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AN ENANTIOSPECIFIC NITRONE CYCLOADDITION ROUTE TO 3-HYDROXY-2-AZETIDINONES

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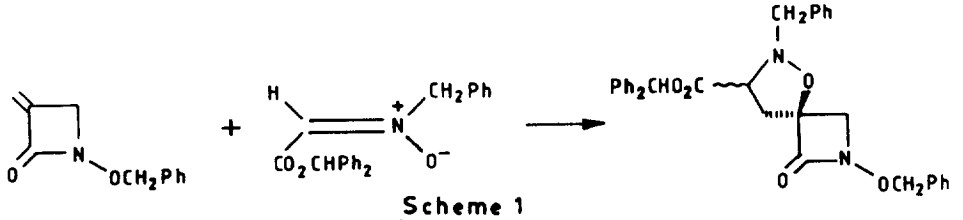
Abstract : 4-Aryl or heteroaryl 3-methylene β-lactams **2a-2c** underwenthighly stereospecific cycloaddition with various nitrones **3a-3c**. The method offers an enantiospecific route to 3-hydroxy-β-lactams.

3-Hydroxy or 3-alkoxyazetidin-2-one moiety, representing an efficient carboxylate mimic[1], is present in several monobactams such as Sulphazecin[2], Tabtoxin and related microbial products[3]. Design of substrates incorporating such entities is also a recent topic of interest[4]. Thus construction of such structural units would be useful and, indeed, several synthetic approaches have been reported[5]. However, none of these methods addressed the problem of making such units in enantiomerically pure forms. Herein we report our attempt to reach that goal.

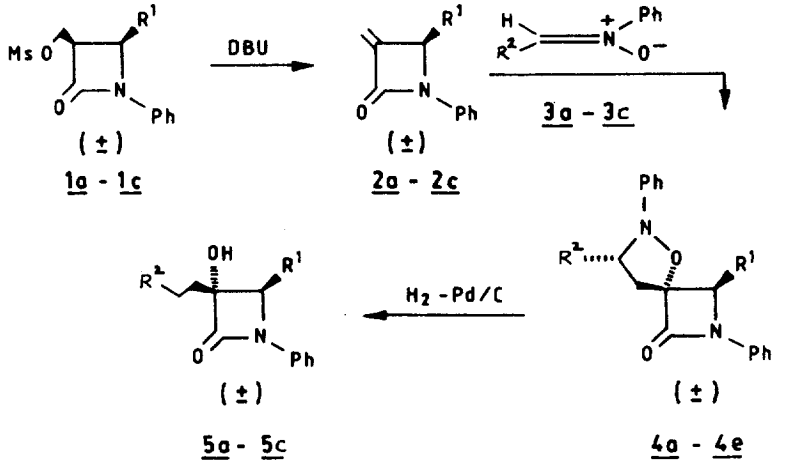
Previously Baldwin et al[5a] reported the nitrone cycloaddition route to 3-hydroxy-β-lactams. The addition was highly regiospecific; however due to rapid equilibration of E and Z nitrones, a mixture of diastereomeric products was obtained (Scheme 1). We reasoned that by



Scheme 1

keeping a substituent at C-4 we might be able to add stereoselectively to the cycloaddition which would ultimately pave the way towards enantiomerically pure products. With the above intention, we prepared several C-4 substituted methylene β-lactams **2a-2c** in racemic forms

starting from the corresponding mesylates 1a-1c by a DBU-promoted elimination. The alkenyl β-lactams 2a-2c were then subjected to cycloaddition conditions (benzene/toluene, reflux, argon), along with various nitrones 3a-3c. The addition products (Scheme 2), the spiro β-lactams 4a-4e, were isolated pure by column chromatography followed by crystallization. As revealed in Table 1, the reaction proceeded with a high degree of regio and stereoselectivity, with the nitrone approaching the dipolarophile from a face opposite to that of the C-4 substituent. Moreover, the cycloaddition showed excellent diastereofacial selectivity with respect to the dipolar component as shown by the formation of practically a single product. The stereochemistry at C-3 was established by the absence of any NOE enhancement for the signals at ~δ 2.5 and ~3.1 for the methylene hydrogens when the C-4 hydrogen was irradiated. The stereochemistry at C-7 has been tentatively assigned as shown (structure 4a-4e) which is based on the favourable secondary interactions[6] between the orbitals of the C-aryl ring of the nitrone in the E form and the oxygen of the carbonyl group of the β-lactam (Figure 1). The various cycloadducts underwent smooth hydrogenolysis (H_2-Pd/C) to furnish 3-(2-phenylethyl)-3-hydroxy- 4-substituted β-lactams 5a-5c.



Scheme 2

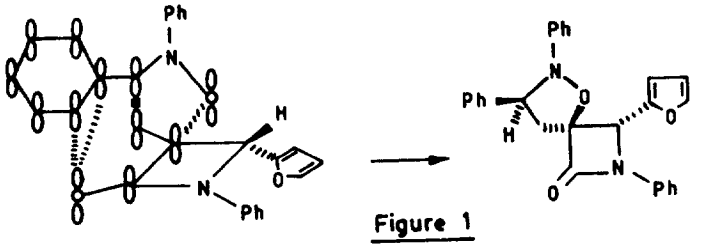
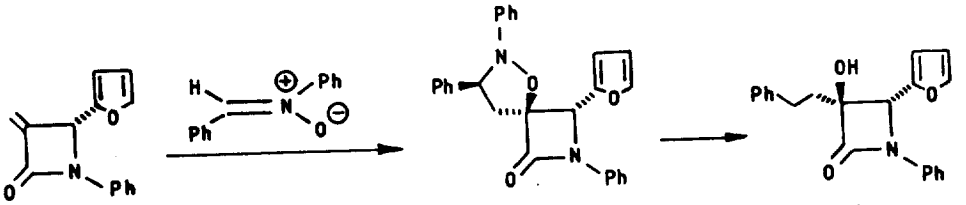


Figure 1



(+) 2a (+) 4a (+) 5a

Scheme 3

The methodology was repeated starting from enantiomerically pure (3S, 4R)-3-hydroxymethyl-4-furyl azetidinone[7]. There was no loss of stereochemical integrity during the entire procedure as revealed by the formation of essentiallv enantiomerically pure 3-hydroxy β-lactam 5a[8], confirmed by ^{1}H NMR in the presence of chiral shift reagent[9].

Table 1

Substituents	β-lactam	Nitrone	Cycloadduct (% yield)	Hydrogenolysed product (% yield)
R^1 =  , R^2 = Ph	2a	3a	4a (89)	5a (95)
R^1 = R^2 = 	2a	3b	4b (93)	—
R^1 =  R^2 = 	2a	3c	4c (72)[a]	5b (93)
R^1 =  R^2 = 	2b	3c	4d (74)[a]	5c (92)
R^1 = R^2 = Ph	2c	3a	4e (91)	—

a Isomeric cycloadducts were produced to the extent of ~15%

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8. Selected Spectral data : For **(+)2a** δ_H 5.33 (1H, *bs*), 5.49 (1H, *bs*), 5.93 (1H, *bs*), 6.39 (1H, *m*), 6.45 (1H, *d*, J = 3.7 Hz), 7.05 - 7.85 (6H, *m*), $[\alpha]_D^{28}$ + 11.6° (C 0.62, $CHCl_3$). For **(+)4a** δ_H 2.49 (1H, *dd*, J = 5.4, 13.2 Hz), 3.01 (1H, *dd*, J = 6.1, 13.2 Hz), 4.82 (1H, *dd*, J = 5.4, 6.1 Hz), 5.23 (1H, *s*), 6.02 (1H, *d*, J = 3.2 Hz), 6.36 (1H, *dd*, J = 2.0, 3.2 Hz), 7.0 - 7.63 (16H, *m*), $[\alpha]_D^{28}$ + 71.3° (C 0.16, $CHCl_3$). For **(+)5a** δ_H 1.93-2.03 (2H, *m*), 2.29-2.44 (1H, *m*), 2.76-2.88 (1H, *m*), 5.06 (1H, *s*), 6.31 (2H, *s*), 6.98-7.45 (11H, *m*); $[\alpha]_D^{28}$ + 22.1° (C 0.19, $CHCl_3$).
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