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# Temperature- and Time-Dependent Stereochemical Control in Thermally Induced Keto−Ene Cyclizations

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Reaction conditions determine the stereoselection in the intramolecular keto−ene reaction. The thermolysis of chiral 2-acyl-3-allyl-substituted 1,3-perhydrobenzoxazines derived from (−)-8-aminomenthol gives a mixture of only two *cis*-3-hydroxy-3,4-disubstituted pyrrolidine nuclei. The stereochemistry of the major diastereoisomer depends on both the temperature and the reaction time.

## Introduction

The intramolecular ene reaction has been extensively used in the formation of cyclic systems because it allows the formation of a single carbon−carbon bond with concomitant construction of two contiguous stereocenters.[1] In addition, the relative stereochemistry in the cyclization products is dependent on the ring size. The cis adduct is the major product formed for cyclopentane derivatives but the trans diastereoisomer predominates in the formation of cyclohexanes. The absolute configuration of both of them is also controlled by the presence of stereocenters or chiral templates on the tether between the ene and the enophile,[2] or by the use of chiral Lewis acids as promoters.[3]

The interest of the type I carbonyl ene reaction lies in the fact that macrocyclic alcohols[4] and cyclohexanol[1,5] and cyclopentanol[6] derivatives can be prepared in high yield and diastereoselectivities. The Lewis acid or thermally induced cyclizations of unsaturated aldehydes have been profoundly studied, but there are no antecedents on the intramolecular carbonyl ene reactions of unsaturated ketones[1,2] due to their low electrophilicity. In general, the reaction is restricted to electron-deficient ketones which cyclize to cyclohexanol or cyclopentanol derivatives, in moderate yields, under Lewis acid mediated conditions. Recently, intramolecular type II carbonyl ene reaction on α,α′-alkoxy-disubstituted ketones leading to cyclohexanols[7] and type I carbonyl ene reactions on α-oxoesters yielding cyclopentanol derivatives[6] have been described.

As part of a project directed to the use of perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol as chiral inductors in the synthesis of enantiopure nitrogen heterocycles, we have demonstrated that these systems are specially prone to participate in concerted,[8] anionic,[9] and radical[10] mediated cyclizations when two substituents are placed in positions 2 and 3.

On the basis of these previous results, now we have tested the carbonyl ene cyclization of 2-acyl-3-allyl-substituted perhydro-1,3-benzoxazines, directed to the synthesis of enantiopure 3-hydroxypyrrolidines.

## Results and Discussion

The preparation of 2-formyl-3-prenyl derivative **3** was attempted as summarize in Scheme 1. The 2-hydroxymethyl perhydro-1,3-benzoxazine **1**[11] was alkylated by reaction with prenyl bromide and potassium carbonate in acetonitrile at reflux to give **2** in 91%. Swern oxidation of **2** gave the formyl derivative **3**, which cannot be isolated because it immediately suffers the carbonyl ene reaction to yield the cyclized compound **4** (85% after purification) as a single enantiopure diastereoisomer. The absolute stereochemistry of **4** was determined by X-ray crystallography.[12]

The formation of the five-membered ring is very interesting because there are few precedents on the formation of cyclopentanols in Lewis acids[13] or ther-

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(1) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, p 527.

(2) (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(3) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. N. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(4) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1993**, *58*, 3912.

(5) (a) Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* **2001**, *3*, 4205. (b) Robertson, J.; O'Connor, G.; Ringrose, C. L.; Middleton, D. S. *Tetrahedron* **2000**, *56*, 8321. (c) Kocovsky, P.; Ahmed, G.; Srogl, J.; Malkov, A. V.; Steele, J. *J. Org. Chem.* **1999**, *64*, 2765 and references therein.

(6) Hiersemann, M. *Eur. J. Org. Chem.* **2001**, 483.

(7) Cheung, C.-M.; Craig, D.; Todd, R. *Synlett* **2001**, 1611.

(8) Pedrosa, R.; Andrés, C.; Nieto, J. *J. Org. Chem.* **2002**, *67*, 782.

(9) Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817.

(10) Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem.* **1999**, *64*, 4282.

(11) Pedrosa, R.; Andrés, C.; de las Heras, L.; Nieto, J. *Org. Lett.* **2002**, *4*, 2513.

(12) See Supporting Information

(13) (a) Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144. (b) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358. (c) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.

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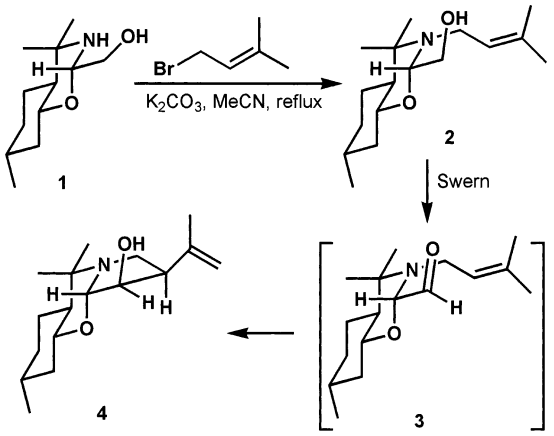
**SCHEME 1**




mally[14] promoted processes, and the type I carbonyl ene reaction failed when the tether between the formyl group and the enophile takes part of a $\beta$-lactam system.[5a] The stereochemical outcome in our system is also very noticeable because the process is diastereospecific, leading to only one of the two possible cis-disubstituted diastereoisomers formed in a concerted ene reaction.

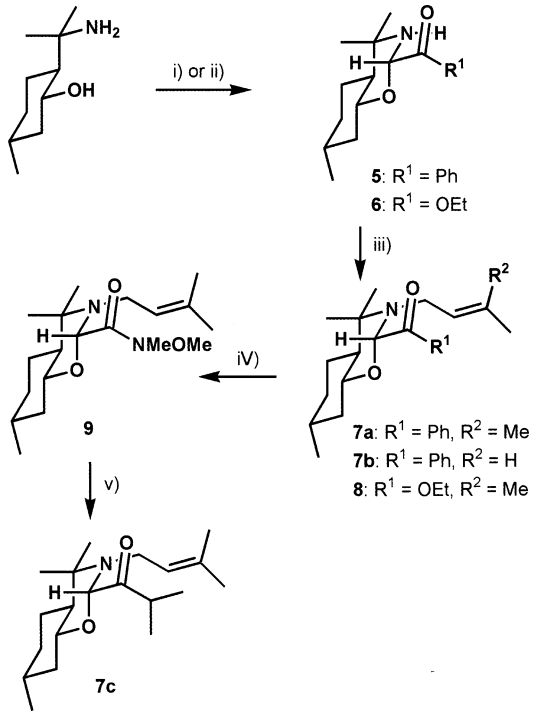
Because of the easy reaction of **3** and the total control of the stereoselection, we envisaged that the thermally induced reaction could be extended to perhydro-1,3-benzoxazines bearing different acyl substituents at C-2. This methodology implies the participation of a ketonic group as the enophile component, and provides a route to the formation of a 3,4-disubstituted hydroxy pyrrolidine system with a quaternary stereocenter. To this end, 2-benzoyl and 2-isobutanoyl perhydro-1,3-benzoxazines **7a**−**c** were prepared as summarized in Scheme 2.

2-Benzoyl derivatives **7a**,**b** were prepared from (−)-8-aminomenthol, in two steps, by sequential condensation with phenylglyoxal to **5** and alkylation with prenyl or crotyl bromide and potassium carbonate in refluxing acetonitrile, respectively. **7c** was also obtained from the amino alcohol and the hemiacetal of the ethyl glyoxylate of **6** followed by alkylation with prenyl bromide to **8**. This compound was transformed[15] into the Weinreb amide **9** by reaction with *N*,*O*-dimethyl hydroxylamine hydrochloride and isopropylmagnesium chloride. Compound **7c** was obtained (59% from **8**) by treatment of **9** with isopropylmagnesium chloride.

Compounds **7a**−**c** lead to mixtures of diastereomeric 3-hydroxypyrrolidines **10a**−**c** and **11a**−**c** under different thermal conditions (Scheme 3). The results depend on the experimental conditions and are collected in Table 1.

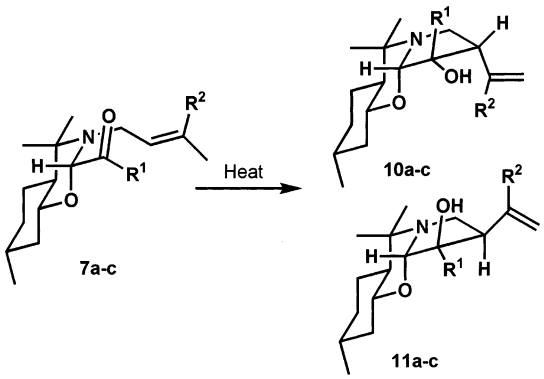
The results summarized in Table 1 are noteworthy. Compounds **7a**−**c** are *N*,*O*-acetals of α-formyl ketones, and this is the first case of thermally induced type I carbonyl ene reaction of this type of compounds leading to cyclopentanol derivatives. This fact points to the presence of *vicinal* oxygen and nitrogen substituents α to the carbonyl group activating the ketone to participate in the thermal reaction. As expected, *N*-prenyl-substituted compound **7a** is more reactive than *N*-crotyl

**SCHEME 2**[a]




[a] Conditions: (i) HOCCOPh, $CH_2Cl_2$, rt, quant. (ii) HO(EtO)CH-$CO_2$Et, benzene, Dean−Stark, quant. (iii) Prenyl or crotyl bromide, $K_2CO_3$, acetonitrile, rt or reflux, **7a** (95%), **7b** (88%), **8** (88%). (iv) MeNHOMe, $^i$PrMgCl, THF, −20 °C to room temperature. (v) $^i$PrMgCl, THF, rt, **7c** (59% from **8**).

**SCHEME 3**




derivative **7b**. The former was totally transformed into the cyclization compounds **10a** and **11a** after heating in toluene at 150 °C for 3 h (entry 6), whereas 36% of unreacted **7b** was isolated after 18 h in the same experimental conditions (entry 12).

The most surprising results refer to the stereochemical outcome of the reactions. In this way, these thermal carbonyl ene reactions are diastereoselective, giving a mixture of *cis*-3,4-disubstituted pyrrolidine systems with a cis fusion to the perhydro-1,3-benzoxazine nucleus. These facts suggest that the reaction is a concerted process that occurs when the ene component on the nitrogen atom is axially oriented. In addition, the ratio of diastereoisomers obtained is dependent on both the reaction conditions and the nature of the substituents. 2-Benzoyl-3-crotyl perhydro-1,3-benzoxazine **7b** yielded mixtures of *all-cis*-**10b** and *trans*,*cis*-**11b** diastereoiso-

(14) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.
(15) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

**TABLE 1. Intramolecular Carbonyl Ene Reactions of Compounds 7a−c**

| entry | substrate | $R^1$ | $R^2$ | reaction conditions[a] | yield[b] | products (ratio)[c] |
|---|---|---|---|---|---|---|
| 1 | **7a** | Ph | Me | 170 °C, 1 h | 88 | **10a**, **11a** (44:56) |
| 2 | | | | 170 °C, 2 h | 86 | **10a**, **11a** (55:45) |
| 3 | | | | 170 °C, 3 h | 88 | **10a**, **11a** (63:37) |
| 4 | | | | 170 °C, 8 h | 85 | **10a**, **11a** (70:30) |
| 5 | | | | 170 °C, 21 h | 80 | **10a**, **11a** (75:25) |
| 6 | | | | toluene, 150 °C, 3 h | 84 | **10a**, **11a** (32:68) |
| 7 | | | | xylene, reflux, 218 h | 85 | **10a**, **11a** (70:30) |
| 8 | **7b** | Ph | H | 170 °C, 1h | 20 | **10b**, **11b** (70:30)[d] |
| 9 | | | | toluene, reflux, 120 h | 40 | **10b**, **11b** (75:25)[e] |
| 10 | | | | toluene, reflux, 240 h | 50 | **10b**, **11b** (77:23)[f] |
| 11 | | | | xylene, reflux, 218 h | 80 | **10b**, **11b** (88:12) |
| 12 | | | | toluene, 150 °C, 18 h | 40 | **10b**, **11b** (72:28)[g] |
| 13 | **7c** | i Pr | Me | 170 °C, 3 h | 70 | **10c**, **11c** (41:59)[h] |
| 14 | | | | 170 °C, 8 h | 88 | **10c**, **11c** (50:50) |
| 15 | | | | 170 °C, 18 h | 50 | **10c**[i] |

[a] The reactions, with or without solvent, were performed in a pressure tube. [b] Yields refer to isolated compounds after column chromatography. [c] Determined by $^1$H NMR of the reaction mixture. [d] Extensive decomposition of **7b** was observed. [e] 36% of **7b** was recovered. [f] 26% of **7b** was recovered. [g] 36% of **7b** was recovered. [h] 15% of **7c** was recovered. [i] 40% of decomposition products was formed.

mers in ratios which vary from 3:1 to 7:1 depending on the experimental conditions, although it was necessary to reflux a solution of **7b** in xylene for 218 h to complete the reaction. Compound **7b** suffered extensive decomposition with heating at 170 °C for 1 h (entry 8).

The behavior of **7a** is quite different because it is more reactive than **7b** and the ratio of diastereoisomers depends on the reaction conditions. The carbonyl ene cyclization for **7a** is a fast reaction giving quantitatively a mixture (44:56) of diastereomeric adducts **10a**:**11a** with heating for 1 h at 170 °C. A mixture (32:68) of the same diastereoisomers was formed after heating a solution of **7a** in toluene at 150 °C in a sealed tube. The most important and unprecedented feature of the reaction refers to the change in the diastereoselection with the reaction time. Thus, the ratio of diastereoisomers **10a**:**11a** varies when the reaction time increases (entries 1−5 in Table 1), changing from 44:56 after 1 h to 75:25 after 21 h of heating at 170 °C without solvent. Some decomposition was observed for longer periods of heating. A quite similar ratio (70:30, entry 7 in Table 1) of diastereoisomers was obtained after a solution of **7a** in xylene was refluxed for 218 h.

Once isolated, compound **10a** isomerized to a mixture of **10a**:**11a** (70:30) after being heated at 170 °C for 9 h, and **11a** also gave to the same equilibrium mixture under the same experimental conditions. The same behavior was observed for compound **7c**, although it reacted more slowly than **7a**. Isobutanoyl derivative **7c** was transformed into a mixture of **10c** and **11c** (41:59, entry 13) after 3 h at 170 °C, and quantitatively (entry 14) in an equimolar mixture of the same diastereoisomers after thermolysis for 8 h at the same temperature. Compound **10c** was the only isomer isolated when **7c** was thermolyzed for 18 h, but only at 50% because extensive decomposition products were observed after this period of heating.

The stereochemistry of compounds **10a**−**c** and **11a**−**c** was determined on the basis of nOe experiments. First, a strong nOe effect was observed between the protons at the acetallic and C-4 positions (pyrrolidine numbering) for compounds **10a**−**c**, but no nOe effect was observed for the same protons in compounds **11a**−**c**. Further support of the assignment comes from nOe difference spectra, showing a strong (7%) nOe effect between the acetallic and hydroxylic protons for **11a**−**c**, but a weak (2%) nOe effect between the same protons for **10a**−**c**. These observations, corroborated by X-ray diffraction analysis[12] for **10c**, indicate that in compounds **10a**−**c** the acetallic proton and the proton at C-4 are cis, and both of them are trans to the OH at C-3. On the other hand, for compounds **11a**−**c** the acetallic proton and the OH at C-3 are cis but both of them are trans with respect to the proton at C-4.

Both the stereochemical outcome and the change in the stereoselection depend on the experimental conditions, and can be explained by accepting that the carbonyl−ene cyclization in these compounds is a reversible process[16] (Scheme 4). The cyclization leading to the *cis*-3,4-disubstituted pyrrolidine system occurs through the unstrained[17] *endo* transition states **A** and **B** which only differ in the relative orientation of the diastereofaces of the ene and enophile components.

The formation of diastereoisomers **11a** and **11c** was favored, in low selectivity, under kinetic reaction conditions because the chairlike[18] transition state **A** is more stable than **B**. This one suffers from steric repulsion between the perhydro-1,3-benzoxazine nucleus and the methyl group at $R^2$. On the other hand, compounds **10a** and **10c** should be more stable probably due to the establishment of a hydrogen bond between the OH group and the oxygen atom of the *N*,*O*-acetal, and consequently were the major diastereoisomers formed under thermodynamically controlled reactions.

By contrast, the formation of **10b** as the major diastereoisomer under any assayed experimental conditions can be explained as a consequence of the lack of steric interactions in the transition structure **B** ($R^2$ = H) making compound **10b** both kinetic and thermodynamically favored. The isolation of the kinetic compound **4** as a single diastereomer from the oxidation of **2** is a consequence of the mild reaction conditions.

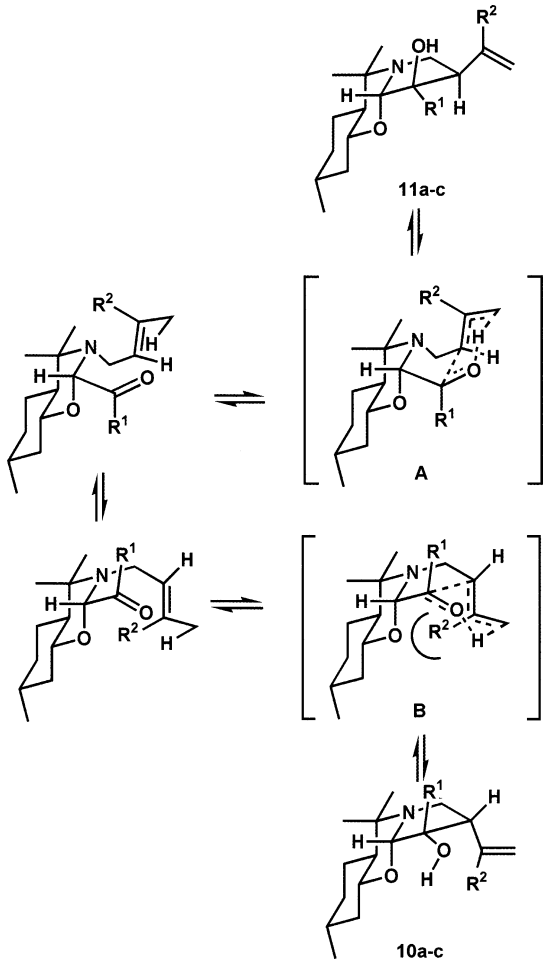
The major diastereoisomers **10a**−**c**, once isolated, were transformed into the enantiopure 3,4-disubstituted-3-

(16) (a) Warrington, J. M.; Yap, G. P. A.; Barriault, L. *Org. Lett.* **2000**, *2*, 663. (b) Ripoll, J. L.; Valée, Y. *Synthesis* **1993**, 659.

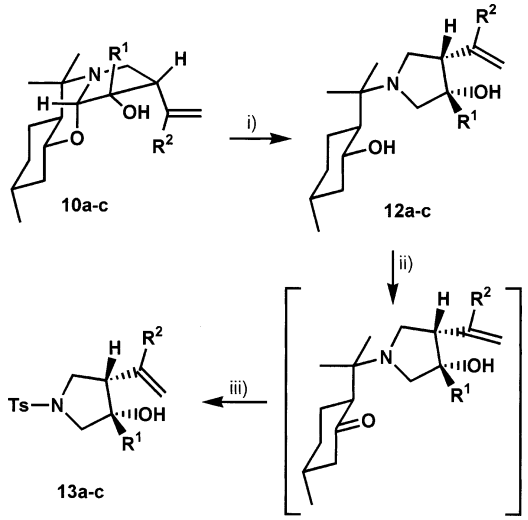
(17) (a) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947. (b) Oppolzer, W.; Pfenninger, E.; Keller, K. *Helv. Chim. Acta* **1973**, *56*, 1807.

(18) Braddock, D. C.; Hii, K. K.; Brown, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1720.

**SCHEME 4**




**SCHEME 5**[a]




[a] Conditions: (i) $AlH_3$, THF, −10 °C, 30 min. (ii) PCC, $CH_2Cl_2$, rt. (iii) 2.5 M KOH, $H_2O$, MeOH, THF (1:1:2), rt, 12 h, then TsCl, DIPEA, EtOAc, rt, 36 h (**13a**, 39%; **13b**, 45%; **13c**, 42% from **10a**−**c**, respectively).

hydroxy pyrrolidines **13a**−**c** as summarized in Scheme 5. Reductive ring opening of **10a**−**c** with aluminum hydride yielded 8-aminomenthols **12a**−**c**. The elimination of the chiral moiety was achieved, in moderate yields, by oxidation with PCC of **12a**−**c** to 8-aminomentone derivatives, which, without isolation, were transformed into the final pyrrolidines **13a**−**c** by elimination with KOH and tosylation.

In summary, we have reported herein several noteworthy features of the thermally induced intramolecular carbonyl−ene reaction in 2-acyl-3-allyl-substituted 1,3-perhydrobenzoxazines derived from (−)-8-aminomenthol. Specially interesting and unreported facts follow: (1) the participation of a ketone as an enophile under moderate thermal conditions, giving the formation of five-membered rings; (2) the good stereoselection observed in the cyclization process; (3) the reversibility of the reaction, and consequently the dependence of the stereoselection on both the structure of the starting compounds and the experimental conditions; and (4) the cyclization products that are easily transformed into enantiopure 3-hydroxy-3,4-substituted pyrrolidines.

## Experimental Section

**General.** All reactions were carried out under argon atmosphere, in oven-dried glassware. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were registered in $CDCl_3$ as solvent, and TMS as internal standard, and chemical shifts are given in ppm. Specific rotations were determined on a digital polarimeter using a Na lamp, and concentration is given in g per 100 mL. Melting points were obtained with open capillary tubes and are uncorrected. Solvents were dried by standard methods. TLC was performed on glass-backed plates coated with silica gel 60 with $F_{254}$ indicator; the chromatograms were visualized under UV light and/or by staining with a Ce/Mo reagent. Flash column chromatography was carried out on silica gel 60 (230−240 mesh).

**Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-[4,4,7-Trimethyl-3-(3-methylbut-2-enyl)octahydrobenzo[*e*][1,3]oxazin-2-yl]methanol (2).** A mixture of benzoxazine **1**[11] (3.0 g, 14.1 mmol), potassium carbonate (4.3 g, 31.0 mmol), and prenyl bromide (28.2 mmol) in dry acetonitrile (8 mL) was heated in an oil bath at 80−90 °C until the reaction was completed (TLC, 30 h). The reaction mixture was diluted with ethyl acetate, and the solid was separated by filtration and washed with hot ethyl acetate (3 × 25 mL). The solvents were evaporated under vacuum and the residue was purified by flash chromatography on silica gel, using hexanes−ethyl acetate 15:1 as eluent. Compound **2** was isolated as a colorless solid (91%), mp 64−65 °C (from ethanol). $[\alpha]^{25}_D$ −46.9 (*c* 0.9, $CHCl_3$). $^1$H NMR: $\delta$ 0.89−1.15 (m, 3H), 0.92 (d, 3H, $J$ = 6.5 Hz), 1.11 (s, 3H), 1.15 (s, 3H), 1.32−1.53 (m, 2H), 1.60−1.71 (m, 2H), 1.61 (d, 3H, $J$ = 0.7 Hz), 1.67 (d, 3H, $J$ = 1.3 Hz), 1.87−1.94 (m, 1H), 2.20 (br s, 1H), 3.02 (dd, 1H, $J_1$ = 6.1 Hz, $J_2$ = 17.1 Hz), 3.34 (dd, 1H, $J_1$ = 6.1 Hz, $J_2$ = 17.1 Hz), 3.46 (dt, 1H, $J_1$ = 4.1 Hz, $J_2$ = 10.6 Hz), 3.55 (d, 2H, $J$ = 5.6 Hz), 4.55 (t, 1H, $J$ = 5.6 Hz), 5.17 (m, 1H, $J_1$ = 1.3 Hz, $J_2$ = 6.1 Hz). $^{13}$C NMR: $\delta$ 17.8 ($CH_3$), 18.4 ($CH_3$), 22.1 ($CH_3$), 25.0 ($CH_2$), 25.7 ($CH_3$), 26.9 ($CH_3$), 31.2 (CH), 34.8 ($CH_2$), 41.0 ($CH_2$), 41.2 ($CH_2$), 47.6 (CH), 56.8 (C), 63.5 ($CH_2$), 75.6 (CH), 87.1 (CH), 126.5 (CH), 130.4 (C). IR: 3300, 3060, 840 cm$^{-1}$. CIMS (*m*/*z*, %): 282 (M + 1, 100%). Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.38; H, 11.39; N, 5.19.

**Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-Phenyl-(4,4,7-trimethyloctahydrobenzo[*e*][1,3]oxazin-2-yl) Ketone (5).** A mixture of (−)-8-aminomenthol (2.5 g, 15 mmol) and phenylglyoxal (2.01 g, 15 mmol) in dichloromethane (75 mL) was stirred for 24 h at room temperature. The solvent was removed under vacuum, yielding quantitatively the perhydrobenzoxazine **5**. An analytical sample was recrystallized from EtOH. Colorless solid, mp 69−70 °C (from ethanol). $[\alpha]^{25}_D$ −1.3 (*c* 1.1, $CHCl_3$). $^1$H NMR: $\delta$ 0.92 (d, 3H, $J$ = 6.5 Hz), 0.95−1.15 (m, 4H), 1.19 (s, 3H), 1.21 (s, 3H), 1.45−1.55 (m, 1H), 1.69−1.72 (m, 2H),

1.93−1.97 (m, 1H), 2.38 (br s, 1H, NH), 3.69 (dt, 1H, $J_1$ = 4.2 Hz, $J_2$ = 10.4 Hz), 5.64 (s, 1H), 7.42−7.56 (m, 3H), 8.06 (d, 2H, $J$ = 7.9 Hz). $^{13}$C NMR: $\delta$ 19.5 ($CH_3$), 22.2 ($CH_3$), 25.5 ($CH_2$), 29.6 ($CH_3$), 31.4 (CH), 34.8 ($CH_2$), 41.4 ($CH_2$), 51.1 (C), 51.4 (CH), 75.9 (CH), 80.6 (CH), 128.4 (2CH), 129.3 (2CH), 133.5 (CH), 134.6 (C), 193.0 (C═O). IR: 3320, 1680, 1590, 790, 700 cm$^{-1}$. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.40; H, 8.79; N, 4.78.

**Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-4,4,7-Trimethyloctahydrobenzo[*e*][1,3]oxazine-2-carboxylic Acid Ethyl Ester (6).** A mixture of (−)-8-aminomenthol (5.01 g, 30 mmol) and the hemiacetal of ethyl glyoxylate (4.44 g, 30 mmol) in benzene (75 mL) was refluxed in a Dean−Stark trap for 24 h. The solvent was removed under vacuum yielding quantitatively the perhydrobenzoxazine **6**. Colorless oil. $[\alpha]^{25}_D$ +20.22 (*c* 1.5, $CHCl_3$). $^1$H NMR: $\delta$ 0.85−1.05 (m, 2H), 0.87 (d, 3H, $J$ = 6.5 Hz), 1.06−1.16 (m, 2H), 1.06 (s, 3H), 1.09 (s, 3H), 1.26 (t, 3H, $J$ = 7.2 Hz), 1.35−1.50 (m, 1H), 1.60−1.65 (m, 2H), 1.87−1.94 (m, 1H), 1.99 (br s, 1H), 3.46 (dt, 1H, $J_1$ = 4.2 Hz, $J_2$ = 10.5 Hz), 4.13 (q, 2H, $J$ = 7.1 Hz), 4.83 (s, 1H). $^{13}$C NMR: $\delta$ 13.9 ($CH_3$), 19.2 ($CH_3$), 22.1 ($CH_3$), 25.3 ($CH_2$), 29.4 ($CH_3$), 31.2 (CH), 34.7 ($CH_2$), 41.1 ($CH_2$), 51.0 (C), 51.3 (CH), 61.5 ($CH_2$), 75.5 (CH), 81.1 (CH), 168.2 (C═O). IR: 3320, 2920, 1740 cm$^{-1}$. CIMS (*m*/*z*, %): 256 (M + 1, 100%). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 66.08; H, 10.01; N, 5.31.

**Alkylation of 5 and 6. General Procedure.** A mixture of benzoxazine **5** or **6** (14.1 mmol), potassium carbonate (4.3 g, 31.0 mmol), and the corresponding allyl bromide (28.2 mmol) in dry acetonitrile (8 mL) was heated in an oil bath at 80−90 °C until the reaction was completed (TLC, 30−80 h). The reaction mixture was diluted with ethyl acetate, and the solid was separated by filtration and washed with hot ethyl acetate (3 × 25 mL). The solvents were evaporated under vacuum and the residue was purified by flash chromatography on silica gel, using hexanes−ethyl acetate 15:1 as eluent.

**(2*S*,4a*S*,7*R*,8a*R*)-Phenyl-[4,4,7-trimethyl-3-(3-methylbut-2-enyl)octahydrobenzo[*e*] [1,3]oxazin-2-yl] Ketone (7a).** Colorless solid (95%), mp 65−66 °C (from ethanol). $[\alpha]^{25}_D$ −16.6 (*c* 1.2, $CHCl_3$). $^1$H NMR: $\delta$ 0.93−1.03 (m, 2H), 0.94 (d, 3H, $J$ = 6.5 Hz), 1.18−1.29 (m, 1H), 1.19 (s, 3H), 1.27 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.43−1.76 (m, 4H), 2.01−2.05 (m, 1H), 3.19 (dd, 1H, $J_1$ = 6.5 Hz, $J_2$ = 16.6 Hz), 3.32 (dd, 1H, $J_1$ = 6.5 Hz, $J_2$ = 16.6 Hz), 3.57 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.4 Hz), 4.71 (m, 1H), 5.66 (s, 1H), 7.39 (t, 2H, $J$ = 7.2 Hz), 7.50 (t, 1H, $J$ = 7.2 Hz), 8.20 (d, 2H, $J$ = 7.2 Hz). $^{13}$C NMR: $\delta$ 17.5 ($CH_3$), 19.8 ($CH_3$), 22.2 ($CH_3$), 25.0 ($CH_2$), 25.3 ($CH_3$), 26.8 ($CH_3$), 31.3 (CH), 34.9 ($CH_2$), 41.3 ($CH_2$), 42.3 ($CH_2$), 46.2 (CH), 57.5 (C), 76.2 (CH), 88.7 (CH), 126.2 (CH), 127.8 (2CH), 129.2 (2CH), 130.8 (C), 132.7 (CH), 135.4 (C), 194.6 (C═O). IR: 3100, 1680, 1600, 1500, 830, 750, 690 cm$^{-1}$. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.39; H, 9.11; N, 4.00.

**(2*S*,4a*S*,7*R*,8a*R*)-(3-But-2-enyl-4,4,7-trimethyloctahydrobenzo[*e*][1,3]oxazin-2-yl)phenyl Ketone (7b).** Yellowish oil (88%). $[\alpha]^{25}_D$ −18.0 (*c* 0.9, $CHCl_3$). $^1$H NMR: $\delta$ 0.87−1.05 (m, 2H), 0.93 (d, 3H, $J$ = 6.5 Hz), 1.12−1.32 (m, 1H), 1.19 (s, 3H), 1.27 (d, 3H, $J$ = 6.1 Hz), 1.37 (s, 3H), 1.39−1.57 (m, 2H), 1.61−1.73 (m, 2H), 1.99−2.04 (m, 1H), 3.16 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 16.8 Hz), 3.31 (dd, 1H, $J_1$ = 5.9 Hz, $J_2$ = 16.8 Hz), 3.57 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.5 Hz), 4.99−5.20 (m, 2H), 5.71 (s, 1H), 7.37−7.52 (m, 3H), 8.17 (d, 2H, $J$ = 7.1 Hz). $^{13}$C NMR: $\delta$ 17.4 ($CH_3$), 20.1 ($CH_3$), 22.2 ($CH_3$), 24.9 ($CH_2$), 26.7 ($CH_3$), 31.3 (CH), 34.9 ($CH_2$), 41.2 ($CH_2$), 46.1 (2CH), 57.7 (C), 76.2 (CH), 88.2 (CH), 125.8 (CH), 127.8 (2CH), 129.3 (2CH), 131.3 (CH), 132.8 (CH), 135.4 (C), 195.0 (C═O). IR: 3080, 1690, 1610, 1480, 1350, 980 cm$^{-1}$. CIMS (*m*/*z*, %): 342 (M + 1, 100%). Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.54; H, 9.32; N, 3.91.

**(2*S*,4a*S*,7*R*,8a*R*)-4,4,7-Trimethyl-3-(3-methylbut-2-enyl)-octahydrobenzo[*e*][1,3]oxazine-2-carboxylic Acid Ethyl Ester (8).** Colorless oil (88%). $[\alpha]_D^{25}$ −35.0 (*c* 1.1, $CHCl_3$). $^1$H NMR: $\delta$ 0.87−1.13 (m, 2H), 0.93 (d, 3H, $J$ = 6.5 Hz), 1.17 (s, 3H), 1.21 (s, 3H), 1.27 (t, 3H, $J$ = 7.2 Hz), 1.30−1.53 (m, 2H), 1.56 (s, 3H), 1.64 (s, 3H), 1.60−1.75 (m, 3H), 1.95−2.02 (m, 1H), 3.22 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 7.0 Hz), 3.34 (dd, 1H, $J_1$ = 6.2 Hz, $J_2$ = 7.0 Hz), 3.49 (dt, 1H, $J_1$ = 4.1 Hz, $J_2$ = 10.7 Hz), 4.13 (dq, 1H, $J_1$ = 7.1 Hz, $J_2$ = 10.8 Hz), 4.23 (dq, 1H, $J_1$ = 7.1 Hz, $J_2$ = 10.7 Hz), 5.06 (s, 1H), 5.16−5.36 (m, 1H). $^{13}$C NMR: $\delta$ 13.8 ($CH_3$), 17.5 ($CH_3$), 19.6 ($CH_3$), 21.9 ($CH_3$), 24.7 ($CH_2$), 25.4 ($CH_3$), 26.2 ($CH_3$), 31.0 (CH), 34.6 ($CH_2$), 40.8 ($CH_2$), 42.4 ($CH_2$), 45.6 (CH), 56.7 (C), 60.6 ($CH_2$), 75.7 (CH), 85.3 (CH), 126.1 (CH), 129.8 (C), 168.5 (C═O). IR: 3080, 2920, 1740, 830 cm$^{-1}$. CIMS (*m*/*z*, %): 324 (M + 1, 100%). Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.72; H, 10.09; N, 4.21.

**Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-4,4,7-Trimethyl-3-(3-methylbut-2-enyl)octahydrobenzo[*e*][1,3]-2-carboxylic Acid Methoxy Methyl Amide (9).** This compound was prepared by reaction of **8** with *N*,*O*-dimethyl hydroxylamine hydrochloride as previously described.[15] Colorless oil. $[\alpha]_D^{25}$ 39.6 (*c* 0.6, $CHCl_3$). $^1$H NMR: $\delta$ 0.87−1.02 (m, 2H), 0.92 (d, 3H, $J$ = 6.5 Hz), 1.08−1.31 (m, 2H), 1.15 (s, 3H), 1.25 (s, 3H), 1.40−1.65 (m, 2H), 1.55 (s, 3H), 1.63 (s, 3H), 1.65−1.76 (m, 1H), 1.92−2.02 (m, 1H), 3.13 (s, 3H), 3.15−3.36 (m, 1H), 3.40−3.80 (m, 2H), 3.81 (s, 3H), 5.17 (m, 1H), 5.62 (br s, 1H). $^{13}$C NMR: $\delta$ 17.6 ($CH_3$), 21.1 ($CH_3$), 22.1 ($CH_3$), 24.8 ($CH_2$), 25.6 ($CH_3$), 26.6 ($CH_3$), 31.3 (CH), 32.2 ($CH_3$), 34.9 ($CH_2$), 41.0 ($CH_2$), 41.9 ($CH_2$), 45.0 (CH), 57.3 (C), 61.5 ($CH_3$), 76.6 (CH), 82.8 (CH), 126.6 (CH), 129.5 (C), 169.9 (C═O). IR: 3080, 1640, 830 cm$^{-1}$.

**Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-2-Methyl-1-[4,4,7-trimethyl-3-(3-methylbut-2-enyl)octahydrobenzo[*e*][1,3]-oxazin-2-ylpropan-1-one (7c).** To a cooled (0 °C) solution of **9** (6.24 mmol, 2.1 g) in anhydrous THF (200 mL) was added a 2 M solution (18.72 mmol, 9.36 mL) of isopropylmagnesium chloride in $Et_2O$ and the mixture was stirred for 30 min. The reaction mixture was quenched by addition of a saturated solution of $NH_4Cl$ (200 mL). The aqueous phase was extracted with $Et_2O$ (4 × 25 mL), and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvents, the residue was recrystallized, giving to **7c** (59% from **8**) as a colorless solid, mp 61−62 °C (from ethanol). $[\alpha]^{25}_D$ −82.1 (*c* 0.9, $CHCl_3$). $^1$H NMR: $\delta$ 0.90−1.02 (m, 2H), 0.93 (d, 3H, $J$ = 6.5 Hz), 1.01 (d, 3H, $J$ = 6.9 Hz), 1.05−1.25 (m, 1H), 1.10 (d, 3H, $J$ = 6.9 Hz), 1.13 (s, 3H), 1.25 (s, 3H), 1.42−1.50 (m, 2H), 1.50 (s, 3H), 1.52−1.63 (m, 1H), 1.63 (d, 3H, $J$ = 1.3 Hz), 1.67−1.74 (m, 1H), 1.95−2.02 (m, 1H), 3.03 (dd, 1H, $J_1$ = 6.1 Hz, $J_2$ = 17.4 Hz), 3.10 (m, 1H, $J$ = 6.9 Hz), 3.26 (dd, 1H, $J_1$ = 4.9 Hz, $J_2$ = 17.4 Hz), 3.47 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.5 Hz), 5.13 (ddd, 1H, $J_1$ = 1.3 Hz, $J_2$ = 4.9 Hz, $J_3$ = 6.2 Hz), 5.15 (s, 1H). $^{13}$C NMR: $\delta$ 17.4 ($CH_3$), 17.8 ($CH_3$), 19.6 ($CH_3$), 21.5 ($CH_3$), 22.2 ($CH_3$), 24.9 ($CH_2$), 25.6 ($CH_3$), 26.6 ($CH_3$), 31.4 (CH), 35.0 ($CH_2$), 36.3 (CH), 41.1 ($CH_2$), 43.1 ($CH_2$), 44.9 (CH), 57.2 (C), 76.3 (CH), 88.4 (CH), 126.8 (CH), 130.2 (C), 210.9 (C═O). IR: 3060, 1680, 830 cm$^{-1}$. CIMS (*m*/*z*, %): 322 (M + 1, 100%). Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.54; H, 10.78; N, 4.56.

**Synthesis of (1*R*,2*R*,4a*S*,7*R*,8a*R*,9a*S*)-2-Isopropenyl-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (4).** To a cooled (−78 °C) solution of oxalyl chloride (15 mmol, 1.9 g, 1.32 mL) in $CH_2Cl_2$ (32 mL) was slowly dropped dimethyl sulfoxide (32 mmol, 2.5 g, 2.26 mL). After 15 min of stirring, a solution of **2** (12 mmol, 3.37 g) in $CH_2Cl_2$ (32 mL) was added and the mixture was stirred for 25 min and triethylamine (45 mmol, 6.26 mL) was added. The stirred mixture was allowed to reach rt, and then quenched by addition of $H_2O$ (32 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 25 mL), and the organics were washed with a solution of $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was recrystallized giving to **4** as a colorless solid (85%), mp 118−119 °C (from ethanol). $[\alpha]^{25}_D$ +6.85 (*c* 1.1, $CHCl_3$). $^1$H NMR: $\delta$ 0.81−1.07 (m, 3H), 0.84 (d, 3H, $J$ = 6.5 Hz), 1.08 (s, 3H), 1.09 (s, 3H), 1.31−1.39 (m, 2H), 1.49−1.65 (m, 2H), 1.74 (s, 3H), 1.76−1.82 (m, 1H), 2.00 (br s, 1H, OH), 2.92−3.10 (m, 3H),

3.36 (dt, 1H, $J_1 = 4.1$ Hz, $J_2 = 10.5$ Hz), 3.94 (br s, 1H), 4.62 (s, 1H), 4.81 (s, 1H), 4.93 (s, 1H). $^{13}$C NMR: $\delta$ 20.8 ($CH_3$), 22.2 ($CH_3$), 23.4 ($CH_3$), 24.7 ($CH_2$), 26.3 ($CH_3$), 31.2 (CH), 35.0 ($CH_2$), 41.4 ($CH_2$), 43.7 (CH), 45.4 ($CH_2$), 46.6 (CH), 52.9 (C), 74.5 (2CH), 91.5 (CH), 111.8 ($CH_2$), 142.9 (C). IR: 3450, 3100, 2940, 1630, 880 cm$^{-1}$. CIMS (*m*/*z*, %): 280 (M + 1, 100%). Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.31; H, 10.59; N, 5.20.

**Keto−Ene Cyclizations. General Procedure.** A 5-mmol sample of the corresponding compound **7a−c** was introduce in a pressure tube, under argon atmosphere, and heated as pure or in the corresponding solvent (25 mL) at the temperature and for the time indicated in Table 1. When the reactions were finished, the reaction mixtures were purified by flash chromatography or by recrystallization on the appropriate solvents.

**(1*R*,2*S*,4a*S*,7*R*,8a*R*,9a*S*)-2-Isopropenyl-4,4,7-trimethyl-1-phenyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (10a).** Yellow oil (60%, entry 5). $[\alpha]^{25}_D$ −25.7 (*c*=0.9, $CHCl_3$). $^1$H NMR: $\delta$ 0.86−0.99 (m, 2H), 0.91 (d, 3H, $J = 6.5$ Hz), 1.02−1.14 (m, 1H), 1.16 (s, 3H), 1.20 (s, 3H), 1.46−1.51 (m, 2H), 1.60 (s, 3H), 1.60−1.64 (m, 1H), 1.70−1.72 (m, 1H), 1.85−1.88 (m, 1H), 2.94 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 9.1$ Hz), 3.09 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 8.3$ Hz), 3.36 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 9.1$ Hz), 3.45 (dt, 1H, $J_1 = 4.1$ Hz, $J_2 = 10.4$ Hz), 3.73 (s, 1H, OH), 4.62 (s, 1H), 4.69 (s, 1H), 4.87 (s, 1H), 7.19−7.34 (m, 3H), 7.67 (dd, 2H, $J_1 = 1.4$ Hz, $J_2 = 7.1$ Hz). $^{13}$C NMR: $\delta$ 20.2 ($CH_3$), 22.3 ($CH_3$), 23.5 ($CH_3$), 24.8 ($CH_2$), 27.0 ($CH_3$), 31.2 (CH), 35.0 ($CH_2$), 41.2 ($CH_2$), 44.5 (CH), 47.1 ($CH_2$), 53.5 (C), 56.9 (CH), 75.0 (CH), 79.9 (C), 91.9 (CH), 111.3 ($CH_2$), 124.7 (2CH), 126.4 (CH), 127.8 (2CH), 143.6 (C), 147.9 (C). IR: 3300, 1600, 1500, 1480, 900, 760, 690 cm$^{-1}$. CIMS (*m*/*z*, %): 356 (M + 1, 100%). Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.54; H, 9.52; N, 4.12.

**(1*S*,2*R*,4a*S*,7*R*,8a*R*,9a*S*)-2-Isopropenyl-4,4,7-trimethyl-1-phenyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (11a).** Colorless solid (57%, entry 6), mp 75−76 °C (from ethanol). $[\alpha]^{25}_D$ −116.2 (*c* 1.0, $CHCl_3$). $^1$H NMR: $\delta$ 0.88−1.09 (m, 2H), 0.89 (d, 3H, $J = 6.5$ Hz), 1.16 (s, 3H), 1.18 (s, 3H), 1.38−1.48 (m, 1H), 1.48 (s, 3H), 1.48−1.61 (m, 3H), 1.69−1.72 (m, 1H), 1.78−1.83 (m, 1H), 2.88 (br s, 1H), 3.08 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 9.3$ Hz), 3.28 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 10.3$ Hz), 3.39 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 9.9$ Hz), 3.54 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 9.9$ Hz), 4.46 (s, 1H), 4.84 (s, 1H), 4.89 (s, 1H), 7.23−7.33 (m, 3H), 7.69 (dd, 2H, $J_1 = 1.5$ Hz, $J_2 = 7.1$ Hz). $^{13}$C NMR: $\delta$ 20.0 ($CH_3$), 22.3 ($CH_3$), 23.9 ($CH_3$), 24.8 ($CH_2$), 26.3 ($CH_3$), 31.3 (CH), 35.2 ($CH_2$), 41.2 ($CH_2$), 43.1 (CH), 46.7 ($CH_2$), 51.5 (CH), 53.3 (C), 74.6 (CH), 81.5 (C), 93.3 (CH), 112.6 ($CH_2$), 126.7 (CH), 127.2 (4CH), 139.9 (C), 143.0 (C). IR: 3350, 1600, 1480, 910, 760, 700 cm$^{-1}$. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.36; H, 9.10; N, 3.87.

**(1*R*,2*S*,4a*S*,7*R*,8a*R*,9a*S*)-4,4,7-Trimethyl-1-phenyl-2-vinyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (10b).** Colorless solid (70%, entry 11), mp 52−53 °C (from ethanol). $[\alpha]^{25}_D$ −35.0 (*c* 1.0, $CHCl_3$). $^1$H NMR: $\delta$ 0.85−1.02 (m, 2H), 0.90 (d, 3H, $J = 6.5$ Hz), 1.06−1.16 (m, 1H), 1.12 (s, 3H), 1.16 (s, 3H), 1.39−1.48 (m, 2H), 1.57−1.69 (m, 2H), 1.86−1.90 (m, 1H), 2.87 (q, 1H, $J = 8.4$ Hz), 3.09 (t, 1H, $J_1 = 8.4$ Hz), 3.15 (t, 1H, $J_1 = 8.4$ Hz), 3.44 (dt, 1H, $J_1 = 4.1$ Hz, $J_2 = 10.5$ Hz), 3.67 (s, 1H, OH), 4.67 (s, 1H), 4.86 (ddd, 1H, $J_1 = 0.8$ Hz, $J_2 = 1.8$ Hz, $J_2 = 16.4$ Hz), 5.00 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 10.3$ Hz), 5.91 (ddd, 1H, $J_1 = 8.4$ Hz, $J_2 = 10.3$, $J_3 = 16.4$ Hz), 7.16−7.31 (m, 3H), 7.58 (d, 2H, $J = 8.0$ Hz). $^{13}$C NMR: $\delta$ 19.0 ($CH_3$), 22.2 ($CH_3$), 24.8 ($CH_2$), 26.7 ($CH_3$), 31.2 (CH), 34.9 ($CH_2$), 41.2 ($CH_2$), 45.3 (CH), 48.8 ($CH_2$), 53.6 (C), 53.9 (CH), 75.2 (CH), 80.4 (C), 91.2 (CH), 116.2 ($CH_2$), 124.9 (2CH), 126.6 (CH), 127.8 (2CH), 136.1 (CH), 146.1 (C). IR: 3250, 1500, 930, 760, 690 cm$^{-1}$. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.16; H, 9.16; N, 4.49.

**(1*S*,2*R*,4a*S*,7*R*,8a*R*,9a*S*)-4,4,7-Trimethyl-1-phenyl-2-vinyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (11b).** Colorless solid (11%, entry 10), mp 109−110 °C (from ethanol). $[\alpha]^{25}_D$ −98.1 (*c* 0.5, $CHCl_3$). $^1$H NMR: $\delta$ 0.88−1.09 (m, 3H), 0.89 (d, 3H, $J = 6.5$ Hz), 1.17 (s, 3H), 1.18 (s, 3H), 1.29−1.54 (m, 2H), 1.57−1.62 (m, 1H), 1.67−1.73 (m, 1H), 1.77−1.84 (m, 1H), 2.91 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 9.1$ Hz), 2.97 (s, 1H, OH), 3.31 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 10.4$ Hz), 3.42 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 10.1$ Hz), 3.52 (m, 1H), 4.55 (s, 1H), 5.00 (dd, 1H, $J_1 = 0.8$ Hz, $J_2 = 17.2$ Hz), 5.03 (dd, 1H, $J_1 = 0.8$ Hz, $J_2 = 10.5$ Hz), 5.93 (ddd, 1H, $J_1 = 7.9$ Hz, $J_2 = 10.5$, $J_3 = 17.2$ Hz), 7.21−7.34 (m, 3H), 7.63 (d, 2H, $J = 7.1$ Hz). $^{13}$C NMR: $\delta$ 22.3 ($CH_3$), 22.4 ($CH_3$), 24.8 ($CH_2$), 26.1 ($CH_3$), 31.2 (CH), 35.1 ($CH_2$), 41.3 ($CH_2$), 43.0 (CH), 48.0 ($CH_2$), 48.7 (CH), 53.3 (C), 74.5 (CH), 82.3 (C), 92.6 (CH), 117.0 ($CH_2$), 127.0 (CH), 127.3 (2CH), 127.4 (2CH), 135.9 (CH), 138.8 (C). IR: 3450, 1600, 1500, 920, 760, 690 cm$^{-1}$. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.02; H, 8.92; N, 4.12

**(1*S*,2*S*,4a*S*,7*R*,8a*R*,9a*S*)-2-Isopropenyl-1-isopropyl-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-1-ol (10c).** Colorless solid (50%, entry 15), mp 64−65 °C (from ethanol). $[\alpha]^{25}_D$ −44.3 (*c* 0.8, $CHCl_3$). $^1$H NMR: $\delta$ 0.87−1.18 (m, 3H), 0.92 (d, 3H, $J = 6.5$ Hz), 0.96 (d, 3H, $J = 7.3$ Hz), 0.98 (d, 3H, $J = 7.0$ Hz), 1.09 (s, 3H), 1.11 (s, 3H), 1.43−1.56 (m, 2H), 1.57−1.61 (m, 1H), 1.70−1.75 (m, 1H), 1.78−1.94 (m, 2H), 1.82 (s, 3H), 2.74 (t, 1H, $J = 8.3$ Hz), 2.89 (t, 1H, $J = 8.3$ Hz), 3.09 (s, 1H, OH), 3.13 (t, 1H, $J = 8.3$ Hz), 3.47 (dt, 1H, $J_1 = 4.2$ Hz, $J_2 = 10.5$ Hz), 4.47 (s, 1H), 4.86 (s, 1H), 4.93 (s, 1H). $^{13}$C NMR: $\delta$ 17.2 ($CH_3$), 17.6 ($CH_3$), 20.1 ($CH_3$), 22.2 ($CH_3$), 22.9 ($CH_3$), 24.8 ($CH_2$), 26.4 ($CH_3$), 31.2 (CH), 35.0 ($CH_2$), 36.3 (CH), 41.3 ($CH_2$), 44.0 (CH), 48.3 ($CH_2$), 48.9 (CH), 53.1 (C), 74.9 (CH), 81.9 (C), 87.1 (CH), 113.0 ($CH_2$), 145.1 (C). IR: 3540, 3060, 2920, 1630, 930 cm$^{-1}$. CIMS (*m*/*z*, %): 322 (M + 1, 100%). Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.89; H, 11.05; N, 4.18.

**(1*R*,2*R*,4a*S*,7*R*,8a*R*,9a*S*)-2-Isopropenyl-1-isopropyl-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[*b*]naphthalene-1-ol (11c).** Colorless oil (41%, entry 13). $[\alpha]^{25}_D$ −11.2 (*c* 0.9, $CHCl_3$). $^1$H NMR: $\delta$ 0.87−1.04 (m, 2H), 0.88 (d, 3H, $J = 6.5$ Hz), 0.94 (d, 3H, $J = 6.8$ Hz), 0.96 (d, 3H, $J = 6.8$ Hz), 1.06 (s, 3H), 1.11 (s, 3H), 1.38−1.68 (m, 5H), 1.80−1.83 (m, 1H), 1.83 (s, 3H), 1.95 (hept, 1H, $J = 6.8$ Hz), 2.07 (s, 1H, OH), 2.76 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 9.0$ Hz), 2.95 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 10.1$ Hz), 3.17 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 10.1$ Hz), 3.28 (dt, 1H, $J_1 = 4.1$ Hz, $J_2 = 10.4$ Hz), 4.38 (s, 1H), 4.78 (s, 1H), 4.87 (s, 1H). $^{13}$C NMR: $\delta$ 16.7 ($CH_3$), 18.4 ($CH_3$), 21.8 ($CH_3$), 22.2 (2$CH_3$), 24.8 ($CH_2$), 26.1 ($CH_3$), 31.2 (CH), 32.0 (CH), 35.1 ($CH_2$), 41.4 ($CH_2$), 42.8 (CH), 49.0 ($CH_2$), 50.1 (CH), 52.9 (C), 74.3 (CH), 84.1 (C), 92.2 (CH), 113.9 ($CH_2$), 145.8 (C). IR: 3520, 3060, 2920, 1630, 1450, 1380, 990, 880 cm$^{-1}$. CIMS (*m*/*z*, %): 322 (M + 1, 100%). Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.58; H, 10.81; N, 4.22.

**Synthesis of Amino Alcohols 12a−c. General Method.** To a suspension of $LiAlH_4$ (0.57 g, 15 mmol) in anhydrous THF (40 mL) cooled to −10 °C was added, in portions, dry $AlCl_3$ (0.67 g, 5 mmol). The mixture was stirred for 10 min, and a solution of the corresponding adduct (3 mmol) in dry THF (20 mL) was slowly added. The reaction mixture was stirred fo 8 min at −10 °C and quenched by addition of $H_2O$ (4 mL). The resulting mixture was filtered, the solid was washed with EtOAc, and the organic layer was dried ($MgSO_4$). The solvent was eliminated under reduced pressure, and the residue was chromatographed on silica gel with hexane/EtOAc 3/1 as eluent.

**(3*R*,4*S*,1′*S*,2′*R*,4′*R*)-1-[1′-(2′-Hydroxy-4′-methylcyclohexyl)-1′-methylethyl]-4-isopropenyl-3-phenylpyrrolidin-3-ol (12a).** Colorless solid, mp 78−79 °C (from hexane). $[\alpha]^{25}_D$ +9.3 (*c* 0.9, $CHCl_3$). $^1$H NMR (333 K): $\delta$ 0.89 (d, 3H, $J = 6.5$ Hz), 0.93−1.01 (m, 2H), 1.05 (s, 3H), 1.22 (s, 3H), 1.21−1.28 (m, 1H), 1.31 (s, 3H), 1.36−1.43 (m, 2H), 1.56−1.68 (m, 2H), 1.92−1.97 (m, 1H), 2.28 (s, 1H, OH), 3.07−3.19 (m, 4H), 3.36 (d, 1H, $J = 10.8$ Hz), 3.67 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 10.2$ Hz), 4.86 (s, 1H), 4.99 (s, 1H), 7.18−7.33 (m, 3H), 7.49 (d, 2H, $J = 7.2$ Hz), 8.40 (br s, 1H). $^{13}$C NMR (333 K): $\delta$ 17.1 ($CH_3$), 21.4

($CH_3$), 21.9 ($CH_3$), 24.2 ($CH_3$), 25.6 ($CH_2$), 31.0 (CH), 35.1 ($CH_2$), 44.3 ($CH_2$), 48.5 ($CH_2$), 48.9 (CH), 56.3 (CH), 59.5 (C), 62.3 ($CH_2$), 72.8 (CH), 79.2 (C), 113.8 ($CH_2$), 125.0 (2CH), 126.7 (CH), 128.0 (2CH), 141.4 (C), 144.2 (C). IR: 3500, 3060, 1600, 1500, 900, 760, 690 $cm^{-1}$. Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87; N, 3.73. Found: C, 77.48; H, 9.85; N, 3.70.

**(3*R*,4*S*,1′*S*,2′*R*,4′*R*)-1-[1′-(2′-Hydroxy-4′-methylcyclohexyl)-1′-methylethyl]-3-phenyl-4-vinylpyrrolidin-3-ol (12b).** Colorless solid, mp 61−62 °C (from hexane). $[\alpha]^{25}_D$ −20.1 (*c* 1.0, $CHCl_3$). $^1H$ NMR (333 K): $\delta$ 0.87−1.01 (m, 2H), 0.89 (d, 3H, $J$ = 6.5 Hz), 1.04 (s, 3H), 1.21 (s, 3H), 1.25−1.36 (m, 1H), 1.37−1.47 (m, 2H), 1.55−1.69 (m, 2H), 1.88−1.96 (m, 1H), 2.05−2.40 (br s, 1H, OH), 3.00−3.15 (m, 4H), 3.32 (d, 1H, $J$ = 10.9 Hz), 3.65 (dt, 1H, $J_1$ = 4.0 Hz, $J_2$ = 10.3 Hz), 5.02 (dd, 1H, $J_1$ = 1.3 Hz, $J_2$ = 17.2 Hz), 5.13 (dd, 1H, $J_1$ = 1.3 Hz, $J_2$ = 10.8 Hz), 5.73 (ddd, 1H, $J_1$ = 6.3 Hz, $J_2$ = 10.8 Hz, $J_3$ = 17.2 Hz), 7.19−7.35 (m, 3H), 7.46 (d, 2H, $J$ = 7.3 Hz). $^{13}C$ NMR (333 K): $\delta$ 17.0 ($CH_3$), 21.3 ($CH_3$), 21.9 ($CH_3$), 25.6 ($CH_2$), 31.0 (CH), 35.1 ($CH_2$), 44.3 ($CH_2$), 48.8 ($CH_2$), 49.0 (CH), 52.8 (CH), 59.5 (C), 61.3 ($CH_2$), 72.8 (CH), 80.7 (C), 118.7 ($CH_2$), 125.2 (2CH), 127.0 (CH), 128.1 (2CH), 133.0 (CH), 143.3 (C). IR: 3200, 3060, 1600, 1500, 900, 760, 690 $cm^{-1}$. Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.01; H, 9.86; N, 3.77.

**(3*S*,4*S*,1′*S*,2′*R*,4′*R*)-1-[1′-(2′-Hydroxy-4′-methylcyclohexyl)-1′-methylethyl]-4-isopropenyl-3-isopropylpyrrolidin-3-ol (12c).** Colorless oil. $[\alpha]^{25}_D$ −41.6 (*c* 0.9, $CHCl_3$). $^1H$ NMR (333 K): $\delta$ 0.84−1.29 (m, 3H), 0.90 (d, 3H, $J$ = 6.5 Hz), 1.00 (d, 3H, $J$ = 6.9 Hz), 1.01 (d, 3H, $J$ = 6.9 Hz), 1.09 (s, 3H), 1.29 (s, 3H), 1.38−1.52 (m, 2H), 1.61−1.70 (m, 2H), 1.84 (hept, 1H, $J$ = 6.9 Hz), 1.85 (s, 3H), 1.94−2.01 (m, 1H), 2.74 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 11.2 Hz), 3.02−3.17 (m, 3H), 3.08 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 9.4 Hz), 3.73 (dt, 1H, $J_1$ = 4.1 Hz, $J_2$ = 10.4 Hz), 4.93 (s, 1H), 5.03 (s, 1H). $^{13}C$ NMR (333 K): $\delta$ 17.5 ($CH_3$), 17.8 ($CH_3$), 18.1 ($CH_3$), 20.8 ($CH_3$), 21.7 ($CH_3$), 23.8 ($CH_3$), 25.6 ($CH_2$), 31.0 (CH), 34.6 (CH), 34.7 ($CH_2$), 44.2 ($CH_2$), 48.4 (CH), 49.7 ($CH_2$), 50.2 (CH), 54.3 ($CH_2$), 62.3 (C), 72.0 (CH), 81.6 (C), 115.0 ($CH_2$), 141.4 (C). IR: 3300, 2940, 1630, 1450, 1370, 880 $cm^{-1}$. CIMS (*m*/*z*, %): 324 (M + 1, 100%). Anal. Calcd for $C_{20}H_{37}NO_2$: C, 74.25; H, 11.53; N, 4.33. Found: C, 74.12; H, 11.68; N, 4.19.

**Elimination of the Menthol Appendage. General Method.** A solution of amino derivatives **12a**−**c** (1.0 mmol) and PCC (1.3 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 (TCL, 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 EtOAc. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solvents were eliminated under vacuum, 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 dissolved in 50 mL of $CH_2Cl_2$ and washed with $H_2O$. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was eliminated under vacuum to give an oily residue that was treated with an excess of tosyl chloride in diisopropylethylamine for 36 h. After elimination of the solvents the residues were purified by recrystallization or flash chromatography.

**(3*R*,4*S*)-4-Isopropenyl-3-phenyl-1-tosylpyrrolidin-3-ol (13a).** Colorless solid (39% from **10a**), mp 90−91°C (from pentane). $[\alpha]^{25}_D$ +24.7 (*c* 0.3, $CHCl_3$). $^1H$ NMR: $\delta$ 1.23 (s, 3H), 2.09 (s, 1H, OH), 2.46 (s, 3H), 3.15 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 11.4 Hz), 3.48 (dd, 1H, $J_1$ = 9.5 Hz, $J_2$ = 11.4 Hz), 3.61 (d, 1H, $J$ = 11.2 Hz), 3.71 (d, 1H, $J$ = 11.2 Hz), 3.76 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 9.5 Hz), 4.74 (s, 1H), 4.98 (s, 1H), 7.25−7.37 (m, 7H), 7.77 (d, 2H, $J$ = 8.0 Hz). $^{13}C$ NMR: $\delta$ 21.6 ($CH_3$), 24.2 ($CH_3$), 50.1 ($CH_2$), 55.6 (CH), 62.8 ($CH_2$), 79.8 (C), 114.7 ($CH_2$), 125.0 (2CH), 127.5 (CH), 127.6 (2CH), 128.3 (2CH), 129.7 (2CH), 133.9 (C), 139.6 (C), 141.5 (C), 143.5 (C═). IR: 3400, 3100, 1620, 1500, 1180, 900, 830 $cm^{-1}$. CIMS (*m*/*z*, %): 358 (M + 1, 100%). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 66.97; H, 6.02; N, 4.10.

**(3*R*,4*S*)-3-Phenyl-1-tosyl-4-vinylpyrrolidin-3-ol (13b).** Yellowish oil (45% from **10b**). $[\alpha]^{25}_D$ +4.6 (*c* 0.7, $CHCl_3$). $^1H$ NMR: $\delta$ 2.01 (s, 1H, OH), 2.44 (s, 3H), 3.06−3.47 (m, 1H), 3.44 (dd, 1H, $J_1$ = 9.5 Hz, $J_2$ = 10.6 Hz), 3.59 (d, 1H, $J$ = 11.4 Hz), 3.66 (d, 1H, $J$ = 11.4 Hz), 3.73 (dd, 1H, $J_1$ = 7.7 Hz, $J_2$ = 9.5 Hz), 4.99 (d, 1H, $J$ = 17.4 Hz), 5.13 (d, 1H, $J$ = 10.7 Hz), 5.57 (ddd, 1H, $J_1$ = 6.6 Hz, $J_2$ = 10.7 Hz, $J_3$ = 17.4 Hz), 7.25−7.36 (m, 7H), 7.76 (d, 2H, $J$ = 8.2 Hz). $^{13}C$ NMR: $\delta$ 21.5 ($CH_3$), 50.1 ($CH_2$), 52.5 (CH), 61.9 ($CH_2$), 81.1 (C), 120.1 ($CH_2$), 125.1 (2CH), 127.5 (2CH), 127.7 (CH), 128.4 (2CH), 129.7 (2CH), 130.9 (CH), 134.0 (C), 140.5 (C), 143.6 (C). IR: 3380, 3100, 2960, 1620, 1500, 1180, 990, 830 $cm^{-1}$. CIMS (*m*/*z*, %): 344 (M + 1, 100%). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.28; H, 6.32; N, 3.91.

**(3*S*,4*S*)-4-Isopropenyl-3-isopropyl-1-tosylpyrrolidin-3-ol (13c).** Colorless solid (42% from **10c**), mp 139−140 °C (from hexane). $[\alpha]^{25}_D$ −4.8 (*c* 0.7, $CHCl_3$). $^1H$ NMR: $\delta$ 0.90 (d, 3H, $J$ = 6.9 Hz), 0.94 (d, 3H, $J$ = 6.9 Hz), 1.48 (d, 1H, $J$ = 0.8 Hz, OH), 1.69 (hept, 1H, $J$ = 6.9 Hz), 1.78 (s, 3H), 2.43 (s, 3H), 2.72 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 11.0 Hz), 3.18 (d, 1H, $J$ = 10.8 Hz), 3.30 (dd, 1H, $J_1$ = 9.3 Hz, $J_2$ = 11.0 Hz), 3.39 (dd, 1H, $J_1$ = 0.8 Hz, $J_2$ = 10.8 Hz), 3.51 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 9.3 Hz), 4.80 (s, 1H), 5.03 (s, 1H), 7.33 (d, 2H, $J$ = 8.2 Hz), 7.73 (d, 2H, $J$ = 8.2 Hz). $^{13}C$ NMR: $\delta$ 17.5 ($CH_3$), 18.0 ($CH_3$), 21.5 ($CH_3$), 24.3 ($CH_3$), 34.3 (CH), 49.9 (CH), 50.9 ($CH_2$), 55.3 ($CH_2$), 82.4 (C), 115.2 ($CH_2$), 127.4 (2CH), 129.6 (2CH), 133.8 (C), 140.4 (C), 143.4 (C). IR: 3400, 3100, 1620, 1160, 890, 820 $cm^{-1}$. CIMS (*m*/*z*, %): 324 (M + 1, 100%). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33. Found: C, 63.01; H, 7.96; N, 4.17.

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**Supporting Information Available:** Ortep representation of X-ray structures of **4** and **10c**, and $^1H$ NMR and $^{13}C$ NMR for compounds **2**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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