Synthesis of Enantiopure Highly Substituted *trans*-8a-Hydroxydecahydroisoquinolines by Sequential Diastereoselective IMDA Reaction and Oxanorbornene Nucleophilic Ring Opening

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The decahydroisoquinoline system, a component of more than 500 alkaloids,[1] has attracted a lot of synthetic interest. Some of the synthetic approaches are the hydrogenation of isoquinoline derivatives,[2] reductive cyclizations of disubstituted cyclohexanes,[3] and intramolecular Mannich reaction or related processes.[4] Nevertheless, the most efficient and stereoselective method to prepare saturated isoquinolines is the intramolecular Diels−Alder reaction of 1,3,9-trienes with a nitrogen at a suitable position.[5]

In previous work,[6] we have shown that the chiral perhydrobenzoxazines, derived from (−)-8-aminomenthol (**1**), was a useful chirality inductor in asymmetric transformations. This heterocycle **3**, bearing a furan ring at C-2 as diene and a 3-butenyl substituent at the nitrogen atom as dienophile, would serve as a nitrogen source and chiral inductor in the stereoselective synthesis of enantiopure decahydroisoquinolines. The initial key step of our approach is an intramolecular Diels−Alder reaction, directed to assemble the bicyclic structure.[7] Other important transformations are the stereoselective ring opening of the cyclic N,O-acetal[8] to introduce the substituent at C-2, the highly regio- and stereoselective oxanorbornene nucleophilic ring opening[9] with triethylaluminum, and the elimination of the chiral appendage.

Attempts to prepare **3** by condensation of 2-furaldehyde with (−)-8-((3′-butenyl)amino)menthol (**2**), obtained by alkylation of (−)-8-aminomenthol (**1**) with 4-bromo-1-butene (K_2CO_3, toluene, reflux), under standard conditions failed.[8a] However, the heating of a mixture of 2-furaldehyde and **2** for 9 days in toluene at reflux led to **3**, which immediately cyclized in these conditions to the diastereomeric *exo* adducts **4a**,**b**, isolated as a mixture 4:1 in 90% total yield. The stereoselectivity of the IMDA reaction is highly increased (9:1 **4a**/**4b**) when the reaction was carried out by heating a mixture of the reactants, without solvent, at 160 °C for 4 days, although the chemical yield decreased to 70%, probably as a consequence of decomposition of starting material under those somewhat harsh reaction conditions (Scheme 1). Flash chromatography on silica gel using hexanes−EtOAc as eluent allowed the isolation of the pure diastereoisomers **4a**,**b** as colorless solids.[10]

The predominance of the diastereomer **4a** is a result of the thermodynamic conditions used in the cyclization reaction, and it is in accord with the results obtained in the formation of isoindoline derivatives.[6a]

Reduction of **4a**,**b** with 1.5 equiv of aluminum hydride (prepared from LAH and $AlCl_3$) in THF at −10 °C for 15 min furnished the amino alcohols **5a,b**, respectively, which upon oxidation with PCC in CH_2Cl_2 at room temperature and treatment with 2.5 M solution of KOH in THF−methanol afforded the enantiomeric epoxyisoquinoline derivatives **6a** and *ent*-**6a** in excellent chemical yields (Scheme 2). Otherwise, the treatment of the cycloadducts **4a**,**b** with 3 equiv of AlH_3 at room temperature for 6 h led to the amino diols **7a**,**b** (92% total yield), respectively, resulting from the ring opening of the N,O-cyclic acetal moiety and the regio- and stereoselective reduction of the oxanorbornene system.[9] The mild reduction conditions contrast with those previously reported for the reaction of related oxanorbornenes with DIBAL-H.[11] These amino diols were transformed into the enantiopure *trans*-8a-hydroxydecahydroisoquinolines **9a** and *ent*-**9a** by sequential hydrogenation (PtO_2/H_2, ethanol, room temperature, 24 h) to **8a**,**b** and elimination of the menthol appendage as described for **5a**,**b** (Scheme 2).

The stepwise reductive ring opening described opens the possibility to introduce different substituents at C-1 and C-8 in the final isoquinolines regio- and stereoselectively by a careful control of the reaction conditions. In fact, the adduct **4a** reacted with 4 equiv of trimethylaluminum in toluene, at room temperature, for 15 min leading to the open epoxy amino alcohol **10** as a single stereoisomer in 80% yield. This compound was transformed into the enantiopure epoxy isoquinoline **11** by the oxidation−elimination protocol described above.

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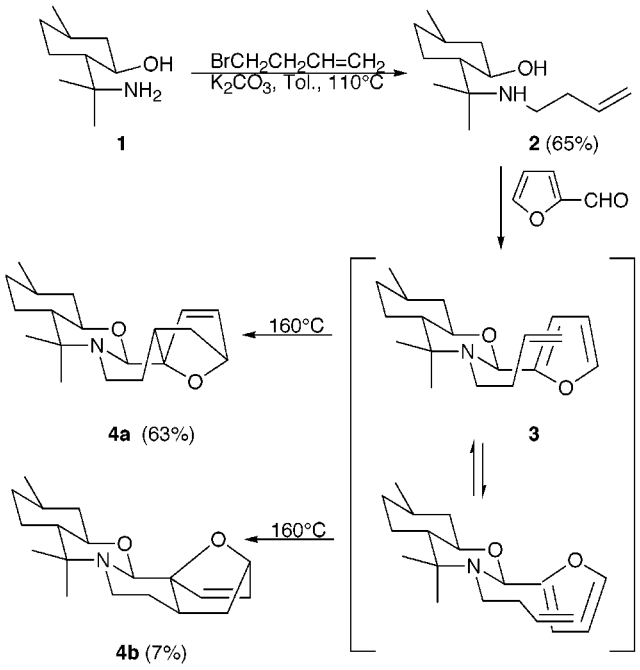
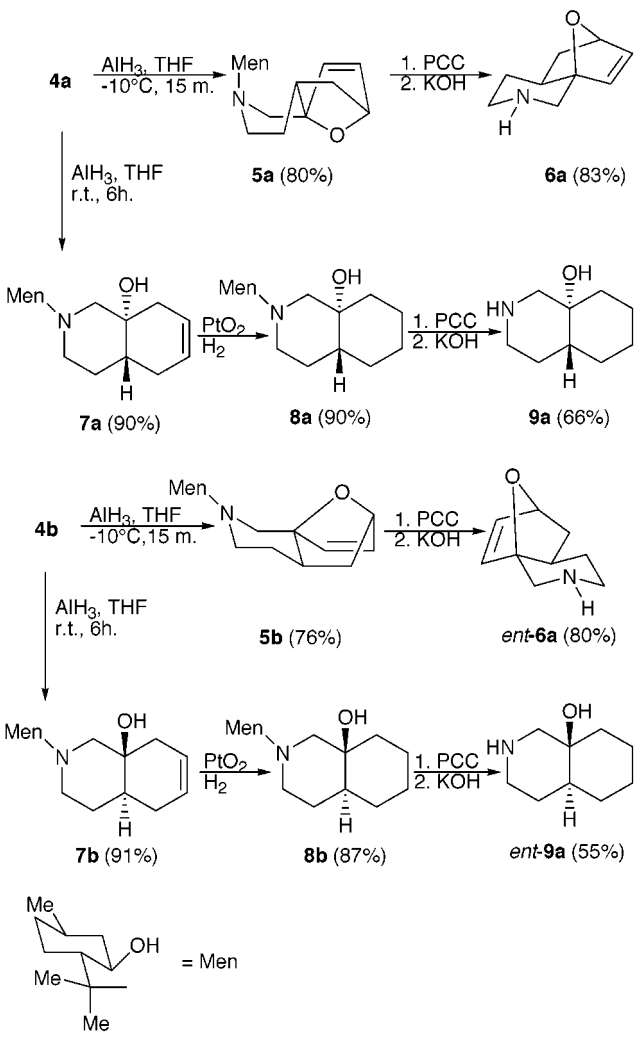
Scheme 1

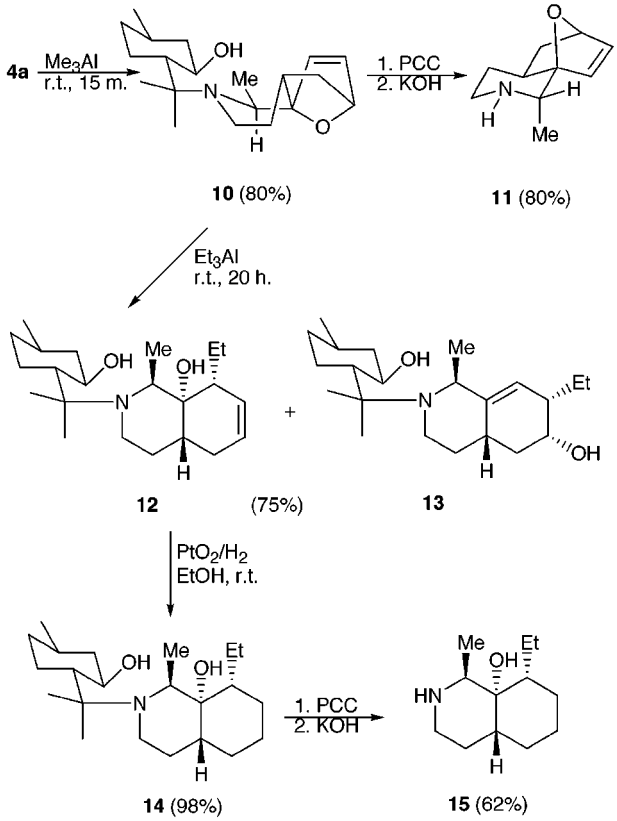


Scheme 2



The configuration of the newly created stereocenter was determined as *S* by NOESY experiments, showing that the nucleophilic ring opening of the N,O-acetal occurred by the oxygen face in the perhydrobenzoxazine by a synchronous retentive alkylation process, as previously noted for related systems.[12]

Scheme 3



The compound **10** was subjected to the reaction with an excess (8 equiv) of triethylaluminum in toluene for 20 h, at room temperature, leading to a mixture (4:1) of the regioisomers **12** and **13** in 75% combined yield (Scheme 3). It is worthy to note that, although the *exo* S_N2' ring opening of the oxanorbornene system occurs with total stereoselectivity by the β face of the double bond as described for related oxatricyclo derivatives,[13,8e] the regiochemistry was just the contrary.[14] To our knowledge, this is the first case where the nucleophilic attack yields the open compound **12** with the OH at the angular carbon as major regioisomer with good selectivity. As previously reported for alkoxy derivatives, electrostatic repulsions or changes in the LUMO coefficients caused by the nitrogen substituent could be responsible for the change in the observed regioselectivity.[15]

Compound **12** was isolated from the reaction mixture by flash chromatography (silica gel, 30:1 $CHCl_3$/EtOH) and subjected to hydrogenation (PtO_2, 1 atm, EtOH, room temperature, 24 h) to **14**, which, upon elimination of the chiral appendage, led to the enantiopure (1*S*,4a*R*,8*R*,8a*R*)-8-ethyl-1-methyl-8a-hydroxydecahydroisoquinoline (**15**) in 62% yield from **12** (Scheme 3).

In summary, a concise diastereoselective synthesis of enantiopure decahydroisoquinolines has been achieved in five steps from easily accessible (−)-8-aminomenthol.

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The described protocol allows to prepare a variety of enantiopure isoquinoline derivatives with four stereocenters, three of which are contiguous, and with known absolute configuration. The method opens a way to the stereocontrolled synthesis of potentially important biologically active molecules.

Experimental Section

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

Synthesis of (−)-8-((3′-Butenyl)amino)menthol (2). A mixture of (−)-8-aminomenthol (17.1 g, 100 mmol), 4-bromo-1-butene (11.16 mL, 110 mmol), and anhydrous K_2CO_3 (15.18 g, 110 mmol) in toluene (60 mL) was refluxed for 65 h. The mixture was filtered, and the solid was washed with EtOAc. The solvents were evaporated on a rotavapor, and the residue was chromatographed on a column packed with silica gel and eluted with 1:8 EtOAc/hexane. Yield: 65%, colorless oil. $[\alpha]^{25}_D$ = −19.81 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ): 5.81−5.67 (m, 1H); 5.11−5.02 (m, 2H,); 3.60 (dt, J_1 = 10.2 Hz, J_2 = 4.1 Hz, 1H); 2.73 (m, 1H); 2.62 (m, 1H); 2.19 (m, 2H); 1.93 (m, 1H); 1.70−1.60 (m, 2H); 1.42 (m, 1H); 1.26 (m, 1H); 1.10 (s, 3H); 1.09 (s, 3H); 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR (δ): 135.2; 116.1; 71.8; 55.7; 48.8; 43.8; 39.2; 34.4; 33.9; 30.3; 25.5; 25.0; 21.5; 20.9. IR (film): 3150, 1625, 1190, 1050, 1020 cm^{-1}. MS (CI) (m/z, %): 226 (M^+ + 1, 100); 210 (11); 184 (34); 149 (15); 137 (33). Anal. Calcd for $C_{14}H_{27}NO$: C, 74.6; H, 12.1; N, 6.2. Found: C, 74.3; H, 12.4; N, 5.8.

Synthesis of Cycloadducts 4a,b. A mixture of amino alcohol **2** (11.7 g, 52 mmol) and recently distilled furfural (13 mL, 157 mmol) was heated at 160 °C (oil bath) for 4 days. The excess of aldehyde was distilled, and the oily residue was subjected to flash chromatography (silica gel, 8:1, 5:1, 3:1 hexane/EtOAc and pure EtOAc) to give, in order of elution, **4a** and **4b**. Data for **4a** (9.93 g, 63%) as a colorless solid; mp 102−103 °C (from pentane)) are as follows. $[\alpha]^{25}_D$ = − 100.2 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ): 6.35 (d, J = 5.8 Hz, 1H); 6.33 (dd, J_1 = 1.5 Hz, J_2 = 5.8 Hz, 1H); 5.13 (s, 1H); 4.93 (dd, J_1 = 1.5 Hz, J_2 = 4.3 Hz, 1H); 3.58 (dt, J_1 = 3.9 Hz, J_2 = 10.5 Hz, 1H); 3.05 (dt, J_1 = 2.1 Hz, J_2 = 11.3 Hz, 1H); 2.78 (dt, J_1 = 3.5 Hz, J_2 = 11.3 Hz, 1H); 1.97−1.88 (m, 2H); 1.75−1.65 (m, 3H); 1.65−1.45 (m, 7H); 1.24 (s, 3H); 1.17 (s, 3H); 1.12−0.94 (m, 1H); 0.94 (d, J = 6.5 Hz, 3H). ^{13}C NMR (δ): 136.4; 136.0; 86.2; 82.3; 78.9; 76.8; 55.6; 44.4; 41.3; 38.6; 35.0; 34.6; 31.7; 31.3; 30.6; 27.4; 25.1; 22.2; 21.6. MS [m/z (%)]: 303 (3) (M^+), 150 (18), 121 (17), 109 (76), 41 (100). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.6; H, 9.3; N, 4.2.

Data for **4b** (1.10 g, 7%, colorless solid; mp 119−120 °C (from pentane)) are as follows. $[\alpha]^{25}_D$ = + 24.1 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ): 6.32 (dd, J_1 = 1.7 Hz, J_2 = 5.7, Hz, 1H); 6.12 (d, J = 5.7 Hz, 1H); 5.00 (dd, J_1 = 1.7 Hz, J_2 = 4.4 Hz, 1H); 4.53 (s, 1H); 3.43 (dt, J = 4.3 Hz, 10.5 Hz, 1H); 2.99 (dt, J_1 = 3.3 Hz, J_2 = 12.0 Hz, 1H); 2.18 (dt, J_1 = 1.8 Hz, J_2 = 12.0 Hz, 1H); 1.95 (m, 1H); 1.85 (m, 1H); 1.75−1.35 (m, 9H); 1.25−1.15 (m, 1H); 1.18 (s, 3H); 1.05−0.95 (m, 1H); 0.94 (s, 3H); 0.90 (d, J = 6.5 Hz, 3H). ^{13}C NMR (δ): 136.2; 135.6; 86.8; 85.4; 78.8; 74.7; 55.6; 49.0; 42.3; 41.0; 35.7; 34.3; 34.1; 31.1; 30.8; 25.5; 24.7; 21.7; 10.6. MS [m/z (%)]: 303 (4) (M^+), 288 (41), 150 (10), 121 (17), 109 (24), 55 (100). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.5; H, 9.9; N, 4.3.

Reduction of 4a,b to the Amino Alcohols 5a,b. To a suspension of LAH (0.60 g, 15.8 mmol) in dry THF (40 mL) at −10 °C was added $AlCl_3$ (0.70 g, 5.25 mmol) in small portions. The mixture was stirred for 10 min, a solution of the adduct **4a** or **4b** (0.96 g, 3.17 mmol) in THF (20 mL) was slowly dropped, and then the mixture was stirred for 15 min. The reaction mixture was quenched by addition of H_2O (4 mL), the solid was separated by filtration, and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, the solvent was eliminated on Rotavapor, and the residue was purified by flash chromatography on silica gel using EtOAc as eluent.

Amino Alcohol 5a. Yield: 80%, colorless solid. Mp: 113−114 °C (from hexane). $[\alpha]^{25}_D$ = −6.40 (c = 1.16, CH_2Cl_2). ^{1}H NMR (δ): 7.81 (s, 1H); 6.34 (dd, J_1 = 5.7 Hz, J_2 = 1.7 Hz, 1H); 5.99 (d, J = 5.7 Hz, 1H); 4.99 (dd, J_1 = 4.4 Hz, J_2 = 1.7 Hz, 1H); 3.75 (d, J = 12.9 Hz, 1H); 3.58 (dt, J_1 = 10.3 Hz, J_2 = 4.2 Hz, 1H); 3.14 (m, 1H); 2.71 (d, J = 12.9 Hz, 1H); 2.29 (m, 1H); 1.97−1.87 (m, 2H); 1.75−1.30 (m, 8H); 1.18 (s, 3H); 1.10−0.90 (m, 4H); 0.95 (s, 3H); 0.87 (d, 3H, J = 6.5 Hz). ^{13}C NMR (δ): 137.5; 135.9; 85.5; 79.3; 72.2; 60.2; 48.0; 46.4; 45.0; 44.6; 35.1; 34.3; 34.0; 32.6; 30.9; 26.0; 22.1; 21.6; 18.5. IR (Nujol): 3020 cm^{-1}. MS (CI) (m/z, %): 307 (M^+ + 2, 22); 306 (M^+ + 1, 100); 192 (44); 152 (32).

Amino Alcohol 5b. Yield: 76%, colorless solid. Mp: 130−131 °C (from pentane). $[\alpha]^{25}_D$ = −16.89 (c = 1.1, CH_2Cl_2). ^{1}H NMR (δ): 8.12 (s, 1H); 6.35 (dd, J_1 = 5.8 Hz, J_2 = 1.7 Hz, 1H); 5.98 (d, J = 5.8 Hz, 1H); 4.91 (dd, J_1 = 4.3 Hz, J_2 = 1.7 Hz, 1H); 3.59 (d, J = 12.5 Hz, 1H); 3.57 (dt, J_1 = 10.2 Hz, J_2 = 4.0 Hz, 1H); 3.21 (m, 1H); 2.80 (d, J = 12.5 Hz, 1H); 2.10 (m, 1H); 1.96−1.89 (m, 2H); 1.74−1.52 (m, 4H); 1.52−1.32(m, 4H); 1.16 (s, 3H); 1.05−0.90 (m, 3H); 0.93 (s, 3H); 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (δ): 137.7; 135.7; 85.8; 78.9; 71.8; 60.0; 47.4; 47.0; 46.2; 44.6; 35.2; 34.6; 33.6; 31.4; 30.9; 25.8; 22.2; 20.9; 18.0. IR (Nujol): 3140 cm^{-1}. MS (CI) (m/z, %): 307 (M^+ + 2, 21); 306 (M^+ + 1, 100); 304 (15); 192 (33).

Synthesis of Amino Alcohols 7a,b. To a mixture of LAH (1.2 g, 31.6 mmol) and $AlCl_3$ (1.4 g, 10.5 mmol) in THF (50 mL) prepared as described above was added the adduct **4a** or **4b** (0.96 g, 3.17 mmol) in THF (20 mL). The mixture was heated to room temperature, stirred for 6 h, and then cooled to 0 °C and quenched by addition of a 15% solution of NaOH (50 mL). The solids were filtered off and washed with EtOAc (4 × 30 mL), and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were eliminated on rotavapor, and the residue was purified by flash chromatography (silica gel, 1:25 EtOH−$CHCl_3$).

Amino Alcohol 7a. Yield: 90%, colorless solid. Mp: 72−74 °C (from pentane). $[\alpha]^{25}_D$ = −15.95 (c = 0.78, CH_2Cl_2). ^{1}H NMR (δ): 5.83 (ddd, J_1 = 9.8 Hz, J_2 = 4.2 Hz, J_3 = 2.8 Hz, 1H); 5.62 (ddd, J_1 = 9.8 Hz, J_2 = 2.1 Hz, J_3 = 1.9 Hz, 1H); 3.61 (dt, J_1 = 10.2 Hz, J_2 = 4.0 Hz, 1H); 3.19 (m, 1H); 3.17 (d, J = 11.5 Hz, 1H); 2.24 (m, 1H); 2.13 (m, 1H); 2.07 (d, J = 11.5 Hz, 1H); 1.91 (m, 1H); 1.80−1.55 (m, 6H); 1.50−1.22 (m, 6H); 1.18 (s, 3H); 1.08−0.95 (m, 3H); 0.91 (s, 3H); 0.90 (d, J = 6.5 Hz, 3H). ^{13}C NMR (δ): 131.5; 131.0; 72.8; 66.2; 60.8; 55.9; 46.4; 45.7; 44.3; 41.9; 35.0; 31.0; 28.0; 26.2; 25.9; 22.9; 22.1; 21.3; 18.6. IR (Nujol): 3360, 1195 cm^{-1}. MS (CI) (m/z, %): 309 (M^+ + 2, 21); 308 (M^+ + 1, 100); 306 (21); 290 (24); 194 (62).

Amino Alcohol 7b. Yield: 91%, colorless oil. $[\alpha]^{25}_D$ = +10.15 (c = 0.7, CH_2Cl_2). ^{1}H NMR (δ): 8.45 (broad s, 1H); 5.83 (ddd, J_1 = 9.8 Hz, J_2 = 4.0 Hz, J_3 = 2.9 Hz, 1H); 5.59 (dt, J_1 = 9.8 Hz, J_2 = 2.1 Hz, 1H); 3.61 (dt, J_1 = 10.3 Hz, J_2 = 4.0 Hz, 1H); 3.32 (m, 1H); 3.03 (dd, J_1 = 11.0 Hz, J_2 = 2.1 Hz, 1H); 2.22−2.02 (m, 3H); 1.93 (m, 1H); 1.80−1.50 (m, 6H); 1.50−1.19 (m, 5H); 1.17 (s, 3H); 1.05−0.90 (m, 3H); 0.91 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR (δ): 131.9; 130.7; 71.8; 66.0; 62.0; 55.4; 46.8; 46.2; 44.5; 41.6; 35.0; 31.0; 26.9; 26.2; 26.0; 23.0; 22.1; 21.1; 19.1. IR (film): 3400, 1190, 1170 cm^{-1}. MS (CI) (m/z, %): 309 (M^+ + 2, 21); 308 (M^+ + 1, 100); 306 (17); 290 (20); 194 (27).

Reduction of 7a,b to Amino Alcohols 8a,b. A mixture of the corresponding amino alcohol (0.6 g) and a spatula of PtO_2 in ethanol (20 mL) was stirred for 24 h under H_2 atmosphere at room temperature. The catalyst was separated by filtration over a pad of Celite, the solvent was eliminated on rotavapor, and the residue was flash chromatographed on silica gel using 1:10 EtOH−$HCCl_3$ as eluent.

Amino Alcohol 8a. Yield: 90%, colorless oil. $[\alpha]^{25}_D$ = +24.81 (c = 1.6, CH_2Cl_2). ^{1}H NMR (δ): 8.52 (broad s, 1H); 3.61 (dt, J_1 = 10.3 Hz, J_2 = 4.0 Hz, 1H); 3.17 (m, 1H); 3.05 (dd, J_1 = 11.8 Hz, J_2 = 2.2 Hz, 1H); 2.21 (dt, J_1 = 11.5 Hz, J_2 = 2.9 Hz, 1H); 2.00 (d, J = 11.8 Hz, 1H); 1.90 (m, 1H); 1.80−1.55 (m, 8H); 1.55−0.90 (m, 11H); 1.18 (s, 3H); 0.91 (s, 3H); 0.90 (d, J = 6.5 Hz, 3H). ^{13}C NMR (δ): 72.9; 68.4; 61.0; 57.5; 46.3, 45.7; 44.0; 43.3; 36.8; 34.9; 30.9; 28.7; 27.0; 26.0; 25.8; 22.0; 21.0; 20.8; 18.5.

IR (film): 3240, 1190, 1170 cm^{-1}. MS (CI) (*m*/*z*, %): 311 (M^+ + 2, 23); 310 (M^+ + 1, 100); 308 (30); 196 (66).

Amino Alcohol 8b. Yield: 87%, colorless oil. $[\alpha]^{25}_D$ = −36.78 (*c* = 2.1, CH_2Cl_2). ^1H NMR (*δ*): 8.37 (broad s, 1H); 3.60 (dt, J_1 = 10.2 Hz, J_2 = 4.1 Hz, 1H); 3.28 (m, 1H); 2.86 (dd, J_1 = 11.2 Hz, J_2 = 2.0 Hz, 1H); 2.07 (dt, J_1 = 11.7 Hz, J_2 = 2.4 Hz, 1H); 2.04 (d, *J* = 11.2 Hz, 1H); 1.95 (m, 2H); 1.78−1.45 (m, 9H); 1.45−1.10 (m, 6H); 1.14 (s, 3H); 1.10−0.90 (m, 3H); 0.91 (d, *J* = 6.5 Hz, 3H); 0.90 (s, 3H). ^{13}C NMR (*δ*): 72.0; 68.5; 60.3; 57.0; 46.5, 46.2; 44.3; 43.2; 36.3; 34.9; 30.8; 27.8; 27.0; 25.9; 25.8; 22.0; 21.1; 20.8; 18.3. IR (film): 3220, 1010, 980 cm^{-1}. MS (CI) (*m*/*z*, %): 311 (M^+ + 2, 23); 310 (M^+ + 1, 100); 308 (29); 196 (44).

Synthesis of Amino Alcohol 10. To a solution of **4a** (0.76 g, 2.5 mmol) in toluene (30 mL) was slowly added a 2 M solution (5 mL, 10 mmol) of trimethylaluminum in toluene, and the mixture was stirred at room temperature for 15 min. The solution was quenched by addition of a mixture of saturated solution of ammonium chloride and ice and the solid separated by filtration and washed with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated on a rotavapor, and the residue was flash chromatographed on silica gel, using a mixture of 1:20 EtOH−$CHCl_3$ as eluent. Yield: 80%, colorless solid. Mp: 90−91 °C (from pentane). $[\alpha]^{25}_D$ = −28.02 (*c* = 1.1, CH_2Cl_2). ^1H NMR (*δ*): 8.46 (broad s, 1H); 6.30 (dd, J_1 = 5.8 Hz, J_2 = 1.6 Hz, 1H); 6.20 (d, *J* = 5.8 Hz, 1H); 4.89 (dd, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 1H); 3.71 (q, *J* = 6.7 Hz, 1H); 3.67 (dt, J_1 = 10.4 Hz, J_2 = 4.2 Hz, 1H); 2.98−2.86 (m, 2H); 2.04−1.89 (m, 2H); 1.83−1.50 (m, 6H); 1.50−1.37 (m, 2H); 1.38 (d, *J* = 6.7 Hz, 3H), 1.24 (s, 3H); 1.10−0.88 (m, 3H); 1.05 (s, 3H); 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (*δ*): 137.2; 136.3; 90.1; 77.4; 72.6; 61.3; 48.2; 47.2; 44.1; 44.0; 36.7; 36.0; 35.5; 31.2; 29.4; 26.2; 22.3; 22.1; 22.0; 20.5. IR (Nujol): 3090, 1050, 935 cm^{-1}. MS (CI) (*m*/*z*, %): 321 (M^+ + 2, 23); 320 (M^+ + 1, 100); 206 (64); 166 (67).

Synthesis of Amino Alcohol 12. To a solution of **10** (1 g, 3.13 mmol) in toluene (50 mL) was added a 2 M solution (12.5 mL, 25 mmol) of triethylaluminum in toluene. The mixture was stirred at room temperature for 20 h and manipulated as described for the preparation of **10** to yield a colorless oil. $[\alpha]^{25}_D$ = − 82.38 (*c* = 1.0, CH_2Cl_2). ^1H NMR (*δ*): 5.80 (ddd, J_1 = 9.9 Hz, J_2 = 4.8 Hz, J_3 = 0.6 Hz, 1H); 5.51 (dd, J_1 = 9.9 Hz, J_2 = 1.3 Hz, 1H); 4.20 (broad s, 2H); 3.56 (dt, J_1 = 10.3 Hz, J_2 = 3.9 Hz, 1H); 3.39 (q, *J* = 6.6 Hz, 1H); 2.83 (m, 1H); 2.75 (m, 1H); 2.02 (m, 1H); 1.92 (m, 1H); 1.86−1.50 (m, 6H); 1.50−1.15 (m, 6H); 1.21 (s, 3H); 1.11 (s, 3H); 1.05−0.90 (m, 2H); 1.01 (d, *J* = 6.6 Hz, 3H); 0.94 (t, *J* = 7.3 Hz, 3H); 0.90 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (*δ*): 135.2; 131.2; 72.8; 70.6; 59.9; 56.7; 49.9; 45.3; 38.9; 36.4; 35.3; 31.4; 30.5; 28.4; 27.9; 27.2; 26.8; 24.4; 23.9; 22.1; 12.5; 11.1. IR (film): 3320, 1185, 965 cm^{-1}. MS (CI) (*m*/*z*, %): 351 (M^+ + 2, 23); 350 (M^+ + 1, 100); 348 (52); 332 (22).

Amino Alcohol 14. Compound **14** was obtained by hydrogenation of **12** as described for **8a**,**b**. Yield: 98%, colorless oil. $[\alpha]^{25}_D$ = +1.06 (*c* = 1.9, CH_2Cl_2). ^1H NMR (*δ*): 5.33 (broad s, 2H); 3.99 (q, *J* = 6.7 Hz, 1H); 3.57 (dt, J_1 = 10.4 Hz, J_2 = 4.0 Hz, 1H); 3.27 (m, 1H); 3.12 (m, 1H); 2.10−1.88 (m, 4H); 1.80−1.20 (m, 13H); 1.45 (s, 3H); 1.30 (d, *J* = 6.7 Hz, 3H); 1.29 (s, 3H); 1.10−0.90 (m, 3H); 0.93, (d, *J* = 6.5 Hz, 3H); 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (*δ*): 72.6; 72.2; 68.5; 61.9; 46.7; 42.6; 40.6; 34.1; 34.0; 31.6; 30.5; 29.3; 27.7; 27.1; 26.5; 23.7; 23.6; 22.9; 22.8; 21.5; 12.4; 10.3. IR (film): 3200, 1140 cm^{-1}. MS (CI) (*m*/*z*, %): 353 (M^+ + 2, 19); 352 (M^+ + 1, 77); 350 (35); 238 (100); 198 (34).

Elimination of the Menthol Appendage. General Method. A mixture of the corresponding amino alcohol (1.65 mmol), PCC (1.41 g., 6.56 mmol), and 4 Å molecular sieves (1 g) in CH_2Cl_2 was stirred at room temperature for 6 h. The mixture was filtered through a pad of Celite, the solvent was eliminated, and the residue was redissolved in 15% aqueous solution of NaOH with the aqueous phase was extracted with Et_2O (5 × 20 mL). The organics were washed with brine and dried over anhydrous $MgSO_4$. After elimination of the solvent and pyridine under vacuum, the residue was redissolved in a mixture of THF (8 mL), MeOH (4 mL), and a 2.5 M solution of KOH (4 mL) and stirred at room temperature for 5 h. After elimination of the THF and MeOH under vacuum, the aqueous residue was acidified to pH = 2 by addition of a 10% solution of HCl. The aqueous phase was washed with Et_2O (4 × 10 mL) and then basified to pH = 12 by addition of 15% solution of NaOH. The basic solution was extracted with $CHCl_3$ (4 × 15 mL), and the organic layer was dried over anhydrous $MgSO_4$. After elimination of the solvent, the residue was purified by flash chromatography (silica gel, 1:10 EtOH−$CHCl_3$).

(4a*S*,6*R*,8a*S*)-6,8a-Epoxy-4a,5,6,8-tetrahydroisoquinoline (6a). Yield: 83%, colorless oil. $[\alpha]^{25}_D$ = + 27.96 (*c* = 1.0, CH_2Cl_2). ^1H NMR (*δ*): 6.38 (dd, J_1 = 5.7 Hz, J_2 = 1.6 Hz, 1H); 5.94 (d, *J* = 5.7 Hz, 1H); 4.95 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H); 3.53 (d, *J* = 14.7 Hz, 1H); 3.27 (d, *J* = 14.7 Hz, 1H); 3.05 (m, 1H); 2.61 (dt, J_1 = 13.2 Hz, J_2 = 2.3 Hz, 1H); 2.39 (broad s, 1H); 1.91 (m, 1H); 1.62 (m, 1H); 1.53 (dd, J_1 = 11.0 Hz, J_2 = 7.2 Hz, 1H); 1.44 (ddd, J_1 = 11.0 Hz, J_2 = 4.4 Hz, J_3 = 2.8 Hz, 1H); 1.34 (m, 1H). ^{13}C NMR (*δ*): 137.6; 135.6; 84.0; 79.0; 48.1; 45.6; 35.1; 33.5; 33.0. IR (film): 3320, 1315 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.9; H, 9.0; N, 9.7.

(4a*R*,6*S*,8a*R*)-6,8a-Epoxy-4a,5,6,8-tetrahydroisoquinoline (*ent*-6a). Yield: 80%, colorless oil. $[\alpha]^{25}_D$ = −28.22 (*c* = 0.98, CH_2Cl_2). Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.5; H, 9.1; N, 9.2.

(4a*R*,8a*R*)-8a-Hydroxydecahydroisoquinoline (9a). Yield: 66%, colorless oil. $[\alpha]^{25}_D$ = +29.74 (*c* = 1.27, CH_2Cl_2). ^1H NMR (*δ*): 3.45 (broad s, 2H); 3.05−2.95 (m, 1H); 2.69 (d, *J* = 11.5 Hz, 1H); 2.60 (dt, J_1 = 11.9 Hz, J_2 = 3.0 Hz, 1H); 2.42 (d, *J* = 11.5 Hz, 1H); 1.74−1.12 (m, 11H). ^{13}C NMR (*δ*): 67.9; 57.6; 46.6; 42.7; 35.6; 28.2; 28.0; 26.1; 21.2. IR (film): 3320, 1610, 1445 cm^{-1}. MS (CI) (*m*/*z*, %): 157 (M^+ + 2, 45); 156 (M^+ + 1, 100); 155 (M^+, 38). Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 70.0; H, 10.6; N, 9.3.

(4a*S*,8a*S*)-8a-Hydroxydecahydroisoquinoline (*ent*-9a). Yield: 55%, colorless oil. $[\alpha]^{25}_D$ = −28.17 (*c* = 0.65, CH_2Cl_2). Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.9; H, 11.4; N, 9.2.

(1*S*,4a*S*,6*R*,8a*S*)-1-Methyl-6,8a-epoxy-4a,5,6,8-tetrahydroisoquinoline (11). Yield: 80%, colorless oil. $[\alpha]^{25}_D$ = +15.08 (*c* = 1.1, CH_2Cl_2). ^1H NMR (*δ*): 6.42 (dd, J_1 = 5.8 Hz, J_2 = 1.6 Hz, 1H); 6.07 (d, *J* = 5.8 Hz, 1H); 4.94 (dd, J_1 = 4.5 Hz, J_2 = 1.6 Hz, 1H); 3.53 (q, *J* = 7.2 Hz, 1H); 3.49 (broad s, 1H); 2.96−2.77 (m, 2H); 1.87 (m, 1H); 1.76 (m, 1H), 1.53 (dd, J_1 = 11.2 Hz, J_2 = 7.1 Hz, 1H); 1.46 (d, *J* = 7.2 Hz, 3H); 1.43 (m, 1H); 1.39 (m, 1H). ^{13}C NMR (*δ*): 138.4; 134.4; 87.4; 78.6; 49.3; 38.5; 35.7; 32.4; 30.3; 17.1. IR (film): 3320, 1140 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.1; N, 8.5. Found: C, 72.9; H, 9.4; N, 8.7.

(1*S*,4a*R*,8*R*,8a*R*)-1-Methyl-8-ethyl-8a-hydroxydecahydroisoquinoline (15). Yield: 62%, colorless oil. $[\alpha]^{25}_D$ = −3.38 (*c* = 0.68, CH_2Cl_2). ^1H NMR (*δ*): 3.02 (broad s, 2H); 2.91 (dt, J_1 = 12.2 Hz, J_2 = 3.2 Hz, 1H); 2.74 (q, *J* = 7.0 Hz, 1H); 2.67 (ddd, J_1 = 12.2 Hz, J_2 = 5.5 Hz, J_3 = 1.5 Hz, 1H); 1.70 (m, 1H); 1.71−1.17 (m, 11H); 1.17 (d, *J* = 7.0 Hz, 3H); 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (*δ*): 71.1; 57.6; 38.8; 34.6; 31.9; 30.1; 28.9; 28.7; 24.5; 23.8; 10.0; 12.6. IR (film): 3280, 1440, 1100 cm^{-1}. MS (CI) (*m*/*z*, %): 199 (M^+ + 2, 19); 198 (M^+ + 1, 100); 197 (M^+, 17); 180 (82). Anal. Calcd for $C_{12}H_{23}NO$: C, 73.1; H, 11.7; N, 7.1. Found: C, 72.8; H, 11.4; N, 6.8.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **4a**,**b**, **5a**,**b**, **6a**, **7a**,**b**, **8a**,**b**, **9a**, **10**−**12**, **14**, and **15**, as well as COSY, NOESY, and heteronuclear correlation experiments for **4a**,**b**, **6a**, and **11** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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