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

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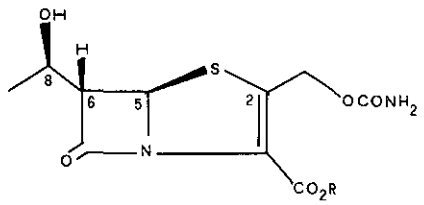
Abstract - The synthesis of two new 6α-hydroxyethyl penem esters, with the relevant feature of a carbamoyloxymethyl moiety in position 2, is described.

Among non classical β-lactams, penems are recognized as potent antibiotics.[1-4] As continuing part of our work on penems,[3] 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[5-6] (R = Na).

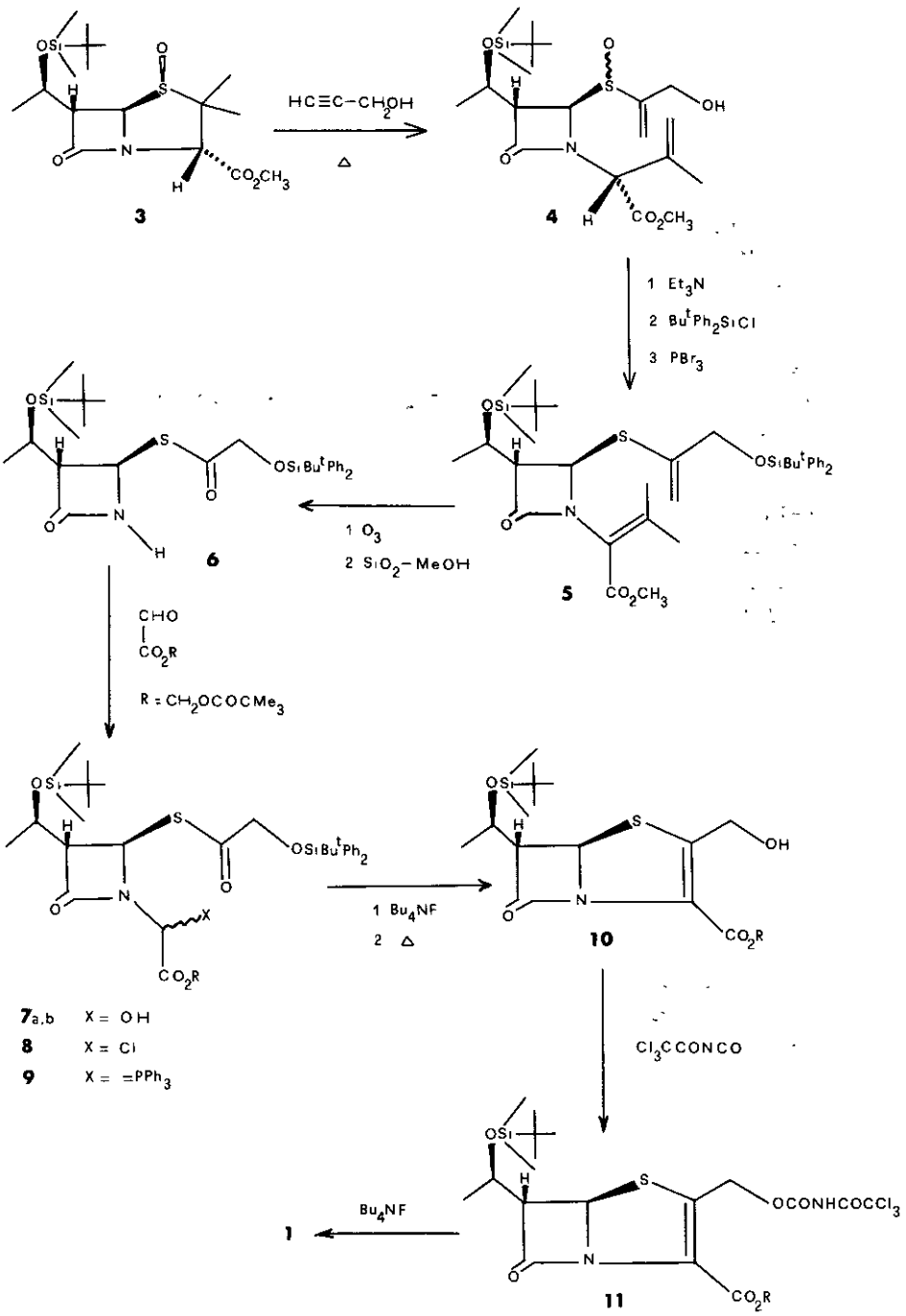


R = Na FCE 22101

1 R = $CH_2OCOCMe_3$ FCE 22553

2 R = CH_2OCOCH_3 FCE 22891

We chose compound (3) as available[7] starting material: the sulphenic acid obtained by thermolysis of the sulphoxide was trapped[8] by propargyl alcohol (refl. toluene) to give the allylic sulphoxide (4) in 80% yields. PMR (60 MHz, $CDCl_3$) δ 0.03 (s, 6H, $Si(\underline{CH_3})_2$); 0.82 (s, 9H, $Si\underline{Bu^t}$); 1.03 (d, J = 6 Hz, 3H, $CH\underline{CH_3}$); 1.91 (s, 3H, $\underline{CH_3}$); 3.2-3.8 (m, 2H, H-6, OH); 3.75 (s, 3H, $COO\underline{CH_3}$); 4.1-4.4 (m, 1H, $\underline{CH}OSi$); 4.45 (br s, 2H, $\underline{CH_2}OH$); 5.0-5.1 (m, 3H, $\underline{CH_3}\underline{CH_2}$, $\underline{CH}$); 5.38 (d, J = 2 Hz, 1H, H-5); 5.86 (br s, 2H, $=\underline{CH_2}$). Quantitative isomerization of the isopropenyl double bond (TEA, r.t.), protection of the alcohol function with diphenyltertbutylchlorosilane and reduction of the sulphoxide (PBr_3, DMF, -20°C, 90% yields) gave sulphide (5). Ozonolysis on both double bonds (CH_2Cl_2, -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, $CDCl_3$) δ 0.07 (s, 6H, $Si(\underline{CH_3})_2$); 0.88, 1.11 (two s, 18H, $SiC(\underline{CH_3})_3$ x2); 1.23 (d, J = 5.5 Hz, 3H, $\underline{CH_3}CH$); 3.24 (dd, J = 2.5 Hz, 1H, H-6); 4.15-4.20 (m, 1H, $CH_3\underline{CH}$); 4.24 (s, 2H, $C{=}O\underline{CH_2}O$); 5.24 (d, J = 2 Hz, 1H, H-5); 7.30-7.70 (m, 10H, $Si(\underline{Ph})_2$). 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[9] diastereomeric carbinolamides


HC≡C–CH2OH
△
3
4
1 Et3N
2 Bu^tPh2SiCl
3 PBr3
5
1 O3
2 SiO2–MeOH
6
CHO
CO2R
R = CH2OCOCMe3
7a,b X = OH
8 X = Cl
9 X = =PPh3
1 Bu4NF
2 △
10
Cl3CCONCO
Bu4NF
1
11
OCONHCOCCl3

(7a) and (7b). The crude mixture was chlorinated to (8) and then transformed into the phosphorane (9). Selective desilylation of the primary alcohol (Bu_4NF, 1 hour) and subsequent cyclisation by simple heating in refluxing xylene, afforded the important and versatile (10). PMR (200 MHz, $CDCl_3$)δ0.07 (s, 6H, $Si(\underline{CH_3})_2$); 0.88 (s, 9H, $SiC(\underline{CH_3})_3$); 1.22 (s, 9H, $OCOC(\underline{CH_3})_3$); 1.23 (d, J = 6.2 Hz, 3H, $\underline{CH_3}CH$); 3.11 (br t, J = 6.7 Hz, 1H, $CH_2\underline{OH}$); 3.71 (dd, J = 1.6, 4.6 Hz, 1H, H-6); 4.22 (dq, J = 4.6,6.2 Hz, 1H, $CH_3\underline{CH}$); 4.62 (d, J = 6.7 Hz, 2H, $\underline{CH_2}OH$); 5.58 (d, J = 1.6 Hz, 1H, H-5); 5.80, 5.90 (two d, J = 5.5 Hz, 2H, $COO\underline{CH_2}O$).

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 Bu_4NF afforded also at the same time deblocking of the trichloroacetyl residue, eventually giving our target (1). PMR (200 MHz, $CDCl_3$)δ1.21 (s, 9H, $C(\underline{CH_3})_3$); 1.33 (d, J = 6.0 Hz, 3H, $\underline{CH_3}CH$); 1.61 (br s, 1H, OH); 3.74 (dd, J = 1.6, 6.0 Hz, 1H, H-6); 4.22 (bm, 1H, $CH_3\underline{CH}$); 4.79 (br s, 2H, $CO\underline{NH_2}$); 5.08, 5.42 (two s, J = 15.8 Hz, 2H, $\underline{CH_2}OCONH_2$); 5.62 (d, J = 1.6 Hz, 1H, H-5); 5.78, 5.94 (two d, J = 5.5 Hz, 2H, $COO\underline{CH_2}O$).

Analogously, compound (2) was also obtained starting from the N-H free azetidinone (6) and acetoxymethyl glyoxylate. PMR (200 MHz, acetone-d_6)δ1.26 (d, J = 6.0 Hz, 3H, $\underline{CH_3}CH$); 2.06 (s, 3H, $COCH_3$); 3.78 (s, 1H, OH); 3.80 (dd, J = 1.7, 6.4 Hz, 1H, H-6); 4.14 (m, 1H, $CH_3\underline{CH}$); 5.08, 5.34 (two d, J = 16.0 Hz, 2H, $\underline{CH_2}OCONH_2$); 5.69 (d, J = 1.7 Hz, 1H, H-5); 5.80, 5.86 (two d, J = 5.8 Hz, 2H, $COO\underline{CH_2}OCO$); 6.10 (bs, 2H, $\underline{NH_2}$).

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9. PMR (200 MHz, $CDCl_3$) (7a isomer) :

δ0.07 (s, 6H, $Si(\underline{CH_3})_2$); 0.88, 1.11, 1.19 (three s, 27H, $SiC(\underline{CH_3})_3$ x 2, $COC(\underline{CH_3})_3$); 1.20 (d, J = 5.5 Hz, 3H, $\underline{CH_3}CH$); 3.34 (dd, J = 2.6, 4.7 Hz, 1H, H-6); 4.10-4.35 (m, 2H, $CH_3\underline{CH}$, CHOH); 4.21, 4.35 (two d, J = 16.6 Hz, 2H, $\underset{O}{\overset{\|}{C}}\underline{CH_2}OSi$); 5.47 (bd, J = 10 Hz, 1H, CHOH); 5.55 (d, J = 2.6 Hz, 1H, H-5); 5.64, 5.82 (two d, J = 5.4 Hz, 2H, $COO\underline{CH_2}O$); 7.38-7.67 (m, 10H, $Si(\underline{Ph})_2$).

(7b isomer) :

δ0.06 (s, 6H, $Si(\underline{CH_3})_2$); 0.87, 1.11, 1.20 (three s, 27H, $SiC(\underline{CH_3})_3$ x 2, $COC(\underline{CH_3})_3$; 1.23 (d, J = 5.5 Hz, 3H, $\underline{CH_3}CH$); 3.34 (dd, J = 2.8, 4.1 Hz, 1H, H-6); 3.62 (bd, J = 6 Hz, 1H, CHOH); 4.25 (m, 3H, $\underset{O}{\overset{\|}{C}}\underline{CH_2}OSi$, $\underline{CH}CH_3$); 5.21 (d, J = 6 Hz, 1H, CHOH); 5.50 (d, J = 2.8 Hz, 1H, H-5); 5.80, 5.95 (two d, J = 5.4 Hz, 2H, $COO\underline{CH_2}O$); 7.38-7.68 (m, 10H, $Si(\underline{Ph})_2$).

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