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.

Acknowledgment. We express appreciation to the National Institutes of Health (Grants GM 30255 and 34442) for financial support of this research. R.A. also thanks the Burroughs Wellcome Fund for a graduate fellowship. The 300-MHz NMR spectra and mass spectra were obtained at NCSU instrumentation laboratories which were established by grants from the North Carolina Biotechnology Center.

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]

Richard P. Polniaszek*,[†] and Lawrence W. Dillard[‡]

Department of Chemistry, Duke University, Durham, North Carolina 27706

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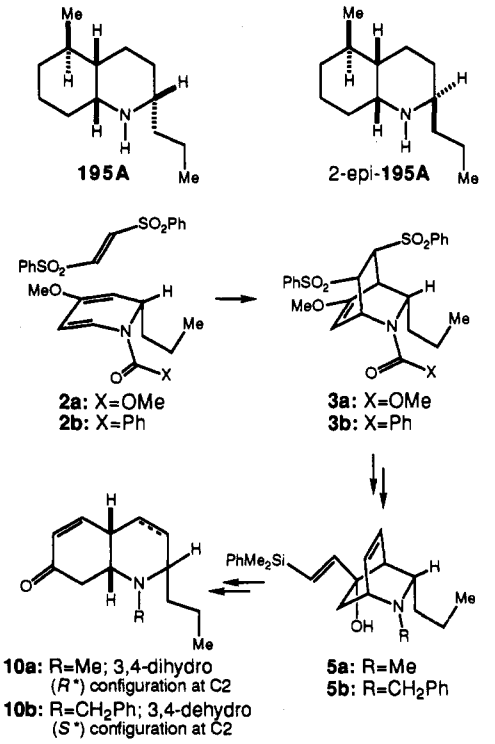
The total syntheses of decahydroquinoline alkaloids (±)-**195A** (pumiliotoxin C) and (±)-2-*epi*-**195A** are described. An unexpected, *stereospecific* epimerization of the C2 stereocenter of intermediate **6a** occurred during its reduction. The isomerization resulted in ultimate production of 2-*epi*-**195A**. 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-

[†] Recipient of a Junior Faculty Research Award of the American Cancer Society, 1990–1993.

[‡] Charles R. Hauser Fellow, 1990–1991.

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

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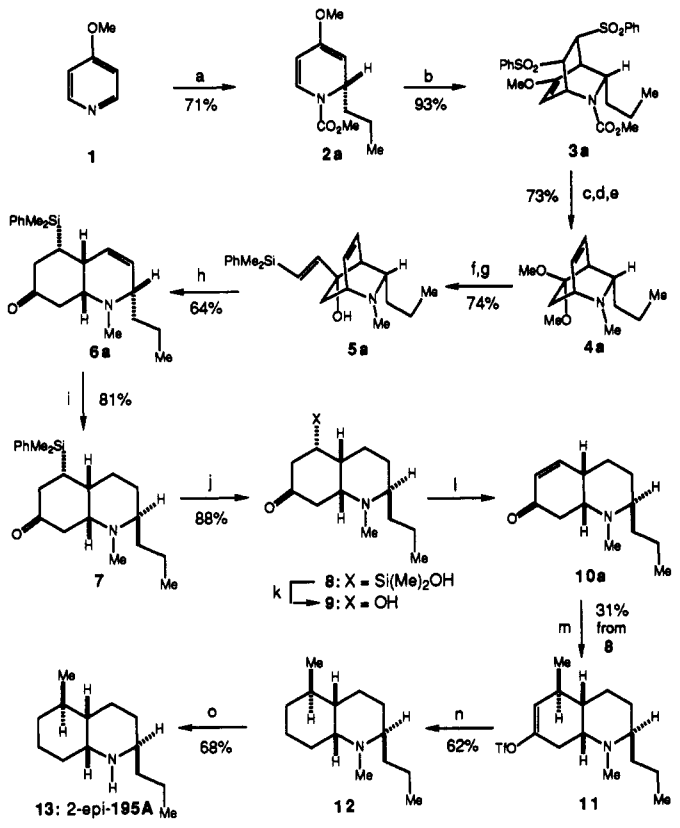
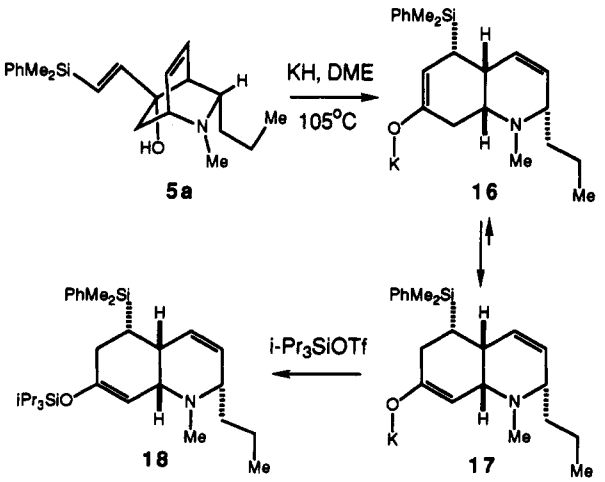
Scheme I[a]



[a] (a) $ClCO_2CH_3$, THF, −78 to −20 °C then *n*-PrMgCl, −78 to 0 °C; (b) (*E*)-bis(phenylsulfonyl)ethylene, 2.5:1 benzene–THF, 65 °C, 26.5 h; (c) MeOH, 1 equiv of camphorsulfonic acid, 25 °C, 5 d; (d) excess Na(Hg), 1:1 MeOH–THF, −30 °C, 1.75 h; (e) 5 equiv of $LiAlH_4$, THF, reflux 10 h; (f) 2:1 THF–10% HCl, 4.5 h; (g) 1.5 equiv of (*E*)-(phenyldimethylsilyl)vinyllithium, THF, −78 °C, 1.75 h; (h) 10 equiv of KH, DME, 105 °C, 8 h; (i) MeOH, 10% Pd/C, 1 atm of H_2, 25 min; (j) excess HBF_4-Et_2O, CH_2Cl_2, rt, 4 h; (k) 3.3 equiv of H_2O_2, 10 equiv of KF, DMF, 40 °C, 4 h; (l) 2.5 equiv of MsCl, 3.5 equiv of NEt_3, CH_2Cl_2, −78 °C to rt, then 1 h; (m) Me_2CuLi, THF–Et_2O, −78 to 0 °C, then $PhN(Tf)_2$, 0 °C; (n) MeOH, 10% Pd on C, 1 atm of H_2, 2 h; (o) excess PhSeH, 160 °C, 5 d.

silyl)vinyllithium.[15] The divinyl carbinol **5a** underwent anionic oxy-Cope rearrangement[6] in DME at 105 °C.



Interestingly, when the potassium enolate generated in this reaction was trapped with TIPS triflate a single silyl enol ether, the Δ-7,8 isomer (**18**), was obtained. In his earliest publication, Evans[6a] reported enolate equilibration under anionic oxy-Cope conditions. Apparently, enolate **17** is more stable than **16**. This observation was discouraging, since it was necessary to install a 7-keto-Δ-5,6 enone function (cf. **10a**). Consequently, the Δ-3,4 olefin moiety of octahydroquinolone **6a** (Scheme I) was reduced catalytically to afford the saturated derivative **7**.

Quite unexpectedly, the C2 stereocenter of **6a** underwent stereospecific inversion of configuration during the reduction step. The epimerization of C2 did not become evident until the completion of the synthesis. It seems reasonable to assume that the phenyldimethylsilyl moiety attached to C5 of the octahydroquinolone **6a** serves to fix the cis-fused ring system into conformation **19**. A destabilizing 1,3 $CH_2 \leftrightarrow CH_2$ diaxial interaction is present in conformation **19**. Thus, palladium-catalyzed double-bond isomerization may have occurred to produce enamines **20** and/or **21**. Catalytic reduction of **20** and/or **21** presumably occurred to produce decahydroquinolone **7**, present in solution as conformation **22**, wherein the destabilizing 1,3-diaxial interaction has been removed.

Controlled oxidation[16] of the phenyldimethylsilyl moiety of **7** (Scheme I) afforded the labile hydroxy ketone **9** which was immediately dehydrated to enone **10a** with mesyl

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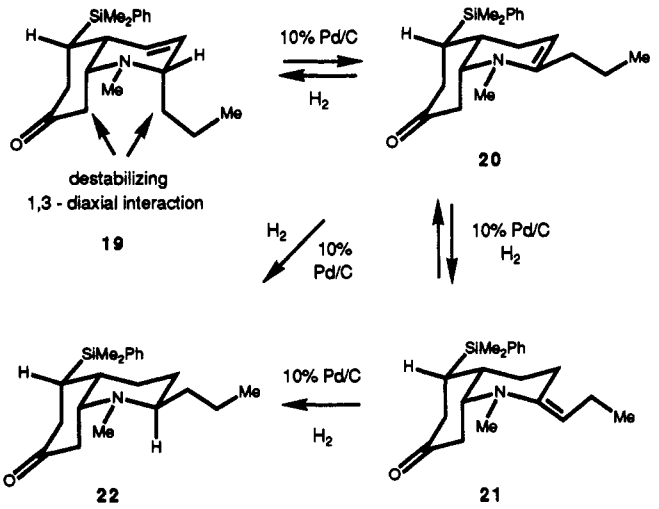
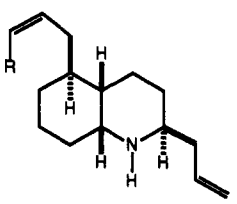


chloride.[17] The **7** to **9** transformation proved interesting in that fluoroboric acid promoted desilylations of alkylphenyldimethylsilanes normally afford fluorosilanes[16a] which then undergo oxidation to an alcohol in a separate step.[16a,b] The fluorosilane derived from **7** is apparently very labile toward hydrolysis,[18] since aqueous workup of the protodesilylation reaction afforded the dimethylsilanol **8**.

The enone **10a** underwent smooth 1,4-addition of lithium dimethylcuprate, and the resultant copper enolate was trapped in situ with *N*-phenyltriflamide,[19] affording enol triflate **11**. The conjugate addition reaction was stereospecific. The enol triflate **11** was catalytically reduced[20] to afford decahydroquinoline **12**. Demethylation of **12** by treatment with excess selenophenol at elevated temperature[21] afforded an alkaloid isomeric with **195A**, according to comparison of its ^1H and ^{13}C NMR with published data.[5]

The assignment of the alkaloid **13** as the 2-epi-isomer of **195A** was supported by the similarity in chemical shift and coupling patterns of its C8a and C2 protons to those present in alkaloids *cis*-**219A** and *cis*-**243A**.[22] In each of

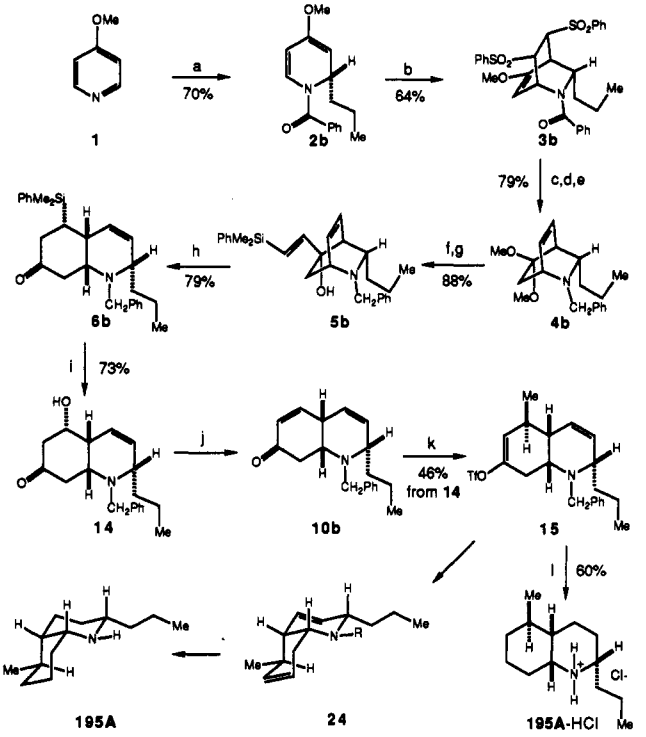


R = H: cis **219A**

R = -C≡CH: cis **243A**

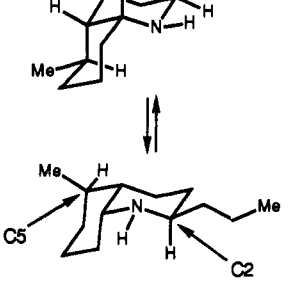
these three compounds, the C8a proton resonated at ca. 3.1 ppm and possessed one large and two small coupling constants. These coupling constants are due to a large coupling of H8a with a trans-axial C7 proton and two axial–equatorial couplings between H8a and either H7eq or H4a. This behavior is consistent with a cis-fused ring junction of the decahydroquinoline ring. Another similarity involved the C2 proton resonance in 2-*epi*-**195A**, *cis*-**219A**, and *cis*-**243A** which occurred between 2.8 and 2.9 ppm and appeared as an unresolved multiplet. Further evidence consistent with the assignment of 2-*epi*-**195A** was the similarity in the behavior of its ^{13}C spectrum with those of the two other alkaloids *cis*-**219A** and *cis*-**243A**.

Scheme II[a]



[a] (a) ClCOPh, THF, −78 to −20 °C then *n*-PrMgCl, −78 to 0 °C; (b) (*E*)-bis(phenylsulfonyl)ethylene, 2.5:1 benzene–THF, 80 °C, 66 h; (c) MeOH, 1 equiv of camphorsulfonic acid, 25 °C, 2.5 d; (d) excess Na(Hg), 1:1 MeOH–THF, −30 °C, 7 h; (e) 5 equiv of $LiAlH_4$, THF, reflux 9 h; (f) 2:1 THF–10% HCl, 6 h; (g) 1.5 equiv of (*E*)-(dimethylphenylsilyl)vinyllithium, THF, −78 °C, 2 h, then 0 °C, 15 min; (h) 10 equiv of KH, DME, 105 °C, 8.5 h; (i) (1) excess $HBF_4{\cdot}Et_2O$, CH_2Cl_2, rt, 21 h, (2) 3.3 equiv of H_2O_2, 10 equiv of KF, DMF, 40 °C, 4.5 h; (j) MsCl, NEt_3, −78 to 0 °C, then 5 equiv of DBN, −78 °C; (k) Me_2CuLi, THF–Et_2O, −78 to 0 °C, then PhN-$(Tf)_2$, 0 °C to rt; (l) MeOH, 10% Pd on C, 1 atm of H_2, 20 h, then HCl(g)/Et_2O.

Because of the cis-ring fusion in 2-*epi*-**195A** and the stereochemical relationship between the C2 and C5 stereocenters, either the C2 or C5 substituent must be axial while the other remains equatorial if the cis-fused rings are to remain in a chair–chair conformation. This feature leads to conformational inversion of both rings, producing a statistical distribution of two equilibrating chair–chair cis-fused decahydroquinoline rings. The dynamic conformational behavior results in broadening of several carbon resonances in each alkaloid.[24]



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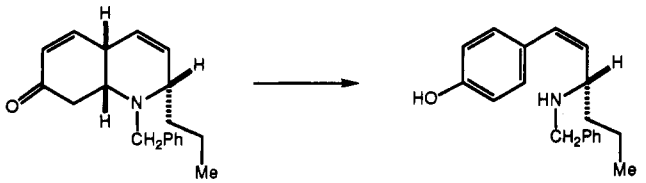
Although the sequence of reactions appearing in Scheme I did not provide *cis*-**195A**, the protocol has established a working method for preparing the correct substitution pattern and relative configuration common to other naturally occurring *cis*-decahydroquinoline alkaloids (**219A**, **243A**)[22] and the decahydroquinoline subunit of gephyrotoxin.[4b]

Reasoning that epimerization of the C2 stereocenter of **6a** occurred by double-bond isomerization to form an enamine, followed by catalytic reduction of the enamine, it seemed the most obvious solution to the epimerization problem would be reduction of **6a** over a catalyst less prone toward double-bond isomerization. In the event, neither rhodium, platinum, nor nickel catalysts were successful. Realizing that it was necessary to defer the double-bond reduction to a later stage in the overall synthetic sequence, we opted to attempt to increase the efficiency of the synthesis by changing the nitrogen protecting group from *N*-Me to *N*-CH_2Ph (Scheme II). Thus, by simply acylating 4-methoxypyridine with benzoyl chloride and performing all chemical operations as before it was possible to prepare octahydroquinolone **6b**. The phenyldimethylsilyl moiety of **6b** was then oxidized via the fluorodesilylation-oxidation procedure[16] to afford the β-hydroxy ketone **14**. It was necessary to carry out the dehydration of **14** under strictly controlled conditions in that the enone **10b** was extremely labile. Exposure of **10b** to silica gel or excess DBN resulted in quantitative conversion of **10b** to phenol **23** resulting from retro-Michael reaction of the β-amino ketone moiety, followed by tautomerization of the resulting dienone.



10b **23**

Nevertheless, the enone **10b** could be worked up under controlled conditions of pH with aqueous NaH_2PO_4 and isolated. The unpurified enone **10b** was then subjected to the conjugate addition with lithium dimethyl cuprate and the resultant copper enolate trapped with *N*-phenyltriflamide[19] as before. Catalytic hydrogenation of diene triflate **15** resulted in hydrogenolysis of both the *N*-benzyl and enol triflate moieties, with concomitant reduction of both double bonds and produced alkaloid (±)-**195A** which was characterized as its hydrochloride salt. The synthetic material had a high-field ^1H NMR identical to that of an authentic sample kindly provided by Professor Larry Overman. The ^{13}C spectrum of the synthetic material also matched the published values. The hydrogenation of enol triflate **15** presumably proceeds via diene **24** (R = CH_2Ph or H). The preferred conformation of **24** (Scheme II) places both the propyl chain attached to C2 and the methyl group attached to C5 in equatorial positions. The success of the hydrogenation of **24** (as opposed to that of **6a** in Scheme I) lies in the fact that **24** does not provide a steric driving force for double-bond isomerization/epimerization of the C2 stereocenter.

In summary, a single synthetic approach has provided stereospecific access to the decahydroquinoline skeleta of both the pumiliotoxin C and gephyrotoxin families.

Experimental Section

General. Melting points are uncorrected. ^1H data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, dd = doublet of doublets), integration, coupling (in Hz), and interpretation. Combustion analyses were performed either by Spang Microanalytical Laboratory (Eagle Harbor, MI), or MHW Laboratories (Phoenix, AZ). Dichloromethane, 1,2-dimethoxyethane, and triethylamine were distilled from calcium hydride prior to use. Ethyl ether, tetrahydrofuran, and benzene were distilled from sodium/benzophenone ketyl. Grignard and alkyl lithium reagents were assayed for molarity according to the method of Bergbreiter.[23] All glassware was oven dried and stored in dessicators prior to use. Flash chromatography was carried out with Kieselgel 60 (2300–400 mesh) silica gel.

(1*R,3*S**,4*S**,7*S**,8*S**)-2-(Methoxycarbonyl)-3-(1-propyl)-5-methoxy-7,8-bis(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-5-ene (3a).** 4-Methoxypyridine (3.01 g, 27.6 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. Methyl chloroformate (2.6 mL, 1.2 equiv) in THF (15 mL) was added. After 15 min, the reaction was allowed to warm to −20 °C over 15 min and immediately recooled to −78 °C before adding propylmagnesium chloride (33 mmol, 1.2 equiv). After 15 min, the reaction was warmed to 0 °C and stirred for 1.75 h before quenching with 5% Na_2CO_3. The THF was removed in vacuo and the residue diluted with 1:1 5% Na_2CO_3–0.2 M Na_2EDTA and extracted with 1:1 CH_2Cl_2–pentane. The combined extracts were dried (K_2CO_3), filtered, and concentrated to give a residue which was chromatographed on silica gel with 10:90 EtOAc–hexane affording 4.12 g of an oil which was immediately combined with (*E*)-1,2-bis(phenylsulfonyl)ethylene (6.02 g, 195 mmol) in a mixture of benzene (90 mL) and THF (30 mL). The reaction was heated at 65 °C for 26.5 h, cooled to 0 °C, and filtered. The filtrate was concentrated to give a residue that was flash chromatographed on silica with a gradient of 20:80–50:50 EtOAc–hexane affording 9.41 g (66% from 4-methoxypyridine) of a white foam, mp 121–124 °C: IR (CH_2Cl_2) 1690 (s), 1650 (m) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 7.72 (d, 2 H, *J* = 7 Hz, ArH_2), 7.67 (d, 2 H, *J* = 7 Hz, ArH_2), 7.11–6.94 (m, 6 H, 2 × ArH_3), 5.36 (dd, 1 H, *J* = 5.5, 3 Hz, C=CH), 5.00 (dd, 1 H, *J* = 7, 2.5 Hz, C_1-H), 4.62–4.49 (m, 2 H, C_3-H and C_7-H), 4.26 (dd, 1 H, *J* = 5, 3 Hz, C_8-H), 3.56 (s, 3 H, CO_2CH_3), 3.42–3.36 (m, 1 H, C_4-H), 3.26 (s, 3 H, C_5-OCH_3), 1.44–1.23 (m, 4 H, CH_2CH_2), 0.91 (t, 3 H, *J* = 7 Hz, CH_2CH_3); MS (CI, NH_3) *m/e* 537 ($(M + NH_4)^+$, base peak). Anal. Calcd for $C_{25}H_{29}NO_7S_2$: C, 57.78; H, 5.64. Found: C, 57.51; H, 5.73.

(1*R,3*S**,4*S**,7*S**,8*S**)-2-(Methoxycarbonyl)-3-(1-propyl)-5,5-dimethoxy-7,8-bis(phenylsulfonyl)-2-azabicyclo[2.2.2]octane (3a-2).** Enol ether **3a** (8.70 g, 16.8 mmol) and (±)-10-camphorsulfonic acid (3.93 g, 1 equiv) were dissolved in MeOH (150 mL), and the mixture was stirred at room temperature for 114 h, poured onto aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford a solid which was recrystallized from EtOAc–hexane affording 7.72 g (84%) of a white solid, mp 179–180 °C: IR (CH_2Cl_2) 1699 (s) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 7.82–7.78 (m, 4 H, 2 × ArH_2), 7.11–6.97 (m, 6 H, 2 × ArH_3), 4.87 (dd, 1 H, *J* = 6, 2.5 Hz, C_8-H), 4.76 (dd, 1 H, *J* = 6, 3 Hz, C_2-H), 4.66–4.58 (m, 1 H, C_3-H), 4.38–4.33 (m, 1 H, C_7-H), 3.49 (s, 3 H, CO_2CH_3), 3.09–3.04 (m, 1 H, C_4-H), 3.03 (s, 3 H, C_5-OCH_3), 2.95 (s, 3 H, C_5-OCH_3), 2.90 (dd, 1 H, *J* = 14.5, 4 Hz, C_6-H), 2.01–1.88 (m, 2 H, $CH_2CH_2CH_3$), 1.79 (ddd, 1 H, *J* = 14.5, 2.5, 1.5 Hz, C_6-H), 1.52–1.35 (m, 2 H, CH_2CH_3), 0.99 (t, 3 H, *J* = 7 Hz, CH_2CH_3); MS (CI, NH_3) *m/e* 569 ($(M + NH_4)^+$, base peak). Anal. Calcd for $C_{26}H_{33}NO_8S_2$: C, 56.60; H, 6.04. Found: C, 56.62; H, 6.11.

(1*R,3*S**,4*S**)-2-(Methoxycarbonyl)-3-(1-propyl)-8,8-dimethoxy-2-azabicyclo[2.2.2]oct-5-ene (3a-3).** Ketal **3a-2** (2.85 g, 5.17 mmol) and $NaHCO_3$ (2.17 g, 5 equiv) were dissolved in a mixture of MeOH (90 mL) and THF (70 mL) and cooled to −35 °C. Three portions (35 g each) of sodium amalgam (2% Na) were added at 30-min intervals keeping the temperature strictly between −30 and −40 °C. After being stirred at −30 °C for an additional 45 min, the mixture was then filtered through alumina

(24) We thank Dr. Spande, Dr. Daly, and Dr. Yeh of the Laboratory of BioOrganic Chemistry of the National Institutes of Health for ^1H and ^{13}C spectral accumulation and analyses of both *N*-Me-2-*epi*-**195A** and 2-*epi*-**195A**.

and the filtrate concentrated to leave a residue which was flash chromatographed on silica gel with a gradient of 20:80–40:60 EtOAc–hexane affording 1.34 g (97%) of an oil: IR (NaCl) 1701 (s) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 6.19–6.07 (m, 2 H, C*H*=C*H*), 4.75–4.68 (m, 1 H, C_1-H), 3.51 (s, 3 H, CO_2CH_3), 3.25 (ddd, 1 H, J = 10.5, 4.5, 2.5 Hz, C_3-H), 3.00 (s, 3 H, $-C_8$-OCH_3), 2.93 (s, 3 H, C_8-OCH_3), 2.84–2.76 (m, 1 H, C_4-H), 2.28–2.15 (m, 1 H, CH*H*CH_2CH_3), 1.99–1.85 (m, 1 H, C*H*HCH_2CH_3), 1.91 (dd, 1 H, J = 13, 2.5 Hz, C_7-H), 1.64–1.46 (m, 1 H, C*H*HCH_3), 1.54 (dd, 1 H, J = 13, 3 Hz, C_7-H), 1.45–1.26 (m, 1 H, CH*H*CH_3), 0.99 (t, 3 H, J = 7.5 Hz, CH_2CH_3); MS (CI, NH_3) m/e 270 (MH^+, base peak). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61. Found: C, 62.40; H, 8.43.

(1*R,3*S**,4*S**)-2-Methyl-3-(1-propyl)-8,8-dimethoxy-2-azabicyclo[2.2.2]oct-5-ene (4a).** To an ice-cooled solution of LAH (1.11 g, 29.3 mmol) in THF (20 mL) was added carbamate **3a-3** (1.46 g, 5.46 mmol) as a solution in THF (25 mL). The reaction was then heated to reflux for 10 h, cooled, and cautiously quenched with saturated Na_2SO_4 and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to leave a residue which was distilled (120 °C (0.4 mm)) affording 1.11 g (90%) of an oil: IR (NaCl) 1456 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (t, 1 H, J = 8 Hz, C_6-H), 6.17 (dd, 1 H, J = 8, 5 Hz, C_5-H), 3.45–3.35 (m, 1 H, C_1-H), 3.17 (s, 3 H, OCH_3), 3.12 (s, 3 H, OCH_3), 2.69 (d, 1 H, J = 7 Hz, C_4-H), 2.26 (s, 3 H, NCH_3), 2.07 (dd, 1 H, J = 13, 3 Hz, C_7-H), 1.76–1.61 (m, 3 H, C*H*$CH_2CH_2CH_3$), 1.57 (dd, 1 H, J = 13, 3.5 Hz, C_7-H), 1.49–1.23 (m, 2 H, CH_2CH_3), 0.93 (t, 3 H, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 129.3, 103.0, 64.2, 56.3, 48.4, 48.0, 45.1, 40.2, 39.6, 36.1, 20.7, 14.5; MS (CI, NH_3) m/e 226 (MH^+, base peak). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.15; H, 10.38.

(1*R,3*S**,4*S**)-2-Methyl-3-(1-propyl)-2-azabicyclo[2.2.2]-oct-7-en-5-one (4a-2).** Ketal **4a** (514 mg, 2.28 mmol) was dissolved in a mixture of THF (20 mL) and 10% HCl (10 mL). The mixture was stirred at room temperature for 4.5 h and then diluted with CH_2Cl_2 (100 mL), and solid anhydrous K_2CO_3 was added to basify and dry the solution. Filtration and concentration of the filtrate gave a pale yellow oil which was chromatographed on silica gel with EtOAc affording 345 mg (85%) of an oil: IR (NaCl) 1729 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (t, 1 H, J = 6.5 Hz, C_7-H), 6.43 (t, 1 H, J = 7 Hz, C_8-H), 3.74–3.67 (m, 1 H, C_1-H), 3.01 (d, 1 H, J = 6 Hz, C_4-H), 2.39 (s, 3 H, N-CH_3), 2.32 (d, 1 H, J = 18 Hz, C_6-H), 2.14–2.02 (m, 2 H, C_6-H + C_3-H), 1.58–1.21 (m, 4 H, $CH_2CH_2CH_3$), 0.91 (t, 3 H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 134.3, 128.2, 64.2, 57.8, 53.2, 45.2, 42.1, 38.7, 19.7, 13.9; MS (CI, NH_3) m/e 180 (MH^+, base peak). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.68; H, 9.58. Found: C, 68.42; H, 8.87.

(1*R,3*S**,4*S**,5*S**)-2-Methyl-3-(1-propyl)-5-[(*E*)-2-(dimethylphenylsilyl)-1-ethenyl]-2-azabicyclo[2.2.2]oct-7-en-5-ol (5a).** (*E*)-1-(Tri-*n*-butylstannyl)-2-(dimethylphenylsilyl)ethene[15] (2.22 g, 4.92 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. *n*-Butyllithium (4.90 mmol) was added and the mixture stirred for 1.5 h, allowed to warm to −30 °C over 15 min, and immediately recooled to −78 °C. Ketone **4a-2** (571 mg, 3.19 mmol) in THF (9 mL) was added and the mixture stirred for 1.75 h before being quenched with saturated $NaHCO_3$ and removing THF in vacuo. The aqueous residue was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to given an oil which was chromatographed on silica with a gradient of 40:60 EtOAc–hexane to 40:60 MeOH–EtOAc affording 950 mg (87%) of an oil: IR (NaCl) 3360 (br), 1611 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.45 (m, 2 H, ArH_2), 7.38–7.31 (m, 3 H, ArH_3), 6.43 (t, 1 H, J = 7.5 Hz, C_8-H), 6.11 (t, 1 H, J = 6.5 Hz, C_7-H), 6.08 (d, 1 H, J = 19 Hz, SiC=CH), 5.87 (d, 1 H, J = 19 Hz, SiCH=C), 3.44–3.37 (m, 1 H, C_1-H), 2.37 (d, 1 H, J = 7 Hz, C_4-H), 2.29 (s, 3 H, N-CH_3), 2.10–1.94 (m, 2 H, C_3-H + C_6-H), 1.90–1.73 (m, 3 H, C_6-H + $CH_2CH_2CH_3$), 1.53–1.22 (m, 2 H, CH_2CH_3), 0.94 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 0.31 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 138.8, 135.0, 133.7, 129.0, 128.9, 127.7, 121.9, 75.0, 66.4, 56.3, 45.0, 44.2, 44.0, 36.4, 20.8, 14.4, 2.5, 2.4; MS (CI, isobutane) m/e 342 (MH^+, base peak). Anal. Calcd for $C_{21}H_{31}NOSi$: C, 73.83; H, 9.16. Found: C, 73.89; H, 9.17.

(2*S,4a*R**,5*S**,8a*R**)-1-Methyl-2-(1-propyl)-(Δ-3,4)-5-(dimethylphenylsilyl)-7-oxooctahydroquinoline (6a).** Hydroxy diene **5a** (332 mg, 0.97 mmol) in DME (4 mL) was added to a suspension of KH (415 mg, 11 equiv) in DME (2.5 mL). The resulting suspension was heated at 105 °C for 8 h, cautiously poured onto 50:50 ice–saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue which was chromatographed on silica gel with a gradient of 10:90–30:70 EtOAc–hexane affording 213 mg (64%) of an oil: IR (NaCl) 1711 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.44 (m, 2 H, ArH_2), 7.37–7.31 (m, 3 H, ArH_3), 5.80 (dt, 1 H, J = 10.5, 2.5 Hz, C*H*=C), 5.66 (d, 1 H, J = 10.5 Hz, C*H*=C), 2.96 (dt, 1 H, J = 11, 4.5 Hz, C_{8a}-H), 2.88–2.78 (m, 1 H, C_2-H), 2.78–2.69 (m, 1 H, C_{4a}-H), 2.51 (t, 1 H, J = 13 Hz, C_8-H), 2.41 (s, 3 H, NCH_3), 2.35 (dd, 1 H, J = 13.5, 4.5 Hz, C_8-H), 2.29–2.08 (m, 2 H, C_6-H_2), 1.52–1.23 (m, 5 H, C_5-H and $CH_2CH_2CH_3$), 0.87 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.37 (s, 3 H, $SiCH_3$), 0.36 (s, 3 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 137.1, 133.7, 132.2, 129.3, 127.9, 124.4, 62.6, 58.5, 43.9, 42.7, 38.3, 37.0, 32.0, 26.7, 20.1, 14.2, −3.5, −3.8; MS (CI, NH_3) m/e 342 (MH^+, base peak). Anal. Calcd for $C_{21}H_{31}NOSi$: C, 73.83; H, 9.16. Found: C, 73.62; H, 9.08.

(2*R,4a*R**,5*S**,8a*R**)-1-Methyl-2-(1-propyl)-5-(dimethylphenylsilyl)-7-oxodecahydroquinoline (7).** 10% Palladium on carbon (43 mg) was suspended in MeOH (2 mL) and stirred under 1 atm of H_2 for 2.5 h before adding ketone **6a** (26.0 mg) in MeOH (3 mL). The reaction was stirred under 1 atm of H_2 for 25 min. The catalyst was filtered off and the filtrate concentrated to give a residue which was flash chromatographed on silica gel with a gradient of 30:70–40:60 EtOAc–hexane affording 21.3 mg (81%) of an oil: IR (NaCl) 1707 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2 H, ArH_2), 7.35–7.29 (m, 3 H, ArH_3), 3.14 (dt, 1 H, J = 12, 4 Hz, C_{8a}-H), 2.64 (t, 1 H, J = 12.5 Hz, C_5-H), 2.44–2.26 (m, 3 H), 2.24 (s, 3 H, NCH_3), 2.18–2.02 (m, 2 H), 1.77–1.44 (m, 4 H), 1.38–1.12 (m, 4 H), 1.30 (dt, 1 H, J = 15, 3.5 Hz, C_5-H), 0.86 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.30 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 137.0, 133.7, 129.2, 127.9, 67.7, 53.9, 39.1, 37.8, 36.5, 35.8, 35.4, 30.6, 28.5, 21.6, 18.3, 14.5, −3.8, −3.9; MS (CI, NH_3) m/e 344 (MH^+, base peak). Anal. Calcd for $C_{21}H_{33}NOSi$: C, 73.40; H, 9.70. Found: C, 73.31; H, 9.73.

(2*R,4a*R**,5*S**,8a*R**)-1-Methyl-2-(1-propyl)-5-(hydroxydimethylsilyl)-7-oxodecahydroquinoline (8).** To a solution of ketone **7** (65.3 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added 85% HBF_4·OEt_2 (0.65 mL) and the mixture stirred at ambient temperature for 4 h. After being shaken with 10% HCl (10 mL) for 5 min, the mixture was basified with 15% KOH and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to give a yellow oil which was flash chromatographed on silica gel with a gradient of EtOAc to 10:90 MeOH–EtOAc affording 47.1 mg (88%) of an oil: IR (NaCl) 3400 (br), 1701 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (dt, 1 H, J = 12.5, 4 Hz, C_{8a}-H), 2.68 (t, 1 H, J = 12.5 Hz, C_8-H), 2.46–2.29 (m, 3 H, C_2-H + C_{4a}-H + C_8-H), 2.26 (s, 3 H, NCH_3), 2.24–2.10 (m, 2 H, C_6-H_2), 1.83–1.62 (m, 3 H), 1.58–1.47 (m, 1 H), 1.42–1.16 (m, 4 H), 1.06 (dt, 1 H, J = 15, 3.5 Hz, C_5-H), 0.87 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 0.13 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 67.7, 54.3, 39.1, 37.1, 35.7, 35.6, 35.5, 30.4, 30.1, 21.7, 18.4, 14.5, −0.7, −0.9; MS (CI, NH_3) m/e 284 (MH^+, base peak).

(2*R,4a*S**,5*S**,8a*R**)-1-Methyl-2-(1-propyl)-5-methyl-(Δ-6,7)-7-[(trifluoromethanesulfonyl)oxy]decahydroquinoline (11).** Ketone **8** (98 mg, 0.34 mmol) and KF (202 mg, 10 equiv) were stirred in DMF (1 mL) for 15 min before 30% H_2O_2 (0.13 mL, 3.3 equiv) was added and the mixture was heated to 40 °C. After 4 h the mixture was poured onto saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil which was immediately dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. Triethylamine (0.17 mL, 3.5 equiv) and mesyl chloride (0.07 mL, 2.5 equiv) were added and the mixture stirred for 1 h each at −78, 0 °C, and room temperature. The reaction was poured onto saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a yellow oil which was immediately dissolved in THF (10 mL) and added to a cooled (−78 °C) solution of lithium dimethylcuprate (2.5 equiv) in Et_2O (10 mL). After 20 min the reaction was warmed to 0 °C. After 35 min, $PhNTf_2$ (369 mg,

3 equiv) in THF (8 mL) was added. After 1.75 h the mixture was filtered through a glass frit and the filtrate concentrated to give a residue which was flash chromatographed on silica gel with a gradient of 30:70 EtOAc–hexane to 10:90 MeOH–EtOAc affording 38.5 mg (31% from 8) of an oil: IR (NaCl) 1692 (m), 1416 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, 1 H, J = 5, 1.5 Hz, C=CH), 3.47–3.33 (m, 1 H, C_{8a}-H), 2.67–2.57 (m, 1 H, C_8-H), 2.55–2.40 (m, 1 H, C_2-H), 2.45 (s, 3 H, NCH_3), 2.33 (dd, 1 H, J = 17.5, 6.5 Hz, C_8-H), 2.27–2.14 (m, 1 H, C_5-H), 1.92–1.70 (m, 2 H, C_{4a}-H and $CHHCH_2CH_3$), 1.67–1.54 (m, 1 H), 1.52–1.18 (m, 5 H), 1.12 (d, 3 H, J = 7 Hz, C_5-CH_3), 0.92 (t, 3 H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 145.3, 122.0, 57.1, 55.6, 39.7 (two coincident signals), 35.5, 35.0, 30.4, 25.6, 21.9, 21.0, 18.4, 14.4; MS (CI, isobutane) m/e 356 (MH^+, base peak). HRMS m/e calcd for $C_{15}H_{24}F_3NO_3S$ 355.1429, found 355.1425.

(2*R,4a*S**,5*R**,8a*R**)-1-Methyl-2-(1-propyl)-5-methyldecahydroquinoline (12).** Palladium on carbon (10% Pd) (76 mg) was suspended in MeOH (3 mL) and prereduced under 1 atm of H_2 for 2 h before adding enol triflate 11 (27.5 mg, 0.08 mmol) in MeOH (3 mL). After being stirred for 2 h under 1 atm H_2, the mixture was filtered through a pad of Celite and the filtrate concentrated to give a residue which was partitoned between saturated $NaHCO_3$ and CH_2Cl_2 and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give an oil which was chromatographed on silica gel with a gradient of 10:90–40:60 MeOH–EtOAc affording 10.0 mg (62%) of an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.87–2.76 (m, 1 H, C_{8a}-H), 2.48–2.33 (m, 1 H, C_2-H), 2.27 (s, 3 H, NCH_3), 1.78–1.03 (m, 16 H), 0.93 (d, 3 H, J = 7 Hz, C_5-CH_3), 0.83 (t, 3 H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.3, 55.5, 41.4 (br), 40.3, 39.2, 38.9, 35.8, 35.1, 29.6, 28.8, 25.2, 20.2, 19.2, 14.4; MS (CI, isobutane) m/e 210 (MH^+, base peak); HRMS m/e calcd for $C_{14}H_{27}N$ 209.2143, found 209.2140.

(2*R,4a*S**,5*R**,8a*R**)-2-(1-Propyl)-5-methyldecahydroquinoline (2-*epi*-195A).** A mixture of amine 12 (10.0 mg, 0.048 mmol) and benzeneselenol (0.25 mL) was sealed under argon in a thick-walled glass vessel and heated to 160 °C with stirring for 119 h. The mixture was cooled, partitioned between 15% KOH and CH_2Cl_2, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue which was flash chromatographed on silica gel with 40:60 MeOH–EtOAc affording 6.4 mg (68%) of an oil: GC IR 1458 (w), 1372 (w), 1142 (w), 1078 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (dt, 1 H, J = 10.5, 4 Hz, C_{8a}-H), 1.86–1.56 (m, 5 H), 1.56–1.40 (m, 3 H), 1.40–1.16 (m, 6 H), 1.12–0.98 (m, 2 H), 0.92 (d, 3 H, J = 7 Hz, C_5-CH_3), 0.88–0.78 (m, 3 H, CH_2CH_3); MS (CI, isobutane) m/e 196 (MH^+, base peak). 2-*epi*-195A·HCl: ^{13}C NMR (75 MHz, D_2O) δ 52.0, 51.2, 38.9, 34.2 (br), 31.7 (br), 26.9 (br) (two peaks), 23.8 (br), 22.4 (br), 19.2, 18.2, 18.0, 13.0.

(1*R,3*S**,4*S**,7*S**,8*S**)-2-Benzoyl-3-(1-propyl)-5-methoxy-7,8-bis(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-5-ene (3b).** 4-Methoxypyridine (3.03 g, 27.8 mmol) was dissolved in THF (15 mL) and cooled to −78 °C. Benzoyl chloride (3.6 mL, 1.1 equiv) in THF (17 mL) was added. After 15 min, the solution was warmed to −20 °C over 10 min and immediately recooled to −78 °C before propylmagnesium chloride (1.1 equiv) was added. After 10 min, the reaction was warmed to 0 °C and stirred 1 h before being quenched with 5% Na_2CO_3. The THF was removed in vacuo and the residue partitioned between 1:1 5% Na_2CO_3–0.2 M Na_2EDTA and 1:1 CH_2Cl_2–pentane. The mixture was extracted, and the combined extracts were dried (K_2CO_3), filtered, and concentrated to give a yellow liquid. Flash chromatography on silica gel with a gradient of 10:90–20:80 EtOAc–hexane afforded 4.97 g of a yellow oil which was immediately combined with (*E*)-1,2-bis(phenylsulfonyl)ethylene (5.96 g, 1 equiv) in a mixture of benzene (75 mL) and THF (50 mL). The reaction was warmed to 80 °C and stirred for 66 h before being cooled to 0 °C and filtering. The filtrate was concentrated to give a residue that was chromatographed on silica gel with a gradient of 20:80–50:50 EtOAc–hexane affording 6.99 g (44% from 4-methoxypyridine) of a white solid: mp 169–170 °C; IR (NaCl) 1734 (w), 1642 (s) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 7.74 (d, 2 H, J = 7.5 Hz, ArH_2), 7.62 (d, 2 H, J = 7.5 Hz, ArH_2), 7.53–7.45 (m, 2 H, ArH_2), 7.18–6.93 (m, 9 H, 3 × ArH_3), 5.68–5.42 (m, 1 H, C=CH), 5.03 (dd, 1 H, J = 7, 2.5 Hz, C_1-H), 4.86–4.74 (m, 1 H, C_3-H), 4.55–4.47 (m, 1 H, C_7-H), 4.30 (dd, 1 H, J = 5, 3 Hz, C_8-H), 3.48–3.43 (m, 1 H, C_4-H), 3.27 (s, 3 H, OCH_3), 1.76–1.52 (m, 1 H, $CHHCH_2CH_3$), 1.40–1.06 (m, 3 H, $CHHCH_2CH_3$), 0.84–0.65 (m, 3 H, CH_2CH_3); MS (CI, NH_3) m/e 566 (MH^+, 16). Anal. Calcd for $C_{30}H_{31}NO_6S_2$: C, 63.68; H, 5.53. Found: C, 63.67; H, 5.70.

(1*R,3*S**,4*S**,7*S**,8*S**)-2-Benzoyl-3-(1-propyl)-5,5-dimethoxy-7,8-bis(phenylsulfonyl)-2-azabicyclo[2.2.2]octane (3b-2).** Enol ether 3b (6.99 g, 12.35 mmol) was dissolved, in MeOH (150 mL), and (±)-10-camphorsulfonic acid (2.87 g, 1 equiv) was added. The mixture was stirred at room temperature for 62 h and then poured onto saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford 6.70 g (91%) of a white solid, mp 188–189 °C (EtOAc–hexane): IR (NaCl) 1645 (s) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 7.90 (d, 2 H, J = 7.5 Hz, ArH_2), 7.59 (d, 2 H, J = 7.5 Hz, ArH_2), 7.30 (d, 2 H, J = 7.5 Hz, ArH_2), 7.15–6.91 (m, 9 H, 3 × ArH_3), 4.99–4.86 (m, 2 H, C_7-H + C_3-H), 4.76–4.69 (m, 1 H, C_1-H), 4.29–4.22 (m, 1 H, C_8-H), 3.15–3.10 (m, 1 H, C_4-H), 3.01 (s, 3 H, OCH_3), 2.98 (s, 3 H, OCH_3), 2.88 (dd, 1 H, J = 15, 3.5 Hz, C_6-H), 2.03–1.87 (m, 3 H, C_6-H + $CH_2CH_2CH_3$), 1.48–1.24 (m, 2 H, CH_2CH_3), 0.90 (t, 3 H, J = 7.5 Hz, CH_2CH_3); MS (CI, NH_3) m/e 598 (MH^+, 12%). Anal. Calcd for $C_{31}H_{35}NO_7S_2$: C, 62.28; H, 5.91. Found: C, 62.41; H, 6.10.

(1*R,3*S**,4*S**)-2-Benzoyl-3-(1-propyl)-8,8-dimethoxy-2-azabicyclo[2.2.2]oct-5-ene (3b-3).** Ketal 3b-2 (3.42 g, 5.72 mmol) and $NaHCO_3$ (2.40 g, 5 equiv) were dissolved in a mixture of MeOH (75 mL) and THF (70 mL) and cooled to −35 °C. Three portions (30 g each) of sodium amalgam (2% Na) were added at 1 h intervals keeping the temperature strictly between −30 and −40 °C. After being stirred at −30 °C for an additional 30 min, the mixture was then filtered through alumina and the filtrate concentrated to leave a residue which was flash chromatographed on silica with a gradient of 30:70–50:50 EtOAc–hexane affording 1.79 g (99%) of an oil: IR (NaCl) 1738 (m), 1633 (s) cm^{-1}; ^1H NMR (300 MHz, 105 °C, toluene-d_8) δ 7.43–7.36 (m, 2 H, ArH_2), 7.16–7.06 (m, 3 H, ArH_3), 6.15 (t, 1 H, J = 8 Hz, C_5-H), 5.82 (t, 1 H, J = 6.5 Hz, C_6-H), 4.33–4.25 (m, 1 H, C_1-H), 3.76 (ddd, 1 H, J = 10, 7.5, 2.5 Hz, C_3-H), 3.05 (s, 3 H, OCH_3), 2.93 (s, 3 H, OCH_3), 2.92–2.86 (m, 1 H, C_4-H), 2.37–2.23 (m, 1 H, $CHHCH_2CH_3$), 2.05 (dd, 1 H, J = 13, 2.5 Hz, C_7-H), 2.02–1.87 (m, 1 H, $CHHCH_2CH_3$), 1.68–1.34 (m, 2 H, CH_2CH_3), 1.50 (dd, 1 H, J = 13, 3.5 Hz, C_7-H), 1.01 (t, 3 H, J = 7.5 Hz, CH_2CH_3); MS (CI, NH_3) m/e 316 (MH^+, base peak). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.34; H, 8.00. Found: C, 72.32; H, 8.17.

(1*R,3*S**,4*S**)-2-Benzyl-3-(1-propyl)-8,8-dimethoxy-2-azabicyclo[2.2.2]oct-5-ene (4b).** Amide 3b-3 (626 mg, 1.99 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. LAH (384 mg, 5 mol equiv) was added and the reaction refluxed for 9 h and then cooled to 0 °C before being quenched with saturated Na_2SO_4 (50 mL). The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue which was flash chromatographed on silica gel with a gradient of 30:70–40:60 EtOAc–hexane affording 536 mg (89%) of an oil: IR (NaCl) 1604 (w), 1494 (m), 1455 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.16 (m, 5 H, ArH_5), 6.48 (t, 1 H, J = 6.5 Hz, C_5-H), 6.13 (dd, 1 H, J = 8, 5 Hz, C_6-H), 3.55 (d, 1 H, J = 13.5 Hz, $CHHPh$), 3.33–3.26 (m, 1 H, C_1-H), 3.27 (d, 1 H, J = 13.5 Hz, $CHHPh$), 3.16 (s, 3 H, OCH_3), 3.09 (s, 3 H, OCH_3), 2.73 (d, 1 H, J = 6.5 Hz, C_4-H), 2.02–1.89 (m, 2 H, C_7-H + C_3-H), 1.86–1.60 (m, 2 H, $CH_2CH_2CH_3$), 1.48 (dd, 1 H, J = 12.5, 3.5, C_7-H), 1.44–1.25 (m, 2 H, CH_2CH_3), 0.93 (t, 3 H, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 132.9, 129.4, 128.4, 127.9, 126.5, 103.6, 62.6, 60.4, 50.7, 48.2, 47.7, 39.9, 39.5, 36.3, 20.4, 14.4; MS (CI, NH_3) m/e 302 (MH^+, base peak). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.69; H, 9.05. Found: C, 75.65; H, 8.89.

(1*R,3*S**,4*S**)-2-Benzyl-3-(1-propyl)-2-azabicyclo[2.2.2]-oct-7-en-5-one (4b-2).** Ketal 4b (1.20 g, 3.99 mmol) was dissolved in THF (25 mL), 10% HCl (15 mL) was added, and the mixture was stirred at room temperature for 6 h. The reaction was diluted with CH_2Cl_2 (150 mL), and solid anhydrous K_2CO_3 was added to basify and dry the solution. Filtration and concentration afforded a pale yellow oil which was chromatographed on silica gel with 10:90 EtOAc–hexane affording 0.98 g (96%) of an oil: IR (NaCl) 1726 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.20 (m 5 H, ArH_5), 6.53–6.42 (m, 2 H, HC=CH), 3.65–3.63 (m, 1 H, C_1-H), 3.64 (d, 1 H, J = 13.5 Hz, $CHHPh$), 3.51 (d, 1 H, J = 13.5 Hz, $CHHPh$), 3.11–3.05 (m, 1 H, C_4-H), 2.35–2.28 (m, 1 H, C_3-H),

2.23 (dd, 1 H, J = 18, 2.5 Hz, C_6-H), 2.00 (dd, 1 H, J = 18, 3 Hz, C_6-H), 1.59–1.25 (m, 4 H, CH_2CH_2), 0.89 (t, 3 H, J = 7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 139.6, 134.8, 129.0, 128.7, 128.4, 127.2, 63.4, 61.1, 53.6, 52.9, 42.4, 39.2, 19.7, 14.3; MS (CI, NH_3) m/e 256 (MH^+, base peak). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.94; H, 8.30. Found: C, 80.03; H, 8.37.

(1*R,3*S**,4*S**,5*S**)-2-Benzyl-3-(1-propyl)-5-[(*E*)-2-(dimethylphenylsilyl)-1-ethenyl]-2-azabicyclo[2.2.2]oct-7-en-5-ol (5b).** (*E*)-1-(Tri-*n*-butylstannyl)-2-(dimethylphenylsilyl)ethene[15] (1.74 g, 3.85 mmol) was dissolved in THF (30 mL) and cooled to −78 °C. *n*-Butyllithium (3.87 mmol) was added and the mixture stirred for 2 h, allowed to warm to −30 °C over 15 min and immediately recooled to −78 °C. Ketone **4b-2** (644 mg, 2.52 mmol) in THF (17 mL) was added and the mixture stirred for 2 h and then warmed to 0 °C over 15 min before quenching with saturated $NaHCO_3$. The THF was removed in vacuo, the aqueous residue diluted with saturated $NaHCO_3$, and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to given an oil which was chromatographed on silica gel with a gradient of hexane to 10:90 EtOAc–hexane affording 975 mg (92%) of an oil: IR (NaCl) 3471 (br), 1608 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.09 (m, 10 H, ArH_5 + ArH_5), 6.37 (t, 1 H, J = 7 Hz, C_8-H), 6.04–5.94 (m, 2 H, C_7-H + SiC=CH), 5.76 (dd, 1 H, J = 19, 3 Hz, SiCH=C), 3.53 (d, 1 H, J = 14 Hz, C*H*HPh), 3.27–3.21 (m, 1 H, C_1-H), 3.46 (d, 1 H, J = 14 Hz, CH*H*Ph), 2.32 (d, 1 H, J = 6.5 Hz, C_4-H), 2.07–1.88 (m, 2 H, C_3-H + C*H*CH_2CH_3), 1.82–1.53 (m, 3 H, C*H*HCH_2CH_3 + C_6-H + OH), 1.48–1.12 (m, 2 H, CH_2CH_3), 0.84 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 0.22 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 140.5, 138.8, 135.2, 133.7, 129.4, 128.9, 128.6, 128.1, 127.7, 126.7, 121.7, 75.9, 64.9, 60.3, 51.2, 44.5, 44.2, 36.8, 20.6, 14.5, −2.4, −2.5; MS (CI, NH_3) m/e 418 (MH^+, base peak). Anal. Calcd for $C_{27}H_{35}NOSi$: C, 77.63; H, 8.46. Found: C, 77.44; H, 8.25.

(2*S,4a*R**,5*S**,8a*R**)-1-Benzyl-2-(1-propyl)-(Δ-3,4)-5-(dimethylphenylsilyl)-7-oxooctahydroquinoline (6b).** Hydroxy diene **5b** (265 mg, 0.63 mmol) in DME (5 mL) was added to a suspension of KH (252 mg, 10 equiv) in DME (2 mL). The resulting suspension was stirred at 105 °C for 8.5 h, cautiously poured onto 50:50 ice–saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography on silica with a gradient of 100% hexane to 10:90 EtOAc–hexane afforded 209 mg (79%) of an oil: IR (NaCl) 1710 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.20 (m, 10 H, ArH_5 + ArH_5), 5.88 (dt, 1 H, J = 10.5, 3 Hz, C_4-H), 5.69 (d, 1 H, J = 10.5 Hz, C_3-H), 3.83 (d, 1 H, J = 14 Hz, C*H*HPh), 3.73 (d, 1 H, J = 14 Hz, CH*H*Ph), 3.09–2.97 (m, 2 H, C_2-H + C_{8a}-H), 2.79–2.70 (m, 1 H, C_{4a}-H), 2.60 (t, 1 H, J = 12.5 Hz, C_8-H), 2.29 (dd, 1 H, J = 13, 4.5 Hz, C_8-H), 2.24–2.09 (m, 2 H, C_6-H_2), 1.59–1.24 (m, 4 H, CH_2CH_2), 1.60 (ddd, 1 H, J = 12, 5, 3.5 Hz, C_5-H), 0.84 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.40 (s, 3 H, $SiCH_3$), 0.37 (s, 3 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 139.8, 137.1, 133.8, 132.8, 129.3, 128.34, 128.27, 128.0, 127.0, 124.2, 60.0, 59.8, 57.5, 44.8, 38.5, 38.4, 31.3, 26.9, 20.3, 14.1, −3.4, −3.8; MS (CI, NH_3) m/e 418 (MH^+, base peak). Anal. Calcd for $C_{27}H_{35}NOSi$: C, 77.63; H, 8.46. Found: C, 77.73; H, 8.57.

(2*S,4a*R**,5*S**,8a*R**)-1-Benzyl-2-(1-propyl)-(Δ-3,4)-5-hydroxy-7-oxooctahydroquinoline (14).** To a solution of ketone **6b** (206 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added 85% HBF_4·Et_2O (0.55 mL) and the reaction stirred at ambient temperature for 21 h. The mixture was then shaken for 2 min with 10% HCl (15 mL), basified with 15% KOH, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to give a yellow oil (161.6 mg) which was dissolved in DMF (40 mL). KF (274 mg, 10 equiv) was added and the solution stirred at room temperature for 15 min before 30% H_2O_2 (0.18 mL, ~3.5 equiv) was added. The mixture was stirred at 45 °C for 4.5 h, partitioned between saturated $NaHCO_3$ and CH_2Cl_2, and extracted. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography on silica gel with a gradient of 20:80–30:70 EtOAc–hexane afforded 108 mg (73%) of an oil: IR (NaCl) 3386 (br), 1713 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.12 (m, 5 H, ArH_5), 5.92–5.77 (m, 2 H, HC=CH), 5.25 (br s, 1 H, OH), 4.14–4.06 (m, 1 H, C_5-H), 3.97 (d, 1 H, J = 16 Hz, C*H*HPh), 3.69 (d, 1 H, J = 16 Hz, CH*H*Ph), 3.43–3.35 (m, 1 H, C_{8a}-H), 3.09–3.00 (m, 1 H, C_2-H), 2.96–2.85 (m, 1 H, C_8-H), 2.65–2.55 (m, 2 H, C_6-H + C_{4a}-H), 2.49–2.36 (m, 2 H, C_6-H + C_8-H), 1.63–1.42 (m, 2 H, $CH_2CH_2CH_3$), 1.37–1.17 (m, 2 H, CH_2CH_3), 0.80 (t, 3 H, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 138.2, 131.9, 128.4, 128.2, 127.1, 124.3, 70.5, 60.1, 59.3, 54.7, 49.1, 44.4, 39.8, 36.2, 18.4, 14.5; MS (CI, NH_3) m/e 300 (MH^+, base peak). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.20; H, 8.43. Found: C, 74.55; H, 8.62.

(2*S,4a*S**,5*S**,8a*R**)-1-Benzyl-2-(1-propyl)-(Δ-3,4)-5-methyl-(Δ-6,7)-7-[(trifluoromethanesulfonyl)oxy]hexahydroquinoline (15).** The β-hydroxy ketone **14** (92.4 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C before NEt_3 (0.21 mL, 5 equiv) was added followed by mesyl chloride (49 μL, 2 equiv). After 50 min at 0 °C the solution was cooled to −78 °C and DBN (0.19 mL, 5 equiv) was added. After 15 min the mixture was poured onto ice-cold 5% NaH_2PO_4 and quickly extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to give 108 mg of a dark yellow oil which was immediately dissolved in THF (7 mL) and added to a −78 °C solution of lithium dimethylcuprate (1.5 equiv) in Et_2O (9 mL). The mixture was stirred at −78 °C for 45 min and then warmed to 0 °C and stirred for 35 min before $PhNTf_2$ (114 mg, 1 equiv) in THF (5 mL) was added. The reaction was stirred at 0 °C for 2 h, warmed to ambient temperature and stirred 1 h and then filtered through a glass frit. The filtrate was concentrated to a brown oil which was flash chromatographed on silica gel with a gradient of hexane to 10:90 EtOAc–hexane affording 61 mg (46% from **14**) of an oil: IR (NaCl) 1692 (w), 1417 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.12 (m, 5 H, ArH_5), 5.64 (s, 2 H, HC=CH), 5.48 (d, 1 H, J = 4 Hz, C_6-H), 3.77 (d, 1 H, J = 15 Hz, C*H*HPh), 3.64 (d, 1 H, J = 15 Hz, CH*H*Ph), 3.02–2.95 (m, 2 H, C_2-H + C_{8a}-H), 2.50–2.40 (m, 1 H, C_5-H), 2.34 (dd, 1 H, J = 18, 7 Hz, C_8-H), 2.12 (dd, 1 H, J = 18, 6 Hz, C_8-H), 2.03–1.96 (m, 1 H, C_{4a}-H), 1.51–1.17 (m, 4 H, CH_2CH_2), 0.99 (d, 3 H, J = 7 Hz, C_5-CH_3), 0.82 (t, 3 H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 140.6, 130.9, 128.3, 127.9, 126.9, 121.8, 120.5, 116.2, 60.3, 59.1, 53.2, 39.1, 36.7, 35.0, 30.9, 20.1, 19.3, 14.3; MS (CI, NH_3) m/e 430 (MH^+, base peak). Anal. Calcd for $C_{21}H_{26}F_3NO_3S$: C, 58.71; H, 6.11. Found: C, 58.90; H, 6.31.

(2*S,4a*S**,5*S**,8a*R**)-2-(1-Propyl)-5-methyldecahydroquinoline, Hydrochloride Salt (195A·HCl).** 10% Palladium on carbon (54 mg) was suspended in MeOH (2 mL) and stirred under 1 atm of H_2 for 2.5 h before the enol triflate **15** (29 mg, 0.068 mmol) was added in MeOH (3.5 mL). After being stirred under 1 atm of H_2 for 20 h, the mixture was filtered through a pad of Celite and the filtrate concentrated to give a residue which was basified with 15% KOH and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to give 9.2 mg of an oil which was treated with HCl–saturated Et_2O and concentrated to give a waxy solid. Trituration with hexane afforded 10.2 mg (60%) of a white solid, mp 238–239 °C (2-methylpropanol) (lit.[50] mp 231–233 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (br s, 1 H, NH), 8.21 (br s, 1 H, NH), 3.26 (d, 1 H, J = 10.5 Hz, C_{8a}-H), 3.00–2.83 (m, 1 H, C_2-H), 2.48–1.13 (m, 16 H), 0.86 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.83 (d, 3 H, J = 6.5 Hz, C_5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.0, 57.9, 40.8, 34.8, 34.4, 29.1, 27.1, 25.2, 23.1, 20.5, 19.7, 19.1, 13.7; MS (free base) (CI, NH_3) m/e 196 (MH^+, base peak).

(2*S,4a*R**,5*S**,8a*S**)-1-Methyl-2-(1-propyl)-(Δ-3,4)-5-(dimethylphenylsilyl)-7-(triisopropylsiloxy)-(Δ-7,8)-hexahydroquinoline (18).** Hydroxy diene **5a** (75 mg, 0.22 mmol) in DME (3 mL) was added to a suspension of KH (92 mg, 10 equiv) in DME (2 mL). The resulting suspension was heated at 105 °C for 7 h before being cooled to 0 °C and adding triisopropylsilyl trifluoromethanesulfonate (89 μL, 1.5 equiv). After 30 min, NEt_3 (1 mL) was added and the mixture poured onto saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), filtered, and concentrated to give a yellow oil that was flash chromatographed on silica gel using 10:90 EtOAc–hexane affording 50 mg (46%) of an oil: IR (NaCl) 1664 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2 H, ArH_2), 7.40–7.33 (m, 3 H, ArH_3), 5.70 (dt, 1 H, J = 10.5, 3 Hz, C_4-H), 5.50 (d, 1 H, J = 10.5 Hz, C_3-H), 4.75 (br s, 1 H, C_8-H), 3.46–3.39 (m, 1 H, C_{8a}-H), 2.83–2.74 (m, 1 H, C_2-H), 2.74–2.66 (m, 1 H, C_{4a}-H), 2.50 (s, 3 H, N-CH_3), 2.15–2.01 (m, 1 H, C_6-H), 1.89–1.75 (m, 1 H, C_6-H), 1.68–1.56 (m, 1 H, C*H*HCH_2CH_3), 1.45–1.21 (m, 4 H, CH*H*CH_2CH_3 + C_5-H), 1.17–0.98 (m, 21 H, $((CH_3)_2CH)_3Si$), 0.87 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.38 (s, 3 H, $SiCH_3$), 0.36 (s, 3 H, $SiCH_3$); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 150.7, 138.2, 133.8, 130.9, 129.0, 127.8, 124.2, 106.2, 58.9 (two coincident peaks), 43.1, 36.7, 31.6, 29.6, 27.8, 26.0, 22.6, 20.7, 17.9, 14.1, 12.6, -3.4, -3.7; MS (CI, isobutane) *m/e* 498 (MH^+, base peak).

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A Novel Stereospecific Rearrangement of 3-Substituted B-Homo 5-Azasteroids to Their A-Nor Analogues. Preparation, Stereochemistry, and Conformational Studies

Thomas G. Back,* Joseph H.-L. Chau, Penelope W. Codding, Patricia L. Gladstone,[1a] David H. Jones, Jacek W. Morzycki,[1b] and Aleksander W. Roszak[1c]

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

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The novel 3α- and 3β-hydroxy-*B*-homo-5-azasteroid lactams **4** and **5** were prepared from testosterone. When the hydroxyl group in these compounds is converted into a leaving group, rearrangement to the corresponding A-nor azasteroids occurs under a variety of conditions, along with competing substitution with inversion of configuration at C-3. The rearrangements proceed with complete stereospecificity and are faster and more efficient in the 3α-series. The observed stereochemistry, as well as the results of molecular modeling, low-temperature NMR, and X-ray crystallographic studies support a mechanism involving neighboring-group participation by the nitrogen atom in the departure of the nucleofuge from C-3 via the formation of aziridinium ion intermediates. Compounds in the 3α-series require prior ring-flipping to the A-boat conformation, while those in the 3β-series react through the corresponding A-chairs. The differences in the free energies of the A-boat and A-chair forms are greater in the 3β-compounds (1.6-3.4 kcal/mol) than in the corresponding 3α-isomers (0.1-1.3 kcal/mol). The 3α-chloro derivative **19** exists mainly as the A-chair in solution (ΔG = 0.3 kcal/mole; ΔG^* = 12.2 kcal/mol), but crystallizes in the A-boat conformation. Molecular modeling studies of several 3-substituted derivatives and X-ray investigations of **19** and its 3β-isomer **20** also reveal separate flip forms of the B-rings associated with the A-chair and A-boat conformations in each case. Relief of steric hindrance between one of the hydrogen atoms at C-19 and the β-hydrogen at C-7 (this H-H contact is only 1.98 Å in the crystal structure of **19**) in the A-boat conformations of the 3α-series enhances anchimeric assistance to the departure of the leaving group and facilitates the rearrangements of these compounds relative to their 3β-counterparts.

Azasteroids display diverse types of biological activity,[2] and consequently their preparation and further transformations are of importance.[3] Our work with azasteroids[4] has been directed toward the design and synthesis of novel analogues where the nitrogen atom is part of a latent or existing reactive functionality that can be used to form covalent bonds with complementary groups within the active sites of receptor proteins or enzymes involved in steroid biosynthesis.

Such compounds have possible uses as affinity labels, enzyme inhibitors, and anticancer agents. In particular, we wished to determine whether neighboring group participation by a nitrogen atom placed at the 5-position would affect the behavior of nucleofugal substituents attached at C-3. By analogy, the alkylating properties of

(1) (a) Summer undergraduate research assistant, 1989. (b) Visiting scientist on sabbatical leave (1990-1991) from the University of Warsaw, Bialystok Branch, Institute of Chemistry, Al. J. Pilsudskiego 11/4, 15-443 Bialystok, Poland. (c) Present address: Department of Chemistry, Queen's University, Kingston, Ontario, Canada.

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