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Palladium-Catalyzed Asymmetric Allylic Substitution of 2-Arylcyclohexenol Derivatives: Asymmetric Total Syntheses of (+)-Crinamine, (−)-Haemanthidine, and (+)-Pretazettine

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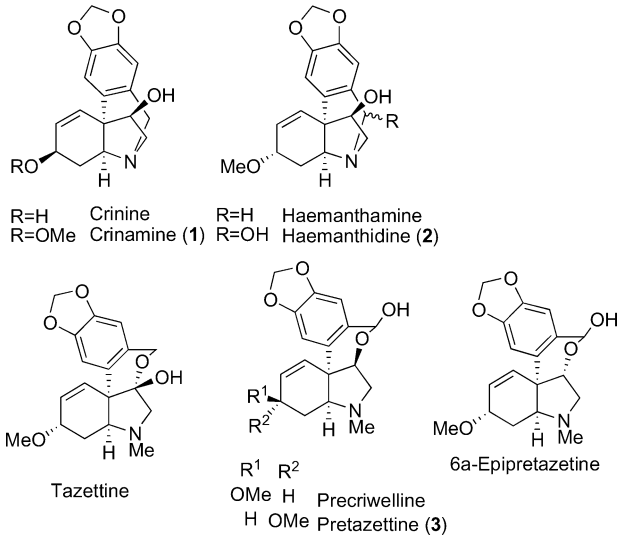
Received September 30, 2003

Much interest has been shown in *Amaryllidaceae* alkaloids as synthetic targets due to their wide range of biological activities. Over 100 alkaloids have been isolated from members of the *Amaryllidaceae* family; most of them can be classified into eight skeletally homogeneous groups. We have succeeded in the first asymmetric total syntheses of the crinane-type alkaloids (+)-crinamine (**1**), (−)-haemanthidine (**2**), and (+)-pretazettine (**3**). The starting cyclohexenylamine **14** was obtained from allyl phosphonate **11c** by palladium-catalyzed asymmetric amination in 82% yield and with 74% ee. The product was recrystallized from MeOH. Interestingly, (−)-**14** with 99% ee was obtained from the mother liquor (74% recovery). Intramolecular carbonyl−ene reaction of (−)-**10** proceeds in a highly stereoselective manner to give hexahydroindole derivative **9** as the sole product. In the Lewis-acid-catalyzed carbonyl−ene reaction, an interesting rearrangement product, **20**, was isolated in high yield. From **9**, (+)-crinamine was synthesized. Thus, the asymmetric total synthesis of (+)-crinamine was achieved in 10 steps from **11c**, and the overall yield is 19%. The total synthesis of (−)-haemanthidine was also achieved from **9** by a short sequence of steps.

Amaryllidaceae alkaloids constitute an important group of naturally occurring bases, and much interest has been shown in them due to the wide range of biological activities they exhibit.[1] Over 100 alkaloids have been isolated from members of the *Amaryllidaceae* family, and most of these compounds can be classified into eight skeletally homogeneous groups. Crinine-type alkaloids such as crinamine (**1**),[2] haemanthidine (**2**),[3] and pretazettine (**3**)[4] (Scheme 1) have a perhydroindole skeleton connected to an aromatic ring at the ring junction. The antineoplastic activity exhibited, in particular, by pretazettine, has stimulated interest in the synthesis of these compounds. The total synthesis of haemanthidine was achieved by Hendrickson.[3d] Several groups later succeeded in the total syntheses of these alkaloids.[2−4] Very recently, Baldwin reported the asymmetric syntheses of these alkaloids.[3k]

SCHEME 1



We have already reported[5] the asymmetric synthesis of a 2-arylcyclohexenylamine derivative, **6**, via π-allylpalladium complex **5** generated from **4a**, Pd(0), and (*S*)-BINAPO. In the palladium-catalyzed allylic substitution of **4** using Pd(0), the starting material **4** is racemic and

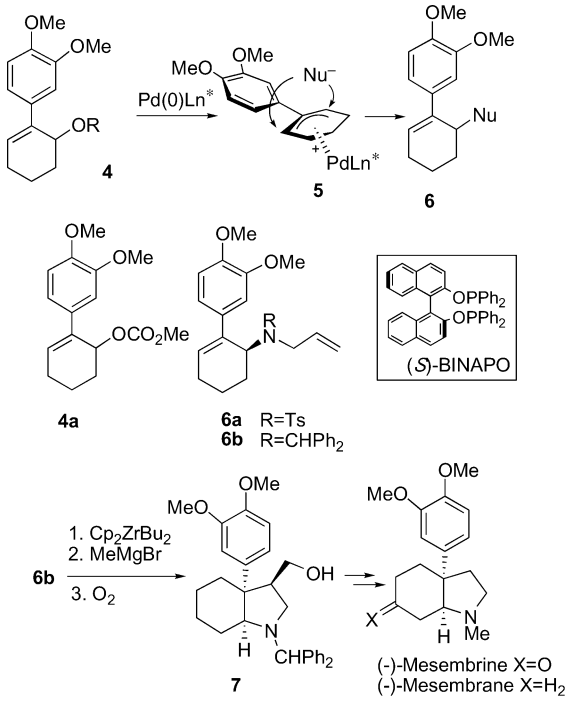
(1) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323. (c) Jin, Z.; Li, Z.; Huang, R. *Nat. Prod. Rep.* **2002**, *19*, 454.

(2) Isolation 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.

(3) Isolation of (−)-haemanthidine: (a) Boit, H. G. *Chem. Ber.* **1954**, *87*, 1339. (b) Takagi, S.; Yamaki, M. *Yakugaku Zasshi* **1974**, *94*, 617; *Chem. Abstr.* **1974**, *81*, 74924y. Isolation of (+)-pretazettine: (c) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749. Total syntheses of (±)-haemanthidine and (±)-pretazettine: (d) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5538. (e) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781. (f) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (g) Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431. (h) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962. Formal total syntheses of (±)-haemanthidine and (±)-pretazettine: (i) Ishibashi, H.; Nakatani, H.; Iwatani, S.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Chem. Soc., Chem. Commun* **1989**, 1767. (j) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360. Total syntheses of (−)-haemanthidine, (+)-prettazetine, and (+)-tazettine: (k) Baldwin, S. W.; Debenham, J. S. *Org. Lett.* **2000**, *2*, 99.

10.1021/jo030309b CCC: $27.50
Published on Web 02/14/2004

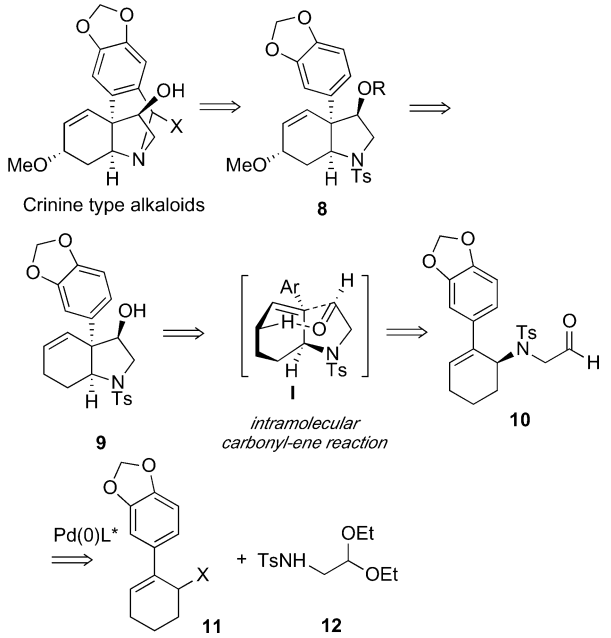
SCHEME 2. Asymmetric Allylic Substitution



the intermediary π-allylpalladium complex **5** is meso type (Scheme 2). Thus, a nucleophile attacks from both sides of π-allylpalladium complex **5** to give racemic **6**. However, if a chiral ligand is used for this reaction, the intermediary π-allylpalladium complex should be a chiral form. Thus, the nucleophile attacks preferentially from one side to give **6** enantioselectively. Using this strategy, we synthesized **6a** in an enantioriched form from **4a**. After conversion of **6a** into **6b**, zirconium-mediated cyclization of **6b** was carried out, and hexahydroindole derivative **7** was obtained. From **7**, (−)-mesembrane and (−)-mesembrine were synthesized.[5a]

Here, we report the first asymmetric total syntheses[6] of the crinine-type alkaloids (+)-crinamine ((+)-**1**), (−)-haemanthidine ((−)-**2**), and (+)-pretazettine ((+)-**3**). In the previous natural product syntheses,[5a] we used zirconium-mediated cyclization for the synthesis of a hexahydroindole derivative. However, for the synthesis of crinine-type alkaloids, a hydroxymethyl group of **7** must be converted into a hydroxyl group. Thus, an alternative route was considered. The retrosynthetic analysis of these alkaloids is shown in Scheme 3.

SCHEME 3. Retrosynthetic Analysis of Crinine-Type Alkaloids



If aldehyde (*S*)-**10** was obtained from **11** and **12** using this palladium-catalyzed asymmetric allylic substitution, the intramolecular carbonyl−ene reaction[7] of **10** would construct a quaternary carbon center of **9** in a stereoselective manner via **I**. From this compound, the target alkaloids **1**−**3** would be synthesized as chiral forms in a short numbers of steps.

Results and Discussion

Asymmetric Allylic Substitution of a Cyclohexenol Derivative Having an Aromatic Ring at the 2-Position. Initially, **4a** was used as a model compound to synthesize a chiral cyclohexenylamine derivative, **14**. When a THF solution of **4a** (1 equiv), acetal **12**[8] (1.1 equiv), Pd_2dba_3·$CHCl_3$ (2.5 mol %), and dppb (5.0 mol %) was stirred at 60 °C for 2 h, a cyclohexenylamine derivative, **13**, was obtained in 40% yield (Table 1, run 1). When the ligand was changed to (*S*)-BINAPO[9] and the reaction was carried out under similar conditions, the yield was increased to 83% and the ee[10] was 76% (run 2). The ee was increased to 84% when the reaction was carried out at room temperature (run 3), but the reaction rate decreased at the lower temperature (run 4). In the

(4) Total syntheses of (±)-tazettine and/or (±)-6a-epipretazettine: (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (b) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (c) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300. (d) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. (e) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848. (f) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc* **1998**, *120*, 3664. For the formal total synthesis of (±)-6a-epipretazettine (synthetic compound by Wildman) see: Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150). (g) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647. Efforts for syntheses: (h) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662. (i) Baldwin, S. W.; Aube, J.; McPhail, A. T. *J. Org. Chem.* **1991**, *56*, 6546. (j) Watson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 1519.

(5) (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (b) Preliminary report: Nishimata, T.; Mori, M. J. *Org. Chem.* **1998**, *63*, 7586. (c) Nishimata, T.; Yamaguchi, K.; Mori, M. *Tetrahedron Lett.* **1999**, 40, 5713. (d) Mori, M.; Nishimata, T.; Nagasawa, Y.; Sato, Y. *Adv. Synth. Catal.* **2001**, *343*, 34.

(6) Asymmetric total syntheses of crinine-type alkaloids: (a) [(+)-Maritidine] Yamada, S.-I.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, 57; *Chem. Pharm. Bull.* **1977**, *25*, 2681. (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; *J. Org. Chem.* **1998**, *63*, 3607. (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.

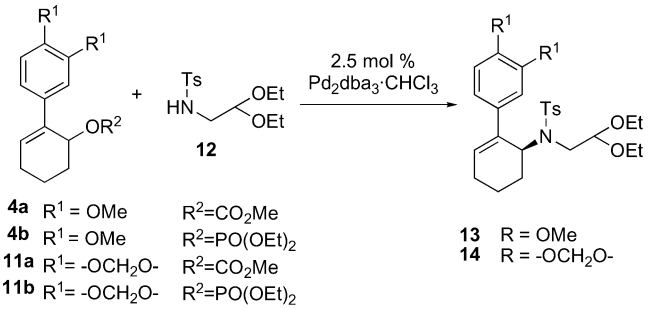
(7) Recent review: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(8) 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.

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

(10) The ee values of **13** and **14** were determined by HPLC analysis (DAICEL Chiralpak AD, hexane/2-propanol (9:1) and DAICEL CHIRALPAK AS, hexane/2-propanol (9:1), respectively).

TABLE 1. Palladium-Catalyzed Asymmetric Amination



4a R^1 = OMe R^2=CO_2Me
4b R^1 = OMe R^2=$PO(OEt)_2$
11a R^1= -OCH_2O- R^2=CO_2Me
11b R^1= -OCH_2O- R^2=$PO(OEt)_2$

13 R = OMe
14 R = -OCH_2O-

run	substrate	ligand	solvent	temp (°C)	time (h)	yield[a] (%)	ee (%)
1	**4a**	dppb	THF	60	2	40	
2	**4a**	(*S*)-BINAPO	THF	60	2	83	76
3	**4a**	(*S*)-BINAPO	THF	rt	19	87	84
4	**4a**	(*S*)-BINAPO	THF	0	330	30 (31)	88
5	**4b**	(*S*)-BINAPO	THF	0	2	84	88
6	**11a**	dppb	THF	60	3	51	
7	**11a**	(*S*)-BINAPO	THF	rt	18	68	60
8	**11a**	(*S*)-BINAPO	THF	0	106	31 (38)	68
9	**11b**	(*S*)-BINAPO	THF	0	4	73	69
10	**11b**	(*S*)-BINAPO	THF	−20	48	80	74
11	**11b**	(*S*)-BINAPO	DMF	−20	91	65	67
12	**11b**	(*S*)-BINAPO	EtCN	−20	310	48 (21)	68
13	**11b**	(*S*)-BINAP	THF	rt	160	43 (28)	75

[a] The numbers in parentheses show the yields of recovered starting material.

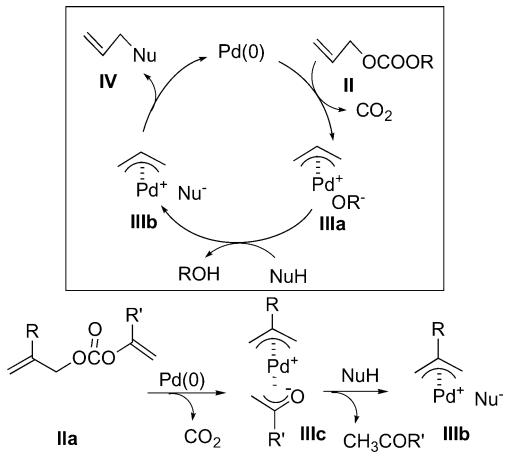
case of phosphonate **4b**, the desired compound **13** with high ee was obtained in high yield (run 5). When a cyclohexenol derivative, **11a**, having a methylenedioxyphenyl group at the 2-position was treated in a similar manner, both the yield and the ee were decreased (runs 7 and 8).

The reaction was carried out under various conditions. Surprisingly, when phosphonate **11b** was used instead of methyl carbonate **11a**, the reaction rate increased, and after 4 h, the desired compound **14** was obtained in 73% yield (run 9). Even at the lower temperature, the reaction proceeded, and desired compound **14** with 74% ee was obtained in 80% yield after 48 h (run 10). THF was found to be the most suitable solvent (runs 10−12), and the use of (*S*)-BINAP as a ligand gave **14** with 75% ee, but the yield was only moderate (run 13).

Development of a Novel Leaving Group for Palladium-Catalyzed Allylic Substitution. The reaction of an allylic compound with a nucleophile using a stoichiometric amount of palladium catalyst was developed by Tsuji.[11] Subsequently, this reaction was carried out as a catalytic reaction using alkyl allyl carbonate.[12]

Although phosphonate is a good leaving group in palladium-catalyzed allylic substitution, we searched for another effective leaving group. Among the many leaving groups for palladium-catalyzed allylic substitution, alkyl allyl carbonate is unique because an alkoxide anion is generated and thus a base is not required. The reaction of palladium-catalyzed allylic substitution proceeds via the formation of a π-allylpalladium complex. If alkyl allyl carbonate **II** is used for this reaction, π-allylpalladium

SCHEME 4. Plan for the Use of Vinyl Carbonate as a Leaving Group



complex **IIIa** is formed from **II** and Pd(0), and it is converted into complex **IIIb** by abstraction of a proton from the nucleophile (Scheme 4). Thus, the nucleophile can react with the π-allylpalladium complex without a base to form **IV**. If vinyl carbonate **IIa** is used for this reaction, oxo-π-allylpalladium complex **IIIc** is formed.[13] Since **IIIc** should be a stable palladium enolate complex, it was expected that the reaction rate might be accelerated.

When a THF solution of allyl vinyl carbonate **4c** and tosyl amide **12** was stirred in the presence of Pd_2dba_3·$CHCl_3$ and (*S*)-BINAPO at 0 °C, surprisingly, the desired product **13** with 88% ee was obtained in 90% yield after only 2 h, while the reaction of methyl carbonate **4a** gave **13** in 30% yield after 330 h under the same reaction conditions (Table 2, runs 1 and 2). Even at −20 °C, the reaction proceeded and the desired product **13** with 92% ee was obtained in 78% yield (run 3). The reactivity of isopropenyl carbonate **4d** was slightly lower than that of vinyl carbonate **4c** because of the steric hindrance (runs 2 and 4).

Similar results were obtained when vinyl carbonate **11c** was used for this reaction. The desired product **14** was obtained in 69% yield after 2.5 h (run 7), while the reaction of methyl carbonate **11a** with **12** afforded **4** in 31% yield after 106 h (run 6). The reactivity of isopropenyl carbonate **11d** was lower than that of vinyl carbonate **11c** (runs 8 and 9). In each case, the leaving group did not affect the enantioselectivity of **13** or **14**, but it was affected by the reaction temperature. Thus, compound **14** was obtained in high yield by use of vinyl carbonate compared with use of methyl carbonate, and the reactivity would be almost the same as that of phosphonate.

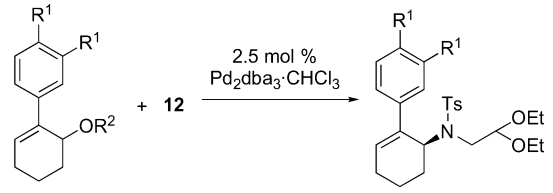
Synthesis of Hexahydroindole Derivatives Using Carbonyl-Ene Reaction. Since the desired compound **14** was obtained from **11b** or **11c** in an enantioriched form, the usefulness of a carbonyl−ene reaction for

(11) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: West Sussex, England, 1995; p 290.

(12) (a) Hata, G.; Takahashi, K.; Miyake, A. *Chem. Commun.* **1970**, 1392. (b) Atkin, K. E. W.; Walker, E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821.

(13) A palladium-catalyzed reaction using allyl carbonate has been reported: (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. Palladium-catalyzed allylation using allyl vinyl carbonate has been reported: (c) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (d) Shimizu, I.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 1797.

TABLE 2. Reaction of Vinyl Carbonate with 12 in the Presence of Pd(0)

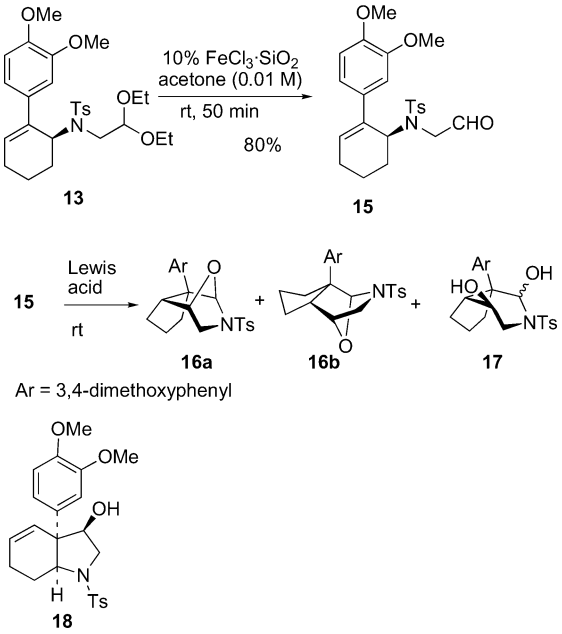


4a R^1 = OMe R^2=CO_2Me
4c R^1 = OMe R^2=$CO_2CH{=}CH_2$
4d R^1 = OMe R^2=$CO_2CMe{=}CH_2$
11a R^1= -OCH_2O- R^2=CO_2Me
11c R^1= -OCH_2O- R^2=$CO_2CH{=}CH_2$
11d R^1= -OCH_2O- R^2=$CO_2CMe{=}CH_2$

13 R = OMe
14 R = -OCH_2O-

run	substrate	temp (°C)	time (h)	product	yield (%)	ee (%)
1	**4a**	0	330	**13**	30	88
2	**4c**	0	2	**13**	90	88
3	**4c**	−20	116	**13**	78	92
4	**4d**	0	5	**13**	67	88
5	**4d**	−20	145	**13**	50	91
6	**11a**	0	106	**14**	31	68
7	**11c**	0	2.5	**14**	69	68
8	**11c**	−20	53	**14**	82	74
9	**11d**	−20	245	**14**	39	74

SCHEME 5. Treatment of 15 with Lewis Acid



constructing a hexahydroindole skeleton was next examined. A model compound, **13**, was converted into **15** in high yield by treatment with $FeCl_3$·SiO_2[14] (Scheme 5). Initially, Lewis-acid-promoted carbonyl−ene reactions of **15** were carried out. When a CH_2Cl_2 solution of **15** was stirred in the presence of a Lewis acid such as $TiCl_4$, $FeCl_3$, Me_2AlCl, Et_2AlCl, and MAD at room temperature, the desired product **18** was not obtained and a complex mixture was formed. However, when $AlCl_3$ was used as a Lewis acid, an unexpected product, **17**, was obtained after hydrolysis with aqueous $NaHCO_3$ solution (Table 3, run 1).

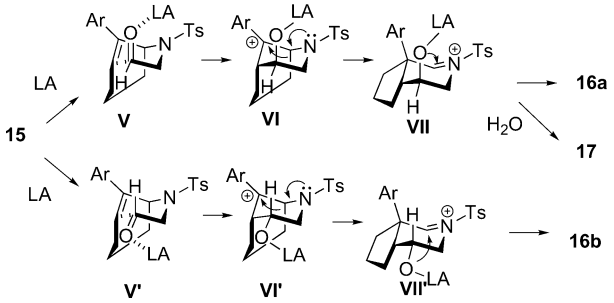
(14) Fadel, A.; Yefsah, R.; Salaun, J. *Synthesis* **1987**, 37.

TABLE 3. Lewis-Acid-Promoted Reaction of 15

run	Lewis acid	equiv	yield (%) 16a	16b	17
1	$AlCl_3$	1	3	2	50
2	$AlCl_3$[a]	1	67	5	
3	$SnCl_4$	1	13	6	29
4	$SnCl_4$	0.1	84	5	

[a] The reaction mixture was treated with $^iPr_2NEt$.

SCHEME 6. Possible Mechanism of Lewis-Acid-Promoted Rearrangement



On the other hand, when the reaction mixture was treated with $^iPr_2NEt$, two compounds, **16a** and **16b**, were obtained as an inseparable mixture (run 2). Treatment of **15** with $SnCl_4$ afforded the same products, but the yield was low (run 3). However, the use of a catalytic amount of $SnCl_4$ (10 mol %) afforded **16** in 85% yield (run 4).

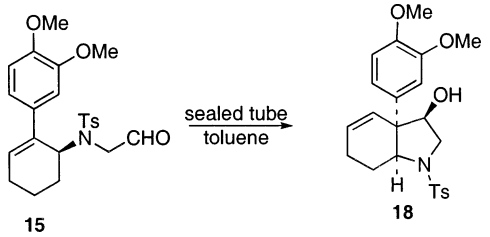
The structures of **16** and **17** were determined by NMR spectroscopic data, including NOESY and HMBC data. The possible reaction course for the formation of **16** and **17** is shown in Scheme 6. Coordination of a Lewis acid to the carbonyl group of **15** gives **V** and **V′**. Carbon−carbon bond formation between the carbonyl carbon coordinated by the Lewis acid and the double bond occurs to form the six-membered cation **VI**, and the generated cation **VI** should be stabilized by an adjacent aryl group.[15] Carbon−carbon bond fission of **VI** is accelerated by the formation of imminium cation, and then oxygen attacks the imminium cation of **VII** or **VII′**, resulting in the formation of **16a** or **16b**. Compound **17** would be formed by hydrolysis of **VII**.

Since Lewis-acid-catalyzed carbonyl−ene reactions gave undesired rearrangement products, carbonyl−ene reactions were carried out under thermal conditions. When a toluene solution of **15** was heated in a sealed tube at 180 °C for 15 h, only a small amount of desired hexahydroindole derivative **18** was obtained (Table 4, run 1). A higher reaction temperature increased the yield of the desired compound **18** (run 2), but reproducibility was not achieved. Thus, molecular sieves were added to the reaction mixture. When the solution was heated at 230 °C for 45 min, **18** was obtained in 40% yield in the presence of 4 Å molecular sieves (run 3). Furthermore, when dried molecular sieves were used, **18** was obtained in 60% yield and reproducibility was achieved (run 4).

Since the thermal carbonyl−ene reaction of **15** afforded desired hexahydroindole derivative **18**, an attempt was made to convert **14** into hexahydroindole derivative **9** for

(15) A similar rearrangement has been reported. See: Csuzdi, E.; Pallagi, I.; Jerkovich, G.; Solyom, S. *Synlett* **1994**, 429.

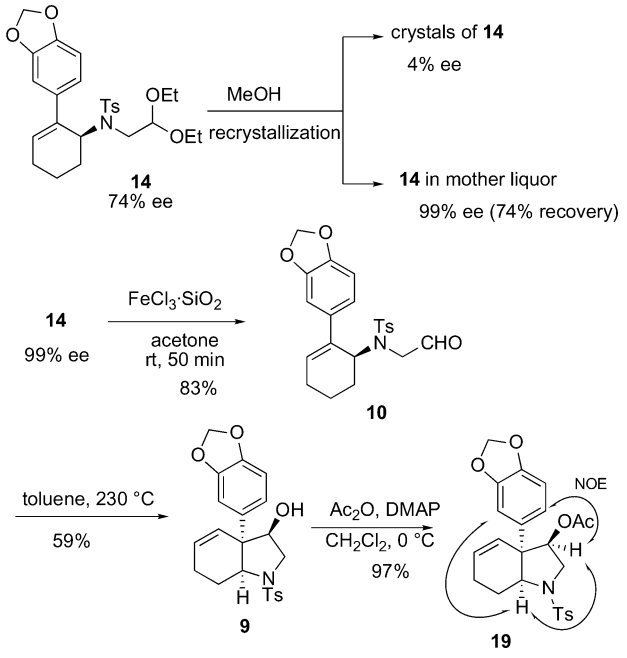
TABLE 4. Intramolecular Carbonyl−Ene Reactions under Thermal Conditions



entry	temp (°C)	time (h)	additive	SM (%)	yield (%)
1	180	15			5
2	200−230	3			26
3	230	0.5	4 Å molecular sieves	51	40
4	230	1.1	4 Å molecular sieves[a]		60

[a] 4 Å molecular sieves were dried at 180 °C under reduced pressure.

SCHEME 7. Construction of a *cis*-3a-Aryloctahydroindole Moiety



the total syntheses of crinine-type alkaloids as enantiomerically pure forms. Surprisingly, when compound **14** with 74% ee was recrystallized from MeOH, racemic **14** was obtained as a colorless crystal, and concentration of the mother liquor gave oily (−)-**14** with 99% ee in 74% recovery.

Next, the intramolecular carbonyl−ene reaction of enantiopure **10** was carried out. Deacetalization of **14** (99% ee) with $FeCl_3$·SiO_2[14] gave the aldehyde **10** in high yield (Scheme 7).

As expected, when a toluene solution of **10** was heated at 230−240 °C in the presence of dried 4 Å molecular sieves for several hours, the desired hexahydroindole **9** was obtained in 59% yield as an identifiable product. Results of the NOE experiments using acetylated compound **19** indicated that the ring junction of the five,six-membered ring is *cis* and that an acetoxy group is *trans* to an aryl group. The stereochemistry of the ring junction

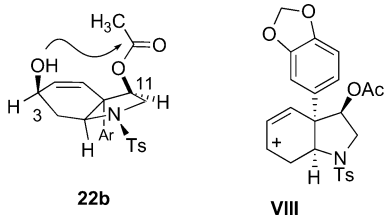
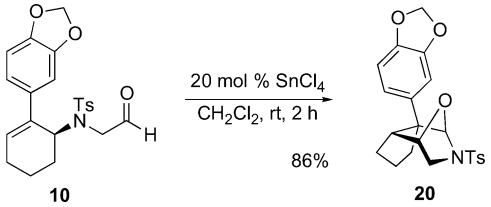
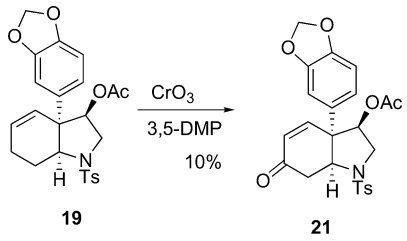


FIGURE 1. Formation of **22b** and allyl cation.

SCHEME 8. $SnCl_4$-Catalyzed Rearrangement



SCHEME 9. Allylic Oxidation of 19



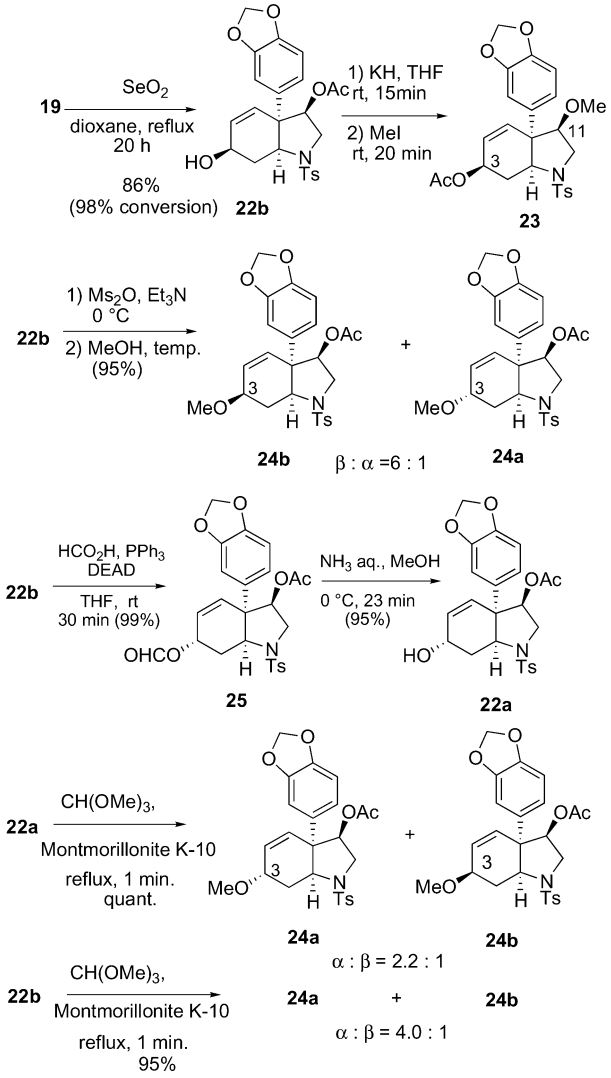
and the acetoxy group of **19** is consistent with that of the target alkaloids **1**−**3**. In contrast to thermal conditions, the $SnCl_4$-catalyzed (20 mol %) carbonyl−ene reaction of **10** in CH_2Cl_2 at 0 °C for 3 h gave a rearrangement product, **20**, in 86% yield (Scheme 8).

Total Syntheses of (+)-Crinamine, (−)-Haemanthidine, and (+)-Pretazetine. Finally, we turned our attention to the syntheses of crinine-type alkaloids such as (+)-**1**, (−)-**2**, and (+)-**3**. Since these alkaloids have a hydroxyl group or methoxy group at the 3-position, allylic oxidation was carried out. Treatment of **19** with CrO_3 in the presence of 3,5-dimethylpyrazole[16] gave desired compound **21** in only 10% yield (Scheme 9).

Subsequently, **19** was treated with SeO_2 in dioxane to afford allyl alcohol **22b** in high yield, but the stereochemistry of the hydroxyl group could not be determined (Scheme 10). Methylation of this compound with KH afforded an unexpected product, **23**, whose acetyl group migrates onto the 3-position of **23**. Since the β-hydroxyl group at the 3-position in the concave face is near the β-acetoxy group at the 11-position, migration of the acetyl group to the hydroxyl group at the 3-position occurred, and then methylation proceeded as shown in Figure 1. This means that the hydroxyl group at the 3-position should be placed at the β-position. Mesylation followed by treatment with MeOH at 0 °C afforded β-methoxylated compound **24b** (ratio of α to β 1:6) as a major product. Presumably, allylic cation **VIII** is formed (Figure 1), and then methanol attacks from the concave face to produce β-hydroxyl compound. This is an unexpected result

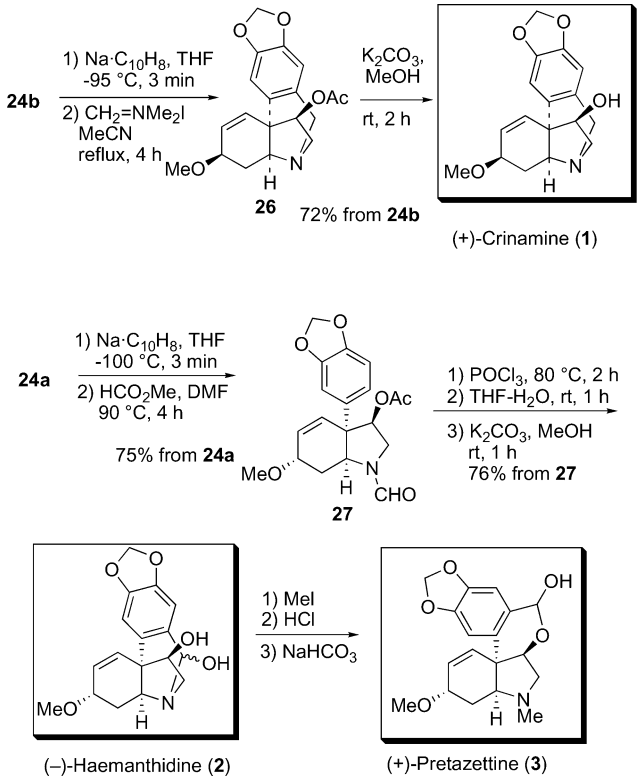
(16) (a) Corey, E. J.; Fleet, W. J. *Tetrahedron Lett.* **1973**, 4499. (b) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *21*, 1357.

SCHEME 10. Methoxylation of the C-3 Position of 22b



because it was thought that methanol would attack from the convex face to give an α-methoxylated compound.[17] For the synthesis of crinine-type alkaloids, it is important to introduce α- and *β*-methoxy groups at the C-3 position in a stereoselective manner. Thus, an α-methoxylated compound was synthesized. Mitsunobu reaction of **22b** in the presence of formic acid smoothly proceeded to give formylated compound **25**, which was treated with NH_3 in MeOH to afford α-hydroxylated compound **22a** in high yield. Many attempts for methylation of the α-hydroxyl group were then made, but all attempts were fruitless. Fortunately, a methyl orthformate solution of **22b** was refluxed in the presence of Montmorillonite K-10[18] for 1 min to give α-methoxylated compound **24a** as a major product (ratio of α to *β* 2.2:1) in quantitative yield. In a similar treatment of *β*-hydroxylated compound **22b**, **24a** was also obtained as a major product (ratio of α to *β* 4:1) in 95% yield. In the reaction of a mesylated compound of **22b** with MeOH, an allylic cation, **VIII**, was formed,

SCHEME 11. Total Syntheses of (+)-Crinamine, (−)-Haemanthidine, and (+)-Pretazetine



and **24b** was obtained as the main product (ratio of 6:1) via S_N1. However, the reaction of **22a**, obtained by Mitsunobu reaction with **22b**, with $HC(OMe)_3$ gave **24a** and **24b** in a ratio of 2.2:1. Moreover, the reaction of **22b** with $HC(OMe)_3$ gave **24a** as the main product in a ratio of 4:1.

It is difficult to explain these results. Presumably, the reaction of **22a** or **22b** with $HC(OMe)_3$ in the presence of Montmorillonite K-10 proceeds via both S_N1 and S_N2.

Finally, we tried to synthesize (+)-**1**, whose methoxy group is placed at the *β*-position. Detosylation of **24b** followed by methylenation with an Eschenmoser reagent afforded **26** (Scheme 11). Deacetylation of **26** afforded **1**, whose $[\alpha]_D$ value and spectral data agreed with those of (+)-crinamine reported in the literature.[2b] Thus, we succeeded in the first asymmetric total synthesis of (+)-crinamine from cyclohexenol derivative **11c** via 10 steps in 19% overall yield.

Subsequently, we tried to synthesize crinine-type alkaloids having α-methoxy groups at the C-3 positions. Detosylation of **24a** followed by treatment with methyl formate[19] afforded **27**, which was treated with $POCl_3$ followed by deacetylation to give alcohol **2**, whose $[\alpha]_D$ values and spectral data agreed with those reported in the literature.[3a−c] (+)-**3** was synthesized from (−)-**2** by the known method.[3c−f]

Thus, we succeeded in short asymmetric total syntheses of crinine-type alkaloids (+)-**1**, (−)-**2**, and (+)-**3**, using palladium-catalyzed asymmetric allylic substitution developed by us and carbonyl−ene reaction as key steps.

(17) In previous studies,[3g,h,4a−c] a compound having the methyl group on nitrogen (in our case, the tosyl group) was treated under the same reaction conditions to give only an 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.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 09470478) from the Ministry of Education, Science, Sports and Culture, Japan, which is gratefully acknowledged.

Supporting Information Available: Information on experimental procedures and spectral data for substrates **4c**−**d**, **9**, **10**, **11a**−**d**, **13**−**21**, **23a**,**b**, **24**, **25a**,**b**, **26**, and **28** and **(+)**-crinamine, (−)-haemanthidine, and (+)-pretazettine. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030309B