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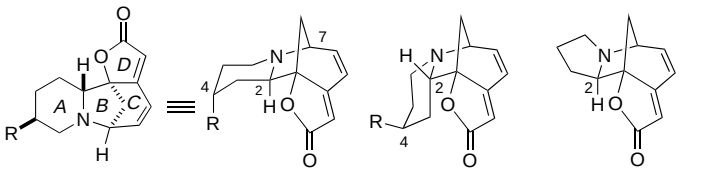
A New Enantioselective Approach to Total Synthesis of the Securinega Alkaloids: Application to (−)-Norsecurinine and Phyllanthine**

Gyoonhee Han, Matthew G. LaPorte, James J. Folmer, Kim M. Werner, and Steven M. Weinreb*

Dedicated to the memory of Professor George Buchi

The securinega alkaloids are a family of approximately 20 tetracyclic compounds produced by several *Securinega* and *Phyllanthus* species of the Euphorbiaceae plant family.[1] The major securinega alkaloid is securinine (**1**), isolated from the leaves of *Securinega suffruticosa*. Its enantiomer, virosecurinine, is also naturally occurring, as are the antipodes of



1 R = H: securinine
2 R = OMe: phyllanthine
3 R = H: allosecurinine **5**: (–)-norsecurinine
4 R = OMe: securitinine

several other alkaloids of this class. Allosecurinine (**3**), which is the C2 epimer of **1**, is also a common alkaloid of this group, as is securitinine (**4**). The enantiomer of **3** (viroallosecurinine) is a natural product as well. Some additional common alkaloids of this group are (−)-norsecurinine (**5**), whose (+)-enantiomer is also naturally occurring, and phyllanthine (**2**).

These alkaloids are associated with a wide range of biological activity. Securinine causes central nervous system stimulation and clonic – tonic convulsions in laboratory animals. This activity is due to the alkaloid acting as a γ-amino butyric acid (GABA) receptor antagonist.[2] These alkaloids have found a sporadic use clinically for such diseases as poliomyelitis, ALS (amyotrophic lateral sclerosis) and chronic aplastic anemia.[1] Securinine has also been found to be an antimalarial agent[3] and to have antibacterial activity.[4]

To date there has been only limited synthetic work in this area. A nonstereoselective total synthesis of racemic securinine (**1**) was described by Horii et al. in 1966.[5] More recently, Heathcock and coworkers devised a clever route to racemic norsecurinine (**5**).[6] In this synthesis, both the A-ring and the configuration of the C2 atom of **5** were derived from L-proline, although unfortunately optical activity was lost by the racemization of an intermediate. Jacobi et al.[7] have developed an innovative route to both (+)- and (−)-norsecurinine,

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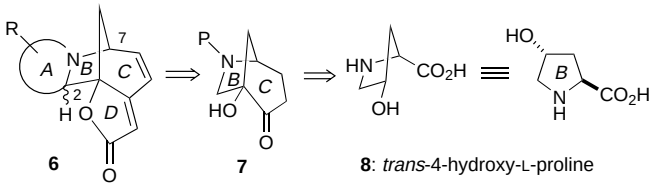
starting from L- and D-proline, respectively, once again as a source of the five-membered A-ring and the absolute configuration of the C2 atom. Finally, the Magnus group[8] has reported an elegant synthesis of racemic norsecurinine via the related securinega alkaloid nirurine, starting from 3-hydroxypyridine.

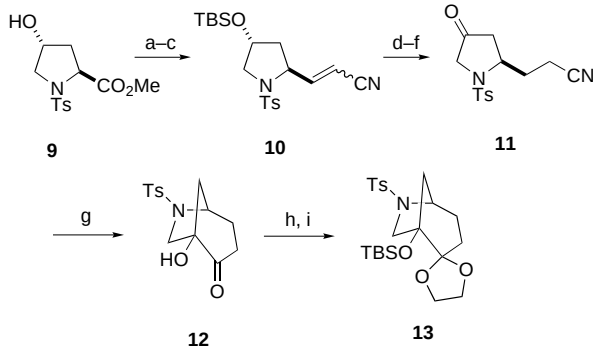
We have been attempting to develop a novel, general strategy for construction of the securinega alkaloids and have established two fundamental design criteria: 1) since most members of this family differ only in the A-ring size and functionality, as well as the C2 configuration (compare **1**–**5**), the strategy should be flexible enough to allow for the variations in these areas of the molecules; 2) the approach should provide access to both enantiomeric series of alkaloids. With these points in mind, our basic strategy (Scheme 1) was to use readily available *trans*-4-hydroxy-L-proline (**8**) (or the



Scheme 1. Retrosynthetic pathway for securinega alkaloids **6** using 4-hydroxy-L-proline (**8**) as a starting material.

commercially available D-enantiomer) as a source of the alkaloid B-ring and the C7 configuration.[9] The intent was to first elaborate **8** into a BC-ring fragment like **7**, followed by annulation of the desired A-ring having the appropriate stereogenicity at C2. Finally, the butenolide D-ring would be appended at a late stage to afford the alkaloids **6**. Herein we describe the successful application of this concept to a new enantioselective total synthesis of (−)-norsecurinine (**5**) and the first total synthesis of phyllanthine (**2**).

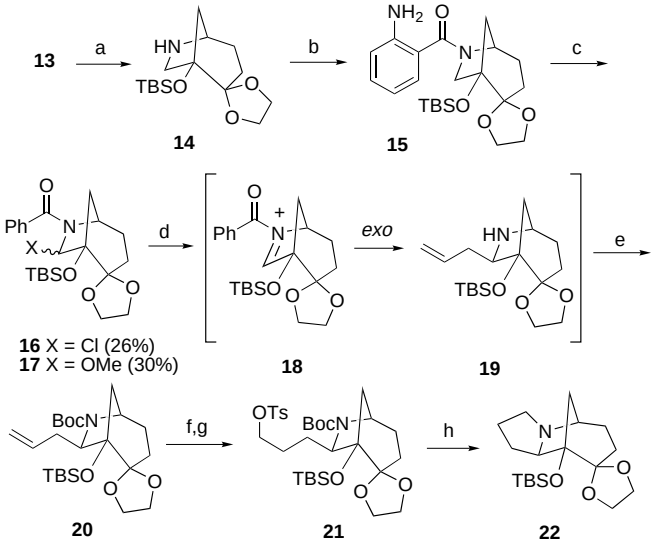
The enantiomerically pure ester **9**, prepared from *trans*-4-hydroxy-L-proline (**8**),[10] was converted via the α,β-unsaturated nitrile **10** to ketonitrile **11** (Scheme 2). We were pleased to find that exposure of **11** to SmI_2, followed by acidic



Scheme 2. a) TBSCl, imidazole, CH_2Cl_2, 88%; b) DIBAL-H, PhMe, −78 °C→rt, 98%; c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C/Ph_3P=CHCN, CH_2Cl_2, −78 °C→rt, 90% (7:2 *E*/*Z* mixture); d) 1 atm H_2, 10% Pd-C, EtOAc, 98%; e) Bu_4NF, THF, rt, 100%; f) Jones reagent, acetone, rt, 84%; g) SmI_2, MeOH, THF, −78 °C→rt/H_3O^+, 78%; h) TBSOTf,*i*Pr_2NEt, CH_2Cl_2, 0 °C→rt, 91%; i) $(CH_2OH)_2$, *p*-TsOH, PhH, reflux, 100%.

hydrolysis, provided the key scalemic bicyclic BC-ring system **12** in good yield.[11] Hydroxyketone **12** was then transformed into protected ketal silyl ether derivative **13**.

Intermediate **13** was converted to the (−)-norsecurinine ABC-ring synthon as outlined in Scheme 3. The *N*-tosyl group of **13** was removed to afford amine **14**, which was acylated with isatoic anhydride to yield the *ortho*-aminobenzamide



Scheme 3. a) Na, naphthalene, DME, −78 °C, 88%; b) isatoic anhydride, DMAP, MeCN, rt, 87% from **13**; c) $NaNO_2$, HCl, CuCl, MeOH, rt; d) allylmagnesium bromide, $BF_3 \cdot Et_2O$, THF, −78→0 °C; e) $(Boc)_2O$, NEt_3, CH_2Cl_2, reflux, 68%; f) disiamyl borane, THF, 0 °C→rt/H_2O_2, NaOH; g) TsCl, DMAP, NEt_3, CH_2Cl_2, 71% from **20**; h) 3% HCl, MeOH, 60 °C, 81%.

derivative **15**. In a key step which utilizes our recently reported method,[12] amide **15** could be regioselectively converted to a mixture of α-chloro- and α-methoxybenzamides **16** and **17**, respectively, in a good combined yield. Subsequent treatment of this mixture with excess allylmagnesium bromide/$BF_3 \cdot Et_2O$ stereoselectively afforded the allyl amine **19**, which was transformed without purification into the *tert*-butyloxycarbonyl (Boc) derivative **20**. Formation of alkylation product **19** undoubtedly proceeds via the *N*-acyliminium species **18**, which is exclusively *exo*-attacked by the Grignard reagent, followed by debenzoylation by the excess organometallic reagent. The configuration of **20** was established by X-ray analysis of the derivative **25a** (see below). To complete formation of the requisite tricyclic ABC-species, olefin **20** underwent hydroboration, followed by treatment of the resulting primary alcohol with tosylate, giving sulfonate **21**. Removal of the Boc group from **21** resulted in direct in situ cyclization to ketal silyl ether **22**.

Mild acidic hydrolysis of **22** then led to the pivotal tricyclic α-hydroxy ketone **23a** (Scheme 4). This compound could be reacted with the ketene ylide reagent of Bestmann,[13] a reaction which is best conducted in this case at high pressure (12 kbar), to afford (+)-14,15-dihydronorsecurinine (**25a**), a naturally occurring minor alkaloid isolated along with (−)-norsecurinine from the root bark of *Securinega virosa*.[14] The structure of the synthetic alkaloid **25a** was firmly established by an X-ray analysis of its hydrochloride salt.[15]

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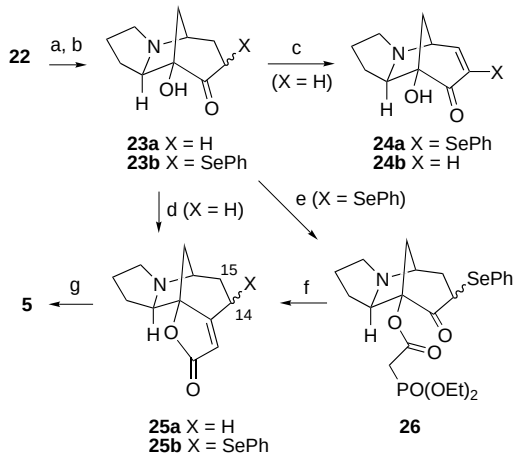
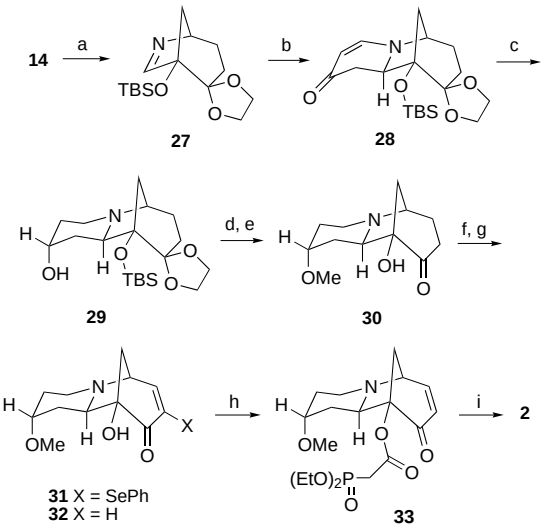


Scheme 4. a) 3 N HCl, 95 °C, 74 %; b) PhSeCl, EtOAc, NEt_3, reflux, 60 %; c) PhSeCl, EtOAc, py, reflux, 67 %; d) $Ph_3P{=}C{=}C{=}O$, PhMe, CH_2Cl_2, 12 kbar, rt, 89 %; e) $(EtO)_2POCH_2CO_2H$, CMC, CH_2Cl_2, 0 °C → rt, 88 %; f) K_2CO_3, [18]crown-6, PhMe, 0 °C → rt, 95 %; g) dimethyldioxirane, CH_2Cl_2/Me_2CO, −78 °C, 39 %.



Scheme 5. a) PhIO, CH_2Cl_2, rt, 87 %; b) Danishefsky's diene, $Yb(OTf)_3$, MeCN, 84 %; c) L-selectride (2 equiv.), THF, −78 °C, 85 %; d) NaH, MeI, THF, 0 °C → rt, 87 %; e) 3 N HCl, reflux, 78 %; f) $(PhSe)_2$, SeO_2, MsOH, CH_2Cl_2, 0 °C → rt, 58 %; g) NaI, $BF_3 \cdot Et_2O$, MeCN, 0 °C, 84 %; h) $(EtO)_2POCH_2CO_2H$, DCC, THF, 0 °C → rt, 67 %; i) K_2CO_3, [18]crown-6, PhMe, 0 °C → rt, 84 %.

In order to prepare (−)-norsecurinine itself, we next investigated conversion of hydroxy ketone **23a** to the corresponding enone **24b** (Scheme 4). Despite extensive effort we were unable to effect the α-phenylselenation of **23a**, or any hydroxyl-protected derivatives, using standard enolate selenation methods.[16] On the other hand, we did find that application of an alternate method based on the work of Liotta[17] (PhSeCl, EtOAc, pyridine, reflux) to substrate **23a** did not afford the anticipated α-selenophenylketone **23b**, but surprisingly gave α-selenophenylenone **24a** as the only discernible product. However, we have been unable to remove the selenophenyl group from **24a** to produce the enone **24b**. Interestingly, we also discovered that simply changing the selenation base from pyridine to triethylamine allowed conversion of ketone **23a** to the desired α-phenylselenoketone **23b**. Disappointingly, all attempts to effect elimination of the selenophenyl group from **23b** via the corresponding selenoxide species[16a] led to a number of decomposition products, probably due to the instability of the resulting enone **24b**. Despite these problems, it was possible to successfully complete the alkaloid total synthesis by converting the keto selenide **23b** to the phosphonate species **26**, which could then be cyclized to butenolide derivative **25b**.[18] Finally, treatment of the butenolide **25b** with dimethyldioxirane at low temperature led directly to (−)-norsecurinine (**5**) having spectral data identical with those of authentic material.[16c, 19]

In order to test the generality of our strategy for synthesis of the securinega alkaloids, we have extended the approach to phyllanthine (**2**). Thus, the bicyclic amine **14** could be cleanly oxidized with iodosobenzene[20] to afford the imine **27** (Scheme 5). We were pleased to find that this imine undergoes an *exo*-stereoselective hetero Diels–Alder reaction with Danishefsky's diene under high pressure (yield ca. 70 %), or more conveniently and efficiently upon catalysis by $Yb(OTf)_3$,[21, 22] to afford the tricyclic vinylogous amide **28** after aqueous workup (yield 84 %).[23] Treatment of **28** with two equivalents of L-selectride effected both conjugate reduction and subsequent stereoselective reduction of the ketone group, yielding the axially oriented alcohol **29**. This compound could then be O-methylated and the protecting groups removed by acid hydrolysis to afford hydroxyketone **30**. Attempted application to ketone **30** of the phenylselenation method[17] used for **23a** (see above) resulted in a complex mixture of products. However, using the selenation procedure reported by Sonoda's group (PhSeSePh, MsOH, SeO_2),[24] **30** was transformed to the α-phenylselenoenone **31**, which was deselenated in good yield with $NaI/BF_3 \cdot Et_2O$[25] to provide the required enone **32**. To complete the synthesis, hydroxyenone **32** was esterified to give phosphonate **33**.[26] Cyclization of **33**, promoted by potassium carbonate/[18]crown-6, then afforded phyllanthine (**2**) which had ^1H and ^{13}C NMR data in good accord with those reported for the natural product.[27]

In summary, we have successfully implemented a new general strategy for enantioselective construction of the securinega alkaloids. Key steps in the total synthesis of (−)-norsecurinine (**5**) include an intramolecular SmI_2-catalyzed ketonitrile coupling and application of our new method for generation of *N*-acylimines.[12] The total synthesis of phyllanthine (**2**) features a stereoselective imino Diels–Alder reaction for construction of the A-ring.

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Formal Three-Electron Reduction by an f-Element Complex: Formation of $[\{(C_5Me_5)(C_8H_8)U\}_2(C_8H_8)]$ from Cyclooctatetraene and $[(C_5Me_5)_3U]$**

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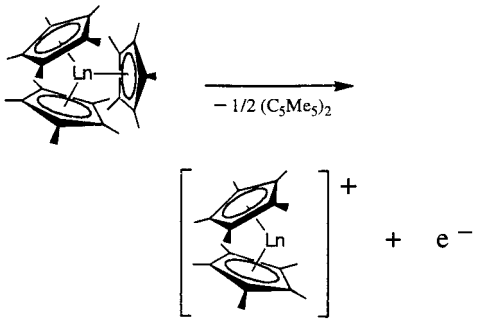
Reduction reactions involving more than two electrons are not common for metal complexes containing just one metal.[1] In f-element chemistry, multielectron reductions from monometallic species are particularly rare[2] since the common low-valent ions Th^{III}, U^{III}, Eu^{II}, Yb^{II}, Sm^{II}, and Tm^{II} typically react as one-electron An^{IV}/An^{III} or Ln^{III}/Ln^{II} redox couples.[3–5] Recently however, we have shown that there is a new way of accomplishing reductive chemistry with f-element complexes by steric crowding[6, 7] and we report here how this method can be coupled with a traditional one-electron redox couple to accomplish multielectron reduction with a monometallic uranium complex.

It has recently been discovered that the sterically crowded $[(C_5Me_5)_3Ln]$ complexes (Ln = Sm,[6] Nd[7]) can act as one-electron reductants as shown in Equation (1). The reductive reactivity of the $[(C_5Me_5)_3Ln]$ complexes can be rationalized



(1)

by the fact that the $C_5Me_5^-$ ions are not well-stabilized electrostatically in these compounds due to the long $Ln-C(C_5Me_5)$ distances caused by steric congestion. If the redox reaction in Equation (1) is coupled to a one-electron metal-based reduction, for example, the U^{IV}/U^{III} couple[8] of uranium, then a complex such as $[(C_5Me_5)_3U]$[9] could be a two-electron reducing agent. This concept was tested by reacting $[(C_5Me_5)_3U]$ with 1,3,5,7-cyclooctatetraene (C_8H_8). It had been shown that U^{III} complexes would act as one-electron reductants with cyclooctatetraene.[10] Our efforts to couple that reactivity with sterically induced reduction are reported here.

Reaction of $[(C_5Me_5)_3U]$ with C_8H_8 in a 1:1 stoichiometry formed $(C_5Me_5)_2$ and a new product, **1**, but residual $[(C_5Me_5)_3U]$ remained at the end of the reaction. Subsequently, it was determined that a 2:3 $[(C_5Me_5)_3U]:C_8H_8$

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