Synthesis of Tricyclic Cephalosporins

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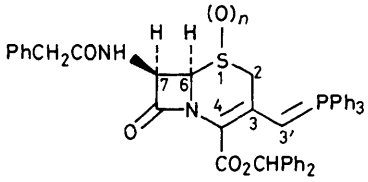
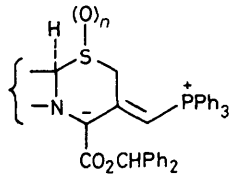
Cephalosporin 3'-triphenylphosphonium ylide (**1**) reacted with acrylaldehyde to give the C-3,C-4 tricyclic compound (**3**), while the sulphoxide of the ylide (**1**) upon similar treatment gave the C-2,C-3 tricyclic compound (**4**) which was converted into the ring-fused analogue (**7**) of nocardicin; desulphurization of this compound afforded the nocardicin nucleus (**10**).

Although reaction of cephalosporin 3'-triphenylphosphonium ylide (**1**) with aldehydes is a useful tool for elongation at C-3', such reactions are accompanied by formation of the C-2 and/or C-4 substituted products arising from the resonance-stabilized tautomers [*e.g.*, (A) and (B)].[1] Here we report that the ylide (**1**) is also a useful precursor for preparation of tricyclic cephalosporins, which are bridged by a cyclohexene ring between the C-2 and C-3 positions or between the C-3 and C-4 positions.[2]

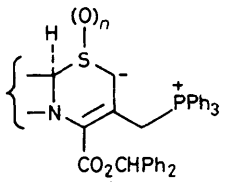
An excess of acrylaldehyde was treated with a suspension of (**1**) in dichloromethane to give the C-3,C-4 tricyclic compound (**3**)† [56% yield, m.p. 143—145 °C]. In contrast, the sulphoxide (**2**) [readily available in 86% yield from (**1**) by peracid oxidation in the presence of hydrochloric acid] gave the C-2,C-3 tricyclic compound (**4**) [62% yield, m.p. 228—230 °C (decomp.)] upon similar treatment with acrylaldehyde. These tricyclic compounds appear to arise from initial Michael addition at C-4 or C-2 followed by intramolecular Wittig reaction. The complete switching of the reaction course in the Michael addition from C-4 to C-2 by the sulphoxidation of (**1**)



(**1**) n = 0
(**2**) n = 1

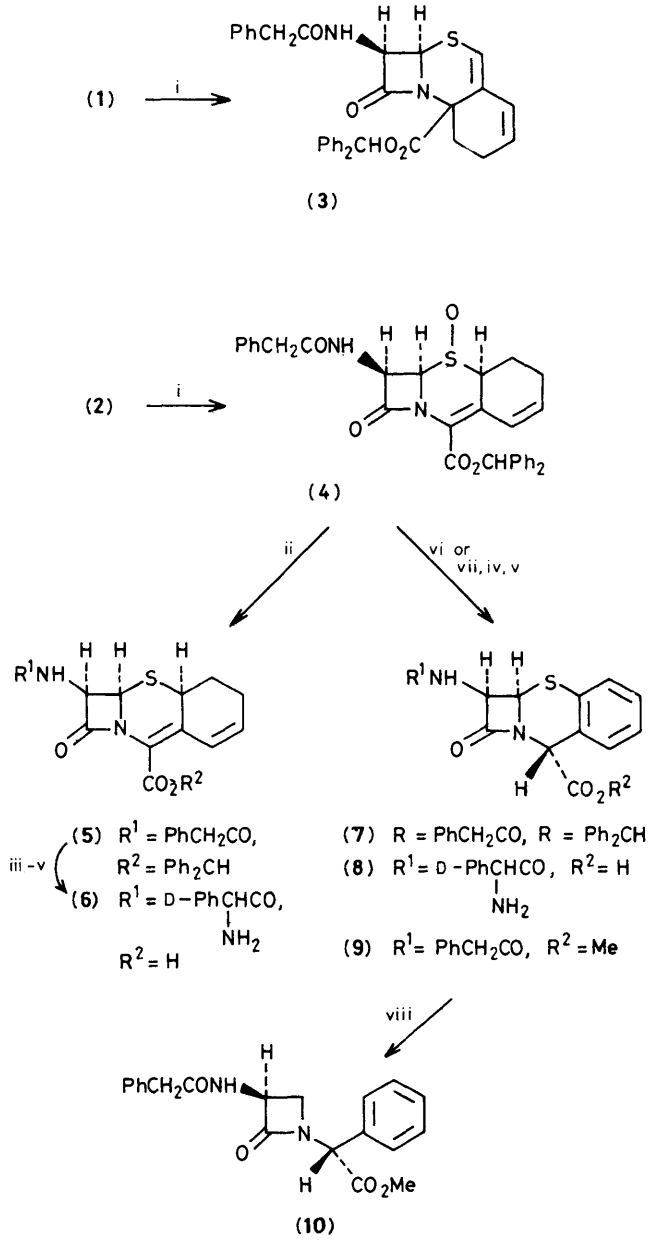


(A)



(B)

† All new compounds were fully characterized by spectroscopic and microanalytical methods. However the stereochemistry of the carboxy moieties of compound (**3**) was not determined. Selected physical data: (**3**): colourless amorphous solid; i.r. (Nujol) 1770, 1735, and 1670 cm^{-1}; $\lambda_{max.}$ (EtOH) 274 nm (log ε 4.17); ^1H n.m.r. ($CDCl_3$) δ 2.08 (m, 1H), 2.20 (m, 1H), 2.50 (m, 1H), 2.76 (br. d, *J* 5.0 and 13.4 Hz, 1H), 3.62 (dd, 2H), 4.69 (d, *J* 4.2 Hz, 1H), 5.37 (dd, *J*, 4.2 and 8.6 Hz, 1H), 5.62 (m, 1H), 6.08 (br. dd, *J* 8.7 Hz, 1H), 6.15 (d, *J* 8.7 Hz, 1H), and 7.2—7.4 (m, 16H), (**4**): colourless needles; i.r. (Nujol) 1775, 1720, and 1650 cm^{-1}; $\lambda_{max.}$ (EtOH) 317 nm (log ε 4.20); ^1H n.m.r. [$(CD_3)SO$] δ 1.82 (m, 1H), 2.33 (m, 1H), 3.63 (dd, 2H), 3.70 (br.d, *J* 14.2 Hz, 1H), 5.08 (dd, *J* 1.5 and 4.8 Hz, 1H), 5.90 (dd, *J* 4.8 and 8.3 Hz, 1H), 6.12 (m, 1H) 6.74 (d, *J* 10.0 Hz, 1H), 6.94 (s, 1H), and 7.2—7.6 (m, 15H). (**7**): fine needles; i.r. (Nujol) 1775, 1742, and 1655 cm^{-1}; $\lambda_{max.}$ (EtOH) 287 nm (log ε 2.98); ^1H n.m.r. ($CDCl_3$) δ 3.61 (s, 2H), 5.43 (d, *J* 3.8 Hz, 1H), 5.56 (s, 1H), 5.64 (dd, *J* 3.8 and 8.6 Hz, 1H), 6.32 (d, *J* 8.6 Hz, 1H), and 6.8—7.7 (m, 20H).



Scheme 1. i, acrylaldehyde (3.0 equiv.), CH_2Cl_2, room temp., 1 h; ii, PBr_3, CH_2Cl_2, −20 °C, 1 h; iii, PCl_5 (1.1 equiv.), pyridine, 0 °C, work-up with MeOH, −50 to 0 °C, 1 h, and then with H_2O, 0 °C, 30 min; iv, *N*-t-butoxycarbonyl-D-phenylglycine (1 equiv.), dicyclohexylcarbodiimide (1 equiv.), 1-hydroxybenzotriazole (1 equiv.), CH_2Cl_2, room temp., 3 h; v, CF_3CO_2H, anisole, CH_2Cl_2, room temp., 30 min; vi, $(CF_3CO)_2O$ (2 equiv.), CH_2Cl_2, 0 °C, 1 h, and then pyridine (2 equiv.), 0 °C, 1 h; vii, PCl_5 (2.1 equiv.), pyridine (6 equiv.), 0 °C, work-up with MeOH, −50 to 0 °C, 1 h, and then H_2O, 0 °C, 30 min; viii, Raney Ni, dioxane, 50 to 60 °C, 2 h.

is attributable to stabilization of the resonance form (**B**) by the sulphoxide group. Attempted reactions with other vinyl aldehydes including crotonaldehyde and methacrylaldehyde failed and (**1**) was recovered. The stereochemistry at C-2 of (**4**) was determined on the basis of its 360 MHz ^{1}H n.m.r. spectrum, which showed long-range W coupling ($J_{2,6}$ 1.5 Hz) between H-2 and H-6.[3]

Deoxygenation of (**4**) with phosphorus tribromide afforded (**5**) [64% yield, m.p. 220—223 °C], which was then transformed to (**6**) by the standard sequence consisting of cleavage of the 7-amide bond, acylation, and subsequent deprotection. Alternatively, reaction of (**4**) with trifluoroacetic anhydride and pyridine resulted in aromatization of the newly formed cyclohexene ring *via* the carbosulphonium ion to give (**7**) [35% yield, m.p. 158—161 °C]. The aromatization was also effected by phosphorus pentachloride and pyridine. Finally, interchange of the acyl groups as above gave (**8**) (32%). These compounds can be regarded as fused analogues of the monocyclic β-lactam antibiotics, nocardicins.[4] The diphenylmethyl ester (**7**) was converted into the methyl ester (**9**) by treatment with trifluoroacetic acid and then diazomethane. Desulphurization of (**9**) with Raney nickel afforded (**10**)[5] [30% yield, m.p. 143—145 °C] which possessed the nocardicin nucleus. Thus a simple transformation of a cephalosporin to the nocardicin nucleus was achieved, in which the full carbon skeleton of the cephalosporin nucleus was retained.

The *in vitro* biological activities of (**6**) and (**8**) were poor and almost same as that of Δ^2-cephalosporins.[6]

Received, 6th August 1984; Com. 1151

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5 Compound (**10**) was identical in all respects with that prepared from L-2,3-diaminopropanoic acid, benzaldehyde, and butyl isocyanide by the reported method: M. Hatanaka, N. Noguchi, and T. Ishimaru, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1234.
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