Nitroalkene Inter [4 + 2]/Intra [3 + 2] Tandem Cycloadditions. 7. Application of (*R*)-(−)-2,2-Diphenylcyclopentanol as the Chiral Auxiliary

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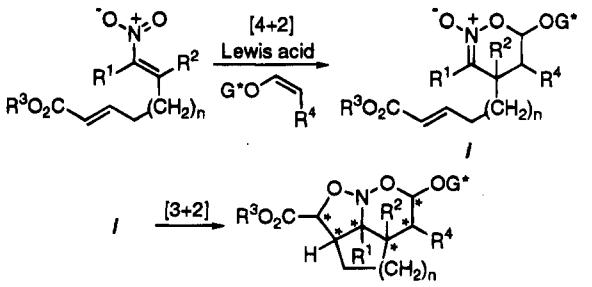
Chiral enol ethers derived from (*R*)-(−)-2,2-diphenylcyclopentanol ((−)-**3**) have been found to provide high levels of asymmetric induction in tandem inter [4 + 2]/intra [3 + 2] nitroalkene cycloadditions. The chiral auxiliary (>97% ee) is readily prepared in three steps from diphenylacetonitrile employing an asymmetric oxazaborolidine-catalyzed borane reduction. Either enantiomeric series of tandem cycloaddition/hydrogenolysis product **7** is available from the chiral auxiliary of a single absolute configuration by judicious selection of the Lewis acid promoter, Ti(O-*i*-Pr)$_2$Cl$_2$ (98% ee, (−)-**7**) or MAPh (93% ee, (+)-**7**). Propenyl ethers derived from (−)-**3** undergo endo selective [4 + 2] cycloadditions (2.3/1 − 8.2/1) in the presence Ti(O-*i*-Pr)$_2$Cl$_2$; however, exo selective [4 + 2] cycloadditions (10.2/1 − 54.8/1) are observed in the presence of MAPh.

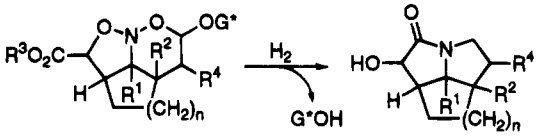
Introduction and Background

Tandem cycloaddition strategy allows for the rapid construction of subsets of polycyclic systems starting from a single acyclic design.[1] In a tandem reaction, each subsequent step occurs by virtue of structural changes in the components as a result of the previous reaction. The tandem heterodiene [4 + 2]/dipolar [3 + 2] cycloaddition chemistry of nitroalkenes is a representative example of this reaction class.[2] The inverse electron-demand [4 + 2] cycloaddition of a 1-nitroalkene with an electron-rich enol ether promoted by a Lewis acid affords a cyclic nitronic ester (nitronate) ***i***, Scheme 1. Subsequent dipolar [3 + 2] cycloaddition of the nitronate with a tethered olefin leads to the construction of a tricyclic nitroso acetal. Variations in the system such as dienophile substitution and geometry, tether length, and dipolarophile substitution and geometry allow for access to a wide range of structural motifs. By virtue of the tandem process, six contiguous stereogenic centers are formed, three of which are controlled by the outcome of the [4 + 2] cycloaddition. The use of a chiral, nonracemic enol ether as the dienophile for the [4 + 2] cycloaddition allows for control of these stereogenic centers in an absolute sense. Recently, the ability to modify the sense of asymmetric induction by changing the Lewis acid promoter, Ti(O-*i*-Pr)$_2$Cl$_2$ or methyl aluminum bis(2,6-diphenylphenoxide) (MAPh), was documented.[2c,e,3] The resulting nitroso acetals may be transformed into tricyclic α-hydroxy lactams by hydrogenolysis with recovery of the chiral auxiliary, Scheme 2.

Scheme 1



Scheme 2



In the original demonstration of this approach, vinyl and propenyl ethers prepared from camphor-derived chiral auxiliary **1** were employed.[2b] The tandem cycloaddition between vinyl ether **4** and nitroalkene **6** promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ followed by intramolecular [3 + 2] cycloaddition and hydrogenolysis afforded tricyclic α-hydroxy lactam (−)-**7** in 98% enantiomeric excess (1*S*,5a*S*,7a*S*,7b*R*), Scheme 3. In contrast, the same cycloaddition promoted by MAPh afforded the α-hydroxy lactam (+)-**7** of the opposite configuration (1*R*,5a*R*,7a*R*,7b*S*) in 99% ee. Through the use of propenyl ethers this reversal of stereoselectivity has been attributed to a highly endo selective [4 + 2] cycloaddition in the case of Ti(O-*i*-Pr)$_2$Cl$_2$ as opposed to an exo selective cycloaddition with MAPh.[2e] Despite the high asymmetric induction afforded by auxiliary **1**, it was not ideal from a synthetic

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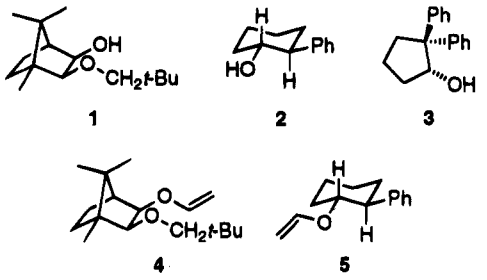
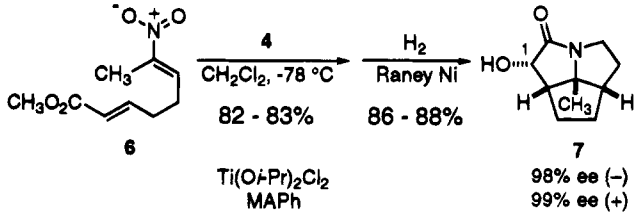


standpoint for several reasons: (1) the chiral auxiliary is of high molecular weight thus necessitating large quantities of material for synthetic applications, (2) the synthesis of auxiliary **1** involves six steps from (+)-camphor,[4] (3) the expense of using (−)-camphor to access the complementary enantiomeric series is prohibitive, and (4) low selectivity was observed in cycloadditions involving the (*Z*)-propenyl ether derived from **1**.[2e]

To address the limitations of auxiliary **1**, several other chiral alcohols including (1*R*,2*S*)-(−)-2-phenylcyclohexanol (**2**) were examined. The lower molecular weight and relative ease of synthesis (two steps and an enzymatic resolution)[5] augured well for the practical applications of **2**. The Ti(O-*i*-Pr)$_2$Cl$_2$-promoted tandem [4 + 2]/[3 + 2] cycloaddition of (−)-2-phenylcyclohexanol-derived vinyl ether **5** with nitroalkene **6** followed by hydrogenolysis again afforded the α-hydroxy lactam in high enantiomeric enrichment ((−)-**7**, 98% ee); however, when promoted by MAPh, an erosion of selectivity occurred ((+)-**7**, 79% ee).[2e] Although selectivity in the cycloaddition of the corresponding (*Z*)-propenyl ether (82% ee) was superior to the camphor derivative, a general erosion in endo/exo selectivity in the propenyl ethers was observed. Also, due to low reactivity, the [4 + 2] cycloadditions of the 2-phenylcyclohexanol-derived propenyl ethers could not be promoted by MAPh. Therefore, problems still plagued auxiliary **2** including: (1) the selectivity of the vinyl ether in exo mode [4 + 2] cycloadditions, (2) the maintenance of high endo/exo selectivity in propenyl ether cycloadditions, and (3) insufficient reactivity of the propenyl ethers in MAPh-promoted [4 + 2] cycloadditions. These problems notwithstanding, the use of (−)-2-phenylcyclohexanol as an auxiliary addressed many practical aspects of the methodology,[6] but it still does not meet the demands of a general chiral auxiliary for the tandem nitroalkene cycloaddition.

On the basis of these foregoing studies, several important design criteria have been identified for the ideal chiral auxiliary in nitroalkene cycloadditions: (1) the auxiliary must be readily available in enantiomerically enriched form in a minimal number of synthetic steps from commercially available starting materials, (2) the auxiliary itself must be compatible with the reaction conditions of the [4 + 2] cycloaddition, (3) the design should impart conformational restrictions on the vinyl ether moiety to reduce the number of possible reactive conformations, (4) a rigid backbone is desirable to maintain high dissymmetry, and (5) a large shielding moiety proximal to the reaction center is required to block one face of the enol ether double bond. One approach to

Scheme 3



improve the 2-phenylcyclohexanol auxiliary has been to replace phenyl with larger aryl systems such as 4-isopropylphenyl or 4-phenylphenyl;[7] however, this approach only extends the steric shield away from the reaction center. Since the double bond of vinyl ether **5** is relatively close (ca. 3 Å) to the chiral backbone (cyclohexane ring) a more appropriate approach in our case would be to increase the effective steric size of the shielding element in the immediate vicinity of the reaction arena, e.g., (−)-8-phenylmenthol.[8,9]

Recently, d'Angelo[7] has reported the use of (*R*)-(−)-2,2-diphenylcyclopentanol (**3**) as a chiral auxiliary in the hydrogenation of β-acetamidocrotonates to afford β-amido esters in high selectivity (96% de). Also, **3** has shown modest diastereoselection (60% de) as a chiral auxiliary in Mn(III)-based oxidative free-radical cyclizations.[10] Alcohol **3** is intriguing in that it bears only one stereogenic center and also fits well into our model. The geminal phenyl substituents would create a concave pocket adjacent to the stereogenic center covering a wide cone angle to shield the enol ether double bond. Optically active alcohol (−)-**3** has been prepared by (+)-β-chlorodiisopinocampheylborane reduction of the corresponding ketone.[7] The preparation of 2,2-diphenylcyclopentanone (**9**) has been reported several times previously.[11] One approach involves ring closure of a dinitrile by Thorpe–Ziegler cyclization followed by acid hydrolysis and decarboxylation.[11a-c,12] Alternatively, the ketone has been prepared by allylation of diphenylacetic acid followed by Lewis acid-promoted Friedel–Crafts acylation to afford 5,5-diphenyl-2-cyclopentenone.[11d,13] Subsequent reduction provided the ketone, however, only in 20% overall yield.[11d] Recently, the one-step diphenylation of cyclopentanone trimethylsilyl enol ether with diphenyliodonium fluoride (DIF) has been reported affording ketone **9** in 51% yield;[11e] however, the expense in preparing the DIF reagent makes this approach impractical on a preparative scale.

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(5) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1. See also: King, S. B.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 5611.

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(9) (a) Early work showed that this auxiliary was not compatible in our Ti(O-*i*-Pr)$_2$Cl$_2$-promoted [4 + 2] cycloaddition.[2b] The vinyl ether derived from the simplified analog 2-(1-methyl-1-phenylethyl)-cyclohexanol[9b] has shown high stereoselectivity in MAPh-promoted cycloadditions. (b) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.

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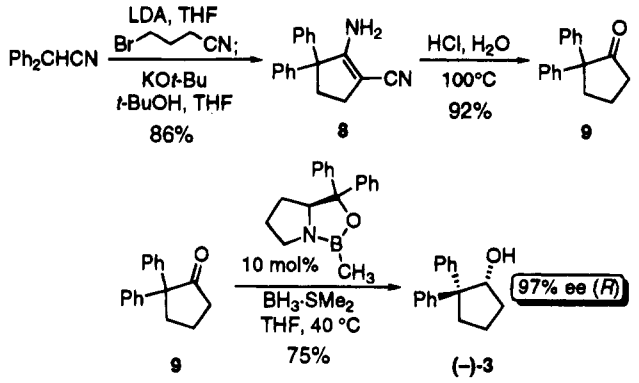
(12) Salmon-Legagneur, F.; Neveu, C. *Bull. Soc. Chim. Fr.* **1956**, 929.

(13) Craig, P. N.; Witt, I. H. *J. Am. Chem. Soc.* **1950**, *72*, 4925.

Scheme 4



Recently, we have reported the application of 2-acetoxyvinyl ethers derived from alcohol (−)-**3** in the highly stereoselective synthesis of 3-hydroxypyrrolidines (96% ee).[14] Therefore, it was of interest to examine the potential of this alcohol as a general auxiliary in the Lewis acid-promoted tandem [4 + 2]/dipolar [3 + 2] cycloadditions with nitroalkenes. Several synthetic and mechanistic issues have been explored including (1) the large scale preparation of (*R*)-(−)-2,2-diphenylcyclopentanol, (2) the synthetic utility of vinyl ethers derived from (−)-**3** in nitroalkene [4 + 2] cycloadditions and subsequent hydrogenolysis of the resulting nitroso acetals to provide α-hydroxy lactams, (3) the synthetic potential and mechanistic implications of propenyl ethers derived from (−)-**3** in the [4 + 2] cycloaddition, and (4) the influence of the Lewis acid, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ or MAPh, on the stereochemical outcome. A preliminary report of tandem cycloadditions for the vinyl ether derived from (−)-**3** has appeared.[2g]

Results

Synthesis of Chiral Auxiliary (−)-3. (*R*)-(−)-2,2-Diphenylcyclopentanol (**3**) was prepared by an asymmetric, oxazaborolidine-catalyzed borane reduction of 2,2-diphenylcyclopentanone (**9**), available in two steps from diphenylacetonitrile, Scheme 4. In our hands, the previously published procedures to prepare ketone **9** were plagued with two difficulties: (1) undesired fragmentation of enamino nitrile **8** under alkylation conditions and (2) incomplete consumption of intermediate cyano ketone in the hydrolysis of **8**. To obtain large quantities of ketone **9**, an optimized procedure based on the alkylation/Thorpe−Ziegler approach has been developed to circumvent these problems.

The anion of diphenylacetonitrile was generated with LDA (1.0 equiv) in THF at 0 °C, Scheme 4. Subsequent alkylation with 4-bromobutyronitrile afforded the dinitrile which was not purified. Direct Thorpe−Ziegler ring closure of the dinitrile in a mixture of tetrahydrofuran (THF) and *tert*-butyl alcohol at 60 °C with potassium *tert*-butoxide as base[11c] afforded enamino nitrile **8** in 86% yield. Attempts to perform the Thorpe−Ziegler cyclization with LDA encountered a rapid fragmentation of the resulting enamino nitrile under the reaction conditions to afford 1,1-dicyano-4,4-diphenylbutane. The same fragmentation pathway was observed with sodium amide; however, it does not occur with the weaker base potassium *tert*-butoxide. As a result, it is essential to use exactly 1 equiv of LDA/diphenylacetonitrile to perform the alkylation since subsequent Thorpe−Ziegler cyclization of the intermediate dinitrile in the presence of excess LDA is not advantageous. The choice of 4-halobutyronitrile was also found to be important. Under the same reaction conditions, 4-chlorobutyronitrile failed to undergo alkylation while 4-iodobutyronitrile provided low yields.[15] Hydrolysis of **8** with hydrochloric acid[16] was found to be superior to previously reported methods which led to incomplete consumption of the intermediate cyano ketone. Heating a 0.27 M solution of **8** in 6 N aqueous hydrochloric acid at reflux with vigorous stirring for 4 days provided ketone **9** in 92% yield. The ratio of solvent volume to enamino nitrile is very important and more concentrated reaction mixtures resulted in incomplete conversion of the cyano ketone even after prolonged heating.

Table 1. Asymmetric Reduction of 9

solvent	mol % catalyst	temp, °C	addition order[a]	**3**, yield, %	% ee[b]
toluene	15	−10	a	94	60
CH_2Cl_2	15	−10	a	99	66
THF	15	−10	a	100	70
CH_2Cl_2	5	25	b	100	82
THF	5	40	b	81	90
THF	10	40	b	97	92

[a] (a) Borane (1.2 equiv) added to ketone and catalyst over 20 min. (b) Ketone added to catalyst and borane over 6 h. [b] Determined from crude product by chiral HPLC.

The previously described asymmetric reduction of ketone **9** with (+)-β-chlorodiisopinocampheylborane affords (*R*)-(−)-**3** of high optical purity (96% ee),[7,17] but the reaction is extremely slow and inefficient (70% yield, 5 days, 2.6 equiv of (+)-β-chlorodiisopinocampheylborane). Enzymatic resolution of **3** also suffers from low conversion (28%, 96.5% ee (*R*)).[18] The oxazaborolidine-catalyzed borane reduction of **9** provides an efficient, catalytic alternative for the asymmetric synthesis of (−)-**3** on a preparative scale.[19] The addition of a solution of ketone **9** over 8 h to a solution of *B*-methyloxazaborolidine catalyst[20] (10 mol %) and borane−methyl sulfide complex (1.0 equiv) in THF at 40 °C afforded (−)-**3** in 97% yield (92% ee).[21] Subsequent recrystallization afforded (−)-**3** (>97% ee) in 75% yield. The catalyst precursor, (*S*)-α,α-diphenylpyrrolidinemethanol, was recovered in 93% yield.

To achieve selectivity exceeding 90% ee, the reaction required the use of 10 mol % of oxazaborolidine catalyst, Table 1. When using a lower catalyst loading a significant decrease in selectivity was observed (5 mol % catalyst provides 90% ee (*R*)-**3**). The oxazaborolidine catalyst used in these experiments was purified by bulb-to-bulb distillation prior to use and quickly weighed in

(14) (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576. (b) See also: Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, xxxx.

(15) Procedures to prepare **8** from 4-chlorobutyronitrile via the iodide have been developed requiring inverse addition at −78 °C.

(16) Snider, T. E.; Morris, D. L.; Srivastava, K. C.; Berlin, K. D. *Organic Syntheses;* Wiley: New York, 1988; Coll. Vol. 6, p 932.

(17) The absolute configuration of **3** has been determined by an X-ray crystal structure of the (*R*)-MTPA derivative; see ref 7.

(18) Randrianasolo-Rakotozafy, L. R.; Azerad, R.; Dumas, F.; Potin, D.; d'Angelo, J. *Tetrahedron Asymmetry* **1993**, *4*, 761.

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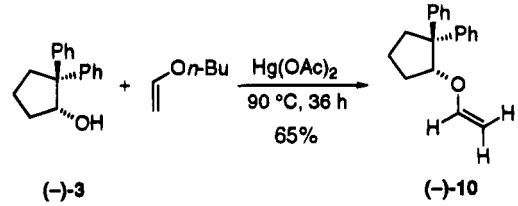
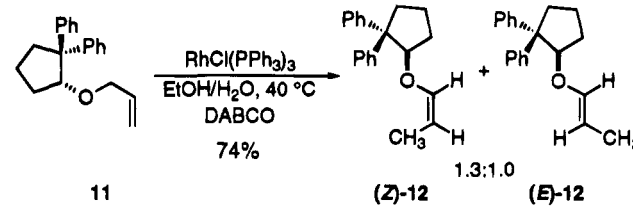
(20) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock; T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

(21) Determined by chiral HPLC analysis, t_R (*S*)-**3** 8.8 min, t_R (*R*)-**3** 17.9 min (Diacel Chiralcel OJ; hexane/ethanol, 70/30, 1.0 mL/min).

Scheme 5



Scheme 6



the open atmosphere. Examination of the purified catalyst by ^{1}H NMR confirmed the presence of *B*-methyloxazaborolidine as well as varying amounts of the hydrated adduct (approximately 7−20%).[20] Unfortunately, it is not clear if the hydrated adduct was the result of trace amounts of water in the NMR solvent, exposure to atmospheric moisture, or simply insufficient purification. Regardless, the use of different batches of the catalyst provided reproducible results that were within experimental error (91−94% ee). Several solvents such as toluene, dichloromethane, and THF were examined;[22] however, for the reduction of **9** the use of THF was found to provide the highest enantioselectivity. The reaction temperature was found to be the crucial parameter for reproducible, high selectivities. The reaction displays an inverse temperature effect with respect to enantioselectivity, where decreased selectivity is observed at lower temperatures. This interesting phenomenon in oxazaborolidine-catalyzed reductions is precedented[23] and can be attributed to the slow breakdown of the catalyst−product complex at low temperatures. The catalyst−product complex is a highly active but less selective catalyst for the reduction of the starting ketone.[24] Accumulation of this undesired intermediate can be avoided by performing the reaction at higher temperatures (40 °C) as well as using a slow inverse addition of the ketone to the catalyst−borane mixture.

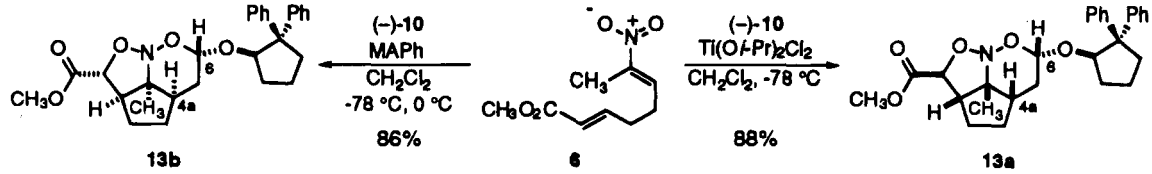
Synthesis of Enol Ethers of (−)-3. Alcohol (−)-**3** was transformed to the corresponding vinyl ether (−)-**10** by a mercuric acetate catalyzed transetherification reaction with *n*-butyl vinyl ether in 65% yield, Scheme 5.[25] Previously, the propenyl ethers of auxiliaries **1** and **2** had been prepared by stereoselective reduction of their corresponding propynyl ethers.[2e,26] In the case of alcohol (−)-**3**, however, selective reduction to afford the (*E*)-propenyl ether failed.[27] Therefore, the well-known isomerization of allyl ethers to the corresponding propenyl ethers was examined.[28] A solution of allyl ether **11**[14a] in ethanol/water (9/1) was heated to 40 °C in the presence of 7 mol % $RhCl(PPh_3)_3$ (Wilkinson's catalyst) and DABCO (0.4 equiv) for 9 h to afford a 1.3:1.0 mixture of propenyl ethers (*Z*)- and (*E*)-**12**, Scheme 6. After separation by MPLC, isomerically pure (>98/1, HPLC) (*E*)- and (*Z*)-**12** were obtained in 74% combined yield. The geometry of the olefin was determined by comparison of the vicinal ^{1}H NMR coupling constants, J = 12.5 Hz for (*E*)-**12** and J = 6.1 for (*Z*)-**12**. Temperature was found to be very important in the isomerization. Below 30 °C the reaction did not proceed; however, above 40 °C increasing amounts of saturated *n*-propyl ether were observed.

Tandem Cycloadditions of (−)-10. The Lewis acids $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, MAPh, and methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) were each examined for their ability to promote the [4 + 2] cycloaddition between nitroalkene **6**[2d] and vinyl ether (−)-**10**. In the case of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, a solution of the Lewis acid (3.0 equiv) was added to a solution of nitroalkene **6** and vinyl ether (−)-**10** (3.0 equiv) in dichloromethane at −78 °C, and the reaction solution was maintained at that temperature for 2 h, Table 2. Subsequent [3 + 2] cycloaddition of the intermediate nitronate at room temperature after workup afforded a mixture of three nitroso acetal diastereomers in a ratio of 48:1:1 (^{1}H NMR) and 88% combined yield. Lower yields were observed when the ratio of vinyl ether to nitroalkene substrate was reduced (76%, 1.5 equiv). Four possible diastereomers can arise from the tandem [4 + 2]/[3 + 2] cycloaddition sequence, two as a result of endo or exo approach of the dienophile and two as a result of α or β facial approach to the heterodiene. Facial approach of the dipolarophile is stereoselective as a result of tether length and is defined by the configuration of the newly formed C(4a) stereogenic center in the [4 + 2] cycloaddition. As shown in earlier cycloadditions with achiral vinyl ethers, the fold of the tether in the [3 + 2] cycloaddition is exclusively endo.[2a] The anomeric center, C(6), is known to be susceptible to epimerization in the presence of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$.[2b]

Assignment of the configuration of the anomeric center (alkoxy group cis or trans with respect to the C(4a) ring junction proton) was determined by comparison of the ^{1}H NMR coupling pattern for HC(6), Figure 1. The anomeric proton of the major diastereomer was observed as a doublet of doublets at 4.87 ppm (J = 6.6, 3.2 Hz) while the two minor diastereomers were observed as triplets at 4.66 ppm (J = 7.5 Hz) and 5.15 ppm (J = 8.0 Hz). The observed coupling patterns can be rationalized in terms of a twist-boat conformation[2b] of the six-membered N−O heterocyclic ring which places the alkoxy group in a pseudoequatorial (dd) or pseudoaxial (t) orientation for the trans and cis configurations, respectively. On the basis of this analysis, the major diastereomer (**13a**) bears a trans relationship between the C(4a) proton and the pseudoequatorial alkoxy group. The configurations of the remaining stereogenic centers were assumed on the basis of prior studies of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$-promoted cycloadditions[2e] and will be subsequently confirmed by hydrogenolysis. The trans relationship of the alkoxy group and HC(4a) suggests that, if produced

(22) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.
(23) Stone, G. B. *Tetrahedron Asymmetry* **1994**, *5*, 465.
(24) Personal communication with Dr. David J. Mathre of Merck Research Laboratories.
(25) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.
(26) Solà, L.; Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1992**, *33*, 2863.
(27) Hydride-based reductions afforded mixtures of (*E*)-**12**, (*Z*)-**12**, and regenerated alcohol **3**. Dissolving metal reduction afforded significant quantities of 1,1-diphenylcyclopentane.
(28) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Arnold, T.; Reissig, H.-U. *Synlett* **1990**, 514. (c) McGrath, D. V.; Grubbs, R. H. *J. Am. Chem. Soc.* **1991**, *113*, 3611. (d) Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 277. (e) Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 83. (f) Taskinen, E. *Tetrahedron* **1993**, *49*, 11389.

Table 2. Influence of Lewis Acid on Cycloadditions of Vinyl Ether (−)-10



Lewis acid	equiv	(−)-10, equiv	13, yield, %	ratio[a] 13a:13a′:13b	7, yield, %	% ee 7[b] (confign)
$Ti(O\text{-}i\text{-}Pr)_2Cl_2$	3.0	3.0	88	48:1:1	70	98 (−)
MAPh	3.0	3.0	86	1:2:122	74	93 (+)

[a] Determined by ^1H NMR. [b] Determined by chiral HPLC analysis.

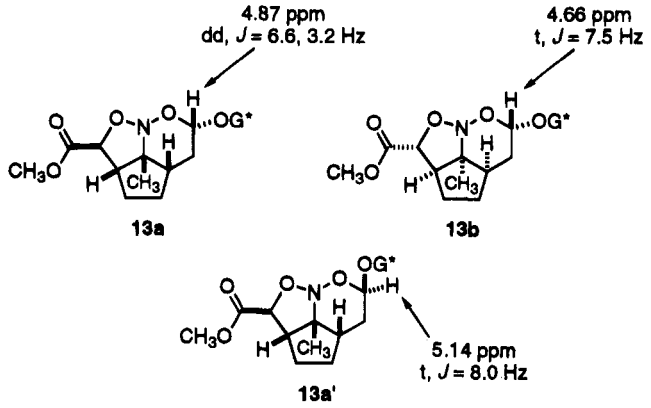


Figure 1. Characteristic 400 MHz ^1H NMR data for nitroso acetals **13a**, **13b**, and **13a′**.

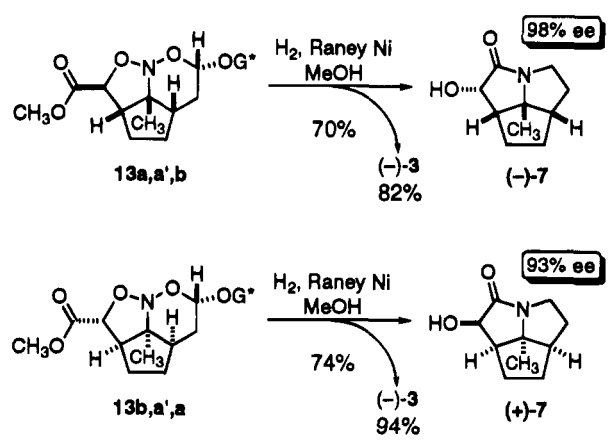
kinetically, **13a** would have arisen from an endo approach of the dienophile in the [4 + 2] cycloaddition. The minor two diastereomers bearing a cis relationship would represent exo approach diastereomers, if produced kinetically, and necessarily with opposite facial approach.

Similarly, for MAPh a solution of vinyl ether (−)-**10** (3.0 equiv) followed by nitroalkene **6** were added to a solution of the Lewis acid (3.0 equiv) at −78 °C, Table 2. The reaction mixture was then allowed to warm to 0 °C and was held at that temperature for 45 min. Subsequent [3 + 2] cycloaddition of the intermediate nitronate after workup afforded a mixture of three nitroso acetal diastereomers in a ratio of 1:2:122 (^1H NMR) and 86% combined yield. Again, the use of fewer equivalents of chiral vinyl ether resulted in diminished yields. Also, if the temperature was maintained at −78 °C, the cycloaddition did not proceed to completion even after extended reaction times. Interestingly, analysis of the ^1H NMR spectra revealed a triplet at 4.66 ppm (J = 7.5 Hz) for the anomeric proton HC(6) of the major nitroso acetal diastereomer, therefore identifying it as **13b**, a minor diastereomer from the previous $Ti(O\text{-}i\text{-}Pr)_2Cl_2$-promoted cycloaddition. The two minor diastereomers were likewise identified as **13a** and **13a′**.

The corresponding cycloaddition employing MAD as the Lewis acid afforded a mixture of three nitroso acetal diastereomers in the ratio of 3:3:1 (**13a**:**13a′**:**13b**, ^1H NMR) in low yield (48%), and further examination was not pursued.

Hydrogenolysis of Vinyl Ether Cycloadducts. To determine the extent of asymmetric induction, the mixture of nitroso acetal diastereomers obtained from the $Ti(O\text{-}i\text{-}Pr)_2Cl_2$-promoted cycloaddition was transformed to a single tricyclic α-hydroxy lactam **7** by hydrogenolysis (1 atm) over Raney nickel catalyst in 70% yield, Scheme 7.[29] The chiral auxiliary (−)-**3** was recovered in 82% yield. Analysis of the corresponding 3,5-dinitrophenyl carbamate derivative of **7** (**14**) by chiral HPLC analysis[30] revealed the lactam to be highly enantiomerically enriched (98% ee). The major enantiomer ((−)-**7**) possessed the (1*S*,5a*S*,7a*S*,7b*R*) configuration as was previously established from the *O*-methyl mandelate esters.[2b,31]

Scheme 7



In a similar fashion, the mixture of nitroso acetal diastereomers obtained from the MAPh-promoted cycloaddition was transformed to tricyclic α-hydroxy lactam **7** by hydrogenolysis (1 atm) over Raney nickel catalyst in 74% yield. The chiral auxiliary (−)-**3** was recovered in 94% yield. Analysis of the corresponding 3,5-dinitrophenyl carbamate derivative of **7** (**14**) by chiral HPLC analysis revealed the lactam again to be highly enantiomerically enriched (93% ee); however, the major enantiomer ((+)-**7**) possessed the (1*R*,5a*R*,7a*R*,7b*S*) configuration. *Therefore, when promoted by MAPh the [4 + 2] cycloaddition afforded nearly the same magnitude of asymmetric induction as observed with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ but now in the opposite sense.*

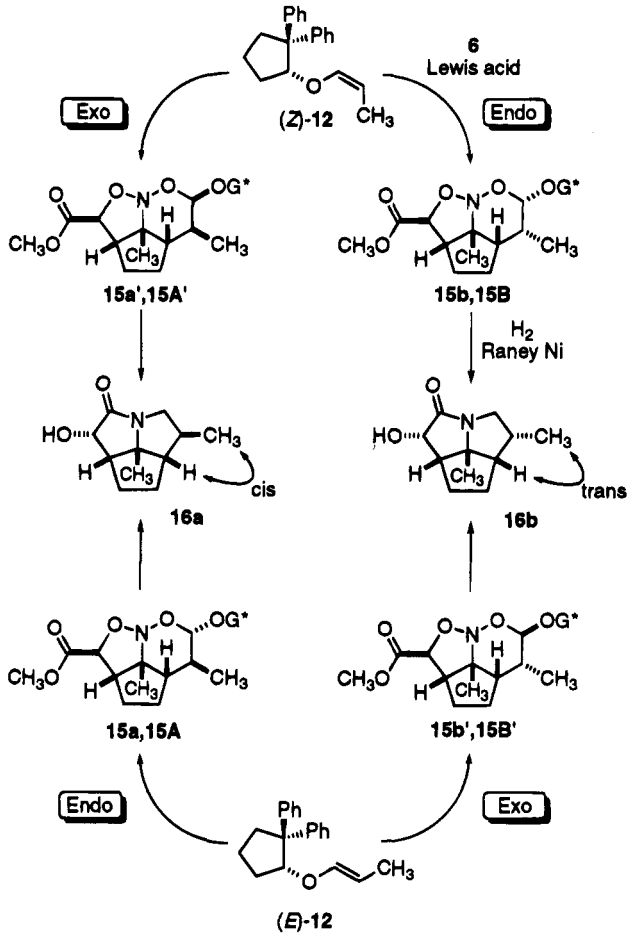
Cycloadditions with (*Z*)-Propenyl Ether and Hydrogenolysis of Cycloadducts. The use of chiral propenyl ethers in the [4 + 2] cycloaddition allows for the installation of an additional stereogenic center in the tandem cycloadducts. The methyl substituent also pro-

(29) For a discussion of the mechanism of this transformation see ref 2b.

(30) (a) Pirkle, W. H.; Mahler, G.; Hyun, M. H. *J. Liquid 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.

(31) (a) 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. (b) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Scheme 8



vides a stereochemical marker to allow for the determination of endo/exo selectivity in the [4 + 2] cycloaddition. Since the anomeric center C(6) is susceptible to epimerization, it is not a reliable indicator of reaction selectivity. The corresponding endo and exo approaches of the dienophile in the [4 + 2] cycloaddition would afford after subsequent [3 + 2] cycloaddition and hydrogenolysis α-hydroxy lactam methyl epimers **16a** and **16b**, Scheme 8. Therefore, cycloadditions of nitroalkene **6** with propenyl ethers (*E*)- and (*Z*)-**12** promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ and MAPh were examined.

Following the optimized conditions found for vinyl ether **10**, a solution of Ti(O-*i*-Pr)$_2$Cl$_2$ (3.0 equiv) was added to a solution of nitroalkene **6** and propenyl ether (*Z*)-**12** (2.0 equiv) in dichloromethane at −78 °C, and the reaction solution was maintained at that temperature for 4 h, Scheme 9. Subsequent [3 + 2] cycloaddition after workup afforded a mixture of five diastereomeric nitroso acetals in the ratio of 26:1:1:1:1 (^{1}H NMR) in 95% combined yield, Table 3. Stereochemical assignments for the nitroso acetal diastereomers were not possible on the basis of NMR data.[32] The additional methyl stereogenic center and the potential for epimerization of C(6) now provides the possibility of eight diastereomers from the [4 + 2]/[3 + 2] cycloaddition. *Isolation of unreacted (Z)-12 indicated that double bond isomerization had not occurred under the reaction conditions.*[2e] Likewise, for MAPh a solution of propenyl ether (*Z*)-**12** followed by nitroalkene **6** were added to a solution of the Lewis acid in dichloromethane at −78 °C. The reaction mixture was allowed to warm to −10 to 0 °C and was held at that temperature for 3 h. Subsequent [3 + 2] cycloaddition after workup afforded a mixture of three nitroso acetal diastereomers in a ratio of 12:1:1 (^{1}H NMR) and a combined yield of 84%.

To determine the endo/exo selectivity and the extent of asymmetric induction, the mixture of nitroso acetals, **15**, obtained from the Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloaddition was transformed into a mixture of α-hydroxy lactam methyl epimers in a ratio of 9:1 (**16b**:**16a**, ^{1}H NMR) by hydrogenolysis (1 atm) over Raney nickel catalyst in 78% yield, Scheme 9. The configurational assignment of the C(5) methyl group of **16a** and **16b** had previously been established by ^{1}H NOE experiments.[2d] To avoid unintentional enrichment of either α-hydroxy lactam diastereomer, **16a** and **16b** were directly converted to the corresponding 3,5-dinitrophenyl carbamates (**17a** and **17b**), and the mixture was submitted to chiral HPLC analysis. Analysis confirmed a ratio of 8.2:1.0 (**17b**:**17a**) which was in close agreement to the ratio of **16a** and **16b** obtained by ^{1}H NMR integration. Therefore, a corresponding endo/exo selectivity of 8.2:1.0 was observed in the [4 + 2] cycloaddition, Table 3. The diastereomer derived from endo mode approach in the [4 + 2] cycloaddition (**16b**) was found to be highly enantiomerically enriched (92% ee). The major enantiomer ((−)-**16b**) belonged to the (1*S*) configurational family as determined on the basis of HPLC elution order in analogy to the products of the vinyl ether series. An erosion of selectivity was observed in the exo mode-derived diastereomer ((−)-**16a**) which was enriched to the extent of 65% ee and was of the same enantiomeric series as the endo-derived diastereomer.

Hydrogenolysis of the mixture of nitroso acetal diastereomers obtained from the MAPh-promoted cycloaddition afforded a mixture of α-hydroxy lactam methyl epimers in a ratio of 17:1 (**16a**:**16b**, ^{1}H NMR) in 78% combined yield, Scheme 9. The chiral auxiliary was recovered in quantitative yield. Conversion of the epimeric mixture to their corresponding 3,5-dinitrophenyl carbamates (**17a** and **17b**) and chiral HPLC analysis revealed an endo/exo selectivity of 1.0:10.2 (**17b**:**17a**). The diastereomer derived from exo mode approach in the [4 + 2] cycloaddition (**16a**) was found to be enriched to the extent of 83% ee, and the major enantiomer ((+)-**16a**) belonged to the (1*R*) configurational family. Low asymmetric induction (38% ee) was observed in the corresponding endo mode-derived diastereomer ((−)-**16b**) although primarily of the (1*S*) enantiomeric series. *Therefore, the MAPh-promoted cycloaddition of propenyl ether (Z)-12 proceeded primarily through an exo [4 + 2] transition state while the Ti(O-i-Pr)$_2$Cl$_2$-promoted cycloaddition proceeded primarily through an endo selective [4 + 2] cycloaddition.*

Cycloadditions with (*E*)-Propenyl Ether and Hydrogenolysis of Cycloadducts. Tandem [4 + 2]/[3 + 2] cycloadditions were also performed with propenyl ether (*E*)-**12** and nitroalkene **6** using the previously optimized conditions. In the case of Ti(O-*i*-Pr)$_2$Cl$_2$, a solution of the Lewis acid (3.0 equiv) was added to a solution of nitroalkene **6** and propenyl ether (*E*)-**12** (2.0 equiv) in dichloromethane at −78 °C, and the mixture was main-

(32) In some instances the configuration of the nitroso acetals could be inferred assuming the absence of C(6) epimerization on the basis of the configurational distribution of **16** obtained after hydrogenolysis. For the eight possible diastereomers of **15**, the letter designator (a or b) refers to the relative C(4a)/C(5) configuration, lowercase and uppercase designators refer to diastereomers obtained from opposite facial approach, and (') refers to the relative C(4a)/C(6) configuration.

Scheme 9

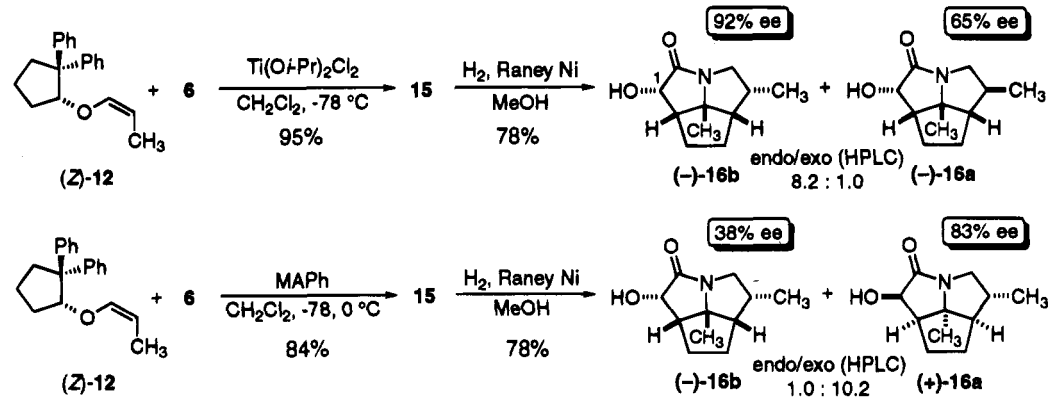


Table 3. Influence of Lewis Acid on Cycloadditions of Propenyl Ether (Z)-12

Lewis acid	equiv	(Z)-12, equiv	15, yield, %	16, yield %	endo/exo ratio[a] 16b:16a	endo % ee[a]	exo % ee[a]
Ti(O-*i*-Pr)$_2$Cl$_2$	3.0	2.0	95	78	8.2:1.0	92 (−)	65 (−)
MAPh	3.0	2.0	84	78	1.0:10.2	38 (−)	83 (+)

[a] Determined by chiral HPLC analysis of **17a/17b**.

tained at that temperature for 3 h, Scheme 10. Subsequent [3 + 2] cycloaddition after workup afforded a mixture of three diastereomeric nitroso acetals in a ratio of 14:2:1 (^{1}H NMR) and a combined yield of 93%. *Again, isolation of unreacted (E)-12 indicated that double bond isomerization had not occurred under the reaction conditions.* Likewise for MAPh, a solution of propenyl ether (*E*)-**12** followed by nitroalkene **6** were added to a solution of the Lewis acid in dichloromethane at −78 °C. The reaction mixture was allowed to warm to −10 to 0 °C and was held at that temperature for 2 h. Subsequent [3 + 2] cycloaddition after workup afforded a mixture of diastereomeric nitroso acetals in a ratio of 7:1 (^{1}H NMR) and a combined yield of 83%.

To determine the endo/exo selectivity and extent of asymmetric induction, the mixture of nitroso acetals obtained from the Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloaddition was transformed to a mixture of α-hydroxy lactam methyl epimers in a ratio of 2.8:1 (**16a**:**16b**, ^{1}H NMR) and 84% combined yield by hydrogenolysis (1 atm) over Raney nickel catalyst. The chiral auxiliary was recovered in 98% yield. Chiral HPLC analysis of the 3,5-dinitrophenyl carbamate derivatives of **16** revealed an endo/exo selectivity of 2.3:1.0, Table 4. The diastereomer derived from endo approach in the [4 + 2] cycloaddition (**16a**) was again found to be highly enantiomerically enriched (96% ee). The major enantiomer ((−)-**16a**) belonged to the (1*S*) configurational family. An erosion of selectivity was observed in the exo-derived diastereomer (−)-**16b** (66% ee); however, it exhibited the same sense of asymmetric induction.

In contrast, hydrogenolysis of the mixture of nitroso acetal diastereomers obtained from the MAPh-promoted cycloaddition afforded a single α-hydroxy lactam by ^{1}H NMR analysis in 77% yield. It was identified as **16b** and, therefore, derived from exclusive exo approach of the dienophile in the [4 + 2] cycloaddition. The chiral auxiliary was recovered in 90% yield. Chiral HPLC analysis of the 3,5-dinitrophenyl carbamate derivative of **16b**, however, did reveal a minor component of **16a** to afford an endo/exo selectivity of 1.0:54.8. Moderate asymmetric induction (74% ee) was observed in the diastereomer derived from exo mode approach in the [4 + 2] cycloaddition (**16b**). The major enantiomer ((+)-**16b**) belonged to the (1*R*) configurational family. The minor endo-derived product (−)-**16a** also showed low asymmetric induction (41% ee) and primarily belonged to the opposite configurational series. Therefore, in cycloadditions of propenyl ether (*E*)-**12**, MAPh again promoted a highly exo-selective [4 + 2] cycloaddition in contrast to Ti(O-*i*-Pr)$_2$Cl$_2$ which induced low endo selectivity.

Discussion

The stereochemical outcome of the [4 + 2] cycloaddition is governed by two factors: (1) the orientation of dienophile approach to the heterodiene, endo or exo with respect to the alkoxy group, and (2) the facial selectivity of the dienophile. The accessible face of the dienophile π-system is defined by the design of the auxiliary as well as the conformation of the vinyl ether moiety, s-cis or s-trans. Previous studies have shown that the Lewis acid promoter has a profound effect not only on the rate of the [4 + 2] cycloaddition but also on the endo/exo selectivity and the reactive conformation of the dienophile.[2e] These effects have now been observed with vinyl and propenyl ethers of 2,2-diphenylcyclopentanol. To understand the origin of asymmetric induction as a result of the chiral auxiliary and its Lewis acid dependence, the conformational preference of enol ethers **10** and (*E*)- and (*Z*)-**12** as well as the endo/exo selectivity of the [4 + 2] cycloaddition must be examined.

Dienophile Conformation. A vinyl ether derived from a secondary alcohol may exist in four possible limiting conformations: s-cis (**a**) or s-trans (**b**) with a synclinal ($\theta \sim 60°$) relationship between the hydrogen and the α-carbon and s-cis (**c**) or s-trans (**d**) with an antiperiplanar ($\theta \sim 180°$) relationship between these atoms, Figure 2. Studies of the conformational preferences of simple vinyl and 2-substituted vinyl ethers by spectroscopic and computational methods have been reported.[33] Methyl vinyl ether is believed to exist in two rapidly interconverting rotamers. On the basis of spec-

(33) (a) Owen, N. L.; Sheppard, N. *Trans. Faraday Soc.* **1964**, *60*, 634. (b) Cahill, P.; Gold, L. P. *J. Chem. Phys.* **1968**, *48*, 1620. (c) Marsault-Herail, F.; Chiglien, G. S.; Dorie, J. P.; Martin, M. L. *Spectrochim. Acta* **1973**, *29A*, 151. (d) Charles, S. W.; Cullen, F. C.; Owen, N. L. *J. Mol. Struct.* **1973**, *18*, 183. (e) Sullivan, J. F.; Dickson, T. J.; Durig, J. R. *Spectrochim. Acta* **1986**, *42A*, 113. (f) Bond, D.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1003. (g) Gallinella, E.; Cadioli, B. *J. Mol. Struct.* **1991**, *249*, 343. (h) For a review see: Fischer, P. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and Their Sulphur Analogs, Part 2*; Patai, S., Ed.; Wiley: New York, 1980; p 761.

Scheme 10

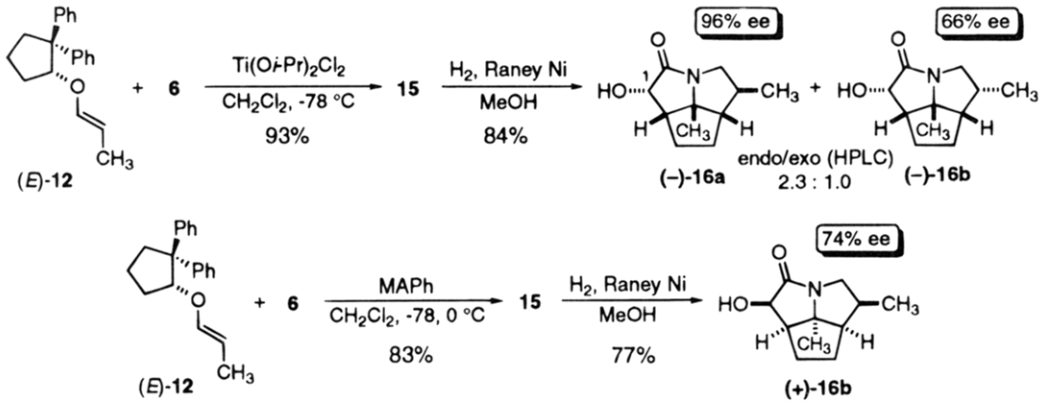


Table 4. Influence of Lewis Acid on Cycloadditions of Propenyl Ether (*E*)-12

Lewis acid	equiv	(*E*)-**12**, equiv	**15**, yield, %	**16**, yield %	endo/exo ratio[a] **16a:16b**	endo % ee[a]	exo % ee[a]
$Ti(O\text{-}i\text{-}Pr)_2Cl_2$	3.0	2.0	93	84	2.3:1.0	96 (−)	66 (−)
MAPh	3.0	2.0	83	77	1.0:54.8	41 (−)	74 (+)

[a] Determined by chiral HPLC analysis of **17a**/**17b**.

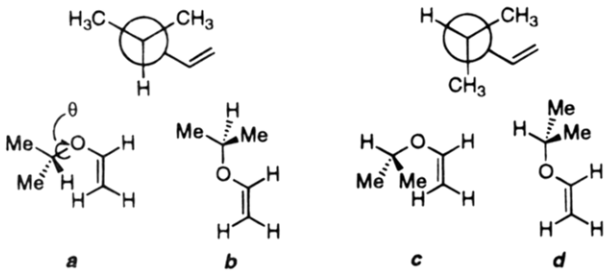


Figure 2. Limiting conformations of isopropyl vinyl ether.

troscopic evidence, the s-cis conformation predominates while the minor component (less stable by 1.15 kcal/mol experimentally[33a]) is believed to be a nonplanar s-trans conformation.[33g] Evidence suggests, however, that sterically larger alkoxy groups (i.e., *tert*-butyl) favor the s-trans conformation.[34] Studies of propenyl ethers indicate an s-trans conformation is favored for (*Z*)-propenyl ethers while the conformer population for (*E*)-propenyl ethers[33d] mimics that of vinyl ethers.

The relative contribution of the synclinal and antiperiplanar s-cis and s-trans conformations was assessed by ab initio calculations[35] (MP2/6-31G*) of isopropyl vinyl ether, Table 5. Calculations supported the synclinal s-cis conformation (**a**) as the most stable with the nonplanar s-trans conformation (**b**) 1.2 kcal/mol less stable. As expected on the basis of steric and molecular orbital[36] arguments antiperiplanar ($\theta = 180°$) s-trans (**d**) and s-cis (**c**) conformations were less stable by 3.4 and 4.6 kcal/mol, respectively. The ground state conformer population, however, is not a governing factor in the determination of the stereochemical course of the reaction. Rather, the reactive conformation as dictated by steric and electronic factors in the [4 + 2] cycloaddition transition state must be considered. On the basis of the above evidence, both s-cis and s-trans conformations must be considered as potential reactive conformations.

To ascertain the conformational preference and the mode of stereodifferentiation of the 2,2-diphenylcyclopentanol auxiliary, molecular mechanics (MM2) calculations were performed on vinyl ether **10** and propenyl ethers (*E*)- and (*Z*)-**12**, Table 6.[37] The ground state conformation of vinyl ether **10** was identified as a synclinal s-cis conformation (**a**, Figure 3). Modeling predicted the vinyl ether moiety and the trans phenyl to

Table 5. Isopropyl Vinyl Ether Conformational Energies

conformer	θ (°)	HF/6-31G* HF (au)	HF/6-31G* E_{rel} (kcal/mol)	MP2/6-31G* MP2 (au)	MP2/6-31G* E_{rel} (kcal/mol)
s-cis (**a**)	41.2	−269.992 30	0.00	−270.844 41	0.00
s-trans (**b**)	45.4	−269.991 85	0.28	−270.842 55	1.17
s-cis (**c**)	180.0	−269.984 98	4.59	−270.837 15	4.56
s-trans (**d**)	−180.0	−269.988 00	2.70	−270.839 00	3.40

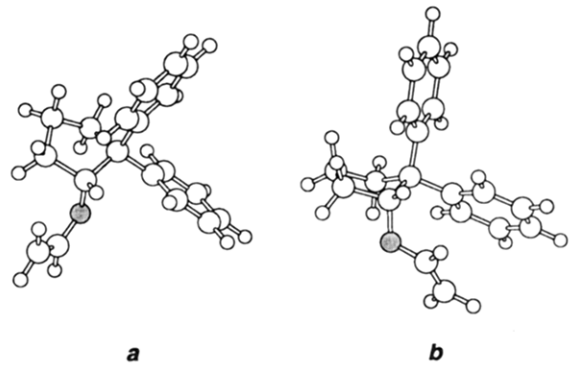


Figure 3. Synclinal s-cis (a) and s-trans (b) conformations of **10**.

Table 6. Molecular Mechanics (MM2) Calculations for 10 and 12

conformer	E_{rel} (kcal/mol) **10**	(*E*)-**12**	(*Z*)-**12**
s-cis	0.00	0.00	4.31
s-trans	1.30	0.69	0.00
s-trans ($\theta = 180°$)	3.65	3.21	2.47
s-cis ($\theta = 180°$)	8.79	8.37	

(34) (a) Afonin, A. V.; Khil'ko, M. Y.; Komel'kova, V. I.; Shafeev, M. A.; Nedolya, N. A. *Zh. Org. Khim.* **1991**, *27*, 161. (b) Kalabin, G. A.; Krivdin, L. B.; Shcherbakov, V. V.; Trofimov, B. A. *J. Mol. Struct.* **1986**, *143*, 569. (c) Taskinen, E. *Tetrahedron* **1978**, *34*, 353.

(35) Gaussian 90, Revision F: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1990.

(36) Bernardi, F.; Epiotis, N. D.; Yates, R. L.; Schlegel, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 2385.

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

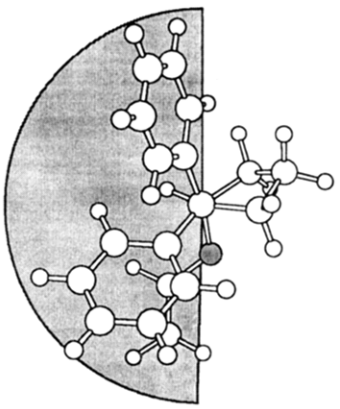


Figure 4. Shielding of the vinyl ether in the s-trans conformation of **10**.

be pseudoaxial which is consistent with X-ray structural evidence.[7,14a] As a consequence of the geminal phenyl substituents, the *si* face of the enol ether olefin is predicted to be shielded from approach;[38] however, the olefin is canted away from the shielding moiety. The conformation in which the vinyl ether moiety is canted toward the phenyl rings incurs a 2.8 kcal/mol energy penalty due to steric congestion. In contrast, the synclinal s-trans conformation (1.3 kcal/mol less stable) orients the olefin toward the shielding phenyl rings establishing a potential π-overlap (**b**, Figure 3). The auxiliary now effectively shields the *re* face of the vinyl ether. The modeling results suggest the utility of auxiliary **3** in exo mode cycloadditions. The approach of the dienophile in an exo orientation places the bulk of the auxiliary away from the heterodiene, therefore, limiting steric interactions. In the case of the s-trans conformation of **10**, however, the trans phenyl substituent reaches across toward the diene and establishes a wide cone angle for steric shielding of the vinyl ether double bond, Figure 4. Orientation of the vinyl ether substituent between the two ring carbons represents a 2.3 and 8.7 kcal/mol energy penalty over the ground state s-trans and s-cis conformations, respectively. Similar overall predictions were made for propenyl ether (*E*)-**12**.

Molecular mechanics calculations for propenyl ether (*Z*)-**12** predicted the ground state to be the s-trans conformation; however, the pseudoequatorial and pseudoaxial orientations of the vinyl ether exhibited similar energies. Examination of the ^{1}H NMR spectra of (*Z*)-**12** revealed a triplet for the ring methine suggesting a predominance of the axial conformation in solution. The corresponding s-cis conformation was predicted to be 4.3 kcal/mol less stable. Interestingly, the antiperiplanar s-trans conformation was only 2.5 kcal/mol less stable.

Endo/Exo Selectivity. The preference for the endo orientation of a vinyl ether in an inverse, electron-demand Diels–Alder reaction has been documented in general[39] and in our own studies employing Ti(O-*i*-Pr)$_2$Cl$_2$ as the Lewis acid promoter.[2d] For both propenyl ethers (*E*)- and (*Z*)-**12**, Ti(O-*i*-Pr)$_2$Cl$_2$ preferentially promoted an endo selective cycloaddition on the order of 2.3/1 and 8.2/1, respectively. Although the anomeric center of the vinyl ether cycloadducts is susceptible to epimerization, the observation of a very highly selective cycloaddition (24/1) favoring a trans relationship between the C(6) alkoxy substituent and the hydrogen at C(4a) in nitroso acetal **13a** is consistent with a highly endo selective approach. The observation that an aluminum-based Lewis acid could alter the endo/exo selectivity in nitroalkene [4 + 2] cycloadditions was previously documented in propenyl ether cycloadditions promoted by MAD.[2e] MAPh has now been shown to afford even higher levels of exo selectivity in the cycloaddition for propenyl ethers (*E*)- and (*Z*)-**12**, 10.2/1 and 54.8/1 (exo/endo), respectively. Again the observation of very high selectivity (>100/1) in the vinyl ether cycloaddition promoted by MAPh favoring the cis relationship between the C(6) alkoxy group and the hydrogen at C(4a) in nitroso acetal **13b** is consistent with a highly exo selective approach of the dienophile.

The orientation of a large, chiral auxiliary endo to the Lewis acid-nitroalkene complex would be expected to be energetically unfavorable on the basis of steric considerations. Houk and Hehre have proposed that coulombic interactions between the diene and dienophile in the transition state influence the endo/exo selectivity of [4 + 2] cycloadditions.[40] Coulombic interactions between the electron poor nitrogen of the heterodiene and the partially electron rich enol ether oxygen would stabilize an endo approach over the corresponding exo cycloaddition where this interaction would be absent, Figure 5. In MAPh-promoted cycloadditions, the large steric demand of the bulky aluminum Lewis acid now overrides the attractive coulombic interaction thus favoring the exo transition state. Changes in the electronic environment of nitrogen and the extent of charge delocalization in the two nitroalkene–Lewis acid complexes formed from MAPh and Ti(O-*i*-Pr)$_2$Cl$_2$ cannot be ruled out as contributing factors.

Asymmetric Induction. To rationalize the stereochemical outcome of the [4 + 2] cycloaddition the contributions of three components must be considered: (1) the absolute configuration of the product α-hydroxy lactam, (2) the facial approach (endo or exo) of the dienophile, and (3) the π-facial preference of the dienophile as dictated by the chiral auxiliary. It is assumed on the basis of molecular mechanics calculations that approach to the dienophile π-system is from the side opposite to the geminal phenyl substituents in the reactive conformation. Therefore, if dienophile approach (endo or exo) is constant but the vinyl ether conformation were switched (i.e., s-cis to s-trans), enantiomeric α-hydroxy lactams would be produced after hydrogenolysis of the nitroso acetal cycloadducts. Likewise, if the enol ether conformation were constant but dienophile approach was switched (i.e., endo to exo), again enantiomeric α-hydroxy lactams would be produced.

The cycloaddition of vinyl ether (−)-**10** with nitroalkene **6** promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ afforded α-hydroxy lactam (−)-**7** with very high selectivity (98% ee). Endo approach of the dienophile is inferred from the C(6)–C(4a) relationship in the nitroso acetal cycloadduct. To obtain the observed sense of asymmetric induction, the cycloaddition must occur through an approach of the s-trans vinyl ether

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

(39) (a) Boger, D. L. In *Comprehensive Organic Chemistry, Combining C–C π-Bonds*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 451-512. (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (c) Desimoni, G.; Gamba, A.; Monticelli, M.; Nicola, M.; Tacconi, G. *J. Am. Chem. Soc.* **1976**, *98*, 2947. (d) Desimoni, G.; Colombo, G.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1973**, *29*, 2635.

(40) (a) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (b) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.

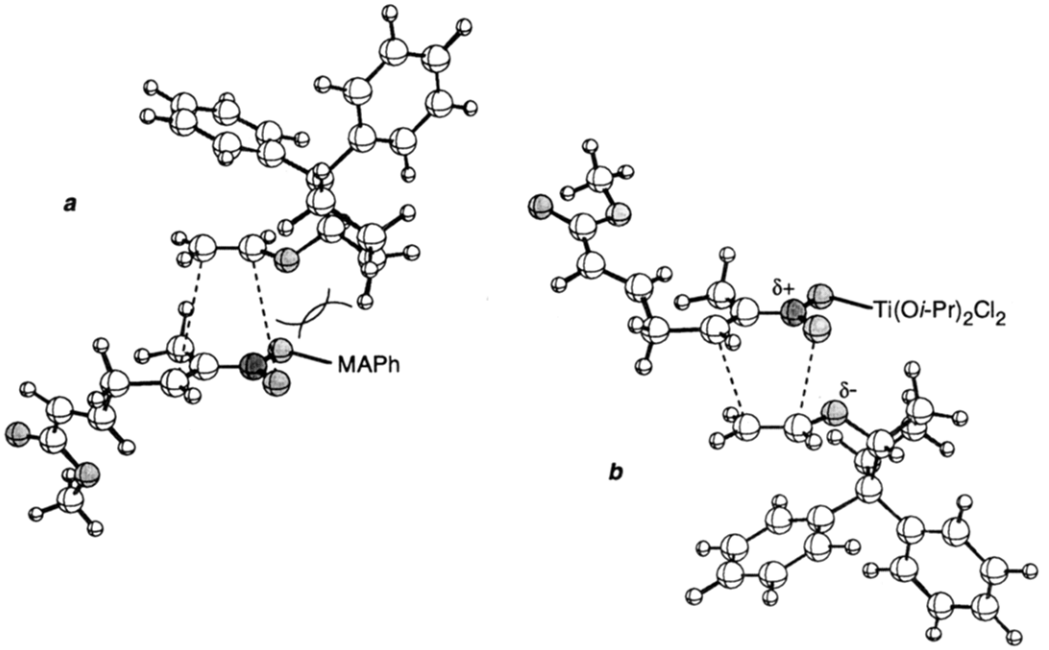
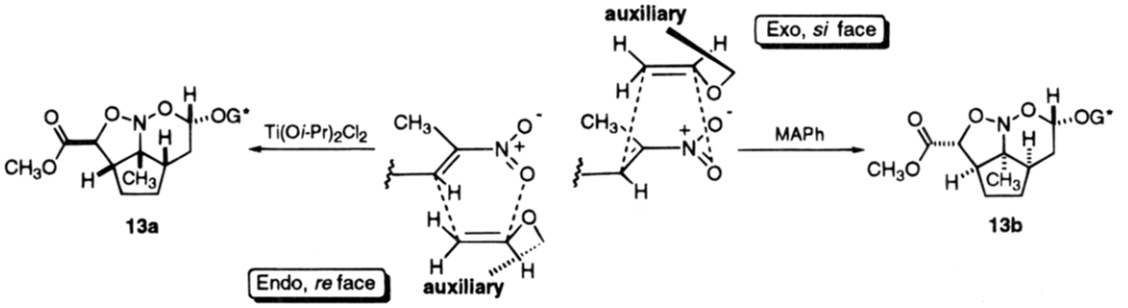


Figure 5. Exo (**a**) and endo (**b**) transition states for reaction of s-trans vinyl ether **10** and nitroalkene **6**.

Scheme 11



conformation to the *re* face of the nitroalkene[41] (Scheme 11, Figure 5). The analogous cycloaddition promoted by MAPh afforded the α-hydroxy lactam (+)-**7** with high selectivity (93% ee). Exo approach of the dienophile was inferred from the conformation of the resulting nitroso acetal. To afford the opposite enantiomeric series with respect to the Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloaddition, the enol ether must remain in the s-trans conformation and approach the *si* face of the nitroalkene as dictated by the auxiliary. *Therefore, changing the Lewis acid promoter from Ti(O-i-Pr)$_2$Cl$_2$ to MAPh only changes the endo/exo selectivity of the cycloaddition while the reactive enol ether conformation remains s-trans.*

The same concepts also apply in the cycloadditions of the (*E*)- and (*Z*)-propenyl ethers. In the case of cycloadditions promoted by Ti(O-*i*-Pr)$_2$Cl$_2$, the endo approach of the dienophile was favored for both (*E*)- and (*Z*)-**12**, and the resulting α-hydroxy lactams were highly enantiomerically enriched (96% and 92% ee, respectively). In both cases the major enantiomer belonged to the (1*S*) enantiomeric family as was observed for the vinyl ether cycloadduct. Therefore, as with **10**, (*E*)- and (*Z*)-**12** react through a highly selective s-trans enol ether conformation when approaching in an endo orientation.

In contrast to the exo-selective, MAPh-promoted cycloaddition of the vinyl ether affording the (1*R*) enantiomeric series, the exo-derived cycloadducts from the Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloadditions of (*E*)- and (*Z*)-**12** were found to belong to the same enantiomeric series as the endo cycloadducts (1*S*) in 65−66% ee. If the propenyl ethers again reacted through the s-trans conformation, the (1*R*) enantiomeric series would have been expected. The observed sense of asymmetric induction would be consistent with a reactive s-cis or cisoid-like conformation approaching the *re* face of the nitroalkene. The erosion of selectivity (66% ee) observed in the exo mode would be anticipated from the modeling studies since in the s-cis conformations of **10** and **12** the enol ether double bond is canted away from the shielding phenyl rings.

In the case of the MAPh-promoted cycloadditions of (*E*)- and (*Z*)-**12**, the exo approach of the dienophile was favored in both instances and the resulting α-hydroxy lactams were afforded in moderate asymmetric induction (74% and 83% ee, respectively). The major enantiomer belonged to the (1*R*) series as was observed in the vinyl ether study. Also, in the minor endo-derived product, the major enantiomer belonged to the (1*S*) series as observed in the vinyl ether cycloaddition promoted by Ti(O-*i*-Pr)$_2$Cl$_2$. Therefore in both the exo and endo approaches, the reactive propenyl ether conformation was s-trans. The low asymmetric induction in the endo-derived products (38% and 41% ee) can be attributed to deformation of the chiral auxiliary caused by proximity to the large aluminum Lewis acid. From these results it can be

(41) The *re* and *si* faces of the diene are defined with respect to the nitroalkene β-carbon atom.

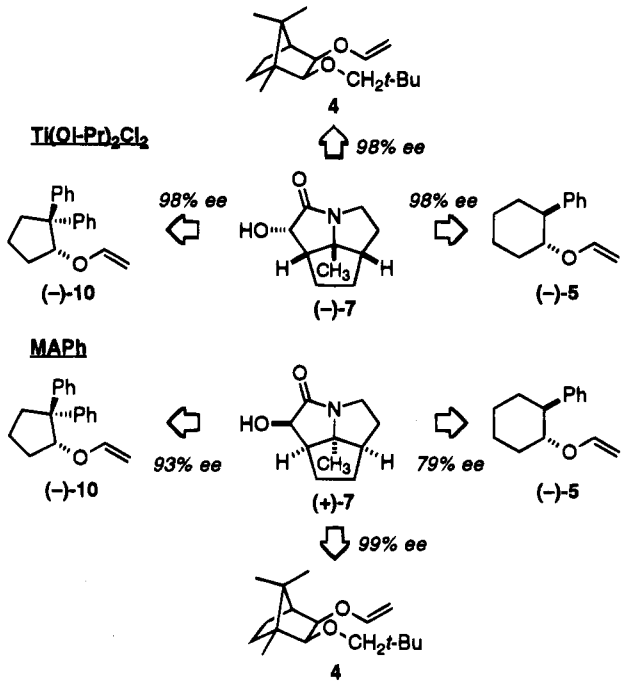


Figure 6. Comparison of chiral auxiliary efficiency in vinyl ether cycloadditions.

concluded that propenyl ethers (*E*)- and (*Z*)-**12** react through an s-trans conformation when approaching the heterodiene in an endo orientation. However, the reactive conformation in the exo approach is Lewis acid dependent being s-trans for MAPh and s-cis or cisoid-like for Ti(O-*i*-Pr)$_2$Cl$_2$.

Comparison of Auxiliaries in Nitroalkene [4 + 2] Cycloadditions. Three chiral auxiliaries (**1**, **2**, and **3**) have now shown the ability to afford high levels of stereoselection in nitroalkene [4 + 2] cycloadditions.[2b,e] Vinyl ethers derived from all three chiral auxiliaries have shown nearly identical selectivities in Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloadditions with nitroalkene **6** to afford α-hydroxy lactam (−)-**7**, Figure 6. The differences, however, manifest themselves when one considers exo selective cycloadditions. The reaction promoted by MAPh with the camphor-derived vinyl ether **4** afforded very high asymmetric induction ((+)-**7**, 99% ee), Scheme 3. However, vinyl ether **5** derived from the more readily available chiral auxiliary **2** provided only moderate selectivity (79% ee). The vinyl ether (−)-**10** derived from 2,2-diphenylcyclopentanol, on the other hand, provided nearly equal selectivity to that obtained from **4** while being easily prepared in three steps from commercial starting materials.

The success of cycloadditions of chiral propenyl ethers derived from the three auxiliaries may be similarly compared, Figure 7. To access the fused hydroxy lactam (−)-**16a**, chiral auxiliaries **1** and **2** (as their (*E*)-propenyl ethers) still provide the highest selectivities since (*E*)-**12** (derived from (−)-**3**) suffered from low endo/exo selectivity when promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ (not shown). In contrast, for the methyl epimer (−)-**16b**, the Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloaddition of the (*Z*)-propenyl ether (*Z*)-**12** derived from chiral auxiliary (−)-**3** clearly provided the highest level of asymmetric induction (92% ee) when compared to the (*Z*)-propenyl ethers derived from auxiliaries **1** or **2** (50% and 82% ee, respectively, not shown). Chiral auxiliary (−)-**3** also allowed for access to the dextrorotatory enantiomers of **16a** and **16b** through the use of MAPh to promote the cycloaddition in 83% and 74% ee, respectively.

Conclusion

Chiral vinyl and propenyl ethers derived from (*R*)-2,2-diphenylcyclopentanol, (−)-**3**, have been found to provide significant improvements over the shortcomings of previously examined auxiliaries **1** and **2**. The optically active alcohol (>97% ee) is available in three steps from commercially available starting materials employing an asymmetric, oxazaborolidine-catalyzed, borane reduction of the corresponding ketone. The vinyl ether derived from (−)-**3** has shown high π-facial selectivities in endo and exo mode [4 + 2] cycloadditions comparable to those previously obtained with camphor-derived vinyl ether **4**. Likewise, asymmetric induction in Ti(O-*i*-Pr)$_2$Cl$_2$-promoted cycloadditions of propenyl ether (*Z*)-**12** is the highest observed to date (92% ee). Additional evidence obtained through cycloadditions of propenyl ethers derived from (−)-**3** support the observation that Ti(O-*i*-Pr)$_2$Cl$_2$ promotes a highly endo-selective [4 + 2] cycloaddition while MAPh promotes a highly exo-selective cycloaddition. Unfortunately, 2,2-diphenylcyclopentanol does not satisfy all of the criteria for a general chiral auxiliary in nitroalkene [4 + 2] cycloadditions. Endo/exo erosion in the corresponding propenyl ethers compared to the vinyl ether is still observed, and the opposite enantiomer of the auxiliary is expensive to prepare by the asymmetric borane reduction. Nonetheless, alcohol (−)-**3** has expanded the utility of the tandem nitroalkene cycloaddition especially in the application of (*Z*)-propenyl ethers and exo mode [4 + 2] cycloadditions.

Experimental Section

General. Bulb-to-bulb distillations were performed on a Kugelrohr apparatus; bp refers to air bath temperatures which are uncorrected. Melting points are uncorrected. Analytical HPLC employed a Pirkle Covalent L-naphthylalanine column (250 × 4.5 mm, 5 μm (Regis)) or an Excalibar alumina column (250 × 4.5 mm). MPLC employed a 40 × 5 cm silica gel (Kieselgel 60G) column. Column (flash) chromatography was performed using 230−400 mesh silica gel. All reactions were performed in oven- (140 °C) or flame-dried glassware under an inert atmosphere of dry N_2 unless performed in H_2O. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$), CH_2Cl_2 ($CaCl_2$), *tert*-butyl methyl ether (MTBE) ($CaSO_4/FeSO_4$), and EtOAc (K_2CO_3). Reaction solvents were distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5), EtOH (Mg), MeOH (Mg), THF (Na, benzophenone), toluene (Na). *n*-Butyllithium was titrated according to the method of Gilman.[42] Optical rotations are reported in the form $[\alpha]^{temp}_D$ (solvent, concn). IR spectra 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) as an internal standard in $CDCl_3$ unless otherwise specified. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants, *J*, are reported in Hertz. Low-resolution EI mass spectra were obtained with an ionization voltage of 70 eV. Low-resolution 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

(42) Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 447.

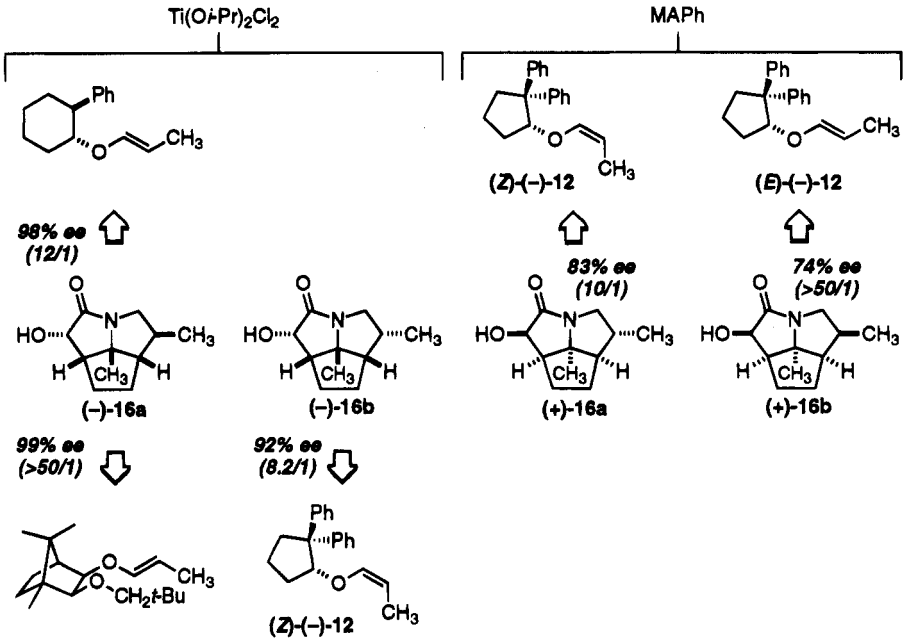


Figure 7. Isomeric α-hydroxy lactams accessible through propenyl ether cycloadditions.

were performed by the University of Illinois Microanalytical Service Laboratory.

2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile (8). A solution of diisopropylamine (39.9 mL, 0.29 mol, 1.1 equiv) in THF (200 mL) was cooled to 0 °C, and *n*-BuLi (101.6 mL, 2.55 M in hexane, 0.26 mol, 1.0 equiv) was slowly added. After 10 min, a solution of diphenylacetonitrile (50.0 g, 0.26 mol) in THF (200 mL) was added over 30 min forming a deep yellow solution. A solution of 4-bromobutyronitrile (28.3 mL, 0.29 mol, 1.1 equiv) in THF (200 mL) was added over 20 min. The resulting bright yellow solution was allowed to slowly warm to rt over 10 h. The reaction mixture was quenched by the slow addition of H_2O (25 mL), was diluted with MTBE (400 mL), and washed with H_2O (2 × 100 mL) and brine (100 mL). The aqueous layers were back-extracted with MTBE (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the resulting crude dinitrile was placed under high vacuum (0.2 Torr) for 1 h. The dinitrile was dissolved in a mixture of *tert*-butyl alcohol (400 mL) and THF (200 mL). Potassium *tert*-butoxide (23.25 g, 0.21 mol, 0.8 equiv) was added, and the suspension was heated at 60 °C (internal temperature) for 2 h. The reaction mixture was quenched at rt with H_2O (25 mL), diluted with MTBE (500 mL), and washed with H_2O (100 mL) and brine (3 × 100 mL). The aqueous layers were back-extracted with MTBE (100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was suspended in MTBE (75 mL), cooled (0 °C), filtered, and recrystallized from absolute ethanol (400 mL). The concentrated mother liquor was purified by column chromatography (hexane/EtOAc, 4/1) and was recrystallized (absolute EtOH) to afford a combined yield of 57.7 g (86%) of the enamino nitrile **8** as a white solid. Data for **8**: mp 145–148 °C (EtOH); ^{1}H NMR 7.37–7.23 (m, 10 H), 4.38 (br, 2 H), 2.63 (dd, J = 7.6, 6.3, 2 H), 2.46 (dd, J = 6.8, 5.6, 2 H); ^{13}C NMR 164.78, 142.82, 128.40, 128.19, 127.08, 118.77, 76.19, 62.76, 41.48, 27.94; IR 3490 (w), 2197 (m), 1643 (s); MS (EI) 260 (M^+, 100); TLC R_f 0.38 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{18}H_{16}N_2$ (260.34): C, 83.05; H, 6.19; N, 10.76. Found: C, 83.34; H, 6.07; N, 10.84.

2,2-Diphenylcyclopentanone (9). A mixture of enamino nitrile **8** (57.5 g, 0.22 mol) and 800 mL of concd HCl was mechanically stirred for 5 min, and 800 mL of H_2O was added. The reaction mixture was heated to reflux (heating mantle, 110 °C internal temperature) with vigorous stirring for 4 days. After being cooled to rt, the reaction mixture was extracted with CH_2Cl_2 (5 × 200 mL). The organic layers were washed with sat. aq $NaHCO_3$ (100 mL) and brine (100 mL), and the aqueous layers were back-extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was recrystallized from MTBE (300 mL). The concentrated mother liquor was purified by column chromatography (hexane/EtOAc, 4/1), decolorized with carbon, and recrystallized (MTBE) to afford a combined yield of 48.2 g (92%) of the ketone **9** as a white solid. Data for **9**: mp 85–88 °C (MTBE); ^{1}H NMR 7.32–7.21 (m, 10 H), 2.73 (t, J = 6.6, 2 H), 2.46 (t, J = 7.7, 2 H), 1.95 (dt, J_d = 13.4, J_t = 7.3, 2 H); ^{13}C NMR 217.77, 142.02, 128.31, 127.96, 126.69, 62.44, 38.16, 38.07, 18.79; IR 3033 (m), 1744 (s), 1494 (s); MS (EI) 236 (M^+, 47), 180 (100); TLC R_f 0.48 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{17}H_{16}O$ (236.31): C, 86.41; H, 6.82. Found: C, 86.57; H, 6.75.

***(R)*-(−)-2,2-Diphenylcyclopentanol ((−)-3).** To a solution of (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-1,3,2-oxazaborole (1.76 g, 6.34 mmol, 0.1 equiv) in THF (86 mL) was added borane–methyl sulfide complex (6.34 mL, 63.4 mmol, 1.0 equiv), and the solution was warmed to 40 °C (internal temperature). A solution of ketone **9** (15.0 g, 63.4 mmol) dissolved in THF (121 mL) was added dropwise over 8 h to the stirred catalyst solution maintained at 40 °C, and the mixture was stirred at 40 °C for an additional 30 min. The reaction mixture was cooled to 0–5 °C and carefully quenched with 100 mL of MeOH. The cold bath was removed, and the reaction was left to stir until gas evolution ceased. The resulting solution was concentrated by simple distillation such that 100 mL of solvent was distilled. An additional 100 mL of fresh MeOH was added, and 100 mL of solvent was distilled off again. The remaining solution was concentrated in vacuo to afford a slightly yellow oil. The oil was dissolved in MTBE (250 mL) and washed with 0.1 N aqueous HCl (3 × 100 mL), and the combined acidic, aqueous phases were back-extracted with MTBE (100 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 15.1 g of an off-white solid. The solid was purified by bulb-to-bulb distillation to afford 14.7 g (97%) of (*R*)-(−)-**3** (92% ee) as a white solid. Multiple recrystallizations of the product from hexane afforded 11.3 g (75%) of (*R*)-(−)-**3** (>97% ee). To recover (*S*)-α,α-diphenyl-2-pyrrolidinemethanol, the acidic, aqueous phase was made basic (blue to litmus) by addition of 25 mL of aqueous 25% NaOH solution and was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a clear oil which crystallized under high vacuum (0.1 Torr, several hours). The solid was

recrystallized (hexane) to afford 1.5 g (93% recovery) of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol as a white crystalline solid. Data for (−)-**3**: bp 180 °C (0.2 Torr); mp 76−77 °C (hexane); ^{1}H NMR 7.33−7.14 (m, 10 H), 4.88 (dd, J = 9.7, 4.8, 1 H), 2.66 (dt, J_d = 8.9, J_t = 12.9, 1 H), 2.32 (ddd, J = 12.9, 8.7, 3.3, 1 H), 2.10 (m, 1 H), 1.93 (m, 1 H), 1.75−1.55 (m, 2 H), 1.28 (dd, J = 4.9, 0.7, 1 H); ^{13}C NMR 146.87, 144.26, 128.53, 128.44, 128.17, 126.92, 126.33, 125.89, 77.57, 76.69, 59.71, 34.60, 31.67, 19.95; IR 3585 (m), 2967 (s), 1495 (s), 1446 (s); MS (EI) 238 (M^+, 44), 167 (100); TLC R_f 0.49 (hexane/EtOAc, 4/1); $[\alpha]^{26}_D$ = −114.8° (c = 1.17, EtOH). Anal. Calcd for $C_{17}H_{18}O$ (238.33): C, 85.67; H, 7.61. Found: C, 85.65; H, 7.59.

(*R*)-(−)-(2,2-Diphenylcyclopentoxy)ethene ((−)-10). (*R*)-(−)-2,2-Diphenylcyclopentanol (**3**) (3.56 g, 15.0 mmol) was dissolved in *n*-butyl vinyl ether (125 mL), and $Hg(OAc)_2$ (1.20 g, 3.75 mmol, 0.25 equiv) was added. The solution was heated to reflux for 12 h. An additional portion of $Hg(OAc)_2$ (1.20 g, 3.75 mmol, 0.25 equiv) was added, and the solution was heated to reflux for an additional 12 h. The reaction mixture was cooled to approximately 40 °C and was quenched with a saturated aqueous solution of K_2CO_3 (50 mL). The mixture was poured into (200 mL) MTBE and washed with saturated aqueous K_2CO_3 (3 × 25 mL). The aqueous layers were back-extracted with MTBE (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on basic alumina (pentane/MTBE, 100/0, 95/5; MTBE) and distillation to afford 2.78 g (70%) of vinyl ether (−)-**10** and 0.58 g of recovered alcohol. Data for (−)-**10**: bp 175 °C (0.2 Torr); ^{1}H NMR 7.30−7.09 (m, 10 H), 6.30 (dd, J = 14.4, 6.8, 1 H), 4.95 (m, 1 H), 4.20 (dd, J = 14.4, 1.7, 1 H), 3.99 (dd, J = 6.8, 1.7, 1 H), 2.58−2.52 (m, 2 H), 1.97−1.83 (m, 3 H), 1.68−1.61 (m, 1 H); ^{13}C NMR 150.30, 146.12, 145.17, 128.28, 128.24, 127.76, 126.61, 125.94, 125.61, 87.46, 83.69, 59.16, 34.57, 28.67, 20.27; IR 3061 (s), 2970 (s), 1607 (s), 1495 (s); MS (EI) 264 (M^+, 3), 117 (100); $[\alpha]^{25}_D$ = −40.4° (CH_2Cl_2, c = 1.18); TLC R_f 0.44 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{19}H_{20}O$ (264.37): C, 86.32; H, 7.63. Found: C, 86.08; H, 7.65.

(*R*)-2,2-Diphenyl-1-(1(*E*)-propenyloxy)cyclopentane ((*E*)-(−)-12) and (*R*)-2,2-Diphenyl-1-(1(*Z*)-propenyloxy)cyclopentane ((*Z*)-(−)-12). To a solution of allyl ether (−)-**11** (1.00 g, 3.59 mmol) dissolved in ethanol (45 mL) was added $RhCl(PPh_3)_3$ (233 mg, 0.25 mmol, 0.07 equiv), DABCO (161 mg, 1.44 mmol, 0.40 equiv), and H_2O (5 mL). The solution was heated to 40 °C (internal temperature) for 9 h. The reaction mixture was allowed to cool to rt, filtered through Florisil, and concentrated in vacuo. The crude product was filtered through a plug of basic alumina (2 cm diameter, 1.5 cm) eluting with pentane (200 mL) and concentrated in vacuo. The crude product was purified by MPLC (12 mL/min, hexane/MTBE, 99.9/0.1) and distillation to afford 443 mg of (*Z*)-(−)-**12** as a white solid, 212 mg of (*E*)-(−)-**12** as a white solid, and 104 mg of a mixture of *E* and *Z* isomers in a combined yield of 76%. Data for (*Z*)-(−)-**12**: bp 150 °C (0.1 Torr); ^{1}H NMR 7.31−7.12 (m, 10 H), 5.98 (dq, J_d = 6.1, J_q = 1.7, 1 H), 4.69 (t, J = 4.4, 1 H), 4.35 (quint, J = 6.6, 1 H), 2.69−2.62 (m, 1 H), 2.44−2.37 (m, 1 H), 2.00−1.87 (m, 2 H), 1.82−1.73 (m, 1 H), 1.70−1.60 (m, 1 H), 1.36 (dd, J = 1.7, 6.8, 3 H); ^{13}C NMR 146.78, 144.83, 143.98, 128.17, 127.46, 126.78, 125.82, 125.50, 101.90, 86.63, 58.78, 34.91, 29.38, 19.81, 9.28; IR 3036 (s), 1664 (s), 1599 (s), 1495 (s); MS (EI) 278 (M^+, 1), 117 (100); $[\alpha]^{25}_D$ = −128.4° (CH_2Cl_2, c = 1.19); HPLC t_R 8.99 min (alumina; hexane/MTBE, 99.9/0.1, 1.0 mL/min); TLC R_f 0.46 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{20}H_{22}O$ (278.39): C, 86.29; H, 7.97. Found: C, 86.32; H, 8.00. Data for (*E*)-(−)-**12**: bp 170 °C (0.1 Torr); ^{1}H NMR 7.31−7.11 (m, 10 H), 6.09 (dq, J_d = 12.5, J_q = 1.6, 1 H), 4.82 (m, 1 H), 4.77 (dq, J_d = 12.5, J_q = 6.6, 1 H), 2.60−2.46 (m, 2 H), 1.98−1.78 (m, 3 H), 1.70−1.58 (m, 1 H), 1.53 (dd, J = 1.7, 6.8, 3 H); ^{13}C NMR 146.35, 145.24, 144.93, 128.32, 128.22, 127.68, 125.85, 125.53, 99.90, 84.56, 59.09, 34.54, 28.71, 20.17, 12.75; IR 3030 (s), 1672 (s), 1653 (s), 1495 (s); MS (EI) 278 (M^+, 1), 117 (100); $[\alpha]^{25}_D$ = −35.7° (CH_2Cl_2, c = 1.18); HPLC t_R 10.62 min (alumina; hexane/MTBE, 99.9/0.1, 1.0 mL/min); TLC R_f 0.46 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{20}H_{22}O$ (278.39): C, 86.29; H, 7.97. Found: C, 86.31; H, 7.93.

Tandem Cycloadditions Promoted by $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ with Vinyl Ether (−)-10. (2*S*,2a*S*,4a*S*,6*S*,7a*R*,7b*R*)-6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-7b-methyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (13a). To a cold (−78 °C) solution of nitroalkene **6** (199 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL) was added a solution of vinyl ether (−)-**10** (790 mg, 3.00 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL). A freshly prepared solution of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (3.00 mmol, 3.0 equiv) in CH_2Cl_2 (1.5 mL) was added dropwise to the solution over 5 min. The resulting pale yellow solution was stirred at −78 °C for 2 h. The reaction mixture was quenched with a 1 N solution of NaOH in MeOH (6.0 mL) and allowed to warm for 5 min. The mixture was diluted with CH_2Cl_2 (200 mL) and was washed with H_2O (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 ($MgSO_4$/$NaHCO_3$,1/1) and concentrated in vacuo. The crude concentrate was allowed to stand at rt for 10 h to allow for the [3 + 2] cycloaddition to occur. The crude products were then purified by column chromatography (hexane/EtOAc, 8/1, 6/1, 4/1) to afford 410 mg (89%) of a mixture of nitroso acetals **13a**, **13a′**, and **13b** (48:1:1, ^{1}H NMR) and 15 mg of recovered nitroalkene. An analytical sample of **13a** was prepared by recrystallization from EtOAc/hexane. Data for **13a**: mp 48−52 °C (hexane/EtOAc); ^{1}H NMR 7.26−7.11 (m, 10 H), 4.87 (dd, J = 3.2, 6.6, 1 H), 4.83 (d, J = 8.3, 1 H), 4.75 (dd, J = 2.7, 5.9, 1 H), 3.79 (s, 3 H), 2.67 (dt, J_d = 3.2, J_t = 8.1, 1 H), 2.57 (dt, J_d = 12.5, J_t = 9.0, 1 H), 2.27 (ddd, J = 2.9, 7.8, 11.5, 1 H), 2.20−2.15 (m, 1 H), 2.03−1.96 (m, 1 H), 1.94−1.86 (m, 1 H), 1.85−1.73 (m, 4 H), 1.53−1.25 (m, 4 H), 1.23 (s, 3 H); ^{13}C NMR 170.18, 146.50, 145.29, 128.58, 128.09, 127.45, 126.92, 125.79, 125.41, 101.18, 87.07, 86.74, 83.19, 59.81, 57.20, 52.30, 43.33, 35.01, 34.00, 32.34, 28.14, 28.05, 24.48, 20.21; IR 2932 (s), 1744 (s), 1449 (s), 1199 (s); MS (FAB) 464 (MH^+, 21), 221 (100); $[\alpha]^{25}_D$ = −31.4° (CH_2Cl_2, c = 0.99); TLC R_f 0.26 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{28}H_{33}NO_5$ (463.57): C, 72.55; H, 7.18; N, 3.02. Found: C, 72.56; H, 7.29; N, 2.97.

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-7b-methyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((−)-7). To a solution of the mixture of nitroso acetals **13a**, **13a′**, and **13b** (345 mg, 0.75 mmol) in MeOH (50 mL) was added a catalytic amount of Raney nickel (W-2). The suspension was stirred for 36 h under 1 atm of hydrogen pressure at rt and was filtered though Celite and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 1/1, 1/3) to afford 92 mg (70%) of (−)-**7** as a white solid along with 145 mg (82%) of recovered alcohol (−)-**3**. Data for (−)-**7**:[2b] ^{1}H NMR 4.68 (d, J = 7.1, 1 H), 3.91 (ddd, J = 3.9, 8.5, 12.0, 1 H), 2.98−2.90 (m, 2 H, OH), 2.63 (q, J = 7.3, 1 H), 2.25 (m, 1 H), 2.15 (m, 1 H), 1.85−1.70 (m, 3 H), 1.50 (m, 1 H), 1.32 (s, 3 H), 1.25 (m, 1 H); ^{13}C NMR 176.40, 75.73, 72.86, 51.17, 49.24, 42.17, 31.49, 31.08, 24.82, 22.94; IR 2961 (m), 1707 (s), 1406 (m), 1334 (m); $[\alpha]^{25}_D$ = −35.1° (CH_2Cl_2, c = 1.13); TLC R_f 0.10 (hexane/EtOAc, 1/1).

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-7b-methyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (14). A solution of 3,5-dinitrobenzoyl azide (29 mg, 0.12 mmol, 1.1 equiv) in toluene (5.0 mL) was heated to reflux for 15 min, and a solution of (−)-**7** (20 mg, 0.11 mmol) in toluene (1.0 mL) was added. The solution was heated to reflux for 90 min and then was allowed to cool to rt. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (hexane/EtOAc, 3/1, 1/2) to afford 36 mg (84%) of **14** as a white solid. Data for **14**:[2b] ^{1}H NMR 10.24 (br, 1 H), 8.61 (t, J = 2.0, 1 H), 8.55 (d, J = 2.0, 2 H), 5.95 (d, J = 7.1, 1 H), 3.95 (ddd, J = 8.5, 3.9, 12.2, 1 H), 3.08 (dt, J_d = 12.2, J_t = 7.6, 1 H), 2.81 (q, J = 7.3, 1 H), 2.40 (m, 1 H), 2.29−2.21 (m, 1 H), 1.65 (m, 3 H), 1.45 (s, 3 H), 1.43 (m, 1 H), 1.27 (m, 1 H); ^{13}C NMR 172.10, 152.46, 148.62, 141.14, 118.05, 112.44, 76.68, 74.87, 49.48, 49.26, 42.93, 31.63, 31.03, 25.79, 22.69; IR 3024 (s), 1547 (s), 1226 (s); HPLC t_R (1*R*,3*S*,5a*R*,7a*R*,7b*S*)-**14**, 7.1 min (1.0%); t_R (1*S*,3*R*,5a*S*,7a*S*,7b*R*)-**14**, 20.3 min (99.0%) (Pirkle covalent L-naphthylalanine; hexane/EtOAc, 7/3, 1.5 mL/min); TLC R_f 0.35 (hexane/EtOAc, 1/1).

With Propenyl Ether (*E*)-12. (2*S*,2a*S*,4a*S*,5*S*,6*S*,7a*R*,-7b*R*)- and *rel*-(2*S*,2a*S*,4a*S*,5*R*,6*R*, 7a*R*,7b*R*)-6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-5,7b-dimethyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (15a, 15b′, 15B′). To a cold (−78 °C) solution of nitroalkene **6** (199 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of propenyl ether (*E*)-**12** (557 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL). A freshly prepared solution of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (3.00 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise to the solution over 10 min. The resulting pale-yellow solution was stirred at −78 °C for 3 h. The reaction mixture was quenched with a 1 N solution of NaOH in MeOH (6.0 mL) and allowed to warm for 5 min. The mixture was diluted with CH_2Cl_2 (300 mL) and was washed with H_2O (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 ($MgSO_4$/$NaHCO_3$, 1/1) and were concentrated in vacuo. The crude concentrate was allowed to stand at rt for 12 h to allow for the [3 + 2] cycloaddition to occur. The crude products were then purified by column chromatography (hexane/EtOAc, 6/1, 4/1) to afford 445 mg (93%) of nitroso acetals **15a**, **15b′**, and **15B′** as a mixture of diastereomers in a ratio of 14:2:1 (^1H NMR). Data for **15a**, **15b′**, **15B′**: ^1H NMR 7.44−7.09 (m, 10 H), 5.14 (d, J = 6.8, 0.1 H), 5.01 (t, J = 4.9, 0.2 H), 4.98 (d, J = 8.3, 0.2 H), 4.83 (m, 1.4 H), 4.76 (m, 0.1 H), 4.64 (d, J = 7.1, 0.2 H), 4.41 (d, J = 6.3, 0.7 H), 4.35 (d, J = 6.8, 0.1 H), 3.83 (s, 2.5 H), 3.79 (s, 0.5 H), 2.80−2.45 (m, 2 H), 2.35−2.18 (m, 2 H), 2.00−1.20 (m, 8.5 H), 1.32 (s, 2.5 H), 0.92−0.80 (m, 1 H), 0.42 (d, J = 7.2, 2.5 H), 0.39 (d, J = 7.2, 0.3 H), 0.37 (d, J = 6.8, 0.2 H); ^{13}C NMR 170.36, 170.28, 147.28, 146.53, 145.43, 145.43, 145.18, 129.28, 128.42, 128.07, 128.02, 127.64, 127.14, 127.11, 126.73, 125.71, 125.40, 106.53, 105.77, 103.24, 100.74, 86.92, 86.40, 85.46, 84.46, 82.76, 79.24, 59.91, 58.73, 56.79, 52.29, 50.81, 50.13, 49.68, 36.99, 36.10, 34.88, 34.41, 32.44, 31.77, 28.27, 28.12, 27.98, 27.43, 23.75, 20.11, 19.70, 17.15; IR 2957 (s), 1744 (s), 1495 (s), 1446 (s); MS (FAB) 478 (MH^+, 50), 258 (100); TLC R_f 0.27 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.60): C, 72.93; H, 7.39; N, 2.93. Found: C, 72.95; H, 7.42; N, 2.93.

(1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)- and (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]-pyrrolizin-2-one (16a, 16b). Hydrogenolysis of nitroso acetals **15a** and **15b′** (344 mg, 0.72 mmol) in MeOH (50 mL) as described for **13** afforded 118 mg (84%) of hydroxy lactams **16a** and **16b** as a white solid as a mixture of diastereomers (2.8:1.0, ^1H NMR) along with 168 mg (98%) of recovered alcohol (−)-**3**. Data for **16a**, **16b**:[2d] ^1H NMR 4.64 (m, 1 H), 4.04 (dd, J = 7.3, 12.0, 0.7 H), 3.20 (d, J = 9.0, 0.5 H), 2.90 (br, 0.2 H, OH), 2.82 (br, 0.8 H, OH), 2.78−2.60 (m, 0.5 H), 2.53 (m, 1.4 H), 2.11 (m, 0.7 H), 1.85−1.39 (m, 5.2 H), 1.36 (s, 0.9 H), 1.33 (s, 2.1 H), 1.06 (d, J = 6.6, 2.1 H), 1.02 (d, J = 6.8, 0.9 H); ^{13}C NMR 177.21, 77.50, 71.88, 54.19, 50.22, 47.31, 33.99, 25.44, 24.77, 21.98, 14.88, 176.03, 75.33, 72.40, 58.05, 51.85, 50.42, 42.06, 30.81, 25.33, 24.12, 17.47; IR 3377 (s), 2961 (s), 1701 (s), 1452 (s); TLC R_f 0.13 (hexane/EtOAc, 1/1).

(1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)- and (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (17a, 17b). Derivatization of hydroxy lactams **16a** and **16b** (20 mg, 0.10 mmol) as described for **7** afforded 37 mg (92%) of **17a** and **17b** as a white solid. Data for **17a**, **17b**:[2e] ^1H NMR 10.50 (br, 0.2 H), 10.28 (br, 0.8 H), 8.75−8.48 (m, 3 H), 6.00 (d, J = 8.1, 0.2 H), 5.97 (d, J = 6.8, 0.8 H), 4.08 (dd, J = 7.3, 12.0, 0.8 H), 3.40−3.17 (m, 0.5 H), 2.98−2.64 (m, 2.4 H), 2.24 (m, 0.3 H), 2.08−1.45 (m, 5 H), 1.47 (s, 0.6 H), 1.46 (s, 2.4 H), 1.13 (d, J = 6.6, 2.4 H), 1.05 (d, J = 7.1, 0.6 H); ^{13}C NMR 173.47, 172.33, 152.99, 152.83, 148.82, 141.70, 141.64, 118.25, 118.17, 112.49, 112.43, 78.29, 76.24, 75.02, 74.09, 58.34, 54.45, 51.10, 50.33, 49.01, 47.97, 42.88, 34.33, 31.34, 26.61, 26.15, 25.87, 24.12, 21.73, 17.43, 15.18; IR 3115 (m), 1741 (s), 1691 (s); HPLC t_R (1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)-**17a**, 13.5 min (1.4%); t_R (1*R*,3*S*,5*S*, 5a*R*,7a*R*,7b*S*)-**17b**, 15.5 min (5.2%); t_R (1*S*,3*R*,5*S*,5a*S*,7a*S*, 7b*R*)-**17a**, 35.2 min (67.9%); t_R (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-**17b**, 40.0 min (25.5%) (Pirkle covalent L-naphthylalanine; hexane/EtOAc, 85/15, 2.0 mL/min, 25 min; ramp for 2 min to hexane/EtOAc, 75/25, 2.0 mL/min); TLC R_f 0.36 (hexane/EtOAc, 1/1).

With Propenyl Ether (*Z*)-12. 6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-5,7b-dimethyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (15). To a cold (−78 °C) solution of nitroalkene **6** (199 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of propenyl ether (*Z*)-**12** (557 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL). A freshly prepared solution of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (3.00 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise to the solution over 10 min. The resulting pale-yellow solution was stirred at −78 °C for 4 h. The reaction mixture was quenched with a 1 N solution of NaOH in MeOH (6.0 mL) and allowed to warm for 5 min. The mixture was diluted with CH_2Cl_2 (300 mL) and was washed with H_2O (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 ($MgSO_4$/$NaHCO_3$, 1/1) and were concentrated in vacuo. The crude concentrate was allowed to stand at rt for 12 h to allow for the [3 + 2] cycloaddition to occur. The crude products were then purified by column chromatography (hexane/EtOAc, 6/1, 4/1) to afford 453 mg (95%) of nitroso acetals **15** as a mixture of diastereomers in a ratio of 26:1:1:1:1 (^1H NMR). Data for **15**: ^1H NMR 7.44−7.07 (m, 10 H, phenyl), 5.29 (d, J = 5.9, 0.1 H), 5.14 (d, J = 6.6, 0.9 H), 5.10−4.99 (m, 0.3 H), 4.83 (d, J = 7.6, 0.9 H), 4.82 (d, J = 8.1, 0.1 H), 4.76 (dd, J = 5.8, 2.9, 0.9 H), 4.69 (d, J = 6.6, 0.1 H), 4.64 (d, J = 7.1, 0.1 H), 4.41 (d, J = 6.3, 0.1 H), 3.83 (s, 0.1 H), 3.83 (s, 0.1 H), 3.81 (s, 0.1 H), 3.79 (s, 2.6 H), 3.77 (s, 0.1 H), 2.68 (dt, J_d = 2.9, J_t = 7.8, 1 H), 2.55 (dt, J_d = 12.5, J_t = 9.3, 1 H), 2.33 (m, 1 H), 2.18 (m, 1 H), 2.10−1.30 (m, 8.5 H), 1.25 (s, 3 H), 0.90 (d, J = 7.1, 0.1 H), 0.83 (d, J = 7.1, 0.1 H), 0.74 (d, J = 7.3, 0.1 H), 0.66 (d, J = 7.1, 0.1 H), 0.39 (d, J = 7.1, 2.6 H); ^{13}C NMR 170.34, 146.58, 145.62, 128.39, 128.10, 127.55, 126.67, 125.71, 125.35, 103.24, 87.08, 86.96, 85.44, 59.80, 56.65, 52.29, 50.13, 34.97, 32.33, 31.08, 29.25, 28.59, 23.96, 19.97, 12.78; IR 2957 (s), 1743 (s), 1446 (s); MS (FAB) 478 (MH^+, 25), 221 (100); TLC R_f 0.27 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.60): C, 72.93; H, 7.39; N, 2.93. Found: C, 72.96; H, 7.38; N, 2.91.

(1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)- and (1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]-pyrrolizin-2-one (16a, 16b). Hydrogenolysis of nitroso acetal diastereomers **15** (374 mg, 0.78 mmol) in MeOH (50 mL) as described for **13** afforded 119 mg (78%) of hydroxy lactams **16a** and **16b** as a white solid consisting of a mixture of diastereomers in a ratio of 8.7:1.0 (^1H NMR) along with 170 mg (91%) of recovered alcohol (−)-**3**. Data for **16a**, **16b**: ^1H NMR 4.65 (d, J = 8.1, 1 H), 4.04 (dd, J = 7.3, 11.7, 0.1 H), 3.19 (d, J = 8.3, 1.8 H), 3.10 (br, 0.9 H), 2.98 (br, 0.1 H), 2.74 (m, 1 H), 2.65 (m, 0.9 H), 2.53 (m, 0.1 H), 2.19−2.04 (m, 1.8 H), 1.82−1.45 (m, 2.6 H), 1.35 (s, 2.7 H), 1.33 (s, 0.3 H), 1.05 (m, 1 H), 1.02 (d, J = 6.8, 2.7 H); ^{13}C NMR 177.25, 77.49, 71.88, 54.19, 50.21, 47.29, 33.97, 25.43, 24.77, 21.97, 14.88, 72.40, 58.04, 51.85, 50.41, 42.05, 30.80, 25.23, 24.10, 17.46; IR 3358 (w), 2963 (s), 1693 (s), 1404 (s); TLC R_f 0.13 (hexane/EtOAc, 1/1).

(1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*), and (1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (17a, 17b). Derivatization of hydroxy lactams **16a** and **16b** (20 mg, 0.10 mmol) as described for **7** afforded 36 mg (90%) of **17a** and **17b** as a white solid. Data for **17a**, **17b**: ^1H NMR 10.54 (br, 1 H), 8.56 (t, J = 2.1, 1 H), 8.51 (d, J = 2.0, 2 H), 6.00 (d, J = 8.1, 1 H), 4.10 (dd, J = 8.4, 12.0, 0.1 H), 3.35 (ddd, J = 1.3, 12.0, 9.3, 0.9 H), 3.22 (dd, J = 11.4, 8.4, 1 H), 2.91 (m, 1 H), 2.80−2.65 (m, 1 H), 2.22 (dt, J_d = 10.3, J_t = 6.6, 1 H), 2.08−1.60 (m, 3 H), 1.47 (s, 3 H), 1.15 (m, 1 H), 1.05 (d, J = 7.1, 3 H); ^{13}C NMR 173.54, 152.87, 148.88, 141.77, 118.30, 112.52, 78.30, 74.12, 58.37, 54.49, 51.12, 50.33, 49.05, 47.99, 42.85, 34.35, 31.27, 26.54, 26.21, 26.21, 26.05, 24.12, 21.76, 17.43, 15.17; IR 3013 (s), 1689 (s), 1549 (s); HPLC t_R (1*R*,3*S*,5*R*,5a*R*,7a*R*, 7b*S*)-**17a**, 13.6 min (1.9%); t_R (1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-**17b**, 15.8 min (3.6%); t_R (1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)-**17a**, 35.5 min (9.0%); t_R (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-**17b**, 39.7 min (85.6%) (Pirkle covalent L-naphthylalanine; hexane/EtOAc, 85/15, 2.0

mL/min, 25 min; ramp for 2 min to hexane/EtOAc, 75/25, 2.0 mL/min); TLC R_f 0.36 (hexane/EtOAc, 1/1).

Tandem Cycloadditions Promoted by Methyl Aluminum Bis(2,6-diphenylphenoxide) with Vinyl Ether (−)-10. (2*R*,2a*R*,4a*R*,6*S*,7a*S*,7b*S*)-6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-7b-methyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (13b). To a solution of 2,6-diphenylphenol (1.48 g, 6.0 mmol, 6.0 equiv) in CH_2Cl_2 (12 mL) was added dropwise Me_3Al (2.0 M in toluene, 1.50 mL, 3.0 mmol, 3.0 equiv). The solution was allowed to stir at rt for 30 min and then was cooled to −78 °C. A solution of vinyl ether (−)-**10** (790 mg, 3.0 mmol, 3.0 equiv) in CH_2Cl_2 (1.5 mL) was added dropwise, and then a solution of nitroalkene **6** (199 mg, 1.00 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise resulting in a deep, red-colored solution. The reaction mixture was allowed to stir at −78 °C for 10 min. The cooling bath was removed, and the reaction mixture was allowed to warm until all precipitated solids dissolved. The reaction mixture was then allowed to stir at 0 °C for 45 min and was quenched with H_2O (1.0 mL). The reaction mixture was diluted with CH_2Cl_2 (200 mL) and then was washed with H_2O (2 × 50 mL) and brine (50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$/$NaHCO_3$, 1/1) and concentrated in vacuo. The crude concentrate was allowed to stand at rt for 12 h to allow for the [3 + 2] cycloaddition to occur and then was purified by column chromatography (hexane/EtOAc, 10/1, 8/1, 6/1, 4/1) to afford 400 mg (86%) of nitroso acetal diastereomers **13a**, **13a′**, and **13b** in a ratio of 1:2:122 (^{1}H NMR) along with 1.30 g of recovered 2,6-diphenylphenol. An analytical sample of **13b** was obtained after recrystallization from hexane/EtOAc. Data for **13b**: mp 40−45 °C (hexane/EtOAc); ^{1}H NMR 7.28−7.09 (m, 10 H), 4.81 (d, J = 7.7, 1 H), 4.70 (dd, J = 5.8, 2.3, 1 H), 4.66 (t, J = 7.5, 1 H), 3.78 (s, 3 H), 2.68 (m, 1 H), 2.59 (dt, J_d = 12.3, J_t = 8.8, 1 H), 2.28−2.11 (m, 3 H), 1.85−1.68 (m, 6 H), 1.49−1.35 (m, 3 H), 1.28 (s, 3 H); ^{13}C NMR 170.39, 146.74, 145.67, 128.58, 128.02, 127.42, 127.02, 125.72, 125.34, 99.96, 87.16, 85.17, 85.03, 60.00, 56.84, 52.35, 42.90, 35.22, 31.71, 31.50, 28.87, 26.57, 23.69, 20.46; IR 2955 (s), 1743 (s), 1493 (s); MS (FAB) 464 (MH^+, 10), 226 (100); TLC R_f 0.26 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{28}H_{33}NO_5$ (463.57): C, 72.55; H, 7.18; N, 3.02. Found: C, 72.54; H, 7.24; N, 2.95.

(1*R*,3*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-hydroxy-7b-methyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((+)-7). Hydrogenolysis of nitroso acetals **13a**, **13a′**, and **13b** (380 mg, 0.71 mmol) in MeOH (50 mL) as described above afforded 93 mg (74%) of hydroxy lactam (+)-**7** as a white solid along with 160 mg (94%) of recovered alcohol (−)-**3**. Data for (+)-**7**: mp 110−115 (hexane/EtOAc); ^{1}H NMR 4.68 (d, J = 10.0, 1 H), 3.91 (ddd, J = 8.5, 3.9, 12.2, 1 H), 2.98 (d, J = 2.7, 1 H), 2.93 (dt, J_d = 12.0, J_t = 8.0, 1 H), 2.63 (q, J = 7.3, 1 H), 2.26 (m, 1 H), 2.12 (m, 1 H), 1.81−1.69 (m, 3 H), 1.49 (m, 1 H), 1.32 (s, 3 H), 1.32−1.25 (m, 1 H); ^{13}C NMR 176.37, 75.68, 72.84, 51.14, 49.22, 42.14, 31.47, 31.05, 24.81, 22.91; IR 3360 (s), 2959 (s), 1695 (s), 1452 (m); $[\alpha]^{25}_D$ = +32.0° (CH_2Cl_2, c = 1.14); TLC R_f 0.10 (hexane/EtOAc, 1/1).

(1*R*,3*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-7b-methyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (14). Derivatization of hydroxy lactam (+)-**7** (20 mg, 0.11 mmol) as described above afforded 35 mg (81%) of **14** as a white solid. Data for **14**: ^{1}H NMR 10.38 (br, 1 H), 8.35 (t, J = 2.2, 1 H), 8.50 (d, J = 2.0, 2 H), 6.01 (d, J = 7.1, 1 H), 3.93 (ddd, J = 8.5, 3.7, 12.2, 1 H), 3.08 (dt, J_d = 12.0, J_t = 7.8, 1 H), 2.80 (q, J = 7.1, 1 H), 2.40 (m, 1 H), 2.28−2.19 (m, 1 H), 1.93−1.42 (m, 3 H), 1.44 (s, 3 H), 1.43 (m, 1 H), 1.27 (m, 1 H); ^{13}C NMR 172.71, 152.94, 148.86, 141.71, 118.71, 112.48, 76.54, 75.22, 49.74, 49.60, 42.81, 31.94, 31.35, 26.19, 22.74; IR 3026 (s), 1549 (s), 1346 (s), 1228 (s); HPLC t_R (1*R*,3*S*,5a*R*,7a*R*,7b*S*)-**14**, 6.8 min (96.4%); t_R (1*S*,3*R*,5a*S*,7a*S*,7b*R*)-**14**, 20.2 min (3.6%) (Pirkle covalent L-naphthylalanine; hexane/EtOAc, 7/3, 1.5 mL/min); TLC R_f 0.35 (hexane/EtOAc, 1/1).

With Propenyl Ether (*E*)-12. *rel*-(2*R*,2a*R*,4a*R*,5*S*,6*S*,7a*S*,7b*S*)-6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-5,7b-dimethyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (15B′, 15b′). To a solution of 2,6-diphenylphenol (1.48 g, 6.00 mmol, 6.0 equiv) in CH_2Cl_2 (20 mL) was added Me_3Al (2.0 M in toluene, 1.50 mL, 3.0 mmol, 3.0 equiv) dropwise. The pale yellow solution was allowed to stir at rt for 1 h before being cooled to 0 °C. A solution of propenyl ether (*E*)-**12** (557 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (3.0 mL) was added. The solution was cooled to −78 °C, and a solution of nitroalkene **6** (199 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise resulting in a deep red solution. The solution was stirred at −78 °C for 10 min, −10 °C for 1 h, and 0 °C for 1 h. The reaction mixture was quenched with H_2O (1.0 mL), diluted with CH_2Cl_2 (200 mL), and then washed with H_2O (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 ($MgSO_4$/$NaHCO_3$, 1/1) and concentrated in vacuo. The crude concentrate was allowed to stand at rt for 12 h to allow for the [3 + 2] cycloaddition to occur and then was purified by column chromatography (hexane/EtOAc, 6/1, 4/1) to afford 395 mg (83%) of a diastereomeric mixture of nitroso acetals **15B′** and **15b′** in a ratio of 7:1 (^{1}H NMR) along with 1.41 g of recovered 2,6-diphenylphenol. Data for **15B′**, **15b′**: ^{1}H NMR 7.44−7.06 (m, 10 H), 5.01 (t, J = 4.9, 0.1 H), 4.90 (d, J = 8.3, 0.1 H), 4.83 (d, J = 8.1, 0.9 H), 4.71 (dd, J = 2.4, 4.6, 0.9 H), 4.64 (d, J = 7.1, 0.1 H), 4.35 (d, J = 6.8, 0.9 H), 3.83 (s, 2.7 H), 3.79 (s, 0.3 H), 2.70 (m, 0.1 H), 2.68 (dt, J_d = 7.8, J_t = 2.9, 0.9 H), 2.65−2.54 (m, 0.9 H), 2.54−2.44 (m, 0.1 H), 2.34−2.16 (m, 3 H), 1.94−1.62 (m, 7 H), 1.42−1.29 (m, 1.3 H), 1.29 (s, 2.7 H), 0.90 (d, J = 7.1, 0.3 H), 0.37 (d, J = 6.6, 2.7 H); ^{13}C NMR 170.34, 146.79, 145.98, 129.29, 128.29, 128.30, 128.00, 127.64, 127.15, 127.12, 126.80, 125.62, 125.27, 105.78, 100.74, 87.10, 86.92, 85.90, 84.47, 79.25, 60.13, 56.81, 52.34, 49.72, 35.07, 34.43, 31.91, 28.31, 28.13, 27.99, 26.24, 23.73, 20.43, 19.70, 15.92, 16.71; IR 2959 (s), 1743 (s), 1446 (s), 1199 (s); MS (FAB) 478 (MH^+, 10), 240 (100); TLC R_f 0.27 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.60): C, 72.93; H, 7.39; N, 2.93. Found: C, 72.94; H, 7.38; N, 2.93.

(1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (16b). Hydrogenolysis of nitroso acetals **15B′** and **15b′** (322 mg, 0.67 mmol) in MeOH (50 mL) as described for **13** afforded 101 mg (77%) of hydroxy lactam **16b** as a white solid along with 144 mg (90%) of recovered alcohol (−)-**3**. Data for **16b**: ^{1}H NMR 4.65 (d, J = 8.1, 1 H), 3.19 (d, J = 8.6, 2 H), 3.09 (br, 1 H), 2.74 (t, J = 8.1, 1 H), 2.65 (m, 1 H), 2.11 (m, 2 H), 1.75-1.55 (m, 2 H), 1.35 (s, 3 H), 1.05 (m, 1 H), 1.02 (d, J = 7.1, 3 H); ^{13}C NMR 177.32, 77.40, 71.84, 54.15, 50.21, 47.26, 33.92, 25.40, 24.76, 21.94, 14.86; IR 3358 (m), 2963 (s), 1693 (s), 1452 (s); TLC R_f 0.13 (hexane/EtOAc, 1/1).

(1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolidin-2-one (17b). Derivatization of hydroxy lactam **16b** (20 mg, 0.10 mmol) as described for **7** afforded 38 mg (95%) of **17b** as a white solid. Data for **17b**: ^{1}H NMR 10.54 (br, 1 H), 8.75−8.50 (m, 3 H), 6.01 (d, J = 8.1, 1 H), 3.36 (t, J = 10.6, 1 H), 3.22 (dd, J = 8.5, 11.7, 1 H), 2.91 (t, J = 9.5, 1 H), 2.77 (quint, J = 6.6, 1 H), 2.21 (m, 1 H), 2.02 (m, 1 H), 1.82 (m, 1 H), 1.68 (m, 1 H), 1.47 (s, 3 H), 1.12 (m, 1 H), 1.05 (d, J = 7.1, 3 H); ^{13}C NMR 173.54, 152.86, 148.84, 141.74, 118.28, 112.51, 78.31, 74.10, 54.45, 49.02, 47.97, 34.33, 26.19, 26.06, 21.72, 15.16; IR 3109 (w), 1689 (s), 1549 (s), 1346 (s); HPLC t_R (1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)-**17a**, 12.9 min (0.5%); t_R (1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-**17b**, 14.0 min (85.3%); t_R (1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)-**17a**, 34.7 min (1.3%); t_R (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-**17b**, 38.7 min (12.9%) (Pirkle Covalent L-naphthylalanine; hexane/EtOAc, 85/15, 2.0 mL/min, 25 min; ramp for 2 min to hexane/EtOAc, 75/25, 2.0 mL/min); TLC R_f 0.36 (hexane/EtOAc, 1/1).

With Propenyl Ether (*Z*)-12. *rel*-(2*R*,2a*R*,4a*R*,5*R*,6*S*,7a*S*,7b*S*)- and *rel*-(2*S*,2a*S*,4a*S*,5*S*,6*R*,7a*R*,7b*R*)-6-[(*R*)-2,2-Diphenylcyclopentoxy]octahydro-5,7b-dimethyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester (15A′, 15a′, 15b). To a solution of 2,6-diphenylphenol (1.48 g, 6.00 mmol, 6.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise Me_3Al (2.0 M in toluene, 1.50 mL, 3.0 mmol, 3.0 equiv). The pale yellow solution was allowed to stir at rt for 1 h before being cooled to 0 °C. A solution of propenyl ether (*Z*)-**12** (557 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (3.0 mL) was added. The solution was cooled to −78 °C, and a solution of

nitroalkene **6** (199 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise resulting in a deep red solution. The solution was stirred at −78 °C for 10 min, −10 °C for 30 min, and 0 °C for 2.5 h. The reaction mixture was quenched with H_2O (1.0 mL), diluted with CH_2Cl_2 (300 mL), and then washed with H_2O (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 ($MgSO_4$/$NaHCO_3$, 1/1) and concentrated in vacuo. The crude concentrate was allowed to stand at rt for 12 h to allow for the [3 + 2] cycloaddition to occur and then was purified by column chromatography (hexane/EtOAc, 6/1, 4/1) to afford 402 mg (84%) of a diastereomeric mixture of nitroso acetals **15A′**, **15a′** and **15b** in a ratio of 12:1:1 (^{1}H NMR) along with 1.31 g of recovered 2,6-diphenylphenol. Data for **15A′, 15a′, 15b**: ^{1}H NMR 7.45−7.07 (m, 10 H), 5.29 (d, J = 6.5, 0.1 H), 5.14 (d, J = 6.6, 0.1 H), 5.08 (m, 0.1 H), 4.88 (m, 0.1 H), 4.83 (d, J = 7.6, 0.1 H), 4.78 (d, J = 4.9, 0.8 H), 4.75 (t, J = 4.6, 0.8 H), 4.69 (d, J = 6.8, 0.1 H), 4.51 (d, J = 6.1, 0.8 H), 3.81 (s, 0.2 H), 3.79 (s, 0.2 H), 3.77 (s, 2.6 H), 2.70 (m, 1 H), 2.64−2.54 (m, 1 H), 2.36−2.10 (m, 2 H), 2.24−1.38 (m, 7 H), 1.29 (s, 3 H), 1.16-1.10 (m, 2 H), 0.65 (d, J = 7.1, 2.8 H), 0.39 (d, J = 7.3, 0.2 H); ^{13}C NMR 171.16, 146.90, 145.55, 128.58, 128.37, 127.99, 127.93, 127.42, 126.95, 126.88, 125.66, 125.34, 103.22, 101.11, 96.30, 87.06, 86.95, 85.63, 83.95, 82.97, 79.78, 78.72, 77.51, 59.75, 58.31, 58.10, 56.63, 52.32, 50.10, 47.41, 46.56, 35.48, 35.23, 34.95, 34.53, 34.05, 33.81, 33.54, 33.23, 31.62, 31.19, 29.22, 28.57, 26.91, 26.27, 23.93, 20.12, 19.90, 19.16, 15.56, 15.34, 12.76; IR 2953 (s), 2874 (s), 1741 (s), 1493 (s), 1446 (s); MS (FAB) 478 (MH^+, 9), 117 (100); TLC R_f 0.27 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{29}H_{35}NO_5$ (477.60): C, 72.93; H, 7.39; N, 2.93. Found: C, 73.16; H, 7.47; N, 2.82.

(1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)- and (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]-pyrrolizin-2-one (16a, 16b). Hydrogenolysis of nitroso acetals **15a′** and **15b** (250 mg, 0.52 mmol) in MeOH (50 mL) as described for **13** afforded 80 mg (78%) of **16a** and **16b** as a mixture of diastereomers in a ratio of 17.2:1.0 (^{1}H NMR) along with 124 mg (100%) of recovered alcohol (−)-**3**. Data for **16a, 16b**: ^{1}H NMR 4.64 (m, 1 H), 4.04 (dd, J = 7.3, 11.7, 0.9 H), 3.19 (d, J = 8.3, 0.1 H), 2.96 (br, 0.9 H), 2.89 (br, 0.1 H), 2.53 (m, 2 H), 2.11 (m, 0.1 H), 1.78 (m, 1.9 H), 1.65−1.38 (m, 3 H), 1.35 (s, 0.2 H), 1.33 (s, 2.8 H), 1.06 (d, J = 6.6, 2.8 H), 1.02 (d, J = 6.8, 0.2 H); ^{13}C NMR 176.02, 75.34, 72.40, 58.05, 54.19, 51.88, 50.42, 47.31, 42.06, 33.99, 30.81, 25.44, 25.23, 24.77, 24.11, 21.98, 17.47, 14.89; IR 3377 (m), 2961 (s), 1699 (s), 1462 (s); TLC R_f 0.13 (hexane/EtOAc, 1/1).

(1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)- and (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-[*N*-(3,5-dinitrophenyl)carbamoxy]-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (17a, 17b). Derivatization of hydroxy lactams **16a** and **16b** (20 mg, 0.10 mmol) as described for **7** afforded 38 mg (95%) of **17a** and **17b** as a white solid. Data for **17a, 17b**: ^{1}H NMR 10.23 (br, 1 H), 8.52 (t, J = 2.2, 1 H), 8.47 (d, J = 2.0, 2 H), 5.96 (d, J = 6.8, 1 H), 4.08 (dd, J = 11.7, 7.3, 1 H), 2.69 (m, 2 H), 2.00−1.78 (m, 3 H), 1.55 (m, 3 H), 1.45 (s, 3 H), 1.12 (d, J = 6.8, 3 H); ^{13}C NMR 172.28, 152.98, 148.82, 141.62, 118.17, 112.43, 76.23, 75.03, 58.34, 51.09, 50.33, 42.88, 31.36, 26.64, 24.13, 17.43; IR 3028 (s), 1693 (s), 1547 (s), 1346 (s); HPLC t_R (1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)-**17a**, 12.3 min (83.3%); t_R (1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-**17b**, 15.4 min (2.8%); t_R (1*S*,3*R*,5*S*,5a*S*,7a*S*,7b*R*)-**17a**, 35.0 min (7.9%);t_R (1*S*,3*R*,5*R*,5a*S*,7a*S*,7b*R*)-**17b**, 39.4 min (6.1%) (Pirkle covalent L-naphthylalanine; hexane/EtOAc, 85/15, 2.0 mL/min, 25 min; ramp for 2 min to hexane/EtOAc, 75/25, 2.0 mL/min); TLC R_f 0.36 (hexane/EtOAc, 1/1).

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Supplementary Material Available: Complete ^{1}H and ^{13}C NMR assignments and IR and MS data for all characterized compounds (14 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.

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