Synthesis of Chiral Hydroxylated Quinolizidines via Vinylogous Bischler-Napieralski Nitrilium Ion Cyclizations

Angela L. Marquart, Brent L. Podlogar, Edward W. Huber, David A. Demeter, Norton P. Peet, Herschel J. R. Weintraub, and Michael R. Angelastro*

Marion Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, Ohio 45215-6300

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Treatment of the amido esters **9** and **17** with PPSE (polyphosphoric acid trimethylsilyl ester) followed by $NaBH_4$ in ethanol gave the quinolizidinones **11-14** and **19** via a vinylogous Bischler-Napieralski nitrilium ion cyclization-reductive lactamization two-step process. Subsequent ozonolysis and reduction afforded chiral hydroxylated quinolizidines in moderate to good yield. In contrast to five-membered-ring formation, six-membered-ring formation via nitrilium-ion cyclization requires a *p*-methoxy-substituted styryl terminator. The effect para-substituted styryl terminators have on the energy of activation and ΔH for the cyclization process has been calculated by semiempirical and *ab initio* methods.

Introduction

Pyrrolizidine, indolizidine, and quinolizidine alkaloids are prevalent natural products found in plants and microorganisms. Several of these alkaloids display biological activities of current interest.[1,2] A number of interesting approaches for the construction of hydroxylated indolizidines and pyrrolizidines have recently been developed,[3-10] whereas relatively few syntheses of hydroxylated quinolizidine systems have been reported. The isosteric homologue of castanospermine, the (1*R*, 2*R*, 3*S*, 9*S*, 9a-*R*)-1,2,3,9-tetrahydroxyquinolizidine,[11] was synthesized from D-glucofuranurono-6,3-lactone, and the quinolizidine analog of α-homonojirimycin has been obtained from a multiply protected iminoheptitol.[12] Several quinolizidine hemiaminals have been prepared from the enamine of (+)-nupraridine.[13] Likewise, perchlorate oxidation of 2,3,4,5,5a,6,7,8-octahydrocyclopent-[*b*]azepine gave the *N*-acylhemiaminal 1,2,3,6,7,8,9,9a-octahydro-9a-hydroxy-4*H*-quinolizidin-4-one.[14] Electroorganic reduction of a bicyclic pyridinium salt gave 1-hydroxyquinolizidine.[15] Preparation of 1-hydroxyquinolizidine has also been achieved by a two-step reduction of ethyl 3-(2-pyridyl)-3-oxobutyrate.[16] Additionally, the quinolizidine corresponding to 6-epicastanospermine and its 1-epi isomer have been prepared from 2,3,4-tri-*O*-benzyl-D-glucopyranose.[17]

We were intrigued by a route to pyrrolizidines and indolizidines reported by Gawley and Chemburker[18a] based on an intramolecular nitrilium ion cyclization followed by reductive lactamization. A potential advantage of this route over iminium and acyliminium ion cyclization routes is that a stereogenic center is formed in the cyclization which is amenable to asymmetric or stereospecific reduction or bridgehead elaboration.

The nitrilium ion route has been reported to fail for the construction of quinolizidines.[18a] Since the nitrilium ion cyclization route has potential for the preparation of chiral hydroxylated quinolizidines, we have studied this process. In this report we describe a novel route to chiral hydroxylated quinolizidines using vinylogous Bischler-Napieralski nitrilium ion cyclizations.

Results and Discussions

Our efforts to extend nitrilium ion cyclizations to the synthesis of quinolizidines began with the attempted PPSE (polyphosphoric acid trimethyl silyl ester)-mediated cyclization of the amido ester **3a** (Scheme 1), which was readily prepared by acylation of (*Z*)-5-phenyl-4-pentylamine[19] with glutaric anhydride in CH_2Cl_2, followed by esterification with triethyloxonium tetrafluorobate. All attempts to cyclize **3a** were unsuccessful.

During the course of our investigation, Gawley and Chemburker[18b] reported that nitrilium ion cyclizations

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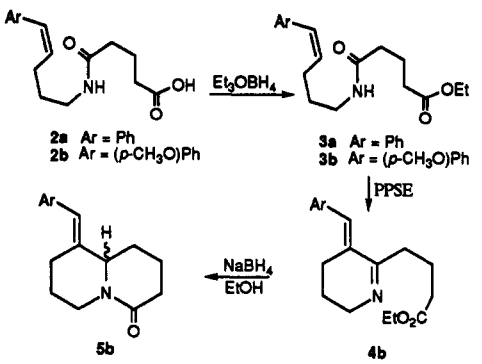
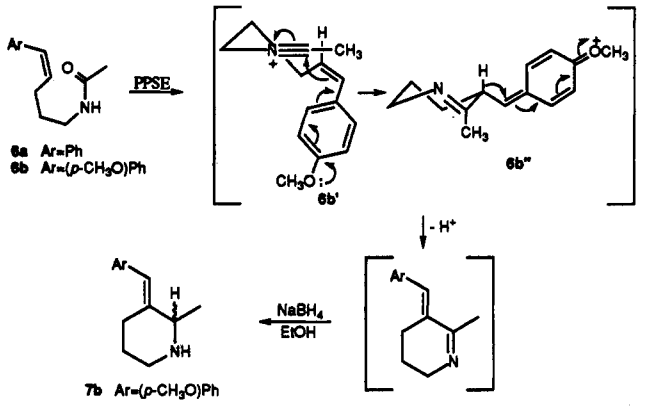
Scheme 1



Scheme 2



did not generate six-membered rings, based on the failure of methyl amide **6a** to cyclize (Scheme 2). These authors suggest that this failure stems from the inability of **6a** to achieve the appropriate orbital overlap geometry. Since the 6-*endo-dig* cyclization[20] is a favored process, we felt that its inability to undergo cyclization was related to its decreased rate of cyclization relative to that of five-membered-ring formation. A rate dependency for six-membered-ring formation has been reported in relation to biomimetic polyene cyclizations, in which the desired cyclizations are achieved provided the olefinic terminator is sufficiently nucleophilic to react with the cationic center at a rate greater than deprotonation.[21] In an effort to increase the rate of reaction via an increase in the nucleophilic character of the styryl terminator, we have incorporated a *p*-methoxy substituent. *We now wish to report that this modification has enabled six-membered ring formation via a vinylogous Bischler–Napieralski nitrilium ion cyclization.*

The amido ester **3b** was prepared in an analogous fashion to that of **3a**. Treatment of **3b** with PPSE afforded **4b** which was subjected to reductive lactamization with $NaBH_4$ in ethanol to afford the quinolizidinone **5b** in 80% overall yield from **3b**. For direct comparison to published results,[18b] the *N*-[5-(4-methoxyphenyl)-4-pentenyl]methylamide (**6b**) was prepared. Treatment of **6b** with PPSE followed by reduction with $NaBH_4$ gave the expected 3-[(4-methoxyphenyl)methylene]-2-methylpyrrolidine (**7b**) in 66% overall yield (Scheme 2).

To study the effect of the electron-donating substituent on the cyclization process, we have performed semiempirical charge density calculations for **3a** and **3b** (Figure 1). These calculations indicate that the ring substituent confers no significant effect upon the electron density at the nucleophilic carbon atom of the styryl terminator. There is, however, an approximate 2-fold increase in electron density at the carbon atom of the phenyl ring para to the methoxy group which may stabilize the incipient carbocation and reduce the energy of activation. This increase in electron density has been demonstrated by the effect of *p*-methoxy substitution in Pictet–Spengler cyclizations.[22]

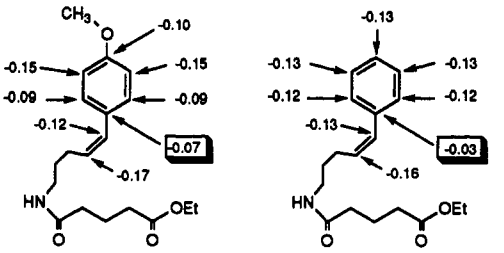
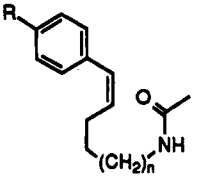


Figure 1. Semiempirical molecular orbital charge density calculations for **3a** and **3b**.

Table 1. Energy of Activation Values and Changes in Enthalpy Calculated for *N*-(5-Aryl-4-pentenyl)methylamides and *N*-(4-Aryl-3-butenyl)methylamides Undergoing PPSE-Mediated Nitrilium Ion Cyclization



compd no.	*n*	*R*	ΔH semiempirical	ΔH *ab initio*	E_a (kcal/mol) semiempirical	E_a (kcal/mol) *ab initio*
6b	1	OCH_3	−7.32	−8.96	14.55	18.22
6c	1	CH_3	−1.59	−1.55	16.58	20.51
6a	1	H	1.72	3.76	17.82	23.43
6d	1	CF_3	9.54	11.95	22.24	26.73
6e	0	OCH_3	0.65	−7.47	17.96	14.67
6f	0	H	8.25	3.14	20.70	20.80

To quantitate the effect para-substituted styryl terminators have on the energy of activation (E_a) and ΔH for the cyclization process described by **6b′** → **6b″** (Scheme 2), reaction coordinate calculations were conducted for a series of analogs containing substituents with sequentially decreasing electron-donating capabilities [i.e., OCH_3 (**6b**) > CH_3 (**6c**) > H (**6a**) > CF_3 (**6d**)] using semiempirical and *ab initio* molecular orbital theory (Table 1). The transition-state structure for **6b** and interatomic distances between the atoms undergoing ring closure for **6a–f** are shown in Figure 2. The calculations indicate that the E_a decreases as the electron-donating capacity of the para-substituent increases. This trend is also observed for the chain-shortened analogs **6e** and **6f** which undergo five-membered-ring formation. For the experimentally observed process **6b′** → **6b″**, the *ab initio* E_a is 5.21 kcal/mol lower than the unsubstituted system **6a**. This translates to an approximate 10 000-fold increase in the relative rate of reaction and is consistent with the difference in reactivity between substituted and unsubstituted systems. It is interesting to note that the ΔH for the process also increases as the electron-donating capacity of the sub-

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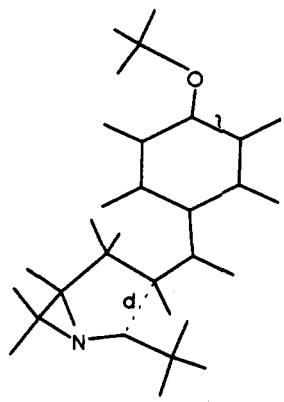


Figure 2. "Transition-state structure" for **6b**. The interatomic distances between the ring closure atoms are as follows: **6a**, 2.05 Å; **6b**, 2.04 Å; **6c**, 2.00 Å; **6d**, 1.93 Å; **6e**, 1.89 Å; and **6f**, 1.96 Å.

stituent decreases. This may suggest thermodynamic control if **6b′** and **6b″** are in equilibrium until quenching of the reaction. However, it is our opinion that **6b″** undergoes a rapid and exothermic deprotonation to form product. Kinetic control is supported by the reported[18] cyclization of **6f** despite a calculated positive ΔH of 3.14 kcal/mol.

We next turned our attention to the synthesis of chiral hydroxylated quinolizidines. The preparation of the chiral precursors was accomplished utilizing (*R*)- and (*S*)-γ-(alkoxycarbonyl)-γ-butyrolactones as the source of chirality (Scheme 3). The 3-substituted (benzoyloxy)quinolizidinones **11** and **12** were obtained via the treatment of **1b** with (*S*)-γ-(ethoxycarbonyl)-γ-butyrolactone to give the hydroxy ester **8a** which was benzoylated and then subjected to PPSE cyclization and reductive lactamization to give a 1:1 epimeric ratio of **11** and **12** in 56% yield from **9a**. Because it was not possible to definitively assign the bridgehead (C-9a) stereochemistry of **11** and **12**, **11** was reduced with $LiAlH_4$ to the amino alcohol **11b** (Scheme 4). The relative stereochemistry and olefin geometry of **11b** was assigned on the basis of NMR data. Coupling constants (see Experimental Section) indicated a chair–chair conformation of the bicyclic system. The bridgehead methine (H-9a, δ = 2.44, d, J = 10.8 Hz) and hydroxy methine (H-7, δ = 3.86, tt, J = 10.7 and 4.4 Hz) protons were both assigned as axial on the basis of the large coupling constants which were observed. These assignments were confirmed by a NOESY spectrum wherein typical NOE correlations were observed between 1,3-diaxial protons. Thus, NOE correlations were observed between H-9a and the protons H-8 axial, H-6 axial, and H-2 axial, consistent with the trans-fused ring junction shown. Similarly, an NOE correlation was observed between H-7 and H-9 axial confirming that H-7 is an axial proton. Since the absolute stereochemistry of H-7 was known to be *S* from the chiral γ-butyrolactone starting material, the absolute stereochemistry at C-9a was assigned as *R*.

The olefin geometry of **11b** was determined to be *E* based on these same NMR experiments. In the NOESY spectrum, NOE correlations were observed between the vinyl proton and the H-9a, H-9 equatorial and H-9 axial protons, which was consistent with a *cis* relationship between these protons. Similarly, an NOE correlation was observed between the aromatic protons and H-2 equatorial. On the basis of the assignments made for **11b**, the absolute stereochemistry of C-9a was assigned as *S* for **12** and the olefin geometry was confirmed as *E* based on the NOESY spectrum which was analogous to that above.

Quinolizidinones **13** and **14** were prepared in a similar fashion to **11** and **12** with the acyclic precursor **9b** being generated from **1b** and (*R*)-γ-(methoxycarbonyl)-γ-butyrolactone. In the two-step cyclization process, **13** and **14** were each produced in 24% yield.

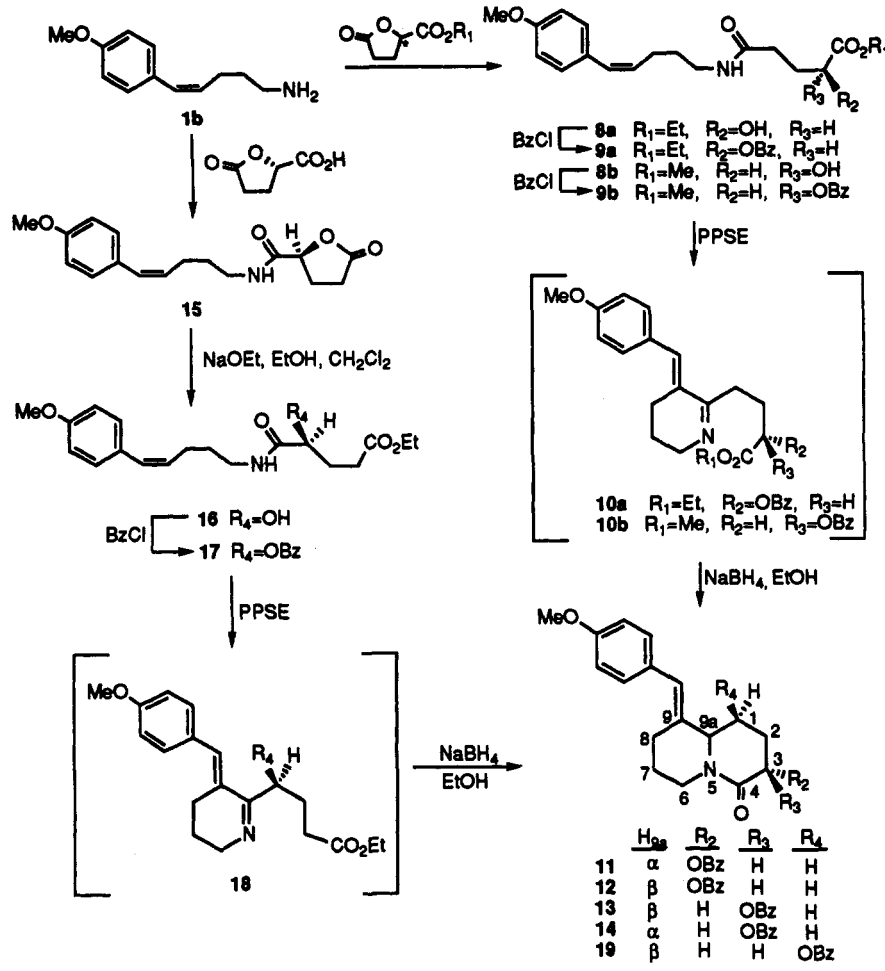
The synthesis of 1-(benzoyloxy)-substituted quinolizidinone **19** was achieved by the acylation of **1b** with the acid chloride derived from (*S*)-γ-carboxyl-γ-butyrolactone. The consecutive ethanolysis, benzoylation, cyclization, and reductive lactamization gave **19** in 43% yield from **17** as a single diastereomer. The stereochemistry of this diastereomer was shown to be 1*S* (1β,9a-β) after conversion to quinolizidinone **20b** and quinolizidine **23** as discussed below.

Treatment of **12** with ozone in CH_2Cl_2 at −78 °C followed by $NaBH_4$ reduction gave **20a** as a 9:1 (R:S) mixture of inseparable epimers at C-9 (Scheme 4). The relative stereochemistry of C-9 in the major epimer was determined by NMR based on the observed coupling constants of H-9 (δ 3.56, td, J = 10.0 and 4.3 Hz) and NOESY data. The 10.0-Hz coupling constant between H-9 and H-9a and the absence of an NOE correlation in the NOESY spectrum indicated a diaxial arrangement between these protons. Since the absolute stereochemistry at C-9a is *S* (see above), C-9 was assigned as *R*. Inversion of **20a** using DIAD/PPh_3/$PhCO_2H$ yielded the corresponding bis(benzoyloxy quinolizidinone (**21**) which was reduced with BH_3–SMe_2 to give diol **22** as a single isomer with 1*S* (1α,7α,9a-β) stereochemistry. Treatment of **19** with ozone followed by $NaBH_4$ reduction gave **20b** as a single diastereomer. NMR analysis indicated that in solution this quinolizidinone assumes a chair–boat-like configuration and not a chair–chair conformation as observed for **20a**. The stereochemistry was determined to be 1*S* (1β,9β,9a-β) on the basis of the observed coupling constants ($J_{1,9a} \simeq 1$ Hz and $J_{9,9a}$ = 10.1 Hz) and NOE correlations (H-1 to both H-9a and H-9; H-9a to H-6 axial). This assignment was confirmed by the direct conversion of **20b** to **23** by BH_3–SMe_2 reduction. Only five signals were observed in the ^{13}C NMR spectrum of **23**, which indicated a meso compound. In the ^1H NMR spectrum, H-9a was not resolved but H-1/H-9 were observed with two axial–axial couplings (11.1 and 8.5 Hz) and one axial–equatorial coupling (4.6 Hz), which was consistent with the diaxial stereochemistry shown between H-9a and H-1/H-9.

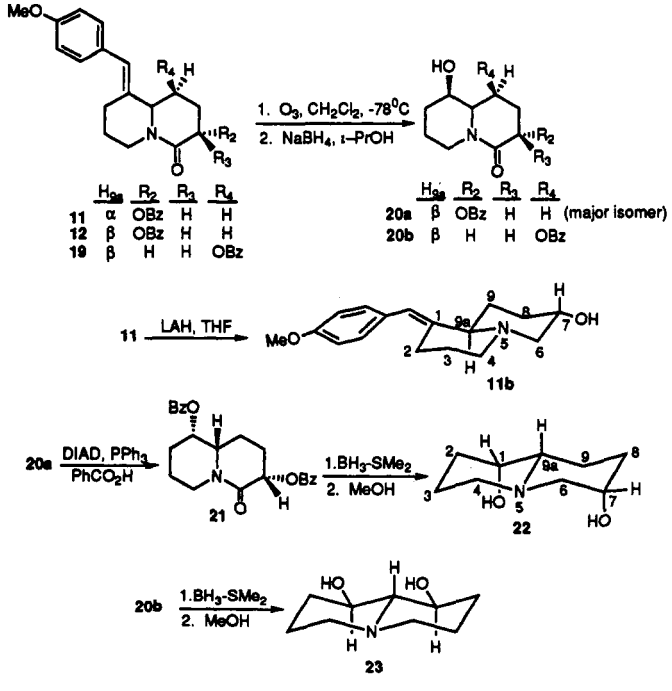
Conclusions

The incorporation of a *p*-methoxy substituent into a styryl terminator has allowed the generation of a six-membered ring via a vinylogous Bischler–Napieralski nitrilium ion cyclization, and this methodology has been applied to the synthesis of chiral hydroxylated quinolizidinones and quinolizidines. Semiempirical and *ab initio* molecular orbital calculations indicate that an increase in the electron-donating capacity of the ring substituent corresponds to a decrease in the calculated E_a and ΔH values. Because systems with large and positive ΔH values have been observed to undergo cyclization, we suggest that the overall reaction is under kinetic rather than thermodynamic control. The *p*-methoxy-substituted styryl group may also be the terminator of choice for other cationic cyclizations.

Scheme 3



Scheme 4



Experimental Section

TLC analyses were performed with Merck DC-F_{254} silica gel plates, with visualization by alkaline permanganate and UV irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040–0.063 mm). ^{13}C NMR spectra were recorded at 75 MHz and ^{1}H NMR spectra at 300 or 500 MHz. IR spectra were recorded with a Perkin-Elmer Model 1800 spectrophotometer; MS were recorded at 70 eV with a Finnigan MAR 4600 and HRMS at 70 EV with a VG ZAB2-SE spectrometer using computerized peak matching with perfluorokerosene as the reference. All reactions were run under inert atmosphere. The organic extracts were dried over anhydrous $MgSO_4$ prior to solvent removal on a rotary evaporator. All reagents were obtained from commercial sources and used without further purification.

Semiempirical calculations were carried out using the AM1 Hamiltonian[23] of the UNICHEM-MNDO/91 module[24] on a Cray YMP-2E. Approximate transition-state geometries were located by the reaction coordinate method[25] using the distance between the ring-closure atoms as the reaction coordinate. The reaction profile was determined by successively incrementing the C–C bond of the cyclized **6b″** by 0.01 Å from the equilibrium distance (1.52 Å) to a distance of 3.2 Å. (See Scheme 2, **6b′** → **6b″**.) With the exception of the reaction coordinate, all degrees of freedom were optimized. In accordance with Boyd et al.,[26] the PRECISE convergence option was employed.

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The initial "reactant" and final "product" were fully optimized without any constraints. The crude transition-state geometries were refined using the algorithms supplied in UNICHEM. Subsequent normal-mode analyses demonstrated that the transition states were truly hypersurface maxima along the desired reaction coordinate *via* the existence of one and only one imaginary frequency.[27] Single-point energy determinations of the AM1-minimized structures were conducted using the UHF 6-31G basis function in SPARTAN 2.0.[28]

General Procedure for PPSE Cyclization of Amides. A suspension of P_2O_5 (0.100 mol) and hexamethyldisiloxane (30 mL) was refluxed in CCl_4 (70 mL) for 1.5 h. The resulting clear, colorless solution was cooled to room temperature, and the amide (7.5 mmol) was added. The reaction mixture was heated at reflux for 1 h during which time the solution turned bright yellow and a gummy precipitate formed. After being cooled to room temperature the viscous solution was poured into a mixture of CH_2Cl_2 and 10% NaOH (1:1, 800 mL). The organic phase was washed with brine and dried and the solvent removed *in vacuo* to give the corresponding imine.

(*Z*)-5-(4-Methoxyphenyl)-4-penten-1-amine (1b). Triphenylphosphine (27.9 g, 0.106 mol) and *N*-5-(4-bromobutyl)phthalimide (30.0 g, 0.106 mol) were refluxed in xylene (150 mL) with vigorous stirring for 14 h. The reaction was filtered and the white solid dried over P_2O_5 under high vacuum to give 48.6 g (90%) of [4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyl]triphenylphosphonium bromide as a white powder.

The phosphonium salt (49.1 g, 96.6 mmol) was suspended in THF (500 mL), and *p*-anisaldehyde (13.2 g, 96.6 mmol) was added. The reaction was cooled to 0 °C, and potassium *tert*-butoxide (10.8 g, 96.6 mmol) was slowly added. The reaction was stirred at 0 °C for 15 min, allowed to warm to room temperature, and then refluxed for 1 h. The reaction mixture was cooled to room temperature and poured into a mixture of Et_2O, pentane, and H_2O (2:1:2, 1l total). The layers were separated, and the organic phase washed with H_2O, brine, and dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography (4:1 hexane:EtOAc) to afford 16.5 g (53%) of (*Z*)-2-[5-(4-methoxyphenyl)-4-pentenyl]-1*H*-isoindole-1,3(2*H*)-dione as a white solid.

To a suspension of (*Z*)-2-[5-(4-methoxyphenyl)-4-pentenyl]-1*H*-isoindole-1,3-(2*H*)-dione (16.5 g, 50.0 mmol) in EtOH (175 mL) was added hydrazine (2.4 mL), and the suspension stirred with a mechanical stirrer under reflux for 1 h. The reaction was cooled to room temperature and diluted with EtOH (150 mL), and concd. HCl (10 mL) was added. The reaction mixture was filtered and the solvent removed *in vacuo* to give the crude hydrochloride salt. The salt was taken up in a mixture of Et_2O:H_2O (1:1 400 mL) and the pH adjusted to 10 with 50% NaOH. The aqueous phase was extracted with Et_2O (2 × 100 mL), the combined organic extracts were washed with brine and dried, and the solvent was removed *in vacuo* to give 6.39 g (60%) of **1b** as a pale yellow oil. (Note: the carbonate of the amine forms rapidly upon exposure to air): IR (film) 3374, 3310, 1608, 1574, 1512, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 11.4 Hz, 1H), 5.56 (dt, J = 11.4, 7.2 Hz, 1H), 3.80 (s, 3 H), 2.72 (t, J = 7.2 Hz, 2H), 2.36 (q, J = 7.2 Hz, 2H), 1.60 (p, J = 7.2 Hz, 2H), 1.47 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 158.17, 130.70, 130.22, 129.87, 128.60, 113.54, 55.19, 41.72, 33.81, 25.87; CIMS (CH_4) 232 (M + $C_3H_5^+$), 220 (M + $C_2H_5^+$), 192 (MH^+, base), 175 (M + H − NH_3^+); HRMS calcd for $C_{12}H_{18}NO$ 192.1388, found 192.1379.

(*Z*)-5-[(5-Phenyl-4-pentenyl)amino]-5-oxopentanoic Acid (2a). To a stirred solution of (*Z*)-5-phenyl-4-penten-1-amine[19] (**1a**) (1.75 g, 10.9 mmol) in EtOH was added glutaric anhydride (1.49 g, 13.0 mmol). The solution was stirred at room temperature for 4 h, the solvent removed *in vacuo*, and the residue taken up in 0.5 M NaOH. The aqueous phase was washed with Et_2O, acidified with concd HCl, and extracted with Et_2O. The combined organic extracts were washed with brine and dried and the solvent removed *in vacuo* to afford 1.78 g (64%) of **2a** as a viscous, pale yellow oil: IR (film) 3294, 1710, 1624, 1554 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.20 (m, 5 H), 6.47 (d, J = 11.5 Hz, 1H), 5.63 (dt, J = 11.5, 7.1 Hz, 1H), 5.64 (br s, 1H), 3.23 (q, J = 6.9 Hz, 2H), 2.36 (t, J = 7.1 Hz, 2H), 2.35 (qd, J = 7.3, 1.7 Hz, 2H), 2.15 (t, J = 7.1 Hz, 2H), 1.89 (p, J = 7.2 Hz, 2H), 1.63 (p, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 177.54, 172.64, 137.32, 131.44, 129.83, 128.67, 128.23, 126.70, 38.91, 35.20, 33.06, 29.28, 25.47, 20.77; CIMS (CH_4) 276 (MH^+, base), 258, 162; HRMS for $C_{16}H_{22}NO_3$ calcd 276.1600, found 276.1591.

(*Z*)-Ethyl 5-[(5-Phenyl-4-pentenyl)amino]-5-oxopentanoate (3a). To a solution of **2a** (1.75 g, 6.36 mmol) in CH_2Cl_2 (30 mL) was added Et_3O–BF_4 (7.0 mL, 1.0 M in CH_2Cl_2) followed by dropwise addition of diisopropylethylamine (0.903 g, 6.99 mol, 1.22 mL). After being stirred at room temperature for 6 h the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 10% HCl, saturated $NaHCO_3$, and brine. The organic phase was dried, the solvent removed *in vacuo*, and the residue purified by flash chromatography (1:1 hexane:EtOAc) to afford 0.96 g (52%) of **3a** as a viscous, pale yellow oil: IR (film) 1734, 1644, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) 7.37–7.20 (m, 5H), 6.48 (d, J = 11.6 Hz, 1H), 5.64 (dt, J = 11.6, 7.4 Hz, 1H), 5.49 (br s, 1H), 4.12 (q, J = 7.4 Hz, 2H), 3.24 (q, J = 6.7 Hz, 2H), 2.36 (qd, J = 7.4, 1.7 Hz, 2H), 2.32 (t, J = 7.1 Hz, 2H), 2.12 (t, J = 7.1 Hz, 2H), 1.90 (p, J = 7.2 Hz, 2H), 1.64 (p, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.21, 172.01, 137.33, 131.51, 129.75, 128.65, 128.19, 126.64, 60.36, 38.79, 35.44, 33.29, 29.46, 25.54, 20.90, 14.19; EIMS 70 EV 303 (M^+), 258, 143, 115 (base). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.04; H, 8.35; N, 4.56.

(*Z*)-5-[[5-(4-Methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoic Acid (2b). To a stirred solution of glutaric anhydride (3.30 g, 28.8 mmol) in CH_2Cl_2 (130 mL) was added **1b** (5.00 g, 26.1 mmol). After 16 h the solvent was removed *in vacuo* and the residue taken up in 0.5 N NaOH (200 mL). The aqueous layer was washed with Et_2O and then acidified with concd HCl. The aqueous layer was extracted with Et_2O (3 × 75 mL), and the combined organic extracts washed were with brine and dried. Removal of the solvent *in vacuo* gave 5.61 g (70%) of **2b** as a white solid: IR (film) 3310, 1710, 1642, 1608, 1542, 1512, 1254 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.67–8.37 (br s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.40 (d, J = 11.6 Hz, 1H), 5.67 (br t, J = 5.5 Hz, 1H), 5.53 (dt, J = 11.6, 7.3 Hz, 1H), 3.81 (s, 3H), 3.28 (q, J = 6.9 Hz, 2H), 2.42–2.33 (m, 4H), 2.17 (t, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ

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(28) SPARTAN 2.0, Wavefunction, Inc., Irvine, CA 92715.

177.68, 172.62, 158.26, 129.88, 129.23, 127.03, 113.89, 113.63, 55.24, 38.97, 35.22, 33.05, 29.35, 25.51, 20.77; HRMS calcd for $C_{17}H_{23}NO_4$ 306.1705, found 306.1687.

(*Z*)-Ethyl 5-[[5-(4-Methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoate (3b). To a stirred solution of **2b** (5.60 g, 18.3 mmol) was added $Et_3O{\cdot}BF_4$ (27.5 mL, 27.5 mmol, 1.0 M in CH_2Cl_2). To the mixture was added diisopropylethylamine (3.55 g, 27.5 mmol, 4.80 mL) dropwise and the reaction stirred at room temperature for 1 h. The reaction was diluted with CH_2Cl_2 (100 mL) and washed with 10% HCl, saturated $NaHCO_3$, and brine and dried. Removal of the solvent *in vacuo* and purification by flash chromatography (1:1 hexane:EtOAc) gave 2.73 g (44%) of **3b** as a white solid: IR (film) 1732, 1646, 1608, 1548, 1512, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.40 (d, J = 11.7 Hz, 1H), 5.58–5.50 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.25 (q, J = 7.1 Hz, 2H), 2.40–2.29 (m, 4H), 2.14 (t, J = 7.3 Hz, 2H), 1.90 (p, J = 7.1 Hz, 2H), 1.64 (p, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.19, 172.02, 158.27, 129.98, 129.86, 129.16, 127.00, 113.60, 60.34, 55.20, 38.87, 35.47, 33.30, 29.55, 25.61, 20.93, 14.18; HRMS calcd for $C_{19}H_{27}NO_4$ 334.2018, found 334.2002.

(*E*)-Ethyl 4-[3,4,5,6-Tetrahydro-3-[(4-methoxyphenyl)methylene]-2-pyridinyl]butanoate (4b). PPSE cyclization of **3b** (2.5 g, 7.50 mmol) as described above gave 2.30 g (97%) of **4b** as a yellow oil: IR (film) 1732, 1648, 1602, 1510 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.97 (s, 1H), 6.91 (d, J = 8.6 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.84 (S, 3H), 3.67 (t, J = 5.8 Hz, 2H), 2.67–2.60 (m, 4H), 2.41 (t, J = 7.3 Hz, 2H), 1.98 (p, J = 7.3 Hz, 2H), 1.66 (p, J = 6.0 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ 173.61, 167.24, 159.05, 131.09, 130.54, 129.53, 128.93, 113.71, 60.25, 55.29, 49.63, 35.53, 34.02, 25.98, 23.11, 22.45, 14.26; HRMS calcd for $C_{19}H_{25}NO_3$ 316.1913, found 316.1908.

(*E*)-(±)-Octahydro-9-[(4-methoxyphenyl)methylene]-4*H*-quinolizin-4-one (5b). To a stirred solution of **4b** (2.30 g, 7.28 mmol) in EtOH (85 mL) was added $NaBH_4$ (0.57 g, 14.5 mmol). The reaction mixture was stirred for 2 h at room temperature, cooled to 0 °C, and quenched with 1% HOAc. The mixture was poured into H_2O (100 mL) and extracted with EtOAc (2 × 100 mL) and the combined organic layer washed with saturated $NaHCO_3$ and brine and dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography (49:1 CH_2Cl_2:MeOH) to give 1.62 g (82%) of **5b** as a viscous, clear colorless oil: ^1H NMR ($CDCl_3$) δ 7.14 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.40 (s, 1H), 4.65 (dt, J = 13.2, 4.5 Hz, 1H), 4.04 (t, J = 6.5 Hz, 1H), 3.82 (s, 3H), 2.85–2.72 (m, 2H), 2.54–2.21 (m, 3H), 2.12–1.92 (m, 3H), 1.85–1.58 (m, 3H), ^{13}C NMR ($CDCl_3$) δ 169.41, 158.28, 138.05, 129.98, 129.54, 122.71, 113.62, 60.10, 55.23, 41.83, 32.74, 26.70, 26.63, 24.52, 19.37; HRMS calcd for $C_{17}H_{22}NO_2$ 272.1651, found 272.1639.

***N*-[5-(4-Methoxyphenyl)-4-pentenyl]methylamide (6b).** To a stirred solution of **1b** (0.500 g, 2.61 mmol) and triethylamine (0.290 g, 2.87 mmol, 0.40 mL) in CH_2Cl_2 (10 mL) was added acetic anhydride (0.293 g, 2.87 mmol) dropwise. After being stirred at room temperature for 0.5 h, the reaction mixture was diluted with additional CH_2Cl_2 (50 mL), washed with 10% HCl (2 × 25 mL), saturated $NaHCO_3$ (2 × 25 mL), and brine (2 × 25 mL), and dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography (1:4 hexane:EtOAc) to give 0.44 g (72%) of **6b** as a pale yellow solid: IR (film) 1652, 1512, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) 7.21 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.41 (d, J = 11.6 Hz, 1H), 5.55 (dt, J = 11.6, 7.3 Hz, 1H), 5.48 (br s, 1H), 3.82 (s, 3H), 3.25 (q, J = 7.1 Hz, 2H), 2.37 (qd, J = 7.3, 1.8 Hz, 2H), 1.90 (s, 3H), 1.65 (p, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.04, 158.29, 129.98, 129.87, 129.19, 127.01, 113.62, 55.24, 39.00, 29.48, 25.58, 23.21; HRMS calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1411. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21, N, 6.00. Found: C, 71.91; H, 8.16; N, 6.17.

3-[2-(4-Methoxyphenyl)methylene]-2-methylpyrrolidine (7b). PPSE cyclization of **6b** (0.300 g, 1.29 mmol) as described above, except using benzene as the reaction and workup solvents, gave the imine as a yellow oil.

To the imine in EtOH (15 mL) at 0 °C was added $NaBH_4$ (97.3 mg, 2.58 mmol) and the reaction stirred at room temperature for 72 h. After being cooled to 0 °C the reaction was quenched with 1% HOAc and poured into H_2O (50 mL). The aqueous layer was washed with EtOAc (2 × 20 mL), made basic (pH 10) with 10% NaOH, and saturated with NaCl. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic extracts were dried, and the solvent was removed *in vacuo* to give 0.184 g (66%) of **7b** as a clear, colorless oil: IR (film) 3290, 1608, 1510, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.27 (s, 1H), 3.80 (s, 3H), 3.37 (q, J = 6.6 Hz, 1H), 3.13 (dt, J = 12.4, 4.3 Hz, 1H), 2.94–2.79 (m, 2H), 2.18–2.04 (m, 2H), 1.76–1.50 (m, 2H), 1.33 (d, J = 6.6 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ 157.93, 142.16, 130.32, 130.03, 120.10, 113.48, 56.21, 55.21, 45.67, 29.16, 27.55, 18.84; HRMS calcd for $C_{14}H_{19}NO$ 217.1467, Found, 217.1459.

[*S*-(*Z*)]-Ethyl 2-Hydroxy-5-[[5-(4-methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoate (8a). To a stirred solution of (*S*)-γ-(ethoxycarbonyl)-γ-butyrolactone (20.0 g, 0.126 mol) in CH_2Cl_2 (500 mL) was added 5-(4-methoxyphenyl)pent-4-enylamine (**1b**) (24.1 g, 0.126 mol). The reaction mixture was stirred at room temperature for 90 h and concentrated and the residue purified by flash chromatography (1:4 hexane:EtOAc) to give 31.5 g (86%) of **8a** as a viscous, yellow oil: IR (film) 3306, 1736, 1646, 1608, 1550, 1512, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.40 (d, J = 11.4 Hz, 1H), 5.55 (br s, 1H), 5.54 (dt, J = 11.4, 7.3 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.21–4.14 (m, 1H), 3.82 (s, 3H), 3.48 (s, 1H), 3.25 (q, J = 7.3 Hz, 2H), 2.35 (qd, J = 7.4, 1.8 Hz, 2H), 2.30–2.10 (m, 3H), 1.95–1.82 (m, 1H), 1.64 (p, J = 7.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.92, 172.59, 158.63, 130.28, 130.20, 129.58, 113.97, 70.18, 62.04, 55.57, 39.32, 32.38, 30.10, 29.77, 25.89, 14.49; CIMS (CH_4) 350 (MH^+, base), 192. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01: Found: C, 64.91; H, 7.95, N, 4.16.

[*R*-(*Z*)]-Methyl 2-Hydroxy-5-[[5-(4-methoxyphenyl)-pentenyl]amino]-5-oxopentanoate (8b). Treatment of 5-(4-methoxyphenyl)pent-4-enylamine (**1b**) (7.00 g, 36.8 mmol) as described in **8a** except using (*R*)-γ-(methoxycarbonyl)-γ-butyrolactone gave, after purification by flash chromatography (gradient, 70–90% EtOAc in hexane), 6.05 g (49%) of **8b** as a viscous yellow oil as well as 1.6 g of recovered amine: IR (film) 3304, 1740, 1644, 1608, 1550, 1512, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.41 (d, J = 11.5 Hz, 1H), 5.55 (br s, 1H), 5.54 (dt, J = 11.5, 7.3 Hz, 1H), 4.26–4.17

(m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.63 (br s, 1H), 3.24 (q, J = 6.8 Hz, 2H), 2.35 (qd, J = 7.3, 1.7 Hz, 2H), 2.30–2.09 (m, 3H), 1.97–1.83 (m, 1H), 1.64 (p, J = 7.3 Hz, 2H), ^{13}C NMR ($CDCl_3$) δ 174.99, 172.32, 158.32, 129.95, 129.89, 129.28, 113.66, 69.94, 55.26, 52.51, 39.01, 32.04, 29.67, 29.42, 25.55; HRMS calcd for $C_{18}H_{25}NO_5$ 336.1811, found 336.1817.

[S-(*Z*)]-Ethyl 2-(Benzoyloxy)-5-[[5-(4-methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoate (9a). To a stirred solution of **8a** (31.5 g, 90.1 mmol) in CH_2Cl_2 (360 mL) were added benzoyl chloride (14.0 g, 99.2 mmol, 11.6 mL) and triethylamine (10.1 g, 99.2 mmol, 13.9 mL). The reaction mixture was stirred at room temperature for 48 h and concentrated and the residue purified by gravity chromatography (1:1 hexane:EtOAc) to give 32.1 g (76%) of **9a** as a viscous, yellow oil: IR (film) 1752, 1726, 1648, 1608, 1548, 1512, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09–8.04 (m, 2H), 7.59 (H, J = 7.5, 1.4 Hz, 1H), 7.49–7.42 (m, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.39 (br d, J = 11.6 Hz, 1H), 5.51 (dt, J = 11.6, 7.3 Hz, 1H), 5.47–5.39 (m, 1H), 5.27–5.21 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.24 (q, J = 6.6 Hz, 2H), 2.41–2.23 (m, 6H), 1.61 (p, J = 7.2 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H): ^{3}C NMR (CDCl) δ 171.10, 169.70, 165.93, 158.33, 133.42, 129.94, 129.86, 129.38, 129.23, 128.43, 113.64, 72.09, 61.56, 55.23, 39.05, 32.00, 29.51, 26.95, 25.62, 14.12; CIMS (CH_4) 454 (MH^+, base), 408, 332; HRMS calcd for $C_{26}H_{32}NO_6$ 454.2230, found 454.2212.

[*R*-(*Z*)]-Methyl 2-(Benzoyloxy)-5-[[5-(4-methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoate (9b). Treatment of **8b** (6.00 g, 12.9 mmol) as described in **9a** gave, after purification by flash chromatography (gradient, 60–80% EtOAc in hexane), 6.51 g (83%) of **9b** as a viscous, pale yellow oil: IR (film) 1756, 1724, 1648, 1608, 1512, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09–8.04 (m, 2H), 7.58 (tt, J = 7.4, 1.4 Hz, 1H), 7.48–7.42 (m, 2H), 7.18 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 11.6 Hz, 1H), 5.51 (dt, J = 11.6, 7.3 Hz, 1H), 5.49 (br s, 1H), 5.30–5.23 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.23 (q, J = 6.9 Hz, 2H), 2.41–2.19 (m, 6H), 1.60 (p, J = 7.0 Hz, 2H), ^{13}C NMR ($CDCl_3$) δ 171.04, 170.18, 165.87, 158.29, 133.45, 129.92, 129.86, 129.19, 129.16, 128.43, 113.61, 71.95, 55.20, 52.41, 39.01, 31.87, 29.47, 26.91, 25.58; HRMS calcd for $C_{25}H_{29}NO_6$ 440.2076, found 440.2068.

[*S*-(*E*)]-Ethyl 4-[2-(Benzoyloxy)-3,4,5,6-tetrahydro-3-[(4-methoxyphenyl)methylene]-2-pyridinyl]butanoate (10a). PPSE cyclization of **9a** (6.00 g, 13.2 mmol) as described above gave 4.7 g (82%) of **10a** as a viscous, yellow oil: IR (film) 1750, 1724, 1602, 1510, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.5 Hz, 2H), 7.00 (s, 1H), 7.46 (d, J = 8.7 Hz, 2H), 5.33 (dd, J = 9.9, 6.1 Hz, 1H), 4.23 (qd, J = 7.3, 1.5 Hz, 2H), 3.82 (s, 3H), 3.69 (t, J = 5.8 Hz, 2H), 2.93–2.82 (m, 2H), 2.65 (t, J = 6.1 Hz, 2H), 2.45–2.33 (m, 2H), 1.68 (p, J = 6.1 Hz, 2H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.48, 166.41, 166.25, 159.39, 133.47, 131.25, 130.38, 130.07, 129.93, 129.73, 128.90, 128.58, 113.85, 72.66, 61.34, 55.19, 49.62, 31.07, 28.75, 25.76, 22.21, 13.91; CIMS (CH_4) 436 (MH^+, base), 314.

[3*S*-(3α,9*E*,9a-α)(and 9a-β)]-3-(Benzoyloxy)octahydro-9-[(4-methoxyphenyl)methylene]-4*H*-quinolizin-4-one (11 and 12). Reduction of **10a** as described in **5b** gave, after flash chromatography (gradient, 40–70% EtOAc in hexane), 1.47 g (35%) of **11** and 1.46 g (35%) of **12** as white foams. **11 (9a-α)**: $[\alpha]^{20}_D$ = −11.4° (c = 0.8, $CHCl_3$); IR (film) 1722, 1656, 1606, 1510, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14–8.08 (m, 2H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.47–7.40 (m, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.44 (s, 1H), 5.53 (dd, J = 10.4, 5.7 Hz, 1H), 4.62 (dt, J = 13.3, 4.2 Hz, 1H), 4.12–4.05 (m, 1H), 3.82 (s, 3H), 2.91–2.76 (m, 2H), 2.44–2.08 (m, 5H), 1.88–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.57, 165.92, 158.43, 137.49, 133.02, 130.02, 129.93, 129.30, 128.24, 123.38, 113.69, 69.77, 60.19, 55.25, 42.07, 26.57, 25.96, 24.38, 24.34; HRMS calcd for $C_{24}H_{23}NO_4$ 392.1862, found 392.1861. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.51; H, 6.54, N, 3.41.

[3*S*-(3α,9*E*,9a-α)]-Octahydro-9-[(4-methoxyphenyl)methylene]-2*H*-quinolizin-3-ol (11b). To a stirred solution of **11** (0.500 g, 1.28 mmol) in THF (15 mL) at 0 °C was added LAH (0.190 g, 5.11 mmol) in several portions. After vigorous gas evolution had ceased, the reaction was refluxed for 16 h. The reaction was quenched with 10% $KHSO_4$ at 0 °C, poured into H_2O (75 mL), and washed with Et_2O (1 × 75 mL). After the pH was adjusted to 10 with 50% NaOH and saturating with NaCl, the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined Et_2O layer was dried and the solvent removed *in vacuo* to give 0.27 g (77%) of the amino alcohol as a pale yellow wax: ^{1}H NMR ($CDCl_3$) 7.10 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 H, 2H), 6.35 (s, 1H), 3.86 (tt, J = 10.7, 4.4 Hz, 1H), 3.80 (s, 3H), 3.11 (ddd, J = 10.7, 4.4, 2.2 Hz, 1H), 3.01–2.89 (m, 2H), 2.66 (br s, 1H), 2.44 (br d, J = 10.8 Hz, 1H), 2.35 (td, J = 11.5, 3.9 Hz, 1H), 2.23–2.13 (m, 1H), 2.07 (t, J = 10.5 Hz, 1H), 2.01 (dq, J = 13.3, 3.5 Hz, 1H), 1.91–1.56 (m, 4H), 1.42–1.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 158.02, 139.26, 130.38, 130.09, 121.94, 113.48, 66.91, 64.40, 64.01, 56.62, 55.22, 33.68, 28.41, 26.64, 26.10; CIMS (CH_4) 210 (M + $C_3H_5^+$, 3), 198 (M + $C_2H_5^+$, 11), 170 (MH^+, base), 152 ($MH^+ - H_2O$, 63); HRMS calcd for $C_{17}H_{23}NO_2$ 274.1807, found 274.1796.

12 (9a-β): $[\alpha]^{20}_D$ = −29.8° (c = 1.0, $CHCl_3$); IR (film) 1722, 1652, 1606, 1510, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.13–8.07 (m, 2H), 7.55 (dt, J = 7.4, 1.4 Hz, 1H), 7.46–7.39 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.44 (s, 1H), 5.58 (dd, J = 8.3, 5.7 Hz, 1H), 4.63 (dt, J = 13.1, 4.3 Hz, 1H), 4.17–4.11 (m, 1H), 3.82 (s, 3H) 2.94–2.80 (m, 2H), 2.46–2.09 (m, 5H), 1.83–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 165.95, 165.85, 158.46, 136.87, 133.05, 130.07, 129.94, 129.22, 128.27, 122.83, 113.71, 69.67, 59.75, 55.27, 42.87, 27.04, 25.13, 24.70, 22.34; HRMS calcd for $C_{24}H_{25}NO_4$ 392.1862, found 392.1855.

[3*R*-(3β,9*E*,9a-β (and 9a-α))]-3-(Benzoyloxy)octahydro-9-[(4-methoxyphenyl)methylene]-4*H*-quinolizin-4-one (13 and 14). PPSE cyclization of **9b** (4.75 g, 10.8 mmol) as described above gave 4.50 g of the crude imine as a yellow oil. Reduction of the imine as described in **5b** gave, after purification by flash chromatography (1:1 hexane:EtOAc), 1.00 g (24%) of **13** and 1.03 g (24%) of **14** as white foams: **13 (9a-β)**: IR (film) 1720, 1654, 1606, 1510, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14–8.07 (m, 2H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.46–7.40 (m, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H) 6.44 (s, 1H), 5.53 (dd, J = 10.3, 5.8 Hz, 1H), 4.61 (dt, J = 13.2, 4.3 Hz, 1H), 4.13–4.05 (m, 1H), 3.83 (s, 3H), 2.92–2.76 (m, 2H), 2.44–2.10 (m, 5H), 1.86–1.55 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 166.57, 165.93, 158.44, 137.50, 133.03, 129.98, 129.94, 129.31, 128.25, 123.39, 113.70, 69.78, 60.20, 55.27, 42.08, 26.58, 25.97, 24.39,

24.35. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.45; H, 6.77; N, 3.28.

14 (9a-α): $[\alpha]^{20}_D$ = +22.6° (c = 0.42, $CHCl_3$); IR (film) 1722, 1652, 1606, 1512, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13–8.07 (m, 2H), 7.57 (tt, J = 7.3, 1.5 Hz, 1H), 7.45–7.39 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.44 (s, 1H), 5.60 (dd, J = 8.3, 5.6 Hz, 1H), 4.63 (dt, J = 13.2, 4.3 Hz, 1H), 4.17–4.10 (m, 1H), 3.81 (s, 3H), 2.94–2.82 (m, 2H), 2.46–2.07 (m, 5H), 1.84–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$) 165.98, 165.84, 158.45, 136.84, 133.05, 130.06, 129.93, 129.20, 128.32, 128.26, 122.83, 113.70, 69.66, 59.75, 55.26, 42.87, 27.03, 25.12, 24.69, 22.33; HRMS calcd for $C_{24}H_{25}NO_4$ 392.1862, found 392.1875.

[*S*-(*Z*)]-Tetrahydro-*N*-[5-(4-methoxyphenyl)-4-pentenyl]-5-oxo-2-furancarboxamide (15). A solution of (*S*)-γ-carboxy-γ-butyrolactone (1.50 g, 11.5 mmol) in $SOCl_2$ (3 mL) was refluxed until gas evolution ceased and the excess $SOCl_2$ removed *in vacuo* to give the crude acid chloride. A solution of (*Z*)-5-(4-methoxyphenyl)-4-penten-1-amine (**1b**) (2.21 g, 11.5 mmol) and TEA (2.33 g, 23.1 mmol, 3.22 mL) in CH_2Cl_2 (40 mL) was cooled to 0 °C and a solution of the acid chloride in CH_2Cl_2 (10 mL) added dropwise. The mixture was warmed to room temperature and the solvent removed *in vacuo* to give the crude product as a dark orange oil. Purification by flash chromatography (9:1 EtOAc:hexane) gave **15**, 2.72 g (78%), as an off-white solid (compound contains ~20% trans isomer by NMR): IR (film) 3314, 1786, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) 7.19 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.50–6.33 (m, 1H), 6.40 (d, J = 11.6 Hz, 1H), 5.53 (dt, J = 11.6, 7.2 Hz, 1H) 4.79 (t, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.31 (q, J = 7.2 Hz, 2H), 2.68–2.46 (m, 3H), 2.40–2.19 (m, 3H), 1.68 (p, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 175.66, 169.14, 158.28, 130.14, 129.88, 129.83, 129.56, 129.38, 127.03, 113.60, 77.42, 55.21, 38.82, 29.45, 27.50, 25.78, 25.69; HRMS calcd for $C_{17}H_{21}NO_4$ 304.1549, found 304.1538.

[*S*-(*Z*)]-Ethyl 4-Hydroxy-5-[[5-(4-methoxyphenyl)-4-pentenyl]amino-5-oxopentanoate (16). To a solution of **15** (2.40 g, 7.91 mmol) in CH_2Cl_2 (20 mL) and EtOH (30 mL) was added a small amount of EtO-Na^+ and the reaction stirred at room temperature for 0.5 h. The reaction was diluted with additional CH_2Cl_2 (60 mL), washed with H_2O (1 × 30 mL) and brine, and dried. Solvent removal *in vacuo* gave the crude product which was purified by flash chromatography (17:3 EtOAc:hexane) to yield 2.07 g (75%) of **16** as a viscous, yellow oil: IR (film) 3380, 1732, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) 7.20 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.82–6.73 (m, 1H), 6.39 (d, J = 11.5 Hz, 1H), 5.55 (dt, J = 11.5, 7.2 Hz, 1H), 4.38 (d, J = 4.5 Hz, 1H), 4.40–4.06 (m, 3H), 3.81 (s, 3H), 3.29 (q, J = 7.3 Hz, 2H), 2.57–2.48 (m, 2H), 2.22–2.09 (m, 1H), 2.00–1.85 (m, 1H), 7.09 (qd, J = 7.5, 1.7 Hz, 2H), 1.67 (p, J = 7.2 Hz, 2H), 1.26 (t, J = 2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 175.36, 173.11, 158.27, 129.87, 129.20, 113.61, 71.95, 61.15, 55.22, 38.63, 30.82, 29.70, 29.16, 25.76, 14.09; CIMS (CH_4) 390 ($M + C_3H_5^+$, 4), 378 ($M + C_2H_5^+$, 16), 350 (MH^+, base), 332 ($MH^+ - H_2O^{1+}$, 17), 304 (MH^+ – EtOH, 26); HRMS calcd for $C_{19}H_{27}NO_5$ 350.1967, found 350.1964. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.03; H, 7.70; N, 3.91.

[*S*-(*Z*)-Ethyl 4-(Benzoyloxy)-5-[[5-(4-methoxyphenyl)-4-pentenyl]amino]-5-oxopentanoate (17). Treatment of **6** (200 g, 5.72 mmol) as described in **9a** gave, after purification by flash chromatography (gradient, 1:1–4:1 EtOAc:hexane), 2.01 g (77%) of **17** as an off-white solid (compound contains ~20% *trans* isomer by NMR): IR (film) 3312, 1728, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) 8.03 (dd, J = 7.7, 1.4 Hz, 2H), 7.62 (tt, J = 7.4, 1.4 Hz, 1H), 7.51–7.44 (m, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.34 (d, J = 11.6 Hz, 1H), 6.21–6.10 (m, 1H), 5.52 (dt, J = 11.6, 7.2 Hz, 1H), 5.42 (dd, J = 7.0, 5.1 Hz, 1H), 4.11–4.02 (m, 2H), 3.80 (s, 1H), 3.31 (q, J = 6.7 Hz, 2H), 2.51–2.28 (m, 6H), 1.71–1.60 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$) 172.49, 168.94, 165.17, 158.26, 133.69, 129.84, 129.73, 129.24, 129.01, 128.62, 127.02, 113.59, 73.42, 60.59, 55.20, 39.03, 29.96, 29.60, 27.10, 25.84, 14.08; HRMS calcd for $C_{26}H_{31}NO_6$ 454.2230, found 454.2205. Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.62; H, 7.19; N, 3.00.

[1*R*-(1β,9*E*,9a-β)]-1-(Benzoyloxy)octahydro-9-[(4-methoxyphenyl)methylene]-4*H*-quinolizin-4-one (19). PPSE cyclization of **17** (1.45 g, 3.20 mmol) as described above, except reflux for 24 h, gave the crude imine as a yellow oil. Reduction of the imine as described in **5b** yielded, after purification by flash chromatography (gradient 1:1–4:1 EtOAc:hexane), 0.537 g (43%) of **19** as a white foam: IR (film) 1719, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 8.05 (dd, J = 8.4, 1.4 Hz, 2H), 7.59 (tt, J = 7.4, 1.4 Hz, 1H), 7.49–7.43 (m, 2H), 7.06 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.40 (s, 1H), 5.78–5.73 (m, 1H), 4.75 (dt, J = 13.1, 4.3 Hz, 1H), 4.23 (d, J = 4.1 Hz, 1H), 3.80 (s, 3H), 2.80–2.66 (m, 3H), 2.60–2.50 (m, 1H), 2.41–2.27 (m, 2H), 2.26–2.13 (m, 1H), 1.82–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$) 167.81, 165.64, 158.51, 135.36, 133.38, 129.94, 129.68, 128.85, 128.49, 124.32, 113.66, 67.81, 64.57, 55.23, 41.89, 28.16, 26.17, 24.64, 24.16; HRMS calcd for $C_{24}H_{25}NO_4$ 392.1862, found 392.1858.

[3*S*-(3α,9β,9a-β)]-3-(Benzoyloxy)octahydro-9-hydroxy-4*H*-quinolizin-4-one (20a). A solution of **12** (1.00 g, 2.55 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C and treated with ozone until the appearance of a blue color. Argon was then passed through the reaction vessel for several minutes followed by the addition of 2-propanol (50 mL) and $NaBH_4$ (0.48 g, 12.8 mmol). The reaction was stirred at −78 °C for 15 min, allowed to warm to room temperature, and stirred an additional 1.0 h. The reaction was cooled to 0 °C, quenched with 1% HOAc, diluted with CH_2Cl_2 (150 mL), and washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried, the solvent removed *in vacuo*, and the residue purified by flash chromatography (3:7 hexane:EtOAc) to give 0.37 g (50%) of **20a** as a white foam (contains 10% 9α-OH by NMR): IR (film) 3390, 1726, 1628, 1478, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11–8.06 (m, 2H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.46–7.40 (m, 2H), 5.44 (dd, J = 9.5, 5.5 Hz, 1H), 4.65 (d of mult, J = 12.9 Hz, 1H), 3.56 (td, J = 10.0, 4.3 Hz, 1H), 3.17–3.09 (m, 1H), 2.59–1.38 (series of mult, 10 H); ^{13}C NMR ($CDCl_3$) δ 166.07, 165.83, 133.10, 129.88, 128.28, 69.82, 69.59. 62.21, 43.22, 34.50, 23.86, 23.70, 20.25. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.09; H, 6.66; N, 4.53.

[3*S*-(3α,9α,9a-β)]-3,9-Bis(benzoyloxy)octahydro-4*H*-quinolizin-4-one (21). To a stirred solution of **20** (0.200 g, 0.691 mmol), in THF (7 mL) PPh_3 (0.361 g, 1.38 mmol), and benzoic acid (0.169 g, 1.38 mmol) was added diisopropyl azodicarboxylate (0.279 g, 1.38 mmol, 0.27 mL). The resulting bright yellow solution was stirred at room temperature for 2 h, poured into H_2O (25 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried and the solvent

removed *in vacuo*. Purification of the residue by flash chromatography (gradient, 60–80% EtOAc in hexane) gave 0.125 g (46%) of **21** as a white foam: $[\alpha]^{20}_D = -16.5°$ (c = 1.0, $CHCl_3$), IR (film) 1720, 1654, 1602, 1584, 1452, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16–8.11 (m, 2H), 7.98–7.92 (m, 2H), 7.63 (tt, J = 7.4, 1.3 Hz, 1H), 7.53–7.43 (m, 3H), 7.31–7.24 (m, 2H), 5.59 (dd, J = 7.1, 4.8 Hz, 1H), 5.32–5.28 (m, 1H), 4.90 (d of mult, J = 13.2 Hz, 1H), 3.68 (td, J = 6.4, 1.5 Hz, 1H), 2.66 (td, J = 13.2, 3.0 Hz, 1H), 2.30–2.14 (m, 2H), 2.13–1.61 (series of mult, 6H); ^{13}C NMR ($CDCl_3$) δ 177.79, 166.45, 165.61, 165.56, 133.39, 132.98, 129.83, 129.79, 128.67, 128.18, 71.14, 69.41, 58.09, 42.86, 29.39, 25.23, 22.16, 19.63; HRMS calcd for $C_{23}H_{23}NO_3$ 394.1654, found 394.1653.

[1*S*-(1α,7α,9a-β)]-Octahydro-2*H*-quinolizine-1,7-diol (22). To a stirred solution of **21** (0.21 g, 0.534 mmol) in THF at 0 °C was added dropwise BH_3–SMe_2 (2.67 mL, 5.34 mmol, 2.0 M in THF) and the reaction stirred at room temperature for 15 min and then slowly heated to reflux. After 2 h the solvent was removed *in vacuo* and the residue refluxed in MeOH (20 mL) for 1 h. The solvent was removed *in vacuo* and the residue purified by ion-exchange chromatography using Biorad A6 500-X8 200–400-mesh H^+ form resin (gradient, 0.5–1.0 M $N^+H_4OH^-$) to give after lyophilization 59.5 mg (65.1%) of **22** as a white solid: $[\alpha]^{20}_D = -20.6°$ (c = 0.1, MeOH); IR (film) 3381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90–3.85 (m, 1H), 3.58–3.53 (m, 1H), 2.86 (dt, J = 12.0, 2.7 Hz, 1H), 2.80 (s, 2H), 2.74–2.67 (m, 1H), 2.18 (dd, J = 12.0, 1.8 Hz, 1H), 2.12–1.80 (series of mult, 6H), 1.55–1.29 (series of mult, 4H); ^{13}C NMR ($CDCl_3$) 68.50, 65.30, 64.93, 61.58, 56.23, 31.41, 30.15, 22.12, 19.29; HRMS calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1253.

[1*R*-(1β,9β,9a-β)]-1-(Benzoyloxy)octahydro-9-hydroxy-4*H*-quinolizin-4-one (20b). Treatment of **19** (0.400 g, 1.02 mmol) as described in **20a** gave, after purification by flash chromatography (hexane:EtOAc, gradient 85–100% EtOAc) 0.130 g (44%) of **20b** as a white foam: $[\alpha]^{20}_D = -40.5°$ (c = 0.65, $CHCl_3$); IR (film) 3366, 2942, 1717, 1618, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06–8.00 (dm, J = 8.0 Hz, 2H), 7.59 (tm, J = 7.4 Hz, 1H), 7.45 (tm, J = 7.6 Hz, 2H), 5.86 (br s, 1H), 4.79 (dm, J = 13.1 Hz, 1H), 3.50 (td, J = 9.7, 4.6 Hz, 1H), 3.37 (dm, J = 10.0 Hz, 1H), 2.69 (ddd, J = 17.8, 12.4, 6.6 Hz, 1H), 2.51–2.04 (series of mult, 5H), 1.82–1.71 (series of mult, 4H); ^{13}C NMR ($CDCl_3$) 168.05, 165.97, 133.40, 129.68, 128.49, 69.62, 67.14, 66.86, 42.83, 35.07, 27.07, 23.95, 22.37; CIMS (CH_4) 330 (M + $C_3H_5^+$, 5), 318 (M + $C_2H_5^+$, 20), 290 (MH^+, base), 272 ($MH^+ - H_2O$, 18), 168 ($MH^+ - HO_2CPh$, 35); HRMS calcd for $C_{16}H_{20}NO_4$ 290.1392, found 290.1380.

[1*R*-(1β,9β,9a-β)]-Octahydro-2*H*-quinolozine-1,9-diol (23). Treatment of 20b (85.0 mg, 0.294 mmol) as described in **22** gave a viscous, clear, colorless oil. Purification by ion-exchange chromatography using Biorad AG 500-X8 200–400-mesh H^+ form resin (0.5 M $NH_4^+OH^-$) gave, after lyophilization, 19.0 mg (38%) of **23** as a white solid: $[\alpha]^{20}_D = -0.7°$ (C = 0.86, $CHCl_3$); IR (KBr) 3364 cm^{-1}; ^1H NMR ($CDCl_3$) 4.10 (very br s, 2H), 3.72 (ddd, J = 11.1, 8.5, 4.6 Hz, 2H), 2.77 (dm, J = 11.3 Hz, 2H), 2.14–2.04 (m, 2H), 2.00 (dm, J = 12.1 Hz, 2H), 1.73–1.59 (m, 5H), 1.43–1.25 (m, 2H); ^{13}C NMR ($CDCl_3$) 74.14, 71.49, 55.33, 33.64, 23.00; EIMS 171 (45), 153 (74), 114 (base), 99 (65), 96 (83); HRMS calcd for $C_9H_{18}NO_2$ 172.1338, found 172.1348.

Supplementary Material Available: 1D and 2D NMR spectra (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.