

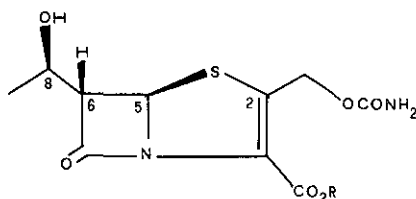
## SYNTHESIS OF NEW ORALLY ABSORBED PENEM ESTERS, STRUCTURALLY RELATED TO THIENAMYCIN AND CEPHAMYCINS

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*Abstract* - The synthesis of two new 6 $\alpha$ -hydroxyethyl penem esters, with the relevant feature of a carbamoyloxymethyl moiety in position 2, is described.

Among non classical  $\beta$ -lactams, penems are recognized as potent antibiotics.<sup>1-4</sup> As continuing part of our work on penems,<sup>3</sup> we wish to describe here the synthesis of new penem esters, well absorbed in animals, and then enzymatically converted to the parent free carboxylate FCE 22101<sup>5-6</sup> (R = Na).

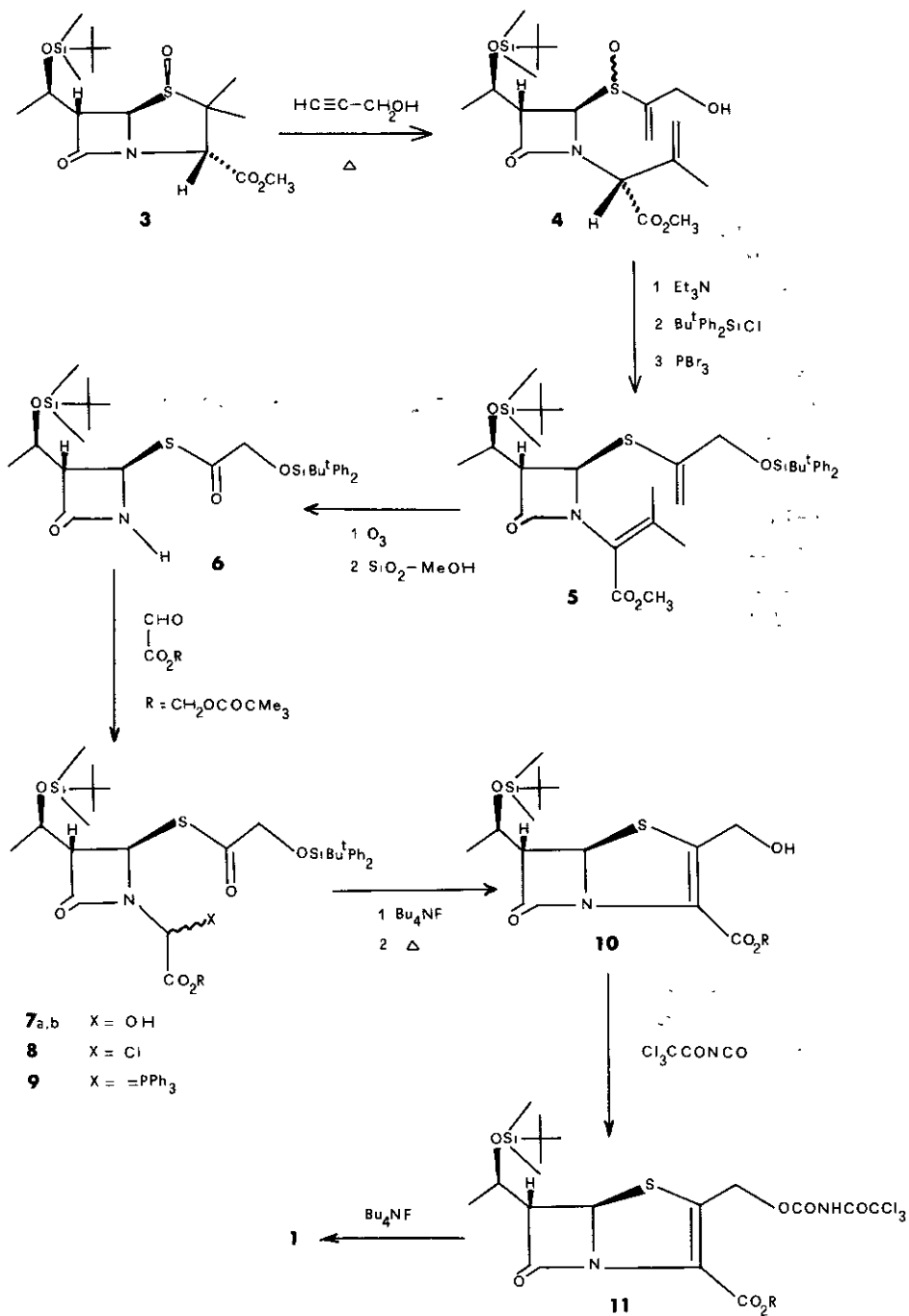


1 R = CH<sub>2</sub>OCOCMe<sub>3</sub> FCE 22553

2 R = CH<sub>2</sub>OCOCH<sub>3</sub> FCE 22891

R = Na FCE 22101

We chose compound (3) as available<sup>7</sup> starting material: the sulphenic acid obtained by thermolysis of the sulphoxide was trapped<sup>8</sup> by propargyl alcohol (refl. toluene) to give the allylic sulphoxide (4) in 80% yields. PMR (60 MHz, CDCl<sub>3</sub>) $\delta$  0.03 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>); 0.82 (s, 9H, SiBu<sup>t</sup>); 1.03 (d, J = 6 Hz, 3H, CHCH<sub>3</sub>); 1.91 (s, 3H, CH<sub>3</sub>); 3.2-3.8 (m, 2H, H-6, OH); 3.75 (s, 3H, COOCH<sub>3</sub>); 4.1-4.4 (m, 1H, CHOSi); 4.45 (br s, 2H, CH<sub>2</sub>OH); 5.0-5.1 (m, 3H, CH<sub>2</sub>, CH); 5.38 (d, J = 2 Hz, 1H, H-5); 5.86 (br s, 2H, =CH<sub>2</sub>). Quantitative isomerization of the isopropenyl double bond (TEA, r.t.), protection of the alcohol function with diphenyltertbutylchlorosilane and reduction of the sulphoxide (PBr<sub>3</sub>, DMF, -20°C, 90% yields) gave sulphide (5). Ozonolysis on both double bonds (CH<sub>2</sub>Cl<sub>2</sub>, -78°C) followed by methanolysis of the oxamide moiety in the presence of silica gel, afforded the N-H free azetidinone (6); PMR (200 MHz, CDCl<sub>3</sub>) $\delta$  0.07 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>); 0.88, 1.11 (two s, 18H, SiC(CH<sub>3</sub>)<sub>3</sub> x2); 1.23 (d, J = 5.5 Hz, 3H, CH<sub>3</sub>CH); 3.24 (dd, J = 2.5 Hz, 1H, H-6); 4.15-4.20 (m, 1H, CH<sub>3</sub>CH); 4.24 (s, 2H, C=OCH<sub>2</sub>O); 5.24 (d, J = 2 Hz, 1H, H-5); 7.30-7.70 (m, 10H, Si(Ph)<sub>2</sub>). Compound (6) was then condensed with pivaloyloxymethyl glyoxylate (prepared by ozonolysis of the corresponding fumarate), following the well established Woodward's procedure, to give the separable<sup>9</sup> diastereomeric carbinolamides



(7a) and (7b). The crude mixture was chlorinated to (8) and then transformed into the phosphorane (9). Selective desilylation of the primary alcohol ( $\text{Bu}_4\text{NF}$ , 1 hour) and subsequent cyclisation by simple heating in refluxing xylene, afforded the important and versatile (10). PMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.07 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ); 0.88 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ); 1.22 (s, 9H,  $\text{OCOC}(\text{CH}_3)_3$ ); 1.23 (d,  $J = 6.2$  Hz, 3H,  $\text{CH}_3\text{CH}$ ); 3.11 (br t,  $J = 6.7$  Hz, 1H,  $\text{CH}_2\text{OH}$ ); 3.71 (dd,  $J = 1.6, 4.6$  Hz, 1H, H-6); 4.22 (dq,  $J = 4.6, 6.2$  Hz, 1H,  $\text{CH}_3\text{CH}$ ); 4.62 (d,  $J = 6.7$  Hz, 2H,  $\text{CH}_2\text{OH}$ ); 5.58 (d,  $J = 1.6$  Hz, 1H, H-5); 5.80, 5.90 (two d,  $J = 5.5$  Hz, 2H,  $\text{COOCH}_2\text{O}$ ).

The introduction of the carbamoyl moiety was successfully achieved by reacting the alcohol group of (10) with trichloroacetyl isocyanate (r.t., 2-3 hours) giving (11). Deprotection of the silyl moiety in position 8 by  $\text{Bu}_4\text{NF}$  afforded also at the same time deblocking of the trichloroacetyl residue, eventually giving our target (1). PMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.21 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ); 1.33 (d,  $J = 6.0$  Hz, 3H,  $\text{CH}_3\text{CH}$ ); 1.61 (br s, 1H, OH); 3.74 (dd,  $J = 1.6, 6.0$  Hz, 1H, H-6); 4.22 (br s, 1H,  $\text{CH}_3\text{CH}$ ); 4.79 (br s, 2H,  $\text{CONH}_2$ ); 5.08, 5.42 (two s,  $J = 15.8$  Hz, 2H,  $\text{CH}_2\text{OCONH}_2$ ); 5.62 (d,  $J = 1.6$  Hz, 1H, H-5); 5.78, 5.94 (two d,  $J = 5.5$  Hz, 2H,  $\text{COOCH}_2\text{O}$ ).

Analogously, compound (2) was also obtained starting from the N-H free azetidinone (6) and acetoxymethyl glyoxylate. PMR (200 MHz, acetone- $d_6$ )  $\delta$  1.26 (d,  $J = 6.0$  Hz, 3H,  $\text{CH}_3\text{CH}$ ); 2.06 (s, 3H,  $\text{COCH}_3$ ); 3.78 (s, 1H, OH); 3.80 (dd,  $J = 1.7, 6.4$  Hz, 1H, H-6); 4.14 (m, 1H,  $\text{CH}_3\text{CH}$ ); 5.08, 5.34 (two d,  $J = 16.0$  Hz, 2H,  $\text{CH}_2\text{OCONH}_2$ ); 5.69 (d,  $J = 1.7$  Hz, 1H, H-5); 5.80, 5.86 (two d,  $J = 5.8$  Hz, 2H,  $\text{COOCH}_2\text{OCO}$ ); 6.10 (bs, 2H,  $\text{NH}_2$ ).

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#### REFERENCES AND NOTES

1. H.R. Pfaendler, J. Gosteli and R.B. Woodward, *J. Am. Chem. Soc.* 1980, 102, 2039.
2. V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto and R. Rizvi, 21th Intersci. Conf. Antimicr. Agents & Chemoth., Abstract 829 and following papers, Chicago Nov. 1981.
3. A. Sanfilippo, C. Della Bruna, D. Jabes, E. Morvillo, G. Schioppacassi, G. Franceschi, F. Arcamone, C. Battistini, M. Foglio and F. Zarini, *J. Antib.*, 1982, 35 1248.
4. T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara and E. Ohki, *Chem. Pharm. Bull.*, 1981, 29, 3158.
5. C. Della Bruna, D. Jabes, A. Sanfilippo, G. Schioppacassi, F. Arcamone, M. Foglio and G. Franceschi, 22nd Intersci. Conf. Antimicr. Agents & Chemoth., Abstract 216, Miami Oct. 1982.
- 6) Submitted to *J. Antibiotics* for publication.
- 7) M. Foglio, C. Battistini, F. Zarini and G. Franceschi, *Heterocycles*, 1982, 19, 485.
- 8) M. Foglio, G. Franceschi, C. Scarafile and F. Arcamone, *J. Chem. Soc. Chem. Commun.*, 1980, 70.

9. PMR (200 MHz,  $\text{CDCl}_3$ ) (7a isomer) :

$\delta$  0.07 (s, 6H,  $\text{Si}(\underline{\text{CH}_3})_2$ ); 0.88, 1.11, 1.19 (three s, 27H,  $\text{SiC}(\underline{\text{CH}_3})_3 \times 2$ ,  $\text{COC}(\underline{\text{CH}_3})_3$ ); 1.20 (d,  $J = 5.5$  Hz, 3H,  $\underline{\text{CH}_3\text{CH}}$ ); 3.34 (dd,  $J = 2.6, 4.7$  Hz, 1H,  $\underline{\text{H-6}}$ ); 4.10-4.35 (m, 2H,  $\underline{\text{CH}_3\text{CH}}$ ,  $\underline{\text{CHOH}}$ ); 4.21, 4.35 (two d,  $J = 16.6$  Hz, 2H,  $\overset{\text{O}}{\text{CCH}_2\text{OSi}}$ ); 5.47 (bd,  $J = 10$  Hz, 1H,  $\underline{\text{CHOH}}$ ); 5.55 (d,  $J = 2.6$  Hz, 1H,  $\underline{\text{H-5}}$ ); 5.64, 5.82 (two d,  $J = 5.4$  Hz, 2H,  $\text{COO}\underline{\text{CH}_2\text{O}}$ ); 7.38-7.67 (m, 10H,  $\text{Si}(\underline{\text{Ph}})_2$ ).

(7b isomer) :

$\delta$  0.06 (s, 6H,  $\text{Si}(\underline{\text{CH}_3})_2$ ); 0.87, 1.11, 1.20 (three s, 27H,  $\text{SiC}(\underline{\text{CH}_3})_3 \times 2$ ,  $\text{COC}(\underline{\text{CH}_3})_3$ ); 1.23 (d,  $J = 5.5$  Hz, 3H,  $\underline{\text{CH}_3\text{CH}}$ ); 3.34 (dd,  $J = 2.8, 4.1$  Hz, 1H,  $\underline{\text{H-6}}$ ); 3.62 (bd,  $J = 6$  Hz, 1H,  $\underline{\text{CHOH}}$ ); 4.25 (m, 3H,  $\overset{\text{O}}{\text{CCH}_2\text{OSi}}$ ,  $\underline{\text{CHCH}_3}$ ); 5.21 (d,  $J = 6$  Hz, 1H,  $\underline{\text{CHOH}}$ ); 5.50 (d,  $J = 2.8$  Hz, 1H,  $\underline{\text{H-5}}$ );  $\overset{\text{O}}{\text{O}}$  5.80, 5.95 (two d,  $J = 5.4$  Hz, 2H,  $\text{COO}\underline{\text{CH}_2\text{O}}$ ); 7.38-7.68 (m, 10H,  $\text{Si}(\underline{\text{Ph}})_2$ ).

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