An Intramolecular Diels-Alder/Retro-Mannich Approach to the *cis*-Perhydroquinoline Ring System. Model Studies toward the Synthesis of *Lycopodium* Alkaloids

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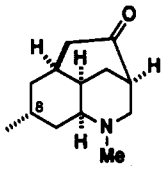
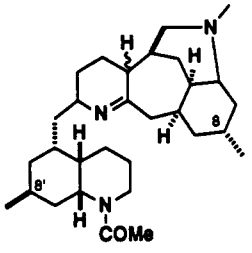
Model studies toward the preparation of *cis*-decahydroquinoline derivatives using an IMDA/retro-Mannich strategy were carried out. Tricyclic amino ester **13**, prepared via an IMDA reaction of 1,2-dihydropyridine **11**, was ring-opened on treatment with excess LDA. Trapping the intermediate dianion **17** with TMSCl gave the polysilylated derivatives **18**. Subsequent N-acylation with benzyl chloroformate provided ene carbamate **19**, which on catalytic hydrogenation gave the desired decahydroquinoline **21**. In a similar manner, 1,2-dihydropyridine **22** was cyclized and ring-opened in two steps to give the desired *cis*-hexahydroquinolone **25**. N-Acylation of **25** with LDA and benzyl chloroformate provided the benzyl carbamate **26** in quantitative yield. The target model compounds, **21** and **26**, were prepared with complete control of relative stereochemistry at their three contiguous stereogenic centers. The mechanisms for the retro-Mannich ring-openings are discussed.

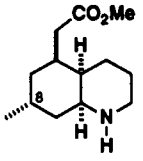
The alkaloids isolated from *Lycopodium* are numerous and include various structural types.[1] The simplest *Lycopodium* alkaloid, luciduline (**1**), and the complex lucidines, i.e., lucidine B (**2**), contain a *cis*-perhydroquinoline fragment within their skeletons. A *cis*-perhydroquinoline derivative can be a viable building block for certain *Lycopodium* alkaloids. Schumann[2] has described a racemic synthesis of luciduline (**1**) from the *cis*-perhydroquinoline **3**, and MacLean[3] has reported lactam **4** as an intermediate in his synthesis of **1**.



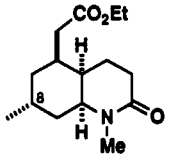
1
luciduline



2
lucidine B



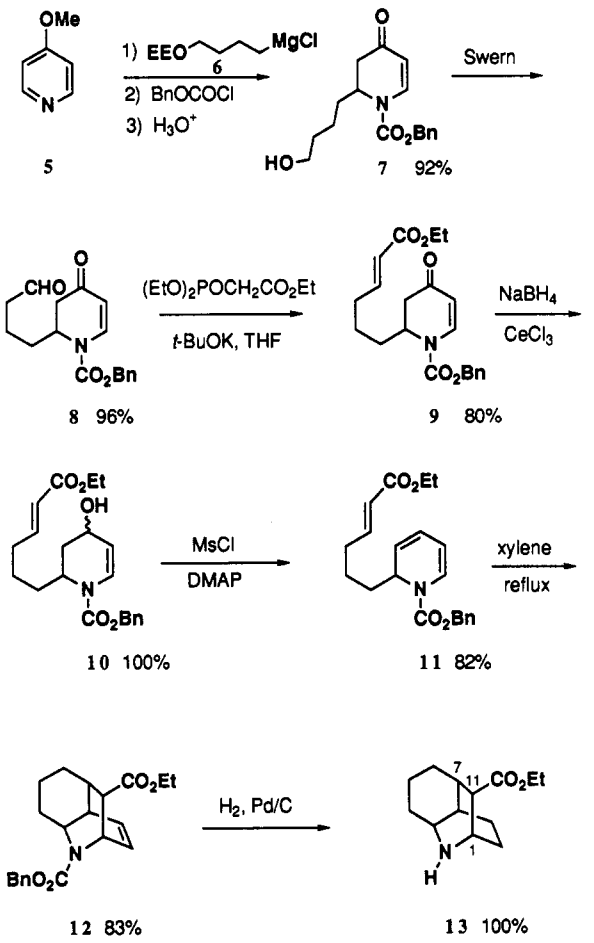
3



4

Previously in our laboratories the intramolecular Diels-Alder reaction of 1-acyl-2-alkenyl-1,2-dihydropyridines was examined. We reported that a derivative of a dihydropyridine Diels-Alder product could be ring-opened through a retro-Mannich reaction to give a *cis*-decahydroquinoline derivative.[4] The potential of this methodology for the synthesis of various alkaloids containing the *cis*-perhydroquinoline ring system prompted us to carry out the model studies described in this paper.

Scheme I



For simplicity, we examined the formation of normethyl bicyclic intermediates similar to **3** and **4** but having no stereogenic center at C-8.

Results and Discussion

The addition of organometallics to 1-acylpyridinium salts is a convenient method for the synthesis of substituted dihydropyridines.[5] Starting with this reaction, the required 1-acyl-2-alkenyl-1,2-dihydropyridine **11** was

(1) For reviews on the *Lycopodium* alkaloids, see: (a) Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185-240. (b) Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 489-515.

(2) Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1984**, 1519.

(3) Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1979**, *57*, 1631.

(4) Comins, D. L.; Abdullah, A. H.; Smith, R. K. *Tetrahedron Lett.* **1983**, *24*, 2711.

(5) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199 and references cited therein. For an efficient asymmetric synthesis of 1-acyl-2-alkyl-1,2-dihydropyridines, see: Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.

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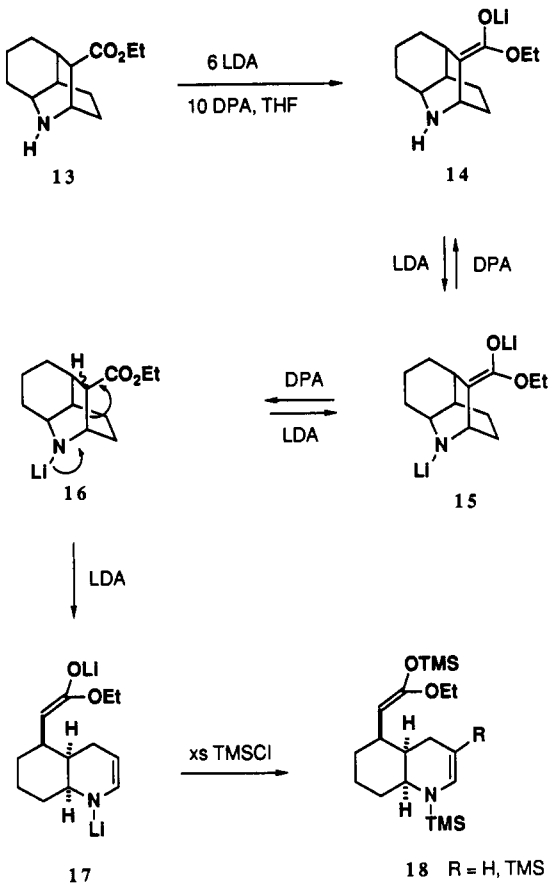
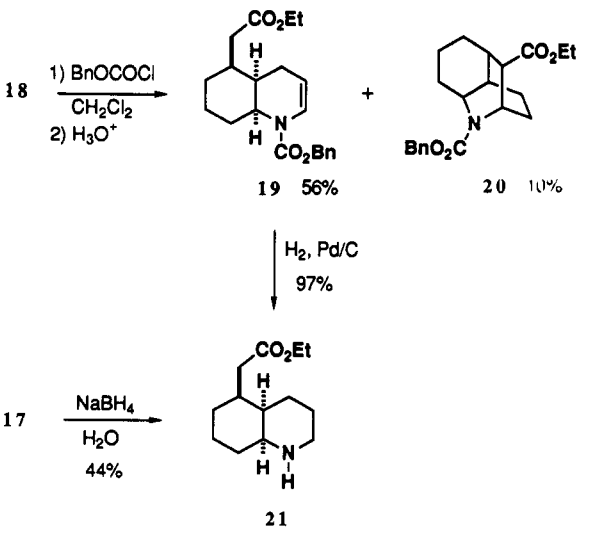
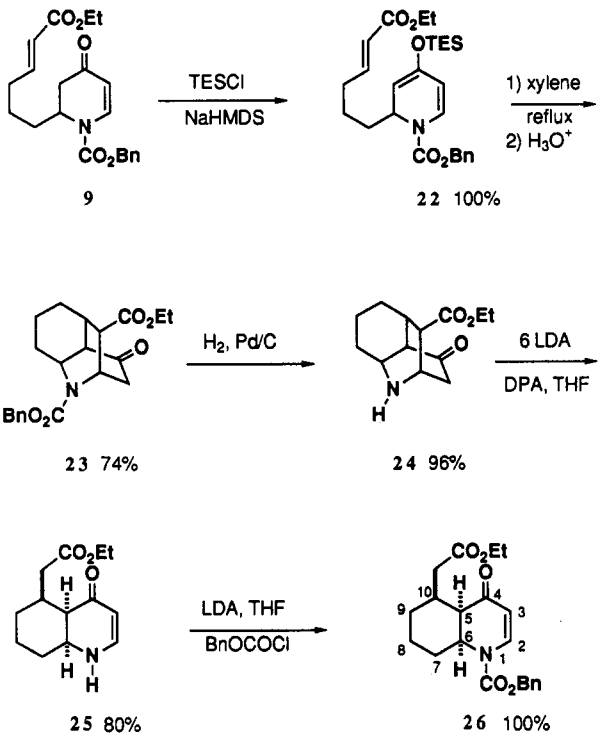
Scheme II



Scheme III



Scheme IV

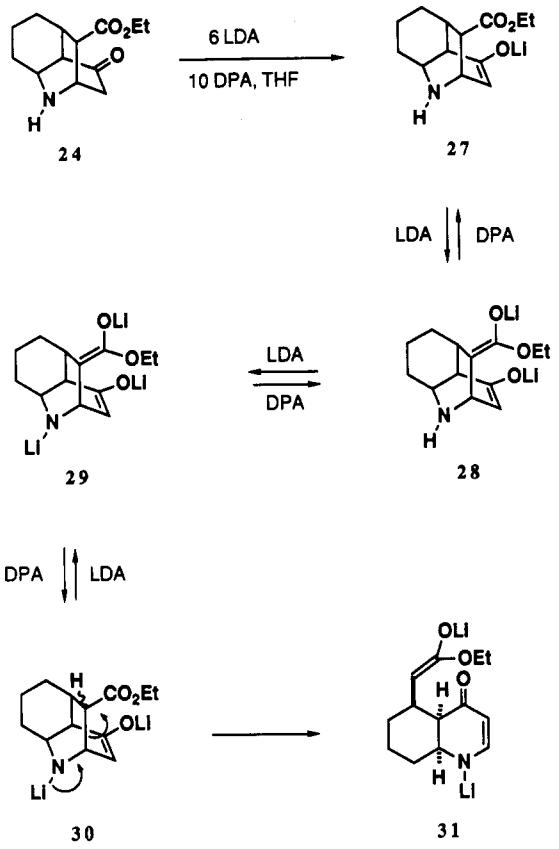


prepared in five steps as shown in Scheme I. Treatment of 4-methoxypyridine (**5**) with Grignard reagent **6** and benzyl chloroformate gave on workup with aqueous acid a 92% yield of dihydropyridone **7**.[6] Swern oxidation[7] of **7** provided a near-quantitative yield of aldehyde **8**. Chemoselective olefination occurred on treatment of **8** with triethyl phosphonoacetate/potassium *tert*-butoxide in THF to give ester **9**. To prepare the required precursor to the intramolecular Diels–Alder step, we needed to convert dihydropyridone **9** into 1,2-dihydropyridine **11**. This was accomplished in two steps with a 82% overall yield by reducing the dihydropyridone carbonyl of **9** with $NaBH_4/CeCl_3$ and dehydrating the resulting alcohol **10** with Furukawa's reagent.[8] The intramolecular Diels–Alder reaction of triene **11** was carried out in refluxing xylene for 6 days to provide an 83% yield of the desired tricyclic carbamate **12**.[4,9] Catalytic hydrogenation of **12** over palladium on carbon in ethyl acetate gave a quantitative yield of amino ester **13**. The anticipated structure of amine **13** was in agreement with ^1H and ^{13}C NMR data. The stereochemistry at C-11 was assigned on the basis of the H-1, H-11 and H-7, H-11 coupling constants (J_{1-11} = 3.6 Hz and J_{7-11} = 4.4 Hz), which corresponds well to the calculated values (J_{1-11} = 2.3 Hz and J_{7-11} = 2.6 Hz).[10]

As previously reported from our laboratories, ring-opening occurs on treatment of **13** with excess lithium diisopropylamide (LDA) as shown in Scheme II.[4] The best conditions found for this retro-Mannich ring-opening required 6 equiv of LDA and 10 equiv of diisopropylamine (DPA) in THF at −78 °C. Presumably, dianion **15** is formed in equilibrium with enolate anion **14** and excess LDA. Dianion **15** is slowly protonated by DPA at the α-position of the ester enolate to give **16**, which undergoes ring-opening and deprotonation to provide dianion **17**. Quenching the reaction with chlorotrimethylsilane and anhydrous workup provided a mixture of polysilylated derivatives **18**. Without purification, mixture **18** was N-acylated[11] with benzyl chloroformate in refluxing methylene chloride to give the ene carbamate **19** in 56%

(6) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.
(7) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(8) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440.
(9) Several variations of the intramolecular Diels–Alder reaction of 1-acyldihydropyridines have been examined, see: (a) Comins, D. L.; Abdullah, A. H.; Mantlo, N. B. *Tetrahedron Lett.* **1984**, *25*, 4867. (b) Krow, G. R.; Lee, Y. B.; Raghavachari, R. *Tetrahedron Lett.* **1988**, *29*, 3187 and references cited therein.
(10) Molecular modeling and calculations of coupling constants were performed using PCMODEL (Serena Software, Bloomington, IN).
(11) *N*-Silylenamines have been N-acylated with acyl halides, see: (a) Ando, W.; Tsumaki, H. *Tetrahedron Lett.* **1982**, *23*, 3073. (b) Akiba, K.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994.

Scheme V



yield after chromatography (Scheme III). Approximately 10% of carbamate **20** is also formed in this reaction by acylation of N-silylated unopened amine **13**, which was present in crude **18**. Catalytic hydrogenation of **19** provided a near-quantitative yield of amino ester **21**. The in situ protonation/reduction of dianion **17** with $NaBH_4/H_2O$ gave amino ester **21** in 44% yield after purification via its benzyl carbamate. This procedure is less convenient than the one described above for the preparation of **21** from **18**.

To determine if a more functionalized *cis*-perhydroquinoline derivative could be prepared using the IMDA/retro-Mannich strategy, we examined the formation and cyclization of triene **22** (Scheme IV). Dihydropyridone **9** was treated with chlorotriethylsilane (TESCl) and sodium hexamethyldisilazane (NaHMDS) to give **22** in quantitative yield. The IMDA reaction was performed by refluxing a xylene solution of **22** for 6 days followed by an acidic workup. In this manner, a 74% yield of the desired tricyclic ketoester **23** was obtained. The benzyl carbamate group of **23** was cleaved by catalytic reduction to provide amine **24** in 96% yield. Retro-Mannich ring-opening was effected as before using excess LDA in DPA/THF. Aqueous workup gave a good yield of hexahydroquinolone **25**. Since analogous dihydropyridones are more synthetically useful as their *N*-acyl derivatives,[12] we examined the conversion of **25** to **26**. N-Acylation of **25** in the presence of the ester function was effected by deprotonation with LDA and addition of benzyl chloroformate to give *N*-acylhexahydroquinolone **26** in quantitative yield. The ring-opening of **24** probably proceeds as depicted in Scheme V. Initial deprotonation of the keto function of **24** gives enolate **27**. On further reaction with LDA, dianion **28** and trianion **29** are formed in equilibrium. Protonation of **29** by DPA at the α-position of the ester enolate provides dianion **30**, which suffers ring-opening to give **31** in situ. An alternative pathway involving a retro-Michael ring-opening of anion **27** is apparently not operating, for treatment of **24** with an excess of the weaker base, LiHMDS, gave mainly recovered starting material.

Despite the use of excess strong base in the ring-opening step, no epimerization occurred at the stereogenic centers. The N-acylated product **26**[13] (Scheme IV) was isolated as one diastereomer with the relative stereochemistry shown as determined by ^1H NMR coupling constants, $J_{5-6} = 5.1$ Hz and $J_{5-10} = 2.9$ Hz, which showed good correlation with values derived from molecular mechanics calculations.[10]

In summary, the IMDA/retro-Mannich strategy for the preparation of *cis*-decahydroquinoline derivatives has been successfully carried out on model systems with complete stereochemical control. This approach should be amenable to the synthesis of viable building blocks for certain *Lycopodium* alkaloids, once the C-8 methyl group (see structures **1–4**) can be incorporated stereoselectively.[14]

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-(4-hydroxybutyl)-2,3-dihydro-4-pyridone (7).** The 1-ethoxyethyl ether of 4-chlorobutanol (1.07 mL, 6.0 mmol) and 1,2-dibromoethane (0.1 mL, 1.16 mmol) was added with stirring to magnesium turnings (0.438 g, 18.0 mmol) in 6 mL of THF. The temperature during the addition was controlled using an ice/water bath. The resulting mixture was stirred at room temperature for 1 h and at reflux for 2 h. To a stirred solution of 4-methoxypyridine (0.47 mL, 4.6 mmol) in 25 mL of THF was added the Grignard reagent via a double-tipped needle. The mixture was cooled to −23 °C, and benzyl chloroformate (0.66 mL, 4.6 mmol) was added dropwise. The solution was stirred at −23 °C for 45 min and poured into 100 mL of aqueous 10% HCl. The resulting mixture was stirred at room temperature for 1 h. 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 and silica, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 40% EtOAc/hexanes) gave 1.289 g (92%) of alcohol **7** as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78–7.76 (d, 1 H, J = 7.34 Hz), 7.45–7.35 (m, 5 H), 5.33–5.22 (m, 3 H), 4.70–4.55 (bm, 1 H), 3.58 (bs, 2 H), 2.86–2.78 (dd, 1 H, J = 16.14, 6.60 Hz), 2.48–2.43 (d, 1 H, J = 16.14 Hz), 1.80–1.20 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.15, 152.21, 141.52, 134.61, 128.50, 128.44, 128.24, 106.69, 68.73, 61.75, 52.96, 39.26, 31.93, 29.96, 21.66; IR (neat) 3400, 2900, 2830, 1720, 1660, 1600, 1420, 1380, 1330, 1265, 1230, 1195, 1110, 1075 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1469.

(12) (a) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (b) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053. (d) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (e) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (f) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (g) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (h) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919.

(13) To avoid confusion, the numbering system used in Scheme IV for structure **26** is the same as used for the *Lycopodium* alkaloids. A more appropriate numbering system for reduced quinolone derivatives, i.e., **25** and **26**, is used in the Experimental Section.

(14) A formal total synthesis of (+)-luciduline (**1**) has been achieved in our laboratories using the IMDA/retro-Mannich strategy. Comins, D. L.; Goehring, R. R., paper presented at the 201st National Meeting of the American Chemical Society, Atlanta, GA, April 14–19, 1991; ORGN 182.

***N*-[(Benzyloxy)carbonyl]-2-(3-formylpropyl)-2,3-dihydro-4-pyridone (8).** To a stirred solution of oxalyl chloride (0.58 mL, 6.64 mmol) in 30 mL of CH_2Cl_2 at −50 °C to −60 °C was added DMSO (1.0 mL, 14.6 mmol). The mixture was stirred for 5 min, and alcohol **7** (2.014 g, 6.64 mmol) in 20 mL of CH_2Cl_2 was added dropwise. After the mixture was stirred for 15 min, triethylamine (4.6 mL, 33.2 mmol) was added. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature, and the reaction was quenched with 50 mL of water. The layers were separated, and 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 1.914 g (96%) of crude aldehyde **8** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 7.78–7.76 (bd, 1 H, J = 6.60 Hz), 7.45–7.35 (m, 5 H), 5.34–5.18 (m, 3 H), 4.65–4.50 (bs, 1 H), 2.87–2.80 (dd, 1 H, J = 6.60, 16.13 Hz), 2.47–2.41 (m, 3 H), 1.80–1.40 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.26, 192.67, 152.18, 141.29, 134.57, 128.60, 128.53, 128.34, 106.89, 68.89, 52.67, 42.95, 39.49, 29.73, 17.88; IR (neat) 3070, 3040, 3010, 3100, 2800, 2700, 2220, 1690, 1600, 1490, 1450, 1415, 1380, 1300, 1200, 1105, 1080 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1314.

***N*-[(Benzyloxy)carbonyl]-2-[(*E*)-5-(ethoxycarbonyl)-4-pentenyl]-2,3-dihydro-4-pyridone (9).** Triethyl phosphonoacetate (1.4 mL, 6.99 mmol) was added dropwise to a stirred solution of potassium *tert*-butoxide (0.713 g, 6.35 mmol) in 50 mL of THF at 0 °C. The resulting solution was stirred for an additional 10 min at 0 °C and cooled to −78 °C. Crude aldehyde **6** (1.914 g, 6.35 mmol) in 25 mL of THF was added dropwise via a double-tipped needle. The mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature. The reaction mixture was stirred an additional 7 h at room temperature and was quenched with 30 mL of water. The aqueous layer was separated and extracted with ether (2 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through silica and Celite, and evaporated in vacuo to yield the crude α,β-unsaturated ester **9**. Purification by radial PLC (silica gel, 20% EtOAc/hexanes) gave 1.87 g (80%) of **9** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.76 (bd, 1 H, J = 7.33 Hz), 7.45–7.35 (m, 5 H), 6.91–6.81 (m, 1 H), 5.80–5.75 (d, 1 H, J = 15.4 Hz), 5.34–5.23 (m, 3 H), 4.70–4.55 (bs, 1 H), 4.23–4.16 (q, 2 H), 2.87–2.80 (dd, 1 H, J = 6.60, 16.13 Hz), 2.45–2.40 (d, 1 H, J = 16.13 Hz), 2.25–2.10 (m, 2 H), 1.80–1.35 (m, 4 H), 1.32–1.27 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.34, 165.95, 152.05, 147.47, 141.00, 134.54, 128.40, 128.34, 128.15, 121.49, 106.72, 68.63, 59.75, 52.61, 39.46, 31.28, 29.76, 23.79, 13.87; IR (neat) 3040, 3005, 2940, 2920, 2840, 1720, 1665, 1605, 1495, 1450, 1420, 1385, 1295, 1195, 1110, 1045, 995 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.89; H, 6.79; N, 3.77. Found: C, 67.79; H, 6.80; N, 3.81.

***N*-[(Benzyloxy)carbonyl]-2-[(*E*)-5-(ethoxycarbonyl)-4-pentenyl]-4-hydroxy-1,2,3,4-tetrahydropyridine (10).** To a stirred solution of pure **9** (1.78 g, 4.81 mmol) in 75 mL of MeOH at 0 °C was added cerium(III) chloride heptahydrate (1.972 g, 5.29 mmol), and stirring was continued for 10 min. Sodium borohydride (0.273 g, 7.22 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 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to yield 1.797 g (100%) of crude alcohol **10** as a clear oil. Purification of a small amount of **10** by radial PLC (silica gel, 10–20% EtOAc/hexanes) provided an analytical sample as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5 H), 6.98–6.75 (m, 2 H), 5.82–5.77 (d, 1 H, J = 15.4 Hz), 5.19–5.18 (d, 2 H, J = 2.2 Hz), 4.95–4.85 (bs, 1 H), 4.50–4.24 (m, 2 H), 4.23–4.16 (q, 2 H), 2.30–2.10 (bs, 3 H), 1.76–1.40 (m, 6 H), 1.32–1.27 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.50, 152.86, 148.34, 135.71, 128.40, 128.15, 127.98, 124.07, 121.46, 109.66, 67.63, 61.17, 60.07, 51.35, 33.64, 31.70, 30.64, 24.30, 14.06; IR (neat) 3440, 2940, 2860, 1700, 1650, 1495, 1445, 1395, 1380, 1330, 1265, 1215, 1190, 1160, 1100, 1050, 985, 915, 865 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.42; H, 7.32; N, 3.74.

***N*-[(Benzyloxy)carbonyl]-2-[(*E*)-5-(ethoxycarbonyl)-4-pentenyl]-1,2-dihydropyridine (11).** To a solution of crude alcohol **10** (1.797 g, 4.95 mmol) in 40 mL of CH_2Cl_2 was added 11 mL of Furukawa's reagent.[8] The resulting mixture was stirred for 2 h at room temperature, quenched with 20 mL of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, and evaporated in vacuo to yield crude triene **11** in quantitative yield. Purification by radial PLC (silica gel, hexanes–10% EtOAc/hexanes) gave 1.396 g (82%) of pure 1,2-dihydropyridine **11** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5 H), 6.98–6.82 (m, 1 H), 6.80–6.67 (dd, due to rotamers, 1 H, J = 7.33 Hz), 5.95–5.88 (m, 1 H), 5.82–5.73 (dd, due to rotamers, 1 H, J = 11.73 Hz), 5.61–5.48 (m, 1 H), 5.35–5.20 (m, 3 H), 4.90–4.70 (m, 1 H), 4.22–4.14 (q, 2 H), 2.25–2.05 (m, 2 H), 1.70–1.40 (m, 4 H), 1.31–1.26 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.56, 153.99 and 153.28 (due to rotamers), 148.69 and 148.43 (due to rotamers), 135.87 and 135.71 (due to rotamers), 128.44, 128.27 and 128.15 (due to rotamers), 127.98, 125.43 and 124.59 (due to rotamers), 122.56, 122.01 and 121.78 (due to rotamers), 121.39 and 121.30 (due to rotamers), 106.21 and 105.88 (due to rotamers), 67.69, 60.04, 51.93 and 51.67 (due to rotamers), 33.74 and 33.16 (due to rotamers), 31.99 and 31.90 (due to rotamers), 22.75 and 22.59 (due to rotamers), 14.16; IR (neat) 3040, 2980, 2930, 2860, 1710, 1645, 1575, 1495, 1450, 1420, 1395, 1365, 1315, 1260, 1190, 1145, 1110, 1040, 975, 910, 860 cm^{-1}; HRMS calcd for $C_{21}H_{25}NO_4$ 355.1784, found 355.1781.

***N*-[(Benzyloxy)carbonyl]-11-(ethoxycarbonyl)-2-azatricyclo[5.3.1.0^{3,8}]undec-9-ene (12).** A solution of triene **11** (1.032 g, 2.90 mmol) in degased xylenes was refluxed for 6 consecutive days under an argon atmosphere. The xylenes were evaporated in vacuo to yield crude **12** in quantitative yield. Purification by radial PLC (silica gel, 10% EtOAc/hexanes) gave 0.854 g (83%) of pure **12** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5 H), 6.46–6.30 (m, 2 H), 5.30–5.06 (m, 3 H), 4.20–4.00 (m, 2 H), 3.40–3.30 (bs, 1 H), 2.79–2.77 (t, 1 H, J = 3.66 Hz), 2.45–2.15 (m, 3 H), 1.80–1.28 (m, 5 H), 1.25–1.21 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.63 and 172.54 (due to rotamers), 156.09 and 154.96 (due to rotamers), 136.71 and 136.54 (due to rotamers), 136.06 and 135.96 (due to rotamers), 130.96 and 130.54 (due to rotamers), 128.24, 127.66, 127.43, 66.73 and 66.47 (due to rotamers), 60.39, 51.22 and 50.89 (due to rotamers), 48.34 and 48.05 (due to rotamers), 47.57, 38.91 and 38.55 (due to rotamers), 31.51 and 31.09 (due to rotamers), 28.44 and 28.08 (due to rotamers), 26.92, 14.64 and 14.58 (due to rotamers), 14.00; IR (neat) 3050, 2930, 2860, 1730, 1695, 1495, 1450, 1405, 1370, 1355, 1330, 1300, 1275, 1245, 1220, 1190, 1175, 1110, 1070, 1055, 1025, 965, 920, 885, 860, 820, 800 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09; N, 3.94. Found: C, 71.06; H, 7.11; N, 3.96.

11-(Ethoxycarbonyl)-2-azatricyclo[5.3.1.0^{3,8}]undecane (13). A solution of **12** (1.596 g, 4.49 mmol) in 40 mL of ethyl acetate was hydrogenated at room temperature (balloon pressure) in the presence of 0.798 g of 5% palladium on carbon for 3 h. Filtration through Celite and removal of the solvent in vacuo resulted in 0.978 g (98%) of amine **13** as a grayish solid, which was used directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19–4.09 (m, 2 H), 3.30–3.25 (bs, 1 H), 3.20–3.15 (bs, 1 H), 2.65–2.63 (t, 1 H, J = 3.66 Hz), 2.48–2.40 (bs, 1 H), 2.20–2.00 (bs, 1 H), 1.80–1.30 (m, 11 H), 1.28–1.23 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.67, 60.01, 49.47, 48.54, 45.95, 31.96, 31.54, 31.28, 30.06, 24.24, 22.79, 14.52, 13.90; IR ($CHCl_3$) 3020, 2930, 2860, 1715, 1460, 1440, 1425, 1420, 1380, 1365, 1345, 1335, 1320, 1285, 1260, 1235, 1190, 1160, 1140, 1090, 1070, 1055, 1040, 1025, 985, 960, 915, 890, 860 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1573.

1,4,4a,5,6,7,8,8a-Octahydro-1-[(benzyloxy)carbonyl]-5-[1-(ethoxycarbonyl)methyl]quinoline (19). To a stirred solution of amine **13** (0.270 g, 1.21 mmol) in 15 mL of THF at −78 °C was added diisopropylamine (1.7 mL, 12.1 mmol) followed by LDA in THF (12.1 mL, 12.1 mmol). After the solution was stirred at −78 °C for 8 h, chlorotrimethylsilane (1.6 mL, 12.7 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 10 min and was warmed to room temperature over a period of 45 min. The solvent was evaporated in vacuo, the residue was diluted with dry hexanes, and the mixture was filtered through a disposable pipet packed with Celite under an argon atmosphere. The resulting filtrate was concentrated in vacuo to yield intermediate **18**, which was dried under high vacuum for 2 h. Benzyl chloroformate was added to a solution of **18** in 30 mL of CH_2Cl_2,

and this mixture was refluxed for 12 h. After the solution was cooled to room temperature, 40 mL of 10% HCl was added and stirring was continued for 2.5 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine, dried over anhydrous K_2CO_3, filtered through Celite and silica, and concentrated in vacuo to yield crude ene carbamate **19** and carbamate **20**. Purification by radial PLC (silica gel, hexanes–5% EtOAc/hexanes) gave 0.344 g (80%) of a mixture of **19** and **20** in an 85:15 ratio. Repeated purification (2 ×) by radial PLC (silica gel/$AgNO_3$, 2–5% EtOAc/hexanes) gave 0.241 g (56%) of pure **19** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H), 6.84–6.72 (dd, due to rotamers, 1 H, J = 8.8 Hz), 5.27–5.15 (m, 2 H), 4.94–4.76 (m, 1 H), 4.20–4.02 (m, 3 H), 2.30–1.30 (m, 12 H), 1.27–1.23 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.47 and 172.38 (due to rotamers), 153.12 and 152.51 (due to rotamers), 136.35 and 136.29 (due to rotamers), 128.40, 127.98 and 127.92 (due to rotamers), 127.63, 123.72 and 123.20 (due to rotamers), 103.98 and 103.85 (due to rotamers), 67.31 and 67.15 (due to rotamers), 60.23, 53.93 and 53.48 (due to rotamers), 38.55, 36.81, 34.64 and 34.48 (due to rotamers), 25.89 and 25.79 (due to rotamers), 24.89 and 24.27 (due to rotamers), 24.21 and 24.14 (due to rotamers), 17.81 and 17.68 (due to rotamers), 14.16; IR (neat) 2840, 1720, 1700, 1650, 1485, 1455, 1435, 1405, 1380, 1330, 1295, 1270, 1255, 1200, 1155, 1115, 1100, 1085, 1030, 1015, 995, 965, 945, 810 cm^{-1}; HRMS calcd for $C_{21}H_{27}NO_4$ 357.1940, found 357.1939.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[1-(ethoxycarbonyl)methyl]quinoline (21). A solution of **19** (1.234 g, 3.47 mmol) in 30 mL of ethyl acetate was hydrogenated for 4 h at room temperature under balloon pressure in the presence of 0.617 g of 5% palladium on carbon. Filtration through Celite and removal of the solvent in vacuo resulted in 0.753 g (97%) of amine **21** as a grayish solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21–4.06 (m, 2 H), 2.94–2.68 (m, 2 H), 2.30–2.15 (m, 2 H), 2.05–1.30 (m, 13 H), 1.28–1.23 (t, 3 H, J = 7.33 Hz), 1.2–1.0 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 60.07, 54.84, 39.91, 39.72, 38.42, 37.74, 26.63, 26.27, 24.89, 24.63, 18.46, 14.13; IR (neat) 3320, 2930, 2850, 1725, 1465, 1445, 1370, 1275, 1215, 1170, 1110, 1070, 1030, 845 cm^{-1}; HRMS calcd for $C_{13}H_{23}NO_2$ 225.1729, found 225.1728.

***N*-[(Benzyloxy)carbonyl]-2-(*trans*-5-(ethoxycarbonyl)-4-pentenyl)-4-(triethylsilyloxy)-1,2-dihydropyridine (22).** Chlorotriethylsilane (0.16 mL, 0.974 mmol) was added to a solution of pure **9** (0.302 g, 0.812 mmol) in 10 mL of THF at –78 °C. Sodium bis(trimethylsilyl)amide (1.01 mL, 1.01 mmol), as a 1.0 M solution in THF, was added dropwise over a period of 1 h. The resulting solution was stirred at –78 °C for 1 additional hour. After being quenched with saturated aqueous $NaHCO_3$, the mixture was extracted with ether (2 × 30 mL), and the combined organic layers were washed with 30-mL portions of water and brine. After being dried over anhydrous K_2CO_3, the solution was filtered through Celite and concentrated in vacuo to yield 0.394 g (100%) of the desired silyl enol ether **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 7.00–6.85 (m, 1 H), 6.83–6.68 (dd, due to rotamers, 1 H, J = 7.33 Hz), 5.82–5.73 (dd, due to rotamers, 1 H, J = 15.4 Hz), 5.25–5.16 (s, 2 H), 5.14–5.02 (dd, due to rotamers, 1 H, J = 8.06 Hz), 4.90–4.65 (m, 2 H), 4.25–4.15 (q, 2 H), 2.25–2.00 (m, 2 H), 1.75–1.35 (m, 4 H), 1.30–1.25 (t, 3 H, J = 7.33 Hz), 1.0–0.95 (t, 9 H, J = 7.33 Hz), 0.70–0.65 (q, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.41 and 152.60 (due to rotamers), 148.40 and 148.18 (due to rotamers), 147.01 and 146.53 (due to rotamers), 135.58 and 135.41 (due to rotamers), 128.18, 127.89, 127.69, 127.05 and 126.01 (due to rotamers), 121.13, 106.76 and 106.43 (due to rotamers), 98.87 and 98.55 (due to rotamers), 76.39, 67.47, 59.72, 52.35, 34.55 and 33.90 (due to rotamers), 31.74 and 31.61 (due to rotamers), 22.59 and 22.43 (due to rotamers), 13.87, 6.21, 4.47; IR (neat) 3000, 2930, 2880, 2850, 1700, 1645, 1385, 1365, 1325, 1210, 1100 cm^{-1}; HRMS calcd for $C_{27}H_{39}NSiO_5$ 485.2598, found 485.2599.

***N*-[(Benzyloxy)carbonyl]-11-(ethoxycarbonyl)-2-azatricyclo[5.3.1.0^{3,8}]undecan-9-one (23).** A solution of silyl enol ether **22** (0.394 g, 0.812 mmol) in degased xylenes was refluxed for 6 consecutive days under an argon atmosphere. After concentration under reduced pressure, the crude Diels–Alder product was diluted with 50 mL of ether and hydrolyzed with 20 mL of aqueous 10% HCl at room temperature for 7 h. The organic layer was separated and washed with 20-mL portions of saturated $NaHCO_3$ and brine. After the organic layer was dried over anhydrous K_2CO_3, filtration through Celite and silica and concentration in vacuo provided 0.302 g (100%) of crude **23**. Purification by radial PLC (silica gel, 20–30% EtOAc/hexanes) gave 0.223 g (74%) of pure **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5 H), 5.25–5.11 (m, 2 H), 5.07–4.90 (m, 1 H), 4.21–4.13 (m, 2 H), 4.05–3.98 (bd, 1 H), 2.98–2.95 (t, 1 H, J = 3.66 Hz), 2.78–2.66 (bd, 1 H), 2.50–2.20 (m, 4 H), 1.80–1.48 (m, 5 H), 1.29–1.25 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.99 and 210.63 (due to rotamers), 171.79, 155.41 and 154.44 (due to rotamers), 136.26 and 136.03 (due to rotamers), 128.44, 128.02, 127.76 and 127.69 (due to rotamers), 67.31 and 67.05 (due to rotamers), 61.17, 51.83 and 51.67 (due to rotamers), 49.80 and 49.54 (due to rotamers), 48.99, 46.27 and 46.21 (due to rotamers), 40.78 and 40.52 (due to rotamers), 29.31 and 28.89 (due to rotamers), 28.38 and 27.95 (due to rotamers), 26.66, 14.61, 14.03; IR (neat) 2930, 2860, 1730, 1700, 1495, 1445, 1405, 1370, 1335, 1305, 1280, 1205, 1105, 1075, 1055, 1025, 970 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.89; H, 6.79; N, 3.77. Found: C, 67.68; H, 6.83; N, 3.66.

11-(Ethoxycarbonyl)-2-azatricyclo[5.3.1.0^{3,8}]undecan-9-one (24). A solution of **23** (0.188 g, 0.506 mmol) in 50 mL of ethyl acetate was hydrogenated at room temperature under balloon pressure in the presence of Li_2CO_3 (0.075 g, 1.01 mmol) and 0.132 g of 5% palladium on carbon for 12 h. Filtration through Celite and removal of the solvent in vacuo gave 0.116 g (96%) of amine **24** as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20–4.10 (m, 2 H), 3.76–3.73 (q, 1 H), 3.45–3.40 (bs, 1 H), 2.86–2.84 (t, 1 H, J = 3.66 Hz), 2.73–2.65 (bs, 1 H), 2.35–2.34 (d, 2 H, J = 2.93 Hz), 2.20–2.18 (t, 1 H, J = 2.56 Hz), 2.00–1.30 (m, 7 H), 1.28–1.23 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.34, 172.76, 60.78, 50.93, 49.15, 48.24, 46.60, 41.82, 30.31, 29.09, 28.34, 14.06; IR ($CDCl_3$) 2980, 2930, 2860, 1720, 1395, 1370, 1350, 1330, 1315, 1290, 1255, 1195, 1135, 1080, 1065, 1045, 1025 cm^{-1}; HRMS calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1361.

5α,6,7,8,9α,10α-Hexahydro-5-[1-(ethoxycarbonyl)methyl]-4-quinolone (25). To a stirred solution of amine **24** (0.064 g, 0.270 mmol) in 10 mL of THF at –78 °C was added diisopropylamine (0.38 mL, 2.70 mmol) followed by a THF solution of LDA (2.2 mL, 1.08 mmol). The resulting mixture was stirred at –78 °C for 4 h and quenched with cold saturated aqueous $NaHCO_3$. Once at room temperature, the mixture was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine and dried over anhydrous K_2CO_3. The dry organic extracts were filtered through Celite and concentrated in vacuo to yield 0.070 g of crude **25**. Purification by radical PLC (silica gel, 50% EtOAc/hexanes) gave 0.051 g (80%) of pure **25** as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.03 (t, 1 H, J = 6.96 Hz), 5.85–5.70 (bs, 1 H), 4.87–4.84 (d, 1 H, J = 7.33 Hz), 4.14–4.07 (q, 2 H), 3.65–3.61 (m, 1 H), 2.95–2.80 (m, 3 H), 2.15–1.30 (m, 7 H), 1.26–1.22 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.06, 173.76, 149.15, 98.61, 60.01, 54.84, 47.76, 37.74, 35.06, 27.37, 25.82, 22.88, 14.13; IR ($CHCl_3$) 3450, 3010, 2930, 2860, 1720, 1630, 1595, 1500, 1460, 1445, 1400, 1380, 1370, 1355, 1340, 1300, 1235, 1200, 1135, 1120, 1085, 1030 cm^{-1}; HRMS calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1363.

5α,6,7,8,9α,10α-Hexahydro-1-[(benzyloxy)carbonyl]-5-[1-(ethoxycarbonyl)methyl]-4-quinolone (26). A THF solution of LDA (1.9 mL, 0.190 mmol) was added to a stirred solution of ester **25** (0.041 g, 0.173 mmol) in 8 mL of THF at –78 °C. After this mixture was stirred at –78 °C for 30 min, benzyl chloroformate (0.03 mL, 0.225 mmol) was added dropwise. Continuous stirring at –78 °C for an additional 2 h was followed by quenching with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous K_2CO_3, and filtered through Celite. Concentration in vacuo and purification by radial PLC (silica gel, hexanes–5–30% EtOAc/hexanes) gave 0.064 g (100%) of **26** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.50 (bs, 1 H), 7.48–7.30 (m, 5 H), 5.30–5.10 (m, 3 H), 4.55–4.35 (bs, 1 H), 4.15–4.07 (q, 2 H), 3.05–3.02 (t, 1 H, J = 4.4 Hz), 3.01–2.93 (dd, 1 H, J = 7.33, 16.86 Hz), 2.83–2.75 (dd, 1 H, J = 7.33, 16.86 Hz), 2.05–1.95 (bs, 1 H), 1.85–1.35 (m, 6 H), 1.26–1.21 (t, 3 H, J = 7.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.06, 173.41, 151.70, 140.07 and 139.16 (due to rotamers), 135.03, 128.69, 128.31, 107.47 and 107.08 (due to rotamers), 68.83, 60.13, 56.90, 47.08, 38.71, 36.06, 29.64, 26.86, 24.63, 14.19; IR (neat) 3090, 3070, 3030, 2930, 2860,

1725, 1665, 1610, 1485, 1450, 1420, 1385, 1330, 1295, 1270, 1250, 1195, 1140, 1125, 1090, 1035, 955, 915, 860, 820 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.89; H, 6.79; N, 3.77. Found: C, 67.76; H, 6.83; N, 3.69.

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Registry No. **5**, 620-08-6; (±)-**7**, 141584-00-1; (±)-**8**, 141584-01-2; (±)-**9**, 141584-02-3; **10**, 141584-03-4; (±)-**11**, 141584-04-5; (±)-**12**, 141660-71-1; (±)-**13**, 141660-72-2; (±)-**18** (R = H), 141584-05-6; (±)-**18** (R = TMS), 141584-06-7; (±)-**19**, 141584-07-8; (±)-**20**, 141584-08-9; (±)-**21**, 141584-09-0; (±)-**22**, 141584-10-3; (±)-**23**, 141584-11-4; (±)-**24**, 141584-12-5; (±)-**25**, 141584-13-6; (±)-**26**, 141584-14-7; (±)-EEO$(CH_2)_4$Cl, 116725-73-6.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **7**, **8**, **11**, **13**, **19**, **21**, **22**, **24**, and **25** (18 pages). This material is contained in many 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.

Stereospecific Total Syntheses of Decahydroquinoline Alkaloids (±)-195A and (±)-2-*epi*-195A[1]

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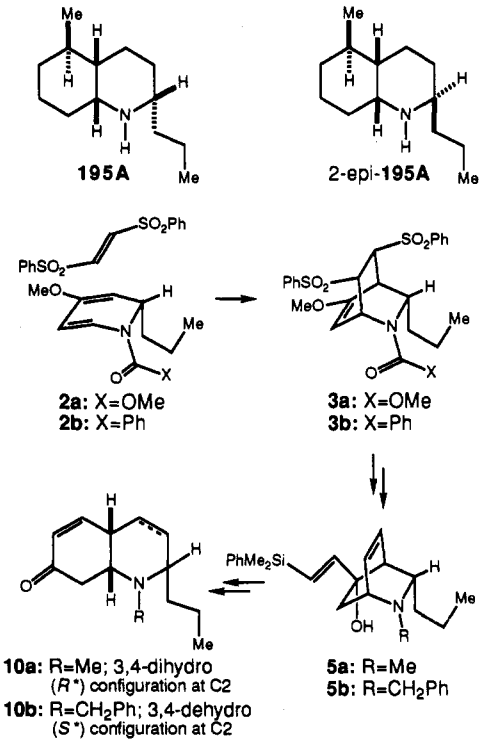
The total syntheses of decahydroquinoline alkaloids (±)-**195A** (pumiliotoxin C) and (±)-2-*epi*-**195A** are described. An unexpected, *stereospecific* epimerization of the C2 stereocenter of intermediate **6a** occurred during its reduction. The isomerization resulted in ultimate production of 2-*epi*-**195A**. The stereochemical relationship of the C2, C4a, C5, and C8a stereocenters in 2-*epi*-**195A** is common to other decahydroquinoline alkaloids and gephyrotoxin. The 2-*epi*-**195A** synthesis demonstrated the viability of an *N*-Me group as a nitrogen protecting group. Alkaloid **195A** was prepared in 5.0% overall yield by minor modification of the protocol established in the 2-*epi*-**195A** synthesis.

Substituted, functionalized derivatives of the cis-fused decahydroquinoline ring system occur as discrete natural products[2,3] or as subunits[4] of natural products. We have developed a general strategy with which to prepare decahydroquinoline alkaloids and describe herein the total syntheses of alkaloid **195A** (pumiliotoxin C)[3,5] and 2-*epi*-**195A**. The key element of our strategy involved establishing the cis-fused hydroquinoline ring via a [3,3] sigmatropic rearrangement[6] of isoquinuclidines[7] **5a** and **5b**. Controlled functionalization of enones **10a** and **10b** via the principal of convex face attack then afforded both **195A** (from **10b**) and 2-*epi*-**195A** (from **10a**).

Treatment of 4-methoxypyridine[8] with methyl chloroformate (Scheme I) formed an intermediate *N*-acylpyridinium ion which was intercepted with *n*-propylmagnesium chloride.[9] The resultant *N*-acyl-1,2-dihydropyridine[10] **2a** engaged in a stereospecific Diels–Alder reaction[11] with (*E*)-bis(phenylsulfonyl)ethylene.[12] We reason that the substrate **2a** assumed a conformation which placed the C2 propyl substituent in an orientation which is perpendicular to the plane defined by the heterocycle in order to minimize A1,3 strain.[13] The dienophile then attacked the least hindered face of the diene. Methanol was added across the enol ether moiety of **3a**, the sulfone moieties of the resultant ketal were then reductively eliminated,[12] and the urethane moiety of the resultant olefin was reduced with lithium aluminum hydride.[14] Aqueous hydrolysis of the amino acetal **4a** afforded the



corresponding ketone, which underwent a stereospecific carbonyl addition reaction with (*E*)-2-(phenyldimethyl-

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(1) Dedicated to the late Robert V. Stevens, a dearly missed colleague and friend.

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