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SYNTHESIS OF CARBAPENEM-3-PHOSHPONIC ACID DERIVATIVES

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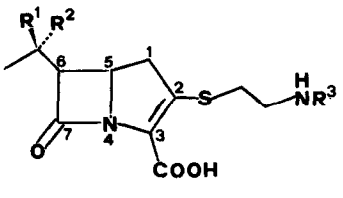
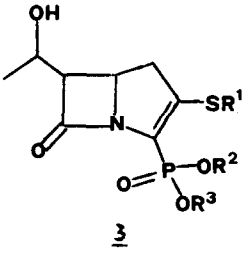
Abstract: The synthesis of 6-(1-hydroxyethyl)-2-oxocarbapenem-3-phosphonic acid derivatives, starting from 3-iodomethyl-2-oxoazetidine is described.

Thienamycin (1), PS-5 (2) and other carbapenem antibiotics[1] belong to a novel class of natural ß-lactams. Compared with the penicillins and cephalosporins, they have an extremely broad antimicrobial spectrum against Gram-positive and Gram-negative bacteria, as well as potent inhibitory activity of bacterial ß-lactamases[2]. Ironically, despite their excellent stability towards bacterial inactivating enzymes, naturally occuring carbapenems have been found to be metabolically unstable to certain mammalian dehydro-peptidases[3a,b]. We decided to investigate the possibility of obtaining non-substrates for these inactivating enzymes by substituting a phosphonate moiety for the carboxyl group in carbapenems (e.g. 3). Phosphonic acid derivatives of penicillins and cephalosporins are known in the literature[4] and they have been shown to be less active than their corresponding carboxylic acid counterparts. However, in view of the high intrinsic antibiotic activity of the carbapenems, one might sacrifice part of this potency on one hand for the benefit of metabolic stability. Herein we report the synthesis of such derivatives.



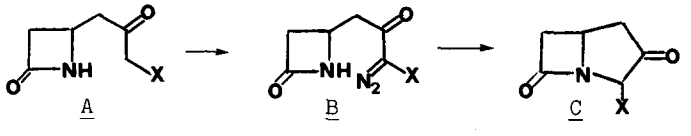
1 R^1 = OH, R^2 = R^3 = H

2 R^1 = R^2 = H, R^3 = $COCH_3$



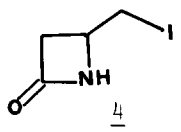
3

Following the work of the Merck group[5] and others, who have established that the synthesis of the carbapenem bicyclic structure can be efficiently obtained by the formation of the 3,4-bond via carbene insertion as the final step (Scheme 1), we have chosen the azetidinone acetic acid 5[5] as our starting material for the preparation of compound type A [X = $PO(OR^2)_2$].



A B C

Scheme 1



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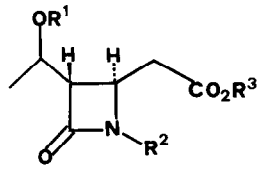
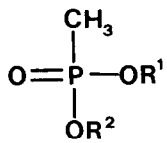
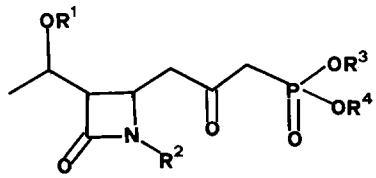


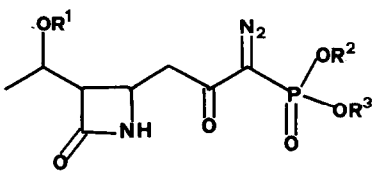
5 $R^1 = R^2 = H$, $R^2 = TBDMS$
6 $R^1 = H$, $R^2 = TBDMS$, $R^3 =$
7 $R^1 = R^2 = TBDMS$, $R^3 = CH$



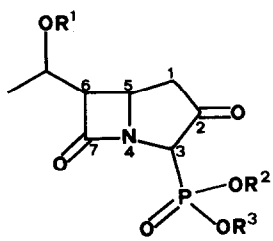
8a $R^1 = R^2 = CH_3$
8b $R^1 = R^2 = Bz$
8c $R^1 = CH_3$, $R^2 = Bz$



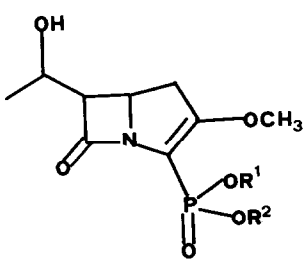
9 $R^1 = R^2 = TBDMS$, $R^3 = R^4 = CH_3$
10 $R^1 = R^2 = TBDMS$, $R^3 = R^4 = Bz$
11 $R^1 = R^2 = TBDMS$, $R^3 = CH_3$, $R^4 = Bz$
12 $R^1 = TBDMS$, $R^2 = H$, $R^3 = R^4 = CH_3$
13 $R^1 = TBDMS$, $R^2 = H$, $R^3 = R^4 = Bz$
14 $R^1 = TBDMS$, $R^2 = H$, $R^3 = CH_3$, $R^4 = Bz$
15 $R^1 = R^2 = H$, $R^3 = R^4 = Bz$
16 $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = Bz$



17 $R^1 = TBDMS$, $R^2 = R^3 = CH_3$
18 $R^1 = TBDMS$, $R^2 = R^3 = Bz$
19 $R^1 = H$, $R^2 = R^3 = Bz$
20 $R^1 = H$, $R^2 = CH_3$, $R^3 = Bz$



21 $R^1 = TBDMS$, $R^2 = R^3 = CH_3$
22 $R^1 = TBDMS$, $R^2 = R^3 = Bz$
23 $R^1 = H$, $R^2 = R^3 = Bz$
24 $R^1 = H$, $R^2 = Bz$, $R^3 = CH_3$
25 $R^1 = H$, $R^2 = R^3 = Na$
26 $R^1 = H$, $R^2 = CH_3$, $R^3 = Na$



27 $R^1 = R^2 = Bz$
28 $R^1 = Bz$, $R^2 = CH_3$
29 $R^1 = Bz$, $R^2 = Na$
30 $R^1 = CH_3$, $R^2 = Na$

TBDMS = 

Bz = CH_2Ph

Racemic acid 5 was prepared from iodomethylazetidinone 4[6] in 5 steps, applying essentially the Merck's procedure. Esterification of 5 with excess diazomethane afforded the crystalline ester 6[7], which on treatment with tert-butyldimethylsilyl chloride/triethylamine (two-fold excess, DMF, 25°C) gave the bis-silylated azetidinone 7 (89 % yield from 5). The remaining carbon atoms necessary to construct the bicyclic nucleus were introduced via acylation of the anion derived from methylphosphonates[8]. Thus, dimethyl ester 9, dibenzyl ester 10, and the mixed ester 11 were obtained from the corresponding phosphonates 8a, 8b and 8c in 34 %, 64 % and 45 % yield, respectively (nBuLi, THF, -78°C to 25°C). Complete desilylation of these phosphonates was not successful under acidic conditions[5], leading only to extensive decomposition. However, stepwise deprotection could be achieved by using one equivalent of tetrabutylammonium fluoride at low temperature (CH_2Cl_2, -78°C), giving first the O-silylated products 12 (93 %), 13 (95 %), 14 (80 %) . On subsequent treatment with methanolic HCl (0°C, 4 h), 13 and 14 were smoothly converted to the alcohols 15 (80 %) and 16 (57 %).

Introduction of the diazo function was more sluggish than with the corresponding ß-keto ester[5,9], probably due to the reduced acidity of the methylene protons involved. Nevertheless, exposure of phosphonates 13/14 to an excess of p-carboxybenzenesulfonylazide/triethylamine (CH_3CN, 15 h, 15°C) did give the diazoketones 17/18 in about 55 % yield, while the unprotected phosphonates 15/16 gave 19/20 as yellow foams in 75 % and 54 % yield, respectively. The final ring closure went uneventful. On thermal decomposition (80°C, benzene, $Rh_2(OAc)_4$ 10 min) of the diazoketones 17-20, the corresponding bicyclic keto-phosphonates were obtained in 60-90 % yield.

What remained to be accomplished was the introduction of the proper side-chain into C-2. Conversion of the keto function into either an enol phosphate or enol triflate[10], followed by displacement with sulfur nucleophiles under a variety of conditions failed to provide any substitution products, and resulted mainly in complete destruction of the bicyclic ring. Efforts to thio-ketalize the ketone were also unsuccessful. The only derivatives that could be prepared proved to be enol methyl ethers 27/28 (40 %, CH_2Cl_2, diazomethane, 25°C, 48 h).

Attempts to hydrolyse the methyl ester 21 (TMSBr, TMSI, t-butylamine etc.) gave only decomposition products, whereas hydrogenation of the benzyl esters (23, 24, 27, 28) gave the corresponding phosphonic acids, isolated as their sodium salts (H_2, Pd/C, THF/H_2O, 25°C, one atmosphere). It is worth noting that the mono sodium salt 29 could be obtained from di-ester 27 by stopping the process after one equivalent of hydrogen was consumed. To our disappointment, the esters 21-24, 27, 28 and the acids 25, 26, 29, 30 exhibited only weak or no antibacterial activities.

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Notes and References:

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6. J. Brennan, G. Richardson and R.J. Stoodley, J.Chem.Soc., Chem.Comm., 49 (198o).
7. All compounds reported are racemic. For simplicity, only one of the isomers was depicted. The hydroxy group on the alkyl side chain has the relative 'R' configuration. Selected physical data: - 1o: mp 87°; IR(KBr) 1735, 125o, 1ooo cm^{-1}, NMR($CDCl_3$)δo.o, o.o3, o.1, o.14 (each 3H, s), o.84 (s, 9), o.88 (s, 9), 1.18 (d, 3, J = 6), 2.71 (dd, 1, J = 2.5,4), 2.78 (dd, 1, J = 8, 17), 2.95 (dd, 1, J = 4.5, 17), 3.o4 (d, 2, J = 23), 3.92 (ddd, 1, J = 2.5, 4.5, 8), 4.11 (dq, 1, J = 4.5, 17), 3.o4 (d, 2, J = 23), 3.92 (ddd, 1, J = 2.5, 4.5, 8), 4.11 (dq, 1, J = 4,6), 4.82-5.21 (m, 4), 7.34 (s, 1o). 13: oil; IR($CHCl_3$) 3415, 1755, 1715, 125o, 12o5, 995 cm^{-1}; NMR($CDCl_3$) δ o.o7, o.o8, (each 3H, s), o.88 (s, 9), 1.16 (d, 3, J = 6), 2.68 (dd, 1, J = 2, 5), 2.72 (dd, 1, J = 1o, 18), 2.95 (dd, 1, J = 4, 18), 3.o9 (d, 2, J = 23), 3.92 (ddd, 1, J = 2, 4, 1o), 4.17 (dq, 1, J = 5, 6), 5.o6 (m, 4), 6.oo (br, 1), 7.4o (s, 1o). 15: mp 119-2o; IR(KBr) 339o, 322o, 1745, 171o, 1245, 995 cm^{-1}, NMR($CDCl_3$-D_2O) δ 1.27 (d, 3, J = 6), 2.72 (dd, 1, J = 2,7), 2.84-2.98 (m, 2), 3.o8 (d, 2, J = 22.5), 3.82 (dt, 1, J = 2, 7), 4.12 (quint. 1, J = 6), 5.o4 (m, 4), 6.16 (br, 1), 7.37 (s, 1o). 19: foam; IR($CHCl_3$)341o, 213o, 1755, 1645, 1265, 99o cm^{-1}; NMR($CDCl_3$) δ 1.24 (d, 3, J = 6),2.56-3.oo (m, 4), 3.77 (td, 1, J = 2, 6), 4.o4 (quint. 1, J = 6), 5.16 (d, 4, J = 11), 6.2o (br, 1), 7.4o (s, 1o). 23: foam; IR($CHCl_3$) 34o5, 176o, 126o, 12o5, 1ooo cm^{-1}; NMR($CDCl_3$) δ 1.32 (d, 3, J = 6.3), 2.36 (dd, 1, J = 7.4, 19.2), 2.83 (dd, 1, J = 7.3, 19.2), 3.12 (dd, 1, J = 7, 1.3), 4.o1 (td, 1, J = 1.3, 7.3), 4.19 (quint., 1, J = 6.5), 4.46 (d, 1, J = 18.3), 5.o-5.1 (m, 4), 7.35 (s, 1o); ^{13}C ($CDCl_3$) δ 21.9 (q), 41.3 (d), 51.8 (d), 61.o (dd, J_{CP} = 161), 65.8 (d), 68.5 (d), 69.o (dt, J_{CP} = 6.9), 69.3 (dt, J_{CP} = 6.7), 173.2 (s), 2o7.3 (s). 26: IR(KBr) 3464, 34oo, 174o, 1o95, 975 cm^{-1}; NMR(D_2O) δ 1,32 (d, 3, J = 7), 2.57 (dd, 1, J = 7, 19), 2.84 (dd, 1, J = 7, 19), 3.31 (d, 1, J = 2, 6), 4.16 (dt, 1, J = 2, 7), 4.32 (dq, 1, J = 6, 7); ^{13}C($CDCl_3$) δ 21.3 (CH_3), 42.8 (C-1), 52.4 (C-6), 66.1 (C-5), 66.2 (C-3), 66.7 (C-OH), 177.6 (C-7), 216.6 (C-2). 27: foam; IR($CHCl_3$) 341o, 177o, 16o5, 1345, 1235, 121o, 1o1o cm^{-1}; NMR($CDCl_3$) δ 1.29 (d, 3, J = 5.5), 2.76-2.94 (m, 2), 3.o9 (dd, 1, J = 2, 7), 3.4o (br, 1), 3.68 (s, 3), 3.9o-4.25 (m, 2), 5.11 (d, 2, J = 3, 8), 5.13 (d, 2, J = 8), 7.2o-7.5o (m, 1o). 29: IR(KBr) 343o, 3275, 174o, 161o, 138o, 1335, 1o75, 1o2o cm^{-1}; NMR(D_2O) δ 1.27 (d, 1, J = 6.3), 2.8-3.o (m, 2), 3.25 (dd, 1, J = 2.4, 6.3), 3.69 (s, 3), 3.98 (td, J = 2.3, 9.1), 4.14 (quint., 1, J = 6.3), 4.8-5.o (m, 2), 7.4-7.5 (m, 5); ^{13}C($CDCl_3$) δ 21.o (CH_3), 34.1 (C-1), 53.7 (C-5), 58.9 (OCH_3), 65.1 (C-OH), 66.o (C-6), 67.6 (OCH_2Ph), 166.6 (C-2), 181.o (C-7), C-3 was not detected.
8. Methyl phosphonate 8b (166°/o.28 mm) was prepared by the reaction of dibenzyl phosphite with methyl iodide (NaH, DMF, 0°). Alkaline hydrolysis (THF, 1N NaOH, 2 days) of 8b gave the monoester, which on treatment with diazomethane gave 8c (12o°/o,1 mm).
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