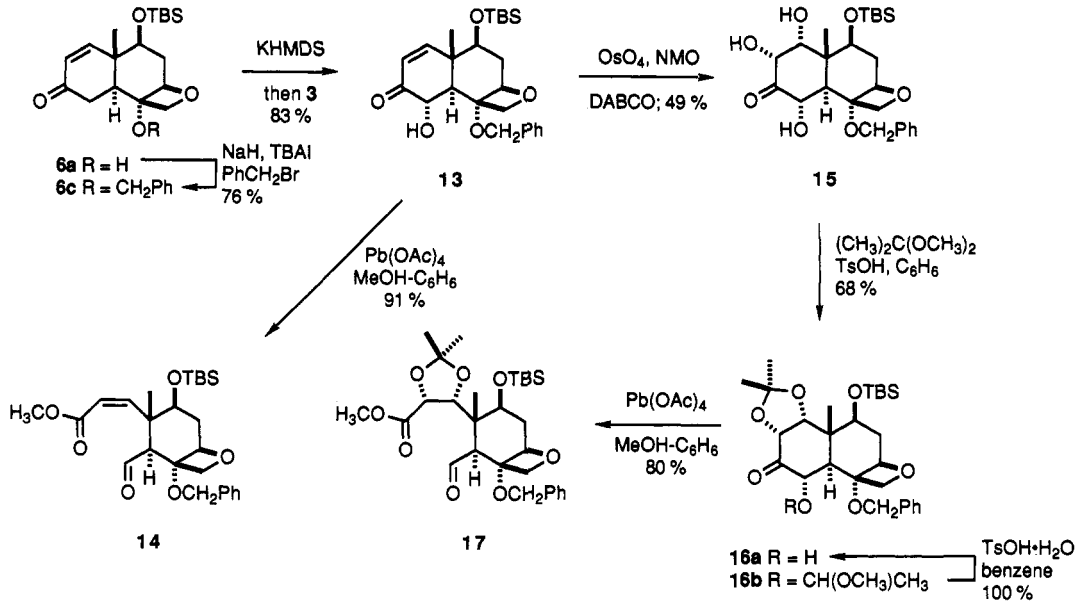
Scheme 3



3.80 (br s, 1H), 2.25–2.47 (m, 5H), 1.82–1.92 (m, 1H), 1.43 (s, 3H), 0.88 (s, 18H), 0.12 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 209.2, 86.9, 77.2, 76.6, 75.9, 75.1, 69.1, 43.5, 42.4, 37.2, 34.6, 25.8, 25.6, 18.0, 17.9, 10.3, –3.1, –3.4, –4.3, –5.1. IR (cm^{-1}): 3466, 1725, 1255, 1100.

Aldehyde Ester 8. Dihydroxy ketone **7** (13.7 mg; 0.028 mmol) was dissolved in 1:1/MeOH:benzene (0.5 mL) and cooled to 0 °C whereupon LTA (31.0 mg; 0.069 mmol) in the same mixture (0.5 mL) was added all at once. After 5 min, SiO_2 and ether were added. The suspension was concentrated to a fine white powder and loaded onto a SiO_2 pad. Elution of this pad with 3:7/EtOAc:hexanes gave pure **8** as a colorless oil (11.9 mg; 87%). TLC: R_f = 0.70 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H), 4.87–4.89 (dd, 1H, J = 2.7, 9 Hz), 4.47–4.49 (d, 1H, J = 7.3 Hz), 4.32–4.34 (d, 1H, J = 7.3 Hz), 4.10–4.15 (m, 1H), 3.59 (s, 3H), 2.46–2.49 (m, 1H), 2.20–2.45 (m, 3H), 1.85–1.97 (m, 1H), 1.57 (s, 3H), 0.89 (s, 9H), 0.81 (s, 9H), 0.19 (s, 6H), 0.03 (s, 3H), 0.005 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 204.3, 172.5, 85.9, 78.6, 70.6, 54.5, 51.9, 43.1, 36.4, 30.4, 25.6, 25.5, 17.9, 6.8, –2.9, –3.0, –3.9, –5.1. IR (cm^{-1}): 1737, 1256, 1100. HRMS: calcd for $C_{24}H_{46}O_6Si_2$ (M^+ + 1) 487.2911; found 487.2907.

Epoxide 9. Enone **6a** (884.6 mg; 2.61 mmol) was dissolved in a 1:1 mixture of $MeOH/CH_2Cl_2$ (20 mL), cooled to 0 °C, and further diluted with 1 N NaOH (0.5 mL). Following the addition of aqueous H_2O_2 (30%; 0.8 mL; 7.04 mmol) the ice bath was removed and the reaction was stirred for 2 h. A mixture of ice, saturated NaCl, and saturated thiosulfate was then added to quench and the product was isolated by CH_2Cl_2 extraction. The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Pure epoxide **9** was isolated by flash SiO_2 column chromatography eluting with 3:7/EtOAc:hexanes (759.8 mg; 82%). TLC: R_f = 0.29 (1:2/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 4.75–4.80 (m, 1H), 4.46–4.49 (d, 1H, J = 7.9 Hz), 4.27–4.28 (d, 1H, J = 7.9 Hz), 3.88–3.92 (m, 1H), 3.58–3.59 (d, 1H, J = 4.2 Hz), 3.34–3.35 (d, 1H, J = 4.2 Hz), 2.42–2.52 (m, 2H), 2.20–2.28 (m, 1H), 1.80–2.08 (m, 3H), 1.26 (s, 3H), 0.91 (s, 9H), 0.087 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 204.7, 87.6, 77.3, 74.6, 71.3, 60.5, 55.9, 38.5, 37.5, 37.1, 32.9, 25.8, 18.0, 9.4, –4.1, –5.1. HRMS: calcd for $C_{18}H_{30}O_5Si$ (M^+ + 1) 355.1941; found 355.1952.

Diol 10. Epoxide **9** (75.9 mg; 0.21 mmol) was dissolved in anhydrous DMF (Aldrich Sure-Seal; 2 mL) and treated with neat hydrazine monohydrate (0.052 mL; 1.07 mmol) at rt. To this pale yellow solution was then added neat, distilled (CaH_2) TMS-Cl (0.055 mL; 0.43 mmol). A precipitate formed almost immediately during this addition but the reaction became homogeneous within 5 min. At this point TLC indicated the reaction to be complete. Water (20 mL) was added and the product was isolated by ether extraction (3 × 20 mL). The combined organic layers were then back extracted with water (2 × 20 mL), saturated NaCl (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on SiO_2 using a gradient elution (1:4 to 2:3/EtOAc:hexanes) afforded pure allylic alcohol **10** (51.8 mg; 72%). TLC: R_f = 0.20 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 5.92–5.83 (m, 2H), 4.73–4.75 (d, 1H, J = 7.7 Hz), 4.68–4.71 (dd, 1H, J = 4.4, 9.5 Hz), 4.29–4.31 (d, 1H, J = 7.7 Hz), 3.99–4.04 (dd, 1H, J = 6, 12.3 Hz), 3.79 (br s, 1H), 2.75 (br s, 1H), 2.31–2.43 (m, 1H), 2.08–2.21 (m, 1H), 1.95–2.07 (m, 1H), 1.77–1.88 (m, 2H), 1.66 (br s, 1H), 1.03 (s, 3H), 0.89 (s, 9H), 0.093 (s, 3H), 0.081 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 129.7, 127.3, 88.0, 79.0, 75.4, 69.1, 69.0, 40.8, 39.3, 37.0, 25.8, 22.8, 18.0, 10.0, –3.7, –5.0. IR (cm^{-1}): 3410, 1254, 1103, 1082. HRMS: calcd for $C_{18}H_{32}O_4Si$ (M^+ + 1) 341.2148; found 341.2150.

Bissilyl Ether 11. A solution of diol **10** (193.4 mg; 0.57 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and treated with 2,6-lutidine (0.2 mL; 1.72 mmol). Despite precipitation of the starting material, TES-OTf (0.32 mL; 1.42 mmol) was added dropwise during which time a clear homogeneous solution resulted. After approximately 0.75 h, the reaction was quenched with saturated $NaHCO_3$ and warmed to rt. The product was then isolated by ether extraction followed by silica gel chromatography (ether:hexanes/1:19) to give pure bissilyl ether **11** in quantitative yield. TLC: R_f = 0.25 (1:9/ether:petroleum ether). ^{1}H NMR ($CDCl_3$): δ 5.80–5.89 (m, 2 H), 4.70–4.73 (dd, 1 H, J = 3.6, 9.2 Hz), 4.61–4.63 (d, 1 H, J = 7 Hz), 4.28–4.30 (d, 1 H, J = 7 Hz), 4.16–4.20 (m, 1 H), 3.88–3.90 (d, 1 H, J = 5.2 Hz), 2.30–2.36 (m, 1 H), 2.07–2.15 (m, 2 H), 1.87–1.94 (m, 1 H), 1.73–1.83 (m, 1 H), 0.91–0.98 (m, 21 H), 0.87 (s, 9 H), 0.56–0.67 (m, 12 H), 0.056 (s, 3 H), 0.049 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 130.4, 127.9, 86.8, 79.5, 69.7, 68.1, 41.5, 39.1, 38.0, 25.9, 23.5, 18.1, 10.0, 7.1, 7.0, 6.5, 6.3, –3.7, –4.6. IR (cm^{-1}): 2952, 1461, 1093.

Aldehyde Ester 12. Allyl silyl ether **11** (512.1 mg; 0.90 mmol) was dissolved in a mixture of $MeOH/CH_2Cl_2$ (1:5; 3.6 mL), solid $NaHCO_3$ was added, and the mixture was cooled to –78 °C. Ozone was then bubbled through the solution until a blue color persisted. The excess oxidant was removed in a stream of nitrogen and the reaction was filtered (CH_2Cl_2 rinse), diluted with benzene, and concentrated *in vacuo*. The resulting residue was dissolved in dry CH_2Cl_2 (5 mL), cooled to 0 °C, and treated sequentially with TEA (0.19 mL; 1.36 mmol) and Ac_2O (0.25 mL; 2.65 mmol). After 5 h, TLC indicated that no ozonide remained. The reaction was concentrated *in vacuo* diluted with saturated $NaHCO_3$ (10 mL) and extracted with ether (3 × 20 mL). The combined ether layers were washed with saturated $NaHCO_3$ (1 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on silica gel (ether:petroleum ether/1:19) gave pure aldehyde ester **12** (369.0 mg; 65%). TLC: R_f = 0.50 (1:4/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 9.78–9.79 (d, 1 H, J = 1.7 Hz), 4.74–4.77 (dd, 1 H, J = 3, 8 Hz), 4.64–4.66 (d, 1 H, J = 7.3 Hz), 4.29–4.31 (d, 1 H, J

= 7.3 Hz), 4.19–4.20 (d, 1 H, J = 1.7 Hz), 3.90–3.94 (m, 1 H), 3.60 (s, 3 H), 2.61–2.69 (m 1 H), 2.22–2.31 (m, 1 H), 1.87–2.15 (m, 3 H), 1.19 (s, 3 H), 0.93–0.99 (m, 18 H), 0.90 (s, 9 H), 0.61–0.69 (m, 12 H), 0.098 (s, 3 H), 0.073 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 204.2, 172.5, 85.1, 81.3, 79.6, 77.9, 70.3, 51.4, 48.4, 42.5, 36.4, 32.8, 26.0, 18.2, 11.9, 6.9, 6.8, 6.2, 5.4, −3.3, −4.5. IR (cm^{-1}): 2953, 1745, 1730, 1462, 1255. HRMS: calcd for $C_{31}H_{62}O_7Si_3$ (M^+) 630.3803; found 630.3798.

Benzyl Ether 6c. Enone **6a** (104 mg; 0.31 mmol) was dissolved in dry THF (3.5 mL), cooled to 0 °C, and treated with solid NaH (9.7 mg; 0.4 mmol). After 10 min, neat benzyl bromide (0.044 mL; 0.37 mmol) and tetrabutylammonium iodide (28.3 mg; 0.077 mmol) were added. The ice bath was removed and the reaction was warmed to rt. After 3 h the reaction was quenched with saturated NH_4Cl (5 mL) and extracted into ether (3 × 10 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from hexanes to give pure **6c** (74.4 mg) as bright yellow needles (mp = 140.5–141.5 °C). The mother liquor was concentrated *in vacuo* and chromatographed on SiO_2, eluting first with 1:9/EtOAc:hexanes to furnish an additional sample of benzyl ether **6c** (25.4 mg; total yield 76%) and then with 2:3/EtOAc:hexanes to give unreacted **6a** (12.2 mg; 12%). TLC: R_f = 0.58 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5H), 7.13–7.15 (d, 1H, J = 10.2 Hz), 5.91–5.93 (d, 1H, J = 10.2 Hz), 5.06–5.08 (d, 1H, J = 8.1 Hz), 4.60–4.63 (d, 1H, J = 11.6 Hz), 4.57–4.58 (d, 1H, J = 7.4 Hz), 4.52–4.55 (d, 1H, J = 11.6 Hz), 4.45–4.47 (d, 1H, J = 7.4 Hz), 3.62–3.66 (m, 1H), 2.34–2.49 (m, 4H), 1.95–2.05 (m, 1H), 1.44 (s, 3H), 0.93 (s, 9H), 0.083 (s, 3H), 0.073 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 198.8, 156.9, 137.8, 128.5, 127.8, 127.1, 126.9, 82.1, 78.4, 73.0, 72.2, 65.2, 42.2, 41.0, 37.7, 33.1, 25.8, 18.0, 11.6, −3.9, −5.0. IR (cm^{-1}): 1681, 1607, 1496, 1255, 1091.

α-Hydroxy Enone 13. Enone **6c** (192.6 mg; 0.45 mmol) in dry THF (5 mL) was cooled to −78 °C and treated with KHMDS in toluene (0.5 M; 1.8 mL; 0.9 mmol). The potassium enolate was allowed to form over 45 min at this temperature. To this bright yellow solution was added oxaziridine **3** (175.0 mg; 0.67 mmol) in dry THF (4 mL) via cannula. The reaction was quenched with water (5 mL) after 30 min and warmed to rt. Following dilution with saturated NaCl (5 mL), the product was isolated by ether extraction (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography using gradient elution (1:9 to 1:4 EtOAc/hexanes) afforded pure α-hydroxy enone **13** (165.5 mg; 83%). TLC: R_f = 0.46 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 7.28–7.35 (m, 5H), 7.18–7.20 (d, 1H, J = 10.1 Hz), 5.98–6.00 (d, 1H, J = 10.1 Hz), 5.10–5.12 (d, 1H, J = 8.8 Hz), 4.86–4.88 (d, 1H, J = 8.1 Hz), 4.69–4.72 (d, 1H, J = 11.3 Hz), 4.64–4.68 (d, 1H, J = 8.1 Hz), 4.58–4.61 (d, 1H, J = 12.6 Hz), 4.57–4.60 (d, 1H, J = 11.3 Hz), 3.61–3.65 (m, 1H), 2.36–2.39 (d, 2H, J = 12.6 Hz), 2.25–2.35 (m, 1H), 1.90–2.05 (m, 1H), 1.55 (s, 3H), 0.92 (s, 9H), 0.065 (s, 6h). ^{13}C NMR ($CDCl_3$): δ 199.8, 157.3, 137.3, 128.5, 127.9, 127.5, 127.0, 82.5, 78.3, 72.8, 71.7, 65.2, 48.9, 43.3, 37.0, 25.7, 18.0, 12.2, −3.9, −5.0. IR (cm^{-1}): 3460, 1682, 1462, 1254, 1091.

Aldehyde Ester 14. Hydroxy ketone **13** (19.8 mg; 0.044 mmol) was dissolved in a 1:1/MeOH:benzene mixture (2 mL) and cooled to 0 °C. To this was added solid LTA (49.6 mg; 0.11 mmol). After 45 min, ether (5 mL) and Celite were added and the mixture was filtered through a silica gel plug (ether wash). Concentration *in vacuo* gave a pale yellow oil which was chromatographed on SiO_2 eluting with 1:9/EtOAc:hexanes to give pure enoate aldehyde **14** (19.3 mg; 91%). TLC: R_f = 0.37 (1:4/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 1H), 7.25–7.38 (m, 5H), 6.16–6.19 (d, 1H, J = 13.2 Hz), 5.85–5.88 (d, 1H, J = 13.2 Hz), 4.99–5.02 (dd, 1H, J = 3.1, 8.8 Hz), 4.77–4.79 (d, 1H, J = 8 Hz), 4.57–4.71 (m, 4H), 3.96 (s, 1H), 3.67 (s, 3H), 2.22–2.28 (m, 1H), 1.93–2.00 (m, 1H), 1.52 (s, 3H), 0.86 (s, 9H), 0.039 (s, 36H), 0.014 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 201.5, 166.4, 155.8, 138.2, 128.4, 127.6, 127.3, 120.5, 83.2, 78.2, 70.6, 65.6, 58.5, 51.7, 43.8, 36.4, 25.7, 18.5, 18.0, 17.6, −4.1, −5.1. IR (cm^{-1}): 1723, 1714, 1202, 1090. HRMS: calcd for $C_{26}H_{38}O_6Si$ (M^+ + 1) 475.2516; found 475.2521.

Triol 15. Enone **13** (101.4 mg; 0.23 mmol) was dissolved in a 4:1 mixture of THF:H_2O (5 mL) and treated with NMO (135.6 mg; 1.16 mmol), DABCO (78.2 mg; 0.70 mmol), and OsO_4 in tBuOH (2.5 wt%; 0.12 mL; 0.012 mmol). The reaction was stirred at rt for 5.5 h at which point no starting material remained by TLC. Saturated $NaHSO_3$ (3 mL) was added, and the mixture was poured into saturated NaCl (5 mL) and then extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with saturated $NaHSO_3$ (1 × 15 mL), water (2 × 15 mL), and saturated NaCl (1 × 10 mL), drived over $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on SiO_2 using 2:3/EtOAc:hexanes gave pure triol **15** (53.5 mg; 49%). TLC: R_f = 0.12 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 7.28–7.35 (m, 5H), 5.06–5.08 (d, 1H, J = 8.0 Hz), 4.79–4.81 (d, 1H, J = 8 Hz), 4.68–4.71 (d, 1H, J = 11.3 Hz), 4.60–4.65 (m, 3H), 4.51–4.55 (m, 2H), 4.16–4.17 (d, 1H, J = 3 Hz), 4.08–4.14 (m, 1H), 3.78–3.79 (d, 1H, J = 2.6 Hz), 3.49–3.50 (d, 1H, J = 4.2 Hz), 2.62–2.65 (d, 1H, J = 11.9 Hz), 2.56 (s, 1H), 2.25–2.33 (m, 2H), 1.91–1.98 (m, 1H), 1.50 (s, 3H), 0.88 (s, 9H), 0.060 (s, 3H), 0.052 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 208.4, 136.9, 128.6, 128.1, 127.7, 82.5, 80.1, 76.4, 74.1, 73.5, 72.0, 69.0, 65.4, 44.1, 41.3, 36.7, 25.7, 18.0, 11.3, −4.2, −5.1. IR (cm^{-1}): 3451, 1731, 1470, 1388, 1255, 1093.

Aldehyde Ester 17. Triol **15** (10.0 mg; 0.021 mmol) was dissolved in benzene (2 mL) and treated with dimethoxypropane (0.6 mL). To this mixture was added 4-Å molecular sieves (beads) and $TsOH·H_2O$. The reaction was stirred for 1.5 h and quenched with saturated $NaHCO_3$, and the product was isolated by ether extraction. The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude mixture on silica gel using 1:3/EtOAc:hexanes gave compounds **16a** (7.3 mg; 68%) and **16b** (3.9 mg; 31%).

Fully protected ketone **16b** (15.0 mg; 0.025 mmol) was dissolved in benzene (1 mL), and $TsOH·H_2O$ (5 mg; 0.025 mmol) was added. The reaction was stirred at rt until TLC indicated that starting material had been consumed (approximately 18 h) whereupon saturated $NaHCO_3$ was added and the product was isolated by ether extraction. This procedure afforded a quantitative crude yield of α-hydroxy ketone **16a**.

Pure **16a** (36.1 mg; 0.07 mmol) was dissolved in a 1:1/MeOH:benzene mixture (5 mL) and treated with solid LTA (78.0 mg; 0.18 mmol). TLC indicated complete consumption of starting material within 5 min. The reaction was diluted with ether and filtered through SiO_2 (ether wash) to give essentially pure product. Flash chromatography using 1:9/EtOAc:hexanes gave pure aldehyde ester **17** as a colorless oil (30.7 mg; 80%). TLC: R_f = 0.64 (2:3/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 10.09–10.10 (d, 1H, J = 4 Hz), 7.25–7.35 (m, 5H), 4.95–4.96 (d, 1H, J = 5.9 Hz), 4.56–4.59 (d, 1H, J = 11.6 Hz), 4.47–4.49 (d, 1H, J = 7.2 Hz), 4.25–4.38 (m, 4H), 4.08–4.10 (d, 1H, J = 6.2 Hz), 3.75 (s, 3H), 3.10–3.11 (d, 1H, J = 3.6 Hz), 2.05–2.18 (m, 1H), 1.93–2.00 (m, 1H), 1.58 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.095 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 204.2, 137.6, 128.3, 127.7, 127.6, 109.9, 82.7, 79.7, 75.7, 75.0, 68.4, 65.9, 55.1, 52.4, 42.6, 32.7, 26.5, 25.8, 25.4, 15.4, −4.4, −4.8. IR (cm^{-1}): 1760, 1725, 1708, 1256, 1078. HRMS: calcd for $C_{29}H_{44}O_8Si$ (M^+) 548.2806; found 548.2787.

Acknowledgment. C.A.C. is grateful to the National Science Foundation for a Postdoctoral Fellowship award. We thank V. Parmakovich and B. Sporer of the Department of Chemistry of Columbia University for mass spectral analyses.

Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of **5**, **7–15**, **17**, and **6c** (26 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.

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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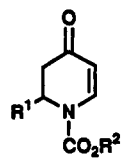
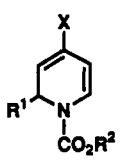
Received August 17, 1993•

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 ($ClCHCCl_2$, 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 heterocycles[1] 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 ($NaBH_4/CeCl_3$; 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[8g] 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.

(1) Dihydropyridones **1** are conveniently prepared by the addition of Grignard reagents to 1-acyl-4-methoxypyridinium chloride; see: (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053.

(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.

(4) (a) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. (b) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035. (c) Chiral piperidines have been prepared from *N*-alkyl-2,3-dihydro-4-pyridones; see: Kunz, H., Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067. Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468. Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264 and references cited therein. (d) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetrahedron Lett.* **1992**, *33*, 7635.

(5) (a) Comins, D. L.; Abdullah, A. H.; Smith, R. K. *Tetrahedron Lett.* **1983**, *24*, 2711. (b) Comins, D. L.; Abdullah, A. H. *Tetrahedron Lett.* **1985**, *26*, 43. (c) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (d) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098.

(6) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574.

(7) For reviews on dihydropyridines, see: Stout, D. E.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291. Also see: Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.

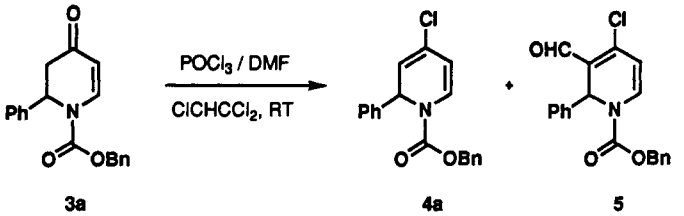
(8) (a) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094. (b) Comins, D. L.; O'Connor, S. *Tetrahedron Lett.* **1987**, *28*, 1843. (c) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292. (d) Ogawa, M.; Natsume, M. *Heterocycles* **1985**, *23*, 831. (e) Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S. *Tetrahedron* **1985**, *41*, 2115 and references cited therein. (f) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawansi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215. (g) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506.

(9) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.

(10) (a) Brown, P. E.; Marcus, W. Y.; Anastasis, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1127. (b) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753. (c) Kozhich, D. T.; Vasilevskii, V. I.; Mironov, A. F.; Evstigneeva, R. P. *Zh. Org. Khim.* **1980**, *16*, 849; *Chem. Abst.* **1980**, *93*, 46309f. (d) For an excellent review on the reactions of carbonyl compounds with Vilsmeier reagents, see: Marson, C. M. *Tetrahedron* **1992**, *48*, 3659.

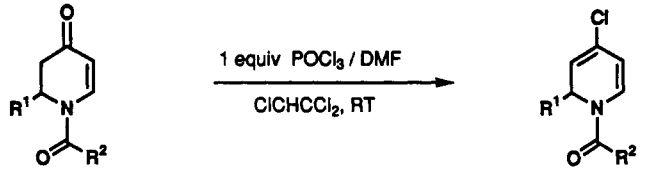
0022-3263/93/1958-7732$04.00/0

Scheme I

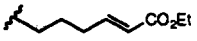


3a 4a 5

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



3 4

entry[a,b]	R^1	R^2	yield,[c] %
a	Ph	OBn	85
b	*n*-Pr	OBn	96
c	*c*-Hex	$(CH_2)_3Br$	83
d	*c*-Hex		92
e		OBn	83

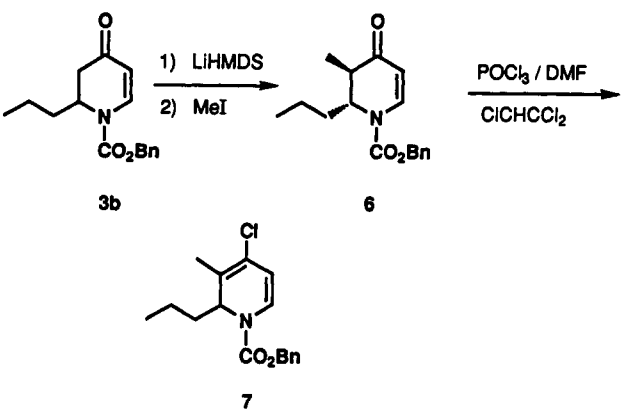
[a] The reactions were generally performed on a 1–2 mmol scale in trichloroethylene. [b] The workup consisted of concentration, addition of aqueous sodium bicarbonate, and extraction with methylene chloride; see Experimental Section. [c] Yield of products obtained from radial preparative-layer chromatography (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 (R^1) of **3** is also tolerated (entry e). It is noteworthy that dihydropyridone **3a** and $POCl_3$ 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 $POCl_3$/DMF using the

Scheme II



3b 6 7

standard conditions gave a 90% yield of 1,2-dihydropyridine **7**. The addition of Grignard reagents to the 1-phenoxycarbonyl 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-methoxypyridine[1] represents a regiospecific 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-pyridones[6] 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.[8g] 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

(11) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.
(12) Comins, D. L.; Mantlo, N. B. *J. Org. Chem.* **1985**, *50*, 4410.
(13) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. (b) Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1987**, *28*, 759 and references cited therein.
(14) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
(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.