

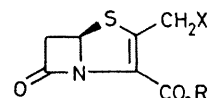
Synthesis of Optically Active (5*R*)-2-Penem-3-carboxylates from Penicillanic Acid Derivatives: New Potent Anti-bacterial Agents

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Summary A novel synthesis of optically active (5*R*)-2-penem-3-carboxylates (**1a—d**) (same configuration as in natural penicillins) starting from the penicillanic acid derivative (**3**), is described.

RECENT efforts in the β -lactam field have been increasingly focused on the synthesis of new and novel structures, of which the 'penem' class, whether as 6-acylamino¹ or 6-unsubstituted^{2,3,4} derivatives, has drawn attention.

As part of our continuing interest in this area,⁵ we report the first synthesis of optically active (5*R*)-2-acetoxymethyl-2-penem-3-carboxylates (**1a—c**) and (5*R*)-2[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl-2-penem-3-carboxylate (**1d**). We treated (5*R*)-methylpenicillanate *S*-oxide (**3**) with suitable alkynes,⁶ and obtained the new key intermediates (**2**). To prepare (**1a**), (**3**) was refluxed in toluene with 1,4-diacetoxymethyl-2-yne to give (**2a**)† in 60% yield as a nonseparable mixture of chiral sulphoxides (80:20) (from ¹³C- and ¹H-n.m.r. data†) having a *cis*-configuration about the double bond derived from the alkyne, the reaction proceeding *via* a regioselective *cis*-addition: δ (CDCl₃) 2.88 (1 H, dd, *J* 4 and 14 Hz, H-3 β), 3.38 (1 H, dd, *J* 2 and 14 Hz, H-3 α), 4.88 (2H, d, *J* 6 Hz, =CH-CH₂-), 4.92 (2 H, s, =C-CH-), 5.32 (1 H, dd, *J* 4 and 2 Hz, H-4), and 6.47 (1 H, d, *J* 6 Hz,

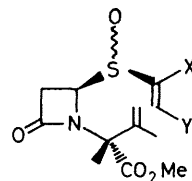
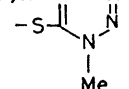


(1) a; X = OAc, R = O₂NC₆H₄CH₂-*p*

b; X = OAc, R = H

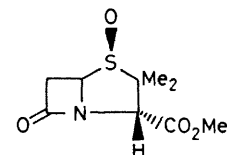
c; X = OAc, R = CH₂OCOMe

d; X = N-N, R = CH₂OCOMe



(2) a; X = Y = CH₂OAc

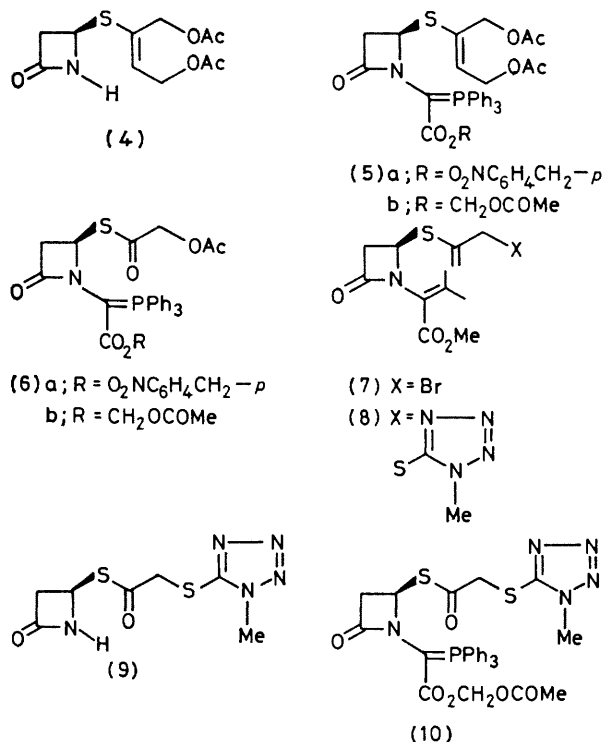
b; X = CH₂OH, Y = H



(3)

CH=C-), (major isomer); field desorption mass spectrum (FD-MS): *m/e* 401 (*M*⁺), 219 and 182 (C-4-S bond cleavage). Compound (**2a**) then isomerized to its $\alpha\beta$ -unsaturated ester, was selectively ozonized (CH₂Cl₂, -78 °C), reduced to the

corresponding sulphide (PBr₃, -20 °C in dimethylformamide (DMF), 80%), and cleaved by removing the oxalo group (MeOH, silica gel) to give (4). The azetidinone (4) containing a free N-H group was condensed with *p*-nitrobenzyl glyoxylate (or alternatively with its acetoxymethyl ester) in refluxing benzene and was chlorinated using SOCl₂-pyridine-tetrahydrofuran. Reaction with PPh₃ and pyridine afforded the ylides (5a,b). The phosphorane function of



(5a) was protected as its phosphonium salt (20% CF₃CO₂H in CH₂Cl₂), and was treated with ozonized oxygen at -40 °C to give (6a) after restoring the phosphorane group with aqueous sodium hydrogen carbonate. Intramolecular Wittig cyclisation (refluxing toluene, 2 h) gave (1a):[†] m.p.

122–123 °C; [α]_D +87° (CHCl₃); λ_{max} 265 (ε 11000) and 322 nm (ε 7000); ν_{max} (CHCl₃) 1800 (β lactam), 1750, and 1720 cm⁻¹; δ (CDCl₃) 3.75 (1 H, dd, *J* 2.3 and 16.8 Hz, H-6α), 3.87 (1H, dd, *J* 3.6 and 16.8 Hz, H-6β), 5.14 and 5.50 (both H, d, *J* 15.8 Hz, =C-CH₂-O), and 5.71 (1 H, dd, *J* 2.3 and 3.6 Hz, H-5); ¹³C-n.m.r. [(CD₃)₂CO] 20.26 (COCH₃), 51.09 (COCH₂CHS), 59.99 (CH₂OCOME), 62.13 (CH₂-CHS), 65.87 (COOCH₂Ph), 124.21 (Ph, 2', 6'), 129.18 (Ph, 3', 5'), 144.47 (Ph, 4'), 154.66 (S-C=), 159.71 (-C-COO), 170.22 (OCOME₃), and 173.89 p.p.m. (N-CO and COOCH₂); (FD-MS): *m/e* 378 (M⁺).

Finally, hydrogenolysis (AcOEt, aqueous NaHCO₃, Pd-C 10%) of (1a) afforded crude (1b):[†] λ_{max} (EtOH) 258 and 301 nm; ν_{max} (CHCl₃) 1790 (β-lactam), 1735, and 1700 cm⁻¹.

Analogously, (1c)[†] was obtained from (5b) following the same route, [α]_D +110° (CHCl₃). Compound (1d) was prepared by a slightly different and in some ways more efficient route.

Compound (2b) was obtained in very good yield by heating (3) with prop-2-yn-1-ol (toluene, 8 h).

After isomerisation of its isopropenyl double bond, reaction with PBr₃ (-20 °C, DMF) reduced the sulphoxide and brominated the alcoholic function of (2b) to give (7) in 70% yield. Nucleophilic displacement of bromine from (7) with the sodium salt of 1-methyltetrazole-5-thiol gave (8), which, after ozonization of both double bonds and cleavage of the oxalo residue, afforded product (9).

Compound (9) was condensed with acetoxymethyl glyoxylate, chlorinated, and treated with PPh₃-pyridine finally to give the thioester-phosphorane (10). Compound (1d)[†] was then obtained from (10) by heating (toluene, 100 °C, 2 h).

Compound (6) was also obtained by a parallel route, starting from the versatile intermediate (2b). Acetylation of (2b), reduction of the sulphoxide, removal of the group attached to N, followed by glyoxylation, chlorination, and treatment with PPh₃, afforded (6) in better yield than before.

Compounds (1b–d), in some ways similar to the cephalosporin skeleton, showed remarkable antibacterial activity.

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[†] Satisfactory spectroscopic data were obtained for all new compounds.

[‡] *syn* Orientation of S-O, C3-H3α, C4-H4α bonds was strongly suggested by H-3α shielding in (2) and its analogues and by the net negative solvent effect observed in (2b) for H-4. The source of chirality was identified as the sulphur atom by ¹³C n.m.r. spectroscopy.

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³ P. C. Cherry, C. E. Newall, and N. S. Watson, *J.C.S. Chem. Comm.*, 1979, 663; C. M. D. Bells and M. Said Abu-Rabie, *ibid.*, p. 665.

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⁵ P. Lombardi, G. Franceschi, and F. Arcamone, *Tetrahedron Letters*, 1979, 3777.

⁶ This trapping reaction was described by D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Chem. Comm.*, 1973, 303, on 6-acylaminopenicillates.

⁷ The preparation of racemic (1a), by a different route has been described recently (CIBA-Geigy AG, German OLS, No. 2,819,655).