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Stereoselective Formal [3 + 3] Cycloaddition Approach to *cis*-1-Azadecalins and Synthesis of (−)-4*a*,8*a*-*diepi*-Pumiliotoxin C. Evidence for the First Highly Stereoselective 6π-Electron Electrocyclic Ring Closures of 1-Azatrienes

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Abstract: Evidence is described here to support that a highly stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes is a key step in formal [3 + 3] cycloaddition or annulation reactions of chiral vinylogous amides with α,β-unsaturated iminium salts. This would represent the first highly stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes. We have also unambiguously demonstrated that these specific ring closures are reversible, leading to the major diastereomer that is also thermodynamically more stable, and that a rotation preference likely also plays a role. A synthetic application is illustrated here to stereoselectively transform the resulting dihydropyridines to *cis*-1-azadecalins with unique anti relative stereochemistry at C2 and C2a, leading to synthesis of epi isomers of (−)-pumiliotoxin C.

Introduction

Annulation reactions of vinylogous amides with α,β-unsaturated carbonyl systems represent a powerful synthetic approach for constructing nitrogen heterocycles and related nitrogen alkaloids.[1,2] Most of these reactions have led to pyridines, and in some cases, 2-pyridones, 4-pyridones, and 1,4-dihydropyridines have been reported (Figure 1).[1] The attractive aspect of these reactions is that the formation of the six-membered nitrogen heterocycle ultimately constitutes a formal hetero [3 + 3] cycloaddition.[3,4] Two of the five carbons along with the nitrogen atom in the resulting six-membered nitrogen heterocycle come from the vinylogous amide with the remaining three carbons from the α,β-unsaturated carbonyl system. Two possible regiochemical alignments can be commonly found in these reactions. The formation of pyridines or 4-pyridones mainly results from a *head-to-head* (both carbonyls are in the same direction) regiochemical alignment, and products such as 2-pyridones and 1,4-dihydropyridines are results from a *head-to-tail* (carbonyls are in opposite directions) alignment. Despite that a variety of different α,β-unsaturated carbonyl systems have been employed in these reactions, α,β-unsaturated iminium salts have not been used,[5] nor have 1,2-dihydropyidines been found in these reactions.

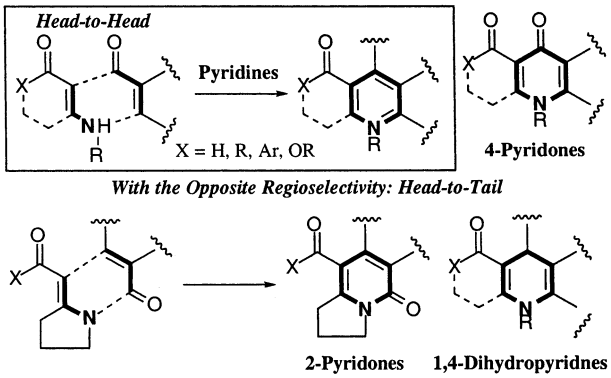

Figure 1. Precedents in formal aza-[3 + 3].

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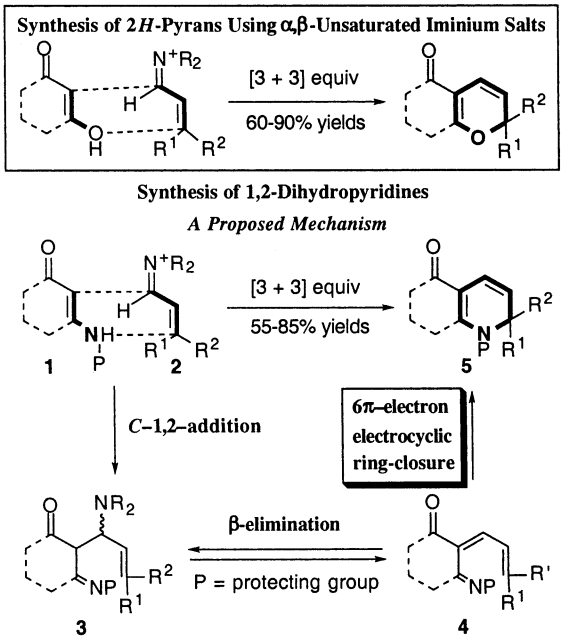
(3) For the term "formal [3 + 3]" used to describe [3 + 3] carbo-cycloadditions, see: (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. For earlier studies on [3 + 3] carbo-cycloadditions, see: (b) Landesman, H. K.; Stork, G. *J. Am. Chem. Soc.* **1956**, *78*, 5129. (c) Hendrickson, J. B.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1307. (d) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H. *Tetrahedron Lett.* **1978**, *19*, 4209.
(4) For recent reviews on stepwise [3 + 3] carbo-cycloadditions using enamines, enol ethers, or β-keto esters, see: (a) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27. (b) Rappoport, Z. The Chemistry of Enamines. In *The Chemistry of Functional Groups*; John Wiley & Sons: New York, 1994. (c) Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872, and see refs 21−33 cited therein. For reviews on metal mediated stepwise [3 + 3] cycloaddition reactions, see: (d) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

Scheme 1



Our interest in this area commenced with an investigation involving condensations of α,β-unsaturated aldehydes with 4-hydroxy-2-pyrones and 1,3-cyclohexanediones (Scheme 1). These reactions have been known for the almost 50 years since Link's first report using 4-hydroxycoumarins[6] and have been extensively examined by Moreno-Mañas.[7] However, these reactions also suffer from problems caused by the competing 1,2- versus 1,4-additions and *C*- versus *O*-addition, thereby providing a synthetically less useful process.[7] Our initial contribution was to recognize that instead of generating α,β-unsaturated iminium ions in situ, the direct use of iminium salts provided a highly efficient entry to 2*H*-pyrans in favor of the *head-to-head* alignment (Scheme 1).[8−12]

At the heel of the success in using α,β-unsaturated iminium salts, first reactions of vinylogous amides **1** with α,β-unsaturated iminium salts **2** were explored and found to be very efficient, leading exclusively to 1,2-dihydropyridines **5** (Scheme 1).[13] The regiochemistry of these reactions is the same (head-to-head) as those using 1,3-diketo systems but opposite of Hickmott−Stille's aza-annulation using acid anhydrides or chlorides.[14] Thus, mechanistically, these new reactions of vinylogous amides **1** were thought to involve a sequence that consists of a Knoevenagel condensation followed by a key 6π-electron electrocyclic ring closure of 1-azatrienes **4**.[15] The net result of this sequential anionic−pericyclic strategy[16] is the formation of two σ-bonds in addition to an important carbocenter adjacent to the nitrogen atom that could be controlled stereochemically.[17] It provides a rapid construction of 1,2-dihydropyridines from simple and accessible vinylogous amides. In this paper, we disclose full details of this stereoselective formal [3 + 3] cycloaddition reaction, mechanistic evidences for the first stereoselective ring closure of 1-azatrienes, and applications of this methodology in stereoselective constructions of *cis*-1-azadecalins.

Results and Discussions

(1) Stereoselectivity and Mechanism. (a) Stereoselective Formal [3 + 3] Formal Cycloaddition Using Chiral Vinylogous Amides. Having established the synthetic feasibility in accessing 1,2-dihydropyridines, a stereoselective variant of this formal [3 + 3] cycloaddition using chiral vinylogous amides such as **5** and **6** was developed to give 1,2-dihydropyridines **7** and **8,** respectively, in high diastereoselectivity and good yields when reacted with a range of different α,β-unsaturated iminiums salts (Scheme 2).[17] Given the vast number of nitrogen alkaloids that are known to possess this important stereogenic center adjacent to the nitrogen atom, this stereoselective reaction represents an attractive and novel entry to natural products with the 1-azadecalinic structural motif.[2,18,19] Most significantly, this stereoselective manifold potentially represents the first examples

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(12) For other studies using 2-pyrones and 1,3-cyclohexanones, see: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Moorhoff, C. M. *Synthesis* **1997**, 685. (c) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473. (d) Krasnaya, Z. A.; Bogdanov, V. S.; Burova, S. A.; Smirnova, Y. V. *Russ. Chem.* **1995**, *44*, 2118. (e) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1990**, *73*, 1865. (f) Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972. (g) Tietze, L. F.; v. Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683. (h) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, *16*, 3407.

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(14) (a) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112. (b) Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493. (c) Paulvannan,; K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215, 6677. (d) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (e) Greenhill, J. V.; Mohamed, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1411. (f) Chaaban, J.; Greenhill, J. V.; Rauli, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3120. (g) Greenhill, J. V.; Moten, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 287. (h) Heber, D.; Berghaus, Th. *J. Heterocycl. Chem.* **1994**, *31*, 1353.

(15) For leading references on electrocyclic ring-closures involving 1-azatrienes, see: (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763. (b) de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4051. (c) Okamura, W. H.; de Lera, A. R.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 4462. For an earlier account, see: (e) Oppolzer, V. W. *Angew. Chem.* **1972**, *22*, 1108. For a recent account similar to Okamura's elegant studies, see: (f) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

(16) For a review on synthetic methods involving sequential transformations, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47.

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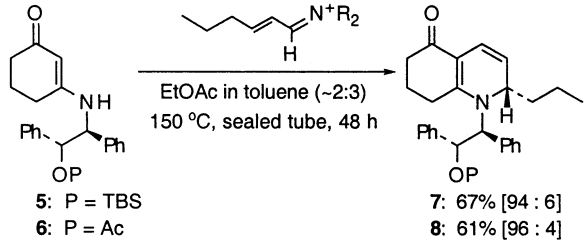
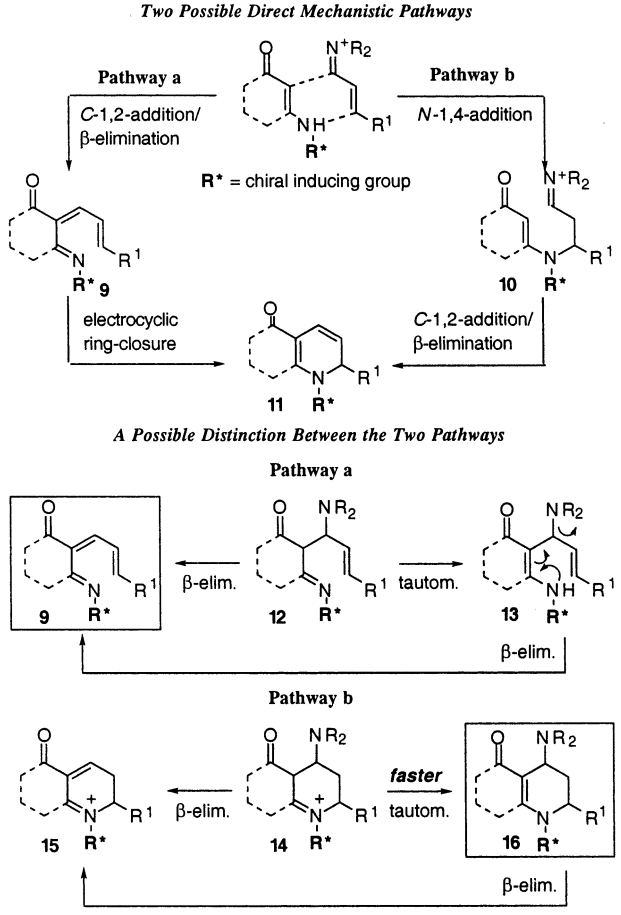
(18) For a recent review on preparations of piperidines, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.

Scheme 2. Stereoselective Formal [3 + 3] Cycloadditon



Scheme 3



of stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes.

(b) Evidence for the 6π-Electron Electrocyclic Ring Closure of 1-Azatrienes. (1) Mechanistic Analysis. Although the mechanism described in Scheme 1 provides a reasonable pathway leading to the dihydropyridine **5** that is in agreement with the assigned regiochemistry (head-to-head), there are other possible mechanistic pathways that could also lead to such conclusions. While it is not possible to completely rule out all mechanistic possibilities, two pathways could be assigned as the major possibilities (Scheme 3). One would involve pathway a with the key step being the 6π-electron electrocyclic ring closure of 1-azatrienes **9** after the Knoevenagel condensation. Pathway b, the most likely alternative pathway, would involve an *N*-1,4-addition followed by the Knoevenagel-type condensation via the intermediate **10**.

A closer analysis of these two possibilities would reveal that to distinguish them, one could attempt to detect and/or isolate intermediates related to **9** and **16** (Scheme 3). The major difference in the two possibilities would reside in the *C*-1,2-addition step. For pathway a, the initial *C*-1,2-addition intermediate would be **12**. While an ensuing β-elimination could lead to the 1-azatriene intermediate **9**, a tautomerization could first give **13** and a subsequent β-elimination would then provide **9**. It is also noteworthy that the intermediate **13** itself could also undergo an intramolecular S_N2 displacement to give the dihydropyridine product **11**. This would lead to a mechanistic possibility that cannot be completely ruled out even if the 1-azatriene intermediate **9** can be detected.

On the other hand, for pathway b, the *C*-1,2-addition step via **10** after the initial *N*-1,4-addition would lead to an iminium type intermediate **14**. While **14** could undergo β-elimination to directly give the vinyl iminium intermediate **15** that could further tautomerize to the dihydropyridine **11**, simple intuitions suggest that tautomerization of **14** could proceed faster, leading to the neutral allylamine **16**, and that β-elimination of the NR_2 group in this case could be slower. It could be further suggested that allylic amines such as **16** could be isolated or trapped. Evidence in differentiating these two pathways can lend support to whether this reaction does involve a 6π-electron electrocyclic ring closure of 1-azatrienes.

(2) Isolation of an Intermediate Related to 16. Although we have never spectroscopically observed or isolated any intermediates related to **16** *in intermolecular reactions* of vinylogous amides under any conditions, this can only serve as a negative support. However, *an intramolecular variant* of this annulation reaction using vinylogous amides tethered with α,β-unsaturated iminium salt as in **17** provided an opportunity to isolate an intermediate related to **16** (Scheme 4).[11d]

For the intramolecular reaction, the mechanism could also proceed via two possibilities: Pathway c and pathway d with distinctions similar to those described for pathways a and b. However, intuitions would support pathway d (corresponding to pathway b *in intermolecular reactions*) since it *does not require an initial counterintuitive formation* of a macrocycle **18** as suggested in the pathway c (corresponding to pathway a). If this intuitive assertion is valid, then the intermediate **21** in pathway d, related to **16** in pathway b, should be detectable or attainable by isolation, thereby leading to positive support for an *N*-1,4-/*C*-1,2-addition pathway.

To achieve this task, the vinylogous amide **24** tethered with the enal was prepared as a 3:1 *E/Z* mixture from **22** using standard conditions (Scheme 5).[20] While the intramolecular formal [3 + 3] cycloaddition reaction of **24** under the conditions using piperidinium acetate salt[20] at 150 °C gave the desired product **25** in 55% yield as a single diastereomer, the intermediate **26** was isolated in 40% yield also as a single diastereomer

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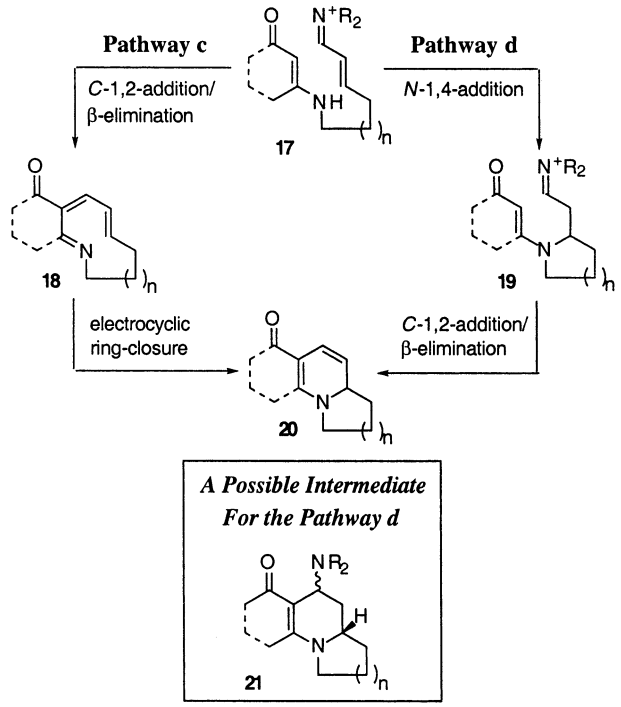
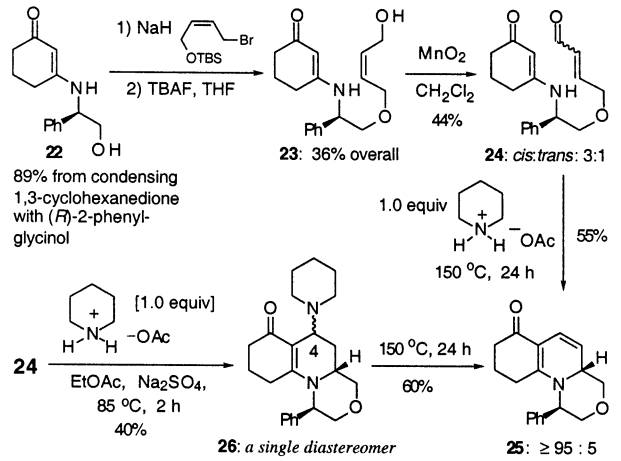
(20) See Supporting Information for preparations of all relevant new compounds and details of their full characterizations along with their ^{1}H NMR spectra. These reactions are best carried out in toluene and/or EtOAc using piperidine/Ac_2O. L-Proline does not work well for this reaction contrary to literature accounts due to low solubility in EtOAc. We can also use piperidinium salts as well as other amine salts.

Scheme 4



Scheme 5

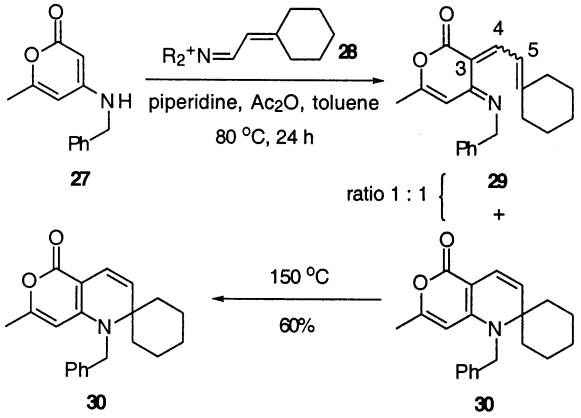


when the reaction was carried out at 85 °C. The intermediate **26** was fully characterized, although stereochemistry at C4 was not vigorously assigned. Further heating of **26** at higher temperature and/or for a longer reaction time, the tricycle **25** was isolated in comparable yield as a single diastereomer in favor of the same major isomer.

This experiment suggests that if the mechanistic pathway would involve an *N*-1,4-addition/*C*-1,2-addition as described for pathway d, **21** is a viable reaction intermediate that could be isolated. Thus, inability to observe or attain the proposed intermediate **16**, corresponding to **21** in pathway d, under any reaction conditions suggests that an *N*-1,4-addition/*C*-1,2-addition as described in pathway b is likely not involved in intermolecular formal [3 +3] cycloadditions.

(3) Identification of the 1-Azatriene Intermediate Related to 9. Finding and/or isolating 1-azatriene intermediates such as **9** were not trivial, although we have on occasions isolated and trapped 1-oxatriene intermediates in related reactions.[8] These 1-heterotrienes are usually very reactive and undergo ring

Scheme 6



closure readily.[15,21] We were, however, able to isolate successfully in one case the 1-azaztriene **29** partially containing the ring-closed product **30** in ~50−60% yield from reactions of the aminopyrone **27** with the α,β-unsaturated iminium salt **28** at 80 °C (Scheme 6). Although the stereochemistry of C3−C4 olefin was not vigorously assigned, there appeared to be mainly just one isomer of **29**, as suggested in ^{1}H NMR and LCMS.[20]

On the basis of literature precedents of related 1-heterotrienes,[8,15,21] this assignment of the 1-azatriene **29** is well-substantiated, although attempts to separate **29** and **30** for further characterizations failed. In addition, the mixture of **29** and **30** could be resubjected to reaction conditions at higher temperature (150 °C) and/or with a longer reaction time (48 h) to give **30** quantitatively (an overall yield of 60% from **27**).

This collective evidence suggests that, while not completely ruling out other mechanistic pathways, this formal [3 + 3] cycloaddition of vinylogous amides proceeds via a Knoevenagel condensation followed by an electrocyclic ring closure of 1-azatrienes analogous to those described by Link and Moreno-Mañas using 4-hydroxy-2-pyrones. Although 6π-electron electrocyclic ring closure of 1-azatrienes has been elegantly studied by Okamura,[15] and although Okamura has also made the first attempts in effecting these ring closures stereoselectively,[22] the diastereoselectivity observed using chiral vinylogous amides represents the first highly stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes.

(c) Rotational Preference and Reversibility of the Ring Closure. (1) Rotational Preference. Having established evidence to support that the stereoselective formal [3 + 3] cycloaddition reaction of vinylogous amides involves a key stereoselective ring closure of 1-azatrienes, the observed high diastereoselectivity could be proposed as a result of a key rotational preference in the 1-azatriene **31** (Figure 2). Rotational preferences leading to stereoselective constructions of sp^2 and sp^3 hybirdized stereocenters have excellent precedents in various pericyclic processes, and such stereoselectivity has been appropriately termed as torquoselectivity.[23,24]

Rotations of the vinyl strand in **31** along in directions a and b would lead to diastereomers **32a** and **32b**, respectively. It was

(21) For leading references on electrocyclic ring-closures involving 1-oxatrienes, see: (a) Kametani, T.; Kajiwara, M.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1053. (b) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943. (c) Shishido, K.; Shitara, E.; Fukumoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 5810. (d) Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1986**, *27*, 971.

(22) Professor Bill Okumura performed the first attempts at effecting these ring closures of 1-azatrienes stereoselectively using optically active phenylethylamine: A personal communication.

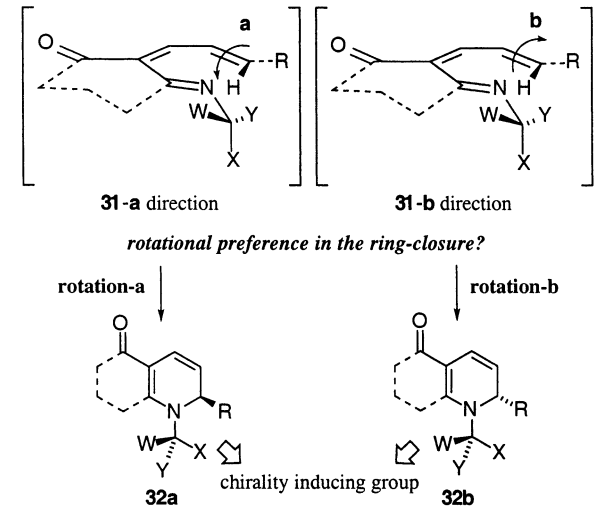


Figure 2. Stereoselective ring closure of 1-azatriene.

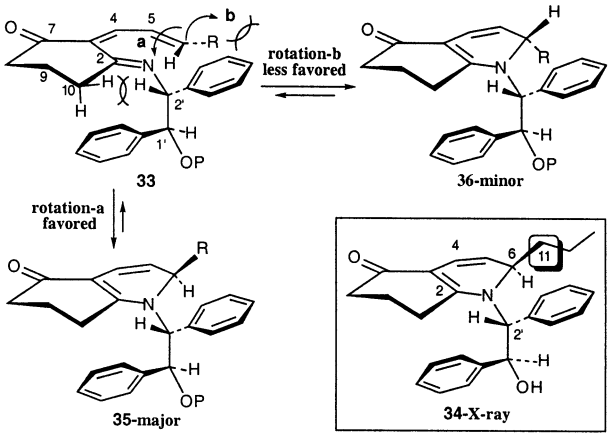


Figure 3. Mechanistic proposal.

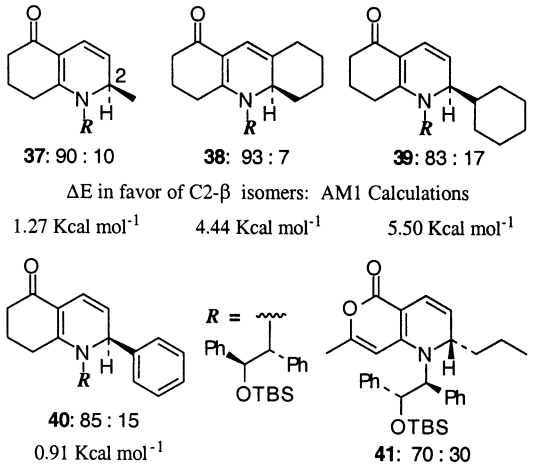
not readily apparent how such rotational preferences could be evoked and what chirality inducing groups on the nitrogen atom should be employed. However, on the basis of much trial and error, it became clear that the protected 1-hydroxy-1,2-bisphenylethyl group is unique in this stereoselective ring closure.

On the basis of the X-ray structure of the desilylated dihydropyridine **34**, a mechanistic model is proposed in Figure 3 to describe such rotational preferences. X-ray structure of **34** reveals that the C2′−N and C1′−OH are anti to one another and that the two phenyl groups are completely anti to one another with the C2′ phenyl group being in close proximity to C6. The correlation of this solid-phase conformation to the one possibly present in the solution phase would be that the chemical shift of the C11 methylene in **34** is absolutely upfield shifted, suggesting an anisotropic effect from the proximal C2′ phenyl ring. This upfield shift was also observed in other dihydropyridine substrates with a range of −0.11 to +0.27 ppm for the δ values.

(23) For a review on rotational preferences leading to diastereomeric induction during a 6π-electron electrocyclic ring closure, see: Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Paquette, L. A., Vol. Ed.; Pergamon Press: New York, 1991; Vol. 5, pp 699−750.

(24) For some examples involving torquoselective processes, see: (a) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1970. (b) Hsung, R. P.; Quinn, J. F.; Weisenberg, B. A.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *J. Chem. Soc., Chem. Commun.* **1997**, 615.

Chart 1



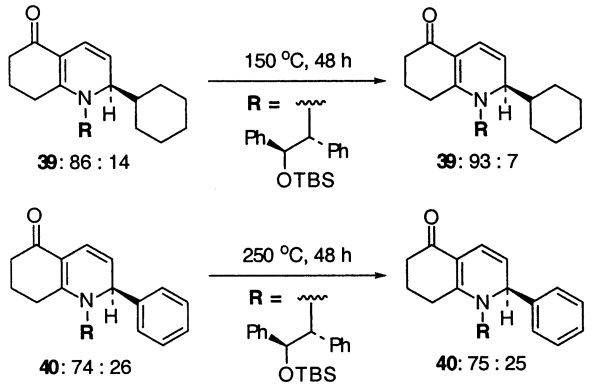
It could be proposed that the 1-azatriene **33** also assumes such a conformational preference prior to the ring closure. This assumption would then render **33** with a conformation where the C2′ phenyl is almost π-stacked with the C5−C6 alkene, and there can be two possible rotations for the C5−C6 vinyl strand in **33** during the ring closure. The rotation a should be favored, leading to isomer **35** that is the observed major diastereomer, while rotation b is less favored for it leads to the severe steric interaction between the R and the C2′-phenyl group.

This assertion also implies that the level of diastereoselectivity should be a function of the size of the R group. The diastereomeric ratios of dihydropyridines **34** and **37**−**39** (Chart 1), with R groups being Me, *n*-Pr, -$(CH_2)_4$, and cyclohexyl (or primary, secondary, and tertiary carbons), respectively, reveal that this trend is in part true with the sole exception of **39**, suggesting that there are other factors. In addition, the diastereoselectivity for **40** is much lower despite the R group being a large phenyl ring. This is actually in agreement with the aforementioned conformational assumption and rotation preference. An extended $\pi-\pi$ interaction could exist with the C2′ phenyl ring, the C5−C6 vinyl strand, and the R (=Ph) group in the 1-azatriene precursor corresponding to the dihydropyridine **40**, thereby providing less steric interaction and lower diastereoselectivity.

The proposed conformation for the 1-azatriene intermediate **33** is key to the rotational preference illustrated above in rationalizing the observed high diastereoselectivity. In addition to the chemical shift data, the observation that any perturbations of this conformational preference lead to loss of stereoselectivity also lends support to this conformation. The steric interaction (pseudo $A^{1,3}$) between the methylene at C10 and the entire substituent on the nitrogen atom appears to be significant. Presumably, to alleviate this interaction, the substituent on the nitrogen atom moves or rotates away, but as a result, a closer proximity of the C2′ phenyl to the C5−C6 vinyl strand is gained. This assertion is supported by the observation that the diastereoselectivity is significantly reduced when the steric presence of the C10 carbon is reduced to a sp^2 carbon as in the 1-azatriene precursor corresponding to the dihydropyridine **41** (Chart 1).

(**2) Reversibility of the Ring Closure.** While the rotational preference provides one explanation for the observed diastereoselectivity in the ring closure of 1-azatrienes, the reversibility of ring closure likely plays a significant role because there is ample precedent regarding the reversibility in the ring closure

Scheme 7



of 1-heterotrienes. In addition, since the rotational preference leads to the major product with the least amount of steric congestion between the R and C2′ phenyl group, the major isomer of **35** is the thermodynamically more stable one. ΔE values from AM1 calculations (Spartan) for the major isomers of **37**−**39** are shown in Scheme 7, and the ΔE value for **34** is 1.66 kcal mol^{-1} also in favor of the substituent at C2 being β. We pursued the following studies to establish such reversibility, thereby suggesting that the overall stereoselectivity is a result of thermodynamic equilibration.

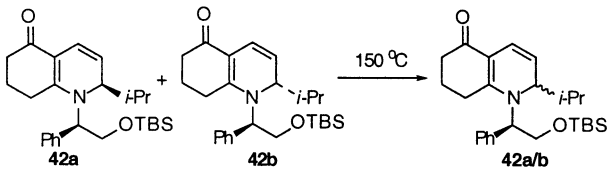
The first study was motivated by the observation that the diastereomeric ratio (dr) of the dihydropyridine **39** did not follow suit as suggested by the proposed rotational preference. Reheating a sample of **39** with a dr of 84:16 at 150 °C for 48 h in toluene-d_8 led to no significant loss of materials but a noticeably improved dr of 93:7 in favor of the same major isomer (Scheme 7). This improved ratio provides a better agreement for the assertion that the level of diastereoselectivity should be a function of the size of the R group in lieu of the rotation preference. It is also in good agreement in terms of the energetic difference of major and minor isomers of **39** relative to those of **37** or **38** (relative ΔE values).

The second study involved heating a sample of **40** that has a ratio of 74:26 at 250 °C for 48 h. This in fact led to no improvement of the dr, suggesting that having the R group being a phenyl (sp^2) indeed led to lower ratios than when R contained an sp^3 carbon and that it is actually lower than the ratio we had obtained initially but reflects well of a potential prediction from the ΔE value.

To further verify the reversibility of this ring closure involving these 1-azatrienes, we heated samples of pure major isomer of **42** (≥95:5 major to minor) at 150 °C for an overall of 60 h in toluene-d_8. The reaction was monitored using ^{1}H NMR, and ratios as a function of time are displayed in Scheme 8. Although the rate of equilibration through a sequence of ring opening and ring closure appeared to be slow, it is unambiguous that the ring closure is reversible and ultimately led to **42a/b** with a ratio befitting of its original thermodynamic distributions. A similar study was carried out using an enriched minor isomer of **34** (28:72 major to minor) in toluene-d_8 for 66 h, but temperature was varied (Scheme 9). Although the final isomeric ratio of **34** eventually matched that observed from the reaction, the rate of equilibration from the minor isomer to the major isomer appeared to slow especially at a temperature well below that of 150 °C.

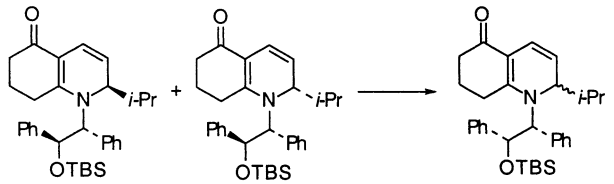
These studies suggest that the reversibility of ring closure ultimately provides the diastereomeric ratio based on the

Scheme 8



time	ratio of 42a:b
1.5 h	93 : 7
12	82 : 18
20	77 : 23
36	66 : 34
The observed ratio from the reaction was 55 : 45	60	60 : 40

Scheme 9



temp	time	34a : 34b
80 °C	20 h	30 : 70
110	28	44 : 56
110	43	51 : 49
110-5	49	61 : 39
The observed ratio was ≥96 : 4	150	66	≥96 : 4

thermodynamic stability of the two diastereomers, a rotational preference during the ring closure of 1-azatrienes also likely plays a role in setting up an initial ratio close to the thermodynamic ratio.

(2) Applications in Constructing *cis*-1-Azadecalin. Having achieved a mechanistic understanding of this annulation reaction of chiral vinylogous amides with α,β-unsaturated iminium salts, we pursued a synthetic application to illustrate the utility of dihydropyridines such as **7** in constructing *cis*-1-azadecalin related to the dendrobatid alkaloid pumiliotoxin C (Figure 4).[25−27]

Such an approach represents an attractive and stereoselective entry to *cis*-1-azadecalins because of its ability to achieve high diastereomeric control of the stereogenic center at C2. To achieve this task, two major issues need to be addressed. They

(25) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1983; Vol. 4, pp 124−162. (b) Garaffo, H. M.; Simon, L. D.; Daly, J. W.; Spande, T. F.; Jones, T. H. *Tetrahedron* **1994**, *50*, 11329.

(26) For earlier total syntheses, see: (a) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 593. (b) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48. (c) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204. (d) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 179.

(27) For recent approaches and total syntheses, see: (a) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2001**, *66*, 7873. (b) Oppolzer W.; laskamp E.; Bieber L. W. *Helv. Chim. Acta* **2001**, *84*, 141. (c) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368. (d) Shieh, Y. S.; Yeh, M. C. P.; Rao, U. N. *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 283. (e) Kunz, H.; Weymann, M.; Follmann, M.; Allef, P.; Oertel, K.; Schultz-Kukula, M.; Hofmeister, A. *Pol. J. Chem.* **1999**, *73*, 15. (f) Riechers, T.; Krebs, H. C.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem.* **1946**, *11*, 2641. (g) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566. (h) Toyota, M.; Asoh, T.; Fukumoto, K.; *Heterocycles* **1997**, *45*, 147. (i) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, *11*, 2007. (j) Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595. (k) Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279. (l) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838. (m) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.

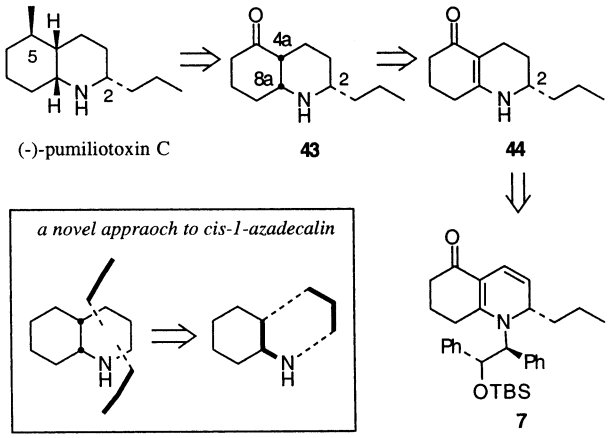
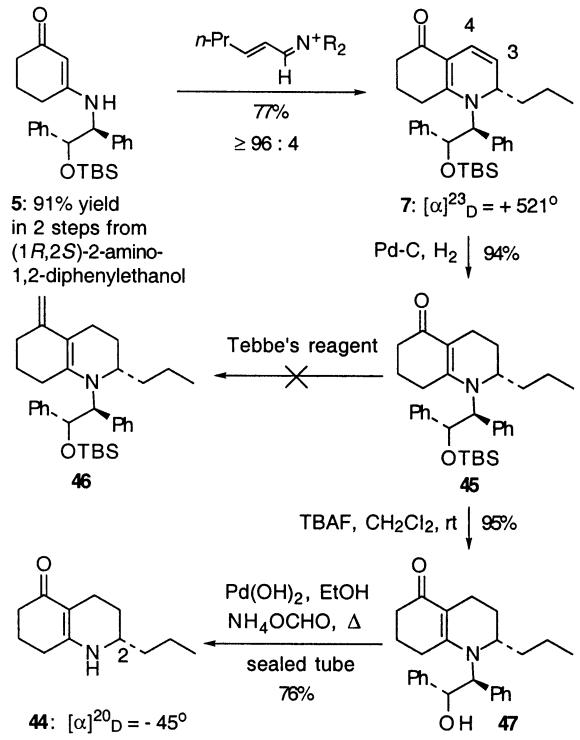


Figure 4. Constructions of *cis*-1-azadecalins.

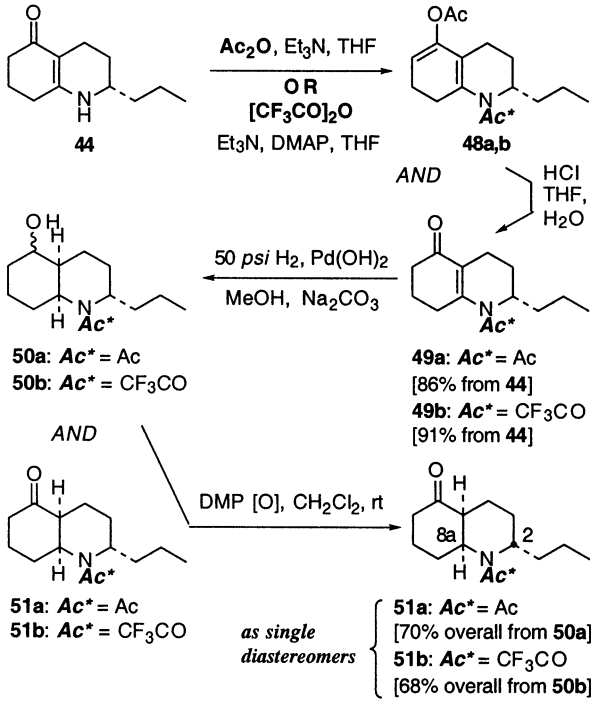
Scheme 10



entail (1) removal of the chiral inducing group that was not trivial and (2) a stereoselective reduction of the C4a−C8a tetrasubstituted olefin.

As shown in Scheme 10, the dihydropyridine **7** could be readily brought up in large quantities, and an ensuing hydrogenation would give **45** in 94% yield. Tebbe's olefination[28] was attempted on the vinylogous amide carbonyl of **45** but failed to give any olefination product **46**. Removal of the TBS group followed by hydrogenation using $Pd(OH)_2$ and NH_4OCHO[29] at 140 °C successfully gave the key 1-azadecalinone **44** in 68% overall yield from **7**. The C3−C4 olefin in **7** was quickly removed at first due to the fear of ring opening under various reaction conditions, leading to loss of stereointegrity at C2. However, a more efficent sequence via TBAF desilylation of **7** followed by a single hydrogenation using NH_4OCHO and $Pd(OH)_2$ could be carried out to afford **44** in 70% overall yield from **7**, and the stereointegrity at C2 of **44** did not appear to suffer.

Scheme 11



Attempts to hydrogenate **44** using various conditions failed but led to the speculation that the nitrogen atom may need to be protected. Capping the nitrogen atom could be achieved using either Ac_2O or TFAA to give **49a** and **49b** (Scheme 11). In the case of using Ac_2O, some enol acetate **48a** was also found but could be readily hydrolyzed to **49a** under mild acidic conditions. Having protected the vinylogous amide nitrogen, high-pressure hydrogenation of **49a** and **49b** proceeded smoothly to give a mixture of alcohols **50a** and **50b** and ketones **51a** and **51b**, respectively. Further Dess−Martin periodinane (DMP) oxidation of the respective mixtures gave **51a** in 70% overall yield from **49a** and **51b** in 68% overall yield from **49b**. Both **51a** and **51b** were isolated as single diastereomers, and no detectable amount of the corresponding minor isomers was observed in ^{1}H NMR. This completes a highly stereoselective transformation of the dihydropyridine **7** to *cis*-1-azadecalins **51a** and **51b**.

The stereochemical outcome deserves some comments since the relative stereochemistry based on nOe experiments (see Supporting Information) revealed that it is anti at C2 and C8a in **51a** and **51b**. Evidently, out of four possible conformations of **49a** (or **49b**), the conformer D clearly predominated to provide the observed stereochemistry in the hydrogenation (Figure 5). Conformer D is favored (Spartan AM1 calculations: a minimum of 2.01 kcal mol^{-1} over conformers A−C) because it alleviates much of the well-known pseudo $A^{1,2}$ strain (or the gauche interaction) between the *N*-acyl group and the *n*-Pr group at C2.[30] This presents a rare and highly stereoselective entry to such anti relative stereochemistry at C2 and C8a of *cis*-1-azadecalins.

cis-1-Azadecalinones **51a** and **51b** could be further elaborated to provide (−)-4*a*,8*a*-*diepi*-pumiliotoxin along with 2-*epi*-(+)-

(28) (a) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *109*, 3270.
(29) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.
(30) Kolocouris, A.; Outeirino, J. G.; Anderson, J. E.; Fytas, G.; Foscolos, G. B.; Kolocouris N. *J. Org. Chem.* **2001**, *66*, 4989.

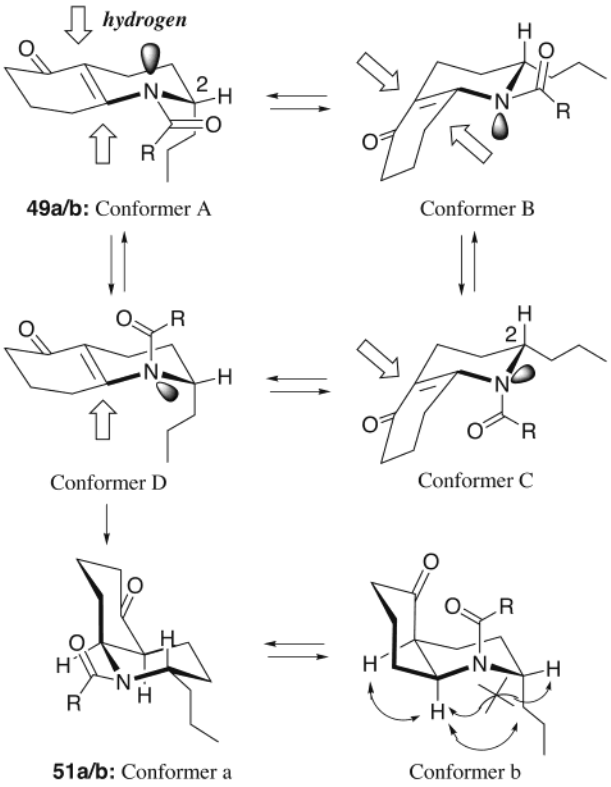


Figure 5. Proposed hydrogenation mechanism.

pumiliotoxin C,[20] thereby illustrating synthetic potential of this formal [3 + 3] cycloaddition methodology in constructing *cis*-1-azadecalin related natural products.

Conclusion

We have described here mechanistic evidence for the first highly stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes, a key step in formal [3 + 3] cycloaddition or annulation reactions of chiral vinylogous amides with α,β-unsaturated iminium salts. We have unambiguously demonstrated that the 6π-electron electrocyclic ring closure is reversible, leading to the thermodynamically more stable major isomer and that a rotation preference also plays a role in this stereoselective ring closure. A synthetic application is illustrated here to transform the resulting dihydropyridines to *cis*-1-azadecalins with unique anti relative stereochemistry at C2 and C2a, leading to an efficient synthesis of epi isomers of (−)-pumiliotoxin C.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and copies of ^{1}H NMR (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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