Tetrahedron Letters 50 (2009) 4654–4657

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Alternative synthetic path to (−)-adalinine via a SmI_2-promoted fragmentation of a 3-oxopyrrolidine derivative

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ARTICLE INFO

Article history:
Received 7 May 2009
Revised 28 May 2009
Accepted 29 May 2009
Available online 6 June 2009

Keywords:
Adalinine
Coccinellid alkaloid
Fragmentation
Samarium diiodide
C–N bond cleavage

ABSTRACT

A novel and stereocontrolled synthetic path to a coccinellid alkaloid, (−)-adalinine, was established by employing the reductive carbon–nitrogen bond cleavage reaction and subsequent recyclization of a 3-oxopyrrolidine derivative with samarium diiodide, as key steps, where water was found to be the best proton source.

(−)-Adalinine **1** was isolated from secretion of the European two-spotted ladybird beetle, *Adalia bipunctata*, as a minor piperidine alkaloid having a chiral quaternary carbon center, together with a major alkaloid, (−)-adaline **2** (Fig. 1).[1] This alkaloid **1** has also been proposed to be biosynthetically derived from adaline **2** via a retro-Mannich reaction.[1]

In 2000, we established a novel synthetic procedure for (−)-adalinine, in which a SmI_2-promoted regioselective carbon–nitrogen bond cleavage reaction of the α-amino ester derived from pyroglutamic acid followed by recyclization of the fragmentation product providing the corresponding δ-lactam was involved as the key reactions (Fig. 2).[2]

During the course of our studies directed toward the total synthesis of bioactive alkaloids employing cyclic amino acids as starting materials,[3] we became interested in developing an alternative method for the stereoselective synthesis of (−)-adalinine.[4]

We thought that the most straightforward way to achieve this goal was carbon–nitrogen bond cleavage of a 3-oxopyrrolidine derivative having a butyric acid moiety at the 5-position and subsequent cyclization of the resulting primary amine with the ester function, based on the consideration of its retrosynthetic route depicted in Figure 3.

Prior to the synthesis of (−)-adalinine, we attempted to find optimal reaction conditions for a SmI_2-promoted fragmentation reaction employing a readily accessible 3-oxopyrrolidine derivative **3** having a quaternary carbon center at the 5-position.[5]

First, the fragmentation of **3** was carried out by using SmI_2 (5.0 equiv) in THF–HMPA at 0 °C for 15 h; however, only decomposition of the starting material was observed (entry 6). We note in advance that proton sources play an important role in this fragmentation reaction. We therefore decided to find the best proton source in THF solution by screening, and the results obtained are summarized in Table 1. In the presence of MeOH as the proton donor in THF–HMPA, the reaction of **3** with SmI_2 (5.0 equiv) at 0 °C for 5 min gave the secondary alcohols **5** as an inseparable diastereoisomeric mixture in 85% yield in a ratio of ca. 1:1 (entry 1). As can be seen in Table 1, almost all of the proton sources, such as

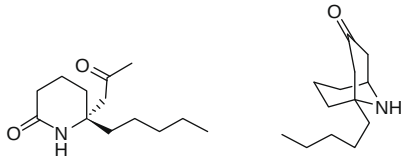

Figure 1. Structures of (−)-adalinine and (−)-adaline.

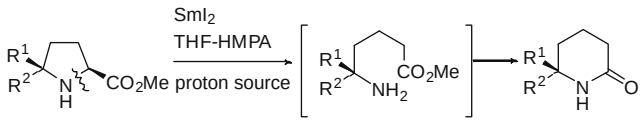

Figure 2. SmI_2-promoted fragmentation of α-amino ester.

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doi:10.1016/j.tetlet.2009.05.114

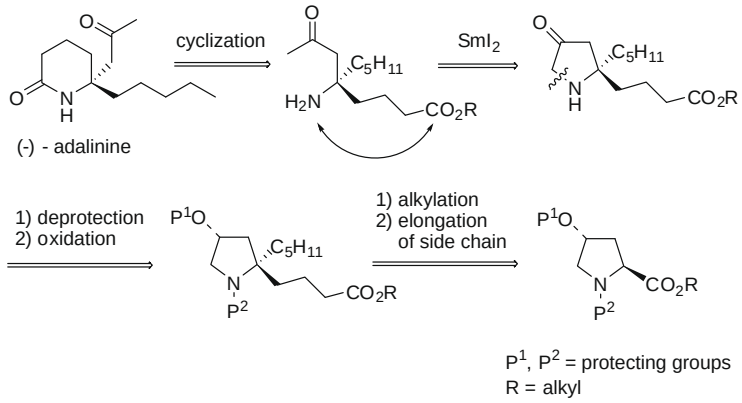
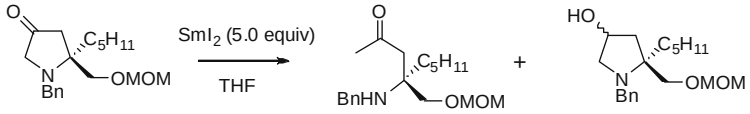


Figure 3. Retrosynthetic analysis of (−)-adalinine.

Table 1
Screening of proton sources for SmI_2-promoted fragmentation



Entry	Additive (equiv)	Time	Temperature	Products (yield)
1	HMPA (5.0) + MeOH (2.5)	5 min	0 °C	**5** (85%)
2	DMEA (10)	10 min	0 °C	**5** (75%)
3	MeOH (2.5)	2 h	0 °C	**4** (trace), **5** (50%)
4	NiI_2 (0.05)	6 h	0 °C–rt	**5** (25%), **3** (58%)
5	NiI_2 (0.05) + MeOH (2.5)	4 h	0 °C	**5** (43%)
6	HMPA (5.0)	15 h	0 °C	Decompose
7	HMPA (5.0) + *tert*-BuOH (2.5)	6 h	0 °C	**5** (68%)
8	*tert*-BuOH (2.5)	15 h	0 °C	**5** (10%)
9	*tert*-BuOH (2.5)	2 h	Reflux	**5** (60%)
10	H_2O (2.5)	2 h	0 °C	**4** (50%)

N,N-dimethylethanolamine (DMEA), NiI_2, *tert*-BuOH, and the combination of those proton sources, were also found to be ineffective for this fragmentation (entries 2, 4, 5, and 7–9).

When MeOH (2.5 equiv) was employed as the proton source in THF solution, the desired product **4** was obtained in a trace amount (<3%) (entry 3). Unfortunately, the yield of **4** could not be improved under various reaction conditions attempted by the use of MeOH. We were pleased to find that the choice of water as a proton source afforded the desired carbon–nitrogen bond cleavage product **4** in moderate yield (entry 10). Although its pivotal role is still unclear at present, it has been shown that the use of water as the proton donor sometimes had a profound impact on various factors, such as the reaction rate, mechanism, and stereoselectivity of SmI_2-mediated one-electron transfer reactions.[6]

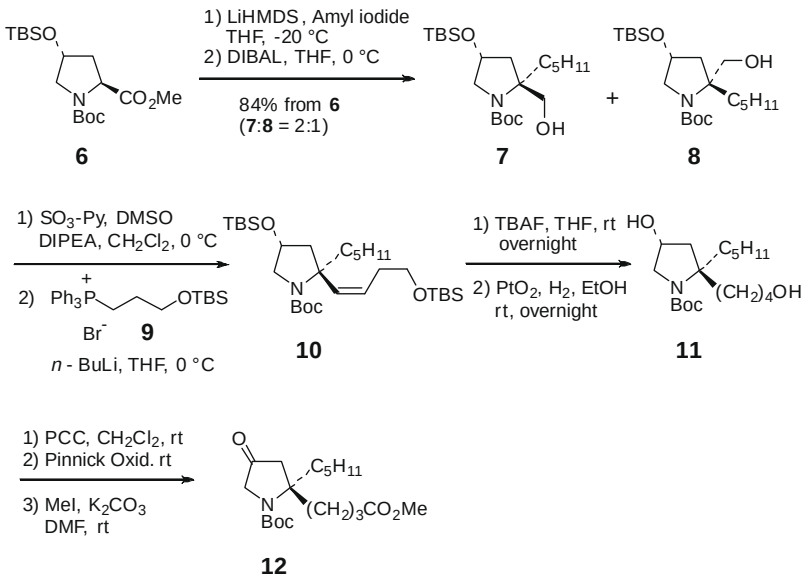
Given these considerations, we started to prepare a key precursor for a SmI_2-promoted carbon–nitrogen bond cleavage reaction as follows (Scheme 1).

The known ester **6**[7] readily accessible from (4*R*)-hydroxy-L-proline was alkylated with *n*-amyl iodide in the presence of LiHMDS as the base in THF to give a mixture of diastereomers, which, without separation, was reduced with DIBAL to give primary alcohols **7** and **8** in 56% and 28% yields, respectively. Oxidation of the major alcohol **6** followed by Wittig reaction of the resulting aldehyde with the phosphonium salt **9** afforded the olefin **10** in 80% yield from **7**. After treatment of **10** with TBAF, the resulting olefin was hydrogenated over platinum oxide to furnish the saturated alcohol **11** in 70% yield from **10**. Subsequent oxidation of **11** in two steps via the corresponding aldehyde provided an acid, which was further transformed to the ester **12**[8] in 39% yield from **11**.

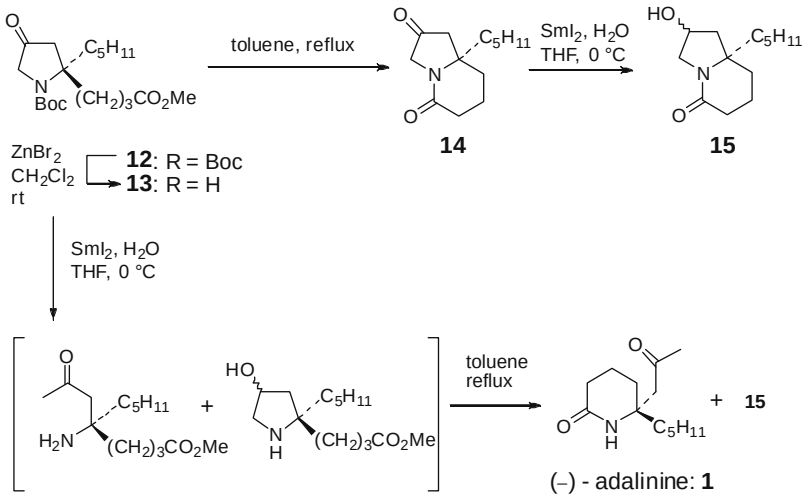
The desired precursor thus obtained was subjected to SmI_2-mediated reductive carbon–nitrogen bond cleavage reaction exploiting water as the proton donor by two routes (Scheme 2).

First, the *N*-Boc group of ester **12** was removed by treatment with $ZnBr_2$ to give the amine **13**, which on heating in toluene furnished the lactam **14**[9] in 86% yield from **12**. Treatment of **14** with 5.0 equiv of SmI_2 in THF in the presence of 2.5 equiv of water at 0 °C for 3 h, however, afforded the reduction product **15** as the major product in 61% yield as a mixture of diastereoisomers, together with 22% of the recovered starting material. On the other hand, a reductive carbon–nitrogen bond cleavage reaction of the amine **13** with 5.0 equiv of SmI_2 in THF in the presence of 2.5 equiv of water at 0 °C for 30 min generated two products, which, without separation, were heated at reflux in toluene to give (−)-adalinine in 16% yield from **12** and the bicyclic compound **15** in 38% yield from **12**.[10] The spectroscopic data for the synthesized compound **1** including its specific optical rotation were identical to those reported in the literature,[4d] $[\alpha]_D$ −24.2 (*c* 1.50, CH_2Cl_2), {lit.[4d] $[\alpha]_D$ −28.3 (*c* 1.6, CH_2Cl_2)}.

The poor yield of the fragmentation product in this reaction compared to that in a similar reaction for α-amino esters as shown in Figure 2 was rationalized by assuming that the formation of samarium-involved five-membered chelation intermediate, which



Scheme 1. Preparation of the key precursor **12**.



Scheme 2. Synthesis of (−)-adalinine.

might facilitate the fragmentation reaction, seemed to have difficulties due to steric strain observed for a 3-oxopyrrolidine derivative compared to α-amino esters (Fig. 4).

In summary, we were able to establish an alternative stereoselective chiral synthesis of (−)-adalinine **1** by employing reductive carbon–nitrogen bond cleavage reaction of a 3-oxopyrrolidine derivative as a key reaction. In this synthesis, we assumed that the formation of samarium-involved chelation intermediate plays an important role for the desired fragmentation. It is also noteworthy that water was found to be the best proton source in this reaction. This methodology seems to be applicable to various types of 3-oxopyrrolidine and 3-oxopiperidine derivatives, and its application is now under investigation in our laboratory.

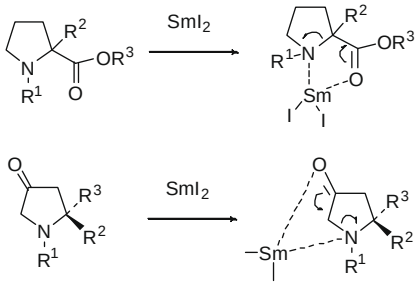


Figure 4. Assumed chelation intermediates.

Acknowledgments

This research was supported financially in part by a grant for the Open Research Center Project and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

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. Honda, T.; Kimura, M. *Org. Lett.* **2000**, *2*, 3925.

3. (a) Katoh, M.; Matsune, R.; Nagase, H.; Honda, T. *Tetrahedron Lett.* **2004**, *45*, 6221; (b) Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499; (c) Katoh, M.; Mizutani, H.; Honda, T. *Tetrahedron Lett.* **2005**, *46*, 5161; (d) Katoh, M.; Hisa, C.; Honda, T. *Tetrahedron Lett.* **2007**, *48*, 4692.
4. For the synthesis of racemic adalinine, see: (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; (c) Wardrop, D. J.; Landrie, C. L.; Ortiz, J. A. *Synlett* **2003**, 1352; For the synthesis of (−)-adalinine, see: (d) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739; For a recent review of the coccinellied alkaloids, see: (e) King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105.
5. Compound **3** was prepared from methyl *N*-benzyl-(4*R*)-*tert*-butyldimethylsilyloxyprolinate by alkylation with amyl iodide in the presence of LiHMDS and subsequent $LiAlH_4$ reduction.
6. (a) Hasegawa, E.; Ishiyama, K.; Fujita, T.; Kato, T.; Abe, T. *J. Org. Chem.* **1997**, *62*, 2396; (b) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172; (c) Dahlën, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123; (d) Chopade, P. R.; Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 44; (e) Farran, H.; Shmaryahu Hoz, S. *J. Org. Chem.* **2009**, *74*, 2075; (f) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 1865.
7. Enders, D.; Kirchhoff, J. H.; Koebberling, J.; Peiffer, T. H. *Org. Lett.* **2001**, *3*, 1241.
8. *Selected data for* **8**: colorless oil. $[\alpha]_D$ −4.32 (*c* 1.02, $CHCl_3$); IR (thin film): 2956, 2930, 2860, 1763, 1740, 1703, 1455, 1439, 1393, 1367, 1256, 1170, 1138, 1107, 994, 873 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 1H), 3.82 (s, 1H), 3.67 (s, 3H), 2.70–2.47 (m, 2H), 2.27–2.43 (m, 2H), 2.17–2.26 (m, 1H), 2.05 (br s, 1H), 1.56–1.89 (m, 4H), 1.48 (d, *J* = 19.5 Hz, 9H), 1.08–1.37 (m, 8H), 0.84–0.92 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 210.3, 209.5, 173.7, 173.4, 154.2, 153.1, 80.7, 79.8, 64.8, 64.3, 56.6, 56.5, 51.5, 48.0, 47.2, 39.7, 39.2, 38.3, 37.8, 33.9, 33.8, 32.0, 31.8, 28.44, 28.37, 23.5, 23.3, 22.5, 19.4, 13.9; MS (EI) (*m*/*z*): 355 (M^+); HRMS *m*/*z* calcd for $C_{19}H_{33}NO_5$ (M^+): 355.2344, found: 355.2358.
9. *Selected data for* **9**: colorless solid. Mp 50–52 °C; $[\alpha]_D$ −131.1 (*c* 1.04, $CHCl_3$); IR (thin film): 2955, 2933, 2860, 1763, 1644, 1456, 1409, 1181, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (d, *J* = 20.0 Hz, 1H), 3.67 (d, *J* = 20.0 Hz, 1H), 2.75 (dt, *J* = 4.4, 18.6 Hz, 1H), 2.67 (d, *J* = 17.5 Hz, 1H), 2.64 (dd, *J* = 8.9, 18.7 Hz, 1H), 2.47 (d, *J* = 17.6 Hz, 1H), 2.24 (dt, *J* = 3.4, 13.6 Hz, 1H), 1.89–1.96 (m, 2H), 1.68–1.77 (m, 2H), 1.53–1.60 (m, 1H), 1.14–1.37 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.3, 171.1, 64.2, 51.5, 30.4, 37.5, 31.8, 31.5, 30.4, 24.0, 22.4, 16.5, 13.9; MS (EI) (*m*/*z*): 223 (M^+); HRMS *m*/*z* calcd for $C_{13}H_{21}NO_2$ (M^+): 223.1572, found: 223.1557. Anal Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.79; H, 9.30; N, 6.18.
10. *Typical experimental procedure for a SmI_2-promoted fragmentation reaction*: To a stirred solution of **12** (200.0 mg, 0.56 mmol) in CH_2Cl_2 (6.00 mL) was added $ZnBr_2$ (254 mg, 1.12 mmol) at room temperature, and the resulting mixture was stirred overnight. After removal of the insoluble materials by filtration, the filtrate was treated with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extract was concentrated, and the residue was dissolved in THF (6.0 mL). To this solution were added SmI_2 (0.2 M in THF, 14.0 mL, 2.8 mmol) and H_2O (25 μL, 1.4 mmol) at 0 °C, and the whole mixture was stirred for a further 30 min at the same temperature. The mixture was treated with aqueous $NaHCO_3$ and Et_2O, and the whole mixture was filtered through a pad of Celite to remove insoluble materials. The filtrate was extracted with Et_2O, and the ethereal solution was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved in toluene. After heating the toluene solution at reflux for 10 min, the solvent was removed to leave a residue, which was purified by column chromatography on silica gel to afford (−)-adalinine **1** and alcohols **15**.