182 (M^+ - HF, 31), 103 (100), 102 (20), 77 (23).

10,11-Dibromoundecan-1-ol[31] **(7c).** This compound was further confirmed by comparison with an authentic sample prepared by bromination of 10-undecen-1-ol: ^{1}H NMR δ 2.2 (m, 16 H, CH_2), 3.65 (t, 2 H, J = 2.6 Hz, CH_2OH), 3.4-3.7 (m, 1 H, J = 10.2, 5.2 Hz, CH_ABr), 3.84 (dd, 1 H, J = 10.2, 4.4 Hz, CH_BBr), 4.15 (m, 1 H, $CHBrCH_2Br$); MS m/z (%) 244 (14), 242 (33), 240 (19), 229 (14), 205 (21), 203 (26), 177 (40), 175 (40), 163 (23), 161 (25), 151 (96), 149 (27), 147 (20), 123 (63), 109 (70), 95 (100), 83 (56), 81 (87), 69 (68), 67 (55), 55 (97), 41 (85).

11-Bromo-10-fluoroundecan-1-yl acetate (8a): ^{1}H NMR δ 1.1-2.0 (m, 16 H, CH_2), 2.03 (s, 3 H, CH_3CO), 3.45 (dd, 2 H, J = 21, 5.2 Hz, CH_2Br), 4.04 (t, 2 H, J = 6.3 Hz, CH_2O), 4.6 (dm, 1 H, J = 46 Hz, CHF); ^{19}F NMR -101.5 (m); MS m/z (%) 252 (3), 250 (3), 182 (6), 180 (5), 168 (16), 166 (16), 151 (17), 109 (25), 95 (33), 81 (22), 69 (17), 67 (15), 61 (16), 55 (29), 43 (100), 41 (28). Anal. Calcd for $C_{13}H_{24}O_2BrF$: C, 50.16; H, 7.71; Br, 25.72. Found: C, 50.21; H, 7.92; Br, 25.25.

10-Bromo-11-fluoroundecan-1-yl acetate (8b). Assignment by MS only: MS m/z (%) 250 (4), 224 (5), 222 (6), 182 (21), 180 (24), 167 (10), 151 (10), 109 (17), 95 (17), 81 (15), 69 (14), 68 (11), 67 (14), 61 (22), 55 (29), 43 (100), 41 (31).

3-Bromo-2-fluoro-2-methylbutane[32] **(9a):** ^{1}H NMR δ 1.52 (d, 3 H, J_{CH_3F} = 21.6 Hz, CH_3F), 1.48 (d, 3 H, J_{CH_3F} = 21.6 Hz, CH_3F), 1.70 (d, 3 H, J = 6.9 Hz, CH_3CH), 4.13 (dq, 1 H, J = 9.4, 6.9 Hz, CHBr); ^{19}F NMR -62.0 (m); MS m/z (%) 151 (M^+ + 2 - 19, 89), 149 (M^+ - 19, 100), 69 (34), 41 (37).

3-Fluoro-4-bromo-1-cyclooctene (10a): ^{1}H NMR δ 1.25-1.9 (m, 4 H, 2 CH_2), 1.9-2.4 (m, 4 H, CH_2CBr and CH_2C=C), 4.2 (m, 1 H, CHBr), 5.1-6.1 (m, 3 H, CHF and CH=CH); ^{19}F NMR -96.2 (d, J = 48.6 Hz); MS m/z (%) 208 (M^+ + 2, 25), 206 (M^+, 28), 180 (40), 178 (48), 127 (83), 107 (100), 97 (21), 91 (21), 85 (63), 79 (87), 77 (20), 72 (35), 67 (31), 65 (22), 59 (34), 41 (33); exact mass m/z 206.0103 (calcd for $C_8H_{12}BrF$ 206.0106).

5-Bromo-6-fluoro-1-cyclooctene[14] **(11a):** ^{1}H NMR δ 1.8-2.9 (m, 8 H, CH_2), 4.40 (m, 1 H, CHBr), 4.8 (dm, 1 H, J = 47 Hz, CHF), 5.53 (m, 2 H, CH=CH); ^{19}F NMR -86.3 (m); MS m/z (%) 208 (M^+ + 2, 35), 206 (M^+, 36), 180 (13), 178 (13), 127 (17), 107 (100), 91 (22), 85 (36), 79 (92), 67 (32), 59 (19), 53 (21), 41 (26).

Reaction of TBABF/NBS with Dihydropyran 6. The reaction was carried out as described above although the crude reaction mixture could not be purified by column chromatography due to the instability of the resulting compounds. GLC analysis on a SE-30 25 m × 0.25 mm i.d. fused silica capillary column showed a major compound with a 72% estimated purity. The compound was identified as the Markovnikov-oriented stereoisomer ***trans*-3-bromo-2-fluorotetrahydropyran (6a)** in base to the ^{1}H and ^{19}F NMR spectra of the crude product.

6a: ^{1}H NMR δ 1.2-2.7 (m, 4 H, CH_2CH_2CBr), 3.5-4.3 (m, 3 H, CHBr and CH_2O), 5.56 (b d, 1 H, J = 51.8 Hz, CHF); ^{19}F NMR -46.3 (dm, J = 51.9 Hz); MS m/z (%) 184 (M^+ + 2, 30), 182 (M^+, 24), 164 (4), 162 (4), 136 (83), 134 (100), 108 (50), 106 (55), 55 (81), 53 (17).

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Studies on the Synthesis of 1-Azaspiro[5.5]undecanes Related to Histrionicotoxin

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3-Methoxybenzaldehyde was converted into 4-(3-methoxyphenyl)butylamine (**4**), and the derived hydrochloride was reduced with Li/NH_3/EtOH to give the spirocyclic keto amine **6**. The reduction of **6** and urethane derivatives **13** and **14** to give the corresponding cis and trans alcohols **9**/**10**, **15**/**16**, and **17**/**18** was studied. The keto amine **6** upon attempted ketalization underwent rearrangement to give the α,β-unsaturated imine **11**. Treatment of **6** with *N*-chlorosuccinimide, followed by DBU, gave the aziridine **21**. The amide **25** was converted directly into 1-azaspiro[5.5]undecane-2,8-dione (**24**) by Birch reduction and acid hydrolysis. The dione **24** underwent stereospecific reduction with LS-Selectride to give the cis alcohol **30**.

Histrionicotoxin (**1**) has generated an enormous amount of synthetic interest during the last decade or so because of its important inhibitory action on electrogenic membranes and unique molecular structure.[2] Most of the synthetic work has been directed toward perhydrohistrionicotoxin (**3**),[3] and only recently has the first and only total synthesis of histrionicotoxin (**1**) itself been reported by Kishi.[4] The large body of literature associated with this area has been reviewed in detail.[5]

(1) Taken in part from the Ph.D. Thesis of J. J. Venit, Ohio State University, Department of Chemistry, 140 West 18th Avenue, Columbus, Oh 43210.
(2) For a comprehensive review of work before 1985, see: Daly, J. W. *Progress in the Chemistry of Natural Products*; Herz, W., Grisebach, H., Kirby, G., Eds.; Springer-Verlag: Vienna, 1982; Vol. 41, pp 206-340. Witkop, B.; Gossinger, E. *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1983; Vol. 21, pp 139-251. Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507.
(3) For references since 1982, see: Holmes, A. B.; Russell, K.; Stern, E. S.; Stubbs, M. E.; Welland, N. K. *Tetrahedron Lett.* **1984**, 4163. Evans, D. A.; Thomas, E.; Cherpeck, R. *J. Am. Chem. Soc.* **1982**, *104*, 3695. Ibuka, T.; Minakata, H.; Hashimoto, M.; Overman, L.; Freerks, R. *Heterocycles* **1984**, *22*, 485. Tanner, D.; Somfai, *Tetrahedron Lett.* **1985**, 3883. Koft, E.; Smith, A. B. *J. Org. Chem.* **1984**, *49*, 832. Butlin, R. J.; Holmes, A. B.; McDonald, E. *Tetrahedron Lett.* **1988**, *29*, 2989. Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177. Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque *Helv. Chim. Acta* **1982**, *65*, 252. Godleski, S. A.; Heacock, D. J.; Meinhart, J. D.; Wallendael, S. V. *J. Org. Chem.* **1983**, *48*, 2101. Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590. Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, 2495.
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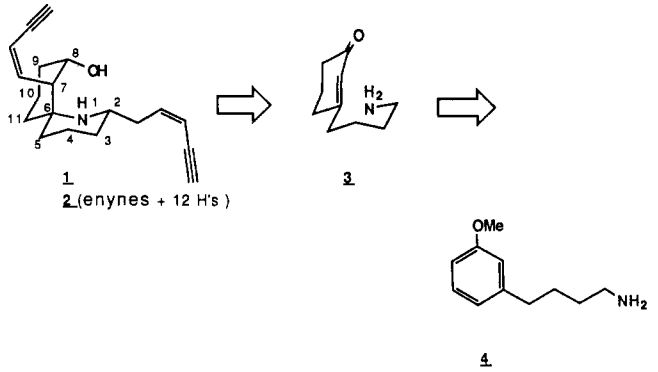
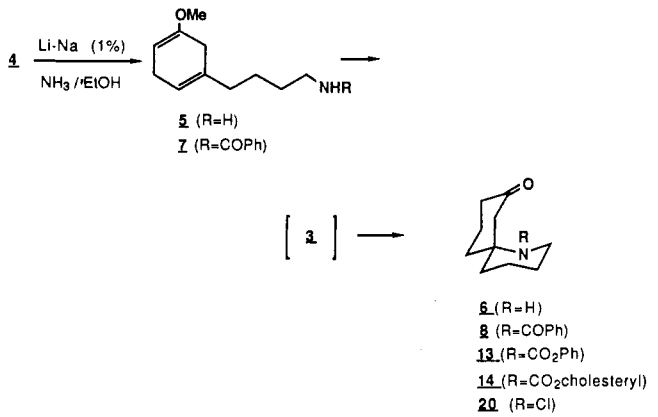
0022-3263/89/1954-4298$01.50/0

Scheme I



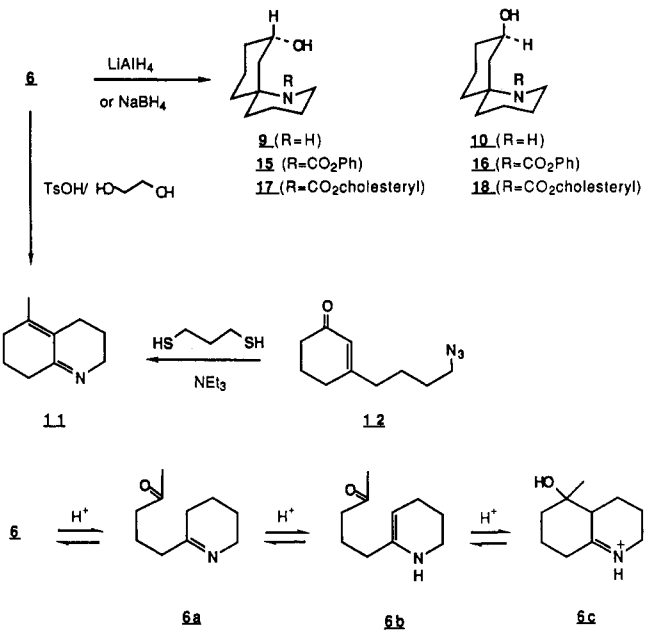
In this paper we describe a new route to the 1-azaspiro[5.5]undecane ring system that implements the retrosynthetic analysis shown in Scheme I.

3-Methoxybenzaldehyde was converted into 4-(3-methoxyphenyl)butylamine (**4**) in six steps, overall yield 31%.[6] Birch reduction of the hydrochloride of **4** using Li–Na (1%)/NH_3/EtOH/Et_2O gave the expected dihydro compound **5** (90%), which on acid hydrolysis with 2 N HCl/THF gave **6** (94.5%). There was no evidence that the intermediate α,β-unsaturated ketone **3** could be detected. N-Benzoylation of **5** gave **7**, which on acid hydrolysis gave the *N*-benzoyl derivative of **3** but resisted attempts to transform it into the corresponding 1-azaspirocyclic analogue **8**. Reduction of **6** with $LiAlH_4$/THF/−70 °C or $NaBH_4$ gave the epimeric alcohols **9** and **10** (1:1, 74%).

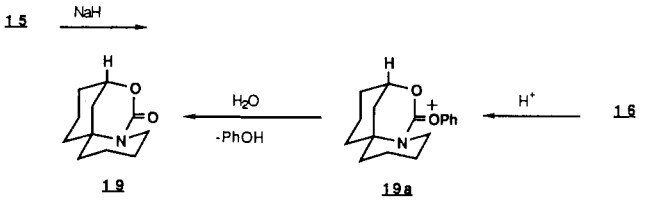


Interestingly, attempted ketalization of **6**, $HOCH_2CH_2OH$/TsOH/PhH, gave the rearranged α,β-unsaturated imine **11**, whose structure was confirmed by dehydrogenation to 5-methylquinoline.[7] Reduction of the azide **12** using Knowles procedure,[8] $HS(CH_2)_3SH$, also gave **11**. The formation of **11** involves a retro-Mannich reaction to give the imine **6a** (after enol–ketone tautomerism), which through a series of imine **6a** ⇌ enamine **6b** ⇌ iminium ion **6c** transformations leads to the rearranged octahydroquinoline **11**.

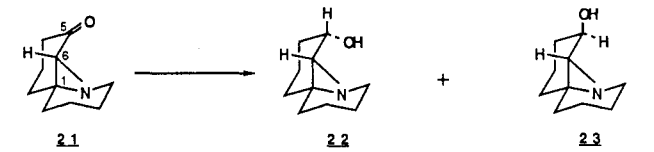
In order to make the reduction of the 8-ketone in **6** more stereoselective we examined the effect of placing a large



group, in the form of urethane derivatives, on the amino group. Reduction of **13** with $Li(t\text{-}BuO)_3AlH$ gave a mixture of epimeric alcohols **15** and **16** (99%, 3:1), whereas, reduction of **13** with L-Selectride (Aldrich) gave only **16** (63%) and the cyclic urethane **19** (19%). When the mixture of **15** and **16** was treated with NaH/THF heated at reflux, **15** was converted into the cyclic urethane **19** (29%), and **16** remained unchanged. Interestingly, when **16** was treated with 9 M H_2SO_4 in THF it was cleanly converted into the cyclic urethane **19**, presumably via participation of the urethane carbonyl leading to the intermediate **19a**. These transformations also allow the assignments of relative configuration at C-8 to be made without complete recourse to ^1H NMR. Reduction of the cholesterylurethane derivative **14** using L-Selectride at −70 °C gave predominantly **18** with traces (2–5%) of the epimeric alcohol **17** detected by ^{13}C NMR.



Treatment of **6** with *N*-chlorosuccinimide/CCl_4 gave the *N*-chloro derivative **20**, which on exposure to freshly distilled DBU (2.1 equiv) gave the aziridine **21** (65%). The C-6 proton appeared as a singlet at δ 2.07 in the ^1H NMR spectrum. Reduction of the 5-ketone group in **21** using either $NaBH_4$ or $Li(t\text{-}BuO)_3AlH$ gave a mixture of **22**/**23** (92%), whereas L-Selectride gave only **22** (35%).



While we could achieve stereoselective reduction of the carbamate derivatives **13** and **14**, the difficulties associated with the removal of these protecting groups did not make this route to a stereocontrolled synthesis of 8-hydroxy-1-azaspiro[5.5]undecanes with a free NH viable. Consequently, it was decided to investigate the synthesis and reduction of 1-azaspiro[5.5]undecane-2,8-dione (**24**).[9]

(5) For a review of earlier synthetic work, see: Corey, E. J.; Balanson, R. D. *Heterocycles* **1976**, *5*, 445; *Synform*, Vol. 2, No. 1, 1984, p 1.

(6) References to the conversion of 3-methoxybenzaldehyde into 4-(3′-methoxyphenyl)butylamine (**4**): Tiemann, R.; Ludwig, R. *Ber.* **1882**, *15*, 2052. Cohen, A. *J. Chem. Soc.* **1935**, 429. Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738.

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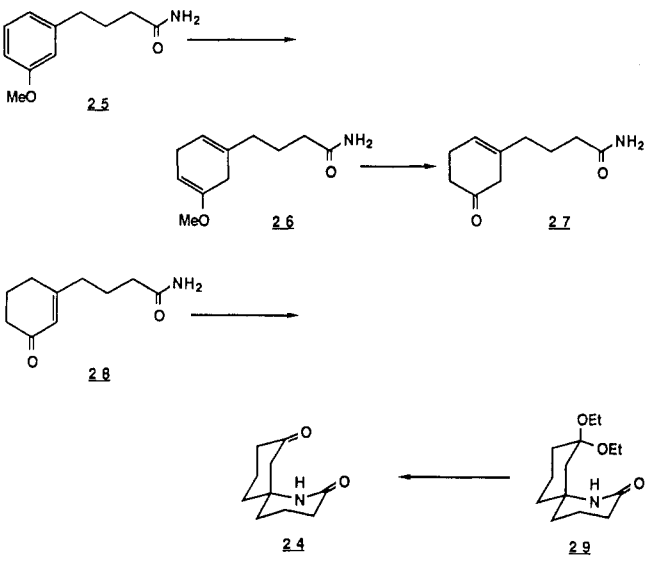
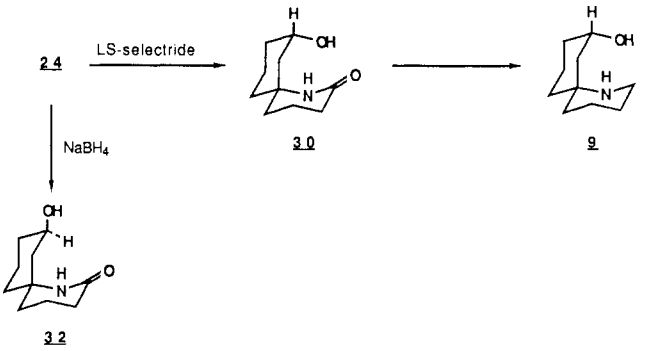
3-(3′-Methoxyphenyl)-1-butyronitrile was converted into the amide **25** by treatment with hydrogen peroxide under phase-transfer conditions. The amide **25** can be converted, without isolation of intermediates, into the spiroketolactam **24** in 50% yield. The procedure involves Birch reduction of **25** using Na/*t*-BuOH/Et_2O, hydrolysis of **26** to a mixture of β,α-unsaturated ketone **27** and α,β-unsaturated ketone **28**, followed by treatment with EtOH/triethyl orthoformate/camphorsulfonic acid, to give **29**, which on mild acid hydrolysis, CH_2Cl_2 aqueous HCl, gave **24**. Reduction of **24** with LS-Selectride in CH_2Cl_2 at −78 °C gave the *cis*-hydroxy lactam **30** with 97% diastereoselectivity in 75% yield. Further reduction of **30** with $LiAlH_4$ gave the known amino alcohol **9**,[10] thus confirming the relative stereochemistry of **30**. Reduction of **24** with $NaBH_4$/MeOH gave predominantly the *trans*-hydroxy lactam **32**, along with the cis isomer **30** (ca. 65:35). Brossi has described the preparation of **30** and **32** using the acyliminium ion cyclization route.[9]





In summary, the Birch reduction route to azaspiro[5.5]undecanes provides a short concise route to these dealkyl analogues of histrionicotoxin (**1**).

Experimental Section

4-(3-Methoxyphenyl)butylamine (4). 3-Methoxybenzaldehyde was condensed with malonic acid in pyridine/piperidine (catalyst) to give 3-methoxycinnamic acid (94.8%), mp 118–119 °C (lit.[6] mp 115 °C). Hydrogenation of 3-methoxycinnamic acid over 10% Pd/C in methanol gave 3-(3-methoxyphenyl)propanoic acid (96.3%), mp 43–46 °C (lit.[6] mp 51 °C), which was reduced with $LiAlH_4/Et_2O$ to give 3-(3′-methoxyphenyl)-1-propanol (87.2%), bp 96–98 °C at 0.16 Torr (lit. 147 °C at 10.5 Torr). The above alcohol was converted into its *p*-toluenesulfonate derivative using standard methodology and treated with potassium cyanide to give 3-(3′-methoxyphenyl)-1-butyronitrile (88%), bp 113–115 °C at 0.25 Torr (lit.[6] bp 164–170 °C at 11 Torr). Reduction of the nitrile with $LiAlH_4/Et_2O$ gave **4**, isolated as its hydrochloride (81%): mp 132–133 °C; IR ($CHCl_3$) 2950, 1600, 1485, 1260, 1150, and 1040 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 8.25 (2 H, br s), 7.30–6.53 (4 H, m), 3.72 (3 H, s), 3.20–2.40 (4 H, m), 1.97–1.50 (4 H, m). Anal. Calcd for $C_{11}H_{18}NOCl$: C, 61.25; H, 8.41; N, 6.49; Cl, 16.43. Found: C, 61.16; H, 8.54; N, 6.36; Cl, 16.26.

1-Methoxy-5-(4′-aminobutyl)cyclohexa-1,3-diene (5) (R = H). Treatment of **4**·HCl salt (15.00 g, 69.5 mmol) with Li–Na alloy (0.01% Na, 3.4 g) in anhydrous ammonia (700 mL), ethanol (85 mL), and Et_2O (150 mL) under Birch reduction conditions gave **5** (11.40 g, 90% crude): IR (neat) 3300, 1695, 1665, 1220 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.30 (1 H, br s), 4.45 (1 H, br s), 3.46 (3 H, s), 2.80–2.30 (6 H, m), 2.17–1.69 (3 H, m), 1.67–1.15 (5 H, m); MS calcd for $C_{11}H_{19}NO$ *m/e* 181.147, found 181.147.

1-Azaspiro[5.5]undecan-8-one (6) (R = H). A solution of **5** (R = H) (1.50 g, 8.3 mmol) in THF (12 mL) was treated with 2 N HCl (15 mL). After 1 h at 20 °C the mixture was brought to pH 10 with 10% aqueous KOH solution and saturated with NaCl. The mixture was extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo to give **6** (R = H) (1.26 g, 94.5%): IR (neat) 3290, 2920, 1710, 1660 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.90–2.60 (2 H, m), 2.37–2.00 (4 H, m), 2.10–0.70 (11 H, m); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 210.6 (s), 55.9 (s), 51.9 (t), 40.9, 40.6, 36.9 (t), 34.7 (t), 26.7 (t), 20.7, 20.1; MS calcd for $C_{10}H_{17}NO$ *m/e* 167.131, found 167.131.

1-Azaspiro[5.5]undecan-8-ol (9/10). 1-Azaspiro[5.5]undecan-8-one (**6**) (R = H) (0.50 g, 3.0 mmol) in THF (10 mL) at −78 °C was treated with $LiAlH_4$ (0.19 g) and slowly (1.5 h) warmed to 10 °C. Water (0.80 mL) was added to the mixture, and the precipitate was washed with Et_2O (2 × 5 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give **9/10** (1:1) (0.38 g, 74%), which was directly acetylated with acetic anhydride (3 mL) in pyridine (6 mL). The mixture had the following properties: IR (neat) 2940, 1730, 1640 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.00–4.55 (1 H, m), 3.49–3.23 (2 H, m), 2.09–1.98 (6 H, m), 1.84–1.34 (15 H, m); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 171.6 (s), 170.8 (s), 170.6 (s), 170.5 (s), 71.0 (d), 60.7 (s), 43.2, 42.1, 37.9, 36.1, 34.4, 33.9, 30.8, 30.6, 29.6, 25.6, 24.8, 22.6, 21.4, 21.3, 19.3, 19.5, 18.1, 15.6. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.69; H, 9.34; N, 5.60.

5-Methyl-2,3,4,6,7,8-hexahydroquinoline (11). A mixture of 1-azaspiro[5.5]undecan-8-one (**6**) (0.44 g, 2.63 mmol), ethylene glycol (6.50 g), and *p*-toluenesulfonic acid (20 mg) in benzene (50 mL) was heated at reflux for 15 h with provision for the azeotropic removal of water. Workup gave **11** (0.33 g, 84%): IR (neat) 2930, 1680, 1630 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 3.43 (2 H, t, J = 6 Hz), 2.40–2.00 (6 H, m), 2.00–1.13 (4 H, m), 1.73 (3 H, s); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 164.9 (s), 141.2 (s), 123.5 (s), 49.0 (t), 35.1 (t), 24.1, 22.4, 22.1, and 19.1; MS calcd for $C_{10}H_{15}N$ *m/e* 149.120, found 149.121. Dehydrogenation of **11** (0.36 g) over 10% palladium on charcoal (0.10 g) in *p*-cymene (20 mL) gave 5-methylquinoline, picrate, mp 217–220 °C (lit.[7] mp 221 °C).

1-Carbophenoxy-1-azaspiro[5.5]undecan-8-one (13). The amine **6** (1.00 g, 5.98 mmol) in THF (50 mL) was treated with triethylamine (1.7 mL) and phenyl chloroformate (1.88 g, 12.0 mmol). The mixture was stirred at room temperature for 24 h, quenched with water (100 mL), and extracted with dichloromethane (30 mL). The dried (Na_2SO_4) extract was evaporated in vacuo to give an oil, which was purified by flash column chromatography over silica gel to give **13** (0.85 g, 50%): IR (neat) 2940, 1710, 1600, 1390, 1210 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.41–6.82 (5 H, m), 3.91–3.33 (2 H, m), 2.41–1.33 (14 H, m); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 208.6, 154.4, 151.2, 129.3, 125.3, 121.9, 60.5, 50.9, 41.6, 39.9, 34.8, 30.8, 23.4, 20.2, 17.4. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 71.05; H, 7.37; N, 4.88. Found: C, 71.26; H, 7.45; N, 5.07. 1-Carbocholestoxy-1-azaspiro[5.5]undecan-8-one (**14**) was made in an identical fashion.

Reduction of 1-Carbophenoxy-1-azaspiro[5.5]undecan-8-one (13) with Li(*t*-BuO)$_3$AlH. To a solution of **13** (0.25 g, 0.87 mmol) in THF (10 mL) was added Li(*t*-BuO)$_3$Al (0.30 g, 1.2 mmol). After 45 min at 20 °C, water (20 mL) was added, and the mixture

(9) Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96.
(10) Gessner, W.; Takahashi, K.; Witkop, B.; Brossi, A. *Helv. Chim. Acta* **1985**, *68*, 49.

worked up in the usual way to give **15/16** (0.25 g, 99%, ca. 3:1). A single alcohol **16** (0.081 g) crystallized from Et_2O/petroleum ether (9:1): mp 100–103 °C; IR (neat) 3420, 2940, 1725 cm^{-1}; ^{13}C NMR (20.1 MHz, $CDCl_3$) 154.1 (s), 151.5 (s), 129.3 (d), 125.1 (d), 122.0 (d), 67.5 (d), 60.9 (s), 44.3 (t), 42.5 (t), 36.7 (t), 34.6, 34.2, 25.3 (t), 19.7, 19.4; MS calcd for $C_{17}H_{23}NO_3$ m/e 289.168, found 289.168. We could not isolate **15** in a pure form.

Reduction of **13** (0.20 g, 0.69 mmol) with L-Selectride (0.77 mL) gave **16** (0.138 g, 63%) and the carbamate **19** (0.026 g, 19%): IR (neat) 2950, 1680 cm^{-1}; ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 72.2 (d), 52.9 (s), 40.1, 38.7, 37.6, 31.5, 30.8, 25.2 (t), 19.1 (t), 16.6 (t); MS calcd for $C_{11}H_{17}NO_2$ m/e 195.126, found 195.126.

To a THF (2.5 mL) solution of **15/16** [0.073 g from the Li(t-BuO)$_3$AlH reduction] was added sodium hydride (0.029 g), and the mixture was heated at reflux for 3 h. The carbamate **19** (0.014 g, 29%) was isolated, and the alcohol **16** (0.026 g, **35**) was recovered unchanged. Treatment of **16** (0.010 g, 0.34 mmol) in THF (4 mL) with 9 M H_2SO_4 (5 mL) for 10 h at 20 °C gave **19** (40 mg) together with unreacted **16**.

Reduction of 1-Carbocholestoxy-1-azaspiro[5.5]undecan-8-one (14) with L-Selectride. To a solution of **14** (0.12 g, 0.19 mmol) in THF (2 mL) at −70 °C was added L-Selectride (0.22 mL). After 1.5 h at 0 °C workup gave **18** (0.11 g, 99%) as a foam: IR (neat) 2940, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (1 H, d, J = 4.5 Hz), 4.60–4.17 (2 H, m), 4.33–4.00 (3 H, m), and 2.57–0.57 (57 H, m, singlets at 1.13, 0.90, 0.85, and 0.66). We were unable to obtain satisfactory microanalytical or mass spectral data on **14**. The ^{13}C spectrum indicated the **18** was contaminated by approximately 2–5% of the C-8 epimer **17**.

7-Azatricyclo[5.4.0.0^{1,6}]undecan-5-one (21). To a solution of **6** (R = H) (2.00 g, 11.9 mmol) in CCl_4 (50 mL) at 0 °C was added N-chlorosuccinimide (2.00 g, 15.0 mmol) and DBU (3.80 g, 25.0 mmol) in rapid succession. The above mixture was warmed to 20 °C, after 4 h the solution was filtered, and the filtrate was concentrated in vacuo to approximately 8 mL. The resulting dark-colored oil was purified by flash chromatography over silica gel eluting with 10% Et_2O/petroleum ether to give **21** (1.28 g, 65%): IR (neat) 2940, 1705 cm^{-1}; ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 209.7 (s), 51.3 (d), 49.0 (t), 44.6 (s), 36.3 (t), 31.2 (t), 37.6 (t), 20.9 (t), 18.1, and 17.5; MS calcd for $C_{10}H_{15}NO$ m/e 165.116, found 165.115. The intermediate N-chloro compound **20** can be isolated if the DBU is omitted.

Reduction of 7-Azatricyclo[5.4.0.0^{1,6}]undecan-5-one (21). Treatment of **21** (0.32 g, 1.96 mmol) in EtOH (5 mL) at 0 °C with $NaBH_4$ (0.083 g, 2.2 mmol) gave **22/23** (0.30 g, 92%), whereas L-Selectride gave **22** (35%): IR (neat) 3320, 2920, 1450 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.00 (1 H, br s), 3.60–3.20 (1 H, m), 3.17–2.40 (2 H, m), 2.15 (1 H, d, J = 6 Hz), and 2.10–1.00 (12 H, m); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 63.4 (d), 49.4 (t), 47.1 (d), 41.8 (s), 32.4 (t), 31.3 (t), 28.7 (t), 21.4 (t), 18.3 (t), 15.3 (t); MS calcd for $C_{10}H_{17}NO$ 167.131, found 167.131.

4-(3-Methoxyphenyl)butyramide (25). A mixture of 3-(3′-methoxyphenyl)-1-butyronitrile (37.90 g, 0.22 mL) and n-$Bu_4N^+HSO_4^-$ (14.67 g, 20 mol %) in CH_2Cl_2 (125 mL) was treated with 20% NaOH (100 mL) and 30% H_2O_2 (120 mL). After 2 h at room temperature, standard workup gave **25** (29.8 g, 71%): mp 102–103.5 °C (from Et_2O); IR ($CHCl_3$) 3530, 3410, 3350, 3195, 1680, 1600, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.17 (1 H, m), 6.82–6.72 (3 H, m), 5.63 (1 H, br s), 5.43 (1 H, br s), 3.79 (3 H, s), 2.65 (2 H, t, J = 7.5 Hz), 2.22 (2 H, t, J = 7.5 Hz), 1.97 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 175.6, 159.5, 143.0, 129.2, 120.8, 114.1, 111.2, 55.0, 35.0, 34.9, 26.6. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.54; N, 7.16.

1-Azaspiro[5.5]undecane-2,8-dione (24). The aromatic amide **25** (31.21 g, 162 mmol) was added to an anhydrous NH_3 (400 mL), t-BuOH (200 mL), and ether (200 mL) mixture, containing sodium (17.5 g, 760 mmol) at −70 °C. After 18 h the cooling bath was removed, and the mixture was allowed to evaporate over 10 h. Water (150 mL) was added to the residue, and the mixture was extracted with EtOAc (1 L). The dried ($MgSO_4$) extract was evaporated in vacuo to give **26** as off-white crystals: mp 108–109 °C (from $CHCl_3$/petroleum ether); IR ($CHCl_3$) 3540, 3420, 3350, 3000, 1680, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.64 (1 H, br s), 5.44 (1 H, br s), 5.48–5.40 (1 H, m), 4.65–4.60 (1 H, m), 3.55 (3 H, s), 2.83–2.75 (2 H, m), 2.61 (2 H, t, J = 7.5 Hz), 2.20 (2 H, t, J = 7.5 Hz), 2.06 (2 H, t, J = 7.5 Hz), 1.78 (2 H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.18. Found: C, 67.57; H, 8.75; N, 7.27.

The crude product **26** was dissolved in THF (1 L) and 1 N HCl (200 mL) and stirred at room temperature for 30 min. Solid sodium bicarbonate (100 g) was slowly added, and the mixture was extracted with EtOAc (2 × 750 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a mixture of **27** and **28** as a pale yellow oil. The crude mixture was dissolved in EtOH/HC(OEt)$_3$ (1:1, 400 mL), and camphor sulfonicacid (2.00 g) and 3-Å molecular sieves (10 g) were added. After 15 h at 20 °C the mixture was filtered and washed with ethanol (100 mL), and the filtrate was evaporated to give the crude diethyl ketal **29**. A sample of **29**, purified by flash chromatography, has mp 97–98.5 °C (from EtOAc/petroleum ether): IR ($CHCl_3$) 3345, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (1 H, br s), 3.57–3.38 (4 H, m), 2.42–2.20 (2 H, m), 2.11–2.00 (2 H, m), 1.94–1.72 (4 H, m), 1.68–1.51 (4 H, m), 1.50–1.35 (1 H, m), 1.32–1.25 (1 H, m), 1.24 (3 H, t, J = 7.0 Hz), 1.15 (3 H, t, J = 7.0 Hz). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 66.07; H, 9.67; N, 5.49.

The crude ketal **29** was dissolved in CH_2Cl_2 (250 mL), and 1 N HCl (100 mL) was added. After 10 h at room temperature the CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (750 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated in vacuo to give the crude keto lactam **24**. The material was triturated with petroleum ether (4 × 300 mL), and the remaining solid (21.42 g) crystallized from 2-propanol to give **24** (15.14 g). Sublimation of **24** (0.40 mmHg, 180 °C) gave pure **24** (14.22 g, 48%): mp 184–186 °C (lit.[9] mp 185–186 °C); IR ($CHCl_3$) 3380, 3200, 1712, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (1 H, br s), 2.58–2.41 (2 H, AB, J = 13.6 Hz), 2.40–2.25 (4 H, m), 2.04–1.94 (1 H, m), 1.94–1.87 (2 H, m), 1.86–1.68 (3 H, m), 1.66–1.53 (2 H, m). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.17; H, 7.98; N, 7.59.

***cis*-8-Hydroxy-1-azaspiro[5.5]undecan-2-one (30).** The keto amide **29** (5.50 g, 30.3 mmol) in CH_2Cl_2 (100 mL) at −78 °C was treated with LS-Selectride (30.8 mL 1 M in THF). After 1 h the mixture was quenched with saturated aqueous ammonium chloride (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 600 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give a residue, which was crystallized from EtOAc/petroleum ether to give **30** (4.88 g). Recrystallization from EtOAc (ca. 60 mL) gave pure **30** (4.15 g, 75%): mp 177–178 °C (lit.[9] 178–179 °C); IR ($CHCl_3$) 3295, 2940, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1 H, br s), 4.32 (1 H, br s), 4.18 (1 H, m), 2.40–2.18 (2 H, m), 2.00–1.67 (6 H, m), 1.67–1.42 (5 H, m), 1.38–1.24 (1 H, m). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.36; N, 7.64. Found: C, 65.38; H, 9.08; N, 7.58.

***cis*-8-Hydroxy-1-azaspiro[5.5]undecane (9).** The hydroxy lactam **30** (2.00 g, 10.9 mL) in dry THF (50 mL) was treated with $LiAlH_4$ (828 mg), and the mixture heated at reflux for 24 h. Conventional workup gave **9** (1.39 g), mp 75–84 °C, which was purified by sublimation to give **9** (1.18 g, 64%), mp 85.5–87.5 °C (lit.[10] mp 82 °C).

***trans*-8-Hydroxy-1-azaspiro[5.5]undecan-2-one (32).** The keto lactam **24** (4.00 g, 2.21 mmol), in dry methanol (120 mL) at −78 °C was treated with $NaBH_4$ (1.00 g, 2.64 mmol), and the mixture was slowly warmed to room temperature. Workup gave a mixture of *trans*- and *cis*-hydroxy lactams (3.87 g, 96%; 73:27). They were separated by column chromatography (SiO_2) to give **32** (953 mg after sublimation and crystallization from EtOAc), mp 156–157 °C (lit.[9] 156–158 °C); IR ($CHCl_3$) 3600, 3380, 3320, 1630, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.06 (1 H, br s), 3.82 (1 H, m), 2.42–2.26 (2 H, m), 2.07–1.90 (3 H, m), 1.90–1.60 (6 H, m), 1.52–1.19 (4 H, m). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.01; N, 7.64. Found: C, 65.48; H, 9.36; N, 7.63.

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