First Diastereoselective Chiral Synthesis of (–)-Securinine
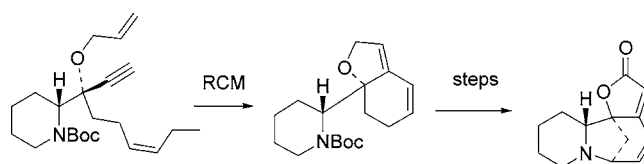
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ABSTRACT

A diastereoselective total synthesis of securinine in optically pure form was achieved by employing ring-closing metathesis of the corresponding dienyne compound as a key step.

Naturally occurring Securinega alkaloids, such as securinine **1**, virosecurinine **2**, allosecurinine **3**, and viroallosecurinine **4**, with their wide range of structural and stereochemical features, continue to provide challenging synthetic targets,[1] since these alkaloids exhibit attractive biological activities.

Securinine **1**, embodying the basic structural features of this class of alkaloids, was first isolated from *Securinega suffruticasa* in 1956.[2] Its structure (Figure 1) was determined
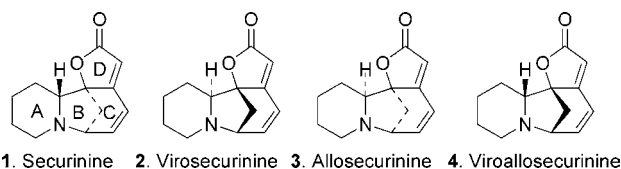

1. Securinine **2.** Virosecurinine **3.** Allosecurinine **4.** Viroallosecurinine

Figure 1.

by chemical and spectroscopic studies in 1963,[3] and later verified by X-ray crystallography in 1965.[4] It contains an indolizidine skeleton that forms part of an azabicyclo[3.2.1]-octane system fused onto an α,β-unsaturated γ-lactone ring.

This alkaloid has been clinically used in Russia as a CNS stimulating drug,[5] acting as a stereospecific antagonist at the GABA binding site of the GABA$_A$–receptor complex.[6] Since it would appear to be a fairly rigid molecule with a well-defined geometry, this alkaloid might aid in understanding the shape of the GABA$_A$ receptor site.[6]

Due to its interesting biological activities, a number of total and formal syntheses have appeared[7] for racemic securinine including the first total synthesis by Horii et al.[8] However, no asymmetric synthesis has so far been achieved.[9]

(1) Snieckus, V. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 425–503 and references therein.

(2) Murav'eva, V. I.; Ban'kovskii, A. I. *Dokl. Acad. Nauk SSSR* **1956**, *110*, 998–1000.

(3) (a) Saito, S.; Kotera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085–2099. (b) Horii, Z.; Ikeda, M.; Sugimito, N.; Tamura, Y.; Saito, S.; Kotera, K. *Tetrahedron* **1963**, *19*, 2101–2110. (c) Sakoda, I.; Maruyama, M.; Tsuji, J.; Yoshii, E. *Tetrahedron Lett.* **1962**, 1199–1206. (d) Parello, J.; Melera, A.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1963**, 898–910. (e) Chen, S.-F.; Hsieh, C.-H.; Liang, H.-T. *Yaoxue Xuebao* **1963**, *10*, 225–236. (f) Nakano, T.; Yang, T. H.; Terao, S. *Tetrahedron* **1963**, *19*, 609–619. (g) Nakano, T.; Yang, T. H.; Terao, S. *J. Org. Chem.* **1963**, *28*, 2619–2621.

(4) Imado, S.; Shiro, M.; Horii, Z. *Chem. Pharm. Bull.* **1965**, *13*, 643–651.

(5) *Russian Pharmacopeia*, 10th ed.; Ministry of Health of the USSR: Moscow, 1968; pp 612–614.

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

(7) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703–706 and references therein.

(8) 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.

(9) Recent approach to asymmetric synthesis of securinega alkaloids, see: (a) Wanner, K. Th. *Eur. J. Pharm. Sci.* **1994**, *2*, 62–64. (b) Kammler, R.; Polborn, K.; Wanner, K. Th. *Tetrahedron* **2003**, *59*, 3359–3368 and references therein.

Recently, we became involved in the synthesis of this alkaloid, and successfully accomplished a formal synthesis where an intramolecular Diels−Alder cycloaddition was exploited as a key reaction.[10]

As part of our continuing effort to synthesize and study the biological activity of compounds related to important CNS stimulating drugs, we aimed at developing a new and improved general strategy for obtaining securinine and its relatives in optically active form.

In our retrosynthetic scheme, (+)-pipecolinic acid was chosen as the starting material; its chirality would be transferred to the quaternary carbon center of (−)-securinine as shown in Scheme 1. For forming the conjugated diene system

Scheme 1. Retrosynthetic Analysis
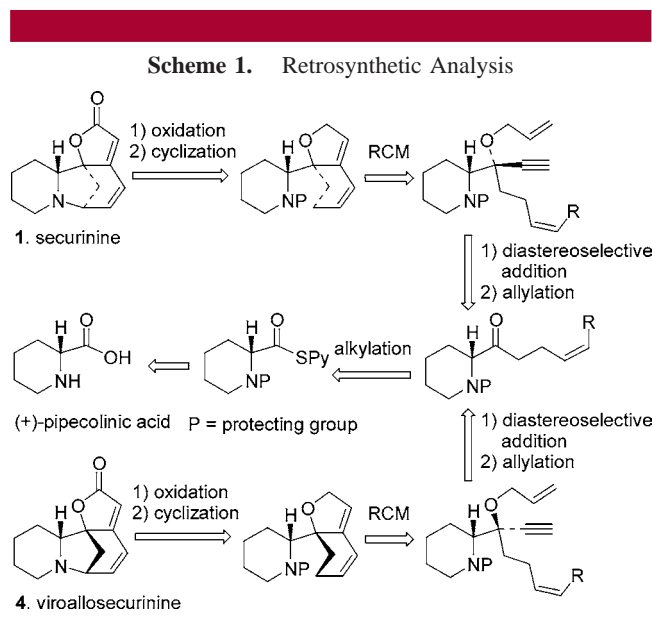
we intended to exploit a tandem ring-closing metathesis (RCM) of a dienyne system as a key reaction,[11] and allylic oxidation and ring closure would complete the sequence.

Thus, the optically active thioester **5**[12] was treated with 3-butenylmagnesium bromide to give ketone **6**, which, on treatment with lithium trimethylsilylacetylide in the presence of cerium(III) chloride, gave tertiary alcohol **7** as the sole product. The observed stereoselectivity was rationalized by assuming that the addition of the lithium reagent to **6** would proceed via the Felkin−Anh model. After deprotection of the silyl group with tetrabutylammonium fluoride, the resulting alkyne **8** was further transformed into ester **9** by acylation with acryloyl chloride. Attempted RCM of ester **9** with the highly active ruthenium catalyst (**A**),[13] however,

afforded the δ-lactonic compound **10** instead of the desired compound, where a ruthenium carbene complex generated from the terminal alkene in the butenyl group reacted with alkyne prior to the olefin in the α,β-unsaturated ester.

Scheme 2[a]
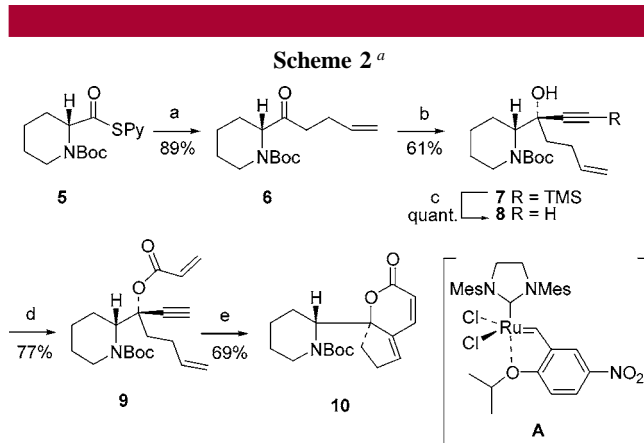
[a] Reaction conditions: (a) 3-butenylmagnesium bromide, THF, 0 °C; (b) n-BuLi, CeCl₃, trimethylsilylacetylene, THF −78 °C; (c) TBAF, THF, rt; (d) acryloyl chloride, EtMgBr, THF −78 °C; (e) catalyst **A**, CH₂Cl₂, rt.

Thus, we focused our attention on the introduction of a less reactive alkene moiety into **5**. Treatment of **5** with 3(Z)-hexenylmagnesium bromide gave ketone **11**, which, on alkynylation with lithium trimethylsilylacetylide in the presence of a stoichiometric amount of cerium(III) chloride as described above, provided tertiary alcohol **12** as the sole product via the Felkin−Anh model. By way of contrast, the addition of lithium trimethylsilylacetylide to amine **13**, derived from ketone **11** by acid treatment, afforded the chelation-controlled product **14**,[14] as expected.

It is noteworthy that the construction of the desired stereochemistry at the quaternary carbon center for both securine and viroallosecurinine can easily be achieved from the same starting material depending on the substituents on the piperidine nitrogen.

Two RCM strategies were investigated for obtaining securinine. In the first we investigated the RCM of the α,β-unsaturated ester **17**, derived from **15** by acylation with acryloyl chloride. For this, catalyst **A** was employed. However, none of the desired product could be isolated under a range of reaction conditions, presumably due to the presence of a less reactive conjugated ester function. We, therefore, turned our attention to employing a more reactive allyl ether as the precursor for RCM.

Although difficulties were initially encountered in the O-allylation of **15**,[15] we did eventually find that the reaction of **15** with allyl trichloroacetimidate[16] afforded the desired allyl ether **16** in fairly good yield. The diastereomeric

(10) Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2000**, *41*, 5927−5930.

(11) For reviews on enyne metathesis, see: Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. For other reviews on metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Trunka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (e) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945−950.

(12) Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem.* **1998**, *41*, 591−601.

(13) Grela, K.; Harutyunyan, S.; Michrewska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4039−4040.

(14) Tramontini, M. *Synthesis* **1982**, 604−644.

(15) O-Allylation of **15** with allyl bromide under basic conditions afforded the corresponding oxazolidinone arising from the reaction of tertiary alcohol with a Boc group.

Scheme 3 [a]
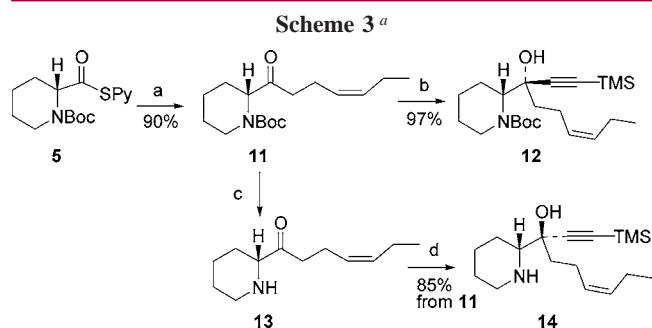
[a] Reaction conditions: (a) (Z)-3-hexenylmagnesium bromide, THF, 0 °C; (b) n-BuLi, CeCl₃, trimethylsilylacetylene, THF −78 °C; (c) TFA, CH₂Cl₂, 0 °C; (d) trimethylsilylacetylene, n-BuLi, THF, −78 °C.

N-acetyl allyl ether **19** was also prepared from **14**, via **18**, by employing the same procedure as above (Scheme 4).

Scheme 4 [a]
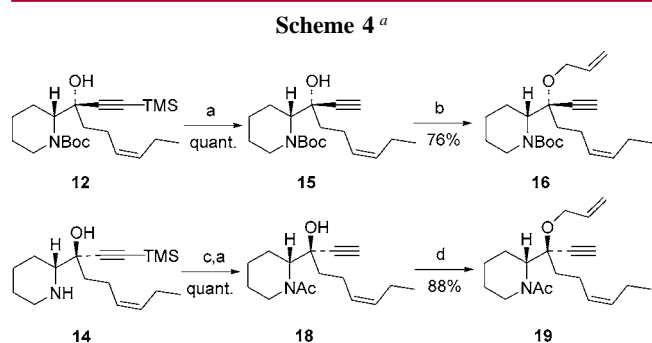
[a] Reaction conditions: (a) TBAF, THF, 0 °C; (b) CH₂=CH-CH₂OC(=NH)CCl₃, TfOH, CH₂Cl₂, rt; (c) Ac₂O, Et₃N, CH₂Cl₂, rt; (d) NaH, allyl bromide, THF−HMPA, rt.

The tandem RCM of **16** was again conducted with the highly active ruthenium catalyst (**A**) in dichloromethane at room temperature; it afforded the cyclized compound **20**, in 74% yield. Thus, the stereoselective construction of the A, C, and D rings of securinine was achieved in a relatively short sequence.

To accomplish the total synthesis of securinine, diene **20** was oxidized at the allylic position with chromium trioxide and 3,5-dimethylpyrazole at −20 °C to provide lactone **21**. Finally, allylic bromination of **21** with NBS and AIBN,[17] followed by removal of the protecting group with TFA and subsequent cyclization of the resulting amino

(16) (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240−1241. (b) Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247−2250.

(17) The stereochemistry of the bromide could not be determined at this stage, unfortunately. However, the following cyclization of allylic bromide would be assumed to proceed with both S$_N$2 and S$_N$1-like reaction mechanisms. Thus, we used the crude material in the next reaction as reported previously: see refs 7 and 8.

bromide with potassium carbonate furnished (−)-securinine **1**, mp 142−143 °C (n-hexane) (lit.[18] mp 139−141 °C; lit.[7] mp 143−144 °C). The spectroscopic data of **1** including optical rotation {[α]$_D$ −1082 (c 1.0, CHCl₃) {lit.[2] [α]$_D$ −1106 (CHCl₃)} were identical with those reported.[3] Thus, we were

Scheme 5 [a]
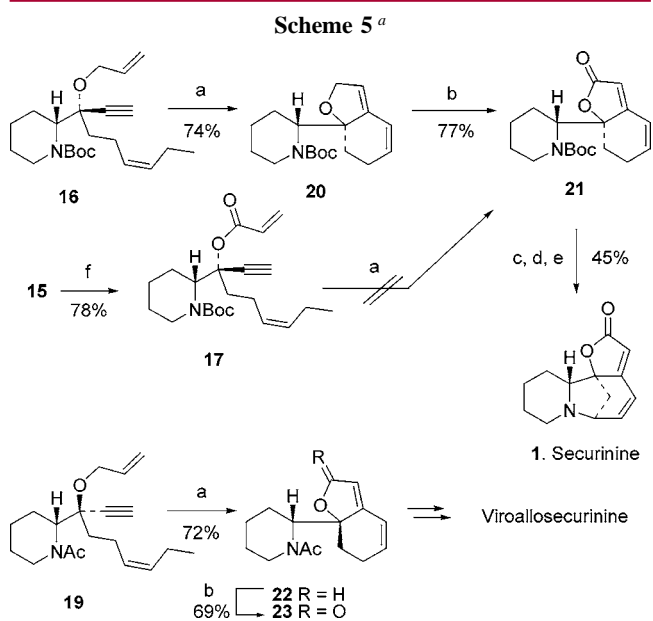
[a] Reaction conditions: (a) catalyst **A**, CH₂Cl₂, rt; (b) CrO₃, 3,5-dimethylpyrazole, CH₂Cl₂, −20 °C; (c) NBS, AIBN, CCl₄, reflux; (d) TFA, CH₂Cl₂, rt; (e) K₂CO₃, THF; (f) acryloyl chloride, EtMgBr, THF −78 to 0 °C.

able to establish a facile synthetic route to the *Securinega* alkaloids, and this is the first synthesis of optically pure securinine.

The diastereomeric N-acetyl tertiary alcohol **18**[19] was also converted into lactone **23**, a potential intermediate for the synthesis of viroallosecurinine, via the allyl ether **19** and the diene **22**, by adopting the same procedures as described above.

In conclusion, we have completed a facile chiral synthesis of (−)-securinine by using a tandem RCM reaction on a dienyne derivative as a key step. This strategy should be applicable to the synthesis of other *Securinega* alkaloids, and this is currently under investigation.

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

OL0361251

(18) Krivut, B. A.; Perel'son, M. E. *Khim.-Farm. Zh.* **1967**, *1*, 44−46.

(19) To investigate RCM for the diastereomerical compound, a readily accessible racemic N-acetyl compound **18** was employed.