Access to Enantiopure 4-Substituted 1,5-Aminoalcohols from Phenylglycinol-Derived δ-Lactams. Synthesis of *Haliclona* Alkaloids

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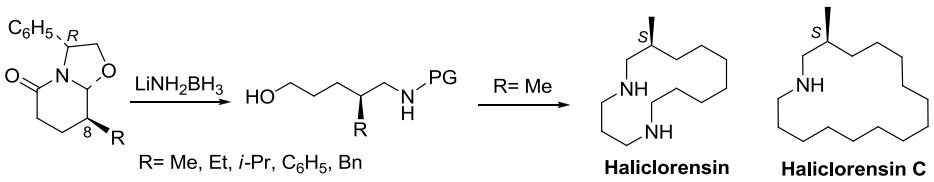
Abstract



$LiNH_2BH_3$-promoted reductive opening of 8-substituted phenylglycinol-derived oxazolopiperidone lactams leads to enantiopure 4-substituted-5-aminopentanols, which are used as starting building blocks in the synthesis of the *Haliclona* alkaloids haliclorensin C, haliclorensin, and halitulin (formal). The starting lactams are easily accessible by a cyclocondensation reaction of (*R*)-phenylglycinol with racemic γ-subtituted δ-oxoesters, in a process that involves a dynamic kinetic resolution.

Phenylglycinol-derived oxazolopiperidone lactams have proven to be multipurpose enantiomeric scaffolds for the synthesis of diversely substituted piperidine, indolizidine, quinolizidine, decahydroquinoline, tetrahydroisoquinoline, and tetrahydro-β-carboline derivatives, as well as complex polycyclic piperidine-containing alkaloids.[1] These lactams are easily accessible by a cyclocondensation reaction between the amino alcohol and a δ-oxoacid derivative and, due to their versatile functionality and conformational rigidity, allow the regio- and stereocontrolled introduction of substituents at the

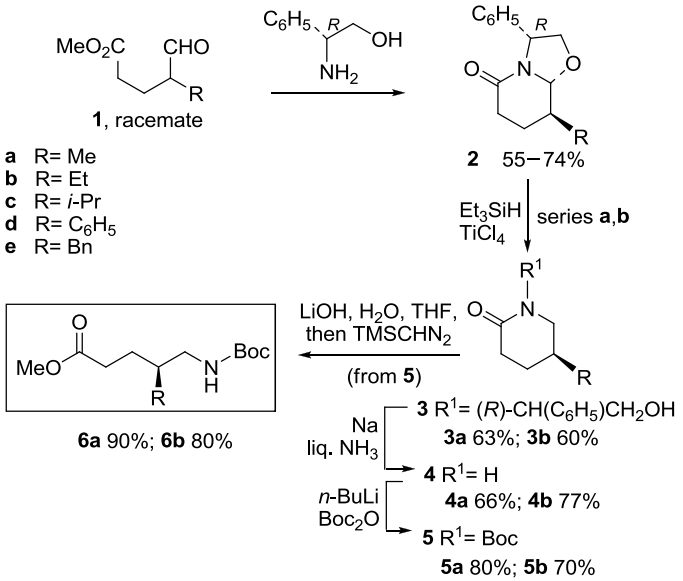
different positions of the piperidine ring to ultimately provide enantiopure piperidine derivatives bearing virtually any type of substitution pattern.

Taking into account that the stereocontrolled generation of chiral centers is generally more efficient and easier to accomplish in conformationally rigid cyclic systems than in acyclic compounds, we envisaged the above δ-lactams as potential building blocks for the synthesis of enantiopure substituted 1,5-aminoalcohols or δ-amino acid derivatives. Our approach would involve the stereoselective formation of the appropriate substituted lactam and then the opening of the lactam ring, with prior or subsequent removal of the phenylethanol moiety of the chiral inductor.

We report herein our studies aimed at developing this concept from lactams **2**, which incorporate a substituent at the 5 position of the 2-piperidone ring, and illustrate the usefulness of the resulting substituted linear-chain amino intermediates in the total synthesis of natural products.

Lactams **2** were stereoselectively prepared[2] by cyclocondensation of racemic δ-oxoesters **1**,[3] which bear a substituent (alkyl, phenyl, benzyl) at the epimerizable carbon α to the aldehyde carbonyl group, with (*R*)-phenylglycinol, in a process that involves a dynamic kinetic resolution of the racemic substrate[4,5] (Scheme 1).

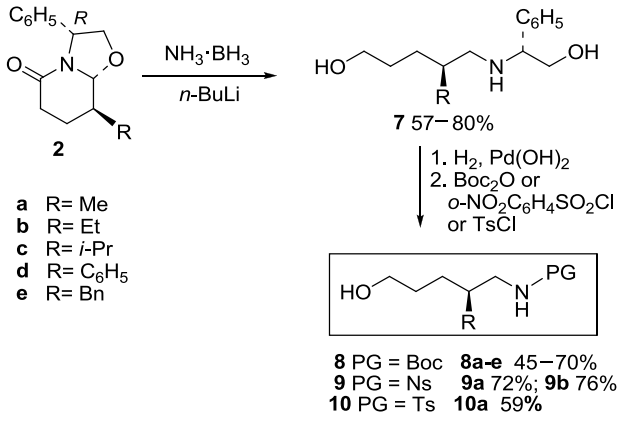
Scheme 1. Synthesis of Enantiopure 4-Substituted 5-Aminopentanoic Acid Derivatives



Initially, the conversion of lactams **2** into functionalized linear-chain amino derivatives was performed by the four-step sequence outlined in Scheme 1, involving the hydrolytic opening of a 2-piperidone as the key step. Thus, removal of the chiral auxiliary from lactams **2a** and **2b** was accomplished by successive treatment with triethylsilane in the presence of $TiCl_4$, which brought about the reductive cleavage of the oxazolidine C–O bond, and sodium in liquid NH_3, which caused the cleavage of the benzylic C–N bond. After the resulting *N*-unsubstituted 2-piperidones **4a** and **4b** were converted to the corresponding *N*-Boc derivatives **5a** and **5b**, a final alkaline hydrolysis with lithium hydroxide in aqueous THF at room temperature,[6] followed by esterification of the resulting crude δ-amino acids with trimethylsilyldiazomethane, led to esters **6a** and **6b**. The overall process **1** → **6** can be envisaged as a reductive amination of racemic aldehyde-esters **1** using a chiral latent form of ammonia, with concomitant dynamic kinetic resolution.

A more straightforward preparation of substituted linear-chain functionalized amino derivatives was accomplished by treatment of lactams **2** with lithium amidotrihydroborate ($LiNH_2BH_3$), which was generated in situ by deprotonation of the borane-ammonia complex with *n*-BuLi[7] (Scheme 2).

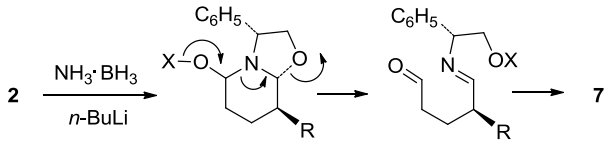
Scheme 2. Synthesis of Enantiopure 4-Substituted 5-Aminoalcohols



Although this reagent has been used to reduce acyclic tertiary amides to primary alcohols,[8] *N*-alkyl δ-lactams are usually reduced to the corresponding cyclic amines,[9] and there are only a few examples in the literature of the $LiNH_2BH_3$ reductive opening of crowded δ-lactams.[10]

Under $LiNH_2BH_3$ reduction conditions, bicyclic lactams **2a**–**e** were directly converted into *N*-substituted 1,5-aminoalcohols **7a**–**e** in an unprecedented process featuring the reductive opening of both the oxazolidine and lactam rings,[11] most probably through a stepwise sequence involving a 3-aza-Grob fragmentation,[12] as outlined in Scheme 3.

Scheme 3. Proposed Mechanism for the $LiNH_2BH_3$ Reduction of Lactams **2**

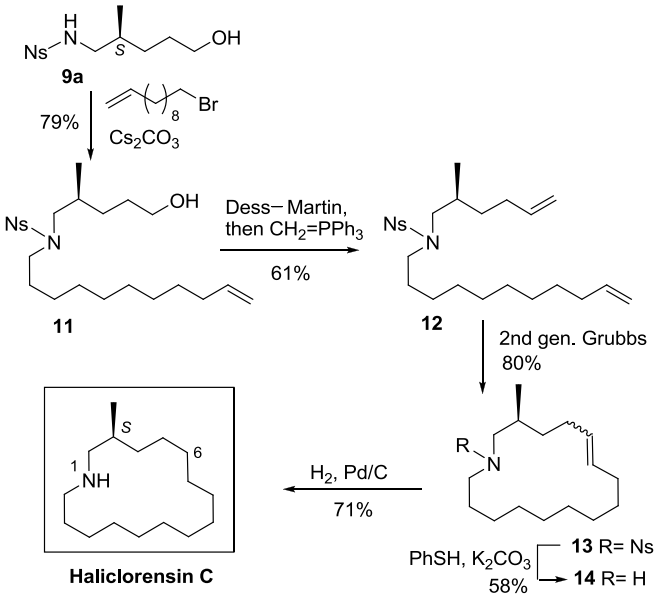


A subsequent removal of the phenylethanol moiety by hydrogenolysis, followed by protection of the resulting primary amines, led to the enantiopure *N*-protected 4-substituted-5-aminopentanols **8**–**10**. These aminoalcohols possess a stereogenic center with a well-defined configuration at the position β to the nitrogen atom, a structural motif (when R = methyl) found in several macrocyclic alkaloids, such as haliclorensin C,[13] halitulin,[14] and haliclorensin,[15] isolated from the marine sponge *Haliclona tulearensis*. The synthesis of these alkaloids from the above aminoalcohols would require the latter to be converted into appropriate long-chain secondary amino derivatives bearing two terminal alkene functionalities, which would allow the target azacyclic structures to be assembled using a ring-closing metathesis reaction as the key step.

Thus, the methyl substituted aminopentanol **9a** was envisaged as the N_1–C_6 fragment of haliclorensin C (Scheme 4). Alkylation of **9a** with 10-undecenyl bromide, followed by Dess–Martin oxidation of the resulting alcohol **11** and subsequent Wittig methylenation from the resulting aldehyde, gave the required *N*-hexenyl *N*-undecenyl amino derivative **12**. As expected, a ring-closing metathesis reaction provided the 16-membered azacycle **13**[16] in excellent yield. Removal of the nosyl group followed by catalytic

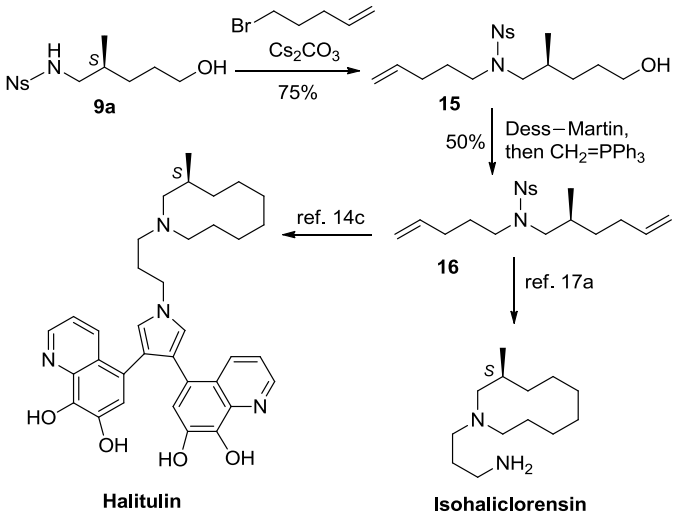
hydrogenation completed the first total synthesis of haliclorensin C. Unfortunately, haliclorensin C had been isolated[13] only in minute amounts (2 mg), and the ^{1}H and ^{13}C NMR spectra included in the paper show considerable contamination. These spectra probably correspond to a protonated sample since they essentially coincide with the spectra of the hydrochloride of our synthetic material (see Experimental Section and Supporting Information).

Scheme 4. Enantioselective Synthesis of Haliclorensin C



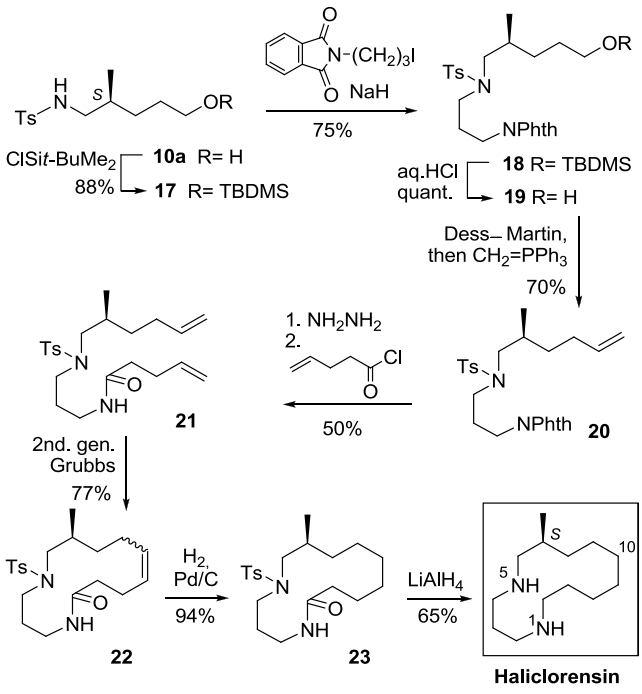
A conceptually similar strategy from the same aminoalcohol **9a**, but using 4-pentenyl bromide as the alkylating agent, can be used for the synthesis of halitulin and isohaliclorensin,[17] the latter being the structure initially proposed[15a] for haliclorensin (Scheme 5). Oxidation of alcohol **15** under Dess–Martin conditions, followed by Wittig methylenation of the resulting aldehyde, led to the *N*-hexenyl *N*-pentenyl amino derivative **16**, from which the synthesis of halitulin and isohaliclorensin has already been reported[14c,17a] using a ring-closing metathesis reaction to construct the azacyclodecane ring.

Scheme 5. Formal Syntheses of Halitulin and Isohaliclorensin



Similarly, the protected aminopentanol **10a** was envisaged as the N_5–C_{10} fragment of haliclorensin. The synthesis of this alkaloid from **10a** was also planned via a ring-closing metathesis reaction from an appropriate long-chain amino derivative, **21**, bearing two terminal carbon–carbon double bonds. The synthesis is outlined in Scheme 6.

Scheme 6. Enantioselective Synthesis of Haliclorensin



Alkylation of the tosylamide moiety of the silyl derivative **17** with 3-(phthalimido)propyl iodide,[18] followed by removal of the silyl protecting group and, as in the above syntheses, a Dess–Martin oxidation–Wittig methylenation sequence, led to the orthogonally protected diamino derivative **20**. Hydrazinolysis of the phthalimido group, followed by acylation of the resulting primary amine with 4-pentenoyl chloride, installed the required terminal alkene functionality in **21**. The synthesis of haliclorensin was completed by a ring-closing metathesis reaction, followed by catalytic hydrogenation of the carbon–carbon double bond of the resulting diazacyclotetradecane derivative **22**[19] and $LiAlH_4$ reduction, which brought about both the reductive removal of the tosyl group and the reduction of the lactam carbonyl. The NMR spectroscopic data of our synthetic haliclorensin were coincident with those reported for previously synthesized haliclorensins,[15b,c] whereas the $[\alpha]^{22}_D$ value of our sample [– 17.2 (*c* 0.5, MeOH)] was consistent with that of both the natural product[13] [– 19 (*c* 0.57, MeOH)] and synthetic haliclorensins.[15b,c,20.]

In summary, we have developed a straightforward procedure for the preparation of enantiopure 1,5-aminoalcohols from phenylglycinol-derived oxazolopiperidone lactams. Starting from 8-substituted lactams **2**, lithium amidotrihydroborate ($LiNH_2BH_3$) induces the reductive opening of both the oxazolidine and lactam rings in a single synthetic step. A subsequent removal of the phenylethanol moiety by hydrogenolysis leads to 4-substituted-5-aminopentanols, whose value as chiral building blocks is illustrated by the synthesis of the marine alkaloids haliclorensin C, haliclorensin, and halitulin (formal).

Experimental Section

Methyl 4-Isopropyl-5-oxopentanoate (1c): Isovaleraldehyde (7.54 mL, 69.7 mmol) was added dropwise to a cooled (0 ºC) mixture of piperidine (10.3 mL, 104.5 mmol) and K_2CO_3 (3.47 g, 25.1 mmol) and the mixture was stirred for 18 h at room temperature. Insoluble material was filtered through Celite®, and the filtrate was washed with Et_2O, dried, filtered, and concentrated in vacuum to remove

the excess of piperidine. Methyl acrylate (7.64 mL, 84.8 mmol) was slowly added to a stirred solution of the resulting residue in anhydrous acetonitrile (21 mL) at 0 ºC. The mixture was stirred at reflux overnight. Glacial acetic acid (4.8 mL) and water (21 mL) were added, and the resulting solution was heated at reflux for 2 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with NaCl, and the solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (8:2 hexane-Et_2O) afforded compound **1c** (8.7 g, 73 %) as a colorless oil: IR (film) 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.97 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.00 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.74-1.83 (m, 1H, H-3), 1.90-1.99 (m, 1H, H-3), 2.02-2.10 (m, 1H, C*H*Me_2), 2.12-2.18 (m, 1H, H-4), 2.25 (ddd, *J* = 16.1, 8.5, 7.4 Hz, 1H, H-2), 2.38 (ddd, *J* = 16.1, 8.9, 6.0 Hz, 1H, H-2), 3.67 (s, 3H, CH_3O), 9.65 (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (CH_3), 19.9 (CH_3), 20.8 (C-3), 28.3 ($CHMe_2$), 31.8 (C-2), 51.3 (CH_3O), 57.3 (C-4), 173.3 (CO_2), 204.4 (CHO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{17}O_3$ 173.1172; Found 173.1168.

Methyl 4-Benzyl-5-oxopentanoate (1e): Operating as above, from 3-phenylpropanal (5.89 mL, 44.7 mmol), piperidine (6.61 mL, 67.1 mmol), K_2CO_3 (2.23 g, 15.6 mmol), and methyl acrylate (7.0 mL, 77.5 mmol) in anhydrous acetonitrile (20 mL), with subsequent treatment with a mixture of glacial acetic acid (5 mL) and water (20 mL), compound **1e** (5.58 g, 57 %) was obtained as a yellow oil after flash chromatography (from 95:5 hexane-Et_2O to 9:1 hexane-Et_2O): IR (film) 1732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.76-1.85 (m, 1H, H-3), 1.93-2.01 (m, 1H, H-3), 2.34 (m, 2H, H-2), 2.66-2.71 (m, 1H, H-4), 2.71-2.77 (m, 1H, CH_2Ar), 3.02 (dd, *J* = 13.4, 6.6 Hz, 1H, CH_2Ar), 3.65 (s, 3H, CH_3), 7.15-7.32 (m, 5H, ArH), 9.68 (d, *J* = 2.0 Hz, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.5 (C-3), 31.3 (C-2), 35.1 (CH_2Ar), 51.6 (CH_3), 52.4 (C-4), 126.5 (C-*p*), 128.6, 128.8 (C-*o*, C-*m*), 138.1 (C-*i*), 173.2 (CO_2), 203.5 (CHO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}O_3$ 221.1099; Found 221.1089.

(3*R*,8*S*,8a*R*)-8-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo [3,2-*a*]pyridine (2a): <u>*Method A:*</u> A mixture of racemic oxoester **1a**[21] (565 mg, 3.92 mmol), (*R)*-phenylglycinol (537 mg, 3.92

mmol) and anhydrous Na_2SO_4 (2.17 g, 15.3 mmol) in Et_2O (10 mL) was stirred at 0 ºC for 5 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 90 ºC for 5 h under vacuum (10-15 mm Hg). Column chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) of the residue afforded lactam **2a** (670 mg, 74 %) and its **(3*R*,8*R*,8a*S*) diastereoisomer** (85 mg, 9 %). **2a**: $[\alpha]^{22}_D$ – 43.7 (*c* 1.0, MeOH); IR (film) 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.20 (d, *J* = 6.3 Hz, 3H, CH_3), 1.46-1.58 (m, 1H, H-7), 1.88-1.94 (m, 1H, H-7), 1.95-2.00 (m, 1H, H-8), 2.28-2.44 (m, 2H, H-6), 4.00 (dd, *J* = 8.8, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 8.8, 6.4 Hz, 1H, H-2), 4.43 (d, *J* = 8.8 Hz, 1H, H-8a), 4.92 (d, *J* = 7.2 Hz, 1H, H-3), 7.21-7.40 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.6 (CH_3), 26.9 (C-7), 31.4 (C-6), 34.5 (C-8), 59.1 (C-3), 73.7 (C-2), 93.5 (C-8a), 126.3 (C-*o*), 127.4 (C-*p*), 128.4 (C-*m*), 141.5 (C-*i*), 167.3 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1332; Found 232.1325. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.66; H, 7.20; N, 5.98. (**3*R*,8*R*,8a*S*) diastereoisomer**: $[\alpha]^{22}_D$ – 115.3 (*c* 1.0, MeOH); IR (film) 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.18 (d, *J* = 6.0 Hz, 3H, CH_3), 1.42-1.63 (m, 1H, H-7), 1.65-1.71 (m, 1H, H-8), 1.80-1.85 (m, 1H, H-7), 2.34-2.44 (m, 1H, H-6), 2.53 (dd, *J* = 18.0, 6.0 Hz, 1H, H-6), 3.75 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.60 (d, *J* = 8.0 Hz, 1H, H-8a), 5.25 (t, *J* = 7.8 Hz, 1H, H-3), 7.20-7.45 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 25.9 (C-7), 31.5 (C-6), 34.9 (C-8), 58.4 (C-3), 72.4 (C-2), 93.7 (C-8a), 126.1 (C-*o*), 127.5 (C-*p*), 128.7 (C-*m*), 139.5 (C-*i*), 168.7(CO). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.56; H, 7.35; N, 5.81.

Method B: (*R*)-Phenylglycinol (1.97 g, 14.4 mmol) was added to a solution of racemic oxoester **1a**[21] (1.9 g, 14.4 mmol) in anhydrous toluene (45 mL), and the mixture was heated at reflux for 25 h with azeotropic elimination of water produced by a Dean-Stark apparatus. The resulting mixture was cooled and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N;

gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **2a** (1.7 g, 56 %) as a brown solid and its **(3*R*,8*R*,8a*S*) diastereoisomer** (0.55 g, 18 %).

Method C: (*R*)-Phenylglycinol (190 mg, 1.39 mmol) and oxoester **1a**[21] (200 mg, 1.39 mmol) in toluene (4.5 mL) were mixed in a capped 10 mL microwave vessel. The mixture was heated at 110 ºC (average effective ramp time = 5 min). The power was set at 100 W and the pressure at 218 psi for 10 min. The reaction mixture was then concentrated under reduced pressure and the crude product was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried, filtered, and concentrated. Flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **2a** (185 mg, 58 %) and its (**3*R*,8*R*,8a*S*) diastereoisomer** (70 mg, 22 %).

(3*R*,8*R*,8a*R*)-8-Isopropyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2c): Operating as described in the above Method A, from racemic oxoester **1c** (1.07 g, 6.18 mmol), (*R*)-phenylglycinol (848 mg, 6.18 mmol), and anhydrous Na_2SO_4 (3.43 g, 24.1 mmol) in Et_2O (20 mL), lactam **2c** (1.16 g, 73 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer** (white solid, 180 mg, 11 %) were obtained after flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc). **2c**: $[\alpha]^{22}_D$ – 18.6 (*c* 1.2, MeOH); IR (film) 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98 (d, *J* = 6.9 Hz, 3H, CH_3), 1.07 (d, *J* = 6.9 Hz, 3H, CH_3), 1.50-1.61 (m, 1H, H-7), 1.76-1.83 (m, 1H, H-8), 1.86-1.93 (m, 1H, H-7), 2.08-2.16 [m, 1H, C*H*$(CH_3)_2$], 2.30 (ddd, *J* = 17.9, 11.2, 6.8 Hz, 1H, H-6), 2.43 (ddd, *J* = 17.9, 6.8, 2.4 Hz, 1H, H-6), 4.01 (d, *J* = 9.0 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.67 (d, *J* = 9.2 Hz, 1H, H-8a), 4.92 (d, *J* = 6.6 Hz, 1H, H-3), 7.22-7.32 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.6 (C-7), 20.5 (CH_3), 27.7 [*C*H$(CH_3)_2$], 31.6 (C-6), 44.6 (C-8), 58.9 (C-3), 73.8 (C-2), 90.6 (C-8a), 126.3 (C-*o*), 127.4 (C-*p*), 128.5 (C-*m*), 141.6 (C-*i*), 167.3 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; Found 260.1640. **(3*R*,8*S*,8a*S*) diastereoisomer**: $[\alpha]^{22}_D$ – 87.7 (*c* 1.2, MeOH); IR (film) 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.96 (dd, *J* = 6.9, 2.1 Hz, 3H, CH_3), 1.05 (dd, *J* = 6.9, 2.1 Hz, 3H, CH_3), 1.47-1.63 (m, 2H, H-7, H-8), 1.83-1.88 (m, 1H, H-7), 2.01-2.05 [m, 1H, C*H*$(CH_3)_2$],

2.30-2.39 (m, 1H, H-6), 2.59 (dm, *J* = 18.5 Hz, 1H, H-6), 3.74 (dt, *J* = 8.2, 2.1 Hz, 1H, H-2), 4.48 (dt, *J* = 8.2, 2.1 Hz, 1H, H-2), 4.80 (dd, *J* = 8.2, 2.1 Hz, 1H, H-8a), 5.26 (t, *J* = 7.8 Hz, 1H, H-3), 7.26-7.37 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0 (CH_3), 19.2 (C-7), 20.6 (CH_3), 28.1 [*C*H(CH_3)$_2$], 31.7 (C-6), 45.3 (C-8), 58.1 (C-3), 72.4 (C-2), 90.7 (C-8a), 126.1 (C-*o*), 127.5 (C-*p*), 128.8 (C-*m*), 139.7 (C-*i*), 169.1 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; Found 260.1639.

Method B: Operating as described in the above Method B, from racemic oxoester **1c** (1.09 g, 6.32 mmol) and (*R*)-phenylglycinol (867 mg, 6.32 mmol) in toluene (20 mL), lactam **2c** (white solid, 1.06 g, 64 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer** (230 mg, 14 %) were obtained after flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc).

(3*R*,8*R*,8a*R*)-8-Benzyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo [3,2-*a*] pyridine (2e): Operating as described in the above Method A, from racemic oxoester **1e** (626 mg, 2.84 mmol), (*R*)-phenylglycinol (390 mg, 2.84 mmol), and anhydrous Na_2SO_4 (1.57 g, 11.1 mmol) in Et_2O (9 mL), lactam **2e** (478 mg, 55 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer** (white solid, 80 mg, 9 %) were obtained after flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc). **2e:** $[\alpha]^{22}_D$ – 144.8 (*c* 0.1, MeOH); IR (film) 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.39-1.51 (m, 1H, H-7), 1.83-1.88 (m, 1H, H-7), 2.08-2.13 (m, 1H, H-8), 2.21 (ddd, *J* = 18.2, 11.6, 6.9 Hz, 1H, H-6), 2.36 (ddd, *J* = 18.2, 6.9, 1.8 Hz, 1H, H-6), 2.54 (dd, *J* = 13.5, 9.7 Hz, 1H, CH_2Ar), 3.27 (dd, *J* = 13.5, 3.5 Hz, 1H, CH_2Ar), 4.06 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.18 (dd, *J* = 9.0, 6.4 Hz, 1H, H-2), 4.58 (d, *J* = 9.0 Hz, 1H, H-8a), 4.94 (d, *J* = 6.4 Hz, 1H, H-3), 7.23-7.35 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4 (C-7), 31.3 (C-6), 37.2 (*C*H_2Ar), 41.0 (C-8), 59.1 (C-3), 73.9 (C-2), 91.9 (C-8a), 126.3 (C-*o*), 126.5 (C-*p*), 127.5 (C-*p*), 128.5 and 129.2 (2C-*m*, C-*o*), 138.2 and 141.4 (2C-*i*), 167.2 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; Found 308.1645. **(3*R*,8*S*,8a*S*) diastereoisomer**: $[\alpha]^{22}_D$ – 45.0 (*c* 0.15, MeOH); IR (film) 1659 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.43-1.55 (m, 1H, H-7), 1.79-1.90 (m, 2H, H-7, H-8), 2.26 (dd, *J* = 12.1, 6.6 Hz, 1H, H-6), 2.47-2.54 (m, 2H, H-6, CH_2Ar), 3.23 (dd, *J* = 13.5, 3.4 Hz, 1H, CH_2Ar), 3.81 (dd, *J* = 8.9, 7.8 Hz, 1H, H-2), 4.53 (dd, *J* = 8.9, 7.8 Hz, 1H, H-2), 4.76 (d, *J* = 8.4 Hz, 1H, H-8a), 5.28

(t, J = 7.8 Hz, 1H, H-3), 7.19-7.36 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.4 (C-7), 31.4 (C-6), 37.7 (CH_2Ar), 41.6 (C-8), 58-5 (C-3), 72.5 (C-2), 92.1 (C-8a), 126.1 (C-*o*), 126.5 (C-*p*), 127.6 (C-*p*), 128.5 (C-*o*), 128.8, 129.4 (C-*m*), 138.4 and 139.5 (2C-*i*), 168.7 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; Found 308.1644.

Method B: Operating as in the preparation of **2a** in the above Method B, from racemic aldehyde ester **1e** (627 mg, 2.85 mmol) and (*R*)-phenylglycinol (391 mg, 2.85 mmol) in toluene (9 mL), lactam **2e** (white solid, 483 mg, 55 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer** (white solid, 122 mg, 14 %) were obtained after flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc).

(*S*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-methyl-2-piperidone (3a): Triethylsilane (0.52 mL, 3.24 mmol) and $TiCl_4$ (0.52 mL, 4.76 mmol) were added to a solution of lactam **2a** (500 mg, 2.16 mmol) in anhydrous CH_2Cl_2 (35 mL), and the mixture was stirred at 50 ºC for 24 h. Then, additional $TiCl_4$ (0.52 mL, 4.76 mmol) and triethylsilane (0.52 mL, 3.24 mmol) were added and the stirring was continued at 50 ºC for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was filtered over Celite® and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give a residue, which was chromatographed (from 8:2 hexane-EtOAc to EtOAc) to afford **3a**[22] (315 mg, 63 %) as a colorless oil: $[\alpha]^{22}_D$ – 150.4 (*c* 0.1, MeOH); $[\alpha]^{22}_D$ – 88.3 (*c* 1.1, CH_2Cl_2), lit.[22] $[\alpha]_D$ – 86.8 (*c* 1.1, CH_2Cl_2); IR (film) 3372, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (d, J = 6.4 Hz, 3H, CH_3), 1.44-1.54 (m, 1H, H-4), 1.77-1.86 (m, 2H, H-4, H-5), 2.48 (ddd, J = 17.9, 11.4, 6.5 Hz, 1H, H-3), 2.59 (ddd, J = 17.9, 6.3, 2.9 Hz, 1H, H-3), 2.85 (dd, J = 11.8, 10.2 Hz, 1H, H-6), 2.98 (ddd, J = 11.8, 4.8, 2.1 Hz, 1H, H-6), 4.09 (dd, J = 11.4, 9.6 Hz, 1H, CH_2O), 4.17 (dd, J = 11.4, 5.1 Hz, 1H, CH_2O), 5.81 (dd, J = 9.6, 5.1 Hz, 1H, CHN), 7.17-7.38 (m, 5H, ArH); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 18.6 (CH_3), 28.9 (C-5), 29.1 (C-4), 32.0 (C-3), 50.3 (C-6), 58.5 (CHN), 61.6 (CH_2O), 127.6 (C-*o*), 127.7 (C-*p*), 128.7 (C-*m*), 137.0 (C-*i*), 171.5 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1489; Found 234.1484.

(*S*)-5-Ethyl-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone (3b): Operating as above, from lactam **2b** (500 mg, 2.12 mmol) in CH_2Cl_2 (32 mL), $TiCl_4$ (1.20 mL, 11.03 mmol), and Et_3SiH (1.02 mL, 9.54 mmol), lactam **3b**[22] was obtained (316 mg, 60 %) after flash chromatography (from hexane-EtOAc 8:2 to EtOAc-EtOH 8:2) as a yellow oil: $[\alpha]^{22}_D$ – 127.2 (*c* 0.9, EtOH), $[\alpha]^{22}_D$ – 73.5 (*c* 1.1, CH_2Cl_2), lit.[22] $[\alpha]_D$ – 74.2 (*c* 1.1, CH_2Cl_2); IR (film) 3360, 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *g*-HSQC) δ 0.84 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.17-1.35 (m, 2H, CH$_3$C*H*$_2$), 1.37-1.49 (m, 1H, H-4), 1.50-1.60 (m, 1H, H-5), 1.88-1.93 (m, 1H, H-4), 2.44 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H, H-3), 2.57 (ddd, *J* = 18.0, 6.0, 3.6 Hz, 1H, H-3), 2.90 (dd, *J* = 12.0, 9.6 Hz, 1H, H-6), 3.03 (ddd, *J* = 12.0, 5.0, 2.0 Hz, 1H, H-6), 4.05 (t, *J* = 10.4 Hz, 1H, CH_2O), 4.16 (dd, *J* = 11.6, 5.0 Hz, 1H, CH_2O), 5.86 (dd, *J* = 9.6, 5.0 Hz, 1H, CHN), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 26.0 (CH$_3$*C*H$_2$), 26.5 (C-4), 31.8 (C-3), 35.6 (C-5), 48.3 (C-6), 58.2 (CHN), 61.2 (CH_2O), 127.5 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 137.1 (C-*i*), 171.8 (CO). Anal. Calcd for $C_{15}H_{21}NO_2 \cdot 1/2\ H_2O$: C, 70.28; H, 8.65; N, 5.46. Found: C, 70.36; H, 8.37; N, 5.27.

(*S*)-5-Methyl-2-piperidone (4a): Into a three-necked, 100 mL, round-bottomed flask equipped with a coldfinger condenser charged with dry-ice acetone were condensed 30 mL of NH_3 at – 78 ºC. A solution of **3a** (290 mg, 1.24 mmol) in dry THF (5 mL) was added, and the temperature was raised to – 33 ºC. Sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at – 33 ºC for 3 minutes. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and then the mixture was stirred at room temperature for 5 h. CH_2Cl_2 was added, the solid was filtered, and the solvent was removed under reduced pressure. The resulting oil was chromatographed (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) to afford **4a**[23] (93 mg, 66 %): $[\alpha]^{22}_D$ – 29.0 (*c* 0.55, MeOH), $[\alpha]^{22}_D$ – 80.0 (*c* 1.0, $CHCl_3$), lit.[23] $[\alpha]^{23}_D$ – 82.5 (*c* 1.0, $CHCl_3$); IR (film) 3232, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 (d, *J* = 6.6 Hz, 3H, CH_3), 1.45-1.51 (m, 1H, H-4), 1.83-1.99 (m, 2H, H-4, H-5), 2.34 (ddd, *J* = 17.8, 10.8, 6.4 Hz, 1H, H-3), 2.43 (ddd, *J* = 17.8, 6.4, 3.5 Hz, 1H, H-3), 2.92 (t, *J* = 10.8 Hz, 1H, H-6), 3.26-3.33 (m, 1H, H-6), 6.10 (br.s, 1H, NH);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.2 (CH_3), 28.0 (C-5), 28.8 (C-4), 30.6 (C-3), 48.8 (C-6), 172.6 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_6H_{12}NO$ 114.0914; Found 114.0913.

(S)-5-Ethyl-2-piperidone (4b): Operating as above, from lactam **3b** (300 mg, 1.21 mmol) in THF (5 mL), sodium, and liquid NH_3 (35 mL) at – 33 ºC for 5 minutes, lactam **4b**[24] was obtained (119 mg, 77 %) after column chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH): $[\alpha]^{22}_D$ – 58.3 (*c* 0.75, MeOH); IR (film) 1665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.95 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.34-1.50 (m, 3H, CH$_3$C*H*$_2$, H-4), 1.62-1.78 (m, 1H, H-5), 1.87-1.98 (m, 1H, H-4), 2.25-2.50 (m, 2H, H-3), 2.94 (t, *J* = 12.0 Hz, 1H, H-6), 3.35 (m, 1H, H-6), 5.93 (br.s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 25.9 (CH$_3$*C*H$_2$), 26.6 (C-4), 30.7 (C-3), 34.7 (C-5), 47.3 (C-6), 172.7 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_{14}NO$ 128.1070; Found 128.1067.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-methyl-2-piperidone (5a): *n*-BuLi (1.6 M in hexanes, 0.55 mL, 0.88 mmol) was added at – 78 ºC to a solution of lactam **4a** (100 mg, 0.88 mmol) in THF (2.5 mL), and the mixture was stirred at this temperature for 30 minutes. Then, a cooled (– 78 ºC) solution of di-*tert*-butyl dicarbonate (289 mg, 1.32 mmol) in dry THF (1.2 mL) was added, and the resulting mixture was stirred for 90 minutes at this temperature. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. The residue was chromatographed (95:5 hexane-EtOAc) affording lactam **5a** (150 mg, 80 %) as a colorless oil: $[\alpha]^{22}_D$ – 19.5 (*c* 0.3, $CHCl_3$); IR (film) 1770, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.04 (d, *J* = 6.6 Hz, 3H, CH_3), 1.41-1.50 (m, 1H, H-4), 1.52 [s, 9H, $(CH_3)_3$], 1.84-1.92 (m, 1H, H-4), 1.93-2.03 (m, 1H, H-5), 2.47 (ddd, *J* = 17.4, 10.8, 6.5 Hz, 1H, H-3), 2.57 (ddd, *J* = 17.4, 6.5, 4.0 Hz, 1H, H-3), 3.11 (dd, *J* = 12.6, 10.4 Hz, 1H, H-6), 3.79 (ddd, *J* = 12.6, 4.8, 2.0 Hz, 1H, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (CH_3), 28.0 [$(CH_3)_3$], 28.7 (C-4), 28.7 (C-5), 34.2 (C-3), 52.8 (C-6), 82.8 [*C*$(CH_3)_3$], 152.7 (NCO), 172.6 (CO); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{19}NO_3Na$ 236.1257; Found 236.1258.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-ethyl-2-piperidone (5b): Operating as above, from lactam **4b** (180 mg, 1.4 mmol), *n*-BuLi (1.6 M in hexanes, 0.57 mL, 1.4 mmol), and di-*tert*-butyl dicarbonate (309 mg, 1.4

mmol) in THF (5 mL), lactam **5b** was obtained (221 mg, 70 %) as a colorless oil after flash chromatography (from 9:1 hexane-EtOAc to 1:1 hexane-EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.96 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.30-1.46 (m, 3H, CH$_3$C*H*$_2$, H-4), 1.53 [s, 9H, (CH$_3$)$_3$], 1.68-1.77 (m, 1H, H-5), 1.89-1.98 (m, 1H, H-4), 2.45 (ddd, *J* = 17.3, 10.6, 6.4 Hz, 1H, H-3), 2.55 (ddd, *J* = 17.3, 6.4, 4.3 Hz, 1H, H-3), 3.17 (dd, *J* = 12.7, 10.1 Hz, 1H, H-6), 3.82 (ddd, *J* = 12.7, 4.8, 1.7 Hz, 1H, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (*C*H$_3$CH$_2$), 26.2 (C-4), 26.3 (CH$_3$*C*H$_2$), 28.0 [(CH$_3$)$_3$], 34.1 (C-3), 35.2 (C-5), 50.9 (C-6), 82.8 [*C*(CH$_3$)$_3$], 152.8 (NCO), 171.5 (CO); HRMS (ESI-TOF) m/z: [M – *t*Bu]$^+$ Calcd for $C_8H_{12}NO_3$ 170.0812; Found 170.0808.

Methyl (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-methylpentanoate (6a): A solution of LiOH (50.2 mg, 1.20 mmol) in water (1.25 mL) was added to a solution of lactam **5a** (85 mg, 0.40 mmol) in THF (19 mL), and the mixture was stirred at room temperature for 4 h. THF was removed under reduced pressure, and the residue was dissolved in Et_2O. The organic extract was washed with aqueous 1 N HCl, dried, filtered, and concentrated to afford a carboxylic acid (85 mg) as a colorless oil, which was used without purification in the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 1.44 [s, 10H, (CH$_3$)$_3$, C*H*$_2$) 1.58-1.76 (m, 2H), 2.32-2.45 (m, 2H), 2.95-3.05 (m, 2H), 4.65 (br.s, 1H, NH); HRMS (ESI-TOF) m/z: [M - H]$^+$ Calcd for $C_{11}H_{20}NO_4$ 230.1392; Found: 230.1397. $TMSCHN_2$ (0.28 mL, 0.55 mmol) was added at 0 ºC to a solution of the above carboxylic acid (85 mg) in toluene-methanol (2.5:1, 12.3 mL), and the mixture was stirred at this temperature for 1 h, quenched with some drops of AcOH, and concentrated under reduced pressure to afford pure ester **6a** (88 mg, 90 %): $[\alpha]^{22}_D$ – 5.45 (*c* 0.8, MeOH); IR (film) 3375, 1735, 1715 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.38 [s, 10H, (CH$_3$)$_3$, H-3], 1.52-1.61 (m, 1H, H-4), 1.62-1.71 (m, 1H, H-3), 2.20-2.37 (m, 2H, H-5), 2.92-3.02 (m, 2H, H-2), 3.61 (s, 3H, CH$_3$O), 4.71 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 28.3 [(CH$_3$)$_3$], 28.9 (C-3), 31.4 (C-5), 33.2 (C-4), 45.9 (C-2), 51.4 (CH$_3$O), 78.9 [*C*(CH$_3$)$_3$], 156.0 (NCO), 174.1 (CO_2); HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{23}NO_4Na$ 268.1519; Found 268.1527.

Methyl (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethylpentanoate (6b): Operating as above, from lactam **5b** (80 mg, 0.35 mmol) in THF (1.7 mL) and a solution of LiOH (44.3 mg, 1.06 mmol) in water (1.1 mL), a carboxylic acid (80 mg) was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.25-1.36 (m, 2H, CH$_3$C*H*$_2$), 1.44 [s, 9H, $(CH_3)_3$], 1.43-1.48 (m, 1H, H-4), 1.55-1.67 (m, 2H, H-3), 2.30-2.42 (t, *J* = 7.6 Hz, 2H, H-2), 2.90-3.17 (m, 2H, H-5), 6.07 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (*C*H$_3$CH$_2$), 24.0 (CH$_3$*C*H$_2$), 25.9 (C-3), 28.4 [$(CH_3)_3$], 31.3 (C-2), 39.3 (C-4), 42.9 (C-5), 79.3 [*C*$(CH_3)_3$], 156.2 (NCO), 179.0 (CO_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{23}NO_4Na$ 268.1519; Found 268.1519. Operating as in the preparation of **6a**, from the above crude carboxylic acid (80 mg) and $TMSCHN_2$ (0.24 mL, 0.47 mmol) in a mixture of toluene-methanol (2.5:1, 11 mL), ester **6b** (73 mg, 80 %) was obtained: $[\alpha]^{22}_D$ – 8.4 (c 0.58, MeOH); IR (film) 3371, 1740, 1715 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.32 (m, 2H, CH$_3$C*H*$_2$), 1.44 [s, 9H, $(CH_3)_3$], 1.46 (m, 1H, H-4), 1.62 (m, 2H, H-3), 2.34 (t, *J* = 7.7 Hz, 2H, H-2), 3.02 (m, 1H, H-5), 3.09 (m, 1H, H-5), 3.70 (s, 3 H, CH_3O), 4.67 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.9 (CH$_3$*C*H$_2$), 26.0 (C-3), 28.3 [$(CH_3)_3$], 31.2 (C-2), 39.3 (C-4), 42.9 (C-5), 51.5 (CH_3O), 79.0 [$(CH_3)_3$], 156.0 (NCO), 174.2 (CO_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{26}NO_4$ 260.1856; Found 260.1852.

(*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-methyl-1-pentanol (7a): *n*-BuLi (4.13 mL of a 2.5 M solution in hexanes, 10.3 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (319 mg, 10.3 mmol) in anhydrous THF (9.0 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, a solution of lactam **2a** (555 mg, 2.40 mmol) in THF (4.5 mL) was added, and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave **(*S*)-[(*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine**[22] (40 mg, 7%) as a colorless oil, and aminoalcohol **7a** (425 mg, 75 %): $[\alpha]^{22}_D$ – 50.9 (*c* 0.68, MeOH); IR (film) 3314 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.4 Hz, 3H, CH_3), 1.13-1.21 (m, 1H, H-2), 1.44-1.56 (m,

2H, H-2, H-3), 1.57-1.67 (m, 2H, H-3, H-4), 2.31 (br.s, 3H, OH, NH), 2.33 (dd, *J* = 11.7, 6.0 Hz, 1H, H-5), 2.43 (dd, *J* = 11.7, 7.0 Hz, 1H, H-5), 3.55 (dd, *J* = 10.6, 8.8 Hz, 1H, CH_2O), 3.61 (t, *J* = 6.0 Hz, 2H, H-1), 3.70 (dd, *J* = 10.6, 4.4 Hz, 1H, CH_2O), 3.75 (dd, *J* = 8.8, 4.4 Hz, 1H, CHN), 7.25-7.37 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.6 (CH_3), 29.7 (C-3), 30.3 (C-2), 32.8 (C-4), 53.4 (C-5), 62.6 (C-1), 64.7 (CHN), 66.5 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 140.4 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; Found 238.1799.

(*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (7b): Operating as above, from lactam **2b** (200 mg, 0.82 mmol), *n*-BuLi (1.40 mL of a 2.5 M solution in hexanes, 3.51 mmol), and $NH_3{\cdot}BH_3$ (108 mg, 3.51 mmol) in anhydrous THF (3 mL), aminoalcohol **7b** (165 mg, 80 %) was obtained after flash chromatography (from EtOAc to EtOAc-EtOH 8:2): $[\alpha]^{22}_D$ – 44.9 (*c* 0.16, MeOH); IR (film) 3330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.82 (t, *J* = 7.6 Hz, 3H, CH_3), 1.23-1.40 (m, 3H, H-3, CH_3CH_2), 1.42-1.50 (m, 4H, H-2, H-3, H-4), 2.40 (dd, *J* = 11.6, 6.4 Hz, 1H, H-5), 2.46 (dd, *J* = 11.6, 5.0 Hz, 1H, H-5), 3.41 (br.s, 3H, OH, NH), 3.57-3.64 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 10.8, 4.0 Hz, 1H, CH_2O), 3.77 (dd, *J* = 8.8, 4.0 Hz, 1H, CHN), 7.24-7.38 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (CH_3), 24.9 (CH_3CH_2), 27.4 (C-3), 29.2 (C-2), 38.8 (C-4), 50.2 (C-5), 60.3 (C-1), 64.8 (CHN), 66.5 (CH_2O), 127.3 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 139.9 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_2$ 252.1958; Found 252.1947.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-isopropyl-1-pentanol (7c): Operating as described for preparation of **7a**, from lactam **2c** (400 mg, 1.54 mmol), *n*-BuLi (4.14 mL of a 2.5 M solution in hexanes, 6.6 mmol), and $NH_3{\cdot}BH_3$ (205 mg, 6.6 mmol) in anhydrous THF (9 mL), **(*S*)-[(*R*)-2-hydroxy-1-phenylethyl]-3-isopropylpiperidine** (30 mg, 7 %) and aminoalcohol **7c** (292 mg, 71 %) were obtained as colorless oils after flash chromatography (from hexane-EtOAc 1:1 to EtOAc-EtOH 8:2). **(*S*)-[(*R*)-2-hydroxy-1-phenylethyl]-3-isopropylpiperidine**: $[\alpha]^{22}_D$ – 47.5 (*c* 0.25, MeOH); IR (film) 3406 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78-0.84 (m, 1H, H-4), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 0.88 (d, *J* = 6.4 Hz, 3H, CH_3), 1.35-1.47 [m, 3H, H-3, H-5, $CH(CH_3)_2$], 1.60-1.70 (m, 3H, H-4, H-5, H-6), 2.03 (t, *J* = 10.5 Hz, 1H, H-2), 2.82 (br.m, 2H, H-2, H-6), 3.61 (dd, *J* = 10.3, 5.2 Hz, 1H,

CH_2O), 3.70 (dd, *J* = 10.2, 5.2 Hz, 1H, CHN), 3.98 (t, *J* = 10.2 Hz, 1H, CH_2O), 7.17-7.19 (m, 2H, ArH), 7.30-7.37 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.9 (CH_3), 20.3 (CH_3), 25.8 (C-5), 27.9 (C-4), 30.9 [*C*H(CH_3)$_2$], 43.3 (C-3), 46.6 (C-6), 57.1 (C-2), 59.9 (CH_2O), 70.3 (CHN), 127.7 (C-*p*), 128.0, 128.9 (C-*o*, C-*m*), 135.5 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO$ 248.2009; Found 248.2005. **7c**: $[\alpha]^{22}_D$ – 44.9 (*c* 0.65, MeOH); IR (film) 3320 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78 (d, *J* = 6.8 Hz, 3H, CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 1.31-1.41 (m, 3H, H-3, H-4), 1.45-1.52 (m, 1H, H-2), 1.54-1.61 (m, 1H, H-2),1.64-1.72 (m, 1H, C*H*CH_3), 2.31 (dd, *J* = 11.8, 4.2 Hz, 1H, H-5), 2.48 (dd, *J* = 11.8, 7.7 Hz, 1H, H-5), 3.54-3.65 (m, 3H, H-1, CH_2O), 3.68 (dd, *J* = 10.8, 4.0 Hz, 1H, CH_2O), 3.76 (dd, *J* = 9.1, 4.0 Hz, 1H, CHN), 7.24-7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (CH_3), 19.4 (CH_3), 25.3 (C-3), 29.3 (*C*HCH_3), 30.2 (C-2), 43.2 (C-4), 48.8 (C-5), 61.8 (C-1), 64.9 (CHN), 66.5 (CH_2O), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.1 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_2$ 266.2115; Found 266.2109.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-phenyl-1-pentanol (7d): Operating as described for preparation of **7a**, from lactam **2d** (200 mg, 0.68 mmol), *n*-BuLi (1.17 mL of a 2.5 M solution in hexanes, 2.93 mmol), and $NH_3{\cdot}BH_3$ (91 mg, 2.93 mmol) in anhydrous THF (5 mL), aminoalcohol **7d** (116 mg, 57 %) was obtained as a colorless oil after flash chromatography (from hexane-EtOAc 1:1 to EtOAc-EtOH 8:2): $[\alpha]^{22}_D$ – 48.1 (*c* 0.4, MeOH); IR (film) 3323 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.39-1.46 (m, 2H, H-3), 1.54-1.61 (m, 1H, H-2), 1.66 (br.s, 3H, OH, NH), 1.76-1.80 (m, 1H, H-2), 2.65-2.72 (m, 2H, H-4, H-5), 2.78-2.82 (m, 1H, H-5), 3.44 (dd, *J* = 10.2, 8.5 Hz, 1H, CH_2O), 3.56 (t, *J* = 6.4 Hz, 2H, H-1), 3.60-3.68 (m, 2H, CH_2O, CHN), 7.13-7.34 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 30.1 (C-2), 30.5 (C-3), 46.0 (C-4), 53.3 (C-5), 62.7 (C-1), 64.8 (CHN), 66.4 (CH_2O), 126.5, 126.9 (C-*p*), 127.2, 127.7, 128.6, 128.6 (C-*o*, C-*m*), 140.4, 143.4 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}NO_2$ 300.1958; Found 300.1952.

(*R*)-4-Benzyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (7e): Operating as described for the preparation of **7a**, from lactam **2e** (324 mg, 1.05 mmol), *n*-BuLi (2.83 mL of a 2.5 M solution in hexanes, 4.53 mmol), and $NH_3{\cdot}BH_3$ (140 mg, 4.53 mmol) in anhydrous THF (4 mL), aminoalcohol **7e**

(233 mg, 70 %) was obtained as a colorless oil after flash chromatography: $[\alpha]^{22}_D$ – 35.8 (*c* 1.15, MeOH); IR (film) 3331 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.23-1.40 (m, 1H, H-3), 1.44-1.59 (m, 3H, H-3, H-2), 1.84 (br.s, 1H, H-4), 2.35-2.47 (m, 2H, H-5), 2.48-2.63 (m, 2H, CH_2Ar), 2.92 (br.s, 3H, OH, NH), 3.50-3.63 (m, 3H, H-1, CH_2O), 3.64-3.73 (m, 2H, CH_2O, CHN), 7.05-7.33 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.8 (C-3), 29.3 (C-2), 39.2 (CH_2Ar), 39.6 (C-4), 50.1 (C-5), 62.4 (C-1), 64.8 (CHN), 66.5 (CH_2O), 125.8 (C-*p*), 127.3 (C-*m*), 127.6 (C-*p*), 128.2 (C-*m*), 128.5, 128.9 (C-*o*), 140.1, 140.5 (C-*i*); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{28}NO_2$ 314.2115; Found 314.2111.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-methyl-1-pentanol (8a): A solution of aminodiol **7a** (1.4 g, 5.9 mmol) in anhydrous MeOH (35 mL) containing 45 % $Pd(OH)_2$ (630 mg) was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyl dicarbonate (1.55 g, 7.08 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **8a** (893 mg, 70 %) as a colorless oil: $[\alpha]^{22}_D$ – 2.89 (*c* 1.0, MeOH); IR (film) 3355, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 1.05-1.18 (m, 1H, H-3), 1.30-1.40 (m, 1H, H-3), 1.38 [s, 9H, $(CH_3)_3$], 1.45-1.57 (m, 3H, H-2, H-4), 2.60 (br.s, 1H, OH), 2.88 (ddd, *J* = 13.2, 6.4, 6.4 Hz, 1H, H-5), 2.99 (ddd, *J* = 13.2, 6.4, 6.4 Hz, 1H, H-5), 3.55 (t, *J* = 6.4 Hz, 2H, H-1), 4.77 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 28.3 [$C(CH_3)_3$], 29.8 (C-3), 30.1 (C-2), 33.4 (C-4), 46.3 (C-5), 62.6 (C-1), 79.1 [$C(CH_3)_3$], 156.3 (CO); HRMS (ESI-TOF) m/z: $[M – Boc + 2H]^+$ Calcd for $C_6H_{16}NO$ 118.1226; Found 118.1227.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-1-pentanol (8b): Operating as above, from a solution of aminodiol **7b** (325 mg, 1.29 mmol) in anhydrous MeOH (10 mL), 45 % $Pd(OH)_2$ (146 mg), and Boc_2O (339 mg, 1.55 mmol), alcohol **8b** (195 mg, 65 %) was obtained as a colorless oil after column chromatography (from hexane-EtOAc 7:3 to hexane-EtOAc 1:1): $[\alpha]^{22}_D$ – 3.3 (*c* 0.84, MeOH); IR (film) 3348, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.4 Hz, 3H, CH_3), 1.24-

1.37 (m, 5H, CH_3CH_2, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.56-1.63 (m, 2H, H-3), 2.21 (br.s, 1H, OH), 3.03-3.15 (m, 2H, H-5), 3.64 (t, *J* = 6.3 Hz, 2H, H-1), 4.54 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.9 (CH_3), 24.1 (CH_3CH_2), 26.9 (C-2), 28.4 [$(CH_3)_3$], 29.5 (C-3), 39.6 (C-4), 43.0 (C-5), 62.9 (C-1), 79.0 [$C(CH_3)_3$], 156.3 (NCO); HRMS (ESI-TOF) m/z: $[M - t\text{Bu} + 2H]^+$ Calcd for $C_8H_{18}NO_3$ 176.1281; Found 176.1279.

(*R*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-isopropyl-1-pentanol (8c): Operating as described for the preparation of **8a**, from a solution of **7c** (500 mg, 1.88 mmol) in anhydrous MeOH (12 mL), 45 % $Pd(OH)_2$ (225 mg), and Boc_2O (493 mg, 1.2 mmol), alcohol **8c** (208 mg, 45 %) was obtained after column chromatography (from hexane-EtOAc 8:2 to EtOAc): $[\alpha]^{22}_D$ + 2.5 (*c* 1.25, MeOH); IR (film) 3347, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 1.24-1.33 (m, 3H, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.59-1.63 (m, 2H, H-3), 1.67-1.74 [m, 1H, $CH(CH_3)_2$], 3.06-3.17 (m, 2H, H-5), 3.64 (t, *J* = 6.4 Hz, 2H, H-1), 4.52 (br.s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 (CH_3), 19.5 (CH_3), 24.6 (C-3), 28.4 [$CH(CH_3)_2$, $(CH_3)_3$], 30.5 (C-2), 41.4 (C-5), 44.3 (C-4), 62.9 (C-1), 79.1 [$C(CH_3)_3$], 156.2 (NCO); HRMS (ESI-TOF) m/z: $[M - t\text{Bu} + 2H]^+$ Calcd for $C_9H_{20}NO_3$ 190.1438; Found 190.1438.

(*R*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-phenyl-1-pentanol (8d): Operating as described for the preparation of **8a**, from a solution of **7d** (193 mg, 0.65 mmol) in anhydrous MeOH (16 mL), 45 % $Pd(OH)_2$ (86 mg), and Boc_2O (169 mg, 0.77 mmol), alcohol **8d** (97 mg, 53 %) was obtained after column chromatography (from hexane-EtOAc 8:2 to hexane-EtOAc 1:1): $[\alpha]^{22}_D$ + 10.9 (*c* 0.65, MeOH); IR (film) 3363, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.40 [s, 9H, $(CH_3)_3$], 1.43-1.49 (m, 2H, H-2), 1.57-1.67 (m, 1H, H-3), 1.73-1.80 (m, 1H, H-3), 2.76 (br.s, 1H, H-4), 3.18 (ddd, *J* = 13.6, 8.7, 4.9 Hz, 1H, H-5), 3.47-3.42 (m, 1H, H-5), 3.57 (t, *J* = 6.4 Hz, 2H, H-1), 4.43 (br.s, 1H, NH), 7.15-7.17 (m, 2H, ArH), 7.21-7.27 (m, 1H, H-*p*), 7.30-7.34 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.3 [$(CH_3)_3$], 29.6 (C-3), 30.4 (C-2), 45.9 (C-4), 46.2 (C-5), 62.6 (C-1), 79.2 [$C(CH_3)_3$], 126.7 (C-*p*), 127.8, 128.6 (C-*o*, C-*m*), 142.6 (C-*i*), 156.0 (NCO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_3$ 280.1907; Found 280.1905.

(*R*)-4-Benzyl-5-[(t*ert*-butoxycarbonyl)amino]-1-pentanol (8e): Operating as described for the preparation of **8a**, from a solution of **7e** (260 mg, 0.83 mmol) in anhydrous MeOH (10 mL), 45 % $Pd(OH)_2$ (117 mg), and Boc_2O (217 mg, 1.0 mmol), alcohol **8e** (123 mg, 51 %) was obtained as a colorless oil after column chromatography (from hexane-EtOAc 8:2 to EtOAc): $[\alpha]^{22}_D$ – 1.87 (*c* 0.8, MeOH); IR (film) 3348, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.33-1.39 (m, 2H, H-3), 1.43 [s, 9H, $(CH_3)_3$], 1.54-1.68 (m, 2H, H-2), 1.82-1.86 (m, 1H, H-4), 2.04 (br.s., 1H, OH), 2.57 (d, *J* = 7.2 Hz, 2H, CH_2Ar), 3.09 (t, *J* = 5.6 Hz, 2H, H-5), 3.58 (t, *J* = 6.3 Hz, 2H, H-1), 4.62 (br.s, 1H, NH), 7.14-7.20 (m, 3H, ArH), 7.25-7.29 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.2 (C-3), 28.3 [$(CH_3)_3$], 29.5 (C-2), 38.6 (CH_2Ar), 40.4 (C-4), 43.2 (C-5), 62.7 (C-1), 79.2 [$C(CH_3)_3$], 126.0 (C-*p*), 128.3, 129.0 (C-*o*, C-*m*), 140.3 (C-*i*), 156.3 (NCO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{28}NO_3$ 294.2064; Found 294.2063.

(*S*)-4-Methyl-5-[(2-nitrobenzenesulfonyl)amino]-1-pentanol (9a): A solution of aminodiol **7a** (1.36 g, 5.73 mmol) in anhydrous MeOH (35 mL) containing 20 % $Pd(OH)_2$ (272 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in CH_2Cl_2 (19 mL). 2-Nitrobenzenesulfonyl chloride (1.4 g, 6.3 mmol) and Et_3N (0.88 mL, 6.3 mmol) were added, and the mixture was allowed to react at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed (from 7:3 hexane-EtOAc to EtOAc) to give alcohol **9a** (1.25 g, 72 %) as a colorless oil: $[\alpha]^{22}_D$ + 2.66 (*c* 1.05, MeOH); IR (film) 3349 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 1.22-1.28 (m, 1H, H-3), 1.42-1.54 (m, 3H, H-3, H-2, OH), 1.55-1.62 (m, 1H, H-2), 1.64-1.74 (m, 1H, H-4), 2.92 (ddd, *J* = 13.2, 6.8, 6.8 Hz, 1H, H-5), 3.01 (ddd, *J* = 13.2, 6.8, 6.8 Hz, 1H, H-5), 3.61 (t, *J* = 6.4 Hz, 2H, H-1), 5.35 (t, *J* = 6.2 Hz, 1H, NH), 7.73-7.75 (m, 2H, H-5Ns, H-6Ns), 7.85 (m, 1H, H-4Ns), 8.12 (m, 1H, H-3Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 29.6 (C-2), 29.9 (C-3), 33.1 (C-4), 49.5 (C-5), 62.8 (C-1), 125.3, 131.1 (C-3Ns, C-6Ns), 132.7 (C-4Ns), 133.5 (C-1Ns), 133.7 (C-5Ns), 148.1 (C-2Ns); HRMS (ESI-TOF) m/z: [M + H] Calcd for $C_{12}H_{19}N_2O_5S$ 303.1009; Found 303.1008.

(*S*)-4-Ethyl-5-[(2-nitrobenzenesulfonyl)amino]-1-pentanol (9b): Operating as above, from a solution of **7b** (1.15 g, 4.56 mmol) in anhydrous MeOH (25 mL), 20 % $Pd(OH)_2$ (230 mg), 2-nitrobenzenesulfonyl chloride (1.12 g, 5.0 mmol), and Et_3N (0.7 mL, 5.0 mmol) in CH_2Cl_2 (16 mL), alcohol **9b** (1.09 g, 76 %) was obtained as a colorless oil after column chromatography (from 7:3 hexane-EtOAc to EtOAc): $[\alpha]^{22}_D$ + 0.95 (*c* 0.84, MeOH); IR (film) 3348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (t, *J* = 7.6 Hz, 3H, CH_3), 1.30-1.40 (m, 4H, H-3, CH_3CH_2), 1.47-1.54 (m, 3H, H-2, H-4), 1.65 (br.s, 1H, OH), 3.02 (dt, *J* = 6.1, 3.7 Hz, 2H, H-5), 3.60 (t, *J* = 6.4 Hz, 2H, H-1), 5.41 (t, *J* = 6.0 Hz, 1H, NH), 7.76 (m, 2H, H-5Ns, H-6Ns), 7.85 (m, 1H, H-4Ns), 8.13 (m, 1H, H-3Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.7 (CH_3), 23.9 (CH_3CH_2), 26.9 (C-3), 29.3 (C-2), 33.1 (C-4), 46.2 (C-5), 62.8 (C-1), 125.3, 131.1 (C-3 Ns, C-6Ns), 132.7 (C-4Ns), 133.5 (C-1Ns), 133.6 (C-5Ns), 148.0 (C-2Ns); HRMS (ESI-TOF) m/z: [M + H] Calcd for $C_{13}H_{21}N_2O_5S$ 317.1166; Found 317.1161.

(*S*)-4-Methyl-5-[(*p*-methylbenzenesulfonyl)amino]-1-pentanol (10a): A solution of aminodiol **7a** (1.5 g, 6.32 mmol) in anhydrous MeOH (110 mL) containing 20 % $Pd(OH)_2$ (300 mg) was hydrogenated at 68 °C for 19 h under 11 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH, and the combined organic solutions were concentrated. The resulting residue was dissolved in $CHCl_3$ (30 mL), and *p*-toluenesulfonyl chloride (1.33 g, 6.96 mmol) and Et_3N (1.06 mL, 7.56 mmol) were added. The mixture was allowed to react at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed (from 9:1 hexane-EtOAc to EtOAc) to give alcohol **10a** (1.01 g, 59 %) as a yellow oil: $[\alpha]^{22}_D$ + 0.61 (*c* 0.8, MeOH); IR (film) 3507, 3286 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.09-1.16 (m, 1H, H-3), 1.38-1.48 (m, 1H, H-3), 1.50-1.64 (m, 3H, H-2, H-4), 2.42 (s, 3H, CH_3Ts), 2.74 (dd, *J* = 12.5, 6.4 Hz, 1H, H-5), 2.79 (dd, *J* = 12.5, 6.8 Hz, 1H, H-5), 3.57 (t, *J* = 6.1 Hz, 2H, H-1), 5.32 (br.s, 1H, NH), 7.24 (d, *J* = 8.3 Hz, 2H, H-3 Ts, H-5 Ts), 7.74 (d, *J* = 8.3 Hz, 2H, H-2 Ts, H-6 Ts); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.4 (CH_3Ts), 29.4 (C-3), 29.7 (C-2), 32.8 (C-4), 48.7 (C-5), 62.6 (C-1), 126.9 and 129.6 (CHTs), 136.9 (C-4Ts), 143.2 (C-1Ts); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_3S$ 272.1315; Found 272.1317.

(*S*)-4-Methyl-5-[*N*-(2-nitrobenzenesulfonyl)-10-undecenylamino]-1-pentanol (11): 11-Bromo-1-undecene (0.10 mL, 0.44 mmol) was added to a suspension of alcohol **9a** (110 mg, 0.36 mmol) and Cs_2CO_3 (154 mg, 0.47 mmol) in anhydrous DMF (2.5 mL), and the resulting mixture was stirred at 55 ºC for 3 h. The mixture was cooled to room temperature, poured into brine, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (7:3 hexane-EtOAc) afforded alkene **11** (130 mg, 79 %) as a colorless oil: $[\alpha]^{22}_D$ – 10.2 (*c* 1.25, MeOH); IR (film) 3334 cm^{-}1; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (d, *J* = 6.6 Hz, 3H, CH_3), 1.05-1.13 (m, 1H, H-3), 1.15-1.29 (m, 9H, H-3, 4CH_2), 1.32-1.38 (m, 2H, CH_2), 1.40-1.52 (m, 5H, CH_2), 1.58-1.67 (m, 1H, CH_2), 1.71-1.80 (m, 1H, H-4), 1.99-2.05 (m, 2H, CH_2=CHC*H*$_2$), 3.12 (dd, *J* = 14.2, 8.1 Hz, 1H, H-5), 3.20 (dd, *J* = 14.2, 7.1 Hz 1H, H-5), 3.18-3.32 (m, 2H, CH_2N), 3.61 (t, *J* = 6.4 Hz, 2H, H-1), 4.91-5.02 (m, 2H, C*H*$_2$=CH), 5.81 (qt, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1H, CH_2=C*H*), 7.60-7.70 (m, 3H, H-3Ns, H-5Ns, H-6Ns), 7.99-8.02 (m, 1H, H-4Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.6 (CH_2), 27.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 31.0 (C-4), 33.7 (CH_2=CH*C*H$_2$), 47.2 (CH_2N), 53.2 (C-5), 62.9 (C-1), 114.1 (*C*H_2=CH), 124.1 and 130.9 (C-3Ns, C-6Ns), 131.4 (C-4Ns), 133.2 (C-1Ns), 133.8 (C-5Ns), 139.1 (CH_2=*C*H), 148.0 (C-2Ns); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{39}N_2O_5S$ 455.2574; Found 455.2570.

***N*-[2-Methyl-5-hexenyl)-*N*-(2-nitrobenzenesulfonyl)-10-undecenamine (12):** Dess–Martin reagent (168 mg, 0.40 mmol) was added to a solution of alcohol **11** (90 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1.5 mL), and the mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous $Na_2S_2O_4$ (0.75 mL) and saturated aqueous $NaHCO_3$ (0.75 mL) were added, and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to give an aldehyde, which was used without purification in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 8.8 Hz, 3H, CH_3), 1.12-1.29 (m, 9H), 1.31-1.51 (m, 6H), 1.73-1.84 (m, 2H), 1.99-2.07 (m, 2H, CH_2=CHC*H*$_2$), 2.37-2.58 (m, 2H, C*H*$_2$COH), 3.10-3.28 (m, 4H, 2CH_2N), 4.91-5.02 (m, 2H, C*H*$_2$=CH), 5.80 (qt, *J* = 16.9, 10.1, 6.7, 6.7 Hz, 1H, CH_2=C*H*),

7.60-7.70 (m, 3H, H-Ns), 7.99-8.02 (m, 1H, H-Ns), 9.76 (s, 1H, COH). *t*-BuOK (0.99 mL of a 1 M solution in THF, 0.99 mmol) was added to a solution of methyltriphenylphosphonium bromide (497 mg, 1.38 mmol) in THF (10 mL) at room temperature, and the mixture was stirred for 1 h. Then, a solution of the above aldehyde in THF (10 mL) was added via cannula, and the resulting mixture was stirred at room temperature for 3 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were dried, filtered, and concentrated. The residue was chromatographed (9:1 hexane-EtOAc) to give diene **12** (55 mg, 61 %) as a colorless oil: $[\alpha]^{22}_D$ – 3.58 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.09-1.30 (m, 11H, CH_2), 1.32-1.33 (m, 2H, CH_2), 1.41-1.50 (m, 3H, CH_2), 1.70-1.75 (m, 1H, CH), 1.95-2.06 (m, 3H, CH_2), 2.08-2.17 (m, 1H, CH_2), 3.12 (dd, *J* = 14.2, 8.3 Hz, 1H, CH_2N), 3.18 (dd, *J* = 14.2, 8.8 Hz, 1H, CH_2N), 3.13-3.21 (m, 2H, CH_2N), 4.91-5.02 (m, 4H, CH_2=$CHCH_2$), 5.74 (qt, *J* = 17.0, 10.1, 10.1, 6.7 Hz, 1H, CH_2=C*H*), 5.80 (qt, *J* = 17.3, 10.3, 10.3, 7.0 Hz, 1H, CH_2=C*H*), 7.59-7.62 (m, 1H, H-3Ns), 7.63-7.70 (m, 2H, H-5Ns, H-6Ns), 7.99-8.03 (m, 1H, H-4Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.6 (CH_2), 27.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.4 (CH), 31.1 (CH_2), 33.0 (CH_2=CH*C*H_2), 33.8 (CH_2=CH*C*H_2), 47.1 (C-1), 53.1 (CH_2N), 114.1 (*C*H_2=CH), 114.7 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.4 (C-4Ns), 133.2 (C-5Ns), 133.9 (C-1Ns), 138.4 (CH_2=*C*H), 139.1 (CH_2=*C*H), 148.0 (C-2Ns); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{39}N_2O_4S$ 451.2625; Found 451.2622.

(*S*)-3-Methyl-1-(2-nitrobenzenesulfonyl)azacyclohexadec-6-ene (13): A solution of **12** (58 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of second-generation Grubbs catalyst (16.4 mg, 0.02 mmol) in CH_2Cl_2 (650 mL) at reflux. The resulting mixture was stirred at reflux temperature for 14 h. The solvent was evaporated, and the resulting residue was chromatographed (95:5 hexane-EtOAc) to yield a 86:14 (calculated by GC/MS) mixture of *E/Z* diastereoisomers **13** (44 mg, 80 %). Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (d, *J* = 6.6 Hz, 3H, CH_3), 1.06-1.18 (m, 1H, H-4), 1.19-1.59 (m, 15H, H-4, 7CH_2), 1.78-1.87 (m, 1H, H-3), 1.97-2.10 (m, 3H, H-5, H-8), 2.12-2.18 (m, 1H, H-8), 3.08 (dd, *J* = 13.9, 6.7 Hz, 1H, H-2), 3.14-3.24 (m, 3H, H-2, H-

16), 5.26-5.45 (m, 2H, H-6, H-7), 7.59-7.62 (m, 1H, H-3Ns), 7.64-7.69 (m, 2H, H-5Ns, H-6Ns), 7.97-8.02 (m, 1H, H-4Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH_3), 24.4 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 27.4 (CH_2), 28.1 (C-3), 28.9 (*C*H_2CH=), 30.9 (*C*H_2CH=), 33.3 (C-4), 46.5 (C-16), 54.1 (C-2), 124.0 (C-3Ns), 130.0 (CH=), 130.8 (C-6Ns), 131.3 (CH=), 131.4 (C-4Ns), 133.1 (C-5Ns), 133.6 (C-1Ns), 148.1 (C-2Ns); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{35}N_2O_4S$ 423.2312; Found 423.2301.

(*S*)-3-Methylazacyclohexadec-6-ene (14): K_2CO_3 (194 mg, 1.41 mmol) and thiophenol (0.058 mL, 0.56 mmol) were added to a solution of **13** (198 mg, 0.47 mmol) in anhydrous DMF (9 mL), and the mixture was stirred at room temperature for 14 h. The reaction was quenched by the addition of aqueous 2 M NaOH, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) to afford compound **14** (64 mg, 58 %) as a 84:16 (calculated by GC/MS) mixture of *E/Z* diastereoisomers as a brown oil. Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (d, *J* = 6.6 Hz, 3H, CH_3), 1.14-1.22 (m, 1H, H-4), 1.24-1.54 (m, 15H, H-4, 7CH_2), 1.68-1.77 (m, 1H, H-3), 1.95-2.16 (m, 4H, H-5, H-8), 2.46 (m, 2H, H-2), 2.48-2.58 (m, 1H, H-16), 2.62-2.72 (m, 1H, H-16), 5.35-5.40 (m, 2H, H-6, H-7); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.8 (CH_3), 25.0 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 30.1 (C-3), 31.9 (*C*H_2CH=), 34.0 (*C*H_2CH=), 47.0 (C-16), 55.4 (C-2), 130.7 (CH=), 130.9 (CH=); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{32}N$ 238.2529; Found 238.2523.

Haliclorensin C: A solution of alkene **14** (46 mg, 0.19 mmol) in anhydrous MeOH (10 mL) containing 25% Pd/C (12 mg) was hydrogenated at room temperature for 14 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH, and the combined organic solutions were concentrated. Flash chromatography (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) of the residue gave haliclorensin C (**15a**, 33 mg, 71 %) as a brown oil: $[\alpha]^{22}_D$ – 6.04 (*c* 0.85, MeOH), lit[13] $[\alpha]^{20}_D$ + 53 (*c* 0.15, MeOH). ^{1}H NMR [500 MHz, 4:1 $CDCl_3$-CD_3OD, COSY, *g*-HSQC; see Table 1 in Supporting Information] δ 0.73 (d, *J* = 6.8 Hz, 3H, CH_3), 1.08-1.22 (m, 1H, H-4), 1.30-1.41 (m, 20H, 10CH_2), 1.42-

1.56 (m, 3H, H-4, CH_2), 1.60-1.63 (m, 1H, H-3), 2.30 (dd, *J* = 11.8, 7.7 Hz, 1H, H-2), 2.36 (dd, *J* = 11.8, 5.2 Hz, 1H, H-2), 2.48-2.54 (m, 1H, H-16), 2.64-2.70 (m, 1H, H-16); ^{13}C NMR [125 MHz, 4:1 $CDCl_3$-CD_3OD; see Table 2 in Supporting Information] δ 18.2 (CH_3), 24.2 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 26.1 ($2CH_2$), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 27.0 ($2CH_2$), 30.7 (C-3), 32.4 (C-4), 47.0 (C-16), 53.8 (C-2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{34}N$ 240.2686; Found 240.2681. Haliclorensin C hydrochloride: ^{1}H NMR [400 MHz, 4:1 $CDCl_3$-CD_3OD, COSY, *g*-HSQC; see Table 1 in Supporting Information] δ 1.06 (d, *J* = 6.8 Hz, 3H, CH_3), 1.26-1.40 (m, 22H, $11CH_2$), 1.75 (m, 2H, H-15), 1.89 (m, 1H, H-3), 2.78-2.84 (m, 2H, H-2), 2.89-2.99 (m, 2H, H-16); ^{13}C NMR [100.6 MHz, 4:1 $CDCl_3$-CD_3OD; see Table 2 in Supporting Information] δ 17.9 (CH_3), 23.7 (C-15), 24.7 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 28.7 (C-3), 32.6 (C-4), 45.6 (C-16), 50.9 (C-2).

(*S*)-4-Methyl-5-[*N*-(2-nitrobenzenesulfonyl)-4-pentenylamino]-1-pentanol (15): Operating as described for the preparation of alcohol **11**, from **9a** (1.15 g, 3.80 mmol), Cs_2CO_3 (1.61 g, 4.95 mmol), and 5-bromo-1-pentene (0.54 mL, 4.56 mmol) in anhydrous DMF (25 mL), compound **15** (1.06 g, 75 %) was obtained as a yellow oil after flash chromatography (from 7:3 hexane-EtOAc to 1:1 hexane-EtOAc): $[\alpha]^{22}_D$ – 13.4 (*c* 1.85, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.7 Hz, 3H, CH_3), 1.05-1.14 (m, 1H, H-3), 1.40-1.52 (m, 2H, H-2, H-3), 1.55-1.66 (m, 4H, H-2, CH_2, OH), 1.71-1.80 (m, 1H, H-4), 1.95-2.00 (m, 2H, CH_2=CHCH_2), 3.11 (dd, *J* = 14.2, 8.1 Hz, 1H, H-5), 3.20 (dd, *J* = 14.2, 7.1 Hz, 1H, H-5), 3.19-3.33 (m, 2H, CH_2N), 3.59 (t, *J* = 6.4 Hz, 2H, H-1), 4.93-4.99 (m, 2H, CH_2=CH), 5.69 (qt, *J* = 16.9, 10.2, 10.2, 6.6, Hz, 1H, CH_2=C*H*), 7.59-7.63 (H-3Ns), 7.64-7.71 (m, 2H, H-5Ns, H-6Ns), 7.97-8.02 (m, 1H, H-4Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.8 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.6 (CH_2=CH*C*H_2), 31.1 (C-4), 46.8 (CH_2N), 53.5 (C-5), 62.9 (C-1), 115.4 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.5 (C-4Ns), 133.3 (C-5Ns), 133.6 (C-1Ns), 137.1 (CH_2=*C*H), 147.9 (C-2Ns); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}N_2O_5S$ 371.1635; Found 371.1635.

(*S*)-2-Methyl-*N*-(2-nitrobenzenesulfonyl)-*N*-(4-pentenyl)-5-hexenamine (16): Operating as described for the preparation of **12**, from alcohol **15** (355 mg, 1.0 mmol) and Dess–Martin reagent (1.49 g, 3.52 mmol) in anhydrous CH_2Cl_2 (9 mL), an aldehyde was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H, CH_3), 1.33-1.39 (m, 1H), 1.53-1.63 (m, 2H), 1.74-1.83 (m, 2H), 1.95-2.02 (m, 2H), 2.40-2.52 (m, 2H, C*H*$_2$COH), 3.11-3.30 (m, 4H, 2CH_2N), 4.94-5.00 (m, 2H, C*H*$_2$=CH), 5.64-5.75 (m, 1H, CH_2=C*H*), 7.50-7.60 (m, 3H, H-Ns), 7.99-8.00 (m, 1H, H-Ns), 9.75 (s, 1H, COH). Then, from the above aldehyde, *t*-BuOK (5.9 mL of a 1 M solution in THF, 5.9 mmol), and methyltriphenylphosphonium bromide (2.94 g, 8.22 mmol) in anhydrous THF (60 mL), diene **16**[14c] (175 mg, 50 %) was obtained as a colorless oil after flash chromatography (9:1 hexane-EtOAc): $[\alpha]^{22}_D$ – 12.0 (*c* 1.3, $CHCl_3$), lit[14c] $[\alpha]^{22}_D$ – 15.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.09-1.18 (m, 1H), 1.41-1.50 (m, 1H), 1.53-1.65 (m, 2H), 1.70-1.79 (m, 1H), 1.95-2.02 (m, 3H, CH_2=CHC*H*$_2$, CH_2), 2.07-2.17 (m, 1H, CH_2=CHC*H*$_2$), 3.13 (dd, *J*= 14.2, 8.3 Hz, 2H, C-1), 3.19 (dd, *J*= 14.2, 7.2 Hz, 2H, C-1), 3.26 (m, 2H, CH_2N), 4.92-4.97 (m, 3H, C*H*$_2$=CHCH_2), 4.99-5.01 (m, 1H, C*H*$_2$=CHCH_2), 5.65-5.72 (m, 1H, CH_2=C*H*), 5.72-5.79 (m, 1H, CH_2=C*H*), 7.59-7.62 (m, 1H, H-3Ns), 7.65-7.68 (m, 2H, H-5Ns, H-4Ns), 7.99-8.02 (m, 1H, H-4Ns); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.9 (CH_3), 26.8 (CH_2), 30.4 (CH), 30.7 (CH_2), 30.9 (CH_2), 33.0 (CH_2), 46.7 (CH_2), 53.4 (CH_2), 114.7 (*C*H_2=CH), 115.4 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.4 (C-4Ns), 133.3 (C-5Ns), 133.7 (C-1Ns), 137.1 (CH_2=*C*H), 138.3 (CH_2=*C*H), 147.9 (C-2Ns).

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-*N*-tosylpentanamine (17): *tert*-Butyldimethylsilyl chloride (773 mg, 5.13 mmol) was added to a solution of alcohol **10a** (870 mg, 3.20 mmol) and imidazole (349 mg, 5.13 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was heated at reflux for 15 h. The reaction was quenched by a saturated aqueous solution of NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give an oil (1.2 g). Purification by flash chromatography (from 9:1 hexane-EtOAc to 1: 1 hexane-EtOAc) afforded pure compound **17** (1.09 g, 88 %) as a colorless oil: $[\alpha]^{22}_D$ = – 0.19 (*c* 1.02, MeOH); IR (film) 3564, 3282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ – 0.01 (s, 6H, CH_3Si), 0.84 [s, 9H,

$(CH_3)_3$], 0.86 (d, J = 6.0 Hz, 3H, CH_3), 1.07-1.09 (m, 1H, H-3), 1.28-1.45 (m, 3H, H-4, H-3), 1.52-1.59 (m, 1H, H-2), 2.39 (s, 3H, CH_3Ts), 2.69 (ddd, J = 12.5, 6.8, 6.8 Hz, 1H, H-1), 2.79 (ddd, J = 12.5, 5.6, 5.6 Hz, 1H, H-1), 3.50 (dt, J = 6.4, 1.5 Hz, 2H, H-5), 5.18 (br.s, 1H, NH), 7.26 (d, J = 8.4 Hz, 2H, H-3Ts, H-5Ts), 7.73 (d, J = 8.4 Hz, 2H, H-2Ts, H-6Ts); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ – 5.4 (CH_3Si), 17.4 (CH_3), 18.2 [*C*$(CH_3)_3$], 21.3 (CH_3Ts), 25.8 [C(*C*$H_3)_3$], 29.8 (C-3), 30.0 (C-4), 32.8 (C-2), 48.8 (C-1), 63.1 (C-5), 126.9 (C-HTs), 129.5 (C- HTs), 137.0 (C-4Ts), 143.0 (C-1Ts); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{36}NO_3SSi$ 386.2180; Found 386.2179.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-*N*-[3-(phthalimido)propyl]-*N*-tosylpentanamine (18): NaH (95 %, 136 mg, 5.39 mmol) was added to a solution of compound **17** (562 mg, 1.46 mmol) and 3-(phthalimido)propyl iodide[18] (964 mg, 3.06 mmol) in anhydrous DMF (9 mL), and the mixture was stirred at room temperature for 17 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting oil (1.03 g) was chromatographed (from 9:1 hexane-EtOAc to 8: 2 hexane-EtOAc) to give compound **18** (630 g, 75 %) as a colorless oil: $[\alpha]^{22}_D$ – 4.61 (*c* 1.65, MeOH); IR (film) 1773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 (s, 6H, CH_3Si), 0.88 [s, 9H, $(CH_3)_3$], 0.91 (d, J = 6.6 Hz, 3H, CH_3), 1.03-1.12 (m, 1H), 1.36-1.50 (m, 2H), 1.55-1.61 (m, 1H), 1.74 (m, 1H, H-4), 1.84-1.95 (m, 2H, C*H*$_2$CH$_2$N), 2.41 (s, 3H, CH_3Ts), 2.91 (d, J = 7.5 Hz, 2H, H-1), 3.12-3.17 (m, 2H, CH_2NTs), 3.56 (t, J = 6.5 Hz, 2H, H-5), 3.66 (t, J = 7.1 Hz, 2H, CH_2NPhth), 7.27 (d, J = 8.3 Hz, 2H, H-3Ts, H-5Ts), 7.64 (d, J = 8.3 Hz, 2H, H-2Ts, H-6Ts), 7.73 (dd, J = 5.4, 3.0 Hz, 2H, H-Phth), 7.84 (dd, J = 5.4, 3.0 Hz, 2H, H-Phth); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ – 5.3 (CH_3Si), 17.3 (CH_3), 18.2 [*C*$(CH_3)_3$], 21.5 (CH_3Ts), 25.9 [C(*C*$H_3)_3$], 27.9 (*C*H_2CH_2N), 30.1 (C-3), 30.3 (C-4), 31.9 (C-2), 35.6 (CH_2NPhth), 46.7 (CH_2NTs), 55.2 (C-1), 63.2 (C-5), 123.2 (CH-Phth), 127.1 (C-HTs), 129.6 (C-HTs), 131.9 (C-Phth), 133.9 (CH-Phth), 136.4 (C-4Ts), 143.1 (C-1Ts), 168.1 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{45}N_2O_5SSi$ 573.2813; Found 573.2813.

(*S*)-4-Methyl-5-{*N*-[3-(phthalimido)propyl]-*N*-tosylamino}-1-pentanol (19): A solution of compound **18** (450 mg, 0.79 mol) in 1.0 N aqueous HCl (10 mL) was stirred at room temperature for 20 minutes.

Then, the solution was concentrated to give alcohol **19** (360 mg, quantitative), which was used in the next step without purification: $[\alpha]^{22}_{D}$ – 1.32 (*c* 1.12, MeOH); IR (film) 3542, 1770, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10-1.17 (m, 1H), 1.44-1.56 (m, 2H), 1.60-1.66 (m, 1H), 1.66-1.78 (m, 2H, H-4, OH), 1.89 (quint, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_2$N), 2.40 (s, 3H, CH_3Ts), 2.85 (dd, *J* = 13.6, 7.5 Hz, 1H, H-5), 2.95 (dd, *J* = 13.6, 7.5 Hz, 1H, H-5), 3.14 (m, 2H, CH_2NTs), 3.62 (t, *J* = 6.2 Hz, 2H, H-1), 3.67 (t, *J* = 7.2 Hz, 2H, CH_2NPhth), 7.27 (d, *J* = 8.2 Hz, 2H, H-3Ts), 7.64 (d, *J* = 8.2 Hz, 2H, H-2Ts), 7.72 (m, 2H, H-Phth), 7.84 (m, 2H, H-Phth); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.5 (CH_3Ts), 27.9 (*C*H$_2$CH$_2$N), 29.8 (CH_2), 30.1 (CH_2), 31.9 (CH), 35.8 (CH_2NPhth), 46.9 (CH_2NTs), 55.4 (C-5), 62.9 (C-1), 123.3 (CH-Phth), 127.2 (CHTs), 129.6 (CHTs), 131.9 (C-Phth), 134.0 (CH-Phth), 136.2 (C-4Ts), 143.2 (C-1Ts), 168.2 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_5S$ 459.1948; Found 459.1941.

(*S*)-2-Methyl-*N*-[3-(phthalimido)propyl]-*N*-tosyl-5-hexenamine (20): Operating as described for the preparation of compound **12**, from alcohol **19** (95 mg, 0.21 mmol) and Dess–Martin reagent (220 mg, 0.52 mmol) in anhydrous CH_2Cl_2 (2 mL), an aldehyde was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 1.78-1.93 (m, 4H), 2.39-2.51 (m, 5H), 2.40 (s, 3H, CH_3Ts), 2.87 (dd, 1H, *J* = 13.6, 7.6 Hz, CH_2N), 2.98 (dd, *J* = 13.6, 7.2 Hz, 1H, CH_2N), 3.13-3.19 (m, 2H, CH_2N), 3.67 (t, *J* = 6.8 Hz, 2H, CH_2N), 7.27 (d, 2H, *J* = 8.2 Hz, H-Ts), 7.64 (d, *J* = 8.2 Hz, 2H, H-Ts), 7.75 (dd, *J* = 5.6, 3.2 Hz, 2H, H-Phth), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H, H-Phth), 9.75 (s, 1H, COH). Then, from the above aldehyde (95 mg), *t*-BuOK (0.62 mL of a 1 M solution in THF, 0.62 mmol), and methyltriphenylphosphonium bromide (296 mg, 0.83 mmol) in anhydrous THF (5 mL), alkene **20** (66 mg, 70 %) was obtained as a colorless oil after flash chromatography (from 9:1 hexane-EtOAc to 85:15 hexane-EtOAc): $[\alpha]^{22}_{D}$ + 2.71 (*c* 0.65, EtOH); IR (film) 1772, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.3 Hz, 3H, CH_3), 1.15 (m, 1H, H-3), 1.45 (m, 1H, H-3), 1.65 (m, 1H, H-2), 1.90 (m, 2H, C*H*$_2$CH$_2$N), 1.95 (m, 1H, H-4), 2.15 (m, 1H, H-4), 2.41 (s, 3H, CH_3Ts), 2.91 (m, 2H, H-1), 3.14 (m, 2H, CH_2NTs), 3.64 (m, 2H, CH_2NPhth), 4.86-4.99 (m, 2H, H-6), 5.73 (m, 1H, H-5), 7.26 (d, *J* = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.65 (d, *J* = 8.2 Hz, 2H, H-2Ts, H-6Ts), 7.72 (dd, *J* = 5.8, 3.3 Hz,

2H, H-Phth), 7.84 (dd, J = 5.8, 3.3 Hz, 2H, H-Phth); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.3 (CH_3), 21.4 (CH_3Ts), 27.9 (CH_2CH_2N), 31.0 (C-3), 31.5 (C-2), 33.4 (C-4), 35.8 (CH_2NPhth), 46.7 (CH_2NTs), 55.1 (C-1), 114.5 (C-6), 123.2 (CH-Phth), 127.2 (CHTs), 129.6 (CHTs), 132.2 (C-Phth), 133.9 (CH-Phth), 137.5 (C-4Ts), 138.5 (C-5), 143.1 (C-1Ts), 168.1 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}N_2O_4S$ 455.1999; Found 455.2024.

(*S*)-*N*-[3-(2-Methyl-*N*-tosyl-5-hexenylamino)propyl]-4-pentenamide (21): A solution of hydrazine monohydrate (56 mg, 1.1 mmol) in ethanol (1.3 mL) was added to a solution of alkene **20** (506 mg, 1.1 mmol) in ethanol (4.5 mL), and the mixture was heated at reflux for 2.5 h. Insoluble material was removed by filtration, and the filtrate was concentrated to give the primary amine as a yellow oil (420 mg), which was used without purification in the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.5 Hz, 3H, CH_3), 1.10-1.15 (m, 1H), 1.42-1.46 (m, 1H), 1.70-1.75 (m, 3H), 1.95-2.00 (m, 1H), 2.06-2.13 (m, 1H), 2.42 (s, 3H, CH_3Ts), 2.66 (br.s., 2H, NH_2), 2.80 (m, 2H, CH_2N), 2.87-2.90 (m, 2H, CH_2N), 3.12-3.19 (m, 2H, CH_2N), 4.91-5.00 (m, 2H, CH_2=CH), 5.70-5.75 (m, 1H, CH_2=C*H*), 7.20-7.30 (m, 2H, H-Ts), 7.60-7.70 (m, 2H, H-Ts). 4-Pentenoyl chloride (0.15 mL, 1.34 mmol) and Et_3N (0.2 mL, 1.45 mmol) were slowly added to a solution of the above amine in CH_2Cl_2 (3 mL), and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched with water, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated under vacuum to give an oil. Flash chromatography (from 9:1 hexane-EtOAc to 1:1 hexane-EtOAc) afforded diene **21** (224 mg, 50 %) as a colorless oil: $[\alpha]^{22}_D$ + 1.9 (*c* 1.6, MeOH); IR (film): 3305, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, J = 6.6 Hz, 3H, CH_3), 1.08-1.17 (m, 1H, CHC*H*$_2$), 1.40-1.49 (m, 1H, CHC*H*$_2$), 1.70-1.76 (m, 3H, C*H*$_2$CH$_2$N, CH), 1.92-2.00 (m, 1H, H-2), 2.07-2.16 (m, 1H, H-2), 2.28-2.31 (m, 2H, CH_2=CHC*H*$_2$), 2.38-2.41 (m, 2H, H-3), 2.43 (s, 3H, CH_3Ts), 2.84-2.95 (m, 2H, CHC*H*$_2$N), 3.10 (t, J = 6.7 Hz, 2H, TsNC*H*$_2$CH$_2$), 3.35 (m, 2H, C*H*$_2$NH), 4.93-5.10 (m, 4H, C*H*$_2$=CH), 5.73 (m, 1H, CH_2=C*H*), 5.84 (m, 1H, CH_2=C*H*), 6.36 (br.s, 1H, NH), 7.31 (d, J = 8.1 Hz, 2H, H-Ts), 7.66 (d, J = 8.1 Hz, 2H, H-Ts); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.2 (CH_3), 21.4 (CH_3Ts), 28.6 ($CH_2CH_2CH_2$), 29.5 (CH_2=CH*C*H$_2$), 30.8 (C-3), 31.4 (CH), 33.2 (*C*H$_2$CH$_2$CH=), 35.8 (C-2), 36.0

(CH_2NH), 46.8 (TsN*C*H_2CH_2), 55.9 (CH*C*H_2N), 114.6 (*C*H_2=CH), 115.3 (*C*H_2=CH), 127.0 (CH-Ts), 129.6 (CH-Ts), 135.9 (C-4Ts), 137.0 (CH_2=*C*H), 138.3 (CH_2=*C*H), 143.3 (C-1Ts), 172.4 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{35}N_2O_3S$ 407.2363; Found 407.2361.

(*S*)-13-Methyl-6-oxo-1-tosyl-1,5-diaza-9-cyclotetradecene (22): Operating as described in the preparation of macrocycle **13**, from compound **21** (101 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) and second-generation Grubbs catalyst (32 mg, 0.037 mmol) in anhydrous CH_2Cl_2 (1.24 L), diazacycle **22** (72 mg, 77 %) was obtained as a 91:9 mixture (calculated by GC/MS) of *E/Z* diastereoisomers after flash chromatography (from 8:2 hexane-EtOAc to 3:7 hexane-EtOAc). Major diastereoisomer: IR (film): 3300, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10-1.27 (m, 2H, H-4), 1.49-1.65 (m, 2H, H-3, H-13), 1.65-1.73 (m, 1H, H-13), 1.92-2.04 (m, 2H, C*H*$_2$CH=), 2.05-2.13 (m, 1H, H-9), 2.19-2.30 (m, 2H, C*H*$_2$CH=, H-9), 2.33-2.38 (m, 1H, C*H*$_2$CH=), 2.40 (s, 3H, CH_3Ts), 2.75 (dd, *J* = 12.6, 5.9 Hz, 1H, H-2), 2.86-2.90 (m, 1H, H-12), 2.95 (dd, *J* = 12.6, 9.1 Hz, 1H, H-2), 2.98-3.02 (m, 1H, H-14), 3.16-3.24 (m, 1H, H-12), 3.29-3.37 (m, 1H, H-14), 5.22-5.36 (m, 2H, C*H*=C*H*), 5.96 (br.s, 1H, NH), 7.26 (d, *J* = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.62 (d, *J* = 8.2 Hz, 2H, H-2Ts, H-6Ts); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.4 (CH_3Ts), 26.9 (C-3), 28.0 (*C*H_2CH=), 28.3 (C-13), 28.9 (*C*H_2CH=), 32.0 (C-4), 36.2 (C-9), 36.4 (C-14), 44.8 (C-12), 53.5 (C-2), 127.0 (CH-Ts), 129.5 (CH=), 129.6 (CH-Ts), 131.7 (CH=), 136.5 (C-4Ts), 143.1 (C-1Ts), 172.4 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{31}N_2O_3S$ 379.2053; Found 379.2051.

(*S*)-13-Methyl-6-oxo-1-tosyl-1,5-diazacyclotetradecane (23): A solution of alkene **22** (79 mg, 0.21 mmol) in anhydrous MeOH (7 mL) containing 10 % Pd-C (8 mg) was stirred under hydrogen at room temperature for 48 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give pure compound **23** (74 mg, 94 %) as a brown oil: $[\alpha]^{22}_D$ – 12.7 (*c* 1.18, $CHCl_3$); IR (film): 3410, 1643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.10-1.20 (m, 1H, 1H-CH_2), 1.22-1.35 (m, 6H, 3CH_2), 1.36-1.62 (m, 3H, CH_2, 1H-CH_2), 1.65-1.92 (m, 3H, H-3, CH_2), 2.10-2.27 (m, 2H, H-9), 2.42 (s, 3H, CH_3Ts), 2.76 (dd, *J* = 12.9, 5.5 Hz, 1H, H-2), 2.99 (dd, *J* = 12.9, 8.5 Hz, 1H, H-2), 2.95-2.98 (m, 1H, H-14), 3.07-3.14 (m, 2H, H-

12), 3.42-3.54 (m, 1H, H-14), 6.10 (br.s, 1H, NH), 7.29 (d, J = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.65 (d, J = 8.2 Hz, 2H, H-2Ts, H-6Ts); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 21.4 (CH_3Ts), 23.3 (CH_2), 24.3 (CH_2), 25.1 (CH_2), 25.8 (CH_2), 27.7 (C-3), 28.7 (CH_2), 30.9 (CH_2), 35.1 (C-9), 36.6 (C-14), 45.9 (C-12), 54.8 (C-2), 127.1 (CH-Ts), 129.6 (CH-Ts), 136.1 (C-4Ts), 143.2 (C-1Ts), 173.1 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{33}N_2O_3S$ 381.2206; Found 381.2207.

(*S*)-Haliclorensin: A solution of diazacycle **23** (74 mg, 0.19 mmol) in dry THF (3.5 mL) was added to a suspension of $LiAlH_4$ (74 mg, 1.95 mmol) in dry THF (4.5 mL) at 0 ºC, and the mixture was heated at reflux for 21 h. After cooling to room temperature, the reaction was quenched by water (7 mL), and the pH value was adjusted to 4 by adding 2 M aqueous HCl solution (2 mL). The mixture was extracted with Et_2O, and the aqueous phase was basified with a saturated aqueous solution of K_2CO_3 to reach pH 12. The solution was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated under vacuum to give a yellow oil. Flash chromatography (SiO_2 previously washed with 18:1:1 CH_2Cl_2-MeOH-NH_4OH; gradient from 19:1 CH_2Cl_2-MeOH to 17:3 CH_2Cl_2-MeOH) afforded haliclorensin (26 mg, 65 %) as a colorless oil: $[\alpha]^{22}_D$= – 17.2 (*c* 0.5, MeOH), lit[15a] $[\alpha]_D$ – 2.2 (*c* 1.3, MeOH), lit[13] $[\alpha]^{20}_D$ – 19 (*c* 0.57, MeOH), lit[15b] $[\alpha]_D$ – 18.5 (*c* 0.6, MeOH), lit[15b] $[\alpha]_D$ – 8.5, lit[15b] $[\alpha]^{20}_D$ + 7.0 (1M HCl), lit[15c] $[\alpha]^{20}_D$ – 18.2 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, CD_3OD, *g*-HSQC; see Table 3 in Supporting Information) δ 0.89 (d, J = 6.9 Hz, 3H, CH_3), 1.24-1.31 (m, 1H), 1.36-1.51 (m, 9H), 1.55-1.61 (m, 2H), 1.70-1.77 (m, 3H), 2.40 (dd, J = 11.8, 9.7 Hz, 1H), 2.55 (dd, J = 11.8, 3.8 Hz, 1H), 2.58-2.63 (m, 1H), 2.64-2.68 (m, 2H), 2.71-2.73 (m, 2H), 2.82 (ddd, J = 11.2, 6.8, 4.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3OD; see Table 4 in Supporting Information) δ 18.8 (CH_3), 22.0 (CH_2), 23.2 (CH_2), 24.7 (CH_2), 27.3 (CH_2), 27.7 (CH_2), 29.3 (CH_2), 30.5 (CH), 32.7 (CH_2), 47.5 (CH_2N), 49.8 (CH_2N), 50.5 (CH_2N), 55.6 (CH_2N).

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Supporting Information Available

Copies of the ^{1}H and ^{13}C spectra of all new compounds and tables with NMR data for halicloresin C and haliclorensin. This material is available free of charge via the Internet at http://pubs.acs.org.

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