Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions. 17. The Spiro Mode. Efficient and Highly Selective Synthesis of Azapropellanes

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Received October 15, 1997

A new variant of the tandem inter [4 + 2]/intra [3 + 2] nitroalkene cycloaddition has been developed. Intermolecular [4 + 2] cycloaddition of a 2-nitroalkene (bearing an unsaturated ester moiety, the dipolarophile) with a vinyl ether produces a cyclic nitronate substituted at C(3) wherein the only stereogenic center is the anomeric carbon C(6). Since the dipolarophile is attached to a tether extending from the C(3) of the nitronate (α-carbon of the nitroalkene), the intramolecular [3 + 2] cycloaddition affords a spiro tricyclic nitroso acetal. The cycloaddition proceeds smoothly for three- and four-atom tethers to afford five- and six-membered rings. Both *E*- and *Z*-unsaturated esters serve well as dipolarophiles, but the *E*-isomers react more selectively. Hydrogenolysis of the nitroso acetals affords the spiro tricyclic α-hydroxy lactams in good yield. Remarkably high levels of asymmetric induction are observed with the use of a chiral vinyl ether derived from (1*R*,2*S*)-2-phenylcyclohexanol. The origin of asymmetric induction is a combination of the established face selectivity of the enol ether and the preference for a distal fold of the tether away from the substituent on the anomeric carbon. The scope and limitations of this transformation and an analysis of the origin of stereoselectivity are provided.

Introduction

In recent years, the development and application of tandem reactions has emerged as a powerful strategy for increasing efficiency in organic synthesis.[1] In our laboratories, the tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkenes have proven extremely versatile for the stereoselective construction of a diverse array of highly functionalized polycyclic compounds.[2] The structural virtuosity of the tandem [4 + 2]/[3 + 2] cycloaddition sequence derives from the number of permutations possible for attachment of the various components (nitroalkene, dienophile, and dipolarophile).

As for any tandem cycloaddition protocol, there are in principle four different permutations that arise from the pairwise combinations of inter- and intramolecularity for each event, Figure 1. While all permutations have been documented in our laboratories, our efforts have primarily focused on the tandem inter [4 + 2]/intra [3 + 2] variant. The overwhelming superiority of this process is in large measure due to the existence of four distinct subclasses of cycloadditions that encompass remarkable structural diversity. These subclasses arise from the various points of attachment of the dipolarophilic tether to the intermediate nitronate as illustrated in Figure 2. These can be seen to arise from two distinct types of precursors: nitroso acetals **A** and **B**, which arise from dipolarophile-tethered nitroalkenes, and nitroso acetals **C** and **D**, which arise from dipolarophile tethered dienophiles.

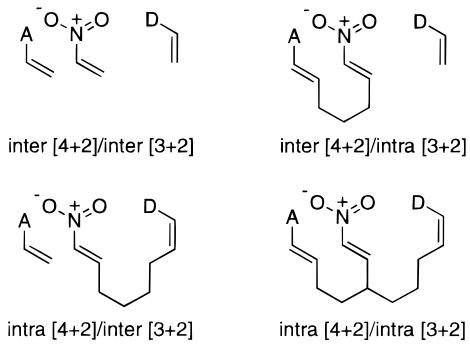

Figure 1. Family of tandem [4 + 2]/[3 + 2] cycloadditions.

Extensive investigations from these laboratories have illustrated the scope and utility of the fused mode cycloaddition for asymmetric synthesis of various nitrogen-containing polycyclic compounds.[2b−e] Furthermore, recent disclosures have demonstrated the potential for the two variants of bridged mode process for the synthesis of five- and six-membered carbocycles.[2f,g] In this report, we disclose, in full, our studies on the scope and limitations of the spiro mode cycloaddition between 2-nitroalkenes bearing dipolarophilic tethers at C(2) and (chiral) vinyl ethers, Scheme 1.[3]

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(1) (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Ziegler, F. E. In *Comprehensive Organic Synthesis, Combining C−C π-Bonds*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5; Chapter 7.3. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Grigg, R., Ed. Cascade Reactions. *Tetrahedron Symposium in Print No. 62* **1996**, *52* (35).

(2) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 137. (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (c) Denmark, S. E.; Thorarensen. A. *J. Am. Chem. Soc.* **1997**, *119*, 127. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (f) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (g) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 7086.

(3) For preliminary reports see: (a) Denmark, S. E.; Senanayake, C. B. W.; Schnute, M. E.; Moon, Y. C.; Ho, G. D.; Middleton, D. S. *Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry*; VCH Verlagsgesellschaft and Kodansha Ltd.: Weinhein, 1992. (b) Denmark, S. E.; Schnute, M. E.; Thorarensen, A.; Middleton, D. S.; Stolle, A. *Pure Appl. Chem.* **1994**, *66*, 2041.

S0022-3263(97)01905-1 CCC: $15.00
Published on Web 02/14/1998

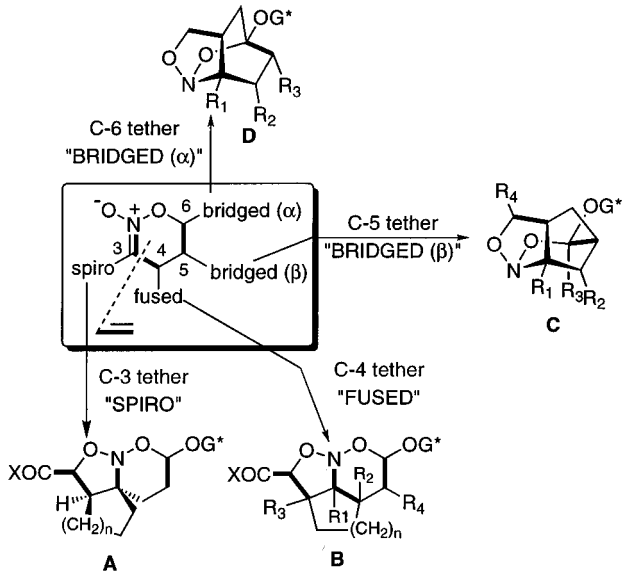
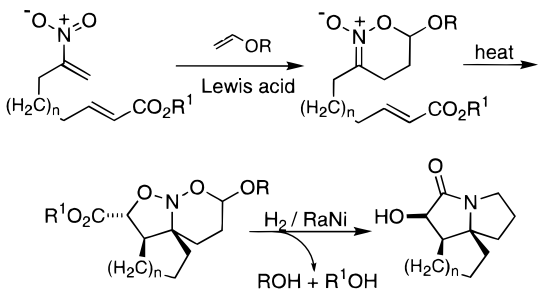


Figure 2. Subclasses of the inter [4 + 2]/intra [3 + 2] cycloadditions.

Scheme 1

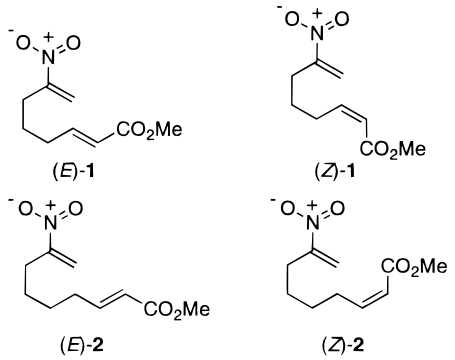


This work addresses several topics related to the spiromode tandem [4 + 2]/[3 + 2] cycloaddition process, including the following: (1) the preparation of α-branched nitroalkenes bearing an intramolecularly tethered dipolarophile, (2) the feasibility of employing such α-branched nitroalkenes in tandem cycloaddition reactions, (3) the effect of tether length and dipolarophile geometry on the diastereoselectivity of the process, (4) the feasibility of preparing spiro-fused α-hydroxy lactams from the nitroso acetal products of the cycloaddition sequence, and (5) the application of auxiliary-based asymmetric synthesis to the preparation of enantiomerically enriched α-hydroxy lactams.

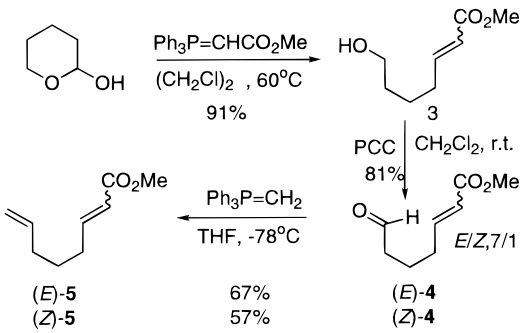
Results

Synthesis of α-Branched Nitroalkenes. The pronounced reactivity of α-substituted nitroalkenes as Michael acceptors dictated that formation of the nitro olefin function constitute the final step in the preparation of the nitro dienoate substrates (*E*)- and (*Z*)-**1** and (*E*)- and (*Z*)-**2** required for this study, Chart 1. The added complication of the intramolecularly tethered enoate group precluded the use of nucleophile-based introduction of the nitro olefin via Seebach's NPP method.[4] Instead, we considered a two-step procedure involving nitromercuration[5] and tertiary-amine-mediated elimination that has been successfully applied to the synthesis of both

Chart 1



Scheme 2



cyclic and α-substituted nitroalkenes derived from simple olefins.[6] Reaction of the olefin with mercuric chloride or mercuric perchlorate (1 equiv) and sodium nitrite (2 equiv) in water for 30 h affords nitromercurials that upon treatment with aqueous hydroxide (2.5 N) or a tertiary amine give the nitroalkenes.

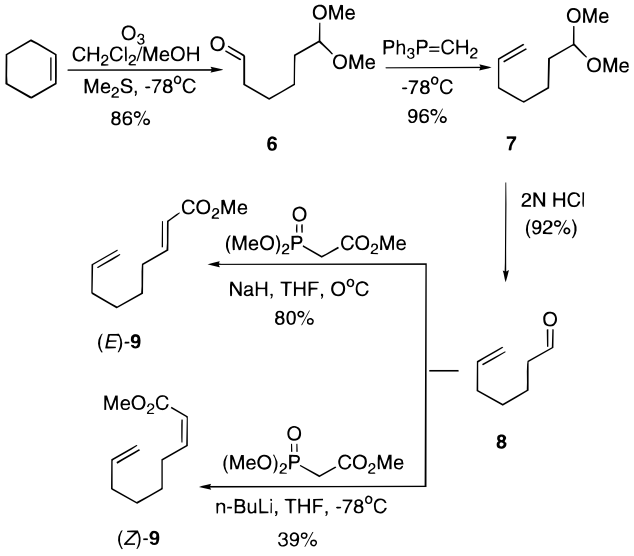
The application of this nitromercuration−elimination procedure to the preparation of the α-substituted nitroalkenes **1** and **2** required the synthesis of octa- and nonadienoates with both *E* and *Z* geometries, Chart 1.

The preparation of both (*E*)- and (*Z*)-1,7-octadienoates **5** was achieved from 1-hydroxypyran. Treatment of the latent aldehydes with (carbomethoxymethylene)triphenylphosphorane afforded 7-hydroxyheptenoate (**3**) in 91% yield as a 7/1 mixture of *E* and *Z* isomers. This mixture of alcohols was then oxidized with PCC to the corresponding aldehydes (*E*)-**4** and (*Z*)-**4**, which were found to be chromatographically separable. Conversion to the dienoates (*E*)-**5** and (*Z*)-**5** was then accomplished in each case by treatment with the ylide generated in situ from methyl triphenylphosphonium bromide and *n*-butyllithium, Scheme 2. The higher homologs (*E*)-**9** and (*Z*)-**9** were prepared as shown in Scheme 3. Ozonolysis of cyclohexene provided monoprotected 1,6-dialdehyde **6** in good yield, which was then converted to the terminal olefin **7** via simple Wittig methylenation.[7] The acetal protecting group was then removed by treatment with 0.1 N HCl in THF to afford 6-heptenal (**8**) in 76% overall yield from cyclohexene. Conversion to nonadienoates (*E*)-**9** and (*Z*)-**9** was then achieved by Horner−Emmons olefination with trimethyl phosphonoacetate.

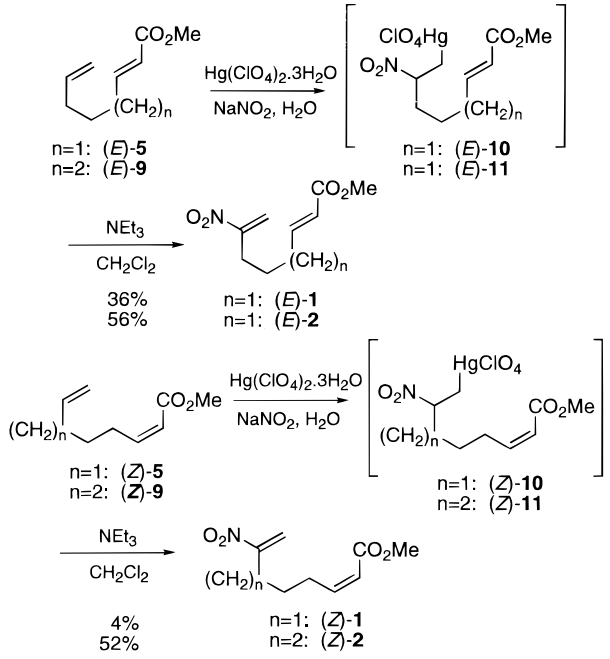
Reaction of methyl (*E*)-2,7-octadienoate ((*E*)-**5**) with sodium nitrite (2 equiv) and mercuric perchlorate trihydrate (1 equiv) in water for 24 h afforded, after aqueous workup, nitromercurial **10** as a viscous yellow oil. This

(4) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261.
(5) Bachman, G. B.; Whitehouse, M. L. *J. Org. Chem.* **1967**, *32*, 2303.
(6) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294.
(7) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

Scheme 3



Scheme 4



was immediately treated with triethylamine in CH_2Cl_2 to afford nitroalkene (*E*)-**1** in 36% overall yield. By using a similar two-step sequence, (*Z*)-**5** was converted to nitroalkene (*Z*)-**1**, via nitromercurial (*Z*)-**10**, Scheme 4, albeit in poor yield.

Attempts to improve the disappointing overall yield for these two sequences by changing reaction time, concentration, and stoichiometry were all unsuccessful. Nitroalkenes (*E*)-**2** and (*Z*)-**2** were prepared by an analogous procedure in 56% and 52% yield, respectively.

The generally modest overall yields for the nitromercuration−elimination protocol prompted a brief investigation into alternative approaches to the synthesis of these nitroalkenes. Tomoda has reported the synthesis of 2-nitroalkyl phenylselenides and their subsequent conversion to nitroalkenes.[8] Thus, treatment of octadienoate (*E*)-**5** with phenylselenenyl bromide, silver nitrite, and mercuric chloride in CH_3CN/THF (1/1) at −78 °C for 85 min, afforded nitroselenide **12** in 32% yield (55% based on recovered starting material), Scheme 5. The hydroxy selenide, formed by nucleophilic attack of the ambident nitrite anion, through oxygen, on the intermediate selenonium ion, was also observed. Attempts to improve the yield of **12** by modifying the reaction time and temperature were unsuccessful. The attempted selenoxide elimination of **12** using hydrogen peroxide was unsuccessful. Other viable approaches exist to improve the yield in the nitroalkene preparations; however, such studies did not constitute the focal point of this work.

Scheme 5

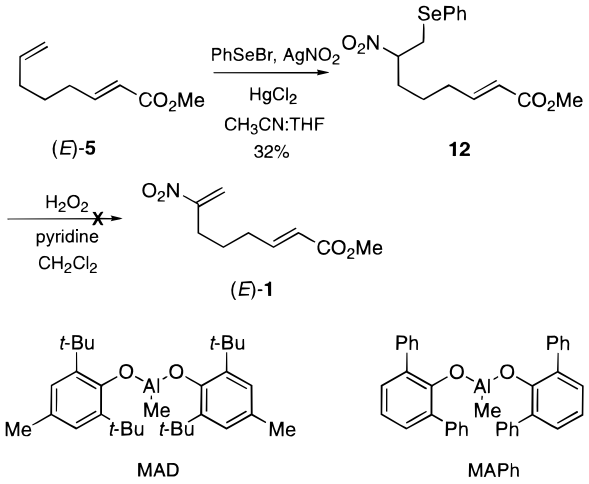


Figure 3. Bulky monomeric aluminum Lewis acids.

The nitromercuration−elimination strategy, although proceeding in disappointing yield, was sufficiently concise to allow adequate quantities of nitroalkenes to be synthesized for the subsequent tandem cycloaddition studies, and therefore, studies to optimize or improve the yields were not pursued.

Tandem Cycloaddition Reactions with *n*-Butyl Vinyl Ether. For orienting experiments to establish the ability of α-substituted nitroalkenes to engage in [4 + 2] cycloaddition with *n*-butyl vinyl ether we first examined the use of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$. This Lewis acid has served admirably in our previous studies of nitroalkene cycloadditions.[9] Surprisingly, this Lewis acid failed to induce cycloaddition of (*E*)-**1** with *n*-butyl vinyl ether under various combinations of time, temperature, stoichiometry, and addition order. In all instances (*E*)-**1** was recovered, albeit in modest yield (70%).

Our ongoing parallel investigations of fused and bridged mode cycloadditions have established that the bulky, aluminum-based Lewis acids methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and methylaluminum bis(2,6-diphenylphenoxide) (MAPh), Figure 3, are excellent alternatives to $TiCl_2(O\text{i-}Pr)_2$ for this process.[10]

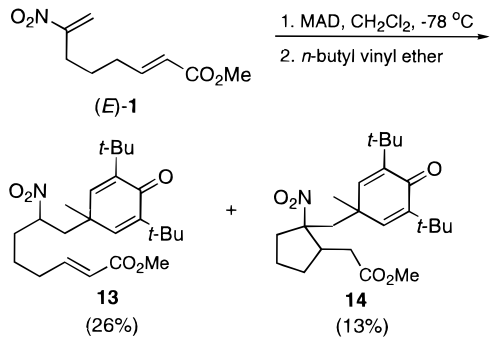
Addition of in situ generated MAD to nitroalkene (*E*)-**1** at −78 °C in CH_2Cl_2 followed by the addition of butyl

(8) Hayama, T.; Tomoda, S.; Takeuchi, Y.; Nomura, Y. *Chem. Lett.* **1982**, 1109 and references therein.

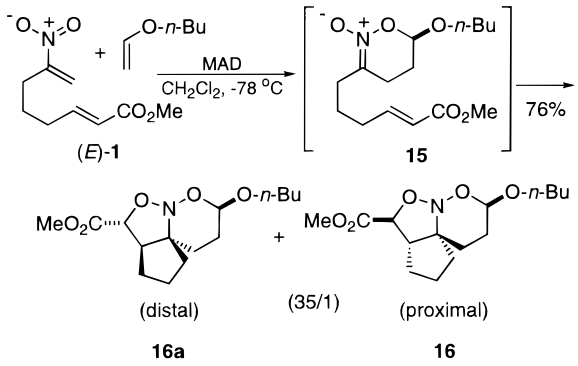
(9) (a) Denmark, S. E.; Moon, Y. C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311 and references therein. (b) Denmark, S. E.; Senanayake, C. B. W.; Ho, G. D. *Tetrahedron* **1990**, *46*, 4857. (c) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853.

(10) (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738. (b) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (c) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (d) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1996**, *61*, 6727.

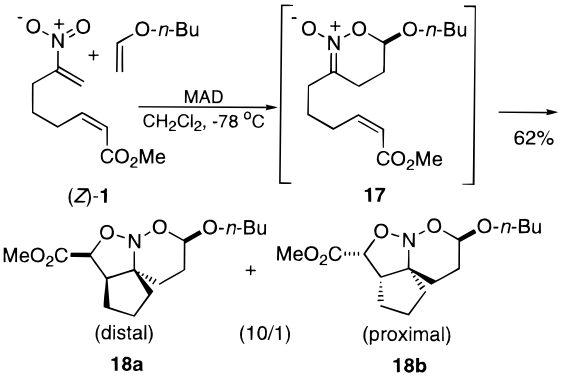
Scheme 6



Scheme 7



Scheme 8

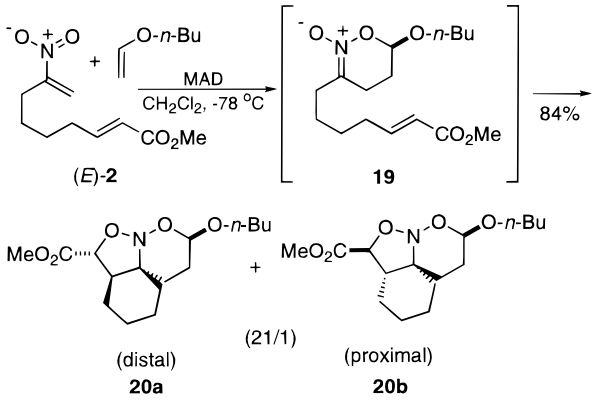


vinyl ether afforded **13** and **14** in 26% and 13% yield, respectively, but with no cycloaddition products, Scheme 6. These unwanted products arose from Michael addition of the aluminum phenoxide to the reactive acceptor double bonds in (*E*)-**1**. This problem could be overcome by simply having the dienophile present as the Lewis acid was added to the nitroalkene.

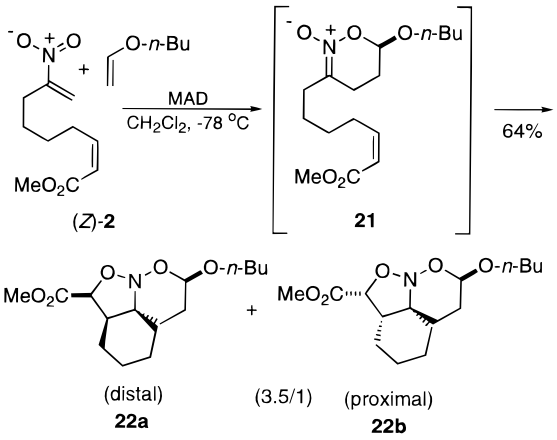
Thus, addition of MAD (3 equiv) to a solution of nitroalkene and *n*-butyl vinyl ether (6 equiv) at −78 °C resulted in the complete consumption of starting nitroalkene and the formation of the more polar nitronate product **15**. Intramolecular [3 + 2] cycloaddition of the crude nitronate **15** (isolated after aqueous extraction to remove aluminum salts) was facilitated by warming in toluene at 75 °C for 85 min. The nitroso acetal **16** was isolated as an inseparable 35/1 mixture of diastereomers with the distal isomer **16a** predominating, Scheme 7. The assignment of relative configuration was made by analogy to the nonracemic series, vide infra.

Treatment of the nitroalkene (*Z*)-**1** with MAD (3 equiv) in the presence of *n*-butyl vinyl ether gave, after workup and warming in toluene, nitroso acetal **18** in 62% yield

Scheme 9



Scheme 10



as an inseparable 10/1 mixture of diastereomers with the distal isomer **18a** predominating, Scheme 8.

Nitroalkenes (*E*)-**2** and (*Z*)-**2** were similarly converted to nitroso acetals **20** and **22**, respectively, with an erosion of diastereoselectivity relative to their respective lower homologs, Schemes 9 and 10.

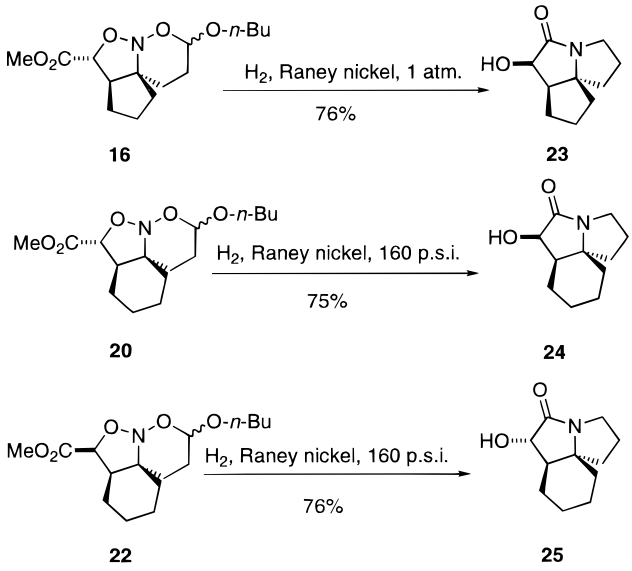
Intermediate nitronate **19**, in contrast to the lower homolog **15**, did not undergo the intramolecular [3 + 2] cycloaddition at room temperature and could be readily isolated. Interestingly, nitronate **21** required prolonged heating (230 min) in toluene at 100 °C to achieve complete conversion to the nitroso acetals **22a** and **22b**. Diastereomeric ratios in all cases were established by integration of the diagnostic anomeric protons.

In view of the difficulties encountered in preparing nitroalkene substrate (*Z*)-**1** and more importantly the relatively poor diastereoselectivity (compared to (*E*)-**1**) observed in the cycloaddition leading to **18**, further studies on this substrate in the tandem cycloaddition were not undertaken.

Hydrogenolytic Cleavage of Nitroso Acetals: Preparation of α-Hydroxy Lactams. The conversion of nitroso acetals **16**, **20**, and **22** to their respective α-hydroxy lactams **23**, **24**, and **25** was accomplished using our standard hydrogenolysis reaction, Scheme 11.

The diastereomeric mixture of nitroso acetals **16** was treated with a catalytic amount of Raney nickel in methanol under 1 atm of hydrogen for 37.5 h to afford the α-hydroxy lactam **23** as a single isomer. Conducting the hydrogenolysis reaction at 1 atm, the reaction was found to be somewhat capricious depending upon substrate. This problem of irreproducibility was solved,

Scheme 11



however, by conducting the reaction at 160 psi, to furnish the α-hydroxy lactams **24** and **25**, both as single isomers, in 75% and 76% yield, respectively.

Radical Deoxygenation of α-Hydroxy Lactams. We assumed that the isomeric α-hydroxy lactams **24** and **25** differed only at the hydroxyl bearing center. This would be a simple consequence of the different dipolarophile geometries in (*E*)-**2** and (*Z*)-**2** if both substrates underwent [3 + 2] cycloaddition via the same (exo-fold) transition structure. To establish this (and thereby establish the identity of reaction pathways), the hydroxyl groups were removed from **24** and **25**.

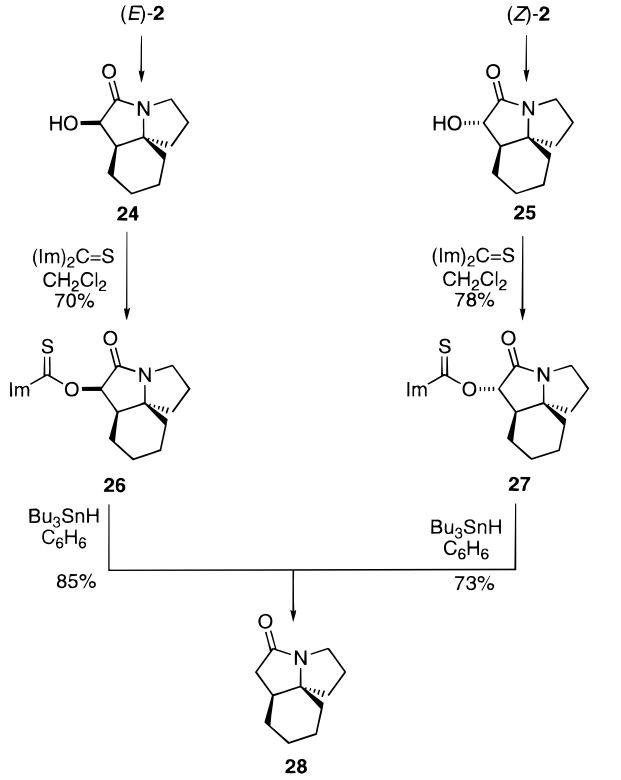
Thus, alcohols **24** and **25** were converted to their corresponding xanthates **26** and **27** by reaction with 1,1′-(thiocarbonyl)diimidazole in boiling CH_2Cl_2, Scheme 12. Slow addition of a benzene solution of Bu_3SnH and AIBN over 4 h to a refluxing solution of **26** in benzene yielded tricyclic lactam **28** in 85% yield. Similarly, deoxygenation of light sensitive **27** using Bu_3SnH and AIBN in refluxing benzene yielded a tricyclic lactam **28** identical with that prepared from **26**.

The observation that both **26** and **27** ultimately yield the identical tricyclic lactam after radical deoxygenation establishes that a single (exo) (vide infra) folding orientation of the dipolarophile tether occurs in the [3 + 2] cycloaddition independent of double bond geometry.

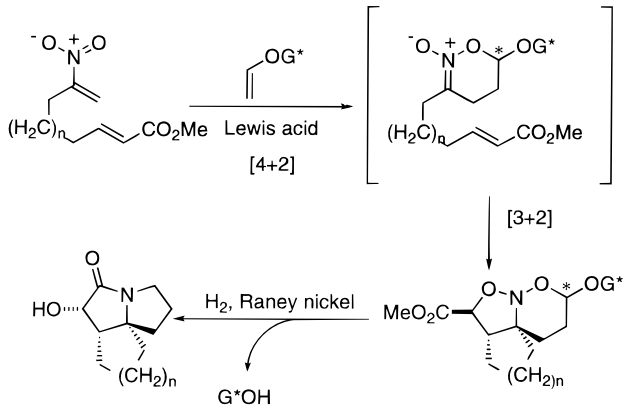
Asymmetric Synthesis of α-Hydroxy Lactams. Tandem Cycloadditions Using a Nonracemic Vinyl Ether. The unexpectedly high diastereoselectivities observed for the tandem cycloaddition reaction with *n*-butyl vinyl ether, particularly for nitrodienoates (*E*)-**1** and (*E*)-**2**, made the possibility of auxiliary-controlled asymmetric synthesis an attractive avenue for investigation, Scheme 13.

Unlike the fused-mode tandem cycloadditions, the spiro-mode creates only a single stereogenic center in the [4 + 2] process, that at the anomeric position. Since this center is ultimately destroyed in the hydrogenolysis, the stereoinduction (relative to this center) in the [3 + 2] cycloaddition creates all of the centers that persist. Thus, successful enantioselective synthesis of α-hydroxy lactams using this approach depended critically on achieving the following: (1) highly diastereofacial reaction of the chiral vinyl ether in the initial [4 + 2] cycloaddition

Scheme 12



Scheme 13



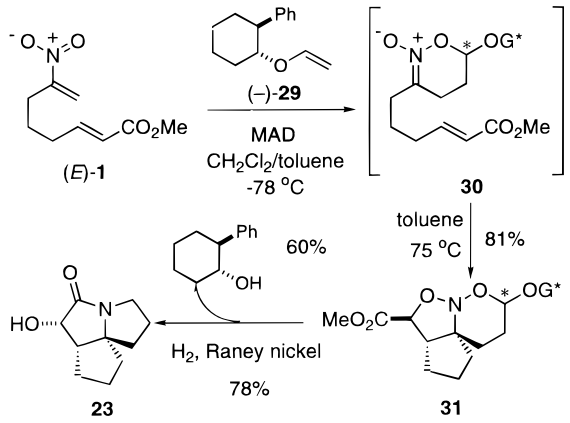
to create the anomeric center with high selectivity and (2) selective alkoxy-controlled distal side approach of the dipolarophile to the nitronate in the [3 + 2] step.

To test the viability of this approach, we chose (−)-(1*R*,2*S*)-2-phenylcyclohexanol as the chiral auxiliary. The corresponding vinyl ether (−)-**29** has been employed with good success in all modes of tandem-cycloaddition and has served admirably in a number of total synthesis efforts.[2c,d,10b] While it is not, in fact, the optimal auxiliary for the MAD- or MAPh-promoted cycloadditions used herein,[10d] it is easily accessible[11] and allows us to evaluate proof of principle.

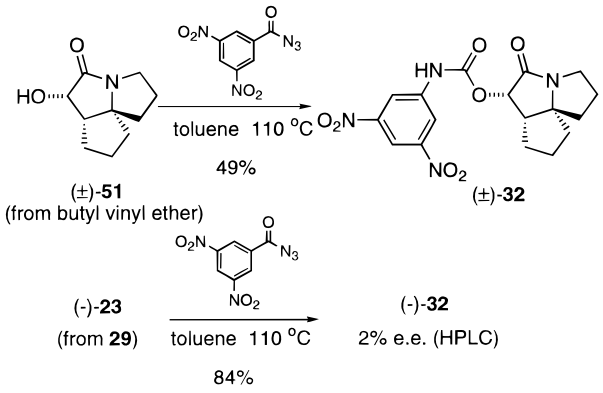
Addition of MAD (3.0 equiv) to a solution of nitroalkene (*E*)-**1** and chiral vinyl ether (−)-**29** (3.0 equiv) in CH_2Cl_2 at −78 °C provided an approximately 1/1 mixture of diastereomeric nitronate **30**, which after aqueous workup and warming in toluene at 75 °C for 60 min, afforded

(11) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.

Scheme 14



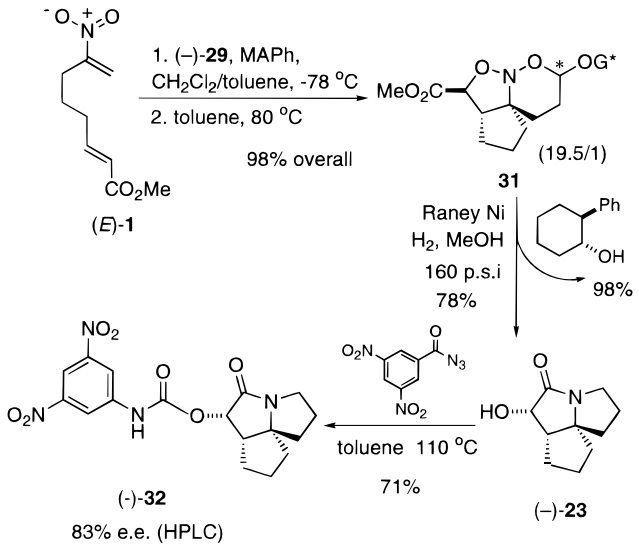
Scheme 15



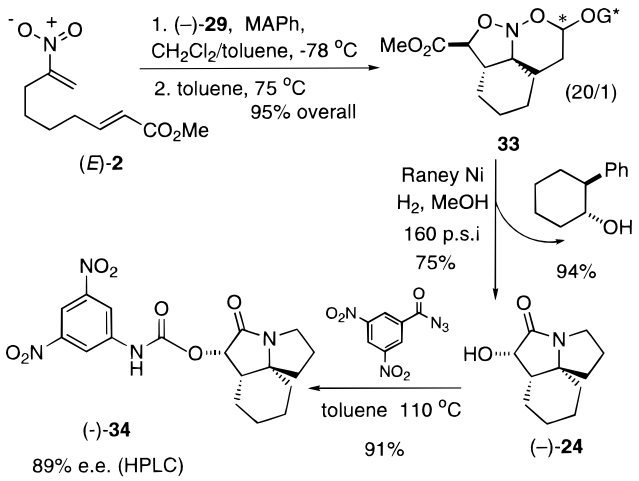
nitroso acetal **31** in 81% yield. The ^{1}H NMR spectrum of this material showed two major products in approximately equal amounts. Hydrogenolytic cleavage of this nitroso acetal mixture was performed as described above to afford α-hydroxy lactam **23** along with the recovered auxiliary, Scheme 14. The enantiomeric excess of the hydroxy lactam was established by conversion to the 3,5-dinitrophenyl carbamate derivative **32** using 3,5-dinitrobenzoyl azide in refluxing toluene, Scheme 15. Comparison of the chiral stationary phase HPLC[12] traces of this derivative with those of racemic carbamate (±)-**32**, prepared from (±)-**23**, established the enantiomeric excess as 2%.

A spectacular improvement in stereoselectivity was observed for the tandem process upon changing the Lewis acid from MAD to MAPh. Thus, addition of MAPh (3.0 equiv) to a solution of (*E*)-**1** and vinyl ether (−)-**29** in CH_2Cl_2 at −78 °C gave, after workup and warming in toluene, nitroso acetal **31** in 98% yield. The ^{1}H NMR spectrum of this highly crystalline solid showed it to be an approximately 19.5/1 mixture of diastereomers. Hydrogenolytic cleavage to the hydroxy lactam (Raney nickel, methanol, 160 psi) afforded (−)-**23** in 78% yield along with an almost quantitative recovery of (−)-2-phenylcyclohexanol. Conversion to the carbamate derivative **32** as above (71% yield) and chiral HPLC analysis revealed an enantiomeric enrichment of 83% in the more strongly retained enantiomer, Scheme 16.

Scheme 16



Scheme 17



Similarly, addition of MAPh (2.8 equiv) to a solution of nitroalkene (*E*)-**2** and vinyl ether (−)-**29** (3.0 equiv) in CH_2Cl_2 at −78 °C afforded nitroso acetal **33** in 95% yield. The ^{1}H NMR spectrum of this material showed it to be an approximately 20/1 mixture of diastereomers. Hydrogenolysis afforded hydroxy lactam (−)-**24** in 75% yield together with the recovered alcohol (−)-2-phenylcyclohexanol, again in very high yield. Transformation to the carbamate derivative (−)-**34** and chiral HPLC analysis (with comparison to the racemic carbamate derivative prepared independently from (±)-**24**) showed it to be 89% enantiomerically enriched in the more strongly retained enantiomer, Scheme 17.

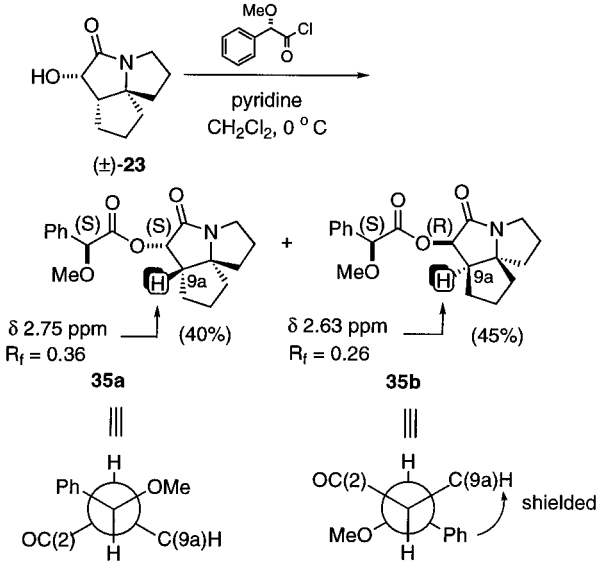
Determination of Absolute Configuration. The absolute configurations of α-hydroxy lactams (−)-**23** and (−)-**24** were established by using two empirical techniques; chemical shift nonequivalence and chiral HPLC elution order. The (*S*)-*O*-methylmandelate esters of *racemic* α-hydroxy lactams **23** and **24** were readily prepared by the method of Trost,[13] and the diastereomers were easily separated, Schemes 18 and 19.

For both hydroxy lactams, the more polar diastereomer (i.e., **35b** and **36b**) displayed an upfield shift for the

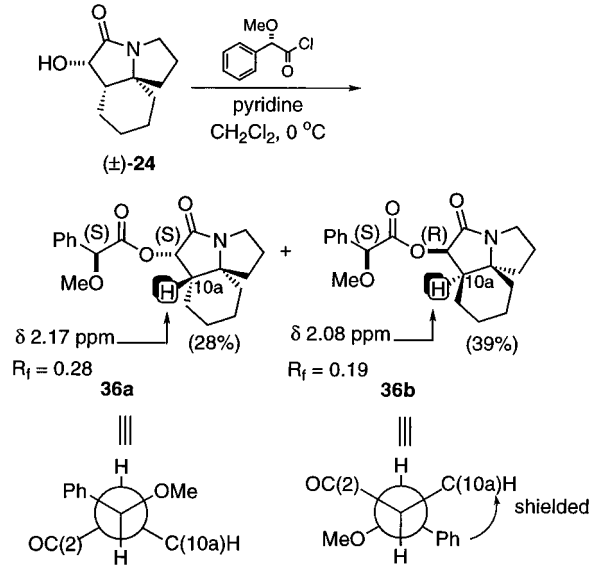
(12) (a) Pirkle, W. H.; Mahler, G.; Hyun, M. H. *J. Liq. Chromatogr.* **1986**, *9*, 443. (b) Pirkle, W. H.; Pochapsky, T. C.; Burke, J. A.; Deming, K. C. In *Chiral Separations*; Stevenson, D., Wilson, I. D., Eds; Plenum: New York, 1988; p 23. (c) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347.

(13) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J Org. Chem.* **1986**, *51*, 2370.

Scheme 18



Scheme 19

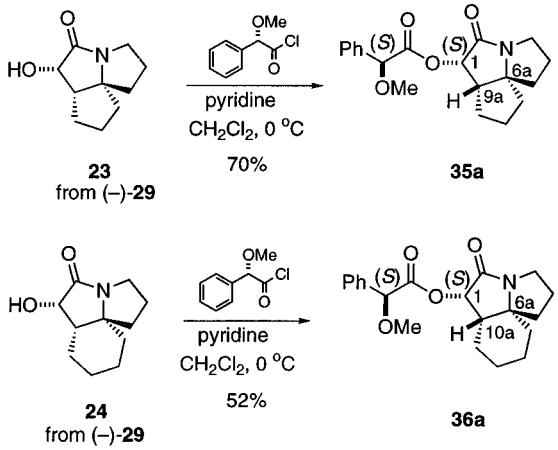


proton at HC(9a) and HC(10a), respectively, relative to their less polar diastereomeric partner. Examination of an "extended Newman projection" for these diastereomers shows that a shielding of HC(9a) and HC(10a), in **23** and **24**, respectively, by the phenyl ring is expected in the isomer with the 1*R*-configuration.

Treatment of enantiomerically enriched α-hydroxy lactams (−)-**23** and (−)-**24** with (S)-*O*-methylmandaloyl chloride and pyridine in CH_2Cl_2 afforded, by TLC and ^{1}H NMR comparison with authentic samples, esters **35a** and **35b** respectively, Scheme 20.

On the basis of this analysis, the enantiomerically enriched α-hydroxy lactams (−)-**23** and (−)-**24** obtained from the cycloaddition using MAPh and (−)-2-phenylcyclohexyl vinyl ether were assigned as possessing the (1*S*,6a*S*,9a*S*) and (1*S*,6a*S*,10a*S*) configurations, respectively. These assignments were corroborated by the observed chiral HPLC elution order for these compounds relative to their minor enantiomers. A large body of empirical data, recently supported by modeling, shows that, generally, the *S*-enantiomer is more strongly retained.[12b,c]

Scheme 20



Discussion

Preparation of 2-Nitroalkenes. Several problems became apparent with this nitromercuration strategy. First, incomplete conversion of the starting dienoates **5** and **9** to the intermediate nitromercurial was encountered. This may be a consequence of the insolubility of the nitromercurial causing entrainment of the starting material in the heterogeneous mixture. Unreacted starting material was recovered in all cases (ca. 10%) after chromatography. The addition of an organic solvent was not deemed suitable since it is known to retard the rate of nitromercuration.[5] Second, the nitromercuration step was found to give the products derived from both Markovnikov and anti-Markovnikov addition, thus necessitating a chromatographic separation after conversion to the nitroalkene. Third, base-mediated intramolecular (or intermolecular) Michael-addition to the α,β-unsaturated ester by the α-nitro anion competes with the desired elimination. The higher yields for the nonadienoate products (*E*)-**2** and (*Z*)-**2** relative to their octadienoate analogues (*E*)-**1** and (*Z*)-**1** may be ascribed, at least in part, to a reduction in the likelihood of the (proposed) intramolecular Michael addition upon increasing the chain length. The improvement in yield upon lengthening the methylene tether from three to four units is particularly apparent for the preparation of (*Z*)-**1** (4% yield) and (*Z*)-**2** (52%).

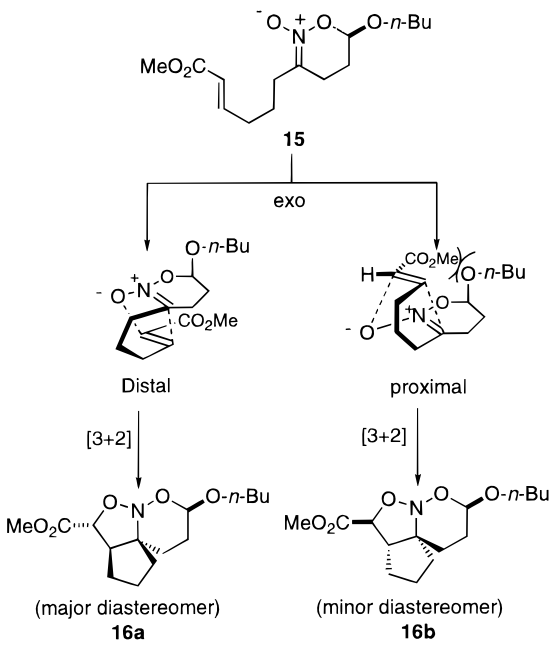
Tandem Cycloadditions. Our previous experience with 2,2-disubstituted 1-nitroalkenes[14] showed that the rate of the [4 + 2] cycloaddition is severely retarded by bulky substituents on the nitroalkene. Accordingly, we expected that substrates **1** and **2** should react rapidly. We were surprised, therefore, that the mild Lewis acid Ti(*i*-OPr)$_2$Cl$_2$ failed to induce reaction. Indeed, recent studies in these laboratories with nitroethylene have shown that aluminum and tin-based Lewis acids are the most effective for promoting [4 + 2] cycloaddition.[15] Presumably, this is related to the low Lewis basicity of unsubstituted nitroalkenes, which gives rise to a low equilibrium concentration of the reactive complex.[16] Accordingly, the [4 + 2] cycloaddition of **1** and **2** with both butyl vinyl ether and (−)-**29** proceeded readily at

(14) (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576. (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.

(15) Denmark, S. E.; Hurd, A. R. Manuscript submitted.

(16) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912.

Scheme 21



−78 °C with MAD and MAPh. The intermediate nitronates were not characterized as they underwent cycloaddition at room temperature or on warming in toluene. The overall chemical yield for this sequence was good (62−84%).

For the three-methylene-tethered precursors (*E*)-**1** and (*Z*)-**1**, the spirocyclic nitroso acetals **16** and **18** were formed with surprisingly high diastereoselectivities (distal/proximal, 35/1 and 10/1, respectively). The origin of the diastereoselectivity in this variant of the tandem inter [4 + 2]/intra [3 + 2] is fundamentally different from either the fused or the bridged modes and merits careful analysis. In the spiro-mode, the [4 + 2]-cycloaddition creates a single, new stereogenic center at the anomeric position (C(6)). Thus, unlike the fused mode or bridged mode, the dipolarophilic tether is not automatically predisposed to fold on one side or the other of the nitronate. Rather, the facial selectivity of the folding of the chain is solely controlled by the disposition of the substituent (butoxy group) on the anomeric center. The preferred pathway is that in which the dipolarophile tether approaches that face of the nitronate ring in the half-space opposite the butoxy group, Scheme 21.

The initial [4 + 2] cycloaddition between the nitroalkene and butyl vinyl ether results in the formation of nitronate **15** with a single stereogenic center at the anomeric position. Folding of the dipolarophile tether can then occur in an exo or endo fashion to either the proximal or the distal face of the nitronate ring. Exo folding is a significantly lower energy process, since the tether is attached to an sp^2 center. Endo folding is mechanically very difficult and would lead to a trans-fused 3.3.0 system. Should the dipolarophile tether fold to the proximal face of the nitronate, a significant unfavorable steric interaction results between the ester linkage on the tether and the butoxy group. However, folding of the dipolarophile tether to the distal face of the nitronate, opposite the butoxy group, alleviates this steric interaction and ultimately results in the formation of the major nitroso acetal **16a**. This also explains the observation that the (*Z*)-enoates display lower diastereoselectivities than their (*E*)-analogues. For the (*Z*)-enoate, proximal orientation of the dipolarophile tether positions the ester group on the same face but *away* from the butoxy substituent, Figure 4. This reduced steric interaction makes a proximal orientation of the (*Z*)-enoate less disfavored than the same orientation for the (*E*)-analogue resulting in reduced facial selectivity and, therefore, lower diastereoselectivity.

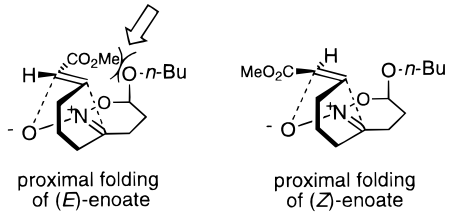
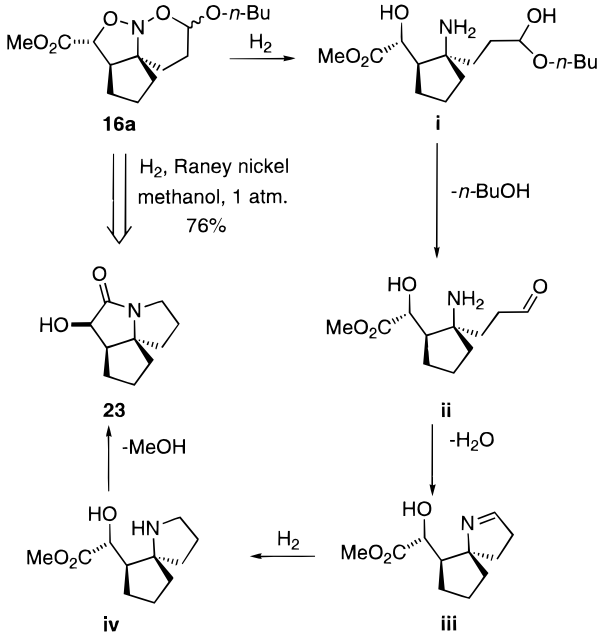


Figure 4. Steric interactions for (*Z*)- and (*E*)-enoates in a proximal folding alignment.

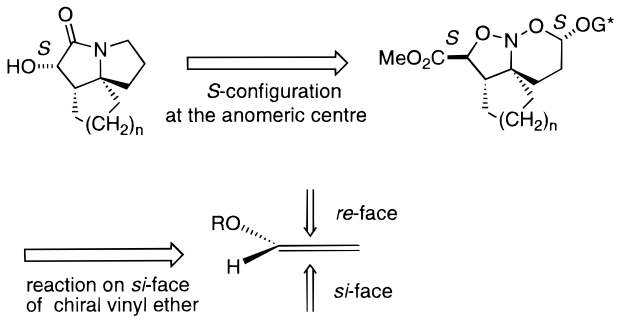
Scheme 22



The reduced diastereoselectivities for both (*E*)- and (*Z*)-nonadienoate substrates **2** relative to their respective lower homologs **1** (21/1 vs 35/1 and 3.5/1 vs 10/1) may be rationalized by the increased geometrical freedom attendant with increasing the length of the dipolarophile tether from three to four methylene units. This increased flexibility permits the enoate tether to more readily adopt an alignment that allows for effective orbital overlap but reduces unfavorable steric interactions. This ability to minimize these steric interactions, the origin of the diastereoselectivity, results in poorer distal/proximal face differentiation relative to the three methylene tether analogs and hence lower stereoselectivities.

The formation of the α-hydroxy lactam from the nitroso acetal is believed to proceed through a number of discrete intermediates. A plausible sequence of events for this transformation is shown in Scheme 22. Hydrogenolytic N−O bond cleavage of **16a** would form hemiacetal **i**, which upon loss of butanol would give amino aldehyde **ii**. Intramolecular imine formation **iii** and subsequent reduction would give amine **iv**, which upon lactamization yields α-hydroxy lactam product **23**. The α-hydroxy

Scheme 23



lactams formed were all colorless highly crystalline solids that were found to be stable indefinitely when stored in the freezer. The observation that mixtures of nitroso acetals give a single α-hydroxy lactam product indicates that the nitroso acetals generated in the tandem cycloaddition differ stereochemically only at the anomeric center (which, of course, is destroyed in the hydrogenolysis step).

Origin of Stereoselectivity in the Asymmetric Tandem Cycloaddition. With the knowledge of the absolute configuration of the α-hydroxy lactams (−)-**23** and (−)-**24** it is possible to infer the configuration of the anomeric center in the nitroso acetal from which it was created and from this identify which face of the vinyl ether is involved in the initial [4 + 2] cycloaddition reaction. This stereochemical "lineage" is shown in Scheme 23. The 1*S*-configuration at the secondary hydroxyl center in the α-hydroxy lactam products must necessarily derive from the nitroso acetal bearing the *S*-configuration at the anomeric center. Modeling shows that this configuration originates from a *si*-face attack on (−)-(1*R*,2*S*)-*trans*-2-phenylcyclohexyl vinyl ether (−)-**29** in the [4 + 2] cycloaddition step.

MM2 energy-minimized ground-state structures for the s-cis and s-trans conformations of (−)-**29** shows that in the s-cis conformation the phenyl ring shields the *si*-face of the vinyl ether; the *re*-face being exposed. In contrast, the s-trans conformation effectively shields the *re*-face; the *si*-face being readily accessible. Interestingly, MM2 calculations show that the two limiting conformations have almost identical energies in the ground state (s-cis 14.16 kcal/mol, s-trans 14.66 kcal/mol).

With the knowledge that to obtain the observed configuration in the α-hydroxy lactam products it is necessary to access the *si*-face of the vinyl ether (Scheme 23), four possible limiting transition-state complexes may be proposed to account for the observed configuration of the product nitroso acetal. These molecular "aggregations" are constructed by pairwise combinations of two vinyl ether conformations and exo or endo orientation of the auxiliary relative to the nitroalkene. For clarity, the bulky monomeric aluminum Lewis acid has been omitted, Scheme 24.

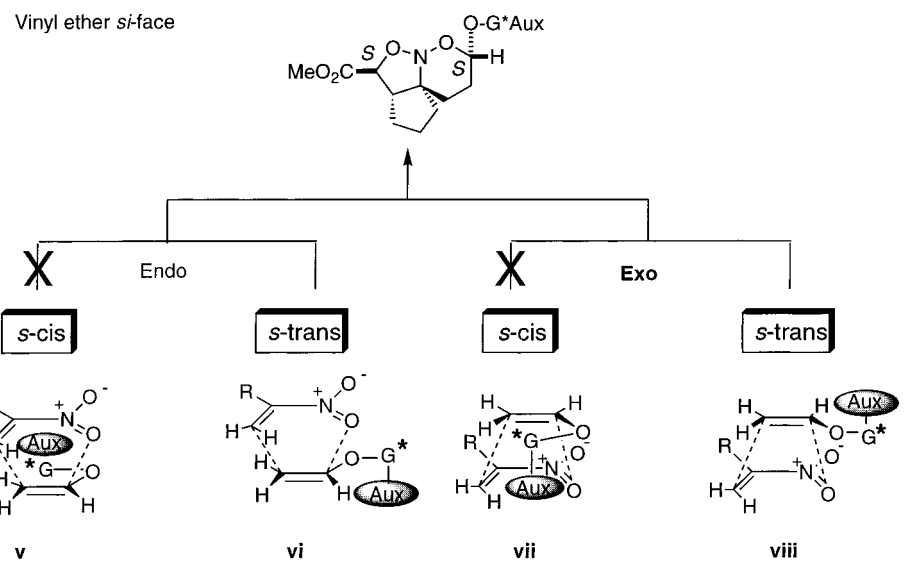
An endo orientation of vinyl ether (−)-**29** in the s-cis conformation **v** clearly places the phenyl ring directly between the vinyl ether and the diene, preventing reaction between the [2π]-system of the vinyl ether and the nitroalkene. A similar analysis for the s-cis conformation in the exo-mode **vii** again places the phenyl ring between the vinyl ether *si*-face and the nitroalkene. On the other hand, the s-trans conformation of the vinyl ether, in either the endo or exo mode (**vi** and **viii** respectively), places the phenyl ring away from the reacting vinyl ether *si*-face and the nitroalkene, making either of these pathways viable; both ultimately leading to the same product.

Thus, on the basis of this analysis, the [4 + 2] cycloaddition reaction, which leads to the *S*-configuration at the anomeric center, proceeds through either the s-trans-exo **viii** or the s-trans-endo **vi** orientation. It is impossible to unambiguously distinguish between these two pathways using this steric model alone. However, previous studies carried out in these laboratories have established the high exo-preference of MAPh, relative to MAD, in tandem [4 + 2]/[3 + 2] cycloaddition reactions using β-substituted nitroalkenes.

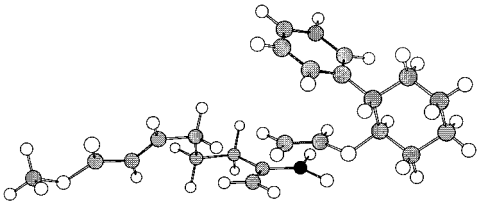
A similar exo preference may be reasonably expected with MAPh employing an α-substituted nitroalkene, and thus, by analogy with these previous studies, the initial [4 + 2] in the asymmetric spiro-mode tandem cycloaddition may be reasonably assumed to proceed through the s-trans-exo orientation **viii**. As pictorially represented in Scheme 25, this creates the anomeric center with the *S*-configuration.

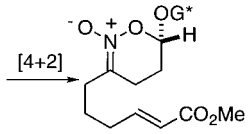
In an analogous fashion to the racemic variant discussed earlier, the [3 + 2] cycloaddition can then occur

Scheme 24



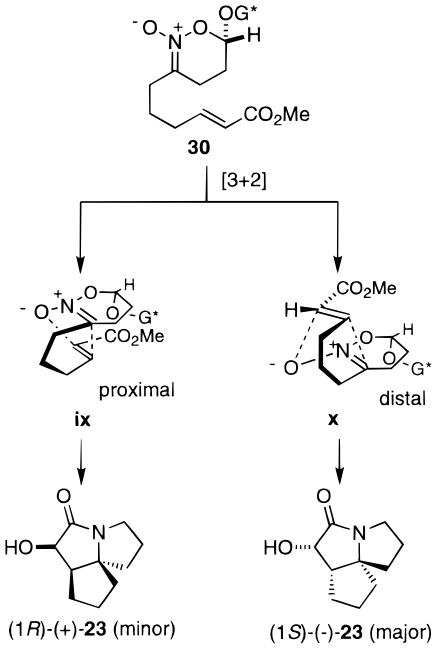
Scheme 25





30

Scheme 26



to either the distal or the proximal face of the nitronate ring in **30** relative to the auxiliary. A distal orientation places the dipolarophile tether on the opposite face of the nitronate ring relative to the auxiliary **x**, ultimately leading to the major α-hydroxy lactam. Folding of the dipolarophile tether to the proximal face of the nitronate ring relative to the auxiliary, **ix**, invokes an unfavorable steric interaction between the enoate and the auxiliary. The [3 + 2] cycloaddition via this latter pathway would lead to the minor α-hydroxy lactam enantiomer, Scheme 26.

On the basis of the product distribution alone, it is not possible to identify the origin of the erosion of diastereoselectivity in the tandem cycloaddition; imperfect asymmetric induction in the initial [4 + 2] cycloaddition and/or imperfect proximal/distal nitronate face selectivity in the [3 + 2] cycloaddition. Both are possible contributors and could be distinguished if the diastereomeric ratio of **30** were known.

The observation that asymmetric tandem cycloaddition using MAD as the Lewis acid produces α-hydroxy lactam **23** in racemic form (Schemes 14 and 15) can be understood on the basis of the poor diastereofacial bias found for (−)-**29** with this Lewis acid.[10a,b] With MAPh, the chiral vinyl ether (−)-**29** reacts in a highly *exo*-selective fashion via the s-trans conformation, thus exposing the *si*-face of the vinyl ether for cycloaddition. With MAD, on the other hand, (−)-**29** exhibits poor exo/endo and diastereofacial selectivity. In the exo-mode, the s-cis conformation of the vinyl ether is accessed, exposing the *re*-face of the vinyl ether (leading to the *R*-configuration at the anomeric center). In the endo-mode, the s-trans conformation of the vinyl ether is accessed, exposing the *si*-face of the vinyl ether (leading to the *S*-configuration at the anomeric center). This facial selectivity, which leads to enantiomorphic anomeric centers, explains the formation of racemic α-hydroxy lactam with MAD. The isolation of **30** from these reactions as a 1/1 mixture of diastereomers confirms the poor facial selectivity of the [4 + 2] event.

Conclusion

The spiro mode variant of the tandem inter [4 + 2]/intra [3 + 2] cycloaddition has been documented. 2-Nitroalkenes bearing unsaturated esters with three and four methylene tethers underwent tandem cycloaddition with vinyl ethers in the presence of MAD or MAPh as the Lewis acids. The stereochemical course of the intramolecular [3 + 2] reaction is determined by (1) the configuration of the anomeric center, (2) the length of the tether, and (3) the geometry of the dipolarophile. *E*-Dipolarophiles react more selectively than the *Z*-isomers and particularly when tethered to the nitronate by three methylene groups. The tandem sequence can be carried out with high enantioselectivity with chiral vinyl ether (−)-**29**. The origin of selectivity is the high diastereofacial bias for [4 + 2] cycloaddition with MAPh as the Lewis acid. This process allows simple access to azapropellanes with high selectivity.

Improvements in the overall process will require newer methods for the synthesis of 2-nitroalkenes and the employment of chiral auxiliaries of greater facial bias.[10d] In addition, applications to the synthesis of spirocyclic alkaloids are planned.

Experimental Section

General Methods. See the Supporting Information.

Methyl (*E*)-7-Nitro-2,7-octadienoate ((*E*)-1). To a stirred solution of sodium nitrite (1.29 g, 18.70 mmol) in distilled water (6 mL) at rt was added, dropwise, a solution of mercuric perchlorate trihydrate (4.25 g, 9.35 mmol) in water (6 mL). After 10 min, this clear yellow solution was added dropwise to a foil-covered flask containing a heterogeneous mixture of methyl (*E*)-2,7-octadienoate ((*E*)-**5**) (1.44 g, 9.35 mmol) and water (6 mL). The mixture was then mechanically stirred. After 24 h, CH_2Cl_2 (50 mL) was added and the organic layer washed with water (20 mL). The combined aqueous layers were then re-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phase was dried ($MgSO_4$). Removal of the solvent in vacuo afforded a viscous yellow oil (3.46 g) that was used immediately.

To a solution of this nitromercurial in CH_2Cl_2 (25 mL) in a foil-covered flask at rt was added, dropwise, triethylamine (957 μL, 6.92 mmol). After 20 min, the crude reaction mixture was filtered through a short pad of silica (40 mm × 60 mm), eluting with CH_2Cl_2 (100 mL) to remove precipitated mercury. Removal of the solvent by rotary evaporation and silica gel column chromatography (5%, 10%, 15% EtOAc/pentane) gave 162 mg (11%) of recovered methyl (*E*)-2,7-octadienoate (*E*)-**5** followed by the nitroalkene (*E*)-**1** 675 mg (36%), as a pale

yellow oil: ^{1}H NMR (300 MHz) δ 6.84 (m, 1 H,), 6.35 (s, 1 H), 5.75 (d, J = 15.5, 1 H), 5.50 (s, 1 H), 3.61 (s, 3 H), 2.53 (t, J = 7.7, 2 H), 2.19 (m, 2 H), 1.63 (m, 2 H); ^{13}C NMR (75.5 MHz) δ 166.44, 157.10, 147.44, 121.56, 117.38, 51.13, 30.88, 29.19, 25.22; IR (CCl_4) 1729 (s), 1661 (w), 1534 (s) cm^{-1}; MS (70 eV) m/z 168 (35), 91 (100); TLC R_f 0.28 (hexane/EtOAc, 4/1). Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.17; H, 6.59; N, 7.13.

Methyl (*Z*)-7-Nitro-2,7-octadienoate ((*Z*)-1). To a stirred solution of sodium nitrite (1.49 g, 21.58 mmol) in distilled water (6 mL) at rt was added, dropwise, a solution of mercuric perchlorate trihydrate (4.90 g, 10.79 mmol) in distilled water (6 mL). After 15 min, this clear yellow solution was added dropwise to a foil-covered flask containing a heterogeneous mixture of methyl (*Z*)-2,7-octadienoate ((*E*)-**5**) (1.51 g, 9.81 mmol) and water (6 mL). The mixture was then mechanically stirred. After 39 h, CH_2Cl_2 (80 mL) was added and the organic layer washed with water (60 mL). The combined aqueous layers were then back-extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic phase was dried ($MgSO_4$). Removal of the solvent in vacuo afforded a viscous yellow oil that was used immediately.

To a solution of this nitromercurial in CH_2Cl_2 (30 mL) in a foil-covered flask at rt was added, dropwise, triethylamine (1.09 mL, 7.90 mmol). After 30 min, the crude reaction mixture was filtered through a short pad of Florisil (50 mm × 60 mm), eluting with CH_2Cl_2 (300 mL) to remove precipitated mercury. Removal of the solvent by rotary evaporation and silica gel column chromatography (5%, 10%, 15% EtOAc/pentane) gave 74 mg (4%) of nitroolefin (*Z*)-**1** as an impure yellow oil: ^{1}H NMR (200 MHz) δ 6.43 (d, J = 1.6, 1 H), 6.24−6.14 (m, 1 H), 5.83 (br d, J = 11.9, 1 H), 5.58 (br s, 1 H), 3.70 (s, 3 H), 2.77−2.59 (m, 4 H), 1.77−1.66 (m, 2 H).

Methyl (*E*)-8-Nitro-2,8-nonadienoate ((*E*)-2). To a stirred solution of sodium nitrite (1.20 g, 17.38 mmol) in distilled water (8 mL) at rt was added, dropwise, a solution of mercuric perchlorate trihydrate (3.94 g, 8.69 mmol) in water (8 mL). After 10 min, this clear yellow solution was added dropwise to a foil-covered flask containing a heterogeneous mixture of methyl (*E*)-2,8-nonadienoate ((*E*)-**9**) (1.46 g, 8.69 mmol) and water (8 mL). The mixture was then mechanically stirred. After 22 h, CH_2Cl_2 (100 mL) was added and the organic layer washed with water (100 mL). The combined aqueous layers were then re-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phase was dried ($MgSO_4$). Removal of the solvent in vacuo afforded a viscous yellow oil (3.92 g) that was used immediately.

To a solution of this nitromercurial in CH_2Cl_2 (45 mL) in a foil-covered flask at rt was added, dropwise, triethylamine (1.05 mL, 7.62 mmol). After 25 min, the crude reaction mixture was filtered through a short pad of silica (40 mm × 50 mm), eluting with CH_2Cl_2 (200 mL) to remove precipitated mercury. Removal of the solvent by rotary evaporation and silica gel column chromatography (5%, 10%, 15% EtOAc/hexane) yielded 1.04 g (56%) of nitroolefin (*E*)-**2** as a pale yellow oil: ^{1}H NMR (300 MHz) δ 6.93 (dt, J = 7.0, 1 H), 6.42 (d, J = 1.5, 1 H), 5.82 (dt, J = 15.6, 1.1, 1 H), 5.54 (s, 1 H), 3.71 (s, 3 H), 2.60 (t, J = 6.3, 2 H), 2.23 (m, 2 H), 1.56 (m, 4 H); ^{13}C NMR (75.5 MHz) δ 166.64, 157.54, 148.35, 121.12, 117.03, 51.13, 31.13, 29.60, 27.02, 26.40; IR (CCl_4) 1728 (s), 1659 (s), 1532 (s) cm^{-1}; MS (70 eV) m/z 182 (37), 79 (100); TLC R_f 0.29 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.30; H, 7.09; N, 6.60.

Methyl (*Z*)-8-Nitro-2,8-nonadienoate ((*Z*)-2). To a stirred solution of sodium nitrite (541 mg, 7.83 mmol) in distilled water (3 mL) at rt was added, dropwise, a solution of mercuric perchlorate trihydrate (1.78 g, 3.92 mmol) in water (3 mL). After 10 min, this clear yellow solution was added dropwise to a foil-covered flask containing a heterogeneous mixture of methyl (*Z*)-2,8-nonadienoate ((*Z*)-**9**) (658 mg, 3.92 mmol) and water (3 mL). The mixture was then mechanically stirred. After 24 h, CH_2Cl_2 (40 mL) was added and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were then dried ($MgSO_4$). Removal of the solvent in vacuo afforded a viscous yellow oil (1.64 g) that was used immediately. To a solution of this nitromercurial in CH_2Cl_2 (12 mL) in a foil-covered flask at rt was added, dropwise, triethylamine (441 μL, 3.19 mmol). After 15 min, the crude reaction mixture was filtered through a short pad of silica (30 mm × 30 mm), eluting with CH_2Cl_2 (100 mL) to remove precipitated mercury. Removal of the solvent by rotary evaporation and silica gel column chromatography (5%, 10% EtOAc/hexane) afforded 437 mg (52%) of nitroolefin (*Z*)-**2** as a pale yellow oil: ^{1}H NMR (300 MHz) δ 6.33 (d, J = 1.5, 1 H), 6.14 (dt, J = 7.5, 1 H), 5.71 (dd, J = 11.5, 1.3, 1 H), 5.50 (s, 1 H), 3.61 (s, 3 H), 2.65−2.52 (m, 4 H), 1.54−1.42 (m, 4 H); ^{13}C NMR δ (75.5 MHz) 166.44, 157.70, 149.55, 119.55, 116.98, 50.77, 29.56, 28.07, 27.84, 26.45; IR (CCl_4) 1724 (s), 1701 (m), 1646 (s), 1530 (s) cm^{-1}; MS (70 eV) m/z 182 (26); TLC R_f 0.50 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.33; H, 7.08; N, 6.56.

Methyl (2*R,2a*R**,5a*R**)-8-Butoxyoctahydro-1,9-dioxa-9a-azacyclopent[*c*]indene-2-carboxylate (16).** To a solution of BHT (5.28 g, 24.0 mmol) in toluene (18 mL) at rt was slowly added Me_3Al (6.00 mL, 12 mmol, 2 M solution in toluene). The solution was then stirred at rt for 60 min.

To a solution of methyl (*E*)-7-nitro-2,7-octadienoate ((*E*)-**1**) (597 mg, 3.0 mmol) and butyl vinyl ether (2.43 mL, 18.0 mmol, 6.0 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added slowly, dropwise, freshly prepared MAD solution (18 mL, 9.0 mmol, 3.0 equiv). After 40 min, H_2O (20 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 3 min. CH_2Cl_2 (80 mL) was added and the organic phase washed with H_2O (2 × 60 mL). The combined aqueous phase was re-extracted with CH_2Cl_2 (50 mL), and the combined organic phase was washed with aqueous sodium potassium tartrate solution (100 mL) and dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo and the remaining toluene solution heated to 75 °C for 85 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (5%, 10%, 15% TBME/pentane) to furnish 677 mg (76%) of nitroso acetal **16** as a colorless viscous oil: ^{1}H NMR (300 MHz) δ 4.75 (br t, J = 2.5, 1 H), 4.31 (d, J = 3.1, 1 H), 3.87 (ddd, J = 10.0, 6.8, 4.9, 1 H), 3.74 (s, 3 H), 3.39 (ddd, J = 10.0, 6.8, 4.9, 1 H), 3.28 (m, 1 H), 2.15 (m, 1 H), 1.96−1.46 (m, 11 H), 1.35 (m, 2 H), 0.87 (t, J = 7.3, 3 H); ^{13}C NMR (75.5 MHz) δ 171.90, 99.68, 87.94, 84.07, 67.33, 52.26, 47.65, 38.71, 31.90, 31.41, 27.59, 25.41, 23.47, 19.15, 13.84; IR (CCl_4) 1738 (s), 1455 (m) cm^{-1}; MS (70 eV) m/z 226 (11); TLC R_f 0.41 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{15}H_{25}NO_5$ (299.37): C, 60.18; H, 8.42; N, 4.68; Found: C, 60.06; H, 8.37; N, 4.72.

Methyl (2*R,2a*S***S*,5a*S**)-8-Butoxyoctahydro-1,9-dioxa-9a-azacyclopent[*c*]indene-2-carboxylate (18).** To a solution of BHT (354 mg, 1.61 mmol) in toluene (1.6 mL) at rt was slowly added Me_3Al (402 μL, 0.80 mmol, 2 M solution in toluene). The solution was then stirred at rt for 20 min.

To a solution of methyl (*Z*)-7-nitro-2,7-octadienoate ((*Z*)-**1**) (40 mg, 0.2 mmol) and butyl vinyl ether (163 mL, 1.21 mmol, 6.0 equiv) in CH_2Cl_2 (1 mL) at −78 °C was added slowly, dropwise, freshly prepared MAD solution (1.5 mL, 0.6 mmol, 3.0 equiv). After 30 min, H_2O (2 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 5 min. CH_2Cl_2 (10 mL) was added and the organic phase washed with H_2O (2 × 5 mL). The combined aqueous phase was re-extracted with CH_2Cl_2 (5 mL), and the combined organic phase was washed with aqueous sodium potassium tartrate solution (100 mL) and dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo, and the remaining toluene solution was heated to 70 °C for 55 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (5%, 10% TBME/pentane) to furnish 37.4 mg (62%) of nitroso acetal **18** as a colorless viscous oil (isolated as an inseparable ca. 10/1 mixture of diastereomers): ^{1}H NMR (200 MHz) δ 5.30 (d, J = 7.6, 1 H), 4.88 (m, 1 H), 3.91−3.83 (m, 1 H), 3.77 (s, 3 H), 3.50−3.41 (m, 1 H), 2.86−2.72 (m, 1 H), 1.98−1.20 (m, 16 H), 0.90 (t, J = 7.3, 3 H); TLC R_f 0.61 (hexane/EtOAc, 4/1).

Methyl (2*R,2a*R**,6a*R**)-9-Butoxyoctahydro-1,10-dioxa-10a-azacyclohex[*c*]indene-2-carboxylate (20).** To a solution of BHT (2.32 g, 10.56 mmol) in toluene (5 mL) at rt was slowly added Me_3Al (2.64 mL, 5.28 mmol, 2 M solution in toluene). The solution was then stirred at rt for 45 min.

To a solution of methyl (*E*)-8-nitro-2,8-nonadienoate ((*E*)-**2**) (281 mg, 1.32 mmol) and butyl vinyl ether (1.07 mL, 7.92 mmol, 6.0 equiv) in CH_2Cl_2 (3 mL) at −78 °C was added slowly, dropwise, the freshly prepared MAD solution (5.6 mL, 3.9 mmol, 2.9 equiv). After 55 min, H_2O (20 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 2 min. CH_2Cl_2 (10 mL) was added and the organic phase washed with H_2O (2 × 10 mL). The combined aqueous phase was re-extracted with CH_2Cl_2 (10 mL) and the combined organic phase dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo, and the remaining toluene solution was heated to 70 °C for 240 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (10%, 15%, 20% EtOAc/pentane) to give nitroso acetal **20** 347 mg (84%) as a colorless viscous oil: ^{1}H NMR (300 MHz) δ 4.83 (t, J = 4.6, 1 H), 4.56 (d, J = 9.7, 1 H), 3.92 (ddd, J = 11.7, 6.9, 4.9, 1 H), 3.76 (s, 3 H), 3.43 (ddd, J = 11.7, 6.9, 4.9, 1 H), 2.92 (m, 1 H), 2.04−1.44 (m, 10 H), 1.41−1.19 (m, 6 H), 0.88 (t, J = 7.3, 3H); ^{13}C NMR (75.5 MHz) δ 171.60, 100.64, 82.61, 71.90, 67.49, 52.35, 43.44, 31.44, 30.67, 26.12, 24.19, 22.12, 21.03, 20.28, 19.15, 13.86; IR (CCl_4) 1736 (s), 1455 (s) cm^{-1}; MS (70 eV) *m*/*z* 240 (34), 121 (100); TLC R_f 0.26 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{16}H_{27}NO_5$ (313.40): C, 61.32; H, 8.68; N, 4.47. Found: C, 61.22; H, 8.68; N, 4.47.

Methyl (2*R,2a*S**,6a*S**)-9-Butoxyoctahydro-1,10-dioxa-10a-azacyclohex[*c*]indene-2-carboxylate (22).** To a solution of BHT (1.88 g, 8.56 mmol) in toluene (6 mL) at rt was slowly added Me_3Al (2.14 mL, 4.28 mmol, 2 M solution in toluene). The solution was then stirred at rt for 30 min.

To a solution of methyl (*Z*)-8-nitro-2,8-nonadienoate ((*E*)-**2**) (227 mg, 1.07 mmol) and butyl vinyl ether (860 mL, 6.39 mmol, 6.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C was added slowly, dropwise, the freshly prepared MAD solution (6 mL, 3.2 mmol, 3.0 equiv). After 40 min, H_2O (10 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 3 min. CH_2Cl_2 (10 mL) was then added, the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phase was dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo, and the remaining toluene solution was heated to 100 °C for 230 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (5%, 10% TBME/pentane) to afford 215 mg (64%) of nitroso acetal **22** as a colorless viscous oil (isolated as an inseparable ca.. 3.5:1 mixture of diastereomers): ^{1}H NMR (300 MHz) δ 4.98 (d, J = 11.4, 1 H), 4.84 (t, J = 5.2, 1 H), 4.69 (dd, J = 9.5, 1.9, 0.3 H), 3.94−3.85 (m, 1.3 H), 3.78 (s, 1.05 H), 3.77 (s, 3 H), 3.54 (m, 0.3 H), 3.43 (m, 1 H), 3.16 (m, 0.3 H), 2.31−1.18 (m, 20.2 H), 0.97−0.83 (m, 4 H); ^{13}C NMR (75.5 MHz) δ (major diastereomer) 170.92, 100.30, 81.67, 71.64, 67.44, 52.20, 42.65, 31.50, 30.34, 26.68, 24.30, 21.10, 20.85, 20.62, 19.27, 13.90. (minor diastereomer) 100.54, 81.30, 70.54, 69.50, 38.85, 33.10, 31.63, 27.06, 26.14, 21.15, 21.05, 19.08, 13.84, three carbons missing ((C(1″)), (C(2″)) and one CH_2)); IR (CCl_4) 1761 (s), 1736 (s) cm^{-1}; MS (70 eV) *m*/*z* 240 (35), 121 (100); TLC R_f 0.45 (EtOAc/hexane, 7/3). Anal. Calcd for $C_{16}H_{27}NO_5$ (313.40): C, 61.32; H, 8.68; N, 4.47. Found: C, 61.21; H, 8.74; N, 4.52.

(1*R,6a*R**,9a*R**)-Octahydro-1-hydroxy-2*H*-cyclopenta[*h*]pyrrolizin-2-one (23).** A heterogeneous mixture of nitroso acetal **16** (251 mg, 0.84 mmol) and methanol-washed Raney nickel (spatula tip) in methanol (15 mL) was stirred at rt under 1 atm of hydrogen for 37.5 h. The reaction mixture was filtered through a short pad of silica (30 mm × 40 mm), eluting with CH_2Cl_2 (150 mL) to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (40%, 60%, 80%, 100% EtOAc/pentane) and recrystallization (EtOAc/pentane) to yield 116 mg (76%) of hydroxy lactam **23** as a white crystalline solid: mp 139−140 °C; ^{1}H NMR (300 MHz) δ 5.55 (d, J = 5.2, 1 H), 4.41 (dd, J = 9.7, 5.2, 1 H), 3.57−3.47 (m, 1 H), 3.08−2.99 (m, 1 H), 2.55 (dt, J = 9.3, 2.7, 1 H), 2.20−2.15 (m, 1 H), 2.07−1.98 (m, 2 H), 1.81−1.63 (m, 2 H), 1.61−1.43 (m, 4 H), 1.36−1.26 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.55, 77.43, 72.64, 43.73, 40.46, 37.56, 35.61, 25.53, 25.30, 24.85; IR (KBr) 3287 (br), 1680 (s) cm^{-1}; MS (70 eV) *m*/*z* 182 (M^+ + 1, 12), 181 (M^+, 90), 152 (100); TLC R_f 0.18 (EtOAc). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.24): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.26; H, 8.38; N, 7.74.

(1*R,6a*R**,10a*R**)-Octahydro-1-hydroxy-2*H*-cyclohexa[*h*]pyrrolizin-2-one (24).** A hetereogeneous mixture of nitroso acetal **20** (593 mg, 1.89 mmol) and methanol-washed Raney nickel (spatula tip) in methanol (20 mL) was stirred at rt under an atmosphere of hydrogen at 160 psi for 21 h. The reaction mixture was filtered through a short pad of silica (30 mm × 15 mm), eluting with CH_2Cl_2 (150 mL) to remove the catalyst. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc) and recrystallization (EtOAc/hexane) to give 227 mg (75%) of hydroxy lactam **24** as a white crystalline solid: mp 180.5−182 °C; ^{1}H NMR (300 MHz) δ 5.77 (d, J = 4.9, 1 H), 4.13 (dd, J = 5.0, 6.1, 1 H), 3.46 (m, 1 H), 3.14 (m, 1 H), 2.52−1.41 (m, 11 H), 1.39−1.27 (m, 1 H), 1.20−1.03 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 174.51, 79.12, 69.82, 45.67, 39.87, 35.03, 34.69, 25.70, 23.17, 23.07, 22.13; IR (KBr) 3250 (br), 1671 (s) cm^{-1}; MS (70 eV) *m*/*z* 195 (M^+, 76), 152 (100); TLC R_f 0.22 (EtOAc). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.73; H, 8.72; N, 7.20.

(1*R,6a*S**,10a*S**)-Octahydro-1-hydroxy-2*H*-cyclohexa[*h*]pyrrolizin-2-one (25).** A hetereogeneous mixture of nitroso acetal **22** (141 mg, 0.45 mmol) and methanol-washed Raney nickel (spatula tip) in methanol (10 mL) was stirred at rt under an atmosphere of hydrogen at 160 psi for 36 h. The reaction mixture was filtered through a short pad of silica (10 mm × 10 mm), eluting with CH_2Cl_2 (400 mL) to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc) and recrystallization (EtOAc/hexane) to furnish 59 mg (76%) of hydroxy lactam **25** as a white crystalline solid: mp 106−108 °C; ^{1}H NMR (300 MHz) δ 4.52 (dd, J = 3.1, 11.2, 1 H), 3.93 (d, J = 3.5, 1 H), 3.57 (m, 1 H), 3.13 (m, 1 H), 2.19−1.12 (m, 13 H); ^{13}C NMR (125.8 MHz) δ 174.13, 73.65, 65.27, 51.97, 41.03, 35.43, 34.98, 25.03, 23.61, 22.79, 20.85; IR ($CDCl_3$) 1684 (s) cm^{-1}; MS (70 eV) *m*/*z* 196 (M^+ + 1, 11), 195 (M^+, 90), 152 (100); TLC R_f 0.23 (EtOAc). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.76; H, 8.78; N, 7.20.

(1*S,6a*R**,10a*R**)-Octahydro-1-*O*-[imidazoyl(thiocarbonyl)]-2*H*-cyclohexa[*h*]pyrrolizin-2-one (26).** A solution of hydroxy lactam (±)-**24** (71 mg, 0.36 mmol) and 1,1′-(thiocarbonyl)diimidazole (97 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) was heated under reflux for 44 h. The solution was cooled, the solvent removed in vacuo, and the residue purified by silica gel column chromatography (80%, EtOAc/hexane) and recrystallization (EtOAc/hexane) to give 44 mg (78%) of xanthate ester **26** as a white crystalline solid: mp 148−149 °C; ^{1}H NMR (300 MHz) δ 8.35 (s, 1 H), 7.64 (s, 1 H), 7.00 (s, 1 H), 6.58 (d, J = 11.6, 1 H), 3.64 (ddd, J = 13.8, 5.0, 4.1, 1 H), 3.16 (m, 1 H), 2.39 (br dd, J = 11.3, 3.2, 1 H), 2.22−1.38 (m, 11 H), 1.27−1.18 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 184.03, 166.90, 137.00, 130.79, 118.21, 81.63, 64.87, 50.04, 41.35, 35.39, 35.08, 24.90, 23.54, 22.46, 20.84; IR (CCl_4) 1721 (s) cm^{-1}; MS (70 eV) *m*/*z* 305 (M^+, 4), 194 (100). Anal. Calcd for $C_{15}H_{19}N_3O_5S$ (305.39): C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.80; H, 6.33; N, 13.65; S, 10.44.

(6a*R,10a*R**)-Octahydro-2*H*-cyclohexa[*h*]pyrrolizin-2-one (28).** To a refluxing solution of xanthate ester **26** (89 mg, 0.29 mmol) in benzene (12.5 mL) was added a solution of Bu_3SnH (102 μL, 0.35 mmol, 1.2 equiv) and AIBN (10 mg, 0.06 mmol, 5 mol %) in benzene (2.5 mL) over 4 h via syringe pump. The reaction was then heated under reflux for a further 13.5 h and cooled and the solvent removed in vacuo. The residue was then purified by silica gel column chromatography (40%, 60%, 80%, 100% EtOAc/hexane) to give 38 mg (73%) of tricyclic

lactam **28** as a colorless oil: ^{1}H NMR (300 MHz) δ 3.54−3.47 (m, 1 H), 3.08 (m, 1 H), 2.75 (m, 1 H), 2.29−2.04 (m, 4 H), 1.90−1.83 (m, 1 H), 1.74−1.33 (m, 8 H), 1.19−1.10 (m, 1 H); ^{13}C NMR (125.8 MHz) δ 173.45, 68.95, 43.09, 40.53, 39.17, 35.11, 33.33, 26.30, 25.56, 22.32, 20.53; MS (70 eV) *m*/*z* 179 (19), 137 (10), 136 (100), 95 (11), 67 (8), 42 (14).

(1*R,6a*R**,10a*R**)-Octahydro-1-*O*-[imidazoyl(thiocarbonyl)]-2*H*-cyclohexa[*h*]pyrrolizin-2-one (27).** A solution of hydroxy lactam (±)-**25** (40 mg, 0.21 mmol) and 1,1′-(thiocarbonyl)diimdazole (77 mg, 0.43 mmol, 2.1 equiv) in CH_2Cl_2 (5 mL) was heated under reflux for 16 h. The solution was cooled, the solvent removed in vacuo, and the residue purified by silica gel column chromatography (50%, 70%, 80%, 100% EtOAc/hexane) and recrystallization (EtOAc/hexane) to give 44 mg (78%) of xanthate ester **27** as a white crystalline solid: mp 141−143 °C; ^{1}H NMR (300 MHz) δ 8.35 (s, 1 H), 7.64 (m, 1 H), 7.06 (m, 1 H), 6.36 (d, J = 6.7, 1 H), 3.65 (ddd, J = 12.3, 8.0, 6.1, 1 H), 3.26 (m, 1 H), 2.46−2.41 (m, 1 H), 2.31−2.17 (m, 2 H), 2.15−1.88 (m, 3 H), 1.79−1.42 (m, 5 H), 1.37−1.11 (m, 2 H); ^{13}C NMR (75.5 MHz) δ 183.36, 167.45, 137.05, 131.08, 118.25, 86.67, 69.03, 44.65, 40.91, 35.06, 34.77, 25.82, 23.13, 22.65, 21.71; IR (KBr) 1694 (s) cm^{-1}; MS (10 eV) *m*/*z* 305 (M$^+$, 7), 194 (100); TLC R_f 0.24 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{15}H_{19}N_3O_2S$ (305.39): C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.88; H, 6.29; N, 13.68; S, 10.47.

(6a*R,10a*R**)-Octahydro-2*H*-cyclohexa[*h*]pyrrolizin-2-one (28).** To a refluxing solution of xanthate ester **27** (90 mg, 0.29 mmol) in benzene (12.5 mL) was added a solution of Bu_3SnH (112 μL, 0.38 mmol) and AIBN (9.8 mg, 0.06 mmol, 5 mol %) in benzene (2.5 mL) over 4 h by syringe pump. The reaction was then heated under reflux for a further 14 h and cooled and the solvent removed in vacuo. The residue was then purified by silica gel column chromatography (EtOAc) to give 44 mg (85%) of tricyclic lactam **28** as a colorless oil. The chromatographic and spectroscopic data for **28** were consistent with those for **28** isolated from the reaction of xanthate **26**.

Methyl (2*S*,2a*S*,5a*S*,8*S*)-8-[[(1*R*,2*S*)-2-Phenylcyclohexyl]oxy]-1,9-dioxa-9a-azacyclopent[*c*]indene-2-carboxylate (31). To a solution of 2,6-diphenylphenol (2.85 g, 11.60 mmol) in toluene (17.1 mL) at rt was slowly added Me_3Al (2.90 mL, 5.80 mmol, 2 M solution in toluene). The solution was then stirred at rt for 25 min.

To a solution of methyl (*E*)-7-nitro-2,7-octadienoate ((*E*)-**1**) (289 mg, 1.45 mmol) and (1*R*,2*S*)-[(2-phenylcyclohexyl)oxy]-ethene (−)-**29** (880 mg, 4.36 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added slowly, dropwise, the freshly prepared MAPh solution (15 mL, 4.35 mmol, 3.0 equiv). After 55 min, H_2O (20 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 3 min. CH_2Cl_2 (30 mL) and water (50 mL) were then added, the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phase dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo, and the remaining toluene solution was heated to 80 °C for 135 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (10%, 20%, 30% EtOAc/hexane) to give 569 mg (98%) of nitroso acetal **31** as a white solid as a mixture of diastereomers: mp 111−122 °C. A portion (58 mg) of this material was recrystallized (EtOAc/hexane) to give 47 mg of a highly crystalline white solid: mp 135−137 °C; ^{1}H NMR (300 MHz) δ 7.27−7.14 (m, 5 H), 4.27 (d, J = 3.0, 1 H), 3.98 (t, J = 3.9, 1 H), 3.72 (s, 3 H), 3.69−3.60 (m, 1 H), 3.16−3.13 (m, 1 H), 2.56−2.47 (1 H, m), 2.42−2.38 (1 H, m), 2.03−1.18 (17 H, m); ^{13}C NMR (75.5 MHz) δ 171.96, 144.58, 127.94, 127.88, 126.08, 100.47, 87.93, 84.08, 81.00, 52.26, 51.42, 47.98, 38.75, 34.08, 32.93, 32.07, 27.70, 25.91, 25.25, 25.03, 23.62; IR (KBr) 1728 (s), 1447 (s) cm^{-1}; MS (70 eV) *m*/*z* 195 (13), 91 (100); TLC R_f 0.49 (major diastereomer), 0.45 (minor diastereomer) (EtOAc/hexane, 7/3). Anal. Calcd for $C_{23}H_{31}NO_5$ (401.50): C, 68.80; H, 7.78; N, 3.49. Found: C, 68.74; H, 7.80; N, 3.52.

Methyl (2*S*,2a*S*,6a*S*,9*S*)-9-[(1*R*,2*S*)-2-Phenylcyclohexyoxy]-1,10-dioxa-10a-azacyclohex[*c*]indene-2-carboxylate (33). To a solution of 2,6-diphenylphenol (2.74 g, 11.12 mmol) in toluene (17.2 mL) at rt was slowly added Me_3Al (2.78 mL, 5.56 mmol, 2M solution in toluene). The solution was then stirred at rt for 25 min.

To a solution of methyl (*E*)-8-nitro-2,8-nonadienoate (*E*)-**2** (296 mg, 1.39 mmol) and (1*R*,2*S*)-[(2-phenylcyclohexyl)oxy]-ethene (−)-**29** (842 mg, 4.17 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added slowly, dropwise, the freshly prepared MAPh solution (14 mL, 3.9 mmol, 2.8 equiv). After 40 min, H_2O (20 mL) was added at −78 °C, the cooling bath removed, and the mixture allowed to stir for 2 min. Water (30 mL) was then added, the aqueous phase extracted with CH_2Cl_2 (2 × 60 mL), and the combined organic phase dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo, and the remaining toluene solution was heated to 75 °C for 240 min. The mixture was cooled, the toluene removed in vacuo, and the residue purified by silica gel column chromatography (10%, 15%, 20%, TBME/pentane) to afford 545 mg (95%) of nitroso acetal **33** as a colorless, viscous oil: ^{1}H NMR (300 MHz) δ 7.38−7.13 (m, 5 H), 4.52 (d, J = 9.8, 1 H), 4.09 (t, J = 5.2, 1 H), 3.77 (s, 3 H), 3.71−3.63 (m, 2 H), 2.77 (br dd, J = 9.6, 3.7, 1 H), 2.57−2.40 (m, 2 H), 1.97−1.17 (m, 18 H); ^{13}C NMR (75.5 MHz) δ 171.29, 144.23, 127.69, 127.59, 125.71, 101.35, 82.28, 81.20, 71.62, 52.02, 51.09, 43.57, 34.07, 32.50, 30.19, 25.99, 25.65, 24.98, 23.65, 21.77, 20.80, 20.03; IR (CCl_4) 1734 (s), 1451 (s) cm^{-1}; MS (70 eV) *m*/*z* 209 (11), 91 (100); TLC R_f 0.43 (hexane/EtOAc, 7/3). Anal. Calcd for $C_{24}H_{33}NO_5$ (415.53): C, 69.37; H, 8.01; N, 3.37. Found: C, 69.52; H, 8.23; N, 3.25.

(−)-(1*S*,6a*S*,9a*S*)-Octahydro-1-hydroxy-2*H*-cyclopenta[*h*]pyrrolizin-2-one ((−)-23). A heterogeneous mixture of nitroso acetal **31** (161 mg, 0.40 mmol) and methanol-washed Raney nickel (spatula tip) in methanol (15 mL) was stirred at room under an atmosphere of hydrogen (160 psi) for 14.5 h. The reaction mixture was filtered through a short pad of silica (20 mm × 10 mm, eluting with CH_2Cl_2 (200 mL)) to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (80%, 100% EtOAc/pentane) to give 70 mg (98%) of recovered (−)-2-phenylcyclohexanol and 57 mg (78%) of hydroxy lactam (−)-**23** as a white crystalline solid. The chromatographic and spectroscopic data for hydroxy lactam (−)-**23** were consistent with those for (±)-**23** isolated from the reaction of (±)-**16** and it also displayed $[\alpha]_D$ −90.65° (1.0, $CHCl_3$).

(−)-(1*S*,6a*S*,9a*S*)-Octahydro-1-hydroxy-2*H*-cyclohexa[*h*]pyrrolizin-2-one ((−)-24). A heterogeneous mixture of nitroso acetal **33** (247 mg, 0.60 mmol) and methanol-washed Raney nickel (spatula tip) in methanol (15 mL) was stirred at room under an atmosphere of hydrogen (160 psi) for 17 h. The reaction mixture was filtered through a short pad of silica (20 mm × 10 mm, eluting with CH_2Cl_2 (150 mL)) to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc) to give 99 mg (94%) of recovered (−)-2-phenylcyclohexanol and 87 mg (75%) of hydroxy lactam (−)-**24** as a white crystalline solid. The chromatographic and spectroscopic data for hydroxy lactam (−)-**24** were consistent with those for (±)-**24** isolated from the reaction of (±)-**20**, and it also displayed $[\alpha]_D$ −83.27° (1.0, $CHCl_3$).

(1*R,6a*R**,9a*R**)-3,5-Dinitro-*N*-[(octahydro-2-oxo-2*H*-cyclopenta[*h*]pyrrolizin-1-yl)oxy]benzamide (32).** A solution 3,5-dinitrobenzoyl azide (170 mg, 0.716 mmol) in toluene (6 mL) was heated under reflux for 10 min. To this was added a solution of hydroxy lactam (±)-**23** (108 mg, 0.60 mmol) in toluene (2 mL) and the mixture refluxed for 75 min during which time a pale yellow precipitate formed. The solution was cooled, the solvent removed in vacuo, and the residue was purified by silica gel column chromatography (50%, 100%, EtOAc/hexane) and recrystallization (EtOAc/hexane) to give 171 mg (73%) of carbamate (±)-**32** as a pale yellow crystalline solid: mp 241−243 °C; ^{1}H NMR (300 MHz) δ 10.14 (br, 1 H), 8.66 (s, 2 H), 8.64 (s, 1 H), 5.55 (d, J = 10, 1 H), 3.75 (m, 1 H), 3.17 (m, 1 H), 2.87 (m, 1 H), 2.72 (m, 1 H), 2.18 (m, 1 H), 1.95 (m, 1 H), 1.83−1.43 (m, 6 H); ^{13}C NMR (125.8 MHz) δ 171.68, 152.56, 148.71, 141.27, 117.97, 112.48, 78.12, 74.95, 42.37, 41.12, 37.66, 35.63, 26.47, 25.51, 25.11; IR (KBr) 3196 (m), 1740 (s), 1680 (s) cm^{-1}; MS (70 eV) *m*/*z* 209 (100); TLC R_f 0.27

(hexane/EtOAc, 2/1); HPLC t_R (±)-**32** 6.93 and 15.28 min (column B, hexane/EtOAc, 65/35, 1.5 mL/min). Anal. Calcd for $C_{17}H_{18}N_4O_7$ (390.35): C, 52.31; H, 4.65; N, 14.35. Found: C, 52.29; H, 4.62%, N, 14.33.

(1*R,6a*R**,10a*R**)-3,5-Dinitro-*N*-[(octahydro-2-oxo-2*H*-cyclohexa[*h*]pyrrolizin-1-yl)oxy]benzamide (34).** A solution 3,5-dinitrobenzoyl azide (158 mg, 0.67 mmol) in toluene (7 mL) was heated under reflux for 10 min. To this was added a solution of hydroxy lactam (±)-**24** (118 mg, 0.61 mmol) in toluene (2 mL) and the mixture refluxed for 75 min, during which time a pale yellow precipitate formed. The solution was cooled, the solvent removed in vacuo, and the residue purified by silica gel column chromatography (50%, 100% EtOAc/hexane) and recrystallization (EtOAc/hexane) to yield 223 mg (91%) of carbamate (±)-**34** as a pale yellow crystalline solid: mp 262−265 °C; ^{1}H NMR (300 MHz) δ 10.11 (br s, 1 H), 8.70−8.63 (m, 3H), 5.62 (d, J = 6.9, 1 H), 3.64 (ddd, J = 12.2, 8.0, 6.2, 1 H), 3.17 (m, 1 H), 2.31−2.26 (m, 2 H), 2.10−2.02 (m, 1 H), 1.94−1.20 (m, 10 H); ^{13}C NMR (125.8 MHz) δ 169.47, 152 37, 148.76, 141.24, 117.84, 112.60, 80.31, 70.06, 44.23, 40.50, 35.15, 34.69, 26.03, 22.78, 22.68, 22.26; IR (KBr) 3193 (m), 1738 (s), 1676 (s) cm^{-1}; MS (70 eV) *m*/*z* 209 (100); TLC R_f 0.26 (hexane/EtOAc, 2/1); HPLC t_R (±)-**34** 9.06 and 17.35 min (column B, hexane/EtOAc, 7/3, 1.5 mL/min). Anal. Calcd for $C_{18}H_{20}N_4O_7$ (404.38): C, 53.46; H, 4.99; N, 13.86. Found: C, 53.35; H, 4.94; N, 13.83.

(−)-(1*S*,6a*S*,9a*S*)-3,5-Dinitro-[(octahydro-2-oxo-2*H*-cyclopenta[*h*]pyrrolizin-1-yl)oxy]benzamide ((−)-32). A solution 3,5-dinitrobenzoyl azide (25 mg, 0.11 mmol) in toluene (2 mL) was heated under reflux for 10 min. To this was added a solution of hydroxy lactam (−)-**23** (16 mg, 0.09 mmol) in toluene (1 mL) and the mixture refluxed for 110 min during which time a solid precipitated. The solution was cooled, the solvent removed in vacuo, and the residue purified by silica gel column chromatography (50%, 70%, 100% EtOAc/hexane) to give benzamide **32** 24 mg (71%) as a white solid. The chromatographic and spectroscopic data for benzamide (−)-**32** were consistent with those for (±)-**32** isolated from the reaction of (±)-**23**: TLC R_f 0.30 (hexane/EtOAc, 1/1); HPLC t_R (1*R*)-**32**, 7.08 min (8.2%); t_R (1*S*)-**32**, 15.20 min (91.8%) (column B, hexane/EtOAc, 65/35, 1.5 mL/min).

(−)-(1*S*,6a*S*,10a*S*)-3,5-Dinitro-*N*-[(octahydro-2-oxo-2*H*-cyclohexa[*h*]pyrrolizine-1-yl)oxy]benzamide ((−)-34). A solution of 3,5-dinitrobenzoyl azide (15 mg, 0.06 mmol) in toluene (1 mL) was heated under reflux for 10 min. To this was added a solution of hydroxy lactam (−)-**24** (10 mg, 0.05 mmol) in toluene (1 mL), and the mixture was heated to reflux for 65 min. The solution was cooled, the solvent removed in vacuo, and the residue purified by silica gel column chromatography (50%, 70%, 100% EtOAc/hexane) to give carbamate (−)-**34** (19 mg, 91%) as an off-white solid. The chromatographic and spectroscopic data for carbamate (−)-**34** were consistent with those for (±)-**34** isolated from the reaction of (±)-**34**: TLC R_f 0.22 (hexane/EtOAc, 1/1); HPLC t_R (1*R*)-**34**, 9.3 min (5.6%); t_R (1*S*)-**34**, 17.2 min (94.4%) (column B, 30% hexane/EtOAc, 7/3, 1.8 mL/min).

(1*S*,6a*S*,9a*S*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclopenta[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (35a) and (1*R*,6a*R*,9a*R*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclopenta-[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (35b). To a solution of DMF (93 μL, 1.20 mmol) in acetonitrile (3 mL) at 0 °C was added oxalyl chloride (77 μL, 0.88 mmol) dropwise. After 2 min, a solution of (S)-(+)-α-methoxyphenylacetic acid (133 mg, 0.80 mmol, 1 equiv) in acetonitrile (1 mL) was added and the mixture allowed to stir at 0 °C for 15 min. To this was then added a solution of hydroxy lactam (±)-**23** (145 mg, 0.80 mmol) and pyridine (129 μL, 1.60 mmol, 2 equiv) in acetonitrile (1 mL). After 55 min, CH_2Cl_2 (30 mL) was added and the organic layer washed with aqueous saturated $CuSO_4$ solution (2 × 30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (40%, 50%, 605, 70% EtOAc/pentane) to give 105 mg (40%) of **35a** and 118 mg (45%) of **35b** as a separable mixture of diastereomers. Data for less polar diastereomer **35a**: mp 101−102 °C; ^{1}H NMR (300 MHz) δ 7.51−7.47 (m, 2 H), 7.40−7.32 (m, 3 H), 5.38 (d, J = 9.8, 1 H), 4.90 (s, 1 H), 3.63 (m, 1 H), 3.48 (s, 3 H), 3.11 (m, 1 H), 2.74 (m, 1 H), 2.15−2.03 (m, 2 H), 1.86−1.77 (m, 2 H), 1.63−1.33 (m, 6 H); ^{13}C NMR (125.8 MHz) δ 170.74, 170.22, 135.72, 128.70, 128.51, 126.87, 82.64, 77.33, 74.84, 57.61, 42.75, 41.02, 37.58, 35.88, 26.11, 25.41, 25.39; IR (KBr) 3457 (m), 1715 (s), 1455 (s) cm^{-1}; MS (70 eV) 121 (100); TLC R_f 0.36 (hexane/EtOAc, 7/3); HPLC t_R 9.28 min (column A, EtOAc/hexane, 1/1, 1.5 mL/min). Anal. Calcd for $C_{19}H_{23}NO_4$ (329.40): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.25; H, 7.09; N, 4.21.

Data for more polar diastereomer **35b**: mp 98−99 °C; ^{1}H NMR (300 MHz) δ 7.49−7.45 (m, 2 H), 7.39−7.33 (m, 3 H), 5.40 (d, J = 9.7, 1 H), 4.93 (s, 1 H), 3.63 (m, 1 H), 3.44 (s, 3 H), 3.13 (m, 1 H), 2.65 (m, 1 H), 2.13−1.98 (m, 2 H), 1.82−1.76 (m, 1 H), 1.66−1.48 (m, 2 H), 1.28−1.06 (m, 4 H), 0.72−0.66 (m, 1 H); ^{13}C NMR (125.8 MHz) δ 170.83, 169.79, 136.10, 128.81, 128.56, 127.41, 81.81, 77.37, 74.96, 57.40, 42.91, 40.98, 37.44, 35.90, 25.58, 25.41, 25 17; MS (70 eV) *m*/*z* 121 (100); TLC R_f 0.26 (hexane/EtOAc, 7/3); HPLC t_R 24.30 min (column A, EtOAc/hexane, 1/1, 1.5 mL/min). Anal. Calcd for $C_{19}H_{23}NO_4$ (329.40): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; H, 6.99; N, 4.21.

(1*S*,6a*S*,10*S*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclohexa-[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (36a) and (1*R*,6a*R*,10*R*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclohexa-[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (36b). To a solution of DMF (77 μL, 0.93 mmol) in acetonitrile (2 mL) at 0 °C was added oxalyl chloride (63 μL, 0.73 mmol) dropwise. After 2 min, a solution of (*S*)-(+)-α-methoxyphenylacetic acid (110 mg, 0.66 mmol) in acetonitrile (1 mL) was added and the mixture allowed to stir at 0 °C for 15 min. To this was then added a solution of hydroxy lactam (±)-**24** (145 mg, 0.66 mmol) and pyridine (107 μL, 1.32 mmol, 2 equiv) in acetonitrile (1 mL). After 70 min, CH_2Cl_2 (20 mL) was added and the organic layer washed with aqueous saturated $CuSO_4$ solution (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (40%, 50%, 60%, 70% EtOAc/pentane) to give 63 mg (28%) of **36a** and 89 mg (39%) of **36b** as a separable mixture of diastereomers.

Data for less polar diastereomer **36a** (contaminated with an inseparable, unidentified, impurity): ^{1}H NMR (300 MHz) δ 7.46−7.31 (m, 5 H), 5.40 (d, J = 6.6, 1 H), 4.86 (s, 1 H), 3.60−3.51 (m, 1 H), 3.46 (s, 3 H), 3.18 (m, 1 H), 2.23−1.07 (m, 13 H); ^{13}C NMR (100 MHz) δ 170.08, 160.06, 135.64, 128.71, 128.58, 126.90, 82.81, 80.17, 69.01, 57.11, 44.56, 40.58, 35.10, 34.50, 25.85, 22.85, 22.30, 1.97; IR (CCl_4) 1736 (s), 1709 (s) cm^{-1}; MS (70 eV) *m*/*z* 122 (15), 121 (100); TLC R_f 0.28 (hexane/EtOAc, 3/2). Data for more polar diastereomer **36b**: mp 120.5−121 °C; ^{1}H NMR (300 MHz) δ 7.47−7.28 (m, 5 H), 5.53 (d, J = 6.7, 1 H), 4.84 (s, 1 H), 3.61−3.45 (m, 1 H), 3.43 (s, 3 H), 3.21−3.12 (m, 1 H), 2.20−2.04 (m, 3 H), 1.89−1.82 (m, 1 H), 1.50−1.18 (m, 6 H), 1.03−0.85 (m, 2 H), 0.25−0.16 (m, 1 H); ^{13}C NMR (125 MHz) δ 169.64, 168.91, 135.83, 128.86, 128.61, 127.62, 82.23, 79.96, 69.00, 57.63, 44.66, 40.55, 34.97, 33.62, 25.77, 22.23, 21.52, 20.96; MS (70 eV) *m*/*z* 299 (4), 121 (100); TLC R_f 0.19 (hexane/EtOAc, 3/2). Anal. Calcd for $C_{20}H_{25}NO_4$ (343.42): C, 69.95; H, 7.34; N, 4.08. Found: C, 69.80; H, 7.33; N, 3.99.

(1*S*,6a*S*,9a*S*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclopenta[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (35a). To a solution of (*S*)-(+)-α-methoxyphenylacetyl chloride (13 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a solution of hydroxy lactam (−)-**51** (11 mg, 0.06 mmol) and pyridine (10 μL, 0.12 mmol, 2 equiv) in CH_2Cl_2 (0.2 mL). After 65 min, CH_2Cl_2 (5 mL) was added and the organic phase washed with aqueous copper sulfate solution (2 × 5 mL). The aqueous phase was reextracted with CH_2Cl_2 (5 mL) and dried and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (40%, 50%, 60% EtOAc/hexane) to give 14 mg (70%) of mandelate ester **35a**. The chromatographic and spectroscopic data for mandelate **35a** were consistent with those for the less polar diastereomer **35a** derived from the reaction of (±)-**23**.

(1*S*,6a*S*,10*S*)-α-Methoxyoctahydro-2-oxo-2*H*-cyclohexa-[*h*]pyrrolizin-1-ylbenzeneacetic Acid Ester (36a). To a solution of (*S*)-(+)-α-methoxyphenylacetyl chloride (12.5 mg, 0.07 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C was added a solution of hydroxy lactam (−)-**24** (12 mg, 0.06 mmol) and pyridine (10 μL, 0.12 mmol) in CH_2Cl_2 (0.5 mL). After 70 min, CH_2Cl_2 (5 mL) was added and the organic phase washed with aqueous copper sulfate solution (2 × 5 mL). The aqueous phase was reextracted with CH_2Cl_2 (5 mL) and dried and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (40%, 50%, 60% EtOAc/hexane) to give 11 mg (52%) of mandelate ester **36a**. The chromatographic and spectroscopic data for mandelate **36a** were consistent with those for the less polar diastereomer **36a** derived from the reaction of (±)-**24**.

Acknowledgment. We are grateful to the National Institutes of Health (GM-30938) for generous financial support. We also thank Alexander R. Hurd for a critical reading of the manuscript.

Supporting Information Available: General experimental details, complete ^1H and ^{13}C NMR assignments, and IR and MS data for all characterized compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9719057