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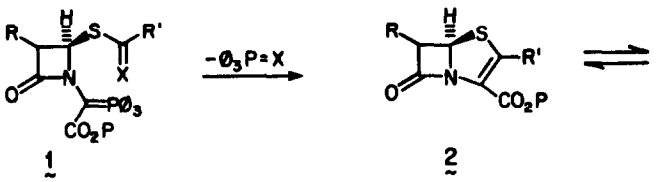
A CONVENIENT SYNTHESIS OF RACEMIC 6-HYDROXYETHYL-2-ALKYLTHIO-SUBSTITUTED PENEMS

Frank DiNinno,* David A. Muthard, Ronald W. Ratcliffe and Burton G. Christensen

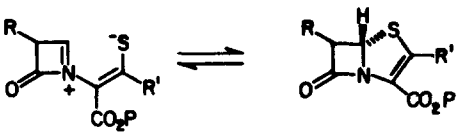
Merck Sharp & Dohme Research Laboratories, P. O. Box 2000, Rahway New Jersey 07065

Racemic 6-hydroxyethyl-2-alkylsulfinylpenems undergo a facile displacement with mercaptans under basic conditions to conveniently provide new 2-alkylthiopenems.

Penems, a novel class of bicyclic β-lactam antibiotics, have received extensive attention[1] since the first announcement of their synthesis in 1976.[2] One result of this effort has been the advancement of sodium (5R,6S)-6-[(R)-1-hydroxyethyl]-2-ethylthiopen-2-em-3-carboxylate (Schering-29,482), a potent, broad spectrum, orally active antibiotic, as the first penem clinical candidate.[3] The synthesis of the latter compound[1e] and penems in general[1a,b,c,e,f] usually relies on the formation and cyclization of a stabilized phosphorane **1**. However, it has been observed[1c,e] that certain 2-alkylthio-6-substituted



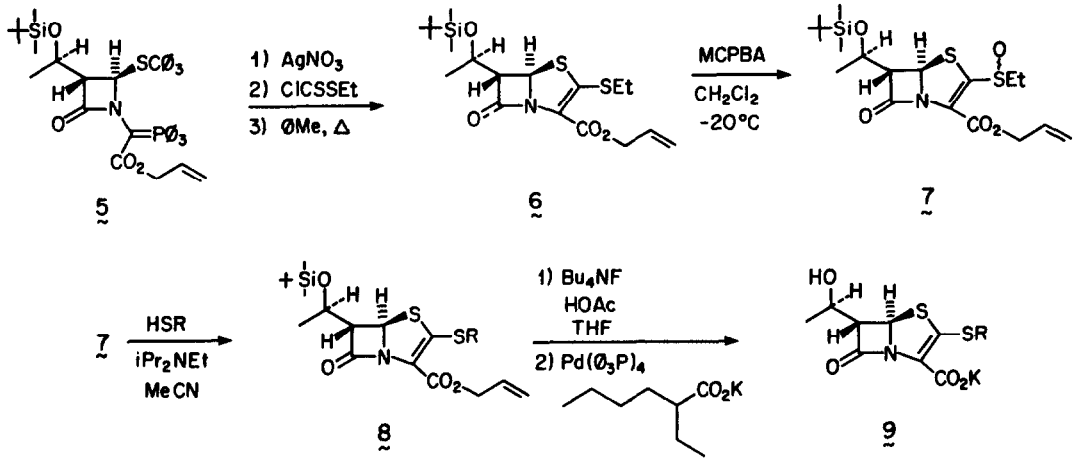
1 **2**



3 **4**

penems undergo a novel thermal isomerization, presumably via betaine **3**, during the course of the intramolecular Wittig reaction to provide mixtures of **2** and the undesired isomer **4**. Thus, as part of a derivative program designed to produce "2-SR" penem variants, which parallels our efforts in carbapenems,[4] we have devised a route which minimizes this problem by obviating the need to synthesize and cyclize **1** for every derivative, and which, in addition, may provide derivatives unobtainable by the Wittig process.

Penem **6**[5] was synthesized from the phosphorane azetidinone **5**[6,11] by initial silver thiolate formation ($AgNO_3$, MeOH-CH_2Cl_2, pyridine, RT), followed by thioacylation (ClCSSEt, CH_2Cl_2, pyridine, 0°C, 74% overall) and cyclization (ØMe, 140°C, 40 hr, 59%).[7] Exposure of **6** to 1.1 equivalents of m-chloroperoxybenzoic acid in methylene chloride solution at -20°C resulted predominantly in oxidation of the exocyclic



5 **6** **7** **8** **9**

sulfur[8] to provide a 1:1 mixture of diastereomeric sulfoxides **7**[9] (63% after chromatography), thereby setting the stage for displacement reactions of the newly generated sulfinyl group.[10] Indeed, treatment of acetonitrile solutions of **7** with a variety of thiols in the presence of Hunig's base at -40°C to -20°C affected a facile transformation to penems **8**.[11] Table 1 summarizes the results of this novel "side-chain interchange" process with several representative mercaptans.

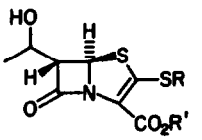
Table 1. Synthesis of Penems 8

R	Isolated[a] Yield (%)
a. $-CH(CH_3)_2$	69
b. $-CH_2CH_2NHCO_2PNB$[b]	70
c. $-CH_2\overset{O}{\overset{\|}{C}}NH_2$	43
d. $-CH_2-$ 	74
e. $-CH(CH_3)CH_2OH$[c]	67
f. $-CH_2CH_2OH$	69

[a] Unoptimized. [b] PNB = p-nitrobenzyl.
[c] Separable diastereomers.

Penems **8** were converted into their biologically active forms **9**[11] by sequential desilylation (Bu_4NF, HOAc, THF, RT)[12] and deallylation ($[\phi_3P]_4Pd$, ϕ_3P, $Me(CH_2)_3CH(Et)CO_2K$, EtOAc).[13] The p-nitrobenzyloxycarbonyl protecting group of compound **9b** was removed by catalytic hydrogenation (10% Pd/C, 0.1M pH 7.1 phosphate buffer) to afford (±)-"thiathienamycin,"[1c] which was subsequently formimidoylated to provide the penem analog of N-formimidoylthienamycin (MK-787).[14] Table 2 summarizes the results of these transformations.

Table 2. Deprotection Results.



R	Isolated Yield (%)	
	R' = $CH_2CH=CH_2$	R' = K
a. $-CH(CH_3)_2$	84	81
b. $-CH_2CH_2NHCO_2PNB$	56	72
c. $-CH_2\overset{O}{\overset{\|}{C}}NH_2$	73	87
d. $-CH_2-$	32	37
e. $-CH(CH_3)CH_2OH$	84	44

The penem antibiotics afforded by these procedures were, in general, less active than their carbapenem counterparts against a wide variety of microorganisms but were more stable toward the dehydropeptidase-I enzyme. The biological results will be the subject of a forthcoming publication from these laboratories.

References and Notes

1) For leading references see: a) H. R. Pfaendler, J. Gosteli and R. B. Woodward, J. Amer. Chem. Soc., **102**, 2039 (1980); b) M. Lang, K. Prasad, J. Gosteli and R. B. Woodward, Helv. Chim. Acta, **63**, 1093 (1980); c) T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara and E. Ohki, Chem. Pharm. Bull., **29**, 3158 (1981); d) T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura and T. Miyadera, Tet. Lett., 1075 (1982); e) V. M. Girijavallabhan, A. K. Ganguly, S. W. McCombie, P. Pinto and R. Rizvi, Tet. Lett., 3485 (1981); f) M. Foglio, G. Franceschi, G. Serra-Errante, M. Ballabio and F. Arcamone, Heterocycles, **15**, 785 (1981); g) P. C. Cherry, D. N. Evans, C. E. Newall and N. S. Watson, Tet. Lett., 561 (1980).

2) R. B. Woodward, Recent Advances in the Chemsitry of β-Lactam Antibiotics, p. 167, J. Elks, Ed., Chemical Society, London (1977).

3) See J. Antimicrobial Chemotherapy, **9**, Suppl. C (1982).

4) a) R. W. Ratcliffe, T. N. Salzmann and B. G. Christensen, Tet. Lett., 31 (1980); b) T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, J. Amer. Chem. Soc., **102**, 6161 (1980); c) The extension of the methodology of the latter references to the synthesis of 2-SR side chain analogs of thienamycin will be reported shortly.

5) Reference 1e describes penem **6** in which the t-butyldimethyl silyl group is replaced with a trichloroethyloxycarbonyl group; pertinent spectroscopic data: IR (CH_2Cl_2) 1790 cm^{-1}; NMR δ 5.64 (d, J = 1.0 Hz, H-5); λ_{max}^{diox} 337 nm.

6) Compound **5** may be prepared according to M. Menard and A. Martel, U.K. Patent No. 2,042,514 (1980), Bristol-Meyers Co.

7) The corresponding cis-penem **6** was isolated in 16% yield after chromatography and may be conveniently separated from **6** by fractional crystallization.

8) A small yield (5%) of a ring sulfur oxide was isolated and characterized spectroscopically: IR (CH_2Cl_2) 1819 cm^{-1}; pertinent NMR ($CDCl_3$) δ 1.3 (d, J = 6.5 Hz, 3H), 1.46 (t, J = 7.0 Hz, 3H), 3.26 and 3.46 (dq's, J = 7 and 12.5 Hz, 2H), 3.9 (app. t, J = 3.0 Hz, H-6), 5.16 (d, J = 4.0 Hz, H-5); λ_{max}^{diox} 298 nm.

9) IR (CH_2Cl_2) 1800 cm^{-1}; NMR δ 1.26 (2 d's, J = 5 and 7 Hz, 3H), 1.44 (2 t's, J = 7 Hz, 3H), 3.14 (m, 2H), 3.86 (2 dd's, J = 1.5, 4.0 and J = 1.0, 3.0, H-6), 5.7 and 5.84 (2 d's, J = 1.5 and J = 1.0 respectively, H-5); λ_{max}^{diox} 347 nm. In our experience, side chain sulfur oxidation vs. ring sulfur oxidation products can be readily distinguished by the chemical shifts of the H-5 protons. Relative to the parent sulfides the former S-oxides exhibit downfield shifts for H-5 and for the latter dramatic upfield shifts.

10) During the preparation of this manuscript, an analogous process was described for carbapenems: K. Yamamoto, T. Yoshioka, Y. Kato, K. Isshiki, M. Nishino, F. Nakamura, Y. Shimauchi and T. Ishikura, Tet. Lett., 897 (1982); and identically for penems: N. Broom, European Patent Publication No. 0,046,363 (1982), Beecham Group Limited.

11) All new compounds exhibited spectroscopic properties consistent with the structures given.

12) G. Just and T.-J. Liak, Can. J. Chem., **56**, 211 (1978) and reference 1c.

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