Tetrahedron Letters, Vol.22, No.36, pp 3485 - 3488, 1981
Printed in Great Britain

0040-4039/81/363485-04$02.00/0

SYNTHESIS OF OPTICALLY ACTIVE PENEMS

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ABSTRACT: A general synthesis for optically active penems is described. Penems undergo a novel thermal isomerisation reaction.

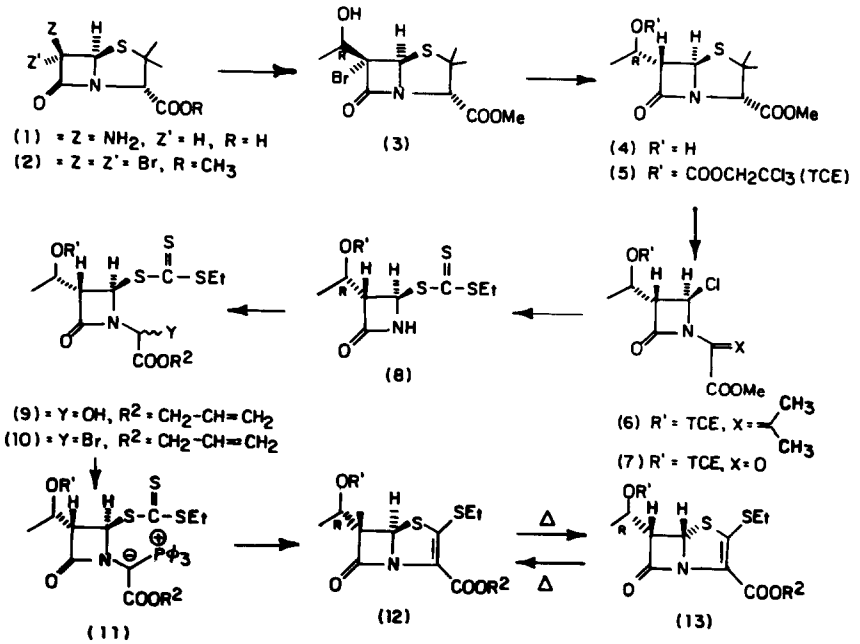
Non-classical β-lactams, exemplified by thienamycin[1], olivanic acid[2] and the Woodward's novel synthetic "penem"[3] have all been described as potent antimicrobial agents. Recently, several papers have appeared on the syntheses of C_6-substituted penems[4-8]. A Merck group[9] has also announced a chiral synthesis for penems, which is now established to be inoperative[10-11]. In this communication, we wish to report a general chiral synthesis for novel C_6-carbon substituted penems.

The relatively inexpensive and readily available 6-amino penicillanic acid (1) (6-APA) was diazotized and brominated using a modified[12] Clayton procedure[13]. The crystalline methyl ester (2) was obtained (~70%) by esterification of the dibromo penicillanic acid with methyl iodide in the presence of K_2CO_3 in DMF. Introduction of a hydroxyethyl group at C_6 was achieved by following the Merck procedure[14]. The desired 8R isomer (3) was crystallized (ethylacetate-hexane) in pure form from a mixture of four possible isomers (55-60%). Hydrogenation of (3) with 10% $Pd/CaCO_3$ afforded a mixture of cis and trans penams. The trans isomer (4)[15] was separated by silica gel chromatography (~60%). The hydroxy group in (4) was next protected as its TCE derivative (5)[16] (CCl_3CH_2-O-COCl + pyridine in CH_2Cl_2). The fully protected penam (5) was then chlorinated[17] (2.5 equivalents of Cl_2/CCl_4) at -20°C to get the azetidinone (6)[18] in nearly quantitative yield. Ozonolysis of (6) in CH_2Cl_2 at -70°C yielded the oxamide (7)[19], which readily reacted with excess (3-6 molar equivalents) potassium ethyl trithiocarbonate (EtSK + CS_2 in EtOH) to give the non-crystalline azetidinone trithiocarbonate (8)[20] in 80-85% yield. In practice, conversion of (5) to (8) could be easily conducted without isolation of intermediates (6) and (7).

Azetidinone (8) readily added to allyl glyoxylate to generate the diastereomeric carbinolamides (9)[3,7,8]. Conversion of (9) to the bromo derivative (10) was carried out by reacting with mesylbromide and triethylamine in CH_2Cl_2 at 0°C. The highly reactive bromide (10)

(unstable to storage) was immediately reacted with triphenylphosphine[3,7,8] in DMF (2 hrs) yielding the phosphorane (11)[12] in an overall 50-55% yield from (8). Cyclisation to the penem was achieved by heating in either toluene or xylene.

Scheme 1

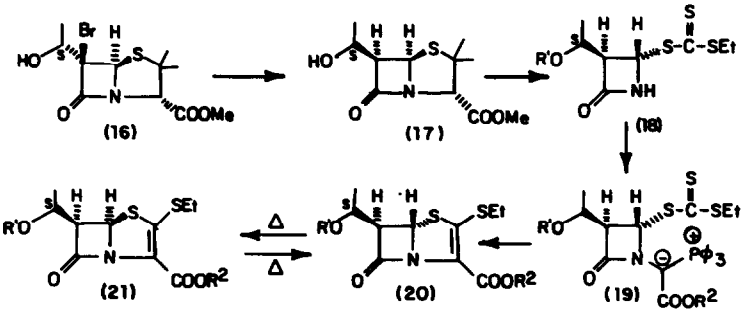


In the above cyclisation process, an unusual isomerisation was observed. In addition to the trans penem (12) (major component), a cis penem was also isolated[21], the ratio of which depended on the temperature and duration of heating. When either of the pure isomers (12)[22] or (13)[23] was heated, a similar equilibrium was established[24]. It was, at this stage, unclear to us at which carbon center has the isomerisation occurred (at C_5 or C_6)[25].

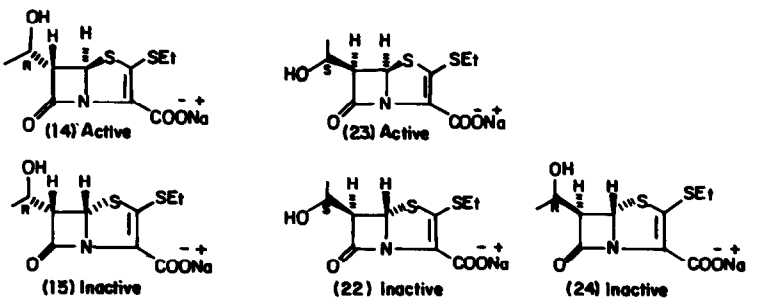
Both the trans and cis penems (12) and (13) were then deprotected, first by zinc reduction to remove the TCE group (desthioethyl penem[26] was isolated as a byproduct), followed by the McCombie procedure[27] for allyloxy cleavage. Whereas the trans penem (14) showed remarkable antimicrobial properties, the cis penem (15) was devoid of any significant activity[12].

The biological activity profile of (14) and (15) was in agreement with the observation made by Woodward and co-workers for C_6 unsubstituted penems. In the same paper[4], Woodward also stated "5R configuration in penems is the sole essential stereochemical requirement for antibiotic activity .... this requirement may be obscured by the presence of other chiral centers". We have now synthesized a few 5S penems having chiral substituents at C_6 and C_8. For example, enantiomer of (14) was synthesized as shown in Scheme 2.

SCHEME 2



SCHEME 3



The 8S bromohydrin (16) (a byproduct from Grignard reaction) was reduced with tri-n-butyl tin-hydride[28] to get predominantly the cis isomer (17). The hydroxy group in (17) was protected as its TCE derivative, and then converted to the azetidinone (18), following the general procedure. The phosphorane (19), prepared from (18), was cyclised to a mixture of trans and cis penems[29]. Both were deprotected to afford the corresponding sodium salts (22) and (23). [Trans penem (20) is the enantiomer of (12).] In a similar manner, (24) was also prepared. The cis isomer (23) showed good antimicrobial activity, whereas (15) was "inactive" Penems (22)[30] and (24) were also found to be inactive.

These observations lead us to believe that 5S isomers of penems will have little microbiological activity irrespective of the chirality at other centers, and that the corresponding 5R isomers are entirely responsible for the observed activity[31].

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11. S. Oida, A. Yoshida, T. Hayashi, E. Nakayama, S. Sato and E. Ohki, Tet. Lett. 21, 619 (1980).
12. Details will be published in a full paper.
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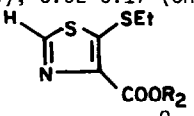
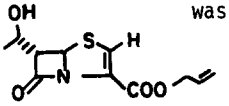
15. $[\alpha]_D^{26}$ = +145.5; ν max 3300, 1780, 1735, NMR ($CDCl_3$) δ = 5.25 (1H, d, J = 1.5 c/s), 4.41 (1H, s), 4.19 (1H, m), 3.74 (3H, s), 3.33-3.2 (1H, q, J = 1.5, 6 c/s), 1.61 (3H, s), 1.44 (3H, s), 1.13 (3H, d, J = 6 c/s).
16. M.P. = 77.5-78.5°C, $[\alpha]_D^{26}$ = +160.26; ν max 1780, 1765, 1735.
17. S. Kukolja and S.R. Lammert, Croatica Chemica Acta, 44, 299 (1972).
18. ν max 1775-1760, 1720; NMR ($CDCl_3$) 5.8 (1H, d, J = 2 c/s), 5.15 (1H, m), 4.75 (2H, s), 3.74 (3H, s), 3.6 (1H, q), 2.27 (3H, s), 2 (3H, s), 1.5 (3H, d, J = 9 c/s).
19. NMR ($CDCl_3$) δ = 5.98 (1H, d, J = 2.2 c/s), 5.1 (1H, m), 4.75 (2H, s), 3.9 (3H, s), 3.8 (1H), 1.45 (3H, d).
20. $[\alpha]_D^{26}$ = +154.2 (.4% in dioxane); NMR ($CDCl_3$) δ=5.62 (1H, d, J = 2 c/s), 5.2 (1H, m), 4.76 (2H, s), 3.52-3.17 (3H), 1.54-1.22 (6H).
21. Thiazole  was also isolated as a minor fragmentation product.
22. Free acid M.P. = 89-91.5°C, $\nu_{max}^{CHCl_3}$ 3350, 1805, 1715, 1690 cm^{-1}; salt $[\alpha]_D^{26}$ = +246.3 (H_2O), NMR (D_2O) δ = 5.66 (1H, d, J = 1.5 c/s), 4.25 (1H, m), 3.88 (1H, q, J = 1.5, 6 c/s), 2.95 (2H, m), 1.33 (3H, t), 1.31 (3H, d, J = 6 c/s).
23. Na^+ salt, $[\alpha]_D^{26}$ = +145 (H_2O), NMR (D_2O) δ = 5.76 (1H, d, J = 4 c/s), 4.3 (1H, m), 3.93 (1H, q, J = 4, 10 c/s), 2.96 (2H, m), 1.41 (3H, d, J = 6 c/s), 1.35 (3H, t).
24. Phosphorane (11) did not isomerise under the cyclisation conditions.
25. We thank Prof. J. Meinwald for discussions.
26. Desthioethyl penem  was formed as a minor component, presumably by a reductive elimination.
27. P. Jeffrey and S. McCombie, in press. European patent application E.P. 13-663.
28. J.A. Ametti, E.S. Hamanaka, D.A. Johnson and M.S. Kellog, Tet. Lett. 48, 4631 (1979).
29. X-Ray determination of the structure in the racemic series has been done - subject of a forthcoming publication.
30. Sodium salt $[\alpha]_D^{26}$ -243 (H_2O).

31. We thank the Chemical Development Division for their support and the Chemotherapy Division for the biology results.

(Received in USA 4 May 1981)