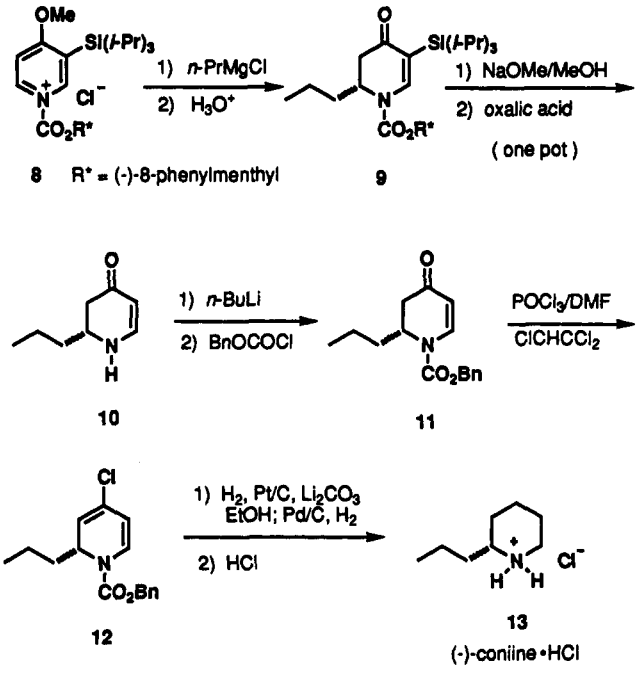
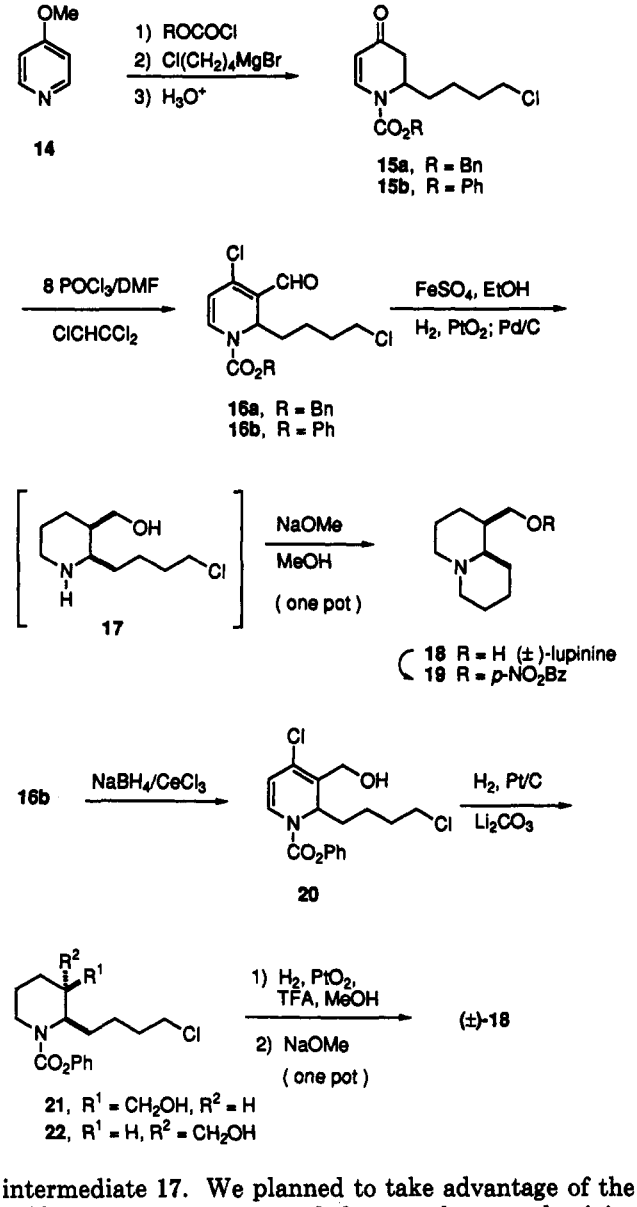
Scheme III



Scheme IV



dihydropyridone ring. The stereoselectivity has been explained using steric approach control arguments.[6] Treatment of **9** with sodium methoxide in MeOH, followed by oxalic acid, effects removal of the chiral auxiliary and the TIPS group via a one-pot reaction to provide dihydropyridone **10** in 86% yield. Reacylation of **10** to give enantiopure **11** in 94% yield was performed using *n*-butyllithium and benzyl chloroformate. The Vilsmeier reaction transformed **11** into 4-chloro-1,2-dihydropyridine **12** in 92% yield. Catalytic reduction of **12** using a combination of Pt/C and Pd/C gave (−)-coniine hydrochloride (**13**) in 83% yield. Our synthetic (−)-coniine hydrochloride was prepared from 4-methoxy-3-(triisopropylsilyl)pyridine in 54% overall yield. Spectral and optical properties of **13** were in agreement with literature values.[14,15]

Synthesis of the Quinolizidine Alkaloid, (±)-Lupinine. The use of excess Vilsmeier reagent with an *N*-acyl-2,3-dihydropyridone results in formation of a 4-chloro-3-formyl-1,2-dihydropyridine as the major product. To determine if these formylated dihydropyridines could be utilized as building blocks for alkaloids, we investigated an approach to the synthesis of the quinolizidine alkaloid, (±)-lupinine.[16] A synthesis was accomplished according to the route depicted in Scheme IV.

Reaction of 4-methoxypyridine (**14**) with benzyl or phenyl chloroformate and (4-chlorobutyl)magnesium bromide[3b,17] in Et_2O/THF at −23 °C gave the dihydropyridones **15** in 74% and 73% yield, respectively. Treatment of **15a** and **15b** with 8.0 equiv of Vilsmeier reagent in trichloroethylene at room temperature provided an 84% and a 73% yield of the corresponding 3-formyl-1,2-dihydropyridines **16**. At this point the synthetic plan called for transforming **16a** to lupinine **18** using a one-pot reaction involving cleavage of the benzyl carbamate, conversion of the aldehyde group to an alcohol function, stereoselective reduction of the chlorodiene moiety, and ring formation via intramolecular S_N2 cyclization of intermediate **17**. We planned to take advantage of the $A^{(1,3)}$ strain present in **16a** to help control stereoselectivity during the reduction step. It was anticipated that the axial C-2 chlorobutyl group of **16a** would sterically hinder catalytic hydrogenation from the top face, producing the intermediate *cis*-piperidine alcohol **17** in situ. Initial attempts using PtO_2 and Pd/C were successful but only with low stereoselectivity. We were able to increase the selectivity by using a ferrous salt as a promoter in the hydrogenation reaction. Catalytic hydrogenation of **16a** in the presence of ferrous sulfate[18] provided, after workup with sodium methoxide, (±)-lupinine (**18**) and (±)-epilupinine as a 4:1 mixture that was difficult to purify by chromatography. The purification problem was circumvented by treating the crude product mixture with *p*-nitrobenzoyl chloride to give a 49% yield of the amino ester **19** and 9% of the corresponding epilupinine derivative.

The synthesis was improved by using **16b** as an intermediate. Luche reduction[19] of **16b** gave a 90% yield

(17) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.

(18) For the use of ferrous salts as promoters in the catalytic reduction of α,β-unsaturated aldehydes, see: Bray, R. H.; Adams, R. *J. Am. Chem. Soc.* **1927**, *49*, 2101 and references cited therein.

(19) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

of the alcohol **20**, which was subjected to catalytic hydrogenation over 5% Pt/C to provide a 4:1 mixture of diastereomeric alcohols **21** and **22**. Pure **21** was isolated (37%) by HPLC and subjected to the final cyclization step. Cleavage of the phenyl carbamate group via catalytic hydrogenolysis over platinum oxide,[5c] followed by addition of sodium methoxide, gave (±)-lupinine (**18**) in 84% yield. Spectral properties of **18** were in agreement with literature values.[16]

Conclusion

The conversion of 2,3-dihydro-4-pyridones to other piperidine derivatives is useful synthetically.[20] Piperidine alkaloids have been prepared in an asymmetric fashion by reduction of enantiopure 2-substituted 2,3-dihydro-4-pyridones. For example, Kunz has reported the synthesis of (*S*)-anabasin from an *N*-acyl-2,3-dihydropyridone precursor by a reduction sequence involving L-Selectride (Aldrich) 1,4-reduction, dithioketal formation, and Raney nickel desulfurization.[21] Waldmann has used a similar three-step reduction to arrive at (*S*)-coniine and (*R*)-coniceine from *N*-acyl-2,3-dihydro-4-pyridone intermediates.[22]

The two-step reduction using our Vilsmeier reaction/hydrogenation procedure is economical, convenient, and high yielding. The utility of this conversion was demonstrated in a short synthesis of (−)-coniine hydrochloride. When 2,3-dihydro-4-pyridones are treated with excess Vilsmeier reagent, good yields of 4-chloro-3-formyl-1,2-dihydropyridines result. These heterocycles are useful building blocks for alkaloids, as was demonstrated by our synthesis of (±)-lupinine. The methodology and syntheses presented in this paper expand the utility of *N*-acyl-2,3-dihydro-4-pyridones as intermediates in organic synthesis.

Experimental Section

Reactions were performed in oven-dried glassware under an atmosphere of dry argon and were magnetically stirred. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl under nitrogen immediately prior to use. Other solvents were dried over 3-Å molecular sieves prior to use. Radial preparative-layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1-, 2-, or 4-mm thicknesses of Kieselgel 60 PF_{254} containing gypsum.

***N*-[(Benzyloxy)carbonyl]-2-phenyl-2,3-dihydro-4-pyridone (3a).** Benzyl chloroformate (1.4 mL, 10 mmol) was added dropwise to a solution of 4-methoxypyridine (1.0 mL, 10 mmol) in 80 mL of THF at −23 °C. The resulting salt was stirred for 30 min at −23 °C before the dropwise addition of phenylmagnesium chloride (7.5 mL, 15 mmol) as a 2.0 M solution in THF. The solution was stirred for 45 min at −23 °C and 30 min at room temperature and then was poured into 30 mL of aqueous 10% HCl. The resulting mixture was stirred at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with ether (5 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 20% EtOAc/hexanes) gave 2.87 g (93%) of pure **3a** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (d, 1 H, *J* = 8.8 Hz), 7.40–7.18 (m, 10 H), 5.75–5.73 (d, 1 H, *J* = 7.34 Hz), 5.41–5.39 (d, 1 H, *J* = 8.07 Hz), 5.28–5.19 (m, 2 H), 3.20–3.12 (dd, 1 H, *J* = 7.33, 16.87 Hz), 2.83–2.78 (d, 1 H, *J* = 16.87 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.57, 152.44, 142.10, 138.23, 134.61, 128.66, 128.60, 128.40, 128.02, 127.76, 125.66, 107.73, 68.86, 55.71, 41.53; IR (KBr) 1720, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.24; H, 5.58; N, 4.56. Found: C, 74.14; H, 5.66; N, 4.53.

***N*-[(Benzyloxy)carbonyl]-2-propyl-2,3-dihydro-4-pyridone (3b).** By use of a procedure similar with that described for the preparation of **3a**, benzyl chloroformate (2.9 mL, 20 mmol), 4-methoxypyridine (2.0 mL, 20 mmol), and an etherial solution of *n*-propylmagnesium chloride (15 mL, 30 mmol) gave, after purification by radial PLC (silica gel, 10–20% EtOAc/hexanes), 4.9 g (90%) of **3b** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.75 (d, 1 H, *J* = 7.34 Hz), 7.45–7.35 (m, 5 H), 5.35–5.25 (m, 3 H), 4.67–4.55 (m, 1 H), 2.84–2.76 (dd, 1 H, *J* = 6.59, 16.14 Hz), 2.47–2.42 (d, 1 H, *J* = 16.86 Hz), 1.70–1.10 (m, 4 H), 0.90–0.85 (t, 3 H, *J* = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.79, 152.25, 141.26, 134.74, 128.53, 128.44, 128.18, 106.79, 68.66, 52.90, 39.36, 32.32, 18.62, 13.48; IR (neat) 1725, 1665 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13. Found: C, 70.11; H, 7.04; N, 5.04.

***N*-(4-Bromobutyryl)-2-cyclohexyl-2,3-dihydro-4-pyridone (3c).** By use of a procedure similar to that described for the preparation of **3a**, 4-bromobutyryl chloride (1.2 mL, 10 mmol), 4-methoxypyridine (1.0 mL, 10 mmol), and an etherial solution of cyclohexylmagnesium chloride (7.5 mL, 15 mmol) gave, after purification by radial PLC (silica gel, 40% EtOAc/hexanes), 2.86 g (87%) of **3c** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.60 (bd, 1 H, *J* = 5.87 Hz), 5.36–5.33 (bd, 1 H, *J* = 8.07 Hz), 4.85–4.65 (bs, 1 H), 3.57–3.53 (t, 2 H, *J* = 6.6 Hz), 2.90–2.60 (m, 4 H), 2.40–2.20 (m, 2 H), 1.85–0.85 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.12, 169.99, 140.71, 107.82, 55.42, 37.87, 37.62, 32.83, 30.93, 29.18, 28.89, 27.02, 25.56, 25.50, 25.37; IR (neat) 1670, 1595 cm^{-1}; HRMS calcd for $C_{15}H_{22}NO_2Br$ 326.0756, found 326.0736.

***N*-[(Allyloxy)carbonyl]-2-cyclohexyl-2,3-dihydro-4-pyridone (3d).** By use of a procedure similar to that described for the preparation of **3a**, allyl chloroformate (1.1 mL, 10 mmol), 4-methoxypyridine (1.0 mL, 10 mmol), and an etherial solution of cyclohexylmagnesium chloride (7.5 mL, 15 mmol) gave, after purification by radial PLC (silica gel, 40% EtOAc/hexanes), 2.28 g (87%) of **3d** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (d, 1 H, *J* = 8.07 Hz), 6.04–5.91 (m, 1 H), 5.42–5.30 (m, 3 H), 4.74–4.72 (d, 2 H, *J* = 5.86 Hz), 4.42–4.30 (m, 1 H), 2.81–2.73 (dd, 1 H, *J* = 6.6, 16.13 Hz), 2.65–2.60 (d, 1 H, *J* = 16.13 Hz), 1.90–0.90 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.31, 152.64, 141.88, 131.31, 119.03, 107.66, 67.53, 57.81, 38.33, 38.00, 29.28, 29.09, 25.76; IR (neat) 1725, 1670 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.66; H, 7.69; N, 5.34. Found: C, 68.47; H, 8.04; N, 5.27.

***N*-[(Benzyloxy)carbonyl]-4-chloro-2-phenyl-1,2-dihydropyridine (4a).** Phosphorus oxychloride (0.15 mL, 1.63 mmol) was added to a solution of DMF (0.13 mL, 1.63 mmol) in 5 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **3a** (0.50 g, 1.63 mmol) in 10 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then warmed to room temperature. Following 2 d of stirring at room temperature, the solution was concentrated in vacuo, carefully quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude dihydropyridine as a yellow oil. Purification by radial PLC (silica gel, 5% EtOAc/hexanes) gave 0.454 g (85%) of pure **4a** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.10 (m, 10 H), 7.07–6.80 (m, 1 H), 6.02–5.62 (m, 2 H), 5.35–5.11 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.60 and 152.89 (due to rotamers), 141.33, 140.20, 135.35, 135.19, 128.60, 128.44, 128.31, 128.18, 128.08, 127.79, 126.98, 126.79, 126.53, 126.17, 117.77, 106.40, 68.21, 58.00 and 57.16 (due to rotamers); IR (neat) 1710, 1635 cm^{-1}; HRMS calcd for $C_{19}H_{16}NO_2Cl$ 325.0870, found 325.0866.

***N*-[(Benzyloxy)carbonyl]-4-chloro-2-propyl-1,2-dihydropyridine (4b).** By use of a procedure similar to that described for the preparation of **4a**, dihydropyridone **3b** (0.51 g, 1.87 mmol) was converted to the crude dihydropyridine **4b**. Purification by

(20) For a recent monograph on piperidone and piperidine chemistry, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine, Structure, Preparation, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.

(21) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261.

(22) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444 and references cited therein.

radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.526 g (96%) of **4b** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5 H), 6.87–6.73 (dd, due to rotamers, 1 H, J = 7.33 Hz), 5.64–5.51 (m, 1 H), 5.30–5.12 (m, 3 H), 4.92–4.72 (m, 1 H), 1.75–1.20 (m, 4 H), 1.00–0.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.64 and 152.80 (due to rotamers), 135.61, 135.51, 128.50, 128.31, 128.08, 127.56 and 127.08 (due to rotamers), 126.59 and 126.43 (due to rotamers), 118.13 and 117.64 (due to rotamers), 107.47 and 107.14 (due to rotamers), 68.02, 53.71, 36.49 and 35.81 (due to rotamers), 17.36, 13.84; IR (neat) 1710, 1630 cm^{-1}; HRMS calcd for $C_{16}H_{18}NO_2Cl$ 291.1026, found 291.1006.

***N*-(4-Bromobutyryl)-4-chloro-2-cyclohexyl-1,2-dihydropyridine (4c).** Phosphorus oxychloride (0.11 mL, 1.21 mmol) was added to a solution of DMF (0.09 mL, 1.21 mmol) in 5 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **3c** (0.396 g, 1.21 mmol) in 10 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then was warmed to room temperature. Following 3 d of stirring at room temperature, the solution was concentrated in vacuo and quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude dihydropyridine as a yellow oil. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.349 g (83%) of pure **4c** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64–6.61 (d, 1 H, J = 8.07 Hz), 5.72–5.69 (dd, 1 H, J = 2.2, 6.59 Hz), 5.34–5.31 (dd, 1 H, J = 2.2, 7.33 Hz), 5.04–5.00 (t, 1 H, J = 6.6 Hz), 3.60–3.47 (m, 2 H), 2.72–2.52 (m, 2 H), 2.32–2.15 (m, 2 H), 1.90–0.95 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.50, 126.69, 125.92, 119.03, 109.66, 56.32, 42.37, 33.32, 31.22, 28.18, 27.53, 27.24, 26.11, 25.82, 25.69; IR (neat) 1670, 1630 cm^{-1}; HRMS calcd for $C_{15}H_{21}NOClBr$ 347.0474, found 347.0473.

N-[(Allyloxy)carbonyl]-4-chloro-2-cyclohexyl-1,2-dihydropyridine (4d). By use of a procedure similar to that described for the preparation of **4a**, dihydropyridone **3d** (0.668 g, 2.54 mmol) was converted to the crude dihydropyridine **4d**. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.659 g (92%) of pure **4d** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.78 (dd, 1 H, due to rotamers, J = 8.07 Hz), 6.01–5.88 (m, 1 H), 5.65–5.55 (bm, 1 H), 5.40–5.17 (m, 3 H), 4.77–4.55 (m, 3 H), 1.95–0.95 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.86 and 153.05 (due to rotamers), 131.99, 128.37 and 127.37 (due to rotamers), 127.18 and 126.46 (due to rotamers), 118.23, 116.87 and 116.35 (due to rotamers), 108.21 and 107.76 (due to rotamers), 66.82, 58.42 and 58.29 (due to rotamers), 43.27 and 42.78 (due to rotamers), 27.95, 27.34, 26.15, 25.89, 25.73; IR (neat) 1715, 1630 cm^{-1}; HRMS calcd for $C_{15}H_{20}NO_2Cl$ 281.1183, found 281.1183.

***N*-[(Benzyloxy)carbonyl]-4-chloro-2-[(*E*)-5-(ethoxycarbonyl)-4-pentenyl]-1,2-dihydropyridine (4e).** Phosphorus oxychloride (0.10 mL, 1.07 mmol) was added to a solution of DMF (0.08 mL, 1.07 mmol) in 5 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **3e**[5d] (0.397 g, 1.07 mmol) in 10 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then was warmed to room temperature. Following 2 d of stirring at room temperature, an additional mixture of phosphorus oxychloride (0.10 mL, 1.07 mmol) and DMF (0.08 mL, 1.07 mmol) in 5 mL of trichloroethylene was added. Following an additional 3 d of stirring at room temperature, the solution was concentrated in vacuo, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude dihydropyridine as a yellow oil. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.347 g (83%) of pure **4e** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5 H), 7.00–6.70 (m, 2 H), 5.85–5.70 (m, 1 H), 5.62–5.50 (m, 1 H), 5.32–5.15 (m, 3 H), 4.95–4.74 (m, 1 H), 4.23–4.16 (q, 2 H), 2.28–2.05 (m, 2 H), 1.75–1.35 (m, 4 H), 1.32–1.27 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.33, 153.41 and 152.73 (due to rotamers), 148.21 and 147.98 (due to rotamers), 135.38 and 135.25 (due to rotamers), 128.44, 128.27, 128.15, 128.02, 127.50, 126.72, 126.50, 121.52, 117.55 and 117.06 (due to rotamers), 107.50 and 107.14 (due to rotamers), 68.05, 59.97, 53.48 and 53.38 (due to rotamers), 33.74 and 33.16 (due to rotamers), 31.74, 22.53, 14.06; IR (neat) 1710, 1630 cm^{-1}; HRMS calcd for $C_{21}H_{24}O_4NCl$ 389.1394, found 389.1369.

***N*-[(Benzyloxy)carbonyl]-*trans*-3-methyl-2-propyl-2,3-dihydro-4-pyridone (6).** Lithium bis(trimethylsilyl)amide (4.1 mL, 4.12 mmol) as 1.0 M solution in THF was added dropwise to a solution of dihydropyridone **3b** (1.02 g, 3.74 mmol) in 50 mL of THF at −78 °C. Continued stirring for 45 min at −78 °C was followed by addition of methyl iodide (0.70 mL, 11.2 mmol). The resulting mixture was stirred for an additional 1 h at −78 °C before being warmed to room temperature. Water (30 mL) was added, the two layers were separated, and the aqueous layer was extracted with ether (4 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through Celite, and concentrated in vacuo to yield crude **6**. Purification by radial PLC (silica gel, 5–10% EtOAc/hexanes) yielded 0.938 g (87%) of pure **6** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.60 (bs, 1 H), 7.45–7.35 (m, 5 H), 5.35–5.15 (m, 3 H), 4.35–4.20 (bs, 1 H), 2.47–2.35 (m, 1 H), 1.70–1.25 (m, 4 H), 1.20–1.17 (d, 3 H, J = 7.34 Hz), 0.95–0.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.51, 152.86, 140.23, 140.13, 134.87, 128.57, 128.15, 104.98, 68.79, 59.23, 43.46, 32.74, 18.81, 16.87, 13.64; IR (neat) 1725, 1665 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.04; H, 7.37; N, 4.88. Found: C, 70.92; H, 7.37; N, 4.81.

N-[(Benzyloxy)carbonyl]-4-chloro-3-methyl-2-propyl-1,2-dihydropyridine (7). Phosphorus oxychloride (0.12 mL, 1.26 mmol) was added to a solution of DMF (0.10 mL, 1.26 mmol) in 5 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **6** (0.362 g, 1.26 mmol) in 10 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then warmed to room temperature. Following 3 d of stirring at room temperature, the solution was concentrated in vacuo and quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude dihydropyridine as a yellow oil. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.348 g (90%) of pure **7** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.28 (m, 5 H), 6.74–6.60 (dd, due to rotamers, 1H, J = 7.33 Hz), 5.34–5.16 (m, 3 H), 4.81–4.63 (m, 1 H), 1.88 and 1.85 (s, due to rotamers, 3 H), 1.70–0.57 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.86 and 153.15 (due to rotamers), 135.80, 135.58, 128.53, 128.37, 128.27, 128.05, 126.04 and 125.33 (due to rotamers), 124.82 and 123.85 (due to rotamers), 122.36 and 121.68 (due to rotamers), 109.41 and 109.11 (due to rotamers), 67.99 and 67.92 (due to rotamers), 58.20 and 57.87 (due to rotamers), 34.03 and 33.64 (due to rotamers), 18.30 and 18.10 (due to rotamers), 18.00 and 17.94 (due to rotamers), 14.03; IR (neat) 1710, 1635 cm^{-1}; HRMS calcd for $C_{17}H_{20}NO_2Cl$ 305.1183, found 305.1181.

(*R*)-2-Propyl-1-[((1*R*,2*S*,5*R*)-8-phenylmenthoxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (9). To a solution of 4-methoxy-3-(triisopropylsilyl)pyridine[6] (1.33 g, 5.0 mmol) in 25 mL of toluene at −23 °C was added (−)-8-phenylmenthyl chloroformate[6] (10.0 mL, 5.0 mmol) as a 0.5 M solution in toluene. The resulting mixture was stirred at −23 °C for 45 min and cooled to −78 °C. *n*-Propylmagnesium chloride (3.0 mL, 6.0 mmol) as a 2.0 M solution in diethyl ether was added dropwise over a period of 30 min, and the resulting solution was stirred at −78 °C for 1.5 h. After being quenched with 50 mL of aqueous 10% HCl, the mixture was allowed to warm to room temperature and was stirred for 1 h. The aqueous layer was separated and extracted with ether (4 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product as a yellow solid. HPLC analysis (silica gel, 5% EtOAc/hexane) showed a 91% de. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 2.44 g (88%) of the major diastereomer **9** as a white solid and 0.08 g (3%) of the minor diastereomer as a clear oil. Major diastereomer (**9**): $[\alpha]^{25}_D$ −73.1° (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.40–7.05 (m, 5 H), 5.00–4.80 (m, 1 H), 2.80–2.60 (bs, 1 H), 2.45–0.80 (m, 47 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.06, 152.60, 152.31, 147.47, 128.05, 125.01, 110.05, 77.52, 51.12, 50.38, 41.65, 40.26, 39.17, 34.45, 32.67, 31.35, 30.99, 26.21, 21.69, 21.46, 18.78, 18.58,

13.90, 11.06; IR (KBr) 2930, 2850, 1700, 1650, 1565, 1480, 1455, 1445, 1380, 1350, 1320, 1295, 1250, 1235, 1175, 1145, 1130, 1110, 1010, 970, 950, 930, 920, 875 cm^{-1}. Anal. Calcd for $C_{34}H_{55}NO_3Si$: C, 73.73; H, 10.02; N, 2.53. Found: C, 73.79; H, 10.03; N, 2.50. Minor diastereomer: $[\alpha]^{23}_D$ +112.7° (*c* 1.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.00 (m, 6 H), 4.99–4.90 (m, 1 H), 4.38–4.35 (m, 1 H), 2.72–2.65 (dd, 1 H, *J* = 6.6, 15.4 Hz), 2.39–2.34 (d, 1 H, *J* = 15.4 Hz), 2.10–0.80 (m, 45 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.77, 151.28, 150.63, 146.69, 127.85, 125.17, 109.50, 77.16, 52.57, 50.96, 42.20, 39.81, 39.62, 34.16, 32.35, 31.32, 27.63, 26.57, 25.08, 21.62, 18.81, 18.72, 13.74, 11.12; IR (neat) 1705, 1650 cm^{-1}. Anal. Calcd for $C_{34}H_{55}NO_3Si$: C, 73.73; H, 10.02; N, 2.53. Found: C, 73.70; H, 10.07; N, 2.49.

(*R*)-2-Propyl-2,3-dihydro-4-pyridone (10). To a solution of dihydropyridone **9** (0.545 g, 0.984 mmol) in 30 mL of methanol was added NaOMe (2.3 mL, 9.84 mmol) as a 4.37 M solution in methanol. The resulting mixture was refluxed for 12 h and then cooled to room temperature. Solid oxalic acid (2.66 g, 29.5 mmol) was added, and stirring was continued at room temperature for 5 h. The mixture was concentrated in vacuo, carefully quenched with aqueous saturated $NaHCO_3$, and extracted with EtOAc (7 × 20 mL). The combined organic layers were washed with brine, dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to yield 0.562 g of the crude product as a yellow oil. Purification by radial PLC (silica gel, 20–30–50% EtOAC/hexanes) gave 0.118 g (86%) of **10** as a clear oil: $[\alpha]^{23}_D$ +405.1 (*c* 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.21 (t, 1 H, *J* = 13.93 Hz), 6.50–6.30 (bs, 1 H), 4.95–4.92 (d, 1 H, *J* = 7.33 Hz), 3.72–3.62 (m, 1 H), 2.46–2.28 (m, 2 H), 1.80–1.35 (m, 4 H), 0.98–0.93 (t, 3 H, *J* = 13.93 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.02, 151.96, 97.52, 52.67, 41.56, 35.84, 18.36, 13.71; IR (neat) 1570 cm^{-1}; HRMS calcd for $C_8H_{13}NO$ 139.0997, found 139.0984.

(*R*)-1-[(Benzyloxy)carbonyl]-2-propyl-2,3-dihydro-4-pyridone (11). A 1.59 M solution of *n*-BuLi in hexanes (1.1 mL, 1.76 mmol) was added dropwise to a solution of **10** (0.233 g, 1.67 mmol) in THF at −78 °C. After the mixture was stirred at −78 °C for 20 min, benzyl chloroformate (0.29 mL, 2.01 mmol) was added. Continuous stirring at −78 °C for 30 min was followed by warming the mixture to room temperature. After being quenched with aqueous saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over K_2CO_3, and filtered through Celite/silica gel. Concentration in vacuo and purification by radial PLC (silica gel, hexanes-20–30% EtOAc/hexanes) gave 0.428 g (94%) of **11** as a clear oil: $[\alpha]^{26}_D$ −121.2° (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.75 (d, 1 H, *J* = 7.34 Hz), 7.45–7.35 (m, 5 H), 5.35–5.25 (m, 3 H), 4.67–4.55 (m, 1 H), 2.84–2.76 (dd, 1 H, *J* = 6.59, 16.14 Hz), 2.47–2.42 (d, 1 H, *J* = 16.86 Hz), 1.70–1.10 (m, 4 H), 0.90–0.85 (t, 3 H, *J* = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.79, 152.25, 141.26, 134.74, 128.53, 128.44, 128.18, 106.79, 68.66, 52.90, 39.36, 32.32, 18.62, 13.48; IR (neat) 1725, 1665 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13. Found: C, 70.11; H, 7.04; N, 5.04.

(*R*)-1-[(Benzyloxy)carbonyl]-4-chloro-2-propyl-1,2-dihydropyridine (12) was prepared from **11** by a procedure identical with that described for the preparation of racemic **4b** to give 0.53 g (96%) of **12** as a clear oil: $[\alpha]^{24}_D$ −1028° (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5 H), 6.87–6.73 (dd, due to rotamers, 1 H, *J* = 7.33 Hz), 5.64–5.51 (m, 1 H), 5.30–5.12 (m, 3 H), 4.92–4.72 (m, 1 H), 1.75–1.20 (m, 4 H), 1.00–0.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.64 and 152.80 (due to rotamers), 135.61 and 135.51 (due to rotamers), 128.50, 128.31, 128.08, 127.56 and 127.08 (due to rotamers), 126.59 and 126.43 (due to rotamers), 118.13 and 117.64 (due to rotamers), 107.47 and 107.14 (due to rotamers), 68.02, 53.71, 36.49 and 35.81 (due to rotamers), 17.36, 13.84; IR (neat) 1710, 1630 cm^{-1}; HRMS calcd for $C_{16}H_{18}NO_2Cl$ 291.1026, found 291.1006.

(−)-Coniine Hydrochloride (13). A solution of dihydropyridine **12** (1.02 g, 3.50 mmol) in 60 mL of ethanol was hydrogenated at room temperature under balloon pressure in the presence of Li_2CO_3 (0.259 g, 3.51 mmol) and 0.30 g of 5% Pt/C for 6 h. Following the addition of 0.30 g of 5% Pd/C the hydrogenation was continued for another 3 h. The solution was filtered through Celite, most of the solvent was removed by distillation at atmospheric pressure, and the final 1 mL was distilled using a spinning band column (20 mmHg) to yield 0.396 g (89%) of (−)-coniine as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30–2.90 (m, 1 H), 2.85–2.18 (m, 2 H), 1.67–1.01 (m, 11 H), 0.92 (bt, 3 H). In 10 mL of dry ether, 0.30 g of (−)-coniine was dissolved and dry HCl gas was bubbled through the solution for 40 min. The solution was concentrated in vacuo, and the salt was recrystallized from 2-propanol to yield 0.371 g of **13** as a white solid (96%). After three recrystallizations 0.321 g (83%) of pure **13** was obtained: $[\alpha]^{24}_D$ −5.6 (*c* 1, EtOH); mp 218–219 °C [lit.[14,15] $[\alpha]^{20}_D$ −5.8 (*c* 1, EtOH), mp 217–220 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (bs, 2 H), 3.98–2.56 (bm, 3 H), 2.50–1.02 (bm, 10 H), 0.97 (bt, 3 H).[15]

***N*-[(Benzyloxy)carbonyl]-2-(4-chlorobutyl)-2,3-dihydro-4-pyridone (15a).** To magnesium turnings (1.07 g, 44.0 mmol) in 5.0 mL of THF was added 1,2-dibromoethane (0.34 mL, 4.0 mmol). The reaction temperature during the addition was controlled using an ice/water bath. After all the effervescence had stopped, the solvent was removed by syringe, and the magnesium turnings were washed with dry THF (2 × 5 mL). To the washed magnesium was added 50 mL of anhydrous ether. The mixture was cooled to 0 °C, and 1-bromo-4-chlorobutane (4.6 mL, 40.0 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 6 h.

To a stirred solution of 4-methoxypyridine (2.0 mL, 20.0 mmol) in 120 mL of THF at −23 °C was added benzyl chloroformate (2.8 mL, 20.0 mmol) dropwise. The resulting mixture was stirred at −23 °C for 1 h followed by the dropwise addition of the Grignard reagent via a double-tipped needle. The mixture was stirred at −23 °C for 1 h and at room temperature for 30 min. The solution was poured into 50 mL of aqueous 10% HCl and stirred at room temperature for 45 min. The layers were separated, and the aqueous phase was extracted with ether (5 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 10–20% EtOAc/hexanes) gave 4.89 g (76%) of dihydropyridone **15a** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.76 (bd, 1 H, *J* = 8.07 Hz), 7.45–7.35 (m, 5 H), 5.35–5.23 (m, 3 H), 4.65–4.56 (m, 1 H), 3.48–3.44 (t, 2 H, *J* = 13.2 Hz), 2.87–2.79 (dd, 1 H, *J* = 6.6, 16.14 Hz), 2.47–2.42 (d, 1 H, *J* = 16.86 Hz), 1.80–1.25 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.79, 152.47, 141.39, 134.83, 128.79, 128.73, 128.50, 107.14, 69.05, 53.06, 44.43, 39.68, 31.96, 29.73, 22.95; IR (neat) 1720, 1660 cm^{-1}; HRMS calcd for $C_{17}H_{20}NO_3Cl$ 321.1132, found 321.1132.

***N*-[(Benzyloxy)carbonyl]-4-chloro-2-(4-chlorobutyl)-3-formyl-1,2-dihydropyridine (16a).** Phosphorus oxychloride (6.6 mL, 70.9 mmol) was added to a solution of DMF (5.5 mL, 70.9 mmol) in 80 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **15a** (2.85 g, 8.86 mmol) in 30 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then warmed to room temperature. After being stirred at room temperature for 3.5 d, the solution was concentrated in vacuo and slowly quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (6 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 2–5% EtOAc/hexanes) gave 2.84 g (87%) of dihydropyridine **16a** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1 H), 7.48–7.30 (m, 5 H), 5.60–5.15 (m, 4 H), 3.60–3.25 (bs, 2 H), 1.90–1.20 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.98, 152.83 and 152.12 (due to rotamers), 144.72 and 143.98 (due to rotamers), 134.77, 133.61, 128.66, 128.50, 123.72, 107.89, 68.92, 51.06, 44.50, 31.93, 21.72; IR (neat) 1725, 1655 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_3Cl_2$ 367.0742, found 367.0741.

***p*-Nitrobenzoate Derivatives of Lupinine and Epilupinine.** To a solution of aldehyde **16a** (0.155 g, 0.422 mmol) in 20 mL of absolute ethanol was added ferous sulfate (0.021 g, 0.076 mmol), lithium carbonate (0.031 g, 0.422 mmol) and 0.155 g of PtO_2. The resulting mixture was hydrogenated under balloon pressure for 12 h, 0.078 g of 5% Pd/C was added, and the hydrogenation was continued for an additional 1.5 h. The solution was filtered through Celite and concentrated in vacuo, and 15 mL of sodium methoxide in methanol (1.03 mL, 4.49 mmol, 4.37 M) was added. The reaction mixture was stirred for 12 h at room

temperature and then refluxed for 12 h. The solution was concentrated in vacuo, 3.0 mL of 4 N NaOH was added, and the solution was extracted with ether (10 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to yield 0.054 g of the crude product. To a solution of the crude amine in 10 mL of CH_2Cl_2 was added *p*-nitrobenzoyl chloride (0.071 g, 0.383 mmol), triethylamine (0.09 mL, 0.638 mmol), and two crystals of DMAP. The mixture was stirred at room temperature for 2 d. The solution was concentrated in vacuo, and 3.0 mL of 4 N NaOH was added. The mixture was extracted with ether (10 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 50% EtOAc/hexanes) gave 0.066 g (49%) of **19** as a gray solid: mp 94–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40–8.10 (m, 4 H), 4.71–4.66 (dd, 1 H, *J* = 11.00, 5.14 Hz), 4.56–4.50 (dd, 1 H, *J* = 11.00, 8.07 Hz), 2.86–2.83 (d, 2 H, *J* = 11.00 Hz), 2.20–1.20 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.57, 150.35, 135.84, 130.54, 123.47, 65.27, 64.27, 57.26, 56.84, 37.93, 29.86, 27.24, 25.43, 24.95, 21.07; IR (neat) 1725 cm^{-1}; HRMS calcd for $C_{17}H_{22}N_2O_4$ 318.1578, found 318.1588.

The *p*-nitrobenzoate derivative of epilupinine [0.012 g (9%)] was isolated as a gray solid: mp 66–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40–8.15 (m, 4 H), 4.40–4.27 (m, 2 H), 2.88–2.81 (t, 2 H, *J* = 9.7 Hz), 2.20–1.20 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.61, 150.53, 135.67, 130.60, 123.55, 67.66, 64.60, 56.81, 56.58, 41.41, 29.96, 28.73, 25.57, 24.95, 24.51; IR ($CHCl_3$) 1725 cm^{-1}; HRMS calcd for $C_{17}H_{22}N_2O_4$ 318.1578, found 318.1585.

2-(4-Chlorobutyl)-1-(phenoxycarbonyl)-2,3-dihydro-4-pyridone (15b). To magnesium turnings (0.583 g, 24.0 mmol) in 5.0 mL of THF was added 1,2-dibromoethane (0.34 mL, 4.0 mmol). The reaction temperature during the addition was controlled using an ice/water bath. After all the effervescence had stopped, the solvent was removed by syringe and the magnesium turnings were washed with THF (2 × 5 mL). To the washed magnesium was added 25 mL of anhydrous ether. The mixture was cooled to 0 °C, and 1-bromo-4-chlorobutane (2.3 mL, 20.0 mmol) was added dropwise. The resulting Grignard reagent was stirred at 0 °C for 6 h.

To a stirred solution of 4-methoxypyridine (0.81 mL, 8.0 mmol) in 60 mL of THF at −23 °C was added phenyl chloroformate (1.1 mL, 8.0 mmol) dropwise. The resulting mixture was stirred at −23 °C for 1 h followed by the dropwise addition of the Grignard reagent via a double-tipped needle. The mixture was stirred at −23 °C for 1 h and then at room temperature for 30 min. The solution was poured into 50 mL of aqueous 10% HCl and stirred at room temperature for 45 min. The layers were separated, and the aqueous phase was extracted with ether (4 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 10–20% EtOAc/hexanes) gave 1.79 g (73%) of dihydropyridone **15b** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.88 (dd, 1 H, *J* = 1.46, 8.8 Hz), 7.50–7.14 (m, 5 H), 5.46–5.43 (bd, 1 H, *J* = 8.06 Hz), 4.77–4.75 (bm, 1 H), 3.56–3.52 (t, 2 H, *J* = 6.23 Hz), 2.98–2.91 (dd, 1 H, *J* = 6.6, 16.13 Hz), 2.56–2.51 (dd, 1 H, *J* = 1.46, 16.13 Hz), 2.00–1.40 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.52, 151.00, 150.19, 140.72, 129.44, 126.18, 121.04, 107.73, 53.32, 44.37, 39.62, 31.73, 29.66, 22.85; IR (neat) 1735, 1670 cm^{-1}. Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.52; H, 5.91; N, 4.56. Found: C, 62.54; H, 6.02; N, 4.55.

4-Chloro-2-(4-chlorobutyl)-3-formyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (16b). Phosphorus oxychloride (0.62 mL, 6.66 mmol) was added to a solution of DMF (0.52 mL, 6.66 mmol) in 3.0 mL of trichloroethylene at 0 °C. After the mixture was stirred at 0 °C for 30 min, dihydropyridone **15b** (0.256 g, 0.833 mmol) in 5 mL of trichloroethylene at 0 °C was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 °C for 30 min and then warmed to room temperature. Following 3.5 d of stirring at room temperature, the solution was concentrated in vacuo and quenched slowly with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (6 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite/silica gel, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 2–5% EtOAc/hexanes) gave 0.215 g (73%) of dihydropyridine **16b** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1 H), 7.45–7.10 (m, 5 H), 5.75–5.50 (bs, 2 H), 3.54–3.50 (t, 2 H, *J* = 6.60 Hz), 1.90–1.20 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.99, 151.74 and 150.64 (due to rotamers), 150.16, 144.57 and 143.60 (due to rotamers), 134.23 and 133.13 (due to rotamers), 129.44, 126.18, 124.21, 121.04, 109.02 and 108.54 (due to rotamers), 51.73 and 51.12 (due to rotamers), 44.53, 32.09 and 31.57 (due to rotamers), 31.76, 21.78; IR (neat) 1735, 1655 cm^{-1}; HRMS calcd for $C_{17}H_{17}NO_3Cl_2$ 353.0586, found 353.0583.

4-Chloro-2-(4-chlorobutyl)-3-(hydroxymethyl)-1-(phenoxycarbonyl)-1,2-dihydropyridine (20). To a stirred solution of pure **16b** (0.352 g, 0.99 mmol) in 14 mL of MeOH at 0 °C was added cerium(III) chloride heptahydrate (0.426 g, 1.41 mmol), and stirring was continued for 10 min. Sodium borohydride (0.045 g, 1.19 mmol) was added in small portions over a 5-min period. After all the effervescence had stopped, the reaction mixture was stirred for an additional 5 min at 0 °C and was quenched with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to yield the crude alcohol. Purification by radial PLC (silica gel, 5–20% EtOAc/hexanes) gave 0.318 g (90%) of alcohol **20** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.10 (m, 5 H), 6.92–6.86 (dd, due to rotamers, 1 H, *J* = 8.06 Hz), 5.49–5.40 (dd, due to rotamers, 1 H, *J* = 8.06 Hz), 5.28–5.17 (m, 1 H), 4.49–4.30 (m, 2 H), 3.62–3.48 (m, 2 H), 1.98–1.48 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.51 and 151.80 (due to rotamers), 150.51 and 150.28 (due to rotamers), 129.35, 128.34 and 127.83 (due to rotamers), 126.18 and 125.95 (due to rotamers), 125.86 and 125.24 (due to rotamers), 124.11 and 123.50 (due to rotamers), 121.27, 110.12 and 109.77 (due to rotamers), 60.36, 55.00 and 54.45 (due to rotamers), 44.69, 32.02, 31.63 and 31.18 (due to rotamers), 22.36 and 22.13 (due to rotamers); IR (neat) 3470, 1715 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_3Cl_2$ 355.0742, found 355.0744.

(2*R,3*R**)-2-(4-Chlorobutyl)-3-(hydroxymethyl)-1-(phenoxycarbonyl)piperidine (21).** A solution of dihydropyridine **20** (0.186 g, 0.52 mmol) in 10 mL of EtOAc was hydrogenated in the presence of Li_2CO_3 (0.019 g, 0.26 mmol) and 0.056 g of 5% Pt/C for 20 h at room temperature and under balloon pressure. Filtration through Celite and removal of the solvent in vacuo gave the crude piperidine. Purification by radial PLC (silica gel, 5–10–20% EtOAc/hexanes) gave 0.104 g (61%) of alcohol as a 80:20 mixture of trans to cis isomers by HPLC analysis (silica gel, 40% EtOAc/hexanes, 1.0 mL/min). Separation of the diastereomers by preparative HPLC (silica gel, 20% EtOAc/hexanes, 6.0 mL/min) yielded 0.063 g (37%) of the cis diastereomer **21** as a white solid: mp 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.05 (m, 5 H), 4.68–4.50 (m, 1 H), 4.28–4.14 (m, 1 H), 3.65–3.45 (m, 4 H), 3.02–2.76 (m, 1 H), 2.15–1.25 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.19, 151.35, 129.12, 125.08, 121.62, 64.24, 52.48 and 51.89 (due to rotamers), 44.91 and 44.82 (due to rotamers), 42.01 and 41.84 (due to rotamers), 39.45 and 38.74 (due to rotamers), 32.15 and 32.05 (due to rotamers), 25.40 and 24.82 (due to rotamers), 23.30 and 23.01 (due to rotamers), 22.81 and 22.49 (due to rotamers), 21.94; IR ($CHCl_3$) 3480, 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{24}NO_3Cl$: C, 62.74; H, 7.44; N, 4.31. Found: C, 62.56; H, 7.49; N, 4.35.

(±)-Lupinine (18). A solution of **21** (0.021 g, 0.065 mmol) in 6.0 mL of methanol was hydrogenated for 24 h at room temperature under balloon pressure in the presence of trifluoroacetic acid (0.1 mL, 1.29 mmol) and 0.04 g of PtO_2. The hydrogen balloon was removed, and sodium methoxide in methanol (0.74 mL, 3.23 mmol, 4.37 M) was added. The resulting mixture was stirred for 24 h at room temperature under argon. The solution was filtered through Celite and concentrated in vacuo. About 2.0 mL of aqueous 25% NaOH was added, and the solution was extracted with ether (6 × 10 mL). The combined organic layers were washed with brine, dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to yield 0.011 g of lupinine **18** as a yellow oil. Chromatographic purification using a disposable pipet (basic alumina, 2% MeOH/CH_2Cl_2) yielded 9.2 mg (84%) of pure (±)-lupinine as a white solid: mp 57–58

°C (lit.[23] mp 57.5–58.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20–4.14 (ddd, 1 H, J = 11.0, 4.4, 1.47 Hz), 3.72–3.68 (d, 1 H, J = 11.0 Hz), 2.90–2.78 (m, 2 H), 2.30–1.20 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.05, 65.04, 57.00, 38.03, 31.44, 29.63, 25.56, 24.56, 22.91; IR ($CHCl_3$) 3200, 2940, 1465, 1445, 1350, 1150, 1125, 1105, 1085, 1050, 1015, 1005 cm^{-1}.[16d]

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Supplementary Material Available: ^{1}H NMR spectra of **3c**, **4a-e**, **7**, **10**, **12**, **15a**, **16a,b**, **20**, lupinine *p*-nitrobenzoate, and epilupinine *p*-nitrobenzoate, ^{13}C NMR spectra of **15a** and **16b**, and tables of physical properties and spectroscopic data for **13** and **18** and corresponding literature values (19 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 page for ordering information.

Synthesis of Doubly Bridged Prismanes: An Investigation of the Photochemical Behavior of Doubly Bridged Dewar Benzenes

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Starting from cyclic acetylenes, two stereoisomeric doubly bridged Dewar benzenes of type **14** and **15** were synthesized, and the effects of the chain length and the nature of two other functional groups on their photochemical behavior were examined. The isomers with bridges spanning the 1,4- and 2,3-positions, **14b,c** and **25b**, reacted to form the respective prismanes, **17b,c** and **27b**. Isomers **15b–d**, with bridges spanning the 1,2- and 3,4-positions, revealed a more complex photochemistry: through consecutive transposition reactions via a total of five intermediates, an unexpected phthalic/terephthalic ester rearrangement was observed. Prismane **38b** and Dewar benzenes **39b,c** could be characterized directly, and the existence of the other intermediates was deduced indirectly.

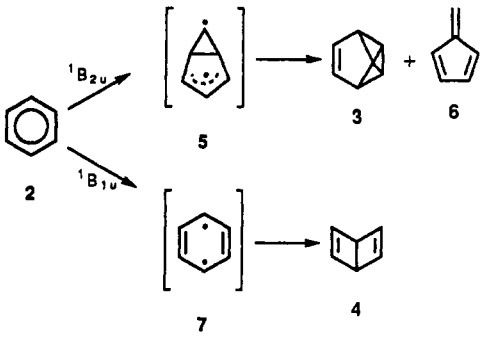
Introduction

Tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane, [3]prismane (**1**, "prismane") was first mentioned conceptually by Ladenburg in 1869.[1] Almost a century passed before the first synthesis of a prismane derivative, tri-*tert*-butylprismane, was reported in 1965.[2] Since then, a series of papers has been published dealing with syntheses,[3,4] theoretical aspects,[5] chemical behavior,[6] and molecular structures[4,7] of prismane derivatives. As irradiation of benzene (**2**) itself does not afford parent compound **1**, it was not synthesized until 1972, when an indirect synthesis starting from benzvalene (**3**) via an azo compound was successful.[8] Later it was shown that under certain conditions Dewar benzene (**4**) can be transformed into prismane (**1**).[9]

1 **2** **3** **4**

Irradiation of alkylbenzenes in solution at 254 nm leads to a positional isomerization of the alkyl groups.[10] These isomerizations, which were assumed to have occurred via valence isomers of benzene such as benzvalene (**3**), Dewar benzene (**4**), and prismane (**1**), gave the first hints of their existence.[10,11]

Scheme I. Photochemistry of Benzene



Concerning the mechanistic aspects, it is assumed that excitation of the $^1B_{2u}$ state (S_1 in benzene, 254-nm band) produces "prefulven" biradical **5** as a short-lived intermediate, which may adiabatically convert to benzvalene (**3**) and fulvene (**6**) Scheme I.[13] Excitation of the $^1B_{1u}$ state (S_2 in benzene, 204-nm band) is thought to generate the biradical **7**, which may then form Dewar benzene **4**.[12] In the case of benzene, this mechanism has been experimentally substantiated.[13] However, for substituted benzenes the mechanism may be more complicated. As a result of substitution, the bands of the different excited states may overlap. Consequently, selective excitation is no longer possible, and the irradiation products are no longer predictable.[10]

Our interest in prismanes was aroused by the synthesis of **8** some 5 years ago.[14] We named **8** propella[3$_4$]prismane because it possesses the structural features of a propellane as well as those of a prismane, in this case a [4]prismane (cubane). The on-line number 3 indicates the length of the bridges, and the subscript 4 designates the symmetry of the prismane core. Compound **8** represented the first and, at that time, the only member of this family, and we

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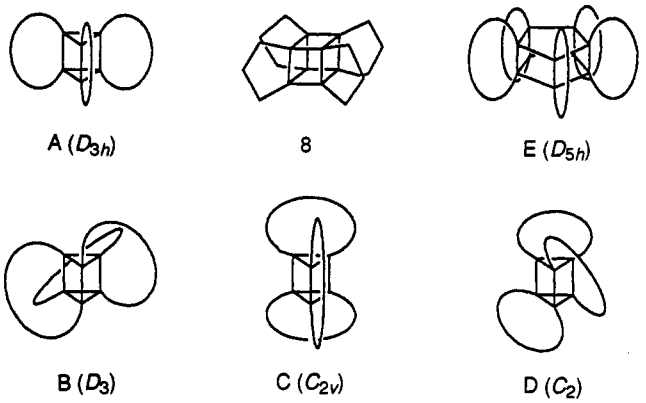
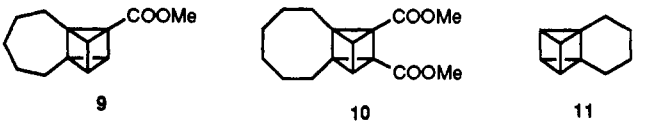
Scheme II. Propellaprismanes



hoped to synthesize further congeners of this family by homologation of the prismane core (**A**, **E**) and/or variation of the chain length. As the first synthetic goal, a propella-[n_3]prismane, with a [3]prismane as the central body, was tackled. At this point, it should be mentioned that there are four conceivable stereoisomers (**A**–**D**) which are depicted in Scheme II. Because of the arrangement of the chains, their symmetry decreases from D_{3h} via D_3 and C_{2v} to C_2.

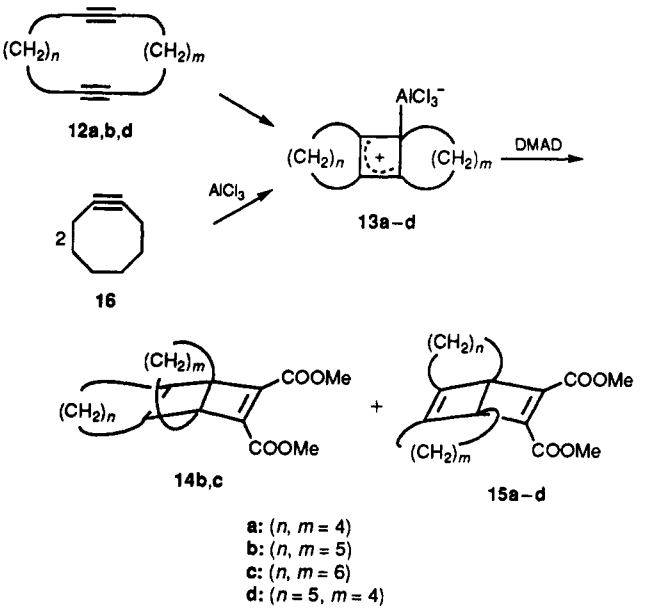
Prismanes with one methylene chain have been obtained by Y. Tobe et al.,[15] W. Tochtermann et al.,[16,17] and F. Bickelhaupt et al.[18] In all three cases, the irradiation of a bridged Dewar benzene precursor yielded a bridged prismane (e.g., **9**–**11**).



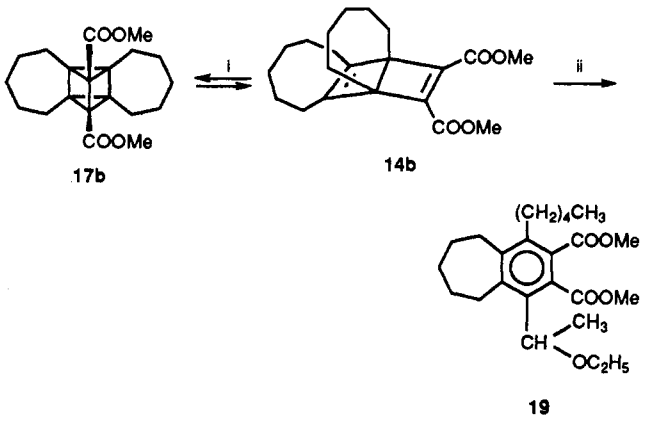
Results and Discussion

Doubly Bridged Prismanes with Acceptor Substituents. We joined this field of research with the synthesis of doubly bridged Dewar benzenes. To reach this goal we chose a synthetic route that was discovered in 1971[19] and has been widely extended since then.[20] 1,8-Cyclotetradecadiyne (**12b**)[21] and cyclooctyne (**16**)[22] serve as starting materials. The reactions of these acetylenes with $AlCl_3$ in CH_2Cl_2 yield the cyclobutadiene–$AlCl_3$ σ-complexes **13b** and **13c**, respectively (Scheme III). Addition of dimethyl acetylenedicarboxylate (DMAD) and dimethyl sulfoxide results in the formation of the isomeric doubly bridged Dewar benzenes **14b**, **15b** (60% yield) and **14c**, **15c** (31% yield), respectively. When the same reaction sequence is carried out with 1,7-cyclododecadiyne (**12a**)

Scheme III. Synthesis of Doubly Bridged Dewar Benzenes



Scheme IV. Photochemistry of Dewar Benzene 14b



or 1,7-cyclotridecadiyne (**12d**)[21] only Dewar benzenes of type **15** with the bridges in the 1,2- and 3,4-positions are obtained. The cyclizations of **12a**, **12b**, and **12d** have already been carried out by Driessen and Hogeveen, but their results have never been published in detail.[20,23] The elegance of this route lies in the fact that the desired Dewar benzenes are accessible in only one step from readily available starting materials.[21a] Furthermore, the length of the bridges is controllable with the exception of the lower homologues 1,6-cyclodecadiyne and 1,6-cycloundecadiyne do not react in this fashion.[24] The versatility of the route is further enhanced by the fact that the two ester groups can be easily converted into other functional groups. The homologous Dewar benzenes of type **14**, with the bridges spanning the 1,4- and 2,3-positions, are suitable model compounds for studying the factors that influence prismane formation.

(a) Photochemistry of Dewar benzene 14b. The photochemistry of Dewar benzene **14b**, with pentamethylene bridges, is depicted in Scheme IV. When **14b** is irradiated at $\lambda \geq 320$ nm, we obtain 15% of prismane **17b** and 25% of **19**, as well as 30% of recovered starting material **14b**.[25] Two facts are remarkable: Firstly, there is a

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