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Enantioselective Approach to Securinega Alkaloids. Total Synthesis of Securinine and (−)-Norsecurinine

David González-Gálvez, Elena García-García, Ramon Alibés, Pau Bayón,* Pedro de March, Marta Figueredo,* and Josep Font

Universitat Autònoma de Barcelona, Departament de Química, 08193 Bellaterra, Spain

marta.figueredo@uab.es

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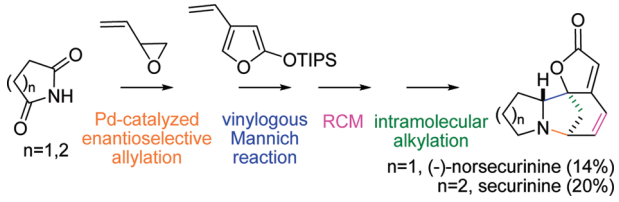

The most representative securinega alkaloids have been synthesized through a new strategy involving the palladium-catalyzed enantioselective allylation of a cyclic imide, a vinylogous Mannich reaction, and a ring-closing metathesis process, as the key steps. The diastereoselectivity of the vinylogous Mannich reaction was in partial agreement with DFT theoretical calculations performed in a model system. The synthesis of (−)-norsecurine has been accomplished in nine steps from succinimide and 14% overall yield and that of securinine in 10 steps from glutarimide and 20% overall yield. Both syntheses compare favorably with those previously described. The three key transformations have been performed in a synthetically useful scale (more than 500 mg). Moreover, since the enantioselectivity was originated by a chiral phosphine ligand, the antipode of which is readily available, the same route is expected to give access to (+)-norsecurinine and virosecurinine.

Introduction

The securinega alkaloids[1] comprise a group of compounds initially isolated from some plants of the *Securinega* (also named *Flueggea*) and *Phyllanthus* species, belonging to the Euphorbiaceae family, and later also found in other Euphorbiaceae species, such as *Margaritaria* and *Breynia*, and in *Zygogynum pauciflorum* (Winteraceae). Due to their medicinal properties, some of these plants have been widely used for years in traditional folk medicine in China and Amazonia. In particular, they have found application as diuretics[2] and antipyretics,[3] in the treatment of hepatic disorders,[4] and against skin eruptions.[5] Securinine (**1**, Chart 1), the most abundant of these alkaloids, was first isolated in 1956, and its structure was fully established in the 1960s.[6] Since then, around 30 related alkaloids have been isolated and characterized.[7] Typically, the skeleton of

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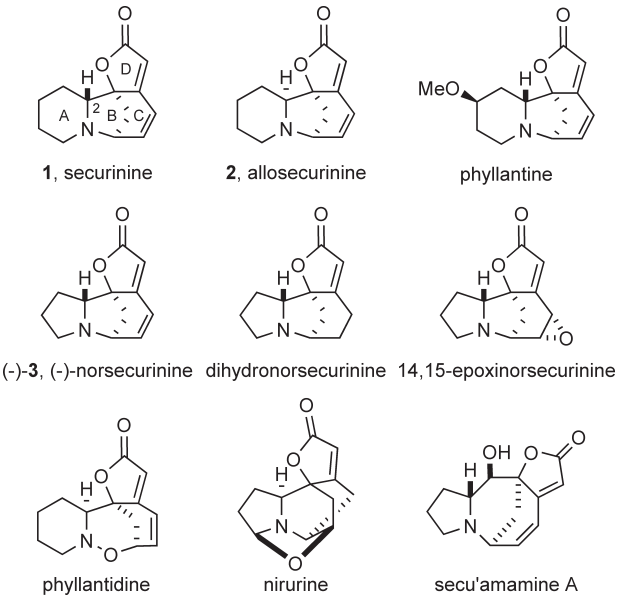
CHART 1. Representative Examples of Securinega Alkaloids



securinega alkaloids encloses a 6-azabicyclo[3.2.1]octane system (rings B and C) fused to a 2-furanone (ring D) and either a piperidine or pyrrolidine (ring A), with the size of this last ring characterizing the securinine and norsecurinine type subgroups, respectively. The members within each one of these subgroups differ in the configuration of their stereogenic centers and/or they present slight functionality alterations. The enantiomer of securinine, virosecurinine, and their epimers at C2, allosecurinine (**2**) and viroallosecurinine, have all been isolated from natural sources. (−)-Norsecurinine [(−)-**3**], the first isolated and most representative member of its subgroup,[8] and its antipode (+)-norsecurinine are both naturally occurring too. There are also several securinega alkaloids that show significant modifications of the typical structural framework, as is the case of phyllantidine, which presents rings A and C connected through an oxygen bridge; nirurine, where the benzofuranone moiety (rings C and D) is connected to the nitrogen atom of the pyrrolidine subunit through a different position, or secu'amamine A, wherein rings B and C conform an azabicyclo[4.2.1]octane system.

The securinega alkaloids have been associated with a number of biological activities, some of which are well documented. Securinine is an ACE inhibitor[9] and a stimulant of the central nervous system[10] and has shown antimalarial[11] and antibacterial activities.[12] It has been described that several securinega alkaloids are specific $GABA_A$ receptor antagonists,[13] and some of them act also as antitumor agents.[14] (+)-Norsecurinine inhibits spore germination of some plant pathogenic fungi.[15]

Despite their attractive potential as pharmacological agents, published synthetic investigations related to the securinega alkaloids are rather limited. Racemic securinine was synthesized by Horii et al. a few years after its isolation,[16] while in 1987 Heathcock and von Geldern disclosed the first synthesis of racemic norsecurinine.[17] Two additional total syntheses[18] and one formal synthesis[19] of (±)-securinine have since been reported, as well as one total synthesis of (±)-norsecurinine.[20] In this last work, a small quantity of the oxygen-bridged alkaloid (±)-nirurine was also obtained. The first nonracemic total synthesis of a securinega alkaloid was reported in 1989 by Jacobi and co-workers, who described the enantioselective syntheses of (+)- and (−)-norsecurinine, starting from L- and D-proline, respectively.[21] In 2000, the Weinreb group described the second successful approach to (−)-norsecurinine,[22] together with the first preparation of (−)-dihydronorsecurinine, both alkaloids derived from a common synthetic intermediate. Simultaneously, and through an analogous sequence, these authors also reported the preparation of phyllantine, the first nonracemic synthesis among the securinine subgroup, and more recently, they disclosed the first synthesis of secu'amamine A.[23] Two rather

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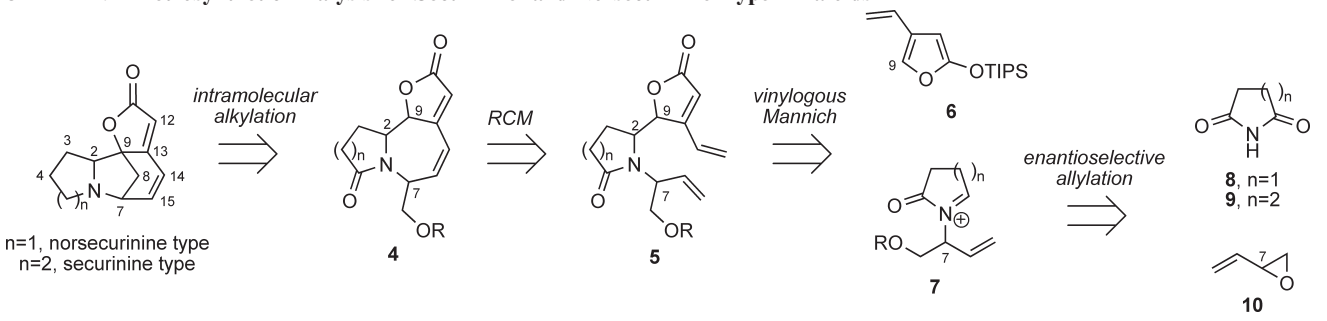
SCHEME 1. Retrosynthetic Analysis for Securinine- and Norsecurinine-Type Alkaloids

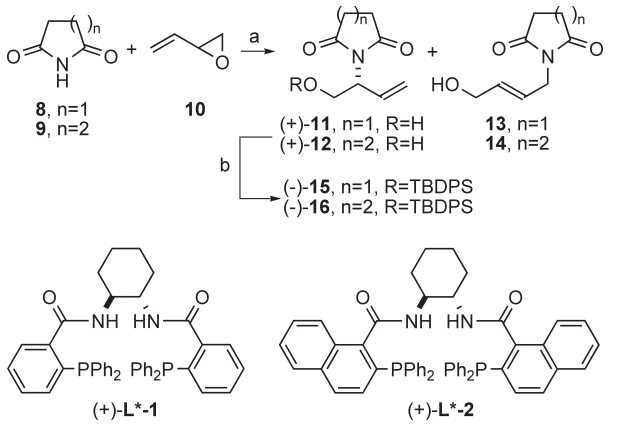


similar diastereoselective syntheses of securinine have been developed by the group of Honda[24] and ours,[25] both of them starting from (*R*)-pipecolinic acid. As part of the same investigations, the Japanese group has also accomplished the synthesis of (+)-viroallosecurinine,[26] and we have obtained a previously unknown epimer at C2 of (−)-norsecurinine, named (−)-allonorsecurinine.[25] Starting from 4-hydroxypyroglutamic acid, and through a closely related strategy, a third synthesis of securinine has been disclosed very recently.[27] Also in recent publications,[28] Kerr and co-workers described the syntheses of (+)-phyllantidine and (−)-allosecurinine from enantiopure cyclopropane precursors, which were prepared through multistep sequences from commercially available materials. Making use of a chiral auxiliary approach, we have also accomplished the asymmetric syntheses of allosecurinine and viroallosecurinine.[29] In parallel to these studies, we were trying to develop a general and enantioselective strategy for the synthesis of both types of securinega alkaloids. Our goal was originating enantioselectivity in a catalytic process rather than deriving it from a chiral pool material, in order to make either antipode of the target alkaloid equally available. The efficiency of our enantioselective approach has been illustrated by concluding the total syntheses of (+)-securinine and (−)-norsecurinine[30] in a small number of steps and excellent overall yields. A full account of this work is reported herein.

Results and Discussion

Synthetic Plan. Scheme 1 shows the retrosynthetic analysis of our enantioselective approach, where key steps are a vinylogous Mannich reaction between an acyliminium cation **7** and silyloxyfuran **6**, providing, respectively, rings A and D of the alkaloid, and a ring-closing metathesis (RCM) reaction, which would furnish the seven-membered cycle containing rings B and C. The stereogenic center of the iminium intermediate **7** would furnish the configuration at C7 in the alkaloid, while the diastereoselectivity of its addition to **6** would determine the relative configuration at C2. The additional stereocenter simultaneously generated at C9 will be lost in the formation of the enolate, which is required for the final intramolecular alkylation leading to the tetracyclic skeleton of the alkaloid. Therefore, the main challenges for the stereochemical control of the synthesis were an enantioselective preparation of a suitable precursor of **7** and getting a good diastereoselectivity in the vinylogous Mannich reaction. The final cyclization step parallelizes that used by Jacobi and co-workers in their synthesis of norsecurinine, where, except for the nitrogen protection, for $n = 1$ and R = Ms the last intermediate is identical to **4**.

SCHEME 2. Enantioselective Allylation of Imides 8 and 9[a]



[a]Key (a) $[\eta^3\text{-}C_3H_5PdCl]_2$, **L***, $NaHCO_3$, solvent, room temperature; (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C → room temperature.

The Enantioselective Imide Allylation. According to the above synthetic plan, our first task was the enantiodirected introduction of the alkyl substituent at the *N*-position of the starting imides. Recently, Trost et al. described the conversion of racemic butadiene monoepoxide (**10**) into a single enantiomeric product through a palladium-catalyzed asymmetric allylic alkylation of phthalimide in the presence of a chiral diphosphine ligand.[31] With this work in mind, we studied the reaction of succinimide (**8**) and glutarimide (**9**) with epoxide **10** (Scheme 2) as the starting point for the

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TABLE 1. Enantioselective Allylation of Imides 8 and 9[a]

entry	imide	ligand	solvent	conversion (%)	C:T[b]	ee of (+)-**11** or **12** (%)
1	**8**	(+)-**L*-1**	CH_2Cl_2	92	10:1	64
2	**8**	(+)-**L*-1**	toluene	100	16:1	29
3	**8**	(+)-**L*-1**	THF	96		46
4	**8**	(+)-**L*-1**	CH_3CN	45		81
5	**8**	(+)-**L*-1**	CH_3CN/H_2O 3/1	15		90
6	**8**	(+)-**L*-2**	CH_2Cl_2	99	90:1	87
7	**9**	(+)-**L*-2**	CH_2Cl_2	64	10:1	
8[c]	**9**	(+)-**L*-2**	CH_2Cl_2	100		>99

[a] Standard conditions: 0.4 mol % of $[(C_3H_5)PdCl]_2$; 1.2 mol % of ligand*; 5.0 mol % of Na_2CO_3; room temperature. [b]Ratio between central and terminal attack product (**11**:**13** or **12**:**14**). [c]In this experiment, double concentration of Pd complex, ligand, and base were used.

syntheses of norsecurinine and securinine, respectively. The results are summarized in Table 1. The initial experiments were performed using the most readily available ligand **L*-1**.[32] From the reaction between **8** and **10**, under the conditions previously described for phthalimide (entry 1) (0.4 mol % of the π-allylpalladium chloride dimer, 1.2 mol % of the chiral diphosphine ligand, and 5.0 mol % of Na_2CO_3, in dichloromethane), after 14 h, the expected alkylation product (+)-**11** was isolated in 83% yield, along with a minor quantity (9%) of its regioisomer **13**, resulting from the terminal attack of the imide to the intermediate palladium complex. In this run, the enantiomeric excess of (+)-**11** was only moderate (64%). In an effort to improve this result, the same reaction was performed in different solvents (entries 2−5). It was observed that an increase in polarity was beneficial for the enantioselectivity, reaching 90% ee in acetonitrile/water 3/1, but unfortunately, in polar solvents the reaction became too slow. Consequently, we went back to dichloromethane and changed the ligand to the bulkier diphosphine **L*-2**, which was prepared as described.[31] From this last experiment (entry 6), the desired regioisomer (+)-**11** could be isolated in 91% yield with 87% ee. Surprisingly, when the same conditions were applied to glutarimide (entry 7), we observed that both the regio- and enantioselectivity decreased disappointingly. After some experimentation, it was found that excellent yield, regioselectivity, and ee can be obtained by using double catalyst loading while keeping the Pd/ligand/base stoichiometry. In this way, the allylated glutarimide (+)-**12** was obtained in almost quantitave yield with >99% ee, and no traces of its regioisomer **14** were detected (entry 8). The same modification was then applied to the allylation of succinimide, but intriguingly, no improvement in the regio- or enantioselectivity of the reaction was observed for this substrate.

The ee of the glutarimide derivative (+)-**12** was determined by CHPLC. Surprisingly, in the case of the succinimide derivative (+)-**11** the peak resolution was not possible and the ee was established by NMR through preparation of the diastereomeric Mosher's esters. The absolute configuration of the major enantiomers (+)-**11** and (+)-**12** was tentatively assigned as *R* by analogy to the phthalimide derivative obtained by Trost in the presence of the same ligand. The enantiomerically enriched alcohols (+)-**11** and (+)-**12** obtained under the conditions of entries 6 and 8 were converted into the corresponding *tert*-butyldiphenylsilyl (TBDPS) ethers (−)-**15** and (−)-**16**. Crystallization of (−)-**15** from 2-propanol furnished enantiomerically pure material in overall 81% yield from succinimide, while enantiopure silylether (−)-**16** was obtained in quantitative yield from glutarimide.

The Vinylogous Mannich Reaction. According to the plan, we next performed the regioselective reduction of the *N*-alkylated imides (−)-**15** and (−)-**16** to the corresponding hemiaminals, required to generate the acyliminium Mannich acceptors. For this transformation, $LiEt_3BH$ in THF worked more efficiently than other attempted reducing agents ($NaBH_4$ or DIBALH), furnishing the mixtures of epimeric hemiaminals **17** and **18** in 87% and 90% yield, respectively (Scheme 3). Triisopropylsilyloxyfuran **6** was prepared in 97% yield from 4-vinyl-2(5*H*)-furanone, which was in turn synthesized from β-tetronic acid in two steps and 68% overall yield following a previously reported procedure.[33]

In the last years, the vinylogous Mannich reaction has attracted the attention of several researchers in the field of natural product synthesis.[34] In relation to our work, particularly interesting were those precedents using a pyrrolinium cation and a 2-silyloxyfuran as the reaction partners. Studies on the stereochemical induction produced by a stereogenic center enclosed in the pyrrolinium ring[34e] or by a chiral auxiliary group attached to a carbamate nitrogen protection[34c] have been reported, but to the best of our knowledge, an example with the stabilizing acyl group inside the ring and the stereogenic motif outside has not been described yet. A priori, the vinylogous Mannich reaction between silyloxyfuran **6** and the iminium ions derived from **17** or **18** may produce up to four diastereomers of **20** or **21**, respectively, among which the (2*R*,7*R*,9*R*) and (2*R*,7*R*,9*S*) isomers correlate with (−)-norsecurinine ($n=1$) or securinine ($n=2$), while the (2*S*,7*R*,9*S*) and (2*S*,7*R*,9*R*) isomers of **21** correlate with allosecurinine. To synthesize the corresponding, and also natural, enantiomeric alkaloids, (+)-norsecurinine, virosecurinine, and viroallosecurinine, a starting hemiaminal with the opposite configuration at C7 would be required. We anticipated that the configurational assignment of adducts **20**/**21** would be quite complex, and hence, we decided to acquire some theoretical knowledge on the stereochemical course of the reaction.

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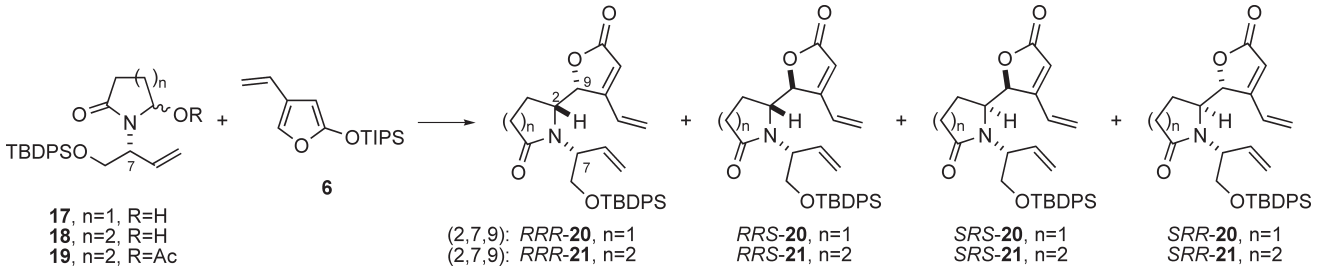
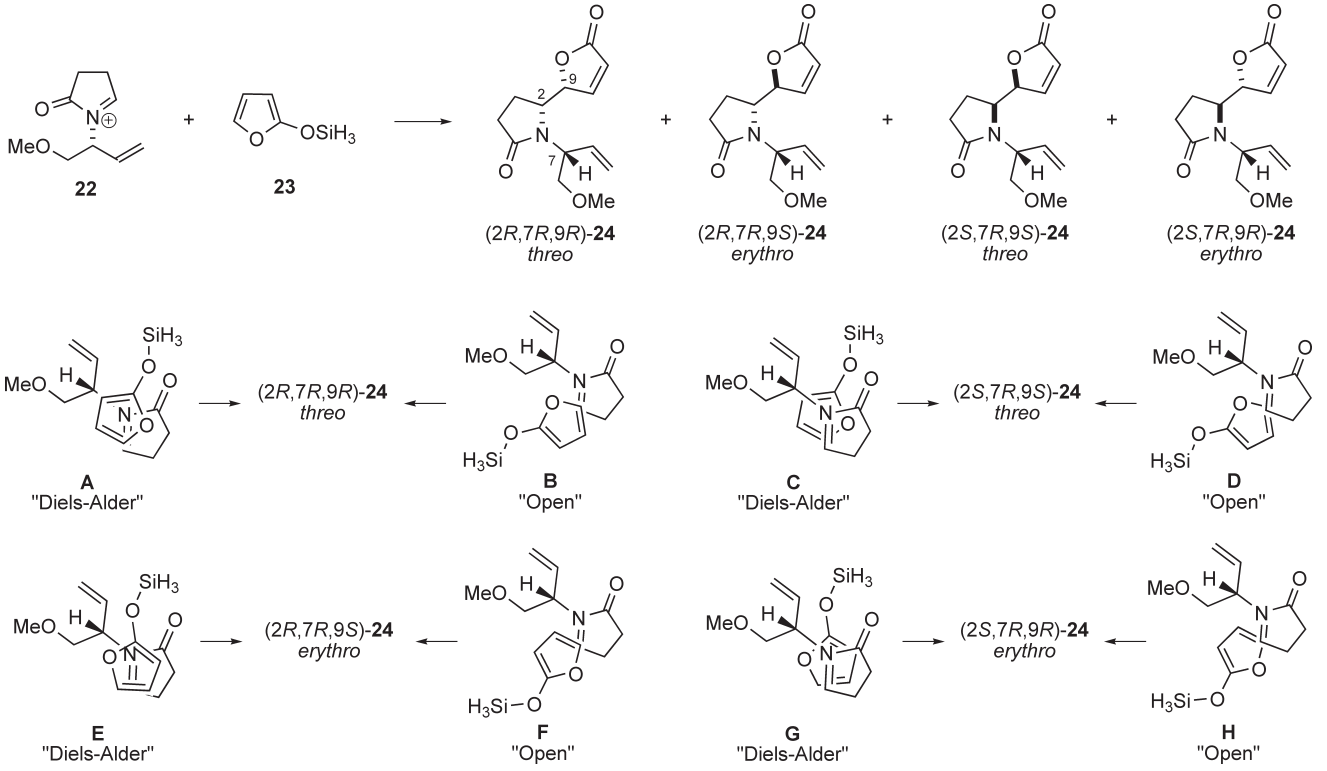
SCHEME 3. Vinylogous Mannich Reaction Leading to Trienes 20 and 21



SCHEME 4. Models for the Density Functional Theory Calculations on the Vinylogous Mannich Reaction



Some years ago, Martin and Bur reported the results of ab initio calculations concerning the vinylogous Mannich reaction between 2-methoxyfuran and an achiral pyrrolinium ion. These authors envisaged two kinds of transition states (TS), "Diels−Alder-like TS" and "open-like TS", and rationalized the empirical preference of the process to result in *threo* over *erythro* products.[34a,34d] Taking this work as a reference, we analyzed the reaction between the acyliminium ion **22** and the furanyloxysilane **23** (Scheme 4), which we judged appropriate models for our reagents, as a way to evaluate the influence that the stereogenic center external to the pyrrolinium ring may have on the stereoselectivity of the process. Density functional theory calculations were carried out to identify the structures of the eight competitive transition states A−H considered, using the program package Gaussian 03 (rev E.01),[35] the B3LYP[36] combination of functionals, and the 6-31G(d) as the basis. The relative energies calculated for the eight saddle points suggested that orientation **A** had the lowest energy, followed by **C** (0.3 kcal/mol higher). This result predicted that *threo* adducts would predominate, with the stereogenic center of the iminium cation favoring (2*R*,7*R*,9*R*) over (2*S*,7*R*,9*S*) relative configuration in a ratio of 2:1 at 0 °C. The preferred adduct, (2*R*,7*R*,9*R*)-**24**, had a suitable relative configuration to be used as a precursor in the synthesis of norsecurinine. Orientations **H** and **E**, coming next in stability (2.7 and 3.0 kcal/mol higher than **A**, respectively), would lead to *erythro* diastereomers, which, consequently, would be less expected among the reaction products. Finally, orientations **D**, **B**, **F**, and **G** gave energies between 4.4 and 6.0 kcal/mol higher than **A**. These values are too far from the minimum to have an important effect on the diastereomeric ratio.

To prove that the optimized geometries of the eight calculated TS match the hybridization change on going from the reactants to the product, the dihedral angles $N-C_2-C_3-C_4$ were observed. All of them were between 6° (TS **C**) and

(35) Calculations using B3LYP/6-31G* as implemented by Gaussian 03, Revision E.01 : Frisch, M. J. et al. Gaussian, Inc., Wallingford, CT, 2004.

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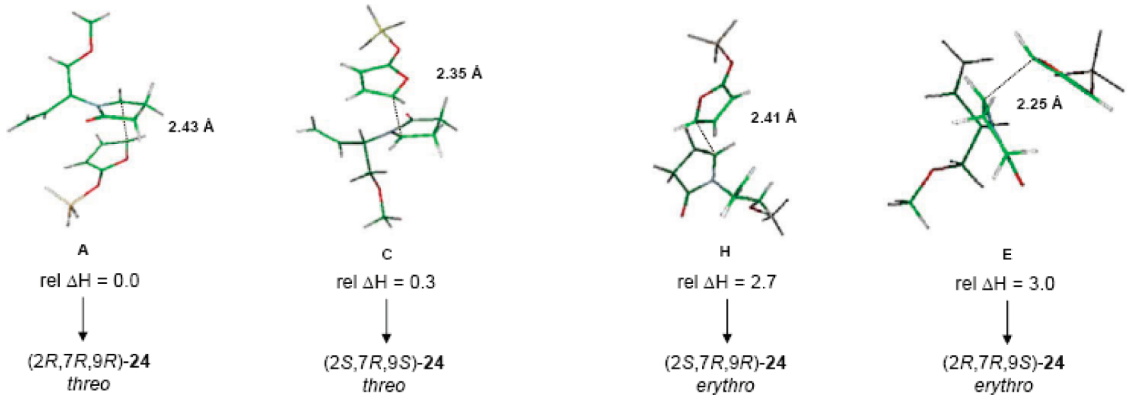


FIGURE 1. Stick drawings of the saddle point structures of the most representative TS. Relative energies (rel ΔH) are given in kcal/mol.

TABLE 2. Vinylogous Mannich Reaction between Silyloxyfuran 6 and Iminium Precursors 17−19[a]

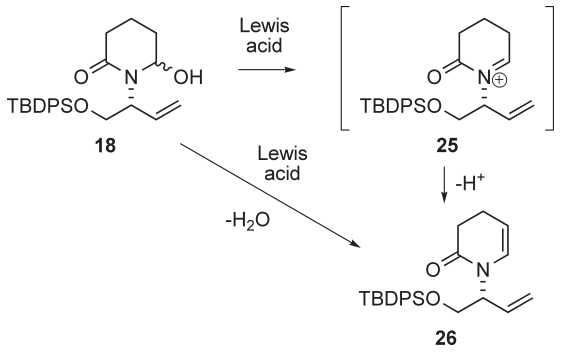
entry	iminium precursor	Lewis acid	T (°C)	conversion (%)	products (ratio)	**20** or **21***RRR*:*RRS*:*SRS*:*SRR*[b]
1	**17**	TIPSOTf[c]	−78	75	**20**	
2	**17**	TIPSOTf[c]	0	85	**20**	43:29:14:14
3	**17**	$Cu(OTf)_2$[c]	0	0		
4	**17**	$Sn(OTf)_2$[c]	0	0		
5	**17**	$BF_3 \cdot OEt_2$	0	>99	**20**	57: 29:5:9
6	**17**	$BF_3 \cdot OEt_2$	−10	92	**20**	62: 25:4:9
7	**17**	$BF_3 \cdot OEt_2$	−20	85	**20**	
8[d]	**17**	$BF_3 \cdot OEt_2$	0	90	**20**	
9[e]	**17**	$BF_3 \cdot OEt_2$	0	95	**20**	
10	**17**	$BF_3 \cdot OEt_2$[f]	0	60	**20**	
11	**17**	$BF_3 \cdot OEt_2$[g]	0	85	**20**	
12	**18**	$BF_3 \cdot OEt_2$	0	>99	**21**/**26** (1:1.5)	48:4:24:24
13[h]	**18**	$BF_3 \cdot OEt_2$	0	>99	**26**	
14	**18**	TIPSOTf	0	>99	**26**	
15	**18**	$Sn(OTf)_2$	0	>99	**26**	
16[i]	**18**	$BF_3 \cdot OEt_2$	0	>99	**21**/**26** (1.5:1)	48:4:24:24
17	**18**	$BF_3 \cdot OEt_2$[c]	−20	>99	**21**/**26** (2.3:1)	48:4:24:24
18	**18**	$BF_3 \cdot OEt_2$[c]	−40	20	**21**/**26** (3:1)	48:4:24:24
19	**18**	$BF_3 \cdot OEt_2$	−78	<2		
20[j]	**18**	$BF_3 \cdot OEt_2$	−20	>99	**21**/**26** (4:1)	48:4:24:24
21[j]	**19**	$BF_3 \cdot OEt_2$	−20	>99	**21**/**26** (>20:1)	50:−:35:15
22[j]	**19**	*n*-Bu_2BOTf	−20	>99	**21**/**26** (>20:1)	59:−:24:17
23[j]	**19**	(*R*,*R*)-IpcBCl[k]	−20	>99	**26**	
24[i]	**19**	(*R*,*R*)-IpcBOTf[k]	−20	>99	**21**/**26** (1:2.3)	60:−:22:18
25	**19**	*n*-Bu_2BOTf	−40	25	**21**/**26** (4:1)	53:−:33:14
26	**19**	*n*-Bu_2BOTf	−78	<2		

[a]Standard conditions: 1 equiv of aminal (**17**, **18**, or **19**); 1.2 equiv of **6** (prepared from 1.2 equiv of 4-vinyl-2(5*H*)-furanone, 1.6 equiv of Et_3N, and 1.3 equiv of TIPSOTf); 2.5 equiv of Lewis acid; diethyl ether; 30 min. [b]Diastereomeric ratio was measured by ^1H NMR analysis of the crude product of the vinylogous Mannich reaction. [c]Reaction time 120 min. [d]1 equiv of **6** was used. [e]1.1 equiv of **6** was used. [f]1 equiv of Lewis acid was used. [g]1.75 equiv of Lewis acid were used. [h]A 3-fold excess of Et_3N was used in the preparation of **6**. [i]Furan **6** was prepared in situ. [j]The reaction was run in CH_3CN. [k]Ipc = isopinocamphenyl.

20° (TS **E**), indicating that the five-membered ring adopts a shallow envelop conformation. The formation-bond distances were also analyzed, with the shortest being 2.25 Å and the longest 2.43 Å, but no relation between this parameter and the relative stability of the TS was observed. Figure 1 shows the saddle point structures for the most representative TS. The calculated data show that a stereogenic center attached to the five-membered ring by the nitrogen atom could affect the diastereoselectivity of the reaction, despite its distance to the reactant carbon atom and even neither of the faces of the pyrrolinium cation being clearly blocked.

Table 2 summarizes the experimental results of the vinylogous Mannich reactions leading to trienes **20** and **21**. The first experiment was performed with hemiaminal **17**, using a 20% excess of furan **6** and 2.5 equiv of triisopropyl triflate (TIPSOTf) as the Lewis acid promoter, in diethyl ether at −78 °C (entry 1). Under these conditions, after 2 h of reaction, the conversion of the hemiaminal was incomplete (around 75%), and a complex mixture of products was formed. Increasing the temperature to 0 °C (entry 2) improved the conversion, but still some unreacted hemiaminal remained. Next, alternative Lewis acid promoters were tried (entries 3−5), and it was found that $BF_3 \cdot Et_2O$ furnished the best conversion, with a moderate enhancement of the diastereoselectivity compared to the reactions promoted by TIPSOTf. Attempts to enhance it further by lowering the temperature (entries 6 and 7) led to lower conversions of **17**, probably due to the competitive hydrolysis of the silyloxyfuran. Some experiments were also performed by decreasing the relative amounts of furan **6** (entries 8 and 9) or Lewis acid (entries 10 and 11), but none of them improved the

SCHEME 5. Pathways for the Formation of Enamide 26



results attained under the conditions established in entry 5. All attempts to separate the isomers of **20** by chromatography on silica gel or alumina or by fractional crystallization met with failure, due to the low stability of these compounds, but a purified mixture of all the isomers could be obtained by quick filtration of the crude product through silica gel. On the other hand, on standing at room temperature overnight, the major adduct crystallized from a reaction mixture without any solvent, and it could be separated by filtration in 51% yield. The relative configuration of the isomers of **20** was established by performing a RCM experiment with a mixture containing all the isomers (vide infra). By correlation, the isolated vinylogous Mannich adduct was identified as *RRR*-**20** and the second most abundant one as its *erythro* epimer *RRS*-**20**. This stereochemical assignment is in partial agreement with the theoretical calculations, which anticipated the preferential formation of the major adduct *RRR*-**20** but predicted a stronger predominance of *threo* over *erythro* isomers. Hence, it has to be concluded that the DFT calculations underestimate the influence of the stereogenic center external to the ring on the *threo*/*erythro* selectivity of the process.

The first trials with the six-membered cyclic hemiaminal **18** were performed under the best conditions found for its five-membered analogue (entry 12). Disappointingly, we found that, instead of the expected vinylogous Mannich adducts **21**, the major product of the reaction was enamide **26** (Scheme 5), resulting from dehydration of **18** through direct β-elimination or with the intermediacy of the iminium cation **25**. A control experiment under the same conditions, except for the absence of furan **6**, rendered enamide **26** quantitatively after only 5 min. To preclude silyloxyfuran hydrolysis as the cause of the undesired pathway, furan **6** was prepared in the presence of a large excess of triethylamine,[37] but the formation of the enamide was even more favorable (entry 13). The same occurred when TIPSOTf or $Sn(OTf)_2$ were used as the reaction promoters (entries 14−15). Certain improvement was accomplished when furan **6** was prepared in situ (entry 16), and a decrease in the formation of enamide was also observed performing the reaction at −20 °C, but lowering further the temperature stopped the conversion (entries 17−19). As it was obvious that the stability of the iminium cation **25** played a crucial role, we decided to assay the reaction in a more polar solvent, which could stabilize this intermediate. Thus, the change to acetonitrile favored the formation of adducts **21** over enamide **26** (entry 20).

Since hemiaminal analogues lacking the free hydroxyl group are often used as precursors of acyliminium ions,[38] we performed the acetylation of hemiaminal **18** under standard conditions,[39] and the reaction was attempted starting from its acetyl derivative **19** (entry 21). Rewardingly, with this new substrate, only trace amounts of enamide **26** were detected, and the diastereoselectivity of the addition process was also improved. Encouraged by this good result, we decided to study the effect of the boron substituents over the reaction (entries 22−24). The best result was obtained with $^{n}Bu_2BOTf$, which gave good conversion, negligible enamide formation, and the higher proportion of the major isomer of **21**. A pair of experiments at lower temperatures were also carried on (entries 25−26), but further improvement was not accomplished.

For synthetic purposes, the conditions of entry 22 were found to be the most convenient. As in the case of their five-membered-ring analogues **20**, the vinylogous Mannich adducts **21** are not stable to long contact with silica gel or alumina, but a fast flash chromatography on silica gel allowed the separation of the mixture in two fractions with two diastereomers in each, *RRR*- and *RRS*-**21** (50% yield) and *SRS*- and *SRR*-**21** (35% yield). We attribute the formation of small quantities of adduct *RRS*-**21**, which was not present in the reaction crude material, to partial epimerization of C-9 in *RRR*-**21** during the chromatographic purification. Fortunately, both isomers correlate with securinine and the synthesis could therefore be continued with the mixture. As above, the stereochemical assignment of the isomeric adducts was established after the subsequent RCM step, when the more rigid tricyclic structures facilitated their elucidation.

Ring-Closing Metathesis Process. In order to determine the relative configuration of the vinylogous Mannich adducts **20** and **21**, RCM reactions[40] starting from mixtures containing diverse proportions of two, three, or four isomers of **20** and **21** were performed (Scheme 6). These reactions were run in dichloromethane at room temperature, with 15% molar of the second-generation Grubbs' catalyst. Starting from a mixture of the four diastereomers of **20**, we obtained **27**, also as a mixture of four diastereomers, matching the relative proportion of the starting trienes, in ca. 70% yield.

The tricyclic olefins **27** could be chromatographically separated in three fractions (*RRR*, *SRR*+*SRS*, and *RRS*) and their configuration determined with the help of NOESY experiments (Figure 2). For the major isomer of **27**, a clear interaction was observed between the three protons at the stereogenic centers, H2, H7, and H9, indicating that they are sharing the same face of the tricycle, and hence, it was assigned as the *threo* isomer *RRR*-**27**. The NOE interactions shown by the other isomer isolated as a single compound, which correlates with the second most abundant product of the vinylogous Mannich reaction, were only consistent with the *erythro* isomer *RRS*-**27**. Hence, both isolated isomers

(37) The isolation of furan **6** is problematic because it hydrolyzes very fast in the presence of any trace of acid.

(38) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.

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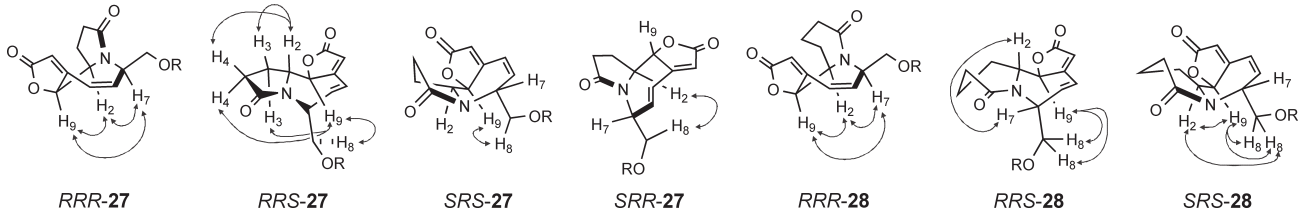
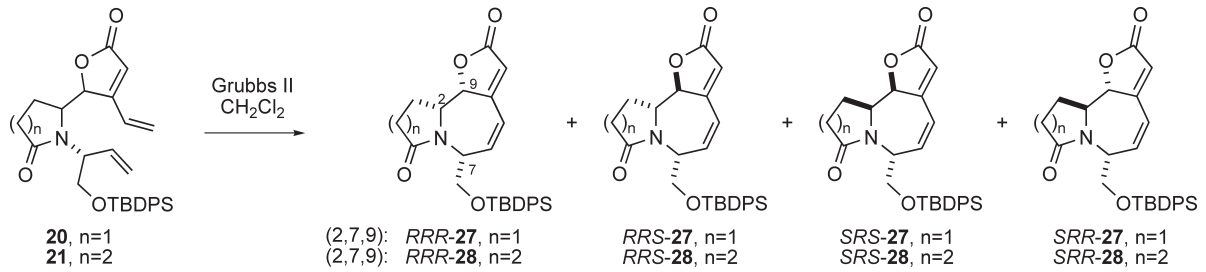


FIGURE 2. Significant NOEs observed in compounds **27** ($CDCl_3$) and **28** (C_6D_6), R = TBDPS.

SCHEME 6. RCM Reaction of the Mixtures of Isomers 20 and 21



present the same C2/C7 relative configuration as in norsecurinine.

When the RCM reaction was applied to the crystallized isomer *RRR*-**20**, the expected diene *RRR*-**27**, [α] = +118 (*c* 0.61, $CHCl_3$), was isolated in nearly quantitative yield.[41]

The RCM reaction of a mixture of the four diastereomers of **21** furnished the corresponding mixture of **28**. Unfortunately, it was not possible to separate the diastereomers of **28** because prolonged contact with silica gel or alumina led to partial decomposition, with the isolated yield dropping under 20%. However, starting from the mixture of *RRR*- and *RRS*-**21**, after quick filtration through silica gel, we isolated a mixture of *RRR*- and *RRS*-**28** in the same ratio as the starting trienes and 97% total yield. Unexpectedly, the complementary mixture of *SRS*- and *SRR*-**21** reacted in the presence of the second-generation Grubbs' catalyst to give the diastereomer *SRS*-**28**, [α] = +87 (*c* 1.45, $CHCl_3$), as the only reaction product in 98% yield. In view of the high yield isolated, this fact was attributed to epimerization of the allylic stereocenter C9 in the presence of the RCM catalyst. In fact, epimerization of vinylcyclopropanes in the presence of the first-generation Grubbs' catalyst or first-generation Hoveyda−Grubbs' catalyst has previously been described,[42] and these catalysts have also been used for olefin isomerization in substrates bearing an oxygen or nitrogen atom at the allylic position,[43] a process that has even been applied to total syntheses.[44] As above, the relative 2*R*,7*R*,9*R* configuration of the major isomer of **28** was deduced from the NOEs observed between the protons at these positions. The relative configuration of the other isomer accompanying the former was more difficult to ascertain, but a NOE interaction between H2 and H7 pointed to the 2*R*,7*R*,9*S* relative configuration, meaning that both isomers of the mixture would correlate with securinine. For the second major isomer, which was the one isolated as a single product, positive NOE's between protons H2, H9, and H8 were consistent with the relative 2*S*,7*R*,9*S* configuration as in allosecurinine.

Completion of the Synthesis of (−)-Norsecurinine. With the tricyclic diene *RRR*-**27** in hands, the two transformations required to conclude the synthesis of (−)-norsecurinine were reducing the lactam to amine and connecting the stereogenic centers C7 and C9 through the one-carbon bridge to complete the tetracyclic skeleton (Scheme 7). Conversion of *RRR*-**27** into the corresponding thiolactam **29** was accomplished in 82% yield by reaction with Lawesson's reagent in refluxing THF, but treatment of **29** with Raney nickel or other reducing agents (including $LiAlH_4$, AlH_3, $NaBH_4$, and $BH_3 \cdot THF$ under different reaction conditions) ended up with decomposition products. Apparently, the lactone and/or olefin functionalities were more reactive toward these reducing agents than the thiolactam moiety. In view of these failures, we decided to attempt the direct reduction of the lactam to amine, which a priori had been judged more problematic. Recently, it was reported the use of borane to reduce a lactam without affecting neither the ester moiety nor the olefins present in the substrate,[45] but lactam *RRR*-**27** displayed low reactivity and poor selectivity toward $BH_3 \cdot THF$. It is also known that AlH_3 is able to reduce lactams much faster than esters and that it does not react with olefins, conjugated or not.[46] The exclusive reduction of an ester with this reagent in a substrate containing an olefin was also described,[47] but the selective reduction of a lactam in a substrate bearing additional ester and olefin functionalities has not been published. After extensive

(41) In a work scale below 100 mg, the yield was quantitative, although for larger quantities of starting material (around 500 mg), the yield was somewhat lower (around 80%).

(42) Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 8864–8875.

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(44) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848–14849.

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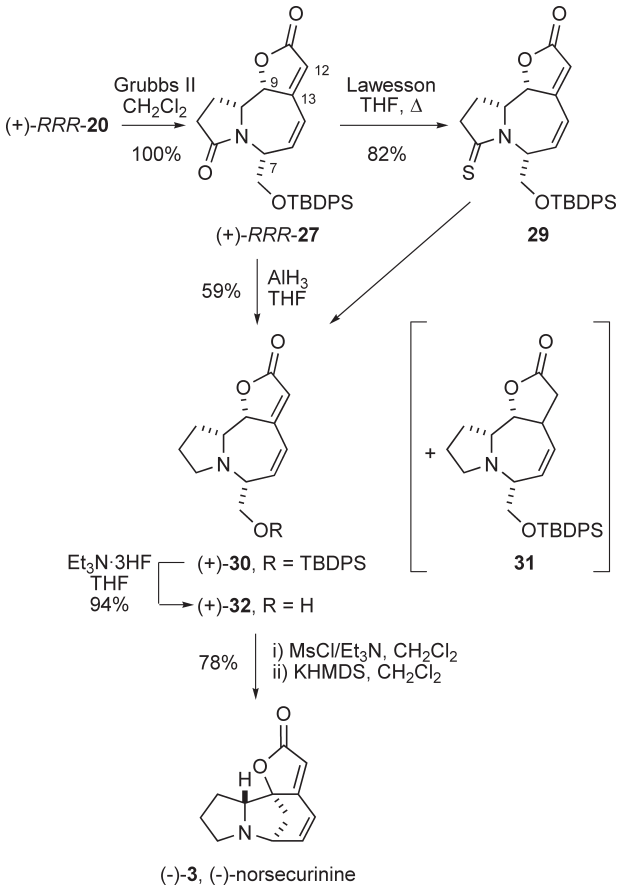
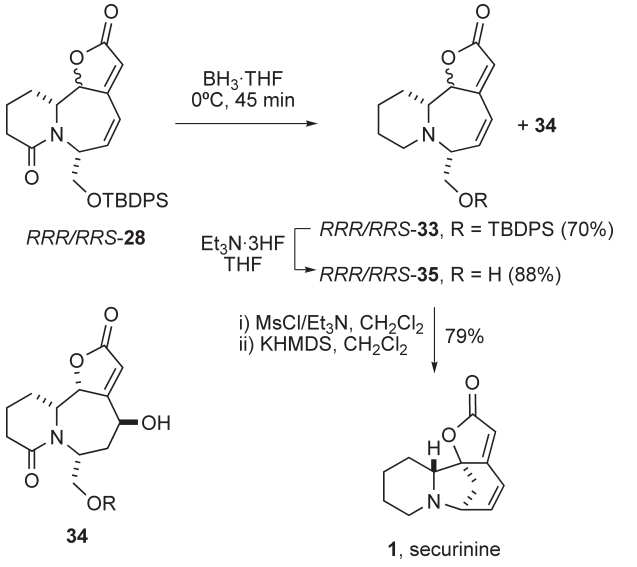
(46) Brown, H. C.; Yoon, N. M. *J. Am. Soc. Chem.* **1966**, *88*, 1464–1472.

(47) Giraud, L.; Huber, V.; Jenny, T. *Tetrahedron* **1998**, *58*, 11899–11906.

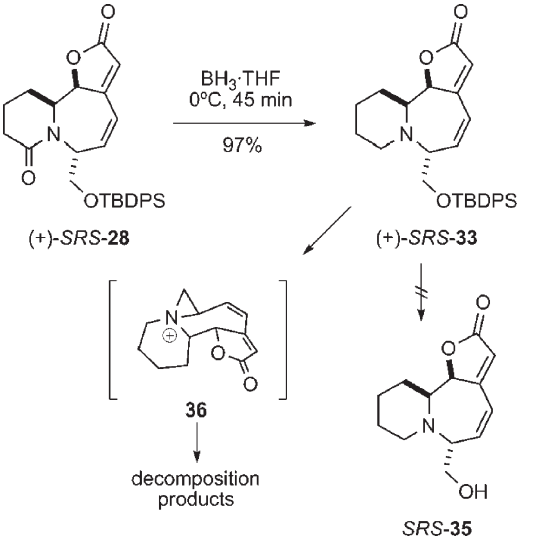
SCHEME 7. Completion of the Synthesis of (−)-Norsecurinine



SCHEME 8. Completion of the Synthesis of Securinine



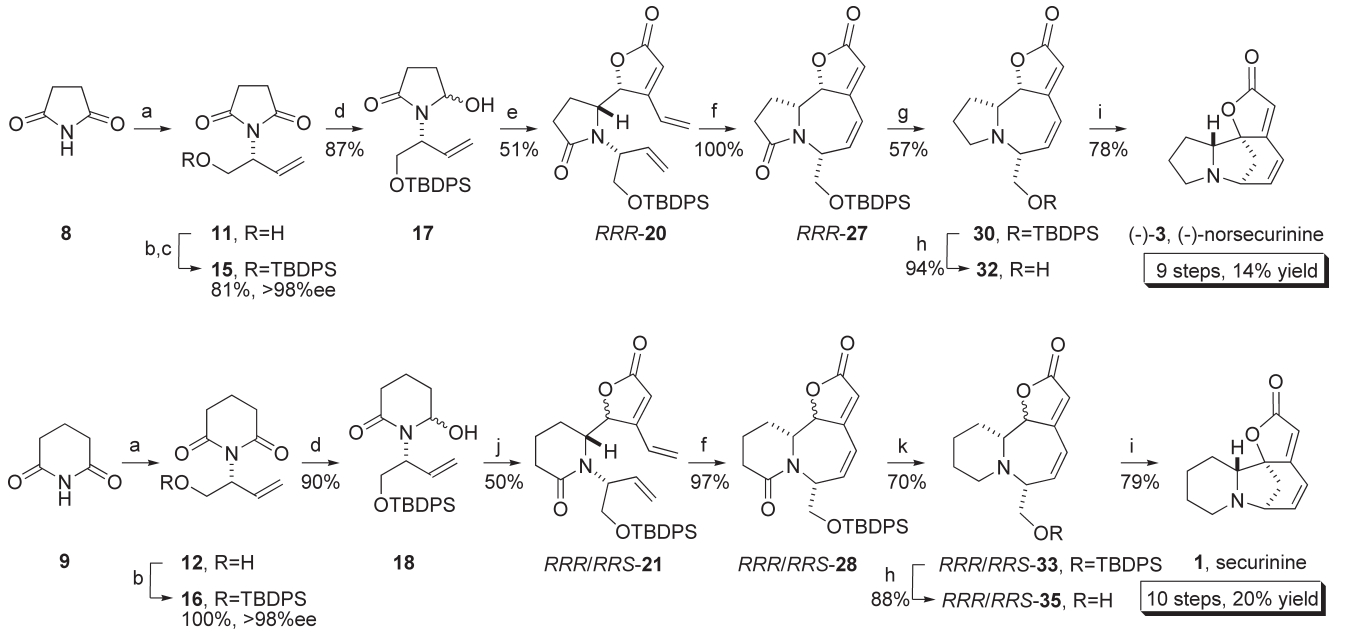
SCHEME 9. Attempted Preparation of *SRS*-35 en Route to Allosecurinine, 2



experimentation, we found that treatment of lactam *RRR*-**27** with freshly prepared 1 M AlH_3 in THF at 0 °C for 5 min produced the desired amine **30**, [α] = +89 (*c* 1.39, $CHCl_3$), in 59% yield after chromatographic purification over silica gel, with 10% of the starting lactam being recovered. The 12,13-saturated amine **31** was identified as the main byproduct of this reaction. Desilylation of **30** by different standard protocols (including treatment with TBAF in various solvents and $BF_3 \cdot OEt_2$ in the presence of silica gel) met with failure, but the free alcohol **32**, [α] = +123 (*c* 0.60, CH_2Cl_2), could be finally obtained in 94% yield by reaction of **30** with an excess of $Et_3N \cdot 3HF$ in THF at room temperature. Although alcohol **32** is the penultimate intermediate in the synthesis of (−)-norsecurinine published by Jacobi et al.,[21] its optical rotation value was not given. Hence, to assess the absolute configuration of our synthetic material we completed the synthesis of the alkaloid by mesylation and subsequent treatment with potassium bis(trimethylsilyl)amide, according to Jacobi's protocol. These transformations were satisfactorily reproduced in 78% yield for the two steps, and we ended up with the levorotatory enantiomer of norsecurinine, [α] = −270 (*c* 0.20, EtOH), lit.[8b] [α] = −270 (*c* 6.9, EtOH). Overall, the synthesis of (−)-norsecurinine was completed in nine steps from succinimide and 14% total yield.

Completion of the Synthesis of Securinine. To conclude the synthesis of securinine, we sought to elaborate the mixture of tricyclic dienes *RRR*- and *RRS*-**28** (Scheme 8). Considering the previous results within the norsecurinine sequence, the reduction of the lactam was first attempted by treatment with AlH_3 in THF, but in this case the reaction was much slower, even at higher temperatures, and we were unable to obtain the corresponding isolated amines in more than 40% yield. Among many alternative reducing agents and conditions tried, the best results were obtained when the mixture of *RRR*- and *RRS*-**28** was treated with a 7.5-fold molar amount of $BH_3 \cdot THF$ at 0 °C for 45 min. This reaction furnished amines *RRR*- and *RRS*-**33** in 70% isolated yield, along with another product identified as alcohol **34** (10% yield), and recovered starting lactam (10%). Performing the reaction at room temperature led to decomposition products, while at lower temperatures (−20 °C) the conversion was very slow and borane addition to the olefins was observed at prolonged reaction times. It is worth mentioning that the ratio *RRR*-**33**:*RRS*-**33** of isolated amines was not the same as the ratio of the starting lactams, and the yield of the reduction diminished if the initial mixture had a higher proportion of

SCHEME 10. Complete Optimized Route to (−)-Norsecurinine and Securinine[a]



[a]Key: (a) (±)-**10**, $[\eta^3\text{-}C_3H_5PdCl]_2$, (+)-**L*-2**, $NaHCO_3$, CH_2Cl_2, room temperature; (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C → room temperature; (c) crystallization from 2-propanol; (d) $LiHBEt_3$, THF, −78 °C; (e) **6**, $BF_3 \cdot OEt_2$, Et_2O, 0 °C; (f) Grubbs II, CH_2Cl_2, room temperature; (g) AlH_3, THF, 0 °C; (h) $Et_3N \cdot HF$, THF, room temperature; (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, then KHMDS, CH_2Cl_2, −78 °C → room temperature; (j) Ac_2O, DMAP, CH_3CN, 0 °C, then **6**, *n*-Bu_2OTf, CH_3CN, −20 °C; (k) $BH_3 \cdot THF$, THF, 0°C.

RRS-**28**. Intrigued by the formation of alcohol **34**, we investigated if this product was formed in the reaction medium or during the methanolic workup by performing ^1H NMR analysis of the reaction mixture before the quenching, and we observed that alcohol **34** was already present in the reaction medium. A reference experiment showed that, under the reduction conditions, the lactam moiety of alcohol **34** remains unchanged. As a plausible explanation for the formation of **34**, we visualize a hydroboration−oxidation process, in which residual traces of ruthenium species from the former RCM step would act as the oxidizing agent.[48]

Cleavage of the silyl ether in *RRR*/*RRS*-**33** by treatment with $Et_3N \cdot 3HF$ in THF at room temperature for 7 h delivered the expected alcohols *RRR*/*RRS*-**35** in 88% yield after chromatographic purification. The alcohols were converted in the corresponding mesylates, which showed low stability and were therefore immediately treated with KHMDS in dichloromethane, giving securinine as the unique product in 79% yield from the alcohols **35**. The NMR spectra of the synthetic material matched that of the natural alkaloid, and its specific rotation, [α] = −1061 (*c* 1.08, $CHCl_3$), was in agreement with the previously reported values for securinine, [α] = −1082 (*c* 1.0, $CHCl_3$).[24] Overall, the synthesis of securinine was completed in 10 steps from glutarimide and 20% total yield.

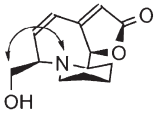
Attempted Synthesis of Allosecurinine. We then intended to perform a parallel sequence starting from the tricyclic diene *SRS*-**28**, in order to complete the synthesis of allosecurinine (Scheme 9). Promisingly, treatment of *SRS*-**28** with $BH_3 \cdot THF$ in THF at 0 °C for 45 min furnished the corresponding amine *SRS*-**33**, [α] = +63 (*c* 0.73, CH_2Cl_2), in 97% yield, but all attempts to desilylate *SRS*-**33** with different reagents and conditions failed. Although most standard desilylation protocols were tried, the starting material remained unchanged or it delivered complex mixtures of products, among which the expected aminoalcohol *SRS*-**35** was never detected. Trials to trap the alcohol by in situ mesylation were also unsuccessful. A plausible explanation to this pitfall could be the inherent instability of amino alcohol *SRS*-**35**, which may be prone to undergo skeletal rearrangements with the intermediacy of an aziridinium cation such as **36**.[49] A related process has been postulated for the biogenetic transformation of 3-β-hydroxyallosecurinine into secu'amamine A.[50]

Conclusion

In summary, we have developed a new synthetic strategy for securinega alkaloids. The key transformations are an enantioselective allylation of a cyclic imide, a vinylogous Mannich reaction, and a ring-closing metathesis process. The palladium-catalyzed enantioselective allylation of phthalimide developed by Trost[31] has been extended to succinimide and glutarimide, providing a new and

(48) For a related process, see: Yates, M. H. *Tetrahedron Lett*. **1997**, *38*, 2813–2816.

(49) In *SRS*-**35**, the nitrogen lone pair and the "activated" hydroxyl group are suitably oriented for an intramolecular S_N2 displacement leading to an aziridinium cation. This is not the case for *RRR*-**35**.



RRR-**35**

SRS-**35**

(50) Magnus, P.; Padilla, A. I. *Org. Lett*. **2006**, *8*, 3569–3571.

convenient access to enantiopure pyrrolidine and piperidine derivatives. DFT calculations performed in a model system predicted the predominance of the (2*R*,7*R*,9*R*) diastereoselectivity experimentally observed in the vinylogous Mannich reaction. Extremely concise syntheses of the most representative members of each subtype of the securinega alkaloids have been completed (Scheme 10). Thus, (−)-norsecurine has been prepared from succinimide in nine steps and 14% overall yield, while the synthesis of securinine has been accomplished starting from glutarimide in 10 steps and 20% overall yield. The absolute configuration of the final alkaloids has demonstrated that the stereochemical assignments of all the intermediates were correct. Both syntheses can be performed in a synthetically useful scale and compare favorably with the previously described routes, which were more complicated and long and with significantly lower overall yields. Moreover, all the previous syntheses directed to a single enantiomer of the target alkaloid made use of chiral pool precursors, while in our approach, the enantioselectivity was originated by the phosphine ligand (+)-(*S*,*S*)-**L*-2**, the antipode of which is equally available. Consequently, the same route is expected to provide also access to (+)-norsecurinine and virosecurinine.

Experimental Section

General experimental details are provided in the Supporting Information. Securinine numbering was used for the signal assignment of ^{1}H and ^{13}C NMR spectra of compounds **21**, **28**, **33**, and **35**.

1-[(1*R*)-1-(Hydroxymethyl)-2-propenyl]-2,6-piperidinedione [(+)-12]. A mixture of 33 mg (0.090 mmol) of π-allylpalladium chloride dimer, 220 mg (0.278 mmol) of (+)-**L*-2**, 122 mg (1.15 mmol) of sodium carbonate, and 1.3 g (11.7 mmol) of glutarimide, **9**, was purged with nitrogen for 1 h. Dry CH_2Cl_2 (93 mL) was added, and the mixture was stirred at room temperature for 10 min. Then, 950 μL (11.8 mmol) of butadiene monoepoxide, **10**, was added, and the resulting mixture was efficiently stirred under nitrogen for 14 h. The solvent was removed under vacuum, and the oily residue was purified by flash chromatography on silica gel (gradient hexanes/ethyl acetate 1:1 to ethyl acetate) to give 2.14 g (11.7 mmol, 100%) of (+)-**12** (99% ee) as a colorless oil: R_f = 0.30 (ethyl acetate); $[\alpha]^{20}_D$ = +35 (*c* 0.95, $CHCl_3$); IR (ATR) 3272, 2961, 1639, 1562, 1384, 1111; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.03 (dddd, J = 17.6, 10.6, 7.0, 1.5 Hz, 1H:$H_{2'}$), 5.31 (bqd, J = 6.8, 1.2, 1H:$H_{1'}$), 5.13 (bdd, J = 17.6, 1.2 Hz, 1H:$H_{3'}$), 5.12 (bdd, J = 10.6, 1.2 Hz, 1H:1$H_{3'}$), 3.93 (m, 1H:$H_{1''}$), 3.75 (dd, J = 11.4, 5.0 Hz, 1H:$H_{1''}$), 2.98 (bs, 1H:H_{OH}), 2.60 (t, J = 6.4 Hz, 4H:2H_3, 2H_5), 1.88 (qn, J = 6.3 Hz, 2H:2H_4); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.2 (C_2,C_6), 133.1 ($C_{2'}$), 118.3 ($C_{3'}$), 62.6 ($C_{1''}$), 56.3 ($C_{1'}$), 33.2 (C_3,C_5), 16.9 (C_4); HRMS (ESI+) calcd. for $C_9H_{13}NO_3$ 206.0793 [M + Na]$^+$, found 206.0788.

For preparative purposes, the crude material can be used in the next step without chromatographic purification, with the overall yield being unaffected.

1-[(1*R*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-2-propenyl]-2,6-piperidinedione [(−)-16]. Imidazole (3.74 g, 54.9 mmol) and TBDPSCl (5.7 mL, 21.9 mmol) were added to a solution of (+)-**12** (2.00 g, 10.9 mmol) in dry CH_2Cl_2 (97 mL) under nitrogen at 0 °C. Then, the cooling bath was removed and the mixture stirred at room temperature, under nitrogen, for 14 h. The solvent was evaporated under vacuum and replaced by ethyl acetate (55 mL). The resulting mixture was stirred vigorously and the insoluble fine white powder (imidazole·HCl) filtered trough Celite. The filtrate was concentrated under vacuum, and the resulting yellowish wax was purified by flash chromatography on silica gel (gradient, hexanes/ethyl acetate 9:1 to 8:2) to give (−)-**16** (4.60 g, 10.9 mmol, 100%) as a white solid: R_f = 0.58 (hexanes/ethyl acetate 1:1); mp = 88−89 °C (2-propanol); $[\alpha]^{20}_D$ = −13 (*c* 1.20, $CHCl_3$); IR (ATR) 2960, 2856, 1679, 1467, 1386, 1351, 1177, 1109; ^{1}H NMR (250 MHz, $CDCl_3$) 7.61 (m, 4H), 7.36 (m, 6H), 6.04 (ddd, J = 17.5, 10.4, 7.3 Hz, 1H:H2'), 5.52 (m, 1H:$H_{1'}$), 5.15 (dt, J = 17.5, 1.4 Hz, 1H:$H_{3'}$), 5.11 (dt, J = 10.4, 1.4 Hz, 1H:$H_{3'}$), 4.20 (t, J = 9.7 Hz, 1H:$H_{1''}$), 3.81 (dd, J = 9.7, 6.3 Hz, 1H:$H_{1''}$), 2.60 (t, J = 6.6 Hz, 4H:2H_3,2H_5), 1.88 (qn, J = 6.6 Hz, 2H:2H_4), 1.00 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3 (C_2,C_6), 135.3 (C_{Ph}), 135.2 (C_{Ph}), 133.4 (C_{Ph}), 133.3 (C_{Ph}), 133.1 (C_{Ph}), 129.5 (C2'), 129.4 (C_{Ph}), 127.6 (C_{Ph}), 118.4 ($C_{3'}$), 62.9 ($C_{1''}$), 56.1 ($C_{1'}$), 33.4 (C_3,C_5), 26.7 (C_{Me}), 19.1 (C_{tBu}), 17.2 (C_4); HRMS (ESI+) calcd for $C_{25}H_{31}NO_3Si$ 444.1965 [M + Na]$^+$, found 444.1957. Anal. Calcd for $C_{25}H_{31}NO_3Si$: C, 71.22; H, 7.41; N, 3.32. Found: C, 71.22; H, 7.41; N, 3.39.

(6*RS*)-1-[(1*R*)-1-(1-*tert*-Butyldiphenylsilyloxymethyl)-2-propenyl]-6-hydroxyhexahydro-2-pyridinone (18). A solution of $LiBEt_3H$ in THF (1M, 14 mL, 14 mmol) was added dropwise to a solution of **16** (3.70 g, 8.78 mmol) in dry THF (34 mL) at −78 °C, and the reaction mixture was stirred at the same temperature for 1 h. Keeping the temperature at −78 °C, saturated aqueous $NaHCO_3$ (66 mL) and H_2O_2 (16.4 mL) were added, and the mixture was allowed to warm slowly to room temperature and then stirred for an additional 1 h. After filtration through Celite, the solution was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The oily residue was purified by flash chromatography on silica gel (gradient, hexanes/ethyl acetate 9:1 to 7:3) to give a mixture of isomers **18** (3.46 g, 8.17 mmol, 93%) as a colorless oil: IR (ATR) 3391, 3072, 2956, 2857, 1619, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) isomers A (major) and B (minor) δ 7.65 (m, 4H_A + 4H_B: 4H_{PhA},4H_{PhB}), 7.42 (m, 6H_A + 6H_B: 6H_{PhA},6H_{PhB}), 6.15 (ddd, J = 17.5, 10.5, 7.2 Hz, 1H_B:$H_{2'B}$), 5.76 (ddd, J = 17.3, 10.6, 5.9 Hz, 1H_A:$H_{2'A}$), 5.28−5.15 (complex, 3H_A:$H_{2'A}$,$H_{1'A}$,OH_A), 5.15−5.03 (complex, 2H_A+3H_B:$H_{2'A}$,H_{6A},2$H_{2'B}$,H_{6B}), 4.30 (dd, J = 10.3, 9.3 Hz, 1H_B:$H_{1''B}$), 4.26 (bs, 1H_B:OH_B), 3.94 (dd, J = 11.3, 3.4 Hz, 1H_A:$H_{1''A}$), 3.82 (dd, J = 11.3, 6.0 Hz, 1H_A:$H_{1''A}$), 3.62 (dd, J = 10.3, 4.0 Hz, 1H_B:$H_{1''B}$), 2.62 (m, 1H_A:H_{3A}), 2.52 (m, 1H_B), 2.41 (m, 1H_A:H_{3A}), 2.31 (m, 1H_A:H_{3A}), 2.17 (m, 1H_B), 2.10 (m, 1H_A:H_{4A}), 2.08 (m, 1H_B), 1.92 (m, 1H_B), 1.82 (m, 1H_B) 1.73 (m, 2H_A:2H_{5A}), 1.07 (s, 9H_B:9H_{tBuB}), 1.06 (s, 9H_A:9H_{tBuA}); ^{13}C NMR (100 MHz, CDCl3) isomer A δ 170.7 (C_2), 135.7 (C_{Ph}), 135.5 (C_{Ph}), 132.8 ($C_{2'}$), 131.9 (C_{Ph}), 130.2 (C_{Ph}), 127.9 (C_{Ph}), 127.9 (C_{Ph}), 118.7 ($C_{3'}$), 75.4 (C_6), 64.9 ($C_{1''}$), 56.0 ($C_{1'}$), 32.4 (C_3), 29.5 (C_5), 26.8 (C_{Me}), 19.2 (C_{tBu}), 15.4 (C_4); HRMS (ESI+) calcd for $C_{25}H_{33}NO_3Si$ 446.2122 [M + Na]$^+$, found 446.2109.

(6*R*)-1-[(1*R*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-2-propenyl]-6-[(2*RS*)-5-oxo-3-vinyl-2,5-dihydro-2-furyl]hexahydro-2-pyridinone (*RRR*/*RRS*-21). In a 250 mL Schlenk vessel, hemiaminal **18** (1.66 g, 3.92 mmol) was dissolved in dry acetonitrile (21.6 mL) under nitrogen. The solution was cooled to 0 °C, dimethylaminopyridine (527 mg, 4.31 mmol) and acetic anhydride (1.5 mL, 15.68 mmol) were added, and the reaction mixture was kept at the same temperature for 15 min. After this time, the cooling bath was removed, and the mixture was kept at room temperature for 1 h. It was then treated with a mixture of ice and water (approx 10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and cold water (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum.

The colorless oily residue that contained hemiaminal **19** (TLC analysis) was immediately used in the next step to avoid decomposition. In a 250 mL Schlenk vessel connected to a nitrogen line, 4-vinyl-2(5*H*)-furanone (510 mg, 4.63 mmol) was dissolved in dry diethyl ether (14 mL). The solution was cooled to 0 °C, triethylamine (840 μL, 6.03 mmol) was added, and the reaction mixture was kept at the same temperature for 30 min. After this time, TIPSOTf (1.37 mL, 5.09 mmol) was slowly added; the mixture was warmed to room temperature and left until complete butenolide disappearence (basic alumina TLC analysis). Next, the solution was cooled down to −20 °C, a solution of hemiaminal **19** in acetonitrile (22 mL) and $^{n}Bu_2$-BOTf (10.1 mL, 1 M in CH_2Cl_2) were slowly added, and the reaction mixture was kept at the same temperature for 30 min. Then, it was treated with saturated aqueous $NaHCO_3$ (30 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The brownish oily residue was purified by flash chromatography on silica gel (gradient, hexanes/ethyl acetate 4:1 to 2:1) to give a 3.5:1 mixture of isomers *RRR*-**21** and *RRS*-**21** (983 mg, 1.96 mmol, 50%) as a colorless oil, a 6:1 mixture of isomers *SRS*-**21** and *SRR*-**21** (687 mg, 1.37 mmol, 35%) as a colorless oil, and a fraction with enamide **26** (65 mg, 0.16 mmol, 4%) as a colorless oil. *RRR*-**21** and *RRS*-**21**: R_f = 0.4 (hexanes/ethyl acetate 1:1); $[\alpha]^{20}_D = -25$ (*c* 1.2, $CHCl_3$); IR (ATR) 2929, 2856, 1757, 1639, 1259, 1104; ^{1}H NMR (400 MHz, CD_2Cl_2) isomers *RRR*-**21** (A, major) and *RRS*-**21** (B, minor) δ 7.65 (m, $4H_A$ + $4H_B$:$4H_{PhA}$,$4H_{PhB}$), 7.47 (m, $6H_A$ + $6H_B$:$6H_{PhA}$,$6H_{PhB}$), 6.58 (ddt, *J* = 17.8, 11.2, 0.7 Hz, 1H $_B$:H_{14B}), 6.57 (ddt, *J* = 18.5, 11.0, 0.7 Hz, $1H_A$:H_{14A}), 6.22 (ddd, *J* = 17.8, 10.4, 6.5 Hz, $1H_B$:H_{15B}), 6.21 (ddd, *J* = 17.6, 10.5, 7.3 Hz, $1H_A$:H_{15A}), 6.06 (m, $1H_B$:H_{12B}), 5.98 (bd, *J* = 1.1 Hz, $1H_A$:H_{12A}), 5.74 (d, *J* = 17.8 Hz, $1H_A$:$H_{14'A}$), 5.69 (d, *J* = 11.2 Hz, $1H_A$:$H_{14'A}$), 5.67 (d, *J* = 11.2 Hz, $1H_B$:$H_{14''B}$), 5.65 (d, *J* = 17.8 Hz, $1H_B$:$H_{14'B}$), 5.48 (m, $1H_B$:H_{9B}), 5.22 (dt, *J* = 17.8, 1.4 Hz, $1H_B$:$H_{15'B}$), 5.21 (dt, *J* = 10.4, 1.4 Hz, $1H_B$:$H_{15'B}$), 5.18 (m, $1H_A$:H_{9A}), 5.03 (dt, *J* = 10.6, 1.2 Hz, $1H_A$:$H_{15'A}$), 5.03 (dt, *J* = 17.6, 1.3 Hz, $1H_A$:$H_{15'A}$), 4.38 (dd, *J* = 10.2, 8.2 Hz, $1H_B$:H_{8B}), 4.32 (dd, *J* = 10.1, 9.1 Hz, $1H_B$:H_{8B}), 4.12 (m, $1H_A$:H_{2A}), 3.97 (m, $1H_B$:H_{2B}), 3.88 (dd, *J* = 10.2, 5.6 Hz, $1H_B$:H_{8B}), 3.70 (m, $1H_B$:H_{7B}), 3.62 (dd, *J* = 10.3, 4.7 Hz, $1H_A$:H_{8A}), 3.44 (m, $1H_A$:H_{7A}), 2.31 (m, $2H_A$ + $2H_B$:$2H_{5A}$, $2H_{5B}$), 1.97 (m, $2H_A$ + $2H_B$:H_{3A},H_{4A},H_{3B},H_{4B}), 1.85 (m, $1H_A$ + $1H_B$:H_{3A},H_{3B}), 1.70 (m, $1H_A$:H_{4A}), 1.60 (m, $1H_B$:H_{4B}), 1.07 (s, $9H_B$:$9H_{tBuB}$), 1.06 (s, $9H_A$:$9H_{tBuA}$); ^{13}C NMR (100 MHz, CD_2Cl_2) isomers *RRR*-**21** (A, major) and *RRS*-**21** (B, minor) δ 171.6 (C_{11B}), 171.2 (C_{11A}), 170.6 (C_{6A}), 170.4 (C_{6B}), 162.3 (C_{13A}), 161.8 (C_{13B}), 135.3 (C_{Ph}), 135.2 (C_{Ph}), 134.4 (C_{15A}), 134.3 (C_{15B}), 133.1 (C_{Ph}), 133.0 (C_{Ph}), 129.5 (C_{Ph}), 127.4 (C_{Ph}), 127.3 (C_{14A}), 126.9 (C_{14B}), 124.0 ($C_{14'A}$+$C_{14'B}$), 117.90 (C_{12B}), 117.87 (C_{12A}), 117.0 ($C_{15'B}$), 116.4 ($C_{15'A}$), 82.3 (C_{9A}), 81.4 (C_{9B}), 68.6 (C_{7A}), 65.1 (C_{7B}), 64.1 (C_{8A}), 63.9 (C_{8B}), 61.4 (C_{2A}), 59.3 (C_{2B}), 32.4 (C_{5B}), 31.8 (C_{5A}), 26.38 (C_{3A}), 26.36 (C_{MeA}), 26.31 (C_{MeB}), 21.3 (C_{3B}), 18.7 (C_{tBuB}), 18.6 (C_{tBuA}), 18.2 (C_{4B}), 17.2 (C_{4A}); HRMS (ESI+) calcd for $C_{31}H_{37}NO_4Si$: 538.2384 $[M + Na]^+$, found 538.2397.

(6*R*,11a*R*,11b*RS*)-6-*tert*-Butyldiphenylsilyloxymethyl-2,6,8,9,10,11,11a,11b-octahydrofuro[2,3-*c*]pyrido[1,2-*a*]azepine-2,8-dione (*RRR*/*RRS*-28). A solution of second-generation Grubbs' catalyst (46 mg, 0.054 mmol) in degassed anhydrous CH_2Cl_2 (14 mL) was slowly added to a solution of a 3.5:1 mixture of *RRR*-**21** and *RRS*-**21** (170 mg, 0.34 mmol) in degassed CH_2Cl_2 (34 mL) under argon, and the reaction mixture was stirred for 14 h at room temperature. Then, the solvent was evaporated under vacuum, and the dark brown oily residue was purified by flash chromatography (gradient, hexanes to hexanes/ethyl acetate 1:1) to furnish a 3.5:1 mixture of compounds *RRR*-**28** and *RRS*-**28** (161 mg, 0.33 mmol, 97%) as a pale brownish oil: R_f = 0.41 (hexanes/ethyl acetate 1:1); IR (ATR) 2930, 2857, 1754, 1629, 1427, 1110; ^{1}H NMR (400 MHz, C_6D_6) isomers *RRR*-**28** (A, major) and *RRS*-**28** (B, minor) δ 7.70 (m, $4H_A$ + $4H_B$:$4H_{PhA}$,$4H_{PhB}$), 7.24 (m, $6H_A$ + $6H_B$:$6H_{PhA}$,$6H_{PhB}$), 6.40 (dd, *J* = 10.1, 4.1 Hz, $1H_A$:H_{15A}), 5.92 (dd, *J* = 11.2, 5.2 Hz, $1H_B$:H_{15B}), 5.78 (d, *J* = 11.2 Hz, $1H_B$:H_{14B}), 5.75 (dd, *J* = 10.1, 2.4 Hz, $1H_A$:H_{14A}), 5.43 (bs, $1H_A$:H_{12A}), 5.36 (bs, $1H_B$:H_{12B}), 4.66 (bd, *J* = 7.9 Hz, $1H_A$:H_{9A}), 4.52 (dd, *J* = 10.0, 7.2 Hz, $1H_A$:H_{8A}), 4.38 (bd, *J* = 10.1 Hz, $1H_B$:H_{9B}), 4.32 (dd, *J* = 10.0, 6.0 Hz, $1H_A$:H_{8A}), 4.19 (dd, *J* = 8.6, 5.8 Hz, $1H_B$:H_{8B}), 4.13 (m, $1H_B$:H_{7B}), 4.08 (dd, *J* = 8.6, 5.4 Hz, $1H_B$:H_{8B}), 3.54 (ddd, *J* = 10.9, 7.9, 5.5 Hz, $1H_A$:H_{2A}), 3.42 (m, $1H_A$:H_{7A}), 2.81 (dt, *J* = 10.1, 5.0 Hz, $1H_B$:H_{2B}), 2.06−1.91 (complex, $2H_A$ + $1H_B$:$2H_{5A}$,H_{5B}), 1.68−1.46 (complex, $2H_A$ + $2H_B$:$1H_{3A}$,$1H_{4A}$,$2H_{3B}$), 1.25 (m, $1H_B$:H_{5B}), 1.16 (s, $9H_A$:$9H_{tBuA}$), 1.12 (s, $9H_B$:$9H_{tBuB}$), 1.10−0.85 (complex, $1H_A$ + $2H_B$:H_{4A},$2H_{4B}$), 0.60 (m, $1H_A$:H_{3A}); ^{13}C NMR (100 MHz, C_6D_6) isomers *RRR*-**28** (A, major) and *RRS*-**28** (B, minor) δ 171.8 (C_{11A}), 171.0 (C_{11B}), 170.0 (C_{6B}), 169.0 (C_{6A}), 164.2 (C_{13B}), 161.8 (C_{13A}), 146.3 (C_{15A}), 139.5 (C_{15B}), 136.0 (C_{Ph}), 134.0 (C_{Ph}), 133.8 (C_{Ph}), 133.6 (C_{Ph}), 130.3 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 122.7 (C_{14B}), 121.8 (C_{14B}), 117.3 (C_{12A}), 117.2 (C_{12B}), 82.1 (C_{9A}), 81.2 (C_{9B}), 65.4 (C_{8B}), 65.0 (C_{8A}), 62.8 (C_{2B}), 60.8 (C_{7B}), 59.7 (C_{7A}), 59.5 (C_{2A}), 33.3 (C_{5A}), 32.2 (C_{5B}), 27.2 (C_{Me}), 27.1 (C_{Me}), 26.4 (C_{3B}), 22.9 (C_{3A}), 19.5 (C_{tBu}), 19.4 (C_{tBu}), 18.1 (C_{4A}), 17.5 (C_{4B}); HRMS (ESI+) calcd for $C_{29}H_{33}NO_4Si$: 510.2071 $[M + Na]^+$, found 510.2062.

This reaction has been performed with quantities of *RRR*-**21** + *RRS*-**21** up to 700 mg. Yields of different runs range from 80% to >98%.

(6*R*,11a*R*,11b*RS*)-6-*tert*-Butyldiphenylsilyloxymethyl-2,6,8,9,10,11,11a,11b-octahydrofuro[2,3-*c*]pyrido[1,2-*a*]azepin-2-one (*RRR*/*RRS*-33). In a 10 mL Schlenk vessel, a 3.5:1 mixture of *RRR*-**28** and *RRS*-**28** (80 mg, 0.16 mmol) was dissolved in dry THF (3.2 mL) under nitrogen. The solution was cooled to 0 °C, a solution of $BH_3 \cdot$THF (1 M in THF, 820 μL, 0.82 mmol) was added, and the reaction mixture was kept at the same temperature for 2 h. It was then treated with 1 M NaOH, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The brownish oily residue was purified by flash chromatography (gradient, hexanes/ethyl acetate 49:1 to 1:1) to furnish a 9:1 mixture of *RRR*- and *RRS*-**33** (54 mg, 0.11 mmol, 70%) as a colorless oil, alcohol **34** (8.0 mg, 0.016 mmol, 10%) as a yellow oil, and recovered *RRR*/*RRS*-**28** (8 mg, 0.016 mmol, 10%). An analytical sample of *RRR*-**33** could by obtained by repeated flash chromatography. *RRR*-**33** and *RRS*-**33**: R_f = 0.66 (hexanes/ethyl acetate 1:1); IR (ATR) 2927, 1750, 1427, 1113; HRMS (ESI+) *m*/*z* calcd for $C_{29}H_{35}NO_3Si$ 474.2459 $[M + H]^+$, found:474.2457. *RRR*-**33**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.68 (m, 4H:$4H_{Ph}$), 7.42 (m, 6H:$6H_{Ph}$), 6.58 (dd, *J* = 12.8, 2.4 Hz, 1H:H_{14}), 6.25 (dd, *J* = 12.8, 4.1 Hz, 1H:H_{15}), 5.77 (bs, 1H:H_{12}), 5.39 (dd, *J* = 11.5, 1.7 Hz, 1H:H_9), 3.76 (dd, *J* = 11.1, 8.6 Hz, 1H:H_8), 3.73 (dd, *J* = 11.0, 7.1 Hz, 1H:H_8), 3.52 (m, 1H:H_7), 3.06 (dt, *J* = 11.8, 4.1 Hz, 1H:H_2), 2.80 (m, 1H:H_6), 2.57 (m, 1H:H_6), 1.95 (m, 1H:H_3), 1.78 (m, 1H:H_3), 1.67−1.47 (complex, 4H:$2H_4$,$2H_5$), 1.05 (s, 9H:$9H_{tBu}$); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 172.9 (C_{11}), 165.9 (C_{13}), 140.6 (C_{15}), 135.6 (C_{Ph}), 134.7 (C_{Ph}), 133.5 (C_{Ph}), 129.7 (C_{Ph}), 129.6 (C_{Ph}), 127.7 (C_{Ph}), 123.0 (C_{14}), 115.7 (C_{12}), 78.0 (C_9), 65.8 (C_8), 64.5 (C_7), 63.4 (C_2), 42.6 (C_6), 29.7 (C_3), 28.3 (C_5), 26.6 (C_{Me}), 19.1 (C_4), 18.8 (C_{tBu}). *RRS*-**33**: ^{13}C NMR (100 MHz, CD_2Cl_2), observed significant signals, δ 116.4 (C_{12}), 66.5 (C_8), 65.1 (C_2), 65.0 (C_7).

(6*R*,11a*R*,11b*RS*)-6-Hydroxymethyl-2,6,8,9,10,11,11a,11b-octahydrofuro[2,3-*c*]pyrido[1,2-*a*]azepin-2-one (*RRR*/*RRS*-35). In a 10 mL Schlenk vessel, a 9:1 mixture of *RRR*-**33** and *RRS*-**33** (40 mg, 0.085 mmol) was dissolved in THF (1.1 mL) under nitrogen, $Et_3N \cdot 3HF$ (83 μL, 0.51 mmol) was added, and the

reaction mixture was kept at room temperature for 7 h. It was then treated with saturated aqueous $NaHCO_3$ (1 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The brownish oily residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH 99:1 to 20:1) to furnish a 9:1 mixture of *RRR*- and *RRS*-**35** (17.6 mg, 0.075 mmol, 88%) as a brownish oil. R_f = 0.46 (CH_2Cl_2/acetone 7:3); IR (ATR) 3423, 2927, 1749, 1629, 1102; ^{1}H NMR (600 MHz, $CDCl_3$) *RRR*-**35** δ 6.61 (ddd, J = 11.6, 1.1, 0.4 Hz, 1H:H_{14}), 5.83 (dd, J = 0.6, 0.4 Hz, 1H:H_{12}), 5.79 (dd, J = 11.3, 3.9 Hz, 1H:H_{15}), 5.46 (bdd, J = 10.6, 1.1 Hz, 1H:H_9), 3.62−3.49 (complex, 3H:H_7,2H_8), 3.16 (ddd, J = 10.7, 3.8, 3.0 Hz, 1H:H_2), 2.82 (bs, 1H:OH), 2.78 (td, J = 11.8, 2.8 Hz, 1H:H_6), 2.68 (dt, J = 11.8, 3.9 Hz, 1H:H_6), 2.14 (dddd, J = 14.0, 6.6, 3.0, 1.4 Hz, 1H:H_3), 1.91 (m, 1H:H_3), 1.80 (m, 1H:H_5), 1.73 (m, 2H:2H_4), 1.66 (m, 1H:H_5); *RRS*-**35** observed significant signals, 6.49 (d, J = 12.4 Hz, 1H:H_{14}), 6.07 (dd, J = 12.4, 5.6 Hz, 1H:H_{15}), 5.78 (m, 1H:H_{12}), 5.50 (bd, J = 10.5 Hz, 1H:H_9); ^{13}C NMR (100 MHz, CD_2Cl_2) *RRR*-**35**, δ 172.2 (C_{11}), 164.9 (C_{13}), 137.3 (C_{15}), 124.3 (C_{14}), 116.5 (C_{12}), 77.2 (C_9), 63.7 (C_2), 63.2 (C_7), 59.8 (C_8), 53.2 (C_6), 28.1 (C_3), 25.8 (C_5), 18.9 (C_4); HRMS (ESI+) m/z calcd for $C_{13}H_{17}NO_3$ 236.1287 $[M + H]^+$, found 236.1300.

Securinine (1). In a 10 mL Schlenk vessel, a 9:1 mixture of *RRR*-**35** and *RRS*-**35** (17 mg, 0.073 mmol) was dissolved in anhydrous CH_2Cl_2 (2.6 mL) under nitrogen. The solution was cooled at 0 °C, and Et_3N (45 μL, 0.328 mmol) and MsCl (25 μL, 0.219 mmol) were added. The reaction mixture was kept at the same temperature for 30 min. It was then treated with saturated aqueous $NaHCO_3$ (1 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The brownish oily residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH 99:1 to 20:1) to furnish the mesylate as a brownish oil. R_f = 0.82 (CH_2Cl_2/acetone 7:3). Immediately, this mesylate was dissolved in dry CH_2Cl_2 (13 mL), and a solution of KHMDS in toluene (0.5 M, 200 μL, 0.10 mmol) was added at −78 °C. After being stirred for 15 min, the mixture was warmed to room temperature and stirred for an additional 45 min. The reaction mixture was then cooled again to −78 °C, and cold (0 °C) saturated aqueous $NaHCO_3$ (13 mL) was added. After the mixture was warmed to room temperature, the organic phase was decanted and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the remaining oily material was purified by flash chromatography on silica gel (gradient, hexanes/AcOEt 1:1 to AcOEt) to furnish **1** (12.6 mg, 0.058 mmol, 79%) as a yellow solid: R_f = 0.18 (ethyl acetate); $[\alpha]^{20}_D$ = −1061 (*c* 1.08, $CHCl_3$); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.59 (d, J = 9.1, Hz, 1H:H_{14}), 6.39 (dd, J = 9.1, 5.3 Hz, 1H:H_{15}), 5.49 (s, 1H:H_{12}), 3.80 (t, J = 4.6 Hz, 1H:H_7), 2.95 (dt, J = 10.5, 3.7 Hz, 1H:H_6), 2.44 (dd, J = 9.2, 4.1 Hz, 1H:H_8), 2.39 (ddd, J = 10.5, 6.5, 4.9 Hz, 1H:H_6), 2.07 (dd, J = 11.3, 2.3 Hz, 1H:H_2), 1.85 (m, 1H:H_4), 1.75 (dd, J = 9.2, 0.6 Hz, 1H:H_8), 1.62−1.54 (complex, 2H:H_3,H_5), 1.54 (dd, J = 7.6, 3.8 Hz, 1H:H_5), 1.50 (qd, J = 12.1, 3.8 Hz, 1H:H_3), 1.22 (m, 1H:H_4); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 173.1 (C_{11}), 169.9 (C_{13}), 139.9 (C_{15}), 120.9 (C_{14}), 104.5 (C_{12}), 89.1 (C_9), 62.7 (C_2), 58.5 (C_7), 48.4 (C_6), 42.1 (C_8), 27.1 (C_3), 25.8 (C_5), 24.4 (C_4).

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Supporting Information Available: Experimental procedure for the preparation of *SRS*-**28** and *SRS*-**33** and listing of their physical data; physical data of *SRS*/*SRR*-**21**, **26**, and **34**; significant ^{1}H and ^{13}C NMR spectra of new compounds and synthetic securinine, CHPLC analysis of (+)-**12**, Cartesian coordinates, and imaginary frequencies of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.