A General Enantioselective O-2-Isocephem Synthesis

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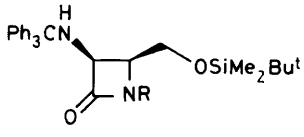
A simple procedure for the conversion of the readily available chiral azetidinone (**2**) into the O-2-isocephem (**5**) is described.

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 synthesis[1] 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.

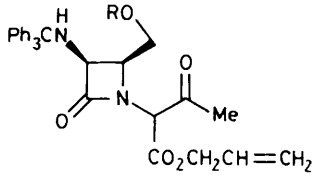
The approach which we adopted took advantage of the fact that several good enantioselective syntheses[2] of derivatives of (3*S*,4*S*)-3-amino-4-hydroxymethylazetidin-2-ones have recently appeared. We thought that if it were possible to react successfully the enolate[3] of an acetate derivative such 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



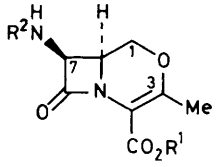
(**1**) R = H

(**2**) R = $CH_2CO_2CH_2CH{=}CH_2$



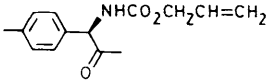
(**3**) R = $SiMe_2Bu^t$

(**4**) R = H

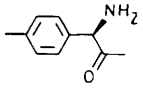


(**5**) $R^1 = CH_2CH{=}CH_2$, $R^2 = CPh_3$

(**6**) $R^1 = CH_2CH{=}CH_2$, $R^2 = HO$



(**7**) $R^1 = H$, $R^2 = HO$



† 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 conditions[4] in 66% yield (90% conversion). The enolate of (**2**) was generated [$LiN(SiMe_3)_2$ (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**) → (**3**) → (**4**) → (**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-$MeC_6H_4SO_3H{\cdot}H_2O$, 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 (EEDQ)] gave the protected product (**6**) in 76% yield from (**5**). Deprotection[5] [catalytic $Pd(PPh_3)_4$, 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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‡ M.p. 88—89 °C; $[\alpha]_D$ + 90° (*c* 0.5, $CHCl_3$); $\nu_{max.}$ (KBr) 3340, 1760, 1710, 1610 cm^{-1}; ^1H n.m.r. (C_6D_6 + D_2O) 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).

References

1 (a) Racemic syntheses: T. W. Doyle, J. L. Douglas, B. Belleau, T. T. Conway, C. F. Ferrari, D. E. Horning, G. Lim, B.-Y. Luh, A. Martel, M. Menard, and L. R. Morris, *Can. J. Chem.*, 1980, **58**, 2508, and earlier papers in this series; C. H. Hakimelahi, G. Just, and A. Ugolini, *Helv. Chim. Acta*, 1982, **65**, 1368; S. W. McCombie, W. A. Metz, and A. Afonso, *Tetrahedron Lett.*, 1986, 305. (b) Enantioselective synthesis: S. M. Tenneson and B. Belleau, *Can. J. Chem.*, 1980, **58**, 1605. (c) After completion of this work, another enantioselective O-2-isocephem synthesis was reported: H. Natta, M. Hatanaka, and T. Ishimaru, *J. Chem. Soc., Chem. Commun.*, 1987, 51.

2 (a) C. Hubschwerlen, *Synthesis*, 1986, 962, and references therein; (b) D. A. Evans and E. B. Sjogren, *Tetrahedron Lett.*, 1985, 3783.

3 A similar condensation has been used to synthesize a clavulanic acid derivative: J. Eglington, *J. Chem. Soc., Chem. Commun.*, 1977, 720.

4 D. Reuschling, H. Pietsch, and A. Linkies, *Tetrahedron Lett.*, 1978, 615.

5 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.