Determination of Configuration and Conformation of Isoxazolidines by Nuclear Overhauser Effect Difference Spectroscopy

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The configurations of isoxazolidines **2**, **3**, **5**, **7**, and **10–12** have been assigned by analysis of NMR coupling constants and by nuclear Overhauser effect difference spectroscopy (NOEDS). The preferred solution conformations of isoxazolidines **3** and **5** were determined to be as in **3A**/**5A**. It is proposed that these conformations are adopted to take advantage of the anomeric effect and to alleviate the unfavorable stereoelectronic lone pair–lone pair interaction in the N–O portion of the molecule (gauche effect).

Introduction

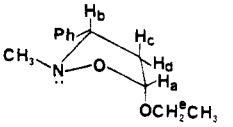
During the course of synthetic studies, a variety of isoxazolidines were prepared in our laboratories by [3 + 2] dipolar cycloadditions of nitrones and nitronates with olefins. It was critical to the success of these projects that the configurations of the cycloadducts be firmly established. However, analysis of the ^{1}H NMR coupling constants of the various isoxazolidines often did not result in unambiguous assignment of configuration because of the limitations of applying the Karplus equation to five-membered ring systems.[1] On the other hand, the application of nuclear Overhauser effect difference spectroscopy (NOEDS)[2] in combination with analysis of proton coupling constants has allowed facile determination of both the configuration and conformation of these various isoxazolidines. As demonstrated in this paper, we believe that such methods are generally useful for establishing the stereochemistry of substituted isoxazolidines.

Results and Discussion

Dipolar cycloaddition of nitrone **1**[3] and ethyl vinyl ether at 80 °C for 72 h resulted in the formation of a 1:1 mixture of cycloadducts **2** and **3** in 78% yield (Scheme I). The regiochemistry of the cycloaddition was readily deduced from the ^{1}H NMR spectrum of the pure cycloadducts. In each case, there was a one proton signal at δ ~5.15 which corresponded to the C-5 acetal proton in **2** and **3**. The alternative regioisomeric cycloadduct is not expected to show a signal at this chemical-shift value. The regiospecificity observed in this cycloaddition was expected based upon earlier studies of similar nitrone cycloadditions by Huisgen.[3]

The NMR signal multiplicities of the acetal proton for **2** and **3** were remarkably different. Isomer **2** displayed a doublet of doublets of δ 5.15 with coupling constants of 3 and 6 Hz, while isomer **3** showed only a doublet (J = 5 Hz) at δ 5.16. Similar patterns have been consistently obtained in our laboratories for various isoxazolidine stereoisomers.[4] It was clear from the proton NMR spectrum that one cycloadduct has a dihedral angle between the C-5 proton and one of the C-4 protons of ~90°, resulting in no observed coupling between these two nuclei. Unfortunately, this information could not be employed in conjunction with other coupling constants to yield a unique stereochemical assignment, since Dreiding models indicated that both isoxazolidines **2** and **3** are capable of attaining conformations in which one C-4 proton and the proton at C-5 have a dihedral angle of ~90°. Thus, since the configurations of the two cycloadducts could not be definitively assigned from analysis of proton coupling

Table I. NOE Difference Spectral Data of Isoxazolidine 2[a]

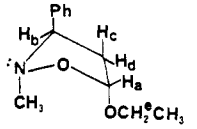


2

	X[b]				
	H_a	N-CH_3	H_e^{uf}, H_b[c]	H_c	H_d
H_a			3.0[e]	6.6	1.8
H_e^{uf}, H_b[c]	4.2[d]	10.7[g]		4.8[g]	3.6[g]
H_c	6.0		4.8		14.9
H_d	0.8		2.4[e]	10.7	
H_ϕ			8.9[f]		4.2[f]

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated. [c] uf = upfield; H_e^{uf} and H_b are overlapping. [d] Irradiation affects both H_e^{uf} and H_b. [e] Includes effect of irradiation on H_e^{uf}. [f] Ortho protons on phenyl ring. [g] For H_b only.

Table II. NOE Difference Spectral Data of Isoxazolidine 3[a]



3

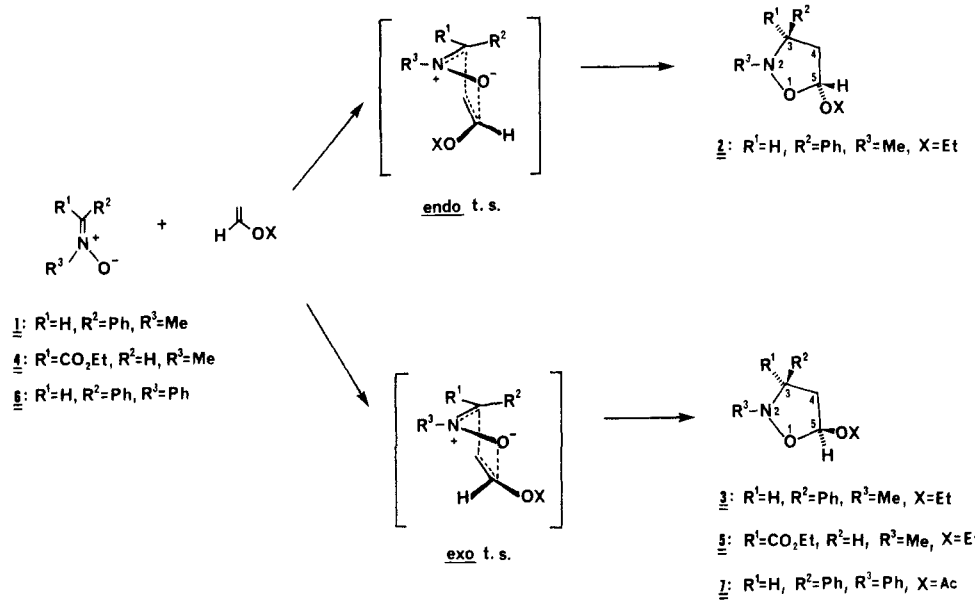
	X[b]			
	H_a	N-CH_3	H_b	H_c, H_d[c]
H_a				8.4
N-CH_3			2.4	
H_e^{uf}	8.8			
H_e^{df}		2.2		
H_b		10.6		6.5[f]
H_c, H_d[c]	3.2		1.9	
H_ϕ			1.6[e] 3.9[d]	1.7[d]

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated. [c] H_c and H_d are overlapping. [d] Ortho protons on phenyl ring. [e] Meta, para protons on phenyl ring. [f] Includes NOE from irradiation of N-CH_3.

(1) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Permagon Press: Oxford, 1969; pp 286–294.
(2) Williamson, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580. Kotovych, G.; Aarts, G. H. M. *Org. Magn. Reson.* **1982**, *18*, 77. Mersh, J. D.; Sanders, J. K. M. *Ibid.* **1982**, *18*, 122.
(3) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565, and references cited therein. Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2548.
(4) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Stauffer, D., unpublished results.

0022-3263/82/1947-4397$01.25/0

Scheme I



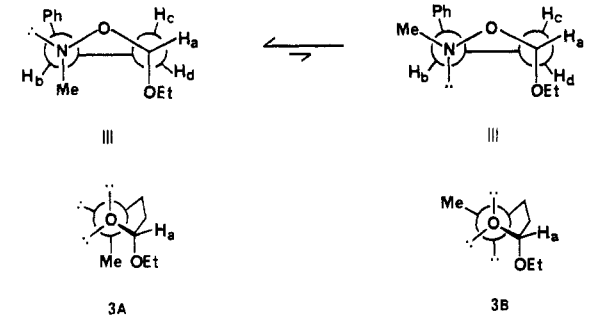
constants, an alternative method was sought.

Tables I and II contain the results obtained when isoxazolidines **2** and **3**, respectively, were analyzed by NOEDS. Irradiation of proton H_a of **2** resulted in enhancement of the signals for H_b, H_c, H_d, and the upfield proton of the ethyl ether methylene. Likewise, when H_b was irradiated, the signals corresponding to H_a, H_c, H_d, and the ortho protons of the phenyl ring were enhanced. These results are possible only for the cis stereoisomer **2** because there is no possible conformation of the trans isomer **3** in which H_a and H_b are close enough to induce enhancements in their respective signals.[5] This conclusion was confirmed by noting the magnitude of the NOE for H_c/H_d caused by irradiation of either H_a or H_b. Irrespective of whether H_a or H_b was irradiated, the H_c signal displayed a greater enhancement than that of H_d, and this can only occur when H_a and H_b are syn on the five-membered ring.

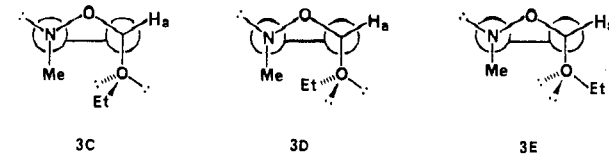
The magnitude of the observed NOE for H_b/H_e^{uf} in **2** cannot be measured with precision due to signal overlap. However, from partial irradiation experiments with **2** it has been determined that H_e^{uf} makes a minimal contribution to the NOE of H_d. Therefore, the NOE observed for H_d upon complete irradiation of the H_b/H_e^{uf} region must result from the proximity of H_b and H_d.

The data in Table II clearly correspond to that expected for the trans isomer **3**. Irradiation of H_a has no effect upon the intensity of H_b, suggesting that they are not topologically close. Similarly, the signal for H_a was unaffected by irradiation of H_b. As mentioned above, the trans stereoisomer **3** is not able to attain a conformation whereby H_a and H_b are near enough to display a NOE enhancement.

There is a second feature of the data in Table II which is also important because it gives information concerning the preferred conformation of **3** in solution. Irradiation of the signal corresponding to the protons of the *N*-methyl group resulted in enhancements of the two signals H_b and H_e^{df}. For irradiation of the *N*-methyl protons to affect H_e^{df}, the *N*-methyl group and H_e have to be within 3.5 Å[5], indicating that the *N*-methyl and *O*-ethyl groups of **3** occupy pseudoaxial positions on the five-membered ring. When this information is taken in conjunction with the $\theta \simeq 90°$ Karplus relationship between H_a and H_d ($J_{a,d} \simeq 0$ Hz), it becomes clear that the solution conformation of the trans isomer is as depicted in **3A**. The alternative conformation **3B** with the nitrogen lone-pair pseudoaxial cannot display a N-CH_3/H_e NOE and maintain $\theta_{a,d} \simeq 90°$.



Although conformation **3A** would not appear to be the most favorable conformation of **3** based on steric grounds (two large groups in a 1,3-dipseudoaxial orientation), there are overriding electronic factors that are expected to favor **3A** over **3B**. Thus, the trans isomer adopts the pseudoaxial orientation **3A** to take advantage of the stabilization of an anomeric effect between a lone pair on the ring oxygen and the pseudoaxial *O*-ethyl substituent at C-5. This anomeric effect is probably worth about 1.2–1.5 kcal/mol[6] and offsets the minor repulsions that are incurred in this conformation. Furthermore, it is probable that the *O*-ethyl substituent adopts a conformation about the C_6–O bond such that an exo-anomeric effect is able to impart additional stabilization (cf. conformations **3C** and **3D**). Both **3C** and



3D would result in the "pushing" of the *O*-ethyl substituent under the ring, hence, forcing the *O*-ethyl and *N*-methyl substituents into close proximity. However, conformation **3E**, in which an exo-anomeric effect is not possible, allows the *O*-ethyl group to adopt an orientation that could not

(5) From the magnitude of the NOE between the vicinal protons H_a and H_c/H_d or H_b and H_c/H_d, it is possible to calculate the maximum distance across which a detectable enhancement can be observed. In all of the systems studied, this was ~3.5 Å.

(6) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105, and references cited therein. Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

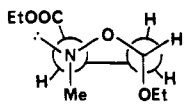
result in a NOE enhancement. Involvement of the anomeric and exo-anomeric effects in **3** readily explains why the *O*-ethyl group adopts the pseudoaxial orientation on the five-membered ring, and a NOE enhancement is observed between the two substituents.

Once it was recognized that **3** adopts conformations **3C/3D** to take advantage of an anomeric/exo-anomeric effect, an explanation for the favoring of the pseudoaxial *N*-methyl group became clear: invertomer **3A** avoids the destabilizing N lone pair/O lone pair interaction found in **3B**. Hydrazines, hydroxylamines, hydroperoxides, and similar compounds are known to adopt ground-state conformations in which the lone pairs of the heteroatoms are arranged gauche to each other.[7] This conformation avoids the unfavorable electronic interaction arising from anti- or syn-periplanar arrangement of the lone pairs. In **3A**, the lone pairs on oxygen and nitrogen have the gauche relationship. However, there is an antiperiplanar orientation of the lone pairs in **3B**; therefore, conformation **3B** is disfavored with regard to **3A**.

Dipolar cycloaddition of nitrone **4**[8] and ethyl vinyl ether at 80 °C for 72 h resulted in formation of a single isoxazolidine stereoisomer in 92% yield. The regiochemistry of the cycloaddition is shown in **5** as evidenced by a one-proton signal at δ 5.20 corresponding to the acetal proton. In analogy with the results obtained for isoxazolidines **2/3**, the multiplicity of this signal (doublet, J = 5 Hz) suggests that only the trans isomer **5** was produced. This assignment was confirmed by NOEDS (Table III).

Irradiation of H_a resulted in the observation of a large signal enhancement for H_c and a smaller enhancement for H_d, which implied that H_c was closer to H_a than was H_d. Similarly, when the resonance for H_c was irradiated, a large NOE was obtained for H_a, while a peak enhancement was observed for H_b upon irradiation of H_d. These results are only possible for the regioisomer **5** which has H_a and H_b in the anti relationship.

As in the case of isoxazolidine **3**, when the *N*-methyl region of adduct **5** was irradiated, a large enhancement in the H_e region was observed. This fact suggested that **5**, in analogy with **3**, exists in conformation **5A** with the



5A

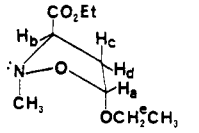
O-ethyl and the *N*-methyl adopting pseudoaxial positions. As discussed above, preference for conformation **5A** can be rationalized as a result of the stabilizing anomeric and gauche effects of this conformation.

A single isoxazolidine was obtained in 70% yield from cycloaddition of nitrone **6**[8] with vinyl acetate. The regiochemistry of this cycloaddition product was assigned as shown in **7**, since the compound displayed a one-proton signal at δ 6.57 due to the acetal proton. As in the above cases, the stereochemistry of the cycloadduct could not be unambiguously assigned from analysis of the proton coupling constants. However, NOEDS clearly showed that the stereoisomer **7** was produced in the cycloaddition (Table IV). As discussed in earlier examples, the data indicate that protons H_a and H_b are syn on the five-membered ring. Unfortunately, little conformational information concerning **7** was available from the NOEDS experiments, since it was not possible to unambiguously assign the proton resonances of the two aromatic rings.

Knowing the configurations of cycloadducts **2**, **3**, **5**, and **7**, we can draw some conclusions concerning the transition-state geometries of the nitrone cycloaddition reactions. We found that nitrone **1** exists exclusively in the *Z* conformation as shown by NOEDS, and **1** did not isomerize during the course of cycloaddition.[9] Yet, this geometrically pure nitrone reacted with ethyl vinyl ether to give a 1:1 mixture of cycloadducts **2** and **3** which means that there was no discrimination between the endo and exo transition states[10] during cycloaddition (Scheme I). This result is not surprising, since there is no potential for secondary orbital overlap to favor the endo transition state[11] nor is there obvious steric congestion developed in either transition state.

The results obtained from reaction of nitrone **4** and ethyl vinyl ether differed from those with nitrone **1**. Unlike **1**,

Table III. NOE Difference Spectral Data of Isoxazolidine 5[a]

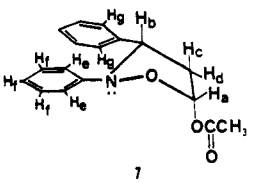


5

	X[b]					
	H_a	N-CH_3	$H_e^{uf\,c}$	H_e^{df}, H_b^{c}	H_c	H_d
H_a			2.5	0.7	2.1	0.6
N-CH_3			0.5			
$H_e^{uf\,c}$	3.7			3.7		
$H_e^{df\,c}$		3.6	5.0			
H_b		6.3				2.2
H_c	3.0					2.6
H_d	0.4				2.2	

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated. [c] uf = upfield; df = downfield; H_e^{df} and H_b are overlapping.

Table IV. NOE Difference Spectral Data of Isoxazolidine 7[a]



7

	X[b]						
	H_a	H_b	H_c	H_d	H_e	H_f	H_g
H_a			3.7				
H_b			1.9		1.6		2.1
H_c	2.0	2.9		1.2			
H_d			4.3				0.7
H_e						3.1	
H_f					3.5		
H_g		1.5					

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated.

(7) Riddell, F. G. "The Conformational Analysis of Heterocyclic Compounds"; Academic Press: London, 1980; and references cited therein.

(8) Inouye, T.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763.

(9) Variable-temperature ^{1}H NMR (360 MHz) spectrum of nitrone **1** showed that only the *Z* isomer was present, even after heating for 72 h at 80 °C.

(10) The terms endo and exo are applied in analogy with those accepted in Diels–Alder chemistry.

(11) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; 1st ed.; Verlag: Weinheim, Germany, 1970; pp 145–151.

nitrone 4 exists as a mixture of *E* and *Z* isomers, with the *E* isomer predominating. This mixture of isomers could be thermally isomerized to yield solely the *Z* isomer. The half-life of this rearrangement is 65 h at 100 °C. When the mixture of isomers was allowed to react with ethyl vinyl ether, (*E*)-nitrone 4 underwent cycloaddition more readily than the *Z* isomer. If the reaction mixture was analyzed prior to the completion of cycloaddition (6 h), the *E* isomer had been consumed, while a substantial quantity of the *Z* isomer remained. Thermal isomerization of (*E*)-4 to (*Z*)-4 cannot account for the rapid disappearance of the *E* isomer, since its rate of isomerization was an order of magnitude slower than its rate of disappearance. Also, the amount of 5 produced during the abbreviated cycloaddition corresponded to the quantity of (*E*)-4 that had disappeared. Therefore, unlike nitrone 1, the *E* isomer of 4 appears to react stereospecifically with ethyl vinyl ether through the exo transition state to give 5. However, when pure (*Z*)-4 was resubjected to the cycloaddition conditions, it too gave 5. Thus, formation of 5 from (*Z*)-4 has to occur via an endo transition state. Control experiments conclusively showed that 5 was the kinetic product of cycloaddition in both instances. Therefore, the observed stereospecificity could not have arisen from a postcycloaddition process, although these experiments do not preclude the conversion of (*Z*)-4 to 5 by way of minute amounts of the more reactive and thermodynamically less stable (*E*)-4 and an exo transition state. We are currently more closely investigating the factors that influence the stereospecificity of this cycloaddition.

Nitrone 6, which is exclusively the *Z* isomer, produced only 7 upon reaction with vinyl acetate. Cis isomer 7 must arise from an exo transition state as depicted in Scheme I. As in the case above, the factors responsible for control of stereospecificity during these cycloadditions are not clear, since secondary orbital considerations obviously play a small role and steric repulsions appear to be minimal in either the exo or endo transition state.

Based upon these results, confident prediction of nitrone cycloaddition stereoselectivity based upon nitrone geometry may not be generally feasible as in the Diels–Alder reaction. Instead, the stereochemistry of each cycloadduct will have to be rigorously determined by the sort of spectroscopic means described here.

The NOEDS method used above has also been found valuable in establishing the configurations of some isoxazolidines derived from cycloaddition of nitronates and alkenes. Nitronate 8 (40:60 *E*/*Z* mixture)[12] added to α,β-unsaturated ketone 9 at room temperature in benzene to produce what proved to be a 50:15:35 mixture of three *N*-methoxyisoxazolidines 10–12, respectively, in 84% yield (Scheme II). The regiochemistry of these adducts was established by inspection of their ^{1}H NMR spectra, each of which showed an ABX pattern due to the protons at C-3 and C-4. The regioisomeric series of cycloadducts would not show such coupling, and none of these isomers could be detected. The regiospecificity of this addition was anticipated based upon related reactions of α,β-unsaturated carbonyl compounds with methyl nitronates.[13-15]

Scheme II

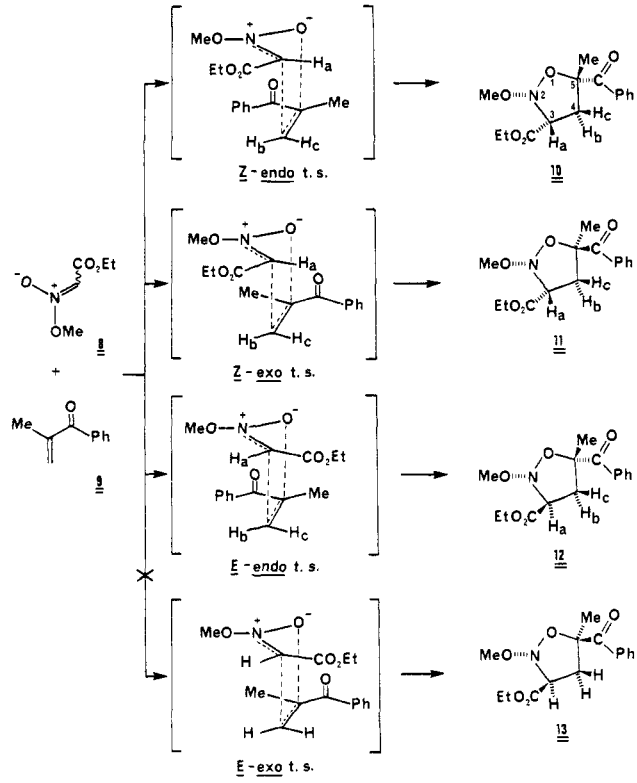
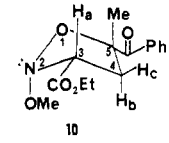


Table V. NOE Difference Spectral Data of Isoxazolidine 10[a]



10

	X[b]			
	H_a	H_b	H_c	C_5-Me
H_a			12.8	4.5
H_b			15.7	
H_c	1.9	12.8		6.4

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated.

These results are also in accord with the predictions of FMO theory.[14c]

It has been established that *N*-methoxyisoxazolidines are configurationally stable at nitrogen even at room temperature and that the methoxy group always assumes a pseudoaxial position in these compounds, presumably to take advantage of anomeric effect stabilization. These conclusions are based upon X-ray analyses and extensive NMR studies of *N*-methoxyisoxazolidines.[13-15]

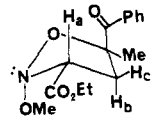
Since compounds 10–12 all incorporate a quaternary carbon in the isoxazolidine ring, it was impossible to fully establish relative configuration based upon proton coupling constants. However, NOE methodology did allow unambiguous assignments of configurations to be made.

Table V shows the results of a NOEDS experiment on the major isoxazolidine isomer 10. Irradiation of the C-5 methyl group of 10 resulted in signal enhancement of H_a and H_c. Similarly, irradiaton of H_c resulted in signal enhancement of H_a and H_b. Thus, the carbethoxy and benzoyl groups are syn in isoxazolidine 10.

Interestingly, irradiaiton of the *N*-methoxy group of 10 did not result in signal enhancement of any other protons,

(12) Gree, R.; Carrie, R. *Bull. Soc. Chim. Fr.* **1975**, 1314.
(13) (a) Müller, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1823. (b) Müller, K. *Ibid.* **1970**, *53*, 1112. (c) Müller, K. Ph.D. Thesis, Eidg. Technische Hochschüle, Zurich, 1970.
(14) (a) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron Lett.* **1973**, 453. (b) Gree, R.; Carrie, R. *Bull. Soc. Chim. Fr.* **1975**, 1319. (c) Gree, R.; Tonnard, F.; Carrie, R. *Ibid.* **1975**, 1325. (d) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675. (e) Gree, R.; Carrie, R. *Ibid.* **1976**, *32*, 683.
(15) Kamernitzky, A. V.; Levina, I. S.; Mortikova, E. I.; Shitkin, V. M.; El'Yanov, B. S. *Tetrahedron* **1977**, *33*, 2135.

Table VI. NOE Difference Spectral Data of Isoxazolidine 11[a]

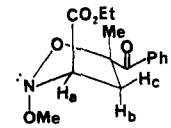


11

	X[b]			
	H_a	H_b	H_c	C_5-Me
H_a			11.7	
H_b			15.9	8.6
H_c	4.7	13.3		

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated.

Table VII. NOE Difference Spectral Data of Isoxazolidine 12[a]

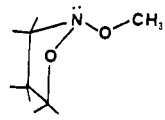


12

	X[b]			
	H_a	H_b	H_c	C_5-Me
H_a		13.2		
H_b	4.6		6.6	
H_c		13.2		5.3

[a] % η_{obsd} values; recorded as percent of η_{max}. [b] Proton that was irradiated.

and similar results were found in isomers **11** and **12**. This result is not surprising, since Müller and Eschenmoser have found via X-ray crystallography of several *N*-methylisoxazolidines that these systems have a conformation, as



14

shown in **14**, in which the *O*-methyl group is spatially removed from the five-membered ring.[13] Also, Müller has calculated that in order to minimize lone-pair repulsions on nitrogen and oxygen such a conformation is energetically favored.[13b,c] Although NOEDS methods could thus not be used to assign configuration at nitrogen, it was possible to do so based upon proton coupling constant data (vide infra).

Irradiation of the C-5 methyl group of the minor adduct **11** (Table VI) led to an increase in the H_b signal but *not* of H_a. Consistent with the configuration in **11**, saturation of H_c led to enhancement of H_a. The NOEDS results for the intermediate adduct **12** were similar to that for **11** and are shown in Table VII. Thus, irradiation of the C-5 methyl produced enhancement of H_c but not of H_a.

Establishment of the *N*-methoxy configuration was easily effected based upon observed coupling constants between H_a, H_b, and H_c in the isoxazolidines.[14d] For example, in the minor isomer **11**, large coupling constants are observed between these three nuclei. As can be seen from Dreiding models, in **11** the dihedral angles between H_a/H_b and H_a/H_c are nearly 180 and 0°, respectively. Thus, one can rationalize couplings of the magnitude observed (12 and 7 Hz) when H_a is pseudoaxial.

If isoxazolidine **11** was epimeric at nitrogen to the structure drawn and if one assumes that the five-membered ring will exist in a conformation having the methoxy group pseudoaxial because of the anomeric effect, then one would expect a small H_c/H_a coupling constant (dihedral angle $\cong$ 90°). It turns out that isoxazolidine **12** is, in fact, this isomer, being epimeric to **11** only at nitrogen. Compound **12** does show the small (3 Hz) H_c/H_a coupling constant predicted for this stereochemical arrangement.[14]

One can make similar arguments for assigning the configuration at nitrogen in the major adduct **10**. This isoxazolidine shows large coupling constants between H_b, H_c, and H_a, indicative of a pseudoaxial H_a as shown in structure **10**. The nitrogen epimer of **10** (i.e., **13**) was not isolated in this cycloaddition.

The products of cycloaddition of nitronate **8** and α,β-unsaturated ketone **9** can be rationalized as shown in Scheme II. The major stereoisomer **10** is derived from an endo transition state involving the (*Z*)-nitronate **8**.[10] Similarly, minor adduct **11** is produced via the *Z*-exo transition state. The intermediate adduct **12** results from the *E*-endo transition state shown in Scheme II. It has been previously observed[14,15] that (*E*)-nitronates react much slower than *Z* in [3 + 2] cycloadditions, and it is often possible to isolate pure unreacted (*E*)-nitronate from these reaction mixtures. In our case, the (*E*)-nitronate could, in fact, be isolated, and upon resubjection to the cycloaddition reaction conditions produced *only* adduct **12**. There is clearly a preference for endo transition states in these reactions (85% of the cycloaddition products.) These results appear to be generally in accordance with related nitronate cycloadditions,[13-15] although our unsaturated ketone system **9** appears to show somewhat better endo stereospecificity than those cases previously described. This result may be due to a subtle combination of steric and secondary orbital effects in the transition states (Scheme II).

Experimental Section

Proton and carbon NMR spectra were obtained with Bruker WP-200 and WM-360 spectrometers. Proton relaxation measurements were made on carefully degassed solutions with the inversion–recovery (180°–τ–90°–T) sequence and calculations of T_1's were done by a three-parameter, nonlinear least-squares analysis. The proton NOE measurements were made at 200 or 360 MHz by the FT difference method. The data were obtained by the PAPS sequence. Four FID's were acquired with the decoupler set exactly on a given resonance; four FID's with the decoupler off-resonance were then subtracted. This procedure was repeated until an adequate signal to noise ratio was achieved. A 90° observation pulse and a recovery time of $10T_1$ were used.

Infrared spectra were recorded on a Perkin-Elmer Model 197, 267, or 580 diffraction grating spectrophotometer. Mass spectral data were obtained on a KRATOS MS-950 double-focusing high-resolution spectrometer or a Finnigan 3200 twin EI and CI quadrupole mass spectrometer equipped with a Digital Equipment Corp. PDP 8/I computer. Chemical-ionization spectra used isobutane as the carrier gas. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL. Melting points were taken on a Thomas-Hoover "Uni-Melt" capillary melting point apparatus and are corrected.

Gas chromatography (GLC) was performed on either a Varian Model 920 or a 3200 gas chromatograph equipped with a thermal-conductivity detector using one of the following columns: 5 ft × 0.25 in. 30% SE-30 on Gas Chrom Q, 100–120 mesh or 5 ft × 0.25 in. 1.5% OV-101 on Chrom G, 100–120 mesh (stainless-steel columns). Analytical and preparative thin-layer chromatography were performed on silica gel 60 PF-254 (Merck). Column chromatography was done on 70–230 mesh silica gel 60 (Merck). Medium-pressure liquid chromatography was performed as described by Meyers et al.[16] Flash chromatography was performed

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with thick-walled glass columns on silica gel (Merck, 32–63 μm) according to the method of Still et al.[17]

Preparation of α-Carbethoxy-*N*-methylnitrone (4). The procedure of Inouye et al. for the preparation of the corresponding *N*-benzylnitrone was followed.[8] *N*-Methylhydroxylamine hydrochloride (3.60 g, 43.1 mmol), calcium chloride (3.00 g), and sodium bicarbonate (10.50 g) were stirred in ether (50 mL) at 0 °C. Ethyl glyoxylate (4.50 g, 44.1 mmol) was added, and the reaction mixture was stirred for 1.5 h. The mixture was filtered, and the filtrate was evaporated in vacuo. White crystals of the addition product were obtained: mp 72–78 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 4.3 (q, 2 H), 4.4 (br s, 3 H), 4.7 (s, 1 H). The crystals were dissolved in toluene, and the solution was evaporated in vacuo. The procedure was repeated three times to yield yellow oily **4** (4.2 g, 75%) as a 3.5:1 mixture of (*E*)- and (*Z*)-nitrone isomers, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 3.9 (s, 3 H, *Z* isomer), 4.2 (s, 3 H, *E* isomer), 4.2 (q, 2 H, both isomers), 7.1 (s, 1 H, *Z* isomer), 7.2 (s, 1 H, *E* isomer); IR (CCl_4) 3000–2800 (s), 1750–1700 (vs), 1400–1300 (s), 1200–1100 (vs) cm^{-1}.

Synthesis of Phenylisoxazolidines 2 and 3. α-Phenyl-*N*-methylnitrone (**1**)[3] (1.00 g, 7.4 mmol) was dissolved in an excess of freshly distilled ethyl vinyl ether (25.0 mL, 161 mmol), and the solution was sealed in a thick-walled glass reaction tube. The tube was heated at 80 °C for 72 h and cooled, and excess vinyl ether was removed by evaporation under high vacuum. The residue was chromatographed (CH_2Cl_2) to remove unreacted nitrone, followed by bulb to bulb distillation at 145 °C (1 torr) to give a yellow oil (1.19 g, 78%). As evidenced by GLC (SE-30 column/140 °C) and NMR analysis, the reaction mixture contained a 50:50 mixture of cis (**2**) and trans isomers (**3**) (retention times of 4.0 and 5.4 min, respectively). The isomers were separated by column chromatography (120 g; 10:1 hexane/EtOAc). The less polar isomer was the cis-isomer **2**, while the more polar compound was the trans-isomer **3**.

Cis-isomer **2** (oil): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3 H, *J* = 7 Hz), 2.32 (ddd, 1 H, *J* = 3, 10, and 13 Hz), 2.55 (s, 3 H), 2.86 (ddd, 1 H, *J* = 6, 10, and 13 Hz), 3.34 (t, 1 H, *J* = 10 Hz), 3.45 (dq, 1 H, *J* = 7 and 14 Hz), 3.93 (dq, 1 H, *J* = 7 and 14 Hz), 5.15 (dd, 1 H, *J* = 3 and 6 Hz), 7.33 (m, 5 H); IR (CCl_4) 3100–3000 (m), 3000–2800 (vs), 1455 (s), 1370 (s), 1100 (vs) cm^{-1}; mass spectrum (EI), *m*/*z* (relative intensity) 207 (M^+, 4), 161 (36), 118 (100), 77 (75). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.44; H, 8.10; N, 6.69.

Trans-isomer **3** (oil): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, 3 H, *J* = 7 Hz), 2.41 (ddd, 1 H, *J* = 5, 9, and 13 Hz), 2.57 (dd, 1 H, *J* = 6 and 13 Hz), 2.78 (s, 3 H), 3.48 (dq, 1 H, *J* = 7 and 10 Hz), 3.86 (dq, 1 H, *J* = 7 and 10 Hz), 4.03 (dd, 1 H, *J* = 6 and 9 Hz), 5.16 (d, 1 H, *J* = 5 Hz), 7.30 (m, 5 H); IR (CCl_4) 3100–3000 (m), 3000–2800 (vs), 1455 (s), 1370 (s), 1100 (vs) cm^{-1}; mass spectrum (EI), *m*/*z* (relative intensity) 207 (M^+, 9), 161 (100), 134 (63), 118 (53), 77 (48). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.37; H, 8.10; N, 6.77.

Preparation of Carbethoxyisoxazolidine 5. Following the above procedure, isoxazolidine **5** was prepared from α-carbethoxy-*N*-methylnitrone[8] **4** (0.70 g, 5.3 mmol) and ethyl vinyl ether (25 mL, 161 mmol). Flash chromatography (hexane/ethyl acetate, 3:1) and bulb to bulb distillation of the reaction mixture [115 °C (1 torr)] gave isoxazolidine **5** as a yellow oil (1.06 g, 92%). GLC (OV-101 column/130 °C) and NMR analysis indicated that the product consisted of one isomer (retention time 3.4 min), which was assigned the trans configuration: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.21 (t, 3 H, *J* = 7 Hz), 1.29 (t, 3 H, *J* = 7 Hz), 2.55 (dd, 1 H, *J* = 8 and 13 Hz), 2.71 (ddd, 1 H, *J* = 5, 8, and 13 Hz), 2.95 (s, 3 H), 3.48 (dq, 1 H, *J* = 7 and 10 Hz), 3.75 (dd, 1 H, *J* = 8 and 8 Hz), 3.81 (dq, 1 H, *J* = 7 and 10 Hz), 4.21 (q, 2 H, *J* = 7 Hz), 5.20 (d, 1 H, *J* = 5 Hz); IR (CCl_4) 3000–2800 (s), 1750–1700 (vs), 1450–1400 (s), 1200–1150 (vs), 1100–1000 (vs) cm^{-1}; mass spectrum (EI), *m*/*z* (relative intensity) 203 (M^+, 5), 157 (5), 130 (100), 102 (17), 84 (24).

Preparation of *cis*-α,*N*-Diphenylisoxazolidine (7). Using the method outlined above, we prepared isoxazolidine **7** from α,*N*-diphenylnitrone (**6**)[3] (1.00 g, 5.1 mmol) and vinyl acetate (25 mL). The reaction mixture was kept in the dark during the heating period. After standard workup, flash chromatography (hexane/ethyl acetate, 2:1), and recrystallization (hexane/CH_2Cl_2), white crystals of isoxazolidine **7** were obtained (1.05 g, 70%), mp 103–105 °C. TLC and NMR analysis (^{1}H and ^{13}C) indicated that only the cis isomer was produced: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3 H), 2.51 (ddd, 1 H, *J* = 2, 7, and 14 Hz), 3.19 (ddd, 1 H, *J* = 6, 10, and 14 Hz), 4.39 (dd, 1 H, *J* = 7 and 10 Hz), 6.57 (dd, 1 H, *J* = 2 and 6 Hz), 7.28 (m, 5 H), 7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, ^{1}H decoupled) δ 21.28, 46.15, 69.29, 95.54, 117.10, 123.34, 127.25, 127.87, 128.53, 128.87, 140.39, 149.57, 170.30; IR (CCl_4) 3100–3000 (m), 3000–2800 (m), 1750 (vs), 1500–1450 (m), 1400–1350 (m), 1250–1200 (s) cm^{-1}; mass spectrum (EI), *m*/*z* (relative intensity) 283 (M^+, 62), 224 (15), 206 (4), 77 (61). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.02; H, 6.01; N, 4.80.

1-Phenyl-2-methyl-2-propen-1-one (9). To a solution of 5.5 mL (0.067 mol) of methacrolein in 20 mL of dry THF under a dry nitrogen atmosphere at 0 °C was added dropwise, with stirring, a solution of 23 mL (0.069 mol, 3 M in diethyl ether) of phenylmagnesium bromide in 10 mL of dry THF. After the addition was complete, the yellow solution was allowed to warm to room temperature, and stirring was continued for 2 h. The reaction mixture was quenched with 50 mL of saturated NH_4Cl solution and was diluted with 200 mL of water. The layers were separated, and the aqueous phase was extracted twice with 20-mL portions of diethyl ether. The organic phases were combined and washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give 8.79 g (90%) of allylic alcohol as an oil: ^{1}H NMR ($CDCl_3$) δ 7.30 (5 H, s), 4.82–5.27 (3 H, m), 1.60 (3 H, s); IR (film) 3400 (br), 3070, 3040, 2980, 1495, 1450 cm^{-1}.

The crude alcohol was taken up in 10 mL of methylene chloride and was added in one portion at room temperature with stirring to a suspension of 20 g (0.093 mol) of pyridinium chlorochromate in 100 mL of methylene chloride.[18] The mixture was stirred for 2 h and then filtered through a pad of Florisil, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (200 g), eluting with 15% ethyl acetate/hexane, to give 5.77 g (67% from the crude allylic alcohol) of unsaturated ketone **9**: bp 101–103 °C (13 torr); ^{1}H NMR ($CDCl_3$) δ 7.90–7.20 (5 H, m), 5.89 (1 H, m), 5.60 (1 H, m), 2.07 (3 H, br s); IR (film) 1660, 1440, 1330, 1200 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O$: C, 82.15; H, 6.91. Found: C, 82.33; H, 6.98.

Isoxazolidine Adducts 10–12. To a solution of 1.170 g (8.00 mmol) of unsaturated ketone **9** in 15 mL of dry benzene under a dry nitrogen atmosphere at room temperature was added 0.634 g (4.31 mmol) of the nitronic ester mixture **8** (*Z*/*E* = 60:40).[12] After the solution was stirred for 48 h at room temperature, an additional 0.657 g (4.47 mmol) of the nitronic ester mixture in 2 mL of dry benzene was added. The solution was stirred for 24 h and a further 0.603 g (4.11 mmol) of the nitronate mixture in 3 mL of dry benzene was added. This solution was stirred at room temperature for an additional 48 h. The solvent was evaporated in vacuo, and the residue was purified by medium-pressure liquid chromatography on silica gel, eluting with 10% ethyl acetate/hexane, to give 0.162 g of unreacted unsaturated ketone **9**, 0.2175 g of unreacted (*E*)-nitronic ester **8**, and three isomeric isoxazolidine adducts **10–12** [total yield 1.698 g (84%) based on unrecovered ketone **9**] in a 50:15:35 ratio, respectively.

Isoxazolidine **10** (0.841 g, 50%): recrystallized from hexane; mp 77.2–78.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.15–7.27 (5 H, m), 4.31–4.12 (3 H, m), 3.67 (1 H, dd, *J* = 13 and 11 Hz), 3.06 (3 H, s), 2.30 (1 H, dd, *J* = 13 and 9 Hz), 1.75 (3 H, s), 1.27 (3 H, t); IR (KBr) 3070, 2970, 2940, 1740, 1670, 1600, 1580, 1440 cm^{-1}; mass spectrum (CI), *m*/*z* (relative intensity) 294 (11, $M^+ + 1$), 278 (9), 262 (22), 190 (100), 105 (79). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54. Found: C, 61.16; H, 6.52.

Isoxazolidine **12** (0.586 g, 35%): recrystallized from hexane; mp 66.0–67.2 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.20–7.26 (5 H, m), 4.31–4.21 (3 H, m), 3.63 (1 H, dd, *J* = 13 and 9 Hz), 3.04 (3 H, s), 2.48 (1 H, dd, *J* = 13 and 3 Hz), 1.79 (3 H, s), 1.33 (3 H, t); IR (KBr) 3070, 2970, 2940, 1740, 1670, 1590, 1570, 1440 cm^{-1}; mass spectrum (CI), *m*/*z* (relative intensity) 294 (5, $M^+ + 1$), 278

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(18), 262 (71), 190 (45), 105 (100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54. Found: C, 61.17; H, 6.51.

Isoxazolidine 11 (0.270 g, 15%): recrystallized from hexane, mp 67.5–69.0 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.11–7.26 (5 H, m), 4.34–4.16 (2 H, m), 3.99 (1 H, dd, J = 12 and 7 Hz), 3.72 (3 H, s), 3.38 (1 H, dd, J = 13 and 7 Hz), 2.81 (1 H, m), 1.84 (3 H, s), 1.30 (3 H, t); IR (KBr) 3070, 2980, 2950, 2900, 1745, 1680, 1600, 1580, 1440 cm^{-1}; mass spectrum (CI), m/z (relative intensity) 294 (14, M^+ + 1), 262 (89), 190 (100), 105 (88). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54. Found: C, 31.03; H, 6.31.

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Registry No. 1, 7372-59-0; 2, 83077-18-3; 3, 83077-19-4; (*E*)-4, 81206-60-2; (*Z*)-4, 81206-61-3; 5, 83095-76-5; 6, 1137-96-8; 7, 19744-05-9; (*E*)-8, 83148-36-1; (*Z*)-8, 65628-23-1; 9, 769-60-8; 10, 83077-20-7; 11, 83077-21-8; 12, 83077-22-9; methacrolein, 78-85-3; phenylbromide, 108-86-1; 2-methyl-1-phenyl-2-propenol, 4383-08-8; vinyl acetate, 108-05-4; ethyl vinyl ether, 109-92-2; *N*-methylhydroxylamine hydrochloride, 4229-44-1; ethyl glyoxylate, 924-44-7.

Supplementary Material Available: The NOE difference spectra (stack plots) of compounds 2, 3, 5, 7, and 10–12 (7 pages). Ordering information is given on any current masthead page.

Stereoselective Indolizidine Synthesis: Preparation of Stereoisomers of Gephyrotoxin-223AB

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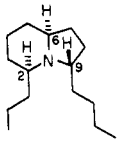
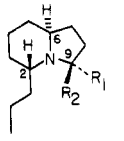
Indolizidines 2 and 3 were prepared and shown to be stereoisomers of the Dendrobatid alkaloid gephyrotoxin-223AB. A potentially useful entry to the 5-hexenyl radical manifold and an unusual ester to ketone transformation are described.

Over 90 alkaloids, several of which possess interesting pharmacological properties, have been detected in extracts from the skins of frogs belonging to the genus *Dendrobates*.[1,2] The structures of several of these alkaloids have been determined. A lack of sufficient quantities of pure substances, however, has obstructed structure determination of most of these alkaloids. On the basis of a gas chromatography–mass spectrometry survey, Daly and his co-workers suggested 2,9-disubstituted 1-azabicyclo-[4.3.0]nonane structures for several Dendrobatid alkaloids.[1] As part of a cooperative effort that led to the suggestion that gephyrotoxin-223AB (GTX-223AB) has structure 1,[3] we prepared the GTX-223AB stereoisomers 2 and 3. This report presents the details of our syntheses and discusses chemical and spectral data that support the stereochemical assignments.[4]



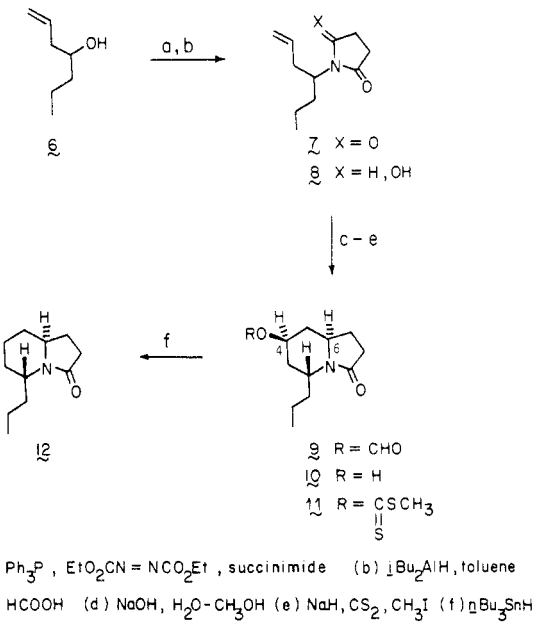
1



2 R_1 = H, R_2 = n-C_4H_9

3 R_1 = n-C_4H_9, R_2 = H

Scheme I



Our approach to the synthesis of 2 and 3 was based on the discovery that formic acid induced cyclizations[5] of

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