Synthesis of Stenusine, the Spreading Agent of the Beetle *Stenus comma*

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Stenusine [1-ethyl-3-(2-methylbutyl)piperidine], the spreading agent of *Stenus comma*, was synthesized by a six-step sequence in 21% overall yield from acetaldehyde. Acetaldehyde was converted into the corresponding *N-tert*-butyl aldimine, which was sequentially alkylated via its 1-azaallylic anion with 1-bromo-2-methylbutane and 1-bromo-3-chloropropane. The resulting δ-chloro aldimine was hydrolyzed into the δ-chloro aldehyde, which was converted into the corresponding *N*-ethyl aldimine. The latter labile δ-chloro aldimine was cyclized with lithium aluminum hydride to afford stenusine. The 1-*tert*-butyl analogue of stenusine was synthesized using an analogous route.

Introduction

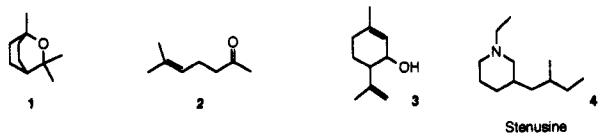
Stenus comma, a black staphynilid beetle with two yellow spots on its wings, does not have the ability to swim, although it often falls into the water while hunting for its prey.[1] In order to avoid drowning, the beetle presses its abdomen into the water the expels an oily mixture onto the water surface. This enables the 2.5-mg beetle to ski over the water with a speed of 75 cm/s. The beetle jets to the river bank and to safety while using the flotation activity of the excreted oil. From the small pygidial glands that excrete part of this oil responsible for the spreading activity, three compounds were isolated: eucalyptol [1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane, 1], 6-methyl-5-hepten-2-one (2), and an isopiperitenol (3).[2]

The larger pygidial glands excreted a 1,3-disubstituted piperidine 4, named stenusine. Stenusine exhibits a high spreading capacity on the water surface and is the active compound which propels the beetle over the water. The ratio between the surface-active (1) and the more active stenusine (4) in the excreted oil is 1:14. In this paper, a convenient synthesis of the 1,3-disubstituted piperidine 4 (stenusine) and its 1-*tert*-butyl analogue is disclosed using a mild synthetic route via δ-chloro aldimines.

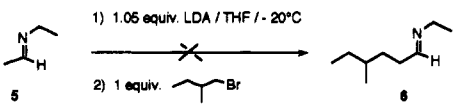
Results and Discussion

Up to now, only one synthesis of stenusine was published.[2] However, this synthetic sequence was not fully detailed in the literature and consists of seven steps often using sensitive reactions. The lack of a facile route to stenusine (4) left the opportunity to apply our recently developed ω-halo imine chemistry[3,4] in the synthesis of stenusine. The synthetic problem is therefore shifted to the synthesis of a suitable δ-chloro aldimine using the 1-azaallyl anion methodology.[5-7] However, alkylation of

Scheme I



Scheme II



the labile *N*-(ethylidene)ethylamine, 5, synthesized by condensation of ethylamine and acetaldehyde in toluene with magnesium sulfate as drying agent, with 1-bromo-2-methylbutane at low temperature did not lead to the alkylated aldimine 6. Several reaction conditions were evaluated without success, due to the lability of the imines 5 and 6. The competing acidity of the *N*-ethyl substituent in 5 and 6 certainly plays a major role in the failure. The reaction of aldimine 5 with lithium diisopropylamide and 1-bromo-2-methylbutane led to irreproducible results and to tar formation (Scheme II). Therefore, the more stable *N-tert*-butylamine 8 was chosen as alternative starting material for the alkylation with 1-bromo-2-methylbutane. The *N-tert*-butylimine 8 was synthesized by condensation of acetaldehyde and *tert*-butylamine without solvent at −10 °C.[8,9] The use of a solvent, e.g. dichloromethane, leads to an unseparable mixture of imine 8 and the solvent (an unacceptably low yield of some pure aldimine was obtained).

Deprotonation of aldimine 8 in THF at 0 °C using the strong nonnucleophilic base lithium diisopropylamide and alkylation with 1-bromo-2-methylbutane at −60 °C results in a mixture of the desired aldimine 9, the α,α-dialkylated aldimine 10, and some starting material 8 (Scheme III). α,α-Dialkylation occurs due to the competing acidity of the α-monoalkylated aldimine 9 compared to the starting material and could never be totally suppressed by altering the reaction conditions. The mixture of mono- and dialkyl imines 9 and 10 was fractionally distilled under reduced pressure in order to isolate the α-monoalkyl aldimine 9.

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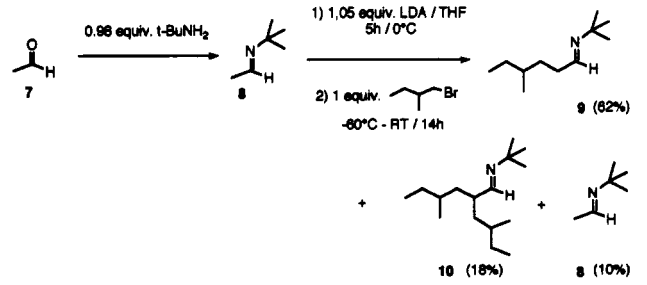
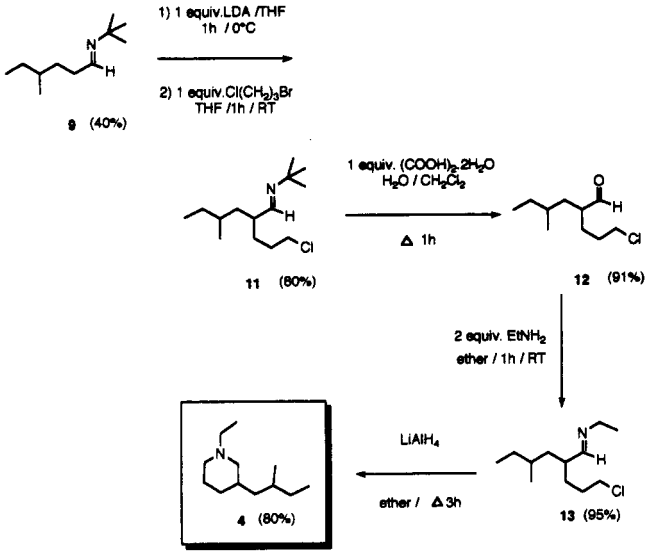
Scheme III



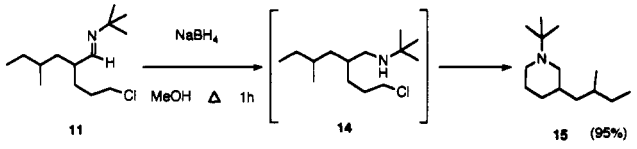
Scheme IV



This separation decreased the yield of the monoalkyl imine from 62% to 40% (pure aldimine **9**). Subsequent deprotonation of aldimine **9** by lithium diisopropylamide and reaction with 1-bromo-3-chloropropane leads to *N*-[2-(3-chloropropyl)-4-methyl-1-hexylidene]-*tert*-butylamine (**11**) in 80% yield (Scheme IV). In this reaction, no side products due to double alkylation were formed. This can be explained by steric hindrance and is especially a result of the reduced acidity of α-methine hydrogens as compared to α-methylene hydrogens.[6] δ-Chloro imine **11** occurs as a mixture of diastereoisomers (≈1:1) as evidenced by ^{13}C-NMR spectroscopy. In order to introduce the right *N*-alkyl substituent, the δ-halo imine **11** was hydrolyzed in a two-phase system (water/dichloromethane 1/1) using oxalic acid as an acid catalyst. The resulting δ-chloro aldehyde **12** was also obtained as a mixture of diastereoisomers (≈1:1) and could be used in the next step without further purification. Condensation of δ-chloro aldehyde **12** with ethylamine in ether leads to δ-chloro aldimine **13** in 95% yield. Noteworthy is the use of 2 equiv of ethylamine due to its high volatility. Also for δ-chloro aldimine **13**, two diastereoisomers (≈1:1) were detected by ^{13}C NMR. No purification was performed on this compound due to the extreme lability of the δ-chloro aldimine **13**. The spectral analysis proving the structure was done using the crude imine which was possible by the high degree of purity of the reaction mixture.

The final ring closure of the δ-chloro aldimine **13** to stenusine was accomplished by intramolecular nucleophilic substitution using lithium aluminum hydride in ether under reflux (yield: 80%). The fast reduction of the imino bond is followed by the intramolecular nucleophilic substitution. Purification of stenusine was performed by flash chromatography. The structural assignment is in accordance with the literature.[2] The diastereoisomers of stenusine (≈1:1) could be separated on a capillary GC column (RSL 150; 15 m; FID detector). The reaction route via δ-chloro aldimines resulted in a facile synthesis of stenusine (**4**) in 21% overall yield from acetaldehyde.

Scheme V



The 1-*tert*-butyl analogue of stenusine was synthesized from the intermediate **11**. Intramolecular nucleophilic substitution of imine **11** by reaction with sodium borohydride leads to 1-*tert*-butyl-3-(2-methylbutyl)piperidine (**15**) in 95% yield (Scheme V). This new piperidine also shows a tensioactive activity and a high spreading ability. In general, this methodology provides an entry to a diversity to 1,3-disubstituted piperidines.

The absolute and relative stereochemistry of stenusine are not known. The natural compound displays an optical rotation of $[\alpha]^{20}_{546}$ 5.8°.[2]

Although stenusine was synthesized by using (−)-1-bromo-2-methylbutane, no attention was paid to the stereochemistry at the 3-position of the piperidine ring.[2] Efforts are underway to synthesize the four possible stereoisomers of 1-ethyl-3-(2-methylbutyl)piperidine and to compare them with the naturally occurring stenusine.

Experimental Section

General Methods. ^{1}H-NMR spectra were recorded at 60 MHz with $CDCl_3$ as solvent. ^{13}C-NMR spectra were recorded at 20, 90, or 67.8 MHz. All solvents were dried extensively over sodium (ether), sodium/benzophenone ketyl (THF), or CaH_2 (CH_2Cl_2). The alkylation experiments of imines were performed under N_2.

***N*-Ethylideneethylamine (5).** To a solution of 15.38 g (0.35 mol) of acetaldehyde in 10 mL of toluene and 10 g (0.083 mol) of $MgSO_4$ was added 14.7 g (0.315 mol) of ethylamine at −40 °C, and the mixture was subsequently stirred for 1 h at rt. The mixture was filtered and distilled, yielding 4.36 of pure aldimine **5** (yield: 17% bp 58–60 °C (760 mm)). ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 3 H, J = 7.2 Hz), 1.90 (dt, 3 H, J = 4.8, 1 Hz), 3.33 (qt, 2 H, J = 7.2, 1.2 Hz), 7.63 (qxt, 1 H, J = 4.8, 1.2 Hz). IR (NaCl): 1650 cm^{-1} (broad) (C=N). ^{13}C NMR: δ 16.14 (q, Me), 21.93 (q, Me), 55.35 (t, CH_2), 159.71 (d, CH=N).

***N*-(4-Methyl-1-hexylidene)-*tert*-butylamine (9).** To a stirred solution of LDA, prepared from 6.79 g (0.068 mol) of diisopropylamine and 26.9 mL of *n*-butyllithium (2.5 N in hexane) in 80 mL of dry THF, was added dropwise at 0 °C a solution of 6.53 g (0.066 mol) of *N*-ethylidene-*tert*-butylamine (**5**) in 10 mL of THF. Stirring was continued at 0 °C for 5 h. Afterward a solution of 9.97 g (0.066 mol) of 1-bromo-2-methylbutane in 10 mL of THF was added in one portion at −60 °C, and the reaction mixture was allowed to warm up to rt and was stirred for 16 h. The mixture was then poured into 200 mL of aqueous NaOH (1 N) and extracted with ether (3 × 100 mL). After drying ($MgSO_4$), the solvent was removed leaving a mixture of **9** (62%), *N*-[2-(2-methylbutyl)-4-methyl-1-hexylidene]-*tert*-butylamine (**10**) (18%), and 10% of *N*-ethylidene-*tert*-butylamine (10%). High-vacuum distillation of the mixture yielded 4.46 of **9** (40%) (purity >98%; GC) (bp: 27–36 °C (0.01 mmHg)). ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 9 H, Me_3), 0.7–1.6 (m, 11 H), 2.0–2.4 (m, 2 H, CH_2C=N), 7.67 (t, 1 H, J = 5.0 Hz). IR (NaCl): 1672 cm^{-1} (C=N). MS: m/z 169 (3, M^+), 154 (30), 112 (19), 99 (100), 84 (92), 58 (27), 57 (26), 56 (46). Anal. Calcd for $C_{11}H_{23}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 78.2; H, 13.8; N, 8.1.

***N*-[2-(2-Methylbutyl)-4-methyl-1-hexylidene]-*tert*-butylamine (10)** was isolated by preparative GC from the

reaction mixture or from the remaining residue from the vacuum distillation. ^{1}H NMR ($CDCl_3$): 1.13 (s, 9 H, Me_3), 0.7–1.5 (m, 22 H), 2.35–2.6 (m, 1 H, CHC=N), 7.34 (dq, J = 7.0, 1.6 Hz). IR (NaCl): 1772 cm^{-1} (C=N). MS: m/z 238 (0.8, $M^+ - 1$), 183 (8), 169 (9), 154 (17), 112 (100), 57 (38), 56 (60).

***N*-[2-(3-Chloropropyl)-4-methyl-1-hexylidene]-*tert*-butylamine (11).** As described above 4.0 g (0.024 mol) of **9** in 50 mL of dry THF was deprotonated with 0.025 mol of LDA during 1 h at 0 °C and was subsequently alkylated with 3.71 g (0.024 mol) of 1-bromo-3-chloropropane at 0 °C and stirred for 2 h. The reaction mixture was then poured into 100 mL of aqueous NaOH (1 N) and extracted with ether (3 × 100 mL). After drying ($MgSO_4$), filtration, evaporation of the solvent, and distillation, 4.62 g (80%) of **11** was obtained with a purity of 97% (bp 68–70 °C 0.08 mmHg)). ^{1}H NMR ($CDCl_3$) δ 0.6–1.9 (m, 15 H), 1.18 (s, 9 H, tBu), 2.0–2.6 (m, 1 H, C*H*C=N), 3.55 (≈t, 2 H, J = 6 Hz), 7.39 and 7.41 (2 isomers; 1:1) (each d, 1 H, each J = 6.8 Hz). ^{13}C NMR (C_6D_6) 2 isomers (ratio ≈1:1): δ 11.17 and 11.43 (q, Me), 19.13 and 19.80 (t, CH_2), 29.07, 29.74 (q, tBu), 30.37 and 30.47, 32.20 and 32.31, 40.06 (t), 42.25 (d), 44.61 (t, CH_2Cl), 56.41 (s, *C*Me_3), 160.36 and 160.47 (d, *C*=N). IR (NaCl): 1670 cm^{-1} (C=N). MS: m/z 245/47 (1.6, M^+), 211 (12), 210 (12), 188/90 (13), 175/77 (29), 160/62 (50), 152/54 (54), 132/34 (25), 112 (96), 96 (100), 57 (86), 56 (64). Anal. Calcd for $C_{14}H_{28}ClN$: C, 68.40; H, 11.48; N, 5.70. Found: C, 68.2; H, 11.4; N, 5.5.

2-(3-Chloropropyl)-4-methylhexanal (12). A solution of 4.62 g (0.019 mol) of amine **11** in 46 mL of CH_2Cl_2 was stirred with a solution of 2.39 g (0.019 mol) of oxalic acid in 24 mL of water. The two-phase mixture was stirred and heated under reflux for 1 h and subsequently extracted with CH_2Cl_2. After drying ($MgSO_4$), filtration, and evaporation of the solvent in vacuo, compound **12** was obtained with a purity > 98%. Distillation yielded 3.28 g of the aldehyde **12** in 91% yield (purity: 99%; 2 isomers; ratio 1:1) (bp 58–61 °C (0.008 mmHg)). ^{1}H NMR ($CDCl_3$): δ 0.7–2.0 (m, 15 H), 2.2–2.7 (m, 1 H, C*H*C=O), 3.56 (≈t, 2 H, J = 6 Hz), 9.43 and 9.46 (each d, 1 H, each J = 2 Hz, 1:1). ^{13}C NMR (90 MHz) (2 diastereoisomers): δ 11.15 and 11.17, 19.03 and 19.22, 26.16 and 26.83, 29.35 and 29.75, 29.89 and 29.99, 32.11 and 32.22, 35.81 and 36.27, 44.66 and 44.71, 49.11 and 49.17, 204.68 and 204.76. IR (NaCl): 1727 cm^{-1} (CHO). MS: m/z 154 (2, M^+ – HCl) 133/35 (2), 120/2 (50), 71 (50), 70 (35), 57 (100). Anal. Calcd for $C_{10}H_{19}ClO$: C, 62.98; H, 10.04. Found: C, 63.0; H, 10.2.

***N*-[2-(3-Chloropropyl)-4-methyl-1-hexylidene]ethylamine (13).** To a solution of 3.26 g (0.017 mol) of δ-chloro aldehyde **12** in 30 mL of dry ether and 2 g of $MgSO_4$ was added dropwise 1.53 g (0.034 mol) of ethylamine, and the reaction mixture was stirred for 1 h. Filtration and evaporation yielded 1.38 g of **13** in 95% yield (purity >98%). ^{1}H NMR ($CDCl_3$) (2 isomers; 1:1): δ 0.6–2.0 (m, 15 H), 1.19 (t, 3 H, J = 7 Hz, NCC*H*$_3$), 2.0–2.6 (m, 1 H, C*H*C=N), 3.41 (qd, 2 H, J = 7 Hz, J ≈ 1.5 Hz), 3.56 (m, 2 H, CH_2Cl), 7.43 and 7.48 (each dt, overlap, 1 H, J ≈ 6 Hz). ^{13}C NMR (90 MHz) (C_6D_6) (2 isomers; 1:1): δ 11.22 and 11.45, 16.66 and 16.69, 19.01 and 19.21, 29.18 and 29.63, 30.36 and 30.46, 30.42, 32.05 and 32.21, 39.79 and 39.93, 41.82 and 41.85, 44.93, 55.81, 166.16 and 166.32. IR (NaCl) 1670 cm^{-1} (C=N). MS: m/z 217/19 (0.9, M^+), 202/04 (1), 160.62 (10), 147/49 (21), 124 (82), 84 (100), 56 (36), 44 (23), 41 (27). Anal. Calcd for $C_{12}H_{24}ClN$: C, 66.18; H, 11.11; Cl, 16.28; N, 6.43. Found: C, 66.3; H, 11.0; N, 6.6.

1-Ethyl-3-(2-methylbutyl)piperidine (Stenusine, 4). δ-Chloro aldimine **13** (1.13 g, 5.2 mmol) in 15 mL of dry ether was treated with 0.20 g (5.2 mmol) of lithium aluminum hydride, and the reaction mixture was stirred under reflux for 3 h. The mixture was then poured into 30 mL of aqueous sodium hydroxide (1 N) and extracted with ether (3 × 30 mL). After drying ($MgSO_4$), filtration, and evaporation of the solvent, the crude stenusine was purified by flash chromatography (silica gel, length 15 cm, eluent: ether/pentane, 1/1; R_f = 0.20) yielding 0.86 g (80%) of pure stenusine (purity >98%; GC). The isolation was monitored by TLC, whereby stenusine was visualized by cobalt(II) thiocyanate staining. ^{1}H NMR (270 MHz) ($CDCl_3$): δ 0.78 (d, 3 H, J = 6.2 Hz), 0.78 (t, 3 H, J = 7.2 Hz), 1.01 (t, 3 H, J = 7.2 Hz, C*H*$_3$CN), 1.0–1.75 (m, 10 H), 2.2–2.35 (m, 2 H), 2.7–2.9 (m, 4 H). ^{13}C NMR (67.8 MHz) ($CDCl_3$; 2 isomers; ratio ≈ 1:1): δ 11.49 and 11.57 (q, Me), 12.29 and 12.31 (q, Me), 19.56 and 19.75 (q, Me), 25.89 and 25.94, 29.88 and 30.23, 31.88 and 31.47, 32.29, 33.83 and 33.93, 42.18 and 42.39, 53.11 and 53.13, 54.13 and 54.18 (t, CH_2N), 60.65 and 61.33 (t, CH_2N). IR (NaCl): 2930, 1460, 1380, 1148, 1089 cm^{-1}. MS: m/z 183 (25, M^+), 182 (19), 168 (100), 155 (11), 136 (5), 113 (6), 112 (9), 98 (17), 96 (7), 85 (15), 84 (11), 72 (44), 71 (7), 70 (6), 69 (8), 58 (75), 57 (17), 44 (24), 42 (13), 41 (16). Anal. Calcd for $C_{12}H_{25}N$: C, 78.62: h, 13.75; N, 7.64. Found: C, 78.7; H, 13.9; N, 7.5.

1-*tert*-Butyl-3-(2-methylbutyl)piperidine (15). To a solution of 0.74 g (3 mmol) of *N*-[2-(3-chloropropyl)-4-methyl-1-hexylidene]-*tert*-butylamine (**11**) in 10 mL of methanol was added 125 mg (3.3 mmol) of sodium borohydride, and the mixture was refluxed for 1 h. The reaction mixture was then poured into 200 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). After drying ($MgSO_4$), filtration, and evaporation of the solvent, the crude product was purified by flash chromatography (silica gel, length 19 cm, eluent: ether/pentane, 1/1, R_f = 0.22) yielding 0.6 g (95%) of 1-*tert*-butyl-3-(2-methylbutyl)piperidine, **15**. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9 H), 0.7–2.0 (m, 16 H), 2.2–3.2 (m, 4 H). ^{13}C NMR (90 MHz) ($CDCl_3$; 2 isomers, ratio ≈ 1:1): δ 11.24 and 11.34, 19.29 and 19.59, 26.12, 26.48 and 26.50, 29.18, 29.57 and 30.15, 31.35, 32.27, 34.35 and 34.42, 42.17 and 42.37, 46.75, 53.11 and 53.81. IR (NaCl): 2960, 1465, 1379, 1359, 1222, 1210 cm^{-1}. MS: m/z 211 (6 M^+), 196 (100), 69 (8), 58 (10), 57 (15), 56 (6), 55 (13), 44 (23), 41 (20). Anal. Calcd for $C_{14}H_{29}N$: C, 79.55; H, 13.83; N, 6.63. Found: C, 79.4; H, 13.7; N, 6.4.

Registry No. (±)-**4** (isomer 1), 144301-02-0; (±)-**4** (isomer 2), 144301-03-1; **5**, 1190-79-0; **7**, 75-07-0; **8**, 7020-80-6; (±)-**9**, 144226-82-4; **10**, 144226-83-5; (±)-**11** (isomer 1), 144226-84-6; (±)-**11** (isomer 2), 144226-85-7; (±)-**12** (isomer 1), 144226-86-8; (±)-**12** (isomer 2), 144226-87-9; (±)-**13** (isomer 1), 144240-88-0; (±)-**13** (isomer 2), 144240-89-1; (±)-**15** (isomer 1), 144226-88-0; (±)-**15** (isomer 2), 144226-89-1; $Cl(CH_2)_3Br$, 109-70-6; ethylamine, 75-04-7; (±)-1-bromo-2-methylbutane, 5973-11-5.