JOC Article
pubs.acs.org/joc

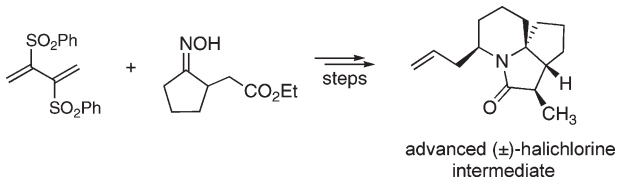
2,3-Bis(phenylsulfonyl)-1,3-butadiene as a Reagent for the Synthesis of the Azatricyclic Core of (±)-Halichlorine

Andrew C. Flick, Maria José Arevalo Caballero, Hyoung Ik Lee, and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

Received January 13, 2010



An efficient stereocontrolled route to the azatricyclic core of an advanced halichlorine intermediate is described. Reaction of the oxime derived from 2-(oxo-cyclopentyl)acetic acid ethyl ester with 2,3-bis(phenylsulfonyl)-1,3-butadiene gives rise to a 7-oxa-1-azanorbornane cycloadduct in high yield. The formation of the bicyclic isoxazolidine arises from conjugate addition of the oxime onto the diene to afford a transient nitrone that then undergoes an intramolecular dipolar cycloaddition. Treatment of the cycloadduct with 5% Na/Hg results in reductive nitrogen−oxygen bond cleavage to furnish a spirocyclic piperidinone, which was further elaborated to an advanced intermediate employed in an earlier synthesis of halichlorine.

Introduction

Over the past several years, our research group has developed a tandem conjugate addition/dipolar cycloaddition protocol that generates 2,2-disubstituted 4-piperidinones of type **4**.[1−5] In this cascade sequence, a bicyclic isoxazolidine **3** is first formed by conjugate addition of an oxime with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**)[2] to produce the transient nitrone **2**, which then undergoes a further intramolecular 1,3-dipolar cycloaddition onto the adjacent vinyl sulfone. Raney-Ni reduction of the 7-oxa-1-azanorbornane cycloadduct **3** results in sequential nitrogen−oxygen bond cleavage followed by a subsequent desulfonylation to furnish the 2,2-disubstituted 4-piperidinone (Scheme 1). This reaction sequence proved to be very effective for the synthesis of several alkaloids and related nitrogen-containing heterocyclic compounds.[3−5] Thus, by using this protocol, we have accomplished the total synthesis of (±)-cylindricine C,[3] yohimbenone[4] as well as 2,7,8-epi-perhydrohistrionicotoxin.[5] Since oximes possessing functionalized substituent groups on the side chain are particularly appealing for the cascade sequence, we became interested in making further use of this operation for the synthesis of other alkaloidal skeletons. In this paper we demonstrate that the methodology based on conjugate addition/dipolar cycloaddition can facilitate the rapid assembly of the central tricyclic core structure of halichlorine.

Results and Discussion

Halichlorine (**5**) is an alkaloid that was isolated from the marine sponge *Halichondria okadai* Kadota in 1996 by Uemura and co-workers.[6] The 15-membered macrolide has been shown to significantly inhibit vascular cell adhesion with reasonable efficiency.[6,7] Two structurally related alkaloids, pinnaic acid (**6**) and tauropinnaic acid (**7**), were discovered later by the Uemura group (Figure 1).[8] Owing to their intriguing structures and biological activity, these

(1) (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett*. **1988**, *29*, 2417. (b) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem*. **1991**, *56*, 2154.
(2) Padwa, A.; Watterson, S. H.; Ni, Z. *Org. Synth*. **1997**, *74*, 147.
(3) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett*. **2008**, *10*, 1871.
(4) Stearman, C. J.; Wilson, M. S.; Padwa, A. *J. Org. Chem*. **2009**, *74*, 3491.
(5) Wilson, M. S.; Padwa, A. *J. Org. Chem*. **2008**, *73*, 9601.
(6) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett*. **1996**, *37*, 3867.
(7) (a) Bevilacqua, M. P.; Nelson, R. M.; Mannori, G.; Cecconi, O. *Annu. Rev. Med*. **1994**, *45*, 361. (b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068. (c) Foster, C. A. *J. Allergy Clin. Immunol*. **1996**, *98*, S270. (d) Yusuf-Makagiansar, H.; Anderson, M. E.; Yakovleva, T. V.; Murray, J. S.; Siahaan, T. J. *Med. Res. Rev*. **2002**, *22*, 146.
(8) (a) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett*. **1996**, *37*, 3871. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett*. **1998**, *39*, 861.

Published on Web 02/12/2010 DOI: 10.1021/jo100055u

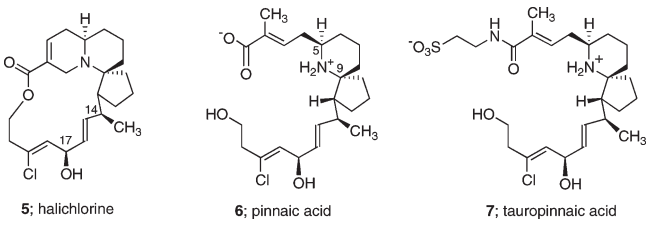
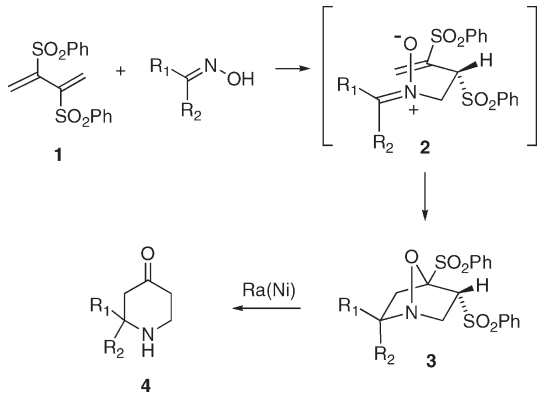


FIGURE 1. Natural products containing 6-azaspiro[4.5]decane.

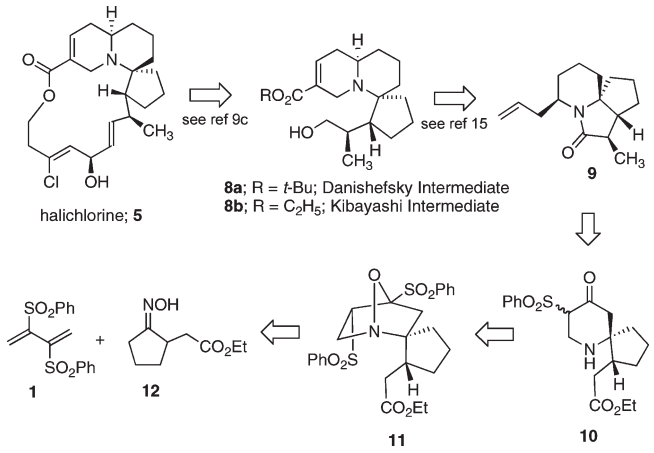
SCHEME 1



natural products have received considerable attention from members of the synthetic community. Since the first total synthesis of halichlorine (**5**) by the Danishefsky group,[9c] two other syntheses have been reported by Heathcock[10] and more recently by Clive.[11] Numerous approaches to **5** have also been reported and have dealt primarily with the construction of the 6-azaspiro[4.5]decane skeleton[12] and with formal syntheses[13] reliant on the Danishefsky route.[9] We were attracted to a synthesis of halichlorine in the more general context of our longstanding interest in developing new cycloaddition approaches to alkaloid natural products.[14] The 6-azaspiro[4.5]decane core embedded within halichlorine served as our inspiration for a possible synthetic route which is based on the conjugate addition/dipolar cycloaddition strategy. The essential elements of our plan are outlined in retrosynthetic format in Scheme 2.

The lactone belt of halichlorine (**5**) can eventually be installed via Danishefsky's intermediate **8a**, an advanced compound that was used by his group in the total synthesis[9c]

SCHEME 2



and that contains three of the five stereogenic centers of the natural product. This spirocycle can, in turn, be envisioned to be derived from the tricyclic lactam **9**, a species that encompasses the 6-azaspiro[4.5]decane core of the target molecule. Lactam **9** had previously been converted by Feldman[15] to another advanced intermediate **8b** used by the Kibayashi group[13b] in their approach to Danishefsky's intermediate **8a**.[9c] We felt as though compound **9** could be easily derived from piperidin-4-one **10**, a direct product of the reductive cleavage of isoxazolidine **11**. By analogy with our earlier studies, we reasoned that this 7-oxa-1-azanorbornane intermediate could be readily accessed from the conjugate addition/cycloaddition protocol using oxime **12** and butadiene **1**. Thus, our immediate goal was directed toward the preparation of lactam **9**,[13b,15] which we viewed as an engaging intermediate for an eventual synthesis of halichlorine (**5**). To establish the underlying feasibility of our strategy to access the tricyclic skeleton of **9**, oxime **12** was heated with bis(phenylsulfonyl)-1,3-butadiene (**1**) in refluxing toluene for 24 h. The resulting cascade sequence gave rise to a 1.3:1 mixture of diastereomeric cycloadducts **11** in 95% yield. Considering that the construction of the 7-oxa-1-azanorbornane core is highly stereoselective,[1] four diastereomers are thus possible from this reaction cascade, but only two cycloadducts were formed, which were readily separable by silica gel chromatography. More than likely, steric repulsion between the attached CH_2CO_2Et side chain and the adjacent substituents on the norbornane skeleton prevents formation of the more sterically crowded diastereomers. Although the assignment is tentative, we believe that the major diastereomer **11a** has the CH_2CO_2Et group oriented in the less congested *exo* orientation. The mixture of diastereomers was then reduced under controlled conditions with sodium amalgam to furnish the expected phenylsulfonyl substituted piperidin-4-one **10**, also as a mixture of diastereomers. Further reduction of the phenylsulfonyl group present in **10** could be carried out using radical reduction conditions[16] (i.e., n-Bu_3SnH, AIBN) that afforded the tricyclic amide **13** in good yield and possessing the relative configuration required for the halichlorine framework (Scheme 3).

(9) (a) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450. (b) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453. (c) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (d) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344.

(10) Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079.

(11) Liu, D.; Acharya, H. P.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S.; Chiruta, C.; Jachak, S. M.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 7417.

(12) Review: (a) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483. (b) Roulland, E.; Chiaroni, A.; Husson, H.-P. *Tetrahedron Lett.* **2005**, *46*, 4065. (c) Keck, G. E.; Heumann, S. A. *Org. Lett.* **2008**, *10*, 4783. (d) Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4131. (e) Sinclair, A.; Arini, L. G.; Rejzek, M.; Szeto, P.; Stockman, R. A. *Synlett* **2006**, 2321. (f) Yang, S.-H.; Caprio, V. *Synlett* **2007**, 1219.

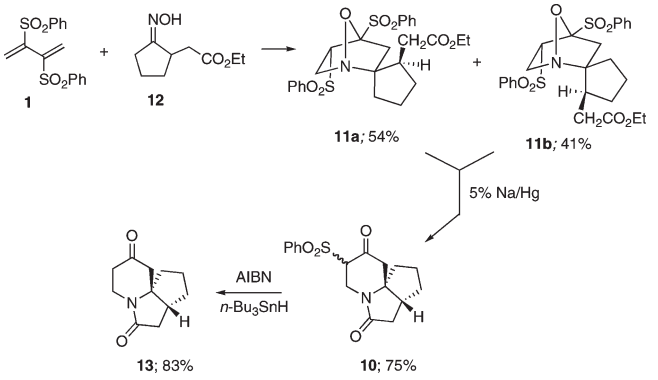
(13) (a) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441. (b) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2004**, *6*, 965. (c) Zhang, H.-L.; Zhao, G.; Ding, Y.; Wu, B. *J. Org. Chem.* **2005**, *70*, 4954. (d) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733. (e) Wu, H.; Zhang, H.; Zhao, G. *Tetrahedron* **2007**, *63*, 6454.

(14) Padwa, A. *J. Org. Chem.* **2009**, *74*, 6421.

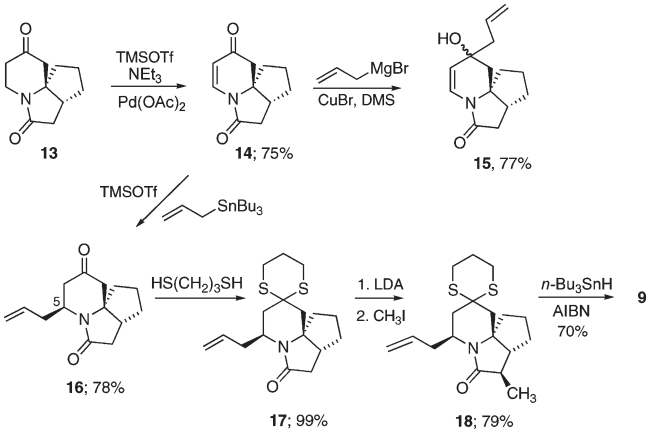
(15) Feldman, K. S.; Perkins, A. L.; Masters, K. M. *J. Org. Chem.* **2004**, *69*, 7928.

(16) Smith, A. B.; Hale, K. J.; McCauley, J. P. *Tetrahedron Lett.* **1989**, *30*, 5579.

SCHEME 3



SCHEME 4



Our construction of the critical tricyclic lactam **9** from **13** is presented in Scheme 4. Introduction of the allyl group adjacent to the nitrogen atom was believed to be possible by an initial oxidation of **13** to the corresponding 2,3-dihydropyridin-4(1*H*)-one **14** followed by a conjugate addition of allyl cuprate in order to introduce the necessary side chain. We were pleased to find that dihydro-4-pyridin-4(1*H*)-one **14** could be easily obtained in 75% yield from **13** under Saegusa oxidation conditions.[17] Surprisingly, the reaction of allyl cuprate with **14** gave only the 1,2-addition product **15** as a 1:1 mixture of diastereomers. However, when **14** was allowed to react with allyl stannane and TMSOTF, the desired conjugate addition product **16** was obtained in 78% yield as a 15:1 mixture of diastereomers. The major diastereomer formed can be attributed to approach of the stannyl group from the convex face of the tricyclic system, thereby leading to the requisite stereogenicity at the C_5 center. Reaction of 4-piperidonone **16** with 1,3-propane thiol gave in nearly quantitative yield the expected dithiane **17**, which underwent smooth alkylation with LDA/CH_3I from the least-hindered convex face to furnish **18** in 79% yield. Reduction of **18** with *n*-Bu_3SnH/AIBN afforded the desired tricyclic lactam **9**, whose spectral properties were identical to those reported by Feldman.[15] Thus, acquisition of this advanced intermediate sets the stage for completion of the synthesis of halichlorine in the near future.

In summary, the central tricyclic core of an advanced halichlorine intermediate has been synthesized through the use of a conjugate addition/dipolar cycloaddition cascade between 2,3-bis(phenylsulfonyl)-1,3-butadiene and the oxime derived from 2-(oxocyclopentyl)acetic acid ethyl ester.

Experimental Section

(2-Hydroxyiminocyclopentyl)acetic Acid Ethyl Ester (12). To a round-bottom flask charged with 1.0 g (5.9 mmol) of (2-oxocyclopentyl)acetic acid ethyl ester[18] in 25 mL of ethanol were added 0.82 g (11.8 mmol) of hydroxylamine hydrochloride and 1.4 mL (17.6 mmol) of pyridine. The solution was allowed to stir at rt for 24 h and was then concentrated under reduced pressure. The resulting reside was taken up in ethyl acetate and transferred to a separatory funnel. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give 0.97 g (89%) of oxime **12** as a colorless oil: IR ($CHCl_3$) 3298, 2956, 1677, and 930 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.25 (t, $J = 6.8$ Hz, 3H), 1.34−1.44 (m, 1H), 1.58−1.70 (m, 1H), 1.84−1.91 (m, 1H), 2.32−2.45 (m, 2H), 2.55−2.74 (m, 1H), 2.70 (dd, $J = 16.4$ and 5.2 Hz, 1H), 2.87−2.91 (m, 1H), 4.12 (q, $J = 6.8$ Hz, 2H), and 8.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 22.4, 27.0, 31.9, 36.6, 39.6, 60.4, 167.3, and 172.4.

Formation of Cycloadduct 11. To a solution containing 2.0 g (10.8 mmol) of oxime **12** in 50 mL of toluene was added 3.6 g (10.8 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**)[2] and the mixture was heated at reflux for 24 h, cooled to rt, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 5.6 g (95%) of a 1.3:1 diastereomeric mixture of cycloadducts **11**. The two diastereomers were separated by silica gel chromatography, and the major isomer **11a** could be obtained pure as a colorless oil: IR (neat) 2965, 1729, and 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H, $J = 7.6$ Hz), 1.56−1.78 (m, 5H), 1.80−1.92 (m, 2H), 2.02 (dd, 1H, $J = 15.6$ and 3.6 Hz), 2.09 (dd, 1H, $J = 12.8$ and 2.4 Hz), 2.14−2.22 (m, 1H), 3.24 (d, 1H, $J = 12.8$ Hz), 3.66 (dd, 1H, $J = 12.4$ and 10.8 Hz), 3.83 (dd, 1H, $J = 12.4$ and 4.8 Hz), 4.00 (dd, 1H, $J = 7.2$ and 2.0 Hz), 4.04 (dd, 1H, $J = 7.2$ and 2.0 Hz), 4.33 (ddd, 1H, $J = 10.8$, 4.8, and 2.0 Hz), 7.53 (t, 2H, $J = 7.6$ Hz), 7.60−7.70 (m, 3H), 7.73 (t, 1H, $J = 7.6$ Hz), 7.78 (d, 2H, $J = 7.6$), and 7.98 (d, 2H, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.3, 28.7, 31.4, 34.4, 40.5, 48.2, 55.0, 60.0, 66.5, 80.2, 103.9, 128.3, 128.8, 129.0, 129.3, 130.2, 134.2, 134.6, 134.8, 139.1, and 173.0; HRMS calcd for [$C_{25}H_{29}NO_7S_2 + H^+$] 520.1464, found 520.1460.

The minor isomer could not be completely separated from the major isomer, and so the above 1.3:1 mixture was used in the next step.

7-Benzenesulfonylhexahydro-5a-aza-cyclopenta[*c*]indene-5,8-dione (10). To a solution containing 2.6 g (5.0 mmol) of the above cycloadduct **11** in 100 mL of THF was added 5.8 g (12.5 mmol) of 5% Na/Hg at rt. The mixture was stirred at rt for 12 h, and then 30 mL of a 1 N solution of HCl was added. The resulting mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1.25 g (75%) of an inseparable 1:1 diastereomeric mixture of phenylsulfonyl substituted piperidin-4-one **10** as a pale yellow oil: IR (neat) 2943, 1716, and 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44−1.55

(17) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635. (c) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.

(18) Molander, G. A.; Harris, C. R. J. *Am. Chem. Soc.* **1995**, *117*, 3705.

(m, 2H), 1.56−1.76 (m, 3H), 1.96−2.07 (m, 1H), 2.22−2.30 (m, 1H), 2.43−2.52 (m, 1H), 2.58 (dd, 1H, J = 13.2 and 0.8 Hz), 2.95 (dd, 1H, J = 17.6 and 10.0 Hz), 3.12 (dd, 1H, J = 15.2 and 4.8 Hz), 3.31 (d, 1H, J = 13.2 Hz), 3.73 (d, 1H, J = 4.8 Hz), 4.78 (d, 1H, J = 15.2 Hz), 7.62 (t, 2H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), and 8.02 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 34.3, 35.9, 36.7, 36.9, 41.6, 52.3, 70.7, 72.6, 129.4, 129.6, 134.7, 136.4, 173.7, and 197.3; HRMS calcd for [$C_{17}H_{19}NO_4S + H^+$] 334.1113, found 334.1117.

Hexahydro-5a-aza-cyclopenta[*c*]indene-5,8-dione (13). To a solution containing 1.2 g (3.60 mmol) of the above mixture of substituted piperidin-4-ones in 50 mL of benzene were added 4.8 mL (18 mmol) of *n*-tributyltin hydride and 1.2 g (7.2 mmol) of AIBN. The mixture was heated at reflux for 36 h and then cooled to rt. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography to give 0.58 g (83%) of **13** as a colorless oil: IR (neat) 1729, and 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39−1.55 (m, 2H), 1.60−1.68 (m, 2H), 1.72 (dd, 1H, J = 12.0 and 6.0 Hz), 1.92−2.03 (m, 1H), 2.21 (ddd, 1H, J = 18.0, 3.2, and 1.2 Hz), 2.29−2.46 (m, 4H), 2.53 (d, 1H, J = 13.6 Hz), 2.78 (dd, 1H, J = 18.0 and 10.4 Hz), 2.91 (tdd, 1H, J = 13.6, 5.2, and 0.8 Hz), and 4.44 (ddd, 1H, J = 13.6, 7.6, and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 34.2, 35.6, 35.9, 37.3, 40.1, 41.5, 53.0, 72.6, 172.8, and 206.3; HRMS calcd for [$C_{11}H_{15}NO_2 + H^+$] 194.1181, found 194.1186.

2,3,3*a*,4-Tetrahydro-1*H*-5a-aza-cyclopenta[*c*]indene-5,8-dione (14). To a solution containing 1.7 g (8.8 mmol) of piperidin-4-one **13** in 50 mL of CH_2Cl_2 were added 2.9 mL (21 mmol) of triethylamine and then 1.9 mL (10.6 mmol) of TMSOTf at 25 °C. The solution was stirred at room temperature for 12 h and was subsequently quenched by the addition of 10 mL of a saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to give 1.3 g (75%) of 2,3-dihydropyridin-4(1*H*)-one **14** as a white solid: mp 67−68 °C; IR (KBr) 1705 and 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.62−2.01 (m, 7H), 2.28 (dd, 1H, J = 18.8 and 6.4 Hz), 2.51 (dd, 1H, J = 16.0 and 0.8 Hz), 2.54−2.62 (m, 1H), 2.75 (d, 1H, J = 16.0 Hz), 2.93 (dd, 1H, J = 18.8 and 10.8 Hz), 5.49 (dd, 1H, J = 8.0 and 0.8 Hz), and 7.66 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 32.4, 37.0, 38.1, 41.2, 48.5, 71.5, 109.8, 137.5, 171.4, and 193.7. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.86; N, 7.33. Found: C, 69.13; H, 6.72; N, 7.41.

8-Allyl-8-hydroxy-2,3,3*a*,4,8,9-hexahydro-1*H*-5a-aza-cyclopenta[*c*]inden-5-one (15). To a solution containing 0.12 g (0.6 mmol) of 2,3-dihydropyridin-4(1*H*)-one **14** in 5 mL of THF at −78 °C was added 0.9 g (0.63 mmol) of copper bromide-dimethyl sulfide complex. The resulting mixture was stirred for 20 min at −78 °C, and then 7.6 mL (0.76 mmol) of a 1.0 M solution of allyl magnesium bromide was added. The solution was allowed to warm slowly to 25 °C, and to this mixture was added a saturated solution of NH_4Cl. The resulting mixture was extracted with EtOAc, and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.11 g (77%) of an inseparable 1:1 diastereomeric mixture of alcohols **15** as a colorless oil: IR (neat) 3402, 2948, and 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54−1.66 (m, 3H), 1.70−1.81 (m, 3H), 1.82−1.98 (m, 3H), 2.05 (dd, 1H, J = 13.6 and 1.6 Hz), 2.17 (dd, 1H, J = 18.4 and 6.0 Hz), 2.24−2.34 (m, 2H), 2.39−2.48 (m, 1H), 2.76 (dd, 1H, J = 18.4 and 10.8 Hz), 5.19−5.22 (m, 3H), 5.82 (ddt, 1H, J = 17.2, 10.0, and 7.2 Hz), and 6.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 32.9, 37.1, 38.3, 42.4, 46.6, 47.7, 68.8, 69.1, 115.2, 119.6, 122.8, 132.8, and 172.2.

6-Allyl-hexahydro-5a-aza-cyclopenta[*c*]indene-5,8-dione (16). To a solution containing 0.75 g (3.9 mmol) of 2,3-dihydropyridin-4(1*H*)-one **14** in 15 mL of CH_2Cl_2 at 0 °C were added 1.3 mL (4.3 mmol) of allyltributyltin and 0.8 mL (4.3 mmol) of TMSOTf. After stirring for 1 h at 0 °C, the mixture was warmed to rt and was stirred for an additional 10 min at 25 °C. To this solution was added 10 mL of a 1.0 N solution of HCl, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.87 g (78%) of a 15:1 diasteromeric mixture of piperidin-4-one **16**. The major diastereomer was purified by silica gel chromatography to give 0.74 g (72%) of **16** as a colorless oil: IR (neat) 2958, 1718, 1685, and 1396 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34−1.45 (m, 1H), 1.52−1.66 (m, 1H), 1.69−1.86 (m, 3H), 2.00−2.09 (m, 1H), 2.20−2.48 (m, 7H), 2.57 (dd, 1H, J = 14.8 and 7.6 Hz), 2.74 (dd, 1H, J = 17.2 and 10.4 Hz), 4.67 (ddd, 1H, J = 14.8, 8.4, and 4.0 Hz), 5.04−5.13 (m, 2H), and 5.64−5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 34.0, 37.3, 39.1, 39.3, 42.9, 43.1, 48.8, 53.0, 72.3, 118.4, 133.9, 173.9, and 206.8. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21; N, 6.00. Found: C, 71.94; H, 8.08; N, 6.33.

6-Allyl-hexahydro-5a-aza-cyclopenta[*c*]indene-5,8-dithiaspiro-[5.5]undecane (17). To a solution containing 0.74 g (3.2 mmol) of piperidin-4-one **16** in 12 mL of CH_2Cl_2 at rt were added 0.6 mL (5.5 mmol) of 1,3-propanedithiol and a catalytic amount of $BF_3 \cdot OEt_2$. The solution was stirred for 12 h at rt, and the solvent was then removed under reduced pressure. The crude residue was purified by silica gel chromatography to give 1.03 g (97%) of dithiane **17** as a colorless oil: IR (neat) 2948, 1689, and 1397 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32−1.42 (m, 1H), 1.55−1.74 (m, 2H), 1.76−1.94 (m, 3H), 1.96−2.30 (m, 7H), 2.37 (dd, 1H, J = 14.8 and 6.0 Hz), 2.46 (dt, 1H, J = 14.4 and 8.1 Hz), 2.56−2.68 (m, 2H), 2.68−2.79 (m, 2H), 2.89 (ddd, 1H, J = 14.4, 10.0, and 2.8 Hz), 2.98 (ddd, 1H, J = 14.8, 10.0, and 2.8 Hz), 4.20 (quintet, 1H, J = 7.2 Hz), 5.20−5.13 (m, 2H), and 5.72−5.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 25.4, 26.9, 27.0, 33.4, 36.6, 37.3, 39.3, 41.4, 44.4, 46.3, 48.5, 50.4, 69.7, 117.6, 134.9, and 174.6; HRMS calcd for [$C_{17}H_{25}NOS_2 + H^+$] 324.1456, found 324.1460.

6-Allyl-4-methyl-octahydro-5a-azacyclopenta[*c*]inden-5-one (9). To a solution containing 0.5 mL (3.6 mmol) of diisopropylamine in 10 mL of THF at −78 °C was added 1.5 mL (3.7 mmol) of a 2.5 M solution of *n*-BuLi. After stirring for 30 min, a solution containing 1.0 g (3.2 mmol) of dithiane **17** in 5 mL of THF was added. The mixture was allowed to stir for 30 min at −78 °C, and 21 mL (3.4 mmol) of iodomethane was then added. The solution was stirred at −78 °C for an additional 3 h and was allowed to slowly warm to rt. To this mixture was added a saturated solution of NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.9 g (79%) of 6-allyl-4-methyl-hexahydro-5a-aza-cyclopenta[*c*]inden-5,8-dithiaspiro[5.5]undecane (**18**) as a colorless oil: IR (neat) 2950, 1690, and 1397 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, 3H, J = 7.2 Hz), 1.40−1.49 (m, 1H), 1.58−1.73 (m, 2H), 1.78−1.95 (m, 4H), 1.96−2.08 (m, 3H), 2.14−2.25 (m, 2H), 2.33 (d, 1H, J = 14.4 Hz), 2.39 (dd, 1H, J = 14.0 and 9.2 Hz), 2.50 (dt, 1H, J = 14.0 and 8.4 Hz), 2.61−2.70 (m, 1H), 2.70−2.81 (m, 2H), 2.91 (ddd, 1H, J = 14.4, 10.0, and 2.8 Hz), 3.00 (ddd, 1H, J = 14.8, 10.0, and 2.8 Hz), 4.22 (quintet, 1H, J = 7.2 Hz), 5.03−5.15 (m, 2H), and 5.74−5.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 24.8, 25.6, 26.9, 27.0, 32.1, 36.9, 39.1, 41.4, 43.5, 46.5, 48.4, 51.7, 54.7, 67.8, 117.6, 135.0, and 177.0.

To a solution of 0.34 g (1 mmol) of **18** and 0.58 g (2 mmol) of tri-*n*-butyltin hydride was added 30 mg of AIBN in 5 mL of benzene, and the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel chromatography to give 0.16 g

(70%) of **9** as a pale yellow oil:[15] IR (neat) 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 6.6 Hz), 1.28−1.50 (m, 5H), 1.50−1.87 (m, 7H), 1.90 (m, 1H), 2.15 (m, 1H), 2.65 (dt, 1H, J = 14.3 and 7.5 Hz), 3.20 (m, 1H), 3.35 (dt, 1H, J = 14.3 and 6.5 Hz), 5.05 (dd, 1H, J = 10.0 and 1.0 Hz), 5.13 (dd, 1H, J = 17.0 and 1.5 Hz) and 5.85 (dddd, 1H, J = 17.0, 10.0, 7.5, and 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 22.0, 25.2, 30.8, 32.8, 32.9, 35.4, 36.7, 38.7, 44.5, 51.6, 55.9, 71.6, 116.3, 137.0, and 176.3; HRMS calcd for [$C_{15}H_{23}NO + H^+$] 234.1857, found 234.1854.

Acknowledgment. The financial support provided by the National Science Foundation (CHE-0742663) is greatly appreciated.

Supporting Information Available: ^1H and ^{13}C NMR data of various key compounds lacking CHN. This material is available free of charge via the Internet at http://pubs.acs.org.