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A New Synthetic Approach to the Carbapenem Antibiotic PS-5 from Ethyl (S)-3-Hydroxybutanoate

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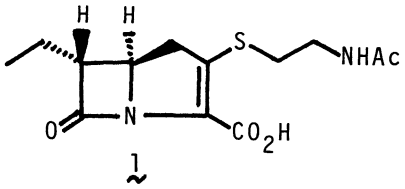
A new synthetic route to the PS-5 key precursor is described which involves the fully stereocontrolled transformation of the optically active 2-azetidinone derivative easily obtainable from ethyl (S)-3-hydroxybutanoate.

The carbapenem antibiotic (+)-PS-5 (1)[1] has currently been the focus of considerable synthetic activities.[2] In an effort to develop new synthetic routes to carbapenem antibiotics from (R)- or (S)-3-hydroxybutanoic esters (2)[3] which are commercially available in large quantity, we have recently reported that the enolate-imine condensation of (S)-2 with the silylimine generated in situ from trimethylsilylpropynal affords the 2-azetidinone derivative (+)-3 as a major product.[4] We now wish to report a facile scheme for the stereocontrolled transformation of (+)-3 to a PS-5 key precursor.



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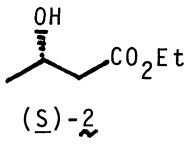
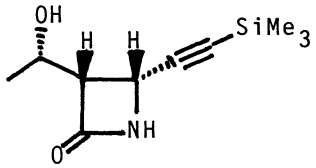


(S)-2



(+)-3

The following scheme depicts the newly-developed sequence starting with (+)-3 prepared from (S)-2 of ca. 80% ee.[5] First, the hydroxy group on the side chain was removed by bromination followed by reduction with zinc to give the 3-ethyl derivative (4);[6] $[\alpha]_D^{20}$ -41.1° (c 1.08, $CHCl_3$), which was then subjected to the hydration/Baeyer-Villiger sequence[7] to afford the 4-acetoxy derivative (5)[6] with 3,4-cis configuration ($J_{3,4}$=4.2 Hz); $[\alpha]_D^{22}$ -113.9° (c 0.99, $CHCl_3$). The reaction of 5 with the silyl enol ether (6), prepared by the reported method,[2a] proceeded with complete inversion of configuration at C-4 to give the 3,4-trans adduct (7);[6] $[\alpha]_D^{17}$ +47.8° (c 0.60, $CHCl_3$).[8] The thermal cyclization of 7 carried out according to the reported procedure[9] gave rise to the desired PS-5 precursor (8), of which the IR and NMR data are in accord with the reported values.[2a] Since the precursor 8 has already been converted to (+)-PS-5,[2] we have now completed the formal synthesis of (+)-PS-5 from the easily available (S)-3-hydroxybutanoic ester.

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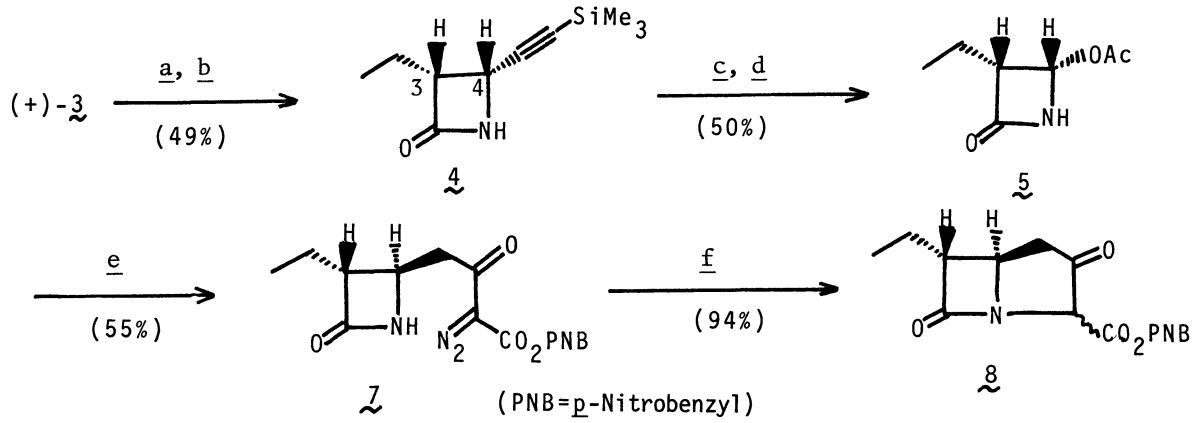

a: CBr_4/PPh_3, THF; b: Zn/HCO_2H, N,N-Dimethylformamide; c: $H_2SO_4/HgSO_4$, aq. THF; d: m-Chloroperbenzoic acid, AcOEt; e: $CH_2=C(OSiMe_3)-CN_2-CO_2PNB$ (6)/$Me_3SiOSO_2CF_3$, CH_2Cl_2; f: Reflux in hexane in the presence of $Rh_2(OCOC_7H_{15}-n)_4$

In summary, we have now developed a new synthetic route to the optically active PS-5 key precursor from the inexpensive chiral starting material. Further improvement of the present approach is now in progress.

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4) T. Chiba, M. Nagatsuma, and T. Nakai, Chem. Lett., 1985, 1343.
5) The yield of each step has not been optimized yet.
6) The IR and ^1H NMR spectral data of these intermediates are in accord with the reported values[2a,b] and/or the assigned structures.
7) T. Chiba and T. Nakai, Chem. Lett., 1985, 651.
8) Lit.[2b] $[\alpha]_D^{22}$ +64.7° (c 1.0, $CHCl_3$); $J_{3,4}$= 2.0 Hz.
9) T. Salzmann, R. W. Rarcliff, and B. G. Christensen, Tetrahedron Lett., 21, 31 (1980)

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