in calculated positions with the assumption C–H = 0.98 Å. The final full-matrix least-squares refinement yielded agreement indices of R 0.067 and R_w 0.058 for the 1079 intensities with $F_o^2 > 1\sigma(F_o^2)$ and the 163 variables (anisotropic non-hydrogen atoms and hydrogen atoms fixed). The final difference electron density map contained maximum and minimum peak heights of 0.19 and −0.19 e/Å^3.

Acknowledgment. We acknowledge partial support from the National Science Foundation and the National Institutes of Health. J.R. thanks the honors program at The Ohio State University for an undergraduate research scholarship. We wish to thank Judy Gallucci for determination of X-ray structure and Nick Crano for technical assistance.

Supplementary Material Available: Preparation of **2e–g** and 1-chloro-3,3,6,6-tetramethoxy-1,4-cyclohexadiene; monohydrolysis of chloro tetramethyl quinone bis(ketal) and **2h**; addition of phenyllithium to 3-methyl-4,4-dimethoxy-2,5-cyclohexadienone, **2j**, **2k**, *p*-(*tert*-butyldimethylsiloxy)bromobenzene, 4-methyl-4-(*p*-(*tert*-butyldimethylsiloxy)phenyl)-2,5-cyclohexadienone, **5e**, **5f**, **5g**, 4-hydroxy-4-vinyl-2,5-cyclohexadienone ethylene glycol ketal, and 4-methoxy-4-vinyl-2,5-cyclohexadienone; crystallographic details for *rel*-(4*S*,5*S*)-*cis*-4-methoxy-5-propenyl-4-phenylcyclohex-2-en-1-one; and bond lengths, angles, positional and thermal parameters, and diagrams for $C_{16}H_{18}O_2$ (19 pages); tables of structure factors (8 pages). Ordering information is given on any current masthead page.

Highly Stereoselective Ring Contraction of Heterocyclic Enamines: Total Synthesis of Perhydrohistrionicotoxin and Its 2,6-Epimer

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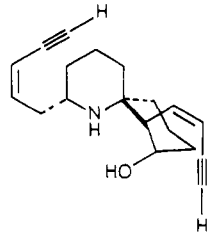
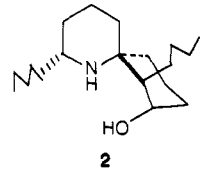
The total syntheses of perhydrohistrionicotoxin (PHTX) and its 2,6-epimer in which the pentyl group, introduced in the early stages, controls the relative configuration of C6 in a highly stereoselective manner are described. Seven-membered heterocyclic enamino ester **8**, enamino aldehyde **9**, and enamino acetal **12** underwent highly stereoselective ring contractions giving gem-bifunctionalized piperidines **10a**, **11a**, and **11b**, respectively. The resultant aldehydes **11a** and **10a** were respectively converted into two diastereoisomeric azaspiro enones **17a** and **17b**. The total synthesis of PHTX and its 2,6-epimer was completed from the azaspiro enone **17b**.

Introduction

Natural histrionicotoxin **1** [(−)-HTX] and its fully hydrogenated unnatural derivative, perhydrohistrionicotoxin (**2**) (PHTX), are now considered to be important biochemical tools for studying the mechanism of the action of cholinergic agonists in the neuromuscular system.[2] Owing to the unusual structure of the azaspiro[5.5]undecane ring system and their remarkable pharmacologic properties as neurotoxins in conjunction with their low natural occurrence, much work over the last 10 years has been devoted to the study of the synthesis of these molecules.[2-8]



1



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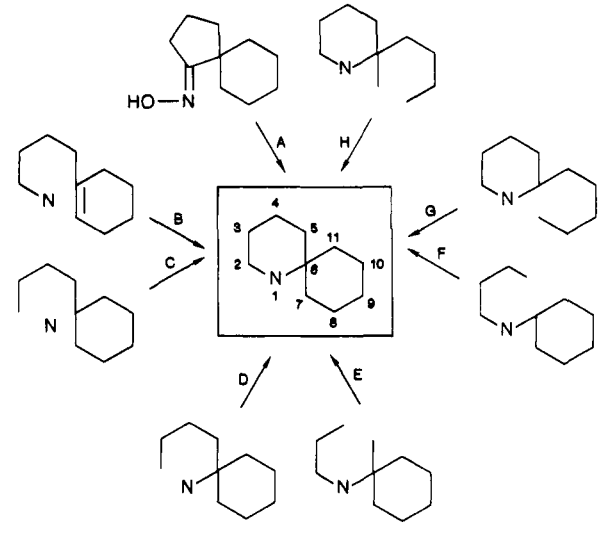
Scheme I



One of the main problems in these studies is how to approach the azaspiro[5.5]undecane ring system with the

(1) (a) Taken in part from the thesis of M.K. Université de Rouen, 1987. (b) Taken in part from the thesis of B.M. Université de Rouen, 1988.

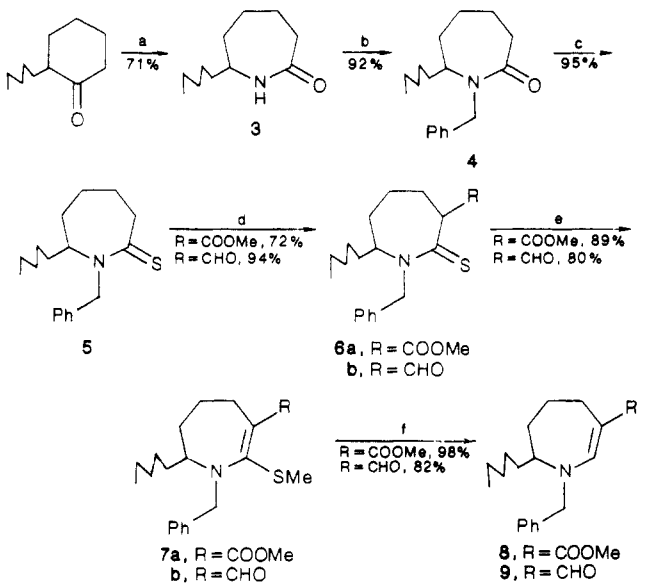
(2) (a) Daly, J. W. Alkaloids of Neotropical Poison Frogs (Dendrobatide). In *Progress in the Chemistry of Organic Natural Products*; Hertz, W., Griesebach, H., Kirby, G. W., Eds.; Springer-Verlag: Vienna, New York, 1982; Vol. 41, pp 206–340. (b) Takahashi, K., Jacobson, A. E.; Mak, C.-P.; Witkop, B.; Brossi, A.; Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Bavoso, A.; Silverton, J. V. *J. Med. Chem.* **1982**, *25*, 919. (c) The total synthesis of (+)- and (−)-PHTX by optical resolution of a hydroxy lactam intermediate: Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.

(3) The total synthesis of (±)-PHTX: (a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (b) Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009. (c) Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2011. (d) Corey, E. J.; Balanson, R. D. *Heterocycles* **1976**, *5*, 445. (e) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

(4) For reviews on synthetic studies until 1981, see: (a) Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507. (b) Witkop, B.; Gössinger, E. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 168. (c) Quinkert, G.; Montforts, F.-P.; Ockenfeld, M.; Rehm, D. *Synform* **1984**, 1.

0022-3263/89/1954-4419$01.50/0

Scheme II[a]



[a] Reagents: (a) H_2NOSO_3H, HCOOH; (b) $PhCH_2Br$, tBuOK; (c) Lawesson's reagent;[12] (d) R = COOMe, iPr_2NMgBr, $(MeO)_2CO$; R = CHO, $tBuOCH(NMe_2)_2$, HCl; (e) Me_2SO_4, NEt_3; (f) Raney nickel, acetone.

appropriate functionalities on it. We have classified about 40 approaches described in over 50 papers[5r,s] for the construction of the azaspiro[5.5]undecane ring system in eight categories shown in Scheme I.

The starting material of the first six approaches (A–F) is a carbocyclic compound and that of the last two (G, H), a heterocyclic compound. Approach B is the best explored strategy and was used for the first and only total synthesis of (±)-HTX (1) by Kishi et al.,[6] for two[3c,d] of five total syntheses of (±)-PHTX (2), and for about 10 formal syntheses[4,5b-i] of 2. The three other total syntheses of 2 used approaches A,[3a] D,[3b] and G.[3e] Only a few examples were reported for the other approaches (C,[5j] E,[5r] F,[5o] H[7]).

In most of these syntheses, the five-carbon unit at C2 was introduced at the very last stage with or without stereoselectivity.

In the previous reports[7,8] we have demonstrated the utility of ring contraction of seven-membered heterocyclic enamines as a method for construction of 2,2-bifunctionalized piperidinic compounds which are direct precursors for azaspiro[5.5]undecane ring systems according to approach H. Here, we describe the stereochemical features of this reaction and its application to the total synthesis of 2 in which the pentyl group, introduced in the early stages, controls the relative configuration of C6 in a highly stereoselective manner.

Results and Discussion

The required enamines 8 and 9 were prepared by methods similar to those used for their analogues without the pentyl group[7,8] (Scheme II).

Formylation and methoxycarbonylation of thiolactam 5 were carried out respectively with methyl carbonate leading to **6a** and with Bredereck's reagent leading to **6b**.

Methylation and deprotonation of the functionalized thiolactam **6a** affords tetrahydroazepine **7a**. Reductive desulfurization of **7a** to the enamino ester 8 was accomplished by deactivated Raney nickel in 62.5% overall yield from thiolactam 5. A similar reaction from the functionalized thiolactam **6b** leads to enamino aldehyde 9 with a 61.5% overall yield from the same thiolactam 5.

On treatment with bromine followed by water/triethylamine, the enamino ester 8 was converted into the formyl ester **10a** in quantitative yield. No detectable amount of the other diastereoisomer was observed in this reaction (Scheme III).

In a similar reaction from the enamino aldehyde 9, treatment with bromine followed by methanol/triethylamine gave aldehyde **11a** as the major product. In this case, the formation of about 5% of minor isomer **11b** was observed. The enamino aldehyde 9 could also be converted to enamino acetal 12, which, on treatment with bromine followed by water/triethylamine, afforded the same ring-contracted piperidines **11a** and **11b** with reversed selectivity. In all cases, the β-substituent of the starting enamine is recovered in the transconfiguration with respect to the pentyl group after ring contraction (Scheme III).

The stereochemical assignment of the diastereoisomeric aldehydes **11a** and **11b** was established by ^1H NMR (500 MHz) spectroscopy. Thus the NOE difference spectra of aldehyde **11a** show a NOE (nuclear Overhauser enhancement) between the CHO proton at 9.7 ppm and the C6 proton at 2.7 ppm, and those of **11b** show equally a NOE between the $CH(OMe)_2$ proton at 4.6 ppm and the C6 proton at 2.6 ppm. The configuration of the formyl ester **10a** was determined by subsequent synthesis of azaspiro enone **17b**, which differs from the isomeric enone **17a** obtained from **11a**. These attributions were also confirmed in the successful synthesis of PHTX from **17b**.

To explain the highly stereoselective formation of formyl ester **10a** from the enamino ester 8, pathways A and B leading respectively to diastereomeric formyl esters **10a** and **10b** were compared (Scheme IV). In both paths, enamino ester 8 is converted into an α-brominated iminium salt **13**, leading through basic treatment to the hydroxy compound **14**. This last material **14** leads to the formyl ester **10** via an aziridinium salt resulting from an intramolecular substitution of bromide ion, with inversion of configuration. On comparison of path A and path B, it can be seen that the preferred formation of **10a** needs as the stereochemical key step a bromine addition on enamine 8 from the same side as the pentyl group, leading to the iminium salt **13a**.

The striking preference for path A can be rationalized by stereoelectronic considerations.[9] Due to benzyl–pentyl

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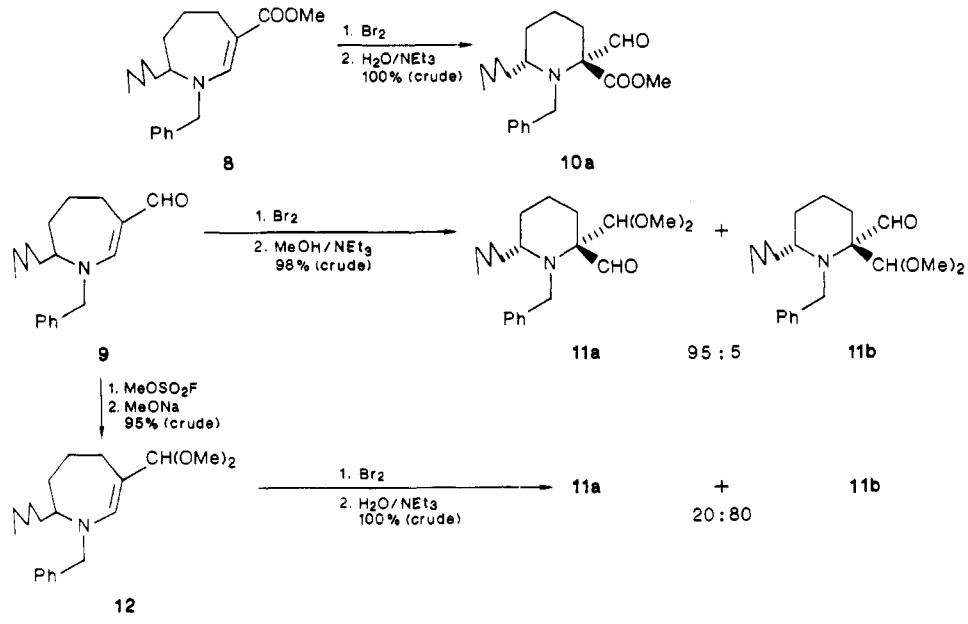
(6) The total synthesis of (±)-HTX: Carey, S. C.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, *26*, 5887.

(7) (a) Duhamel, P.; Kotera, M.; Monteil, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2353. (b) Duhamel, P.; Kotera, M. *J. Org. Chem.* **1982**, *47*, 1688.

(8) Duhamel, P.; Kotera, M. *J. Chem. Res., Synop.* **1982**, 276; *J. Chem. Res., Miniprint* **1982**, 2855.

Scheme III



strain in 8, the conformer **8a** is probably predominant. Axial bromination by a chair-like transition state would occur preferentially from the same side as the pentyl group, affording the iminium salt **13a** as the major intermediate. Another explanation could be the existence of an equilibrium between the salts **13a** and **13b**, the former being consumed faster, during the following steps.

The functionalized piperidines **11a** and **10a** were respectively converted to two isomeric azaspiro enones **17a** and **17b** through the sequences of reactions outlined in Schemes V and VI.

Thus the crude aldehyde **11a** obtained from **9** was condensed with acetone to give the unsaturated keto acetal **16** in 68% yield from **9**, after flash chromatographic removal of the minor stereoisomer. After hydrogenation on 5% Pd/C and hydrolysis of acetal, the resulting keto aldehyde was cyclized to the enone **17a** in 66% yield from **16** (Scheme V). However, the synthesis of the other isomer, **17b**, was carried out from formyl ester **10a** obtained as a single product from **8**. Attempted aldol condensation of **10a** with acetone as described for **11a** was unsuccessful since, with basic treatment, the formyl group cleaved easily. The conversion of **10a** into the unsaturated ketone **18** was achieved by condensation with Tripett–Walker ylide in refluxed toluene. After hydrogenation on 5% Pd/C, the ester function of **19** was reduced to aldehyde in four steps while the keto group was protected, and the resulting keto aldehyde **20** was cyclized as above to the enone **17b** (Scheme VI).

The final steps of total synthesis of PHTX and its 2,6-epimer from **17b** were carried out according to the procedure described by Pearson et al.[5j] for the conversion of the dependyl analogue of **17** to the dependyl-PHTX with slight modifications (Scheme VII).

An attempt at 1,4-addition of lithium dibutylcuprate to the enone **17b** in the usual procedure gave unsatisfactory results due mostly to an extended amount of 1,2-addition. The desired transformation was accomplished by using Normant's procedure[10] in which the mixture of triethylamine/chlorotrimethylsilane was added before the enone **17b** to a solution of lithium dibutylcuprate. The resulting trimethylsilyl enol ether was directly treated with benzeneselenenyl chloride followed by H_2O_2/AcOH[5j] to give butyl enone **21** in 60% overall yield from **17b**. The 9-keto group was then removed to give **22** on treatment with sodium borohydride followed by $LiAlH_4/AlCl_3$. Hydroboration/oxidation of **22** was carried out according to Godleski's procedure[5e] described for its dependyl analogue to yield a 1:2 mixture of alcohols **23a** and **23b**, which were separated by flash chromatography in 17% and 37% yields, respectively (isolated yields). Hydrogenolysis of alcohols **23a** and **23b** over 10% Pd/C affords respectively debenzylated product **2** and its 2,6-epimer **24**. The former product was found to be identical with PHTX by spectroscopic data[11] (IR, ^1H and ^{13}C NMR) and physical data[3b] (melting point of hydrochloric salt) while the latter was assigned as 2,6-epi-PHTX.

Experimental Section

General Methods. All melting points are uncorrected. Infrared spectra (IR) were recorded on a PE 337 spectrophotometer and reported in cm^{-1}. ^1H NMR spectra were taken on PE R12 (60 MHz), Bruker AW80 (80 MHz), and Bruker WM 500 (500 MHz) instruments. ^{13}C NMR spectra were taken on a Varian CFT 20 instrument. The chemical shifts (δ values) are given in parts per million relative to TMS as an internal standard in $CDCl_3$ solutions and coupling constants in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

7-Pentylhexahydroazepin-2-one (3). To a solution of hydroxylamine-*O*-sulfonic acid (12.46 g, 110 mmol) in formic acid (50 mL) was added over 25 min at room temperature a solution of 2-pentylcyclohexanone[8] (16.83 g, 100 mmol). The mixture was refluxed for 1 h. After cooling, the reaction mixture was poured into saturated aqueous NH_4Cl (100 mL)) and water (100 mL), extracted with chloroform (4 × 50 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), dried over Na_2CO_3, and concentrated. The resulting solid was recrystallized from pentane

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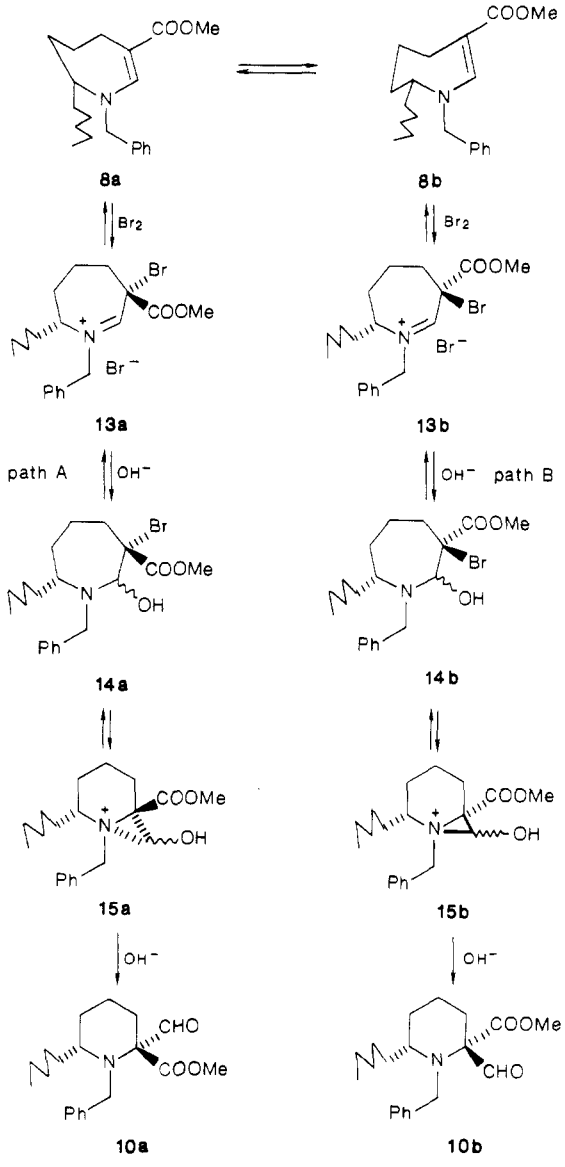
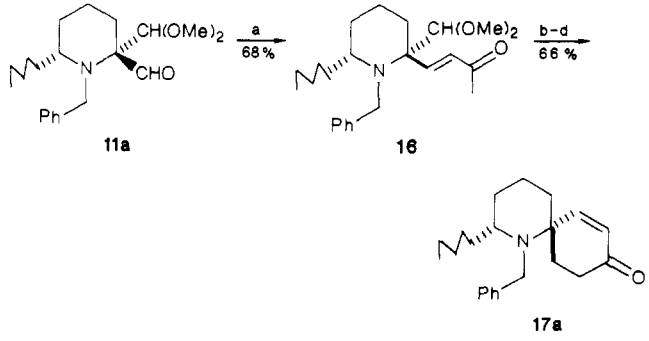
(10) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305.

(11) (a) Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597. (b) Tokuyama, T.; Yamamoto, J.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1983**, *39*, 49.

Scheme IV



Scheme V[a]

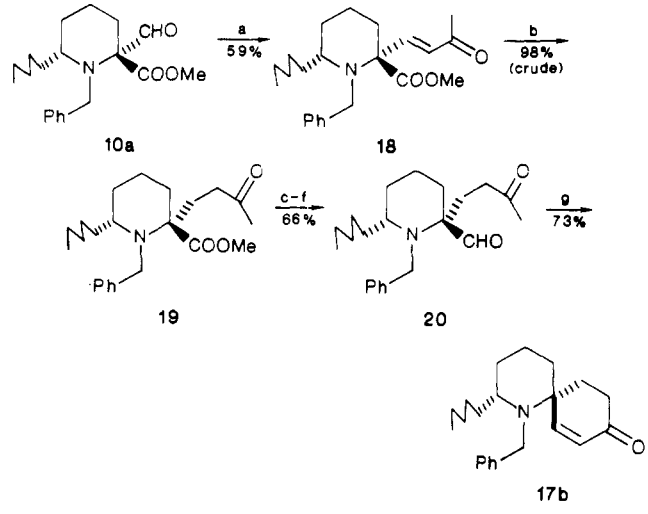


[a] Reagents: (a) acetone/KOtBu; (b) H_2/Pd-C, 5%; (c) *p*-TsOH/acetone; (d) KOtBu.

to yield the lactam **3** (13 g, 71%): mp 57–59 °C; IR (Nujol) 3220, 1665; ^{1}H NMR (60 MHz) 0.6–1.05 (m, 3 H), 1.05–2.15 (m, 14 H), 2.15–2.6 (m, 2 H), 3.0–3.5 (m, 1 H), 5.85–6.35 (m, 1 H).

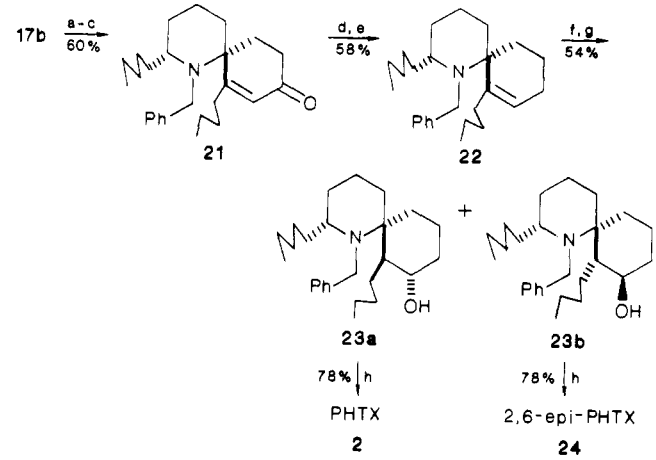
1-Benzyl-7-pentylhexahydroazepin-2-one (4). To a suspension of tBuOK (4.3 g, 38 mmol) in THF (80 mL) was added dropwise over 15 min at room temperature a solution of 7-pentylhexahydroazepin-2-one (**3**) (5.8 g, 31.6 mmol) in THF (40 mL). After 10 min, a solution of benzyl bromide (5.8 g, 33.9 mmol) in THF (5 mL) was added dropwise over 10 min and the mixture

Scheme VI[a]



[a] Reagents: (a) $Ph_3P{=}CHCOCH_3$; (b) H_2/Pd-C, 5%; (c) $(CH_2OH)_2$/*p*-TsOH; (d) Dibal; (e) $(COCl)_2$/DMSO/NEt_3; (f) HCl; (g) KOtBu.

Scheme VII[a]



[a] Reagents: (a) $Bu_2CuLi/NEt_3/TMSCl$; (b) PhSeCl; (c) H_2O_2/AcOH; (d) $NaBH_4$; (e) $LiAlH_4/AlCl_3$; (f) BH_3/Me_2S; (g) H_2O_2/NaOH; (h) H_2/Pd-C, 5%.

was refluxed for 1 h. After cooling, the reaction mixture was poured into water (100 mL), extracted with chloroform, dried over $MgSO_4$, and concentrated. The oily residue was distilled (165–170 °C/0.15 mmHg) to yield the benzyl lactam **4** (7.96 g, 92%): IR (neat) 1635; ^{1}H NMR (60 MHz) 0.7–1.0 (m, 3 H), 1.0–1.9 (m, 14 H), 2.45–2.75 (m, 2 H), 3.15–3.5 (m, 1 H), 4.05 and 5.05 (AB q, J = 15 Hz, 2 H), 7.25 (s, 5 H).

1-Benzyl-7-pentylhexahydroazepine-2-thione (5). According to a previous procedure, a solution of the 1-benzyl-7-pentylcaprolactam **4** (13.6 g, 49.7 mmol) and the Lawesson's reagent[12] (6.0 g, 14.8 mmol) in HMPA (60 mL) was heated at 100 °C for 2.5 h. After cooling, the mixture was poured into water (250 mL), extracted with ether (4 × 70 mL), washed with saturated NH_4Cl solution (2 × 100 mL), dried over Na_2CO_3, and concentrated to yield the thiolactam **5** (13.65 g, 95%), which was utilized without further purification: IR (Nujol) 1608, 1499, 1453, 1380; ^{1}H NMR (60 MHz) 0.6–1.05 (m, 3 H), 1.05–2.05 (m, 14 H), 2.5–4.0 (m, 3 H), 4.72 and 5.97 (AB q, J = 15 Hz, 2 H), 7.3–7.6 (m, 5 H).

Methyl 1-Benzyl-7-pentyl-2-thioxohexahydroazepine-3-carboxylate (6a). To a solution of ethylmagnesium bromide (85.5 mmol) in THF (50 mL) was added dropwise at room temperature diisopropylamine (8.7 g, 85.5 mmol), and the mixture refluxed

(12) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chem. Belg.* **1978**, *87*, 229.

for 1 h. After cooling, a solution of 1-benzyl-7-pentylhexahydroazepine-2-thione (**5**) (8.2 g, 28.3 mmol) in THF (10 mL) was added. The mixture was stirred for 1 h at room temperature and refluxed for 20 min. A solution of methyl carbonate (6.84 g, 85.4 mmol) in THF (10 mL) was added dropwise at −15 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The hydrolysis was carried out by addition of 2 M hydrochloric acid (60 mL) at 0 °C, the solution was extracted with dichloromethane and dried over $MgSO_4$, and the solvent was removed by evaporation. The oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (4:1) as the eluant to yield 7.05 g (72%) of an oily mixture of two diastereoisomeric esters **6a** (ratio ≃ 1:1): IR (neat) 1750; ^{1}H NMR (60 MHz) 0.7–1.05 (m, 3 H), 1.05–2.1 (m, 15 H), 3.75 (s, 3 H), 4.25–4.5 (m, 1 H), 4.62 and 5.95 (AB q, J = 14 Hz, 1 H), 5.15 and 5.55 (AB q, J = 14 Hz, 1 H), 7.1–7.5 (m, 5 H).

Methyl 1-Benzyl-2-(methylthio)-7-pentyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carboxylate (7a). The above mixture of esters **6a** (2.77 g, 7.97 mmol) was heated with dimethyl sulfate (1.1 g, 8.7 mmol) at 65–70 °C for 3 h. After cooling, the mixture was diluted with 30 mL of dichloromethane and triethylamine (1.6 g, 15.7 mmol) was slowly added with stirring at room temperature. After 1 h, the solvent was removed in vacuo and the residual oil was extracted with ether (20 mL × 6) to give β-methylthio ester **7a** (2.57 g, 89%) as an oil, which was utilized without further purification: IR (neat) 1690, 1615; ^{1}H NMR (60 MHz) 0.7–1.05 (m, 3 H), 1.05–1.65 (m, 14 H), 2.23 (s, 3 H), 3.1–3.6 (m, 1 H), 3.72 (s, 3 H), 4.38 and 4.8 (ABq, J = 16 Hz, 2 H), 7.38 (s, 5 H).

Methyl 1-Benzyl-7-pentyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carboxylate (8). To about 10 g of Raney nickel W2, previously refluxed in acetone (150 mL) for 45 min, was added a solution of the β-methylthio ester **7a** (2.57 g, 7.1 mmol) in acetone (10 mL), and the mixture was refluxed for 4 h. After cooling, the solution was decanted and the catalyst was washed five times with acetone. The decanted solution and washings were together filtered and concentrated. The resulting oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (4:1 to 2:1) as the eluant to give enamino ester **8** (2.19 g, 98%) as an oil: IR (neat) 1690, 1615; ^{1}H NMR (60 MHz) 0.7–1.05 (m, 3 H), 1.05–1.6 (m, 8 H), 1.6–1.8 (m, 4 H), 2.0–3.0 (m, 1 H), 3.6 (s, 3 H), 4.25 (s, 2 H), 7.25 (s, 5 H), 7.45 (s, 1 H). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.96; H, 9.40; N, 4.70.

1-Benzyl-2-thioxo-7-pentylhexahydroazepine-3-carbaldehyde (6b). A mixture of 1-benzyl-7-pentylhexahydroazepine-2-thione (**5**) (15.1 g, 52.3 mmol) and Bredereck's reagent[13] [tBuOCH(NMe_2)$_2$, 10.9 g, 62.5 mmol] was heated at 150 °C until most of the *tert*-butyl alcohol had been removed by distillation (about 1 h). An additional amount of Bredereck's reagent (total 10.1 g, 57.9 mmol) was added in four portions and the heating repeated. After cooling, the reaction mixture was poured into 2N HCl (200 mL), stirred overnight at room temperature, then extracted with ether, washed with brine, dried over 4-Å molecular sieves, and concentrated at reduced pressure to yield 15.7 g (94%) of an oily mixture of two diastereoisomeric aldehydes **6b** (ratio ≃ 7:3), which was utilized without further purification: IR (neat) 1722, 1606; ^{1}H NMR (60 MHz) 0.84 (br t, J = 6 Hz, 3 H), 1.0–2.2 (m, 14 H), 3.5–4.0 (m, 2 H), 4.69 and 5.91 (AB q for major isomer, J = 15 Hz), 5.20 and 5.33 (AB q for minor isomer, J = 15 Hz), 7.2–7.5 (m, 5 H), 9.95 (d, J = 1 Hz, 1 H).

1-Benzyl-2-(methylthio)-7-pentyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carbaldehyde (7b). The above mixture of aldehydes **6b** (15.7 g, 49.0 mmol) was diluted with dimethyl sulfate (12.6 g, 0.1 mol) in 15 mL of dichloromethane and stirred at room temperature overnight. To this mixture was slowly added triethylamine (10.0 g, 0.1 mol) at room temperature with stirring. After 1 h, the oily residue was extracted four times with hot petroleum ether and the combined extracts were filtered and concentrated at reduced pressure to yield 13.1 g (80%) of β-methylthio aldehyde **7b** as an oil, which was utilized without further purification: IR (neat) 1630; ^{1}H NMR (60 MHz) 0.88 (br t, J = 5 Hz, 3 H), 1.0–2.3 (m, 12 H), 2.26 (s, 3 H), 2.6–3.9 (m, 3 H), 4.73 and 4.76 (AB q, J = 15 Hz, 2 H), 7.35 (s, 5 H), 10.10 (s, 1 H); ^{13}C NMR (20 MHz) 13.2, 17.4, 19.5, 21.7, 24.9, 25.6, 29.7, 30.8, 30.8, 53.6, 61.9, 120.3, 126.9, 127.6, 127.8, 137.5, 165.7, 189.3.

1-Benzyl-7-pentyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carbaldehyde (9). To about 50 g of Raney nickel W2, previously refluxed in acetone (100 mL) for 1.5 h, was added a solution of the β-methylthio aldehyde **7b** (13.1 g, 39.5 mmol) in acetone (50 mL), and the mixture was refluxed for 2 h. After cooling, the solution was decanted and the catalyst was washed nine times with acetone. The decanted solution and washings were together filtered and concentrated. The resulting oily residue was purified by flash chromatography on silica gel with ether as the eluant to give enamino aldehyde **9** (9.3 g, 82%) as an oil: IR (CCl_4) 1660, 1609; ^{1}H NMR (60 MHz) 0.88 (br t, 3 H), 1.0–2.0 (m, 12 H), 2.0–2.9 (m, 2 H), 3.0–3.7 (m, 1 H), 4.46 (s, 2 H), 6.73 (s, 1 H), 7.2–7.5 (m, 5 H), 8.86 (s, 1 H); ^{13}C NMR (20 MHz) 14.0, 20.1, 22.5, 24.2, 26.3, 30.8, 30.8, 31.7, 61.0, 61.6, 114.6, 127.2, 128.0, 128.9, 137.3, 160.0, 190.8. Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.90; H, 9.70; N, 5.09.

1-Benzyl-7-pentyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carbaldehyde Dimethyl Acetal (12). A solution of the enamino aldehyde **9** (160 mg, 0.559 mmol) and methyl fluorosulfate (90 mg, 0.79 mmol) in dichloromethane (1 mL) was stirred at room temperature for 1 h. To this mixture was added a methanolic solution (0.8 M) of sodium methoxide (1.0 mL, 0.8 mmol) with stirring. After 10 min, the solvent was removed in vacuo and the residue was extracted three times with 5 mL of ether. The combined extracts were together filtered, and the ether was removed in vacuo to give 176 mg (95%) of **12** as an oil, which was utilized without further purification: IR (neat) 1670, 1610; ^{1}H NMR (60 MHz, CCl_4), 0.88 (br t, J = 5 Hz, 3 H), 1.0–2.3 (m, 14 H), 3.11 (s, 3 H) 3.16 (s, 3 H), 4.08 (s, 2 H), 4.31 (s, 1 H), 5.88 (br s, 1 H), 7.27 (s, 5 H).

(2*R,6*R**)-Methyl 1-Benzyl-2-formyl-6-pentylpiperidine-2-carboxylate (10a).** To a solution of enamino ester **8** (3.16 g, 10.0 mmol) in ether (100 mL) was added dropwise at −70 °C 1.8 g (11 mmol) of bromine in 5 mL of dichloromethane and 10 mL of ether. After the addition had been completed (about 10 min), the resulting yellow suspension of iminium salt was stirred at this temperature for 1.5 h. To this suspension was added a mixture of water (216 mg, 12 mmol) and triethylamine (3.05 g, 30 mmol) at −70 °C, and the reaction mixture was allowed to warm to room temperature, stirred for 2 h, and filtered. The filtrate was concentrated at reduced pressure, and dry cold ether was added to the residue. The triethylamine hydrobromide was filtered off and the solvent evaporated at reduced pressure to give 3.32 g (100%) of **10a** as an oil, which was utilized without further purification: IR (neat) 1750, 1730, 1610; ^{1}H NMR (60 MHz) 0.6–0.9 (m, 3 H), 0.9–2.3 (m, 14 H), 2.6–3.05 (m, 1 H), 3.75 (s, 3 H), 4.15 and 4.85 (AB q, J = 18 Hz, 2 H), 7.05–7.5 (m, 5 H), 9.45 (s, 1 H).

(2*S,6*R**)-1-Benzyl-2-(dimethoxymethyl)-6-pentylpiperidine-2-carbaldehyde (11a).** To a solution of enamino aldehyde **9** (1.45 g, 5.1 mmol) in ether (60 mL) was added dropwise at −70 °C 0.84 g (5.3 mmol) of bromine in 15 mL of ether. After the addition had been completed (about 10 min), the resulting yellow suspension of iminium salt was stirred at this temperature for 1.5 h. To this suspension was added a mixture of methanol (38 g, 1.2 mol) and triethylamine (3.1 g, 30 mmol) at −70 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 48 h. The solution was concentrated at reduced pressure, and ether (50 mL) was added to the residue. The triethylamine hydrobromide was filtered off and the solvent evaporated at reduced pressure to give 1.74 g (98%) of **11a** as an oil, which was utilized without further purification. This crude product contained about 5% of the other isomer **11b**: IR (neat) 1737, 1609; ^{1}H NMR (500 MHz) 0.81 (t, J = 7 Hz, 3 H), 1.1–2.0 (m, 14 H), 2.6–2.7 (m, 1 H), 3.09 (s, 3 H), 3.35 (s, 3 H), 3.97 (br d, J = 15 Hz, 1 H), 4.05–4.15 (m, 1 H), 4.28–4.38 (m, 1 H), 7.20 (t, J = 9 Hz, 1 H), 7.31 (t, J = 9 Hz, 2 H), 7.50 (d, J = 9 Hz, 2 H), 9.64 (s, 1 H); ^{13}C NMR (20 MHz) 13.6, 19.2, 22.3, 22.6, 26.4, 26.7, 31.6, 33.5, 49.9, 56.5, 58.1, 58.8, 72.9, 109.0, 126.9, 127.5, 142.6, 204.1.

(2*R,6*R**)-1-Benzyl-2-(dimethoxymethyl)-6-pentylpiperidine-2-carbaldehyde (11b).** To a solution of enamino acetal **12** (176 mg, 0.531 mmol) in ether (2 mL) was added at −70

(13) Bredereck, H.; Simchen, G.; Funke, B. *Chem. Ber.* **1971**, *104*, 2709.

°C 86 mg (0.54 mmol) of bromine in 1 mL of ether. The resulting yellow suspension of iminium salt was stirred at this temperature for 40 min. To this suspension was added a mixture of water (12 mg, 0.67 mmol) and triethylamine (0.1 g, 1 mmol) at −70 °C, and the reaction mixture was allowed to warm to room temperature, stirred overnight, and filtered. The filtrate was concentrated at reduced pressure, and dry cold ether was added to the residue. The triethylamine hydrobromide was filtered off and the solvent evaporated at reduced pressure to give 200 mg (100%) of **11b** as an oil, which contained about 20% of isomer **11a**. A TLC separation from 80 mg of crude product gave 16 mg of sample **11b**, which contained about 5% of **11a**: IR (neat) 1730, 1605; ^{1}H NMR (500 MHz) 0.81 (t, J = 7 Hz, 3 H), 1.0–2.0 (m, 14 H), 2.8 (m, 1 H), 3.43 (s, 3 H), 3.51 (s, 3 H), 3.96 and 4.05 (AB q, J = 16 Hz, 2 H), 4.61 (s, 1 H), 7.18 (t, J = 9 Hz, 1 H), 7.29 (t, J = 9 Hz, 2 H), 7.42 (d, J = 9 Hz, 2 H), 9.72 (s, 1 H).

(2′*R,6′*S**)-(*E*)-4-[1′-Benzyl-2′-(dimethoxymethyl)-6′-pentylpiperidin-2′-yl]buten-2-one (16).** To a suspension of tBuOH (2.83 g, 25.2 mmol) in anhydrous THF (55 mL) was rapidly added at −5 °C a solution of acetone (1.05 g, 18.0 mmol) in THF (6 mL). After cooling to −10 °C, a solution of **11a** (1.74 g, 5.00 mmol) in THF (11 mL) was added. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then poured into 2 M HCl (220 mL). After neutralization with Na_2CO_3, the aqueous solution was extracted with ether, dried over Na_2CO_3, and concentrated. The resulting oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (1:1) as the eluant to yield 1.33 g (68%) of **16** as an oil: IR (neat) 1680, 1630; ^{1}H NMR (80 MHz) 0.7–1.0 (m, 3 H), 1.0–2.0 (m, 14 H), 2.1 (s, 3 H), 2.6–2.9 (m, 1 H), 3.0 (s, 3 H), 3.25 (s, 3 H), 3.8 (s, 2 H), 4.05 (s, 1 H), 6.45 and 7.0 (AB q, J = 17 Hz, 2 H), 7.2–7.6 (m, 5 H); ^{13}C NMR (20 MHz) 14.0, 18.8, 22.6, 26.8, 27.3, 27.9, 32.0, 32.8, 51.1, 56.9, 57.1, 59.2, 66.6, 110.9, 126.0, 127.9, 132.2, 142.9, 151.4, 198.7.

(2′*R,6′*S**)-4-[1′-Benzyl-2′-(dimethoxymethyl)-6′-pentylpiperidin-2′-yl]butan-2-one.** A suspension of 67 mg of Pd/C, 5%, in ethanolic KOH, 0.3 N (5 mL), was saturated with hydrogen. A solution of enone **16** (453 mg, 1.17 mmol) in ethanolic KOH, 0.3 N (5 mL), and ethyl acetate (7 mL) was added and the mixture hydrogenated at room temperature and atmospheric pressure until 1 equiv of hydrogen (32 mL) was absorbed (35 min). The catalyst was filtered, and the filtrate was concentrated to about 5 mL. After addition of water (20 mL), the aqueous solution was extracted with ether and dried over Na_2CO_3. Removal of the solvent in vacuo gave the keto acetal (430 mg, 94%) as an oil, which was utilized without further purification: IR (neat) 1720; ^{1}H NMR (80 MHz) 0.8–1.0 (m, 3 H), 1.0–1.8 (m, 16 H), 2.05 (s, 3 H), 2.45–2.95 (m, 3 H), 3.4 (s, 3 H), 3.55 (s, 3 H), 4.0 (d, J = 2 Hz, 2 H), 4.45 (s, 1 H), 7.2–7.6 (m, 5 H).

(2*R,6*S**)-1-Benzyl-2-(3-oxobutyl)-6-pentylpiperidine-2-carbaldehyde.** To a solution of the above keto acetal (90 mg, 0.23 mmol) in benzene (15 mL) was added at room temperature 5 mL of 1% solution of *p*-toluenesulfonic acid in acetone. The mixture was heated at 50 °C for 12 h. After cooling, 20 mL of a saturated solution of Na_2CO_3 was added. The aqueous solution was extracted with ether and dried over Na_2CO_3. Removal of the solvent in vacuo gave the keto aldehyde, which was purified by flash chromatography on silica gel with petroleum ether/ether (4:1) as the eluant to yield 68 mg (87%): IR (neat) 1735, 1725; ^{1}H NMR (80 MHz) 0.75–0.95 (m, 3 H), 0.95–2.0 (m, 16 H), 2.1 (s, 3 H), 2.3–2.9 (m, 3 H), 3.85 (s, 2 H), 7.15–7.55 (m, 5 H), 9.65 (s, 1 H).

(2*S,6*R**)-1-Benzyl-2-pentyl-1-azaspiro[5.5]undec-7-en-9-one (17a).** To a suspension of tBuOK (37 mg, 0.33 mmol) in anhydrous THF (8 mL) was dropwise added at −10 °C a solution of the above keto aldehyde (68 mg, 0.20 mmol) in THF (8 mL). After 15 min, the reaction mixture was allowed to warm to room temperature, stirred for 12 h, and then poured into 2 M HCl (10 mL). After neutralization with Na_2CO_3, the aqueous solution was extracted with ether, dried over Na_2CO_3, and concentrated. The resulting oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (9:1) as the eluant to yield 52 mg (80%) of **17a** as an oil: IR (neat) 1695, 1675; ^{1}H NMR (80 mHz) 0.6–2.0 (m, 19 H), 2.0–2.8 (m, 3 H), 3.55 and 3.8 (AB q, J = 16 Hz, 2 H), 5.85 (d, J = 11 Hz, 1 H), 6.85 (d, J = 11 Hz, 1 H), 7.1–7.6 (m, 5 H); ^{13}C NMR (20 MHz) 13.9, 20.7, 22.6, 23.3, 26.0, 31.6, 31.9, 32.4, 34.7, 35.0, 54.6, 57.8, 60.2, 126.3, 126.8, 128.1, 128.7, 146.3, 160.0, 198.7. Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 80.77; H, 9.04; N, 4.08.

(2*R,6*R**)-(*E*)-Methyl 1-Benzyl-2-(3-oxobutenyl)-6-pentylpiperidine-2-carboxylate (18).** A mixture of 3.32 g (10 mmol) of aldehyde **10a** and 8.48 g (22.0 mmol) of Tripett–Walker ylide (Ph_3P=$CHCOCH_3$) in toluene (30 mL) was heated at 110 °C for 40 h. After cooling, the solvent was removed in vacuo and the residue was passed through a column of silica gel with petroleum ether/ether (1:4) as the eluant to yield 2.2 g (59%) of enone **18** as an oil: IR (neat) 1735, 1680, 1625; ^{1}H NMR (80 MHz) 0.6–0.9 (m, 3 H), 0.9–2.3 (m, 14 H), 2.6–3.05 (m, 1 H), 3.75 (s, 3 H), 4.15 and 4.85 (AB q, J = 18 Hz, 2 H), 7.05–7.5 (m, 5 H), 9.45 (s, 1 H).

(2*R,6*R**)-(*E*)-Methyl 1-Benzyl-2-(3-oxobutyl)-6-pentylpiperidine-2-carboxylate (19).** Under the same conditions as in the above hydrogenation of the enone **16**, 2.12 g (5.7 mmol) of enone **18** was hydrogenated on 200 mg of Pd/C (5%) to give 2.08 g (98%) of keto ester **19** as an oil, which was utilized without further purification: IR (neat) 1730, 1725; ^{1}H NMR (80 MHz) 0.6–0.95 (m, 3 H), 0.95–2.55 (m, 18 H), 1.75 (s, 3 H), 2.6–3.05 (m, 1 H), 3.75 (s, 3 H), 3.85 (s, 1 H), 4.05 (s, 1 H), 7.15–7.65 (m, 5 H).

(2*R,6*R**)-1-Benzyl-2-(3-oxobutyl)-6-pentylpiperidine-2-carbaldehyde (20).** A solution of 0.42 g (2.68 mmol) of keto ester **19**, 0.42 g (6.8 mmol) of ethylene glycol, and about 5 mg of *p*-toluenesulfonic acid in 10 mL of toluene was refluxed for 6 h, while the water formed was azeotropically eliminated. After removal of toluene in vacuo, the oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (3:1) as the eluant to yield 914 mg (82%) of the acetal of **19** as an oil: IR (neat) 1730; ^{1}H NMR (80 MHz) 0.6–0.95 (m 3 H), 0.95–2.15 (m, 18 H), 1.05 (s, 3 H), 2.55–2.9 (m, 1 H), 3.15–4.1 (m, 6 H), 3.70 (s, 3 H), 7.0–7.5 (m, 5 H). This product was stirred in ether (20 mL) at −78 °C while Dibal (10 mL of a 20 wt % solution in toluene, 12.0 mmol) was added. After 6 h at −78 °C, excess Dibal was decomposed by addition of methanol at −78 °C and the solution was allowed to attain ambient temperature. The resulting mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted twice with ether and once with dichloromethane. The combined extracts were dried (Na_2CO_3), and solvents were removed under reduced pressure to yield 0.82 g (96%) of the crude alcohol: IR (neat) 3400; ^{1}H NMR (80 MHz) 0.65–0.9 (m, 3 H), 0.9–1.95 (m, 18 H), 1.20 (s, 3 H), 2.6–2.9 (m, 2 H), 2.9–3.2 (m, 1 H), 3.2–4.0 (m, 7 H), 7.05–7.2 (m, 5 H).

To a solution of oxalyl chloride (0.84 g 6.6 mmol) in dichloromethane (6 mL) was added at −60 °C dimethyl sulfoxide[14] (1.0 g, 12.8 mmol) in dichloromethane (4 mL). After 10 min at −60 °C, the crude alcohol was added and the mixture was stirred at this temperature for 30 min. After addition of triethylamine (1.34 g, 13.2 mmol) in dichloromethane (2 mL), the mixture was allowed to warm to room temperature. To this was added 20 mL of 4 M HCl, the mixture was vigorously stirred for 3 h, neutralized with sodium carbonate, extracted with dichloromethane, and dried (Na_2CO_3), and solvents were removed in vacuo. The oily residue was purified by flash chromatography on silica gel with petroleum ether/ether (3:1) as the eluant to yield 0.61 g (84%) of keto aldehyde **20** as an oil: IR (neat) 1725; ^{1}H NMR (80 MHz) 0.65–1.0 (m, 3 H), 1.0–2.8 (m, 19 H), 1.85 (s, 3 H), 3.7–3.9 (m, 2 H), 7.1–7.6 (m, 5 H), 9.55 (s, 1 H).

(2*R,6*R**)-1-Benzyl-2-pentyl-1-azaspiro[5.5]undec-7-en-9-one (17b).** Under the same conditions as in the above preparation of the azaspiro enone **17a**, 0.59 g (1.72 mmol) of keto aldehyde **20** was cyclized to give 0.41 g (73%) of azaspiro enone **17b** as an oil: IR (neat) 1690, 1680; ^{1}H NMR (80 MHz) 0.6–1.0 (m, 3 H), 1.0–2.75 (m, 19 H), 3.74 (s, 2 H), 5.90 (d, J = 10 Hz, 1 H), 6.89 (d, J = 10 Hz, 1 H), 7.0–7.4 (m, 5 H); ^{13}C NMR (20 MHz) 13.6, 17.0, 22.3, 27.3, 29.0, 29.5, 30.3, 31.7, 33.1, 34.7, 52.2, 54.8, 57.8, 126.2, 127.1, 127.8, 128.8, 141.2, 159.6, 198.5. Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.14; H, 9.63; N, 4.31.

(2*R,6*R**)-1-Benzyl-7-butyl-2-pentyl-1-azaspiro[5.5]undec-7-en-9-one (21).** To a suspension of copper(I) iodide (0.72 g, 3.8 mmol) in ether (15 mL) was added dropwise at −30 °C

(14) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

butyllithium (2.7 mL of a 2.3 M solution in hexane, 6.2 mmol). Stirring was continued at −30 °C for a further 15 min, then the mixture was cooled to −78 °C, and triethylamine (0.38 g, 3.7 mmol), chlorotrimethylsilane (0.49 g, 4.5 mmol), and enone **17b** (188 mg, 0.58 mmol) were added successively. The reaction mixture was stirred for 5 min at −78 °C and allowed to warm to room temperature during 1.5 h. The resulting mixture was poured into saturated aqueous ammonium chloride (30 mL)/concentrated ammonium solution (30 mL), extracted with ether, and dried over Na_2CO_3. Removal of solvent in vacuo afforded a 3:1 mixture of two isomeric trimethylsilyl enol ethers (265 mg, 100%), which was used immediately without further purification. This crude product was stirred in THF (5 mL) at −78 °C, and benzeneselenenyl chloride (140 mg, 0.73 mmol) was added in THF (2 mL). After 5 min at −78 °C, the solution was allowed to warm to room temperature and stirred for 15 min, then again cooled to 0 °C, when a mixture of hydrogen peroxide solution (0.1 mL, 100 volumes), glacial acetic acid (0.05 mL), and water (1 mL) was added. After being stirred for 15 min at room temperature, the mixture was poured into saturated aqueous sodium carbonate, extracted with ether, dried over Na_2CO3, and concentrated under reduced pressure. Purification of the oily residue by flash chromatography on silica gel with ether/petroleum ether (1:9) as the eluant afforded 132 mg (60%) of butyl enone **21** as an oil: IR (neat) 1680, 1610; ^1H NMR (80 MHz) 0.6–2.8 (m, 31 H), 3.38 and 3.63 (AB q, J = 15 Hz, 2 H), 5.89 (s, 1 H), 7.0–7.3 (m, 5 H).

(2*R,6*R**)-1-Benzyl-7-butyl-2-pentyl-1-azaspiro[5.5]undec-7-ene (22).** According to Pearson's procedure[4j] described for the depentyl analogue, butyl enone **21** (243 mg, 0.635 mmol) was reduced at 0 °C for 30 min with $NaBH_4$ (65 mg, 1.72 mmol) in methanol (10 mL) to give after workup the corresponding alcohol (244 mg, 100%): IR (neat) 3420–3280; H^1 NMR (80 MHz) 0.6–2.8 (m, 31 H), 3.38 and 3.63 (AB q, J = 15 Hz, 2 H), 5.89 (s, 1 H), 7.0–7.3 (m, 5 H). This crude alcohol was then reduced with $AlCl_3$ (0.96 g, 7.2 mmol)/$LiAlH_4$ (91 mg, 2.4 mmol) in ether (15 mL) at room temperature for 1.5 h to yield, after purification by flash chromatography (eluant = ether/petroleum ether, 1:49), azaspiro olefin **22** (135 mg, 58%) as an oil: IR (neat) 3060, 3020, 2950, 2920, 2850, 1490, 1445, 1360, 1255, 1205, 1190, 1150, 1080, 1060, 1025, 880, 790, 725, 695; ^1H NMR (80 MHz) 0.55–0.95 (m, 6 H), 0.95–2.30 (m, 26 H), 2.40–2.70 (m, 1 H), 3.57 (s, 2 H), 5.41–5.59 (m, 1 H), 6.97–7.36 (m, 5 H).

1-Benzylperhydrohistrionicotoxin (23a) and 1-Benzyl-2,6-epiperhydrohistrionicotoxin (23b). To a solution of **22** (133 mg, 0.36 mmol) in THF (4 mL) was added at room temperature BH_3/Me_2S (0.4 mL of a 2 M solution in THF, 0.8 mmol), and the mixture was heated at 40 °C for 24 h. After removal of solvent in vacuo, a mixture of diglyme (3.2 mL), hydrogen peroxide solution (0.25 mL, 100 volumes), and sodium hydroxide (10% solution, 0.8 mL) was added, and the mixture was heated at 80 °C for 14 h. After cooling, the mixture was poured into saturated aqueous NaCl (30 mL), extracted with ethyl acetate, dried over Na_2CO_3, and concentrated in vacuo. The resultant mixture of diastereoisomers was separated by flash chromatography (eluant = ether/petroleum ether, 5–10%), affording the less polar isomer **23a** (25 mg, 17%) as an oil [IR ($CDCl_3$) 3600, 1600; ^1H NMR (80 MHz) 0.7–1.1 (m, 6 H), 1.1–1.8 (m, 26 H), 2.5–2.95 (m, 1 H), 3.4–4.1 (m, 2 H), 3.9 (s, 2 H), 7.1–7.5 (m, 5 H), 7.65 (br d, J = 9.5 Hz, 1 H)] and the more polar isomer **23b** (52 mg, 37%) as an oil [IR ($CDCl_3$) 3610, 1600; ^1H NMR (80 MHz) 0.65–1.05 (m, 6 H), 1.05–1.8 (m, 26 H), 2.4–2.6 (m, 2 H), 2.6–3.1 (m, 1 H), 3.70 (s, 2 H), 4.0–4.2 (m, 1 H), 7.05–7.50 (m, 5 H)].

Perhydrohistrionicotoxin (2). A solution of alcohol **23a** (42 mg, 0.109 mmol) in ethanol (4 mL) with 10% Pd/C (24 mg) was stirred under a hydrogen atmosphere at room temperature and under ordinary pressure for 2 h. The mixture was directly passed through a short alumina column (activity = 1) with dichloromethane/methanol (9:1; 50 mL) as the eluant. After removal of solvents, the oily residue was further purified by flash chromatography on silica gel with chloroform as the eluant to give 24.8 mg (78%) of PHTX (**2**) as an oil: IR (CCl_4) 3610, 3240, 3220, 2960, 2930, 2870, 2860, 1505, 1460, 1425, 1380, 1350, 1250, 1220, 1070, 1005, 975, 910, 865; ^1H NMR (80 MHz) 0.67–1.04 (m, 6 H), 1.04–2.06 (m, 28 H), 2.06–2.35 (m, 1 H), 2.7–3.15 (m, 1 H), 3.77–3.95 (m, 1 H); ^{13}C NMR (100 MHz) 14.1, 14.1, 15.2, 22.5, 23.1, 25.6, 27.6, 27.7, 30.3, 32.2, 33.2, 37.0, 37.0, 37.8, 38.1, 50.0, 55.2, 69.8. Hydrochloride of **2**, a colorless solid: mp 157–159 °C (lit.[3b] mp 159–161 °C). Anal. Calcd for $C_{19}H_{27}NO$: C, 68.74; H, 11.54; N, 4.22. Found: C, 68.48; H, 11.44; N, 4.07.

2,6-Epiperhydrohistrionicotoxin (24). Debenzylation of **23b** (77 mg, 0.20 mmol) under the same conditions as in the above debenzylation of **23a** afforded 45 mg (78%) of 2,6-epi-PHTX (**24**) as an oil: IR (CCl_4) 3630, 3380–3230, 2960, 2930, 2870, 2860, 1550, 1460, 1380, 1330, 1250, 1220, 1135, 1105, 1060, 990, 910, 865; ^1H NMR (80 MHz) 0.7–1.06 (m, 6 H), 1.06–1.89 (m, 26 H), 1.89–2.17 (m, 2 H), 2.37–2.80 (m, 2 H), 3.98–4.15 (m, 1 H). Hydrochloride of **24**, a colorless solid: mp 259–261 °C. Anal. Calcd for $C_{19}H_{27}NO$: C, 68.74; H, 11.54; N, 4.22. Found: C, 68.54; H, 11.57; N, 4.18.