

## Penems: some recent advances

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**Abstract** - Recent advances in penem synthesis are presented, with particular attention to the "2-CH<sub>2</sub>X" derivatives. Two main approaches to the thiazoline ring of penems are discussed, the desulphurization or desulphonylation of their six-membered sulphur analogues and a double-bond forming strategy based on a new type of reductive carbonyl condensation. Generation of the appropriate azetidione thioester intermediates from penicillins has become the discriminating step for the selection of the manufacturing procedure of our clinical candidate, FCE 22101.

The penems are not found in nature. They were created as a "nuclear hybrid" by combining in a single molecule both structural elements essential for the chemical reactivity and biological activity of penicillins and cephalosporins: namely, the hindered amide resonance imposed by the nonplanar skeleton of the former and the competing enamine resonance operative in the latter (ref. 1). Beside the nucleus, a second combination of structural elements appeared appropriate for the side chains. Today, the structure of many remarkable penems reveals something that I venture to call a "double hybrid" nature: a first group of biologically promising products are inspired by thienamycin at C<sub>6</sub> and cephalosporins at C<sub>2</sub>, and a second one by thienamycin alone for both substituents (Fig. 1).

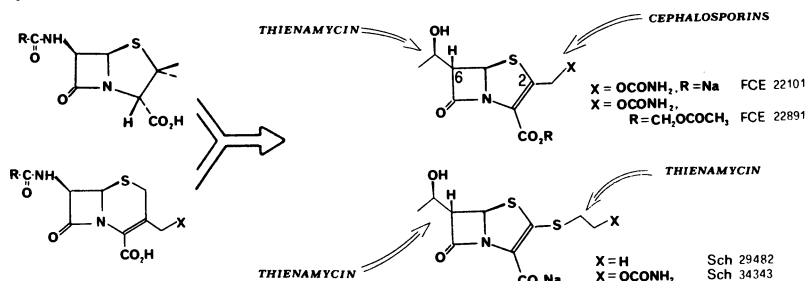


Fig. 1. Remarkable penems from "double hybridization".

We focused our research in the former direction, in the effort of reproducing the enhancement of antibacterial activity that in cephalosporins is associated with the inductive effect and leaving group ability of the C<sub>3</sub>' substituent (ref. 2). The carbamate FCE 22101 is the most advanced product along this line, together with its orally adsorbed acetoxymethyl ester pro-drug FCE 22891 (ref. 3), and newer products are being actively examined.

In ten years, some advances over the pioneering Woodward's work have been achieved. Nonetheless, the chemical ways by which this highly strained skeleton can be assembled remain very limited in number. If we arrange them according to the bond which is made last (Fig. 2), we are left with only two main approaches: the 2,3 and the 1,5 bond-forming strategies. The latter suffers from obvious problems of stereocontrol and we shall marginally discuss it when dealing with the 2-thiacephem ring contraction. The former can be divided into Wittig-type reactions (the phosphorane-thioester approach originally devised by Woodward) and "carbanionic routes", where the active N-acetate methylene acts as a nucleophile on a trigonal carbon centre. The thienamycin-inspired penems are conveniently prepared from 2-thioxopenams (ref. 4) arising through carbanionic routes (Fig. 2, X = S, X' = OPh), but this is not the case for other types of 2-substituted penems, and the products object of our interest had to wait for the inventiveness of Prof. Hanessian before being accessible by this strategy (ref. 5).

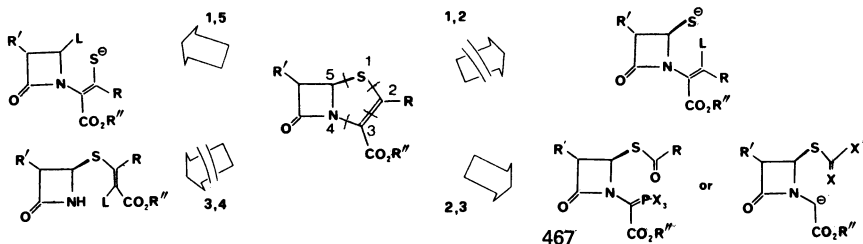


Fig. 2. Penem nucleus: retrosynthetic analysis.

No wonder, therefore, that we concentrated our efforts on the phosphorane-thioester approach. When amino acids (aspartic acid, L-threonine) or 3S-hydroxybutyric acid are used as the starting material, the sequence begins with a *N*-unsubstituted azetidinone, the thioester is introduced by nucleophilic displacement (stereocontrolled by the adjacent hydroxyethyl group), and the *N*-appendage by condensation with a glyoxylate (Fig. 3). On the other hand, starting from penicillins a number of possibilities are opened. Thus, the entire thiazolidine ring can be demolished to furnish the same *N*-unsubstituted azetidinone, ready for thioester introduction. Better, the sulphur atom of the penam skeleton can be preserved, together with the natural chirality of the C<sub>5</sub> centre, by developing convenient methods for converting penams into azetidyl thioesters. Best, also part of the butenoate *N*-appendage can be incorporated into the penem nucleus. All these possibilities have been explored.

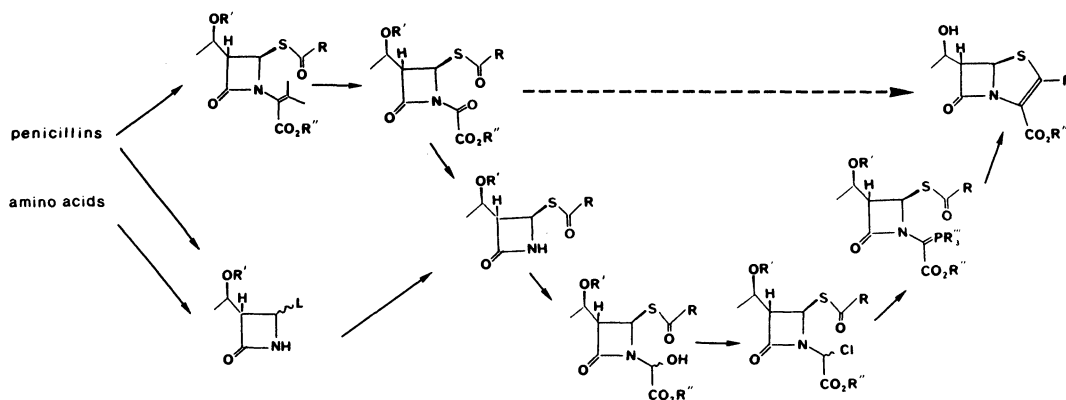


Fig. 3. The phosphorane-thioester approach and the concept of the "conservative" penam-penem route.

One way of retaining the penicillanic sulphur was exploited in the synthetic procedure to optically active penems that we originally developed. This can be divided into three consecutive blocks. In the first (Fig. 4), the hydroxyethyl group was stereoselectively introduced at the 6 $\alpha$  position of a penicillanic sulphoxide (ref. 6). The resulting mixture of 8R and 8S carbinols was separated by TLC, and the latter converted into the former *via* hydrolytic inversion of the triflate (ref. 7).

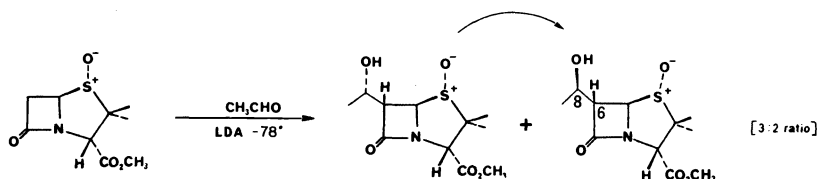


Fig. 4. A route to 6 $S$ ,8 $R$ -hydroxyethylpenam-1-oxides.

Then, following the track of another pioneer of penicillin chemistry, Sir Derek Barton, we trapped with functionalized alkynes the sulphenic acid existing in equilibrium with penam sulphoxide through a six-electron sigmatropic transition state. In particular, the vinyl sulphoxide obtained with propargyl alcohol, after double bond isomerization and hydroxyl protection, could be reduced to the corresponding sulphide and finally converted into the desired azetidinone thioester intermediate by double ozonolysis followed by cleavage of the *N*-oxalyl moiety (Fig. 5).

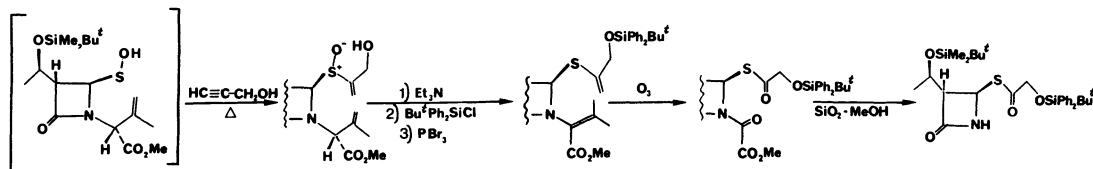


Fig. 5. Synthesis of *N*-unsubstituted azetidinone thioester intermediates.

In the third block, the phosphorane appendage was built up according to Woodward's methodology and finally condensed with the thioester carbonyl (Fig. 6). The 2-hydroxymethyl penem thus constructed is a pivotal intermediate for a variety of "2-CH<sub>2</sub>X" penem targets, including, in this specific instance, the carbamates FCE 22101 and 22891 (ref. 8).

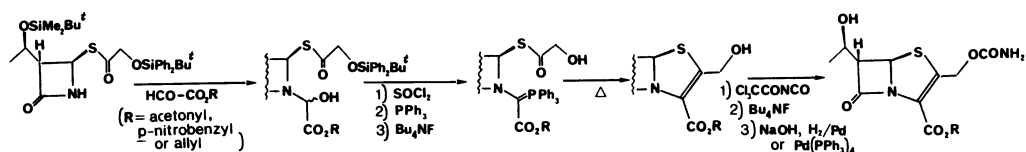


Fig. 6. Synthesis of 6-hydroxyethyl-2-carbamoyloxymethyl penems.

In order to improve this multistep synthesis, a more expeditious conversion of penicillins into azetidiny thioesters was desired. But, above all, a way of incorporating part of the N-appendage of secopenicillins into the final penem was actively looked for. Again, we are indebted to Prof. Woodward for the first, albeit limited, "conservative" penam-penem route: he was able to reduce the oxalimido carbonyl with diborane, thereby obtaining the corresponding carbinolamide, the first intermediate in the phosphorane sequence. In this way two more carbon atoms (and a mere single step over the whole synthesis) might be saved. But a more striking link holds between two other entries of the sequence (Fig. 3): having conceived the double ozonolysis procedure to prepare the oxalimido-thioesters, we could not fail to recognize the latter as the products of an ideal penem ozonization. Would the reverse, a deoxygenative cyclization, be possible? There are few examples of reductive dicarbonyl coupling in the literature; fewer are compatible with  $\beta$ -lactam substrates; one is the triethyl phosphite-induced dimerization of phthalic anhydride into biphtalyl. Rewardingly, prolonged heating of a variety of oxalimido-thioesters and triethyl phosphite (2 mol equiv.) enabled us to obtain the corresponding penems in satisfactory yields (40-90%). This result (ref. 9) was promptly extended to the carbapenem nucleus, and recently the same methodology was exploited by Stoodley for a cephem synthesis (ref. 10).

Similar oxalimido cyclization procedures were conceived at Sankyo and Schering (ref. 11). Schering's substrates, however, were trithiocarbonates instead of thioesters, aldehydes or ketones, and the products were restricted to the 2-alkylthio penem family (Fig. 7).

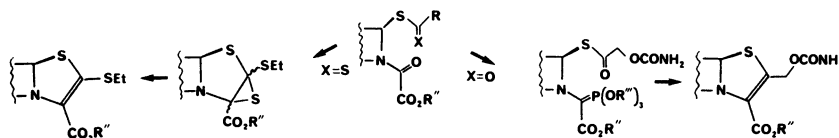


Fig. 7. The "thiocarbonyl-carbonyl" and the "carbonyl-carbonyl" reductive condensations.

The mechanisms differ as well: the CO/CS coupling proceeds through a carbene-thiono insertion followed by desulphurization of the resulting fused thirane, while the CO/CO coupling is a strategically modified Wittig reaction involving an unusual trialkoxyphosphorane (ref. 12). The stepwise nature of this condensation was unequivocally laid open by the results of a competitive phosphine/phosphite trapping performed on the first-formed carbene, and by the full chemical characterization (ozonolysis, hydrolysis, thermolysis) carried out on the successively generated ylid intermediate (Fig. 8).

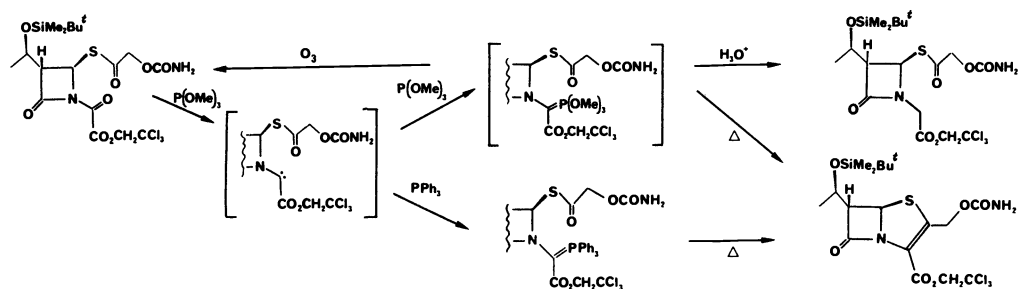


Fig. 8. Chemical characterization of intermediates involved in the CO/CO coupling.

With the powerful tool of this new oxalimido-thioester cyclization procedure in hands, the emphasis in "conservative" penem routes was shifted to an efficient and stereocontrolled generation of butenoate-thioesters. The problem with azetidiny thioesters lies in the instability of the corresponding mercaptides. Usually, thioesters are obtained through the generation and collapse of acyloxyphosphonium azetidiny mercaptides III (X=O, Fig. 9); however, the available procedures (Hatfield, Woodward, Prasad; ref. 1, 13) fail to a greater or less extent when the classical acylamino side chains are missing or replaced by the hydroxyethyl group. In these instances, 4-acyloxyazetidinyones are formed, clearly through the competitive collapse of the more stable azetidinythiophosphonium ion pair I.

Substitution of sulphur for oxygen does not solve the problem when ionic species **I** are involved: 4-acylthioazetidiones are obtained, but they are epimeric (ref. 14). Rather, we have observed that a possible solution is aiming at the pentacovalent phosphorus species **II** ( $X = O$  or  $S$ , Fig. 9).

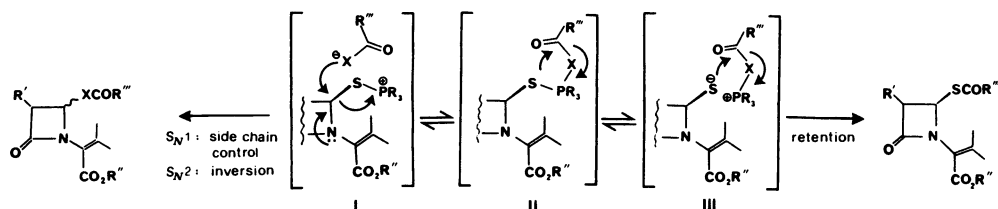


Fig. 9. The role of phosphorus intermediates in the stereospecific synthesis of 4-acylthioazetidiones.

Such species for  $X = S$  are the formal result of treating acyl azetidiny disulphides with triphenylphosphine; in fact, this reaction leads to azetidiny thioesters with substantial retention of configuration, irrespective of side chain type and orientation (ref. 15). A convenient access to the disulphide substrates was therefore needed. In the original procedure from sulphonyl chlorides, three equivalents of the thioacid are consumed; we postulate that the second acts as a thiophile and the third as a sulphenic acid trapper (Fig. 10). Both reaction modes were separately tested, and the result are two new routes to acyl azetidiny disulphides: the first by intercepting thermally generated sulphenic acids with thioacids (ref. 14), the second merely by adding thioacids to the easily accessible benzothiazolyl azetidiny disulphides, and letting a virtually quantitative thioacid-mercaptane exchange take place (ref. 16).

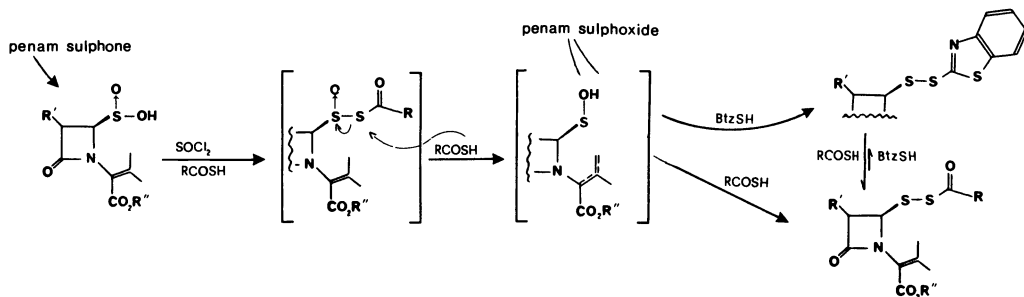


Fig. 10. Three routes to acyl azetidiny disulphides.

More recently, we succeeded in arranging a new set of conditions for the stereocontrolled reductive acylation of the benzothiazolyl azetidiny disulphide intermediates. We presume that under such conditions (diluted solutions in non-polar solvents, triethyl phosphite instead of triphenylphosphine, excess of the appropriate carboxylic anhydride and absence of the corresponding acid) the pentacovalent phosphorus species **II** wherein  $X = O$  is preferentially generated (Fig. 9; ref. 17).

Any further improvement in the thioester synthesis could not come from penicillin sulphoxides but had to be looked for at the sulphide level. This goal was finally achieved (ref. 18) through the combination of a heavy metal thiophile and a non-nucleophilic base: the latter abstracts the  $C_3$  hydrogen of the sulphonium salt existing in mobile equilibrium with the penicillin substrate, thus promoting 1,2-bond cleavage; the resulting mercaptide is then acylated *in situ* by simple addition of the appropriate acyl chloride (Fig. 11).

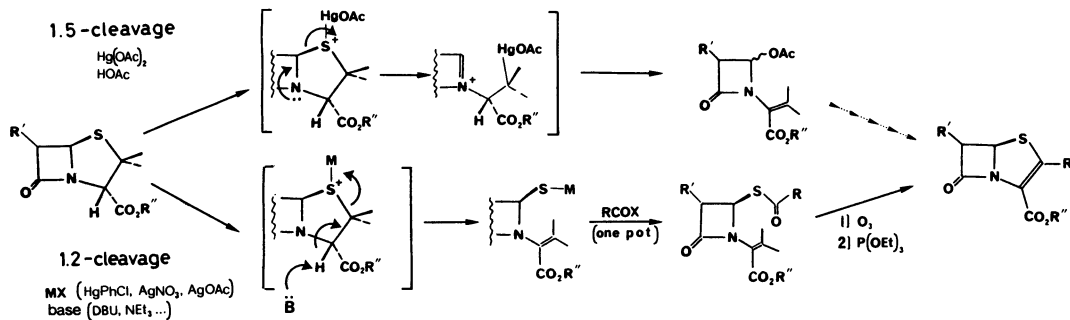


Fig. 11. 4-Acylthioazetidiones via heavy-metal assisted 1,2-cleavage of penicillins. A three step penam-penam conversion.

Interestingly, the base is essential for addressing the course of the  $\beta$ -eliminative pathway, which would otherwise be promoted by the nitrogen lone pair and result in a much less useful 1,5-bond cleavage (ref. 19).

The achievement of stereoselective routes to azetidinyl thioesters, in combination with ozonolysis and the carbonyl coupling, allowed us to assemble, scrutinize and put into practice a number of "conservative" penem syntheses. Two of them are presented here; in the first (Fig. 12) the emphasis is placed on the simultaneous generation of the thioester and oxalo carbonyl, ready to be condensed, and in the second (Fig. 13) on the complete utilization of the penam framework elements (geminal methyls included, which end up as an easily cleavable acetylonyl ester after consecutive incorporation in a cepham and in a lactone ring; ref. 20).

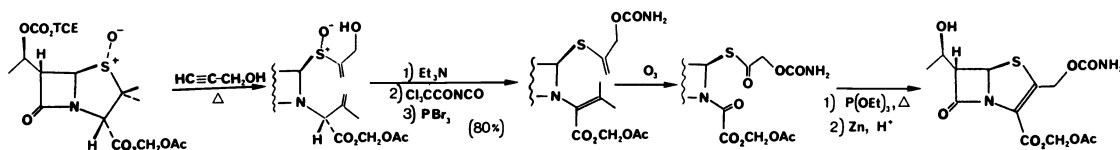


Fig. 12. "Conservative" route from penams to FCE 22891 via the trapping reaction with alkynes.

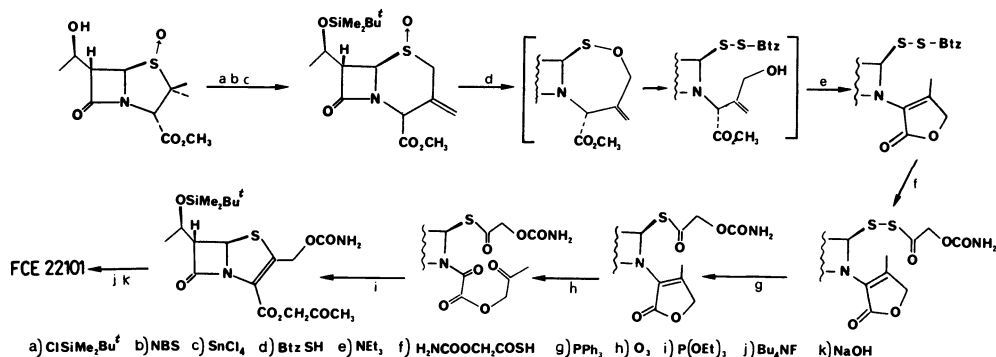


Fig. 13. From penam methyl esters to penem acetylonyl esters: a fully "conservative" conversion.

Newer routes entail the exploitation of the heavy-metal assisted 1,2-cleavage of penicillins, capable of performing the skeletal transformation in just three isolated steps (Fig. 11). These recent advances basically reduce the chemist's choice to solving a problem of multiple functional group protection.

Our original contribute to the 1,5-ring closure, the second possible strategy to the penem nucleus, stems from attempts to accomplish a 1,2 cyclization by condensing a mercaptide at  $C_4$  with an enol mesylate at nitrogen. Penems did not show more propensity than penams for a birth disfavoured by Baldwin's rules.

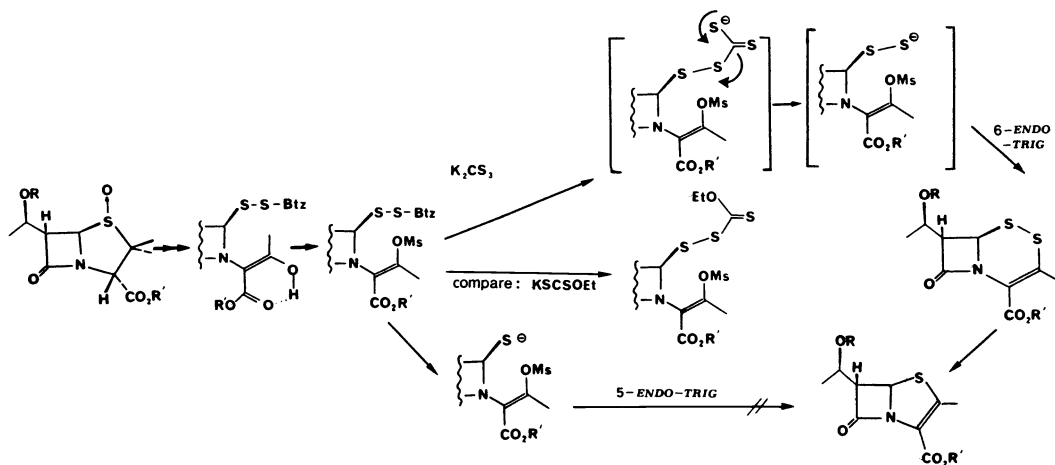


Fig. 14. The 2-thiacephem approach to penems.



affording "hot" penems, established the 1,1-dioxide structure of the intermediate thiosulpho-nate. That implies a sulphur dioxide extrusion preserving the configuration of the adjacent chiral centre, a result without precedents. More mechanistic intricacies reside in the oxidative step, where regio- and stereoisomeric thiosulphinates, vic-dioxides and O,S-sulphenyl sulphinates are involved: a speculative delight (Fig. 16).

For preparative purposes, the non-stereoselective PPh<sub>3</sub> route may turn of more avail, as shown by the synthesis of a "2-CH<sub>2</sub>X" penem not accessible otherwise (Fig. 17).

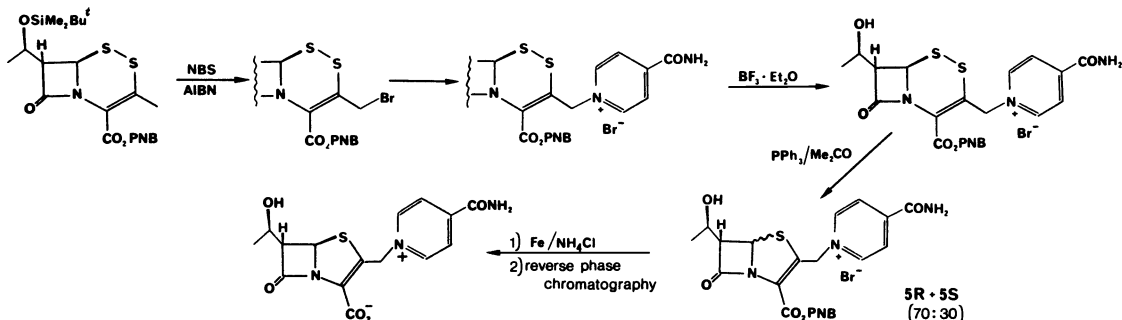


Fig. 17. A useful application of the 2-thiacephem route to penems.

And this leads us back to our targets and to the practice of "peripheral" chemistry. After the "2-CH<sub>2</sub>X" penem family where X is an oxa radical, the thia, aza and azonium classes have been explored, mainly through mesylate, triflate or Mitsunobu activation of the common

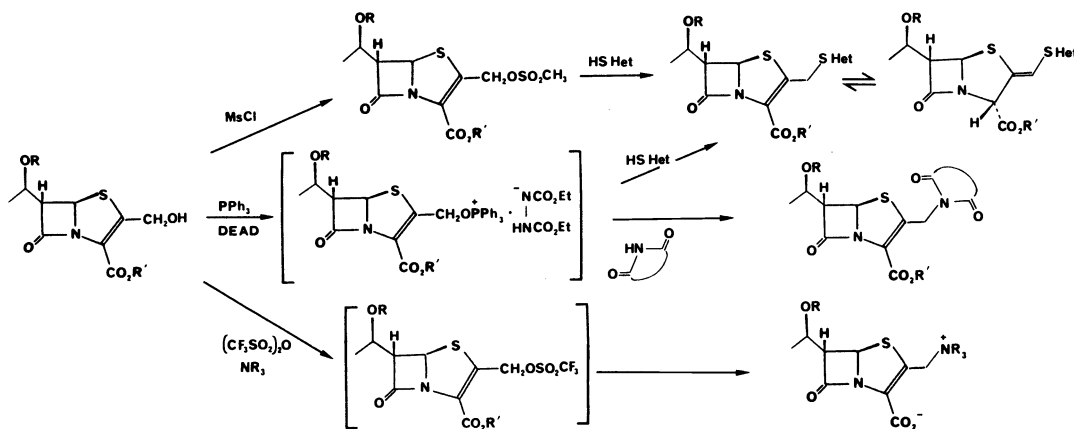
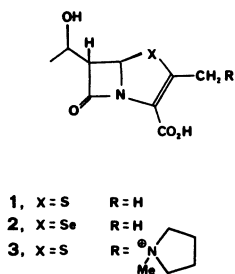


Fig. 18. Synthesis of 2(functionalized)methyl penems.

hydroxyethyl precursor (Fig. 18; ref. 25). The antibacterial potency conferred by some substituents (ref. 26, 27) demonstrates the potentialities of the newest products and serves here as a concluding remark.

Table 1. Effects of nuclear and peripheral substitution on the activity of penems.



MICROORGANISM	MICs (µg/ml)		
	1	2	3
<i>Staphylococcus aureus</i> Smith	0.39	0.39	≤0.006
<i>Streptococcus pyogenes</i> ATCC 12384	0.09	0.19	≤0.006
<i>Klebsiella aerogenes</i> 1522 E	3.1	12.5	0.19
<i>K. aerogenes</i> 1082 E (β-lact.+)	3.1	12.5	0.049
<i>Enterobacter cloacae</i> 1321 E	3.1	12.5	0.049
<i>E. cloacae</i> P 99 (β-lact.+)	3.1	12.5	0.049
<i>Escherichia coli</i> B	3.1	12.5	0.024
<i>E. coli</i> B cef R (β-lact.+)	3.1	12.5	0.049
<i>Salmonella typhimurium</i> ATCC 14028	1.55	6.25	0.049
<i>Shigella flexneri</i> ATCC 11836	3.1	12.5	0.049
<i>Proteus mirabilis</i> FI 7474	6.2	25	0.19

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