Synthesis of Enantiopure Primary Amines by Stereoselective Ring Opening of Chiral Octahydro-1,3-benzoxazines by Grignard and Organoaluminum Reagents†

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Chiral 1,3-perhydrobenzoxazines **1**, **2**, and **9**−**14**, prepared by condensation of 8-(benzylamino)-menthol with different aldehydes, react with alkylmagnesium bromides and trimethylaluminum leading to the open amino alcohols **3a**−**d**, **4a**−**d**, and **15**−**20** in excellent chemical yields and good to excellent diastereomeric excess. The sequential elimination of the menthol appendage by heating with P_2O_5 and the benzyl group by hydrogenolysis lead to primary amines **7a**−**d**, **8a**−**d**, and **27**−**30** in excellent chemical yields and ee. The addition of the alkyl group from the Grignard derivatives and the methyl group from the trimethylaluminum occurs from opposite sides of the heterocycle, yielding the final primary amines with the same stereochemistry.

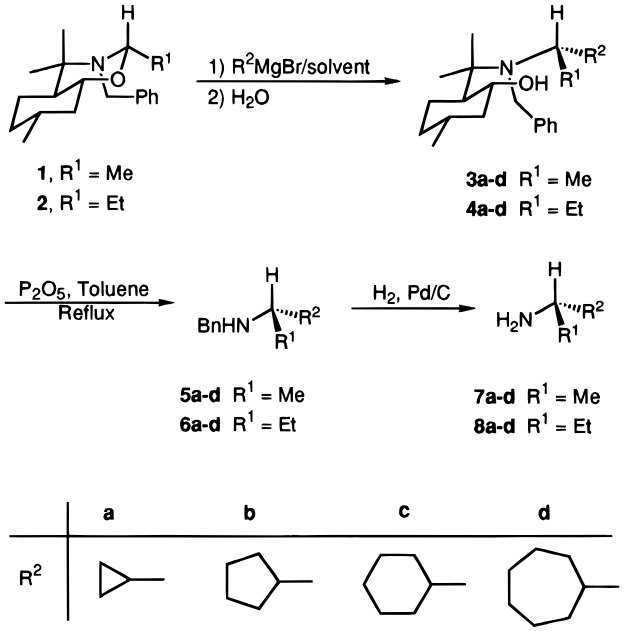
Introduction

Diastereoselective ring opening of chiral 1,3-oxazolidines directed to the synthesis of enantioenriched secondary amines was first reported more than 20 years ago.[1] The heterocycle, formed by condensation of an aldehyde with a chiral N-substituted 1,2-amino alcohol, yields hydroxyamines in moderate to good de when reacted with organometallics.[2] On the other hand, treatment of an aldehyde with chiral unsubstituted 1,2-amino alcohols leads to equilibrium mixtures of hydroxyimines and N-unsubstituted 1,3-oxazolidines, which have been also used as starting material in the synthesis of homochiral amines with good ee.[3]

In the ring-opening reactions the configuration at the newly created stereocenter in the final amine depends on both the configuration of the chiral centers in the heterocycle and the nature of the organometallic, but the final ee's are always limited by the ratio of the C-2 epimers present in the starting mixture of chiral 1,3-oxazolidine.[4]

In contrast, condensation of aldehydes with the *5c-methyl-2t-[1-methyl-1-(benzylamino)ethyl]-cyclohexan-1r-ol* ("*(−)-8-benzylaminomenthol*"), easily prepared[5] from (+)-pulegone, leads to chiral 2-alkyloctahydro-1,3-benzoxazines **1**, **2**, and **9**−**14** as single diastereomers that we have previously used as chiral adjuvants in the asymmetric synthesis of primary amines.[6] On the other hand, the enantiomers of compounds **1**, **2**, and **9**−**14** could be obtained by reaction of aldehydes with (+)-8-(benzylamino)menthol, derived from unnatural (−)-pulegone.[7]

Scheme 1



Results and Discussion

We have now extended our method to the synthesis of different primary amines with cycloalkyl (**7a**−**d**, **8a**−**d**) or methyl (**27**−**30**) substituents at the stereogenic center. To this end, 2-methyl- (**1**) and 2-ethylperhydrobenzoxazine (**2**) were reacted with Grignard derivatives prepared from magnesium and cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl bromides. In addition, 1,3-perhydrobenzoxazines **2** and **9**−**14** bearing different substituents at C-2 were also tested toward trimethylaluminum.

Initially, the reactions with Grignard derivatives (Scheme 1) were carried out on **1** and **2** with 4 equiv of

† Dedicated in memory of Prof. Félix Serratosa.

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(1) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256.

(2) For recent references see: (a) Higashiyama, H.; Inoue, H.; Yamauchi, T.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 111. (b) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083. (c) Davidsen, S. K.; Chu-Moyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558.

(3) See, for instance: (a) Takahashi, H.; Niva, H.; Higashiyama, K. *Heterocycles* **1988**, *27*, 2099. (b) Wu, M. J.; Pridgen, L. N. *Synlett* **1990**, 636. (c) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (d) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489. (e) Scialdone, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 7533.

(4) (a) Agami, C.; Meynier, F. *J. Org. Chem.* **1986**, *51*, 73. (b) Agami, C.; Rizk, C. *Tetrahedron* **1985**, *41*, 537. (c) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 1803.

(5) He, X.-C.; Eliel, E. *Tetrahedron* **1987**, *43*, 4979.

(6) Alberola, A.; Andrés, C.; Pedrosa, R. *Synlett* **1990**, 763.

(7) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380.

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Table 1. Stereoselective Ring Opening of Perhydrobenzoxazines 1 and 2 by Cycloalkylmagnesium Bromides, Followed by Transformation into the Chiral Primary Amines

				3a−d, 4a−d		**5a−d, 6a−d**		**7a−d, 8a−d**	
entry	oxazine	solvent	R^2MgBr	yield (%)	(de)[a]	yield (%)	(ee)[b]	yield (%)	(confgn)[c]
1	**1**	Et_2O	**a** (c-C_3H_5)	(**3a**) 88	(6)				
2	**1**	Et_2O	**d** (c-C_7H_{13})	(**3d**) 40	(60)				
3	**2**	Et_2O	**a** (c-C_3H_5)	(**4a**) 86	(20)				
4	**2**	Et_2O	**d** (c-C_7H_{13})	(**4d**) 28	(84)				
5	**1**	benzene	**a** (c-C_3H_5)	(**3a**) 96	(18)	(**5a**) 68	(>99)[d]	(**7a**) 98	*S*
6	**1**	benzene	**b** (c-C_5H_9)	(**3b**) 81	(96)	(**5b**) 98	(96)	(**7b**) 98	*S*
7	**1**	benzene	**c** (c-C_6H_{11})	(**3c**) 77	(76)	(**5c**) 98	(>99)[d]	(**7c**) 96	*S*
8	**1**	benzene	**d** (c-C_7H_{13})	(**3d**) 67	(80)	(**5d**) 97	(80)	(**7d**) 95	*S*
9	**2**	benzene	**a** (c-C_3H_5)	(**4a**) 95	(34)	(**6a**) 64	(>99)[d]	(**8a**) 96	*S*
10	**2**	benzene	**b** (c-C_5H_9)	(**4b**) 79	(>99)	(**6b**) 96	(>99)	(**8b**) 96	*S*
11	**2**	benzene	**d** (c-C_7H_{13})	(**4d**) 58	(86)	(**6d**) 97	(>99)[d]	(**8d**) 95	*S*

[a] Determined by integration of the H-NMR signals. [b] Measured by HPLC using a Pirkle CSP column. [c] Assigned by comparison of the sign of the specific rotation with those previously described. [d] After separation of the major diastereoisomers (**3a**, **3c**, **4a**, and **4d**) by flash chromatography.

cyclopropyl- or cycloheptylmagnesium bromide at reflux for 2 h in diethyl ether as solvent (entries 1−4 in Table 1). The effect of temperature was studied by repeating these experiments at room temperature. In this case it was necessary to increase the reaction time to 12 h to force the reactions to completion, but the effect on the stereochemical outcome was negligible.

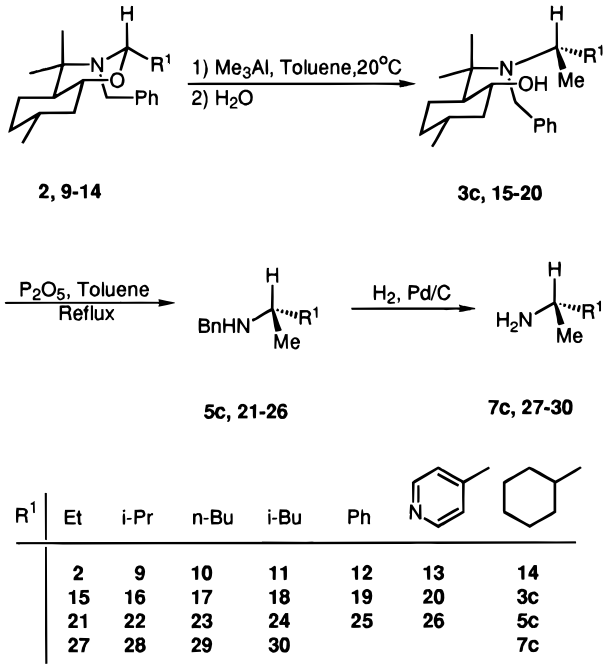
Because of the low stereoselectivity observed, the experimental conditions were changed by using benzene as solvent at 78 °C. In this solvent, not only the diastereomeric excess but also the chemical yields were improved (compare entries 1−4 versus 5, 8, 9, and 11 in Table 1). These improved conditions were used for the reactions of perhydrobenzoxazines **1** and **2** with cyclopentyl- and cyclohexylmagnesium bromide.

As shown in Table 1, the efficiency and the stereoselectivity in the ring-opening reactions were found to be dependent on both the solvent used and the magnesium derivative. Thus, cyclopentylmagnesium bromide yields the best diastereomeric excess (96−100%), whereas the reactions with cyclopropylmagnesium bromide gave a low stereochemical discrimination (de 6−34%). Cyclohexylmagnesium bromide behaves differently because it is the only reagent that shows a better face discrimination in diethyl ether[6] than in benzene. Compounds **3a**, **3c**, **4a**, and **4d** were isolated as pure diastereomers from the reaction mixtures by flash column chromatography using a 3/1 mixture of hexane/ethyl acetate as eluent.

In order to test the generality of the ring opening of these heterocycles, we explored the behavior of these compounds toward a different organometallic compound. To this end, perhydrobenzoxazines **2** and **9**−**14** were reacted with 4 equiv of trimethylaluminum in toluene at 20 °C (Scheme 2). In striking contrast with the reported[8] nonstereoselective reactions of chiral acetals with trimethylaluminum, compounds **2** and **9**−**14** were completely transformed in these experimental conditions into the open amino alcohols **3c** and **15**−**19**, with excellent chemical yields and good to complete stereochemical differentiation (Table 2).

The stereodiferentiation is better, in general, for reactions with trimethylaluminum than for magnesium derivatives (compare the data from Table 2 and Table 1). An exception to this behavior was the 4-pyridyl derivative **13**, which gave a diastereomeric mixture of **20** in only 33% de. However, the major diastereomers (**19** and **20**) could be isolated from the reaction mixtures by flash chromatography.

Scheme 2



It is interesting to note that the single diastereomer **3c**, obtained by reaction of 2-cyclohexylperhydrobenzoxazine **14** (entry 7 in Table 2) with trimethylaluminum has physical and spectral characteristics identical to those of the major diastereomer prepared from 2-methylperhydrobenzoxazine **1** and cyclohexylmagnesium bromide (entry 7 in Table 1), indicating that they are the same compound and not the expected epimer.

In order to determine the configuration of the new stereocenter as well as to establish the synthetic potential of the reaction, the open amino alcohols were transformed into the primary amines **7**, **8**, and **27**−**30**. A previously described[6] two-step procedure, consisting of dehydration−deamination and subsequent hydrogenolytic debenzylation, yielded the primary amines. The transformation of amino alcohols **3**, **4**, and **15**−**20** into benzylamines **5**, **6**, and **21**−**26** was carried out in good chemical yields by refluxing in toluene with phosphorus pentoxide for 2 h. The stereochemical integrity at the stereocenter was maintained as demonstrated by analytical HPLC through

(8) Mori, A.; Fugiwara, J.; Maruoka, K.; Yamamoto, M. *J. Organomet. Chem.* **1985**, *285*, 83.

Table 2. Stereoselective Ring Opening of Perhydrobenzoxazines 2 and 9−14 by Trimethylaluminum in Toluene at 20 °C, Followed by Transformation into the Chiral Primary Amines

			3c, 15−20		**5c, 21−26**		**7c, 27−30**	
entry	oxazine	time (min)	yield (%)	(ee)[a]	yield (%)	(ee)[b]	yield (%)	(confgn)[c]
1	**2**	10	(**15**) 95	(89)	(**21**) 96	(89)	(**27**) 98	*S*
2	**9**	60	(**16**) 95	(>99)	(**22**) 82	(>99)	(**28**) 96	*S*
3	**10**	10	(**17**) 93	(61)	(**23**) 95	(61)	(**29**) 95	*S*
4	**11**	10	(**18**) 97	(90)	(**24**) 97	(90)	(**30**) 94	*S*
5	**12**	10	(**19**) 97	(74)	(**25**) 85	(>99)[d]		*S*
6	**13**	60	(**20**) 90	(33)	(**26**) 50	(>99)[d]		*S*
7	**14**	60	(**3c**) 94	(>99)	(**5c**) 98	(>99)	(**7c**) 98	*S*

[a] Determined by integration of the H-NMR signals. [b] Measured by HPLC using a Pirkle CSP column. [c] Assigned by comparison of the sign of the specific rotation with those previously described. [d] After separation of the major diastereoisomers (**19** and **20**) by flash chromatography.

a column packed with a CSP of the α-naphthamides[9] for compounds **5b**, **5d**, **21**, **23**, and **24**. Debenzylation by hydrogenolysis using 10% palladium on carbon as catalyst led to the final amines in nearly quantitative yields.

It is important to note that, contrary to our expectations, all the primary amines prepared from the magnesium or aluminum reagents were of the *S* configuration, as determined by comparison of the sign of specific rotation with those previously reported. This indicates that the sense of asymmetric induction in the ring opening of the perhydrobenzoxazines is profoundly affected by the nature of the organometallic: the trimethylaluminum opens the heterocycle from the oxygen face, whereas the magnesium derivatives predominantly attack from the nitrogen side. Similar reactions have been previously observed in the opening of chiral oxazolidine[10−12] and acetals.[13] As previously noted for the ring opening of chiral acetals,[14−16] an increase in the nucleophilicity of the alkylating reagent increases the stereoselectivity of the reactions.[17] A similar increase in the stereoselectivity has been observed in relation to the chelating ability of Lewis acids in additions of Grignard reagents to chiral oxazolidines.[18]

The stereochemical results of the reactions can be rationalized by an initial complexation of the organometallics to the oxygen atom in the heterocycle leading to the complex **A** or **B** (Figure 1); the timing of bond breaking and bond making in **A** or **B**, depending on the nucleophilicity of the reagent, could explain the differences in both the degree and the sense of diastereoselection. Thus, the observed S_N2-like alkylation (inversion) with alkylmagnesium bromide occurs, after breaking the C−O bond, in a late iminium-type transition state (**A′**). The magnesium reagent then attacks the less hindered *Re* face of C-2. A similar chelated transition state has been proposed for the addition of Grignard reagents to oxazolidine−hydroxyimine tautomers.[18]

On the contrary, although the opposite stereochemical outcome of the reactions with trimethylaluminum could be explained as an internal alkylation on (**A′**), the faster reaction and the better discrimination with an excess of this organometallic implies a syncronous retentive alkylation (S_Ni-like) in the early transition state (**B**), when the heterocycle is still essentially intact.

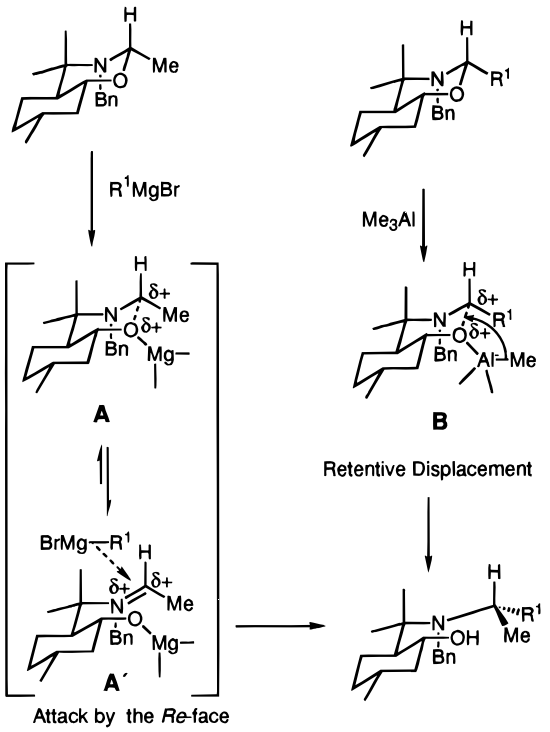


Figure 1.

In summary, this paper describes a new methodology for the enantioselective synthesis of primary amines. The reported results reflect the unusual diastereofacial discrimination in the heterocycle, depending on the nature of the organometallic acting as nucleophile. Further work is in progress on this matter.

Experimental Section

General. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 80 and 20 MHz, respectively, in $CDCl_3$ with $SiMe_4$ as internal standard. *J* values are given in Hz. Optical rotations were measured on a digital polarimeter in a 1 dm cell. Melting points were determined in a capillary tube and are uncorrected.

Chromatographic separations were done by flash chromatography using 240−400 mesh silica gel. The enantiomeric purity was determined by chiral HPLC using a Pirkle (0.46 × 25 cm) column on the amines derivatized as α-naphthamides.[9] For this purpose, the corresponding racemic amines were prepared, derivatized, and coinjected with our samples.

(9) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138.
(10) Fuganti, C.; Ghiringhelli, D.; Grasselli, D. *Tetrahedron Lett.* **1974**, *15*, 2264.
(11) Takahashi, H.; Suzuki, Y.; Kametani, T. *Heterocycles* **1983**, *20*, 607.
(12) Takahashi, H.; Niwa, H.; Higashiyama, K. *Heterocycles* **1988**, *27*, 2099.
(13) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074.
(14) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.
(15) Sato, T.; Otera, J.; Nozaki, M. *J. Org. Chem.* **1990**, *55*, 6116.
(16) (a) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089.
(17) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.
(18) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340.

Anhydrous solvents were distilled prior to use from benzophenone ketyl. All the reactions were carried out in oven-dried glassware under a nitrogen atmosphere. The experimental methods for the reactions with Grignard derivatives (20 mmol scale), elimination of the menthol appendage, and debenzylation have been previously described.[6]

Synthesis of Perhydrobenzoxacines 1, 2, and 9−14. A mixture of 8-(benzylamino)menthol[5] (5.22 g, 20 mmol) and the appropriate aldehyde (25 mmol), in toluene (100 mL) was refluxed under nitrogen until the reaction was completed (TLC). The mixture was filtered trough a pad of Celite, and the Celite was washed with toluene. The solvent was evaporated, and the residue was purified by recrystallization from the solvent given below.

(−)-*N*-Benzyl-2α,4,4,7α-tetramethyl-*trans*-octahydro-1,3-benzoxazine (1): yield 86%; colorless solid; mp 43−44 °C (from EtOH); $[\alpha]^{25}_D = -37.8$ (*c* 3.0, EtOAc); ^{1}H NMR δ 7.45−7.05 (m, 5H), 4.84 (q, 1H, *J* = 6.0), 4.06 (d, 1H, *J* = 17.7), 3.67 (d, 1H, *J* = 17.7), 3.46 (dt, 1H, *J* = 10.1, 3.9), 1.21 (s, 3H,), 1.09 (d, 3H, *J* = 6.0), 1.05 (s, 3H), 0.93 (d, 3H, *J* = 5.6); ^{13}C NMR δ 144.3, 127.9, 126.6, 125.6, 83.4, 75.6, 56.7, 46.4, 46.0, 41.4, 34.9, 31.3, 27.1, 24.9, 22.2, 20.9, 19.7; IR (Nujol) 3060, 3020, 1020 cm^{-1}; MS *m/z* 287 (M$^+$, 1), 272 (52), 146 (15), 134 (14), 91 (100), 41 (13). Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.27; H, 10.39; N, 4.71.

(−)-*N*-Benzyl-2α-ethyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (2): yield 94%; colorless solid; mp 34−35 °C (from EtOH); $[\alpha]^{25}_D = -51.6$ (*c* 4.4, EtOAc); ^{1}H NMR δ 7.48−7.12 (m, 5H), 4.55 (t, 1H, *J* = 5.7), 3.71 (d, 1H, *J* = 17.8), 4.04 (d, 1H, *J* = 17.8), 3.45 (dt, 1H, *J* = 10.1, 3.7), 1.27 (s, 3H), 1.05 (s, 3H), 0.93 (d, 3H, *J* = 5.7), 0.81 (t, 3H, *J* = 7.6); ^{13}C NMR δ 144.5, 127.9, 126.9, 125.7, 89.5, 76.3, 57.0, 46.4, 46.2, 41.7, 35.3, 31.6, 27.4, 27.2, 25.3, 22.3, 21.0, 10.6; IR (Nujol) 3060, 3020, 1020 cm^{-1}; MS *m/z* 301 (M$^+$, 1), 272 (68), 148 (13), 136 (14), 91 (100), 81 (16), 41 (22). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.57; H, 10.25; N, 4.58.

(−)-*N*-Benzyl-2α-isopropyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (9): yield 80%; colorless solid; mp 47−48 °C (from EtOH); $[\alpha]^{25}_D = -40.7$ (*c* 3.0, EtOAc); ^{1}H NMR δ 7.46−7.08 (m, 5H), 4.17 (d, 1H, *J* = 8.4), 4.07 (d, 1H, *J* = 18.1), 3.76 (d, 1H, *J* = 18.1), 3.43 (dt, 1H, *J* = 10.1, 3.6), 1.26 (s, 3H), 1.00 (s, 3H), 0.93 (d, 3H, *J* = 5.6), 0.89 (d, 3H, *J* = 6.4), 0.73 (d, 3H, *J* = 6.5); ^{13}C NMR δ 144.1, 127.8, 127.0, 125.6, 93.7, 77.0, 57.1, 46.5, 44.7, 41.5, 35.2, 31.4, 30.7, 27.3, 25.0, 22.2, 20.0, 19.4; IR (Nujol) 3080, 3060, 1090, 1025 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54; N, 4.44. Found: C, 80.07; H, 10.68; N, 4.32.

(−)-*N*-Benzyl-2α-butyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (10): yield 75%; colorless solid; mp 51−52 °C (from EtOH); $[\alpha]^{25}_D = -46.1$ (*c* 3.0, EtOAc); ^{1}H NMR δ 7.45−7.12 (m, 5H), 4.66 (t, 1H, *J* = 5.1), 4.09 (d, 1H, *J* = 18.0), 3.76 (d, 1H, *J* = 18.0), 3.49 (dt, 1H, *J* = 9.9, 3.8), 1.27 (s, 3H), 1.03 (s, 3H), 0.93 (d, 3H, *J* = 5.6); ^{13}C NMR δ 144.4, 127.9, 126.8, 125.6, 87.9, 76.2, 56.9, 46.1, 45.6, 41.6, 35.1, 34.0, 31.4, 28.4, 27.3, 25.0, 22.5, 22.3, 21.4, 13.9; IR (Nujol) 3060, 3020, 1260, 1025 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.32; H, 10.59; N, 4.38.

(−)-*N*-Benzyl-2α-isobutyl-4,4,7a-trimethyl-*trans*-octahydro-1,3-benzoxazine (11): yield 78%; colorless oil; bp 157−160 °C/2 mmHg; $[\alpha]^{25}_D = -45.4$ (*c* 3.2, EtOAc); ^{1}H NMR δ 7.43−7.12 (m, 5H), 4.76 (t, 1H, *J* = 5.8), 3.69 (d, 1H, *J* = 17.9), 3.77 (d, 1H, *J* = 17.9), 3.49 (dt, 1H, *J* = 10.0, 3.6), 1.28 (s, 3H), 1.00 (s, 3H), 0.98 (d, 3H, *J* = 6.6), 0.84 (d, 3H, *J* = 6.5), 0.74 (d, 3H, *J* = 6.4); ^{13}C NMR δ 144.4, 127.8, 126.7, 125.6, 86.1, 76.3, 57.0, 46.0, 45.2, 42.9, 41.5, 35.1, 31.4, 27.2, 24.9, 22.8, 22.5, 22.2, 21.7; IR (neat) 3060, 3020, 1180, 1050, 1025 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N 4.25. Found: C, 80.41; H, 10.52; N, 4.39.

(−)-*N*-Benzyl-2α-phenyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (12): yield 66%; colorless solid; mp 90−91 °C (from EtOH); $[\alpha]^{25}_D = -40.0$ (*c* 3.0, EtOAc); ^{1}H NMR δ 7.52−7.07 (m, 10H), 5.77 (s, 1H), 3.86 (d, 1H, *J* = 17.2), 3.62 (d, 1H, *J* = 17.2), 3.58 (m, 1H), 1.37 (s, 3H), 0.99 (s, 3H), 0.96 (d, 3H, *J* = 5.5); ^{13}C NMR δ 144.1, 140.4, 127.6, 127.5, 127.3, 126.9, 125.4, 88.2, 76.5, 57.4, 47.4, 45.3, 41.5, 35.2, 31.5, 27.7, 25.1, 22.4, 21.0; IR (Nujol) 3060, 3020, 1025 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO$: C, 82.48; H, 8.94; N, 4.01. Found: C, 82.29; H, 8.76; N, 4.14.

(−)-*N*-Benzyl-2α-pyridyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (13): yield 90%; colorless solid; mp 101−102 °C (from EtOH); $[\alpha]^{25}_D = -44.3$ (*c* 1.3, EtOAc); ^{1}H NMR δ 8.42−8.35 (m, 2H), 7.41−7.09 (m, 7H), 5.76 (s, 1H), 3.71 (s, 2H), 3.63 (m, 1H), 1.39 (s, 3H), 1.01 (s, 3H), 0.98 (d, 3H, *J* = 5.7); ^{13}C NMR δ 149.2, 143.2, 127.7, 126.6, 125.7, 121.9, 86.8, 76.6, 57.5, 47.5, 44.9, 41.3, 35.1, 31.4, 27.4, 25.0, 22.3, 21.6; IR (Nujol) 3080, 3020, 1180, 1050,1030 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.98; H, 8.78; N, 8.11.

(−)-*N*-Benzyl-2α-cyclohexyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (14): yield 84%; colorless oil; bp 143−145 °C/0.5 mmHg; $[\alpha]^{25}_D = -38.8$ (*c* 2.0, EtOAc); ^{1}H NMR δ 7.46−7.07 (m, 5H), 4.27 (d, 1H, *J* = 8.1), 4.08 (d, 1H, *J* = 17.8), 3.76 (d, 1H, *J* = 17.8), 3.41 (dt, 1H, *J* = 10.2, 3.7), 1.24 (s, 3H), 1.01 (s, 3H), 0.93 (d, 3H, *J* = 5.7); ^{13}C NMR δ 144.0, 127.7, 127.0, 125.6, 92.2, 76.7, 57.0, 46.6, 44.9, 41.4, 40.0, 35.1, 31.4, 29.8, 29.2, 27.5, 26.4, 25.7, 25.5, 25.0, 22.2; IR (Nujol) 3060, 3020 cm^{-1}. Anal. Calcd for $C_{24}H_{37}NO$: C, 81.07; H, 10.49; N, 3.94. Found: C, 80.91; H, 10.32; N, 4.07.

8-[*N*-Benzyl-*N*-[(*S*)-1-cyclopropylethyl]amino]menthol (3a). Major diastereomer: colorless solid; mp 69−70 °C (from pentane); $[\alpha]^{25}_D = +15.3$ (*c* 0.7, hexane); ^{1}H NMR δ 7.81 (s, 1H), 7.50−7.14 (m, 5H), 3.91 (d, 1H, *J* = 15.1), 3.83 (d, 1H, *J* = 15.1), 3.54 (dt, 1H, *J* = 9.7, 3.6), 2.64 (m, 1H), 1.13 (s, 3H), 1.12 (d, 3H, *J* = 6.4), 1.08 (s, 3H), 0.89 (d, 3H, *J* = 5.7); ^{13}C NMR δ 142.2, 128.4, 128.2, 126.4, 72.5, 62.7, 56.7, 48.4, 47.7, 44.8, 35.2, 30.8, 26.1, 22.8, 22.0, 17.5, 5.8, 4.2; IR (Nujol) 3160, 3050, 1160, 1010 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.27; H, 10.60; N, 4.12.

8-[*N*-Benzyl-*N*-[(*R*)-1-cyclopropylethyl]amino]menthol. Minor diastereomer: ^{1}H NMR δ 8.23 (s, 1H), 7.57−7.15 (m, 5H), 4.13 (d, 1H, *J* = 15.5), 3.18 (d, 1H, *J* = 15.5), 3.59 (dt, 1H, *J* = 10.2, 3.8), 2.66 (m, 1H), 1.21 (d, 3H, *J* = 5.9), 1.18 (s, 6H), 0.88 (d, 3H, *J* = 5.8); ^{13}C NMR δ 141.9, 128.6, 128.2, 126.6, 72.8, 62.6, 57.7, 48.0, 47.2, 44.9, 35.3, 31.0, 26.1, 23.5, 22.1, 17.1, 17.3, 5.6. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.08; H, 10.62; N, 4.14.

8-[*N*-Benzyl-*N*-[(*S*)-1-cyclopentylethyl]amino]menthol (3b): colorless solid; mp 83−84 °C (from pentane); $[\alpha]^{25}_D = -6.6$ (*c* 0.7, hexane); ^{1}H NMR δ 7.60 (s, 1H), 7.39−7.13 (m, 5H), 3.83 (d, 1H, *J* = 15.4), 3.72 (d, 1H, *J* = 15.4), 3.63−3.19 (m, 2H), 1.09 (d, 3H, *J* = 6.6), 1.08 (s, 3H), 1.05 (s, 3H), 0.89 (d, 3H, *J* = 5.7); ^{13}C NMR δ 142.5, 128.2, 126.3, 125, 63.6, 55.7, 48.8, 47.8, 46.7, 44.7, 35.3, 32.0, 30.8, 28.5, 26.2, 25.4, 24.5, 23.2, 22.5, 22.0, 14.7; IR (Nujol) 3140, 1160, 1130 cm^{-1}. Anal. Calcd for $C_{24}H_{39}NO$: C, 80.62; H, 10.99; N, 3.92. Found: C, 80.53; H, 10.88; N, 4.04.

8-[*N*-Benzyl-*N*-[(*S*)-1-cyclohexylethyl]amino]menthol (3c): colorless solid; mp 88−89 °C (from hexane); $[\alpha]^{25}_D = -12.9$ (*c* 0.7, hexane); ^{1}H NMR δ 7.77 (s, 1H), 7.42−7.17 (m, 5H), 3.90 (d, 1H, *J* = 15.1), 3.75 (d, 1H, *J* = 15.1), 3.40 (dt, *J* = 9.8, 3.7), 3.17 (m, 1H), 1.08 (s, 3H), 1.07 (d, 3H, *J* = 6.8), 0.97 (s, 3H), 0.88 (d, 3H, *J* = 5.6); ^{13}C NMR δ 142.9, 128.3, 127.8, 126.3, 72.4, 64.1, 56.7, 49.8, 47.9, 44.7, 44.3, 35.2, 32.2, 30.8, 27.5, 26.9, 26.6, 26.3,23.2, 22.1, 21.1, 13.1; IR (Nujol) 3150, 1140, 1080, 1020 cm^{-1}. Anal. Calcd for $C_{25}H_{41}NO$: C, 80.81; H, 11.12; N, 3.77. Found: C, 80.73; H, 11.19; N, 3.66.

8-[*N*-Benzyl-*N*-[(*S*)-1-cycloheptylethyl]amino]menthol (3d): colorless oil; ^{1}H NMR δ 7.68 (s, 1H), 7.37−7.21 (m, 5H), 3.98 (d, 1H, *J* = 16.0), 3.67 (d, 1H, *J* = 16.0), 3.64−3.15 (m, 2H), 1.05 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 142.9, 128.1, 127.4, 126.0, 72.2, 64.1, 57.3, 49.5, 47.6, 45.1, 44.6, 35.1, 34.1, 30.6, 29.5, 28.1, 27.6, 27.2, 26.9, 25.9, 22.9, 21.9, 20.5, 12.3; IR (neat) 3180, 1220, 1185, 1075, 1030 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO$: C, 80.98; H, 11.24; N, 3.63. Found: C, 80.89; H, 11.12; N, 3.74.

8-[*N*-Benzyl-*N*-[(*S*)-1-cyclopropylpropyl]amino]menthol (4a). Major diastereomer: colorless oil; $[\alpha]^{25}_D = +11.9$ (*c* 0.7, hexane); ^{1}H NMR δ 8.23 (s, 1H), 7.60−7.16 (m, 5H), 4.15 (d, 1H, *J* = 14.7), 3.80 (d, 1H, *J* = 14.7), 3.59 (dt, 1H, *J* = 10.0, 3.8), 1.20 (s, 6H), 0.95 (t, 3H, *J* = 7.2), 0.88 (d, 3H, *J* = 5.7); ^{13}C NMR δ 141.5, 128.3, 127.8, 126.2, 72.1, 63.6, 62.1,

48.7, 47.5, 44.6, 34.9, 30.5, 27.3, 25.8, 22.2, 21.7, 15.6, 12.8, 5.7, 3.8; IR (Nujol) 3170, 3090, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{23}H_{37}NO$: C, 80.41; H, 10.86; N, 4.08. Found: C, 80.29; H, 10.97; N, 3.93.

8-[*N*-Benzyl-*N*-[(*R*)-1-cyclopropylpropyl]amino]menthol. Minor diastereomer: colorless oil; $[\alpha]^{25}_D = -31.1$ (*c* 0.8, hexane); ^{1}H NMR δ 7.93 (s, 1H), 7.48−7.10 (m, 5H), 3.93 (s, 2H), 3.60 (m, 1H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (d, 3H, J = 5.8); ^{13}C NMR δ 141.5, 128.8, 127.8, 126.3, 72.5, 65.1, 61.9, 48.4, 48.0, 44.9, 35.1, 30.7, 26.5, 26.0, 23.7, 21.9, 16.6, 12.2, 8.3, 3.3. Anal. Calcd for $C_{23}H_{37}NO$: C, 80.41; H, 10.86; N, 4.08. Found: C, 80.21; H, 10.62; N, 4.26.

8-[*N*-Benzyl-*N*-[(*S*)-1-cyclopentylpropyl]amino]menthol (4b): colorless solid; mp 81−82 °C; $[\alpha]^{25}_D = -18.6$ (*c* 0.7, hexane); ^{1}H NMR δ 7.51 (s, 1H), 7.38−7.15 (m, 5H), 3.81 (s, 2H), 3.47 (dt, 1H, J = 9.8, 3.5), 3.00 (m, 1H), 1.13 (s, 3H), 1.07 (s, 3H), 0.88 (d, 3H, J = 5.6); ^{13}C NMR δ 142.5, 128.3, 126.4, 72.7, 63.3, 62.8, 49.7, 48.0, 46.5, 44.8, 35.3, 32.5, 30.9, 28.3, 26.3, 25.5, 24.1, 23.3, 22.9, 22.0, 22.1, 13.9; IR (Nujol) 3150, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{25}H_{41}NO$: C, 80.81; H, 11.12; N, 3.77. Found: C, 80.98; H, 10.97; N, 3.96.

8-[*N*-Benzyl-*N*-[(*S*)-1-cycloheptylpropyl]amino]menthol (4d). Major diastereomer: colorless solid; mp 102−104 °C (hexane); $[\alpha]^{25}_D = -5.4$ (*c* 0.7, hexane); ^{1}H NMR δ 7.63 (s, 1H), 7.40−7.26 (m, 5H), 3.90 (d, 1H, J = 17.1), 3.78 (d, 1H, J = 15.8), 3.50 (dt, 1H, J = 9.9, 3.6), 2.94 (m, 1H), 1.11 (s, 3H), 1.06 (s, 3H), 0.87 (d, 3H, J = 5.8); ^{13}C NMR δ 142.7, 128.2, 128.0, 126.3, 72.7, 65.7, 63.7, 49.9, 48.0, 44.8, 44.3, 35.5, 35.3, 30.8, 29.0, 28.1, 27.8, 27.5, 27.3, 26.2, 22.8, 22.3, 22.0, 13.7; IR (Nujol) 3140, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N 3.51. Found: C, 81.26; H, 11.22; N, 3.64.

8-[*N*-Benzyl-*N*-[(*R*)-1-cyclopropylpropyl]amino]menthol. Minor diastereomer: colorless oil; $[\alpha]^{25}_D = -16.0$ (*c* 0.6, hexane); ^{1}H NMR δ 7.55 (s, 1H), 7.39−7.22 (m, 5H), 3.94 (d, 1H, J = 15.5), 3.69 (d, 1H, J = 15.5), 3.52 (dt, 1H, J = 9.5, 3.6), 2.95 (m, 1H), 1.10 (s, 6H), 0.88 (d, 3H, J = 5.7); ^{13}C NMR δ 142.5, 128.4, 128.2, 126.4, 72.6, 65.0, 63.5, 48.5, 47.9, 44.6, 43.0, 36.6, 35.2, 30.8, 28.7, 27.6, 26.6, 26.3, 24.6, 22.9, 22.0, 13.8. Anal. Calcd for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N, 3.51. Found: C, 81.28; H, 11.21; N, 3.67.

General Method for the Reaction of 2 and 9−14 with Trimethylaluminum. To a stirred solution of trimethylaluminum in toluene (10 mL; 20 mmol) was added dropwise a solution of the corresponding perhydrobenzoxazine (5 mmol) in anhydrous toluene (20 mL). The mixture was stirred at room temperature until the reaction was finished (TLC) and then was treated with a saturated solution of NH_4Cl and crushed ice and filtered to eliminate the aluminum hydroxides. The aqueous solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield a crystalline mass that was recrystallized from hexane or chromatographed on silica gel using hexane−ether as eluent.

8-[*N*-Benzyl-*N*-[(*S*)-1-methylpropyl]amino]menthol (15): colorless solid; mp 97−98 °C (from hexane); ^{1}H NMR δ 8.04 (s, 1H), 7.37−7.21 (m, 5H), 3.79 (s, 2H), 3.55−3.12 (m, 2H), 1.09 (s, 6H); ^{13}C NMR δ 142.2, 128.2, 126.4, 72.4, 63.2, 53.7, 47.7, 44.6, 35.2, 30.8, 30.2, 26.0, 22.5, 22.0, 16.7, 11.7; IR (Nujol) 3100, 1160, 1135 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.23; H, 11.27; N, 4.28.

8-[*N*-Benzyl-*N*-[(*S*)-1-methyl-2-methylpropyl]amino]-menthol (16): colorless solid; mp 86−87 °C (from hexane); $[\alpha]^{25}_D = -5.4$ (*c* 0.7, hexane); ^{1}H NMR δ 7.81 (s, 1H), 7.42−7.19 (m, 5H), 3.90 (d, 1H, J = 16.0), 3.71 (d, 1H, J = 16.0), 3.58−3.18 (m, 2H), 2.30 (m, 1H); ^{13}C NMR δ 142.9, 128.3, 127.7, 126.3, 72.4, 64.2, 56.4, 49.5, 47.8, 44.6, 35.2, 33.6, 30.8, 26.1, 23.1, 22.1, 21.0, 16.2, 11.4; IR (Nujol) 3090, 1160, 1095, 1080 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.62; H, 11.39; N, 4.41.

8-[*N*-Benzyl-*N*-[(*S*)-1-methylpentyl]amino]menthol (17): colorless oil; ^{1}H NMR δ 8.05 (s, 1H), 731−7.21 (m, 5H), 3.79 (s, 2H), 3.68−3.08 (m, 2H), 1.09 (s, 6H); IR (neat) 3170, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 80.16; H, 11.20; N, 4.26.

8-[*N*-Benzyl-*N*-[(*S*)-1-methyl-3-methylbutyl]amino]-menthol (18): colorless solid; mp 94−95 °C (from hexane); $[\alpha]^{25}_D = -17.0$ (*c* 0.7, hexane); ^{1}H NMR δ 7.98 (s, 1H), 7.35−7.21 (m, 5H), 3.77 (s, 2H), 3.70−3.29 (m, 2H); ^{13}C NMR δ 142.5, 128.3, 126.5, 72.5, 63.5, 49.7, 47.9, 46.6, 44.8, 35.4, 30.9, 26.1, 25.4, 24.3, 22.9, 22.5, 22.1, 21.1, 17.5; IR (Nujol) 3080, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N 4.05. Found: C, 79.76; H, 11.26; N, 4.22.

8-[*N*-Benzyl-*N*-[(*S*)-1-phenylethyl]amino]menthol (19). Major diastereomer: colorless solid; mp 66−67 °C (from hexane); $[\alpha]^{25}_D = -18.3$ (*c* 0.7, hexane); ^{1}H NMR δ 7.42−7.17 (m, 11H), 4.64 (q, 1H, J = 7.0), 4.15 (d, 1H, J = 15.3), 3.72 (d, 1H, J = 15.3), 3.51 (dt, 1H, J = 10.0, 3.8), 1.44 (d, 3H, J = 7.0), 1.15 (s, 3H), 1.09 (s, 3H), 0.90 (d, 3H, J = 5.6); ^{13}C NMR δ 143.4, 141.9, 128.8, 128.2, 126.9, 126.5, 72.6, 63.7, 55.3, 48.5, 48.3, 44.8, 35.3, 30.9, 26.2, 23.1, 22.1, 18.5; IR (Nujol) 3210, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{25}H_{35}NO$: C, 82.14; H, 9.65; N, 3.83. Found: C, 82.27; H, 9.51; N, 4.01.

8-[*N*-Benzyl-*N*-[(*R*)-1-phenylethyl]amino]menthol. Minor diastereoisomer: ^{1}H NMR δ 7.86 (s, 1H), 7.35−7.09 (m, 5H), 4.75 (q, 1H, J = 6.8), 4.15 (d, 1H, J = 15.4), 3.84 (d, 1H, J = 15.4), 3.59 (dt, 1H, J = 10.2, 3.9), 1.54 (d, 3H, J = 6.8), 1.29 (s, 3H), 1.07 (s, 3H), 0.83 (d, 3H, J = 5.9). Anal. Calcd for $C_{25}H_{35}NO$: C, 82.14; H, 9.65; N, 3.83. Found: C, 82.02; H, 9.73; N, 3.71.

8-[*N*-Benzyl-*N*-[(*S*)-1-(4-pyridyl)ethyl]amino]menthol (20). Major diastereoisomer: colorless solid; mp 88−89 °C (from hexane); $[\alpha]^{25}_D = +5.5$ (*c* 0.7, hexane); ^{1}H NMR δ 8.53−8.45 (m, 2H), 7.29−7.05 (m, 8H), 4.55 (q, 1H, J = 7.0), 4.08 (d, 1H, J = 15.1), 3.75 (d, 1H, J = 15.1), 3.53 (dt, 1H, J = 10.0, 3.8), 1.49 (d, 3H, J = 7.0), 1.15 (s, 3H), 1.12 (s, 3H), 0.91 (d, 3H, J = 5.7); ^{13}C NMR δ 152.3, 149.5, 140.7, 128.2, 126.7, 123.5, 72.4, 63.9, 54.2, 48.8, 48.3, 44.5, 35.0, 30.7, 26.0, 23.0, 21.9, 16.7; IR (Nujol) 3220, 1160, 1030 cm^{-1}. Anal. Calcd for $C_{24}H_{34}NO$: C, 81.77; H, 9.72; N 3.97. Found: C, 81.62; H, 9.89; N, 3.83.

8-[*N*-Benzyl-*N*-[(*R*)-1-(4-pyridyl)ethyl]amino]menthol. Minor diastereoisomer: colorless solid; mp 102−103 °C (from hexane); $[\alpha]^{25}_D = -32.8$ (*c* 0.7, hexane); ^{1}H NMR δ 8.40−8.32 (m, 2H), 7.69 (s, 1H), 7.18−7.08 (m, 7H), 4.68 (q, 1H, J = 7.0), 4.21 (d, 1H, J = 15.1), 3.78 (d, 1H, J = 15.1), 3.66 (dt, 1H), 1.56 (d, 3H, J = 7.0), 1.35 (s, 3H), 1.14 (s, 3H), 0.87 (d, 3H, J = 5.9). Anal. Calcd for $C_{24}H_{34}NO$: C, 81.77; H, 9.72; N, 3.97. Found: C, 81.59; H, 9.83; N, 4.10.

(*S*)-*N*-Benzyl-1-cyclopropylethylamine hydrochloride (5a): colorless solid; mp 153−155 °C (from EtOH−ether); $[\alpha]^{25}_D = -9.3$ (*c* 1.0, MeOH); ^{1}H NMR δ 9.87 (s, 2H), 7.73−7.27 (m, 5H), 4.08 (t, 2H, J = 5.7), 2.29 (m, 1H), 1.48 (d, 3H, J = 6.6), 1.39−0.12 (m, 5H); IR (Nujol) 2720, 1570, 1130, 1030 cm^{-1}.

(*S*)-*N*-Benzyl-1-cyclopentylethylamine hydrochloride (5b): colorless solid; mp 163−165 °C (from EtOH−ether); $[\alpha]^{25}_D = +8.0$ (*c* 1.5, MeOH); ^{1}H NMR δ 9.91 (s, 1H), 9.19 (s, 1H), 7.76−7.27 (m, 5H), 4.13 (m, 2H), 2.80 (m, 1H), 1.38 (d, 3H, J = 6.5); IR (Nujol) 2550, 2420, 1585 cm^{-1}; chiral HPLC analysis of α-naphthamide ee 96% (UV detector 254 nm, t_R 12.41 min, 0.6 mL/min, 85:15 hexane/2-propanol).

(*S*)-*N*-Benzyl-1-cyclohexylethylamine (5c): colorless oil; bp 112−113 °C/0.25 mmHg; $[\alpha]^{25}_D = +16.6$ (*c* 2.0, EtOH); ^{1}H NMR δ 7.53−7.05 (m, 5H), 3.87 (d, 1H, J = 13.1), 3.66 (d, 1H, J = 13.1), 2.45 (m, 1H), 1.02 (d, 3H, J = 6.4); IR (Nujol) 3300, 3020 cm^{-1}.

(*S*)-*N*-Benzyl-1-cycloheptylethylamine hydrochloride (5d): colorless solid; mp 179−181 °C (from EtOH−ether); $[\alpha]^{25}_D = -6.13$ (*c* 1.4, MeOH); ^{1}H NMR δ 9.56 (m, 2H), 7.75−7.27 (m, 5H), 4.23 (d, 1H, J = 13.8), 3.99 (d, 1H, J = 13.8), 2.85 (m, 1H), 1.30 (d, 3H, J = 6.8); IR (Nujol) 2680, 2480, 1585, 1145 cm^{-1}; chiral HPLC analysis of α-naphthamide ee 80% (UV detector 254 nm, t_R 15.62 min, 0.9 mL/min, 95:5 hexane/2-propanol).

(*S*)-*N*-Benzyl-1-cyclopropylpropylamine hydrochloride (6a): colorless solid; mp 134−136 °C (from EtOH−ether); $[\alpha]^{25}_D = +7.1$ (*c* 0.7, MeOH); ^{1}H NMR δ 9.6 (s, 2H), 7.67−7.23 (m, 5H), 4.19 (s, 2H), 1.06 (t, 3H, J = 6.9); IR (Nujol) 2720, 2430, 2370, 1565, 1020 cm^{-1}.

(*S*)-*N*-Benzyl-1-cyclopentylpropylamine hydrochloride (6b): colorless solid; mp 115−117 °C (from EtOH−ether); $[\alpha]^{25}_D = +3.4$ (*c* 1.5, MeOH); ^{1}H NMR δ 9.71 (s, 1H), 9.38 (s,

1H), 7.79−7.27 (m, 5H), 4.20 (m, 2H), 2.65 (m, 1H), 1.07 (t, 3H, J = 7.2); IR (Nujol) 2390, 1585, 1205 cm^{-1}.

(*S*)-*N*-Benzyl-1-cycloheptylpropylamine hydrochloride (6d): colorless solid; mp 179−181 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −7.8 (*c* 1.0, MeOH); ^{1}H NMR δ 9.40 (m, 2H), 7.78−7.30 (m, 5H), 4.40 (d, 1H, J = 13.6), 4.12 (d, 1H, J = 13.6), 2.56 (m, 1H), 0.96 (t, 3H, J = 7.3 Hz); IR (Nujol) 2650, 2330, 1580, 1205 cm^{-1}.

(*S*)-*N*-Benzyl-2-butylamine hydrochloride (21): colorless solid; mp 142−143 °C (from EtOH−ether); $[\alpha]^{25}_D$ = +2.1 (*c* 2.5, EtOH); ^{1}H NMR δ 9.77 (s, 2H), 7.72−7.21 (m, 5H), 4.01 (s, 2H), 2.86 (m, 1H), 1.38 (d, 3H, J = 6.5), 0.92 (t, 3H, J = 7.4); IR (Nujol) 2580, 2485, 1590 cm^{-1}; chiral HPLC analysis of α-naphthamide ee >99% (UV detector 254 nm, t_R 19.88 min, 1.0 mL/min, 98:2 hexane/2-propanol).

(*S*)-*N*-Benzyl-3-methyl-2-butylamine hydrochloride (22): colorless solid; mp 169−170 °C (from EtOH−ether); $[\alpha]^{25}_D$ = +2.4 (*c* 1.7, EtOH); ^{1}H NMR δ 7.75−7.29 (m, 5H), 4.25 (d, 1H, J = 13.8), 3.98 (d, 1H, J = 13.8), 2.79 (m, 1H), 2.17 (m, 1H), 1.29 (d, 3H, J = 6.7), 1.09 (d, 3H, J = 6.7), 0.95 (d, 3H, J = 6.8); IR (Nujol) 2690, 2550, 2490, 1585 cm^{-1}.

(*S*)-*N*-Benzyl-2-hexylamine (23): colorless oil; $[\alpha]^{25}_D$ = +0.6 (*c* 3.0, EtOH); ^{1}H NMR δ 7.38−7.24 (m, 5H), 3.81 (d, 1H, J = 13.8), 3.75 (d, 1H, J = 13.8), 2.66 (m, 1H), 1.08 (d, 3H, J = 6.2); IR (neat) 3300, 3060, 3020, 1450, 1370 cm^{-1}; chiral HPLC analysis of α-naphthamide ee 61% (UV detector 254 nm, t_R 30.86 min, 0.5 mL/min, 98.5:1.5 hexane/2-propanol).

(*S*)-*N*-Benzyl-4-methyl-2-pentylamine hydrochloride (24): colorless solid; mp 182−183 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −7.3 (*c* 0.6, EtOH); ^{1}H NMR δ 9.73 (s, 2H), 7.73−7.28 (m, 5H), 4.02 (t, 2H, J = 5.2), 3.01 (m, 1H), 1.40 (d, 3H, J = 6.5), 0.88 (d, 3H, J = 5.8), 0.74 (d, 3H, J = 5.9); IR (Nujol) 2650, 1575 cm^{-1}; chiral HPLC analysis of α-naphthamide ee 90% (UV detector 254 nm, t_R 43.44 min, 0.4 mL/min, 98.8:0.2 hexane/2-propanol).

(*S*)-*N*-Benzyl-1-phenylethylamine (25): colorless oil; bp 82−85 °C/0.25 mmHg; $[\alpha]_D^{25}$ = −59.9 (*c* 2.4, EtOH) (lit.[19] $[\alpha]^{25}_D$ = −56.1 (*c* 3.1, EtOH)); ^{1}H NMR δ 7.41−7.19 (m, 5H), 3.81 (q, 1H, J = 6.6), 3.62 (s, 2H), 1.61 (s, 1H), 1.36 (d, 3H, J = 6.6); IR (neat) 3310, 3060, 3020, 1595, 1485 cm^{-1}.

(*S*)-*N*-Benzyl-1-(4-pyridyl)ethylamine (26): colorless oil; $[\alpha]^{25}_D$ = −60.4 (*c* 1.1, EtOH); ^{1}H NMR δ 8.59−8.51 (m, 2H), 7.33−7.18 (m, 7H), 3.80 (q, 1H, J = 6.6), 3.61 (s, 2H), 1.93 (s, 1H), 1.34 (d, 3H, J = 6.6); IR (neat) 3280, 3060, 3020, 1450, 1410 cm^{-1}.

(*S*)-1-Cyclopropylethylamine hydrochloride (7a): colorless solid; mp 173−175 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −3.6 (*c* 1.5, MeOH) (lit.[20] free base $[\alpha]^{23}_D$ = −21.3 (neat)); ^{1}H NMR δ 8.39 (s, 3H), 2.65 (m, 1H), 1.46 (d, 3H, J = 6.6), 1.40−0.13 (m, 5H); IR (Nujol) 2600, 2540, 2050, 1120, 1050 cm^{-1}.

(*S*)-1-Cyclopentylethylamine hydrochloride (7b): colorless solid; mp 210−211 °C (from EtOH−ether); $[\alpha]^{25}_D$ = +4.8 (*c* 2.0, MeOH); ^{1}H NMR δ 8.32 (s, 3H), 3.14 (m, 1H), 1.42 (d, 3H, J = 6.6); IR (Nujol) 2705, 2580, 2020, 1510 cm^{-1}.

(*S*)-1-Cyclohexylethylamine hydrochloride (7c): colorless solid; mp 221−223 °C (from EtOH−ether); $[\alpha]_D^{25}$ = −6.0 (*c* 0.7, MeOH); ^{1}H NMR δ 8.33 (s, 3H), 3.14 (m, 1H), 1.16 (d, 3H, J = 6.7); IR (Nujol) 2720, 2560, 2010, 1510, 1065 cm^{-1}; chiral HPLC analysis of α-naphthamide ee >99% (UV detector 254 nm, t_R 12.28 min, 2.0 mL/min, 95:5 hexane/2-propanol).

(*S*)-1-Cycloheptylethylamine hydrochloride (7d): colorless solid; mp 229−231 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −4.4 (*c* 2.2, MeOH); ^{1}H NMR δ 8.30 (s, 3H), 3.24 (m, 1H), 1.34 (d, 3H, J = 6.7); IR (Nujol) 2880, 2705, 2515 cm^{-1}.

(*S*)-1-Cyclopropylpropylamine hydrochloride (8a): colorless solid; mp 253−255 °C (from EtOH−ether); $[\alpha]^{25}_D$ = +5.2 (*c* 1.5, MeOH); ^{1}H NMR δ 8.48 (s, 3H), 2.34 (m, 1H), 1.93 (m, 2H, J = 7.1), 1.11 (t, 3H, J = 7.1); IR (Nujol) 2710, 2560, 1510, 1020 cm^{-1}.

(*S*)-1-Cyclopentylpropylamine hydrochloride (8b): colorless solid; mp 238−239 °C (from EtOH−ether); ^{1}H NMR δ 8.36 (s, 3H), 3.01 (m, 1H), 1.12 (t, 3H, J = 7.2); IR (Nujol) 2600, 2520, 1510 cm^{-1}.

(*S*)-1-Cycloheptylpropylamine hydrochloride (8d): colorless solid; mp 243−245 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −6.1 (*c* 0.4, MeOH); ^{1}H NMR δ 8.32 (s, 3H), 3.00 (m, 1H), 0.98 (t, 3H, J = 6.8); IR (Nujol) 2620, 2540, 1520 cm^{-1}.

(*S*)-2-Butylamine hydrochloride (27): colorless solid; mp 149−150 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −2.3 (*c* 4.0, MeOH) (lit.[21] $[\alpha]^{23}_D$ = −2.64 (*c* 4.0, MeOH)); ^{1}H NMR δ 8.28 (s, 3H), 3.29 (m, 1H), 1.74 (m, 2H), 1.41 (d, 3H, J = 6.6), 1.04 (t, 3H, J = 7.3); IR (Nujol) 2790, 2620, 2540, 1510, 1010 cm^{-1}.

(*S*)-3-Methyl-2-butylamine hydrochloride (28): colorless solid; mp 198−199 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −2.1 (*c* 4.0, MeOH) (lit.[21] $[\alpha]^{23}_D$ = −2.19 (*c* 4.0, MeOH)); ^{1}H NMR δ 8.36 (s, 3H), 3.26 (m, 1H, J = 6.7), 1.97 (m, 1H), 1.36 (d, 3H, J = 6.7), 1.07 (d, 3H, J = 6.8), 1.04 (d, 3H, J = 6.8); IR (Nujol) 2630, 2530, 1500, 1190 cm^{-1}.

(*S*)-2-Hexylamine hydrochloride (29): colorless solid; mp 102−103 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −3.4 (*c* 0.7, EtOH) (lit.[22] $[\alpha]_D$ = −5.68 (MeOH)); ^{1}H NMR δ 8.3 (s, 3H), 3.29 (m, 1H), 1.40 (d, 3H, J = 6.4); IR (Nujol) 2580, 2510, 1510 cm^{-1}.

(*S*)-4-Methyl-2-pentylamine (30): colorless oil; bp 42−43 °C; $[\alpha]^{25}_D$ = +3.7 (*c* 1.0, MeOH) (lit.[23] $[\alpha]_D$ = +4.2 (MeOH)). Hydrochloride: colorless solid; mp 219−22 °C (from EtOH−ether); $[\alpha]^{25}_D$ = −7.3 (*c* 0.3, MeOH); ^{1}H NMR δ 8.32 (s, 3H), 3.40 (m, 1H), 1.41 (d, 3H, J = 6.5), 0.96 (d, 3H, J = 6.0), 0.92 (d, 3H, J = 5.9); IR (Nujol) 2700, 2580, 2490, 1510, 1160 cm^{-1}.

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(19) Terashima, S.; Wagatsuma, M.; Yamada, S. *Chem. Pharm. Bull.* **1970**, *18*, 1137.

(20) Vogel, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 2262.

(21) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaran, B. *J. Am. Chem. Soc.* **1986**, *108*, 6764.

(22) *Dictionary of Organic Compounds*; Eyre and Spottiswood Pub.: London, 1965; Vol. 1, p 135.

(23) *Dictionary of Organic Compounds*; Eyre and Spottiswood Pub.: London, 1965; Vol. 1, p 160.