187. Synthesis of (±)-*trans*-2,5-Dialkylpyrrolidines from the *Lukes-Šorm* Dilactam: Efficient Preparation of (±)-*trans*-2-Butyl-5-heptylpyrrolidine and Analogs Present in Ant Venoms

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A 7-step synthesis of (±)-*trans*-2-butyl-5-heptylpyrrolidine (**14**) from the *Lukes-Šorm* dilactam **1** was accomplished in 6% overall yield without counting for a reconversion of *cis*-isomer **13** into *trans*-isomer **14** which was also accomplished. Reduction of pyrroline **12**, the precursor of **14**, with $NaBH_4$ afforded a 1:1 mixture of *cis*-isomer **13** and *trans*-isomer **14** separated by chromatography. Reductive *N*-methylation of **14** afforded the *N*-methyl analog **15**, another ant alkaloid. The synthetic route to **14** was extended to a similar synthesis of analogs **23–25** and is representative for the synthesis of *trans*-2,5-diakyl-substituted pyrrolidines. Results on the screening of a few compounds for the effect on vascular permeability are reported.

1. Introduction. – Thief ants steal larvae from nests of other ant species [1], secreting a powerful venomous scent [2]. *Solenopsis* species use 2-butyl-5-heptylpyrrolidine (**14**), possibly as an enantiomer[1]), to effectively attack host ants [4]. Ants of *Solenopsis punctaticeps*, a species closely related to thief ants also sting humans [5], resulting in transient edema and pruritus. Other ants of the genus *Solenopsis* called fire ants contain potent venoms which exhibit necrotic [6] and haemolytic effects [7]. Ant alkaloids so far have only been available in very small amounts, and their biological effects, therefore, were not fully investigated. Ant alkaloids are composed of several classes of heterocyclic compounds [12–14]: 2,5-dialkyl-substituted pyrrolidines [8], 2,6-disubstituted piperidines [9], 3,5-disubstituted pyrrolidines [10], and 3,5-disubstituted indolizidines (= octahydroindolizines) [11]. The *trans*-2,5-disubstituted pyrrolidines, recently also found in skin extracts of the poison frogs of the family *Dendrobatidae* [15], represent the largest group of ant toxins and we, therefore, decided to prepare representative members for biological studies.

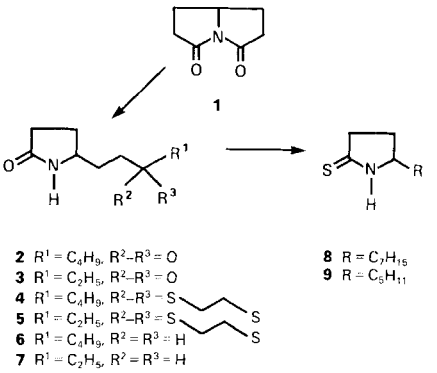
2. Results. – 2.1. *Chemistry.* The *trans*-2,5-disubstituted pyrrolidines were prepared previously by a *Hofmann-Löffler-Freytag* reaction [16], by reduction of pyrrols with borohydride [17], by C-alkylation of *N*-nitrosopyrrolidines [18a–c], by catalytic hydrogenation of pyrrols [19], and by reductive amination of 1,4-diketones [20]. These reactions afforded besides the desired *trans*-toxins also the corresponding unnatural *cis*-isomers,

[1]) Although natural ant toxins so far were never assessed for optical properties, it has to be assumed that they are optically active [3].

which were found to be less polar and separable from their *trans*-isomers by chromatographic procedures [19]. Attempts of stereoselective synthesis of *trans*-substituted 2,5-dialkylpyrrolidines were only recently reported and are multistep reaction sequences [21] [22]. The only enantioselective synthesis of representative ant pyrrolidine toxins is that reported by *Shiosaki* and *Rapoport* [3] which may allow preparation and testing of optically active compounds for biological effects [3].

We report here a versatile synthesis of 2,5-disubstituted ant pyrrolidines from the *Lukes-Šorm* dilactam **1**, already used to prepare 3-alkyl-substituted pyrrolizidines (= hexahydro-1*H*-pyrrolizine) [24], by a route which should be amenable to the synthesis of all saturated 2,5-dialkylpyrrolidines so far reported [14] [25]. Dilactam **1** smoothly reacted with *Grignard* reagents to afford in high yield ketones of type **2** and **3** (*Scheme 1*), which were converted into 2,5-dialkylpyrrolidines by the route described here

Scheme 1



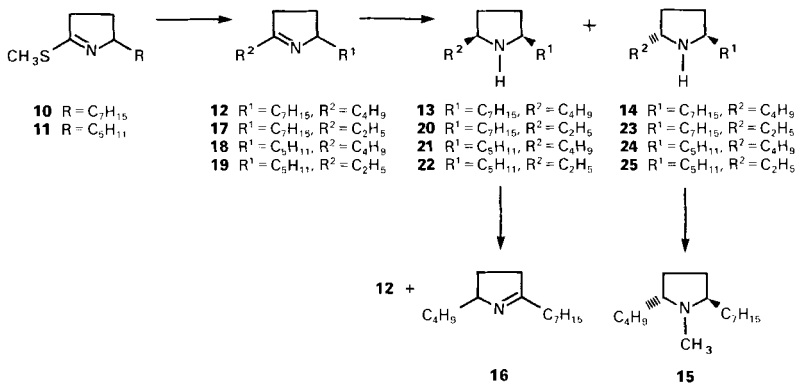
in detail for the conversion of **2** into **14**[2]). Reaction of **1** with BuMgCl in CH_2Cl_2 yielded ketone **2** in 89% yield. Protection of **2** with ethanedithiol in the presence of $BF_3 \cdot Et_2O$ afforded dithioacetal **4** as a solid, which was converted by treatment with *Raney*-Ni in a H_2 atmosphere into lactam **6** (analogously: **3**→**5**→**7**). Refluxing of **6** with P_2S_5 in benzene gave thiolactam **8** which was converted into thioether **10** by treatment with MeI in CH_2Cl_2 (analogously: **7**→**9**→**11**).

Successful replacement of the thiomethyl group with an alkyl group, applied successfully previously in the synthesis of perhydrohistrionicotoxins [26a–e], was accomplished with BuMgCl when CH_2Cl_2 was used as a solvent, affording pyrroline **12** in 30% yield, but failed to give practical results when Et_2O or tetrahydrofuran was used as a reaction medium.

Reduction of pyrroline **12** with $NaBH_4$ in MeOH afforded a 1:1 mixture of *cis*-pyrrolidine **13** and *trans*-pyrrolidine **14** separated by chromatography on silica gel, with **13** being the faster moving isomer [19]. Reductive *N*-methylation of **14** afforded the pyrrolidine **15**, an ant toxin occurring in *Monomorium latinode* [25]. Reconversion of *cis*-isomer **13** into *trans*-isomer **14** was accomplished by *N*-chlorination of **13** with chloro-

[2]) The 3,4-dihydro-2*H*-pyrrols and pyrrolidines prepared are racemic mixtures and the structures shown in *Scheme 2*, therefore, represent one of the two enantiomers.

Scheme 2[2])



succinimide followed by dehydrochlorination with KOH [27], yielding a 1:1 mixture of 3,4-dihydro-2*H*-pyrrols **12** and **16**, which was reduced with $NaBH_4$ to give a 1:1 mixture **13**/**14**. Attempts to resolve pyrrolidine **14** *via* diastereoisomeric ureas obtained from **14** and 1-phenylethyl isocyanate [28] failed since the ureas could not be separated on TLC or HPCL.

Using similar routes to that described above, pyrrolines **17–19** (**17** and **19** were isolated previously from *Solenopsis punctaticeps* [25]), the *cis*-2,5-dialkyl-substituted pyrrolidines **20–22**, and the *trans*-2,5-dialkylpyrrolidines **23–25** were also prepared in amounts sufficient for biological evaluation.

2.2. *Biological Effects of Synthetic Ant-Venom Alkaloids.* 2.2.1. *Method.* Stinging by fire ant results in painful burning in the skin and is followed by subsequent formation of a sterile pustule within 24 h. A biopsy study [29] demonstrated sequential development of superficial pustule with necrotic material infiltrated by leukocytes. Although stinging by fire ants, besides local discomfort, is not toxic by itself in the majority of individuals, there is a small population of subjects in whom sensitivity reaction to fire-ant venom may occur. In these cases symptoms of hypersensitivity include generalized urticaria, angio-edema, dyspnea, nausea, and even collapse and unconsciousness.

Alkaloids comprise about 95% of the fluid phase of fire-ant venom and up to 19 μg of alkaloids may be present in the poison gland of a single worker ant [12]. However, the biological effects of these compounds have not been elucidated so far. The synthesis of fire ant-venom alkaloids reported made it possible for the first time to test some of their biological effects. In order to determine biological effects of the ant-venom alkaloids, we measured the capacity of these compounds to induce vascular permeability response in rat skin by the *Evans* blue dye extravasation technique [30].

The dorsal skin of Et_2O-anaesthetized rats (300 g *Sprague Dawley*) was shaven the day before the study. On the day of skin testing, animals were anaesthetized with sodium pentobarbitone (50 mg/kg i.p.), and 200 μl of 0.5% *Evans* blue dye was injected intravenously. Immediately thereafter, 0.05 ml of ant-venom alkaloids or histamine prepared in PBS solution were injected intradermally. Three alkaloids **13**, **14**, and **17** in various concentrations (0.5 μg, 5 μg, and 50 μg per injection) were studied. Twenty min later, the animals were sacrificed, the dorsal skin reflected, and the largest diameter of blueing determined.

2.2.2. *Results.* The intradermal injection of increasing concentrations of the synthetic ant-venom alkaloids resulted in dose-dependent vascular permeability responses in the rat skin as measured by the diameter of blueing (*Table*). Control injections of solvent produced only slight, usually unmeasurable responses.

Table. *Vascular Permeability of (±)-Pyrrolidines* **13** *and* **14** *and (±)-3,4-Dihydro-2*H*-pyrrol* **17**[a])

Compounds	Vascular permeability[b])		
	0.5 μg	5.0 μg	50 μg
13	3.2 ± 0.6	3.8 ± 0.7	6.9 ± 0.9
14	3.4 ± 0.3	5.9 ± 0.7	9.2 ± 0.4
17	4.1 ± 0.4	5.2 ± 0.4	7.7 ± 1.0
Histamine	6.1 ± 0.4	9.1 ± 0.6	13.7 ± 1.0
Compound 48/80[c])	–	11.2 ± 0.5	

[a]) Capacity of ant alkaloids tested in form of an aqueous solution of their hydrochlorides prepared *in situ* with reference compounds histamine and compound 48/80 to induce vascular permeability in rat skin.

[b]) Millimeters of blueing.

[c]) Compound 48/80 is the condensation product of *N*-methyl-*p*-methoxyphenylamine with formaldehyde (*Sigma* catalogue 1987, page 436).

When cutaneous blueing responses to alkaloids were compared to the effects of equivalent concentrations of histamine, a reference permeability agent, the alkaloids demonstrated 50–67% of histamine capacity to induce vascular permeability in the rat skin. The (±)-*trans*-pyrrolidine **14** of the natural series was clearly the most potent compound, followed by (±)-3,4-dihydro-2*H*-pyrrol **17** and (±)-*cis*-pyrrolidine **13** which were similarly potent.

Conclusions. – The *Lukes-Šorm* dilactam **1** has served here as a useful compound to prepare *cis*-2,5-dialkyl-substituted pyrrolidines (**13** and **20–22**), and *trans*-substituted isomers occurring in ant species of the genus *Solenopsis* (**14** and **23–25**). Reductive N-methylations of either of these pyrrolidines, examplified here with the conversion of **14** into **15**, should readily afford the corresponding *N*-methylpyrrolidines which in the *trans*-series also occur in ant species. *N*-Chlorination of *cis*-isomers, followed by dehydrochlorination and reduction of the intermediate 3,4-dihydro-2*H*-pyrrolines, examplified here with the conversion of **13** into **14** *via* **12**/**16**, should result in a considerably improved yield of desired *trans*-isomers, allowing preparation in amounts suitable for biological testing. Several of these compounds have, for the first time, been obtained as crystalline fumarate salts particularly useful for biological screening. Although no serious attempts were made to separate racemic mixtures by chemical methods, this possibility can not be excluded. The urea-fragmentation method which recently was successfully applied for preparing optically active secondary amines [28], failed to give urea diastereoisomers separable by TLC or HPLC. Resolution of 5-alkyl-substituted pyrrolidin-2-ones obtained as intermediates in this synthesis, by direct or indirect methods, however, provides other possibilities to enter the optically active series of ant alkaloids, and this will be investigated.

We were able to demonstrate that synthetic 2,5-disubstituted 2,3-dihydro-2*H*-pyrrols and pyrrolidines when tested as racemates and occurring in ants possibly as enantiomers act as relatively potent vasodilators inducing plasma protein extravasation in rat skin in

microgram quantities. In this respect, the alkaloids tested including 3,4-dihydro-2*H*-pyrrol **17**, *cis*-pyrrolidine **13**, and *trans*-pyrrolidine **14** were only one order less potent than histamine. Taking into account that a poison gland of a single ant contains micrograms of such alkaloids and probably as enantiomers makes it likely that these agents may play a role in the inflammatory response which results after the stinging of humans.

Venom alkaloids do not contribute to allergenicity of fire-ant venom, and the antigen responsible for the allergic reactions are found in trace amount of proteins within the aqueous phase of the venom [31]. However, vasopermeability effect of alkaloids suggest that they may contribute to the allergic reaction by allowing larger amount of allergen to reach tissues and the bloodstream.

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Experimental Part[2])

General. Silica gel *60* for short column chromatography (0.015–0.040 nm) was from *E.M. Reagents.* M.p.: *Fisher-Johns* apparatus; corrected. IR spectra (cm^{-1}): $CHCl_3$ solns.; *Beckman-4230* instrument. ^{1}H-NMR spectra ($CDCl_3$): *Varian-XL-300* or *Varian-HR-220* spectrometer; TMS (δ in ppm) as internal standard. ^{13}C-NMR spectra ($CDCl_3$): *Varian-XL-300* or *JEOL-FX-100* spectrometer; TMS as internal reference. CI-MS (*m/z*): *Finnigan 1015 D* spectrometer; NH_3 the reagent gas; model *6000* data collection system. EI-MS (*m/z*): double focusing *V.G. Micromass 7070F* spectrometer (70 eV). Elemental analyses were performed by the *Atlantic Microlab Inc.*, Atlanta, Georgia.

5-(3'-Oxoheptyl)pyrrolidin-2-one (**2**) *and 5-(3'-Oxopentyl)pyrrolidin-2-one* (**3**). Dilactam **1** (20.98 g, 0.15 mol) in 600 ml of anh. CH_2Cl_2 was cooled to 0° with an ice bath. BuMgCl (75 ml of a 2M soln. in Et_2O) was added dropwise with stirring and the mixture left overnight at r.t. A sat. aq. soln. of NH_4Cl was then added, the mixture stirred for 30 min, separated, and the aq. layer extracted 3x with $CHCl_3$. The combined org. extracts were dried and evaporated to yield 26.39 g (89%) of a pinkish crystalline material, which was used in the next step without further purification (97% purity by GC). An anal. sample was crystallized twice from cyclohexane: colorless crystals of **2**. M.p. 52–54°. IR: 3440, 3200, 2960, 2925, 2870, 1770, 1680, 1455, 1405, 1365, 1300, 1200. ^{1}H-NMR: 7.35 (br. *s*, NH); 3.65 (*quint.* J = 6.5, H–C(5)); 2.55–2.15 (*m*, 7 H); 1.90–1.65 (*m*, 3 H); 1.56 (*quint.*, J = 7, 2 H–C(5')); 1.31 (*sext.*, J = 7, 2 H–C(6')); 0.91 (*t*, J = 7, 3 H–C(7')). ^{13}C-NMR: 210.21; 178.61; 54.06; 42,53; 38.61; 36.45; 30.36; 28.96; 27.03; 25.86; 22.23; 13.75. CI-MS: 198 (M^+ + 1). Anal. calc. for $C_{11}H_{19}NO_2$(197.16): C 66.95, H 9.71, N 7.10; found: C 66.70, H 9.74, N 7.01.

Similarly, reaction of 13.9 g of **1** with EtMgBr yielded 15.83 g (94%) of **3** as an almost colorless, crystalline solid. After crystallization from cyclohexane/$(i\text{-}Pr)_2O$, m.p. 47–49°. ^{1}H-NMR: 7.70 (br. *s*, NH); 3.66 (*quint.*, J = 6.5, H–C(5)); 2.56–2.42 (*m*, 4 H); 2.38–2.18 (*m*, 3 H); 1.90–1.63 (*m*, 3 H); 1.05 (*t*, J = 7.0, 3 H–C(5')). ^{13}C-NMR: 210.45; 178.58; 53.91; 53.83; 38.12; 38.05; 35.92, 35.85; 30.22; 26.94; 26,86; 7.63. CI-MS: 170 (M^+ + 1). Anal. calc. for $C_9H_{15}NO_2$ (169.13): C 63.86, H 8.94, N 8.28; found: C 63.76, H 8.54, N 8.26.

5-[3',3'-(Ethylenedithio)heptyl]pyrrolidin-2-one (**4**) *and 5-[3',-(Ethylenedithio)pentyl]pyrrolidin-2-one* (**5**). A soln. of **2** (26.30 g) in 30 ml of ethane-1,2-dithiol was cooled with an ice bath, and 20 ml of $BF_3 \cdot Et_2O$ were added slowly. The mixture was left overnight at r.t. then evaporated. Crushed ice was added to the residue and the product extracted twice with Et_2O. The org. extracts were washed with a sat. aq. soln. of $NaHCO_3$, dried, and evaporated to yield 30.60 g (84%) of **4** as a colorless oil which became crystalline while standing in the refrigerator. M.p. 65–67°. IR: 3440, 3220, 2940, 2880, 1690, 1460, 1415, 1385, 1340, 1310, 1280, 1200. ^{1}H-NMR: 6.63 (br. *s*, NH); 3.65 (*quint.* J = 7, H–C(5)); 3.25 (*s*, SCH_2CH_2S); 2.40–2.20 (*m*, 3 H); 1.95–1.85 (*m*, 4 H); 1.85–1.60 (*m*, 3H); 1.55–1.25 (*m*, 4 H); 0.90 (*t*, J = 7, 3 H–C(7')). ^{13}C-NMR: 178.26; 54.53; 43,53; 39.66; 39.37; 33.82; 30.25; 29.08; 27.15; 22.88; 14.04. CI-MS: 274 (M^+ + 1). Anal. calc. for $C_{13}H_{23}NOS_2$(273.31): C 57.08, H 8.48, N 5.12; found: C 57.19, H 8.52, N 5.08.

Similarly, reaction of 2.10 g of **3** with ethane-1,2-dithiol yielded 3.02 g (95%) of crystalline **5**. M.p. 51–53°. ^{1}H-NMR: 7.44 (br. *s*, NH); 3.63 (*quint.*, J = 6.5, H–C(5)); 2.36–2.19 (*m*, 4 H); 1.70–1.23 (*m*, 10 H); 0.89 (*t*, J = 7.0, 3 H–C(5')). ^{13}C-NMR: 178.51; 54.66; 36.55; 31.52; 30.27; 27.07; 25.26, 22.31; 13.80. CI-MS: 246 (M^+ + 1). Anal. calc. for $C_{11}H_{19}NOS_2$ (245.28): C 53.82, H 7.81, N 5.71; found: C 53.73, H 7.82, N 5.69.

5-Heptylpyrrolidin-2-one (**6**) *and 5-Pentylpyrrolidin-2-one* (**7**). To a soln. of **4** (30.0 g) in 750 ml of EtOH, 150 g of *Raney* Ni (*Aldrich*) washed with EtOH was added and the mixture refluxed with stirring under H_2 for 12 h. Then, another 100 g of *Raney* Ni was added and reflux continued for 8 h. It was then cooled, filtered, and evaporated: 17.5 g (87%) of crude **6** as a colorless oil. This was used for the next step without further purification. A sample was purified by column chromatography on SiO_2 to yield a colorless crystalline product. M.p. 47–48° (hexane). IR: 3440, 3220, 2930, 1680, 1455, 1410, 1380, 1310, 1190. ^{1}H-NMR: 7.16 (br. *s*, NH); 3.62 (*quint.* J = 6.5, H–C(5)); 2.20–2.10 (*m*, 4 H); 1.90–1.10 (*m*, 12 H); 0.88 (*t*, J = 7, 3 H–C(7')). ^{13}C-NMR: 178.42; 54.65; 36.68; 31.67; 30.27; 29.38; 29.04; 27.19; 25.71, 22.52; 13.96. CI-MS: 174 (M^+ + 1). Anal. calc. for $C_{11}H_{21}NO$ (183.17): C 72.06, H 11.56, N 7.65; found: C 71.99, H 11.52, N 7.61.

Similarly, conversion of 21.5 g of **5** over 180 g of *Raney* yielded 16.3 g of **7**. M.p. 30–31° (hexane). ^{1}H-NMR: 7.07 (br. *s*, NH); 3.27 (*quint.* J = 6.5, H–C(5)); 2.40–2.20 (*m*, 3 H); 2.00–1.87 (*m*, 4 H); 1.83–1.64 (*m*, 3 H); 1.05 (*t*, J = 7, 3 H–C(5')). ^{13}C-NMR: 178.25; 54,38; 39.60; 38.69; 36.36; 33.64; 30.11; 26,96; 11.00. CI-MS: 156 (M^+ + 1). Anal. calc. for $C_9H_{17}NO$ (155.14): C 69.61, H 11.05, N 9.03; found: C 69.51, H 11.12, N 9.10.

5-Heptylpyrrolidine-2-thione (**8**) *and 5-Pentylpyrrolidine-2-thione* (**9**). To crude **6** (17.5 g) in 200 ml of benzene, 20.0 g of P_2S_5 were added, and the mixture was refluxed with stirring for 1 h, then cooled and evaporated. Then, 50 ml of sat. aq. $NaHCO_3$ and 50 ml of $CHCl_3$ were added and stirred at r.t. for 15 min. The org. layer was separated and the aq. layer extracted 3 × with $CHCl_3$. The combined org. extracts were dried and evaporated to yield 20.99 g of yellow, milky oil which was chromatographed on a SiO_2 column to give 15.11 g (75%) of **8** as colorless oil, which became crystalline during standing. M.p. 48–49° (hexane). IR: 3410, 2930, 2860, 1490, 1415, 1310, 1270, 1190. ^{1}H-NMR: 8.46 (br. *s*, NH); 3.91 (*quint.* J = 7 H–C(5)); 3.05–2.85 (*m*, 2 H–C(2)); 2.40–2.25 (*m*, 1 H); 1.90–1.20 (*m*, 13 H); 0.89 (*t*, 3 H–C(7')). ^{13}C-NMR: 205.18; 62.78; 43.00; 35.45; 31.71; 29.40; 29.14; 26.03; 22.58; 14.04. CI-MS: 200 (M^+ + 1). Anal. calc. for $C_{11}H_2NS$ (199.36): C 66.27, H 10.62, N 7.03; found: C 66.20, H 10.65, N 7.03.

Similarly, conversion of 12.92 of **7** with P_2S_5 yielded 12.42 g (82%) of crystalline **9**. M.p. 40–42° (hexane). ^{1}H-NMR: 9.33 (br. *s*, NH); 3.93 (*quint.*, J = 7, H–C(5)); 3.05–2.80 (*m*, 2 H); 2.40–2.25 (*m*, 1 H); 1.90–1.25 (*m*, 10 H); 0.89 (*t*, J = 7, 3 H–C(5')). ^{13}C-NMR: 204.35; 62.75; 43.02; 35.15; 31.39; 29.09; 25.47; 22.32; 13.81. CI-MS: 172 (M^+ + 1). Anal. calc. for $C_9H_{17}NS$ (171.20): C 63.08, H 10.01, N 8.18; found: C 62.96, H 10.05, N 8.09.

*2-Heptyl-3,4-dihydro-5-thiomethyl-2*H*-pyrrol* (**10**) *and 3,4-Dihydro-2-pentyl-5-thiomethyl-2*H*-pyrrol* (**11**). To a soln. of **8** (4.22 g) in 50 ml of CH_2Cl_2, 2.5 ml of CH_3I were added. The mixture was kept at r.t. overnight, then evaporated to dryness, the residue dissolved in $CHCl_3$, the org. phase washed with sat. aq. $NaHCO_3$ soln., dried, and evaporated to yield 4.19 g (93%) of **10** as a yellow oil, used for the next step without further purification. A small sample was converted into **10** · HCl. M.p. 118–120° ((i-Pr)$_2$O/EtOH). **10**: IR: 2960, 2930, 2860, 1585, 1450, 1425, 1285, 1180. ^{1}H-NMR: 3.95 (*quint.*, J = 7, H–C(5)); 2.68–2.50 (*m*, 2 H); 2.44 (*s*, CH_3S); 2.25–2.05 (*m*, 2 H); 1.80–1.20 (*m*, 12 H); 0.87 (*t*, J = 7, 3 H–C(7')). ^{13}C-NMR: 171.30; 72.78; 38.38; 36.74; 31.85; 29.72; 29.60; 29.31; 26.62; 22.70; 14.04; 13.51. CI-MS: 214 (M^+ + 1). Anal. calc. for $C_{12}H_{24}ClNS \cdot 1/2H_2O$ (258.72): C 55.66, H 9.74, Cl 13.70; N 5.41; found: C 55.62, H 9.76, Cl 13.64, N 5.41.

Similarly, **9** (13.0 g) was converted by treatment with CH_3I into **11** (11.7 g, 83%), orange oil. ^{1}H-NMR: 3.96 (*quint.*, J = 7, H–C(5)); 2.71–2.50 (*m*, 2 H); 2.45 (*s*, CH_3S); 2.26–2.08 (*m*, 1 H); 1.82–1.68 (*m*, 1 H); 1.64–1.50 (*m*, 1 H); 1.46–1.24 (*m*, 7 H); 0.89 (*t*, J = 7, 3 H–C(5')). ^{13}C-NMR: 171.22; 72.62; 38.22; 38.14; 36.52; 31.84; 29.43; 29.36; 26.14; 22.49; 13.91; 13.40. CI-MS: 816 (M^+ + 1).

A small sample of **11** was converted into **11** · HCl which was crystallized from (i-Pr)$_2$O/EtOH to yield colorless crystals. M.p. 115–117°. Anal. calc. for $C_{10}H_{20}ClNS \cdot 1/2H_2O$ (230.69): C 52.02, H 9.18, Cl 15.137; N 6.07; found: C 51.82, H 9.22, Cl 15.27, N 6.06.

*5-Butyl-2-heptyl-3,4-dihydro-2*H*-pyrrol* (**12**) *and 5-Ethyl-2-heptyl-3,4-dihydro-2*H*-pyrrol* (**17**). To a soln. of **10** (430 mg) in 80 ml of anh. CH_2Cl_2, 20 ml of 2M BuMgCl in Et_2O are added, and the mixture was refluxed with stirring for 48 h. It was then cooled, and 50 ml of a sat. aq. NH_4Cl soln. added. The mixture was stirred for 15 min, separated, and the aq. layer extracted 3 × with Et_2O. The combined org. extracts were dried and evaporated to yield 0.68 g of an orange oil. It was chromatographed on a SiO_2 column (hexane/i-PrOH 98:2) to yield 130 mg (29%) of **12** as a colorless oil. IR: 2960, 2930, 2860, 1635, 1455, 1370. ^{1}H-NMR: 3.90 (*m*, H–C(2)); 2.56–2.28 (*m*, 3 H); 2.08–1.94 (*m*, 1 H); 1.78–1.66 (*m*, 1 H); 1.62–1.50 (*m*, 2 H); 1.50–1.20 (*m*, 12 H); 0.98–0.84 (*m*, 6 H). ^{13}C-NMR: 177.00; 72.59; 36.95; 36.76; 33.73; 31.90; 29.82; 29.33; 28.85; 28.65; 28.71; 26.71; 22.68; 14.10; 13.89. EI-MS: 223.2289 ($C_{15}H_{29}N$, calc. 223.2300).

Similarly, using EtMgBr in Et_2O instead of BuMgCl, and starting from 419 mg of **10**, 124 mg (32%) of **17** were obtained as a colorless oil. ^{1}H-NMR: 3.90 (*m*, 1 H); 2.60–2.30 (*m*, 3 H); 2.12–1.98 (*m*, 1 H); 1.80–1.65 (*m*, 1 H); 1.50–1.20 (*m*, 9 H); 1.74 (*t*, J = 7.5, 3 H); 0.88 (*t*, J = 7, 3 H). ^{13}C-NMR: 178.07; 72.60; 36.74; 36.68; 31.92; 29.82; 29.33; 28.66; 27.06; 26.73; 22.71; 14.12; 10.99. EI-MS: 195.1996 ($C_{13}H_{25}N$, calc. 195.1987).

*5-Butyl-3,4-dihydro-2-pentyl-2*H*-pyrrol* (**18**) *5-Ethyl-3,4-dihydro-2-pentyl-2*H*-pyrrol* (**19**). Starting from 3.05 g of **11** and 70 ml of 2M BuMgCl in Et_2O, the procedure described above gave 820 mg (26%) of **18** as a colorless oil. ^{1}H-NMR: 3.92 (*m*, 1 H); 2.57–2.28 (*m*, 4 H); 2.08–1.74 (*m*, 1 H); 1.78–1.66 (*m*, 1 H); 1.60–1.50 (*m*, 2 H); 1.46–1.24 (*m*, 1 OH); 0.98–0.84 (*m*, 6 H). ^{13}C-NMR: 176.88; 72.40; 36.76; 36.55; 33.55; 31.88; 28.65; 28.46; 26.20; 22.48; 13.89; 13.71. EI-MS: 195.1971 ($C_{13}H_{25}N$, calc. 195.1987).

Similarly, using EtMgBr instead of BuMgCl, and starting from 3.51 g of **11**, 990 mg (31%) of **19** were obtained as a colorless oil. ^{1}H-NMR: 3.90 (*m*, 1 H); 2.58–2.28 (*m*, 4 H); 2.30–1.98 (*m*, 1 H); 1.78–1.66 (*m*, 1 H); 1.49–1.24 (*m*, 8 H); 1.94 (*t*, *J* = 7.5, 3 H); 0.89 (*t*, *J* = 7, 3 H). ^{13}C-NMR: 177.96; 72.60; 36.68; 32.06; 28.65; 27.04; 26.38; 22.66; 14.06; 10.97. EI-MS: 167.1667 ($C_{11}H_{21}N$, calc. 167.1674).

cis-*2-Butyl-5-heptylpyrrolidine* (**13**) *and* trans-*2-Butyl-5-heptylpyrrolidine* (**14**). To a soln. of **12** (350 mg) in 20 ml of MeOH, 100 mg of $NaBH_4$ were added in small portions over 5 min. The mixture was then stirred at r.t. for 30 min and evaporated. It was dissolved in Et_2O, washed with H_2O, dried, and evaporated to yield a colorless oil. The mixture **13**/**14** (1:1 by GC) was separated on a SiO_2 column ($CHCl_3$/MeOH 99:1) to yield first 93 mg of **13**, followed by **13**/**14** (91 mg) and **14** (95 mg).

13: ^{1}H-NMR: 5.3 (br. *s*, 1 H); 3.23–3.10 (*m*, 2 H); 2.05–1.90 (*m*, 2 H); 1.85–1.68 (*m*, 2 H); 1.65–1.45 (*m*, 4 H); 1.45–1.20 (*m*, 14 H); 0.98–0.83 (*m*, 6 H). ^{13}C-NMR: 59.43; 36.69; 36.37; 31.87; 31.33; 29.84; 29.78; 29.73; 29.33; 27.54; 22.91; 22.70; 14.09. EI-MS: 224.2397 ($M^+ - 1$, $C_{15}H_{30}N$, calc. 224.2378), 168, 126, 96, 82, 69, 55. Fumarate salt of **13**: M.p. 116–118° (AcOEt).

14: ^{1}H-NMR: 3.28–3.13 (*m*, 2 H); 2.4 (very br. *s*, 1 H); 2.06–1.92 (*m*, 2 H); 1.68–1.52 (*m*, 2 H); 1.50–1.20 (*m* 16 H); 0.96–0.83 (*m*, 6 H). ^{13}C-NMR: 58.47; 35.91; 35.58; 31.91; 29.70; 29.32; 27.20; 22.78; 22.68; 14.11. EI-MS: 224.2351 ($M^+ - 1$, $C_{15}H_{30}N$, calc. 224.2378), 168, 126, 82, 73, 55. Fumarate salt of **14**: M.p. 119–122° (AcOEt).

Conversion of **13** *into* **14**. A soln. of **13** (75 mg, 0.33 mmol) in 5 ml of abs. EtOH was, cooled to 0°, and *N*-chlorosuccinimide (48 mg, 0.36 mmol) was added in one portion. The mixture was then stirred for 15 min at 0° and 2 h at r.t. A soln. of KOH (30 mg) in EtOH (0.3 ml) was then added and the mixture stirred at r.t. for 3 h. It was then evaporated, dissolved in Et_2O, washed with H_2O, dried, and evaporated to yield 70 mg of colorless oil. GC/MS: **12**/**16** 1:1 with identical M^+ (223). The mixture **12**/**16** in MeOH was reduced with 30 mg of $NaBH_4$ to yield a 1:1 mixture **13**/**14** as compared with anal. standards.

trans-*2-Butyl-5-heptyl-1-methylpyrrolidine* (**15**). To a soln. of **14** (40 mg) in 5 ml of 30% AcOH, 0.1 ml of a 37% formaldehyde soln. and 25 mg of 10% Pd/C are added, and the mixture was stirred at r.t. under H_2 for 6 h. It was then filtered, alkalinized with 2N NaOH and extracted with Et_2O. The Et_2O extract was dried and evaporated to yield **15** as a colorless oil. ^{1}H-NMR: 2.77 (*m*, 2 H); 2.35 (*s*, 3 H); 1.92 (*m*, 2 H); 1.61 (*m*, 2 H); 2.35 (*s*, 3 H); 1.92 (*m*, 2 H); 1.16 (*m*, 2 H); 1.47 (*m*, 2 H); 1.38–1.06 (*m*, 16 H); 0.90 (*m*, 6 H). ^{13}C-NMR: 63.36; 35.12; 31.85; 30.54; 30.23; 29.97; 29.32; 29.08; 28.71; 26.89; 23.05; 22.66; 14.09. EI-MS: 238.2512 ($M^+ - 1$, $C_{16}H_{32}N$, calc. 238.2535), 182, 140.

cis-*2-Ethyl-5-heptylpyrrolidine* (**20**) *and* trans-*2-Ethyl-5-heptylpyrrolidine* (**23**). Using the procedure described above for **12**→**13** + **14**, starting from 800 mg of **17**, 238 mg of **20**, 112 mg of **20**/**23**, and 233 mg of **23** were obtained.

20: ^{1}H-NMR: 2.90 (*m*, 2 H); 2.05 (br. *s*, NH); 1.82 (*m*, 2 H); 1.65–1.20 (*m*, 16 H); 0.90 (*m*, 6 H). ^{13}C-NMR 61.01; 59.53; 36.79; 31.91; 31.40; 30.99; 29.88; 29.50; 29.35; 27.58; 22.72; 14.14; 11.74. EI-MS: 196.2067 ($M^+ - 1$, $C_{13}H_{26}N$, calc. 196.2065), 182, 168, 112, 98, 82, 69, 55, 41.

23: ^{1}H-NMR: 3.9 (br. *s*, NH); 3.16 (*m*, 2 H); 1.98 (*m*, 2 H); 1.70–1.20 (*m*, 16 H); 0.90 (*m*, 6 H). ^{13}C-NMR: 59.89; 58.40; 36.40; 32.16; 31.89; 31.71; 29.76; 29.33; 29.18; 27.28; 22.69; 14.11; 11.44. EI-MS: 196.2054 ($M^+ - 1$, $C_{13}H_{26}N$, calc. 196.2065), 168, 98, 82, 68, 55, 41.

cis-*2-Butyl-5-pentylpyrrolidine* (**21**) *and* trans-*2-Butyl-5-pentylpyrrolidine* (**24**). Reduction of 400 mg of **18** in the manner described for the conversion **12**→**13** + **14** gave a 1:1 mixture **21**/**24** which, after chromatography, yielded 50 mg of **21**, 85 mg of **21**/**24**, and 68 mg of **24**.

21: ^{1}H-NMR: 2.93 (*m*, 2 H); 1.83 (*m*, 3 H); 1.60–1.20 (*m*, 16 H); 0.89 (*m*, 6 H). ^{13}C-NMR 59.47; 36.81; 36.53; 32.13; 31.43; 29.76; 27.25; 22.95; 22.69; 14.09. EI-MS: 196.2050 ($M^+ - 1$, $C_{13}H_{26}N$, calc. 96.2065), 140, 126, 82, 67, 55, 41.

24: ^{1}H-NMR: 3.14 (*m*, 2 H); 2.85 (br. *s*, NH); 1.95 (*m*, 2 H); 1.65–1.20 (*m*, 16 H); 0.88 (*m*, 6 H). ^{13}C-NMR: 58.18; 36.89; 36.62; 32.41; 32.06; 29.54; 27.03; 22.89; 22.71; 14.11. EI-MS: 196.2070 ($M^+ - 1$, $C_{13}H_{26}N$, calc. 196.2065), 140, 126, 82, 67, 55, 41.

cis-*2-Ethyl-5-pentylpyrrolidine* (**22**) *and* trans-*2-Ethyl-5-pentylpyrrolidine* (**25**). Reduction of 600 mg of **19** with $NaBH_4$ in MeOH, followed by a column chromatography on SiO_2 yielded 139 mg of **22**, 41 mg of **22**/**25** and 143 mg of **25**.

22: ^{1}H-NMR: 2.94 (*m*, 2 H); 2.25 (br. *s*, NH); 1.84 (*m*, 2 H); 1.65–1.20 (*m*, 12 H); 0.93 (*m*, 6 H). ^{13}C-NMR: 60.98; 59.50; 36.66; 32.09; 31.34; 30.93; 29.43; 27.20; 22.66; 14.05; 11.70. EI-MS: 168.1750 ($M^+ - 1$, $C_{11}H_{22}N$, calc. 168.1752), 140, 112, 98, 82, 55, 44.

25: ^{1}H-NMR: 3.11 (*m*, 2 H); 2.38 (br. *s*, NH); 1.94 (*m*, 2 H); 1.60–1.20 (*m*, 12 H); 0.89 (*m*, 6 H). ^{13}C-NMR: 59.73; 58.20; 37.11; 32.54; 32.07; 29.84; 27.09; 22.74; 14.12; 11.55. EI-MS: 168.1750 ($M^+ - 1$, $C_{11}H_{22}N$, calc. 168.1752), 140, 126, 112, 98, 81, 68, 55, 44.

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