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A New General Access to Either Type of *Securinega* Alkaloids: Synthesis of Securinine and (−)-Allonorsecurinine

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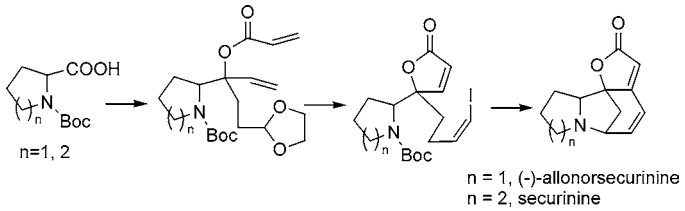
ABSTRACT



The syntheses of securinine and (−)-allonorsecurinine have been achieved starting from easily available α-amino acid derivatives and using as key steps a RCM and a Heck reaction for the formation of rings D and C, respectively.

The *Securinega* alkaloids are a group of polycyclic compounds elaborated by plants of the *Securinega* and *Phyllanthus* species belonging to the Euphorbiaceae family.[1] Most of these natural products present a tetracyclic structure formed by an α,*β*-butenolide (ring D), a 6-azabicyclo[3.2.1]-octane (rings B and C), and a piperidine or pyrrolidine (ring A) (Figure 1). According to the size of this last heterocycle, they are classified in two main groups: securinine- and norsecurinine-type alkaloids, respectively.

Securinine, **1**, was first isolated in 1956 by Russian workers[2] and its structure and absolute configuration (2*R*,9*S*) were established in the early 60's.[3] All four possible stereoisomers of **1** have been isolated from natural sources, a quite unusual fact: its epimer at C-2, allosecurinine, **2**, and the corresponding enantiomers, virosecurinine and viroallosecurinine, respectively. The isolation of (−)-norsecurinine, (−)-**3**, was first reported in 1963[4] and its absolute configuration was secured two years later.[5] Its antipode, (+)-norsecurinine, is also a natural product, but until now the other two stereoisomers of **3** were unknown.

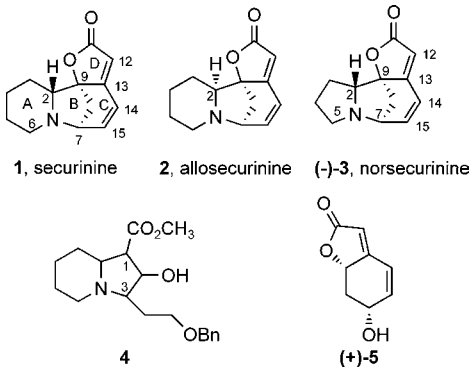


Figure 1.

Although the *Securinega* alkaloids have been known for more than four decades and even though they exhibit a large

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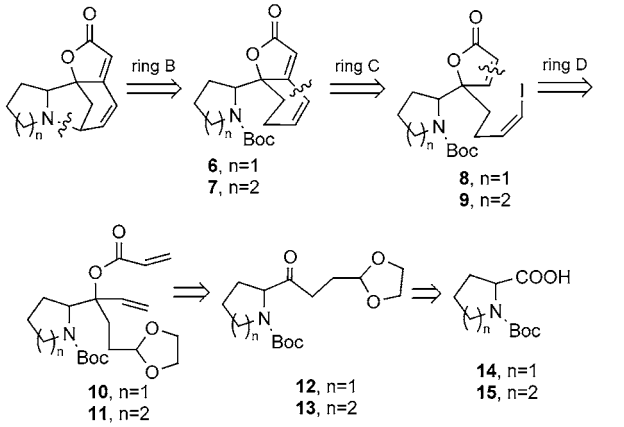
number of biological activities,[6] only a few total syntheses of some compounds of this family have been reported, and with a unique exception, they were all reported during the last two decades. Regarding norsecurinine, two racemic[7,8] and two enantioselective[6,9] syntheses have been reported, while the total synthesis of racemic securinine has been accomplished by three groups[10−12] and only very recently the first enantioselective synthesis of securinine has been described.[13] This last work has prompted us to disclose some of our results in this field.[14]

During the last few years we have been engaged in a project with the aim of developing general synthetic strategies that will allow access to both groups of *Securinega* alkaloids. One of our approaches involves the use of indolizidines **4** as key intermediates, prepared through a sequence involving the 1,3-dipolar cycloaddition of a cyclic nitrone to a nonracemic olefin.[15] A second ongoing route contemplates the intermediacy of the natural product menisdaurilide, **5**, which structure matches rings C and D of the target alkaloids. We have recently published the first synthesis of (+)- and (−)-**5**.[16] Herein we present the results of our third strategy, in close similarity to Honda's approach,[13] since it also makes use of a ring closing metathesis (RCM) for the formation of ring D.

The retrosynthetic analysis began with the disconnection of ring B, followed by the opening of rings C and D in this order (Scheme 1). Consequently, the tricyclic compounds **6** and **7**, the disubstituted α,β-butenolides **8** and **9**, and the functionalized pyrrolidine **10** and piperidine **11** were visualized as the key intermediates for the syntheses of norsecurinine- and securinine-type alkaloids, respectively. A RCM reaction of **10**/**11** followed by acetal hydrolysis and Wittig reaction would furnish the iodoolefins **8**/**9**, adequate substrates for closing ring C through a Heck reaction. Finally, formation of ring B would arise from an intramolecular nucleophilic substitution on the allylic bromo derivatives of **6**/**7**, as already described for securinine.[10,13] The required

Scheme 1. Retrosynthetic Analysis



substituents at the pyrrolidine **10** and piperidine **11** may be incorporated to the *N*-protected proline **14** and pipecolinic acid **15** via the corresponding ketones **12** and **13**, respectively, using Grignard reagents. Both enantiomers of the starting proline and pipecolinic acid derivatives are commercially available.

For the synthesis of norsecurinine-type alkaloids, we started our studies with the cheaper pyrrolidine derivative (*S*)-*N*-*tert*-butoxycarbonyl proline, (*S*)-**14**. Thus, reduction with BH_3·THF, followed by oxidation with Dess−Martin reagent afforded the commercially available aldehyde **16** in 82% overall yield (Scheme 2). The reaction of **16** with the Grignard derivative **17** furnished a mixture of diastereomeric alcohols **18**, which was submitted, without separation, to Dess−Martin oxidation giving rise to the new enantiopure ketone (*S*)-**12** in 60% overall yield. Starting from (*R*)-**14**, we have also prepared (*R*)-**12** and the optical integrity of **12** was checked by CHPLC. In the ^{1}H NMR spectrum of **12** proton H-2 displays signals at δ 4.32 and 4.20 due to the existence of both carbamate rotamers in a ratio ca. 2:3. Pairs of signals at δ ca. 209, 154, and 103 in the ^{13}C NMR spectrum evidence the presence of the ketone, the *N*-protecting group, and the ketal, respectively.

The required olefin moieties for the RCM reaction were incorporated by sequential treatment of (*S*)-**12** with vinylmagnesium bromide and acryloyl chloride in a one-pot procedure at room temperature. This reaction afforded a 6:1 mixture of both diastereomeric acrylates in 71% overall yield. The major and less polar isomer was isolated, and although the absolute configuration of the new stereocenter could not be determined by nOe experiments, it has been established as *S* on the tricyclic compound **6** (vide infra). All our attempts to improve the yield and the diastereoselectivity of this addition reaction were unsuccessful. The synthesis was continued with a RCM reaction[17] of **10**, using the Grubbs second generation catalyst **19**. The best results were obtained by consecutive addition of a 2% molar amount of catalyst

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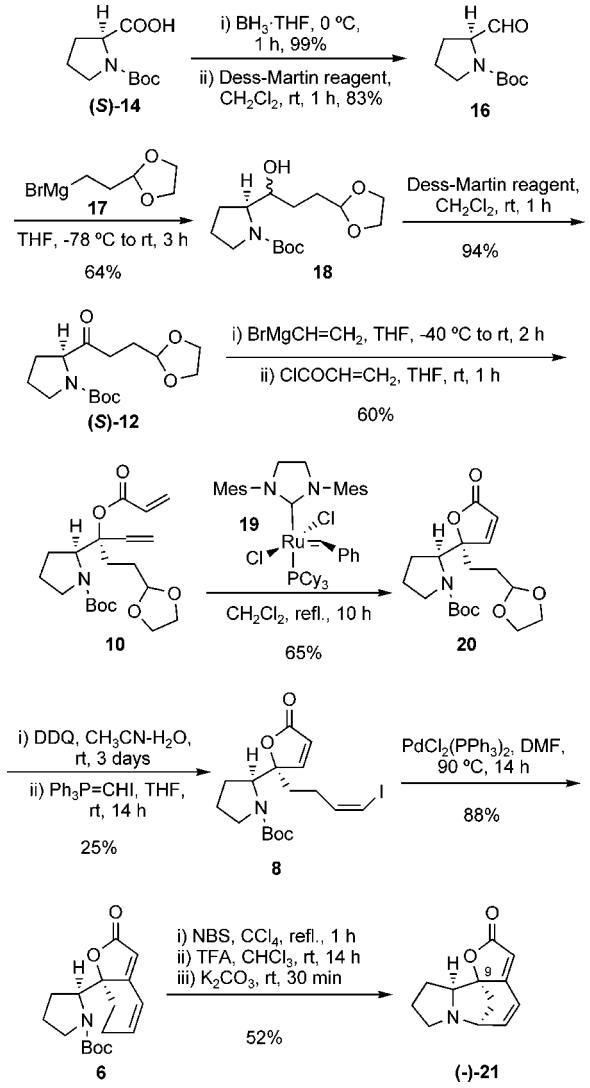
Scheme 2



every 2 h until reaching 10%. Under these conditions we isolated butenolide **20** in 65% yield. Two conformers in a ratio of 9:1 are observed in its ^{1}H NMR spectrum, with the signals at δ 173.0, 155.1, and 103.4 in the ^{13}C NMR spectrum revealing the presence of the lactone, the carbamate, and the acetal groups. The synthesis of the enantiomer of **20** has also been performed and the enantiomeric purity of either enantiomer has been established (ee >95%) by ^{1}H NMR (500 MHz) at 250 K, using europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as a chiral shift reagent.

Next, the dioxolane system was hydrolyzed by treatment with dichlorodicyanoquinone (DDQ)[18] and the resulting aldehyde was treated with iodomethylenetriphenylphosphonium iodide[19] to furnish the (*Z*)-iodoolefin **8** in 25% overall yield. Two signals in its ^{13}C NMR spectrum at δ 139.7 and 84.6 indicate the formation of the new double bond. The poor yield in the preparation of **8** is the result of the troublesome acetal hydrolysis, which has been attempted under a large series of conditions.

Closing of the ring C under Heck conditions was accomplished by reaction with dichlorobis(triphenylphosphine)-palladium(II) in the presence of sodium carbonate.[20] The new tricyclic compound **6** was isolated in 88% yield. Its NOESY spectrum shows a correlation between the α-carbonyl proton of the butenolide and the methyl groups of the carbamate function, which is only consistent with the *S* configuration of C-9 (norsecurinine numbering). Consequently, the diastereoselectivity of the Grignard reaction to **12** is opposite that required for the synthesis of norsecurinine. The stereochemical assignment of **6** was confirmed when the synthetic sequence was completed. Allylic bromination of **6** with NBS and benzoyl peroxide, removal of the carbamate group with trifluoroacetic acid (TFA), and treatment of the resulting crude material with potassium carbonate afforded a new compound, which we have denominated (−)-allonorsecurinine (−)-**21**, {[α]$_D$ −441.3 (*c* 0.3, EtOH)}, by analogy to allosecurinine, in 52% overall yield. Like norsecurinine, allonorsecurinine and most of the intermediates involved in the synthetic sequence are relatively unstable compounds.

Simultaneously, we have also undertaken the synthesis of securinine, **1**, using a parallel pathway (Scheme 3). To this end, (*R*)-(−)-*N*-*tert*-butoxycarbonyl pipecolinic acid, (*R*)-**15**, was converted into the known aldehyde **22**[21] {[α]$_D$ +49.1 (*c* 0.5, $CHCl_3$) [lit.[21] for (*S*)-**22** [α]$_D$ −45.4 (*c* 0.5, $CHCl_3$)]} in 73% yield, using the same reagents previously employed for the proline derivative. Other trials to prepare **22** with use of Swern or PCC oxidation led always to partial racemization. The reaction of **22** with the Grignard reagent **17** provided a mixture of diastereomeric alcohols **23**, which was oxidized to the unknown ketone (*R*)-**13** in 66% overall yield. We have also prepared (*S*)-**13** and the stereochemical integrity of both enantiomers (ee >95%) has been established by CHPLC. The NMR spectra of **13** show two carbamate rotamers in a ca.1:1 ratio.

Sequential treatment of ketone (*R*)-**13** with vinylmagnesium bromide and acryloyl chloride afforded an inseparable mixture of the diastereomeric acrylates **11** in a 6:1 ratio and 57% overall yield. The RCM reaction was performed as above and the butenolides **24** were obtained in 78% yield as an inseparable mixture of diastereomers in a 6:1 ratio. Treatment of **24** with DDQ followed by Wittig reaction gave rise to the (*Z*)-iodoolefins **9** in 35% overall yield, from which each stereoisomer could be separated with the major and more polar being obtained in 28% yield. Although the absolute configuration of this isomer could not be established by nOe experiments, it was later assigned as (2*R*,2′*S*) according to the synthesized natural product (vide infra). When (2*R*,2′*S*)-**9** was submitted to the Heck reaction under the above-mentioned conditions, the known tricyclic com-

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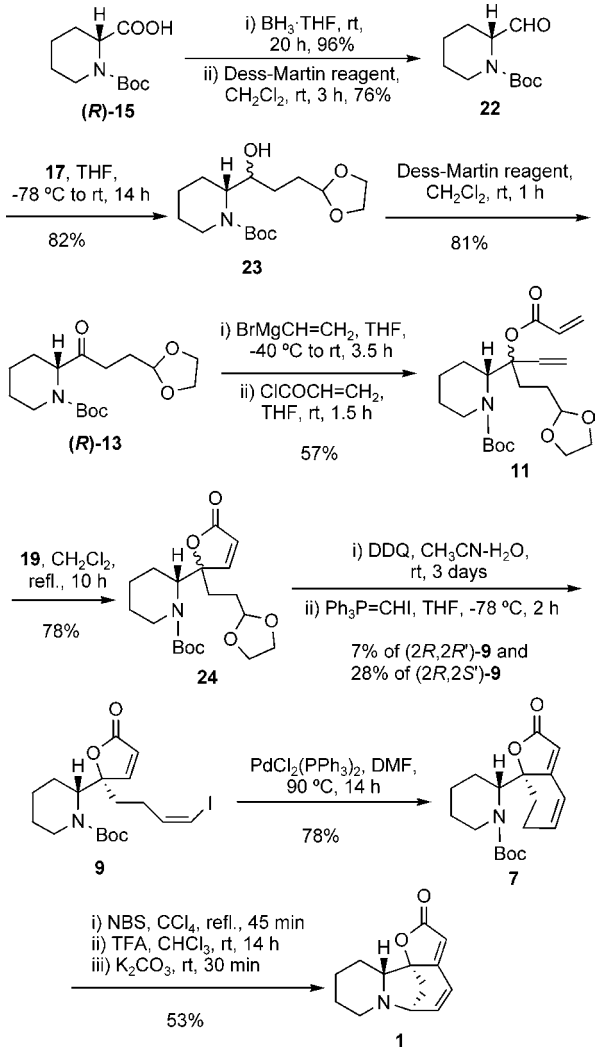
Scheme 3



pound **7**[13] {[α]$_D$ −14.1 (*c* 0.26, $CHCl_3$) [lit.[13] [α]$_D$ −12.5 (*c* 1.00, $CHCl_3$)]} was isolated in 78% yield. This fact indicates that the addition of the Grignard reagent occurs mainly at the *re* face of the piperidinyl ketone **13**, in strong contrast with the facial selectivity observed in the analogous addition to the pyrrolidinyl ketone **12**. The addition of the Grignard reagent follows the Felkin−Anh model for **13**, in which the molecular models show a clear steric hindrance of the carbamate group to the attack from the *si* face. By contrast, in the case of ketone **12**, the attack from the *si* face is not sterically hindered by the carbamate group and one of the pyrrolidine H-3 protons might hinder the *re* approach. Finally, the total synthesis of the target alkaloid was accomplished by sequential allylic bromination of **7**, removal of the carbamate group, and basic treatment with potassium carbonate. These conditions, very similar to those reported by Honda et al.,[13] yielded securinine, **1**, in 53% overall yield {[α]$_D$ −1042 (*c* 1.0, $CHCl_3$) [lit.[10] [α]$_D$ −1045 (*c* 1, EtOH)}; lit.[13] [α]$_D$ −1082 (*c* 1.0, $CHCl_3$)]}.

In conclusion, a new and general strategy for the synthesis of either type of *Securinega* alkaloids has been developed by using a RCM and a Heck reaction for the formation of rings D and C, respectively. Securinine and the hitherto unknown (−)-allonorsecurinine have been synthesized with this approach. Work is in progress in our laboratories to achieve a synthesis of norsecurinine through a similar sequence and opening new synthetic routes to this family of alkaloids.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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