A Novel Approach to Chiral, Nonracemic Pyrrolidines by 5-exo-trig Diastereoselective Radical Cyclization on Acrylamides Derived from (−)-8-Aminomenthol

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α,β−Unsaturated amides supported on perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol as chiral auxiliaries undergo regio- and stereoselective 5-*exo-trig* radical cyclization leading to diastereomeric five-membered lactams. These cyclization products are transformed into enantiopure 3,4-disubstituted pyrrolidines by reduction with aluminum hydride followed by removal of the menthol appendage.

Introduction

Asymmetric formation of carbon−carbon bonds by free-radical addition is one of the most attractive, contemporary topics in organic synthesis, and high levels of stereoselectivity have been reported for intermolecular addition of alkyl radicals to carbon−carbon double bonds.[1] In this respect, α,β-unsaturated amides attached to a chiral auxiliary (e.g., C_2-pyrrolidine, camphorsultam, oxazolidine, and oxazolidinones) have been used for stereoselective free-radical addition due to their excellent diastereoselection.[2] More recently, enantioselective catalysis using N-acyloxazolidinones as radical acceptors has also been reported.[3]

The intramolecular version of these reactions remains essentially unexplored,[4] although some macrocyclizations[5] and intramolecular aryl radical additions directed to the synthesis of lactams[6] have been reported. Nevertheless, 5-hexenyl radical cyclizations concerning acrylamide moieties as acceptors have not been described so far.[7]

As a part of an ongoing project on the synthesis of enantiopure nitrogen heterocycles,[8] we have recently demonstrated[8b] that a radical centered at a substituent in C-2 of N-acryloyl-perhydro-1,3-benzoxazines cyclized regioselectively in a 5-exo way leading to γ-lactams. Now we report in full the results on the regio- and stereoselective cyclizations of radicals derived from chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol directed to the synthesis of chiral, nonracemic C-3- and C-4-substituted pyrrolidines.[10]

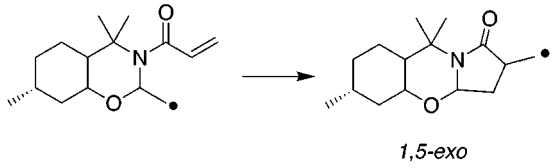

Figure 1.

Results

The synthesis of the starting perhydro-1,3-benzoxazines **3a**−**e** starting from (−)-8-aminomenthol, prepared from (+)-pulegone[9] is summarized in Scheme 1. Condensation of some α-phenylselenoaldehydes[11] with (−)-8-aminomenthol **1** afforded the N-unsubstituted perhydrobenzoxazines **2a**−**c** in excellent yield.[12] Obviously, perhydrobenzoxazines **2b** and **2c** were obtained as equimo-

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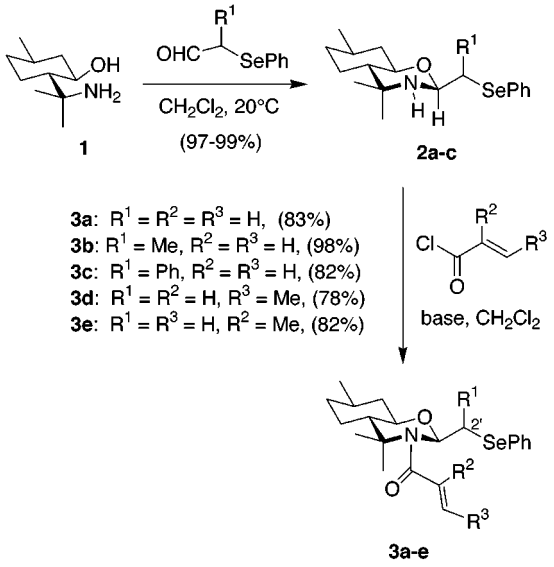
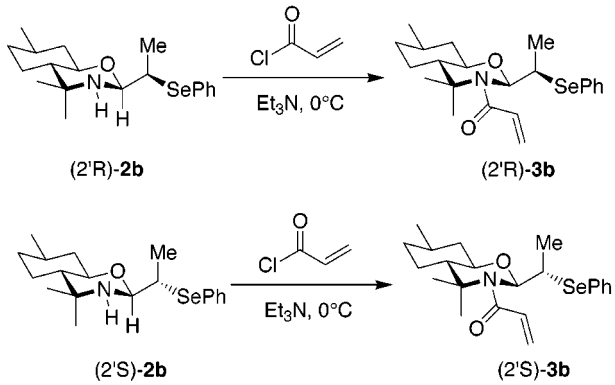
Scheme 1



Scheme 2



lar mixture of epimers at the carbon attached to selenium (C-2′) because racemic α−selenoaldehydes were used. At this stage, both diastereomers of **2b** could be separated by crystallization from hexanes and characterized by hydrolysis into (+) and (−)-2-phenylselenopropanal.[13]

The introduction of the α,*β*-unsaturated amide group was performed on **2a**−**c** by treatment with acryloyl chloride and triethylamine leading to **3a**−**c**, whereas **3d** was obtained by reaction of **2a** with crotonyl chloride in the presence of pyridine and **3e** by reaction of **2a** with methacryloyl chloride and TMEDA (Scheme 1). In a similar way, diastereomerically pure (2′*R*)-**3b** and (2′*S*)-**3b** were obtained from (2′*R*)-**2b** and (2′*S*)-**2b**, respectively, by stirring with acryloyl chloride and triethylamine (Scheme 2). In contrast with previous observations about the acylation of related auxiliaries,[14] the reaction of **2a**-**c** occurs in high to excellent chemical yield (78−98%).

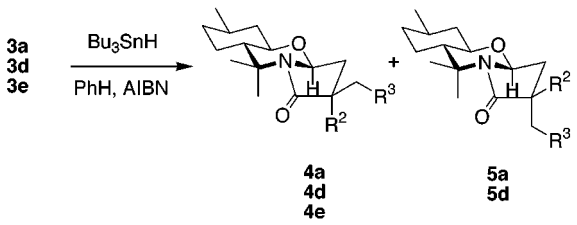
The radical cyclization was initially examined on acrylamide **3a**. After testing some experimental reaction conditions, the best chemical yield and stereoselectivity (81:19) were achieved by refluxing a 0.004 M solution of **3a**, tributyltin hydride (1.2 equiv), and AIBN (0.1 equiv) in benzene. The chemical yield decreased when the reaction was performed at higher concentration (Table 1, entry 3), whereas both the yield and the stereoselection

Table 1. Radical Cyclization of Amides 3a-e

entry	amide	solvent[a]	concn (M)	products ratio[b]	yield[c] (%)
1	3a	PhMe	0.2	**4a** (76), **5a** (24)	64
2	3a	PhMe	0.02	**4a** (78), **5a** (22)	66
3	3a	PhH	0.02	**4a** (81), **5a** (19)	70
4	3a	PhH	0.004	**4a** (81), **5a** (19)	94
5	3b	PhH	0.02	**4b** (48), ***epi*-4b** (33), **5b** (11), ***epi*-5b** (8)	87
6	3c	PhH	0.03	**4c** (72), **5c**(28)	82
7	3d	PhH	0.02	**4d** (81), **5d** (19)	84
8	3e	PhH	0.02	**4e**	81

[a] All reactions have been carried out at reflux of the specified solvent. [b] Determined in the crude reaction mixture by integration of the ^{1}H NMR 300 MHz spectrum. [c] Combined percent yield after chromatographic purification.

Scheme 3



4a, 5a: $R^2 = R^3 = H$; **4d, 5d**: $R^2 = H$, R^3 = Me; **4e**: R^2 = Me, $R^3 = H$

lowered when the reaction was carried out in refluxing toluene (entries 1 and 2). Some other reagents such as tristrimethylsilylsilane (TTMS)[15] or nonthermal initiation attempts (ultraviolet, triethylborane)[16] failed to promote the homolysis of the C−Se bond and therefore the subsequent cyclization.

The N-crotonyl perhydro-1,3-benzoxazine **3d** behaves in a similar way as described for **3a**. In this case, the slow addition (6−7 h, syringe pump) of a 0.02 M solution of tributyltin hydride and catalytic AIBN in benzene to a refluxing 0.02 M solution of **3d** in the same solvent yielded a mixture of two diastereomeric lactams **4d** and **5d** in 81:19 ratio and 84% combined yield (Table 1, entry 7).

It is worthy to note that the cyclization of **3a** and **3d** occurred with complete regioselectivity in a 5-exo way leading to the five-membered lactams **4a**, **5a** and **4d**, **5d**, respectively, in good diastereomeric excess. In this sense, our system resembles another related 3-aza-5-hexenyl radicals, in which 1,5 ring closure is the only observed cyclization.[9] To probe the reliability of the 5-exo attack on α,*β*-unsaturated amides, we tested the cyclization of methacrylamide **3e**, whose internal methyl group should disfavor the 5-exo addition process.[17] Interestingly, the reaction of **3e** with tributyltin hydride-AIBN (0.02 M, syringe pump) afforded a single product corresponding to the five-membered lactam **4e** (Scheme 3). No traces of 6-endo regioisomers[18] or another byproduct were observed by ^{1}H NMR analysis (Table 1, entry 8).

The stereochemistry of the diastereomers formed in the reactions of **3a** and **3d** was assigned on the basis of NOESY experiments. The cis-relationship between the acetalic proton and the α-H of the amide in major lactams **4a** and **4d** led us to assign the R configuration for the

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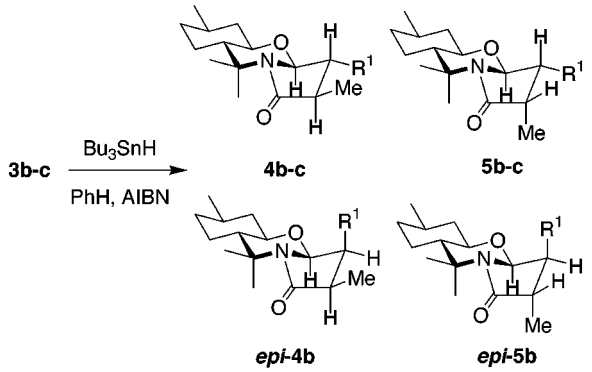
Scheme 4



stereocenters in these compounds. Conversely, the configuration of the α-carbon in the lactamic ring for the minor diastereomers **5a** and **5d** was assigned as S.

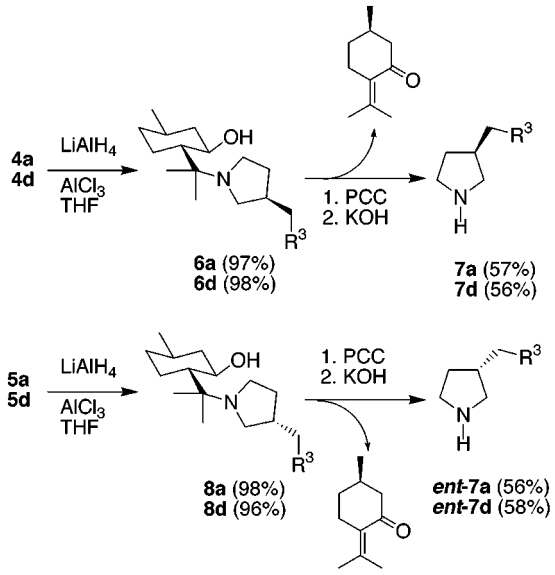
To our knowledge these are the first examples of stereoselective 5-exo-trig cyclizations performed on acrylamide acceptors as well as one of the few radical approaches to nonracemic lactams. In view of the good level of diastereoselection (i.e., 62%), we considered the preparation of 3,4-disubstituted nonracemic lactam derivatives by simultaneous formation of two stereocenters in the cyclization. This method required the generation of a secondary carbon-centered radical, so we first tried the reaction on the (C-2′)-substituted perhydrobenzoxazine **3b**. When the 1:1 epimeric mixture of this compound was refluxed with tributyltin hydride and AIBN (0.02 M, syringe pump 8 h) in benzene, a set of four cyclization products **4b**, ***epi*-4b**, **5b**, and ***epi*-5b** was formed in 48:33:11:8 ratio (Table 1, entry 5) corresponding to diastereomeric five-membered lactams (Scheme 4). The same distribution was obtained when pure (2′*R*)-**3b** or (2′*S*)-**3b** were independently subjected to the cyclization conditions.

All four diastereomers were separated by flash chromatography, and their structure was elucidated by NOE-difference and NOESY experiments. The all-trans relationship found in lactam **4b** and the all-cis relation observed in ***epi*-4b** allowed us to assign α-R,*β*-R configurations for the former and α-R,*β*-S for the latter. Similarly, the assigned configuration for diastereoisomer **5b** was α-S,*β*-R whereas ***epi*-5b** shows the *β*-opposite configuration, α-S,*β*-S. These data demonstrate that facial discrimation of the acrylamide acceptor is maintained at good levels (ca.. 81:19) but stereoselection at the radical site is somewhat disappointing (59:41).

Surprisingly, cyclization of the (C-2′)-phenyl benzoxazine **3c** led to a mixture of only two products **4c** and **5c** in a ratio 72:28 (Table 1, entry 6). Once isolated, these compounds were characterized as diastereomeric five-membered lactams and their stereochemistry was assigned as α-R,*β*-S, and α-S,*β*-S, respectively. In this case, the cyclization proceeds with total stereoselectivity at the radical site.

Some attempts to increase the diastereoselection by Lewis acid complexation[3] failed because no modification of the diastereomeric ratio has been currently observed.[19]

Scheme 5



The transformation of cyclization products into the final chiral, nonracemic pyrrolidines was carried out in two steps. Treatment of major diastereomers **4a** and **4d** with lithium aluminum hydride (5 equiv) and aluminum chloride (2 equiv) in THF produced ring opening of the N,O-acetalic moiety with concomitant reduction of the amide group, yielding 8-pyrrolidinylmenthols **6a** and **6d** in 95−99% yield (Scheme 5). Analogous cleavage reduction on minor lactams **5a** and **5d** led to pyrrolidinylmenthols **8a** and **8d**, respectively. Removal of the menthol appendage was achieved by PCC oxidation followed by *β*-elimination with KOH in H_2O/MeOH/THF. According to this protocol, (R)-3-alkylpyrrolidines **7a** and **7d** were obtained as pure enantiomers from pyrrolidinylmenthols **6a** and **6d**, whereas the (S)-3-alkyl series (***ent*-7a**, ***ent*-7d**) was isolated from **8a** and **8d**. These menthol derivatives and substituted pyrrolidines have been previously described.[9]

A similar procedure was followed for isolation of 3,4-disubstituted pyrrolidines (Scheme 6). Thus, (3R,4R)-3,4-dimethylpyrrolidine **10b** and (3S,4R)-4-methyl-3-phenylpyrrolidine **10c** were obtained from **9b** and **9c**, prepared by reduction of lactams **4b** and **4c**, respectively. In the same way (3S,4S)-4-methyl-3-phenylpyrrolidine **12c** was obtained from lactam **5c**, whereas the symmetrical cis-3,4-dimethylpirrolidine **12b** arises from **5b** or ***epi*-4b**. Finally (3S,4S)-3,4-dimethylpyrrolidine ***ent*-10b** was the final reduction−elimination product of the minor lactam ***epi*-5b**.

It is interesting to note the total regioselective 5-exo ring closure for the intramolecular radical additions in all the amides presented here. Frontier orbital theory has been used to justify the preferential 5-exo over 6-endo attack in 5-hexenyl radicals because the SOMO−LUMO interactions in the 5-exo transition state are more favorable than in the 6-endo pathway.[20] Our results suggest that this effective overlap should be also preferred when an unsaturated amide is placed on the structure and that the torsional strain controls the addition path.[21]

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(20) Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*, J. Wiley and Sons, 1978. For an aplication of the Frontier Orbital Theory to radical additions, see Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(21) A new set of MM2-parameters introduced by Houk indicate the crucial role of the C(acyl)-C(rad)-C(alkene) torsion angle in related acyl-5-hexenyl radical cyclizations. See Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651. For early MM2 calculation on amides, see Schnur, D. M.; Yuh, Y. H.; Dalton, D. R. *J. Org. Chem.* **1989**, *54*, 3779.

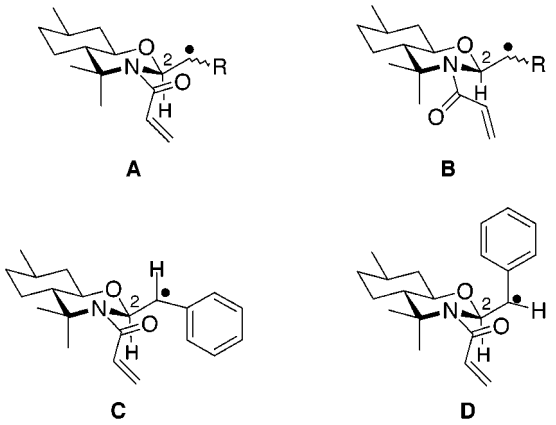
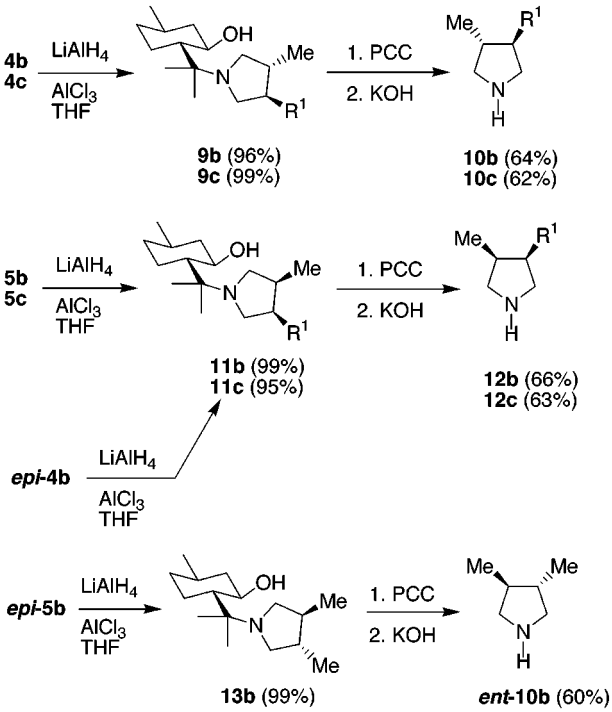


Figure 2.

Scheme 6



The stereochemical results for the cyclization of acrylamide **3a** could be explained on the basis of two different radical intermediates **A** and **B** (Figure 2). The major cyclization product **4a** was formed from the most stable[22] conformer **A**, whereas the less stable conformer **B** will be the responsible for the formation of the minor diastereoisomer **5a**. The isolation of four diastereoisomers from **3b** (R = Me) could be also explained on the basis of the same intermediates. Taking into account the pyramidal structure of the carbon bearing the unpaired electron, the facial discrimination on the acrylamide double bond is maintained, whereas the stereoselection at the stereogenic radical center is very poor.

By contrast, when a phenyl group is attached to the radical center, the intermediate adopts a planar structure,[23] which is responsible for the total stereocontrol at the benzylic stereocenter observed in the cyclization of **3c**. In this case, two planar conformations **C** and **D** can be proposed, but only **C** is highly stabilized by minimum allylic strain.[1a]

In summary, α,β-unsaturated amides attached to an (−)-8-aminomenthol-derived perhydro-1,3-benzoxazine system have been shown as excellent radical acceptors in intramolecular alkyl radical addition, providing five-membered lactams in high yield. Removal of the menthol auxiliary opens an access to enantiopure pyrrolidines.

Experimental Section

General methods have been previously specified.[9] Synthesis and characterization of compounds **1**, **2a**, **6a**, **6d**, **7a**, **7d**, ***ent*-7a**, ***ent*-7d**, **8a**, and **8d** are found in the preceding paper in this issue.[9]

(±)-2-Phenylselenopropionaldehyde.[11] To a solution of phenylselenyl bromide (3.78 g, 16 mmol) and diisopropylamine (4.5 mL, 32 mmol) in anhydrous THF (50 mL), stirred under argon atmosphere, was added propionaldehyde (1.2 mL, 16 mmol) at room temperature. The mixture was stirred for 1 h, the solid was eliminated by filtration, and the solution was concentrated in a vacuum. The oily residue was chromatographed on silica gel (Et_2O/hexane, 1/30) giving a racemic mixture of 2-phenylselenopropionaldehyde (2.9 g, 86%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.45 (d, 3H, J = 7.5 Hz), 3.75 (dq, 1H, J = 7.5 Hz, J = 2.8 Hz), 7.20−7.50 (m, 5H), 9.45 (d, 1H, J = 2.8 Hz). IR (neat, cm^{-1}): 2800, 2700, 1690, 735, 690.

(±)-2-Phenylselenophenylacetaldehyde.[11] This compound was prepared from acetaldehyde as described above. Yield: 64%. Pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.74 (d, 1H, J = 4.9 Hz), 7.1−7.6 (m, 10H), 9.63 (d, 1H, J = 4.9). IR (neat, cm^{-1}): 2800, 2720, 1700, 740, 690.

Perhydro-1,3-benzoxazine (2b). A solution of (−)-8-aminomenthol **1** (0.91 g, 5.3 mmol) and 2-phenylselenopropionaldehyde (1.2 g, 5.9 mmol) in anhydrous benzene (40 mL) was stirred overnight at room temperature. The solvent was removed under vacuum to give a mixture of epimeric perhydro-1,3-benzoxazines **2b** (1.9 g). The isolation of the diastereoisomers was carried out by flash chromatography (silica gel, EtOAc/Hexane, 1/15) yielding (2′*R*)-**2b** (672 mg, 1.85 mmol, 35%) as white solid, mp 62−63 °C (hexanes); $[\alpha]^{20}_D$ = +2.80 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 4H), 0.91 (d, 3H, J = 6.5 Hz), 1.09 (s, 3H), 1.10 (s, 3H), 1.45 (br. s., 1H), 1.54 (d, 3H, J = 7.1 Hz), 1.60−1.70 (m, 2H), 1.85−1.95 (m, 1H), 2.00−2.10 (m, 1H), 3.30 (dq, 1H, J = 7.1 Hz, J = 2.4 Hz), 3.40 (dt, 1H, J = 4.2 Hz, J = 10.7 Hz), 4.31 (d, 1H, J = 2.4 Hz), 7.20 (m, 3H), 7,65 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.8; 22.2; 25.4; 29.8; 31.3; 34.8; 41.5; 46.1; 51.1; 51.5; 74.8; 84.6; 127.1; 128.8; 129.9; 134.1; 134.3. IR (neat, cm^{-1}): 3265, 1575, 735, 690. CIMS (*m*/*z*, %): 368 (M + 1, 100), 210 (40), 182 (53). Anal. Calcd for $C_{19}H_{29}NOSe$: C, 62.28; H, 7.98; N, 3.82. Found: C, 62.38; H, 7.84; N, 3.84. (2′*S*)-**2b** (576 mg, 16 mmol, 30%): colorless oil, $[\alpha]^{20}_D$ = +20.1 (*c* 1.14, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.00 (m, 4H), 0.90 (d, 3H, J = 6.5 Hz), 1.07 (s, 3H), 1.09 (s, 3H), 1.37 (d, 3H, J = 7.1 Hz), 1.40−1.50 (m, 1H), 1.60−1.70 (m, 3H), 1.85−1.95 (m, 1H), 3.35−3.45 (m, 2H), 4.40 (d, 1H, J = 4.6 Hz), 7.20 (m, 3H), 7.65 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.2; 19.8; 22.2; 25.3; 29.8; 31.3; 34.9; 41.4; 43.2; 51.3; 51.6; 75.2; 85.0; 127.2; 128.7; 129.6; 134.8. IR (neat, cm^{-1}): 3260, 1570, 735, 690. CIMS (*m*/*z*, %): 368 (M + 1, 100), 210 (31), 182 (41). Anal. Calcd for $C_{19}H_{29}NOSe$: C, 62.28; H, 7.98; N, 3.82. Found: C, 62.37; H, 7.94; N, 3.83.

Perhydro-1,3-benzoxazine (2c). A mixture of of (−)-8-aminomenthol **1** (1.03 g, 6 mmol) and 2-phenylselenophenylacetaldehyde (1.82 g, 6.6 mmol) in anhydrous benzene (40 mL) was stirred at room temperature for 10 h. The solvent was evaporated under vacuum giving an equimolar mixture of epimeric perhydro-1,3-benzoxazines **2c** (2.68 g, 5.7 mmol, 95%), which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 0.80−1.10 (m, 4H), 0.92 and 0.93 (d, 3H, J = 6.5 Hz and J = 6.8 Hz), 0.96 and 1.07 (s, 3H), 1.08 and 1.13 (s, 3H), 1.40−

(22) Conformational searching and single point energy calculation were performed using UHF/PM3 Hamiltonian and then submitted to UHF/6-31G* optimization, as implemented in PcSpartan *Plus* (Wave function Inc., 1997).

(23) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064.

1.60 (m, 1H), 1.60−1.80 (m, 2H), 1.90−2.20 (m, 2H), 3.40 (m, 1H), 4.30 and 4.65 (d, 1H, J = 1.9 Hz and J = 3.8 Hz), 4.40 and 4.95 (d, 1H, J = 1.9 Hz and J = 3.8 Hz), 7.20 (m, 6H), 7.45 (m, 4H). Anal. Calcd for $C_{24}H_{31}NOSe$: C, 67.28; H, 7.29; N, 3.27. Found: C, 67.03; H, 7.51; N, 3.46.

***N*-Acryloyl-perhydro-1,3-benzoxazine (3a). General Procedure:** To a solution of benzoxazine **2a** (1.0 g, 2.8 mmol) and triethylamine (3.2 mmol, 0.260 mL) in dry dichloromethane (20 mL) under Ar at 0 °C was slowly added neat acryloyl chloride (0.435 mL, 3.1 mmol). The mixture was stirred for additional 30 min at room temperature and then was diluted with hexane (50 mL). The solid was eliminated by filtration, and the solvent was evaporated under vacuum. The residue was chromatographed on silica gel using CH_2Cl_2 as eluent, yielding the acrylamide **3a** (1.1 g, 2.5 mmol, 90%) as a pale yellow oil, $[\alpha]^{20}_D$ = +71.5 (*c* 1.12, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.20 (m, 3H), 0.94 (d, 3H, J = 6.5 Hz), 1.40−1.50 (m, 1H), 1.45 (s, 3H), 1.59 (s, 3H), 1.65−1.80 (m, 2H), 1.90 (m, 1H); 2.05 (m, 1H), 3.15 (dd, 1H, J = 5.0 Hz, J = 13.0 Hz), 3.49 (dd, 1H, J = 9.0 Hz, J = 13.0 Hz), 3.66 (dt, 1H, J = 4.0 Hz, J = 10.5 Hz), 5.40 (dd, 1H, J = 2.5 Hz, J = 9.9 Hz), 5.50 (dd, 1H, J = 9.0 Hz, J = 5.0 Hz), 6.05 (dd, 1H, J = 2.5 Hz, J = 16.6 Hz), 6.14 (dd, 1H, J = 9.9 Hz, J = 16.6 Hz), 7.30 (m, 3H), 7.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.1; 22.2; 25.3; 25.6; 31.2; 34.1; 38.0; 43.0; 47.1; 58.2; 72.3; 82.2; 125.9; 126.8; 128.7; 128.9; 131.0; 134.1; 166.7. IR (neat, cm^{-1}): 1635, 1600, 1570, 730, 685. EIMS (*m*/*z*, %): 407 (M, 0.36), 236 (94), 182 (89), 137 (30), 81 (57), 55 (100). Anal. Calcd for $C_{21}H_{29}NO_2Se$: C, 62.06; H, 7.19; N, 3.45. Found: C, 61.94; H, 7.11; N, 3.41.

***N*-Crotonyl-perhydro-1,3-benzoxazine (3d)**. To a stirred solution of **2a** (1.8 g, 5.2 mmol) and pyridine (0.85 mL, 10.5 mmol) in dichloromethane (15 mL) at 0 °C under Ar atmosphere was slowly added crotonyl chloride (1.1 mL, 10.4 mmol). The stirring was continued for 2 h at room temperature, the solvent was removed under vacuum, and the residue was chromatographed (silica gel, CH_2Cl_2) to afford **2a (**1.6 g, 75%) as oil, $[\alpha]^{20}_D$ = +57.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.20 (m, 3H), 0.93 (d, 3H, J = 6.4 Hz), 1.35−1.45 (m, 1H), 1.44 (s, 3H), 1.59 (s, 3H), 1.65 (d, 3H, J = 6.6 Hz), 1.70−1.80 (m, 2H), 1.90 (m, 1H), 2.10 (m, 1H), 3.15 (dd, 1H, J = 4.9 Hz, J = 12.8 Hz), 3.48 (dd, 1H, J = 9.1 Hz, J = 12.8 Hz), 3.65 (dt, 1H, J = 4.0 Hz, J = 10.3 Hz), 5.48 (dd, 1H, J = 9.1 Hz, J = 4.9 Hz), 5.80 (d, 1H, J = 14.8 Hz), 6.65 (m, 1H), 7.30 (m, 3H), 7.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.9; 19.0; 22.1; 25.6; 25.7; 31.2; 34.1; 38.0; 42.8; 47.0; 58.3; 72.2; 82.3; 125.0; 127.2; 129.2; 129.4; 133.0; 140.4; 166.8. IR (neat, cm^{-1}): 1650, 1620, 1575, 735, 685. CIMS (*m*/*z*, %): 422 (M + 1, 3), 268 (100), 250 (42), 222 (63), 137 (20). $C_{22}H_{31}NO_2Se$. Anal. Calcd for $C_{22}H_{31}NO_2Se$: C, 62.85; H, 7.43; N, 3.33. Found: C, 62.46; H, 7.18; N, 3.25.

***N*-Methacryloyl-perhydro-1,3-benzoxazine (3e)**. To a solution of **2a** (1.9 g, 5.3 mmol), TMEDA (1.2 mL, 8.2 mmol) in dry dichloromethane (15 mL), was dropped methacryloyl chloride (0.863 mL, 8.0 mmol), and the stirring was continued at room temperature for 30 min. Then, the solvent was removed and the residue was chromatographed (silica gel, CH_2Cl_2/hexane: 1/1) leading to **2a** (1.82 g, 82%) as oil, $[\alpha]^{20}_D$ = +87.0 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.00 (m, 2H), 0.93 (d, 3H, J = 6.6 Hz), 1.15 (m, 2H), 1.41 (s, 3H), 1.60 (s, 3H), 1.75 (m, 2H), 1.84 (s, 3H), 1.90 (m, 1H), 2.10 (m, 1H), 3.17 (dd, 1H, J = 6.0 Hz, J = 12.6 Hz), 3.43 (dd, 1H, J = 8.3 Hz, J = 12.6 Hz), 3.68 (dt, 1H, J = 4.1 Hz, J = 10.3 Hz), 4.97 (d, 2H, J = 18.8 Hz), 5.50 (dd, 1H, J = 9.1 Hz, J = 4.9 Hz), 7.20 (m, 3H), 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 18.0; 20.1; 21.9; 25.6; 25.9; 31.0; 34.2; 38.0; 43.3; 47.1; 57.8; 72.2; 83.0; 114.9; 127.0; 128.9; 130.1; 133.3; 142.4; 172.8. IR (neat, cm^{-1}): 1630, 1620, 730. 685. CIMS (*m*/*z*, %): 422 (M + 1, 5), 268 (100), 250 (31), 222 (45), 137 (32). Anal. Calcd for $C_{22}H_{31}NO_2Se$: C, 62.85; H, 7.43; N, 3.33. Found: C, 62.52; H, 7.21; N, 3.25.

(2′*R*)-*N*-Acryloyl-perhydro-1,3-benzoxazine [(2′*R*)-3b]. To a mixture of (2′*R*)-**2b** (826 mg, 2.26 mmol) and triethylamine (0.47 mL, 3.4 mmol) in dichloromethane (15 mL), at 0 °C, under argon, was slowly added acryloyl chloride (0.27 mL, 3.3 mmol), the reaction mixture was stirred for additional 30 min, and the solvent was evaporated under vacuum. The amide (2′*R*)-**3b** (936 mg) was obtained as a pale yellow oil and used without further purification: $[\alpha]^{20}_D$ = +115.0 (*c* 1.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.80−1.00 (m, 2H), 0.91 (d, 3H, J = 6.5 Hz), 1.10−1.30 (m, 1H), 1.16 (d, 3H, J = 7.0 Hz), 1.35−1.50 (m, 1H), 1.43 (s, 3H), 1.62 (s, 3H), 1.70 (m, 2H), 1.80−2.00 (m, 2H), 3.65 (dt, 1H, J = 4.6 Hz, J = 11.1 Hz), 3.90 (dq, 1H, J = 7.0 Hz, J = 10.3 Hz), 5.33 (d, 1H, J = 10.3 Hz), 5.50 (dd, 1H, J = 1.8 Hz, J = 10.5 Hz), 6.10 (dd, 1H, J = 1.8 Hz, J = 16.7 Hz), 6.37 (dd, 1H, J = 10.5 Hz, J = 16.7 Hz), 7.30 (m, 3H), 7.65 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 18.5; 18.9; 21.9; 25.4; 25.6; 31.1; 34.2; 42.5; 47.3; 47.8; 58.5; 71.7; 86.2; 126.7; 128.0; 128.1; 128.9; 131.7; 136.7; 167.8. IR (neat, cm^{-1}): 1640, 1600, 735, 690. CIMS (*m*/*z*, %): 422 (M + 1, 10), 268 (63), 264 (62), 236 (44), 208 (100). Anal. Calcd for $C_{22}H_{31}NO_2Se$: C, 62.85; H, 7.43; N, 3.33. Found: C, 63.09; H, 7.62; N, 3.16.

(2′*S*)-*N*-Acryloyl-perhydro-1,3-benzoxazine [(2′*S*)-3b]. The named compound was obtained from (2′*S*)-**2b** by the above procedure in 98% yield as a pale yellow oil, $[\alpha]^{20}_D$ = +42.4 (*c* 1.43, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.80−1.05 (m, 2H), 0.93 (d, 3H, J = 6.5 Hz), 1.10−1.25 (m, 2H), 1.45 (s, 3H), 1.47 (d, 3H, J = 7.0 Hz), 1.63 (s, 3H), 1.70 (m, 2H), 1.85 (m, 1H), 2.05 (m, 1H), 3.66 (dt, 1H, J = 4.6 Hz, J = 11.0 Hz), 3.80 (dq, 1H, J = 7.0 Hz, J = 10.3 Hz), 5.33 (d, 1H, J = 10.3 Hz), 5.65 (dd, 1H, J = 1.8 Hz, J = 10.5 Hz), 6.20 (dd, 1H, J = 1.8 Hz, J = 16.8 Hz), 6.61 (dd, 1H, J = 10.5 Hz, J = 16.8 Hz), 7.20 (m, 3H), 7.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.2; 20.1; 21.9; 25.5; 25.7; 31.1; 34.4; 43.3; 47.6; 49.4; 58.3; 71.9; 86.0; 126.3; 128.1; 129.0; 129.2; 132.3; 135.9; 167.9. IR (neat, cm^{-1}): 1640, 1600, 735, 690. CIMS (*m*/*z*, %): 422 (M + 1, 9), 268 (45), 266 (27), 236 (29), 208 (100). Anal. Calcd for $C_{22}H_{31}NO_2Se$: C, 62.85; H, 7.43; N, 3.33. Found: C, 62.68; H, 7.59; N, 3.49.

***N*-Acryloyl-perhydro-1,3-benzoxazine (3c)**. To a mixture of epimeric benzoxazines **2c** (856 mg, 2 mmol) and triethylamine (0.24 mL, 3 mmol) in anhydrous CH_2Cl_2, cooled to 0 °C, under argon, was slowly added acryloyl chloride (0.3 mL, 2.2 mmol), and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure giving an equimolar mixture of epimeric **3c** (935 mg, 1.94 mmol, 97%) as pale yellow oil. ^{1}H NMR ($CDCl_3$) mixture of epimers at C-2′: δ 0.70−1.00 (m, 2H), 0.84 and 0.98 (d, 3H, J = 6.6 Hz and J = 6.0 Hz), 1.10−1.35 (m, 2H), 1.40 and 1.46 (s, 3H), 1.67 and 1.72 (s, 3H), 1.80−2.10 (m, 4H), 3.60 and 3.75 (m, 1H), 4.76 and 5.01 (d, 1H, J = 9.6 Hz), 5.13 and 5.71 (dd, 1H, J = 1.6 Hz, J = 10.8 Hz, and J = 1.7 Hz, J = 10.6 Hz), 5.50 and 6.26 (dd, 1H, J = 1.6 Hz, J = 16.8 Hz, and J = 1.7 Hz, J = 16.8 Hz), 5.83 and 5.99 (d, 1H, J = 9.6 Hz), 5.97 and 6.74 (dd, 1H, J = 10.8 Hz, J = 10.6 Hz and J = 10.8, J = 16.8 Hz), 7.00−7.30 (m, 10H). Anal. Calcd for $C_{27}H_{33}NO_2Se$: C, 67.21; H, 6.89; N, 2.90. Found: C, 67.14; H, 7.02; N, 3.14.

Cyclization of Acrylamides (3a−d). General Procedure: A 0.02 M solution (20 mL) of the corresponding amides **3a**−**d** in benzene was placed in a two-necked flask equipped with a reflux condenser and a magnetic bar, under argon atmosphere. The solution was heated to reflux, and a 0.08 M solution of Bu_3SnH (6 mL, 1.2 equiv) and AIBN (0.1 equiv) in benzene was slowly added (syringe pump, 7−12 h). The heating was continued until disappearance of starting material (TLC). When the reaction was finished, the solvent was removed under vacuum, and the residues chromatographed on silica gel using ethyl acetate/hexanes or dichloromethane mixtures as eluent.

Lactam (4a). White solid, mp 64−65 °C (from pentane), $[\alpha]^{20}_D$ = −35.8 (*c* 0.99, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.95 (d, 3H, J = 6.6 Hz), 0.95−1.20 (m, 3H), 1.18 (s, 3H), 1.20−1.50 (m, 2H), 1.21 (d, 3H, J = 7.0 Hz), 1.39 (ddd, 1H, J = 7.5 Hz, J = 10.0 Hz, J = 12.5 Hz), 1.60−1.90 (m, 2H), 1.73 (s, 3H), 2.05 (m, 1H), 2.24 (ddq, 1H, J = 7.0 Hz, J = 10.0 Hz, J = 9.0 Hz), 2.41 (ddd, 1H, J = 6.0 Hz, J = 12.5 Hz, J = 9.0 Hz), 3.41 (dt, 1H, J = 4.1 Hz, J = 10.3 Hz), 4.89 (dd, 1H, J = 6.0 Hz, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 16.0; 18.2; 21.9; 24.0; 24.9; 31.1; 33.8; 34.4; 36.3; 41.1; 41.9; 58.0; 76.2; 84.1; 175.7. IR (neat, cm^{-1}): 1680, 1270, 735. CIMS (*m*/*z*, %): 252 (M + 1, 100), 236 (4), 139 (3). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.39; H, 9.79; N, 5.39.

Lactam (5a). Colorless oil; $[\alpha]^{20}_D$ = −61.5 (*c* 1.22, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 3H), 0.93 (d, 3H, J = 6.6 Hz), 1.13 (d, 3H, J = 7.4 Hz), 1.19 (s, 3H), 1.20−1.35 (m, 2H), 1.40−1.55 (m, 2H), 1.73 (s, 3H), 1.83 (ddd, 1H, J = 6.2 Hz, J = 6.6 Hz, J = 13.7 Hz), 1.90−2.05 (m, 1H), 1.99 (ddd, 1H, J = 13.7 Hz, J = 5.0 Hz, J = 9.4 Hz), 2.55 (ddq, 1H, J = 7.4 Hz, J = 6.6 Hz, J = 9.4 Hz), 3.42 (dt, 1H, J = 4.0 Hz, J = 10.2 Hz), 5.02 (dd, 1H, J = 6.2 Hz, J = 5.0 Hz). ^{13}C NMR ($CDCl_3$): δ 17.0; 18.9; 22.1; 24.0; 25.1; 31.2; 33.0; 34.1; 35.8; 41.0; 49.9; 57.0; 76.2; 84.1; 176.5. IR (neat, cm^{-1}): 1680, 1270, 735. CIMS (*m*/*z*, %): 252 (M + 1, 100), 137 (15), 139 (12). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.57; H, 9.66; N, 5.21.

Lactam (4b). White solid, mp 68−69 °C (pentane), $[\alpha]^{20}_D$ = −54.5 (*c* 2.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 3H), 0.94 (d, 3H, J = 6.5 Hz), 1.15 (d, 3H, J = 6.7 Hz), 1.16 (s, 3H), 1.17 (d, 3H, J = 7.3 Hz), 1.30 (m, 1H), 1.40−1.55 (m, 1H), 1.60−1.85 (m, 4H), 1.72 (s, 3H), 2.05 (m, 1H), 3.37 (dt, 1H, J = 4.2 Hz, J = 10.5 Hz), 4.42 (d, 1H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.0; 14.8; 17.9; 21.7; 23.6; 25.3; 30.9; 34.2; 40.8; 41.3; 43.5; 49.3; 56.3; 75.8; 89.3; 174.7. IR (neat, cm^{-1}): 1690. CIMS (*m*/*z*, %): 266 (M + 1, 100), 153 (4), 112 (18). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.22; H, 9.99; N, 5.41.

Lactam *epi*-(4b). Colorless oil; $[\alpha]^{20}_D$ = −36.0 (*c* 2.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, J = 7.0 Hz), 0.90−1.15 (m, 3H), 0.95 (d, 3H, J = 6.5 Hz), 1.10 (d, 3H, J = 7.0 Hz), 1.16 (s, 3H), 1.20−1.35 (m, 1H), 1.40−1.55 (m, 1H), 1.60−1.80 (m, 2H), 1.70 (s, 3H), 2.05 (m, 1H), 2.30−2.50 (m, 2H), 3.39 (dt, 1H, J = 4.2 Hz, J = 10.5 Hz), 4.85 (d, 1H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 8.2; 10.3; 18.0; 22.1; 23.9; 25.7; 31.2; 34.4; 34.5; 40.4; 41.0; 49.6; 56.4; 75.6; 85.6; 175.7. IR (neat, cm^{-1}): 1690. CIMS (*m*/*z*, %): 266 (M + 1, 100), 153 (14), 112 (18). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.58; H, 10.08; N, 4.92.

Lactam (5b). Colorless oil; $[\alpha]^{20}_D$ = −80.8 (*c* 3.50, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.15 (m, 3H), 0.94 (d, 3H, J = 6.6 Hz), 1.01 (d, 3H, J = 7.7 Hz), 1.05 (d, 3H, J = 7.1 Hz), 1.16 (s, 3H), 1.30 (m, 1H), 1.40−1.55 (m, 1H), 1.70−1.80 (m, 2H), 1.72 (s, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 2.51 (dq, 1H, J = 8.7 Hz, J = 7.7 Hz), 3.38 (dt, 1H, J = 4.2 Hz, J = 10.5 Hz), 4.52 (d, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 11.4; 11.8; 18.5; 21.9; 23.9; 25.4; 31.1; 34.3; 36.0; 39.7; 40.9; 49.7; 56.5; 76.1; 90.0; 176.3. IR (neat, cm^{-1}): 1690. CIMS (*m*/*z*, %): 266 (M + 1, 100), 153 (7), 112 (8). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.60; H, 10.42; N, 5.14.

Lactam *epi*-(5b). Colorless oil; $[\alpha]^{20}_D$ = −81.5 (*c* 0.52 CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.05 (m, 3H), 0.93 (d, 3H, J = 6.6 Hz), 1.04 (d, 3H, J = 7.0 Hz), 1.11 (d, 3H, J = 7.3 Hz), 1.20 (s, 3H), 1.20−1.35 (m, 1H), 1.35−1.55 (m, 1H), 1.65−1.75 (m, 2H), 1.72 (s, 3H), 1.80−1.95 (m, 2H), 2.14 (quintuplet, 1H, J = 7.3 Hz), 3.43 (dt, 1H, J = 4.2 Hz, J = 10.5 Hz), 4.91 (d, 1H, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 12.6; 14.8; 20.1; 22.0; 24.2; 25.5; 31.2; 34.5; 38.0; 41.0; 44.1; 50.5; 57.3; 76.1; 85.3; 177.0. IR (neat, cm^{-1}): 1690. CIMS (*m*/*z*, %): 266 (M + 1, 100), 153 (6), 112 (15). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.63; H, 10.38; N, 5.09.

Lactam (4c). White solid, mp 111−112 °C (hexanes), $[\alpha]^{20}_D$ = −63.3 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 3H), 0.92 (d, 3H, J = 6.5 Hz), 1.21 (s, 3H), 1.22 (d, 3H, J = 7.0 Hz), 1.30−1.50 (m, 2H), 1.65−1.75 (m, 2H), 1.78 (s, 3H), 1.95 (m, 1H), 2.44 (dq, 1H, J = 10.8 Hz, J = 7.0 Hz), 2.80 (dd, 1H, J = 10.8 Hz, J = 7.2 Hz), 3.33 (dt, 1H, J = 4.3 Hz, J = 10.5 Hz), 4.84 (d, 1H, J = 7.2 Hz), 7.30−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.8; 18.4; 22.0; 23.9; 25.6; 31.2; 34.4; 41.0; 43.3; 49.6; 52.8; 57.0; 76.3; 89.1; 127.3; 127.9; 128.7; 138.8; 174.1. IR (neat, cm^{-1}): 1700, 690. CIMS (*m*/*z*, %): 328 (M + 1, 100), 282 (19). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.92; N, 4.27. Found: C, 77.24; H, 8.73; N, 4.31.

Lactam (5c). White solid, mp 94−95 °C (hexanes), $[\alpha]^{20}_D$ = −172 (*c* 0.74, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.76 (d, 3H, J = 7.5 Hz), 0.85−1.10 (m, 3H), 0.92 (d, 3H, J = 6.5 Hz), 1.28 (s, 3H), 1.30−1.55 (m, 2H), 1.70−1.90 (m, 2H), 1.80 (s, 3H), 1.95 (m, 1H), 2.86 (dq, 1H, J = 9.2 Hz, J = 7.5 Hz), 3.39 (dd, 1H, J = 9.2 Hz, J = 5.3 Hz), 3.49 (dt, 1H, J = 4.1, J = 10.7), 5.22 (d, 1H, J = 5.3 Hz), 7.10−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.6; 19.2; 22.0; 24.1; 25.6; 31.2; 34.4; 40.7; 41.0; 47.5; 50.0; 57.3; 76.4; 87.8; 126.9; 128.2; 128.4; 137.4; 175.7. IR (neat, cm^{-1}): 1680, 695. CIMS (*m*/*z*, %): 328 (M + 1, 100), 211 (22), 172 (24), 137 (12).

Lactam (4d). Colorless oil; $[\alpha]^{20}_D$ = −53.8 (*c* 1.11, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, J = 7.5 Hz), 0.95 (d, 3H, J = 6.4 Hz), 0.95−1.15 (m, 3H), 1.17 (s, 3H), 1.20−1.35 (m, 1H), 1.35−1.50 (m, 3H), 1.65−1.80 (m, 2H), 1.72 (s, 3H), 1.83−2.05 (m, 2H), 2.10−2.25 (m, 1H), 2.30−2.45 (m, 1H), 3.40 (dt, 1H, J = 4.0 Hz, J = 10.2 Hz), 4.88 (dd, 1H, J = 6.4 Hz, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 10.9; 18.1; 22.2; 23.9; 24.1; 25.0; 30.9; 31.1; 33.9; 41.2; 42.1; 50.1; 56.7; 76.2; 84.0; 175.0. IR (neat, cm^{-1}): 1685, 1265. CIMS (*m*/*z*, %): 266 (M + 1, 100), 112 (16). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.19; H, 9.98; N, 5.07.

Lactam (5d). Colorless oil, $[\alpha]^{20}_D$ = −29.9 (*c* 0.85, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.90−1.10 (m, 3H), 0.93 (t, 3H, J = 7.3 Hz), 0.95 (d, 3H, J = 6.5 Hz), 1.19 (s, 3H), 1.25−1.55 (m, 4H), 1.65−1.80 (m, 2H), 1.74 (s, 3H), 1.90−2.00 (m, 3H), 2.45 (m, 1H), 3.43 (dt, 1H, J = 4.0 Hz, J = 10.2 Hz), 4.98 (t, 1H, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 11.3; 18.9; 22.0; 24.1; 24.7; 25.3; 30.0; 30.7; 33.9; 41.1; 42.1; 50.1; 56.8; 76.2; 84.2; 176.1. IR (neat, cm^{-1}): 1685, 1265. CIMS (*m*/*z*, %): 266 (M + 1, 100), 112 (17).

Cyclization of Amide (3e). A solution of **3e** (99 mg, 0.24 mmol) in refluxing benzene (12 mL) was treated with tributyltin hydride (0.1 mL, 0.35 mmol) and AIBN (3 mg) for 8 h. After evaporation of the solvent under vacuum, the residue was chromatographed on silica gel yielding the lactam **4e** (51 mg, 81%) as a white solid, mp 58−59 °C (hexanes); $[\alpha]^{20}_D$ = −39.1 (*c* 1.03, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 3H), 0.95 (d, 3H, J = 6.5 Hz), 1.05 (s, 3H), 1.17 (s, 3H), 1.19 (s, 3H), 1.20−1.35 (m, 1H), 1.40−1.50 (m, 1H), 1.65 (dd, 1H, J = 13.0 Hz, J = 6.8 Hz), 1.70−1.80 (m, 2H), 1.73 (s, 3H), 1.95 (m, 1H), 2.08 (dd, 1H, J = 6.1 Hz, J = 13.0 Hz), 3.40 (dt, 1H, J = 4.0 Hz, J = 10.3 Hz), 4.93 (t, 1H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 18.1; 22.2; 24.0; 25.1; 25.4; 25.7; 31.1; 34.2; 40.1; 40.3; 41.0; 50.1; 55.8; 76.2; 83.2; 178.0. IR (neat, cm^{-1}): 1685, 1275. CIMS (*m*/*z*, %): 266 (M + 1, 100), 153 (11), 112 (54). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.14; H, 10.04; N, 4.93.

Reductive Cleavage of Lactams (4−5). General Procedure: To a mixture of $LiAlH_4$ (0.5 g, 13.1 mmol) and $AlCl_3$ (713 mg, 5.34 mmol) in anhydrous THF (30 mL) at 0 °C was slowly injected a solution of the corresponding lactams **4** or **5** (2.7 mmol). The solution was stirred for 10 min at 0 °C, and then the mixture was carefully quenched with water (40 mL) and extracted with chloroform (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent evaporated under vacuum giving pure pyrrolidinylmentols **6a**,[9] **6d**,[9] **8a**,[9] **8d**,[9] **9b**, **9c**, **11b**, **11c**, and **13b**.

(3′*R*,4′*R*)-8-(3′,4′-Dimethylpyrrolidinyl)-menthol (9b). Yield: 96%. Colorless oil, $[\alpha]^{20}_D$ = −0.55 (*c* 2.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.90−1.05 (m, 15H), 1.14 (s, 3H), 1.45−1.70 (m, 7H), 1.95 (m, 1H), 2.20 (m, 1H), 2.65 (m, 1H), 2.95 (m, 2H), 3.50−3.60 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 15.9; 16.3; 17.5; 21.3; 22.0; 25.4; 30.9; 35.0; 40.0; 40.1; 44.2; 48.4; 52.6; 54.1; 59.0; 72.7. IR (neat, cm^{-1}): 3100, 1450. CIMS (*m*/*z*, %): 254 (M + 1, 100), 238 (8), 140 (90). Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 75.68; H, 12.21; N, 5.65.

(3′*R*,4′*S*)-8-(3′-Methyl-4′-phenylpyrrolidinyl)-menthol (9c). Yield: 99%. Colorless oil, $[\alpha]^{20}_D$ = −11.5 (*c* 1.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.10 (m, 4H), 0.90 (d, 3H, J = 6.4 Hz), 0.91 (s., 6H), 1.18 (s, 3H), 1.35−1.50 (m, 2H), 1.55−1.70 (m, 2H), 1.95−2.25 (m, 2H), 2.30−2.95 (m, 3H), 3.05−3.25 (m, 2H), 3.66 (dt, 1H, J = 4.2 Hz, J = 10.5 Hz), 7.20−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.5; 18.0; 21.5; 22.1; 25.5; 31.0; 35.1; 44.3; 48.5; 52.4; 52.8; 53.7; 54.5; 59.4; 72.9; 126.3; 127.6; 128.4. IR (neat, cm^{-1}): 3100, 1490, 700. CIMS (*m*/*z*, %): 316 (M + 1, 100), 202 (24). Anal. Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54; N, 4.44. Found: C, 80.11; H, 10.68; N, 4.29.

8-(3′,4′-*cis*-Dimethylpyrrolidinyl)-menthol (11b). The general cleavage-reduction protocol was followed starting from lactam **5c**. Yield: 99%. Oil, $[\alpha]^{20}_D$ = −17.1 (*c* 1.70, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.80−1.10 (m, 15H), 1.15 (s, 3H), 1.20 (s,

1H), 1.35−1.70 (m, 4H), 1.90 (m, 1H), 2.00−2.30 (br., 3H), 2.50−3.30 (m, 3H), 3.56 (dt, 1H, $J = 4.2$ Hz, $J = 11.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 13.7; 14.0; 16.7; 21.2; 22.0; 25.5; 29.6; 30.9; 33.2; 34.9; 35.1; 44.2; 48.4; 52.6; 59.0; 72.6. IR (neat, cm^{-1}): 3200, 1450, 1200. CIMS (*m/z*, %): 254 (M + 1, 100), 140 (47). Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 75.62; H, 12.15; N, 5.68. The same product was obtained from lactam ***epi*-4c** by similar reduction.

(3′*S*,4′*S*)-8-(4′-Methyl-3′-phenylpyrrolidinyl)-menthol (11c). Yield: 95%. Oil, $[\alpha]^{20}_D = -69.8$ (*c* 0.56, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.55−0.80 (m, 3H), 0.85−1.10 (m, 3H), 0.93 (d, 3H, $J = 6.5$ Hz), 1.03 (s, 3H), 1.21 (s, 3H), 1.28 (s, 1H), 1.40−1.70 (m, 4H), 1.98 (m, 1H), 2.30−2.50 (br., 6H), 3.68 (dt, 1H, $J =$ 4.3 Hz, $J = 10.5$ Hz), 7.10−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 15.8; 17.5; 21.5; 22.1; 25.6; 29.7; 31.0; 35.1; 44.3; 48.8; 53.2; 59.1; 72.8; 126.2; 128.1; 128.5. IR (neat, cm^{-1}): 3100, 1490, 695. CIMS (*m/z*, %): 316 (M + 1, 100), 202 (25). Anal. Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54; N, 4.44. Found: C, 79.79; H, 10.72; N, 4.28.

(3′*S*,4′*S*)-8-(3′,4′-Dimethylpyrrolidyl)-menthol (13b). Yield: 99%, oil; $[\alpha]^{20}_D = -37.7$ (*c* 2.30, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85−1.05 (m, 15H), 1.13 (s, 3H), 1.25 (s, 1H), 1.45−1.70 (m, 6H), 1.95 (m, 1H), 2.00−2.15 (br., 1H), 2.40−2.60 (br., 1H), 2.75−2.90 (br., 1H), 3.10−3.30 (br., 1H), 3.62 (dt, 1H, *J* = 4.2 Hz, $J = 11.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 16.9; 17.4; 19.4; 21.3; 22.2; 25.7; 31.1; 35.2; 39.3; 40.2; 44.4; 48.4; 52.3; 53.8; 58.7; 72.8. IR (neat, cm^{-1}): 3150, 1450. CIMS (*m/z*, %): 254 (M + 1, 100), 140 (41). Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 76.02; H, 12.14; N, 5.39.

Elimination of the Menthol Appendage. Synthesis of Pyrrolidine Derivatives. The elimination of the chiral appendage was carried out as previously described,[9] and now we describe the transformation of the pyrrolidinylmenthol **9b** into the dimethylpyrrolidine **10b** as an example.

(3*R*,4*R*)-3,4-Dimethylpyrrolidine (10b). To a solution of 8-pyrrolidinylmenthol **9b** (190 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) were added a solution of PCC (680 mg) in CH_2Cl_2 (5 mL) and molecular sieves (500 mg), and the mixture was stirred at room temperature for 2 h. The mixture was poured into aqueous NaOH solution and extracted with $CHCl_3$ (3 × 25 mL). The solvent was eliminated under vacuum at low temperature (10−20 °C), and the residue was treated with a 2.5 M solution (8 mL) of KOH in THF/MeOH/H_2O (2/1/1) for 3 h at room temperature. After that, the solution was acidified with diluted hydrochloric acid and concentrated under vacuum. The residue was extracted with EtO_2 (2 × 15 mL) to recover the (+)-pulegone. The aqueous phase was alkalinized by addition of diluted aqueous NaOH solution, and extracted with chloroform (3 × 25 mL). Isolation of the pyrrolidine, as hydrochloride, was accomplished by bubbling dry hydrogen chloride through the chloroformic solution giving **10b·HCl** (65 mg, 64%) as hygroscopic oil. $[\alpha]^{20}_D = +35$ (*c* 1.30, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.09 (d, 6H, $J = 5.2$ Hz), 1.87 (m, 2H), 2.86 (m, 2H), 3.54 (m, 2H), 9.3−9.9 (br.s., 2H). ^{13}C NMR ($CDCl_3$): δ 14.8; 39.9; 51.5. Benzoylation of this salt afforded the following compound.

(3′*R*,4′*R*)-*N*-benzoyl-3,4-dimethylpyrrolidine: Colorless oil, $[\alpha]^{20}_D = +117$ (*c* 1.83, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3H, $J = 6.2$ Hz), 1.08 (d, 3H, $J = 6.2$ Hz), 1.60−1.90 (m, 2H), 3.07 (t, 1H, $J = 10.2$ Hz), 3.20 (dd, 1H, $J = 12.1$ Hz, $J =$ 9.8 Hz), 3.56 (dd, 1H, $J = 10.2$ Hz, $J = 6.9$ Hz), 3.88 (dd, 1H, $J = 12.1$ Hz, $J = 7.3$ Hz), 7.30 (m, 3H), 7.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.1; 15.5; 39.3; 41.1; 53.6; 56.9; 127.1; 128.2; 129.7; 136.8; 169.4. IR (neat, cm^{-1}): 1620, 1570, 720, 700. EIMS (*m/z*, %): 203 (M, 47), 188 (47), 105 (100), 77 (35), 51 (7). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.23; H, 8.25; N, 6.83.

(3*R*,4*R*)-4-Methyl-3-phenylpyrrolidine (10c). *N*-Benzamide: oil, $[\alpha]^{20}_D = +63.1$ (*c* 0.32, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) mixture of rotamers: δ 0.89 and 1.00 (d, 3H, $J = 6.5$ Hz), 2.28 and 2.45 (m, 1H), 2.81 and 2.90 (dt, 1H, $J = 7.5$ Hz, $J = 10.9$ Hz and $J = 8.2$ Hz, $J = 10.6$ Hz), 3.22 and 3.54 (t, 1H, $J =$ 10.6 Hz), 3.35 and 3.75 (dd, 1H, $J = 12.0$ Hz, $J = 10.6$ Hz), 3.70−3.80 (m, 1H), 4.06 and 4.09 (t, 1H, $J = 12.7$ Hz and $J =$ 12.4 Hz), 7.10−7.60 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 15.1 and 15.5; 39.0 and 41.5; 51.1 and 52.7; 53.5; 56.8 and 57.1; 127.1; 127.2; 127.5; 127.6; 128.2; 128.6; 129.9; 136.5 and 136.7; 138.7 and 139.4; 169.4. IR (neat, cm^{-1}): 3060, 3020, 1625, 1575, 720, 700. EIMS (*m/z*, %): 265 (M, 21), 134 (9), 117 (11), 105 (100), 91 (14), 77 (54), 51 (16). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.31; H, 7.39; N, 5.14.

***cis*-3,4-Dimethylpyrrolidine (12b). Hydrochloride**: 72% yield. ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 6H, $J = 6.6$ Hz), 2.42 (m, 2H), 3.00 (m, 2H), 3.43 (m, 2H), 9.20−10.10 (br.s., 2H). ^{13}C NMR ($CDCl_3$): δ 12.1; 35.3; 50.2. *N*-Benzoyl-*cis*-3,4-dimethylpyrrolidine: ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 3H, $J = 6.9$ Hz), 1.00 (d, 3H, $J = 6.9$ Hz), 2.23 (septuplet, 1H, $J = 6.5$ Hz), 2.34 (septuplet, 1H, $J = 6.6$ Hz), 3.14 (dd, 1H, $J = 10.5$ Hz, $J = 6.1$ Hz), 3.38 (dd, 1H, $J = 12.2$ Hz, $J = 6.0$ Hz), 3.52 (dd, 1H, $J =$ 10.5 Hz, $J = 6.5$ Hz), 3.74 (dd, 1H, $J = 12.2$ Hz, $J = 7.1$ Hz), 7.30−7.60 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.7; 13.3; 34.8; 36.7; 52.4; 55.6; 127.1; 128.2; 129.7; 137.0; 169.8. IR (neat, cm^{-1}): 1620, 1570, 715, 695. EIMS (*m/z*, %): 203 (M, 47), 188 (47), 105 (100), 77 (35), 51 (7). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.58; H, 8.35; N, 6.53.

(3*S*,4*S*)-4-Methyl-3-phenylpyrrolidine (12c). ***N*-Benzamide**: oil, $[\alpha]^{20}_D = -56.8$ (*c* 0.84, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), mixture of rotamers: δ 0.69 and 0.81 (d, 3H, $J = 6.5$ Hz and J = 7.0 Hz), 2.56 and 2.69 (septuplet, 1H, $J = 6.5$ Hz and $J =$ 7.0 Hz), 3.25 and 3.45 (dd, 1H, $J = 10.5$ Hz, $J = 6.5$ Hz and J = 12.2 Hz, $J = 7.0$ Hz), 3.38 and 3.51 (q, 1H, $J = 6.5$ Hz and $J = 7.0$ Hz), 3.63 and 3.90 (dd, 1H, $J = 10.5$ Hz, $J = 6.5$ Hz and $J = 12.2$ Hz, $J = 7.0$ Hz), 3.76 and 3.85 (dd, 1H, $J = 10.9$ Hz, $J = 7.0$ Hz), 4.04 (d, 1H, $J = 6.5$ Hz), 6.90−7.60 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 13.5 and 14.3; 36.1 and 37.7; 46.2 and 47.9; 50.3 and 52.4; 53.5 and 55.4; 126.7; 127.1; 127.2; 127.7; 128.0; 128.3; 128.4; 128.5; 129.9; 130.0; 136.8; 139.2; 139.3; 170.0. IR (neat, cm^{-1}): 3060, 3020, 1620, 1570, 725, 695. CIMS (*m/z*, %): 266 (M + 1, 100), 188 (3), 105 (2). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.25; H, 7.36; N, 5.42.

(3*S*,4*S*)-3,4-Dimethylpyrrolidine (*ent*-10b). ***N*-Benzamide**: oil, $[\alpha]^{20}_D = -104.4$ (*c* 2.93, CH_2Cl_2). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.17; N, 6.72. The spectral data are identical to those described for the benzamide of **10b**.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C DEPT spectra of compounds **2b**, **3a**−**b**, **3d**−**e**, **4a**−**e**, ***epi*-4b**, **5a**−**d**, ***epi*-5b**, **9b**−**c**, **10c**, **11b**−**c**, **12b**−**c**, **13b**, and ***ent*-10b**; NOESY spectra of **4a**, **4c**, and **5a**; NOE difference spectra of **4b**, ***epi*-4b**, **5b**−**c**, and ***epi*-5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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