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# TOTAL SYNTHESIS OF A 1α-HYDROXY-1-CARBACEPHEM

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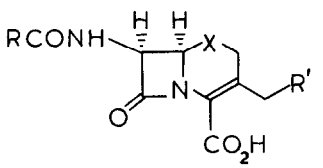
Summary: Sodium (d, l)-7β-phenoxyacetamido-1α-hydroxy-1-carbacephalosporanate (16) has been synthesised from acyclic precursors. In surprising contrast to its non-hydroxylated analogue (4), it did not show significant antibacterial activity against Staphylococcus aureus.

The synthesis of 1-carbacephem[1] (1) and 1-oxacephem[2] (2) systems, coupled with the observation of their high levels of antibacterial activity, made a 1-hydroxy-1-carbacephem (3) system an attractive synthetic goal. It was hoped that such a target molecule would show not only the antibacterial properties[3] of the biologically active 1-carbacephem (4), but also, as its α-epimer, enhanced activity by analogy[4] with cephem R-sulphoxides. Additionally, molecular models indicated that both epimers had the potential to form OH-to-π intramolecular hydrogen bonds,[5] which would reduce the electron density in the $\Delta^3$-double bond, and possibly result in further enhancement of activity. In approaching such a goal, we modelled our route on the Merck procedure,[1,2] which involves assembly of an imine, followed by reaction with an azido-ketene equivalent to form a monocyclic β-lactam. This protocol defined the required components for imine formation as the aldehyde (5), in suitably protected form, and the amine (6).

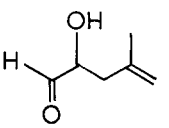


(1), X = $CH_2$, R' = OAc

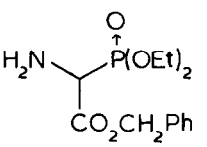
(2), X = O, R' = OAc

(3) X = CHOH, R = $PhOCH_2$, R' = H

(4), X = $CH_2$, R = $PhOCH_2$, R' = H



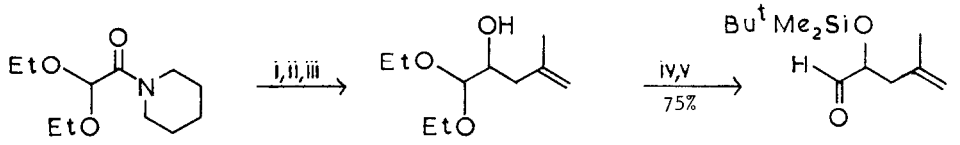
(5)



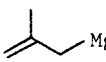
(6)

The aldehyde (5) was prepared readily (Scheme 1), with the intermediate hydroxyacetal (7) being obtained in an overall yield of 72%. After several faulty choices of protecting group for the alcohol functionality, with ensuing problems of over-stability being revealed only at a late stage in the synthesis, ideal protection was found to be provided by the t-butyldimethyl-

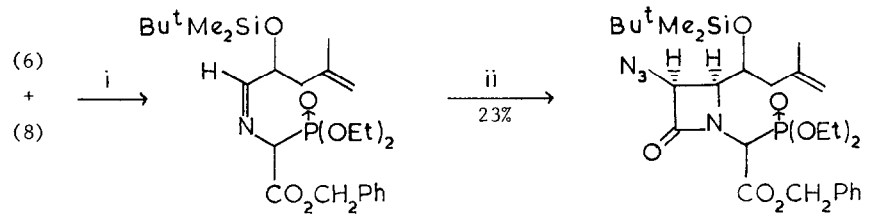
silyl group, as in aldehyde[6] (8). Amine (6) was prepared either by a published route[7] from phthalimide, or, more conveniently, by direct reaction[8] of the sodium salt of benzyl (diethoxyphosphinyl)acetate with O-(diphenylphosphinyl)hydroxylamine.



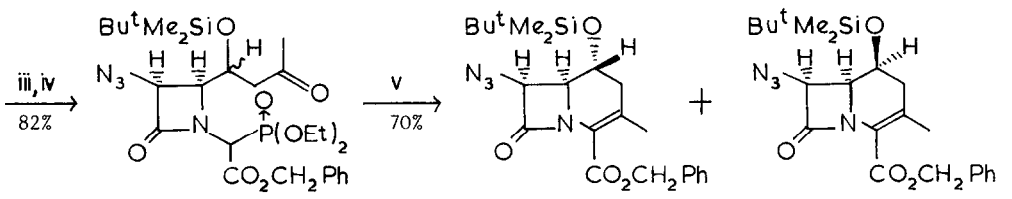

(7) (8)

Scheme 1. Reagents: i,  MgCl, $Et_2O$, 35°C, 24h; ii, aq $NH_4Cl$, 0°C; iii, $NaBH_4$, EtOH, $H_2O$, 0°C, 15 h; iv, Bu$^t$Me$_2$SiCl, imidazole, DMF; v, acetone, ptsa.$H_2O$.

Reaction between aldehyde (8) and amine (6) rapidly gave the unstable imine (9), and thence the β-lactam[6] (10), as an inseparable mixture of stereoisomers (Scheme 2); these stereoisomers were uniformly cis-1,2-disubstituted, as evidenced by $^1$H n.m.r. vicinal coupling constants of 4.5 Hz shown by all subsequent compounds. Ozonolysis of this mixture gave the methyl ketone[6] (11) as two separable epimers. Without separation, treatment with one equivalent of NaH in DME at 50°C for 5 h induced cyclization of one epimer, to produce, on work-up, a mixture of the bicyclic β-lactam[6] (12), m.p. 144-145°C, and the other, unreacted epimer; cyclization of this




(9) (10)

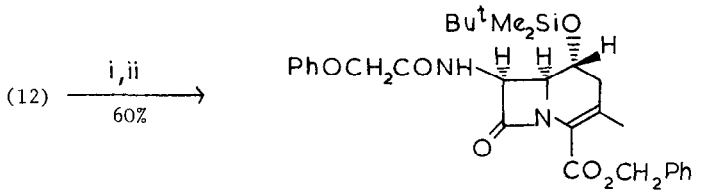



(11) (12) (13)

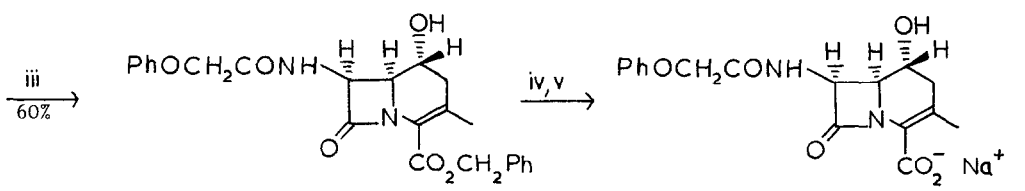
Scheme 2. Reagents: i, $PhCH_3$, 3 x azeotrope; ii, $N_3CH_2COCl$, $Et_3N$, cyclohexane-$PhCH_3$ (4:1), 20°C, 1 h; iii, $O_3$, MeOH; iv, $Me_2S$; v, NaH, DME, 85°C, 6 h (see text).

recovered epimer, by similar treatment with base but at reflux, yielded a second bicyclic β-lactam[6] (13), m.p. 150-151°C. Alternatively, direct treatment at reflux, followed by chromatographic separation, gave the same two epimeric compounds (12) and (13). Based on the relative ease of their formation and consideration of transition state interactions, their $^1$H n.m.r. spectra (in particular, $H_1$-$H_6$ vicinal coupling constants of 8.5 and 1 Hz, respectively), and subsequent reactions, these two compounds are assigned the respective relative configurations shown.

The azide moiety of the α-epimer[6] (12) was reduced[9] and acylated to give the phenoxy acetamide[6] (14), m.p. 147-148°C, as shown in Scheme 3. Desilylation to the 1α-hydroxy-1-carbacephem ester[6] (15), m.p. 149-150°C, followed by hydrogenolysis, ultimately gave the desired free acid, which was isolated, characterised, and tested biologically as its sodium salt (16). The structure of ester (15) was confirmed in all detail by X-ray analysis, which also showed the absence of any through-space interaction between the hydroxyl group and the $\Delta^3$-double bond. The sodium salt (16), fully characterised by 250 MHz $^1$H n.m.r. spectroscopy, was inactive against S. aureus (Oxford) at 500 μg/ml; it also failed to induce enhancement in




(14)




(15) (16)

Scheme 3. Reagents: i, $H_2S$, $Et_3N$, $CH_2Cl_2$, ii, $PhOCH_2COCl$, $Et_3N$, $CH_2Cl_2$, iii, HCl, MeOH; iv, $H_2$, 10% Pd/C, 40 lb in$^{-2}$, 35 min; v, $NaHCO_3$.

the activity of ampicillin against a β-lactamase producing strain of S. aureus. In light of ester (15) possessing a β-lactam i.r. carbonyl absorption at 1777 $cm^{-1}$, and X-ray analysis showing a β-lactam nitrogen h value[10] of 0.204 Å, this result was disappointing.[11] Steric bulk in the C6-S1 region on the α-face of the parent cephem system has recently been suggested[12] to disfavour high biological activity: such an effect may be operating here.

Treatment of the β-epimer (13) in an analogous manner proved successful up to the 1β-epimer of ester (14). Employment of a wide range of desilylation conditions caused either no reaction or total decomposition of the substrate. The lack of significant biological activity shown by the α-epimer (16) did not encourage further study.

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10. h is the distance of the β-lactam nitrogen above the plane defined by the three atoms to which it is bonded.
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