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A Novel and Highly Stereoselective Approach to Aza-Spirocycles. A Short Total Synthesis of 2-*epi*-(±)-Perhydrohistrionicotoxin and an Unprecedented Decarboxylation of 2-Pyrones

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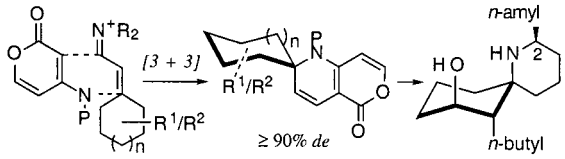
ABSTRACT

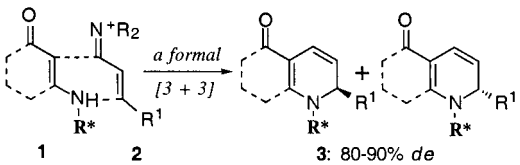


A novel and highly stereoselective synthesis of aza-spirocycles is described. An application of this methodology is illustrated as a short and concise total synthesis of 2-*epi*-(±)-perhydrohistrionicotoxin with high diastereomeric control at the aza-spirocenter. An unprecedented decarboxylation of the 2-pyrone ring is observed in this total synthesis effort.

Annulation reaction of vinylogous amides **1** with α,β-unsaturated iminium salts **2** represents a highly convergent approach to dihydropyridines **3** (Scheme 1).[1−3] This reaction involves a Knoevenagel condensation followed by a 6π-electron electrocyclic ring closure of the 1-azatriene intermediate.[4] This sequential anionic−pericyclic strategy[5] constitutes a stepwise formal [3 + 3] cycloaddition[6−8] in which two σ-bonds are constructed in addition to a new stereocenter adjacent to nitrogen. Not only have we demonstrated that

Scheme 1

Approach I: chiral vinylogous amides



1 **2** **3**: 80-90% *de*

R* = chiral group — *highly stereoselective*

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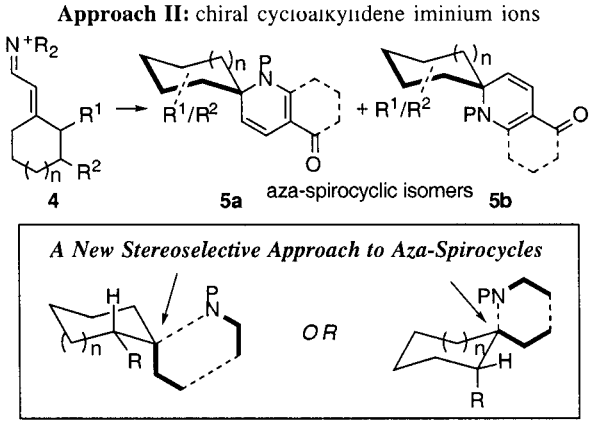
(1) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.
(2) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J.; Mulder, J. A. *Org. Lett.* **2000**, *2*, 1161.
(3) For applications in natural product synthesis, see: (a) Zehnder, L. R.; Hsung, R. P.; Wang, J.-S.; Golding, G. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3876. (b) McLaughlin, M. J.; Hsung, R. P. *J. Org. Chem.* **2001**, *42*, 1049. (c) Wang, J.; Cole, K. P.; Wei, L. L.; Zehnder, L. R.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 3337. (d) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 3341.
(4) For electrocyclic ring closures involving 1-oxa- or 1-aza-trienes, see: (a) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943. (b) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763.
(5) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; *Angew. Chem.* **1993**, *105*, 137.
(6) (a) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. In *Trends in Heterocyclic Chemistry*; Research Trends: Poojapura, Trivandrum, India, 2001; Vol. 7, pp 1−24. (b) For [3 + 3] carbocycloaddition, see: Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27. Also see: (c) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (d) Landesman, H. K.; Stork, G. *J. Am. Chem. Soc.* **1956**, *78*, 5129.

this reaction can be rendered intramolecular,[9] but more significantly, a highly stereoselective variant of this reaction (**1** + **2** → **3**) was recently unveiled using chiral vinylogous amides.[2]

Using cycloalkylidene α,β-unsaturated iminium salts in this formal cycloaddition has efficiently led to aza- and oxa-spirocycles.[1,10] However, it has not been possible to achieve good diastereomeric control at the new hetero spirocenter.[11] Achieving such a diastereomeric control would signify a novel and stereoselective formation of hetero spirocenters, particularly the aza-spirocenter (**4** → **5a/b** in Scheme 2).[12]

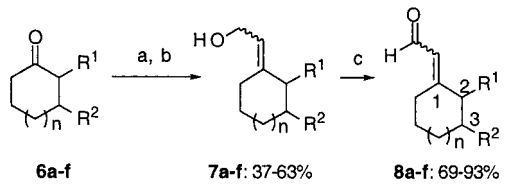
Scheme 2



We report here this highly diastereoselective approach to aza-spirocycles, an application to total synthesis of 2-*epi*-(±)-perhydrohistrionicotoxin, and an unprecedented decarboxylation of 2-pyrones.

To demonstrate the feasibility of such a stereoselective approach to aza-spirocycles, a variety of cycloalkylidene α,β-unsaturated aldehydes **8a**−**f**,[13] precursors to iminium salts **9a**−**f** that contain a substituent at either C-2 or C-3 position, were prepared from corresponding cycloalkanones **6a**−**f** in three efficient steps (Scheme 3). Cycloalkylidene α,β-unsaturated iminium salts **9a**−**f**, prepared from **8a**−**f** using piperidine and Ac_2O, were reacted with aminopyrones **10**, and **15**−**17**[14] (Table 1).

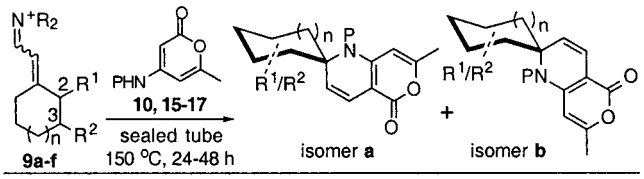
Scheme 3[a]



[a] (a) NaH, $(EtO)_2POCH_2COOEt$, THF, reflux, 4 h; (b) DIBAL-H, CH_2Cl_2, 0 °C, 2 h; (c) Dess-Martin periodinane, CH_2Cl_2, rt, 30 min.

Cyclopentylidene α,β-unsaturated iminium salts **9a** and **9b** gave encouraging but different results. The C-2 methyl group of **9a** effectively led to aza-spirocycle **11** with a

Table 1



entry	iminium ions[a]	pyrones	products	yield[b]	a : b[c]
1	**9a**: R^1 = Me; R^2 = H; n = 0	**10** P = Bn	**11**	82%	90 : 10
2	**9b**: R^1 = H; R^2 = Me; n = 0	**10**	**12**	72	50 : 50
3	**9c**: R^1 = Me; R^2 = H; n = 1	**10**	**13**	85	> 95 : 5
4	**9d**: R^1 = Bu; R^2 = H; n = 1	**10**	**14**	63[d]	≥ 96 : 4
5	**9c**	**15**: P = Me	**18**	74%	95 : 5
6	**9a** or **9c** n = 0 or 1	**16**: P = $CHPh_2$	**19**	ND[d]	–
7	**9c** n = 1	**17**: P = Ac	**20**	ND[d]	–
8	**9e**: R^1 = H; R^2 = Me [*R*] n = 1	**10**	**21**[e]	69	≥ 96 : 4
9	**9e**	Note f	**22**	69	70 : 30[f]
10	**9f**: R^1 = Me; R^2 = H; n = 2	**10**	**23**	57	85 : 15

[a] Iminium salts were generated using 1.0 equiv of piperidine and 1.0 equiv of Ac_2O at 85 °C for 1 h. Reaction time is 62 h for entry 5. [b] Isolated yields. [c] Rations were determined using $^1H/^{13}C$ NMR. Stereochemistry was assigned via X-ray of **14** and **21**, NOE, and ^1H NMR correlations. [d] At 250 °C. ND: not detected. [e] $[\alpha]^{20}_D = 55.0°$. [f] 6-Methyl-4-hydroxy-2-pyrone was used. Stereochemistry of **22** was unassigned [ref 11].

(7) For recent notable studies, see: (a) Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, 49. (b) Hua, D. H.; Chen, Y.; Sin, H.-S.; Robinson, P. D.; Meyers, C. Y.; Perchellet, E. M.; Perchellet, J.-P.; Chiang, P. K.; Biellmann, J.-P. *Acta Crystallogr.* **1999**, *C55*, 1698 and reference therein. (c) Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493. (d) Moorhoff, C. M. *Synthesis* **1997**, 685. (e) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473. (f) Heber, D.; Berghaus, Th. *J. Heterocycl. Chem.* **1994**, *31*, 1353.

(8) For some earlier studies, see: (a) de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 1369. (b) Tietze, L. F.; Kiedrowski, G. v.; Berger, B. *Synthesis* **1982**, 683. (c) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, *16*, 3407.

(9) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516.

(10) (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (b) Zehnder, L. R.; Dahl, J. W.; Hsung, R. P. *Tetrahedron Lett.* **2000**, *41*, 1901.

(11) McLaughlin, M. J.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609.

(12) Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370.

(13) New compounds are characterized by ^1H and ^{13}C NMR, IR, and MS. See Supporting Information for procedures and yields.

90:10 diastereomeric ratio (entry 1), whereas the remote C-3 methyl group in **9b** did not influence the stereoselectivity in **12** (entry 2). On the other hand, aza-spirocycles **13** and **14** were obtained as single diastereomers when cyclohexylidene iminium salts **9c** and **9d** were used, respectively (entries 3 and 4). The nitrogen and alkyl groups are *trans* for major isomers of **11**, **13**, and **14**.

The size of the P group in aminopyrones did not appear to affect stereochemical outcome. As shown in entry 5 in Table 1, aminopyrone **15**[14c] with a smaller methyl group on the nitrogen atom also led to **18** in 74% yield with a ratio of 95:5. However, in this case, the minor isomer could be observed when the reaction was prematurely terminated. The minor isomer was found to equilibrate completely to the major isomer after heating in toluene-d_8 at 150 °C for 19 h. While a large dibenzylidene group in aminopyrone **16** effectively shut down the cycloaddition, the aminopyrone **17** containing an acetyl group also appeared to be ineffective in this reaction (entries 6 and 7). These results suggest that a bulky nitrogen substituent does hinder the ring closure of the 1-azatriene intermediate[4b,10a] and that an electron-deficient nitrogen substituent could impede the initial Knoevenagel condensation.

Most intriguingly, enantiomerically pure cyclohexylidene iminium salt **9e** with a C-3 methyl group led to aza-spirocycle **21** as a single diastereomer (entry 8). It is noteworthy that the nitrogen and methyl groups are now *cis* for the major isomer of **21**. This finding is in contrast with not only the result from cyclopentylidene iminium salt **9b** (entry 2) but also the result we obtained earlier using 6-methyl-4-hydroxy-2-pyrone (entry 9).[11] This represents a unique asymmetric construction of aza-spiroundecanes.[12] Finally, cycloheptylidene iminium salt **9f** also effectively gave aza-spirocycle **23**, although in lower diastereoselectivity (entry 10). The generality of this stereoselective reaction is established using vinylogous amide **24** or urethane **26** (derived from tetronic acid **25**) as shown in Scheme 4. Aza-spirocycles **27**−**29** were obtained in good yields as well as high diastereoselectivities.

The diastereoselectivity is most likely determined during 6π-electron electrocyclic ring closure of 1-azatriene intermediates **30**/**31** and **32**/**33** derived from the initial Knoevenagel condensation of the amino pyrone **10** with cycloalkylidene iminium salts **9c** and **9e**, respectively (Figure 1). Both sets of 1-azatrienes **30**/**31** and **32**/**33** represent two possible conformers with **30** or **32** having either R^1 or R^2 in an equatorial position and with **31** or **33** having either R^1 or R^2 in an axial position for each set. PM3 calculations indicate that the 1-azatriene conformers **30** and **31** (R^1 = Me and R^2 = H) are quite comparable energetically (~0.11 Kcal mol^{-1} in favor of **31**) presumably because **30** experiences some $A^{1,3}$ strain at the exocyclic olefin and **31** suffers from flagpole interactions. On the other hand, the 1-azatriene conformer **32** (R^1 = H and R^2 = Me) is favored over **33** by 1.12 Kcal mol^{-1} given a stronger equatorial preference for the R^2 group in **32**.

From the onset, on the basis of a similar assumption made by Stork regarding a preferred equatorial approach of the nitrogen atom in an imino allyl sulfide [2,3] sigmatropic rearrangement,[15] these equilibrating conformers could have played a significant role in the stereochemical outcome as observed in our previous work using 4-hydroxy-2-pyrones.[11] However, in these current reactions using amino pyrones, both aza-spirocycles **13** and **21** were obtained in high diastereoselectivity (in favor of the stereoisomer **a**) independent of the initially preferred conformation of 1-azatrienes. Thus, it could be more cleanly explained that the observed high stereoselectivity for these reactions is a result of thermodynamic control based on the reversibility of such pericyclic ring closures.[2] This mechanistic assertion is supported by the aforementioned equilibration study using **18**. In addition, AM1 calculations indicate that the aza-spirocycle **18a** is favored over **18b** by 2.8 Kcal mol^{-1}, while **13a** is more favored by 4.2 Kcal mol^{-1}.

To demonstrate synthetic potential of this new approach to aza-spirocycles, cyclohexylidene α,β-unsaturated iminium salt **34** was obtained from 2-cyclohexenone in 51% overall

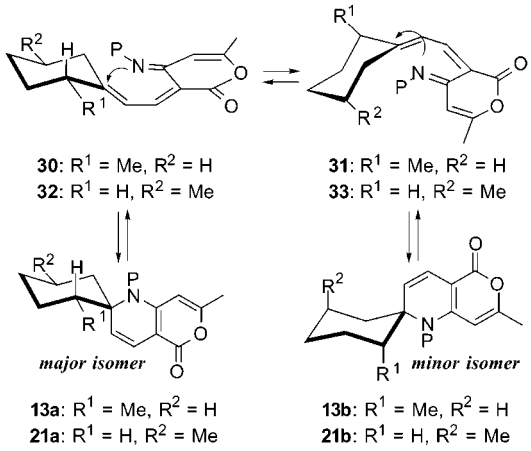
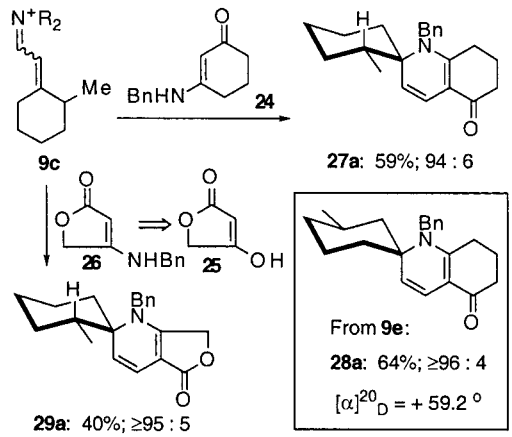


Figure 1. Equatorial approach of the N atom during ring closure.

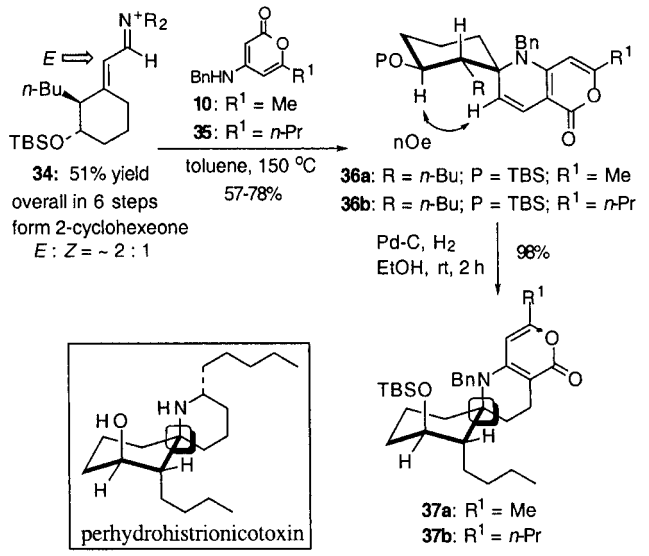
Scheme 4



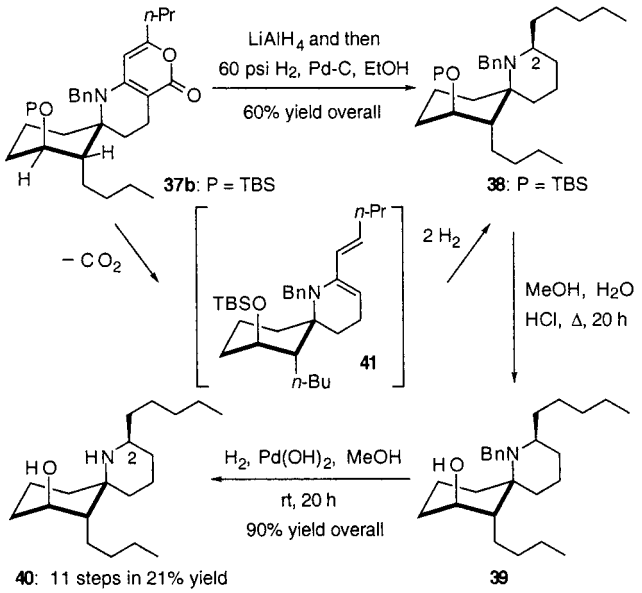
(14) (a) Cervera, M.; Moreno-Mañas, M.; Pleixats, R. *Tetrahedron* **1990**, *46*, 7885. (b) Sato, A.; Morone, M.; Azuma, Y. *Heterocycles* **1997**, *45*, 2209. (c) Cimarelli, C.; Palmieri, G. *Tetrahedron* **1997**, *53*, 6893.

(15) Cvetovich, R. J. *Diss. Abstr. Int. B.* **1979**, *39*(8), 3837; *Chem. Abstr.* **1979**, *90*, 186758q.

Scheme 5



Scheme 6



yield for the six steps[16,17] with an *E:Z* ratio of 2:1 (Scheme 5). The *E*-isomer of **34** (readily separable from the *Z*-isomer) reacted with **10** and **35**[18] to give aza-spirocycles **36a** and **36b** in 57−78% yield as single diastereomers unambiguously assigned using NOE experiment. Hydrogenation of **36a** and **36b** led to **37a** and **37b** quantitatively, thereby furnishing in a very short sequence three contiguous stereocenters of perhydrohistrionicotoxin.[12,19−22] In comparison to known approaches to this natural product,[12,20−22] this represents a novel approach to aza-spiroundecane ring systems with a high level of diastereomeric control at the aza-spiro center.

Transformation of the 2-pyrone ring of **37b** to the desired simple *n*-amyl side chain proved to be challenging. However, we encountered a unique if not unprecedented decarboxylation protocol when **37b** was treated with LAH. After a simple quenching with ethanol followed by filtration through Celite, the crude mixture was subjected to 60 psi of H_2 in the presence of Pd−C (Scheme 6). The product **38** was isolated in a repeatable manner with a consistent yield in the range of 40−60%. The compound **38** was not unambiguously assigned until the subsequent acidic desilylation followed by debenzylation of **39** using Pearlman's catalyst led to 2-*epi*-(±)-perhydrohistrionicotoxin **40**[22] in 90% overall yield. This completes an 11-step total synthesis of **40** in 21% yield.

It is not clear, however, how the decarboxylation of the 2-pyrone ring had occurred. To simply balance the equation, losing CO_2 from **37b** could give an amino diene intermediate **41**, and addition of 2 equiv of hydrogen would then lead to **38**. Although any discussions at this point are all quite speculative, the presence of this amino diene intermediate **41** does lend support to the observed stereochemical outcome in the hydrogenation. The subsequent hydrogenation of **41** should occur from the back face away from the TBSO (and/or *n*-Bu) group, leading to **38** with an exclusive *epi* stereoselection at C2.

We have described here a highly stereoselective and novel approach to aza-spirocycles. An application toward synthesis of 2-*epi*-perhydrohistrionicotoxin was completed with the finding of an unprecedented decarboxylation of the 2-pyrone ring. Efforts toward synthesis of relevant spirocyclic nitrogen alkaloids and understanding of this decarboxylation process are underway.

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Supporting Information Available: Experimental procedures, NMR spectral characterization data, and X-ray data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Wender, P. A.; Erhardt, J. M.; Letendre, L. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

(17) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427.

(18) The *N*-benzyl aminopyrone **35** was prepared by treating 4-trimethylsilyloxy-6methyl-2-pyone with *n*-BuLi followed by quenching with EtI. Subsequent transformation to the corresponding *N*-benzyl aminopyrone was carried according to ref 14a.

(19) For isolation, see: Daly, J. W.; Karle, I.; Myer, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci.* U.S.A. **1971**, *68*, 1870.

(20) For the first syntheses of (±)-perhydrohistrionicotoxin, see: (a) Coery, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (b) Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009.

(21) For recent efforts in total synthesis of perhydrohistrionicotoxin or histrionicotoxin, see: (a) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (b) Comins, D. L.; Zhang, Y.-M.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1998**, 2509. (c) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. (d) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (e) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (f) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852. (g) Tanner, D.; Sellén, M.; Bäckvall, J.-E. *J. Org. Chem.* **1989**, *54*, 3374. (h) Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B. *J. Org. Chem.* **1989**, *54*, 4419. For the first synthesis of (±)-histrionicotoxin, see: (i) Carey, S. C.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, *26*, 5887.

(22) For matching the characterization 2-*epi*-(±)-perhydrohistrionicotoxin, see: Takahashi, K.; Wiktop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *6*, 252.