

Conversion of *N*-Acyl-2,3-dihydro-4-pyridones to 4-Chloro-1,2-dihydropyridines Using the Vilsmeier Reagent. Synthesis of (–)-Coniine and (±)-Lupinine

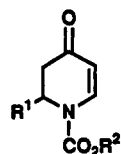
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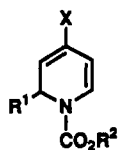
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The full details are given of a study on the conversion of dihydropyridones of the type 3 to 4-chloro-1,2-dihydropyridines 4 using a Vilsmeier reagent. The use of 1 equiv of Vilsmeier reagent under mild conditions (ClCHCl₂, rt) transformed several racemic *N*-acyl-2,3-dihydro-4-pyridones 3 to dihydropyridines 4 in very good to excellent yields (83–96%). A C-3 methyl group can be tolerated as was demonstrated in the preparation of 4-chloro-3-methyl-1,2-dihydropyridine 7 from dihydropyridone 6 in 90% yield. The utility of this conversion was demonstrated in the synthesis of the piperidine alkaloid, (–)-coniine. The synthesis of (–)-coniine was completed in five steps from 4-methoxy-3-(triisopropylsilyl)pyridine in 54% overall yield. 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 intermediates for alkaloid preparation, as was shown by two syntheses of the quinolizidine alkaloid, (±)-lupinine, carried out in three and five steps, respectively.

Recently we have been studying the synthesis and synthetic utility of *N*-acyl-2-alkyl-2,3-dihydro-4-pyridones 1. These readily available heterocycles¹ are useful building blocks for the preparation of indolizidine,² quinolizidine,³ piperidine,⁴ and *cis*-decahydroquinoline alkaloids.⁵ The dihydropyridones 1 can be prepared enantiopure by a method recently described by us involving the addition of Grignard reagents to chiral, nonracemic 1-acylpyridinium salts.⁶



1



2a, X = H
2b, X = OTES
2c, X = Cl

The related 1-acyl-1,2-dihydropyridines 2 are also very useful intermediates for alkaloid synthesis,^{7–9} and a reduction–elimination sequence (NaBH₄/CeCl₃; MsCl/

DMAP) for converting enantiopure 2,3-dihydropyridones 1 to 1,2-dihydropyridines 2a has been reported.⁹ In the course of model studies directed toward the synthesis of *Lycopodium* alkaloids, a 4-[(triethylsilyl)oxy]-1,2-dihydropyridine of the type 2b was prepared from a 2,3-dihydropyridone precursor (NaHMDS, TESCl) and utilized in an intramolecular Diels–Alder/retro-Mannich approach to the *cis*-perhydroquinoline ring system.^{5d} The 4-chloro-1,2-dihydropyridines 2c have been used in the preparation of quinolizidine^{8b} and piperidine^{8c} alkaloids. The considerable synthetic potential of dihydropyridines 2 prompted us to find other methods of preparing them from *N*-acyl-2,3-dihydro-4-pyridones. In this paper we report the full details of a study^{4d} on the conversion of dihydropyridones of the type 1 to 4-chloro-1,2-dihydropyridines, i.e., 2c, using a Vilsmeier reagent. This methodology was utilized in the synthesis of the piperidine alkaloid, (–)-coniine, and the quinolizidine alkaloid, (±)-lupinine.

Results and Discussion

Although vinyl chlorides have been formed in a few cases,¹⁰ the reaction of formamide-derived Vilsmeier reagents with ketones and amides generally results in products containing a β-chlorovinyl aldehyde group.^{10d}

- * Abstract published in *Advance ACS Abstracts*, December 1, 1993.
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(2) (a) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* 1991, 113, 6672. (b) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* 1991, 32, 5919. (c) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* 1991, 32, 5889.
(3) (a) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* 1988, 110, 7445. (b) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* 1992, 57, 5807. (c) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* 1993, 115, 8851. (d) See ref 1.
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Scheme I

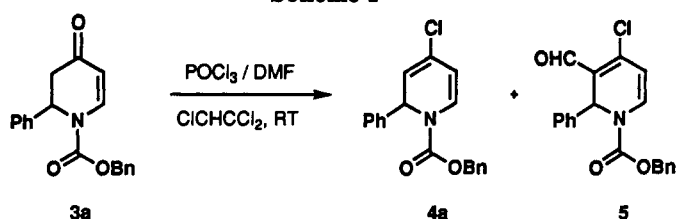


Table I. Preparation of 4-Chloro-1,2-dihydropyridines 4

entry ^{a,b}	R ¹	R ²	yield, % ^c
a	Ph	OBn	85
b	<i>n</i> -Pr	OBn	96
c	<i>c</i> -Hex	(CH ₂) ₃ Br	83
d	<i>c</i> -Hex		92
e		CO ₂ Et OBn	83

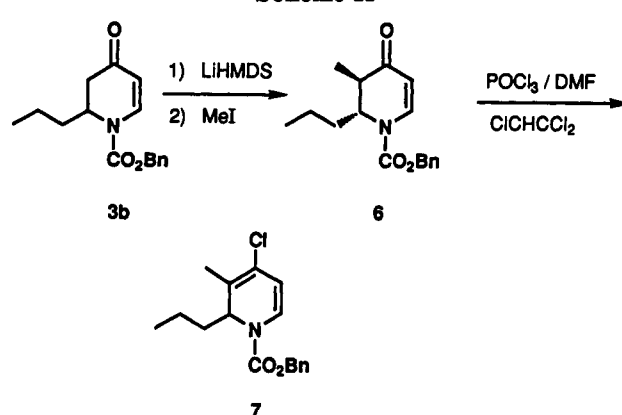
^a The reactions were generally performed on a 1–2 mmol scale in trichloroethylene. ^b The workup consisted of concentration, addition of aqueous sodium bicarbonate, and extraction with methylene chloride; see Experimental Section. ^c Yield of products obtained from radial preparative-layer chromatography (silica gel, EtOAc/hexanes).

When we initially performed this reaction on **3a** using excess Vilsmeier reagent, the vinyl chloride **4a** was obtained along with the anticipated 3-formyl-4-chloro derivative **5** (Scheme I). Since this indicated that the vinyl chloride **4a** was a likely intermediate leading to **5**, we pursued conditions that would favor the formation of **4a** but inhibit subsequent formylation of the vinyl chloride group. The use of 1 equiv of Vilsmeier reagent under mild conditions allowed us to obtain the desired result. This transformation on several racemic *N*-acyl-2,3-dihydro-4-pyridones **3** was investigated, and the results are given in Table I.

The reaction is easy to perform, and the purified yields of dihydropyridines **4** are very good to excellent (83–96%). Only small amounts (<5%) of formylated compounds were observed in the crude products by ¹H NMR analysis. The reaction conditions are mild and compatible with various *N*-acyl groups. An α,β -unsaturated ester in the side chain (R¹) of **3** is also tolerated (entry e). It is noteworthy that dihydropyridone **3a** and POCl₃ under the usual conditions but in the absence of DMF gave no reaction. Also, isolated vinyl chloride **4a** on treatment with Vilsmeier reagent provides the 3-formyl-4-chloro-1,2-dihydropyridine **5**.

To investigate whether the presence of a C-3 alkyl group would affect the conversion, the 2,3-dialkyl-2,3-dihydro-4-pyridone **6** was prepared and subjected to the Vilsmeier-chlorination reaction as shown in Scheme II. Methylation of dihydropyridone **3b** was carried out using LiHMDS/MeI to provide *trans*-2,3-dialkyl-2,3-dihydro-4-pyridone **6** in 87% yield.^{2c} The high stereoselectivity observed in this alkylation reaction of **3b** is due to a conformational bias resulting from A^(1,3) strain forcing the C-2 substituent into an axial orientation. Stereoelectronically preferred axial alkylation at C-3 from the least sterically hindered face of the intermediate enolate leads to the *trans* product.¹¹ Reaction of **6** with POCl₃/DMF using the

Scheme II



standard conditions gave a 90% yield of 1,2-dihydropyridine **7**. The addition of Grignard reagents to the 1-phenoxy-carbonyl salt of 4-chloropyridine gives 3-unsubstituted 1-acyl-4-chloro-1,2-dihydropyridines in good yield.¹² This approach to 3-substituted derivatives is limited, however, for the analogous reaction using a 3-alkyl-4-chloropyridine would lead to a mixture of regioisomers due to nucleophilic attack at C-2 and C-6 of the pyridinium salt.^{7,13} Our three-step preparation of **7** from 4-methoxypyridine¹ represents a regioselective method for the synthesis of 2,3-dialkyl-1,2-dihydropyridines of this type.

By combining our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones⁶ and the above methodology, enantiopure 1-acyl-4-chloro-1,2-dihydropyridines of considerable synthetic potential^{7–9} can be prepared. In addition, the Vilsmeier reaction can be used in a facile, two-step conversion of homochiral dihydropyridones of the type **3** to enantiopure 2-alkylpiperidines by catalytic reduction of a 1-acyl-4-chloro-1,2-dihydropyridine intermediate.^{8c} The utility of this conversion is demonstrated in the following syntheses of (-)-coniine^{14,15} and (±)-lupinine.¹⁶

Synthesis of (-)-Coniine. The synthesis of the piperidine alkaloid, (-)-coniine, was completed as shown in Scheme III. Reaction of chiral 1-acylpyridinium salt **8**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and the chloroformate of (-)-8-phenylmenthol,⁶ with *n*-propylmagnesium chloride in THF/toluene at -78 °C gave the dihydropyridone **9** in 96% crude yield and 91% de. After purification by chromatography, an 88% yield of diastereomerically pure **9** was obtained as a white solid. The major diastereomer resulting from addition of an aliphatic Grignard reagent to chiral 1-acyl salt **8** is known to possess the *R* configuration at C-2 of the

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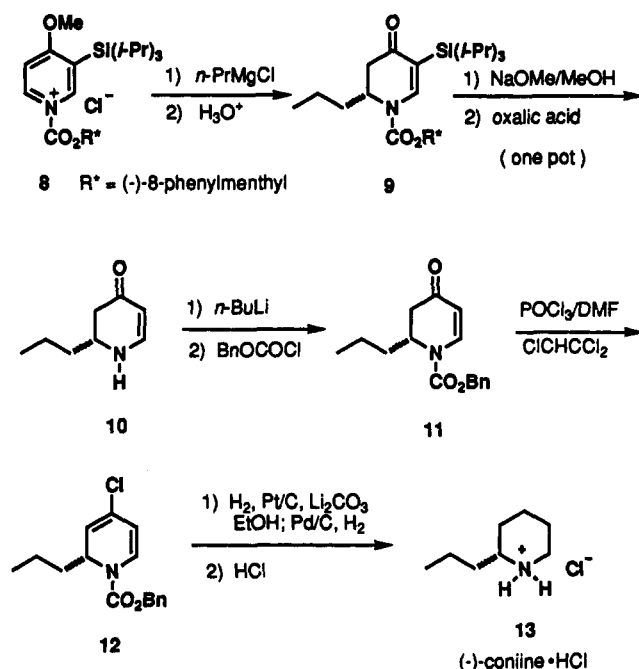
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(15) (a) Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.* 1992, 33, 3765 and references cited therein. (b) For comparison of the physical properties and ¹H NMR data of **13** with literature values, see Table 1 in the supplementary material.

(16) For previous syntheses of lupinine, see: (a) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* 1993, 34, 215. (b) Gesson, J. P.; Jacquesy, J. C.; Rambaud, D. *Tetrahedron Lett.* 1992, 33, 3633. (c) Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron: Asymmetry* 1990, 1, 147 and references cited therein. (d) For comparison of the physical properties and NMR data of **18** with literature values, see Table 2 in the Supplementary Material.

Scheme III

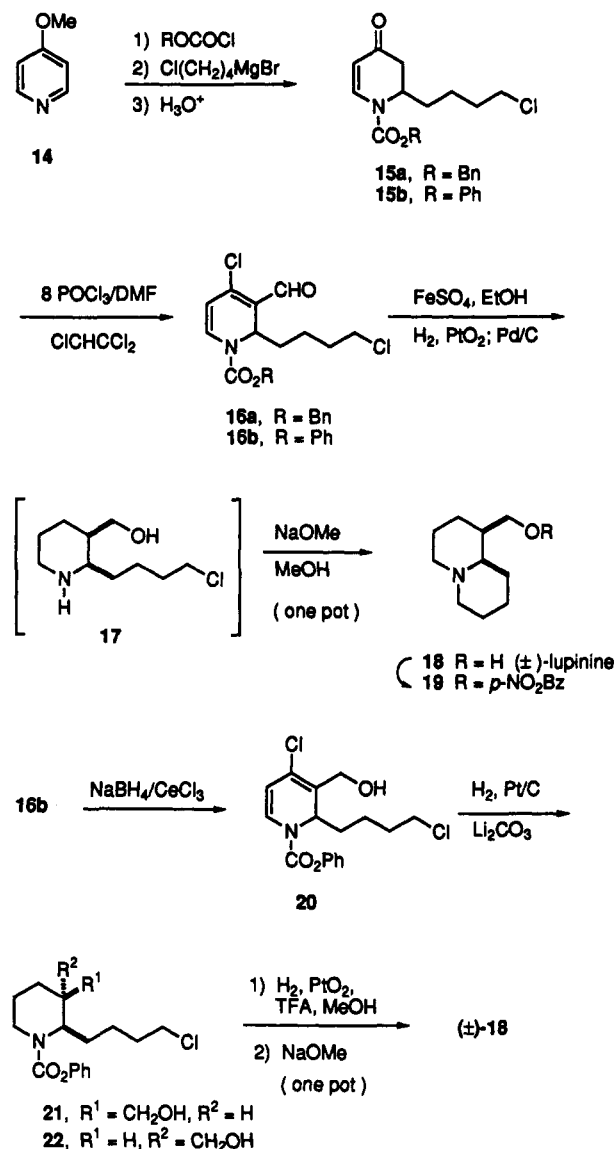


dihydropyridone ring. The stereoselectivity has been explained using steric approach control arguments.⁶ Treatment of 9 with sodium methoxide in MeOH, followed by oxalic acid, effects removal of the chiral auxiliary and the TIPS group via a one-pot reaction to provide dihydropyridone 10 in 86% yield. 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^{9b,17} in $\text{Et}_2\text{O}/\text{THF}$ 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 $\text{S}_{\text{N}}2$ cyclization of

Scheme IV



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 sulfate¹⁸ 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 reduction¹⁹ of 16b gave a 90% yield

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(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.

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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.¹⁸

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, dithioacetal formation, and Raney nickel desulfurization.²¹ Waldmann has used a similar three-step reduction to arrive at (S)-coniine and (R)-coniine 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 PF₂₅₄ 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 MgSO₄, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₉H₁₇NO₃: 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 ethereal 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₁₉NO₃: 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 ethereal 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₂NO₂Br 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 ethereal 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₁NO₃: 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 NaHCO₃, and extracted with CH₂Cl₂ (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K₂CO₃, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₉H₁₆NO₂Cl 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) Pfeigle, 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: ^1H 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 $\text{C}_{16}\text{H}_{18}\text{NO}_2\text{Cl}$ 291.1026, found 291.1006.

N-[(4-Bromobutyl)-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 \times 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: ^1H 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 $\text{C}_{15}\text{H}_{21}\text{NOCIBr}$ 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: ^1H 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 $\text{C}_{15}\text{H}_{20}\text{NO}_2\text{Cl}$ 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** (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 \times 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: ^1H 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 $\text{C}_{21}\text{H}_{24}\text{O}_4\text{NCl}$ 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 \times 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: ^1H 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 $\text{C}_{17}\text{H}_{21}\text{NO}_3$: 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 \times 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: ^1H NMR (300 MHz, CDCl_3) δ 7.50–7.28 (m, 5 H), 6.74–6.60 (dd, due to rotamers, 1 H, $J = 7.33$ 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 $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{Cl}$ 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)pyridine⁶ (1.33 g, 5.0 mmol) in 25 mL of toluene at –23 °C was added (–)-8-phenylmenthyl chloroformate⁶ (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 \times 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**): $[\alpha]_D^{25} -73.1^\circ$ (c 1.04, CHCl_3); ^1H 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 $\text{C}_{24}\text{H}_{35}\text{NO}_3\text{Si}$: C, 73.73; H, 10.02; N, 2.53. Found: C, 73.79; H, 10.03; N, 2.50. Minor diastereomer: $[\alpha]_D^{25} +112.7^\circ$ (c 1.46, CHCl_3); ^1H 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 $\text{C}_{24}\text{H}_{35}\text{NO}_3\text{Si}$: 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 \times 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: $[\alpha]_D^{25} +405.1$ (c 0.59, CHCl_3); ^1H 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 $\text{C}_8\text{H}_{13}\text{NO}$ 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 \times 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: $[\alpha]_D^{25} -121.2^\circ$ (c 0.84, CHCl_3); ^1H 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 $\text{C}_{18}\text{H}_{21}\text{NO}_3$: 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: $[\alpha]_D^{25} -1028^\circ$ (c 1.09, CHCl_3); ^1H 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 $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{Cl}$ 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: ^1H 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: $[\alpha]_D^{25} -5.6$ (c 1, EtOH); mp 218–219 $^\circ\text{C}$ [lit.^{14,15} $[\alpha]_D^{25} -5.8$ (c 1, EtOH), mp 217–220 $^\circ\text{C}$]; ^1H 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 \times 5 mL). To the washed magnesium was added 50 mL of anhydrous ether. The mixture was cooled to 0 $^\circ\text{C}$, and 1-bromo-4-chlorobutane (4.6 mL, 40.0 mmol) was added dropwise. The resulting mixture was stirred at 0 $^\circ\text{C}$ 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 \times 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: ^1H 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 $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{Cl}$ 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 $^\circ\text{C}$. After the mixture was stirred at 0 $^\circ\text{C}$ for 30 min, dihydropyridone 15a (2.85 g, 8.86 mmol) in 30 mL of trichloroethylene at 0 $^\circ\text{C}$ was added dropwise via a double-tipped needle. The resulting solution was stirred at 0 $^\circ\text{C}$ 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 \times 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: ^1H 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 $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{Cl}_2$ 367.0742, found 367.0741.

p-Nitrobenzoate Derivatives of Lupinine and Epi-lupinine. To a solution of aldehyde 16a (0.155 g, 0.422 mmol) in 20 mL of absolute ethanol was added ferrous 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 K₂CO₃, 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 CH₂Cl₂ 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 K₂CO₃, 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₂N₂O₄ 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CHCl₃) 1725 cm⁻¹; HRMS calcd for C₁₇H₂₂N₂O₄ 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 MgSO₄, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₁₈NO₃Cl: 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 NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂ (6 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K₂CO₃, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₁₇NO₃Cl₂ 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 NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K₂CO₃, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₁₉NO₃Cl₂ 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 Li₂CO₃ (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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CHCl₃) 3480, 1700 cm⁻¹. Anal. Calcd for C₁₇H₂₄NO₃Cl: 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 PtO₂. 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 K₂CO₃, 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/CH₂Cl₂) yielded 9.2 mg (84%) of pure (±)-lupinine as a white solid: mp 57–58

°C (lit.²³ mp 57.5–58.5 °C); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 66.05, 65.04, 57.00, 38.03, 31.44, 29.63, 25.56, 24.56, 22.91; IR (CHCl₃) 3200, 2940, 1465, 1445, 1350, 1150, 1125, 1105, 1085, 1050, 1015, 1005 cm⁻¹.^{16d}

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Supplementary Material Available: ¹H NMR spectra of **3c**, **4a–e**, **7**, **10**, **12**, **15a**, **16a,b**, **20**, lupinine *p*-nitrobenzoate, and epilupinine *p*-nitrobenzoate, ¹³C 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.

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