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HIGHLY DIASTEREOSELECTIVE INTRAMOLECULAR NITRONE CYCLOADDITIONS TO α,β-UNSATURATED ESTERS.

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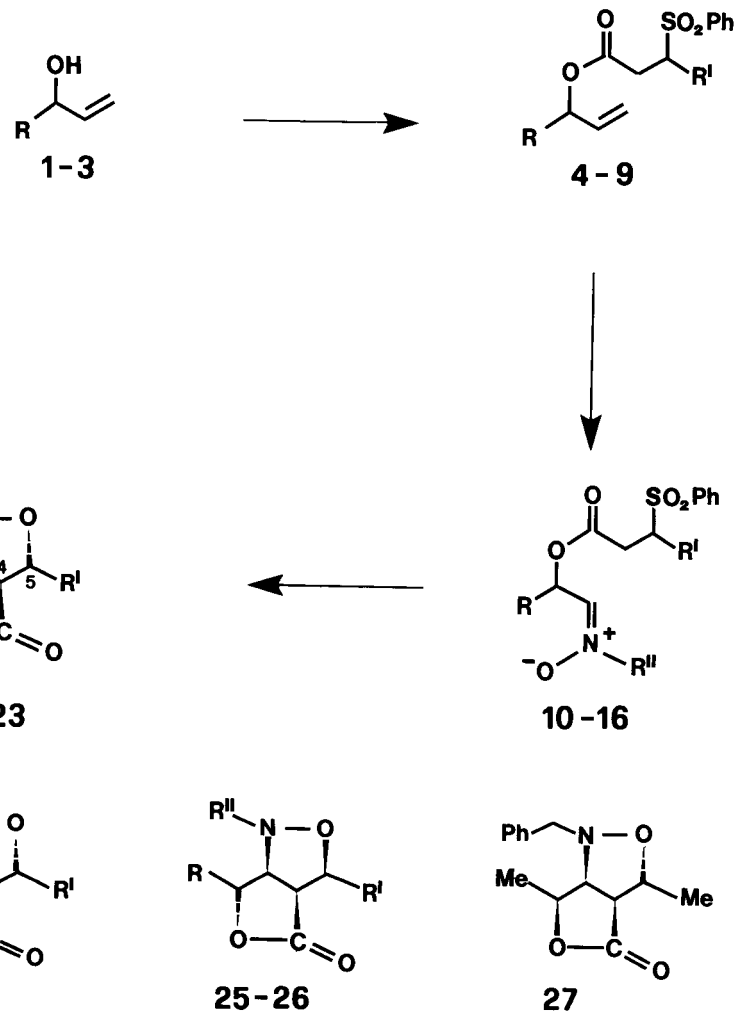
Abstract. Intramolecular cycloaddition of chiral α-acyloxynitrones to in situ generated α,β-unsaturated esters occurs with very high diastereoselectivity to afford useful precursors for the synthesis of β-lactam antibiotics.

The cycloaddition of nitrones[1] to α,β-unsaturated esters has been extensively studied in connection with the synthesis of key intermediates of penem and carbapenem antibiotics.[2-8] While reaction of achiral nitrones with crotonates occurs with high[4] or complete[5] stereoselection to give isoxazolidines featuring the desired relative stereochemistry, attempts to exploit chiral nitrones to control also the absolute configuration of the stereocenters were faced by almost total lack of stereocontrol.[6-8]

Here we report that intramolecular[9] cycloaddition of chiral but racemic α-acyloxy-nitrones[10] can be conveniently used to prepare diastereoisomerically pure cycloadducts with the stereochemistry required to obtain precursors of the above mentioned β-lactams. The synthetic approach to the desired nitrones is outlined in Scheme 1.[11] Allylic alcohols 1-3 were converted into β-phenylsulfonyl esters 4-9 by reaction with 1 mol. equiv. of acid chloride (CH_2Cl_2, 1.0 mol. equiv. of pyridine, 0° to room temperature, 30 min.) in 70-94% yield. Treatment of 4-9 with ozone (CH_2Cl_2, -78°C, 30 min.) followed by dimethylsulfide quenching gave the crude aldehydes. These were reacted as such with 1 mol. equiv. of N-benzyl- or N-methylhydroxylamine (9:1 Et_2O:THF mixture, room temperature, 15h) to afford the expected Z-nitrones[1,10,12] 10-16 in 55-65% overall yield from 4-9. Finally, addition of 1.1 mol. equiv. of DBU to a refluxing mixture of nitrones in CCl_4 delivered the unsaturated esters that underwent intramolecular cycloaddition to give bicyclic isoxazolines 17-23, as single or largely predominant isomers. Indeed, compounds 17, 18, 21, and 23 were the only detectable products within the limit of 300 MHz ^1H and 75.4 MHz ^{13}C n.m.r. spectroscopy. In the cycloadditions leading to 19, 20, and 22 trace amounts of isomers 24-26 were also obtained (diastereoisomeric ratios: 19:24 = 21:1; 20:25 = 24:1; 22:26 = 28:1). To isoxazolidines 17-26 the 3,4-syn configuration (see scheme 1 for numbering) can be assigned

Scheme 1.



	R	R'	R''
1, 4, 10, 17	Me	H	$PhCH_2$
2, 5, 11, 18	Ph	H	$PhCH_2$
3, 6, 12, 19, 24	$PhCH_2OCH_2$	H	$PhCH_2$
7, 13, 20, 25	Me	Me	$PhCH_2$
8, 14, 21	Me	Ph	$PhCH_2$
9, 15, 22, 26	Ph	Me	$PhCH_2$
16, 23,	Ph	H	Me

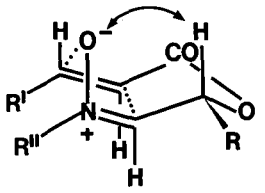
Table 1. Synthesis of nitrones 10-16 and isoxazolidines 17-23.

Compound	Yield %	m.p.°C (n_D^{25})	compound	yield %[a]	m.p.°C (n_D^{25})
10	55	127[b]	17	70	68-69
11	55	140[b]	18	74	75-76
12	60	106-107[b]	19	96	(1.5540)
13	57	(1.5570)[a,c]	20	50	99-100
14	55	108-111[b,c]	21	63	118-119
15	64	166-168[b,c]	22	65	119-120
16	57	(1.5522)[a]	23	50	(1.5490)

[a] Isolated yields after flash chromatography. [b] Isolated by filtration of reaction mixture. [c] As roughly 1:1 mixture of diastereoisomers.

since it is well known that intramolecular cycloaddition of nitrones affording fused five-membered rings gives exclusively 3,4-syn products.[1,13] N.O.e. experiments[14] carried out on cycloadducts 17, 20, and 25 are in agreement with this attribution and also allow to assign the anti relative stereochemistry at C-3 and C-3' to the same products . On the reasonable assumption that all these intramolecular cycloadditions proceed through the same stereochemical path, the 3,3'-anti configuration was assigned to 17-23, 25, and 26, and the 3,3'-syn one to 24. The isoxazolidines deriving from esters 7-9 possess an additional stereocenter at C-5. According to literature data[15] and to control experiments carried out on 8 and 9 with DBU in refluxing CCl_4, base promoted elimination of sulfinic acid from β-sulfonyl esters afford almost exclusively E-alkenes. Therefore 4,5-anti configuration was assigned to 20-22, as confirmed by n.O.e. experiments on 20. This technique was also used to elucidate the 4,5-syn stereochemistry of isomer 25 and, by extension, of related 26. These two very minor products likely derive from interception of small amounts of Z esters formed in the elimination reaction. That 25, a thick oil, has the indicated structure was also confirmed by independent synthesis of another isomer of 20, i.e. 3,3'-syn-3,4-syn-4,5-anti-27, m.p. 136-137°C, via an intermolecular reaction.[10,16]

The stereochemical outcome of the synthesis of 17-23 can be rationalized either by a transition structure such as 28 (Z-nitrone) or 29 (E-nitrone).[10] In both the 1,3-allyl-type interactions between the R group and the nitrogen substituents (oxygen for Z-nitrone, R" for E-nitrone) are minimized.



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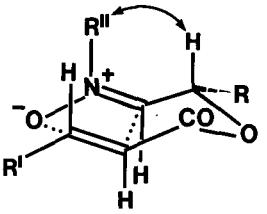

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The application of this method to the synthesis of enantio- and diastereoisomerically pure intermediates for the synthesis of carbapenem antibiotics from easily available chiral non racemic allylic alcohols is under active investigation in our laboratories.

References and Notes

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11) All new compounds gave satisfactory analytical and spectral data.
12) Nitrones 10-16 were obtained only as Z-isomer as demonstrated by n.O.e. data.
13) N.A. Le Bel, E.G. Banucci, J. Org. Chem., 36, 2440, 1971; for a recent example see: R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, Tetrahedron, 43, 4051, 1987.
14) N.O.e. experiments were used throughout this work since they were found much more reliable for stereochemical assignment than the use of coupling contant values. Observed J values for major isomers: J HC-3/HC-4 = 8.0-8.5 Hz; J HC-3/HC-3' = 0.7-5,3 Hz; J HC-4-HC-5 = 5.2-6.0 Hz. For 24: J HC-3/HC-3' = 3.0 Hz. For 25, 26, 27: J HC-4/HC-5 = 8.3, 8.1, 5.0 Hz, respectively).
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16) Compound 27 was prepared by cycloaddition of E-benzyl crotonate with N-benzylnitrone of lactaldehyde, and subsequent lactonization.[10] Three cycloadducts were obtained but only the minor 3,4-syn isomer gave the lactone 27. Its structure was established by n.O.e. as above.

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