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SYNTHESIS OF (5R) (E)-6-[(1-METHYL-1,2,3-TRIAZOL-4-YL)METHYLENE]-7-OXO-1-AZABICYCLO[3.2.0]HEPT-2-ENE-2-CARBOXYLIC ACID, A NOVEL CARBAPENEM DERIVATIVE, FROM 6-AMINOPENICILLANIC ACID

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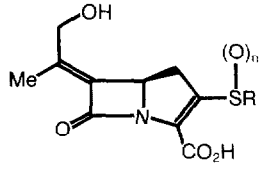
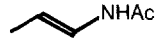
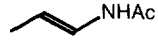
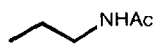
Summary: The title compound has been prepared from 6-aminopenicillanic acid via the novel intermediate, p-methoxybenzyl (5R,6R) 6-bromo-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (10).

The ability of bacteria to produce β-lactamases poses a continuing threat to the clinical utility of β-lactam antibiotics. The past several years have witnessed the discovery of a number of naturally occurring and semi-synthetic β-lactam derivatives which inhibit these β-lactamase enzymes. They include clavulanic acid, sulbactam, the olivanic acids and the asparenomycins.[1]



R =  , n = 1 **Asparenomycin A**

R =  , n = 0 **Asparenomycin B**

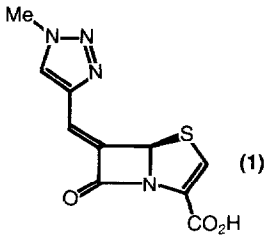
R =  , n = 1 **Asparenomycin C**

The alkylidene carbapenem derivatives, Asparenomycin A, B and C have been shown to exert their β-lactamase inhibitory effect by acylating the β-lactamase enzyme.[2] The acyl-enzyme complex thus formed is believed to be stable to subsequent hydrolytic breakdown, thereby disrupting the catalytic activity of the enzyme.

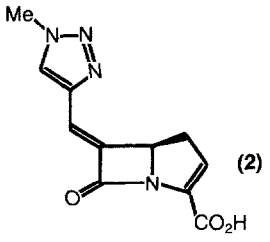
This, together with a recent report from these laboratories that the triazolylmethylene penem, BRL 42715 (1) is a potent inhibitor of both penicillinases and cephalosporinases,[3] prompted us to incorporate the triazolylmethylene moiety into the carbapenem nucleus.

The great potential of 6-aminopenicillanic acid (6-APA) for the synthesis of non-classical β-lactams has been recognised on numerous occasions.[4]

We also have utilized this readily available, chiral starting material to prepare the triazolylmethylene carbapenem (2), via the 6(R)-bromocarbapenem (10).



(1)

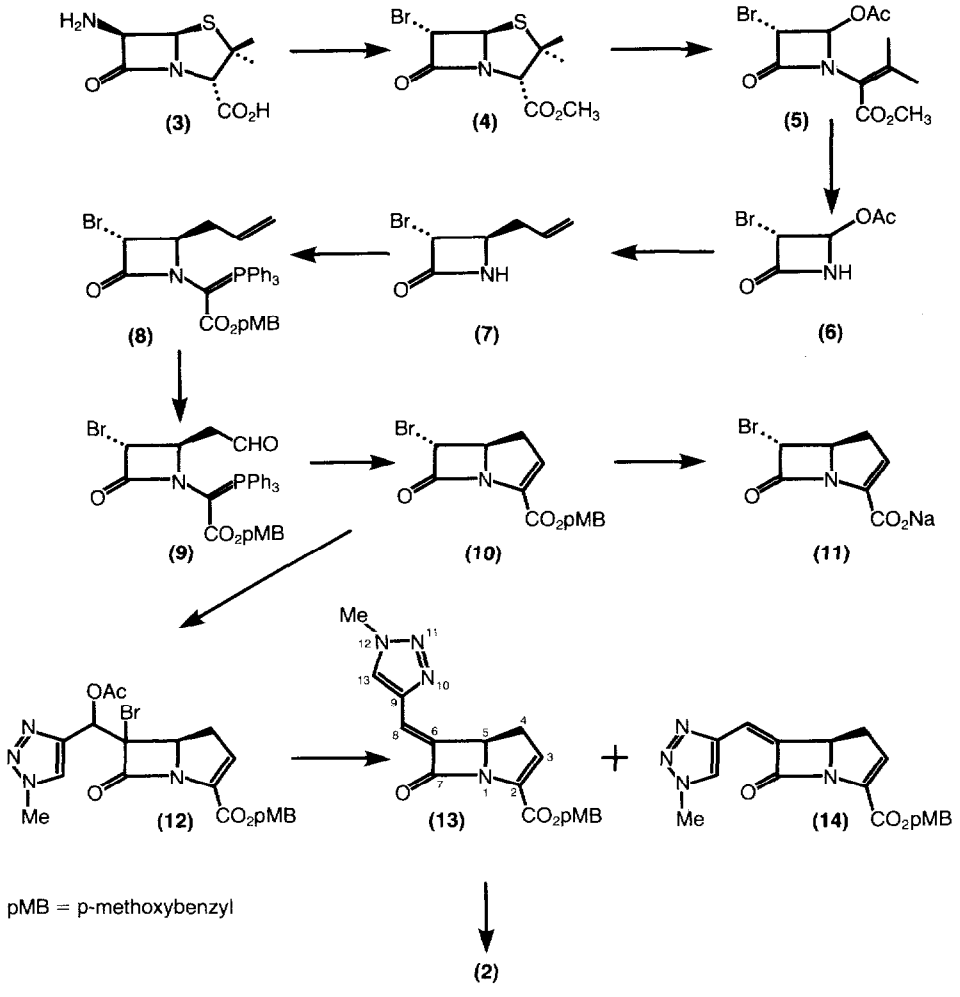


(2)

Accordingly, 6-APA (3) was converted to the known methyl 6(S)-bromopenicillanate (4) by the method of John et al.[5] Treatment with acetyl nitrate (1,2-dichloroethane, 5°C, 3h) and triethylamine (5°C, 4h) provided a diastereoisomeric mixture of 4-acetoxyazetidin-2-ones (5). This procedure was first reported by the Schering group[6] for the preparation of 3-(1-hydroxyalkyl)-4-acyloxyazetidin-2-ones. Ozonolysis, followed by methanolysis then afforded the diastereoisomeric azetidinones (6) in 45% yield from (4).

The introduction of carbon substituents at the C-4 position of azetidin-2-one derivatives is well documented.[7] Indeed, the diastereospecific allylation of 3(R)-bromo-4(R,S)-acetoxyazetidin-2-one (6) was achieved in 60% yield by the use of boron trifluoride etherate (1.2 equiv.) and allyltrimethylsilane (CH_2Cl_2, 20°C, 16h).[7a] The trans β-lactam orientation in the product (7)[8] $[\alpha]_D^{20}$ + 39.6° (c 1.0, CH_3OH) was apparent from the H_3-H_4 vicinal coupling constant of 1.7 Hz.

The 3(R)-bromo-4(R)-allylazetidin-2-one (7) was then progressed to the bicyclic carbapenem (10) using the well established intramolecular Wittig cyclisation first reported by Woodward.[9] Selective oxidation of the terminal double bond of phosphorane (8), prepared in 56% yield by condensation of (7) with p-methoxybenzyl glyoxalate,[9] could be achieved by ozonolysis in ethyl acetate (-78°C, 6min) in the presence of trifluoroacetic acid (40 equiv.); the phosphorane group was protected by protonation.[10] Reduction of the ozonide (PPh_3) followed by regeneration of the phosphorane with aqueous sodium hydrogen carbonate provided the aldehyde (9), which spontaneously cyclised to yield the crystalline p-methoxybenzyl (5R,6R) 6-bromocarbapenem (10)[11] m.p. 104-105°C, $[\alpha]_D^{20}$ + 149° (c 1.0, CH_2Cl_2), in 64% yield. Lewis acid-mediated deprotection[12] of the ester (10) (i. 2.5 equiv. $AlCl_3$, anisole, CH_2Cl_2, -40°C, 10min; ii. Na_2HPO_4) afforded the sodium salt of (5R,6R) 6-bromo-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (11) $[\alpha]_D^{20}$ + 93° (c 0.5, H_2O) (69% yield).



The bromocarbapenem ester (10) was elaborated to the triazolylmethylene carbapenem ester (13) by that procedure previously reported for the synthesis of the triazolylmethylene penem (1).[13]

Sequential treatment of the bromocarbapenem (10) with lithium diphenylamide (THF, -78°C, 2min), 1-methyl-1,2,3-triazole-4-carbaldehyde[14] (-78°C, 2min) and acetic anhydride (-78°C to 20°C over 20min) gave a diastereoisomeric mixture of acylated bromohydrins (12). Reductive elimination of this mixture (Zn, acetic acid, THF, 20°C, 30min) provided a 3:1 mixture of the (E)- and (Z)-triazolylmethylene carbapenem esters, (13) m.p. 115-117°C, $[\alpha]_D^{20}$ + 253° (c 1.0, CH_2Cl_2) and (14), which were separated by silica gel

column chromatography [32% total yield from (10)]. The structural assignment of (13), especially the (E)-geometry of the C-6,8 double bond, was based on a comparison of its ^{1}H n.m.r. spectrum with that of (14). The 8-H vinyl proton of the (E)-isomer (13) appears at δ7.05, downfield from that of the (Z)-isomer (14) (δ6.88), due to the anisotropic deshielding effect of the β-lactam carbonyl on this proton (solvent $CDCl_3$). In the (Z)-isomer (14) it is the triazole proton that is deshielded by the β-lactam carbonyl and appears at δ8.76, downfield from that of the (E)-isomer, which appears at δ7.64.

Finally, deprotection of the ester (13) by reaction with $AlCl_3$ in anisole/CH_2Cl_2[12] provided the sodium salt of (5R) (E)-6-[(1-methyl-1,2,3-triazol-4-yl)methylene]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (2) $[\alpha]_D^{20}$ + 224° (c 0.25, H_2O) in 68% yield, after Diaion HP 20 column chromatography and lyophilisation.

Neither the bromocarbapenem (11) nor the triazolylmethylene carbapenem (2) displayed any significant antibacterial or β-lactamase inhibitory activity.

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