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Diastereoselection in Intermolecular Nitrile Oxide Cycloaddition (NOC) Reactions: Confirmation of the “Anti-Periplanar Effect” through a Simple Synthesis of 2-Deoxy-D-ribose†

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We have initiated recently a program to examine the extent to which an allylic asymmetric center can control diastereoface selection in both inter- and intramolecular additions of nitrile oxides to olefins.¹ While the extent of such diastereoselection appears to be relatively small when there is little to distinguish the allylic groups on a steric or electronic basis (except in intramolecular cyclizations where the allylic center is within the nonisoxazoline ring being formed),² we now report that an allylic oxygen substituent can, on the other hand, serve as a useful control element for achieving diastereoface selectivity in [3 + 2] cycloaddition reactions. We illustrate this new concept in stereocontrol through a simple synthesis of 2-deoxy-D-ribose.

Optically active (+)-(*S*)-isopropylidene-3-butene-1,2-diol, prepared from isopropylidene D-glyceraldehyde by reaction with methylenetriphenylphosphorane,³ was reacted with (carboethoxy) formonitrile oxide⁴ to afford an 80:20 mixture of diastereomeric cycloadducts. These products were separated by gravity chromatography, and the major isomer **3** (Scheme I) was heated with sodium hydroxide to effect the following transformations: (a) ester hydrolysis; (b) decarboxylative ring opening of the isoxazoline to a β -hydroxy nitrile; (c) hydrolysis of nitrile to carboxylate. Acidification and diazomethane treatment then yielded **4** (74% overall yield from **3**).⁵ On converting this compound to its acetate and stirring with trifluoroacetic acid, the acetate of 2-deoxy-D-ribo-1,4-lactone(**5**) was formed (71%). The NMR of this compound was identical with that reported previously by Mukaiyama;⁶ $[\alpha]^{24}_D = -12^\circ$ (*c* 0.75, CH₂Cl₂); IR (thin film) 3450, 1785, 1740, 1240 cm⁻¹; ¹H NMR (CDCl₃) δ 2.07 (s, 3 H), 2.55 (dd, 1 H, *J* = 2.5, 18 Hz), 2.95 (dd, 1 H, *J* = 7, 18 Hz), 3.40–3.60 (m, 1 H), 3.85 (d, 2 H, *J* = 2.5 Hz), 4.40–4.60 (m, 1 H), 5.20–5.50 (m, 1 H); mass spectrum (15 eV), *m/e* 143, 84, 83, 53.

Trifluoroacetic acid treatment of **4** followed by bis(3-methyl-2-butyl)borane reduction of the intermediate lactone gave 2-deoxy-D-ribose(**7**).^{6,7} The synthetic material was identical with authentic 2-deoxy-D-ribose by the standard criteria of comparison. Alternatively, the lactone **6** was silylated to give the crystalline bis(*tert*-butyldimethylsilyl) derivative **8** (mp 76 °C). Reduction of this product with Dibal gave the disilyl derivative **9** in 92% yield $[[\alpha]^{24}_D = +23.6^\circ$ (after 8 h, *c* 0.096, MeOH)]. The 300-MHz ¹H NMR of **9** was identical with that

†Dedicated to the memory of Dr. Anthony Ames.

obtained for the product generated by silylating authentic 2-deoxy-D-ribose and chromatographically separating out the disilyl derivative.

Additionally, it was observed that acetonitrile oxide reacted with **2** to deliver after N–O bond hydrogenolysis the erythro β -hydroxy ketone as the major product (^1H NMR ratio 88:12).⁸ By reacting **2** with the nitrile oxide derived from the tetrahydropyranyl derivative of 2-nitroethanol⁴ and then effecting both cleavage of the THP group and hydrogenolysis of the isoxazoline by Raney nickel/ AlCl_3 /MeOH/ H_2O treatment, we generated nearly a single dihydroxy ketone (>94% by HPLC analysis).⁹ Sodium periodate cleavage of this α -hydroxy ketone followed by diazomethane treatment yielded **4** as the major isomer. These studies thus reveal that the sense of the addition of a nitrile oxide to **2** is independent of the nature of the nitrile oxide employed.

One can rationalize the production of 2-deoxy-D-ribose as the major product of the above scheme through the following two factors: (a) cycloaddition occurs preferentially through a transition state resembling conformer A;¹⁰ (b) addition of the nitrile oxide occurs anti to the C–O bond (the anti-periplanar effect).¹¹ This latter factor is due presumably to the minimization of secondary antibonding orbital interactions as predicted on a theoretical basis by the work of Houk et al. The explanation for such stereoselection is, of course, related closely to that offered by Anh in support of the Felkin type transition state, i.e., the addition of a nucleophile to a carbonyl compound (bearing an α -asymmetric center) anti to the large group (the one having the lowest energy $\sigma^*_{\text{C}_2-\text{X}}$ orbital).¹²

For comparison with current aldol technology, we list in Table I the erythro/threo ratios observed for the reactions of **1** with various carbon nucleophiles.

In conclusion, we suggest that the anti-directing effect of an allylic oxygen should be very useful in cycloadding chiral or achiral nitrile oxides to chiral olefinic units so as to produce β -hydroxy carbonyl compounds (aldol fragments) in a stereopredictable fashion. A variety

of molecular systems that can be constructed through applications of this stereochemical concept are now under study.¹⁵

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Scheme I.

Table I.

Aldol Stereoselection Observed in the Addition of Various Carbon Nucleophiles to **1**

nucleophile	erythro/threo, %	ref
93/7 (+acetate >90:10)	6
>95/<5	13
85/15	14
66/34	14
66/34	14
>95/<1	14