Tetrahedron Letters, Vol.27, No.2, pp 247-250, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A STEREOCONTROLLED ROUTE TO OPTICALLY ACTIVE 1-METHYL CARBAPENEMS

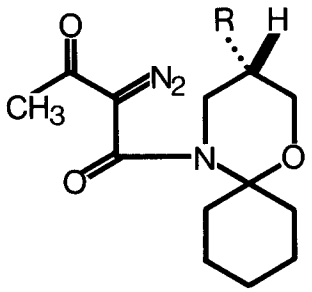
Pamela Brown* and Robert Southgate

Beecham Pharmaceuticals Research Division,
Brockham Park, Betchworth, Surrey, RH3 7AJ, U.K.

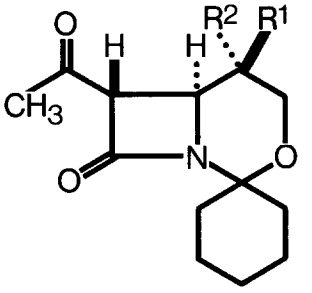
Summary:

Using a stereoselective carbene insertion reaction to form the β-lactam ring, optically active 1-methyl carbapenems have been prepared.

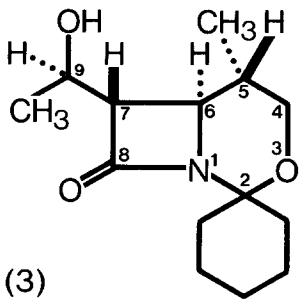
We have previously shown[1] that the cyclisation of α-diazoamides of type (1a) in the presence of rhodium (II) acetate gives the trans-β-lactam (2a) in good yield. We have now found that the presence of a methyl group at C-5 of the tetrahydro-1,3-oxazine ring system has a directing influence on the insertion reaction. Thus use of an optically active diazoketone (1b) gives rise to optically active β-lactam products in a stereocontrolled manner. This methodology has now been extended to prepare optically active (2b) and thence (3), a key intermediate in the synthesis of 1-methyl carbapenems[2].



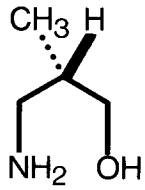
(1a) R=H
(1b) R=CH_3



(2a) $R^1=R^2=H$
(2b) $R^1=H$, $R^2=CH_3$
(2c) $R^1=CH_3$, $R^2=H$



(3)



(4)

Initial experiments were carried out in the racemic series. Thus (±)-3-amino-2-methylpropan-1-ol was converted to the (±)-diazoketone (1b). Cyclisation of (1b) in the presence of rhodium (II) acetate gave racemic (2b) (63% yield) together with a small amount of (2c) (6.3%), which were readily separable by column chromatography. Reduction of (2b) with potassium-tri-sec-butyl borohydride gave the desired alcohol (3) (50%), m.p. 133-4°C.

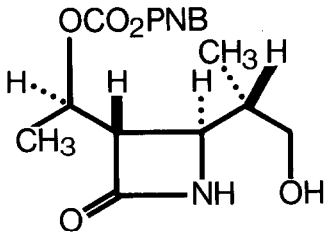
The stereochemical assignments of (3) and its C-5 epimer were based upon ^{1}H n.m.r. coupling constants[3] and we concluded that the major product from the carbene insertion reaction was the α-methyl compound (2b).

We deduced that (S)-3-amino-2-methylpropan-1-ol (4) was the required starting material for the preparation of optically active (3), in which the stereochemistry at C-6 as shown would give rise to carbapenems having the natural configuration at C-5 required for biological activity.

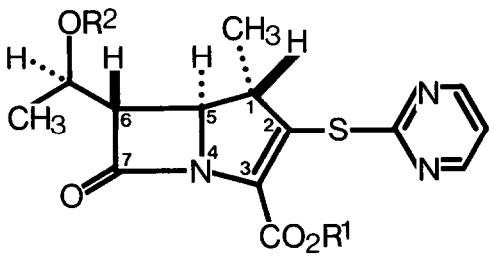
The racemic aminopropanol was resolved as its salt with N-[(S)-(1-phenylethyl)]succinamic acid[4] giving, after regeneration, the (S)-aminopropanol (4) b.p. 82°C (7mm.), $[\alpha]_D^{20}$ -7.05°(c 1.05 in H_2O), +11.33°(c 1.8 in $CHCl_3$) . The stereochemical assignment was made by correlation with the previously reported (R)-3-amino-2-methylpropan-1-ol[5].

The (S)-alcohol (4) was elaborated *via* our established route[1] to the optically active α-diazoketone (1b), which, after cyclisation and reduction as described above gave optically active (3), $[\alpha]_D^{20}$ -36.3° (c 1 in $CHCl_3$) . Protection of the alcohol function with the p-nitrobenzyloxycarbonyl group, followed by cleavage of the tetrahydro-1, 3-oxazine ring, gave the intermediate (5), $[\alpha]_D^{20}$ -16.0° (c 1 in $CHCl_3$) . This was progressed to the bicyclic carbapenem (6), $[\alpha]_D^{20}$ -138.8° (c 1 in $CHCl_3$) *via* our previously-described intramolecular Wittig cyclisation route[6]. During this reaction sequence no evidence of epimerisation at any of the chiral centres was observed. Hydrogenolysis of (6) gave the biologically active salt (7).

In a similar manner, (R)-3-amino-2-methylpropan-1-ol was progressed to the antibacterially inactive enantiomer of (7).



(5)



(6) R^1 = PNB, R^2 = CO_2PNB

(7) R^1 = Na, R^2 = H

PNB = *p*-nitrobenzyl

Acknowledgements:

The authors thank Drs. A.J. Eglington and J.H. Bateson for helpful discussions, and Mr.J.W.Tyler for 250MHz ^{1}H n.m.r. spectra.

References and notes:

1. R.J. Ponsford and R. Southgate, J. Chem. Soc., Chem. Commun., 1979, 846.

2. A similar intermediate has recently been prepared in racemic form by workers at Merck Sharp and Dohme; D.H. Shih, J.A. Fayter, L.D. Cama, B.G. Christensen and J. Hirshfield, Tetrahedron Lett., 1985, 26, 583.

3. All compounds were characterised by infra-red and 250MHz ^{1}H n.m.r. spectra plus mass spectral and/or microanalytical evidence. Some selected physical data for compound (3) and its C-5 epimer are as follows: (3): $\delta(CDCl_3)$ 0.92 (3H, d, J 6.0Hz, 5-CH_3), 1.32 (3H, d, J 6.0 Hz, 9-CH_3), 2.79 (1H, dd, J 5.0, 1.5Hz, 7-H), 3.14 (1H, dd, J, 1.5, 9.8 Hz, 6-H), C-5 epimer (β-methyl): $\delta(CDCl_3)$ 1.13 (d, J 7Hz, 5-CH_3), 1.30 (3H, d, J 7Hz, 9-CH_3), 3.03 (1H, dd, J 6.6, 2.0Hz, 7-H), 3.75 (1H, dd, J 5.1, 2.0 Hz, 6-H).

4. E. Felder, D. Pitrè and S. Boveri, Helv. Chim. Acta. 1969, 52, 329.

5. K. Balenović and N. Bregant, Croat. Chem. Acta., 1960, 32, 57.

6. A.J.G. Baxter, P. Davis, R.J. Ponsford and R.Southgate, Tetrahedron Lett., 1980, 21, 5071; M.J. Basker, R.J. Boon, S.J. Box, A.G. Brown, P. Davis, R.J. Ponsford, R. Southgate and S.R. Spear, J. Antibiotics, 1983, 36, 1357.

(Received in UK 21 October 1985)