

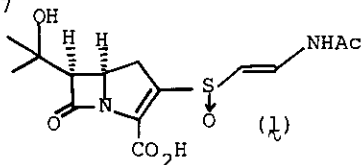
A FORMAL TOTAL SYNTHESIS OF ( $\pm$ )-CARPETIMYCIN A (C-19393 H<sub>2</sub>):  
 STEREOSELECTIVE SYNTHESIS OF ( $\pm$ )-CIS-4-CARBOXYMETHYL-3-(1-  
 METHYL-1-TRIMETHYLSILYLOXYETHYL)-2-AZETIDINONE VIA AN ISO-  
 XAZOLINE DERIVATIVE

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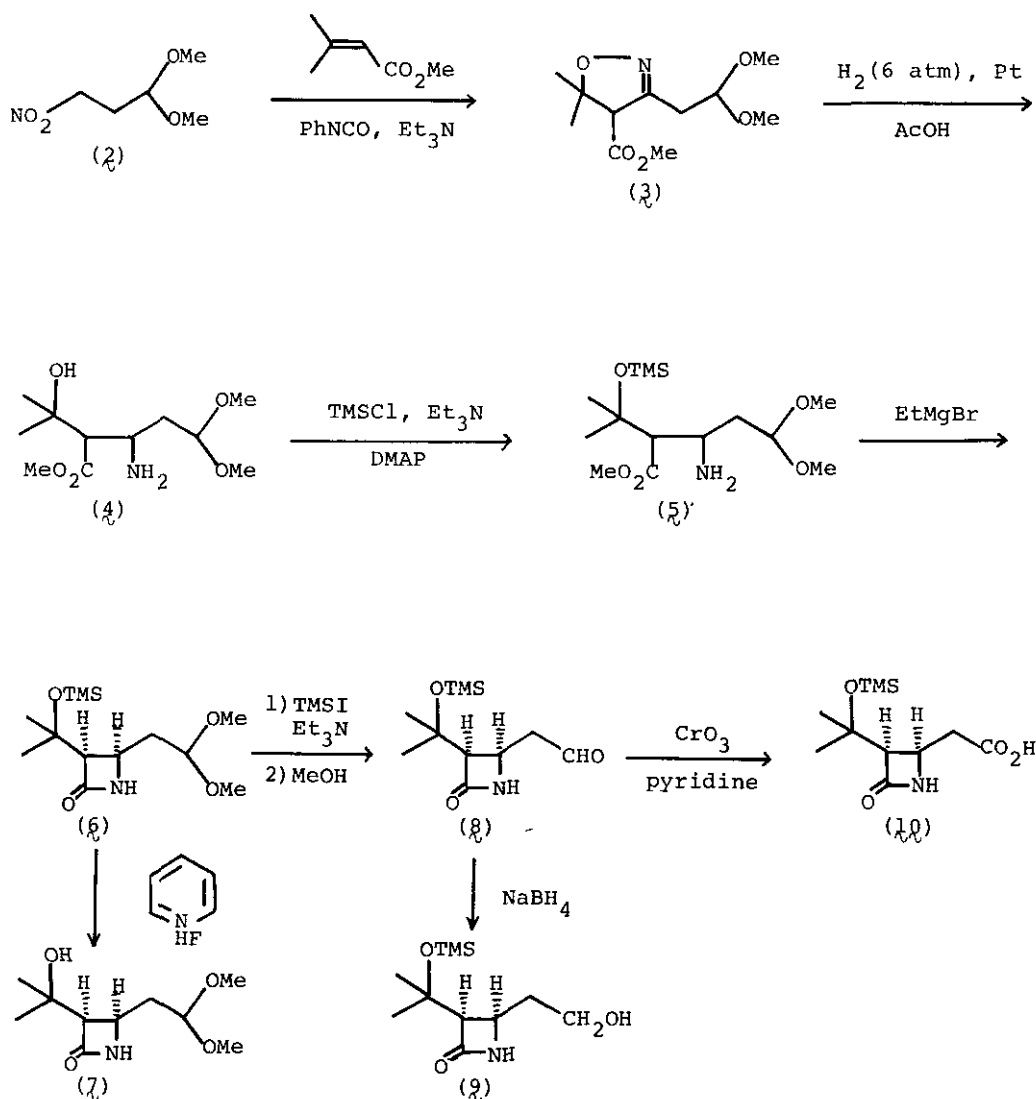
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Abstract — The synthetic intermediate, ( $\pm$ )-cis-4-carboxymethyl-  
 3-(1-methyl-1-trimethylsilyloxyethyl)-2-azetidinone (1), of the  
 carbapenem antibiotics, carpetimycin A, was stereoselectively  
 prepared via an isoxazoline derivative (3).

The carbapenem antibiotics carpetimycin A<sup>1</sup> and C-19393 H<sub>2</sub><sup>2</sup> were isolated by two independent groups and assigned to the same structure (1). This cis-substituted carbapenem was reported to possess not only a highly potent, broad-spectrum antibacterial activity, but also a strong  $\beta$ -lactamase inhibitory activity. Recently its racemate was synthesized by the Takeda's group<sup>3</sup> while the synthesis of the natural levorotatory form was achieved by Ohno and his coworkers.<sup>4</sup> On the other hand, in the case of our synthesis of thienamycin and its derivatives via isoxazoline derivatives,<sup>5</sup> we realized that a cis-substituted  $\beta$ -lactam could be preferentially obtained if a less bulky ester of the isoxazoline derivative was used as a synthetic precursor.<sup>6</sup> On the basis of this knowledge, we have planned a stereoselective synthesis of carpetimycin A and its related compounds and here wish to report the successful result.<sup>7</sup>



Heating 3-nitropropanal dimethyl acetal (2) in the presence of two molar equivalents of phenyl isocyanate and catalytic amount of triethylamine<sup>8</sup> in large excess methyl 3,3-dimethylacrylate at 130 - 140°C for 6.5 h followed by chromatography on neutral alumina eluting with hexane - ether (1 : 1 v/v) gave the desired isoxazoline (3) in 56 % yield and no regio-isomer was obtained. Such high regio-selectivity on the 1,3-dipolar cycloaddition between some nitrile oxides and 3,3-dimethylacrylate was observed by Christl and Huisgen.<sup>9</sup> Catalytic hydrogenation of the isoxazoline (3) in the presence of Adams catalyst in acetic acid under a medium pressure of hydrogen (6 atm) at room temperature for 3 days afforded quantitatively the corresponding amino-ester (4). Without purification, the ester (4) was treated



with excess trimethylsilyl chloride and triethylamine in the presence of catalytic amount of 4-N,N-dimethylaminopyridine in benzene at room temperature for 8 h. After filtration to remove a solid formed, evaporation of the filtrate gave an oily residue, whose NMR spectrum indicated the O-monosilylated structure ( $\xi$ ). The product was then cyclized by the reaction with ethylmagnesium bromide<sup>10</sup> in tetrahydrofuran at room temperature for 2 days. The cis-substituted  $\beta$ -lactam ( $\zeta$ ), IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3450 (NH), 1758 (C=O); NMR (CDCl<sub>3</sub>)  $\delta$ : 0.13 (9H, s, TMS), 1.32 (3H, s, Me), 1.52 (3H, s, Me), 3.14 (1H, d, J = 5.5 Hz, C<sub>3</sub>-H), 3.32 (6H, s, 2  $\times$  OMe); FD-MS m/e 289 (M<sup>+</sup>), was obtained in 61 % yield from  $\xi$  after purification by silica gel column chromatography eluting with acetone - benzene (1 : 4 v/v). But the trans-isomer formed in less than 12 % yield could not be gained as a pure form.

Trimethylsilyl group of  $\zeta$  was removed by the action of pyridinium hydrofluoride<sup>11</sup> in tetrahydrofuran at room temperature for 12 h to give, in 79 % yield, the alcohol ( $\eta$ ), mp 97 - 98°C; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3450 (NH), 1758 (C=O); NMR (CDCl<sub>3</sub>)  $\delta$ : 1.33 (3H, s, Me), 1.50 (3H, s, Me), 3.33 (6H, s, 2  $\times$  OMe), 4.47 [1H, t, J = 6 Hz, CH(OMe)<sub>2</sub>], 7.66 (1H, br s, NH). However selective deprotection of the acetal group was difficult under the acidic reaction conditions. The conversion of the acetal ( $\zeta$ ) into the aldehyde ( $\theta$ ) was achieved by the reaction using three molar equivalents of trimethylsilyl iodide<sup>12</sup> and four molar equivalents of triethylamine in methylene chloride at room temperature for 30 min. Since N-trimethylsilylation also effectively occurred, the product was successively treated with methanol giving in 83 % yield the aldehyde ( $\theta$ ); NMR (CDCl<sub>3</sub>)  $\delta$ : 0.11 (9H, s, TMS), 1.30 (3H, s, Me), 1.54 (3H, s, Me), 9.75 (1H, s, CHO); FD-MS m/e 243 (M<sup>+</sup>). When the deprotection reaction using trimethylsilyl iodide was carried out without triethylamine, no desired product formed.

Reduction of  $\theta$  with sodium borohydride produced the alcohol ( $\varrho$ ), mp 112 - 115°C, NMR (CDCl<sub>3</sub>)  $\delta$ : 0.12 (9H, s, TMS), 1.34 (3H, s, Me), 1.51 (3H, s, Me), 3.17 (1H, d, J = 5.0 Hz, C<sub>3</sub>-H) in 88 % yield. Oxidation of  $\theta$  with excess chromic anhydride in pyridine at room temperature for 16 h furnished in 71 % yield the corresponding acid ( $\rho$ ), mp 135 - 136°C, whose IR (CHCl<sub>3</sub>) and NMR (CDCl<sub>3</sub>) spectra were identical with those of the authentic optically active compound.<sup>4</sup> Since the dextrorotatory compound of  $\rho$  was transformed into (-)-carpetimycin A ( $\rho$ )<sup>4</sup>, a formal total synthesis of the racemate has been accomplished.

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