A Chiral Synthesis of *trans*-Carbapenam-3-carboxylic Acid and the Assignment of (3*S*,5*S*) Configuration to the Corresponding Product from *Serratia* and *Erwinia* Species

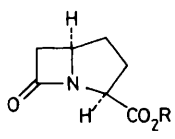
Barrie W. Bycroft and Siri Ram Chhabra

Department of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RD, U.K.

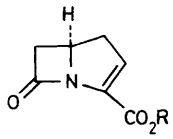
A convenient stereoselective synthesis of (3*R*,5*R*)-carbapenam-3-carboxylic acid from D-(*R*)-glutamic acid is described and the product shown to be enantiomeric with that isolated from *Serratia* and *Erwinia* species; this represents the first naturally occurring carbapenem or carbapenam with (5*S*) ring junction geometry to be reported.

In a recent communication we reported the isolation and characterisation of the two isomeric carbapenam-3-carboxylic acids as their *p*-nitrobenzyl esters from various *Serratia* and *Erwinia* species, as well as their possible role in carbapenem biosynthesis.[1] The (3*S*,5*R*) absolute configuration for the minor *cis*-isomer (**1**) followed from chemical correlation with the co-occurring antibiotic (5*R*)-carbapen-2-em-3-carboxylic acid (**2**) of established chirality.[2] The major *trans*-isomer, which was obviously epimeric with (**1**) at either the C-3 or C-5 position, was provisionally assigned the (3*R*,5*R*) configuration on the basis of comparative circular dichroism (c.d.) data. The stereochemistry at the ring junction for all three compounds was also consistent with that of all the reported carbapenem antibiotics.[3] More recently we have published details of experiments which conclusively establish that all three compounds are intimately related biosynthetically and are derived from an acetate unit and L-(*S*)-glutamic acid.[4]

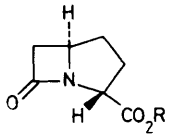
In order to explore further the biosynthesis and ascertain whether the antibiotic (**2**) and the carbapenams are derived from a common precursor or sequentially related, we required an efficient and unambiguous synthesis of both isomers of carbapenam-3-carboxylic acid, as well as putative biosynthetic



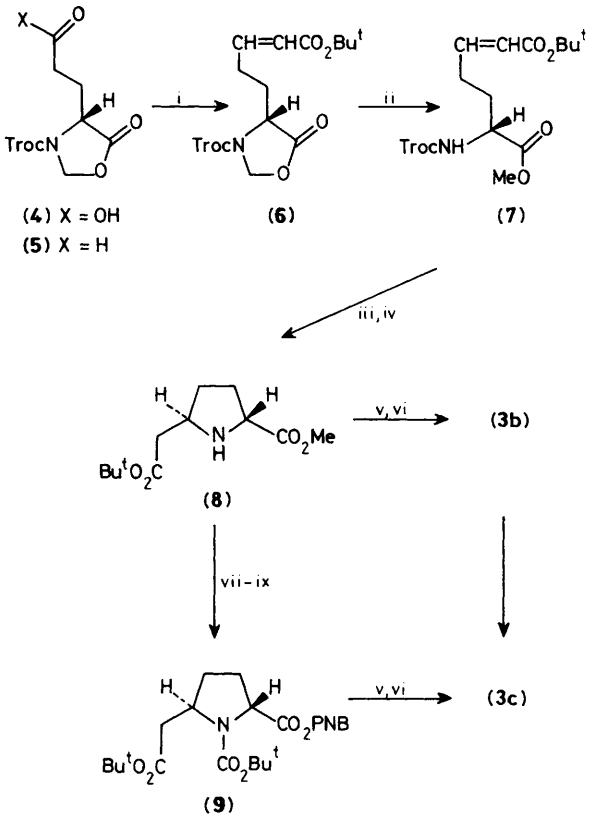
(**1**)



(**2**)

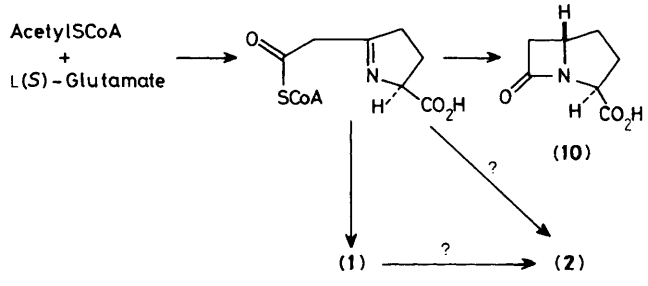


(**3**)
a; R = H
b; R = Me
c; R = PNB



Troc = trichloroethoxycarbonyl, PNB = *p*-nitrobenzyl

Scheme 1. *Reagents and conditions:* i, $Ph_3PCHCO_2Bu^t$, CH_2Cl_2, 20 °C, 20 h, 85%; ii, 0.1 M NaOMe in MeOH, 0 °C, 2 h, 90%; iii, Zn, AcOH, 20 °C, 4 h, 90%; iv, pyridine, CH_2Cl_2, 20 °C, 48 h, 60%; v, HCl in Et_2O, 20 °C, 2 h, 100%; vi, Et_3N, Ph_3P, $(2\text{-PyS})_2$, MeCN, reflux, 16 h, 25%; vii, 1 M-NaOH, MeOH, 20 °C, 5 h, 90%; viii, $(Bu^tOCO)_2O$, Bu^tOH, H_2O, 20 °C, 16 h, 90%; ix, $p\text{-}NO_2C_6H_4CH_2Br$, Et_3N, EtOAc, reflux, 24 h, 43%.



Scheme 2. Possible biosynthetic sequence for the formation of (**1**), (**2**), and (**10**).

intermediates. Although a number of syntheses had already been reported,[5] they lacked significant stereocontrol and were unsuitable for our purposes. We now report a convenient synthesis of the major isomer with the (3*R*,5*R*) configuration (**3a**) from an acetate equivalent and an appropriately protected (*R*)-glutamic acid derivative (see Scheme 1).

Reduction of the γ-carboxylic acid group of the oxazolidinone derivative (**4**),† prepared from *N*-trichloroethoxycarbonyl-(*R*)-glutamic acid[6] and paraformaldehyde to the corresponding aldehyde (**5**) was achieved using *N*,*N*-dimethylchloromethyleneammonium chloride ($ClCH{=}NMe_2{}^+Cl^-$) and lithium tri-t-butoxyaluminohydride[7] in a one-pot operation. The resulting crude aldehyde was condensed with the Wittig reagent derived from t-butyl bromoacetate to afford the *trans*-alkene (**6**), careful alcoholysis of which with sodium methoxide in methanol provided the triester (**7**) containing the complete carbon backbone for the construction of the bicyclic system. Reductive deprotection of (**7**) released the α-amino group which in the presence of pyridine underwent an internal Michael addition to yield the *trans*-proline derivative (**8**)‡ as the major product. The free acid, prepared by treatment of (**8**) with hydrogen chloride gas in ether, cyclised with Mukaiyama's reagent[8] to give the β-lactam methyl ester (**3b**). Enzymic hydrolysis of (**3b**) with pig liver esterase in NaH_2PO_4/Na_2HPO_4 buffer yielded the sodium salt of (**3a**) which was converted using phase transfer catalysis (Aliquat 336) to the *p*-nitrobenzyl ester (**3c**). In addition (**3c**) was also prepared by the completely chemical sequence from (**8**) *via* the *N*-protected intermediate (**9**) as shown in Scheme 1.

Samples of (**3c**) derived from both routes were identical in all respects and possessed the same chromatographic, mass, and n.m.r. spectral properties as the *trans*-isomer obtained from the natural source. They differed however in that the c.d. spectra of the synthetic compounds displayed a differential absorbance at 230 nm (Δε +3.46) equal and opposite to that of the natural product. It follows therefore that the major isomer of carbapenam-3-carboxylic acid from *Serratia* and *Erwinia* species possesses the enantiomeric (3*S*,5*S*) configuration (**10**) from that originally proposed. Thus (**10**) represents the first authenticated example of a naturally occurring carbapenem or carbapenam with 5*S* ring junction geometry.§ The previously reported observations that this compound lacks any notable antibacterial activity and neither induces β-lactamases nor is a substrate for a range of these enzymes[1,4] now finds a plausible explanation. It would also seem highly unlikely that (**2**) and

† All new compounds described here gave satisfactory spectroscopic and analytical data. Selected physical data: unless otherwise stated, n.m.r. spectra were recorded in $CDCl_3$ at 90 MHz.

(**3b**), oil; $[\alpha]_D^{28}$ −197° (*c* 0.5 in $CHCl_3$); *m/z* 169.0737 (M^+, $C_8H_{11}NO_3$ requires *M*, 169.0738), $\nu_{max.}$ ($CHCl_3$) 1740 (C=O), 1640 cm^{-1}; δ_H 1.2—1.7 (1H, m), 2.0—2.75 (3H, m), 2.61 (1H, dd, *J* 16.0 and 2.0 Hz), 3.30 (1H, dd, *J* 16.0 and 5.0 Hz), 3.75 (3H, s), 3.86 (1H, m), 4.42 (1H, t, *J* 7.5 Hz).

(**4**), m.p. 117—119 °C; $[\alpha]_D^{28}$ −89.8° (*c* 0.85 in MeOH); $\nu_{max.}$ (KBr) 3650—2250 (CO_2H), 1792, 1700 cm^{-1} (C=O); δ_H 2.1—2.7 (4H, m), 4.45 (1H, t, *J* 6 Hz), 4.70 and 4.86 (2H, ABq, *J* 13 Hz), 5.31 and 5.59 (2H, ABq, *J* 4 Hz), 10.50 (1H, s).

(**6**), m.p. 82—84 °C; $[\alpha]_D^{28}$ −80.9° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$ (KBr) 1785, 1735, 1705, 1655 cm^{-1} (C=O); δ_H 1.52 (9H, s), 1.8—2.5 (4H, m), 4.40 (1H, t, *J* 6 Hz), 4.70 and 4.93 (2H, ABq, *J* 12 Hz), 5.28 and 5.59 (2H, ABq, *J* 4 Hz), 5.79 (1H, dt, *J* 16 and 1.5 Hz), 6.80 (1H, dt, *J* 16.0 and 6.8 Hz).

(**8**), oil; $[\alpha]_D^{28}$ +18.75° (*c* 1.52 in $CHCl_3$); *m/z* 243.1485 (M^+, $C_{12}H_{21}NO_4$ requires *M*, 243.1468); ν_{max} (thin film) 3340 (NH), 1730 (C=O) cm^{-1}; δ_H 1.50 (9H, s), 1.60—2.25 (4H, m), 2.40 (2H, dd, *J* 8.5 and 6.8 Hz), 2.53 (1H, br. s), 3.51 (1H, m) 3.75 (3H, s), 3.80 (1H, m).

‡ It was expected that the ring closure would afford the thermodynamically more stable isomer, but at this stage it was not possible to determine the stereochemistry conclusively and this subsequently followed from the analysis of the ^1H n.m.r. spectra of the resultant β-lactam (see refs. 1 and 4 and refs. cited therein).

§ A number of naturally occurring clavams with 5*S* ring junction geometry are known.[9]

(**10**) are sequentially related to one another on the biosynthetic pathway but probably derived from a common intermediate in the manner outlined in Scheme 2.

Received, 10th October 1988; Com. 8/04028A

References

1 B. W. Bycroft, C. Maslen, S. J. Box, A. G. Brown, and J. W. Tyler, *J. Chem. Soc., Chem. Commun.*, 1987, 1623.
2 Y. Ueda, C. E. Damas, and V. Vinet, *Can. J. Chem.*, 1983, **61**, 2257; M. Miyashita, N. Chida, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 1984, 195.
3 J. M. Williamson, *CRC Crit. Rev. Biotechnol.*, 1986, **4**, 111.
4 B. W. Bycroft, C. Marslen, S. J. Box, A. G. Brown, and J. W. Tyler, *J. Antibiot.*, 1988, **41**, in the press.
5 T. Nagasaka, A. Tsakada, and F. Hamaguchi, *Heterocycles*, 1986, **24**, 2015; S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135; S. R. Berryhill, T. Price, and M. Rosenblum, *ibid.*, 1983, **48**, 158; T. Ohta, A. Hosoi, and S. Nozoe, Abstracts of the 106th Meeting of Pharmaceutical Society of Japan, Chiba, 1986, p. 218.
6 J. F. Carson, *Synthesis*, 1981, 268.
7 T. Fujisawa, T. Mori, S. Tsuge, and T. Sato, *Tetrahedron Lett.*, 1983, **24**, 1543; T. Fujisawa and T. Sato, *Org. Synth.*, 1987, **66**, 121.
8 S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 2405; S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *ibid.*, 1981, **103**, 2406.
9 See R. Southgate and S. Elson, *Fortscher. Chem. Org. Naturst.*, 1985, **47**, 1; 'Dictionary of Antibiotics,' ed. B. W. Bycroft, Chapman and Hall, London, 1987, p. 916.