Tetrahedron Letters,Vol.24,No.31,pp 3179-3182,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF OPTICALLY ACTIVE PENEMS[3] - II

V. M. Girijavallabhan*, A. K. Ganguly, P. Pinto, R. Versace

Chemical Research, Schering Corporation, Bloomfield, NJ 07003

ABSTRACT: A chiral synthesis of 2-thioxopenam, a highly useful synthon for penems, is described. S-allyl penems undergo facile molecular rearrangements.

Penems, first described by Woodward[1] as a novel class of β-lactam antibiotics, have since been a center of attention[2] by virtue of their potency, broad-spectrum activity and stability to β-lactamases. We have reported earlier a chiral synthesis[3] of penems, exemplified by sodium 5R, 6S, 8R-6 (1-hydroxyethyl)-2-ethylthio penem 3 carboxylate (Sch 29482[4]), which has undergone clinical evaluation and was found efficacious. In continuation of our efforts on penems, we have early on recognized the need to discover a more efficient route for their synthesis. As the phosphorane cyclization was often accompanied by partial isomerization[3] at C_5 and the carbene ring closure[5] required specific structural features, an efficient chiral synthesis of the 'synthon' 2-mercapto penem[6] 9 which could be derivatized conveniently appeared attractive to us. Here we wish to report a novel chiral synthetic route[7] to penems by way of the versatile 2-thioxo penam 9.

The trityl protected acetoxyazetidinone[8] 1 readily added to diallylketomalonate[9] under base catalysis (THF, triethylamine) to afford the amidol 2a (>85%). The hydroxy group in 2a was converted to a chloro group ($SOCl_2$,Py,CH_2Cl_2) and the resultant reaction mixture was reduced (zinc,CH_2Cl_2,isopropanol,AcOH) to obtain the malonate 3a. Deprotection of the trityl group[8] ($AgNO_3$,MeOH,pyridine), followed by reaction of the silver thiolate 4a with thiocarbonyl diimidazole (2 equivalents in CH_2Cl_2) spontaneously generated the thiolactone 7a (>80%), presumably via 5a[10].

Deprotection of the allyl group[11] has worked exceedingly well in our hands. However, attempted deblocking of the thiolactone 7a using Pd^0 catalyst mostly gave the S-allyl penem 8 (R=R¹=allyl). The incipient allyl-Pd complex, being a powerful alkylating agent appeared to have transferred the allyl group to the sulfur atom intramolecularly[12]. The allyl thiopenem 8 (R=R¹=allyl) had only limited stability; it further underwent a facile thermal rearrangement (>55°C) to the thermodynamically more stable thiolactone 10

(Scheme 2). Furthermore, 10 rearranges to 11 via the corresponding penem when treated with Pd^0.

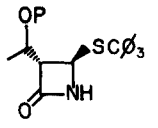
Having realized that deblocking the allyl group of 7a using Pd^0 is a futile exercise, we investigated the use of β-trimethylsilyl ethyl (TMSE) group[13] as a protecting group (often used in peptides). The sequence from 1 to 7b (via 2b,3b,4b) proceeded uneventfully. Fluoride ion (2.5 eq. tetrabutylammonium fluoride, THF, r.t., 15 minutes) rapidly monodeprotected the malonate 7b to afford the desired thiolactone 9 (R=TMSE) (~80% yield - a 10 to 15% loss of β-lactam was found unavoidable), which exhibited all the reaction properties of a thiol[6] (e.g. alkylating and acylating agents gave the corresponding expected penems). Here we observed a remarkable fluoride ion reaction selectivity in that while the deblocking of 7b was rapid and efficient, the penems[14] (especially when the C_2 substituent is a more complex functionality) reacted sluggishly,often resulting in poor yields.

The above problem was essentially solved by using the mixed ester ketomalonate[9], such as allyl trimethylsilyl ethyl ketomalonate and running the sequence from 1 to 7c (via 2c, 3c,4c). Fluoride ion induced deprotection of 7c, as expected was rapid to afford 9 (R= allyl, 65-70% - a slight lowering of yield due to β-lactam loss[15] was observed when mixed ester was used). The allyl protected thiolactone is a stable compound, and, indeed, we found it to be a highly desirable intermediate for the synthesis of a variety of penems[16].

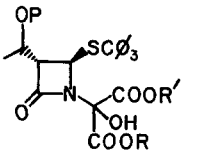
REFERENCES, NOTES AND SPECTRAL DATA

1. R. B. Woodward, Recent Advances in the Chemistry of β-Lactam Antibiotics, p. 167, Chemical Society, London (1977).
2. Lead references: a) H. R. Pfaendler, J. Gosteli and R. B. Woodward, J. Amer. Chem. Soc., 101, 6306 (1979); b) M. Lang, K. Prasad, J. Gosteli and R. B. Woodward, Hel Chim. Acta 63, 1093 (1980); c) A. L. P. Lombardi, C. Giandolfi, G. Franseschi, Tet. Lett., 22, 235 (1981) and the cited references; d) T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara and E. Ohki, Chem. Pharm. Bull., 29, 3158 (1981); e) P. C. Cherry, D. N. Evans, C. E. Newall and N. S. Watson, Tet. Lett., 561 (1980).
3. V. M. Girijavallabhan, A. K. Ganguly, S. W. McCombie, P. Pinto and R. Rizvi, Tet. Lett., 3485 (1981)
4. A. K. Ganguly, V. M. Girijavallabhan, S. McCombie, P. Pinto, R. Rizvi, P. D. Jeffrey and S. Lin, J. Antimicrobial-Chemotherapy, 9, Suppl., 1 (1981).
5. A. Afonso, F. Hon, J. Weinstein, A. K. Ganguly and A. McPhail, J. Am. Chem. Soc., 6138 (1982) - This process has allowed us large-scale preparation of Sch 29482.
6. Very recently publications appeared on the same intermediate which exists mostly in the thioxo form - both gave C_5 isomeric products because of 1-5 bond formation. a) T. Tanaka, T. Hashimoto, K. Lino, Y. Sugimura and T. Miyadera, J. Chem. Soc. Chem. Comm. 713 (1982); b) N. J. Daniels, G. Johnson, B. C. Ross and M. S. Yeomens, Ibid, 1119 (1982).
7. Recognizing that 1-5 bond formation can lead to R,S isomer distribution at C_5, we have relied on 2-3 ring closure.
8. M. Menard and A. Martel, U. K. Patent No. 2041524 1980 - Bristol Meyers Co.
9. The ketomalonates were made by acid catalyzed esterification of ketomalonic acid with the desired alcohol. The mixed ester was made by ester exchange using K_2CO_3 in ~60% yield from the symmetrical esters.
10. Though less likely, an intermediate such as 6 is not entirely ruled out. No intermediates other than traces of C_8-O-CO-imidazole were isolable under the reaction conditions.

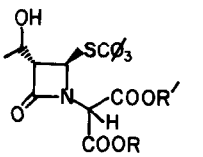
SCHEME I



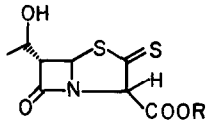
1
P=COOCH$_2$CCl$_3$



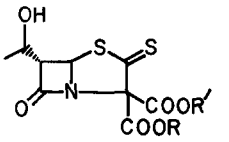
2a, R=R′=ALLYL
2b, R=R′=CH$_2$—CH$_2$—Si(CH$_3$)$_3$ (TMSE)
2c, R/R′=ALLYL/TMSE (ISOMERIC)



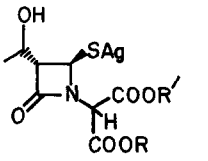
3a, 3b, 3c



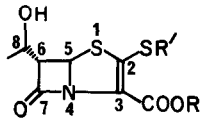
9



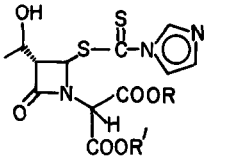
7a, 7b, 7c



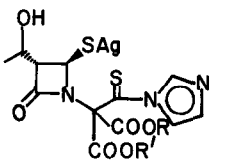
4a, 4b, 4c



8



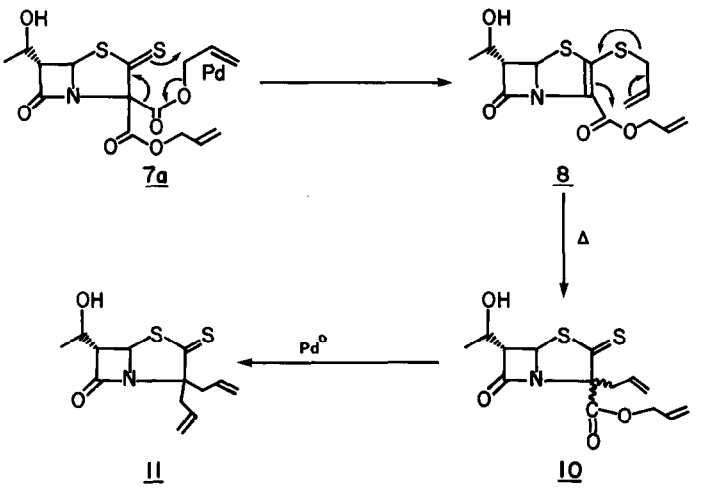
5a, 5b, 5c



6a, 6b, 6c

a, b, c, as in 2 for 3, 4, 5, 6 or 7

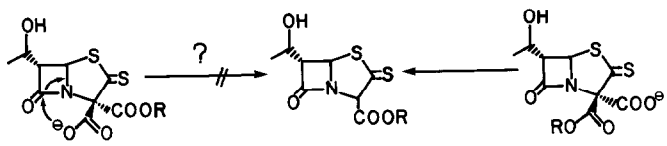
SCHEME 2



7a 8 10 11

11. a) P. D. Jeffrey and S. W. McCombie, J. Org. Chem., 47, 587 (1982); b) S. W. McCombie, A. K. Ganguly, V. M. Girijavallabhan, P. D. Jeffrey, S. Lin and P. Pinto, Tet. Lett., 3489 (1981).
12. Many attempts to trap the allyl-Pd complex failed to give any of the desired thione 9.
13. The authors thank Dr. T. L. Nagabhushan for discussions.
14. A. Martel, P. Dextraze, J. P. Daris, R. Saintonge, P. Lapointe, T. Conway, I. Monkovic, G. Kavadias, Y. Ueda, P. Elie, S. Patil, G. Caron, J. C. Douglas, M. Menard and B. Belleau, Can. J. Chem., 60, 942 (1982).

15.



We speculate that as in penicillins, the β carboxylate is unstable and attacks the β-lactam ring intramolecularly to a certain extent.

16. Details will be published elsewhere.

SALIENT SPECTRAL DATA:

IR in $CHCl_3$, Cm^{-1}; UV in $CHCl_3$, λmax-nm; PMR in $CDCl_3$, δppm, C^{13} in $CDCl_3$:

7a (R=R^1=allyl) PMR 5.8, 1H, d (J=1.5 Hz)-$C_5\underline{H}$; 3.75, dd (J=1.5 and 7 Hz) $C_6\underline{H}$; 1.4, 3H, d (J=7 Hz). 7b and 7c have similar features; IR 1790 (β-lactam); 1745 (ester). UV 319 nm.

8 (R=R^1=allyl) 5.6, 1H, d (J=1.5 Hz); 3.65, 1H, dd (J=1.5 and 7 Hz); 3.5, 2H, m (S-$\underline{CH_2}$-); 1.3, 3H, d (J=7 Hz). IR 1790 (β-lactam), 1690 (ester). UV 340 nm.

9 (R=allyl) PMR 5.85, 1H, d (J=1.5 Hz); 5.35, 1H S ($C_3\underline{H}$); 4.3, 1H, m; 3.65, 1H, dd (J=1.5 and 7 Hz); 1.35, 3H, d (J=7 Hz). IR 1792, 1742. UV 313 nm. C^{13}NMR 230.25 (C=S); 170.19 (ester); 164.21 (β-lactam).

10 PMR Two sets of β-lactam peaks. 5.65, 1H, d (J=1.5 Hz); 3.7 and 3.5, 2 dd (J=1.5 and 7 Hz); 3.2-2.8, 2H, m (-$\underline{CH_2}$-CH=CH_2); 1.4-1.2, 2 doublets, 3H (J=7 Hz). IR 1790, 1745; UV 317 nm; C^{13}NMR 2 sets of peaks. 237.46 and 232.88 (C=S), 168 (ester), 164.77 and 164.53 (β-lactam).

11 PMR 5.3, 1H, d (J=1.5 Hz), 5.2, 4H, m; 4.2, 1H, m; 3.5, 1H, dd (J=1.5 and 7 Hz); 3.2-2.5, 2Q, 2H; (-$\underline{CH_2}$-CH=CH_2) 2.4, 2H, m (-CH_2-C=C); 1.3, 3H, d (J=7 Hz).

NOTE: All new compounds were characterized by High Resolution Mass Spectrometry, H' NMR, C^{13} NMR, IR and UV data.

(Received in USA 6 April 1983)