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A NEW APPROACH TO THE CARBAPENAM NUCLEUS THROUGH AN INTRAMOLECULAR N-HETEROCYCLIZATION

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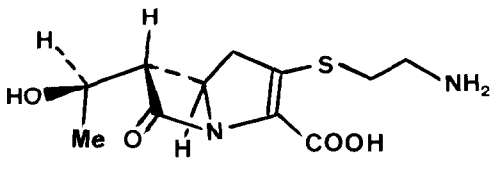
Summary : *A new approach to the carbapenam nucleus is described. The starting ester 4a was converted, via a solvomercuration process, to a mixture of the iodoesters 11 and 12. Base-induced cyclization of epimer 11 led to carbapenam derivative 14.*

Since the discovery by a Merck group of thienamycin 1 [1], an exceptionally potent and broad-spectrum antibacterial agent, a special interest has been focused on the carbapenem class of antibiotics.

We have recently described two methods [2] for the stereoselective introduction of the hydroxyethyl side chain of compound 1. In this paper we wish to report a new approach to type 2 carbapenam derivatives, precursors of the carbapenem moiety 3 [3] in that they are "oxidized" at C-2 position, based on an intramolecular N-heterocyclization that makes use of the nucleophilicity of the nitrogen atom of the ß-lactam ring.



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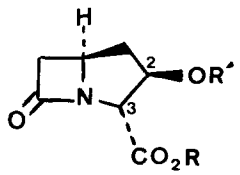

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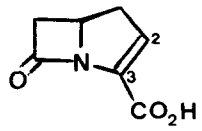
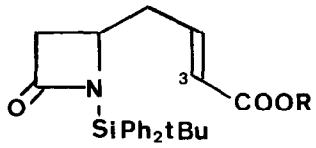
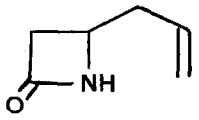


3

The starting compounds, racemic esters 4 [4], were obtained either from the known ß-lactam derivative 5 [5] [(i) $tBuPh_2SiCl/Et_3N$, (ii) O_3/CH_2Cl_2 -78°C then Me_2S, (iii) Ph_3P=CH-COOR, 90 % overall yield] or, more economically, through a known route from the corresponding sorbic esters [6].

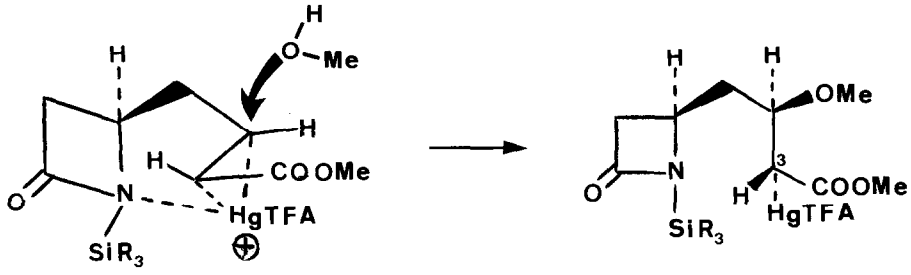




4 a R = Me b R = CH_2Ph **5**

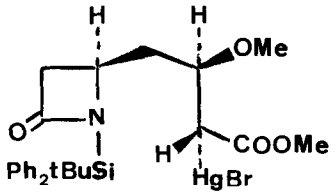
The introduction of a leaving group at the C-3 position of esters 4 is required for their transformation into the corresponding carbapenam derivatives. This crucial functionalization of the electron-deficient double bond of compound 4a [4] was efficiently performed by solvomercuration [7] using mercuric trifluoroacetate in methanol [$Hg(TFA)_2$, MeOH/THF, 20°C 48 h or 1 h under sonication, 98 % yield]. This reaction is highly stereoselective and gives mainly the organomercurial 7 [8]. The relative configuration of the three asymmetric centers in 7 were deduced from the subsequent transformations (*vide infra*).

The highly selective conversion (4a → 7) can tentatively be interpreted by assuming that the nitrogen atom of the β-lactam ring directs the formation of the intermediate mercurinium ion [9] in a complex such as that depicted in scheme 6. A molecule of methanol then attacks the rigid mercurinium ion regioselectively (β to the ester group) and stereoselectively (on the opposite side) to produce compound 7.



6 **R_3Si = Ph_2tBuSi** **7**

Organomercurial trifluoroacetate 7 was converted [10] to the corresponding organomercurial bromide 8 [11] (KBr, H_2O/CH_2Cl_2, 97 % yield) and then the cleavage of the carbon-mercury bond was performed by using one equiv of molecular bromine or iodine either in the dark [10] (CH_2Cl_2, 20°C, 17 h, 98 % yield) or in the presence of UV light [10] (300 nm, pyrex, degassed CH_2Cl_2, 20°C, 5 min, 98 % yield). Unfortunately, both methods were non-selective and gave an equimolar mixture of the two isomers 9 and 10, epimerization at the C-3 center cannot be avoided in such processes.



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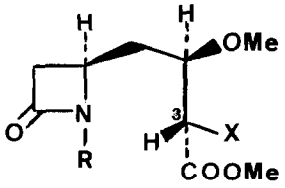


9 R = SitBuPh$_2$ 10

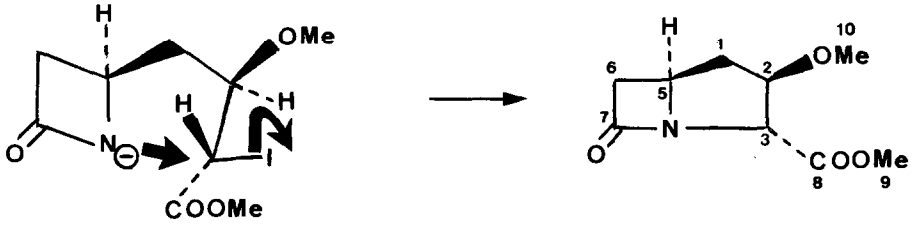
a X = Br

b X = I

11 R = H X = I 12

After separation by preparative HPLC [12], compounds 9b [13] and 10b [14] were subjected to desilylation. KF, either in the presence of 18-crown-6 or the less expensive TAD [15] (THF/MeOH/H_2O, 85 % yield), although efficient, could not be used because of epimerization at C-3. In contrast, hydrofluoric acid (5 % aqueous HF/MeCN, 20°C, 5 min, 85 % yield) was non-epimerizing, and gave the pure compounds 11 and 12 as oils, which were then submitted to an intramolecular cyclization process [16] (0.95 equiv of Triton B, MeCN/H_2O, 20°C, 5 min). Remarkably, this last process is highly dependent on the configuration at C-3 in the starting material. While one of the epimers cyclized rapidly to produce the target carbapenam 14 [17] in 80 % yield, the other polymerized completely under the same reaction conditions.

Structure 11 can be tentatively assigned to the carbapenam-generating epimer, assuming that : (i) epimerization at C-3 does not take place prior to cyclization, and (ii) a completely intramolecular SN_2 mechanism is involved in the cyclization process, as depicted in scheme 13.



13 14

Acknowledgments : *We thank the CNRS for financial support (PIRMED Grant)*

References and Notes

1 *Structure of thienamycin* : G. Albers-Schönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkle, R.B. Morin, B.G. Christensen, *J. Am. Chem. Soc.*, 100, 6491 (1978).
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4 4a : mp 93°C, 4b : mp 102°C. In this paper the subsequent transformations of esters 4 are only reported for methyl ester 4a ; comparable results were obtained for benzyl ester 4b. Stereochemical designations refer to one enantiomer only.

5 A.J.G. Baxter, K.H. Dickinson, P.M. Roberts, T.C. Smale, R. Southgate, *J. Chem. Soc. Chem. Comm.*, 236 (1979).

6 Y. Ueda, C.E. Damas, B. Belleau, *Can. J. Chem.*, 61, 1996 (1983).

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8 7 : mp 68°C, ^{13}C NMR ($CDCl_3$) δ ppm : 173.1 171.5 161.0 135.9 135.8 131.9 131.7 130.4 128.2 77.2 57.2 52.2 46.9 43.7 43.1 27.7 19.2.

9 For a similar O-assistance of a mercurinium ion in sugars, see, for example : S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.*, 16, 2623 (1975).

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11 8 : mp 58°C.

12 Partisil 10μ, 22 mm ID x 50 cm, cyclohexane/CH_2Cl_2/MeOH 50:50:0.3, flow rate 20 ml/min, retention times 9b : 13.4 min, 10b : 14.7 min.

13 9b : mp 102°C, ^{13}C NMR ($CDCl_3$) δ ppm : 172.4 169.7 135.8 131.8 130.2 128.1 128.0 78.5 56.9 53.0 47.2 43.5 37.5 27.7 24.6 19.2.

14 10b : mp 106°C, ^{13}C NMR ($CDCl_3$) δ ppm : 172.6 170.3 135.8 131.8 130.2 128.1 79.4 57.9 52.9 46.8 43.6 37.7 27.7 22.4 19.2.

15 G. Soula, *J. Org. Chem.*, 50, 3717 (1985).

16 For a similar cyclization in oxapenams, see : A.G. Brown, D.F. Corbett, T.T. Howarth, *J. Chem. Soc. Chem. Comm.*,359 (1977).

17 14 : oil, IR (neat) : 1765, 1745 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$, double resonance assignments) δ ppm : 1.83 (ddd, J = 13.5 10 4.5 Hz, 1 $H_{1\alpha}$) 2.31 (broad dd, J = 13.5 5 Hz 1 $H_{1\beta}$) 2.77 (dd, J = 15.5 2.5 Hz, 1 $H_{6\beta}$) 3.18 (ddd, J = 15.5 4.5 1.5 Hz 1 $H_{6\alpha}$) 3.34 (s, 3 H_{10}) 3.79 (s, 3 H_9) 3.92 (m, 1 H_5) 3.93 (broad s 1 H_3) 4.22 (broad d, J = 4.5 Hz, 1 H_2). ^{13}C NMR ($CDCl_3$, off-resonance assignments) δ ppm : 172.7 (C_8) 168.7 (C_7) 91.7 (C_2) 65.6 (C_3) 57.1 (C_9) 52.6 (C_{10}) 52.4 (C_5) 41.7 (C_1 or C_6) 36.4 (C_1 or C_6).

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