

First Asymmetric Total Syntheses of (+)-Crinamine, (–)-Haemanthidine, and (+)-Pretazettine

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The *Amaryllidaceae* alkaloids have been of interest as synthetic targets due to the wide range of biological activities they exhibit.¹ Over 100 alkaloids have been isolated from members of the *Amaryllidaceae*, and most of these compounds may be classified into eight skeletally homogeneous subgroups. Here, we report the first asymmetric total syntheses² of the crinane-type alkaloid, (+)-crinamine (**1**),³ (–)-haemanthidine (**2**), and (+)-pretazettine (**3**)^{4,5} in a few efficient steps (Scheme 1).

Our plan is shown in Scheme 2. We have already reported the asymmetric synthesis of 2-arylcylohexenylamine derivatives *via* π -allylpalladium complex generated from **4**, Pd(0), and (*S*)-BINAPO.⁷ There are many alkaloids containing the hexahydroindole skeleton that have an aryl group at the ring junction. We were stimulated to synthesize some of these alkaloids in optically pure form. If aldehyde (*S*)-**6** is obtained using this asymmetric amination procedure, the intramolecular carbonyl-ene reaction⁸ of **6** would construct the quaternary carbon center of **7** in a stereoselective manner *via* **I**. From this compound, the target alkaloids would be synthesized in an optically pure form in short steps.

Initially, we tried to synthesize cyclohexenylamine derivative **9** from **4**⁹ and **8** (Scheme 3).¹⁰ When a THF solution of **4a** (1 equiv), acetal **8** (1.1 equiv), Pd₂dba₃·CHCl₃ (2.5 mol

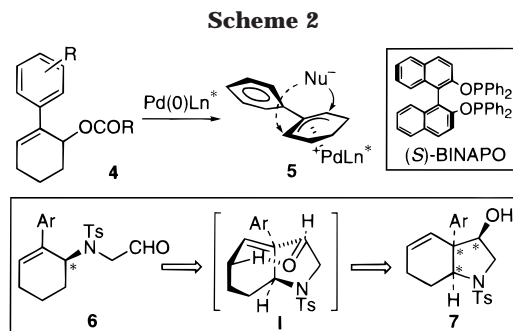
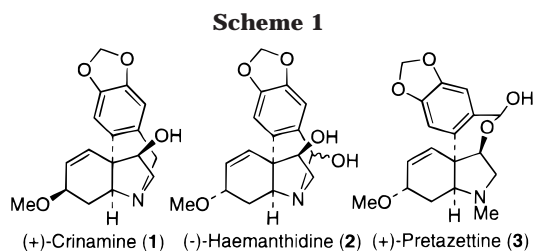


Table 1. Reaction of **4 with **8** in the Presence of Palladium Complex**

run	X	solv	temp (°C)	time (h)	yield (%) ^a	ee (%)
1	CO ₂ Me (4a)	THF	rt	18	68	60
2			0	106	31 (38)	68
3	PO(OEt) ₂ ^b (4b)	THF	0	4	73	69
4		THF	–20	48	80	74
5		DMF	–20	91	65	67
6		EtCN	–20	310	48 (21)	68
7 ^c		THF	rt	160	43 (28)	75

^a The number in parenthesis shows the yield of recovered starting material. ^b NaH was used as a base. ^c (*S*)-BINAP was used as a ligand.

%), and (*S*)-BINAPO¹¹ (5.0 mol %) was stirred at room temperature for 18 h, cyclohexenylamine derivative **9** was obtained in 68% yield with 60% ee as a crystalline product (Table 1, run 1).¹² The ee of **9** was slightly increased when the reaction was carried out at a low temperature, although the reaction time was long and the yield was moderate (run 2). Then the leaving group was changed to phosphonate, and the reaction of **4b** with **8** was carried out in the presence of NaH. At a low temperature, the reaction proceeded smoothly, and the desired product **9** was obtained in 80% yield with 74% ee (run 4). As a solvent, THF was the most suitable (runs 4–6), and with (*S*)-BINAP as the ligand the reaction gave **9** with a high ee, although the yield was only moderate (run 7).

Surprisingly, when compound **9** with 74% ee was recrystallized from MeOH, racemic **9** was obtained as colorless

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(2) Asymmetric total syntheses of crinine-type alkaloids: (a) (+)-Maritidine: Yamada, S.-I.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, *57*. (b) (–)-Crinine: Overman, L. E.; Sugai, S. *Helv. Chem. Acta* **1985**, *68*, 745. (c) (–)-Amabiline and (–)-augustamine: Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (d) Formal total synthesis of (+)-Maritidine: Kita, Y.; Takeda, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857.

(3) Isolations of (+)-crinamine: (a) Mason, L. H.; Puschett, E. R.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 1253. (b) Kobayashi, S.; Tokumoto, T.; Kihara, M.; Imakura, Y.; Shingu, T.; Taira, Z. *Chem. Pharm. Bull.* **1984**, *32*, 3015. Total synthesis of (±)-crinamine: (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976**, 2331.

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(6) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.

(7) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263.

(8) Recent review; Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

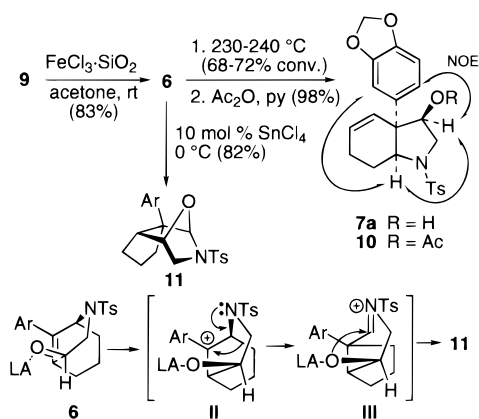
(9) Substrate **4a** and **4b** were synthesized by the same procedure as that previously reported.⁷ For experimental details, see Supporting Information.

(10) Hall, R. J.; Dharmasena, P.; Marchant, J.; Oliveira-Campos, A.-M. F.; Queiroz, M.-J. R. P.; Raposo, M. M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1879.

(11) Grubbs, R. H.; DeVries, R. A. *Tetrahedron Lett.* **1977**, *26*, 1879.

(12) The ee value of **9** was determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane/2-propanol 9/1).

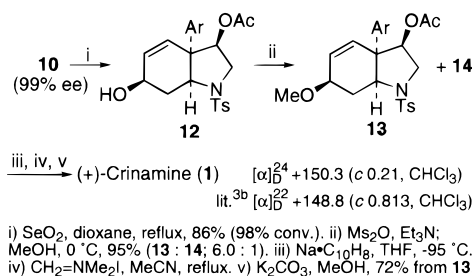
Scheme 4



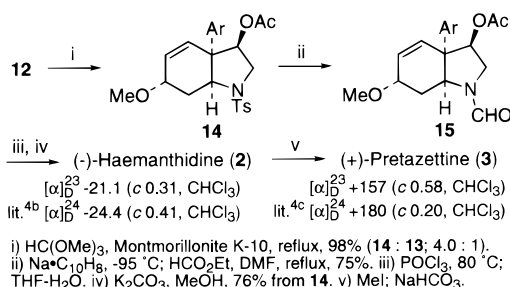
crystals, and the concentration of the mother liquor gave the oily (–)-**9** with 99% ee.

Next the intramolecular carbonyl-ene reaction of enantiopure **9** was carried out. Deacetalization of **9** with $\text{FeCl}_3 \cdot \text{SiO}_2$ ¹³ gave the aldehyde **6** in high yield. As expected, when a toluene solution of **6** was heated at 230–240 °C in the presence of 4 Å molecular sieves for several hours, the desired hexahydroindole **7** was obtained in 51–59% yield (68–72% conversion) as a sole product. The NOE experiment with acetylated compound **10** indicates that the ring junction of the five- and six-membered ring is *cis* and that the acetoxy group is *trans* to the aryl group. The stereochemistry of this compound is consistent with that of the target alkaloids. On the other hand, the SnCl_4 -catalyzed (10 mol %) carbonyl-ene reaction of **6** in CH_2Cl_2 at 0 °C for 3 h gave an unusual rearrangement product **11** in 82%

Scheme 5



Scheme 6



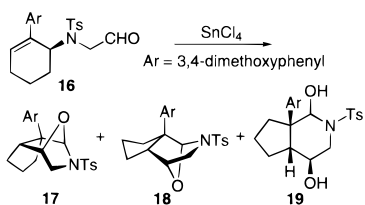
yield.¹⁴ From the spectral data, the structure of this compound was assigned to be **11**, as shown in Scheme 4.¹⁵ Presumably, the six-membered ring formation is promoted by the coordination of SnCl_4 to the carbonyl group, and the generated cation **II** is stabilized by an adjacent aryl group. Carbon–carbon bond fission of **II** is accelerated by the formation of an imminium cation, and then oxygen attacks **III** to give cyclic ether **11**.¹⁶

The alkaloids **1–3** were synthesized from the key intermediate **10** (Scheme 5). Allylic oxidation of **10** with SeO_2 gave alcohol **12** in a highly stereoselective manner as the sole product because SeO_2 approached the olefin from the face opposite of the large phenyl group. It is quite interesting that the reaction of Ms_2O with **12** in the presence of NEt_3 , followed by treatment with MeOH , gave **13** as the main product (**13**:**14**, 6.0:1).¹⁷ Detosylation of **13** followed by methylenation and deacetylation smoothly proceeded to give (+)-crinamine, whose $[\alpha]_D$ value, melting point, and spectral data agreed with those reported in the literature.^{3a,b} Thus, the asymmetric total synthesis of (+)-crinamine was achieved in nine steps from **4b** in 20% overall yield, and this establishes the absolute configuration of C-3 in (–)-**9** to be *S*.

For the synthesis of (–)-haemanthidine (**2**) and (+)-pretazettine (**3**), the Mitsunobu reaction of **12** with formic acid, followed by hydrolysis, was carried out to give the epimeric alcohol of **12** in 94% yield. However, treatment of *epi*-**12** with MeI in the presence of KH or NaH gave **14** in low yield. After various attempts, and it was found that treatment of **12** with $\text{HC}(\text{OMe})_3$ in the presence of Montmorillonite K-10¹⁸ gave **14** in high yield (**14**:**13**, 4.0:1) (Scheme 6). Detosylation of **14**, followed by formylation,¹⁹ gave compound **15**. Treatment of **15** with POCl_3 , followed by deacetylation, gave (–)-haemanthidine (**2**), which could be converted into (+)-pretazettine (**3**) by a known method.^{4c,f} The $[\alpha]_D$ value, melting point, and spectral data of synthetic **2** and **3**, respectively, agreed with those reported in the literature.^{4a–c} Further studies are in progress.

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Supporting Information Available: The experimental procedures for the synthesis of **1–3** and spectral data (9 pages).

Table 2 SnCl_4 -Promoted Carbonyl-ene Reaction of **16**

SnCl_4 (mol %)	temp (°C)	yield (%)		
		17	18	19
100	–5	13	6	29
10	rt	89	0	0

However, this reaction was carried out using 10 mol % of SnCl_4 to give **17** in 89% yield as a single product. By comparing with the spectral data of **17** and **18** and the spectra of the NOE experiments on them, the stereochemistry of these compounds could be determined. The stereochemistry of **11** was confirmed by a comparison with the above data.

(16) A similar rearrangement has been reported: cf. Csuzdi, E.; Pallagi, I.; Jerkovich, G.; Sólyom, S. *Synlett* **1994**, 429.

(17) In previous reports,^{4f,5a,b} compounds having the methyl group on nitrogen (in our case, tosyl group) were treated under the same reaction conditions to give only α -methoxylated product.

(18) Kumar, H. M. S.; Reddy, B. V. S.; Mohanty, J. S.; Yadav, J. S. *Tetrahedron Lett.* **1997**, 38, 3619.

(19) Schmidhammer, H.; Brossi, A. *Can. J. Chem.* **1982**, 60, 3055.