5. Probes for a Regulatory Site on the Nicotinic Acetylcholine Receptor-Channel. Synthesis of (±)-7-Debutylperhydrohistrionicotoxin, (±)-2-Depentyl-7-debutylperhydrohistrionicotoxin, and their Analogues

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Reaction of glutarimide with pent-4-enylmagnesium bromide, followed by cyclization of intermediate ketoamide, and hydrolysis of the formates **10** and **13** led to the mixture of the hydroxylactams **11** *(cis)* and **14** *(trans)* which could be separated *via* their benzenecarbamates. Reduction of *cis*-hydroxylactam **11** with $LiAlH_4$ yielded 2-depentyl-7-debutylperhydrohistrionicotoxin (**6**), whereas reduction of *trans*-isomer **14** gave the epimeric alcohol **9**. *cis*-Hydroxylactam **11** was converted *via* thiolactam **17** and the methylthio derivative **18** to ketimine **19** which was reduced with $NaBH_4$ yielding a mixture of natural **4** and unnatural **7**, analogues of perhydrohistrionicotoxin (**2**). Reduction of **4** with H_2 in the presence of Pd/C yielded (±)-7-debutylperhydrohistrionicotoxin (**5**).

Perhydrohistrionicotoxin (**2**) is the fully hydrogenated isomer of histrionicotoxin (**1**) and related alkaloids isolated from skin extracts of some Colombian frogs [1–3]. Compounds **1** and **2** represent interesting models to study structural and stereochemical features as they relate to the mechanism of action of cholinergic agonists in the neuromuscular system.

It was found that the (±)-2-depentyl derivative **3**, lacking the C_5 side-chain of **2** has effects similar to those of (±)-**2** on the neuromuscular transmission of the frog nerve-muscle preparation [4] [5]. It was also found that natural (–)-**2** behaved in a manner remarkably similar in this assay to its synthetic, unnatural (+)-enantiomer [6] [7], suggesting that the binding sites of **2** on the acetylcholine receptor interact in a two-point fashion [2].

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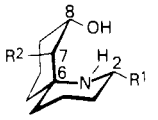
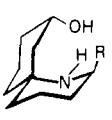
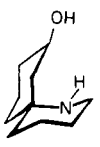
Scheme 1



1 $R^1 = CH_2CH{=}CH{-}C{\equiv}CH$
$R^2 = CH{=}CH{-}C{\equiv}CH$
2 $R^1 = C_5H_{11}$
$R^2 = C_4H_9$
3 $R^1 = H$
$R^2 = C_4H_9$
4 $R^1 = (CH_2)_3CH{=}CH_2$
$R^2 = H$
5 $R^1 = C_5H_{11}$
$R^2 = H$
6 $R^1 = R^2 = H$



7 $R = (CH_2)_3CH{=}CH_2$
8 $R = C_5H_{11}$



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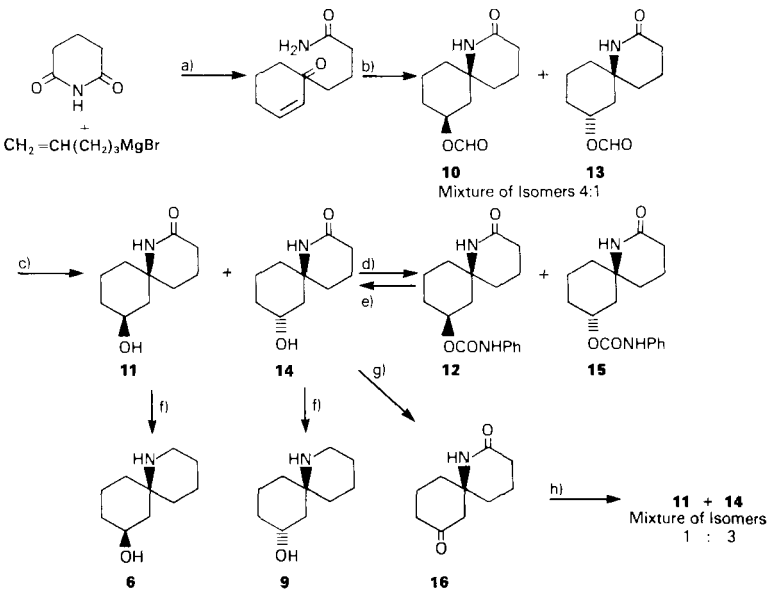
These results prompted an extension of our investigations to other members of this series of spiroamines. In this paper, we would like to report the synthesis of the two diastereoisomeric (±)-alcohols **6** and **9** of the unsubstituted series, the synthesis of the (±)-7-debutyl derivative **5**, its unsaturated derivative **4** with a double bond in ω-position of the C_5 side-chain, and the synthesis of the unnatural analogues **7** and **8**, having a different relative configuration than **4** and **5** at C(2).

The key compound for the synthesis of all analogues in the natural *cis*-series (*cis* refers to the senior substituents at C(6) and C(8)) was the hydroxylactam **11**[3]), which was

Scheme 2



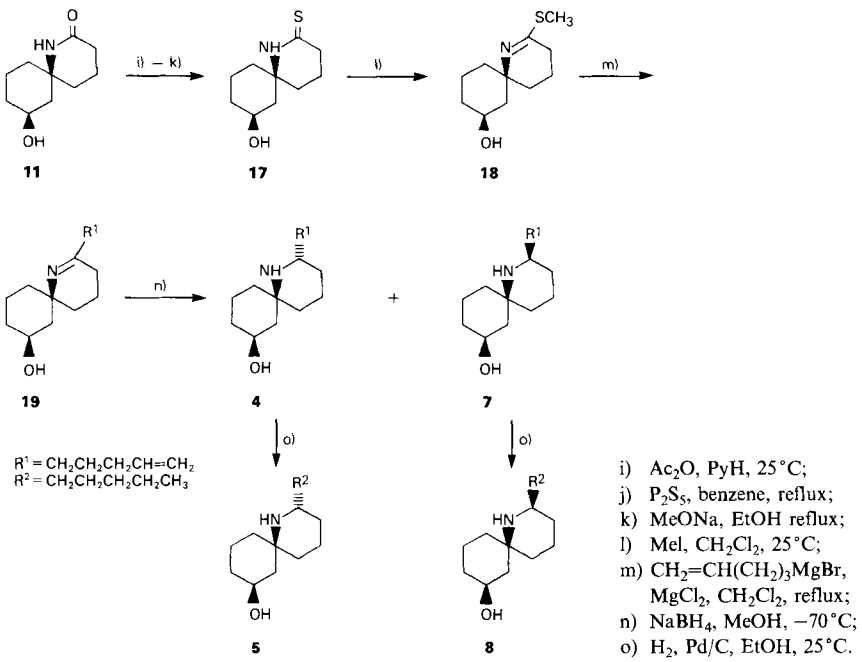
a) THF, 40–60°C; b) HCOOH anh. 25°C; c) KOH/EtOH/H_2O; d) PhNCO, PyH, 25°C; e) MeONa/EtOH, reflux; f) $LiAlH_4$, THF, reflux; g) DMSO/$(COCl)_2$, CH_2Cl_2, −60°C; h) $NaBH_4$, MeOH, −70°C.

[3]) The structures shown in the schemes represent one series of enantiomers. Compounds **4**–**19** described in this paper were prepared as racemates.

prepared by a modified *Speckamp* procedure [8]. Reaction of glutarimide with pent-4-enylmagnesium bromide followed by treatment with anhydrous formic acid led in 42% yield to a 4:1 mixture of the formates **10** *(cis)* and **13** *(trans)*. Although pure *cis*-isomer **10**[4]) could be isolated from the reaction mixture after several crystallizations from AcOEt, it was necessary to find an effective method to separate these two isomers, and to obtain also the *trans*-isomer in pure form. Because **10** and **13** as well as hydroxylactams **11** and **14** (obtained by hydrolysis with KOH/EtOH/H_2O) could not be separated by chromatography, the benzenecarbamates **12** and **15** were synthesized. Chromatographic separation of **12** and **15** followed by hydrolysis in the presence of MeONa in EtOH yielded pure **11** *(cis)* and **14** *(trans)*. Larger amounts of **14** could be obtained by oxidation (see method described in [10]) of an original 4:1 mixture **11**/**14** to ketolactam **16** which when reduced with $NaBH_4$ in MeOH yielded the mixture **11**/**14** in a ratio of 1:3.

Reduction of *cis*-hydroxylactam **11** with $LiAlH_4$ in refluxing THF yielded (±)-2-depentyl-7-debutylperhydrohistrionicotoxin (**6**), whereas the reduction of *trans*-isomer **14** gave the epimeric alcohol **9**. The *cis*-alcohol **6** representing the configuration of histrionicotoxin was previously obtained by *Gössinger et al.* [9].

Scheme 3



[4]) The structural assignments of isomers **10** and **13** were made by comparison of the spectroscopic data of compounds **6** and **9** obtained by $LiAlH_4$ reduction of **10** and **13**, with the data published for the *cis*-alcohol by *Gössinger et al.* [9]. These results were later confirmed by X-ray analysis of hydroxylactam **11**.

Conversion of *cis*-hydroxylactam **11** to *cis*-thiolactam **17** followed by methylation with CH_3I yielded the methylthio derivative **18**, which when reacted with pent-4-enyl magnesium bromide in the presence of anhydrous $MgCl_2$ gave ketimine **19** in 18% yield. The later compound when reduced with $NaBH_4$ in MeOH, at −70°C, yielded a mixture of two diastereoisomeric spiroamines **4** and **7** in a ratio of 3:2. The isomer **4** having the natural configuration of histrionicotoxin was reduced with H_2 in the presence of 10% Pd/C yielding the fully saturated isomer **5**, which is (±)-7-debutylperhydrohistrionicotoxin. Similarly, reduction of **7** gave **8**.

Similar reactions could not be accomplished starting from *trans*-hydroxylactam **14**, since the *trans*-methylthio analog to **18** did not react with the *Grignard* reagent. This can be explained by the inability of the methylthio derivative to form the magnesium-imide complex [11] when the OH-group at C(8) is in *trans*-configuration.

C-alkylation of ketolactam **16** and the results of the biological evaluation of these compounds in frog sciatic nerve muscle preparations will be described in another paper.

Experimental Part

General. Thin-layer chromatography plates (silica gel *GF*) were purchased from *Analtech, Inc.* and silica gel *60* for short column flash chromatography (0.015–0.040 mm) was from *E. M. Reagents*. Melting points were determined on a *Fisher-John* apparatus and are corrected. IR spectra (in cm^{-1}) were obtained on a *Beckman-4230* instrument. ^{1}H-NMR spectra were recorded using a *Varian-HR-220* spectrometer or a *JEOL-FX-100* spectrometer with TMS (= 0 ppm) as the internal reference. ^{13}C-NMR spectra were recorded using a *JEOL-FX-100* spectrometer with TMS (= 0 ppm) as the internal reference. Chemical ionization (CI) MS (*m/z*) were obtained on a *Finnigan-1015D* spectrometer with a model *6000* data collection system. Elemental analysis were performed by the Section on Microanalytical Services and Instrumentation, Laboratory of Chemistry, NIADDK, NIH.

2-Oxo-1-azaspiro[5.5]undec-8-yl Formates (**10** *and* **13**). A solution of pent-4-enylmagnesium bromide (prepared in the usual way from 31.5 g (25 ml, 0.21 mol) of 5-bromo-1-pentene) in 200 ml of THF was added dropwise under Ar at 50–60° to a mechanically stirred solution of 11.3 g (0.1 mol) of glutarimide in 700 ml of THF. The mixture was stirred for 20 h at 40° (oil bath) and evaporated to dryness under reduced pressure (bath temp. 20°) to yield white crystalline material (23.0 g) which was dissolved in 900 ml of anh. HCOOH and kept at r.t. for 4 days. The mixture was then evaporated under reduced pressure, dissolved in $CHCl_3$, washed with a sat. aq. solution of $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness yielding a colorless crystalline product which was recrystallized 3× from AcOEt giving 4.5 g of **10**. The mother liquors gave, after evaporation, 7.4 g of yellowish crystalline product which was chromatographed on silica gel (CH_2Cl_2/MeOH/conc. NH_4OH 240:9:1) yielding 4.5 g of a 3:2 mixture **10**/**13** (ratio determined by ^{1}H-NMR). Total yield of **10** and **13**: 9.0 g (43%). cis-*Isomer* **10**: m.p. 153–155. ^{1}H-NMR ($CDCl_3$): 8.08 (*s*, CHO); 6.55 (br. *s*, NH); 5.15 (*m*, H–C(8)); 2.35 (*t*, *J* = 6, 2H–C(3)); 2.0–1.5 (*m*, 12H). MS (CI): 212 (M^+ + 1). Anal. calc. for $C_{11}H_{17}NO_3$ (211.26): C 62.53, H 8.11, N 6.63; found: C 62.40, H 7.91, N 6.56.

8-Hydroxy-1-azaspiro[5.5]undecan-2-one (**11**; cis). *cis*-Isomer **10** (3.0 g, 14 mmol) was added to a solution of KOH (0.9 g, 16 mmol) in 40 ml of EtOH/H_2O 1:1 and stirred at r.t. for 6 h. Then, the mixture was adjusted to pH 7 with 2N HCl and extracted 4× with $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated to dryness yielding colorless crystalline product which was recrystallized from AcOEt giving 2.02 g (78%) of **11**: m.p. 178–179° IR ($CHCl_3$): 3360, 3300, 1635. ^{1}H-NMR ($CDCl_3$): 8.08 (br. *s*, NH); 4.90 (*s*, 1H, OH); 4.20 (br. *s*, H–C(8)); 2.32 (*m*, 2H–C(3)); 2.1–1.1 (*m*, 12H). MS (CI): 184 (M^+ + 1). Anal. calc. for $C_{10}H_{17}NO_2$ (183.25): C 65.54, H 9.35, N 7.64; found: C 65.72, H 9.40, N 7.62.

1-Azaspiro[5.5]undecan-2,8-dione (**16**). The crude mixture **11**/**14** (4:1) was obtained by hydrolysis of the mixture **10**/**13** as described above. A solution of oxalyl chloride (2.5 ml, 27.5 mmol) in 70 ml of CH_2Cl_2 was placed in a 250-ml flask equipped with two dropping funnels containing DMSO (4.25 ml, 55 mmol) in 25 ml of CH_2Cl_2 and **11**/**14** (4.58 g, 25 mmol) in 50 ml of CH_2Cl_2 resp. The flask was cooled with a dry ice/i-PrOH bath, and the solution of DMSO was added dropwise to the oxalyl chloride at −60°. The mixture was then stirred for

2 min, **11**/**14** added dropwise within 15 min, and stirring continued for an additional 15 min. Et_3N (17.5 ml, 125 mmol) was added, the mixture was stirred for 5 min at −60°, and then allowed to warm to r.t. H_2O (125 ml) was then added, the org. layer separated, and the aq. layer extracted 3× with CH_2Cl_2. The combined org. extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure yielding 3.8 g (84%) of solid, creme-colored product which was used in the next step without purification. A small anal. sample was purified by short-column chromatography (SiO_2, CH_2Cl_2/MeOH/conc. NH_4OH 390:9:1) and crystallized from AcOEt yielding colorless crystals, m.p. 185–186°. IR ($CHCl_3$): 3390, 1714, 1657. ^{1}H-NMR ($CDCl_3$): 7.50 (br. *s*, NH); 2.52 (*m*, 2H–C(7)); 2.35 (*m*, 2H–C(3), 2H–C(9)); 2.1–1.6 (*m*, 8H). MS (CI): 182 ($M^+ + 1$). Anal. calc. for $C_{10}H_{15}NO_2$ (181.24): C 66.27, H 8.34, N 7.73; found: C 66.14, H 8.18, N 7.48.

Reduction of **16** *with* $NaBH_4$. A solution of **16** (900 mg, 5 mmol) in MeOH (30 ml) was cooled with a dry ice/acetone bath, and $NaBH_4$ (200 mg, 5.4 mmol) was added with stirring in one portion. The mixture was stirred for 2 h, while the temp. was rising slowly to r.t. It was then evaporated under reduced pressure, dissolved in $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated to dryness yielding 820 mg (90%) of colorless crystalline material which was used in the next step (separation of *cis*- and *trans*-isomers) without purification. ^{1}H-NMR: mixture of **14** (73%) and **11** (27%).

Separation of Hydroxylactams (cis) **11** *and* **14** (trans). a) *2-Oxo-1-azaspiro[5.5]undec-8-yl Benzenecarbamates* (**12** *and* **15**). A mixture (1.8 g, 9.8 mmol) of **11** (27%) and **14** (73%) was dissolved in 50 ml of dry pyridine. Then, phenyl isocyanate (13 g, 12 ml, 11 mmol) was added and the mixture kept at r.t. for 2 h. It was then evaporated to dryness, dissolved in $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure yielding **12**/**15**. The mixture was separated by short-column chromatography (SiO_2, benzene/acetone 3:1) yielding 0.74 g (25%) of **12** as colorless crystals; m.p. 197–199° (from $(i\text{-}Pr)_2O$). TLC (SiO_2, benzene/acetone 1:1) R_f 0.53. ^{1}H-NMR ($CDCl_3$): 8.55 (br. *s*, H–C(1)); 7.5–7.0 (*m*, 6H, PhNH); 5.13 (br. *s*, H–C(8)); 2.34 (*t*, J = 5.5, 2H–C(3)); 1.9–1.4 (*m*, 12H). MS (CI): 303 ($M^+ + 1$). Anal. calc. for $C_{17}H_{22}N_2O_3$ (302.37): C 67.53, H 7.33, N 9.26; found: C 67.38, H 7.45, N 9.03.

Further elution gave 2.08 g (70%) of **15** as colorless crystals, m.p. 196–198° from $(i\text{-}Pr)_2O$. TLC (SiO_2, benzene/acetone 1:1): R_f 0.31. ^{1}H-NMR ($CDCl_3$): 7.45–6.95 (*m*, PhNH); 6.8 (very br. *s*, H–C(1)); 5.1 (very br. *s*, H–C(8)); 2.35 (*t*, J = 5.5, 2H–C(3)); 2.15–1.25 (*m*, 12H). MS (CI): 303 ($M^+ + 1$). Anal. calc. for $C_{17}H_{22}N_2O_3$ (302.37): C 67.53, H 7.33, N 9.26; found: C 67.71, H 7.34, N 9.24.

b) *Hydrolysis of* **15** *and* **12**, *resp. trans*-Carbamate **15** (1.7 g, 5.6 mmol) was dissolved in 50 ml of 99% EtOH, then 0.45 g (8.2 mmol) of NaOMe was added, and the mixture was refluxed for 20 h. After evaporation under reduced pressure, the residue was dissolved in H_2O, neutralized with 2N HCl and extracted 3× with $CHCl_3$. The org. extracts were combined, dried over Na_2SO_4, evaporated, and chromatographed on silica gel (CH_2Cl_2/MeOH/conc. NH_4OH 190:9:1) yielding colorless solid product which was crystallized from AcOEt giving 0.78 g (76%) of **14** as colorless crystals, m.p. 156–158°. ^{1}H-NMR ($CDCl_3$): 6.45 (*s*, H–C(1)); 3.85 (br. *s*, H–C(8)); 3.30 (*s*, OH); 2.35 (*t*, J = 5.5, 2H–C(3)); 2.1–1.2 (*m*, 12H). MS (CI): 184 ($M^+ + 1$). Anal. calc. for $C_{10}H_{17}NO_2$ (183.25): C 65.54, H 9.35, N 7.64; found: C 65.39, H 9.41, N 7.67.

cis-Carbamate **12** was hydrolyzed in similar manner yielding a product identical with that obtained by hydrolysis of *cis*-formate **10**.

(6RS,8SR)-1-Azaspiro[5.5]undecan-8-ol (**6**). *cis*-Hydroxylactam **11** (915 mg, 5 mmol) and $LiAlH_4$ (190 mg, 5 mmol) were refluxed in THF (50 ml) for 12 h. After cooling, 1.3 ml of H_2O was added dropwise, the mixture was filtered through *Celite*, dried over Na_2SO_4, and evaporated. The product was purified by short-column chromatography (SiO_2, CH_2Cl_2/MeOH/conc. NH_4OH 190:9:1) yielding **6** as colorless oil (790 mg, 93%) which crystallized slowly during standing in the refrigerator. The crystals were washed with Et_2O/hexane and dried, m.p. 80–82° ([8]: 82°). TLC (SiO_2, $CHCl_3$/MeOH/conc. NH_4OH 35:15:3): R_f 0.49. IR (CCl_4): 3300, 2930, 1443, 1175, 1160, 1130, 1118, 1082, 974. ^{1}H-NMR ($CDCl_3$): 3.88 (br. *s*, H–C(8)); 3.63 (br. *s*, OH, NH); 2.80 (br. *s*, 2H–C(2)); 2.4–1.0 (*m*, 14H). ^{13}C-NMR ($CDCl_3$): 67.35, 52.29, 40.64, 39.57, 38.16, 37.13, 33.48, 27.09, 19.73, 15.79. MS (CI): 170 ($M^+ + 1$).

Hydrochloride salt of **6**: m.p. 214–216° ($(i\text{-}Pr)_2O$/EtOH). Anal. calc. for $C_{10}H_{20}ClNO$ (205.73): C 58.38, H 9.80, N 6.81, Cl 17.24; found: C 58.56, H 9.66, N 6.68, Cl 17.15.

(6RS,8RS)-1-Azaspiro[5.5]undecan-8-ol (**9**). The *trans*-isomer **9** was obtained in 79% yield by reduction of **14** in the manner similar to that described above: colorless crystals, m.p. 83–84° (Et_2O/hexane). TLC (SiO_2, $CHCl_3$/MeOH/conc. NH_4OH 35:15:3): R_f 0.61. IR (CCl_4): 3370, 2930, 1452, 1441, 1160, 1130, 1105, 1071, 1047, 1021, 1009. ^{1}H-NMR ($CDCl_3$): 3.82 (*m*, H–C(8)); 2.75 (*m*, 2H–C(2)); 2.25–1.90 (*m*, NH, OH, 2H–C(7)); 1.9–1.0 (*m*, 12H). ^{13}C-NMR ($CDCl_3$): 66.33, 52.83, 44.84, 40.50, 39.52, 35.57, 33.77, 26.80, 20.13, 19.35. MS (CI): 170 ($M^+ + 1$). Anal. calc. for $C_{10}H_{19}NO$ (169.27): C 70.96, H 11.31, N 8.28; found: C 70.58, H 11.69, N 8.32.

8-Hydroxy-1-azaspiro[5.5]undecane-2-thione (**17**; cis). *cis*-Hydroxylactam **11** (1.43 g, 7.8 mmol) was suspended in 20 ml of dry pyridine/Ac_2O 3:1, the mixture stirred overnight, evaporated, taken up in pyridine, evaporated, and finally evaporated with toluene. The product was dissolved in 50 ml of benzene, 0.75 g (3.4 mmol) of P_2S_5 was added, and the mixture was refluxed for 2 h. After cooling, the mixture was diluted with CH_2Cl_2 and the solution washed with sat. aq. solution of $NaHCO_3$ and concentrated to a small volume. MeOH/H_2O 8:2 (100 ml) and K_2CO_3 (2.0 g, 14.5 mmol) were then added, and the mixture was stirred overnight. The mixture was concentrated, and $CHCl_3$ and brine were added. The org. layer was dried over Na_2SO_4 and concentrated under reduced pressure yielding 1.48 g (95%) of colorless solid product which was crystallized from benzene giving colorless crystals of **17**, m.p. 134–135°. ^{1}H-NMR ($CDCl_3$): 10.00 (br. *s*, NH); 4.25 (*s*, H–C(8)); 3.30 (br. *s*, OH); 2.85 (*m*, 2H–C(3)); 2.10–1.25 (*m*, 12H). MS (CI): 200 ($M^+ + 1$). Anal. calc. for $C_{10}H_{17}NOS$ (199.31): C 60.26, H 8.26, N 7.03, S 16.09; found: C 60.45, H 8.92, N 6.93, S 16.19.

2-Methylthio-1-azaspiro[5.5]undec-1-en-8-ol (**18**; cis). *cis*-Lactam **17** (4.85 g, 24 mmol) was dissolved in 50 ml of CH_2Cl_2, 2 ml (5.56 g, 39 mmol) of CH_3I was added, and the mixture was kept overnight at r.t. It was then evaporated under reduced pressure, the residue dissolved in CH_2Cl_2, washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to yield 5.10 g (98%) of **18** as almost colorless oil which was used in the next step without purification. A small anal. sample was purified by short-column chromatography (SiO_2, CH_2Cl_2), converted to the **18** · HCl, and crystallized from acetone yielding colorless crystals, m.p. 193–196°. ^{1}H-NMR ($CDCl_3$, free base): 6.02 (br. *s*, OH); 4.10 (br. *s*, H–C(8)); 2.27 (*s*, CH_3S); 2.3–1.2 (*m*, 14H). MS (CI, free base): 214 ($M^+ + 1$). Anal. calc. for $C_{11}H_{20}ClNOS$ (250.97): C 53.08, H 8.03, N 5.58, Cl 14.13; found: C 52.87, H 8.26, N 5.67, Cl 14.25.

2-(Pent-4'-enyl)-1-azaspiro[5.5]undec-1-en-8-ol (**19**; cis). Compound **18** (4.9 g, 23 mmol) was dissolved in 750 ml of CH_2Cl_2 and 16.0 g (0.17 mmol) of anh. $MgCl_2$ was added. To the stirred solution was added dropwise the solution of *Grignard* reagent (prepared from 30.0 g (0.2 mol) of 5-bromo-1-pentene) in 120 ml of THF/Et_2O 1:1. The mixture was refluxed for 24 h, then cooled, and 60 ml of sat. NH_4Cl solution was added. It was filtered and the filter-cake washed with CH_2Cl_2. The combined org. solutions were dried over Na_2SO_4 and evaporated under reduced pressure yielding an orange oil which was chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH 970:27:3) yielding 3.18 g of unreacted **18**. Further elution gave **19** (0.97 g, 18%) as colorless oil. IR (CCl_4): 3300, 3075, 2925, 1664, 1442, 1415, 1350, 1137, 1088, 950, 908. ^{1}H-NMR ($CDCl_3$): 5.76 (*m*, H–C(4')); 4.95 (*m*, 2H–C(5')); 4.09 (*m*, H–C(8)); 2.12 (*m*, 2H–C(3), 2H–C(1'), 2H–C(3')); 1.90–1.15 (*m*, 14H). MS (CI): 236 ($M^+ + 1$). Anal. calc. for $C_{15}H_{25}NO$ (235.37): C 76.55, H 10.71, N 5.95; found: C 76.52, H 10.80, N 5.78.

(2RS,6RS,8SR)-2-(Pent-4'-enyl)-1-azaspiro[5.5]undecan-8-ol (**4**) *and (2RS,6SR,8RS)-2-(Pent-4'-enyl)-1-azaspiro[5.5]undecan-8-ol* (**7**). Compound **19** (970 mg, 4.13 mmol) was dissolved in 50 ml of MeOH and cooled to –70°. To the stirred solution, 200 mg (5.4 mmol) of $NaBH_4$ was added in one portion. The mixture was then stirred for 2 h while it was warming slowly to r.t. The mixture was evaporated under reduced pressure, dissolved in $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure yielding an oil which was chromatographed on silica gel (CH_2Cl_2/MeOH/conc. NH_4OH (190:9:1) yielding **7** (333 mg, 34%) as colorless oil. IR (CCl_4): 3300, 3080, 2935, 1642, 1450, 1354, 1319, 1187, 1137, 1120, 1085, 1067, 990, 950, 912. ^{1}H-NMR ($CDCl_3$): 5.80 (*m*, H–C(4')); 4.75 (*m*, 2H–C(5')); 4.00 (br. *s*, H–C(8)); 2.80 (*m*, H–C(2)); 2.45–0.75 (*m*, 21H). MS (CI): 238 ($M^+ + 1$).

Hydrochloride salt of **7**, m.p. 172–174° (MeOH/Et_2O). Anal. calc. for $C_{15}H_{28}ClNO$ (273.85): C 65.79, H 10.31, N 5.11; found: C 65.74, H 10.46, N 4.91.

Further elution gave 459 mg (47%) of **4** as a colorless oil. IR (CCl_4): 3320, 3078, 2925, 1640, 1450, 1350, 1320, 1265, 1215, 1200, 1122, 1065, 1047, 971, 910. ^{1}H-NMR ($CDCl_3$): 5.76 (*m*, H–C(4')); 4.95 (*m*, 2H–C(5')); 4.00 (br. *s*, H–C(8)); 3.10 (very br. *s*, OH); 2.60 (*m*, H–C(2)); 2.25–0.75 (*m*, 20H). MS (CI): 238 ($M^+ + 1$).

Hydrochloride salt of **4**, m.p. 186–188° (MeOH/Et_2O). Anal. calc. for $C_{15}H_{28}ClNO$ (273.85): C 65.79, H 10.31, N 5.11; found: C 65.65, H 9.97, N 5.39.

(2RS,6RS,8SR)-2-Pentyl-1-azaspiro[5.5]undecan-8-ol (= (±)-*7-Debutylperhydrohistrionicotoxin;* **5**). Compound **4** (100 mg, 0.42 mmol) was dissolved in EtOH (10 ml), then 100 mg of 10% Pd/C was added and the mixture stirred overnight at r.t. under H_2. The catalyst was then filtered off and the solution evaporated to dryness yielding 100 mg (99%) of **5** as a colorless oil. IR (CCl_4): 3340, 2937, 2865, 2730, 1460, 1370, 1280, 1264, 1200, 1122, 1082, 985. ^{1}H-NMR ($CDCl_3$): 6.25 (br. *s*, OH, NH); 3.98 (br. *s*, H–C(8)); 2.85 (*m*, H–C(2)); 2.07 (*m*, 3H); 1.70 (*m*, 11H); 1.30 (*m*, 8H); 0.88 (*m*, 3H–C(5')). MS (CI): 240 ($M^+ + 1$).

Hydrochloride salt of **5**, m.p. 203–204° (MeOH/Et_2O). Anal. calc. for $C_{15}H_{30}ClNO$ (275.86): C 65.31, H 10.96, N 5.08, Cl 12.85; found: C 65.55, H 10.67, N 5.13, Cl 13.08.

(2RS,6SR,8RS)-2-Pentyl-1-azaspiro[5.5]undecan-8-ol (**8**). Compound **7** (70 mg, 0.30 mmol) was reduced with H_2 in the presence of 10% Pd/C as described above yielding 68 mg (97%) of **8** as colorless oil. IR (CCl_4):

3300, 2935, 1450, 1135, 1120. ^{1}H-NMR ($CDCl_3$): 4.05 (*s*, H–C(8)); 2.90 (*m*, H–C(2)); 2.40–1.00 (*m*, 22H); 0.88 (*m*, 3H–C(5')). MS (CI): 240 ($M^+ + 1$).

Hydrochloride salt of **8**, m.p. 207–209° (MeOH/Et_2O). Anal. calc. for $C_{15}H_{30}ClNO$ (275.86): C 65.31, H 10.96, N 5.08, Cl 12.85; found: C 65.32, H 10.96, N 5.01, Cl 12.97.

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