Nitroalkene [4 + 2] Cycloadditions with 2-(Acyloxy)vinyl Ethers. Stereoselective Synthesis of 3-Hydroxy-4-substituted-pyrrolidines

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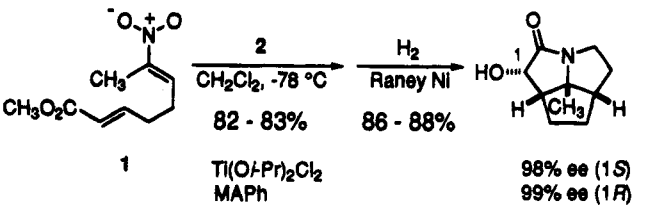
2-(Acyloxy)vinyl ethers undergo regioselective [4 + 2] cycloadditions with nitroalkenes (promoted by $SnCl_4$) to afford substituted 5-acetoxy nitronates in good yields (68–91%). Endo/exo selectivity in the cycloadditions has been found to be dependent on the nitroalkene substitution; 2-aryl-1-nitroalkenes provided exclusively exo cycloadducts while 2-cyclohexyl-1-nitroalkene **28** afforded predominately endo cycloadducts in a ratio of 12:1. The resulting nitronates can be elaborated to *N*-tosyl-4-substituted-3-hydroxypyrrolidines by hydrogenolysis (160 psi of H_2/PtO_2) or to bicyclic α-hydroxy lactams by [3 + 2] cycloaddition followed by hydrogenation (14.7 psi of H_2/Raney nickel). A chiral 2-acetoxyvinyl ether derived from (*R*)-2,2-diphenylcyclopentanol has been employed in the cycloaddition–hydrogenation sequence to prepare an optically active *N*-tosyl-3-hydroxypyrrolidine in 96% ee.

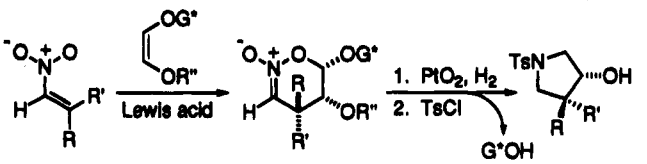
Introduction

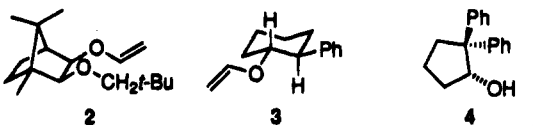
The stereoselective construction of highly functionalized, oxygen-substituted nitrogen heterocycles is a challenging task with many potential rewards in the fields of medicinal and natural product chemistry. The hetero Diels–Alder reaction of nitroalkenes provides a convenient route to this class of compounds, allowing for the simultaneous construction of carbon–carbon bonds and installation of several stereogenic centers about the newly formed heterocyclic ring. Tandem inter [4 + 2]/intra [3 + 2] cycloadditions between nitroalkenes (as diene components) and chiral vinyl ether dienophiles proceed with high stereoselectivity in a predictable fashion.[1] For example, [4 + 2] cycloaddition of nitroalkene **1** with camphor-derived vinyl ether **2** affords the nitroso acetal cycloadducts with excellent π-facial differentiation when promoted by $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ or methylaluminum bis(2,6-diphenylphenoxide), MAPh, Scheme 1.[1a] After hydrogenolytic cleavage of the resulting nitroso acetal, a tricyclic α-hydroxy lactam is produced in high enantiomeric excess (98–99% ee) whose absolute configuration is dependent on the Lewis acid promoter employed. The reversal of selectivity has been attributed to a highly endo selective cycloaddition in the case of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ compared to high exo selectivity in the case of MAPh. A simplified auxiliary (1*R*,2*S*)-2-phenylcyclohexanol (**3**) has shown similar selectivities in the nitroalkene cycloaddition. In addition to vinyl ethers it has been shown that β-substitution of the enol ether as in 1-(*E*)- and 1-(*Z*)-propenyl ethers is feasible and also provides high stereocontrol.[1a,e] Recent disclosures from these laboratories have shown that protected 3,4-disubstituted pyrrolidines can be obtained in good yield and high stereoselectivity by hydrogenolysis of the intermediate nitronate cycloadducts.[2]

Scheme 1



Scheme 2





2 3 4

The incorporation of an oxygen substituent into the nitrogen heterocycle in a stereocontrolled fashion using this procedure can be approached from two directions: (1) inclusion of the oxygen functionality into the precursor nitroalkene[3] or (2) inclusion in the chiral enol ether component of the [4 + 2] cycloaddition. Both routes have been found to be viable and each has unique advantages. This paper will describe our development of the latter approach. The concept of a nitroalkene [4 + 2] cycloaddition followed by hydrogenolysis of the resulting nitronate has now been extended to include the use of chiral 2-(acyloxy)vinyl ethers, Scheme 2. Several important synthetic and mechanistic aspects have been explored including (1) the synthesis and [4 + 2] cycloaddition behavior of 2-(acyloxy)vinyl ethers derived from achiral and chiral alcohol precursors, (2) the synthesis of protected 3-hydroxypyrrolidines by hydrogenolytic

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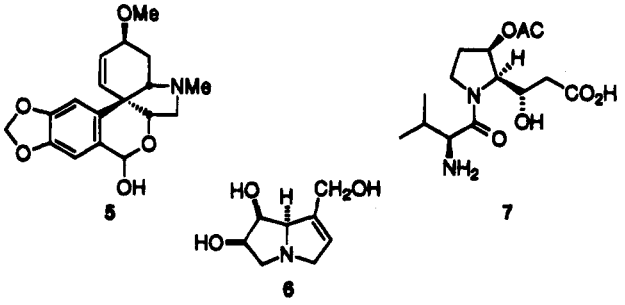
cleavage of substituted acyloxy nitronates, (3) the utilization of 2,2-diphenylcyclopentanol (**4**) as a chiral auxiliary for the preparation of optically active 3-hydroxypyrrolidines, (4) elaboration of the nitronate cycloadducts through an intermolecular [3 + 2] cycloaddition and hydrogenolysis to provide α-hydroxy lactams, and (5) the reversal of endo/exo selectivity in the [4 + 2] cycloaddition depending on nitroalkene substitution. This paper represents a full account of the use of 2-(acyloxy)vinyl ethers in nitroalkene [4 + 2] cycloadditions. The enantioselective synthesis of 3,4-disubstituted-pyrrolidines is the subject of an independent report.[4]

Background

The hydroxypyrrolidine subunit is found in a wide range of naturally occurring alkaloids and biologically active molecules. One such example of a highly substituted pyrrolidinol nucleus can be found in the Amaryllidaceae alkaloid (+)-pretazettine.[5] (+)-Pretazettine (**5**), which has shown anticancer and antiviral activity, not only offers the challenge of controlling the configuration of the hydroxy-bearing center but also possesses two additional contiguous stereogenic centers, one of which is a stereogenic quaternary carbon.[6] Other interesting hydroxylated pyrrolidines include crotanecine (**6**),[7] a pyrrolizidine necine base, and detoxin A_1 (**7**),[8] a natural chemical detoxification agent.



Several approaches to the stereoselective synthesis of 3-hydroxypyrrolidine and its derivatives have appeared, Figure 1.[9] The intramolecular displacement of a tosyl, mesyl, or benzoyl leaving group by an amine has offered one route to highly oxygenated 3-hydroxypyrrolidine systems.[10] Generally the configuration of the hydroxy-bearing center arises from diethyl tartrate or a carbohydrate starting material. Another route involves an intramolecular olefin cyclization mediated by iodine or mercuric acetate between an allylic alcohol and the amine

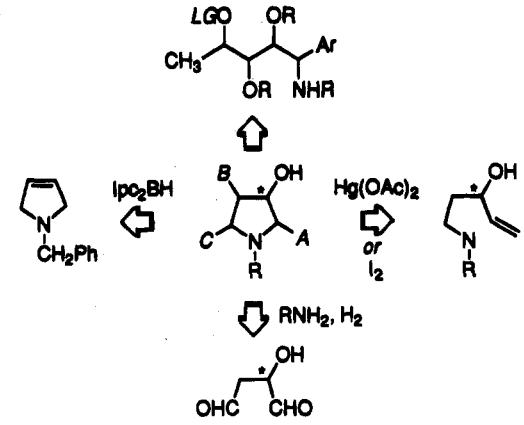


Figure 1. Existing routes to chiral 3-hydroxypyrrolidines.

functionality.[11] Amidomercurations and haloamidations have been found to be cis selective for carbons C(2) and C(3), while haloamination was found to be trans selective. Sharpless asymmetric epoxidation (in the kinetic resolution mode) has been employed to provide optically active allylic alcohol precursors and, therefore, provide optically active pyrrolidines.[11c] Hydroboration of *N*-benzyl-3-pyrroline with Ipc_2BH has provided enantiomerically pure *N*-benzyl-3-hydroxypyrrolidine; however, more substituted cases were not examined.[12] Optically active *N*-protected 3-hydroxypyrrolidines have also been obtained through inter- or intramolecular condensation followed by reduction of the resulting lactams starting from L-malic acid or L-glutamic acid, respectively.[13]

In none of the above cases, however, does the ring formation event coincide with installation of the C(3) and C(4) stereogenic centers. In many cases these stereogenic centers are introduced in high stereocontrol by the fact that they arise from chiral pool starting material. On the other hand this has limited the range of functionalization at C(4) to simple alkyl, hydroxy,[10,11b] or acyl[14] groups. To our knowledge, C(4)-disubstituted-pyrrolidinols have only been prepared unselectively.[15] Therefore, a general route to optically active 3,4-disubstituted-hydroxypyrrolidines is lacking. The use of the [4 + 2] cycloaddition between a nitroalkene and a 2-(acyloxy)-vinyl ether offers the advantage of direct stereocontrol of the C(3) and C(4) centers in the carbon–carbon bond forming event.

In considering the design for a suitable 1,2-dioxyethylene dienophile, the following criteria needed to be satisfied. First, the substituents must fulfill the electronic requirements for the inverse, electron-demand Diels–Alder reaction. Therefore, the groups must make the olefin sufficiently electron rich to act as a heterodienophile; however, if the C(1) and C(2) substituents are different, their electronic nature must impart significant differentiation to the dienophile HOMO to afford high regioselectivity. Second, at least one of the oxygen groups

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must be capable of being derived from a chiral alcohol or otherwise capable of asymmetric induction. Third, the oxygen substituents must be compatible with the reaction conditions required for the [4 + 2] cycloaddition, namely, stability in the presence of a Lewis acid.

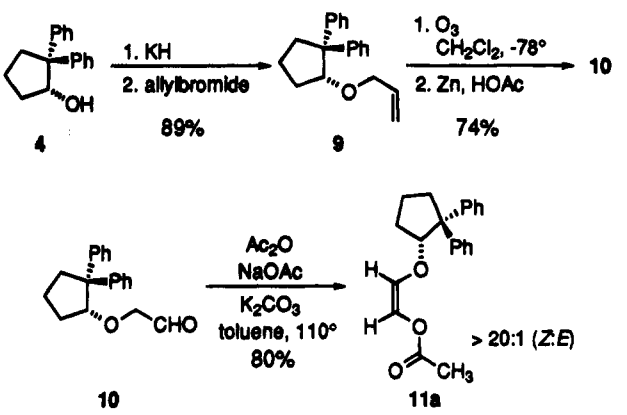
The hetero Diels–Alder cycloaddition reactions of 1,2-dialkoxyethylene has been studied in combination with α,β-unsaturated ketones,[16] α,β-unsaturated pyrazolones,[17] 3-sulfonyl-2-pyrones,[18] diiminosuccinonitriles,[19] azodicarboxylates,[20] and tetrazines[21] under thermal conditions. Alkyl substitution has been limited to symmetric cases including dimethoxy and diethoxy as well as cyclic examples[18,21] with 1,3-dioxole and 1,4-dioxene. The use of 1,2-dialkoxyethylene as the dienophile for our nitroalkene cycloadditions offers two disadvantages. To prepare a symmetric chiral example, 2 equiv of the precious chiral auxiliary would be required and, therefore, not synthetically efficient. Also, deprotection of the resulting alkyl ether for further manipulation could prove synthetically challenging.

A second alternative is the use of 1-(acyloxy)-2-alkoxyethenes as the dienophile. First reported by Alder,[22] 1-acetoxy-2-ethoxyethene was found to undergo a thermally-promoted [4 + 2] cycloaddition with acrolein in moderate yield (55–65%) affording 2-ethoxy-3-acetoxytetrahydropyran. More recently, Tietze[23] has examined the reactivity of both the *E* and *Z* isomers in cycloadditions with 1-oxa-1,3-butadienes. Only one regioisomer was observed, and when conducted under thermal conditions the cycloadditions were endo selective while under Lewis acid catalysis the orientation was dependent on the Lewis acid promoter, $SnCl_4$ or Me_2AlCl. Likewise, Boger[24] has explored the cycloadditions of (*E*)- and (*Z*)-1-acetoxy-2-(benzyloxy)ethene with 1-aza-1,3-butadienes. Thermal, high-pressure cycloadditions produced a single regioisomer with generally high endo selectivity. The use of 1-oxa-1,3-butadienes has lead to a synthetic route for the synthesis of carbohydrates.[24b] Therefore, on the basis of high regioselectivity in the orientation desired for our nitroalkene [4 + 2] cycloadditions and stability toward Lewis acids, 2-(acyloxy)vinyl ethers were chosen to be the framework of our heterodienophile.

Results

Preparation of Enol Ethers. 1-Acetoxy-2-(benzyloxy)ethene (**8**) was chosen as the achiral 2-(acyloxy)vinyl ether to be examined and was prepared as previously reported by heating 2-(benzyloxy)ethanal in the presence of acetic anhydride, K_2CO_3, and a catalytic amount of sodium acetate in toluene.[24b] For the chiral 2-(acyloxy)-vinyl ether, 2,2-diphenylcyclopentanol (**4**) was chosen as the auxiliary. Alcohol **4** has been reported to provide high selectivity as a chiral auxiliary in the asymmetric hydrogenation of β-acetamidocrotonates.[25] Racemic alcohol **4** was obtained by $NaBH_4$ reduction of the corresponding ketone,[25a] which is available in three steps from diphenylacetonitrile as follows: alkylation (LDA) with 4-bromobutyronitrile followed by direct Thorpe–Ziegler condensation with potassium *tert*-butoxide afforded the enaminonitrile which was converted to the ketone by acid (HCl) hydrolysis in an overall yield of 77%.[26] For the optically active alcohol, the reported chiral borane reduction[25a] and enzymatic resolution[27] suffer from long reaction times and low conversion. Asymmetric oxazaborolidine reduction has been found to afford (*R*)-2,2-diphenylcyclopentanol in moderate yield and 98% ee as determined by chiral HPLC analysis.[26c,28] Chiral 2-(acyloxy)vinyl ethers derived from 2,2-diphenylcyclopentanol were prepared by analogy to **8**. Allylation of the potassium alkoxide of alcohol **4** followed by ozonolysis with zinc/acetic acid reductive workup afforded the chiral aldehyde **10**, Scheme 3. Heating aldehyde **10** with acetic anhydride, K_2CO_3, and a catalytic amount of sodium acetate for 24 h at 110 °C afforded 1-acetoxy-2-((2,2-diphenylcyclopentyl)oxy)ethene in 80% yield with greater than 20:1 *Z*-selectivity. Pivaloyloxy (**11b**) and benzoyloxy derivatives (**11c**) were prepared in the same manner using the corresponding anhydride and sodium salt of the carboxylic acid in much lower yields of 39% and 17%, respectively, with high *Z*-selectivity. Of the three derivatives, acetoxy analog **11a** was found to be the most convenient to prepare and the *E* and *Z* isomers are easily separable by silica gel column chromatography. In contrast, the 2-(benzoyloxy)vinyl ether **11c** required medium pressure silica gel chromatography to purify it from side products. The *Z* olefin configuration was determined from the olefinic proton coupling constant of 3.6 Hz for (*Z*)-2-acetoxyvinyl ether **11a** as compared to 13.5 Hz for the corresponding *E* isomer.

Scheme 3



Preparation of Nitroalkenes. All nitroalkenes were prepared by published procedures. (*E*)-1-Nitro-2-phenylethene was prepared by nitro aldol condensation between

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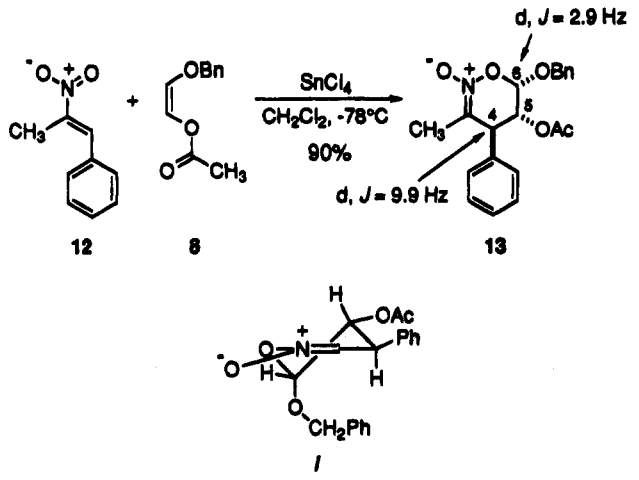
(28) HPLC conditions: Chiralcel OD, 70/30, hexane/isopropyl alcohol, 0.5 mL/min.

Scheme 4



benzaldehyde and nitromethane.[29] Other mono-2-substituted-1-nitroalkenes were prepared by KO-*t*-Bu/*tert*-butyl alcohol catalyzed Henry reactions between the corresponding aldehyde and nitromethane or nitroethane followed by DMAP-promoted elimination of the derived acetate, or triethylamine promoted elimination of the trifluoroacetate.[30] Employing a method recently developed in these laboratories, 2,2-disubstituted-1-nitroalkenes were prepared by 1,4-conjugate addition of ethylzinc cuprate to the corresponding mono-2-substituted-1-nitroalkene followed by trapping with benzeneselenyl bromide and subsequent oxidative elimination.[30a]

Cycloadditions of 2-Acetoxyvinyl Ether 8. To initially explore the feasibility of nitroalkene cycloadditions with 2-(acyloxy)vinyl ethers, (*E*)-1-methyl-1-nitro-2-phenylethene (**12**) was chosen as the diene component and (*Z*)-1-acetoxy-2-(benzyloxy)ethene (**8**) as the dienophile. Initial attempts were discouraging as neither Ti(O-*i*-Pr)$_2$Cl$_2$ nor methylaluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) (MAD) induced cycloaddition even at room temperature. In the case of MAD there appeared to be competitive coordination between the acyl carbonyl and the nitroalkene. For example, when the ratio of Lewis acid to enol ether was greater than 1, a characteristic red nitroalkene–Lewis acid complex was observed. However, when the amount of enol ether exceeded that of Lewis acid, the color disappeared and presumably an insufficient amount of nitroalkene was complexed. Fortunately, however, cycloaddition of nitroalkene **12** with (*Z*)-**8** could be promoted by $SnCl_4$ (3.0 equiv) at −78 °C to afford a single nitronate (**13**) in 90% yield, Scheme 4. The relative configuration of the substituents about the six-membered ring was established on the basis of ^{1}H NMR coupling constants. A cis relationship between HC(5) and HC(6) was indicated by a coupling constant of 2.9 Hz, while a 9.9 Hz coupling constant between the protons at C(4) and C(5) suggested a trans relationship. The nitronate ring is believed to adopt a twist boat conformation (*i*, Scheme 4) placing the C(6) alkoxy group in a pseudoaxial position to provide stabilization by the anomeric effect. This would place the acetoxy and C(4) substituents in pseudoequatorial positions in the trans diastereomer. The alternative boat conformations would suffer from either one or two more severe gauche interactions. The proposed configuration suggests a highly exo-selective cycloaddition which was not unexpected on the basis of previous $SnCl_4$-promoted cycloadditions with cyclopentene;[30b] however, this represents the first use of $SnCl_4$ to promote a nitroalkene cycloaddition with an enol ether dienophile. The analogous cycloaddition of nitroalkene **12** with the *E* isomer of enol ether **8** resulted in a complex mixture of products along with an approximately 1:1 mixture of recovered (*E*)- and (*Z*)-1-acetoxy-2-(benzyloxy)ethene. On the basis of this result, isomerization of the enol ether appears to have occurred under the reaction conditions leading to the more stable *Z* configuration (cf. the preferred *Z* configuration in the preparation of **8**). Therefore, all subsequent cycloadditions will employ the *Z* configuration of the 2-(acyloxy)vinyl ether exclusively.

To further explore the scope of this new cycloaddition, pure (*E*)-2,2-disubstituted-1-nitroalkene (*E*)-**14** was treated with $SnCl_4$ (3.0 equiv) at −78 °C to provide a deep purple Lewis acid complex. The addition of enol ether (*Z*)-**8** (1.5 equiv) to the complex afforded a single nitronate diastereomer in 88% yield, Scheme 5. Employing 1.5 equiv of enol ether was found to be optimal since both lower and higher ratios resulted in diminished yields. In the latter case, this is presumably do to competitive coordination with the Lewis acid. Once again the cis relationship between HC(5) and HC(6) was indicated by a vicinal coupling constant of 2.4 Hz. The configuration at C(4) was tentatively assigned by analogy to the presumed exo cycloaddition of nitroalkene **12**. When the (*Z*)-nitroalkene isomer was employed under the same conditions, a nitronate diastereomer was produced in 83% yield whose spectral data surprisingly were identical to that of the nitronate produced from (*E*)-**14**. Therefore, it is possible to obtain the same nitronate diastereomer in extremely high stereoselectivity starting from either the *E* or *Z* isomer of nitroalkene **14**. To clarify the origin of this behavior, isomerically pure nitroalkene (*Z*)-**14** was subjected to the reaction conditions but in the absence of the enol ether. After 30 min the mixture was quenched and the recovered nitroalkene was analyzed by ^{1}H NMR spectroscopy. A 17:1 mixture of isomers now favoring the *E* configuration was observed. Thus, under the reaction conditions a rapid isomerization of (*E*)- and (*Z*)-nitroalkene isomers occurred which heavily favored the more stable *E* isomer. Presumably this configuration eliminates peri interactions between the aryl hydrogens and the nitro functionality. In addition, the *Z* isomer must be significantly less reactive in the cycloaddition in order to obtain the high diastereoselectivity. The isomerization most likely occurs through a reversible conjugate addition of a nucleophile, presumably chloride, to the nitroalkene–Lewis acid complex.

Hydrogenation to Pyrrolidines. Previous experience with hydrogenolysis of 3,3- and 3,4-dialkyl nitronates has shown that catalytic hydrogenation employing platinum oxide (Adams' catalyst) at elevated pressures provides a route to substituted pyrrolidines.[2,31] In a similar fashion, a solution of nitronate **15** in methanol was reduced in the presence of 15 mol % platinum oxide at a pressure of 160 psi to afford a white solid in low yield, Scheme 6. On the basis of infrared and NMR spectral analysis, this compound was identified as the

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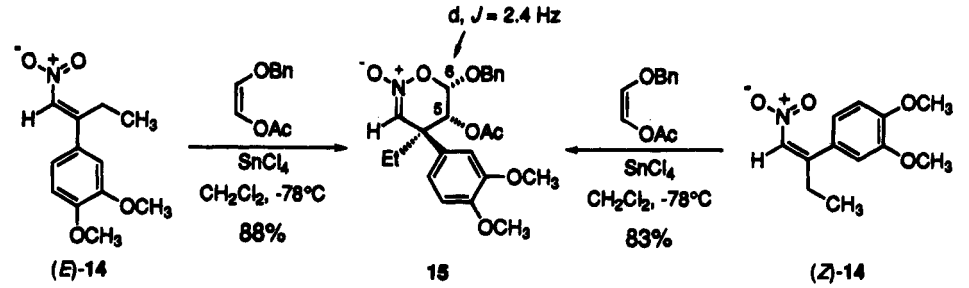
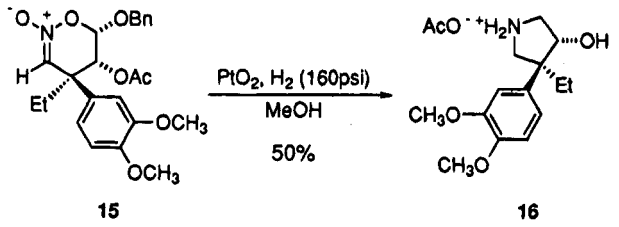
(31) (a) Thurston, J. T.; Shriner, R. L. *J. Org. Chem.* **1937**, *2*, 183. (b) Young, A.; Levand, O.; Luke, W. K. H.; Larson, H. O. *J. Chem. Soc., Chem. Commun.* **1966**, 230. (c) Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 7569.

Scheme 5



Scheme 6



corresponding 3-hydroxypyrrolidine acetate salt **16**. During the course of the hydrogenation, partial saponification of the acetate had occurred, liberating acetic acid and trapping the pyrrolidine product. To facilitate isolation of the pyrrolidines, *p*-toluenesulfonamides were prepared directly after reduction. Therefore, hydrogenation of nitronate **15** under the same conditions for a period of 24 h at room temperature followed by filtration of the clear solution to remove the catalyst, evaporation of the solvent, and treatment with tosyl chloride in the presence of triethylamine afforded a 32% yield of the desired *N*-tosyl-3-acetoxy pyrrolidine **17** along with a 43% yield of the corresponding *N*-protected-3-hydroxy pyrrolidine **18**, Scheme 7. Variation in pressure had no significant influence on the ratio of **17** to **18**, though lower pressures generally resulted in lower combined yields. Employing a nonprotic solvent such as ethyl acetate or methylene chloride in the reduction failed to provide the desired products.

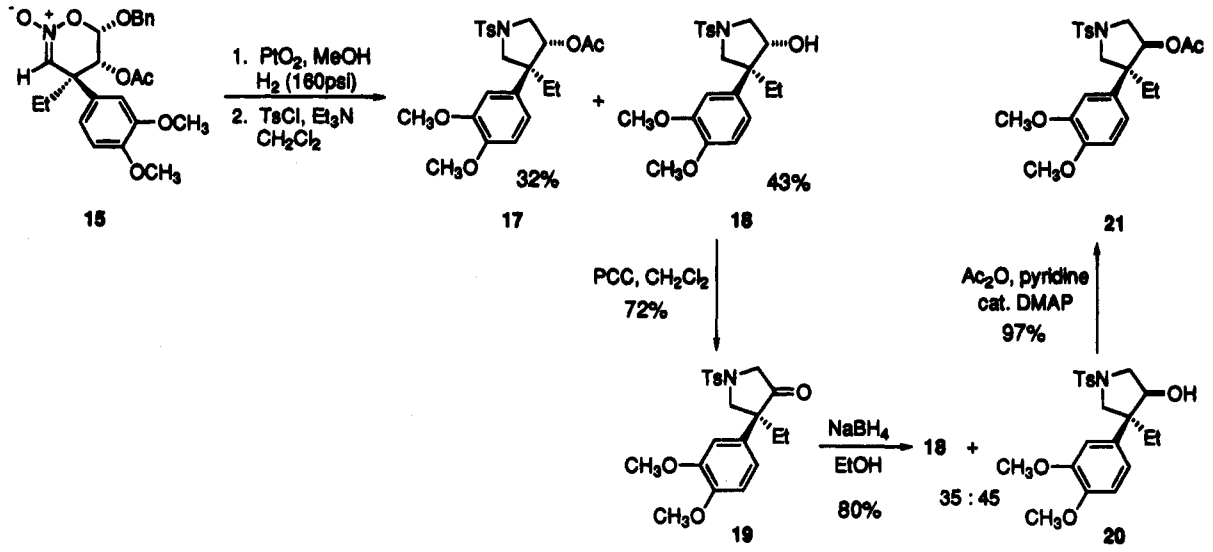
The stereochemical integrity of the oxygen-bearing stereogenic center in **17** and **18** was of concern. It was necessary to unambiguously establish that both products possessed the same relative configuration. To accomplish this, the preparation of both cis and trans *N*-protected-3-hydroxypyrrolidines and the corresponding acetoxy diastereomers was required. *N*-Tosyl-3-hydroxypyrrolidine **18** was oxidized with pyridinium chlorochromate to afford pyrrolidinone **19** in 72% yield, Scheme 7. Subsequent reduction with $NaBH_4$ afforded two isomeric *N*-tosyl-3-hydroxypyrrolidines in 80% combined yield and a ratio of 35:45 (**18**:**20**). The minor diastereomer exhibited spectral characteristics that exactly matched those of the 3-hydroxypyrrolidine obtained in the original hydrogenation. The reduction selectivity while modest is consistent with the stereochemical assignment of **18** since hydride approach to the carbonyl from the less hindered face opposite to the aryl ring would be expected to give the aryl, hydroxy cis diastereomer. Acetylation of the major diastereomer **20** with acetic anhydride in the presence of pyridine and a catalytic amount of DMAP afforded a single *N*-tosyl-3-acetoxypyrrolidine (**21**), in 97% yield. By spectroscopic comparison, it was confirmed that **21** and **17** were diastereomeric, thus providing conclusive proof that both the *N*-tosyl-3-hydroxy- and *N*-tosyl-3-acetoxypyrrolidines formed in the reduction of nitronate **15** exhibit the same relative configuration *tentatively* assigned with the aryl group at C(4) and the hydroxy group at C(3) in a trans relationship. An attempt to assign the configuration by NOE experiments on diastereomers **17** and **21** was unfortunately inconclusive.

Cycloadditions of Chiral 2-(Acyloxy)vinyl Ethers and Nitronate Hydrogenations. With the encouraging results of high regioselectivity and diastereoselectivity in the [4 + 2] cycloadditions of 1-acetoxy-2-(benzyloxy)-ethene and the demonstration that the resulting nitronate can be reduced to a 3-hydroxypyrrolidine, studies toward an asymmetric variant of the cycloaddition were undertaken. Nitroalkene **14** was used in this series as well for optimization with a chiral 2-(acyloxy)vinyl ether. The high selectivities observed in vinyl ether cycloadditions employing (1*R*,2*S*)-2-phenylcyclohexanol as a chiral auxiliary prompted us to explore this controller as a first approach.[1a] 1-Acetoxy-2-((2-phenylcyclohexyl)oxy)ethene was prepared by the route described above involving allylation, ozonolysis, and acetoxylation. Unfortunately, diastereoselectivity in the [4 + 2] cycloaddition was low (64% de). In light of the fact these are believed to be exo selective cycloadditions, this result should have been anticipated on the basis of previous experience with this auxiliary in MAPh-promoted cycloadditions.[1a] Recently, we have found that the vinyl ether derived from (*R*)-2,2-diphenylcyclopentanol (**4**) is capable of providing very high diastereoselectivity in exo mode cycloadditions[32] and, therefore, the corresponding 2-acetoxyvinyl ether **11a** was prepared.

Cycloaddition of either pure (*E*)-**14** or pure (*Z*)-**14** with racemic 2-acetoxyvinyl ether **11a** promoted by $SnCl_4$ at −78 °C provided the same nitronate **22** in high selectivity (35−42:1) and an excellent yield of 86% and 91%, respectively (Scheme 8). Modification of the acyl group in the enol ether was found to have detrimental results. Cycloaddition of nitroalkene **14** with enol ethers **11b** and **11c** under the same conditions afforded high yields of the nitronate cycloadduct, however, in significantly lower selectivities, 8.7:1 for 2-(pivaloyloxy)vinyl ether **11b** and 3.7:1 for 2-(benzoyloxy)vinyl ether **11c** (Table 1). Enol ethers **11b** and **11c** react essentially instantaneously at −78 °C as compared to approximately 15 min for complete consumption of nitroalkene with **11a**. All three are considerably more reactive than 1-acetoxy-2-(benzyloxy)-ethene, which requires 3 h for complete reaction with the same substrate. Much of the rate enhancement can be attributed to the extent of $SnCl_4$ coordination to the Lewis basic oxygens of the 2-(acyloxy)vinyl ether. Increasing the size of the acyl group reduces the deactivating coordination to the acyl carbonyl. Likewise, increasing the size of the ether substituent (notably to the bulky

(32) Denmark, S. E.; Schnute, M. E. Unpublished results.

Scheme 7



Scheme 8

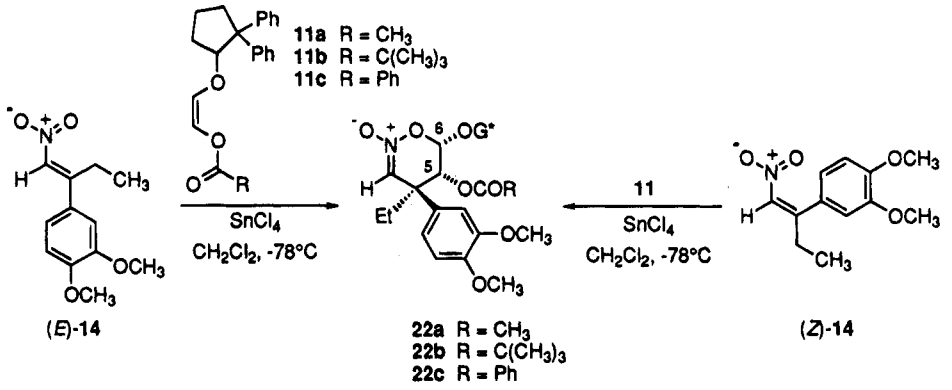


Table 1. Influence of Acyloxy Substituent on Selectivity of [4 + 2] Cycloaddition

nitroalkene	enol ether	R	product	yield (%)	diastereomer ratio[a]
(*E*)-**14**	**11a**	CH_3	**22a**	86	35:1
(*Z*)-**14**	**11a**	CH_3	**22a**	91	42:1
(*Z*)-**14**	**11b**	$C(CH_3)_3$	**22b**	90	8.7:1
(*E*)-**14**	**11c**	Ph	**22c**	96	3.7:1

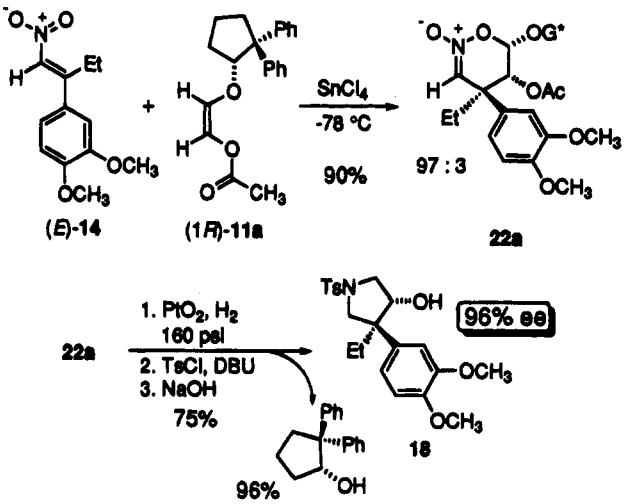
[a] Determined by ^1H NMR of crude product.

2,2-diphenylcyclopentyl auxiliary) reduces coordination to the ethereal oxygen. On the basis of these results 2-acetoxyvinyl ether **11a** was the dienophile of choice, providing high stereocontrol and ease of preparation.

Reduction of acetoxy nitronate **22a** containing a chiral auxiliary was next examined. To obtain a single product in the acetoxy nitronate reductions, hydroxy-deprotection would be done in situ to provide the alcohol directly. A methanolic solution of nitronate (±)-**22a** was allowed to stir at room temperature under 160 psi of hydrogen pressure for 24–36 h in the presence of 10 mol % of platinum oxide and acetic acid (1.0 equiv). The catalyst was filtered off and to the cold (0 °C) methanolic solution were added DBU and *p*-toluenesulfonyl chloride. The reaction mixture was then quenched with 20–30 equiv of NaOH solution in methanol (1 N) to deprotect the acetate and afford the *N*-tosyl-3-hydroxypyrrolidine in 61% yield.

Likewise, employing (*R*)-**11a**, nitronate (−)-**22a** was obtained in 90% yield and a diastereomer ratio of 97:3, Scheme 9. Subsequent hydrogenation, in situ tosylation,

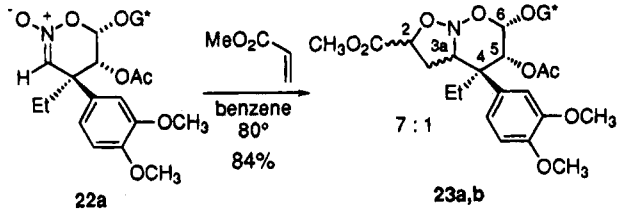
Scheme 9



and deprotection afforded the optically active *N*-tosyl-3-hydroxypyrrolidine in 75% overall yield. The final product was found to be enantiomerically enriched to the extent of 96% ee on the basis of chiral HPLC analysis (Chiralcel AD column). The chiral auxiliary was also recovered in 96% yield.

[3 + 2] Cycloaddition and Proof of Stereochemistry. To confirm the tentative stereochemical assignments for nitronate **22a** and the resulting pyrrolidine, a crystalline derivative was prepared. Thus, [3 + 2] cycloaddition of nitronate **22a** with methyl acrylate in

Scheme 10



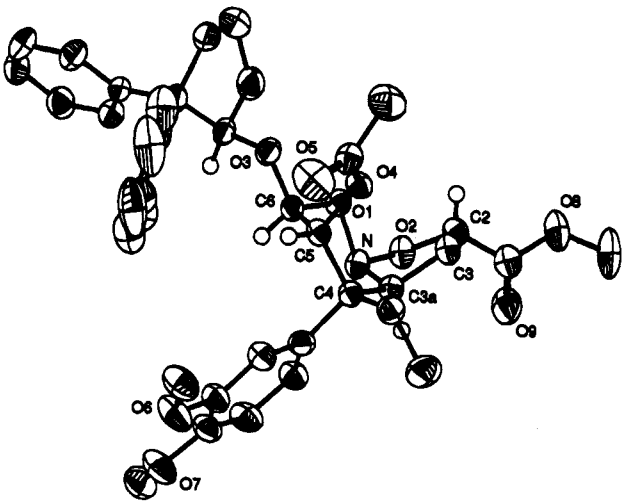
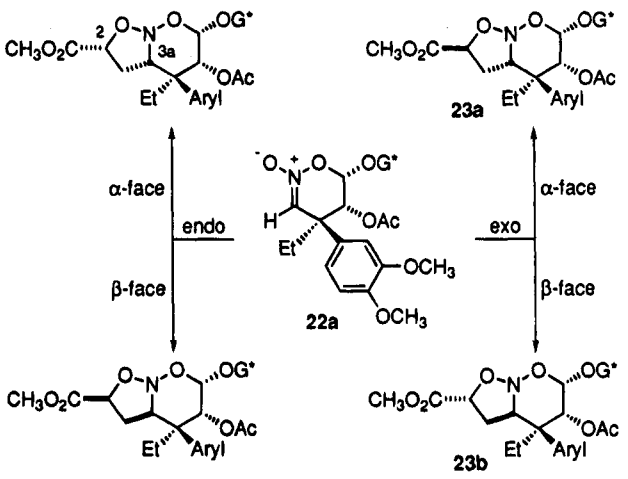


Figure 2. ORTEP representation of **23a** (40% thermal ellipsoids).

refluxing benzene afforded a 7:1 mixture of nitroso acetals **23** in 84% yield, Scheme 10. An X-ray crystal structure was obtained of the major nitroso acetal cycloadduct, **23a**, Figure 2.[33] The X-ray analysis confirmed the structure of **23a** to be consistent with the previously anticipated configuration made on the basis of proton NMR coupling constants. A cis relationship existed between the substituents at C(5) and C(6) as expected from the (*Z*)-configuration of the starting 2-acetoxyvinyl ether. The trans relationship between the C(4) veratryl and the C(5) acetoxy substituents is consistent with a highly exo-selective [4 + 2] cycloaddition assuming the (*E*)-configured nitroalkene is the reactive diene component. The configurations at C(2) and C(3a) arise from the [3 + 2] cycloaddition. On the basis of the X-ray structure, it can be concluded that the predominant diastereomer produced in the [3 + 2] cycloaddition resulted from an exo approach of methyl acrylate to the 1,3-dipole from the face opposite the aryl ring, Scheme 11. Since the absolute configuration of the oxygen-bearing stereogenic center in the auxiliary is known (*R*)[34] and nitronate **22a** was highly enantiomerically enriched, the configurations of the remaining stereogenic centers can be deduced. Therefore, the configuration of the stereogenic centers constructed in the [4 + 2] cycloaddition are as shown in **23a** and **23b** as (4*S*,5*R*,6*S*).

The minor diastereomer from the [3 + 2] cycloaddition could have resulted from three possible pathways (Scheme 11): (1) endo approach to the face opposite the aryl ring, (2) endo approach to the same side as the aryl ring, or

Scheme 11



(3) exo approach to the same side as the aryl ring. Since the configurations at C(2) and C(3a) are coupled by the endo/exo preference and the facial approach, the deduction of the configuration of the minor isomer is difficult since two variables are involved. If, however, the stereogenic center at C(2) were removed after the fact, the problem simplifies to one variable and allows for the facial preference to be determined. To accomplish this, both major and minor diastereomers must be reduced to their corresponding α-hydroxy lactams and then the hydroxyl-bearing stereogenic center would need to be deoxygenated. If the same bicyclic lactam results from both diastereomers, then the C(3a) stereogenic center is the same in both, and endo approach has occurred. On the other hand, if two different bicyclic lactams are produced, then the C(3a) stereogenic center is different in the diastereomers and facial erosion has occurred. In this case, however, the endo or exo orientation in the β-approach cannot be distinguished.

The major nitroso acetal **23a** was reduced at 1 atm of hydrogen pressure in the presence of Raney nickel catalyst, Scheme 12. Initial cleavage of both nitrogen, oxygen heterocyclic bonds followed by breakdown of the resulting hemiacetal would form an intermediate amino alcohol aldehyde. Subsequent intramolecular imine formation, saturation, and lactamization afforded the observed α-hydroxy lactam **24a** in 58% yield.[35] As seen previously in hydrogenolysis of the precursor nitronates, significant amounts (20–30%) of deacylated product were observed. The chiral auxiliary was recovered in 96% yield. Derivatization of **24a** with 1,1′-(thiocarbonyl)-diimidazole afforded the xanthate ester **25a** in 91% yield. Subsequent deoxygenation with tributyltin hydride and 2,2′-azobis(isobutyronitrile) (AIBN) provided the bicyclic lactam **26a** in 85% yield as a high-boiling oil.

In a similar fashion, an inseparable mixture of nitroso acetal diastereomers **23a** and **23b** favoring the minor diastereomer (1:6) was reduced to the corresponding α-hydroxy lactam in 52% yield and (after partial resolution) in an 8:1 ratio. Formation of the xanthate ester **25b** occurred in 54% yield after removal of the final traces of ester derived from **23a**. Deoxygenation of **25b** afforded bicyclic lactam **26b** in 83% yield as a white solid. Spectral data confirmed that bicyclic lactams **26a** and **26b** were two distinct diastereomers. Therefore, the

(33) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(34) Determined by X-ray crystal structure of (*R*)-MTPA derivative, see ref 25a.

(35) For a discussion of the mechanism of this transformation, see ref 1c.

Scheme 12

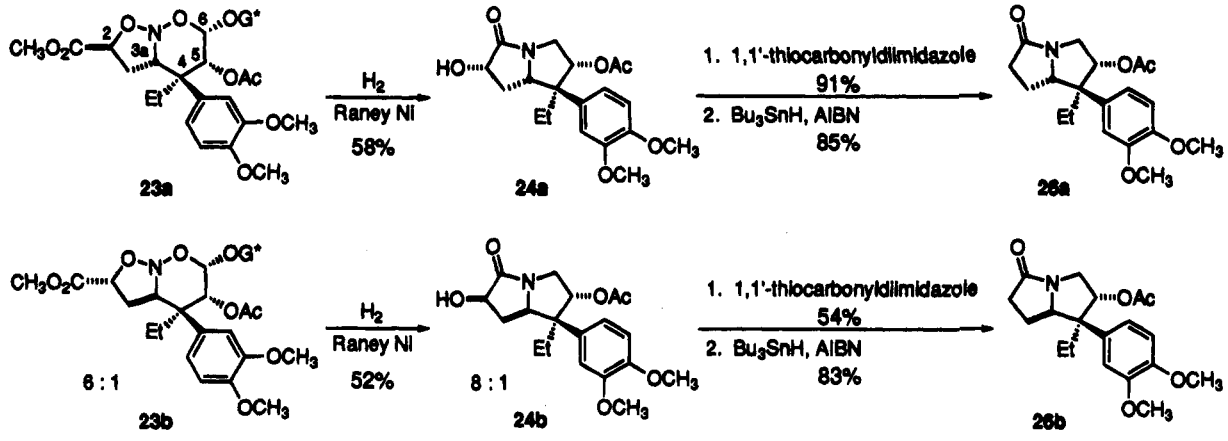
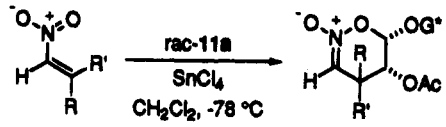


Table 2. Preparation of Acetoxy Nitronates



nitroalkene	R	R'	time (h)	yield (%)	product	diastereomer ratio
(*Z*)-**14**	ethyl	veratryl	0.50	90	**22a**	40:1
27	phenyl	H	0.25	86	**31**	1:1
28	cyclohexyl	H	8	68	**32a,b**	12:1[a]
29	*n*-pentyl	H	8	82	**33**	1:3.5:1.5:2
30	cyclohexyl	ethyl		NR		

[a] Diastereomers separated.

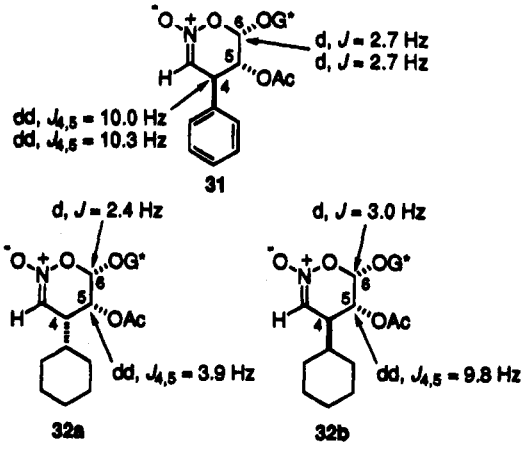
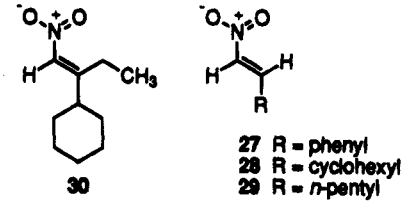


Figure 3. Spectral data for nitronates **31**, **32a**, and **32b**.

minor diastereomer obtained in the [3 + 2] cycloaddition arises from approach of methyl acrylate to the face of the 1,3-dipole on the same side as the aryl moiety. On the basis of the observed preference of exo mode [3 + 2] cycloadditions of nitronates,[36] in most likelihood the minor diastereomer is also a result of exo approach of the dipolarophile.

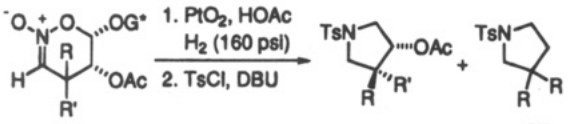
3,4-Disubstituted-pyrrolidines. A survey of nitroalkene substitution patterns was next undertaken employing racemic 2-acetoxyvinyl ether (±)-**11a** to determine the scope of sequential nitroalkene [4 + 2] cycloaddition and reduction to prepare 3-hydroxypyrrolidines. Four additional nitroalkenes were examined including a 2-aryl-1-nitroalkene (**27**), mono 2-alkyl-1-nitroalkenes **28** and **29**, and a 2,2-dialkyl-1-nitroalkene (**30**). Nitroalkene **27** underwent [4 + 2] cycloaddition with enol ether (*Z*)-**11a** in the presence of $SnCl_4$ at −78 °C to afford a 1:1 mixture of nitronates **31** in 86% yield, Table 2. The HC(4) and HC(5) proton coupling constant for both diastereomers of 10.0 and 10.3 Hz suggested that both possess the trans configuration, Figure 3. Likewise, a 2.7 Hz coupling constant between HC(5) and HC(6) in both suggested the same cis relationship between these centers. Thus, the low selectivity must result from low diastereofacial selectivity with respect to the auxiliary in the cycloaddition. This was proven by hydrogenolysis of the nitronate mixture (160 psi H_2, rt, 36 h, 10 mol % PtO_2, and 5.0 equiv of glacial acetic acid) followed by direct tosylation to afford a single *N*-protected-3-acetoxypyrrolidine in 51% yield, Table 3. Interestingly, no *O*-deprotected product was observed as in the 3,4,4-trisubstituted pyrrolidine series; however, a substantial amount (13%) of deoxygenated product **37** was isolated. The addition of glacial acetic acid was essential to obtain the 3-acetoxypyrrolidine. In its absence, only the deoxygenated product was isolated. Employing more than 5 equiv had a negligible effect on the product distribution.



Nitroalkene **28** was found to be much less reactive than its aryl predecessors requiring 8 h at −78 °C to afford a 68% yield of two separable nitronates **32a** and **32b** in a ratio of 12:1. For 2-alkyl-1-nitroalkenes, best results were obtained if $SnCl_4$ (3.0 equiv) was added to the mixture of nitroalkene and enol ether (1.5 equiv) at −78 °C. No reaction was observed if 1-acetoxy-2-(benzyloxy)-ethene was employed as the dienophile. Unlike the phenyl series, the observed HC(4) and HC(5) coupling constants were 3.9 and 9.8 Hz for the major and minor diastereomers, respectively, Figure 3. This suggested that the relative configuration of these centers differed in the two diastereomers. The small coupling constants of 2.4 and 3.0 Hz for HC(5) and HC(6) indicated that the cis relationship was maintained. Hydrogenolysis and *N*-protection of the major nitronate cycloadduct afforded

(36) (a) Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306. (b) Rudchenko, V. F. *Chem. Rev.* **1993**, *93*, 725. (c) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675.

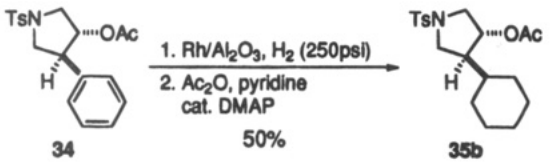
Table 3. Preparation of 3-Acetoxypyrrolidines



nitronate	product	R	R′	yield (%)	diastereomer ratio	37, yield (%)
22a	**18**	veratryl	ethyl	75[a]		0
31	**34**[b]	phenyl	H	51		13
32a	**35a**	H	cyclohexyl	44		19
32b	**35b**	cyclohexyl	H	60		0
33	**36**[c]	H[d]	*n*-pentyl	14	3:1	30

[a] After deprotonation. [b] 1:1 mixture of diastereomers. [c] 1:3.5:1.5:2 mixture of diastereomers. [d] Relative configuration could not be established.

Scheme 13



the *N*-tosyl-3-acetoxypyrrolidine in 44% yield accompanied by 19% of *N*-tosyl-3-cyclohexylpyrrolidine. Hydrogenolysis and *N*-protection of the minor nitronate diastereomer, however, afforded a different *N*-tosyl-3-acetoxypyrrolidine in 60% yield with no detectable deoxygenation product. To confirm the relative stereochemistry of the 4-cyclohexylpyrrolidines, a correlation was made to the 4-phenylpyrrolidine **34** by saturation of the aromatic ring. The configuration of **34** was relatively certain by analogy to the structure of **23a** which was established by X-ray crystallography. A methanolic solution of **34** was stirred for 36 h under 250 psi of hydrogen pressure in the presence of 5% Rh/Al_2O_3 catalyst, Scheme 13. Subsequent reacylation of the 3-hydroxy substituent afforded in 50% yield a single *N*-tosyl-4-cyclohexyl-3-acetoxypyrrolidine whose spectral data exactly matched that of the pyrrolidine obtained from the minor nitronate, **35b**. On the basis of this correlation and the proton coupling constants, the relative configuration of the major pyrrolidine and consequently nitronate can be assigned as cis while the minor is trans. *It should be noted that the observed selectivity in the [4 + 2] cycloaddition of 2-cyclohexyl-1-nitroalkene* ***28*** *is opposite to that of the 2-aryl-1-nitroalkenes previously examined.*

1-Nitroheptene (**29**) also reacted very slowly with enol ether (*Z*)-**11a** to afford a mixture of all four possible diastereomers in 82% yield. Analysis of the stereochemical composition was not possible due to overlapping resonances in the ^1H NMR spectrum. Subsequent hydrogenation of the inseparable mixture followed by *N*-protection afforded a 3:1 mixture of *N*-tosyl-3-acetoxypyrrolidines in 14% yield. Assignment of the relative configuration of the two diastereomers was again not possible since HC(3) and HC(4) coupling constants were very similar, 3.9 and 3.4 Hz. A deoxygenated pyrrolidine was also isolated in 30% yield. Nitroalkene **30** was found to be unreactive and was recovered unchanged from attempted cycloadditions.

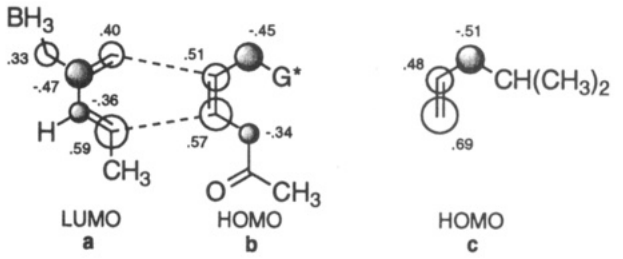


Figure 4. AM1 molecular orbital coefficients for (a) BH_3–nitropropene complex, (b) **11a**, and (c) isopropyl vinyl ether.

Discussion

[4 + 2] Cycloaddition. Regioselectivity. Both 1-acetoxy-2-(benzyloxy)ethene and chiral 2-acetoxyvinyl ether **11a** underwent highly regioselective cycloadditions with 2-aryl- and 2-alkyl-1-nitroalkenes. In no case could diastereomers related to the opposite regiochemistry be identified. The observed regioselectivity can be easily explained on the basis of frontier molecular orbital theory. AM1 molecular orbital calculations[37] were performed to identify the HOMO and LUMO orbitals for enol ether **11a**, isopropyl vinyl ether, and the Lewis acid complex between 1-nitropropene and BH_3, Figure 4.[38] In comparison to the HOMO molecular orbital for isopropyl vinyl ether, the presence of the 2-acetoxy substituent attenuates the difference between the orbital coefficients; however, sufficient differentiation is still provided to obtain high regiocontrol.

Endo/Exo Selectivity. Cycloadditions of 2-phenyl- and 2-veratryl-1-nitroalkenes were found to undergo exclusive exo mode cycloadditions with enol ethers (*Z*)-**8** and (*Z*)-**11a**. On the other hand, 2-alkyl-1-nitroalkenes showed low to moderate endo/exo selectivity and in the case of cyclohexyl-substituted nitroalkene **27**, the endo approach dominated in a ratio of 12:1. Previously, enol ethers have shown high endo selectivity in nitroalkene [4 + 2] cycloadditions when promoted with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$; however, this phenomenon is Lewis acid dependent.[1a] In contrast, the Lewis acid MAPh was found to promote an exo-selective cycloaddition. Unfortunately, a direct comparison for a $SnCl_4$-promoted cycloaddition with a vinyl ether is not available. Cycloadditions promoted by $SnCl_4$ employing cyclohexene as the dienophile have been found to provide exo products exclusively with 2-aryl-1-nitroalkenes but erosion of selectivity occurred with 2-cyclohexyl-1-nitroalkene **28** (9:1 exo/endo).[30b] This behavior is similar to that observed with 2-acetoxyvinyl ethers, but not as pronounced an effect. These observations suggest that secondary interactions between substituents of the dienophile and the diene play an important role in determining exo/endo selectivity.

Steric effects should favor the exo approach of the dienophile since this would minimize nonbonded interactions between the nitroalkene and the enol ether. In comparing a cyclohexane ring to a planar, conjugated phenyl ring in terms of Taft steric parameters ($-E_s$ = 2.03 and 1.01, respectively),[39] a cyclohexyl substituent would be predicted to impose the greater steric influence.

(37) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Jie, C.; Zoebisch, E. G. *Organometalics* **1988**, *7*, 513.

(38) (a) MOPAC 6.0 as implemented in CAChe MOPAC Version 94 was employed for these calculations. (b) BH_3 was employed as the Lewis acid since AM1 calculations with $SnCl_4$ predict an Sn–O distance outside their van der Waals radii.

(39) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.

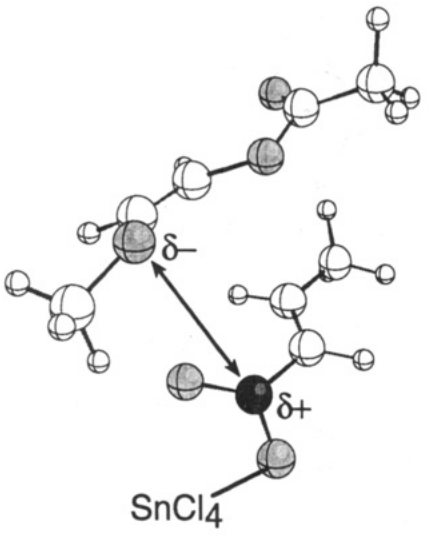


Figure 5. Representation of the proposed endo approach to 1-nitropropene.

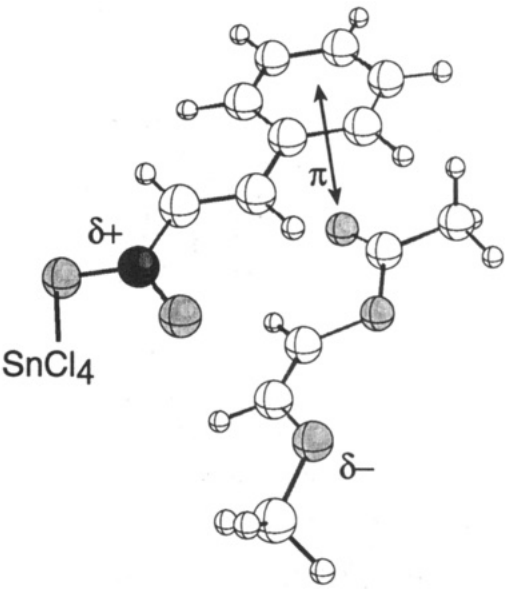


Figure 6. Representation of the proposed exo approach to β-nitrostyrene.

This is counter to the observation that 2-cyclohexyl-1-nitroalkene **28** favors the endo approach of the dienophile. Houk[40] has proposed that Coulombic interactions between the diene and dienophile in the transition state govern the endo/exo selectivity in [4 + 2] cycloadditions. In the case of nitroalkene cycloadditions, attractive Coulombic interactions between the electropositive nitrogen of the diene and a partially electronegative enol ether oxygen would facilitate endo approach, Figure 5. However, if the electronic environment of nitrogen is changed such that the extent of charge delocalization is altered, the endo/exo selectivity would consequently also be altered. The extended π-conjugation present in 2-aryl-1-nitroalkenes would allow for delocalization of the positive charge from nitrogen into the aryl ring. The reduced attractive electrostatic interaction is therefore no longer sufficient to overcome the steric demands of endo approach and the exo orientation is observed, Figure 6. Though exo approach does not benefit from the stabilizing interaction between nitrogen and oxygen, the potential for π–π interactions between the aryl ring and the acyl carbonyl may help to stabilize this approach.

The role of the Lewis acid in determining endo or exo approach, however, should not be overlooked. The exact nature of the nitroalkene–Lewis acid complex is uncertain. Early studies which employed variable-temperature NMR experiments suggested that the $SnCl_4$ complex with 1-nitrocyclohexene has a 1:1 stoichiometry; however, the complex was still dynamic at −120 °C.[41] An X-ray crystal structure of a $TiCl_4$–nitromethane complex has been reported and shows a 1:1 stoichiometry with monodentate coordination;[42] however, a crystal structure of a zinc complex indicated bidentate coordination.[43] Previous studies with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ and MAPh have shown that the Lewis acid plays an important role in the endo/exo selectivity. The fact that alkyl nitroalkenes are significantly less reactive than the aryl derivatives may suggest a weaker complex between the Lewis acid and nitroalkene.[44] As a result delocalization of the electropositive charge on nitrogen into the Lewis acid is attenuated. The persistence of a localized positive charge on nitrogen therefore helps to stabilize the endo approach of the dienophile.

Facial Selectivity. The facial selectivity of the [4 + 2] cycloaddition is governed by three factors: (1) the exo or endo approach of the dienophile, (2) the conformation of the enol ether, s-cis or s-trans, and (3) the inherent facial bias of the auxiliary, 2,2-diphenylcyclopentanol. The endo/exo preference of the cycloaddition was discussed above. Enantiomerically enriched pyrrolidine **18** arises from an exo [4 + 2] cycloaddition as confirmed by X-ray analysis of **23a** and the assumption that the *E* configuration of nitroalkene **14** is the reactive species.

Two conformational issues must be considered with 2-acetoxyvinyl ethers, the conformation of the enol ether fragment and the conformation of the vinyl ester half of the molecule. The most important question in relation to the sense of asymmetric induction is that of the enol ether. If the auxiliary provides perfect shielding, the two enol ether conformations, s-cis and s-trans, present a different face of the olefin toward the diene and therefore opposite configuration of products can be obtained. Spectroscopic studies have suggested that the s-trans conformation of vinyl and propenyl ethers predominates in the ground state as the steric size of the ether substituent increases.[45] Molecular mechanics calculations[46] for **11a** predicted an s-trans ground-state conformation with the corresponding s-cis conformation only 0.3 kcal/mol higher in energy. AM1 calculations[37a,38a] however predicted the opposite, with the s-cis conformation lower in energy by 0.9 kcal/mol. The discrepancy

(40) (a) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. (b) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.

(41) Cramer, C. J. Ph.D. Thesis, University of Illinois, Urbana, IL 1988.

(42) Boyer, M.; Jeannin, Y.; Rocchiccioli-Deltcheff, C.; Thouvenot, R. *J. Coord. Chem.* **1978**, *7*, 219.

(43) Hurlburt, P. K.; Kellett, P. J.; Anderson, O. P.; Strauss, S. H. *J. Chem. Soc., Chem. Commun.* **1990**, 576.

(44) A Hammett study of the influence of nitroalkene C(2) substituent on reactivity has been examined, see ref 30b.

(45) (a) Atoni, A. V.; Khil'ko, M. Y.; Komel'kova, V. I.; Shafeev, M. A.; Nedolya, N. A. *Zh. Org. Khim.* **1991**, *27*, 161. (b) Bond, D.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1003. (c) For a review, see: Fischer, P. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and Their Sulphur Analogs*; Patai, S., Ed.; Wiley: New York, 1980; Part 2, p 761.

(46) The program Macromodel version 3.5a, Columbia University, was employed for these calculations.

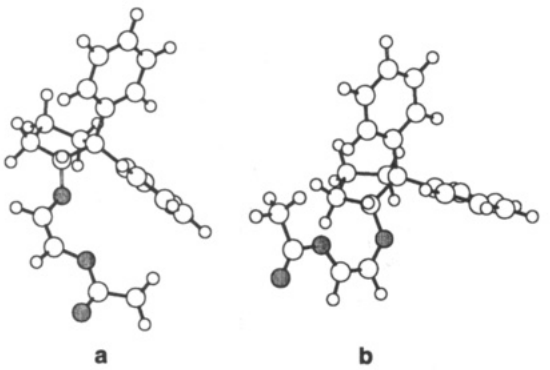
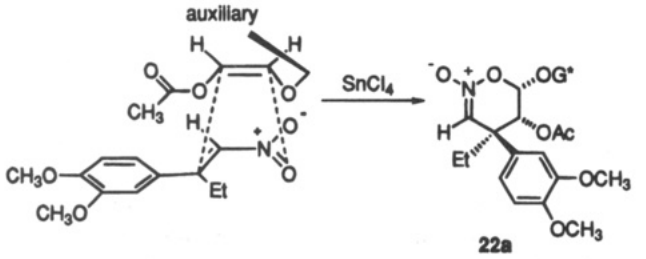


Figure 7. Representations of enol ether **11a** (a) s-trans and (b) s-cis conformations from MM2 calculations.

Scheme 14



punctuates the fine balance of steric and stereoelectronic factors present in **11a** and dictates that both conformations must be considered as the potentially reactive conformation in the [4 + 2] cycloaddition.

The conformation of enol esters has been studied computationally by Houk.[47] These calculations indicate that the most stable conformation corresponds to a vinylic C—O torsion angle of approximately 180° and a carbonyl C_{sp^2}—O dihedral angle of 0°. These results are reproduced in molecular mechanics calculations predicting an 8.7 kcal/mol energy penalty for adopting the anti conformation.

As depicted by the representations of the molecular mechanics calculations in Figure 7, limited facial shielding would be expected for the s-cis conformation (Figure 7b). In the case of the s-trans conformation (Figure 7a), the phenyl moieties of the auxiliary would be expected to provide shielding to the *re* face[48] of the enol ether. Therefore, the [4 + 2] cycloaddition would be expected to occur to the *si* face. This is indeed the case for the cycloaddition of enol ether (*R*)-**11a** with nitroalkene (*E*)-**14**. Exo approach of the enol ether in the s-trans conformation to the *si* face of the nitroalkene would afford the observed configuration for the nitronate cycloadduct, Scheme 14. The same absolute configuration could be obtained through an s-cis conformation; however, this would force one to invoke nonbonded steric interactions between the auxiliary cyclopentyl ring and the nitroalkene as the stereocontrolling element. It is unlikely that this interaction would afford the high enantiomeric enrichment observed (96% ee).

Several observations about the requirements for facial selectivity in this system can be made on the basis of nitroalkene and enol ether surveys (Tables 1 and 2). First, a small acyl substituent is required for good selectivity. Selectivity rapidly decreased in the series methyl > pivaloyl > benzoyl in the range of 40:1 to 3.7:1. It is believed that increasing the size of the enol ether β substituent results in steric interactions between the substituent and the phenyl rings of the auxiliary which compromises their shielding ability for the enol ether olefin. Also, in exo-mode cycloadditions, a 2,2-disubstituted-1-nitroalkene is required for high facial selectivity. This is exemplified by the comparison of nitroalkene **14** affording 97:3 selectivity while nitroalkene **27** provides essentially no facial preference (1:1). This suggests that the primary steric interaction is between the *Z*-configured ethyl substituent and the auxiliary when the enol ether is in an exo orientation since the nitroalkene itself is too far removed to provide high discrimination. In the case of 2-alkyl-substituted nitroalkenes, α-branching is necessary for high facial selectivity. Though endo/exo selectivity was only moderate for nitroalkene **28**, a single diastereomer was isolated from each mode.

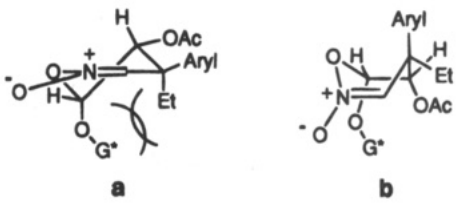


Figure 8. Proposed twist chair and boat conformations for **22a**.

[3 + 2] Cycloaddition. As discussed above, [3 + 2] cycloaddition of nitronate **22a** proceeded with high stereoselectivity (7:1) with exo approach of the dipolarophile. The exo selectivity of the cycloaddition has been rationalized by a mismatched secondary orbital interaction between the nitronate nitrogen and the C_{sp^2} center of the dipolarophile in addition to steric interactions which would destabilize the endo approach.[36c] On the basis of our stereochemical analysis of the cycloadducts, approach of the dipolarophile occurs preferentially from the face opposite to the aryl moiety. If one were to invoke the same twist chair as for nitronates derived from mono-2-substituted-1-nitroalkenes, the selectivity would not be expected to be high, Figure 8a. This conformation would place the veratryl substituent in a pseudoequatorial position. The twist chair conformation, however, introduces a destabilizing 1,3-diaxial interaction in nitronate **22a** between the C(4) ethyl substituent and the anomeric alkoxy substituent. As a result, the boat conformation (Figure 8b) which maintains the alkoxy group axial for anomeric stabilization becomes the more favored conformation. This conformation may also exhibit a stabilizing "gauche effect" [49] interaction between the C(5) and C(6) heteroatom substituents. High selectivity from this conformation can be easily explained since the aryl ring is now placed in an axial position.

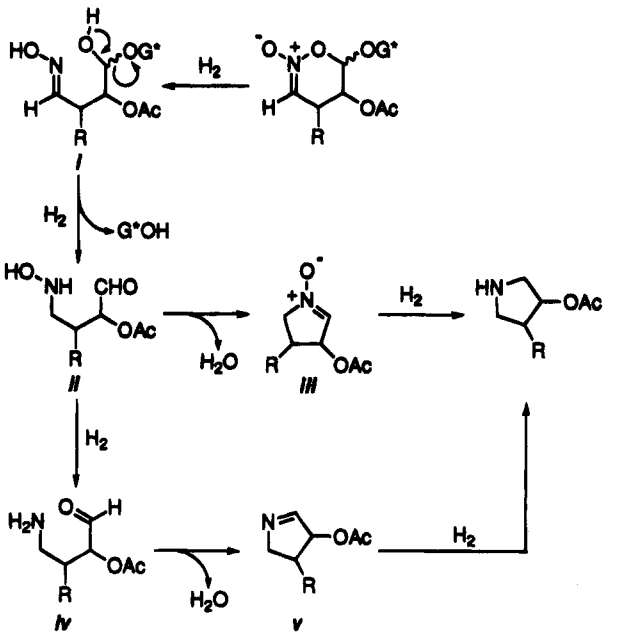
Hydrogenation of Acetoxy Nitronates. A detailed mechanistic study of the hydrogenolysis has not been conducted; however, a proposed route is presented in Scheme 15. The initial step is believed to involve saturation of the carbon—nitrogen bond followed by elimination to cleave the oxazine nitrogen—oxygen bond. Tautomerization would afford the unstable oxime hemiacetal (***i***) which, upon breakdown, would provide the

(47) Tucker, J. A.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1990**, *112*, 5465.

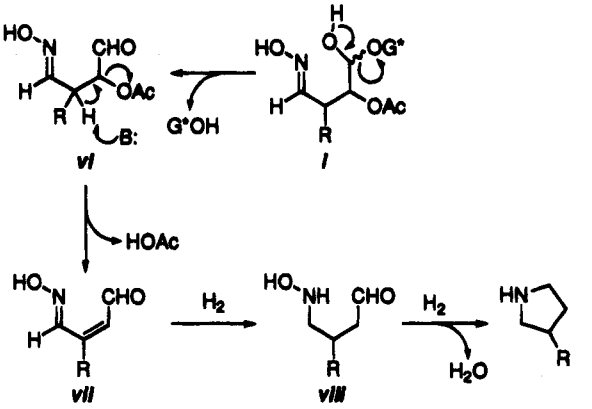
(48) The *re* and *si* faces of the olefin are defined with respect to the C(1) alkoxy bearing carbon atom.

(49) (a) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. (b) Amos, R. D.; Handy, N. C.; Jones, P. G.; Kirby, A. J.; Parker, J. K.; Percy, J. M.; Su, M. D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 549.

Scheme 15



Scheme 16



parent aldehyde and the chiral alcohol auxiliary. Further reduction of the oxime would afford the intermediate hydroxylamine aldehyde (*ii*). Two potential routes can be envisioned for collapse to the observed pyrrolidine. Condensation and subsequent reduction of the resulting nitrone (*iii*) would afford the pyrrolidine directly. On the other hand, hydrogenolysis of the hydroxylamine aldehyde would afford amino aldehyde (*iv*). Subsequent condensation and saturation via the intermediate imine (*v*) would also form the pyrrolidine product.

Competitive deprotection of the acetate was found to be a problem in the hydrogenolysis of 4,4,5-trisubstituted nitronate **22a** and their corresponding nitroso acetals **23a,b**. Both the starting nitroso acetal and the α-hydroxy lactam product were found to be stable in methanol solution indefinitely; however, it is impossible to ascertain the susceptibility of the numerous intermediates along the reaction pathway to methanolysis. Interestingly, hydrogenation of *N*-tosyl-3-acetoxypyrrolidine **34** with Rh/Al_2O_3 also resulted in deprotection of the acetate. Therefore, methanolysis of the acetate promoted by base or pressure is the most likely pathway. The addition of acetic acid to the reduction of nitronate **15** did suppress deprotection to an extent, 57:43 (**18**:**17**) without acetic acid and 46:54 (**18**:**17**) with acetic acid, but the addition of any acid to the nitroso acetal hydrogenolysis retarded the reaction. The incorporation of in situ deprotection of the product mixture is convenient if the hydroxylated pyrrolidine or lactam is desired.

In the case of nitronates derived from 2-substituted-1-nitroalkenes, saponification was not observed; however, competitive deoxygenation was. Deoxygenation could be suppressed by the addition of 5 equiv of glacial acetic acid, but the side product still accounted for 13–30% of the isolated material. Several possible mechanistic explanations are offered. First, the fact that deoxygenation was not observed when a quaternary carbon center is adjacent to the acetoxy substituent implies that the presence of a β-proton is important. The hydrogen at an α-carbon center to an oxime is susceptible to deprotonation. With the pyrrolidine product acting as the base, deprotonation and subsequent elimination of the acetate would form a highly conjugated oxime aldehyde (*vii*, Scheme 16). Further hydrogenolysis would afford the observed deoxygenated product. The role of acetic acid in suppressing deoxygenation arises from trapping of the pyrrolidine product as the acetate salt, preventing deprotonation. Intramolecular deprotonation at an intermediate state in the hydrogenation cannot be ruled out and in this case acetic acid is an intermolecular competitor. Alternatively, tertiary alcohols and esters are known to be reduced to alkanes by platinum oxide and trifluoroacetic acid at atmospheric pressure of hydrogen.[50] It is believed that the trifluoroacetate and alkene are intermediates. A similar process could be occurring for the secondary acetate in our nitronate reductions. The presence of the β-quaternary center would prevent alkene formation. The reason for suppression of the deoxygenation by the addition of acetic acid however is not clear in this case.

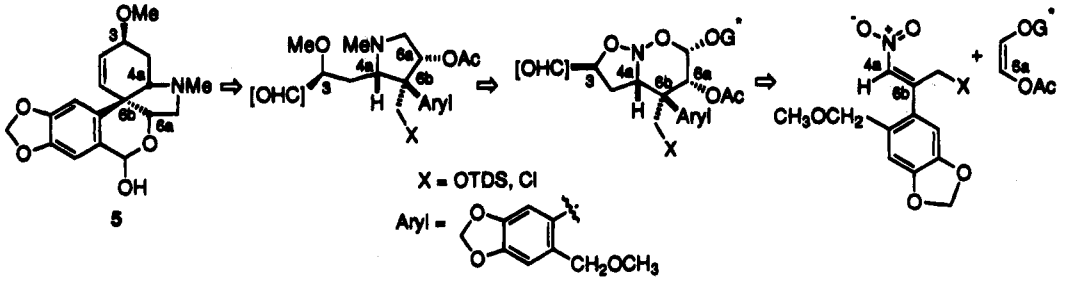
The stereoselective [4 + 2] cycloaddition of nitroalkene (*E*)-**13** followed by the exo-selective [3 + 2] cycloaddition of the resulting nitronate with methyl acrylate demonstrated the ability to construct four stereogenic centers three of which are contiguous and provided an excellent model system for a proposed total synthesis of (+)-pretazettine (**5**), Scheme 17. The stereogenic centers C(6a) and C(6b) of pretazettine are envisioned to arise from the initial [4 + 2] cycloaddition to afford a trans relationship between the aryl ring and the oxygen functionality as demonstrated in nitroso acetal **23a**. An exo-selective [3 + 2] cycloaddition would allow introduction of the stereogenic centers at C(4a) and C(3) where the hydroxyl functionality at C(3) would be unmasked in the hydrogenolysis of a nitrogen–oxygen heterocyclic bond. Therefore, the model system has demonstrated that all four stereogenic centers of (+)-pretazettine can be installed in the proper relative and absolute configuration. By employing the three basic reactions, [4 + 2] cycloaddition, hydrogenolysis of nitroso acetals, and [3 + 2] dipolar cycloaddition, (+)-pretazettine would arise from a properly substituted nitroalkene and the corresponding β-acetoxy enol ether **11a**.

Conclusion

2-(Acyloxy)vinyl ethers have been found to act as heterodienophiles in $SnCl_4$-promoted [4 + 2] cycloadditions with nitroalkenes. The [4 + 2] cycloadditions studied have provided exclusively one regioisomer. The mode of dienophile approach, endo or exo, has been found to be dependent on the nitroalkene substitution and is

(50) Peterson, P. E.; Casey, C. *J. Org. Chem.* **1964**, *29*, 2325.

Scheme 17



rooted in the extent of charge delocalization within the nitroalkene–Lewis acid complex. The resulting nitronates can be elaborated by direct hydrogenolysis to *N*-protected-3-hydroxypyrrolidines or through [3 + 2] cycloaddition followed by hydrogenolysis to afford bicyclic α-hydroxy lactams. A chiral 2-acetoxyvinyl ether derived from (*R*)-2,2-diphenylcyclopentanol (**11a**) has been found to provide high facial selectivity with 2,2-disubstituted aryl-1-nitroalkenes from which *N*-tosyl-4,4-disubstituted-3-hydroxypyrrolidines can be prepared with high enantiomeric excess (96% ee). Currently, the application of chiral 2-acetoxyvinyl ethers is being applied toward the total synthesis of (+)-pretazettine.

Experimental Section

General. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures and are uncorrected. Melting points (mp) are uncorrected. Analytical high-pressure liquid chromatography (HPLC) employed a Chiralcel AD column (250 × 4.5 mm) and a solvent system of hexane/EtOH, 66.6/33.4, 0.75 mL/min (wavelength = 254 nm). Medium-pressure chromatography (MPLC) employed a 40 × 5 cm silica gel (Kieselgel 60G) column. All reactions were performed in oven- (140 °C) or flame-dried glassware under an inert atmosphere of dry N_2. Reaction solvents were distilled from the indicated drying agent: CH_2Cl_2 (P_2O_5), THF (Na, benzophenone), and toluene (Na). Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); dichloromethane ($CaCl_2$); *tert*-butyl methyl ether (MTBE) ($CaSO_4/FeSO_4$); ethyl acetate (K_2CO_3). Column (flash) chromatography was performed by the method of Still,[51] using 32–63 μm silica gel (Woelm). Brine refers to a saturated aqueous solution of sodium chloride. Ozonolyses were performed with an oxygen pressure of 8 psi and 70 W, producing an ozone flow rate of 1.5 mmol/min.

Optical rotations were performed in CH_2Cl_2 (l = 5 cm, T = 25 °C). Infrared spectra (IR) were obtained in CCl_4 unless otherwise specified. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34-66%), w (weak, 0–33%). ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz ^1H (100 MHz ^{13}C) with chloroform (δ 7.26 ppm for ^1H, 77.0 ppm for ^{13}C) or tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). Coupling constants, J, are reported in hertz. Unassigned ^{13}C resonances are noted with their multiplicities from DEPT spectra. Electron-impact (EI) mass spectra were obtained with an ionization voltage of 70 eV. Chemical ionization (CI) mass spectra were obtained using methane. Low- and high-resolution fast atom bombardment (FAB) spectra were obtained in Magic Bullet (3:1, dithiothreitol: dithioerythitol). Data are reported in the form m/z (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

(51) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3-((*R*)-2,2-Diphenylcyclopentoxy)-1-propene (9). In a 100 mL three-neck flask, potassium hydride (802 mg, 20.0 mmol, 2.0 equiv) was washed three times with pentane and suspended in THF (20 mL). Alcohol **4** (2.38g, 10.0 mmol) in THF (20 mL) was added dropwise by addition funnel at 20 °C. The suspension was allowed to stir at 20 °C for 1 h. Allyl bromide (1.30 mL, 15.0 mmol, 1.5 equiv) in THF (10 mL) was added dropwise, maintaining a temperature less than 30 °C. The resulting cloudy white solution was allowed to stir at rt for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL), diluted with 150 mL of MTBE, and washed with water (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (8/1)) and crystallized from hexane/EtOAc to afford 2.45g (89%) of allyl ether **9** as a white solid. Data for **9**: mp 30–32 °C (hexane/EtOAc); ^1H NMR (400 MHz) 7.10–7.31 (m, 10 H), 5.81 (dddd, J = 17.3, 10.5, 5.4, 5.4, 1 H), 5.13 (dq, J_q = 1.7, J_d = 17.1, 1 H), 5.07 (dq, J_q = 1.7, J_d = 10.5, 1H), 4.44 (t, J = 4.9, 1H), 4.00, 3.83 (ABq, J_d = 13.2, 5.4, J_t = 1.5, 2H), 2.57-2.64 (m, 1H), 2.30–2.36 (m, 1H), 1.92–2.01 (m, 1H), 1.83–1.90 (m, 1H), 1.71–1.79 (m, 1H), 1.56–1.64 (m, 1H); ^{13}C NMR (100 MHz) 147.45, 145.22, 135.18, 128.78, 128.06, 127.42, 126.93, 125.69, 125.45, 116.06, 84.84, 70.17, 58.91, 35.16, 28.62, 19.88; IR 2966 (s), 1493 (s), 1446 (s); MS (EI) 278 (M^+, 10); $[\alpha]^{25}_D$ = −109.8° (CH_2Cl_2, c = 1.05); TLC R_f 0.16 (hexane). Anal. Calcd for $C_{20}H_{22}O$ (278.393): C, 86.29; H, 7.97. Found: C, 86.33; H, 7.97.

2-((*R*)-2,2-Diphenylcyclopentoxy)ethanal (10). Allyl ether **9** (0.98g, 3.50 mmol) was dissolved in CH_2Cl_2 (35 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue color appeared. The solution was purged with oxygen. Zinc (332 mg, 5.24 mmol, 1.5 equiv) was added followed by 15 mL of 50% acetic acid. The suspension was allowed to slowly warm to 0 °C, stirred for 30 min, and then allowed to stir at rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (20 mL), saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and brine (10 mL). The aqueous layers were back-extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (4/1, 2/1)) and distilled to afford 720 mg (74%) of aldehyde **10** as a clear oil. Data for **10**: bp 200 °C (0.1 Torr); ^1H NMR (400 MHz) 9.50 (t, J = 1.2, 1 H), 7.10–7.31 (m, 10 H), 4.51 (dd, J = 3.7, 4.9, 1 H), 3.95, 3.83 (ABq, J = 17.6, 1.2, 2 H), 2.60-2.68 (m, 1 H), 2.35–2.41 (m, 1 H), 1.77–2.08 (m, 3 H), 1.52–1.63 (m, 1 H); ^{13}C NMR (100 MHz) 201.99, 146.59, 144.78, 128.58, 128.22, 127.69, 126.76, 125.95, 125.79, 86.96, 75.05, 58.35, 34.87, 28.84, 19.86; IR 2967 (s), 1738 (s), 1599 (m), 1493 (s), 1446 (s); MS (EI) 280 (M^+, 2); $[\alpha]^{25}_D$ = −114.4° (CH_2Cl_2, c = 1.12); TLC R_f 0.22 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{19}H_{20}O_2$ (280.366): C, 81.40; H, 7.19. Found: C, 81.24; H, 7.16.

(*Z*)-1-(Acetyloxy)-2-((*R*)-2,2-diphenylcyclopentoxy)-ethene (11a). Aldehyde **10** (1.84 g, 6.55 mmol) was dissolved in toluene (100 mL). To the solution were added K_2CO_3 (4.52 g, 32.75 mmol, 5.0 equiv), NaOAc (67 mg, 0.66 mmol, 0.1 equiv), and acetic anhydride (6.18 mL, 65.5 mmol, 10.0 equiv). The mixture was heated at reflux for 24 h. After being allowed to cool, the reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude reaction mixture was

purified by column chromatography (hexane/EtOAc (8/1)) and distilled to afford 1.69 g (80%) of enol ether **11a** as a clear oil. Data for **11a**: bp 225 °C (0.1 Torr); mp 35–37 °C; ^{1}H NMR (400 MHz) 7.10–7.29 (m, 10 H), 6.35 (d, J = 3.7, 1 H), 5.60 (d, J = 3.6, 1 H), 4.79 (dd, J = 5.2, 3.2, 1 H), 2.63–2.71 (m, 1 H), 2.40–2.46 (m, 1 H), 2.03 (s, 3 H), 1.85–2.05 (m, 3 H), 1.54–1.65 (m, 1 H); ^{13}C NMR (100 MHz) 167.75, 146.21, 144.39, 132.04, 128.57, 128.26, 127.55, 127.55, 126.70, 125.99, 125.70, 118.09, 88.51, 59.10, 34.67, 29.55, 19.86; IR 3026 (s), 2969 (s), 1755 (s), 1684 (s), 1495 (s); MS (EI) 322 (M^+, 1); $[\alpha]^{25}_D$ = −165.0° (CH_2Cl_2, c = 0.75); TLC R_f 0.39 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{21}H_{22}O_3$ (322.403): C, 78.24; H, 6.88. Found: C, 78.12; H, 6.94.

***rac*-(*Z*)-1-((2,2-Dimethyl-1-oxopropyl)oxy)-2-(2,2-diphenylcyclopentoxy)ethene (11b).** Aldehyde **10** (3.75 g, 13.36 mmol) was dissolved in toluene (200 mL). Trimethylacetic anhydride (27.1 mL, 133.6 mmol, 10.0 equiv) was added followed by K_2CO_3 (9.23 g, 66.8 mmol, 5.0 equiv) and pivalic acid, sodium salt (189 mg, 1.34 mmol, 0.1 equiv). The mixture was heated at 110 °C for 36 h, allowed to cool to rt, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (12/1)) and distilled to afford 1.91 g (39%) of **11b** as a clear oil. Data for **11b**: bp 220 °C (0.1 Torr); ^{1}H NMR (400 MHz) 7.12–7.31 (m, 10 H), 6.40 (d, J = 3.4, 1 H), 5.67 (d, J = 3.4, 1 H), 4.80 (t, J = 4.9, 1 H), 2.67 (ddd, J = 13.2, 9.2, 7.7, 1 H), 2.40 (ddd, J = 13.1, 8.0, 4.0, 1 H), 1.78–2.10 (m, 3 H), 1.65 (m, 1 H), 1.17 (s, 9 H); ^{13}C NMR (100 MHz) 175.18, 146.49, 144.30, 131.86, 128.56, 128.21, 127.53, 126.71, 125.94, 125.66, 118.50, 87.64, 58.62, 38.71, 34.79, 29.17, 26.93, 19.60; IR 3060 (s), 2972 (s), 1739 (s), 1679 (s), 1494 (s); MS (EI) 364 (M^+, 0.2); TLC R_f 0.40 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{24}H_{28}O_3$ (364.483): C, 79.09; H, 7.74. Found: C, 79.10; H, 7.75.

***rac*-(*Z*)-1-(Benzoyloxy)-2-(2,2-diphenylcyclopentoxy)ethene (11c).** Aldehyde **10** (4.98 g, 17.76 mmol) was dissolved in toluene (250 mL). Benzoic anhydride (20.1 g, 88.81 mmol, 5.0 equiv) was added followed by K_2CO_3 (12.30 g, 88.81 mmol, 5.0 equiv) and benzoic acid, sodium salt (512 mg, 3.55 mmol, 0.2 equiv). The mixture was heated at 110 °C for 48 h, allowed to cool to rt, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (12/1)) followed by MPLC (12 mL/min, 30:1 (hexane/EtOAc)) and distilled to afford 1.15 g (17%) of **11c** as a clear oil. Data for **11c**: bp 250 °C (0.2 Torr); ^{1}H NMR (400 MHz) 7.94 (dd, J = 8.3, 1.0, 2 H), 7.57 (t, J = 7.3, 1 H), 7.42 (t, J = 7.8, 2 H), 7.10–7.34 (m, 10 H), 6.72 (d, J = 3.4, 1 H), 5.80 (d, J = 3.6, 1 H,), 2.73 (m, 1 H), 2.44 (m, 1 H), 2.07 (m, 1 H), 1.85–2.02 (m, 2 H), 1.67 (m, 1 H); ^{13}C NMR (100 MHz) 162.99, 146.43, 144.39, 133.14, 132.16, 129.91, 129.15, 128.63, 128.30, 128.24, 127.52, 126.71, 125.97, 125.66, 118.24, 87.88, 58.77, 34.96, 29.34, 19.69; IR 2971 (s), 1736 (s), 1494 (s), 1273 (s); MS (EI) 384 (M^+, 0.3); TLC R_f 0.53 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{26}H_{24}O_3$ (384.474): C, 81.22; H, 6.29. Found: C, 81.11; H, 6.85.

***rel*-(4*R*,5*S*,6*S*)-5-(Acetyloxy)-3-methyl-4-phenyl-6-(phenylmethoxy)-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (13).** To a cold (−78 °C) solution of nitroalkene **12** (163 mg, 1.0 mmol) in CH_2Cl_2 (2.5 mL) was added $SnCl_4$ (350 μl, 3.0 mmol, 3.0 equiv) in CH_2Cl_2 (1.0 mL). The resulting yellow-brown solution was stirred at −78 °C for 10 min and then a solution of enol ether (*Z*)-**8** (288 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise. The color of the solution gradually changed to red. After 30 min, the reaction mixture was quenched with a 1 N solution of NaOH in methanol (6.0 mL) and allowed to warm for 5 min. The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (2 × 75 mL) and brine (75 mL). The aqueous layers were back-extracted with MTBE (2 × 100 mL). The combined organic layers were dried ($MgSO_4$/$NaHCO_3$ (1:1)) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (4/1, 1/1)) to afford 321 mg (90%) of nitronate **13** as a white solid. Data for **13**: mp 120–122 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 7.30–7.37 (m, 8 H), 7.18–7.20 (m, 2 H), 5.53 (d, J = 2.9, 1 H), 5.07 (dd, J = 9.9, 2.9, 1 H), 5.05, 4.79 (ABq, J = 12.1, 2 H), 3.88 (dd, 1 H, J = 9.9, 1.5), 1.91 (s, 3 H), 1.83 (d, J = 1.5, 1 H); ^{13}C NMR (100 MHz) 169.56, 136.69, 135.94, 129.11, 128.49, 128.32, 128.30, 128.19, 128.05 121.08, 97.70, 70.68, 70.46, 45.49, 20.36, 17.33; IR 3034 (w), 1753 (s), 1618 (m), 1230 (s); MS (EI) 265 (3), 91 (100); TLC R_f 0.16 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{20}H_{21}NO_5$ (355.390): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.66; H, 5.95; N, 3.95.

***rel*-(4*S*,5*S*,6*R*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-4-ethyl-6-(phenylmethoxy)-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (15) from Nitroalkene (*Z*)-14.** To a cold (−78 °C) solution of nitroalkene (*Z*)-**14** (237 mg, 1.0 mmol) in CH_2Cl_2 (4.0 mL) was added a solution of $SnCl_4$ (1.0 mL, 3.0 mmol, 3.0 equiv) prepared by dissolving $SnCl_4$ (701 μl, 6.0 mmol) in CH_2Cl_2 (1.3 mL). The resulting deep purple solution was stirred at −78 °C for 5 min and then a solution of enol ether (*Z*)-**8** (288 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. After 3 h, the reaction mixture was quenched with a 1 N solution of NaOH in methanol (12.0 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (3 × 75 mL) and brine (75 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (1/1, 1/3)) and recrystallized from EtOAc/hexane to afford 355 mg (83%) of nitronate **15** as a white solid. Data for **15**: mp 140–143 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.24–7.33 (m, 5 H), 6.83 (d, J = 8.3, 1 H), 6.79 (dd, J = 8.3, 2.2, 1 H), 6.70 (d, J = 2.0, 1 H), 6.58 (s, 1 H), 5.42 (d, J = 2.4, 1 H), 5.29 (J = 2.7, 1 H), 4.98, 4.61 (ABq, J = 11.9, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.14 (s, 3 H), 2.08 (dq, J_d = 2.9, J_q = 7.3, 2 H), 0.70 (t, J = 7.6, 3 H); ^{13}C NMR (100 MHz) 170.09, 149.34, 148.47 135.84, 132.66, 128.31, 127.99, 127.53, 119.23, 114.47, 111.21, 109.31, 99.36, 71.49, 71.00, 55.92, 55.74, 47.16, 26.97, 20.58, 7.65; IR 2970 (m), 1749 (s), 1622 (s), 1516 (s); MS (EI) 429 (M^+, 3); TLC R_f 0.58 (EtOAc). Anal. Calcd for $C_{23}H_{27}NO_7$ (429.469): C, 64.32; H, 6.34: N, 3.26. Found: C, 64.41; H, 6.37; N, 3.24.

***rel*-(4*S*,5*S*,6*R*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-4-ethyl-6-(phenylmethoxy)-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (15) from Nitroalkene (*E*)-14.** As above to nitroalkene (*E*)-**14** (237 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) were added $SnCl_4$ (350 μL, 3.0 mmol, 3.0 equiv) and a solution of enol ether (*Z*)-**8** (288 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). Recrystallization from EtOAc/hexane afforded 379 mg (88%) of nitronate **15** as a white solid. Data for **15**: mp 142–144 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.24–7.31 (m, 5 H), 6.82 (d, J = 8.5, 1 H), 6.78 (dd, J = 8.3, 2.2, 1 H), 6.69 (d, J = 2.0, 1 H), 6.57 (s, 1 H), 5.41 (d, J = 2.4, 1 H), 5.29 (J = 2.4, 1 H), 4.98, 4.60 (ABq, J = 12.0, 2 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 2.14 (s, 3 H), 2.07 (dq, J_d = 2.9, J_q = 7.3, 2 H), 0.70 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 170.06, 149.29, 148.41, 135.81, 132.60, 128.28, 127.96, 127.50, 119.20, 114.44, 111.13, 109.22, 99.33, 71.45, 70.95, 55.88, 55.74, 47.13, 26.93, 20.57, 7.63; IR 3009 (m), 1750 (s), 1621 (s), 1517 (s), 1241 (s); MS (EI) 429 (M^+, 4); TLC R_f 0.23 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{23}H_{27}NO_7$ (429.469): C, 64.32; H, 6.34; N, 3.26. Found: C, 64.30; H, 6.35; N, 3.24.

Isomerization of (*Z*)-1-Nitro-2-(3,4-dimethoxyphenyl)-1-butene ((*Z*)-14). Nitroalkene (*Z*)-**14** (59 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to −78 °C. To the solution was added $SnCl_4$ (88 μL, 0.75 mmol, 3.0 equiv), resulting in a deep purple colored solution, which was stirred for 30 min. The reaction mixture was quenched with a 1 N solution of NaOH in methanol (3.0 mL). The mixture was diluted with 100 mL of CH_2Cl_2 and was washed with water (3 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by being passed through a plug of silica to afford 58 mg (98%) of a mixture of nitroalkenes (*E*)-**14** and (*Z*)-**14** in a ratio of 17:1 (^{1}H NMR). Data for (*E*)-**14** and (*Z*)-**14**: ^{1}H NMR (400 MHz) 7.24 (s, 1 H, 7.07 (dd, J = 2.2, 8.5, 1 H), 6.90–6.94 (m, 2 H), 3.93 (s, 5.6 H), 3.90 (s, 0.2 H), 3.86 (s, 0.2 H), 3.08 (q, J = 7.6, 1.9 H), 2.49 (q, J = 7.3, 0.1 H), 1.17 (t, J = 7.6, 2.8 H), 1.07 (t, J = 7.3, 0.2 H); ^{13}C NMR (100 MHz) 155.78, 151.01, 149.10, 134.62, 133.73, 129.10, 120.39, 119.28, 111.08, 110.83, 109.96, 109.70, 55.93, 55.92,

55.87, 55.75, 30.83, 24.47, 13.01, 11.92; IR 2937 (m), 1612 (m), 1598 (m), 1515 (s); TLC R_f 0.25 (hexane/acetone, 85/15).

***rel*-(3*S*,4*R*)-3-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-4-ethyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (17) and *rel*-(3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-4-ethyl-3-hydroxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (18).** To a suspension of nitronate **15** (1.29 g, 3.0 mmol) in methanol (60 mL) was added a catalytic amount of PtO_2 (102 mg, 0.45 mmol, 0.15 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The solution was filtered through Celite, washed with additional methanol (25 mL), and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (45 mL) and cooled to 0 °C. To the solution was added Et_3N (878 μL, 6.3 mmol, 2.1 equiv) and a solution of *p*-toluenesulfonyl chloride (627 mg, 3.3 mmol, 1.1 equiv) in CH_2Cl_2 (5.0 mL). The reaction mixture was allowed to stir at rt for 2 h. The reaction mixture was poured into 150 mL of CH_2Cl_2 and washed with a 0.1 N solution of HCl (2 × 50 mL) and a saturated aqueous $NaHCO_3$ solution (2 × 50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (2/1, 1/1)) to afford 524 mg (43%) of hydroxypyrrolidine **18** as a white solid and 422 mg (32%) of acetoxypyrrolidine **17** after crystallization from EtOAc/hexane as a white solid. An analytical sample of **17** was obtained after recrystallization from benzene/pentane and for **18** by recrystallization from diethyl ether. Data for **17**: mp 152–155 °C (benzene/pentane); ^{1}H NMR (400 MHz) 7.73 (d, J = 8.3, 2 H), 7.33 (d, J = 8.4, 2 H), 6.76–6.84 (m, 3 H), 5.16 (d, J = 3.5, 1 H), 4.03, 3.23 (ABq, J = 9.8, 2 H), 3.86 (s, 3H), 3.86 (s, 3 H), 3.36, 3.24 (ABq, J_A = 12.2, 3.9, J_B = 12.2, 2 H), 2.44 (s, 3 H), 1.78 (dq, J_d = 11.0, J_q = 7.5, 1 H), 1.77 (s, 3 H), 1.61 (dq, J_d = 11.0, J_q = 7.3, 1 H), 0.55 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz) 170.00, 148.96, 147.99, 143.36, 133.99, 132.27, 129.52, 127.48, 118.94, 110.92, 109.63, 78.93, 55.86, 55.74, 54.76, 52.45, 27.18, 21.41, 20.52, 9.12; IR 2967 (m), 1746 (s), 1234 (s), 1170 (s); MS (EI) 447 (M^+, 13); TLC R_f 0.39 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{23}H_{29}NO_6S$ (447.545): C, 61.73; H, 6.53; N, 3.13. Found: C, 61.71; H, 6.56; N, 3.12. Data for **18**: mp 139–142 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.73 (d, J = 8.3, 2 H), 7.31 (d, J = 7.8, 2 H), 6.83 (s, 1 H), 6.75 (s, 2 H), 4.20 (dt, J_d = 2.4, J_t = 4.9, 1 H), 3.85, 3.35 (ABq, J = 9.8, 2 H), 3.86 (s, 3H), 3.85 (s, 3 H), 3.39 (dd, J = 11.2, 4.6, 1 H), 3.22 (dd, J = 2.2, 11.0, 1 H), 2.42 (s, 3 H), 1.81 (dq, J_d = 13.7, J_q = 7.6, 1 H), 1.68 (dq, J_d = 13.7, J_q = 7.3, 1 H), 1.57 (m, 1 H), 0.59 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz) 148.71, 147.55, 143.36, 134.26, 134.08, 129.56, 127.20, 118.67, 110.72, 109.79, 77.40, 55.80, 55.68, 54.21, 54.21, 53.09, 26.16, 21.45, 9.05; IR 3505 (w), 2965 (w), 1597 (m), 1255 (m); MS (EI) 405 (M^+, 9); TLC R_f 0.29 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{21}H_{27}NO_5S$ (405.508): C, 62.20; H, 6.71; N, 3.45. Found: C, 62.16; H, 6.81; N, 3.42.

4-(3,4-Dimethoxyphenyl)-4-ethyl-1-[(4-methylphenyl)-sulfonyl]-3-pyrrolidinone (19). Pyridinium chlorochromate (1.29 g, 5.98 mmol, 3.0 equiv) and molecular seives (4 Å, 1.30 g) were suspended in CH_2Cl_2 (20 mL). Alcohol **18** (808 mg, 1.99 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise. The suspension was allowed to stir for 2 h as it gradually turned black. The reaction mixture was filtered through Florosil, washing with CH_2Cl_2 (20 mL), MTBE (20 mL), and EtOAc (20 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (2/1, 1/1)) and recrystallized (Et_2O) to afford 578 mg (72%) of **19** as a white solid. Data for **19**: mp 102–105 °C (Et_2O); ^{1}H NMR (400 MHz) 7.73 (d, J = 8.3, 2 H), 7.37 (d, J = 8.1, 2 H), 6.96 (d, J = 2.2, 1 H), 6.92 (dd, J = 8.3, 2.2, 1 H), 6.82 (d, J = 8.5, 1 H), 4.12, 3.30 (ABq, J = 10.2, 2 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 3.69, 3.45 (ABq, J = 17.5, 2 H), 2.46 (s, 3H), 2.07 (ddd, J = 7.3, 14.9, 14.2, 1 H), 1.66 (ddd, J = 7.3, 14.6, 14.1, 1 H), 0.69 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 208.68, 148.98, 148.34, 144.32, 131.49, 129.91, 128.25, 127.76, 119.06, 110.98, 109.79, 57.16, 55.82, 55.74, 54.43, 53.25, 29.32, 21.49, 8.64; IR 2967 (m), 1757 (s), 1520 (s), 1163 (s); MS (EI) 403 (M^+, 26), TLC R_f 0.52 (hexane/EtOAc). Anal. Calcd for $C_{21}H_{25}NO_5S$ (403.492): C, 62.51; H, 6.25; N, 3.47. Found: C, 62.48; H, 6.25; N, 3.44.

***rel*-(3*R*,4*R*)-4-(3,4-Dimethoxyphenyl)-4-ethyl-3-hydroxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (20) and *rel*-(3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-4-ethyl-3-hydroxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (18).** Ketone **19** (750 mg, 1.86 mmol) was dissolved in EtOH (37 mL) and cooled to 0 °C. $NaBH_4$ (140 mg, 3.72 mmol, 2.0 equiv) was added, and the solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 5 °C, and the reaction was quenched with 0.2 N HCl (10 mL). The mixture was poured into CH_2Cl_2 (150 mL) and washed with 0.2 N HCl (2 × 25 mL) and brine (25 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by column chomatography (hexane/EtOAc (1/1)) and recrystallized from Et_2O to afford 260 mg (35%) of **18** and 336 mg (45%) of **20** as white solids. Data for **18**: mp 139–142 °C (Et_2O, pentane); ^{1}H NMR (400 MHz) 7.72 (d, J = 8.3, 2 H), 7.30 (d, J = 8.3, 2 H), 6.83 (s, 1 H), 6.74 (s, 2 H), 4.20 (dt, J_d = 2.4, J_t = 4.9, 1 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.85, 3.35 (ABq, J = 9.9, 2 H), 3.38, 3.21 (ABq, J_A = 4.6, 11.1, J_B = 2.4, 11.1, 2 H,), 2.43 (s, 3 H), 1.64–1.85 (m, 3 H), 0.58 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 148.73, 147.59, 143.40, 134.25, 134.02, 129.60, 127.24, 118.69, 110.72, 109.74, 77.53, 55.82, 55.71, 54.24, 54.13, 53.02, 26.19, 21.49, 9.08; IR ($CHCl_3$) 3609 (m), 3513 (m), 3010 (s), 2938 (s), 1519 (s); TLC R_f 0.46 (hexane/EtOAc, 1/1). Data for **20**: mp 137–139 °C (Et_2O); ^{1}H NMR (400 MHz) 7.77 (d, J = 8.3, 2 H), 7.31 (d, J = 7.9, 2 H), 6.83 (d, J = 8.3, 1 H), 6.61 (dd, J = 8.2, 2.1, 1 H), 5.56 (d, J = 2.2, 1 H), 4.21 (m, 1 H), 3.86 (s, 6 H), 3.72, 3.53 (ABq, J = 9.1, 2 H), 3.71, 3.35 (ABq, J_A = 11.3, 4.3, 1.6, J_B = 11.2, 0.8, 2 H), 2.41 (s, 3 H), 1.36–1.56 (m, 2 H), 1.33 (s, 1 H), 0.58 (s, 3 H); ^{13}C NMR (100 MHz) 149.35, 148.03, 143.36, 134.21, 131.1, 129.60, 127.31, 119.63, 111.44, 110.30, 76.71, 55.98, 55.93, 55.80, 53.71, 51.40, 29.70, 21.49, 8.58; IR 3626 (w), 3518 (w), 2965 (w), 1520 (m); MS (EI) 405 (M^+, 15); TLC R_f 0.20 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{21}H_{27}NO_5S$ (405.508): C, 62.20; H, 6.71; N, 3.45. Found: C, 62.13; H, 6.78; N, 3.35.

***rel*-(3*R*,4*R*)-3-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-4-ethyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (21).** Alcohol **20** (233 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (20 mL). Pyridine (98 μL, 1.21 mmol, 2.1 equiv) was added followed by acetic anhydride (109 μL, 1.15 mmol, 2.0 mmol) and DMAP (7 mg, 0.06 mmol, 0.1 equiv). The solution was allowed to stir at rt for 2 h and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (2/1, 1/1)) and crystallized from benzene/pentane to afford 250 mg (97%) of **21** as a white solid. Data for **21**: mp 146–147 °C (benzene, pentane); ^{1}H NMR (400 MHz) 7.76 (d, J = 8.2, 2 H), 7.32 (d, J = 8.0, 2 H), 6.75 (d, J = 8.0, 1 H), 6.45 (dd, J = 7.9, 2.2, 1 H), 6.43 (s, 1 H), 5.40 (d, J = 3.8, 1 H), 3.84 (s, 3 H), 3.83, 3.54 (ABq, J = 9.3, 2 H), 3.81 (s, 3 H), 3.77, 3.33 (ABq, J_A = 12.3, 4.0, J_B = 12.2, 2 H), 2.40 (s, 3 H), 1.46 (s, 3 H), 1.54–1.34 (m, 2 H), 0.57 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz) 169.87, 148.47, 147.41, 143.48, 133.73, 131.79, 129.57, 127.42, 119.07, 110.54, 109.85, 76.91, 55.81, 55.66, 54.16, 53.06, 52.92, 30.31, 21.39, 20.38, 8.23; IR 2967 (m), 1746 (s), 1522 (m), 1232 (s); MS (EI) 447 (M^+, 25); TLC R_f 0.39 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{23}H_{29}NO_6S$ (447.545): C, 61.73; H, 6.53; N, 3.13. Found: C, 61.81; H, 6.57; N, 3.09.

***rel*-(4*R*,5*S*,6*R*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-6-(2,2-diphenylcyclopentoxy)-4-ethyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (22a) from Nitroalkene (*E*)-14.** To a cold (−78 °C) solution of nitroalkene (*E*)-**14** (355 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) was added $SnCl_4$ (526 μL, 4.50 mmol, 3.0 equiv) dropwise, resulting in a deep purple colored solution. After the solution was allowed to stir for 5 min, a solution of enol ether **11a** (725 mg, 2.25 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. The color of the solution faded to yellow after 15 min. After the mixture was stirred for 30 min at −78 °C, the reaction was quenched with a 1 N solution of NaOH in methanol (18.0 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (4 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried

(Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (1/1)) to afford 723 mg (86%) of nitronate **22a** as an amorphous solid. Data for **22a**: mp 80–85 °C (hexane/EtOH); ^{1}H NMR (400 MHz) 6.98–7.38 (m, 10 H), 6.79 (d, J = 8.5, 1 H), 6.62 (dd, J = 2.2, 8.3, 1 H), 6.53 (d, J = 2.2, 1 H), 6.46 (s, 1 H), 5.02 (d, J = 2.2, 1 H), 4.82 (d, J = 2.0, 1 H), 4.77 (dd, J = 2.9, 5.4, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.54 (dt, J_d = 12.7, J_t = 9.0, 1 H), 2.20–2.34 (m, 2 H), 2.04 (s, 3 H), 2.00–2.07 (m, 1 H), 1.81–1.88 (m, 3 H), 1.44–1.47 (m, 1 H), 0.59 (t, J = 7.6); ^{13}C NMR (100 MHz) 169.85, 149.27, 148.35, 145.83, 144.09, 132.83, 128.10, 128.00, 127.44, 126.50, 125.91, 125.53, 119.34, 114.09, 110.03, 109.03, 100.99, 87.71, 70.68, 59.55, 55.79, 55.74, 46.69, 34.63, 31.40, 26.34, 20.61, 19.82, 7.56; IR 2961 (s), 1751 (s), 1618 (s), 1514 (s); MS (CI) 560 (MH^+, 1); TLC R_f 0.10 (hexane/acetone, 85/15). Anal. Calcd for $C_{33}H_{37}NO_7$ (559.658): C, 70.82; H, 6.66; N, 2.50. Found: C, 70.87; H, 6.90; N, 2.47.

***rel*-(4*R*,5*S*,6*R*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-6-(2,2-diphenylcyclopentoxy)-4-ethyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (22a) from Nitroalkene (*Z*)-14.** As above to nitroalkene (*Z*)-**14** (355 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) were added $SnCl_4$ (526 μl, 4.50 mmol, 3.0 equiv) and a solution of enol ether **11a** (725 mg, 2.25 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL), which afforded 760 mg (91%) of nitronate **22a** as an amorphous solid. Data for **22a**: mp 75–82 °C (hexane/EtOH); ^{1}H NMR (400 MHz) 6.98–7.38 (m, 10 H,), 6.79 (d, J = 8.3, 1 H,), 6.62 (dd, J = 2.2, 8.3, 1 H), 6.53 (d, J = 2.2, 1 H), 6.47 (s, 1 H), 5.02 (d, J = 2.2, 1 H), 4.82 (d, J = 2.0), 4.77 (dd, J = 2.9, 5.6, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.54 (dt, J_d = 12.7, J_t = 9.0, 1 H), 2.20–2.35 (m, 2 H), 2.04 (s, 3 H), 2.01–2.07 (m, 1 H), 1.82–1.89 (m, 3), 1.44–1.47 (m, 1 H), 0.59 (t, J = 7.3, $H_3C(8)$); ^{13}C NMR (100 MHz) 169.93, 149.33, 148.41, 145.90, 144.14, 132.88, 128.16, 128.06, 127.49, 126.56, 125.98, 125.60, 119.40, 114.15, 110.91, 109.07, 101.05, 87.77, 70.73, 59.61, 55.86, 55.81, 46.75, 34.69, 31.47, 26.40, 20.66, 19.88, 7.61; IR 2963 (s), 1751 (s), 1620 (s), 1516 (s); MS (CI) 560 (MH^+, 1); TLC R_f 0.10 (hexane/acetone, 85/15). Anal. Calcd for $C_{33}H_{37}NO_7$ (559.658): C, 70.82; H, 6.66; N, 2.50. Found: C, 70.53; H, 6.85; N, 2.32.

(4*S*,5*R*,6*S*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-6-((1*R*)-2,2-diphenylcyclopentoxy)-4-ethyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (22a). As above to nitroalkene (*Z*)-**14** (356 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) were added $SnCl_4$ (526 μL, 4.50 mmol, 3.0 equiv) and a solution of enol ether (1*R*)-**11a** (725 mg, 2.25 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). Recrystallization from diethyl ether/pentane afforded 753 mg (90%) of nitronate **22a** as a white solid. Data for **22a**: mp 85–90 °C (pentane/Et_2O); ^{1}H NMR (400 MHz) 6.98–7.23 (m, 10 H), 6.79 (d, J = 8.5, 1 H), 6.62 (dd, J = 2.2, 8.3, 1 H), 6.53 (d, J = 2.2, 1 H,), 6.47 (s, 1 H), 5.02 (d, J = 2.0, 1 H), 4.82 (d, J = 2.0, 1 H), 4.77 (dd, J = 2.9, 5.4, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.54 (dt, J_d = 12.7, J_t = 9.0, 1 H), 2.22–2.28 (m, 2 H), 2.04 (s, 3 H), 2.00–2.08 (m, 1 H), 1.80–1.90 (m, 3 H), 1.43–1.49 (m, 1 H), 0.59 (t, J = 7.3, $H_3C(8)$); ^{13}C NMR (100 MHz) 169.97, 149.36, 148.44, 145.93, 144.18, 132.91, 128.19, 128.09, 127.53, 126.60, 126.01, 125.63, 119.44, 114.14, 110.93, 109.10, 101.08, 87.81, 70.77, 59.65, 55.89, 55.84, 46.79, 34.73, 31.51, 26.43, 20.71, 19.92, 7.65; IR 2963 (s), 1751 (s), 1620 (s), 1516 (s); MS (CI) 560 (MH^+, 17); $[\alpha]^{25}_D$ = −15.1° (CH_2Cl_2, c = 1.28); TLC R_f 0.10 (hexane/acetone, 85/15). Anal. Calcd for $C_{33}H_{37}NO_7$ (559.658): C, 70.82; H, 6.66; N, 2.50. Found: C, 70.90; H, 6.68; N, 2.51.

***rel*-(4*R*,5*S*,6*R*)-5-(Acetyloxy)-6-(2,2-diphenylcyclopentoxy)-4-phenyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (31).** To a cold (−78 °C) solution of nitroalkene **27** (149 mg, 1.00 mmol) in CH_2Cl_2 (8 mL) was added $SnCl_4$ (350 μl, 3.00 mmol, 3.0 equiv) dropwise, resulting in a dark yellow colored solution. After the mixture was allowed to stir for 5 min, a solution of enol ether **11a** (484 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. After addition of the enol ether, the now clear, colorless solution was stirred at −78 °C for 15 min and then the reaction was quenched with a 1 N solution of NaOH in methanol (12.0 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (3 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (3/1, 1/1)) followed by recrystallization from hexane/EtOAc to afford 403 mg (86%) of nitronate **31** as a mixture of two diastereomers (1.2:1.0, ^{1}H NMR). Data for **31**: mp 128–135 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 7.09–7.37 (m, 15 H), 6.16 (dd, J = 3.3, 0.9, 0.5 H), 5.72 (dd, J = 3.2, 1.0, 0.5 H), 5.62 (d, J = 2.7, 0.5 H), 5.55 (d, J = 2.7, 0.5 H), 5.30 (m, 0.5 H), 4.94 (m, 0.5 H), 4.87 (ddd, J = 2.9, 10.2, 1.0, 1 H), 3.77 (dd, J = 10.0, 3.2, 0.5 H), 3.31 (dd, J = 10.3, 3.2, 0.5 H), 2.65–2.78 (m, 1 H), 2.52-2.60 (m, 0.5 H), 2.26–2.40 (m, 1 H,), 1.80–2.05 (m, 2 H), 1.92 (s, 1.5 H), 1.78 (s, 1.5 H,), 1.60–1.73 (m, 2 H); ^{13}C NMR (100 MHz) 169.80, 169.70, 146.42, 145.23, 145.12, 144.35, 136.20, 136.17, 128.94, 128.90, 128.45, 128.25, 128.23, 128.19, 128.16, 128.14, 128.12, 127.86, 127.55, 127.53, 126.48, 126.47, 126.01, 125.97, 125.79, 125.46, 112.26, 112.22, 100.34, 95.90, 85.95, 81.59, 69.35, 69.27, 59.71, 59.11, 41.13, 40.88, 34.91, 34.46, 30.93, 28.03, 20.53, 20.34, 20.30, 19.62; IR 3032 (m), 1753 (s), 1632 (s), 1225 (s), 1136 (s); MS (CI) 472 (MH^+, 3); TLC R_f 0.10 (hexane/acetone, 85/15). Anal. Calcd for $C_{29}H_{29}NO_5$ (471.552): C, 73.87; H, 6.20; N, 2.97. Found: C, 73.86; H, 6.25; N, 3.01.

***rel*-(4*R*,5*R*,6*S*)- and *rel*-(4*R*,5*S*,6*R*)-5-(Acetyloxy))-4-cyclohexyl-6-[*rel*-(*R*)-2,2-diphenylcyclopentoxy]-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (32a and 32b).** To a cold (−78 °C) solution of nitroalkene **28** (155 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added enol ether **11a** (484 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). $SnCl_4$ (350 μL, 3.00 mmol, 3.0 equiv) was added dropwise over 10 min. After 90 min the solution became a white emulsion which was then stirred at −78 °C for an additional 6.5 h. The reaction was quenched with a 1 N solution of NaOH in methanol (12.0 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (3 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was crystallized from hexane to afford 300 mg (63%) of the major diastereomer **32a** as a white solid. After column chromatography (hexane/EtOAc (2/1)) of the mother liquor followed by recrystallization from hexane/EtOAc, 25 mg (5%) of the minor diastereomer **32b** was afforded as a white solid. Data for **32a**: mp 187–189 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 7.08–7.27 (m, 10 H), 5.73 (d, J = 1.3, 1 H), 5.31 (d, J = 2.4, 1 H), 5.29 (d, J = 4.8, 1 H), 4.72 (ddd, J = 3.9, 2.4, 1.1,1 H), 2.50–2.61 (m, 1 H), 2.33–2.42 (m, 1 H), 2.03–2.12 (m, 1H), 2.08 (s, 3 H), 1.09–1.87 (m, 13 H), 0.65–0.82 (m, 2 H); ^{13}C NMR (100 MHz) 170.40, 145.39, 145.21, 128.22, 127.67, 127.61, 126.57, 126.01, 125.38, 111.79, 96.33, 80.91, 62.44, 59.98, 38.05, 34.74, 34.49, 30.28, 29.79, 28.24, 25.96, 25.58, 25.50, 20.75, 20.57; IR 2932 (s), 2855 (s), 1740 (s), 1630 (s), 1495 (s); MS (CI) 478 (MH^+, 2); TLC R_f 0.35 (hexane/EtOAc (1/1)). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.599): C, 72.93; H, 7.39; N, 2.93. Found: C, 72.84 ; H, 7.45; N, 2.96. Data for **32b**: mp 145–147 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 7.13–7.26 (m, 10 H), 6.11 (d, J = 2.9, 1 H), 5.44 (d, J = 3.0, 1 H), 4.88 (t, J = 5.1, 1 H), 4.83 (dd, J = 9.8, 3.0, 1 H), 2.52–2.63 (m, 2 H), 2.22–2.34 (m, 2 H), 1.89 (s, 3 H), 0.86–1.87 (m, 14 H); ^{13}C NMR (100 MHz) 170.24, 146.63, 144.40, 128.25, 127.62, 127.57, 126.00, 125.84, 112.25, 100.04, 85.79, 62.92, 59.05, 40.10, 34.61, 30.95, 30.39, 28.64, 26.33, 26.11, 25.99, 20.93, 19.61; IR 2930 (s), 1749 (s), 1632 (s), 1225 (s), 1062 (s); MS (CI) 478 (MH^+, 4); TLC R_f 0.40 (hexane/EtOAc (1/1)). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.599): C, 72.93; H, 7.39; N, 2.93. Found: C, 72.82; H, 7.37; N, 2.92.

***rel*-(4*R*,5*R*,6*S*)- and *rel*-(4*R*,5*S*,6*R*)-5-(Acetyloxy)-6-(2,2-diphenylcyclopentoxy)-4-*n*-pentyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (33).** To a cold (−78 °C) solution of nitroalkene **29** (143 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added enol ether **11a** (484 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (0.5 mL). $SnCl_4$ (350 μL, 3.00 mmol, 3.0 equiv) was added dropwise over 10 min. After 1 h the solution became a white emulsion which was then stirred at −78 °C for an additional 7 h. The reaction mixture was quenched with a 1 N solution of NaOH in methanol (12.0 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (3 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted

with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (4/1, 1/1)) to afford 381 mg (82%) of a mixture of diastereomers **33** as a foaming oil. Data for **33**: ^{1}H NMR (400 MHz) 7.08–7.31 (m, 10 H), 6.11 (d, J = 2.7, 0.1 H), 6.04 (m, 0.1 H), 6.00 (d, J = 3.9, 0.1 H), 5.65 (d, J = 3.2, 0.1 H), 5.89–5.60 (m, 0.6 H), 5.52 (d, J = 2.4, 0.1 H), 5.47 (d, J = 3.1, 0.1 H), 5.43 (d, J = 2.5, 0.1 H), 5.31 (m, 1.2 H), 5.22 (m, 0.1 H), 5.17 (m, 0.1 H), 5.11 (m, 0.1 H), 4.88 (m, 0.2 H), 4.65–4.69 (m, 1 H), 2.52–2.62 (m, 1 H), 2.11–2.43 (m, 0.7 H), 2.09 (s, 2.1 H), 1.79–2.07 (m, 4.2 H), 1.50–1.62 (m, 1 H), 1.06–1.37 (m, 8 H), 0.88 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 170.28, 146.48, 145.29, 145.15, 145.08, 144.32, 128.18, 127.64, 127.54, 126.46, 125.94, 125.30, 112.96, 112.88, 101.70, 99.89, 96.72, 95.37, 87.60, 85.77, 81.31, 80.97, 67.50, 67.40, 63.24, 59.80, 59.59, 58.96, 34.64, 34.13, 33.74, 32.59, 31.00, 28.09, 26.69, 25.46, 22.18, 20.57, 20.41, 13.81; IR 2959 (s), 1748 (s), 1634 (s), 1446 (s); MS (CI) 466 (MH^+, 5); TLC R_f 0.13 (hexane/acetone, 85/15). Anal. Calcd for $C_{28}H_{35}NO_5$ (465.588): C, 72.23; H, 7.58; N, 3.01. Found: C, 72.16; H, 7.60; N, 2.97.

***rel*-(4*S*,5*S*,6*R*)-4-(3,4-Dimethoxyphenyl)-5-[(2,2-dimethyl-1-oxopropyl)oxy)-6-(*rel*-(*S*)-2,2-diphenylcyclopentoxy)-4-ethyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (22b).** To a cold (−78 °C) solution of nitroalkene (*Z*)-**14** (464 mg, 1.96 mmol) in CH_2Cl_2 (20 mL) was added $SnCl_4$ (685 μL, 5.87 mmol, 3.0 equiv) dropwise, resulting in a deep purple colored solution. After the solution was allowed to stir for 5 min, a solution of enol ether **11b** (1.07 g, 2.93 mmol, 1.5 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise. The color of the solution faded on completion of enol ether addition. After the solution was stirred for 15 min at −78 °C, the reaction was quenched with a 1 N solution of NaOH in methanol (23.5 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (4 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (1/1)) to afford a diasteriomeric mixture of nitronates **22b** in a ratio of 8.7:1.0 by ^{1}H NMR. Recrystallization afforded 875 mg (75%) of nitroanate **22b** as a white solid and 175 mg (15%) of a mixture of diastereomers. Data for **22b**: mp 161–163 °C (EtOAc, hexane); ^{1}H NMR (400 MHz) 6.84–7.21 (m, 10 H), 6.76 (d, J = 8.5, 1 H), 6.54 (dd, J = 8.3, 2.2, 1 H), 6.47 (d, J = 2.2, 1 H), 6.43 (s, 1 H), 4.77 (d, J = 1.5, 1 H), 4.75 (m, 1 H), 4.73 (t, J = 1.2, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.51 (m, 1 H), 2.15–2.30 (m, 2 H), 1.98 (m, 1 H), 1.64–1.85 (m, 3 H), 1.37 (m, 1 H), 1.23 (s, 9 H), 0.54 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 177.47, 149.41, 148.43, 145.62, 143.70, 132.67, 128.15, 127.95, 127.37, 126.63, 125.97, 125.58, 119.87, 113.64, 110.72, 109.02, 100.94, 87.62, 69.79, 59.81, 55.85, 55.82, 47.39, 39.09, 34.41, 31.58, 27.01, 26.64, 19.92, 7.42; IR 2972 (s), 1738 (s), 1616 (s), 1518 (s); MS (CI) 602 (MH^+, 1); TLC R_f 0.10 (hexane/acetone, 85/15). Anal. Calcd for $C_{36}H_{43}NO_7$ (601.738): C, 71.86; H, 7.20; N, 2.33. Found: C, 71.88; H, 7.24; N, 2.32.

***rel*-(4*S*,5*S*,6*R*)- and *rel*-(4*R*,5*R*,6*S*)-5-(Benzoyloxy)-4-(3,4-dimethoxyphenyl)-6-(*rel*-(*S*)-2,2-diphenylcyclopentoxy)-4-ethyl-5,6-dihydro-3*H*-1,2-oxazine *N*-Oxide (22c).** To a cold (−78 °C) solution of nitroalkene (*E*)-**14** (237 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added $SnCl_4$ (350 μL, 3.0 mmol, 3.0 equiv) dropwise, resulting in a deep purple colored solution. After 5 min of stirring, a solution of enol ether **11c** (576 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise. The solution faded to colorless on completion of enol ether addition. After 15 min of stirring at −78 °C, the reaction was quenched with a 1 N solution of NaOH in methanol (12 mL). The mixture was diluted with 200 mL of CH_2Cl_2 and was washed with water (3 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with MTBE (2 × 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (1/1)) to afford 608 mg (98%) of a diastereomeric mixture of nitronates **22c** in a ratio of 3.8:1.0 by ^{1}H NMR as a foamy solid. Data for **22c**: ^{1}H NMR (400 MHz) 8.03 (d, J = 8.3, 1.6 H), 7.97 (d, J = 8.3, 0.4 H), 7.62 (m, 1 H), 7.49 (m, 2 H), 7.34 (t, J = 8.3, 1 H), 7.22 (t, J = 7.6, 1 H), 7.02–7.18 (m, 6 H), 6.90 (t, J = 7.3, 1.6 H), 6.76–6.82 (m, 2 H), 6.67 (dd, J = 2.0, 8.3, 1 H), 6.58 (d, J = 2.0, 0.8 H), 6.55 (s, 0.8 H), 6.37 (s, 0.2 H), 5.62 (d, J = 3.4, 0.2 H), 5.32 (m, 0.4 H), 5.18 (d, J = 2.4, 0.8 H), 5.07 (d, J = 2.2, 0.8 H), 4.80 (dd, J = 3.2, 5.6, 0.8 H), 3.88 (s, 2.4 H), 3.83 (s, 0.6 H), 3.75 (s, 2.4 H), 3.68 (s, 0.6 H), 2.42–2.64 (m, 1 H), 2.25 (m, 2 H), 2.02 (m, 3 H), 1.20–1.84 (m, 4 H), 0.62 (t, J = 7.3, 2. H), 0.37 (t, J = 7.6, 0.6 H); ^{13}C NMR (100 MHz) 165.30, 165.10, 149.28, 149.11, 148.33, 148.21, 145.87, 145.14, 144.86, 144.05, 133.61, 133.58, 133.50, 133.05, 129.82, 129.45, 128.96, 128.82, 128.55, 128.41, 128.23, 128.03, 127.86, 127.79, 127.65, 127.39, 126.45, 126.17, 125.89, 125.81, 125.48, 125.46, 119.15, 118.57, 114.72, 114.33, 111.05, 110.87, 108.95, 101.06, 96.71, 87.73, 82.77, 72.02, 71.56, 59.48, 59.44, 55.70, 55.62, 46.78, 45.96, 34.67, 34.14, 31.38, 27.27, 26.43, 25.54, 22.19, 19.86, 19.77, 7.90, 7.70; IR 2963 (m), 1730 (s), 1621 (s), 1519 (s), 1264 (s); MS (CI) 622 (MH^+, 6); TLC R_f 0.12 (hexane/acetone, 85/15). Anal. Calcd for $C_{38}H_{39}NO_7$ (621.729): C, 73.41; H, 6.32; N, 2.25. Found: C, 73.55; H, 6.40; N, 2.20.

Representative Procedure for Reduction of Nitronates. *rel*-(3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-4-ethyl-3-hydroxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (18). To a solution of nitronate **22a** (560 mg, 1.0 mmol) in methanol (25 mL) were added a catalytic amount of PtO_2 (23 mg, 0.1 mmol, 0.1 equiv) and glacial acetic acid (57 μL, 1.0 mmol, 1.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The solution was filtered through a plug of glass wool/Celite into a 100 mL three-neck flask and washed with additional methanol (5 mL). The solution was cooled to 0 °C, and to it were added DBU (449 μL, 3.0 mmol, 3.0 equiv) and a solution of *p*-toluenesulfonyl chloride (380 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min before the addition of a 1 N solution of NaOH in methanol (20 mL, 20 equiv). After 10 min the reaction mixture was poured into 200 mL of CH_2Cl_2 and washed with water (50 mL), saturated aqueous NH_4Cl solution (2 × 50 mL), and brine (50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography (hexane/EtOAc (4/1, 1/1, 1/2)). The resulting pyrrolidine was crystallized from diethyl ether/hexane to afford 245 mg (61%) of **18** as a white solid. Also, 228 mg (95%) of diphenylcyclopentanol was recovered after distillation. Data for **18**: mp 135–138 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.73 (d, J = 8.3, 2 H), 7.31 (d, J = 8.3, 2 H), 6.83 (s, 1 H), 6.75 (s, 2 H), 4.20 (dt, J_d = 2.4, J_t = 4.9, 1 H), 3.85, 3.34 (ABq, J = 10.0, 2 H), 3.86 (s, 3H), 3.85 (s, 3 H), 3.38 (dd, J = 11.2, 4.6, 1 H), 3.21 (dd, J = 2.4, 11.2, 1 H), 2.43 (s, 3 H), 1.80 (dq, J_d = 13.7, J_q = 7.6, 1 H), 1.69 (dq, J_d = 13.9, J_q = 7.3, 1 H), 1.57 (m, 1 H), 0.58 (t, J = 7.6, 3 H); ^{13}C NMR (100 MHz) 148.73, 147.59, 143.41, 134.26, 134.01, 129.62, 127.26, 118.69, 110.70, 109.72, 77.55, 55.83, 55.72, 54.24, 54.14, 53.01, 26.20, 21.50, 9.09; IR 3510 (S), 2963 (s), 1520 (s), 1464 (s); MS (EI) 405 (M^+, 12); TLC R_f 0.29 (hexane/EtOAc, 1/1); HPLC (Chiralcel AD; hexane/EtOH, 66.6/33.4, 0.75 mL/min) t_R((3*S*,4*R*)-**18**) 9.5 min (49.1%), t_R((3*R*,4*S*)-**18**) 16.8 min (50.9%). Anal. Calcd for $C_{21}H_{27}NO_5S$ (405.508): C, 62.20; H, 6.71; N, 3.45. Found: C, 62.26; H, 6.80; N, 3.46.

(3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-4-ethyl-3-hydroxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (18). To a solution of nitronate **22a** (560 mg, 1.0 mmol) in methanol (25 mL) were added a catalytic amount of PtO_2 (23 mg, 0.1 mmol, 0.1 equiv) and glacial acetic acid (57 μL, 1.0 mmol, 1.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The filtered solution was cooled to 0 °C, and to it were added DBU (449 μL, 3.0 mmol, 3.0 equiv) and a solution of *p*-toluenesulfonyl chloride (380 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (2.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min before the addition of a 1 N solution of NaOH in methanol (30 mL, 30 equiv). After workup the crude product was purified by column chromatography (hexane/EtOAc (4/1, 1/1, 1/2)). The resulting pyrrolidine was crystallized from ethyl acetate/hexane to afford 305 mg (75%)

of **18** as a white solid. Also, 228 mg (96%) of diphenylcyclopentanol was recovered after distillation. Data for **18**: mp 158–160 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.73 (d, J = 8.3, 2 H), 7.31 (d, J = 8.3, 2 H), 6.83 (s, 1 H), 6.75 (d, J = 0.7, 2 H), 4.19 (m, 1 H), 3.85, 3.34 (ABq, J = 9.8, 2 H), 3.86 (s, 3H), 3.85 (s, 3 H), 3.39 (dd, J = 11.2, 4.6, 1 H), 3.21 (dd, J = 2.4, 11.2, 1 H), 2.43 (s, 3 H), 1.80 (dq, J_d = 13.7, J_q = 7.6, 1 H), 1.69 (dq, J_d = 13.9, J_q = 7.3, 1 H), 1.55 (m, 1 H), 0.58 (t, J = 7.6, 3 H); ^{13}C NMR (100 MHz) 148.72, 147.57, 143.40, 134.22, 133.99, 129.60, 127.24, 118.68, 110.69, 109.71, 77.55, 55.81, 55.71, 54.24, 54.13, 53.01, 26.19, 21.49, 9.08; IR 3512 (m), 2965 (s), 1520 (s), 1464 (s); MS (EI) 405 (M^+, 13), 42 (54); $[\alpha]^{25}_D$ = −27.3° (CH_2Cl_2, c = 1.15); TLC R_f 0.29 (hexane/EtOAc, 1/1); HPLC (Chiralcel AD; hexane/EtOH, 66.6/33.4, 0.75 mL/min) t_R((3*S*,4*R*)-**18**) 9.6 min (2.0%), t_R((3*R*,4*S*)-**18**) 16.8 min (98.0%). Anal. Calcd for $C_{21}H_{27}NO_5S$ (405.508): C, 62.20; H, 6.71; N, 3.45. Found: C, 62.23; H, 6.76; N, 3.48.

***rel*-(3*S*,4*S*)-3-(Acetyloxy)-1-[(4-methylphenyl)sulfonyl]-4-phenylpyrrolidine (34).** To a solution of nitronate **31** (707 mg, 1.5 mmol, 1.0 equiv) in methanol (25 mL) were added a catalytic amount of PtO_2 (34 mg, 0.15 mmol, 0.1 equiv) and glacial acetic acid (431 μL, 7.5 mmol, 5.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The filtered solution was cooled to 0 °C, and to it were added DBU (1.57 mL, 10.5 mmol, 7.0 equiv) and a solution of *p*-toluenesulfonyl chloride (570 mg, 3.0 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min. After workup the crude product was purified by column chromatography (hexane/acetone (90/10, 85/15)). The resulting acetoxypyrrolidine was crystallized from diethyl ether/pentane to afford 270 mg (51%) of **34** as a white solid. The deoxygenated pyrrolidine was distilled to afford 45 mg (13%) of a clear oil. Also, 275 mg (77%) of diphenylcyclopentanol was recovered after distillation. Data for **34**: mp 98–100 °C (Et_2O/pentane); ^{1}H NMR (400 MHz) 7.76 (d, J = 8.3, 2 H), 7.37 (d, J = 8.1, 2 H), 7.15–7.30 (m, 5 H), 4.94–4.96 (m, 1 H), 3.70, 3.52 (ABq, J_A = 10.0, 7.2, J_B = 10.0, 4.5, 2 H), 3.62, 3.37 (ABq, J_A = 12.0, 5.2, J_B = 12.1, 2.6, 0.9, 2 H), 3.42 (ddd, J = 4.5, 7.2, 4.2, 1 H), 2.47 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR (100 MHz) 170.02, 143.67, 137.98, 132.97, 129.62, 128.77, 127.65, 127.41, 127.02, 78.22, 51.69, 51.19, 48.73, 21.43, 20.58; IR 3032 (s), 1740 (s), 1599 (s), 1495 (s); MS (EI) 299 (26); TLC R_f 0.20 (hexane/acetone, 85/15). Anal. Calcd for $C_{19}H_{21}NO_4S$ (359.439): C, 63.49; H, 5.89; N, 3.90. Found: C, 63.66; H, 5.95; N, 3.88.

***rel*-(3*S*,4*S*)-3-(Acetyloxy)-4-cyclohexyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (35a).** To a solution of nitronate **32a** (955 mg, 2.0 mmol) in methanol (30 mL) were added a catalytic amount of PtO_2 (45 mg, 0.2 mmol, 0.1 equiv) and glacial acetic acid (575 μL, 10.0 mmol, 5.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The filtered solution was cooled to 0 °C, and to it were added DBU (2.09 mL, 14.0 mmol, 7.0 equiv) and a solution of *p*-toluenesulfonyl chloride (760 mg, 4.0 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min. After workup the crude product was then purified by column chromatography (hexane/acetone (90/10)). The resulting acetoxypyrrolidine was crystallized from diethyl ether/hexane to afford 322 mg (44%) of **35a** as a white solid. *N*-Tosyl-3-cyclohexylpyrrolidine was crystallized from diethyl ether/hexane to afford 116 mg (19%) as a white solid. Also, 355 mg (75%) of diphenylcyclopentanol was recovered after distillation. Data for **35a**: mp 90–94 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.70 (d, J = 8.3, 2 H), 7.33 (d, J = 7.9, 2 H), 5.10 (t, J = 3.6, 1 H), 3.64 (dd, J = 9.0, 7.8, 1 H), 3.48 (dd, J = 6.4, 12.5, 1 H), 3.39 (d, J = 12.6, 1 H), 2.99 (dd, J = 9.2, 11.5, 1 H), 2.42 (s, 3 H), 1.81 (m, 1 H), 1.71 (s, 3 H), 1.52–1.70 (m, 4 H), 1.31 (m, 1 H), 1.04–1.24 (m, 3 H), 0.79–0.98 (m, 2 H); ^{13}C NMR (100 MHz) 170.06, 143.27, 133.64, 129.49, 127.36, 72.43, 54.54, 50.22, 48.59, 35.06, 31.64, 30.96, 25.94, 25.66, 25.53, 21.32, 20.37; IR 2920 (s), 1740 (s), 1599 (s), 1495 (s); MS (EI) 222 (100); TLC R_f 0.29 (hexane/acetone, 85/15). Anal. Calcd for $C_{19}H_{27}NO_4S$ (365.487): C, 62.44; H, 7.45; N, 3.83. Found: C, 62.17; H, 7.48; N, 3.62.

***rel*-(3*S*,4*R*)-3-(Acetyloxy)-4-cyclohexyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (35b).** To a solution of nitronate **32b** (120 mg, 0.25 mmol) in methanol (10 mL) were added a catalytic amount of PtO_2 (6 mg, 0.03 mmol, 0.1 equiv) and glacial acetic acid (72 μL, 1.25 mmol, 5.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The filtered solution was cooled to 0 °C, and to it were added DBU (267 μL, 1.75 mmol, 7.0 equiv) and a solution of *p*-toluenesulfonyl chloride (95 mg, 0.5 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min. After workup the crude product was purified by column chromatography (hexane/acetone (90/10)). The resulting acetoxy pyrrolidine was crystallized from diethyl ether/hexane to afford 55 mg (60%) of **35b** as a white solid. Also, 54 mg (91%) of diphenylcyclopentanol was recovered after distillation. Data for **35b**: mp 107–109 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.69 (d, J = 8.9, 2 H), 7.34 (d, J = 7.9, 2 H), 4.90 (ddd, J = 2.9, 6.1, 4.2, 1 H), 3.47 (dd, J = 7.5, 9.9, 1 H), 3.37 (dd, J = 6.1, 11.6, 1 H), 3.23 (dd, J = 2.8, 11.5, 1 H), 2.88 (dd, J = 6.4, 9.8, 1 H), 2.44 (s, 3 H), 2.00 (ddd, J = 7.5, 6.4, 4.4, 1 H), 1.91 (s, 3 H), 1.52–1.72 (m, 5 H), 0.80–1.18 (m, 6 H); ^{13}C NMR (100 MHz) 170.43, 143.67, 133.48, 129.65, 127.79, 75.30, 53.01, 49.63, 49.28, 38.76, 30.85, 30.74, 26.05, 25.93, 25.86, 21.53, 20.89; IR 2928 (s), 1741 (s), 1599 (s), 1448 (s); MS (EI) 222 (100); TLC R_f 0.25 (hexane/acetone, 85/15). Anal. Calcd for $C_{19}H_{27}NO_4S$ (365.487): C, 62.44; H, 7.45; N, 3.83. Found: C, 62.31; H, 7.46; N, 3.79.

Stereochemical Assignment of *rel*-(3*S*,4*R*)-3-(Acetyloxy)-4-cyclohexyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (35b). Pyrrolidine **34** (50 mg, 0.139 mmol) was dissolved in methanol (10 mL) and 5% Rh/Al_2O_3 catalyst (500 mg) was added. The solution was allowed to stir at rt under 250 psi H_2 pressure for 36 h. The solution was filtered through a plug of glass wool/Celite and concentrated *in vacuo*. The crude *N*-tosylhydroxypyrrolidine was then dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0 °C. To the solution were added pyridine (23 μL, 0.278 mmol), acetic anhydride (30 μL, 0.278 mmol), and a catalytic amount of DMAP. The reaction mixture was allowed to stir at 0 °C for 30 min and then was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone (85/15)) to afford 25 mg (50%) of pyrrolidine **35b** as a white solid after recrystallization from diethyl ether/hexane. Data for **35b**: mp 105–108 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.69 (d, J = 8.3, 2 H), 7.33 (d, J = 8.1, 2 H), 4.89 (m, 1 H), 3.46 (dd, J = 7.6, 10.0, 1 H), 3.37 (dd, J = 6.1, 11.7, 1 H), 3.22 (dd, J = 2.7, 11.5, 1 H), 2.88 (dd, J = 6.4, 9.8, 1 H), 2.43 (s, 3 H), 1.95–2.02 (m, 1 H), 1.90 (s, 3 H), 1.54–1.67 (m, 5 H), 0.83–1.11 (m, 6 H); ^{13}C NMR (100 MHz) 170.42, 143.67, 133.45, 129.64, 127.78, 75.29, 53.00, 49.62, 49.27, 38.75, 30.84, 30.73, 26.04, 25.92, 25.86, 21.52, 20.88; IR 2930 (s), 1741 (s), 1358 (s), 1236 (s); TLC R_f 0.25 (hexane/acetone, 85/15).

***rel*-(3*S*,4*R*)- and *rel*-(3*S*,4*S*)-3-(Acetyloxy)-1-[(4-methylphenyl)sulfonyl]-4-*n*-pentylpyrrolidine (36).** To a solution of nitronate **33** (1.28 g, 2.75 mmol) as a mixture of four diastereomers in methanol (30 mL) were added a catalytic amount of PtO_2 (62 mg, 0.28 mmol, 0.1 equiv) and glacial acetic acid (790 μL, 13.75 mmol, 5.0 equiv). The reaction mixture was allowed to stir at rt under 160 psi H_2 pressure for 36 h. The filtered solution was cooled to 0 °C, and to it were added DBU (2.88 mL, 19.25 mmol, 7.0 equiv) and a solution of *p*-toluenesulfonyl chloride (1.05 g, 5.50 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL). The reaction mixture was allowed to stir at 0 °C for 30 min. After workup the crude product was then purified by column chromatography (hexane/acetone (90/10)). The resulting acetoxypyrrolidine was fractionally distilled to afford 140 mg (14%) of **36** as a mixture of diastereomers (3:1, ^{1}H NMR). *N*-Tosyl-3-*n*-pentylpyrrolidine was crystallized from diethyl ether/hexane to afford 240 mg (30%) as a white solid. Also, 583 mg (89%) of diphenylcyclopentanol was recovered after distillation. Data for **36**: bp 220 °C (0.1 Torr); ^{1}H NMR (400 MHz) 7.69 (d, J = 8.3, 2 H), 7.31 (d, J = 8.1, 2 H), 5.04 (t, J = 3.9, 0.7 H), 4.73 (ddd, J = 5.1, 2.2, 3.4, 0.3 H), 3.58 (dd, J = 7.7, 9.2, 0.7 H), 3.50 (dd, J = 3.9, 12.5, 0.7 H), 3.46 (dd, J = 11.7, 5.2, 0.3 H), 3.43 (dd, J = 10.4, 6.7, 0.3 H), 3.36 (dd, J = 0.7, 12.5, 0.7 H), 3.29 (dd, J = 2.3, 11.9, 0.3 H), 3.00 (dd, J = 2.3, 9.9, 0.3 H), 2.92 (dd, J = 11.4, 9.4, 0.7 H), 2.41 (s, 3 H), 2.07 (m, 1 H), 1.84 (s, 0.9 H), 1.72 (s, 2.1 H), 1.15–1.35 (m, 8

H), 0.83 (t, J = 6.8, 3 H); ^{13}C NMR (100 MHz) 170.17, 143.37, 133.21, 129.56, 127.58, 73.80, 54.31, 51.28, 42.64, 31.65, 27.36, 26.15, 22.34, 21.43, 20.47, 13.90, 170.26, 143.53, 133.08, 129.58, 127.49, 77.17, 52.14, 51.09, 43.70, 31.51, 27.01, 30.89, 22.36, 21.45, 20.75, 13.94; IR 2930 (s), 1740 (s), 1462 (s); MS (EI) 293 (13), 222 (100); TLC R_f 0.32 (hexane/acetone, 85/15). Anal. Calcd for $C_{18}H_{27}NO_4S$ (353.476): C, 61.16; H, 7.70; N, 3.96. Found: C, 61.04; H, 7.71; N, 3.96.

(2*S*,3a*S*,4*S*,5*R*,6*S*)- and (2*R*,3a*R*,4*S*,5*R*,6*S*)-5-(Acetyloxy)-4-(3,4-dimethoxyphenyl)-6-((*R*)-2,2-diphenylcyclopentoxy)-4-ethylhexahydroisoxazolo[2,3-*b*]oxazine-2-carboxylic Acid Methyl Ester (23a and 23b). Nitronate **22a** (279 mg, 0.5 mmol) was dissolved in benzene (25 mL). Methyl acrylate (270 μL, 3.0 mmol, 6.0 equiv) was added along with a crystal of 2,5-di-*tert*-butylhydroquinone and the solution was heated at 80 °C for 4 h. The reaction mixture was allowed to cool, concentrated *in vacuo*, and crystallized from hexane/EtOAc (2/1) to afford 225 mg (70%) of nitroso acetal **23a** as a white solid. An additional 45 mg (14%) of a diastereomeric mixture of **23a** and **23b** was obtained after column chromatography (hexane/EtOAc (2/1)). Data for **23a**: mp 168–170 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 7.07–7.16 (m, 5 H), 6.92–7.00 (m, 6 H), 6.79 (m, 2 H), 5.11, 5.08 (ABq, J = 2.8, 1 H), 4.67 (s, 1 H), 4.64 (dd, J = 3.4, 5.6, 1 H), 4.29 (d, J = 1.2, 1 H), 3.92 (3, 3 H), 3.90 (s, 3 H), 3.91 (m, 1 H), 3.79 (s, 3 H), 3.14 (q, J = 11.7, 1 H), 2.47 (dt, J_d = 12.5, J_t = 9.0, 1 H), 2.23–2.28 (m, 1 H), 2.04–2.16 (m, 2 H), 2.09 (s, 3 H), 1.62–1.87 (m, 4 H), 1.33–1.41 (m, 1 H), 0.47 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 171.09, 170.23, 148.65, 147.66, 146.39, 144.03, 133.39, 128.23, 127.98, 127.18, 126.76, 125.73, 125.40, 120.98, 110.63, 110.39, 97.18, 86.73, 79.56, 73.09, 69.83, 59.39, 55.80, 55.78, 52.54, 46.47, 34.73, 31.58, 30.03, 28.23, 20.93, 19.85, 7.11; IR 2959 (s), 1746 (s), 1520 (s), 1495 (s); MS (EI) 645 (M^+, 3); $[\alpha]^{25}_D$ = −42.9° (CH_2Cl_2, c = 1.68); TLC R_f 0.25 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{37}H_{43}NO_9$ (645.748): C, 68.82; H, 6.71; N, 2.17. Found: C, 68.92; H, 6.76; N, 2.15. Data for **23a,b:** ^{1}H NMR (400 MHz) 6.61–7.30 (m, 10 H), 6.79 (m, 1 H), 6.62 (m, 1 H), 5.51 (d, J = 4.4, 0.6 H), 5.30 (dd, J = 1.0, 4.4, 0.6 H), 5.10 (dd, J = 2.9, 10.5, 0.4 H), 4.92 (dd, J = 3.4, 10.5, 0.6 H), 4.77 (t, J = 5.1, 0.6 H), 4.67 (s, 0.4 H), 4.64 (dd, J = 3.2, 5.6, 0.4 H), 4.30 (d, J = 1.0, 0.4 H), 3.92 (s, 1.2 H), 3.90 (s, 1.2 H), 3.85 (s, 1.8 H), 3.80 (s, 1.2 H), 3.50 (m, 0.4 H), 3.15 (q, J = 11.7, 0.4 H), 2.10–2.65 (m, 4 H), 2.09 (s, 1.2 H), 1.71 (s, 1.8 H), 1.55–2.00 (m, 4 H), 0.69 (t, J = 7.3, 1.8 H), 0.47 (t, J = 7.3, 1.2 H); ^{13}C NMR (100 MHz) 171.14, 170.27, 148.72, 147.72, 146.44, 144.08, 133.45, 128.28, 128.02, 127.23, 126.81, 125.79, 125.44, 121.03, 110.72, 110.47, 97.22, 86.77, 79.61, 73.12, 69.88, 59.45, 55.86, 55.81, 52.57, 46.52, 34.79, 31.63, 30.07, 28.28, 20.98, 19.89, 7.15, 170.78, 170.60, 148.98, 147.54, 147.06, 145.30, 133.77, 128.47, 128.19, 127.70, 126.60, 125.50, 117.63, 111.24, 108.55, 99.14, 85.92, 80.22, 79.94, 68.48, 59.20, 55.71, 52.51, 43.96, 34.96, 31.45, 30.83, 30.19, 20.96, 19.20, 10.73; IR 2955 (m), 1746 (s), 1521 (s), 1464 (s); MS (FAB) 646 (MH^+, 28); TLC R_f 0.32 (hexane/EtOAc, 2/1); HRMS calcd for $C_{37}H_{44}NO_9$ 646.3016, found 646.3023.

***rel*-(1*S*,3*R*,5*R*,6*S*,6a*S*)-5-(Acetyloxy)-6-(3,4-dimethoxyphenyl)-6-ethyl-1-hydroxyhexahydro-1*H*-pyrrolizin-2-one (24a).** Nitroso acetal **23a** (646 mg, 1.0 mmol) was added to a suspension of a catalytic amount of Raney Nickel in methanol (40 mL). The suspension was allowed to stir at rt under 1 atm of H_2 pressure for 24 h. The reaction mixture was filtered through Celite, washed with CH_2Cl_2 (25 mL)/Et_3N (5 mL), and concentrated *in vacuo*. The crude products were purified by column chromatography (hexane/EtOAc (1/1), EtOAc, EtOAc/IPA (2/1)) to afford 210 mg (58%) of **24a** after recrystallization from hexane/EtOAc, 95 mg (30%) of lactam diol, and 225 mg (96%) of alcohol **4**. Data for **24a**: mp 170–172 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 6.78–6.85 (m, 3 H), 5.47 (m, 1 H), 4.64 (dd, J = 10.5, 7.1, 1 H), 4.19 (J = 10.0, 4.6, 1 H), 3.88 (s, 6 H), 3.64 (dd, J = 3.7, 12.5, 1 H), 3.39 (dd, J = 4.9, 12.5, 1 H), 2.74 (ddd, J = 11.5, 7.1, 5.4, 1 H,), 2.23 (ddd, J = 11.2, 11.2, 10.3, 1 H), 2.13 (s, 3 H), 1.76–2.04 (m, 2 H), 0.68 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 176.52, 170.15, 149.01, 147.92, 134.52, 118.65, 110.86, 109.80, 79.03, 71.33, 62.01, 55.89, 55.78, 52.79, 47.08, 35.32, 23.30, 20.94, 9.80; IR 3028 (s), 1697 (s), 1520 (s), 1464 (s); MS (EI) 363 (M^+, 21); TLC R_f 0.20 (EtOAc). Anal. Calcd for $C_{19}H_{25}NO_6$ (363.410): C, 62.80; H, 6.93; N, 3.85. Found: C, 62.79; H, 6.96; N, 3.79.

***rel*-(1*S*,3*R*,5*R*,6*S*,6a*S*)-5-(Acetyloxy)-6-(3,4-dimethoxyphenyl)-6-ethyl-1-((imidazoyl(thiocarbonyl)oxy)-hexahydro-1*H*-pyrrolizin-2-one (25a).** Hydroxy lactam **24a** (250 mg, 0.69 mmol) and 1,1′-thiocarbonyldiimidazole (257 mg, 1.45 mmol, 2.1 equiv) were dissolved in CH_2Cl_2 (20 mL) and heated at reflux for 2.5 h. The mixture was allowed to cool to rt and was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (1/1, 1/2, 1/4), EtOAc) and recrystallized from hexane/EtOAc to afford 295 mg (91%) of **25a** as a white solid. Data for **25a**: mp 156–159 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 8.58 (s, 1 H), 7.76 (s, 1 H), 7.15 (s, 1 H), 6.86–6.77 (m, 3 H), 6.30 (dd, J = 9.8, 8.1, 1 H), 5.55 (dd, J = 4.2, 5.1, 1 H), 4.31 (dd, J = 9.3, 5.9, 1 H), 3.89 (s, 6 H), 3.70 (dd, J = 12.7, 4.2, 1 H), 3.52 (dd, J = 12.7, 5.4, 1 H), 3.07–3.12 (m, 1 H), 2.42-2.48 (m, 1 H), 2.16 (s, 3 H), 1.79–2.05 (m, 2 H), 0.72 (t, J = 7.1, 3 H); ^{13}C NMR (100 MHz) 183.06, 169.85, 169.09, 149.09, 148.08, 136.91, 133.92, 130.94, 118.56, 118.11, 110.94, 109.67, 79.28, 78.87, 61.81, 55.91, 55.77, 52.97, 47.42, 32.49, 23.33, 20.92, 9.80; IR 2936 (s), 1734 (s), 1518 (s), 1460 (s); MS (EI) 473 (M^+, 6); TLC R_f 0.35 (EtOAc). Anal. Calcd for $C_{23}H_{27}N_3O_6S$ (473.543): C, 58.34; H, 5.75; N, 8.87. Found: C, 58.34; H, 5.77; N, 8.87.

***rel*-(2*R*,4*R*,5*S*,5a*S*)-4-(Acetyloxy)-5-(3,4-dimethoxyphenyl)-5-ethylhexahydro-1*H*-pyrrolizin-2-one (26a).** Xanthate ester **25a** (234 mg, 0.49 mmol) was dissolved in benzene (40 mL) and heated to reflux. A mixture of Bu_3SnH (173 μL, 0.64 mmol, 1.3 equiv) and AIBN (17 mg, 0.1 mmol, 0.2 equiv) in benzene (2.5 mL) was added over 1 h. The mixture was heated at reflux for an additional 8 h, allowed to cool to rt, and concentrated *in vacuo*. The crude product was purified by column chromatography (KF pad above silica, EtOAc) and distilled to afford 145 mg (85%) of **26a** as a glass. Data for **26a**: bp 200 °C (0.1 Torr); ^{1}H NMR (400 MHz) 6.75–6.84 (m, 3 H), 5.49 (t, J = 5.6, 1 H), 4.29 (t, J = 7.4, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.48 (d, J = 5.4, 2 H), 2.70 (dt, J_d = 16.1, J_t = 9.6, 1 H), 2.46 (ddd, J = 7.9, 3.1, 6.3, 1 H), 2.27–2.36 (m, 2 H), 2.14 (s, 3 H), 1.75–1.96 (m, 2 H), 0.71 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 175.93, 170.03, 148.87, 147.79, 134.83, 118.62, 110.86, 109.82, 79.86, 66.68, 55.81, 55.74, 52.29, 46.35, 33.25, 24.05, 22.81, 20.94, 9.93; IR 2972 (s), 1737 (s), 1690 (s), 1519 (s); MS (EI) 347 (M^+, 18); TLC R_f 0.25 (EtOAc). Anal. Calcd for $C_{19}H_{25}NO_5$ (347.410): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.71; H, 7.28; N, 4.00.

***rel*-(1*R*,3*S*,5*R*,6*S*,6a*R*)-5-(Acetyloxy)-6-(3,4-dimethoxyphenyl)-6-ethyl-1-hydroxyhexahydro-1*H*-pyrrolizin-2-one (24b).** A mixture of nitroso acetals **23a** and **23b** (646 mg, 1.0 mmol) was added to a suspension of a catalytic amount of Raney nickel in methanol (40 mL). The suspension was allowed to stir at rt under 1 atm of H_2 pressure for 24 h. The reaction mixture was filtered through Celite, washed with CH_2Cl_2 (25 mL)/Et_3N (5 mL), and concentrated *in vacuo*. The crude products were purified by column chromatography (hexane/EtOAc (1/1), EtOAc, EtOAc/IPA (9/1)) to afford 128 mg (35%) of a diastereomeric mixture of hydroxy lactams **24a** and **24b** in a ratio of 1.0:8.0 (^{1}H NMR) after recrystallization from hexane/EtOAc. Also, 63 mg (17%) of **24a** was obtained after recrystallization from hexane/EtOAc. Data for **24a/b**: mp 78–85 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 6.76–6.87 (m, 1.3 H), 6.64 (dd, J = 2.4, 7.7 H), 6.54 (d, J = 2.2, 0.8 H), 5.64 (d, J = 5.1, 0.8 H), 5.47 (dd, J = 3.7, 4.9, 0.2 H), 4.63 (dd, J = 7.3, 10.5, 0.2 H), 4.50 (t, J = 9.3, 0.8 H), 4.20 (dd, J = 5.4, 14.3, 1 H), 4.00 (dd, J = 6.4, 8.5, 0.8 H), 3.88 (s, 1.2 H), 3.87 (s, 2.4 H), 3.86 (s, 2.4 H), 3.64 (dd, J = 3.7, 12.5, 0.2 H), 3.39 (dd, J = 5.1, 12.5, 0.2 H), 3.18 (d, J = 13.9, 0.8 H), 2.74 (m, 0.2 H), 2.50 (m, 0.8 H), 2.42 (br, 1 H), 1.50–2.30 (m, 6 H), 0.73 (t, J = 7.3, 0.8 H), 0.68 (t, J = 7.3, 0.2 H); ^{13}C NMR (100 MHz) 172.83, 169.93, 148.92, 148.05, 129.37, 120.09, 111.17, 111.05, 79.06, 72.57, 64.97, 56.03, 55.77, 54.55, 49.17, 32.91, 25.42, 21.05, 9.44; IR 2965 (s), 1697 (s), 1518 (s), 1462 (s); MS (EI) 363 (M^+, 23); HRMS calcd for ($C_{19}H_{25}NO_6$) 363.1682, found 363.1695; TLC R_f 0.20 (EtOAc).

***rel*-(1*R*,3*S*,5*R*,6*S*,6a*R*)-5-(Acetyloxy)-6-(3,4-dimethoxyphenyl)-6-ethyl-1-((imidazoyl(thiocarbonyl)oxy)-hexahydro-1*H*-pyrrolizin-2-one (25b).** Hydroxy lactam

24b (71 mg, 0.20 mmol) and 1,1′-thiocarbonyldiimidazole (73 mg, 0.41 mmol, 2.1 equiv) were dissolved in CH_2Cl_2 (5.0 mL) and heated at reflux for 2.5 h. The mixture was allowed to cool to rt and was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc (1/1, 1/2, 1/4), EtOAc) and recrystallized from hexane/EtOAc to afford 50 mg (54%) of **25b** as a white solid. Data for **25b**: mp 188 °C (hexane/EtOAc); ^{1}H NMR (400 MHz) 8.21 (s, 1 H), 7.32 (s, 1 H), 7.01 (s, 1 H), 6.82 (d, J = 8.5, 1 H), 6.64 (dd, J = 8.3, 2.2, 1 H), 6.50 (d, J = 2.2, 1 H), 5.97 (t, J = 8.1, 1 H), 5.65 (dd, J = 5.6, 1.0, 1 H), 4.45 (dd, J = 14.4, 5.9, 1 H), 4.05 (t, J = 6.6, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.22 (d, J = 14.4, 1 H,), 2.83 (ddd, J = 13.7, 8.8, 7.1, 1 H), 2.18 (s, 3 H), 1.91–2.10 (m, 2 H), 1.65 (ddd, J = 13.9, 7.8, 6.6, 1 H), 0.76 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 181.55, 169.87, 148.98, 148.28, 137.08, 128.53, 120.29, 117.66, 111.09, 111.02, 79.96, 78.40, 65.23, 56.12, 55.74, 55.21, 50.56, 28.78, 24.38, 21.02, 9.38; IR 1751 (m), 1464 (m), 1230 (s); MS (EI) 473 (M^+, 3); TLC R_f 0.35 (EtOAc). Anal. Calcd for $C_{23}H_{27}N_3O_6S$ (473.543): C, 58.34; H, 5.75; N, 8.87. Found: C, 58.38; H, 5.76; N, 8.86.

***rel*-(2*S*,4*R*,5*S*,5a*R*)-4-(Acetyloxy)-5-(3,4-dimethoxyphenyl)-5-ethylhexahydro-1*H*-pyrrolizin-2-one (26b).** Xanthate ester **25b** (40 mg, 0.08 mmol) was dissolved in benzene (10 mL) and heated to reflux. A mixture of Bu_3SnH (30 μL, 0.11 mmol, 1.3 equiv) and AIBN (3 mg, 0.02 mmol, 0.2 equiv) in benzene (1.0 mL) was added over 1 h. The mixture was heated at reflux for an additional 10 h, allowed to cool to rt, and concentrated *in vacuo*. The crude product was purified by column chromatography (KF pad above silica, EtOAc) and recrystallized from hexane/EtOAc to afford 25 mg (83%) of **26b** as a white solid. Data for **26b**: mp 180–182 °C (hexane, EtOAc); ^{1}H NMR (400 MHz) 6.84 (d, J = 8.5, 1 H), 6.60 (dd, J = 10.7, 2.4, 1 H), 6.57 (d, J = 2.4, 1 H), 5.60 (dd, J = 5.9, 1.2, 1 H), 4.41 (dd, J = 14.2, 5.9, 1 H), 4.00 (dd, J = 8.3, 3.9, 1 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 3.08 (d, J = 14.2, 1 H), 2.34 (ddd, J = 16.6, 10.0, 5.4, 1 H), 2.15 (s, 3 H), 1.94–2.08 (m, 3 H), 1.63–1.72 (m, 1 H), 1.36 (ddd, J = 16.8, 10.5, 5.9, 1 H), 0.78 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) 175.80, 169.99, 148.76, 148.03, 129.22, 120.06, 111.01, 110.89, 78.21, 69.12, 56.00, 55.72, 54.85, 51.13, 31.83, 23.76, 21.04, 19.12, 9.24; IR 3007 (s), 1734 (s), 1520 (s), 1464 (s); MS (EI) 347 (M^+, 19); TLC R_f 0.25 (EtOAc). Anal. Calcd for $C_{19}H_{25}NO_5$ (347.410): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.67; H, 7.29; N, 4.01.

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Supplementary Material Available: Complete ^{1}H and ^{13}C NMR (with assignments), IR, and MS data for all characterized compounds, ^{1}H NMR spectra for mixtures **23b/a** and **24b/a**, and coordinates for the X-ray crystal structure of **23a** (22 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.