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A Short Synthesis of an Important Precursor to a New Class of Bicyclic β-Lactamase Inhibitors

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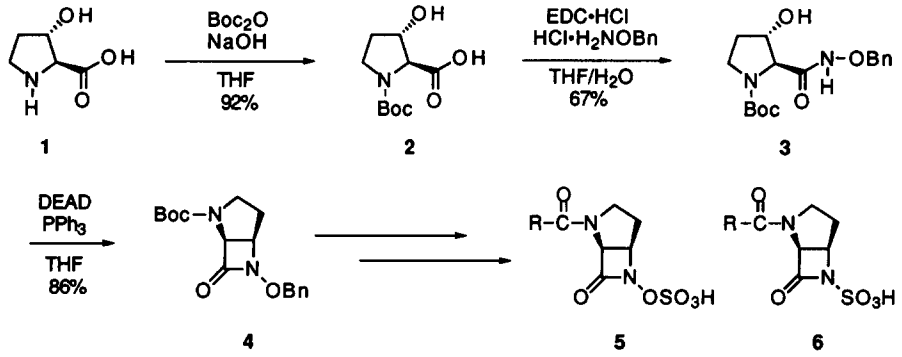
Abstract: A short synthesis of an important precursor to known bicyclic β-lactamase inhibitors is described. The synthesis uses commercially available *trans*-3-hydroxy-L-proline **1**. Protection of the amino group followed by formation of the hydroxamate and cyclization using Mitsunobu conditions afforded bicyclic β-lactam **4** in three steps in 53% overall yield. Copyright © 1996 Elsevier Science Ltd

The emergence of resistance by bacteria to many of the currently used β-lactam antibiotics has led the scientific community to search for new and effective antibacterial agents and inhibitors of β-lactamase enzymes that are responsible for most resistance.[1] Recently workers at F. Hoffmann-LaRoche have reported the synthesis and biological evaluation of a variety of bicyclic β-lactams **5** and **6**.[2] These bicyclic β-lactams were shown to have activity against the class C β-lactamases. We were particularly interested in synthesizing a precursor to these bicyclic β-lactams using the hydroxamate-mediated cyclization approach developed previously in our laboratory.[3] We reasoned that we should be able to quickly and efficiently construct a precursor to these bicyclic β-lactams from commercially available *trans*-3-hydroxy-L-proline **1** (Fluka).

The amine of *trans*-3-hydroxy-L-proline **1** was protected by treatment with Boc anhydride to afford **2** in 92% yield. The carboxylic acid was then coupled with *O*-benzylhydroxylamine using the water soluble carbodiimide 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC) to afford hydroxamate **3** in 67% yield. Finally, the hydroxamate was cyclized using Mitsunobu conditions (diethylazodicarboxylate, PPh_3)[4] to afford bicyclic β-lactam **4** in 86% yield. We anticipated that the cyclization would afford the *N*-cyclized product **4** over the carbonyl *O*-cyclized product based upon precedent from our previous work.[3] However, we had never before attempted to form a bicyclic system using the Mitsunobu conditions. The structure of the cyclization product was indeed confirmed to be **4** by X-ray crystallography indicating that the *N*-cyclized product was the exclusive cyclization product.

In summary, bicyclic β-lactam **4** was synthesized in three steps with an overall yield of 53%.[5] The previous route to bicyclic β-lactam **4** required 12 steps with an overall yield of 1.3%.[2a] Bicyclic β-lactam **4** can be used for the synthesis of a large number of important β-lactamase inhibitors. We are currently investigating the preparation of other bicyclic β-lactams from intermediate **4** for use as β-lactamase inhibitors.



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References and Notes

1. Davies, J. *Science* **1994**, *264*, 375-382.
2. (a) Angehrn, P.; Gubernator, K.; Gutknecht, E.-M.; Heinze-Krauss, I.; Hubschwerlen, C.; Kania, M.; Page, M. G. P.; Specklin, J.-L. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy **1995**, Program and Abstracts, F147. (b) Charnas, R.; Gubernator, K.; Heinze, I.; Hubschwerlen, C. European patent serial No. 0508234A2 **1992**.
3. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49-56.
4. (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335-656.
5. Characterization data: (**2**) recrystallized from EtOAc-hexanes: mp 156-157 °C; IR (KBr) 3180, 1755, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 90 °C) δ 1.38 (s, 9H), 1.72-1.80 (m, 1H), 1.86-1.99 (m, 1H), 3.41 (apparent dd, J = 9.0, 5.0 Hz, 2H), 3.96 (s, 1H), 4.24 (s, 1H), 5.13 (br s, 1H, D_2O exchangeable), 12.14 (br s, 1H, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6, 22 °C) mixture of rotomers δ 27.94, 28.11, 31.63, 32.32, 44.16, 44.45, 67.75, 67.96, 72.79, 73.78, 78.60, 78.69, 153.26, 153.70, 172.12, 172.46; $[\alpha]^{25}_D$ = -9.9° (c = 1, MeOH); HRMS (FAB) calcd for $C_{10}H_{18}NO_5$ (MH^+) 232.1185, found 232.1190; Anal. calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.94; H, 7.30; N, 6.08. (**3**) recrystallized from EtOAc-hexanes: mp 158-160 °C; IR (KBr) 3520, 3200, 1700, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 90 °C) δ 1.38 (s, 9H), 1.68-1.76 (m, 1H), 1.91-2.01 (m, 1H), 3.35-3.47 (m, 2H), 3.87 (br s, 1H), 4.10 (s, 1H), 4.81 (s, 2H), 5.00 (s, 1H, D_2O exchangeable), 7.25-7.50 (m, 5H), 10.92 (s, 1H, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6, 22 °C) mixture of rotomers δ 28.02, 28.13, 31.80, 32.51, 44.38, 44.65, 66.62, 66.74, 73.27, 74.27, 76.72, 76.86, 78.65, 78.72, 128.23, 128.28, 128.73, 128.87, 135.85, 153.27, 153.68, 167.25, 167.40; $[\alpha]^{25}_D$ = -75.2° (c = 1, $CHCl_3$); HRMS (FAB) calcd for $C_{17}H_{25}N_2O_5$ (MH^+) 337.1763, found 337.1761; Anal. calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.61; H, 7.03; N, 8.27. (**4**) recrystallized from hexanes: mp 88-89 °C; R_f 0.39 (2:3 EtOAc:hexanes); IR (KBr) 1770, 1685 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 45 °C) δ 1.39 (s, 9H), 1.58-1.67 (m, 1H), 1.85 (apparent dd, J = 13.8 Hz, 6.0 Hz, 1H), 3.00 (ddd, J = 11.4, 11.4, 6.0 Hz, 1H), 3.74 (apparent t, J = 10.8, 9.0 Hz, 1H), 4.42 (apparent t (probable multiplet), J = 4.8, 4.2 Hz, 1H), 4.80 (br, 1H), 4.93 (d, J_{AB}= 11.4 Hz, 1H), 4.97 (d, J_{AB} = 11.4 Hz, 1H), 7.35-7.44 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) mixture of rotomers δ 25.37, 26.09, 28.24, 43.39, 43.80, 63.40, 64.25, 64.41, 78.27, 80.69, 128.69, 129.14, 135.19, 153.35, 162.12, 162.56; $[\alpha]^{25}_D$ = -214.9° (c = 1, $CHCl_3$); HRMS (FAB) calcd for $C_{17}H_{23}N_2O_4$ (MH^+) 319.1658, found 319.1641; Anal. calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 63.92, H, 6.99; N, 8.70.

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