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Short synthesis of stenusine and norstenusine, two spreading alkaloids from *Stenus* beetles (Coleoptera: Staphylinidae)

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Abstract—Each of the both spreading alkaloids stenusine and norstenusine could be synthesized starting from commercially available 3-picoline in a two-step synthesis in yields of 74% and 67% in gram scale. The stereoisomeric ratio of the synthesized (+)-stenusine is similar to that of stenusine from *Stenus comma*.

1. Introduction

The rove beetle genus *Stenus* comprises 1990 species worldwide[1] and about 120 species in Central Europe. *Stenus comma* LeConte, the most common species of the genus, lives in sandy banks of ponds and sluggishly flowing rivers.[2] The beetle has no ability to swim, but during its hunting for its prey, it often falls into the water. In order to avoid drowning, the beetle releases a surface-active fluid from the pygidial glands. This fluid propels the beetle over the water with a speed up to 75 cm/s. The Schildknecht group found that stenusine exhibits a high spreading capacity.[2] The surface-active oil contains some other compounds such as 1,8-cineol, isopiperitenol and 6-methyl-5-hepten-2-one.[3] Norstenusine[4] and actinidine[5] could be detected in other *Stenus* species. Actinidine shows a knock-down effect to other insects.

Our objectives are the determination of the repellent activity of stenusine and norstenusine against predators and the analysis of their surface activity. For these reasons we were interested in the synthesis of stenusine (**1**) and norstenusine (**2**) (Fig. 1).

Numerous preparations of stenusine have been developed. The enantioselective 12-step synthesis of Enders et al.[6] started from 5-*tert*-butyldimethylsilyloxypentanol[7] and gave (2′*S*,3*S*)- and (2′*S*,3*R*)-stenusine in total yields of 7.8% and 5.7%. By means of the both diastereomeric compounds, the ratio of the four stereoisomers (2′*R*,3*R*):(2′*S*,3*R*):(2′*S*,3*S*):(2′*R*,3*S*) of natural stenusine from *S. comma* could be determined by chiral GC: 13%:40%:43%:4%. These four stenusine isomers in a ratio of 9%:36%:43%:12% could also be obtained in a two-step biomimetic route with a yield of 26% starting from (*R*)-phenylglycinol and glutaraldehyde. Since the found ratio of stereoisomers is similar to that of natural stenusine from *S. comma*, the authors consider this as a confirmation of their hypothesis for the biosynthesis of stenusine.[8]

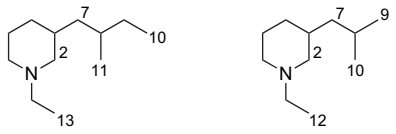

Figure 1. Stenusine (**1**) and norstenusine (**2**). The numbering of the N- and C-atoms of **1** and **2** is used for the NMR assignments.

2. Results and discussion

As we could demonstrate other *Stenus* species show completely different stenusine stereoisomer ratios.[9] Stenusine from *Stenus juno* possesses mainly (2′*R*,3*R*)-configuration (88%), whereas in *Stenus clavicornis*, *Stenus providus* and *Stenus bimaculatus* the (2′*S*,3*R*)-stereoisomer dominates (95%, 95%, 76%). For *Stenus fulvicornis* (2′*R*,3*S*)-stenusine was found as the main peak (90%). This shows that the biosynthesis of stenusine in other *Stenus* species than *S. comma* is highly enantio- and diastereoselective.

Although our synthesis of stenusine (**1**) is not based on a biomimetic route, it leads also to a stereoisomer ratio (2′*R*,3*R*):(2′*S*,3*R*):(2′*S*,3*S*):(2′*R*,3*S*) of 10%:29%:54%:7%, which is similar to the natural stenusine from *S. comma* (Fig. 2).

Keywords: Alkaloids; Asymmetric synthesis; Stenusine; *Stenus comma*; Staphylinidae.
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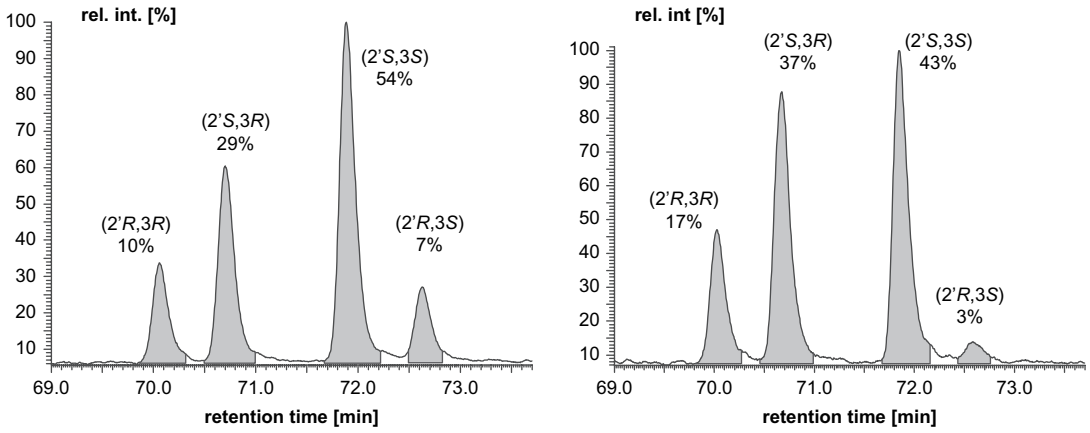
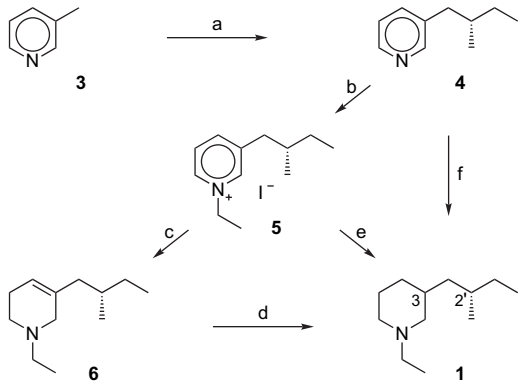


Figure 2. Gas chromatogram of synthetic (left) and natural (right) stenusine (**1**) from *S. comma*, fused with silica capillary column (30 m, 0.25 mm ID), coated with 0.25 µm film of 0.4% heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)β-cyclodextrin (30%) in SE 52 (70%), carrier gas He, temperature program 60 °C (20 min isothermal), heating rate 2 °C/min to 200 °C. Capillary column was self-prepared by D. Burkhardt and A. Mosandl, University of Frankfurt am Main.

The alkylation of the methyl group of 3-picoline (**3**) with (*R*)-2-bromobutane gives 82% yield with 66% ee (*S*)-3-(2′-methylbutyl)pyridine (**4**, 83%) and its (*R*)-enantiomer (**4**, 17%). This enantiomeric mixture reacts with ethyl iodide quantitatively to yield 1-ethyl-3-(2′-methylbutyl)pyridinium iodide (**5**). Reduction of **5** with $NaBH_4$ leads to 3,4-didehydrostenusine (**6**), which can be transformed by catalytic hydrogenation under normal pressure to four stereoisomers of stenusine (**1**). Catalytic hydrogenation of the pyridinium salt **5** at a hydrogen pressure of 10 bar gives 90% yield of the four stenusine isomers (**1**) and so the total yield over three steps starting from 3-picoline is 74% (Scheme 1).



Scheme 1. Synthesis of stenusine (**1**). Reagents and conditions: (a) LDA, THF, 0 °C; (*R*)-2-bromobutane, THF, −78 °C to room temperature, 82%; (b) EtI, 90 °C, 0.5 h, 100%; (c) $NaBH_4$, MeOH/THF 2:1, −78 °C to room temperature, 96%; (d) H_2 (normal pressure), Pd/C, EtOAc, 35 °C, 89%; (e) H_2 (10 bar), Pd/C, MeOH, room temperature, 16 h, 90%; (f) H_2 (20 bar), Pd/C, MeCHO, MeCOOH, 30 °C, 24 h, 90%.

A further distinct improvement of the stenusine synthesis can be achieved by reaction of 3-(2′-methylbutyl)pyridine (**4**) with acetaldehyde under hydrogenating conditions. In this way **1** can be synthesized in two steps with 74% yield (Scheme 1).

The use of 2-bromopropane instead of (*R*)-2-bromobutane for the alkylation of 3-picoline methyl group gives 81% yield of 3-isopropylpyridine (**7**), which can be transformed in an analogous way as **4** with comparable yields in a three- or two-step reaction sequence to racemic norstenusine (**2**).

In order to demonstrate that stenusine (**1**) and norstenusine (**2**) are surface-active compounds, the surface tension was determined by means of the pendant drop tensiometry at 22 °C. At a concentration of 0.125% of stenusine (**1**) or norstenusine (**2**) in an aqueous 0.1 M phosphate buffer, a surface tension of about 60 mN/m is observed (Fig. 3). Even at 0.05% stenusine concentration, a distinct lowering of the surface tension (65 mN/m) compared with water (72.8 mN/m) is observed. Sodium phosphate is as electrolyte surface inactive, so that the comparison of the surface tensions of stenusine (**1**) and norstenusine (**2**) in phosphate buffer with water is justified.

3. Experimental

3.1. Alkylation of 3-picoline (3)

3.1.1. Alkylation with (*R*)-2-bromobutane. A mixture of diisopropylamine (7.4 ml, 5.3 g, 52.5 mmol) in abs THF (120 ml) under argon is cooled to −30 °C. To this mixture *n*-BuLi (21.0 ml, 2.5 M, 52.5 mmol) is added under stirring. After 1 h, 3-picoline (**3**, 4.8 ml, 4.7 g, 50 mmol) is slowly added and stirring is continued for 1 h at 0 °C. (*R*)-2-Bromobutane (5.5 ml, 6.9 g, 50 mmol) is slowly added to the deep brown solution at −78 °C and the mixture is warmed to room temperature overnight. The reaction mixture is diluted with half saturated NH_4Cl solution, the organic phase is separated and the aqueous phase extracted three times with EtOAc. The combined organic phases are washed with saturated NaCl solution and dried with $MgSO_4$. After filtration through Celite® and removing the solvent under vacuum, 3-(2′-methylbutyl)pyridine (**4**, 6.95 g, 47 mmol, 93%, crude product) is obtained. Distillation gives **4** (6.10 g, 40.9 mmol, 82%) as colourless oil. $[\alpha]_D^{23}$ +5.8 (*c* 2.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.38 (dd, 1H, 6-H, $^3J_{6,5}$=4.9 Hz, $^4J_{6,4}$=1.6 Hz), 8.36 (br s, 1H, 2-H), 7.40 (dd, 1H, 4-H, $^3J_{4,5}$=7.8 Hz, $^4J_{4,6}$=1.6 Hz), 7.14 (ddd, 1H, 5-H, $^3J_{5,4}$=7.8 Hz, $^3J_{5,6}$=4.9 Hz, $^5J_{5,2}$=1.0 Hz), 2.58 (dd, 1H, 7-H_a, $^2J_{7a,7b}$=13.7 Hz, $^3J_{7a,8}$=6.1 Hz), 2.32 (dd, 1H, 7-H_b, $^2J_{7a,7b}$=13.7 Hz, $^3J_{7b,8}$=8.2 Hz), 1.59 (m_c, 1H, 8-H), 1.34, 1.14 ($2m_c$, 2H, 9-H), 0.87 (dd, 3H, 10-H, $^3J_{10,9}$=7.5 Hz), 0.80 (d, 3H, 11-H, $^3J_{11,8}$=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=150.3 (2-C), 146.9 (6-C), 136.5 (3-C),

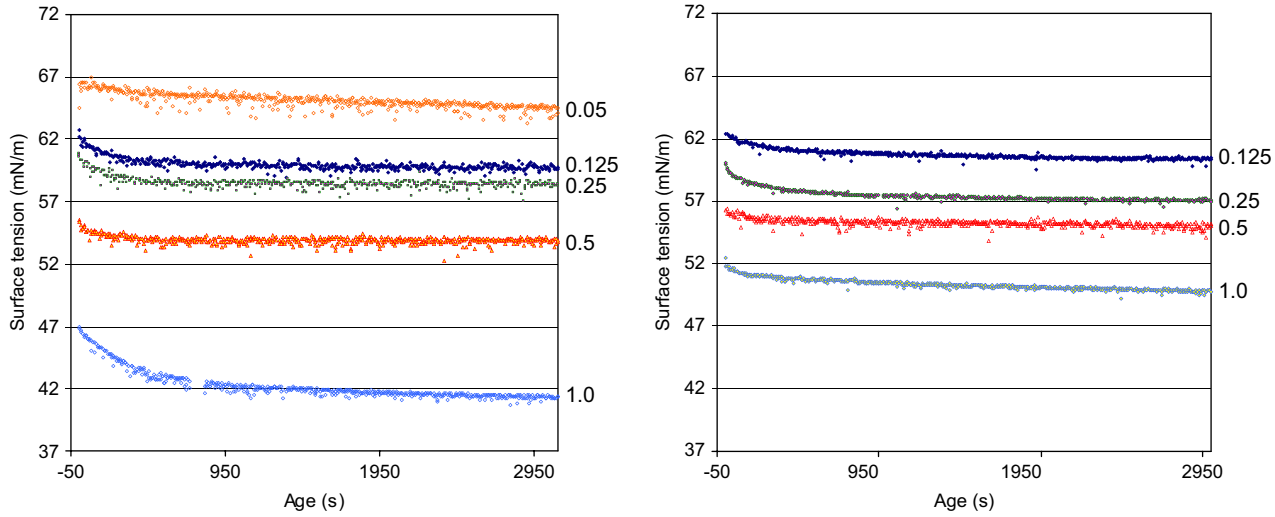


Figure 3. Surface tension of stenusine (**1**) (left) and norstenusine (**2**) (right) in 0.1 M phosphate buffer (pH 6) determined by means of pendant drop tensiometry at 22 °C.

136.2 (4-C), 122.9 (5-C), 40.0 (7-C), 36.2 (8-C), 28.8 (9-C), 18.5 (11-C), 11.1 (10-C); GC–MS, EI$^+$: *m/z* (%)=150 (4) [M+H$^+$], 149 (28) [M$^+$], 118 (5), 93 (100) [$C_6H_7N^+$], 92 (18), 65 (13), 57 (21) [$C_4H_9^+$], 41 (20) [$C_3H_5^+$]; HRMS (70 eV): 149.1204 [$C_{10}H_{15}N^+$] (calcd 149.1205), 93.0579 [$C_6H_7N^+$] (calcd 93.0579), 57.0704 [$C_4H_9^+$] (calcd 57.0704).

3.1.2. Alkylation with isopropyl bromide. 3-Picoline (**3**, 4.8 ml, 4.7 g, 50 mmol), isopropyl bromide (4.7 ml, 6.15 g, 50 mmol). Yield of 3-isobutylpyridine (**7**): 6.26 g, 46.3 mmol, 93%, crude product; after distillation 5.48 g, 40.5 mmol, 81%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 8.28 (dd, 1H, 6-H, $^3J_{6,5}$=4.9 Hz, $^4J_{6,4}$=1.7 Hz), 8.26 (br s, 1H, 2-H), 7.30 (dd, 1H, 4-H, $^3J_{4,5}$=7.8 Hz, $^4J_{4,6}$=1.7 Hz), 7.04 (dd, 1H, 5-H, $^3J_{5,4}$=7.8 Hz, $^3J_{5,6}$=4.9 Hz), 2.32 (d, 2H, 7-H, $^3J_{7,8}$=7.5 Hz), 1.72 (m$_c$, 1H, 8-H), 0.73 (d, 6H, 9-H, 10-H, $^3J_{8,9/10}$=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=150.2 (2-C), 146.9 (6-C), 136.3 (3-C), 136.0 (4-C), 122.7 (5-C), 42.0 (7-C), 29.7 (8-C), 21.8 (9-C, 10-C); GC–MS, EI$^+$: *m/z* (%)=135 (41) [M$^+$], 118 (3), 93 (100) [$C_6H_7N^+$], 92 (27), 66 (6), 65 (14), 51 (4), 43 (20), 41 (10) [$C_3H_5^+$], 39 (13); HRMS (70 eV): 135.1048 [$C_9H_{13}N^+$] (calcd 135.1048), 93.0578 [$C_6H_7N^+$] (calcd 93.0579), 41.0391 [$C_3H_5^+$] (calcd 41.0391).

3.2. N-Ethylation

3.2.1. N-Ethylation of 3-(2′-methylbutyl)pyridine (4) with ethyl iodide. Under argon, ethyl iodide (2.90 ml, 5.57 g, 35.7 mmol) is added to 3-(2′-methylbutyl)pyridine (**4**, 3.55 g, 23.8 mmol) and heated for 30 min under reflux (temperature of the oil bath 90 °C). The surplus ethyl iodide is distilled off under vacuum and 1-ethyl-3-(2′-methylbutyl)-pyridinium iodide (**5**) is obtained in quantitative yield (7.27 g, 23.8 mmol, 100%) as viscous pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=9.23 (br s, 1H, 2-H), 9.13 (d, 1H, 6-H, $^3J_{6,5}$=6.1 Hz), 8.10 (d, 1H, 4-H, $^3J_{4,5}$=8.0 Hz), 7.91 (dd, 1H, 5-H, $^3J_{5,6}$=6.1 Hz, $^3J_{5,4}$=8.0 Hz), 4.79 (q, 2H, 12-H, $^3J_{12,13}$=7.4 Hz), 2.73 (dd, 1H, 7-H$_a$, $^2J_{7a,7b}$=13.8 Hz, $^3J_{7a,8}$=6.1 Hz), 2.50 (dd, 1H, 7-H$_b$, $^2J_{7b,7a}$=13.8 Hz, $^3J_{7b,8}$=8.3 Hz), 1.61 (m$_c$, 1H, 8-H), 1.52 (t, 3H, 13-H, $^3J_{13,12}$=7.4 Hz), 1.18, 1.01 (2m$_c$, je 1H, 9-H), 0.69 (dd, 3H, 10-H, $^3J_{10,9}$=7.3 Hz), 0.66 (d, 3H, 11-H, $^3J_{11,8}$=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=145.1 (2-C), 143.5 (6-C), 142.7 (3-C), 141.5 (4-C), 127.5 (5-C), 56.4 (12-C), 38.9 (7-C), 35.3 (8-C), 28.3 (9-C), 18.0 (11-C), 16.9 (13-C), 10.7 (10-C).

3.2.2. N-Ethylation of 3-isobutylpyridine (7) with ethyl iodide. 3-Isobutylpyridine (**7**, 3.92 g, 29.0 mmol), ethyl iodide (3.50 ml, 6.74 g, 43.2 mmol). Yield of 1-ethyl-3-isobutylpyridinium iodide (**8**): 8.44 g, 29.0 mmol, 100%, crude product. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=9.03 (br s, 1H, 2-H), 8.99 (d, 1H, 6-H, $^3J_{6,5}$=6.1 Hz), 7.94 (d, 1H, 4-H, $^3J_{4,5}$=7.9 Hz), 7.80 (dd, 1H, 5-H, $^3J_{5,6}$=6.1 Hz, $^3J_{5,4}$=7.9 Hz), 4.63 (q, 2H, 11-H, $^3J_{11,12}$=7.2 Hz), 2.50 (d, 2H, 7-H, $^3J_{7,8}$=7.6 Hz), 1.76 (m$_c$, 1H, 8-H), 1.43 (t, 3H, 12-H, $^3J_{12,11}$=7.2 Hz), 0.72 (2d, 6H, 9-H, 10-H, $^3J_{9/10,8}$= 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=144.6 (2-C), 144.5 (6-C), 142.8 (3-C), 142.3 (4-C), 127.7 (5-C), 56.8 (11-C), 41.0 (7-C), 29.3 (8-C), 21.6 (9-C, 10-C), 16.9 (12-C).

3.3. Partial reduction of the pyridinium salts to the tetrahydropyridines

3.3.1. Reduction of 1-ethyl-3-(2′-methylbutyl)pyridinium iodide (5). Compound **5** (3.51 g, 11.5 mmol) is dissolved under argon in MeOH/THF (2:1, 120 ml) and cooled to −78 °C. $NaBH_4$ (1.30 g, 34.5 mmol) is added, the mixture is stirred for 20 min at −78 °C, warmed to room temperature overnight and cooled again to −78 °C. $NaBH_4$ (0.87 g, 23 mmol) is added and the reaction mixture is warmed to room temperature for 5 h. To stop the reaction, 2 N HCl (125 ml, 250 mmol) is added and stirred for 1 h at room temperature. To prevent the oxidation of iodide by air, a small amount of Na_2SO_3 is added, the volume of the reaction mixture is reduced to about 1/5 and 2 N KOH (about 100 ml) is added (pH>10). The mixture is extracted three times with EtOAc (50 ml), the combined organic layers are washed with saturated NaCl solution and dried with $MgSO_4$. After filtration through Celite® and removing the solvent crude

product (2.09 g, 11.5 mmol, 100%), from which **5** (91 mg, 0.30 mmol, 3%) is separated as viscous oil. The resulting 1-ethyl-3-(2′-methylbutyl)-1,2,5,6-tetrahydropyridine (**6**, 3,4-didehydrostenusine, 2.00 g, 11.0 mmol, 96%) is not further purified. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=5.35 (m_c, 1H, 4-H), 2.74 (m_c, 2H, 2-H), 2.41 (m_c, 2H, 6-H), 2.40 (q, 2H, 12-H, $^3J_{12,13}$=7.3 Hz), 2.10 (m_c, 2H, 5-H), 1.89 (dd, 1H, 7-H_a, $^2J_{7a,7b}$=13.6, $^3J_{7a,8}$=6.3 Hz), 1.65 (dd, 1H, 7-H_b, $^2J_{7b,7a}$=13.6, $^3J_{7b,8}$=8.2 Hz), 1.40 (m_c, 1H, 8-H), 1.30, 1.02 (2m_c, 2H, 9-H), 1.06 (t, 3H, 13-H, $^3J_{13,12}$=7.3 Hz), 0.80 (dd, 3H, 10-H, $^3J_{10,9a}$=$^3J_{10,9b}$=7.5 Hz), 0.76 (d, 3H, 11-H, $^3J_{11,8}$=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=135.0 (3-C), 120.1 (4-C), 55.5 (2-C), 52.2 (12-C), 49.7 (6-C), 43.3 (7-C), 32.4 (8-C), 29.3 (9-C), 26.0 (5-C), 19.0 (11-C), 12.2 (13-C), 11.3 (10-C); GC–MS, EI$^+$: *m/z* (%)=181 (17) [M^+], 180 (7) [M^+-H], 166 (19) [M^+-CH_3], 152 (3) [$M^+-C_2H_5$], 124 (100) [$M^+-C_4H_9$], 110 (35) [$M^+-C_5H_{11}$], 96 (7) [$C_6H_{10}N^+$], 82 (4) [$C_5H_8N^+$], 68 (13) [$C_5H_8^+$], 56 (7) [$C_3H_6N^+$], 42 (12) [$C_2H_4N^+$], 41 (11); HRMS (70 eV): 181.1831 [$C_{12}H_{23}N^+$] (calcd 181.1831), 166.1596 [$C_{11}H_{20}N^+$] (calcd 166.1596), 124.1126 [$C_8H_{14}N^+$] (calcd 124.1126), 110.0970 [$C_7H_{12}N^+$] (calcd 110.0970), 68.0628 [$C_5H_8^+$] (calcd 68.0626).

3.3.2. Reduction of 1-ethyl-3-isobutylpyridinium iodide (8). 1-Ethyl-3-isobutylpyridinium iodide (**8**, 4.22 g, 14.5 mmol). Yield of 1-ethyl-3-isobutyl-1,2,5,6-tetrahydropyridine (**9**, 3,4-didehydronorstenusine): 2.27 g, 13.6 mmol, 94%, crude product. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.30 (m_c, 1H, 4-H), 2.70 (m_c, 2H, 2-H), 2.36 (m_c, 2H, 6-H), 2.36 (q, 2H, 11-H, $^3J_{11,12}$=7.3 Hz), 2.06 (m_c, 2H, 5-H), 1.70 (d, 2H, 7-H, $^3J_{7,8}$=6.8 Hz), 1.60 (m_c, 1H, 8-H), 1.01 (t, 3H, 12-H, $^3J_{12,11}$=7.3 Hz), 0.76 (d, 6H, 9-H, 10-H, $^3J_{9/10,8}$=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 135.0 (3-C), 119.9 (4-C), 55.3 (2-C), 52.0 (11-C), 49.6 (6-C), 45.2 (7-C), 26.0 (8-C), 25.9 (5-C), 22.3 (9-C, 10-C), 12.1 (12-C); GC–MS, EI$^+$: *m/z* (%)=167 (32) [M^+], 166 (23) [M^+-H], 152 (11) [M^+-CH_3], 136 (3) [$M^+-CH_2CH_3$], 124 (100) [$M^+-C_3H_7$], 122 (9), 110 (83) [$M^+-CH_3-C_3H_6$], 108 (13), 95 (23) [$C_7H_{11}^+$], 81 (13), 68 (33) [$C_4H_6N^+$], 67 (18), 58 (12), 56 (7) [$C_3H_6N^+$], 55 (9), 42 (34) [$C_2H_4N^+$], 41 (23), 39 (8).

3.4. Catalytic hydrogenation of the tetrahydropyridines

3.4.1. Hydrogenation of 3,4-didehydrostenusine (6). Compound **6** (2.00 g, 11.0 mmol) is dissolved in EtOAc (30 ml) and palladium on charcoal (10%, 585 mg, 0.55 mmol, 5 mol %) is added under argon. After four evacuations and fillings with hydrogen, the mixture is heated to 35 °C and stirred until the appropriate amount of hydrogen (250 ml) is consumed. The reaction mixture is filtered through Celite®, the solvent is removed and the crude product (1.97 g, 10.7 mmol, 98%) is purified by column chromatography on silica gel with EtOAc as solvent to yield stenusine (**1**, 1.79 g, 9.8 mmol, 89%) as a colourless oil.

3.4.2. Hydrogenation of 3,4-didehydronorstenusine (9). 3,4-Didehydronorstenusine (**9**, 4.54 g, 27.2 mmol). Yield of 1-ethyl-3-isobutylpiperidine (**2**, norstenusine): 4.47 g, 26.4 mmol, 97%, crude product; after distillation 3.64 g, 21.5 mmol, 79%.

3.5. Hydrogenation and N-ethylation of the 3-alkylpyridines

3.5.1. Hydrogenation and N-ethylation of 3-(2′-methylbutyl)pyridine (4). Since the acid amount is critical for a fast reaction the amount of 3-(2′-methylbutyl)pyridine (**4**, 6.95 g, 46.6 mmol) is divided into two parts and each of them (**4**, 3.47 g, 23.3 mmol) is dissolved in concentrated acetic acid (80 ml). After the addition of palladium on charcoal (10%, 620 mg, 0.58 mmol, 2.5 mol %) and acetaldehyde (2.0 ml, 1.54 g, 35.0 mmol), the mixture is hydrogenated for 24 h in an autoclave at a hydrogen pressure of 20 bar and 30 °C. The two reaction mixtures are combined, filtered through Celite® and evaporated under vacuum to a volume of about 20 ml. Solid KOH is added until pH value of 10 is reached. The mixture is extracted four times with EtOAc (100 ml), the organic layer is dried with $MgSO_4$, evaporated and the crude product (8.36 g, 45.6 mmol, 98%) is degassed (inhibition of foam formation) by cooling three times with liquid nitrogen and slow heating to room temperature under vacuum. Distillation gives stenusine (**1**, 7.70 g, 42.0 mmol, 90%) as colourless oil. Bp 75 °C (15 Torr); $[\alpha]_D^{26}$ +10.3 (*c* 2.01, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=2.83 (m_c, 2H, 6-H_a), 2.81 (m_c, 1H, 2-H_a, (2′*S*,3*S*)-diastereomer), 2.77 (m_c, 1H, 2-H_a, (2′*S*,3*R*)-diastereomer), 2.32 (m_c, 4H, 12-H), 1.71 (m_c, 2H, 6-H_b), 1.70 (m_c, 1H, 4-H_a, (2′*S*,3*R*)-diastereomer), 1.64 (m_c, 1H, 4-H_a, (2′*S*,3*S*)-diastereomer), 1.58 (m_c, 2H, 8-H), 1.56 (m_c, 2H, 5-H_a), 1.52 (m_c, 2H, 5-H_b), 1.42 (m_c, 1H, 2-H_b, (2′*S*,3*R*)-diastereomer), 1.40 (m_c, 1H, 2-H_b, (2′*S*,3*S*)-diastereomer), 1.33 (m_c, 2H, 3-H), 1.23 (m_c, 2H, 9-H_a), 1.07 (m_c, 2H, 7-H_a), 1.05 (m_c, 2H, 9-H_b), 1.00 (t, 6H, 13-H, $^3J_{13,12}$=7.3 Hz), 0.88 (m_c, 2H, 7-H_b), 0.78 (m_c, 12H, 11-H, 10-H), 0.77 (m_c, 1H, 4-H_b, (2′*S*,3*S*)-diastereomer), 0.73 (m_c, 1H, 4-H_b, (2′*S*,3*R*)-diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$): (2′*S*,3*S*)-diastereomer: δ (ppm)= 60.3 (2-C), 53.8 (6-C), 52.8 (12-C), 42.1 (7-C), 33.5 (8-C), 31.9 (4-C), 31.1 (3-C), 29.5 (9-C), 25.6 (5-C), 19.4 (11-C), 12.0 (13-C), 11.1 (10-C); (2′*S*,3*R*)-diastereomer: δ (ppm)= 61.0 (2-C), 53.8 (6-C), 52.8 (12-C), 41.8 (7-C), 33.6 (8-C), 31.1 (3-C), 31.0 (4-C), 29.9 (9-C), 25.5 (5-C), 19.2 (11-C), 12.0 (13-C), 11.2 (10-C); GC–MS, EI$^+$: *m/z* (%)=183 (23) [M^+], 182 (23) [M^+-H], 168 (100) [M^+-CH_3], 154 (14) [$M^+-C_2H_5$], 126 (7) [$M^+-C_4H_9$], 124 (9), 112 (10) [$M^+-C_5H_{11}$], 110 (4), 98 (14) [$M^+-CH_3-C_5H_{10}$], 96 (8), 85 (10) [$C_5H_{11}N^+$], 84 (9) [$C_5H_{10}N^+$], 72 (33) [$C_4H_{10}N^+$], 58 (44) [$C_3H_8N^+$], 57 (13) [$C_4H_9^+$], 44 (5), 42 (10), 41 (11); HRMS (70 eV): 183.1987 [$C_{12}H_{25}N^+$] (calcd 183.1987), 168.1752 [$C_{11}H_{22}N^+$] (calcd 168.1752), 126.1283 [$C_8H_{16}N^+$] (calcd 126.1283), 112.1126 [$C_7H_{14}N^+$] (calcd 112.1126), 98.0969 [$C_6H_{12}N^+$] (calcd 98.0970), 85.0892 [$C_5H_{11}N^+$] (calcd 85.0892), 72.0813 [$C_4H_{10}N^+$] (calcd 72.0813).

3.5.2. Hydrogenation and N-ethylation of 3-isobutylpyridine (7). 3-Isobutylpyridine (**7**, 6.26 g, 46.3 mmol) is divided into two parts and to each of them (**7**, 3.13 g, 23.1 mmol) acetaldehyde (2.0 ml, 1.54 g, 35.0 mmol) is added. Yield of 1-ethyl-3-isobutylpiperidine (**2**, norstenusine): 7.46 g, 44.0 mmol, 95%, crude product; after distillation 6.52 g, 38.5 mmol, 83%. Bp 69 °C (15 Torr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.83 (m_c, 1H, 6-H_a), 2.78 (m_c, 1H, 2-H_a), 2.31 (m_c, 2H, 11-H), 1.73 (m_c, 1H, 6-H_b), 1.66 (m_c, 1H, 4-H_a), 1.57 (m_c, 3H, 3-H, 5-H_a, 8-H), 1.48 (m_c, 1H, 5-H_b), 1.42 (dd, 1H, 2-H_b, $^2J_{2b,2a}$=$^3J_{2b,3}$=10.8 Hz), 1.02 (t, 3H,

12-H, $^3J_{12,11}$=7.3 Hz), 0.97 (dd, 2H, 7-H, $^3J_{7,8}$=$^3J_{7,3}$= 6.8 Hz), 0.81, 0.79 (2d, 6H, 9-H, 10-H, $^3J_{9,8}$=$^3J_{10,8}$= 6.3 Hz), 0.74 (m_c, 1H, 4-H_b); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=60.6 (2-C), 53.8 (6-C), 52.8 (11-C), 44.2 (7-C), 33.7 (3-C), 31.4 (4-C), 25.6 (5-C), 24.7 (8-C), 23.0 (9-C), 22.7 (10-C), 12.0 (12-C); GC–MS, EI$^+$: *m*/*z* (%)=169 (32) [M^+], 168 (31) [M^+-H], 154 (100) [M^+-CH_3], 140 (5) [$M^+-C_2H_5$], 126 (8) [$M^+-C_3H_7$], 112 (7) [$M^+-C_4H_9$], 110 (5), 98 (14) [$M^+-CH_3-C_4H_8$], 96 (8), 85 (11) [$C_5H_{11}N^+$], 84 (10) [$C_5H_{10}N^+$], 72 (39) [$C_4H_{10}N^+$], 69 (10), 58 (73) [$C_3H_8N^+$], 57 (17) [$C_4H_9^+$], 55 (11), 42 (15) [$C_2H_4N^+$], 41 (15); HRMS (70 eV): 169.1830 [$C_{11}H_{23}N^+$] (calcd 169.1831), 154.1596 [$C_{10}H_{20}N^+$] (calcd 154.1596), 126.1283 [$C_8H_{16}N^+$] (calcd 126.1283), 112.1126 [$C_7H_{14}N^+$] (calcd 112.1126), 98.0969 [$C_6H_{12}N^+$] (calcd 98.0970).

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