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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF TWO CATECHOL-BEARING PENEMS

Arun C. Kaura* and Michael J. Pearson

SmithKline Beecham Pharmaceuticals, Department of Medicinal Chemistry, Brockham Park, Betchworth, Surrey RH3 7AJ, U.K.

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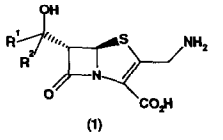
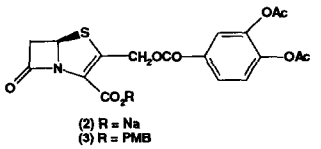
Abstract: The penems (**2**) and (**4**), attached to a catechol group *via* an ester linkage at C-2, have been prepared and evaluated as antibacterial agents.

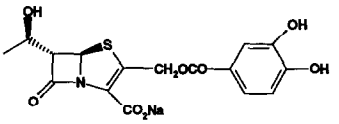
The penems are a group of synthetic antibiotics displaying potent *in vitro* activity against a broad range of bacteria. However with the exception of C-2-aminomethyl derivatives (**1**) none are reported to possess useful anti-pseudomonal activity.[1] Various studies on the cephalosporin nucleus[2-5] have demonstrated that attachment of a catechol moiety enhanced potency against Gram-negative bacteria, including *Pseudomonas aeruginosa*, relative to corresponding structures which lack the vicinal hydroxy groups. Such catecholic agents penetrate the bacterial outer membrane *via* the *ton B* dependent high-affinity iron-transport systems which are derepressed when bacteria are grown under conditions of iron-limitation.[6,7] In the hope that the advantageous biological properties conferred by such chemical modification could be extended to the penem system, the compounds (**2**)[8] and (**4**) were identified as key targets. The incorporation of a 6*S*-(1*R*-hydroxyethyl) substituent is widely known to increase both chemical and ß-lactamase stability of the penem system.[9]



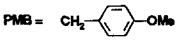
(1)



(2) R = Na
(3) R = PMB

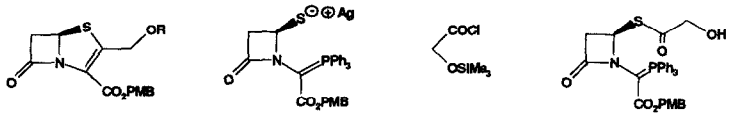


(4)

PMB = 

The 2-hydroxymethylpenem (**5**),[10,11] required for preparation of the ester (**3**) was synthesised initially using literature precedent.[12] Thus the silver salt (**7**)[13] was transformed into (**5**) in 23% overall yield in three steps *via* the *tert*-butyldiphenylsilyl ether (**6**) [(i) $Bu^t(Ph)_2SiOCH_2COCl$/pyridine/CH_2Cl_2/O°C, 42%; (ii) toluene/110°C, 69%; (iii) Bu_4NF/HOAc/THF/RT, 79%]. Subsequently we developed a new two-step procedure which employs transient trimethylsilyl protection of the hydroxyl group and provides (**5**) in 37% overall yield. Thus, the salt (**7**) was acylated with *O*-trimethylsilyl protected acid chloride (**8**), itself prepared from glycollic acid by sequential trimethylsilylation and thionyl chloride treatment.[14] The resulting

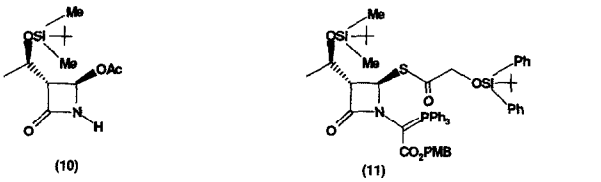
phosphorane (**9**; 48%), obtained following a hydrolytic work up, was then subjected to intramolecular Wittig cyclisation [toluene/110°C] to give the desired ester (**5**; 78%). We attribute the efficient preparation of the acid chloride (**8**) to our adventitious selection of *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (MSTFA) as the silylating species. This is in contrast to an unsuccessful attempt to prepare (**8**) from glycollic acid using trimethylchlorosilane/triethylamine prior to reaction with thionyl chloride.[15]



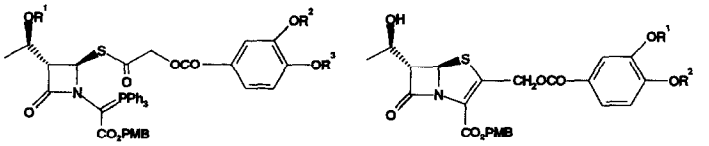
(5) R = H
(6) R = Si(Ph)$_2$Bu^t (7) (8) (9)

O-Acylation[16] of the penem (**5**) with 3,4-diacetoxybenzoyl chloride provided the derivative (**3**; 71%). Removal of PMB ester [$EtAlCl_2$/Anisole/CH_2Cl_2/-20°C] and neutralisation of the resulting acid [Na_2HPO_4] gave the salt (**2**; 17%).

The synthesis of (**4**) utilised the commercially available azetidinone (**10**)[17] which was converted into the phosphorane (**11**) following a known procedure.[18] The primary hydroxyl group in (**11**) was then selectively unmasked (Bu_4NF)[19] and acylated as above to give the derivative (**12**; 88%). Attempted fluoride-ion mediated desilylation of (**12**) was complicated by concomitant partial cleavage of the acetate protecting groups. Prolonged treatment (3 days) with excess Bu_4NF [14 mol. eq.] thus provided the phosphoranes (**13**; 53%) as a mixture of catecholic esters. Cyclisation [toluene/110°C] then afforded a 3:1 mixture of the respective penem esters (**14**) and (**15**) in 57% overall yield, the regiochemistry being established by an n.O.e. difference experiment. Cleavage of PMB protecting group as described above gave the corresponding C-3 carboxylic acid which was neutralised [$NaHCO_3$]. During this procedure the remaining acetyl group was hydrolysed to give the catechol-bearing penem(**4**; 42%) as the final product.



(10) (11)

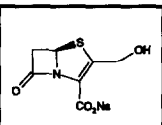
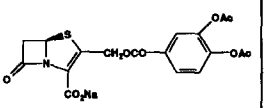
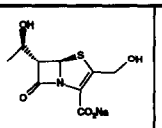
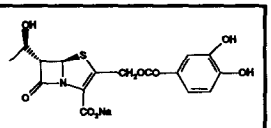


(12) R^1 = Si(Me)$_2$Bu^t ; $R^2 = R^3$ = Ac
(13) R^1 = H; $R^2 = R^3$ = H,Ac
(14) R^1 = Ac; R^2 = H
(15) R^1 = H; R^2 = Ac

The Table shows the *in vitro* antibacterial activities of catecholic penems (**2**) and (**4**) compared to the corresponding C-2-hydroxymethyl derivatives (**16**)[20] and (**17**)[21] respectively. It can be seen that the catechol group in (**2**) and (**4**) causes a significant improvement in their antimicrobial activity against *E. coli* presumably as a result of uptake by iron-regulated outer membrane proteins, in addition to the conventional porin

pathways.[7] However this was not apparent with the other Gram-negative bacteria in the screen, including *Pseudomonas aeruginosa*, for which we have no explanation. This is in contrast to cephalosporins with a catechol group attached at C-3' *via* an ester linkage, which show a marked improvement in *in vitro* antimicrobial activity against this organism when compared to their non-catecholic analogues.[22]

Table: The relative antimicrobial activities[a] of catechol-bearing penems and their precursors.

	 (16)	 (2)	 (17)	 (4)
E. coli NCTC 10418	16	8	8	0.5
E. coli DC2 [b]	32	0.5	8	0.12
E. coli DC0	32	>32	8	1.0
P. mirabilis 977	32	16	16	32
P. stuartii T90	32	>32	16	32
P. aeruginosa. NCTC 10662	>64	8	64	32
P. aeruginosa K799 wt	>64	>32	64	>64
P. aeruginosa Dagleish [c]	>64	>32	64	>64

[a] MICs (μg/ml) determined by serial dilution in nutrient agar

[b] cell-wall deficient mutant

[c] ß-lactamase producer

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10. All new compounds gave satisfactory spectral data. The sodium salts (**2**) and (**4**) were pure by reverse phase HPLC and gave the expected mass by FAB mass spectroscopy.

11. $[\alpha]_D^{25}$ + 107° ($CHCl_3$). We believe this is the first report of a 6-unsubstituted 5*R*-2-(hydroxymethyl)-penem ester.

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14. Glycollic acid was *bis*-silylated by reaction with MSTFA (2.2 mol. eq.) and Me_3SiCl (0.1 mol. eq.) in dry CH_2Cl_2 under inert atmosphere. The mixture was stirred at RT (2 hrs.), heated under reflux (4 hrs.) and stirred at RT (7 days) before evaporation under red. press. at 60°C (IR 1735cm^{-1}). The residue in dry CH_2Cl_2 was reacted with thionyl chloride (1.2 mol. eq.) at RT (18 hrs.) before evaporation to a clear syrup which solidified upon storage under argon at RT (IR 1810cm^{-1}). This acid chloride (**8**) was used without further purification.

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