Cu^{I}/Cu^{II} mixed-valence complex $\mathbf{C^{12m}}$: A solution of ferrocenium (BF_4 salt) (0.003 g, 0.01 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of $\mathbf{C^{12}}$ (0.04 g, 0.01 mmol) in anhydrous CH_2Cl_2 (10 mL) at 20 °C. After stirring for 2 h, the solvent was removed. Crystallisation from hexane afforded 0.035 g (88% yield) of a dark-brown powder. UV/Vis (CH_2Cl_2): λ_{max} (ε): 279 (137000), 450 (6700), 500 nm ($4600\,\text{M}^{-1}\,\text{cm}^{-1}$); IR (KBr): $\tilde{\nu} = 2925$ (s), 2855 (s), 1731(m, ester), 1590 (m, imine), 1500 (m), 1465 (w), 1433 (m), 1385 (w), 1336 (s), 1190 (s), 1113 (s), 862 cm^{-1} (w); ES-MS (CH_2Cl_2): m/z: 1892.7 $[M-2\,BF_4]^{2+}$, 1233.0 $[M-3\,BF_4]^{3+}$; elemental analysis calcd for $C_{230}H_{346}N_{10}O_{20}Cu_2B_3F_{12} \cdot CH_2Cl_2$ ($M_r = 3958.882 + 84.933$): C 68.61, H 8.67, N 3.46; found: C 68.22, H 8.41, N 3.08.

The synthesis and characterization of additional ligands and complexes, as well as their mesomorphic behavior, will be reported in full elsewhere. Equipment used: DSC: Perkin-Elmer DSC 7, heating/cooling rate $10\,\text{K}\,\text{min}^{-1}$; POM: Leitz Orthoplan, Mettler FP 82 hot stage; XRD: Guinier focusing camera, $Cu_{K\alpha 1}$ radiation, powder samples in Lindemann capillaries, INSTEC hot-stage, INEL CPS-120 curved position-sensitive detector.

Received: September 24, 1999 [Z 14067]

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An Expeditious Total Synthesis of the Natural Stereomeric Mixture of Stenusine Following a Possible Biogenetic Pathway[**]

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Henri-Philippe Husson[*]

Dedicated to Professor Pierre Potier
on the occasion of his 65th birthday

Stenus comma (Coleoptera, Staphylinidae) is a familiar beetle encountered on the sandy banks of stagnant ponds and sluggishly flowing rivers in Eastern and Central Europe. The beetle propels itself over the water surface by an unusual biological phenomenon in which it expels an oily substance with a high spreading capacity onto the aqueous surface. Since the isolation and structure elucidation of stenusine **1** (see Scheme 1; $[\alpha]^{20}_{365} = +5.8$, $c = 0.115$ in EtOH) as the main component of the propulsion fluid and a toxic chemical substance by Schildknecht et al.,[1] numerous preparations have been developed based on racemic[2] and asymmetric[1a, 3] strategies. Finally the enantioselective syntheses of isomeric (2*S*,3*S*)-1-ethyl-3-(2-methylbutyl)piperidine and (2*S*,3*R*)-1-ethyl-3-(2-methylbutyl)piperidine by Enders, De Kimpe et al.[3a] accompanied by chiral GC for both synthetic and natural samples helped to establish that natural stenusine is a mixture of the four possible stereomers in a ratio of 43:40:13:4 = (*S*,*S*):(*S*,*R*):(*R*,*R*):(*R*,*S*) with predominance (83:17) of the two epimers with *S* configuration on the side chain.

It is unusual that an organism produces a natural compound as a mixture of two pairs of enantiomers in a particular ratio. This intriguing observation led us to reflect on the biogenetic origin of the compound. Although Schildknecht et al.[1a] suggested a terpenoid origin, the biosynthesis of stenusine has not yet been elucidated by incorporation experiments. In continuation of our research on the biomimetic synthesis of piperidine alkaloids,[4] we sought a rapid access to natural stenusine. The essence of our biogenetic postulate and strategy for synthesis is that structure **1** derives most likely from lysine and isoleucine and could be considered as the biological condensation of their metabolites, 1,2,3,4-tetrahydropyridine and aldehyde (−)-**2** (Scheme 1). The inter-

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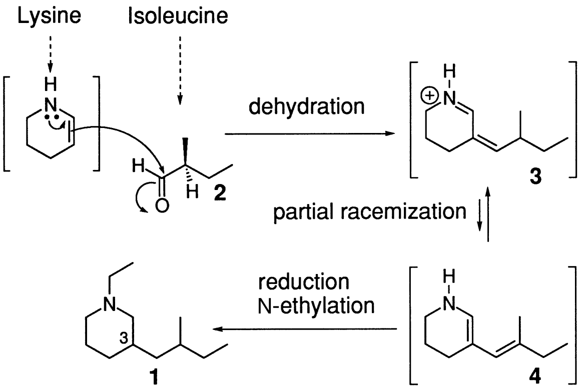
[**] We are grateful to Prof. Dr. Dieter Enders for fruitful discussions.

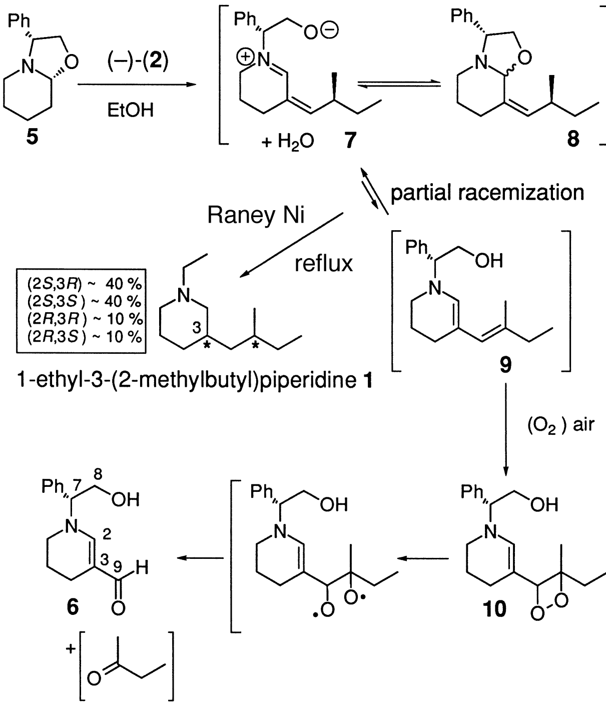


Scheme 1. Possible biogenetic pathway for the synthesis of **1**.

mediates **3** and **4** resulting from the iminium–enamine equilibrium (Scheme 1) could explain the formation of enantiomers at the stereogenic center C-3 and the partial racemization on the side chain leading to the natural stereomeric mixture.

To test the chemical basis of the hypothesis outlined in Scheme 1, we decided to use a stable surrogate of 1,2,3,4-tetrahydropyridine as starting material. We chose compound **5**,[5] which is easily obtained from (*R*)-(−)-phenylglycinol as chiral nitrogen source and glutaraldehyde as C_5 unit biogenetically derived from lysine. The potential enamine functionality of **5** through the oxazolidine/alcohol–enamine equilibrium in protic media was revealed by its ability to react with electrophiles such as aldehydes.

Reaction of **5** with an excess of (*S*)-(−)-2-methylbutyraldehyde ((−)-**2**)[6] in ethanol at room temperature led to the total consumption of the starting material (monitored by TLC) and isolation of only small quantities of compound **6** (Scheme 2) instead of the expected oxazolidine **8**. A modification of the reaction conditions (refluxing in EtOH in the presence of air/molecular sieves) afforded **6** in 60% yield. The formation of this new compound provides strong support for the sequence depicted in Schemes 1 and 2, in which the intermediate conjugate iminium ion **7** (synthetic equivalent of **3**) is in equilibrium with tautomeric dienamine **9** (synthetic equivalent of **4**). The unexpected oxidative degradation of dienamine **9** can be rationalized by the formation of a dioxetane **10**, which produces two carbonyl fragments by a stepwise mechanism in which a 1,4-diradical[7] is formed by cleavage of the oxygen bond, followed by double β-cleavage. This sequence leads to aldehyde **6**, an optically active synthetic equivalent of 1,4,5,6-tetrahydronicotinaldehyde,[8] and butan-2-one (not isolated).[9]



Scheme 2. Synthesis of **1**.

To synthesize stenusine **1**, it was necessary to perform the reaction in the total absence of oxygen. Moreover, for stenusine bearing an ethyl chain at the nitrogen atom the chiral appendage of phenylglycinol had to be properly exchanged. We have shown that the phenylethanol moiety of phenylglycinol can be replaced easily by an alkyl chain under hydrogenolytic conditions by treatment with the corresponding primary alcohol in the presence of Raney nickel.[4b, 10] Thus, in a one-pot procedure, addition of Raney nickel to the reaction mixture of (−)-**2** and **5** in EtOH under argon (Scheme 2) afforded directly stenusine **1** ($[\alpha]^{20}_{365} = +5$ ($c = 0.115$ in EtOH), 51%). It is noteworthy that a series of eight steps is performed in a single operation: oxazolidine ring opening, condensation, dehydration, reduction, debenzylation, oxidation of ethanol to ethanal, Schiff base formation, and reduction to give an *N*-ethyl group.

Our initial hypothesis gained further support when we measured an optical rotation for **1** identical to that reported by Schildknecht[1] for natural stenusine. We thus decided to investigate more accurately the diastereomeric ratio of our mixture by NMR spectroscopy, taking advantage of the easy formation of a chloroform-soluble salt after addition of Mosher acid to synthetic stenusine **1** in a 1:1 ratio. This chiral solvating agent has been already used to induce nonequivalence in the ^{1}H NMR spectra of several racemic tertiary amines, usually in the signals of the protons adjacent to the amino group.[11] While no significant information could be deduced from the ^{1}H NMR spectrum, an excellent resolution of several signals was displayed by the ^{13}C NMR spectrum. Interestingly, those two resonances corresponding to C-2[12] were split into four signals of different intensity. Quantitative evaluation of the stereomeric composition of mixtures by ^{13}C NMR spectroscopy is a known technique.[13] To this end, racemic stenusine (±)-**1** was prepared by the same one-pot procedure by using **5** and racemic 2-metylbutyraldehyde. After addition of one equivalent of Mosher acid to a 0.01 mM solution of (±)-**1** in $CDCl_3$, a ^{13}C NMR spectrum was recorded. As expected, the resonances of C-2 were split into four signals of equal intensity.

The spin-lattice relaxation time T_1 of each signal was measured by the inversion–recovery method[13] and was shown to be identical (0.6 s) under the experimental conditions. Taking into account the identical value of T_1 for the four C-2 signals in (±)-**1**, a comparison of the peak areas of these signals gave a 25/26/25/24 ratio for the diastereomers in the racemic stenusine and a 9/36/43/12 ratio in the compound derived from (−)-**2**. Although these values were obtained with moderate accuracy (percentage error ±2%) as expected for ^{13}C NMR spectroscopy, they are in good agreement with the data for natural stenusine. These results indicated that the synthesis afforded no stereochemical control at one center and partial control at the other. The starting material being (−)-**2**, one might expect total absence of control at the stereogenic center C-3 and partial racemization at the chiral carbon atom of the 2-methylbutyl moiety during the reaction (Scheme 2). Thus, the major diastereomers should be (2*S*,3*S*)-**1** and (2*S*,3*R*)-**1** as observed by Enders, De Kimpe et al.[3a] in the natural stenusine.

In conclusion, racemic stenusine, (±)-**1**, could be synthesized in a one-pot procedure using simple reagents—the shortest synthesis hitherto of (±)-**1**. Moreover, the same strategy using (*S*)-(−)-2-methylbutyraldehyde afforded a disproportionate mixture of the four stereomers in a ratio analogous to that of natural stenusine as demonstrated by optical rotation and NMR studies. The efficiency and shortness of this first synthesis of the natural stenusine mixture might confirm the likelihood of our biogenetic hypothesis. The latter is also supported by the isolation of the new conjugated aldehyde **6**.

Experimental Section

5: To a solution of (*R*)-(−)-phenylglycinol (200 mg, 1.45 mmol) in methanol (10 mL) cooled to −5 °C was added dropwise over 10 min under vigourous stirring glutaraldehyde (25% aqueous solution, 0.6 mL, 1.45 mmol) diluted in methanol (3 mL). The mixture was stirred for another 10 min before it was cooled to −50 °C. Sodium borohydride (26 mg, 0.619 mmol) was added gradually over 2 h. Then a saturated aqueous solution of sodium hydrogencarbonate was added and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue (290 mg) was purified by flash chromatography on silica gel (90/10 cyclohexane/diethyl ether). Crystallization from cyclohexane afforded **5** (147 mg, 50%) as colorless crystals. M.p. 38–41 °C; $[\alpha]_D^{20} = -103$ ($c = 1$, in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.30$–1.45 (m, 1H; H-4), 1.48–1.61 (m, 3H), 1.85–1.89 (m, 1H), 1.97–2.05 (m, 2H), 2.85 (br d, ^3J(H,H) = 10.5 Hz, 1H; H-6), 3.53 (t, ^3J(H,H) = 8 Hz, 1H; H-7), 3.65 (t, ^3J(H,H) = 8, ^2J(H,H) = 8 Hz, 1H; H-8), 3.68 (dt, ^3J(H,H) = 3, 9 Hz, 1H; H-2), 4.17 (t, ^3J(H,H) = 8, ^2J(H,H) = 8 Hz, 1H; H-8), 7.26–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 22.5$, 24.8, 30.3, 47.8, 67.1, 72.9, 94.6, 127.6, 127.7, 128.4, 138.9; MS: *m*/*z*: 204 [M^++1]; elemental analysis for $C_{13}H_{17}NO$: calcd: C 76.81, H 8.43, N 6.89; found: C 76.75, H 8.15, N 6.96.

1: Compound **5** (600 mg, 2.95 mmol) was dissolved in ethanol (50 mL). The resulting solution was degassed with argon and (−)-**2** was added (29.5 mmol, 3.16 mL). The mixture was stirred at room temperature in darkness for 5 d. Raney nickel (W2, 50% slurry in water, 11 g) was added and the suspension refluxed for 24 h before being filtered over celite. After addition of a saturated solution of sodium hydrogencarbonate, the cloudy solution was extracted with dichloromethane (3 ×). The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum to give an oily residue. Purification by flash chromatography over silica gel (dichloromethane/methanol, 92/8) followed by ion-exchange chromatography (amberlyst OH^-) led to **1**[1, 2, 3] as a colorless oil (108 mg, 20%). When the reaction was performed in EtOH/H_2O (3/1) followed by extraction (Et_2O), evaporation and dissolving in EtOH before treatment with Raney nickel, compound **1** was obtained in 51% yield. ^{13}C NMR (75 MHz, $CDCl_3$, 0.01 mM solution of **1** and Mosher acid, 25 °C) C-2: $\delta = 57.8$ (9%), 57.7 (36%), 57.5 (43%), 57.4 (12%).

6: Compound **5** (400 mg, 1.97 mmol) and (±)-**2** (10 equiv, 19.7 mmol, 2.11 mL) were dissolved in dry ethanol (30 mL). Molecular sieves (3 Å, 1 g) were added and the mixture was refluxed for 48 h under air bubbling. Filtration and concentration gave a yellowish oil which was submitted to flash chromatography (dichloromethane/methanol, 95/5). Compound **6** was obtained from trituration in diethyl ether as white crystals (273 mg, 60%). M.p. 116–118 °C; $[\alpha]_D^{20} = 52$ ($c = 1$, in $CHCl_3$); IR ($CHCl_3$, film): $\tilde{\nu}$ [cm^{-1}] = 1578 (CHO); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.69$–1.77 (m, 2H; H-5), 2.22–2.29 (m, 2H; H-4), 3.06–3.29 (m, 2H; H-6), 4.10–4.14 (m, 2H; H-8), 4.49–4.54 (bt, ^3J(H,H) = 8.5 Hz, 1H; H-7), 7.20–7.40 (m, 6H; H_{ar}, H-2), 8.71 (s, 1H; H-9); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 18.0$ (C-5), 20.3 (C-4), 44.9 (C-6), 61.3 (C-8), 70.1 (C-7), 110.6 (C-3), 126.9 (HC_{ar}), 128.3 (HC_{ar}), 128.8 (HC_{ar}), 136.2 (C_{ar}), 156.5 (C-2), 186.9 (C-9); MS (EI): *m*/*z*: 231 [M^+]; HRMS (EI): *m*/*z*: [M^+] for $C_{14}H_{17}NO_2$: calcd: 231.1259; found: 231.1255.

Received: October 4, 1999 [Z14095]

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