STUDIES ON THE TOTAL SYNTHESIS OF 6-AMIDO-1-METHYLCARBAPENEMS

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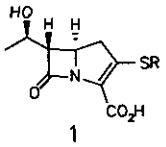
Abstract- The synthesis of 6-acylamino- and 6-phthalimido-1-methylcarbapenem derivatives via intramolecular Wittig cyclization is described.

Since the discovery of thienamycin, there has been considerable interest in the synthesis of structural hybrids of the carbapenems (**1**) and the classical penicillin (**2**) and cephalosporin (**3**) β-lactam antibiotics. Penams and cephems possessing the hydroxyethyl side-chain of the carbapenems have been prepared but were found to have only marginal antibacterial activity.[1] On the other hand, attempts to prepare carbapenems endowed with the amido side-chain of the penicillins and cephalosporins have been largely unsuccessful due to the instability of such compounds.[2] The recent discovery of the stabilizing effect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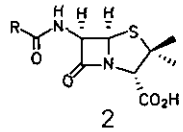
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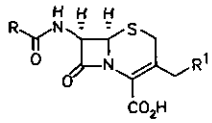
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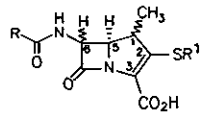
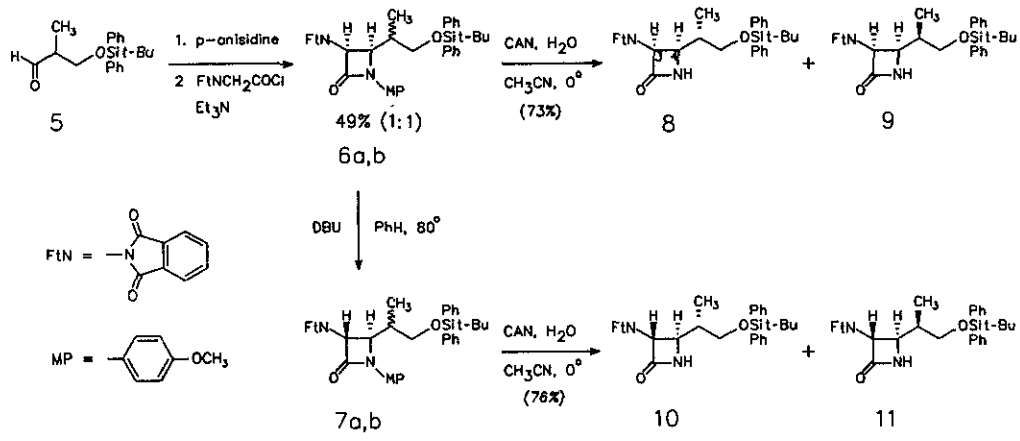

4

of a C-1-methyl substituent on the carbapenem ring system[3] prompted us to investigate the synthesis of *6-amido-1-methylcarbapenems represented by structure* **4**. It was hoped that such compounds would demonstrate enhanced antibacterial activity due to the activating effect of the amido-substituent on the β-lactam ring, but possess adequate chemical stability as a result of the protective influence of the C-1-methyl group. Since it was not obvious apriori what the optimal relative stereochemical arrangement of the C-1-methyl and the C-6-amido substituents would be, we chose to investigate the synthesis of each of the four possible stereoisomers of **4**.

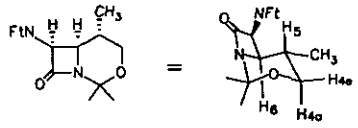
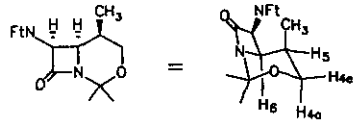
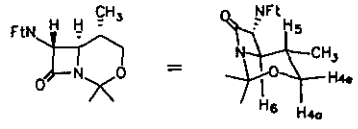
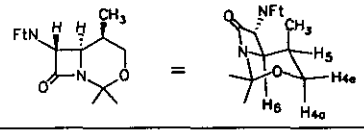
Scheme 1 shows the preparation of a set of monocyclic azetidinone intermediates possessing suitable functionallity to allow for their elaboration into the target carbapenems. Thus, condensation of aldehyde **5** [4,5] with p-anisidine ($MgSO_4$, CH_2Cl_2, r.t.) followed by reaction of the resulting aldimine with phthalimidoacetyl chloride and triethylamine (CH_2Cl_2, 0 °C) produced an inseparable mixture of the cis-cycloadducts **6a,b** (1:1 ratio) in 49% yield. After oxidative removal of the p-methoxyphenyl group from the azetidinone nitrogen (ceric ammonium nitrate, H_2O, CH_3CN, 0 °C; 73%)[6] the α- and β-methyl isomers **8** and **9** could be separated chromatographically. The cis stereochemistry of these adducts was established by ^{1}H-nmr spectroscopy ($J_{3,4}$ = 5.65 and 5.05 Hz for **8** and **9** respectively). The trans-isomers **10** and **11** were obtained by base catalyzed epimerization of **6a,b** (DBU, PhH, 80 °C, 72h)[7] followed by removal of the p-methoxyphenyl group as before (76% overall yield, trans : cis = 30:1; $J_{3,4}$ = 2.54 Hz for each isomer).

Scheme 1



Assignment of the methyl stereochemistry of the above compounds was based upon the ^{1}H-nmr coupling constants of acetonides **12-15** (Chart 1), which were prepared from **8-11** respectively in a straightforward manner (1. n-Bu_4NF, HOAc, THF; 2. $Me_2C(OMe)_2$, p-TsOH, CH_2Cl_2). Thus, the α–methyl isomers **12** and **14** showed a large axial-axial coupling constant between H_5 and H_6 (10.3 and 12.0 Hz respectively) while the β-methyl compounds **13** and **15** showed a smaller equatorial-axial coupling constant (6.65 and 5.08 Hz respectively).[8,9]

Chart 1

		H_{4a}	H_{4e}	H_5	H_6
12		3.43, dd $J_{4a,4e}$ = 12.1 $J_{4a,5}$ = 10.7	3.74, dd $J_{4e,4a}$ = 12.1 $J_{4e,5}$ = 4.58	2.0~2.1, m	3.50, dd $J_{6,5}$ = 10.3 $J_{6,7}$ = 4.76
13		3.70 – 3.80, m		2.1~2.2, m	4.13, dd $J_{6,5}$ = 6.65 $J_{6,7}$ = 4.88
14		3.50, dd $J_{4a,4e}$ = 12.1 $J_{4a,5}$ = 12.1	3.78, dd $J_{4e,4a}$ = 12.1 $J_{4e,5}$ = 4.55	1.9~2.0, m	3.53, dd $J_{6,5}$ = 12 $J_{6,7}$ = 1.90
15		3.61, dd $J_{4a,4e}$ = 12.1 $J_{4a,5}$ = 2.85	3.96, dd $J_{4e,4a}$ = 12.1 $J_{4e,5}$ = 2.23	1.9~2.0	4.17, dd $J_{6,5}$ = 5.08 $J_{6,7}$ = 2.22

Chemical shifts are reported in ppm downfield from TMS. Coupling constants are in Hertz.
Spectra were obtained in $CDCl_3$ at 300 MHz (12 & 13) and 200 MHz (14 & 15)

Initial investigations into the preparation of 6-amido-1-methylcarbapenems **4** *from intermediates* **8-11** by employing the carbene-insertion route originally developed for the total synthesis of thienamycin[10] were unprofitable due to the unstable nature of the bicyclic β-ketoester intermediates.[11] Thus, we turned our attention to the intramolecular Wittig-type construction of the carbapenem nucleus.[12] As shown in Scheme 2, the trans-β-methylazetidinone intermediate **11** was converted to thioester **17** by a straightforward sequence of reactions. Thus, desilylation of **11** with tetra-n-butylammonium fluoride - acetic acid (THF, 55 °C, 18h; 97%) followed by oxidation of the resulting alcohol with catalytic ruthenium tetroxide *employing the Sharpless procedure* ($RuCl_3/NaIO_4$, $CH_3CN/H_2O/CCl_4$; 97%)[13] provided the carboxylic acid **16**. Thioesterification with thiophenol (DCC/DMAP, CH_3CN/DMF; 66%) then gave **17**. Phosphorane formation was accomplished by acylating **17** with allyl chloroglyoxylate (pyridine, CH_2Cl_2, 0 °C) to yield the oxalimide intermediate which, without purification, was heated with excess triethyl phosphite in toluene (90 °C, 5h) to give phosphorane **18**.[12] Cyclization of **18** in refluxing p-xylene in the presence of a trace amount of hydroquinone as a *radical scavenger (138 °C, 12h) yielded the carbapenem* **19** in 60% overall yield from **17**. Palladium(0) catalyzed deallylation of **19** [$Pd(PPh_3)_4$, PPh_3, potassium 2-ethylhexanoate, CH_2Cl_2, EtOAc; 50%)[14] gave the carbapenem potassium salt **20** as a stable white solid.[15] Other 1-methyl-6-phthalimido-2-thioalkylcarbapenems which were similiarly prepared are shown in Table 1.

Scheme 2

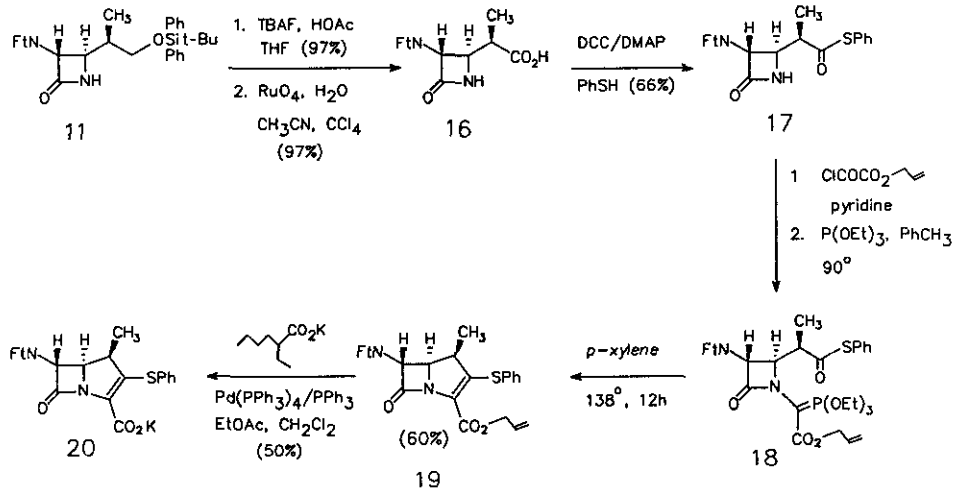
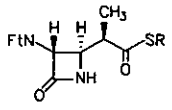
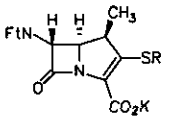
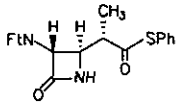
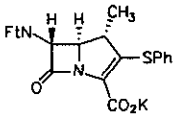
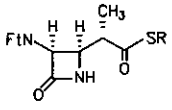
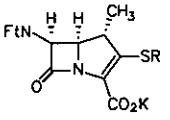
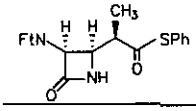


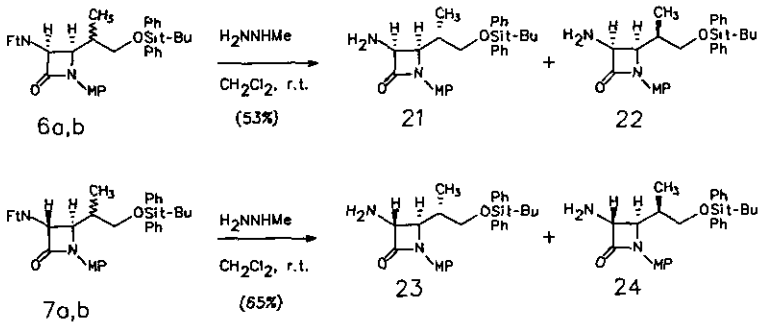
Table 1

STARTING MATERIAL	CYCLIZATION	DEPROTECTION	PRODUCT
			
SR = SPh	138°, 12h; 60%	50%	SR = SPh
SR = S⌒CN	138°, 9.5h; 60%	71%	SR = S⌒CN
SR = S⌒$NHCO_2PNB$	125°, 22h; 20%	--	
	120°, 1h; 31%	33%	
			
SR = SPh	138°, 2h; 63%	31%	SR = SPh
SR = S⌒CN	138°, 1.5h; 60%	62%	SR = S⌒CN
	178°, 11h; --	--	---

Of the four stereoisomeric permutations, only the cis-β-methyl orientation failed to yield a carbapenem product. This was evidently due to the unfavorable steric interaction of the β-methyl- and phthalimido-groups in the transition state for cyclization. In vitro screening of the carbapenems shown in Table 1 revealed only a low level of antibacterial activity against a variety of bacterial organisms. Thus, we turned our attention to replacing the phthalimido-group with a more bioactive amido side-chain.

As shown in Scheme 3, reaction of **6a,b** with excess methylhydrazine (CH_2Cl_2, r.t., 96h) gave the chromatographically separable cis-amines **21** and **22** in 53% combined yield. Similiar treatment of the trans-phthalimido compounds **7a,b** provided the trans-amines **23** and **24** (65% combined yield).

Scheme 3



Acylation of the trans-β-methyl-amine **24** with p-nitrobenzyl chloroformate (pyridine, CH_2Cl_2, 0 °C; 92%) followed by oxidative removal of the p-methoxyphenyl group (ceric ammonium nitrate, H_2O, CH_3CN, 0 °C; 74%) gave the carbamate **25** (Scheme 4). Elaboration of **25** to the phosphorane **27** proceeded in a manner analogous to that described above for the corresponding phthalimido compound. However, in contrast to its phthalimido-substituted analog, cyclization of **27** was accompanied by substantial thermal decomposition of the carbapenem product leading to, inter alia, the pyrrole **29**. By carefully monitoring the progress of the reaction it was possible to obtain an 18% yield of the carbapenem ester **28** [16] along with 15% of **29**. Deallylation of **28** gave the 6-acylamino-1-methylcarbapenem **30** [17] which showed significant antibacterial activity against *S. aureus*, but only very limited chemical stability. Other 6-acylamino-1-methylcarbapenem analogs which were similiarly prepared are shown in Table 2. It is noteworthy that only the trans-β-methyl stereochemical configuration led to successful cyclizations. In both the cis-α-methyl and the trans-α-methyl cases, the carbapenem products were seemingly too unstable to survive under the conditions of the cyclization.

Scheme 4

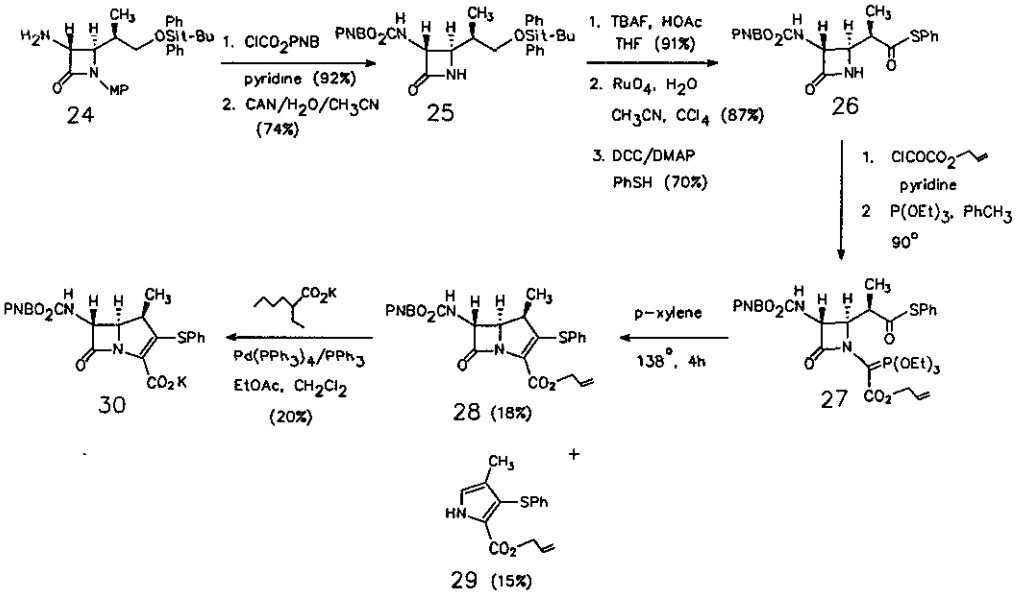
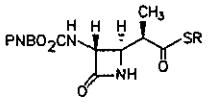
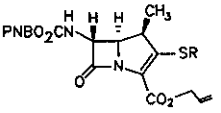
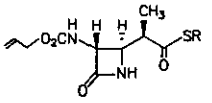
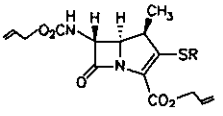
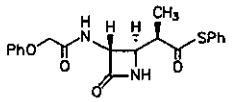
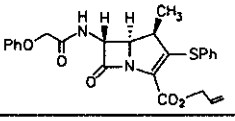
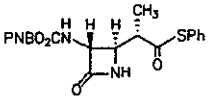
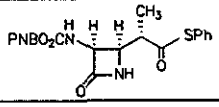


Table 2

STARTING MATERIAL	CYCLIZATION	PRODUCT	DEPROTECTION
			
SR = SPh	138°, 4h; 18%		20%
SR = S 	138°, 8h; 5%		10%
			
SR = SPh	138°, 4h; 20%		--
SR = S 	138°, 6h; 12%		--
	138°, 3h; 5%		--
	90°, 2h; --	---	--
	90°, 2h; --	---	--

In conclusion, the introduction of a 1-methyl-substituent does not appear to significantly enhance the chemical stability of 6-amidocarbapenems. The results of related approaches to the stabilization of 6-amidocarbapenems will be reported in due course.

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3. *D. H. Shih, F. Baker, L. D. Cama, and B. G. Christensen, Heterocycles, 1984, 21, 29.*
4. All compounds described herein are racemic. Spectral data consistant with the assigned structure were obtained for each new compound.
5. (RS)- **5** was prepared in a manner analogous to that described by Kishi for the preparation of racemic 3-benzyloxy-2-methylpropanal: M. R. Johnson and Y. Kishi, Tetrahedron Lett., 1979, 4347. (S)-**5** has been prepared previously from (S)-methyl 3-hydroxy-2-methylpropionate: W. R. Roush, A. D. Palkowitz, and M. A. J. Palmer, J. Org. Chem., 1987, 52, 316.
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9. The methyl stereochemistry of **8** and **11** was subsequently confirmed in each case by X-ray crystallographic analysis of a derivative. These results will be reported separately.

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14. P. D. Jeffrey and S. W. McCombie, J. Org. Chem., 1982, 47, 587.

15. Spectral data for **20**; ^{1}H-nmr (200 MHz, D_2O): δ1.21 (d, J = 7.2 Hz, $-CH_3$), 3.20 (m, H_1), 4.60 (dd, J = 3.3, 9.4 Hz, H_5), 5.57 (d, J = 3.3 Hz, H_6), 7.50-8.00 (m, ArH); uv (H_2O): λmax = 306 nm (ε = 9,800).

16. Spectral data for **28**; ^{1}H-nmr (200 MHz, $CDCl_3$): δ1.07 (d, J = 7.0 Hz, $-CH_3$), 3.10 (m, H_1), 4.11 (dd, J = 2.9, 10.2 Hz, H_5), 4.65-4.95 (m, $-OCH_2C{=}C$), 4.93 (dd, J = 2.9, 8.3 Hz, H_6), 5.18 (s, $-NCO_2CH_2-$), 5.20-5.60 (m, 3H, NH, $-C{=}CH_2$), 5.90-6.10 (m, -CH=C), 7.30-8.30 (m, 9H, ArH); ir ($CHCl_3$): 3440, 1780, 1725 cm^{-1}; uv (EtOH): λmax = 263 nm (ε = 10,200), 322nm (ε = 8,000).

17. Spectral data for **30**; ^{1}H-nmr (300 MHz, D_2O): δ1.07 (d, J = 6.6 Hz, $-CH_3$), 3.10 (m, H_1), 4.27 (dd, J = 2.0, 8.8 Hz, H_5), 4.90 (H_6, *obscured by HOD*), 5.30 (*s*, $-CH_2O-$), 7.40-8.40 (m, 9H, ArH); uv (H_2O): λmax = 270 nm (ε = 13,000), 300 nm (shoulder, ε = 12,000).

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