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Articles

Total Syntheses of the *Securinega* Alkaloids (+)-14,15-Dihydronorsecurinine, (−)-Norsecurinine, and Phyllanthine†

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A new strategy for enantiospecific construction of the *Securinega* alkaloids has been developed and applied in total syntheses of (+)-14,15-dihydronorsecurinine (**8**), (−)-norsecurinine (**6**), and phyllanthine (**2**). The B-ring and C7 absolute stereochemistry of these biologically active alkaloids originated from *trans*-4-hydroxy-L-proline (**10**), which was converted to ketonitrile **13** via a high-yielding eight-step sequence. Treatment of this ketonitrile with SmI_2 afforded the 6-azabicyclo-[3.2.1]octane B/C-ring system **14**, which is a key advanced intermediate for all three synthetic targets. Annulation of the A-ring of (−)-norsecurinine (**6**) with the required C2 configuration via an *N*-acyliminium ion alkylation was accomplished using radical-based amide oxidation methodology developed in these laboratories as a key step, providing tricycle **33**. Annulation of the D-ring onto α-hydroxyketone **33** with the Bestmann ylide **45** at 12 kbar gave (+)-14,15-dihydronorsecurinine (**8**). In the securinine series, the D-ring was incorporated using an intramolecular Wadsworth−Horner−Emmons olefination of phenylselenylated α-hydroxyketone **47**. The C14,15 unsaturation was installed late in the synthesis by an oxidative elimination of the selenoxide derived from tetracyclic butenolide **50** to give (−)-norsecurinine (**6**). The A-ring of phyllanthine (**2**) was formed from hydroxyketone **14** using a stereoselective $Yb(OTf)_3$-promoted hetero Diels−Alder reaction of the derived imine **34** with Danishefsky's diene, affording adduct **35**. Conjugate reduction and stereoselective equatorial ketone reduction of vinylogous amide **35** provided tricyclic intermediate **36**, which could then be elaborated in a few steps to stable hydroxyenone **53** via α-selenophenylenone intermediate **52**. The D-ring was then constructed, again using an intramolecular Wadsworth−Horner−Emmons olefination reaction to give phyllanthine (**2**).

Introduction and Background

Various plants of the Euphorbiaceae family, particularly those of the *Securinega* and *Phyllanthus* genera, produce a group of tetracyclic compounds classified as the *Securinega* alkaloids.[1] Securinine (**1**), the major alkaloid isolated from the leaves of *Securinega suffruc-*

† Dedicated to the memory of Professor Arthur G. Schultz, a superb chemist and friend.

(1) For excellent reviews, see: (a) Snieckus, V. The *Securinega* Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, p 425. (b) Beutler, J. A.; Brubaker, A. N. *Drugs Fut.* **1987**, *12*, 957.

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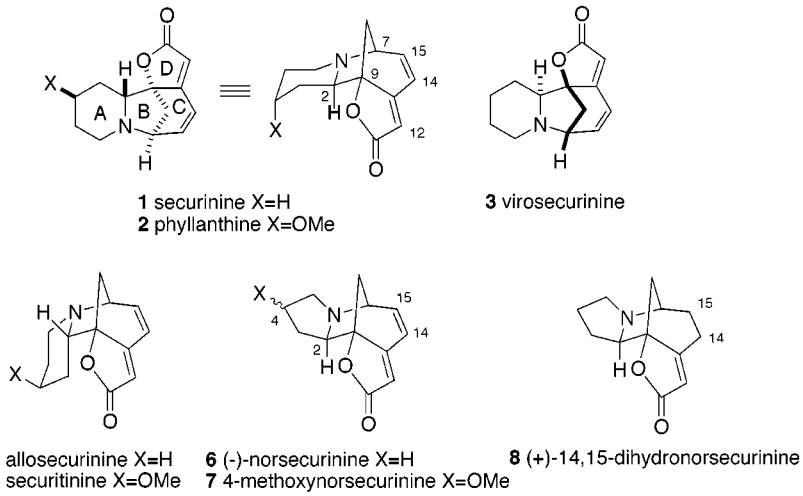


Figure 1.

ticosa, was structurally characterized in the early 1960s and is the most common member of this family (Figure 1).[2] Around the same time, allosecurinine (**4**), the C2 epimer of securinine, was isolated in minor quantities from the same plant and later from a *Phyllanthus* species.[1] Interestingly, the enantiomers of both of these compounds (i.e., virosecurinine (**3**) and viroallosecurinine) were subsequently discovered in related Euphorbiaceae species. During the succeeding years, a number of other *Securinega* alkaloids were found, including the A-ring methoxylated compounds phyllanthine (**2**)[3] and securitinine (**5**).[4] Moreover, the A-ring contracted alkaloids (−)-norsecurinine (**6**),[5] its enantiomer (+)-norsecurinine, and 4-methoxynorsecurinine (**7**)[6] have also been reported. In addition, a number of saturated congeners such as (+)-14,15-dihydronorsecurinine (**8**)[7] have been described. To date, approximately 20 different members of this family of alkaloids have been isolated and characterized.

The *Securinega* alkaloids display an impressive range of biological activity.[1b] The most widely studied of these alkaloids, securinine, is a specific GABA receptor antagonist[8] and has been found to have significant in vivo CNS activity. The compound has been studied clinically in treating paralysis following Bell's palsy and poliomyelitis, and in treatment of the symptoms of ALS and chronic aplastic anemia.[1b] More recently, reports have appeared indicating that securinine is also an antimalarial,[9a] an antibacterial agent,[9b] and causes apoptosis in leukemia cells.[9c]

Considering the extensive body of work in the literature on alkaloid total synthesis, it is surprising that relatively little research has been directed toward these interesting compounds, particularly in view of their wide profile of biological activity. In 1966, starting from (±)-pipecolic acid as the source of the A-ring, Horii and co-workers completed a nonstereoselective, low-yielding total synthesis of racemic securinine, which could be resolved by classical procedures into securinine and virosecurinine.[10] The field lay dormant for over 15 years until synthetic work resumed, when Heathcock et al. in 1983 described the first total synthesis of norsecurinine (**6**) starting from L-proline.[11] The intent was to have this scalemic amino acid provide the A-ring and the C2 absolute stereochemistry of the alkaloid. Unfortunately a racemization occurred during the synthesis, which eventually led to racemic **6**. A few years later, Jacobi and co-workers devised an elegant oxazole/acetylene intramolecular Diels−Alder-based strategy to both (+)- and (−)-norsecurinine starting from L- and D-proline, respectively.[12] Once again, the amino acids provided the A-ring and C2 absolute stereochemistry. Shortly thereafter, Magnus et al. reported a total synthesis of racemic norsecurinine,[13] along with the related *Securinega* alkaloid nirurine,[14] starting from 3-hydroxypyridine as the A-ring precursor. This synthetic route to norsecurinine

(2) Saito, S.; Kodera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoaka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085 and references cited.

(3) Parello, J. *Bull. Soc. Chim. Fr.* **1968**, 1117. Arbain, D.; Birkbeck, A. A.; Byrne, L. T.; Sargent, M. V.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1863.

(4) Horii, Z.; Ikeda, M.; Hanaoka, M.; Yamauchi, M.; Tamura, Y.; Saito, S.; Tanaka, T.; Kodera, K.; Sugimoto, N. *Chem. Pharm. Bull.* **1967**, *15*, 1633 and references cited.

(5) Joshi, B. S.; Gawad, D. H.; Pelletier, S. W.; Kartha, G.; Bhandary, K. *J. Nat. Prod.* **1986**, *49*, 614 and references cited.

(6) Mulchandani, N. B.; Hassarajani, S. A. *Planta Med.* **1984**, *50*, 104.

(7) (a) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.-I.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1964**, *12*, 1520. (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.-I.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1965**, *13*, 786.

(8) (a) Rognan, D.; Boulanger, T.; Hoffmann, R.; Vercauteren, D. P.; Andre, J.-M.; Durant, F.; Wermuth, C.-G. *J. Med. Chem.* **1992**, *35*, 1969. (b) Galvez-Ruano, E.; Aprison, M. H.; Robertson, D. H.; Lipkowitz, K. B. *J. Neurosci. Res.* **1995**, *42*, 666.

(9) (a) Weenen, H.; Nkunya, M. H. H.; Bray, D. H.; Mwasumbi, L. B.; Kinabo, L. S.; Kilimali, V. A.; Wijnberg, J. B. *Planta Med.* **1990**, *56*, 371. (b) Mensah, J. L.; Lagarde, I.; Ceschin, C.; Michel, G.; Gleye, J.; Fouraste, I. *J. Ethnopharmacol.* **1990**, *28*, 129. (c) Dong, N. Z.; Gu, Z. L.; Chou, W. H.; Kwok, C. Y. *Chung Kuo Li Hsueh Pao* **1999**, *20*, 267; *Chem Abstr.* **1999**, *130*, 346993n.

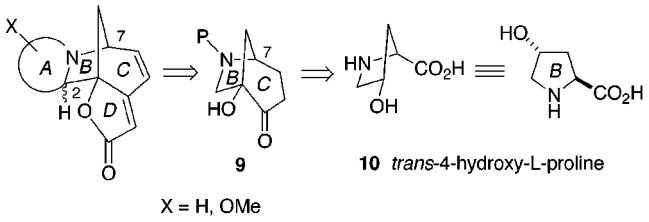
(10) Saito, S.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N.; Horii, Z.; Hanaoka, M.; Tamura, Y. *Chem. Pharm. Bull.* **1966**, *14*, 313. See also: Horii, Z.; Imanishi, T.; Tanaka, T.; Mori, I.; Hanaoka, M.; Iwata, C. *Chem. Pharm. Bull.* **1972**, *20*, 1768. Horii, Z.; Imanishi, T.; Hanaoka, M.; Iwata, C. *Chem. Pharm. Bull.* **1972**, *20*, 1774.

(11) (a) Heathcock, C. H.; Jennings, R. A.; von Geldern, T. W. *J. Org. Chem.* **1983**, *48*, 3428. (b) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75. (c) Heathcock, C. H.; von Geldern, T. W.; Librilla, C. B.; Maier, W. F. *J. Org. Chem.* **1985**, *50*, 968.

(12) (a) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173. (b) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384. (c) We are grateful to Professor Jacobi for providing spectra of authentic norsecurinine.

(13) Magnus, P.; Rodriguez-Lopez, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059.

Scheme 1



featured a clever biogenetically inspired[15] rearrangement of an azabicyclo[2.2.2]octane to an azabicyclo[3.2.1]octane system.

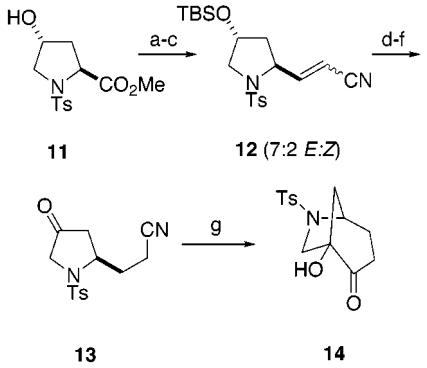
Synthetic Strategy

The goal of this program was to devise a new general synthetic strategy to the *Securinega* alkaloids that would allow a simple entry to any of the compounds of the family in enantiomerically pure form starting from a common advanced intermediate.[16,17] We recognized that most members of this group differ only in the A-ring size and functionality, as well as the C2 configuration (cf. **1**−**8**), and thus, we attempted to devise a strategy with the flexibility to allow for the variations in this portion of the molecules. Also, since in most instances both enantiomers of a given alkaloid are known, we felt the approach should in principle provide access to either antipode starting from readily available chiral pool compounds. We therefore investigated the retrosynthetic plan shown in Scheme 1. The idea was to first generate a 6-azabicyclo[3.2.1]octane B/C moiety like **9** starting from enantiomerically pure *trans*-4-hydroxyl-L-proline (**10**), or its commercially available D-enantiomer, which would provide the B-ring and the absolute chirality at C7. It might be noted that for the Heathcock[11] and Jacobi[12] strategies to produce the more common enantiomeric alkaloid series related to securinine D-proline is required, whereas our proposed approach would use the less expensive L-amino acid. Our objective was to then develop methodology to annulate an appropriate A-ring onto the pivotal bicycle **9**, followed by the D-ring. This order was chosen since the conjugated dienic γ-lactone functionality, particularly in the case of norsecurinine, adds an element of instability to the system, and it seemed prudent to leave introduction of this sensitive array until the final stages of the synthesis. In this paper, we descibe the successful application of this strategy to enantiospecific total syntheses of three *Securinega* alkaloids (+)-14,15-dihydronorsecurinine (**8**), (−)-norsecurinine (**6**), and phyllanthine (**2**).

Results and Discussion

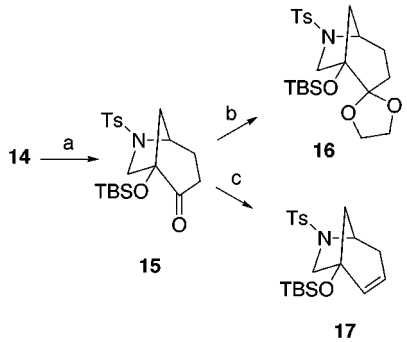
Construction of a 6-Azabicyclo[3.2.1]octane B/C Ring Synthon. The first objective of the project was to access an enantiomerically pure B/C ring intermediate such as **9**. Our starting material was the known ester sulfonamide **11**,[18] easily prepared from *trans*-4-hydroxy-L-proline (**10**). This compound was first converted to the TBS ether, and after ester reduction followed by Swern oxidation the resulting aldehyde was subjected to a Wittig reaction to produce α,β-unsaturated nitrile **12** as a 7:2 mixture of *E*/*Z* isomers (Scheme 2). Catalytic hydrogenation of isomer mixture **12**, silyl ether removal, and alcohol oxidation led to the ketonitrile **13** in high overall yield. We were pleased to find that upon subjection of compound **13** to samarium diiodide in THF containing methanol as a proton source, followed by acidic hydrolysis, the desired azabicyclic α-hydroxyketone **14** was formed in 78% isolated yield.[19]

Scheme 2[a]



[a] Reagents: (a) TBSCl, imid., CH_2Cl_2, 88%; (b) DIBALH, PhMe, −78 °C to rt, 98%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C/Ph_3P=CHCN, CH_2Cl_2, −78 °C to rt, 90%; (d) 1 atm H_2, 10% Pd−C, EtOAc, 98%; (e) Bu_4NF, THF, rt, 100%; (f) Jones reagent, Me_2CO, rt, 84%; (g) SmI_2, MeOH, THF, −78 °C to rt; then H_3O^+, 78%.

Scheme 3[a]



[a] Reagents: (a) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 91%; (b) $(CH_2OH)_2$, *p*-TsOH, PhH, Δ, 100%; (c) $TsNHNH_2$, MeOH, 0 °C to rt; NaH, PhMe, Δ, 78%.

Since we entertained a number of possibilities for eventual annulation of the D-ring (vide infra), it was decided to prepare two differently functionalized C-ring systems for future study. Therefore, hydroxyketone **14** was first silylated to produce TBS ether **15**, which could then be converted to ketal **16** in high yield (Scheme 3). The second system was produced by conversion of ketone **15** to the corresponding tosylhydrazone, which cleanly

(14) Petchnaree, P.; Bunyapraphatsara, N.; Cordell, G. A.; Cowe, H. J.; Cox, P. J.; Howie, R. A.; Patt, S. L. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1551.

(15) For studies on the biosynthesis of the *Securinega* alkaloids, see: Parry, R. J. *Bioorg. Chem*. **1978**, *7*, 277 and references cited.

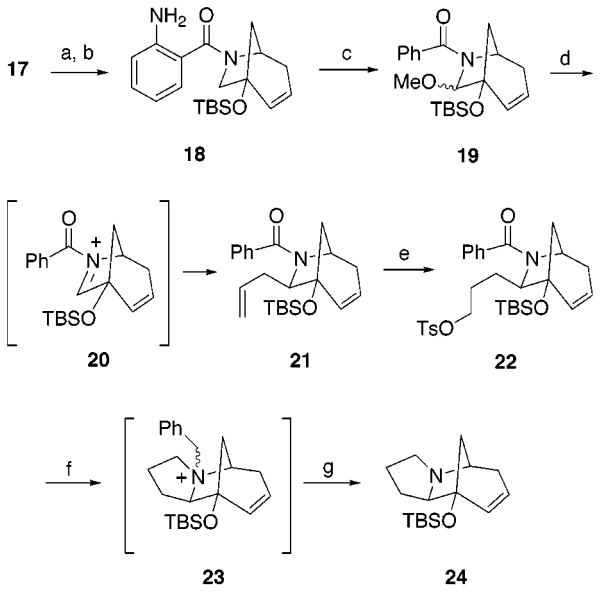
(16) Preliminary accounts of portions of this research have appeared: (a) Weinreb, S. M. *J. Heterocycl. Chem*. **1996**, *33*, 1437. (b) Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 237.

(17) This work is taken in part from: (a) Folmer, J. J. Ph.D. Thesis, The Pennsylvania State University, 1994. (b) Han, G. Ph.D. Thesis, The Pennsylvania State University, 1997. (c) LaPorte, M. G. Ph.D. Thesis, The Pennsylvania State University, 2000.

(18) Andreatta, R. H.; Nair, V.; Robertson, A. V.; Simpson, W. R. J. *Aust. J. Chem*. **1967**, *20*, 1493.

(19) cf. Molander, G. A.; Wolfe, C. N. *J. Org. Chem*. **1998**, *63*, 9031 and references cited.

Scheme 4[a]



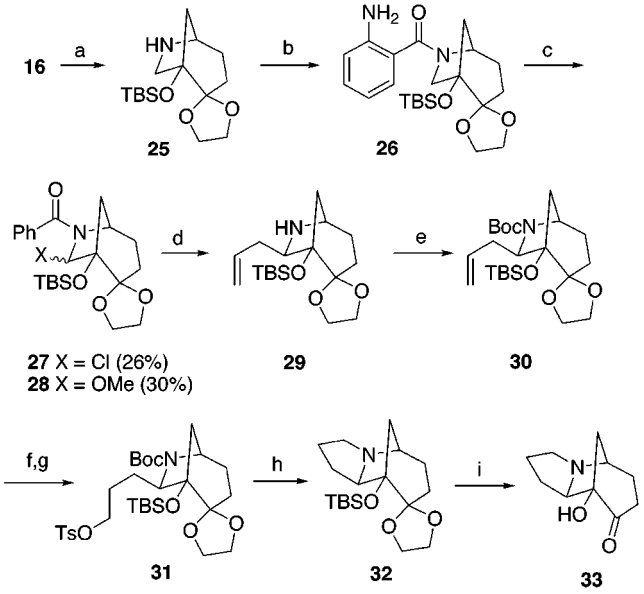
[a] Reagents: (a) Na, naphthalene, DME, −78 °C; (b) isatoic anhydride, MeCN, DMAP, 0 °C to rt, 79% from **17**; (c) $NaNO_2$, HCl, CuCl (20 mol %); MeOH, rt, 61%; (d) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C to rt, 91%; (e) disiamylborane, THF; H_2O_2, NaOH; TsCl, DMAP, NEt_3, CH_2Cl_2, 0 °C to rt, 64%; (f) DIBALH, PhMe, −70 to −15 °C; (g) NaI, NEt_3, PhMe, Δ, 59% from **22**.

afforded the bicyclic olefin **17** using a modification of the Shapiro reaction described by Jung.[20]

Annulation of the Norsecurinine A-Ring. With azabicyclics **16** and **17** in hand, we next turned to studying routes for annulation of the norsecurinine pyrrolidine A-ring. It was our intention here to make use of our recently developed radical-based methodology for generation of *N*-acyliminium ions from simple secondary amines.[21] Thus, the sulfonamide group of **17** was reductively cleaved to afford the corresponding amine, which was acylated with isatoic anhydride to yield *o*-aminobenzamide **18** (Scheme 4). When this compound was subjected to diazotization conditions in the presence of CuCl (∼20 mol %) in methanol, the desired α-methoxybenzamide **19** was formed regioselectively (61%). Treatment of **19** with allyltrimethylsilane and $TiCl_4$ then led to a single stereoisomeric allylation product **21** in high yield. We believe that **21** results from exo attack on an intermediate *N*-acyliminium salt **20**. Although the stereochemistry of **21** was not firmly established, this transformation is in accord with later results discussed below. To complete annulation of the A-ring, olefin **21** was hydroborated and the resulting primary alcohol was converted to tosylate **22**. However, all attempts to remove the *N*-benzoyl group by basic hydrolysis failed. Alternatively, it was possible to reduce the benzoyl substituent with DIBALH to give ammonium salt **23**, which without characterization was dealkylated with sodium iodide, affording the requisite norsecurinine tricyclic amine **24**.

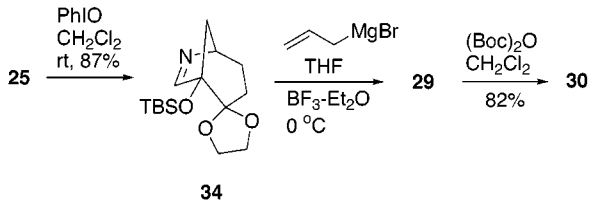
We have also investigated a similar annulation strategy in the C-ring ketal azabicyclic series. Therefore, sulfonamide **16** was first converted to amine **25** and then to *o*-aminobenzamide **26** (Scheme 5). Interestingly, the

Scheme 5[a]



[a] Reagents: (a) Na, naphthalene, DME, −78 °C; (b) isatoic anhydride, DMAP, MeCN, rt, 87% from **16**; (c) $NaNO_2$, HCl, CuCl (100 mol %), MeOH, rt; (d) allylmagnesium bromide, $BF_3{-}Et_2O$, THF, −78 to 0 °C; (e) $(Boc)_2O$, NEt_3, CH_2Cl_2, reflux, 68% from **27**/**28**; (f) disiamyl borane, THF, 0 °C to rt/H_2O_2, NaOH; (g) TsCl, DMAP, NEt_3, CH_2Cl_2, 71% from **30**; (h) 0.8 N HCl, MeOH, 60 °C, 81%; (i) 3 N aqueous HCl, 95 °C, 74%.

Scheme 6

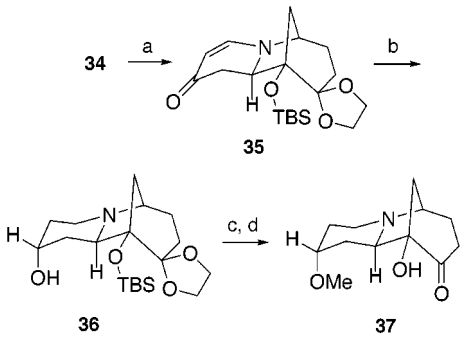


conversion of **26** to the desired α-methoxybenzamide proved messy under our standard conditions and required a significantly larger amount of CuCl than we have usually employed, perhaps due to complexation of the catalyst by the ketal moiety.[21] The reaction could be promoted by using 100 mol % of CuCl, but under these conditions the product consisted of a nearly 1:1 mixture of the α-methoxybenzamide **28** and the α-chloro compound **27**. However, it was possible to effect the next step in the sequence using the mixture of **27** and **28**. Treatment of this mixture with a large excess of allylmagnesium bromide in the presence of boron trifluoride etherate afforded the allylated product **29** and also conveniently led to removal of the benzoyl group. Amine **29** is a single stereoisomer, whose C2 configuration was eventually proven to be exo by X-ray crystallography (vide infra). This amine was next converted to the Boc-protected derivative **30** which, after hydroboration of the olefin, could be transformed to tosylate **31**. Finally, acidic cleavage of the Boc group and in situ cyclization led to tricycle **32**. Further hydrolysis of the TBS and ketal groupings, which required more stringent conditions, yielded α-hydroxyketone **33**.

An alternative and more convenient route has also been developed to convert secondary amine **25** to intermediate **30** (Scheme 6). It was found that **25** could be cleanly oxidized to chromatographically stable imine **34**

(20) Jung, M. E.; Gomez, A. V. *Tetrahedron Lett.* **1991**, *34*, 2891.
(21) (a) Han, G.; McIntosh, M. C.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 5813. (b) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 9483.

Scheme 7[a]



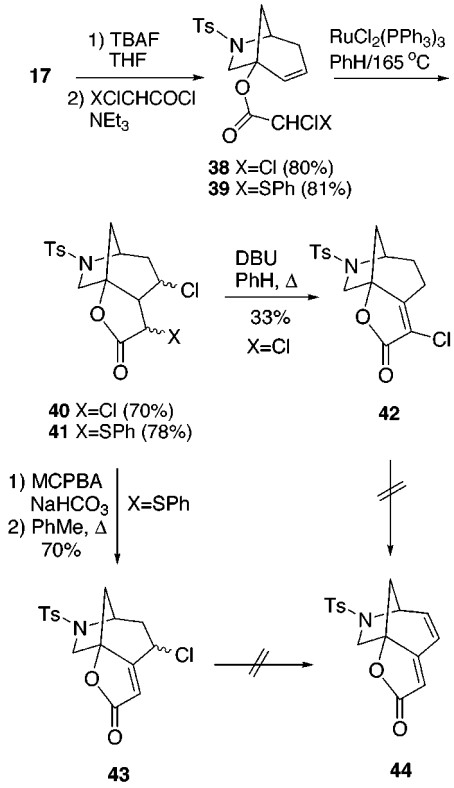
[a] Reagents: (a) Danishefsky's diene, $Yb(OTf)_3$, MeCN, 84%, or CH_2Cl_2, 12 kbar, 71%; (b) L-Selectride (2 equiv), THF, −78 °C, 85%; (c) NaH, MeI, THF, 0 °C to rt, 87%; (d) 3 N HCl, reflux, 78%.

using iodosobenzene.[22,23] Attempts to allylate **34** with allyltributylstannane and ytterbium triflate as the catalyst led to about a 30% yield of **29** along with 60% of unreacted starting material.[24] However, the imine could be cleanly alkylated with allylmagnesium bromide/boron trifluoride etherate to produce amine **29**, which was then Boc protected to yield **30** (82% from **34**).

Annulation of the Phyllanthine A-Ring. Our strategy of choice for annulating the phyllanthine A-ring was to effect a hetero Diels−Alder reaction using imine **34** as a dienophile.[25] We had some initial concerns about the feasibility of this approach since this unactivated bicyclic imine is more complex than any imino dienophile previously used for this type of cycloaddition, and we felt it was possible that it might be too sterically hindered to participate effectively in the reaction. Initial experiments with imine **34** and Danishefsky's diene using a variety of common Lewis acid catalysts (e.g., $SnCl_4$, $TiCl_4$, etc.) produced only low yields of the desired cycloadduct **35** (Scheme 7), possibly due in part to the sensitivity of the ketal and silyl ether functionality to strong acids. However, it was eventually discovered that ytterbium triflate catalyzes the [4 + 2]-cycloaddition affording **35** in 84% yield.[24] It was also found that the Diels−Alder reaction can be run without a catalyst at high pressure (12 kbar, 71% yield). The structure of tricycle **35** was confirmed by X-ray crystallography, indicating that as had been anticipated the diene attacks the imine from the less congested exo direction with the regiochemistry shown, thereby setting the correct C2 stereochemistry of phyllanthine (see the Supporting Information).

To further elaborate the A-ring functionality, vinylogous amide **35** was treated with 2 equiv of L-Selectride, leading to stereoselective formation of the axial alcohol **36** in high yield. This result was rather surprising since one would anticipate that conjugate reduction of **35** produces an enolate which should be resistant to further reduction.[26] It is possible here that the second reduction step actually occurs upon enolate protonation during the aqueous workup. Finally, O-methylation of alcohol **36** afforded the corresponding methyl ether, which upon acid hydrolysis led to the desired tricyclic α-hydroxyketone **37**.

Scheme 8



D-Ring Model Studies with Azabicyclic Olefin 17. An attractive strategy which we wished to explore was the possibility of utilizing a metal-catalyzed atom transfer radical reaction[27] to construct the requisite *Securinega* alkaloid D-ring, and we opted to investigate the basic approach using bicyclic olefin **17** as a model system. In our initial experiments, the silyl ether group of **17** was removed with TBAF to give the tertiary alcohol, which could then be acylated with dichloroacetyl chloride to afford ester olefin **38** (Scheme 8). Exposure of this compound to a catalytic amount of ruthenium dichloride tris-triphenylphosphine at 165 °C in a sealed tube indeed led to the desired α,γ-dichlorolactone **40**. However, we have been unable to effect a double elimination to produce the desired diene **44**. The only characterizable product obtained in any of these experiments was α-chlorobutenolide **42**, which could not be converted to **44**.

In an attempt to circumvent the elimination problem, compound **17** was converted to the α-chloro-α-thiophenylacetate **39**. Ruthenium-catalyzed cyclization of this intermediate proceeded cleanly to afford the expected lactone **41**, which could be oxidized to the sulfoxide and thermally eliminated to give γ-chloro butenolide **43**. Unfortunately, we have been unable to eliminate HCl

(22) Muller, P.; Gilabert, D. M. *Tetrahedron* **1988**, *44*, 7171. Larsen, J.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1213.

(23) This transformation could also be effected, but less conveniently, with diphenylseleninic anhydride: Czarny, M. R. *J. Chem. Soc., Chem. Commun.* **1976**, 81. Czarny, M. R. *Synth. Commun.* **1976**, *6*, 285.

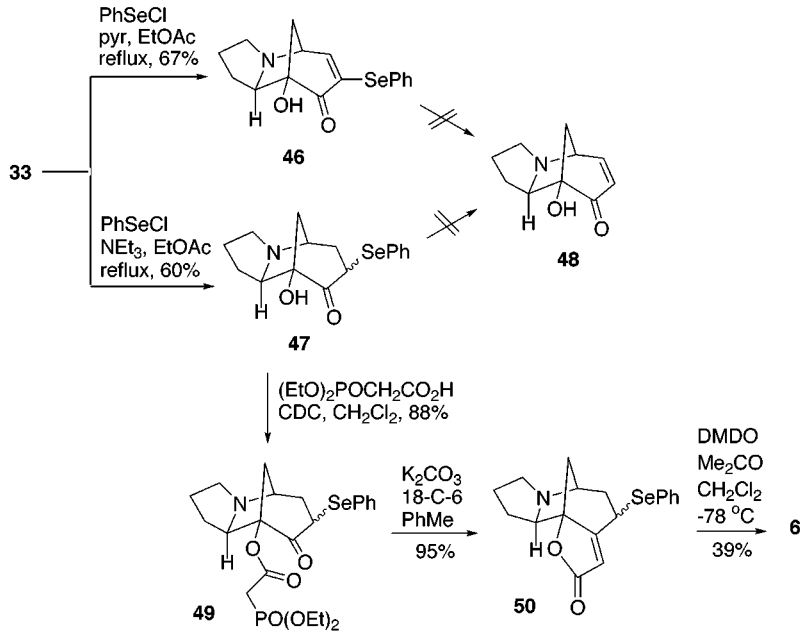
(24) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049.

(25) For reviews of the imino Diels−Alder reaction, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987; Chapter 2. (b) Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 401.

(26) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184 and references cited.

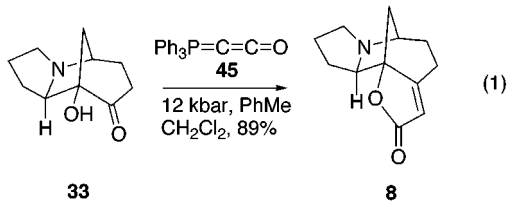
(27) For lead references, see: (a) Ishibashi, H.; Nakatani, H.; Iwami, S.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1767. (b) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464. (c) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625.

Scheme 9



from **43** to form diene lactone **44**. Moreover, it has not been possible to displace the chlorine in tricycle **43** with any nucleophile. In view of these disappointing results, we decided to abandon the idea of using an olefin as a handle to elaborate the D-ring and have instead concentrated on the compounds bearing a C-ring ketone substituent.

Synthesis of (+)-14,15-Dihydronorsecurinine (8) and (−)-Norsecurinine (6). At this point, we chose to return to the tricyclic α-hydroxyketone **33** and investigate the D-ring annulation of this key intermediate via a strategy based upon the methodology of Bestmann.[28] Thus, treatment of hydroxyketone **33** with the Bestmann ylide **45** under the usual conditions for butenolide formation (CH_2Cl_2, reflux, NEt_3) gave 14,15-dihydronorsecurinine (**8**) but in only ~25% yield (eq 1). This reaction has



(1)

apparently not been used previously with a tertiary α-hydroxyketone, and it is possible that the initial alcohol acylation step with **45** is slow with substrate **33**. However, we were pleased to find that if the reaction is run at 12 kbar in the absence of an added base, alkaloid **8** is formed in 89% yield. 14,15-Dihydronorsecurinine was isolated in 1964 from the root bark of *Securinega virosa*, but only scant data are provided for this alkaloid.[7] In fact, no D-line optical rotation is available for the natural material, but rather an ORD spectrum was reported. The ORD spectrum of our synthetic material is in accord with that described, thereby confirming the assigned absolute configuration.[29] Furthermore, X-ray analysis of the hydrochloride salt of **8** unambiguously established the structure of our synthetic material, and also confirmed that the allylation of the *N*-acyliminium salt derived from benzamides **27/28** (Scheme 5) had occurred exo as was assumed (see Supporting Information).

Several attempts were made to directly oxidize the dihydro compound **8** to (−)-norsecurinine (**6**) using reagents such as DDQ, or by a Saegusa-type oxidation. However, in all cases either starting material was recovered unchanged or complete decomposition occurred. It therefore became necessary to introduce the norsecurinine C-ring double bond at the tricycle stage using ketone **33** or a related compound. Effecting this transformation in fact turned out to be much more difficult than was envisioned.

A number of experiments were conducted using both α-hydroxyketone **33** and model bicyclic ketone **14**, along with some alcohol-protected derivatives, with the idea of generating an enolate which could then be selenylated or sulfenylated.[30] In no case, however, could any useful product be isolated in acceptable yield. We were also unable to prepare a silylenol ether from any of these ketones.[17]

Since these compounds did not appear to form well-behaved metal enolates, we turned to an alternative neutral method for α-phenylselenation of ketones described by Sharpless.[31] Surprisingly, refluxing hydroxyketone **33** in ethyl acetate in the presence of excess phenylselenyl chloride did not produce the desired α-phenylselenyl ketone **47**, but in fact gave the α-phenylselenoenone **46** (Scheme 9). However, the reaction was sluggish, requiring several days of heating, and moreover, yields of product **46** were quite variable. It was eventually found that addition of pyridine increased the rate of the reaction and also led to a reproducible 67% yield of the

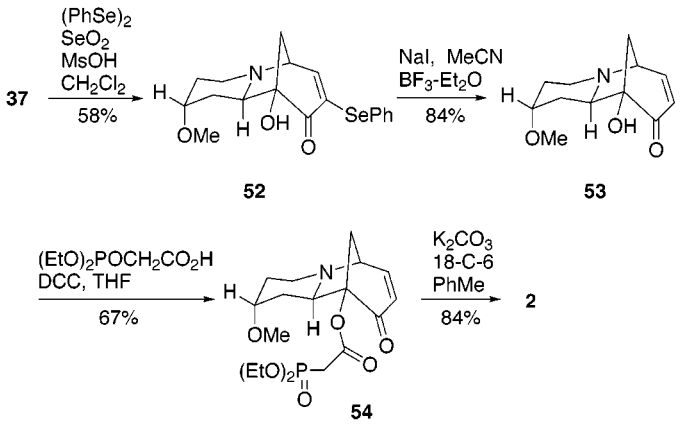
(28) Bestmann, H. J.; Sandmeier, D. *Chem Ber*. **1980**, *113*, 274. Nickisch, K.; Klose, W.; Bohlmann, F. *Chem Ber*. **1980**, *113*, 2038.

(29) We are indebted to Dr. C. J. Easton and J. Kelly (Australian National University) for recording the ORD spectrum of synthetic (+)-14,15-dihydronorsecurinine (**8**).

(30) Reich, H. J.; Wollowitz, S. *Org. React*. **1993**, *44*, 1.

(31) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

Scheme 10

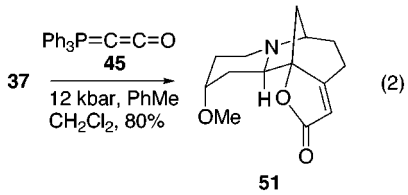


selenoenone **46**. Liotta and co-workers[32a] have previously investigated the reaction of this combination of PhSeCl/pyridine with some enolizable ketones, and observed direct formation of α,*β*-unsaturated ketones. To explain these results, it was suggested that initial ketone α-phenylselenylation occurs, followed by a "nonoxidative" elimination to an α,*β*-unsaturated ketone. However, the reaction does not occur with simple ketones such as cyclohexanone, and it is not clear why this transformation seems to be happening with α-hydroxyketone **33**. Liotta has also found that α,*β*-unsaturated ketones react with PhSeCl/pyridine to produce α-selenophenylenones analogous to **46**, thus suggesting transient formation of the enone **48**.[32b]

Inexplicably, when the base used for the selenylation step was changed from pyridine to triethylamine, α-phenylselenyl ketone **47** was formed from ketone **33** (mixture of epimers, 60%) rather than the selenoenone **46**. However, despite some considerable effort we have been unable to convert either **46** or **47** to the requisite enone **48**. We believe that the difficulty here is that **48** is probably unstable and polymerizes, as is the case with the free base of norsecurinine itself. Based upon this supposition, we chose to delay introduction of the C14,15 double bond until after butenolide formation.

Attempts were first made to combine hydroxyketone **47** with the Bestmann reagent **45**, but in no case did we detect the desired butenolide **50**. Alternatively, tricyclic selenide alcohol **47** was esterified with commercially available diethylphosphonoacetic acid to produce phosphonate **49** in high yield. Exposure of **49** to potassium carbonate/18-crown-6 in toluene led to an efficient intramolecular Wadsworth−Horner−Emmons cyclization, giving the tetracyclic butenolide **50** (95%) as a chromatographically separable mixture of selenide epimers. To complete the total synthesis all that remained was to effect a selenide oxidation/elimination sequence. Disappointingly, the usual selenide oxidants (*m*-CPBA, H_2O_2, $NaIO_4$, Oxone, ozone, *tert*-butylhydroperoxide, etc.)[30] all led to only poor yields (<30%) of norsecurinine. In addition, there was no discernible improvement in yield by first converting **50** to an amine salt. It was finally found that oxidation of the mixture of selenides **50** with dimethyldioxirane at −78 °C produces (−)-norsecurinine (**6**) in moderate 39% yield.[33] To our knowledge, this reagent has not previously been used for the oxidation of selenides to selenoxides.[30] Our synthetic material had spectral data identical with those of an authentic sample of norsecurinine.[12c]

Synthesis of 14,15-Dihydrophyllanthine (51) and Phyllanthine (2). To test the D-ring annulation in the phyllanthine series, α-hydroxyketone **37** was reacted under high pressure with the Bestmann ylide **45**, providing 14,15-dihydrophyllanthine (**51**) in 80% yield (eq 2).



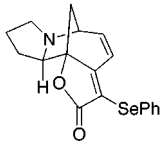
(2)

Although this compound is not a natural product, it has been previously prepared by partial reduction of phyllanthine (**2**).[3] Our compound had data in good accord with those reported for naturally derived material.

Some of the same problems as described above for norsecurinine arose with regard to introducing C-ring unsaturation into the phyllanthine intermediate. Once again, enolate chemistry with hydroxyketone **37** and derivatives proved fruitless. More surprising was the fact that exposure of **37** to the selenation procedures used for **33** (Scheme 9) gave complex mixtures of products. In exploring other neutral or acidic methods for α-phenylselenylation of ketones, we turned to the procedure of Sonoda *et al.*[34] Thus, ketone **37** was treated with diphenyldiselenide, selenium dioxide, and methanesulfonic acid, leading to selenoenone **52** in 58% yield (Scheme 10). This was an unexpected result since the Sonoda protocol has been used previously for forming an α-phenylselenoketone from a ketone, but direct formation of an α-selenophenylenone has apparently not been observed. For-

(32) (a) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III. *J. Org. Chem.* **1981**, *46*, 2920. (b) Zima, G.; Liotta, D. *Synth. Commun.* **1979**, *9*, 697.

(33) A byproduct in this reaction has been tentatively identified as the phenylselenonorsecurinine **i**. We are uncertain as to the genesis of this compound.



i

(34) Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1982**, *23*, 4813. Watanabe, M.; Awen, B. Z.; Kato, M. *J. Org. Chem.* **1993**, *58*, 3923.

tunately, in a crucial experiment selenoenone **52** could be converted to the stable tricyclic enone **53** using NaI/BF_3 etherate in 84% yield.[35,36] This procedure has previously been used for dehalogenation of an α-bromoenone, but not for deselenylation.

Attempted condensation of hydroxyenone **53** with the Bestmann reagent **45** under a variety of conditions did not produce any phyllanthine, and it was therefore necessary to pursue a Wadsworth−Horner−Emmons approach for annulation of the D-ring. Thus, hydroxyenone **53** was first converted to the phosphonate **54**, which upon exposure to potassium carbonate/18-crown-6 yielded phyllanthine (**2**). Although we could not obtain a sample of the natural alkaloid, the synthetic phyllanthine had spectral data in close agreement with those published.[3]

Conclusion

Described here is a conceptually new, general strategy for enantiospecific construction of the biologically active *Securinega* family of plant alkaloids starting from *trans*-L-4-hydroxyproline (**10**). Total syntheses of (+)-14,15-dihydronorsecurinine (**8**) and (−)-norsecurinine (**6**), along with the first total synthesis of phyllanthine (**2**) have been achieved via this approach. Novel chemical steps include: (1) an intramolecular pinacol-type coupling of ketonitrile **13** using samarium diiodide to efficiently generate the pivotal B/C azabicyclo[3.2.1]octane nucleus **14** common to all these alkaloids; (2) application of our recently developed radical-based methodology for regioselective generation of *N*-acyliminium ions from simple amines as a key step in the syntheses of the norsecurinine series; and (3) stereoselective imino Diels−Alder reaction catalyzed by $Yb(OTf)_3$ of the hindered, highly functionalized bicyclic imine **34** for efficient annulation of the A ring of phyllanthine. We also hope to modify the approach described here so that A-rings bearing the endo C2 stereochemistry found in allosecurinine (**4**) and securitinine (**5**) can be annulated onto key bicyclic hydroxyketone **14**.

Experimental Section

General Methods. Reactions were run under an atmosphere of argon. Low-resolution mass spectra were obtained at 50−70 eV by electron impact (EIMS). Chemical ionization mass spectra (CIMS) were obtained using isobutane as a carrier gas. Optical rotations were obtained at ambient temperature. Reactions under high pressure were conducted in a LECO model PG-200-HPC apparatus at room temperature. Flash chromatography was performed using EM Sciences silica gel 60 (25−40 mm). Preparative TLC was done with EM Silica Gel 60 PF_{254}. Melting points are uncorrected. Combustion analyses were carried out by Atlantic Microlab.

Synthesis of α,β-Unsaturated Nitrile 12. To a solution of *trans*-4-hydroxy-L-proline-derived alcohol sulfonamide **11**[18] (11.6 g, 38.7 mmol) in 300 mL of CH_2Cl_2 at 0 °C was added imidazole (6.3 g, 92.5 mmol), followed by *tert*-butyldimethylsilyl chloride (8.4 g, 55.7 mmol). The mixture was stirred at 0 °C for 45 min and then at room temperature for 16 h. The solution was concentrated under reduced pressure, and the residue was filtered through a silica gel plug eluting with ethyl acetate. The eluent was concentrated in vacuo, and the residue was purified by flash chromatography (ethyl acetate/hexanes, 1/9) to give the silyl ether as a white solid (14.1 g, 88%): $[\alpha]^{20}_D = -82.2$ (*c* 0.64, $CDCl_3$); mp 45−47 °C; IR (film) 2950, 2840, 1750, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.42−4.32 (m, 1H), 4.24 (t, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 3.66 (dd, *J* = 4.3, 10.7 Hz, 1H), 3.18 (dd, *J* = 1.9, 10.8 Hz, 1H), 2.40 (s, 3H), 2.11−2.04 (m, 2H), 0.69 (s, 9H), −0.072 (s, 3H), −0.084 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 143.6, 134.3, 129.6, 127.7, 70.3, 59.7, 56.7, 52.5, 40.2, 25.5, 21.5, 17.8, −5.0, −5.1; EIMS *m/z* (relative intensity) 412 ($M^+ - H$, 0.1), 356 ($M^+ - t$-Bu, 100). Anal. Calcd for $C_{19}H_{31}NO_5SSi$: C, 55.17; H, 7.55; N, 3.39. Found: C, 55.19; H, 7.62; N, 3.32.

To a −78 °C solution of the silyl ether (15.0 g, 36.3 mmol) in 450 mL of dry toluene was added neat DIBALH (20.0 mL, 0.11 mol) dropwise over 30 min. The solution was stirred at −78 °C for 1 h and then warmed to 0 °C. The reaction mixture was diluted with 100 mL of saturated sodium potassium tartrate (Rochelle salt). Ethyl acetate (100 mL) was added, and the cloudy mixture was stirred at room temperature for 2 h. The organic layer was washed with saturated Rochelle salt solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1/3) to give the alcohol as a white solid (13.7 g, 98%): $[\alpha]^{20}_D = -26.8$ (*c* 0.55, $CDCl_3$); mp 83−85 °C; IR (film) 3510−3480, 2930, 2810, 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.30−4.23 (m, 1H), 3.92−3.87 (m, 1H), 3.73−3.62 (m, 3H), 3.22 (dt, *J* = 1.7, 11.2 Hz, 1H), 3.09−3.00 (m, 1H), 2.42 (s, 3H), 1.91−1.86 (m, 1H), 1.79−1.75 (m, 1H), 0.71 (s, 9H), −0.078 (s, 3H), −0.098 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 133.1, 129.7, 127.8, 69.4, 65.2, 60.9, 58.6, 38.7, 25.6, 21.5, 17.9, −5.0, −5.1; EIMS *m/z* (relative intensity) 384 ($M^+ - H$, 0.3), 370 ($M^+ - Me$, 4), 354 ($M^+ - CH_2OH$, 64), 328 ($M^+ - t$-Bu, 100). Anal. Calcd for $C_{18}H_{31}NO_4SSi$: C, 56.07; H, 8.10; N, 3.63. Found: C, 55.98; H, 8.05; N, 3.71.

To a solution of oxalyl chloride (12.0 mL, 2.0 M in CH_2Cl_2) in 50 mL of dry CH_2Cl_2 at −78 °C was added a solution of DMSO (4.0 mL, 56.3 mmol) in 7.0 mL of CH_2Cl_2. The mixture was stirred for 10 min, and a solution of the above alcohol (5.3 g, 13.8 mmol) in 30 mL of dry CH_2Cl_2 was added dropwise over 30 min. The mixture was stirred for an additional 30 min, and triethylamine (9.0 mL, 64.7 mmol) was added over 10 min. The solution was stirred for 35 min, and (triphenylphosphoranylidene)acetonitrile (9.4 g, 31.2 mmol) in 100 mL of dry CH_2Cl_2 was added via cannula. The reaction mixture was stirred for an additional 3 h at room temperature and was diluted with 50 mL of brine. The organic layer was washed twice with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in ethyl acetate and hexanes (1/4), filtered through a silica gel plug, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1/8) to give (*E*)-olefin (3.9 g, 70%) and (*Z*)-olefin (1.1 g, 20%) (**12**) as white solids.

(*E*)-Olefin: mp 84−87 °C; IR (CCl_4) 2952, 2856, 2224, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.72 (dd, *J* = 7.2, 16.2 Hz, 1H), 5.58 (dd, *J* = 1.3, 16.2 Hz, 1H), 4.25 (m, 1H), 4.17 (q, *J* = 7.5 Hz, 1H), 3.62 (dd, *J* = 4.4, 11.1 Hz, 1H), 3.19 (d, *J* = 11.1 Hz, 1H), 2.41 (s, 3H), 1.86−1.80 (m, 2H), 0.70 (s, 9H), −0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 143.9, 133.7, 129.8, 127.7, 116.7, 100.2, 69.5, 59.6, 57.4, 41.9, 25.5, 21.5, 17.8, −5.0, −5.2; CIMS *m/z* (relative intensity) 407 (MH^+, 33), 349 ($M^+ - t$-Bu, 15); EIMS *m/z* (relative intensity) 391 ($M^+ - Me$, 3), 349 ($M^+ - t$-Bu, 100).

(*Z*)-Olefin: mp 98−100 °C; IR (CCl_4) 2950−2856, 2218, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.66 (dd, *J* = 9.1, 10.9 Hz, 1H), 5.40 (d, *J* = 10.9 Hz, 1H), 4.44 (m, 1H), 4.23 (m, 1H), 3.66 (dd, *J* = 3.6, 11.3 Hz, 1H), 3.14 (d, *J* = 11.3 Hz, 1H), 2.37 (s, 3H), 2.02−1.88 (m, 1H), 1.87−1.72 (m, 1H), 0.61 (s, 9H), −0.14 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 143.9, 133.7, 129.8, 127.9, 115.7, 98.9, 69.7, 58.5, 58.3, 41.8, 25.4, 21.4, 17.6, −5.0, −5.2; CIMS *m/z* (relative intensity) 407 (MH^+, 57), 349 ($M^+ - t$-Bu, 27); EIMS *m/z* (relative intensity) 391 ($M^+ - Me$, 2), 349 ($M^+ - t$-Bu, 100).

(35) Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293.

(36) Attempted application of this procedure to convert norsecurinine intermediate **46** to enone **48** failed.

Preparation of Ketonitrile 13. To a solution of an *E*/*Z* mixture of unsaturated nitriles **12** (10.4 g, 25.6 mmol) in 200 mL of ethyl acetate was added 3 g of 10% Pd/C. The mixture was stirred under 1 atm of H_2 for 12 h and filtered through a short plug of Celite which was washed with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (ethyl acetate/hexanes, 1/3) to give the saturated nitrile as a white solid (10.2 g, 98%): $[\alpha]^{29}_D = -64.6$ (*c* 0.55, $CDCl_3$); mp 83−87 °C; IR (KBr) 2958, 2852, 2246, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.25 (ddd, J = 3.9, 4.3, 4.3 Hz, 1H), 3.71−3.62 (m, 1H), 3.58 (dd, J = 4.6, 11.2 Hz, 1H), 3.16 (dd, J = 1.1, 11.2 Hz, 1H), 2.60−2.44 (m, 2H), 2.40 (s, 3H), 2.26−2.20 (m, 1H), 2.18−2.01 (m, 1H), 1.81−1.74 (m, 2H), 0.69 (s, 9H), −0.10 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 133.4, 129.7, 127.8, 119.6, 69.4, 57.7, 57.3, 40.5, 30.6, 25.5, 21.5, 17.8, 13.2, −5.0, −5.1; CIMS *m*/*z* (relative intensity) 409 (MH^+, 80), 351 ($M^+ - t$-Bu, 34). Anal. Calcd for $C_{20}H_{32}N_2O_3SSi$: C, 58.79; H, 7.89; N, 6.86. Found: C, 58.85; H, 7.92; N, 6.82.

To a solution of the saturated nitrile (8.0 g, 19.6 mmol) in 200 mL of THF was added tetrabutylammonium fluoride (1 M in THF, 20 mL) at room temperature. The amber solution was stirred at room temperature for 0.5 h and concentrated. The residue was diluted with brine and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was then purified by flash chromatography (ethyl acetate/CH_2Cl_2, 1/2) to give the hydroxynitrile as a white solid (5.7 g, 100%): $[\alpha]^{20}_D = -56.3$ (*c* 0.52, $CDCl_3$); mp 101−103 °C; IR (film) 3506 (br), 2939, 2852, 2247, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 4.37−4.28 (m, 1H), 3.85−3.76 (m, 1H), 3.52 (dd, J = 4.1, 12.0 Hz, 1H), 3.31 (ddd, J = 1.6, 2.6, 12.0 Hz, 1H), 2.58−2.44 (m, 2H), 2.41 (s, 3H), 2.24−2.13 (m, 1H), 2.03−1.91 (m, 1H), 1.89−1.85 (m, 1H), 1.82−1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 133.6, 129.7, 127.8, 119.5, 69.4, 57.5, 56.9, 39.9, 31.1, 21.5, 13.4; ^{13}C NMR DEPT (75 MHz) δ 129.7 (CH), 127.8 (CH), 69.4 (CH), 57.5 (CH), 56.9 (CH_2), 39.9 (CH_2), 31.1 (CH_2), 21.5 (CH_3), 13.4 (CH_2); EIMS *m*/*z* (relative intensity) 294 (M^+, 3), 240 ($M^+ - C_3H_4N$, 100).

To a solution of the hydroxynitrile (7.2 g, 24.5 mmol) in 200 mL of acetone was added Jones reagent (0.91 M, 32 mL, 29 mmol). The mixture was stirred at room temperature for 30 min, and 5 mL of 2-propanol was then added. The mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated to give ketonitrile **13** as a white solid (6.0 g, 84%) which was recrystallized from ethyl acetate/hexanes (1/1): mp 165−166 °C; IR ($CDCl_3$) 2926, 2254, 1766, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 4.32−4.21 (m, 1H), 3.83 (d, J = 19.3 Hz, 1H), 3.66 (d, J = 19.5 Hz, 1H), 2.69−2.60 (m, 2H), 2.45 (s, 3H), 2.20−2.08 (m, 2H), 1.94−1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 144.9, 133.8, 130.4, 127.3, 118.9, 56.4, 52.7, 42.1, 31.3, 21.5, 14.2; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 130.4 (CH), 127.3 (CH), 56.4 (CH), 52.7 (CH_2), 42.1 (CH_2), 31.3 (CH_2), 21.5 (CH_3), 14.2 (CH_2); EIMS *m*/*z* (relative intensity) 292 (M^+, 29), 155 (*p*-$MePhSO_2$, 100); HRMS ($C_{14}H_{16}N_2O_3S$) calcd 292.0882, found 292.0901. Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.41; H, 5.49; N, 9.51.

Cyclization of Cyanoketone 13 to α-Hydroxyketone 14. To a slurry of Sm powder (stored and weighed in a glovebox and then flame dried under Ar, 2.9 g, 19.3 mol) in THF (200 mL) was added CH_2I_2 (1.40 mL, 17.4 mmol) dropwise at 0 °C. After the mixture was stirred for 30 min, the ice bath was removed. The reaction mixture was stirred for an additional 2 h at room temperature and cooled to −78 °C. To the SmI_2 solution was added dropwise a solution of ketonitrile **13** (2.10 g, 7.19 mmol) in THF (100 mL) and MeOH (0.90 mL) over 30 min via cannula. The reaction mixture was allowed to warm to room temperature overnight, diluted with saturated $NaHCO_3$ solution (50 mL), and concentrated at reduced pressure. The residue was acidified with 5% HCl solution and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (ethyl acetate/CH_2Cl_2, 1/8) to give α-hydroxyketone **14** as a white solid (1.65 g, 78%): $[\alpha]^{20}_D = -13.3$ (*c* 0.052, $CDCl_3$); recrystallization of the solid (benzene/hexanes, 1/1) gave material with mp 199−202 °C dec; IR (film) 3480, 2971, 2877, 1717, 1598 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 4.39−4.30 (m, 1H), 3.91 (s, 1H), 3.45 (d, J = 10.0 Hz, 1H), 3.19 (d, J = 10.0 Hz, 1H), 2.71−2.61 (m, 2H), 2.44 (s, 3H), 1.95−1.78 (m, 1H), 1.75−1.65 (m, 1H), 1.63 (s, 1H), 1.58 (d, J = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 144.0, 134.7, 130.0, 127.2, 80.8, 57.4, 53.9, 41.5, 33.4, 33.0, 21.6; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 130.0 (CH), 127.2 (CH), 57.4 (CH), 53.9 (CH_2), 41.5 (CH_2), 33.4 (CH_2), 33.0 (CH_2), 21.5 (CH_3); CIMS *m*/*z* (relative intensity) 296 (MH^+, 100). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.68; H, 5.71; N, 4.83.

Preparation of Silyl Ether 15. To a solution of hydroxyketone **14** (1.40 g, 4.74 mmol) in 120 mL of dry CH_2Cl_2 was added *N*,*N*-diisopropylethylamine (2.60 mL, 14.96 mmol), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.20 mL, 5.23 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h and at room temperature for 15 h. Another portion of *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.70 mL, 3.05 mmol) was added at 0 °C, and the solution was stirred at 0 °C for 2 h and at room temperature for 15 h. The reaction mixture was diluted with 2 mL of methanol, and the solvent was removed in vacuo. The residue was filtered through a silica gel pad, eluting with ethyl acetate/hexanes (1/2), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1/4) to give the silyl ether **15** as a white solid (1.76 g, 91%): $[\alpha]^{20}_D = -11.2$ (*c* 0.55, $CDCl_3$); mp 69−72 °C; IR (CCl_4) 2955, 2887, 1731, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 4.32 (m, 1H), 3.50 (d, J = 7.8 Hz, 1H), 3.15 (d, J = 7.8 Hz, 1H), 2.48−2.40 (m, 5H), 2.38−2.22 (m, 1H), 1.70−1.58 (m, 3H), 0.72 (s, 9H), 0.039 (s, 3H), 0.012 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 143.9, 134.7, 129.9, 127.1, 83.8, 57.8, 56.1, 42.9, 34.6, 32.4, 25.6, 21.4, 18.4, −3.4; CIMS *m*/*z* (relative intensity) 410 (MH^+, 100), 352 ($M^+ - t$-Bu, 83).

Synthesis of Ketal 16. A solution of the TBS ether ketone **15** (1.23 g, 3.01 mmol), ethylene glycol (1.50 mL, 26.9 mmol), and *p*-toluenesulfonic acid monohydrate (126 mg, 0.66 mmol) in 60 mL of dry benzene was heated at reflux for 15 h. After being cooled to room temperature, the reaction mixture was concentrated. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1/4) to give ketal **16** as a white solid (1.36 g, 100%): $[\alpha]^{20}_D = 8.8$ (*c* 1.2, CH_2Cl_2); mp 103−105 °C; IR (CCl_4) 2957, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.14 (t, J = 5.7 Hz, 1H), 4.04−3.84 (m, 4H), 3.54 (d, J = 9.9 Hz, 1H), 2.92 (d, J = 9.9 Hz, 1H), 2.39 (s, 3H), 1.90−1.78 (m, 2H), 1.70−1.61 (m, 2H), 1.53−1.36 (m, 2H), 0.72 (s, 9H), −0.11 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 135.5, 129.8, 127.1, 110.6, 82.8, 65.9, 65.5, 58.0, 54.4, 40.3, 30.5, 30.1, 25.7, 21.5, 18.0, −2.8, −2.9; CIMS *m*/*z* (relative intensity) 454 (MH^+, 100), 396 ($M^+ - t$-Bu, 23); HRMS ($C_{22}H_{35}NO_5SiS$) calcd 453.2005, found 453.1995.

Preparation of Olefin 17. To a solution of TBS ether ketone **15** (1.7 g, 4.23 mmol) in 90 mL of dry methanol was added *p*-toluenesulfonylhydrazine (0.94 g, 45.05 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h and at room temperature for 18 h. The solvent was removed, and the residue was dried in vacuo. The crude tosylhydrazone was used without further purification.

To a solution of the crude tosylhydrazone in 100 mL of dry toluene was added NaH (0.97 g, 0.95%, 38.4 mmol). The mixture was heated at reflux for 3 h, cooled to 0 °C, and diluted with brine/aqueous NH_4Cl solution (10 mL/10 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by

flash chromatography (ethyl acetate/hexanes, 1/8) to give alkene **17** as a light yellow solid (1.3 g, 78%): mp 67−69 °C; $[\alpha]^{20}_D = -15.1°$ (*c* 0.67, $CDCl_3$); IR (CCl_4) 2956, 2858 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.90−5.83 (m, 1H), 4.29−4.21 (m, 1H), 3.50 (d, J = 7.9 Hz, 1H), 3.00 (d, J = 7.9 Hz, 1H), 2.40 (s, 3H), 2.38−2.11 (m, 2H), 1.73 (d, J = 10.0 Hz, 1H), 1.62−1.54 (m, 1H), 0.79 (s, 9H), 0.00 (s, 3H), −0.037 (s, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 143.2, 137.3, 135.7, 129.6, 127.1, 123.9, 61.3, 57.4, 53.4, 40.9, 35.3, 25.5, 21.4, 17.7, −2.8; HRMS ($C_{20}H_{31}NO_3SSi$) calcd 393.1793, found 393.1769.

Preparation of *o*-Aminobenzamide 18. A solution of sodium naphthalenide was made by adding sodium metal (0.3 g, 13 mol) to a solution of naphthalene (2.1 g, 16.4 mmol) in 10 mL of dry DME at room temperature. The dark blue solution was stirred at room temperature for 3 h and added dropwise to a −78 °C solution of the sulfonamide olefin **17** (0.82 g, 2.09 mmol) in 40 mL of dry DME until a dark blue color persisted. The mixture was stirred at −78 °C for 15 min and quenched with 10 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extract was dried over $MgSO_4$ and concentrated, and the residue was dried in vacuo. The crude amine was used without further purification.

To a solution of isatoic anhydride (0.84 g, 5.2 mmol) and DMAP (61 mg, 0.5 mmol) in 50 mL of dry MeCN was added a solution of the above crude amine in 50 mL of dry MeCN at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 2 d. The solvent was removed in vacuo, and the residue was filtered through a silica gel pad, eluting with ethyl acetate/hexanes (1/1), and the filtrate was concentrated. The residue was purified by column chromatography (ethyl acetate/hexanes, 1/3) to give amide **18** as a yellow oil (0.59 g, 79%): IR (film) 3451, 3349, 2953, 2856, 1737, 1613 cm^{-1}; ^1H NMR (300 MHz/DMSO-d_6, 75 °C) δ 7.10−7.07 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 5.91 (d, J = 9.9 Hz, 1H), 5.53 (d, J = 9.5 Hz, 1H), 4.93 (br s, 2H), 4.43 (m, 1H), 3.33 (d, J = 9.3 Hz, 1H), 2.24−2.12 (m, 3H), 1.91 (d, J = 9.9 Hz, 1H), 0.87 (s, 9H), 0.11 (s, 6H); EIMS *m*/*z* (relative intensity) 358 (M^+, 20); HRMS ($C_{20}H_{30}N_2O_2Si$) calcd 358.2076, found 358.2098.

Oxidation of *o*-Aminobenzamide 18. To a solution of amide **18** (230 mg, 0.64 mmol) in 30 mL of dry MeOH at room temperature were added $NaNO_2$ (96 mg, 1.41 mmol), CuCl (14 mg, 0.14 mmol), and 3.9 mL of an 0.83 M solution of HCl in MeOH. The mixture was stirred at room temperature for 1 h and diluted with 5 mL of saturated $NaHCO_3$ solution. The MeOH was removed at reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (ethyl acetate/hexanes, 1/3) to give α-methoxybenzamide **19** as a yellow solid (138 mg, 59%): $[\alpha]^{20}_D = -7.1°$ (*c* 0.46, $CDCl_3$); mp 74−78 °C; IR (CCl_4) 2955, 2858 1651 cm^{-1}; ^1H NMR (300 MHz/DMSO, 75 °C) δ 7.45−7.39 (m, 5H), 5.82−5.72 (m, 1H), 5.62−5.52 (m, 1H), 4.71−4.64 (m, 1H), 4.19 (s, 1H), 2.94 (s, 3H), 2.61−2.48 (m, 1H), 2.40−2.29 (m, 1H), 2.21−2.10 (m, 1H), 1.79 (d, J = 10.1 Hz, 1H), 0.88 (s, 9H), 0.11 (s, 6H); EIMS *m*/*z* (relative intensity) 373 (M^+, 4), 316 (M^+ − *t*-Bu, 60); HRMS ($C_{21}H_{31}NO_3Si$) calcd 373.2073, found 373.2075.

Allylation of α-Methoxybenzamide 19. To a solution of α-methoxyamide **19** (141 mg, 0.38 mmol) in 30 mL of dry CH_2Cl_2 at −78 °C was added allyltrimethylsilane (0.8 mL, 5.03 mmol), followed by $TiCl_4$ (0.8 mL, 1 M in CH_2Cl_2, 0.8 mmol). After the mixture was stirred for 4 h at −78 °C, the bath was removed and the solution was stirred for 2 d at room temperature. The reaction mixture was diluted with 10 mL of saturated $NaHCO_3$ solution at 0 °C and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was washed brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (ethyl acetate/hexanes, 1/3) to give olefin **21** as a colorless oil (132 mg, 91%): $[\alpha]^{20}_D = -57.9°$ (*c* 0.50, $CDCl_3$); IR (film) 2954, 2856 1633 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 7.48−7.35 (m, 5H), 6.05−5.91 (m, 2H), 5.52−5.39 (m, 1H), 5.18−5.02 (m, 1H), 4.79−4.72 (m, 1H), 4.55−3.85 (m, 2H), 2.81−2.69 (m, 1H), 2.47−1.26 (m, 9H), 0.20−0.11 (m, 6H); CI MS *m*/*z* (relative intensity) 384 (MH^+), 368 (M^+ − Me); EIMS *m*/*z* (relative intensity) 383 (M^+, 13), 342 (M^+ − allyl, 74), 326 (M^+ − *t*-Bu, 24); HRMS ($C_{23}H_{33}NO_2Si$) calcd 383.2280, found 383.2283.

Preparation of Tosylate 22. To a solution of BH_3·THF (1.8 mL, 1 M in ether, 1.8 mmol) in 5 mL of THF was added 2-methyl-2-butene (1.8 mL, 2 M in THF, 3.6 mmol) dropwise at 0 °C. The solution was stirred at 0 °C for 2 h and cooled to −23 °C. To the borane solution was added dropwise olefin **21** (130 mg, 0.34 mmol) in 5 mL of THF over 10 min. The reaction mixture was stirred at −23 °C for 2 h and allowed to warm to room temperature. H_2O_2 (2.3 mL, 30%, 22.9 mmol) and aqueous NaOH solution (2M, 2.3 mL) were added at room temperature, and the mixture was stirred for 30 min. Aqueous 2 M $NaHSO_3$ solution was added until effervescence ceased. The mixture was extracted with ethyl acetate (30 mL × 3), and the combined organic extract was washed with 2M $NaHSO_3$, solution and brine, dried over $MgSO_4$ and concentrated. The crude alcohol was used without further purification.

To a solution of the crude alcohol in 25 mL of CH_2Cl_2 were added DMAP (20 mg, 0.16 mmol) and triethylamine (1 mL, 7.2 mmol) followed by *p*-toluenesulfonyl chloride (168 mg, 0.88 mmol) at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with 1 mL of MeOH, and the solvent was removed in vacuo. The residue was filtered through a silica gel pad which was washed with ethyl acetate/hexanes (1/2), and the filtrate was concentrated. The residue was purified by preparative TLC (ethyl acetate/hexanes, 1/3) to give tosylate **22** as a colorless oil (120 mg, 64%): IR (film) 2954, 2856 1738, 1633 cm^{-1}; ^1H NMR (200 MHz/$CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.40−7.28 (m, 7H), 5.90 (d, J = 9.7 Hz, 1H), 5.60 and 5.36 rotamers (br d, J = 9.1 Hz, 1H), 4.65 and 4.29 rotamers (br d, J = 8.4 Hz, 1H), 4.05 (m, 2H), 3.50 (m, 1H), 2.59−2.24 (m, 5H), 1.83−1.76 (m, 5H), 1.51−1.30 (m, 1H), 0.85 and 0.77 rotamers (m, 9H), 0.06 (s, 6H); EIMS *m*/*z* (relative intensity) 555 (M^+, 4), 498 (M^+ − *t*-Bu, 44), 105 ($PhCO^+$, 100); HRMS ($C_{30}H_{41}NO_5SSi$) calcd 555.2475, found 555.2485.

Preparation of Tricycle 24. To a −78 °C solution of benzamide tosylate **22** (190 mg, 0.34 mmol) in 25 mL of dry toluene was added DIBALH (1.7 mL, 1 M in hexanes, 1.7 mmol) dropwise over 30 min. The solution was stirred at −78 °C for 1 h and was allowed to warm to room temperature. The reaction was quenched with 1 mL of MeOH, and the mixture was stirred at room temperature for 4 h. The mixture was diluted with 10 mL of ethyl acetate, filtered through a Celite pad, and concentrated in vacuo. The crude compound was used without further purification.

To a solution of the above crude product in 25 mL of dry toluene were added NaI (50 mg, 0.33 mmol) and triethylamine (1 mL, 9.67 mol). The solution was heated at reflux for 17 h and cooled to room temperature. The reaction mixture was concentrated in vacuo, and the residue was filtered through a silica gel pad which was washed with ethyl acetate/triethylamine (9/1). After concentration of the filtrate, the residue was purified by flash column chromatography (ethyl acetate/CH_2Cl_2/triethylamine, 4/4/1) to give tricycle **24** as a yellow oil (56 mg, 59%): IR (CCl_4) 2958, 2858 cm^{-1}; ^1H NMR (300 MHz/$CDCl_3$) δ 6.00 (dddd, J = 7.4, 2.1, 2.1, 2.1 Hz, 1H), 5.45 (dddd, J = 7.4, 4.4, 4.4, 2.1 Hz, 1H), 3.49−3.40 (m, 1H), 3.38−3.28 (m, 1H), 3.05−2.98 (m, 1H), 2.21 (m, 2H), 2.01−1.92 (m, 1H), 1.81−1.51 (m, 6H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 140.7, 123.3, 77.3, 62.3, 57.4, 35.9, 35.1, 29.2, 26.4, 25.7, 18.0, −2.6, −2.8; EIMS *m*/*z* (relative intensity) 279 (M^+, 88); HRMS ($C_{16}H_{29}NOSi$) calcd 279.2018, found 279.2029.

Preparation of *o*-Aminobenzamide 26. A solution of sodium naphthalenide was made by adding sodium metal (0.3 g, 13 mol) to a solution of naphthalene (2.1 g, 16.4 mmol) in 10 mL of dry DME at room temperature. The dark blue solution was stirred at room temperature for 3 h and added dropwise to a −78 °C solution of the sulfonamide **16** (1.5 g,

3.31 mmol) in 80 mL of dry DME until a dark blue color persisted. The mixture was stirred at −78 °C for 15 min and quenched with 10 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extract was dried over $MgSO_4$ and concentrated, and the residue was dried in vacuo. The crude amine **25** was used without further purification.

To a solution of isatoic anhydride (0.60 g, 3.7 mmol) and DMAP (86 mg, 0.7 mmol) in 80 mL of dry MeCN was added a solution of the amine **25** in 50 mL of dry MeCN at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 3 d. The solvent was removed in vacuo, and the residue was filtered through a silica gel pad, eluting with ethyl acetate/hexanes (1/1), and the filtrate was concentrated. The residue was purified by flash column chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to give benzamide **26** as a yellow oil (1.2 g, 87%): IR (film) 3469, 3372, 2957, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 62 °C) δ 8.18−8.11 (m, 1H), 7.70−7.61 (m, 1H), 7.58−7.48 (m, 1H), 7.35 (d, J = 7.8 Hz, 1H), 4.08−3.81 (m, 5H), 3.62−3.51 (m, 1H), 3.26 and 2.92 rotamer (d, J = 8.2 Hz, 1H), 2.08−1.97 (m, 2H), 1.83−1.18 (m, 6H), 0.88 and 0.71 rotamer (s, 9H), 0.070, 0.063 and −0.023 rotamer (s, 6H); EIMS m/z (relative intensity) 418 (M^+, 10), 361 (M^+ − t-Bu, 11), 120 (o-NH_2PhCO^+, 100); HRMS ($C_{22}H_{34}N_2O_4Si$) calcd 418.2288, found 418.2267.

Oxidation of *o*-Aminobenzamide 26. To a solution of amide **26** (590 mg, 1.41 mmol) in 40 mL of dry MeOH at room temperature were added $NaNO_2$ (195 mg, 2.82 mmol), CuCl (140 mg, 1.41 mmol), and 16 mL of methanolic HCl (0.81 M). The mixture was stirred at room temperature for 15 min and diluted with 5 mL of saturated $NaHCO_3$ solution. The MeOH was removed in vacuo, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (ethyl acetate/CH_2Cl_2, 1/4) to give α-methoxybenzamide **28** (178 mg, 30%) and α-chlorobenzamide **27** (157 mg, 26%).

Data for **28**: $[\alpha]^{20}_D$ = −54.3 (c 1.3, CH_2Cl_2); IR (CCl_4) 2956, 1703, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.38 (m, 5H), 4.28−3.82 (m, 6H), 3.52 and 3.75 (d, rotamers, 1H), 3.66 and 2.79 (s, rotamers, 3H), 2.28−1.78 (m, 3H), 1.68−1.46 (m, 2H), 0.85 (two s, 9H), 0.11 (four s, 6H); EIMS m/z (relative intensity) 433 (M^+, 60), 376 (M^+-t-Bu, 92), 105 ($PhCO^+$, 100); HRMS ($C_{23}H_{35}NO_5Si$) calcd 433.2284, found 433.2270.

Data for **27**: IR (CCl_4) 2953, 1658 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.63−7.39 (m, 5H), 4.11−3.86 (m, 3H), 3.76−3.47 (m, rotamers, 2H), 3.08 and 2.36 (m, rotamers, 2H), 2.62 (s, 1H), 2.02−1.22 (m, 4H), 0.88 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H); EIMS m/z (relative intensity) 437 (M^+, 4), 439 (M^+ + 2, 2), 402 (M^+ − Cl, 8), 105 ($PhCO^+$, 100).

Allylation of α-Methoxybenzamide 28 and α-Chlorobenzamide 27. To a solution of a mixture of α-methoxybenzamide **28** and α-chlorobenzamide **27** (251 mg, 0.58 mmol) in THF (20 mL) at −78 °C was added allyltrimethylsilane as a fluoride ion scavenger (1.6 mL, 10.1 mmol), followed by BF_3·etherate (0.8 mL, 6.31 mmol) and allylmagnesium bromide (1 M in ether, 8 mL, 8.0 mmol). After 2 h at −78 °C, the reaction mixture was allowed to warm to −5 °C, and diluted with saturated NH_4Cl solution (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was used without further purification.

To a solution of crude secondary amine **29** in CH_2Cl_2 (20 mL) were added di-*tert*-butyl dicarbonate (0.8 mL, 3.48 mmol) and triethylamine (2.0 mL, 14.3 mmol) at room temperature. The reaction mixture was refluxed for 14 h and concentrated. The residue was diluted with brine (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexanes, 1/8) to give carbamate **30** as a light yellow oil (180 mg, 68%): $[\alpha]^{20}_D$ = −48.9 (c 1.3, CH_2Cl_2); IR (film) 2958, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00−5.80 (m, 1H), 5.11−4.91 (m, 2H), 4.08−3.89 (m, 6H), 2.61−2.48 (m, 1H), 2.30−1.90 (m, 6H), 1.74−1.62 (m, 1H), 1.45 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); EIMS m/z (relative intensity) 439 (M^+, 8), 382 (M^+ − t-Bu, 3), 105 ($PhCO^+$, 100); HRMS ($C_{23}H_{41}NO_5Si$) calcd 439.2754, found 439.2726.

Formation of Imine 34. Amine **25** (570 mg, 1.91 mmol) in 20.0 mL of CH_2Cl_2 was treated with iodosobenzene (928 mg, 4.22 mmol, obtained from TCI) at room temperature. After 3.5 h, the solution was filtered through Celite, rinsed with CH_2Cl_2 (3 × 50 mL), and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexanes, 1/3) afforded imine **34** (496 mg, 87%) as a yellow oil: IR (neat) 1604, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 4.35 (m, 1H), 4.15−3.80 (m, 4H), 2.09−2.01 (m, 2H), 1.72−1.62 (m, 4H), 0.89 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 108.0, 89.9, 66.3, 65.9, 65.6, 45.4, 31.3, 25.7, 22.9, 18.0, −2.6, −2.7; CIMS m/z (relative intensity) 298 (MH^+, 100); HRMS ($C_{15}H_{27}NO_3Si$) calcd 297.1760, found 297.1754.

Preparation of Boc Carbamate 30 from Imine 34. To a solution of imine **34** (150 mg, 0.51 mmol) in THF (2 mL) at 0 °C was added BF_3·etherate (64 μL, 0.51 mmol) followed by allylmagnesium bromide (1.52 mL, 1 M in Et_2O). After 1.5 h, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (CH_2Cl_2 to 2.5% NH_4OH/10% MeOH/87.5% CH_2Cl_2 gradient) gave the amine as a yellow oil. To a solution of this amine in CH_2Cl_2 (2.5 mL) was added di-*tert*-butyl dicarbonate (110 mg, 0.50 mmol). The reaction mixture stirred at room temperature for 16 h and was then concentrated in vacuo. The crude residue was purified by flash chromatography (3 to 6% ethyl acetate/hexanes) to afford 183 mg (82%) of carbamate **30** as a yellow oil.

Preparation of Tosylate 31. To a solution of BH_3−THF complex (5 mL, 1 M in ether, 5 mmol) in 5 mL of THF was added 2-methyl-2-butene (5 mL, 2 M in ether, 10 mmol) dropwise at 0 °C. After 2 h at 0 °C, carbamate **30** (165 mg, 0.38 mmol) in 5 mL of THF was added dropwise to the borane solution over 10 min. The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature. After 9 h at room temperature, H_2O_2 (2 mL, 30%, 20 mmol) and 1 N aqueous NaOH solution (2 mL) were added at room temperature, and the mixture was stirred for 50 min. Aqueous 1 M $Na_2S_2O_3$ solution was added until effervescence ceased. The mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with 1 M $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$ and concentrated. The crude alcohol was used without further purification.

To a solution of the above crude alcohol in 25 mL of CH_2Cl_2 was added DMAP (150 mg, 1.20 mmol) and followed by *p*-toluenesulfonyl chloride (155 mg, 0.81 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with 1 mL of MeOH, and the solvent was removed in vacuo. The residue was filtered through a silica gel pad, eluting with ethyl acetate/hexanes (1/2), and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/hexanes, 1/4) to give tosylate **31** as a colorless oil (164 mg, 71%): $[\alpha]^{20}_D$ = −32.9 (c 1.1, CH_2Cl_2); IR (film) 2961, 1694, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 4.03−3.82 (m, 8H), 2.40 (s, 3H), 2.10−1.24 (m, 11H), 1.36 (s, 9H), 0.82 and 0.79 (s, rotamers, 9H), 0.09 (s, 6H); EIMS m/z (relative intensity) 611 (M^+, 10); HRMS ($C_{30}H_{49}NO_8SSi$) calcd 611.2948, found 611.2950.

Preparation of Tricycle 32 from Tosyl Carbamate 31. To a solution of the tosylate **31** (155 mg, 0.25 mmol) in 20 mL of MeOH was added methanolic HCl (0.8 N, 0.9 mL, 0.73 mmol) at room temperature. The reaction mixture was heated at 60 °C for 9 h. After being cooled to room temperature, the mixture was concentrated and the residue was purified by flash column chromatography (ethyl acetate/CH_2Cl_2/triethylamine, 4/4/1) to give the tricyclic ketal **32** (69 mg, 81%) as a colorless oil: $[\alpha]^{20}_D$ = −38.4 (c 0.96, CH_2Cl_2); IR (CCl_4) 2960,

1694, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09−3.83 (m, 4H), 3.46−3.25 (m, 2H), 2.93 (m, 1H), 2.50−2.40 (m, 1H), 1.97−1.34 (m, 10H), 0.85 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.8, 85.4, 68.6, 65.1, 64.2, 60.9, 56.7, 34.7, 30.5, 30.2, 29.4, 26.4, 26.2, 18.4, −1.5, −2.8; EIMS *m/z* (relative intensity) 339 (M^+, 51), 282 (M^+-*t*-Bu, 66), 169 (100); HRMS ($C_{18}H_{33}NO_3Si$) calcd 339.2230, found 339.2221.

Synthesis of Hydroxyketone 33. A solution of TBS ether ketal **32** (40 mg, 0.12 mmol) in 3 N HCl (20 mL) was heated at 95 °C for 17 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. The resulting HCl salt was converted to the free amine by ion-exchange chromatography (Dowex 1 × 8−400 ion-exchange resin, MeOH eluant). After concentration, the residue was purified by flash column chromatography (MeOH/triethylamine/CH_2Cl_2, 1/1.5/20) to give hydroxyketone **33** (16 mg, 74%, white solid): mp 118−119 °C; $[\alpha]^{20}_D = -62.6$ (*c* 0.35, CH_2Cl_2); IR ($CDCl_3$) 3479, 2955, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 1H), 3.34 (t, *J* = 7.8 Hz, 1H), 3.20 (t, *J* = 7.8 Hz, 1H), 3.11 (br s, 1H), 2.75−2.56 (m, 2H), 2.51 (dd, *J* = 7.8, 16.1 Hz, 1H), 2.32−2.26 (m, 1H), 2.14−2.09 (m, 1H), 1.92−1.88 (m, 1H), 1.79−1.61 (m, 4H), 1.47 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 84.8, 68.3, 60.6, 57.4, 36.9, 33.9, 32.8, 28.5, 26.4; EIMS *m/z* (relative intensity) 181 (M^+, 53), 96 (100); HRMS ($C_{10}H_{15}NO_2$) calcd 181.1103, found 181.1097.

Synthesis of (+)-14,15-Dihydronorsecurinine (8). A solution of hydroxyketone **33** (6 mg, 0.033 mmol) and the Bestmann reagent **45**[28] (25 mg, 0.083 mmol) in toluene/CH_2Cl_2 (1.5 mL/1.5 mL) was subjected to 12 kbar of pressure for 21 h at room temperature. After removal of the solvent, the residue was purified by preparative TLC (CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5 and then ethyl acetate/triethylamine, 9/1) to give (+)-14,15-dihydronorsecurinine (**8**) as a white solid (6 mg, 89%): mp 124−127 °C (lit.[7] mp 135−136 °C); ORD in dioxane (*c* = 0.25); $[\alpha]_{500}$ −20°, $[\alpha]_{300}$ −910°; $[\alpha]^{20}_D = +10$ (*c* 0.35, dioxane); IR ($CDCl_3$) 2955, 1752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 3.34 (t, *J* = 7.9 Hz, 1H), 3.20−3.11 (m, 2H), 2.87−2.50 (m, 5H), 2.09−1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 129.7, 109.3, 92.2, 66.5, 60.8, 57.2, 34.8, 31.5, 29.0, 26.6, 22.8; EIMS *m/z* (relative intensity) 205 (M^+, 17), 96 (100).

The HCl salt of **8** was prepared by 5−7 cycles of dissolution in $CHCl_3$ and removal of solvent under reduced pressure.[37] The crude solid was dried in vacuo for 10 h to give a white solid. Recrystallization of the crude solid by dissolving in 1 mL of CH_2Cl_2 and addition of hexanes by slow diffusion gave crystals suitable for X-ray analysis (see Supporting Information).

Preparation of α-Selenophenylenone 46. To a solution of hydroxyketone **33** (9.0 mg, 0.050 mmol) in 5 mL of ethyl acetate was added phenylselenyl chloride (38 mg, 0.20 mmol) followed by pyridine (20 μL, 0.25 mmol). The reaction mixture was heated at reflux, stirred for 16 h, and then concentrated. The crude residue was purified by column chromatography (CH_2Cl_2 to 2.5% NH_4OH (concd)/10% MeOH/87.5% CH_2Cl_2 gradient) to give 11.3 mg (67%) of vinylselenide **46** as a dark yellow oil: IR ($CDCl_3$) 3491, 2971, 1679 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62−7.57 (m, 2H), 7.48−7.34 (m, 3H), 6.78 (d, *J* = 7.0 Hz, 1H), 3.46 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.27−3.18 (m, 2H), 2.55−2.42 (m, 1H), 2.32 (dd, *J* = 12.7, 4.8 Hz, 1H), 2.04−1.80 (m, 6H); CIMS *m/z* (relative intensity) 336 (MH^+, 31), 332 (MH^+ + 2, 10), 267 (100).

α-Phenylselenoketone 47. To a solution of hydroxyketone **33** (60 mg, 0.33 mmol) in 6.5 mL of ethyl acetate was added phenylselenyl chloride (190 mg, 0.99 mmol) followed by triethylamine (184 μL, 1.32 mmol). The solution was heated at 86 °C for 48 h and concentrated. The residue was purified by flash chromatography (0−5% MeOH/CH_2Cl_2 gradient) to give 67 mg (60%) of α-phenylselenoketone **47** as a mixture of diastereomers. The major diastereomer was separated by preparative TLC (two elutions with 4% MeOH/ CH_2Cl_2) for characterization: $[\alpha]^{20}_D = -65.1$ (*c* 0.55, $CHCl_3$); IR (film) 3477, 2957, 1713, 1579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.6 Hz, 2H), 7.27 (m, 3H), 4.43 (dd, *J* = 11.4, 8.8 Hz, 1H), 3.50 (br s, 1H), 3.33 (t, *J* = 7.6 Hz, 1H), 3.27 (t, *J* = 8.0 Hz, 1H), 3.07 (m, 1H), 2.58 (ddd, *J* = 11.3, 9.6, 5.6 Hz, 1H), 2.48 (dddd, *J* = 12.5, 8.8, 3.7, 3.7 Hz, 1H), 2.33 (ddd, *J* = 12.0, 5.2, 3.0 Hz, 1H), 1.93 (m, 1H), 1.86−1.66 (m, 4H), 1.50 (d, *J* = 12.0 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 135.8, 129.1, 128.2, 127.2, 85.1, 68.2, 60.7, 57.3, 45.1, 42.5, 37.2, 28.5, 26.4; CIMS *m/z* (relative intensity) 205 (MH^+, 12), 180 (M^+ − SePh, 65), 70 (100); HRMS ($C_{16}H_{19}NO_2Se$) calcd 338.0659, found 338.0658.

Butenolide 50. A solution of epimeric α-phenylselenoketones **47** (47 mg, 0.14 mmol) in 1 mL of CH_2Cl_2 was cooled to 0 °C. To this mixture was added diethylphosphonoacetic acid (45 μL, 0.28 mmol) followed by 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (130 mg, 0.31 mmol), and the solution was warmed to room temperature overnight. After 20 h, the solution was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (4% MeOH/CH_2Cl_2) to give 63 mg (88%) of phosphonate **49** as a mixture of diastereomers.

A solution of phosphonate **49** (63 mg, 0.12 mmol) in toluene (3 mL) was added to a suspension of 18-crown-6 (97 mg, 0.37 mmol) and K_2CO_3 (67 mg, 0.49 mmol) in 7 mL of toluene at 0 °C which had been stirred at room temperature for 15 min. After 4 h, the mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (4% MeOH/CH_2Cl_2) to give 42 mg (95%) of butenolide **50** as a mixture of diastereomers which was separated by preparative TLC (2 elutions with 4% MeOH/ CH_2Cl_2) for characterization.

Major diastereomer: IR ($CDCl_3$) 2942, 1752, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.41−7.30 (m, 3H), 4.81 (s, 1H), 4.31 (d, *J* = 8.1 Hz, 1H), 3.88 (t, *J* =7.7 Hz, 1H), 3.38 (ddd, *J* = 8.7, 5.7, 2.6 Hz, 1H), 3.19 (m, 1H), 2.63 (ddd, *J* = 5.8, 5.8, 4.0 Hz, 1H), 2.51 (ddd, *J* = 10.9, 5.9, 1.4 Hz, 1H), 2.43 (br d, *J* = 14.8 Hz, 1H), 2.19 (ddd, *J* = 14.8, 8.2, 2.3 Hz, 1H), 1.94 (m, 2H), 1.78 (m, 2H), 1.40 (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.5, 135.8, 130.9, 129.4, 128.9, 108.4, 91.8, 68.1, 61.4, 57.7, 39.4, 34.8, 34.7, 29.2, 26.6; EIMS *m/z* (relative intensity) 362 (MH^+, 6), 206 (MH^+ − SePh, 33), 70 (100); HRMS ($C_{18}H_{19}NO_2Se$) calcd 362.0659, found 362.0641.

Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.34−7.30 (m, 3H), 5.94 (d, *J* = 2.4 Hz, 1H), 4.33 (t, *J* = 8.9 Hz, 1H), 3.36 (m, 1H), 3.24 (m, 1H), 3.16 (m, 1H), 2.62−2.50 (m, 3H), 1.98−1.90 (m, 2H), 1.77−1.68 (m, 3H), 1.42 (d, *J* = 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 171.7, 134.6, 129.4, 128.3, 127.7, 112.9, 91.7, 66.7, 61.3, 57.2, 40.6, 34.8, 34.6, 28.9, 26.5.

(−)-Norsecurinine (6). To a solution of butenolides **50** (19 mg, 0.053 mmol) in CH_2Cl_2 at −78 °C was added dimethyldioxirane (1.16 mL, 0.059 M in acetone). After 1 h, the reaction was quenched with dimethyl sulfide (40 μL, 0.54 mmol) followed by triethylamine (10 μL, 0.071 mmol). The mixture was concentrated and the residue was purified by flash chromatography (9% MeOH/CH_2Cl_2) to give 4.2 mg (39%) of (−)-norsecurinine (**6**) as a yellow oil: $[\alpha]^{20}_D = -256$ (*c* 5.6, EtOH) (lit.[12b] $[\alpha]^{20}_D = -262$ (*c* 0.06, EtOH)); IR (neat) 1748, 1633, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.51 (d, *J* = 9.0 Hz, 1H), 5.68 (s, 1H), 3.67 (t, *J* = 5.5 Hz, 1H), 3.30 (m, 1H), 3.19 (t, *J* = 7.7 Hz, 1H), 2.61−2.50 (m, 2H), 2.10−1.94 (m, 3H), 1.84−1.74 (m, 2H), 1.72 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 168.2, 143.5, 120.6, 108.0, 91.6, 65.1, 59.8, 55.3, 35.8, 29.3, 26.8; ESIMS *m/z* (relative intensity) 204 ($[M + H]^+$, 100); HRMS calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1018; UV (EtOH) λ_{max} 255 nm.

(−)-Norsecurinine hydrochloride was prepared by dissolving (−)-norsecurinine (**6**) in CH_2Cl_2 and adding HCl (1 N in Et_2O) until the pH reached 2: mp 220 °C dec; ^1H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 9.1 Hz, 1H), 6.80 (dd, *J* = 9.0, 6.3 Hz,

(37) Formation of the amine hydrochloride by this procedure was fortuitous but was not planned.

1H), 6.12 (s, 1H), 4.54 (t, J = 5.5 Hz, 1H), 4.01 (t, J = 8.6 Hz, 1H), 3.90 (dd, J = 11.6, 6.8 Hz, 1H), 3.25 (dt, J = 11.9, 5.7 Hz, 1H), 3.01 (dd, J = 12.3, 4.9 Hz, 1H), 2.38−2.15 (m, 3H), 2.21 (d, J = 12.1 Hz, 1H), 1.97−1.83 (m, 1H).

Dihydropyridinone 35. Procedure A. A solution of imine **34** (56 mg, 0.19 mmol) in 0.50 mL of CH_2Cl_2 and Danishefsky's diene (75 mg, 0.44 mmol, distilled prior to use at 65−66 °C/6 mmHg) in 1.0 mL of CH_2Cl_2 was sealed in a 5 mL plastic Luerlock syringe and subjected to 12 kbar of pressure for 48 h at room temperature. The resulting red solution was concentrated in vacuo, and the residue was purified by flash chromatography (hexanes/acetone, 1/1) to give 49 mg (71%) of dihydropyridinone **35** as a tan solid: $[\alpha]^{20}_D = -327$ (c 0.554, CH_2Cl_2); mp 149−151 °C; IR ($CDCl_3$) 1634, 1567 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 6.8 Hz, 1H), 4.90 (d, J = 6.8 Hz, 1H), 4.11−3.83 (m, 6H), 2.37−2.30 (m, 2H), 2.24−2.17 (m, 2H), 1.85−1.69 (m, 3H), 1.67−1.49 (m, 1H), 0.88 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 149.2, 110.9, 97.8, 82.6, 65.4, 64.8, 61.3, 59.6, 40.8, 36.8, 30.1, 29.3, 26.1, 18.4, −1.2, −2.7; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 149.2 (CH), 97.8 (CH), 65.4 (CH_2), 64.8 (CH_2), 61.3 (CH), 59.6 (CH), 40.8 (CH_2), 36.8 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 26.1 (CH_3), −1.2 (CH_3), −2.7 (CH_3); CIMS m/z (relative intensity) 366 (MH^+, 100); HRMS ($C_{19}H_{31}NO_4Si$) calcd 365.2022, found 365.2018; Anal. Calcd for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 61.98; H, 8.72; N, 3.71. A sample of **35** was recrystallized from ethyl acetate/hexanes for X-ray analysis (see Supporting Information).

Procedure B. A solution of imine **34** (299 mg, 1.0 mmol) in 20.0 mL of dry CH_3CN was treated with $Yb(OTf)_3$ (134 mg, 0.22 mmol) and Danishefsky's diene (253 mg, 1.47 mmol) in 10.0 mL of CH_3CN at 0 °C. The solution was allowed to warm to room temperature overnight and then concentrated. The residue was extracted with CH_2Cl_2 (3 × 50 mL), washed with saturated $NaHCO_3$, dried over K_2CO_3, and concentrated in vacuo. Purification of the residual oil by flash chromatography (hexanes/acetone, 2/1) provided dihydropyridinone **35** as tan solid (308 mg, 84%).

Synthesis of Piperidinol 36. To a −78 °C solution of dihydropyridinone **35** (153 mg, 0.42 mmol) in 20.0 mL of dry THF was added L-Selectride (1.0 mL, 1.0 M in THF). After 30 min, the solution was diluted with brine (10 mL), warmed to room temperature, and extracted with EtOAc (3 × 50 mL). The combined organics were dried with K_2CO_3 and concentrated in vacuo. Purification of the oil by flash chromatography (CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5) afforded 132 mg (85%) of alcohol **36** as an orange oil: $[\alpha]^{20}_D = +12.4$ (c 0.294, CH_2Cl_2); IR (neat) 3403 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (m, 1H), 4.06−3.83 (m, 5H), 3.30 (dd, J = 2.6, 12.3 Hz, 1H), 3.13 (m, 1H), 2.93 (ddd, J = 3.5, 9.3, 11.3 Hz, 1H), 2.67 (m, 1H), 2.10−2.04 (m, 1H), 1.98−1.85 (m, 2H), 1.80−1.63 (m, 5H), 1.56−1.38 (m, 2H), 0.88 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.6, 84.1, 65.1, 65.0, 64.5, 59.4, 58.5, 44.1, 39.2, 34.9, 32.7, 31.3, 28.1, 26.2, 18.5, −1.4, −2.7; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 65.1 (CH_2), 65.0 (CH), 64.5 (CH_2), 59.4 (CH), 58.5 (CH), 44.1 (CH_2), 39.2 (CH_2), 34.9 (CH_2), 32.7 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 26.2 (CH_3), −1.4 (CH_3), −2.7 (CH_3); CIMS m/z (relative intensity) 370 (MH^+, 100), 352 (M^+-OH, 60); HRMS ($C_{19}H_{35}NO_4Si$) calcd 369.2335, found 369.2333. Anal. Calcd for $C_{19}H_{35}NO_4Si$: C, 61.75; H, 9.55; N, 3.79. Found: C, 61.63; H, 9.52; N, 3.73.

Preparation of Ketone Methyl Ether 37. To a solution of alcohol **36** (59 mg, 0.16 mmol) in 15.0 mL of dry THF was added NaH (12 mg, 60% dispersion in mineral oil) at room temperature. After 10 min, a solution of CH_3I in THF (0.20 M, 2.0 mL) was slowly added via syringe pump (20 min). After 1 d, TLC indicated starting material remained. An additional 1.0 mL of CH_3I in THF (0.20 M) was slowly added. After being stirred at room temperature overnight, the solution was diluted with brine and extracted with EtOAc (3 × 25 mL). The combined organics were dried with K_2CO_3 and concentrated in vacuo. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5) gave the methyl ether (53 mg, 87%) as a yellow oil: $[\alpha]^{20}_D = +19.7$ (c 0.206, CH_2Cl_2); IR (neat) 2928, 1472, 1462 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04−3.81 (m, 4H), 3.68 (dddd, J = 2.7, 2.9, 3.7, 3.7 Hz, 1H), 3.29 (s, 3H), 3.27 (dd, J = 2.9, 12.4 Hz, 1H), 3.06 (m, 1H), 2.85 (ddd, J = 3.6, 8.9, 11.2 Hz, 1H), 2.66 (ddd, J = 5.4, 5.4, 10.9 Hz, 1H), 2.06−2.01 (m, 1H), 1.91−1.64 (m, 7H), 1.40−1.24 (m, 2H), 0.88 (s, 9H), 0.12 (s, 3H), 0.073 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.5, 84.6, 74.2, 65.2, 64.5, 59.4, 58.4, 55.8, 44.4, 38.8, 31.2, 30.4, 30.3, 28.8, 26.2, 18.6, −1.4, −2.7; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 74.2 (CH), 65.2 (CH_2), 64.5 (CH_2), 59.4 (CH), 58.4 (CH), 55.8 (CH_3), 44.4 (CH_2), 38.8 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 28.8 (CH_2), 26.2 (CH_3), −1.4 (CH_3), −2.7 (CH_3); CIMS m/z (relative intensity) 383 (M^+, 40), 326 (M^+-t-Bu, 70); HRMS ($C_{20}H_{37}NO_4Si$) calcd 383.2492, found 383.2491. Anal. Calcd for $C_{20}H_{37}NO_4Si$: C, 62.62; H, 9.72; N, 3.65. Found: C, 62.77; H, 9.85; N, 3.70.

To a solution of the methyl ether (26 mg, 0.068 mmol) was added 3 N HCl (8.0 mL). The solution was heated to reflux, stirred for 26 h, and concentrated in vacuo. The residue was dissolved in MeOH and filtered through ion-exchange resin (Dowex-strongly basic, 1 × 8−400, 200−400 mesh) eluting with MeOH (20 mL), and the eluent was concentrated. Purification of the residual oil by flash chromatography (CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5) gave hydroxyketone **37** (12 mg, 78%) as an amorphous solid: $[\alpha]^{20}_D = 24.9$ (c 0.167, CH_2Cl_2); IR (neat) 3367, 1711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (m, 1H), 3.29 (s, 3H), 3.28−3.27 (m, 1H), 3.07 (dd, J = 3.2, 12.2 Hz, 1H), 3.02 (ddd, J = 3.6, 9.2, 11.7 Hz, 1H), 2.74−2.65 (m, 2H), 2.51 (dd, J = 8.0, 17.4 Hz, 1H), 2.38 (ddd, J = 2.7, 5.4, 11.4 Hz, 1H), 2.13−2.08 (m, 1H), 1.84−1.72 (m, 3H), 1.66−1.62 (m, 1H), 1.60 (d, J = 11.3 Hz, 1H), 1.53 (dddd, J = 1.8, 3.5, 12.2, 12.2 Hz, 1H); ^{1}H NMR (500 MHz, C_6D_6) δ 3.80 (bs, 1H), 3.38 (dddd, J = 4.1, 4.1, 4.1, 4.1 Hz, 1H), 3.17 (dd, J = 3.2, 12.0 Hz, 1H), 3.04 (s, 3H), 2.95 (dddd, J = 3.3, 3.3, 9.8, 9,8 Hz, 1H), 2.74−2.73 (m, 1H), 2.37−2.29 (m, 2H), 2.24 (ddd, J = 2.7, 5.5, 11.2 Hz, 1H), 2.17 (dd, J = 8.0, 17.2 Hz, 1H), 1.93 (dddd, J = 1.4, 1.4, 3.0, 13.9 Hz, 1H), 1.64−1.55 (m, 2H), 1.52−1.45 (m, 2H), 1.24 (d, J = 11.2 Hz, 1H), 1.04−0.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 83.7, 73.9, 59.4, 58.0, 56.3, 44.5, 39.8, 34.3, 31.2, 29.9, 29.6; ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 73.9 (CH), 59.4 (CH), 58.0 (CH), 56.3 (CH_3), 44.5 (CH_2), 39.8 (CH_2), 34.3 (CH_2), 31.2 (CH_2), 29.9 (CH_2), 29.6 (CH_2); CIMS m/z (relative intensity) 226 (MH^+, 50); HRMS ($C_{12}H_{19}NO_3$) calcd 225.1365, found 225.1372.

14,15-Dihydrophyllanthine (51). A solution of tricyclic hydroxyketone **37** (11 mg, 0.049 mmol) and the Bestmann reagent **45** (30 mg, 0.099 mmol) in 4.0 mL of PhMe/CH_2Cl_2 (1/1) was sealed in a 5 mL Luerlock syringe and subjected to 12 Kbar of pressure for 25 h at room temperature. The solution was then concentrated, and the residue was purified by flash chromatography (ether/acetone, 2/1) followed by preparative TLC (1% TEA/ethyl acetate) to give dihydrophyllanthine (**51**, 9.8 mg, 80%) as a tan solid: $[\alpha]^{20}_D = -12°$ (c = 0.85, $CHCl_3$) (lit. $[\alpha]^{20}_D = -8.5°$ (c 0.94, $CHCl_3$)), mp 55−58 °C (lit.[3] mp 66−68 °C), IR (neat) 2929, 1758 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.60 (s, 1H), 3.73 (m, 1H), 3.30 (s, 3H), 3.24 (dd, J = 3.8, 12.6 Hz, 1H), 3.11 (ddd, J = 3.6, 7.9, 11.8 Hz, 1H), 2.79−2.71 (m, 2H), 2.69−2.60 (m, 2H), 2.05−1.96 (m, 1H), 1.91−1.71 (m, 3H), 1.67−1.56 (m, 2H), 1.52−1.46 (m, 2H); ^{13}C NMR (125 MHz) δ 173.0, 171.3, 109.0, 89.0, 70.3, 60.4, 55.5, 55.1, 44.3, 35.9, 29.9, 27.0, 26.8, 21.8; CIMS m/z (relative intensity) 250 (MH^+, 60); HRMS ($C_{14}H_{19}NO_3$) calcd 249.1365, found 249.1371.

Formation of Vinylselenide 52. To a solution of hydroxyketone **37** (21 mg, 0.093 mmol) in 3.0 mL of dry CH_2Cl_2 was added methanesulfonic acid (12 μL, 0.19 mmol) at room temperature. After 20 min, the solution was cooled to 0 °C and then treated with selenium dioxide (13 mg, 0.12 mmol) and diphenyl diselenide (31 mg, 0.099 mmol). The mixture was slowly warmed to room temperature overnight. The solution was diluted with saturated $NaHCO_3$ (10 mL) and extracted exhaustively with CH_2Cl_2 (3 × 50 mL). The aqueous layer was back-extracted with Et_2O (20 mL) and ethyl acetate (20 mL). The combined organics were dried with K_2CO_3 and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexanes, 2/1) provided vinylselenide **52** as a yellow oil (20.3 mg, 58%): IR (neat) 3474, 2926, 2819, 1682, 1567 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.57 (m,

2H), 7.38−7.33 (m, 3H), 6.37 (d, J = 5.6 Hz, 1H), 3.74 (t, J = 4.8 Hz, 1H), 3.64 (m, 1H), 3.29 (s, 3H), 2.75−2.71 (m, 1H), 2.54−2.47 (m, 2H), 2.25 (dd, J = 5.1, 10.1 Hz, 1H), 1.97−1.92 (m, 2H), 1.83−1.79 (m, 1H), 1.75−1.60 (m, 3H); ^{13}C NMR DEPT (100 MHz, $CDCl_3$) δ 198.4, 143.6 (CH), 136.1 (CH), 133.1, 129.7 (CH), 129.3 (CH), 126.5, 82.4, 74.6 (CH), 59.2 (CH), 56.1 (CH_3), 55.2 (CH), 45.7 (CH_2), 44.9 (CH_2), 31.1 (CH_2), 30.3 (CH_2); CIMS m/z (relative intensity) 380 (MH^+, 3).

Preparation of Hydroxy Enone 53. A solution of vinylselenide **52** (14.5 mg, 0.038 mmol) and sodium iodide (22 mg, 0.15 mmol) in 3.0 mL of dry CH_3CN was cooled to 0 °C and treated with freshly distilled boron trifluoride etherate (12 μL, 0.098 mmol). The yellow solution immediately turned orange. After 1.5 h, the reaction mixture was diluted with 10% NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried over K_2CO_3 and concentrated in vacuo. Purification of the residual oil by flash chromatography (CH_2Cl_2−CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5) to give hydroxyenone **53** as a yellow oil (7.1 mg, 84%): IR (neat) 3465, 1689, 1457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, J = 5.7, 9.4 Hz, 1H), 6.19 (d, J = 9.4 Hz, 1H), 3.87 (t, J = 4.5 Hz, 1H), 3.66 (m, 1H), 3.62 (s, 1H), 3.28 (s, 3H), 2.83 (ddd, J = 2.3, 3.0, 10.2 Hz, 1H), 2.57 (ddd, J = 3.4, 7.5, 10.9 Hz, 1H), 2.44 (dd, J = 2.3, 12.1 Hz, 1H), 2.26 (dd, J = 4.1, 10.9 Hz, 1H), 1.97−1.60 (m, 5H); CIMS m/z (relative intensity) 224 (MH^+, 23).

Formation of Ester 54. A solution of hydroxyenone **53** (6.0 mg, 0.027 mmol) in 2.0 mL of dry THF was cooled to 0 °C. To this mixture was added diethylphosphonoacetic acid (35 mg, 0.18 mmol) in THF (1.5 mL) followed by DCC (26 mg, 0.13 mmol). The solution was allowed to warm to room temperature overnight. After 20 h, the solution was diluted with saturated $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organics were dried over K_2CO_3 and concentrated. Purification of the residue by flash chromatography (CH_2Cl_2/ethyl acetate, 1/1 CH_2Cl_2/MeOH/NH_4OH (concd), 92.5/5/2.5) followed by preparative TLC (acetone/CH_2Cl_2, 2/1) afforded ester **54** (7.3 mg, 67%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.75 (dd, J = 4.4, 9.5 Hz, 1H), 6.17 (d, J = 9.7 Hz, 1H), 4.26−4.11 (m, 4H), 3.90 (t, J = 4.9 Hz, 1H), 3.66−3.62 (m, 1H), 3.28 (s, 3H), 3.13 (d, J = 7.2 Hz, 1H), 3.02 (d, J = 7.2 Hz, 1H), 2.89−2.52 (m, 3H), 2.24−2.12 (m, 1H), 1.88−1.60 (m, 5H), 1.35 (t, J = 7.0 Hz, 6H).

Preparation of Phyllanthine (2). A solution of 18-crown-6 (16 mg, 0.061 mmol) and K_2CO_3 (12 mg, 0.087 mmol) in 2.0 mL of dry PhMe was stirred at room temperature for 15 min. To this mixture was added ester **54** (7.3 mg, 0.018 mmol) in dry PhMe (2.0 mL) at 0 °C. The solution was allowed to warm to room temperature overnight. After 20 h, the mixture was diluted with saturated $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were dried over K_2CO_3 and concentrated. Purification of the residual oil by flash chromatography (4% MeOH in CH_2Cl_2) provided phyllanthine (**2**, 3.7 mg, 84%) as a yellow oil: $[\alpha]^{20}_D$ = −791 (*c* 0.090, $CHCl_3$) (lit.[3] $[\alpha]^{20}_D$ = −898 (*c* 0.98, $CHCl_3$)); IR (neat) 1754, 1663, 1456, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, J = 9.2 Hz, 1H), 6.43 (dd, J = 5.3, 9.2 Hz, 1H), 5.55(s, 1H), 3.80 (t, J = 4.7 Hz, 1H), 3.63 (dddd, J = 3.0, 3.0, 3.1, 3.1 Hz, 1H), 3.26 (s, 3H), 2.79 (ddd, J = 3.3, 5.4, 10.6 Hz, 1H), 2.67 (ddd, J = 3.8, 10.2, 10.2 Hz, 1H), 2.59 (dd, J = 2.4, 12.2 Hz, 1H), 2.52 (dd, J = 4.1, 9.3 Hz, 1H), 1.94 (dddd, J = 1.4, 2.5, 2.5, 13.1 Hz, 1H), 1.87−1.73 (m, 2H), 1.78 (d, J = 8.9 Hz, 1H), 1.68 (ddd, J = 2.9, 12.4, 12.4 Hz, 1H); ^{13}C NMR DEPT (100 MHz, $CDCl_3$) δ 140.7 (CH), 122.1 (CH), 105.8 (CH), 74.7 (CH), 59.2 (CH), 56.7 (CH), 56.5 (CH_3), 44.9 (CH_2), 42.4 (CH_2), 31.5 (CH_2), 31.1 (CH_2); CIMS m/z (relative intensity) 248 (MH^+, 8).

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Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds and X-ray data including ORTEP drawings for compounds **35** and **8**·HCl. Also included are experimental details for the reactions in Scheme 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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