A General Synthesis of Chiral C-4-Alkylated Azetidin-2-ones which are of Potential Use as Intermediates for 1β-Heteroatom-substituted Carbapenems

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A highly diastereocontrolled alkylation at the C-4 position of 4-acetoxyazetidin-2-one (**5**) employing chiral tin(II) enolates of heteroatom-substituted acetyl derivatives (**3a—e**) furnishes new synthetic intermediates (**6a—e**) for 1β-heteroatom-substituted carbapenems (**2**).

1β-Substituted carbapenems are potential candidates for the new generation of β-lactam antibiotics.[1] Recently, Nagao and Lederle (Japan) group,[2] the Merck, Sharp & Dohme research group,[3] and the Shibasaki group[4] have independently developed a highly diastereoselective synthetic method for the synthesis of 1β-methyl carbapenems (**1**). However, there are no previous reports of a highly stereospecific chiral induction method for the synthesis of 1β-heteroatom substituted carbapenems (**2**).[5]

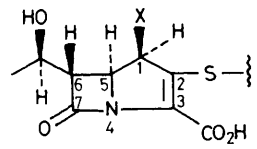
In this communication we describe a highly diastereocontrolled alkylation at the C-4 position of 4-acetoxyazetidin-2-one (**5**) with tin(II) enolates of 3-(heteroatom substituted acetyl)-(4*S*)-4-isopropyl-1,3-thiazolidine-2-thiones (**3a—e**).

Firstly, we attempted the alkylation under similar enolate formation conditions to earlier work[2] but the yield of desired alkylation product was less than 30%. After several trials, we realised that the mixing order of the reagents is critical for tin(II) enolate formation in these particular heteroatom-substituted acetyl derivatives (**3a—e**). Thus, a solution of 3-benzyloxyacetyl-(4*S*)-4-isopropyl-1,3-thiazolidine-2-thione (**3a**) (1.09 mmol) in anhydrous tetrahydrofuran (THF) (1.2 ml) was added to a solution of tin(II) trifluoromethanesulphonate (1.40 mmol) in THF (2.3 ml) at −78 °C under N_2. After adding *N*-ethylpiperidine (1.47 mmol), the mixture was stirred at −78 °C for 30 min to form the tin(II) enolate (**4a**). To the solution of enolate (**4a**) was added at −40 °C a solution of 4-acetoxyazetidin-2-one (**5**) (0.78 mmol) in THF (1.2 ml). After stirring at 0 °C for 30 min, the reaction was quenched with 0.1 M phosphate buffer solution (pH 7.0) and the mixture was treated as usual to give a crude product (**6a**) in a highly diastereoselective ratio (Scheme 1, Table 1). Purification of the crude product (**6a**) on a silica gel column ($CHCl_3$–acetone, 95 : 5) gave a pure compound (**6a**) as yellow needles ($CHCl_3$–Pr^i_2O) in 79% yield. Other chiral alkylations of (**5**) with tin(II)

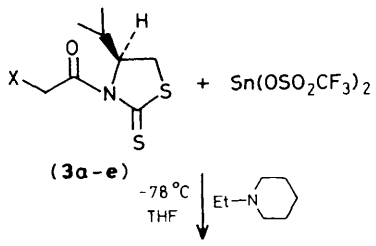
Table 1. Diastereocontrolled alkylation of 4-acetoxyazetidin-2-one (**5**) with tin(II) enolates (**4a—e**).

Tin(II) enolate	Diastereoisomer selectivity[a] (**6**) : other isomers	Isolated yield/%[b]	M.p./°C	$[\alpha]_D^{26}$ (*c* in $CHCl_3$)
(**4a**)	97 : 3	79 (**6a**)	104—105	+407.0° (0.29)
(**4b**)	97 : 3	55 (**6b**)	150—151	+561.1° (0.22)
(**4c**)	97 : 3	84 (**6c**)	oil	+252.8° (0.36)
(**4d**)	96 : 4	72 (**6d**)	147—148	+247.6° (0.25)
(**4e**)[c]	99 : 1	52 (**6e**)	oil	+219.7° (0.38)

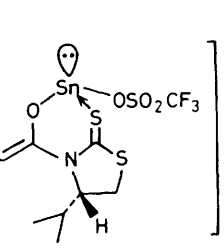
[a] Determined by h.p.l.c. analysis (u.v. 305 nm). [b] Based on 4-acetoxyazetidin-2-one (**5**). [c] Reaction time 10 min.



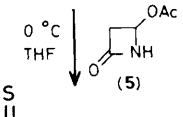
(1) X = Me
(2) X = OCH_2Ph, OMe, SCH_2Ph, SMe, $NHCO_2CH_2Ph$



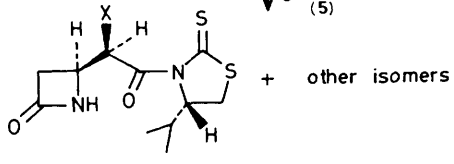
(3a-e)



(4a-e)



(5)



(6a-e)

a; X = OCH_2Ph
b; X = OMe
c; X = SCH_2Ph
d; X = SMe
e; X = $NHCO_2CH_2Ph$

Scheme 1

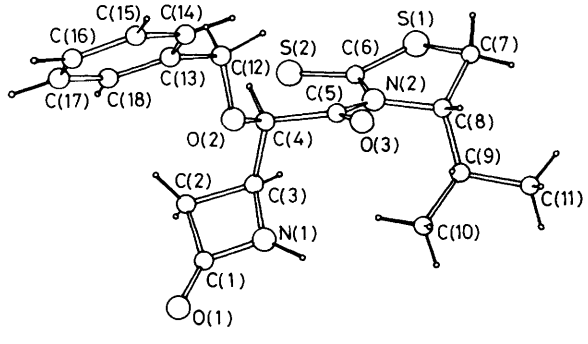
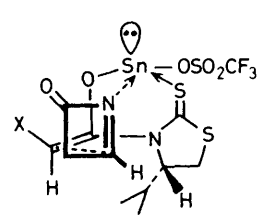
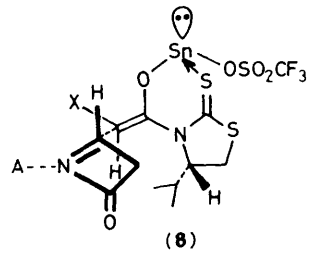


Figure 1. Perspective view of the crystal structure of (**6a**).



(7)



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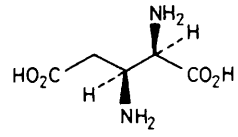

(9)

A = acidic group

enolates (**4b—e**) were similarly carried out to give the desired major products (**6b—e**), respectively, in 52—84% yields with excellent diastereoselectivity (Table 1).

The absolute configuration of the newly formed asymmetric centres in (**6a**) may be assumed by comparison with the known chirality of the asymmetric centre in the starting material. This comparison was achieved *via* the *X*-ray crystallographic analysis of (**6a**). The structure is shown in Figure 1.†

The stereochemistry of the other compounds (**6b—e**) was tentatively assigned from their ^1H n.m.r. spectra and similar mechanistic considerations to those for (**6a**). The excellent diastereofacial selectivity obtained for the major products (**6a—e**) can be explained by postulation of a six-membered chelating transition state (**7**)[2,6] or non-chelation transition state (**8**).

Interestingly, (**6e**) can be regarded as the compound obtained by differentially protecting similar kinds of functional groups in (**9**).

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† *Crystal data:* $C_{18}H_{22}N_2O_3S_2$, M_r = 378.5, space group $P2_1$, monoclinic, a = 10.053(1), b = 7.784(3), c = 12.509(3) Å, β = 96.28(8)°, U = 973 Å^3, Z = 2, D_x = 1.292 g cm^{-3}. 2529 Reflections measured on a Rigaku AFC-5RU diffractometer (Mo-K_α) had $F_o > 3\sigma(F_o)$, and were used in the refinement of the structure. The least-squares refinement including the hydrogen atoms located in the difference Fourier map gave R = 0.064. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.