Regio- and Stereoselective Control in the Addition of Grignard Reagents to the Pyridine Ring System

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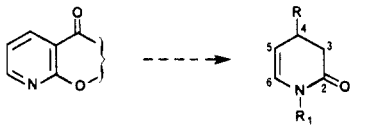
The *N*-methyl and *N*-benzyl salts of nicotinic acid derivative **7a** (e.g., **8** and **9**) undergo regio- and stereoselective addition with Grignard reagents to give **10** as the major reaction product. Selectivities as high as >99:1 are observed. Addition of alkyllithium reagents to **8** and **9** are regio- and stereorandom. The major diastereoisomer, **10**, resulting from Grignard reagent addition to **8** and **9**, has the group R_1 oriented anti to the hydrogen atom at the chiral center of the L-prolinol auxiliary. Chelation control is proposed to account for the regio- and stereoselectivity observed with Grignard reagent additions. Removal of the chiral auxiliary is demonstrated by conversion of **10a** to **16** in 83% overall yield via hydrogenation and acid-catalyzed methanolysis.

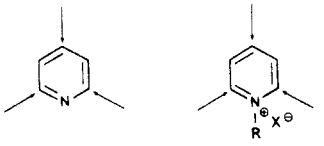
We are interested in the regio- and enantioselective conversion of 2-substituted nicotinic acid derivatives A into C(4) substituted dihydropyridones B. The multifunctional



A B

nature of B suggests that subsequent stereocontrolled bond formations at C(2), C(3), C(5), and C(6) should be possible. Consequently, synthetic intermediates of type B should be of use in the enantioselective construction of alkaloids containing the piperidine ring system.

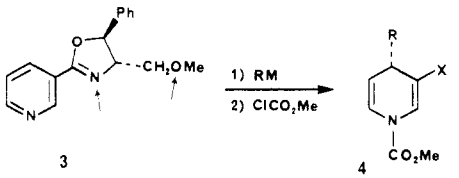
A remarkable number of studies concerned with the addition of carbon nucleophiles to pyridines have been reported.[2] Both the "free-base" 1 and the activated py-



1 2

ridinium salts **2** undergo 1,2- and 1,4-additions as shown; 1,6-additions also have been observed in appropriately substituted systems. Except for the recent work of Comins, very little effort has been directed at the application of this chemistry to natural products synthesis.

In 1981, Meyers and co-workers reported the addition of organometallic reagents to a chiral 3-pyridyloxazoline, **3**, to give the 1,4-addition product **4** with excellent regio-

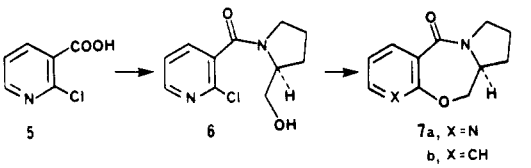


3 4

chemical and stereochemical control.[3] Diastereoselectivities were reported to be in the range 91:9 to 97:3. Reagent chelation at the sites indicated in the drawing was suggested to be responsible for the high regio- and stereoselectivities observed in this study.

Results and Discussion

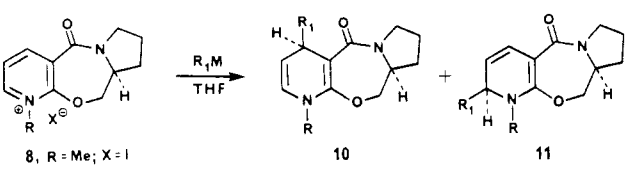
Pyridoxazepinone **7a** was selected as the substrate for our initial organometallic addition studies. This decision was influenced by the observation of excellent diastereoselection obtained in the Birch reductive alkylation of the related benzoxazepinone **7b**.[4,5] An important distinction



5 6 7a, X=N b, X=CH

between the two processes, however, is that the Birch reductive alkylation of **7b** relies on 1,4-diastereoselection mediated by the chiral center in the L-prolinol residue, while organometallic addition to the pyridine ring in **7a** would require 1,5-diastereoselection.[6] Heterocycle **7a** is prepared in 86% yield from 2-chloronicotinic acid (**5**) and L-prolinol. The amide bond in the intermediate **6** is fashioned by use of a standard peptide-forming process (DCC, 1-hydroxybenzotriazole, and *N*-methylmorpholine), and cyclization involves sodium hydride initiated addition–elimination.

The *N*-methyl and *N*-benzyl derivatives of **7a** (e.g., **8** and **9**) undergo highly regioselective and stereoselective addition with Grignard reagents to give **10** as the major re-



8, R = Me; X = I
9, R = CH₂Ph; X = Br

10 11

(1) Author to whom inquiries regarding X-ray crystallographic analysis should be directed.

(2) (a) Ziegler, K; Zeiser, H. *Ber. Dtsch. Chem. Ges. B* **1930**, *63*, 1847. (b) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 224. (c) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (d) Meyers, A. I.; Stout, D. M. *Chem. Rev.* **1982**, *82*, 223. (e) Comins, D. L.; Abdullah, A. H.; Mantlo, N. B. *Tetrahedron Lett.* **1984**, *25*, 4867 and references cited therein.

(3) Meyers, A. I.; Natale, N. R.; Wattlaufer, D. G.; Rafii, S.; Clardy, J. *Tetrahedron Lett.* **1981**, *22*, 5123.

(4) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591.

(5) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915.

(6) Morrison, J. D., Ed. "Asymmetric Synthesis–A Multivolume Treatise"; Academic Press: New York, 1984.

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Table I. Addition of Grignard and Organolithium Reagents to 8 and 9

R_1M	substrate	regioisomer ratio (10:11)[a]	diastereoisomer ratio 10 (β:α)[a]	diastereoisomer ratio 11 (β:α)[a]	isolated yield of 10, %
MeLi	8	1:1	3:1	3:1	
MeLi	9	1.75:1	3:0.5	1:1	
n-BuLi	8	3:1	2:1	1:0	
MeMgBr	8	19:1	19:0	1:0	**10a**, 72
MeMgBr	9	15:1	75:0	4:1	**10b**, 87
n-BuMgBr	8	57:1	57:0	1:0	**10c**, 60
Me_2CHCH_2MgBr	8	>99:1	>99:0	<1:0	**10d**, 95
CH_2=$CHCH_2MgBr$	8	5.5:1	4:1.5	1:0	
CH_2=$CHMgBr$	8	>99:1	>99:0	<1:0	**10e**, 74
PhMgBr	8	98:2	98:0	2:0	**10f**, 88
PhMgBr	9	>99:1	>99:0	<1:0	**10g**, 83

[a] Determined by ^{1}H NMR integration.

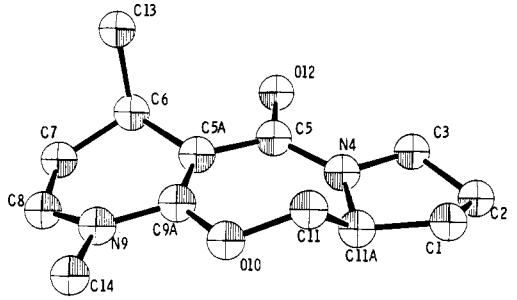
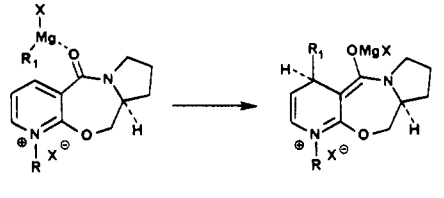


Figure 1. Computer-generated drawing of **10a** derived from the X-ray coordinates with hydrogens omitted for clarity.

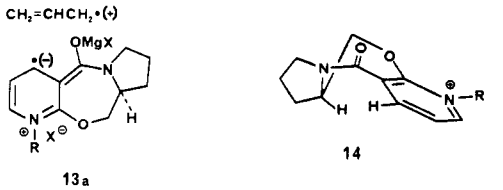
action product (Table I). While MeMgBr is quite selective (19:1), the bulkier reagents PhMgBr, CH_2=$CHMgBr$, and Me_2CHCH_2MgBr result in remarkably high selectivities of >99:1. Isolated yields of **10** are generally in excess of 85%. It is noteworthy that the alkyllithium reagents are nearly regio- and stereorandom.

A single-crystal X-ray structure determination for **10a** (R = R_1 = Me) was performed, and the molecular structure is shown in Figure 1. Stereochemical assignments for other members of the series were made by comparisons of ^{1}H NMR spectral data. Thus, the major diastereoisomer resulting from Grignard reagent addition to **8** and **9** has the group R_1 oriented anti to the hydrogen atom at the chiral center of the L-prolinol auxiliary. This configuration is opposite to that obtained with **3** in the Meyers study.

The high regio- and stereoselection for addition of Grignard reagents to **8** and **9** may be a result of coordination between the Grignard reagent and the amide oxygen atom as shown in structure **12**. Conjugate delivery of the organic ligand from magnesium to C(4) of the pyridine ring would generate the magnesium enolate **13**.



12 **13**

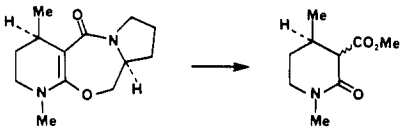


13a **14**

Dreiding stereomodels indicate that there is very little flexibility in the seven-membered ring of **8** and **9**. In fact, only two conformational minima appear to be possible. One of these is shown as **14**, in which the amide carbonyl group is above the plane of the pyridine ring anti to the hydrogen atom at the chiral center; the other conformer has the carbonyl group and pyridine ring coplanar. Significantly, there is no conformation available that positions the amide carbonyl group below the plane of the pyridine ring. Thus, intramolecular delivery of R_1 in **12** via a six-centered transition state can only give the stereochemistry shown in **13**. To complete this mechanistic hypothesis, we would suggest that the minor products formed in the Grignard additions and the random addition products encountered with alkyllithium reagents would result from pathways not involving the type of chelation control shown in **12**.

Allylmagnesium bromide is unique among the Grignard reagents studied because of the poor regio- and stereocontrol observed on reaction with **8**. Perhaps intermediate **12** (R_1 = allyl) experiences transfer of the organic ligand by a dissociative mechanism involving allylic radicals or allylic carbocations; see hypothetical intermediates **13a** (radical pair or nitrogen "ylide-like" ion pair, respectively).

Removal of the chiral auxiliary is demonstrated by conversion of **10a** (R = R_1 = Me) to 1,4(*R*)-dimethyl-3-carbomethoxypiperdin-2-one (**16**), which is accomplished by hydrogenation with 5% Pd on carbon in ethyl acetate to give **15** (93% yield) and acid-catalyzed methanolysis of



15 **16**

15 to give **16** (89%). While the conversion of **10a** into **16** represents an efficient method for removal of the chiral auxiliary, complementary protocols which liberate other functionality in **10** are also under exploration. We expect that this chemistry will find application in the enantioselective synthesis of alkaloids.

Experimental Section

Instrumentation. ^{1}H NMR spectra were recorded on Varian XL 200 (200-MHz) or Hitachi-Perkin-Elmer R-600 (60-MHz) NMR spectrometers by using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on an IBM WP-100 SY (25-MHz) spectrometer. X-ray diffraction data were obtained with an EnrafNonius CAD4 diffractometer by using Cu Kα (λ = 1.5418 Å) radiation. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer. Melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus and were reported uncorrected. Mass spectra were obtained on a Hewlett-Packard 5987A GC–MS system.

Microanalysis were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN.

Solvents. Tetrahydrofuran (THF) was dried by distillation in the presence of sodium metal under a nitrogen atmosphere with benzophenone ketyl as indicator. Benzene was distilled from calcium hydride and stored over 4-Å molecular sieves. Acetone was dried by storage over 4-Å molecular sieves. Aldrich HPLC-grade ethyl acetate was used without further purification. Dry methanol was obtained via distillation over magnesium turnings.

Solvents were removed at reduced pressure with a Buchi Rotavapor-R rotary evaporator. The last traces of solvent were removed by evacuation at room temperature by using a Welch Duo-Seal floor pump (~0.05 mmHg).

2-Chloro-3-[L-2-(hydroxymethyl)pyrrolidinyl]nicotinamide (6). To a stirred solution of 2-chloronicotinic acid (**5**) (3.1520 g, 20.00 mmol) and *N*-methylmorpholine (4.048 g, 40.02 mmol) in THF (60 ml) under N_2 was added *N,N'*-dicyclohexylcarbodiimide (4.12 g, 20.00 mmol) and 1-hydroxybenzotriazole hydrate (2.7019 g, 20.00 mmol). The solution was then cooled to 0 °C, and L-prolinol (2.0230 g, 20.00 mmol) dissolved in THF (7 mL) was added. After 2 h, the reaction mixture was allowed to slowly warm to room temperature, after which stirring was continued for an additional 18 h. The *N,N'*-dicyclohexylurea was removed by filtration, and the filtrate was concentrated under reduced pressure to a viscous red-orange oil. Flash chromatography on silica gel (ethyl acetate–acetone, 4:1) afforded the amide alcohol as a viscous oil which solidified to a colorless solid (monohydrate) upon standing (4.18 g, 86.8%, mp 61–62 °C): $[\alpha]^{25}_D$ −72.3° (*c* 0.845, $CHCl_3$); IR (KBr) 3400, 2980, 2960, 2882, 1620, 1583, 1561, 1460, 1429, 1396, 1075, 1055, 918, 812, 730 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 8.46 (1 H, dd, *J* = 1.9, 4.9 Hz), 7.75 (1 H, dd, *J* = 1.9, 7.6 Hz), 7.36 (1 H, dd, *J* = 4.9, 7.6 Hz), 4.50–4.31 (2 H, m), 3.90–3.80 (2 H, m), 3.38–3.32 (2 H, m), 2.26–2.13 (1 H, m), 1.95–1.68 (3 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 241 (M + 1, 100).

Anal. Calcd for $C_{11}H_{13}N_2O_2Cl{\cdot}H_2O$: C, 51.06; H, 5.84; N, 10.83. Found: C, 51.11; H, 5.83; N, 10.89.

1,2,3,10,11,11a(*S*)-Hexahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (7a). A mixture of **6** (1.4552 g, 6.04 mmol) and sodium hydride (0.18 g, 7.55 mmol) in 70 mL of dry THF was refluxed under N_2 for 18 h. Sodium chloride and unreacted NaH were removed by filtration; solvent evaporation and crystallization (ethyl acetate) afforded 1.230 g of analytical pure **7a** (99%, mp 144–145 °C): $[\alpha]^{25}_D$ +220.2° (*c* 1.55, $CHCl_3$); IR (KBr) 3060, 2800, 1621, 1578, 1458, 1427, 1380, 1270, 1208, 1110, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.65 (1 H, dd, *J* = 2, 7.9 Hz), 8.39 (1 H, dd, *J* = 2, 4.6 Hz), 7.13 (1 H, dd, *J* = 4.6, 7.9 Hz), 4.64 (1 H, d, *J* = 11.4 Hz) 4.14, (1 H, dd, *J* = 8.2, 11.8 Hz), 4.08–3.95 (1 H, m), 3.88–3.71 (2 H, m), 2.35–2.18 (1 H, m), 2.10–1.80 (2 H, m), 1.78–1.60 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 162.7 (s, C=O), 160.6 (s), 151.4 (d), 143.7 (d), 118.2 (d), 115.9 (s), 73.3 (t, OCH_2), 57.4 (d), 48.3 (t, NCH_2), 29.3 (t), 22.5 (t); chemical ionization mass spectrum, *m/e* (relative intensity) 205 (M + 1, 100).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.34; H, 5.93.

1,2,3,10,11,11a(*S*)-Hexahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one, Methyl Iodide Salt (8). To a stirred solution of **7a** (0.50 g, 2.46 mmol) in 20.0 mL of dry benzene at room temperature was added 2.30 mL of iodomethane (36.9 mmol, 15 equiv). The reaction mixture was heated at 38 °C for 22 h. After cooling to room temperature, the resulting precipitate was collected by filtration to afford the *N*-methylpyridinium-oxazepenone iodide **8a** as a yellow-tinted white solid (0.55 g, 100% based on recovered starting material, mp 150–151 °C): $[\alpha]^{25}_D$ +135° (*c* 1.30, $CHCl_3$); IR (KBr) 3078, 3058, 3025, 2980, 2955, 1640, 1605, 1578, 1500, 1440, 1385, 1354, 1258, 1120, 1047, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.04 (1 H, dd, *J* = 1.8, 6.5 Hz), 8.99 (1 H, dd, *J* = 1.8, 9.6 Hz), 7.62 (1 H, dd, *J* = 6.2, 8.0 Hz), 5.19 (1 H, dd, *J* = 1.7, 11.4 Hz), 4.95 (1 H, m), 4.64 (1 H, dd, *J* = 9.1, 11.4 Hz), 4.36 (3 H, s), 3.92–3.64 (2 H, m), 2.48–2.30 (1 H, m), 2.04–1.97 (2 H, m), 1.84–1.62 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 159.8 (d), 158.6 (s, C=O), 157.4 (s), 151.5 (d), 121.6 (s), 119.0 (d), 78.6 (t, OCH_2), 55.9 (d), 48.7 (t, NCH_2), 44.0 (q, NCH_3), 28.6 (t), 22.6 (t); chemical ionization mass spectrum, *m/e* (relative intensity) 347 (M + 1, 100), 219 (66.7), 205 (6.7), 136 (9.6).

Anal. Calcd for $C_{12}H_{15}N_2O_2I$: C, 41.63; H, 4.37; N, 8.09. Found: C, 41.73; H, 4.44; N, 8.10.

1,2,3,10,11,11a(*S*)-Hexahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one, Benzyl Bromide Salt (9). To a stirred solution of **7a** (0.5 g, 2.46 mmol) in 13.0 mL of dry acetone was added 0.29 mL of benzyl bromide (2.46 mmol, 1.0 equiv). The reaction mixture was heated to reflux for 6 h. Upon cooling the benzyl bromide pyridinium salt crystallized. Filtration, washing of the collected precipitate with chilled acetone, and vacuum drying afforded 0.74 g of **9** as a colorless solid (80.3%, mp 145–146 °C): $[\alpha]^{25}_D$ +260.2° (*c* 1.02, $CHCl_3$); IR (KBr) 3100, 3076, 2982, 2950, 2874, 1652, 1611, 1580, 1444, 1400, 1373, 1216, 1158, 1095, 968, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.93 (1 H, dd, *J* = 1.7, 7.6 Hz), 8.80 (1 H, dd, *J* = 1.7, 6.5 Hz), 7.54 (1 H, dd, *J* = 6.3, 7.9 Hz), 7.50–7.40 (5 H, m, phenyl ring protons), 6.01 (2 H, s, CH_2Ph), 5.29 (1 H, dd, *J* = 2, 11 Hz), 5.09 (1 H, m), 4.63 (1 H, dd, *J* = 10.3, 10.3 Hz), 3.94–3.64 (2 H, m), 2.51–2.33 (1 H, m), 2.09–1.93 (2 H, m), 1.84–1.62 (1 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 377 (28.7), 375 (82.2), 295 (100), 212 (16.5), 205 (26.4), 91 (18.4).

Anal. Calcd. for $C_{18}H_{19}N_2O_2Br$: C, 57.61; H, 5.10; N, 7.47. Found: C, 57.51; H, 5.21; N, 7.43.

General Procedure for Grignard Additions to 8 and 9. To a stirred suspension of the pyridinium salt (0.27 mmol) of THF (4.5 mL) under N_2 at −20 °C (CCl_4/dry ice) was added slowly via syringe the desired Grignard reagent (1.1 to 1.5 equiv). After 2 h at −20 °C, the solution was quenched with cold saturated aqueous ammonium chloride. Water (3 mL) was added, and the resulting homogeneous solution was poured into a 30-mL separatory funnel containing 10 mL of water. The aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to afford a mixture of **10** and **11**. Isolation of **10** was accomplished by flash chromatography on neutral alumina (Brockman Activity Grade 1) eluting with 100% ethyl acetate, followed by recrystallization. Direct crystallization of **10** was possible in cases of high regio- and stereoselectivity.

6(*R*),9-Dimethyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[1,2-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10a) was prepared according to the general procedure from **8** and 3 M methylmagnesium bromide as colorless needles (72%, mp 149–150 °C, ethyl acetate/hexanes, 1:1): $[\alpha]^{25}_D$ −675.0° (*c* 1.00, $CHCl_3$); IR (KBr) 2944, 2935, 2910, 2888, 2878, 1672, 1550, 1410, 1363, 1242, 1086, 1010, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.80 (1 H, d, *J* = 6.9 Hz), 4.95 (1 H, t, *J* = 6.9 Hz), 4.43 (1 H, dd, *J* = 0.8, 11.5 Hz), 3.97 (1 H, dd, *J* = 7.6, 11.5 Hz), 3.78–3.50 (4 H, m), 3.01 (3 H, s) 2.17–2.02 (1 H, m), 1.98–1.42 (3 H, m), 0.99 (3 H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 165.0 (s, C=O), 156.1 (s), 128.7 (d), 109.5 (d), 84.9 (s), 72.8 (t, OCH_2), 58.4 (d), 48.1 (t, NCH_2), 35.5 (q, NCH_3), 29.9 (d), 29.6 (t), 23.3 (q), 22.6 (t); chemical ionization mass spectrum, *m/e* (relative intensity) 235 (100, M + 1), 2.19 (12.3).

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.78; H, 7.62; N, 12.00.

Suitable crystals of **10a** for X-ray diffraction studies formed from ethyl acetate and hexane mixtures with space group symmetry of $P2_12_12_1$ and cell constants of a = 7.402 (2) Å, b = 12.248 (2) Å, and c = 14.079 (2) Å for Z = 4 and a calculated density of 1.219 g/cm^3. Of the 1018 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 965 were observed ($I > 3\ \sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[7] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.049. No abnormally short intermolecular contacts were noted. Tables II, III, and IV containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-

(7) The following library of crystallographic programs was used: MULTAN 80, Main, P. et al., University of York, York, England, 1980; ORTEP-II, Johnson, C. K. Oak Ridge National Laboratory, Oak Ridge, TN, 1970; SDP PLUS V1.1, Okaya, Y. et al., Frenz, B. A. and associates, College Station, TX, 1984.

generated perspective drawing of **10a** from the final X-ray coordinates showing the relative stereochemistry.

6(*R*)-Butyl-9-methyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10c) was obtained from **8** and 1.5 M *n*-butylmagnesium bromide as light yellow needles (59.5%, mp 131–132 °C, ether/pet ether): $[\alpha]^{25}_D$ −482.7° (*c* 1.04, $CHCl_3$); IR (KBr) 2966, 2921, 2878, 2856, 1676, 1550, 1410, 1364, 1283, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (1 H, d, *J* = 7.3 Hz), 4.98 (1 H, t, *J* = 6.9 Hz), 4.44 (1 H, dd, *J* = 0.8, 11.5 Hz), 3.97 (1 H, dd, *J* = 7.6, 11.5 Hz), 3.80–3.50 (4 H, m), 3.00 (3 H, s), 2.16–2.02 (1 H, m), 1.98–1.42 (3 H, m), 1.36–1.16 (6 H, m), 0.87 (3 H, t, *J* = 6.1 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 277 (M + 1, 88), 219 (100).

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.42; H, 8.81; N, 10.02.

6(*R*)-Isobutyl-9-methyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10d) was obtained from **8** and 1.6 M isobutylmagnesium bromide as colorless crystals (94.8%, mp 181–183 °C, ethyl acetate/hexanes, 1:1): $[\alpha]^{25}_D$ −515.7° (*c* 0.83, $CHCl_3$); IR (KBr) 2966, 2950, 2894, 2828, 1668, 1540, 1459, 1414, 1368, 1250, 1008, 869 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.82 (1 H, d, *J* = 7.1 Hz), 5.01 (1 H, t, *J* = 6.9 Hz), 4.43 (1 H, dd, *J* = 0.9, 11.5 Hz), 3.95 (1 H, dd, *J* = 7.6, 11.5 Hz), 3.76–3.59 (4 H, m), 3.01 (3 H, s), 2.14–2.00 (1 H, m), 1.94–1.40 (4 H, m), 1.21 (2 H, m, *J* = 1.1, 6.6 Hz), 0.97 (3 H,d, *J* = 6.6 Hz), 0.87 (3 H, d, *J* = 6.6 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 277 (M + 1, 100), 219 (59.8).

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.68; H, 8.67; N, 10.20.

6(*R*)-Vinyl-9-methyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10e) was obtained from **8** and 1.0 M vinylmagnesium bromide as colorless crystals (74.3%, mp 100–101 °C, hexanes/ethyl acetate, 2:1): $[\alpha]^{25}_D$ −405.1° (*c* 0.78, $CHCl_3$); IR (KBr) 2968, 2924, 2882, 1669, 1548, 1411, 1348, 1237, 1074, 1009, 904 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (1 H, d, *J* = 7.1 Hz), 5.98–5.82 (1 H, m, *J* = 9.1, 17.1 Hz), 5.04–4.91 (2 H, m, *J* = 0.8, 9.1, 17.1 Hz), 4.90 (1 H, t, *J* = 6.9 Hz), 4.45 (1 H, dd, *J* = 0.8, 11.5 Hz), 4.32 (1 H, t, *J* = 4.2 Hz), 3.99 (1 H, dd, *J* = 7.8, 11.5 Hz), 3.80–3.60 (3 H, m), 3.01 (3 H, s), 2.16–2.02 (1 H, m), 1.92–1.40 (3 H, m); electron impact mass spectrum, *m/e* (relative intensity) 246 (M^+, 9.0), 219 (9), 205 (12), 163 (22), 136 (100), 106 (8).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.38. Found: C, 68.21; H, 7.47; N, 10.99.

6(*R*)-Phenyl-9-methyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10f) was obtained from **8** and 0.9 M phenylmagnesium bromide as yellow crystals (87.9%, mp 181–182 °C, ethyl acetate/hexanes, 2:1): $[\alpha]^{27}_D$ −735.4° (*c* 0.82, $CHCl_3$); IR (KBr) 3052, 2985, 2942, 2878, 1673, 1560, 1448, 1410, 1365, 1350, 1268, 1230, 1076, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.09 (5 H, m, phenyl ring), 5.93 (1 H, d, *J* = 7.0 Hz), 5.08 (1 H, t, *J* = 6.8 Hz), 4.91 (1 H, d, *J* = 6.5 Hz), 4.46 (1 H, d, *J* = 11.4 Hz), 4.00 (1 H, dd, *J* = 7.8, 11.4 Hz), 3.83–3.70 (1 H, m), 3.68–3.48 (2 H, m), 3.06 (3 H, s), 2.13–2.00 (1 H, m), 1.93–1.66 (2 H, m), 1.64–1.40 (1 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 297 (M + 1, 100), 219 (14).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.70; H, 6.77; N, 9.34.

6(*R*)-Methyl-9-benzyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10b) was obtained from **9** and 3 M methylmagnesium bromide as yellow crystals (86.6%, mp 108–110 °C, ethyl acetate/hexanes, 1:1): $[\alpha]^{28}_D$ −265.5° (*c* 2.06, $CHCl_3$); IR (KBr) 3064, 3026, 2976, 2962, 2922, 2884, 1622, 1549, 1377, 1346, 1238, 1159, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.18 (5 H, m, phenyl ring), 5.87 (1 H, d, *J* = 7.3 Hz), 5.00 (1 H, t, *J* = 7.2 Hz), 4.56 (2 H, AB quartet, *J* = 15.9 Hz), 4.34 (1 H, dd, *J* = 0.9, 11.4 Hz), 3.90 (1 H, dd, *J* = 7.8, 11.5 Hz), 3.78–3.53 (4 H, m), 2.14–2.00 (1 H, m), 1.96–1.66(2 H, m), 1.64–1.42 (1 H, m), 1.01 (3 H, d, *J* = 6.5 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 311 (M + 1, 100), 295 (11), 219 (2).

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.41; H, 7.18; N, 8.91.

6(*R*)-Phenyl-9-benzyl-1,2,3,6,9,10,11,11a(*S*)-octahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (10g) was obtained from **9** and 0.9 M phenylmagnesium bromide as a yellow solid (82.9%, bp 140 °C, 0.8 mmHg): $[\alpha]^{28}_D$ −215.1° (*c* 2.52, $CHCl_3$); IR (KBr) 3068, 3016, 2982, 2954,2884, 1652, 1557, 1420, 1377, 1350, 1216, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) 7.48–7.13 (10 H, m), 6.00 (1 H, d, *J* = 7.3 Hz), 5.11 (1 H, t, *J* = 6.7 Hz), 4.92 (1 H, d, *J* = 6.5 Hz), 4.61 (2 H, AB quartet, *J* = 15.9 Hz), 4.40 (1 H, dd, *J* = 0.9, 11.5 Hz), 3.96 (1 H, dd, *J* = 7.8, 11.5 Hz), 3.88–3.73 (1 H, m), 3.70–3.52 (2 H, m), 2.14–2.00 (1 H, m),1.96–1.70 (2 H, m), 1.63–1.40 (1 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 373 (M + 1, 100), 295 (7.4), 281 (6.3), 205 (8.1), 131 (7.2).

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.27; H, 6.40; N, 7.62.

6(*R*),9-Dimethyl-1,2,3,6,7,8,9,10,11,11a(*S*)-decahydro-5*H*-pyrrolo[2,1-*c*]pyrido[3,2-*f*][1,4]oxazepin-5-one (15). A solution of **10a** (20.5 mg, 0.088 mmol) in ethyl acetate (3.0 mL), to which 5% Pd on carbon (14.9 mg) had been added, was hydrogenated at atmospheric pressure and room temperature for 45 min. Removal of the catalyst by filtration through Celite, followed by solvent evaporation, afforded **18** as a colorless solid (19.3 mg, 92.8%, mp 120–125 °C): $[\alpha]^{25}_D$ −146.8° (*c* 1.11, $CHCl_3$); IR (KBr) 3018, 2977, 2870, 1624, 1571, 1539, 1415, 1354, 1331, 1215, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (1 H, dd, *J* = 1.2, 11.4 Hz), 3.90 (1 H, dd, *J*= 8.0, 11.4 Hz), 3.76–3.48 (4 H, m), 3.35–3.07 (4 H, m), 2.85 (3 H, s), 2.14–2.00 (1 H, m), 1.93–1.70 (2 H, m), 1.63–1.41 (1 H, m), 1.09 (3 H, d, *J* = 6.7 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 237 (M + 1, 100).

1,4(*R*)-Dimethyl-3-carbomethoxypiperidin-2-one (16). To a solution of **15** (20.0 mg, 0.085 mmol) in MeOH (2.5 mL) was added H_2O (0.3 mL) and concentrated H_2SO_4 (0.5 mL). The resulting solution was heated and stirred at 80 °C for 21 h. Upon cooling the solution was neutralized with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$. Water was added to give a total solution volume of 10 mL. Extraction with chloroform (3 × 8 mL), drying ($MgSO_4$), solvent removal, and distillation in a Kugelrohr apparatus afforded **16** as a 5:1 mixture of diastereomers (colorless oil, 13.9 mg, 88.5%, bp 85–87 °C at 0.5 mmHg): IR (neat) 2960, 2936, 2880, 1740, 1642, 1504, 1436, 1342, 1259, 1207, 1164, 1014 cm^{-1}; ^1H NMR of major diastereomer ($CDCl_3$) δ 3.78 (3 H, s), 3.53–3.22 (2 H, m), 3.00 (1 H, d, *J* = 10.9 Hz), 2.96 (3 H, s), 2.42–2.22 (1 H, m), 1.97–1.83 (1 H, m), 1.64–1.42 (1 H, m), 1.02 (3 H, d, *J* = 6.5 Hz); chemical ionization mass spectrum *m/e* (relative intensity) 186 (M + 1, 100), 154 (14).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.31; H, 8.17.

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Registry No. 5, 2942-59-8; **6**, 100044-95-9; **7a**, 100044-96-0; **8**, 100044-97-1; **9**, 100044-98-2; **10** (R = Me, R′ = CH_2=$CHCH_2$) (isomer 1), 100045-04-3; **10** (R = Me, R′ = CH_2=$CHCH_2$) (isomer 2), 100163-43-7; **10a** (isomer 1), 100044-99-3; **10a** (isomer 2), 100163-41-5; **10b** (isomer 1), 100045-08-7; **10b** (isomer 2), 100163-44-8; **10c** (isomer 1), 100045-01-0; **10c** (isomer 2), 100163-42-6; **10d**, 100045-03-2; **10e**, 100045-06-5; **10f**, 100045-07-6; **10g**, 100045-10-1; **11** (R = R′ = Me), 100045-00-9; **11** (R = CH_2Ph, R′ = Me), 100045-09-8; **11** (R = Me, R′ = Bu), 100045-02-1; **11** (R = Me, R′ = CH_2=$CHCH_2$), 100045-05-4; **15**, 100045-11-2; **16**, 100045-12-3; MeLi, 917-54-4; *n*-BuLi, 109-72-8; MeBr, 74-83-9; *n*-BuBr, 109-65-9; Me_2CHCH_2Br, 78-77-3; CH_2=$CHCH_2Br$, 106-95-6; CH_2=CHBr, 593-60-2; PhBr, 108-86-1; $PhCH_2Br$, 100-39-0; L-prolinol, 23356-96-9.

Supplementary Material Available: Complete listings of positional parameters, bond angles and distances, and thermal parameters for structure **10a** (3 pages). Ordering information is given on any current masthead page.