80664-52-4; (±)-*cis*-**30e**, 80664-51-3; (±)-*trans*-**30e**, 80664-50-2; (±)-**31**, 92721-39-6; (±)-**32**, 92721-40-9; **33**, 2555-14-8; (±)-**34**, 92721-41-0; **35**, 2687-97-0; (±)-**36**, 92721-42-1; (±)-**36** (X = CH_3, OH), 92721-43-2; (±)-**37**, 92721-44-3; **38**, 92721-45-4; (±)-**39**, 80664-60-4; **40**, 80664-61-5; (±)-**41**, 92721-46-5; **43**, 92721-47-6; (±)-**43** (hydroxy lactam), 92721-59-0; (±)-**44**, 92721-48-7; (±)-**45**, 92721-49-8; (±)-**46**, 92721-50-1; (±)-**47**, 92762-55-5; **48**, 92721-51-2; (±)-$\Delta^{7,8}$-**49**, 92721-52-3; (±)-**50**, 92721-53-4; (±)-**51**, 92721-54-5; (±)-**52**, 92721-60-3; (±)-**53**, 83004-66-4; (±)-**55**, 92721-55-6; (±)-**56**, 92721-56-7; (±)-**57**, 92721-61-4; (±)-**58**, 92721-57-8; (±)-**59**, 92721-58-9; PhSH, 108-98-5; PhSeH, 645-96-5; 2,4-$(NO_2)_2C_6H_3F$, 70-34-8; CH_2=C=$CHCH_2OH$, 18913-31-0; PhSeCl, 5707-04-0; CH_2=$CHCH$=$CH(CH_2)_2OH$, 5747-07-9; succinimide, 123-56-8; 1-(3-pentynyl)-2,5-pyrrolidinedione, 63838-13-1.

Supplementary Material Available: Experimental procedures for the preparation of **4c**, **7b–e**, **10–14**, **25b**, **26b**, **27b–e**, **28b–e**, **29b–e**, **30b–e**, **34–41**, **44–46**, **48**, and **49** (17 pages). Ordering information is given on any current masthead page.

α-Acylamino Radical Cyclizations: Syntheses of Isoretronecanol

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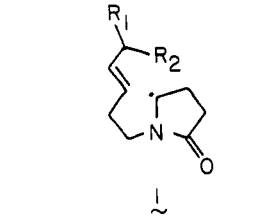
Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received February 27, 1984. Revised Manuscript Received May 29, 1984*

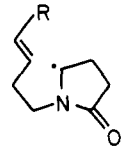
Abstract: α-Acylamino radicals **1–3** can be generated by tri-*n*-butyltin radical mediated cleavage of a carbon–sulfur bond. These radicals cyclize with good regio- and stereoselectivity to afford pyrrolizidinones. Cyclization products **12a** and **23a** were converted to the alkaloid isoretronecanol (**4**).

In the preceding paper in this issue we reported a new entry to pyrrolizidinones and indolizidinones by the cyclization of *N*-acyl-2-aza-5-hexenyl radicals.[4] Our initial studies showed that by placing methyl groups appropriately on the double bond, one could direct the regiochemical course of cyclization toward either pyrrolizidinone or indolizidinone formation. In subsequent studies, with an eye on using this methodology in pyrrolizidine alkaloid synthesis, we have focused on olefin substitution patterns which permit the introduction of the C(1)-hydroxymethyl group which appears in many of these natural products.[5] Specifically, this article describes the behavior of α-acylamino radicals **1–3** within the context of syntheses of the pyrrolizidine base isoretronecanol (**4**). For the sake of clarity, the synthesis and properties of radicals **1–3** will be discussed individually.

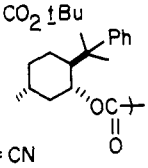


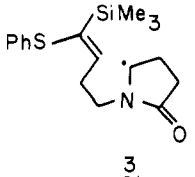
1

a R_1 = Me, R_2 = OAc
b R_1 = H, R_2 = OAc
c R_1 = R_2 = H

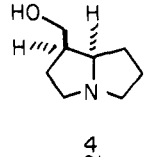


2

a R = CO_2 tBu
b R = 
c R = CN

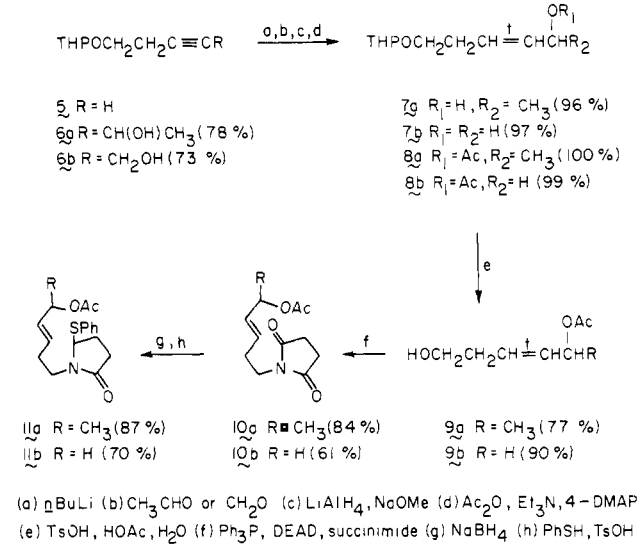


3



4

Scheme I



(a) nBuLi (b) CH_3CHO or CH_2O (c) $LiAlH_4$, NaOMe (d) Ac_2O, Et_3N, 4-DMAP (e) TsOH, HOAc, H_2O (f) Ph_3P, DEAD, succinimide (g) $NaBH_4$ (h) PhSH, TsOH

Results and Discussion

Generation and Cyclization of 1. The precursors of radicals **1a,b** were prepared in a straightforward manner as outlined in Scheme I. Sequential treatment of terminal acetylene **5**[6] with *n*-butyllithium and acetaldehyde gave alcohol **6a** (78%) which was reduced with lithium aluminum hydride–sodium methoxide to give trans allylic alcohol **7a** (96%).[7] The alcohol was acetylated by using the Steglich procedure,[8] and the resulting acetate **8a** (100%) was converted to alcohol **9a** upon treatment with aqueous acetic acid in tetrahydrofuran (77%). Coupling of **9a** with succiminide using the Mitsunobu procedure[9] gave imide **10a** (84%) which was converted to radical precursor **11a** by sequential reduction with sodium borohydride[10] and hydroxy–thiophenoxy exchange (87%).[4] Lactam **11b**, the precursor of **1b**, was prepared by using a similar

(1) Alfred P. Sloan Foundation Fellow, 1983–1985.
(2) McPherson-Evans Scholar, 1981–1982.
(3) Taken in part from: Tsai, Y.-M. Ph.D. Thesis, Ohio State University, 1983.
(4) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.*, preceding paper in this issue.
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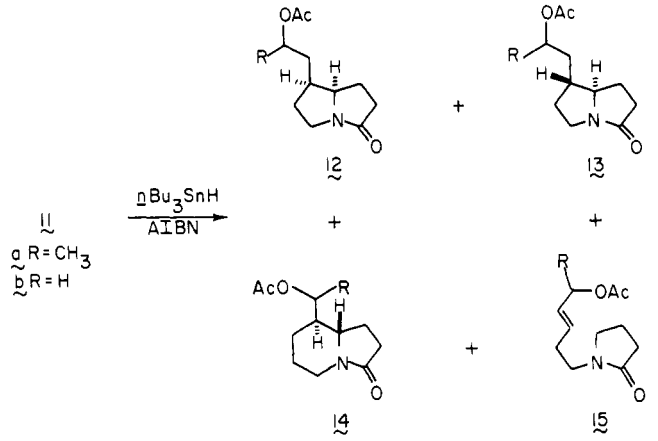
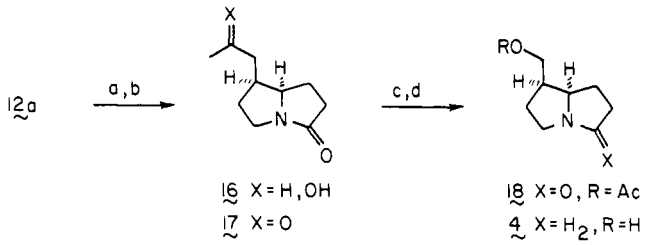
Scheme II



Scheme III



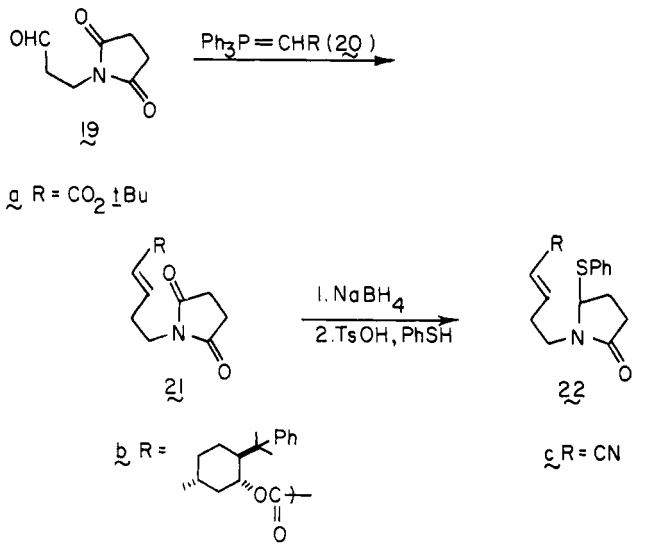
(a) NaOH, H_2O, MeOH (b) $(COCl)_2$, DMSO, Et_3N (c) CF_3CO_3H (d) $LiAlH_4$

reaction sequence. The yields of intermediates are documented in Scheme I.

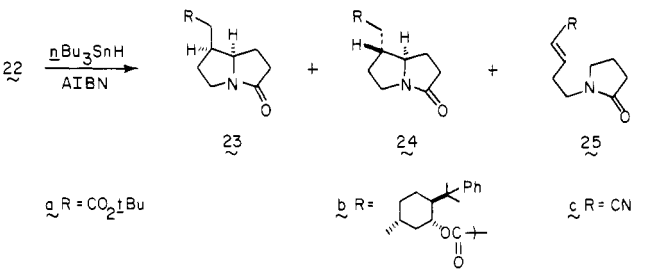
Our early studies suggested that the radicals derived from **11** would cyclize to mixtures of pyrrolizidinones and indolizidinones with little regioselectivity. For example, radical **1c** affords a 2:1 mixture of the exo and endo cyclization products, respectively.[4] Therefore it was surprising to find that treatment of **11a** with tri-*n*-butyltin hydride and AIBN gave a 9:1 ratio of diastereomeric pyrrolizidinones **12a** and **13a**, respectively, in an 86% yield. Indolizidinone **14a** (4%) and reduction product **15a** (5%) were only detected in minor amounts (Scheme II). The unexpected high exo–endo regioselectivity (21:1) in this reaction could be attributed to stabilization of the developing radical by the acetoxy group in the transition state of the exo cyclization.[11,12] We favor an alternative explanation, however, and suggest that steric effects probably decrease the rate of the endo cyclization. This would also account for the increase in regioselectivity observed for **1a** relative to **1c**. In agreement with this suggestion, treatment of **11b** with tri-*n*-butyltin hydride and AIBN gave a 64% yield of **12b + 13b**, **14b**, and **15b** in a 75:17:8 ratio, respectively. Thus, **1b** shows regioselectivity (exo:endo = 4.5:1) which falls between that shown by **1a** and **1c**.

From a synthetic standpoint, pure **12a** could be isolated from the cyclization of **11a** in a 71% yield. The structure assignment for **12a** was confirmed by completion of a synthesis of *dl*-isoretronecanol (**4**) as outlined in Scheme III. Hydrolysis of **12a** with sodium hydroxide in aqueous methanol gave a mixture of diastereomeric alcohol **16** (83%) which was converted to ketone **17** by using a Swern oxidation (89%).[13] Baeyer–Villager oxidation[14] of **17** with trifluoroperacetic acid gave **18** (56%) which was reduced with lithium aluminum hydride to afford isoretronecanol (**4**) in an 86% yield.[15]

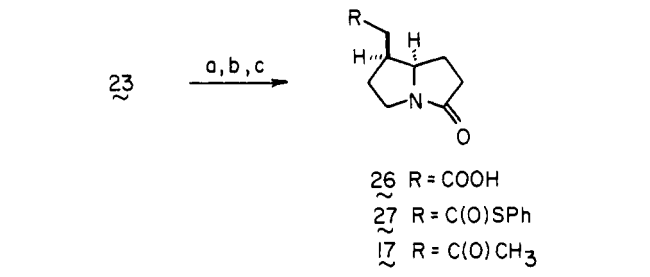
Scheme IV



Scheme V



Scheme VI



(a) TFA (b) DCC, 4-DMAP, Et_3N, PhSH (c) Me_2CuLi

Generation and Cyclization of 2. One problem associated with free radical cyclizations in media where hydrogen-atom-transfer reactions are possible is reduction of the radical prior to cyclization. The preceding example illustrates that this problem can be dealt with by using high-dilution techniques, although such conditions can become operationally cumbersome (see Experimental Section for details). However, the cyclization of radicals of type **2**, where a good donor–acceptor relationship is present, is quite fast, and high-dilution techniques are unnecessary.[16]

Precursors to radicals of type **2** were prepared as shown in Scheme IV. Aldehyde **19**, prepared from acrolein and succinimide,[17] was treated with phosphoranes **20a–c** to afford imides **21a–c** in 92%, 84%, and 76% yields, respectively. Reduction of **21** with sodium borohydride[10] followed by treatment of the crude carbinolamides with thiophenol and a catalytic amount of *p*-

(11) For an explanation of endo–exo terminology, see: Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.
(12) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447.
(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.
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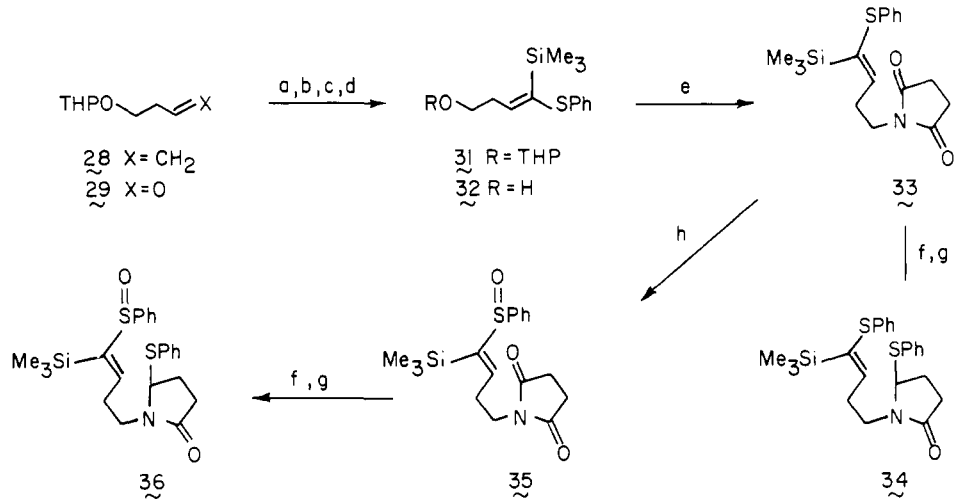
(15) Data on our material compared favorably to that reported elsewhere. Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783. Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230.
(16) For an appropriate discussion, see: Huyser, E. S. "Free-Radical Chain Reactions"; Wiley-Interscience: New York, 1970.
(17) Moe, O. A.; Warner, D. T. *J. Am. Chem. Soc.* **1949**, *71*, 1251. This procedure was capricious and at best gave a 50% yield of **19**.

Scheme VII



(a) O_3 (b) H_2, Pd on C (c) $(Me_3Si)_2C(Li)SPh$ (30) (d) TsOH, MeOH (e) Ph_3P, succinimide, DEAD (f) $NaBH_4$ (g) PhSH, TsOH (h) MCPBA

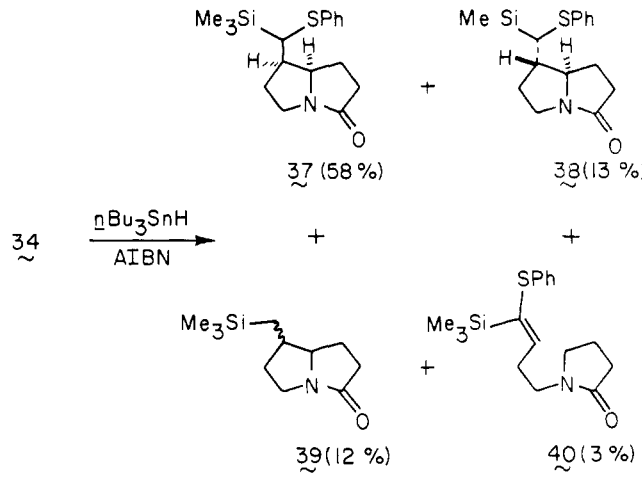
toluenesulfonic acid gave radical precursors **22a–c** in 91%, 87%, and 45% yields, respectively.[18]

Treatment of **22a** with neat tri-*n*-butyltin hydride and AIBN gave a 72% yield of a mixture of diastereomeric pyrrolizidinones **23a** and **24a** in a 9:1 ratio. In addition, reduction product **25a** was obtained in a 12% yield (Scheme V). Thus, cyclization of **2a** competed very favorably with reduction. As expected, the production of **25** could be reduced by simply running the reaction at higher dilution. For example, a 0.5 M benzene solution of **22a** containing 1.5 equiv of tri-*n*-butyltin hydride and 6 mol % of AIBN gave an 81% yield of **23a** and **24a** (9:1) containing no **25a**. The structure of the major cyclization product (**23a**) was proven by conversion to ketolactam **17** as shown in Scheme VI. Treatment of a 9:1 mixture of **23a** and **24a** with trifluoroacetic acid gave pure acid **26** in a 70% yield after recrystallization. Coupling of **26** with thiophenol in the presence of DCC and a catalytic amount of 4-(dimethylamino)pyridine gave thioester **27** (89%).[19] Treatment of **27** with lithium dimethyl cuprate completed the correlation with methyl ketone **17** (84%).[20]

Treatment of **22b** with tri-*n*-butyltin hydride and AIBN also gave a mixture of products **23b** and **24b** (9:1) in an 85% yield. Hydrolysis of the mixture with ethanolic potassium hydroxide gave **26** which did not show any significant optical activity. Thus, no notable asymmetric induction was observed in the cyclization of **22b**. Finally, treatment of **22c** with tri-*n*-butyltin hydride and AIBN gave nitriles **23c** and **24c** (9:1, respectively) in an 85% yield.

Generation and Cyclization of 3. The syntheses of isoretronecanol presented above were instructive from the standpoint of learning about steric and electronic effects on exo–endo partitioning in α-acylamino radical cyclizations. They suffered, however, from the standpoint of synthesis design in that a two-carbon unit was introduced at C(1) of the pyrrolizidine nucleus rather than the desired one-carbon unit. In an attempt to avoid the use of carbon–carbon bond breaking reactions in the synthetic sequence, radical precursors **34** and **36** were prepared as outlined in Scheme VII. Ozonolysis of **28** followed by a reductive workup gave the known aldehyde **29** (57%).[21] Treatment of **29** with anion **30** gave α-trimethylsilylvinyl sulfide **31** as a mixture of geometrical isomers.[22] Deprotection of **31** with *p*-toluenesulfonic acid in methanol gave alcohol **32** in a 92% yield. Mitsunobu coupling[9] of **32** with succinimide gave imide **33** (93%) which was reduced (sodium borohydride, methanol)[4] and followed by the exchange reaction to give **34** in an 89% yield as a 1:1 mixture of geometrical isomers. Alternatively, oxidation of **33** with *m*-chloroperbenzoic acid[23] gave an easily separable mixture of sulfoxide geometrical isomers **35a** (42%) and **35b** (42%) which were independently converted to the corresponding radical precursors **36a** and **36b** (64–69%) in the usual manner.

Scheme VIII



We had hoped that treatment of **36** with excess tri-*n*-butyltin hydride in benzene under reflux would trigger sequential radical formation, cyclization, sila–Pummerer rearrangement,[24] and subsequent carbon–sulfur bond cleavage[25] to afford a C(1)-hydroxymethyl side chain after a hydrolytic workup. Unfortunately, the thermal sensitivity of α-trimethylsilylvinyl sulfoxides[26] and other trouble we encountered while trying to generate α-acylamino radicals in the presence of sulfoxides prevented detailed examination of this sequence. We found, however, that radical precursor **34** behaved normally upon treatment with tri-*n*-butyltin

(18) Radical precursors **22a** and **22b** were contaminated by less than 10% of material in which the carbon–carbon double bond was also reduced. The reduction of **21c** and subsequent hydroxythiophenoxy exchange gave 21% of material resulting from conjugate reduction of the α,β-unsaturated nitrile (see Experimental Section for details).

(19) Lloyd, K.; Young, G. T. *J. Chem. Soc. C* **1971**, 2890.

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(21) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037.

(22) Grobel, B.-T.; Seebach, D. *Chem. Ber.* **1977**, *110*, 852.

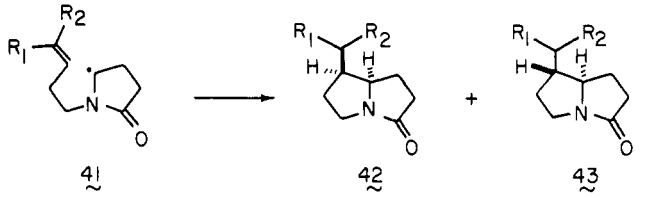
(23) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.

(24) For a review, see: Brook, A. G.; Bassindale, A. R. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 149–227.

(25) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, *45*, 3393.

(26) Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1983**, 4387.

Table I. Diastereoselectivity in Exo Cyclizations



41 42 43

entry[a]	R_1	R_2	42:43
1	H	H	11:1
2	H	Me	8:1
3	Me	H	6.5:1
4	Me	Me	4:1
5	H	$CH_2CH(OAc)CH_3$	9:1
6	H	CH_2CH_2OAc	9:1
7	H	CO_2tBu	9:1
8	H	CO_2Et	9:1
9	H(CN)	CN(H)	9:1
10	$SiMe_3(SPh)$	$SPh(SiMe)_3$	4.5:1

[a] Entries 1–4 are taken from the preceding article in this issue. Entries 5–7, 9, and 10 come from this work. For entry 8 see ref 3.

hydride and AIBN, giving the products shown in Scheme VIII in the indicated yields. We were able to transform diastereomeric silyl sulfides **37** into the corresponding aldehyde by oxidation to the sulfoxides, sila–Pummerer rearrangement, and hydrolysis.[27] The overall yield (30%) for this process, however, was not acceptable. Nonetheless, the chemistry presented in Schemes VII and VIII introduces a potentially useful olefin terminator for radical cyclizations and adds to the array of functional groups which will withstand α-acylamino radical precursor and radical generation conditions.

One notable feature of all the cyclizations presented above and in the preceding article is the relative invariance of the diastereomer ratios obtained in the exo cyclization process (Table I). Although this stereochemical result is consistent with results reported for carbocyclic systems,[28,29] the reason for this preference is not clear. Two basic arguments have been advanced by others to explain this pattern. The first suggests that secondary orbital interactions are responsible for the observed selectivity.[28,30] The second suggests that polar effects in the transition state may be the dominant factor.[31] Our studies show that the electronic nature of the olefin substituents seems to have little effect on the stereochemical course of the α-acylamino radical cyclizations. What little variance in the **42:43** ratio is observed seems to follow a pattern which depends on geometrical rather than electronic factors. These results suggest that varying the olefin HOMO and LUMO energy levels has little effect on the cyclization stereoselectivity in this system.

Summary and Conclusions. It has been shown that 2-aza-5-hexenyl radical cyclizations can provide a stereoselective entry to the pyrrolizidine nucleus. The factors which control the regiochemical course of these cyclizations are reasonably well understood. A pattern of stereoselectivity has also evolved although the reasons underlying this selectivity have not been uncovered. Finally, two syntheses of isoretronecanol have been accomplished by using a strategy which differs considerably from past syntheses,[5,15] yet competes reasonably in terms of length (13 steps from 3-butyn-1-ol or 10 steps from acrolein) and overall yield (11% or 9%). Studies directed toward establishing the general utility of α-acylamino radical cyclizations in alkaloid synthesis are under way.

Experimental Section

All melting points are uncorrected as are boiling points. ^1H NMR spectra are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constant in hertz, integration, interpretation]. Mass spectra were recorded at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at *m/e* greater than that of the parent. The parent ions of phenylthiolactams (e.g., **11a**) and a few other compounds were too small for exact mass measurements to be obtained. In these cases, the fragmentation patterns were in accord with the assigned structures. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether (distilled from Na metal); benzene, dimethyl sulfoxide, pyridine (distilled from calcium hydride); methanol (distilled from magnesium methoxide); chloroform, dichloromethane (passed through activity I alumina). All reaction temperatures refer to those of the reaction mixture. Reactions requiring an inert atmosphere were run under a blanket of argon. Tri-*n*-butyltin hydride was prepared according to a known procedure.[32] Column chromatography was performed over EM Laboratories silica gel (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed by using EM Laboratories Lobar prepacked silica gel columns. GLC analysis was done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector.

Procedures for the preparation of **6b–11b** and ylide **20b** appear in the supplementary material.

6-(Tetrahydro-2*H*-pyran-2-yloxy)-3-hexyn-2-ol (6a). To a solution of 7.99 g (51.9 mmol) of **5**[6] in 50 mL of dry tetrahydrofuran cooled in a dry ice–acetone bath under argon was added dropwise 51 mL of a 1.06 N solution of *n*-butyllithium in hexane over a period of 25 min. The resulting solution was stirred at −78 °C for 30 min and at −20 °C (dry ice–carbon tetrachloride bath) for 10 min followed by the addition of a solution of 5.8 mL (104 mmol) of fresh distilled acetaldehyde in 25 mL of dry tetrahydrofuran over a 20-min period. The reaction mixture was stirred at −20 °C for 20 min and partitioned between 300 mL of ether and 50 mL of water. The aqueous phase was extracted with 100 mL of ether. The combined organic layers were washed with 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 11.4 g of a pale-yellow oil. The oil was vacuum distilled to yield 8.06 g (78%) of alkynol **6a** as a pale-yellow oil: bp 100–101 °C/0.3 mmHg; IR (CCl_4) 3620, 3450 (br) cm^{-1}; NMR (CCl_4) δ 1.10–2.15 (m with d, *J* = 7 Hz, at 2.35, 10 H, CH_3, OH, and CH_2 manifold), 2.41 (dt, *J* = 7, 2 Hz, 2 H, ≡CCH_2), 3.30–3.95 (m, 4 H, OCH_2), 4.33 (br s, 1 H, ≡CH), 4.67 (br s, 1 H, OCHO); mass spectrum, *m/e* (rel intensity) 99 (12), 96 (7), 84 (100), 83 (49), 69 (23).

6-(Tetrahydro-2*H*-pyran-2-yloxy)-3(*E*)-hexen-2-ol (7a). To a mixture of 4.90 g (129 mmol) of lithium aluminum hydride in 400 mL of dry tetrahydrofuran under argon was added 13.8 g (255 mmol) of sodium methoxide. The resulting mixture was stirred at room temperature for 10 min followed by the addition of a solution of 8.53 g (43.1 mmol) of alkynol **6a** in 50 mL of dry tetrahydrofuran over a 40-min period. The reaction mixture was heated to reflux for 1 h. The reaction flask was cooled in an ice–water bath, and 4.5 mL of water, 4.5 mL of 3 N sodium hydroxide solution, and 13.4 mL of water were carefully added in sequence. The resulting mixture was stirred at room temperature for 90 min, filtered, and concentrated in vacuo. The residual colorless oil was distilled to afford 8.31 g (96%) of allylic alcohol **7a** as a colorless oil: bp 94 °C/0.4 mmHg; IR (CCl_4) 3610, 3430 (br) cm^{-1}; NMR (CCl_4) δ 1.20 (d, *J* = 7 Hz, 3 H, CH_3), 1.33–2.00 (m, 7 H, CH_2 manifold and OH), 2.27 (br q, *J* = 6 Hz, 2 H, CH_2C=), 3.20–3.95 (m, 4 H, OCH_2), 4.15 (br s, 1 H, =CCH), 4.53 (br s, 1 H, OCHO), 5.50–5.67 (m, 2 H, =CH); mass spectrum *m/e* (rel intensity) 98 (M^+ − (THP)OH, 19), 84 (100), 83 (62).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.11; H, 10.10.

6-(Tetrahydro-2*H*-pyran-2-yloxy)-3(*E*)-hexen-2-yl Acetate (8a). To a solution of 8.02 g (40.1 mmol) of allyl alcohol **7a** and 47.4 mg (0.390 mmol) of 4-(dimethylamino)pyridine in 40 mL of dry pyridine under argon was added 6.7 mL (71.0 mmol) of dry acetic anhydride. The reaction mixture was stirred at room temperature for 1.5 h. The resulting solution was diluted with 300 mL of ether, shaken with 20 mL of water for a few minutes in a separatory funnel, and washed with 180 mL of 3 N aqueous hydrochloric acid. The aqueous phase was extracted with 200 mL of ether. The combined organic layers were washed with 100 mL of water, 100 mL of saturated aqueous sodium bicarbonate, and 100 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to yield 9.68 g (100%) of allylic acetate **8a** as a colorless oil. This material was used directly in subsequent reactions: IR (CCl_4) 1730 cm^{-1}; NMR (CCl_4) δ 1.27 (d, *J* = 6 Hz, 3 H, CH_3), 1.40–1.95 (m, 6 H,

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CH_2 manifold), 1.96 (s, 3 H, $COCH_3$), 2.29 (br q, J = 6 Hz, 2 H, $=CCH_2$), 3.15–3.89 (m, 4 H, OCH_2), 4.52 (br s, 1 H, OCHO), 5.10–5.95 (m, 3 H, CHOAc and =CH); mass spectrum, *m/e* (rel intensity) 98 (12), 84 (100), 83 (55), 80 (12), 79 (17), 69 (22), 68 (23), 67 (28).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.36; H, 9.40.

3(*E*)-Hexen-1-ol-5-yl Acetate (9a). A solution of 3.12 g (12.9 mmol) of allylic acetate **8a** in 80 mL of acetic acid, 40 mL of tetrahydrofuran, and 25 mL of water was heated at 45 °C for 4 h and 40 min. The resulting solution was diluted with 200 mL of ether and 300 mL of water. Sodium bicarbonate (120 g) was added in portions with stirring. The resulting mixture was filtered. The filtrate was diluted with 100 mL of ether. The organic layer was washed with three 50-mL portions of saturated aqueous sodium bicarbonate, three 200-mL portions of water, and 100 mL of saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo to give 1.18 g of a pale-yellow liquid. The aqueous washes and filter cake were combined and extracted with 500 mL of ether. The ether layer was washed with 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.09 g of a colorless liquid. The combined aqueous phases were extracted again with 500 mL of dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford 0.494 g of a colorless liquid. The combined crude product was distilled to give 1.80 g of a colorless liquid: bp 75–77 °C/0.75 mmHg. This material was chromatographed over 35 g of silica gel (ethyl acetate–hexane, 3:7, followed by ethyl acetate–hexane, 4:6) to yield 1.57 g (77%) of alcohol **9a** as a colorless liquid: IR (CCl_4) 3480 (br), 1730 cm^{-1}; NMR (CCl_4) δ 1.27 (d, J = 6 Hz, 3 H, CH_3), 1.96 (s, 3 H, $COCH_3$), 2.09–2.37 (m, 3 H, $CH_2C=$ and OH), 3.53 (br t, J = 6 Hz, 2 H, OCH_2), 5.00–5.85 (m, 3 H, CHOAc and =CH); mass spectrum, *m/e* (rel intensity) 115 ($M^+ - COCH_3$, 12), 98 (42), 83 (38), 81 (12), 80 (19), 79 (31), 77 (8), 71 (15), 70 (4), 69 (23), 68 (100), 67 (77), 66 (8), 65 (15).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 59.88; H, 9.06.

1-(5-Acetoxy-3(*E*)-hexenyl)-2,5-pyrrolidinedione (10a). To a solution of 2.99 g (19.0 mmol) of alcohol **9a**, 1.87 g (18.9 mmol) of succinimide, and 4.96 g (18.9 mmol) of triphenylphosphine in 24 mL of dry tetrahydrofuran cooled in an ice–water bath under argon was added dropwise a solution of 3.29 g (18.9 mmol) of diethyl azodicarboxylate in 7 mL of dry tetrahydrofuran over a period of 40 min. The resulting solution was stirred at room temperature for 2 min, and the solvent was removed in vacuo. The residue was triturated with 65 mL of ethyl acetate–hexane (3:7) and filtered. The filter cake was triturated again with 30 mL of the same solvent pair. The combined extracts were concentrated in vacuo, suspended in 60 mL of ethyl acetate–hexane (3:7), and filtered. The filtrate was concentrated in vacuo to afford 6.75 g of a pale-yellow oil. The oil was chromatographed over 90 g of silica gel (dichloromethane followed by 0.25% methanol in dichloromethane and finally 0.5% methanol in dichloromethane) to yield 2.91 g (61%) of imide **10a** as a pale-yellow oil. Collection of latter fractions gave 1.81 g of a mixture of yellow oil and white solid. This material was suspended in carbon tetrachloride and filtered twice to remove insoluble solids. The filtrate was concentrated in vacuo to afford a pale-yellow oil. The oil was bulb-to-bulb distilled at 0.5 mmHg at 110 °C to trap 209 mg of a colorless liquid identified as unreacted alcohol **9a** with 1.03 g (23%) of imide **10a** left in the distillation flask as a pale-yellow oil: IR (CCl_4) 1740, 1705 cm^{-1}; NMR (CCl_4) δ 1.28 (d, J = 6 Hz, 3 H, CH_3), 1.93 (s, 3 H, $COCH_3$), 2.30 (br q, J = 6 Hz, 2 H, $=CCH_2$), 2.57 (s, 4 H, $NCOCH_2$), 3.48 (t, J = 6 Hz, 2 H, NCH_2), 4.95–5.75 (m, 3 H, CHOAc and =CH); mass spectrum, *m/e* (rel intensity) 197 (23), 196 ($M^+ - COCH_3$, 17), 179 (53), 140 (10), 136 (10), 127 (13), 113 (8), 112 (8), 100 (40), 98 (13), 97 (20), 85 (13), 84 (20), 83 (12), 82 (5), 81 (33), 80 (100), 79 (20).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16. Found: C, 60.06; H, 7.22.

1-(5-Acetoxy-3(*E*)-hexenyl)-5-(phenylthio)-2-pyrrolidinone (11a). To a solution of 3.82 g (16.0 mmol) of imide **10a** in 90 mL of absolute ethanol cooled in an ice–water bath under argon was added 1.78 g (47.2 mmol) of sodium borohydride. A 1.49 N solution of hydrogen chloride was added at a rate of 3 drops every 5 min over a period of 2 h and 15 min. The resulting mixture was partitioned between 50 mL of water, 50 mL of saturated sodium chloride solution, and 150 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 3.76 g of crude carbinollactam as a colorless oil. The oil was stirred with 60 mg (0.32 mmol) of *p*-toluenesulfonic acid monohydrate and 1.61 mL (15.7 mmol) of thiophenol at room temperature for 2 h and chromatographed over 100 g of silica gel (ethyl acetate–hexane, 4:6, followed by ethyl acetate–hexane, 1:1) to afford 4.63 g (86%) of thiophenoxylactam **11a** as a colorless oil: IR (CCl_4) 1740, 1700 cm^{-1}; NMR (CCl_4) δ 1.27 (d, J = 6 Hz, 3 H, CH_3), 1.42–2.55 (m with s at 1.97, 9 H, $COCH_3$ and CH_2 manifold), 3.20 (dt, J = 12, 6 Hz, 1 H, NCH), 3.80 (dt, J = 12, 6 Hz, 1 H, NCH), 4.82 (dd, J = 8, 3 Hz, 1 H, NCHS), 4.95–5.40 (m, 1 H, CHOAc), 5.40–5.70 (m, 2 H, =CH), 7.31 (br s, 5 H, ArH); mass spectrum, *m/e* (rel intensity) 224 (M^+ – SPh, 29), 164 (44), 163 (27), 110 (53), 109 (16), 96 (100), 81 (36), 68 (49).

1-(5-Acetoxy-3(*E*)-hexenyl)-2-pyrrolidinone (15a), *rel*-(1*R*,7a*R*)-Hexahydro-1-(2-acetoxypropyl)-1*H*-pyrrolizin-5-one (13a), and *rel*-(1*S*,7a*R*)-Hexahydro-1-(2-acetoxypropyl)-1*H*-pyrrolizin-5-one (12a). To a solution of 4.61 g (13.8 mmol) of thiophenoxylactam **11a** in 200 mL of dry benzene heated under argon at 80 °C was added a solution of 5.1 mL (19.3 mmol) of tri-*n*-butyltin hydride and 72 mg (0.44 mmol) of AIBN in 120 mL of dry benzene over a 23-h period. The solvent was removed in vacuo, and the residue was chromatographed over 120 g of silica gel (ethyl acetate followed by ethyl acetate–methanol, 9:1) and then over a Lobar size C column (ethyl acetate–hexane, 85:15, followed by ethyl acetate) to afford a total of 2.85 g (95%) of lactams **15a**, **14a**, **12a**, and **13a** in a ratio of 5:4:82:9, respectively, by NMR integration. The isomeric lactams eluted in the order presented above. A pure sample of the least polar isomer (**15a**) was difficult to obtain, and it was characterized only by its ^1H NMR: ^1H NMR (CCl_4) δ 1.23 (d, J = 6 Hz, 3 H, CH_3), 1.73–2.36 (m with s at 1.82, 9 H, $COCH_3$ and CH_2 manifold), 3.10–3.37 (m, 4 H, NCH_2), 5.00–5.60 (m, 3 H, CHOAc and =CH). Lactam **14a** was not completely separable from **12a** and was characterized only after hydrolysis of the acetate (vide infra). Lactam **12a** (2.22 g, 71%): IR (CCl_4) 1740, 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.21–1.28 (two overlapping d's, J = 6 Hz, at 1.24 and 1.25, 3 H, CH_3), 1.30–2.80 (m with s at 2.05, 12 H, CH_3 and CH_2 manifold), 2.88–3.07 (m, 1 H, NCH), 3.47–3.72 (m, 1 H, NCH), 4.02 (q, J = 6 Hz, 1 H, angular NCH), 4.89–5.03 (m, 1 H, CHOAc). Exact mass calcd for $C_{12}H_{19}NO_3$: *m/e* 225.1365. Found: *m/e* 225.1371. Lactam **13a** (279 mg, 9%): IR (CCl_4) 1740, 1700 cm^{-1}; NMR (CCl_4) δ 1.25 (d, J = 6 Hz, 3 H, CH_3), 1.36–2.83 (m with s at 1.89, 12 H, CH_3 and CH_2 manifold), 3.05 (br t, J = 11 Hz, 1 H, NCH), 3.23–3.66 (m, 2 H, NCH and angular NCH), 4.67–5.00 (br s, 1 H, CHOAc). Exact mass calcd for $C_{12}H_{19}NO_3$: *m/e* 225.1365. Found: *m/e* 225.1369.

***rel*-(1*S*,7a*R*)-Hexahydro-1-(2-hydroxypropyl)-1*H*-pyrrolizin-5-one (16) and *rel*-(8*S*,8a*R*)-Hexahydro-8-(2-hydroxypropyl)-2*H*-indolizin-3-one.** To 2.15 g (9.54 mmol) of lactam acetate **12a** was added 25 mL of a 1.04 N solution of sodium hydroxide in aqueous methanol (H_2O–MeOH, 1:5). The resulting solution was stirred at room temperature for 15 min, diluted with 700 mL of dichloromethane, saturated with sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 1.69 g of a pale-yellow oil. The oil was chromatographed over a Lobar size C column (ethyl acetate–methanol, 92:8). Overlapping fractions were rechromatographed over a Lobar size B column (5% methanol in ethyl acetate), and the overlapping part was chromatographed again over the same column (2% methanol in ethyl acetate) to yield 60 mg (3%) of the alcohol derived from hydrolysis of **14a** as a colorless oil: IR (CCl_4) 3400 (br), 1670 cm^{-1}; NMR ($CDCl_3$) 1.00–2.90 (m with two d, J = 6 Hz at 1.09 and 1.21, 13 H, OH, CH_3, and CH_2 manifold), 2.90–4.25 (m with br d, J = 14 Hz, 4 H, NCH, NCH_2, and CHOAc). Exact mass calcd for $C_{10}H_{17}NO_2$: *m/e* 183.1259. Found: *m/e* 183.1264. Continued elution gave 1.46 g (83%) of pure **16** as a pale-yellow oil: IR (CH_2Cl_2) 3520 (br), 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.80–3.15 (m with d, J = 6 Hz, at 1.21, 14 H, CH_3, OH, CHN, and CH_2 manifold), 3.40–4.20 (m, 3 H, CHOAc and NCH). Exact mass calcd for $C_{10}H_{17}NO_2$: *m/e* 183.1259. Found: *m/e* 183.1266.

***rel*-(1*S*,7a*R*)-Hexahydro-1-(2-oxopropyl)-1*H*-pyrrolizin-5-one (17).** To a solution of 0.79 mL (9.05 mmol) of oxalyl chloride in 20 mL of dry dichloromethane cooled in a dry ice–acetone bath was added dropwise a solution of 1.34 mL (18.9 mmol) of dimethyl sulfoxide in 4 mL of dichloromethane over a period of 30 min. The resulting solution was stirred at −78 °C for 10 min followed by the addition of a solution of 1.40 g (7.67 mmol) of carbinollactam **16** in 8 mL of dry dichloromethane over a 30-min period. The reaction mixture was stirred at −78 °C for 30 min followed by the addition of 5.5 mL (39.5 mmol) of triethylamine over a 7-min period. After the solution was stirred at −78 °C for 5 min and at room temperature for 1 h, the reaction mixture was quenched with 10 mL of water. The resulting mixture was stirred until it turned clear, saturated with sodium chloride, and extracted with three 100-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a solid residue. This material was triturated with 500 mL of ethyl acetate and filtered. The filtrate was concentrated in vacuo to give 1.94 g of a brown liquid which was chromatographed over 60 g of silica gel (2% methanol in ethyl acetate) to yield 1.24 g (89%) of **17** as a pale-yellow oil. Later fractions contaminated with dimethyl sulfoxide were purified by dissolving in 25 mL of

1,2-dichloroethane and washing with 5 mL of water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to provide an additional 64 mg (5%) of pure **17** as a pale-yellow oil: IR (CCl_4) 1720, 1695 cm^{-1}; NMR (CCl_4) δ 1.35–3.07 (m with s at 2.11, 13 H, CH_3, NCH, and CH_2 manifold), 3.49 (td, J = 11, 7 Hz, 1 H, NCH), 4.01 (q, J = 6 Hz, 1 H, angular NCH). Exact mass calcd for $C_{10}H_{15}NO_2$: m/e 181.1103. Found: m/e 181.1111.

***rel*-(1*R*,7a*R*)-Hexahydro-1-(acetoxymethyl)-1*H*-pyrrolizin-5-one (18).** A solution of trifluoroperacetic acid was prepared by dropwise addition of 7 mL of trifluoroacetic anhydride into an ice–water bath cooled mixture of 1 mL of 90% hydrogen peroxide in 5 mL of dichloromethane over a 20-min period. After the solution was stirred at 0 °C for another 10 min, the resulting solution was ready for use.

Part of the solution prepared above (1.5 mL, 4.25 mmol) was added dropwise into an ice–water bath cooled solution of 97.6 mg (0.539 mmol) of methyl ketone **17** in 2 mL of dry dichloromethane over 5 min. The resulting solution was stirred at room temperature for 3 h and then poured into a mixture of 20 mL of water and 30 mL of dichloromethane. Solid sodium bicarbonate was added with stirring until no gas formation was observed. The mixture was saturated with sodium chloride and extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 99 mg of pale-yellow oil. The oil was chromatographed over 5 g of silica gel (2% methanol in ethyl acetate) to afford 59 mg (56%) of lactam acetate **18** as a pale-yellow oil: IR (CH_2Cl_2) 1740, 1685 cm^{-1}; NMR (CCl_4) δ 1.50–3.10 (m with s at 1.98, 11 H, CH_3, NCH, and CH_2 manifold), 3.55 (td, J = 11, 7 Hz, 1 H, NCH), 3.77–4.17 (m, 3 H, CH_2OAc and angular NHC). Exact mass calcd for $C_{10}H_{15}NO_3$: m/e 197.1052. Found m/e 197.1057.

(±)-Isoretronecanol (4). To a solution of 74.0 mg (0.376 mmol) of lactam acetate **18** in 5.5 mL of dry tetrahydrofuran was added 97.6 mg (2.56 mmol) of lithium aluminum hydride. The reaction mixture was heated to reflux under argon for 30 min and diluted with 30 mL of ether followed by the addition of 69 μL of water and 69 μL of 3 N sodium hydroxide solution. After the solution was stirred at room temperature for 1 h, the resulting mixture was filtered. The filtrate was concentrated in vacuo to yield 45.5 mg (86%) of **4** as a pale-yellow oil: picrate mp 188 °C (lit.[15] 189.5–191 °C); IR (CCl_4) 3360 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.03–2.17 (m, 7 H, CH_2 manifold), 2.12–2.77 (m, 2 H, NCH), 2.77–3.27 (m, 2 H, NCH), 3.27–3.85 (m with d at 3.59, J = 7 Hz, 3 H, OCH_2 and angular NCH), 4.33 (br s, 1 H, OH); mass spectrum, m/e (rel intensity) 141 (24), 140 (12), 124 (18), 83 (100). Exact mass calcd for $C_8H_{15}NO$: m/e 141.1154. Found: m/e 141.1158.

The high-field NMR spectrum compared favorably with that reported in the literature.[15]

1-(5-Acetoxy-3(*E*)-pentenyl)-2-pyrrolidinone (15b), *rel*-(8*R*,8a*R*)-Hexahydro-8-(acetoxymethyl)-2*H*-indolizin-3-one (14b), *rel*-(1*R*,7a*R*)-Hexahydro-1-(2-acetoxyethyl)-1*H*-pyrrolizin-5-one (13b) and *rel*-(1*S*,7a*R*)-Hexahydro-1-(2-acetoxyethyl)-1*H*-pyrrolizin-5-one (12b). To a solution of 155 mg (0.49 mmol) of **11b** in 6.5 mL of benzene was added a solution of 0.26 mL (0.99 mmol) of tri-*n*-butyltin hydride and 6 mg of AIBN in 6 mL of benzene over a 28-h period. The resulting solution was concentrated in vacuo, and the residue was partitioned between 10 mL of hexane and 10 mL of acetonitrile. The hexane layer was extracted with two 10-mL portions of acetonitrile. The acetonitrile layers were concentrated in vacuo, and the residue was chromatographed over 6 g of silica gel (ethyl acetate–hexane, 1:1, followed by ethyl acetate and finally ethyl acetate–methanol, 9:1) to give 39 mg (25%) of recovered **11b** and 65 mg (64%) of a mixture of **12b + 13b**, **14b**, and **15b** in a ratio of 75:17:8, separable by GLC (6 ft × $^1/_8$ in. 3% SE-30 on WAW, DMCS 80–100; column temperature = 200 °C, flow rate = 25 mL He min^{-1}). Pure samples of **15b**, **14b**, and **13b + 12b** were obtained by preparative GLC. Lactam **15b**: t_R = 5.8 min; IR (CCl_4) 1745, 1690 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.95–2.10 (m overlapping with s at 2.07, 5 H, CH_3 and CH_2), 2.25 (m, 4 H, $COCH_2$ and CH_2C=), 3.34–3.41 (two overlapping t's, J = 7.5 Hz, at 3.37 and 3.38, 4 H, NCH_2), 4.51 (d, J = 5 Hz, 2 H, CH_2OAc), 5.53–5.82 (m, 2 H, =CH). Exact mass calcd for $C_{11}H_{17}NO_3$: m/e 211.1209. Found: m/e 211.1196. Lactam **14b**: t_R = 6.75 min; IR (CCl_4) 1750, 1695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.20–2.42 (m with s at 2.08, 12 H, CH_3, CH, and CH_2 manifold) 2.58 (br t, J = 10 Hz, 1 H, axial NC(5)H), 3.20 (td, J = 10, 6 Hz, 1 H, equatorial NC(5)H), 4.04 (br d, 2 H, J = 5 Hz, CH_2OAc), 4.16 (br d, J = 12 Hz, 1 H, NC(9)H). Exact mass calcd for $C_{11}H_{17}NO_3$: m/e 211.1209. Found: m/e 211.1196. Lactam **12b**: t_R = 7.9 min; IR (CCl_4) 1745, 1695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.25–2.25 (m with s at 2.05, 10 H, CH_3 and CH_2 manifold), 2.39 (ddd, J = 15, 10, 3 Hz, 1 H, COCH), 2.69 (td, J = 15, 10 Hz, 1 H, COCH), 3.00 (td, J = 12, 6 Hz, 1 H, NCH), 3.50–3.70 (m, 1 H, NCH), 3.99–4.18 (m, 3 H, CH_2OAc and NHC). Exact mass calcd for $C_{11}H_{17}NO_3$: m/e 211.1209. Found: m/e 211.1192. A broad triplet at δ 3.15 indicated the presence of a small amount of 13b. The ratio of **12b**:**13b** was 9:1 by NMR.

***cis*- and *trans*-1-(4-(*tert*-Butoxy)carbonyl)-3-butenyl)-2,5-pyrrolidinedione (21a).** To a mixture of 395 mg (2.55 mmol) of aldehyde **19**[17] and 843 mg (2.24 mmol) of (*tert*-butoxycarbonyl)methylidenetriphenylphosphorane (**20a**)[33] under argon was added 2.3 mL of dry dichloromethane. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with 16 mL of dichloromethane and chromatographed directly over 25 g of silica gel (ethyl acetate–hexane, 47:53) to afford 519 mg (92%) of imide **21a** (cis:trans = 15:85) as a colorless oil: IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 1.47 (s, 9 H, CH_3), 2.43 (br q, J = 7 Hz, 2 H, CH_2C=), 2.63 (s, 4 H, $NCOCH_2$), 3.57 (br t, J = 7 Hz, 2 H, NCH_2), 5.55–6.90 (m, with trans signals shown as br d, J = 16 Hz, at 5.70 and td, J = 16, 7 Hz, at 6.67, 2 H, =CH). Exact mass calcd for $C_{13}H_{19}NO_4$: m/e 253.1314. Found: m/e 253.1320.

Ester 21b. To 5.10 g (9.56 mmol) of ylide **20b**[34] was added a solution of 1.78 g (11.5 mmol) of aldehyde **19**[17] in 18 mL of dry dichloromethane. The resulting yellow solution was stirred at room temperature for 1 h and 20 min. The solution was diluted with 50 mL of dichloromethane and 50 mL of ethyl acetate–hexane (4:6) and directly chromatographed over 140 g of silica gel (ethyl acetate–hexane, 4:6) to give 3.31 g (84%) of imide **21b** (cis:trans = 15:85) as a colorless oil. The pure trans isomer could be crystallized from 3 mL of ethyl acetate and 70 mL of hexane as white needles: mp 119–120 °C; IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 0.65–2.13 (m with br d, J = 6 Hz, at 0.90 and two br s at 1.20 and 1.29, 17 H, CH_3CH, $Ph(CH_3)_2C$, and cyclohexyl), 2.30 (br q, J = 7 Hz, 2 H, CH_2C=), 2.63 (s, 4 H, $NCOCH_2$), 3.48 (t, J = 7 Hz, 2 H, NCH_2), 4.70 (dt, J = 11, 4 Hz, 1 H, OCH), 5.20 (br d, J = 16 Hz, 1 H, COCH=), 6.27 (td, J = 16, 7 Hz, 1 H, =CH), 7.15 (br s, 5 H, ArH).

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08. Found: C, 72.66; H, 8.02.

The pure cis isomer could be isolated by MPLC (Lobar size B column, ethyl acetate–hexane, 3:7) as a colorless oil: IR (CH_2Cl_2) 1710 cm^{-1}; NMR (CCl_4) δ 0.67–2.15 (m with br d, J = 6 Hz, at 0.85 and two br s at 1.19 and 1.27, 17 H, CH_3CH, $Ph(CH_3)_2C$, and cyclohexyl), 2.45–2.90 (m with s at 2.59, 6 H, CH_2C= and $NCOCH_2$), 3.50 (t, J = 7 Hz, 2 H, NCH_2), 4.70 (dt, J = 11, 4 Hz, 1 H, OCH), 5.10 (br d, J = 12 Hz, 1 H, COCH=), 5.90 (td, J = 12, 7 Hz, 1 H, =CH), 7.13 (br s, 5 H, ArH). Exact mass calcd for $C_{25}H_{33}NO_4$: m/e 411.2409. Found: m/e 411.2417.

***cis*- and *trans*-1-(4-Cyano-3-butenyl)-2,5-pyrrolidinedione (21c).** A mixture of 356 mg (2.30 mmol) of aldehyde **19** and 694 mg (2.30 mmol) of cyanomethylidenetriphenylphosphorane (**20c**)[35] in 2.3 mL of dichloromethane was stirred under argon at room temperature for 2 h and concentrated in vacuo. The resulting pale-yellow solid was chromatographed over 18 g of silica gel (methanol in dichloromethane) to yield 311 mg (76%) of imide **21c** (cis:trans = 4:6) as a pale-yellow oil: IR (CH_2Cl_2) 2220, 1705 cm^{-1}; NMR ($CDCl_3$) δ 2.30–2.85 (m with s at 2.70, 6 H, CH_2C= and $NCOCH_2$), 3.50–3.80 (two overlapping t's, J = 7 Hz, at 3.63 and 3.69, 2 H, *trans*- and *cis*-NCH_2), 5.20–5.60 (two overlapping d's, J = 12 Hz at 5.35 and J = 16 Hz at 5.39, 1 H, *cis*- and *trans*-=CHCN), 6.25–6.90 (m with the trans signal clearly displayed as td, J = 16, 7 Hz, at 6.63, 1 H, CH=CHCN). Exact mass calcd for $C_9H_{10}N_2O_2$: m/e 178.0742. Found: m/e 178.0747.

***cis*- and *trans*-1-(4-(*tert*-Butoxycarbonyl)-3-butenyl)-5-(phenylthio)-2-pyrrolidinone (22a).** To a solution of 4.32 g (17.1 mmol) of imide **21a** in 100 mL of absolute ethanol cooled in an ice–water bath under argon was added 1.90 g (50.3 mmol) of sodium borohydride. Over a period of 3 h, a 1.94 N solution of hydrogen chloride in absolute ethanol was added at a rate of 2 drops every 5 min. The resulting solution was poured into a mixture of 50 mL of water, 50 mL of saturated aqueous sodium chloride, and 100 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 4.33 g of a colorless oil. The oil was stirred with 130 mg (0.680 mmol) of *p*-toluene sulfonic acid monohydrate and 1.74 mL (17.0 mmol) of thiophenol under argon at room temperature for 3 h and 20 min. The mixture was diluted with 100 mL of dichloromethane and washed with 50 mL of 1 N aqueous sodium hydroxide. The aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford a pale-yellow oil which was chromatographed over 130 g of silica gel

(33) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Tetrahedron* **1976**, *32*, 275.

(34) Prepared from (1*R*,2*R*,5*R*)-2-(2-phenyl-2-propyl)-5-methylcyclohexanol (Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908) by using the following reaction sequence: (1) $BrCH_2CO_2H$, DCC, 4-DMAP, (2) Ph_3P, (3) NaOH, H_2O. The details appear in the supplementary material.

(35) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1959**, 3874.

(ethyl acetate-hexane, 45:55) to yield 5.19 g (91%) of **22a** as a colorless oil (cis:trans = 15:85) contaminated with a small amount of 1-(4-(*tert*-butoxycarbonyl)butenyl)-5-(phenylthio)-2-pyrrolidinone. This material was used directly in the cyclization reaction. A pure sample of **22a** was obtained by MPLC (Lobar size A column, eluted with ethyl acetate–hexane, 3:7). The less polar cis isomer of **22a**: IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) 1.50 (s, 9 H, CH_3), 1.53–3.45 (m, 7 H, NCH and CH_2 manifold), 3.67–4.07 (m, 1 H, NCH), 5.00 (dd, J = 7, 2 Hz, 1 H, NCHS), 5.67 (br d, J = 12 Hz, 1 H, COCH=), 6.08 (ddd, J = 12, 8, 7 Hz, 1 H, =CH), 7.28 (br s, 5 H, ArH); mass spectrum, m/e (rel intensity) 274 (5), 238 (M^+ – SPh, 26), 218 (5), 182 (33), 181 (21), 164 (21), 163 (16), 136 (15), 110 (100), 109 (22), 96 (8). Trans isomer of **22a**: IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) 1.50 (s, 9 H, CH_3), 1.53–2.60 (m, 6 H, CH_2 manifold), 3.30 (td, J = 14, 7 Hz, 1 H, NCH), 3.82 (td, J = 14, 7 Hz, 1 H, NCH), 4.83 (dd, J = 8, 3 Hz, 1 H, NCHS), 5.75 (br d, J = 16 Hz, 1 H, COCH=), 6.71 (td, J = 16, 7 Hz, 1 H, =CH), 7.33 (br s, 5 H, ArH); mass spectrum, m/e (rel intensity) 274 (7), 238 (M^+ – SPh, 15), 182 (43), 181 (27), 164 (53), 163 (27), 136 (30), 110 (100), 109 (23), 96 (90).

Lactam 22b. Imide **21b** (2.7 g, 6.58 mmol) was reduced with 706 mg (18.7 mmol) of sodium borohydride as described for **21a**. The resulting crude carbinolamide was stirred with 0.67 mL (6.57 mmol) of thiophenol and 50 mg (0.26 mmol) of *p*-toluenesulfonic acid for 2.5 h to give, after chromatography (70 g of silica gel; ethyl acetate–hexane 3:7), 2.90 g (87%) of a colorless oil as a mixture of cis and trans isomers of **22b** (15:85, respectively) contaminated with small amount of material in which the double bond had been reduced. This material was used directly in the cyclization reaction. Pure samples of *cis*- and *trans*-**23b** could be separated by MPLC (Lobar size B column, eluted with ethyl acetate–hexane, 3:7). The less polar cis isomer of **22b**: IR (CCl_4) 1705 cm^{-1}; NMR (CCl_4) δ 0.67–3.49 (m, 25 H), 3.49–4.07 (m, 1 H, NCH), 4.50–5.20 (m, 3 H, OCH, COCH= and NCHS), 5.80–6.13 (m, 1 H, =CH), 6.90–7.45 (two overlapping s's at 7.13 and 7.30, 10 H, ArH); mass spectrum, m/e (rel intensity) 250 (17), 218 (75), 125 (75), 110 (100), 109 (100). Trans isomer of **22b**: IR (CCl_4) 1705 cm^{-1}; NMR (CCl_4) δ 1.60–2.50 (m with br d, J = 7 Hz, at 0.87 and two br s at 1.20 and 1.27, 23 H, CH_3CH, $Ph(CH_3)_2C$, and CH_2 manifold), 3.20 (td, J = 14, 7 Hz, 1 H, NCH), 3.73 (td, J = 14, 7 Hz, 1 H, NCH), 4.52–4.89 (m with dd, J = 7, 3 Hz, at 4.77, 2 H, OCH and NCHS), 5.21 (br d, J = 16 Hz, 1 H, COCH=), 6.30 (td, J = 16, 7 Hz, 1 H, =CH), 6.90–7.40 (two overlapping br s's at 7.17 and 7.33, 10 H, ArH); mass spectrum, m/e (rel intensity) 218 (5), 121 (36), 119 (100), 117 (91).

***cis* and *trans*-1-(4-Cyano-3-butenyl)-5-(phenylthio)-2-pyrrolidinone (22c).** Imide **21c** (306 mg, 1.72 mmol) was reduced with 190 mg (5.0 mmol) of sodium borohydride as described for **21a**. The resulting crude carbinolamide was stirred with 168 mg (1.64 mmol) of thiophenol and 15 mg (0.08 mmol) of *p*-toluenesulfonic acid monohydrate for 1 h to give, after chromatography over silica gel, 210 mg (45%) of **22c** as a colorless oil: IR (CH_2Cl_2) 2215, 1700 cm^{-1}; NMR (CCl_4) δ 1.40–2.70 (m, 6 H, CH_2 manifold), 3.10–3.49 (m, 1 H, NCH), 3.59–4.00 (m, 1 H, NCH), 4.70–5.05 (two dd, J = 8, 3 Hz, at 4.80 and 4.98, 1 H, *trans*- and *cis*-NCHS), 5.17–5.43 (two overlapping d's, J = 12 Hz at 5.29 and J = 16 Hz at 5.33, 1 H, *cis*- and *trans*-NCCH=), 6.29–6.80 (m, 1 H, NCC=CH), 7.33 (br s, 5 H, ArH); mass spectrum, m/e (rel intensity) 163 (M^+ – SPh, 100), 109 (8), 108 (4), 95 (6), 83 (7), 79 (5). Later fractions gave 100 mg (21%) of overreduction product 1-(4-cyanobutyl)-5-(phenylthio)-2-pyrrolidinone as a colorless oil: IR (CCl_4) 2240, 1700 cm^{-1}; NMR (CCl_4) δ 1.40–1.80 (m, 4 H, $NCCH_2CH_2CH_2$), 1.80–2.60 (m, 6 H, CH_2 manifold), 3.10–3.42 (m, 1 H, NCH), 3.48–3.80 (m, 1 H, NCH), 4.85 (dd, J = 7, 3 Hz, 2 H, NCH_2), 7.30 (br s, 5 H, ArH); mass spectrum, m/e (rel intensity) 165 (M^+ – SPh, 100), 137 (14), 110 (16), 109 (13), 84 (16), 69 (14), 68 (16).

***rel*-(1*R*,7a*R*)-Hexahydro-1-((*tert*-butoxycarbonyl)methyl)-1*H*-pyrrolizin-5-one (24a), and *rel*-(1*S*,7a*R*)-Hexahydro-1-((*tert*-butoxycarbonyl)methyl)-1*H*-pyrrolizin-5-one (23a).** To a solution of 5.19 g (15.5 mmol) of thiophenoxylactam **22a** in 320 mL of dry benzene under argon was added 5.80 mL (22.0 mmol) of tri-*n*-butyltin hydride and 127 mg (0.770 mmol) of AIBN. The resulting solution was heated to reflux for 1.5 h and cooled to room temperature. The solvent was removed in vacuo to give 12.5 g of a colorless oil. The oil was chromatographed over 130 g of silica gel (ethyl acetate) to yield 3.48 g (86%) of a colorless oil composed of **23a** and **24a** containing 6% of the compound derived from reduction of the double bond in **25a**. This contaminant arises from reduction of the corresponding contaminant in the starting **22a**. A pure sample of **23a + 24a** was obtained by GLC (2 m × $^1/_8$ in. column packed with 10% OV-101 on Chrom W, Hp 80/100; column temperature = 220 °C, flow rate = 25 mL/min): t_R = 6.0 min; IR (CCl_4) 1730, 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9 H CH_3), 1.64–1.85 (m, 2 H), 1.95–2.48 (m, 5 H), 2.48–2.79 (m, 2 H), 3.02 (dddd, J = 12, 8.5, 5, 1 Hz, 1 H, NCH), 3.57 (td, J = 12, 7.5 Hz, 1 H, NCH), 4.09 (td, J = 8, 6.5 Hz, 1 H, NCH), characteristic signals of **24a** could be detected at δ 3.15 as br t, J = 9.5 Hz. Exact mass calcd for $C_{13}H_{21}NO_3$: m/e 239.1521. Found: m/e 239.1529. The ratio of **23a**:**24a** was 9:1 by NMR. For practical purposes, the mixture of cyclization products was used directly in the next reaction.

***rel*-(1*S*,7a*R*)-Hexahydro-1-(carboxymethyl)-1*H*-pyrrolizin-5-one (26).** A solution of 936 mg (3.90 mmol) of the **23a** and **24a** obtained above in 2 mL of trifluoroacetic acid was stirred at room temperature under argon for 30 min. The trifluoroacetic acid was removed in vacuo to afford 948 mg of pale-yellow oil which partially solidified. This material was recrystallized from 5 mL of dichloromethane and 10 mL of ether to yield 504 mg (71%) of **26** as a white solid: mp 144–145 °C; IR (CH_2Cl_2) 3000 (br), 1720, 1680, 1645 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.65–1.91 (m, 2 H), 2.00–2.83 (m, 7 H), 3.05 (dddd, J = 12, 8.5, 5, 1 Hz, 1 H, NCH), 3.58 (td, J = 12, 7.5 Hz, 1 H, NCH), 4.14 (td, J = 8.5, 6.5 Hz, 1 H, NCH) 12.0 (br s, 1 H, COOH). Exact mass calcd for $C_9H_{13}NO_3$: m/e 183.0895. Found: m/e 183.0910.

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 59.21; H, 7.24.

***rel*-(1*S*,7a*R*)-Hexahydro-1-((phenylthiocarboxy)methyl)-1*H*-pyrrolizin-5-one (27).** To a mixture of 706 mg (3.86 mmol) of acid **26** in 11 mL of dry dichloromethane was added 0.4 mL (3.86 mmol) of thiophenol, 797 mg (3.87 mmol) of dicyclohexylcarbodiimide, and 5.5 mg (0.045 mmol) of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 4 h, filtered, and concentrated in vacuo. The residue was suspended in carbon tetrachloride and filtered. The filtrate was concentrated in vacuo to give 1.27 g of a pale-yellow oil which was chromatographed over 60 g of silica gel (ethyl acetate-hexane, 9:1, followed by ethyl acetate) to afford 943 mg (89%) of **27** as a colorelss oil; IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.20–3.10 (m, 10 H), 3.27–4.15 (m, 2 H, NCH), 7.25 (s, 5 H, ArH). Exact mass calcd for $C_{15}H_{17}NO_2S$: m/e 275.0980. Found: m/e 275.0988.

Methyl Ketone 17 from Thioester 27. To a mixture of 443 mg (2.33 mmol) of cuprous iodide in 6.2 mL of dry tetrahydrofuran cooled in an ice–water bath under argon was added in a single portion 3.5 mL of a 1.33 N solution of methyllithium in ether. The resulting black mixture was stirred at 0 °C for 5 min and then cooled in a dry ice–carbon tetrachloride bath for 5 min. A solution of 214 mg (0.777 mmol) of thioester **27** in 3.7 mL of dry tetrahydrofuran was added in one portion and stirred at the same temperature for 5 min. Methanol (1.25 mL) was added carefully, and the resulting mixture was warmed to room temperature and partitioned between 25 mL of saturated ammonium chloride solution and 50 mL of dichloromethane. The aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 145 mg of a yellow oil. The oil was chromatographed over 6 g of silica gel (5% methanol in ethyl acetate) to yield 119 mg (84%) of **17** as a yellow oil.

Lactams 23b and 24b. A solution of 2.89 g (5.73 mmol) of thiophenoxylactam **22b**, 2.12 mL (8.04 mmol) of tri-*n*-butyltin hydride, and 37.2 mg (0.227 mmol) of AIBN in 115 mL of dry benzene was heated under argon at reflux temperature for a 1.5-h period. The solvent was removed in vacuo to give 5.68 g of a colorless oil. The oil was chromatographed over 70 g of silica gel (ethyl acetate–hexane, 45:55, followed by ethyl acetate) to yield 2.44 g (94%) of a mixture of **23b** and **24b** containing 9% (by NMR) of the compound derived from reduction of the double bond in **25b**. This contaminant arises from reduction of the corresponding contaminant in the starting **22b**. A pure sample of **23b + 24b** was obtained by MPLC (Lobar size B column, ethyl acetate–hexane, 7:3): IR (CCl_4) 1725, 1695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.80–2.45 (m with d, J = 7 Hz, at 0.88 and two br s at 1.19 and 1.29, 25 H, CH_3CH, $Ph(CH_3)_2C$, and CH_2 manifold), 2.75 (m, 1 H), 2.85–3.03 (m, 1 H, NCH), 3.43 (tt, J = 11, 7 Hz, 1 H, NCH), 3.96 (dq, J = 8.5, 2 Hz, 1 H, angular NCH), 4.97 (dt, J = 10.5, 4 Hz, 1 H, OCH), 7.06–7.35 (m, 5 H, ArH). Signals due to **24b** were detected at δ 3.09 as a br t, J = 12 Hz. Exact mass calcd for $C_{25}H_{35}NO_3$: m/e 397.2617. Found: m/e 397.2626. The ratio of **23a**:**24a** was 9:1 by NMR.

***rel*-(1*R*,7a*R*)-Hexahydro-1-cyanomethyl-1*H*-pyrrolizin-5-one (24c) and *rel*-(1*S*,7a*R*)-Hexahydro-1-cyanomethyl-1*H*-pyrrolizin-5-one (23c).** To a solution of 206 mg (0.756 mmol) of thiophenoxylactam **22c** in 16 mL of dry benzene was added 0.40 mL (1.5 mmol) of tri-*n*-butyltin hydride and 8.5 mg (0.052 mmol) of AIBN. The resulting solution was heated at 80 °C for 1 h and 30 min. The solvent was removed in vacuo to yield 658 mg of a colorless liquid. This material was chromatographed over 8 g of silica gel (ethyl acetate followed by 6% methanol in ethyl acetate) and distilled bulb-to-bulb to afford 106 mg (85%) of a mixture of **24c** and **23c** (1:9, respectively, by NMR) as a colorless oil: bp 140–145 °C/0.17 mmHg; IR (CH_2Cl_2) 2290, 2240, 1690 cm^{-1}; NMR ($CDCl_3$, 200 MHz, characteristic signals for **23c**) δ 1.70–2.84 (m, 9 H), 3.11 (dddd, J = 12, 8.5, 4, 1 Hz, 1 H, NCH), 3.60 (td, J = 12, 7 Hz,

1 H, NCH), 4.13 (q, J = 7 Hz, 1 H, angular NCH). Lactam **24c** could be detected by the signal at δ 3.21 (br t, J = 11 Hz, 1 H, NCH). Exact mass calcd for $C_9H_{12}N_2O$: m/e 164.0950. Found: m/e 164.0954.

β-(Tetrahydro-2*H*-pyran-2-yloxy)propanal (29).[21] Through 20.78 g (0.133 mol) of the appropriate olefin in 170 mL of dry toluene cooled in a dry ice–acetone bath was passed a stream of ozone prepared with a Welsbach ozone generator for a period of 2 h and 15 min (the reaction was monitored for disappearance of alkene by TLC, silica gel, ethyl acetate–hexane, 1:9). The solution was stirred at −78 °C for another 15 min and then warmed to room temperature. Palladium on charcoal (2.8 g of 10% Pd on C) was added, and the mixture was stirred under a balloon of hydrogen for 3 h. An additional 0.9 g of 10% Pd on C was added, and the mixture was stirred for another 6 h. To the resulting mixture was added a spatula of $MgSO_4$. The mixture was stirred for 15 min and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the colorless residue was distilled through a small Vigreux column to give 11.0 g (52%) of the aldehyde as a colorless liquid (bp 75 °C at 3.5 mm): NMR (CCl_4) δ 1.4–2.0 (m, 6 H, CH_2 manifold), 2.5 (td, J = 9.3 Hz, 2 H, CH_2CHO), 3.2–4.2 (m, 4 H, CH_2O), 4.5 (br t, J = 3 Hz, 1 H, OCHO), 9.65 (t, J = 3 Hz, 1 H, CHO).

1-(Phenylthio)-1-(trimethylsilyl)-4-(tetrahydro-2*H*-pyran-2-yloxy)-1-butene (31). To a solution of 11.3 g (42.4 mmol) of phenylthiobis(trimethylsilyl)methane (**30**)[22] in 80 mL of dry tetrahydrofuran cooled in a dry ice–acetone bath under argon was added dropwise 42 mL of a solution of 1.03 N *n*-butyllithium in hexane (43.3 mmol) over a 15-min period. The resulting yellow solution was stirred at room temperature for 2 h and cooled again in a dry ice–acetone bath. A solution of 6.83 g (43.2 mmol) of aldehyde **29** in 40 mL of dry tetrahydrofuran was added dropwise over an 85-min period. The reaction mixture was stirred at −78 °C for 10 min and then at room temperature for 1 h. The resulting solution was poured into 200 mL of water and extracted with 400 mL of hexane. The aqueous phase was extracted with two 100-mL portions of hexane. The combined organic layers were washed with three 200-mL portions of water and 100 mL of saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo to give 13.9 g of a yellow oil. The oil was chromatographed over 140 g of silica gel (hexane followed by ethyl acetate–hexane, 1:9) to yield 4.77 g (42%) of phenylthiobis(trimethylsilyl)methane. Continued elution gave 7.71 g (54%) of **31** (E:Z = 1:1) as a pale-yellow liquid: IR (CCl_4) 1580, 1480, 1440, 1250 cm^{-1}; NMR (CCl_4) δ 0.00–0.25 (two s's at 0.00 and 0.16, 9 H, (E)- and (Z)-$SiMe_3$), 1.17–1.77 (m, 6 H, CH_2 manifold), 2.27–2.77 (two overlapping q's, J = 7 Hz, at 2.45 and 2.57, 2 H, (E)- and (Z)-CH_2C=), 3.07–3.92 (m, 4 H, OCH_2), 4.47 (br s, 1 H, OCH), 6.09–6.67 (two t's, J = 7 Hz, at 6.22 and 6.53, 1H, (E)- and (Z)-=CH), 6.92–7.22 (two overlapping br s's at 7.01 and 7.07, 5 H, ArH). Exact mass calcd for $C_{18}H_{28}O_2SSi$: m/e 336.1579. Found: m/e 336.1588.

4-(Phenylthio)-4-(trimethylsilyl)-3-buten-1-ol (32). To a solution of 7.71 g (22.9 mmol) of **31** in 120 mL of methanol was added 83 mg (0.44 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was stirred at room temperature for 6 h, poured into 50 mL of saturated sodium bicarbonate solution, and diluted with 400 mL of ether. The resulting mixture was filtered. The filtrate was washed with four 100-mL portions of water and 100 mL of saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo to afford a pale-yellow oil. The oil was chromatographed over 100 g of silica gel (ethyl acetate–hexane, 15:85) to yield 5.34 g (92%) of alcohol **32** as a colorless oil: IR (CCl_4) 3630, 3400 (br), 1580, 1480, 1440, 1250 cm^{-1}; NMR (CCl_4) δ 0.00–0.20 (two s's at 0.05 and 0.13, 9 H, (E)- and (Z)-$SiMe_3$), 1.50 (br s, 1 H, OH), 2.20–2.73 (overlapping td, J = 8, 7 Hz, at 2.39 and q, J = 7 Hz, at 2.51, 2 H (E)- and (Z)-CH_2C=), 3.35–3.75 (m, 2 H, OCH_2), 5.99–6.68 (two t's, J = 8 Hz, at 6.13 and J = 7 Hz, at 6.50, 1 H, =CH), 6.95–7.10 (two overlapping br s's at 7.01 and 7.10, 5 H, ArH). Exact mass calcd for $C_{13}H_{20}OSSi$: m/e 242.1004. Found: m/e 252.1011.

1-(4-(Phenylthio)-4-(trimethylsilyl)-3-butenyl)-2,5-pyrrolidinedione (33). To a mixture of 2.00 g (7.59 mmol) of alcohol **32**, 0.866 g (8.74 mmol) of succinimide, and 2.29 g (8.75 mmol) of triphenylphosphine in 11.5 mL of dry tetrahydrofuran cooled in an ice–water bath under argon was added dropwise a solution of 1.52 g (8.76 mmol) of diethyl azodicarboxylate in 4 mL of dry tetrahydrofuran over a period of 35 min. The resulting solution was stirred for 5 min, and the solvent was removed in vacuo. The residue was triturated twice with ethyl acetate–hexane (3:7, 40 mL followed by 20 mL). The combined extracts were concentrated in vacuo, and the residue was triturated again with 30 mL of ethyl acetate–hexane (3:7) and filtered. The filtrate was concentrated in vacuo and chromatographed over 60 g of silica gel (dichloromethane) to afford 2.47 g (93%) of imide **33** (E:Z = 1:1 by NMR) as a yellow oil: IR (CCl_4) 1780 (w), 1710 cm^{-1}; NMR (CCl_4) δ 0.00–0.20 (two s's at 0.00 and 0.18, 9 H, $SiMe_3$), 2.35–2.80 (m with s at 2.50, 6 H, CH_2C= and $NCOCH_2$), 3.30–3.60 (two overlapping t's, J = 6 Hz, at 3.43 and 3.53, 2 H, NCH_2), 5.80–6.55 (two t's, J = 8 Hz at 5.90 and J = 7 Hz, at 6.40, 1 H, vinyl), 7.00–7.20 (two overlapping br s's at 7.03 and 7.15, 5 H, ArH). Exact mass calcd for $C_{17}H_{23}NO_2SSi$: m/e 333.1219. Found: 333.1227.

1-(4-(Phenylthio)-4-(trimethylsilyl)-3-butenyl)-5-(phenylthio)-2-pyrrolidinone (34). To a solution of 2.48 g (7.43 mmol) of imide **33** in 15 mL of methanol cooled in an ice–water bath under argon was added four portions of sodium borohydride at 10-min intervals (205, 175, 195, and 191 mg in sequence). The resulting mixture was stirred at 0 °C for another 45 min followed by the addition of 201 mg of sodium borohydride. After 45 min the reaction mixture was partitioned between 15 mL of water, 15 mL of saturated sodium chloride solution, and 50 mL of dichloromethane. The aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil. To this oil was added 27.5 mg (0.145 mmol) of *p*-toluenesulfonic acid monohydrate and 0.762 mL (7.43 mmol) of thiophenol. The resulting mixture was stirred at room temperature for 3 h and chromatographed over 70 g of silica gel (ethyl acetate–hexane, 25:75) to yield 2.82 g (89%) of thiophenoxylactam **34** (E:Z = 1:1) as a colorless oil: IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 0.00–0.25 (two s's at 0.00 and 0.20, 9 H, $SiMe_3$), 1.10–4.20 (m, 8 H, CH_2 manifold), 4.60–4.95 (m, 1 H, NCHS), 5.75–6.60 (two t's, J = 8 Hz at 5.90 and J = 7 Hz at 6.47, 1 H, =CH), 6.90–7.30 (m, 10 H, ArH); mass spectrum, m/e (rel intensity) 412 (3), 318 (M^+ − SPh, 95), 302 (3), 278 (1), 235 (36), 208 (9), 162 (19), 149 (13), 110 (100), 96 (22), 84 (27), 73 (82).

1-(4-(Phenylsulfinyl)-4-(trimethylsilyl)-3-butenyl)-2,5-pyrrolidinedione (35). To a solution of 1.5 g (4.49 mmol) of imide **33** in 60 mL of dry dichloromethane cooled in an ice–water bath under argon was added dropwise a solution of 0.85 g (4.94 mmol) of *m*-chloroperbenzoic acid in 30 mL of dichloromethane over a 3-h period. The resulting mixture was stirred at 0 °C for 8 h and washed with 25 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a pale-yellow oil. The oil was chromatographed over 80 g of silica gel (ethyl acetate–hexane, 65:35, followed by ethyl acetate) to afford 174 mg (12%) of recovered **33**. Continued elution gave 671 mg (43%) of one geometrical isomer of **35**: mp 105–107 °C; IR (CCl_4) 1710, 1050 cm^{-1}; NMR (CCl_4) δ 0.06 (s, 9 H, $SiMe_3$), 2.13–2.73 (m with s at 2.65, 6 H, $NCOCH_2$ and CH_2C=), 3.03–3.80 (m, 2 H, NCH_2), 6.33 (t, J = 7 Hz, 1 H, =CH), 7.30 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{23}NO_3SSi$: m/e 349.1168. Found: m/e 349.1177.

Anal. Calcd for $C_{17}H_{23}NO_3SSi$: C, 58.42; H, 6.63. Found: C, 58.29; H, 6.45.

Continued elution gave 637 mg (41%) of the other isomer of **35** as a colorless oil: IR (CCl_4) 1710, 1050 cm^{-1}; NMR (CCl_4) δ 0.00 (s, 9 H, $SiMe_3$), 2.37–2.82 (m with s at 2.55, 6 H, $NCOCH_2$ and CH_2C=), 3.59 (t, J = 7 Hz, 2 H, NCH_2), 6.85 (t, J = 7 Hz, 1 H, =CH), 7.21–7.55 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{23}NO_3SSi$: m/e 349.1168. Found: m/e 349.1177.

1-(4-(Phenylsulfinyl)-4-(trimethylsilyl)-3-butenyl)-5-(phenylthio)-2-pyrrolidinone (36). To a solution of 622 mg (1.78 mmol) of the noncrystalline isomer of imide **35** in 7 mL of methanol cooled in an ice–water bath under argon was added 311 mg of sodium borohydride in one portion. The resulting mixture was stirred at 0 °C for 15 min, 28 mg of sodium borohydride was added, and stirring was continued at 0 °C for 15 min. The reaction was worked up as described for the preparation of **34** and the crude carbinolamide was treated with 0.183 mL (1.79 mmol) of thiophenol and 13 mg (0.068 mmol) of *p*-toluenesulfonic acid monohydrate for 3 h at room temperature. The resulting mixture was chromatographed over 25 g of silica gel (ethyl acetate–hexane, 6:4) to yield 548 mg (69%) of **36** as a colorless oil: IR (CCl_4) 1690, 1050 cm^{-1}; NMR (CCl_4) δ 0.05 (s, 9 H, $SiMe_3$), 1.22–2.95 (m, 6 H, CH_2 manifold), 3.23 (td, J = 14, 7 Hz, 1 H, NCH), 3.69 (td, J = 14, 7 Hz, 1 H, NCH), 4.75 (br d, J = 6 Hz, 1 H, NCHS), 6.79 (br t, J = 8 Hz, 1 H, =CH), 7.00–7.45 (m, 10 H, ArH); mass spectrum, m/e (rel intensity) 354 (2), 334 (M^+ − SPh, 29) 262 (54), 152 (41), 136 (18), 124 (66), 110 (100), 96 (22), 84 (22), 77 (21), 73 (30). Similar treatment of the crystalline isomer of **35** gave the corresponding thiophenoxylactam in a 64% yield.

1-(4-(Phenylthio)-4-(trimethylsilyl)-3-butenyl)-2-pyrrolidinone (40), *rel*-(1*S*,7a*R*)-Hexahydro-1-[(phenylthio)(trimethylsilyl)methyl]-1*H*-pyrrolizin-5-one (38), *rel*-(1*R*,7a*R*)-Hexahydro-1-[(phenylthio)(trimethylsilyl)methyl]-1*H*-pyrrolizin-7-one (37), and Hexahydro-1-((trimethylsilyl)methyl)-1*H*-pyrrolizin-5-one (39). A solution of 2.81 g (6.57 mmol) of thiophenoxylactam **34**, 2.60 mL (9.86 mmol) of tri-*n*-butyltin hydride, and 23.3 mg (0.142 mmol) of AIBN in 130 mL of dry benzene was heated at reflux temperature for 16.5 h with the addition of a few crystals of AIBN at the end of the first 8 h. The solvent was removed in vacuo, and the residue was dissolved in 100 mL of hexane. The hexane solution was extracted with three 50-mL portions of acetonitrile. The

combined acetonitrile layers were concentrated in vacuo to afford 2.68 g of a pale-yellow oil. The oil was chromatographed first over 50 g of silica gel (ethyl acetate–hexane, 25:75, followed by ethyl acetate–hexane, 1:1, and finally ethyl acetate) and then over a Lobar size C column (ethyl acetate–hexane, 25:75, followed by ethyl acetate) to yield 241 mg (8%) of unreacted starting material **34** as a pale-yellow oil. Continued elution gave a fraction which was recrystallized from 4 mL of hexane to yield 627 mg (30%) of one diastereoisomer of **37** as a white solid: mp 93.5–94.5 °C; IR (CCl_4) 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.13 (s, 9 H, $SiMe_3$), 1.24–2.71 (m, 8 H), 2.82 (dt, J = 11, 5 Hz, 1 H, NCH), 3.95 (dd, J = 11, 5 Hz, NCH), 4.25 (ddd, J = 11, 7, 5 Hz, 1 H, angular NCH), 7.10–7.40 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: m/e 319.1426. Found: m/e 319.1447.

Anal. Calcd for $C_{17}H_{25}NOSSi$: C, 63.90; H, 7.89. Found: C, 64.00; H, 8.07.

The mother liquor was concentrated in vacuo to give 86.6 mg (4%) of a colorless oil composed of **37** and **40** (35:65, respectively, by NMR). Characteristic signals of **40**: NMR ($CDCl_3$) δ 3.30–3.45 (two overlapping t's, J = 7 Hz, at 3.35 and 3.40, 4 H, NCH_2), 6.55 (t, J = 7 Hz, 1 H, =CH). Further elution gave 445 mg (25%) of a mixture of **38** and **39** (3:2, respectively, by NMR). A small amount of pure **38** was obtained by further chromatography over a Lobar column as a colorless oil: IR (CCl_4) 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.19 (s, 9 H, $SiMe_3$), 1.37–2.75 (m, 8 H), 3.15 (br t, J = 12 Hz, 1 H, NCH), 3.54 (dt, J = 12, 8 Hz, 1 H, NCH), 3.80 (td, J = 9, 7 Hz, 1 H, angular NCH), 7.13–7.40 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: m/e 319.1426. Found: m/e 319.1474. Only an enriched sample of **39** could be obtained: NMR ($CDCl_3$, 200 MHz) δ 3.00 (ddd, J = 11, 8, 5 Hz, 1 H, NCH), 3.56 (td, J = 11, 8 Hz, 1 H, NCH), 3.96 (q, J = 6 Hz, 1 H, angular NCH).

Final elution gave 596 mg (28%) of the most polar diastereoisomer of **37** as a white solid: mp 87–88.5 °C; IR (CCl_4) 1695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.18 (s, 9 H, $SiMe_3$), 1.42–2.05 (m, 4 H), 2.13–2.71 (m, 4 H), 2.93 (td, J = 12, 7 Hz, 1 H, NCH), 3.78 (ddd, J = 12, 8, 5 Hz, 1 H, NCH), 4.01 (td, J = 9, 7 Hz, 1 H, angular NCH), 7.11–7.50 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: m/e 319.1426. Found: m/e 319.1452.

Anal. Calcd for $C_{17}H_{25}NOSSi$: C, 63.90; H, 7.89. Found: C, 63.86; H, 7.69.

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Registry No. (±)-**4**, 18929-90-3; (±)-**5**, 92845-54-0; **6a**, 92844-96-7; (±)-**6b**, 92844-97-8; **7a**, 92844-98-9; (±)-**7b**, 92844-99-0; **8a**, 92845-00-6; (±)-**8b**, 92845-01-7; (±)-**9a**, 92845-02-8; **9b**, 70255-35-5; (±)-**10a**, 92845-03-9; **10b**, 92845-04-0; **11a**, 92845-05-1; (±)-**11b**, 92845-06-2; **12a**, 92845-07-3; (±)-**12b**, 92845-15-3; (±)-**13b**, 92845-16-4; (±)-**14b**, 92845-14-2; (±)-**15a**, 92845-08-4; **15b**, 92845-13-1; (±)-**16** (isomer 1), 92845-09-5; (±)-**16** (isomer 2), 92845-10-8; (±)-**17**, 92845-11-9; (±)-**18**, 92845-12-0; **19**, 5615-85-0; **20a**, 35000-38-5; **20c**, 16640-68-9; (*Z*)-**21a**, 92845-17-5; (*E*)-**21a**, 92845-18-6; (±)-(*E*)-**21a**-ol, 92845-47-1; (±)-(*Z*)-**21a**-ol, 92845-48-2; (*Z*)-**21b**, 92845-19-7; (*E*)-**21b**, 92845-20-0; **21b**-ol, 92845-49-3; (*Z*)-**21c**, 92845-21-1; (*E*)-**21c**, 92845-22-2; (±)-(*E*)-**21c**-ol, 92845-50-6; (±)-(*Z*)-**21c**-ol, 92845-51-7; (±)-(*Z*)-**22a**, 92845-23-3; (±)-(*E*)-**22a**, 92845-24-4; **22b**, 92845-25-5; (*Z*)-**22c**, 92845-26-6; (*E*)-**22c**, 92845-27-7; (±)-**23a**, 92845-29-9; **23b**, 92845-33-5; (±)-**23c**, 92845-35-7; (±)-**24a**, 92845-28-8; (±)-**24c**, 92845-34-6; **25a**, 92845-30-2; (±)-**26**, 92845-31-3; (±)-**27**, 92845-32-4; (±)-**29**, 89922-81-6; **30**, 62761-90-4; (±)-(*E*)-**31**, 92845-36-8; (±)-(*Z*)-**31**, 92845-37-9; (*E*)-**32**, 92845-38-0; (*Z*)-**32**, 92845-39-1; (*E*)-**33**, 92845-40-4; (*Z*)-**33**, 92845-41-5; (±)-(*E*)-**34**, 92845-42-6; (±)-(*Z*)-**34**, 92845-43-7; (*Z*)-**35**, 88695-24-3; (*E*)-**35**, 88850-04-8; (*E*)-**35**-ol, 92845-52-8; (*Z*)-**35**-ol, 92845-53-9; (*Z*)-**36**, 92900-58-8; (*E*)-**36**, 92900-59-9; **37**, 92845-44-8; **39**, 92845-46-0; **40**, 92845-45-9; (1*R*,2*S*,5*R*)-2-(2-phenyl-2-propyl)-5-methylcyclohexanol, 65253-04-5; (1*R*,2*S*,5*R*)-2-(2-phenyl-2-propyl)-5-methylcyclohexanol bromoacetate, 80595-59-1; acetaldehyde, 75-07-0; paraformaldehyde, 30525-89-4; succinimide, 123-56-8; thiophenol, 108-98-5; bromoacetic acid, 79-08-3.

Supplementary Material Available: Experimental procedures for the preparation of **6b**–**11b** and **20b** (6 pages). Ordering information is given on any current masthead page.

Total Synthesis of Guaianolides: (±)-Dehydrocostus Lactone and (±)-Estafiatin

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Abstract: The total synthesis of two guaianolide sesquiterpenes, (±)-dehydrocostus lactone and (±)-estafiatin, is described. The synthesis starts with 2,4,6-cycloheptatrien-1-one (tropone) and introduces the elements of the five-membered ring through a 1,8-addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane. A stereocontrolled Lewis acid mediated cyclization reaction generates the requisite cis-fused hydroazulene intermediate. Regio- and stereoselective γ-butyrolactone formation via epoxide opening with dilithioacetate followed by the introduction of three exocyclic methylene groups completes the synthesis of (±)-dehydrocostus lactone in twelve steps from tropone. (±)-Estafiatin is constructed in two additional steps from dehydrocostus lactone.

The guaianolides comprise one of the largest and most widely distributed groups of naturally occurring sesquiterpene lactones.[1] A majority of these species feature a cis-fused hydroazulene skeleton in which a trans-fused γ-butyrolactone moiety is appended to the seven-membered carbocycle. With approximately 200 representatives currently identified, the great structural diversity exhibited by this class of natural products stems principally from the level and variety of functionalization that can be located at a number of positions in the molecules. Many guaianolides are endowed with an impressively rich spectrum of biological activity. Tumor inhibitory[2] and schistosomicidal[3] as well as plant growth

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