Concise Enantiospecific Synthesis of a Coccinellied Alkaloid, (–)-Adalinine
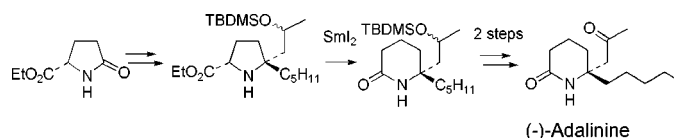
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ABSTRACT

An enantiospecific synthesis of a coccinellied alkaloid, (–)-adalinine, was established starting from (*S*)-(–)-pyroglutamic acid, where a stereoselective Michael addition and a samarium iodide-promoted regioselective carbon–nitrogen bond cleavage reaction were involved as the key reactions.

(−)-Adalinine **1**, a simple piperidine alkaloid with a chiral quaternary carbon center, was isolated from the secretion of the European two-spotted ladybird beetle, *Adalia bipunctata*, as a minor component, together with major alkaloid (−)-adaline **2**, and the structure of **1** was determined by spectroscopic methods.[1] This alkaloid was shown to be present in all of the life cycle stages of *Adalia bipunctata*, as well as in the adults of a related species, *A. decempunctata*.[1] Adalinine **1** has also been proposed to be biosynthetically derived from the major alkaloid adaline via a retro-Mannich reaction.[1]

(-)-Adalinine **1**   (-)-Adaline **2**
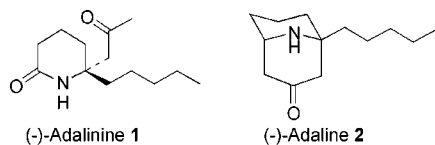
The relatively simple alkaloid **1** seems to be the target molecule for the application of newly developed synthetic methods and strategies. Consequently, one chiral synthesis[2]

of **1** leading to the determination of its absolute configuration and two syntheses of its racemate[3] have so far been reported.

Recently we have developed a general carbon−nitrogen bond cleavage reaction of α-amino carbonyl compounds by using samarium iodide as a one-electron reducing agent, as shown in Figure 1.[4]
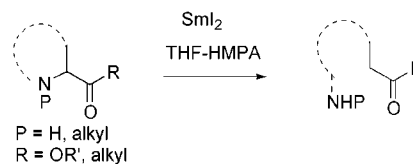

Figure 1. Deamination reaction of α-amino carbonyl compounds.

Because this fragmentation reaction seems to be widely applicable to the synthesis of various types of alkaloids, we planned its utilization for the synthesis of (−)-adalinine.[5]

(1) Lognay, G.; Hemptinne, J. L.; Chan, F. Y.; Gasper, CH.; Marlier, M.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Nat. Prod.* **1996**, *59*, 510.

(2) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739.

(3) (a) Broeders, F.; Braekman, J. C.; Daloze, D. *Bull. Soc. Chim. Belg.* **1997**, *106*, 377. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Synlett* **1999**, 37.

(4) Honda, T.; Ishikawa, F. *Chem. Commun*. **1999**, 1065.

(5) For a recent review of the coccinellied alkaloids, see: King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105.
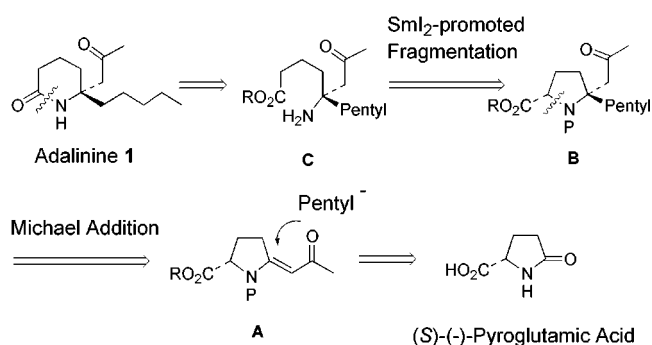
Figure 2. Retrosynthetic route to (−)-adalinine.

The retrosynthetic route to (−)-adalinine is depicted in Figure 2, in which we envisaged that a chiral quaternary carbon center could be constructed with the desired stereochemistry via Michael addition of a pentyl group to enaminone **A**, readily accessible from (S)-(−)-pyroglutamic acid, by the control of the stereochemistry of the ester function on the pyrrolidine ring. Moreover, a ring enlargement of pyrrolidine derivative **B** to δ-lactam would easily be achieved by application of a samarium-promoted fragmentation reaction,[4] followed by recyclization of the resulting amino ester **C**.

Thus, the requisite optically active pyrrolidine derivative bearing a chiral quaternary carbon center was prepared as follows. Treatment of thiolactam **3**, derived from ethyl (S)-(−)-pyroglutamate **2** with phosphorus pentasulfide[6] and bromoacetone and subsequent desulfurization of thioether **4** with triphenylphosphine[7] gave (Z)-enaminone **5**. The stereochemistry of the olefin was assumed to be Z by observation of an absorption at 1630 cm^{-1} for an intramolecular hydrogen bond between the enaminone carbonyl and NH groups in its IR spectrum. This fact was already reported by Eschenmoser.[7] After protection of the amino group of **5** as a carbamoyl group, (E)-Boc-enaminone **6** was subjected to Michael addition with pentylmagnesium bromide in the presence of a copper sulfide−dimethyl sulfide complex[8] to provide the desired pyrrolidine **7** in 87% yield. Although the stereochemistry of the newly generated chiral center could not be determined at this stage, it was assumed that the major product **7** should have the correct stereochemistry for natural product synthesis, since Michael addition of a pentyl group would be expected to take place from the less hindered side of enaminone **6**.

With the desired pyrrolidine derivative available, we first investigated a samarium-promoted carbon−nitrogen bond cleavage reaction for keto ester **7** or its de-Boc derivative; however, the reactions were found to be sluggish. We thought

that this result might be caused by the presence of another reactive site, such as a ketone carbonyl function. Ketone **7** was, therefore, reduced with NaBH$_4$ to give alcohol **8** as an inseparable diastereoisomeric mixture (ca. 1:1).

After deprotection of the Boc group on treatment with TFA, the resulting alcohol **9** was further converted to silyl ether **10** in the usual manner (Scheme 1). Attempted

Scheme 1
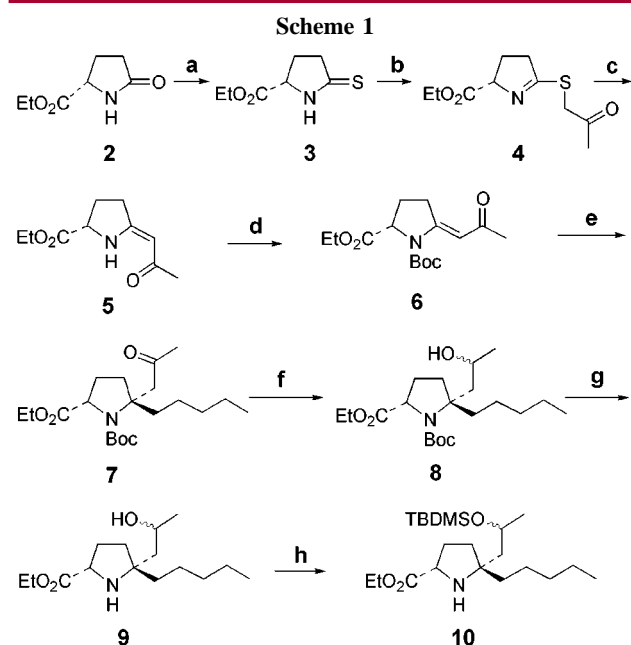
(a) P$_4$S$_{10}$, THF, reflux, 87%; (b) BrCH$_2$COCH$_3$, CH$_2$Cl$_2$, 93%; (c) Ph$_3$P, N-methylpiperidine, benzene, reflux, 69%; (d) (Boc)$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 97%; (e) C$_5$H$_{11}$MgBr, CuBr·SMe$_2$, BF$_3$·OEt$_2$, THF, -78°C, 87%; (f) NaBH$_4$, EtOH, 0°C, 100%; (g) TFA, CH$_2$Cl$_2$, 95%; (h) TBDMSCl, DMAP, CH$_2$Cl$_2$, 91%.

fragmentation reaction of **10** with 5 equiv of samarium iodide in THF−HMPA (7:1) in the presence of pivalic acid as a proton source brought about the carbon−nitrogen bond cleavage smoothly, and simultaneous cyclization of the resulting δ-amino ester to give the desired δ-lactam **11** in 70% yield.[9] In our previous study on this fragmentation reaction,[4] a cosolvent HMPA usually required only 5 equiv; however, it was found that the use of a smaller amount of HMPA or its absence in the conversion of **10** to **11** decreased the yield, remarkably. The exact reason for this observation is still obscure at the present time; however, the presence of the disubstituents at the α-position to an amino group may have some effect on this reaction.

Finally, desilylation of **11** on acid hydrolysis with hydrochloric acid, followed by oxidation of the resulting alcohol **12** with TPAP and NMO according to the reported procedure[2] (Scheme 2) gave (−)-adalinine **1**, whose spectroscopic

(6) Peterson, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.

(7) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(8) For Michael addition of Grignard reagent to enaminones, see: Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182.

(9) A small amount of uncyclized δ-amino ester could also be isolated from this reaction; however, the uncyclized compound was easily transformed to the cyclization product by heating in benzene or by standing at room temperature for few days. The yield was demonstrated as the combined yield.

Scheme 2
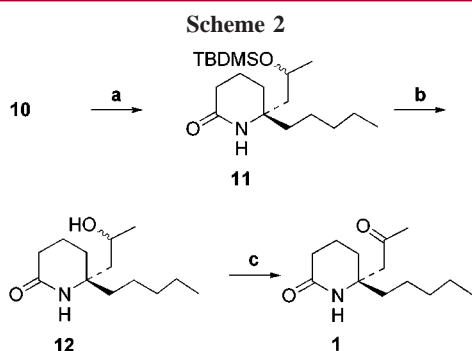
(a) SmI$_2$, Pivalic acid, THF-HMPA (7:1), 0°C to room temp., 70%; (b) conc.HCl, THF, 97%;(c) TPAP, NMO, CH$_2$Cl$_2$, 100%.

data (^{1}H and ^{13}C NMR, MS, IR) including specific optical rotation {[α]$_D$ −30.4 (c 0.8, CH$_2$Cl$_2$); lit.[2] [α]$_D$ −28.3 (c 1.6, CH$_2$Cl$_2$)} were identical with those provided by Professor Kibayashi.[2]

In summary, we were able to disclose a chiral synthesis of **1** by employing a samarium iodide promoted reductive carbon−nitrogen bond cleavage as the key reaction. Further application of this methodology to various types of alkaloid syntheses is now under investigation in this laboratory.

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

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