Asymmetric Synthesis. 29.[1] Preparation of 1,8-Diazaspiro[5.5]undecane Derivatives

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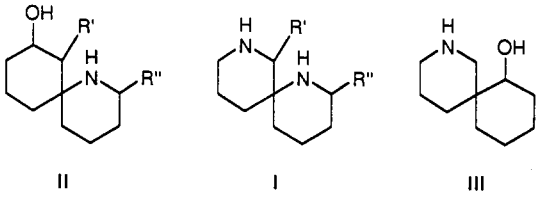
From 2-cyano-6-phenyl oxazolopiperidine 1, two highly efficient routes have been developed for the asymmetric synthesis of the spiropiperidine system: 1,8-diazaspiro[5.5]undecane. The key step was generation of the imine salts 6 and 17 from the functionalized α-amino nitrile 2, by nucleophilic addition of a suitable organometallic reagent to the nitrile group followed by, in situ, intramolecular nucleophilic alkylation. A reductive-cyclization procedure allowed the preparation of nonsubstituted and monosubstituted spiro compounds 5 and 10, respectively, while an alkylation–cyclization procedure led to the disubstituted spiro derivative 15, an aza analog of perhydrohistrionicotoxin.

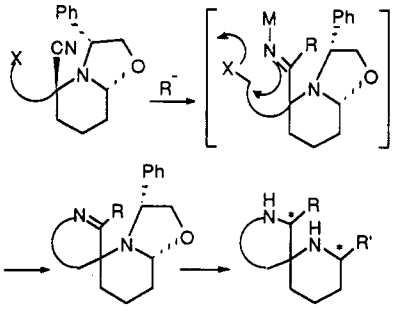
Naturally occurring histrionicotoxin (HTX)[2] and its perhydro analog (PHTX) both possess skeleton **II** conferring neurotoxic activities. Structure–activity relationship studies show that both heteroatoms, as well as their distance,[2b] are important in the mode of action of this series of alkaloids. However, no interesting pharmacological activity has been observed for alkaloids in the *Nitraria* family,[3] although the structure **III** presents structural similarities with **II**.Due to the unique structure and potential biological activity, studies on the synthesis of azaspiropiperidine[4] were performed long before histrionicotoxin and nitramine were isolated. Recently,[5] we reported the first synthesis of a new 1,8-diazaspiro[5.5]-undecane system (I) which represents a skeletal hybrid of both HTX (**II**) and nitramine (**III**). The promising pharmacological activity of this compound on synaptic conductance[6] encouraged us to develop a new strategy that would potentially lead to a range of different substituted spiropiperidines. Detailed herein is the asymmetric synthesis of three new types of substitution in this series. The interesting outcome of this study was the facile generation of imine salts from the corresponding functionalized α-amino nitrile by hydride reduction or



II I III

Figure 1.

Scheme I



organometallic attack at the nitrile group and subsequent easy intramolecular nucleophilic alkylation (Scheme I). This strategy was previously[7] unknown due to the facile decyanation tendency of such compounds.[8]

Results and Discussion

Synthesis of 1,8-Diazaspiro[5.5]undecane. It was decided to prepare compound 2 as the key intermediate in the synthesis of different substituted spiro derivatives (Scheme II). This was achieved by stereoselective alkylation of 2-cyano-6-phenyloxazolopiperidine synthon 1[9] with 1-chloro-3-iodopropane. The chloro derivative 2 was obtained as a single isomer in 91% yield after crystallization. The absolute configuration at C-2 was *R* in accordance with our previous results.[9b] First we decided to cyclize compound 2 by hydride reduction of the nitrile group. It is known that α-amino nitriles can be reduced

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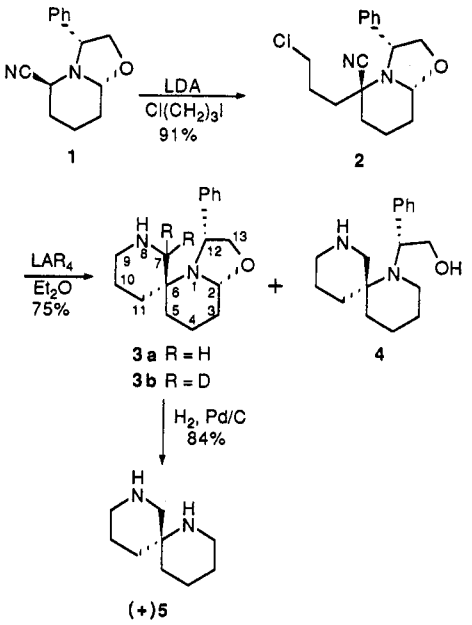
Scheme II



with $LiAlH_4$, either to diamines by reduction of the nitrile moiety or into monoamines by a decyanation process. The reaction product depends on the substitution pattern of the α-amino nitrile,[8] the stereoelectronic effect,[10] and the I strain of the molecule.[11] It was concluded that reduction of disubstituted α-amino nitriles with $LiAlH_4$ gave the decyanation product while monosubstituted α-amino nitrile yielded the diamine.[8]

It has been established that the nitrile group of compound **2**, a disubstituted α-amino nitrile, occupies an axial position and is antiparallel to the lone-pair electrons of nitrogen.[9] Thus, according to previous results, the decyanation route could be further facilitated by the stereoelectronic effects.[10] However, when this compound was treated with $LiAlH_4$ in Et_2O at O °C, two products **3a** and **4** were isolated in 70 and 5% yield, respectively. Inferior results were obtained when the reduction was carried out either in THF or when other reducing agents (e.g., $NaBH_3CN$ and DIBAL[7]) were employed. No decyanation product was found. The unusual result observed was tentatively explained by the strong $A^{1,3}$ interaction[12] in iminium compound **7**, a well-accepted intermediate for the decyanation process, which could in turn favor the alternative pathway, i.e., reduction of nitrile into imine salt **6**. In addition one could expect dehalogenation and/or reduction of the oxazolidine compound **2** with $LiAlH_4$. This was the first time we observed an oxazolidine which was reduced in low yields (5%) under these conditions. To confirm structure **3a**, reductive cyclization of **2** was conducted with $LiAlD_4$ under otherwise identical conditions. Compound **3b** was obtained which differed from **3a** in ^1H NMR only by the disappearance of the AB system of the two protons H-7 at 2.79 and 3.35 ppm and by an increase of 2 mu in mass spectrometry. This result opened a route to the 2-substituted-1,8-diazaspiro[5.5]undecane (vide infra). Finally hydrogenolysis of compound **3a** furnished the expected (6*R*)-1,8-diazaspiro[5.5]undecane (+)-**5** (84%).

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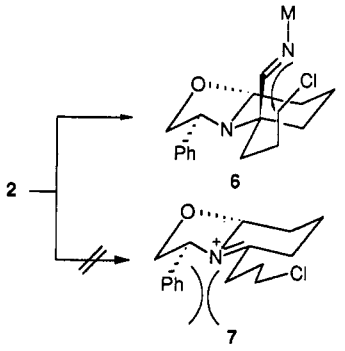
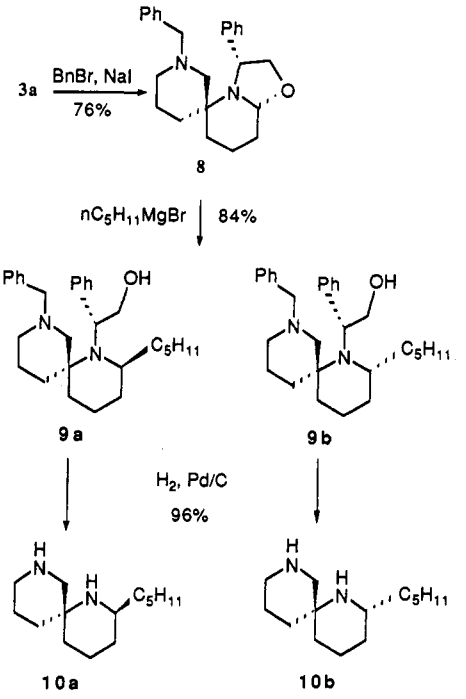
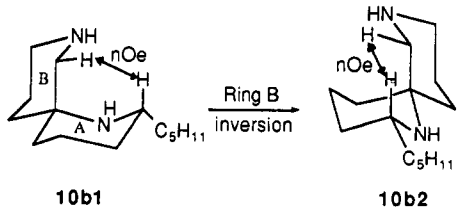


Figure 2.

Scheme III



Synthesis of 2-Pentyl-1,8-diazaspiro-[5.5]undecane. The pentyl side chain of PHTX was introduced in **9** by utilizing the potential iminium function of compound **3a** (Scheme III). Alkylation of compound **3a** using a Grignard reagent furnished a mixture of inseparable epimers. In contrast, reaction of *N*-benzyl derivative **8** with *n*-pentylmagnesium bromide in Et_2O/THF solution afforded a mixture of two separable isomers, **9a** (68%) and **9b** (16%). The relative stereochemistry of these two products could not be determined at this point. However, on hydrogenation over Pd/C (96% yield), the two products (**10a**, **10b**) exhibited important NMR differences. Only the spectrum of **10b** was entirely interpretable. Because of the failure of obtaining a crystalline derivative, we decided to study the stereochemistry by means of conformational analysis and NMR techniques. The two products differed only by the stereochemistry of C-2. Each can adopt four conformations by ring A and B inversions. The first problem needed to be resolved was the position of the *n*-pentyl chain. Proton H-2 in compound **10b** gave a complex signal at 2.6 ppm which did not offer any indication on the stereochemistry of this center. However by means of the ^1H–^1H COSY spectrum, one of the protons H-3 was identified as a well-resolved signal at 0.98 ppm (qd, J = 12.2 and 4.1 Hz) indicating an axial position. The large coupling constant between this proton and H-2 (J =12.2



10b1 10b2

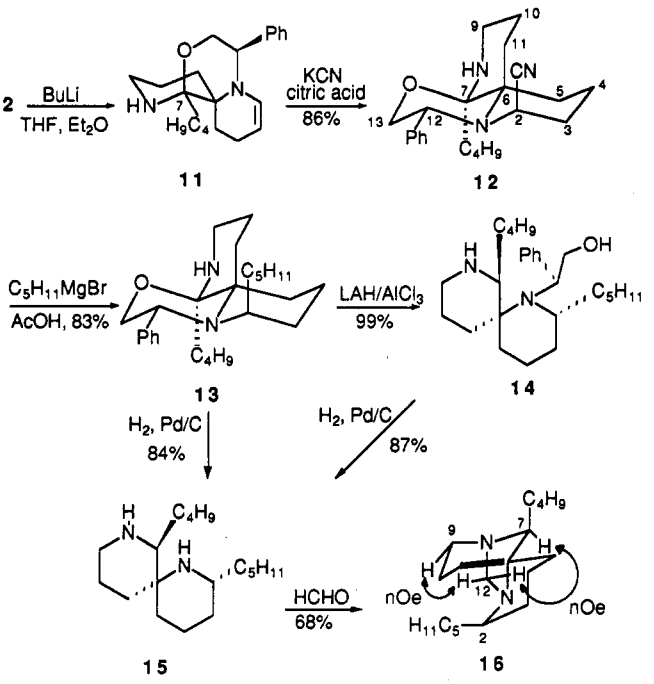
Figure 3.

Hz) showed that proton H-2 is also axial. The stereochemistry was determined by a phase-sensitive NOESY experiment in which a correlation between H-2 and one of the H-7 protons was observed. This spatial relationship being only possible for conformers **10b1** and **10b2**, it was concluded that product **10b** was the epimer having the pentyl chain in a *trans* relationship with respect to the C-6,C-7 bond. Thus the absolute stereochemistry of these products are (2*R*,6*R*) for **10b** and (2*S*,6*R*) for **10a**.

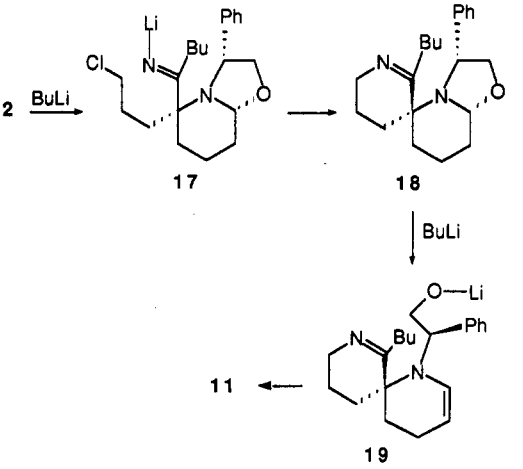
Synthesis of 2-Pentyl-7-butyl-1,8-diazaspiro[5.5]-undecane (15). For the synthesis of dialkylated spiro compound analog of PHTX we wished to explore the intramolecular reaction of imine salt **17**, generated by nucleophilic attack of a suitable organometallic reagent at the nitrile. A similar reaction has been carried out for the synthesis of tetrahydroisoquinolines; however in this case, the aryl nitrile was used as an external electrophile.[13] There are four possible electrophilic sites (CN, C-9, and two potential iminium functions) in compound **2**; thus the difficulty in obtaining the desired intermediate amino imine is obvious. A chemoselective nucleophile for attack at the nitrile moiety of compound **2** was required. While it is known that Grignard reagents react with both α-amino nitrile (Bruylants reaction)[14] and α-amino ether moieties,[9b] via an iminium ion, reaction with organolithium reagents is more highly substrate dependent.[15,16] Indeed it has been shown that organolithium reagents gave substitution products with elimination of cyanide in the case of disubstituted α-amino nitrile.[15] However, we have recently reported that reaction of synthon **1** (a monosubstituted-α-amino nitrile) with organolithium or organocuprate reagents provided the α-amino imine.[16] On the basis of this result, and encouraged by our experience on the reductive cyclization of compound **2** (vide supra), we investigated the reaction of compound **2** with BuLi. This proved to be a highly efficient route to prepare 1,7-disubstituted-1,8-diazaspiro[5.5]undecane derivatives.

Our synthesis started from compound **2** which was submitted to the reaction with BuLi in an Et_2O/THF solution. Enamine **11** (Scheme IV)was isolated in 61% yield as an unstable oil. Particulary diagnostic of structure **11** in the ^1H NMR were two olefinic protons with a typical splitting pattern (H-2: δ = 5.47 ppm, dt, J = 8.2 and 1.7 Hz; H-3: δ = 4.34 ppm, ddd, J = 8.2, 4.7 and 2.3 Hz). The coupling constants of H-12 and H-13 (J = 12.0, 11.1, and 4.9 Hz) are characteristic of a morpholine system. The ^{13}C spectrum exhibited a quaternary carbon (δ = 87.4 ppm) and two olefin signals (δ = 98.4 and 133.50 ppm) of the enamine system.

Scheme IV



Scheme V



Formation of enamine **11** could be explained by intramolecular alkylation of imine salt **17**, resulting from addition of BuLi onto the nitrile group (Scheme V). Ring opening of oxazolidine **18** under basic conditions[17] would lead to enamine **19** in the presence of excess BuLi. The stereochemistry of the newly created asymmetric center (C-7) was necessarily 7(*R*) as depicted in Scheme IV. Exclusive addition of the nucleophile onto the nitrile group could again be explained by the important $A^{1,3}$ interaction for the intermediate iminium **7**[15] which disfavors the decyanation process.

Due to the instability of compound **11**, it was directly transformed to amino nitrile **12** without purification in a biphasic system (CH_2Cl_2/H_2O) under acidic conditions in the presence of KCN. Compound **12** was obtained as a single isomer (86%). The remarkable stereoselectivity observed for the addition of CN^- to the intermediate tetrahydropyridinium salts was in accordance with stereoelectronic control.[18] Thus, β-attack to the sterically

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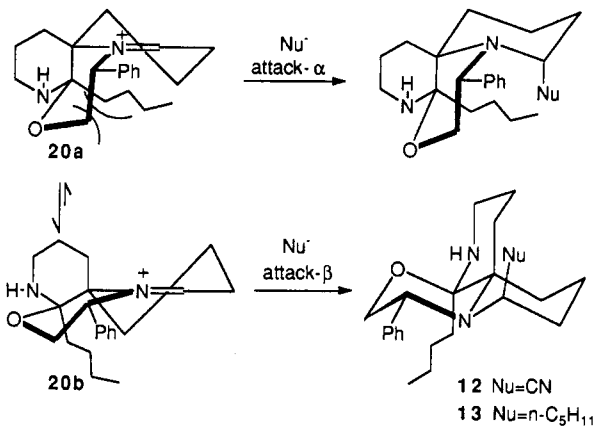
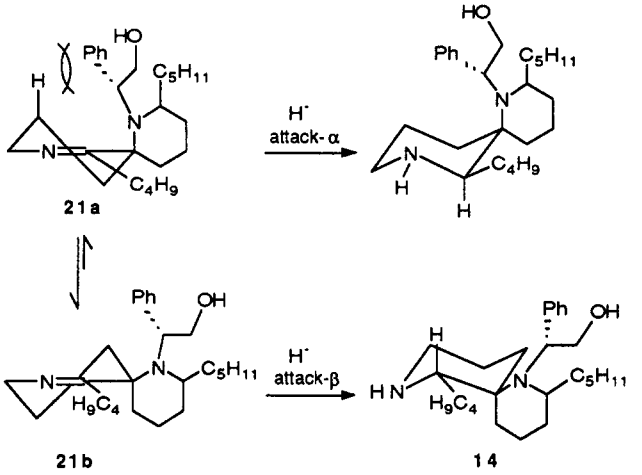
Scheme VI



Scheme VII



more favored conformer **20b** led to amino nitrile **12** (Scheme VI). The axial position of the nitrile was confirmed by ^{1}H NMR. Indeed H-2 had a chemical shift and coupling constants typical of an equatorial proton (δ = 3.58 ppm, br d, J = 6.1 Hz). It is worthy of noting that there are four new bonds created (two cyclizations) in this simple one-pot reaction.

The next step was introduction of the alkyl chain at C-2. Two methods were envisaged. All attempts to introduce a substituent by deprotonation and alkylation failed, probably due to steric hindrance of the amino nitrile. We then turned our attention to the second method in which the substituent was introduced by means of a Grignard reagent.[9,14] Classical conditions led only to poor yields of substitution product **13**. Prior formation of the iminium salt by complexation with $AgBF_4$[9] or $TiCl_4$[19] also proved unsuitable. The difficulty in this reaction is evident when one considers the steric hindrance of the intermediate iminium salt; tautomerization of iminium to enamine by deprotonation was favored over nucleophilic addition. This problem was solved by displacing the enamine–iminium equilibrium with repeated sequential additions of HCl and nucleophile.[20] We modified this procedure, and after three cycles of alternative addition of Grignard reagent (1 equiv) and acetic acid (1 equiv) compound **13** was isolated in 59% yield as a single isomer (83% in reacted material). The configuration at C-2 was proposed again according to the principle of stereoelectronic control (Scheme VI). Hydrogenation of compound **13** allowed reduction of the amino ether function and hydrogenolysis of the benzylamine in one step. Only one stereoisomer **15** was obtained in 84% yield. The same result was obtained *via* a two-step process involving reduction with $LiAlH_4/AlCl_3$ followed by hydrogenolysis of amino alcohol **14**. hydrogenation of the amino ether moiety (steric control) and nucleophilic attack at the imine (stereoelectronic control) led to the same stereochemistry at C-7 giving important information concerning the stereochemistry of this center. It is well known that reduction of amino ethers by hydride involves an intermediate iminium salt[21] and the approach of hydride is controlled by stereoelectronic effect.[18] On the basis of this assumption, we reasoned that **14** was the most probable structure resulting from the β-attack of hydride on the conformer **21b** (Scheme VII).

Due to possible ring inversion of the piperidine rings in compound **15**, it was not feasible to study the stereochemistry by NMR. In order to rigidify the molecule, aminal **16** was prepared by condensation of diamine **15** with formaldehyde. Examination of the Dreiding model shows that there are four possible conformers for the two diastereoisomers. Final confirmation of the structure was obtained from NOESY experiments conducted on aminal **16**. Strong NOE correlations were observed between H-7 and one of the two H-12 protons and between the other H-12 and H-9 protons. These correlations can be observed only in the isomer depicted for formula **16** which possesses the stereochemistry of C-2 and C-7 predicted on the basis of mechanistic hypothesis. Thus, it was concluded that the absolute configuration of diamine **15** was (2*R*,6*R*,7*S*). It is interesting to note that this stereochemistry is identical to that of (−)-perhydrohistrionicotoxin.

In conclusion, starting from synthon **1**, we have developed an efficient and general method for the asymmetric synthesis of different substituted 1,8-diazaspiro[5.5]-undecanes. The intriguing result is formation of an amino imine salt by nucleophilic addition to the nitrile group of a functionalized α-amino nitrile. These observations are contrary to what has been reported hitherto in the literature and have been rationalized by means of the $A^{1,3}$ interaction. The usefulness of α-amino nitriles, usually considered only as protected iminium functions, is thus increased.

Experimental Section

^{1}H NMR were recorded at 200, 250, or 400 MHz and at 62.5 MHz for ^{13}C NMR in $CDCl_3$ or CD_3OD solution. Chemical shifts were measured as ppm downfield of internal tetramethylsilane. Infrared spectra were recorded as solutions in $CHCl_3$. Unless otherwise noted, mass spectral data were recorded in the electron-impact (EI) mode (70eV). Analytical TLC was performed on glass plates coated with silica gel 60 F_{254} (Merck). Optical rotations of $CHCl_3$ solutions were measured at 20 ± 3 °C. Reaction solvents were distilled under N_2 from various drying agents. All reactions were performed under an atmosphere of dry N_2. In order to make easier comparison of NMR data the products are described with the numbering of the final products as indicated for **3** in Scheme II.

2*H*-Hexahydro-2-(3-Chloropropyl)-2-cyano-6-phenyloxazolo[3,2-*a*]pyridine (2) (nonsystematic numbering). To a solution of LDA, prepared from diisopropylamine (48.4 mmol, 6.68 mL) and BuLi (1.6 M in hexane, 44 mmol, 27.5 mL) in THF (80 mL) at −20°C was added a solution of 2-cyano-6-phenyloxazolopiperidine **1** (4.56 g, 20 mmol) in THF (20 mL) at −78 °C.

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(21) Bergmann, E. D. *Chem. Rev.* **1953**, *53*, 309.

After 30 min 1-chloro-3-iodopropane (30 mmol, 3.21 mL) in THF (5 mL) was added slowly. The mixture was stirred for 3 h at this temperature. The dry ice–acetone bath was removed and the mixture was warmed to rt and was quenched by aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the crude material on SiO_2 [ether/heptane (1:2 then 1:1)] afforded chloro derivative **2** which was crystallized from ether/hexane (3:2) (5.55 g, 91%): mp 122–124 °C; $[\alpha]_D$ −145° (c = 1.38); IR 2200 cm^{-1} (CN); MS m/z (rel inten) 306 (3), 305 (10), 304 (10), 303 (10), 227 (100); ^1H NMR (200 MHz) δ 1.3–2.3 (10 H), 2.85 (CH_2Cl), 3.75 (H-13), 4.00 (H-13), 4.14 (dd, J = 9.8, 2.0 Hz, H-2 ax), 4.22 (H-12), 7.10–7.15 (5 H); ^{13}C NMR (50.3 MHz) δ 20.1, 26.7, 29.4, 34.2, 36.7 (5 CH_2), 43.7 (CH_2Cl), 61.9 (C-6), 62.5 (C-12), 74.8 (C-13), 92.3 (C-2), 118.6 (CN), 127.3, 127.8, 128.7, 143.7 (Ar). Anal. Calcd for $C_{17}H_{21}N_2ClO$: C, 66.99; H, 6.94; O, 5.25. Found: C, 67.28; H, 6.81; O, 5.07.

Preparation of 3a via Cyclization of Halogeno Nitrile 2. To a suspension of $LiAlH_4$ (898 mg, 2.24 mmol) in ether (30 mL) was added a solution of compound **2** (1.8 g, 5.9 mmol) in ether (10 mL) and THF (2 mL) at 0 °C. After stirring the mixture for 3 h, NaOH (10%) (2 mL) was carefully added, followed by water (2 mL). After filtration, concentration of organic phases gave an oil which was purified by SiO_2 flash chromatography [CH_2Cl_2/MeOH/NH_4OH (95:5:0.1)] affording **3a** (1.13 g, 70%) and **4** (81 mg, 5%). **3a**: Amorphous powder, $[\alpha]_D$ −157° (c = 1.1); IR 3300 cm^{-1}; MS m/z (rel inten) 272 (6), 229 (80), 228 (100), 215 (100), 214 (100), 104 (78); HRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1894; ^1H NMR (250 MHz) δ 1.1–2.4 (10H), 2.48 (H-9 ax), 2.79 (d, J = 11.8 Hz, H-7 ax), 3.05 (H-9 eq), 3.35 (d, J = 11.8 Hz, H-7 eq), 3.68 (H-12), 4.05 (H-13), 4.11 (br s, NH), 4.25 (H-13), 4.35 (d, J = 8.0, 2.6 Hz, H-2 ax), 7.20–7.50 (5 H); ^{13}C NMR (62.5 MHz) δ 19.1, 23.2, 31.2, 31.5, 38.8, 44.3 (C-7), 46.8 (C-9), 55.8 (C-6), 58.5 (C-12), 75.0 (C-13), 88.2 (C-2), 126.6, 126.9, 128.2, 147.9. **4**: Amorphous solid; $[\alpha]_D$ −53° (c = 0.3); IR 3350 cm^{-1}; MS m/z (rel inten) 274 (2), 243 (8), 230 (100), 217 (55); HRMS calcd for $C_{17}H_{28}N_2O$ 274.2045, found 274.1894; ^1H NMR (250 MHz) δ 1.1–1.9 (10H), 2.55 (d, J = 12.1 Hz, H-7), 2.70–3.00 (4H, 2 H-2 and 2 H-9), 3.50 (d, J = 12.1 Hz, H-7), 3.58 (H-13), 3.75 (br s, NH and OH), 3.92 (H-13), 4.42 (H-12), 7.1–7.5 (5H); ^{13}C NMR (62.5 MHz) δ 20.1, 22.4, 25.7, 31.2, 35.0, 39.4 (C-9), 46.7 (C-2), 53.2 (C-7), 54.7 (C-6), 59.8 (C-12), 61.6 (C-13), 127.3, 128.3, 128.7, 141.4.

(6*R*)-1,8-Diazaspiro[5.5]undecane (5). Hydrogenolysis of compound **3a** (35 mg, 1.3 mmol) in methanol (5 mL) in the presence of HCl (0.1 mL) and 5% Pd/C (10 mg) for 6 h afforded a compound, which after filtration and concentration, was dissolved in ether and extracted three times with HCl solution. Aqueous layers were made basic (NaOH, 10%) and then extracted with CH_2Cl_2. Evaporation of the organic solvent afforded pure **5** (17 mg, 84%) as an oil: $[\alpha]_D$ +18° (c = 0.3); IR 3300 cm^{-1}; MS m/z (rel inten) 154 (15), 126 (36), 110 (100), 96 (80); HRMS calcd for $C_9H_{18}N_2$ 154.1470, found 154.1475; ^1H NMR (250 MHz) δ 1.2-1.7 (11H), 2.05 (br s, 2 NH), 2.48 (d, J = 12.2 Hz, H-7), 2.60 (ddd, J = 12.2, 9.1, 3.0 Hz, H-2 ax), 2.82 (H-9 eq), 2.90 (d, J =12.2 Hz, H-7), 2.91 (dt, J = 12.2, 4.2 Hz, H-2 eq); ^{13}C NMR (62.5 MHz) δ 20.2, 22.3, 26.9, 34.8, 35.5, 40.7 and 47.3 (C-2 and C-9), 49.6 (C-6), 54.8 (C-7).

***N*-8-Protected Amine 8.** To a solution of amine **3a** (510 mg, 1.9 mmol), $NaHCO_3$ (315 mg, 3.75 mmol), and sodium iodide (281 mg, 1.87 mmol) in acetonitrile (10 mL) was added benzyl bromide (0.45 mL, 3.75 mmol). After refluxing for 16 h under N_2, the mixture was diluted with aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. SiO_2 flash chromatography [ether/hexane (1:10)] of oily residue furnished 516 mg of amine **8** (76%) as an amorphous powder: $[\alpha]_D$ −163° (c = 4.3); MS m/z (rel inten) 362 (18), 318 (80), 228 (100); ^1H NMR (200 MHz) δ 0.9–1.4 (9H), 1.98 (d, J = 10.8 Hz, H-7), 1.9–2.0 (H-3), 2.45 (H-5 eq), 2.74 (H-9 eq), 2.95 (d, J = 10.8 Hz, H-7), 3.37 and 3.60 (AB system, J = 13.4 Hz, NCH_2Ph), 3.62 (H-13), 3.95 (H-13), 4.18 (br d, J = 9.1 Hz, H-2 ax), 4.28 (H-12), 7.1–7.5 (10H); ^{13}C NMR (50.3 MHz) δ 19.3, 22.5, 31.2, 32.9, 38.5, 51.6 (C-7), 54.9 (C-9), 56.8 (C-6), 58.7 (C-12), 63.4 (NCH_2Ph), 72.1 (C-13), 88.3 (C-2), 126.7, 127.0, 128.3, 128.7, 139.3, 148.2. Anal. Calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.72. Found: C, 79.38; H, 8.40; N, 7.56.

1-(1′-Phenyl-2′-hydroxyethyl)-2-pentyl-8-benzyl-1,8-diazaspiro[5.5]undecanes 9a and 9b. A solution of n-pentylmagnesium bromide (0.77 mmol) in THF was added dropwise to a solution of oxazolidine **8** (70 mg, 0.19 mmol) in THF (5 mL) at rt. The solution was stirred at rt for 24 h and then hydrolyzed with aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by SiO_2 flash chromatography [ether/heptane (1:2 then 1:1)] and **9a** (57 mg, 68%) and **9b** (13 mg, 16%) were isolated. **9a**: oil; $[\alpha]_D$ −34° (c = 0.2); IR 3350 cm^{-1}; MS m/z (rel inten) 434 (4), 403 (2), 300 (100); HRMS calcd for $C_{29}H_{24}N_2O$ 434.3297, Found 434.3300; ^1H NMR (250 MHz) δ 0.60 (H-3 ax), 0.85 (t, J = 7.0 Hz, CH_3), 1.0–2.2 (21 H), 2.62 (H-2 eq), 2.70 (br s, O-H), 3.37 and 3.58 (AB system, J = 12.5 Hz, NCH_2-PH), 3.90 (2 H-13), 4.45 (H-12), 7.1–7.5 (10 H); ^{13}C NMR (62.5 MHz) δ 14.2 (CH_3), 16.4, 22.7, 22.9, 26.2, 28.9, 32.2, 37.2, 37.5, 51.2 (C-2), 54.2 (C-9), 54.6 (C-6), 59.7 (C-12), 61.9 (C-13), 64.0 (NCH_2Ph), 64.9 (C-7), 126.8, 127.4, 128.1, 128.3, 130.0, 137.8, 142.6. **9b**: oil, $[\alpha]_D$ −53° (c = 0.3); IR 3400 cm^{-1}; MS m/z (rel inten) 434 (4), 403 (10), 300 (100); HRMS calcd for $C_{29}H_{42}N_2O$ 434.3297, found 434.3293; ^1H NMR (250 MHz) δ 0.72 (t, J = 7.1 Hz, CH_3), 0.9-2.0 (19 H), 2.05 (d, J = 11.5 Hz, H-7), 2.32 and 2.60 (2 H-9), 2.70 (d, J = 11.5 Hz, H-7), 2.75 (H-2 eq), 3.45 and 3.55 (AB system, J = 12.8 Hz, NCH_2Ph), 3.71 (2 × H-13), 4.68 (H-12), 7.1–7.5 (10 H).

(2*S*,6*R*)-2-Pentyl-1,8-diazaspiro[5.5]undecane (10a). Hydrogenolysis of 50 mg of **9a** in the manner described in the preparation of **5** afforded **10a** in 96% yield: oil; $[\alpha]_D$ +9° (c = 0.7); IR 3330 cm^{-1}; MS m/z (rel inten) 224 (3), 180 (100); MS (CI) 225 (MH^+, 100); ^1H NMR (250 MHz) δ 0.88 (t, J = 6.5 Hz, CH_3), 0.9–2.05 (18 H), 1.85 (br s, 2 NH), 2.50–2.70 (2 H-7, H-2, H-9 ax), 2.91 (H-9 eq); ^{13}C NMR δ (62.5 MHz) 14.1 (CH_3), 20.1, 22.3, 22.7, 25.8, 29.2, 32.2, 33.6, 35.4, 37.8, 47.4 (C-9), 49.6 (C-2), 50.1 (C-6), 60.5 (C-7). Anal. Calcd for $C_{14}H_{28}N_2$: C, 74.94; H, 12.58; N, 12.48. Found: C, 74.46; H, 12.18; N, 12.24.

(2*R*,6*R*)-2-Pentyl-1,8-diazaspiro[5.5]undecane (10b). The same procedure conducted on 25 mg of **9b** afforded **10b** in 96% yield: oil; $[\alpha]_D$ +13° (c = 0.52); IR 3350 cm^{-1}; MS m/z (rel inten) 224 (8), 180 (100), 167 (20); ^1H NMR (250 MHz) δ 0.88 (t, J = 6.8 Hz, CH_3), 0.98 (qd, J = 12.2, 4.1 Hz, H-3 ax), 1.10–1.70 (17 H), 1.92 (br s, 2 NH), 2.50 (d, J = 12.2 Hz, H-7), 2.58 (H-2 ax), 2.62 (H-9 ax), 2.85 (dt, J = 11.5, 5.0 Hz, H-9 eq), 3.05 (d, J = 12.2 Hz, H-7); ^{13}C NMR (62.5 MHz) δ 14.4 (CH_3), 20.8, 22.7, 22.9, 26.0, 32.4, 33.2, 35.3, 38.1, 40.2, 47.5 (C-9), 50.4 (C-2), 50.6 (C-6), 51.3 (C-7).

Preparation of 11 by Cyclization of Halogeno Nitrile 2. BuLi (1.6 N in hexane, 12.1 mL, 19.4 mmol) was added dropwise at −78 °C to a solution of **2** in ether/THF (2:1) (1.97 g, 6.45 mmol). The mixture was stirred at this temperature for 1 h and then at 0 °C for 14 h. It was then quenched by addition of aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phases were dried and concentrated. An analytical sample was chromatographed on a short SiO_2 column [ether/heptane (1:2)]. Enamine **11** was obtained as an unstable oil: $[\alpha]_D$ −211° (c = 2.01, MeOH); IR 1646 cm^{-1}; MS m/z (rel inten) 326 (80), 295 (5), 108 (90), 104 (100); ^1H NMR (200 MHz) δ 0.95 (t, J = 8.0 Hz, CH_3), 1.2–2.55 (14 H), 2.70 (H-9 eq), 3.13 (H-9 ax), 3.53 (H-13 ax), 3.69 (H-13 eq), 4.22 (H-12), 4.34 (ddd, J = 8.2, 4.7, 2.3 Hz, H-3), 5.47 (dt, J = 8.2, 1.7 Hz, H-2), 7.2–7.5 (5 H); ^{13}C NMR (50.3 MHz) δ 14.1 (CH_3), 19.3, 19.7, 22.0, 23.3, 23.5, 25.7, 29.9, 40.0 (C-9), 56.3 (C-6), 57.6 (C-12), 69.0 (C-13), 87.4 (C-7), 98.4 (C-3), 133.5 (C-2), 127.8, 128.7, 139.5.

Amino Nitrile 12. Crude material from the preceding experiment was dissolved in CH_2Cl_2 (40 mL). Water (30 mL) was added and then citric acid to pH 2–3. KCN (624 mg, 9.6 mmol) was then cautiously added. The resulting mixture was stirred for 2 h at rt, was then made alkaline with aqueous $NaHCO_3$, and was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by SiO_2 flash chromatography [ether/heptane (1:2)] afforded **12** (1.95 g, 86%): mp 88–90 °C (ether); $[\alpha]_D$ −137° (c = 0.7); IR 2200 cm^{-1}; MS m/z (rel inten) 353 (18), 327 (10), 104 (100); ^1H NMR (200 MHz) δ 0.95 (t, J = 7.0 Hz, CH_3), 1.1–2.5 (16 H), 2.60 (H-9 eq),

3.10 (H-9 ax), 3.58 (H-2 eq), 3.60 (H-13 ax), 3.72 (H-13 eq), 4.28 (H-12), 7.20–7.50 (5 H); ^{13}C NMR δ 14.2 (CH_3), 17.2, 19.6, 22.3, 23.4, 23.7, 27.5, 29.2, 29.7, 39.3 (C-9), 46.2 (C-2), 58.6 (C-12), 59.0 (C-6), 66.3 (C-13), 87.8 (C-7), 120.4 (CN), 128.5, 129.2, 138.8. Anal. Calcd for $C_{22}H_{31}N_3O$: C, 74.75; H, 8.84; N, 11.89; O, 4.53. Found: C, 74.83; H, 9.00; N, 11.62; O, 4.48.

Preparation of 13 by Reaction of Amino Nitrile 12 with *n*-Pentylmagnesium Bromide. *n*-Pentylmagnesium bromide in Et_2O (1.0 mmol) was added dropwise to a solution of amino nitrile **12** (340 mg, 0.96 mmol) in ether (10 mL) at −40 °C. After stirring at this temperature for 30 min, the mixture was stirred 30 min at rt. Acetic acid (5.5 × 10^{-2} mL, 0.96 mmol) was added and after 5 min, the reaction mixture was cooled to −40 °C and the Grignard reagent (1 equiv) was added. This procedure was repeated three times after which the mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2, and the organic phases were concentrated under reduced pressure. The crude mixture was purified by SiO_2 flash chromatography [ether/heptane (1:2)], affording unreacted **12** (35 mg) and alkylated product **13** (318 mg, 83%): oil; $[\alpha]_D$ −67° (*c* = 3.5); IR 3350 cm^{-1}; MS *m/z* (rel inten) 398 (10), 341 (10), 167 (100); ^{1}H NMR (400 MHz) δ 0.74 (t, *J* = 7.5 Hz, CH_3), 0.93 (t, *J* = 7.5 Hz, CH_3), 1.1–2.3 (23 H), 1.98 (br s, NH), 2.65 (H-2 and H-9 eq), 2.85 (H-5 ax), 3.10 (H-9 ax), 3.44 (H-13 ax), 3.58 (H-13 eq), 3.98 (H-12 ax), 7.10–7.50 (5H); ^{13}C NMR (50.3 MHz) δ 14.0 and 14.2 (2 CH_3), 18.4, 19.6, 22.4, 22.6, 23.4, 23.5, 27.1, 28.0, 29.3, 29.7, 31.8, 38.1, 39.5 (C-9), 57.2 (C-2), 58.8 (C-6), 59.2 (C-12), 69.6 (C-13), 88.0 (C-7), 126.6, 127.6, 128.0, 145.5. Anal. Calcd for $C_{28}H_{24}N_2O$: C, 78.34; H, 10.62; N, 7.03. Found: C, 78.43; H, 10.49; N, 6.67.

1-(1′-Phenyl-2′-hydroxyethyl)-2-pentyl-7-butyl-1,8-diazaspiro[5.5]undecane (14). To a suspension of $LiAlH_4$ (96 mg, 2.52 mmol) and $AlCl_3$ (335 mg, 2.52 mmol) in THF (5 mL) at −40 °C was added a solution of amino ether **13** (250 mg, 0.63 mmol) in THF (−40 °C). The reaction mixture was stirred for 4 h at this temperature. A solution of NaOH (10%) (0.5 mL) was added, followed by addition of water (0.5 mL). After stirring for 5 min, the mixture was filtered. The filtrate was concentrated and the residue was purified by column chromatography on Al_2O_3 [CH_2Cl_2/MeOH (98/2)], affording 250 mg of **14** (99%): oil; $[\alpha]_D$ −21° (*c* = 1.2); IR 3430 cm^{-1}; MS *m/z* (rel inten) 400 (2), 369 (25), 300 (100); ^{1}H NMR (200 MHz) δ 0.8 (t, *J* = 7.0 Hz, CH_3), 0.92 (t, *J* = 7.0 Hz, CH_3), 1.1–1.9 (24 H), 2.1 (br s, NH and OH), 2.60–2.90 (2 H-9, H-2), 3.10 (br d, *J* = 11.2 Hz, H-7), 3.95 (2 H-13), 4.50 (H-12), 7.1–7.4 (5 H); ^{13}C NMR (50.3 MHz) δ 14.2, 14.2 (2 × CH_3), 15.4, 22.9, 23.0, 23.1, 25.8, 27.5, 28.8, 29.2, 29.8, 32.3, 32.8, 38.8 (C-9), 51.8 (C-2), 57.5 (C-2), 59.3 (C-7), 60.8 (C-12), 63.7 (C-13), 126.7, 128.2, 128.4, 143.1. Anal. Calcd for $C_{26}H_{44}N_2O$: C, 77.95; H, 11.07; N, 6.99. Found: C, 77.58; H, 11.10; N, 6.90.

(2*R*,6*R*,7*S*)-2-Pentyl-7-butyl-1,8-diazaspiro[5.5]undecane (15). Hydrogenolysis according the conditions described for **3a** from either **13** (158 mg, 0.4 mmol) or **14** (210 mg, 0.52 mmol) furnished the same diamine **15** in 84 and 87% yield, respectively; oil; $[\alpha]_D$ −60° (*c* = 0.4); IR 3330 cm^{-1}; MS m/z (rel inten) 280 (12), 236 (5), 180 (100), 167 (81); HRMS calcd for $C_{18}H_{36}N_2$ 280.2879, found 280.2888; ^{1}H NMR (200 MHz) δ 0.9 (6H, 2 × CH_3), 1.1–1.9 (24H), 2.25 (dd, *J* = 10.0, 2.7 Hz, H-7), 2.50–2.70 (H-2 and H-9 ax), 2.85 (H-9 eq); ^{13}C NMR (50.3 MHz) δ 14.0, 14.1 (2 × CH_3), 19.4, 20.6, 22.7, 22.8, 25.5, 25.7, 25.9, 29.0, 30.1, 31.0, 31.9, 36.0, 40.6 (C-9), 50.8 (C-2), 56.0 (C-6), 62.6 (C-7).

Preparation of Aminal 16 by Reaction of Diamine 15 with Formaldehyde. To a solution of diamine **15** (40 mg, 0.14 mmol) in formaldehyde (40% aqueous solution) (2 mL) was added AcOH (0.1 mL). The solution was stirred for 2 h at rt and then made alkaline with aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography [Al_2O_3, CH_2Cl_2/MeOH (99:1)], yielding compound **16** (28 mg, 68%): oil; $[\alpha]_D$ +43° (*c* = 1.2); MS *m/z* (rel inten) 292 (32), 235 (71), 180 (100); ^{1}H NMR (200 MHz) δ 0.9 (6H, 2 × CH_3), 1.2–2.1 (24 H), 2.5–2.6 (H-7 eq and H-9 eq), 2.7 (H-2 eq), 3.02 (H-9 ax), 3.80 and 4.15 (AB system, *J* =7.5 Hz, NCH_2N); ^{13}C NMR (50.3 MHz) δ 14.1 (2 CH_3), 17.9, 19.9, 22.2, 22.8, 23.1, 25.1, 25.5, 29.2, 32.3, 32.4, 33.9, 35.2, 45.8 (C-9), 52.4 (C-2), 57.9 (C-6), 66.5 (NCH_2N), 70.5 (C-7).

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Supplementary Material Available: NMR spectra for compounds **3a**, **4**, **5**, **9a**, **9b**, **10b**, **11**, **15**, and **16a** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.