Amino Acid-Derived Chiral Acyl Nitroso Compounds: Diastereoselectivity in Intermolecular Hetero Diels–Alder Reactions

Allen R. Ritter and Marvin J. Miller*

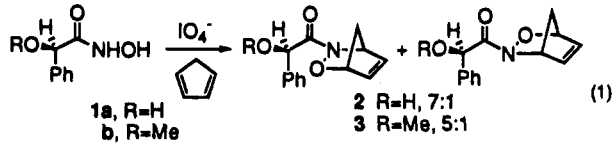
Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received March 23, 1994®

The diastereoselectivities of chiral acyl nitroso dienophiles derived from optically pure *N*-protected α-amino hydroxamic acids have been determined in intermolecular hetero Diels–Alder reactions. The cycloaddition reactions afforded synthetically useful quantities of functionally rich, optically pure cycloadducts, useful for the preparation of a variety of compounds of potential biological interest. Molybdenum hexacarbonyl reduction of the cycloadducts gave optically pure allylic alcohols. Osmium tetraoxide-catalyzed dihydroxylation of several bis-allylically substituted intermediates gave only the diastereomerically pure diols corresponding to naturally occurring 2′,3′-dihydroxynucleoside analogs.

Introduction

The use of hetero Diels–Alder reactions in the syntheses of natural products and in the preparation of useful synthetic intermediates has been studied extensively.[1] The development of asymmetric Diels–Alder reactions, using either chiral auxiliaries or chiral catalysts has further extended the utility of the Diels–Alder process to include the formation of enantiomerically enriched compounds. One of the more recently exploited classes of dienophiles has been acyl nitroso-containing compounds used in both intermolecular[2] and intramolecular[3] versions of the hetero Diels–Alder reaction. The highly functionalized cycloadducts provide valuable synthetic intermediates to a variety of biologically interesting molecules.[4] The cycloadditions of chiral mandelic acid-derived acyl nitroso compounds (**1a** and **1b**)[2] with simple dienes gave reasonable diastereoselectivity (7:1 and 5:1, respectively) and provided highly functionalized, optically active synthetic intermediates **2** and **3** (eq 1). Removal of the mandelic acid auxiliary is typically required for the preparation of compounds with interesting biological activity.

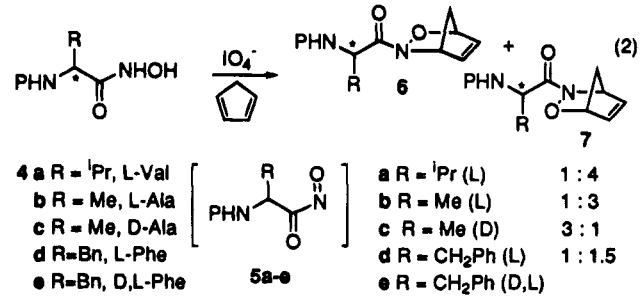


(1)

Amino acids offer several advantages as auxiliaries. They are readily available in both optically pure forms, they are relatively inexpensive, and most importantly, they can serve as chiral educts in the preparation of compounds with interesting biological activity. Apparently proline hydroxamic acid is the only amino acid that has been studied for use in the asymmetric acyl nitroso hetero Diels–Alder reaction.[5] Here we report on the diastereoselectivity of several optically pure acyl nitroso compounds **5a–e** derived from α-amino hydroxamic acids **4a–e** (P = *tert*-butyloxycarbonyl, Boc, or benzyloxycarbonyl, Cbz) in the intermolecular asymmetric hetero Diels–Alder reaction with cyclopentadiene (eq 2).[6] We also describe the chemoselective reduction and stereoselective dihydroxylation of hetero Diels–Alder adducts **6** and **7**.

Results and Discussion

Amino acid-derived hydroxamic acids were obtained by hydroxaminolyses of the corresponding *N*-protected amino acid methyl esters. Thus, L- and D-alanine, L- and D,L-phenylalanine, and L-valine were *N*-protected, esterified, and hydroxaminolyzed under standard conditions.[7] Oxidation of hydroxamic acids **4a–e** to acyl nitroso dienophiles **5a–e** in the presence of excess freshly distilled cyclopentadiene afforded a mixture of chromatographically separable diastereomers **6a–e** and **7a–e** in 65 to 90% yield (eq 2).[8] The ratio of diastereomers was



(2)

determined by HPLC analysis.[9] The absolute structure

® Abstract published in *Advance ACS Abstracts,* July 1, 1994.

(1) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987.

(2) (a) Kirby, G. W.; Nazeer, M. *Tetrahedron Lett.* **1988**, *29*, 6173. (b) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1043. (c) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1041. (d) Miller, A.; MacPaterson, T.; Procter, G. *Synlett* **1989**, *1*, 32. (e) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (f) Defoin, A.; Pines, J.; Streith, J. *Synlett* **1991**, *2*, 417.

(3) (a) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (c) Aoyagi, S.; Shishido, Y.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4325. (d) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083.

(4) Kim, C. U.; Luh, B. Y.; Martin, J. C. *J. Org. Chem.* **1991**, *56*, 2642.

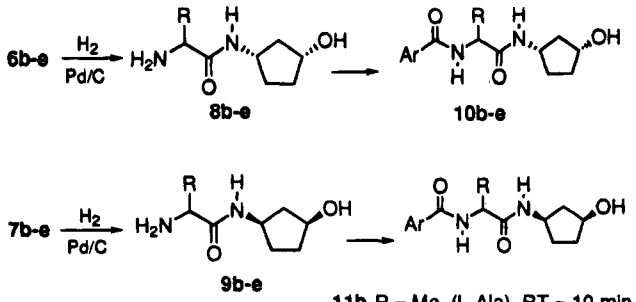
(5) Brouillard-Poichet, A.; Defoin, A.; Streith, J. *Tetrahedron Lett.* **1989**, *30*, 7061.

(6) Our study using proline as the auxiliary verified the results reported by Streith (see ref 5).

(7) (a) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571. (b) Fishbein, W. N.; Daly, J.; Streeter, C. L. *Anal. Biochem.* **1969**, *28*, 13.

0022-3263/94/1959-4602$04.50/0

Scheme 1



11b R = Me, (L-Ala), RT = 10 min
11c R = Me, (D-Ala), RT = 47 min
11d R = Bn, (L-Phe), RT = 14 min
11e R = Bn, (D-Phe), RT = 54 min

of the major diastereomer formed in the cycloaddition process was determined by X-ray crystal structure analysis on **6c**, the major diastereomer formed using D-alanine as the chiral auxiliary.[10]

We next determined the optical purity of cycloadducts **6b–d** and **7b–d** (Scheme 1). While each of the cited reports on the use of chiral acyl nitroso compounds disclose a ratio of diastereomers isolated, none have shown that racemization of the chiral acyl nitroso intermediate, potentially giving rise to mixtures of enantiomers, does not occur. While the cycloaddition reaction was expected to be a fast, concerted process, the highly electrophilic nature of acyl nitroso intermediates **5** makes them potentially prone to racemization in the same manner that some carboxyl-activated amino acids or their derivatives are labile to racemization.

Diastereomerically pure cycloadducts derived from L- and D-alanine and L- and D,L-phenylalanine (**6b–e** and **7b–e**) were subjected to hydrogenation (1 atm) in CH_3OH with 10% palladium on carbon as a catalyst, to give *cis* amino cyclopentanols **8b–e** and **9b–e**, respectively. Amino alcohols **9b–e** were then acylated with 3,5-dinitrobenzoyl chloride to provide dinitrobenzamides **11b–e**, which were chromatographically purified. Chiral HPLC analysis[11,12] of each of the derivatives formed showed that the L-alanine-derived diastereomers did not coelute with or contain the D-alanine diastereomers. From this analysis, and as expected, no racemization of the amino acid-derived acyl nitroso intermediate was observed. The separate diastereomers obtained from the cycloaddition were essentially optically pure. The addition of 1% D-alanine-derived benzamide **11c** to L-alanine-derived benzamide **11b** was detected, demonstrating enantiomeric purity of greater than 98%. In the same manner, L-phenylalanine-derived benzamide **11d** was determined to be greater than 98% enantiomerically pure.

(8) The cyclopentadiene adducts were separable by simple column chromatography. Boc-protected amino acid-derived hydroxamic acids reacted with the same diastereoselectivity as Cbz-protected hydroxamic acids.

(9) Normal phase HPLC was performed on a 25.4 cm × 4.6 mm 5 μm Econosil silica gel column with 20% 2-propanol in hexanes as eluent and 254 nm detection. The difference in retention time of the two diastereomers was greater than 3 min.

(10) While the X-ray analysis can only prove relative stereochemistry, the stereochemistry of the chiral auxiliary was known. As discussed, the optical purity of the auxiliary was maintained in the cycloaddition process.

(11) Only data for the major diastereomer is shown. Similar results were obtained for the minor, less polar diastereomers.

(12) Chiral HPLC conditions: The 3,5-dinitrobenzoylated *cis*-aminocyclopentanol derivatives were analyzed on a Rexachrom Pirkle Covalent D-Naphthylalanine 5 μm, 100 Å, 25 cm × 4.6 mm column. A solution of 2% 2-propanol in hexanes was used as eluent at a flow rate of 2 mL/min. Detection was by UV at 254 nm.

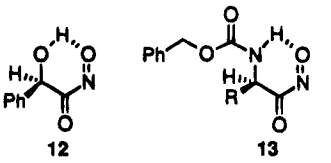
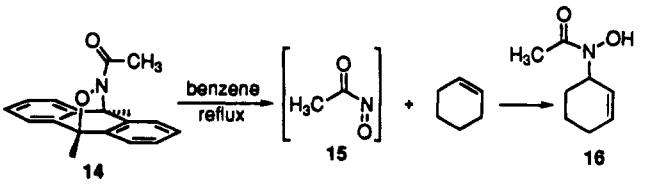


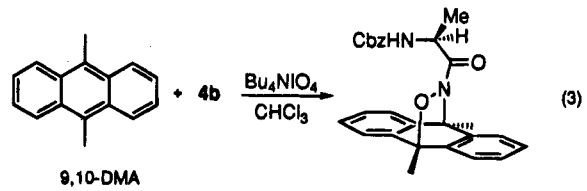
Figure 1. Proposed stabilization of transition state conformation.

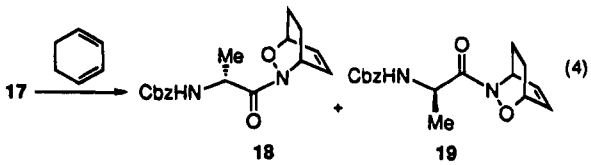
Scheme 2



The diastereoselectivity observed in the mandelic acid-derived systems is reported to result from the intramolecular hydrogen bonding as shown in structure **12** (Figure 1).[2d] Lower diastereoselectivity obtained with amino acids as auxiliaries suggests less stabilization of the reactive intermediate by intramolecular hydrogen bonding as in **13**.

An alternative source of the reactive acyl nitroso intermediate was based on Keck and co-worker's study of the ene reaction of acyl nitroso compounds derived from dimethylanthracene acyl nitroso adduct **14** (Scheme 2).[13] In that case, eneophile **15** was liberated by a retro Diels–Alder reaction on heating the dimethylanthracene adduct. Oxidation of L-alanine-derived hydroxamic acid **4b** in the presence of dimethylanthracene gave Diels–Alder adduct **17** (eq 3). Heating adduct **17** in refluxing benzene in the presence of cyclohexadiene gave a separable 1.1:6 mixture of diastereomers **18** and **19** (eq 4).



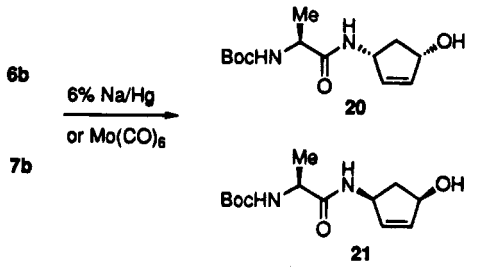


With the desired, diastereomerically separated, optically pure cycloadducts in hand, the chemistry of the functionally rich chiral educts was considered. The compatability of the novel amino acid-containing adducts with known conditions for N–O bond reduction and subsequently with the potential for stereoselective diol formation on the resulting bis-allylically substituted systems was particular of interest.

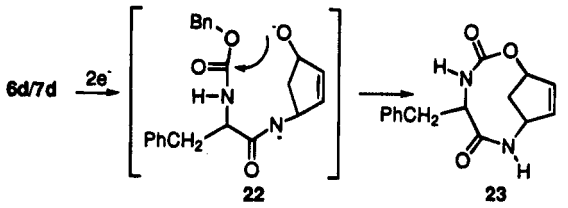
N–O Bond Reduction. As indicated earlier, palladium-catalyzed reduction of cycloadducts **6** and **7** with hydrogen gave saturated amino alcohols **8** and **9**. While the amino alcohols are themselves useful intermediates for the preparation of 2′,3′-dideoxy carbocyclic nucleoside analogs and conformationally restricted, CNS-active

(13) (a) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007. (b) Keck, G. E. *Tetrahedron Lett.* **1978**, *48*, 4767.

Scheme 3



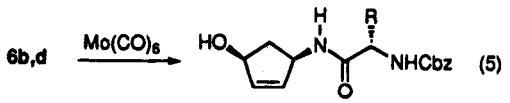
Scheme 4



γ-aminobutyric acid (GABA) analogs,[5] more synthetically versatile compounds could be obtained if the olefin was not reduced in the N—O bond reduction process.

The N—O bond of the oxazine cycloadducts derived from mandelic acid has been reduced using sodium or aluminum amalgam.[14] Using sodium amalgam, *tert*-butyloxycarbonyl (Boc)-protected cycloadducts **6b** and **7b** afforded allylic alcohols **20** and **21** in 50–85% yields, respectively (Scheme 3). Reduction of the benzyloxycarbonyl (Cbz)-protected cycloadduct **6d** (derived from L-phenylalanine) with sodium amalgam gave a 77% yield of a compound tentatively assigned as macrocyclic carbamate **23** (Scheme 4). The same process was not observed for Boc-protected cycloadducts, such as **6b** (P = Boc) due, presumably, to the steric hindrance of the *tert*-butyl carbamate.

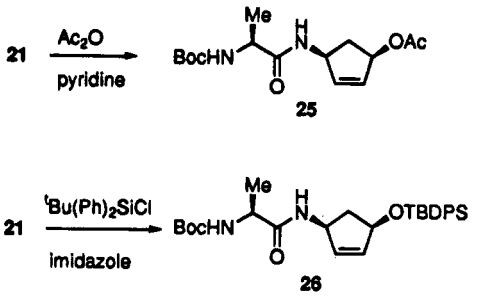
In contrast to the basic sodium amalgam conditions, use of neutral molybdenum hexacarbonyl efficiently cleaved the N—O bond without induction of competitive reactions.[15] This reaction was much cleaner and was easier to work up, and the yield was consistently higher than when sodium amalgam was used as the reducing agent. The best yields (90–95%) and fastest reactions were obtained when 1 full equivalent of molybdenum hexacarbonyl was employed. More importantly, the N—O bond of Cbz-protected amino acid-containing cycloadducts **6b,d** were cleanly reduced to alcohols **24b,d** when molybdenum hexacarbonyl was used as the reducing agent (eq 5).[16]



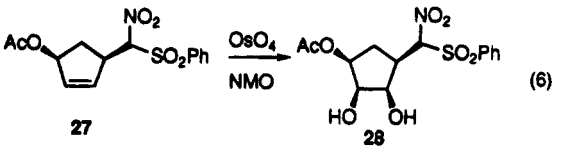
24b R = Me, 75%
d R = Bn, 88%

Allylic Alcohol Chemistry. Optically pure allylic alcohol **21** was converted to allylic acetate **25** (85% yield) and silyl ether **26** (92% yield), useful substrates for the study of the *cis*-dihydroxylation of the bis-allylically

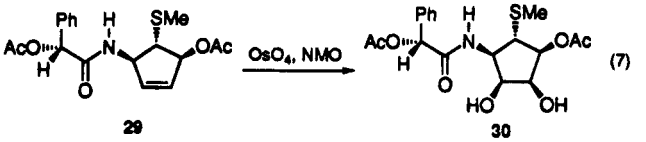
Scheme 5



subtituted systems (Scheme 5). In related studies reported by Trost (eq 6)[17] and Ganem (eq 7),[18] the osmium tetraoxide-catalyzed dihydroxylation of bis-allylically substituted systems **27** and **29** resulted in the predominant formation of the all *cis*-substituted cyclopentane ring systems **28** and **30**, respectively. Anchimeric assistance by the nitromethyl substituent in Trost's case, and by the acetate in Ganem's case, was suggested to be the source of the stereoselectivity observed in these dihydroxylation processes.

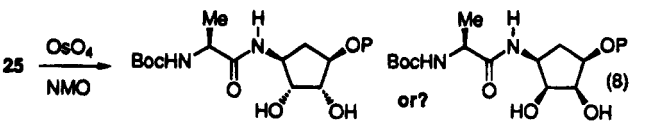


27 28



29 30

If the allylic acetate does in fact direct dihydroxylation, then allylic acetate **25** was anticipated to osmylate in a similar fashion to give all *syn* diol **31b** (eq 8). Subjection of **25** to catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide afforded a single diastereomerically pure diol. The stereochemistry tentatively assigned to product **31b** was based on the precedent set in Ganem's work.

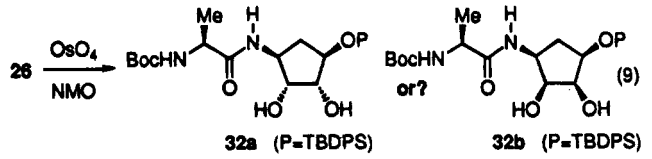


31a (P=Ac) 31b (P=Ac)

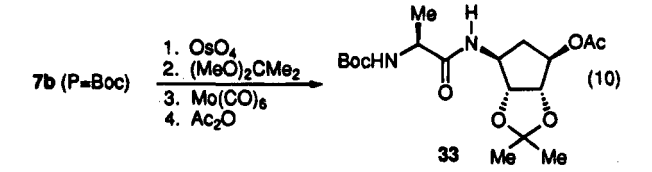
More importantly, osmylation of allylic silyl ether **26**, which lacks the potential for anchimeric assistance as in allylic acetate **25**, was expected to occur on the face opposite the two allylic substituents and provide access to diol **32a**. Simply changing protecting groups was anticipated to allow selective diastereomeric diol synthesis. In fact, a single diastereomerically pure diol was obtained on osmylation of **26** and was tentatively assigned structure **32a**.

A diastereomerically pure diol was also obtained in the catalytic osmylation of hetero Diels–Alder cycloadduct **7b** (eq 10). Literature precedent suggested that the *exo* diol should result from osmylation of the norbornadiene-

(14) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(15) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; DeSarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.
(16) For a discussion about the mechanism of metal-carbonyl-induced reduction of isoxazoles, see Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401.
(17) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621.
(18) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089.



like system.[19] Acetonide formation followed by N–O bond reduction and acylation of the alcohol resulted in the formation of a single acetate, tentatively assigned structure **33**.



To our surprise, a compound (**33**) identical to that obtained from **7b** (by ^{1}H and ^{13}C NMR, and optical rotation) was isolated following acetonide formation on diol acetate **31**. Moreover, acetonide formation, fluoride deprotection, and acylation of the diol tentatively assigned structure **32a** gave an acetate acetonide identical to that obtained from both **25** (through **31**) and **7b**.

If anchimeric assistance were involved, dihydroxylation of the allylic acetate and the allylic silyl ether was expected to have occurred on opposite faces of *bis*-allylically substituted systems **25** and **26**. Two diastereomeric acetates were expected from the transformations described above. However, the acetate acetonides formed from all three bis allylically substituted systems were identical.

Fortuitously, X-ray analysis of a single crystal of acetonide **33** revealed that osmylation in all three systems occurred on the face opposite the two allylic substituents.[20a] Clearly anchimeric assistance by the allylic acetate is not involved in the dihydroxylation of allylic acetate **25**, and diol **31a** was actually obtained. Apparently, in the osmylation described by Ganem, an electronic-directing effect by the allylic acetate does not induce dihydroxylation to occur on the more sterically hindered face, but may instead result from a directing effect by the methyl thio group.

Conclusion

We have determined the diastereoselectivity of a number of amino acid-derived acyl nitroso dienophiles in the hetero Diels–Alder reaction. The chromatographically separable cycloadducts are novel, enantiomerically pure chiral educts, easily accessible from readily available amino acid hydroxamates. The chemoselective reduction and stereospecific dihydroxylation of the cycloadducts was carried out efficiently. We are currently studying the conversion of these functionally rich synthetic intermediates to novel, optically pure carbocyclic nucleoside analogs. Applications to other systems of biological interest will be reported in due course.

(19) (a) For a review on the *cis* hydroxylation of unsaturated substrates, see: Schroder, M. *Chem. Rev.* **1980**, *80*, 187. (b) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. (c) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075.

(20) (a) The author has deposited atomic coordinates for structures **33** and **6c** with the Cambridge Crystallographic Date Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.

Experimental Section

General Methods. Instruments and general chromatographic methods used have been described previously.[20b] Reaction solvents and reagents were used as obtained from commercial sources unless otherwise noted.[21] Anhydrous procedures were performed with purified solvents, oven-dried syringes stored in a dessicator, and oven-dried glassware. Reactions were run under argon unless otherwise noted. Solutions were concentrated *in vacuo* on a rotary evaporator.

Methyl Ester Precursors to Hydroxamic Acids. Methyl ester synthesis was performed by adding a methanolic solution of the *N*-protected amino acid to be esterified to a methanolic solution of thionyl chloride (several drops of thionyl chloride for 0.5 g scale reaction, more if the CH_3OH was not dry). The reaction was followed by TLC. On completion, the reaction mixture was concentrated, dissolved in EtOAc, washed with saturated $NaHCO_3$ and then brine, dried over $MgSO_4$, and chromatographed on silica gel, if necessary. Acetyl chloride in CH_3OH also was used for the acid-catalyzed esterification.[22]

General Procedure for Hydroxamic Acid Preparation. A methanolic solution of *N*-protected amino acid methyl ester, cooled in an ice bath, was charged with a preformed methanoic slurry of hydroxylamine hydrochloride (300 mol %) and KOH (600 mol %). The reaction mixture was stirred under argon. When the reaction was complete, as indicated by TLC analysis, the reaction mixture was acidified to an apparent pH of 4 with concentrated HCl. The resulting solution was then concentrated to give a white solid. The solid was repeatedly boiled in EtOAc and filtered until TLC analysis of the filtrate revealed that no ferric chloride-positive component remained in the filtrate. The combined filtrates were concentrated to give the desired hydroxamic acid as a white powder or glassy solid.

***N*-Carbobenzyloxy-L-alanine *N*-Hydroxyamide (4b, R = Me, P = Cbz).** Following the general procedure on a 2.5 g scale, 2.4 g (96%) of an off-white solid was isolated: $R_f = 0.57$ (10% MeOH, 2% AcOH in CH_2Cl_2); ^{1}H NMR (DMSO-d_6) 1.19 (d, J = 6.9 Hz, 3 H), 3.96 (m, 1 H), 5.00 (s, 2 H), 7.34 (s, 5 H), 7.5 (d, 1 H), 10.7 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 18.4, 48.1, 65.5, 127.8, 127.9, 128.5, 137.1, 155.7, 169.6; MS m/z calcd for $C_{11}H_{14}N_2O_4$ 238.0954, found 238.0956.

***N*-(*tert*-Butoxycarbonyl)-L-alanine *N*-Hydroxyamide (4b, R = Me, P = Boc).** Following the usual procedure, 15.0 g of *N*-Boc-L-alanine methyl ester gave a 98% yield of the hydroxamic acid (14.8 g): $R_f = 0.26$ (100% EtOAc); IR (KBr) 3300, 2990, 1690, 1660, 1515, 1373, 1175 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.30 (d, J = 7.2 Hz, 3 H), 1.42 (s, 9 H), 4.11 (m, 1 H), 5.92 (d, J = 7.8 Hz, 1 H), 10.49 (m, 1 H); ^{13}C NMR δ 18.0, 27.4, 46.9, 78.1, 154.2, 169.4; MS m/z calcd for $C_4H_8N_2O_4$ 148.0481, found 148.0486.

***N*-(Carbobenzyloxy)-D-alanine *N*-Hydroxyamide (4c, R = Me, P = Cbz).** Prepared as described above using 1.20 g of methyl ester precursor, 0.97 g (81%) of the desired hydroxamic acid was obtained as an off-white solid: $R_f = 0.55$ (10% MeOH, 2% AcOH in CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.17 (d, J = 7.2 Hz, 3 H), 3.94 (m, 1 H), 5.00 (s, 2 H), 7.34 (s, 5 H), 7.46 (d, J = 7.8 Hz, 1 H), 8.8 (s, 1 H), 10.61 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 18.4, 48.0, 65.4, 127.8, 127.8, 128.4, 137.1, 155.6, 169.4; MS m/z calcd for $C_{11}H_{14}N_2O_4$ 238.0954, found 238.0951.

***N*-(Carbobenzyloxy)-L-phenylalanine *N*-Hydroxyamide (4d, R = Bn, P = Cbz).** Prepared as described above on 1.00 g (3.2 mmol) of ester, 0.96 g of product (92% yield) was isolated: $R_f = 0.19$ (10% MeOH, 1% AcOH in CH_2Cl_2); IR (KBr) 3310, 1710, 1650, 1255, 1025 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.88 (m, 2 H), 4.15 (m, 1 H), 4.94 (s, 2 H), 7.26 (m, 10 H), 7.64 (d, J = 5.7 Hz, 1 H), 8.94 (s, 1 H), 10.77 (s, 1 H); ^{13}C δ 37.8, 54.1, 65.3, 126.4, 127.6, 127.8, 128.2, 128.4, 129.3, 137.1, 138.0, 155.8, 168.3; MS m/z calcd for $C_{17}H_{18}N_2O_4$ 314.1267, found 314.1270.

***N*-(Carbobenzyloxy)-D,L-phenylalanine *N*-Hydroxyamide (4e, R = Bn, P = Cbz).** Prepared as described above

(21) Perrin, D. D; Armarego, W. L. F.; Perrin, D. R. In *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1980.

(22) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.

on 2.70 g (8.63 mmol) of ester, 2.51 g of product (93% yield) was isolated as a white solid: $R_f = 0.19$ (10% MeOH, 1% AcOH in CH_2Cl_2); IR (KBr) 3300 (br), 1720, 1650, 1155 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.89 (m, 2 H), 4.15 (m, 1 H), 4.94 (s, 2 H), 7.28 (m, 10 H), 7.65 (d, $J = 5.7$ Hz, 1 H), 10.79 (s, 1 H); ^{13}C (DMSO-d_6) δ 37.8, 54.2, 65.3, 126.4, 127.6, 127.8, 128.2, 128.4, 129.3, 137.1, 138.0, 155.8, 168.3; MS m/z calcd for $C_{17}H_{18}N_2O_4$ 314.1267, found 314.1270.

General Procedure for the Hetero Diels–Alder Reaction. A 0.1 M methanolic solution of hydroxamic acid was cooled under argon in an ice–water bath. Freshly distilled cyclopentadiene (500 mol %) and 100 mol % of tetrabutylammonium periodate were added. Within 5 min a yellow color began to appear in the reaction as did a fine white precipitate. TLC analysis indicated that the reaction was complete within 1 h, sooner if the ice bath was removed after the first 10 min. The reaction was quenched by cooling in ice–water followed by the slow addition of concentrated (approximately 2.0 M) sodium metabisulfite until the reaction color disappeared. The reducing quench was exothermic and was generally allowed to proceed for 5–10 min. Water or saturated sodium chloride was then added and the mixture was extracted with CH_2Cl_2 until no additional color was extracted. Drying and concentration usually gave a tan solid. The product was not stable if heated during concentration and was chromatographed immediately. Two diastereomers were formed in all cycloaddition reactions. Typically the mixture of diastereomers was isolated followed by a second chromatography to separate the diastereomers. The products appear to be stable for an extended period after the first chromatography. If any color remained after the first chromatography, the product was not stable for extended periods. The yields were typically between 75 and 90%. The more polar diastereomer crystallized much more easily than the less polar diastereomer. A dilute sample of the crude cycloadducts, dissolved in CH_2Cl_2, was analyzed by HPLC (25 cm × 4.6 mm Econosil 5 μm silica gel column with 10% 2-propanol in hexanes at 1.5 mL/min and monitoring at 254 nm. Both phenylalanine (23 and 33 min retention times) and alanine (11.3 and 14.7 min) cycloadducts were separated under these conditions.

(1*S*,4*R*)-*N*-[*N*-(Carbobenzyloxy)-L-valinyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6a, R = ^{i}Pr, P = Cbz, minor diastereomer). The minor diastereomer was isolated as an oil by silica gel chromatography from the reaction described in the previous experimental: $R_f = 0.27$ (50% EtOAc in hexanes); IR (neat) 3315, 2965, 1715, 1655, 1510, 1235, 845 cm^{-1}; ^1H NMR δ 0.84 (d, $J = 6.7$ Hz, 3 H), 0.97 (d, $J = 6.7$ Hz, 3 H), 1.83 (d, $J = 8.6$ Hz, 1 H), 1.99 (d, $J = 8.6$ Hz, 1 H), 2.21 (m, 1 H), 4.37 (m, 1 H), 5.06 (dd, $J = 12.3$ Hz, 2 H), 5.31 (s, 2 H), 5.48 (m, 1 H), 6.34 (m, 1 H), 6.56 (m, 1 H), 7.33 (m, 5 H); ^{13}C NMR δ 16.5, 19.4, 30.8, 48.3, 58.4, 62.3, 66.6, 84.6, 127.8, 128.3, 132.6, 136.3, 136.5, 156.2, 175.2; MS m/z (M^+) calcd for $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1576. The minor diastereomer had $t_R = 8.8$ min using the standard HPLC analysis.

(1*R*,4*S*)-*N*-[*N*-(Carbobenzyloxy)-L-valinyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (7a, R = ^{i}Pr, P = Cbz, major diastereomer). Following the usual procedure, 2.36 g (8.87 mmol) of hydroxamic acid was oxidized in the presence of 5.85 g (88.7 mmol) of freshly distilled cyclopentadiene to give 2.49 g (85%) of a 4:1 mixture of cycloadducts. The more polar diastereomer was isolated by silica gel chromatography as an oil (35% EtOAc in hexanes): $R_f = 0.20$ (50% EtOAc in hexanes); IR (neat) 3320, 2965, 1720, 1655, 1515, 1235, 850 cm^{-1}; ^1H NMR δ 0.76 (m, 3 H), 0.92 (m, 3 H), 1.84 (d, $J = 8.4$ Hz, 1 H), 1.97 (m, 2 H), 4.54 (m, 1 H), 5.34 (s, 2 H), 5.41 (m, 1 H), 5.51 (m, 1 H), 6.37 (m, 1 H), 6.55 (m, 1 H), 7.34 (m, 5 H); ^{13}C NMR δ 16.4, 19.4, 28.5, 48.3, 57.2, 61.5, 66.6, 84.5, 127.8, 127.9, 128.3, 133.4, 135.7, 136.3, 156.2, 171.5; MS m/z (M^+) calcd for $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1572. The major diastereomer had $t_R = 13$ min using the standard HPLC analysis.

(1*S*,4*R*)-*N*-[*N*-(Carbobenzyloxy)-L-alanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6b, R = Me, P = Cbz, minor diastereomer). The minor diastereomer was isolated as an oil by chromatography from the reaction described above: $R_f = 0.26$ (50% EtOAc in hexanes); IR (thin film) 3410, 3310, 3060, 1960, 1720, 1650, 1450, 1325, 1240, 1050 cm^{-1}; ^1H NMR δ 1.39 (d, $J = 6.9$ Hz, 3 H), 1.85 (d, $J = 8.7$ Hz, 1 H), 2.00 (d, $J = 8.4$ Hz, 1 H), 4.41 (m, 1 H), 5.07 (s, 2 H), 5.31 (s, 2 H), 5.65 (m, 1 H), 6.36 (m, 1 H), 6.57 (m, 1 H), 7.34 (m, 5 H); ^{13}C NMR δ 19.0, 37.6, 48.4, 49.7, 62.3, 66.6, 80.3, 84.7, 128.0, 128.4, 132.6, 136.4, 155.3, 176.1; MS m/z (M^+) calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1267.

(1*S*,4*R*)-*N*-[*N*-*tert*-Butyloxycarbonyl-L-alanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6b, P = Boc). Following the usual procedure, 16.1 g (78%) of a 3:1 mixture of diastereomers was isolated from the hetero Diels–Alder reaction of 14.4 g (97.3 mmol) of *N*-Boc-L-alanine hydroxamic acid with cyclopentadiene. The less polar diastereomer was isolated as an oil following silica gel chromatography and was crystallized from EtOAc and hexanes: $R_f = 0.40$ (25:75 hexanes:EtOAc); $[\alpha]^{20}_D$ +100.2° ($c = 0.206$, $CHCl_3$); IR (KBr) 3445, 2990, 1720, 1655, 1495, 1170, 845 cm^{-1}; mp 76–78 °C; ^1H NMR δ 1.35 (d, $J = 6.9$ Hz, 3 H), 1.42 (s, 9 H), 1.85 (d, $J = 9.0$ Hz, 1 H), 2.01 (d, $J = 9.0$ Hz, 1 H), 4.33 (m, 1 H), 5.33 (m, 3 H), 6.38 (m, 1 H), 6.57 (m, 1 H); ^{13}C NMR δ 19.0, 28.3, 48.4, 49.1, 62.3, 79.3, 84.6, 132.8, 136.6, 154.9, 176.4; MS m/z calcd for $C_9H_{12}N_2O_4$ 212.0797, found 212.0794. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.31; H, 7.51; N, 10.44. Found: C, 58.35; H, 7.68; N, 10.51.

(1*R*,4*S*)-*N*-[*N*-(Carbobenzyloxy)-L-alanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (7b, R = Me, P = Cbz, major diastereomer). Using the general procedure on 1.00 g of hydroxamic acid, 1.14 g (90%) of a 3:1 mixture of diastereomers was isolated. The major diastereomer was isolated as an oil by silica gel chromatography. $R_f = 0.19$ (50% EtOAc in hexanes); IR (neat) 3260, 3047, 2986, 1714, 1630, 1537, 1378, 1258 cm^{-1}; ^1H NMR δ 1.12 (d, $J = 5.7$ Hz, 3 H), 1.85 (d, $J = 5.7$ Hz, 1 H), 1.99 (m, 1 H), 4.57 (dq, $J = 5.7$, 7.5 Hz, 1 H), 5.09 (s, 2 H), 5.35 (m, 2 H), 5.61 (d, $J = 7.5$ Hz, 1 H), 6.37 (m, 1 H), 6.54 (m, 1 H), 7.32 (s, 5 H); ^{13}C NMR δ 16.0, 48.3, 48.5, 61.8, 66.6, 84.6, 128.0, 128.4, 133.0, 136.1, 136.4, 155.4, 173.2; MS m/z (M^+) calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1270.

(1*R*,4*S*)-*N*-(*N*-(*tert*-Butyloxycarbonyl)-L-alanine)-2,3-oxazabicyclo[2.2.1]hept-5-ene (7b, P = Boc). The more polar diastereomer was isolated as an oil by column chromatography from the reaction described in the general experimental procedure. The product was crystallized from EtOAc and hexanes: mp 112–113 °C; $R_f = 0.34$ (25:75 hexanes: EtOAc); $[\alpha]^{20}_D$ −90.9° ($c = 0.78$, $CHCl_3$); IR (neat) 3340, 2985, 1720, 1655, 1525, 1175, 850 cm^{-1}; ^1H NMR δ 1.09 (d, $J = 6.9$ Hz, 3 H), 1.43 (s, 9 H), 1.87 (d, $J = 5.7$ Hz, 1 H), 2.02 (d, $J = 5.7$ Hz, 1 H), 4.51 (m, 1 H), 5.26 (d, $J = 4.5$ Hz, 1 H), 5.35 (m, 2 H), 6.39 (m, 1 H), 6.55 (m, 1 H); ^{13}C NMR δ 173.8, 154.9, 136.0, 133.0, 84.4, 79.3, 61.7, 48.2, 47.9, 28.2, 15.9; MS m/z calcd for $C_9H_{12}N_2O_4$ 212.0797, found 212.0796. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.31; H, 7.51; N, 10.44. Found: C, 58.54; H, 7.81; N, 10.26.

(1*S*,4*R*)-*N*-[*N*-(Carbobenzyloxy)-D-alanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6c, R = Me, P = Cbz, major diastereomer). Isolated as the more polar diastereomer from the reaction described in the previous experimental, the major diastereomer was isolated as an oil after column chromatography and was obtained as needles from EtOAc/hexanes: mp 118–120 °C; $R_f = 0.19$ (50% EtOAc in hexanes); IR (KBr) 3260, 1715, 1645, 1535, 1255, 1045, 1020, 845, 800, 700 cm^{-1}; ^1H NMR δ 1.11 (d, $J = 4.8$ Hz, 3 H), 1.84 (d, $J = 8.7$ Hz, 1 H), 1.99 (d, $J = 8.1$ Hz, 1 H), 4.56 (dq, $J = 7.5$ Hz, 1 H), 5.08 (s, 2 H), 5.32 (m, 2 H), 5.65 (d, $J = 6.3$ Hz, 1 H), 6.36 (m, 1 H), 6.53 (m, 1 H), 7.32 (m, 5 H); ^{13}C NMR δ 15.8, 48.2, 48.5, 61.7, 66.5, 84.5, 127.8, 128.3, 132.9, 136.0, 136.3, 155.4, 173.2; MS m/z (M^+) calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1270. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.63; H, 6.18; N, 9.36.

(1*R*,4*S*)-*N*-[*N*-(Carbobenzyloxy)-D-alanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (7c, R = Me, P = Cbz, minor diastereomer). Following the general procedure on 0.30 g (1.26 mmol) of hydroxamic acid, we isolated 296 mg (78%) of a 3:1 mixture of cycloadducts. The less polar diastereomer was isolated by silica gel chromatography as an oil. The less polar diastereomer gave the following data: $R_f = 0.26$ (50% EtOAc in hexanes); IR (thin film) 3315, 1720, 1655, 1240, 845, 800, 740 cm^{-1}; ^1H NMR δ 1.39 (d, $J = 6.9$ Hz, 3 H), 1.84 (d, $J = 8.7$

Hz, 1 H), 1.99 (d, J = 5.7 Hz, 1 H), 4.39 (dq, J = 6.9 Hz, 1 H), 5.07 (s, 2 H), 5.31 (m, 2 H), 5.62 (d, J = 7.2 Hz, 1 H), 6.35 (m, 1 H), 6.57 (m, 1 H), 7.33 (s, 5 H); ^{13}C NMR δ 18.9, 48.3, 49.7, 62.3, 66.5, 84.7, 127.9, 128.4, 132.7, 136.4, 136.5, 155.3, 176.1; MS m/z calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1264.

(1*S*,4*R*)-*N*-[*N*-(Carbobenzyloxy)-L-phenylalanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6d, R = Bn, P = Cbz, minor diastereomer). Using the general Diels–Alder procedure on 1.30 g (4.14 mmol) of hydroxamic acid, 1.24 g (79%) of a 2:1 mixture of diastereomeric cycloadducts was isolated. The minor diastereomer was isolated as an oil following silica gel chromatography: R_f = 0.28 (5% EtOAc in CH_2Cl_2); IR (thin film) 3310, 3035, 1720, 1655, 1500, 1050, 700 cm^{-1}; ^{1}H NMR δ 1.72 (m, 1 H), 1.82 (d, J = 8.4 Hz, 1 H), 1.95 (d, J = 8.4Hz, 1 H), 3.01 (dd, J = 6.3, 12.9 Hz, 1 H), 3.16 (dd, J = 6.0, 16.5 Hz, 1 H), 4.66 (m, 1 H), 5.04 (dd, J = 12.0, 21.6 Hz, 2 H), 5.33 (m, 2 H), 6.38 (m, 1 H), 6.59 (m, 1 H), 7.3 (m, 10 H); ^{13}C NMR δ 37.9, 48.3, 54.6, 62.7, 66.5, 84.8, 126.67, 126.8, 127.8, 127.9, 128.3, 129.5, 132.7, 136.2, 136.5, 155.4, 174.1; MS m/z (M$^+$) calcd for $C_{22}H_{22}N_2O_4$ 378.15796, found 378.1577.

(1*R*,4*S*)-*N*-[*N*-(Carbobenzyloxy)-L-phenylalanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (7d, R = Bn, P = Cbz, major diastereomer). The major diastereomer was isolated as an oil by silica gel chromatography of the product from the reaction described in the previous experimental: R_f = 0.22 (50% EtOAc in hexanes); IR (KBr) 3310, 3040, 1728, 1660, 1503, 1250, 740, 700 cm^{-1}; ^{1}H NMR δ 1.84 (d, J = 8.4 Hz, 1 H), 1.99 (d, J =8.4 Hz, 1 H), 2.65 (m, 1 H), 2.93 (m, 1 H), 4.89 (m, 1 H), 5.04 (m, 2 H), 5.34 (s, 1 H), 5.41 (s, 1 H), 6.31 (m, 1 H), 6.52 (m, 1 H), 7.29 (m, 10 H); ^{13}C NMR δ 35.8, 48.3, 48.5, 53.4, 61.5, 66.6, 84.8, 126.6, 127.9, 128.2, 128.4, 129.4, 133.2, 136.1, 136.3, 155.6, 170.9; MS m/z (M$^+$) calcd for $C_{22}H_{22}N_2O_4$ 378.15796, found 378.1577.

***N*-[*N*-(Carbobenzyloxy)-D,L-phenylalanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6e/7e, R = Bn, P = Cbz, minor racemic diastereomer).** A 75% yield of cycloadducts was isolated following the standard Diels–Alder reaction procedure. The minor diastereomer was isolated as an oil by silica gel chromatography of the crude reaction mixture: R_f = 0.28 (50% EtOAc in hexanes); IR (KBr) 3315, 3035, 1715, 1655, 1525, 1262, 1038 cm^{-1}; ^{1}H NMR δ 1.80 (d, J = 8.4 Hz, 1 H), 1.92 (d, J = 8.4 Hz, 1 H), 2.99 (dd, J = 6.0, 13.5 Hz, 1 H), 3.16 (dd, J = 6.0, 13.5 Hz, 1 H), 4.66 (dd, J = 6.0, 14.4 Hz, 1 H), 5.02 (dd, J = 12.3, 22.5 Hz, 2 H), 5.29 (s, 2 H), 5.44 (m, 1 H), 6.34 (m, 1 H), 6.55 (m, 1 H), 7.24 (m, 10 H); ^{13}C NMR δ 38.0, 48.3, 54.6, 62.3, 66.5, 84.8, 126.7, 127.8, 127.9, 128.0, 128.2, 128.3, 129.5, 132.7, 136.1, 136.3, 155.4, 174.1; MS m/z (M$^+$) calcd for $C_{22}H_{22}N_2O_4$ 378.1580, found 378.1577.

***N*-[*N*-(Carbobenzyloxy)-D,L-phenylalanyl]-2,3-oxazabicyclo[2.2.1]hept-5-ene (6e/7e, R = Bn, P = Cbz, major racemic diastereomer).** The major diastereomer from the reaction described in the previous experimental was isolated as an oil by silica gel chromatography of the crude reaction mixture: R_f = 0.22 (50% EtOAc in hexanes); IR (KBr) 3310, 3030, 2960, 1710, 1655, 1525, 1260, 1040 cm^{-1}; ^{1}H NMR δ 1.76 (d, J = 8.4 Hz, 1 H), 1.89 (d, J = 8.4 Hz, 1 H), 3.00 (m, 1 H), 3.16 (dd, J = 6.0, 16.5 Hz, 1 H), 4.65 (m, 1 H), 5.02 (dd, J = 12.3, 23.1 Hz, 2 H), 5.27 (s, 2 H), 5.55 (m, 1 H), 6.31 (s, 1 H), 6.52 (s, 1 H), 7.29 (m, 10 H); ^{13}C NMR δ 37.8, 48.2, 54.5, 62.2, 66.3, 84.7, 126.5, 127.7, 127.8, 127.9, 128.0, 128.2, 129.4, 132.6, 136.1, 136.4, 155.3, 174.0; MS m/z (M$^+$) calcd for $C_{22}H_{22}N_2O_4$ 378.1580, found 378.1573.

General Procedure for Aminocyclopentanol Synthesis via Hydrogenation of Diels–Alder Adducts. A 1:1 CH_3OH/EtOAc solution (10 mL) of 145 mg (0.48 mmol) of D-alanine-derived cyclopentadiene diastereomer **6c** (P = Cbz) was reduced on 30 mg of 10% Pd/C under 1 atm of H_2. When complete by TLC analysis, 1 mL of ethyldiisopropylamine was added (to prevent the primary amine formed in the reaction from adhering to the surface of the catalyst) and the solution was stirred for 10 min. The catalyst was then removed by filtration, the solution was concentrated and the resulting oil was chromatographed on silica gel (5% CH_3OH in CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2 as eluent) to obtain 82 mg of product **8c** as a semisolid (86% yield).

***cis*-3(*S*)-(*N*-L-Alanylamino)cyclopentan-1(*R*)-ol (8b, R = Me).** Less polar diastereomer **6b** (45 mg, 0.15 mmol) was reduced to give a 66% yield (17 mg) of semisolid after chromatography on silica gel: R_f = 0.34 (20% CH_3OH in CH_2Cl_2, with a trace of triethylamine); IR (KBr) 3340, 3300, 2965, 1630, 1560, 1095, 965 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.21 (d, J = 6.9 Hz, 3 H), 1.48 (dt, J = 5.2, 13.5 Hz, 1 H), 1.69 (m, 3 H), 1.91 (m, 1 H), 2.03 (ddd, J = 5.4, 7.8, 13.5 Hz, 1 H), 3.32 (q, J = 6.9 Hz, 1 H), 4.20 (m, 2 H), 7.83 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 20.0, 29.6, 32.5, 40.4, 47.0, 48.9, 69.9, 173.2; MS m/z (M$^+$) calcd for $C_8H_{16}N_2O_2$ 172.1212, found 172.1212.

***cis*-3(*R*)-(*N*-L-Alanylamino)cyclopentan-1(*S*)-ol (9b, R = Me).** Following the general reduction procedure, 60 mg of **7b** was reduced and chromatographed to give 25 mg of a waxy white solid (74% yield): R_f = 0.31 (20% CH_3OH in CH_2Cl_2, 2% Et_3N); IR (KBr) 3290, 2970, 1640, 1555, 1080, 975 cm^{-1}; ^{1}H NMR (1:1 DMSO-d_6:$CDCl_3$) δ 1.20 (d, J = 6.9 Hz, 3 H), 1.47 (dt, J = 3.9, 13.5 Hz, 1 H), 1.67 (m, 3 H), 1.89 (m, 1 H), 2.03 (ddd, J = 5.4, 8.1, 13.5 Hz, 1 H), 3.15 (q, J = 6.9 Hz, 1 H), 4.18 (m, 2 H), 7.84 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 20.1, 29.6, 32.5, 40.4, 47.0, 48.9, 69.8, 173.2; MS m/z (M$^+$) calcd for $C_8H_{16}N_2O_2$ 172.1212, found 172.1210.

***cis*-3(*S*)-(*N*-D-Alanylamino)cyclopentan-1(*R*)-ol (8c, R = Me).** From **6c**, the more polar cyclopentanol was prepared as described in the general procedure above: R_f = 0.2 (10% CH_3OH in CH_2Cl_2 with 1% Et_3N); IR (KBr) 3285, 2965, 1640, 1555, 1240, 1075, 970 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.17 (d, J = 6.9 Hz, 3 H), 1.43 (dt, J = 4.2, 13.5 Hz, 1 H), 1.65 (m, 4 H), 1.86 (m, 1 H), 2.02 (ddd, J = 5.7, 8.1, 13.5 Hz, 1 H), 3.27 (q, J = 6.9 Hz, 1 H), 4.10 (m, 1 H), 4.17 (m, 1 H), 7.85 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 19.6, 29.0, 32.0, 39.9, 46.5, 48.3, 69.1, 172.8; MS m/z (M$^+$) calcd for $C_8H_{16}N_2O_2$ 172.1212, found 172.1210.

***cis*-3(*R*)-(*N*-D-Alanylamino)cyclopentan-1(*S*)-ol (9c, R = Me).** Following the general procedure on cycloadduct **7c**, 50 mg of substrate (0.166 mmol) was reduced, and following chromatography, gave 25 mg of product as a waxy solid (87% yield): R_f = 0.11 (10% CH_3OH in CH_2Cl_2 with 1% diisopropylethylamine); IR (KBr) 3280, 2965, 1640, 1560, 1095, 970 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.15 (d, J = 6.9 Hz, 3 H), 1.40 (dt, J = 13.5 Hz, 1 H), 1.62 (m, 4 H), 1.84 (m, 1 H), 2.01 (ddd, J = 5.7, 7.8, 13.5 Hz, 1 H), 3.26 (q, J = 6.9 Hz, 1 H), 4.07 (m, 1 H), 4.15 (m, 1 H), 7.85 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 19.5, 29.0, 32.0, 39.9, 46.4, 48.3, 69.0, 172.0; MS m/z (M$^+$) calcd for $C_8H_{16}N_2O_2$ 172.1212, found 172.1209.

***cis*-3(*S*)-(*N*-L-Phenylalanylamino)cyclopentan-1(*R*)-ol (8d, R = Bn).** Following the general procedure, 120 mg (0.32 mmol) of **6d** was reduced to give 60 mg (76%) of a waxy solid after chromatography: R_f = 0.25 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3330, 3300, 1645, 1550, 1360, 1100, 700 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.44 (dt, J = 3.0, 13.5 Hz, 1 H), 1.66 (m, 3 H), 1.9 (m, 1 H), 2.01 (ddd, J = 5.4, 7.8, 19.2 Hz, 1 H), 2.69 (dd, J = 8.4, 13.5 Hz, 1 H), 3.07 (dd, J = 4.5, 13.5 Hz, 1 H), 3.47 (dd, J = 4.5, 8.7 Hz, 1 H), 4.20 (m, 2 H), 7.25 (m, 5 H), 7.83 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 29.7, 32.7, 39.7, 40.4, 47.3, 54.8, 70.1, 125.0, 126.9, 127.9, 136.8, 171.8; MS m/z (M$^+$ + 1) calcd for $C_{14}H_{21}N_2O_2$ 249.1603, found 249.1599.

***cis*-3(*R*)-(*N*-L-Phenylalanylamino)cyclopentan-1(*S*)-ol (9d, R = Bn).** Following the general procedure, 100 mg (0.26 mmol) of **7d** was reduced to afford 46 mg (70%) of waxy white solid that was isolated after chromatography: R_f = 0.10 (10% CH_3OH in CH_2Cl_2); IR (KBr) 3310, 3290, 3085, 2965, 1650, 1545, 1100, 1075, 740, 695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.40 (dt, J = 3.9, 13.5 Hz, 1 H), 1.62 (m, 3 H), 1.83 (m, 1 H), 2.02 (ddd, J = 5.7, 7.8, 13.5 Hz, 1 H), 2.65 (dd, J = 8.4, 13.2 Hz, 1 H), 3.01 (dd, J = 4.8, 13.2 Hz, 1 H), 3.42 (m, 1 H), 4.14 (m, 2 H), 7.21 (m, 5 H), 7.84 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 29.2, 32.2, 29.4, 40.0, 54.5, 69.4, 90.1, 124.4, 126.4, 127.5, 136.7, 171.4; MS m/z (M$^+$ + 1) calcd for $C_{14}H_{21}N_2O_2$ 249.16030, found 249.1604.

***cis*-3-(*N*-D,L-Phenylalanylamino)cyclopentan-1-ol (8e, R = Bn, more polar diastereomer).** A 46% yield of the primary amine was isolated as a waxy white solid using the general procedure on 100 mg of the major cycloadduct: R_f = 0.10 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3305, 3200, 2910,

1648, 1565, 935, 750, 705 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.58 (d, J = 14.1 Hz, 1 H), 1.73 (m, 3 H), 2.01 (m, 2 H), 2.25 (m, 3 H), 2.70 (dd, J = 9.0, 13.5 Hz, 1 H), 3.17 (dd, J = 4.5, 13.5 Hz, 1 H), 3.51 (dd, J = 4.5, 8.7 Hz, 1 H), 4.29 (m, 1 H), 4.34 (m, 1 H), 7.27 (m, 5 H), 7.60 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 29.4, 32.5, 39.5, 40.2, 47.1, 54.6, 69.7, 124.7, 126.7, 127.7, 136.7, 171.42; MS m/z (M$^+$+ 1) calcd for $C_{14}H_{21}N_2O_2$ 249.1603, found 249.1601.

***cis*-3-(*N*-D,L-Phenylalanylamino)cyclopentan-1-ol (9e, R = Bn, less polar diastereomer).** A 60% yield of the primary amine was isolated as a waxy white solid from 170 mg of the minor cycloadduct using the general procedure: R_f = 0.25 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3340, 3315, 1639, 1560, 1350, 1100, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.56 (d, J = 15 Hz, 1 H), 1.75 (m, 3 H), 2.00 (m, 5 H), 2.71 (dd, J = 9.0, 13.5 Hz, 1 H), 3.18 (dd, J = 4.5, 13.5 Hz, 1 H), 3.53 (dd, J = 4.2, 8.7 Hz, 1 H), 4.26 (m, 1 H), 4.35 (m, 1 H), 7.26 (m, 5 H), 7.57 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 30.9, 34.4, 41.1, 42.0, 49.2, 56.4, 72.8, 126.7, 128.6, 129.3, 137.8, 173.3; MS m/z (M$^+$ + 1, self CI) calcd for $C_{14}H_{21}N_2O_2$ 249.16030, found 249.1601.

Derivatization for Pirkle Column Analysis. The free amines isolated from the hydrogenation of the Diels–Alder adducts were dissolved in a mixture of CH_2Cl_2, CH_3CN, and pyridine (2:5:1) and were charged with 110 mol % of 3,5-dinitrobenzoyl chloride (freshly crystallized from hexanes). The mixture was stirred under argon until TLC showed no remaining starting material, typically for less than 1 h. The mixture was concentrated and chromatographed (gradient from 20% EtOAc in hexanes to 50% CH_3OH in CH_2Cl_2). A waxy white solid was isolated in 50–80% yield. The isolated material was analyzed by elution through a "Rexachrom" Pirkle Covalent D-Napthylalanine 5 μm, 100 Å, 25 cm by 4.6 mm column with UV detection at 254 nm; 20% 2-propanol in hexanes as eluent, 2 mL/min. Retention times are as noted in the text. Enantiomeric purity was proven to be greater than 98% by standard coinjection experiments.

***cis*-3(*S*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-L-alanyl]amino]cyclopentan-1(*R*)-ol (10b, R = Me, less polar diastereomer).** A 55% yield of the desired benzamide was obtained using the general derivatization procedure on 100 mg of the less polar primary amine substrate: R_f = 0.26 (20% CH_3OH in CH_2Cl_2); IR (KBr) 3400, 3300, 1655, 1540, 1340, 725 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.31 (m, 1 H), 1.34 (d, J = 7.2 Hz, 3 H), 1.59 (m, 2 H), 1.80 (m, 1 H), 2.04 (ddd, J = 13.5, 5.7, 7.8 Hz, 1 H) 4.04 (m, 2 H), 4.49 (m, 1 H), 4.61 (d, J = 3.9 Hz, 1 H), 7.93 (d, J = 7.8 Hz, 1 H), 8.95 (t, J = 2.1 Hz, 1 H), 9.11 (d, J = 2.1 Hz, 2 H), 9.29 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 16.0, 28.5, 31.9, 39.7, 46.9, 47.6, 68.7, 118.8, 126.0, 135.0, 146.2, 160.0, 169.1; MS m/z (M$^+$) calcd for $C_{15}H_{18}N_4O_7$ 366.1176, found 366.1174.

***cis*-3(*R*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-L-alanyl]amino]cyclopentan-1(*S*)-ol (11b, R = Me, more polar diastereomer).** Following the general procedure, a 68% yield of the benzamide was isolated as a waxy solid from the acylation of 25 mg of substrate. HPLC analysis on the chiral Pirkle column showed a single compound eluting with a retention time of 10.04 min: R_f = 0.11 (20% CH_3OH in CH_2Cl_2); IR (KBr) 3300, 3085, 1648, 1625, 1537, 1343, 1050, 1026, 723 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.44 (d, J = 7.2 Hz, 3 H), 1.50 (m, 1 H), 1.67 (m, 1 H), 1.86 (m, 1 H), 2.05 (ddd, J = 13.5, 7.8, 6.0 Hz, 1 H), 4.16 (m, 2 H), 4.57 (m, 2 H), 7.82 (d, J = 8.1 Hz, 1 H), 9.04 (t, J = 2.1 Hz, 1 H), 9.25 (d, J = 2.1 Hz, 2 H), 9.30 (d, J = 7.5 Hz, 1 H); ^{13}C NMR δ 16.3 29.3, 32.4, 40.0, 47.6, 48.2, 69.7, 119.0, 126.6, 135.8, 146.6, 160.5, 169.5; MS m/z (M$^+$) calcd for $C_{15}H_{18}N_4O_7$ 366.1176, found 366.1174.

***cis*-3(*S*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-D-alanyl]amino]cyclopentan-1(*R*)-ol (10c, R = Me, more polar diastereomer).** Using the general procedure, a yield of 84% of benzamide was obtained as a white waxy solid from 72 mg of primary amine substrate: R_f = 0.11 (20% CH_3OH in CH_2Cl_2); IR (KBr) 3300, 3045, 1648, 1625, 1535, 1345, 1050, 1026, 723 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.46 (d, J = 6.9 Hz, 3 H), 1.55 (m, 1 H), 1.70 (m, 3 H), 1.90 (m, 1 H), 2.05 (ddd, J = 13.5, 5.7, 7.8 Hz, 1 H), 4.21 (m, 2 H), 4.48 (d, J = 6.9 Hz, 1 H), 4.61 (m, 1 H), 7.74 (d, J = 7.5 Hz, 1 H), 9.06 (t, J = 1.8 Hz, 1 H), 9.23 (d, J = 1.8 Hz, 2 H), 9.29 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 18.0, 30.4, 33.7, 41.5, 48.8, 49.5, 70.5, 120.9, 127.9, 136.7, 148.1, 162.0, 171.1; MS m/z (M$^+$) calcd for $C_{15}H_{18}N_4O_7$ 366.1176, found 366.1174.

***cis*-3(*R*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-D-alanyl]amino]cyclopentan-1(*S*)-ol (11c, R = Me, less polar diastereomer).** A 50% yield of a waxy solid was obtained from the acylation of 47 mg of primary amine substrate using the usual acylation procedure: R_f = 0.25 (20% CH_3OH in CH_2Cl_2); IR(KBr) 3400, 3300, 1655, 1540, 1340, 725 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.42 (d, J = 7.2 Hz, 3 H), 1.46 (m, 1 H), 1.68 (m, 4 H), 1.90 (m, 1 H), 2.06 (ddd, J = 13.5, 6.0, 7.8 Hz, 1 H), 4.14 (m, 2 H), 4.59 (m, 2 H), 7.85 (d, J = 7.8 Hz, 1 H), 9.03(t, J = 2.1 Hz, 1 H), 9.21 (d, J = 2.1 Hz, 2 H), 9.31 (d, J = 7.2 Hz, 1 H); ^{13}C NMR δ 16.2, 29.1, 32.3, 40.1, 47.5, 48.1, 69.5, 119.0, 126.4, 135.7, 146.5, 160.4, 169.4; MS m/z (M$^+$) calcd for $C_{15}H_{18}N_4O_7$ 366.1176, found 366.1178.

***cis*-3(*S*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-L-phenylalanyl]amino]cyclopentan-1(*R*)-ol (10d, R = Bn, less polar diastereomer).** Following the usual derivatization procedure, a 50% yield of the product was isolated as a waxy solid from 60 mg of substrate: R_f = 0.15 (20% CH_3OH in CH_2Cl_2); IR (KBr) 3290, 3095, 2965, 2930, 1655, 1635, 1540, 1340, 1075, 920, 730 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ TMS) δ 1.37 (dd, J = 4.8, 13.5 Hz, 1 H), 1.66 (m, 3 H), 2.07 (ddd, J = 6.0, 7.8, 13.5 Hz, 1 H), 3.02 (dd, J = 10.2, 13.5 Hz, 1 H), 3.17 (dd, J = 5.1, 13.8 Hz, 1 H), 4.14 (m, 2 H), 4.58 (d, J = 3.9 Hz, 1 H), 4.82 (m, 1 H), 7.20 (m, 6 H), 8.07 (d, J = 7.5 Hz, 1 H), 8.98 (t, J = 2.1 Hz, 1 H), 9.10 (d, J = 2.1 Hz, 2 H), 9.43 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 28.9, 32.2, 35.9, 39.9, 47.3, 53.7, 69.1, 90.1, 118.9, 124.5, 126.2, 126.3, 127.4, 135.4, 136.2, 146.3, 160.4, 168.2; MS m/z (M$^+$) calcd for $C_{21}H_{22}N_4O_7$ 442.14885, found 442.1489.

***cis*-3(*R*)-[*N*-[*N*-(3,5-Dinitrobenzoyl)-L-phenylalanyl]amino]cyclopentan-1(*S*)-ol (11d, R = Bn, more polar diastereomer).** Following the usual procedure for derivatization, a 60% yield of the 3,5-dinitrobenzamide was isolated from 80 mg of primary amine containing substrate: R_f = 0.23 (20% CH_3OH in CH_2Cl_2); ^{1}H NMR (1:1 $CDCl_3$:DMSO-d_6) δ 1.60 (m, 4 H), 1.85 (m, 1 H), 2.05 (ddd, J = 6.0, 7.8, 13.8 Hz, 1 H), 3.08 (dd, J = 9.0, 13.5 Hz, 1 H), 3.24 (dd, J = 6.0, 15.0 Hz, 1 H), 3.87 (s, 1 H), 4.22 (m, 2 H), 4.85 (dt, J = 5.7, 8.7 Hz, 1 H), 7.27 (m, 5 H), 7.73 (d, J = 8.1 Hz, 1 H), 9.04 (t, J = 2.1 Hz, 1 H), 9.15 (d, J = 2.1 Hz, 2 H), 9.40 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 30.1, 33.1, 37.0, 40.6, 48.5, 54.9, 70.9, 119.6, 125.6, 127.3, 127.2, 128.3, 136.5, 136.6, 147.2, 161.4, 168.9; MS m/z calcd for $C_{21}H_{22}N_4O_7$ 442.1489, found 442.1489.

***cis*-3-[*N*-[*N*-(3,5-Dinitrobenzoyl)-D,L-phenylalanyl]amino]cyclopentan-1-ol (10e/11e, R = Bn, more polar diastereomer).** The general derivatization procedure was followed on 80 mg of primary amine substrate derived from the more polar Diels–Alder adduct to afford a 50% yield of the desired benzamide as a waxy solid: R_f = 0.23 (20% CH_3OH in CH_2Cl_2); IR (KBr) 3340, 3085, 1645, 1540, 1340, 1075, 920, 725, 715 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.47 (dt, J = 4.5, 13.5 Hz, 1 H), 1.59 (m, 3 H), 1.81 (m, 1 H), 2.08 (ddd, J = 6.0, 7.8, 13.8 Hz, 1 H), 3.03 (dd, J = 9.8, 13.8 Hz, 1 H), 3.17 (dd, J = 5.3, 13.8 Hz, 1 H), 4.12 (m, 2 H), 4.55 (d, J = 3.9 Hz, 1 H), 4.83 (m, 1 H), 7.23 (m, 5 H), 8.01 (d, J = 7.8 Hz, 1 H), 9.00 (t, J = 2.1 Hz, 1 H), 9.12 (d, J = 2.1 Hz, 2 H), 9.43 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 29.1, 32.3, 36.1, 39.9, 47.4, 53.9, 69.4, 118.9, 124.7, 126.4, 127.5, 135.6, 136.2, 146.5, 160.5, 168.2; MS m/z (M$^+$) calcd for $C_{21}H_{22}N_4O_7$ 442.14885, found 442.1488.

***cis*-3-[*N*-[*N*-(3,5-Dinitrobenzoyl)-D,L-phenylalanyl]amino]cyclopentan-1-ol (10e/11e, R = Bn, less polar diastereomer).** A 41% yield of product was obtained as a waxy solid by the usual derivatization procedure on 54 mg of primary amine substrate: R_f = 0.15 (20% MeOH in CH_2Cl_2); IR (KBr) 3295, 3110, 1635, 1540, 1344, 1075, 920, 730, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.37 (dt, J = 5.1, 13.5 Hz, 1 H), 1.66 (m, 3 H), 1.87 (m, 1 H), 2.06 (ddd, J = 6.0, 7.8, 13.8 Hz, 1 H), 3.02 (dd, J = 9.9, 13.8 Hz, 1 H), 3.17 (dd, J = 5.1, 13.8 Hz, 1 H), 4.11 (m, 2 H), 4.56 (m, 1 H), 4.82 (m, 1 H), 7.25 (m, 5 H), 8.04 (d, J = 7.8 Hz, 1 H), 9.00 (t, J = 2.1 Hz, 1 H), 9.12 (d, J = 2.1 Hz, 2 H), 9.42 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 28.9, 32.2, 35.4, 35.9, 39.9, 47.3, 53.7, 69.2, 119.0, 124.6, 126.3, 126.3,

127.4, 135.5, 136.2, 146.4, 160.4, 168.1; MS m/z (M^+) calcd for $C_{21}H_{22}N_4O_7$ 442.1489, found 442.1484.

***N*-(Carbobenzyloxy)-L-alanine 9,10-Dimethylanthracene Acyl Nitroso Adduct (17).** A 40 mL 1:1 CH_3OH:CH_2Cl_2 solution containing 730 mg of 9,10-dimethylanthracene (DMA, 3.54 mmol) and 921 mg of tetra-*n*-butylammonium periodate (2.12 mmol) was cooled to 0 °C in an ice–water bath. A 10 mL 1:1 CH_3OH/CH_2Cl_2 solution of *N*-Cbz-L-alanine hydroxamic acid was then added dropwise to the oxidizing solution under argon over 10 min. The ice bath was removed. After 1 h, the reaction mixture was poured into 15 mL of saturated sodium thiosulfate and 30 mL of EtOAc. The aqueous phase was extracted with 3 × 20 mL of EtOAc. The organics were dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting solid was slurried in CH_2Cl_2 and two batches of 9,10-DMA were removed by filtration (273 mg of 9,10-DMA were recovered). The filtrate was concentrated and chromatographed on silica gel using a gradient from 10% EtOAc in hexanes to 40% EtOAc in hexanes. The product was isolated as a foam (630 mg, 78% yield). An additional 208 mg of 9,10-DMA was recovered (total of 481 mg): R_f 9,10-DMA = 0.65, R_f product = 0.38; IR (thin film) 3420, 3340, 3035, 2985, 1720, 1665, 1495, 1455, 1230, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 3 H), 2.23 (s, 3 H), 2.70 (s, 3 H), 4.54 (dq, J = 6.9 Hz, 1 H), 5.00 (s, 2 H), 5.23 (d, J = 8.1 Hz, 1 H), 7.29 (m, 9 H), 7.36 (m, 2 H), 7.45 (m, 2 H); ^{13}C NMR δ 14.9, 16.4, 17.7, 49.4, 60.3, 63.2, 66.4, 80.2, 120.7, 121.0, 121.2, 127.3,127.4, 127.6, 127.6, 127.9, 128.3, 136.5, 140.3, 140.5, 140.6, 140.9, 155.1, 174.9; MS (CI) 443 (MH^+, 5), 206 (100).

***cis*-(1*S*,3*R*)-3-[(*N*-Boc-L-Alanyl)amino]cyclopent-4-enol (20, P = Boc).** A 2:1 THF/EtOH (6 mL total volume) suspension of 24 mg (0.9 mmol) of **6b** (P = Boc) and 500 mol % of sodium phosphate dibasic buffer was charged with 0.85 g (2.2 mmol) of 6% Na/Hg in four portions (not finely ground). The reaction was followed by TLC and was complete in 2 h. The mixture was filtered through Celite and was concentrated to give a tan solid. Silica gel chromatography (EtOAc) gave a 95% yield of the desired *cis*-amino cyclopentenol: R_f = 0.25 (5% CH_3OH in CH_2Cl_2; visualized with $KMnO_4$ in acetone); IR (neat) 3300, 2980, 1700, 1650, 1370, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 6.9 Hz, 3 H), 1.44 (s, 9 H), 1.54 (dt, J = 3.3, 14.4 Hz, 1 H), 2.73 (dt, J = 7.5, 14.4 Hz, 1 H), 4.10 (m, 1 H), 4.72 (m, 2 H), 5.19 (m, 1 H), 5.81 (dd, J = 1.5, 5.4 Hz, 1 H), 6.02 (dt, J = 1.8, 5.4 Hz, 1 H), 6.78 (m, 1 H); ^{13}C NMR δ 18.5, 28.3, 41.1, 50.2, 53.7, 75.2, 80.2, 133.6, 136.7, 155.6, 172.2; MS m/z calcd for $C_{13}H_{22}N_2O_4$ 270.1580, found 270.1579.

***cis*-(1*R*,3*S*)-3-[(*N*-Boc-L-Alanyl)amino]cyclopent-4-enol (21, P = Boc).** An acetonitrile/water solution (16 mL total volume, 15:1) was charged with 540 mg (2.01 mmol) of **7b** (P = Boc) and then with 211 mg (0.4 equiv) of $Mo(CO)_6$. The mixture was heated at reflux for 3 h (100 °C oil bath). The reaction was cooled and poured onto a column of silica gel packed with 100% EtOAc as eluent to give 479 mg (89% yield) of the desired allylic alcohol. The yields with $Mo(CO)_6$ as reducing agent were consistently higher and the reductions easier to work up than when Na/Hg was used as the reducing agent: R_f = 0.20 (EtOAc); IR (neat) 3465, 3340, 3260, 3100, 2980, 1690, 1625, 1525, 1030, 760 cm^{-1}; ^1H NMR ($CDCl_3$ and DMSO-d_6, one drop) δ 1.32 (d, J = 7.2 Hz, 3 H), 1.44 (s, 9 H), 1.50 (dt, J = 3.6, 14.4 Hz, 1H), 2.67 (dt, J = 7.5, 14.4 Hz, 1 H), 3.64 (m, 1 H), 4.1 (m, 1 H), 4.63 (m, 1 H), 4.77 (m, 1 H), 5.70 (m, 1 H), 5.77 (dd, J = 2.1, 5.4 Hz, 1 H), 5.99 (dt, J = 5.4, 1.8 Hz, 1 H), 7.34 (d, J = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$ and DMSO-d_6) δ 18.7, 27.9, 40.5, 49.7, 52.5, 74.4, 78.9, 132.8, 136.4, 154.7, 171.6); MS m/z calcd for $C_{13}H_{22}N_2O_4$ 270.1580, found 270.1579. Anal. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.42; H, 8.11; N, 10.29.

Macrocyclic Carbamates (23, R = Bn). Following the same Na/Hg reduction conditions as used for **6b**, P = Boc, to give **20**, a mixture of diastereomers (114 mg, 0.30 mmol) was dissolved in THF and ethanol (95%) (3:2, 25 mL) and charged with 213 mg of sodium phosphate dibasic (500 mol %) and then with 3.17 g (8.3 mmol) of 6% sodium amalgam. The reaction was stirred under argon, was followed by TLC, and was complete in 2 h. The reaction mixture was filtered through Celite and was concentrated. The resulting semisolid was not very soluble, but was chromatographed on silica to give two compounds that differed by ^1H NMR analysis. A total recovery of 60 mg (0.23 mmol) of product (77% yield) was obtained. The minor product was isolated as an oil by silica gel chromatography: R_f = 0.29 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.72 (dd, J = 7.5, 15.0 Hz, 1 H), 2.64 (ddd, J = 7.8, 15.0 Hz, 1 H), 2.93 (ddd, J = 2.1, 7.5, 14.1 Hz, 1 H), 3.20 (dd, J = 2.4, 14.1 Hz, 1 H), 4.22 (m, 1 H), 4.64 (d, J = 7.5 Hz, 1 H), 4.92 (dd, J = 1.8, 9.6 Hz, 1 H), 5.47 (ddd, J = 2.4, 6.0, 8.4 Hz, 1 H), 5.79 (m, 1 H), 6.15 (m, 1 H), 7.18 (m, 2 H), 7.31 (m, 4 H); ^{13}C NMR δ 37.5, 37.6, 37.7, 37.7, 53.5, 57.5, 57.5, 75.5, 127.6, 128.9, 129.2, 129.4, 129.4, 134.5, 138.7, 138.7, 156.7, 173.2. The second, more polar diastereomeric macrocyclic carbamate was isolated as an oil and consisted of 42 mg of the 60 mg of total product. It had the following spectroscopic data: ^1H NMR ($CDCl_3$) δ 1.70 (dd, J = 9.3, 15.3 Hz, 1 H), 2.63 (ddd, J = 7.5, 7.8, 15.3 Hz, 1 H), 2.94 (ddd, J = 2.4, 7.2, 14.4 Hz, 1 H), 3.18 (dd, J = 3.9, 14.1 Hz, 1 H), 4.22 (m, 1 H), 4.63 (d, J = 8.1 Hz, 1 H), 4.90 (d, J = 9.6 Hz, 1 H), 5.45 (m, 1 H), 6.14 (m, 2 H), 7.17 (m, 2 H), 7.31 (m, 4 H); ^{13}C NMR δ 37.6, 53.4, 57.5, 57.5, 75.4, 127.5, 128.8, 129.2, 129.4, 134.4, 138.6, 138.7, 156.8, 173.2; MS m/z calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1160.

Allylic Alcohol 24b (R = Me). A 20:1 mixture of 20 mg (0.066 mmol) of diastereomeric cycloadducts **6b** and **7b** was reduced with $Mo(CO)_6$ using the same procedure used for the conversion of **6b** to **20**. The usual workup and chromatography were used to isolate 13 mg of the desired product (65% yield) as an oil: R_f = 0.24 (100% EtOAc); IR (neat) 3500, 3290, 1980, 1690, 1645, 1538, 1252 cm^{-1}; ^1H NMR δ 1.35 (d, J = 6.9 Hz, 3 H), 1.38 (d, J = 6.9 Hz, 3 H (other diastereomer)), 1.52 (m, 1 H), 2.68 (m, 1 H), 4.15 (m, 1 H), 4.66 (m, 2 H), 5.09 (s, 2 H), 5.55 (m, 1 H), 5.79 (m, 1 H), 5.94 (m, 1 H), 6.75 (m, 1 H), 7.34 (s, 5 H); ^{13}C NMR δ 18.7, 41.0, 50.6, 53.7, 67.1, 75.2, 128.0, 128.2, 128.5, 133.5, 133.5, 136.1, 136.6, 136.8, 156.0, 171.8; MS m/z (M^+) calcd for $C_{16}H_{20}N_2O_4$ 304.1423, found 304.1430.

Allylic Alcohol (24d, R = Bn). Following the same $Mo(CO)_6$ reduction procedure used for the conversion of **6b** to **20**, 90 mg (0.24 mmol) of Cbz-protected **6d** was reduced with 100 mol % of $MO(CO)_6$. An 88% yield of the desired allylic alcohol was obtained as an oil: R_f = 0.38 (100% EtOAc); IR (neat) 3300, 3070, 1705, 1660, 1540, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (ddd, J = 3.6, 14.4 Hz, 1 H), 2.56 (m, 1 H), 3.02 (m, 3 H), 4.33 (m, 1 H), 4.59 (m, 2 H), 5.04 (d, J = 4.8 Hz, 2 H), 5.64 (m, 1 H), 5.92 (ddd, J = 1.8, 5.4 Hz, 1 H), 6.46 (m, 1 H), 7.32 (m, 11 H); MS m/z (M^+) calcd for $C_{22}H_{22}N_2O_3$ 362.1630, found 362.1630; FAB-MS 381 (MH^+).

1(*R*)-*O*-Acetyl-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopent-2-ene (25). A 2:1 pyridine/CH_2Cl_2 solution (8 mL) of 196 mg (0.73 mmol) of **21** was charged with of acetic anhydride (150 mg, 0.15 mL) and was stirred overnight. The reaction mixture was diluted with EtOAc followed by pouring into 15 mL of 1 N HCl. The organics were washed with 1 N HCl until no pyridine remained in the organic layer. After drying over $MgSO_4$, filtration, and concentration, chromatography on silica gel (EtOAc–hexanes) gave 196 mg (88%) of an oil which was recrystallized from EtOAc and hexanes: mp 86–88 °C; $[\alpha]^{20}_D$ −147.3° (c = 0.0093, $CHCl_3$); R_f = 0.52 (EtOAc); IR (neat) 3305, 2965, 1715, 1655, 1520, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 6.9 Hz, 3 H), 1.44 (s, 9 H), 1.52 (dt, J = 4.5, 14.4 Hz, 1 H), 1.05 (s, 3 H), 2.85 (dt, J = 7.5, 14.4 Hz, 1 H), 4.19 (m, 1 H), 4.92 (dt, J = 4.8, 7.8 Hz, 1 H), 5.39 (d, J = 4.8 Hz, 1 H), 5.55 (dd, J = 4.5, 37.5 Hz, 1 H), 5.96 (s, 2 H), 6.79 (m, 1 H); ^{13}C NMR δ 18.3, 21.0, 28.2, 38.0, 49.8, 52.7, 77.4, 79.8, 132.5, 136.2, 155.4, 170.4, 172.0; MS m/z calcd for $C_{13}H_{21}N_2O_3$ (M^+ − OAc) 253.1552, found 253.1560; 313 (MH^+, 20), 253 (100), 197 (45), 179 (30), 144 (80). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.85; H, 7.95; N, 8.90.

1(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopent-2-ene (26). A solution of DMF and CH_2Cl_2 (1:3, 8 mL) containing **21** (195 mg, 0.73 mmol) was charged with *tert*-butyldiphenylsilyl chloride (220 mg, 1.46 mmol) and then with imidazole (149 mg, 2.19 mmol). The reaction was complete after 17 h. The reaction mixture was poured into water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a clear oil, which after chromatography on silica gel (50% EtOAc in

hexanes) gave a 78% (289 mg) yield of a clear oil which solidified on standing: R_f = 0.5 (50:50 EtOAc:hexanes); IR (neat) 3320, 2940, 1720, 1660, 1510, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.34 (d, J = 7.2 Hz, 3 H), 1.45 (2, 9 H), 1.50 (ddd, J = 5.4, 13.5 Hz, 1 H), 2.60 (ddd, J = 7.2, 7.5, 14.7 Hz, 1 H), 4.15 (m, 1 H), 4.73 (m, 2 H), 5.14 (m, 1 H), 5.71 (m, 1 H), 5.81 (m, 1 H), 6.40 (m, 1 H), 7.38 (m, 6 H), 7.66 (m, 4 H); ^{13}C NMR δ 18.5, 19.0, 26.8, 28.3, 42.1, 50.0, 52.7, 76.4, 80.0, 127.6, 129.7, 133.0, 133.7, 133.9, 135.6, 136.9, 155.4, 171.8; MS m/z (M^+) calcd for $C_{29}H_{40}N_2O_4Si$ 508.2757, found 508.2767.

Diol 31a from 25. A 4 mL THF solution of 49 mg of **25** (0.16 mmol) was charged with 100 mol % of *N*-methylmorpholine *N*-oxide monohydrate and was stirred for 10 min. A 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol was then added (0.2 mL, 10 mol %). After 1 h the reaction was poured into EtOAc and concentrated sodium thiosulfate. The organic extract was chromatographed (100% EtOAc as eluent) after drying and filtration to give 48 mg (87% yield) of the desired diol as an oil: R_f = 0.19 (100% EtOAc); IR (neat) 3310, 2990, 1720, 1695, 1660, 1250 cm^{-1}; $[\alpha]^{20}_D$ −62.76° (c = 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 7.2 Hz, 3 H), 1.44 (s, 9 H), 1.50 (m, 1 H), 2.07 (s, 3 H), 2.74 (ddd, J = 6.9, 8.1, 14.1 Hz, 1 H), 3.67 (m, 2 H), 4.05 (bm, 5 H), 4.97 (m, 1 H), 5.28 (m, 1 H), 7.04 (bs, 1 H); ^{13}C NMR δ 17.7, 21.0, 28.3, 33.8, 49.9, 55.4, 75.5, 77.5, 80.6, 155.8, 170.6, 174.6; MS m/z (M^+ − O − ^{t}Bu) calcd for $C_{11}H_{17}N_2O_6$ 273.1087, found 273.1084.

Diol 32a from 26. A THF solution (10 mL) of **26** (208 mg, 0.41 mmol) was charged with 66.5 mg *N*-methylmorpholine *N*-oxide monohydrate (100 mol %), followed by the addition of 123 μL (2 mol %) of a 2.5% (w/w) solution of OsO_4 in *tert*-butyl alcohol. The reaction was followed by TLC and was complete after 13 h. The reaction was diluted with EtOAc and was quenched by the addition of 3 mL of water, followed by the addition of 3 mL of concentrated sodium thiosulfate. The aqueous solution was washed with 3 × 10 mL of EtOAc. The combined organic solutions were washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated to give 235 mg of a yellow foam. The product was chromatographed on silica gel with 70% EtOAc in hexanes to give 188 mg (85% yield) of the diol product as an oil, which solidified on standing: R_f = 0.18 (3:7 hexanes:EtOAc); IR (neat) 3420, 2930, 1690, 1655, 1525, 1370, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9 H), 1.28 (m, 1 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.43 (s, 9 H), 2.39 (ddd, J = 6.3, 9.0, 14.7 Hz, 1 H), 3.5 (m, 2 H), 3.98 (m, 2 H), 4.16 (m, 3 H), 5.26 (m, 1 H), 6.82 (m, 1 H), 7.39 (m, 6 H), 7.63 (m, 4 H); ^{13}C NMR δ 18.1, 19.0, 26.9, 28.24, 37.4, 49.9, 55.8, 56.1, 76.8, 77.8, 77.9, 78.3, 78.6, 80.3, 127.7, 127.8, 127.86, 129.8, 133.2, 133.6, 133.6, 135.5, 135.6, 135.6, 155.6, 174.44; MS (FAB) m/z MH^+ = 543.

1(*R*)-Acetoxy-2(*R*),3(*R*)-(isopropylidenedioxy)-4(*S*)-[*N*-[*N*-Boc-L-alanyl]amino]cyclopentane (33) from 31a. To 4 mL of 2,2-dimethoxypropane solution containing acetate diol **31a** (28 mg, 0.081 mmol) was added several crystals of *p*-TsOH and the mixture was stirred under argon overnight. The reaction mixture was poured into 20 mL of 1:1 $NaHCO_3$ and EtOAc. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel with 1:1 hexanes: EtOAc to give 30 mg (96% yield) of **33** as a clear oil. The product was crystallized from EtOAc and hexanes: mp 145–146 °C; $[\alpha]^{20}_D$ −55.1° (c = 0.25, $CHCl_3$); R_f = 0.22 (50% EtOAc in hexanes); IR (KBr) 3360, 2985, 1755, 1720, 1670, 1520, 1375, 1245 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.35 (d, J = 6.9 Hz, 3 H), 1.44 (s, 12 H), 1.68 (d, J = 15.0 Hz, 1 H), 2.17 (s, 3 H), 2.42 (ddd, J = 15.0, 6.6, 5.1 Hz, 1 H), 4.11 (m, 1 H), 4.40 (dd, J = 7.2 Hz, 1 H), 4.52 (s, 2 H), 4.92 (m, 1 H), 5.15 (d, J = 4.8 Hz, 1 H), 6.76 (bd, J = 4.8 Hz, 1 H); ^{13}C NMR δ 17.4, 21.1, 23.8, 26.2, 28.3, 33.4, 50.1, 55.0, 79.7, 80.4, 84.1, 85.2, 110.8, 155.7, 169.5, 171.7; MS m/z (M^+ − CH_3) calcd for $C_{17}H_{27}N_2O_7$ 371.1818, found 371.1812. Anal. Calcd for $C_{18}H_{30}N_2O_7$: C, 55.95; H, 7.82; N, 7.25. Found: C, 56.08; H, 8.01; N, 7.13.

Acetonide 33 from Silyl Ether 32a. Diol product **32a** (54 mg) was dissolved in 3 mL of 2,2-dimethoxypropane and under argon and several crystals of *p*-TsOH·H_2O was added. The reaction was incomplete after 30 min, so several more crystals were added. The reaction was then complete in an additional 1 h. Saturated $NaHCO_3$ was added, followed by EtOAc extraction. $MgSO_4$ drying and concentration gave, after chromatography (25% EtOAc in hexanes as eluent), an 83% yield of the desired acetonide as an oil: R_f = 0.25 (70:30 hexanes:EtOAc); IR (neat) 3420, 3325, 2930, 1715, 1680, 1510, 1165, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 and 1.13 (2 singlets, 9 H), 1.19 (s, 3 H), 1.26 (d, J = 7.2 Hz, 3 H), 1.34 and 1.32 (2 singlets, 3 H), 1.44 and 1.43 (2 singlets, 9 H), 1.58 (m, 1 H), 2.14 (m, 1 H), 4.04 (m, 1 H), 4.31 (d, J = 3.9 Hz, 1 H), 4.48 (m, 3 H), 5.18 (m, 1 H), 6.60 (m, 1 H), 7.42 (m, 6 H), 7.64 (m, 4 H); MS m/z (M^+ − ^{t}Bu) calcd for $C_{32}H_{64}N_2O_6Si$ 525.2421, found 525.2408.

To a THF solution (3 mL) of silyl ether acetonide (63 mg, 0.11 mmol) was added a 1 M solution of tetra-*n*-butylammonium fluoride (1.32 mL, 1.32 mmol)) and the mixture was stirred at rt. After 45 min the mixture was poured into EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organics were washed with brine dried over $MgSO_4$. Concentration gave an oil, which after column chromatography gave 30 mg of a white solid (81% yield): R_f = 0.22 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.34 (d, J = 6.9 Hz, 3 H), 1.41 (s, 3 H), 1.44 (s, 9 H), 1.69 (bd, J = 14.4 Hz, 1 H), 2.24 (ddd, J = 4.2, 6.3, 14.1 Hz, 1 H), 4.05 (m, 1 H), 4.28 (d, J = 4.2 Hz, 1 H), 4.37 (dd, J = 6.6, 8.7 Hz, 1 H), 4.51 (s, 2 H), 5.25 (m, 1 H), 7.06 (m, 1 H); ^{13}C NMR δ 18.5, 23.8, 26.2, 28.3, 35.3, 50.3, 55.4, 77.3, 80.1, 85.6, 86.0, 110.3, 155.5, 171.9; MS m/z calcd for $C_{15}H_{25}N_2O_6$ (M^+ − 15) 329.1713, found 329.1713.

A CH_2Cl_2/pyridine (1:1) solution of the alcohol obtained from the fluoride deprotection was charged with Ac_2O (0.016 mL, 0.165 mmol), and several crystals of DMAP·HCl were added. After 4 h, the reaction was diluted with EtOAc and washed with 1 N HCl until the aqueous wash had pH = 2. The organics were dried over $MgSO_4$ and concentrated to give an oil which was chromatographed on silica (25% EtOAc in hexanes) to give the desired product as a clear oil. This product was crystallized from EtOAc and hexanes and was identical in all respects to the acetate acetonide derived from **31a**: $[\alpha]^{20}_D$ −55.0° (c = 0.23, $CHCl_3$).

Conversion of 7b to 33. Following the usual osmylation procedure, 353 mg (1.32 mmol) of olefin **7b** (P = BOC) was dissolved in 10 mL of THF and was oxidized with osmium tetraoxide (0.5 mol %). Following reductive workup and chromatography, the diol was isolated as an oil and was crystallized from EtOAc and hexanes (292 mg, 90% yield): R_f = 0.24 (100% EtOAc); $[\alpha]^{20}_D$ −40.55° (c = 2.01, CCl_4); IR (neat) 3340, 2980, 1700, 1635, 1370, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 6.6 Hz, 3 H), 1.43 (s, 9 H), 1.90 (m, 1 H), 2.24 (m, 1 H), 4.02 (s(b), 2 H), 4.51 (m, 2 H), 4.56 (s(b), 1 H), 4.73 (m, 1 H), 5.54 (m, 1 H); ^{13}C NMR δ 18.0, 28.1, 31.8, 47.0, 58.6, 69.27, 70.6, 79.7, 81.0, 155.1, 171.4; MS m/z (M^+ − C_4H_8) calcd for $C_9H_{14}N_2O_6$ 246.0852, found 246.0849.

To a solution of 126 mg (0.42 mmol) of the diol in 5 mL of 2,2-dimethoxypropane were added several crystals of *p*-TsOH·H_2O. After 1 h the mixture was poured into aqueous saturated $NaHCO_3$ and was extracted with EtOAc. The combined organic layers were washed with brine. The organic solution was dried over $MgSO_4$ and concentrated under vacuum to give a white solid. Chromatography on silica gel (35% EtOAc in hexanes as eluent) gave 120 mg, (86%) of white solid acetonide (crystallized from EtOAc and hexanes): mp 150–151 °C; $[\alpha]^{20}_D$ −81.5° (c = 0.118, $CHCl_3$); R_f = 0.60 (100% EtOAc); IR (KBr) 3405, 2980, 1710, 1655, 1515, 1175, 1075 cm^{-1}; ^{1}H NMR δ 1.30 (s, 3 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.43 (s, 9 H), 1.45 (s, 3 H), 1.81 (m, 1 H), 2.22 (d, J = 11.4 Hz, 1 H), 4.32 (s, 2 H), 4.59 (m, 1 H), 4.69 (s, 1 H), 4.88 (s(b),1 H), 5.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.9, 24.2, 25.5, 28.3, 31.6, 47.3, 57.0, 77.4, 78.2, 78.9, 79.5, 111.8, 155.0, 174.1; MS m/z calcd for $C_{16}H_{26}N_2O_6$ 342.1791, found 342.1784. Anal. Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.95; H, 7.78; N, 8.17. HPLC analysis (10% isopropyl alcohol in hexanes at 2 mL/min) on a 5 μm Econosil silica gel column gave a single peak (254 nm detector) with retention time of 8.8 min.

A 15:1 acetonitrile:water solution of 58 mg (0.17 mmol) of the acetonide was reduced using the standard procedure with 80 mol % of $Mo(CO)_6$. Chromatography on silica gel gave 60 mg (99% yield) of the desired NO reduced product as a white solid: $R_f = 0.08$ (50:50 hexanes:EtOAc); IR (KBr) 3400, 2990, 2940, 1700, 1660, 1545, 1380, 1175 cm^{-1}; ^1H NMR ($CDCl_3$ with one drop of DMSO) δ 1.25 (s, 3 H), 1.32 (d, $J = 7.2$ Hz, 3 H), 1.40 (s, 3 H), 1.44 (s, 9 H), 1.65 (d, $J = 14.4$ Hz, 1 H), 2.19 (ddd, $J = 4.2, 6.3, 14.4$ Hz, 1 H), 4.06 (m, 1 H), 4.20 (d, $J = 3.9$ Hz, 1 H), 4.31 (dd, $J = 6.6, 8.4$ Hz, 1 H), 4.46 (m, 1 H), 5.68 (bd, 1 H), 7.20 (bd, 1 H); ^{13}C NMR δ 18.3, 23.4, 25.8, 27.9, 34.4, 49.9, 54.8, 76.1, 79.0, 85.2, 85.5, 109.4, 154.8, 171.5; MS m/z (M^+) calcd for $C_{16}H_{28}N_2O_6$ 345.2026, found 345.2025.

The resulting alcohol (50 mg, 0.145 mmol) was dissolved in 8 mL of CH_2Cl_2/pyridine (1:1) and excess Ac_2O (0.4 mL, 3.60 mmol) was added. The reaction mixture was stirred at rt for 3 h and poured into EtOAc and aqueous 1 N HCl. The organic layer was extracted with three 10 mL portions of 1 N HCl. The organic layer was dried over $MgSO_4$ and concentrated to an oil. Chromatography on silica gel gave 45 mg (83%) of **33** which was identical to that obtained from **31a** and **32a**.

Acknowledgment. We gratefully acknowledge the NIH and unrestricted funds from Eli Lilly and Co. for partial support of this research. A.R.R. also appreciated financial support from the University of Notre Dame in the form of a Nieuwland Fellowship, and from the Lubrizol Co. for a graduate fellowship.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **4b–d**, **6b** (P = Cbz and P = Boc), **6d**, **7a**, **7b** (P = Cbz and P = Boc), **7d**, **8b**, **8e**, **9b**, **10b**, **10d**, **11b**, **17**, **20**, **21**, **23**, **24b**, **31a**, **32a**, and **33** (51 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.