Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4481–4483

A new synthetic route to (−)-cassine via asymmetric aminohydroxylation

Guncheol Kim* and Nakjeong Kim

Department of Chemistry, College of Natural Science, Chungnam National University, Taejon 305-764, Republic of Korea

Received 5 April 2007; revised 27 April 2007; accepted 2 May 2007
Available online 6 May 2007

Abstract—(−)-Cassine has been synthesized by a new route, asymmetric aminohydroxylation followed by reductive amination.

2,6-Disubstituted piperidin-3-ol alkaloids, displaying attractive structural arrangement, have shown interesting pharmacological activities.[1] For example, (−)-cassine **1** has antimicrobial activity against *Staphylococcus aureus*,[2] prosopinine **2** shows analgesic, anesthetic, and antibiotic activities,[3] and (−)-spectaline **3** offers cytotoxic activity (Fig. 1).[4] (−)-Cassine **1** was isolated from *Cassia excelsa* and the absolute configuration was confirmed by Rice in 1966,[5] and until recently several results of synthetic efforts for **1** have been published.[6]

As we were interested in the arrangement of its ring skeleton, we planned to achieve a new synthesis of **1** via asymmetric aminohydroxylation (AA) and reductive amination reaction. Several asymmetric syntheses of alkaloids based on AA have been reported[7] and the reductive amination reaction has been applied for the synthesis of several alkaloid compounds in our group.[8] We anticipated that AA reaction on **5** would afford **4** with regio- and enantioselectivity[9] and compound **5** could be prepared from the commercially available 11-bromo-1-undecanol through conventional carbon extension and oxidation reactions (Fig. 2).

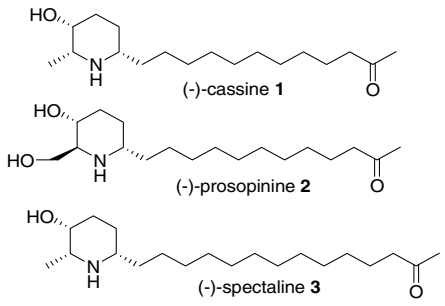


Figure 1.

To perceive chemical features of the AA reaction on the substrate and the products, first we tried to use a simple substrate, 5-heptene-2-one **6**. Compound **6** was readily prepared from *trans*-4-hexenol via a three step sequence (oxidation using tetrapropylammonium perruthenate[10] to aldehyde, MeMgBr addition, and Jones oxidation) in 61% yield. To find out an optimum condition for the regioselective AA reaction on **6**, we tried several conditions by varing ligands and solvents,[9b–d] and obtained **7** and **8** in about 1:1 ratio and 77% yield (Scheme 1). The separated products **7** and **8** were found to be mixtures of about 2:1 isomers, which was assumed to be in equlibrium between **a** and **b**, respectively.

To select the right intermediate for cyclization to the desired piperidine ring, we subjected **7** and **8** to

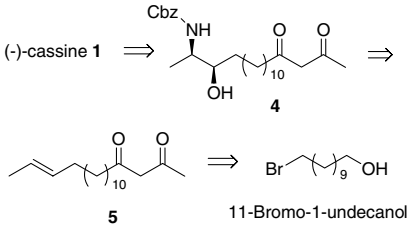
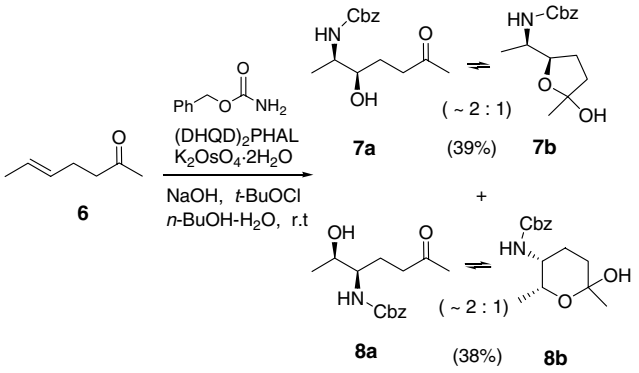


Figure 2.

Keywords: (−)-Cassine; Asymmetric aminohydroxylation; Reductive amination; Hydrogenation.
* Corresponding author. Tel.: +82 042 821 5475; fax: +82 042 823 1360; e-mail: guncheol@cnu.ac.kr

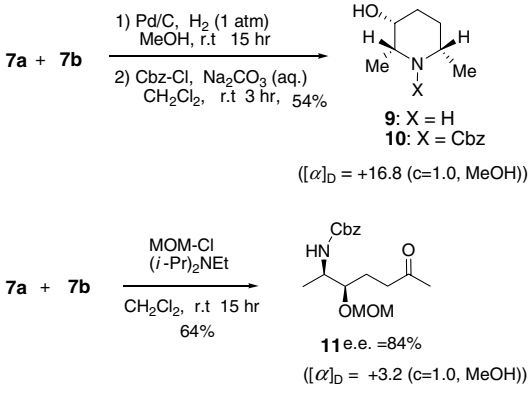
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.05.005



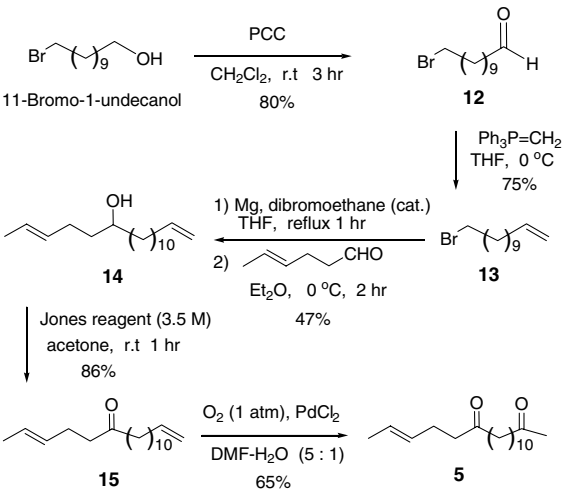
Scheme 1.

hydrogenation condition, respectively. The reductive conditions showed that compounds **7** were the desired intermediates to afford the known 3-hydroxypiperidine **9**,[11] which was protected by benzyloxycarbonyl chloride and purified further to afford **10**, $[\alpha]_D^{24}$ 16.8 (*c* 1.0, MeOH). However, the same reaction condition applied for compounds **8** surprisingly provided the starting mixture **8** back. We assume that the deprotected intermediate of **8** should exist as only a hemi-ketal form, and therefore neither imine formation nor subsequent reductive amination proceeded, and the following protection reaction afforded **8** back. Protection of hydroxyl group of **7a** and **7b** by methoxymethyl chloride yielded convergently **11** in 64% yield and the optical purity of **11** was determined to be 84% ee by chiral HPLC (Scheme 2).[12]

On the basis of the result from the model study, we planned to prepare the proposed template **5** required for the natural product. Commercially available 11-bromo-1-undecanol was oxidized using PCC to the corresponding aldehyde **12** in 80% yield, and the aldehyde was converted to **13** under Wittig reaction with triphenylphosphoranylidene methane in 75% yield. Compound **13** was treated with fresh magnesium in the presence of catalytic amount of dibromoethane to make Grignard reagent and the resulting reagent was added to a solution of *trans*-4-hexenaldehyde in ether to provide **14** in 47% yield. Jones oxidation of **14** provided ketone **15** in 86% yield and the Wacker oxidation[13] of the resulting



Scheme 2.

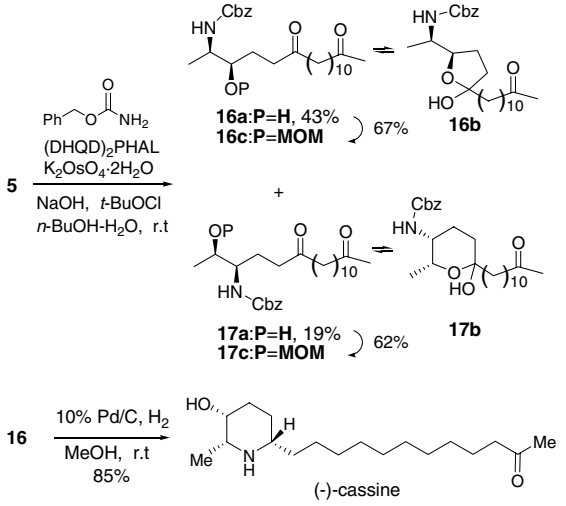


Scheme 3.

diene effectively yielded diketone **5** in 65% yield (Scheme 3).

AA reaction of **5** under the optimized condition afforded **16** in 43% yield and **17** in 19% yield, respectively. Unlike **7** or **8**, the products existed as **16a** and **17a** forms more than 5:1 ratios, respectively. Further characterization of the derivatives was performed after protection with a MOM group to **16c** and **17c**, and the optical purity was detected to be 86% ee and 82% ee by chiral HPLC, respectively. Although we cannot explain the better regioselectivity of AA of **5** than the model substrate and the difference in the equilibrium ratios of isomers **16** and **17**, we assume the longer chain should play certain steric roles on selectivity and equilibrium. The final hydrogenation of **16** provided (−)-cassine in 85% yield. The spectral data (^{1}H and ^{13}C NMR, IR, and MS) were identical to those reported: $[\alpha]_D^{24}$ −0.50 (*c* 0.70, EtOH) [lit. $[\alpha]_D^{25}$ −0.6 (*c* 8.0, EtOH)]; mp 55–57 °C [lit. 54-57 °C] (Scheme 4).

In conclusion, we described a new practical synthetic route to (−)-cassine using AA reaction followed by



Scheme 4.

reductive amination. A room for improvement in the regio- and enantioselectivity has been left, though, the concise route suggested a practical synthetic strategy of the compound. Further application of this reaction for related alkaloid compounds is under study.

Acknowledgement

This work was supported by Grant (R01-2005-000-10032-0) from the Basic Research Program of Korea Science and Engineering Foundation, and we appreciate Center for Research Facilities, CNU, for the permission to NMR.

References and notes

1. Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 89.
2. Peraza, P. S.; Vallado, M. R.; Loeza, W. B.; Mena-Rejón, G. J.; Quijano, L. *Fitoterapia* **2000**, *71*, 690.
3. Fodor, G.; Fumeaux, J.-P.; Sankaran, V. *Synthesis* **1972**, 464.
4. Bolzani, V. S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 5929.
5. Rice, W. Y.; Coke, J. L. *J. Org. Chem.* **1966**, *31*, 1010.
6. (a) Herdeis, C.; Kuepper, P.; Ple, S. *Org. Biomol. Chem.* **2006**, *4*, 524; (b) Tsai, M.-R.; Chen, B.-F.; Cheng, C.-C.; Chang, N.-C. *J. Org. Chem.* **2005**, *70*, 1780; (c) Makabe, H.; Kong, L. K.; Mitsura, H. *Org. Lett.* **2003**, *5*, 27; (d) Oetting, J.; Holzlkamp, J.; Mayer, H. H.; Pahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 477, and references cited therein.
7. (a) Kandula, S. R. V.; Kumar, P. *Tetrahedron* **2006**, *62*, 9942; (b) Chikkanna, D.; Singh, O. V.; Kong, S. B.; Han, H. *Tetrahedron Lett.* **2005**, *46*, 8865; (c) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349; (d) Singh, S.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387; (e) Zhang, H.-X.; Xia, P.; Zhou, W.-S. *Tetrahedron* **2003**, *59*, 2015; (f) Zhang, H.-X.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **2000**, *11*, 3439.
8. (a) Kim, G.; Jung, S.-d.; Lee, E.-j.; Kim, N. *J. Org. Chem.* **2003**, *68*, 5395; (b) Kim, G.; Kim, N. *Tetrahedron Lett.* **2005**, *46*, 423.
9. (a) Nesterenko, V.; Byers, J. T.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 281; (b) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733; (c) O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519; (d) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451.
10. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.
11. Hasseberg, H.-A.; Gerlach, H. *Liebig Ann. Chem.* **1989**, 255.
12. Protection of **8** under the same condition also afforded a single compound, whose optical rotation was detected as $[\alpha]_D^{24}$ 6.8 (*c* 1.0, MeOH) and the enantiomeric excess was found to be 84% ee.
13. Tsuji, J. *Synthesis* **1984**, 384.