A Novel and Stereocontrolled Synthesis of (5*R*)-(*Z*)-6-(1-Methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic Acid, a Potent Broad Spectrum β-Lactamase Inhibitor

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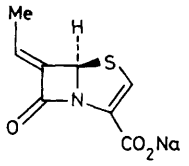
The key step in the preparation of the title compound (BRL 42715) from 6-aminopenicillanic acid was the condensation of the anion, generated by deprotonation of *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate (**10**), with 1-methyl-1,2,3-triazole-4-carbaldehyde; *in situ* acylation, followed by reductive elimination afforded the isomeric (*Z*)- and (*E*)-6-triazolylmethylene penem esters, (**12**) and (**13**) respectively.

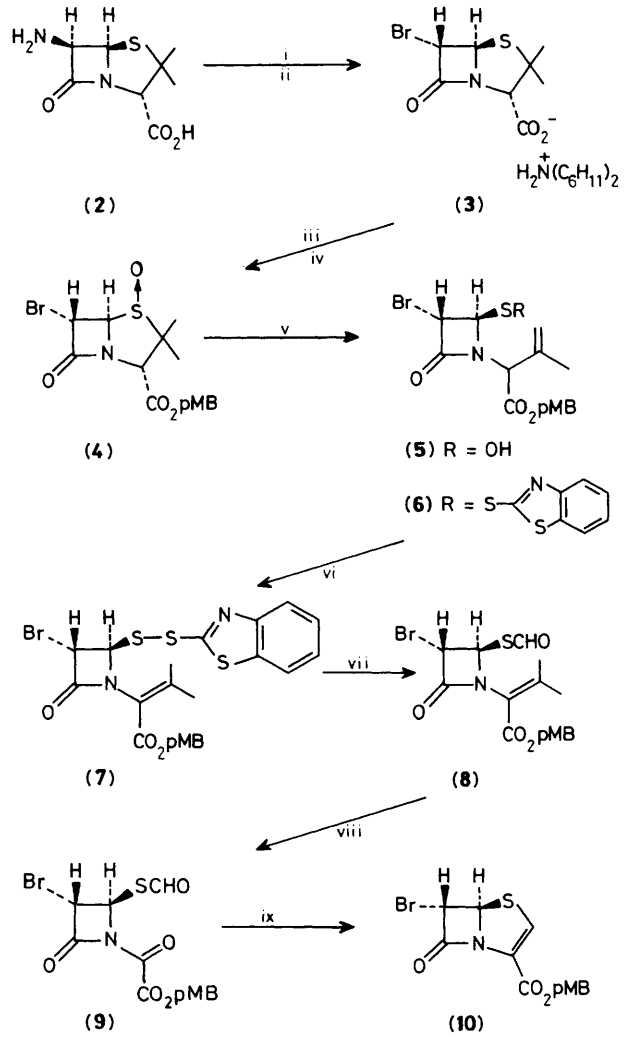
Since the first report by Woodward in 1976,[1] a great deal of interest has been shown by a number of groups in the synthesis of penem derivatives. Whilst most attention has been focused on the antibacterially active 6-(1-hydroxyethyl)penems, we were intrigued to find that the ethylidene penem (**1**) exhibited good β-lactamase inhibitory activity.[2] From further studies involving the preparation of 6-heterocyclylmethylene penems[3] emerged a potent inhibitor of both penicillinases and cephalosporinases, (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid (**14**).



(**1**)

Previous routes to the alkylidene and heterocyclylmethylene penems gave racemic compounds. We now report a facile, chiral synthesis of the title compound from 6-aminopenicillanic acid (6-APA) (**2**), *via* a novel and versatile intermediate, the 6(*S*)-bromopenem ester (**10**).

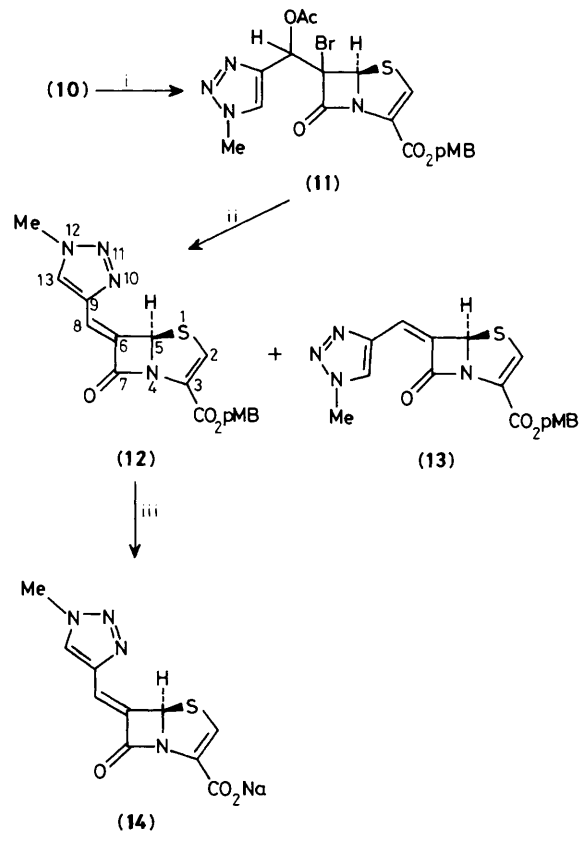
The synthetic strategy ultimately employed for our approach was influenced by the desire to (i) elaborate the inexpensive and readily available chiral synthon, 6-APA (**2**), to the penem (**14**) with the utilisation of as much of the original penam framework as possible; (ii) retain the (5*R*) stereochemical integrity; (iii) introduce the C-6 substituent at a late stage in the synthetic sequence.



pMB = *p*-methoxybenzyl

Scheme 1. *Reagents:* i, HBr, $NaNO_2$, MeOH–H_2O, 5 °C, 1 h; ii, $HN(C_6H_{11})_2$, ether – light petroleum (2 : 1), 5 °C, 16 h; iii, *p*-methoxybenzyl bromide, DMF, 25 °C, 18 h; iv, MCPBA, CH_2Cl_2, 5 °C, 1.5 h; v, 2-mercaptobenzothiazole, toluene, reflux, 2 h; vi, Et_3N (0.1 equiv.), toluene, 5 °C, 2 h; vii, $MeCO_2CHO$ (10 equiv.), NaI (10 equiv.), DMAP (1 equiv.), PPh_3 (1 equiv.), MeCN, −20 °C, 30 min, then 5 °C, 45 min; viii, (a) O_3, EtOAc, −78 °C, 1 h; (b) aq. $NaHSO_3$; ix, $P(OMe)_3$ (4 equiv.), toluene, 95 °C, 30 min.

Abbreviations: DMF = *N*,*N*-dimethylformamide; DMAP = 4-*N*,*N*-dimethylaminopyridine; MCPBA = *m*-chloroperbenzoic acid.



pMB = *p*-methoxybenzyl

Scheme 2. *Reagents:* i, (a) Ph_2NLi, THF, −78 °C immediately followed by 1-methyl-1,2,3-triazole-4-carbaldehyde, −78 °C, 1 min; (b) Ac_2O, −78 to 20 °C over 10 min; ii, Zn, TMEDA·2HCl, NH_4Cl (4 equiv.), DMF, 20 °C, 1 h; iii, (a) $AlCl_3$ (2.5 equiv.), anisole, CH_2Cl_2, −40 °C, 10 min; (b) Na_2HPO_4, −40 to 20 °C over 10 min.

Abbreviations; THF = tetrahydrofuran; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DMF = *N*,*N*-dimethylformamide.

With these considerations in mind, 6-APA (**2**) was converted to 6(*S*)-bromopenicillanic acid by the method of John *et al.*[4] (Scheme 1). Esterification of its dicyclohexylamine salt (**3**) with *p*-methoxybenzyl bromide, followed by oxidation with *m*-chloroperbenzoic acid afforded the sulphoxide (**4**)† in 60% yield from 6-APA. Sulphoxide (**4**) was then heated to reflux in toluene with 2-mercaptobenzothiazole. In this procedure, originally established by Kamiya *et al.*[5] for penicillin sulphoxide esters, the sulphenic acid (**5**) formed from (**4**) at elevated temperatures was intercepted by reaction with the mercaptan, giving the disulphide (**6**). The latter was transformed by base-catalysed double bond isomerisation to the conjugated ester disulphide (**7**) [95% yield from (**4**)]. Reductive formylation of disulphide (**7**) then provided the formylthio-derivative (**8**). Cyclisation of the oxalimide (**9**), obtained by ozonolysis of the formylthio-derivative (**8**), to the crystalline *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate (**10**), m.p. 104—105 °C, $[\alpha]_D^{20}$ +83° (*c* 1.0, $CHCl_3$), was effected by heating a toluene solution of (**9**) at 95 °C for 30 min in the presence of excess trimethyl phosphite [34% from (**7**)]. This carbonyl–carbonyl coupling reaction was first reported for the synthesis of C-2 substituted penem derivatives.[6]

The utility of the 6(*S*)-bromopenem (**10**) was demonstrated by its reaction with 1-methyl-1,2,3-triazole-4-carbaldehyde.[7] Sequential treatment of the bromopenem (**10**) with lithium diphenylamide,‡ 1-methyl-1,2,3-triazole-4-carbaldehyde, and acetic anhydride gave a 4 : 1 : 1 : 1 diastereoisomeric mixture of acylated bromohydrins (**11**) (Scheme 2). Reductive elimination of this mixture using powdered zinc in *N*,*N*-dimethylformamide, in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine dihydrochloride and ammonium chloride afforded an 8 : 1 mixture of the (*Z*)- and (*E*)-triazolylmethylene penem

† Satisfactory spectroscopic data and elemental analysis were obtained for all new compounds.

‡ Prepared by the reaction of n-butyl-lithium with diphenylamine in tetrahydrofuran at −20 °C.

esters, (**12**), m.p. 184—186 °C, $[\alpha]_D^{20}$ + 399° (*c* 1.0, $CHCl_3$), and (**13**), m.p. 183—185 °C, $[\alpha]_D^{20}$ −244° (*c* 1.0, $CHCl_3$), respectively, which were separated by silica gel column chromatography [72% total yield from (**10**)].§ The configurations of the geometrical isomers were assigned by ^1H n.m.r. spectroscopy on the basis of the anisotropic deshielding effect of the β-lactam carbonyl on the 8-H vinyl proton and the 13-H triazole proton. The vinyl proton of the (*Z*)-isomer (**12**) appeared at δ 7.03, downfield from that of the (*E*)-isomer (**13**), which appeared at δ 6.90 (solvent $CDCl_3$). The converse was true of the triazole proton, which appeared at δ 7.70 in (**12**) and δ 8.74 in (**13**).¶

Finally, Lewis acid-mediated deprotection[8] of the ester (**12**) gave the sodium salt of (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid (**14**) in 75% yield, obtained as a crystalline monohydrate from aqueous acetone, $[\alpha]_D^{20}$ +508° (*c* 1.0, H_2O). The β-lactamase inhibitory activity of this penem (**14**) (BRL 42715) represents a significant improvement over that of clavulanic acid, sulbactam, and 2β-[(1,2,3-triazol-1-yl)methyl]-2α-methylpenam-3α-carboxylic acid 1,1-dioxide (YTR-830).[9] Full biological properties of BRL 42715 will be published elsewhere.

§ Reductive elimination of (**11**) using zinc and acetic acid in tetrahydrofuran gave a 5 : 2 mixture of (**12**) and (**13**) in 67% yield from (**10**).

¶ Additional confirmation of assignments was provided by nuclear Overhauser enhancement spectroscopy. Irradiation at 13-H in the isomer (**12**) gave rise to positive enhancements at both 5-H and 8-H, due to the rapid rotation of the C(8)–C(9) bond in solution.

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