Published in final edited form as:

Tetrahedron. 2008 January 28; 64(5): 883–893.

Aza- and Carbo-[3 + 3] Annulations of Exo-Cyclic Vinylogous Amides and Urethanes. Synthesis of Tetrahydroindolizidines and An Unexpected Formation of Hexahydroquinolines

Sunil K. Ghosh, Grant S. Buchanan, Quincy A. Long, Yonggang Wei, Ziyad F. Al-Rashid, Heather M. Sklenicka, and Richard P. Hsung

Division of Pharmaceutical Sciences and Department of Chemistry, 777 Highland Avenue, Rennebohm Hall, University of Wisconsin Madison, WI 53705 USA

Abstract

[3 + 3] Annulations of *exo*-cyclic vinylogous amides and urethanes with vinyl iminium salts are described here. We observed an intriguing dichotomy in their reaction pathways. For pyrrolidine- and azepane-based vinylogous amides or urethanes, *aza*-[3 + 3] annulation would dominate to give tetrahydroindolizidines, whereas, unexpectedly, for piperidine-based vinylogous amides or urethanes, *carbo*-[3 + 3] annulation was the pathway, leading to hexahydroquinolines. The origin for such a contrast is likely associated with a switch in the initial reaction pathway between C-1,2-addition and C-1,4-addition.

Keywords

Aza-[3 + 3] annulation; *carbo*-[3 + 3] annulation; vinylogous amides; quinolines; tetrahydroindolizidines

1. Introduction

Aza-[3 + 3] annulation or formal cycloaddition reaction has emerged as a formidable strategy in the synthesis of alkaloids.^{1–5} Specifically, our intermolecular *aza*-[3 + 3] annulation⁵ involves a Knoevenagel-type condensation of vinyl iminium ions **1** with vinylogous amides or urethanes **2** followed by a 6 π -electron electrocyclic ring-closure of 1-azatrienes **3**^{6,7} en route to 1,2-dihydropyridines **4** [Scheme 1]. This annulation process provides a unique opportunity to develop approaches toward a stereoselective ring-closure of 1-azatrienes, which had represented a real challenge in such pericyclic processes.^{6,8}

Efforts in developing such a torquoselective⁹ reaction have been largely overlooked. An elegant exception would be Tanaka and Katsumura's electrocyclic ring-closure using chiral amines.¹⁰ In our own work, we employed either chiral iminium ions **1** with a preexisting stereogenic center in the β -substituent,¹¹ or 1-azatrienes **5** containing a chiral *N*-auxiliary^{12,13} [see the box in Scheme 1] en route to 1,2-dihydropyridines **4** or 1-azadecalins **6**.

Correspondence to: Richard P. Hsung.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Although by a very different mechanism,¹³ we have exerted much efforts in the last few years in developing both a diastereoselective¹⁴ and an amine salt-catalyzed asymmetric¹⁵ intramolecular *aza*-[3 + 3] annulation reaction employing vinylogous amides tethered with α,β -unsaturated iminium salts **7** [Scheme 2]. This annulation provides a powerful synthetic strategy to construct nitrogen heterocycles **8** that can lead to a range of prevalent structural motifs among alkaloids.

We have already successfully applied this strategy toward total syntheses of several alkaloids such as (+)-gephyrotoxin,¹⁴ ($\pm$)-tangutorine,¹⁶ (+)/(-)-deplancheine,¹⁷ and (-)-cylindricine C,¹⁸ and most recently, five members of the azaphenalene alkaloid family [see Figure 1].¹⁹

Despite our understanding of this annulation reaction, we encountered a rather intriguing and unexpected outcome during our efforts in achieving total syntheses of azaphenalene alkaloids. As shown in Scheme 3, we found that **intramolecular** *aza*-[3 + 3] annulations of *exo*-cyclic vinylogous amides such as **10** would proceed effectively [Scheme 3] to give the key *aza*-tricycle **11** that would subsequently serve as a common intermediate en route to the five azaphenalene alkaloids [Figure 1].¹⁹ On the other hand, **intermolecular** annulations of *exo*-cyclic vinylogous amides **12** [or vinylogous urethanes **13**] with vinyl iminium ion **14** did not give any desired quinolizidine nucleus **15**, thereby thwarting our efforts in the synthesis of members of the quinolizidine and indolizidine families of alkaloids.²⁰ Instead, we identified another product, and we report here our findings in the synthesis of tetrahydroindolizidines accompanied with an unexpected formation of hexahydroquinolines via a *carbo*-[3 + 3] annulation.

2. Results and Discussions

2.1. An Unexpected Formation of Hexahydroquinolines

Preparations of *exo*-cyclic vinylogous amides **12** and **13** are shown in Scheme 4. The synthesis commenced with either 1,3-pentanedione **16a** or ethyl acetoacetate **16b** and followed Carrié's protocol²¹ that features Weiler's dianion²² addition to 1-bromo-2-chloro-propane, azide substitution, and an intramolecular *aza*-Wittig of azides **18a** or **18b**. The *Z*-geometry in **12** and **13** was confirmed via nOe experiments.²¹

Unsuspectingly, with *exo*-cyclic vinylogous amides **12** and **13** in hand, we attempted their *aza*-[3 + 3] annulation reactions using vinyl iminium salts **20a–c** generated from their corresponding enals **19a–c** under standard conditions^{5,11–15} [Scheme 5]. To our surprise, no desired *aza*-[3 + 3] annulation products **15** were formed, and instead, we isolated hexahydroquinolines **21a–c** and **22b–c** in good yields.

We also employed chiral enal **23** in an attempt to detect possible diastereoselectivity. However, while the reaction of chiral enal **23** with **12** led to the isomeric hexahydroquinolines **24** and **25** in good yield, the selectivity was found to be low, and consequently, the relative stereochemistry was not assigned. It is also noteworthy that using more polar solvents such as DMF or EtOH, we still obtained hexahydroquinoline **22** in good yields.

2.2. A Carbo-[3 + 3] Annulation Pathway

A plausible mechanism for the formation of these unexpected hexahydroquinolines is initiated through a C-1,4-addition of the vinylogous amide in a Michael fashion to the iminium salt to give intermediate **B** [Scheme 6]. Tautomerization of **B** could lead to intermediates **C** and **D** with the latter one being de-conjugated, and an ensuing C-1,2-addition to the iminium salt in a Mannich manner would give **E**. A sequence of elimination of the secondary amine in **E** and tautomerization would then afford the observed hexahydroquinolines.

What we have encountered here for the very first time in our own work with *aza*-[3 + 3] annulations, is the competing *carbo*-[3 + 3] annulation pathway.^{23,24} This finding invokes some unique historical perspectives as shown in Figure 2. Prelog²⁵ in 1949 found that instead of the expected Robinson annulation pathway, a *carbo*-[3 + 3] cyclization had occurred to give the bicyclo[5.3.1]undecanone. In 1950, and more relevant to the current study, Stork²⁶ reported the addition of the Stork enamine to acrolein, leading to bicyclo[3.3.1]octanone via a *carbo*-[3 + 3] cyclization. These reactions all share a similar pathway: 1,4-addition followed by 1,2-addition.

Despite the fact that this can be a very useful reaction for constructing highly substituted cyclohexane derivatives to compliment the Diels-Alder Strategy, much of the earlier work focused on the synthesis of bridged bicyclic systems with an interest in accessing Anti-Bredt's olefins.^{23,27} While there has been a surging interest [especially in the synthesis of garsubellin A] given the array of elegant accounts that appeared recently,²⁸ most efforts are still exerted on the synthesis of bridged bicyclic systems.

2.3. Syntheses of Quinolines

One immediate application of this *carbo*-[3 + 3] annulation is in the synthesis of quinolines, which would also be in accord with the theme of this *Symposium-in-Print*. As shown in Scheme 7, treatment of hexahydroquinolines **21b** and **22b** with 3.0 equiv of DDQ at rt led to quinoline **26** and **27** in 50% and 83% yields, respectively. With less DDQ used, we were able to isolate the respective tetrahydroquinolines **28** and **29**, although there was no apparent selectivity over the extent of aromatization.

2.4. A Contrasting Reaction Pathway

When we directed our attention to pyrrolidine-based *exo*-cyclic vinylogous urethane **30**^{21,29} and vinylogous amide **31**,^{21,30} we were fully intending on preparing a series of tetrahydroindoles via the same *carbo*-[3 + 3] annulation [Figure 3]. We were not prepared for additional surprises.

However, as shown in Table 1, reactions of **30** and **31** with achiral enals **19a–c** [entries 1–4], or chiral enals **23** and **33–35** [entries 5–9], led to the respective *aza*-[3 + 3] annulation products: Tetrahydroindolizidines **36–40**. Even when we employed azepane-based *exo*-cyclic vinylogous urethane **32**,^{21,31} we obtained the *aza*-annulation product **41** and **42** in good yields [entries 10–11].

2.5. C-1,2 versus C-1,4-Addition

These two contrasting reaction pathways intrigued us. Although we do not have any definitive understanding at this point, one possible cause for is that they mechanistically differ in the very initial step. As shown in Scheme 8, for the pyrrolidine-based *exo*-cyclic vinylogous amide [left], there appears to be a preference for C-1,2-addition, whereas for piperidine-based *exo*-cyclic vinylogous amide [right], the preference is C-1,4-addition.

Specifically, for the pyrrolidine-based vinylogous amide **G**, it may react through conformer **G-2** because the internal hydrogen-bonding in **G-1** is not as perfectly aligned or tight as in piperidine-based *exo*-cyclic vinylogous amide **J-1**. Thus, the conformational equilibrium does not shift away from **G-2** or at least not completely, thereby freeing the carbonyl group to participate in hydrogen-bonding with protons of the vinyl iminium salt [in green]. This external hydrogen bonding interaction can in fact provide a stabilization of $\sim 14.7 \text{ Kcal mol}^{-1.3}$

With this hydrogen-bonding network in place, C-1,2-addition [red arrow] would be better aligned stereoelectronically than C-1,4-addition [dotted blue arrow], thereby leading to 1-

azatriene **H** after β -elimination and subsequently completing the *aza*-annulation pathway via a pericyclic ring-closure. It is noteworthy that the theoretical observation of this external hydrogen-bonding network likely provides a major rationale for the high level of regioselectivity found in most of our annulation work^{5a,32} involving vinyl iminium salts, especially when comparing with protocols in which vinyl iminium salts are generated *in situ* or not employed.^{33,34}

On the other hand, for piperidine-based *exo*-cyclic vinylogous amide, conformer **J-1** dominates due to the strong internal hydrogen-bonding [in green], which precludes the carbonyl group in **J-1** from participating in the related external hydrogen bonding network. With both options of C-1,2- and C-1,4-additions being available, C-1,4-addition [solid blue arrow] could take precedent based on the “hard-and-soft” concept. This would allow the piperidine-based *exo*-cyclic vinylogous amide [or urethane] to follow the *carbo*-annulation pathway.

In addition, although all of these mechanistic steps are reversible, our calculations using B3LYP/6-31G* [SpartanTM] suggest [Figure 4] that the observed dichotomy of these two reaction pathways cannot be attributed as a result of thermodynamic equilibration. For all three cases, pyrrolidine-, piperidine-, and azepane-based vinylogous amides or urethanes, the respective *carbo*-annulation products are thermodynamically more favored than their corresponding *aza*-annulation products, although in a relatively lesser extent for both the pyrrolidine-based vinylogous amide and azepane-based vinylogous urethane.

3. Conclusion

We have described here [3 + 3] annulations of *exo*-cyclic vinylogous amides and urethanes with vinyl iminium salts and observed an intriguing dichotomy in their reaction pathways. For pyrrolidine- and azepane-based vinylogous amide or urethanes, *aza*-[3 + 3] annulation dominates to give tetrahydroindolizidines, whereas the piperidine-based vinylogous amide or urethane underwent an unexpected *carbo*-[3 + 3] annulation to afford hexahydroquinolines. The origin for such a contrast is not clear at this moment, although we suspect it is associated with an initial preference for either C-1,2-addition or C-1,4-addition. This work provides a useful approach toward either total syntheses of the indolizidine family of natural products, or functionalized quinolines.

4. Experimental Section

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO₂. ¹H and ¹³C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using CDCl₃ (except where noted) with TMS or residual CHCl₃ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT-IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain.

Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported.

4.1. General Procedure for All Annulations

To a solution of an enal [1.40 mmol, 1.40 equiv] in EtOAc/toluene [3.5 to 5 mL with a ratio of 2:3] in a sealed tube were added Na₂SO₄ [400.0 mg], piperidinium acetate [1.40 mmol, 1.40 equiv] and the respective vinylogous amide [1.00 mmol] sequentially. After stirring at rt for 1 min, the mixture was heated at 95 °C –100 °C for 3–4 h. The reaction progress was monitored using TLC analysis and/or crude ¹H NMR. When the starting material completely disappeared, the reaction mixture was cooled and the excess amine salt was filtered off through a small cotton plug [or Celite[™]], and the excess solvent was evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography [gradient eluent: EtOAc in hexanes] to provide the corresponding annulation product.

4.1.1. Carbo-[3 + 3] Annulation Product 21a—*R_f* = 0.10 [30% EtOAc/hexane]; ¹H NMR (400 MHz, CDCl₃) δ 0.96 (d, 3H, *J* = 6.8 Hz), 1.66–1.75 (m, 1H), 1.84 (ddd, 1H, *J* = 4.3, 8.8, 21.8 Hz), 1.94 (s, 1H), 2.05 (dd, 1H, *J* = 6.5, 17.4 Hz), 2.10 (s, 3H), 2.29–2.48 (m, 2H), 2.72 (p, 1H, *J* = 7.0 Hz), 3.32 (ddd, 2H, *J* = 2.7, 3.8, 6.8 Hz), 5.87 (d, 1H, *J* = 6.5 Hz), 11.86 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 22.7, 26.6, 27.7, 28.5, 31.9, 41.5, 102.7, 128.5, 131.9, 154.0, 193.6; IR (neat) cm⁻¹ 2951brm, 2860brm, 1569s, 1550s, 14870m, 1450m, 1364m, 1348m, 1252s; mass spectrum (APCI): *m/e* (% relative intensity) 192 (100) (M+H)⁺, 150 (5), 140 (10); *m/e* (ESI) calcd for C₁₂H₁₇NO 191.1310, found 191.1309.

4.1.2. Carbo-[3 + 3] Annulation Product 21b—*R_f* = 0.26 [30% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 0.89 (t, 3H, *J* = 7.2 Hz), 1.13–1.20 (m, 2H), 1.28–1.32 (m, 1H), 1.38–1.45 (m, 1H), 1.67–1.74 (m, 1H), 1.80–1.85 (m, 1H), 2.09 (s, 3H), 2.19–2.41 (m, 4H), 2.50–2.54 (m, 1H), 3.32 (dd, 2H, *J* = 4.0, 7.0 Hz), 5.85 (d, 1H, *J* = 6.0 Hz), 11.90 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 21.0, 22.8, 26.7, 28.4, 28.6, 32.7, 36.6, 41.6, 102.7, 129.0, 132.2, 154.4, 193.6; IR (neat) cm⁻¹ 2955brm, 2869brm, 1569s, 1543s, 1257s; mass spectrum (APCI): *m/e* (% relative intensity) 220 (100) (M+H)⁺; *m/e* (ESI) calcd for C₁₄H₂₂NO 220.1701, found 220.1703.

4.1.3. Carbo-[3 + 3] Annulation Product 21c—*R_f* = 0.36 [50% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 1.82–1.84 (m, 1H), 1.88–1.98 (m, 1H), 1.97 (s, 3H), 2.41–2.53 (m, 3H), 2.84–2.91 (m, 1H), 3.48–3.50 (m, 2H), 3.99 (d, 1H, *J* = 8.0 Hz), 5.80 (d, 1H, *J* = 5.5 Hz), 7.19–7.31 (m, 5H), 12.06 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 22.9, 27.2, 28.5, 33.4, 38.5, 41.8, 99.1, 126.3, 127.8, 128.3, 128.4, 129.8, 131.1, 145.7, 155.4; IR (neat) cm⁻¹ 2940brm, 2859brm, 1670s, 1577s, 1552, 1273s; mass spectrum (APCI): *m/e* (% relative intensity) 254 (100) (M+H)⁺; *m/e* (ESI) calcd for C₁₇H₂₀NO 254.1545, found 254.1534.

4.1.4. Carbo-[3 + 3] Annulation Product 22b—*R_f* = 0.29 [10% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 0.87 (t, 3H, *J* = 7.0 Hz), 1.16–1.35 (m, 7H), 1.68–1.76 (m, 1H), 1.81–1.87 (m, 1H), 2.16 (dd, 1H, *J* = 6.0, 16.5 Hz), 2.29–2.42 (m, 3H), 2.72 (q, 1H, *J* = 5.0 Hz), 3.29–3.34 (m, 2H), 4.06–4.15 (m, 2H), 5.81 (d, 1H, *J* = 6.0 Hz), 9.17 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 14.8, 20.7, 23.3, 28.3, 29.0, 29.9, 36.3, 41.8, 58.6, 90.7, 128.9, 130.5, 152.6, 170.9; IR (neat) cm⁻¹ 2956brm, 2864brm, 1630s, 1578s, 1243s; mass spectrum (APCI): *m/e* (% relative intensity) 250 (100) (M+H)⁺; *m/e* (ESI) calcd for C₁₅H₂₄NO₂ 250.1807, found 250.1807.

4.1.5. Carbo-[3 + 3] Annulation Product 22c—*R_f* = 0.28 [10% EtOAc/Hexanes]; ¹H NMR (400 MHz, CDCl₃) δ 1.12 (t, 3H, *J* = 7.0 Hz), 1.77–1.93 (m, 2H), 2.39–2.45 (m, 3H), 2.76–2.83 (m, 1H), 3.40–3.44 (m, 2H), 3.95–4.12 (m, 3H), 5.77 (d, 1H, *J* = 5.6 Hz), 7.14–7.24 (m, 5H), 9.42 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.8, 23.3, 29.0, 32.4, 36.2, 41.9, 58.8, 88.1, 125.9, 127.6, 128.0, 129.8, 130.0, 146.9, 153.8, 170.9; IR (neat) cm⁻¹ 2945brm, 2860brm,

1630s, 1584s, 1273s; mass spectrum (APCI): m/e (% relative intensity) 284 (100) (M+H)⁺; m/e (ESI) calcd for C₁₈H₂₂NO₂ 284.1654, found 284.1642.

4.1.6. Chiral Carbo-[3 + 3] Annulation Products 24 and 25 [Characterized as an inseparable mixture]—*R_f* = 0.16 [50% EtOAc/hexane]; ¹H NMR (500 MHz, CDCl₃) δ *Major diastereomer*: 1.30 (s, 3H), 1.39 (s, 3H), 1.69–1.90 (m, 2H), 2.13–2.18 (m, 1H), 2.23 (s, 3H), 2.33–2.45 (m, 3H), 2.86 (t, 1H, *J* = 7.5 Hz), 3.30–3.37 (m, 2H), 3.59 (t, 1H, *J* = 7.5 Hz), 3.91–3.97 (m, 1H), 4.06–4.11 (m, 1H), 5.91 (d, 1H, *J* = 6.0 Hz), 12.1 (s, 1H, NH); *minor diastereomer (partial listing due to unresolved overlapping resonances)*: 1.31 (s, 3H), 1.69–1.90 (m, 3H), 2.20 (s, 3H), 2.33–2.45 (m, 3H), 2.53–2.58 (m, 1H), 2.77 (t, 1H, *J* = 7.5 Hz), 3.30–3.37 (m, 2H), 3.65 (dd, 1H, *J* = 5.5, 8.5 Hz), 3.82 (dd, 1H, *J* = 5.5, 8.5 Hz), 3.95–3.97 (m, 1H), 5.97 (d, 1H, *J* = 5.5 Hz); IR (film): cm^{−1} 2934brw, 1662w, 1609(m), 1571(s), 1554 (s); mass spectrum (APCI): m/e (% relative intensity) 278 (100) (M+H)⁺, 236 (10), 140 (20), 101 (10); m/e (ESI) calcd for C₁₆H₂₄NO₃ 278.1756, found 278.1762.

4.2. General Procedure for the DDQ-Aromatization

To a solution of **21b** [30.0 mg, 0.136 mmol] in CH₂Cl₂ [3 mL] was added DDQ [93.0 mg, 0.40 mmol, 3.00 equiv]. The reaction mixture was stirred at rt for 1 h and the reaction progress was monitored using TLC analysis. When the starting material completely disappeared, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography [gradient eluent: 0% to 25% EtOAc in hexanes] to provide the desired quinoline **26** [14.5 mg, 50%].

4.2.1. Quinoline 26—*R_f* = 0.39 [20% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 0.98 (t, 3H, *J* = 7.5 Hz), 1.69–1.74 (m, 2H), 2.68–2.71 (m, 2H), 2.72 (s, 3H), 7.37 (dd, 1H, *J* = 4.5, 8.5 Hz), 7.41 (d, 1H, *J* = 8.5 Hz), 7.75 (d, 1H, *J* = 8.5 Hz), 8.11 (dd, 1H, *J* = 2.0, 8.5 Hz), 8.86 (dd, 1H, *J* = 1.5, 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 25.0, 33.9, 35.7, 121.0, 126.5, 128.2, 128.8, 135.8, 139.5, 140.3, 145.8, 150.4, 207.8; IR (neat) cm^{−1} 2961m, 2871m, 1705s, 1572m; mass spectrum (APCI): m/e (% relative intensity) 214 (100) (M+H)⁺; m/e (ESI) calcd for C₁₄H₁₅NONa 236.1051, found 236.1053.

4.2.2. Quinoline 27—*R_f* = 0.11 [10% EtOAc/hexane]; ¹H NMR (400 MHz, CDCl₃) δ 1.01 (t, 3H, *J* = 7.2 Hz), 1.46 (t, 3H, *J* = 7.2 Hz), 1.72–1.81 (m, 2H), 2.78 (dt, 2H, *J* = 6.0, 7.6 Hz), 4.59 (q, 2H, *J* = 7.2 Hz), 7.38 (dd, 1H, *J* = 4.0, 8.0 Hz), 7.40 (d, 1H, *J* = 8.8 Hz), 7.79 (d, 1H, *J* = 8.4 Hz), 8.11 (dd, 1H, *J* = 2.0, 8.4 Hz), 8.93 (dd, 1H, *J* = 2.0, 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 14.6, 24.6, 36.3, 61.6, 121.1, 126.5, 128.3, 128.7, 133.1, 135.8, 140.9, 145.7, 151.1, 169.7; IR (film) cm^{−1}: 2962brw, 2872w, 1725s, 1613w, 1569w, 1499w, 1459brw, 1370w, 1265s; mass spectrum (APCI): m/e (% relative intensity) 244 (100) (M+H)⁺, 198 (20), 101 (5); m/e (ESI) calcd for C₁₅H₁₈NO₂ 244.1338, found 244.1349.

4.2.3. Tetrahydroquinoline 28—*R_f* = 0.50 [20% EtOAc/Hexanes]; ¹H NMR (400 MHz, CDCl₃) δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.55–1.61 (m, 2H), 1.84–1.90 (m, 2H), 2.48 (s, 3H), 2.52–2.56 (m, 2H), 2.72 (t, 2H, *J* = 5.6 Hz), 3.27 (t, 2H, *J* = 3.6 Hz), 5.30 (brs, 1H), 6.43 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 3.6 Hz); mass spectrum (APCI): m/e (% relative intensity) 218 (100) (M+H)⁺; m/e (ESI) calcd for C₁₄H₂₀NO 218.1545, found 218.1554.

4.2.4. Tetrahydroquinoline 29—*R_f* = 0.29 [10% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, 3H, *J* = 7.5 Hz), 1.39 (t, 3H, *J* = 7.0 Hz), 1.55–1.61 (m, 2H), 1.88 (dt, 2H, *J* = 5.0, 6.5 Hz), 2.68 (m, 2H), 2.74 (t, 2H, *J* = 6.0 Hz), 3.35 (t, 2H, *J* = 6.0 Hz), 4.35 (q, 2H, *J* = 7.0 Hz), 6.38 (d, 1H, *J* = 7.5 Hz), 6.89 (d, 1H, *J* = 7.5 Hz); IR (film) cm^{−1} 2957m, 2929m, 1725w, 1679m, 1599w, 1582w, 1507m; mass spectrum (APCI): m/e (% relative intensity)

248.2 (100) (M+H)⁺, 202 (65), 101 (5); m/e (ESI) calcd for C₁₅H₂₂NO₂ 248.1651, found 248.1658.

4.3. General Procedure: See Section 4.1

4.3.1. Aza-[3 + 3] Annulation Product 36a—R_f = 0.27 [20% EtOAc/hexane]; ¹H NMR (400 MHz, CDCl₃) δ 0.99 (d, 3H, J = 6.4 Hz), 1.88–2.00 (m, 2H), 2.92 (dt, 1H, J = 9.1, 18.1 Hz), 3.10 (ddd, 1H, J = 4.5, 8.6, 18.1 Hz), 3.29 (q, 1H, J = 9.1 Hz), 3.36 (p, 1H, J = 6.4 Hz), 3.52 (ddd, 1H, J = 4.1, 8.0, 9.1 Hz), 3.65 (s, 3H), 4.88 (dd, 1H, J = 5.5, 7.6 Hz), 5.92 (d, 1H, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.8, 25.0, 28.5, 32.0, 50.5, 51.1, 95.4, 110.6, 125.2, 155.1, 169.2; IR (neat) cm⁻¹ 2947brm, 2862brm, 1672s, 1578s, 1256s, 1219s, 1094s; mass spectrum (APCI): m/e (% relative intensity) 194 (100) (M+H)⁺, 162 (15); m/e (ESI) calcd for C₁₁H₁₆NO₂ 194.1181, found 194.1188.

4.3.2. Aza-[3 + 3] Annulation Product 36b—R_f = 0.22 [10% EtOAc/Hexanes]; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (t, 3H, J = 7.2 Hz), 1.17–1.32 (m, 4H), 1.83–1.94 (m, 2H), 2.87 (ddd, 1H, J = 9.2, 18.0, 36.0 Hz), 3.25 (ddd, 1H, J = 4.4, 8.8, 18.0 Hz), 3.25 (q, 1H, J = 7.2 Hz), 3.30–3.34 (m, 1H), 3.49 (ddd, 1H, J = 4.0, 8.4, 12.0 Hz), 3.61 (s, 3H), 4.87 (dd, 1H, J = 5.6, 7.6 Hz), 5.95 (d, 1H, J = 7.6 Hz); ¹³C NMR (125 MHz, CDCl₃) 14.5, 18.1, 22.0, 32.0, 33.2, 41.2, 50.5, 51.2, 94.2, 108.9, 126.0, 155.6, 169.4; IR (neat) cm⁻¹ 2951brm, 2869brm, 1673s, 1578s, 1194s; mass spectrum (APCI): m/e (% relative intensity) 222 (100) (M+H)⁺; m/e (ESI) calcd for C₁₃H₂₀NO₂ 222.1494, found 222.1504.

4.3.3. Aza-[3 + 3] Annulation Product 36c—R_f = 0.35 [20% EtOAc/Hexanes]; ¹H NMR (500 MHz, CDCl₃) δ 2.02–2.11 (m, 2H), 3.10 (dt, 1H, J = 9.0, 18.0 Hz), 3.28 (ddd, 1H, J = 5.0, 9.0, 18 Hz), 3.45 (q, 1H, J = 8.0 Hz), 3.62 (s, 3H), 3.65 (ddd, 1H, J = 4.5, 9.0, 9.0 Hz), 4.64 (d, 1H, J = 5.5 Hz), 5.08 (dd, 1H, J = 5.0, 7.5 Hz), 6.12 (d, 1H, J = 5.5 Hz), 7.20–7.23 (m, 1H), 7.29–7.35 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 21.9, 32.2, 40.2, 50.7, 51.4, 94.6, 109.6, 125.1, 126.3, 127.7, 128.5, 148.9, 154.9, 169.1; IR (neat) cm⁻¹ 2940brm, 2852brm, 1676s, 1595s, 1273s, 1106s; mass spectrum (APCI): m/e (% relative intensity) 256 (100) (M+H)⁺, 178 (25); m/e (ESI) calcd for C₁₆H₁₇NO₂Na 278.1157, found 278.1165.

4.3.4. Aza-[3 + 3] Annulation Product 36d—R_f = 0.33 [20% EtOAc/hexane]; ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, 3H, J = 7.2 Hz), 1.19–1.41 (m, 4H), 1.92–2.07 (m, 2H), 2.19 (s, 3H), 2.95 (dt, 1H, J = 8.8, 18.0 Hz), 3.19 (ddd, 1H, J = 4.0, 8.0, 18.0 Hz), 3.33 (dt, 1H, J = 8.0, 8.8 Hz), 3.37–3.42 (m, 1H), 3.59 (ddd, 1H, J = 4.0, 8.0, 9.6 Hz), 5.06 (dd, 1H, J = 6.0, 8.0 Hz), 6.03 (d, 1H, J = 8.0 Hz); ¹³C NMR (100MHz, CDCl₃) δ 14.4, 18.1, 21.9, 28.5, 32.9, 33.9, 41.7, 51.1, 105.4, 110.0, 125.9, 155.3, 196.6; IR (film) cm⁻¹ 2953m, 2869m, 2360w, 1659m, 1613m, 1530s, 1395m; mass spectrum (APCI): m/e (% relative intensity) 206 (100) (M+H)⁺; m/e (EI) calcd for C₁₃H₂₀NO 206.1545, found 206.1549.

4.3.5. Aza-[3 + 3] Annulation Product 37 [Characterized as a mixture]—R_f = 0.42 [50% EtOAc/hexane]; ¹H NMR (500 MHz, CDCl₃) δ *Major Diastereomer*: 1.33 (s, 3H), 1.41 (s, 3H), 1.88–2.05 (m, 2H), 2.95 (dt, 1H, J = 9.0 Hz), 3.14 (ddd, 1H, J = 3.5, 8.5, 18.0 Hz), 3.33–3.36 (m, 1H), 3.57 (dt, 1H, J = 3.5, 8.5 Hz), 3.68 (s, 3H), 3.82 (dd, 1H, J = 6.5, 8.0 Hz), 3.86–3.90 (m, 2H), 4.18 (dt, 1H, J = 2.5, 4.5 Hz), 4.96 (dd, 1H, J = 2.0, 5.5 Hz), 6.19 (d, 1H, J = 8.0 Hz); *Minor Diastereomer (partial listing due to unresolved overlapping resonances)*: 1.40 (s, 3H), 1.88–2.05 (m, 2H), 2.91–2.98 (m, 1H), 3.15–3.23 (m, 1H), 3.31–3.38 (m, 1H), 3.60–3.65 (m, 2H), 3.95–4.00 (m, 2H), 4.12–4.14 (m, 1H), 5.01 (dd, 1H, J = 6.0, 7.5), 6.14 (d, 1H, J = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃) δ *From a small sample of resolved major isomer*: 21.8, 25.3, 26.4, 32.2, 36.6, 50.8, 51.2, 66.1, 78.8, 90.1, 94.9, 104.5, 108.8, 128.1, 157.1; IR (film) cm⁻¹ 2984m, 2949w, 1671brs, 1578s, 1414s, 1370s, 1251s; mass spectrum

(APCI): m/e (% relative intensity) 280 (30) (M+H)⁺, 248 (100), 222 (90), 178 (25); m/e (ESI) calcd for C₁₅H₂₁NO₄Na 302.1368, found 302.1375.

4.3.6. Aza-[3 + 3] Annulation Product 38 [Characterized as a mixture]—*R_f* = 0.19 [50% EtOAc/hexane]; ¹H NMR (500 MHz, CDCl₃) δ *Major diastereomer (partial listing due to unresolved overlapping resonances)*: 2.83–2.89 (m, 1H), 2.99–3.03 (m, 1H), 3.09–3.15 (m, 1H), 3.66 (s, 3H), 3.83–3.88 (m, 1H), 4.10–4.20 (m, 2H), 4.35 (dd, 1H, *J* = 2.0, 12.5 Hz), 4.84 (dd, 1H, *J* = 5.5, 7.5 Hz), 5.06 (dd, 1H, *J* = 4.0, 7.0 Hz), 5.27–5.32 (m, 1H), 6.18 (d, 1H, *J* = 7.5 Hz); *minor diastereomer*: 1.95–1.97 (m, 1H), 2.00 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.08–2.1 (m, 1H), 2.94 (dt, 1H, *J* = 9.0, 18 Hz) 3.09–3.15 (m, 1H), 3.37 (dd, 1H, *J* = 8.0, 17.0 Hz), 3.63–3.66 (m, 1H), 3.69 (s, 3H), 3.85–3.87 (m, 1H), 4.10–4.16 (m, 1H), 4.47 (dd, 1H, *J* = 2.5, 12.0 Hz), 4.93 (dd, 1H, *J* = 6.0, 7.5 Hz), 4.98 (dd, 1H, *J* = 5.0, 7.0 Hz), 5.33 (ddd, 1H, *J* = 2.5, 5.0, 7.5 Hz), 6.21 (d, 1H, *J* = 7.5 Hz); IR: (film): cm^{−1} 2950brw, 1742s, 1676m, 1579m, 1435m, 1371m, 1264s; mass spectrum (APCI): m/e (% relative intensity) 396 (100) (M+H)⁺, 336 (20), 194 (5), 101 (10). m/e (ESI) calcd for C₁₉H₂₅NO₈Na 418.1478, found 418.1480.

4.3.7. Aza-[3 + 3] Annulation Product 39a—*R_f* = 0.45 [20% EtOAc/hexane]; [α]_D²⁵ = −303.0 (*c* 0.55, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ *Major Diastereomer*: 1.55–1.69 (m, 1H), 1.72–1.77 (m, 1H), 1.82 (s, 3H), 1.85–1.87 (m, 1H), 1.91 (dddd, 2H, *J* = 8.0 Hz), 2.08–2.21 (m, 2H), 2.28–2.33 (dq, 1H, *J* = 2.8, 13.2 Hz), 2.43 (s, 1H), 2.88 (dt, 1H, *J* = 8.0, 17.6 Hz), 3.08 (dt, 1H, *J* = 7.2, 18.0 Hz), 3.24 (q, 1H, *J* = 8.0 Hz), 3.41 (dt, 1H, *J* = 6.8, 9.2 Hz), 3.55 (dd, 1H, *J* = 3.2, 12.0 Hz), 3.65 (s, 3H), 5.01 (d, 2H, *J* = 6.8 Hz), 5.65 (s, 1H); ¹³C NMR (100MHz, CDCl₃) δ 21.5, 22.8, 28.6, 31.4, 32.1, 33.8, 39.0, 40.5, 50.3, 50.9, 91.7, 111.3, 117.0, 125.3, 146.8, 155.3, 169.5; IR (film) cm^{−1} 2361w, 1709s, 1580w, 1422w, 1360m; mass spectrum (APCI): m/e (% relative intensity) 274 (100) (M+H)⁺; m/e (EI) calcd for C₁₇H₂₃NO₂ 273.1729, found 273.1728.

4.3.8. Aza-[3 + 3] Annulation Product 39b—*R_f* = 0.30 [30% EtOAc/hexane]; [α]_D²⁵ = −449.0 (*c* 0.080, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ *Major Diastereomer*: 1.59–1.76 (m, 2H), 1.84 (s, 3H), 1.92–2.02 (m, 3H), 2.11–2.29 (m, 6H), 2.43 (s, 1H), 2.89 (dt, 1H, *J* = 8.8, 17.6 Hz), 3.11 (dt, 1H, *J* = 6.8, 17.6 Hz), 3.30 (dt, 1H, *J* = 8.0, 9.2 Hz), 3.48 (dt, 1H, *J* = 6.4, 9.2 Hz), 3.65 (dd, 1H, *J* = 3.6, 12.0 Hz), 5.02 (d, 2H, *J* = 10.0 Hz), 5.70 (s, 1H); ¹³C NMR (100MHz, CDCl₃) δ 21.6, 23.1, 28.9, 29.0, 31.8, 33.1, 34.7, 39.4, 40.6, 50.9, 104.2, 111.4, 116.9, 127.0, 147.1, 154.8, 195.6; IR (film) cm^{−1} 2932w, 2360w, 1688m, 1639w, 1540s, 1437m, 1417m, 1276s, 1225m; mass spectrum (APCI): m/e (% relative intensity) 258 (100) (M+H)⁺; m/e (EI) calcd for C₁₇H₂₃NO 257.1780, found 257.1774.

4.3.9. Aza-[3 + 3] Annulation Product 40—*R_f* = 0.30 [25 % EtOAc/hexanes]; [α]_D²⁵ = −95.2 (*c* 2.05, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 0.87 (s, 3H), 1.10 (d, 1H, *J* = 9.5 Hz), 1.28 (s, 3H), 1.86 (m, 1H), 2.04 (ddd, 1H, *J* = 2.5, 6.0, 13.0 Hz), 2.08 (m, 1H), 2.14 (dddd, 1H, *J* = 2.0, 4.0, 6.0, 6.0 Hz), 2.36 (dddd, 1H, *J* = 0.5, 2.5, 4.0, 9.5, 13.5 Hz), 2.63 (dd, 1H, *J* = 5.5, 5.5 Hz), 2.68 (dddd, 1H, *J* = 0.5, 2.0, 6.5, 6.5, 10.0 Hz), 2.90 (ddd, 1H, *J* = 9.5, 11.0, 18.5 Hz), 2.98 (ddd, 1H, *J* = 7.0, 9.5, 11.0 Hz), 3.27 (ddd, 1H, *J* = 2.0, 10.0, 18.5 Hz), 3.52 (ddd, 1H, *J* = 1.5, 8.5, 9.5 Hz) 3.68 (s, 3H), 4.18 (ddd, 1H, *J* = 2.0, 6.0, 9.0 Hz), and 6.13 (d, 1H, *J* = 2.0 Hz); *minor* 2.26 (m, 1H), 2.53 (dd, 1H, *J* = 5.5, 5.5 Hz), 3.43 (ddd, 1H, *J* = 2.0, 8.5, 10.0 Hz), 3.67 (s, 3H), 4.43 (ddd, 1H, *J* = 2.5, 8.5, 8.5 Hz), and 6.02 (d, 1H, *J* = 2.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.0, 24.0, 27.2, 32.6, 33.2, 37.5, 39.8, 42.3, 50.6, 50.7, 50.8, 51.8, 95.5, 116.9, 129.6, 163.8, and 167.4; IR (neat) cm^{−1} 2979w, 2944w, 1732w, 1683s, 1562s, 1435m, 1273s, 1174s, 1116s, 1071s, and 910w; mass spectrum (APCI): m/e (% relative intensity) 274 (100) (M+1)⁺, and 242 (10); (MALDI) mass spectrum (APCI): m/e (% relative intensity) 274 (100) (M+1)⁺, and 242 (10); m/e (MALDI) calcd for C₁₇H₂₄NO₂ (M + H⁺) 274.1802, found 274.1800 and [(M + H⁺) − H₂] 272.1626.

4.3.10. Aza-[3 + 3] Annulation Product 41— $R_f = 0.32$ [10% EtOAc/Hexanes]; ^1H NMR (400 MHz, CDCl_3) δ 1.37 (t, 3H, $J = 7.2$ Hz), 1.62–1.88 (m, 6H), 2.92 (dd, 1H, $J = 8.4, 14.4$ Hz), 3.41–3.61 (m, 3H), 3.97–4.02 (m, 2H), 4.57 (d, 1H, $J = 6.0$ Hz), 4.92 (dd, 1H, $J = 5.6, 7.6$ Hz), 5.94 (d, 1H, $J = 7.6$ Hz), 7.15–7.18 (m, 1H), 7.24–7.29 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 26.5, 27.9, 28.9, 39.9, 52.7, 59.1, 98.3, 107.0, 125.8, 127.2, 128.0, 129.9, 149.0, 155.0, 168.9; IR (neat) cm^{-1} 2927m, 2853brm, 1676s, 1561s, 1186s; mass spectrum (APCI): m/e (% relative intensity) 298 (100) ($\text{M}+\text{H}$) $^+$; m/e (ESI) calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2$ 298.1807, found 298.1812.

4.3.11. Aza-[3 + 3] Annulation Product 42 [Characterized as a mixture]— $R_f = 0.48$ [50% EtOAc/hexane]; ^1H NMR (500 MHz, CDCl_3) δ *Major diastereomer*: 1.25–1.29 (m, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.51–1.78 (m, 6H), 2.73 (dd, 1H, $J = 8.5, 14.5$), 3.39–3.56 (m, 3H), 3.78 (dd, 1H, $J = 6.5, 7.5$ Hz), 3.85 (dd, 1H, $J = 5.0, 6.0$ Hz), 3.89 (dd, 1H, $J = 6.5, 8.0$ Hz), 4.08 (m, 1H), 4.14 (q, 2H, $J = 7.0$ Hz), 4.81 (dd, 1H, $J = 6.0, 7.5$ Hz), 6.07 (d, 1H, $J = 7.5$ Hz); *minor diastereomer (partial listing due to unresolved overlapping resonances)*: 1.51–1.78 (m, 6H), 2.70–2.76 (m, 1H), 3.30 (dd, 1H, $J = 6.0, 10.0$ Hz), 3.39–3.56 (m, 1H), 3.87–3.90 (m, 1H), 4.92 (t, 1H, $J = 7.0$ Hz), 6.05 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ *From a small sample of resolved major isomer*: 14.6, 25.5, 26.5, 26.7, 28.2, 28.9, 29.1, 36.5, 52.6, 59.6, 66.1, 79.2, 94.4, 102.0, 108.7, 133.1, 157.1, 169.1; IR (film) cm^{-1} : 2983w, 2931m, 1675s, 1552s, 1188s; mass spectrum (APCI): m/e (% relative intensity) 322 (100) ($\text{M}+\text{H}$) $^+$, 276 (100), 264 (50), 220 (5), 101 (10); m/e (ESI) calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_4\text{Na}$ 344.1838, found 344.1852.

Acknowledgements

Authors thank the NIH [NS38049], NIH [AI57153-05], and UW-Madison for funding.

References

- For reviews, see: (a) Harrity JPA, Provoost O. *Org Biomol Chem* 2005;3:1349. [PubMed: 15827625] (b) Hsung RP, Kurdyumov AV, Sydorenko N. *Eur J Org Chem* 2005;23. (c) Coverdale HA, Hsung RP. *ChemTracts* 2003;16:238.
- For a review on vinylogous amide chemistry, see: Kucklander UR, Rappoport Z. *Enaminones as Synthons. The Chemistry of Functional Groups: The Chemistry of Enamines Part I* John Wiley & Sons New York 1994;523.
- For a theoretical account, see: Wang Y, De-Cai Fang D-C, Liu R-Z. *Tetrahedron* 2005;61:5663.
- For recent studies in this area, see: (a) Trost BM, Dong G. *Org Lett* 2007;9:2357. [PubMed: 17497869] (b) Schmidt A, Gütlein JP, Mkrrchyan S, Görls H, Langer P. *Synlett* 2007;1305. (c) Pattenden LC, Wybrow RAJ, Smith SA, Harrity JPA. *Org Lett* 2006;8:3089. [PubMed: 16805559] (d) Shintani R, Hayashi T. *J Am Chem Soc* 2006;128:6330. [PubMed: 16683793] (e) Halliday JI, Chebib M, Turner P, McLeod MD. *Organic Lett* 2006;8:3399. (f) Katsuyama I, Funabiki K, Matsui M, Muramatsu H, Shibata K. *Heterocycles* 2006;68:2087. (g) Bose DS, Kumar RK. *Heterocycles* 2006;68:549. (h) Goodenough KM, Raubo P, Harrity JPA. *Org Lett* 2005;7:2993. [PubMed: 15987188] (i) Goodenough KM, Moran WJ, Raubo P, Harrity JPA. *J Org Chem* 2005;70:207. [PubMed: 15624924] (j) Agami C, Dechoux L, Hebbe S, Ménard C. *Tetrahedron* 2004;60:5433. (k) Ji SJ, Jiang ZQ, Lu J, Loh TP. *Synlett* 2004;831. (l) Hedley SJ, Moran WJ, Price DA, Harrity JPA. *J Org Chem* 2003;68:4286. [PubMed: 12762728]
- For our work on intermolecular aza-[3 + 3] annulation, see: (a) Sydorenko N, Hsung RP, Darwish OS, Hahn JM, Liu J. *J Org Chem* 2004;69:6732. [PubMed: 15387597] (b) McLaughlin MJ, Hsung RP, Cole KC, Hahn JM, Wang J. *Org Lett* 2002;4:2017. [PubMed: 12049506] (c) Hsung RP, Wei LL, Sklenicka HM, Douglas CJ, McLaughlin MJ, Mulder JA, Yao LJ. *Org Lett* 1999;1:509.
- For leading references on electrocyclic ring-closures involving 1-azatrienes, see: (a) Maynard DF, Okamura WH. *J Org Chem* 1995;60:1763. (b) de Lera AR, Reischl W, Okamura WH. *J Am Chem Soc* 1989;111:4051. For an earlier account, see: (c) Oppolzer VW. *Angew Chem* 1972;22:1108.
- For some recent studies of the ring-closure of azatrienes, see: (a) Trost BM, Gutierrez AC. *Org Lett* 2007;9:1473. [PubMed: 17362020] (b) Meketa ML, Weinreb SM. *Org Lett* 2007;9:853. [PubMed:

- 17261003] (c) Meketa ML, Weinreb SM. *Org Lett* 2006;8:1443. [PubMed: 16562912] (d) Alajarin M, Ortin MM, Sánchez-Andrada P, Vidal A, Bautista D. *Org Lett* 2005;7:5281. [PubMed: 16268558]
8. For a review on rotational preferences leading to diastereomeric induction during a 6π -electron electrocyclic ring closure see: Okamura WH de Lera ARTrostBMFlemingIPaquetteLA Comprehensive Organic Synthesis Pergamon Press New York 1991:569750
 9. For some examples of torquoselective processes, see: (a) Harmata M, Lee DR, Barnes CL. *Org Lett* 2005;7:1881. [PubMed: 15844930] (b) Harmata M, Schreiner PR, Lee DR, Kirchhoefer PL. *J Am Chem Soc* 2004;126:10954. [PubMed: 15339180] (c) Murakami M, Hasegawa M, Igawa H. *J Org Chem* 2004;69:587. [PubMed: 14725482] (d) Murakami M, Miyamoto Y, Ito Y. *Angew Chem Int Ed* 2001;40:189. (e) Murakami M, Miyamoto Y, Ito Y. *J Am Chem Soc* 2001;123:6441. [PubMed: 11427081] (f) Giese S, Kastrup L, Stiens D, West FG. *Angew Chem, Int Ed Engl* 2000;39:1970. [PubMed: 10940999]
 10. For elegant accounts on stereoselective ring-closure of 1-azatrienes, see: (a) Tanaka K, Katsumura S. *J Am Chem Soc* 2002;124:9660. [PubMed: 12175196] (b) Tanaka K, Mori H, Yamamoto M, Katsumura S. *J Org Chem* 2001;66:3099. [PubMed: 11325275] (c) Tanaka K, Kobayashi T, Mori H, Katsumura S. *J Org Chem* 2004;69:5906. [PubMed: 15373476]
 11. Sydorenko N, Hsung RP, Vera EL. *Org Lett* 2006;8:2611. [PubMed: 16737326]
 12. Wei LL, Hsung RP, Xiong H, Mulder JA, Nkansah NT. *Org Lett* 1999;1:2145.
 13. Sklenicka HM, Hsung RP, McLaughlin MJ, Wei LL, Gerasyuto AI, Brennessel WW. *J Am Chem Soc* 2002;124:10435. [PubMed: 12197745]
 14. Wei LL, Sklenicka HM, Gerasyuto AI, Hsung RP. *Angew Chem Int Ed* 2001;40:1516.
 15. Gerasyuto AI, Hsung RP, Sydorenko N, Slafer BW. *J Org Chem* 2005;70:4248. [PubMed: 15903297]
 16. Luo S, Zifcsak CZ, Hsung RP. *Org Lett* 2003;5:4709. [PubMed: 14627421]
 17. Sydorenko N, Zifcsak CA, Gerasyuto AI, Hsung RP. *Org Biomol Chem* 2005;3:2140. [PubMed: 15917902]
 18. (a) Swidorski JJ, Wang J, Hsung RP. *Org Lett* 2006;8:777. [PubMed: 16468765] (b) Wang J, Swidorski JJ, Sydorenko N, Hsung RP, Coverdale HA, Kuyava JM, Liu J. *Heterocycles* 2006;70:423.
 19. (a) Gerasyuto AI, Hsung RP. *Org Lett* 2006;8:4899. [PubMed: 17020331] (b) Gerasyuto AI, Hsung RP. *J Org Chem* 2007;72:2476. [PubMed: 17338572]
 20. For a review, see: Michael JP. *Nat Prod Rep* 1999;16:675.
 21. Lambert PH, Vaultier M, Carrié R. *J Org Chem* 1985;50:5352. 32. The Z geometry in all the exocyclic vinylogous urethanes or amides we prepared was confirmed through NOE experiments. From B3LYP/6-31G* [SpartanTM] calculations: $\Delta E = 4.62 \text{ Kcal mol}^{-1}$ in favor of the Z-isomer for 31; $\Delta E = 5.93 \text{ Kcal mol}^{-1}$ in favor of the Z-isomer for 13; $\Delta E = 6.68 \text{ Kcal mol}^{-1}$ in favor of the Z-isomer for 32
 22. Huckin SN, Weiler L. *J Am Chem Soc* 1974;96:1082.
 23. For reviews, see: (a) Feist H, Langer P. *Synthesis* 2007:327. (b) Butkus E. *Synlett* 2001:1827. (c) Filippini MH, Rodriguez J. *Chem Rev* 1999;99:27. [PubMed: 11848980] (d) Filippini M-H, Faure R, Rodriguez J. *J Org Chem* 1995;60:6872. and see references 21–33 cited therein. (e) Rappoport Z. *The Chemistry of Enamines. The Chemistry of Functional Groups* John Wiley and Sons New York 1994 (f) Kraus GA, Hon YS, Thomas PJ, Laramay S, Liras S, Hanson J. *Chem Rev* 1989;89:1591. (g) Keese R. *Angew Chem Int Ed* 1975;14:528.
 24. For defining the phrase “[3 + 3] carbo-cyclizations,” see: Seebach D, Missbach M, Calderari G, Eberle M. *J Am Chem Soc* 1990;112:7625.
 25. Prelog V. *J Chem Soc* 1950:420.
 26. (a) Stork G, Brizzolara A, Landesman H, Szmuszkovicz J, Terrell R. *J Am Chem Soc* 1963;85:207. (b) Stork G, Landesman H. *J Am Chem Soc* 1956;78:5129.
 27. For earlier studies, see: (a) Dauben WG, Bunce RA. *J Org Chem* 1983;48:4642. (b) Liu HJ, Ho LK, Lai HK. *Can J Chem* 1981;59:1685. (c) Alexakis A, Chapdelaine MJ, Posner GH. *Tetrahedron Lett* 1978;19:4209. (d) Hajos ZG, Parrish DR. *J Org Chem* 1974;39:1612. (e) Hendrickson JH, Boeckman RK Jr. *J Am Chem Soc* 1971;93:1307. (f) Warnhoff EW, Wong CM, Tai WT. *J Org Chem* 1967;32:2664. (g) Buchanan GL, Maxwell C, Henderson W. *Tetrahedron* 1965;21:3273.
 28. For recent studies, see: (a) Ahmad NM, Rodeschini V, Simpkins NS, Ward SE, Blake AJ. *J Org Chem* 2007;72:4803. [PubMed: 17530804] (b) Hussain I, Nguyen VTH, Yawer MA, Dang TT, Fischer C,

- Reinke H, Langer P. *J Org Chem* 2007;72:6255. [PubMed: 17604399] (c) Hong BC, Wu MF, Tseng HC, Liao JH. *Org Lett* 2006;8:2217. [PubMed: 16706490] (d) Bose G, Nguyen VTH, Ullah E, Lahiri S, Görls H, Langer P. *J Org Chem* 2004;69:9128. [PubMed: 15609946] (e) Dede R, Langer P. *Tetrahedron Lett* 2004;45:9177. (f) Kraus GA, Nguyen TH, Jeon I. *Tetrahedron Lett* 2003;44:659. [PubMed: 16951711] (g) Ciochina R, Grossman RB. *Org Lett* 2003;5:4619. [PubMed: 14627398] (h) Hong BC, Gupta AK, Wu MF, Liao JH, Lee GH. *Org Lett* 2003;5:1689. [PubMed: 12735753] and references cited therein (i) Young DGJ, Zeng D. *J Org Chem* 2002;67:3134. [PubMed: 11975581] (j) Spessard SJ, Stoltz BM. *Org Lett* 2002;4:1943. [PubMed: 12027653] (k) Usuda H, Kanai M, Shibasaki M. *Org Lett* 2002;4:859. [PubMed: 11869146] (l) Ishikawa T, Kadota R, Arai M, Takahashi H, Kashi Y, Mizuta T, Yoshikai K, Saito S. *J Org Chem* 2001;66:8000. [PubMed: 11722197] (m) Filippini M-H, Rodriguez J, Santelli M. *J Chem Soc, Chem Commun* 1993:1647–571. (n) Lapierre JM, Gravel D. *Tetrahedron Lett* 1991;32:2319. Also see: (o) Kuramochi A, Usuda H, Yamatsugu K, Kanai M, Shibasaki M. *J Am Chem Soc* 2005;127:14200. [PubMed: 16218611] (p) Siegal DR, Danishefsky SJ. *J Am Chem Soc* 2006;128:1048. [PubMed: 16433500]
29. For the synthesis of 30: (a) Shiosaki K. *The Eschenmoser Coupling Reaction*. Comp Org Syn Trost BM, Fleming IP, Pergamon Press Oxford 1991:2865 (b) Pinnick HW, Chang YH. *J Org Chem* 1978;43:4662.
30. For the synthesis of 31: Park KH, Marshall WJ. *J Org Chem* 2005;70:2075. [PubMed: 15760190]
31. For the synthesis of 32: (a) Benson RE, Cairns TL. *Organic Syn* 1989;Coll Vol 4:588. (b) Celerier JP, Deloisy-Marchalant E, Lhomme G, Maitte P. *Organic Syn* 1993;Coll Vol 8:263.
32. For our oxa-[3 + 3] annulation work, see: a) Shen HC, Wang J, Cole KP, McLaughlin MJ, Morgan CD, Douglas CJ, Hsung RP, Coverdale HA, Gerasyuto AI, Hahn JM, Liu J, Wei LL, Sklenicka HM, Zehnder LR, Zifcak CA. *J Org Chem* 2003;68:1729. [PubMed: 12608785] (b) Hsung RP, Shen HC, Douglas CJ, Morgan CD, Degen SJ, Yao LJ. *J Org Chem* 1999;64:690. [PubMed: 11674130]
33. For a notable citation in support the usage of α,β -unsaturated iminium salts, see: Cravotto G, Nano GM, Tagliapietra S. *Synthesis* 2001:49.
34. (a) de March P, Moreno-Mañas M, Casado J, Pleixats R, Roca JL. *J Heterocycl Chem* 1984;21:85. Also see: (b) Stevenson R, Weber JV. *J Nat Prod* 1988;51:1215. (c) Schuda PF, Price WA. *J Org Chem* 1987;52:1972. (d) Tietze LF, v Kiedrowski G, Berger B. *Synthesis* 1982:683. (d) de Groot A, Jansen BJM. *Tetrahedron Lett* 1975;16:3407.

Figure 1.
Alkaloids Synthesized via Intramolecular Azide-[3 + 3].

Figure 2.
Aza-[3 + 3] versus *Carbo*-[3 + 3] Annulation.

Figure 3.
A Possible Synthesis of Tetrahydroindoles.

Figure 4.
Energetic Differences in the Annulation Products.

Scheme 1.
 An Aza-[3 + 3] Annulation.

Scheme 2.
An Intramolecular Aza-[3 + 3] Annulation.

Scheme 3.

An Aza-[3 + 3] Pathway to Azaphenalenenes and Quinolizidines.

Scheme 4.
 Syntheses of *Exo*-Cyclic Vinylogous Amide and Urethane.

Scheme 5.
Unexpected Formation of Hexahydroquinolines.

Scheme 6.

A Proposed Pathway for the Hexahydroquinoline Formation.

Scheme 7.
DDQ Aromatization in the Quinoline Synthesis.

Scheme 8.

C-1,2 Addition versus C-1,4-Addition.

Table 1

Aza-[3 + 3] Annulations of *Exo*-Cyclic Vinyllogous Amides.

entry	amides	aldehydes	aza-[3 + 3] products	yield [%] ^a	ratio ^b
1				51	--
2				70	--
3				75	--
4				73	--
5				56	1.5 : 1
6				50	1.3 : 1
7				10	□ 20 : 1
8				7	□ 20 : 1
9				33	2.2 : 1 ^e
10				53	--
11				62	1.2 : 1

^a Isolated Yields.

^b Ratio determined using ¹H NMR, and unless noted otherwise, the relative stereochemistry was not assigned.

^c See references 21 and 29 for the preparation of 30.

^d See references 21 and 30 for the preparation of 31.

^e The ratio was found in crude ¹H NMR but the minor isomer appeared to isomerize to the major isomer during purification. The major isomer shown here was assigned using nOe experiment and the final ratio was 13.8: 1.

^f See references 21 and 31 for the preparation of 32.