Attempts to purify **4a** by distillation resulted in decomposition.

***N*-Isopropyl-4-chloropentanamide (4l).** A solution containing *N*-chloro-*N*-isopropylpentanamide (**1l**; 4.39 g, 24.7 mmol) and potassium acetate (4.4 g) in *tert*-butyl alcohol (330 mL) was irradiated for 15 min. The workup gave a solid that was recrystallized from petroleum ether to give **4l** as colorless needles (3.58 g, 81%): mp 55–56 °C; IR ($CHCl_3$) 3445, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, 6 H), 1.55 (d, 3 H), 1.74–2.20 (m, 2 H), 2.20–2.45 (m, 2 H), 3.84–4.29 (m, 2 H), 5.60 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 58.4, 41.4, 35.9, 33.8, 25.5, 22.8. Anal. Calcd for $C_8H_{16}NOCl$: C, 54.08; H, 9.08; N, 7.89. Found: C, 53.93; H, 8.92; N, 7.96.

Quantitative Irradiations. A Rayonet Model RPR-100 photoreactor fitted with eight PRP-2537 Å lamps was used for all analytical-scale photolyses at 254 nm. The photoreactor was equipped with a Rayonet Model MGR-100 merry-go-round, supporting up to eight test tubes and providing the same light intensity for each tube.

Solutions of *N*-chloro amides (with additives) were normally 7.5×10^{-2} M in methanol. The solutions (2 mL) in 13 mm × 10 mm quartz tubes were deaerated with nitrogen for 15 min prior to irradiation and maintained under a nitrogen atmosphere thereafter. The irradiated samples were neutralized with potassium acetate and yields determined by GC analysis relative to a saturated hydrocarbon standard added after photolysis.

Quantum yields for the decomposition of **1a** (0.1 M) in methanol solution were determined with three PRP-2537 Å lamps. The amount of light absorbed by a sample during the course of an irradiation was determined with use of potassium ferrioxalate actinometry.[20]

Acknowledgment. We thank J. L. Edwards and A. L. Schwartz for technical assistance and A. G. Geigley for ^1H NMR and ^{13}C NMR spectra.

Registry No. **1a**, 10271-71-3; **1b**, 87740-37-2; **1c**, 87740-38-3; **1d**, 87740-39-4; **1e**, 23624-82-0; **1f**, 33744-04-6; **1g**, 54468-04-1; **1h**, 19434-64-1; **1i**, 44639-55-6; **1j**, 87740-40-7; **1k**, 5014-42-6; **1l**, 87740-41-8; **1m**, 36393-98-3; **2a**, 74802-84-9; **2b**, 87740-42-9; **2c**, 87740-43-0; **2d**, 87740-44-1; **2e**, 39057-61-9; **2f**, 63853-74-7; **2g**, 63853-82-7; **2h**, 63853-81-6; **3a**, 6225-10-1; **3b**, 13092-79-0; **3c**, 1540-94-9; **3d**, 7501-79-3; **3e**, 588-46-5; **3h**, 105-60-2; **3i**, 1118-69-0; **3j**, 25291-41-2; **3k**, 1124-53-4; **3l**, 87740-45-2; **3m**, 54385-24-9; **4a**, 10336-07-9; **4l**, 87740-46-3; **5**, 87740-47-4; **6a**, 36394-04-4; **6b**, 36394-03-3; MeOH, 67-56-1; EtOH, 64-17-5; *t*-BuOH, 75-65-0; KOAc, 127-08-2; TMP, 108-75-8; HCl, 7647-01-0; H_2SO_4, 7664-93-9; CH_3CO_2H, 64-19-7; CF_3CO_2H, 76-05-1; O_2, 7782-44-7; 1-dodecanethiol, 112-55-0; trichloroethylene, 79-01-6; 1-methoxycyclohexene, 931-57-7; *N*-(ethoxymethyl)valeramide, 87740-48-5; *N*-(*tert*-butoxymethyl)valeramide, 87740-49-6; 1,1-dimethoxycyclohexane, 933-40-4; valeramide, 626-97-1; 2-chloro-1,1-dimethoxycyclohexane, 65933-44-0.

Aspects of the Intramolecular Diels–Alder Reactions of Some 1,3,9-Trienic Amides, Amines, and Esters. An Approach to the Pentacyclic Skeleton of the Yohimboid Alkaloids

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The intramolecular cycloadditions of a number of 1,3,9-trienes containing an amide, amine, or ester function in the chain linking the dienophile and the diene were examined, and a general preference for the formation of cis cycloadducts was observed. Thus, the aza trienes **7b–h** were found to undergo intramolecular Diels–Alder reaction upon thermolysis at temperatures ranging from 25 to 275 °C to give mixtures of the *cis*- and *trans*-hydroisoquinolines **9b–h** and **10b–h**, respectively, in ratios that varied from about 1.1:1 to 8:1. Thermolysis of the pentadienamide **34** produced the *cis*- and *trans*-hydroisoquinolines **35** and **36** (1.6:1). Interestingly, the aza trienes **13** and **14** in which the internal double bond is *Z* appear to suffer extensive isomerization, presumably via 1,5 hydrogen migration, prior to cyclization to provide isomeric trienes, which have not been isolated but have been tentatively identified as **22** and **25** since they afford corresponding mixtures of the *cis*- and *trans*-hydroisoindoles **20/21** and **23/24** as the principal cycloadducts; only small amounts of the expected *cis*-hydroisoquinolines **9e** and **9h** were obtained in these thermolyses. In order to demonstrate the feasibility of applying intramolecular Diels–Alder reactions of aza trienes to the syntheses of alkaloids containing a hydroisoquinoline ring, the *trans*-hydroisoquinoline **10d** was converted to the yohimbine-related compounds **38** and **39** by cyclization with $POCl_3$ followed by either catalytic hydrogenation or hydride reduction of the intermediate iminium salt. The reactivity of the related esters **40–42** toward intramolecular [4 + 2] cycloaddition was also briefly examined, and it was found that only the acrylate **41** underwent cyclization at temperatures below 275 °C.

Introduction

During the course of a general investigation directed toward the development of new strategies for alkaloid synthesis, we have examined the feasibility of employing intramolecular Diels–Alder reactions[2] for the construction of fused, functionalized nitrogen heterocycles. Our investigations coupled with those of others have now clearly established that the intramolecular [4 + 2] cycloadditions of suitably substituted aza trienes may be utilized for the expeditious construction of hydroindoles, hydroisoindoles, hydroquinolines, indolizidines, and quinolizidines,[3] which are important structural elements common to many al-

(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

(2) For reviews of intramolecular Diels–Alder reactions, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10; *Synthesis* **1978**, 793; *Heterocycles* **1980**, *14*, 1615. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Ciganek, E. *Org. React.*, in press. We thank Dr. Ciganek, for a preprint of this manuscript prior to publication.

(3) For a leading reference of the intramolecular cycloadditions of various aza trienes, see: Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634 and references cited therein. For other recent examples, also see: (a) Takebayashi, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 579. (b) Exon, C.; Gallagher, T.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1982**, 613. (c) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (d) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086.

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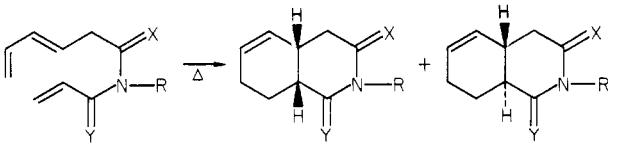
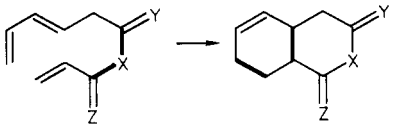
Table I



7 9 10

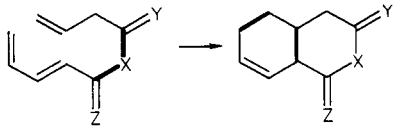
entry	X	Y	R	temp, °C	time, h	yield 9 + 10, %	9/10
a	O	H_2	H	275	120	0	
b	O	H_2	Me	185	60	80	2:1
c	O	H_2	CH_2CH_2Ph	185	60	71	2:1
d	O	H_2	CH_2CH_2-3-indolyl	160	96	74	1.9:1
e	H_2	H_2	Me	140	24	69	1.1:1
f	H_2	H_2	CO_2Me	275	48	74	1.3:1
g	H_2	O	H	85	10	71	7:1
h	H_2	O	Me	80 (25)	2 (20)	83	8:1

kaloids. In contrast to these numerous reports, there is a relative paucity of examples in which simple hydroisoquinolines are created by such processes.[4] Since the hydroisoquinoline ring system is also an important synthon found in these naturally occurring bases, we were prompted to examine synthetic entries to hydroisoquinolines **3** and **4** (X = NR) that featured the thermal cyclization of substituted azatrienes such as **1** and **2** (X = NR) (eq 1 and 2). One significant aspect of this approach to the elaboration of functionalized hydroisoquinolines is that each of the requisite aza trienes **1** and **2** (X = NR) may be readily prepared by two different connective modes (darkened bonds in **1** and **2**) involving the relatively facile construction of a carbon–nitrogen bond. This bimolecular reaction then sets the stage for the subsequent formation of two new carbon–carbon bonds by an entropically favored intramolecular process. In order to demonstrate the potential of employing intramolecular Diels–Alder reactions as the key step in the syntheses of alkaloids containing the hydroisoquinoline ring system, the application of one such process to the construction of the pentacyclic skeleton characteristic of the yohimboid alkaloids was executed.



(1)

1 3



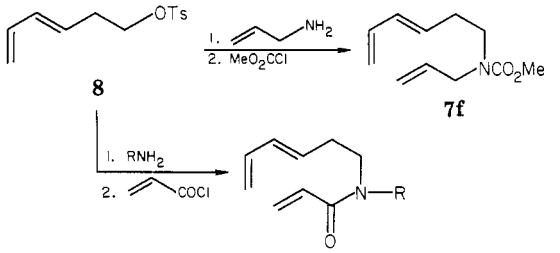
(2)

2 4

X = NR, O
Y, Z = H_2, O

While engaged in these studies, we also became interested in the cycloadditions of the related trienes **1** and **2** (X = O; Y or Z = O) in which the nitrogen atom in the chain linking the diene and dienophile had been replaced with an oxygen atom. The intramolecular cycloadditions of unsaturated esters have not been extensively examined, but we envisioned that such reactions might possess considerable utility for the synthesis of oxygen heterocyclic natural products.

Scheme I

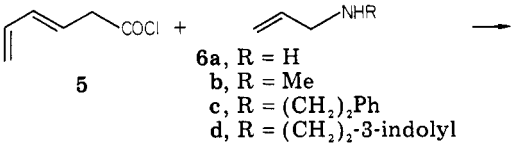


8 7f

7g, R = H
h, R = Me

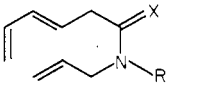
Results

Intramolecular [4 + 2] Cycloadditions of Aza Trienes 1 and 2 (X = NR). In order to investigate the stereochemical course of the intramolecular Diels–Alder reactions of simple aza trienes of the general type **1** and **2** (X = NR), compounds **7a–h** were prepared by standard synthetic techniques. For example, acylation of the alkylallylamines **6a–d** with 3,5-hexadienoyl chloride (**5**)[5] afforded the amides **7a–d** (eq 3) in excellent yields.



5

6a, R = H
b, R = Me
c, R = $(CH_2)_2Ph$
d, R = $(CH_2)_2$-3-indolyl



(3)

7a–d, X = O
e, X = H_2; R = Me

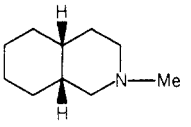
Subsequent reduction of the amide **7b** with alane[6] provided the tertiary amine **7e** (78%). Alkylation of 3,5-hexadienyl tosylate (**8**)[7] with excess allylamine followed by acylation with methyl chloroformate gave the urethane **7f** in 83% overall yield (Scheme I). Similarly, treatment of the tosylate **8** with either excess ammonia or methylamine and then acylation of the intermediate 3,5-hexadienylamines with acryloyl chloride produced the acrylamides **7g,h** in very good yields.

(4) Fused hydroisoquinolines have been prepared by intramolecular Diels–Alder reactions. See: (a) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. (b) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, 903. (c) Cannon, J. G.; Lee, T.; Hsu, F.-L.; Long, J. P.; Flynn, J. R. *J. Med. Chem.* **1980**, *23*, 502. (d) Oppolzer, W.; Francotte, E.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 478. (e) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.

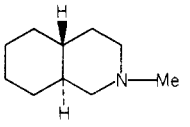
(5) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274.
(6) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.
(7) Howden, M. E. H.; Maercker, A.; Burdon, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732.

With the aza trienes **7a–h** in hand, our attention was focused upon their thermolyses, and the results of these studies are summarized in Table I. Somewhat surprisingly, when the secondary amide **7a** was heated at temperatures as high as 275 °C for up to 5 days, no cycloadduct could be detected. On the other hand, the thermolyses of the secondary amide **7g**, the tertiary amides **7b–e,h**, and the urethane **7f** as 0.05–2% solutions in benzene, toluene, or xylene at temperatures ranging as indicated from 25 to 275 °C afforded mixtures of the expected cis and trans cycloadducts **9b–h** and **10b–h** in good to very good yields. The hydroisoquinolines **9e** and **10e** and **9f** and **10f** were produced as mixtures that proved to be inseparable by conventional chromatographic techniques, but each of the remaining pairs of *cis*- and *trans*-hydroisoquinolines could be readily separated by preparative, normal-phase HPLC. Since it was determined in separate experiments that the cycloadducts **9a–e,g,h** and **10b–e,g,h** did not interconvert under the conditions of the initial cycloaddition, these processes appear to be kinetically controlled. With the exception of the acrylamides **7g,h**, which underwent preferential cyclization to give the corresponding *cis*-hydroisoquinolines **9g,h** and and *trans*-hydroisoquinolines **10g,h** in ratios of approximately 7–8:1, the remaining cycloadditions listed in Table I did not proceed with an appreciable degree of stereoselectivity.

In order to establish unequivocally the stereochemistry of the cycloadducts **9b** and **10b**, they were converted to the known[8] tertiary amines **11** and **12** via **9e** and **10e** by



11



12

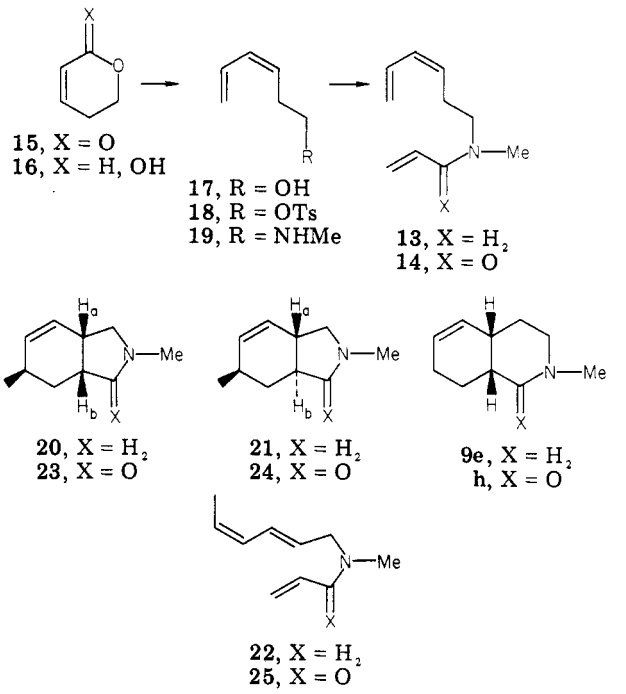
sequential hydride reduction ($LiAlH_4$) and catalytic hydrogenation. The adducts **9f** and **10f** were also reduced ($LiAlH_4$) and then correlated with **9e** and **10e**. The stereochemistry of the hydroisoquinoline **10d** was convincingly secured by its elaboration to yohimban (**38**) (vide infra), and the structural assignments of **9c** and **10c** were then based upon the close similarities of their ^1H NMR and ^{13}C NMR spectra with those of the respective *cis*- and *trans*-hydroisoquinolines **9b,d** and **10b,d**.

Inasmuch as a number of substituted aza trienes of the general type **1** (X = NR) in which the central double bond was *E* did not undergo cyclization with a significant degree of stereocontrol, we decided to examine the intramolecular Diels–Alder reactions of several aza trienes in which the internal double bond was *Z*. Such trienes have been reported to cyclize in a highly stereoselective fashion to provide cis cycloadducts.[9] However, as shall become evident, the incorporation of a *Z*-diene moiety to serve as a stereochemical control element for intramolecular Diels–Alder reactions is not entirely without risk, since thermally allowed 1,5 sigmatropic hydrogen shifts may result in the deleterious isomerization of the dienic moiety prior to the cycloaddition.[9c,10]

In the event, the aza trienes **13** and **14** were readily prepared from 5,6-dihydro-2-pyrone (**15**)[11] by a straightforward sequence of reactions (Scheme II). Thus, reduction of **15** with diisobutylaluminum hydride (1.2 equiv, −78 °C) followed by reaction of the intermediate lactol **16** with excess methylenetriphenylphosphorane under "salt-free" conditions[12] afforded 3(*Z*),5-hexadienol (**17**), which was readily converted into the tosylate **18**. Treatment of **18** with excess allylmethylamine provided the amino triene **13**, whereas reaction of **18** with excess methylamine gave the secondary amine **19**, which gave the acrylamide **14** upon acylation with acryloyl chloride. Thermolysis of the amine **13** required heating at 250 °C for 3 days to effect completion of the reaction, and a mixture of three isomeric cycloadducts (9:1:1) was obtained in 47% total yield. One of the minor adducts, which was separated from the other two by preparative GLC, was shown to be the *cis*-hydroisoquinoline **9e** by direct comparison with an authentic sample that had been prepared from **9h** by hydride reduction. Although the other two cycloadducts could not be separated by conventional chromatographic techniques, the appearance of two methyl doublets at δ 1.03 (minor product) and 0.98 (major product) in the ^1H NMR spectrum of the mixture hinted that they might be the *cis*- and *trans*-hydroisoindoles **20** and **21**, respectively. More compelling evidence for this structural assignment was obtained in other experiments (vide infra).

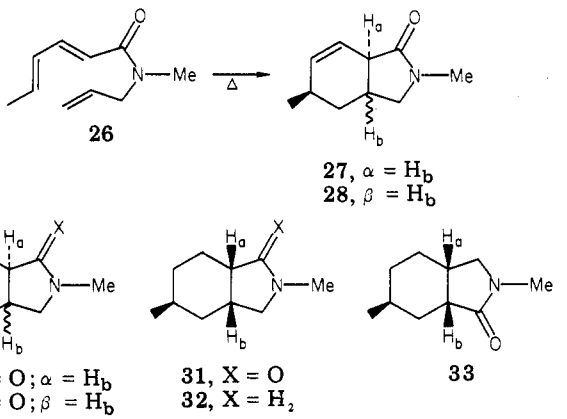
The result obtained in the thermolysis of the amine **13** strongly suggested that the dienic portion of **13** was undergoing thermal rearrangement to provide an isomeric aza triene, to which the structure **22** was tentatively assigned, prior to the expected cyclization. Since we had previously observed that the temperatures required for the cyclization of the acrylamides **7g** and **7h** were less than that required for the related amine **7e**, we anticipated that the acrylamide **14** might undergo an intramolecular Diels–Alder reaction to give the *cis*-hydroisoquinoline **9h** at a sufficiently low temperature that the rearrangement of **14** to the isomeric aza triene **25** would not intervene. However, in contrast to our hopes thermolysis of **14** (190 °C, 3 days)

Scheme II



(8) Witkop, B. *J. Am. Chem. Soc.* **1949**, *71*, 2559.
(9) (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. (c) Boeckman, R. K., Jr.; Alessi, T. R. *Ibid. Soc.* **1982**, *104*, 3216.
(10) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612.
(11) Nakagawa, M.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. *Synthesis* **1974**, 510.
(12) (a) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694. (b) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

Scheme III



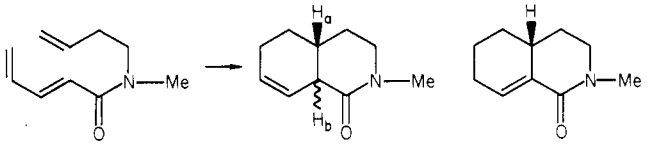
provided a mixture containing three isomeric cycloadducts (10:2:1) in about 90% total yield. The second most abundant product, which exhibited a carbonyl stretching frequency at 1640 cm^{-1}, was separated from the other two cycloadducts by preparative GLC and was positively identified as the *cis*-hydroisoquinolone **9h** by correlation with a sample previously prepared from the triene **7h**. Although the other two cycloadducts could not be separated by conventional chromatographic techniques, the carbonyl stretching frequency that appeared at 1680 cm^{-1} is indicative of a γ-lactam rather than a δ-lactam. Moreover, the ^1H NMR spectrum of this mixture revealed two methyl doublets at δ 1.07 (minor product) and 0.98 (major product). These spectral data suggested that these cycloadducts might be the *cis*- and *trans*-hydroisoindolones **23** and **24** or stereoisomers thereof. By employing off-resonance decoupling techniques, it was possible to determine that $J_{a,b}$ of the major isomer was 7.3 Hz, which corresponds more closely to that which would be expected for a cis ring fusion rather than a trans one. Moreover, the ratio of these two cycloadducts did not change upon treatment with potassium *tert*-butoxide in *tert*-butyl alcohol. This observation indicates that the 10:1 ratio of **23** and **24** obtained from the cycloaddition corresponds approximately to their thermodynamic stability and thus further supports the assignment of a cis ring fusion for the principal adduct.

At this juncture it was deemed desirable to establish more convincingly the structure(s) of one or more of the hydroisoindoles formed upon the thermolyses of the aza trienes **13** and **14**. This would help eliminate any doubts that **13** and **14** underwent isomerization in preference to cyclization to provide the aza trienes **22** and **25**, which we were unable to detect in or isolate from the reaction mixtures but have nevertheless alleged were intermediates. The chemical correlation of **23** with a hydroisoindole of known structure was therefore undertaken. To this end, a solution of *N*-allyl-*N*-methylsorbamide (**26**) was heated at 185 °C (18 h) to provide an approximately 1:1.1 mixture of the *cis*- and *trans*-hydroisoindoles **27** and **28**, which could not be separated by either normal- or reverse-phase HPLC (Scheme III).[13] The IR spectrum of this mixture revealed a carbonyl stretching frequency at 1685 cm^{-1}, and the NMR spectrum of the mixture exhibited two methyl doublets, one at δ 0.99 and the other at δ 1.01. It is noteworthy that these spectral features are reminiscent of those observed for the inseparable mixture of the two cycloadducts obtained from the thermolysis of **14**. Catalytic hydrogenation (H_2, 1 atm/Pd–C/EtOH) of this mixture of **27** and **28** provided the corresponding dihydro derivatives **29** and **30**, which were separated by normal-phase HPLC. The stereochemistry of the ring fusion for **29** and **30** was readily determined by measurement of the coupling constants between the bridgehead protons H_a and H_b, which were 6.2 and 10.2 Hz, respectively. As expected, only the *trans*-hydroisoindole **30** underwent epimerization upon treatment with potassium *tert*-butoxide in *tert*-butyl alcohol, and the *cis*-hydroisoindole **31** thus obtained afforded the tertiary amine **32** upon reduction with lithium aluminum hydride.

In a parallel series of experiments, the mixture of **23** and **24**, which was formed by the thermolysis of **14**, was reduced by catalytic hydrogenation to give a separable mixture of dihydro lactams. On the basis of the observed vicinal coupling constant of 6.2 Hz between the bridgehead protons H_a and H_b, the major component was tentatively identified as the *cis*-hydroisoindole **33**. This assignment was subsequently verified by reduction ($LiAlH_4$) of **33** to give a tertiary amine that was identical in all respects (^1H and ^{13}C NMR, IR, MS) with the sample of **32** prepared independently from **26** as previously described. Furthermore, since the hydride reduction of the mixture of **23** and **24** afforded a mixture of unsaturated amines that was virtually identical with the mixture of hydroisoindoles that was previously obtained upon heating the aza triene **13**, it now seems reasonable to conclude that the major cycloadduct formed by the thermolysis of **13** was the *cis*-hydroisoindole **20**, while the other minor product was presumably the *trans*-hydroisoindole **21**.

Thus, at the elevated temperatures that are necessary to overcome the additional energy of activation that is required as a consequence of the presence of a *Z*-diene moiety in **13** and **14**, there appears to be significant competition between the intramolecular [4 + 2] cycloaddition of **13** and **14** to afford **9e** and **9h**, respectively, and the thermally allowed 1,5 hydrogen shifts of **13** and **14** to give the isomeric aza trienes **22** and **25**, which then cyclize to provide the corresponding hydroisoindoles **20** and **21** or **23** and **24**. In the present instance, the latter pathway is clearly dominant. It is relevant to note that, *under the conditions of the thermolyses of the aza trienes* **7a–h**, *no isomerization of the diene moiety was observed.*

The feasibility of constructing hydroisoquinolines from aza trienes of the general type **2** was also briefly examined as outlined in eq 4. The amide **34** was prepared by



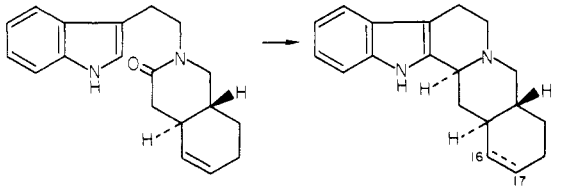
(4)

treatment of 2,4-pentadienoic acid with ethyl chloroformate in the presence of diisopropylethylamine followed by the reaction of the intermediate mixed anhydride with *N*-(3-butenyl)methylamine. Thermolysis of **34** (140 °C, 72 h) provided a mixture (1.6:1) of the *cis*- and *trans*-hydroisoquinolines **35** and **36**, respectively, in 41% yield together with small amounts of the conjugated lactam **37**. When **34** was heated at 300 °C in a sealed tube, **37** was the only product that was isolated. Interestingly, after separation and purification, the cis and trans lactams **35** and **36** were found to interconvert upon heating at 140 °C to provide mixtures of **35** and **36** in the *approximate* ratio of 1.6:1 along with variable quantities of **37**, but the ex-

(13) For closely related cyclizations, see: (a) Fráter, G. *Tetrahedron Lett.* **1976**, 4517. (b) Brettle, R.; Jafri, I. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 387.

tensive decomposition that occurred during these thermolyses unfortunately precluded an accurate and reproducible determination of the equilibrium composition. Although this experiment might suggest that the intramolecular Diels–Alder reaction of **34** is reversible, a prototropic process for effecting the interconversion of **35** and **36** cannot be presently excluded. The stereochemical assignments for **35** and **36** were conclusively established by their respective conversion via catalytic hydrogenation and hydride reduction to the amines **11** and **12**, which had been prepared independently from **9b** and **10b** (vide supra).

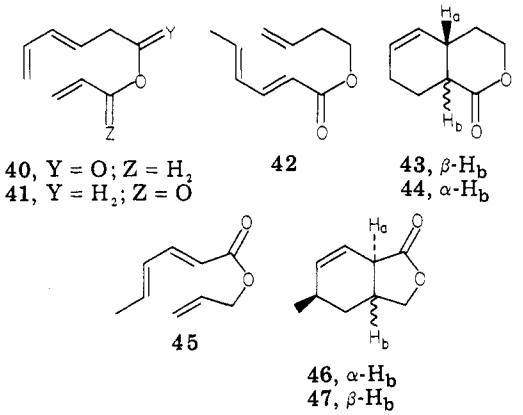
Synthesis of Racemic Yohimban (38) and Δ^{16}-Didehydroyohimban (39). In order to demonstrate the viability of exploiting an intramolecular Diels–Alder reaction according to eq 1 as a key step in the syntheses of alkaloid natural products, the simple conversion of **10d** to yohimban (**38**) and Δ^{16}-didehydroyohimban (**39**) was undertaken. Thus, cyclization of **10d** with $POCl_3$ at 80 °C followed by reduction of the intermediate iminium salt by catalytic hydrogenation afforded racemic yohimban (**38**)[14] in 77% yield. Alternatively, if the iminium salt obtained by reaction of **10d** with $POCl_3$ was reduced with $NaBH_4$, the didehydroyohimban derivative **39** was formed in 71% overall yield.



10d

38
39, Δ^{16}

Intramolecular [4 + 2] Cycloadditions of Esters 1 and 2 (X = O). During the course of our investigations of the intramolecular Diels–Alder reactions of the aza trienes **1** and **2** (X = NR), we also became intrigued with examining the cyclizations of several related esters **1** and **2** (X = O; Y or Z = O) since we reasoned that such processes might be expeditiously applied to the syntheses of natural products containing fused oxygen heterocycles. The requisite esters **40–42** for these preliminary studies were conveniently prepared by standard synthetic reactions involving the acylation of the appropriate acid chlorides with the corresponding unsaturated alcohols. However, at the very inception of our attempts to induce the thermal cyclizations of the esters **40–42**, it became apparent that the conditions that would be necessary to effect their intramolecular [4 + 2] cycloadditions would be considerably more forcing than those that were required for the cyclizations of the related tertiary amides **9b–d,h** and **34**. For example, although heating (5 h, 210 °C) the acrylate ester **41** did afford a 9:1 mixture (42%) of the cis and trans lactones **43** and **44**, no identifiable cycloadducts could be isolated upon thermolyses of the esters **40** and **42** at temperatures up to 275 °C. Variable amounts of starting materials were recovered from these attempts, and decomposition pathways generally prevailed. There was no indication that the diene moiety of either **40** or **41** isomerized. Indeed, it was demonstrated in a separate experiment that allyl sorbate (**45**), which might be formed by isomerization of **40**, underwent cyclization upon thermolysis (250 °C, 120 h) to afford a mixture (1:3.5) of the *cis*- and *trans*-hydroisobenzofurans **46** and **47** (76%).



40, Y = O; Z = H_2
41, Y = H_2; Z = O

42

43, β-H_b
44, α-H_b

45

46, α-H_b
47, β-H_b

Discussion

The intramolecular [4 + 2] cycloadditions of the 1,3-(*E*),9-trienes examined in this study proceeded with a consistent, albeit typically slight, propensity for the formation of the cis cycloadducts, an observation that is in qualitative accord with the recent work of Roush who noted that the thermal cyclizations of several methyl undeca-2,8(*E*),10-trienoates afforded mixtures of *cis*- and *trans*-decalins in ratios ranging from approximately 1:1 for unsubstituted trienes to 3–4:1 for trienes bearing an additional substituent at C-7.[15]

One of the principal objectives of previous investigations of intramolecular Diels–Alder reactions has been the determination of those factors that affect the stereochemical outcome of these processes.[16] On the basis of these studies, it presently appears that a combination of nonbonded interactions, the magnitudes of which depend upon the substitution on the trienic backbone and the extent to which each of the two new carbon–carbon single bonds is formed in the transition state, together with angle and torsional strains in the chain linking the diene and the dienophile are the dominant stereocontrol elements in these intramolecular [4 + 2] cycloadditions. Secondary orbital interactions seem to play only a minimal role for the majority of substrates that have been examined, presumably because most of the cyclizations in which there might have been a significant effect were conducted at higher temperatures wherein the importance of such interactions are known to decrease.[16,17] Oppolzer has noted that the stereochemical course of the thermal cyclizations of certain aza trienes may be affected by the presence and location of the acyl carbon that is attached to the nitrogen atom.[18] Thus, the loss of overlap of the nitrogen lone pair with an adjacent sp^2-hybridized carbon (e.g., amide resonance) in order to attain a particular transition-state ge-

(14) For other syntheses of yohimban see: (a) van Tamelen, E. E.; Shamma, M.; Aldrich, P. *J. Am. Chem. Soc.* **1956**, *78*, 4628. (b) Morrison, G. C.; Cetenko, W. A.; Shavel, J., Jr. *J. Org. Chem.* **1966**, *31*, 2695. (c) Ninomiya, I.; Tada, Y.; Kiguchi, T.; Yamamoto, O.; Naito, T. *Heterocycles* **1978**, *9*, 1527. (d) Suzuki, T.; Tomino, A.; Unno, K.; Kametani, T. *Ibid.* **1979**, *13*, 301.

(15) (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200; (b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825.

(16) For a discussion of the various factors that play a role in governing the stereoselectivity of intramolecular Diels–Alder reactions, see: (a) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273. (b) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (c) Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141. (d) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. See also ref 15a.

(17) The value of 1.2 kcal/mol has been established as the minimum intrinsic energy advantage associated with an electronic explanation of the Alder endo rule. See: Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 4170.

(18) (a) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. (b) Oppolzer W. *Tetrahedron Lett.* **1974**, 1001. (c) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 590.

ometry has an adverse effect upon the energy level of that transition state.

An examination of Dreiding models of the possible transition states for the cyclizations of the aza trienes **7b–h** and **34** to the corresponding *cis*- and *trans*-hydroisoquinolines reveals some discernible differences in the magnitudes of the relevant nonbonded interactions as well as the extent to which amide resonance must be disrupted. For the substrates **7b–h** these differences are visibly dependent upon the presence and location of the acyl carbon atom. However, on the basis of the ratios of cis and trans cycloadducts obtained by the thermolyses of **7b–f** and **34**, which correspond to differences in the energy levels of the respective transition states of less than 0.6 kcal, it is evident that the preferred mode of cyclization for these trienes is determined by a delicate balance of a subtle combination of the effects of the loss of amide resonance together with the magnitudes of the various nonbonded interactions and angle and torsional strains. Consequently, it is not possible to define precisely those factors that generally favor the kinetic production of the cis cycloadducts. The only cyclizations of 1,3(*E*),9-trienes that proceeded with a significant degree of stereoselectivity were those of the acrylamides **7g,h** and the acrylate **41** wherein the dienophile is activated by conjugation with an acyl carbon in the chain linking the diene and the dienophile. Although the preferential formation of the cis cycloadducts **9g,h** and **43** from **7g,h** and **41**, respectively, is consistent with the presence of favorable secondary orbital interactions in the cis transition state, such interactions may not be as important as other effects for the cyclization of **41** since that thermolysis was conducted at 210 °C.

The cyclizations of certain trienes in which the internal double bond is *Z* has been shown to proceed to give cis cycloadducts exclusively, but it is becoming increasingly apparent that the successful utilization of a *Z* diene as a stereocontrol element in intramolecular Diels–Alder reactions is substrate dependent.[9,10] In particular, deleterious side reactions such as 1,5 hydrogen migrations may sometimes intervene to give isomeric trienes, as observed in the thermolyses of the aza 1,3(*Z*),9-trienes **13** and **14**, thereby sabotaging the desired cycloaddition.

Qualitatively, the relative facility with which the N-trisubstituted aza trienes **7b–f,h** undergo intramolecular [4 + 2] cycloaddition is **7h** ≫ **7e** > **34** ≃ **7b–d** > **7f** ≫ **13**, **14**. The ease with which **7h** cyclizes might be attributed to the presence of an activated dienophile, but an examination of Dreiding molecular models reveals that the overlap of the dienophilic double bond with the acyl group of the acrylamide moiety can be accommodated only at the expense of some amide resonance. Since 1,3(*E*),9-decatrien-8-one undergoes a highly stereoselective intramolecular Diels–Alder reaction at 0 °C,[19] this loss of amide resonance in the transition state for the cyclization of **7h** does seem to exact a toll in energy terms, but the additional angle strain that is induced by the presence of an sp^2-hybridized nitrogen in the connecting chain should likewise be a contributing factor. Although the reactivity toward cyclization of **7e** relative to **34** and **7b–d** can be partially ascribed to the reduced angle strain in the connecting chain of **7e** in which all the atoms are sp^3 hybridized, it should again be noted that a loss of amide resonance, in the cases of **7b–d**, and/or loss of overlap with the diene, in the case of **34**, is required for these trienes to adopt the necessary transition-state geometry. The low reactivity of the urethane **7f** toward an intramolecular Diels–Alder reaction would appear to arise principally from the existence in the transition state of two unfavorable steric interactions between the oxygens of the *N*-carbomethoxy group and a hydrogen atom on each of the flanking methylene groups. That the cyclization of **13** and **14**, in which the internal double bond was *Z*, required higher temperatures than was necessary for the corresponding *E* aza trienes **7e** and **7h** is precisely what would be anticipated on the basis of simple steric considerations. The lower reactivity toward cyclization of the secondary amides **7a** and **7g** relative to the tertiary amides **7b** and **7h** is in qualitative accord with the work of Gschwend.[20] Finally, since there have been previous reports of trienic esters, that either failed to undergo intramolecular [4 + 2] cycloaddition or that did so only under forcing conditions,[21] the observed lack of reactivity of the esters **40** and **42** as well as the rather low reactivity of esters **41** and **45** came as no surprise.

The loss of ester overlap in the transition state has been invoked to interpret certain observed differences in the intramolecular Diels–Alder reactions of some trienic esters.[21b] Although the relative reactivities of the esters **40** and **45** as well as that of the tertiary amides **7b** and **26** might arise in part from a loss in overlap between the acyl carbon and the attached heteroatom, such rationalizations are clearly not applicable to the interpretation of other results of this study. For example, an examination of Dreiding molecular models does not reveal any significant differences in these overlap requirements for the cyclizations of (1) the amides **7a–d** and the ester **40**, (2) the amides **7g,h** and the ester **41**, (3) the amide **34** and the ester **42**, and (4) the amide **26** and the ester **45**. Indeed, if the loss of overlap of the oxygen or nitrogen atom with the acyl carbon in the transition state were a major factor in determining the relative reactivities of these trienic esters and amides, then one would anticipate that the cost in energy terms should be considerably greater for amides than for esters because the barrier to rotation, which is a reasonable measure of the resonance energy, is considerably greater for amides (ca. ≤20 kcal/mol) than for esters (ca. ≤10 kcal/mol). This is obviously not the case since the general trend observed for the facility with which these structurally related trienes undergo intramolecular [4 + 2] cycloaddition is that tertiary amides cyclize faster than secondary amides, which cyclize faster than esters. This dramatic difference in the relative reactivities between tertiary amides and esters may be simply rationalized by recognizing that the dipolar interactions, which destabilize the cisoid conformation of esters in the ground state[22] as well as the product lactones[23] and which are absent in the related tertiary amides, are fully manifested in the transition state for cyclization of the trienic esters, thereby resulting in an increase in the energy of activation. Although the reasons for the intermediate reactivity of trienic secondary amides are less easily defined, one likely factor that adversely affects the energy of activation for their

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(20) Gschwend, H. W.; Lee, A. O.; Meier, H.-P. *J. Org. Chem.* **1973**, *38*, 2169.

(21) Cf. (a) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689. (b) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789. (c) Burke, S. D.; Smith Strickland, S. M.; Powner, T. H. *Ibid.* **1983**, *48*, 454. (d) Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *Ibid.* **1983**, *48*, 470.

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(23) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253.

cyclization relative to tertiary amides arises from the loss in the transition state of the intermolecular hydrogen bonding that stabilizes the transoid conformation of secondary amides relative to the cisoid one that is required for cyclization.[20,24]

Further studies of the intramolecular Diels–Alder reactions of other nitrogen- and oxygen-containing trienes are in progress to test the validity of some of the conclusions drawn herein and to explore further the scope and synthetic utility of such processes. The results of these investigations will be reported in due course.

Experimental Section

General Procedures. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ether, tetrahydrofuran (THF), benzene, toluene, and xylene were distilled from either sodium or potassium/benzophenone ketyl immediately prior to use. Phosphorus oxychloride was freshly distilled under dry nitrogen. Triethylamine was distilled from calcium hydride. All reactions involving organometallic reagents or $LiAlH_4$ were executed under an atmosphere of dry nitrogen or argon, using oven-dried glassware. IR spectra were determined as solutions in $CHCl_3$ unless otherwise indicated, using a Beckman Acculab 8 spectrometer. The ^1H NMR spectra were determined as solutions in $CDCl_3$ unless otherwise indicated on a Varian EM-390 (90 MHz) or if indicated a Nicolet NT-200 instrument (a superconducting 200-MHz FT instrument). Chemical shifts are expressed in parts per million (δ units) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Coupling constants are given in hertz (Hz). The ^{13}C NMR spectra were determined in $CDCl_3$ unless otherwise indicated on either a Varian FT-80A or a Bruker WH-90 FT, and the chemical shifts are reported in parts per million (δ units) downfield from internal tetramethylsilane. Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument at an ionizing voltage of 70 eV, and the exact mass determinations were obtained on a DuPont (CEC) 21-110 instrument. Preparative high-performance chromatography (HPLC) was performed on either a Waters Prep LC 500 instrument (sample size > 500 mg) or on a Waters 6000A solvent delivery system equipped with a Model U6K injector and two Porasil A columns (0.6 m × 7.8 mm) (sample size <500 mg). Bulb-to-bulb distillations were executed on a Kügelrohr apparatus.

***N*-Methyl-3(*E*),5-hexadienamine.** Methylamine (ca. 40 mL) was condensed at −78 °C in a dry, resealable glass pressure bomb charged with tosylate 8[7] (5.07 g, 20.1 mmol), and the resulting solution was stirred for 4 days at room temperature. The bomb was cooled to −78 °C and opened, and the excess methylamine was allowed to evaporate at room temperature. A solution of 1 N NaOH saturated with NaCl (20 mL) was added, and the aqueous phase was extracted with ether (4 × 30mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was distilled to give 1.34 g (60%) of pure amino diene as a colorless oil: bp 86–90 °C (60 mm); ^1H NMR δ 6.50–5.45 (comp, 3 H), 5.05 (m, 2 H), 2.63 (m, 2 H), 2.40 (s, 3 H), 2.25 (m, 2 H), 1.20 (s, 1 H); mass spectrum, *m/e* 111.1045 ($C_7H_{13}N$ requires 111.1048), 94, 84, 79, 44 (base).

***N*-Allyl-2-phenylethylamine (6c).** 6c was prepared in 63% yield from 2-phenylethylamine according to the general procedure of Morrison and Rinderknecht:[25] bp 125–128 °C (25 mm); ^1H NMR δ 7.13 (br s, 5 H), 5.78 (m, 1 H), 5.03 (m, 2 H), 3.14 (m, 2 H), 2.71 (m, 4 H); mass spectrum, *m/e* 161.1208 ($C_{11}H_{15}N$ requires 161.1204), 105, 91, 77, 56, 41 (base).

***N*-Allyltryptamine (6d).** 6d was prepared in 87% yield from tryptophyl bromide according to the general procedure of Hoshino and Shinodaira:[26] bulb-to-bulb distillation, 145–150 °C (oven temperature) (0.10 mm); IR ν 3490, 2935 cm^{-1}; ^1H NMR δ 8.88 (br s, 1 H), 7.44 (m, 1 H), 6.97 (m, 4 H), 6.63 (s, 1 H), 5.74 (m, 1 H), 5.00 (m, 2 H), 3.14 (m, 2 H), 2.83 (s, 4 H), 1.33 (br s, 1 H); mass spectrum, *m/e* 200.1319 ($C_{13}H_{16}N_2$ requires 200.1313), 158, 143, 130 (base), 115, 70, 41.

General Procedure for Preparation of Unsaturated Amides 7a–d,g,h and 26. A solution of the appropriate amine (1.0 equiv) and dry triethylamine (1.1 equiv) in dry CH_2Cl_2 was slowly added with stirring to a solution of the appropriate acid chloride (1.0 equiv) in CH_2Cl_2 at −78 °C. The reaction was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous $NaHCO_3$ was added followed by extractive workup with ether. The products were purified by bulb-to-bulb distillation or chromatography as indicated.

***N*-Allyl-3(*E*),5-hexadienamide (7a):** column chromatography [silica gel; hexane/ethyl acetate (3:1)]; 88%; IR ν 1683 cm^{-1}; ^1H NMR δ 7.75 (br t, 1 H), 6.59–5.53 (comp, 4 H), 5.28–4.88 (comp, 4 H), 3.74 (t, 2 H, J = 6 Hz), 2.97 (d, 2 H, J = 7 Hz), mass spectrum, *m/e* 151.0998 ($C_9H_{13}NO$ requires 151.0997), 109, 95, 84, 67, 41 (base).

***N*-Allyl-*N*-methyl-3(*E*),5-hexadienamide (7b):** 95% yield; bulb-to-bulb distillation, 105–118 °C (oven temperature) (0.1 mm); IR ν 1630 cm^{-1}; ^1H NMR δ 6.50–5.44 (comp, 4 H), 5.26–4.83 (comp, 4 H), 3.89 (m, 2 H), 3.07 (m, 2 H), 2.92 (s, 1.6 H), 2.85 (s, 1.4 H); mass spectrum, *m/e* 165.1151 ($C_{10}H_{15}NO$ requires 165.1154), 150, 109, 67, 41 (base).

***N*-Allyl-*N*-(2-phenylethyl)-3(*E*),5-hexadienamide (7c):** 95% yield; bulb-to-bulb distillation, 125–135 °C (oven temperature) (0.1 mm); IR ν 1642 cm^{-1}; ^1H NMR δ 7.23 (br s, 5 H), 6.55–5.47 (comp, 4 H), 5.08 (m, 4 H), 3.76 (m, 2 H), 3.48 (m, 2 H), 3.18–2.67 (comp, 4 H); mass spectrum, *m/e* 255.1628 ($C_{17}H_{21}NO$ requires 255.1623), 214, 164, 105, 91, 77, 67, 41 (base).

***N*-Allyl-*N*-(2-indol-3-ylethyl)-3(*E*),5-hexadienamide (7d):** 95% yield; column chromatography [silica gel; hexane/ethyl acetate (3:1)]; IR ν 1630 cm^{-1}; ^1H NMR δ 8.88 (br d, 1 H, J = 21 Hz), 7.65–6.74 (comp, 5 H), 6.62–5.43 (comp, 4 H), 5.06 (m, 4 H), 390 (m, 2 H), 3.53 (m, 2 H), 3.22–2.83 (comp, 4 H); mass spectrum, *m/e* 294.1738 ($C_{19}H_{22}N_2O$ requires 294.1732), 178, 143 (base), 115, 95, 67, 55, 41.

***N*-Allyl-*N*-methyl-3(*E*),5-hexadienylamine (7e).** A solution of amide **7b** (0.36 g, 2.18 mmol) in dry THF (5.0 mL) was added to a solution of alane[6] (3.00 mmol) in THF (20 mL) at −78 °C under dry nitrogen. The reaction mixture was warmed gradually to room temperature and stirred for 3 h, whereupon THF/H_2O (1:1, 5 mL) was added. The supernatent solution was decanted, and the remaining white residue was washed thoroughly with ether (2 × 20 mL). The combined organic layers were washed with 1 N aqueous HCl (3 × 20 mL). The aqueous solution was then made basic with NaOH pellets at 0 °C, saturated with NaCl, and extracted with ether (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give **7e**, 0.25 g (77%) as a pale, clear oil. An analytical sample could be obtained by bulb-to-bulb distillation: 45–55 °C (oven temperature) (0.1 mm); ^1H NMR δ 6.46–5.43 (comp, 4 H), 5.25–4.82 (comp, 4 H), 2.95 (m, 2 H), 2.52–2.05 (comp, 4 H), 2.18 (s, 3 H); mass spectrum, *m/e* 151.1365 ($C_{10}H_{17}N$ requires 151.1361), 110 (base), 84, 41.

***N*-(3(*E*),5-Hexadienyl)acrylamide (7g):** 85% crude yield as a clear oil, which was used without further purification; IR ν 1675 cm^{-1}; ^1H NMR δ 8.08 (br t, 1 H), 6.48–5.39 (comp, 6 H), 5.24–4.79 (comp, 2 H), 3.32 (q, 2 H, J = 7 Hz), 2.31 (q, 2 H, J = 7 Hz); mass spectrum, *m/e* 151.1001 ($C_9H_{13}NO$ requires 151.0997), 67, 55 (base).

***N*-Allyl-*N*-methylsorbamide (26):** 90% yield; bulb-to-bulb distillation, 95–110 °C (0.15 mm); IR ν 1632 cm^{-1}; ^1H NMR δ 7.11 (m, 1 H), 6.34–5.53 (comp, 4 H), 5.12 (m, 2 H), 3.94 (m, 2 H), 2.92 (s, 3 H), 1.80 (d, 3 H, J = 5 Hz); mass spectrum, *m/e* 165.1155 ($C_{10}H_{15}NO$ requires 165.1154), 150, 109, 41 (base).

***N*-Allyl-*N*-carbomethoxy-3(*E*),5-hexadienylamine (7f).** In a resealable glass pressure bomb, 3(*E*),5-hexadienyl tosylate

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(8; 7.55 g, 30 mmol) and freshly distilled allylamine (8.54 g, 150 mmol) were combined and heated at 60 °C for 20 h with stirring. The crude reaction mixture was cooled to 0 °C, diluted with 2 N aqueous NaOH saturated with NaCl (20 mL), and extracted with ether (3 × 50 mL). The combined organic layers were dried (K_2CO_3) and concentrated by fractional distillation at atmospheric pressure until the head temperature was 65 °C. The crude residue was dissolved in CH_2Cl_2 (125 mL) containing dry triethylamine (3.78 g, 37.5 mmol) and cooled to −78 °C, and freshly distilled methyl chloroformate (11.32 g, 120 mmol) was added dropwise. The reaction was stirred at −78 °C for 0.5 h and then at room temperature for 4 h. The mixture was washed with saturated aqueous $NaHCO_3$ (125 mL), and the layers were separated. The aqueous layer was extracted with ether (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by passing through a column (10 × 1.5 cm) of silica gel [hexane/ethyl acetate (3:1)] and then bulb-to-bulb distillation, 75–80 °C (oven temperature) (0.1 mm), to give **7f** as a colorless oil: 5.02 g (85%); IR ν 1701 cm^{-1}; ^1H NMR δ 6.45–5.37 (comp, 4 H), 5.23–4.83 (comp, 4 H), 3.79 (d, 2 H, J = 6 Hz), 3.65 (s, 3 H), 3.22 (t, 2 H, J = 7 Hz), 2.27 (q, 2 H, J = 7 Hz); mass spectrum, m/e 195.1263 ($C_{11}H_{17}NO_2$ requires 195.1259), 180, 164, 128 (base), 67, 59, 41.

2-Hydroxy-5,6-dihydro-2(2*H*)-pyrone (16). To a solution of 5,6-dihydro-2-pyrone (**15**)[11] (12.74 g, 0.13 mol) in dry toluene (150 mL) at −78 °C was slowly added (30 min) with stirring diisobutylaluminum hydride (0.16 mol, 1 N in toluene). The resulting solution was stirred at −78 °C for 2 h, and the reaction was then quenched by the addition of 2 M isopropyl alcohol in toluene (40 mL). Stirring was continued for 15 min at −78 °C and then for 15 min at 0 °C, whereupon water (9 mL) was added. After the addition of THF (100 mL), anhydrous Na_2SO_4 (54 g) and silica gel (27 g) were added, and the solids were removed by vacuum filtration and washed well with THF (500 mL). The combined filtrates were evaporated under reduced pressure while maintaining the bath temperature below 25 °C to give 12.09 g (93%) of crude **16** as a light yellow oil, which was sufficiently pure for use in the next step: ^1H NMR δ 6.10–5.57 (comp, 2 H), 5.17 (br m, 1 H), 4.80 (d, 1 H, J = 6 Hz), 4.15–3.53 (comp, 2 H), 2.45–1.65 (comp, 2 H); mass spectrum, m/e 100.0522 ($C_5H_8O_2$ requires 100.0524), 83 (base), 55.

3(*Z*),5-Hexadienol (17). Hexamethyldisilazine (65.0 g, 0.40 mol) was added dropwise with stirring to a suspension of potassium hydride (16.3 g, 0.41 mol; as a 35% dispersion in mineral oil that had been washed with hexane to remove the mineral oil) in anhydrous THF (300 mL), and the stirring was continued for an additional 30 min. The resulting solution was then diluted with THF (600 mL) and HMPA (300 mL), and methyl triphenylphosphonium bromide (160.0 g, 0.45 mol) was added in one portion. After stirring at room temperature, the solution of ylide was cooled to −78 °C and crude **16** (10.1 g, 0.1 mol) in anhydrous THF (20 mL) was added slowly (15 min), and the mixture was allowed to warm slowly (10–12 h) to room temperature and then stirred for an additional 12 h at room temperature. Water (3 mL) was then added, the THF was removed under reduced pressure, and saturated NH_4Cl (400 mL) was added. The resulting mixture was extracted with ether (3 × 300 mL), and the combined organic layers were washed with saturated brine (200 mL) and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure afforded a dark yellow oil (ca. 20 g) from which pure **17** (5.2 g, 52%) as a colorless oil was isolated by double distillation: bp 100–103 °C (70 mm); ^1H NMR δ 6.57 (dt, 1 H, J = 16, 10 Hz), 6.00 (t, 1 H, J = 10 Hz), 5.57–4.97 (comp, 3 H), 3.53 (t, 2 H, J = 7 Hz), 3.33 (br s, 1 H), 2.37 (q, 2 H, J = 7 Hz); ^{13}C NMR δ 132.0, 127.9, 118.0, 62.1, 31.3; mass spectrum, m/e 98.0735 ($C_6H_{10}O$ requires 98.0732), 67 (base).

3(*Z*),5-Hexadienyl Tosylate (18). Freshly purified *p*-toluenesulfonyl chloride (13.01 g, 68.2 mmol) was slowly added to a solution of **17** (5.35 g, 54.6 mmol) in dry CH_2Cl_2 (55 mL) containing pyridine (8.60 g, 110 mmol) at 0 °C. The solution was then stirred at room temperature for 6 h, whereupon the excess solvents were removed under reduced pressure, and the residue was dissolved in cold 1 N HCl (125 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL), and the combined organic layers were washed with cold 1 N HCl (75 mL), saturated $NaHCO_3$ (2 × 75 mL), and saturated brine (1 × 75 mL) and dried ($MgSO_4$). Removal of the ether under reduced pressure afforded 9.36 g (68%) of **18**, which was homogeneous by TLC and ^1H NMR and was employed in subsequent reactions without further purification: ^1H NMR δ 7.70 (d, 2 H, J = 8 Hz), 7.25 (d, 2 H, J = 8 Hz), 6.45 (dt, 1 H, J = 16, 10 Hz), 5.97 (t, 1 H, J = 10 Hz), 5.43–4.98 (comp, 3 H), 3.95 (t, 2 H, J = 8 Hz), 2.52 (q, 2 H, J = 7 Hz), 2.45 (s, 3 H).

***N*-Allyl-*N*-methyl-3(*Z*),5-hexadienylamine (13).** A resealable glass pressure bomb was charged with **18** (1.50 g, 5.95 mmol) and *N*-allylmethylamine (1.27 g, 17.86 mmol) dissolved in ether (2 mL) and heated at 50 °C for 44 h. The vessel was then cooled to 0 °C and opened, and 0.5 N HCl (20 mL) was added. The aqueous solution was washed with ether, neutralized with 0.5 N NaOH saturated with NaCl (20 mL), and extracted with ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), and concentration of the organics under reduced pressure followed by Kugelrohr distillation [50 °C (30 mm)] gave 0.81 g (90%) of pure **13**: ^1H NMR δ 6.53 (dt, 1 H, J = 16, 10 Hz), 6.05–4.93 (comp, 7 H), 2.92 (d, 2 H, J = 6 Hz), 2.25 (comp, 4 H), 2.15 (s, 3 H); mass spectrum, m/e 151.1365 ($C_{10}H_{17}N$ requires 151.1361), 150, 84 (base), 41.

***N*-Methyl-3(*Z*),5-hexadienylamine (19).** **19** was prepared in 58% yield from **18** (4.00 g, 15.9 mmol) and methylamine (7 mL) as described previously for the preparation of *N*-methyl-3(*E*),5-hexadienylamine: bp 98–102 °C (140 mm); ^1H NMR δ 6.57 (dt, 1 H, J = 16, 10 Hz), 5.95 (t, 1 H, J = 10 Hz), 5.52–4.97 (comp, 3 H), 2.65–2.12 (comp, 4 H), 2.33 (s, 3 H), 0.95 (br s, 1 H); mass spectrum, m/e 111.1051 ($C_7H_{13}N$ requires 111.1048), 79, 44 (base).

***N*-(3(*Z*),5-Hexadienyl)-*N*-methylacrylamide (14).** **14** was prepared in 76% yield from acryloyl chloride (1.26 g, 13.9 mmol), **19** (1.01 g, 9.10 mmol), and triethylamine (1.38 g, 13.6 mmol) by the same procedure described previously for the preparation of **7g**. An analytical sample was purified by bulb-to-bulb distillation [120 °C (30 mm)]: IR ν 1645 cm^{-1}; ^1H NMR δ 6.79–5.85 (comp, 4 H), 5.65–5.00 (comp, 4 H), 3.38 (t, 2 H, J = 7 Hz), 2.97 (s, 3 H), 2.42 (q, 2 H, J = 7 Hz); mass spectrum, m/e 165.1152 ($C_{10}H_{15}NO$ requires 165.1154), 98, 55 (base), 44.

***N*-(3-Butenyl)-*N*-methyl-2(*E*),4-pentadienamide (34).** To a solution of pentadienoic acid[27] (0.31 g, 3.11 mmol) and diisopropylethylamine (0.84 g, 3.2 mmol) in dry THF (5 mL) at 0 °C was slowly added ethyl chloroformate (0.35 g, 3.2 mmol) dissolved in dry THF (3 mL). The resulting solution was stirred at 0 °C for an additional 3 h, whereupon a solution of 1-(methylamino)-3-butene[28] (0.26 g, 3.11 mmol) in dry THF (3 mL) was added dropwise. The mixture was allowed to warm gradually to room temperature, and the stirring was continued for 2 h. A minimum quantity of H_2O was added to the reaction mixture to dissolve the salts, and the layers were separated. The aqueous layer was extracted with ether (4 × 20 mL), and the combined organics were washed with 1 N HCl (2 × 10 mL), saturated $NaHCO_3$ (1 × 15 mL), and saturated brine (1 × 15 mL) and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure and purification of the residue by HPLC using EtOAc/hexane (1:1) as the eluent provided 0.36 g (71%) of **26** as a colorless oil: IR ν 1650 cm^{-1}; ^1H NMR δ 7.25 (dd, 1 H, J = 7, 15 Hz), 6.65–6.15 (comp, 2 H), 5.93–4.85 (comp, 5 H), 3.42 (m, 2 H), 2.95 (br s, 3 H), 2.23 (br q, 2 H, J = 7 Hz); mass spectrum, m/e 165.1158 ($C_{10}H_{15}NO$ requires 165.1154), 124, 81 (base).

General Procedure for Preparation of Unsaturated Esters 40–42. The esters **40–42** were prepared by coupling the appropriate alcohols with the corresponding acid chlorides in the presence of 1.1 equiv of triethylamine in CH_2Cl_2 at 0 °C followed by extractive workup with ether.

3(*E*),5-Hexadienyl acrylate (41): 80% yield; bp 84–87 °C (15 mm); IR ν 1725 cm^{-1}; ^1H NMR δ 6.55–4.90 (comp, 8 H), 4.20 (t, 2 H, J = 6 Hz), 2.45 (q, 2 H, J = 6 Hz); mass spectrum, m/e 152.0841 ($C_9H_{12}O_2$ requires 152.0837), 107, 80 (base).

Allyl sorbate (45): 94% yield; bulb-to-bulb distillation, 75–85 °C (oven temperature) (2.0 mm); IR ν 1718 cm^{-1}; ^1H NMR δ 7.17 (m, 1 H), 6.37–5.59 (comp, 4 H), 5.21 (m, 2 H), 4.56 (m, 2 H), 1.83 (d, 3 H, J = 5 Hz); mass spectrum, m/e 152.0840 ($C_9H_{12}O_2$ requires 152.0837), 95, 41 (base).

(27) This procedure is an adaptation of Jessup, P. J.; Roos, J.; Overman, L. E. *Org. Synth.* **1981**, *59*, 1.

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Table II. Summary of Experimental Data for Thermolyses of Trienes

triene	concn, %	solv[a]	temp,[c] °C	time, h	chromat solv ethyl acetate/hexane
7b	1	C[b]	185	60	9:1
7c	1	C[b]	185	60	1:2
7d	1	C[b]	160	96	5:1
7e	1	C[b]	140	24	*d*
7f	1	C[b]	275	48	*d*
7g	0.05	B	85	12	9:1
7h	2	A	80 (25)	2 (20)	1:1.4
13	1	C	250	72	*e*
14	1	C	190	72	*e*
26	1	B[b]	185	18	*d*
34	1	C	140	72	1:2
41	2	C	210	5	1:4
45	1	B[b]	250	120	1:9

[a] A, benzene; B, toluene; C, xylene. [b] 0.1–0.5% of bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide added. [c] Oil bath temperature. [d] Cycloadducts could not be separated by normal- or reverse-phase HPLC or GLC. [e] The mixture of *cis*- and *trans*-hydroisoindoles were separated from the *cis*-hydroisoquinoline by preparative GLC, using 1/4 in. × 2 m SE-30 column.

Thermolyses of Unsaturated Amides, Amines, and Esters. General Procedures. A degassed (three freeze–thaw cycles in vacuo) solution (concentration and solvent given) of the appropriate triene was heated in a silylated, sealed glass tube until the reaction was judged complete by TLC (temperature and time given). The addition of bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide as a radical inhibitor had a beneficial affect in some but not all cases. After cooling to room temperature, the tubes were opened, and the excess solvent was removed under reduced pressure. The crude product mixture was separated by HPLC, using ethyl acetate/hexane (ratio given). The general experimental data are summarized in Table II.

***cis*-1,4,4a,7,8,8a-Hexahydro-2-methyl-3(2*H*)-isoquinolone (9b)**: 53% yield; IR ν 1630 cm^{-1}; ^{1}H NMR δ 5.69 (d, 1 H, J = 10 Hz), 5.53 (d, 1 H, J = 10 Hz), 3.41 (dd, 1 H, J = 12, 6 Hz), 3.12 (dd, 1 H, J = 12, 6 Hz), 2.89 (s, 3 H), 2.73–1.48 (comp, 8 H); ^{13}C NMR δ 169.3, 129.6, 127.0, 52.5, 36.3, 34.5, 32.2, 30.8, 23.5; mass spectrum, m/e, 165.1157 ($C_{10}H_{15}NO$ requires 165.1154) (base), 150.

***trans*-1,4,4a,7,8,8a-Hexahydro-2-methyl-3(2*H*)-isoquinolone (10b)**: 27% yield; IR ν 1625 cm^{-1}; ^{1}H NMR δ 5.70 (br d, 1 H, J = 10 Hz), 5.40 (br d, 1 H, J = 10 Hz), 3.40–1.20 (comp, J = 10 Hz), 2.91 (s, 3 H); ^{13}C NMR δ 169.8, 128.5, 127.5, 55.5, 38.3, 36.3, 36.0, 34.4, 25.4, 25.0; mass spectrum, m/e, 165.1157 ($C_{10}H_{15}NO$ requires 165.1154) (base), 150.

***cis*-1,4,4a,7,8,8a-Hexahydro-2-(2-phenylethyl)-3(2*H*)-isoquinolone (9c)**: 47% yield; IR ν 1621 cm^{-1}; ^{1}H NMR δ 7.15 (s, 5 H), 5.63 (d, 1 H, J = 10 Hz), 5.46 (d, 1 H, J = 10 Hz), 3.48 (m, 2 H), 3.05 (dq, 2 H, J = 6, 12 Hz), 2.92–1.22 (comp, 10 H); ^{13}C NMR δ 169.4, 139.2, 129.6, 128.9, 128.4, 127.0, 126.3, 51.4, 49.2, 36.6, 33.7, 32.0, 31.0, 23.5; mass spectrum, m/e, 255.1626 ($C_{17}H_{21}NO$ requires 255.1623), 239, 164 (base), 136.

***trans*-1,4,4a,7,8,8a-Hexahydro-2-(2-phenylethyl)-3(2*H*)-isoquinolone (10c)**: 24% yield; mp 124–125.5 °C (from benzene–hexane, 1:1); IR ν 1628 cm^{-1}; ^{1}H NMR δ 7.18 (s, 5 H), 5.65 (br d, 1 H, J = 10 Hz), 5.41 (d, 1 H, J = 10 Hz), 3.43 (dd, 2 H, J = 6, 9 Hz), 3.11–1.04 (comp, 12 H); ^{13}C NMR δ 169.6, 139.3, 128.9, 128.5, 127.5, 126.3, 54.3, 49.2, 38.6, 36.3, 35.9, 33.5, 25.4, 25.0; mass spectrum, m/e 255.1631 ($C_{17}H_{21}NO$ requires 255.1623), 164 (base), 136.

***cis*-1,4,4a,7,8,8a-Hexahydro-2-(2-indol-3-ylethyl)-3(2*H*)-isoquinolone (9d)**: 49% yield; mp 148–149 °C (from ethanol); IR ν 1625 cm^{-1}; ^{1}H NMR δ 8.90 (br s, 1 H), 7.51 (m, 1 H), 7.42–6.84 (comp, 4 H), 5.64 (d, 1 H, J = 10 Hz), 5.47 (d, 1 H, J = 10 Hz), 3.62 (overlapping d, 2 H, J = 7 Hz), 3.32–1.32 (comp, 12 H); ^{13}C NMR δ 169.6, 136.5, 129.6, 127.5, 127.1, 122.3, 121.7, 119.1, 118.6, 112.7, 111.4, 51.4, 48.3, 36.7, 32.0, 31.0, 23.5, 23.4, 23.3. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.35; H, 7.55; N, 9.52.

***trans*-1,4,4a,7,8,8a-Hexahydro-2-(2-indol-3-ylethyl)-3-(2*H*)-isoquinolone (10d)**: 25% yield; mp 208–209.5 °C (from ethanol); IR ν 1631 cm^{-1}; ^{1}H NMR δ 9.00 (br s, 1 H), 7.65 (m, 1 H), 7.45–6.92 (comp, 4 H), 5.70 (br d, 1 H, J = 10 Hz), 5.42 (br d, 1 H, J = 10 Hz), 3.65 (overlapping d, 2 H, J = 8 Hz), 3.29–1.17 (comp, 12 H); ^{13}C NMR δ 169.8, 136.4, 128.5, 127.5, 122.1, 121.9, 119.2, 118.7, 118.3, 113.0, 111.3, 54.1, 48.3, 36.3, 35.9, 25.4, 25.0, 23.0, 22.7. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.31; H, 7.51; N, 9.40.

***dl*-Yohimban (38).** A solution of dry benzene (20 mL), **10d** (0.20 g, 0.68 mmol), and freshly distilled $POCl_3$ (0.44 mL, 4.7 mmol) was heated at reflux under N_2 for 3 h. The solution was concentrated under reduced pressure to about 10 mL and cooled. The precipitated iminium salt was collected by suction filtration, washed with dry benzene (5 mL), and dried under high vacuum to give a yellow solid (0.27 g). A mixture of the iminium salt (0.20 g, 0.49 mmol), $NaHCO_3$ (0.25g), and PtO_2 (0.025 g) in ethanol (2.5 mL) was stirred under H_2 (1 atm) for 1 h. The mixture was filtered through glass wool and partitioned between 1% aqueous NaOH (25 mL) and $CHCl_3$ (25 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude **38** was purified by column chromatography on neutral alumina with a mixture of ethyl acetate and hexane (3:1) followed by recrystallization from 95% ethanol to give a white solid: 0.11 g (77%); mp 180–182 °C (lit.[14a] mp 181.5–183 °C, lit.[14b] 182.5–183.5 °C); ^{13}C NMR δ 136.1, 135.2, 127.6, 121.2, 119.3, 118.1, 110.7, 108.1, 62.1, 60.3, 53.2, 42.0, 37.0, 32.9, 30.4, 26.5, 26.0, 21.8.

Δ^{16}-Didehydroyohimban (39).[29] To a solution of the iminium salt (prepared as above) (0.24 g) in dry MeOH (15 mL) at −78 °C under N_2 was added $NaBH_4$ (0.50 g, 1.32 mmol) in five portions. Following the addition, the mixture was allowed to warm to room temperature and then heated at reflux for 90 min. The solution was cooled and concentrated to dryness under reduced pressure. Water (30 mL) was added to the white residue and the mixture was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an off-white solid. Recrystallization from 95% ethanol gave 0.12 g (71% from **10d**) of pure **39** as white crystals: mp 129–131 °C; IR ν 3500, 1645 cm^{-1}; ^{1}H NMR δ 7.86 (br s, 1 H), 7.43 (m, 1 H), 7.30–6.93 (comp, 3 H), 5.68 (br d, 1 H, J = 12 Hz), 5.47 (br d, 1 H, J = 11 Hz), 3.43–2.37 (comp, 6 H), 3.40–1.06 (comp, 9 H); ^{13}C NMR δ 136.1, 135.0, 130.1, 127.4, 121.1, 119.3, 118.1, 110.8, 108.0, 61.6, 60.4, 53.0, 40.6, 39.1, 35.8, 26.4, 25.6, 21.8. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.96; N, 10.06. Found: C, 81.66; H, 8.05; N, 9.99.

***cis*-3,4,4a,7,8,8a-Hexahydro-1(2*H*)-isoquinolone (9g)**: 55% yield; mp 136–137 °C (from 3:1 ethyl acetate–hexane); IR ν 3400, 1658 cm^{-1}; ^{1}H NMR δ 7.47 (br s, 1 H), 5.81 (br d, 1 H, J = 10 Hz), 5.52 (br d, 1 H, J = 10 Hz), 3.23 (dt, 2 H, J = 3, 6 Hz), 2.54 (m, 2 H), 2.19–1.48 (comp, 7 H), 7.47 (br s, 1 H); ^{13}C NMR δ 175.1, 129.3, 128.4, 40.4, 40.0, 32.9, 26.8, 23.6, 23.4; mass spectrum, m/e 151.1001 ($C_9H_{13}NO$ requires 151.0997) (base), 150, 136, 122, 93, 79.

***trans*-3,4,4a,7,8,8a-Hexahydro-1(2*H*)-isoquinolone (10g)**:

(29) Reduction of **39** by catalytic hydrogenation afforded (*dl*)-yohimban (**38**).

8% yield; mp 201–202 °C (from 3:1 ethyl acetate–hexane); IR ν 3400, 1661 cm^{-1}; ^{1}H NMR δ 6.15 (br s, 1 H), 5.72 (br d, 1 H, J = 10 Hz), 5.53 (br d, 1 H, J = 10 Hz), 3.37 (m, 2 H), 2.60–1.11 (comp, 8 H); ^{13}C NMR δ 174.3, 129.8, 128.6, 43.9, 41.6, 36.3, 29.0, 26.0, 22.5; mass spectrum, m/e 151.0994 ($C_{19}H_{13}NO$ requires 151.0997) (base), 150, 136, 122, 93, 79.

***cis*-2-Methyl-3,4,4a,7,8,8a-hexahydro-1(2*H*)-isoquinolone (9h)**: 71% yield; bulb-to-bulb distillation, 110 °C (oven temperature) (0.25 mm); IR (film) ν 1640 cm^{-1}; ^{1}H NMR δ 5.80 (br d, 1 H, J = 10 Hz), 5.51 (br d, 1 H, J = 10 Hz), 3.21 (overlapping d, 2 H, J = 6 Hz), 2.90 (s, 3 H), 2.52 (m, 2 H), 2.18–1.60 (comp, 8 H); ^{13}C NMR δ 172.3, 129.3, 128.4, 48.3, 40.4, 34.8, 27.1, 23.8, 23.7; mass spectrum, m/e 165.1151 ($C_{10}H_{15}NO$ requires 165.1154) (base), 150, 136, 110, 79.

***trans*-2-Methyl-3,4,4a,7,8,8a-hexahydro-1(2*H*)-isoquinolone (10h)**: 11% yield; IR ν 1635 cm^{-1}; ^{1}H NMR δ 5.71 (br d, 1 H, J = 10 Hz), 5.48 (br d, 1 H, J = 10 Hz), 3.39 (m, 1 H), 3.27 (d, 1 H, J = 3 Hz), 2.90 (s, 3 H), 2.52 (m, 1 H), 2.40–1.10 (comp, 7 H); ^{13}C NMR δ 171.9, 129.8, 128.6, 49.3, 44.2, 36.5, 34.4, 29.5, 26.2, 23.0; mass spectrum, m/e 165.1151 ($C_{10}H_{15}NO$ requires 165.1154) (base), 136, 79.

***cis*-1,2,3,4,4a,7,8,8a-Octahydro-2-methylisoquinoline (9e).** A solution of the lactam **9b** (0.75 g, 4.55 mmol) in dry ether (25 mL) containing $LiAlH_4$ (0.43 g, 11.36 mmol) was stirred at room temperature for 12 h. The excess $LiAlH_4$ was destroyed by sequential addition of H_2O (0.4 mL) and 15% aqueous NaOH (1.0 mL). The precipitated solids were removed by suction filtration through Celite and washed with CH_2Cl_2 (75 mL). The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to give 0.64 g (93%) of **9e** as a clear, colorless oil: IR ν 1605 cm^{-1}; ^{1}H NMR δ 5.52 (m, 2 H), 2.83 (br t, 2 H, J = 11 Hz), 2.26 (s, 3 H), 2.19–1.10 (comp, 10 H); ^{13}C NMR δ 130.9, 127.0, 59.3, 54.4, 46.9, 33.6, 33.4, 30.5, 24.6, 24.2; mass spectrum, m/e 151.1363 ($C_{10}H_{17}N$ requires 151.1361), 150 (base), 136, 122.

***trans*-1,2,3,4,4a,7,8,8a-Octahydro-2-methylisoquinoline (10e).** **10e** was prepared in 95% yield from **10b** by reduction with $LiAlH_4$ as described for **9e**: IR ν 1605 cm^{-1}; ^{1}H NMR δ 5.56 (m, 2 H), 2.53–1.36 (comp, 12 H), 2.21 (s, 3 H); ^{13}C NMR δ 130.7, 126.9, 62.2, 56.5, 46.3, 40.2, 39.3, 32.0, 26.8, 25.6; mass spectrum, m/e 151.1365 ($C_{10}H_{17}N$ requires 151.1361) (base), 136, 122.

***cis*-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-methylisoquinoline (11).** A mixture of amine **9e** (0.20 g, 1.33 mmol) and 5% Pd/C (0.02 g) in 100% ethanol (2.0 mL) containing excess HCl was stirred under hydrogen (1 atm) at room temperature for 10 h. The reaction mixture was filtered through glass wool, concentrated to a viscous oil, and dissolved in H_2O (5 mL). This solution was made basic with NaOH with NaOH pellets at 0 °C, saturated with NaCl, and extracted with ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a clear oil: 0.19 g (94%); picrate mp 209–210 °C (from ethanol) (lit.[8] mp 210 °C); ^{1}H NMR δ 2.68–2.30 (comp, 2 H). 2.21 (s, 3 H), 2.12–1.04 (comp, 14 H).

***trans*-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-methylisoquinoline (12).** **12** was prepared in 98% yield from **10e** by hydrogenation over 5% Pd/C as described for **11**: picrate mp 234–236 °C (from ethanol) (lit.[8] mp 234–237 °C); ^{1}H NMR δ 2.74 (br t, 2 H, J = 11 Hz), 2.22 (s, 3 H), 2.06–0.53 (comp, 14 H).

(3a*R,5*S**,7a*R**)-2,5-Dimethyl-1,3,3a,4,5,6,7,7a-octahydroisoindol-1-one (29)**: mp 92–93.5 °C; IR ν 1675 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.43 (dd, 1 H, J = 5.3, 9.4 Hz), 3.16 (s, 3 H), 2.76 (d, 1 H, J = 9.4 Hz), 2.43 (br t, 1 H, J = 6.2 Hz), 2.27 (m, 2 H), 1.69 (m, 1 H), 1.48 (m, 2 H), 1.27 (m, 1 H), 0.84 (d, 3 H, J = 6.5 Hz), 0.81 (comp, 2 H); ^{13}C NMR δ 175.4, 54.3, 41.2, 37.8, 33.0, 31.3, 30.5, 30.1, 23.3, 22.7; mass spectrum, m/e 167.1313 ($C_{10}H_{17}NO$ requires 167.1310) (base), 152, 110, 98, 81.

(3a*S,5*S**,7a*R**)-2,5-Dimethyl-1,3,3a,4,5,6,7,7a-octahydroisoindol-1-one (30)**: IR ν 1685 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.23 (dd, 1 H, J = 7.5, 9.6 Hz), 3.17 (dd, 1 H, J = 9.6, 9.8 Hz), 2.83 (s, 3 H), 2.51 (m, 1 H), 2.30 (br d of t, 1 H, J = 6.5, 9.8, 10.2 Hz), 1.95 (m, 1 H), 1.58 (m, 2 H), 1.32 (m, 2 H), 1.02 (m, 2 H), 0.93 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 177.8, 52.2, 41.5, 33.5, 31.6, 31.3, 29.7, 27.5, 23.6, 21.2; mass spectrum, m/e 167.1305 ($C_{10}H_{17}NO$ requires 167.1310) (base), 152, 110, 98, 81.

(3a*S,5*S**,7a*S**)-2,5-Dimethyl-1,3,3a,4,5,6,7,7a-octahydroisoindol-1-one (31)**: IR ν 1675 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.75 (AB q, 2 H, J = 9.5 Hz), 3.02 (s, 3 H), 2.39 (m, 2 H), 2.16 (m, 1 H), 1.83 (comp, 4 H), 1.25 (comp, 3 H), 1.03 (d, 3 H, J = 6.5 Hz), 1.01 (m, 1 H); ^{13}C NMR δ 175.9, 51.8, 41.3, 33.7, 31.2, 31.1, 29.3, 27.5, 23.1, 20.7; mass spectrum, m/e 167.1314 ($C_{10}H_{17}NO$ requires 167.1310) (base), 152, 110, 98, 81.

(3a*S,5*S**,7a*R**)-2,5-Dimethyl-1,3,3a,4,5,6,7,7a-octahydroisoindole (32)**: ^{1}H NMR (200 MHz, C_6D_6) δ 2.70 (dd, 1 H, J = 6.0, 9.0 Hz), 2.64 (d, 1 H, J = 9.0 Hz), 2.46 (t, 1 H, J = 9.0 Hz), 2.38 (dd, 1 H, J = 1.5, 9.0 Hz), 2.32 (s, 3 H), 2.23 (m, 1 H), 1.75 (m, 1 H), 1.65–1.30 (comp, 6 H), 1.16 (m, 1 H), 0.82 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (C_6D_6) δ 62.9, 58.5, 43.2, 38.5, 37.9, 35.0, 33.8, 28.9, 27.4, 22.6; mass spectrum, m/e 153.1515 ($C_{10}H_{19}NO$ requires 153.1517), 138, 57 (base).

(3a*R,6*S**,7a*R**)-2,6-Dimethyl-1,3,3a,4,5,6,7,7a-octahydroisoindol-1-one (33)**: IR (film) ν 1690 cm^{-1}; ^{1}H NMR δ 3.43 (dd, 1 H), J = 5.3, 9.5 Hz), 2.85 (s, 3 H), 2.79 (d, 1 H, J = 9.5 Hz), 2.50 (br t, 1 H, J = 5.8 Hz), 2.23 (br t, 1 H, J = 5.8 Hz), 2.16 (m, 1 H), 1.50 (m, 1 H), 1.39–0.95 (comp, 4 H), 0.89 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 175.7, 54.2, 42.3, 32.8, 32.2, 31.8, 30.0, 29.1 (2 C), 22.3; mass spectrum, m/e 167.1314 ($C_{10}H_{17}NO$ requires 167.1310), 152, 110, 98 (base).

***cis*-2-Methyl-3,4,4a,5,6,8a-hexahydro-1(2*H*)-isoquinolone (35)**: 25% yield; IR ν 1620 cm^{-1}; ^{1}H NMR δ 5.83 (d, 1 H, J = 10 Hz), 5.68 (d, 1 H, J = 10 Hz), 3.28 (overlapping d, 2 H, J = 6 Hz), 3.03 (m, 1 H), 2.90 (s, 3 H), 2.35–1.07 (comp, 7 H); ^{13}C NMR δ 170.9, 127.3, 126.1, 48.5, 43.0, 34.8, 31.4, 25.4, 25.3, 22.1; mass spectrum, m/e 165.1156 ($C_{10}H_{15}NO$ requires 165.1154) (base), 112, 79.

***trans*-2-Methyl-3,4,4a,5,6,8a-hexahydro-1(2*H*)-isoquinolone (36)**: 14% yield; IR ν 1625 cm^{-1}; ^{1}H NMR δ 6.23 (m, 1 H), 5.68 (m, 1 H), 3.30 (m, 2 H), 2.90 (s, 3 H), 2.58 (br s, 1 H), 2.24–1.07 (comp, 7 H); ^{13}C NMR 170.7, 127.3, 124.9, 49.5, 45.7, 35.1, 34.5, 29.8, 29.4, 25.0; mass spectrum, m/e 165.1159 ($C_{10}H_{15}NO$ requires 165.1154) (base), 79.

***cis*-4a,7,8,8a-Tetrahydro-1-isochromanone (43)**: 36% yield; IR ν 1725 cm^{-1}; ^{1}H NMR δ 5.85 (m, 1 H), 5.50 (m, 1 H), 4.23 (t, 2 H, J = 6 Hz), 2.75 (m, 2 H), 2.31–1.50 (comp, 6 H); ^{13}C NMR δ 174.7, 130.4, 129.8, 68.5, 40.4, 33.0, 29.5, 24.8, 23.5; mass spectrum, m/e 152.0840 ($C_9H_{12}O_2$ requires 152.0837), 124, 91, 79 (base).

***trans*-4a,7,8,8a-Tetrahydro-1-isochromanone (44)**: 4% yield; IR ν 1725 cm^{-1}; ^{1}H NMR δ 5.90–5.25 (comp, 2 H), 4.30 (m, 2 H), 2.60–1.10 (comp, 8 H); ^{13}C NMR δ 173.8, 130.4, 129.5, 69.1, 43.8, 35.7, 30.4, 26.6, 23.7; mass spectrum, m/e 152.0840 ($C_9H_{12}O_2$ requires 152.0837), 124, 79 (base).

(3a*S,5*R**,7a*S**)-5-Methyl-1,3,3a,4,5,7a-hexahydroisobenzofuran-1-one (46)**: 17% yield; IR ν 1777 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.86 (m, 1 H), 5.75 (br d, 1 H, J = 10), 4.39 (dd, 1 H, J = 7, 9 Hz), 4.04 (d, 1 H, J = 9 Hz), 3.10 (m, 1 H), 2.67 (m, 1 H), 2.19 (m, 1 H), 1.86 (m, 1 H), 1.13 (m, 1 H), 1.03 (d, 3 H, J = 7 Hz); mass spectrum, m/e 152.0840 ($C_9H_{12}O_2$ requires 152.0837), 108, 93 (base).

(3a*R,5*R**,7a*S**)-5-Methyl-1,3,3a,4,5,7a-hexahydroisobenzofuran-1-one (47)**: 59% yield; IR ν 1770 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.88 (m, 1 H), 5.74 (m, 1 H), 4.39 (dd, 1 H, J = 7, 9 Hz), 4.05 (dd, 1 H, J = 5.7, 9 Hz), 3.12 (m, 1 H), 2.87 (m, 1 H), 2.28 (m, 1 H), 1.74 (m, 1 H), 1.51 (m, 1 H), 1.05 (d, 3 H, J = 7.2 Hz); mass spectrum, m/e 152.0834 ($C_9H_{12}O_2$ requires 152.0837), 108, 93 (base).

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Registry No. **6c**, 5263-58-1; **6d**, 87463-19-2; **7a**, 87463-20-5; **7b**, 87463-21-6; **7c**, 87463-22-7; **7d**, 87463-23-8; **7e**, 87463-24-9; **7f**, 87463-27-2; **7g**, 87463-25-0; **8**, 36206-73-2; (±)-**9b**, 87463-35-2; (±)-**9c**, 87463-37-4; (±)-**9d**, 87463-38-5; (±)-**9e**, 87463-45-4; (±)-**9g**, 87463-41-0; (±)-**9h**, 87463-43-2; (±)-**10b**, 87463-36-3; (±)-**10c**, 87481-46-7; (±)-**10d**, 87463-39-6; (±)-**10e**, 87463-46-5; (±)-**10g**, 87463-42-1; (±)-**10h**, 87463-44-3; (±)-**11**, 87463-47-6; (±)-**12**, 87463-48-7; **13**, 87463-29-4; **14**, 87463-31-8; **15**, 3393-45-1; **16**, 56963-54-3; **17**, 2196-20-5; **18**, 87463-28-3; **19**, 87463-30-7; **26**, 87463-26-1; (±)-**29**, 87463-49-8; (±)-**30**, 87463-50-1; (±)-**31**, 87463-51-2; (±)-**32**, 87463-52-3; (±)-**33**, 87463-53-4; **34**, 87463-32-9; (±)-**35**, 87463-54-5; (±)-**36**, 87463-55-6; (±)-**38**, 10283-60-0; (±)-**39**,

87463-40-9; **40**, 87463-33-0; **41**, 87463-34-1; (±)-**43**, 87481-47-8; (±)-**44**, 87463-56-7; **45**, 7493-75-6; (±)-**46**, 87463-57-8; (±)-**47**, 87463-58-9; (±)-yohimbaniminium ion, 87481-45-6; (*E*)-2,4-pentadienoic acid, 21651-12-7; (*E*)-*N*-methyl-3,5-hexadien-1-amine, 87463-59-0; phenethylamine, 64-04-0; tryptophyl bromide, 55982-76-8; allylamine, 107-11-9; *N*-allyl-*N*-methylamine, 627-37-2; acryloyl chloride, 814-68-6; diisopropylethylamine, 7087-68-5; methyltriphenylphosphonium bromide, 1779-49-3.

A Series of (2*S*)-2-*O*-Protected-2-hydroxypropanals (L-Lactaldehydes) Suitable for Use as Optically Active Intermediates

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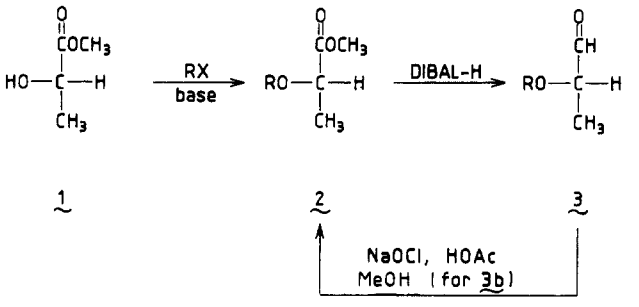
The synthesis and properties of a series of (2*S*)-2-*O*-protected-2-hydroxypropanals, where the protecting groups are *tert*-butyldimethylsilyl (**3a**), *tert*-butyldiphenylsilyl (**3b**), and (methoxyethoxy)methyl (**3c**), are described. A ^{1}H NMR spectroscopic method of determining the optical purity of methyl L-lactate is described.

Short-chain, highly functionalized, optically active compounds are in considerable demand as starting materials in the synthesis of complex natural products via the newer methods developed in the area of stereochemically controlled organic reactions.[1-3] In this laboratory the need for both enantiomers of a protected 2-hydroxypropanal for the synthesis of the possible diastereomers of EHNA,[4,5] a semi-tight-binding inhibitor of adenosine deaminase, was satisfied by deriving both (2*S*)- and (2*R*)-2-benzyloxypropanals from L-rhamnose and D-mannose, respectively. Upon the identification of the biologically more potent isomer as the 2*S*,3*R* isomer,[4] an acute need for its precursor, an *O*-protected (2*S*)-hydroxypropanal developed. Hence a shorter route to this intermediate was sought.

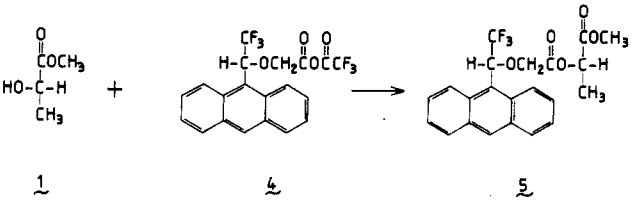
The most logical source of (2*S*)-2-hydroxypropanal derivatives is from (2*S*)-2-hydroxypropionic acid (L-lactic acid), which is available from fermentation of D-glucose using *Lactobacillus delbrueckii*.[6] We chose for our studies a commercial preparation of 2-hydroxypropanoic acid methyl ester (**1**, methyl L-lactate).[7] Inasmuch as the optical rotations for both L-lactic acid and its methyl ester **1** are reported to be low [i.e., $[\alpha]^{22}_D$ +2.67° (*c* 2.5, water)[8] and $[\alpha]^{26}_D$ −8.25° (neat),[9] respectively, for L-lactic acid and **1**], optical methods for determination of the optical purity of the commercial sample were abandoned in favor of a more direct method. Based on the work of Pirkle and Simmons,[10] the optically active mixed anhydride **4** was reacted with **1** in pyridine to give the (trifluoromethyl)anthrylmethyl derivative **5** (Scheme I and II). The product **5** was isolated from the crude reaction mixture by column chromatography, with care being taken to include all material that eluted in the zone for **5** (or its possible diastereomeric contaminant) so that no possible diastereomeric separations would occur.[11] Examination of **5** by

Scheme I



Series	R
a	$Me_2(Me_3C)Si$
b	$Ph_2(Me_3C)Si$
c	$MeOCH_2CH_2OCH_2$
d	$PhCH_2$ (for 3 only)

Scheme II



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(11) The precautions taken in the chromatographic step cannot be overemphasized. Both diastereomeric products (i.e., **5** and its diastereomer from (2*R*)-hydroxypropanoic methyl ester) have been shown to be inseparable by both silica gel (adsorption) and octadecylsilyl (reverse-phase) high-pressure liquid chromatography. This column chromatographic step is necessary to purify **5** from **1** and **4**, as well as decomposition products of **4** and **5**.

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