Synthesis of Optically Active Penems

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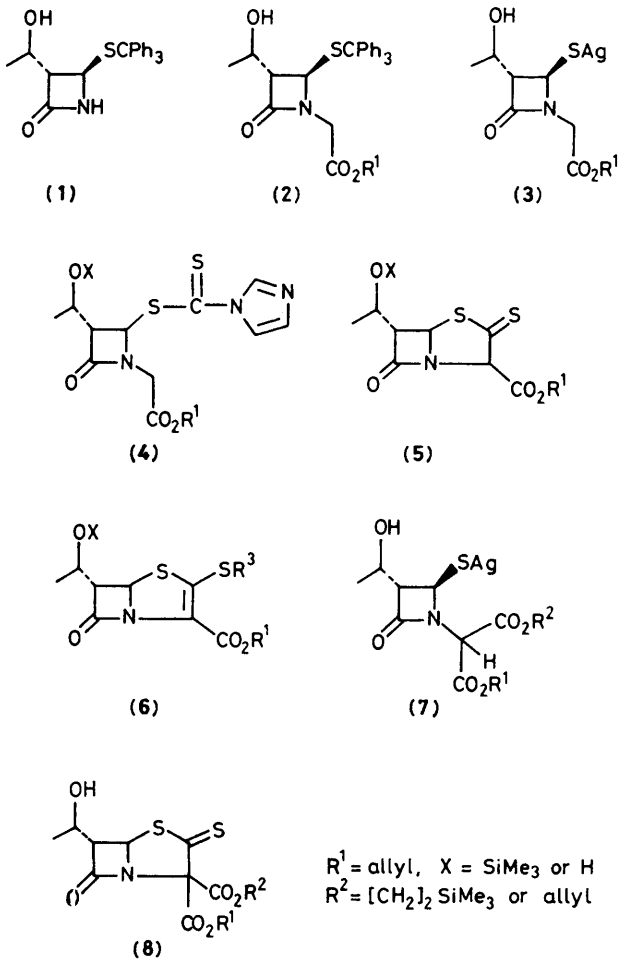
A convenient stereospecific synthesis of optically active penems is described.

Penems,[1,2] a new class of β-lactam antibiotics, have drawn considerable interest during the past few years by virtue of their spectrum and potency[3] against a wide variety of pathogenic micro-organisms. The synthesis of penems requires several chemical transformations, often resulting in overall low yields.[4,5] Recently, a Sankyo[6] and a Hoechst[7] group have described the synthesis of the 2-thioxopenam (**5**) and its conversion to penems. As a consequence of the 1-C_5 ring formation, C_5 epimeric mixtures of penems were formed in both the above procedures. Furthermore, the penems with (5*S*) stereochemistry are biologically inactive compounds, and their conversion to the desired (5*R*)-isomers requires a thermal isomerization step.[4]

More recently, we have reported[8] a stereospecific synthesis of the thioxopenam (**5**) *via* the malonate (**7**); cyclization to (**8**) followed by mono-decarboxylation gave exclusively the desired (5*R*)-isomer. Now we describe a still more convenient and high yielding sequence to the thioxopenam (**5**) and hence to the penems, which are otherwise difficult to obtain by conventional methods.

Alkylation of the hydroxyazetidinone (**1**) with allyl iodoacetate in acetonitrile in the presence of caesium carbonate afforded the β-lactam (**2**) in >80% yield: ^{1}H n.m.r. δ ($CDCl_3$) 7.5—7.1 (15H, m), 5.9 (1H, m), 5.2 (2H, m), 4.5 (1H, d, *J* 1.5 Hz, β-lactam), 4.4 (2H, m, O–CH_2–), 3.95 (1H, m, 8-H), 3.8 (1H, d, *J* 18 Hz, N–CH_2–), 3.45 (1H, dd, *J* 1.5, 6 Hz, β-lactam), 2.85 (1H, d, *J* 18 Hz), and 1.5 (3H, d, *J* 6 Hz).



The silver thiolate (**3**) was then prepared by deblocking the trityl group[9] with silver nitrate in methanol in the presence of an equivalent of pyridine. For the ensuing steps protection of the hydroxy group as a silyl ether was found beneficial. Treatment of the silver salt with bis-trimethylsilylacetamide in methylene dichloride cleanly gave the trimethylsilyl ether, which was (without isolation) further treated with two equivalents of thiocarbonyldi-imidazole[8] to generate the dithiocarbamate (**4**); ^{1}H n.m.r. δ ($CDCl_3$) 8.4 (1H, br. s), 7.6 (1H), 7.05 (1H, d, *J* 1 Hz), 6.05 (1H, d, *J* 2 Hz, β-lactam), 5.9 (1H, m), 5.3 (2H, m), 4.65 (2H, m), 4.3 (1H, m, 8-H), 4.2 (1H, d, *J* 16 Hz), 3.85 (1H, d, *J* 16 Hz, N–CH_2–), 3.4 (1H, dd, *J* 2, 8 Hz, β-lactam), 1.35 (3H, d, *J* 8 Hz), and 0.1 (9H, s). Reaction of (**4**) with two equivalents of lithium hexamethyldisilazane at −76 °C in tetrahydrofuran spontaneously generated the thione as its thiolate salt which after aqueous acidic workup gave (**5**) in about 70% yield; ^{1}H n.m.r. δ ($CDCl_3$) 5.85 (1H, d, *J* 1.5 Hz, 5-H), 5.35 (1H, s, 3-H), 4.3 (1H, m, 8-H), 3.65 (1H, dd, *J* 1.5, 7 Hz, 6-H), and 1.35 (3H, d, *J* 7 Hz); i.r. ν_{max} ($CHCl_3$) 1792 and 1742 cm^{-1}; ^{13}C n.m.r. δ ($CDCl_3$) 230.25 (C=S) and 164.21 p.p.m. (β-lactam).

Deblocking the allyl protecting group had to be performed at the penem stage, as the thione undergoes allylic rearrangements[8] during deprotection. The thioxopenam readily reacted with alkylating and acylating agents to afford the new penems (**6**), which were then deprotected[10] to obtain the desired penem salts. The biological properties of the penems will be published elsewhere.

Received, 19th May 1983; Com. 644

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