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

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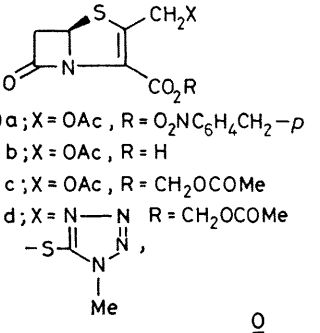
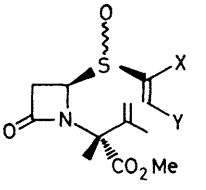
*Summary* A novel synthesis of optically active (5*R*)-2-penem-3-carboxylates (**1a**—**d**) (same configuration as in natural penicillins) starting from the penicillanic acid derivative (**3**), is described.

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-acylamino[1] or 6-unsubstituted[2,3,4] derivatives, has drawn attention.

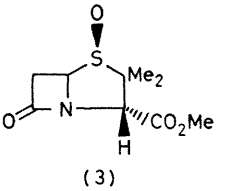
As part of our continuing interest in this area,[5] we report the first synthesis of optically active (5*R*)-2-acetoxymethyl-2-penem-3-carboxylates (**1a**—**c**) and (5*R*)-2[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl-2-penem-3-carboxylate (**1d**). We treated (5*R*)-methylpenicillanate *S*-oxide (**3**) with suitable alkynes,[6] and obtained the new key intermediates (**2**). To prepare (**1a**), (**3**) was refluxed in toluene with 1,4-diacetoxybut-2-yne to give (**2a**)† in 60% yield as a nonseparable mixture of chiral sulphoxides (80:20) (from $^{13}C$- and $^{1}H$-n.m.r. data‡) having a *cis*-configuration about the double bond derived from the alkyne, the reaction proceeding *via* a regiospecific *cis*-addition: δ ($CDCl_3$) 2·88 (1 H, dd, *J* 4 and 14 Hz, H-3β), 3·38 (1 H, dd, *J* 2 and 14 Hz, H-3α), 4·88 (2H, d, *J* 6 Hz, =CH–C$H_2$–), 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, 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 αβ-unsaturated ester, was selectively ozonized ($CH_2Cl_2$, −78 °C), reduced to the




(1) a; X = OAc, R = $O_2NC_6H_4CH_2$–*p*
b; X = OAc, R = H
c; X = OAc, R = $CH_2OCOMe$
d; X = N—N, R = $CH_2OCOMe$
–S
N
N
Me

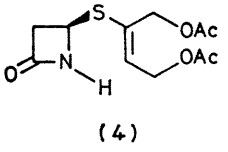



(2) a; X = Y = $CH_2OAc$
b; X = $CH_2OH$, Y = H

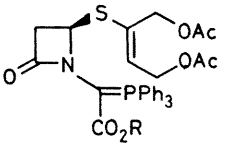



(3)

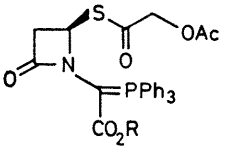
corresponding sulphide ($PBr_3$, −20 °C in dimethylformamide (DMF), 80%), and cleaved by removing the oxalo group (MeOH, silica gel) to give (**4**). The azetidinone (**4**) containing a free N–H group was condensed with *p*-nitrobenzyl glyoxylate (or alternatively with its acetoxymethyl ester) in refluxing benzene and was chlorinated using $SOCl_2$–pyridine–tetrahydrofuran. Reaction with $PPh_3$ and pyridine afforded the ylides (**5a**,**b**). The phosphorane function of



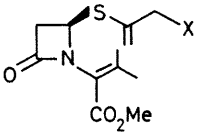
(**4**)

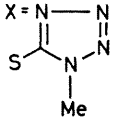


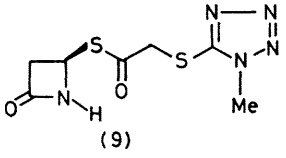
(**5**) a; R = $O_2NC_6H_4CH_2$–*p*
b; R = $CH_2OCOMe$



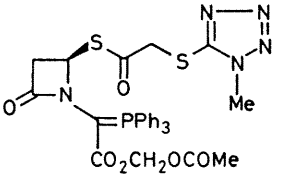
(**6**) a; R = $O_2NC_6H_4CH_2$–*p*
b; R = $CH_2OCOMe$



(**7**) X = Br
(**8**) X = 



(**9**)



(**10**)

(**5a**) was protected as its phosphonium salt (20% $CF_3CO_2H$ in $CH_2Cl_2$), 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**):[7]† m.p. 122—123 °C; $[\alpha]_D$ +87° ($CHCl_3$); $\lambda_{max}$ 265 ($\epsilon$ 11000) and 322 nm ($\epsilon$ 7000); $\nu_{max}$ ($CHCl_3$) 1800 ($\beta$ lactam), 1750, and 1720 $cm^{-1}$; $\delta$ ($CDCl_3$) 3·75 (1 H, dd, *J* 2·3 and 16·8 Hz, H-6$\alpha$), 3·87 (1H, dd, *J* 3·6 and 16·8 Hz, H-6$\beta$), 5·14 and 5·50 (both H, d, *J* 15·8 Hz, =C–C$H_2$–O), and 5·71 (1 H, dd, *J* 2·3 and 3·6 Hz, H-5); $^{13}$C-n.m.r. [$(CD_3)_2CO$] 20·26 ($COCH_3$), 51·09 ($COCH_2CHS$), 59·99 ($CH_2OCOMe$), 62·13 ($CH_2$–CHS), 65·87 ($COOCH_2Ph$), 124·21 (Ph, 2′, 6′), 129·18 (Ph, 3′, 5′) 144·47 (Ph, 4′), 154·66 (S–*C*=), 159·71 (–C–COO), 170·22 ($OCOMe_3$), and 173·89 p.p.m. (N–*C*O and *C*$OOCH_2$); (FD-MS): *m/e* 378 ($M^+$).

Finally, hydrogenolysis (AcOEt, aqueous $NaHCO_3$, Pd–C 10%) of (**1a**) afforded crude (**1b**):† $\lambda_{max}$ (EtOH) 258 and 301 nm; $\nu_{max}$ ($CHCl_3$) 1790 ($\beta$-lactam), 1735, and 1700 $cm^{-1}$.

Analogously, (**1c**)† was obtained from (**5b**) following the same route, $[\alpha]_D$ +110° ($CHCl_3$). 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 $PBr_3$ (−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 $PPh_3$–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 $PPh_3$, 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–H3$\alpha$, C4–H4$\alpha$ bonds was strongly suggested by H-3$\alpha$ 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 $^{13}$C n.m.r. spectroscopy.

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