# Thermal and Lewis Acid Catalyzed Diastereoselective Intramolecular Diels−Alder Reaction on α,β-Unsaturated Amides Derived from (−)-8-Aminomenthol

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*Received March 11, 1999*

Stereochemical aspects of the intramolecular Diels−Alder reaction on perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol bearing α,β-unsaturated amides and the dienic component attached at C-2 are described. The thermal cyclization of 2-(2′-furyl) derivatives **2**, **6**, and **7** exclusively afforded mixtures of *exo* adducts. The product selectivity was highly dependent on the solvent of the reaction. In $CH_2Cl_2$, the kinetic products **3**, **8**, and **9** always predominated, whereas in hexane or toluene, less polar solvents, the thermodynamic adducts **4**, **10**, and **11** were formed as major diastereoisomers. In cyclizations catalyzed with equimolar or 2-fold excess of Lewis acid, the kinetic stereiosomers were predominant. Some Lewis acids catalyzed the reaction, but diethylaluminum chloride was the most effective. The cyclization on the perhydro-1,3-benzoxazine **13**, bearing an open dienic component, was much less stereoselective, and a mixture of two *exo* and two *endo* possible stereoisomers were formed. Elimination of the menthol appendage in two steps by reductive ring opening of the N,O-acetal moiety and oxidation−elimination yielded enantiomerically pure tetrahydroisoindoline derivatives.

## Introduction

The intramolecular Diels−Alder reaction provides a facile and stereoselective access to hetero- and carbopolycyclic structures, and consequently it has been extensively studied.[1] Among different dienic components, furane derivatives have received attention in recent years, and different methodologies to enlarge the limits of this reaction have been recently proposed.[2] In this respect, the effects of the solvent,[3] the substituent at the furane ring[4] or at the dienophile,[5] and the size of the linkage between the two components[6] on the reaction ratio have been well studied. However, the asymmetric version of the Diels−Alder reaction using furan as dienophile is less documented.[7]

Recently, we have reported[8] the synthesis of enantiopure epoxy tetrahydroisoindolines **5** and *ent*-**5** by intramolecular Diels−Alder reaction on the chiral perhydro-1,3-benzoxazine **2** in excellent chemical yield and good de (Figure 1). The reaction is reversible and easily occurs at 0 °C, leading to the kinetically controlled adduct **3** as major stereoisomer. Although the cycloaddition on **2** shows a total *exo*:*endo* selectivity, the ratio of diastereoisomers depends on the nature of the solvent, changing from 71:29 (**3**:**4**) in $CH_2Cl_2$ to 22:78 in hexane.

We present now a full account on the influence in the stereoselectivity of the substituents at the dienophile, the catalyses by Lewis acids, and the behavior of structures with an open dienic component.

## Results and Discussion

The starting chiral 2-(α-furyl)-3-acryloyl-1,3-benzoxazine **2** was prepared by acylation of **1**, in turn obtained

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10.1021/jo9904462 CCC: $18.00 
Published on Web 06/11/1999

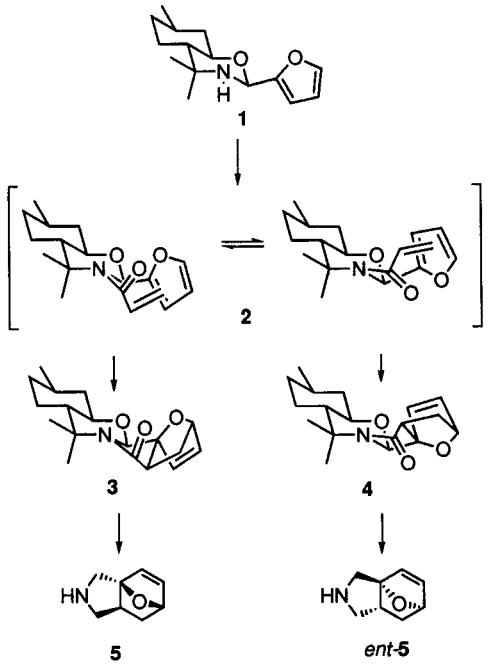


**Figure 1.**

**Table 1. Diels−Alder Reactions of 2 in Different Conditions**

| entry | solvent | Lewis acid (equiv) | temp (°C) | time (h) | yield (%)[a] | products (dr)[b] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | none | 20 | 15 | 96 | **3** (69) **4** (31) |
| 2 | $CH_2Cl_2$ | $ZnCl_2$ (1.1) | 20 | 15 | 86 | **3** (68) **4** (32) |
| 3 | $CH_2Cl_2$ | Ti $(OiPr)_4$ (1.1) | 0 | 120 | 96 | **3** (63) **4** (37) |
| 4 | $CH_2Cl_2$ | $TiCl_4$ (0.5) | 0 | 5 | 31 | **3** (71) **4** (29) |
| 5 | $CH_2Cl_2$ | $BF_3OEt_2$ (2.0) | −23 | 520 | 57 | **3** (78) **4** (22) |
| 6 | $CH_2Cl_2$ | $Et_2AlCl$ (0.2) | −23 | 310 | 94 | **3** (78) **4** (22) |
| 7 | $CH_2Cl_2$ | $Et_2AlCl$ (0.5) | −23 | 310 | 92 | **3** (79) **4** (21) |
| 8 | $CH_2Cl_2$ | $Et_2AlCl$ (1.0) | −23 | 265 | 93 | **3** (81) **4** (19) |
| 9 | $CH_2Cl_2$ | $Et_2AlCl$ (2.0) | −23 | 215 | 96 | **3** (85) **4** (15) |
| 10 | $CH_2Cl_2$ | $Et_2AlCl$ (2.0) | 20 | 6 | 90 | **3** (77) **4** (23) |
| 11 | $CH_2Cl_2$ | $AlCl_3$ (2.0) | −23 | 385 | 91 | **3** (77) **4** (23) |
| 12 | $CH_2Cl_2$ | $Me_3Al$ (2.0) | −23 | 430 | 96 | **3** (76) **4** (24) |
| 13 | hexane | none | 20 | 15 | 96 | **3** (22) **4** (78) |
| 14 | hexane | $Et_2AlCl$ (0.2) | −23 | 430 | 92 | **3** (40) **4** (60) |
| 15 | hexane | $Et_2AlCl$ (0.5) | −23 | 430 | 94 | **3** (60) **4** (40) |
| 16 | hexane | $Et_2AlCl$ (1.0) | −23 | 430 | 88 | **3** (80) **4** (20) |
| 17 | hexane | $Et_2AlCl$ (2.0) | −23 | 430 | 96 | **3** (80) **4** (20) |
| 18 | toluene | none | 20 | 14 | 90 | **3** (38) **4** (62) |
| 19 | toluene | $Et_2AlCl$ (0.2) | −23 | 385 | 93 | **3** (45) **4** (55) |
| 20 | toluene | $Et_2AlCl$ (2.0) | −23 | 335 | 95 | **3** (68) **4** (32) |

[a] Yields refer to pure compounds after column chromatography. [b] Diastereomeric ratios were determined by integration of the signals in the $^1H$ NMR spectra in the reaction mixtures.

by condensation of (−)-8-aminomenthol with furfural. The acylation was carried out with acryloyl chloride at 0 °C, in the presence of triethylamine, using methylene chloride as solvent. In these conditions, compound **2** was not isolated because it immediately cyclized to a mixture of *exo* diastereoisomers **3** and **4** (71:29, 88%). In contrast, when the reaction was carried out in hexane, the stereoselection was reversed and the diastereisomers **3** and **4** were obtained in a 22:78 ratio (98% total yield) (entries 1 and 13 in Table 1).

Because our first concern was to control and improve the stereoselectivity of the cyclization process, we initiated a study on the influence of some Lewis acids of different hardness in the cycloaddition of **2**; the results are collected in Table 1. The first general conclusion derived from these data is that, as previously reported,[9] the reaction occurs at lower temperature than for the uncatalyzed reaction, although the starting product was recovered unchanged after stirring for a long period of time at −23 °C in the presence of titanium tetrachloride or at −78 °C with diethylaluminum chloride.

The use of Lewis acids of moderate acidity, such as zinc or titanium derivatives, did not affect the stereoselectivity of the cycloaddition when methylene chloride was used as solvent (compare entry 1 versus entries 2−4 in Table 1). Nevertheless, the presence of boron trifluoride etherate, diethylaluminum chloride, or aluminum trichloride, stronger Lewis acids,[10] greatly increased the diastereofacial discrimination. The improvement of the diastereomeric ratios were noted even when a substoichiometric quantity of acid was employed (compare entries 6 and 7 versus entry 1), but the best results were obtained by addition of 2-fold excess of diethylaluminum chloride (entry 9).

The reaction temperature also influences the reaction. At room temperature, the reaction was much faster than at −23 °C, but the facial discrimination diminished (compare entries 9 versus 10).

The effect of the Lewis acid has been shown to be much more critical when hexane is used as the reaction solvent. First of all, the presence of diethylaluminum chloride allowed the reaction to proceed at −23 °C, whereas in the absence of the catalyst, the cyclization occurred only at room temperature. In addition, the ratio of diastereoisomers **3**:**4** was changed in favor of the kinetic isomer **3** with the amount of Lewis acid, moving from 22:78 (**3**:**4**) in the absence of catalyst to 80:20 when the reaction was carried out in the presence of equimolar or 2-fold excess of the aluminum derivative (entries 13−17 in Table 1). The same trends were observed when the solvent was toluene (entries 18−20).

The cyclization of α- and β-substituted acrylamides was studied in compounds **6** and **7** (Scheme 1). Methacrylamide **6** was prepared by reaction of **1** with methacryloyl chloride and TMEDA in methylene chloride at 0 °C, whereas **7** was obtained by stirring a mixture of **1**, crotonyl chloride, and pyridine in $CH_2Cl_2$ at 0 °C. It is noteworthy that although crotonylamide **7** can be isolated and characterized, it was not possible to isolate **6** because it cyclized up to 0 °C, and its formation can only be followed by TLC.

Cyclization of methacryloyl amide **6** was much slower than that of the acryloyl derivative **2** (compare entries 1 and 2 in Table 2 versus entries 9 and 13 in Table 1). In hexane as solvent, compound **2** was completely cyclized after 15 h at room temperature, but it was necessary to stir for 130 h to get the total cyclization of **6**. In these conditions, the reaction showed a very low degree of stereoselection as an almost equimolar mixture of diastereoisomers **8** and **10** was obtained. By contrast, in the catalyzed cycloaddition, a good level of stereoselection was maintained. The behavior of crotonyl amide **7** was similar to that observed for **6**. As expected, it reacted slower than **4**, but the stereochemical results were very coincident with those obtained for the acrylamide derivative (compare entries 3−5 in Table 2 versus 13, 18, and 9 in Table 1).

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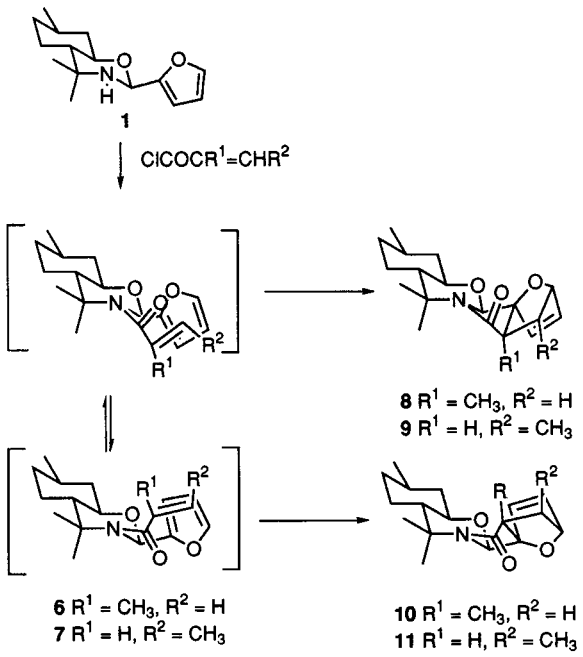
**Scheme 1**




The cycloaddition of perhydro-1,3-benzoxazines bearing an open dienic component was studied on compound **13**, prepared as outlined in Scheme 2. Condensation of (−)-8-aminomenthol with *E*,*E*-2,4-heptadienal, in benzene at room temperature, give the N-unsubstituted perhydro-1,3-benzoxazine **12** in 90% yield. Treatment of **12** with acryloyl chloride and TMDA at room temperature yielded **13**, which could not be isolated because it immediately cyclized to a mixture of the four possible diastereomers **14**−**17** (Scheme 2).

Table 3 summarizes the results obtained in the cyclization of **13** depending on the experimental conditions. It is worthy to note that in this case, both *exo* and *endo* adducts were formed and that the regioselectivity was poor and unaffected by the experimental conditions. The ratio of *exo*/*endo* regioisomers remained practically constant (53−54/47−46) for all of the reactions tested. In addition, the facial discrimination for the *endo* pathway was moderate, and the experimental conditions had little effect on the stereoselectivity for this cyclization mode. By contrast, the *exo* cyclization pathway was profoundly affected by the reaction conditions. In hexane at room temperature or toluene at reflux (entries 2 and 3 in Table 3), **13** cyclized to a mixture of *trans-exo* adducts **14** and **15** with very low stereocontrol, whereas in methylene chloride at −23 °C, in the presence of diethyl aluminum chloride, the all-trans *exo* adduct **14** was formed with good control of facial discrimination.

Diastereoisomers formed in each reaction were separated by flash chromatography, and their stereochemistry was determined at this stage. Thus, the absolute stereochemistry for **3** was established by X-ray crystallography[8] as 3*S*,4*aR*,11*bS* for the newly created stereocenters in the epoxy tetrahydroisoindolone system. The assignation of the contrary configuration at these stereocenters for the minor diastereosiomer **4** was made by chemical correlation (vide infra). The stereochemistry for the major diastereoisomers **8** (3*S*,4*aR*,11*bS*) and **9** (3*R*,4*R*,4*aR*,11*bS*) resulting from the cyclization of **6** and **7** respectively was assigned on the basis of the chemical shift for the hydrogen attached to the N,O-acetalic carbon atom. In this respect, it is noteworthy that the resonance of this proton in the major isomers **3**, **8**, and **9** appears downfield (ca. 0.2 ppm) from that for the minor components **4**, **10**, and **11**, respectively.

COSY and NOESY experiments allowed the assignment of the configuration for the major all-*trans exo*-**14** as 3*R*,4*aR*,11*bR* and for the minor all-*cis endo*-**17** (3*S*,4*aR*,11*bS*) isomers obtained from the cyclization of **13**.

The transformation of the adducts **3**, **4**, **8**−**11**, and **14**−**17** into the final tetrahydroisoindoline derivatives was performed in two steps. Treatment of adducts with aluminum hydride[11] in THF at −10 °C for 10 min led to amino alcohols **18**−**27** in good to excellent yields (Scheme 3), in a process that implies the reductive ring opening of the N,O-acetal moiety and the reduction of the amide group. The elimination of the menthol appendage was carried out by oxidation[12] with PCC of the amino alcohols to the aminomenthone derivatives, followed by elimination with a 2.5 M solution of KOH in THF/MeOH/ $H_2O$ (2/1/1).[13] This protocol allowed the isolation of the final enantiopure tetrahydroisoindoline derivatives **5** and **28**−**31** in good yields and (+)-pulegone, which is the starting compound to prepare the (−)-8-aminomenthol[14] used as chiral adjuvant.

The structure of the final product led us to assign the stereochemistry for adducts **4**, **10**, **11, 15,** and **17**. In fact, spectral, analytical, and optical rotation data showed that the epoxy terahydroisoindolines obtained from **3**, **8**, and **9** are enantiomers to those obtained from **4**, **10**, and **11**, and consequently the configuration of the newly formed stereocenters in these compounds were 3*R*,4*aS*,11*bR* for **4**, 3*R*,4*aS*,11*bR* for **10**, and 3*S*,4*S*,4*aS*,11*bR* for **11**. In the same way, the enantiomeric relationship between the tetrahydroisoindolines resulting from **14** and **17** and those obtained from **15** and **16** respectively, made it possible to establish the configurations of 3*S*,4*aS*,11*bS* for **15** and 3*R*,4*aS*,11*bR* for **16**.

It is also noticeable that cycloaddition of furane derivatives is reversible. We have found that the major diastereoisomers **3**, **8**, and **9**, formed in the reaction in $CH_2Cl_2$ or in any solvent in the presence of Lewis acid, were the kinetically controlled products. After isolation, they were transformed by refluxing in Decalin for 24 h into the same mixture with **4**, **10**, and **11**, obtained as major components in the reaction carried out in hexane under thermodynamic control. This fact had also been observed for some related structures.[15]

The regiospecific formation of *exo* adducts for the furane derivatives[16] is a consequence of the constraints imposed by the connecting bridge of the reacting functions and the fact that the *exo* orientation is energetically more favorable than *endo* in these substrates.[9b] In contrast, the formation of both *exo* and *endo* regioisomers

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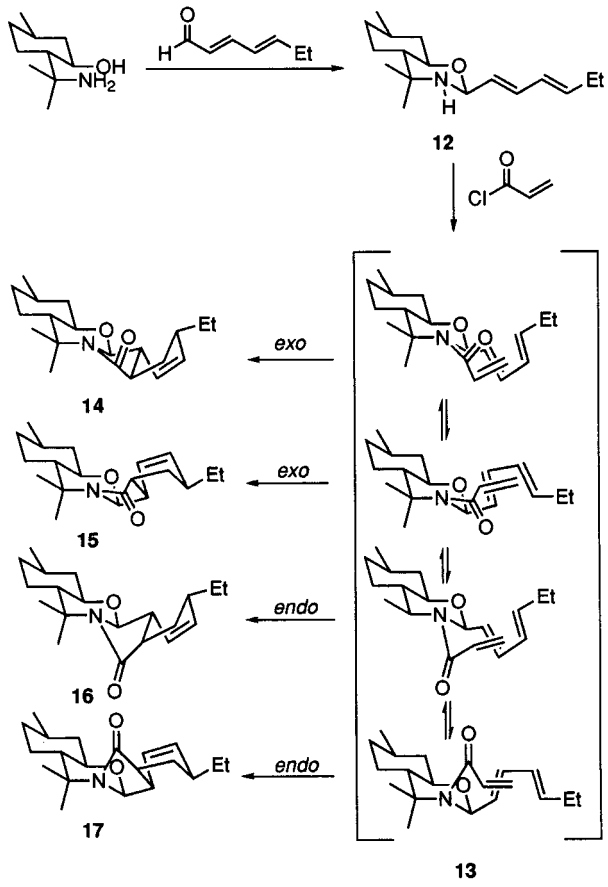
**Table 2. Diels−Alder Reactions of 6 and 7 in Different Conditions**

| entry | amide | solvent | Lewis acid (equiv) | temp (°C) | time (h) | yield (%)[a] | products (dr)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **6** | hexane | none | 20 | 130 | 89 | **8** (45) **10** (55) |
| 2 | **6** | $CH_2Cl_2$ | $Et_2AlCl$ (2.0) | −23 | 430 | 92 | **8** (81) **10** (19) |
| 3 | **7** | hexane | none | 20 | 350 | 82 | **9** (24) **11** (76) |
| 4 | **7** | toluene | none | 110 | 6 | 80 | **9** (40) **11** (60) |
| 5 | **7** | $CH_2Cl_2$ | $Et_2AlCl$ (2.0) | −23 | 530 | 83 | **9** (81) **11** (19) |

[a] Yields refer to pure compounds after column chromatography. [b] Diastereomeric ratios were determined by integration of the signals in the $^1H$ NMR spectra in the reaction mixtures.

**Scheme 2**




in the cyclization of **13** is supported by the fact that the *endo* transition state lies about 1.4 Kcal./mol below *exo* for open dienic components.[17]

The transition state **A** leading to *exo*-**3**, **8**, and **9** has a neat dipole moment about the amide bond higher than **B**, responsible for the formation of **4**, **10**, and **11** (Scheme 4). In these conditions, the formation of **3**, **8**, and **9** will be favored in solvents with high dielectric constants ($CH_2Cl_2$), and **4**, **10**, and **11** will be formed as major diastereoisomers in nonpolar solvents.[18] This fact is also supported by the results obtained from Lewis acid catalyzed reactions. The coordination of the Lewis acid to the oxygen of the amide group and to the heteroatoms of the system favors the displacement of the equilibrium toward **A** even if nonpolar solvents are used, although in our case, at least 1.1 equiv of Lewis acid was necessary to improve the de.[19]

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In summary, this study of an intramolecular Diels−Alder reaction on chiral perhydro-1,3-benzoxazines has demonstrated that the reaction of furane derivatives occurs regiospecifically and with good diastereoselection that is improved by using $Et_2AlCl$ as the Lewis acid catalyst. On the contrary, a mixture of *exo* and *endo* regioisomers is obtained when an open diene derivative **13** is used in the cycloaddition. More important, the results show that both *exo* diastereoisomers can be prepared from a common starting compound by simply changing the solvent of the reaction. The thermodynamically controlled process allows further improvement of the de. Finally, the adducts are easily transformed into enantiopure tetrahydroisoindoline derivatives in good yield by removal of the menthol adjuvant in a two-step process.

## Experimental Section

The reactions were carried out in anhydrous solvents, under an argon atmosphere, and in oven-dried glassware. Melting points were determined in capillary tubes and are uncorrected. The $^1H$ NMR (300 MHz) and $^{13}C$ DEPT-NMR (75 MHz) spectra were registered using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded by electronic impact or chemical ionization. IR spectra were registered as film or in Nujol dispersion. Optical rotations were measured in a 1 dm cell, and concentrations are given in g/100 mL. Products were isolated by flash chromatography using 240−400 mesh silica gel.

**Synthesis of Octahydro-1,3-benzoxazines 1 and 12.** A mixture of (−)-8-aminomenthol (5 g, 29.24 mmol), 4 Å molecular sieves (2 g), and furfural (3.09 g, 32.16 mmol) or *E*,*E*-2,4-heptadienal (3.54 g, 32.16 mmol) in benzene (50 mL) was stirred at room temperature until the reaction was completed (TLC, 30−40 h). The mixture was filtered through a pad of Celite, the solvent was eliminated from the filtrate under vacuum, and the residue was recrystallized from pentane for **1** or purified by flash chromatography on silica gel deactivated with triethylamine with hexane/EtOAc 8/1 as eluent for **12**.

**2α-(2′-Furyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (1).** Yield 96%. Colorless solid, mp 32−34 °C (from pentane). $[\alpha]^{25}_D = +20.4$ ($c = 1.0$, $CH_2Cl_2$). $^1H$ NMR (δ): 0.91−1.04 (m, 2H); 0.93 (d, 3H, $J = 6.5$ Hz); 1.08−1.13 (m, 2H); 1.15 (s, 3H); 1.17 (s, 3H); 1.49 (m, 1H); 1.69−1.71 (m, 2H); 1.98 (m, 1H); 2.10−2.70 (broad s, 1H); 3.59 (dt, 1H, $J_1 = 4.2$ Hz, $J_2 = 10.4$ Hz); 5.43 (s, 1H); 6.31−6.34 (m, 2H); 7.36 (dd, 1H, $J_1 = 0.9$ Hz, $J_2 = 1.6$ Hz). $^{13}C$ NMR (δ): 19.2; 22.1; 25.3; 29.6; 31.2; 34.7; 41.3; 51.2; 51.4; 75.2; 78.2; 106.3; 109.9; 141.8; 152.6. IR (Nujol): 1670, 1200, 1040 $cm^{-1}$. MS (*m*/*z*, %): 249 ($M^+$, 8); 138 (11); 97 (49); 96 (100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.41; H, 9.12; N, 5.78.

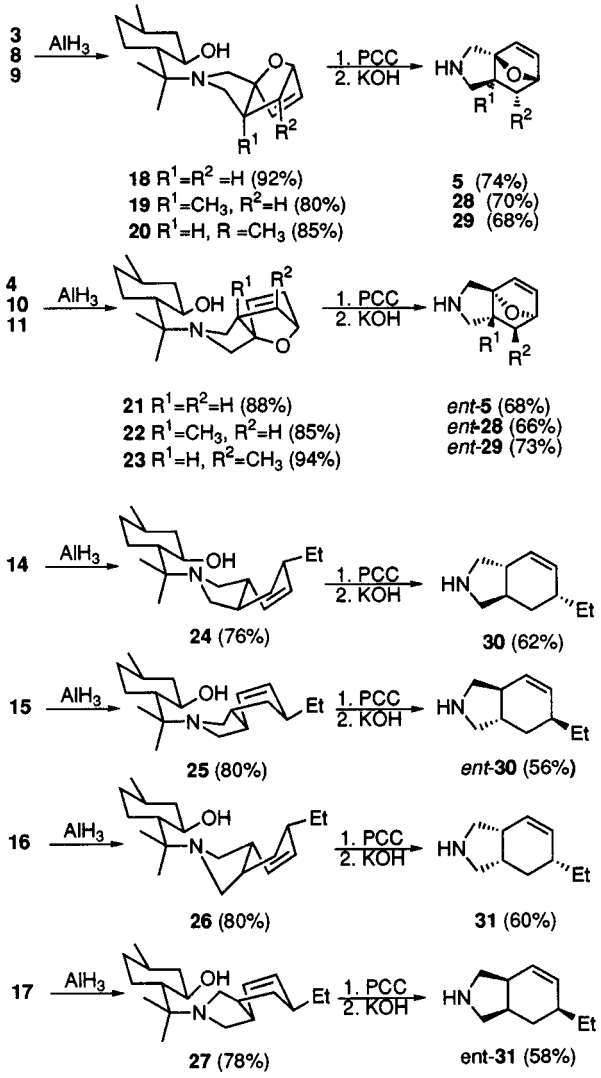
**2α-(*E*,*E*-2′,4′-Heptadienyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (12).** Yield 90%. Colorless oil. $[\alpha]^{25}_D = +18.37$ ($c = 1.2$, $CH_2Cl_2$). $^1H$ NMR (δ): 0.90−1.10 (m, 4H); 0.92 (d, 3H, $J = 6.6$ Hz); 0.97 (t, 3H, $J = 7.4$ Hz); 1.09 (s, 3H); 1.10 (s, 3H); 1.46−1.74 (m, 4H); 1.94 (m, 1H); 2.08 (m, 2H); 3.47 (dt, 1H, $J_1 = 4.1$ Hz, $J_2 = 10.2$ Hz); 4.83 (d, 1H, $J = 4.9$ Hz); 5.53 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 15.4$ Hz); 5.75 (dt, 1H, $J_1 = 6.8$ Hz, $J_2 = 16.1$ Hz); 5.99 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 15.1$ Hz); 6.33 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 15.4$ Hz). $^{13}C$ NMR (δ):

**Table 3. Diels−Alder Reactions of 13 in Different Conditions**

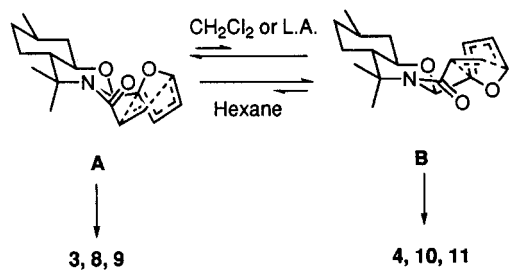
| | | | | | | products (dr)[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| entry | solvent | Lewis acid (equiv) | temp (°C) | time (h) | yield (%)[a] | **14** | **15** | **16** | **17** |
| 1 | $CH_2Cl_2$ | $Et_2AlCl$ (2.0) | −23 | 480 | 90 | (45) | (9) | (35) | (11) |
| 2 | hexane | none | 20 | 96 | 96 | (29) | (24) | (39) | (8) |
| 3 | toluene | none | 110 | 35 | 83 | (32) | (22) | (34) | (12) |

[a] Yields refer to pure compounds after column chromatography. [b] Diastereomeric ratios were determined by integration of the signals in the $^1$H NMR spectra in the reaction mixtures.

**Scheme 3**




**Scheme 4**




13.5; 19.6; 22.3; 25.5; 25.7; 29.9; 31.4; 35.0; 41.6; 51.3; 51.5; 74.8; 81.9; 128.4; 129.0; 132.2; 137.7. IR (neat): 3280, 1200, 1050 cm$^{-1}$. Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.38; H, 11.21; N, 5.17.

**Preparation of Amide Derivatives.** To a mixture of **1** (1 g, 4 mmol) and triethylamine (0.64 mL, 4.62 mmol) in the appropriate anhydrous solvent (20 mL) at 0 °C was slowly added acryloyl chloride (0.36 mL, 4.42 mmol). The stirring was continued until the reaction was finished (TLC, 15−30 min). Attempts to isolate **2** were not successful because the cyclization occurs at temperatures above 0 °C. This fact was also observed in the formation of **6** from **1** (1 g, 4 mmol), methacryloyl chloride (0.45 mL, 4.62 mmol), and TMDA (0.75 mL, 4.83 mmol) or **13** from **12** (1.05 g, 4 mmol), acryloyl chloride (0.36 mL, 4.42 mmol), and TMDA (0.70 mL, 4.62 mmol).

The preparation of **7** was carried out by slow addition of crotonyl chloride (0.42 mL, 4.42 mmol) to a mixture of **1** (1 g, 4.02 mmol) and pyridine (0.37 mL, 4.62 mmol) in dry $CH_2Cl_2$ (20 mL) at 0 °C. The mixture was allowed to reach room temperature and was stirred for an additional 30 min. The solvent was evaporated on a rotary evaporator at room temperature, and the residue was chromatographed on silica gel with hexane/EtOAc 8/1 as eluent. In this way, **7** was isolated after elimination of the eluent by rotary evaporator at room temperature.

***N*-Crotonyl-2α-(2-furyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (7).** Yield 85%. Colorless oil. $[\alpha]^{25}_D$ = −21.23 (*c* = 3.0, hexane). $^1$H NMR (δ): 0.64−0.78 (m, 1H); 0.88−1.21 (m, 2H); 0.89 (d, 3H, *J* = 6.6 Hz); 1.34−1.51 (m, 2H); 1.55 (s, 3H); 1.58 (s, 3H); 1.58−1.76 (m, 2H); 1.79 (dd, 3H, $J_1$ = 1.7 Hz, $J_2$ = 6.9 Hz); 2.04 (m, 1H); 3.75 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.4 Hz); 6.00 (dq, 1H, $J_1$ = 1.7 Hz, $J_2$ = 14.9 Hz); 6.26 (s, 1H); 6.31 (dd, 1H, $J_1$ = 0.8 Hz, $J_2$ = 3.1 Hz); 6.41 (dd, 1H, $J_1$ = 1.7 Hz, $J_2$ = 3.1 Hz); 6.80 (dq, 1H, $J_1$ = 6.9 Hz, $J_2$ = 14.9 Hz); 7.44 (dd, 1H, $J_1$ = 0.8 Hz, $J_2$ = 1.7 Hz).$^{13}$C NMR (δ): 18.2; 19.1; 21.9; 23.9; 25.2; 31.4; 34.3; 42.6; 45.6; 57.9; 73.5; 77.8; 107.7; 110.8; 124.7; 141.0; 142.2; 154.9; 167.1. IR (film): 1650, 1620 cm$^{-1}$. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.06; H, 8.71; N, 4.27.

**General Procedure for Diels−Alder Reactions. (a) Uncatalyzed Reactions.** Once the formation of the amides was observed (TLC), the reaction mixture was stirred in the appropriate solvent for the time and temperature given in Tables 1−3. The formation of cycloadducts was followed by TLC, and after the end of the reaction, the mixture was quenched by addition of $H_2O$. The organic phase was decanted, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic fractions were dried ($MgSO_4$) and filtered, and the solvent was eliminated under reduced pressure to yield a yellow oil. The components were isolated by flash chromatography as described below.

**(b) Lewis Acids Catalyzed Reactions.** After formation of the amide in the appropriate solvent, the solution was cooled to the temperature given in Tables 1−3, and the required amount of Lewis acid was added. The mixture was stirred for the period of time summarized in Tables 1−3, and the evolution of the reaction was followed by TLC. Once finished, the reaction was quenched by addition of $NH_4Cl$ solution, the organic phase was decanted, and the aqueous layer was extracted with $CH_2Cl_2$. The organics were dried ($MgSO_4$) and filtered, and the solvent was eliminated under reduced pressure. Pure compounds were isolated by flash chromatography as described below.

Adducts **3** and **4** were obtained from **2** and isolated by flash chromatography on silica gel deactivated with triethylamine, using hexane/EtOAc 3/1 as eluent.

**(3*S*,4a*R*,6a*S*,9*R*,10a*R*,11a*S*,11b*S*)-5-Oxo-3,11b-epoxy-6,6,9-trimethyl-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (3).** Colorless solid, mp 236−238 °C (from EtOH). $[\alpha]^{25}_D$ = −39.69 (*c* = 1.0, $CH_2Cl_2$).$^1$H NMR

(δ): 0.88−1.13 (m, 2H,); 0.94 (d, 3H, $J$ = 6.5 Hz); 1.13−1.25 (m, 1H); 1.25 (s, 3H); 1.38−1.53 (m, 2H); 1.57 (dd, 1H, $J_1$ = 8.3 Hz, $J_2$ = 11.4 Hz); 1.69−1.74 (m, 2H); 1.76 (s, 3H); 2.05 (m, 1H); 2.19−2.29 (m, 2H); 3.54 (dt, 1H, $J_1$ = 4.3 Hz, $J_2$ = 10.6 Hz); 5.12 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 4.1 Hz); 5.46 (s, 1H); 6.40 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 5.8 Hz); 6.46 (d, 1H, $J$ = 5.8 Hz). $^{13}$C NMR (δ): 18.8; 22.0; 24.0; 25.5; 28.3; 31.2; 34.3; 40.7; 47.8; 49.0; 57.3; 76.8; 79.5; 82.8; 88.3; 132.1; 137.3; 172.6. IR (Nujol): 1680, 1330 cm$^{-1}$. MS (*m*/*z*, %): 303 ($M^+$, 6); 288 (41); 112 (44); 55 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.43; H, 8.16; N, 4.79.

**(3*S*,4a*S*,6a*S*,9*R*,10a*R*,11a*S*,11b*R*)-5-Oxo-3,11b-epoxy-6,6,9-trimethyl-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (4).** Colorless solid, mp 97−98 °C (from hexane). $[\alpha]^{25}_D$ = −45.09 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.91−1.06 (m, 2H); 0.96 (d, 3H, $J$ = 6.5 Hz); 1.06−1.18 (m, 1H); 1.26 (s, 3H); 1.39−1.69 (m, 2H); 1.53 (dd, 1H, $J_1$ = 8.8 Hz, $J_2$ = 11.7 Hz); 1.69−1.83 (m, 2H); 1.73 (s, 3H); 2.03 (m, 1H); 2.12 (ddd, 1H, $J_1$ = 3.7 Hz, $J_2$ = 4.4 Hz, $J_3$ = 11.7 Hz); 2.55 (dd, 1H, $J_1$ = 3.7 Hz, $J_2$ = 8.8 Hz); 3.63 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.6 Hz); 5.07 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 4.4 Hz); 5.19 (s, 1H); 6.34 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 5.8 Hz); 6.57 (d, 1H, $J$ = 5.8 Hz). $^{13}$C NMR (δ): 20.6; 22.0; 24.5; 25.3; 27.8; 31.3; 34.5; 41.1; 47.4; 51.5; 57.8; 77.3; 79.8; 84.4; 89.1; 132.6; 135.9; 173.5. IR (Nujol): 1670, 1040 cm$^{-1}$. MS (*m*/*z*, %): 303 ($M^+$, 8); 191 (49); 136 (53); 112 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.12; H, 8.14; N, 4.76.

Adducts **8** and **10** were obtained from **6** and isolated by flash chromatography on silica gel deactivated with triethylamine, using hexane/EtOAc 5/1 as eluent.

**(3*S*,4a*R*,6a*S*,9*R*,10a*R*,11a*S*,11b*S*)-5-Oxo-3,11b-epoxy-4a,6,6,9-tetramethyl-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (8).** Colorless solid, mp 239−240 °C (from hexane/EtOAc). $[\alpha]^{25}_D$ = −59.20 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.92−1.09 (m, 2H); 0.94 (d, 3H, $J$ = 6.5 Hz); 0.97 (s, 3H); 1.07 (d, 1H, $J$ = 11.8 Hz); 1.17−1.25 (m, 1H); 1.23 (s, 3H); 1.43−1.60 (m, 2H); 1.70−2.00 (m, 2H); 1.77 (s, 3H); 2.05 (m, 1H); 2.48 (dd, 1H, $J_1$ = 4.7 Hz, $J_2$ = 11.8 Hz); 3.53 (dt, 1H, $J_1$= 4.3 Hz, $J_2$ = 10.6 Hz); 5.03 (dd, 1H, $J_1$ =1.3 Hz, $J_2$ = 4.7 Hz); 5.36 (s, 1H); 6.43−6.49 (m, 2H).$^{13}$C NMR (δ): 18.5; 20.4; 21.9; 23.9; 25.5; 31.1; 34.3; 36.3; 40.7; 49.0; 52.4; 56.9; 76.8; 79.3; 82.2; 90.2; 130.3; 137.6; 176.3. IR (Nujol): 1660, 960 cm$^{-1}$. MS (*m*/*z*, %): 317 ($M^+$, 36); 302 (79); 182 (38); 126 (55); 81 (51); 69 (100); 41 (72). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.01; H, 8.69; N, 4.29.

Adducts **9** and **11** were obtained from **7** and isolated by flash chromatography on silica gel deactivated with triethylamine, using hexane/EtOAc 3/1 as eluent.

**(3*R*,4*R*,4a*R*,6a*S*,9*R*,10a*R*,11a*S*,11b*S*)-5-Oxo-3,11b-epoxy-4,6,6,9-tetramethyl-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (9).** Colorless solid, mp 187−188 °C (from hexane). $[\alpha]^{25}_D$ = −4.08 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.88−1.00 (m, 2H); 0.93 (d, 3H, $J$ = 6.6 Hz); 0.97 (d, 3H, $J$ = 7.1 Hz); 1.17−1.24 (m, 1H); 1.24 (s, 3H); 1.37−1.60 (m, 2H); 1.70−1.75 (m, 1H); 1.75 (s, 3H); 1.80 (d, 1H, $J$ = 3.8 Hz); 2.04 (m, 1H); 2.62 (m, 1H); 3.53 (dt, 1H, $J_1$ = 4.2 Hz, $J_2$ = 10.6 Hz); 4.92 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 4.3 Hz); 5.40 (s, 1H); 6.38 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 5.9 Hz); 6.57 (d, 1H, $J$ = 5.9 Hz). $^{13}$C NMR (δ): 17.2; 18.7; 21.1; 23.9; 24.4; 31.1; 34.3; 37.1; 40.7; 49.0; 55.4; 57.2; 76.7; 82.6; 82.9; 88.9; 133.3; 135.4; 172.7. IR (Nujol): 1650 cm$^{-1}$. MS (*m*/*z*, %): 317 ($M^+$, 22); 138 (26); 95 (28); 81 (37); 69 (100); 41 (55). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.72; H, 8.42; N, 4.53.

Adducts **14**−**17** were obtained from **13** and isolated by flash chromatography on silica gel deactivated with triethylamine, using hexane/$CH_2Cl_2$/EtOAc 30/15/1 as eluent.

**(3*R*,4a*R*,6a*S*,9*R*,10a*R*,11a*S*,11b*R*)-3-Ethyl-6,6,9-trimethyl-5-oxo-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (14).** Colorless solid, mp 97−99 °C (from pentane). $[\alpha]^{25}_D$ = +2.21 ($c$ = 1.1, $CH_2Cl_2$). $^1$H NMR (δ): 0.86−1.00 (m, 2H); 0.94 (t, 3H, $J$ = 6.8 Hz); 0.95 (d, 3H, $J$ = 6.3 Hz); 1.00−1.14 (m, 1H); 1.15 (s, 3H); 1.25−1.60 (m, 4H); 1.63−1.77 (m, 3H); 1.71 (s, 3H); 1.87 (dt, 1H, $J_1$ = 3.0 Hz, $J_2$ = 12.5 Hz); 2.05−2.10 (m, 2H); 2.18−2.31 (m, 2H); 3.39 (dt, 1H, $J_1$ = 4.3 Hz, $J_2$ = 10.6 Hz); 4.53 (d, 1H, $J$ = 8.3 Hz); 5.66 (dt, 1H, $J_1$ = 3.0 Hz, $J_2$ = 9.8 Hz); 5.96 (dt, 1H, $J_1$ = 1.0 Hz, $J_2$ = 9.8 Hz). $^{13}$C NMR (δ): 12.2; 18.5; 22.0; 23.8; 25.9; 26.1; 28.7; 31.2; 34.4; 37.2; 41.0; 41.4; 44.6; 49.4; 56.7; 75.8; 86.6; 123.7; 134.6; 173.9. IR (Nujol): 1690, 1050 cm$^{-1}$. MS (*m*/*z*, %): 317 ($M^+$, 24); 182 (100); 81 (47). Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.82; H, 9.71; N, 4.57.

**(3*S*,4a*S*,6a*S*,9*R*,10a*R*,11a*S*,11b*S*)-3-Ethyl-6,6,9-trimethyl-5-oxo-3,4,4a,11b-tetrahydroisoindolyl-[2,3-a]-perhydro-11,5a-benzoxazine (15).** Colorless solid, mp 60−62 °C (from pentane). $[\alpha]^{25}_D$ = −119.11 ($c$ = 1.1, $CH_2Cl_2$). $^1$H NMR (δ): 0.88−0.98 (m, 2H); 0.92 (d, 3H, $J$ = 6.6 Hz); 0.95 (t, 3H, $J$ = 7.4 Hz); 0.98−1.17 (m, 1H); 1.24 (s, 3H); 1.26−1.57 (m, 4H); 1.59−1.74 (m, 3H); 1.71 (s, 3H); 1.90−2.07 (m, 2H); 2.19 (m, 1H); 2.33 (m, 1H); 2.49 (dt, 1H, $J_1$ = 3.0 Hz, $J_2$ = 12.7 Hz); 3.52 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.6 Hz); 5.09 (d, 1H, $J$ = 4.9 Hz); 5.66 (dt, 1H, $J_1$ = 3.0 Hz, $J_2$ = 9.8 Hz); 5.89 (dt, 1H, $J_1$ = 2.0 Hz, $J_2$ = 9.8 Hz). $^{13}$C NMR (δ): 12.3; 21.6; 22.0; 24.6; 25.7; 26.4; 28.8; 31.3; 34.5; 37.4; 41.2; 41.2; 41.6; 51.4; 57.9; 76.4; 84.2; 123.6; 134.7; 176.2. IR (Nujol): 1705, 1330, 1220 cm$^{-1}$. MS (*m*/*z*, %): 317 ($M^+$, 6), 205 (31), 81 (41), 58 (100). Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.56; H, 9.98; N, 4.29.

**Synthesis of Amino Alcohols 18−27. General Method.** To a suspension of $LiAlH_4$ (0.6 g, 15.8 mmol) in anhydrous THF (40 mL) cooled to −10 °C was added, in portions, dry $AlCl_3$ (0.7 g, 5.25 mmol). The mixture was stirred for an additional 10 min, and a solution of the corresponding adduct (3.17 mmol) in dry THF was slowly added. The reaction mixture was stirred for 5 min at −10 °C and quenched by addition of $H_2O$. The resulting mixture was filtered, the solid was washed with EtOAc, and the organic layer was dried ($MgSO_4$). The solvents were eliminated under reduced pressure, and the residue was chromatographed on silica gel using hexane/EtOAc 3/1 as eluent.

***N*-(8-Mentholyl)-(3a*S*,6*S*,7a*S*)-3a,6-epoxy-3a,6,7,7a-tetrahydroisoindoline (18).** Colorless solid, mp 109−111 °C (from hexane). $[\alpha]^{25}_D$ = +4.12 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.88−1.11 (m, 3H); 0.92 (d, 3H, $J$ = 6.5 Hz); 0.97 (s, 3H); 1.19 (s, 3H); 1.30−1.51 (m, 3H); 1.56−1.72 (m, 3H); 1.84−1.96 (m, 2H); 2.34 (m,1H); 3.02 (d, 1H, $J$ = 12.2 Hz); 3.19 (t, 1H, $J$ = 7.6 Hz); 3.62 (m, 1H); 3.66 (dt, 1H, $J_1$ = 4.1 Hz, $J_2$ = 10.3 Hz); 4.98 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 4.4 Hz); 6.30 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 5.8 Hz); 6.39 (d, 1H, $J$ = 5.8 Hz); 8.75 (broad s, 1H). $^{13}$C NMR (δ): 17.1; 21.8; 22.1; 25.5; 29.5; 31.0; 35.0; 42.1; 44.1; 47.2; 48.6; 51.1; 59.4; 73.0; 79.8; 95.1; 135.6; 136.1. IR (Nujol): 3100, 1170, 1080 cm$^{-1}$. CIMS (*m*/*z*, %): 292 ($M^+$ + 1, 100); 178 (41); 138 (41). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.36; H, 10.19; N, 4.65.

***N*-(8-Mentholyl)-(3a*S*,6*S*,7a*S*)-3a,6-epoxy-7a-methyl-3a,6,7,7a-tetrahydroisoindoline (19).** Yield 80%. Colorless solid, mp113−115 °C (from hexane). $[\alpha]^{25}_D$ = −30.06 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.81−1.14 (m, 4H); 0.92 (d, 3H, $J$ = 6.4 Hz); 0.93 (s, 3H); 0.96 (s, 3H); 1.17 (s, 3H); 1.44 (m, 2H); 1.57−1.70 (m, 2H); 1.95 (m, 1H); 2.04 (dd, 1H, $J_1$ = 4.6 Hz, $J_2$ = 11.4 Hz); 2.69 (d, 1H, $J$ = 8.1 Hz); 2.86 (d, 1H, $J$ = 8.1 Hz); 3.09 (d, 1H, $J$ = 12.3 Hz); 3.54 (d, 1H, $J$ = 12.3 Hz); 3.67 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.3 Hz); 4.92 (d, 1H, $J$ = 4.6 Hz); 6.35 (s, 2H); 8.93 (s, 1H). $^{13}$C NMR (δ): 17.0; 21.6; 22.1; 22.5; 25.4; 31.0; 35.0; 38.4; 44.1; 46.2; 47.0; 48.9; 57.7; 59.4; 72.9; 79.8; 96.6; 134.0; 136.1. IR (Nujol): 3085, 1180, 1150 cm$^{-1}$. CIMS (*m*/*z*, %): 306 ($M^+$ + 1, 100); 192 (55); 152 (45). Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.56; H, 10.36; N, 4.42.

***N*-(8-Mentholyl)-(3a*S*,6*R*,7*R*,7a*S*)-3a,6-epoxy-7-methyl-3a,6,7,7a-tetrahydroisoindoline (20).** Yield 87%. Colorless solid, mp 113−115 °C (from hexane). $[\alpha]^{25}_D$ = +36.9 ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (δ): 0.82 (d, 3H, $J$ = 7.1 Hz); 0.85−1.09 (m, 3H); 0.92 (d, 3H, $J$ = 6.5 Hz); 0.96 (s, 3H); 1.19 (s, 3H); 1.39−1.48 (m, 3H); 1.57 (m, 1H); 1.67 (m, 1H); 1.93 (m, 1H); 2.11 (m, 1H); 2.37 (m, 1H); 2.94 (d, 1H, $J$ = 11.9 Hz); 3.26 (t, 1H, $J$ = 7.6 Hz); 3.57 (m, 1H); 3.62 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.3 Hz); 4.80 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 4.3 Hz); 6.29 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 5.8 Hz); 6.48 (d, 1H, $J$ = 5.8 Hz); 8.66 (broad s,

1H). $^{13}$C NMR ($\delta$): 16.6; 17.1; 21.8; 22.1; 25.5; 31.0; 35.0; 37.8; 44.2; 47.6; 48.6; 50.7; 50.7; 59.3; 72.9; 83.5; 96.0; 134.1; 136.8. IR (Nujol): 3060, 1010 cm$^{-1}$. CIMS (*m*/*z*, %): 306 ($M^+ + 1$, 100); 192 (30); 152 (17). Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.58; H, 10.41; N, 4.71.

***N*-(8-Mentholyl)-(3a*R*,6*R*,7a*R*)-3a,6-epoxy-3a,6,7,7a-tetrahydro isoindoline (21).** Colorless solid, mp 125−127 °C (from hexane). $[\alpha]^{25}_D = -11.64$ (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.86−1.06 (m, 3H); 0.91 (d, 3H, *J* = 6.5 Hz); 0.97 (s, 3H); 1.19 (s, 3H); 1.32 (m, 1H); 1.43 (m, 1H); 1.54−1.70 (m, 4H); 1.89−1.95 (m, 2H); 2.23 (t, 1H, *J* = 9.2 Hz); 2.97 (d, 1H, *J* = 11.7 Hz); 3.37−3.50 (m, 2H); 3.65 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.2 Hz); 4.98 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 4.3 Hz); 6.28 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 5.7 Hz); 6.36 (d, 1H, *J* = 5.7 Hz); 8.47 (broad s, 1H). $^{13}$C NMR ($\delta$): 17.8; 21.3; 22.1; 25.8; 28.8; 31.1; 35.1; 42.6; 44.3; 47.4; 48.5; 50.3; 59.6; 72.8; 79.9; 94.8; 135.8; 136.1. IR (Nujol): 3140, 1180 cm$^{-1}$. CIMS (*m*/*z*, %): 292 ($M^+ + 1$, 100); 178 (26); 138 (24). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.02; H, 10.21; N, 4.96.

***N*-(8-Mentholyl)-(3a*R*,6*R*,7a*R*)-6-ethyl-3a,6,7,7a-tetrahydroisoindoline (24).** Colorless solid, mp 79−80 °C (from hexane). $[\alpha]^{25}_D = +32.75$ (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.86−1.04 (m, 3H); 0.90 (d, 3H, *J* = 6.5 Hz); 0.92 (t, 3H, *J* = 6.9 Hz); 0.93 (s, 3H); 1.14 (s, 3H); 1.27−1.79 (m, 9H); 1.93 (m, 1H); 2.14 (m, 2H); 2.33 (m, 1H); 2.62 (m, 1H); 2.93 (m, 1H); 3.01 (m, 1H); 3.63 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.2 Hz); 5.60 (m, 1H); 5.77 (m, 1H); 9.04 (m, 1H). $^{13}$C NMR ($\delta$): 12.3; 16.7; 21.1; 22.2; 25.6; 29.3; 29.6; 31.0; 35.2; 37.2; 38.8; 42.9; 44.3; 49.2; 49.4; 59.6; 72.8; 126.2; 133.2. IR (Nujol): 3120, 1165, 1025 cm$^{-1}$. MS (*m*/*z*, %): 305 ($M^+$, 1); 193 (13); 192 (100). Anal. Calcd for $C_{20}H_{35}NO$: C, 78.63; H, 11.55; N, 4.58. Found: C, 78.48; H, 11.39; N, 4.69.

***N*-(8-Mentholyl)-(3a*S*,6*S*,7a*S*)-6-ethyl-3a,6,7,7a-tetrahydroisoindoline (25).** Colorless oil. $[\alpha]^{25}_D = -49.23$ (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.85−1.07 (m, 3H); 0.91 (d, 3H, *J* = 6.5 Hz); 0.92 (s, 3H); 0.93 (t, 3H, *J* = 7.2 Hz); 1.17 (s, 3H); 1.25−1.65 (m, 6H); 1.65−1.80 (m, 3H); 1.92 (m, 1H); 2.13 (m, 2H); 2.20−2.65 (broad, 2H); 2.91−3.32 (broad, 2H); 3.63 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.3 Hz); 5.58 (m, 1H); 5.76 (m, 1H); 8.00−9.40 (broad s, 1H). $^{13}$C NMR ($\delta$): 12.3; 18.6; 21.6; 22.1; 25.7; 29.1; 29.7; 31.0; 35.1; 37.2; 39.0; 43.1; 44.1; 48.5; 48.7; 59.3; 72.9; 126.3; 132.9. IR (film): 3120, 1160, 1020 cm$^{-1}$. MS (*m*/*z*, %): 305 ($M^+$, 1); 193 (15); 192 (100). Anal. Calcd for $C_{20}H_{35}NO$: C, 78.63; H, 11.55; N, 4.58. Found: C, 78.80; H, 11.72; N, 4.72.

**Elimination of the Menthol Appendage. General Method.** A solution of amino menthol derivatives **18**−**27** (1.0 mmol) and PCC (1.29 g, 6 mmol) in $CH_2Cl_2$ (40 mL) and 4 Å molecular sieves (1 g) was stirred at room temperature until the oxidation was finished (TLC, 6−8 h). The solvent was eliminated under reduced pressure, the residue was dissolved in a 15% aqueous solution of NaOH (25 mL), and the resulting solution was extracted with $Et_2O$. The ethereal solution was separated, washed with brine, and dried over anydrous magnesium sulfate. The solvents were eliminated under vacuum, and the residue was taken up in a 2.5 M solution (16 mL) of KOH in THF/MeOH/$H_2O$ (2/1/1), and the solution was stirred at room temperature for 5−6 h. After elimination of the solvents under reduced pressure, the residue was acidified to pH = 2 by addition of a 10% solution of HCl. The aqueous layer was washed with $Et_2O$ to recover (+)-pulegone, and then the residue was basified to pH = 12 by addition of a 15% solution of NaOH. The basic phase was extracted with $CHCl_3$, the organic layer was dried ($MgSO_4$) and filtered, and the solvent was eliminated under vacuum to give an oily residue, which was purified by flash chromatography on silica gel using a mixture of $CHCl_3$/EtOH (10/1) as eluent.

**(3a*S*,6*S*,7a*S*)-3a,6-Epoxy-3a,6,7,7a-tetrahydroisoindoline (5).** Colorless oil. $[\alpha]^{25}_D = +30.24$ (*c* = 5.6, $CH_2Cl_2$). $^1$H NMR ($\delta$): 1.44 (dd, 1H, $J_1$ = 7.7 Hz, $J_2$ = 11.5 Hz); 1.73 (ddd, 1H, $J_1$ = 3.2 Hz, $J_2$ = 4.4 Hz, $J_3$ = 11.5 Hz); 1.95 (ddt, 1H, $J_1$ = 3.2 Hz, $J_2$ = 7.7 Hz, $J_3$ = 9.5 Hz); 2.63 (t, 1H, *J* = 9.5 Hz); 3.27 (d, 1H, *J* = 12.9 Hz); 3.29 (t, 1H, *J* = 9.5 Hz); 3.39 (d, 1H, *J* = 12.9 Hz); 3.50 (s, 1H); 5.04 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 4.4 Hz); 6.36 (dd, 1H, $J_1$ = 1.6 Hz, $J_2$ = 5.8 Hz); 6.42 (d, 1H, *J* = 5.8 Hz). $^{13}$C NMR ($\delta$): 31.0; 44.7; 47.6; 51.6; 79.9; 98.0; 135.1; 136.5. IR (film): 3350, 1600, 1200 cm$^{-1}$. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.21; H, 8.26; N, 10.09.

**(3a*R*,6*R*,7a*R*)-3a,6-Epoxy-3a,6,7,7a-tetrahydroisoindoline (*ent*-5).** Colorless oil. $[\alpha]^{25}_D = -30.12$ (*c* = 2.0, $CH_2Cl_2$). $^1$H NMR, $^{13}$C NMR, and IR data are coincident with those reported for **5**. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.18; H, 8.18; N, 10.36.

**(3a*S*,6*S*,7a*S*)-3a,6-Epoxy-7a-methyl-3a,6,7,7a-tetrahydroisoindoline (28).** Yield 70%. Colorless oil. $[\alpha]^{25}_D = -23.64$ (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.95 (s, 3H); 1.08 (d, 1H, *J* = 11.4 Hz); 2.10 (dd, 1H, $J_1$ = 4.7 Hz, $J_2$ = 11.4 Hz); 2.97 (d, 1H, *J* = 10.3 Hz); 3.03 (d, 1H, *J* = 10.3 Hz); 3.34 (d, 1H. *J* = 13.1 Hz); 3.45 (d, 1H, *J* = 13.1 Hz); 4.10 (s, 1H); 4.98 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 4.7 Hz); 6.40 (d, 1H, *J* = 5.8 Hz); 6.44 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 5.8 Hz). $^{13}$C NMR ($\delta$): 23.0; 39.5; 46.3; 49.3; 58.6; 79.9; 99.0; 133.6; 136.8. IR (film): 3300, 1305, 1210 cm$^{-1}$. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.31; H, 8.49; N, 9.44.

**(3a*S*,6*R*,7*R*,7a*S*)-3a,6-Epoxy-7-methyl-3a,6,7,7a-tetrahydroisoindoline (29).** Yield 66%. Colorless oil. $[\alpha]^{25}_D = +78.32$ (*c* = 1.8, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.86 (d, 3H, *J* = 7.1 Hz); 1.49 (dt, 1H, $J_1$ = 3.3 Hz, $J_2$ = 8.7 Hz); 2.14 (ddq, 1H, $J_1$ = 3.3 Hz, $J_2$ = 4.4 Hz, $J_3$ = 7.1 Hz); 2.68 (t, 1H, *J* = 8.7 Hz); 3.03 (s, 1H); 3.18 (d, 1H, *J* = 12.6 Hz); 3.29 (d, 1H, *J* = 12.6 Hz); 3.30 (t, 1H, *J* = 8.7 Hz); 4.84 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 4.4 Hz); 6.34 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 5.8 Hz); 6.51 (d, 1H, *J* = 5.8 Hz). $^{13}$C NMR ($\delta$): 16.8; 39.9; 48.0; 51.1; 53.2; 83.4; 99.5; 134.5; 136.1. IR (film): 3300, 1320 cm$^{-1}$. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.37; H, 8.82; N, 9.11.

**(3a*R*,6*R*,7a*R*)-6-Ethyl-3a,6,7,7a-tetrahydroisoindoline (30).** Yield 62%. Pale yellow oil. $[\alpha]^{25}_D = +54.75$ (*c* = 0.5, $CH_2Cl_2$). $^1$H NMR ($\delta$): 0.94 (t, 3H, *J* = 7.3 Hz); 1.23−1.51 (m, 2H); 1.58 (m, 1H); 1.72−1.85 (m, 2H); 2.12−2.31 (m, 2H); 2.66−2.84 (m, 2H); 3.39−3.48 (m, 2H); 5.70 (m, 1H); 5.77 8d, 1H, *J* = 10.0 Hz); 5.98 (broad s, 1H). $^{13}$C NMR ($\delta$): 12.2; 28.6; 28.9; 37.0; 39.0; 43.1; 48.2; 48.8; 123.3; 134.3. IR (film): 3420, 1640 cm$^{-1}$. Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.58; H, 11.50; N, 9.42.

**(3a*S*,6*S*,7a*S*)-6-Ethyl-3a,6,7,7a-tetrahydroisoindoline (*ent*-30).** Yield 56%. Pale yellow oil. $[\alpha]^{25}_D = -52.83$ (*c* = 0.6, $CH_2Cl_2$). $^1$H NMR, $^{13}$C NMR, and IR data are coincident with those reported for **30**. Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.60; H, 11.48; N, 9.40.

**Acknowledgment.** We thank the Spanish DGICYT (Project PB95-707) for the financial support of this work. Predoctoral felloships provided by the Spanish MEC (FPU program) for J.N. and M.G.-V. are also acknowledged.

**Supporting Information Available:** Characterization data (mp or bp, $[\alpha]^{25}_D$, IR, MS, $^1$H and $^{13}$C NMR spectra, and CHN analyses) for compounds **10**, **11**, **16**, **17**, **22**, **23**, **26**, **27**, **ent-28**, **ent-29**, **31**, and **ent-31**; copies of $^{13}$C NMR spectra for compounds **1**, **3**−**5**, **7**−**12**, and **14**−**31**, and COSY and NOESY experiments for **14**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9904462