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Total Synthesis of (−)-Cassine

Hidefumi Makabe,* Looi Kok Kong,[†] and Mitsuru Hirota[†]

Graduate School of Agriculture, Sciences of Functional Foods, Shinshu University, 8304 Minami-minowa Kami-ina, Nagano 399-4598, Japan

makabeh@gipmc.shinshu-u.ac.jp

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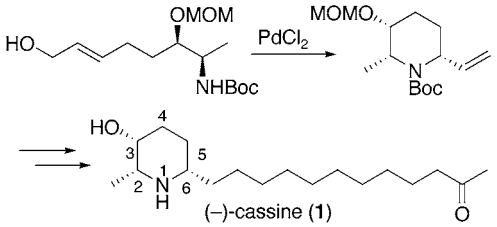
ABSTRACT



The $PdCl_2$-catalyzed cyclization of amino allylic alcohol 16 gave the cyclized product 17a with excellent diastereoselectivity. The versatility of compound 17a as the building block for synthesizing *cis*-2,6-disubstituted piperidine alkaloids has been demonstrated by a total synthesis of (−)-cassine (1).

A number of the piperidine alkaloids, especially 2,6-disubstituted piperidin-3-ols, have been found abundantly in nature, and many of them show interesting pharmacological activities.[1] For example, prosopinine (**2**) displays local anesthetic, analgestic, and antibiotic activities[2] and (−)-spectaline (**3**) shows cytotoxicity (Figure 1).[3]

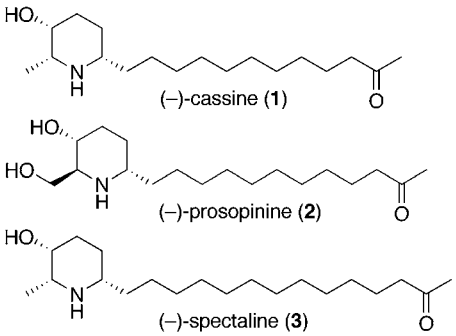


Figure 1.

Although much effort has been directed toward total synthesis of 2,6-disubstituted piperidine alkaloids, the practical method for total synthesis is still limited. Stereoselective synthesis of trans-2,6-disubstituted piperidine alkaloids using Pd(0)-catalyzed N-alkylation was achieved by Tadano in 1993.[4] As to the total synthesis of cis-2,6-disubstituted piperidine alkaloids, racemic cassine was synthesized by Bonte and Hasserburg,[5a,b] and (−)-cassine (**1**) was accomplished by Momose and Oetting using enzymatic optical resolution.[6a−c] Recently, Hirai reported Pd(II)-catalyzed cyclization of piperidines to afford 2-substituted piperidine with excellent diastereoselectivity.[7]

(−)-Cassine (**1**) was isolated from the leaves and twigs of *Cassia excelsa*, and its structure was established in 1963.[8] The absolute configuration was determined by W. Y. Rice

[†] Department of Bioscience and Biotechnology, Faculty of Agriculture, Shinshu University, 8304 Minami-minowa Kami-ina, Nagano 399-4598, Japan.

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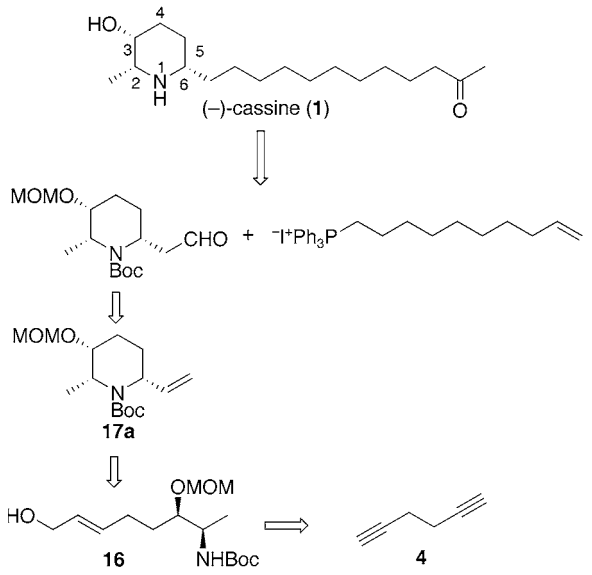
in 1966.[9] Recently, G. J. Mena-Rejon reported that **1** shows antimicrobial activity against *Staphylococcus aureus*.[10] We report here an asymmetric total synthesis of **1** via a diastereoselective Pd(II)-catalyzed cyclization strategy. This cyclization reaction would be attractive as a means to synthesize other 2,6-disubstituted piperidine alkaloids.

Scheme 1 outlines our synthetic strategy. The target compound **1** would be derived from the cyclization product

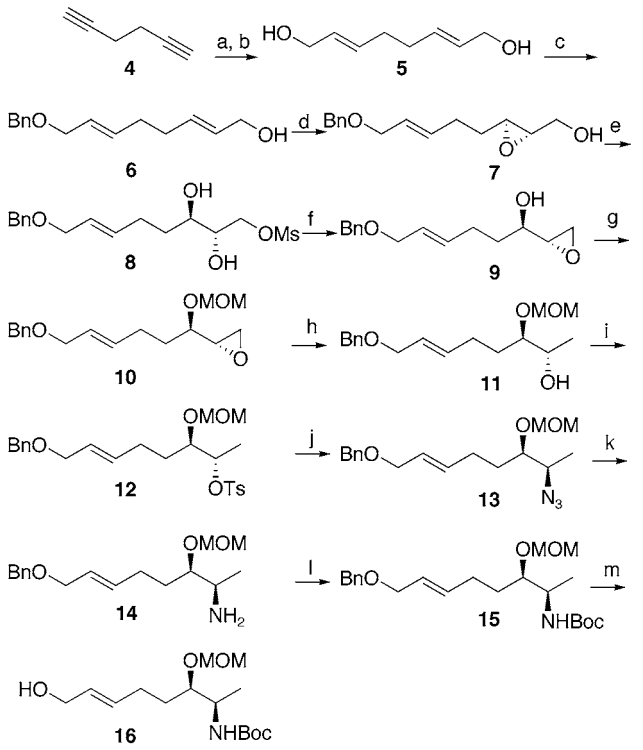
Scheme 1



17a by hydroboration−oxidation of the vinyl group and chain elongation using Wittig reaction. The 2,6-dialkylated piperidine ring of **17a** would be formed by Pd(II)-catalyzed intramolecular N-alkylation. It was expected that the N-alkylation would proceed via an intermediate π-allyl palladium complex. The key intermediate allylic amino alcohol **16** would be synthesized via a multistep procedure from 1,5-hexadiyne (**4**).

As shown in Scheme 2, the key intermediate allylic amino alcohol **16** was constructed as follows. The *trans*,*trans*-dienediol **5** was prepared using Rosenblum's procedure in 51% yield.[11] Monobenzylation of **5** with benzyl bromide, NaH, and a catalytic amount of tetrabutylammonium iodide gave **6** in 56% yield. Sharpless asymmetric epoxidation of **6** with L-(+)-diethyl tartrate gave epoxide **7** in 90% yield,[12] which showed >98% ee by ^{1}H NMR analysis of the corresponding Mosher ester derivative.[13] The hydroxyl group of **7** was converted into a mesylate, which was then treated with perchloric acid to afford dihydroxy sulfonate **8**.[14] Treatment

Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi, $(HCHO)_n$, 71%. (b) Na, NH_3, reflux, 76%. (c) BnBr (1.5 equiv), NaH (2.2 equiv), *n*-Bu_4NI (0.2 equiv), 56%. (d) Ti(O*i*-Pr)$_4$, TBHP, L-(+)-DET, 90%. (e) (i) MsCl, Et_3N; (ii) $HClO_4$, 60 °C, 90%. (f) K_2CO_3, MeOH, 89%. (g) MOMCl, *i*-Pr_2NEt, 99%. (h) $LiAlH_4$, THF, 50 °C, 96%. (i) *p*-TsCl, pyridine, 96%. (j) NaN_3, DMF, 50 °C, 47%. (k) PPh_3, H_2O, 81%. (l) Boc_2O, Et_3N, 81%. (m) Na/NH_3, 90%.

with potassium carbonate gave terminal epoxide **9** in 89% yield. The secondary hydroxyl group of **9** was protected as a MOM ether to give **10**. Regioselective reduction of **10** with $LiAlH_4$ and subsequent tosylation of the resulting secondary hydroxyl group of **11** gave tosylate **12** in 96% yield. Transformation of **12** into azide **13** was achieved in 47% yield by using NaN_3 in DMF. Reduction of azide **13** with PPh_3−H_2O afforded amine **14**, and subsequent protection of the amino group with *tert*-butoxycarbonyl group afforded **15** in high yield. Removal of the benzyl group of **15** with Na in liquid ammonia afforded **16**.

Allyl alcohol **16** was teated with 5 mol % $PdCl_2$ in THF at room temperature to afford cyclized mixtures **17a** and **17b** in 69% yield; the ratio of **17a** and **17b** was >49:1 (Scheme 3).

Switching the catalyst in the above conditions to $Cl_2Pd(CH_3CN)_2$ gave **17a** and **17b** in 51% yield (the ratio of **17a** and **17b** was also >49:1). On the other hand, Pd(II) with bigger ligands such as dppf and PPh_3 did not give any cyclized product. The stereoselective formation of **17a** could be explained by assuming that the cyclization proceeds via transition state A. The chelation effect between the palladium and oxygen atoms of the allyl alcohol is important. This tendency may also be counterbalanced by the chelation effect

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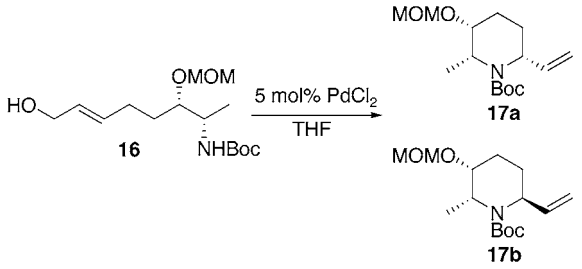
Scheme 3



between the palladium and the oxygen of the Boc group favoring this orientation. Transition state B, which leads to **17b**, would be a disadvantage because of the steric hindrance between the Boc group and the π-allyl palladium complex (Figure 2). Determination of the relative stereochemistry of **17a** was performed by NOE experiments.

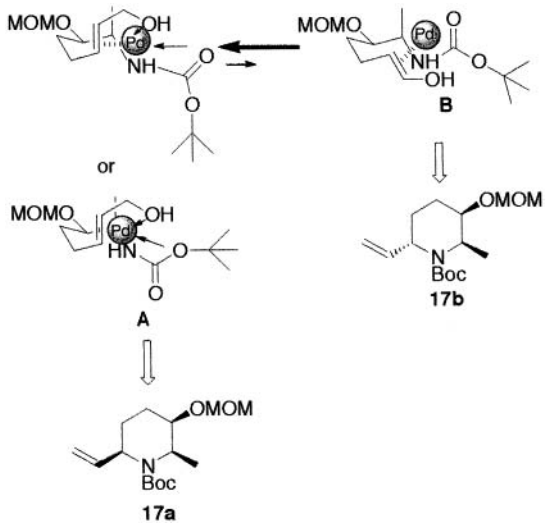


Figure 2.

Hydroboration of **17a** was carried out with 9-BBN to afford primary alcohol **18**, and subsequent oxidation with PCC provided the crude aldehyde. The carbon chain elongation of the piperidine ring appendage at C-6 was accomplished by Wittig reaction using 9-decenyl triphenylphosphonium iodide to afford **19**. Wacker oxidation[15] of the resulting diene effectively afforded **20**, which was subjected to catalytic hydrogenation in the presence of 5% palladium on carbon to give saturated product **21**. Finally, deprotection of the MOM and the Boc groups with a few drops of concentrated HCl in MeOH gave (−)-cassine in quantitative yield (Scheme 4).

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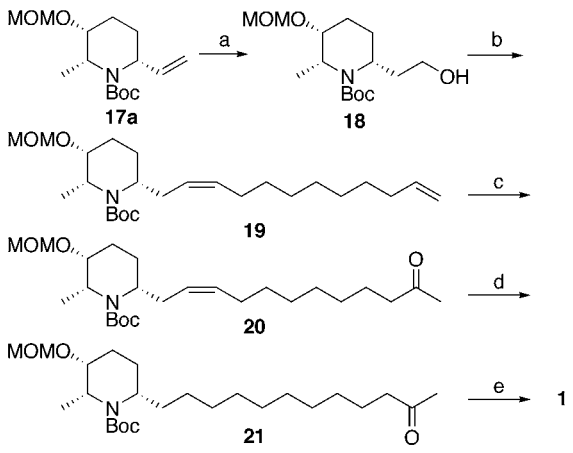
Scheme 4[a]



[a] Regents and conditions: (a) (i) 9-BBN, from 0 °C to room temperature; (ii) NaOH, H_2O_2, 96%. (b) (i) PCC; (ii) $CH_2{=}CH(CH_2)_8PPh_3{}^+I^-$, *n*-BuLi, −40 °C, 67%. (c) O_2, $CuCl_2$, $PdCl_2$, 72%. (d) H_2, 5% Pd−C, 81%. (e) aqueous HCl, MeOH, 100%.

The optical rotation of synthetic **1** ($[\alpha]^{24}_D$ −0.72 (*c* 0.47, EtOH)) was consistent with that reported for natural **1** ($[\alpha]^{25}_D$ −0.6 (*c* 8.0, EtOH)).[8] The ^{1}H NMR, ^{13}C NMR, IR, and MS spectra and melting point of synthetic **1**[16] were also in good agreement with the reported values.[6a−c,8]

In conclusion, we have achieved a total synthesis of (−)-cassine using a diastereoselective $PdCl_2$-catalyzed cyclization. The key intermediate **17a** can be used as a building block for synthesizing other cis-2,6-disubstituted piperidine alkaloids.

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Supporting Information Available: Experimental procedures for compounds **1** and **7**−**21**; ^{1}H and ^{13}C NMR spectra for compounds **1**, **6**−**11**, and **13**−**21**; ^{1}H NMR spectra for compound **12**; and NOESY spectra for compound **17a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Physical and spectroscopic data for **1**. Mp: 54−56 °C, $[\alpha]^{24}_D$ −0.72 (*c* 0.47, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.15 (3H, d, J = 6.6 Hz), 1.15−1.4 (16H, m), 1.46 (9H, s), 1.45−1.65 (5H, m), 1.90−1.95 (1H, m), 2.13 (3H, s), 2.41 (2H, t, J = 7.4 Hz), 2.55−2.65 (1H, br), 2.80−2.85 (1H, qd, J = 6.5, 1.5 Hz), 3.59 (1H, br) ppm. ^{13}C NMR (125 MHz) δ: 18.47, 23.88, 25.80, 29.19, 29.40, 29.44, 29.52, 29.56, 29.77, 29.85, 31.99, 36.72, 43.83, 55.94, 57.34, 67.91, 209.33 ppm. HRFABMS (M + H$^+$): found, 298.2738; calcd for $C_{18}H_{36}NO_2$, 298.2746.