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# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME C-3-LACTONYL SUBSTITUTED CEPHALOSPORINS

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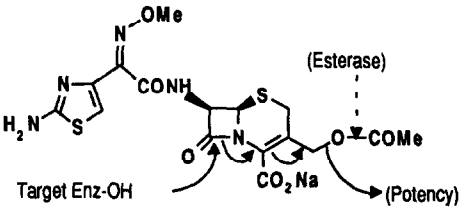
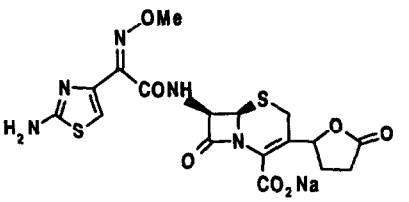
***Abstract:*** *In continuation of our studies of cephalosporins containing novel cyclic 3-substituents,[1] we now report the synthesis of some lactones connected to the cephalosporin dihydrothiazine ring either directly, or through a single carbon spacer.*

The third generation cephalosporins are characterised by broad spectrum antibacterial activity combined with good stability to hydrolysis by β-lactamases. Cefotaxime (**1**), the first of the 3rd generation cephalosporins, shows a high level of activity *in vitro*. However it is vulnerable to esterase hydrolysis[2] *in vivo* and the metabolite has substantially reduced antibacterial activity.




(1)

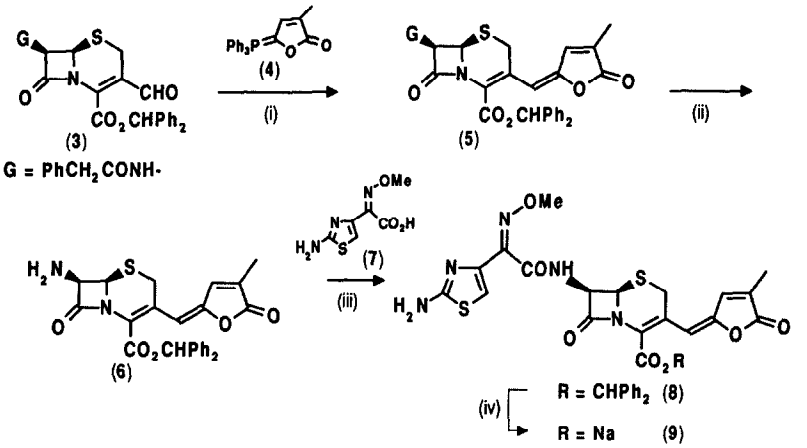
As antibacterial activity is to some extent dictated by the nucleofugacity of the C-3'-substituent[3] we reasoned that a lactone functionality (*cf* **2**) should retain cefotaxime-like activity whilst circumventing the problem of metabolism of the acyloxy linkage, the product at least retaining components which could re-cyclise to the lactone.




(2)

Our deliberations also led us to synthesise a series of highly conjugated butenolides including (**9**). This was obtained (**Scheme 1**) from intermediate (**5**) (26%) derived in turn by reaction of the cephem 3-carboxaldehyde (**3**)[4] with the stabilised Wittig reagent (**4**).[5] Only a trace of the corresponding **Z**-isomer was observed (<1%).

**Scheme 1**

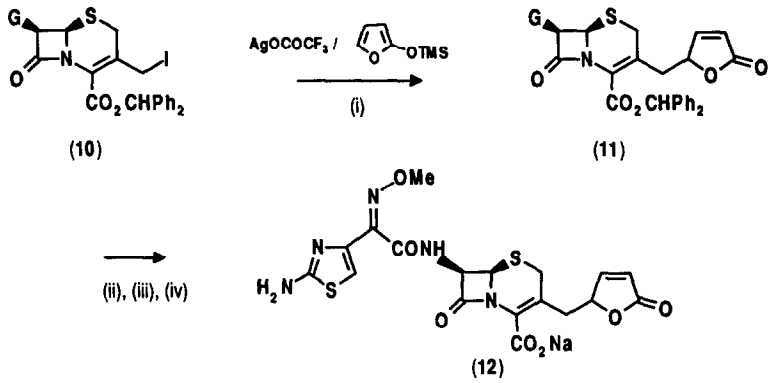



Reagents: (i) DMSO, RT, 1.25h. (ii) $PCl_5$, N-methylmorpholine, $CH_2Cl_2$, -20°C; then MeOH. (iii) (**7**), $MeSO_2Cl$, i-$Pr_2NEt$, $CH_2Cl_2$, -50°C; then (**6**), pyridine. (iv) TFA: $NaHCO_3$.

Standard cephalosporin manipulations, removal of the phenylacetyl group (Delft cleavage[6]), acylation with the acid (**7**) and ester deprotection provided[7] the butenolide (**9**).

A second closely related analogue was provided (**Scheme 2**) by alkylation of 2-trimethylsilyloxyfuran with 3-iodomethylcephem (**10**) in the presence of silver trifluoroacetate using conditions described by Jefford,[8] to give lactone (**11**) as a 2:1 mixture of diastereoisomers. This was then modified at the C-7 position and the ester deprotected as above to give (**12**) still as a 2:1 mixture of lactonyl diastereoisomers.

**Scheme 2**



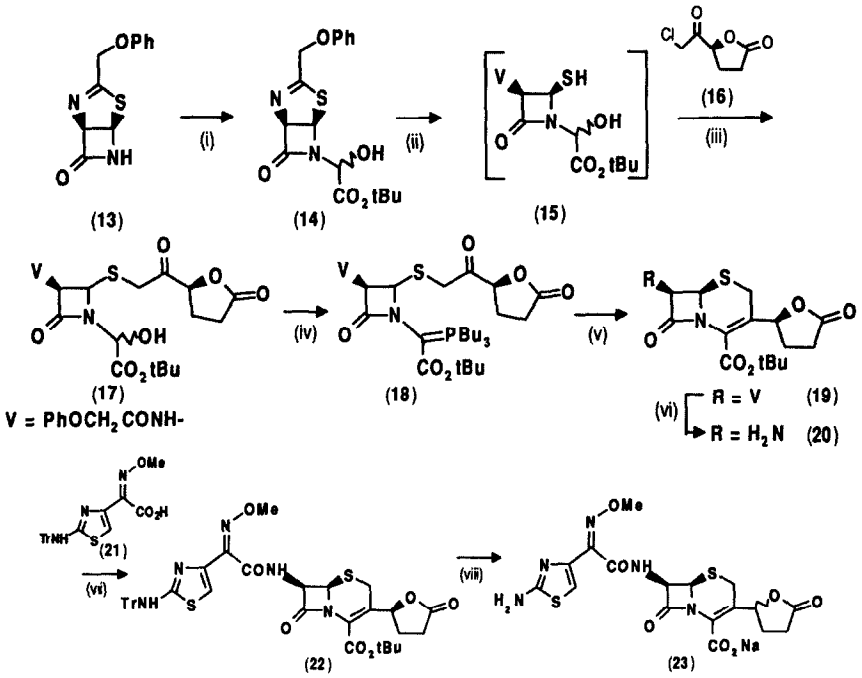

Reagents: (i) $AgOCOCF_3$, $CH_2Cl_2$, -78°C. (ii), (iii), (iv) as for Scheme 1.

These two cephems, (**9**) and (**12**), showed good activity in our primary *in vitro* antibacterial screen (**Table 1**) and this encouraged us to examine the directly linked lactone as originally targeted. When the phosphorane (**4**) was reacted with the 3-keto cephem, obtained by ozonolysis of the exomethylene derivative, no product was obtained using conditions that had been reported[9] as successful with ethyl 2-(triphenylphosphoranylidene)acetate. The reduced reactivity of the secondary phosphorane was thought to be responsible.

The construction of novel 3 substituted cephems by an intramolecular Wittig cyclisation of an appropriately substituted azetidinone is well documented.[10] Our successful synthesis (**Scheme 3**) of the directly linked target cephem (**2**) employed this stratagy. The thiazoline[11] (**13**) was condensed with t-butyl glyoxylate to give the aminol (**14**) and then hydrolysed with aqueous toluene-4-sulphonic acid to the thiol (**15**). This was alkylated *in situ* with (**16**) obtained from (S)-2-oxotetrahydrofuran-5-carboxylic acid via the diazoketone.[12] The hydroxy group could then be chlorinated with thionyl chloride/lutidine and then the chlorine displaced with tri-n-butylphosphine to provide the phosphorane (**18**). When this was heated in toluene at reflux it underwent smooth conversion (<1h) to the cephem (**19**, 74%). The lactonyl (**R**)-isomer (19%) was also produced together with a trace of (RS)-Δ2-mixture. When the more traditional triphenylphosphorane was used, the cyclisation required much longer (~32h) and resulted in a significant reduction in yield (21%). The (S)-lactonyl cephem (**19**) was then subjected to the Delft

cleavage and re-acylation without loss of the chiral integrity of the lactone. However deprotection of the N-trityl t-butyl ester (**22**) with HCl in formic acid followed by formation of the sodium salt also resulted in partial racemisation of the lactonyl asymmetric centre. The final product (**23**) was obtained as a 2:3 mixture of the (R) and (S) diastereoisomers at this chiral centre.

**Scheme 3**




Reagents: (i) t-Butyl glyoxylate, $NEt_3$, 1,2-dichloroethane. (ii) ptsa, $H_2O$, $Me_2CO$, $CH_2Cl_2$. (iii) $K_2CO_3$, $Me_2CO$. (iv) $SOCl_2$, 2,6-lutidine, THF, -10°C; then $PBu_3$, dioxan. (v) PhMe, reflux, 1h. (vi) $PCl_5$, N-methylmorpholine, $CH_2Cl_2$, -20°C; then MeOH. (vii) (**21**), $MeSO_2Cl$, i-$Pr_2NEt$, $CH_2Cl_2$, -10°C; then (**20**), pyridine. (viii) HCl, $HCO_2H$; $NaHCO_3$.

All compounds were characterised by infra red, NMR and mass spectroscopy. Data for compounds (**9**), (**12**) and (**23**) is reported.[13]

The results of the antibacterial testing of the sodium salts (9), (12) and (23) compared to cefotaxime (1) are shown in **Table 1.**[14] Minimum inhibitory concentrations (MIC) were determined at 18 hours by standard techniques using agar dilutions. The results show that for many of the bacterial strains, antibacterial activity equivalent to cefotaxime has been retained with these structurally modified analogues.

**Table 1**
**Antibacterial Activity MIC ($\mu g.ml^{-1}$) of 3-Lactonyl Cephems (9, 12, 23).**

| | (9) | (12) | (23) | (1) |
|---|---|---|---|---|
| *E.coli* 10418 | <0.03 | 0.06 | <0.03 | <0.03 |
| *E.coli* ESS | <0.03 | <0.03 | <0.03 | <0.03 |
| *E.coli* 1077 (a) | 1 | 0.5 | 0.12 | <0.03 |
| *E.coli* JT425 (a) | 2 | 4 | 1 | 0.5 |
| *H.influenzae* Q1 | <0.03 | 0.06 | 0.06 | <0.03 |
| *H.influenzae* NEMC1 (a) | <0.03 | <0.03 | <0.03 | <0.03 |
| *K.pneumoniae* T767 | 1 | 0.5 | 0.06 | 0.06 |
| *M.catarrhalis* Ravasio (a) | 8 | 0.5 | 2 | 0.25 |
| *Morg.morganii* T361 | <0.06 | 0.5 | 0.06 | 2 |
| *Pr.mirabilis* C977 | 0.06 | 0.25 | <0.03 | <0.03 |
| *Ps.aeruginosa* 10662 | 32 | >64 | 64 | 16 |
| *Ent.faecalis* I | 16 | >64 | >64 | >64 |
| *Staph.aureus* Oxford | 1 | 1 | 1 | 2 |
| *Staph.aureus* Russell (a) | 2 | 1 | 1 | 2 |
| *Staph.aureus* MB9 (a) | 4 | 4 | 2 | 4 |
| *S.epidermidis* PHLN 20 | 2 | 4 | 0.5 | 1 |
| *Strep.agalactiae* 2798 | <0.03 | 0.06 | 0.06 | 0.12 |
| *Strep.pneumoniae* 1761 | <0.03 | <0.03 | <0.03 | <0.03 |
| *Strep.pneumoniae* PU 7 (b) | 0.5 | 4 | 2 | 2 |
| *Strep.pyogenes* CN 10 | <0.03 | <0.03 | <0.03 | <0.03 |

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

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**References and Notes:**


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12. Marco, J. L. *Synth. Commun.* **1989**, *19*, 485.
13. (**9**) $\lambda_{max}$ ($H_2O$) 362 (ε 21,740) and 230nm (ε 15,110); $\nu_{max}$ (KBr) 1741 (br), 1679, 1610, 1528 and 1387cm$^{-1}$; $\delta_H$ ($D_2O$) 1.95 (3H, s), 3.64 and 3.80 (2H, ABq, *J* 17.1Hz), 3.97 (3H, s), 5.29 (1H, d, *J* 4.8Hz), 5.82 (1H, d, *J* 4.8Hz), 6.56 (1H, s), 6.97 (1H, s) and 7.56 (1H, s); *m/z* (FAB, +ve ion, thioglycerol) 514 (*MH*$^+$), 536 (*MNa*$^+$). (**12**) $\nu_{max}$ (KBr) 1750 (br), 1663, 1601 (br), 1532, 1458 and 1387cm$^{-1}$; $\delta_H$ ($D_2O$) major diastereoisomer 2.78 (1H, dd, *J* 4.3, 14.5Hz), 2.95 (1H, dd, *J* 7.6, 14.5Hz), 3.37 and 3.59 (2H, ABq, *J* 17.6Hz), 3.95 (3H, s), 5.16 (1H, d, *J* 4.8Hz), 5.45 (1H, m), 5.73 (1H, d, *J* 4.8Hz), 6.17 (1H, dd, *J* 1.8, 5.8Hz), 7.00 (1H, s) and 7.70 (1H, dd, *J* 1.3, 5.8Hz), minor diastereoisomer *inter alia* 2.58 (1H, dd, *J* 7.0, 14.4Hz), 5.36 (1H, m), 6.99 (1H, s) and 7.74 (1H, d, *J* 5.8Hz); *m/z* (FAB, +ve ion, thioglycerol) 502 (*MH*$^+$), 524 (*MNa*$^+$). (**23**) $\nu_{max}$ (KBr) 1758, 1664, 1608, 1533, 1390, 1183 and 1037cm$^{-1}$; $\delta_H$ ($D_2O$) major diastereoisomer 2.0 - 2.8 (4H, m), 3.39 and 3.53 (2H, ABq, *J* 17.5Hz), 3.94 (3H, s), 5.22 (1H, d, *J* 4.9Hz), 5.53 (1H, t, *J* 6.8Hz), 5.78 (1H, d, *J* 4.8Hz) and 6.98 (1H, s), minor diastereoisomer *inter alia* 3.37 and 3.63 (2H, ABq, *J* 17.9Hz), 5.20 (1H, d, *J* 5.0Hz) and 5.57 (1H, t, *J* 6.8Hz); *m/z* (FAB, +ve ion, thioglycerol) 490 (*MH*$^+$).
14. Further details of the Biological properties of these compounds and their pro-drug esters will be reported in a full paper.