Model Studies toward the Synthesis of the *Lycopodium* Alkaloid, Phlegmarine

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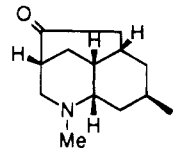
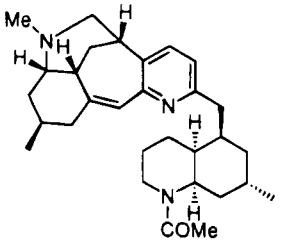
Model studies were carried out toward the preparation of *Lycopodium* alkaloids, i.e. the phlegmarines, which contain a *trans*-decahydroquinoline ring system. The target decahydroquinoline derivative **6** was synthesized stereoselectively in eight steps. The keto aldehyde **10**, prepared in three steps from 4-methoxypyridine, was subjected to an acid-catalyzed Robinson annulation reaction to give bicyclic enone **11**. Copper-mediated 1,4-addition of [(dimethylphenylsilyl)methyl]magnesium chloride and in situ trapping with *N*-(5-chloro-2-pyridyl)triflimide provided vinyl triflate **12**. Conversion to olefin **16** and subsequent hydrolysis gave amine **20**. Stereoselective hydrogenation of **20** over palladium on carbon yielded the *trans*-decahydroquinoline **6** and its cis isomer **21** in a ratio of 89:11. Arguments involving $A^{(1,3)}$ strain are given to explain the observed stereoselectivity.

The *Lycopodium* alkaloids are numerous, contain various structural types, and provide challenging targets for total synthesis.[1] We have previously described an intramolecular Diels–Alder/retro-Mannich approach to the *cis*-decahydroquinoline ring system,[2] which is present in certain *Lycopodium* alkaloids such as luciduline (**1**) and lycolucine (**2**). In 1978, Nyembo and co-workers isolated the *Lycopodium* alkaloid, phlegmarine (**3a**), and several of its derivatives **3b–d**.[3] Unlike most other *Lycopodium* alkaloids, the phlegmarines were shown to possess a *trans*-decahydroquinoline unit in their skeleton rather than the usual cis arrangement.[4] Initial model studies



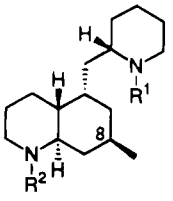
1

luciduline



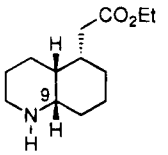
2

lycolucine



3a:	R^1= H, R^2= H	phlegmarine
b:	R^1= H, R^2= Me	Nβ-methylphlegmarine
c:	R^1= Me, R^2= H	Nα-methylphlegmarine
d:	R^1= COMe, R^2= Me	Nα-acetyl-Nβ-methyl-phlegmarine

directed at developing a strategy for the synthesis of phlegmarines involved investigating methods for converting *cis*-decahydroquinoline **4**[2] to its trans isomer **5**. Efforts at inverting the stereochemistry at C-9 of **4** via imine[5] or nitrone[6] formation, followed by dissolving metal reduction,[7] met with little success resulting from poor regioselectivity and/or yield. Although our Diels–Alder/retro-Mannich strategy[2] is attractive for pursuing *Lycopodium* alkaloids containing the *cis*-decahydroquinoline ring system, we decided to develop a new approach to the phlegmarines that would allow a more direct incorporation of the trans stereochemistry at the perhydroquinoline ring juncture. With this goal in mind, model studies were undertaken to prepare decahydroquinoline derivative **6**.



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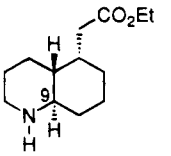

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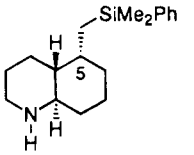

6

Results and Discussions

Our plan for synthesizing **6** centered on the construction of key bicyclic intermediate **11**, which was prepared from 4-methoxypyridine in four steps utilizing *N*-acylpyridinium salt chemistry previously developed in these laboratories (Scheme 1).[8] Addition of the Grignard of 5-bromo-1-pentene to an *N*-acylpyridinium salt, prepared in situ from 4-methoxypyridine (**7**)and methyl chloroformate, gave on acidic aqueous workup 2,3-dihydro-4-pyridone **8** in 93% yield. Conjugate reduction of enone **8** was effected using L-Selectride in THF at −23 °C to

[⊗] Abstract published in *Advance ACS Abstracts*, January 15, 1995.

(1) (a) Ayer, W. A.; Trifonov, L. S. *The Alkaloids*; Cordell, G. A.; Brossi, A., Eds.; Academic Press: San Diego, 1994; Vol. 45, pp 233–274. (b) Blumenkopf, T. A.; Heathcock, C. H. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185–240. (c) Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1984**, 1519. (d) Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1979**, *57*, 1631.

(2) (a) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098. (b) Comins, D. L; Abdullah, A. H.; Smith, R. K. *Tetrahedron Lett.* **1983**, *24*, 2711.

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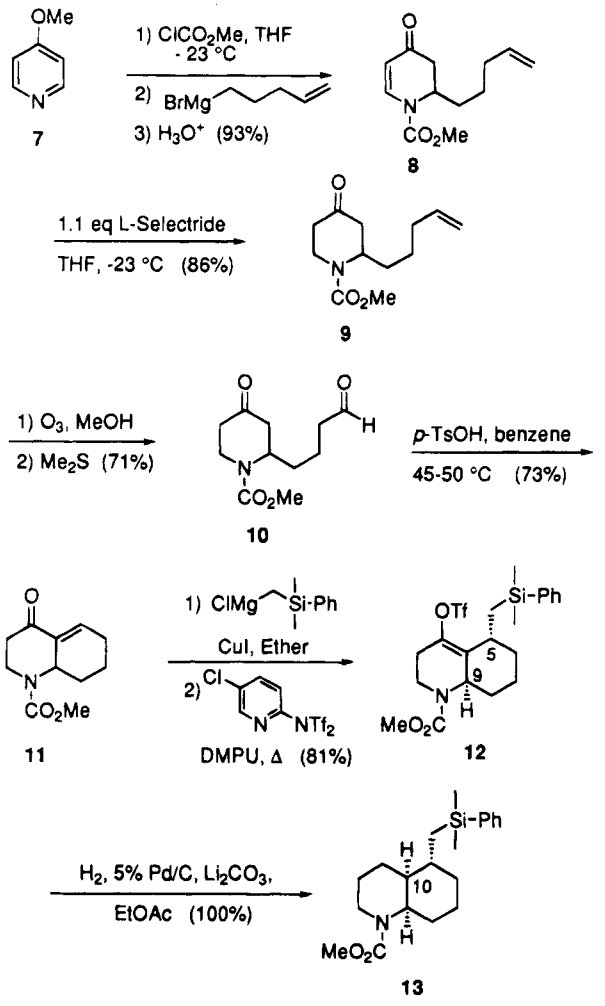
Scheme 1



give an 86% yield of tetrahydropyridone **9**.[9] Ozonolysis of the terminal double bond followed by reductive workup with methyl sulfide provided keto aldehyde **10** in 71% yield. Intramolecular aldol condensation using *p*-toluenesulfonic acid in benzene at 50 °C resulted in a 73% yield of the target bicyclic enone **11**.

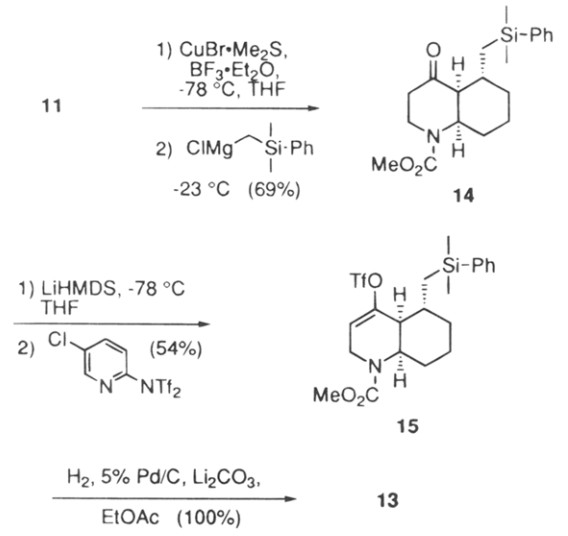
Transformation of enone **11** to vinyl triflate **12** proved to be more challenging than anticipated. Preparation of the Grignard of (chloromethyl)dimethylphenylsilane and its copper-mediated 1,4-addition to enone **11** gave the desired enolate in situ, but simple addition of the triflating reagent, *N*-(5-chloro-2-pyridyl)triflimide,[9a] failed to yield vinyl triflate **12**. Addition of DMPU followed by heating at reflux was necessary to trap the resulting enolate and give **12** in 81% yield.[10,11] The stereochemistry at C-5 was assigned as shown based on previous results from our synthesis of pumiliotoxin C,[12] whereby the key step involved 1,4-addition of lithium dimethylcuprate to the respective bicyclic enone in the presence of boron trifluoride etherate. Even though the use of boron trifluoride etherate is known to affect stereoselectivity in 1,4-additions,[13] we predicted the analogous stereochemical outcome in our conversion of **11** to the vinyl triflate **12** due to the concave shape of our starting enone and stereoelectronic requirements; stereoelectronically preferred axial attack at C-5 by the incoming cuprate would lead to the desired product.[14]

The final stereogenic center at C-10 was to be introduced stereoselectively via catalytic hydrogenation. Our initial attempts at reducing the vinyl triflate **12** involved mild catalytic hydrogenation over platinum on carbon, or platinum oxide, since these two catalysts are known to be effective in olefin reductions while minimizing double bond migration.[15] Under these mild conditions, reduction of an aromatic ring would not be anticipated. Much to our surprise, the crude product from these hydrogenations using Li_2CO_3 as a buffer showed some reduction of the phenyl group, which must be attributed to activation of the phenyl ring by the silicon atom. We then resorted to palladium on carbon as a substitute catalyst to possibly prevent the undesired phenyl ring reduction. The hydrogenation of **12** was accomplished in ethyl acetate using 5% palladium on carbon in the presence of Li_2CO_3 as an acid scavenger to give carbamate **13** in quantitative yield. Initially, we were uncertain of the stereochemistry at the ring junction, but on comparing the ^1H NMR spectrum of **13** with corresponding spectra of the *N*-benzylcarbamates of *cis*- and *trans*-decahydroquinoline, it appeared that our substrate contained the cis arrangement. We looked specifically at the three deshielded protons next to nitrogen and found that their splitting patterns and chemical shifts correlated with a cis ring fused decahydroquinoline.

Although an X-ray structure would have been the ideal method for confirming the suggested relative stereochemistry at the three stereogenic centers, none of the key intermediates was a solid. We therefore set out to confirm the stereochemistry chemically by preparing the cis fused carbamate **13** via a different route, as depicted in Scheme 2. Starting with enone **11**, a cuprate addition was performed in the presence of boron trifluoride etherate, and the resulting enolate was quenched with methanol to yield ketone **14** in 69% yield. The relative stereochemistry was assigned as shown, again based on previous NMR data from the synthesis of pumiliotoxin

(3) Nyembo, L.; Goffin, A.; Hootele, C.; Braekman, J.-C. *Can. J. Chem.* **1978**, *56*, 851.
(4) (a) Leniewski, A.; Szychowski, J.; MacLean D. B. *Can. J. Chem.* **1981**, *59*, 2479. (b) Leniewski, A.; MacLean D. B.; Saunders, J. K. *Ibid.* **1981**, *59*, 2695.
(5) Bartsch, R. A.; Bracken, G. J.; Yilmaz, I. *Tetrahedron Lett.* **1979**, 2109.
(6) (a) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736. (b) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383. (c) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633. (d) Mitsui, H.; Zenki, S.-I.; Shiota, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1984**, 874.
(7) (a) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2734. (b) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
(8) (a) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199 and references cited therein. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053. (d) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (e) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919.
(9) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *42*, 6299. (b) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444 and references cited therein.
(10) A moderate yield of vinyl triflate was reported from reaction of the magnesium enolate of 2-methylcyclohexanone with *N*-phenyltriflimide in ether/HMPA at reflux, see: Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.
(11) For reviews on vinyl triflates, see: (a) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107–114. (b) Stang, P. J.; Hanack M.; Subramanian, L. R. *Synthesis* **1982**, 85–126. (c) Ritter, K. *Synthesis* **1993**, 735–762.
(12) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (b) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838.
(13) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992.
(14) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.
(15) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979.

Scheme 2



C, which was accomplished in these laboratories using a similar approach.[12] Reductive removal of the ketone was accomplished in two steps. Formation of the kinetic enolate using lithium bis(trimethylsilyl)amide at −78 °C, followed by trapping using a pyridyltriflimide,[9a] gave the less substituted vinyl triflate **15** in 54% yield. This was in turn reduced by catalytic hydrogenation using our previous conditions to yield carbamate **13** in quantitative yield. Since the ^{1}H NMR of **13** correlated with the spectrum of the compound from our previous route (Scheme 1), and quantitative olefin migration prior to reduction considered highly unlikely, the relative stereochemistry of the molecule was confirmed.

It was not immediately obvious why the cis ring fused product was obtained exclusively on reduction of **12**. We had hoped the large axial substituent at C-5 would block the "bottom" side of **12** causing hydrogenation to preferentially occur from the top face giving the desired trans ring junction. But when MMX calculations[16] were carried out on vinyl triflate **12**, a low energy conformation depicted in Figure 1 was obtained. Due to $A^{(1,3)}$ strain, the shape of the molecule is concave and the large C-5 substituent is pushed away from the under face of the alkene, providing an explanation as to why hydrogenation occurs solely from its convex face leading to the cis product. Therefore, we decided to remove the $A^{(1,3)}$ strain caused by the *N*-acyl group so that the molecule would flatten and the axial C-5 substituent would move to a more favorable position to direct catalytic hydrogenation from the desired face.

It soon became obvious that the methyl carbamate of substrate **12** could not be easily cleaved in the presence of the vinyl triflate, so the trifluromethanesulfonyloxy group was removed from the olefin. We chose to utilize Cacchi's method for the reduction of enol triflates to alkenes.[17] The palladium-catalyzed reduction of **12** (Scheme 3) using bis(triphenylphosphine)palladium acetate, tri-*n*-butylamine, and formic acid in DMF at 60 °C gave alkene **16** in 93% yield. In our initial attempt at removing the $A^{(1,3)}$ strain from the molecule, we opted to reduce the methyl carbamate of alkene **16** using

(16) Molecular modeling was performed using PCMODEL (Serena Software, Bloomington, IN) and Chem3D (Cambridge Scientific Computing, Inc., Cambridge, MA).

(17) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821.

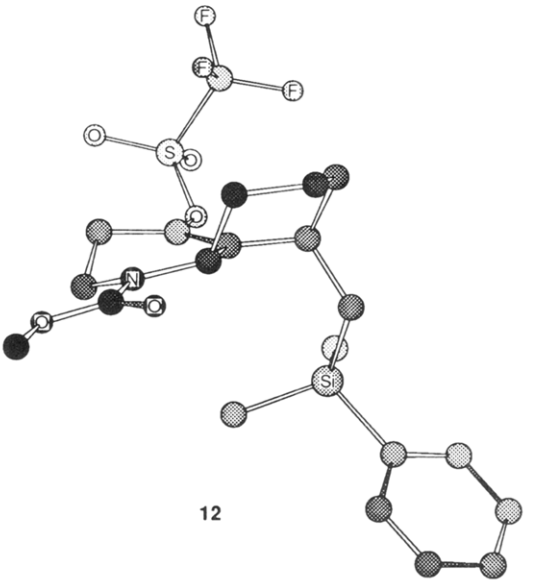
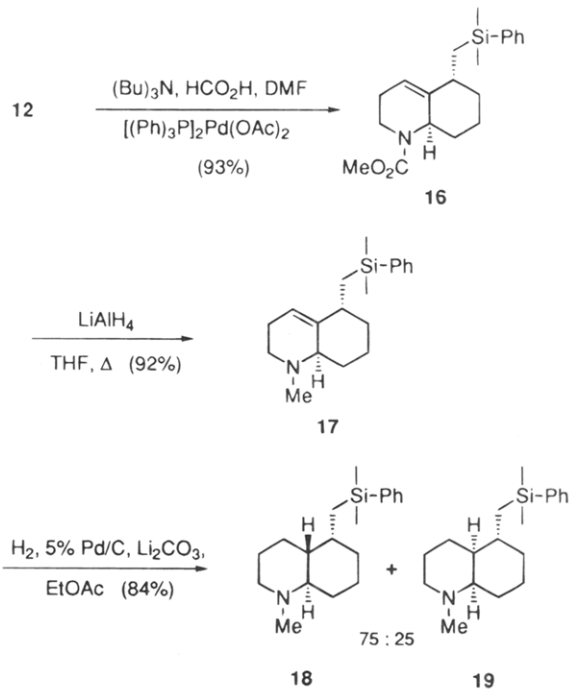


Figure 1. Structure derived from molecular mechanics (MMX).

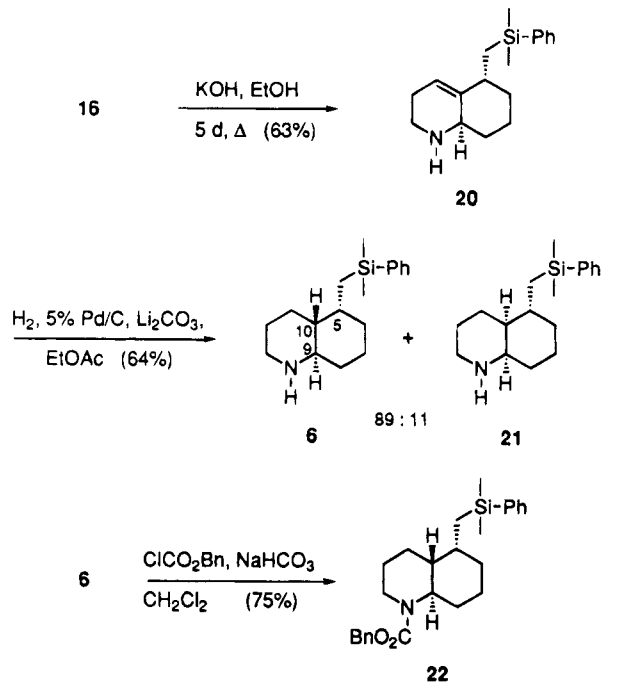
Scheme 3



$LiAlH_4$ under refluxing conditions, thus obtaining tertiary amine **17** in 92% yield. When this amine was subjected to catalytic hydrogenation over palladium on carbon in the presence of lithium carbonate, two products resulted that were easily separated by chromatography. Analysis of the crude mixture by GC showed a 75:25 ratio of trans amine **18** and cis amine **19** as was later confirmed by ^{1}H NMR.

The reversal of the stereoselectivity in favor of the trans product observed from the hydrogenation of substrate **17** confirmed that $A^{(1,3)}$ strain caused by the carbamate group of **12** was creating an unfavorable conformation for the desired stereoselective reduction. In order to carry on our studies, we chose to hydrolyze the methyl carbamate of **16** to amine **20** (Scheme 4). This was accomplished in 63% yield using a concentrated solution of potassium hydroxide in ethanol under reflux

Scheme 4



for 5 days. The resulting alkene **20** was then subjected to catalytic hydrogenation over 5% palladium on carbon in the presence of Li_2CO_3 to give the trans and cis amines **6** and **21** in an 89 to 11 ratio as was determined by GC. Hence, the stereoselectivity improved significantly over our previous reduction of *N*-methyl substrate **17**, a result which is likely due to a further flattening of the molecule. The two diastereomers **6** and **21** were separated by chromatography, and the pure trans amine **6** was treated with benzyl chloroformate in the presence of $NaHCO_3$ in CH_2Cl_2 to give a 75% yield of carbamate **22**.

As before, comparison of the ^1H NMR spectrum of our trans ring fused compound **22** to the spectrum of *trans*-*N*-(benzyloxycarbonyl)decahydroquinoline indicated the stereochemistry shown. The relative stereochemistry at the three contiguous stereogenic centers was later confirmed from the X-ray structure of the hydrochloride salt of trans amine **6**.[18]

In summary, a new strategy for the synthesis of *trans*-decahydroquinoline derivatives has been developed that should be amenable to the preparation of certain *Lycopodium* alkaloids such as the phlegmarines **3**. This approach is particularly attractive as the three contiguous stereocenters of **6** are formed with a high degree of stereocontrol, the C-8 methyl group of **3** can be introduced into the ring system by using the appropriately substituted homochiral Grignard reagent in the first step, absolute stereocontrol can be achieved by incorporating our recently developed asymmetric synthesis of 2,3-dihydro-4-pyridones,[19] and the dimethylphenylsilylmethyl group at C-5 can be utilized as a handle for further elaboration to the phlegmarine alkaloids.

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. NMR spectra were recorded on Varian Gemini 300 MHz and GN 300 instruments in $CDCl_3$ using tetramethylsilane as internal standard. Capillary GC was performed on an HP 5890 using an FID detector on a J & W Scientific DB17 column (30 m × 0.25 mm) at oven temp = 220 °C. 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.

1-(Methoxycarbonyl)-2-(4-pentenyl)-2,3-dihydro-4-pyridone (8). A solution of 5-bromo-1-pentene (1.3 mL, 11.0 mmol) and 1,2-dibromoethane (0.19 mL, 2.2 mmol) in 10 mL of THF was added via a double-tipped needle to magnesium turnings (0.80 g, 33.0 mmol) in 10 mL of THF. The temperature during the addition was controlled using an ice/water bath. The resulting mixture was stirred at rt for 1 h and at reflux for 1.5 h. To a stirred solution of 4-methoxypyridine **6** (1.0 mL, 9.9 mmol) in 40 mL of THF at −23 °C was added methyl chloroformate (0.66 mL, 4.6 mmol) dropwise. The resulting salt was stirred at −23 °C for 1 h before the dropwise addition of the Grignard reagent via a double-tipped needle. The resulting mixture was stirred at −23 °C for 1.5 h and at rt for 0.5 h. The solution was poured into 50 mL of aqueous 10% HCl and stirred at rt 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, 20% EtOAc/hexanes) gave 2.045 g (93%) of dihydropyridone **8** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76−7.73 (bd, 1 H, J = 7.33 Hz), 5.82−5.68 (m, 1 H), 5.33−5.31 (d, 1 H, J = 8.06 Hz), 5.05−4.92 (m, 2 H), 4.65−4.54 (bm, 1 H), 3.88 (s, 3 H), 2.85−2.77 (dd, 1 H, J = 16.87, 6.6 Hz), 2.49−2.43 (d, 1 H, J = 16.87 Hz), 2.08−2.01 (q, 2 H), 1.70−1.60 (m, 2 H), 1.55−1.25 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 152.8, 141.3, 137.6, 114.8, 106.7, 53.7, 52.9, 39.4, 33.0, 29.5, 24.5; IR (neat) 3080, 2930, 2860, 1730, 1670, 1600, 1440, 1335, 1270, 1230, 1190, 1115, 1065 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.68; N, 6.28. Found: C, 64.67; H, 7.73; N, 6.27.

1-(Methoxycarbonyl)-2-(4-pentenyl)-2,3,5,6-tetrahydro-4-pyridone (9). L-Selectride (8.2 mL, 8.20 mmol), as a 1 M solution in THF, was added to a solution of dihydopyridone **8** (1.664 g, 7.45 mmol) in 45 mL of THF at −23 °C. The resulting mixture was stirred at −23 °C for 2.5 h and allowed to warm up to rt. The solution was poured into 100 mL of saturated aqueous $NaHCO_3$ at 0 °C. 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 K_2CO_3, filtered through Celite and silica, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 5−30% EtOAc/hexanes) gave 1.451 g (86%) of tetrahydropyridone **9** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.82−5.68 (m, 1 H), 5.05−4.92 (m, 2 H), 4.75−4.52 (bs, 1 H), 4.48−4.25 (bs, 1 H), 3.76 (s, 3 H), 3.24−3.14 (dt, 1 H, J = 3.67, 13.93 Hz), 2.68−2.61 (dd, 1 H, J = 6.6, 13.94 Hz), 2.54−2.43 (m, 1 H), 2.40−2.25 (m, 2 H), 2.15−1.95 (m, 2 H), 1.60−1.20 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 155.7, 137.8, 114.8, 52.6, 51.8, 45.2, 40.3, 38.0, 32.8, 31.2, 24.5; IR (neat) 3080, 2930, 2860, 1700, 1635, 1445, 1410, 1365, 1340, 1310, 1225, 1185, 1115 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.96; H, 8.51; N, 6.22. Found: C, 63.95; H, 8.52; N, 6.12.

1-(Methoxycarbonyl)-2-(3-formylpropyl)-2,3,5,6-tetrahydro-4-pyridone (10). A solution of alkene **8** (1.585 g, 7.04 mmol) in 60 mL of methanol was cooled to −78 °C, and ozone was bubbled through the solution until a blue color persisted. While still at −78 °C, argon was bubbled through until the excess ozone was removed and the blue color disappeared. To the −78 °C solution was added 10 mL of dimethyl sulfide. The resulting solution was warmed to rt, stirred for 36 h, and

(18) The authors have deposited atomic coordinates for **6**·HCl with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(19) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719 and references cited therein.

subsequently concentrated in vacuo to yield crude aldehyde **10** as a yellow oil. Purification by radial PLC (silica gel, 5–40–50% EtOAc/hexanes) gave 1.113 g (70%) of aldehyde **10** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76–9.75 (t, 1 H, J = 1.47 Hz), 4.75–4.52 (bs, 1 H), 4.48–4.25 (bs, 1 H), 3.76 (s, 3 H), 3.27–3.18 (dt, 1 H, J = 13.93, 3.67 Hz), 2.71–2.64 (dd, 1 H, J = 14.67, 6.6 Hz), 2.60–2.25 (m, 5 H), 1.75–1.40 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 201.5, 155.8, 52.8, 51.7, 45.2, 42.7, 40.3, 38.1, 31.2, 17.7; IR (neat) 2950, 2730, 1700, 1445, 1410, 1365, 1345, 1310, 1240, 1185, 1115, 1075 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.12; H, 7.54; N, 6.17. Found: C, 58.22; H, 7.59; N, 6.07.

2,3,6,7,8,8a-Hexahydro-1-(methoxycarbonyl)-4-quinolone (11). Solid *p*-toluenesulfonic acid monohydrate (0.349 g, 1.83 mmol) was added to a solution of aldehyde **10** (0.417 g, 1.83 mmol) in 25 mL of benzene, and the mixture was stirred at 50 °C for 2 h. The solution was allowed to cool to rt and was carefully quenched with 25 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite and silica, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 5–30–40% EtOAc/hexanes) gave 0.280 g (73%) of enone **11** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74–6.71 (m, 1 H), 4.59–4.53 (m, 1 H), 4.30–4.24 (dd, 1 H, J = 3.67, 13.93 Hz), 3.75 (s, 3 H), 3.17–3.07 (dt, 1 H, J = 3.67, 13.93 Hz), 2.60–2.20 (m, 5 H), 1.95–1.63 (m, 2 H), 1.53–1.38 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 155.4, 139.0, 136.4, 52.4, 52.0, 39.8, 37.5, 27.2, 25.1, 19.9; IR (neat) 2950, 2870, 1690, 1620, 1460, 1440, 1400, 1365, 1345, 1310, 1250, 1210, 1185, 1140, 1110, 1020 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1062.

(5*S,8a*R**)-1,2,3,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]-1-(methoxycarbonyl)-4-[(trifluoromethanesulfonyl)oxy]quinoline (12).** To magnesium turnings (0.229 g, 9.40 mmol) in 10.0 mL of THF were added (chloromethyl)dimethylphenylsilane (6.5 mL, 1.20 mmol) and 1,2-dibromoethane (0.25 mL, 2.86 mmol). The resulting mixture was heated at reflux for 1 h and then cooled to rt. It was added dropwise via a double-tipped needle to a 0 °C solution of copper(I) iodide in 8.0 mL of anhydrous diethyl ether. Enone **11** (0.288 g, 1.38 mmol) in 10 mL of anhydrous diethyl ether was added dropwise to the mixture via a double-tipped needle. The resulting mixture was stirred at 0 °C for 0.5 h and at rt for 2.5 h. Solid *N*-(5-chloro-2-pyridyl)triflimide[9a] (2.552 g, 6.50 mmol) was added followed by DMPU (2.4 mL, 19.5 mmol), and the resulting solution was heated at reflux for 21 h. The mixture was cooled to 0 °C and carefully quenched with 40 mL of aqueous 25% NH_4OH. The layers were separated, and the aqueous phase was extracted with ether (4 × 25 mL). The combined organic layers were washed with water and 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, 5% EtOAc/hexanes) gave 0.548 g (81%) of vinyl triflate **12** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.30 (m, 5 H), 4.75–4.35 (m, 1 H), 4.30–3.95 (m, 1 H), 3.73 (s, 3 H), 3.30–3.20 (m, 1 H), 3.10–2.90 (bt, 1 H, J = 10.27 Hz), 2.40–1.30 (m, 8 H), 1.20–1.00 (m, 2 H), 0.32–0.30 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 138.8, 137.0, 135.1, 133.4 128.8, 127.6, 120.3, 116.1, (124.5, 120.3, 116.1, 111.8) (CF_3), 52.7, 50.2, 37.3, 32.4, 31.5, 29.6, 27.6, 19.2, 18.4, −2.5, −3.4; IR (neat) 3070, 2920, 2835, 1705, 1445, 1405, 1370, 1345, 1330, 1315, 1210, 1140, 1110, 1090, 1050, 1000 cm^{-1}; HRMS calcd for $C_{21}H_{28}F_3NO_5SSi$ 492.1488, found 492.1488.

(4a*S,5*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[(dimethylphenylsilyl)methyl]-1-(methoxycarbonyl)quinoline (13).** A solution of vinyl triflate **12** (0.0508 g, 0.103 mmol) in 6.0 mL of ethyl acetate was hydrogenated at rt under balloon pressure in the presence of Li_2CO_3 (0.0153 g, 0.207 mmol) and (0.040 g) of 5% Pd/C for 2 d. Filtration through Celite and removal of the solvent in vacuo gave crude **13**. Purification by radial PLC (silica gel, 5–20% EtOAc/hexanes) gave 0.0350 g (98%) of **13** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.30 (m, 5 H), 4.50–4.10 (bs, 1 H), 4.08–3.80 (bs, 1 H), 3.68 (s, 3 H), 2.83–2.73 (dt, 1 H, J = 2.2, 13.2 Hz), 1.85–0.85 (m, 14 H), 0.28–0.27 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 139.4, 133.4, 128.7, 127.6, 52.3, 49.1, 42.4, 39.1, 35.5, 26.5, 25.8, 25.4, 23.9, 19.9, 19.7, −2.5, −2.6; IR (neat) 3080, 3050, 2930, 2870, 1700, 1440, 1425, 1410, 1365, 1325, 1300, 1285, 1260, 1250, 1210, 1185, 1165, 1145, 1110, 1045 cm^{-1}; HRMS calcd for $C_{20}H_{31}NO_2Si$ 345.2124, found 345.2123.

(4a*S,5*S**,8a*R**)-1,2,4a,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]-1-(methoxycarbonyl)-4-quinolone (14).** (Chloromethyl)dimethylphenylsilane (0.15 mL, 0.793 mmol) and 1,2-dibromoethane (0.02 mL, 0.24 mmol) were added to magnesium turnings (0.0243 g, 1.00 mmol) in 2.0 mL of THF, and the resulting mixture was heated at reflux for 3.5 h. To a −78 °C solution of enone **11** (0.035 g, 0.167 mmol) and copper bromide dimethyl sulfide complex (0.1375 g, 0.669 mmol) in 3.0 mL of THF was added boron trifluoride etherate (0.10 mL, 0.836 mmol). The resulting mixture was stirred at −78 °C for 1.5 h. The Grignard reagent was diluted with 3.0 mL of THF and was added dropwise to the −78 °C enone/boron trifluoride complex over a period of 1 h. The resulting solution was stirred an additional 1.5 h at −78 °C and overnight at −23 °C before quenching with 1.0 mL of methanol. The solution was warmed to rt, and 20 mL of aqueous 25% NH_4-OH:25% NH_4Cl (50:50) solution was added. The layers were separated, and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite and silica, and concentrated in vacuo to yield the crude product. Purification by radial PLC (silica gel, 5–20% EtOAc/hexanes) gave 0.0413 g (69%) of ketone **14** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.30 (m, 5 H), 4.70–4.44 (bs, 1 H), 4.18–3.96 (bs, 1 H), 3.75 (s, 3 H), 3.40–3.31 (m, 1 H), 2.78–2.65 (m, 1 H), 2.42–2.20 (m, 3 H), 1.80–1.10 (m, 6 H), 0.98–0.80 (m, 2 H), 0.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 155.7, 139.2, 133.3, 128.9, 127.8, 55.4, 52.8, 51.0, 40.0, 39.0, 28.9, 27.6, 27.4, 19.5, 18.6, −2.5, −3.0; IR (neat) 3070, 3050, 2940, 2870, 1700, 1445, 1425, 1400, 1365, 1305, 1280, 1245, 1190, 1110 cm^{-1}; HRMS calcd for $C_{20}H_{29}NO_3Si$ 359.1917, found 359.1894.

(4a*S,5*S**,8a*R**)-1,2,4a,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]-1-(methoxycarbonyl)-4-[(trifluoromethanesulfonyl)oxy]quinoline (15).** Lithium bis(trimethylsilyl)amide (0.13 mL, 0.13 mmol), as a 1 M solution in THF, was added dropwise to a −78 °C solution of ketone **14** (0.041 g, 0.114 mmol) in 6.0 mL of THF. Following 2 h of stirring at −78 °C, *N*-(5-chloro-2-pyridyl)triflimide[9a] (0.094 g, 0.24 mmol) was added and stirring was continued for an additional 3 h. The reaction was quenched with 5 mL of water, and the organic layer was separated and washed with water (2 × 5 mL). The organic layer was finally washed with brine, dried over anhydrous K_2CO_3, filtered through Celite and silica, and concentrated in vacuo to yield 0.048 g of crude **15**. Purification by radial PLC (silica gel, 5–20% EtOAc/hexanes) gave 0.0304 g (54%) of vinyl triflate **15** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.30 (m, 5 H), 5.80–5.60 (bs, 1 H), 4.75–4.25 (m, 2 H), 3.72 (s, 3 H), 3.65–3.60 (bs, 1 H), 2.70–2.60 (bs, 1 H), 2.55–2.45 (m, 1 H), 1.70–1.00 (m, 6 H), 0.91–0.84 (dd, 2 H, J = 5.86, 14.66 Hz), 0.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 148.2 and 147.8 (due to rotamers), 138.8, 133.4, 129.0, 127.8, (124.8, 120.5, 116.3, 112.0) (CF_3), 115.2 and 114.8 (due to rotamers), 52.8, 47.8 and 47.7 (due to rotamers), 44.6, 39.5, 29.4, 26.1, 25.1 and 24.6 (due to rotamers), 18.7, 18.4, −2.7, −2.8; IR (neat) 3020, 2940, 2860, 1695, 1450, 1415, 1365, 1325, 1310, 1270, 1245, 1215, 1140, 1110, 1070, 1050 cm^{-1}.

Reduction of 15 to 13. A solution of vinyl triflate **15** (0.0106 g, 0.0217 mmol) in 4.0 mL of ethyl acetate was hydrogenated for 1 d under balloon pressure in the presence of Li_2CO_3 (0.0032 g, 0.0431 mmol) and 0.02 g of 5% Pd/C. Filtration through Celite and removal of the solvent in vacuo gave 0.0075 g (100%) of crude **13**.

(5*S,8a*R**)-1,2,3,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]-1-(methoxycarbonyl)quinoline (16).** To a mixture of triflate **12** (0.203 g, 0.413 mmol), tributylamine (0.29 mL, 1.24 mmol), bis(triphenylphosphine)palladium acetate (0.015 g, 0.020 mmol) in 1.0 mL of DMF was added formic acid (0.03 mL, 0.824 mmol). The resulting mixture was stirred

at 60 °C for 4.0 h and at rt for 18 h. Ethyl acetate (20 mL) and water (20 mL) were added. The organic layer was separated, washed with 30 mL of water, dried over $MgSO_4$, filtered through Celite and silica, and concentrated in vacuo to yield the crude alkene. Purification by radial PLC (silica gel, 2% EtOAc/hexanes) gave 0.132 g (93%) of **16** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5 H), 5.45–5.25 (bs, 1 H), 4.50–3.80 (m, 2 H), 3.70 (s, 3 H), 2.90–2.68 (m, 1 H), 2.65–2.50 (m, 1 H), 2.15–1.30 (m, 8 H), 1.23–1.14 (dd, 1 H, J = 8.8, 14.66 Hz), 0.92–0.85 (dd, 1 H, J = 6.6, 14.66 Hz), 0.254–0.246 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 142.7 and 142.1 (due to rotamers), 139.3, 133.5, 128.6, 127.5, 116.9 and 116.3 (due to rotamers), 52.3, 50.4, 39.8, 37.1, 34.7, 32.7 and 32.2 (due to rotamers), 29.6, 24.9, 19.7, 19.2, −2.8; IR (neat) 3070, 3050, 3000, 2930, 2870, 1700, 1665, 1440, 1425, 1405, 1365, 1335, 1315, 1290, 1270, 1255, 1245, 1200, 1120, 1110, 1075 cm^{-1}; HRMS calcd for $C_{20}H_{29}NO_2Si$ 343.1968, found 343.1966.

(5*S,8a*R**)-1,2,3,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]-1-methylquinoline (17).** To a solution of alkene **16** (0.075 g, 0.218 mmol) in 10.0 mL of THF was added $LiAlH_4$ (0.87 mL, 0.869 mmol) as a 1.0 M solution in THF. The resulting solution was heated at reflux for 5 h and cooled to 0 °C before the addition of 0.03 mL of water, 0.03 mL of 15% NaOH, and again 0.09 mL of water. The resulting emulsion was filtered through Celite using ether and concentrated in vacuo to yield 0.0649 g (100%) of crude product. Purification by radial PLC (silica gel, 20% EtOAc/hexanes/1% TEA) gave 0.060 g (92%) of **17** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5 H), 5.35–5.33 (bd, 1 H, J = 5.14 Hz), 2.68–2.52 (m, 3 H), 2.31 (s, 3 H), 2.26–2.11 (m, 2 H), 2.05–1.97 (dt, 1 H, J = 10.26, 3.66 Hz), 1.90–1.42 (m, 5 H), 1.18–1.10 (dd, 1 H, J = 14.66, 9.53 Hz), 1.11–0.97 (m, 1 H), 0.98–0.82 (dd, 1 H, J = 14.66, 5.86 Hz), 0.283–0.273 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 139.8, 133.5, 128.6, 127.6, 117.4, 59.8, 51.1, 43.3, 39.3, 34.5, 32.8, 25.2, 20.5, 19.6, −2.4, −2.5; IR (neat) 3070, 3050, 2930, 2860, 2780, 1665, 1485, 1430, 1375, 1290, 1270, 1155, 1110, 1045, 1015 cm^{-1}.

(4a*R,5*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[(dimethylphenylsilyl)methyl]-1-methylquinoline (18).** A solution of alkene **17** (0.040 g, 0.134 mmol) in 6.0 mL of ethyl acetate was hydrogenated at rt under balloon pressure in the presence of Li_2CO_3 (0.020 g, 0.271 mmol) and 0.020 g of 5% Pd/C for 2 d. Filtration through Celite and removal of the solvent in vacuo gave crude **18** and **19** in a 75:25 ratio as determined by GC (**18**, t_R = 23.3 min; **19**, t_R = 19.6 min). Purification by radial PLC (silica gel, 5–20% EtOAc/hexanes/1%TEA) gave 0.024 g (58%) of **18** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.30 (m, 5 H), 2.82–2.77 (td, 1 H, J = 11.73, 2.93 Hz), 2.21 (s, 3 H), 2.10–1.92 (m, 2 H), 1.88–1.75 (m, 1 H), 0.28 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 133.5, 128.7, 127.6, 62.3, 57.5, 45.8, 42.8, 34.4, 31.8, 31.2, 29.4, 25.9, 19.5, 13.0, −2.3, -2.7; IR (neat) 3050, 3030, 2910, 2840, 2760, 2690, 1450, 1435, 1415, 1365, 1330, 1300, 1275, 1235, 1170, 1155, 1120, 1100, 1050 cm^{-1}; HRMS calcd for $C_{19}H_{31}NSi$ 301.2226, found 301.2215.

(5*S,8a*R**)-1,2,3,5,6,7,8,8a-Octahydro-5-[(dimethylphenylsilyl)methyl]quinoline (20).** To a solution of **16** (0.072 g, 0.210 mmol) in 3.0 mL of ethanol were added 3.0 mL of water and 2.1 g of KOH. The resulting mixture was heated at reflux for 5 d, cooled to rt, and concentrated under vacuum. The aqueous layer was extracted with ether (8 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to yield the crude amine **20**. Purification by radial PLC (silica gel, 40% EtOAc/hexanes/1%TEA) gave 0.0375 g (63%) of **20** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.30 (m, 5 H), 5.36–6.32 (m, 1 H), 3.33–3.23 (bm, 1 H), 2.92–2.81 (m, 1 H), 2.55–2.40 (m, 2 H), 2.10–1.40 (m, 8 H), 1.30–1.05 (m, 4 H), 0.86–0.80 (dd, 2 H, J = 5.86, 14.67 Hz), 0.29–0.27 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 139.8, 133.5, 128.6, 127.5, 117.9, 51.3, 41.2, 39.4, 35.5, 34.7, 26.2, 20.3, 19.7, −2.3, −2.7; IR (neat) 3300, 3080, 3060, 2930, 2870, 1730, 1450, 1425, 1330, 1315, 1245, 1215, 1155, 1110, 1070, 1025 cm^{-1}; HRMS calcd for $C_{18}H_{27}NSi$ 285.1913, found 285.1916.

(4a*R,5*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[(dimethylphenylsilyl)methyl]-1-[(benzyloxy)carbonyl]-quinoline (22).** A solution of amine **20** (0.081 g, 0.284 mmol) in 6.0 mL of ethyl acetate was hydrogenated for 4 d under balloon pressure in the presence of Li_2CO_3 (0.042 g, 0.568 mmol) and 0.04 g of 5% Pd/C. Filtration through Celite and removal of the solvent in vacuo gave 0.070 g of crude amines **6** and **21** in an 89:11 ratio as detected by GC (**6**, t_R = 13.1 min; **21**, t_R = 11.7 min). Purification of the mixture by radial PLC (silica gel, 10–20–40% EtOAc/hexanes/1% TEA) gave 0.052 g (64%) of the trans amine **6** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 5 H), 3.03–2.99 (bd, 1 H, J = 11.1 Hz), 2.60–2.53 (dt, 1 H, J = 11.1, 1.5 Hz), 2.49–2.41 (dt, 1 H, J = 11.7, 2.4 Hz), 2.31–1.95 (bs, 2 H), 1.85–0.65 (m, 13 H), 0.278 (s, 6H).

To a solution of amine **6** (0.052 g, 0.181 mmol) in 5.0 mL of CH_2Cl_2 was added solid $NaHCO_3$ (0.076 g, 0.904 mmol) and benzyl chloroformate (0.05 mL, 0.36 mmol). The resulting mixture was stirred at rt for 1 d, filtered through Celite, and concentrated in vacuo. Purification by radial PLC (silica gel, 2–5% EtOAc/hexanes) gave 0.055 g (73%) of carbamate **22** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 10 H), 5.19–5.07 (q, 2 H), 3.88–3.81 (dd, 1 H, J = 13.93, 7.33 Hz), 3.62–3.53 (dt, 1 H, J = 11.73, 3.66 Hz), 3.06–2.96 (m, 1 H), 2.10–1.05 (m, 12 H), 0.90–0.62 (m, 2 H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 139.4, 137.2, 133.4, 128.7, 128.3, 127.6, 127.5, 66.5, 54.5, 42.1, 36.7, 34.4, 31.7, 31.3, 23.4, 22.3, 19.7, 12.2, −2.4, −2.7; IR (neat) 3080, 3040, 2940, 2870, 1695, 1495, 1425, 1355, 1330, 1320, 1290, 1265, 1245, 1215, 1190, 1175, 1135, 1125, 1110, 1090, 1065, 1030 cm^{-1}; HRMS calcd for $C_{26}H_{35}NO_2Si$ 421.2437, found 421.2430.

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Supplementary Material Available: Copies of ^{1}H and/or ^{13}C NMR spectra (300 and 75 MHz) of compounds lacking analyses and the X-ray derived ORTEP diagram of compound **6**·HCl (23 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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