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

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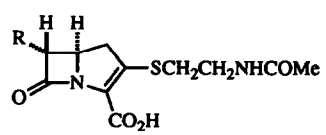
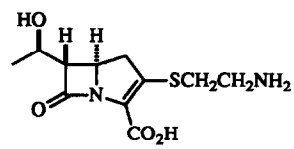
Key Words: Antibiotic; β-Lactam; Ring contraction

Abstract: *Photochemical ring contraction of a cis disubstituted pyrazolidin-3-one, prepared by hydrazinolysis of an α,β-unsaturated δ-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**)[1] is effective against Gram-positive and Gram-negative bacteria,[2] including β-lactamase producing organisms,[3] and together with the related antibiotics PS-6 (**2**)[4] and thienamycin (**3**)[5] **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[6] for construction of the β-lactam ring. These methods have been summarized in a recent review.[7]

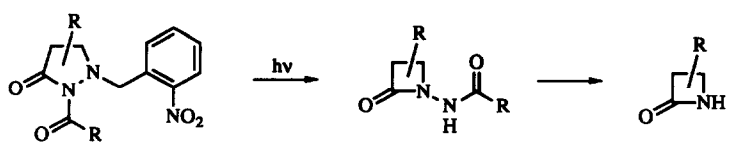


1, R = Et
2, R = *i*-Pr

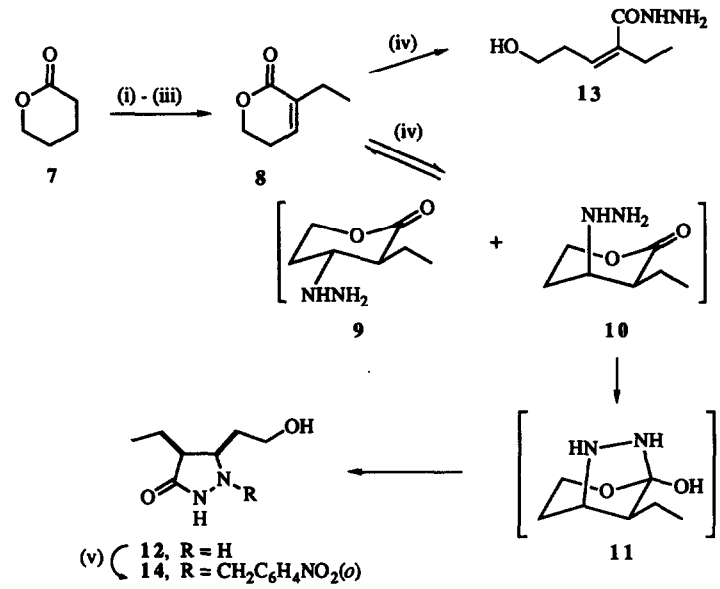


3

A conspicuous difference between **1** and β-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.



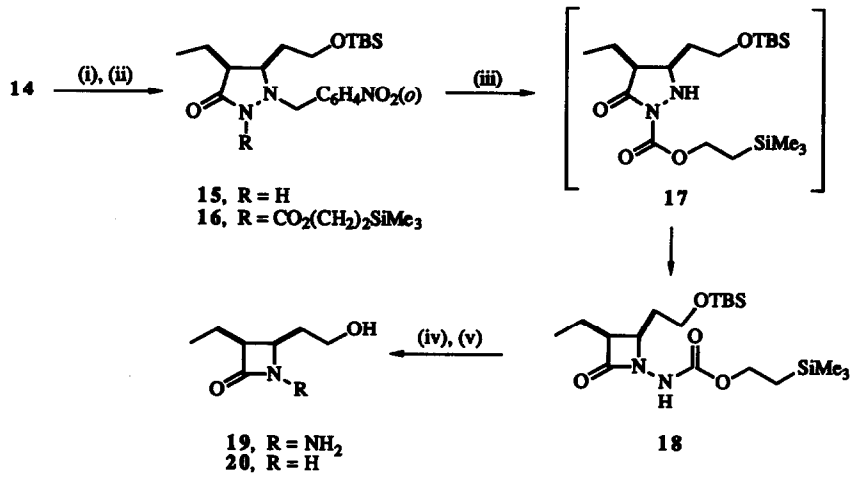
4 **5** **6**



Reagents: (i) LDA, EtI, HMPA, -70 °C, 18 h (65%); (ii) LHMDS, PhSeCl, THF, -70 °C, 1 h (72%); (iii) 30% H_2O_2, 0°→ rt, 20 min (91%); (iv) $H_2NNH_2.H_2O$, EtOH, Δ, 52 h (50%); (v) *o*-$O_2NC_6H_4CH_2Br$, DMF, 25 °C, 96 h (40%).

We recently described a general synthesis of β-lactams in which photochemical contraction of a pyrazolidin-3-one **4** led to a N-acylaminoazetidinone **5**.[8] This synthesis, which extended previous studies on the photochemistry of pyrazolidinones reported by Ege[9] and later by Johnson,[10] 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.[11] 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**,[12] the preparation of **20** constitutes a formal synthesis of the antibiotic (+)-PS-5.

δ-Valerolactone (**7**) was alkylated with ethyl iodide[13] and the resulting product was converted to αβ-unsaturated lactone **8** via oxidation of the α-phenylselenide. On the basis of a previous study of the addition of hydrazine to α,β-unsaturated esters,[14] 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 undergong 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).[15]



Reagents: (i) *t*-BuMe$_2$SiOTf, *i*-Pr$_2$EtN, CH_2Cl_2, 0 °C, 1 h (60%); (ii) NaH, $N_3CO_2(CH_2)_2SiMe_3$, THF, 0 °C, 3 h (95%); (iii) hν (Pyrex), EtOH, 1.5 h, then hν (Vycor), EtOH, 1.5 h (52%); (iv) *n*-Bu$_4$NF (2 equiv), MeCN, rt, 15 h (70%); (v) Ph$_2$NNO, C_6H_6, Δ, 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[16] 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).

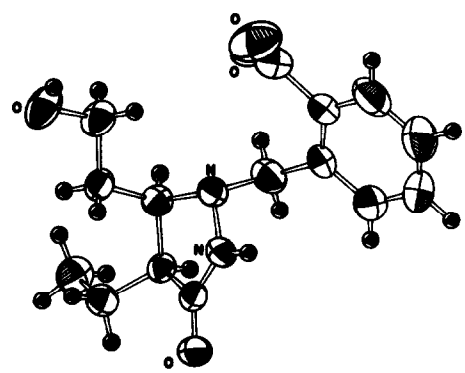


Figure 1. ORTEP representation of **14**

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[11] of this substance then gave β-lactam **20**. The cis azetidinone **20**, after protection, can be epimerized with potassium *tert*-amylate to the more stable trans isomer.[12] The latter has been oxidized to the corresponding carboxylic acid which was resolved and the (+) enantiomer subsequently converted using the Merck method[17] to (+)-PS-5.

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15. 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^3. 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_w = 0.074.
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