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SYNTHESIS OF γ-LACTAM ANALOGUES OF 1-ACETOXY CARBAPENEM DERIVATIVES

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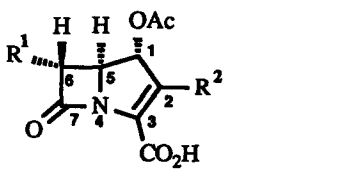
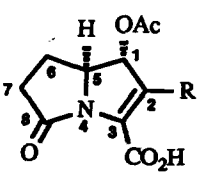
Summary: *The syntheses of γ-lactam analogues of the 1-acetoxy carbapenem esters, from* dl-*pyroglutamic acid are described. Attempted deprotection to provide the free carboxylic acids resulted in degradation. Whilst the free acid of the 1-hydroxy carbapenem analogue was chemically stable, it lacked antibacterial activity.*

The remarkable reactivity of the ß-lactam ring in penicillins has been attributed to a decrease in amide bond resonance due to ring strain in the fused bicyclic ring system. In contrast, the reactivity of the β-lactam ring in cephalosporins is associated with the presence of the Δ^3-double bond; a conjugative interaction of the unshared electron pair on the nitrogen atom with the double bond is possible, thereby opposing the usual stabilisation of the amide bond. This effect is enhanced by the presence of a leaving group at the C-3′ position of the cephalosporin.

These structural features have been incorporated into the carbapenem ring system. The sodium salts of the acids (1)[1] and (2)[2] were found, however, to have limited stability in aqueous solution.



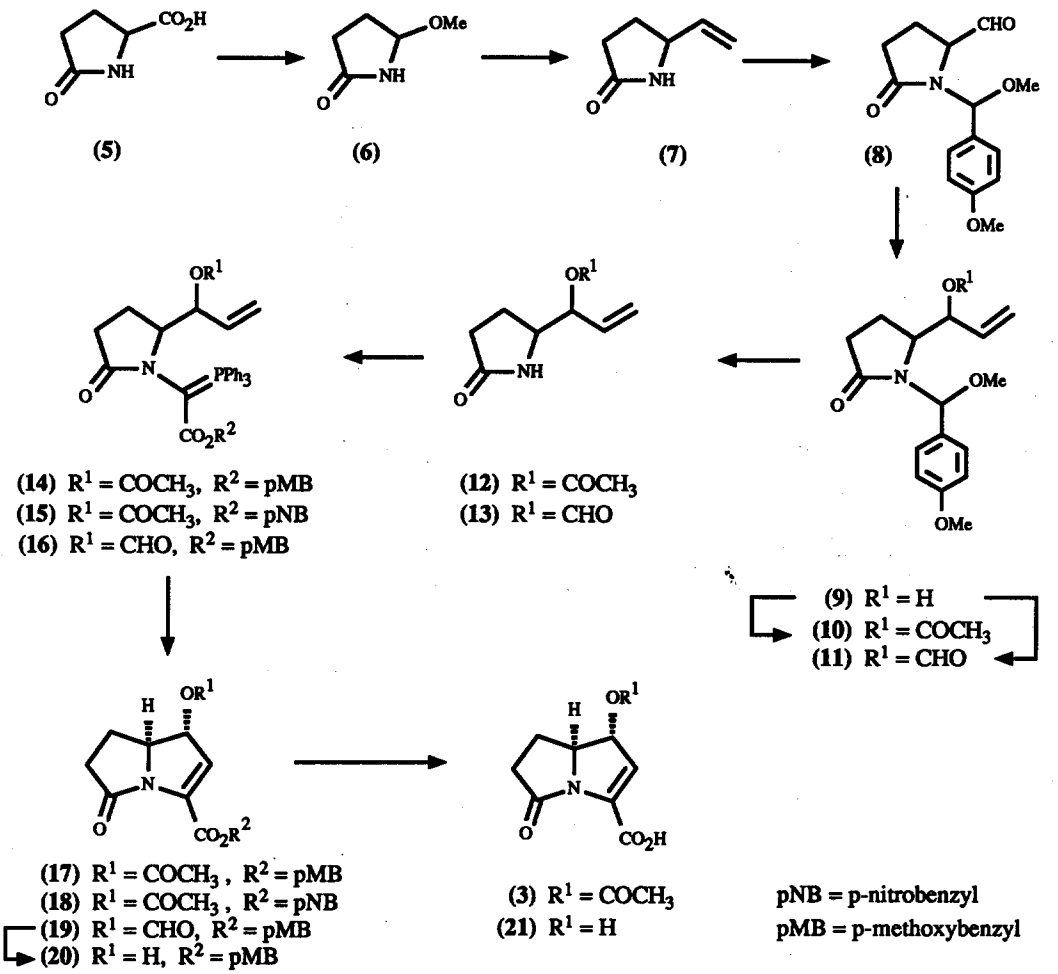
(1) $R^1 = R^2 = H$
(2) $R^1 = CH(OH)CH_3$, $R^2 = S$–(2-pyrimidyl)



(3) R = H
(4) R = SEt

A number of γ-lactam analogues of β-lactam antibiotics have recently been reported.[3] Their inferior antibacterial activity is believed to be due to the lack of reactivity of the γ-lactam ring system compared with that of the β-lactam ring. We reasoned that a γ-lactam analogue of the 1-acetoxy carbapenem derivative might show increased chemical stability whilst improving upon the reactivity of the γ-lactam ring system, owing to delocalisation of the lone pair nitrogen atom electrons through the allylically substituted double bond.

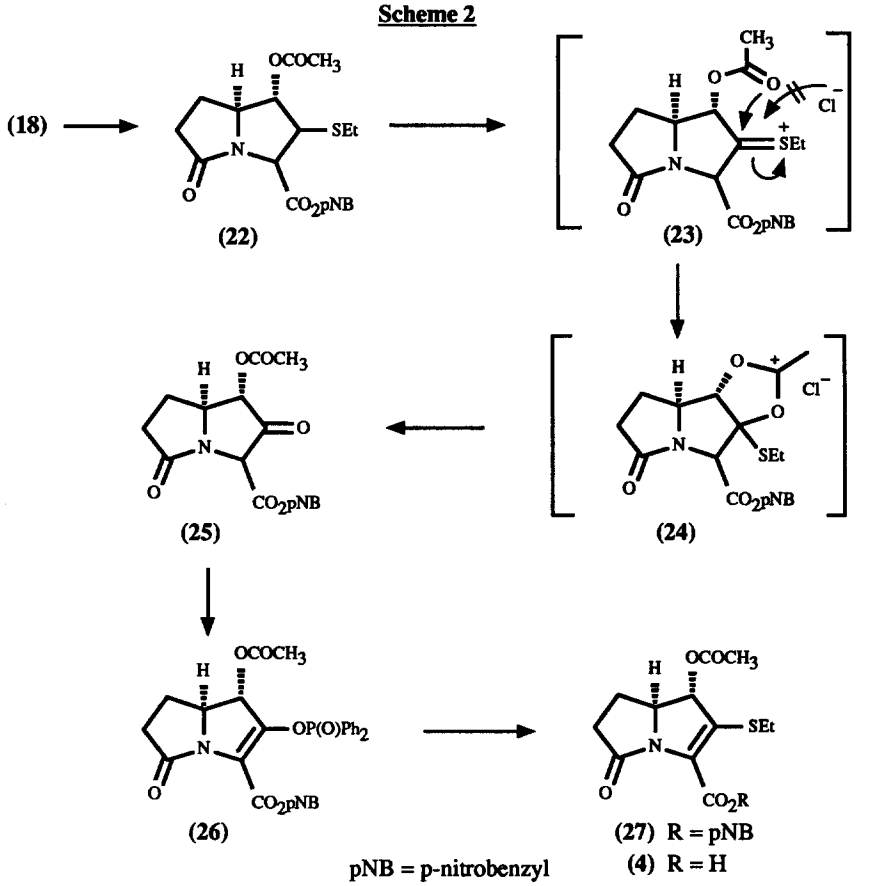
Scheme 1



We now wish to report our approaches to the preparation of such bicyclic γ-lactam derivatives (3) and (4), from pyroglutamic acid (5). Electrolysis of *dl*-pyroglutamic acid (5) (MeOH, Pt electrodes, trace NaOMe, 5°C)[4] afforded 5-methoxy-2-pyrrolidinone (6), which was converted into 5-vinyl-2-pyrrolidinone (7)[5] by treatment with vinyl magnesium bromide (3 equiv., THF, reflux, 2h; 70% overall yield)(Scheme 1). *N*-Protection of the pyrrolidinone (7) (anisaldehyde dimethyl acetal, $BF_3.Et_2O$, r.t., 1h; 56%) followed by ozonolysis [(a) 2:1 MDC/MeOH, 78°C; (b) Me_2S] afforded the aldehyde (8) which was reacted with vinyl magnesium bromide (2 equiv., THF, r.t., 16h) to provide the isomeric mixture of allylic alcohols (9)(52%). Acylation (Ac_2O, Et_3N, 4-DMAP, MDC) provided the isomeric mixture of allylic acetates (10) (77%), which was deprotected by treatment with a saturated solution of SO_2 in wet THF (84%). Reaction of the pyrrolidinone (12) with the

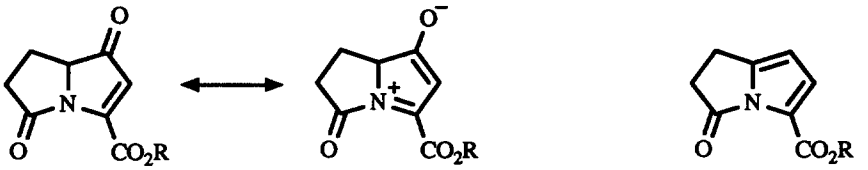
appropriate glyoxalate ester by the established procedure[6] furnished the phosphoranes (**14**) (63%) and (**15**) (40%), which upon cyclisation[6] [(a) 40 equiv. TFA, EtOAc; (b) O_3, -78°C; (c) PPh_3; (d) $NaHCO_3$] provided the bicyclic esters (**17**)[5] (48%) and (**18**) (89%) respectively. Only one diastereoisomer[7] was obtained in each case and this was assumed to be the (1RS,5SR) isomer based on decoupling and n.O.e. experiments.[8]

Scheme 2



The introduction of the C-2 sulphur substituent was pursued *via* the bicyclic ketone (**25**)(Scheme 2). Michael type addition of ethanethiol to the bicyclic compound (**18**) (K_2CO_3, DMF)[6] gave a single diastereoisomeric product (**22**) in 66% yield. Treatment of (**22**) with iodobenzenedichloride and pyridine in anhydrous benzene/MDC provided the keto-ester (**25**) in 53% yield after aqueous work-up.[9] Elaboration to the C-2 ethylthio-derivative (**27**)[5] was achieved *via* the phosphinate ester (**26**), in 47% yield [(a) $Ph_2P(O)Cl$, $^iPr_2NEt$, CH_3CN, 5°C; (b) EtSH, $^iPr_2NEt$, -35°C to r.t., 2h]. Deprotection of esters (**17**), (**18**), and (**27**) by standard procedures (H_2, Pd/C for *p*-nitrobenzyl esters[6] and $AlCl_3$, anisole for *p*-methoxybenzyl esters[10]) failed to yield the desired products (**3**) and (**4**) as their sodium salts. Only pyrrolic degradation products were evident.

In pursuit of a chemically stable γ-lactam system with increased reactivity, we then turned our attention to the preparation of the α,β-unsaturated bicyclic ketone (**29**), which we hoped to prepare by oxidation of the alcohol (**20**).



(28) R = pMB
(29) R = H

(30)

(31) R = pMB
(32) R = H

The 1-oxocarbapenem derivative had already been reported by R.L. Rosati *et al.*,[11] to be chemically labile and we envisaged that the γ-lactam analogue would be more stable. The requisite alcohol (**20**) was obtained *via* the formate ester (**19**), by formylation of the allylic alcohol (**9**) (formic-acetic anhydride, Et_3N, 4-DMAP, MDC, r.t., 4h; 69%). Elaboration of formate ester (**11**) to bicyclic ester (**19**), followed by mild alkaline hydrolysis (1 equiv. NaOH, aq. 1,4-dioxan, 5°C, 5 min) then provided the alcohol (**20**) in 77% yield, which upon oxidation (oxalyl chloride, DMSO, Et_3N, -40°C) afforded the bicyclic pyrrole (**31**) instead of the expected ketone (**28**) (35%). Interestingly, the i.r. carbonyl stretching frequency of the bicyclic pyrrole (**31**) was 1768cm^{-1} (CH_2Cl_2) (c.f. typical i.r. stretching frequency of 1738cm^{-1} in bicyclic γ-lactam derivatives[3]). This would indicate an amide bond of similar reactivity to bicyclic β-lactam derivatives. Deprotection to the sodium salt of (**32**) was therefore investigated ($AlCl_3$, anisole[10]). Whilst the sodium salt of the bicyclic pyrrole (**32**) could be obtained in aqueous solution (λ_{max} 278nm), it rapidly degraded at room temperature. In contrast, the 1-hydroxy ester (**20**) could be deprotected and the resultant acid (**21**) isolated and characterised as its sodium salt. It was however antibacterially inactive.

In conclusion, we have succeeded in increasing the reactivity of the bicyclic γ-lactam ring system. However, we have failed to reach the compromise between increased reactivity and improved chemical stability which is essential for biological activity.

References and Footnotes

1. W. Koller, A. Linkies, H. Peitsch, H. Rehling, and D. Reuschling, *Angew. Chem., Int. Ed. Eng.*, 1982, **21**(7), 537.
2. J.H. Bateson, A.M. Quinn, and R. Southgate, *Tetrahedron Letters*, 1987, **28**(14), 1561.
3. S. Hashiguchi, H. Natsugari, and M. Ochiai, *J. Chem. Soc., Perkin Trans I*, 1988, 2345; J.E. Baldwin, R.T. Freeman, C. Lowe, C.J. Schofield, and E. Lee, *Tetrahedron*, 1989, **45**(14), 4537 and references cited therein.
4. T. Iwasaki, H. Hurikawa, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, 1979, **44**, 1552.
5. All new compounds have satisfactory microanalytical and/or spectroscopic data. For (**17**): $\nu_{max}(CH_2Cl_2)$ 1742, 1720 cm^{-1}. For (**27**): $\nu_{max}(CH_2Cl_2)$ 1740, 1715 cm^{-1}.
6. T.C. Smale and R. Southgate, *J.Chem.Soc., Perkin Trans I*, 1985, 2235.
7. All compounds are racemic; only one enantiomer is depicted for convenience.
8. Irradiation of H-1 showed a large enhancement of βH-6 and a small enhancement of H-5. Irradiation of H-5 showed a small enhancement of H-1 and a large enhancement of αH-6.
9. This reaction usually proceeds directly to the vinylic sulphide, due to base catalysed elimination of HCl from the α-chlorosulphide.[6] In this case, however, neighbouring group participation results in intramolecular attack of the acetoxy group on the intermediate sulphonium cation to provide the intermediate depicted in structure (**24**), instead of the α-chlorosulphide. Hydrolytic work up then yields the ketone (**25**).
10. M. Ohtani, F. Watanabe and M. Narisada, *J. Org. Chem.*, 1984, **49**, 5271.
11. R.L. Rosati, L.V. Kapili, P. Morrissey, and J.A. Retsema, *J. Med. Chem.*, 1990, **33**, 291.

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