NOVEL C-3 CYCLIC ETHER CEPHALOSPORINS AND THEIR ORALLY ABSORBED PRODRUG ESTERS

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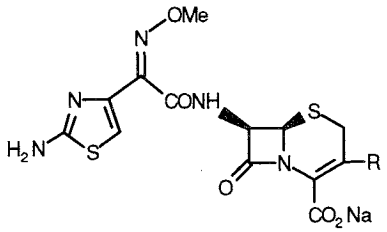
In a previous communication[1] we described analogues of cefotaxime (**1**) in which the C-3 acetoxymethyl group was replaced by a lactone (**2**). In our search for additional metabolically stable analogues, and encouraged by reports of some C-2 substituted penems[2], we targeted the C-3 cyclic ether cephems (**3**, $n=1$, 2). Our synthesis adopted, in modified form, the Wittig cyclisation chemistry of WOODWARD *et al.*[3] and NAYLER *et al.*[4] (Scheme 1).

The racemic acids (**4**) were converted in conventional fashion into the corresponding chloromethyl ketones (**5**), which were then used to alkylate the azetidinone thiol[5] (**6**). Addition of *t*-butyl glyoxylate to the derived ketone (**7**), followed by elaboration of the aminols (**8**) with thionyl chloride and 2,6-lutidine then tri-*n*-butylphosphine, provided the phosphoranes (**9**). On thermolysis in refluxing toluene these phosphoranes cleanly cyclised to the cephems (**10**) in high yields. As reported for the lactonyl derivatives[1], the use of tri-*n*-butyl phosphoranes in place of the triphenyl analogues was advantageous, the latter requiring prolonged reaction times or increased temperatures (thermolysis in xylene) resulting in greatly reduced yields. In addition the incorporation of benzoic acid catalysis[6] in the thermolysis of the tri-*n*-butyl phosphoranes reduced the time required for the completion of the cyclisation.

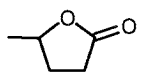
Removal of the 7-phenoxyacetyl group using standard cephalosporin methodology[7] provided the 7-aminocephems. At this stage the (*R*)- (**11**) and (*S*)-diastereoisomers (**12**) at position 2 of the ether ring were readily separated and independently acylated with **13** to give the diastereoisomers (**14a** and **14b**). However subsequent removal of the *N*-trityl and *t*-butyl protecting groups from each of these with hydrochloric acid in formic acid, followed by formation of the sodium salts (**3**) was accompanied by epimerisation of the cyclic ether asymmetric centre. The same 2 : 3 mixture of (*R*) - (*S*) was obtained from both enantiomerically pure intermediates (**14a** and **14b**). The sodium salts were alkylated with iodomethyl pivalate to provide the pivaloyloxymethyl prodrug esters (**15**) for oral absorption studies.

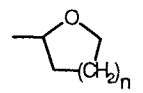
The antibacterial activities of the sodium salts (**3**) (Table 1) show that the tetrahydrofuran (**3**, $n=1$) was significantly more potent than the tetrahydropyranyl analogue (**3**, $n=2$) against several strains, and although it did not match the C-3 lactonyl analogues[1], compared favourably with cefuroxime, and cefetamet.

The oral absorption of the pivaloyloxymethyl prodrug esters (**15**) was examined in mice and compared with the α-acetoxyethyl ester of cefuroxime (cefuroxime axetil[8]) and the pivaloyloxymethyl ester of cefetamet (cefetamet pivoxil[9]). The results (Table 2) dramatically demonstrate that the C-3 cyclic ether cephems give vastly superior AUCs, peak concentrations in blood (C_{max}) and half lives when compared to the standard compounds.



1 R = —CH_2OAc

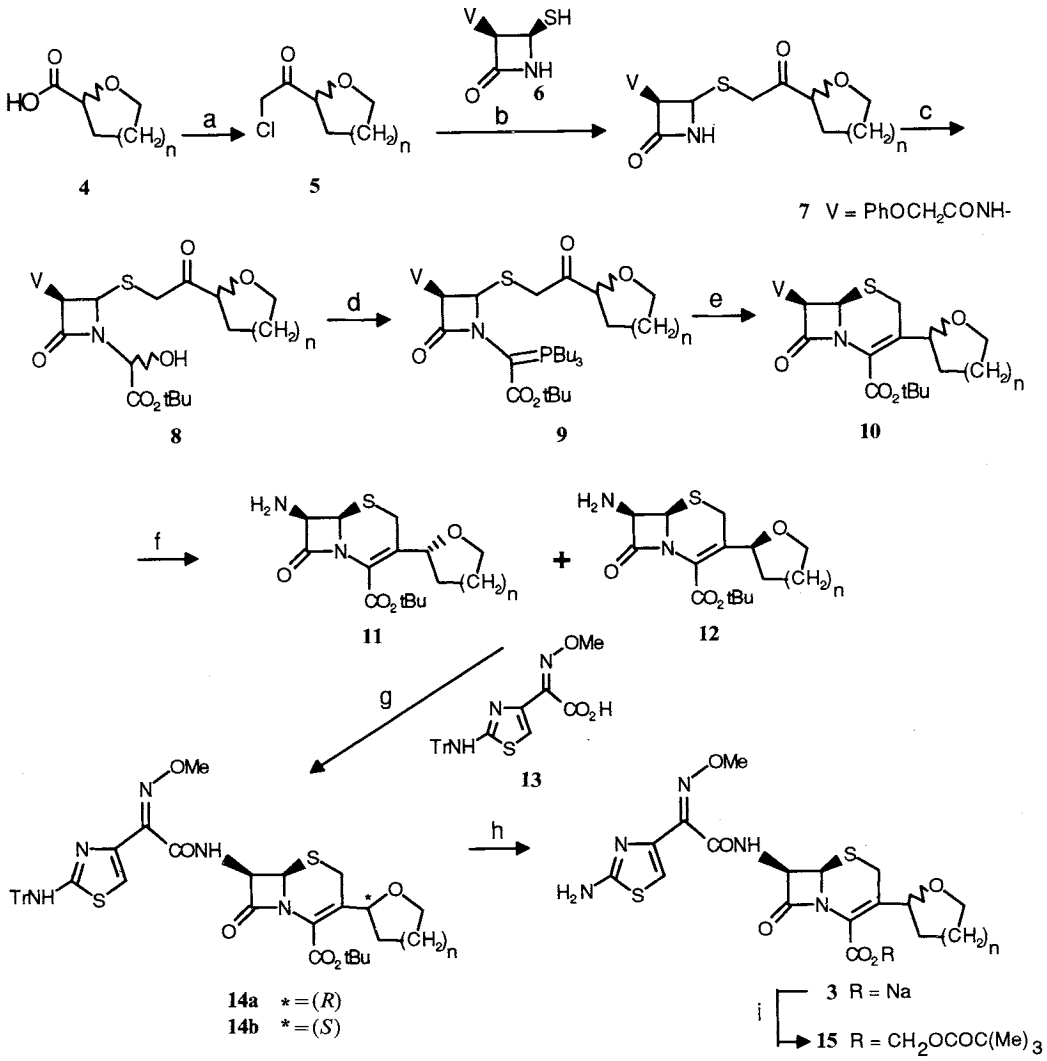
2 R = 

3 R = 

While this manuscript was in preparation, the preparation of a C-3 (3-bromotetrahydrofuran-2-yl)cephem was reported:

JUNG, M. H.; K.-W. CHO, W. J. KIM, J.-S. SHIN & C. S. PARK: Synthesis of cephalosporins having a heterocyclic group at the C-3 position. Bull. Korean Chem. Soc. 14: 32～34, 1993.

Scheme 1.



Reagents: (a) $(COCl_2)$, DMF, CH_2Cl_2; CH_2N_2; HCl. (b) K_2CO_3, DMF. (c) *t*-Butyl glyoxylate, NEt_3, $(CH_2Cl)_2$. (d) $SOCl_2$, 2,6-lutidine, THF; PBu_3, dioxan. (e) Reflux, PhMe, $PhCO_2H$. (f) PCl_5, *N*-methylmorpholine, CH_2Cl_2; MeOH; H_2O. (g) (**13**), $MeSO_2Cl$, iPr_2NEt, DMF; (**11**) or (**12**), pyridine. (h) HCl, HCO_2H; $NaHCO_3$. (i) *t*-$BuCO_2CH_2I$, DMF.

Table 1. Antibacterial activity MIC ($\mu g \cdot ml^{-1}$)[a] of C-3 cyclicether cephems.

	3 ($n=1$)	**3** ($n=2$)	Cefuroxime	Cefetamet
Escherichia coli 10418	0.5	2	0.25	0.12
E. coli ESS	<0.03	0.06	<0.03	0.12
E. coli 1077[b]	1	8	2	0.25
E. coli JT425[b]	8	32	8	16
Haemophilus influenzae Q1	0.25	0.5	0.25	0.25
H. influenzae NEMC1[b]	0.12	0.25	0.25	0.06
Klebsiella pneumoniae T767	1	8	2	0.25
Moraxella catarrhalis Ravasio[b]	0.5	4	2	1
Morganella morganii T361	0.5	4	32	2
Proteus mirabilis C977	0.5	4	2	0.12
Pseudomonas aeruginosa 10662	>64	>64	>64	>64
Enterobacter faecalis I	>64	>64	>64	>64
Staphylococcus aureus Oxford	1	1	0.5	64
S. aureus Russell[b]	1	1	0.5	>64
S. aureus MB9[b]	1	2	2	64
S. epidermidis PHLN 20	0.5	0.5	0.5	16
Streptococcus agalactiae 2798	0.06	0.06	<0.03	2
S. pneumoniae 1761	<0.03	<0.03	<0.03	0.5
S. pneumoniae PU 7[c]	1	1	1	2
S. pyogenes CN 10	<0.03	<0.03	<0.03	0.12

[a] Serial dilution in blood agar base (Oxoid) containing 5% lysed horse blood. Inoculated with 0.001 ml of an overnight broth culture diluted as appropriate.
[b] β-Lactamase mediated resistance.
[c] Target site mediated resistance.

Table 2. *In vivo* data[a] in the mouse of C-3 cyclic ether cephem prodrugs.

	AUC (0~2 hours) ($\mu g \cdot min \cdot ml^{-1}$)	C_{max} ($\mu g \cdot ml^{-1}$)	$T_{1/2}$ (hour)	Bioavail.[b] (%)
15 ($n=1$)	4201 [4264][c]	47.3 [48.8]	1.77	58% [52%]
15 ($n=2$)	4611	52.5	2.0	59%
Cefuroxime axetil	437	8.6	0.3	
Cefetamet pivoxil	1216	23.3	0.46	

[a] Following oral administration of esters (**15**) at a dose equivalent to 50 $mg \cdot kg^{-1}$ of antibiotic (**3**).
[b] Bioavailability (%) $= \frac{\text{AUC of prodrug ester (po)}}{\text{AUC of parent cephem (sc)}} \times 100$.
[c] [HPLC results] Concentrations of antibiotic in blood measured by bioassay and confirmed by HPLC for (**3**, $n=1$).

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-2-methoxyiminoacetamido]-3-[tetrahydrofuran-2-yl]cephem (**3**, $n=1$) has been identified as an analogue of cefotaxime which is well absorbed in the mouse as its pivaloyloxymethyl prodrug ester (**15**, $n=1$) and gives high and prolonged levels of antibiotic in the blood and is worthy of further studies.

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