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Some Observations Regarding the Stereochemical Course of Iminium Ion Reductions: An Example of the Size Difference Between Sodium Cyanoborohydride and Sodium Triacetoxyborohydride

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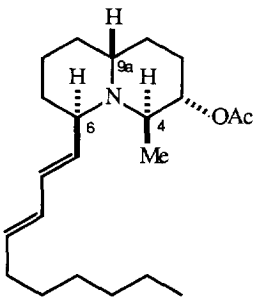
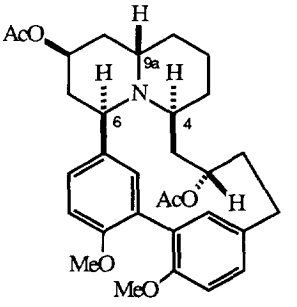
Abstract: The stereochemical course of reductions of iminium ions with sodium cyanoborohydride and sodium triacetoxyborohydride was examined within the context of model studies directed toward the synthesis of the quinolizidine alkaloid clavepictine A. Conformational preferences of the iminium ion and and effective size of the reducing agent were shown play a role in determining reduction stereochemistry.

Introduction. Clavepictine A (**1**) is a quinolizidine alkaloid recently isolated from the tunicate *Clavelina picta*.[1] This alkaloid is structurally related to *Lythraceae* alkaloids, such as lythrancepine-III (**2**), in that the relative stereochemistry of substituents at C_4, C_6, and C_{9a} of the quinolizidine are the same.[2] Several years ago we reported a synthesis of **2** that relied upon a stereoselective iminium ion reduction to establish stereochemistry at C_4 relative to C_6 and C_{9a}.[3] Thus, we decided to undertake a synthesis of the clavepictine A and related alkaloids using a similar strategy. Although this approach to **1** was ultimately unsuccessful, the study provided insight into factors controlling iminium ion reduction stereochemistry.[4] Given that this process plays a central role in many alkaloid syntheses, our results are reported herein.

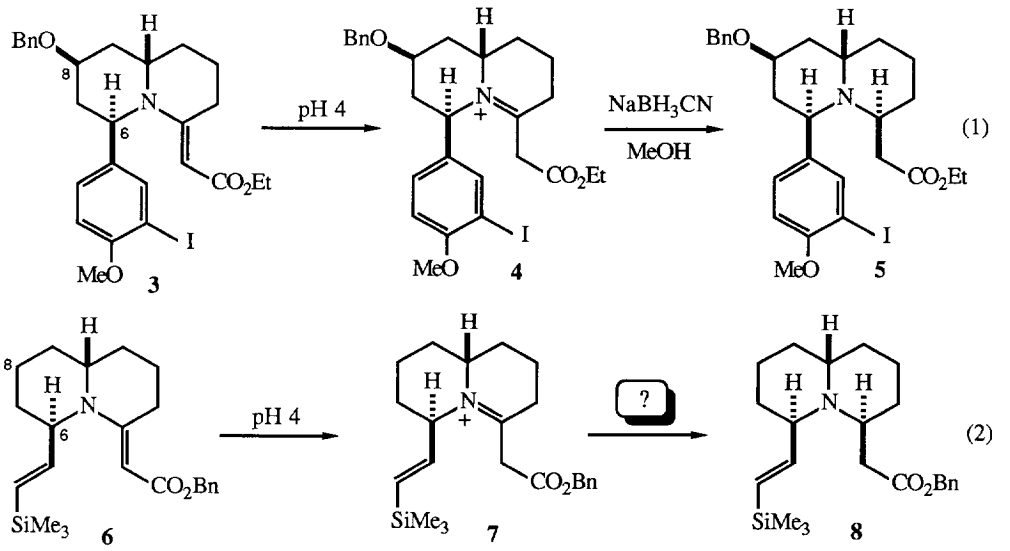


1 Clavepictine A



2 Lythrancepine-III

The stereoselective reduction of vinylogous urethane **3** to tertiary amine **5**, via iminium ion **4**, played a central role in the aforementioned synthesis of lythrancepine-III (eq. 1).[3] Thus, within the context of clavepictine model studies, it was our hope that reduction of **6**, via iminium ion **7**, would provide quinolizidine **8** (eq. 2).

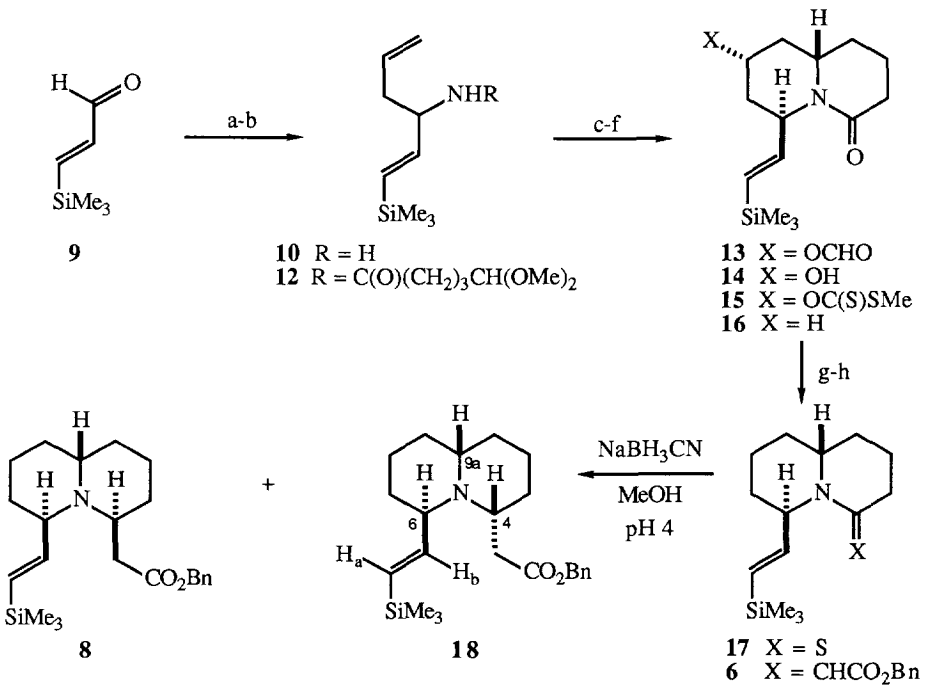


Results and Discusion. The preparation of **6** is outlined in Scheme 1. Sequential treatment of aldehyde **9** with lithium hexamethyldisilazide and allyl magnesium bromide gave homoallylic amine **10** in 80% yield.[5,6] The amine was treated with trimethylaluminum, followed by ester **11**[4b], to afford amide **12** in 84% yield.[7] N-Acyliminium ion cyclization of **12** gave formate ester **13** in 72% yield.[8] Application of the Barton-McCombie deoxygenation protocol to **13** afforded **16** in 71% overall yield via alcohol **14** and xanthate **15**.[9] Conversion of **16** to thiolactam **17** was accomplished in 86% yield with Lawesson's reagent and the synthesis of **6** was completed in 66% yield using an Eschenmoser sulfide contraction.[10,11]

To our surprise, reduction of **6** with sodium cyanoborohydride under acidic conditions gave a 3:1 mixture of **18** and **8**, respectively, in 85% yield (Scheme 1).[12] The stereochemistry of **18** was determined using nOe experiments. Thus, irradiation of H_{9a} gave enhancements of H_4 (6%) and H_b (11%), indicating a cis relation between H_{9a}, H_4, and the vinylsilane unit.

The stereochemical course of the reduction of **6** clearly differed from the reduction of **3**. Specifically, reduction of **6** provided a quinolizidine with a *trans*-relationship between the C_4 and C_6 substituents (**18**), while **3** gave a quinolizidine with a *cis*-relationship between these substituents (**5**). Thus, studies were undertaken to determine the reasons for this difference in behavior. The structural differences between **3** and **6** arise at C_6 and C_8. Therefore we decided to examine the behavior of vinylogous urethanes **19** and **22** (eq. 3).[13] Vinylogous urethane **19** behaved much like **3**, as reduction with sodium cyanoborohydride at pH 4 gave a 5:1 mixture of quinolizidines **20** and **21**, respectively, from which pure **20** was isolated in 70% yield.[14] Based on this result, we conclude that the nature of the C_6 substituent plays an important role in determining reduction stereochemistry.

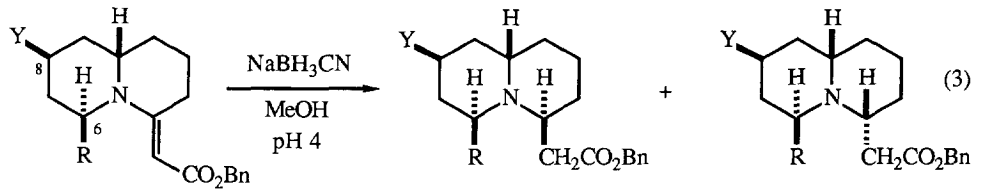
Scheme 1



(a) $LiN(SiMe_3)_2$; $CH_2{=}CHCH_2MgBr$ (b) $AlMe_3$, $(MeO)_2CH(CH_2)_3CO_2Me$ (**11**) (c) HCO_2H (d) NaOH, MeOH, H_2O (e) NaH; CS_2; MeI (f) *n*-Bu_3SnH, AIBN, $PhCH_3$, Δ (g) [*p*-MeOPhP(S)S]$_2$ (h) ICH_2CO_2Bn; Et_3N, Ph_3P

Vinylogous urethane **22**, however, behaved much like **6** as treatment with sodium cyanoborohydride gave a 1:1.7 ratio of **23** and **24**, respectively, in 77% yield. Thus, we conclude that the C_8 substituent has only a minor effect on the stereochemical course of these vinylogous urethane reductions. This was underscored by the observation that reductions of **25** and **26**, prepared from alcohol **14**, with sodium cyanoborohydride gave similar mixtures of reduction products **27-30** (eq. 4).[13, 14]

We decided to next examine sodium triacetoxyborohydride as a reducing agent under acidic conditions.[15] Once again, vinylogous urethanes **6**, **19**, **22**, **25**, and **26** were examined. The results are documented in Table 1. All of these reductions gave quinolizidines with a *cis*-relationship between the C_4 and C_6 substituents as the major products. Thus, *cis*-selectivity was dramatically enhanced, relative to the results obtained with sodium cyanoborohydride. It is clear that the choice of reducing agent also plays a role in determining the stereochemistry of these iminium ion reductions.

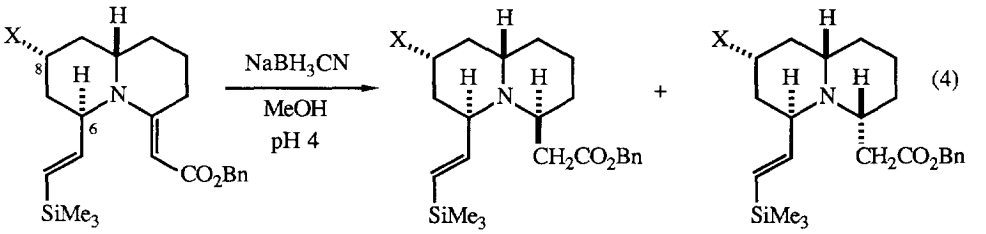


(3)

19 Y = H R = *m*-MeOPh
22 Y = OCOPh
R = (*E*)-$Me_3SiCH{=}CH$

20 Y = H R = *m*-MeOPh
23 Y = OCOPh
R = (*E*)-$Me_3SiCH{=}CH$

21 Y = H R = *m*-MeOPh
24 Y = OCOPh
R = (*E*)-$Me_3SiCH{=}CH$



(4)

25 X = OH
26 X = OAc

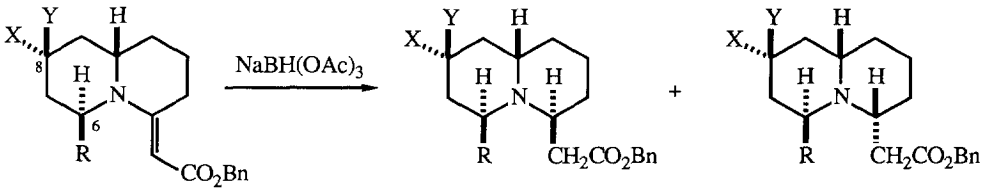
27 X = OH
29 X = OAc

28 X = OH
30 X = OAc

One model that rationalizes these results is outlined in Scheme 2. First, we assume that all of the observed stereoselectivities are kinetically controlled, as has previously been demonstrated for the conversion of **3** to **5**.[3] Next, we presume that the reductions occur via intermediate iminium ions derived from protonation of the starting vinylogous urethanes. We imagine that these ions prefer conformations **31** and **32** in which (i) the C_6-substituent occupies an axial site to avoid $A^{(1,3)}$-strain and (ii) the azomethine-containing ring adopts either of possible two half-chair conformations.[16] Finally, we assume that reduction of **31** and **32** occurs such that the products (**33** and **34**) are born in conformations with an antiperiplanar arrangement of the incoming hydride and the nitrogen lone-pair. This assumption is based on arguments popularized by Delongschamps and Stevens and invoked to explain a variety of iminium ion reductions.[4] Although we have no information regarding which reduction pathway is inherently favored, it does seem reasonable that as the size of the C_6-substituent increases, formation of **34** should become favored at the expense of **33**. For example, it is reasonable to assume that a C_6-aryl group is large relative to a C_6-vinyl group. This assumption is based on the notion that a C_6-aryl group should prefer a conformation in which it is orthogonal to a line passing through C_6 and C_9 while a C_6-vinyl group can easily adopt a conformation in which it is parallel to a line passing through C_6 and C_9.[17] Indeed, substrates **3** and **19** afford larger **34/33** product rations than substrates **6**, **22**, **25** or **26**, regardless of the reducing agent. It is less clear that increasing the effective size of the reducing agent should also favor formation of **34** at the expense of **33**, but this appears to be the case. In a classical test of reducing agent size, Hutchins determined that imines of 4-*tert*-butylcyclohexanone give principally *trans*-amines with sodium cyanoborohydride and *cis*-amines with sodium triacetoxyborohydride.[18,19]

Thus, sodium triacetoxyborohydride appears to be a sterically more demanding reagent than sodium cyanoborohydride. The iminium ions examined in our study all respond to this size difference by affording **34** as the major product. If the model described in Scheme 2 is correct, this means that the path leading from **31** to **33** is more sterically hindered that the path leading from **32** to **34**.

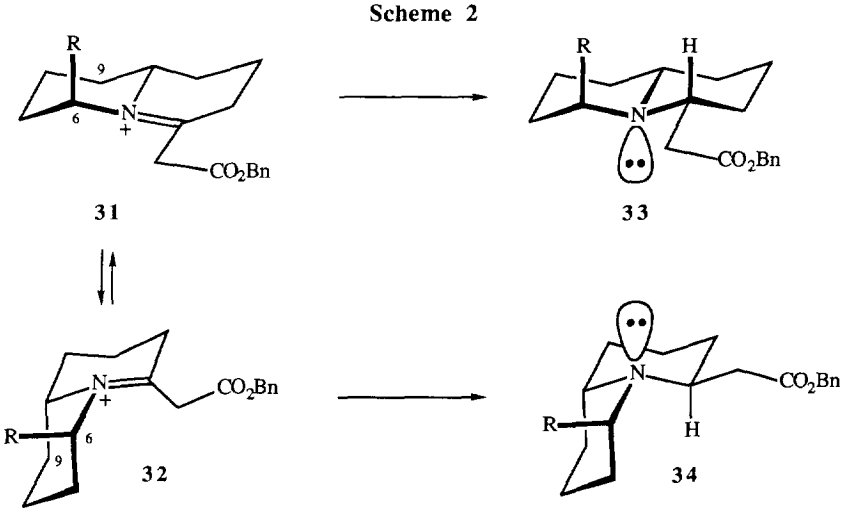
Table 1: Reduction of Iminium Ions with Sodium Triacetoxyborohydride



Substrate	R	X	Y	Products[a]	Yield[b]	Major:Minor[c]
6	(*E*)-TMSCH=CH	H	H	**8 + 18**	91%	3:1 (1:3)
19	*m*-MeOPh	H	H	**20 + 21**	92%	50:1[d] (5:1)
22	(*E*)-TMSCH=CH	H	OBz	**23 + 24**	72%	10:1 (1:2)
25	(*E*)-TMSCH=CH	OH	H	**27 + 28**	91%	5:1 (1: 2)
26	(*E*)-TMSCH=CH	OAc	H	**29 + 30**	96%	3:1 (1:2)

(a) Consult Scheme 1 and Equations 3-4 for specific structures of substrates and products. (b) Combined yield of major and minor products. (c) Product ratios for the sodium cyanoborohydride reductions are shown in parentheses. (d) None of the minor isomer (**21**) was detected.

Scheme 2



Although the aforementioned studies did provide access to a 4,6-disubstituted quinolizidine with the relative stereochemistry required for clavepictine A (**1**), the synthesis was eventually abandoned due to problems associated with introduction of the C_3-acetoxy group. Nonetheless, this study has shed some light on factors of importance in this family of iminium ion reductions and confirms the effective size difference between sodium cyanoborohydride and sodium triacetoxyborohydride. These results have some implications for the development of enantioselective routes to β-amino esters[20], and it is also hoped that these observations will be of some use in general the area of quinolizidine alkaloid synthesis.

Experimental Section

All melting and boiling points are uncorrected. ^{1}H NMR spectral were recorded using 200-300 MHz instruments and are recorded as follows: Chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants in Hz, integration, interpretation]. Interpretations were aided in certain cases by decoupling experiments. ^{13}C NMR spectra are reported as follows: chemical shift (multiplicity from DEPT spectra). Mass spectra were obained at an ionization potential of 70 ev. Solvents and reagents were dried and purified prior to use as necessary. Reactions requiring an inert atmosphere were run under a blanket of argon. Column chromatography was normally performed using flash chromatography conditions over silica gel.

1-(2-(*E*)-(Trimethylsilyl)ethenyl)-3-butenamine (10). To a solution of aldehyde **9**[5] (4.90 g, 38.3 mmol) in 50 mL of dry tetrahydrofuran cooled to 0 °C was added a solution of lithium hexamethyldisilazide [prepared by adding 35.3 mL of *n*-butyllithium (1.3 M in hexanes, 45.9 mmol) to a cooled to 0 °C solution of hexamethyldisilazide (7.39 g, 45.9 mmol) in 30 mL of dry tetrahydrofuran followed by stirring at 0 °C for 1 hour]. The mixture was stirred at rt for 1 h, cooled to 0 °C, and 53 mL of allylmagnesium bromide (0.94 M in diethyl ether, 49.8 mmol) was added. The mixture was stirred at rt for 30 min and then poured into 370 mL of saturated aqueous ammonium chloride. The organic layer was decanted and the aqueous phase extracted with three 120-mL portions of methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 120 g of silica gel, eluted with chloroform : methanol (20:1) to afford 6.47 g (80%) of amine **19** as a yellow liquid. A portion was distilled to afford a colorless liquid: bp 82-84 °C (15 mm); IR (neat) 3500-3100 (broad) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ -0.05 (s, 9H, $SiMe_3$), 1.5 (bs, 2H, NH_2), 1.9-2.2 (m, 2H, CH_2C=), 3.3 (m, 1H, NCH), 5.1 (m, 2H, =CH_2), 5.6 (m, 2H, =CH), 5.9 (dd, *J* = 19, 4 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ -1.4 (q), 41.8 (t), 54.9 (d), 117.3 (t), 127.9 (d), 134.9 (d), 149.9 (d); exact mass calcd. for $C_9H_{19}NSi$ - C_3H_5 *m/z* 128.0896, found *m/z* 128.0894 (base).

N-(3-(1-(*E*)-Trimethylsilyl)-1,5-hexadienyl)-5,5-dimethoxypentanamide (12). To a solution of amine **10** (4.16 g, 24.6 mmol) in 30 mL of dry methylene chloride was added 12.3 mL of trimethylaluminum (2 M in hexanes, 24.6 mmol) via syringe. The resulting mixture was stirred 50 min and followed by addition of methyl 5,5-dimethoxypentanoate[4b] (3.61 g, 20.5 mmol) in 7 mL of methylene chloride. The mixture was heated to reflux for 22.5 h, cooled to room temperature, and 20

mL of 1 M aqueous sodium hydroxide was carefully added. The layers were separated and the organic phase was washed with two 80-mL portions of 1 M hydrochloric acid and two 80-mL portions of water. The combined water layers were extracted with 50 mL of methylene chloride and the combined organics were dried ($MgSO_4$). Evaporation of the solvent afforded 5.37 g (84%) of **12** as a brown liquid, suitable for use in subsequent reactions. Bulb-to-bulb distillation of a small sample (0.5 mm Hg and less than 100 °C) afforded **12** as a colorless liquid: IR (neat) 3282 (broad), 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.05 (s, 9H, SiMe3), 1.6 (m, 4H), 2.2 (m, 4H), 3.2 (s, 6H, OCH_3), 4.3 (m, 1H, OCH), 4.5 (m, 1H, NCH), 5.0 (m, 2H, $=CH_2$), 5.6 (m, 3H, =CH and =CHSi and NH), 5.9 (dd, *J* = 19, 4.2 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ -1.44 (q), 20.7 (t), 31.8 (t), 36.1 (t), 38.9 (t), 51.35 (d), 52.7 (q), 104.3 (d), 117.7 (t), 129.3 (d), 133.9 (d), 145.0 (d), 171.7 (s); exact mass calcd. for $C_{16}H_{31}NO_3Si$ *m/z* 313.2073, found *m/z* 313.2054.

***rel*-(6β,8α,9aα)-8-Formyloxy-6-(2-(*E*)-trimethylsilyl)ethenyloctahydro-4H-quinolizin-4-one (13).** To a solution of acetal **12** (163.9 mg, 0.524 mmol) in 2.0 mL of methylene chloride was added 2.0 mL of formic acid. The mixture was stirred at rt for 2.5 h followed by careful addition of 4 mL of saturated aqueous sodium carbonate. The organic layer was decanted and the aqueous phase was extracted with three 10-mL portions of methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel, eluted with ethyl acetate : hexane (1:3) to afford 110.8 mg (72%) of lactam **12** as a pale yellow oil: IR (CH_2Cl_2) 1720, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 9H, SiMe3), 1.4 (q, *J* = 11.9 Hz, 1H, H(9)ax), 1.5 (m, 1H, H(1)a), 1.7 (m, 2H, H(2) and H(7)ax), 1.8 (m, 1H, H(2)), 2.0 (m, 2H, H(9)eq and H(1)eq), 2.3 (m, 1H, H(7)eq), 2.4 (m, 1H, H(3)), 2.5 (m, 1H, H(3)), 3.5 (m, 1H, H(9a)), 5.0 (tt, *J* = 11.5, 4.5 Hz, 1H, H(8)), 5.6 (m, 1H, H(6), 5.75 (dd, *J* = 19, 2 Hz, 1H, SiCH=), 5.81 (dd, *J* = 19, 2.7 Hz, 1H, CH=), 8.0 (s, 1H, OCHO); ^{13}C NMR ($CDCl_3$) δ -1.3 (q), 19.2 (t), 30.2 (t), 32.9 (t), 33.1 (t), 39.0 (t), 50.1 (d), 50.9 (d), 67.7 (d), 131.8 (d), 142.8 (d), 160.3 (d), 169.5 (s); exact mass calcd. for $C_{15}H_{25}NO_3Si$ *m/z* 295.1604, found *m/z* 295.1605.

***rel*-(6β,8α,9aα)-8-Hydroxy-6-(2-(*E*)-trimethylsilyl)ethenyloctahydro-4H-quinolizin-4-one (14).** To a solution of the formate ester **13** (95.4 mg, 0.32 mmol) in 2 mL of methanol was added 0.2 mL of 4M aqueous sodium hydroxide. The mixture was stirred 30 min at rt and then partitioned between 3 mL of water and 6 mL of methylene chloride. The aqueous phase was extracted with two 6-mL portions of methylene chloride, dried (Na_2SO_4), and concentrated in vacuo to afford 83.8 mg (96%) of **14** as a white powder. An analytically pure sample was prepared by recrystallization from dichloromethane-hexane: mp 119-120 °C; IR ($CHCl_3$) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, SiMe3), 1.25 (q, *J* = 11.7 Hz, 1H, H(9)a), 1.5 (m, 2H), 1.6-2.0 (m, 4H), 2.2 (m, 1H), 2.3-2.5 (m, 3H), 3.4 (m, 1H, H(9a)), 3.8 (m, 1H, H(8)), 5.5 (m, 1H, H(6)), 5.6 (dd, *J* = 18, 2 Hz, 1H, =CH), 5.8 (dd, *J* = 18, 3 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 19.2 (t), 30.4 (t), 33.0 (t), 37.3 (t), 43.0 (t), 50.5 (d), 51.3 (d), 64.7 (d), 130.7 (d), 143.6 (d), 169.8 (s); exact mass calcd. for $C_{14}H_{25}NO_2Si$ *m/z* 267.1655, found *m/z* 267.1656.

Anal. Calcd. for $C_{14}H_{25}NO_2Si$: C 62.87 ; H, 9.42. Found C, 62.78; H, 9.43.

***rel*-(6β,8α,9aα)-6-(2-(*E*)-(Trimethylsilyl)ethenyl)octahydro-4H-quinolizin-4-one-8-S-methyl dithiocarbonate (15).** To a suspension of sodium hydride (404 mg of 60% oil

dispersion rinsed rinsed free of oil with hexane, 10.1 mmol) in 10 mL of dry tetrahydrofuran was added alcohol **13** (1.50 g, 5.62 mmol) and imidazole (10 mg) in 20 mL of dry tetrahydrofuran. The resulting mixture was heated to 50 °C for 2.5 h, cooled to rt, and 1.5 mL of carbon disulfide was added. The mixture was heated to reflux for 30 min, cooled to rt, and 1.5 mL of methyl iodide was added. The mixture was heated to reflux for 30 min, cooled to rt, and then partitioned between 55 mL of water and 55 mL of methylene chloride. The aqueous phase was extracted with two 30-mL portions of methylene chloride and the organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel, eluted with ethyl acetate:hexane (1:2) to afford 1.85 g (93%) of **15** as a yellow solid. This material was suitable for use in subsequent reactions. A small portion was recrystallized from dichloromethane-hexane to afford an analytical sample of colorless crystals : mp 93-95 °C ; IR ($CHCl_3$) 1626 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9H, $SiMe_3$), 1.4-2.2 (m, 7H), 2.4 (m, 3H), 2.5 (s, 3H, SCH_3), 3.5 (m, 1H, H(9a)), 5.7 (m, 4H, H(8), H(6) and CH=CH); ^{13}C NMR ($CDCl_3$) δ -1.35 (q), 18.8 (q), 19.2 (t), 30.2 (t), 32.4 (t), 32.9 (t), 38.6 (t), 50.4 (d), 51.1 (d), 77.0 (d), 131.9 (d), 142.9 (d), 169.4 (s), 215.0 (s); exact mass calcd. for $C_{16}H_{27}NO_2S_2Si$ *m/z* 357.1253, found *m/z* 357.1289.

Anal. Calcd. for $C_{16}H_{27}NO_2S_2Si$: C 53.74 ; H, 7.61. Found C, 53.78; H, 7.65.

***rel*-(6β,9aα)-6-(2-(*E*)-Trimethylsilyl)ethenyloctahydro-4H-quinolizin-4-one (16).** To a solution of 2.44 g of tri-*n*-butyltin hydride (2.26 mL, 8.4 mmol) in 36 mL of dry toluene under reflux was added a solution of xanthate **15** (1.50 g, 4.2 mmol) in 36 mL of toluene dropwise over 1.5 h. The mixture was heated to reflux for another 13 h. The solvent was removed in vacuo and the crude product was chromatographed over silica gel, eluted with ethyl acetate : hexane (1:1.5), to afford 852 mg (81%) of **16** as a colorless oil : IR (neat) 1644 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H, $SiMe_3$), 1.1-2.0 (m, 10H, CH_2), 2.3 (ddd, *J* = 17, 12, 5 Hz, 1H, H(3ax)), 2.45 (dt, *J* = 17, 4.9 Hz, 1H, H(3eq)), 3.35 (b, 1H, H(9a)), 5.45 (b, 1H, H(6)), 5.6 (dd, *J* = 19, 2 Hz, 1H, =CH), 5.85 (dd, *J* = 19, 2.8 Hz, 1H, =CH) ; ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 19.07 (t), 19.7 (t), 28.3 (t), 30.8 (t), 33.1 (t), 34.0 (t), 50.9 (d), 52.0 (d), 130.6 (d), 144.0 (d), 169.6 (s) ; exact mass calcd. for $C_{14}H_{25}NOSi$ *m/z* 251.1706 , found *m/z* 251.1758.

***rel*-(6β,9aα)-6-(2-(E)-Trimethylsilyl)ethenyloctahydro-4H-quinolizin-4-thione (17).** To a solution of lactam **16** (333 mg, 1.33 mmol) in 6 mL of methylene chloride was added 295 mg of Lawesson's reagent (0.73 mmol) in one portion. The mixture was stirred at room temperature for 18 h and chromatographed directly over 20 g of silica gel, eluted with methylene chloride, to afford 304 mg (86%) of thiolactam **17** as a white solid, suitable for use in subsequent reactions. Recrystallization of a sample from methylene chloride-hexanes gave analytically pure material: mp 72 °C ; IR (CH_2Cl_2) 1611, 1476 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9H, $SiMe_3$), 1.3-1.9 (m, 8H, CH_2), 1.9-2.1 (m, 2H), 2.9-3.1 (m, 1H, H(3)), 3.1-3.2 (m, 1H, H(3)), 3.5 (m, 1H, H(9a)), 5.65 (dd, *J* = 19, 2 Hz, 1H, =CH), 5.85 (dd, *J* = 19, 2 Hz, 1H, =CH), 6.8 (m, 1H, H(6)); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 18.4 (t), 19.8 (t), 27.7 (t), 30.5 (t), 34.6 (t), 42.9 (t), 55.4 (d), 59.8 (d), 132.1 (d), 142.4 (d), 200.2 (s); exact mass calcd. for $C_{14}H_{25}NSSi$ *m/e* 267.1477, found *m/e* 267.1488.

Anal. Calcd. for $C_{14}H_{25}NSSi$: C 62.86 ; H, 9.42. Found C, 62.96; H, 9.46.

***rel*-(6β,9aα)-Benzyl α-[Octahydro-6-(2-(*E*)-trimethylsilyl)ethenyl-4H-quinolizin-4-ylidene]acetate (6).** A solution of thiolactam **17** (250 mg, 0.94 mmol) and benzyl iodoacetate (337 mg, 1.22 mmol) in 4.0 mL of methylene chloride was heated to reflux for 4 h. The solution was cooled and triphenylphosphine (319 mg, 1.22 mmol) and then triethylamine (284 mg, 2.81 mmol) were added. After stirring for 18 h, the solution was diluted with 20 mL of methylene chloride and 15 mL of 1M aqueous monobasic sodium phosphate was added. The aqueous layer was extracted with three 15-mL portions of methylene chloride and the organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel, eluted with methylene chloride : hexane (1:1 then 1:0), to afford 236 mg (66%) of **6** as a pale yellow oil: IR (neat) 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9H, SiMe3), 1.3-1.45 (m, 1H), 1.45-1.85 (m, 9H), 2.75 (m, 1H, H(3)a), 3.4 (m, 1H, H(9a)), 3.5 (dt, *J* = 17, 1.6 Hz, 1H, H(3)eq), 4.5 (broad s, 1H, H(6)), 4.7 (s, 1H, =CHCOO), 5.04 (d, *J* = 13 Hz, 1H, OCHPh), 5.07 (d, *J* = 13 Hz, 1H, OCHPh), 5.7 (dd, *J* = 19, 2 Hz, 1H, =CH), 5.8 (dd, *J* = 19, 3 Hz, 1H, =CH), 7.3 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 18.4 (t), 19.6 (t), 28.5 (t), 28.9 (t), 31.3 (t), 34.2 (t), 52.7 (d), 57.0 (d), 64.0 (t), 83.3 (d), 127.4 (d), 127.8 (d), 128.3 (d), 132.2 (d), 138.0 (s), 142.8 (d), 164.0 (s), 169 (s); exact mass calcd. for $C_{23}H_{33}NO_2Si$ *m/e* 383.2280 , found *m/e* 383.2291.

***rel*-(4α,6β,9aα)-Benzyl α-[Octahydro-6-(2-(*E*)-trimethylsilyl)ethenyl-4H-quinolizin-4-yl]acetate (18) and *rel*-(4β,6β,9aα)-Benzyl α-[Octahydro-6-(2-(*E*)-trimethylsilyl)ethenyl-4H-quinolizin-4-yl]acetate (8). A. Reduction of 6 with Sodium Cyanoborohydride:** To a solution of 50 mg of vinylogous urethane **6** (0.131 mmol) in 1.5 mL of dry methanol was added a trace of bromocresol green followed by 12.3 mg of sodium cyanoborohydride (0.196 mmol). The mixture was stirred at rt for 30 min while methanol-acetic acid (1:1) was added dropwise such that the solution maintained a yellow color. The reaction was neutralized with 0.1M aqueous sodium hydroxide. The aqueous layer was extracted with four 5-mL portions of methylene chloride and the organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel, eluted with ethyl acetate:hexane (1:2), to afford a 3:1 (by NMR) mixture of **18** and **8**, respectively (42.6 mg, 85%). Chromatography afforded a pure sample of **18**: IR (neat) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 9H, SiMe3), 1.1-8 (m, 12H), 2.2 (dd, *J* = 13.6, 9 Hz, 1H, CHCOO), 2.55 (br t, *J* = 10 Hz, 1H, H(9a)), 2.72 (br t, *J* = 10 Hz, 1H, H(4)), 2.8 (dd, *J* = 13.6, 3.6 Hz, 1H, CHCOO), 3.65 (m, 1H, H(6)), 5.1 (s, 2H, OCH_2Ph), 5.8 (dd, *J* = 18.7, 0.7 Hz, 1H, =CHSi), 6.5 (dd, *J* = 18.7, 8.7 Hz, 1H, =CH), 7.3 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 19.5 (t), 23.9 (t), 32.5 (t), 32.7 (t), 34.5 (t), 34.7 (t), 38.4 (t), 55.3 (d), 56.1 (d), 60.0 (d), 65.9 (t), 128.0 (d), 128.0 (d), 128.4 (d), 133.5 (d), 136.2 (s), 143.1 (d), 172.1 (s); exact mass calcd. for $C_{23}H_{35}NO_2Si$ *m/z* 385.2437 , found *m/z* 385.2429. Continued elution provided a small sample of **8** of sufficient purity to be characterized by ^1H-NMR: ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, SiMe3), 1.05 (m, 2H, CH_2), 1.25 (m, 2H, CH_2), 1.35-1.9 (m, 8H, CH_2), 2.5 (dd, *J* = 14.1, 7.3 Hz, 1H, CHCOO), 2.8 (dd, *J* = 14.2, 8.5 Hz, 1H, CHCOO), 3.1 (broad d, *J* = 10 Hz, 1H, H(9a)), 3.35 (m, 1H, H(6)), 3.6 (m, 1H, H(4)), 5.7 (d, *J* = 18.5 Hz, 1H, SiCH=), 5.8 (dd, *J* = 18.5, 6.5 Hz, 1H, CH=), 5.1 (d, *J* = 12.5 Hz, 1H, OCHPh), 5.2 (d, *J* = 12.4 Hz, 1H, OCHPh), 7.4 (s, 5H, ArH); The following signals in a ^{13}C-NMR spectrum of a mixture of **18** and **8** were assigned to **8**: ^{13}C NMR ($CDCl_3$) δ -1.1 (q), 19.2

(t), 20.4 (t), 21.7 (t), 23.9 (t), 30.8 (t), 33.4 (t), 37.5 (t), 49.2 (d), 52.4 (d), 60.7 (d), 65.8 (t), 127.9 (d), 128.1 (d), 128.4 (d), 129.6 (d), 136.4 (s), 151.4 (d), 172.3 (s). **B. Reduction of 6 with Sodium Triacetoxyborohydride:** To a solution of 26.5 mg (0.069 mmol) of vinylogous urethane **6** in 0.6 mL of dry acetonitrile was added 36.6 mg (0.176 mmol) of sodium triacetoxyborohydride followed by 0.6 mL of acetic acid. The mixture was stirred at rt for 1h, followed by addition of 3 mL of saturated aqueous sodium carbonate. The aqueous layer was saturated with sodium chloride and extracted with 5 mL of ether and four 5-mL portions of ethyl acetate. The organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was chromatographed over 15 g of silica gel, eluted with ethyl acetate containing 1% Et_3N, to afford 24.1 mg (91%) of a 3:1 mixture (by NMR) of **8** and **18**, respectively, as a colorless oil.

***rel*-(4β,6β,9aα)-Benzyl α-[Octahydro-6-(3-methoxyphenyl)-4H-quinolizin-4-yl]acetate (20). A. Reduction of 19 with Sodium Cyanoborohydride:** To a cooled to 0 °C solution of vinylogous urethane **19**[13] (44.3 mg, 0.113 mmol) and a trace of bromocresol green in 1.0 mL of dry tetrahydrofuran and 1.0 mL of dry methanol was added sodium cyanoborohydride (14.2 mg, 0.226 mmol). The mixture was stirred under argon for 2.5 h at 0 °C while a dry acetic acid-methanol (1:1) was added dropwise to maintain a yellow color. The reaction was neutralized with 1 M sodium hydroxide and the aqueous layer was extracted with four 5-mL portions of methylene chloride. The organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a 5.2:1 mixture (by NMR) of **20** and **21**, respectively. The crude product was chromatographed over 25 g of silica gel, eluted with ethyl acetate : hexane (1:4 + 1% Et_3N), to afford 31 mg (70%) of amino ester **20** as a colorless oil: IR (neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8-2.1 (m, 12H), 2.45 (dd, *J* = 13.6, 6.9 Hz, 1H, CHCO), 2.9 (dd, *J* = 13.6, 8.9 Hz, 1H, CHCO), 3.15-3.4 (m, 2H, H(9a) and H(4)), 3.7 (s, 3H, OMe), 3.9 (m, 1H, H(6)), 4.95 (d, *J* = 12.6 Hz, 1H, OCHPh), 5.25 (d, *J* = 12.6 Hz, 1H, OCHPh), 6.8 (m, 3H, ArH), 7.1-7.4 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.9 (t), 20.4 (t), 21.1 (t), 22.9 (t), 31.1 (t), 37.0 (t), 37.3 (t), 49.6 (d), 51.8 (d), 55.0 (q), 59.6 (d), 65.7 (t), 112.5 (d), 112.7 (d), 119.8 (d), 127.8 (d), 128.4 (d), 129.1 (d), 136.4 (s), 146.9 (s), 159.7 (s), 172.1 (s), the signal at δ 127.8 probably represents two non-equivalent carbons based on its intensity; exact mass calcd. for $C_{25}H_{31}NO_4$ *m/z* 393.2305, found *m/z* 393.2303. Signals at δ 3.75 (OMe) and 4.3 (H(6)) in the crude product mixture were assigned to amino ester **21** and used to determine the product ratio. **B. Reduction of 19 with Sodium Triacetoxyborohydride:** To a solution of 64.2 mg (0.16 mmol) of vinylogous urethane **19** in 0.6 mL of dry acetonitrile was added 86.9 mg (0.41 mmol) of sodium triacetoxyborohydride followed by 0.6 mL of acetic acid. The mixture was stirred at 0 °C for 1h, followed by addition of 5 mL of saturated aqueous sodium carbonate. The aqueous layer was saturated with sodium chloride and extracted with 5 mL of ether and three 5-mL portions of ethyl acetate. The organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was chromatographed over a plug of activity I basic alumina, eluted with ethyl acetate, to afford 59.5 mg (92%) **20** as a colorless oil.

***rel*-(4β,6β,8β,9aα)-Benzyl α-[Octahydro-8-benzoyl-6-(2-((*E*)-trimethylsilyl)-ethenyl)-4H-quinolizin-4-yl]acetate (23) and *rel*-(4α, 6β, 8β, 9aα)-Benzyl α-[octahydro-8-benzoyl-6-(2-((*E*)-trimethylsilyl)ethenyl)-4H-quinolizin-4-yl]acetate (24). A. Reduction of 22 with Sodium Cyanoborohydride:** To a solution of vinylogous urethane **22**[13]

(86.0 mg, 0.17 mmol) and a trace of bromocresol green in 1.7 mL of dry tetrahydrofuran and 1.5 mL of dry methanol at 0 °C was added sodium cyanoborohydride (20.6 mg, 0.34 mmol) in one portion. The mixture was stirred under argon for 1 h at 0 °C with periodic addition of methanol-acetic acid (1:1) such that a yellow color was maintained. The reaction was then neutralized with 1 M sodium hydroxide and the aqueous layer was extracted with four 5-mL portions of methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel, eluted with ethyl acetate:hexane (1:3+ 1% Et_3N), to afford 66.2 mg (77%) of a 1:2 mixture (by NMR) of amino esters **23** and **24** as a colorless oil. Based on this mixture and spectral data collected on pure **23** (*vide infra*), the following spectral assignments were made for amino ester **24**: ^1H NMR ($CDCl_3$) δ -0.1 (s, 9H, $SiMe_3$), 2.3 (dd, *J* = 14, 9 Hz, 1H, CHCO), 6.65 (dd, *J* = 18.5, 9 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ -1.3, 23.7, 24.2, 32.2, 34.2, 38.1, 38.1, 49.8, 55.8, 59.4, 65.9, 68.7, 128.0, 128.2, 128.3, 128.4, 129.5, 129.5, 130.7, 132.7, 136.0, 144.4, 165.8, 172.0. **B. Reduction of 22 with Sodium Triacetoxyborohydride:** To a solution of vinylogous urethane **22** (86.5 mg, 0.17 mmol) in 1.5 mL of dry acetonitrile and 1.5 mL of dry acetic acid at 0 °Cwas added sodium triacetoxyborohydride (97.2 mg, 0.46 mmol) in one portion. The mixture was stirred under argon for 4 h at 0 °C followed by addition of 8 mL of saturated aqueous sodium carbonate. The aqueous layer was extracted with one 6-mL portion of ether and two 6-mL portions of ethyl acetate. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to afford a 10:1 mixture (by NMR) of amino esters **23** and **24**. The crude product was purified over 15 g of silica gel eluted with ethyl acetate:hexane (1:5 + 1% Et_3N) to afford 63 mg (72%) of amine **23** as a colorless solid: mp 88-90 °C; IR (CH_2Cl_2) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9H, $SiMe_3$), 1.0-1.3 (m, 2H), 1.4 (q, *J* = 11.5 Hz, 1H), 1.5-1.20 (m, 7H), 2.45 (dd, *J* = 14, 6.5 Hz, 1H, CHCO), 2.9 (dd, *J* = 14, 9.6 Hz, 1H, CHCO), 3.35 (m, 1H, H(9a)), 3.6 (m, 2H, H(6) and H(4)), 5.1 (d, *J* = 12.4 Hz, 1H, OCHPh), 5.2 (tt, *J* = 11.6, 4.7 Hz, 1H, H(8)), 5.3 (d, *J* = 12.3 Hz, 1H, OCHPh), 5.8 (m, 2H, CH=CH), 7.2-7.6 (m, 8H, ArH), 8.0 (d, *J* = 7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.4 (q), 20.5 (t), 21.0 (t), 24.1 (t), 36.1 (t), 37.5 (t), 38.8 (t), 49.4 (d), 51.8 (d), 59.3 (d), 65.8 (t), 68.8 (d), 127.9 (d), 128.1 (d), 128.3 (d), 128.4 (d), 129.4 (d), 130.6 (s), 130.8 (d), 132.7 (d), 136.3 (s), 149.5 (d), 165.9 (s), 171.9 (s); exact mass calcd. for $C_{30}H_{39}NO_4Si$ *m/z* 505.2650, found *m/z* 505.2652.

***rel*-(4β,6β,8α,9aα)-Benzyl α-[Octahydro-8-hydroxy-6-(2-(*E*)-trimethylsilyl)-ethenyl-4H-quinolizin-4-yl]acetate (27) and *rel*-(4α,6β,8α,9aα)-Benzyl α-[Octahydro-8-hydroxy-6-(2-(*E*)-trimethylsilyl)ethenyl-4H-quinolizin-4-yl]acetate (28). A. Reduction of 25 with Sodium Cyanoborohydride:** To a solution of vinylogous urethane **25**[13] (25.2 mg, 0.063 mmol) in 0.7 mL of tetrahydrofuran and 0.7 mL of dry methanol was added a trace of bromocresol green followed by sodium cyanoborohydride (8.0 mg, 0.13 mmol). The mixture as stirred for 10 min while a mixture of dry acetic acid-methanol (1:1) was added dropwise such that a yellow color was maintained. The mixture was neutralized with saturated aqueous sodium carbonate and extracted with four 5-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel, eluted with ethyl acetate (+ 1% triethylamine), to afford 20 mg (79%) of a 1:1.8 mixture (by NMR) of **27** and **28** as a colorless oil. **B. Reduction of 25 with Sodium Triacetoxyborohydride:** To a solution of vinylogous urethane

25 (41.5 mg, 0.104 mmol) in 2.0 mL of dry acetonitrile and 1.0 mL of dry acetic acid was added sodium triacetoxyborohydride (155 mg, 0.728 mmol) in one portion. The solution was stirred at rt for 2.5 h followed by addition of 3 mL of saturated aqueous sodium carbonate. The aqueous layer was extracted with four 10-mL portions of ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel, eluted with ethyl acetate : hexane (1:1 then 1:0), to afford 32 mg (77%) of **27** as a pale yellow oil: IR (neat) 3416, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H, $SiMe_3$), 1.3-1.8 (m, 11H), 2.4 (dd, *J* = 14.7, 6.8 Hz, 1H, CHCOO), 2.7 (dd, *J* = 14.7, 8 Hz, 1H, CHCOO), 3.05 (m, 1H, H(9a)), 3.45 (m, 1H, H(4)), 3.65 (m, 1H, H(6)), 3.9 (m, 1H, H(8)), 5.05 (d, *J* = 12.3 Hz, 1H, OCHPh), 5.15 (d, *J* = 12.3 Hz, 1H, OCHPh), 5.8 (d, *J* = 19.8 Hz, 1H, =CHSi), 5.95 (dd, *J* = 18.9, 5.3 Hz, 1H, =CH), 7.4 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 19.8 (t), 28.5 (t), 29.7 (t), 36.1 (t), 36.4 (t), 38.6 (t), 49.0 (d), 51.5 (d), 57.8 (d), 65.7 (d), 66.0 (t), 128.1 (d), 128.2 (d), 128.5 (d), 130.0 (d), 136.1 (s), 149.3 (d), 172.3 (s); exact mass calcd. for $C_{23}H_{35}NO_3Si_2$ *m/z* 401.2386, found *m/z* 401.2378. Continued elution afforded 4.5 mg (10%) of amino ester **28** as a pale yellow oil: IR (neat) 3390, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9H, $SiMe_3$), 1.1-1.8 (m, 9H), 1.95 (m, 2H, CH_2), 2.3 (dd, *J* = 14.1, 9.1 Hz, 1H, CHCOO), 2.5-2.8 (m, 3H, H(4), H(9a), CHCOO), 3.85 (m, 2H, H(8), H(6)), 5.1 (s, 2H, OCH_2Ph), 5.8 (dd, *J* = 18.6, 0.7 Hz, 1H, =CHSi), 6.35 (dd, *J* = 18.6, 2.6 Hz, 1H, =CH), 7.3 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.2 (q), 23.8 (t), 32.3 (t), 34.4 (t), 38.5 (t), 41.7 (t), 43.6 (t), 54.0 (d), 55.8 (d), 60.7 (d), 64.8 (d), 66.0 (t), 128.1 (d), 128.3 (s), 128.5 (d), 134.4 (d), 136.1 (s), 142.1 (d), 171.8 (s); exact mass calcd. for $C_{23}H_{35}NO_3Si_2$ *m/z* 401.2386, found *m/z* 401.2375.

***rel*-(4β,6β,8α,9aα)-Benzyl α-[Octahydro-8-Acetoxy-6-(2-(*E*)-trimethylsilyl)-ethenyl-4H-quinolizin-4-yl]acetate (29) and *rel*-(4α,6β,8α,9aα)-Benzyl α-[octahydro-8-Acetoxy-6-(2-(*E*)-trimethylsilyl)ethenyl-4H-quinolizin-4-yl]acetate (30). A. Reduction of 26 with Sodium Cyanoborohydride:** To a solution of vinylogous urethane **26**[13] (31.0 mg, 0.070 mmol) in 0.7 mL of tetrahydrofuran and 0.7 mL of dry methanol was added a trace of bromocresol green followed by sodium cyanoborohydride (8.5 mg, 0.14 mmol). The mixture as stirred for 20 min while a mixture of dry acetic acid-methanol (1:1) was added dropwise such that a yellow color was maintained. The mixture was neutralized with 1M aqueous sodium hydroxide and then extracted with four 5-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over 15 g of silica gel, eluted with ethyl acetate : hexane (1 : 2 + 1% triethylamine), to afford 31 mg (99%) of a 1: 2 mixture (by NMR) of amino esters **29** and **30** as a colorless oil: IR (neat) 1738, 1731, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 and 0.06 (two s, 9H, $SiMe_3$ of **29** and **30**, respectively), 1.2-2.0 (m, 10H, CH_2), 2.01 and 2.03 (two s, 3H, MeCOO of **30** and **29**, respectively), 2.3 (dd, *J* = 14.5, 5 Hz, 0.67H, $CHCO_2Bn$ of **30**), 2.45 (dd, *J* = 14.5, 6 Hz, 0.33H, $CHCO_2Bn$ of **29**), 2.6-2.9 (m , 2H, $CHCO_2Bn$ and NCH of **29** and **30**), 3.25 (m, 0.33H, NCH of **29**), 3.6 (m, 1H, NCH), 3.85 (m, 0.67H, NCH of **30**), 4.9 (m, 1H, H(8)), 5.1 (m, 2H, OCH_2Ph), 5.8 (m, 1.33H, CH=CH of **29** and **30** and =CHSi of **29**), 6.4 (dd, *J* = 16.6, 8.5 Hz, 0.67H, =CH of **30**), 7.2-7.4 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ -1.3 (q), 20.0 (t), 21.3 (q), 21.5 (q), 23.6 (t), 27.9 (t), 31.9 (t), 32.7 (t), 33.4 (t), 33.8 (t), 37.2 (t), 38.0 (t), 39.1 (t), 48.9 (d), 51.7 (d), 54.1 (d), 55.9 (d), 57.1 (d), 60.4 (d), 66.1 (t), 67.7 (d), 68.5 (d), 128.1 (d), 128.3 (d), 128.5 (d),

135.6 (d), 136.0 (s), 136.1 (s), 140.7 (d), 170.4 (s), 170.6 (s), 171.6 (s), 172.1 (s), signals due to **29** and **30** were not completely resolved; exact mass calcd. for $C_{25}H_{37}NO_4Si$ *m/e* 443.2500; found *m/e* 443.2496. **B. Reduction of 26 with Sodium Triacetoxyborohydride:** To a solution of vinylogous urethane **26** (30 mg, 0.068 mmol) in 0.6 mL of dry acetonitrile and 0.6 mL of dry acetic acid was added sodium triacetoxyborohydride (39 mg, 0.184 mmol) in one portion. The solution was stirred at rt for 1.5 h followed by addition of 3 mL of saturated aqueous sodium carbonate. The aqueous layer was extracted with one 5-mL portion of ether and four 5-mL portions of ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel, eluted with ethyl acetate (+ 1% triethylamine), to afford 29 mg (97%) of a 3 : 1 mixture (by NMR) of **29** and **30** as a colorless oil.

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References and Notes

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Yanagida, N. *Bull. Chem. Soc. Jap.* **1976**, *49*, 510) followed by application of a variant of the chemistry described in Scheme 1. Substrates **25** and **26** were prepared from **14** using variants of the route described in Scheme 1. Detailed procedures and spectra will appear in the Ph.D. thesis of V. Leroy (The Ohio State University) and are available from the authors upon request.

14. Stereochemical assignments for **20** and **21** were based on a comparison of NMR data with those of related compounds.[3] Stereochemical assignments for products resulting from reductions of **22**, **25** and **26** were based on a comparison of NMR data with spectra of **8** and **18**, whose structures were secured by nOe experiments as described in the text. For example, H_b for all products belonging to the same stereochemical series as **18** (see Scheme 1) appeared as a distinct doublet of doublets at approximately δ 6.6. This proton always appeared at approximately δ 5.7-5.8 in the diastereomeric reduction product.
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