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SYNTHESIS OF A POTENTIAL INTERMEDIATE TO β-LACTAM ANTIBIOTICS

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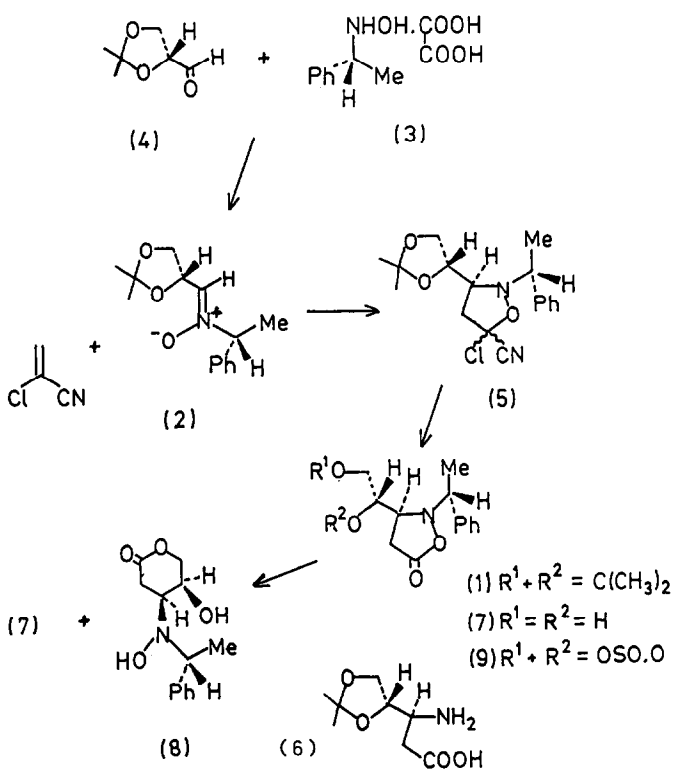
Summary: Cycloaddition of nitrone (2) to α-chloroacrylonitrile followed by hydrolysis afforded the isoxazolidinone (1) as a single diastereomer. The configuration at the new chiral centre (3S), corresponding to that in thienamycin, was established by an X-ray analysis of (9).

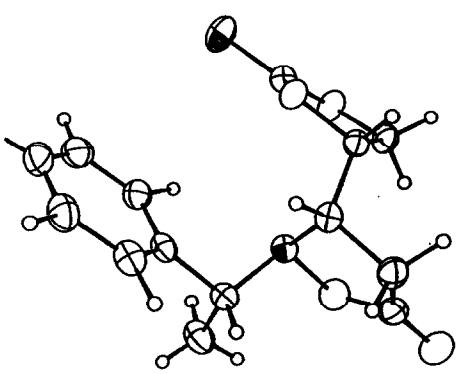
The commercial potential of thienamycin derivatives and other carbapenem antibiotics continues to attract widespread synthetic interest.[1] We here report the formation of the isoxazolidinone (1), a potential carbapenem intermediate, as a single diastereomer from readily available starting materials.



Nitrone (2), prepared (72% yield) from the hydroxylamine oxalate (3)[2] (from (R)-(+)-α-methylbenzylamine) and freshly distilled aldehyde (4)[3] (from D-mannitol), ($CaCl_2$-Et_3N, ether, 0°C) had m.p. 54-55°, $[\alpha]_D$ +127.4° ($CHCl_3$); $(M)^+$ 249.1362 ($C_{14}H_{19}NO_3$ requires 249.1365). Cycloaddition of the nitrone (2) with excess α-chloroacrylonitrile (reflux, 15 m) and hydrolysis (Et_3N, H_2O-THF, 1:4, 20°C, 16 h) of the cycloadduct (mixture of diastereomers) (5), afforded the oily isoxazolidinone (1)[4] (79%) as a single diastereomer (^1H and ^{13}C n.m.r., g.l.c. on 25 m x 0.32 mm CPSIL5 CB fused silica capillary column), $[\alpha]_D$ -16.2° ($CHCl_3$), $(M)^+$ 291.1473 ($C_{16}H_{21}NO_4$ requires 291.1471). Hydrogenolysis ($Pd(OH)_2$-EtOH, 70°C, 48 h) afforded the β-amino acid (6) (84%), $[\alpha]_D$ -27.5° (MeOH), $(M-CH_3)^+$ 174.0762 ($C_7H_{12}NO_4$ requires 174.0766). Deprotection of the isoxazolidinone (1) (TsOH, THF-H_2O, 4:1, reflux, 1 h) gave (70%) a mixture (4:1), separable by silica gel chromatography, of the diol (7), $(M)^+$ 251.1145 ($C_{13}H_{17}NO_4$ requires 251.1158) and the isomeric lactone (8), m.p. 140-2°, $[\alpha]_D$ +112.4°, (MeOH); ν_{max} (KBr) 1731 cm^{-1}, $(M)^+$ 251.1149. The thionocarbonate (9)[5] (diol + $CSCl_2$, DMAP, CH_2Cl_2, 0°C, 1 h)[6] had m.p. 174-5°, $[\alpha]_D$ -10.9° ($CHCl_3$); $(M)^+$ 293.0724 ($C_{14}H_{15}NO_4S$ requires 293.0722). A single crystal structure analysis of (9) showed that the single diastereomer (1) formed in the nitrone cycloaddition had the 3S-configuration (Fig. 1), corresponding to that in thienamycin.

Crystal Data.[7] $C_{14}H_{15}NO_4S$ (8): M = 293.1, monoclinic, space group $P2_1$, a = 5.785(2), b = 10.808(1), c = 11.484(2) A°, β = 103.33(1)°, U = 698.7 $Å^3$, Z = 2, D_c = 1.39 g cm^{-3}, T = 293 K, R = 0.031, R' = 0.034 for 922 independent reflections with $F_o^2 > 3\sigma(F_o^2)$.

Fig. 1. X-Ray Structure of Thionocarbonate (9).



Extensive methodology exists for transforming compounds such as (1) into key intermediates to carbapenems.[8] The two chiral centres present in (1) may be expected to exert further stereo-control, either in concert or singly, in the course of subsequent elaboration.

References and Notes

1. Reviews on the synthesis of carbapenems: R.W. Ratcliffe, G. Albers-Schönberg in Chemistry and Biology of β-Lactam Antibiotics, R.B. Morin, M. Gorman Eds., Academic Press, New York, 1982, Vol. 2, p.227; T. Nagahara, T. Kametani, Heterocycles, 1987, 25, 129; R. Labia, C.J. Morin, J. Antibiot., 1984, 37, 1103.
2. T. Polonsky and A. Chimiak, Bull. Acad. Pol. Sci. Chim., 1979, 27, 459; for experimental details see P.M. Wowkulich and M.R. Uskokovic, Tetrahedron, 1985, 41, 3455.
3. E. Baer and H.O.L. Fischer, J. Biol. Chem., 1939, 128, 463; E. Baer, Biochem. Prep., 1952, 2, 31; D.Y. Jackson, Synthetic Commun., 1988, 18, 337.
4. (1): ^{1}H n.m.r. ($CDCl_3$, 200 MHz): δ 1.26 (s, 6H), 1.53 (d, J = 6.5 Hz, 3H), 2.59 (dd, J = 2.6, 18.1 Hz, 1H), 2.71 (dd, J = 7.7, 18.1 Hz, 1H), 3.32 (m, 2H), 4.05 (m, 3H), 7.2-7.5 (m, 5H); ^{13}C n.m.r. ($CDCl_3$, 50 MHz): δ 20.48, 24.69, 26.25, 29.21, 62.02, 67.01, 67.09, 75.97, 109.78, 127.77, 128.69, 129.08, 139.93, 176.69; IR ($CHCl_3$): ν_{max} 1782, 1490, 1451, 1429, 1382, 1375, 1220, 1170, 1089, 1071, 875, 849, 705 cm^{-1}.
5. (9): ^{1}H n.m.r. ($CDCl_3$, 200 MHz): δ 1.56 (d, J = 6.5 Hz, 3H), 2.65 (dd, J = 1.6, 18.6 Hz, 1H), 2.88 (dd, J = 8.2, 18.6 Hz, 1H), 3.65 (m, 1H), 4.05 (m, 1H), 4.13 (q, J = 6.5 Hz, 1H), 4.75 (m, 2H), 7.1-7.5 (m, 5H); ^{13}C n.m.r. ($CDCl_3$, 50 MHz): δ 19.95, 29.81, 60.67, 66.9, 72.0, 79.66, 127.88, 129.51, 138.62, 175.08, 190.45; IR ($CHCl_3$): 1781, 1431, 1300, 1280, 1155, 1075, 965, 897, 860, 695 cm^{-1}. Found: C, 57.3; H, 5.15; N, 4.6; S, 11.05%; $C_{14}H_{15}NO_4S$ requires C, 57.3; H, 5.15; N, 4.5; S, 10.9%.
6. E.J. Corey and P.B. Hopkins, Tetrahedron Lett., 1982, 23, 1979.
7. Notes. X-ray intensity measurements were made by 2θ-ω scan on a Nonius CAD4 diffractometer using graphite-monochromated Mo-K_α radiation. Unit cell parameters were determined by least-squares refinement of the setting angles for 25 reflections. Hydrogen atom parameters were included, but not refined in the final cycles of least-squares. The principal computer programs used in structure solution and refinement are: MITHRIL, a computer program for the automatic solution of crystal structures from X-ray data:

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8. For examples and leading references see: conversion of isoxazolidinones into azetidinones: S.W. Baldwin, J. Aubé, Tetrahedron Lett., 1987, 179; S. Kim, P.H. Lee, T.A. Lee, Chem. Commun., 1988, 1242; introduction of hydroxyethyl side chain: F.A. Bouffard, T.N. Salzmann, Tetrahedron Lett., 1985, 6285; A.B. Hamlet, T. Durst, Can. J. Chem., 1983, 61, 411; 1β-methyl carbapenems: J.S. Prasad, L.S. Liebeskind, Tetrahedron Lett., 1987, 1857.

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