JOC*Article*

Alkynyliodonium Salts in Organic Synthesis. Application to the Preparation of the Tricyclic Core of (±)-Halichlorine

Ken S. Feldman,* Angela L. Perkins, and Katherine M. Masters

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

ksf@chem.psu.edu

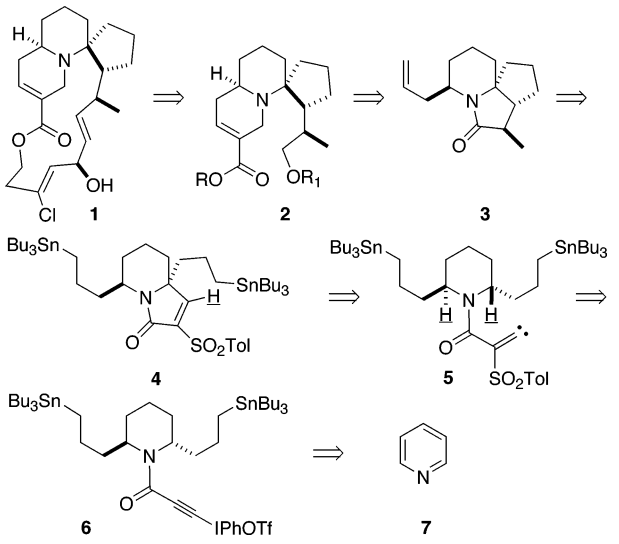
Received July 15, 2004

The tricyclic core of halichlorine has been synthesized through the use of an alkynyliodonium salt/alkylidenecarbene/1,5 C−H insertion sequence that sets the pivotal quaternary center in the target.

Introduction

Alkynyliodonium salts and their derived alkylidenecarbenes provide valuable opportunities for C−C bond formation by carbene insertion into otherwise unactivated C−H bonds.[1] When the scissile C−H bond is positioned on a tertiary carbon, the high energy of the carbene intermediate enables operation in even sterically hindered environments, and insertion with strict retention ensures that quaternary carbon centers can be set with complete control of stereochemistry. A context for exploiting these favorable attributes of alkylidenecarbenes can be found within the tricyclic core of the sponge metabolite halichlorine (**1**).[2] An uncommon selectivity for inhibition of VCAM but not ICAM induction raises the possibility that this unique structure might impact on therapeutic lead development of antiinflammatory agents,[3] and this combination of challenging molecular architecture and intriguing biological activity has stimulated many synthesis approaches[4] and one total synthesis to date.[4a] Alkynyliodonium salt chemistry offers a different perspective on the synthesis of the core of halichlorine, and a distinct strategy toward this target can be envisioned, Scheme 1. The lactone belt of **1** can be installed from the bifunctional tricycle **2**, an advanced intermediate that contains four of the five stereogenic centers of the natural product. This tricycle can, in turn, be assembled from the tricyclic lactam **3**, a species that again encompasses most of the stereochemical information of the target. This lactam might arise from cyclization within the key bicyclic lactam **4**, a direct product of tertiary C−H bond insertion within pseudo-C_2-symmetric piperidine carbene **5**. By analogy with much earlier work, this alkylidenecarbene intermediate should be readily accessed from the simple and symmetrical piperidine alkynyliodonium salt **6**. The conversion of a relatively simple substrate **6** into the more complex bicycle **4**, which features the pivotal *trans*-2,6-piperidine stereochemical relationship required for halichlorine, is a hallmark of alkynyliodonium salt chemistry.

SCHEME 1. Retrosynthesis of Halichlorine



Results and Discussion

The synthesis route commences with pyridine (**7**), which can be processed into *trans*-2,6-diallyltetrahydropyridine (**8**) using allylation conditions described by Bubnov, Scheme 2.[5] Selective functionalization of the

(1) For reviews with leading references, see: (a) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (b) Stang, P. J.; Zhdankin, V. V. *Tetrahedron* **1998**, *54*, 10927. (c) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (d) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.

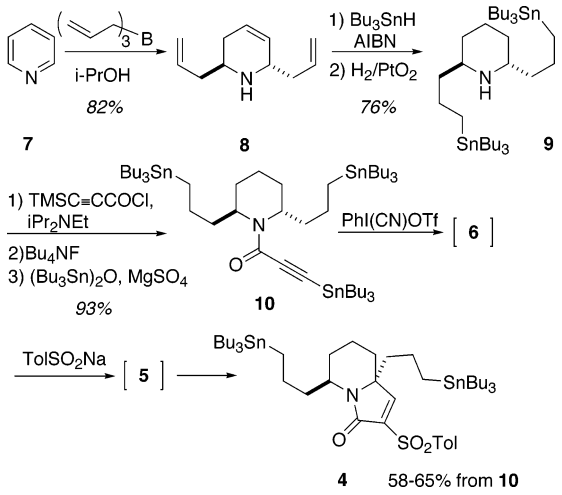
(2) (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.

(3) Foster, C. A. *J. Allergy Clin. Immunol.* **1996**, *98*, S270.

(4) (a) Trauner, D.; Schwartz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (b) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583. (c) Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681. (d) Koviach, J.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (f) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921. (g) Shindo, M.; Fukuda, Y.-i.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929. (h) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (i) Ciblat, S.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2001**, *42*, 4815. (j) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109. (k) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871. (l) Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett.* **2001**, 1506. (m) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249. (n) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017. (o) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2004**, *6*, 965. (p) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879.

10.1021/jo0487911 CCC: $27.50
Published on Web 10/21/2004

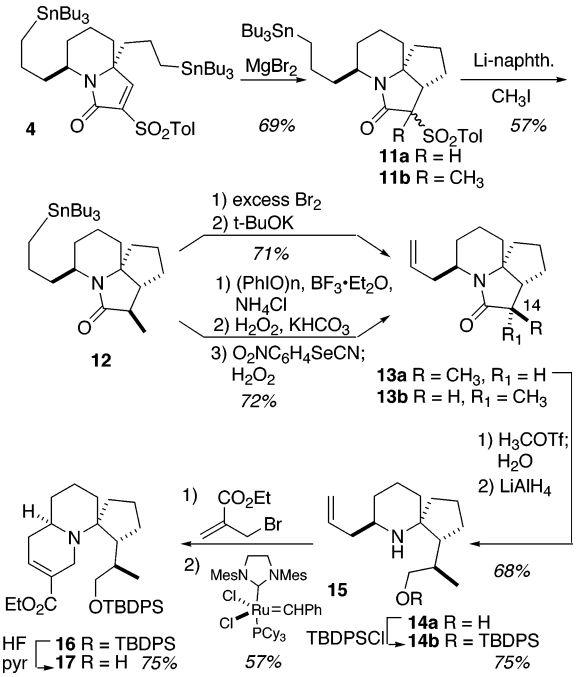
SCHEME 2. Synthesis and Cyclization of Alkynyliodonium Salt 6



terminal alkenes within triene **8** was accomplished via free-radical chemistry. Simply mixing the neat triene **8** with tributyltin hydride and AIBN at 100 °C led to a *trans*-2,6-(tributylstannyl)propyltetrahydropyridine intermediate that was hydrogenated to the piperidine derivative **9**. The product distribution of the tin hydride addition predictably was responsive to concentration, as heating more dilute solutions of Bu_3SnH/**8** led to substantial quantities of bicyclic materials resulting from 5-hexenyl-type radical cyclization of the first-formed secondary alkyl radical into the ring alkene. However, this process was completely suppressed upon reacting neat compounds. Acylation of hindered piperidine **9** with trimethylsilylpropionyl chloride and silicon-for-tin exchange delivered alkynylstannane **10**, the substrate for the key alkynyliodonium salt/alkylidenecarbene cascade sequence.

Treatment of stannane **10** with Stang's reagent, PhI(CN)OTf,[6a] in CH_2Cl_2 at −40 °C furnished a solution of the unisolated alkynyliodonium salt **6**, which was concentrated at −40 °C to an unstable oil. This crude iodonium salt was redissolved in DME at −40 °C and then cannulated into a refluxing solution/suspension of sodium *p*-toluenesulfinate in DME. Chromatographic purification of the crude reaction mixture led routinely

SCHEME 3. Synthesis of the Tricyclic Core of Halichlorine



to 58−65% yields of bicyclic lactam **4**.[6b] This transformation is completely scalable over the range 100 mg to 14 g, and in fact, better yields attended reaction at the higher end of this range.

The use of the pseudo-C_2-symmetric amide **10** contributes to the overall efficiency of the synthesis strategy, but the symmetry-breaking cyclization to form **4** reveals the downside of this approach—the two chemically (nearly) identical propyl(tributylstannane) side chains of **4** must now be distinguished. Fortunately, the proximity of the enone portion of lactam **4** to the "quaternary" propylstannane appendage could be exploited to provide this necessary differentiation, Scheme 3. Exposure of **4** to various Lewis acids activated the enone's β-position to nucleophilic capture by the juxtaposed alkyl−tin bond, as first described by Macdonald.[7] Magnesium bromide performed most consistently in this cyclization, although $Yb(OTf)_3$ was also quite effective as well. The Lewis acids reported by Macdonald in the original work ($TiCl_4$, $SnCl_4$) led to inferior yields of **11a** contaminated by substantial amounts of tricyclized material in which the remaining tin residue has had one butyl fragment replaced by an alcohol (following H_2O workup). Reductive methylation of amidosulfone **11a** afforded the methylamide **12** favoring the desired β-methyl diastereomer by >10:1. This transformation was quite sensitive to the nature of the reductant, and alternative reagents (Li/NH_3, LiDBBP, SmI_2, Kurth's procedure[8]) led to inferior yields and/or eroded stereoselectivity. For example, either (1) large amounts of methylated sulfone **11b**, presumably reflecting facile proton transfer between amide enolate and **11a**, or (2) ∼ 2:1 mixtures of stereoisomers resulted from these other trials. In independent control experiments, either exposure of **12** to *t*-BuOK or reductive desulfonylation of

(5) (a) Bubnov, Y. N.; Shagova, E. A.; Evchenko, S. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1994**, *43*, 645. (b) Bubnov, Y. N. *Pure Appl. Chem.* **1994**, *66*, 235. (c) Bubnov, Y. N. *R. Soc. Chem.* **1997**, *201*, 123. (d) Bubnov, Y. N.; Demina, E. E.; Dekaprilevich, M. O.; Struchkov, Y. T. *Russ. Chem. Bull.* **1997**, *46*, 1356. (e) Bubnov, Y. N.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1998**, *47*, 941. (f) Bubnov, Y. N.; Demina, E. E.; Ignatenko, A. V. *Russ. Chem. Bull.* **1997**, *46*, 1306. (g) Bubnov, Y. N.; Demina, E. E.; Ignatenko, A. V. *Russ. Chem. Bull.* **1997**, *46*, 606. (h) Bubnov, Y. N.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1998**, *47*, 451. (i) Bubnov, Y. N.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1998**, *47*, 1175. (j) Gurskii, M. E.; Potapova, T. V.; Bubnov, Y. N. *Russ. Chem. Bull.* **1998**, *47*, 1410. (k) Bubnov, Y. N.; Demina, E. E.; Bel'sky, V. K.; Zatonsky, G. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1998**, *47*, 2249. (l) Bubnov, Y. N.; Klimkina, E. V.; Lavrinovich, L. I.; Zykov, A. Y.; Ignatenko, A. V. *Russ. Chem. Bull.* **1999**, *48*, 1696. (m) Bubnov, Y. N.; Klimkina, E. V.; Zhun, I. V.; Pastukhov, F. V.; Yampolski, I. V. *R. Soc. Chem.* **2000**, *253*, 446. (n) Bubnov, Y. N.; Pastukhov, F. V.; Starikova, Z. A.; Ignatenko, A. V. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 2172. (o) Bespalova, N. B.; Shuvalova, O. V.; Zaikin, V. G.; Borisov, R. S.; Pastukhov, F. V.; Bubnov, Y. N. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 645.

(6) (a) Stang, P. J.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 4571. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93.

(7) Macdonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc.* **1980**, *102*, 2113.

(8) Kurth, M. J.; O'Brien, M. J. *J. Org. Chem.* **1985**, *50*, 3846.

11b furnished similar diastereomeric mixtures, suggesting that, once again, undesired but competitive proton transfers had intervened in the poorly performing reductive methylations of **11a**.

Reformulation of the original allyl fragment introduced in the Bubnov reaction proved to be quite challenging. Insignificant chemical differences between the propyl chain and the butyl substituents seemed to foil many direct attempts to effect oxidative elimination of the tin residue. For example, treatment of **12** with the hydride abstraction reagent $Ph_3C^+BF_4^-$ led to complex reaction mixtures containing no more than trace amounts of alkene-containing products. Exhaustive bromination of **12** did provide a destannylated propyl bromide-bearing product in good yield, and *tert*-butoxide-mediated elimination of H−Br from this species afforded the required allyl-containing product, but as an approximately 2:1 mixture of diastereomers **13a/13b** at C(14) (halichlorine numbering). Thus, the stereochemical lability of this secondary center, hinted at with the reductive methylation studies, once again proved problematic. This difficulty eventually was overcome by resorting to an indirect Tamao−Fleming-type oxidation sequence.[9,10] Conversion of the propyl(tributylstannyl) chain to its monochlorodibutylstannyl derivative set up the peroxide-mediated oxidative scission of the propyl−tin bond to furnish an intermediate propyl alcohol chain. Indirect elimination of the elements of water from this primary alcohol was achieved by application of Grieco's selenoxide introduction/elimination procedure[11] under conditions mild enough to preserve the stereochemistry at C(14). Thus, the terminal alkene was regenerated in overall good yield by this lengthy but reliable procedure.

Reductive cleavage of the lactam ring using the hydride reagent recommended by Myers[12] for refractory lactams initially proved quite capricious, as unsatisfactory mixtures of the desired amino alcohol **14a** and a pyrrolidine product in overall modest yield were formed. Recourse was made to a two-step procedure involving initial hydrolysis of an iminium ion formed by methylation of **13a** followed by hydride reduction of the liberated ester, a sequence described by Kibayashi et al. in their approach to the halichlorine tricyclic core.[4o] Silylation of the primary alcohol within **14a** then delivered the bicyclic product **14b**, ready for entry into the tetrahydropyridine ring annelation sequence. Allylation of the secondary amine within **14b** provided a bis olefin substrate for Grubbs' second-generation olefin metathesis reagent. Exposure of this diene to catalysis by **15** led smoothly to the tricyclic material **16**, which could be desilylated to furnish the alcohol **17**, a species prepared by Kibayashi[4o] in their halichlorine studies.

In summary, the preparation of halichlorine's tricyclic core in 17 steps from pyridine highlights the value of alkynyliodonium salt chemistry for increasing molecular complexity in a single operation. Acquisition of this advanced intermediate sets the stage for completion of this synthesis effort, and results will be reported in due course.

Experimental Section

Copies of ^1H and ^{13}C NMR spectra are provided in the Supporting Information as criteria of purity for all new titled compounds.

***trans*-2,6-Bis[3-(tributylstannyl)propyl]piperidine (9).** *trans*-2,6-Diallyl-1,2,5,6-tetrahydropyridine[5] (**8**) (2.72 g, 16.7 mmol) was combined with freshly distilled Bu_3SnH (9.9 mL, 37 mmol) and AIBN (112 mg, 0.682 mmol) in a sealed tube. The sealed tube was evacuated and heated to 100 °C. Additional portions of AIBN (60 mg) and Bu_3SnH (6.0 mL) were added after 24, 48, 72, and 96 h. The crude reaction mixture was purified via silica gel chromatography using 0.5% NEt_3/2% ethyl acetate in hexanes−0.5% NEt_3/5% ethyl acetate in hexanes to afford 11.06 g (89%) of bisstannane as a colorless oil: IR (neat) 3406 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 2H), 3.32 (m, 1H), 2.87 (m, 1H), 2.02 (m, 2H), 1.79 (m, 1H), 1.67−1.37 (m, 20H), 1.35−1.23 (m, 12H), 0.91−0.87 (t, J = 7.5 Hz, 18H), 0.84−0.65 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 125.0, 52.4, 47.6, 41.3 ($J_{^{13}C-Sn}$ = 23.5 Hz), 40.6 ($J_{^{13}C-Sn}$ = 23.4 Hz), 32.4, 29.7, 27.8 ($J_{^{13}C-^{119}Sn}$ = 26.4 Hz, $J_{^{13}C-^{117}Sn}$ = 25.3 Hz), 24.3 ($J_{^{13}C-Sn}$ = 9.4 Hz), 23.8 ($J_{^{13}C-Sn}$ = 9.4 Hz), 14.1, 9.4, 9.3, 9.2 ($J_{^{13}C-^{119}Sn}$ = 157.2 Hz, $J_{^{13}C-^{117}Sn}$ = 150.0 Hz); MS APCI$^+$ *m/z* (relative intensity) 746.1 (M + H, 100). Anal. Calcd for $C_{35}H_{73}NSn_2$: C, 56.40; H, 9.87; N, 1.88. Found: C, 56.52; H, 9.79; N, 1.78.

The bis-stannane from above (8.01 g, 10.7 mmol) was dissolved in absolute ethanol (120 mL), and PtO_2 (1.22 g, 5.37 mmol) was added. The reaction mixture was purged of air and stirred at room temperature under a balloon of H_2 for 14 h (frequently recharged H_2 balloon). The mixture was filtered through Celite with ether, and the filtrate was concentrated in vacuo. The resulting crude solution was purified via silica gel chromatography using 1% NEt_3/5% ethyl acetate in hexanes to afford 7.45 g of **9** as a colorless oil (92%): IR (neat) 3448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (m, 2H), 1.66 (m, 3H), 1.56−1.21 (m, 20H), 1.20−1.08 (m, 16H), 0.90−0.85 (t, J = 7.2 Hz, 18H), 0.83−0.69 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 39.2, 31.1, 29.3 ($J_{^{13}C-Sn}$ = 9.9 Hz), 27.4 ($J_{^{13}C-^{119}Sn}$ = 26.6 Hz, $J_{^{13}C-^{117}Sn}$ = 25.5 Hz), 23.7 ($J_{^{13}C-Sn}$ = 9.6 Hz), 19.8, 13.7, 9.0 ($J_{^{13}C-^{119}Sn}$ = 154.0 Hz, $J_{^{13}C-^{117}Sn}$ = 147.2 Hz), 8.7 ($J_{^{13}C-^{119}Sn}$ = 156.9 Hz, $J_{^{13}C-^{117}Sn}$ = 150.0 Hz); MS APCI$^+$ *m/z* (relative intensity) 748.5 (M + H, 100). Anal. Calcd. for $C_{35}H_{75}NSn_2$: C, 56.25; H, 10.11; N, 1.87. Found: C, 56.44; H, 10.23; N, 1.67.

1-[*trans*-2,6-Bis[3-(tributylstannyl)propyl]piperin-1-yl]-3-(tributylstannyl)propynone (10). 1-Chloro-*N*,*N*,2-trimethylpropenylamine (2.13 g, 15.9 mmol) was slowly added to a solution of 3-(trimethylsilyl)propynoic acid (2.09 g, 14.7 mmol) in 75 mL of CH_2Cl_2 at 0 °C. The reaction solution was slowly warmed to room temperature and stirred for 6 h to generate the propynoyl acid chloride. This acid chloride solution was then slowly added to a cooled (−45 °C) solution of amine **9** (7.09 g, 9.47 mmol) and distilled (i-Pr)$_2$NEt (2.5 mL, 14 mmol) in CH_2Cl_2 (95 mL). This yellowish solution was stirred for 12 h at −45 °C. After 12 h, tetrabutylammonium fluoride (1.0 M in THF, 16.2 mL, 16.2 mmol) was added to the solution at −45 °C, and stirring was continued for 30 min, followed by warming to room temperature. The reaction mixture was poured into 100 mL of water, and the organic layer was separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual brown oil was purified via SiO_2 chromatography using 10% ether in hexanes to yield 7.17 g (95%) of alkynyl amide as a colorless oil: IR (neat) 2101, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (m, 1H), 3.89 (m, 1H), 2.97 (s, 1H), 1.90−1.59 (m, 9H), 1.58−1.37 (m, 17H), 1.33−1.22 (m, 12H), 0.90−0.68 (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 77.2, 77.1, 54.7, 51.3, 39.8 ($J_{^{13}C-Sn}$ =

(9) Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4606.
(10) Jones, G. R.; Landis, Y. *Tetrahedron* **1996**, *52*, 7599.
(11) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(12) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

23.5 Hz), 38.0 (J^{13C-Sn} = 25.5 Hz), 29.2 (J^{13C-Sn} = 9.9 Hz), 27.3 (J^{13C-Sn} = 25.8 Hz), 27.3 (J^{13C-Sn} = 25.8 Hz), 24.6 (J^{13C-Sn} = 9.1 Hz), 24.5 (J^{13C-Sn} = 9.2 Hz), 23.7, 23.2, 14.4, 13.7, 8.8, 8.7 ($J^{13C-119Sn}$ = 158.0 Hz, $J^{13C-117Sn}$ = 151.0 Hz), 8.7 ($J^{13C-119Sn}$ = 157.2 Hz, $J^{13C-117Sn}$ = 150.2 Hz), 8.6; MS APCI$^+$ *m/z* (relative intensity) 800.4 (M + H, 100), 742.3 (M − C_4H_9, 100). Anal. Calcd for $C_{38}H_{75}NSn_2$: C, 57.09; H, 9.46; N, 1.75. Found: C, 57.29; H, 9.51; N, 1.58.

To a stirring suspension of the alkyne from above (7.10 g, 8.88 mmol) and magnesium sulfate (4.32 g, 35.9 mmol) in ether (90 mL) was added bis(tributyltin)oxide (4.5 mL, 8.8 mmol). The suspension was stirred at room temperature for 48 h. The reaction mixture filtered through Celite with ether and concentrated in vacuo. The resulting colorless oil was filtered through a SiO_2 plug using 10% ethyl acetate in hexanes to afford 9.46 g (98%) of alkynylstannane **10**: IR ($CHCl_3$) 2244, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (m, 1H), 3.92 (m, 1H), 1.83−1.74 (m, 3H), 1.70−1.64 (m, 5H), 1.62−1.36 (m, 23H), 1.34−1.22 (m, 19H), 1.16−1.02 (m, 6H), 0.98−0.85 (m, 31H), 0.82−0.67 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 102.5, 96.2, 54.7, 51.0, 39.8, 38.3, 29.3 (J^{13C-Sn} = 9.8 Hz, two carbons), 28.9 (J^{13C-Sn} = 11.6 Hz), 27.4, 27.3, 27.1, 24.6 (J^{13C-Sn} = 9.5 Hz, two carbons), 23.4, 23.2, 14.4, 13.7 (two carbons), 13.6, 11.2, 8.9, 8.88, 8.77 ($J^{13C-119Sn}$ = 157.6 Hz, $J^{13C-117Sn}$ = 150.6 Hz), 8.73 ($J^{13C-119Sn}$ = 156.8 Hz, $J^{13C-117Sn}$ = 149.9 Hz); MS APCI$^+$ *m/z* (relative intensity) 1088.5 (M + H, 50), 1030.4 (M − C_4H_9, 50), 748.4 (M − $C_{12}H_{27}Sn$, 100); HRMS calcd for $C_{50}H_{102}NOSn_3$ (M + H) 1088.5041, found 1088.5019.

2-(Toluene-4-sulfonyl)-5,8a-bis[3-(tributylstannyl)propyl]-6,7,8,8a-tetrahydro-5*H*-indolizin-3-propynone (4). To a cooled (−45 °C) suspension of cyanophenyl iodonium triflate (1.79 g, 4.72 mmol) in 15 mL of CH_2Cl_2 was added a solution of alkynylstannane **10** (4.25 g, 3.91 mmol) in 25 mL of CH_2Cl_2. The reaction mixture stirred at −45 °C for approximately 2 h until a yellow homogeneous solution formed and then stirred for an additional 30 min. The solvent was removed in vacuo at −30 °C to give a yellow oil. This oil was then redissolved in DME (prechilled to −30 °C) (30 mL) and slowly added via cannula into a refluxing suspension of anhydrous sodium *p*-toluenesulfinate (842 mg, 4.73 mmol) in DME (50 mL). Upon complete addition, the solution was refluxed for an additional 20 min. The reaction solution was cooled to room temperature, poured into 80 mL of distilled water, and extracted with ether (2 × 100 mL). The organic layer was dried over $MgSO_4$ and concentrated to give an orange oil, which was purified via SiO_2 column chromatography using 10% ether in hexanes to yield 2.52 g (65%) of **4** as a light yellow oil: IR (neat) 1698, 1327, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 3.02 (m, 1H), 2.60 (app dq, J = 14.4, 7.2 Hz, 1H), 2.41 (s, 1H), 1.90−1.38 (m, 24H), 1.31−1.22 (m, 12H), 1.18−1.08 (m, 3H), 0.89−0.84 (m, 18H), 0.81−0.74 (m, 12H), 0.72−0.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 157.6, 144.6, 140.1, 136.3, 129.6, 128.7, 65.9, 55.4, 36.3, 35.9, 34.0, 31.7, 29.2 (J^{13C-Sn} = 9.9 Hz), 29.1 (J^{13C-Sn} = 10.0 Hz), 27.3 ($J^{13C-119Sn}$ = 26.3 Hz, $J^{13C-117Sn}$ = 25.2 Hz), 27.3 ($J^{13C-119Sn}$ = 26.4 Hz, $J^{13C-117Sn}$ = 25.3 Hz), 25.1 (J^{13C-Sn} = 9.0 Hz), 21.6, 20.5, 20.4, 13.7 (two carbons), 8.9, 8.8 ($J^{13C-119Sn}$ = 158.8 Hz, $J^{13C-117Sn}$ = 151.7 Hz), 8.6 ($J^{13C-119Sn}$ = 157.3 Hz, $J^{13C-117Sn}$ = 150.2 Hz), 8.6; MS APCI$^+$ *m/z* (relative intensity) 954.4 (M + H, 100). Anal. Calcd for $C_{45}H_{81}NO_3SSn_2$: C, 56.68; H, 8.56; N, 1.47; S, 3.36. Found: C, 56.80; H, 8.41; N, 1.47; S, 3.33.

4-(Toluene-4-sulfonyl)-6-(3-tributylstannylpropyl)octahydro-5a-azacyclopenta[*c*]inden-5-one (11a). A suspension of **4** (3.87 g, 4.06 mmol) and $MgBr_2$ (896 mg, 4.87 mmol) in dry toluene (40 mL) was refluxed for 14 h. Upon cooling to room temperature, 20 mL of water was added, and the reaction was stirred for 1 h. This mixture was poured into 40 mL of water and extracted with ether (2 × 40 mL). The organic layer was separated, dried via $MgSO_4$, filtered, and concentrated to a yellow oil. The crude oil was purified via SiO_2 column using 15% ether in hexanes to give 1.86 g (69%) of **11a** as a pale yellow oil: IR (neat) 1695, 1317, 1148 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.4, 1.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 3.68 (d, J = 4.0 Hz, 1H), 3.11 (m, 1H), 2.82 (ddd, J = 8.6, 5.8, 4.0 Hz, 1H), 2.56 (app dq, J = 13.8, 6.9 Hz, 1H), 2.42 (s, 3H), 2.16 (m, 1H), 1.78−1.19 (m, 26H), 0.88 (t, J = 7.2 Hz, 9H), 0.79−0.66 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 144.6, 135.4, 129.4, 129.4, 73.8, 71.3, 56.7, 43.3, 36.4, 36.0, 35.6, 31.1, 29.2 (J^{13C-Sn} = 9.9 Hz), 27.3 ($J^{13C-119Sn}$ = 26.4 Hz, $J^{13C-117Sn}$ = 25.3 Hz), 25.0, 24.7, 24.6 (J^{13C-Sn} = 8.9 Hz), 22.4, 21.6, 13.7, 8.6 ($J^{13C-119Sn}$ = 157.2 Hz, $J^{13C-117Sn}$ = 150.1 Hz), 8.4 ($J^{13C-119Sn}$ = 153.9 Hz, $J^{13C-117Sn}$ = 146.9 Hz); MS APCI$^+$ *m/z* 666.4 (M + H, 100). Anal. Calcd for $C_{33}H_{55}NO_3SSn$: C, 59.64; H, 8.34; N, 2.11; S, 4.82. Found: C, 59.76; H, 8.22; N, 2.20; S, 4.95.

4-Methyl-6-(3-tributylstannylpropyl)octahydro-5a-azacyclopenta[*c*]inden-5-one (12). To a solution of naphthalene (212 mg, 1.65 mmol) in THF (2.1 mL) were added lithium beads (40 mg, 5.8 mmol). The reaction mixture was then sonicated for 30 min. An additional 4.5 mL of THF was added, and sonication was continued for an additional 1 h. The dark green reaction mixture was cooled to −78 °C, and a solution of sulfone **11a** (356 mg, 0.536 mmol) in 6.7 mL THF was added dropwise over 30 min. The dark green mixture was stirred for 1 h and then warmed to −60 °C. Methyl iodide (freshly filtered through basic Al_2O_3) (510 μL, 8.0 mmol) was added quickly, and the reaction mixture turned from dark green to yellow. This solution was stirred for 1 h and then diluted at −60 °C with 2.5 mL of methanol and warmed to room temperature. The reaction mixture was poured into 30 mL of water and extracted with ether (2 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to a yellow oil, which was purified via SiO_2 column using 8% ether in hexanes to afford 154 mg (55%) of **12** as a colorless oil: IR (neat) 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (m, 1H), 2.63 (m, 1H), 2.11 (m, 1H), 1.93 (m, 1H), 1.84−1.71 (m, 3H), 1.70−1.34 (m, 18H), 1.33−1.23 (m, 6H), 1.22 (d, J = 7.4 Hz, 3H), 0.87 (t, J = 7.3 Hz, 9H), 0.83−0.71 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 71.5, 55.6, 51.3, 44.5, 38.8, 36.6 (J^{13C-Sn} = 28.0 Hz), 35.4, 33.2, 31.3, 29.2 (J^{13C-Sn} = 9.8 Hz), 27.4 ($J^{13C-119Sn}$ = 26.3 Hz, $J^{13C-117Sn}$ = 25.2 Hz), 25.3, 24.8 (J^{13C-Sn} = 9.1 Hz), 22.5, 18.6, 13.7, 8.7 ($J^{13C-119Sn}$ = 156.7 Hz, $J^{13C-117Sn}$ = 149.7 Hz), 8.6 ($J^{13C-119Sn}$ = 155.2 Hz, $J^{13C-117Sn}$ = 148.7 Hz); MS APCI$^+$ *m/z* (relative intensity) 526.3 (M + H, 100); HRMS calcd for $C_{27}H_{52}NOSn$ (M + H) 526.3065, found 526.3046.

6-Allyl-4-methyloctahydro-5a-azacyclopenta[*c*]inden-5-one (13a). To a stirring suspension of **12** (52 mg, 0.10 mmol) and iodosylbenzene (25 mg, 0.11 mmol) in 2.0 mL of CH_2Cl_2 at 0 °C was added dropwise $BF_3{\cdot}OEt_2$ (14 μL, 0.11 mmol). A bright yellow solution formed which was stirred at 0 °C for 45 min. Saturated aqueous NH_4Cl (3.0 mL) was then added, and the solution was vigorously stirred at 0 °C for 1 h. The reaction mixture was warmed to room temperature, and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give 49 mg of crude chlorostannane as a yellow oil which was used without further purification: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.09 (m, 1H), 2.22 (m, 1H), 2.05 (m, 1H), 1.98−1.50 (m, 16H), 1.48−1.21 (m, 14H), 1.20 (d, J = 7.4 Hz, 3H), 0.94−0.88 (m, 6H); MS APCI$^+$ *m/z* (relative intensity) 504.2 (M + H, 30), 468.3 (M − Cl, 100).

To a solution of the crude chlorostannane from above (49 mg, 0,10 mmol) and $KHCO_3$ (29 mg, 0.29 mmol) in 1.1 mL of THF and 1.1 mL of MeOH was added 30% H_2O_2 (520 μL, 4.5 mmol), and the reaction solution was stirred for 18 h at room temperature. The reaction solution was poured into 5% aqueous Na_2SO_4 (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to afford 25 mg of a crude colorless oil. The alcohol was used without further purification: IR (neat) 3417, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (m, 2H), 3.12 (m, 1H), 2.62 (m, 1H), 2.51 (br s, 1H), 2.11 (m, 1H), 1.92 (m, 1H), 1.86−1.73 (m, 3H), 1.72−1.50

(m, 9H), 1.49−1.35 (m, 3H), 1.21 (d, J = 7.3 Hz, 3H); MS APCI$^+$ *m/z* (relative intensity) 252.1 (M + H, 100).

To a solution of the crude alcohol (25 mg, 0.10 mmol) and 2-nitrophenylselenocyanate (117 mg, 0.515 mmol) in 2.0 mL of THF was slowly added tributylphosphine (130 μL, 0.52 mmol). The dark brown solution was stirred at room temperature. After 10 h, 30% aqueous H_2O_2 (125 μL, 1.10 mmol) was added. After 16 h, the reaction solution was poured into water (10 mL) and extracted with ether (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 157 mg of an orange oil. The crude orange oil was purified via SiO_2 using CH_2Cl_2 and then 1% MeOH in CH_2Cl_2 to give 17 mg (72%) of **13a** as a light yellow oil: IR (neat) 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dddd, J = 17.3, 10.0, 7.5, 6.1 Hz, 1H), 5.11 (dd, J = 17.1, 1.4 Hz, 1H), 5.03 (dd, J = 10.1, 0.9 Hz, 1H), 3.33 (app dt, J = 14.1, 6.3 Hz, 1H), 3.19 (m, 1H), 2.64 (app dt, J = 14.5, 7.5 Hz, 1H), 2.15 (m, 1H), 1.92 (m, 1H), 1.85−1.51 (m, 7H), 1.49−1.26 (m, 5H), 1.24 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 137.0, 116.2, 71.5, 55.8, 51.5, 44.5, 38.7, 36.7, 35.3, 32.9, 30.9, 25.2, 22.1, 18.5; MS APCI$^+$ *m/z* (relative intensity) 234.2 (M + H, 100); HRMS calcd for $C_{15}H_{24}NO$ (M + H) 234.1852, found 234.1858.

2-(7-Allyl-6-azaspiro[4.5]dec-1-yl)propan-1-ol (14a). To a cooled (0 °C) solution of **13a** (11 mg, 0.05 mmol) in 0.9 mL of 1,2-dichloroethane was added methyl triflate (16 μL, 0.14 mmol). The reaction solution was heated to 60 °C for 1 h. Upon cooling to room temperature, the reaction solution was concentrated in vacuo. The residue was redissolved in THF (0.9 mL), distilled H_2O (90 μL) was added, and the solution was stirred for 18 h at room temperature. The reaction solution was then dried over $MgSO_4$, filtered, and concentrated to furnish 18 mg of a crude light yellow solid. The crude solid was dissolved in 0.7 mL of THF and added dropwise to a cooled (0 °C) suspension of lithium aluminum hydride (15 mg, 0.40 mmol) in THF (0.7 mL). The reaction mixture was slowly warmed to room temperature. After 5 h at room temperature, the reaction suspension was treated with 0.3 mL of a saturated aqueous solution of NH_4Cl and filtered through Celite with ethyl acetate (30 mL). The filtrate was washed with brine (10 mL), and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified via SiO_2 using 3% (9:1 MeOH/29% NH_4OH) in CH_2Cl_2 to give 8 mg (68%) of **14a** as a colorless oil: IR (neat) 3304 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dddd, J = 17.2, 9.9, 7.2, 6.2 Hz, 1H), 5.17 (d, J = 17.2 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1H), 3.79 (dd, J = 11.3, 2.1 Hz, 1H), 3.47 (app t, J = 10.7 Hz, 1H), 2.93 (m, 1H), 2.65 (m, 1H), 2.31 (m, 1H), 2.17 (m, 1H), 2.02−1.89 (m, 5H), 1.87−1.14 (m, 10H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 133.9, 118.1, 68.6, 58.3, 54.4, 49.0, 37.2, 35.2, 32.3, 29.3, 28.9, 27.0, 23.7, 21.7, 13.4; MS APCI$^+$ *m/z* (relative intensity) 238.2 (M + H, 100); HRMS calcd for $C_{15}H_{28}NO$ (M + H) 238.2165, found 238.2143.

7-Allyl-1-[2-(*tert*-butyldiphenylsilanyloxy)-1-methylethyl]-6-azaspiro[4.5]decane (14b). To a solution of **14a** (9 mg, 0.04 mmol) in CH_2Cl_2 (0.8 mL) were added 4-(dimethylamino)pyridine (1 mg, 0.008 mmol), distilled triethylamine (9 μL, 0.07 mmol), and *tert*-butylchlorodiphenylsilane (11 μL, 0.042 mmol), and the reaction solution was stirred at room temperature for 2 h. The reaction mixture was diluted with 10 mL of ether and washed with 10 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified via SiO_2 using 2% (9:1 MeOH/29% NH_4OH) in CH_2Cl_2 to give 14 mg (75%) of **14b** as a colorless oil. Analytical data matches that previously reported.[4o]

Ethyl 1′,2′,3′,6′,9′,9′a-Hexahydro-2-[2-[*tert*-butyl(diphenyl)silyloxy]-1-methylethyl]spirocyclopentane-1,4′-[4*H*]-quinolizine-7′-carboxylate (16). To a suspension of **14b** (6 mg, 0.01 mmol) and K_2CO_3 (8 mg, 0.06 mmol) in CH_3CN was added 2-(bromomethyl)acrylic acid ethyl ester (11 mg, 0.058 mmol). The mixture was heated to 60 °C for 14 h. The reaction mixture was poured into water (10 mL) and extracted with 20 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified via SiO_2 using 5% ether in hexanes to give 5 mg (71%) of a colorless oil. Analytical data matches that previously reported.[4o]

To a solution of the silyl ether from above (5 mg, 0.009 mmol) in CH_2Cl_2 (0.8 mL) was added ruthenium complex 15 (1 mg, 0.001 mmol) and the solution was heated to reflux for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by SiO_2 using 5% ether in hexanes to give 4 mg (80%) of **16** as a colorless oil. Analytical data match those previously reported.[4o]

Ethyl 1′,2′,3′,6′,9′,9′a-Hexahydro-2-(2-hydroxy-1-methylethyl)spirocyclopentane-1,4′-[4*H*]quinolizine-7′-carboxylate (17). A solution of **16** (4 mg, 0.007 mmol) and HF·pyridine (2 mg, 0.1 mmol) in CH_3CN was stirred at room temperature for 2 h. The solution was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified with 2% (9:1 MeOH/29% NH_4OH) in CH_2Cl_2 to give 2 mg (75%) of **17** as a colorless oil. Analytical data matches that previously reported.[4o]

Acknowledgment. Funding provided by the General Medical Sciences Division of the National Institutes of Health (GM37681) is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for **4**, **9**, **10**, **11a**, **12**, **13a**, and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0487911