Enantioselective Synthesis and Determination of the Configuration of Stenusine, the Spreading Agent of the Beetle *Stenus comma*

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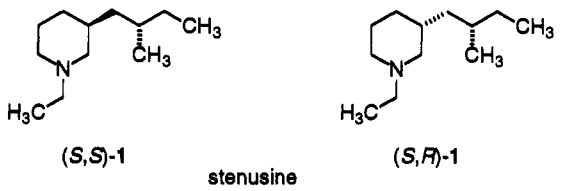
The enantioselective total synthesis of two of the four possible stereoisomers of stenusine (1), the spreading agent of the beetle *Stenus comma*, is described. The silyl ether-substituted aldehyde SAMP hydrazone 2 was alkylated with (*S*)-1-bromo-2-methylbutane (3) yielding the hydrazone 4 in high diastereomeric purity (de > 95%). By several steps including the reduction of the hydrazone functionality and the cleavage of the N–N bond of the intermediates, 4 was converted into the BOC-protected amino alcohol 6. Subsequent cyclization of 6 afforded the (*S,S*) diastereomer of stenusine with 96.6% de, >99.9% ee, and in 11.3% overall yield. Repetition of this synthesis using the aldehyde RAMP hydrazone (*R*)-2 as the starting material produced (*S,R*)-1 with 95.0% de, >99% ee, and in 8.2% overall yield. The synthetic samples of 1 were employed to investigate the stereochemistry of natural stenusine by means of GC analysis on both a chiral and an achiral, stationary phase. As a result of these studies natural stenusine was found to be a mixture of all four stereoisomers in a ratio of (*S,S*)/(*S,R*)/(*R,R*)/(*R:S*) = 43:40:13:4.

Introduction

The staphynilid *Stenus comma*[1] is a beetle found in both Middle and Southern Europe,[2] where it inhabits sandy clay on the edge of ponds.[3] Although a nonswimmer, the beetle is nevertheless able to propel itself over water by means of expelling an oil onto the aqueous surface. The main component of this propulsion fluid, extracted from the pygidial glands of the beetle, is stenusine (1). The 1,3-disubstituted piperidine has an exceptionally high spreading capacity on aqueous surfaces and is chiefly responsible for the propulsion fluids unique properties.[1]

In spite of the unusual biological function of stenusine (1), to date no route has been devised for its diastereoselective preparation nor any investigations on its natural configuration reported. The synthesis reported by Schildknecht et al.[1] as well as that previously developed by two of us (N.D.K. and C.S.)[4] provide 1 as a mixture of diastereomers. Focus was therefore placed on a flexible, overall enantioselective route toward the preparation of (*S,S*)-1 and (*S,R*)-1. Comparison of the synthetic, enantiomerically enriched samples with natural stenusine would then provide an efficient method of determining the naturally occuring configuration.



Results and Discussion

Synthesis of 1. In order to control the stereochemistry of the target molecule 1, it was envisaged that the stereogenic center at the 3 position of the piperidine ring could be created by stereoselective alkylation of hydrazones derived from the enantiomerically pure hydrazines (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP).[5] The electrophile then to be employed would introduce the side chain of the piperidine together with the second stereogenic center. On this basis the hydrazones (*S*)-2 and (*R*)-2, respectively, and the bromide (*S*)-3 were chosen as starting materials (Scheme I). (*S*)-3 resulted from the bromination of the corresponding commercially available alcohol,[6] while the hydrazones (*S*)-2 or (*R*)-2 were readily accessible *via* a known three-step sequence from 1,5-pentanediol.[7]

Lithiation of 2 was performed with lithium diisopropylamide followed by the addition of 1 equiv of *n*-butyllithium in order to deprotonate the formed diisopropyl-

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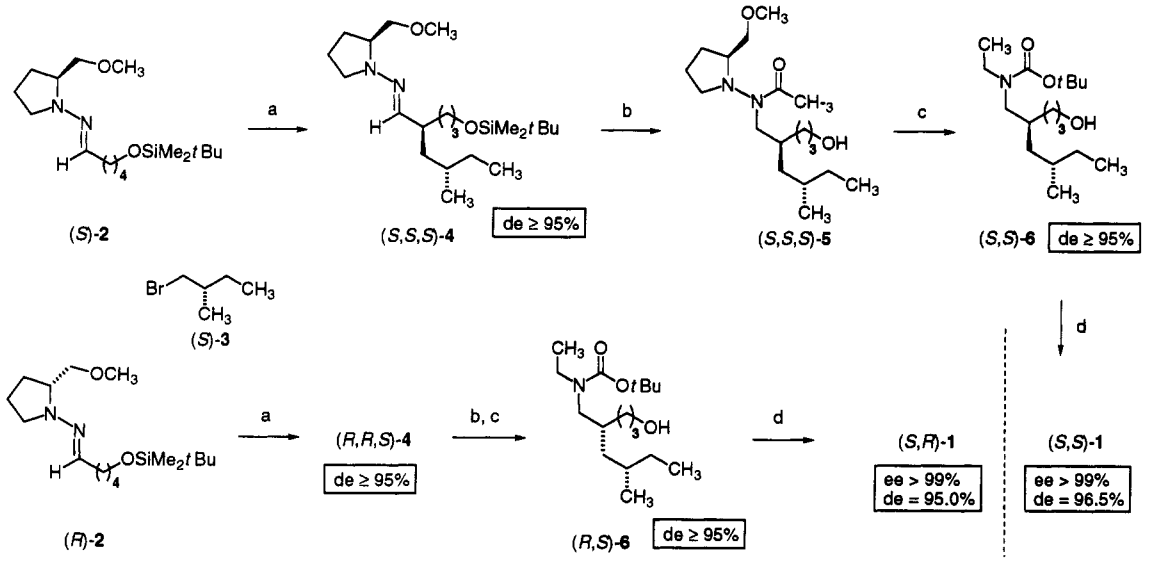
0022-3263/93/1958-4881$04.00/0

Scheme I[a]



[a] (a) (1) LDA, THF, 0 °C, (2) *n*-BuLi, −20 °C, (3) (*S*)-**3**, −100 °C → rt; (b) (1) DIBALH, Et_2O, rt, (2) AcCl, −78 °C → 0 °C, (3) K_2CO_3, $MeOH/H_2O$ (38% based on (*S*)-**2** and 19% based on (*R*)-**2**); (c) (1) Li, NH_3, −33 °C, (2) $LiAlH_4$, THF, Δ, (3) BOC_2O, $NaHCO_3$, MeOH, ultrasound (35% based on (*S,S,S*)-**4** and 45% based on (*R,R,S*)-**4**); (d) (1) MsCl, Et_3N, CH_2Cl_2, 0 °C, (2) TFA, anisole, CH_2Cl_2, rt, and then NaOH and Et_2O/H_2O (85% based on (*S,S*)-**6** and 96% based on (*R,S*)-**6**).

amine.[8] Quenching of the so-produced azaenolate with the bromide (*S*)-**3** yielded (*S,S,S*)-**4** and (*R,R,S*)-**4**, respectively, in high diastereomeric purity (≥95% de). The hydrazones **4** proved to be unstable toward chromatography and were therefore used in subsequent reactions without further purification.

Attempts toward the synthesis of **1** provided the cyclization of the protected amino alcohols **6**. These were prepared from the hydrazones **4** by the reduction of the hydrazone moiety followed by cleavage of the resultant N–N bond.[9] Thus, (*S,S,S*)-**4** and (*R,R,S*)-**4**, respectively, were treated with an excess of DIBALH, which provided simultaneous reduction of the CN double bond and removal of the silyl ether protective group. The resultant, formal aluminum hydrazide was quenched with acetyl chloride. Due to the present basic conditions it was expected that either the hydrazine and the now unprotected hydroxy group would have been acetylated. However, since the reaction mixture was treated with potassium carbonate in aqueous methanol during the workup procedure, hydroxy hydrazides (*S,S,S*)-**5** (38%) and (*R,R,S*)-**5** (19%) were isolated as the final products of this sequence.

The acetyl group of the compounds **5** was necessary as an activating group for the ensuing removal of the chiral auxiliary ((*S*)- or (*R*)-2-(methoxymethyl)pyrrolidine, SMP or RMP) performed with lithium in liquid ammonia at −33 °C.[10] The resulting crude acetamides were then reduced with lithium aluminum hydride, the acetyl functionality now acting as a precursor for the required *N*-ethyl substituent in the target molecules. The final acylation with BOC_2O according to the method of Einhorn et al.[11] led to the N-protected amino alcohols (*S,S*)-**6** [35% based on (*S,S,S*)-**5**] and (*R,S*)-**6** [45% based on (*R,R,S*)-**5**]. The ^{13}C-NMR spectra of these compounds showed the same diastereomeric purity as was determined for the preceding hydrazones **4** (≥95% de).

In order to complete the synthesis of stenusine the hydroxy functionality of the N-protected amino alcohols **6** was mesylated. The following cleavage of the carbamate group by treatment with trifluoroacetic acid and anisole produced a syrupy ammonium salt, which cyclized spontaneously upon basic workup to give (*S,S*)-**1** in 85% yield (11.3% overall) and (*S,R*)-**1** in 96% yield (8.2% overall). GC analysis on a chiral stationary phase[12] showed a de value of 96.5% for (*S,S*)-**1** obtained by this route and a de value of 95.0% for (*S,R*)-**1**. The ee values were shown to be greater than 99% in both cases by GC-CSP.

Determination of the Configuration of Natural Stenusine. With two of the four possible stereoisomers of **1** in hand as well as a racemic sample synthesized according to the literature,[4] the relative and absolute configurations of natural stenusine were investigated. Accordingly, live *Stenus comma* beetles were allowed to slide on water under laboratory conditions. The remaining, oily film on the water surface was collected and analyzed by means of GC on both chiral and nonchiral, stationary phases (Figure 1).

Contrary to initial expectations, naturally occuring stenusine was shown to be not diastereo- and enantiomerically pure, but, as can be seen directly from the GC A in Figure 1, was a mixture of all four stereoisomers. The beetle, however, does not produce racemic mixtures, which was already known based on the optical rotation value [[α]365 = +58° (*c* = 0.115, EtOH)] reported by Schildknecht et a.[1] for natural **1** isolated in pure form. Com-

(8) The advantage of this protocol was demonstrated by the alkylation of **2** with methyl iodide, which can be considered as a model reaction. By means of a simple lithiation of **2** with LDA the alkylation remained incomplete and gave only 58% yield of the methylated product. Additional deprotonation, however, afforded the desired product in 78% yield.

(9) (a) Enders, D.; Schubert, H.; *Angew. Chem.* **1984**, *96*, 368. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 365. (b) Enders, D.; Schubert, H.; Nübling, C. *Angew. Chem.* **1986**, *98*, 1118. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109.

(10) (a) Mellors, J. M.; Smith, N. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2927. (b) Nübling, C. Dissertation, Technical University of Aachen, 1987. (c) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219.

(11) Einhorn, J.; Einhorn, C.; Luche, J. L. *Synlett* **1991**, 37.

(12) Column: Heptakis(2,3,6-tri-*O*-methyl)β-cyclodextrin in OV 1701, 25 m × 0.25 mm; temp 95 °C; carrier gas 0.5 bar H_2.

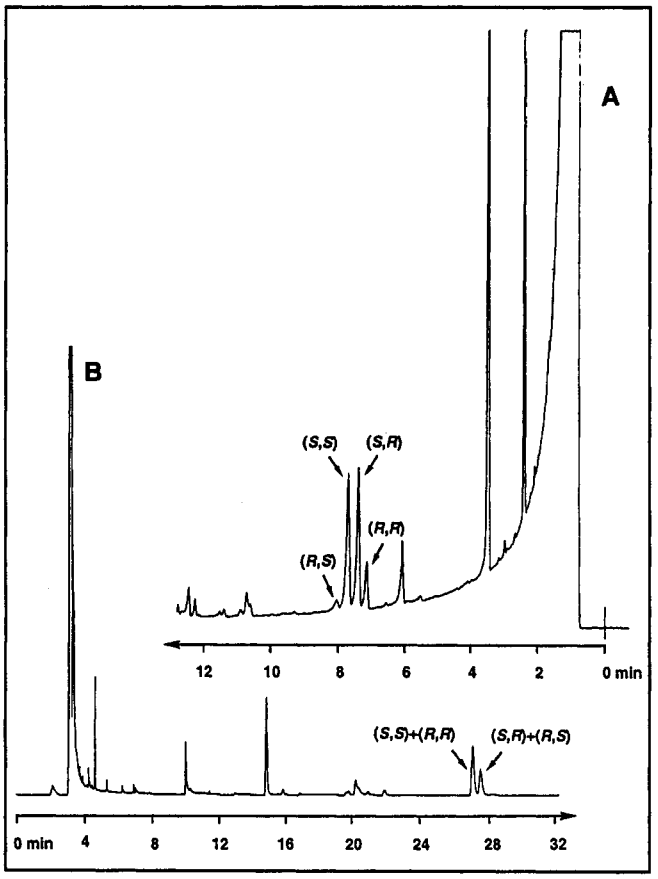


Figure 1. Gas chromatograms of natural stenusine (**A**, chiral phase;[12] **B**, nonchiral phase[13]).

parison of the chromatographs in Figure 1 with those recorded of the synthetic substances led to the indicated assignments, and so a stereoisomeric ratio of 43:40:13:4 = (*S,S*)/(*S,R*)/(*R,R*)/(*R,S*) was determined. Although these values have to be considered with some reservation due to the fact that 1 is only of low concentration in the sample, which makes integration of the chromatogram difficult, it can clearly be said that the epimers, which possess (*S*) configuration in the side chain, are present in excess (83:17). On the other hand there does not seem to be much preference for diastereomers with (*S*) or (*R*) configuration at the ring stereogenic center (53:47). In other words, the enantiomeric excess of (*S,S*)-stenusine is ee = 53% and that of (*S,R*)-stenusine ee = 82%. The here found case that a compound is not produced by nature as a pure stereoisomer is not without literature precedence. A large number of the examples cited are semiochemicals derived from insects (e.g. endo-Brevicomin[14]). However, the fact that an insect uses a particular ratio of stereoisomers of a chiral compound for mechanical purposes, namely to move on the water surface, is surprising. It should be interesting to examine if and how the diastereomeric composition of natural stenusine depends on factors like origin, food or the age of the beetles. Investigations on this matter which take advantage of the herein described methods are currently in program.

(13) Nonchiral phase: column SE 30; temp 90–300 °C, 0.5 °C/min; carrier gas 0.8 bar N_2.

(14) (a) Mori, K. in *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1991; Vol. 4. (b) Weber, R.; Schurig, V. *Naturwissenschaften* **1984**, *71*, 408.

Experimental Section

General Methods. Optical rotation values were recorded on a Perkin-Elmer P241 polarimeter. Elemental analyses: Heraeus CHN-O-Rapid. IR spectra: Beckmann Acculab 4 and Perkin-Elmer FTIR 1750. ^{1}H-NMR spectra (300 MHz) and ^{13}C-NMR spectra (75 MHz): Varian VXR 300 (TMS as internal standard). Mass spectra: Varian MAT 212 (70 eV). All solvents were dried by conventional methods. THF and ether, when used in reactions involving air and moisture-sensitive species, were distilled over sodium/benzophenone under argon. TLC: Merck Kieselgel 60 F254, Art. 5717. Column chromatography: Merck Kieselgel 60, 0.04–0.063 mm (flash) and 0.063–0.1 mm. (*S*)-2-Methylbutan-1-ol was purchased from Merck.

Rearing of *Stenus comma* Beetles and Isolation of the Natural Product. Live *Stenus comma* adults, caught at Niederlamitz/Fichtelgebirge in Northern Bavaria (Germany) during September 1992, were kept under laboratory conditions of 23 °C, 75–85% relative humidity and a photoperiod of 16L:8D. The rearing techniques were generally according to Hertveldt et al.[15] About 40 living adults were kept in a plexiglas cylinder (21 cm diameter, 7 cm high). A 2-cm high ring covered with a fine nylon gauze was placed above and below the adult cage. Inside the cylinder, another ring, covered with a fine nylon gauze was glued at an angle of 45°. On the lower half of the latter ring expanded clay granules (Argex, 1–2 mm diameter, Argex-Sicalex NV, Kraainem, Belgium) were placed to cover half of the cylinder's bottom. The granule layer functioned as a resting and feeding site and as an oviposition substrate. As food for *S. comma* adults and larvae, live 1st and 2nd instar *Spodoptera exigua* larvae (Lepidoptera: Noctuidae) were given *ad libitum*. To collect *S. comma* eggs, the adult cage was placed onto a plexiglas cylinder, possessing a bottom nylon sieve, to retain parts of dead beetles and *S. exigua* larvae. The two cylinders were then placed on a funnel, with a very fine nylon gauze on the funnel stem to collect the eggs. Then the adult cage was gently washed with tap water for about 15 s. Eggs were collected twice a week. Afterwards, the gauze was removed and the eggs were placed in a smaller plexiglas cylinder (9 cm diameter, 2 cm high) on a piece of moist paper toweling. However, egg hatch was never higher than 5%.

Forty living *Stenus comma* beetles, freshly caught from the Northern Bavaria area, were put in a glass petri plate (diameter 15 cm) filled with 100 mL of distilled water. Initially, several beetles moved rapidly over the water surface. After 15 min no more rapid movements were observed and the beetles were removed from the water surface. The water was extracted twice with 15 mL of freshly distilled ether. This procedure was repeated four times (one extraction procedure each day). The combined ethereal extracts were dried ($MgSO_4$) after which the solvent was distilled through a 21-cm Vigreux column until there was 0.5 mL of residual liquid left. This concentrate is a solution of (predominantly) natural stenusine in ether which was used as such for GC analyses.

(2*S*,2′*S*,4′*S*)-1-[[2′-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-4′-methylhexylidene]amino]-2-(methoxymethyl)pyrrolidine [(*S,S,S*)-4]. Hydrazone (*S*)-2 (1.64 g, 5 mmol), dissolved in THF (2 mL), was added to a freshly prepared solution of LDA (5.05 mmol) in THF (8 mL) at 0 °C. After stirring at this temperature for a period of 14–16 h the resulting yellow solution was cooled to −30 °C and *n*-butyllithium (1.55 M in hexane, 3.2 mL, 5 mmol) was added dropwise. The reaction mixture was then cooled to −100 °C and (*S*)-1-bromo-2-methylbutane [(*S*)-3] (1.66 g, 11.0 mmol) was added. The mixture was allowed to warm to rt over 12–15 h and was then poured into saturated ammonium chloride solution and extracted three times with Et_2O. The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give (*S,S,S*)-4 as a crude product which was used in the next step without purification: de > 95% (by ^{13}C NMR); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.25, 11.40, 18.39, 19.02, 22.06, 25.99, 26.53, 30.26, 30.33, 30.85, 31.96, 39.94, 40.83, 50.60, 59.12, 63.26, 63.49, 74.81, 143.71.

(15) Hertveldt, L.; Van Keymeulen, M.; Gillard, A. *J. Econ. Entomol.* **1984**, *77*, 267.

(2*R*,2′*R*,4′*S*)-1-[[2′-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-4′-methylhexylidene]amino]-2-(methoxymethyl)pyrrolidine [(*R*,*R*,*S*)-4]. (*R*,*R*,*S*)-4 was prepared in the same manner as described for the synthesis of (*S*,*S*,*S*)-4 using hydrazone (*R*)-2 (1.64 g, 5 mmol) and (*S*)-1-bromo-2-methylbutane [(*S*)-3] (1.66 g, 11 mmol) as the starting materials: de ≥ 95% (by ^{13}C NMR); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.25, 11.05, 18.34, 19.69, 22.06, 25.98, 26.53, 28.91, 30.24, 31.73, 39.93, 40.83, 50.54, 59.00, 63.27, 63.48, 74.81, 144.01.

(2*S*,2′*S*,4′*S*)-(−)-*N*-[2′-(3′-Hydroxypropyl)-4′-methylhexyl]-*N*-[2-(methoxymethyl)-1-pyrrolidinyl]acetamide [(*S*,*S*,*S*)-5]. DIBALH (1 M in hexane, 8 mL, 8 mmol) was added to an Et_2O solution (10 mL) of the hydrazone (*S*,*S*,*S*)-4 (2/5 of the above obtained crude substance). After stirring at rt for 25 h the reaction mixture was cooled to −78 °C and acetyl chloride (1.9 mL, 26.4 mmol) was slowly added. After a further 30 min at −78 °C and 1 h at 0 °C the reaction was quenched with methanol (10 mL) and subsequently saturated potassium carbonate solution was carefully added to a pH of 10–11. The resulting slurry was stirred for 1 h at rt and then decanted and the remaining precipitate extracted several times with hot THF. The organic phases were combined and concentrated *in vacuo*. The residue was taken up in Et_2O (50 mL), dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography with Et_2O and then EtOAc as eluent to give 250 mg (38% based on (*S*)-2) of (*S*,*S*,*S*)-5 as a viscous, yellow oil: $[\alpha]^{20}_D$ = −5.8° (*c* = 0.55, $CHCl_3$); IR (film) 3400 (m OH), 2960 (s), 2920 (s), 2860 (s), 1640 (s, C=O), 1450 (s), 1405 (s), 1060 (s, br, C–O–C, C–OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.3 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 1.05–2.08 (br m, 14H), 2.14 (s, 3H, $COCH_3$), 2.50 (s, br, 1H, OH), 2.86 (m, 1H), 2.92–3.30 (br m, 5H), 3.33 (s, 3H, OCH_3), 3.38 (dd, *J* = 9.1 Hz, 4.4 Hz, 1H), 3.60 (m, 2H, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.23, 19.56, 21.05, 21.55, 26.70, 28.16, 29.05, 29.68, 31.73, 34.17, 39.83, 44.89, 50.67, 59.06, 59.13, 62.75, 74.32, 175.88. Anal. Calcd for $C_{18}H_{36}N_2O_3$: C, 65.81; H, 11.05; N, 8.53. Found: C, 65.33; H, 11.25; N, 8.22.

(2*R*,2′*R*,4′*S*)-(+)-*N*-[2′-(3′-Hydroxypropyl)-4′-methylhexyl]-*N*-[2-(methoxymethyl)-1-pyrrolidinyl]acetamide (*R*,*R*,*S*)-5. According to the procedure described for the synthesis of (*S*,*S*,*S*)-5, crude (*R*,*R*,*S*)-4 was converted into (*R*,*R*,*S*)-5 (19% yield based on (*R*)-2): $[\alpha]^{27}_D$ = +39.8° (*c* = 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.92–2.08 (br m, 14H), 2.14 (s, 3H, $COCH_3$), 2.87 (m, 1H), 2.92–3.30 (br m, 5H), 3.33 (s, 3H), 3.38 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.60 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 11.32, 19.27, 21.10, 21.52, 26.72, 27.74, 28.84, 30.04, 31.68, 34.23, 39.39, 45.31, 50.80, 58.82, 59.09, 62.73, 74.29, 175.86.

(2*S*,4*S*)-(+)-*tert*-Butyl *N*-Ethyl-*N*-[2-(3-hydroxypropyl)-4-methylhexyl]carbamate [(*S*,*S*)-6]. To liquid ammonia (19 mL) at −78 °C in a three-necked flask fitted with a dry-ice condenser was added a solution of (*S*,*S*,*S*)-5 (0.25 g, 0.76 mmol) in dry THF (3 mL). To this mixture small pieces of lithium wire (28 mg, 4 mmol) were added to give a dark blue suspension. The cooling bath was removed and the suspension was kept under reflux for 1 h. Quenching of the reaction with solid ammonium chloride (1 g) was followed by evaporation of the ammonia at rt. The residue was extracted several times with CH_2Cl_2. After filtration and removal of the solvent *in vacuo* the remaining syrup was dissolved in dry THF (4 mL). Lithium aluminum hydride (65 mg, 1.7 mmol) was added, the reaction mixture was heated under reflux for 4 h, quenched by the addition of EtOAc (3 mL) and sodium hydroxide (1 N, 1 mL), and then filtered. The precipitate was washed, and the washings were combined with the filtrate, dried ($MgSO_4$), and concentrated to yield an oil which was dissolved in methanol (8.5 mL). Sodium bicarbonate (0.43 g) and di-*tert*-butyl dicarbonate (BOC_2O, 0.22 g, 1 mmol) were added, and the suspension was sonicated for 3 h in an ultrasound cleaning bath. The mixture was then filtered, concentrated, and diluted with Et_2O, whereupon all remaining mineral solids precipitated. A second filtration was followed by chromatography on silica gel (Et_2O/petroleum ether = 3/1) to give 80 mg (35%) (*S*,*S*)-6 as a colorless syrup: de ≥ 95% (^{13}C NMR); $[\alpha]^{26}_D$ = +7.0° (*c* = 0.43, $CHCl_3$); IR (film) 3430 (m, br, O–H), 2960 (s), 2930 (s), 2870 (s), 1695, 1670 (s, C=O), 1455 (m), 1420 (s), 1165 (s, CO–O–C), 1070 (m, br, C–OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H), 1.09 (t, *J* = 6.9 Hz, 3H), 1.00–1.68 (br m, 9H), 1.45 (s, 9H, $(CH_3)_3CO$), 1.74 (sept, *J* = 6.8 Hz, 1H), 2.20 (br, 1H, OH), 2.85–3.28 (br m, 4H), 3.62 (m, 2H, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.18, 13.4 (br), 19.69, 27.5 (br), 28.4 (br), 28.52, 29.51, 31.73, 34.0 (br), 39.1 (br), 42.29, 50.5 (br), 63.08, 79.19, 157.5 (br); MS (70 eV) *m*/*z* (%) = 301 (4; M^+), 200 (12), 158 (23), 102 (29), 58 (100), 57 (71), 41 (15). Anal. Calcd for $C_{17}H_{35}NO_3$: C, 67.73; H, 11.70; N, 4.65. Found: C, 67.27; H, 11.52; N, 4.58.

(2*R*,4*S*)-(+)-*tert*-Butyl *N*-Ethyl-*N*-[2-(3-Hydroxypropyl)-4-methylhexyl]carbamate [(*R*,*S*)-6]. According to the procedure described for the synthesis of (*S*,*S*)-6, (*R*,*R*,*S*)-5 (0.29 g, 0.88 mmol) was converted into 120 mg (45%) of (*R*,*S*)-6: de > 95% (^{13}C-NMR); $[\alpha]^{24}_D$ = +24.7° (*c* = 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.95–1.68 (m, 9H), 1.45 (s, 9H), 1.77 (m, 1H), 2.20 (br, 1H), 2.80–3.40 (m, 4H), 3.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.35, 13.4 (br), 19.21, 27.0 (br), 28.7 (br), 28.51, 30.22, 31.68, 34.0 (br), 38.7 (br), 42.23, 50.5 (br), 63.09, 79.18.

(2*S*,3*S*)-1-Ethyl-3-(2-methylbutyl)piperidine [(*S*,*S*)-1]. To a solution of (*S*,*S*)-6 (80 mg, 0.265 mmol) and triethylamine (56 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) was added methanesulfonyl chloride (52 mg, 0.45 mmol) at 0 °C. After stirring for 15 min at 0 °C, the mixture was diluted with an equal amount of Et_2O and filtered through a pad of silica gel. Concentration of the filtrate *in vacuo* gave the crude mesylate, which was dissolved in CH_2Cl_2 (0.3 mL). To this solution, anisole (170 mg, 1.59 mmol) and then trifluoroacetic acid (0.3 mL) were added dropwise followed by stirring for 15 min at rt. Subsequently, all volatile components were removed *in vacuo* until a syrupy residue remained. This was carefully washed with three 1-mL portions of petroleum ether, dissolved in Et_2O (5 mL), and treated with sodium NaOH (5 mL, 1 N) by vigorously stirring for 10 min. Afterwards the ethereal phase was separated and the aqueous phase was additionally extracted three times with Et_2O. All organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (Et_2O/CH_2Cl_2 = 1/1) afforded 41.5 mg (85%) of (*S*,*S*)-1 as a colorless oil: de = 96.5%, ee > 99% (by GC analysis[12]); $[\alpha]^{25}_{365}$ = +34.4° (*c* = 0.27, EtOH); IR (film) ν 2960 (s), 2940 (s), 2770 (s), 1460 (s, br), 1380 (s), 1345, 1195 (m), 1160 (m), 1145 (m), 1090 (s, C–N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.4 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.95–1.82 (br m, 12H), 2.35 and 2.41 (2 dq, each *J* = 12.0 Hz/7.1 Hz, 2H), 2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.24, 12.01, 19.49, 25.65, 32.01, 29.62, 31.21, 33.55, 42.13, 52.87, 53.85, 60.36; MS (70 eV) *m*/*z* (rel inten) 183 (22; M^+), 168 (100), 72 (42), 58 (94). Anal. Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.74; N, 7.64. Found: C, 78.31; H, 14.08; N, 7.66.

(2*S*,3*R*)-1-Ethyl-3-(2-methylbutyl)piperidine [(*S*,*R*)-1]. In the same manner as described for the preparation of (*S*,*S*)-1, (*R*,*S*)-6 (110 mg, 0.365 mmol) was converted into 64 mg of (*S*,*R*)-1 (96%): de = 95.0%, ee > 99% (according to GC analysis[12]); $[\alpha]^{24}_{365}$ = +68.0° (*c* = 0.52, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.7 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.75–1.83 (br m, 12H), 2.34 and 2.40 (2 dq, each *J* = 12.0Hz/7.1 Hz, 2H), 2.83 and 2.91 (2m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.32, 12.04, 19.30, 25.61, 31.12, 29.98, 31.21, 33.65, 41.91, 52.84, 53.91, 61.05.

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Supplementary Material Available: Gas chromatograms of synthetic stenusine samples (racemic, (*S*,*S*), (*S*,*R*), and mixtures of the latter two) recorded on chiral and on nonchiral phases (5 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.