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Ketene Silyl Acetal Chemistry; Diastereofacial Selectivity of 1,3-Addition of Chiral Nitrones

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The reaction of dimethyl-t-butylsiloxy-1-methoxyethene (**1a**) with the *N*-benzylnitrone (**3a**) produced the *syn*-1,3-adduct (**4a**) predominantly, while the reaction of dimethyl-t-butylsiloxy-1-t-butoxyethene (**1b**) with the *N*-diphenylmethylnitrone (**3d**) gave the *anti*-1,3-adduct (**4h**) predominantly; both adducts were readily transformed into the corresponding 3-benzoylamino-2,3-dideoxypentoses (**8a,b**) in fair yields.

In connection with a research programme involving the silyl group-transfer reaction of ketene silyl acetals and their use in natural product synthesis,[1] we have reported[2] the synthesis of *N*-benzoyl-L-daunosamine by the silyl group-transfer 1,3-addition of dimethyl-t-butylsiloxy-1-methoxyethene (**1a**) to the chiral nitrone (**2**). Although highly *anti*-stereoselective 1,3-addition of (**1a**) to (**2**) was observed in the previous investigation, the stereoselectivity of the 1,3-addition of ketene silyl acetals (**1a,b**) to other acyclic nitrones (**3a—d**) has not been investigated and is difficult to predict. We have now found that the bulkiness of the alkyl substituent (R) on the oxygen atom of (**1**), the alkyl substituent of the dioxolane ring, and the alkyl substituent (R′) on the nitrogen atom of the nitrones is significant in determining the diastereofacial selectivity of the reaction; we describe here a highly stereoselective synthesis of the *syn*- and *anti*-adducts (**4a**) and (**4h**) respectively by the addition of (**1a**) to (**3a**) and (**1b**) to (**3d**), respectively. These adducts are readily converted to the corresponding hitherto unknown 5-demethylaminosugars (**8a,b**).

The nitrones (**3a—d**), readily prepared[3] from 2,3-*O*-isopropylidene-D-glyceraldehyde, were treated with (**1a,b**)[4] at −78 °C for 1—15 h in the presence of a catalytic amount of zinc iodide in acetonitrile–methylene chloride (1 : 1). The results are given in Table 1.

It was found that *N*-benzyl- (**3a**) and *N*-(α-phenylethyl)-nitrones (**3b,c**) reacted with (**1a**) to give predominantly the *syn*-adducts (**4a,c,e**). In contrast, the *N*-diphenylmethyl-

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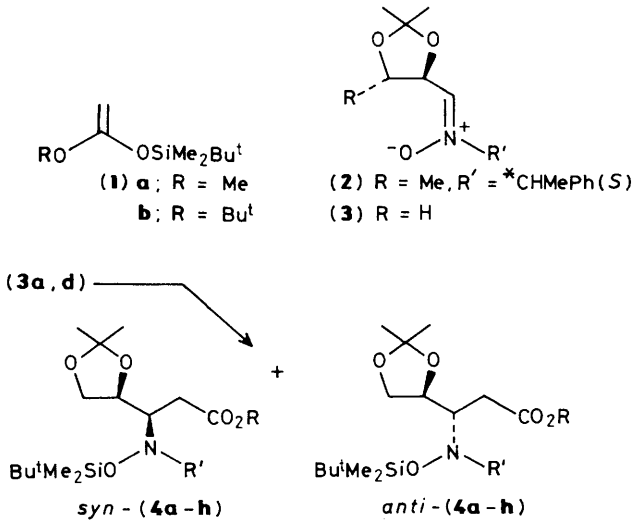
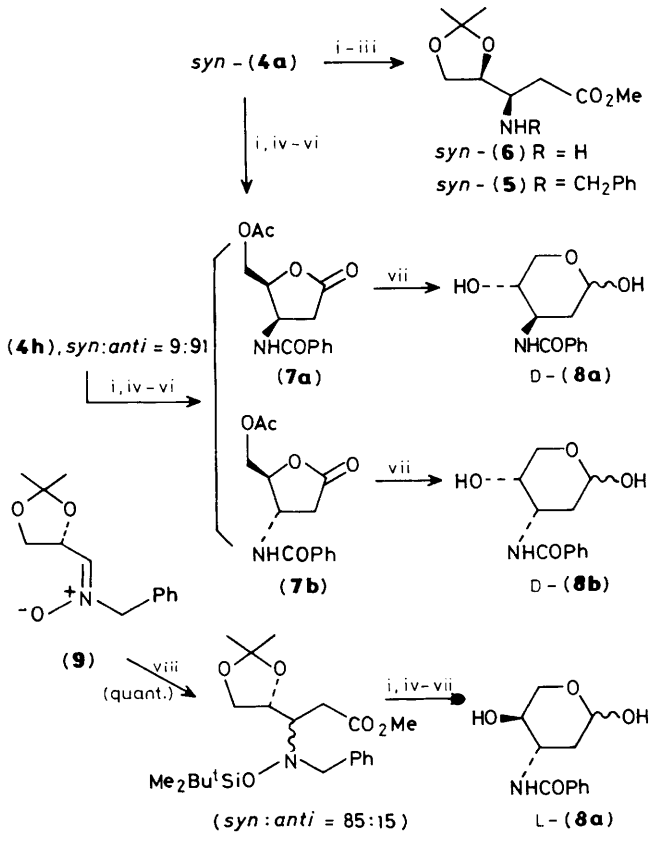
Table 1. Diastereoselectivity of the 1,3-addition of the ketene silyl acetals (**1a,b**) to the chiral nitrones (**3a—d**).

Entry	Nitrone R′		Acetal	Product	Yield[a] (%)	Ratio[b] *syn* : *anti*
1	CH_2Ph	(**3a**)	(**1a**)	(**4a**)	100	89 : 11
2	CH_2Ph	(**3a**)	(**1b**)	(**4b**)	73	53 : 47
3	*CH(Me)Ph (*R*)	(**3b**)	(**1a**)	(**4c**)	75	90 : 10
4	*CH(Me)Ph (*R*)	(**3b**)	(**1b**)	(**4d**)	54	44 : 56
5	*CH(Me)Ph (*S*)	(**3c**)	(**1a**)	(**4e**)	96	74 : 26
6	*CH(Me)Ph (*S*)	(**3c**)	(**1b**)	(**4f**)	74	63 : 37
7	$CH(Ph)_2$	(**3d**)	(**1a**)	(**4g**)	99	29 : 71
8	$CH(Ph)_2$	(**3d**)	(**1b**)	(**4h**)	86	9 : 91

[a] Yields are of chromatographed products. [b] The ratios were determined by h.p.l.c.



Reagents: (**1**), cat. ZnI_2, −78 °C, $MeCN\text{-}CH_2Cl_2$ (1 : 1).



Scheme 1. *Reagents*: i, H_2, 10% Pd–C, AcOH, 3 kg/cm², room temp., 3 days; ii, PhCHO, C_6H_6, reflux, 5 h; iii, $NaBH_4$, MeOH, reflux, 15 min; iv, PhCOCl, Et_3N, cat. 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2, room temp., 15 h; v, 80% AcOH, 40 °C, 1 h → reflux, 5 h; vi, Ac_2O, pyridine, room temp., 15 h; vii, Bu^i_2AlH–tetrahydrofuran, −78 °C, 1 h; viii, (**1a**), 0.1 equiv. ZnI_2, $MeCN\text{–}CH_2Cl_2$ (1 : 1), −78 °C, 1 h.

nitrone (**3d**) gave predominantly the *anti*-adducts (**4g,h**). The best result for the *syn*-adducts was obtained by the reaction of (**1a**) and (**3a**) (entry 1). With the *anti*-adducts, the reaction of (**1b**) and (**3d**) gave the best result (entry 8).

Assignment of the stereochemistry of (**4a**) was based on conversion to the *N*-benzylaminoester (**5**) on the basis of spectroscopic data and chemical correlation. Thus, the major diastereoisomer separated from (**4a**) (*syn* : *anti* 89 : 11) was hydrogenated to give the aminoester (**6**), whose condensation with benzaldehyde followed by reduction furnished *syn*-(**5**) {$[\alpha]_D^{14}$ −8.04° (*c* 1.29, EtOH), lit.[5] $[\alpha]_D$ −8.0° (*c* 1.3, EtOH)}. Similarly, the minor diastereoisomer was converted to *anti*-(**5**) {$[\alpha]_D^{16}$ +14.4° (*c* 0.222, EtOH), lit.[5] $[\alpha]_D$ +14.6° (*c* 1.0, EtOH)}. Stereochemical assignment for (**4h**) was based on conversion to the γ-lactones (**7a,b**). Thus, *syn*-(**6**) obtained from *syn*-(**4a**) was converted into the γ-lactone (**7a**) by benzoylation followed by lactonisation [63% yield based on *syn*-(**4a**), m.p. 148—149 °C]. On the other hand, a 9 : 91 mixture of diastereoisomeric esters (**4h**) provided a mixture of γ-lactones [(**7a**) : (**7b**) 9 : 91, 77% yield based on (**4h**); (**7b**): m.p. 124—126 °C]. Since (**7a**) was converted to *syn*-(**5**), the major diastereoisomer of (**4h**) has *anti* relative stereochemistry. Structures of other adducts (**4b—g**) were similarly determined.

Reduction of (**7a,b**) with Bu^i_2AlH gave 3-benzoylamino-2,3-dideoxy-D-xylose D-(**8a**) and D-ribose D-(**8b**) (demethyl analogue of *N*-benzoyl-L-daunosamine[6]) in 55 and 50% yields, respectively {D-(**8a**): m.p. 153—155 °C, $[\alpha]_D^{11}$ −10.0° (*c* 0.210, EtOH); D-(**8b**): m.p. 207—209 °C, $[\alpha]_D^{25}$ −37.5° (*c* 0.0826, pyridine)}. Similarly, L-(**8a**) (demethyl analogue of *N*-benzoyl-L-acosamine[6]) was obtained from the chiral nitrone (**9**) prepared from 2,3-*O*-isopropylidene-L-glyceraldehyde[7] {L-(**8a**): m.p. 154—156 °C, $[\alpha]_D^{11}$ +9.2° (*c* 0.283, EtOH), 46% overall yield from *syn*-(**4a**)} (Scheme 1).

While the details of the diastereofacial selectivity in the 1,3-addition of (**1**) to (**3**) remain unknown, a working model is

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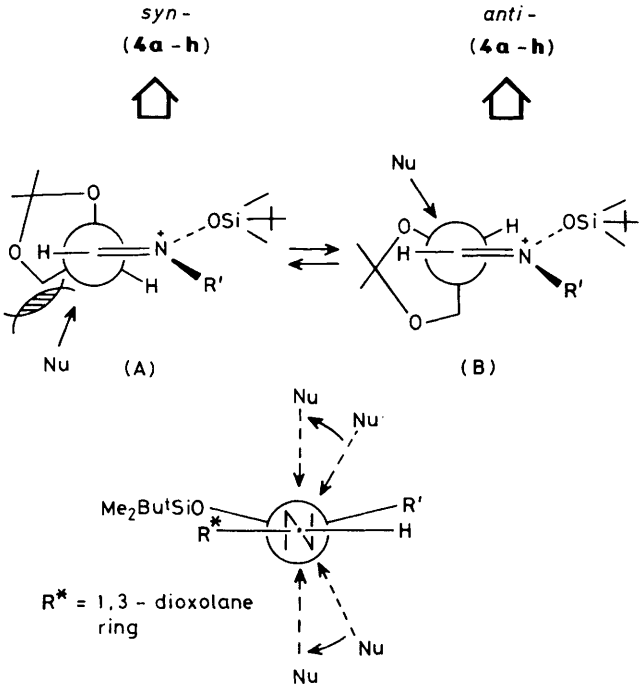

Scheme 2

given in Scheme 2. The selectivity can be explained by assuming that conformations (A) and (B) are the reactive conformations. With regard to the effect of the substituent R in (**1**), the more active conformer (A) (so-called modified Felkin–Anh model) is the preferred form for the smaller nucleophile (**1a**; R = Me), which gives the *syn*-adducts predominantly (entries 1, 3, and 5). In the case of the bulky nucleophile (**1b**; R = Bu^t), the nucleophile may be forced to attack the less reactive but less hindered conformer (B),[8] resulting in lower stereoselection (entries 2, 4, and 6). The *anti*-selectivity on the addition of (**1**) to the bulky nitrone (**3d**; R′ = $CHPh_2$) might be explained by the trajectory.[9] Thus, in the reaction of the nucleophile with the iminium cation, a trajectory is followed that brings the nucleophile at a distance from the bulky substituent on nitrogen [R′ = $CH(Ph)_2$], which emphasizes the steric interaction of conformer (A). Therefore, the matched pair for *anti*-selection *via* conformer (B) may arise from the reaction of the bulky (**1b**) and (**3d**) (entry 8).

Received, 9th December 1987; Com. 1777

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