ORGANIC LETTERS

2005
Vol. 7, No. 22
5107−5109

An Effective Enantioselective Approach to the Securinega Alkaloids: Total Synthesis of (–)-Norsecurinine

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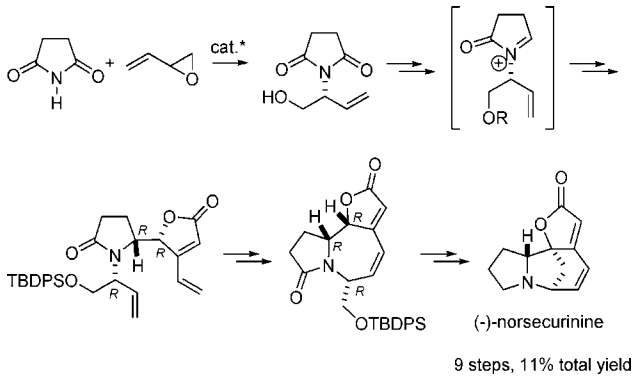
Received September 13, 2005

ABSTRACT



A highly versatile approach to the enantioselective synthesis of securinega alkaloids is presented. Crucial steps are a palladium-catalyzed enantioselective imide alkylation, a vinylogous Mannich reaction, and a ring-closing metathesis process. Through this strategy, the synthesis of (–)-norsecurinine has been accomplished in nine steps and 11% overall yield.

The securinega alkaloids comprise a group of more than 20 tetracyclic compounds produced by some plants of the *Securinega*, *Phyllanthus*, *Margaritaria*, and *Brenia* species, belonging to the Euphorbiaceae family,[1] which have been used for years in traditional folk medicine in China and the Amazonia.[2] Typically, the skeleton of securinega alkaloids (Figure 1) 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. Securinine (**1**) was the first isolated and is the major securinega alkaloid.[3] Its enantiomer, virosecurinine, and their epimers at C2, allosecurinine (**2**) and viroallosecurinine, have also been isolated from natural sources. (−)-Norsecurinine (**3**), the first isolated and most representative member of its subgroup, and its antipode are also both naturally occurring.[4] Herein, we describe an enantioselective synthesis of (−)-**3**, through a highly efficient route, that enables the preparation of either enantiomer of

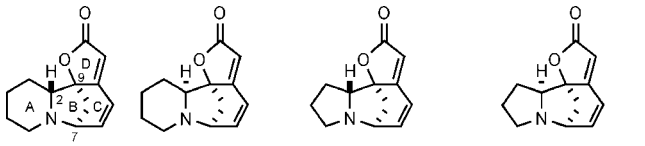


Figure 1. Representative examples of securinega alkaloids.

(1) For a review, see: Snieckus, V. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 425−503.

(2) (a) van der Woerd, L. A. *Genneskd. Tijdschr. Ned.-Indie* **1941**, *81*, 1963−1980. (b) Serra, R. M. *An. Univ. Santo Domingo* **1944**, *8*, 295−297.

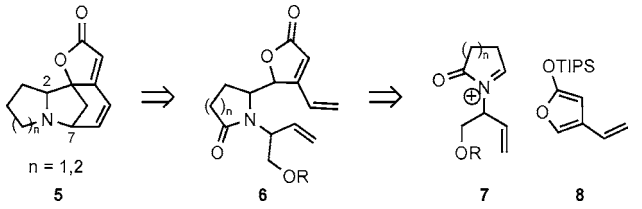
10.1021/ol0522079 CCC: $30.25
Published on Web 10/01/2005

the alkaloid and can be extended to the securinine-type subgroup.

The securinega alkaloids have been associated with a number of biological activities, some of which are well documented. Securinine (**1**) is a stimulant of the central nervous system[5] and has shown antimalarial and antibacterial activities.[6] Several securinega alkaloids act also as antitumor agents.[7] Despite their attractive potential as pharmacological agents, published synthetic investigations related to these alkaloids are quite limited. Racemic securinine was synthesized by Horii et al. a few years after its isolation,[8a] and much more recently, two additional total syntheses[8b,c] and one formal synthesis[8d] were reported. Very recently, two rather similar stereoselective syntheses of **1** have been described by the Honda group and by our group.[9] Both sequences start from (*R*)-pipecolinic acid, which determines the configuration of C2 in **1**. When we performed an analogous sequence starting from (*S*)-proline, we ended up with (−)-allonorsecurinine (**4**), a previously unknown epimer at C2 of (−)-norsecurinine (**3**). The same starting material was used by Heathcock et al. in the first reported successful synthesis of (±)-**3**[10] and by Jacobi and co-workers in the first preparation of (−)-**3**.[11] The groups of Magnus and Weinreb have described alternative successful approaches to (±)-**3** and to (−)-**3**, respectively.[6a,12]

During the past few years, we have been trying to develop new, general strategies for the synthesis of both types of securinega alkaloids. Scheme 1 shows the retrosynthetic analysis for one of the investigated approaches, where key steps are a vinylogous Mannich reaction between an iminium cation **7** and a silyloxyfuran **8**, which would, respectively, provide rings A and D of the alkaloid and a ring-closing

Scheme 1



metathesis (RCM) reaction, which would furnish the seven-membered cycle embracing rings B and C. The stereogenic center of **7** should afford the configuration at C7 in the alkaloid, while the diastereoselectivity of its addition to **8** would determine the relative configuration at C2. Therefore, the main concerns of our investigations were as follows: preparing a suitable precursor of **7** in enantiopure form and getting good steric control in the vinylogous Mannich reaction.

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 some chiral phosphine ligands.[13] Inspired by this work, we investigated the reaction between succinimide (**9**) and epoxide **10** under similar conditions (Scheme 2), and after extensive experimentation, we isolated the alkylated product **11** in 91% yield and 87% ee. We tentatively assigned the *R* configuration to the major enantiomer, by analogy to the phthalimide analogue obtained in the presence of the same ligand. Alcohol **11** was converted into the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether **12**, which upon crystallization in 2-propanol afforded a highly enantiomerically enriched material (>98% ee) in 81% yield from **9**. Reduction of **12** with lithium triethylborohydride furnished a mixture of the epimeric aminals **13** in 87% yield. Triisopropylsilyloxyfuran **8** was prepared in 97% yield from 4-vinyl-2(5*H*)-furanone.[14] Then, the crucial vinylogous Mannich reaction[15] was investigated, and we found that the reaction was best accomplished with 1.2 equiv of **8**, in ether at 0 °C, in the presence of $BF_3 \cdot Et_2O$. Under these conditions, ^{1}H NMR analysis of the crude reaction material evidenced the full conversion of **13** and the formation of a clean mixture of diastereomeric products **14**. All attempts to separate these isomers by chromatography led to complex mixtures of decomposition products, but on standing at room temperature overnight, the major isomer **14a** crystallized and could be separated from the mixture by filtration in 51% yield.

The relative configuration of **14a**−**d** could be established by performing a RCM[16] experiment with the crude reaction material containing the mixture of all the isomers. The olefins

(3) Isolation: (a) Murev'eva, V. I.; Ban'kovskii, A. I.; *Dokl. Akad. Nauk SSSR* **1956**, *110*, 998−1000. Structural assignment: (b) Satoda, I.; Murayama, M.; Tsuji, Y.; Yoshii, E. *Tetrahedron Lett.* **1962**, 1199−1206. (c) Saito, S.; Kotera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085−2099. (d) Horii, Z.; Ikeda, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Kodera, K. *Tetrahedron* **1963**, *19*, 2101−2110. Absolute configuration: (e) Imado, S.; Shiro, M.; Horii, Z.; *Chem. Ind. (London)* **1964**, 1691.

(4) Isolation and structural assignment of (−)-norsecurinine: (a) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. Pharmacol*. **1963**, *15*, 810−815. Absolute configuration: (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull*. **1965**, *13*, 786−796. Isolation of (+)-norsecurinine: (c) Rouffiac, R.; Parello, J. *Plant. Med. Phytother.* **1969**, *3*, 220−223.

(5) Beutler, J. A.; Karbon, E. W.; Brubaker, A. N.; Malik, R.; Curtis, D. R.; Enna, S. J. *Brain Res.* **1985**, *330*, 135−140.

(6) See references in: (a) Han, G.; LaPorte, M. C.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293−6306. (b) Kammler, R.; Polborn, K.; Wanner, K. Th. *Tetrahedron* **2003**, *59*, 3359−3368.

(7) Tatematsu, H.; Mori, M.; Yang, T.-H.; Chang, J.-J.; T. Lee, T.-Y.; Lee, K.-H. *J. Pharm. Sci.* **1991**, *80*, 325−327.

(8) (a) Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Shigematsu, N.; Kotera, K.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N. *Tetrahedron* **1967**, *23*, 1165−1174. (b) Xi, F. D.; Liang, X. T. *Acta Pharm. Sin.* **1992**, *27*, 349−352. (c) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703−706. (d) Honda, T.; Namiki, H.; Kudoh, M.; Nagase, H.; Mizutani, H. *Heterocycles* **2003**, *59*, 169−187.

(9) (a) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87−89. (b) Alibés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813−1816.

(10) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75−78. This synthesis rendered racemic **2** due to racemization of an intermediate.

(11) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384−5392. This paper describes the independent preparation of (+)- and (−)-**3**, starting from L- and D-proline, respectively.

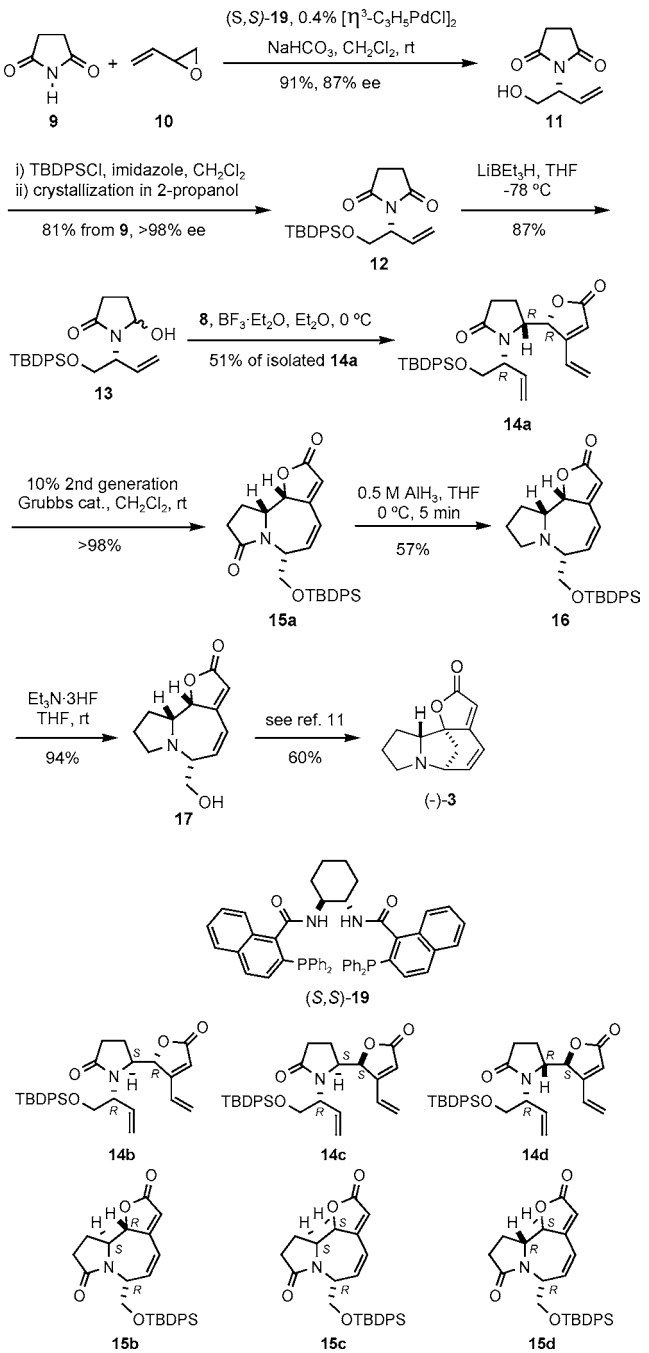
(12) Magnus, P.; Rodríguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059−8072.

(13) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968−5976.

(14) Lattmann, E.; Hoffmann, H. M. R. *Synthesis* **1996**, 155−163.

(15) (a) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773−5776. For a recent review, see: (b) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904.

Scheme 2. Enantioselective Synthesis of (−)-Norsecurinine ((−)-**3**)



15a−**d** could be chromatographically separated in three fractions (**15a**, **15b** + **15c**, and **15d**) and their configuration determined with the help of nOe experiments. We were delighted to discover that the major diastereomer **15a** presented the same relative configuration at C2 and C7 as norsecurinine. When the RCM reaction was applied to the crystallized isomer **14a**, the expected diene **15a** was isolated in nearly quantitative yield. 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. Conversion of **15a** into the corresponding thiolactam, followed by treatment with Raney nickel or other reducing agents, ended up with decomposition products, but direct reduction of the lactam with freshly prepared aluminum hydride[17] allowed the isolation of **16** in 57% yield. Other standard desilylation protocols applied to **16** failed, but the free alcohol **17** was obtained in good yield by reaction of **16** with an excess of $Et_3N{\cdot}3HF$ in THF at room temperature.

Alcohol **17** is the penultimate intermediate in the synthesis of (−)-norsecurinine published by Jacobi et al., who converted it into the alkaloid by mesylation and subsequent treatment with potassium bis(trimethylsilyl)amide in 60% overall yield,[11] but an optical rotation value for **17** was not given. Therefore, to assess the absolute configuration of our synthetic material we completed the synthesis of the alkaloid according to Jacobi's protocol. The yields were satisfactorily reproduced and we obtained the levorotatory enantiomer of norsecurinine, [α] = −270 (*c* 0.20, EtOH) [lit.[4b] [α] = −270 (*c* 6.9, EtOH)].

In summary, we have completed a new synthesis of (−)-norsecurinine in nine steps and 11% total yield. The three crucial steps of this synthesis (enantioselective allylic alkylation of succinimide, vinylogous Mannich reaction, and RCM) have been performed in a synthetically useful scale (more than 500 mg). Since the enantioselectivity was originated by the phosphine ligand (*S*,*S*)-**19**, the antipode of which is equally available, the same route gives access to (+)-norsecurinine. For the preparation of securinine, a parallel sequence starting from glutarimide is currently under study.

Acknowledgment. We acknowledge financial support from DGES (BQU2001-2600) and CIRIT (2001SGR00178) and grants from DGR (to E.G.-G.), MEC (to D.G.-G), and AUR (to P.B.).

Supporting Information Available: Experimental procedures, listing of spectral data, and ^{1}HNMR spectra of compounds **12**, **14a**, **15a**, **16**, **17**, and (−)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0522079

(16) For recent reviews, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140.

(17) (a) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464−1472. (b) Giraud, L.; Huber, V.; Jenny, T. *Tetrahedron* **1998**, *54*, 11899−11906.