The Intramolecular Diels-Alder Cycloaddition of *N*-Dienoyl Acrylimidates. An Efficient Approach for the Synthesis of Hexahydroisoquinolones and Hexahydroisoindolones

Arnold J. Gutierrez, Kenneth J. Shea,* and John J. Svoboda

Department of Chemistry, The University of California Irvine, Irvine, California 92717

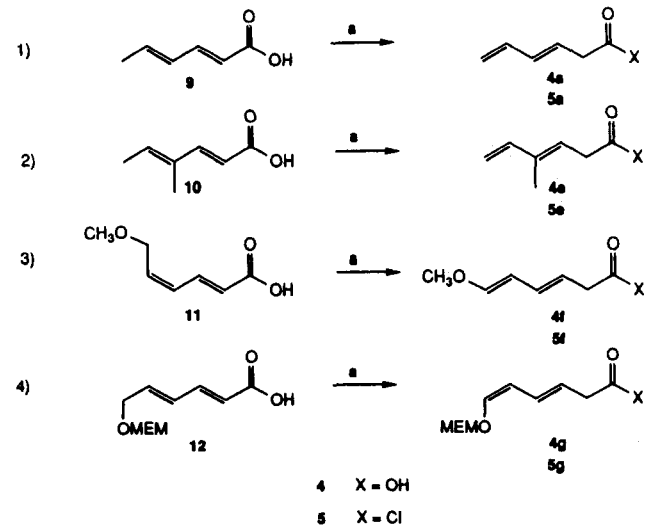
Received February 17, 1989

The intramolecular Diels-Alder reaction of aza trienes featuring the *N*-acyl vinyl imidate moiety in the chain linking the diene and dienophile has been investigated. The acrylimidate bases **3a-d** were synthesized by O-alkylation of the corresponding acrylamides **1a-d** followed by deprotonation of imidate salts **2a-d**. The imidates were efficiently acylated with 3,5-dienoyl chlorides **5a,e-g** in yields ranging from 73 to 87%. The trienes **6a-g** underwent cycloaddition under conditions ranging from 80 to 140 °C, affording mixtures of cis **7a-g** and trans **8a-g** hexahydroisoquinolones, respectively, with a preponderance of the cis cycloadduct. The stereochemistry of the major adduct was determined from proton coupling constants and conversion of **7a** to the known *cis*-perhydroisoquinoline **18**. The cis stereochemistry is understood to originate from cycloaddition in the prefered endo conformation. 2,4-Hexadienoyl imidates **20a,d** also underwent cycloaddition to afford cis hexahydroisoindolones **21a,d** and **22a,d**. The cycloadducts **7a,e-g** were reduced with $NaBH_4$ and $NaCNBH_3$ to the corresponding lactams **24a,e-g**.

Introduction

The intramolecular Diels-Alder cycloaddition of trienes containing nitrogen in the dienophile or diene components has become an important methodology for the synthesis of highly functionalized nitrogen carbocycles for alkaloid synthesis.[1] A number of examples exist using 1-aza-1,3-butadienes as 4π electron components in the intramolecular [4 + 2] cycloaddition to produce functionalized quinolizidine and indolizidine alkaloid precursors.[2] In order to expand the reaction to different nitrogen carbocyclic derivatives, a variation of the intramolecular approach has been developed featuring nitrogen in the tether joining diene and dienophile. This approach has given rise to the synthesis of functionalized hydroindole, hydroisoindole, hydroquinoline, and hydroisoquinoline heterocycles.[3] The latter techniques have relied on amide,[4] amine,[3] ammonium,[5] dienamine,[6] enamide,[7] and imide[8] functional groups to serve as the nexus between diene and dienophile. Bimolecular Diels-Alder reactions of acetylenic and vinyl imidate salts have been reported to exhibit high reactivity as dienophiles.[9] In contrast, the use of vinyl imidates as 2π dienophile components in the intramolecular Diels-Alder reaction and as a means of incorporating nitrogen into a fused bicyclic ring system has not been investigated.[10]

Scheme I[a]



[a] (a) (1) 2.2 equiv of LDA, -78 °C; (2) 3 M HCl, pH = 3.

Not long ago we reported that vinylimidates serve as reactive dienophile 2π components in the intramolecular Diels-Alder reaction to give highly functionalized hexahydroisoquinolone carbocyclic products.[11] This report details the scope of the intramolecular Diels-Alder methodology that has been developed. Attention will be given to the synthesis of the imidate esters and to the diene components as well as the preparation of the Diels-Alder precursors. The scope and selectivity of the intramolecular cycloaddition in terms of the effects of substituents and tether length will be described. Finally, the chemical reduction of the imidate cycloadducts to useful nitrogen carbocyclic intermediates will be presented.

Results and Discussion

Synthesis of Substituted Acrylimidate Esters. Selective O-alkylation[12] of acrylamides **1a-d** with tri-

(1) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (d) Weinreb, S. M.; Levin, J. J. *Heterocycles* **1979**, *12*, 949.

(2) (a) Cheng, Y.-S.; Fowler, F. W.; Lupo, A. T. *J. Am. Chem. Soc.* **1981**, *103*, 2090. (b) Cheng, Y.-S.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696. (c) Fowler, F. W.; Hwang, Y. C. *J. Org. Chem.* **1985**, *50*, 2719.

(3) (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *2*, 183. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (d) Waltanasin, S.; Kathawada, F. G. *J. Org. Chem.* **1985**, *50*, 3810.

(4) (a) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170. (b) Guy, A.; Lemaire, M.; Negre, M.; Guette, J. P. *Tetrahedron Lett.* **1985**, *26*, 3575. (c) Mellor, J. M.; Wagland, A. M. *Tetrahedron Lett.* **1987**, *28*, 5339. (d) Yamaguchi, R.; Otsuji, A.; Utimoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 2186. (e) Kraus, G. A.; Raggon, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605.

(5) Jung, M. E.; Buszek, K. R. *J. Org. Chem.* **1985**, *50*, 5440.

(6) (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (b) Eberle, M. K.; Shapiro, M. J.; Stucki, R. *J. Org. Chem.* **1987**, *52*, 4661.

(7) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

(8) Ciganek, E.; Wong, B. K. U.S. Patent 4 751 306, 1988; *Chem. Abstr.* **1988**, *109*, 128987*p*.

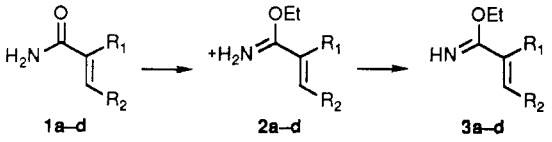
(9) (a) Baum, J. S.; Viehe, H. G. *J. Org. Chem.* **1976**, *41*, 183. (b) Jung, M. E.; Vaccaro, W. D.; Buscek, K. R. *Abstracts of Papers*; 196th National Meeting of the American Chemical Society, Los Angeles, CA; American Chemical Society: Washington, DC, 1988; ORGN 230.

(10) For examples of imidates, thioimidates, and amidines in Diels-Alder chemistry, see: (a) Masataka, I.; Kirihara, T.; Kukumoto, K. *Heterocycles* **1985**, *23*, 1097. (b) Ihara, M.; Tsuruta, M.; Kukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1159. (c) Tamaru, Y.; Ishige, O.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 3583. (d) Widmer, U.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 815.

(11) Shea, K. J.; Svoboda, J. J. *Tetrahedron Lett.* **1986**, *27*, 4837.

0022-3263/89/1954-4335$01.50/0

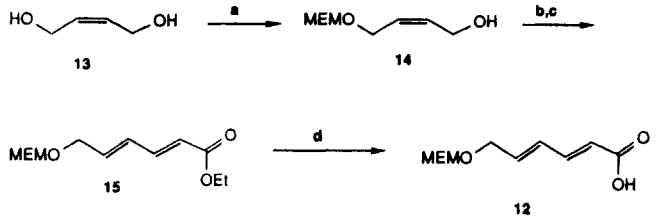
Table I



entry	acrylamide R_1	acrylamide R_2	alkylation conditions[a] (equiv of EtO_3BF_4; time, h)	imidate	isolated yield, %	bp, °C/mmHg
1	H	H	1.1; 12	**3a**	48	70–73/121
2	H	CH_3	1.2; 3	**3b**	39	74–76/100
3	CH_3	H	1.3; 15	**3c**	44	110–120/100
4	H	Ph	1.0; 0.25	**3d**	59	114–115/1

[a] All alkylations were done in CH_2Cl_2 at room temperature under N_2.

Scheme II[a]

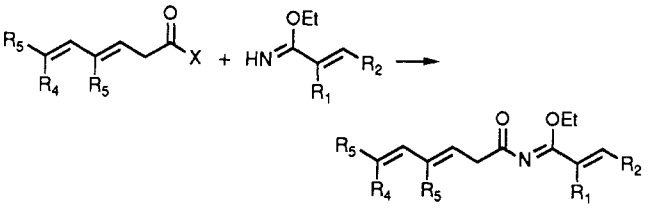


[a] (a) MEM chloride, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C; (b) $C_2O_2Cl_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (c) $(EtO)_2POCH_2COOEt$, NaH, THF, 0 °C; (d) KOH, 1:1 MeOH–H_2O, 25 °C.

ethyloxonium tetrafluorborate[13] followed by deprotonation of the intermediate acrylimidate tetrafluoroborates was the most expedient route for obtaining quantities of the ethyl acrylimidate bases **3a–d** in moderate yield (Table I). In the case of vinyl imidates **3a–c** use of aqueous NaOH was necessary to liberate the monomeric materials. When other bases were tried such as triethylamine or aqueous bicarbonate only large amounts of nonmonomeric materials were obtained. Cinnamimidate **3d** could be acquired from deprotonation of the tetrafluoroborate salt **2d** with aqueous saturated $KHCO_3$. The resulting imidate bases are purified by distillation and, if kept free of water, have a shelf life of several weeks at −20 °C.

Synthesis of Diene Components. The dienes were obtained by kinetic deconjugation of the corresponding conjugated dienoic acids (see Scheme I). 3,5-Hexadienoic acid[7] (**4a**), 4-methyl-3,5-hexadienoic acid[14] (**4e**), and 6-methoxy-3(*E*),5(*E*)-hexadienoic acid[15] (**4f**) were prepared as described by Martin and Grieco and entailed treating the respective acids with 2.2 equiv of LDA followed by quenching with aqueous acid (see Scheme I). MEMoxy acid **4g** was synthesized in a similar manner from acid **12**. Diol **13** was alkylated with MEM chloride in the presence of *N*,*N*-diisopropyl-*N*-ethylamine in dichloromethane to give the monoprotected diol **14** in 56% yield. Swern oxidation[16] of this allylic alcohol gave only the (*E*)-4-MEMoxy-2-butenal and reaction of the α,β-unsaturated aldehyde with the sodium salt of triethyl phosphonoacetate in THF gave the dienoate ester **15** in 64% overall yield. Saponification of the ester with KOH in aqueous methanol gave the acid **12** in 89% yield (Scheme II). Deconjugation of the (*E*,*E*)-dienoic acid in the manner previously described gave exclusively the diene acid **4g** (88%). It has been reported that kinetic deconjugation of 2(*E*),4(*Z*)-6-methoxyhexadienoic acid gives a predominance of 3*E*,5*E*-deconjugated hexadienoic acid (Scheme I). However, deconjugation of 6-methoxy-2(*E*),4(*E*)-hexadienoic acid gave a mixture of deconjugated acids favoring the 6-methoxy-3(*E*),5(*Z*)-hexadienoic acid.[15] In order to realize the deconjugated product **4g**, acid **12** would have to exist predominantly in the rotomer depicted in Scheme I followed by deprotonation. Although the proposed conformation of the diene leading to the *Z* alkoxy dienoic acid **4g** is more sterically congested when viewed with molecular models, possible chelation of the MEMoxy group with the metal carboxylate functionality could favor this conformation. While this seems to be a good working model for the stereoselective deconjugation an investigation in this area is continuing.

Table II



entry	diene	imidate	acylation conditions:[a] time, h	DA precursor	yield,[b] %
1	**5a**	**3a**	1	**6a**	–[c]
2	**5a**	**3b**	0.5	**6b**	–[c]
3	**5a**	**3c**	0.5	**6c**	77
4	**5a**	**3d**	0.5	**6d**	80
5	**5e**	**3a**	2	**6e**	87
6	**4f**	**3a**	12[d]	**6f**	35
7	**5g**	**3a**	3	**6g**	73

[a] 0.98 equiv of acyl chloride; 1.1 equiv of NEt_3; benzene; room temperature. [b] All yields are isolated yields. [c] DA precursor not isolated. [d] Acylation of anhydride; 1.1 equiv of NEt_3, 0.1 equiv of DMAP; room temperature.

Preparation of Diels–Alder Precursors. The N-acylation of the imidate bases was performed utilizing standard procedures.[17] A typical reaction called for adding (0.95–0.98 equiv) of the acid chlorides **5a–g** to the acrylimidates **3a–d** in the presence of triethylamine in benzene at room temperature (Table II). High yields are obtained

(12) Pilloti, A.; Reuterhall, J. C.; Torssell, K.; Lindblad, C.-G. *Acta Chem. Scand.* **1969**, *23*, 818. (b) Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, *33*, 1679. (c) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.

(13) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 1080.

(14) Greico, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897.

(15) Greico, P. A.; Yoshida, K.; He, Z. *Tetrahedron Lett.* **1984**, *25*, 5715.

(16) Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165.

(17) (a) Baccar, B.-G.; Barrans, J. C. *Compt. Rend.* **1964**, *259*, 1340. (b) Baccar, B.-G.; Mathis, F. *Ibid.* **1965**, *261*, 174. (c) Bader, H. *J. Org. Chem.* **1965**, *30*, 707. (d) Lokensgard, J. P.; Fischer, J. W.; Bartz, W. J. *J. Org. Chem.* **1985**, *50*, 5609.

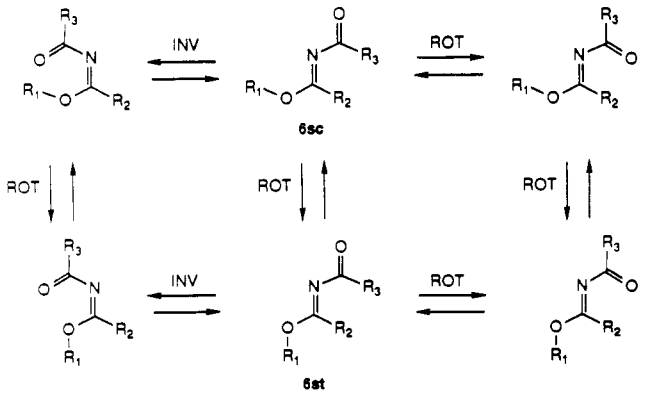
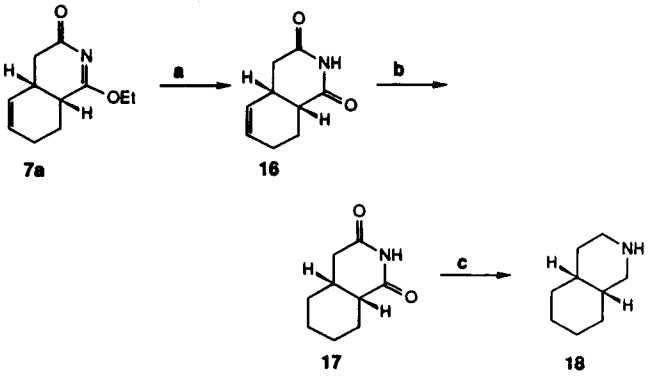


Figure 1.

by this procedure for the synthesis of *N*-dienoyl acrylimidates **6a–e** and **6g**. In the case of Diels–Alder precursors **6a** and **6b**, cycloaddition products were observed under the acylation conditions so their isolation was not achieved. For **6f**, the acid chloride of **4f** could not be successfully prepared so the acid anhydride of **4f** was made with dicyclohexylcarbodiimide in ether. The anhydride, without purification, was added to a stirred solution of imidate **3a**, triethylamine, and a catalytic amount of DMAP in ether to afford 35% yield of **6f** after flash chromatography. Except for **6d,c** the acyl imidates are typically very labile on silica gel and for this reason a low yield of **6f** is obtained. The *N*-dienoyl ethylimidates were characterized by their spectral properties, in particular, ^{13}C NMR absorptions for the >C=O and (EtO)C=N at 184–178 ppm and 158–156 ppm and IR stretching frequencies of 1658–1662 cm^{-1} and 1605–1602 cm^{-1}, respectively.[18] The products of the acylation **6a–g** are reported in the *Z* configuration about the C=N bond. Alternatively the reaction may produce acyl imidates in the *E* configuration. Ab initio 3-21G calculations indicate that the barrier to inversion at nitrogen is from 2.6 to 8.0 kcal/mol.[18] The acylimidates may adopt a number of low energy conformations (Figure 1). These conformations arise from rotation about the N–CO bond and/or nitrogen inversion. The imidate ester may also reside in the s-cis **6sc** or the s-trans **6st** conformation. The s-cis and s-trans conformations may give slight alterations to the rotation/inversion energy barriers. It is important to note that cycloaddition is expected to occur in the *E* configuration as in **6sc** and **6st**. Since barriers to N–CO rotation range from 5.7 to 6.3 kcal/mol,[18] the acyl imidates **6a–g** may explore all conformations including **6sc** and **6st** under thermal reaction conditions.

Synthesis of Hexahydroisoquinol-3-ones by Intramolecular Diels–Alder Cycloaddition. As noted in Table III, high yields are observed for the cycloadditions of *N*-dienoyl acrylimidates under thermal conditions. Furthermore, in each case a predominance of one cycloadduct is evident. Chromatography on silica gel allowed isolation of the pure major isomer. Identification of the major isomer was determined from ^1H NMR by examination of the coupling constants of the bridgehead protons of the major constituent in the cycloadduct mixture. Generally, coupling constants of 5–6 Hz are observed which correspond to a cis-fused hexahydroisoquinolone adduct **7a–g**.[4d] In order to unambiguously identify the stereochemistry of the major cycloadduct, the thermolysis mixture containing **7a** was hydrolyzed with 1% aqueous HCl to give the unsaturated imide **16** (see Scheme III). Hydrogenation of the double bond to give **17** was accomplished with PtO_2 in a hydrogen atmosphere. Finally LAH reduction of the imide mixture furnished the known perhydroisoquinoline **18**. ^1H and ^{13}C NMR of the resulting amine was entirely consistent with *cis*-perhydroisoquinoline[19] and thus establishes the cis geometry of the major cycloadduct.

Scheme III[a]



[a] (a) 1% HCl, MeOH, 25 °C; (b) H_2/Pd-C, 40 psi, EtOH, 25 °C; (c) $LiAlH_4$, THF, 65 °C.

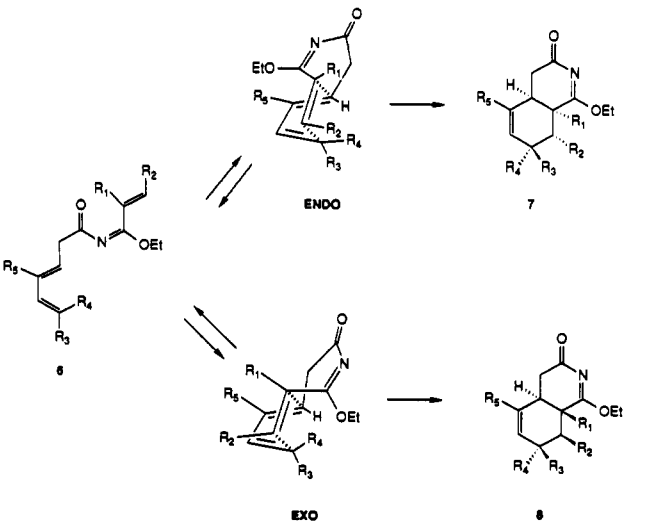


Figure 2.

The intramolecular Diels–Alder cycloaddition may occur from either an endo or exo conformation of the *E*-imidate (Figure 2). The endo conformation is designated as the orientation where the ethyl imidate moiety resides above the plane of the diene. Cycloaddition leads to cis-fused hexahydroisoquinolone **7**. Conversely, in the exo conformation, the imidate is suspended away from the diene, cycloaddition in this manner would give the trans-fused cycloadduct **8**.

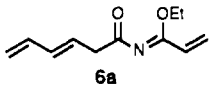
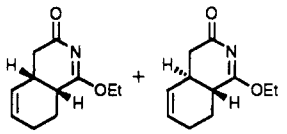
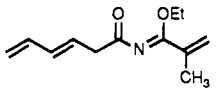
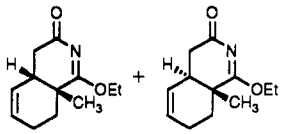
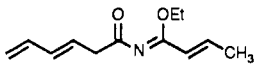
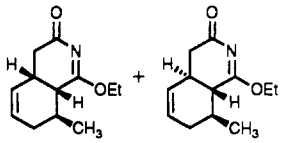
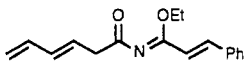
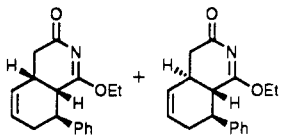
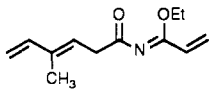
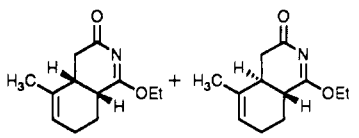
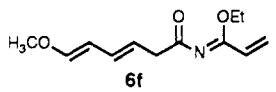
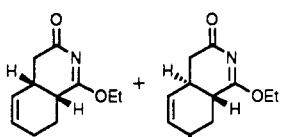
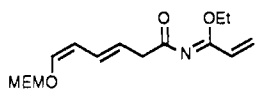
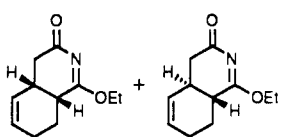
In order to investigate the influence of substituents on the stereochemistry of the cycloaddition, a series of reactions were performed on precursors with variations in the dienophile substituent pattern. In each example (products **7a–d**) a preponderance of cis cycloadduct is observed. The prevalence of cis cycloadduct in all reactions implies the endo transitions state is favored by 1.5–3.5 kcal/mol.

It does appear that substituents at the terminus of the dienophile have the effect of decreasing the endo/exo ratio, however, even in this case the selectivity remains respectable. When a methyl group is substituted at the 2-position of the diene as in **6e** no enhancement in selec-

(18) Kupfer, R.; Nagel, M.; Wurthwein, E.-U.; Allman, R. *Chem. Ber.* **1985**, *118*, 3089.

(19) Booth, H.; Bailey, J. M. *J. Chem. Soc. Perkin Trans. 2* **1979**, 510.

Table III

entry	DA precursor	temp, °C/time, h	product	endo:exo	yield, %
1	 **6a**	80/1	 **7a** **8a**	9:1	85[a]
2	 **6b**	80/12	 **7b** **8b**	5.5:1	83[a]
3	 **6c**	110/9	 **7c** **8c**	3.5:1	83
4	 **6d**	110/17	 **7d** **8d**	4:1	78
5	 **6e**	110/1	 **7e** **8e**	9.5:1	94
6	 **6f**	110/7	 **7f** **8f**	5:1	95
7	 **6g**	140/17	 **7g** **8g**	>20:1	54

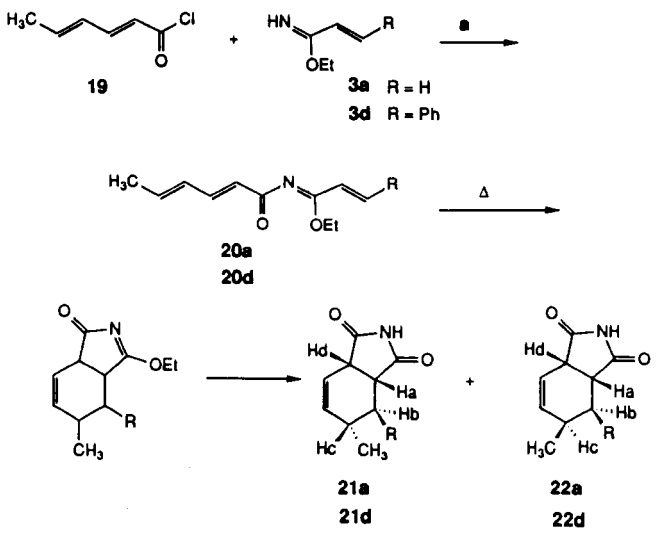
[a] Diels–Alder precursor not isolated. Yield is given for acylation and cycloaddition.

tivity is observed when compared with the unsubstituted case **6a**. An (*E*)-methoxy substituent at the diene terminus as in **6f** gives a slightly lower ratio of cis to trans cycloadduct but the yield remains high. The examples that have been investigated show that when substituents do not exist on the termini of the dienophile or the diene the endo selectivity is high. However a *Z* termally substituted diene in the case of **6g** (R_4 = OMEM, Figure 2) gives a marked increase in the endo/endo ratio. Inspection of molecular models shows that a substantial steric interaction exists between the ethoxy group of the imidate and the (*Z*)-MEMoxy substituent of the diene in the exo conformation. This interaction is completely removed in the endo orientation. Consequently cycloaddition would be expected to occur with a pronounced bias in favor of the endo conformation. The experimental result shows only cis-fused cycloadduct **7g** formed with no trans product **8g** detected.

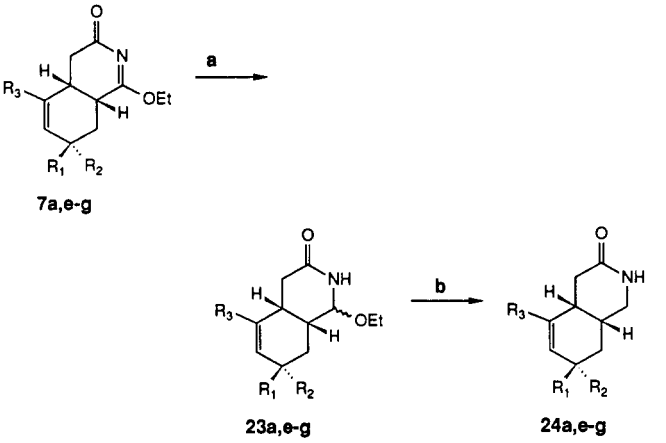
Since cycloadduct **7a** is detected under the acylation conditions for **6a**, proton catalysis via an acyl imidinium intermediate is a possibility. Currently the rate acceleration of the cycloaddition by proton and Lewis acids is being investigated.

Synthesis of Hexahydroisoindolones. As part of this investigation it was desired to explore the effect of decreasing the tether length by one carbon unit as a potential entry to the isoindole ring system. Diels–Alder precursors **3a** and **3d** were acylated as before with sorboyl chloride **19** to afford *N*-sorboyl ethyl acrylimidates **20a** and **20d** in 93 and 91% yield respectively (Scheme IV). It was found that higher temperatures were necessary for cycloaddition to occur. Thermalysis of **20d** in toluene at 200 °C for 16 h gave 83% of three imidate cycloadducts in a ratio of 1:3:3. The isomers could not be separated without hydrolysis which yielded two imide isomers **21d** and **22d** in a ratio of 1:1.3. The stereochemistry was determined from

Scheme IV



Scheme V[a]



[a] (a) $NaBH_4$, EtOH, 0 °C; (b) $NaCNBH_3$, EtOH:TFA 3:1, 25 °C.

^1H NMR and X-ray data which revealed **22d** as a cis isomer in a boat conformation with the phenyl substituent occupying a pseudoaxial orientation. ^1H NMR of this compound showed bridgehead proton coupling constant (H_a–H_d) of 8.2 Hz and a coupling constant for H_a–H_b of 4.1 Hz, and 5.5 Hz for H_b–H_c. Compound **21d** was identified from its ^1H NMR spectrum, which contained a bridgehead proton coupling constant (H_a–H_d) of 8.3 Hz and coupling constants of 8.9 and 9.7 Hz (H_a–H_b; H_b–H_c), indicating pseudoaxial relationships for protons H_a, H_b, and H_c. The syn relationship of the methyl and phenyl group in **22d** can only arise from cycloaddition in the exo conformation followed by proton epimerization during the conversion of acyl imidate to imide. Imide **21d** arises by cycloaddition in the endo conformation followed by hydrolysis of the acyl imidate cycloadduct.

In the same manner *N*-sorboyl ethyl acylimidate **20a** was thermalyzed at 200 °C for 22 h to give two imides **21a** and **22a** in a ratio of 1:1.3. The mixture could not be separated by conventional chromatographic techniques. However ^1H NMR analysis of the product mixture showed chemical shifts and coupling constants for the cis adduct **22a** (H_a–H_d) 8.2 Hz, 3.8 and 5.2 Hz for the H_a–H_b and H_b–H_c coupling. The cis-endo adduct **21a** was also compared with imide **21d** H_a–H_d 8.4 Hz, H_a–H_b 11.4 Hz, and H_b–H_c 9.5 Hz.

Reduction of Imidate Cycloadducts. The acylimidate cycloadducts are chemodifferentiated imides and may be reduced to the corresponding ethoxy lactams with $NaBH_4$[20] (see Scheme V). The imidate cycloadducts are quite labile. In practice it is best to reduce the cycloadducts immediately after isolation. In this manner adducts **7a,e–g** were reduced with $NaBH_4$ in ethanol to ethoxy lactams **23a,e–g**. The ethoxy lactams may be further reduced to lactams **24a,e–g** with $NaCNBH_3$ in ethanolic trifluoroacetic acid.[21] These transformations have been accomplished in two steps. The complete reduction may also be performed in a single-pot reaction by using equal amounts of $NaBH_4$ and $NaCNBH_3$ in ethanol and adding trifluoroacetic acid after a few hours. Compound **24e** was prepared in this manner from imidate **23e**. In effect the cycloaddition of the acylimidates followed by complete reduction of the imidate moiety serves as an allyl amide equivalent in the intramolecular cycloaddition. This approach affords lactams with increased selectivity for the cis isomer and under substantially milder conditions than existing methologies.[12]

Conclusions

Imidates **3a–d** have been synthesized from readily available starting materials. The imidates are acylated in high yield with the corresponding dienoyl chlorides to afford the Diels–Alder precursors **6a–g**. Cycloaddition occurs stereoselectively to give hexahydroisoquinolones **7a–g** and hexahydroisoindoles **21a,d** and **22a,d** in good yield. The imidate cycloadducts may be chemoselectively reduced to the corresponding lactams **24a,e–g**. This methodology is currently being utilized in the synthesis of alkaloid natural products.

Experimental Section

General Procedures. Unless otherwise noted starting materials were obtained from commercial suppliers and were used without further purification. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. All reactions were performed under a N_2 atmosphere in oven-dried glassware. Compounds were purified by silica gel chromatography to purities >98% as established by capillary column gas chromatography. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer and on a Nicolet FTIR spectrophotometer using polystyrene film as standard. ^1H NMR spectra were determined with a Bruker WM 250 spectrometer, Nicolet QE 300 spectrophotometer, and a Nicolet GN 500 spectrometer. Chemical shifts are referenced in parts per million downfield from tetramethylsilane. Splitting patterns are designated as s singlet; d doublet; t triplet; q quartet; m multiplet; br broad. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded using Bruker WM 250 (62.9 MHz), Nicolet QE 300 (75.4 MHz), and Nicolet GN 500 (125.8 MHz) instruments in $CDCl_3$ solvent. Low-resolution mass spectra were obtained with a Finnigan 4000/MS/DS. Chemical ionization was performed using isobutane and a voltage of 100 eV unless otherwise described. Electron impact spectra were determined using a voltage of 70 eV unless otherwise noted. Exact mass determinations were obtained on a VG Analytical 7070e high-resolution mass spectrometer. All mass spectra are reported as mass to charge ratios. GLC analysis was performed with aid of a Hewlett-Packard 5790 instrument equipped with a J & J 30-m capillary column packed with cross-linked methyl silicone. Integration was done on a Hewlett-Packard 3390A integrator. Flash chromatography was performed using 230–400 mesh silica gel (Merck, Sharpe & Dohme). Volatile solvents were removed under reduced pressure using a

(20) (a) Matoba, K.; Yamazaki, T. *Chem. Pharm. Bull.* **1974**, *22*, 2999. (b) Matsuda, F.; Tomiyoshi, N.; Yangiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1982**, *23*, 4043. (c) See ref 15e.

(21) (a) Gribble, G. W.; Nutaitis, F. *Org. Prep. Proc. Int.* **1985**, *17*, 317. (b) Weinreb, S. M.; Orlando, J.; Basha, A. *Synth. Commun.* **1977**, *7*, 549.

Büchi rotary evaporator and is refered to removing solvents in vacuo.

2-Ethoxy-1-aza-1,3-butadiene (3a). Acrylamide **1a** (10.0 g, 0.140 mol) was placed in a 250-mL round-bottom flask furnished with a magnetic stirrer. A solution of triethyloxonium tetrafluorborate[13] in CH_2Cl_2 (68 mL, 0.4360 g/mL, 0.156 mol) was added in one portion. The mixture was stirred under N_2. It became homogeneous within 5 min and was stirred an additional 12 h at room temperature. The solvent was removed in vacuo, and the resulting oil washed with ether (2 × 25 mL). The oil was then added in three portions to a stirred ice-cooled 3 N aqueous NaOH solution (100 mL), which was layered with ether (75 mL). The ether layer was separated, and the aqueous layer was extracted with ether (2 × 75 mL). The combined ether extracts were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to afford 10.32 g of slightly yellow liquid. Distillation yielded 6.74 g (48.6%) of colorless liquid: bp 70–73 °C (121 mmHg); IR (NaCl, film) 3270, 2985, 1915, 1662, 1595, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.15 (br s, 1 H, =N*H*), 6.03 (dd, J = 10.2, 17.2 Hz, 1 H, CH_2=C*H*), 5.86 (dd, J = 16.6, 1.1 Hz, 1 H, CH_2=CH), 5.45 (dd, J = 10.2, 1.7 Hz, 1 H, CH_2=CH), 4.18 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), 1.33 (t, J = 7.0 Hz, 3 H, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.57, 129.89, 121.59, 60.35, 13.19; MS (CI, 100 eV), m/e (relative intensity) 279 (26), 149 (8), 140 (47), 100 (MH^+, 100); high-resolution MS (EI, 70 eV) calculated for C_5H_9NO 99.0684, observed 99.0639.

2-Ethoxy-3-methyl-1-aza-1,3-butadiene (3b). To methacrylamide **1b** (3.0 g, 35.2 mmol) in one portion was added a solution (19.25 mL) of triethyloxonium tetrafluorborate (0.4169 g/mL, 42.2 mmol). The mixture was stirred under N_2 for 3 h. The solvent was removed in vacuo, and the residual salt was washed with ether (1 × 50 mL). The ether was discarded, and the salt was added to ice-cooled 3 M NaOH (50 mL), layered with ether (50 mL). The ether layer was separated, and the aqueous layer was extracted with ether (4 × 50 mL). The combined ether extracts were dried over anhydrous K_2CO_3, and the solvent was carefully removed in vacuo. The residue was dissolved in pentane and dried with K_2CO_3. Removal of solvent and distillation afforded 1.55 g (38.9%) of colorless liquid: bp 74–76 °C (100 mmHg); IR (NaCl, film) 3330, 1603, 1237, 1080, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (s, 1 H, =N*H*), 5.70 (s, 1 H, CH_2=C(CH_3)), 5.28 (d, J = 1.4 Hz, 1 H, CH_2=C(CH_3)), 4.17 (q, J = 6.4 Hz, 2 H, CH_3CH_2O), 1.92 (s, 3 H, CH_3), 1.31 (t, J = 7.0 Hz, 3 H, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.48, 136.14, 118.94, 61.30, 18.80, 13.95; MS (CI, 100 eV) m/e (relative intensity) 113 (MH^+, 100); high-resolution MS (EI, 70 eV) m/e calculated for $C_6H_{11}NO$ 113.0841, observed 113.0859.

2-Ethoxy-4-methyl-1,3(*E*)-butadiene (3c). A solution of EtO_3BF_4 in CH_2Cl_2 (7.0 mL, 0.4169 g/mL, 15.4 mmol) was added in one portion to 3(*E*)-methylacrylamide **1c** (1.00 g, 11.8 mmol). The mixture was stirred in a sealed flask for 15 h at room temperature. The resulting brown solution was concentrated in vacuo. The oily residue was washed with pentane (2 × 20 mL). It was then slowly poured into stirred, ice-cooled 12% aqueous NaOH (30 mL) layered with pentane (30 mL). The layers were separated, and the aqueous layer was extracted with pentane (5 × 25 mL). The combined pentane extracts were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to afford 628 mg of yellow liquid. Kugelrohr distillation provided 576 mg (43.2%) of colorless liquid: bp 110–120 °C (100 mmHg); IR (NaCl, film) 3420, 1679, 1635, 1610, 1385, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.94 (s, 1 H, =N*H*), 6.48 (overlapping q, J = 15.5, 6.8 Hz, 1 H, CH_3CH=CH), 5.78 (m, J = 13.7 Hz, 1 H, CH_3CH=C*H*), 4.17 (q, J = 7.1 Hz, 2 H, CH_3CH_2O), 1.82 (dd, J = 6.8, 1.6 Hz, 3 H, =CH(CH_3), 1.33 (t, J = 7.1 Hz, 3 H, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.01, 135.73, 125.14, 61.18, 17.80, 14.34; MS (CI, 100 eV) m/e (relative intensity) 115 (6), 114 (MH^+, 100); high-resolution MS (EI, 70 eV) m/e calculated for $C_6H_{11}NO$ 113.0841, observed 113.0810.

2-Ethoxy-4-phenyl-1-aza-1,3-butadiene (3d). To a suspension of cinnamamide **1d** (4.50 g, 30.57 mmoles) and CH_2Cl_2 (30 mL) was added dropwise over 10 min a solution of triethyloxonium tetrafluoroborate (5.80 g, 30.6 mmol) in CH_2Cl_2 (11 mL). The solution cleared in about 10 min and was stirred at room temperature for an additional 2 h until a white solid once again appeared. The white solid was filtered and washed with 1:1 ether–CH_2Cl_2 and dried on high vacuum, mp 196–198 °C. The solid was suspended in ether (30 mL) and basified to pH 8 with saturated $KHCO_3$. The ether layer was separated, and the aqueous layer was extracted with ether (3 × 25 mL). The combined extracts were dried over $MgSO_4$. The solvent was removed in vacuo to afford a slightly colored liquid which yielded upon distillation 3.21 g (59.5%) of colorless liquid: bp 95–105 °C (0.87 mmHg); IR (NaCl, film) 3321, 1644, 1627, 1170 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49–7.26 (m, 5 H, C_6H_5), 7.24 (d, J = 15.9 Hz, 1 H, C_6H_5CH=CH), 6.39 (d, J = 15.9 Hz, 1 H, C_6H_5CH=C*H*), 4.24 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.39 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.11, 136.37, 134.95, 128.79, 128.34, 127.05, 120.61, 60.83, 13.85; MS (CI, 70 eV, isobutane) m/e (relative intensity) 177 (12), 176 (MH^+, 100), 148 (7), 130 (24), 89 (8); high-resolution MS (EI, 70 eV) m/e calculated for $C_{11}H_{13}NO$ 175.0997, observed 175.0986.

6-[(2-Methoxyethoxy)methoxy]-3(*E*),5(*Z*)-hexadienoic Acid (4g). Diisopropylamine (5.36 mL, 38.3 mmol) in THF (40 mL) was stirred under N_2 in a dry ice–acetone bath. Added dropwise was 20.1 mL of 1.9 M *n*-butyllithium in hexanes (38.3 mmol). The resulting slightly yellow solution was stirred at this temperature for 40 min. The conjugated acid **12** (3.6 g, 16.65 mmol) in THF (15 mL) was added dropwise over 1 h. The temperature did not rise past −72 °C during addition. Stirring was continued for 3 h. The orange enolate solution was warmed to −40 °C and poured into H_2O (75 mL) and separated. The aqueous layer was washed with 1 × 50 mL of ether, and the aqueous layer was then acidified to pH 3 with 3 M HCl. Extraction with ether (4 × 50 mL) and drying ($MgSO_4$) gave after removal of solvent in vacuo 3.15 g (88%) of deconjugated acid: IR (NaCl, film) 3150, 2910, 1750, 1660, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.46 (dd, J = 10.7, 14.9 Hz, 1 H, C*H*=CHCH$_2$), 6.14 (d, J = 6.3 Hz, 1 H, (MEMO)C*H*=CH), 5.63 (dd, J = 7.2, 14.9 Hz, 1 H, CH=C*H*CH$_2$), 5.19 (dd, J = 6.3, 10.7 Hz, 1 H, (MEMO)CH=C*H*), 4.92 (s, 2 H, OCH_2O), 3.73 (m, 2 H, OCH_2CH_2O), 3.55 (m, 2 H, OCH_2CH_2O), 3.38 (s, 3 H, OCH_3), 3.15 (d, J = 7.2 Hz, 2 H, =CHCH_2CO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.44, 143.58, 127.03, 121.71, 108.09, 95.86, 71.81, 67.74, 59.25, 38.29; MS (EI, 70 eV) m/e (relative intensity) 216 (M^+, 1.7), 89 (41.4), 59 (100).

General Procedures for Preparation of *N*-Hexadienoyl Ethyl Acrylimidates (6c–e,g). A solution of acid chloride (0.95–0.98 equiv) in benzene was added dropwise to a stirred solution of the acrylimidate and triethylamine (1.1 equiv) at room temperature under N_2. The solution was stirred, and the triethylamine hydrochloride salt was filtered with washing (benzene). The solvent was removed in vacuo to afford the products as high-boiling liquids.

***N*-(3,5-Hexadienoyl)-2-ethoxy-4-methyl-1-aza-1,3(*E*)-butadiene (6c).** To a solution of ethyl crotylimidate **3c** (0.45 g, 3.98 mmol) and triethylamine (444 mg, 4.4 mmol) in benzene (100 mL) under N_2 was added a solution of **5a** (0.517 g, 3.98 mmol) in benzene (10 mL). Flash chromatography on silica gel (60 g) using 4:1 hexanes–EtOAc gave 631.2 mg (76.6%) of slightly yellow liquid: IR (NaCl, film) 1680, 1619, 1300, 1093, 968 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.74 (d of q, J = 15,2, 6.9 Hz, 1 H, CH_3CH=CH), 6.35 (d of t, J = 17.0, 10.1 Hz, 1 H, $NCOCH_2CH$=CH), 6.17 (dd, J = 15.0, 10.0 Hz, 1 H, CH=C*H*CH=CH$_2$), 5.82 (m, 2 H, CH_3-CH=C*H*, CH$_2$=C*H*), 5.16 (dd, J = 1.7, 16.4 Hz, 1 H, CH=C*H*$_2$), 5.05 (dd, J = 1.7, 10.1 Hz, 1 H, CH=C*H*$_2$), 4.15 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), 3.25 (d, J = 7.2 Hz, 2 H, =CHCH_2CO), 1.84 (dd, J = 6.9, 1.8 Hz, 3 H, CH_3CH=CH), 1.32 (t, J = 7.0 Hz, 3 H, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 183.66, 156.69, 141.31, 136.58, 134.25, 126.37, 119.96, 116.58, 62.59, 43.10, 18.25, 13.96; MS (CI, 100 eV) m/e (relative intensity) 209 (12), 208 (MH^+, 100), 180 (23), 140 (19), 112 (13); high-resolution MS (EI, 70 eV) m/e calculated for $C_{12}H_{17}NO_2$ 207.1259, observed 207.1277.

***N*-(3,5-Hexadienoyl)-2-ethoxy-4-phenyl-1-aza-1,3(*E*)-butadiene (6d).** The cinnamimidate **3d** (0.268 g, 1.53 mmol) and triethylamine (0.170 g, 1.68 mmol) was dissolved in benzene (90 mL). 3,5-Hexadienoyl chloride **5a** (0.20 g, 1.53 mmol) in benzene (10 mL) was added dropwise over 10 min. Flash chromatography on silica gel using 8:1 hexanes–EtOAc eluent, R_f = 0.41 produced 329 mg (80%) of slightly yellow oil: IR (NaCl, film) 1690, 1649, 1620, 1455, 1376, 1310, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, J = 15.8 Hz, 1 H, PhC*H*=CH), 7.49–7.35 (m, 5 H, C_6H_5),

6.45 (d, J = 15.8 Hz, 1 H, PhCH=C*H*), 6.37 (dd, J = 10.2, 15.8 Hz, 1 H, C*H*=CH_2), 6.18 (dd, J = 15.1, 10.5 Hz, 1 H, C*H*=$CHCH_2CO$), 5.87 (m, 1 H, CH=C*H*CH_2CO), 5.16 (dd, J = 16.5, 1.1 Hz, 1 H, CH=CHCH=C*H*$_2$), 5.02 (dd, J = 10.3, 1.1 Hz, 1 H, CH=CHCH=C*H*$_2$), 4.25 (q, J = 7.1 Hz, 2 H, O*CH*$_2$$CH_3$), 3.31 (d, J = 7.2 Hz, 2 H, CH=CHC*H*$_2$CO), 1.39 (t, J = 7.1 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 183.33, 157.37, 141.43, 136.64, 134.79, 134.43, 130.05, 128.85, 127.99, 126.44, 116.62, 115.76, 62.86, 43.31, 14.07; high-resolution MS (EI, 70 eV) calculated for $C_{17}H_{19}NO_2$ 269.1416, observed 269.1445.

***N*-(4-Methyl-3,5-hexadienoyl)-2-ethoxy-1-aza-1,3-butadiene (6e).** Acid chloride **5e** (2.2 mmol) in benzene (5 mL) was added dropwise to a stirred solution of acrylimidate **3a** (0.222 g, 2.25 mmol) and triethylamine (0.243 g, 2.4 mmol) in benzene (20 mL). Workup afforded 395 mg (87%) of yellow oil: FTIR (NaCl, film) 2981, 29,29, 1695, 1662, 1605, 1283, 1073 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (dd, J = 10.7, 17.4 Hz, 1 H, CH_2=C*H*C(CH_3)=CH), 6.17 (dd, J = 2.6, 17.1 Hz, 1 H, N=C(OEt)CH=C*H*$_2$), 6.08 (dd, J = 9.4, 17.1 Hz, 1 H, N=C(OEt)C*H*=CH_2), 5.69 (dd, J = 2.6, 9.4 Hz, 1 H, N=C(OEt)CH=C*H*$_2$), 5.68 (m, 1 H, =(CH_3)C=C*H*CH_2), 5.16 (d, J = 17.4 Hz, 1 H, C*H*$_2$=CHC(CH_3)=CH), 5.01 (d, J = 10.7 Hz, 1 H, C*H*$_2$=CHC(CH_3)=CH), 4.17 (q, J = 7.1 Hz, 2 H, O*CH*$_2$$CH_3$), 3.32 (d, J = 7.4 Hz, 2 H, =CHC*H*$_2$CO), 1.76 (s, 3 H, C(C*H*$_3$)=CH), 1.34 (t, J = 7.1 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 183.81, 157.02, 127.81, 125.98, 123.98, 112.49, 105.03, 63.20, 39.42, 14.31, 12.47; high-resolution MS (EI, 70 eV) m/e calculated for $C_{12}H_{17}NO_2$ 207.1258, observed 207.1271.

***N*-(6-Methoxy-3(*E*),5(*E*)-hexadienoyl)-2-ethoxy-1-aza-1,3-butadiene (6f).** To acid **4f**, (0.531 g, 3.7 mmol) in ether (10 mL) at room temperature was added dicyclohexylcarbodiimide (0.385 g, 1.86 mmol) in one portion. The resulting suspension was stirred for 10 h. The reaction was filtered with washing, and the filtrate was added dropwise to a solution of acrylimidate **3a** (188 mg, 1.89 mmol), triethylamine (0.197 g, 1.95 mmol), and DMAP (24 g, 0.194 mmol) in ether (15 mL). The reaction was stirred overnight, and the residue was taken up in ether and filtered. The solvent was removed in vacuo. Flash chromatography on silica gel with 3:1 hexanes–EtOAc eluent, R_f = 0.48, gave 158 mg (38%) of slightly yellow liquid: IR (NaCl, film) 2998, 2940, 1660, 1605 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.56 (d, J = 12.6 Hz, 1 H, (CH_3O)C*H*=CH), 6.19–6.12 (m, 2 H, N=C(OEt)C*H*=CH_2), 5.98 (dd, J = 10.5, 15.0 Hz, CH=C*H*CH_2), 5.69 (dd, J = 3.2, 8.9 Hz, 1 H, N=(OEt)CH=C*H*$_2$), 5.60–5.48 (m, 2 H, (CH_3O)CH=C*H*CH=C*H*), 4.17 (q, J = 7.0 Hz, 2 H, O*CH*$_2$$CH_3$), 3.58 (s, 3 H, (C*H*$_3$O)CH=), 3.21 (d, J = 7.3 Hz, 2 H, C*H*$_2$CO), 1.33 (t, J = 7.0 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 184.78, 156.55, 151.66, 130.75, 128.02, 126.41, 120.11, 105.78, 63.43, 57.03, 44.01, 14.59; high-resolution MS (CI, 70 eV, isobutane) m/e calculated for $C_{12}H_{18}NO_3$ 224.1285, observed 224.1276.

***N*-[6-[(2-Methoxyethoxy)methoxy]-3(*E*),5(*Z*)-hexadienoyl]-2-ethoxy-1-aza-1,3-butadiene (6g).** A solution of **5g** (2.08 mmol) in benzene (7 mL) was added dropwise to a stirred solution of acrylimidate **3a** (0.211 g, 0.213 mmol) and triethylamine (0.231 g, 2.28 mmol) in benzene (20 mL) and gave 453 mg (73%) of a liquid: IR (NaCl, film) 22980, 2920, 1657, 1602, 1300, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, J = 11.0, 15.4 Hz, C*H*=$CHCH_2$), 6.19–6.11 (m, 3 H, OCH_2OC*H*=CH, N=C(OEt)C*H*=CH_2), 5.74–5.62 (m, 2 H, N=C(OEt)CH=C*H*$_2$, CH=C*H*CH_2CO), 5.20 (dd, J = 6.2, 10.8 Hz, 2 H, OCH_2OCH=C*H*), 4.94 (s, 2 H, O*CH*$_2$O), 4.18 (q, J = 7.0 Hz, 2 H, O*CH*$_2$$CH_3$), 3.74 (m, 2 H, OCH_2*CH*$_2$O), 3.56 (m, 2 H, OCH_2*CH*$_2$O), 3.41 (s, 3 H, O*CH*$_3$), 3.25 (d, J = 7.3 Hz, 2 H, C*H*$_2$CO), 1.34 (t, J = 7.0 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 184.16, 156.37, 143.25, 127.73, 126.77, 126.15, 122.79, 108.47, 95.96, 71.93, 67.90, 63.17, 59.42, 43.84, 14.29; high-resolution MS (CI, 50 eV) m/e calculated for $C_{15}H_{23}NO_5$ 297.1575, observed 297.1587.

General Procedures for Thermolysis of Ethyl *N*-Dienoyl Acrylimidates (7c–g). The trienes **6c–g** were dissolved in benzene or toluene (0.05 M) and refluxed. The solvent was removed in vacuo and the cycloadducts subjected to Kugelrohr distillation.

(4a*S,8a*S**)-1-Ethoxy-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7a).** To a solution of ethyl acrylimidate **3a** (390.0 mg, 3.94 mmol) and triethylamine (419.0 mg, 4.14 mmol) in benzene (250 mL) was added dropwise a solution of freshly distilled 3,5-hexadienoyl chloride **5a** in benzene (5 mL). The yellow mixture was brought to reflux under N_2 for 1 h. The solution was then cooled, and the solid triethylamine hydrochloride salt was filtered. The yellow solution was concentrated in vacuo to afford 643.4 mg of yellow oil. Kugelrohr distillation gave 587.3 mg (78.2%) of almost colorless oil: bp 150 °C (0.02 mmHg): IR (NaCl, film) 1703, 1578, 1248, 733 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 (m, 1 H, =C*H*CH_2), 5.57 (m, 1 H, =C*H*CH), 4.35 (overlaping q, J = 7.0 Hz, 2 H, CH_3C*H*$_2$O), 2.72 (m, 2 H, =CHC*H*, C*H*C(OEt)=N), 2.58 (dd, J = 5.3, 15.6 Hz, 1 H, CHC*H*$_2$CO), 2.32 (dd, J = 9.2, 15.6 Hz, 1 H, >CHC*H*$_2$CO), 2.07 (m, 2 H, C*H*$_2$CH=CH), 1.90 (m, 2 H, =CHC*H*$_2$C*H*$_2$), 1.31 (t, J = 7.0 Hz, 3 H, C*H*$_3$$CH_2O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.39, 182.33, 128.69, 127.64, 63.80, 37.15, 36.77, 31.77, 23.66, 22.48, 14.04; MS (CI, 100 eV) m/e (relative intensity) 193 (MH^+, 47), 167 (10), 166 (100), 79 (6); (EI, 70 eV) m/e (relative intensity) 193 (M^+, 28), 165 (87), 126 (79), 123 (20), 122 (29), 98 (100), 94 (24), 93 (17), 91 (22), 80 (34), 79 (94), 78 (28), 77 (38); high-resolution MS (EI, 70 eV) m/e calculated for $C_{11}H_{15}NO_2$ 193.1102, observed 193.1096.

(4a*S,8a*S**)-1-Ethoxy-8a-methyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7b).** To a stirred solution of **3b** (483.1 mg, 4.27 mmol) and triethylamine (450.0 mg, 4.44 mmol) in benzene (50 mL) was added dropwise a solution of acid chloride **5a** (550.0 mg, 4.23 mmol) in benzene (5 mL), under N_2 at room temperature. The mixture was stirred an additional 0.5 h. The solid triethylamine hydrochloride was filtered, and the yellow solution was diluted with benzene (200 mL) and refluxed under N_2 an additional 12 h. The solvent was removed in vacuo, and the residual oil was subjected to Kugelrohr distillation to give 724.0 mg (82.6%) of slightly yellow oil: bp 160 °C (0.001 mmHg); An analytical sample was obtained by preparative GC using 5 ft 10% SP2100 column: R_f (1:1 hexanes–EtOAc) = 0.39; IR (NaCl, film) 1710, 1582, 1253, 696 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.82 (m, 1 H, =C*H*CH_2), 5.38 (m, 1 H, =C*H*CH), 4.30 (q, J = 7.0 Hz, 2 H, CH_3C*H*$_2$O), 2.68 (dd, J = 14.3, 6.3 Hz, 1 H, C*H*$_2$CO), 2.40 (m, 1 H, =C*H*), 2.30 (dd, J = 14.3, 6.1 Hz, 1 H, C*H*$_2$CO), 2.00 (m, 3 H, =CHC*H*$_2$C*H*$_2$), 1.52 (m, 1 H, CH_2C*H*$_2$C(CH_3)), 1.25 (overlapping s and t, J = 7.0 Hz, 6 H, CH_2C(C*H*$_3$), C*H*$_3$$CH_2O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 183.92, 182.13, 128.64, 127.87, 63.91, 39.67, 38.69, 37.00, 30.65, 24.10, 22.51, 14.13; MS (CI, 100 eV) m/e (relative intensity) 208 (MH^+, 100), 180 (24); MS (EI, 70 eV) m/e (relative intensity) 207 (M^+, 23), 180 (10), 179 (84), 164 (13), 140 (87), 112 (100), 94 (17), 93 (18); high-resolution MS (EI, 70 eV) m/e calculated for $C_{12}H_{17}NO_2$ 207.12583, observed 207.12590.

(4a*R,8*S**,8a*S**)-1-Ethoxy-8-methyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7c).** A solution of acylimidate **6c** (406 mg, 1.96 mmol) in toluene (250 mL) was heated at reflux under N_2 for 9 h. Preparative GLC employing 5 ft 10% SP2100 column provided some enrichment in the major isomer after two recycles (83:17): bp 130–135 °C (0.015 mmHg): IR (NaCl, film) 1718, 1590, 1360, 1030 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.72 (m, 1 H, CH_2C*H*=CHCH), 5.55 (m, 1 H, CH=C*H*CH), 4.38 (q, J = 7.1 Hz, 2 H, CH_3C*H*$_2$O), 2.85–1.70 (m, 7 H), 1.33 (t, J = 7.1 Hz, 3 H, C*H*$_3$$CH_2O$), 1.04 (d, J = 6.6 Hz, 3 H, C*H*$_3$CH); MS (CI, 100 eV) m/e (relative intensity) 209 (13), 208 (MH^+, 100), 180 (10); high-resolution MS (EI, 70 eV) m/e calculated for $C_{12}H_{17}NO_2$ 207.1259, observed 207.1253.

(4a*R,8*S**,8a*S**)-1-Ethoxy-8-phenyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7d).** A solution of acylimidate **6d** (0.773 g, 2.87 mmol) in toluene (700 mL) was refluxed for 12 h. Flash chromatography with 1:1 hexanes–EtOAc, R_f = 0.41, gave 715 mg (92%) of slightly yellow oil, which partially crystallized with cooling. An analytical sample was prepared as follows: Kugelrohr distillation (bp 140–150 °C (<0.01 mmHg)) of the oil which solidified in the receiver bulb and trituration with pentane to produce a solid. Recrystallization from 1:1 pentane–chloroform gave pure white crystals: mp 151 °C; IR (NaCl, film) 3050, 2930, 1709, 1600, 1415, 1260, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5 H, C_6H_5), 5.93 (d, J = 10.0 Hz, 1 H, CH_2C*H*=CH), 5.70 (dd, J = 3.6, 10.1 Hz, 1 H, CH_2CH=C*H*), 4.08 (q, J = 7.0 Hz, 2 H, O*CH*$_2$$CH_3$), 3.30 (dd, J = 8.0, 6.5 Hz, 1 H, PhC*H*), 2.83 (dd, J = 4.9, 8.7 Hz, 1 H, C*H*C(OEt)=N), 2.69 (m, 2 H, C*H*CH_2CO), 2.50 (dd, J = 18.6, 10.4 Hz, 1 H, CHC*H*$_2$CO), 2.45 (m, 2 H, CH=CHC*H*$_2$CH(Ph)), 0.94 (t, J = 7.1 Hz, 3 H, C*H*$_3$$CH_2O$); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ 182.04, 181.57, 143.22, 128.44, 128.32, 127.88, 127.76, 126.96, 63.71, 43.57, 39.01, 37.12, 30.89, 30.45, 13.49; high-resolution MS (EI, 70 eV) m/e calculated

for $C_{17}H_{19}NO_2$ 269.1416, observed 269.1407.

(4a*S,8a*S**)-1-Ethoxy-5-methyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7e).** The acylimidate **6e** (340 g, 1.64 mmol) was dissolved in toluene (30 mL, 0.055 M). The solution was refluxed for 1 h. Workup gave 321 mg (94%) of slightly yellow liquid: FTIR (NaCl, film) 2972, 2930, 1706, 1586, 1259 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (s, 1 H, C*H*=C(CH_3)), 4.38 (q, J = 7.1 Hz, 2 H, OC$H_2$$CH_3$), 2.74 (dd, J = 4.8, 15.9 Hz, 1 H, CHCH_2CO), 2.62 (ddd, J = 3.5, 5.5, 11.8 Hz, 1 H, C*H*C(OEt)=N), 2.52 (m, 1 H, C*H*CH_2CO), 2.31 (dd, J = 12.1, 15.9 Hz, 1 H, CHCH_2CO), 2.11 (m, 2 H, CH_2CH=C(CH_3)), 1.91 (ddd, J = 3.6, 5.2, 11.0 Hz, 1 H, CH_2CH_2CH), 1.74 (m, 1 H, CH_2CH_2CH), 1.69 (s, 3 H, CH=C(CH_3)), 1.33 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 183.89, 183.09, 134.09, 123.22, 64.27, 37.77, 36.09, 35.37, 24.97, 22.30, 21.78, 14.43; high-resolution MS (EI, 70 eV) m/e calculated for $C_{12}H_{17}NO_2$ 207.1258, observed 207.1256.

(4a*S,7*R**,8a*S**)-1-Ethoxy-7-methoxy-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7f).** The acyl acrylimidate **6f** (0.156 g, 0.70 mmol) was dissolved in toluene (15 mL, 0.047 M) and refluxed for 7 h to produce 148 mg (95%) of slightly yellow liquid: IR (NaCl, film) 2983, 1709, 1580, 1405, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, J = 10.1 Hz, 1 H, (CH_3O)CHC*H*=CH), 5.70 (ddd, J = 1.8, 4.0, 10.1 Hz, 1 H, (CH_3O)CHCH=C*H*), 4.38 (m, 2 H, OC$H_2$$CH_3$), 3.93 (m, 1 H, ($CH_3O$)C*H*), 3.40 (s, 3 H, (C$H_3O$)CH), 2.74–2.65 (m, 2 H, C*H*C*H*), 2.61 (dd, J = 4.7, 15.7 Hz, 1 H, CHCH_2CO), 2.32 (dd, J = 11.5, 15.7 Hz, 1 H, CHCH_2CO), 2.25 (ddd, J = 12.5, 4.7, 3.9 Hz, 1 H, (CH_3O)CHCH_2), 1.78 (ddd, J = 8.6, 11.7, 12.4 Hz, 1 H, (CH_3O)CHCH_2), 1.35 (t, J = 7.2 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 182.18, 182.03, 130.16, 129.91, 74.88, 64.40, 56.45, 36.36, 35.28, 32.04, 27.60, 14.36; high-resolution MS (CI, 70 eV, methane) m/e calculated for $C_{12}H_{18}NO_3$ 224.12856, observed 224.1275.

(4a*S,7*S**,8a*S**)-1-Ethoxy-7-[(2-methoxyethoxy)methoxy]-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (7g).** The acyl acrylimidate **6g** (0.453 g, 1.52 mmol) was dissolved in xylenes (25 mL), and the solution was refluxed with the aid of a soxhlet extractor filled with 4A molecular sieves for 17 h to give 243 mg (54%) of a slightly yellow oil: bp 140–150 °C (>0.01 mmHg); FTIR (NaCl, film) 2961, 1700, 1653, 1260, 1092, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddd, J = 1.1, 4.6, 10.0 Hz, 1 H, (OMEM)CHC*H*=CH), 5.81 (ddd, J = 0.5, 4.1, 10.0 Hz, 1 H, (OMEM)CHCH=C*H*), 4.83 (s, 2 H, OCH_2O), 4.40 (q, J = 7.1 Hz, 2 H, OC$H_2$$CH_3$), 4.16 (dd, J = 4.1, 8.4 Hz, 1 H, (OMEM)C*H*), 3.75 (m, 2 H, OC$H_2$$CH_2$O), 3.58 (m, 2 H, OC$H_2CH_2$O), 3.41 (s, 3 H, CH_2OCH_3), 2.97 (ddd, J = 3.7, 5.7, 11.5 Hz, 1 H, CH=CHC*H*), 2.76 (dd, J = 5.5, 9.7 Hz, 1 H, N=C(OEt)C*H*), 2.60 (dd, J = 4.3, 15.8 Hz, 1 H, CH_2CO), 2.26 (dd, J = 11.5 Hz, 15.6 Hz, 1 H, CH_2CO), 2.10 (ddd, J = 3.6, 3.9, 13.5 Hz, 1 H, (OMEM)-CHCH_2CH), 1.99 (ddd, J = 4.2, 11.5, 13.6 Hz, 1 H, (OMEM)-CHCH_2), 1.35 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.34, 181.91, 131.51, 127.96, 94, 27, 71.57, 68.00, 66.88, 63.95, 58.94, 35.04, 32.71, 31.48, 28.37, 13.91; high-resolution MS (CI, 50 eV, isobutane) m/e calculated for $C_{15}H_{24}NO_5$ 298.1653, observed 298.1639.

4-[(2-Methoxyethoxy)methoxy]-2(*Z*)-butenol (14). To diol **13** (8.8 g, 100 mmol) and *N*,*N*-diisopropylethylamine (8.7 mL, 50 mmol) at room temperature was added neat MEMCl (5.7 mL, 50 mmol) dropwise. The reaction was cooled to 0 °C and stirred for 10 min after addition. The bath was removed and the reaction was stirred an additional 17 h. The reaction was poured into 100 mL of 5% HCl. The layers were separated, and the aqueous extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried ($MgSO_4$). Flash chromatography using EtOAc gave 5.14 g (58%) of a colorless liquid: IR (NaCl, film) 3420, 2930, 2890, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1 H, C*H*=CH), 5.73 (m, 1 H, CH=C*H*), 4.73 (t, J = 4.5, 2 H, OCH_2O), 4.23–4.16 (m, 4 H, OCH_2CH=CHCH_2O), 3.71 (m, 2 H, OCH_2CH_2O), 3.57 (m, 2 H, OCH_2CH_2O), 3.40 (s, 3 H, OCH_3), 2.08 (br s, 1 H, O*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 133.04, 128.18, 94.92, 72.12, 67.26, 63.01, 59.34, 58.79; MS (EI, 70 eV) m/e (relative intensity) 177 (MH^+, 0.12), 101 (6.8), 89 (53), 71 (46), 59 (100).

Ethyl 6-[(2-Methoxyethoxy)methoxy]-2(*E*),4(*E*)-hexadienoate (15). Oxalyl chloride (2.8 mL, 32.12 mmol) in CH_2Cl_2 (75 mL) was stirred under N_2 at −70 °C. DMSO (4.56 mL, 64.24 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 25 min. The resulting white suspension was stirred an additional 30 m. Allyl alcohol **14** (5.14 g, 29.2 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 40 min. The reaction mixture was stirred for 20 min after addition. Neat triethylamine (20.3 mL, 146 mmol) was added dropwise over 15 min, and stirring was continued for 30 min. The reaction was allowed to warm to −20 °C over 20 min and poured into a 0 °C solution of 15 mL of concentrated HCl in H_2O (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford a yellow oil. The oil was dissolved in THF (25 mL). Triethyl phosphonoacetate (6.4 mL, 32.12 mmol) was added dropwise at 0 °C to a stirred suspension of (1.68 g, 35.04 mmol) of a 50% mineral oil dispersion NaH. To the suspension was added the α,β-unsaturated aldehyde over 20 m at 0 °C. The reaction was stirred an additional 1.5 h. The yellow solution was poured into aqueous NH_4Cl. The aqueous extracted with ether (3 × 100 mL) and dried (Mg_4SO_4). Flash chromatography on silica gel with 2:1 hexanes–EtOAc, R_f = 0.38, gave 4.56 g (64%) of slightly yellow liquid: IR (NaCl, film) 2920, 1718, 1653, 1625, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, J = 11.1, 15.1 Hz, 1 H, C*H*=CHCO), 6.39 (m, J = 11.0, 15.3, 0.6 Hz, 1 H, =C*H*CH=CHCO), 6.15 (d of t, J = 15.3, 5.3 Hz, 1 H, OCH_2C*H*=CH), 5.87 (d, J = 15.3 Hz, 1 H, =C*H*CO), 4.75 (s, 2 H, OCH_2O), 4.19 (q, J = 7.1 Hz, 2 H, OC$H_2$$CH_3$), 3.70 (m, 2 H, OC$H_2CH_2$O), 3.55 (m, 2 H, OC$H_2CH_2$O), 3.39 (s, 3 H, OCH_3), 1.29 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.31, 144.01, 138.49, 129.54, 121.96, 95.37, 72.12, 67.35, 67.32, 60.74, 59.44, 14.67; MS (CI, 70 ev) m/e (relative intensity) 245 (4), 215 (28), 169 (7), 157 (15), 139 (68), 89 (100); high-resolution MS (CI, 100 eV) m/e calculated for $C_{12}H_{21}O_5$ 245.1387, observed 245.1381.

6-[(2-Methoxyethoxy)methoxy]-2(*E*),4(*E*)-hexadienoic Acid (12). Diene ester **15** (4.56 g, 18.7 mmol) in methanol (20 mL) was added in one portion to a stirred solution of (2.2 g, 39.3 mmol) of KOH in H_2O (20 mL). The reaction mixture was stirred for 2 h and then concentrated to half volume in vacuo. The solution was washed with ether (25 mL) and then acidified to pH 3 with 3 M HCl. The aqueous solution was extraced with ether (4 × 40 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford 3.6 g (89%) of slightly yellow liquid: IR (NaCl, film) 3010, 2970, 1690, 1645, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 10.9, 15.2 Hz, 1 H, C*H*=CHCOOH), 6.45 (dd, J = 11.0, 15.3 Hz, 1 H, CH=C*H*CH=CHCOOH), 6.22 (d of t, J = 5.2, 15.3 Hz, 1 H, OCH_2C*H*=), 5.89 (d, J = 15.4 Hz, 1 H, =C*H*COOH), 4.23 (dd, J = 1.0, 4.8 Hz, 2 H, CH_2COOH), 3.73 (m, 2 H, OCH_2CH_2O), 3.58 (m, 2 H, OCH_2CH_2O), 3.41 (s, 3 H, OCH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.25, 127.72, 126.76, 126.16, 122.79, 95.98, 71.92, 63.17, 59.41, 43.84; MS (CI, 70 eV) m/e (relative intensity) 217 (MH^+, 1), 111 (11), 89 (100), 77 (25); high-resolution MS (CI, 50 eV) m/e calculated for $C_{10}H_{12}O_5$ 217.1075, observed 217.1081.

(4a*S,8a*S**)-1,2,3,4,4a,7,8,8a-Octahydroisoquinoline-1,3-dione (16).** To a stirred solution of imidate **7a** (512.6 mg, 2.65 mmol) in methanol (25 mL) was added dropwise 10% aqueous HCl (1.5 mL). The mixture was stirred for an additional 5 min at room temperature. Most of the CH_3OH was then removed in vacuo, and H_2O (50 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extracts were washed with saturated aqueous NaCl (20 mL) and dried ($MgSO_4$). The solvent was removed, and the residual yellow oil was triturated with pentane to afford yellow solid. Recrystallization from 2:1 EtOAc–hexanes provided 210 mg (48%) of white solid: mp 134–135 °C; IR (CCl_4) 3375, 1710, 1545, 770 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.10 (s, 1 H, N*H*), 5.84 (m, 1 H, CH=C*H*CH_2), 5.53 (dd, J = 9.9, 2.1 Hz, 1 H, =C*H*CH), 2.85 (m, 2 H, =CHC*H*, C*H*CONH), 2.73 (dd, J = 17.0, 5.3 Hz, 1 H, CH_2CO), 2.56 (dd, J = 17.0, 6.0 Hz, 1 H, CH_2CO), 2.28–2.10 (m, 3 H, CH_2CH_2), 1.92–1.83 (m, 1 H, CH_2CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.54, 171.45, 130.56, 127.22, 40.09, 36.95, 31.03, 22.85, 22.42; MS (CI, 100 eV) m/e (relative intensity) 167 (10), 166 (MH^+, 100); MS (EI, 70 eV) m/e (relative intensity) 166 (11), 165 (M^+, 100), 149 (25), 123 (24), 122 (35), 94 (27), 93 (20), 91 (25); high-resolution MS (EI, 70 eV) m/e calculated for $C_9H_{11}NO_2$ 165.07891, observed 165.07939.

(4a*S,8a*S**)-1,2,3,4,4a,5,6,7,8,8a-Perhydroisoquinoline-1,3-dione (17).** A solution of imide **16** (132.8 mg, 0.804 mmol) in ethanol (35 mL) was added to a prereduced suspension of PtO_2

(20.0 mg, 0.088 mmol) in EtOH (10 mL), (H_2, 40 psi, room temperature, 7 h). The imide/catalyst suspension was then reduced under 40 psi H_2 in a Parr hydrogenator for 12 h. The mixture was filtered through a bed of Celite, the solvent was removed in vacuo, and the residue was recrystallized from 2:1 EtOAc–hexanes to afford 79 mg (58.8%) of white solid: mp 135–136 °C; IR ($CDCl_3$) 3385, 2950, 1720, 1210 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.85 (s, 1 H, N*H*), 2.63 (m, 3 H), 2.27 (m, 2 H), 1.65 (m, 4 H), 1.34 (m, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.46, 172.68, 42.01, 37.74, 32.13, 28.92, 25.48, 24.24, 22.72; MS (CI, 100 eV) *m/e* (relative intensity) 168 (MH^+, 100); MX (EI, 70 eV) *m/e* (relative intensity) 167 (M^+, 64), 139 (46), 138 (17), 125 (41), 124 (13), 112 (100), 109 (19), 108 (10), 99 (15), 96 (16), 95 (13); high-resolution MS (EI, 70 eV) *m/e* calculated for $C_9H_{13}NO_2$ 167.09462, observed 167.09409.

(4a*S,8a*S**)-1,2,3,4,4a,5,6,7,8,8a-Perhydroisoquinoline (18).** To a refluxing suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in THF (25 mL) was added dropwise a solution of imide **17** (58 mg, 0.35 mmol) in THF (10 mL). After the addition was complete the mixture was refluxed an additional 24 h. The mixture was cooled in an ice bath and carefully quenched with H_2O. Sufficient 6 M HCl was added to bring the pH to 1. The aqueous layer was washed with EtOAc (2 × 25 mL), cooled to 0 °C, and basified to pH 14 with 5 N NaOH. The mixture was extracted with ether (6 × 30 mL), dried over anhydrous K_2CO_3, and concentrated to give 42 mg (87.4%) of slightly yellow liquid. An analytical sample was obtained by preparative GC using a 5 ft 10% SP2100 column. The material was identical in all spectral properties with *cis*-perhydroisoquinoline.[19] IR ($CDCl_3$) 3670, 2937, 2190, 1445, 1222, 820 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.97 (m, 1 H, NHC*H*$_2$CH$_2$), 2.84 (dd, *J* = 12.3, 4.0 Hz, 1 H, CHC*H*$_2$NH), 2.73–2.60 (m, 2 H, NHC*H*$_2$CH$_2$, CHC*H*$_2$NH), 1.87–1.25 (m, 12 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 36.66, 34.84.

1-(2(*E*),4(*E*)-Hexadienoyl)-2-ethoxy-1-aza-1,3-butadiene (20a). Sorboyl chloride **19** (256 g, 1.96 mmol) in benzene (5 mL) was added dropwise over 5 min to a solution of acrylimidate **3a** (0.198 g, 2.0 mmol) and triethylamine (0.213 g, 2.1 mmol) in benzene (15 mL). The resulting suspension was stirred for 3 h at room temperature. The solid was filtered and concentrated to afford 353 mg (93%) as a yellow liquid: IR (NaCl, film) 2960, 1643, 1603, 1243, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 9.9, 15.3 Hz, 1 H, C*H*=CHCO), 6.23–6.05 (m, 4 H), 5.93 (d, *J* = 15.5 Hz, 1 H, CH=C*H*CO), 5.67 (dd, *J* = 3.2, 8.9 Hz, 1 H, N=C(OEt)CH=C*H*$_2$), 4.22 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 1.86 (d, *J* = 5.8 Hz, 3 H, C*H*$_3$CH=CH), 1.36 (t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.74, 157.66, 145.58, 140.30, 130.47, 127.54, 126.05, 125.04, 63.13, 19.19, 14.41; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{11}H_{15}NO_2$ 193.1102, observed 193.1107.

1-(2(*E*),4(*E*)-Hexadienoyl)-2-ethoxy-4-phenyl-1-aza-1,3-butadiene (20d). The cinnamimidate **3d** (0.268 g, 1.53 mmol) and triethylamine (0.170 g, 1.68 mmol) were dissolved in toluene (90 mL). Sorboyl chloride **19** (0.200 g, 1.53 mmol) was added in one portion. The mixture was heated to reflux for 4 h. The white ammonium salt was filtered and the solvent removed in vacuo, and the residue was subjected to Kugelrohr distillation to afford 375 mg (91%) of oil: bp 120–130 °C (0.01 mmHg); IR (NaCl, film) 2999, 1658, 1602, 1460 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ 7.47 (d, *J* = 15.8 Hz, 1 H, PhC*H*=CH), 7.44–7.27 (m, 5 H, C$_6$*H*$_5$CH=CH), 7.17 (dd, *J* = 9.9, 15.3 Hz, 1 H, C*H*=CHCON=), 6.47 (d, *J* = 15.8 Hz, 1 H, PhCH=C*H*), 6.23 (dd, *J* = 9.9, 12.1 Hz, 1 H, CH$_3$CH=C*H*), 6.12 (dd, *J* = 12.1, 5.8 Hz, 1 H, CH$_3$C*H*=CH), 6.00 (d, *J* = 15.5 Hz, 1 H, CH=C*H*CON=), 4.30 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 1.85 (d, *J* = 5.8 Hz, 3 H, C*H*$_3$CH=CH), 1.41 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.57, 158.28, 145.19, 141.11, 139.82, 134.90, 130.26, 130.02, 128.85, 128.05, 125.14, 115.70, 62.87, 18.84, 14.25; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{17}H_{19}NO_2$ 269.1416, observed 269.1401.

(3a*R,5*R**,7a*R**)-5-Methyl-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-1,3-dione (22a) and (3a*R**,5*S**,7a*R**)-5-Methyl-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-1,3-dione (21a).** The *N*-sorboyl ethyl acrylimidate **20a** (132 g, 0.68 mmol) in toluene (15 mL, 0.045 M) was placed in a carius tube and heated to 198 °C for 22 h. The solvent was removed in vacuo to give a brown oil. GLPC analysis showed two signals in a ratio of 1.3:1. Flash chromatography on silica gel with 3:1 hexanes–EtOAc, R_f = 0.20, gave 57 mg of oil (51%). **21a** and **22a**: IR (NaCl, film) 3190, 2985, 1773, 1344, 1283 cm^{-1}; high-resolution MS (CI, 50 eV, isobutane) *m/e* calculated for $C_9H_{12}NO_2$ 166.0867, observed 166.0865. **22a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (d, *J* = 10.0 Hz, 1 H, (CH$_3$)CHCH=C*H*), 5.75 (ddd, *J* = 2.5, 4.12, 10.0 Hz, 1 H, (CH$_3$)CHC*H*=CH), 3.45 (ddd, *J* = 2.1, 4.3, 8.2 Hz, 1 H, =CHC*H*), 3.19 (ddd, *J* = 3.8, 5.2, 8.2 Hz, 1 H, CH$_2$C*H*), 2.27 (dddd, *J* = 0.8, 3.8, 4.9, 13.3 Hz, 1 H, (CH$_3$)CHC*H*$_2$), 2.14 (m, 1 H, CH$_3$C*H*), 1.34 (ddd, *J* = 13.4, 10.3, 5.6 Hz, 1 H, CH$_3$CHC*H*$_2$), 1.05 (d, *J* = 7.0 Hz, 1 H, C*H*$_3$CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.81, 177.80, 138.09, 120.72, 42.75, 40.58, 28.81, 26.68, 21.27. **21a**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, 2 H, C*H*=C*H*), 3.37 (ddd, *J* = 8.4, 2.6, 2.6 Hz, 1 H, CH=CHC*H*), 3.04 (ddd, *J* = 5.8, 8.4, 11.4 Hz, 1 H, CH$_2$C*H*), 2.23–2.15 (m, 2 H, CH$_3$C*H*, C*H*$_2$CH), 1.20 (ddd, *J* = 9.5, 12.7, 13.4 Hz, 1 H, (CH$_3$)CHC*H*$_2$, 1.04 (d, *J* = 7.0 Hz, C*H*$_3$CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 179.85, 177.52, 137.72, 119.72, 42.10, 40.82, 32.41, 28.97, 21.39.

(3a*R,5*R**,4*S**,7a*R**)-5-Methyl-4-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-1,3-dione (22d) and (3*R**,5*S**,4*S**,7a*R**)-5-Methyl-4-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-1,3-dione (21d).** A carius tube containing a solution of *N*-sorboyl ethyl cinnamimidate **20d** (0.101 g, 0.37 mmol) in toluene (100 mL) was degassed and heated at 200 °C for 16 h. The solvent removed in vacuo to afford 94 mg of brown oil. The residue was Kugelrohr distilled, bp 130 °C (0.005 mmHg), to give 87 mg (83%) of slightly yellow liquid. GLPC showed three products in the ration 1:3:3. ^1H NMR also showed three imidate cycloadducts. Isolation by flash chromatography with 2:1 hexanes–EtOAc gave only two imide cycloadduct molecules. **22d**: R_f = 0.42; FTIR (KBr) 3185, 3074, 2940, 1702, 1347, 1184 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (br s, 1 H, N*H*), 7.37–7.21 (m, 5 H, C$_6$*H*$_5$), 5.96 (ddd, *J* = 2.7, 4.1, 10.0 Hz, 1 H, (CH$_3$)CHC*H*=CH), 5.88 (dd, *J* = 5.4, 10.0 Hz, 1 H, (CH$_3$)CHCH=C*H*), 3.63 (ddd, *J* = 2.3, 4.2, 8.2 Hz, 1 H, PhCHC*H*), 3.54 (dd, *J* = 5.5, 4.1 Hz, 1 H, C*H*Ph), 3.36 (dd, *J* = 4.0, 8.1 Hz, 1 H, CH=CHC*H*), 2.54 (m, 1 H, CH$_3$C*H*), 0.85 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 178.41, 176.88, 140.46, 136.23, 128.36, 128.94, 126.96, 120.96, 45.93, 42.47, 42.10, 30.86, 17.79; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{15}H_{15}NO_2$ 241.1102, observed 241.1099. **21d**: R_f = 0.30; FTIR (KBr) 3175, 3068, 1698, 1350, 1197 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (br s, 1 H, N*H*), 7.36–7.16 (m, 5 H, C$_6$*H*$_5$), 5.99 (dd, *J* = 2.4, 10.1 Hz, 1 H, (CH$_3$)CHC*H*=CH), 5.95 (dd, *J* = 2.1 10.0 Hz, 1 H, (CH$_3$)CHCH=C*H*), 3.58 (ddd, *J* = 2.9, 3.0, 8.3 Hz, 1 H, CH=CHC*H*), 3.24 (dd, *J* = 8.5, 9.8 Hz, 1 H, CH(Ph)C*H*), 2.49 (dd, *J* = 8.9, 9.7 Hz, 1 H, C*H*(Ph)), 2.43 (m, 1 H, CH$_3$C*H*), 0.88 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.88, 176.40, 141.86, 136.60, 128.61, 127.92, 127.11, 119.34, 48.66, 46.65, 43.11, 35.30, 19.81; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{15}H_{15}NO_2$ 241.1102, observed 241.1113.

Reduction of the Imidate Cycloadduct with $NaBH_4$. General Procedures for 23a,f,g. The acyl imidate cycloadducts **7a,f,g** were added dropwise to a solution of $NaBH_4$ (2 equiv) at 0 °C under N_2. The reactions were stirred for 2 h, and half the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2. The solution was poured into H_2O, extracted with CH_2Cl_2, and dried ($MgSO_4$).

(4a*S,8a*S**)-1-Ethoxy-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (23a).** A solution of **7a** (410.5 mg, 2.13 mmol) in DME (10 mL) was added dropwise to an ice-cooled solution of $NaBH_4$ (100.8 mg, 2.66 mmol) in DME (20 mL). The reaction gave 240 mg (57.7%) of white solid. Recrystallization from 1:1 hexane–EtOAc provided 106.0 mg of white solid: mp 129–131 °C; IR ($CDCl_3$) 3410, 1664, 1097 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.40 (s, 1 H, N*H*), 5.73 (s, 2 H, C*H*=C*H*), 4.76 (dd, *J* = 5.1, 1.4 Hz, 1 H, C*H*(OEt)NH), 3.64 (overlapping q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 2.45 (m, 2 H), 2.18 (m, 4 H), 1.82 (m, 1 H), 1.50 (m, 1 H), 1.23 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.84, 129.49, 127.70, 85.24, 64.00, 36.18, 35.51, 30.36, 24.96, 17.13, 15.34; MS (CI, 100 eV) *m/e* (relative intensity) 197 (11), 196 (MH^+, 100), 166 (7), 150 (17), 149 (9); MS (EI, 70 eV) *m/e* (relative intensity) 195 (M^+, 5), 150 (31), 149 (100), 148 (13), 121 (14), 115 (95), 107 (12), 106 (20), 93 (20), 91 (23), 87 (67); high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{11}H_{17}NO_2$ 195.12592, observed 195.12648.

(4a*S,7*R**,8a*R**)-1-Ethoxy-7-methoxy-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (23f).** To a solution of 50 mg of 98% $NaBH_4$ (1.29 mmol) in absolute ethanol (5 mL) at 0 °C was added dropwise a solution of the acyl imidate cycloadduct **7f** (0.142 g, 0.63 mmol) in ether (5 mL). Flash chromatography on silica gel with 8:1 EtOAc–EtOH, R_f = 0.48, gave 81 mg (57%) of a white solid: mp 98–100 °C; FTIR (KBr) 3185, 3029, 2976, 2945, 1656, 1409, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (br s, 1 H, N*H*), 5.79–5.76 (m, 2 H, C*H*=C*H*), 4.74 (dd, *J* = 1.8, 5.4 Hz, 1 H, (OEt)C*H*NH), 3.93 (ddd, *J* = 1.3, 5.9, 10.2 Hz, 1 H, $(CH_3O)CH$), 3.64 (q, *J* = 7.0 Hz, 1 H, OCH_2CH_3), 3.49 (q, *J* = 7.0 Hz, 1 H, OCH_2CH_3), 3.40 (s, 3 H, OCH_3), 2.47–2.41 (m, 2 H, $CHCH_2CO$), 2.33–2.27 (m, 2 H, $CHCH_2NH$, $CHCH_2CO$), 2.19 (ddd, *J* = 2.3, 6.3, 16.3 Hz, 1 H, $(CH_3O)CHCH_2$), 1.45 (ddd, *J* = 10.2, 12.8, 16.0 Hz, $(CH_3O)CHCH_2$), 1.24 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.80, 131.28, 130.07, 84.55, 76.76, 64.40, 56.11, 35.22, 35.13, 31.09, 23.48, 15.60; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_{12}H_{19}NO_3$ 225.1364, observed 225.1369.

(4a*S,7*S**,8a*R**)-1-Ethoxy-7-[(2-methoxyethoxy)methoxy]-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (23g).** To a solution of $NaBH_4$ (0.070 g, 1.8 mmol) in ethanol (10 mL) at 0 °C was added dropwise MEMoxy imidate cycloadduct **7g** (0.157 g, 0.53 mmol) in Et_2O (5 mL). Workup afforded 132 mg (83%) of an oil: FTIR (NaCl, film) 3218, 2929, 2889, 1652 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.63 (br s, 1 H, N*H*), 5.87 (d, 2 H, C*H*=C*H*), 4.80 (d, *J* = 2.2 Hz, 2 H, OCH_2O), 4.75 (m, 1 H, C*H*(OEt)NH), 4.24 (br m, 1 H, OCH_2OCH), 3.74 (m, 2 H, OCH_2CH_2O), 3.62 (q, *J* = 7.0 Hz, 1 H, OCH_2CH_3), 3.56 (m, 2 H, OCH_2CH_2O), 3.49 (q, *J* = 7.0 Hz, 1 H, OCH_2CH_3), 3.39 (s, 3 H, OCH_3), 2.55 (m, 2 H, C*H*CH), 2.46 (dd, *J* = 6.0, 17.2 Hz, 1 H, CH_2CO), 2.16 (dd, *J* = 11.2, 16.7 Hz, 1 H, CH_2CO), 1.95 (ddd, *J* = 3.4, 3.5, 14.4 Hz, 1 H, $(CH_3O)CHCH_2CH$), 1.71 (ddd, *J* = 4.6, 11.1, 14.4 Hz, 1 H, $(CH_3O)CHCH_2CH$), 1.21 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.80, 133.54, 127.51, 94.51, 85.19, 72.13, 69.04, 67.24, 64.17, 59.46, 34.55, 32.21, 30.34, 24.84, 15.60; high-resolution MS (EI, 50 eV) *m/e* MH^+ calculated for $C_{15}H_{26}NO_5$ 300.1809, observed 300.1781.

(4a*R,8a*S**)-1,2,3,4,4a,7,8,8a-Octahydroisoquinol-3-one (24a).** The ethoxy lactam **23a** (380 mg, 1.95 mmol) was dissolved in 2.0 mL of absolute ethanol. To this solution was added in one portion 367 mg (5.85 mmol) of $NaCNBH_3$. The resulting solution was stirred at 0 °C under N_2; 2.0 mL of trifluoroacetic acid was added dropwise. The reaction mixture was stirred for 0.5 h, and 0.5 mL of H_2O was added with stirring for 10 min. Reaction was extracted with 3 × 50 mL of $CHCl_3$. The chloroform layer was washed with saturated $NaHCO_3$ and 1 × 30 mL saturated NaCl. After drying with $MgSO_4$, removal of solvent in vacuo afforded a light yellow oil. Flash chromatography on silica gel with 8:1 EtOAc–EtOH afforded 176 mg (60%) of white solid: mp 88–90 °C; IR (KBr) 3170, 3050, 2870, 1644, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (br s, 1 H, N*H*), 5.71 (dd, *J* = 1.2, 10.1 Hz, 1 H, C*H*=CHCH), 5.64 (ddd, *J* = 1.5, 3.2, 10.1 Hz, 1 H, CH=C*H*CH), 3.43 (ddd, *J* = 2.3, 5.7, 12.3 Hz, 1 H, $CHCH_2NH$), 3.20 (ddd, *J* = 2.7, 5.7, 12.3 Hz, 1 H, $CHCH_2NH$), 2.61–2.50 (comp, 2 H, $CHCH_2CO$), 2.21 (dd, *J* = 10.7, 20.2 Hz, 1 H, $CHCH_2$), 2.17–2.09 (comp, 3 H), 1.86–1.62 (comp, 2 H, CH_2CH_2CH=CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 190.04, 130.02, 127.49, 45.30, 36.12, 32.06, 30.49, 24.14, 23.64; high-resolution MS (EI, 70 eV) *m/e* calculated for $C_9H_{13}NO$ 151.09971, observed 151.0981.

(4a*S,8a*S**)-5-Methyl-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (24e).** To a solution of $NaBH_4$ (110 mg, 3.1 mmol) and $NaCNBH_3$ (0.193 g, 3.1 mmol) in ethanol (8 mL) at 0 °C was added the imidate **7e** (0.320 g, 1.59 mmol) in ether (8 mL). The solution was stirred (0 °C) for 3 h. To this was carefully added trifluoroacetic acid (2.5 mL) over 5 min. The reaction was stirred for 1 h after vigorous H_2 evolution had ceased. After warming to room temperature, stirring was continued for 2 h, and H_2O (0.1 mL) was added with stirring. The reaction was poured into saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were dried ($MgSO_4$) and concentrated to afford a colorless liquid. Flash chromatography on silica gel with 8:1 EtOAc–EtOH, R_f = 0.47, gave 118 mg (46%) of white solid: mp 92–96 °C; IR (NaCl, film) 3194, 3020, 2910, 1650, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1 H, N*H*), 5.36 (s, 1 H, C*H*=C(CH_3)), 3.53 (dd, *J* = 5.1, 12.1 Hz, 1 H, $CHCH_2NH$), 3.14 (d of t, *J* = 2.9, 12.1 Hz, 1 H, $CHCH_2NH$), 2.63 (dd, *J* = 6.5, 17.8 Hz, 1 H, $CHCH_2CO$), 2.33 (dd, *J* = 5.1, 10.3 Hz, 1 H, $CHCH_2NH$), 2.14 (dd, *J* = 10.8, 17.8 Hz, 1 H, $CHCH_2CO$), 2.12–2.09 (m, 2 H), 2.04 (m, 1 H), 1.70 (m, 1 H), 1.67 (s, 3 H, CH=C(CH_3)), 1.51 (dd, *J* = 3.4 8.2 Hz, 1 H, =$CHCH_2CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.38, 136.51, 121.25, 46.63, 35.98, 34.17, 31.26, 25.15, 22.32, 21.87; high-resolution MS (EI, 60 eV) *m/e* calculated for $C_{10}H_{15}NO$ 165.1152, observed 165.1147.

(4a*S,7*R**,8a*R**)-7-Methoxy-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (24f).** The ethoxy lactam **23f** (0.101 g, 0.45 mmol) and sodium cyanoborohydride (0.113 g, 1.8 mmol) were dissolved in ethanol (3 mL). The solution was stirred under N_2 at 0 °C. Trifluoroacetic acid (1 mL) was added dropwise over 5 min. The resulting solution was stirred for an additional 15 min till evolution of H_2 had ceased. The ice bath was removed, and stirring was continued for 2 h. H_2O (0.1 mL) was added followed by 3 drops of 6 M HCl followed by stirring for 5 min. The mixture was poured into saturated $NaHCO_3$ (30 mL) and extracted (CH_2Cl_2, 4 × 40 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a colorless liquid. Flash chromatography on silica gel (8:1 EtOAc–EtOH, R_f = 0.38) gave 47.5 mg (58%) of colorless oil, which solidified upon standing: IR (NaCl, film) 3280, 2920, 1658, 1495, 1335, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (br s, 1 H, N*H*), 5.81–5.74 (m, 2 H, C*H*=C*H*), 3.89 (ddd, *J* = 1.8, 6.0, 7.9 Hz, 1 H, CH_3OCH), 3.45 (ddd, *J* = 2.2, 5.7, 12.7 Hz, 1 H, $NHCH_2$), 3.36 (s, 3 H, OCH_3), 3.25 (ddd, *J* = 3.0, 4.9, 12.7 Hz, 1 H, $NHCH_2$), 2.52 (m, dd, *J* = 6.5, 19.1 Hz, 2 H, $CHCH_2CO$), 2.21 (dd, *J* = 19.2, 11.1 Hz, 1 H, $CHCH_2CO$), 2.16 (m, 1 H, $CHCH_2NH$), 1.92 (ddd, *J* = 3.1, 5.8, 12.8 Hz, 1 H, $CH(OCH_3)CH_2CH$), 1.71 (ddd, *J* = 8.0, 11.3, 12.9 Hz, 1 H, $CH(OCH_3)CH_2$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.90, 132.51, 129.01, 75.61, 56.56, 46.15, 35.75, 32.60, 29.94, 29.85; high-resolution MS (EI, 100 eV) *m/e* calculated for $C_{10}H_{15}NO_2$ 181.1103, observed 181.1098.

(4a*S,7*S**,8a*R**)-7-[(2-Methoxyethoxy)methoxy]-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (24g).** In a similar manner, ethoxy lactam **23g** (0.020 g, 0.068 mmol) and $NaCNBH_3$ (0.013 g, 0.204 mmol) in ethanol (0.6 mL) gave after flash column chromatography on silica gel with 6:1 EtOAc–EtOH, R_f = 0.32, 17 mg (98%) of a colorless liquid: FTIR (NaCl, film) 3291, 2929, 1661, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (br s, 1 H, N*H*), 5.91 (dd, *J* = 4.1, 9.9 Hz, 1 H, CH=C*H*CH(OMEM)), 5.84 (dd, *J* = 4.0, 9.9 Hz, 1 H, CHC*H*=CHCH(OMEM)), 4.79 (s, 2 H, OCH_2O), 4.19 (dd, *J* = 4.1, 7.9 Hz, 1 H, (MEMO)C*H*), 3.71 (m, 2 H, OCH_2CH_2O), 3.57–3.53 (m, 3 H, OCH_2CH_2O, CH_2NH), 3.15 (ddd, *J* = 3.7, 3.5, 12.6 Hz, 1 H, CH_2NH), 2.62 (m, 1 H, $CHCH_2CO$), 2.53 (dd, *J* = 6.9, 17.7 Hz, 1 H, $CHCH_2CO$), 2.36 (m, 1 H, $CHCH_2NH$), 2.10 (dd, *J* = 9.8, 17.7 Hz, 1 H, $CHCH_2CO$), 1.93 (ddd, *J* = 4.7, 11.7, 14.0 Hz, 1 H, $CHCH_2CH$(OMEM)), 1.77 (ddd, *J* = 3.3, 3.1, 13.9 Hz, 1 H, $CHCH_2CH$(OMEM)); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.20, 134.51, 126.86, 94.52, 72.10, 69.36, 67.32, 59.48, 45.99, 35.44, 31.99, 30.01, 27.25; high-resolution MS (CI, 50 eV, isobutane) *m/e* calculated for $C_{13}H_{22}NO_4$ 256.1547, observed 256.1520.

Acknowledgment. We are grateful to the NIH for support of this research. We also wish to thank Professor Paul Greico for providing us with details for the synthesis of methoxy diene acids.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds **3a–d, 4g, 6c–g, 7a–g, 12, 14–18, 20a,d, 21a,d, 22a,d, 23a,f,g,** and **24a,e–g** (36 pages). Ordering information is given on any current masthead page.