

## A Photochemical Route to Carbapenems from Pyrazolidin-3-ones. Formal Synthesis of PS-5

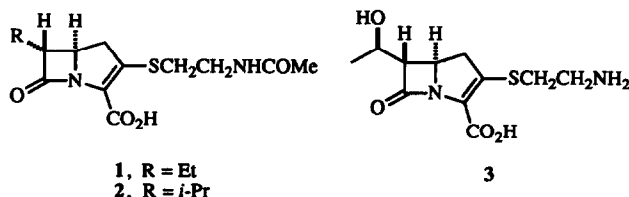
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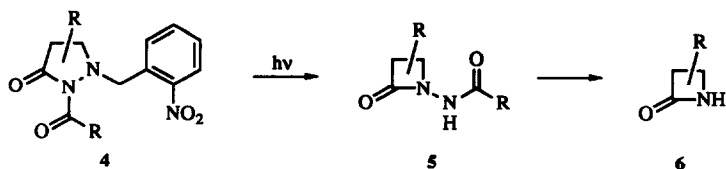
**Key Words:** Antibiotic;  $\beta$ -Lactam; Ring contraction

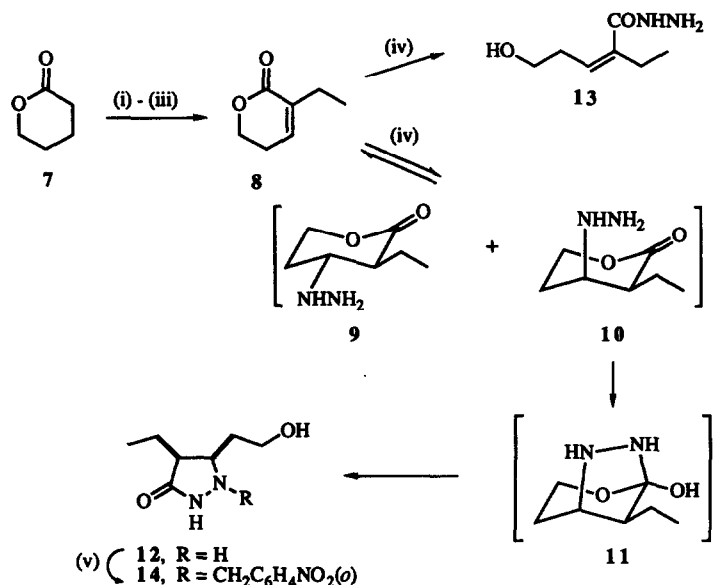
**Abstract:** Photochemical ring contraction of a *cis* disubstituted pyrazolidin-3-one, prepared by hydrazinolysis of an  $\alpha,\beta$ -unsaturated  $\delta$ -lactone, gave the corresponding azetidinone which has been converted previously to the carbapenem antibiotic PS-5.

Carbapenem antibiotics continue to be the center of intense synthetic interest due to the powerful, broad-spectrum antibacterial activity exhibited by many members of this class. The carbapenem PS-5 (**1**)<sup>1</sup> is effective against Gram-positive and Gram-negative bacteria,<sup>2</sup> including  $\beta$ -lactamase producing organisms,<sup>3</sup> and together with the related antibiotics PS-6 (**2**)<sup>4</sup> and thienamycin (**3**)<sup>5</sup> **1** constitutes one of the most important members of this group. Methods for the synthesis of carbapenems have concentrated heavily on enolate-imine cycloaddition and on the hydroxamate approach of Miller<sup>6</sup> for construction of the  $\beta$ -lactam ring. These methods have been summarized in a recent review.<sup>7</sup>



A conspicuous difference between **1** and  $\beta$ -lactam antibiotics such as the carpetimycins and pluracidomycins is the presence of an unusual 5,6-*trans* configuration in the former. Although 5,6-*cis* stereoisomers of **3** exist in the olivanic acids, no corresponding *cis* substituted lactam isomers of **1** or **2** appear to be known. A goal of this research has been to devise routes to hybrid carbapenem structures which embody the unnatural *cis* stereochemistry.

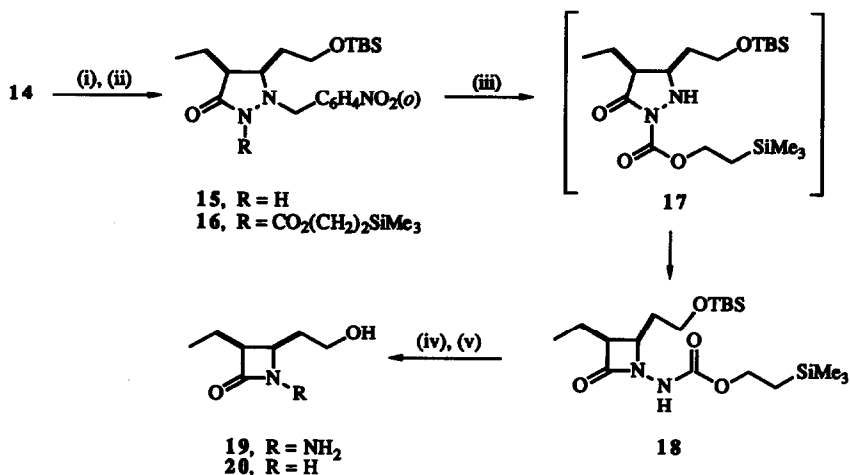




**Reagents:** (i) LDA, EtI, HMPA,  $-70^\circ\text{C}$ , 18 h (65%); (ii) LHMDs, PhSeCl, THF,  $-70^\circ\text{C}$ , 1 h (72%); (iii) 30%  $\text{H}_2\text{O}_2$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 20 min (91%); (iv)  $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ , EtOH,  $\Delta$ , 52 h (50%); (v)  $o\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Br}$ , DMF,  $25^\circ\text{C}$ , 96 h (40%).

We recently described a general synthesis of  $\beta$ -lactams in which photochemical contraction of a pyrazolidin-3-one **4** led to a *N*-acylaminoazetidinone **5**.<sup>8</sup> This synthesis, which extended previous studies on the photochemistry of pyrazolidinones reported by Ege<sup>9</sup> and later by Johnson,<sup>10</sup> relies on the activating influence of an acyl substituent at N2 and a photoremovable blocking group (*o*-nitrobenzyl) at N1 of the pyrazolidinone. Subsequently, we reported a simple procedure for removing the *N*-acylamino group from **5** by nitrosation of the derived *N*-aminoazetidinone with diphenylnitrosamine.<sup>11</sup> We now describe an application of this methodology to the synthesis of the *cis* substituted monocyclic lactam **20**. By virtue of its demonstrated conversion to its *trans* isomer and further transformation of the latter to **1**,<sup>12</sup> the preparation of **20** constitutes a formal synthesis of the antibiotic (+)-PS-5.

$\delta$ -Valerolactone (**7**) was alkylated with ethyl iodide<sup>13</sup> and the resulting product was converted to  $\alpha\beta$ -unsaturated lactone **8** via oxidation of the  $\alpha$ -phenylselenide. On the basis of a previous study of the addition of hydrazine to  $\alpha,\beta$ -unsaturated esters,<sup>14</sup> in which conjugate (but reversible) addition was shown to prevail over carbonyl attack, it was postulated that treatment of **8** with hydrazine would lead initially to **9** and **10**. Only the latter is capable of undergoing transformation via the bicyclic intermediate **11** to a pyrazolidin-3-one which must, in consequence, possess *cis* configuration. In fact, the reaction of **8** with hydrazine hydrate in refluxing ethanol afforded **12** as the sole pyrazolidinone stereoisomer, accompanied by *ca* 10% of the acylhydrazide **13**. Confirmation of the *cis* stereochemistry of **12** was obtained by X-ray crystallographic analysis of *N*-*o*-nitrobenzyl pyrazolidinone **14** (Figure 1).<sup>15</sup>



**Reagents:** (i)  $t\text{-BuMe}_2\text{SiOTf}$ ,  $i\text{-Pr}_2\text{EtN}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 1 h (60%); (ii) NaH,  $\text{N}_3\text{CO}_2(\text{CH}_2)_2\text{SiMe}_3$ , THF, 0 °C, 3 h (95%); (iii) hv (Pyrex), EtOH, 1.5 h, then hv (Vycor), EtOH, 1.5 h (52%); (iv)  $n\text{-Bu}_4\text{NF}$  (2 equiv), MeCN, rt, 15 h (70%); (v)  $\text{Ph}_2\text{NNO}$ ,  $\text{C}_6\text{H}_6$ ,  $\Delta$ , 4 h (76%).

Before activation of N2 of pyrazolidinone 14 the primary alcohol was protected as its *tert*-butyldimethylsilyl ether 15. The latter was then acylated with 2-(trimethylsilyl)ethyl azidoformate<sup>16</sup> in the presence of base to give 16. Irradiation of 16 in ethanol, first through Pyrex and then through a Vycor filter, resulted in its smooth conversion to *cis* azetidinone 18. The tandem optical filtering system employed in this deprotection-contraction sequence ensures that clean removal of the *o*-nitrobenzyl substituent occurs *before* the reaction of unstable intermediate 17 takes place (the latter is inert to Pyrex-filtered light).

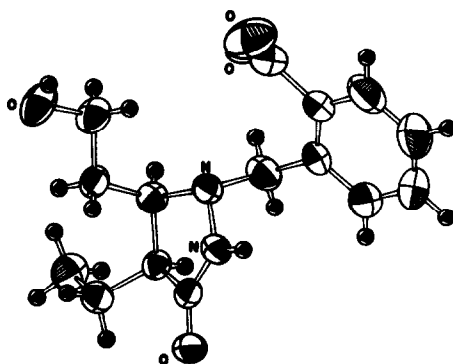


Figure 1. ORTEP representation of 14

Treatment of **18** with tetra-*n*-butylammonium fluoride resulted in removal of both the silyl ether and urethane blocking groups and led to **19** in good yield. Nitrosative deamination<sup>11</sup> of this substance then gave  $\beta$ -lactam **20**. The cis azetidinone **20**, after protection, can be epimerized with potassium *tert*-amylate to the more stable trans isomer.<sup>12</sup> The latter has been oxidized to the corresponding carboxylic acid which was resolved and the (+) enantiomer subsequently converted using the Merck method<sup>17</sup> to (+)-PS-5.

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- Crystals of **14** were triclinic and crystallized in space group P1 with Z = 2 and lattice parameters: a = 10.944 Å, b = 10.203 Å, c = 8.039 Å, V = 757.64 Å<sup>3</sup>. The number of reflections considered observed was 1302. The structure was solved by direct methods and anisotropic refinement full-matrix least-squares at all non-hydrogen atoms converged at R = 0.060, R<sub>w</sub> = 0.074.
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