

Article

## Vicinal Tricarbonyls in Synthesis. New Routes to Indolizidines

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O sistema tricarbonil vicinal tem sido utilizado em duas abordagens diferentes na preparação de indolizidinas funcionalizadas. Numa abordagem, **1** foi usado como trienófilo em reações com aminas primárias contendo certos doadores. Na segunda, **1** foi convertido no 2-carboxilato de 3-hidroxipirrol. Este derivado do pirrol sofreu então uma alquilação intramolecular, produzindo o sistema cíclico indolizidímico.

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

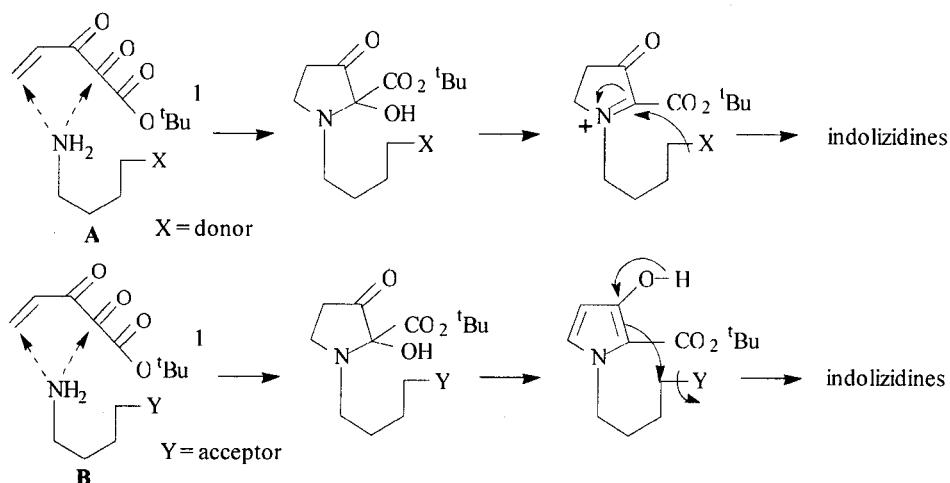
**Keywords:** tricarbonyl, indolizidine, pyrrolidone, iminium ion, pyrrole

### Introduction

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<sup>1</sup>.

In this report we describe the reactions of VTC (**1**)<sup>2</sup> with amines having tethered 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<sup>3a</sup>. 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 initially formed in this process may undergo intramolecular displacement as shown to yield indolizidines<sup>3b</sup>.



## Results and Discussion

### 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 (Fig. 1)<sup>4,5</sup>. As outlined below, the primary amino group at the terminus of each reagent initially takes part in a two-fold addition both to the  $\alpha,\beta$ -unsaturated ketone 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

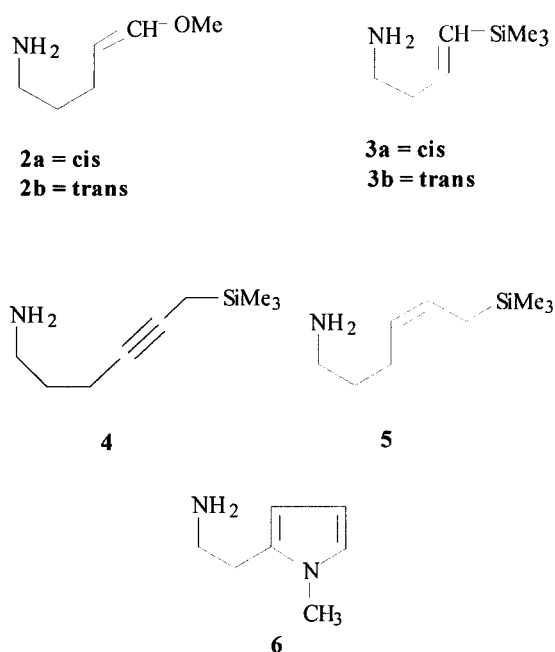
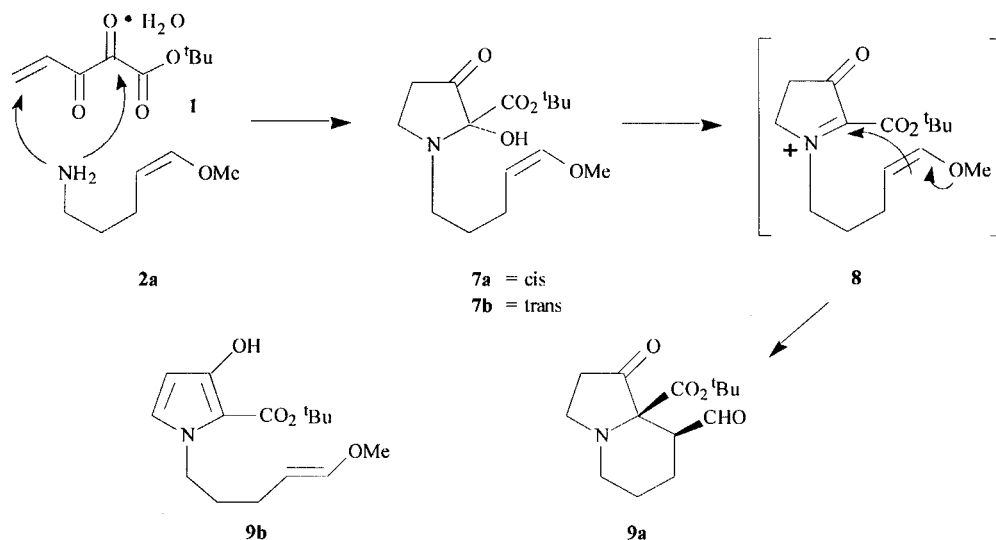


Figure 1.

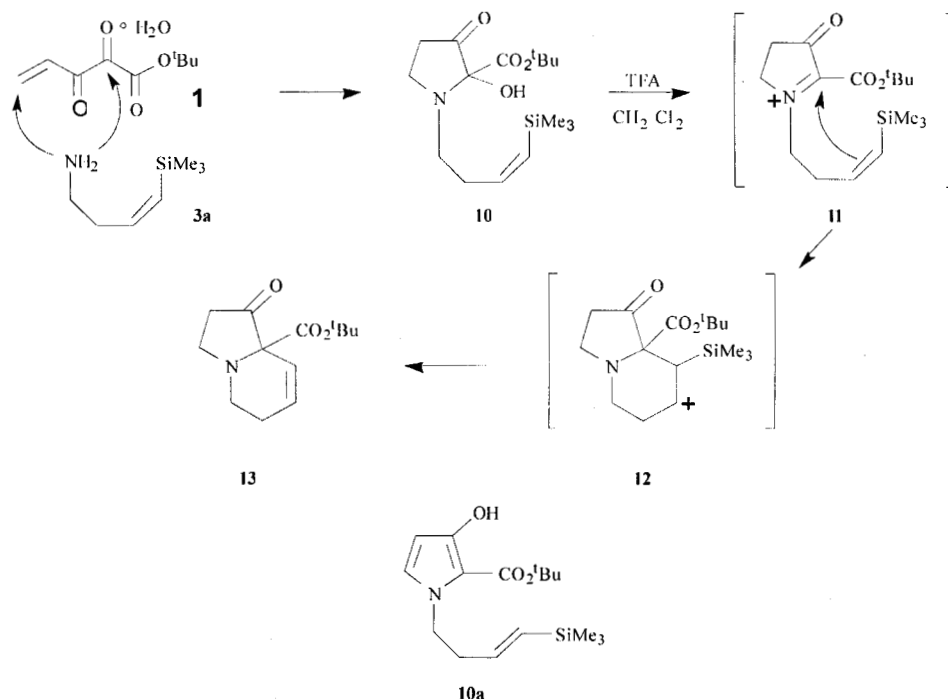


Scheme 1.

third-stage nucleophilic attack. We have found that this third-stage addition takes place readily with an enol ether, a vinylsilane, a propargylsilane, an allylsilane, or a pyrrole to give functionalized indolizidines<sup>3</sup>.

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** underwent reaction with **1** in the indicated fashion to form the hydroxypyrrolidone carboxylate **7a**. In the presence of silica gel, cyclization took place readily to give **9a**, 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 **9a** (20%) and 3-hydroxypyrrole-2-carboxylate **9b** (16%)<sup>7</sup>. Exclusive conversion to the cyclized product **9a** could be achieved by treating the hydroxypyrrolidone **7b** with a Lewis acid such as  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  or  $\text{POCl}_3$  (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<sup>8</sup>. As illustrated in Scheme 2, the cis vinylsilane derivative **3a**<sup>9</sup> could be reacted with **1** to form an intermediate hydroxypyrrolidone **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  $\beta$ -carbocation **12** which undergoes elimination of the silyl residue<sup>10</sup>. 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<sup>9</sup>. In the present work, we found that when the trans analog of **3b** was subjected to this particular procedure, the only isolable product was a small amount of the 3-hydroxypyrrole-2-carboxylate **10a**.



Scheme 2.

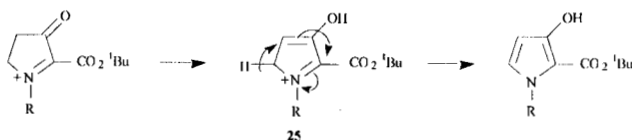
The propargylsilane derivative **4**<sup>11,12</sup> also took part in a related acid-promoted cyclization to give **16** (64%) (Scheme 3). In this case, production of iminium ion **15** and subsequent cyclization generated a vinyl carbonium ion, setting the stage for elimination of the silyl group and the formation of ketene **16**.

Addition of an amine containing an allylsilane residue<sup>13</sup> 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 breakdown of the *t*-butyl ester group took place followed by lactone formation to yield the tricyclic compound **21** (45% overall)<sup>14</sup>.

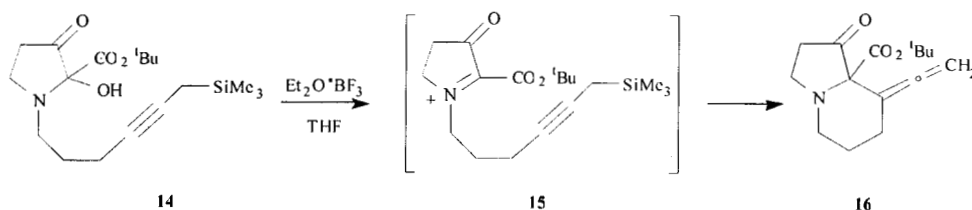
When the electron-rich *N*-methyl pyrrole was appropriately appended to the primary amine as in **6**, a facile reaction with VTC (**1**) took place. The tricyclic system **24** was obtained in 90% overall yield when the intermediate carbinolamine **22** was treated with a mildly acidic reagent such as silica gel (Scheme 5). The fused *N*-methylpyrrole ring thus created provides a reactive site for introduction of functionality into the indolizidine framework<sup>15</sup>.

#### Indolizidines from 3-Hydroxypyrrole-2-carboxylates

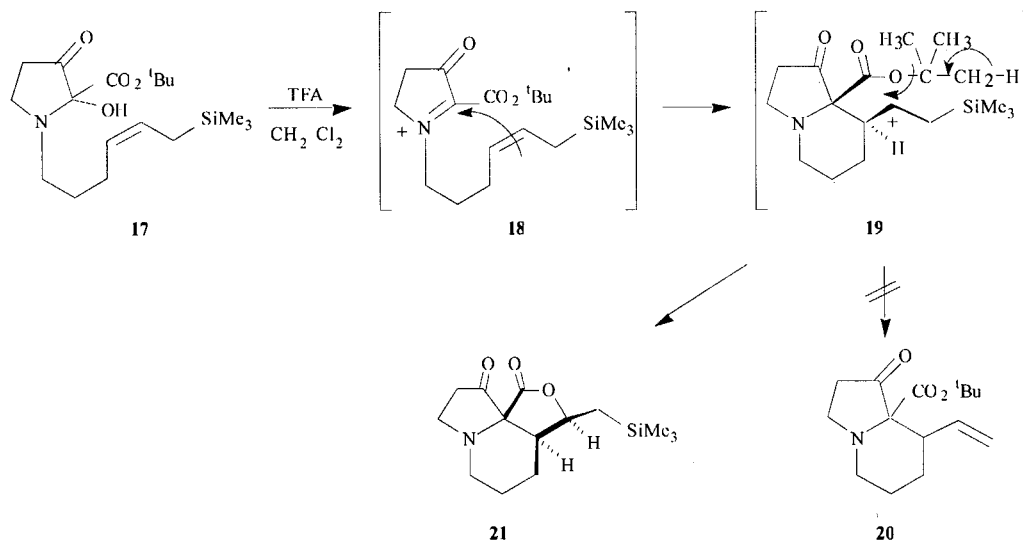
In the second approach to functionalized indolizidines, the vinyl tricarboxyl ester **1** was used to prepare 3-hydroxypyrrole-2-carboxylates<sup>8</sup>. These pyrroles, which always form as trace or minor byproducts in the amine additions, become the dominant reaction products in the presence of acid and/or 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  $\beta$ -keto esters, these hydroxypyrroles undergo ready alkylation at the C-2 position<sup>16</sup>.



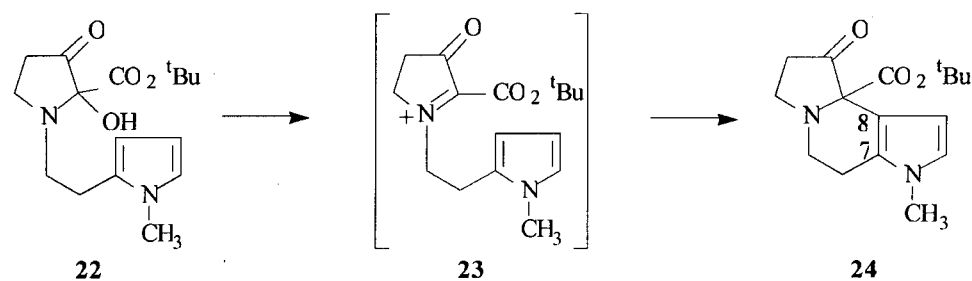
When an electrophile is appropriately attached to the primary amino starting material, the intramolecular alkylation results in a fused-ring system (Scheme 6). In order to construct the indolizidine ring structure using this method,



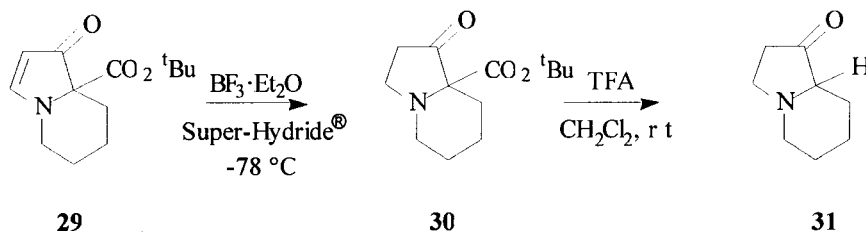
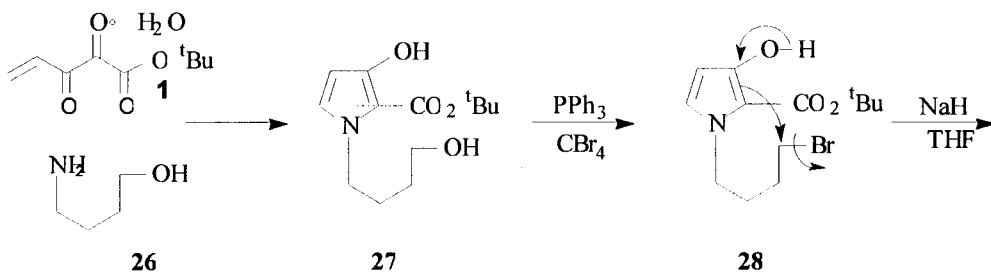
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

we needed to use a primary amine bearing a leaving group separated from the terminal  $\text{NH}_2$  by a four-carbon chain. In practice, we found that it was more convenient to use an amino alcohol such as **26** rather 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%)<sup>17</sup>. As expected, when **28** was treated with NaH, cyclization took place to afford the indolizidine derivative **29** (88%).

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  $-78\text{ }^{\circ}\text{C}$  using Super-Hydride<sup>®</sup> in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (76%)<sup>18</sup>. Upon exposure to excess TFA, compound **30** underwent decarboxylation to give **31** (76%)<sup>19</sup>. This particular derivative has previously been shown to be a key intermediate in the biosynthesis of the indolizidine alkaloids, slaframine and swainsonine<sup>20</sup>.

## Conclusions

We have shown that the vinyl tricarboxyl ester **1** can be used effectively in reactions with substituted primary amines to yield functionalized indolizidines. The two general 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.

## Experimental

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 ( $\delta$  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<sub>254</sub> (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.

### 6-(Trimethylsilyl)-4-hexenylamine (**4**)

A solution containing 410 mg of 6-(trimethylsilyl)-4-hexen-1-ol<sup>12</sup> (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  $0\text{ }^{\circ}\text{C}$  under an atmosphere of nitrogen. With vigorous stirring, 570  $\mu\text{L}$  of diisopropylazodicarboxylate (2.89 mmol, 1.2 equiv) and 650  $\mu\text{L}$  of diphenylphosphoryl azide (2.89 mmol, 1.2 equiv) were added successively at  $0\text{ }^{\circ}\text{C}$ . 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 pressure. 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  $0\text{ }^{\circ}\text{C}$  under an atmosphere of and a 1.0 M solution of  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$  (1.50 mL, 1.5 mmol, 1.0 equiv) was added dropwise. Stirring was continued for an additional 20 min, at which time the reaction was carefully quenched at  $0\text{ }^{\circ}\text{C}$  with 100  $\mu\text{L}$  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: <sup>1</sup>H-NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  2.83 (t, 2H,  $J = 7.0$  Hz), 2.25-2.19 (m, 2H), 1.67-1.56 (m, 2H), 1.50 (br s, 2H), 1.42 (t, 2H,  $J = 2.7$  Hz), 0.09 (s, 9H). IR (neat)  $\nu$  3360, 3300, 2970, 1250, 850  $\text{cm}^{-1}$ . High-resolution MS (CI) calcd. for  $\text{C}_9\text{H}_{19}\text{NSi}$  170.1365 ( $M^+ + 1\text{H}$ ); found 170.1357.

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

A solution containing 550 mg of the alcohol (Z)-6-(trimethylsilyl)-4-hexen-1-ol<sup>12</sup> (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  $\text{LiAlH}_4$  reduction, 280 mg of the product (77%) was obtained as a light yellow oil: <sup>1</sup>H-NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  5.50-5.20 (m, 2H), 2.60-2.71 (t, 2H,  $J = 7.2$  Hz), 2.05 (br s, 2H), 2.02 (g, 2H,  $J = 7.0$  Hz), 0.01 (s, 9H). IR (neat)  $\nu$  3360, 3300, 3020, 2970, 2940, 2870, 1260, 1160  $\text{cm}^{-1}$ . High-resolution MS (CI) calcd. for  $\text{C}_{19}\text{H}_{21}\text{NSi}$  172.1523 ( $M^+ + 1\text{H}$ ); found 172.1521.

### Indolizidine (**9a**)

A solution containing 101 mg of the vinyl tricarboxyl reagent **1** (0.50 mmol, 1.1 equiv) in 5 mL of  $\text{CH}_2\text{Cl}_2$  was stirred at  $0\text{ }^{\circ}\text{C}$  under an 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  $\text{CH}_2\text{Cl}_2$  was then added and the resulting reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 25 min. The reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and  $\text{POCl}_3$  (0.19 mL, 2.0 mmol, 4.0 equiv) was added. The resulting reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 3 h and then poured into 10 mL of saturated aqueous  $\text{NaHCO}_3$ . The two layers were separated and the organic layer was washed with saturated aqueous  $\text{NaHCO}_3$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. Chromatography (1:1  $\text{Et}_2\text{O}$ /hexanes) afforded 41 mg of the product (32%). <sup>1</sup>H-NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $J = 4, 11$  Hz), 2.21-2.13 (m, 1H), 1.69-1.40 (m, 3H), 1.44 (s, 9H). IR (CHCl<sub>3</sub>) 3000, 2960, 2880, 1770, 1730, 1380, 1260, 1160, 1140 cm<sup>-1</sup>. MS (EI, 20 EV) (m/e) 267, 166, 138. High-resolution MS (CI) calcd. for C<sub>14</sub>H<sub>21</sub>NO<sub>4</sub> 268.1549 (M<sup>+</sup> + 1H); 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<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C under an atmosphere of nitrogen. A solution of 11 mg of the amine **3a**<sup>10</sup> (0.079 mmol, 1.0 equiv) in 220 μL of CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>. The two layers were separated and the aqueous layer was extracted with 4 x 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography (1:1 hexanes/EtOAc) afforded 8 mg of the product (42%) as a light yellow oil (TLC, R<sub>f</sub> 0.23, 3:1 EtOAc/hexanes): <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) 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<sub>3</sub>) ν 3020, 2915, 1770, 1730 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) 237 (M<sup>+</sup>, 0.6), 210 (0.7), 209 (2.8), 208 (1.5), 137 (10.6), 136 (M<sup>+</sup> - CO<sub>2</sub><sup>t</sup>Bu, 100.0). High-resolution MS (CI) calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub> 238.1444 (M<sup>+</sup> + 1H); found 238.1446.

*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 atmosphere of nitrogen. A solution of 210 mg of the amine **4** (1.24 mmol, 1.0 equiv) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>•OEt<sub>2</sub> (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<sub>3</sub>. The two layers were separated and the aqueous layer was extracted with 4 x 30 mL of Et<sub>2</sub>O. The organic layer was washed with 50 mL of brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Chromatography (1.5:1 hexanes/EtOAc) yielded 210 mg of the product (64%) as a clear oil (TLC, R<sub>f</sub> 0.47, 2:1 EtOAc/hexanes): <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 4.84-4.68 (m, 2H), 3.30-2.20 (m,

10H), 1.50 (s, 9H). IR (CHCl<sub>3</sub>) ν 2990, 2950, 2870, 1920, 1770, 1740 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) no M<sup>+</sup>, 252 (0.8), 163 (10.1), 162 (M<sup>+</sup> - CO<sub>2</sub><sup>t</sup>Bu, 100). High-resolution MS (CI) calcd. for C<sub>15</sub>H<sub>21</sub>NO<sub>3</sub> 264.1601 (M<sup>+</sup> + 1H); found 264.1609.

*Indolizidine (21)*

A solution of 40 mg of the vinyl tricarbonyl ester **1** (0.198 mmol, 1.0 equiv.) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C under an atmosphere of nitrogen. A solution of 40 mg of the amine **5** (0.198 mmol, 1.0 equiv.) in 600 μL of CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>. The two layers were separated and the aqueous layer was extracted with 3 x 5 mL of Et<sub>2</sub>O. The combined organic layers were washed with 15 mL of brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Chromatography (1.5 hexanes/EtOAc) yielded 25 mg of the product (45%) as a clear oil (TLC, R<sub>f</sub> 0.50, 2:1 EtOAc/hexanes): <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 5.14-5.05 (m, 1H), 3.42-3.35 (m, 1H), 3.23-3.14 (m, 1H), 3.17-2.48 (m, 3H), 2.14-2.07 (m, 1H), 1.94-1.80 (m, 1H), 1.72-1.20 (m, 4H), 1.09 (dd, 1H,  $J = 8.5, 14.4$  Hz), 0.80 (dd, 1H,  $J = 7.3, 14.4$  Hz), 0.088 (s, 9H). IR (CDCl<sub>3</sub>) ν 2960, 2880, 1780, 1755, 1260 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) no M<sup>+</sup>, 237 (M<sup>+</sup> - CO<sub>2</sub>, 100), 164 (21.1), 150 (40.2). High-resolution MS (CI) calcd. for C<sub>14</sub>H<sub>23</sub>NO<sub>3</sub>Si 282.1526 (M<sup>+</sup> + 1H); found 282.1517.

*Indolizidine (24)*

A solution of 1.600 g of the vinyl tricarbonyl reagent **1** (7.91 mmol, 1.0 equiv.) in 250 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C under an 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<sub>2</sub>Cl<sub>2</sub> 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 2.080 g of the product (90%) as a light yellow solid (TLC, R<sub>f</sub> 0.14, 2:1 hexanes/EtOAc), mp 124-126 °C: <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 6.51 (d, 1H,  $J = 3.0$  Hz), 6.25 (d, 1H,  $J = 3.0$  Hz), 3.49 (s, 3H), 3.40-2.30 (m, 8H), 1.47 (s, 9H). IR (CHCl<sub>3</sub>) ν 3050, 2975, 2900, 1770, 1740 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) 290 (M<sup>+</sup>, 0.4), 205 (2.2), 190 (13.2), 189 (M<sup>+</sup> - CO<sub>2</sub><sup>t</sup>Bu, 100.0), 134 (2.4), 133 (6.7). High-resolution MS (CI) calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> 291.1710 (M<sup>+</sup> + 1H); found 291.1720. Anal. Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: 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<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C under an atmosphere of nitrogen. A 0 °C solution containing 200 μL of 4-amino-1-butanol (2.17 mmol, 1.0 equiv) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was then added over a period of 30 min, 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 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<sub>f</sub> 0.45, 2:1 EtOAc/hexanes): <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 6.55 (d, 1H, J = 2.83 Hz), 5.70 (d, 1H, J = 2.90 Hz), 4.07 (t, 2H, J = 7.1 Hz), 3.65 (t, 2H, J = 6.2 Hz), 1.90-1.70 (m, 2H), 1.60 (s, 9H), 1.60-1.50 (m, 2H). IR (neat) ν 3480, 2950, 2880, 1710, 1645, 1560, 850, 780 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) 256 (M<sup>+</sup> + 1, 3.1), 255 (M<sup>+</sup>, 19.9), 199 (100), 181 (47.1). High-resolution MS (EI) calcd. for C<sub>13</sub>H<sub>21</sub>NO<sub>4</sub> 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 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<sub>f</sub> 0.55, 2:1 hexanes/EtOAc), mp 35-35 °C: <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 6.55 (d, 1H, J = 2.9 Hz), 5.74 (d, 1H, J = 2.9 Hz), 4.09 (t, 2H, J = 6.5 Hz), 3.39 (t, 2H, J = 6.2 Hz), 2.00-1.78 (m, 4H), 1.61 (s, 9H). IR (CH<sub>2</sub>Cl<sub>2</sub>) ν 3470, 3250, 3010, 2995, 2950, 2880, 1705, 1650, 1565 cm<sup>-1</sup>. 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<sub>13</sub>H<sub>20</sub>NO<sub>3</sub>Br: 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 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<sub>4</sub>Cl. The two layers were separated and the aqueous layer was extracted with 3 x 20 mL of Et<sub>2</sub>O. The organic layer was washed with 20 mL of brine, dried (Na<sub>2</sub>SO<sub>4</sub>), 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<sub>f</sub> 0.20, 3:1 EtOAc/hexanes), mp 91-91 °C: <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ 7.81 (d, 1H, J = 3.1 Hz), 4.98 (d, 1H, J = 3.1 Hz), 3.66-3.59 (m, 1H), 3.39-3.32 (m, 1H), 2.69-2.63 (m, 1H), 1.92-1.78 (m, 2H), 1.47 (s, 9H), 1.66-1.35 (m, 3H). IR (CH<sub>2</sub>Cl<sub>2</sub>) ν 3120, 3020, 2995, 2960, 2880, 1740, 1665 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) 238 (M<sup>+</sup> + 1, 3.1), 237 (M<sup>+</sup>, 21.5), 178 (4.4), 137 (86.2), 136 (M<sup>+</sup> - CO<sub>2</sub><sup>t</sup>Bu, 100.0). High-resolution MS (EI) calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub> 237.1366; found 237.1361. Anal. Calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub>: 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 atmosphere of nitrogen. At this same temperature, BF<sub>3</sub>·Et<sub>2</sub>O (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<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Chromatography (2:1 EtOAc/hexanes) afforded 72 mg of the product (79%) as a clear oil (TLC, R<sub>f</sub> 0.70, 3:1 EtOAc/hexanes): <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 3.39-3.28 (m, 1H), 3.27-3.03 (m, 2H), 2.92-2.82 (m, 1H), 2.55-2.45 (m, 2H), 2.25-2.15 (m, 1H), 1.80-1.72 (m, 1H), 1.47 (s, 9H), 1.70-1.28 (m, 4H). IR (CH<sub>2</sub>Cl<sub>2</sub>) ν 2990, 2940, 2860, 1770, 1735 cm<sup>-1</sup>. MS (EI, 20 EV) m/e (relative intensity) 239 (M<sup>+</sup>, 0.7), 139 (8.6), 138 (M<sup>+</sup> - CO<sub>2</sub><sup>t</sup>Bu, 100.0). High-resolution MS (EI) calcd. for C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub> 239.1522; found 239.1518.

*1-Oxo*octahydroindolizine (**31**)

Under an atmosphere of nitrogen, excess trifluoroacetic acid (1 mL) was added to a solution containing 50 mg of the ester **30** (0.209 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. 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<sub>3</sub>. The aqueous layer was extracted with 3 x 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 5 mL of brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Chromatography (2:1 methylene chloride/acetone) afforded 22 mg of the known 1-oxooctahydroindolizine (76%)<sup>20</sup> as a clear, volatile oil which rapidly discolored upon exposure to air (R<sub>f</sub> 0.25, 3:1 EtOAc/hexanes). Spectroscopic data for this product were identical to those reported previously<sup>20</sup>.

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