0.11 mmol). The reaction mixture was warmed to 40 °C, and then a second batch of Ph_3P (32 mg, 0.11 mmol) and CBr_4 (41 mg, 0.11 mmol) was added. The solution was stirred for 30 min at 40 °C, allowed to cool to 23 °C, and then filtered through a plug of silica gel (1:1 hexanes–CH_2Cl_2). The filtrate was concentrated and purified by flash chromatography (4:1 hexanes–CH_2Cl_2) to give **1** (6.6 mg, 40%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (ddd, J = 7.4, 7.4, 15.8 Hz, C≡CCH=C*H*) 5.54–5.64 (m, 2 H), 5.27–5.36 (m, 1 H), 5.25 (ddd, J = 2.7, 4.2, 6.9 Hz, H(3)), 3.99–4.04 (m, 2 H), 3.85 (ddd, J = 4.4, 6.1, 7.2 Hz, 1 H), 2.83 (d, J = 2.1 Hz, C≡CH), 2.67–2.72 (m, 2 H), 2.41–2.56 (m, 3 H), 2.01–2.10 (m, 2 H), 2.09 (s, CH_3CO), 1.91 (ddd, J = 2.6, 7.1, 14.5 Hz, 1 H), 1.00 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.44, 141.62, 135.88, 124.75, 111.05, 82.01, 80.20, 79.48, 76.59, 74.12, 56.59, 37.46, 36.48, 32.79, 25.57, 20.99, 13.63; IR (film) 3292, 2926, 1740, 1375, 1240 cm^{-1}; MS (CI) m/z 355.0912 (355.0830 calcd for $C_{17}H_{24}{}^{79}BrO_3$, MH), 357.0900 (357.0830 calcd for $C_{17}H_{24}{}^{81}BrO_3$, MH).

(2*S*)-2-Hydroxy-2-vinylcyclopentanone ((*S*)-22). To a stirring solution of ketoenamine **21** (500 mg, 2.56 mmol)[27] and Et_2O (30 mL) at −78 °C was added dropwise over 30 min a solution of vinylmagnesium bromide (1.0 M in THF, 6.4 mL, 6.4 mmol) and Et_2O (30 mL). The reaction was stirred at −78 °C for 30 min and then quenched by the addition of saturated NH_4Cl solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography using hexanes–Et_2O (1:1) as eluant gave (2*S*)-**22** (210 mg, 65%) as a pale yellow oil: $[\alpha]^{25}_D$ 32.7° (*c* 1.4, $CHCl_3$).

(1*S*,2*R*)-1-Vinylcyclopentane-1,2-diol ((1*S*),(2*R*)-3). Reduction of (2*S*)-**22** (210 mg, 1.67 mmol) under the conditions described previously for the reduction of the related racemic ketone[8] gave (1*S*,2*R*)-**3** (174 mg, 81%) as a viscous, colorless oil: $[\alpha]^{25}_D$ − 58.4° (*c* 1.25, $CHCl_3$).

A solution of this diol sample (10 mg, 0.078 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (13.8 mg, 0.0819 mmol), dicyclohexylcarbodiimide (17 mg, 0.082 mmol), 4-pyrrolidinopyridine (1.1 mg, 0.078 mmol), and dry CH_2Cl_2 (0.5 mL) was maintained at 23 °C for 1.5 h.[31] Concentration followed by purification of the residue by flash chromatography (3:1 hexanes–Et_2O) gave the monoester **23** (18 mg, 86%) as a colorless oil. The enantiomeric excess of **3** was determined to be 84% by ^1H NMR integration of the vinylic hydrogen signals of the major and minor distereoisomers at δ 5.4 and 5.9, respectively.

(2*R*,3a*R*,7a*R*)-Hexahydro-2-[(benzyloxy)methyl]-4(2*H*)-benzofuranone ((−)-5). Reaction of a sample of (1*S*,2*R*)-**3** (55 mg, 0.41 mmol) with α-(benzyloxy)acetaldehyde, under conditions identical with those described[8] for the racemic diol, provided (−)-**5** (64 mg, 57%) as a colorless oil: $[\alpha]^{26}_D$ −8.9° (c, 1.28, $CHCl_3$).

Conversion of (−)-5 to (*R*)-Methylmandelate Ester 25. A mixture of (−)-**5** (64 mg, 0.25 mmol), 10% Pd/C (8 mg), and EtOAc (1.5 mL) was stirred at 23 °C under an atmosphere of H_2 for 18 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (EtOAc) gave alcohol **24** (39 mg, 93%) as a viscous, colorless oil: $[\alpha]^{26}_D$ − 38.4° (*c* 1.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (m, 1 H), 4.00 (m, 1 H), 3.64 (m, 1 H), 3.47 (m, 1 H), 2.78 (m, 1 H), 2.45 (m, 1 H), 2.35 (m, 2 H), 2.08 (m, 1 H), 2.04–1.73 (m, 5 H); IR (film) 3423 (br, OH), 1706, 1048 cm^{-1}, MS (EI, 70 eV) m/z 170.0941 (170.0943 calcd for $C_9H_{14}O_3$, M).

A solution of alcohol **24** (19 mg, 0.188 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (19.5 mg, 0.118 mmol), DCC (24 mg, 0.12 mmol), and 4-pyrrolidinopyridine (2.0 mg, 0.012 mmol) in dry CH_2Cl_2 (1.0 mL) was maintained at 23 °C for 1.5 h.[31] Evaporation of the solvent followed by purification of the residue by flash chromatography (1:1 hexanes–EtOAc) gave **25** (34 mg, 92%) as a colorless oil. The enantiomeric excess of **24** was determined to be 84% by ^1H NMR (500 MHz, $CDCl_3$) comparison of the integrals for the methoxy signlets at δ 3.39 and 3.42 and the methine singlets at δ 4.80 and 4.82 of the major and minor diastereomers of **25**, respectively.

Acknowledgment. We acknowledge the contribution of K. D. Hutchinson in carrying out the chemical correlation that initially established the stereostructure of **11** and S. Joseph for his initial work in optimizing the reaction of **21** with vinylmagnesium bromide. We also thank Professor Etsuro Kurosawa for providing comparison IR and ^1H NMR spectra of natural *trans*-kumausyne. Our investigations in this area were supported by NIH Grant NS-12389. NMR and mass spectra were determined at the University of California at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

Registry No. **1**, 126786-44-5; **3**, 133870-03-8; (1*S*,2*R*)-**3**, 133908-24-4; **5**, 133870-04-9; (−)-**5**, 133908-25-5; **6**, 133870-05-0; **7**, 133870-06-1; **8**, 133870-07-2; **9**, 133870-08-3; **10**, 133870-09-4; **11**, 133870-10-7; **12**, 133870-11-8; **13**, 133870-12-9; *cis*-**14**, 133870-13-0; *trans*-**14**, 133908-26-6; **15**, 133870-14-1; **16**, 133886-79-0; **17**, 133870-15-2; **18**, 133870-16-3; **19**, 133870-17-4; **20**, 133870-18-5; **21**, 96304-33-5; (2*S*)-**22**, 133870-19-6; **23**, 133870-20-9; **24**, 133870-21-0; **25**, 133870-22-1; 1,2-cyclopentanedione, 3008-40-0; (*S*)-*O*-methylprolinol, 63126-47-6.

Bis-Heteroannulation. 15. Enantiospecific Syntheses of (+)- and (−)-Norsecurinine

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Contribution from the Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06457. *Received December 27, 1990*

Abstract: (−)-Norsecurinine (**2a**) has been prepared in a stereospecific fashion with the acetylenic oxazole **39** as the starting material. Diels–Alder cyclization of **39** afforded the furano ketone **45** that was transformed in five steps to the butenolide mesylate **52**. Transannular alkylation of **52** then afforded **2a**. In identical fashion, *ent*-**39** gave (+)-norsecurinine (**2b**).

Introduction

The *Securinega* alkaloids are a family of more than 20 compounds isolated from the *Securinega* and *Phyllanthus* genera of *Euphorbiaceae*,[1] most of which contain either a "securinine-type" skeleton I or a "norsecurinine-type" skeleton II (Figure 1). Members of skeletal class I are built upon an indolizidine nucleus, while those of class II are built upon a pyrrolizidine nucleus. All of these compounds contain an α,β-unsaturated-γ-lactone (butenolide) moiety, and they also share in common the interesting azabicyclo[3.2.1]octane ring system.

Securinine (**1**) is the most abundant of the *Securinega* alkaloids and it was the first member of this group to be isolated (1956) and characterized (1962).[2a-c] The degradative and spectroscopic

(1) Snieckus, V. In *The Alkaloids*; Manske, R. H., Ed.; Academic Press: New York, 1973; Vol. 14, p 425.

(2) (a) Murav'eva, V. I.; Ban'kovskii, A. I. *Dokl. Akad. Nauk. SSSR* **1956**, *110*, 998; *Chem. Abstr.* **1957**, *51*, 8121a. (b) Satoda, I.; Murayama, M.; Tsuji, Y.; Yoshii, E. *Tetrahedron Lett.* **1962**, *3*, 1199. (c) Horii, Z.; Tanaka, T.; Tamura, Y.; Saito, S.; Matsumura, C.; Sugimoto, N. *J. Pharm. Soc. Jpn.* **1963**, *83*, 602; *Chem. Abstr.* **1963**, *59*, 9087c. (d) Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Shigematsu, N.; Kodera, K.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N.; *Tetrahedron*, **1967**, *23*, 1165 and references cited therein.

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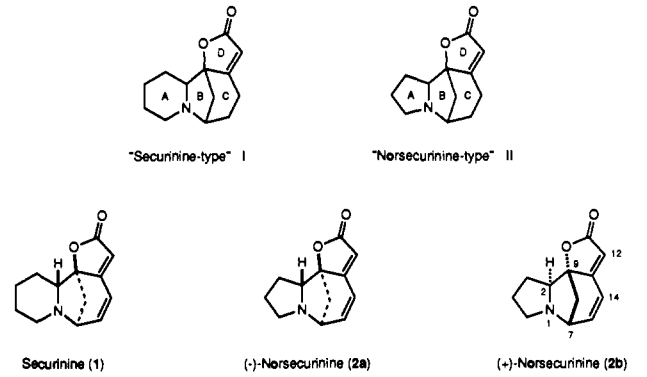


Figure 1.

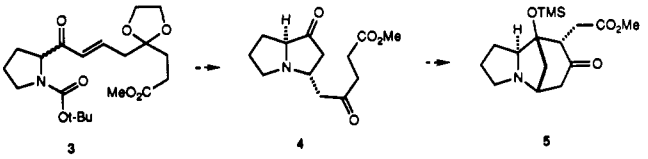


Figure 2.

studies leading to the proposal of structure **1** are now regarded as classics in the field, and they laid the groundwork for subsequent investigations of other members of this class. In 1966, **1** was synthesized by Horii et al., employing a route that closely paralleled the reverse of that followed in the degradation studies.[2d] Norsecurinine (**2**) was initially isolated in the levorotatory form **2a** from the roots of *Securinega virosa* by Iketubosin and Mathiesen (1963),[3a] who correctly deduced that **2a** was a lower ring-A homologue of securinine (**1**) solely on the basis of spectroscopic data. However, definitive proof for this structural assignment came only in 1965 with the work of Saito et al.,[3b] who employed a degradative sequence analogous to that successfully used in the structural studies of **1**. In 1969, Rouffiac and Parello isolated an alkaloid from *Phyllanthus niruri* that they concluded, on the basis of physical and spectral data, to be the optical antipode of **2a**, (+)-norsecurinine (**2b**).[4a] This assignment was confirmed in 1986 when the X-ray crystal structure of **2b** hydrochloride was determined.[4b] To date, there have been no reported pharmacological studies carried out on norsecurinine (**2**), although securinine (**1**) exhibits a broad spectrum of biological activity.[5]

In contrast to the securinine-type alkaloids, which are generally stable, crystalline solids, **2** polymerizes readily and is unstable as the free base. This lack of stability presents a considerable synthetic challenge, and prior to our work only one successful synthesis of (±)-**2** had appeared.[6,7] Thus, in an elegant series of papers, Heathcock et al. described a novel synthesis of (±)-**2** that made use of a tandem Michael addition–aldol condensation for constructing the key intermediate **5**, with the racemic enone **3** as the starting material (Figure 2).[6a] Compound **5** contains three of the four rings present in **2** and it was converted to (±)-**2** by a sequence of steps that included a number of unusual rearrangements. In this paper we provide experimental details for our alternative synthesis of **2**, which culminated in the efficient preparation of both **2a** and **2b** in homochiral form.[7] We believe

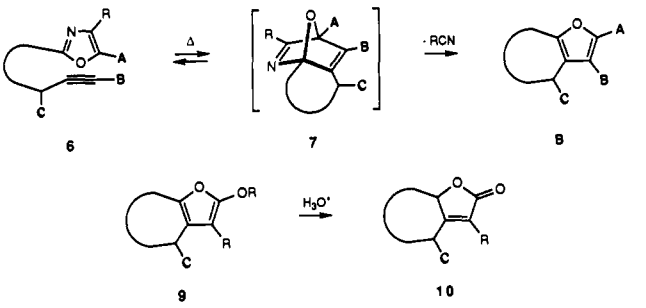
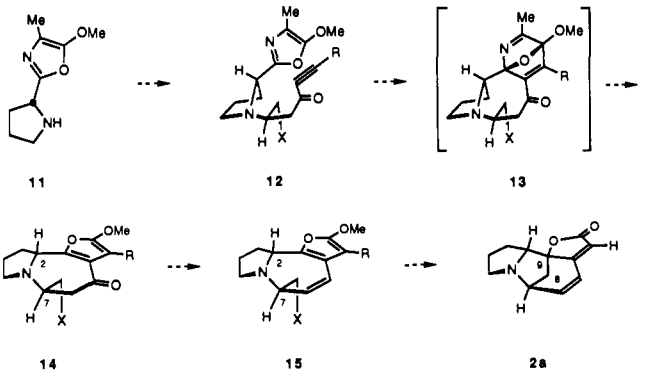


Figure 3.

Scheme I



that the approach described should be applicable to the synthesis of many other members of the Securinega family.

Discussion and Results

For several years we have been developing an unequivocal approach to the synthesis of furano terpenes and related materials, the most notable feature of which is the use of an intramolecular Diels–Alder reaction of acetylenic oxazoles of general structure **6** to afford fused-ring furan derivatives of type **8** (Figure 3).[8] Transformations of this type are of considerable synthetic utility, since the appended groups A, B, and C are transposed in an unequivocal fashion, via intermediate **7**, to the final annulated product **8**. The vast majority of furano terpenes are functionalized at C_3 (B) and $C_{4'}$ (C) of the furan ring (cf. **8**), and a proper choice of substituents A and B allows for the transformation of **8** to butenolides, methylene acids, or lactones.[8e,j] For example with A = OR, B = alkyl (**9**), we have shown that acid-catalyzed hydrolysis proceeds by initial protonation at C_5 to provide butenolides of general structure **10**.[8h,j,9] Butenolide **10**, in turn, embodies the key structural feature found in all of the *Securinega* alkaloids (vide supra).

For norsecurinine (**2**), these observations led in a straightforward fashion to the retro-synthetic analysis depicted in Scheme I. Thus, a key intermediate for our projected synthesis of **2a** was the acetylenic oxazole **12**, which incorporates the correct relative and absolute stereochemistry at C_2 and C_7 found in **2a**. We were confident that **12**, in turn, could be derived from the pyrrolidine oxazole **11**, itself presumably available from D-proline. Diels–Alder cyclization of **12**, followed by loss of MeCN, was expected to give the furano ketone **14**, which appeared to be an ideal

(3) (a) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. Pharmacol.* **1963**, *15*, 810; *Chem. Abstr.* **1964**, *60*, 4370d. (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1965**, *13*, 786.

(4) (a) Rouffiac, R.; Parello, J. *Plant. Med. Phytother.* **1969**, *3*, 220; *Chem. Abstr.* **1970**, *72*, 32094m. (b) Joshi, B. S.; Gawad, D. H.; Pelletier, S. W.; Kartha, G.; Bhandary, K. *J. Nat. Prod.* **1986**, *49*, 614.

(5) (a) Friess, S. L.; Durant, R. C.; Whitcomb, E. R.; Reber, L. J.; Thommesen, W. C. *Toxicol. Appl. Pharmacol.* **1961**, *3*, 347; *Chem. Abstr.* **1961**, *55*, 25053b. (b) Turova, A. D.; Aleshkina, Y. A. *Farmakol. Toksikol. (Moscow)* **1956**, *19*, 11; *Chem. Abstr.* **1956**, *50*, 17201a.

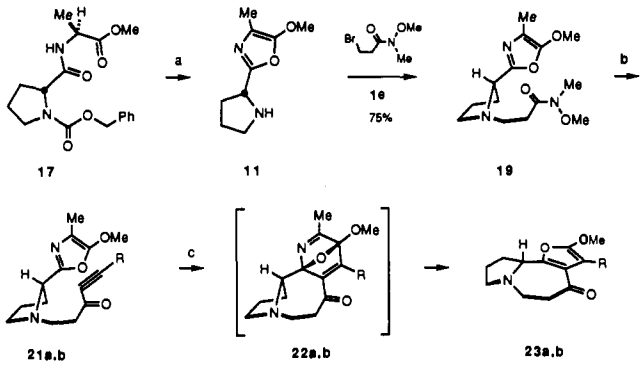
(6) a) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75 and references cited therein. For an unsuccessful approach to (±)-**2**, see: (b) Kucerovy, A. Ph.D. Thesis, Pennsylvania State University, University Park, 1984; *Diss. Abstr. Int., B* **1984**, *45*(6), 1780.

(7) A preliminary account describing portions of this work has appeared: cf. ref 81.

(8) (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (b) Jacobi, P. A.; Ueng, S. N.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042. (c) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (d) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (e) Jacobi, P. A.; Frechette, R.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (f) Jacobi, P. A.; Weiss, K.; Egbertson, M. *Heterocycles* **1984**, *22*, 281. (g) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (h) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, *25*, 4859. (i) Jacobi, P. A.; Frechette, R. F. *Tetrahedron Lett.* **1987**, *28*, 2937. (j) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475. (k) Jacobi, P. A.; Egbertson, M.; Frechette, R. F.; Miao, C. K.; Weiss, K. T. *Tetrahedron* **1988**, *44*, 3327. (l) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. *Tetrahedron Lett.* **1989**, *30*, 7173. (m) Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202.

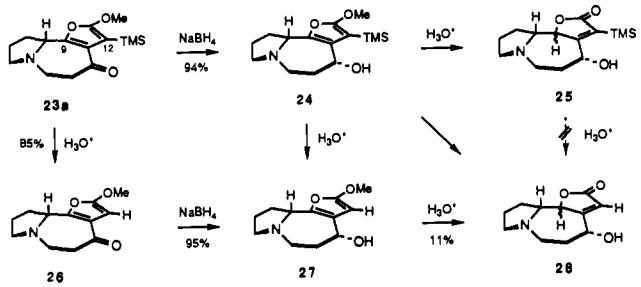
(9) Garst, J. E.; Schmir, G. L. *J. Org. Chem.* **1974**, *39*, 2920.

Scheme II



(a) 1, $POCl_3$; 2, PdH_2, 65%; (b) LiTMSA (**20**), >95%; (c) Δ, 55% **19** → **23a**

Scheme III

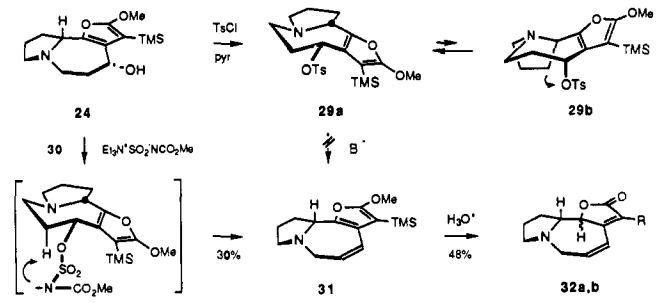


precursor for the alkene derivative **15**. Hydrolysis of **15** to the corresponding butenolide **16**, followed by transannular alkylation (X = leaving group), would then complete the synthesis (geometrical constraints in the transition state that lead to intramolecular alkylation ensure the proper stereochemistry at the newly formed C_8–C_9 bond). Regarding this last step, calculations indicated that the requisite pseudoaxial orientation at C_7–C_8 represented an energetically favorable conformation,[10] thereby providing encouragement that **2a** might be formed under conditions mild enough to assure its survival (vide supra). In addition, a potential competing reaction involving 1,2-elimination appeared to be less favorable due to the fact that H_7 was orthogonal to the π-system of the conjugated butenolide ring.

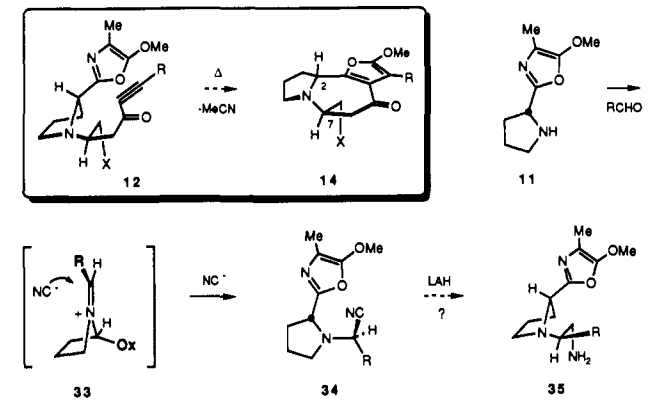
The feasibility of this approach was initially tested with the model system **21a** (R = TMS), which was readily prepared from the known proline derivative **17** (Scheme II).[11,12] Thus, **17** was first converted to the oxazole pyrrolidine derivative **11** by cyclodehydration followed by catalytic hydrogenation,[8] and **11** was directly alkylated with the bromo amide **18** prepared by reaction of 3-bromopropionyl chloride with *N,O*-dimethylhydroxylamine. Condensation of **19** with lithium (trimethylsilyl)acetylide (**20**) then proceeded routinely to afford the acetylenic ketone **21a** (R = TMS)[13] that, upon thermolysis (PhEt, 136 °C), provided the furano ketone **23a** (R = TMS) in 55% overall yield from **19**. Interestingly, acetylenic ketone **21b** (R = H) reacted only sluggishly in the Diels–Alder reaction and gave a much lower yield of the furano ketone **23b** (R = H). A similar rate-enhancing effect of trimethylsilyl groups on acetylenic dienophiles has previously been noted by Nicolaou et al.[14]

Next, valuable information was gained regarding the hydrolytic stability of methoxyfurans of type **23a** (Scheme III). Thus, **23a** gave an excellent yield of the equatorial alcohol **24** upon reduction with $NaBH_4$, and this last material afforded a mixture of butenolides **25** and **28**, as well as the desilylated furan **27**, upon

Scheme IV



Scheme V



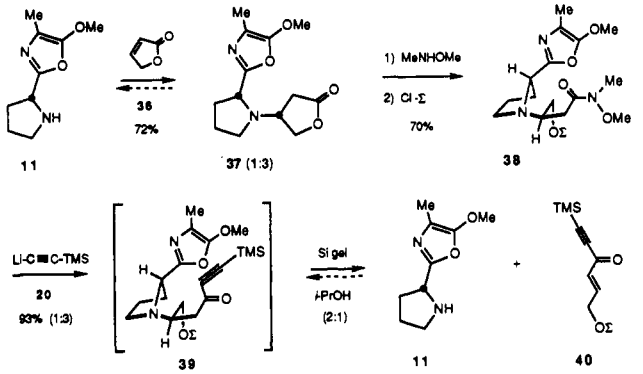
hydrolysis in aqueous acid. Mechanistic studies showed that **28** was derived solely by hydrolysis of **27**, since the (trimethylsilyl)butenolide **25** was completely stable to the reaction conditions. The reaction pathway leading from **24** to **28** must therefore involve an initial protonation at C_{12}, followed by protodesilylation to afford **27**, as opposed to initial protonation at C_9. As expected on the basis of these results, direct hydrolysis of **23a** provided an excellent yield of the methoxyfuran **26** derived by protonation at C_{12}. In this case protonation at C_9 is highly unfavorable due to the inductive effect of the C_{14} carbonyl group, and **26** was stable even in the presence of hot mineral acids. However, **26** could be cleanly reduced to the identical alcohol **27** derived by protodesilylation of **24**, and as previously found, **27** was then rapidly hydrolyzed to the butenolide alcohol **28**, albeit in only 11% yield. The poor yield obtained in this last step is partly due to the inherent instability of **28** under acidic conditions.

Interestingly, **24** proved to be remarkably resistant to dehydration under a variety of experimental conditions (Scheme IV). Tosylate **29**, for example, gave none of the desired alkene **31**, a lack of reactivity that is presumably due to steric compression in the axial conformer **29b** required for trans-elimination. However, reagents that are known to facilitate cis-elimination provided more encouraging results. Thus, the Burgess reagent **30** afforded a modest yield of **31**, which was directly hydrolyzed to a 4/1 mixture of the butenolides **32a** (R = H) and **32b** (R = TMS).[15] As observed with **25** above (Scheme III), it was found that **32b** was completely stable under acidic reaction conditions, thereby indicating that **32a** is formed by initial protodesilylation followed by protonation at C_9. As compared to **27**, C_9 protonation of **31** is facilitated by the formation of a bis-allylic carbocation.

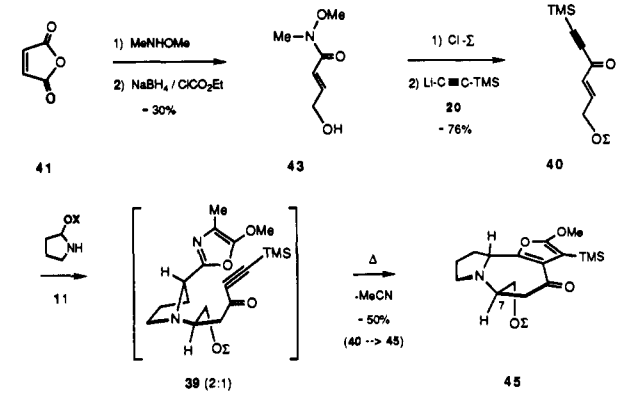
In order for these preliminary results to be extrapolated to the synthesis of (−)-norsecurinine (**2a**), it was first necessary to devise a means for controlling the relative stereochemistry at C_2 and C_7 in the acetylenic oxazole **12** (Scheme V; cf. also Scheme I). Along these lines, we briefly explored the possibility that the pyrrolidine oxazole **11** might be converted to amino nitriles of general structure **34** through a Strecker-like reaction as indicated.[16] Reduction

(10) We are grateful to Mr. Julian Simon, of Columbia University, for carrying out these calculations.
(11) Savige, W. E. *Aust. J. Chem.* **1961**, *14*, 664.
(12) Initial experiments were carried out with **11** derived from the more readily available L-proline. For convenience, structures are represented as those derived from the enantiomeric D-proline. All experimental details are for the L-proline series leading to (+)-norsecurinine (**2b**).
(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(14) Nicolaou, K. C.; Li, W. S. *J. Chem. Soc., Chem. Commun.* **1985**, 421.
(15) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(16) Maigrot, N.; Mazaleyrat, J.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 40.

Scheme VI



Scheme VII



of **34** would then provide the primary amino derivative **35**, which could be suitably modified as necessary. The success of this sequence depended upon the fact that initial condensation of **11** with aldehydes should proceed with high selectivity to afford the *trans*-immonium salt **33**, which upon capture with cyanide anion from the least hindered face would provide **34** having the desired relative stereochemistry.[16] In practice, this strategy worked reasonably well with benzaldehyde (R = Ph), but unfortunately it could not be extended to substrates bearing synthetically useful R groups.

In an alternative approach, **11** gave a 72% yield of the pyrrolidine lactone **37** as an inseparable 1/3 mixture of diastereomers upon Michael addition to the butenolide **36** (Scheme VI). In spite of this disappointing stereoselectivity, **37** was carried on to the Weinreb amide **38** by opening with *N,O*-dimethylhydroxylamine followed by trapping with *tert*-butyldimethylsilyl chloride (Cl-Σ). This latter material then gave a 93% yield of the acetylenic ketone **39**, still as a 1/3 mixture, upon condensation with lithium (trimethylsilyl)acetylide (**20**).[13] Interestingly, however, **39** was rapidly cleaved to the starting pyrrolidine **11** and the novel enynone derivative **40** upon attempted chromatographic purification, and this observation paved the way for our eventual successful route to (−)-norsecurinine (**2a**). Thus, **40** proved to be an exceedingly reactive Michael acceptor that readily combined with **11** in protic solvents to give **39** in the much more favorable ratio of ~2:1. In principle, at least, this last observation provided the basis for a highly convergent approach to **39**, assuming that a preparatively useful synthesis of **40** could be developed.

After considerable experimentation, we found that **40** could be conveniently derived from maleic anhydride (**41**) by the route outlined in Scheme VII. Thus, **41** was reacted with *N,O*-dimethylhydroxylamine and the resulting *E*-amido acid **42** was reduced with $NaBH_4/ClCO_2Et$ to afford the *E*-alcohol **43** in ~30% overall yield (little effort was made to optimize this sequence, which was routinely carried out on multigram scales).[17] Silylation of **43** (*tert*-butyldimethylsilyl chloride, Cl-Σ, 78%),

(17) Ishizumi, K.; Koga, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1968**, *16*, 492.

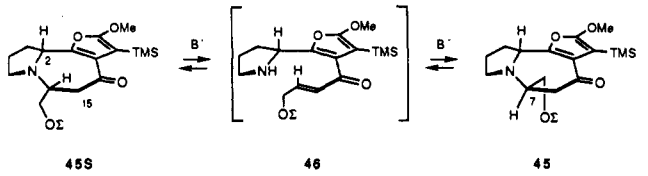
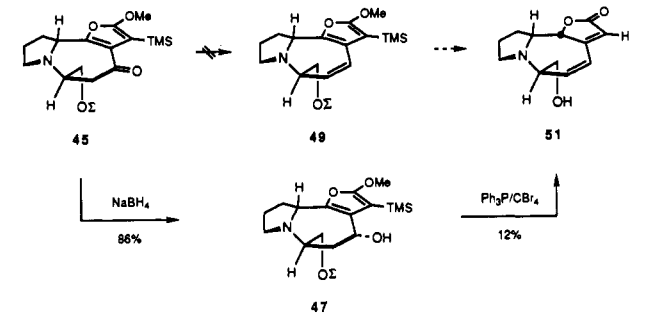
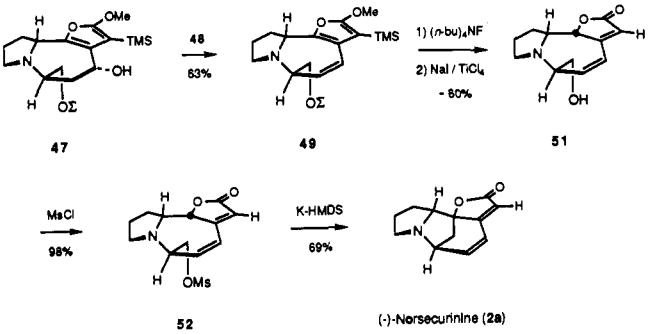


Figure 4.

Scheme VIII



Scheme IX



followed by condensation with lithium (trimethylsilyl)acetylide (**20**) (98% yield), then gave a 76% overall yield of the target enynone **40**, which was identical with the material obtained by retro-Michael addition as described above (Scheme VI). As previously found, **40** underwent a rapid addition of the oxazole pyrrolidine **11** to afford the acetylenic ketone **39**, which without purification was now converted to the furano ketone **45** by brief thermolysis in mesitylene (~50% overall yield from **40**). The material thus obtained consisted of an ~2/1 mixture of **45** together with its C_7 epimer **45S**, which reflects the kinetic bias in the initial condensation of **11** and **40**. In addition, the undesired isomer **45S** could be conveniently recycled by epimerization with Na_2CO_3 in MeOH, which effected a Michael–retro-Michael sequence proceeding through the intermediacy of the enone **46** (Figure 4; **45**:**45S** ≈ 50:50 at thermodynamic equilibrium). The mechanism for this interconversion was established by deuterium-incorporation studies, which showed exclusive incorporation at C_{15}. An alternative mechanism, involving C_2 proton abstraction, would have yielded *ent*-**45** from **45S** and was ruled out on the basis of specific rotations obtained in both the D- and L-proline series (vide infra).

Numerous efforts were made to convert the furano ketone **45** directly to the furano alkene **49**, all without success (Scheme VIII). These included the preparation and reduction of various enol phosphates,[18a-f] phosphorodiamidates,[18b] and triflates,[18g-i] and hydroboration–elimination of silyl enol ethers.[19] By way of

(18) (a) Ireland, R. E.; Kawalski, C. J.; Tilley, J. W.; Walba, D. M. *J. Org. Chem.* **1975**, *40*, 990. (b) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (c) Fetizon, M.; Jurion, M.; Anh, N. T. *J. Chem. Soc., Chem. Commun.* **1969**, 112. (d) Charbonnier, F.; Moyano, A.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2303. (e) Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609. (f) Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 2715. (g) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (h) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (i) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *15*, 4821.

summary, although the requisite enol ethers and esters could be prepared in high yield from **45**, attempted reductive cleavage either had little effect (processes utilizing BR_3, Pd, Ti, or Sn) or brought about overreduction of the double bond (Birch conditions). In addition, an attempt to carry out a Shapiro elimination was thwarted by the lack of reactivity of **45** toward tosylhydrazine.[20] Following a different approach, **45** could be cleanly reduced to the furano alcohol **47** ($NaBH_4$, 86%), and we were intrigued with the finding that **47** gave a modest yield of the butenolide alkene **51** upon treatment with Ph_3P/CBr_4.[21,22] Unfortunately, however, this rather surprising result resisted all attempts at optimization and seemed to depend in an unpredictable fashion on the presence of adventitious HBr and H_2O.

The final route that led to the successful preparation of both **2a** and **2b** is summarized in Scheme IX. Thus, furano alcohol **47** was first converted to the furano alkene **49** by elimination with Martin's reagent ($[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$ (**48**), 63%),[23] which in this case provided better yields than the Burgess reagent employed with the model system **24** (cf. Scheme IV). Removal of the *tert*-butyldimethylsilyl protecting group in **49** (80%), followed by cleavage with $NaI/TiCl_4$ (73%),[24] then afforded the butenolide alcohol **51** as a single isomer (~60% overall yield),[22] which was identical with the material prepared as described in Scheme VIII. Interestingly, direct cleavage of **49**, prior to desilylation, gave much lower yields of the silylated butenolide alcohol corresponding to **51**. We believe that the hydroxyl group facilitates cleavage by initial ligand exchange with $TiCl_4$ followed by intramolecular complexation at C_9. Alcohol **51** was then converted to the corresponding mesylate derivative **52** in virtually quantitative yield. Finally, various combinations of base and solvent were studied in an effort to bring about the desired transannular alkylation of **52** to **2a**. These included LDA and potassium triphenylmethide, both of which afforded small amounts of **2a** by TLC analysis. Eventually, however, we were gratified to find that the desired transformation could be accomplished in 69% yield with 1.2 equiv of K-HMDS/THF, when initial anion generation was carried out at −78 °C and the reaction was briefly allowed to warm to room temperature.[25] (−)-Norsecurinine (**2a**) was most conveniently isolated as its HCl salt (mp 228–30 °C dec, lit.[3b] mp 223–25 °C dec), the free base of which had identical spectral data (NMR, IR, UV, mass spectrum) as that published for the naturally occurring substance ($[\alpha]_D = -262°$, $c = 0.06$ (EtOH), synthetic; $[\alpha]_D = -270°$, $c = 6.9$ (EtOH), natural).[3b] Repetition of the identical reaction sequence described for **2a** but with L-proline as the starting material afforded (+)-norsecurinine (**2b**), also in homochiral form ($[\alpha]_D = +268°$, $c = 0.085$ (EtOH)).

Experimental Section[12]

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on a Varian XL400 spectrometer or a Varian XL200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1500 FT-IR spectrophotometer. Mass spectra were obtained using a Hewlett-Packard HP 38890 GC–MS system. UV spectra were recorded on a Perkin-Elmer Lambda 4B UV–vis spectrophotometer. Optical rotations were determined at either 21 or 25 °C on a Perkin-Elmer 241 polarimeter.

(1′*S*)-2-(2′-Azacyclopentyl)-3-aza-4-methyl-5-methoxyoxacyclopenta-2,4-diene (*ent*-11). A solution of 62.0 g (0.18 mol) of amide ester *ent*-**17**[11] in 300 mL of pyridine was treated at 0 °C, with vigorous stirring, with a total of 20.7 mL (0.22 mol, 1.2 equiv) of freshly distilled $POCl_3$ added in dropwise fashion over a period of 30 min. The reaction mixture was then heated at 60–65 °C for 18 h, during which period the color of the solution turned from light yellow to dark red. The solvent was removed under reduced pressure and the residue was diluted with 380 mL of CH_2Cl_2 and 1200 mL ice water. Powdered $NaHCO_3$ was then added until CO_2 evolution ceased. The organic layer was separated and the aqueous layer was extracted with 4 × 380 mL of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% acetone/hexanes) to afford 51.8 g (88%) of (1′*S*)-2-[*N*-(carbobenzyloxy)-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-**17b**) as an orange-brown oil (mixture of amide rotamers): R_f 0.45 (silica gel, 30% acetone/hexanes); IR ($CHCl_3$) 1696.5, 1415 cm^{-1}; ^1H NMR ($CDCl_3$), (two rotamers) V 1.92–2.25 (m, 4 H), 1.99 (s, 3 H, Me), 2.05 (s, 3 H, Me), 3.45–3.90 (m, 3 H), 3.79 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.8–4.9, (m, 1 H), 5.06 (d, J = 12.5 Hz, 1 H), 5.18 (d, J = 12.5 Hz, 1 H), 5.25 (m, 1 H), 7.32–7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.97, 10.08, 10.11, 23.44, 24.10, 31.13, 32.12, 46.40, 46.85, 54.79, 55.17, 60.88, 61.04, 66.72, 66.83, 111.42, 111.61, 127.51, 127.63, 127.80, 127.97, 128.04, 128.16, 128.32, 128.39, 128.45, 136.63, 136.70, 154.39, 154.42; mass spectrum, m/e 316 (M^+), 225, 204, 160, 133, 91, 70; exact mass calcd for $C_{17}H_{20}N_2O_4$ 316.1423, found 316.1414.

A solution of 27.4 g (0.087 mol) of *ent*-**17b**, prepared as described above, in 200 mL of absolute ethanol was treated with 5.9 g of 10% palladium on activated carbon in a 500-mL hydrogenation flask under N_2. The reaction mixture was then hydrogenated at 46 psi of H_2 for 24 h at room temperature. The mixture was filtered through Celite, the catalyst was washed with 100 mL of ethanol, and the combined filtrates were concentrated under reduced pressure and chromatographed (silica gel, 20% methanol/ethyl acetate) to afford 11.4 g (74%) of *ent*-**11** as a viscous oil: R_f 0.29 (silica gel, 84:8:8 CH_2Cl_2/methanol/acetone); IR ($CHCl_3$) 3333, 1675, 1231 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (m, 2 H), 2.01 (s, 3 H, Me), 2.12 (m, 2 H), 2.95 (m, 1 H), 3.12 (m, 1 H), 3.65 (s, 3 H, OMe), 4.15 (dd, J = 9 Hz, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.71, 24.94, 30.01, 46.26, 55.30, 60.92, 111.10, 154.70, 154.91; mass spectrum, m/e 182 (M^+), 154, 139, 123, 95, 71, 70; exact mass calcd for $C_9H_{14}N_2O_2$ 182.1055, found 182.1057.

***N*-Methyl-*N*-methoxy-3-bromopropionamide (18).** A solution of 15.7 g (0.16 mol, 1.1 equiv) of *N,O*-dimethylhydroxylamine hydrochloride and 25.0 g (0.15 mol) of 3-bromopropionyl chloride in 250 mL of CH_2Cl_2 was treated at 0 °C, with vigorous stirring, with a total of 26 mL (0.32 mol, 2.2 equiv) of pyridine added in dropwise fashion over a period of 30 min. The resulting solution was stirred at room temperature for 1 h before removal of all solvents under reduced pressure. The residue was diluted with 100 mL of 1:1 CH_2Cl_2/Et_2O and 100 mL of brine, and the aqueous layer was extracted with 3 × 100 mL of 1:1 CH_2Cl_2/Et_2O. The combined organic extracts were then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 15% acetone/hexanes) to afford 19.2 g (67%) of **18** as a pale yellow oil (mixture of amide rotamers): R_f 0.5 (silica gel, 15% acetone/hexanes): IR ($CDCl_3$) 1650.1, 1461.9, 1422.7, 1390.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.89 (t, J = 6.8 Hz, 1.5 H), 3.08 (t, J = 6.8 Hz, 0.5 H), 3.17 (s, 3 H), 3.61 (t, J = 6.8 Hz, 0.5 H), 3.68 (s, 3 H), 3.78 (t, J = 6.8 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$) δ 26.10, 28.62, 31.28, 34.28, 34.50, 38.69, 60.66, 131.04, 169.90, 200.57; mass spectrum, m/e 195 (M^+), 135, 107, 88, 86, 61; exact mass calcd for $C_5H_{10}O_2NBr$ 194.9895, found 194.9895.

(1′*S*)-2-[*N*-[3-(*N*-Methyl-*N*-methoxyamino)-3-oxopropyl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-19). A solution of 0.53 g (2.9 mmol) of **11** and 0.45 mL (3.2 mmol, 1.1 equiv) of Et_3N in 2.0 mL of 1:1 CH_2Cl_2/Et_2O was treated at room temperature under N_2 with 0.8 g (4.0 mmol, 1.4 equiv) of **18** with stirring for 36 h. The reaction mixture was then diluted with 2 mL of pH 7 phosphate buffer and 3 mL of CH_2Cl_2, the organic layer was decanted, and the aqueous layer was extracted with 3 × 5 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 1:1 hexanes/acetone) to afford 0.65 g (75%) of *ent*-**19** as a pale yellow oil: R_f 0.32 (silica gel, 1:1 hexanes/acetone); IR ($CHCl_3$) 2825, 1653.7, 1571, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (m, 1 H), 1.88–2.18 (m, 3 H), 1.96 (s, 3 H), 2.36 (q, J = 7.8 Hz, 1 H), 2.56 (m, 2 H), 2.64 (m, 1 H), 2.92 (m, 1 H), 3.10 (s, 3 H), 3.18 (m, 1 H), 3.72 (t, J = 7.8 Hz, 1 H), 3.80 (s, 3 H), 3.86 (s, 3 H); mass spectrum, m/e 297 (M^+), 266, 209, 185, 149, 116, 82, 55; exact mass calcd for $C_{14}H_{23}N_2O_4$ 297.1688, found 297.1682.

(1′*S*)-2-[*N*-[5-(Trimethylsilyl)-3-oxopent-4-ynyl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-21a). A solution of 2.25 g (7.57 mmol) of *ent*-**19** in 110 mL of anhydrous THF under N_2 was treated at −60 °C, with vigorous stirring, with a solution of 28.0 mmol (3.7 equiv) of lithium (trimethylsilyl)acetylide (**20**) in pentane (prepared by treating 4.0 mL (28.0 mmol) of (trimethylsilyl)-acetylene in 95 mL of pentane with 10.7 mL (27.0 mmol) of 2.5 M *n*-butyllithium in hexanes at 0 °C under N_2 for 10 min). The resulting mixture was then warmed to −25 °C over 10 min, cooled to −78 °C,

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(20) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55 and references cited therein.
(21) Mattes, H.; Benezera, C. *Tetrahedron Lett.* **1987**, *28*, 1697.
(22) The structure of butenolide *ent*-**51** was unequivocally proven by single-crystal X-ray analysis. We are grateful to Ms. Gayle Schulte, of Yale University, for carrying out this analysis.
(23) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.
(24) Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293.
(25) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

treated with 5 mL of saturated aqueous NH_4Cl, warmed to 10 °C, and diluted with 80 mL of pH 7 phosphate buffer. The organic layer was separated and the aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organic extracts were washed with 3 × 30 mL of saturated aqueous Na_2CO_3, dried over anhydrous Na_2CO_3, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 2.4 g (95%) of ***ent*-21a** as an unstable dark orange oil that was used without further purification: R_f 0.71 (silica gel, 1:1 hexanes/acetone); ^1H NMR ($CDCl_3$) δ 0.12 (s, 9 H), 1.80–2.20 (m, 3 H), 2.02 (s, 3 H), 2.39 (m, 1 H), 2.72 (m, 3 H), 3.04 (m, 1 H), 3.17 (m, 1 H), 3.57 (t, J = 7.2 Hz, 1 H), 3.92 (s, 3 H).

(13*S*)-3-Methoxy-4-(trimethylsilyl)-6-oxo-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-Δ^{1,5},Δ^{3,4}-diene (*ent*-23a). A solution of 2.4 g (7.2 mmol) of ***ent*-21a** and 40 mg (0.36 mmol) of hydroquinone in 280 mL of ethylbenzene was heated at reflux under N_2 for 7 h. The resulting brown reaction mixture was then concentrated under reduced pressure and chromatographed (silica gel, 9:1 CH_2Cl_2/acetone) to afford 1.2 g (55% from ***ent*-19**) of ***ent*-23a** as a pale yellow oil: R_f 0.59 (silica gel, 9:1 CH_2Cl_2/acetone); IR ($CHCl_3$) 1650.5, 1695.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 9 H), 1.74–2.08 (m, 3 H), 2.20–2.40 (m, 1 H), 2.66 (m, 2 H), 2.72 (m, 2 H), 2.97–3.20 (m, 2 H), 3.68 (t, J = 8.1 Hz, 1 H), 3.87 (s, 3 H). Anal. Calcd for $C_{15}H_{23}NO_3Si$: C, 61.40; H, 7.90; N, 4.77. Found: C, 61.29; H, 7.91; N, 4.83.

(6*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-6-hydroxy-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-Δ^{1,5},Δ^{3,4}-diene (*ent*-24). A solution of 0.21 g (0.72 mmol) of ***ent*-23a** in 5 ml of absolute ethanol was treated with 0.08 g (2.11 mmol, 12 equiv) of $NaBH_4$, and the resulting solution was stirred at room temperature for 15 h. The reaction mixture was then concentrated under reduced pressure and the residue was diluted with 15 mL of CH_2Cl_2 and 15 mL of pH 7 phosphate buffer at 0 °C. The organic layer was decanted and the aqueous layer was extracted with 4 × 10 mL of CH_2Cl_2. The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 1:1 hexanes/acetone) to afford 0.2 g (94%) of ***ent*-24** as a colorless solid. Recrystallization from acetone afforded ***ent*-24** as colorless needles: mp 104–105 °C; R_f 0.68 (silica gel, 1:1 hexanes/acetone); IR ($CHCl_3$) 3369.7, 1626, 1598.6, 1439.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.20 (s, 9 H), 1.60 (m, 2 H), 1.80 (m, 2 H), 2.26 (m, 2 H), 2.40 (q, J = 8.2 Hz, 1 H), 2.50–2.72 (m, 2 H), 3.14 (m, 1 H), 3.32 (m, 2 H), 3.80 (s, 3 H), 4.60 (d, J = 5.0 Hz, 1 H). Anal. Calcd for $C_{15}H_{25}NO_3Si$: C, 60.98; H, 8.53; N, 4.74. Found: C, 60.95; H, 8.57; N, 4.73.

(13*S*)-3-Methoxy-6-oxo-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-Δ^{3,4}-diene (*ent*-26). A solution of 10.0 mg (0.034 mmol) of ***ent*-23a** in 0.3 mL of methanol was treated with 0.3 mL of 1 M aqueous acetic acid, and the resulting solution was allowed to stand for 7 days at room temperature. The reaction mixture was diluted with 1 mL of water and the pH was adjusted to 7.0 with $NaHCO_3$ before extracting with 3 × 2 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 15% acetone/CH_2Cl_2) to afford 7.1 mg (95%) of ***ent*-26** as a yellow solid. Recrystallization from acetone afforded ***ent*-26** as yellow needles: mp 72–74 °C; R_f 0.80 (silica gel, 1:1 CH_2Cl_2/acetone); IR ($CHCl_3$) 1645, 1626, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76–2.03 (m, 3 H), 2.30 (m, 1 H), 2.58 (m, 1 H), 2.64 (m, 1 H), 2.70 (m, 2 H), 2.78 (m, 1 H), 3.10 (m, 1 H), 3.66 (t, J = 8.0 Hz, 1 H), 3.78 (s, 3 H), 5.44 (s, 1 H); mass spectrum, m/e 221 (M^+), 193, 178, 150, 134, 94, 80, 53; exact mass calcd for $C_{12}H_{15}O_3N$ 221.1052, found 221.1048.

(6*S*,13*S*)-3-Methoxy-6-hydroxy-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]-trideca-Δ^{1,5},Δ^{3,4}-diene (*ent*-27). This material was prepared in 95% yield by $NaBH_4$ reduction of ***ent*-26** by following an identical procedure as that described above for ***ent*-24**. Recrystallization from CH_2Cl_2 afforded ***ent*-27** as colorless plates: mp 139–140 °C; IR ($CHCl_3$) 3369.7, 1626, 1598.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66–2.10 (m, 4 H), 2.24 (m, 2 H), 2.62 (q, J = 8.2 Hz, 1 H), 2.58 (m, 1 H), 3.16 (m, 1 H), 3.36 (m, 2 H), 3.80 (s, 3 H), 4.56 (dd, J = 7.5 Hz, 2.0 Hz, 1 H), 5.12 (s, 1 H). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.31; H, 7.73; N, 6.17.

(1*RS*,6*S*,13*S*)-3-Oxo-6-hydroxy-9-aza-2-oxatricyclo[8.3,0^{1,5}.0^{9,13}]-tridec-4-ene (*ent*-28). A solution of 16.7 mg (0.075 mol) of ***ent*-27** in 0.5 mL of MeOH was treated with 0.5 mL of 1 M aqueous acetic acid, and the resulting solution was allowed to stand for 16 h at room temperature. The reaction mixture was then diluted with 1 mL of CH_2Cl_2 and 0.5 mL of water, and the pH was adjusted to 7.0 with $NaHCO_3$ before extraction with 3 × 2 mL of CH_2Cl_2. The combined organic extracts were washed with 2 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 1:1 hexanes/acetone) to afford 1.9 mg (11%) of ***ent*-28** as a yellow oil (mixture of isomers). Major isomer: R_f 0.53 (silica gel, 1:1 hexanes/acetone); IR ($CHCl_3$) 3300, 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 2 H), 1.80 (m, 2 H), 2.06 9q, J = 7.9 Hz, 2 H), 2.40 (m, 2 H), 2.70 (m, 1 H), 3.08 (m, 1 H), 3.24 (m, 1 H), 4.76 (dd, J = 8.4 Hz, 1.5 Hz, 1 H), 4.86 (d, J = 7 Hz, 1 H), 5.80 (s, 1 H).

(13*S*)-3-Methoxy-4-(trimethylsilyl)-9-aza-2-oxatricyclo-[8.3.0^{1,5}.0^{9,13}]trideca-Δ^{1,5},Δ^{3,4},Δ^{6,7}-triene (*ent*-31). A solution of 40.6 mg (0.14 mmol) of alcohol ***ent*-24** in 0.5 mL of benzene was treated with 0.36 g (0.15 mmol, 1.1 equiv) of Burgess's salt **30**, and the resulting mixture was stirred at 36 °C for 2 h. The reaction was then cooled to room temperature, 5 mL of water was added, the organic layer was decanted, and the aqueous layer was extracted with 3 × 5 mL of CH_2Cl_2. The combined organic extracts were washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 37% acetone/hexanes) to afford 11.6 mg (30%) of ***ent*-31** as a yellow oil: R_f 0.57 (silica gel, 37% acetone/hexanes); IR ($CDCl_3$) 2038.0, 1955.3, 1672.2, 1194.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 9 H), 1.66–2.06 (m, 3 H), 2.16 (m, 1 H), 2.48 (t, J = 7.8 Hz, 1 H), 3.02 (m, 1 H), 3.34 (m, 1 H), 3.54 (dd, J = 16.0 Hz, 7.0 Hz, 1 H), 3.84 (t, J = 7.0 Hz, 1 H), 3.96 (s, 3 H), 5.56 (ddd, J = 11.5 Hz, 5.9 Hz, 3.8 Hz, 1 H), 6.4 (dd, J = 11.5 Hz, 3.8 Hz, 1 H); mass spectrum, m/e 277 (M^+), 234, 206, 172, 144, 120, 89, 73; exact mass calcd for $C_{15}H_{23}O_2SiN$ 277.1498, found 277.1501.

(1*RS*,13*S*)-3-Oxo-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-4,6-diene (*ent*-32a). A solution of 9.0 mg (0.032 mmol) of ***ent*-31** in 0.5 mL of MeOH was treated with 0.5 mL of 1 M aqueous acetic acid, and the resulting solution was allowed to stand for 22 h at room temperature. The reaction mixture was then concentrated under reduced pressure and diluted with 1 mL of CH_2Cl_2 and 0.5 mL of water, and the pH was adjusted to 7.0 with $NaHCO_3$ before extraction with 3 × 2 mL of CH_2Cl_2. The combined organic extracts were washed with 2 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 20% acetone/CH_2Cl_2) to afford 3.0 mg (48%) of ***ent*-32a** as a yellow oil (mixture of isomers). Major isomer: R_f 0.64 (silica gel, 20% acetone/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 2.10 (m, 2 H), 2.50 (m, 2 H), 3.10 (dd, J = 18 Hz, 3 Hz, 1 H), 3.12 (dt, J = 10 Hz, 2 Hz, 1 H), 3.66 (dd, J = 18 Hz, 7 Hz, 1 H), 4.66 (dd, J = 10 Hz, 2 Hz, 1 H), 5.75 (s, 1 H), 6.02 (ddd, J = 13 Hz, 7 Hz, 3 Hz, 1 H), 6.40 (dd, J = 13 Hz, 2 Hz, 1 H).

(1′*S*)-2-[*N*-[(4*RS*)-2-Oxo-1-oxacyclopentyl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-37). A mixture of 1.38 g (7.6 mmol) of ***ent*-11** and 1.1 g (13.1 mmol, 1.7 equiv) of butenolide **36** in 0.2 mL of MeOH was stirred for 40 h at room temperature. Concentration and chromatography (silica gel, 30% acetone-/CH_2Cl_2) then afforded 1.46 g (72%) of ***ent*-37** as an inseparable 1/3 mixture of epimers (yellow oil): R_f 0.37 (silica gel, 30% acetone/hexanes); mass spectrum, m/e 266 (M^+); IR ($CHCl_3$) 1776.1, 1678.2, 1580.3 cm^{-1}; ^1H NMR ($CDCl_3$) (major isomer) δ 1.90–2.28 (m, 3 H), 2.00 (s, 3 H), 2.38 (dd, J = 18 Hz, 7.9 Hz, 1 H), 2.52 (m, 1 H), 2.59 (d, J = 7.9 Hz, 1 H), 3.00 (m, 1 H), 3.47 (q, J = 7.9 Hz, 1 H), 3.68 (m, 1 H), 3.90 (s, 3 H), 3.96 (d, J = 7.9 Hz, 1 H), 4.22 (dd, J = 10.2 Hz, 2 Hz, 1 H), 4.34 (dd, J = 13.8 Hz, 7.9 Hz, 1 H).

(1′*S*)-2-[*N*-[(3*RS*)-4-(*N*-Methyl-*N*-methoxyamino)-4-oxo-1-[(*tert*-butyldimethylsilyl)oxy]but-2-yl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-38). A suspension of 0.68 g (6.8 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 9 mL of benzene was treated with 3.44 mL (6.83 mmol, 1 equiv) of 2 M Me_3Al/benzene at 5 °C under N_2, and the resulting mixture was stirred at 5 °C until gas evolution ceased. The mixture was then cannulated into a solution of 0.92 g (3.4 mmol) of ***ent*-37** in 9 mL of benzene at room temperature, and stirring was continued for 3 h. The reaction was then cooled to 0 °C, diluted with 1.1 mL of 10% aqueous acetic acid followed by 20 mL of water, and extracted with 5 × 15 mL of CH_2Cl_2 maintained at −10 °C. The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 0.74 g of alcohol ***ent*-37b** as an extremely unstable mixture of isomers (ring closure readily occurs to regenerate ***ent*-37**): R_f 0.27, 0.39 (silica gel, 20% acetone/CH_2Cl_2).

Crude alcohol ***ent*-37b**, prepared as described above, was dissolved in 3 mL of DMF and treated with 0.39 g (5.67 mmol) of imidazole. The resulting solution was cooled to −10 °C, 0.4 g (2.65 mmol) of *tert*-butyldimethylsilyl chloride was added, and stirring was continued at room temperature for 0.5 h. The reaction solution was then diluted with 20 mL of CH_2Cl_2 and 20 mL of saturated aqueous $NaHCO_3$, the organic layer was decanted, and the aqueous layer was extracted with 3 × 10 mL of CH_2Cl_2. The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% acetone/hexanes) to afford 0.94 g (94%, 70% overall yield from ***ent*-37**) of ***ent*-38** as a 1/3 mixture of isomers. Desired isomer (minor): R_f 0.59 (silica gel, 30% acetone/

hexanes); IR ($CHCl_3$) 1675.1, 1650.6, 1568.0, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (s, 9 H), 0.82 (s, 6 H), 1.72–2.14 (m, 3 H), 1.98 (s, 3 H), 2.50 (dd, J = 15.8 Hz, 7.8 Hz, 1 H), 2.66 (dd, J = 15.8 Hz, 7.8 Hz, 1 H), 2.84 (q, J = 7.8 Hz, 1 H), 3.08 (m, 1 H), 3.12 (s, 3 H), 3.42 (m, 1 H), 3.65 (s, 3 H), 3.70 (m, 2 H), 3.84 (m, 1 H), 3.88 (s, 3 H), 4.08 (t, J = 7.8 Hz, 1 H). Undesired isomer (major): R_f 0.54 (silica gel, 30% acetone/hexanes); ^1H NMR ($CDCl_3$) δ −0.02 (s, 9 H), 0.80 (s, 6 H), 1.64–2.06 (m, 3 H), 1.96 (s, 3 H), 2.48 (dd, J = 16 Hz, 6 Hz, 1 H), 2.70 (dd, J = 16.5 Hz, 7.1 Hz, 1 H), 2.82 (t, J = 8 Hz, 1 H), 3.06 (m, 1 H), 3.10 (s, 3 H), 3.38 (m, 1 H), 3.58 (m, 1 H), 3.62 (s, 3 H), 3.70 (dd, J = 9.5 Hz, 5.5 Hz, 1 H), 3.82 (m, 1 H), 3.84 (s, 3 H), 3.98 (t, J = 7.8 Hz, 1 H).

(1′*S*)-2-[*N*-[(2*RS*)-6-(Trimethylsilyl)-4-oxo-6-[(*tert*-butyldimethylsilyl)oxy]hex-5-yn-2-yl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-39). Method A. A solution of 0.14 g (0.31 mmol) of *ent*-**38** in 5 mL of THF was cooled to −50 °C and treated in a dropwise fashion, with vigorous stirring, with a solution of 0.47 mmol (1.5 equiv) of lithium (trimethylsilyl)acetylide (**20**) in anhydrous THF (prepared by treating 0.11 mL (0.78 mmol) of (trimethylsilyl)acetylene in 3 mL of THF with 0.19 mL (0.47 mmol, 0.7 equiv) of 2.5 M *n*-butyllithium in hexanes at −78 °C under N_2 for 30 min). The resulting mixture was then warmed to −5 °C over 30 min, cooled to −70 °C, treated with 0.03 mL of glacial acetic acid, warmed to −5 °C, and poured into 10 mL of Et_2O and 10 mL of brine. The organic layer was separated and the aqueous layer was extracted with 3 × 10 mL of Et_2O. The combined organic extracts were washed with 2 × 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 0.14 g (93%) of *ent*-**39** as an unstable orange oil (~1/3 mixture of epimers).

(*E*)-3-(*N*-Methyl-*N*-methoxycarbamoyl)propenoic Acid (42). A solution of 33.06 g (0.34 mol) of maleic anhydride (**41**) and 36.18 g (0.37 mol, 1.1 equiv) of dimethylhydroxylamine hydrochloride in 400 mL of EtOH-free $CHCl_3$ was cooled to 0 °C and treated in a dropwise fashion, with vigorous stirring, with 60 mL (0.74 mol, 2.2 equiv) of pyridine added over a period of 1 h. The resulting mixture was then allowed to warm to room temperature and stirring was continued for an additional 26 h. The reaction was concentrated under reduced pressure, and the residue was diluted with 85 mL of brine and 85 mL of water before extraction with 4 × 100 mL of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a solid residue. Crystallization from CH_2Cl_2 afforded 29.0 g (54%) of **42** as a light yellow solid: mp 119–120 °C; IR ($CHCl_3$) 3020, 1708, 1662.9, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, 3 H), 3.75 (s, 3 H), 6.91 (d, J = 15.6 Hz, 1 H), 7.54 (d, J = 15.6 Hz, 1 H). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.37; H, 5.74; N, 8.78.

(*E*)-*N*-Methyl-*N*-methoxy-4-hydroxy-2-butenamide (43). A solution of 12.0 g (0.075 mol) of **42** and 10.5 mL (0.075 mol, 1 equiv) of ET_3N in 160 mL of THF was cooled to −10 °C and treated in a dropwise fashion, with vigorous stirring, with a solution of 7.43 mL (0.075 mol, 1 equiv) of ethyl chloroformate in 36 mL of THF under an atmosphere of N_2. The mixture was stirred for an additional 0.5 h at 0 °C after addition was complete, and was then directly filtered (to remove Et_3N·HCl) into a stirring 0 °C solution of 7.1 g (0.185 mol) of $NaBH_4$ in 160 mL of 1:1 H_2O/THF. After addition was complete, the reaction mixture was allowed to warm to room temperature and was then stirred for an additional 8 h. Solvent was removed under reduced pressure and the pH of the residue was adjusted to 7.0 with concentrated HCl at 0 °C. The aqueous layer was extracted with 4 × 75 mL of CH_2Cl_2, and then continuously extracted for 3 days with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% acetone/CH_2Cl_2) to afford 5.0 g (54%) of **43** as a yellow oil: R_f 0.37 (silica gel, 30% acetone/CH_2Cl_2); IR ($CHCl_3$) 3614.5, 3406.4, 1665.9, 1626.1, 1387.5 cm^{-1}; ^1H NMR δ 3.25 (s, 3 H), 3.70 (s, 3 H), 4.40 (m, 2 H), 6.70 (d, J = 16.5 Hz, 1 H), 7.05 (dt, J = 16.5 Hz, 4 Hz, 1 H). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.43; H, 7.69; N, 9.57.

(*E*)-*N*-Methyl-*N*-methoxy-4-[(*tert*-butyldimethylsilyl)oxy]-2-butenamide (44). A solution of 6.0 g (0.041 mol) of **43** and 7.0 g (0.103 mol, 2.5 equiv) of imidazole in 60 mL of DMF was cooled to 0 °C and treated in a dropwise fashion, with vigorous stirring, with 7.5 g (0.049 mol, 1.2 equiv) of *tert*-butyldimethylsilyl chloride over a period of 15 min. After addition was complete, the reaction was allowed to warm to room temperature and was stirred for an additional 30 min. The resulting mixture was then diluted with 350 mL of CH_2Cl_2 and washed with 350 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with 3 × 175 mL of CH_2Cl_2, and the combined organic extracts were washed with 350 mL of brine, dried over anhydrous Na_2SO_4, and chromatographed (silica gel, 4:1 hexanes/acetone) to afford 8.25 g (78%) of **44** as a yellow oil: R_f 0.39 (silica gel, 4:1 hexanes/acetone); IR ($CHCl_3$) 1730, 1659, 1464 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H), 0.90 (s, 9 H), 3.20 (s, 3 H), 3.66 (s, 3 H), 4.37 (dd, J = 6.5 Hz, 3.5 Hz, 2 H), 6.68 (d, J = 15.6 Hz, 1 H), 6.99 (dt, J = 15.6 Hz, 3.5 Hz, 1 H). Anal. Calcd for $C_{12}H_{25}NO_3Si$: C, 55.56; H, 9.71; N, 5.40. Found: C, 55.64; H, 9.73; N, 5.40.

(*E*)-1-(Trimethylsilyl)-3-oxo-6-[(*tert*-butyldimethylsilyl)oxy]hex-4-en-1-yne (40). A solution of 3.1 g (0.012 mol) of **44** in 300 mL of anhydrous THF under N_2 was treated at −78 °C, with vigorous stirring, with a solution of 0.018 mol (1.5 equiv) of lithium (trimethylsilyl)-acetylide (**20**) in anhydrous THF (prepared by treating 3.7 mL (0.026 mol) of (trimethylsilyl)acetylene in 120 mL of THF with 7.20 mL (0.018 mol, 0.7 equiv) of 2.5 M *n*-butyllithium in hexanes at −78 °C under N_2 for 30 min). The resulting mixture was then warmed to −3 °C over 2 h, cooled to −78 °C, treated with 1.0 mL of glacial acetic acid, warmed to −5 °C, and poured into 150 mL of ether and 150 mL of brine. The organic layer was separated and the aqueous layer was extracted with 3 × 150 mL of Et_2O. The combined organic extracts were washed with 2 × 150 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 10% acetone/hexanes) to afford 3.6 g (99%) of **40** as a yellow oil: R_f 0.50 (silica gel, 2% acetone/hexanes); IR ($CHCl_3$) 2158, 1650.6, 1629.2, 1473.2, 1255.9, 1142.7 cm^{-1}; ^1H NMR δ 0.09 (s, 6 H), 0.25 (s, 9 H), 0.91 (s, 9 H), 4.41 (t, J = 3 Hz, 2 H), 6.40 (dt, J = 15.9 Hz, 3 Hz, 1 H), 7.20 (dt, J = 15.9 Hz, 3 Hz, 1 H). Anal. Calcd for $C_{15}H_{28}O_2Si_2$: C, 60.75; H, 9.52. Found: C, 60.65; H, 9.56.

(1′*S*)-2-[*N*-[(2*RS*)-6-(Trimethylsilyl)-4-oxo-6-[(*tert*-butyldimethylsilyl)oxy]hex-5-yn-2-yl]-2′-azacyclopentyl]-3-aza-4-methyl-5-methoxy-1-oxacyclopenta-2,4-diene (*ent*-39). Method B. A solution of 3.6 g (0.012 mol) of enynone **40** in 6 mL of 2-propanol was treated over a period of 1 h, with vigorous stirring, with a solution of 2.2 g (0.012 mol, 1 equiv) of oxazole *ent*-**11** in 2.5 mL of 2-propanol at room temperature under N_2. After addition was complete, the reaction was allowed to stir for an additional 30 min at room temperature before concentration under reduced pressure. The residue obtained was taken up in 250 mL of ether and washed with 2 × 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 5.8 g (99%) of *ent*-**39** as an unstable orange oil (~2:1 mixture of epimers). Major isomer: IR ($CHCl_3$) 2151.9, 1675.1, 1460.9, 1255.9 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.24 (s, 9 H), 0.87 (s, 9 H), 1.79 (m, 1 H), 1.85–2.10 (m, 2 H), 1.99 (s, 3 H), 2.60 (m, 1 H), 2.70 (m, 1 H), 2.79 (m, 2 H), 3.08 (m, 1 H), 3.55 (m, 2 H), 3.70 (m, 1 H), 3.90 (s, 3 H), 3.99 (dd, J = 3.9 Hz, 2 Hz, 1 H).

In identical fashion, the enantiomeric oxazole **11** (derived from D-proline) afforded **39**, also in homochiral form (~2:1 mixture of epimers).

(8*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-6-oxo-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$-diene (*ent*-45). A solution of 6.3 g (0.013 mol) of *ent*-**39** in 1200 mL of degassed mesitylene containing 68 mg (0.6 mmol) of hydroquinone was heated at reflux for a period of 30 min under N_2. The resulting brown solution was cooled to room temperature, concentrated under reduced pressure, and chromatographed (silica gel, 30% ether/hexanes) to afford 1.60 g of *ent*-**45** and 0.90 g of *ent*-**45S** (46% combined yield, yellow oils).

ent-**45**: R_f 0.58 (silica gel, 30% ether/hexanes); IR ($CHCl_3$) 1665, 1650, 1590.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H, Me of TBDMS), 0.04 (s, 3 H, Me of TBDMS), 0.20 (s, 9 H, TMS), 0.87 (s, 9 H, *t*-Bu of TBDMS), 1.85 (m, 2 H, H_4), 2.10 (m, 1 H, H_3), 2.25 (m, 1 H, H_3), 2.75 (m, 1 H, H_5), 2.80 (dd, J = 16.1 Hz, 5.0 Hz, 1 H, H_{15}), 2.95 (dd, J = 16.1 Hz, 7.71 Hz, 1 H, H_{15}), 3.10 (dd, J = 15.3 Hz, 7.41 Hz, 1 H, H_5), 3.25 (m, 1 H, H_7), 3.47 (dd, J = 10.0 Hz, 7.0 Hz, 1 H, H_8), 3.68 (dd, J = 10.0 Hz, 5.0 Hz, 1 H, H_8), 3.86 (s, 3 H, OMe), 4.27 (dd, J = 5.0 Hz, 3.0 Hz, 1 H, H_2) (norsecurinine numbering); $[\alpha]^{20}_D$ = −16.3°, c = 0.166 (ethanol). Anal. Calcd for $C_{22}H_{39}NO_4Si_2$: C, 60.36, H, 8.98; N, 3.20. Found: C, 60.49; H, 9.02; N, 3.16.

ent-**45S**: R_f 0.24 (silica gel, 30% ether/hexanes): IR ($CHCl_3$) 1662.9, 1590.5, 1464.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H, Me of TBDMS), 0.04 (s, 3 H, Me of TBDMS), 0.20 (s, 9 H, TMS), 0.85 (s, 9 H, *t*-Bu of TBDMS), 1.88 (m, 2 H, H_4), 2.15 (m, 1 H, H_3), 2.37 (m, 1 H, H_3), 2.55 (q, 8.8 Hz, 1 H, H_5), 2.67 (dd, J = 16.5 Hz, 7.75 Hz, 1 H, H_{15}), 2.80 (m, 1 H, H_7), 2.91 (dd, J = 16.5 Hz, 3.5 Hz, 1 H, H_{15}), 3.18 (apparent q, J = 8.8 Hz, 1 H, H_5), 3.61 (dd, J = 10.1 Hz, 6.1 Hz, 1 H, H_8), 3.78 (dd, J = 10.1 Hz, 4.1 Hz, 1 H, H_8), 3.85 (s, 3 H, OMe), 4.41 (dd, J = 7.75 Hz, 4.45 Hz, 1 H, H_2) (norsecurinine numbering); $[\alpha]^{20}_D$ = +3.56°, c = 0.281 (ethanol).

In identical fashion, the enantiomeric oxazole **39** (derived from D-proline) afforded **45**, also in homochiral form ($[\alpha]^{20}_D$ = +17.4°, c = 2.117 (ethanol), and **45S**, $[\alpha]^{20}_D$ = −3.60°, c = 1.352 (ethanol)), as an ~2:1 mixture of epimers.

(8*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-6-oxo-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$-diene (*ent*-45), by Epimerization of (8*R*,13*S*)-3-Methoxy-4-(trimethylsilyl)-6-oxo-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$-diene (*ent*-45S). A solution of 3.7 g (8.49 mmol) of *ent*-**45S** in 50 mL of methanol was treated with 8.9 g (84.9 mmol, 10 equiv) of Na_2CO_3 at room temperature, and the resulting suspension was stirred for 7 days under N_2 at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue was diluted with 50 mL of Et_2O and 50 mL of pH 7 phosphate buffer. The organic layer was separated and the aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% ether/hexanes) to afford 1.5 g of *ent*-**45** and 1.7 g of *ent*-**45S**, both of which were identical in all respects, including optical rotations, with the materials prepared as described above from *ent*-**39**.

In identical fashion, the enantiomeric furan **45S** (derived from D-proline) afforded an equilibrium mixture of **45** and **45S**, both of which were identical in all respects with the materials prepared as described above from oxazole **39**.

(6*S*,8*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-6-hydroxy-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$-diene (*ent*-47). A solution of 0.76 g (1.73 mmol) of ketone *ent*-**45** in 40 mL of absolute ethanol was treated with 0.65 g (17.0 mmol) of $NaBH_4$ with stirring under N_2 at room temperature. Stirring was continued at room temperature until no more *ent*-**45** was present by TLC, approximately 20 h. The reaction mixture was then concentrated under reduced pressure, diluted with 120 mL of CH_2Cl_2, cooled to 0 °C, and neutralized to pH 7.0 with acetic acid. The organic layer was decanted and the aqueous layer was extracted with 3 × 120 mL of CH_2Cl_2. The combined organic extracts were washed with 150 mL of brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% ether/hexanes) to afford 0.65 g (86%) of alcohol *ent*-**47** as a yellow oil: R_f 0.47 (silica gel, 20% ether/hexanes); IR ($CHCl_3$) 3345, 1730, 1577, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 0.08 (s, 3 H, Me of TBDMS), 0.10 (s, 3 H, Me of TBDMS), 0.24 (s, 9 H, TMS), 0.89 (s, 9 H, *t*-Bu of TBDMS), 1.81 (m, 2 H, H_4), 2.00 (m, 2 H, H_{15}, H_3), 2.19 (m, 1 H, H_3), 2.30 (dt, J = 15 Hz, 5 Hz, 1 H, H_{15}), 2.55 (q, J = 8.8 Hz, 1 H, H_5), 2.81 (m, 1 H, H_7), 3.29 (m, 1 H, H_5), 3.57 (t, J = 8.8 Hz, 1 H, H_2), 3.78 (m, 2 H, H_8), 3.85 (s, 3 H, OMe), 4.60 (m, 1 H, H_{14}) (norsecurinine numbering). Anal. Calcd for $C_{22}H_{41}NO_4Si_2$: C, 60.09; H, 9.40; N, 3.19. Found: C, 60.36; H, 9.41; N, 3.03.

In identical fashion, the enantiomeric furan **45** (derived from D-proline) afforded **47**, also in homochiral form.

(8*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$,$\Delta^{6,7}$-triene (*ent*-49). A solution of 1.16 g (2.63 mmol) of *ent*-**47** in 4 mL of CH_2Cl_2 was treated with a solution of 4.42 g (6.61 mmol, 2.5 equiv) of Martin's sulfurane **48**[23] (weighted out under N_2 in a glove box) in 6 mL of CH_2Cl_2 at −48 °C with vigorous stirring. Stirring was continued at −48 °C for 1 h, and the reaction mixture was then poured into 25 mL of saturated aqueous $NaHCO_3$ and extracted with 6 × 15 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 35% ether/hexanes) to afford 0.71 g (63%) of *ent*-**49** as a colorless oil: R_f 0.89 (silica gel, 30% acetone/hexanes); IR (neat) 2958, 2859, 1722, 1633, 1252, 1116, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 H, Me of TBDMS), 0.07 (s, 3 H, Me of TBDMS), 0.21 (s, 9 H, TMS), 0.89 (s, 9 H, *t*-Bu of TBDMS), 1.62 (m, 2 H, H_4), 1.80 (m, 1 H, H_3), 2.10 (m, 1 H, H_3), 2.61 (apparent q, J = 9 Hz, 1 H, H_5), 2.73 (m, 1 H, H_5), 3.65 (m, 2 H, H_8), 3.75 (m, 1 H, H_7), 3.83 (s, 3 H, OMe), 4.54 (d, J = 8.5 Hz, 1 H, H_2), 5.72 (dd, J = 11.0 Hz, 4.1 Hz, 1 H, H_{15}), 6.32 (d, J = 11.0 Hz, 1 H, H_{14}) (norsecurinine numbering). Anal. Calcd for $C_{22}H_{39}NO_3Si_2$: C, 62.66; H, 9.32; N, 3.32. Found: C, 62.64; H, 9.35; N, 3.30.

In identical fashion, the enantiomeric furan **47** (derived from D-proline) afforded **49**, also in homochiral form.

(8*S*,13*S*)-3-Methoxy-4-(trimethylsilyl)-8-(hydroxymethyl)-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-$\Delta^{1,5}$,$\Delta^{3,4}$,$\Delta^{6,7}$-triene (*ent*-50). A solution of 0.45 g (1.10 mmol) of alkene *ent*-**49** in 30 mL of anhydrous THF was treated with 1.3 mL (1.3 mmol, 1.2 equiv) of 1.0 M Bu_4NF/THF at 0 °C with vigorous stirring under N_2 for a period of 2.5 h. The reaction was then quenched with 20 mL of saturated $NaHCO_3$ at 0 °C, the organic layer was decanted, and the aqueous layer was extracted with 4 × 80 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 5% CH_3OH/CH_2Cl_2) to afford 0.28 g (80%) of *ent*-**50** as a yellow oil: R_f 0.39 (5% CH_3OH/CH_2Cl_2), R_f 0.63 (30% acetone/hexanes); IR (neat) 3390, 3030, 1630, 1580, 1115, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9 H, TMS), 1.65 (m, 1 H, H_4), 1.79 (m, 1 H, H_4), 1.85 (m, 1 H, H_3), 2.15 (m, 1 H, H_3), 2.50 (apparent q, J = 9 Hz, 1 H, H_5), 2.73 (m, 1 H, H_5), 3.42 (dd, J = 11 Hz, 10 Hz, 1 H, H_8), 3.53 (dd, J = 10 Hz, 6 Hz, 1 H, H_8), 3.75 (m, 1 H, H_7), 3.82 (s, 3 H, OMe), 4.52 (dd, J = 8 Hz, 1 Hz, 1 H, H_2), 5.24 (dd, J = 11 Hz, 5 Hz, 1 H, H_{15}), 6.45 (dd, J = 11 Hz, 2 Hz, 1 H, H_{14}) (norsecurinine numbering); exact mass calcd for $C_{16}H_{25}NO_3Si$ 307.1604, found 307.1605.

In identical fashion, the enantiomeric furan **49** (derived from D-proline) afforded **50**, also in homochiral form.

(1*S*,8*S*,13*S*)-3-Oxo-8-(hydroxymethyl)-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-4,6-diene (*ent*-51). A solution of 16.6 mg (0.0519 mmol) of *ent*-**50** and 23.4 mg (0.156 mmol, 2.9 equiv) of NaI inn 2 mL of CH_3CN was cooled to 0 °C and was treated, with vigorous stirring, with 1.56 mL (15.6 mmol, 28 equiv) of 1.0 M $TiCl_4/CH_2Cl_2$. The resulting mixture was stirred for approximately 1 min at 0 °C, during which period the color changed from light yellow to black. The reaction was then quenched with 5 mL of saturated aqueous $NaHCO_3$, the organic layer was decanted, and the aqueous layer was extracted with 4 × 20 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 5% CH_3OH/CH_2Cl_2) to afford 8.4 mg (73%) of *ent*-**51** as a colorless solid: mp 128–130 °C; R_f 0.47 (silica gel, 30% acetone/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 1 H, H_3), 1.75 (m, 2 H, H_4), 1.90 (m, 1 H, H_3), 2.29 (m, 1 H, H_5), 2.79 (m, 1 H, H_5), 3.55 (t, J = 11.5 Hz, 1 H, H_8), 3.64 (m, 1 H, H_8), 3.91 (m, 1 H, H_7), 4.19 (apparent q, J = 9.5 Hz, 1 H, H_2), 5.39 (d, J = 9.5 Hz, 1 H, H_9), 5.93 (dd, J = 10.5 Hz, 4.5 Hz, 1 H, H_{15}), 5.99 (s, 1 H, H_{12}), 6.68 (dd, J = 10.5, 3.5 Hz, 1 H, H_{14}) (norsecurinine numbering). The structure of *ent*-**51** was unequivocally proven by single-crystal X-ray analysis.[22]

In identical fashion, the enantiomeric furan **50** (derived from D-proline) afforded **51**, also in homochiral form.

(1*S*,8*S*,13*S*)-3-Oxo-8-[[(methylsulfonyl)oxy]methyl]-9-aza-2-oxatricyclo[8.3.0^{1,5}.0^{9,13}]trideca-4,6-diene (*ent*-52). A solution of 14.9 mg (0.0674 mmol) of butenolide *ent*-**51** in 2.5 mL of CH_2Cl_2 was cooled to 0 °C under N_2 and was treated, with vigorous stirring, with 42 μL (0.3 mmol, 4.5 equiv) of NEt_3 followed by 17.2 μL (0.222 mmol, 3.3 equiv) of methanesulfonyl chloride. The resulting mixture was stirred for an additional 30 min at 0 °C, and was then quenched with 5 mL of saturated aqueous $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted with 4 × 20 mL of CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 30% acetone/CH_2Cl_2) to afford 19.6 mg (98%) of *ent*-**52** as a pale yellow oil: R_f 0.51 (silica gel, 5% CH_3OH/CH_2Cl_2), R_f 0.79 (silica gel, 30% acetone/CH_2Cl_2); IR ($CHCl_3$) 1758, 1365, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 1 H, H_3), 1.66 (m, 2 H, H_4), 1.86 (m, 1 H, H_3), 2.41 (m, 1 H, H_5), 2.73 (m, 1 H, H_5), 3.08 (s, 3 H, Me), 4.12 (m, 2 H, H_7, H_2), 4.28 (dd, J = 11 Hz, 8 Hz, 1 H, H_8), 4.41 (dd, J = 11 Hz, 6 Hz, 1 H, H_8), 5.36 (d, J = 11 Hz, 1 H, H_9), 5.98 (s, 1 H, H_{12}), 6.22 (dd, J = 11 Hz, 5 Hz, 1 H, H_{15}), 6.71 (dd, J = 11 Hz, 3 Hz, 1 H, H_{14}) (norsecurinine numbering); exact mass calcd for $C_{13}H_{17}NO_5S$ 299.0828, found 299.0814

In identical fashion, the enantiomeric butenolide **51** (derived from D-proline) afforded **52**, also in homochiral form.

(+)-Norsecurinine (2b). A solution of 26.0 mg (0.0861 mmol) of mesylate *ent*-**52** in 15 mL of anhydrous THF was cooled to −78 °C under N_2 and was treated, with vigorous stirring, with 206 μL (0.103 mmol, 1.2 equiv of 0.5 M $(TMS)_2NK$/toluene over a period of 1–2 min. The resulting solution was stirred at −78 °C for an additional 15 min, and then at room temperature for 30 min. The reaction was recooled to −78 °C and poured into 20 mL of saturated $NaHCO_3$ cooled to 0 °C. The organic layer was decanted and the aqueous layer was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (preparative TLC, silica gel, 5% CH_3OH/CH_2Cl_2) to afford 10.5 mg (60%) of (+)-norsecurinine (**2b**) as an unstable yellow oil: R_f 0.30 (5% CH_3OH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.72 (d, J = 11 Hz, 1 H, H_8), 1.80 (m, 2 H, H_4), 1.95 (m, 2 H, H_3), 2.57 (m, 2 H, H_5, H_8), 3.23 (m, 1 H, H_2), 3.34 (m, 1 H, H_5), 3.63 (m, 1 H, H_7), 5.67 (s, 1 H, H_{12}), 6.50 (d, J = 10 Hz, 1 H, H_{14}), 6.75 (dd, J = 10 Hz, 5 Hz, 1 H, H_{15}) (norsecurinine numbering); mass spectrum, m/e 203 (M^+, 7), 134 (15), 106 (43), 78 (44), 70 (100); UV (EtOH) λ_{max} 255 nm; $[\alpha]^{20}_D$ = +268.2°, c = 0.085 (ethanol); exact mass calcd for $C_{12}H_{13}NO_2$ 203.0947, found 203.0937.

As an alternative means of isolation, treatment of the ethereal extracts of **2b** with saturated HCl/EtOH until pH 2–3 was reached afforded a 69% yield of **2b**·HCl as a white amorphous solid. Recrystallized from EtOH, **2b**·HCl had the following: mp 228–230 °C dec; IR (KBr) 3524, 2878, 1820, 1780, 1638 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.89 (m, 1 H, H_4), 2.18 (d, J = 11.0 Hz, 1 H, H_8), 2.2–2.4 (m, 3 H, H_3, H_4), 2.99 (dd, J = 11.0 Hz, 6.0 Hz, 1 H, H_8), 3.21 (dt, J = 11 Hz, 5 Hz, 1 H, H_5), 3.82

(dd, J = 11 Hz, 6.5 Hz, 1 H, H_5), 3.95 (t, J = 8 Hz, 1 H, H_2), 4.49 (m, 1 H, H_7), 6.10 (s, 1 H, H_{12}), 6.79 (dd, J = 8.9 Hz, 6 Hz, 1 H, H_{15}), 7.0 (d, J = 8.9 Hz, 1 H, H_{14}) (norsecurinine numbering).

(-)-**Norsecurinine (2a)**. In identical fashion with that described above for **2b**, the enantiomeric mesylate **52** (derived from D-proline) afforded (-)-norsecurinine (**2a**), also in homochiral form: $[\alpha]^{20}_D$ = -262°, c = 0.06 (ethanol); spectral data identical with those given above for **2b**.

Acknowledgment. Financial support of this work by the National Science Foundation, Grant No. CHE-8711922 is gratefully acknowledged.

Supplementary Material Available: Spectroscopic data for compounds *ent*-**11**, *ent*-**15**, **40**, **42**, **43**, **44**, *ent*-**39**, *ent*-**45**, *ent*-**45S**, *ent*-**47**, *ent*-**49**, *ent*-**50**, *ent*-**51**, *ent*-**52**, **2a**, **2b**, and tables of X-ray crystallographic data for compound *ent*-**51** (31 pages). Ordering information is given on any current masthead page.

Solvent Attack in Grignard Reagent Formation from Bromocyclopropane and 1-Bromohexane in Diethyl Ether

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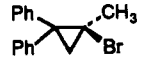
Abstract: In the reaction of magnesium with bromocyclopropane in diethyl ether at reflux, intermediate cyclopropyl radicals attack the solvent, giving cyclopropane (20-30 mol/100 mol of bromocyclopropane consumed) and solvent-derived products. In contrast, the similar reaction of 1-bromohexane gives no more than 0.5 mol of hexane from solvent attack by hexyl radicals. These data are consistent with calculations based on a mechanism (D Model) with freely diffusing intermediate radicals, in which cyclopropyl and hexyl radicals have similar reactivities in their conversions to Grignard reagents, but the cyclopropyl radical is approximately 1000 times as reactive toward the solvent as the hexyl radical.

For Grignard reagent formation from magnesium and an alkyl halide (RX), the extent of reaction of the intermediate alkyl radical (R•) with the solvent (SH) is a critical issue related to the mechanism.[2-6] In general, solvent attack does not appear to be significant for ordinary alkyl halides reacting in diethyl ether. However, it may become significant when R• or SH is sufficiently reactive.[7]

Figures 1 and 2 depict mechanisms currently under consideration. In the D (diffusion) Model (Figure 1), R• diffuses freely in solution at all times.[2] In an A (adsorption) Model, R• remains adsorbed at the magnesium surface. The mechanism proposed by Walborsky (Figure 2) is a basic A Model elaborated with additional hypotheses in order to accommodate certain experimental observations.[3]

The issues addressed here concern those aspects of mechanism and reactivity that determine the extent of solvent attack. In particular, we consider reactions of magnesium with a prototypical alkyl bromide, 1-bromohexane (HxBr), and a prototypical cyclopropyl bromide, bromocyclopropane (CpBr) itself. For these reactions, we have taken great care in analyzing the products.

HxBr provides a calibration point for typical alkyl bromides. CpBr is of particular interest because (1) Walborsky's mechanism is anchored in data for reactions of another cyclopropyl bromide, 1-bromo-1-methyl-2,2-diphenylcyclopropane (**1**),[3] and (2) Cp• is



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more reactive in atom-transfer reactions, by factors of 10^2-10^4, than alkyl radicals such as Hx•.[8]

One question that arises in connection with **1** is that of typicality, that is, the question whether or not the behavior of **1** in Grignard reagent formation is representative of typical (simple) alkyl bromides, e.g., hexyl bromide. Not only is **1** a cyclopropyl bromide, so that the intermediate radical might be unusually reactive, but also it is highly unsaturated. The pseudoconjugation of the cyclopropyl ring with the phenyl groups could lend unusual stability to an intermediate anion radical of **1**, for which there is evidence in reductions in homogeneous solutions.[9]

We find little solvent attack for HxBr but large amounts for CpBr. The latter result contrasts with the data reported for **1** and suggests that the behavior of **1** in Grignard reagent formation

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