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DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. VI.

FROM PENAM METHYL ESTERS TO PENEM ACETONYL ESTERS : A FULLY CONSERVATIVE CONVERSION

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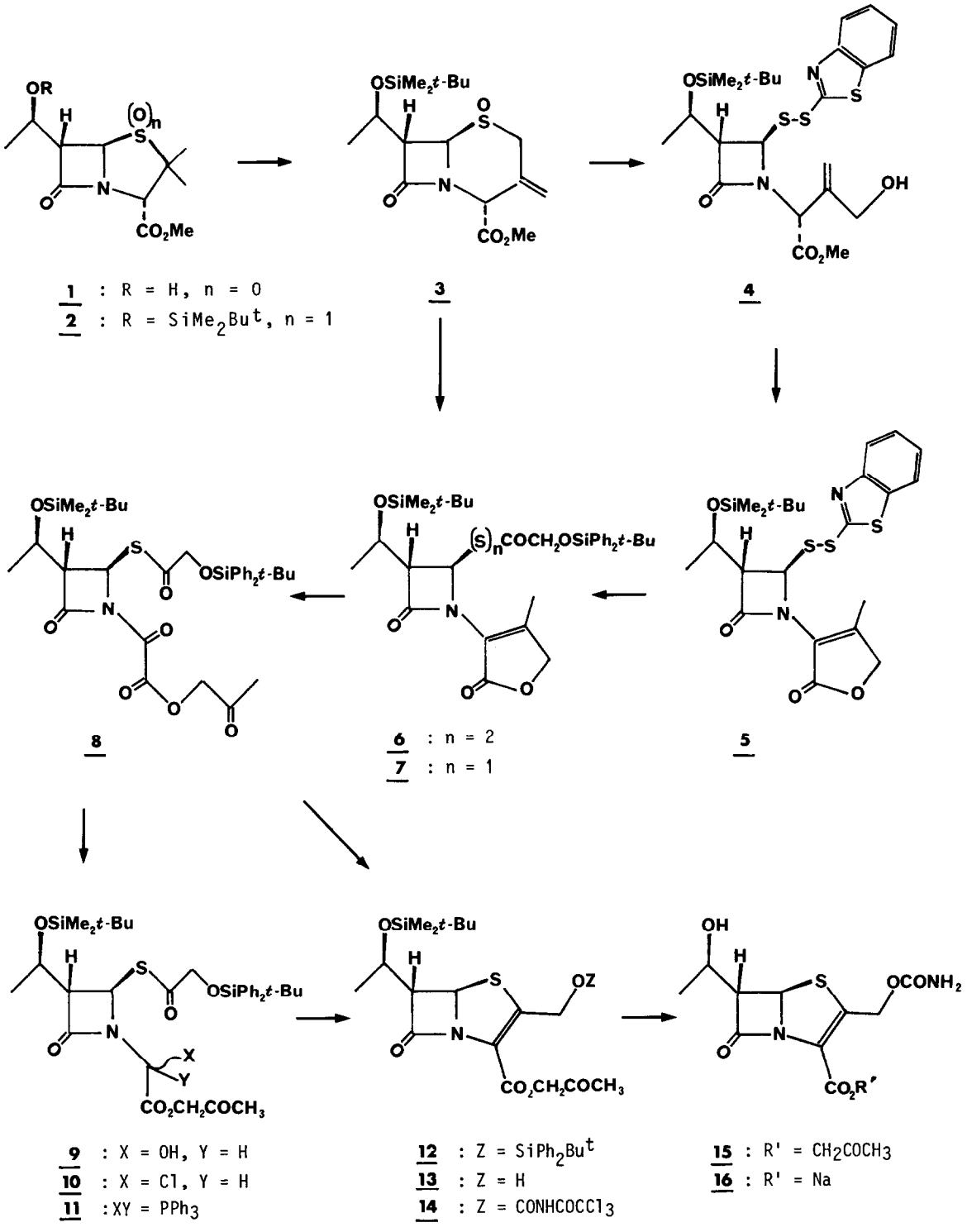
Abstract : A straightforward conversion of penam methyl esters into penem acetonyl esters entailing incorporation of all the elements of the former into the latter is described.

Though formally attractive and preparatively promising, conservative routes from 6-APA to biologically active penem compounds are severely limited by the inadequacy of the existing carboxyl protecting groups. In particular, if the carboxylic portion of the starting penam has to be preserved, it must be protected in such a way as to be resistant towards Grignard reagents (for the introduction of the hydroxyethyl side chain) and oxidative conditions (for the removal of the gem-Me groups), while still permitting a convenient unmasking on the target penem compound. It is a fact that since Woodward's first synthesis[1], every pathway from 6-APA to 6-(1-hydroxyethyl)penem-3-carboxylic acids has involved the total degradation of the thiazolidine ring of the former. On the other hand, new or sophisticated protecting groups stand little chance of development when compared to the cheap methyl ester which, owing to the cristallinity conferred to the bromohydrin intermediate[2], allows chromatography-free preparations of diastereomerically pure methyl (5R,6S)-6-[(1R)-hydroxyethyl]penamcarboxylate 1 in bulk amounts.

In a recent 2-thiacephem synthesis[3], we happened to come across the spontaneous conversion of a penicillin-derived methyl ester, 4, into an azetidinyl lactone, 5. Although related lactones[4,5] have long been known without suscitating synthetic interest, in this speculative context we were prompt to realize that an apparently parasite reaction had cleaved a useless methyl ester to originate, under a masked form, an acetonyl ester plus an oxalimide carbonyl. Oxalimides of this type had been previously converted into phosphoranes[6]; the easy hydrolysis of acetonyl[7] esters had been confirmed in our experience[8]; the missing element, an appropriate thioester at azetidinone C-4, could be provided by our disulphide-exchange/desulphuration techniques[9].

To our end, the key intermediate 1, after conventional oxidation and silylation, was converted into the crystalline 3-methylenecepham-1-oxide 3[3]. Prolonged heating with mercaptobenzothiazole gave a mixture of the alcohol 4 and lactone 5 (approx. 3:2 after 5 hours in refluxing toluene); addition of a catalytic amount of triethylamine,[10] followed by work-up and crystallization (Et_2O) after 3 hours at r.t., afforded the pure disulphide-lactone 5[11] (60% from 3). Exchange of the benzothiazolylthio portion with tert-butyldiphenylsilyloxyethanthioic acid (CH_2Cl_2, immediate) and in situ desulphuration (PPh_3 2 eq., 1 hour r.t.), followed by silica gel chromatography, gave the thioester-lactone 7 (70%). Ozonolysis of this product (CH_2Cl_2, -70°) exposed the oxalimide carbonyl and the acetonyl ester latently present in the lactone moiety; addition of Zn/AcOH and warming up to room temperature afforded the diastereomeric carbinolamides 9 in virtually quantitative yield. Sequential treatment with $SOCl_2$/pyridine and PPh_3 on silica[12] completed the phosphorane synthesis (64% overall from the lactone 7); ring closure of 11 (refluxing toluene, 8 hours) then smoothly furnished the bis-silylated penem acetonyl ester 12 (82%). Selective desilylation of 12 under remarkably mild conditions (tetrabutylammonium fluoride trihydrate in AcOH buffered THF, 15 min. r.t.) liberated the versatile alcohol 13, a key intermediate in the synthesis of penems bearing cephalosporin-like C-2 side chains. In particular, addition of trichloroacetylisocyanate, followed by more prolonged exposure to the fluoride reagent[13] gave 15 (75 % from 12), whose careful alkaline hydrolysis afforded the valuable penem antibiotic 16 (FCE 22101 [13]). Full incorporation of the elements of a penam methyl ester (the gem-Me groups included) into the easily cleavable penem acetonyl esters 13, 15 has therefore been accomplished, if allowance is made for the actual fate of the sulphur atom, still object of speculations.[14]

Shortcuts in the whole process were then examined. The most remarkable one was offered by the recent discovery of a direct thioester - oxalimide dicarbonyl coupling[15]; the acetonyl oxalimide 8 was conveniently cyclized to 12 in a single step thereupon (triethylphosphite, xylene 120°, 8 hours, 50% overall yield from the lactone 7). An additional advantage of the new methodology lies in the chance it offers to suppress the hydroxyl protecting group, formerly required by the carbinol - chloride (9→10) conversion.[16] A further attractive simplification, the trapping of the cyclic sulphenate species[5] with thioacids instead of thiols, proved successful. Although the overall yields were not improved, the acyldithioazetidinone 6 could be directly obtained from the cepham 3 (t-$BuPh_2SiOCH_2COSH$, refluxing toluene, 16 hours under N_2) without the intermediacy of Kamiya's disulphides 4 and 5.



1 : R = H, n = 0
2 : R = $SiMe_2Bu^t$, n = 1

3

4

5

6 : n = 2
7 : n = 1

8

9 : X = OH, Y = H
10 : X = Cl, Y = H
11 : XY = PPh_3

12 : Z = $SiPh_2Bu^t$
13 : Z = H
14 : Z = $CONHCOCCl_3$

15 : R' = CH_2COCH_3
16 : R' = Na

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10. Two pathways warrant consideration for the conversion of type 4 alcohols into type 5 lactones, according to whether double bond migration precedes or follows cyclization; none of the expected intermediates (the conjugate E hydroxybutenoate or the unconjugate lactone) or by-products (the conjugate Z hydroxybutenoate, which cannot lactonize[4]) were however isolated. In order to avoid silica gel artifacts, we have monitored the lactonization of the analogue of 4 bearing a cis-oriented phthalimido chain at C-3 (a model substrate which could be easily isolated pure[3]) in a nmr tube under mild base catalysis ($CDCl_3$, pyridine); under these conditions the starting carbinol was slowly converted into a new product, in turn transformed into the final lactone in a partially superimposing reaction. Although attempted isolation of this intermediate led to lactonization, its nmr signals were fully consistent with the conjugated E hydroxybutenoate structure. The absence of the Z alkene is intriguing; intramolecular hydrogen bonding in the starting hydroxyester could in principle account for the observed geometrical induction, but the above results were not altered by performing the base treatment in deuteroacetone or deuteromethanol.

11. Salient data for new compounds are as follows : 4 : νmax($CHCl_3$ film) 3400, 1765, 1740 cm^{-1}; δ($CDCl_3$) 0.07(6H, s), 0.88(9H, s), 1.28(3H, d, J=6 Hz), 3.40(1H, dd, J=2 and 5 Hz), 3.63(3H, s), 4.25(2H, br), 4.95, 5.15 and 5.30 (each 1H, s), 5.31(1H, d, J=2 Hz), 7.0-7.8(4H, m); 5 : mp 145°;νmax($CHCl_3$) 1775, 1760 cm^{-1};δ($CDCl_3$) 0.06 and 0.10 (each 3 H, s), 0.88(9H, s), 1.3(3H, d, J=6 Hz), 1.8(3H, s), 3.5(1H, dd, J=2 and 3 Hz), 4.15(2H, ABq, J=18 Hz), 4.25(1H, m), 5.9(1H, d, J=2 Hz), 7.0-7.8(4H, m); 6 : νmax ($CHCl_3$ film) 1775, 1760, 1740 cm^{-1}; δ($CDCl_3$) 0.07(6H, s), 0.85(9H, s), 1.1(9H, s), 1.25(3H, d, J=6 Hz), 2.02(3H, s), 3.50(1H, dd, J=2 and 3 Hz), 4.15(1H, m), 4.20(2H, s), 4.45(2H, s), 5.55(1H, d, J=2 Hz), 7.10-7.70(10H, m); 7 : νmax 1780, 1765sh, 1705 cm^{-1}; δ($CDCl_3$) 0.07(6H, s), 0.85(9H, s), 1.1 9H, s), 1.25(3H, d, J=6 Hz), 2.0(3H, s), 3.40(1H, dd, J=2 and 3 Hz), 4.05(2H, s), 4.25(1H, m), 4.50(2H, s), 5.90 1H, d, J=2 Hz), 7.1-7.7(10H, m); 12 : νmax($CHCl_3$) 1785, 1720sh, 1708, 1575 cm^{-1}; δ($CDCl_3$) 0.80 and 0.98(each 9H, s), 1.20(3H, d, J=6 Hz), 2.08(3H, s), 3.68(1H, dd, J=2 and 4 Hz), 4.20(1H, m), 4.53(2H, ABq, J=16 Hz), 4.84(2H, s), 5.55(1H, d, J=2 Hz), 7.3-7.66(10H, m); 13 : νmax($CHCl_3$) 3400, 1785, 1715sh, 1700 cm^{-1}; δ($CDCl_3$) 0.07(6H, s), 0.87 (9H, s), 1.27(3H, d, J=6 Hz), 2.23(3H, s), 3.77(1H, dd, J=2 and 5 Hz), 4.25(1H, m), 4.62(2H, br), 4.76(2H, s), 5.64 (1H, d, J=2 Hz); 15 : mp 155-158° dec.; νmax(KBr) 3550-3170, 1780, 1730, 1710 cm^{-1}; δ(deuteroacetone) 1.25(3H, d, J= 6;5 Hz), 2.12(3H, s), 3.78(1H, dd, J=1.8 and 6.5 Hz), 4.12(1H, m), 4.80(2H, s), 5.20(2H, ABq, J=15.5 Hz), 5.68 (1H, d, J=1.8 Hz), 6.05(2H, br-s).

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