SYNTHESIS OF CARBAPENEMS WITH A $RXCH_2$-SUBSTITUENT IN THE 3-POSITION

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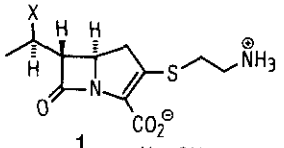
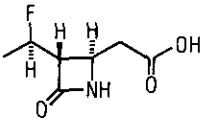
Abstract - Carbapenems 6 were prepared by reacting mercaptans with bromoketone 3 followed by a Wittig sequence, or better through advanced intermediate 9. The carbapenem carboxylates were chemically unstable; stability was not improved by changing the oxidation state of sulfur.

Ever since the discovery of thienamycin (1a) a large number of analogues have been synthesized in an attempt to improve the chemical and metabolical instability of thienamycin while retaining its potent antibacterial activity[2]. Our efforts in this area have been concentrated on carbapenems with an R-1-fluoroethyl side chain in the 6-position[3]. In this paper we report our synthetic work on carbapenems bearing a CH_2XR side chain in the 3-position[4]: we hoped that insertion of a methylene group in between nucleus and sulfur side chain would provide additional chemical and metabolic stability. From the viewpoint of synthetic efficiency introduction of the variable RX group should occur as late as possible in the synthetic sequence. We therefore chose 3-acetoxymethylcarbapenem ester 6a as intermediate, based upon the knowledge that 3-acetoxymethylcephalosporins react with mercaptans to give the thio substituted analogues[5].

Starting with acid 2[3a,b] we were able to synthesize the bromoketone 3[6] (41%[7], mp 71-73°C) by a Nierenstein sequence[8] (see Reaction Conditions). Reaction with NaOAc in DMF gave the acetoxy compound 4a in 88% yield which was transformed into the desired 3-acetoxymethylcarbapenem 6a by the Wittig procedure developed by Woodward[9] (44% over 4 steps). Unfortunately, reaction of 6a with lithium benzyl sulfide (THF, -30°C) led to unidentifiable products and reaction with $PhCH_2SH/Et_3N$ (CH_2Cl_2, RT) gave only recovered 6a. Addition of $Pd(Ph_3P)_4$ to the latter reaction had no beneficial effect. Before investigating other strategies we decided to synthesize one representative of 6 by an alternative route. Reaction of 3 with $PNBO_2CNHCH_2CH_2SH$[10] gave 4b (76%), which was converted to 6b in the usual way (20%, yield over 4 steps). Hydrogenation of 6b gave 6c in 19% yield (purity 80% by ^1H NMR)



1 a. X = OH
b. X = F



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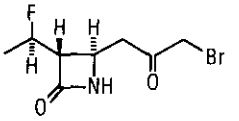

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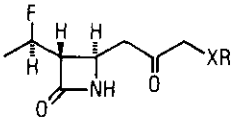

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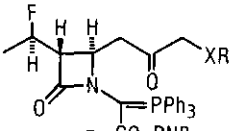

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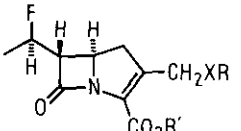
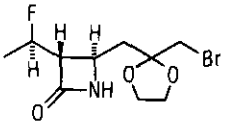


6

4,5: a. RX = OAc
b. RX = $SCH_2CH_2NHCO_2PNB$
c. RX = SCH_2-3-Pyr.

6: a. RX = OAc R' = PNB
b. RX = $SCH_2CH_2NHCO_2PNB$ R' = PNB
c. RX = $SCH_2CH_2NH_2$ R' = H
d. RX = SCH_2-3-Pyr R' = PNB
e. RX = SCH_2-3-Pyr R' = H
f. RX = $SOCH_2CH_2NHCO_2PNB$ R' = PNB
g. RX = $SOCH_2CH_2NH_2$ R' = H
h. RX = $SOCH_2$-3-Pyr R' = PNB
i. RX = $SOCH_2$-3-Pyr R' = H
j. RX = $SO_2CH_2CH_2NHCO_2PNB$ R' = PNB
k. RX = H R' = H
l. RX = SO_2CH_2-3-Pyr R' = PNB
m. RX = SO_2CH_2-3-Pyr R' = H



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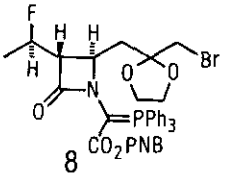

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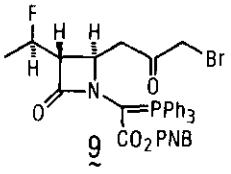

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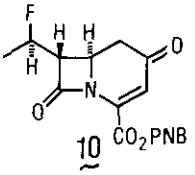

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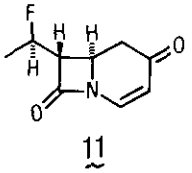

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REACTION CONDITIONS

2 → 3:	i. $(CH_3)_2CHCH_2O_2CCl$, Et_3N, CH_2Cl_2, -78°C. ii CH_2N_2, -30° → -10°C. iii. HBr, -40°C.
3 → 4a:	NaOAc, DMF, RT.
3 → 4b:	$PNBO_2CNHCH_2CH_2SH$, i-Pr_2NEt, CH_2Cl_2, 0°C.
3 → 4c:	3-$PyrCH_2SH$, Et_3N, CH_2Cl_2, 0°C.
4 → 5 :	i $PNBO_2CCH(OH)_2$, benzene, azeotropic reflux. ii $SOCl_2$,
7 → 8	Et_3N, THF, -20°C. iii Ph_3P, THF, RT.
5 → 6:	Toluene, 1% hydroquinone, reflux.
6b,d → 6f,h:	1 eq. MCPBA, CH_2Cl_2, -30°C.
6b,d → 6j,l:	2 eq. MCPBA, CH_2Cl_2, 0°C.
6b,d,f,h,j,l → : 6c,e,g,i,k,m	Pd/C 10% (eq. amount w/w to 6), H_2, THF, Phosphate buffer pH 7.
3 → 7:	$(CH_2OH)_2$, PPTS, benzene, azeotropic reflux.
8 → 9:	70% aq. $HClO_4$, CH_2Cl_2, 8 min.
9 → 10+11:	CH_3CN, RT, 16 hrs.

after RP-18 column chromatography and lyophilization. Though 6c was very unstable[11], we were able to establish that the compound had a satisfactory antibacterial spectrum and had improved renal dehydrogenase stability compared to the fluorinated thienamycin 1b[3b]. Encouraged by this finding we set out to synthesize more analogues, soon to find out that the sequence 4 → 5 is of limited value because of the incompatibility of many functional groups with $SOCl_2$. So, clearly the synthetic sequence had to be adapted in such a way as to allow introduction of the variable side chain at a later stage. Thus we protected bromoketone 3 as the ketal 7 (77 %) which was transformed into phosphorane 8 (74 %). The ketal function in 8 was very stable and deprotection turned out to be a serious problem. After many unsuccessful attempts we found that 8 could be hydrolyzed in CH_2Cl_2 solution by brief treatment with a large excess of 70% aqueous $HClO_4$ (99%)[12]. The resulting bromoketone was very unstable and was best immediately reacted with mercaptan and base. A solution of 9 in CH_3CN left overnight gave 10 and 11 as main products. Reaction of 9 with 3-pyridylmethyl mercaptan and Et_3N gave 5c (100%) which was cyclized to 6d (64%), which we had not been able to obtain by the original sequence: 4c had perished in the second step of the Woodward sequence. Catalytic hydrogenation of 6d did produce the expected carbapenem potassium salt 6e (3%), but this compound was so unstable that no biological data could be obtained. We then sought to find out if the stability of these compounds is influenced by the oxidation state of the sulfur in the side chain. Oxidation of 6b and 6d with 1 eq. of MCPBA gave the sulfoxides 6f (51%) and 6h (61%); with 2 eq. MCPBA the sulfones 6j (41%) and 6l (47%) were obtained. Deprotection of the

sulfoxides 6f and 6h and the sulfone 6l proceeded as usual to give 6g (15%), 6i (46%) and 6m (47%), respectively; but the stability of these compounds was very similar to those of the parent sulfides. Deprotection of 6j was accompanied by reduction of the allylic sulfone, giving 3-methylcarbapenem carboxylate 6k[13].

Since it is possible that the instability of these carbapenems is due to the presence of a potential leaving group on methyl we have now shifted our attention to aminoalkyl substituted carbapenems and we will report on this in due course.

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   (c) J.G. de Vries, G. Hauser, and G. Sigmund, Tetrahedron Lett., 1984, 5989.
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   (c) M. Shiozaki, N. Ishida, H. Maruyama, T. Hiraoka, and S. Sugawara, J. Antibiotics, 1984, 37, 57.
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6. Selected spectral data (NMR in $CDCl_3$ or D_2O, UV, in H_2O): 3: ^{1}H NMR: 6.28 (1H, br s, NH), 4.96 (1H, ddq, J = 48.6, 7.5, 6.3 Hz, HCF), 4.00 (1H, ddd, J = 9.5, 3.5, 2.5 Hz, H-4), 3.91 (s, 2H, CH_2Br), 3.25 and 2.96 (2H, ABX, J_{AB} = 18.5 Hz, J = 7.5, 3.5 Hz, CH_2CO), 3.02 (1H, ddd, J = 18.0, 7.5, 2.5 Hz, H-3), 1.47 (3H, dd, J = 24.5, 6.3 Hz, CH_3). 4a: ^{1}H NMR: 4.66 (2H, s, CH_2O), 2.17 (3H, s, Ac). 4b: ^{1}H NMR: 5.24 (2H, s, OCH_2), 3.29 (2H, s, CH_2S). 4c: ^{1}H NMR: 3.70 (2H, s, CH_2Py), 3.12 (2H, s, CH_2S). 6a: ^{1}H NMR: 5.29 and 5.05 (2H, AB, J = 15.5 Hz, CH_2OAc), 2.10 (3H, s, Ac), IR (KBr): 1783, 1744, 1710 cm^{-1}. 6b: ^{1}H NMR: 3.80 and 3.66 (2H, AB, J = 13.5 Hz, CH_2S). IR (CH_2Cl_2): 1783, 1724 cm^{-1}. 6c: IR (KBr): 1761 cm^{-1}, UV: λ_{max} = 272 (ε=5900) nm. 6d: ^{1}H NMR: 3.70 (2H, s, CH_2Py), 3.82 and 3.69 (2H, AB, J = 14.0 Hz, CH_2S), IR (CH_2Cl_2): 1781, 1721 cm^{-1}. 6e: ^{1}H NMR: 3.32 (1H, ddd, J = 27.4, 5.1, 2.9 Hz, H-6), 1.36 (3H, dd, J = 25.0, 6.3 Hz, CH_3). 6f: IR (CH_2Cl_2): 1789, 1716, 1700,

1048 cm^{-1}. 6g: ^1H NMR: 4.32 and 4.19 (2H, AB, J = 13.5 Hz, CH_2SO). 6h: IR (CH_2Cl_2): 1786, 1718, 1055 cm^{-1}. 6i: IR (KBr): 1762, 1595, 1387, 1029 cm^{-1}. UV: λ_{max} = 263 (6.400), 269 (5900) nm. 6j: ^{1} NMR: 4.59 and 4.27 (2H, AB, J_{AB} = 14.0 Hz, CH_2SO_2). IR (CH_2Cl_2): 1789, 1726, 1320, 1114 cm^{-1}. 6k: ^1H NMR: 2.01 (3H, s, $=C-CH_3$). 6l: ^1H NMR: 4.60 and 4.32 (2H, AB, J_{AB} = 14.2 Hz, CH_2SO_2), 4.30 (2H, s, CH_2Py), IR (CH_2Cl_2): 1787, 1719, 1331, 1120 cm^{-1}. 6m: ^1H NMR: 4.22 (1H, ddd, J = 9.5, 9.0, 3.0 Hz, H-5), 3.61 (1H, ddd, J = 28.1, 4.5, 3.0 Hz, H-6). 7: ^1H NMR: 4.06 (4H, M, CH_2CH_2), 3.36 (2H, s, CH_2Br), 2.42 and 2.13 (2H, ABX, J_{AB} = 14.6 Hz, J = 9.7, 3.2 Hz, CH_2). 10: ^1H NMR: 6.25 (1H, s, =CH), 2.95 and 2.66 (2H, ABX, J_{AB} = 16.2 Hz, J = 5.4 and 13.7 Hz, H-5). 11: ^1H NMR: 7.44 (1H, d, J = 7.6 Hz, H-2), 5.54 (1H, d, J = 7.6 Hz, H-3), 2.67 and 2.84 (2H, ABX, J_{AB} = 16.0 Hz, J = 13.0, 6.2 Hz, H-5). IR (CH_2Cl_2): 1775, 1672, 1585, 1380 cm^{-1}. MS (calcd. for $C_9H_{10}FNO_3$: 183): m/e 183 (M, 18), 136 ($M-CH_3CHF$, 16), 96 (100).

7. The only side product we have been able to isolate was the isobutyl ester of 2, but use of other activated derivatives such as the acid chloride or imidazolide did not lead to improved yields of 3.
8. The synthesis of 3-[2-(tert-butyldimethylsilyloxy)-ethyl]-4-(3-chloro-2-oxo-propyl)-2-azetidinone using the Nierenstein reaction has been described: M. Shiozaki, N. Ishida, T. Hiraoka, and H. Maruyama, Tetrahedron, 1984, 40, 1795.
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11. We were unsuccessful in our attempts to convert 6c to the N-acetimidoyl or N-formimidoyl derivatives, a strategy which was successfully applied by Merck chemists to stabilize thienamycin: W.J. Leanza, K.J. Wildonger, T.W. Miller, and B.G. Christensen, J. Med. Chem. 1979, 22, 1435.
12. We were not able to hydrolyze 8 using milder methods.
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