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A NEW ROUTE TO PENEMS AND CARBAPENEMS

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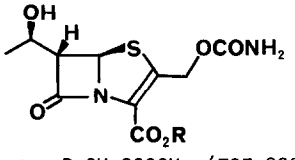
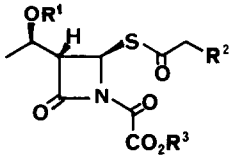
Summary: *A new ring closure by carbonyl-carbonyl reductive coupling is utilized in the synthesis of penem and carbapenem nuclei.*

Our previous syntheses[1,2] of the noticeable penems FCE 22891 (1) and FCE 22101 (2) were based on the total degradation of the thiazolidine ring of the penam nucleus through an oxalimido derivative 3 to an N-unsubstituted azetidin-2-one 4. Successively the new unsaturated five-membered ring was rebuilt up by the Woodward sequence[3].



1 : R=CH_2OCOCH_3 (FCE 22891)
2 : R = Na (FCE 22101)



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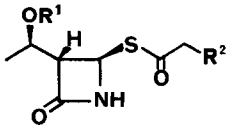

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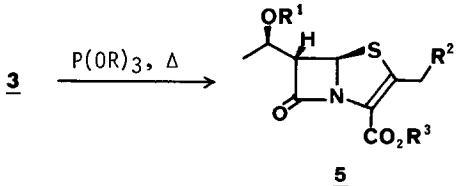
We regarded as a strongly desirable objective the formation of the penem framework directly from the oxalimide 3 by means of a reductive carbonyl-carbonyl coupling. The peculiar reactivity of the thiolester carbonyl[3] and of the oxalimide carbonyl[4] encouraged our efforts in this direction[5]. Gratifyingly we found that addition of trialkylphosphite (two molar equivalent) to a solution of 3 in toluene or xylene and prolonged heating (110-140°C, 1-10 h) afforded cleanly the



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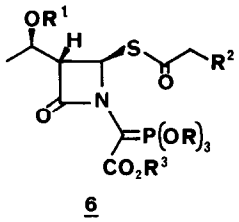

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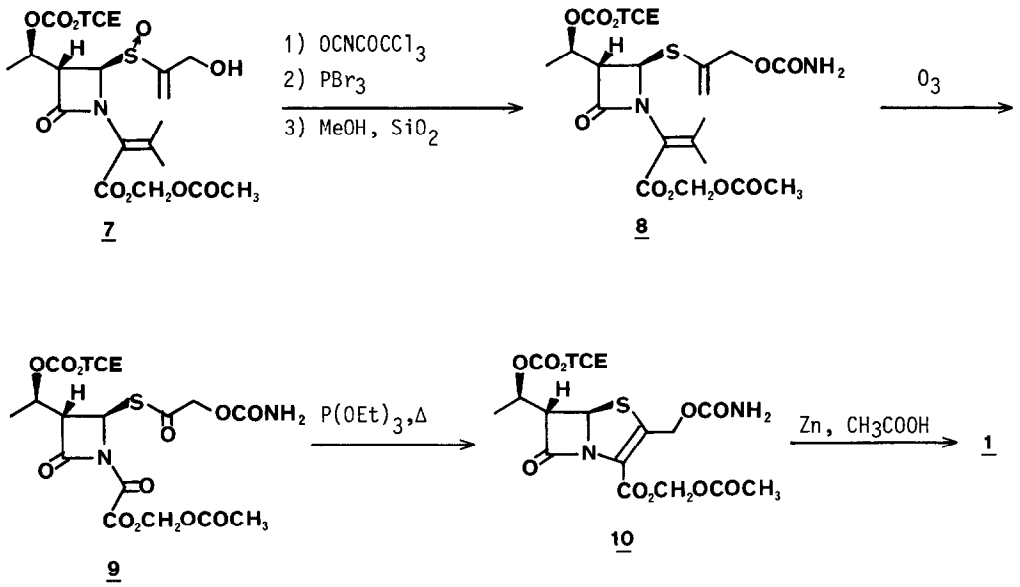
penem derivatives 5 in good yields (40-70%, depending on the nature of R^2 and R^3). The versatility of the reaction was proved by running several experiments with different R^1, R^2 and R^3 groups.

The reaction proceeds through an intermediate 6, which being obtained directly from 3 plays a key role in the path to the penem skeleton. As far as the mechanism[7] of the reaction is concerned, a carbene species[6], generated by a first molecule of trialkylphosphite from the oxalimide 3, is trapped by a second molecule of the reagent to afford the ylide 6, precursor of a final Wittig-type cyclization. During the filing of our patent application[8], Sankyo chemists reported the same reaction for the preparation of a 6-unsubstituted-2-methylpenem[9].

We wish to describe here a new short route to the penem 1, entailing a substantial change also in the introduction of carbamoyl moiety[1,2], performed at an earlier stage.

SCHEME I



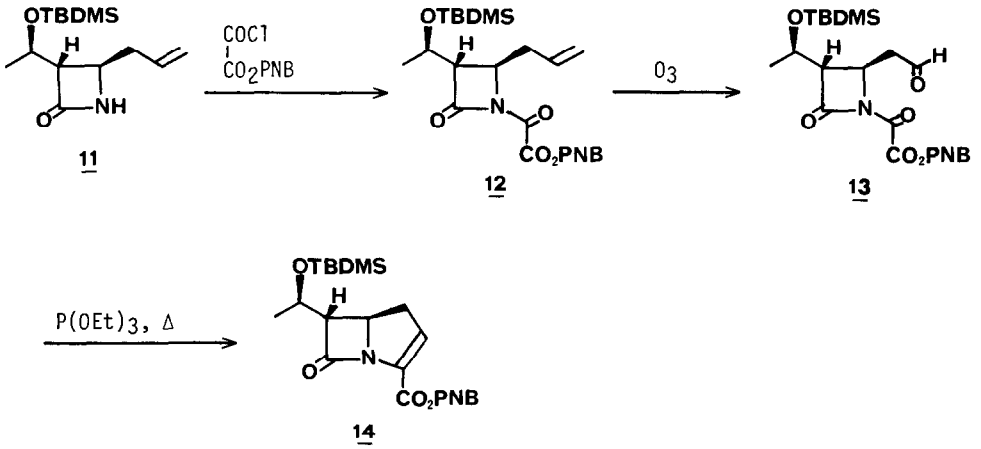
The synthesis outlined in Scheme I utilizes the pivotal intermediate 7 obtained by thermal reaction[2] of the corresponding penam sulphoxide[10] with propargyl alcohol. A high yield (80%) sequence provided the carbamoyl derivative 8.
NMR (60 MHz, $CDCl_3$), δ (ppm): 1.54 (d, J=6.4 Hz, 3H, $\underline{CH_3}CH$), 2.07,2.30 (two s, 6H, $=C(\underline{CH_3})_2$), 2.13 (s, 3H, $CO\underline{CH_3}$), 3.40 (dd, J=2.5, 7 Hz, 1H, H-3), 4.54 (bs, 2H, $\underline{CH_2}OCONH_2$), 4.77 (s, 2H, $\underline{CH_2}CCl_3$), 4.9-5.6 (m, 6H, H-4, $CH_3\underline{CH}$, $\underline{NH_2}$, $=\underline{CH_2}$), 5.77, 5.85 (two d, J=5 Hz, 2H, $\underline{CH_2}OCOCH_3$). Ozonolysis of the two double bonds affor-

ded the key oxalimide 9 prone to be cyclized. Conversion to the penem derivative 10 was performed by refluxing a xylene solution of the precursor with two molar equivalents of triethylphosphite. 10: $[\alpha]_D^{20}$+117°(C 1.00, $CHCl_3$). NMR (60 MHz, $CDCl_3$), δ (ppm): 1.53 (d, J=6.5 Hz, 3H, $\underline{CH_3}CH$), 2.15 (s, 3H, $CO\underline{CH_3}$), 3.95 (dd, J=1.8, 8 Hz, 1H, H-6), 4.77 (s, 2H, $\underline{CH_2}CCl_3$), 5.1 (m, 3H, H-8, $\underline{NH_2}$), 5.08, 5.38 (two d, J= 16 Hz, 2H, $\underline{CH_2}OCONH_2$), 5.60 (d, J=1.8 Hz, 1H, H-5), 5.8 (s, 2H, $\underline{CH_2}OCOCH_3$); IR (KBr) ν (cm^{-1}): 1790, 1755, 1730, 1710. Final deprotection of the hydroxy group afforded the biologically active penem 1, $[\alpha]_D^{20}$ +137° (c 1.00, acetone).

Penem 2 was obtained starting from the azetidinone-thiolester 4[1] by N-acylation with allyloxyoxalyl chloride[4], direct cyclization of the resultant oxalimide with trialkylphosphite, introduction of carbamoyl group at the penem stage and final removal of the protecting groups.

The carbonyl-carbonyl ring closure has been successfully applied also in the synthesis of the carbapenem nucleus (Scheme II). The N-unsubstituted

SCHEME II



azetidinone 11[11] was analogously acylated, the oxalimido derivative 12 was ozonized at -78°C providing the crude intermediate 13 and cyclization by refluxing in toluene with two molar equivalents of triethylphosphite afforded the carbapenem 14, IR ($CHCl_3$) ν (cm^{-1}) 1785, 1735. NMR (200 MHz, $CDCl_3$) δ (ppm): 0.07 (s, 6H, $Si(\underline{CH_3})_2$), 0.86 (s, 9H, $SiC(\underline{CH_3})_3$), 1.23 (d, J=6.2 Hz, 3H, $\underline{CH_3}CH$), 2.78 (ddd, J=2.6, 8.3, 20 Hz, 1H, H-1β), 2.93 (ddd, J=3.1, 10.1, 20 Hz, 1H, H-1α), 3.17 (dd, J=3.2, 5.6 Hz, 1H, H-6), 4.21 (dq, J=6.2, 5.6 Hz, 1H, H-8), 4.25 (ddd, J=3.2, 10.1, 8.3 Hz, 1H, H-5), 5.27, 5.41 (two d, J=13.6 Hz, 2H, $\underline{CH_2}PhNO_2$), 6.54(dd, J=3.1, 2.6 Hz, 1H, H-2), 7.61, 8.21 (two d, J=8.8, $\underline{Ph}NO_2$).

Footnotes and references

1. G. Franceschi, M. Foglio, M. Alpegiani, C. Battistini, A. Bedeschi, E. Perrone, F. Zarini, F. Arcamone, C. Della Bruna and A. Sanfilippo, J.Antibiotics, 36, 938 (1983).

2. M. Foglio, C. Battistini , F. Zarini, C. Scarafile and G. Franceschi, Heterocycles, 20, 1491 (1983).

3. I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R.Pfaendler and R.B. Woodward, J.Am.Chem.Soc., 100, 8214 (1978).

4. A. Afonso, F. Hon, J. Weinstein, A.K. Ganguly and A.T. McPhail, J.Am.Chem.Soc., 104, 6138 (1982).

5. When we started our investigations, to our knowledge, only two cases of C=O/C=O coupling were reported in the literature as rare examples of alkene formation by using trialkylphosphite: B. Arbuzov and V.M. Zoroastrova, Izvest.Akad.Nauk. S.S.S.R., Otdel. Khim. Nauk, 1030 (1960), C.A. 54, 24627g; F. Ramirez, H. Yamanaka and O.H. Basedow, J.Am.Chem.Soc., 83, 173 (1961).

6. Schering chemists[4] proposed that this carbene species interacts with a trithiocarbonate thione group in the cyclization to 2-alkylthiopenems through desulphurisation of an intermediate episulphide.

7. A detailed study of the mechanism is reported in the following paper (E. Perrone et al

8. Conception date FC 151 legalized in U.S. on April 20, 1983; Brit. Pat. Appln. 8321677 filed on August 11, 1983.

9. A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, Chem.Pharm.Bull., 31, 768 (1983).

10. We thank Mr. G.P. Borsotti (Istituto Guido Donegani, Novara) for the preparation of the penam sulphoxide.

11. Japan Patent J80-07251 to Sankyo; C.A.:93, 114310b.

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