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INTRAMOLECULAR [4+2]-CYCLOADDITIONS OF NITROALKENES WITH OLEFINS. 2.

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Abstract: The intramolecular [4+2]-cycloadditions of di- and trisubstituted nitroalkenes with unactivated olefins are described. The cycloadditions proceed readily at low temperatures in the presence of $SnCl_4$. The reactions are shown to be stereospecific in the preservation of dienophile configuration in the product. The configuration of the heterodiene controls the stereochemistry of the ring fusion but the selectivity is high only with trisubstituted nitroalkenes. The rate of cycloaddition of a *cis* dienophile is *ca.* 20-fold faster than a *trans* dienophile. The implications for mechanism and transition structure are discussed.

INTRODUCTION

The cycloaddition reactions of heteroatom containing π-systems constitute versatile and direct methods for the construction of heterocyclic compounds. Beyond providing efficient access to heterocycles, such cycloadditions also function as general methods for creation of difunctional subunits within a carbon framework. Considering a simple olefin as the base unit, the construction of 1,2- and 1,3-difunctional arrays by [1+2]-[1] [2+2]-[2] and [3+2]-cycloaddition[3] processes, as depicted in Scheme I is a well-documented tactic.[4] The advantages of this approach accrue from 1) the stereospecificity and selectivity of pericyclic reactions, 2) the range of heteroatoms X and Y and 3) the availability of unmasking procedures for cleavage at the X-Y linkage.[5] By contrast, the construction of 1,4-difunctional arrays by a [4+2]-cycloaddition[6] with heterodienes is less common. More familiar is the use of heterodienophiles such as nitroso compounds,[7] azodicarboxylates,[8] singlet oxygen,[9] and N-sulfinyl amines[10] in conjunction with 1,3-dienes. In general, heterodienes of sufficient reactivity must be generated *in situ* and efficiently trapped by the dienophile present. Among those heterodienes, the nitrosoalkenes,[11] azoalkenes[12] and vinylnitrosonium cations[13] are suitable for the creation of the desired 1,4-difunctional pattern.

During the past several years we have undertaken a general methodological exploration of heterodiene cycloadditions based on the N=O family of hetero 4π-components, Chart I. Previous reports have described the utility and limitations of *in situ* generated nitrosoalkenes[14a] and vinylnitrosonium cations[14b] in intramolecular cycloadditions. The most recent additions to this family are nitroalkenes. Shelf-stable functions, these readily available substrates react

Scheme I

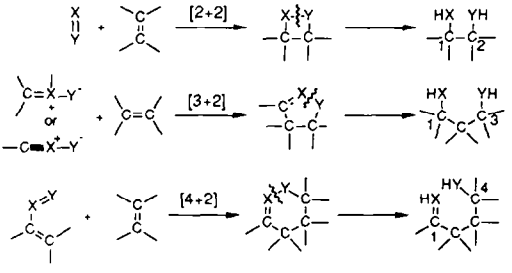
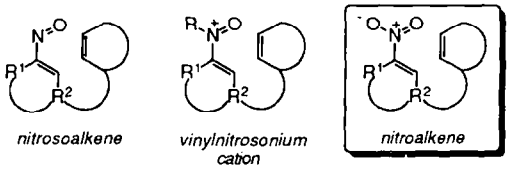
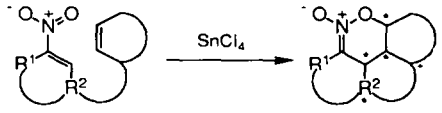


Chart I



both inter-[15] and intramolecularly[16] with unactivated olefins in the presence of $SnCl_4$ to afford cyclic nitronates,[17] Scheme II. The many further transformations and methods for unmasking of these nitronates[15a,15c] make them attractive synthetic intermediates.

Scheme II



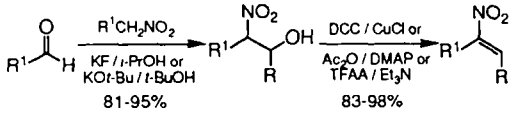
The overall objectives of this investigation are summarized by the general transformation in Scheme II. This report will describe the structural latitude in nitroalkene, dienophile and connecting tether. The stereochemical features of the reaction with acyclic as well as cyclic nitroalkenes and dienophiles will be discussed in future reports.

RESULTS

A. PREPARATION OF NITROALKENES

All of the nitroalkenes used in this study were prepared by modified Henry reaction[18] between nitromethane or nitroethane and the appropriate aldehyde. The resulting nitroalcohols were subjected to dehydration to afford the nitroalkenes in good yield, Scheme III. The preferred reagents for the nitro aldol reaction were either KF/*i*-PrOH[18c] or KO*t*-Bu.[18d] The purified nitroalcohols were transformed into nitroalkenes by elimination employing one of three dehydration protocols: 1) DCC/CuCl, 2) $(CH_3CO)_2O$

Scheme III



/DMAP or 3) $(CF_3CO)_2O/Et_3N$. The Seebach procedure[18e] (DCC/CuCl) worked well on a small scale, but afforded mixtures of nitroalkenes. The anhydride methods we have developed are particularly amenable to large scale preparations and afford di- and trisubstituted nitroalkenes of nearly exclusive *E*-configuration (>98% *E*). The $(CH_3CO)_2O$/DMAP procedure is best run in two stages with isolation of the nitro acetate. Thus, the range of cycloaddition substrates which can be examined is broad and reflects the ease of access to ω-olefinic aldehydes. A full description of the nitroalkene synthetic methods and preparation of the requisite aldehyde precursors will be published elsewhere.

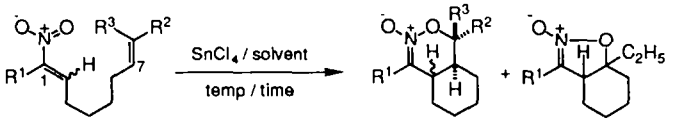
B. CYCLIZATION OF NITROALKENES

1. Optimization of Reaction Conditions. The nitroalkenes were inert to thermal cycloaddition, surviving distillation at >100°C unchanged. Thus, a suitable catalyst and reaction conditions were sought to activate the nitroalkene function. Initial studies employed various Lewis acids in CH_2Cl_2 or toluene solution. Both of these solvents were found to be suitable. Reactions are significantly faster in CH_2Cl_2 but cleaner in toluene (*vide infra*). Other solvents could be used but with no advantage.[19] Of the standard Lewis acids first surveyed $SnCl_4$ emerged as the superior reagent. Titanium tetrachloride was also effective but the reactions were less clean. Ferric chloride, boron trifluoride etherate and aluminium trichloride required ambient temperature for reactions which were nevertheless slow and messy. Recently, however, $TiCl_2(O\text{-}i\text{-}Pr)_2$ has shown promise in a related system. Generally 1.2-2.0 equivalents of $SnCl_4$ gave the best results operating in 0.04-0.1M solutions. The optimal time and temperature for the cycloaddition are highly dependent on dienophile structure and are elaborated below. Generally, the reactions are quenched with aqueous $NaHCO_3$ or methanolic NaOH to suppress acid-catalyzed decomposition of the products.

The cyclic nitronate products obtained from these reactions have only H or CH_3 groups at the nitronic carbon and were surprisingly stable.[20] They could be obtained in analytically pure form after chromatography and distillation. The assignment of structure for the cycloaddition products rests on the characteristic IR stretch (1600-1615 cm^{-1}) and ^{13}C resonance (120-125 ppm) for nitronates. Subsequent transformations and, in one case, X-ray crystallographic analysis provided further support.[16]

2. Cyclization of Disubstituted Nitroalkenes (**1**). The first experiments were performed with the disubstituted nitroalkenes (*E,E*)-**1** and (*E,Z*)-**1** which were > 98% *E* at the nitroalkene. The dienophile configurations were spectroscopically assured and quantified in the aldehydes: (1*E*,7*E*)-**1**, (7*E*/*Z* 96:4)

Table I. Cyclization of Nitroalkenes **1** and **5**

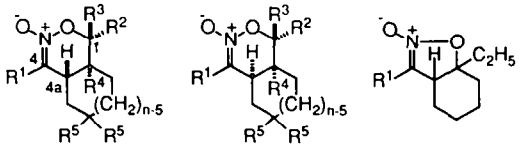


1 (5) **2 (6)** **7**

substrate[a]	R^1	R^2	R^3	*E*/*Z*[b]	solvent	temp, °C	time, h	product	*trans*/*cis*[c]	yield, %
(*E,E*)-**1**	H	CH_3	H	96/4	CH_2Cl_2	-70°→-20°	2.5	**2a**	52/48	59
(*E,Z*)-**1**	H	H	CH_3	17/83	CH_2Cl_2	-70°→-20°	2.5	**2b**	71/29	68
(*E,E*)-**5**	CH_3	CH_3	H	96/4	toluene	-29°→0°	3	**6a**	>98/<2	80[d]
(*E,Z*)-**5**	CH_3	H	CH_3	5/95	toluene	-65°	1.5	**6b**	>98/<2	95
(*Z,E*)-**5**	CH_3	CH_3	H	>98/<2	CH_2Cl_2	-70°	7	**6a**	<2/>98	63

[a] Nitroalkene double bond was >98% homogenous. [b] Ratio for dienophile double bond. [c] Ring fusion. [d] 11% of **7** was isolated.

Table II. Selected Spectroscopic Data for Nitronates



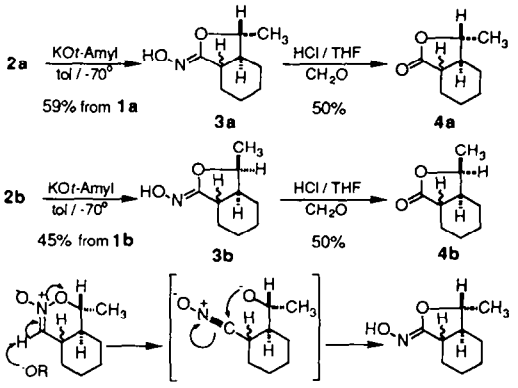
trans cis **7**

structure	R^1	R^2	R^3	R^4	R^5	n	IR, cm^{-1}	^1H NMR (ppm, Hz)		^{13}C NMR (ppm)	
							C=N	δ HC(1)[a] or HC(4a)[b]	$J_{1,8a}$[a] or $J_{4a,5}$[b]	δ C(4)	δ C(1)
trans-**2a**	H	CH_3	H	H	H	6	1616	4.30	9.8		
cis-**2a**	H	CH_3	H	H	H	6	1616	4.56	0		
trans-**2b**	H	H	CH_3	H	H	6	1615				
cis-**2b**	H	H	CH_3	H	H	6	1615				
trans-**6a**	CH_3	CH_3	H	H	H	6	1601	4.21	9.5	123.80	80.80
cis-**6a**	CH_3	CH_3	H	H	H	6	1609	4.64	9.1	c	77.30
trans-**6b**	CH_3	H	CH_3	H	H	6	1599	4.45	4.7	122.32	78.74
7	CH_3						1628			c	77.50
trans-**17**	CH_3	CH_3	CH_3	H	H	6	1601	2.01	12	122.80	83.31
trans-**18**	CH_3	CH_3	CH_3	H	CH_3	6	1601	2.19	12.0	122.75	83.25
trans-**19**	CH_3	CH_3	CH_3	CH_3	H	6	1592	2.33	12.1	122.93	86.97
trans-**21b**	CH_3	CH_3	H	H	H	5	1593	4.58	6.6	126.22	79.48

[a] For compounds **2**, **6** and **21b**. [b] For compounds **17**, **18** and **19**. [c] Not observed.

and (1*E*,7*Z*)-**1** (7*E*/*Z* 17:83). Treatment of these substrates with $SnCl_4$ in CH_2Cl_2 resulted in the rapid cyclization to the nitronates **2a** and **2b**, Table I. Analysis of the ^1H NMR spectra clearly revealed the presence of isomeric mixtures in each case. Although we suspected the mixtures arose from ring-fusion isomerism, the spectroscopic data were inconclusive. Selected spectroscopic data for the cyclic nitronates are collected in Table II. Verification of structure was obtained by transformation of **2a** and **2b** into the known lactones **4a** and **4b** by the interesting base-induced fragmentation to the hydroxamic lactones **3a** and **3b**, Scheme IV. After many failed attempts at acidic or oxidative transformations of the nitronates we discovered that a number of different bases (KOH, Triton-B, KO*t*-Bu) induced the rearrangement of **2** to **3**. Once established as isomers of **2** the products **3** were identified as hydroxamates by their characteristic IR stretches (3585, 3280 and 1694 cm^{-1}) and transformation to the know lactones **4**[21] in acidic formalin solution. The mechanism of fragmentation shown in Scheme IV finds precedent in silyl nitronate chemistry.[22]

Scheme IV



With the lactones **4a** and **4b** in hand, the stereochemical course of [4+2]-cycloaddition could be determined since all of the stereochemical information in **2** is preserved in **4**. The relative configurations of all four diastereomers of **4** had been established previously.[21] In the ^1H NMR spectrum, the chemical shift for HC(3) is diagnostic for each isomer. Quantitative integration was aided by GC analysis. The results, summarized in Table III, clearly established that the configuration of the dienophile was preserved in the products, i.e. the ratio of **4a**/**4b**

Table III. Isomer Ratios for **4a** and **4b**

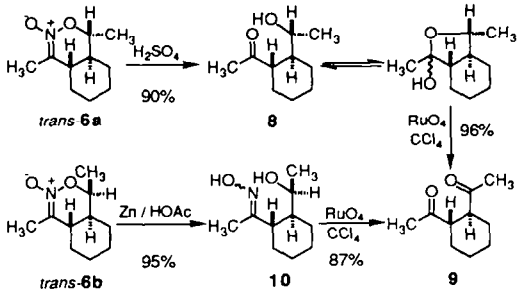
		4a		4b		
educt	*E*/*Z*[a]	*trans*	*cis*	*trans*	*cis*	exo/endo
1a[b]	96/4	52	48	0	0	52/48
1b[c]	17/83	(14.7)[d]		63.5	21.7	71/29

[a] GC analysis of aldehyde. [b] ^1H NMR analysis. [c] GC analysis. [d] Not resolved.

reflects the *E*/*Z* ratio in **1**. Unfortunately, the ring fusion stereochemistry (*trans*/*cis*-**4**) was not controlled (1/1 for (*E*,*E*)-**1**; 3/1 for (*E*,*Z*)-**1**) reflecting a close balance in the energies of the exo and endo folded transition structures. This problem was successfully addressed by use of trisubstituted nitroalkenes as described below.

3. *Cyclization of Trisubstituted Nitroalkenes.* Consideration of the transition structures for cycloaddition suggested the use of trisubstituted nitroalkenes **5** to improve exo/endo selectivity. Preliminary experiments, carried out in dichloromethane, were encouraging as the cycloadditions of **5** were considerably faster and *produced only one ring fusion stereoisomer*. However, cyclization of (*E*,*E*)-**5** gave rise to *trans*-**6a** in only 44% yield along with an isomeric product **7**. The structures of *trans*-**6a** and **7** were established by extensive spectroscopic analysis (Table II). The *trans* relationship of HC(1) and HC(8a) in **6a** was assured by a 9.5 Hz vicinal coupling constant. The *trans* ring fusion was proven by the degradation outlined in Scheme V. Applying the conditions developed in our laboratories,[15a] Nef

Scheme V.



hydrolysis of *trans*-**6a** afforded the hydroxy ketone **8** which was oxidized to the known[23] diketone (*d,l*)-**9** as a single diastereomer.

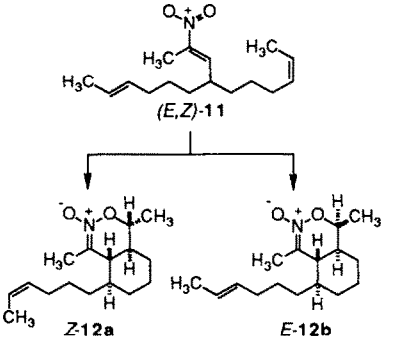
High-resolution mass spectrometry established **7** as an isomer of **6a**, while the IR stretch indicated a five-ring nitronate. The high field ethyl resonances in the ^{1}H NMR spectrum are now diagnostic for this structure. Resubjection of *trans*-**6a** to the reaction conditions did not produce **7** thus proving that the five-ring nitronate is a primary product of the reaction. With the view that **7** must arise from rearrangement of a stable zwitterionic intermediate, the reaction was performed in toluene to disfavor such a pathway. Indeed, in this solvent the yields of *trans*-**6a** and **7** became 58% and 7%, respectively. Further optimization as outlined above and in Table I gave *trans*-**6a** an 80% yield reproducibly with *ca* 11% of **7** as an easily separable by-product.

With an optimized procedure in hand we examined the influence of double bond geometry on product configuration. The data in Table I show clearly that the reactions are stereospecific in the retention of dienophile configuration (*E*→**a** series; *Z*→**b** series) and highly stereoselective in the transmission of diene configuration into ring fusion stereochemistry (*E*→*trans* series; *Z*→*cis* series). We found that *trans*-**6b** retained the *cis* relationship of protons from its precursor (*E,Z*)-**5** ($J_{1,8a}$ = 4.7) and possessed exclusively a *trans* ring fusion as evidenced by the high yield chemical correlation[15a] with diketone (*d,l*)-**9**, Scheme V. Furthermore, in a remarkable transformation (1*Z*,7*E*)-**5**, containing a *cis*-nitroalkene, underwent highly selective cyclization to *cis*-**6a**; no *trans*-**6a** was detected. The product clearly possessed a *cis* ring fusion and the *trans* configuration of the dienophile was preserved ($J_{1,8a}$ = 9.1 Hz).

Thus, the ability to produce all four possible cycloaddition diastereomers by judicious selection of precursor configuration was established.

4. Intramolecular Cis/Trans Competition Experiment. In the course of these studies we observed that, in general, *cis* dienophiles reacted faster than *trans* dienophiles. Compare, for example, the temperature for reactions of (*E,E*)-**5** versus (*E,Z*)-**5**, Table I. Because of the possible mechanistic implications and insight into transition structure we sought to verify and quantify this effect. The "two-armed" nitroalkene (*E,Z*)-**11** was designed for the purpose of evaluating an unbiased competition between *trans* and *cis* olefins, Scheme VI. Ideally the reaction will give a mixture of products *Z*-**12a** and *E*-**12b** resulting from cycloaddition with the *trans* or *cis* olefin respectively. The ratio of these products should reflect the relative rates of cycloaddition with the respective dienophile.

Scheme VI



Synthesis of the requisite aldehyde precursor for (*E,Z*)-**11** involved minor modification of the general route and will be described in detail elsewhere. The *E*-olefin was installed by an orthoester Claisen rearrangement[24a] with *ca.* 96/4 *E*:*Z* selectively while the *Z*-olefin derived from a "salt-free" Wittig ethylidenation[24b] with *ca.* 10/1 *Z*/*E* selectivity. Thus, the nitroalkene **11** constituted a ternary mixture of diolefins whose composition was established by gas chromatography as shown in Table IV. An authentic sample of (*E,E*)-**11** was prepared to allow identification of that component in the mixture.

Cyclization of two samples of **11** with different composition proceeded in good yield. The analysis of product composition relied on the characteristic resonance positions for HC(1) in the **a** and **b** series (Table II). This permitted the ratio of **12a** to **12b** to be established. Since the *E*- and *Z*-isomers of **12a** and **12b** could not be resolved by ^{1}H NMR, the ratio reflects the contribution of both (*E,E*)- and (*E,Z*)-**11** to **12a** and both (*Z,Z*)- and (*E,Z*)-**11** to **12b**. Nonetheless, the selectivity of cyclization of (*E,Z*)-**11** *alone* could be calculated by subtracting the theoretical

Table IV. Intramolecular *Cis/Trans* Competition Experiments with **11**

run	composition of **11**, %[a]			composition of **12**, %[b]				selectivity	yield, %
	(*E,E*)	(*E,Z*)	(*Z,Z*)	*E*-**12a**	*Z*-**12a**	*E*-**12b**	*Z*-**12b**	(*Z*-**12a**/*E*-**12b**)	
1	8.3	86.5	5.2	8	2	85	5	1/42	
2	13.0	83.7	3.3	13	4	80	3	1/20	89%

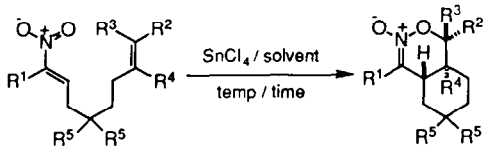
[a] Determined by GC. [b] Determined by ^{1}H-NMR, see text.

contribution of (*E,E*)-**11** from *E*-**12a** and (*Z,Z*)-**11** from *Z*-**12b**. For example, in run 2, the observed ratio of **12a/12b** was 17/83. However 13% of **12a** and 3% of **12b** must arise from the symmetrical precursors. Thus, the cyclization ratio for (*E,Z*)-**11** is (17-13)/(83-3) or 4/80 = 1/20 favoring **12b**. Therefore, the *cis* olefin in (*E,Z*)-**11** reacted twenty-fold faster than the *trans* olefin. The results of run 1 indicate a higher selectivity but we prefer the conservative estimate.

5. Dienophile Substitution. In the foregoing studies, the dienophile was in each case an unactivated, disubstituted olefin. Having established retention of configuration in both *cis* and *trans* isomers, we next explored lower and higher degrees of substitution. Thus, a series of nitroalkenes was prepared bearing pendant mono-, tri- and tetrasubstituted olefins. In all cases, the nitroalkene unit was trisubstituted and reaction partners were connected by four-atom chains. The results of these experiments are summarized in Table V. The cycloadditions proceeded extremely rapidly and in high yield for substrates **14**, **15** and **16** bearing tri- and tetrasubstituted olefins as dienophiles. Selected spectroscopic data for the cycloadducts **17-19** are collected in Table II. The reactions proceeded highly selectively in each case affording a single *trans*-fused product: only with **15** was a small (3%) amount of a *cis*-fused isomer isolated. In these compounds the *trans* ring fusion was suggested by a large (12 Hz) coupling between HC(4a) and HC(5) or HC(8a), Table II. In *cis*-**18**, H-C(4a) appears as broad singlet. The terminal vinyl group in **13** was insufficiently reactive to undergo cycloaddtion although the educt was consumed.

Finally, to evaluate the accelerating effect of $SnCl_4$ a comparison thermal reaction with **15** was performed (Table V). The result was remarkable on two accounts: 1) the isolation of **18** in 92% yield proves that the reaction is thermodynamically favorable *without* $SnCl_4$ (*vide infra*) and 2) the contrast in reaction conditions illustrates the extraordinary activating effect of the $SnCl_4$.

Table V. Dienophile Substitution Effects



13-17 *trans*-**17-19**

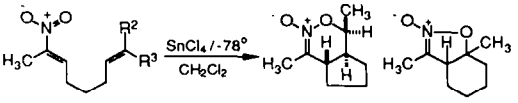
substrate	R^2	R^3	R^4	R^5	solvent	temp, °C	time, min	product	yield, %
13	H	H	H	H	CH_2Cl_2	-18	150		0
14	CH_3	CH_3	H	H	toluene	-70	15	*trans*-**17**	92
15	CH_3	CH_3	H	CH_3	toluene	-76	15	*trans*-**18**	91[a]
15	CH_3	CH_3	H	CH_3	cymene[b]	177	60	*trans*-**18**	92
16	CH_3	CH_3	CH_3	H	toluene	-70	15	*trans*-**19**	92

[a] 3% of *cis*-**18** was isolated. [b] Thermal reaction without $SnCl_4$. $CaCO_3$ added.

6. Variation of Tether Length. An important consequence of the intramolecular cycloaddition is the construction of a carbocycle using the heterocycle formation as a template. Extension of the reaction in this dimension called for the preparation of nitroalkenes with pendant olefins three and five methylene groups removed for the construction of five- and seven-membered rings.

Nitroalkenes **20a** and **20b** were subjected to optimized cycloaddition conditions. The success of the reaction was exquisitely sensitive to dienophile geometry. As shown in Scheme VII, the *E*-olefin (**20a**) gave none of the expected cycloadduct **21a** and only a trace of a rearranged product **22**. By contrast, the *Z*-olefin (**20b**) underwent facile cyclization to afford a single cycloadduct *trans*-**21b**.

Scheme VII



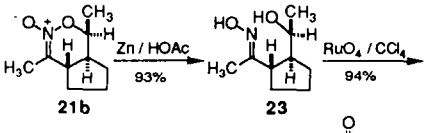
20a R^2=CH_3, R^3=H
20b R^2=H, R^3=CH_3

21a (0%)
21b (70%)

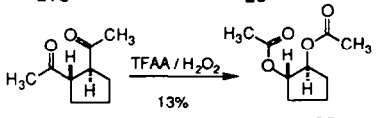
22 (11%)
(0%)

The full stereostructure of **21b** was assigned by spectroscopic and chemical methods. A 6.6 Hz $J_{1,7a}$ coupling constant assured the preservation of the *Z*-dienophile in the product. The ring fusion stereochemistry was established by conversion to cyclopentane-1,2-diol diacetate **25** (Scheme VIII). The diketone **24**, obtained by the reduction/oxidation protocol[15a] described for *trans*-**6b**, was transformed to the diacetate *trans*-**25** by Baeyer-Villiger oxidation. Authentic samples of both *cis*- and *trans*-**25** were prepared[25] and the ^1H and ^{13}C NMR, IR and GC comparisons established the *trans* ring fusion in **21b**.

Scheme VIII

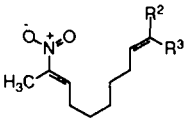


21b **23**

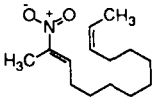


24 *trans*-**25**

To create a seven-membered ring in the cycloaddition, the series of nitroalkenes **26** was prepared. Disappointingly, under no circumstances did any of these substrates display the slightest inclination to undergo cycloaddition. No reaction was observed up to room temperature whereupon the nitroalkene polymerized. The reluctance of **26b** towards intramolecular cycyloaddition was demonstrated in a competition experiment. A 0.05 M dichloromethane solution of **26b** containing five equivalents of cyclopentene[15a] was treated with $SnCl_4$ in the usual fashion. The only products isolated (54%) were derived from intermolecular reaction. One final attempt to construct a ten-membered ring using substrate **27** was also unsuccessful.



26a R^2=CH_3, R^3=H
26b R^2=H, R^3=CH_3
26c R^2=R^3=CH_3



27

DISCUSSION

A. REACTION MECHANISM

Any discussion of this reaction on a molecular level (mechanism, stereochemistry) requires an understanding of the nature of the nitroalkene · $SnCl_4$ complex. An extensive VT-NMR study of the stoichiometry and thermochemistry of complexation[26] provided the following insights: 1) a 1:1 complex is formed; 2) the nitroalkene is a weak Lewis base ($\Delta H°$ = -4.4 - -4.8 Kcal/mol; $\Delta S°$ = 17-18 e.u.); and 3) the complexation is still dynamic at -120°C. The latter fact unfortunately precluded an assignment of structure (mono- vs. bidentate). For purposes of discussion, the complex will be depicted in between these two limits, i.e. primarily monodentate with a weak association to the other oxygen.[27]

The dramatic rate accelerating effect of $SnCl_4$ supports the inverse electron demand[28] classification of this reaction. Accordingly, a $LUMO_{diene}$/ $HOMO_{dienophile}$ frontier interaction should be enhanced by Lewis acid complexation of the diene

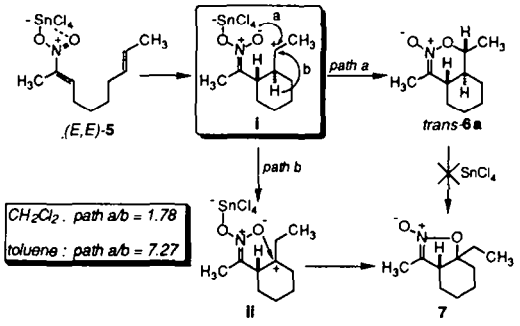
(lower LUMO) and by alkyl substitution on the dienophile (higher HOMO).

Both of these expectations are now well-documented. In addition to a LUMO lowering effect, complexation may also serve a role by bond fixing the resonance delocalized nitro group as a monodentate species. Dienophile reactivity also follows expectation in the series: mono < *trans*-di- < *cis*-di- < tri- ~ tetrasubstituted. Both **14** and **16** reacted so rapidly that relative rates were not discerned.

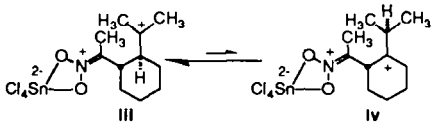
The stereospecific preservation of dienophile configuration in the cycloaddition clearly distinguishes this reaction from the enamine[17e] and enol silane[17b] additions.[29] While this satisfies one of the criteria for a concerted reaction, other features such as the isolation of by-product **7**, the solvent dependence of its formation and *cis*/*trans*-dienophile rate ratio suggest a more asynchronous pathway.

To explain the formation of **7** from (*E*,*E*)-**5** a mechanism involving the initial formation of a zwitterionic intermediate **i** is proposed, Scheme IX. This intermediate can then either collapse directly to the cycloadduct (*path a*) or suffer Wagner-Meerwein

Scheme IX



shift (*path b*) to form a tertiary cation (intermediate **ii**) followed by collapse to **7**. If **i** is indeed formed then the collapse to *trans*-**6a** must occur more rapidly than bond rotation for the olefin configuration to be retained. The formation of **i** in the rate-determining step and its partitioning in the product determining step nicely account for the slower reaction rate in toluene and the increase in the proportion of *trans*-**6a** formed. The diminished ability of toluene to support charge-separated species explains these observations. The proportion of reaction via *path b* is dependent not only on solvent but also on nitroalkene substitution and dienophile substitution and configuration. Factors which stabilize **i** should lead to a greater proportion of rearrangement to **ii** (and thence **7**). Accordingly, the intermediate analogous to **i** derived from (*E*,*E*)-**1** is *less* stable (mono- vs. disubstituted nitronate) and no rearrangement products were detected. Similarly, no ring-contraction products were detected in reactions of **14** and **15**. Although the rate acceleration observed for these substrates is consistent with the stabilization of intermediate **iii**, the Wagner-Meerwein rearrangement to **iv** is in fact thermodynamically unfavorable.[30] In the case of **16**, alkyl migration is not expected to compete with collapse to *trans*-**19**.



The formation of **7** from (*E*,*E*)-**5** but not (*E*,*Z*)-**5** is an interesting consequence of the transition state geometry (*vide infra*). The exo folding of the sidechain places the methyl group of (*E*,*E*)-**5** in the vicinity of the $SnCl_4$ · nitronate complex (see Scheme X) thereby providing a steric deterrent to direct closure via *path a*. In (*E*,*Z*)-**5** the same methyl group is now exo oriented providing a less encumbered approach of the nitronate oxygen.

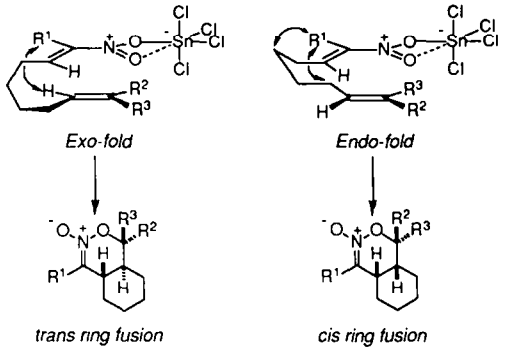
Finally, the relative rate of reaction of *cis* and *trans* dienophiles also has mechanistic implications. In concerted [4+2]-[31a] and [3+2]-[31b] cycloadditions the *trans* dienophiles (dipolarophiles) generally react faster with k_{trans}/k_{cis} ranging from 2-500. Huisgen[31b,31c] has discussed the origins of this effect. In olefins devoid of conjugative activating groups a possible cause is related to the decrease in bond angles from ~120° in the olefin to ~109° in the cycloadduct. Thus, the eclipsing interactions in the *cis*-olefin are intensified if the termini rehybridize synchronously resulting in a faster rate for the *trans* olefin. However, in a highly asynchronous (stepwise) cycloaddition only one terminus of the olefin rehybridizes in the rate

determining step. Thus, the eclipsing interactions in the *cis* olefin are released resulting in a *faster* reaction rate compared to a *trans* olefin.[31d] The observed k_{cis}/k_{trans} > 20 is consistent with the proposed stepwise mechanism. However, the magnitude of the preference may be misleading due to steric effects arising from the terminal methyl group which would also favor a *cis* over a *trans* olefin.

B. STEREOCHEMISTRY

Apart from the dienophile configuration, the only stereochemical issue in these studies is the ring fusion. The two factors shown to influence the ring fusion stereochemistry were the nitroalkene substitution and configuration. It is clear from examination of models that this stereochemical feature arises from the folding of the sidechain in the transition state. Regardless of mechanism, from a *trans* nitroalkene, a *trans* ring fusion arises from an exo fold (sidechain away from diene) and a cis ring fusion arises form an endo fold (sidechain under diene) Scheme X. In a *cis* nitroalkene, only an exo fold can be accommodated leading to a *cis* ring fusion.

Scheme X



The stereoselectivities observed in this study are readily explained by the conformations shown in Scheme X. In the disubstituted nitroalkenes **1**, the higher *trans/cis* ratio for (1*E*,7*Z*)-**1** (R^1=H,R^3=CH_3) is seen to arise from steric effects which are lesser for a *Z*-olefin in an exo (→*trans*) rather than an endo (→*cis*) fold. In the trisubstituted nitroalkenes **5**, the substitutent R^1 changes from H to CH_3. This creates a new set of interactions with the dienophile in the two modes, (arrows, Scheme X), i.e. $R^1 \Leftrightarrow H$ (exo mode) and two different $R^1 \Leftrightarrow CH_2$ (endo mode). Thus, independent of dienophile configuration, the exo fold is expected to be favored and this was the exclusive outcome. The remarkable increase in *trans* selectivity finds ample precedent in the all-carbon intramolecular Diels-Alder reaction (IMDA)[32] where analogous substitution (C(3) of the diene) also gives rise to *trans*-fused products with enhanced selectivity.[33]

With the hope of improving the poor *trans* selectivity observed with disubstituted nitroalkenes, various proton surrogate groups were attached to C(1) of the nitroalkene (Me_3Si, $Me_3SiCH_2CH_2$, $PhSO_2$, PhS, CO_2R). Unfortunately, these substrates proved either difficult to prepare or unreactive towards cycloaddition.[34]

The use of *Z*-dienes to construct *cis*-fused ring system via the IMDA reaction is well-precedented.[35] The remarkable feature of the cyclization of (*Z*,*E*)-**5** is that the nitroalkene retained its configurational identity in presence of $SnCl_4$. A similar observation has been made in the IMDA reaction of *Z*-enals with vinyl sulfides.[36]

The high *trans*-selectivity in the cyclization of **20b** was surprising as related all carbon trienes generally give mixtures.[32] Notable exceptions are highly *trans*-selective reactions in which a stepwise, cationic mechanism is suspected.[37] The failure to generate large ring sizes by this cycloaddition was disappointing, but not unexpected based on the IMDA literature.[32]

In summary, the facility of intramolecular [4+2]-cycloadditions with nitroalkenes as heterodienes has been documented. The reaction is both stereospecific and highly stereoselective in the construction of *trans*-fused bicyclic nitronates. Both five- and six-membered rings can be constructed in the process. Many substitution patterns on the diene and dienophile are tolerated. The nitronates may be unmasked by mild procedures to give keto alcohols, oximino alcohols or 1,4-diketones. Current efforts focus on 1) increasing the complexity of the dienophiles, 2) the asymmetric catalysis of cycloaddition and 3) applications in total synthesis.

EXPERIMENTAL

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian EM-390 (90 MHz ^1H), Varian XL-200 (200 MHz ^1H, 50.4 MHz ^{13}C), General Electric QE-300 (300 MHz ^1H, 75.5 MHz ^{13}C), or a Nicolet NTC-360 (360 MHz ^1H, 90.5 MHz ^{13}C) spectrometer with chloroform (δ 7.26) as an internal standard in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) or br (broadened). Coupling constants, *J*, are reported in Hz. Assignments of individual resonances are supported by APT and HETCOR spectra in most instances. Infrared spectra were obtained on a Perkin-Elmer 1320, or Nicolet 7199c FT IR spectrometer as neat liquids, in chloroform or carbon tetrachloride solutions or KBr pellets. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 34-66%), w (weak, 0-33%). Mass spectra (EI) were obtained on a Finnigan MAT CH-5 spectrometer or a Finnigan MAT 311A with an ionization voltage of 10 or 70 eV. Data are reported in the form *m/z* (intensity relative to base=100). High-resolution (EI) mass spectra were obtained on a Finnnigan MAT 731 spectrometer. High-resolution (FAB) mass spectra were obtained on a VG-ZAB-2F spectrometer.

Melting points were obtained on a Thomas Hoover capillary melting point apparatus in evacuated capillary tubes and are corrected. Bulb-to-bulb distillations were done on a Buchi GKR-50 Kugelrohr; boiling points (bp) refer to air bath temperatures and are uncorrected. Analytical TLC was performed on 0.25 mm silica gel plates (Merck) with QF-254 indicator. Visualization was accomplished with UV light, phosphomolybdic acid, iodine, sulfuric acid/methanol, vanillin and/or 2,4-DNP solution. Column chromatography[38a] was performed on 32-63 μ silica gel (Woelm) with distilled technical grade solvents. Analytical gas chromatography was performed on a Varian 3700 or HP-5890 chromatograph with flame ionization detection. The carrier gas for packed columns was N_2 (30 mL/min) and H_2 (1 mL/min) for capillary columns. Columns used were: packed, 5% TCEP on Chromosorb Q (12 ft. x 1/8 in); capillary, Carbowax 20M (25 m), OV-1 (30 m) and HP-1 (50 m). Retention times (t_R) and integrals were obtained from a Hewlett Packard 3390A or 3393A recorder. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

All reactions were performed in oven (140°C) or flame dried glassware under an inert atmosphere of dry N_2 or Ar. Tin (IV) chloride was freshly distilled for each experiment. Ruthenium (VIII) oxide solutions were prepared by the method of Nakata.[38b]

***rel*-(1*R*,4a*R*,8a*S*)- and *rel*-(1*R*,4a*S*,8a*S*)-4-Methyl-4a,5,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide (2a).** A cold (-70°C) solution of (*E,E*)-**1** (225.6 mg, 1.33 mmol) in 8 mL of dry CH_2Cl_2 was treated dropwise with 187 μL (1.60 mmol, 1.2 equiv) of $SnCl_4$. After stirring for 2.25 h at -70°C, the solution was allowed to warm to -20°C whereupon 1 mL of sat. aq. $NaHCO_3$ solution was added and the solution was allowed to warm to room temeprature. The mixture was poured into 30 mL of water and extracted with CH_2Cl_2 (3 x 30 mL). The individual organic extracts were washed with water (30 mL) and brine (30 mL), then combined and dried (Na_2SO_4). Rotary evaporation of the solvent left 215 mg of crude nitronic ester which was purified by chromatography (acetone/benzene 1/2) to yield 132.9 mg (59%). Data for **2a**: ^1H NMR (200 MHz) 6.25 (d, *J* = 3.8, 0.5 H, HC(4) one diastereomer), 6.18 (d, *J* = 2.5, 0.5 H, HC(4)), 4.56 (quintet, *J* = 6.4, 0.5 H, HC(1), *cis* isomer), 4.30 (dq, *J* = 9.8, 6.4, 0.5 H, HC(1), *trans* isomer), 2.67 (m, 0.5 H, HC(4a)), 2.15 (m, 0.5 H, HC(4a)), 1.94-0.96 (9H), 1.38 (d, *J* = 6.4, 1.5 H, $CH_3C(1)$), 1.33 (d, *J* = 6.4, 1.5 H, $CH_3C(1)$); IR ($CHCl_3$) 2990 (s), 2935 (s), 2860 (s), 1616 (s), 1453 (s), 1382 (m), 1354 (m), 1320 (m), 1285 (m), 1220 (s), 1144 (m), 1132 (m), 1117 (2), 1099 (m), 1075 (w), 1063 (m), 1027 (m), 1008 (m), 909 (s), 880 (w), 844 (w); MS (70 eV) 95 (10), 87 (10), 85 (64), 83 (100), 82 (13), 81 (26), 68 (11), 67 (31), 48 (13), 47 (26), 41 (14).

4a,5,6,7,8,8a-Hexahydro-1-methyl-1*H*-2,3-benzoxazine-3-oxide (2b). A cold (-70°C) solution of (53.1 mg, 0.314 mmol) of (*E,Z*)-**1** in 8 mL of dry CH_2Cl_2 was treated dropwise with 44 μL (0.377 mmol, 1.2 equiv) of $SnCl_4$. After stirring for 2.25 h at -70°C, the solution was allowed to warm to -20°C whereupon 1 mL of a sat. aq. $NaHCO_3$ solution was added and the solution was allowed to warm to room temperature. The mixture was poured into 20 mL of water and extracted with CH_2Cl_2 (3 x 20 mL). The individual organic extracts were washed with water (20 mL) and brine (20 mL), then combined and dried (Na_2SO_4). Rotary evaporation of the solvent left 62 mg of crude nitronic ester which was purified by chromatography (acetone/benzene 1/2) to yield 36.3 mg (68%) of **2b** as a mixture of diastereomers. The major isomer had *rel*-(4*R*,4a*R*,8a*R*) configuration. Data for **2b**: ^1H NMR (200 MHz) 6.24 (d, *J* = 3.8, ~ 0.1 H, HC(1) minor isomer), 6.18 (d, *J* = 2.9, ~ 0.6 H, HC(4) major isomer), 6.14 (d, *J* = 2.9, ~ 0.3 H, HC(4) minor isomer), 4.61-4.50 and 4.32-4.20 (m, 1 H, HC(1)), 2.91 (br s, 0.3 H, HC(4a)), 2.69 (m, 0.1 H, HC(4a)), 2.21 (m, 0.6 H, HC(4a)), 1.90-1.56 (6H), 1.45-0.95 (3.3 H),

1.33 (d, J = 6.7, 1.8 H, $CH_3C(1)$ major isomer), 1.32 (d, J = 6.4, 0.9 H, $CH_3C(4)$); IR ($CHCl_3$) 3000 (s), 2940 (s), 2865 (s), 1615 (s), 1453 (s), 1391 (m), 1377 (m), 1355 (m), 1343 (m), 1336 (m), 1298 (m), 1287 (m), 1137 (s), 1102 (m), 1095 (m), 1075 (m), 1069 (m), 1056 (2), 1021 (s), 972 (m), 913 (s), 879 (m), 849 (m), 838 (m); MS (70 eV) 169 (M^+, 10), 112 (10), 110 (16), 109 (14), 95 (58), 94 (11), 93 (16), 84 (31), 83 (50), 82 (27), 81 (63), 80 (14), 79 (30), 77 (11), 69 (14), 68 (25), 67 (100), 66 (10), 57 (13), 55 (40), 54 (23), 53 (23), 47 (15), 43 (52), 41 (65), 39 (41). TLC R_f 0.40 (acetone/benzene, 1/2).

***rel*-(3*R*,3a*S*,7a*R*) and *rel*-(3*R*,3a*S*,7a*S*)-3-Methylhexahydrophthalhydroximinolide (3a).** Crude nitronic ester **2a**, prepared from 169 mg (1.00 mmol) of (*E*,*E*)-**1**, was dissolved in 40 mL of dry toluene and treated at -78°C with 650 µL (1.20 mmol, 1.2 equiv) of potassium *t*-amylate solution (1.69 M in benzene). The solution was stirred for 2.5 h and then treated with 10 mL of a sat. aq. NH_4Cl solution and allowed to warm to room temperature. The mixture was poured into 40 mL of water and extracted with Et_2O (3 x 40 mL). The individual organic extracts were washed in series with water (40 mL) and brine (60 mL), then combined and dried (Na_2SO_4). Rotary evaporation of the solvent left 166 mg of a crude solid which was purified by chromatography (hexane/EtOAc, 2/3) to yield 73.4 mg (43% from (*E*,*E*)-**1**) of **3a** as a 1:1 mixture of diastereomers. Data for **3a**: ^1H NMR (200 MHz) 8.38 (br s, 1 H, NOH), 4.40 (quintet, J = 6.0, 0.5 H, HC(3) endo isomer), 4.12 (m, 0.5 H, HC(3) exo isomer), 2.89 (q, J = 6.7, 0.5 H, HC(7a) endo isomer), 2.2-1.95 (m, 1.5 H), 1.89-1.60 (2.5 H), 1.50-1.10 (5.5 H), 1.41 (d, J = 6.4, 1.5 H, $CH_3C(3)$ exo isomer), 1.36 (d, J = 6.4, 1.5 H, $CH_3C(3)$ endo isomer); IR ($CHCl_3$) 3590 (m, sh), 3290 (m, br), 2980 (s), 2935 (s), 2865 (s), 1733 (m), 1693 (s), 1450 (s), 1375 (s), 1349 (m), 1317 (m), 1300 (m), 1274 (m), 1163 (m), 1105 (m), 1061 (m), 1042 (s), 1023 (m), 996 (s), 975 (s), 927 (s), 913 (s), 891 (s), 860 (m), 843 (m), 8920 (m), 720 (s); MS (70 eV) 169 (M^+, 19), 152 (11), 124 (12), 110 (10), 109 (67), 95 (11), 86 (17), 84 (28), 82 (36), 81 (46), 80 (13), 79 (25), 77 (10), 68 (13), 67 (100), 60 (23), 55 (29), 54 (21), 53 (23), 43 (34), 41 (59), 39 (39).

3-Methylhexahydrophthalhydroximinolide (3b). Crude nitronic ester **2a**, prepared from 263.8 mg (1.56 mmol) of(*E*,*Z*)-**1**, was dissolved in 40 mL of dry toluene and treated at -78°C with 1.02 mL (1.72 mmol, 1.1 equiv) of potassium *t*-amylate solution (1.69 M in benzene). The resulting yellow solution was stirred for 2.5 h at -78°C at which time the reaction mixture was quenched by addition of 10 mL of a sat. aq. NH_4Cl solution and allowed to warm to room temperature. The mixture was poured into 60 mL of water and extracted with Et_2O (3 x 60 mL). The individual organic extracts were washed in series with water (60 mL) and brine (60 mL), then combined and dried (Na_2SO_4). Rotary evaporation left a crude solid which was purified by chromatography (hexane/EtOAc, 2/3) to yield 156.7 mg (59%) of **3b** as a mixture of 4 diastereomers. The major isomer had *rel*-(3*R*,3a*R*,7a*R*) stereochemistry. Data for **3b**: ^1H NMR (200 MHz) 6.45 (br s, 1 H, NOH), 4.73 (dq, J = 7.3, 6.7, ~ 0.6 H, H-C(3) major diastereomer), 4.47 (dq, J = 4.1, 6.5, ~ 0.3 H, HC(3)), 4.11 (m, ~ 0.1 H, HC(3)), 3.01 (m, ~ 0.3H), 2.35-1.80 (6.7 H), 1.40-1.10 (3H), 1.33 (d, J = 6.5, ~ 0.9 H, $CH_3C(3)$, 1.26 (d, J = 7.0, 0.3 H, $CH_3C(3)$), 1.23 (d, J = 6.7, 1.8 H, $CH_3C(3)$ major isomer); IR ($CHCl_3$) 3585 (m, sh), 3280 (m, br), 2980 (m), 2938 (s), 2861 (s), 1694 (s), 1450 (m), 1388 (m), 1369 (m), 1317 (m), 1275 (w), 1139 (m), 1099 (w), 1062 (w), 1035 (s), 995 (m), 974 (s), 909 (s), 892 (s), 820 (m); MS (70 eV) 169 (M^+, 24), 154 (22), 137 (11), 126 (10), 124 (15), 110 (12), 109 (82), 95 (11), 86 (15), 84 (22), 83 (14), 82 (24), 81 (51), 79 (25), 69 (10), 68 (13), 67 (100), 60 (20), 55 (30), 54 (15), 53 (20), 43 (25), 41 (49), 39 (29). TLC R_f 0.34 ($EtOAc/CH_2Cl_2$, 1/2).

***rel*-(3*R*,3a*S*,7a*R*) and *rel*-(3*R*,3a*S*,7a*S*)-3-Methylhexahydrophthalide (4a).** A cold (0°C) solution of **3a** (73.4 mg, 0.434 mmol) in 2.2 mL of THF was treated with 163 µL (2.2 mmol, 5 equiv) of 37% aq. formalin and 2.2 mL (2.2 mmol) of 1N HCl and was warmed to room temperature. After 6 h, the mixture was poured into 20 mL of water and extracted with Et_2O (3 x 30 mL). The individual ether extracts were washed in series with water (20 mL) and brine (20 mL), then combined and dried ($MgSO_4$). Rotary evaporation of the solvent left a residue which was purified by chromatography (hexane/EtOAc 3/1) to yield 56.6 mg (85%) of **4a** as a mixture of two diastereomers. GC analysis showed 1 peak with the same t_R as the minor diastereomers from **4b** (below). Data for **4a**: ^1H NMR (200 MHz) 4.30 (dq, J = 3.8, 6.4, 0.48 H, H-C(3) endo isomer), 4.11 (dq, J = 9.9, 6.0, 0.5 H, HC(3) exo isomer), 2.73 (q, J = 6.2, 0.48 H, HC(7a)), 2.20-1.15 (9.52 H), 1.40 (d, J = 6.0, 1.56 H, $CH_3C(3)$, exo), 1.35 (d, J = 6.4, 1.5 H, $CH_3C(3)$, endo); IR ($CHCl_3$) 2900 (m), 2940 (s), 2865 (m), 1769 (s), 1401 (m), 1383 (m), 1367 (m), 1324 (w), 1300 (w), 1184 (m), 1163 (m), 1134 (m), 1108 (m), 1059 (m), 1040 (m), 1023 (m), 991 (w), 965 (w), 910 (s); MS (10 eV) 154 (M^+, 1), 110 (15), 95 (24), 86 (14), 84 (23), 82 (67), 81 (82), 69 (12), 68 (34), 67 (100), 55 (10), 54 (26), 54 (26), 41 (11).

3-Methylhexahydrophthalide (4b). A cold (0°C) solution of **3b** (151.4 mg, 0.895 mmol) in 4.5 mL of THF was treated with 337 μL (4.5 mmol, 5 equiv) of 37% aq. formalin and 4.5 mL (4.5 mmol) of 1N HCl and warmed to room temperature. After 4 h, the mixture was poured into 20 mL of water and extracted with Et_2O (3 x 30 mL). The individual ether extracts were washed in series with water (20 mL) and brine (20 mL), then combined and dried ($MgSO_4$). Rotary evaporation of the solvent left a residue which was purified by chromatography (hexane/EtOAc, 3/1) to yield 116.6 mg (85%) of **4b** as a mixture of 4 diastereomers. GC analysis indicated 3 peaks in a ratio of 63.6:21.9:14.5 which were assigned to be the *rel*-(3*R*,3a*R*,7a*R*), *rel*-(3*R*,3a*R*,7a*S*), and a mixture of *rel*-(3*R*,3a*S*,7a*R*) and *rel*-(3*R*,3a*S*,7a*S*) diastereomers, respectively. Data for **4b**: ^{1}H NMR (200 MHz) 4.67 (m, 0.64 H, HC(3) major isomer), 4.44 (dq, J = 4.1, 6.7, 0.22 H, HC(3)), 4.30 (dq, J = 6.4, 3.8, 0.07 H, HC(3)), 4.11 (dq, J = 6.0, 9.7, 0.07 H, HC(3)), 2.75 (m, 0.29 H), 2.30-1.10 (9.68 H), 1.39 (d, J = 6.0, 0.21 H, $CH_3C(3)$), 1.33 (d, J = 6.4, 0.21 H, $CH_3C(3)$), 1.31 (d, J = 6.7, 0.66 H, $CH_3C(3)$), 1.24 (d, J = 6.7, 1.92 H, $CH_3C(3)$); IR ($CHCl_3$) 2995 (s), 2940 (s), 2865 (s), 1763 (s), 1452 (s), 1391 (s), 1367 (s), 1335 (m), 1320 (s), 1182 (s), 1163 (m), 1135 (s), 1114 (s), 1063 (m), 1034 (s), 991 (m), 968 (s), 938 (m), 916 (m), 903 (s); MS (10 eV) 154 (M^+, 1), 110 (15), 95 (21), 82 (59), 81 (82), 69 (11), 68 (31), 67 (100), 66 (12), 55 (10), 54 (23), 43 (16), 41 (13).

***rel*-(1*R*,4a*S*,8a*S*)-1,4-Dimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide (*trans*-6a) and *rel*-(3a*R*,7a*S*)-7a-Ethyl-3-methyl-3a,4,5,6,7,7a-hexahydrobenz[*d*]isoxazole-2-oxide (7).** To a cold (-29°C), magnetically-stirred solution of freshly distilled nitroalkene (2*E*,8*E*)-**5** (300 mg, 1.64 mmol) in dry toluene (41 mL) was added freshly distilled $SnCl_4$ (512 mg, 1.97 mmol, 1.2 equiv). The solution was stirred for 2.5 h, slowly warmed to 0°C and held there for 30 min, then poured into sat. aq. $NaHCO_3$ solution (30 mL), and extracted with CH_2Cl_2 (3 x 80 mL). The CH_2Cl_2 extracts were washed with water (80 mL), brine (80 mL), dried (K_2CO_3), concentrated, and the residue chromatographed on silica gel to afford two fractions. The higher R_f fraction yielded 25 mg (11%) of **7**, and the lower R_f fraction yielded 180 mg (80%) of ***trans*-6a** as a clear, colorless oil which crystallized when stored at -20°C. Data for ***trans*-6a** are reported for a distilled sample: bp 125°C (0.07 Torr); ^{1}H NMR (200 MHz) 4.21 (dq, J = 9.5, 6.1, 1 H, HC(1)), 2.03 (d, J = 1.5, 3 H, $H_3C(9)$), 2.10-1.95 (m, 2 H), 1.95-1.80 (m, 3 H), 1.30 (d, J = 6.1, 3 H, $H_3C(10)$), 1.50-0.85 (m, 5H); ^{13}C NMR (50.4 MHz) 123.80 (C(4)), 80.80 (C(1)), 42.70, 42.50, 28.90, 26.90, 25.70, 25.20, 16.60, 15.00; IR (CCl_4) 2984 (m), 2940 (s), 2861 (m), 1601 (s), 1449 (m), 1383 (w), 1345 (w), 1256 (s), 1146 (w), 1119 (m), 1075 (w), 1053 (w), 1013 (w), 986 (m), 943 (w), 909 (m), 876 (m), 847 (w); MS (10 eV) 183 (M^+, 16), 153 (10), 109 (32), 81 (13), 67 (37), 55 (15), 43 (100); TLC R_f 0.15 (benzene/acetone, 3/1). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.34; H, 9.30; N, 7.67. Data for **7**: ^{1}H NMR (360 MHz) 3.05 (dm, J = 13.1, 1 H, HC(3a)), 2.13 (m, 1H), 1.94 (d, J = 2.3, 3 H, $H_3C(8)$), 1.61 (q, J = 7.4, 2 H, $H_2C(9)$), 1.90-1.30 (m, 7 H), 0.99 (t, J = 7.4, 3 H, $H_3C(10)$); ^{13}C NMR (90.6 MHz) 77.50 C(7a), 55.10 C(3a), 31.00, 24.80, 22.30, 21.60, 20.90, 10.10 C(8), 7.20 C(10), (C(3) was not located); IR (CCl_4) 2942 (s), 2880 (m), 1628 (s), 1464 (m), 1393 (m), 1343 (s), 1327 (w), 1304 (w), 1273 (s), 1250 (m), 1215 (s), 1138 (m), 1080 (w), 934 (m), 909 (s), 885 (m), 847 (s), 831 (m); MS (10 eV) 183 (M^+, 18), 154 (12), 126 (15), 112 (12), 110 (14), 98 (14), 97 (13), 96 (11), 95 (22), 94 (37), 93 (15), 84 (30), 82 (10), 81 (47), 79 (15), 71 (12), 70 (10), 69 (14), 68 (31), 57 (100), 55 (17), 43 (35), 42 (24), 41 (27), 32 (15), 31 (20); high resolution MS calcd for $C_{10}H_{17}NO_2$ 183.12593, found 183.12577; TLC R_f 0.65 (benzene/acetone, 3/1)

***rel*-(1*R*,4a*S*,8a*R*)-1,4-Dimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide(*cis*-6a).** To a cold (-78°C), magnetically-stirred solution of (2*Z*,8*E*)-**5** (30 mg, 0.16 mmol) in dry CH_2Cl_2 (4.1 mL) was added $SnCl_4$ (51 mg, 0.20 mmol, 1.2 equiv). The solution was stirred for 7 h, quenched by addition of sat. aq. $NaHCO_3$ solution (0.5 mL), poured into water (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), concentrated, and the residue chromatographed on silica gel and distilled to afford 19 mg (63%) of *cis*-**6a** as a clear, colorless oil which crystallized when stored at -20°C. Data for *cis*-**6a**: bp 115°C (0.08 Torr); ^{1}H NMR (360 MHz) 4.64 (dq, J = 9.1, 6.2, 1 H, HC(1)), 2.40 (m, 1 H, HC(8a)), 2.04 (s, 3 H, $H_3C(9)$), 1.33 (d, J = 6.2, 3 H, $H_3C(10)$), 2.00-1.20 (m, 9H); ^{13}C NMR (50.4 MHz) 77.30 (C(1)), 37.70, 35.90, 27.30, 25.60, 24.80, 21.40, 17.20, 17.00 (C(4) was not located); IR (CCl_4) 2982 (m), 2938 (s), 2863 (m), 1609 (s), 1451 (m), 1379 (m), 1341 (w), 1273 (s), 1256 (s), 1198 (w), 1132 (w), 1055 (w), 1009 (m), 909 (m), 884 (w), 870 (w), 855 (w); MS (10 eV) 183 (M^+, 13), 109 (32), 81 (12), 67 (31), 55 (14), 43 (100); TLC R_f 0.13 (benzene/acetone, 3/1); Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.39; H, 9.15; N, 7.65.

***rel*-(1*R*,2*R*,9*R*)-1-[2-(Hydroxyethyl)cyclohexyl]ethanone (8).** Nitronate *trans*-**6a** (250 mg, 1.36 mmol) was added in one portion to a cold (0°C), magnetically-stirred solution of 1:1 THF / 0.18 M aq. sulfuric acid (5 mL). After 5 h the reaction mixture was poured into sat. aq. $NaHCO_3$ solution (15 mL) and extracted with ether (3 x 15 mL). The ether extracts were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), concentrated, and the residue sublimed (50°C at 4 Torr) to afford 209 mg (90%) of **8** as white plates. Analytical data are reported for a sample which was further crystallized from hexane. In solution this compound exists as a 54:33:13 equilibrium mixture of open hydroxyketone (33%) and the two anomeric hemiketals (54% and 13%). Data for **8:** mp 64-65°C, ^{1}H NMR (300 MHz) 3.75 (dq, J = 9.5, 6.1, 0.13 H, $HC(1)_{hemi(2)}$), 3.58 (dq, J = 9.5, 6.1, 0.54 H, $HC(1)_{hemi(1)}$), 3.41 (m, 0.33 H, $HC(1)_{open}$), 2.71 (br exch, 0.13 H, $OH_{hemi(2)}$), 2.16 (br exch, 0.33 H, OH_{open}), 1.95-1.65 (m, 5H), 1.42 (br exch, 0.54 H, $OH_{hemi(1)}$), 1.40-0.90 (m, 11 H); ^{13}C NMR (75.5 MHz) 103.49, 79.69, 77.87, 71.84, 54.98, 54.26, 51.38, 49.14, 46.60, 29.77, 28.90, 27.96, 27.48, 27.38, 26.10, 25.93, 25.77, 25.54, 25.41, 25.27, 25.23, 25.13, 24.91, 21.01, 20.51, 18.97, the carbonyl carbon for the free hydroxyketone was not located; IR (CCl_4) 3613 (m), 3403 (m), 2973 (s), 2928 (s), 2857 (s), 1703 (w), 1447 (m), 1375 (s), 1310 (w), 1273 (w), 1246 (m), 1146 (s), 1101 (m), 1061 (s), 1046 (s), 967 (m), 914 (s), 893 (m), 868 (m), 833 (m); MS (10 eV) 126 (71), 111 (28), 110 (51), 109 (34), 97 (23), 95 (40), 83 (15), 82 (39), 81 (100), 71 (23), 69 (19), 68 (49), 67 (75), 66 (12), 59 (10), 58 (11), 55 (13), 54 (10), 43 (42); TLC R_f 0.16 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66. Found: C, 70.33; H, 10.78.

***rel*-(1*R*,2*R*)-1,2-Diacetylcyclohexane (*dl*-9).** To a cold (0°C), magnetically-stirred solution of hydroxy ketone **8** (200 mg, 1.18 mmol) in CCl_4 (20 mL) covered with water (0.2 mL) was added all at once a solution of RuO_4 in CCl_4 (0.06 M, 12.6 mL). After 2 min the cooling bath was removed and the black mixture stirred for 30 min, quenched with excess 2-propanol (0.2 mL) and filtered. The precipitate was washed thoroughly with CCl_4 and the filtrate was then washed with water (20 mL), dried (Na_2SO_4), concentrated. The residue was distilled to afford 190 mg (96%) of *dl*-**9** as a clear, colorless oil. Data for (*d,l*)-**9**: bp 120°C (10 Torr); ^{1}H NMR (300 MHz) 2.71 (m, 2 H), 2.14 (s, 6 H), 2.03 (m, 2 H), 1.80 (m, 2 H), 1.25 (m, 2 H), 1.10 (m, 2 H); ^{13}C NMR (75.5 MHz) 211.45, 51.80, 28.58, 28.28, 25.66; IR (CCl_4) 2938 (s), 2859 (s), 1713 (s), 1449 (s), 1426 (m), 1356 (s), 1314 (m), 1296 (m), 1242 (s), 1169 (s), 1115 (m), 1092 (m), 1044 (s), 1015 (m), 953 (m), 920 (w), 887 (w), 858 (w); TLC R_f 0.34 (hexane/EtOAc, 2/1). For *bis*-2,4-DNP derivative: mp 202°C d; UV ($CHCl_3$) λ_{max}=361nm (ε=46,600).

***rel*-(1*R*,4a*R*,8a*R*)-1,4-Dimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide (*trans*-6b).** To a magnetically-stirred solution of (*E,Z*)-**5** (222.3 mg, 1.21 mmol) in toluene (15 mL) at -62°C was added dropwise $SnCl_4$ (283 µL, 2.42 mmol, 2.0 equiv). The mixture was stirred for 1.5 h at -62~-65°C and quenched with sat. aq. $NaHCO_3$ solution (10 mL) and poured into separatory funnel. The mixture was diluted with CH_2Cl_2 (50 mL), water (30 mL), and separated. The organic layer was washed with sat. aq. $NaHCO_3$ solution (30 mL), and brine (30 mL). The aqueous layers were back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by radial chromatography (hexane/EtOAc, 5/1, 100 mL; hexane/EtOAc, 5/2, 100 mL; hexane/EtOAc, 5/3, 100 mL) afforded 212 mg (96%) of *trans*-**6b** as a viscous oil which was recrystallized from hexane. Data for *trans*-**6a**: mp 42-43°C (hexane); bp 120°C (0.05 Torr); ^{1}H NMR (300 MHz) 4.45 (dq, J = 6.6, 4.7, 1 H, HC(1)), 2.10-2.04 (m, 2 H, HC(4a)), 2.02 (d, J = 1.1, 3 H, $H_3C(9)$), 1.91-1.82 (m, 3 H), 1.67 (d, J =12.3, 1 H), 1.39-1.00 (m, 4 H), 1.26 (d, J = 6.6, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) 122.47 (C(4)), 78.94 (C(1)), 39.25 (C(4a)), 36.74 (C(8a)), 28.51 (C(5)), 27.25 (C(8)), 25.22 (C(6)), 24.83 (C(7)), 14.51 (C(9)), 12.67 (C(10)); IR (CCl_4) 2982 (w), 2937 (s), 2860 (m), 1653 (w), 1599 (s), 1448 (m), 1382 (w), 1338 (w), 1311 (w), 1292 (w), 1270 (m), 1258 (s), 1230 (m), 1148 (w), 1123 (w), 1077 (w), 1059 (w), 1048 (w), 1012 (w), 988 (m), 943 (w), 907 (m), 859 (m), 845 (w); MS (70 eV) 185 (M^+ + 2, 1), 184 (M^+ + 1, 7), 183 (M^+, 55), 168 (1), 166 (2), 154 (4), 153 (37), 140 (4), 122 (3), 121 (3), 111 (5), 110 (11), 109 (100), 107 (7), 97 (7), 95 (9), 93 (9), 82 (6), 81 (30), 80(7), 79 (8), 69 (13), 67 (71), 55 (25); TLC R_f 0.10 (hexane/EtOAc, 1/1), 0.35 (EtOAc). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found : C, 65.26; H, 9.17; N, 7.74

***rel*-(1*R*,2*R*,9*R*)-1-[2-(Hydroxyethyl)cyclohexyl]ethanone Oxime (10).** To a magnetically-stirred solution of *trans*-**6b** (330 mg, 1.80 mmol) in 20 mL of Et_2O was added Zn dust (1.14 g, 17.4 mmol, 9.7 equiv) and 25% aq. acetic acid (1 mL). The mixture was refluxed for 40 min and stirred at room temperature for 1 h. The mixture was filtered and the filtrate was diluted with Et_2O (30 mL) and water (20 mL). The separated organic layer

was washed with sat. aq. $NaHCO_3$ solution (20 mL), and brine (20 mL). The aqueous layers were back extracted with Et_2O (2 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the residue was recrystallized from hexane to afford 328.3 mg (94%) of **10** as a white solid. Data for **10**: mp 77-78.5°C (hexane); ^1H NMR (300 MHz) 7.0-5.0 (br s, 2 H, HONC(9), HOC(7)), 3.67 (quintet, J = 6.5, 1 H, HC(7)), 3.25 (td, J = 11.3, 2.8, 0.33 H, HC(1), *cis* isomer), 2.34 (td, J = 11.1, 0.67 H, HC(1), *trans* isomer), 1.81 (s, 2 H, $H_3C(10)$, *trans* isomer), 1.77 (s, 1 H, $H_3C(10)$, *cis* isomer), 1.89-1.60 (m, 4 H, $H_{eq}C(3)$, $H_{eq}C(4)$, $H_{eq}C(5)$, $H_{eq}C(6)$), 1.43-1.07 (m, 5 H, $H_{ax}C(2)$, $H_{ax}C(3)$, $H_{ax}C(4)$, $H_{ax}C(5)$, $H_{ax}C(6)$), 1.11 (d, J = 6.5, 3 H, $H_3C(8)$); ^{13}C NMR (75.5 MHz) *trans* oxime 162.44 (C(9)), 66.71 (C(7)), 45.55 (C(2)), 44.93 (C(1)), 30.22 (CH_2), 25.81 (CH_2), 25.54 (CH_2), 23.00 (CH_2), 20.01 (C(8)), 10.35 (C(10)); *cis* oxime 162.03 (C(9)), 67.43 (C(7)), 45.23 (C(2)), 38.15 (C(1)), 29.38 (CH_2), 25.68 (CH_2), 25.54 (CH_2), 22.86 (CH_2), 18.34 (C(8)), 16.06 (C(10)); IR (CCl_4) 3594 (w, OH), 3322 (m, br), 2977 (m), 2934 (s), 2859 (m), 1655 (w), 1545 (w), 1449 (m), 1370 (m), 1262 (w), 1156 (w), 1127 (w), 1073 (w), 1042 (m), 995 (w), 968 (m), 922 (w), 897 (w), 851 (w), 835 (w); MS (70 eV) 185 (M^+, 0.4), 171 (0.5), 170 (M^+ - CH_3, 5), 169 (6), 168 (M^+ - OH, 53), 167 (12), 153 (41), 152 (10), 150 (17), 142 (10), 141 (54), 140 (12), 138 (31), 128 (12), 126 (13), 125 (10), 124 (40), 110(20), 10((43), 100 (11), 95 (14), 86 (97), 83 (15), 82 (57), 81 (15), 73 (100), 67 (29), 60 (12); TLC R_f 0.69 (EtOAc). Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.84; H, 10.34; N, 7.56. Found: C, 64.88; H, 10.37; N, 7.56.

***rel*-(1*R*,2*R*)-1,2-Diacetylcyclohexane (9).** To a magnetically-stirred solution of **10** (72.4 mg, 0.39 mmol) in CCl_4 (2 mL) was added a solution of RuO_4 in CCl_4 at 0°C. The oxidant was added until TLC analysis indicated consumption of **10**. The ice bath was then removed and the reaction was quenched with 2-propanol (0.5 mL) and diluted with CH_2Cl_2 (20 mL). The black suspension was passed through short plug (2 x 10 cm) of Celite and concentrated. The crude product was purified by column chromatography (hexane, 100 mL; hexane/EtOAc, 20/1, 100 mL; hexane/EtOAc, 10/1, 100 mL; hexane/EtOAc, 5/1, 300 mL); to afford 59.5 mg (91%) of **9** as a clear, colorless oil. Data for **9**: ^1H NMR (300 MHz): 2.74 (m, 2 H, HC(1), HC(2)), 2.17 (s, 6 H, $H_3C(8)$, $H_3C(10)$), 2.05 (m, 2 H, $H_{eq}C(3)$, $H_{eq}C(6)$), 1.80 (m, 2 H, $H_{eq}C(4)$, $H_{eq}C(5)$), 1.25 (m, 2 H, $H_{ax}C(3)$, $H_{ax}C(6)$), 1.10 (m, 2 H, $HC_{ax}(4)$, $H_{ax}C(5)$); ^{13}C NMR (75.5 MHz) 211.34 (C(7), C(9)), 51.63 (C(1), C(2)), 28.43 (C(8), C(10)), 28.11 (C(3), C(6)), 25.52 (C(4), C(5)); IR (CCl_4) 3006 (w), 2936 (m), 2859 (m), 1713 (s), 1449 (w), 1424 (w), 1356 (m), 1298 (w), 1239 (w), 1169 (m), 1113 (w), 1034 (w), 967 (w), 887 (w).

***rel*-(1*R*,4a*R*,8a*R*,5*S*)-1,4-Dimethyl-5-[(*E*)-4-hexenyl]-4a,5a,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide (*E*-12b).** To a magnetically-stirred solution of (*E*,*Z*)-**11** (145.3 mg, 0.55 mmol) in toluene (18 mL, 0.03 M soution) at -78°C was added dropwise $SnCl_4$ (130 μL, 1.09 mmol, 2.0 equiv). After stirring for 30 min, at -72°C, the mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL). The resulting white emulsion was diluted with CH_2Cl_2 (20 mL) and warmed to room temperature (~20 min). The mixture was filtered and the filtrate was diluted with CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ solution (20 mL). The organic layer was separated and was washed with water (20 mL) and brine (20 mL). The aqueous layers were back extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude, pale-orange oil was purified by chromatography (hexane, 100 mL; hexane/EtOAc, 10/1, 100 mL; hexane/EtOAc, 5/1, 100 mL; hexane/EtOAc, 5/2, 100 mL; hexane/EtOAc, 5/3, 200 mL; hexane/EtOAc, 5/4, 200 mL; hexane/EtOAc, 1/1, 200 mL) to afford 8.0 mg (5.5%) of *E*-**12a**, 5.7 mg (3.9%) of a mixture and 115.0 mg (79.2%) of *E*-**12b**. The major product was distilled under high vacuum. Data for *E*-**12b**: bp 95°C (3.0 x 10^{-5} Torr), 110°C (3 x 10^{-3} Torr); ^1H NMR (300 MHz) 5.42-5.30 (m, 2 H, HC(12), HC(13)), 4.64 (dq, J = 8.4, 6.6, 1 H, HC(1)), 2.04 (s, 3 H, $H_3C(15)$), 1.62 (d, J = 5 6, 3 H, $H_3C(14)$), 1.23 (d, J = 6.6, 3 H, $H_3C(16)$), 2.10-0.87 (m, 15 H, HC(4a), HC(5), $H_2C(6)$, $H_2C(7)$, $H_2C(8)$, HC(8a), $H_2C(9)$,$H_2C(10)$, $H_2C(11)$); ^{13}C NMR (75.5 MHz) 130.52 (C(12)), 130.18 (C(4)), 124.99 (C(13)), 79.84 (C(1)), 43.96 (C(8a)), 43.53 (C(4a)), 37.27 (C(5)), 35.16 (CH_2), 32.26 (CH_2), 31.19 (CH_2), 26.62 (CH_2), 26.23 (CH_2), 24.55 (CH_2), 17.58 (C(14)), 14.17 (C(16)); IR (CCl_4) 2934 (s), 2859 (m), 1595 (s), 1449 (w), 1385 (w), 1254 (m), 1213 (m), 1171 (w), 1136 (w), 1007 (w), 968 (m), 909 (w), 870 (m); MS (70 eV) 267 (M^+ + 2, 3), 266 (M^+ + 1, 17), 265 (M^+, 61), 251 (3), 250 (18), 236 (7), 235 (32), 217 (12), 207 (5), 206 (17), 204 (13), 192 (6), 191 (12), 189 (8), 182 (13), 178 (6), 177 (9), 175 (6), 166 (8), 165 (6), 164 (8), 163 (14), 162 (7), 161 (13), 149 (17), 147 (16), 138 (9), 136 (14), 135 (53), 133 (15), 125 (6), 123 (20), 122 (17), 121 (43), 119 (11), 110 (13), 109 (78), 107 (33), 97 (16), 96 (13), 95 (100), 93 (27), 88 (10), 86 (11), 84 (13), 83 (28), 81 (91), 79 (16), 71 (11), 69 (33); TLC R_f 0.20 (EtOAc). Anal. Calcd for $C_{16}H_{27}NO_2$ (265.39): C, 72.41; H, 10.26; N, 5.28. Found: C, 72.59; H, 10.25; N, 5.21.

***rel*-(1*R*,4a*S*,8a*S*,5*R*)-1,4-Dimethyl-5-[(*E*)-4-hexenyl]-4a,5,6,7,8,8a-hexahydro-1*H*-2,3-benzoxazine-3-oxide (*E*-12a).** To a magnetically-stirred solution of (*E*,*E*)-**11** (84 mg, 0.317 mmol) in toluene (3.2 mL, 0.1 M solution) at -68°C was added $SnCl_4$ (74 μL, 0.633 mmol, 2.0 equiv). After stirring for 1 h at -68°C, the mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and diluted with EtOAc (30 mL). The mixture was allowed warm to room temperature slowly and the white precipitate was filtered off and washed with EtOAc (2 x 10 mL). The collected binary layers were washed with 0.1 NaOH (20 mL), sat. aq. $NaHCO_3$ solution (20 mL), and brine (20 mL). The aqueous layers were back extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford 94.9 mg of nitronate. The pale yellow oil was purified by chromatography (hexane, 100 mL; hexane/EtOAc, 10/1, 100 mL; hexane/EtOAc, 5/1, 100 mL; hexane/EtOAc, 5/2, 100 mL; hexane/EtOAc, 5/3, 200 mL; hexane/EtOAc, 5/4, 200 mL; hexane/EtOAc, 1/1, 200 mL) to afford 8.3 mg (9.9%) of (*E*,*E*)-**11**, 8.5 mg (10.1%) of a rearranged nitronate and 67.7 mg (74.6%) of *E*-**12a.** Data for *E*-**12a**: bp 100°C (1.0 x 10^{-3} Torr); ^{1}H NMR (300 MHz) 5.52-5.30 (m, 2 H, HC(12), HC(13)), 4.09 (qd, *J* = 7.0, 6.4, 1 H, HC(1)), 2.05 (d, *J* = 1.8, 3 H, $H_3C(15)$), 1.62 (d, *J* = 3.8, 3 H, $H_3C(14)$), 1.38 (d, *J* = 7.0, 3 H, H C(16)), 1.96-0.89 (m, 15 H, HC(4a), HC(5), $H_2C(6)$, $H_2C(7)$, $H_2C(8)$, HC(8a), $H_2C(9)$, $H_2C(10)$, $H_2C(11)$); ^{13}C NMR (75.5 MHz) 130.80 (C(12)), 130.08 (C(4)), 125.37 (C(13)), 84.52 (C(1)), 48.52 (C(8a)), 44.80 (C(4a)), 37.03 (C(5)), 35.19 (CH_2)), 32.54 (CH_2), 31.47 (CH_2), 30.41 (CH_2), 26.49 (CH_2), 24.62 (CH_2), 20.41 (C(16)), 17.89 (C(14)), 14.10 (C(15)); IR (CCl_4) 2926 (s), 2859 (m), 1653 (w), 1593 (s, NO_2), 1447 (w), 1379 (w), 1304 (w), 1254 (w), 1215 (m), 1136 (w), 1005 (m), 968 (m), 866 (m); MS (70 eV) 267 (M^+ + 2, 1), 266 (M^+ + 1, 6), 265 (M^+, 31), 250 (9), 235 (32), 234 (18), 220 (3), 217 (4), 209 (3), 207 (8), 206 (8), 204 (9), 192 (5), 191 (9), 182 (12), 177 (14), 164 (21), 163 (13), 151 (47), 149 (13), 135 (38), 123 (15), 122 (14), 121 (32), 109 (56), 107 (22), 97 (11), 95 (72), 93 (14), 83 (15), 81 (53), 69 (23), 68 (21), 67 (22), 57 (17), 55 (19), 41 (100); TLC R_f 0.20 (EtOAc, *E*-**12b**), 0.27 (EtOAc, *E*-**12a**). Anal. Calcd for $C_{16}H_{27}NO_2$ (265.39): C, 72.41; H, 10.26; N, 5.28. Found: C, 72.04; H, 10.07; N, 5.20.

***rel*-(4a*R*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-1,1,4-trimethyl-1*H*-2,3-benzoxazine-3-oxide (*trans*-17).** To a magnetically-stirred solution of **14** (149 mg, 0.76 mmol) in toluene (7.6 mL, 0.1 M solution) was added dropwise $SnCl_4$ (176 μL, 1.52 mmol, 2.0 equiv) at -70°C. After 15 min, the mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and diluted with EtOAc (10 mL). The mixture was allowed warm to room temperature (~20 min) and then was filtered. The white solid was washed with EtOAc (2 x 20 mL) and the combined heterogeneous filtrate washed with sat. aq. $NaHCO_3$ solution (30 mL) and brine (30 mL). The aqueous layers were back extracted with EtOAc(2 x 40 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified by chromatography (hexane/EtOAc, 5/2, 100 mL; hexane/EtOAc, 2/1, 100 mL; hexane/EtOAc, 5/3, 100 mL; hexane/EtOAc, 1/1, 200 mL; EtOAc, 300 mL) to afford 137.5 mg (92 %) of *trans*-**17**. An anlytical sample was recrystallized from hexane. Data for *trans*-**17**: mp 54-56°C (hexane); bp 90°C (5 x 10^{-2} Torr); ^{1}H NMR (300 MHz) 2.01 (s, 3 H, $H_3C(9)$), 2.08-1.94 (m, 2 H, HC(4a) and ?), 1.86-1.77 (m, 3 H), 1.51 (dt, *J* = 11.4, 1.4, 1 H), 1.30 (s, 3 H, $H_3C(10)$), 1.21 (s, 3 H, $H_3C(11)$), 1.38-1.21 (m, 2 H), 1.21-1.11 (m, 1H), 0.94 (dq, *J* = 12.0, *J* = 3.1, 1 H); ^{13}C NMR (75.5 MHz) 122.80 (C(4)), 83.31 (C(1)), 45.11 (C(8a)), 39.19 (C(4a)), 28.87 (C(5)), 26.21 (C(8)), 25.37 (C(6)), 25.15 (C(7)), 24.95 (C(10)), 18.19 (C(11)), 14.67 (C(9)); IR (CCl_4) 2984 (m), 2942 (s), 2861 (m), 1601 (s), 1449 (m), 1387 (m), 1374 (m), 1320 (w), 1266 (s), 1250 (m), 1213 (w), 1190 (m), 1144 (m), 1021 (w), 972 (w), 909 (s), 893 (m), 866 (m), 847 (w). MS (70 eV) 199 (M^+ + 2, 1), 198 (M^+ + 1, 11), 197 (M^+, 60), 168 (7), 166 (5), 152 (6), 149 (17), 135 (8), 126 (6), 125 (5), 124 (9), 123 (22), 122 (7), 121 (8), 111 (7), 110 (17), 109 (84), 108 (14), 107 (20), 102 (6), 100 (8), 98 (9), 97 (17), 96 (13), 95 (28), 93 (25), 85 (11), 83 (16), 82 (19), 81 (55), 80 (11), 71 (11), 70 (9), 69 (49), 68 (13), 67 (100), 59 (14), 57 (11), 56 (11), 55 (45); TLC R_f 0.17 (EtOAc). Anal. Calcd for $C_{11}H_{19}NO_2$ (197.27): C, 66.97; H, 9.63; N, 7.10. Found: C, 66.84; H, 9.67; N, 7.12.

***rel*-(4a*R*,8a*R*)-4a,5,7,8,8a-Pentahydro-1,1,4,6,6-pentamethyl-1*H*-2,3-benzoxazine-3-oxide (*trans*-18).** To a magnetically-stirred solution of **15** (152.3 mg, 0.67 mmol) in toluene (7.0 mL, 0.1 M solution) was added dropwise $SnCl_4$ (156 μL, 1.34 mmol, 2.0 equiv) at -70°C. After 15 min, the mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and diluted with EtOAc (40 mL). The mixture was allowed warm to room temperature (~20 min) and then was filtered. The white solid was washed with EtOAc (2 x 20 mL) and the combined heterogeneous solution was washed with sat. aq. $NaHCO_3$ solution (30 mL) and brine (30 mL). The aqueous layers were back extracted with EtOAc (2 x 40 mL). The combined organic layers were dried (Na_2SO_4) filtered and concentrated. Purification by chromatography (hexane/EtOAc, 10/3, 200 mL; hexane/EtOAc, 2/1, 100 mL; hexane/EtOAc, 5/3, 100 mL; EtOAc, 500 mL) afforded 137.8 mg (91%) of *trans*-**18** and 4.9 mg (3%) of the

cis isomer as a viscous oil. Data for *trans*-**18**: mp 61-62.5°C (hexane); bp 70-80°C (5 x 10^{-4} Torr); ^{1}H NMR (300 MHz) 2.19 (br t, J = 12.0, 1 H, HC(4a)), 1.99 (s, 3 H, $H_3C(11)$), 1.71-1.00 (m, 7 H, $H_2C(5)$, $H_2C(7)$, $H_2C(8)$, HC(8a)), 1.32 (s, 3 H, $H_3C(12)$), 1.24 (s, 3 H, $H_3C(13)$), 0.97 (s, 3 H, $H_3C(9)$), 0.93 (s, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) 122.75 (C(4)), 83.25 (C(1)), 45.60 (C(8a)), 41.56 (C(6)), 38.07 (C(5)), 34.90 (C(4a)), 32.21 (CH_3), 30.56 (C(7)), 25.10 (CH_3), 24.48 (CH_3), 22.38 (C(8)), 18.34 (CH_3), 14.62 (C(11)); IR (CCl_4) 2955 (s), 2869 (m), 1601 (s), 1456 (m), 1386 (m), 1373 (m), 1327 (w), 1310 (w), 1274 (s), 1205 (m), 1154 (m), 1100 (w), 1016 (w), 960 (m), 937 (w), 904 (m), 877 (m), 835 (w), 818 (m); MS (70 eV) 224 (M^+ - 1, 1), 223 (2), 217 (2), 196 (13), 195 (100), 194 (14), 179 (9), 166 (4), 152 (11), 151 (11), 137 (6), 123 (3), 121 (4), 109 (10), 95 (11), 83 (6), 81 (5), 42 (22); TLC R_f 0.42 (EtOAc), 0.10 (hexane/EtOAc, 10/1). Data for *cis*-**18**: ^{1}H NMR (300 MHz) 2.8 (br s, 1 H, HC(4a)), 2.06 (s, 3 H, $H_3C(11)$), 0.85-1.81 (m, 7 H, $H_2C(5)$, $H_2C(7)$, $H_2C(8)$, HC(8a)), 1.35 (s, 3 H, $H_3C(12)$), 1.34 (s, 3 H, $H_3C(13)$), 0.91 (s, 3 H, $H_3C(9)$), 0.81 (s, 3 H, $H_3C(10)$); IR (CCl_4) 2953 (s), 1601 (s), 1460 (w), 1370 (w), 1310 (w), 1285 (m), 1264 (m), 1215 (m), 1146 (m), 1015 (w), 909 (s), 880 (w), 816 (s), 810 (w); TLC R_f 0.31 (EtOAc). Anal. Calcd for $C_{13}H_{23}NO_2$ (225.33): C, 69.29; H, 10.24; N, 6.22. Found: C, 69.11; H, 10.24; N, 6.34.

Thermal Cycloaddition of 15. A magnetically-stirred solution of **15** (64.8 mg, 0.11 mmol) in cymene (5.0 mL, 0.06 M solution) was refluxed in the presence of $CaCO_3$. After 60 min, the mixture was concentrated under reduced pressure (vaccum pump) and diluted with CH_2Cl_2. After filtration and concentration, the resulting oil was purified by chromatography (hexane, 30 mL; hexane/EtOAc, 5/1, 50 mL; hexane/EtOAc, 5/3, 50 mL; EtOAc, 100 mL) to afford 59.3 mg (92%) of *trans*-**18** as a white solid. Yield range : 92-96%

***rel*-(4a*S*,8a*R*)-4a,5,6,7,8-Pentahydro-1,1,4,8a-tetramethyl-1*H*-2,3-benzoxazine-3-oxide (*trans*-19).** To a magnetically-stirred solution of **16** (41.3 mg, 0.195 mmol) in toluene (2.0 mL, 0.1 M solution) was added dropwise $SnCl_4$ (46 μL, 0.39 mmol, 2.0 equiv) at -65°C. After 15 min, the mixture was quenched with sat. aq. $NaHCO_3$ solution (1 mL) and diluted with EtOAc (10 mL). The mixture was allowed warm to room temperature (~20 min) and then was filtered. The white solid was washed with EtOAc (2 x 20 mL) and the combined heterogeneous solution was washed with sat. aq. $NaHCO_3$ solution (25 mL) and brine (25 mL). The aqueous layers were back extracted with EtOAc (2 x 40 mL). The combined organic layers were dried (Na_2SO_4) filtered and concentrated. Purification by chromatography (hexane/EtOAc, 5/1, 50 mL; hexane/EtOAc, 5/2, 50 mL; EtOAc, 100 mL) afforded 37.8 mg (92%) of *trans*-**19** as a colorless oil which solidified. An analytical sample was recrystallized from hexane. Data for *trans*-**19**: mp 94-97°C (hexane); ^{1}H NMR (300 MHz) 2.33 (dm, J = 12.1, 1 H, HC(4a)), 2.01 (d, J = 1.9, 3 H, $H_3C(10)$), 1.91-1.76 (m, 3 H), 1.62-1.04 (m, 5 H), 1.34 (s, 3 H, $H_3C(11)$), 1.26 (s, 3 H, $H_3C(12)$), 1.00 (s, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 122.93 (C(4)), 86.97 (C(1)), 41.24 (C(4a)), 35.45 (C(8a)), 31.67 (C(8)), 25.52 (C(5)), 23.41 (C(7)), 21.24 (C(11)), 20.92 (C(12)), 20.50 (C(6)), 15.07 (C(9)), 13.92 (C(10)); IR (CCl_4) 2988 (m), 2940 (s), 2859 (w), 1592 (s), 1447 (w), 1381 (m), 1339 (m), 1287 (w), 1267 (s), 1256 (s), 1194 (w), 1169 (w), 1154 (m), 984 (w), 949 (w), 893 (m), 872 (m), 849 (w), 818 (m); MS (70 eV) 213 (M^+ + 2, 1), 212 (M^+ + 1, 13), 211 (M^+, 79), 194 (9), 182 (9), 181 (75), 180 (14), 166 (8), 165 (19), 163 (20), 149 (9), 139 (5), 138 (23), 137 (17),136 (15), 135 (6), 126 (6), 125 (24), 124 (17), 123 (84), 122 (13), 121 (18), 116 (5), 112 (5), 111 (15), 110 (40), 109 (25), 108 (8), 107 (30), 100 (8), 99 (17), 98 (6), 97 (16), 96 (139), 95 (60), 94 (11), 93 (15), 86 (5), 85 (9), 84 (8), 83 (46), 82 (13), 81 (100), 80 (5), 79 (10), 71 (13), 70 (7), 69 (32), 68 (13), 67 (28), 59 (7), 57 (50), 56 (5), 55 (23); TLC R_f 0.29 (EtOAc). Anal. Calcd for $C_{12}H_{21}NO_2$ (211.30): C, 68.21; H, 10.02; N, 6.63. Found: C, 68.25; H, 10.01; N, 6.58.

***rel*-(1*R*,4a*R*,7a*R*)-1,4-Dimethyl-1,4a,5,6,7,7a-hexahydro-2,3-cyclopenta[*d*][1,2]-oxazine-3-oxide (*trans*-21b).** To a cold (-78°C) magnetically-stirred solution of (*E*,*Z*)-**20b** (550 mg, 3.25 mmol) in CH_2Cl_2 (60 mL, 0.05M) was added $SnCl_4$ (382 μL, 6.53 mmol, 2 equiv). After stirring at -78°C for 30 min, the reaction was quenched by addition of 0.5N NaOH in methanol (30 mL) and the mixture was allowed to warm to room temperature. The cloudy mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL), sat. aq. $NaHCO_3$ solution (50 mL) and brine (50 mL). The aqueous layers were back extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting pale brown liquid was purified by chromatography (EtOAc) to afford 385 mg (70%) of *trans*-**21b** which was distilled to give a colorless liquid. Data for *trans*-**21b**: bp 85°C (0.05 Torr); ^{1}H NMR (300 MHz) 4.85 (quintet, J = 6.6, 1 H, HC(1)), 2.16 (m, 2 H), 2.03 (s, 3 H, $H_3C(9)$), 1.93 (m, 2 H), 1.80 (m, 2 H), 1.43 (m, 2 H), 1.29 (d, J = 6.6, 3 H, $H_3C(8)$); ^{13}C NMR (75.5 MHz,) 126.22 (C(4)), 79.48 (C(1)), 44.46 (C(4a)), 40.77 (C(7a)), 26.19 (C(7)),

24.99 (C(5)), 23.38 (C(6)), 15.35 C((8)), 14.96 (C(9)); IR (CCl_4) 2971 (m), 2878 (w), 1593 (s), 1458 (w), 1267 (m), 1250 (m), 1231 (m), 1088 (w), 905 (m); MS (70 eV) 170 (M^+ + 1, 5), 169 (12), 95 (100), 93 (14), 79 (12), 68 (22), 67 (83), 55 (36); TLC R_f 0.15 (EtOAc). Anal. Calcd for $C_9H_{15}NO_2$ (169.22): C, 63.88; H, 8.93; N, 8.28. Found: C, 63.52; H, 8.82; N, 8.17.

***rel*-(1*R*,2*R*,8*R*)-[2-(1-Hydroxyethyl)cyclopentyl]ethanone Oxime (23).** To a magnetically-stirred solution of *trans*-**21b** (300 mg, 1.77 mmol) in 25 mL of Et_2O was added Zn dust (1.75 g, 27 mmol, 15 equiv) and 25% aq. HOAc (3.4 mL, 14 mmol, 8 equiv). After stirring at room temperature for 30 min, the reaction mixture was filtered and the residue was washed with Et_2O (25 mL). The combined organic solution was washed with water (50 mL), sat. aq. $NaHCO_3$ solution (50 mL) and brine (50 mL). The aqueous layers were back extracted with Et_2O (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), fitered and concentrated to give a 375 mg (93%) of **23** as a white solid. The solid was recrystallized using hexane with few drops of CH_2Cl_2. Data for *trans*-**23**: mp 84°C (hexane/CH_2Cl_2); ^1H NMR (300 MHz) 4.6-5.4 (broad, 2 H), 3.82 (dq, J = 3.2, 6.4, 1 H, HC(8)), 2.65 (m, 1 H, HC(3)), 1.95 (m, 2 H), 1.88 (d, J = 1.5, 3 H, $H_3C(1)$), 1.18-1.87 (m, 5 H), 1.15 (d, J = 6.4, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 161.73 (C(2)), 65.58 (C(8)), 49.88, 46.45, 30.15, 24.81, 24.18, 21.38, 10.69; IR (CCl_4) 3594-3293 (br w), 2963 (m), 2874 (m), 1453 (w), 1370 (w); MS (70 eV) 171 (M^+,1.2). 154 (36), 136 (47), 126 (72), 125 (68), 124 (64), 110 (3), 108 (43), 95 (95), 86 (100), 67 (37); TLC R_f 0.49 (EtOAc); GC t_R 7.55 min (OV-17 100°C (2 min), 20°C/min, 220°C). Anal. Calcd for $C_9H_{17}NO_2$ (171.22): C, 63.13; H, 10.01; N, 8.18. Found: C, 63.11; H, 10.00; N, 8.15.

***rel*-(1*R*,2*R*)-1,2-Diacetylcyclopentane (24)** To a magnetically-stirred solution of **23** (272 mg, 1.59 mmol) in $CCl_4/CH_3CN/H_2O$ (2 mL/2 mL/3 mL) was added solid $NaIO_4$ (1.80 g, 8.42 mmol, 5.3 equiv), followed by solid RuO_2 (7 mg cat.). The resulting mixture was stirred at room temperature. After 6 h, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL) and brine (25 mL). The aqueous layers were back extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The colorless residue was purified by chromatography (hexane/EtOAc, 2/1) to afford 225 mg (94%) of **24** as a coloress liquid. An analytical sample was prepared by distillation. Data for **24**: bp 115°C (10 Torr); ^1H NMR (300 MHz) 3.31 (t, J = 5.9, 2 H, HC(3)), 2.17 (s, 6 H, $H_3C(1)$), 2.03 (m, 2 H), 1.67 (m, 4 H); ^{13}C NMR (75.5 MHz) 209.42 (C(2)), 53.09 (C(3)), 29.91 (C(1)), 29.11(C(4)), 25.51 (C(5)); IR (CCl_4) 2961 (m), 2874 (m), 1709 (s), 1450 (w), 1423 (w), 1356 (s), 1167 (m); MS (70 eV) 154 (M^+, 2.6), 111 (100), 97 (13), 71 (16); TLC R_f 0.21(hexane/EtOAc, 2/1); GC t_R 5.91 min (OV-17, 100°C (2 min), 10°C/min, 200°C); Anal. Calcd for $C_9H_{14}O_2$ (154.21): C, 70.09; H, 9.15. Found: C, 69.74; H, 9.16.

***rel*-(1*R*,2*R*)-Cyclopentane-1,2-diol Diacetate (*trans*-25).** To a cold (0°C) solution of trifluoroacetic anhydride (0.55 mL, 3.89 mmol, 6 equiv) in CH_2Cl_2 (1 mL) was added H_2O_2 (0.086 mL, 90% aqueous 3.25 mmol, 5 equiv). The mixture was allowed to warm to room temperature after 10 min and was added to a mixture of diketone **24** (190 mg, 0.15 mmol) and Na_2HPO_4 (553 mg, 3.85 mmol, 6 equiv) in CH_2Cl_2 (1 mL). After stirring at room temperature for 12 h, the mixture was diluted with ether (5 mL) and washed with water (15 mL), sat. aq. $NaHCO_3$ solution (15 mL) and brine (15 mL). The aqueous layers were extracted with ether (2 X 20 mL) and the combined organic layers were dried ($MgSO_4$), filterd, and concentrated. The crude residue was purified by chromatography (hexane/EtOAc, 4/1) to afford 16 mg (13%) of *trans*-**25** as a colorless oil. Data for ***trans*-25**: ^1H NMR (300 MHz) 5.04 (t, J = 4.1, 2 H, HC(4)), 2.09 (m, 2 H), 2.02 (s, 6 H, $H_3C(1)$), 1.72 (m, 4 H); ^{13}C NMR (75.5 MHz) 170.35 (C(2)), 78.91 (C(4)), 30.33 (C(1)), 21.46, 21.14.; IR (CCl_4) 2974 (w), 1741 (s), 1437 (w), 1369 (m), 1232 (s), 1084 (m), 1039 (m); TLC R_f 0.70 (hexane/EtOAc, 2/1); GC t_R 6.50 min. (OV-17, 100°C (2 min), 10°C/min, 200°C), 11.30 min (OV-17, 100°C isothermal).

Comparison data for *rel*-(1*R*,2*S*)-Cyclopentane-1,2-diol Diacetate (*cis*-25). bp 100-102°C (8 Torr); ^1H NMR (300 MHz) 5.11 (t, J = 4.0, 2 H, HC(4)), 2.02 (s, 6 H, $H_3C(1)$), 1.93 (m, 2 H), 1.80 (m, 2 H), 1.59 (m, 2 H); ^{13}C NMR (75.5 MHz) 170.28 (C(2)), 73.96 (C(4)), 28.02 (C(1)), 20.82, 18.98; IR (CCl_4) 2980 (w), 1744 (s), 1437 (m), 1250 (s), 1163 (w), 1074 (m), 1049 (w), 1020 (w); TLC R_f 0.68 (hexane/EtOAc, 2/1); GC t_R 11.64 min (OV-17, 100°C isothermal).

Comparison data for *rel*-(1*R*,2*R*)-Cyclopentane-1,2-diol Diacetate (*trans*-25). bp 100-102°C (8 Torr); ^1H NMR (300 MHz) 5.04 (t, J = 4.1, 2 H, HC(4)), 2.08 (m, 2 H), 2.02 (s, 6 H, $H_3C(1)$), 1.75 (m, 4 H); ^{13}C NMR (75.5 MHz) 169.80 (C(2)), 78.56 (C(4)), 30.01 (C(2)), 21.16, 20.69; IR (CCl_4): 2976 (m), 2880 (w),

1744 (s), 1439 (w), 1369 (m), 1238 (s), 1084 (m), 1039 (m).; TLC R_f 0.70 (hexane/ EtOAc , 2/1); GC t_R 11.30 min (OV-17, 100°C isothermal).

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