

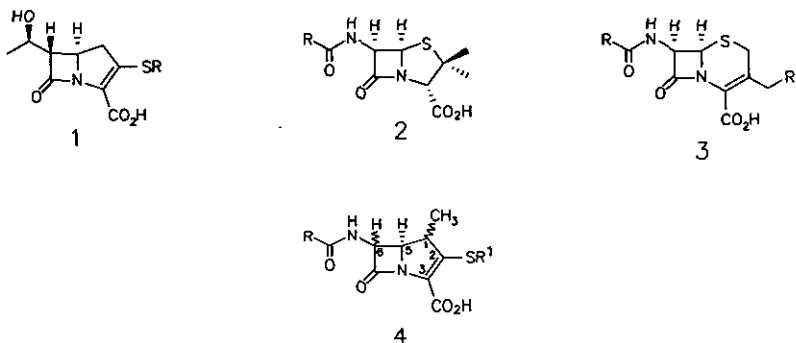
STUDIES ON THE TOTAL SYNTHESIS OF 6-AMIDO-1-METHYLCARBAPENEMS

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

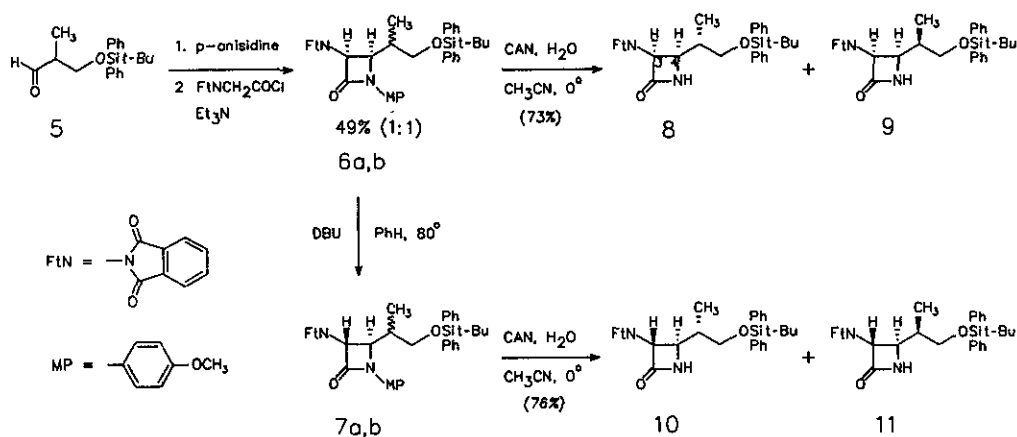
Since the discovery of thienamycin, there has been considerable interest in the synthesis of structural hybrids of the carbapenems (1) and the classical penicillin (2) and cephalosporin (3) β -lactam antibiotics. Penams and cephems possessing the hydroxyethyl side-chain of the carbapenems have been prepared 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



of a C-1-methyl substituent on the carbapenem ring system³ 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 functionality to allow for their elaboration into the target carbapenems. Thus, condensation of aldehyde **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 ^1H -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 ^1H -nmr coupling constants of acetanilides **12-15** (Chart 1), which were prepared from **8-11** respectively in a straightforward manner (1. $n\text{-Bu}_4\text{NF}$, HOAc , THF ; 2. $\text{Me}_2\text{C}(\text{OMe})_2$, $p\text{-TsOH}$, 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}

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 thienamycin¹⁰ 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 (RuCl₃/NaIO₄, CH₃CN/H₂O/CCl₄; 97%)¹³ provided the carboxylic acid **16**. Thioesterification with thiophenol (DCC/DMAP, CH₃CN/DMF; 66%) then gave **17**. Phosphorane formation was accomplished by acylating **17** with allyl chloroglyoxylate (pyridine, CH₂Cl₂, 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(PPh₃)₄, PPh₃, potassium 2-ethylhexanoate, CH₂Cl₂, EtOAc; 50%]¹⁴ gave the carbapenem potassium salt **20** as a stable white solid.¹⁵ Other 1-methyl-6-phthalimido-2-thioalkylcarbapenems which were similarly prepared are shown in Table 1.

Chemical shifts are reported in ppm downfield from TMS. Coupling constants are in Hertz. Spectra were obtained in CDCl₃ at 300 MHz (12 & 13) and 200 MHz (14 & 15).

	12	13	14	15
δ 3.43, dd	δ 3.70 - 3.80, m	δ 3.50, dd	δ 3.61, dd	
$J_{4a,4e} = 12.1$		$J_{4a,4e} = 12.1$	$J_{4a,4e} = 12.1$	
δ 3.74, dd		δ 3.78, dd	δ 3.96, dd	
$J_{4e,5} = 4.58$		$J_{4e,5} = 4.55$	$J_{4e,5} = 2.23$	
δ 3.50, dd	δ 4.13, dd	δ 3.53, dd	δ 4.17, dd	
$J_{5,6} = 10.3$	$J_{5,6} = 6.65$	$J_{5,6} = 12$	$J_{5,6} = 5.08$	
δ 4.76	δ 4.88	δ 3.53, dd	δ 4.17, dd	
$J_{6,7} = 4.76$	$J_{6,7} = 4.88$	$J_{6,7} = 1.90$	$J_{6,7} = 2.22$	

Scheme 2

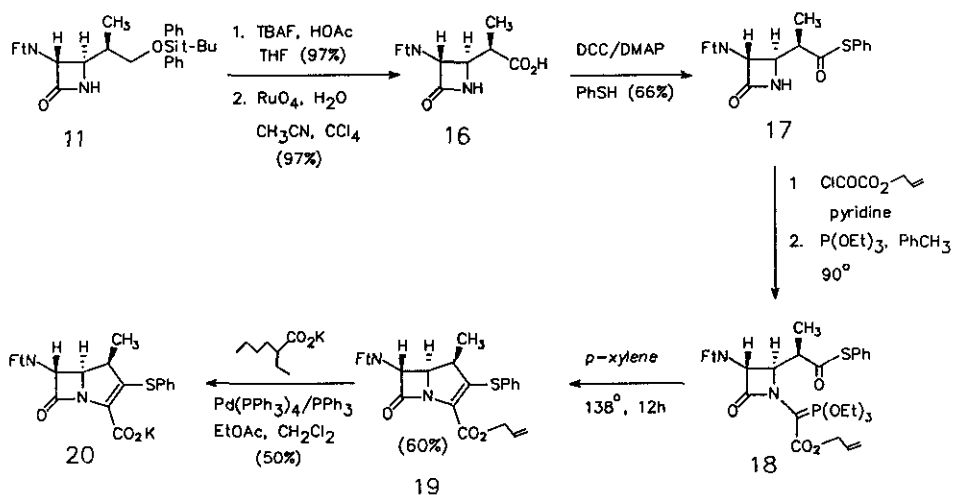
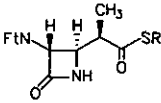
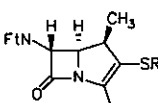
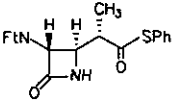
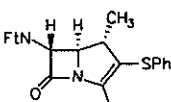
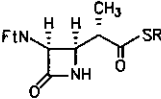
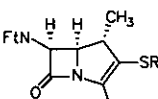
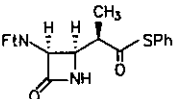


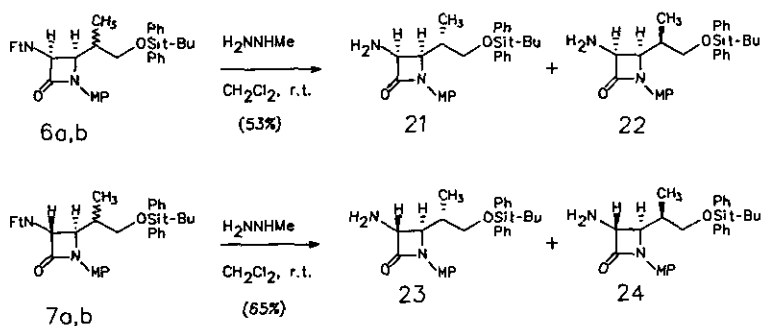
Table 1

STARTING MATERIAL	CYCLIZATION	DEPROTECTION	PRODUCT
 SR = SPh SR = S-CH₂-CN SR = S-CH₂-NHCO₂PNB	138°, 12h; 60% 138°, 9.5h; 60% 125°, 22h; 20%	50% 71% --	 SR = SPh SR = S-CH₂-CN
	120°, 1h; 31%	33%	
 SR = SPh SR = S-CH₂-CN	138°, 2h; 63% 138°, 1.5h; 60%	31% 62%	 SR = SPh SR = S-CH₂-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. Similar 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 similarly 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

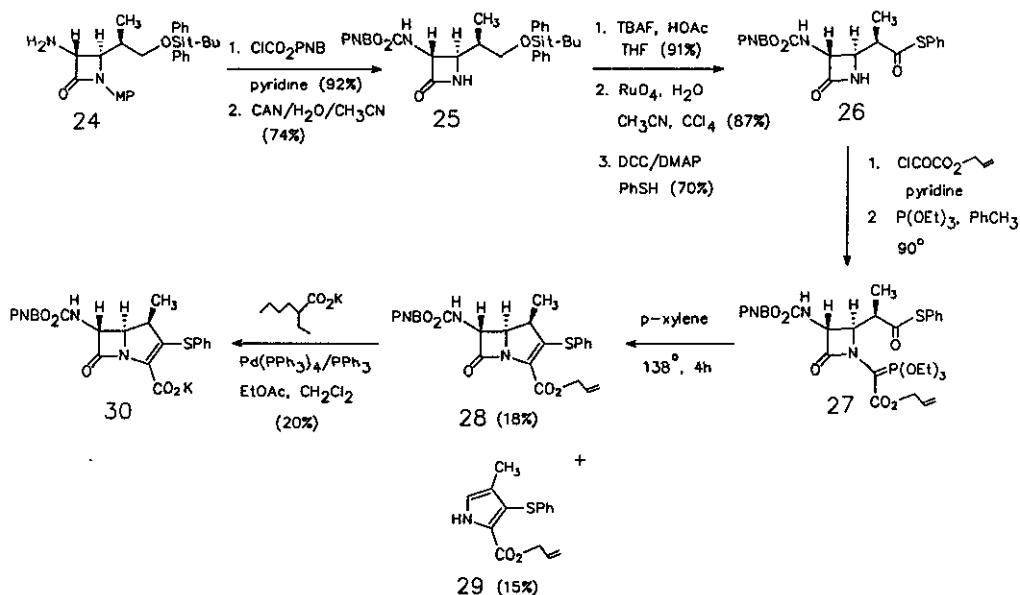
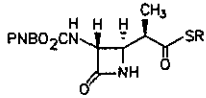
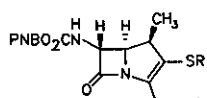
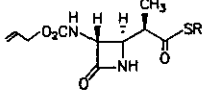
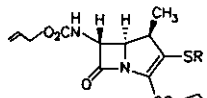
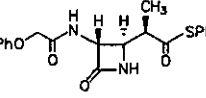
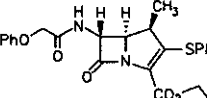
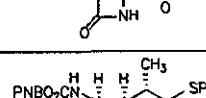


Table 2

STARTING MATERIAL	CYCLIZATION	PRODUCT	DEPROTECTION
 $\text{SR} = \text{SPh}$ $\text{SR} = \text{S}-\text{CH}_2\text{CH}_2\text{CN}$	138° , 4h; 18% 138° , 8h; 5%		20% 10%
 $\text{SR} = \text{SPh}$ $\text{SR} = \text{S}-\text{CH}_2\text{CH}_2\text{CN}$	138° , 4h; 20% 138° , 6h; 12%		-- --
 $\text{SR} = \text{SPh}$	138° , 3h; 5%		--
 $\text{SR} = \text{SPh}$	90° , 2h; --	---	--
 $\text{SR} = \text{SPh}$	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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15. Spectral data for **20**; ^1H -nmr (200 MHz, D_2O): δ 1.21 (d, $J = 7.2$ Hz, $-\text{CH}_3$), 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): $\lambda_{\text{max}} = 306$ nm ($\epsilon = 9,800$).
16. Spectral data for **28**; ^1H -nmr (200 MHz, CDCl_3): δ 1.07 (d, $J = 7.0$ Hz, $-\text{CH}_3$), 3.10 (m, H_1), 4.11 (dd, $J = 2.9, 10.2$ Hz, H_5), 4.65-4.95 (m, $-\text{OCH}_2\text{C}=\text{C}$), 4.93 (dd, $J = 2.9, 8.3$ Hz, H_6), 5.18 (s, $-\text{NCO}_2\text{CH}_2-$), 5.20-5.60 (m, 3H, NH, $-\text{C}=\text{CH}_2$), 5.90-6.10 (m, $-\text{CH}=\text{C}$), 7.30-8.30 (m, 9H, ArH); ir (CHCl_3): 3440, 1780, 1725 cm^{-1} ; uv (EtOH): $\lambda_{\text{max}} = 263$ nm ($\epsilon = 10,200$), 322nm ($\epsilon = 8,000$).
17. Spectral data for **30**; ^1H -nmr (300 MHz, D_2O): δ 1.07 (d, $J = 6.6$ Hz, $-\text{CH}_3$), 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, $-\text{CH}_2\text{O}-$), 7.40-8.40 (m, 9H, ArH); uv (H_2O): $\lambda_{\text{max}} = 270$ nm ($\epsilon = 13,000$), 300 nm (shoulder, $\epsilon = 12,000$).

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