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A Concise Synthesis of Penems

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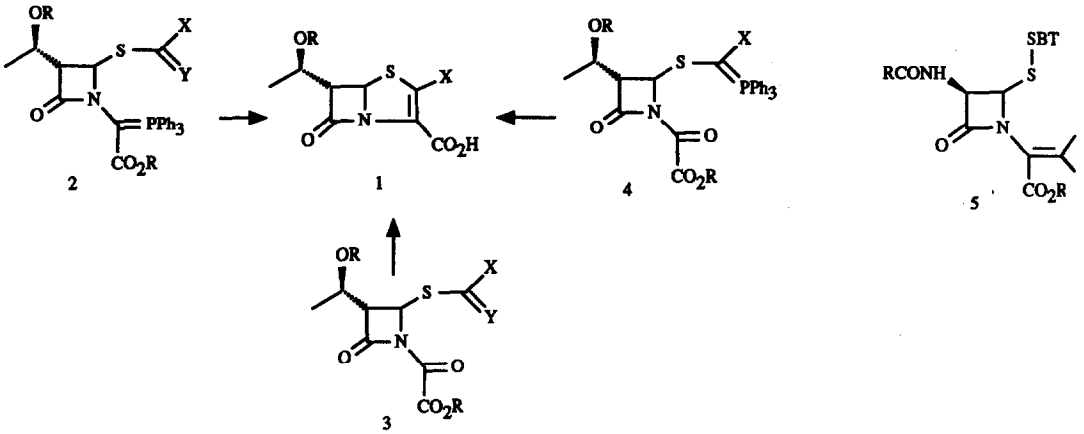
Abstract. A brief and efficient new synthesis of 2-substituted 6-[1(R)-hydroxyethyl]-penems is described. The key step involves reaction of an azetidin-2-one-4-disulphide with either stabilized or unstabilized phosphoranes, giving ylids which cyclize with the 1-oxalimide group to give 2-substituted penems

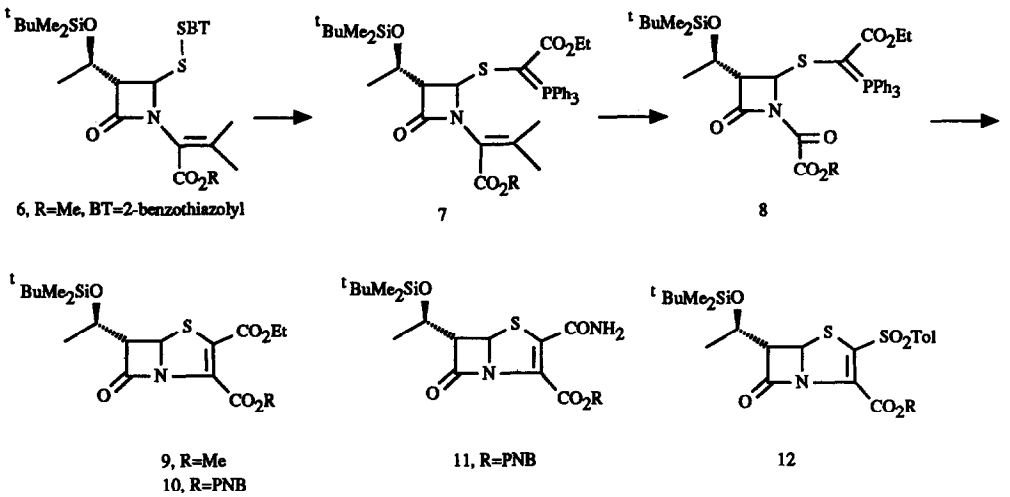
The penems are a class of synthetic β-lactam antibiotics of much current interest because of their potency, spectrum of activity, and resistance to β-lactamase enzymes. Several of the 6-[1(R)-hydroxyethyl]-penems (1) have now reached advanced stages of development.[1] Because they are not naturally occurring a great deal of ingenious synthetic research has emerged in the chiral construction of these β-lactams.[2]

The most widely used approach to the penems involves formation of the C2-C3 bond as the key step, the Wittiz cyclization of phosphoranes (2) being the first class,[3] and the de-oxygenative cyclization of oxalimides (3) being the second class.[4] Our objective was to develop an alternative, brief and flexible Wittig approach from phosphoranes (4). The sythesis of related phosphoranes from azetidinone-4-disulphides (5) has precedent,[5] but the formation of penems by this strategem has not been realized.

Chiral isopropylidene disulphides including (6) are readily available by manipulation of penams.[6] Reaction of (6) with ethoxycarbonylmethylenetriphenylphosphorane resulted in displacement of 2-mercaptobenzothiazole, giving (7) (77%). The phosphorane was protected by protonation (trifluoroacetic acid), and then ozonised (0_3, -20°; Me_2S then $NaHCO_3$) to give oxalimide (8) (quantitative) (υ_{max} 1804, 1754, 1706, 1638 cm^{-1}).[7] Benzene reflux smoothly gave the target bicyclic β-lactam (9) (81%) [υ_{max} 1798, 1726; δ $CDCl_3$), 5.70 (1H, d, J = 1.8Hz), 4.29 (2H, q, J = 7Hz), 4.25 (1H, m,), 3.83 (1H, dd, J = 4.3, 1.8Hz), 3.80 (3H, s), 1.31 (3H, t, J = 7Hz), 1.22 (3H, d, J = 6.3Hz), 0.88 (9H, s), 0.06 (6H, s).]. A similar sequence of reactions gave the PNB ester (10) and the 3-carbamoylpenem ester (11). Subsequent deprotection (Bu_4NF, H_2-Pd/C/3atm./$KHCO_3$ aq.) gave the target penems as their salts. One limitation of this very brief entry was observed.



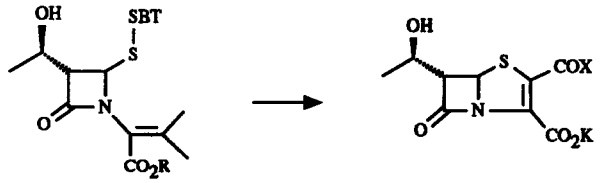
p-Tolysulphonylmethylenetriphenylphosphorane reacted with (6) and was ozonised to the



required oxalimide. However, the very low basicity of the resultant phosphorane precluded cyclization to (12), indicating the lower limit of reactivity for successful penem formation.

The mild nature of the cyclization prompted investigation of the method *without* protection of the 1′-hydroxy group. Thus, (13) was taken by the above procedure through to potassium salts (14) to (17) by an even briefer route (58% typical overall yield).

In a complementary study, less-stabilized phosphoranes were investigated. We considered that a relatively strong base would be required, and decided to reverse the order of



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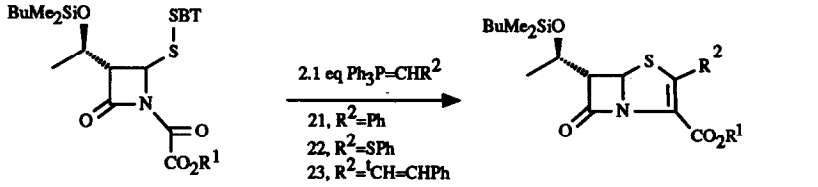
14, X=OEt
15, X=NH_2
16, X=CH_3
17, X=C_6H_5

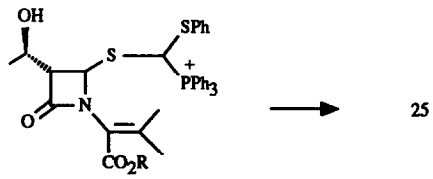


18, R^1=PNB
19, R^1=PNB
20, R^1=TCE

21, R^2=Ph
22, R^2=SPh
23, R^2=^{t}CH=CHPh

24, R^1=PNB, R^2=Ph
25, R^2=PNB, R^2=SPh
26, R^2=PNB, R^2=CH=CHPh

certain steps, and liberate the oxalimide prior to introduction of the phosphorane. The requisite oxalimides (18) - (20) were prepared from (6) by ozonolysis. Reaction at -50° with two equivalents of preformed phosphoranes (21) - (23) gave the target β-lactams (24) - (26) in a single step, on warming to room temperature, in 50-70% yields.



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The disulphide azetidinones (18) - (20) were therefore extremely useful intermediates, allowing the synthesis of a variety of substituted penems, some of which we have described. It was further observed that the isopropylidene disulphide (13, R = PNB) reacted with two equivalents of phenylthiomethylenetriphenylphosphorane at -20° to give, after addition of trifluoroacetic acid, the phosphonium salt (27). Ozonolysis, followed by treatment with phenyl lithium afforded penem (25). The high acidity of the phenylthio methine proton was demonstrated by effecting the reaction with aqueous sodium bicarbonate-dichloromethane.

We have therefore demonstrated a brief entry to the penems, in which the key step

involves formation of the C(2) - C(3) bond by a new variation of the intramolecular Wittig reaction carried out under extremely mild conditions and in good yields.

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(7) Line broadening was observed in the ^1H n.m.r. spectra of all phosphoranes studied.

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