Stereoselectivity of Intramolecular Nitrile Oxide Cycloadditions to *Z* and *E* Chiral Alkenes[1]

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Intramolecular nitrile oxide cycloaddition (INOC) reactions on chiral alkenes were studied in order to evaluate the influence of the double bond configuration on the stereochemical outcome of the process. Oximes **11–16** were prepared, starting from aldehydes **1–4**, via Wittig reaction, isomerization of the double bond for the *E* derivatives, Swern oxidation, and reaction with hydroxylamine. Treatment of oximes **11–16** with sodium hypochlorite gave the nitrile oxides, which were trapped in situ by intramolecular cycloaddition to give the corresponding isoxazolines **17–22** as mixtures of diastereoisomers (Table I). From (*Z*)-alkenyl oximes C-4/C-5 syn products and from (*E*)-alkenyl oximes C-4/C-5 anti products were obtained, while the relative stereochemistry at C-5/C-5′ of the predominant isomers was found to be anti in all cases. The assignment of relative stereochemistry was based on ^{1}H and ^{13}C NMR spectroscopic evidence and on chemical correlations. With Houk's approach, MM2 calculations were performed to evaluate the relative energies of the transition structures. The CNO–ethylene fragment was frozen in the ab initio HCNO–ethylene transition structure model geometry, and the substituents were fully optimized by MM2. With the (*Z*)-alkenes, the "small" group of the allylic stereocenter prefers the inside position, the "medium" the anti, and the "large" the outside, with respect to the forming C–O bond, and the factors controlling the stereoselectivity are mainly steric. On the contrary, with the (*E*)-alkenes the "medium" group will be inside, the "large" anti, and the "small" outside. In the case of allyl ethers this model is mainly ruled by electronic factors. Quite good stereoselectivities were achieved in the INOC reactions using the allyl ethers derived from glyceraldehyde. A rationale for this result has been proposed.

The versatility of 4,5-dihydroisoxazoles (Δ^2-isoxazolines) for the stereocontrolled synthesis of various classes of highly functionalized molecules, such as β-hydroxy ketones and acids, γ-amino alcohols, sugars and amino sugars, and complex heterocycles is well recognized.[2] Δ^2-Isoxazolines are generally synthesized via the cycloaddition of nitrile oxides to olefins,[3] a reaction known to proceed stereospecifically.[4] Attempts to simultaneously control relative and absolute stereochemistry by the use of chiral nitrile oxides[5] have met with limited success so far. On the other hand, cycloadditions to chiral alkenes have been more successful and have received a great deal of attention.[2a-c,6]

Indeed, chiral allyl ethers derived from 3-buten-2-ol and 3-buten-1,2-diol were shown[7,8] to undergo nitrile oxide cycloadditions with diastereoselections ranging from 2:1 up to 9:1. While a variation of the alkoxy group seems to have only negligible effects,[7,8] an increase of the bulkiness of the alkyl group bound to the allylic stereocenter substantially enhances the stereoselectivity.[8] Non-heteroatom-substituted chiral alkenes[9] have generally been found to be less selective.[10,11]

Independently of the nature of the substituents, all these cycloadditions gave C-5/C-5′ anti[12] isomers as major products (see below for isoxazoline numbering). In order to rationalize the results of the cycloaddition on chiral allyl ethers Kozikowski proposed a Felkin-type transition structure where the nitrile oxide attacks the olefin in an anti fashion with respect to the alkoxy group. Houk and Jäger, on the basis of theoretical studies, suggested[8] that the attack occurs anti to the alkyl group, while the allylic ether adopts an inside position ("inside alkoxy effect"). In a recent extension of this model to chiral alkenes[9] Houk proposed that the major product of a nitrile oxide cycloaddition arises from a transition structure featuring the "large" group in the anti and the "medium" group in the inside position, respectively.

Despite this impressive amount of research, the influence of double bond configuration on the stereochemical outcome of the cycloaddition reaction has been studied only to a very limited extent,[2b,7] probably because of the poor regioselectivity observed for the cycloaddition to unsymmetrical disubstituted alkenes. As reported in a preliminary account of this work[1] we thought that an intramolecular nitrile oxide cycloaddition (INOC) reaction,[13] forced to occur in a regiochemical defined fashion, would allow the evaluation of the effect of alkene geometry on the stereochemistry of the process. In this paper we wish to report our experimental results in this area, together with theoretical investigations (MM2) of the cycloaddition transition structures, in order to shed new light on the stereoselectivity of the intramolecular nitrile oxide cycloadditions to chiral alkenes.

(1) A preliminary report of this work has been published: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Chem. Soc., Chem. Commun.* **1987**, 529.

(2) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schroter, D. *Lect. Heterocycl. Chem.* **1986**, *9*, 79. (c) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519. (d) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

(3) Grundmann, C.; Grünanger, P. *The Nitrile Oxides*; Springer Verlag: Berlin, 1971. Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, pp 291–392.

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(6) For an alternative approach to the synthesis of enantio- and diastereoisomerically pure Δ^2-isoxazolines, see: Cinquini, M.; Cozzi, F.; Gilardi, A. *J. Chem. Soc., Chem. Commun.* **1984**, 551. Annunziata, R.; Cinquini, M.; Cozzi, F.; Gilardi, A.; Restelli, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2289.

(7) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762.

(8) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(9) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

(10) For an example of a nitrile oxide cycloaddition on a silicon-substituted chiral alkene, see: Curran, D. P.; Kim, B. H. *Synthesis* **1986**, 312.

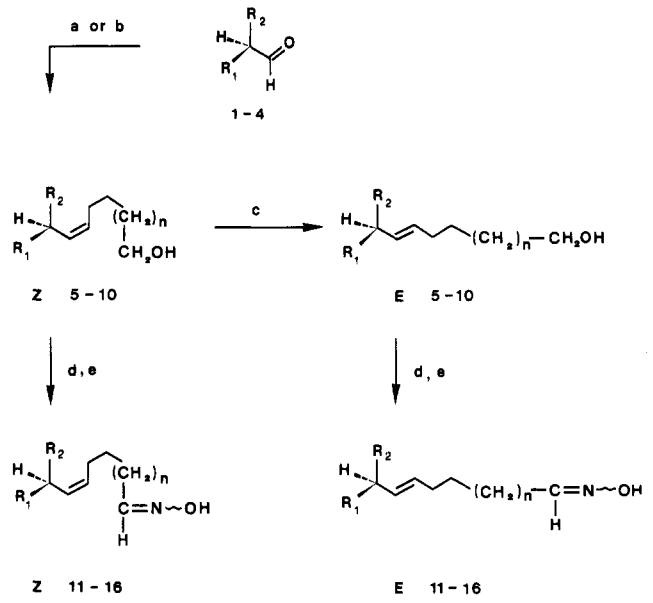
(11) For a cycloaddition on a nitrogen-substituted olefin that occurs with good stereoselectivity, see: Kozikowski, A. P.; Chen, X.-M. *Tetrahedron Lett.* **1985**, *26*, 4047.

(12) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(13) INOC reactions of (*E*)- and (*Z*)-alkenes featuring an allylic stereocenter within the carbon chain connecting dipole and dipolarophile have been reported: Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081.

0022-3263/87/1952-4674$01.50/0

Scheme I[a]



1, 5, 11: $R_1 = OCH_2Ph$, $R_2 = Me$; $n = 2$
2, 6, 12: $R_2 = OCH_2Ph$, $R_1 = CH_2OCH_2Ph$; $n = 2$
3, 7, 13: $R_2,R_1 = OC(CH_2)_5OCH_2$; $n = 2$
4, 8, 14: $R_1 = i$-Pr, $R_2 = Me$; $n = 2$
9, 15: $R_1 = OCH_2Ph$, $R_2 = Me$; $n = 1$
10, 16: $R_2,R_1 = OC(CH_2)_5OCH_2$, $n = 1$

[a] Reagents: (a) $Ph_3P^+(CH_2)_5CH_2OH,Br^-$, *n*-BuLi, THF; (b) $Ph_3P^+(CH_2)_4CH_2OH,Br^-$, *n*-BuLi, THF; (c) PhSH, AIBN, benzene; (d) DMSO, $(COCl)_2$, CH_2Cl_2; (e) NH_2OH·HCl, Py.

Table I. Synthesis of 4,5-Dihydroisoxazoles 17–22 from Oximes 11–16

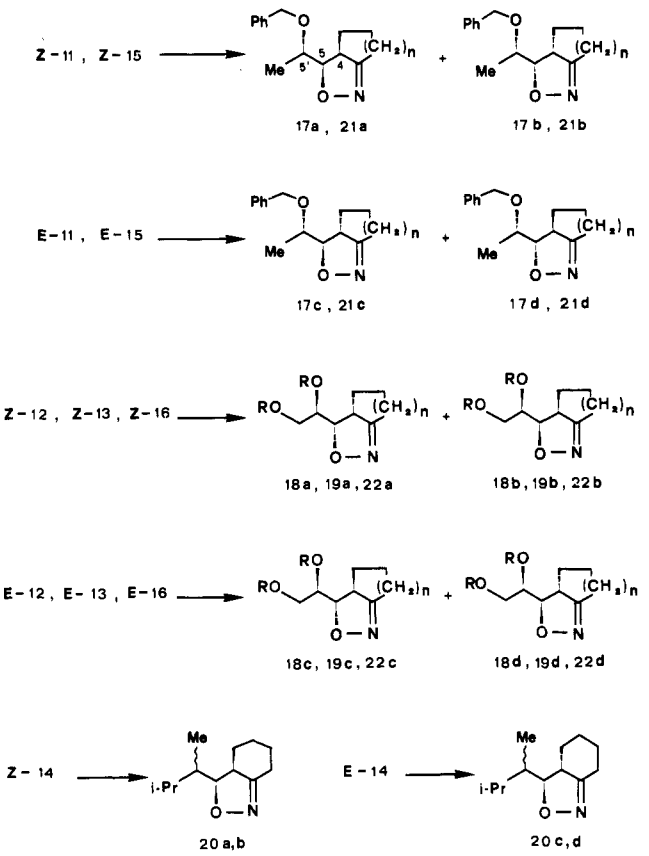
oximes	products	yield, %	diastereoisomeric ratios[a]
(*Z*)-11	**17a,b**	62	80:20[b]
(*E*)-11	**17c,d**	70	60:40
(*Z*)-12	**18a,b**	72	83:17[b]
(*E*)-12	**18c,d**	87	77:23
(*Z*)-13	**19a,b**	63	86:14[b]
(*E*)-13	**19c,d**	84	86:14[b]
(*Z*)-14	**20a,b**	57	66:34
(*E*)-14	**20c,d**	56	66:34
(*Z*)-15	**21a,b**	57	75:25[b]
(*E*)-15	**21c,d**	26	58:42
(*Z*)-16	**22a,b**	58	81:19[b]
(*E*)-16	**22c,d**	43	78:22[b]

[a] As determined by ^1H and ^{13}C NMR spectroscopy. [b] Isomeric products can be separated by flash chromatography.

Results and Discussion

The synthetic route to the desired cycloadduct precursors is reported in Scheme I.[1] *Z* alcohols **6–10** were prepared from (*S*)-*O*-benzyllactaldehyde (**1**), (*R*)-*O*,*O*-dibenzylglyceraldehyde (**2**), (*R*)-*O*,*O*-cyclohexylideneglyceraldehyde (**3**), and (*R*,*S*)-2,3-dimethylbutanal (**4**) by Wittig reaction with the corresponding (ω-(hydroxyalkyl)triphenylphosphonium bromide.[14] From (*Z*)-**5–10** the *E* isomers were obtained by reaction with thiophenol in refluxing benzene in the presence of azoisobutyronitrile (AIBN). Conversion of the alcohols to the oximes **11–16** was readily achieved by Swern oxidation and subsequent reaction with hydroxylamine hydrochloride in pyridine. Treatment of a dichloromethane solution of **11–16** with sodium hypochlorite gave the nitrile oxides which were

Scheme II



17: $n = 2$
18: R = CH_2Ph; $n = 2$
19: R = $C(CH_2)_5$; $n = 2$
21: $n = 1$
22: R = $C(CH_2)_5$; $n = 1$

trapped in situ by intramolecular cycloaddition to give the corresponding isoxazolines **17–22** as mixtures of diastereoisomers (Scheme II).

Chemical yields and diastereoisomeric ratios are collected in Table I. In several cases the products could be separated by flash chromatography, thus affording isomerically pure compounds. In the synthesis of cycloadducts yields were generally good for cyclohexane forming reactions (**17–20**, $n = 2$), while slightly decreased for the cyclopentane forming ones (**21–22**, $n = 1$), probably as the result of the difficulty for dipole and dipolarophile to reach the geometry required by the transition state.[8,15,16] Isomer ratios were determined by high-field ^{13}C and ^1H NMR spectroscopy.

The cycloaddition reaction retains the stereochemistry of the alkene:[3,4] thus from (*Z*)-alkenyl oximes C-4/C-5 syn and from (*E*)-alkenyl oximes C-4/C-5 anti products were obtained, respectively. The assignment of the relative stereochemistry at C-5/C-5′ was based on NMR spectroscopic evidence and chemical correlations.

The relevant NMR data for compounds **17–22** are collected in Table II. Comparison with the literature data[7,17,18] for related substrates was possible only for **17**,

(14) Schlosser, M.; Trong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311.

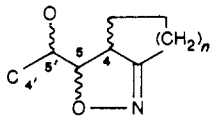
(15) In order to have a homogeneous set of data no attempt to improve chemical yields of cycloadditions of (*E*)-**15** and (*E*)-**16** by changing reaction conditions was made.

(16) INOC reactions leading to isoxazolines with the same structure as **21** and **22** but featuring a sulfur atom instead of a CH_2 group (Scheme II) from the corresponding nitro sulfides occurred only upon overnight refluxing in benzene. Annunziata, R.; Cinquini, M.; Cozzi, F.; Dondio, G.; Raimondi, L. *Tetrahedron* **1987**, *43*, 2369.

(17) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199.

(18) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217.

Table II. Relevant ^{13}C and ^{1}H NMR Data of 4,5-Dihydroisoxazoles 17–22



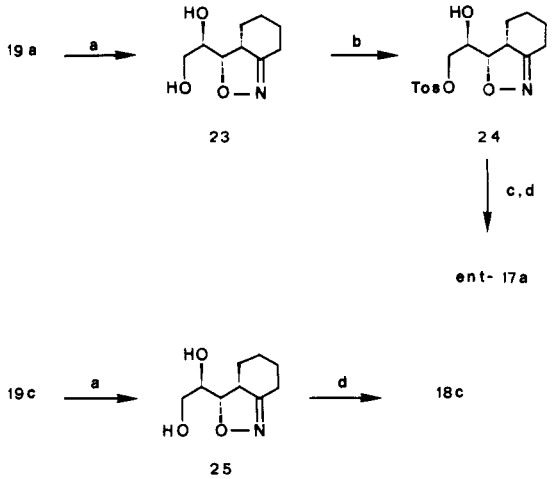
compd	^{13}C NMR, δ				^{1}H NMR, δ		J, Hz	
	C-4	C-5	C-5′	C-4′	HC-5	HC-5′	HC-4/HC-5	HC-5/HC-5′
17a	50.6	83.5	73.6	16.9	4.34	3.70	10.8	8.4
17b	50.1	84.7	73.9	17.3	4.40	3.67	10.3	6.0
17c	49.6	89.1	74.9	16.9	4.02	3.77	8.7	4.8
17d	49.5	88.1	74.8	15.0	4.16	3.74	9.1	6.0
18a	50.7	79.4	77.2	70.5	4.61	3.76	10.0	8.5
18b	49.7	80.5	77.5	70.2	4.66	3.66	10.0	3.8
18c	49.7	85.6	78.0	70.1	4.25	3.85	8.5	4.8
18d	49.7	85.8	77.9	70.1	4.25	3.73	9.8	4.9
19a	50.7	81.6	72.8	67.7	4.37	4.10	10.4	8.6
19b	49.3	80.6	74.9	65.7	4.44	4.14	11.0	5.0
19c	52.1	85.7	76.5	67.0	3.96	4.06	8.0	8.0
19d	49.9	85.1	75.3	64.9	4.18	4.30	9.0	5.5
20a	51.0	84.0	38.4	30.2	4.28	1.63	10.0	7.7
20b	51.5	84.2	37.5	27.7	4.11	1.75	10.0	10.0
20c	51.4	88.1	42.9	28.4	3.96		9.3	8.8
20d	51.9	88.8	43.1	29.4	4.00		9.5	6.6
21a	57.5	83.9	73.3	16.4	4.36	3.60	11.0	8.0
21b	56.7	84.9	73.8	16.4	4.45	3.56	10.7	6.6
21c	55.8	91.4	73.7	17.9	4.16	3.88	11.3	4.5
21d	56.8	91.1	74.9	16.6	4.26	3.82	11.9	6.9
22a	57.8	82.3	71.7	67.5	4.38	4.01	10.0	10.0
22b	56.7	81.1	75.0	65.3	4.45	4.07	10.0	4.5
22c	58.5	87.7	76.1	67.2	4.13	4.28	10.0	8.0
22d	56.2	87.3	75.0	65.2	4.30	4.41	11.0	5.8

19, 21, and **22**. For the products derived from (*R*)-*O*,*O*-cyclohexylideneglyceraldehyde (**4**) (i.e., **19** and **22**) on passing from major (**19a,c, 22a,c**) to minor (**19b,d, 22b,d**) isomers, a decrease of the chemical shift values of C-4, C-5, and C-4′ and an increase of the chemical shift values of *H*C-5 and *H*C-5′ were constantly observed. In addition a common trend was found for the HC-5/HC-5′ coupling constants, which were always larger for the major than for the minor products.[7,16–18] On this basis the C-5/C-5′ anti relative configuration was firmly assigned to predominant isomers of the INOC reaction of (*Z*)- and (*E*)-alkenyl oximes **13** and **16**. For the products derived from (*S*)-*O*-benzyllactaldehyde (**1**) (i.e., **17** and **21**) comparison with the literature[7] was possible only for ^{1}H NMR data. In particular the only reliable[19] feature was found to be the trend of the chemical shift value for HC-5 that always increases on passing from anti (major) **17a,c, 21a,c** to syn (minor) **17b,d, 21b,d** isomers. The attribution of the stereochemistry to (*R*)-*O*,*O*-dibenzylglyceraldehyde derived isoxazolines **18** was not possible on the basis of NMR spectroscopy. The reasonable assumption that also in this case the INOC reactions of both (*Z*) and (*E*)-**12** are anti selective was confirmed by chemical correlation of **19c** with **18c** (Scheme III). As a further proof of the anti diastereoselectivity shared by these cycloadditions, compound **19a** was converted into the enantiomer of **17a** by the reaction sequence outlined in Scheme III.

Finally the stereoselectivity of an INOC reaction dictated by a non-heteroatom-substituted allylic stereocenter was investigated. Both (*Z*)- and (*E*)-alkenyl oximes **14** gave a 2:1 mixture of cycloadducts. The relative configuration at C-5/C-5′ of the prevailing isomers **20a** and **20c** was tentatively assigned by extension to these cycloadditions of the anti diastereoselectivity observed by Houk in intermolecular reactions of *p*-nitrobenzonitrile oxide with

(19) The HC-5/HC-5′ coupling values proved to be misleading (see Table II and ref. 16) and led us to incorrect attribution of the relative stereochemistry to **17c,d**.[1]

Scheme III[a]



[a] Reagents: (a) AcOH, H_2O; (b) TosCl, Et_3N, CH_2Cl_2; (c) $NaBH_4$, DMSO; (d) NaH, catalytic $Bu_4N^+I^-$, $PhCH_2Br$, THF.

3,4-dimethyl-1-pentene and related alkenes.[9] Molecular mechanics calculations of the transition structures of these reactions supported this assignment (see the following section).

In the case of chiral allyl ethers intramolecular cycloadditions of (*Z*)-alkenyl oximes occur with a better diastereoselection than that observed for the corresponding *E* derivatives. This difference is particularly noticeable in the case of lactaldehyde derived products (Table I), the cycloaddition of (*Z*)-**11** and (*Z*)-**15** giving diastereoisomeric ratios which are even higher than those observed in comparable intermolecular cases.[7,8] The stereoselectivity of the INOC reaction of glyceraldehyde derived oximes is less influenced by the double bond geometry and is very similar to that reported in intermolecular reactions.[7,8]

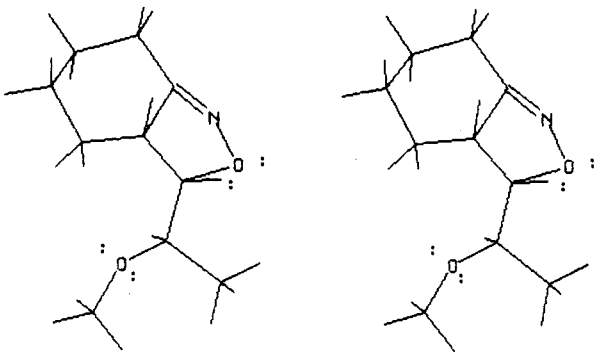
Transition Structure Models. As the sense and the extent of diastereoselection of the INOC reactions of

Table III. Relative Energies of the Transition Structures of the Intramolecular Nitrile Oxide Cycloaddition

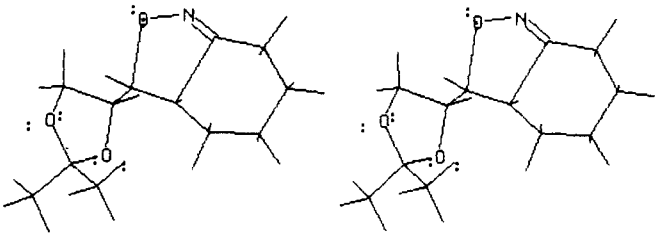
						relative energies, kcal/mol								
						anti			syn			anti/syn		
entry	olefin geometry	R	R′	L	M	A	B	C	A′	B′	C′	calcd[a]	exptl	products
1	*Z*	H	$(CH_2)_4$	Me	OMe	0.0[b]	0.9	4.1	1.2	1.4	4.7	84/16	80/20	**17a/17b**
2	*Z*	H	$(CH_2)_4$	CH_2O	$OCMe_2$	0.0[c]	1.9	3.2	0.2	1.9	4.7	58/42	86/14	**19a/19b**
3	*Z*	H	$(CH_2)_4$	*i*-Pr	Me	0.0[d]	1.3	3.6	0.2	1.8	3.8	60/40	66/34	**20a/20b**
4	*E*	$(CH_2)_4$	H	*i*-Pr	Me	0.5	0.0[e]	3.0	0.1	2.1	1.9	60/40	66/34	**20c/20d**
5	*E*	$(CH_2)_4$	H	Me	OMe	1.2	0.0[f]	2.3	0.0	0.6	1.3		60/40	**17c/17d**
6	*E*	$(CH_2)_4$	H	CH_2O	$OCMe_2$	0.7	0.3[g]	1.3	0.0	0.2	1.1		86/14	**19c/19d**

[a] Stereoselectivity predictions come from calculations of a Boltzmann distribution including all six low-energy conformations. [b] Stereoview 1, Chart I. [c] Stereoview 2, Chart I. [d] Stereoview 3, Chart I. [e] Stereoview 4, Chart I. [f] Stereoview 5, Chart I. [g] Stereoview 6, Chart I.

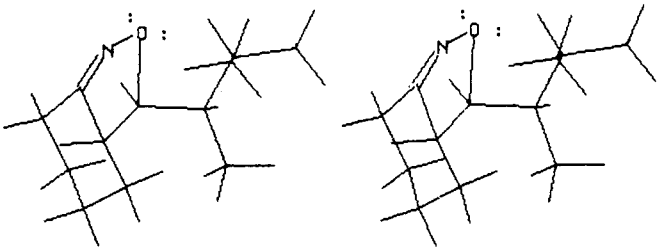
Chart I



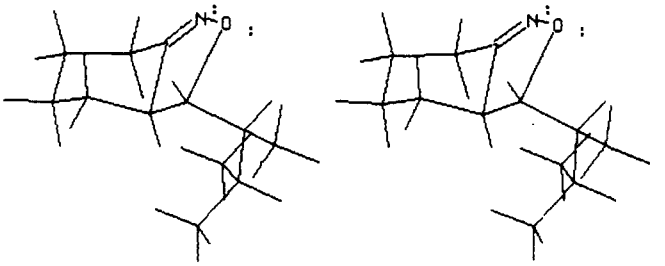
stereoview 1 (Table III, entry 1, conformer A)



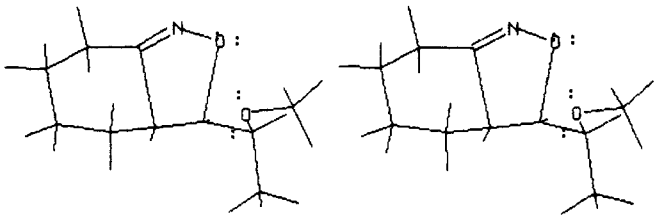
stereoview 2 (Table III, entry 2, conformer A)



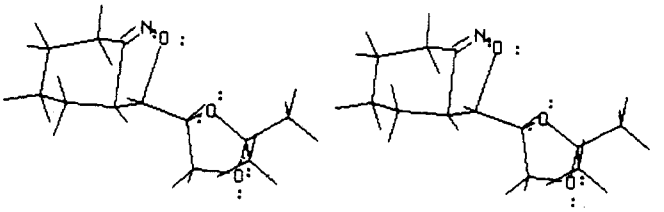
stereoview 3 (Table III, entry 3, conformer A)



stereoview 4 (Table III, entry 4, conformer B)



stereoview 5 (Table III, entry 5, conformer B)

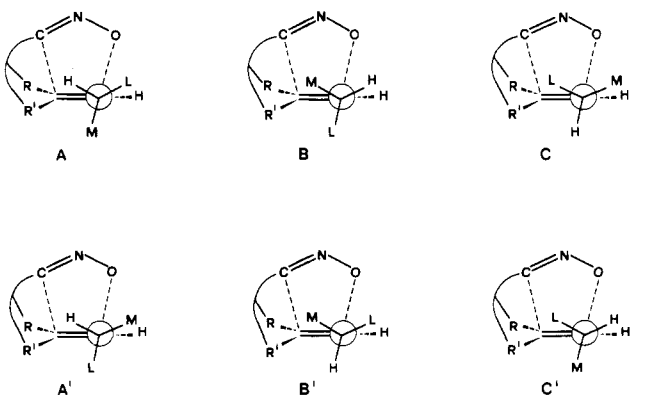


stereoview 6 (Table III, entry 6, conformer B)

(*E*)-alkenyl nitrile oxides closely parallel those of the intermolecular reactions (monosubstituted alkenes), it is reasonable to expect that the same model, featuring the alkoxy or medium group of the allylic stereocenter in the inside and the alkyl or large group in the anti position, is operating.[8,9]

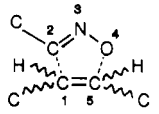
On the contrary no model has yet been proposed in the case of (*Z*)-alkenes, where the presence of substituents cis to the allylic carbon is anticipated to disfavor the "inside alkoxy conformer",[8,20] and it is reasonable to expect a transition structure with the allylic hydrogen in the inside position in order to relieve steric crowding.[1]

Scheme IV



(20) (a) McDougal, P. G.; Rico, J. G.; Van Derveer, D. *J. Org. Chem.* **1986**, *51*, 4492 and references therein. (b) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

Table IV. Input Values for MM2 Calculations



Bond Lengths, Å			
1-2	2.26	1-5	1.35
2-3	1.16	H-5	1.07
3-4	1.32	H-1	1.08
4-5	2.18		
Dihedral Angles, deg			
H-5-1-H (*Z*)	0	H-1-5-C (*E*)	0
C-5-1-C (*Z*)	0	1-2-3-4	0
H-5-1-C (*E*)	0	C-2-3-4	180
Bond Angles, deg			
H-5-1	121	2-1-5	99
C-5-1	121	2-1-C	93
4-5-1	106	2-1-H	93
4-5-H	87	1-2-C	106
4-5-C	87	3-2-1	99
H-5-C	116	3-2-C	155
C-1-5	120	4-3-2	139
H-1-5	120	3-4-5	97
H-1-C	116		

With Houk's approach,[21] MM2 calculations[22] were performed to evaluate the relative energies of the transition structures of the intramolecular nitrile oxide cycloadditions (Scheme IV, Table III, Chart I). The CNO-ethylene fragment was frozen in the ab initio HCNO-ethylene transition structure model geometry,[8,23] and the substituents were fully optimized by MM2 (Table IV).

Our results, in agreement with Houk's postulate of "staggering in transition structures",[24] show that conformations of substituents in the transition structures are quite different from those in the reactants. Alkenes have one allylic bond eclipsed with the double bond in the ground state, while our transition structure conformations, although relatively early in terms in bond breaking and bond making, are more product-like, and allylic substituents are staggered with respect to the forming bonds.

Indeed only the six staggered transition structure conformations shown in Scheme IV (see also Chart I) were found as stable minima in our MM2 calculations.

As can be seen from the reported data (Table III), by the use of a Boltzmann distribution including all six low-energy conformations there is good agreement between experiments and calculations in the case of (*Z*)-alkenes (entries 1-3).

With a *Z* double bond, the most crowded inside position is preferentially occupied by the small group (H) (A and A′, Scheme IV), more than the medium (OMe, entry 1; $OCMe_2$, entry 2; Me, entry 3) (B and B′) and more than the large (Me, entry 1; CH_2O, entry 2; *i*-Pr, entry 3) (C and C′), both for the anti-producing and for the syn-producing transition structures.

This trend is in good agreement with the relative steric bulkiness of the substituents, as can be inferred from their *A* values:[25] *i*-Pr = 2.15 kcal/mol; CH_2OR, Me = 1.7 kcal/mol; OR, OCH_3 = 0.6 kcal/mol. Both conformations A and A′ have H in the inside position, but A is preferred to A′ because of the cis-CH_2/medium (anti) interaction which is smaller than the cis-CH_2/large (anti) interaction suffered by A′. Therefore in this model the inside position is more crowded than the outside, so that the small group will stay inside, the medium anti, and the large outside. Different from the one proposed for monosubstituted[8,9] and disubstituted (*E*)-alkenes (see below), this model is mainly governed by steric factors which overwhelm electronic effects, such as the tendency of the OR substituent for the inside or outside position (see below).[8,24]

With the less sterically requiring *E* double bond (Table III, entries 4-6), the trend, for the transition structures leading to both the syn and the anti isomers, follows the preference of the large substituent for the anti position (B and A′, Scheme IV) more than the outside (A and B′) and more than the inside (C and C′). The experimental differences in energy of activation are well simulated by a Boltzmann distribution of all six MM2-calculated low-energy conformations only in the non-oxygen-substituted case (Table III, entry 4). Both conformations B and A′ (entry 4) have the large group (*i*-Pr) anti to the forming C–O bond. Conformation B, with the medium-sized group (Me) inside, is favored over A′, having Me outside, because of the repulsions between the outside Me group and the nitrile oxide oxygen.[9] Indeed the dihedral angle O—C–C–H is 44° in B, while O—C–C–Me is 66° in A′, thus pushing the *i*-Pr toward the cis-hydrogen substituent.[9]

On the contrary, for entries 5 and 6 (oxygen-substituted cases) calculations do not correctly predict the experimental results. In electrophilic addition to double bonds, the most electropositive allylic group should stay anti in order to maximize the overlap of the olefin π orbital with the highest energy σ orbital belonging to the substituent that most efficently participates in hyperconjugative interactions. As a consequence a more reactive MO will be created. The outside position is second best, and the donor avoids the inside position where the σ overlap with the olefin π orbital is negligible.[8,24]

The electronegative OR group should prefer the inside or outside position in order to minimize the overlap of the σ_{C-O}* with the olefin π orbital,[8,24,26] so that electron withdrawal from the already electron-deficient transition state is avoided.

Both the anti-producing and the syn-producing low-energy conformations B and A′ (entries 5,6) fulfill these requirements, but our MM2 calculations fail to predict the inside position rather than the outside as the best location for OR. Houk's ab initio model calculations indicate that an allylic alkoxy group prefers the inside conformation.[8]

In order to reproduce this result with the MM2 model, an electronic parameter biased to the inside effect should be introduced; i.e., the torsional parameter for the dihedral angle C=C—C—O should be changed.[21,23] Therefore, while the (*Z*)-alkene model seems to be controlled by steric factors, the model for (*E*)-allyl ethers is mainly governed by electronic effects.

The higher selectivity shown by the (*E*)-allyl ether derived from glyceraldehyde compared to the one derived from lactaldehyde (86:14 vs. 60:40, entries 5,6, Table III) could be interpreted either in terms of the stronger donor

(21) We are deeply indebted to Professor K. N. Houk for helpful discussions, sharing of unpublished material, and valuable suggestions.

(22) Calculations were performed with Professor Still's molecular mechanics program MODEL, an improved and graphical version of Allinger's MM2. We thank Professor Still for the gift of his MODEL program and helpful advice on its operation.

(23) Brown, F. K., Ph.D. Thesis, University of Pittsburgh, 1986. In this thesis the fulminic acid–ethylene transition structure was reinvestigated at the 3-21G basis set level with complete optimization of all variables by gradient techniques. Bond lenghts, bond angles, and dihedral angles are reported in the experimental section (Table IV).

(24) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108.

(25) $A = \Delta G = RT \ln K$ for the axial–equatorial equilibrium in the cyclohexane derivatives, see: Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(26) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647.

ability of the CH_2OR group, compared to Me, due to lone pair participation of the homoallylic oxygen,[27] or with a direct through-space interaction of the homoallylic oxygen lone pair with the olefin π bond.[28] The synergic effect of the allylic C–O bond oriented inside, near the plane of the π orbital, and of the CH_2OR group located in the anti position creates a more reactive molecular orbital and is therefore responsible for the high selectivity observed. Allyl ethers with a similar substitution pattern were recently reported by Danishefsky and co-workers[29] to react with electrophiles with very high diastereofacial selectivity through a reactive conformation similar to the one proposed here.

Conclusions

In summary, on the basis of our experiments and calculations we have proposed a new model for INOC reactions with (*Z*)-alkenes. In this model the small group will be inside, the medium anti, and the large outside, and the factors controlling the stereoselectivity are mainly steric.

On the contrary, in the model for (*E*)-alkenes, the medium group will be inside, the large anti, and the small outside. In the case of allyl ethers this model is mainly due to electronic factors. Our experiments have also shown that quite good stereoselectivity can be achieved in the INOC reactions using the allyl ethers derived from glyceraldehyde.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 247 instrument. ^1H and ^{13}C NMR spectra were obtained on a Varian EM-390 or a Varian XL-300 spectrometer with $CDCl_3$ as solvent. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions employing dry solvents were run under argon. THF was distilled from LAH, benzene from Na, DMSO, and CH_2Cl_2 from CaH_2; dry solvents were stored over molecular sieves under argon. Aldehydes (*S*)-**1**,[30] (*R*)-**2**,[31] (*R*)-**3**,[32] and (*R,S*)-**4**[33] were prepared as described.

General Procedure for the Synthesis of *Z* Alcohols 5–10. To a stirred suspension of (ω-hydroxyalkyl)triphenylphosphonium bromide[14] (2 mmol) in THF (20 mL), cooled at 0 °C, was added *n*-BuLi (ca. 1.3 N solution in hexane, 4 mmol) dropwise and the reaction mixture allowed to warm up to room temperature. To the red solution, cooled at 0 °C, a solution of the aldehyde (2 mmol) in THF (5 mL) was added dropwise and the mixture stirred at room temperature for 45 min. Saturated NH_4Cl was then added to quench the reaction; the usual workup afforded the crude alcohol, which was purified by flash chromatography.

(*S*)-8-(Benzyloxy)-(*Z*)-6-nonen-1-ol (5) was obtained in 84% yield (≥10:1 *Z*/*E* ratio) with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 77.34; H, 9.80. $C_{16}H_{24}O_2$ requires: C, 77.36; H, 9.76. IR (thin film) 3400, 3040, 2930, 2860, 1660, 1455, 1070, 740 cm^{-1}; ^1H NMR δ 7.27–7.33 (m, 5 H, Ar protons), 5.50–5.60 (m, 1 H, =C*H*CH_2, *J* (HC=CH) = 10.8 Hz), 5.33–5.40 (m, 1 H, CHC*H*=), 4.47 (AB system, 2 H, PhCH_2O), 4.23–4.33 (m, 1 H, CH–O), 3.63 (t, 2 H, *J* = 7.9 Hz, CH_2OH), 1.93–2.13 (m, 2 H, CH_2C=), 1.27–1.66 (m, 7 H, 3 CH_2 and OH), 1.27 (d, 3 H, *J* = 7.8 Hz, CH_3); $[\alpha]^{22}_D$ −1.01° (*c* 2.08, $CHCl_3$).

(*R*)-8,9-Bis(benzyloxy)-(*Z*)-6-nonen-1-ol (6) was obtained in 73% yield (≥10:1 *Z*/*E* ratio) with a 7:3 diethyl ether/hexanes mixture as eluant. Found: C, 77.96; H, 8.50. $C_{23}H_{30}O_3$ requires: C, 77.91; H, 8.55. IR (thin film) 3420, 3040, 2940, 2860, 1660, 1455, 1080, 740 cm^{-1}; ^1H NMR δ 7.20–7.40 (m, 10 H, Ar protons), 5.60–5.73 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 10.7 Hz), 5.33–5.43 (m, 1 H, CHC*H*=), 4.37–4.67 (m, 5 H, PhCH_2O and CH–O), 3.47–3.67 (m, 4 H, CH_2OH and CHCH_2O), 1.93–2.07 (m, 2 H CH_2C=), 1.20–1.67 (m, 7 H, 3CH_2 and OH); $[\alpha]^{22}_D$ +17.04° (*c* 1.15, $CHCl_3$).

(*R*)-8,9-(Cyclohexylidenedioxy)-(*Z*)-6-nonen-1-ol (7) was obtained in 78% yield (≥10:1 *Z*/*E* ratio) with a 6:4 diethyl ether/hexanes mixture as eluant. Found: C, 70.77; H, 10.28. $C_{15}H_{26}O_3$ requires: C, 70.81; H, 10.32. IR (thin film) 3400, 2960, 2860, 1665, 1455, 1075, 745 cm^{-1}; ^1H NMR δ 5.53–5.77 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 11.0 Hz), 5.33–5.46 (m, 1 H, CHC*H*=), 4.77–4.88 (m, 1 H, CH–O), 4.05 (dd, 1 H, *J* = 8.0, 6.0 Hz, one H of CHCH_2O), 3.63 (t, 2 H, *J* = 6.8 Hz, CH_2OH), 3.50 (t, 1 H, *J* = 8.0 Hz, one H of CHCH_2O), 2.00–2.20 (m, 2 H, CH_2C=), 1.27–1.68 (m, 17 H, 3 CH_2, C_6H_{10}, OH); $[\alpha]^{22}_D$ −7.54° (*c* 0.4 in $CHCl_3$).

(*R,S*)-8,9-Dimethyl-(*Z*)-6-decen-1-ol (8) was obtained in 50% yield (only *Z* isomer detected) with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 78.29; H, 13.06. $C_{12}H_{24}O$ requires: C, 78.17; H, 13.15. IR (thin film) 3400, 2960, 2850, 1660, 1455, 1380, 1170, 745 cm^{-1}; ^1H NMR δ 5.13–5.33 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 11.7 Hz), 5.12–5.27 (m, 1 H, CHC*H*=), 3.63 (t, 2 H, *J* = 7.1 Hz, CH_2–O), 2.13–2.26 (m, 1 H, C*H*CH_3), 1.93–2.06 (m, 2 H, =CCH_2), 1.82 (brs, 1 H, OH), 1.33–1.60 (m, 7 H, 3 CH_2 and C*H*Me_2), 0.80–0.93 (m, 9 H, 3 CH_3).

(*S*)-7-(Benzyloxy)-(*Z*)-5-octen-1-ol (9) was obtained in 73% yield (7:1 *Z*/*E* ratio) with a 4:6 diethyl ether/hexanes mixture as eluant. Found: C, 66.74; H, 9.42. $C_{15}H_{22}O_2$ requires: C, 66.87; H, 9.48. IR (thin film) 3400, 3040, 2930, 2860, 1660, 1455, 1075, 735 cm^{-1}; ^1H NMR δ 7.23–7.40 (m, 5 H, Ar protons), 5.50–5.67 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 10.8 Hz), 5.35–5.40 (m, 1 H, CHC*H*=), 4.47 (AB system, 2 H, PhCH_2O), 4.23–4.33 (m, 1 H, CH–O), 3.60 (t, 2 H, *J* = 7.9 Hz, CH_2OH), 1.93–2.12 (m, 2 H, =CCH_2), 1.70 (brs, 1 H, OH), 1.35–1.60 (m, 4 H, 2 CH_2), 1.27 (d, 3 H, *J* = 6.3 Hz, CH_3); $[\alpha]^{22}_D$ −0.9° (C 1.3, $CHCl_3$).

(*R*)-7,8-(Cyclohexylidenedioxy)-(*Z*)-5-octen-1-ol (10) was obtained in 60% yield (10:1 *Z*/*E* ratio) with a 6:4 diethyl ether/hexanes mixture as eluant. Found: C, 70.03; H, 9.99. $C_{14}H_{24}O_3$ requires: C, 69.95; H, 10.08. IR (thin film) 3400, 2955, 2860, 1660, 1455, 1075, 740 cm^{-1}; ^1H NMR δ 5.53–5.63 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 10.4 Hz), 5.34–5.47 (m, 1 H, CHC*H*=), 4.73–4.83 (m, 1 H, CH–O), 4.03 (dd, 1 H, *J* = 8.2, 6.4 Hz, one H of CHCH_2O), 3.57 (t, 1 H, *J* = 7.1 Hz, CH_2OH), 3.67 (t, 1 H, *J* = 8.2 Hz, one H of CHCH_2O), 2.00–2.23 (m, 2 H, CH_2C=), 2.00 (brs, 1 H, OH), 1.27–1.66 (m, 14 H, 2 CH_2 and C_6H_{10}); $[\alpha]^{22}_D$ −8.93° (*c* 0.5, $CHCl_3$).

General Procedure for the Isomerization of (*Z*)-5–10 to (*E*)-5–10. The described procedure was followed.[34] To a solution of *Z* alcohol (2 mmol) and thiophenol (1 mmol, 0.1 mL) in refluxing benzene (60 mL) was added AIBN (1.2 mmol, 200 mg) in four portions over a period of 8 h. The solvent was evaporated and the crude mixture purified by flash chromatography using the same eluting mixtures employed for *Z* alcohols.

(*S*)-8-(Benzyloxy)-(*E*)-6-nonen-1-ol (5) was obtained in 70% yield (10:1 *E*/*Z* ratio). Found: C, 77.28; H, 9.83. $C_{16}H_{24}O_2$ requires: C, 77.36; H, 9.76. IR (thin film) 3400, 3035, 2930, 2860, 1670, 1455, 1070, 970 cm^{-1}; ^1H NMR δ 7.30–7.36 (m, 5 H, Ar protons), 5.53–5.65 (m, 1 H, =C*H*CH_2, *J*(HC=CH) = 15.5 Hz), 5.34–5.43 (m, 1 H, CHC*H*=), 4.43 (AB system, 2 H, PhCH_2O), 3.80–3.89 (m, 1 H, CH–O), 3.63 (t, 2 H, *J* = 6.8 Hz, CH_2OH), 2.00–2.14 (m, 2 H, CH_2C=), 1.30–1.67 (m, 7 H, 3 CH_2 and OH), 1.27 (d, 3 H, *J* = 7.4 Hz, CH_3); $[\alpha]^{22}_D$ −6.24° (*c* 0.5, $CHCl_3$).

(*R*)-8,9-Bis(benzyloxy)-(*E*)-6-nonen-1-ol (6) was obtained in 75% yield (≥10:1 *E*/*Z* ratio). Found: C, 78.03; H, 8.47. $C_{23}H_{30}O_3$ requires: C, 77.91; H, 8.55. IR (thin film) 3400, 3040, 2940, 2860, 1670, 1455, 1065, 965 cm^{-1}; ^1H NMR δ 7.27–7.40 (m, 10 H, Ar protons), 5.60–5.75 (m, 1 H, =C*H*CH_2, *J*(HC=CH) =

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15.4 Hz), 5.33–5.47 (m, 1 H, CHCH=), 4.40–4.67 (m, 4 H, PhCH$_2$O), 3.90–4.06 (m, 1 H, CH–O), 3.47–3.67 (m, 4 H, CH$_2$OH and CHCH$_2$O), 2.00–2.13 (m, 2 H, CH$_2$C=), 1.28–1.67 (m, 7 H, 3 CH$_2$ and OH); $[\alpha]^{22}_D$ +10.4° (*c* 0.15, $CHCl_3$).

(*R*)-8,9-(Cyclohexylidenedioxy)-(*E*)-6-nonen-1-ol (7) was obtained in 65% yield (10:1 *E*/*Z* ratio). Found: C, 70.72; H, 10.26. $C_{15}H_{26}O_3$ requires: C, 70.81; H, 10.32. IR (thin film) 3400, 2955, 2860, 1670, 1455, 1070, 975 cm^{-1}; ^{1}H NMR δ 5.67–5.80 (m, 1 H, =CHCH$_2$, *J*(HC=CH) = 15.8 Hz), 5.33–5.45 (m, 1 H, CHCH=), 4.37–4.50 (m, 1 H, CH–O), 4.00 (dd, 1 H, *J* = 8.9, 6.8 Hz, one H of CHCH$_2$O), 3.60 (t, 2 H, *J* = 6.5 Hz, CH$_2$OH), 3.51 (t, 1 H, *J* = 8.9 Hz, one H of CHCH$_2$O), 2.00–2.10 (m, 2 H, CH$_2$C=), 1.25–1.68 (m, 17 H, 3 CH$_2$, C$_6$H$_{10}$, OH); $[\alpha]^{22}_D$ +5.75° (*c* 0.1, $CHCl_3$).

(*R*,*S*)-8,9-Dimethyl-(*E*)-6-decen-1-ol (8) was obtained in 71% yield (5:1 *E*/*Z* ratio). Found: C, 78.09; H, 13.26. $C_{12}H_{24}O$ requires: C, 78.17; H, 13.15. IR (thin film) 3400, 2960, 2850, 1670, 1455, 1385, 1170, 970 cm^{-1}; ^{1}H NMR δ 5.27–5.40 (m, 2 H, HC=CH, *J*(HC=CH) = 15.0 Hz), 2.43 (dt, 2 H, *J* = 7.9, 3.1 Hz, CH$_2$OH), 1.96–2.08 (m, 2 H, =CCH$_2$), 1.80–1.91 (m, 1 H, CHCH$_3$), 1.33–1.68 (m, 8 H, 3 CH$_2$, CHMe$_2$, OH), 0.80–0.91 (m, 9 H, 3 CH$_3$).

(*S*)-7-(Benzyloxy)-(*E*)-5-octen-1-ol (9) was obtained in 46% yield (7:1 *E*/*Z* ratio). Found: C, 66.81; H, 9.53. $C_{15}H_{22}O_2$ requires: C, 66.87; H, 9.48. IR (thin film) 3400, 3035, 2940, 2860, 1670, 1455, 1070, 970 cm^{-1}; ^{1}H NMR δ 7.30–7.35 (m, 5 H, Ar protons), 5.55–5.71 (m, 1 H, =CHCH$_2$, *J*(HC=CH) = 16.0 Hz), 5.35–5.45 (m, 1 H, CHCH=), 4.45 (AB system, 2 H, PhCH$_2$O), 3.80–3.95 (m, 1 H, CH–O), 3.10 (t, 2 H, *J* = 5.4 Hz, CH$_2$OH), 2.60 (brs, 1 H, OH), 2.00–2.15 (m, 2 H, CH$_2$C=), 1.30–1.65 (m, 4 H, 2 CH$_2$), 1.27 (d, 3 H, *J* = 7.0 Hz, CH$_3$); $[\alpha]^{22}_D$ −35.36° (*c* 0.9, $CHCl_3$).

(*R*)-7,8-(Cyclohexylidenedioxy)-(*E*)-5-octen-1-ol (10) was obtained in 64% yield (≥10:1 *E*/*Z* ratio). Found: C, 69.86; H, 10.14. $C_{14}H_{24}O_3$ requires: C, 69.95; H, 10.08. IR (thin film) 3400, 2950, 2860, 1675, 1455, 1070, 970 cm^{-1}; ^{1}H NMR δ 5.67–5.80 (m, 1 H, =CHCH$_2$, *J*(HC=CH) = 15.4 Hz), 5.30–5.46 (m, 1 H, CHCH=), 4.35–4.51 (m, 1 H, CH–O), 4.03 (dd, 1 H, *J* = 8.9; 6.1 Hz, one H of CHCH$_2$O), 3.60 (t, 2 H, *J* = 5.4 Hz, CH$_2$OH), 3.50 (t, 1 H, *J* = 8.9 Hz, one H of CHCH$_2$O), 1.93–2.13 (m, 2 H, CH$_2$C=), 1.15–1.68 (m, 15 H, 2 CH$_2$, C$_6$H$_{10}$, OH); $[\alpha]^{22}_D$ +7.7 (*c* 1, $CHCl_3$).

General Procedure for the Synthesis of Cycloadducts 17–22. The products were prepared by a sequence of three reactions from alcohols **5–10** involving (a) Swern oxidation to the aldehydes, (b) conversion of the aldehydes into the oximes, and (c) intramolecular cycloaddition.

Synthesis of Aldehydes. To a stirred solution of oxalyl chloride (1.2 mmol, 0.103 mL) in CH_2Cl_2 (15 mL) cooled at −65 °C was added DMSO (2.5 mmol, 0.180 mL) and the mixture stirred at −65 °C for 20 min. A solution of alcohol (1.0 mmol) in CH_2Cl_2 (5 mL) was then added and the reaction allowed to warm up to −50 °C. After the mixture was stirred 15 min, triethylamine (5 mmol, 0.7 mL) was added and the mixture allowed to warm up to room temperature in about 20 min and kept at that temperature for additional 20 min. The usual workup gave crude aldehydes that were generally used without further purification. Typical yield were in the range 70–90%.

Synthesis of Oximes. To a solution of crude aldehyde (10 mmol) in pyridine (4.0 mL) stirred at room temperature was added NH_2OH·HCl (3.0 mmol, 210 mg) and the mixture stirred overnight. Water was then added and the mixture extracted several time with diethyl ether. Evaporation of the solvent gave the crude oximes as roughly 1:1 mixture of C=N isomers in nearly quantitative yield. They were used without further purification. These products were characterized by their ^{1}H NMR spectra featuring the aldoxime CH signal at δ 7.30–7.50 (syn to OH) and 6.70–6.90 (anti to OH) and the OH signal at δ 7.70–7.90. In the IR spectra ν(OH) stretches were at 3500–3600 cm^{-1}, and ν(C=N) stretches were at 1660–1690 cm^{-1}.

Intramolecular Cycloadditions. To a stirred solution of crude oxime (1 mmol) in CH_2Cl_2 (3.0 mL) cooled at 0 °C was added a 0.3 M solution of NaOCl (1 mmol, 3.4 mL) and stirring continued for 1–3 h at 0 °C. Water was then added and the reaction mixture extracted twice with CH_2Cl_2. The crude products were purified by flash chromatography. Yield and diastereoisomeric ratios are reported in Table I. Relevant NMR data are reported in Table III.

Isoxazolines 17a,b were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 73.96; H, 8.24; N, 5.36. $C_{16}H_{21}NO_2$ requires: C, 74.08; H, 8.18; N, 5.40. IR (thin film) 3040, 2980, 2940, 2880, 1660, 1455, 1105, 910, 730 cm^{-1}. **17a**: $[\alpha]^{22}_D$ +44.8° (*c* 1, $CHCl_3$). **17b**: $[\alpha]^{22}_D$ +20.1° (*c* 0.6, $CHCl_3$).

Isoxazolines 17c,d were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 74.12; H, 8.20; N, 5.33. $C_{16}H_{21}NO_2$ requires: C, 74.08; H, 8.18; N, 5.40. IR (thin film) 3040, 2980, 2940, 2880, 1660, 1455, 1110, 905, 730 cm^{-1}.

Isoxazolines 18a,b were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 75.49; H, 7.40; N, 3.86. $C_{23}H_{27}NO_3$ requires: C, 75.57; H, 7.46; N, 3.83. IR (thin film) 3070, 3040, 2940, 2860, 1650, 1600, 1455, 1100, 730 cm^{-1}. **18a**: $[\alpha]^{22}_D$ −10.8° (*c* 2, $CHCl_3$). **18b**: $[\alpha]^{22}_D$ −64.4° (*c* 0.3, $CHCl_3$).

Isoxazolines 18c,d were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 75.64; H, 7.46; N, 3.80. $C_{23}H_{27}NO_3$ requires: C, 75.57; H, 7.46; N, 3.83. IR (thin film) 3070, 3035, 2940, 2860, 1650, 1600, 1455, 1105, 730 cm^{-1}.

Isoxazolines 19a,b were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 67.94; H, 8.80; N, 5.28. $C_{15}H_{23}NO_3$ requires: C, 67.88; H, 8.75; N, 5.28. IR ($CHCl_3$) 2940, 2860, 1645, 1450, 1105, 940, 735 cm^{-1}. **19a**: $[\alpha]^{22}_D$ +8.8° (*c* 0.4, $CHCl_3$); mp 50 °C. **19b**: $[\alpha]^{22}_D$ −84.2° (*c* 0.4, $CHCl_3$); mp 101 °C.

Isoxazolines 19c,d were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 67.79; H, 8.74; N, 5.30. $C_{15}H_{23}NO_3$ requires: C, 67.88; H, 8.75; N, 5.28. IR (thin film) 2940, 2860, 1650, 1455, 1100, 940, 735 cm^{-1}. **19c**: $[\alpha]^{22}_D$ +108.3° (*c* 0.34, $CHCl_3$). **19d** was obtained only impure from **19c**.

Isoxazolines 20a,b were obtained with 1:4 diethyl ether/hexanes mixture as eluant. Found: C, 73.69; H, 10.79; N, 7.18. $C_{12}H_{21}NO$ requires: C, 73.78; H, 10.86; N, 7.17. IR (thin film) 2960, 2930, 2860, 1640, 1455, 1390, 1370, 870 cm^{-1}.

Isoxazolines 20c,d were obtained with a 1:4 diethyl ether/hexanes mixture as eluant. Found: C, 73.70; H, 10.92; N, 7.23. $C_{12}H_{21}NO$ requires: C, 73.78; H, 10.86; N, 7.17. IR (thin film) 2960, 2930, 2860, 1645, 1450, 1385, 1370, 870 cm^{-1}.

Isoxazolines 21a,b were obtained with a 4:6 diethyl ether/hexanes mixture as eluant. Found: C, 73.36; H, 7.87; N, 5.66. $C_{15}H_{19}NO_2$ requires: C, 73.42; H, 7.82; N, 5.71. IR (thin film) 3070, 3040, 2980, 2870, 1650, 1455, 1110, 910, 730 cm^{-1}. **21a**: $[\alpha]^{22}_D$ +14.6° (*c* 0.8, $CHCl_3$). **21b**: $[\alpha]^{22}_D$ +44.4° (*c* 0.3, $CHCl_3$).

Isoxazolines 21c,d were obtained with a 4:6 diethyl ether/hexanes mixture as eluant. Found: C, 73.48; H, 7.89; N, 5.70. $C_{15}H_{19}NO_2$ requires: C, 73.42; H, 7.82; N, 5.71. IR (thin film) 3065, 3040, 2980, 2940, 2870, 1650, 1455, 1110, 905, 730 cm^{-1}.

Isoxazolines 22a,b were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 66.98; H, 8.40; N, 5.61. $C_{14}H_{21}NO_3$ requires: C, 66.89; H, 8.44; N, 5.57. IR (thin film) 2940, 2860, 1645, 1455, 1110, 940, 735 cm^{-1}. **22a**: $[\alpha]^{22}_D$ +7.5° (*c* 0.2, $CHCl_3$). **22b**: $[\alpha]^{22}_D$ −45.2° (*c* 0.44, $CHCl_3$).

Isoxazolines 22c,d were obtained with a 1:1 diethyl ether/hexanes mixture as eluant. Found: C, 66.80; H, 8.40; N, 5.51. $C_{14}H_{21}NO_3$ requires: C, 66.89; H, 8.44; N, 5.57. IR (thin film) 2940, 2860, 1645, 1455, 1105, 935, 740 cm^{-1}. **22c**: $[\alpha]^{22}_D$ +68.7° (*c* 0.5, $CHCl_3$). **22d**: $[\alpha]^{22}_D$ −11.6° (*c* 0.1, $CHCl_3$).

Correlation of 19a with *ent*-17a. Isoxazoline **19a** was converted into *ent*-**17a** by a four-step procedure. Hydrolysis of the ketal protection (AcOH/H_2O, 4:1; room temperature; 3 days) gave **23** in 75% yield. **23** was monotosylated with *p*-TolSO$_2$Cl (1.2 mol equiv) and triethylamine (3 mol equiv) in CH_2Cl_2 at room temperature to give **24** in 60% yield. Reduction with $NaBH_4$ in DMSO[35] (85 °C, 6 h) and benzylation (NaH, 1.2 mol equiv; catalytic $Bu_4N^+I^-$; benzyl bromide, 1.2 mol equiv; THF; room temperature overnight) afforded *ent*-**17a**, $[\alpha]^{22}_D$ −40.8° (*c* 0.25, $CHCl_3$), in 50% overall yield.

Correlation of 19c with 18c. Compound **25** was obtained from **19c** as described above for the synthesis of **23** from **19a** in 74% yield. The described benzylation procedure gave **18c** in 60% yield. It had $[\alpha]^{22}_D$ −68.5 (*c* 0.3, $CHCl_3$).

MM2 Calculations. The input values collected in Table IV were those found in the ab initio transition structure:[23] they were fixed and not allowed to be minimized. All the remaining pa-

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rameters were fully optimized by MM2.[22]

Registry No. (*S*)-(*Z*)-**5**, 109960-86-3; (*S*)-(*E*)-**5**, 109960-92-1; (*R*)-(*Z*)-**6**, 109960-87-4; (*S*)-(*E*)-**6**, 109960-93-2; (*S*)-(*Z*)-**7**, 109960-88-5; (*S*)-(*E*)-**7**, 109960-94-3; (±)-(*Z*)-**8**, 109960-89-6; (±)-(*E*)-**8**, 109960-95-4; (*S*)-(*Z*)-**9**, 109960-90-9; (*S*)-(*E*)-**9**, 109960-96-5; (*S*)-(*Z*)-**10**, 109960-91-0; (*S*)-(*E*)-**10**, 109960-97-6; (*S*)-(*Z*)-**11**, 109960-71-6; (*S*)-(*E*)-**11**, 109960-72-7; (*S*)-(*Z*)-**12**, 109960-73-8; (*S*)-(*E*)-**12**, 109960-74-9; (*S*)-(*Z*)-**13**, 109960-75-0; (*S*)-(*E*)-**13**, 109975-47-5; (±)-(*Z*)-**14**, 109975-48-6; (±)-(*E*)-**14**, 109960-76-1; (*S*)-(*Z*)-**15**, 109960-77-2; (*S*)-(*E*)-**15**, 109975-49-7; (*S*)-(*Z*)-**16**, 109960-78-3; (*S*)-(*E*)-**16**, 109960-79-4; **17a**, 109960-80-7; **17a** (ent), 110013-46-2; **17b**, 110013-28-0; **17c**, 110013-29-1; **17d**, 110013-30-4; **18a**, 109960-81-8; **18b**, 110013-31-5; **18c**, 110013-32-6; **18d**, 110013-33-7; **19a**, 109960-82-9; **19b**, 110013-34-8; **19c**, 110013-35-9; **19d**, 110013-36-0; **20a**, 109960-83-0; **20b**, 110013-37-1; **20c**, 110013-38-2; **20d**, 110013-39-3; **21a**, 109960-84-1; **21b**, 110013-40-6; **21c**, 110013-41-7; **21d**, 110013-42-8; **22a**, 109960-85-2; **22b**, 110013-43-9; **22c**, 110013-44-0; **22d**, 110013-45-1; **23**, 109960-98-7; **24**, 109960-99-8.

Diastereofacial Selectivity of Enolates

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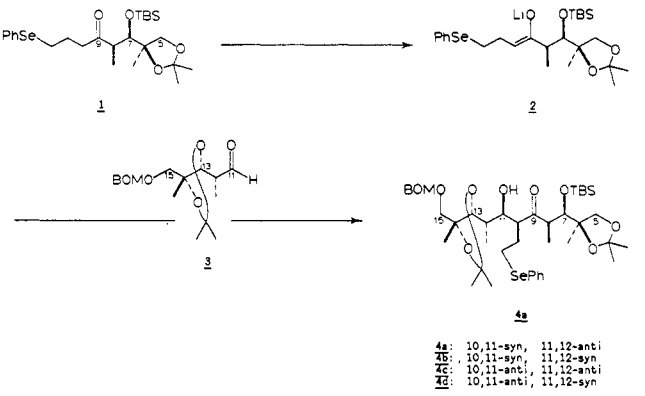
Results from our research in macrolide total synthesis prompted us to investigate ways of altering the diastereofacial selectivity of enolates without making major changes in the enolates' structure. The variation in the diastereofacial selectivity of enolates **7a–g** derived from 3,4-*syn*-3-alkoxy-2,4-dimethylheptan-5-ones (**5a–g**) is presented. The parent enolate **7a** was *si*-facial selective, while protecting the 3-hydroxyl group gave enolates that were *re*-facial selective (**7b–g**). Thus, without changing any chiral centers or backbone functionality, the diastereofacial selectivity of enolates can be varied or reversed. The implications of this finding to natural products synthesis are discussed.

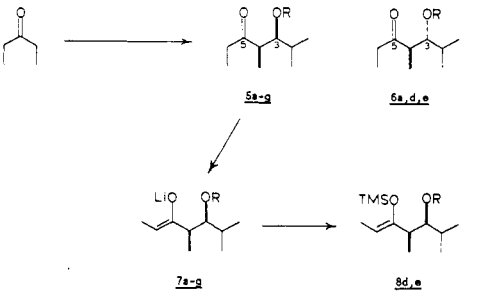
The aldol reaction is of great utility for the total synthesis of complex natural products such as macrolides and ionophores.[2-4] Several investigators have employed aldols for coupling large fragments late in their total syntheses, taking advantage of the reaction's supreme reliability for forming carbon–carbon bonds. Unfortunately, high stereoselectivity from such aldol couplings cannot be relied on. Despite some stunningly good results[5] and a growing understanding of aldol reactions, most aldol reactions used to couple large fragments have resulted in moderate to poor stereoselectivities. Given the potential power of the aldol reaction, it is unfortunate that stereochemical issues limit its utility.

During our study of the total synthesis of streptovaricin A,[6] we investigated the aldol reaction **1** and **3** (Scheme I).[7]

Scheme I



Scheme II



Reaction of ketone **1** with lithium hexamethyldisilazide gave (*Z*)-O-enolate **2** in >20:1 selectivity as judged by enolate-trapping experiments.[11] Reaction of **2** with al-

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