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SYNTHESIS OF CARBAPENEMS WITH CARBON SUBSTITUENTS AT C-3 USING A WITTIG APPROACH

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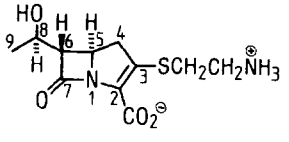
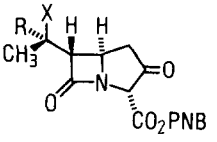
Summary: Reaction of ketone 2 with phosphorane 4 produced a mixture of endocyclic and exocyclic carbapenem esters 5 and 6. Hydrogenolysis of these gave carbapenems 7 and 8 or carbapenams 9 and 10.

Carbapenems are an important new class of antibiotics of which thienamycin (1) is the most well-known example[1]. They distinguish themselves from the classical ß-lactams such as penicillins and cephalosporins by their broad-spectrum antibacterial activity, covering a wide range of both gram-positive and gram-negative bacteria. One of the main obstacles on their way to useful therapeutic agents is their instability towards renal dehydropeptidase leading to low urinary recovery[2]. In an attempt to identify carbapenems with greater metabolic stability we have synthesized carbapenems with fluorine instead of hydroxyl in the 8-position[3]. In this communication we report our synthetic efforts towards syntheses of carbapenems that in addition are devoid of sulphur in the side chain at C-3. Published syntheses of C-3 carbon substituted carbapenems[4] have always relied on variations on the method originally developed by Woodward and coworkers[5].



1



2

a. R=H, X=OR (R=protectivegroup)
b. R=H, X=F
c. $R=CH_3$, X=F

We were intrigued by the possibility of using bicyclic ketone 2 as precursor for this class of carbapenems. This compound (i.e. 2a) was developed by Merck chemists as intermediate for the syntheses of sulphur substituted carbapenems[6]; in our laboratories we have used 2b and 2c for the same purpose[3]. The ketone moiety in 2 is exceptionally reactive for its kind: We found that most nucleophiles react instantaneously with 2b,c giving rise to ring-opened products of type 3 (Scheme 1)[7]. We were therefore gratified to find that stabilized phosphoranes 4 reacted with 2b,c to produce an inseparable mixture of 3-substituted carbapenem esters 5 (endo) and 6 (exo; E and Z)[8,9] (Scheme 2, for conditions and yields see Table 1).

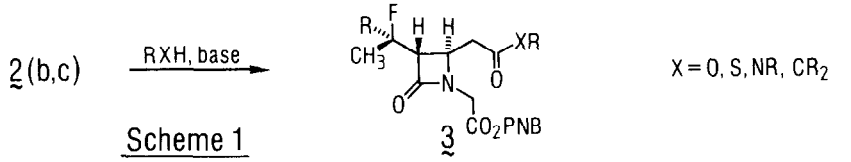
Table 1: Reaction of bicyclic ketone 2 with phosphoranes 4*

Entry	R	Z[11]	Conditions	Yield**	Product Ratio[10] 5	6-E	6-Z	Suffix
1	CH_3	CN	CH_2Cl_2, RT, 20 hrs.	68 %	51	36	13	k
2	CH_3	CO_2Et	CH_2Cl_2, RT, 2 hrs.	94 %	83	12	5	l
3	H	CN	CH_2Cl_2, RT, 2.5 hrs.	82 %	56	34	9	m
4	H	CO_2Et	CH_2Cl_2, RT, 0.75 hrs.	83 %	93	5	2	n
5	H	$COCH_3$	CH_2Cl_2, reflux 5 hrs.	43 %	38	62	--	o

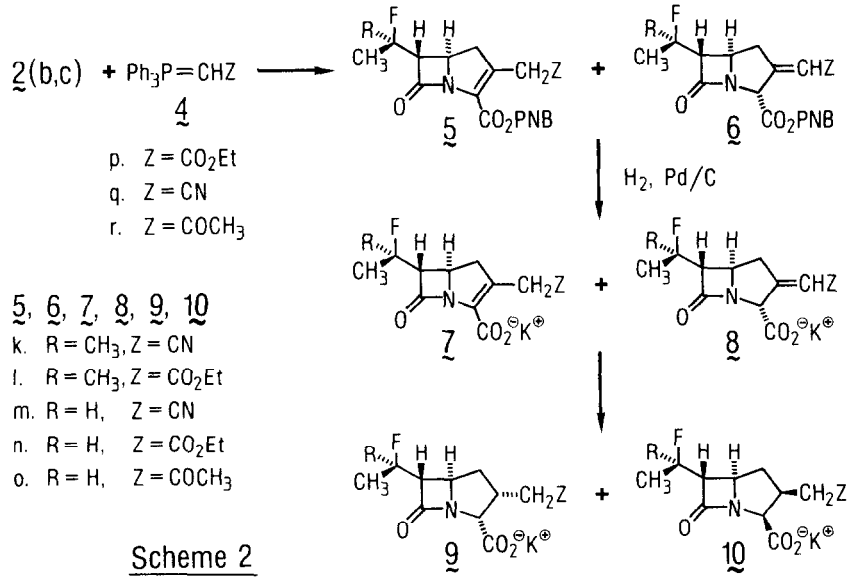
* 1.5 eq of phosphorane, c = 0.05 - 0.07 mol/l

** Yields of purified products (column chromatography: silica, CH_2Cl_2).

With phosphoranes 4p and 4q the reaction proceeded very smoothly at room temperature. Reaction between 2b and 4r was more sluggish and took 5 hrs. at CH_2Cl_2 reflux temperature. Reactions with more basic phosphoranes such as $Ph_3P{=}CHCl$[12] and $Ph_3P{=}CHSCH_3$[13] did not lead to products and bicyclic ketone 2 was recovered in good yield; presumably hydrogen exchange occurred.



Scheme 1



Scheme 2

Unfortunately, hydrogenolytic removal of the p-nitrobenzyl protective ester caused serious problems. Only with the cyanomethyl substituted carbapenem esters (5,6k and 5,6m) were we able to obtain carbapenem potassium salts 7 and 8 as inseparable mixtures in moderate yields, when short hydrogenation times were used (Table 2).

Table 2: Hydrogenolysis of carbapenem p-nitrobenzyl esters (5,6)*

Entry	R	Z	Time	Yield	Product Ratio					Suffix
					7	8E	8Z	9	10	
1	CH_3	CN	1 hr.	43 %	35	53	12	traces		k
2	CH_3	CO_2Et	1.25 hr.	73 %	--	--	--	21	79	l
3	H	CN	5 min.	45 %	15	55	30	traces		m
4	H	CN	1 hr.	60 %		traces		94	6	m
5	H	CO_2Et	15 min.	22 %		traces		65	32	n

* Conditions: 100 mg of the mixture of 5 and 6 and 100 mg of 10 % Pd/C in a mixture of 8 ml of EtOAc and 8 ml of phosphate buffer pH 7 (c = 0.15 M) were hydrogenated at 1 bar H_2 over the period indicated in the table. After filtration the aqueous layer was concentrated and purified over a C-18 column.

However, the already unfavorable endocyclic/exocyclic ratio shifted even further towards the - presumably antibacterially inactive - exocyclic product. Attempted equilibration of the product of entry 3 (Table 2) in D_2O at room temperature over 3 hrs. had the adverse effect and led to a further increase in 8m. Short hydrogenolysis of ethoxycarbonylmethyl substituted carbapenem esters (5,6l and 5,6n) only gave a mixture of carbapenams 9 and 10[14]. Carbapenams were also produced upon prolonged hydrogenation of the 3-cyanomethyl carbapenem esters 5,6m.
None of the product mixtures of Table 2 showed interesting antibacterial activity.

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REFERENCES

1. R.W. Ratcliffe and G. Albers-Schönberg in "Chemistry and Biology of ß-lactam Antibiotics", Vol 2, p 227, edited by R.B. Morin and M. Gorman, Academic Pres, 1982.
2. (a) H. Kropp, J.G. Sundelof, R. Hajdu and F.M. Kahan, Antimicrob. Agents Chemother. 1982, 22, 62 (b) J.S. Kahan, F.M. Kahan, R. Goegelman, S.A. Currie, M. Jackson, E.O. Stapley, T.W. Miller, A.K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H.B. Woodruff, and J. Birnbaum. J. Antibiot., 1979, 32, 1.
3. (a) C.P. Mak, K. Wagner, C. Mayerl, H. Fliri, Heterocycles, 1982, 19, 1399. (b) C.P. Mak, H. Fliri, Belgian Patent 897351-A, 1982
4. (a) S. Oida, A. Yoshida, E. Ohki, Chem. Pharm. Bull. 1980, 28, 3494. (b) J.H. Bateson, A.J.G. Baxter, P.M. Roberts, T.C. Smale, R. Southgate, J. Chem. Soc. Perkin I, 1981, 3242. (c) C.L. Branch, M.J. Pearson, J. Chem. Soc. Perkin I, 1982, 2123. (d) L.D. Cama, K.J. Wildonger, R. Guthikonda, R.W. Ratcliffe, B.G. Christensen, Tetrahedron, 1983, 39, 2531. (e) D.H. Shih, J.A. Fayter, B.G. Christensen, Tetrahedron Lett., 1984, 1639. (f) M. Shiozaki, N. Ishida, H. Maruyama, T. Hiraoka, S. Sugawara, J. Antibiot. 1984, 37, 57. (g) W. Koller, A. Linkies, H. Pietsch, H. Rehling, D. Reuschling. Angew. Chem., 1982, 94, 546. (h) E. Götschi, German Patent 3 201 957 A1, 1982.

5. R. Scartazzini, H. Peter, H. Bickel, K. Heusler, R.B. Woodward, Helv. Chim. Acta, 1972, 55, 408.
6. D.G. Melillo, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger, Tetrahedron Lett., 1980, 2783
7. J.G. de Vries, G. Hauser, G. Sigmund, Heterocycles, submitted for publication.
8. All compounds are racemic mixtures
9. Selected NMR-data (only fully described for 5n, 5l, 9m and 10l. Spectra of PNB esters in $CDCl_3$, salts in D_2O): 5n: δ 8.24 and 7.85 (4H,AA'BB',J=9.0Hz,Ar), 5.47 and 5.26 (2H, AB-q,J=14.0Hz,CH_2Ar), 5.00 (1H,ddq,J=48.3, 7.2, 6.3Hz,HCF), 4.26 (1H,ddd,J=7.3, 6.4, 2.6Hz, H-5), 4.17 (2H,q,J=7.1Hz,OCH_2), 3.82 and 3.63 (2H,AB-q,J=16.5Hz,=C-CH_2), 3.35 (1H,ddd,J=19.0, 7.2, 2.6Hz,H-6), 3.08 and 3.00 (2H,ABX,J_{AB}=18.5Hz,J=7.3, 6.4Hz,H-4), 1.50 (3H,dd,J=23.8, 6.3Hz,CH_3CF), 1.26 (3H,t,J=7.1Hz,CH_3CH_2). 5m: 3.94 and 3.76 (2H, AB-q,t,J_{AB}=18.5Hz,J=1.5Hz,CH_2CN). 6m-E: 5.65 (1H,dt,J=3.1, 2.2Hz,=CH), 5.16 (1H,m, H-2). 6m-Z: 5.60 (1H,dt,J=1.6, 2.0Hz,=CH), 5.40 (1H,m,H-2). 5o: 3.91 and 3.75 (2H, AB-q,J=17.5Hz,CH_2Ac), 2.14 (3H,s,$COCH_3$). 6o-E: 6.07 (1H,m,=CH), 4.60(1H,m,H-2). 5l: 8.23 and 7.66 (4H,AA'BB',J=9.0Hz,Ar), 5.49 and 5.26 (2H,AB-q,J=14.5Hz,CH_2Ar), 4.29 (1H, ddd,J=9.8, 8.5, 3.3Hz,H-5), 4.16 (2H,q,J=7.2Hz,OCH_2), 3.92 and 3.84 (2H, AB-q,J= 16.5Hz,=C-CH_2), 3.36 (1H,dd,J=22.5, 3.3Hz,H-6), 3.09 and 2.97 (2H,ABX,J_{AB}=19.0Hz,J=9.8, 8.5Hz,H-4), 1.57 (3H,d,J=21.3Hz,CH_3CF), 1.48 (3H,d,J=21.3Hz,CH_3CF), 1.26 (3H,t,J= 7.2Hz,CH_2CH_3). 5k: 3.95 and 3.79 (2H,AB-q,t,J_{AB}=18.5Hz,J=1.5Hz,CH_2CN). 6k-E: 5.65 (1H,dt,J=3.0, 2.0Hz,=CH), 5.19 (1H,m,H-2), 6k-Z: 5.59. (1H,dt,J=1.5, 2.5Hz,=CH), 5.41 (1H,m,H-2). 7m: 3.94 and 3.81 (2H,AB-q,J=18.5Hz,CH_2CN). 8m-E: 5.81 (1H,dt,J=3.0, 2.0Hz,=CH), 5.02 (1H,m, H-2), 8m-Z: 5.71 (1H,dt,J=2.0, 2.2Hz), 5.16 (1H,m,H-2). 7k: 4.29 (1H,ddd,J=9.5, 8.5, 3.0Hz,H-5), 3.95 and 3.80 (2H,AB-q,t,J_{AB}=18.3Hz,J=1.2 Hz,CH_2CN), 3.68 (1H,dd,J=27.1, 3.0Hz,H-6). 8k-E: 5.81 (1H,dt,J=3.0, 2.0Hz,=CH), 5.02 (1H,m,H-2), 4.19 (1H,ddd,J=7.0, 7.0, 2.1Hz,H-5), 3.53 (1H,dd,J=27.0, 2.1Hz,H-6). 8k-Z: 5.71 (1H,dt, J=2.0,2.2Hz,=CH), 5.16 (1H,m,H-2), 3.52 (1H,dd,J=26.6, 2.3Hz,H-6). 9n: 4.45 (1H,d,J= 7.4Hz,H-2),4.04-4.21 (5H,m,CH_2CO,H-5), 3.38 (1H,ddd,J=27.3, 4.5, 2.5Hz,H-6), 3.02-3.21 (1H,m,H-3). 10n: 3.92 (1H,d,J=8.5Hz,H-2), 9m: 5.15 (1H,ddq,J=47.8, 5.0, 6.3Hz,HCF), 4.47 (1H,d,J=7.0Hz,H-2), 4.16 (1H,ddd,J=6.3, 6.3, 2.5Hz,H-5), 3.41 (1H,ddd,J=27.3, 5.0, 2.5Hz, H-6), 3.14 (1H,m,H-3), 2.65 and 2.60 (2H,ABX,J_{AB}=17.5Hz,J=9.3, 6.0Hz,CH_2CN), 2.26 and 2.15 (2H,ABXY, J_{AB}=15.5Hz,$J_{2,4}$=$J_{2,4'}$=$J_{3,4}$=$J_{3,4'}$=6.3Hz,H-4),1.45 (3H,dd,J=24.8, 6.3Hz, CH_3CF). 9l: 4.44 (1H,d,J=7.3Hz,H-2), 3.40 (1H,dd,J=27.0, 2.8Hz,H-6). 10l: 4.18 (2H,q, J=7.1Hz,OCH_2), 3.89 (1H,d,J=7.8Hz,H-2), 3.87 (1H,ddd,J=9.8, 5.3, 2.3Hz,H-5), 3.42 (1H, dd,J=27.3, 2.3Hz,H-6), 3.15 (1H,m,H-3), 2.59 and 2.52 (2H,ABX,J_{AB}=16.3,J=7.8, 7.5Hz, CH_2CO_2), 2.14-2.24 (1H,m, H-4), 1.62-1.76 (1H,m,H-4), 1.53 (3H,d,J=22.5Hz,CH_3CF), 1.45 (3H,d,J=22.5Hz,CH_3CF), 1.27 (3H,t,J=7.1Hz,CH_3CH_2). All other spectral data were in agreement with the proposed structures.
10. These were not the thermodynamic equilibria ratios. In most occasions the ratios changed over longer periods of time. Determined by NMR and HPLC.
11. Prepared from the corresponding phosphonium salt and aq. K_2CO_3.
12. R. Appel and W. Morbach, Angew. Chem. 1977, 89, 203.
13. R. Greenwald, M. Chaykovsky, E.J. Corey, J. Org. Chem. 1963, 28, 1128
14. Stereochemical assignment by comparison of NMR data with those published for carbapenams of known stereochemistry: J.H. Bateson, P.M. Roberts, T.C. Smale and R. Southgate, J. Chem. Soc. Chem. Commun. 1980, 185; T. Haneishi, M. Nakajima, N. Serizawa, M. Inukai, Y. Takiguchi, M. Arai, S. Satoh, H. Kuwano, C. Tamura, J. Antibiot. 1983, 36, 1581.

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