

A General Enantioselective O-2-Isocephem Synthesis

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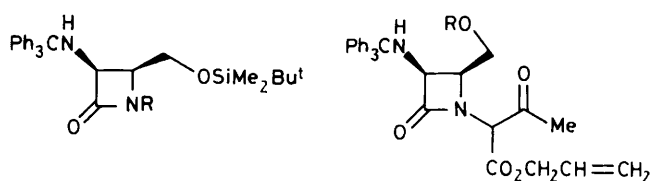
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A simple procedure for the conversion of the readily available chiral azetidinone (2) into the O-2-isocephem (5) is described.

As part of our efforts to find more effective, orally-active anti-infectives, we recently re-examined the O-2-isocephem class, *e.g.* (5), of β -lactam antibiotics. This required an efficient, enantioselective synthesis¹ which would allow us to generate rapidly a variety of analogues with different substituents at the 3-position. The existing enantioselective synthesis^{1b} was considered unsuitable since it relies on a chromatographic separation of diastereoisomers and does not allow for much variation in the 3-substituent.

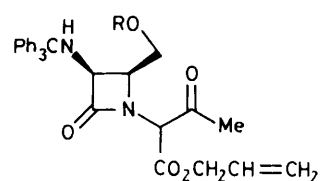
The approach which we adopted took advantage of the fact that several good enantioselective syntheses² of derivatives of (3*S*,4*S*)-3-amino-4-hydroxymethylazetidin-2-ones have recently appeared. We thought that if it were possible to react successfully the enolate³ of an acetate derivative such as (2) with an activated form of a carboxylic acid, the resulting β -ketoester, *i.e.* (3), could then be transformed into an O-2-isocephem.

The required 1-acetate derivative (2) was prepared by reaction of the chiral azetidinone (1)[†] with allyl bromoacetate



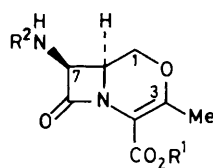
(1) R = H

(2) R = CH₂CO₂CH₂CH=CH₂



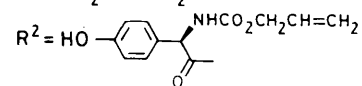
(3) R = SiMe₂Bu^t

(4) R = H



(5) R¹ = CH₂CH=CH₂, R² = CPh₃

(6) R¹ = CH₂CH=CH₂



(7) R¹ = H, R² = HO-C₆H₄-CH(NH₂)-C(=O)-Me

[†] This was derived from (3*S*,4*S*)-3-benzyloxycarboxamido-1-(2,4-dimethoxybenzyl)-4-hydroxymethylazetidin-2-one (ref. 2a) by straightforward protecting group manipulation.

under basic, phase transfer conditions⁴ in 66% yield (90% conversion). The enolate of (2) was generated [$\text{LiN}(\text{SiMe}_3)_2$ (2 equiv.), tetrahydrofuran (THF), -78°C], then quenched with acetyl chloride (1 equiv.) to give what appeared to be the β -ketoester (3). Treatment of this material with tetrabutylammonium fluoride [1 equiv. with HOAc (1 equiv.) in THF] gave a more polar product, presumed to be the alcohol (4). The latter two compounds, although chromatographically homogeneous, were difficult to characterize unambiguously since they existed in their enol forms as mixtures of isomers. However, when (4) was subjected to the conditions of the Mitsunobu reaction (di-isopropyl azodicarboxylate, triphenylphosphine, THF), the O-2-isocephem (5) was cleanly obtained [79% overall yield from (2)].[‡]

This sequence [(2) \rightarrow (3) \rightarrow (4) \rightarrow (5)] was found to be quite general. For example, with chloroacetyl chloride or cyclopropylcarbonyl chloride, the 3-chloromethyl (60% overall yield) or 3-cyclopropyl analogue (86% overall yield) of (5) could be prepared.

Finally, replacement of the trityl group of (5) with the appropriate acyl group proved to be straightforward. Treatment of (5) with acid ($p\text{-MeC}_6\text{H}_4\text{SO}_3\text{H}\cdot\text{H}_2\text{O}$, acetone) gave the toluene- p -sulphonic acid salt of the free amine. Deprotonation (aq. NaHCO_3) of the latter followed by acylation [(*R*)-*N*-allyloxycarbonyl-2-(*p*-hydroxyphenyl)-glycine, ethyl

1,2-dihydro-2-ethoxy-1-quinoline carboxylate (EEDO)] gave the protected product (6) in 76% yield from (5). Deprotection⁵ [catalytic $\text{Pd}(\text{PPh}_3)_4$, PhNHMe (4 equiv), CH_2Cl_2] followed by purification (reverse phase chromatography) gave the O-2-isocephem analogue (7) of cefadroxil.

Using this approach we have been able to prepare a variety of O-2-isocephem analogues.

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References

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- P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, 1982, **47**, 587. We have found that the deprotection proceeds more rapidly when *N*-methylaniline is used as the acceptor for the allyl group.

[‡] M.p. 88–89°C; $[\alpha]_{\text{D}} + 90^\circ$ (c 0.5, CHCl_3); ν_{max} (KBr) 3340, 1760, 1710, 1610 cm^{-1} ; ^1H n.m.r. ($\text{C}_6\text{D}_6 + \text{D}_2\text{O}$) δ 2.23 (s, 3H), 2.36 (dt, 1H, J 9.8, 4.1 Hz), 2.53 (dd, 1H, J 9.8, 4.1 Hz), 2.88 (t, 1H, J 9.8 Hz), 4.29 (d, 1H, J 4.1 Hz), 4.63–6.02 (m, 5H, CH_2CHCH_2), 6.89–7.29 (m, 15H, ArH).