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Phosphonopeptides and 3-Aminophosphononocardicinic Acid

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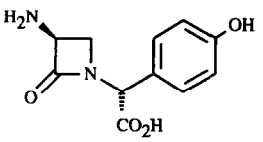
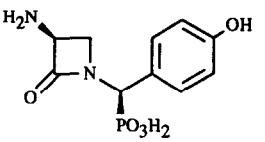
Abstract: *A synthesis of the phosphonic acid analogues of 3-aminonocardicinic acid is described.*

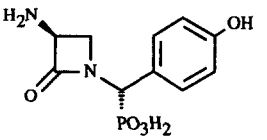
In continuation of our interests in developing new organophosphorus chemistry within the peptide and β-lactam areas,[1] we report routes to the phosphonic acid analogues (2) of 3-aminonocardicinic acid (1).[2] The nocardicins are monocyclic β-lactam antibiotics isolated from *Nocardia* and *Streptomyces* species.[3,4] Synthesis in this area has been reviewed.[5]



(1)

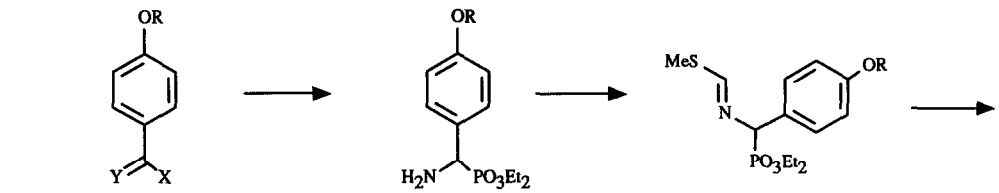


(2a)



(2b)

Our initial stratagem, based on a successful route to the natural nocardicins,[4] involved [2 + 2] cycloaddition of a methyl thioimidate with phthalimidoketene to give a β-lactam. Accordingly acid chloride (3) was reacted with triethylphosphite to give (4) which was reacted immediately with hydroxylamine hydrochloride/pyridine to give (67%) an oxime, (5). Reduction (aluminium amalgam, EtOH) and chromatography gave (81%) the 0,0-dialkylaminophosphonate (6),[6] which was converted to methylthioimidate (7) in 98% yield (ethyl thionoformate, potassium carbonate/methyl iodide). Under a range of conditions (7) did not react with phthalimidoketene to give a β-lactam. However, with azidoacetyl chloride/triethylamine the diastereoisomeric β-lactams (8) and (9) were formed in 47% yield. Apparently only one racemic diastereoisomer in each case was formed (^{31}P nmr and 400MHz nmr). Attempts to desulphurize either (8) and (9) invariably resulted in β-lactam cleavage.



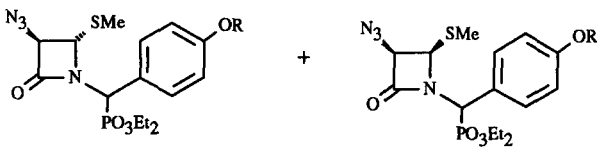
(3) X=Cl, Y=O, R^1=CH_2Ph

(4) X=PO_3Et_2, Y=O, R^1=CH_2Ph

(5) X=PO_3Et_2, Y=NOH, R^1=CH_2Ph

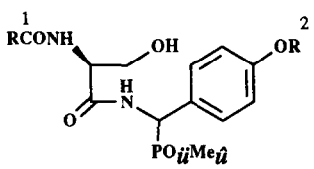
(6)

(7)



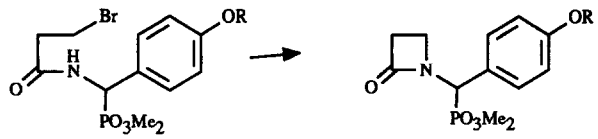
(8) (9)

In an alternative annelation procedure, the Mitsunobu reaction which also has found application in nocardicin synthesis[7] was explored for the seryl-(p-alkoxyphenyl)-phosphonoglycine derivative (10), but resulted in a plethora of products.

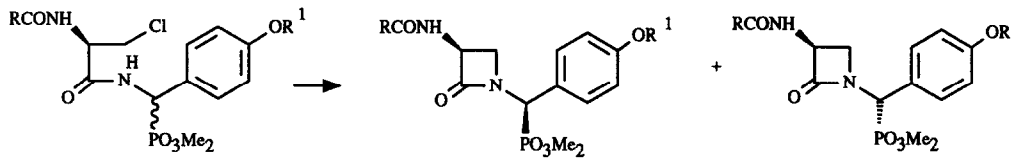


(10), R^1=$PhCH_2O$,R^2=$PhCH_2$

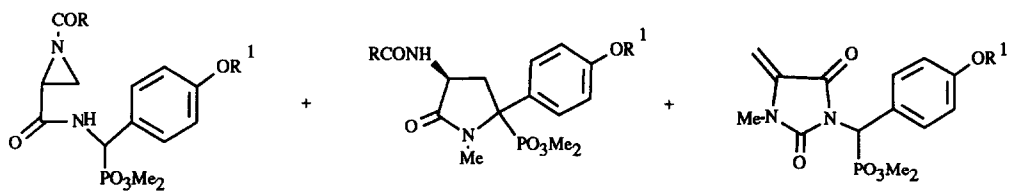
Recourse to the model system (11), prepared from β-bromopropionyl chloride, demonstrated that cyclization could be achieved (73%) by sodium hydride/DMF, CH_2Cl_2; 1:4, to give β-lactam phosphonate (12). Thus, the 0,0-dimethylphosphonic acid corresponding to (6) was reacted with N-carbobenzoxy-L-β-chloroalanine to give the key precursor (13) as an inseparable mixture of diastereoisomers (74%). Cyclisation (NaH/DMF, CH_2Cl_2; 1:1) gave in low yield the target β-lactams (14)[8] (33%) and (15)[9] (28%), which now could be separated chromatographically



(11) R=CH_2Ph (12)



(13) R=$PhCH_2O$, R^1=$PhCH_2$ (14) (15)



(16) (17) (18)

because of accentuation of diastereoisomeric differences due to ring formation. Mobile by-products isolated, in very low yield (<10%), were aziridine (16), lactam (17) and imidazolidindione (18). These products indicate a range of competing mechanisms. Aziridine (16) arises from amide N-anion intramolecular cyclisation. γ-Lactam (17) illustrates the participation of phosphonate carbanions. (Miller *et al*, ref. 7, describe related processes, and further complications). Product (18) involves formation of dehydroalanine, followed by cyclisation of the aminophosphonate nitrogen anion with expulsion of benzyl alcohol. (N-Methylation may involve transfer from another phosphonate).

Completion of the synthesis involved quantitative catalytic transfer hydrogenation ($NH_4^+HCO_2^-$,Pd-C,MeOH) to remove the benzyl ether and the benzyloxycarbonyl groups followed by phosphonate deprotection in high yield by TMSBr-pyridine, allowing isolation of the β-lactams (2a) and (2b) as their pyridinium salts.

All new compounds were characterised spectroscopically and by high resolution mass measurement on homogeneous samples, and/or elemental analysis. Pyridinium salts (2a) and (2b) gave correct FAB molecular ions.

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8. m.p. 104-106°C; υ_{max} 1760 (β-lactam), 1720, 1250 (P-O), 1050 and 1025cm (POMe); δCDCl$_3$ (400MHz) 3.53 (d, 3H, J11Hz, (POMe), 3.65 (m, 2H,H-4), 3.78 (d, 3H, J11Hz, POMe), 4.76 (m, 1H, H-3), 5.00 (s, 2H, OCH_2Ph), 5.06 (s, 2H, CO_2CH_2Ph), 5.19 (d, 1H, J18Hz, CH-P), 5.86 (d, 1H, J6Hz, NH), 6.96-7.34 (m, 14H, arom.). Absolute stereochemistry of phosphonate may be reversed.
9. m.p. 109-100°C; υ_{max} 1760, 1250, 1050 and 1025cm^{-1}; δ 3.24 (dd, 1H, J6, 2Hz, H-4p), 3.50 (d, 3H, J11Hz, POMe), 3.71 (d, 3H, J11Hz, POMe), 3.92 (t, 1H, H-4α), 4.88 (m, 1H, H-3), 5.00 (s, 4H, $PhCH_2O$ and CO_2CH_2Ph), 5.14 (d, 1H, J19Hz, CH-P), 5.71 (d, 1H, J6Hz, NH), 6.92-7.35 (m, 14H, arom). Absolute stereochemistry of phosphonate may be reserved.

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