Tetrahedron Vol. 48, No. 11, pp. 2099-2112, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Vicinal Tricarbonyls in Synthesis. New Routes to Indolizidines.

Harry H. Wasserman *, Chi B. Vu, and Jan D. Cook

Department of Chemistry, Yale University, New Haven, CT 06511, USA

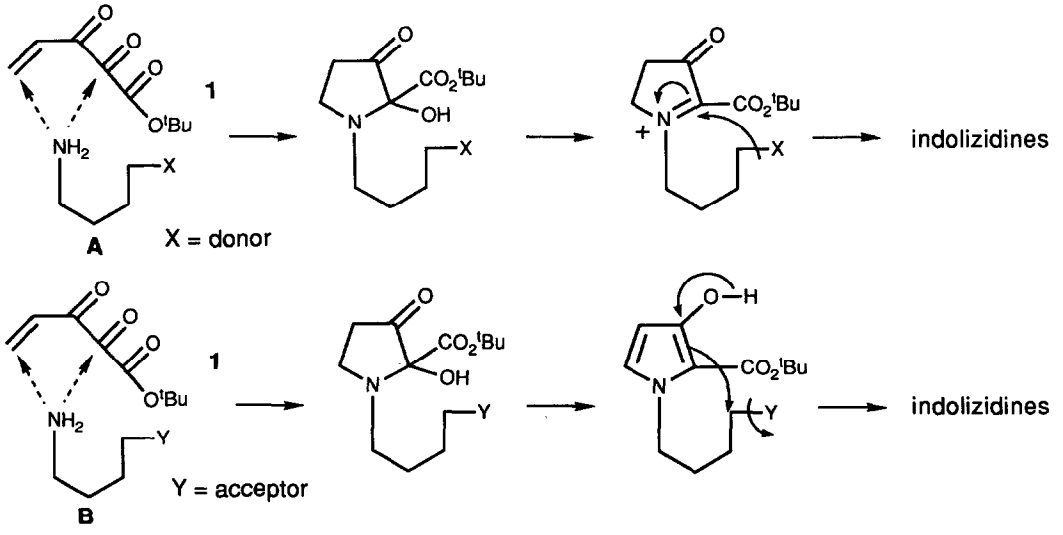
(*Received in USA* 18 *November* 1991)

***Key Words**: indolizidines; vinyl vicinal tricarbonyls; hydroxy pyrroles*

***Abstract**: The vinyl vicinal tricarbonyl system 1 (VTC) has been used in two different approaches to prepare functionalized indolizidines. In one approach, 1 is used as a trielectrophile in reactions with primary amines possessing auxiliary donor sites. In a second approach, 1 is converted to a substituted 3-hydroxypyrrole-2-carboxylate. This pyrrole derivative then undergoes an intramolecular alkylation to give the indolizidine ring system.*

In the course of our studies on the reactions of vicinal tricarbonyl derivatives with nucleophiles we have attached various acceptor units to the 1,2,3-tricarbonyl system to form aggregates of electrophilic functional groups. The vinyl vicinal tricarbonyl reagent **1** (VTC) is one such derivative which reacts with donor systems as a di- or trielectrophile.[1,2]

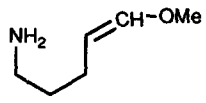
In this report we describe the reactions of VTC (**1**)[3] with amines having auxiliary donor sites (A). The products from these reactions in which the vinyl tricarbonyl reagent behaves like a trielectrophile are indolizidines of potential use in natural products synthesis.[4a] Another route to indolizidines has evolved from the reactions of the VTC reagent with primary amines attached to carbon chains bearing residues easily convertible to good leaving groups (B). The 3-hydroxypyrrole-2-carboxylates formed in this process may undergo intramolecular displacement as shown to yield indolizidines.[4b]



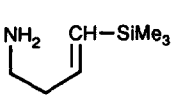
Indolizidines by Iminium Ion Additions

In the first approach to functionalized indolizidines, the VTC reagent **1** was used as a trielectrophile in reactions with primary amines possessing auxiliary donor sites (Figure 1).[5] As outlined below, the primary amino group at the terminus of each reagent initially takes part in a two-fold addition both to the α,β-unsaturated ketone

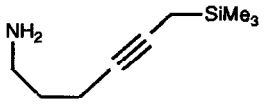
Figure 1



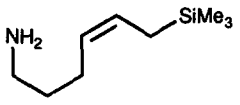
2a = cis
2b = trans



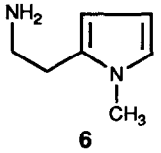
3a = cis
3b = trans



4



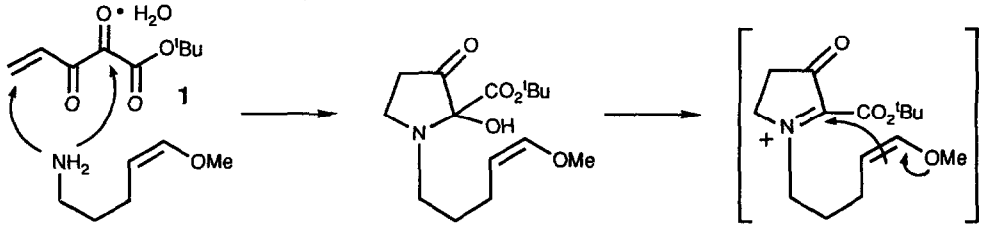
5



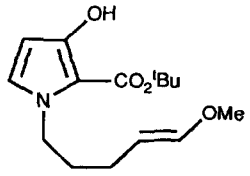
6

and to the central carbonyl group in **1** to give a hydroxypyrrolidone carboxylate. Under mildly acid conditions, this intermediate forms an iminium salt which then acts as an acceptor for a third-stage nucleophilic attack. We have found that this third-stage addition may take place readily with an enol ether, a vinylsilane, a propargylsilane, an allylsilane, or a pyrrole to give functionalized indolizidines.[6]

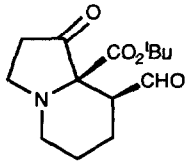
Scheme 1



2a **7** **8**



9a

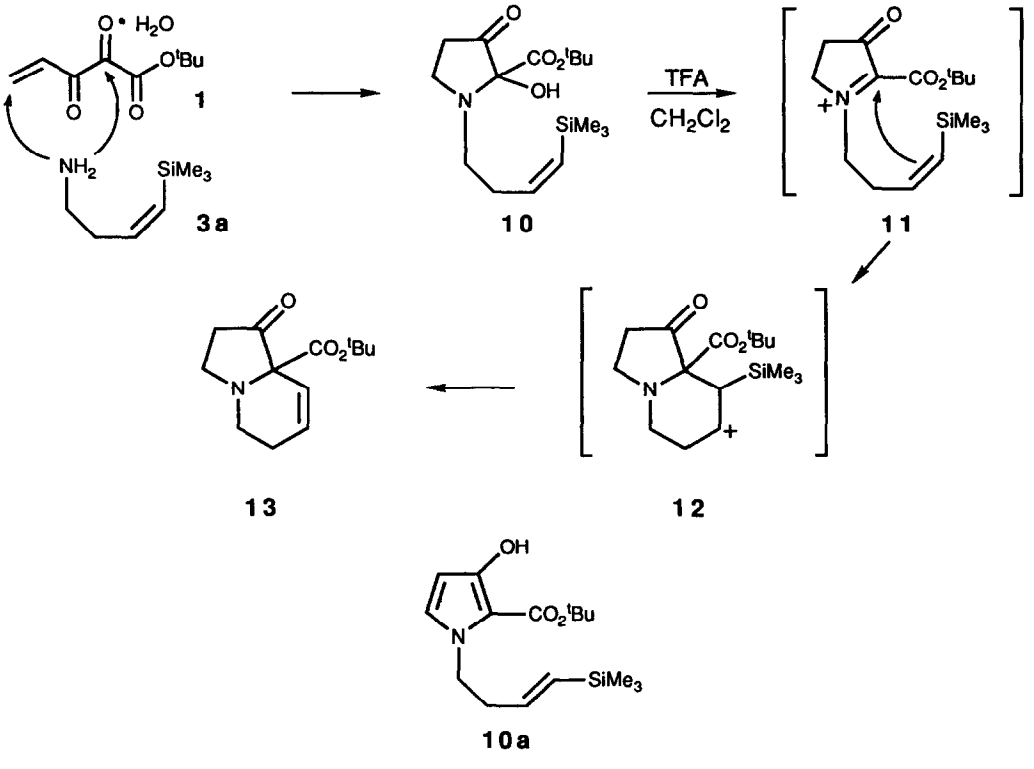


9

In practice, the three-step sequence can be conveniently carried out in a single reaction flask. As shown in Scheme 1, the cis enol ether **2a**[7] underwent reaction with **1** in the indicated fashion to form the hydroxypyrrolidone carboxylate **7**. In the presence of silica gel, cyclization took place readily to give **9**, presumably *via* an iminium ion such as **8** (45% overall). Under the same reaction conditions, the trans enol ether **2b** yielded a mixture of the cyclized product **9** (20%) and 3-hydroxypyrrole-2-carboxylate **9a** (16%).[8] Exclusive conversion to the cyclized product **9** could be achieved by treating the hydroxypyrrolidinone **7** with a Lewis acid such as BF_3•Et_2O or $POCl_3$ (35%).

We next investigated the use of unsaturated silanes as auxiliary donors in the addition to iminium ion intermediates. Recent studies have shown that organosilanes can effectively control both the regio- and stereochemical outcome of cationic cyclization.[9] As illustrated in Scheme 2, the cis vinylsilane derivative **3a**[10] could be reacted with **1** to form an intermediate hydroxypyrrolidinone **10**. Upon treatment of **10** with anhydrous trifluoroacetic acid, cyclization to **13** took place through the iminium ion **11** (42% overall). In this reaction, it can be assumed that the TMS group stabilizes the carbocation formed at the β-position **12** followed by elimination of the silyl residue.[11] Overman has provided a convincing explanation for the fact that this type of hyperconjugative stabilization is more effective in cis vinylsilanes than in trans vinylsilanes.[9b] In the present work, we found that

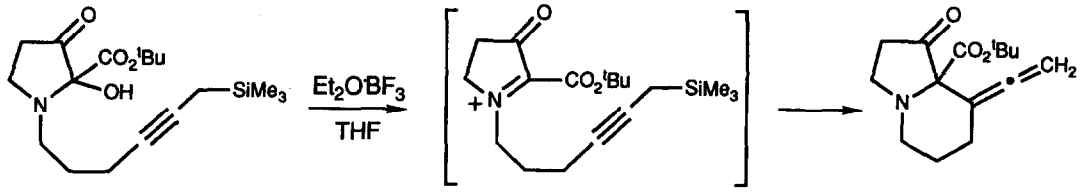
Scheme 2



when the trans analogue of **3b** was subjected to this particular procedure, the only isolable product was a small amount of the 3-hydroxypyrrole-2-carboxylate **10a**.

The propargylsilane derivative **4**[12,13] also took part in a related acid-promoted cyclization to give **16** (64%) (Scheme 3). In this case, production of iminium ion **15** and subsequent cyclization generated a vinyl carbonium ion, setting the stage for the elimination of the silyl group and the formation of the ketene.

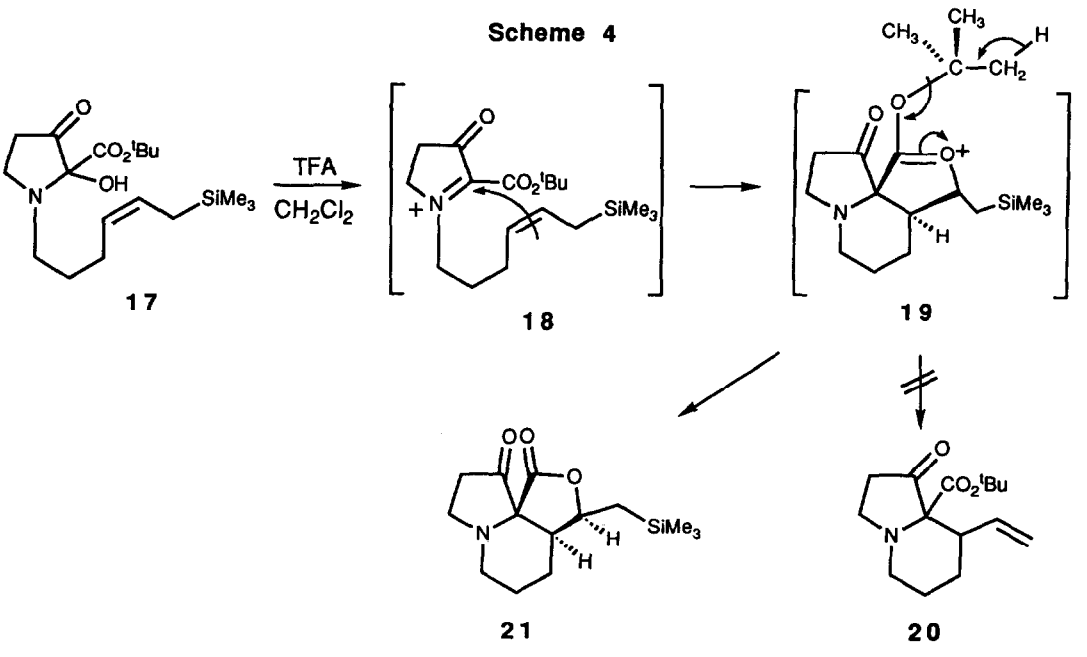
Scheme 3



14 **15** **16**

Addition of an amine containing an allylsilane residue[14] to VTC (**1**) gave the addition product **17**. When this adduct was treated with anhydrous trifluoroacetic acid, the resulting product was not the expected bicyclic system **20**. Instead, a competing decomposition of the *t*-butyl ester group took place followed by lactone formation to yield the tricyclic compound **21** (45% overall).[15]

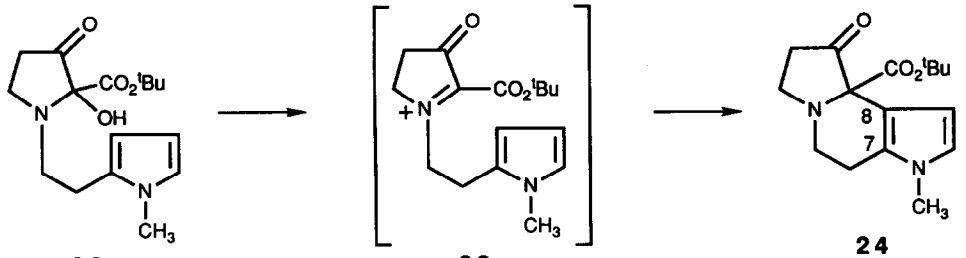
Scheme 4



17 **18** **19** **21** **20**

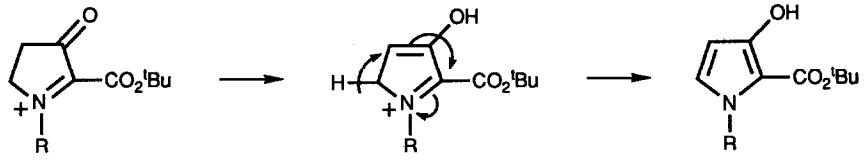
When the electron-rich *N*-methyl pyrrole was appropriately appended to the primary amine as in **6**, a facile reaction with VTC (**1**) took place. The tricyclic system **24** was obtained in 90% overall yield when the intermediate carbinolamine **22** was treated with a mildly acidic reagent such as silica gel (Scheme 5). The fused *N*-methylpyrrole ring thus created, provides a reactive site for introduction of functionality into the indolizidine framework.[16]

Scheme 5



Indolizidines from 3-Hydroxypyrrole-2-carboxylates

In the second approach to functionalized indolizidines, the vinyl tricarbonyl ester **1** was used to prepare 3-hydroxypyrrole-2-carboxylates.[8] These pyrroles, which always form as trace or minor byproducts in the amine additions, become the dominant reaction products in the presence of acid and in the absence of third-stage nucleophiles which can add to iminium ion intermediates. Their formation can be pictured in terms of proton loss from the enol intermediate **25**. As analogues of β-keto esters, these hydroxypyrroles undergo ready alkylation at the C-2 position.[17]

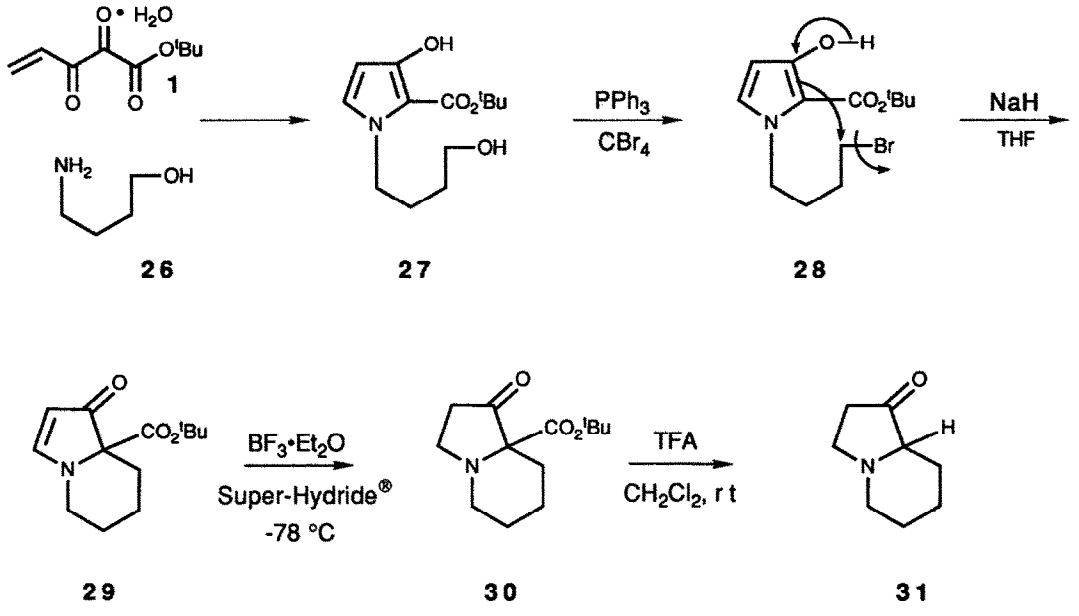


25

When an electrophile is appropriately attached to the primary amino starting material, the intramolecular alkylation results in a fused-ring system (Scheme 6). In order to construct the indolizidine ring structure using this method, we needed to use a primary amine bearing a leaving group separated from the terminal NH_2 by a four-carbon chain. In practice, we found that it was more convenient to use an amino alcohol such as **26** than the hydrochloride salt of 4-bromobutylamine. As shown in the Scheme, the reaction between **26** and the vinyl tricarbonyl **1** took place in the usual fashion to give the 3-hydroxypyrrole-2-carboxylate **27** (64%). The primary alcohol **27** was selectively converted to the corresponding bromide **28** using triphenylphosphine and carbon

tetrabromide (81%).[18] As expected, when **28** was treated with NaH, cyclization took place to afford the indolizidine derivative **29** (88%).

Scheme 6



Compound **29**, in turn, could be converted to derivatives of potential interest in the synthesis of indolizidine alkaloids. For example, the vinylogous amide **29** could be conveniently reduced at -78 °C using Super-Hydride® in the presence of BF_3•Et_2O (76%).[19] Upon exposure to excess TFA, compound **30** underwent decarboxylation to give **31** (76%).[20] This particular derivative has previously been shown to be a key intermediate in the biosynthesis of the indolizidine alkaloids, slaframine and swainsonine.[21]

In summary, we have shown that the vinyl tricarbonyl ester **1** can be used effectively in reactions with substituted primary amines to yield functionalized indolizidines. The two methods which have evolved from this study offer the advantage of placing an oxygen functionality in a key location in the five-membered ring of the indolizidine system. In addition, a variety of functional groups can be installed on the six-membered ring for further elaboration in the synthesis of products of biological interest.

Acknowledgments: This work was supported by NIH Grants GM-07874 and GM-31350. We thank Dr. Roger Frechette for helpful discussions.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus. All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1420 Spectrophotometer or Nicolet S-5X FT-IR. Proton and carbon nuclear magnetic resonance spectra were determined in the indicated solvent on a Bruker HX-270 or Bruker WM-250. In most cases, chloroform was used as the internal standard (δ 7.27 ppm). Low-resolution mass spectra were recorded on a Hewlett Packard 5985A or 5989A mass spectrometer using electron ionization (20 EV). High-resolution mass spectra, using either electron ionization or chemical ionization, were performed by Mr. Dan Pentek on a Kratos MS-80RFA at Yale University, Instrument Center. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. Flash chromatography was performed on silica gel 60 (230-400 mesh, EM laboratories). All chromatographic solvents were distilled prior to use with the exception of diethyl ether which was obtained in anhydrous form. Thin layer chromatography (TLC) was performed on glass plates pre-coated with silica gel 60 F_{254} (0.25 mm, EM laboratories). Anhydrous solvents were distilled prior to use as follows: THF was distilled from sodium/benzophenone ketyl; acetonitrile, benzene, methylene chloride, pyridine, triethylamine and dimethyl sulfoxide were distilled from calcium hydride.

Indolizidine (9):

A solution containing 101 mg of the vinyl tricarbonyl reagent **1** (0.50 mmol, 1.1 equiv) in 5 mL of CH_2Cl_2 was stirred at 0 °C under an inert atmosphere of nitrogen. A solution containing 55 mg of the trans-5-methoxy-4-penten-1-amine (0.48 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2 was then added and the resulting reaction mixture was stirred at 0 °C for 25 min. Next, the reaction mixture was cooled to -78 °C and $POCl_3$ (0.19 mL, 2.0 mmol, 4.0 equiv) was added. The resulting reaction mixture was stirred at -78 °C for 3 h and then poured into 10 mL of saturated aqueous $NaHCO_3$. The two layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (1:1 Et_2O/hexanes) afforded 41 mg of the product (32%). ^1H NMR (250 MHz, $CDCl_3$) δ 10.12 (s, 1H), 3.44-3.35 (m, 1H), 3.28-3.20 (m, 1H), 3.03-2.82 (m, 2H), 2.58-2.53 (m, 2H), 2.29 (dd, 1H, J = 4, 11), 2.21-2.13 (m, 1H), 1.69-1.40 (m, 3H), 1.44 (s, 9H). IR ($CHCl_3$) 3000, 2960, 2880, 1770, 1730, 1380, 1260, 1160, 1140 cm^{-1}. MS (EI, 20 EV) (m/e) 267, 166, 138. High-resolution MS (CI) calcd. for $C_{14}H_{21}NO_4$ 268.1549 (M^+ + 1 H); found 268.1548.

6-*t*-Butoxycarbonyl-7-oxo-1-azabicyclo[4.3.0]non-4-ene (13):

A solution of 16 mg of the vinyl tricarbonyl ester **1** (0.079 mmol, 1.0 equiv) in 1.5 mL of CH_2Cl_2 was cooled to 0 °C under an inert atmosphere of nitrogen. A solution of 11 mg of the amine (0.077 mmol, 1.0 equiv) in 220 μL of CH_2Cl_2 was added dropwise at 0 °C and stirring was continued for an additional 15 min. Anhydrous trifluoroacetic acid (50 μL) was then added and the reaction mixture was warmed to room temperature. After stirring for 2 h at room temperature, the reaction mixture was quenched by adding 3 mL of saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with 4 x 3 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (1:1 hexanes/EtOAc) afforded 8 mg of the product (42%) as a light yellow oil (TLC, R_f 0.23, 3:1 EtOAc/hexanes): ^1H NMR (250 MHz, $CDCl_3$) δ 5.97-6.04 (m, 1H), 5.81-5.76 (m, 1H), 3.27-2.30 (m. 8H),

1.47 (s, 9H). IR ($CHCl_3$) ν 3020, 2915, 1770, 1730 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 237 (M^+, 0.6), 210 (0.7), 209 (2.8), 208 (1.5), 137 (10.6), 136 (M^+ - $CO_2{}^tBu$, 100.0). High-resolution MS (CI) calcd for $C_{13}H_{19}NO_3$ 238.1444 (M^+ + 1H); found 238.1446.

6-(Trimethylsilyl)-4-hexynylamine (4):

A solution containing 410 mg of 6-(trimethylsilyl)-4-hexyn-1-ol[12] (2.41 mmol, 1.0 equiv) and 760 mg of triphenylphosphine (2.89 mmol, 1.2 equiv) in 12 mL of anhydrous THF was cooled to 0 °C under an inert atmosphere of nitrogen. With vigorous stirring, 570 μL of diisopropylazodicarboxylate (2.89 mmol, 1.2 equiv) and 650 μL of diphenylphosphoryl azide (2.89 mmol, 1.2 equiv) were added sucessively at 0 °C. The reaction mixture was warmed to room temperature and stirring was continued for an additional 2 h. The yellow, cloudy reaction mixture was then concentrated under reduced presure. Chromatography (hexanes) afforded 285 mg of the unstable azide (61%) as a clear oil This freshly prepared azide (285 mg, 1.46 mmol, 1.0 equiv) was dissolved in 8 mL of anhydrous THF. The resulting solution was cooled to 0 °C under an inert atmosphere of nitrogen. At this same temperature, a 1.0M solution of $LiAlH_4$ in Et_2O (1.50 mL, 1.5 mmol, 1.0 equiv) was then added dropwise and stirring was continued for an additional 20 min. The reaction was carefully quenched at 0 °C with 100 μL of water and the resulting mixture was filtered through a pad of Celite. The clear filtrate was concentrated under reduced pressure to give 230 mg of the amine (93%) as a light yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 2.83 (t, 2 H, J = 7.0 Hz), 2.25-2.19 (m, 2 H), 1.67-1.56 (m, 2 H), 1.50 (br s, 2 H), 1.42 (t, 2 H, J = 2.7 Hz), 0.09 (s, 9H). IR (neat) ν 3360, 3300, 2970, 1250, 850 cm^{-1}. High-resolution MS (CI) calcd for $C_9H_{19}NSi$ 170.1365 (M^+ + 1H); found 170.1357.

8a-*t*-Butoxycarbonyl-1-oxo-8-vinylideneoctahydroindolizine (16):

A solution of 250 mg of the vinyl tricarbonyl ester **1** (1.24 mmol, 1.0 equiv) in 80 mL of anhydrous THF was cooled to 0 °C under an inert atmosphere of nitrogen. A solution of 210 mg of the amine **4** (1.24 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2 was then added slowly at 0 °C over a period of 10 min and stirring was continued for an additional 15 min. The reaction mixture was then cooled to -78 °C and $BF_3{\cdot}OEt_2$ (0.770 mL, 6.26 mmol, 5.0 equiv) was added. The resulting reaction mixture was then warmed to 0 °C and stirring was continued for an additional 30 min. The slightly yellow reaction mixture was then quenched by pouring into 50 mL of ice-cold saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with 4 x 30 mL of Et_2O. The organic layer was washed with 50 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (1.5:1 hexanes/EtOAc) yielded 210 mg of the product (64%) as a clear oil (TLC, R_f 0.47, 2:1 EtOAc/ hexanes): ^1H NMR (250 MHz, $CDCl_3$) δ 4.84-4.68 (m, 2 H), 3.30-2.20 (m, 10 H), 1.50 (s, 9 H). IR ($CHCl_3$) ν 2990, 2950, 2870, 1920, 1770, 1740 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) no M^+, 252 (0.8), 163 (10.1), 162 (M^+ - CO_2t-Bu, 100). High-resolution MS (CI) calcd for $C_{15}H_{21}NO_3$ 264.1601 (M^+ +1H); found 264.1609.

(*Z*)-6-(Trimethylsilyl)-4-hexenylamine (5):

A solution cantaining 550 mg of the alcohol (Z)-6-(trimethylsilyl)-4-hexen-1-ol[12] (3.20 mmol, 1.0 equiv) in 8 mL of anhydrous THF was subjected to the same reaction conditions used to prepare **4**. After the $LiAlH_4$ reduction, 280 mg of the product (77%) was obtained as a light yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.50-

5.20 (m, 2 H), 2.60-2.40 (m, 2 H), 2.50 (br s, 2 H), 0.006 (s, 9 H). IR (neat) ν 3360, 3300, 3020, 2970, 2940, 2870, 1260, 1160 cm^{-1}. High-resolution MS (CI) calcd for $C_{19}H_{21}NSi$ 172.1523 (M^+ + 1 H); found 172.1521.

Indolizidine (21):

A solution of 40 mg of the vinyl tricarbonyl ester **1** (0.198 mmol, 1.0 equiv) in 10 mL of CH_2Cl_2 was cooled to 0 °C under an inert atmosphere of nitrogen. A solution of 40 mg of the amine **5** (0.198 mmol, 1.0 equiv) in 600 μL of CH_2Cl_2 was then added at 0 °C over a period of 10 min. Stirring was continued at 0 °C for an additional 15 min and anhydrous trifluoroacetic acid (80 μL) was added. The resulting reaction mixture was warmed to room temperature and stirred for 1 h. The slightly yellow solution was then poured into 25 mL of ice-cold saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with 3 x 5 mL of Et_2O. The combined organic layers were washed with 15 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (1.5 hexanes/EtOAc) yielded 25 mg of the product (45%) as a clear oil (TLC, R_f 0.50, 2:1 EtOAc/hexanes): ^1H NMR (250 MHz, $CDCl_3$) δ 5.14-5.05 (m, 1 H), 3.42-3.35 (m, 1 H), 3.23-3.14 (m, 1 H), 3.17-2.48 (m, 3 H), 2.14-2.07 (m, 1 H), 1.94-1.80 (m, 1 H), 1.72-1.20 (m, 1 H), 1.09 (dd, 1 H, J = 8.45, 14.4 Hz), 0.80 (dd, 1 H, J = 7.32, 14.4 Hz), 0.088 (s, 9 H). IR ($CDCl_3$) ν 2960, 2880, 1780, 1755, 1260 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) no M^+, 237 (M^+ - CO_2, 100), 164 (21.1), 150 (40.2). High-resolution MS (CI) calcd for $C_{14}H_{23}NO_3Si$ 282.1526 (M^+ + 1H); found 282.1517.

Indolizidine (24):

A solution of 1.600g of the vinyl tricarbonyl reagent **1** (7.91 mmol, 1.0 equiv) in 250 mL of CH_2Cl_2 was cooled to 0 °C under an inert atmosphere of nitrogen. A solution of 980 mg of 2-(2-aminoethyl)-1-methylpyrrole **6**(7.91 mmol, 1.0 equiv) in 5 ml of CH_2Cl_2 was added slowly over a period of 30 min at 0 °C and stirring was continued for an additional 45 min. The light yellow solution was warmed to room temperature and concentrated under reduced pressure. Chromatography (1:1 hexanes/EtOAc) afforded 2.080g of the product (90%) as a light yellow solid (TLC, R_f 0.14, 2.:1 hexanes/EtOAc), mp 124-126 °C: ^1H NMR (250 MHz, $CDCl_3$) δ 6.51 (d, 1 H, J = 3.0 Hz), 6.25 (d, 1 H, J = 3.0 Hz), 3.49 (s, 3 H), 3.40-2.30 (m, 8 H), 1.47 (s, 9 H). IR ($CHCl_3$) ν 3050, 2975, 2900, 1770, 1740 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 290 (M^+, 0.4),205 (2.2), 190 (13.2), 189 (M^+ - $CO_2{}^tBu$, 100.0), 134 (2.4), 133 (6.7). High-resolution MS (CI) calcd for $C_{16}H_{22}N_2O_3$ 291.1710 (M^+ + 1H); found 291.1720. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64. Found: C, 66.28; H, 7.67.

***t*-Butyl 1-(4-hydroxybutyl)-3-hydroxypyrrole-2-carboxylate (27):**

A solution containing 485 mg of the vinyl tricarbonyl ester **1** (2.17 mmol, 1.1 equiv) in 120 mL of CH_2Cl_2 was cooled to 0 °C under an inert atmosphere of nitrogen. A solution containing 200 μL of 4-amino-1-butanol (2.17 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 was then added over a period of 30 min, at 0 °C, and stirring was continued for an additional 15 min. The reaction mixture was warmed to room temperature and 1 g of silica gel was added. The resulting reaction mixture was stirred vigorously at room temperature for 15 h and then filtered. The yellow filtrate was concentrated under reduced pressure. Purification by chromatography (2:1 hexanes/EtOAc) afforded 357 mg of the hydroxypyrrole **27** (64%) as a light yellow oil (TLC, R_f 0.45, 2:1 EtOAc/hexanes): ^1H NMR (250 MHz, $CDCl_3$) δ 6.55 (d, 1 H, J = 2.83 Hz), 5.70 (d, 1 H, J = 2.90 Hz), 4.07 (t,

2 H, J = 7.14 Hz), 3.65 (t, 2 H, J = 6.22 Hz), 1.90-1.70 (m, 2 H), 1.60 (s, 9 H), 1.60-1.50 (m, 2 H). IR (neat) ν 3480, 2950, 2880, 1710, 1645, 1560, 850, 780 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 256 (M^+ + 1, 3.1), 255 (M^+, 19.9), 199 (100), 181 (47.1). High-resolution MS (EI) calcd for $C_{13}H_{21}NO_4$ 255.1471; found 255.1477.

t-Butyl 1-(4-bromobutyl)-3-hydroxypyrrole-2-carboxylate (28):

A solution containing 120 mg of the alcohol **27** (0.471 mmol, 1.0 equiv) and 220 mg of triphenylphosphine (0.942 mmol, 2.0 equiv) in 20 mL of anhydrous THF was cooled to 0 °C under an inert atmosphere of nitrogen. At this same temperature, 140 mg of carbon tetrabromide (0.471 mmol, 1.0 equiv) was added in a single portion and the resulting reaction mixture was warmed to room temperature. After stirring at room temperature for 2 h, the cloudy reaction mixture was concentrated under reduced pressure. Purification by chromatography (8:1 hexanes/EtOAc) afforded 122 mg of the product (81%) as a white solid (TLC, R_f 0.55, 2:1 hexanes/EtOAc), mp 35-35 °C: ^1H NMR (250 MHz, $CDCl_3$) δ 6.55 (d, 1 H, J = 2.87 Hz), 5.74 (d, 1 H, J = 2.91 Hz), 4.09 (t, 2 H, J = 6.48 Hz), 3.39 (t, 2 H, J = 6.18 Hz), 2.00-1.78 (m, 4 H), 1.61 (s, 9H). IR (CH_2Cl_2) ν 3470, 3250, 3010, 2995, 2950, 2880, 1705, 1650, 1565 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 320 (0.6), 319 (4.3), 318 (0.7), 317 (4.0), 263 (46.3), 245 (100), 243 (97.6). Anal. Calcd for $C_{13}H_{20}NO_3Br$: C, 49.07; H, 6.34. Found: C, 49.15; H, 6.37.

6-t-Butoxycarbonyl-7-oxo-1-azabicyclo[4.3.0]non-8-ene (29):

A suspension containing 60 mg of NaH (60% by weight, 1.5 mmol, 2.2 equiv) in 5 mL of anhydrous THF was cooled to 0 °C under an inert atmosphere of nitrogen. A solution containing 220 mg of the bromide **28** (0.691 mmol, 1.0 equiv) in 12 mL of anhydrous THF was then added at 0 °C and stirring was continued at that temperature until all gas evolution had ceased. The reaction mixture was warmed to 45-50 °C and stirred for an additional 30 min. The cloudy, yellow reaction mixture was then cooled to 0 °C and carefully poured into 20 mL of ice-cold saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was extracted with 3 x 20 mL of Et_2O. The organic layer was washed with 20 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (3:1 EtOAc/hexanes) yielded 144 mg of the product (88%) as a white solid (TLC, R_f 0.20, 3:1 EtOAc/hexanes), mp 91-91 °C: ^1H NMR (250 MHz, $CDCl_3$) δ 7.81 (d, 1 H, J = 3.12 Hz), 4.98 (d, 1 H, J = 3.11 Hz), 3.66-3.59 (m, 1 H), 3.39-3.32 (m, 1 H), 2.69-2.63 (m, 1 H), 1.92-1.78 (m, 2 H), 1.47 (s, 9 H), 1.66-1.35 (m, 3 H). IR (CH_2Cl_2) ν 3120, 3020, 2995, 2960, 2880, 1740, 1665 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 238 (M^+ + 1, 3.1), 237 (M^+, 21.5), 178 (4.4), 137 (86.2), 136 (M^+ - $CO_2{}^tBu$, 100.0). High-resolution MS (EI) calcd for $C_{13}H_{19}NO_3$ 237.1366; found 237.1361. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 65.73; H, 8.06.

6-t-Butoxycarbonyl-7-oxo-1-azabicyclo[4.3.0]nonane (30):

A solution containing 90 mg of compound **29** (0.380 mmol, 1.0 equiv) in 15 mL of anhydrous THF was cooled to -78 °C under an inert atmosphere of nitrogen. At this same temperature, BF_3·Et_2O (61 μL, 0.494 mmol, 1.3 equiv) was added and stirring was continued for about 5 min. A solution of 1.0 M Super-Hydride® in THF (5 mL, 0.500 mmol, 1.3 equiv) was then added and the resulting reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched at -78 °C with 2 mL of brine and warmed to about -30 °C. At this point, 5 mL of

saturated aqueous $NaHCO_3$ was added and the resulting reaction mixture was warmed to room temperature. After dilution with 5 mL of EtOAc, the two layers were separated and the aqueous layer was extracted with 3 x 5 mL of EtOAc. The organic layer was washed with 10 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (2:1 EtOAc/hexanes) afforded 72 mg of the product (79%) as a clear oil (TLC, R_f 0.70, 3:1 EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 3.39-3.28 (m, 1 H), 3.27-3.03 (m, 2 H), 2.92-2.82 (m, 1 H), 2.55-2.45 (m, 2 H), 2.25-2.15 (m, 1 H), 1.80-1.72 (m, 1 H), 1.47 (s, 9 H), 1.70-1.28 (m, 4 H). IR (CH_2Cl_2) ν 2990, 2940, 2860, 1770, 1735 cm^{-1}. MS (EI, 20 EV) m/e (relative intensity) 239 (M^+, 0.7), 139 (8.6), 138 (M^+ - $CO_2{}^tBu$, 100.0). High-resolution MS (EI) calcd. for $C_{13}H_{21}NO_3$ 239.1522; found 239.1518.

1-Oxooctahydroindolizine (31):

Under an inert atmosphere of nitrogen, excess trifluoroacetic acid (1 mL) was added to a solution containing 50 mg of ester **30** (0.209 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 3 h. It was then concentrated under reduced pressure and quenched with 4 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 3 x 3 mL of CH_2Cl_2. The combined organic layers were washed with 5 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (2:1 methylene chloride/acetone) afforded 22 mg of the known 1-oxooctahydroindolizine (76%)[20] as a clear, volatile oil which rapidly discolored upon exposure to air (R_f 0.25, 3:1 EtOAc/hexanes). Spectroscopic data for this product were identical to those reported previously.[20]

References and Notes:

1. Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.

2. Wasserman, H. H.; Frechette, R.; Oida, T.; van Duzer, J. H. *J. Org. Chem.* **1989**, *54*, 6012.

3. For an improved method of preparing **1** using Oxone® see: Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 5205.

4. For preliminary reports on the preparation of functionalized indolizidines, and other pertinent literature references, see: (a) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701. (b) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 4945.

5. For other examples involving the use of **1** as a trielectrophile, see: (a) Wasserman, H. H.; Amici, R. *J. Org. Chem.* **1989**, *54*, 5843. (b) Wasserman, H. H.; Henke, S. L.; Luce, P.; Nakanishi, E. *J. Org. Chem.* **1990**, *55*, 5821.

6. For other examples of π-donor groups used in intramolecular cyclizations, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

7. 5-Methoxy-4-penten-1-amine was prepared from 5-methoxy-4-penten-1-ol by mesylation (94%), phthalimide displacement (90%), and methanolic hydrazinolysis (97%). The alcohol was made by a Wittig reaction of (methoxymethyl)triphenylphosphorane with 2-hydroxyfuran (91%, trans/cis = 2/1) using known procedures (Clive, D. L.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339).

8. Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721.

9. For recent reviews on the chemistry of organosilanes, see: (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

10. Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097.

11. A related iminium ion-initiated, vinylsilane-terminated cyclization reaction to generate indolizidines has recently been reported. Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.

12. Hiemstra, H. Sno, M.; Vijn, R.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

13. 6-(Trimethylsilyl)-4-hexyn-1-ol[12] was converted to the corresponding azide (75%) by treatment with diphenyl phosphorylazide in the presence of diisopropyl azodicarboxylate and triphenylphosphine: Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467. Reduction of the azide with $LiAlH_4$ in Et_2O gave the acetylenic amine **4** (91%).

14. (Z)-6-(Trimethylsilyl)-4-hexen-1-ol was obtained from 6-(trimethylsilyl)-4-hexyn-1-ol by a selective hydrogenation over P_2Ni (Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1977**, *38*, 2226. The alcohol was then converted to the corresponding amine according to the procedure outlined in ref 13.

15. The stereochemical assignment of compound **21** was based on ^1H NMR. Related cis-fused lactones have been trapped by Speckamp and coworkers.[12]

16. We are currently investigating the reaction of singlet oxygen and **24** as a possible route to oxygenation at positions **7** and **8**.

17. (a) Chong, R.; Clezy, P. S. *Aus. J. Chem.* **1967**, *20*, 935. (b) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 2224. (c) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 3521. (d) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1979**, *27*, 1448. (e) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Kobayashi, H.; Takano, S. *Heterocycles* **1981**, *15*, 843.

18. Falorni, M.; Lardicci, L.; Giacomelli, G. *J. Org. Chem.* **1986**, *51*, 5291.

19. Comins, D. L.; LaMuyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053.

20. Leonard, N. J.; Swann, S., Jr.; Figueras, J., Jr. *J. Am. Chem.Soc.* **1952**, *74*, 4620.

21. Harris, M. C.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940 and references cited therein.