92 (100), 91 (81.6), 85 (35.8), 81 (79.9), 77 (89.4), 67 (57.5), 59 (92.2), 55 (79.9); calcd for $C_9H_{14}O_3$, 170.0943; found, 170.0948.

Acknowledgment. We are indebted to the National Science Foundation (CHE-8102944) and to the Research Corporation (Grant 9155) for the financial support of this work and to Prof. Robert Boeckman for the provision of spectral data and for a sample of sarkomycin methyl ester. We are grateful to Frank Koszyk for the preparation of compound **32**. As customary, we thank heartily Dr. James Hudson of University of Texas (Austin) for his determination of mass spectral data. We appreciate further the many heplful suggestions provided to us by colleagues at both IIT and VPI & SU.

Registry No. **4**, 86747-58-2; **8**, 4949-20-6; **9**, 86747-59-3; **10**, 86747-60-6; **11**, 86747-61-7; **12**, 86747-62-8; **13**, 77189-14-1; **14**, 86747-63-9; **15**, 86747-64-0; **15a**, 86747-65-1; **16**, 86747-66-2; **17**, 86747-67-3; **18**, 17102-64-6; **19**, 86747-68-4; **20**, 86747-69-5; **21**, 86747-70-8; **22a**, 86747-71-9; **22b**, 86783-79-1; **23a**, 86747-72-0; **23b**, 86783-80-4; **24**, 86747-73-1; **25**, 86747-74-2; **26**, 86747-75-3; **27**, 86747-76-4; **28**, 86747-77-5; methyl malonate monochloride, 37517-81-0; tosyl azide, 941-55-9; ethyl acetoacetate, 141-97-9.

Studies Directed toward the Total Synthesis of Securinega Alkaloids

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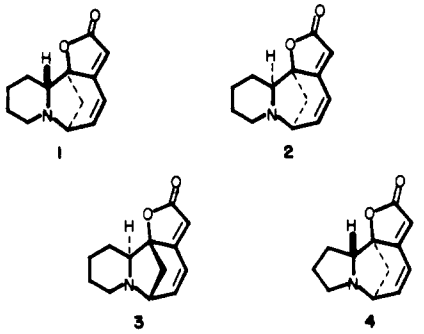
An approach to the synthesis of securinega alkaloids is reported. Reductive amination of ethyl 2-thienylacetoacetate (**12**) with methyl (*S*)-prolinate gives a mixture of diastereomeric amino diesters **6** and **13** in a ratio of 44:56. Dieckmann cyclization of the mixture followed by treatment of the product with acid affords the crystalline (±)-**10** in 64% yield. Separation of **6** and **13** prior to cyclization provides samples of the enantiomers (−)-**10** and (+)-**10**, respectively. Attempts to open the thiophene ring of **10** were not successful. Treatment of (±)-**10** with excess *n*-butyllithium and trimethylsilyl chloride results in a novel fragmentation, leading to the benzothiophene **18**.

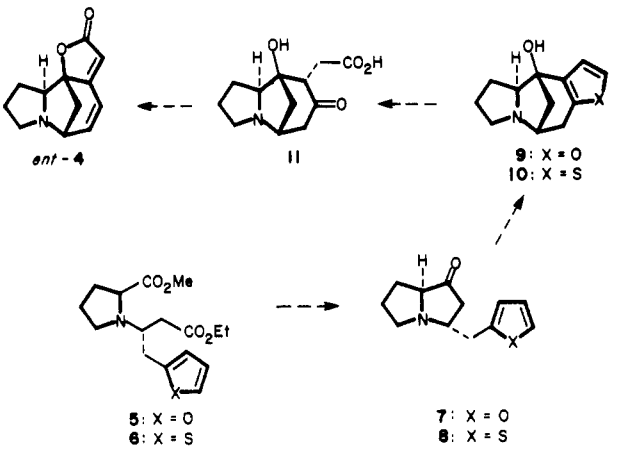
The securinega alkaloids are a group of compounds found in the *Securinega* and *Phyllanthus* genera of the *Euphorbiaceae* family of plants.[1] The most abundant representative, and the first to be isolated and characterized, is securinine (**1**). Other naturally occurring



members of the group are the securinine stereoisomers allosecurinine (**2**) and virosecurinine (**3**) and the *A*-nor compound norsecurinine (**4**). In this paper, we report a simple approach to construction of the skeleton of **4**. Although the approach, which utilizes an intramolecular Friedel–Crafts reaction of a 3-(arylmethyl)pyrrolizid-1-one, has been abandoned for both chemical and stereochemical reasons, some interesting chemistry has emerged from the project. In addition, the current work has led to a more successful approach to norsecurinine, which will be communicated separately.

Our retrosynthetic analysis is summarized in Scheme I. At the outset, we elected to develop a synthesis of *ent*norsecurinine (*ent*-**4**), rather than norsecurinine itself, so that we could employ methyl (*S*)-prolinate, rather than the less readily available methyl (*R*)-prolinate. The decision to mask the γ-keto acid moiety (e.g., in **11**) as a

Scheme I



heteroaromatic ring was made because it was believed that some form of protection would be necessary in any event and that by employing an aromatic ring for this purpose, we would make available a greater range of options for formation of ring C (e.g., **7** or **8** to **9** or **10**). Although some of our exploratory work was done with the furan series (**5**, **7**, **9**), difficulties in working with these exceedingly acid-sensitive compounds encouraged us to concentrate on the thiophene series at an early stage.

Ethyl 2-thienylacetoacetate (**12**) has previously been prepared from (2-thienyl)acetyl chloride and *tert*-butyl ethyl malonate, albeit in only 22% yield.[2] We prepared β-keto ester **12** by the Yonemitsu method[3] in 73% yield. Reductive amination of **12** with methyl (*S*)-prolinate and sodium cyanoborohydride[4] provides a mixture of diaste-

(1) Snieckus, V. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14.

(2) Miller, W. H.; Dessert, A. M.; Anderson, G. W. *J. Am. Chem. Soc.* **1948**, *70*, 500.

(3) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.

(4) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996.

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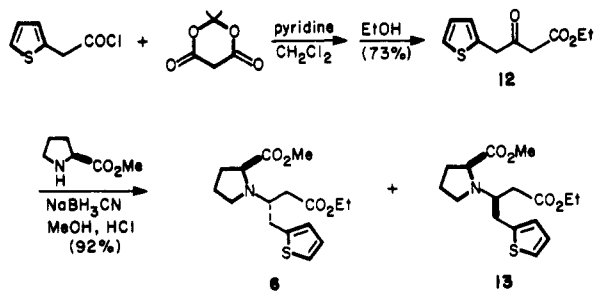
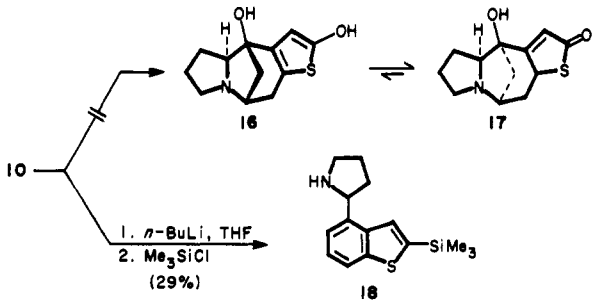


reomeric amino diesters **6** and **13** in 92% yield. Compounds **6** and **13**, which are produced in a ratio of 44:56, may be separated with some difficulty by preparative high-performance liquid chromatography.

Treatment of the foregoing 44:56 mixture of **6** and **13** with potassium *tert*-butoxide in toluene at 0 °C, followed by 6 N hydrochloric acid at reflux affords a crystalline, diastereomerically homogeneous product in 64% yield. The observed zero optical rotation of this material and its formula ($C_{12}H_{15}NOS$) and spectral properties suggest that it is a racemic mixture of (–)-**10** and (+)-**10**. In fact, when the cyclization is carried out with pure samples of **6** and **13**, it is found that diastereomer **6** affords (–)-**10** ($[\alpha]_D$ –43°) and that diastereomer **13** affords (+)-**10** ($[\alpha]_D$ +41°). When the pure diastereomers were cyclized under identical conditions, the conversion of **6** to (–)-**10** was found to proceed in higher yield (63%) than the transformation of **13** into (+)-**10** (46%). Since this approximate ratio of yields (1.37:1) almost exactly balances the ratio of **13**/**6** in the crude reductive amination product (1.27:1), racemic **10** is obtained when the mixture of diastereomers is cyclized.

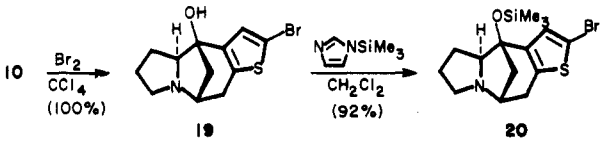
A stereochemical interpretation of the foregoing results is given in Scheme II. Dieckmann cyclization, followed by acid-catalyzed hydrolysis and decarboxylation, presumably converts amino diesters **6** and **13** into pyrrolizidones **8** and **14**, respectively. Isomer **8**, in which the 2-thienyl group is on the convex face of the folded pyrrolizidone system, undergoes Friedel–Crafts cyclization to afford (–)-**10**. However, isomer **14**, in which the 2-thienyl group is on the more hindered concave face, does not cyclize. Instead, epimerization occurs at the bridgehead position, giving *ent*-**8**, which cyclizes to (+)-**10**. As was mentioned earlier, none of the diastereomeric amino alcohol **15** was detected in the crude reaction product. Since the analytical sensitivity (NMR) is probably on the order of 3%, the cyclization of **8** to **10** must be more than 40 times faster than the cyclization of **14** to **15**.

With an effective synthesis of racemic amino alcohol **10** in hand (three steps from (2-thienyl)acetyl chloride, 43% yield) we examined possible ways to open the thiophene ring with a view toward transforming this material into racemic norsecurinine. We first sought to oxidize the thiophene at C-2 to obtain **16** or its tautomer, **17**. Various attempts to lithiate **10** and oxidize the resulting 2-lithiothiophene led only to complex mixtures of aromatic products. Although the products from most of these reactions were not characterized, one reaction did lead to a recognizable product. Treatment of **10** with excess *n*-butyllithium and trimethylsilyl chloride in THF at 25 °C provides benzothiophene **18** in 29% yield. The structure of **18** is assigned on the basis of its molecular weight (M+, 275), ^{1}H NMR spectrum [aromatic signals at δ 7.29 (t, J = 7 Hz), 7.45 (d, J = 7 Hz), 7.65 (s), 7.77 (d, J = 7 Hz)], and UV spectrum [λ_{max} 237 nm (ϵ 12990), 268 (5100), 276 (5315), 298 (2382), 308 (2522)]. The latter data are particularly convincing. For example, the UV spectral data of 2-methylbenzothiophene are λ_{max} 230 nm (ϵ 30000), 259

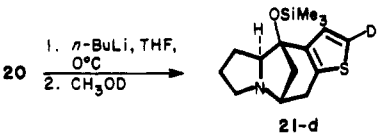


(7500), 288 (2000), and 297 (2400).[5a] The effect of a trimethylsilyl group would seem to be a bathochromic shift of 10 nm (the principle absorptions of benzene are 244, 249, 254, and 259 nm,[6] and those of phenyltrimethylsilane are 253, 259, 264, and 270 nm[5b]). A possible mechanism for the formation of benzothiophene **18** is set forth is Scheme III.

In an attempt to circumvent the surprisingly facile fragmentation of **10**, the thiophene ring was activated by bromination. Treatment of **10** with bromine in CCl_4 affords bromothiophene **19** in quantitative yield. Silylation



of **19** occurs readily upon treatment with *N*-(trimethylsilyl)imidazole. However, treatment of **20** with magnesium or with *n*-butyllithium, followed by addition of various electrophiles (di-*tert*-butyl peroxide, *tert*-butyl perbenzoate, trimethyl borate, methyl iodide, trimethylsilyl chloride) failed to yield any functionalized products. The problem does not seem to be a failure of **20** to undergo metalation, since the trimethylsilyl ether of **10** (**21**) is usually obtained from these reactions. Treatment of **20** with excess *n*-butyllithium in THF at 0 °C, followed by addition of CH_3OD, provides **21**-*d*.



Because of the unexpected difficulties which we have encountered in opening the thiophene ring of **10**, the current approach to norsecurinine has been abandoned. However, the research reported here taught us a valuable lesson. The synthetic plan (Scheme I) called for protection of the keto acid of **11** as an aromatic ring because it was believed that closure of the third ring would be troublesome. In retrospect, it is clear that the synthesis was "over-engineered", since formation of the crucial 6-azabicyclo[3.2.1]octane system proved to be surprisingly easy. A more successful, simplified approach will be reported separately.

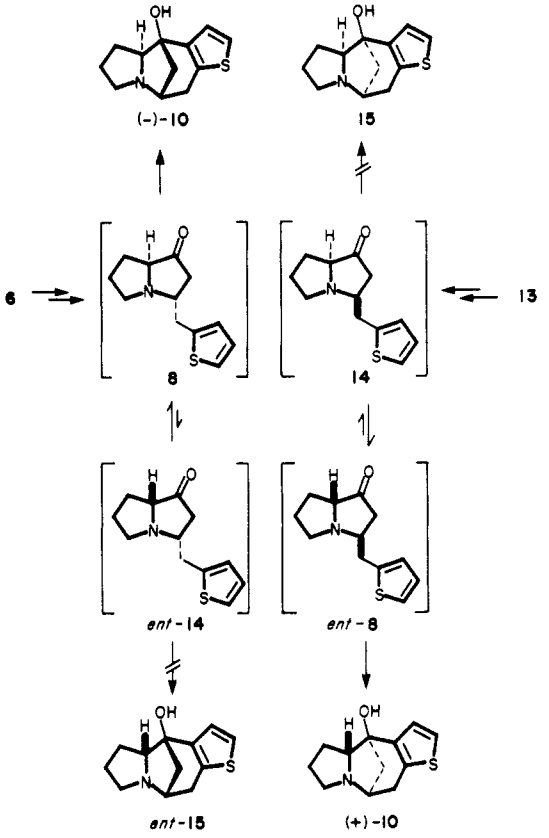
Experimental Section

General Methods. Unless otherwise noted, materials were obtained from suppliers and used without purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Alcoholic solvents were distilled from

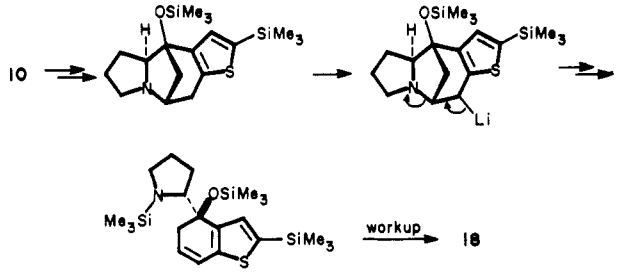
(5) (a) "Absorption Spectra in the Ultraviolet and Visible Region"; Lang, L., Ed.; Academic Press: New York, 1961; Vol. I, 330. (b) *Ibid.*, 1969, Vol. XI, p 9.

(6) Pasto, D.; Johnson, C. "Organic Structure Determination"; Prentice-Hall: Englewood Cliffs, NJ, 1969; p 106.

Scheme II



Scheme III



sodium. Dichloromethane was taken from freshly opened bottles and stored over molecular sieves. Reactions were generally performed under a nitrogen atmosphere. Boiling points and melting points (Pyrex capillary) are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined with either the UCB-200 or UCB-250 spectrometers (superconducting FT instruments operating at 200 and 250 MHz, respectively). Unless otherwise specified, all NMR spectra were recorded in chloroform-*d* as the solvent, with tetramethylsilane as an internal standard. Significant ^{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra (MS) were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as *m/e* (intensity expressed as percent of total ion current). Ultraviolet (UV) spectra were obtained with a Hewlett-Packard 8450A ultraviolet spectrophotometer. UV data are reported as λ_{max} (extinction coefficient). High-performance liquid chromatography (HPLC) was done with a Waters ALC/GPC-244 liquid chromatograph (analytical) or a Waters PrepLC/System 500 (preparative). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

2-(3-Carbethoxy-2-oxopropyl)thiophene (12). A solution of 3.16 g (21.9 mmol, 1.03 equiv) of Meldrum's acid (recrystallized from acetone) in 10 mL of dichloromethane was cooled to 0 °C. Distilled pyridine (4.3 mL, 4.21 g, 53.2 mmol, 2.5 equiv) was added dropwise over a period of 10 min, followed by a solution of 3.42 g (21.3 mmol, 1.0 equiv) of 2-thienylacetyl chloride (unpurified) in 7 mL of dichloromethane over a period of 1 h. The reaction mixture was stirred for 1 h at 0 °C and 1 h at 25 °C and was then poured onto a mixture of 15 mL of 10% aqueous HCl and 10 g of ice. The mixture was extracted three times with dichloromethane, and the combined organic layers were washed sequentially with two portions of 10% aqueous HCl and one of brine. After being dried (Na_2SO_4), the extracts were filtered through Celite and concentrated with a rotary evaporator to give a brown oil. This material was taken up in 50 mL of anhydrous ethanol and refluxed for 2 h. The solvent was concentrated with a rotary evaporator, and the product distilled under vacuum to give 3.30 g (73%) of **12** as a watery white liquid: bp 70–75 °C (0.10 torr); ^{1}H NMR δ 1.27 (t, 3 H, J = 8), 3.50 (s, 2 H), 4.04 (s, 2 H), 4.19 (q, 2 H, J = 8), 6.92 (dd, 1 H, J = 1, 3), 6.98 (dd, 1 H, J = 3, 5), 7.25 (dd, 1 H, J = 1, 5). The compound has previously been prepared in a different manner by Miller and coworkers [lit.[2] bp 143–145 °C (5.5 torr)].

Ethyl (2′*S*,3*R*)-3-(2′-Carbomethoxy-1′-pyrrolidino)-4-(2-thienyl)butanoate (6) and Ethyl (2′*S*,3*S*)-3-(2′-Carbomethoxy-1′-pyrrolidino)-4-(2-thienyl)butanoate (13). To a mixture of 5.13 g (39.7 mmol) of methyl (*S*)-prolinate, 2.81 g (13.2 mmol) of β-keto ester **12**, and 3.6 mL of 2.9 M methanolic HCl (10.4 mmol) in 25 mL of methanol was added 0.82 g (13.2 mmol) of sodium cyanoborohydride. The reaction mixture was stirred at 25 °C for 28 h. After acidification to pH 2 with concentrated hydrochloric acid the mixture was concentrated with a rotary evaporator. Water was added to the residue, and this mixture was extracted twice with ether. The aqueous layer was basified to pH 10 with solid KOH and extracted four times with ether. The combined organic layers were dried ($MgSO_4$), filtered through Celite, and concentrated with a rotary evaporator. Chromatography on 20 g of silica gel, using 20% ether/hexane as the eluant, gave 3.97 g (92%) of **29** as a colorless oil. The ^{1}H NMR spectrum of this product showed a mixture of **6** and **13** in a ratio of 44:56.

Separation of diastereomers was accomplished by HPLC using a Prep-Pak silica column, with 15% ethyl acetate/hexane as the eluant and using a mass-shaving procedure over three recycles.

Compound **6**: IR ($CHCl_3$) 1725, 1435, 1370, 1165, 1030 cm^{-1}; ^{1}H NMR δ 1.23 (t, 3 H, J = 7), 1.73–2.06 (m, 4 H), 2.37 (dd, 1 H, J = 7, 15), 2.50 (dd, 1 H, J = 6, 15), 2.75 (m, 1 H), 2.95–3.16 (m, 3 H), 3.60 (m, 2 H), 3.62 (s, 3 H), 4.08 (q, 2 H, J = 7), 6.84 (dd, 1 H, J = 1, 3), 6.90 (dd, 1 H, J = 3, 5), 7.12 (dd, 1 H, J = 1, 5). Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30. Found: C, 58.96; H, 6.99; N, 4.20.

Compound **13**: IR ($CHCl_3$) 1725, 1435, 1370, 1170, 1035 cm^{-1}; ^{1}H NMR δ 1.22 (t, 3 H, J = 7), 1.73–2.07 (m, 4 H), 2.46 (dd, 1 H, J = 6, 15), 2.52 (dd, 1 H, J = 7, 15), 2.74–2.98 (m, 2 H), 3.03–3.17 (m, 2 H), 3.53–3.66 (m, 2 H), 3.68 (s, 3 H), 4.07 (overlapping dq's, 2 H, J = 7, 14), 6.81 (dd, 1 H, J = 1, 3), 6.90 (dd, 1 H, J = 3, 5), 7.12 (dd, 1 H, J = 1, 5). Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30. Found: C, 58.83; H, 7.10; N, 4.24.

(1*SR*,8*RS*,13*RS*)-9-Aza-1-hydroxy-5-thiatetracyclo-[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene ((±)-10). A solution of 192 mg (0.59 mmol) of a 44:56 mixture of **6** and **13** in 2 mL of toluene was cooled to 0 °C, and 106 mg (0.94 mmol) of potassium *tert*-butoxide was added. The solution was stirred at 0 °C for 3 h, 3 mL of 6 N aqueous HCl was added, and the resulting mixture was heated at reflux for 10 h. After the reaction mixture was allowed to cool to room temperature, the aqueous phase was separated and basified to pH 9 with saturated aqueous K_2CO_3. The mixture was extracted seven times with 10 mL of dichloromethane. The combined extracts were dried (K_2CO_3), filtered through a pad of Celite, and concentrated with a rotary evaporator. Recrystallization of the crude product from chloroform gave 81 mg (64% yield) of a white solid: mp 180–184 °C; IR ($CHCl_3$) 3610, 1510, 1420, 1200, 925 cm^{-1}; ^{1}H NMR δ 1.71 (m, 5 H), 1.89 (m, 1 H), 2.21 (dd, 1 H, J = 6, 10), 2.64 (dt, 1 H, J = 6, 10), 2.95 (d, 2 H, J = 3), 3.30 (dt, 1 H, J = 6, 3), 3.42 (m, 2 H), 7.02 (d, 1 H, J = 5), 7.10 (d, 1 H, J = 5); MS, *m/e* 221 (6.55), 152 (6.31), 151 (6.88), 70 (11.03). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.84; N, 6.23. $[\alpha]^{25}_D$ 0° (*c* 0.5, EtOH).

The foregoing experiment was also performed with pure diastereomers **6** and **13**, producing alcohols (−)-**10** and (+)-**10** in yields of 63% and 46%, respectively.

(−)-**10**: (1*R*,8*S*,13*S*)-isomer; $[\alpha]^{25}_{D}$ −43° (*c* 0.5, EtOH). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 64.91; H, 6.93; N, 6.33.

(+)-**10**: (1*S*,8*R*,13*R*)-isomer; $[\alpha]^{25}_{D}$ +41° (*c* 0.5, Et(OH). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 64.86; H, 6.81; N, 6.11.

4-(2-Pyrrolidino)-2-(trimethylsilyl)benzothiophene ((±)-18). To a solution of 50 mg (0.23 mmol, 1.0 equiv) of thiophene (±)-**10** in 20 mL of THF, stirring at 25 °C, was added 0.62 mL (0.94 mmol, 4.0 equiv) of a 1.50 M solution of *n*-butyllithium in hexane dropwise, generating a yellow color. The solution was stirred for 2 h at room temperature, and then 0.23 mL (0.20 g, 1.84 mmol, 8.0 equiv) of chlorotrimethylsilane was added. The yellow color disappeared, and the solution turned red and then to a vivid purple, which faded as the solution was stirred for an additional 90 min. Reaction was quenched by the addition of 10 mL of distilled water. The reaction mixture was concentrated with a rotary evaporator and was then extracted with three 10-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$), filtered through a pad of Celite, and concentrated with a rotary evaporator to give a reddish oil, which was chromatographed on 3 g of silica gel, using 95% dichloromethane/4.5% methanol/0.5% ammonia as the eluant, to give 18 mg (29%) of a colorless oil: IR ($CHCl_3$) 3300–3000 (br), 1200, 990, 835, 710 cm^{-1}; ^1H NMR δ 0.40 (s, 9 H), 1.74–2.07 (m, 3 H), 2.10 (br s, 1 H), 2.23 (ddd, 1 H, *J* = 6, 7, 8), 3.11 (dt, 1 H, *J* = 9, 7), 3.28 (dt, 1 H, *J* = 9, 7), 4.73 (t, 1 H, *J* = 7), 7.29 (t, 1 H, *J* = 7), 7.45 (d, 1 H, *J* = 7), 7.65 (s, 1 H), 7.77 (d, 1 H, *J* = 7); MS, *m/e* 275 (4.96), 274 (7.07), 202 (3.60), 174 (11.09), 73 (9.10), 70 (3.74); UV λ_{max} 237 (12 990), 268 (5100), 276 (5315), 298 (2382), 308 (2522).

(1*SR*,8*RS*,13*RS*)-9-Aza-4-bromo-1-hydroxy-5-thiatetracyclo[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene (19). Method A. To a solution of 50 mg (0.23 mmol, 1.0 equiv) of thiophene (±)-**10** in 3 mL of glacial acetic acid were added 90 mg (0.56 mmol) of bromine and 1 drop of concentrated hydrobromic acid. The reaction mixture was stirred for 2 h at 25 °C, and then concentrated with a rotary evaporator. The residue was combined with 1 mL of saturated aqueous $Na_2S_2O_3$, 1 mL of saturated aqueous K_2CO_3, and 2 mL of distilled water and was then extracted three times with 5 mL of of a 1:1 solution of dichloromethane and THF. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, leaving 72 mg of a white solid. Recrystallization from methanol gave 62 mg (91%) of a white solid: mp 225 °C dec; IR 3680 (sharp), 2400, 1515, 1425, 1220, 925 cm^{-1}; ^1H NMR (CD_3OD) 1.68 (m, 5 H), 1.91 (m, 1 H), 2.21 (dd, 1 H, *J* = 7, 10), 2.65 (dt, 1 H, *J* = 7, 10), 2.84 (d, 1 H, *J* = 3), 2.86 (d, 1 H, *J* = 3), 3.31 (m, 3 H), 6.94 (s, 1 H); MS, *m/e* 301 (3.78), 299 (3.41), 232 (2.77), 230 (2.83), 150 (3.95), 70 (20.74). Anal. Calcd for $C_{12}H_{14}NOSBr$: C, 48.01; H, 4.70; N, 4.67; Br, 26.62. Found: C, 48.11; H, 4.73; N, 4.53; Br, 26.40.

Method B. To a solution of (±)-**10** (200 mg, 0.90 mmol, 1.0 equiv) in 80 mL of carbon tetrachloride (CCl_4) was added 170 mg (1.07 mmol, 1.2 equiv) of bromine in 5 mL of CCl_4. A fluffy yellowish precipitate appeared almost immediately. After stirring for 20 min at room temperature, the reaction mixture was washed with saturated aqueous $Na_2S_2O_3$, dried ($MgSO_4$), filtered, and concentrated. Recrystallization from methanol gave 270 mg (100%) of **19**, identical by TLC and ^1H NMR with the material prepared by method A.

The dibromo derivative, (1*SR*,8*RS*,13*RS*)-9-aza-3,4-dibromo-1-hydroxy-5-thiatetracyclo[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene, was also prepared by the following procedure. To a solution of 100 mg (0.45 mmol) of thiophene (±)-**10** in 10 mL of glacial acetic acid was added 250 mg (1.56 mmol) of bromine. The reaction mixture was stirred in the dark at room temperature for 7 days and was then quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$. The mixture was concentrated with a rotary evaporator, and the residue was taken up in distilled water and extracted three times with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellowish solid. Chromatography on silica, using 95% dichloromethane/4.5% methanol/0.5% ammonia as eluant, gave 132 mg (77%) of product as a white solid: mp 175–176 °C; IR ($CHCl_3$) 3560 (sharp), 1285, 1130, 995, 905 cm^{-1}; ^1H NMR δ 1.75 (m, 5 H), 1.93 (m, 1 H), 2.24 (dd, 1 H, *J* = 7, 10), 2.67 (m, 1 H), 2.90 (d, 2 H, *J* = 4), 3.30 (m, 3 H); MS, *m/e* 379 (0.95), 310 (1.18), 149 (2.18), 91 (1.99), 70 (6.25). Anal. Calcd for $C_{12}H_{13}Br_2NOS$: C, 38.02; H, 3.46; N, 3.69; Br, 42.15. Found: C, 37.87; H, 3.56; N, 3.51; Br, 42.28.

(1*SR*,8*RS*,13*RS*)-9-Aza-4-bromo-5-thia-1-(trimethylsiloxy)tetracyclo[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene (20). Compound **19** (245 mg, 0.82 mmol) was combined with 15 mL of dichloromethane to give an inhomogeneous mixture, which was cooled to 0 °C. *N*-(Trimethylsilyl)imidazole (145 μL, 137 mg, 0.98 mmol) was added dropwise. The mixture was stirred at 0 °C for 4 h, was allowed to warm to room temperature, and was stirred for an additional 3 h. The now-homogeneous solution was concentrated with a rotary evaporator, and the residue was chromatographed on silica with 95% dichloromethane/4.5% methanol/0.5% ammonia as the eluant to give 281 mg (92%) of **20** as a colorless oil that crystallized upon standing: mp 70–71.5 °C; IR ($CHCl_3$) 2490, 1445, 1330, 1245, 905 cm^{-1}; ^1H NMR δ 0.13 (s, 9 H), 1.55 (dt, 1 H, *J* = 18, 9), 1.78 (m, 4 H), 2.17 (dd, 1 H, *J* = 7, 10), 2.62 (dt, 1 H, *J* = 7, 10), 2.83 (br s, 2 H), 3.32 (m, 3 H), 6.90 (s, 1 H); MS, *m/e* 373 (2.15), 371 (2.07), 304 (3.56), 302 (3.90), 223 (4.42), 83 (5.76), 73 (6.50). Anal. Calcd for $C_{15}H_{22}BrNOSSi$: C, 48.38; H, 5.95; N, 3.76. Found: C, 48.62; H, 5.91; N, 3.71.

(1*SR*,3*RS*,13*RS*)-9-Aza-5-thia-1-(trimethylsiloxy)tetracyclo[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene (21). To 150 mg (0.74 mmol, 3.2 equiv) of *N,O*-bis(trimethylsilyl)acetamide was added 50 mg (0.23 mmol, 1.0 equiv) of alcohol (±)-**10**. The mixture was heated at 95 °C for 15 h in a flask with a reflux condenser attached. The reaction mixture was chromatographed on silica by using 95% dichloromethane/4.5% methanol/0.5% ammonia. After storage overnight on a high-vacuum line to remove traces of acetamide, the major product (45 mg, 68%) was isolated as a colorless oil, which solidified to feathery white crystals (mp 49–50.5 °C) upon standing: IR ($CHCl_3$) 1260, 1140, 905, 825 cm^{-1}; ^1H NMR δ 0.15 (s, 9 H), 1.60 (m, 2 H), 1.81 (m, 3 H), 2.22 (dd, 1 H, *J* = 7, 10), 2.65 (dt, 1 H, *J* = 7, 10), 2.93 (d, 2 H, *J* = 3), 3.36 (m, 3 H), 6.94 (d, 1 H, *J* = 5), 7.04 (d, 1 H, *J* = 5); MS, *m/e* 293 (2.37), 224 (5.81), 148 (1.41), 101 (2.06), 73 (6.30). Anal. Calcd for $C_{15}H_{23}NOSSi$: C, 61.39; H, 7.90; N, 4.77. Found: C, 61.54; H, 7.89; N, 4.64.

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Registry No. (2′*S*,3*R*)-**6**, 86747-47-9; (±)-**10**, 86728-39-4; (−)-**10**, 86782-91-4; (+)-**10**, 86782-92-5; **12**, 86728-40-7; (2′*S*,3*S*)-**13**, 86728-41-8; (±)-**18**, 86728-42-9; (±)-**19**, 86728-43-0; (±)-**20**, 86728-44-1; (±)-**21**, 86728-45-2; 2-thiophenylacetyl chloride, 39098-97-0; Meldrum's acid, 2033-24-1; methyl (*S*)-prolinate, 2577-48-2; *N*-(trimethylsilyl)imidazole, 18156-74-6; (1*RS*,8*RS*,13*RS*)-9-aza-3,4-dibromo-1-hydroxy-5-thiotetracyclo-[6.5.1.0^{2,6}.0^{9,13}]tetradeca-2(6),3-diene, 86728-46-3; *N,O*-bis(trimethylsilyl)acetamide, 10416-59-8.