Chiral Lewis Acid-Mediated Enantioselective Pictet−Spengler Reaction of N_b-Hydroxytryptamine with Aldehydes

Hideki Yamada,† Tomohiko Kawate,† Miyako Matsumizu,† Atsushi Nishida,† Kentaro Yamaguchi,‡ and Masako Nakagawa*,†

Faculty of Pharmaceutical Sciences and Chemical Analytical Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba-shi 263-8522, Japan

Received April 29, 1998

The *first example of a reagent-controlled enantioselective Pictet−Spengler reaction* is demonstrated. Using diisopinocampheylchloroborane as a chiral Lewis acid catalyst, the Pictet−Spengler reaction of N_b-hydroxytryptamine with aldehydes gave the corresponding 2-hydroxytetrahydro-β-carbolines in up to 90% ee. The enantioselective Pictet−Spengler reaction catalyzed by chiral binaphthol-derived Brønsted acid-assisted Lewis acids, with up to 91% ee, is also demonstrated.

Introduction

The Pictet−Spengler (PS) reaction is now established as one of the most powerful methods for the construction of both tetrahydro-β-carboline and tetrahydroisoquinoline frameworks.[1] Numerous naturally occurring indole and isoquinoline alkaloids, with a wide range of important biological and pharmaceutical properties, have been synthesized by this method. Our interest in this area of chemistry arose out of our earlier investigations of the total syntheses of fumitremorgins[2] and eudistomines.[3] Since many indole alkaloids have a stereogenic center at C-1 of the tetrahydro-β-carboline ring system, the synthetic method for preparing this heterocyclic framework in an enantiomerically pure form should be the subject of widespread interest in both organic and medicinal chemistry. Several stereoselective PS reactions have been reported, in which optically active tryptophan esters or chiral aldehydes are used as the origin of chirality to yield optically active tetrahydro-β-carbolines.[4] Recently, Waldmann and co-workers reported the diastereoselective PS reaction of achiral imines, prepared from tryptamine and various aldehydes, using chiral acyl chloride with a *N*,*N*-phthaloylamino group as a removable external mediator.[5] In an investigation of the diastereoselective PS reaction, we found that a chiral α-phenethyl auxiliary group attached to N_b of tryptamine controlled the stereochemistry of the newly formed C-1 stereogenic center in the acid-catalyzed Pictet−Spengler reaction with up to 72% de.[6] Despite active investigation of the asymmetric PS reaction, to our knowledge, no information is currently available on the enantioselective PS reaction. In this paper, we report the chiral Lewis acid-promoted enantioselective cyclization of nitrones to give optically active N_b-hydroxytetrahydro-β-carbolines.[7]

Results and Discussion

We previously found that the PS reaction of N_b-hydroxytryptamine with a chiral aldehyde such as L-cysteinal produced the corresponding tetrahydro-β-carboline in 97% yield with high stereoselectivity (98% de),[3f] and nitrones have proven to be useful intermediates for studying the stereoselective PS reaction. N_b-Hydroxytryptamine was prepared by the reduction of 3-(2-nitroethyl)indole. Nitrones **1**−**6**, prepared from N_b-hydroxytryptamine and corresponding aldehydes, were stable and could be purified by either recrystallization or column chromatography. Moreover, the nitrones were confirmed to have the *Z* configuration by an X-ray analysis of **7**.[3f] A similar result was obtained by differential NOE experiments of **1** between C*H*═N (δ 7.07) and NCH_2 (δ 4.18) in $CDCl_3$, which reflected its *Z* configuration.

The reaction of **1** in CH_2Cl_2 or CH_3CN with an acid such as TFA, $AlCl_3$, $Sn(OTf)_2$, $GaCl_3$, $SbCl_3$, or BF_3·OEt_2 gave (±)-**9** in almost quantitative yield. However, nitrone **1** was less prone to the desired ring closure with the use of other boron reagents such as $(PhO)_3B$, $(C_6F_5O)_3B$, lithium or sodium cobalt−bis-dicarbollide, and $ZnCl_2$. No

† Faculty of Pharmaceutical Sciences.
‡ Chemical Analytical Center.

(1) (a) Whaley, W. M.; Govindachari, T. R. Organic Reactions; John Wiley & Sons: New York, 1951; Vol. 6, pp 151−190. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.

(2) (a) Nakagawa, M.; Kodato, S.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 6217−6220. (b) Kodato, S.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359−377. (c) Hino, T.; Kawate, T.; Nakagawa, M. *Tetrahedron* **1989**, *45*, 1941−1944. (d) Hino, T.; Nakagawa, M. *Heterocycles* **1997**, *46*, 673−704.

(3) (a) Nakagawa, M.; Liu, J.; Hino, T. *J. Am. Chem. Soc.* **1989**, *111*, 2721−2722. (b) Nakagawa, M.; Liu, J.; Ogata, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1988**, 463−464. (c) Liu, J.; Nakagawa, M.; Hino, T. *Tetrahedron* **1989**, *45*, 7729−7742. (d) Hino, T.; Hasegawa, A.; Liu, J.; Nakagawa, M. *Chem. Pharm. Bull.* **1990**, *38*, 59−64. (e) Liu, J.; Nakagawa, M.; Harada, N.; Tsuruoka, A.; Hasegawa, A.; Ma, J.; Hino, T. *Heterocycles* **1990**, *31*, 229−232. (f) Liu, J.; Nakagawa, M.; Ogata, K.; Hino, T. *Chem. Pharm. Bull.* **1991**, *39*, 1672−1676. (g) Hino, T.; Nakagawa, M. *J. Heterocycl. Chem.* **1994**, *31*, 625−630.

(4) Recent reports: (a) Zhang, P.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 6999−7002 and references therein. (b) Waldmann, H.; Schmidt, G. *Tetrahedron* **1994**, *50*, 11865-11884. (c) Bailey, P. D.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 3587−3588. (d) Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron* **1993**, *49*, 8589−8596. (e) Piper, I. M.; MacLean, D. B.; Kvarnström, I.; Szarek, W. A. *Can. J. Chem.* **1983**, *61*, 2721−2728.

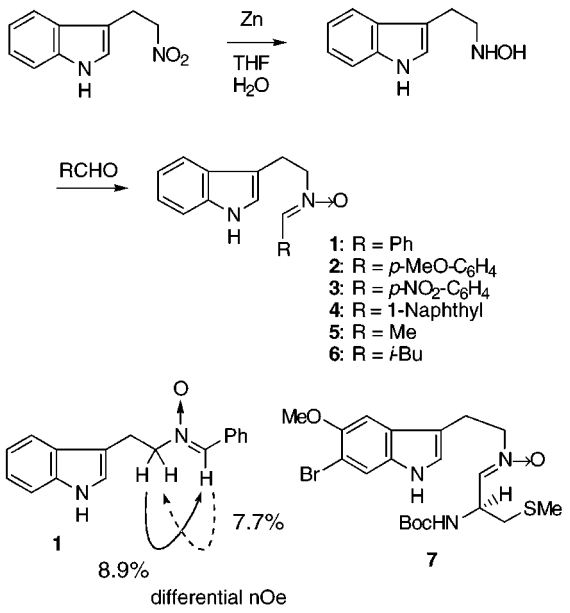
(5) (a) Waldman, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402−2403. (b) Schmidt, G.; Waldman, H.; Henke, H.; Burkard, M. *Chem. Eur. J.* **1996**, *2*, 1566−1571.

(6) (a) Than Soe; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Tetrahedron Lett.* **1995**, *36*, 1857−1860. (b) Than Soe; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347−358.

(7) Part of this work has been published as a preliminary communication: Kawate, T.; Yamada, H.; Than Soe; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249−1252.

S0022-3263(98)00810-X CCC: $15.00
Published on Web 08/20/1998

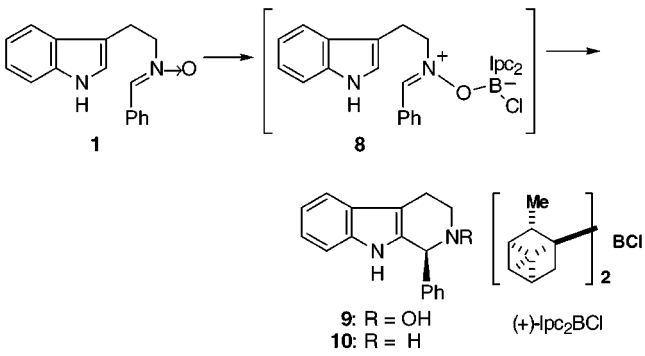
Scheme 1



reaction was observed with $Yb(OTf)_3$, Et_2AlCl, or Et_3Al. The authentic racemic β-carbolines **9** and **15**−**19** were prepared by the reaction with TFA in CH_2Cl_2, and HPLC conditions were examined (see the Experimental Section).

Next, we examined the enantioselective reaction of nitrone **1** with a chiral acid, (+)-diisopinocampheylchloroborane ((+)-Ipc_2BCl). When **1** was stirred in CH_2Cl_2 in the presence 1.9 molar equiv of (+)-Ipc_2BCl at room temperature for 2 h, **1** was smoothly cyclized to give (+)-**9** in 97% yield after silica gel column chromatography. The optical purity of (+)-**9** was determined to be 25% ee (*S*) by HPLC analysis using a chiral column (Daicel Chiralcel-OD). Encouraged by this result, we investigated the effects of temperature and solvent on this reaction (Table 1). Enantioselectivity increased with a decrease in reaction temperature. When the reaction was performed at −78 °C, an appreciable increase in selectivity (75% ee) was observed, while the chemical yield remained as high as 92% (Table 1, entry 4). The highest enantioselectivity, 87% ee, was obtained at −98 °C, although cyclization became sluggish (Table 1, entry 5). Treatment of **1** with (−)-Ipc_2BCl under the same protocol gave (−)-**9** in 94% yield with 83% ee (*R*) (Table 1, entry 6). The configuration at the C-1 stereogenic center could be determined by converting (−)-**9** to optically active **10**. Thus, (−)-**9** (83% ee, Table 1, Entry 6) was refluxed with zinc in MeOH−NH_4OH in the presence of $AcONH_4$ to give optically active **10** in 80% yield. By comparing the specific rotation of **10** ($[\alpha]^{20}_D$ +10.9 (*c* 0.53, EtOH)) with that of authentic (*S*)-**10** ($[\alpha]^{24}_D$ −16.4 (*c* 0.39, EtOH)),[8] the absolute configuration of (−)-**9** was determined to be *R*.[10] Other solvents such as CH_2Cl_2, Et_2O, PhMe, and

Table 1. Pictet−Spengler Reaction of 1 with Diisopinocampheylhaloboranes



entry	Lewis acid	solvent	*T* (°C)	time (h)	**9** yield (%)	**9** % ee
1	(+)-Ipc_2BCl	CH_2Cl_2	rt	2	97	25 (*S*)
2	(+)-Ipc_2BCl	CH_2Cl_2	0	1	97	48 (*S*)
3	(+)-Ipc_2BCl	CH_2Cl_2	−20	1	97	58 (*S*)
4	(+)-Ipc_2BCl	CH_2Cl_2	−78	6	92	75 (*S*)
5	(+)-Ipc_2BCl	CH_2Cl_2	−98	12	31	87 (*S*)
6	(−)-Ipc_2BCl	CH_2Cl_2	−78	3.5	94	83 (*R*)
7	(+)-Ipc_2BCl	Et_2O	−78	6	17	72 (*S*)
8	(+)-Ipc_2BCl	THF	−78	48	61	79 (*S*)
9	(+)-Ipc_2BCl	PhMe	−78	9	44	74 (*S*)
10	(+)-Ipc_2BBr	CH_2Cl_2	−78	24	69	67 (*S*)
11	(+)-Ipc_2BOTf	CH_2Cl_2	−78	28	78	55 (*S*)

THF had little or no effect on enantioselectivity, while the chemical yield of **9** varied from 17% to 92% (Table 1, entries 4 and 7−9). Since replacement of the chlorine atom of Ipc_2BCl was expected to alter the Lewis acidity of the boron, we next used (+)-Ipc_2BBr or (+)-Ipc_2BOTf. However, no improvement was observed (Table 1, entries 10 and 11). Although the enantioselectivity was 85% ee, the PS reaction of **1** gave only an 11% yield of (+)-**9** with 0.5 equiv of (+)-Ipc_2BCl (−78 °C, 4 days). The reaction should proceed via an iminium ion intermediate **8**, in which the boron of Ipc_2BCl is coordinated to the oxygen of the nitrone. The stereochemical outcome can be explained by assuming a transition state involving the nucleophilic attack of indole to the C=N double bond from the less hindered side (**8** → **9**). Preliminary calculations for the cyclization of **8**, from both the *re*- and *si*-faces of the C=N bond attacked by the indole nucleus at the 2-position, were carried out using a semiempirical molecular orbital calculation (MOPAC, AM1),[11] and the results are shown in Figure 1. The transition-state energy for a *re*-face approach (92.044 kcal/mol) to give (*S*)-**9** was less than that for a *si*-face approach (99.327 kcal/mol), which is consistent with experimental results.[12]

We next examined other chiral dialkylchloroboranes, such as dialkylchloroboranes **11** and **12** prepared by hydroboration of the corresponding chiral alkenes **13**[13] and **14**[14] with $H_2BCl{\cdot}SMe_2$,[15] which were used without purification. Compared to the reaction with (−)-Ipc_2BCl,

(8) The authentic samples (*S*)-**10**, $[\alpha]^{24}_D$ −16.4 (*c* 0.39, EtOH), and (*S*)-**21**, $[\alpha]^{26}_D$ −55.4 (*c* 0.41, MeOH), were synthesized from L-tryptophan methyl ester with benzaldehyde and isovaleraldehyde, respectively, according to the synthesis of (*S*)-**20** described in the literature.[9] Details of these syntheses will be reported separately. The specific rotation of (*R*)-**10** is also reported in ref 4b, $[\alpha]^{24}_D$ +15.6 (*c* 0.38, EtOH).

(9) Akimoto, H.; Okamura, K.; Yui, M.; Shioiri, T.; Kuramoto, H.; Kikugawa, Y.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 2614−2623. (*S*)-**20**, $[\alpha]^{24}_D$ −52 (*c* 2.0, EtOH).

(10) The calculated optical purity of **10** suggests partial racemization during zinc reduction of **9**. A reduction procedure without racemization is being actively investigated.

(11) The calculation was carried out using CAChe system Version 3.8, CAChe Scientific Inc., 1995.

(12) A similar result was obtained from a semiempirical molecular orbital calculation of the cyclization of **8** from both the *re*- and *si*-faces of the C=N bond attacked by indole nuclei at the 3-position.

(13) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128−1129.

(14) Dimmel, D. R.; Fu, W. Y. *J. Org. Chem.* **1973**, *38*, 3778−3782.

(15) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Lebelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731−3735.

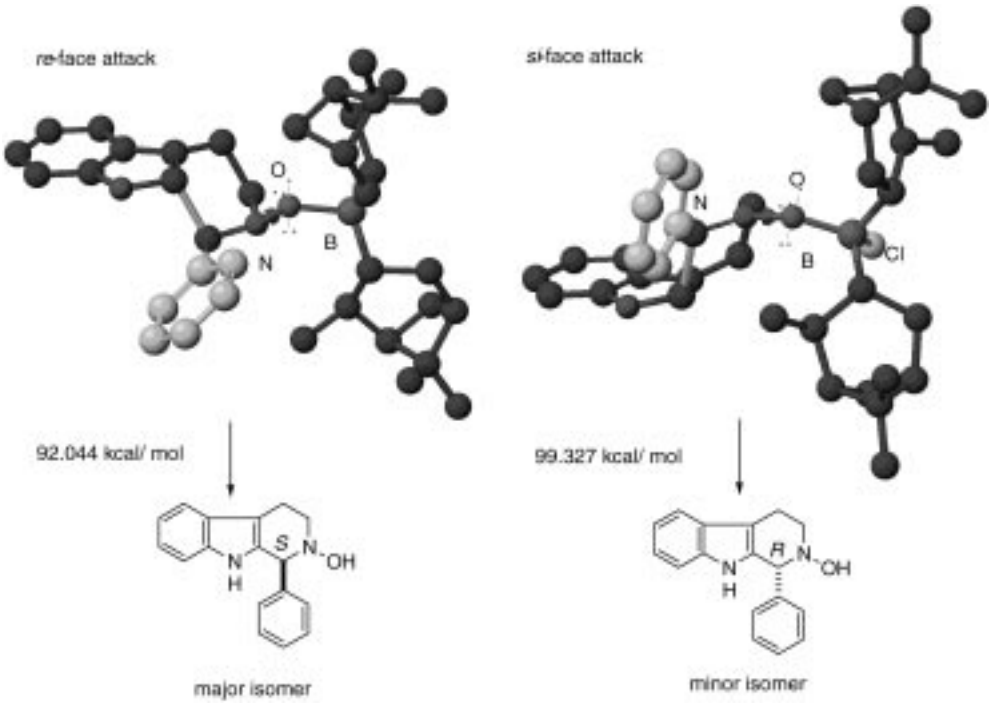
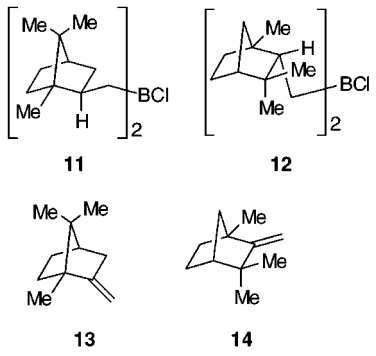


Figure 1. Transition-state model for **1** with (+)-Ipc_2BCl.

although the reaction of **1** catalyzed by **11** or **12** proceeded quantitatively, it gave poor enantioselectivity (less than 5% ee).



11 **12**

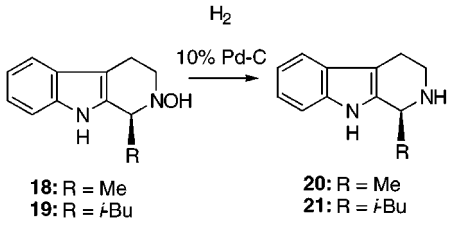
13 **14**

The cyclization of *p*-anisyl and 1-naphthyl nitrones **2** and **4** with (+)-Ipc_2BCl gave **15** and **17** with high enantioselectivity: 90 and 86% ee, respectively. No enantioselectivity was observed in the reaction of nitrone **3**, which has an electron-withdrawing nitro group, although the reaction proceeded more rapidly and gave a high yield. Nitrones **5** and **6**, which have an aliphatic substituent, gave *β*-carbolines **18** and **19** in high yields but with modest enantioselectivity. The absolute configuration of these hydroxy-*β*-carbolines **15** and **17**−**19** were determined by chemical correlation and spectroscopic methods. Hydrogenolysis of **18** and **19** was carried out to give the corresponding *β*-carbolines **20** and **21** in yields of 93 and 57%, respectively (Scheme 2).

Comparison of the specific rotations of **20** and **21** with those of authentic specimens[8,9] showed that the absolute configurations of both **20** and **21** were *S*. On the other hand, the stereochemistries of **15** and **17** were deduced to be *S* by comparison of the CD spectra of **15** and **17** with those of (*S*)- and (*R*)-**9**.

The enantiomeric enrichment of *β*-carbolines was achieved by simple recrystallization. The X-ray crystallographic structure of optically pure (*S*)-**15** indicated a trans configuration for the substituent at the 1-position and the hydroxy group at the 2-position (Figure 2).[16]

Scheme 2



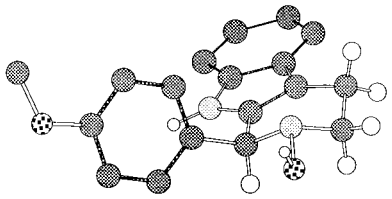
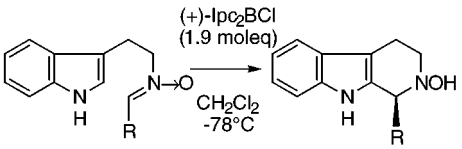


Figure 2. Crystal structure of (*S*)-**15**.

Next, we turned to the newly available Brønsted acid-assisted Lewis acids (BLAs) that were introduced by Yamamoto and co-workers for enantioselective PS reactions. The BLAs (*R*)-**24**, (*S*)-**24**, and (*R*)-**25** were prepared by mixing 2 equiv of optically active 2,2′-binaphthol, (*R*)-

(16) Crystallographic data for (*S*)-**15**: $C_{18}H_{18}N_2O_2$, M_w 294.35, orthorhombic crystal of dimensions 0.40 × 0.08 × 0.40 mm^3 (space group $P2_12_12_1$), with unit cell a = 8.174(2) Å, b = 29.537(3) Å, c = 6.235(2) Å, V = 1505.3(6) Å^3, Z = 4, D_{calcd} = 1.299 g cm^{-3}, F_{000} = 624.00. Lattice constants and intensity data were measured using graphite-monochromated Cu Kα (λ = 1.5418 Å) radiation on a Rigaku AFC5S diffractometer. A total of 1638 unique reflections were obtained using the $\omega-2\theta$ scanning method with a 2θ speed of 32° min^{-1} to $0 < 2\theta < 135.2°$. The structure was solved by a direct method using SIR92 and refined to a final R value of 0.048 and R_w = 0.055.

Table 2. Pictet−Spengler Reaction of Nitrones Catalyzed by (+)-Ipc_2BCl

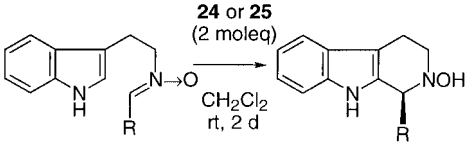


1: R = Ph
2: R = *p*-MeO-C_6H_4
3: R = *p*-NO_2-C_6H_4
4: R = 1-Naphthyl
5: R = Me
6: R = *i*-Bu

9: R = Ph
15: R = *p*-MeO-C_6H_4
16: R = *p*-NO_2-C_6H_4
17: R = 1-Naphthyl
18: R = Me
19: R = *i*-Bu

			β-carboline	
entry	nitrone	time (h)	yield (%)	% ee
1	**1**	6	**9** (92)	75 (*S*)
2	**2**	3	**15** (65)	90 (*S*)
3	**3**	1	**16** (81)	0.6
4	**4**	1	**17** (94)	86 (*S*)
5	**5**	3	**18** (91)	43 (*S*)
6	**6**	4	**19** (75)	35 (*S*)

Table 3. Pictet−Spengler Reaction of Nitrones Catalyzed by Brønsted Acid-Assisted Lewis Acids



1: R = Ph
2: R = *p*-MeO-C_6H_4
3: R = *p*-NO_2-C_6H_4
4: R = 1-Naphthyl
5: R = Me
6: R = *i*-Bu

9: R = Ph
15: R = *p*-MeO-C_6H_4
16: R = *p*-NO_2-C_6H_4
17: R = 1-Naphthyl
18: R = Me
19: R = *i*-Bu

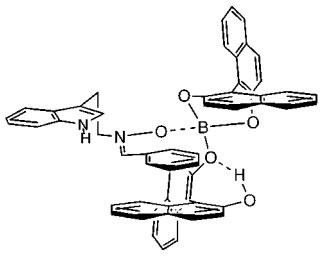
		Lewis	results		recovery of
entry	nitrone	acid	yield (%)	% ee[a]	nitrone (%)
1	**1**	(*R*)-**24**	**9** (81)	73 (*S*)	18
2	**2**	(*R*)-**24**	**15** (39)	91 (*S*)	44
3	**3**	(*R*)-**24**	**16** (75)	74 (*S*)	8
4	**4**	(*R*)-**24**	**17** (59)	31 (*S*)	26
5	**5**	(*R*)-**24**	**18** (94)	15 (*R*)	
6	**6**	(*R*)-**24**	**19** (68)	50 (*S*)	14
7	**1**	(*S*)-**24**	**9** (82)	78 (*R*)	7
8	**1**	(*R*)-**25**	**9** (84)	77 (*S*)	

[a] Enantiomeric excess and absolute configuration were determined by HPLC using a chiral column (Daicel, Chiralcel-OD).

22, (*S*)-**22**, and (*R*)-**23**, respectively, with $(PhO)_3B$ following Yamamoto's procedure.[17] The PS reactions of nitrones **1**−**6** were performed with (*R*)-**24**, (*S*)-**24**, and (*R*)-**25** in CH_2Cl_2 at room temperature for 48 h under an argon atmosphere. Thus, **1** was treated with 2 equiv of (*R*)-**24** to give (S)-**9** in 81% yield with 73% ee (Table 3, entry 1). (*R*)-**9** was obtained with (*S*)-**24** in similar selectivity (Table 3, entry 7). These conditions were also useful for the enantioselective cyclization of **2** and gave enantioselectivity of up to 91% ee (Table 3, entry 2). In particular, the enantioselectivity for the reaction of **3** was greatly improved compared with that using (+)-Ipc_2BCl, which did not show any selectivity (Table 3, entry 3 vs Table 2, entry 3).[18] The introduction of bromine at the

(17) Ishihara, K.; Miyata, M.; Hattori, K.; Toda, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524.

(18) **16** (74% ee) was treated with (+)-Ipc_2BCl under these reaction conditions in CH_2Cl_2 for 1 h. After quenching followed by silica gel column chromatography, **16** was recovered in 94% yield with 73% ee. This indicates that **16** did not undergo racemization by (+)-Ipc_2BCl during the PS reaction of **3** with (+)-Ipc_2BCl.



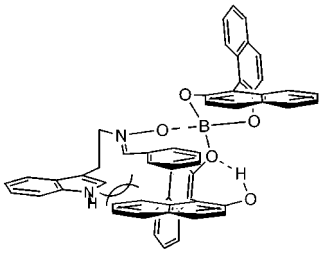
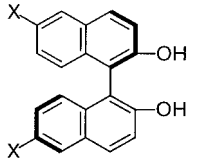
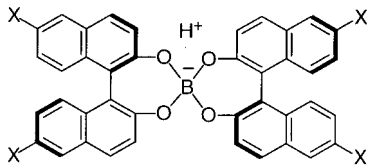


Figure 3. Transition-state model for asymmetric cyclization using BLA.

6- and 6′-positions of binaphthol had little effect on either the chemical yield or enantioselectivity (Table 3, entry 8). In all of the reactions, binaphthol was recovered in 70−80% yield.



(*R*)-**22** : X=H
(*R*)-**23** : X=Br



(*R*)-**24** : X=H
(*R*)-**25** : X=Br

The stereochemical outcome can be explained by assuming a model in which the oxygen of nitrone is coordinated to the boron of BLA, as shown in Figure 3. Transition state A, which shows a *si*-face approach of indole nuclei to the C=N double bond, would be preferred over transition state B due to steric hindrance between the indole ring of the nitrone and the naphthyl ring of the Lewis acid in transition state B.

In summary, a reagent-controlled enantioselective PS reaction was developed in the reaction of nitrones, prepared from N_b-hydroxytryptamine with various aldehydes, catalyzed by diisopinocampheylchloroborane and binaphthol-based Brønsted acid-assisted Lewis acid. The availability of both enantiomers of diisopinocampheylchloroborane as well as binaphthol is an advantage of our findings, and we hope theses results will provide a new strategy for the synthesis of optically active *β*-carboline alkaloids. Application of these results to natural product synthesis and further improvement of the enantioselectivity is in progress.

Experimental Section

Synthesis of Nitrones. Synthesis of *N*-Benzylidene-*N*-[2-(3-indolyl)ethyl]amine Oxide (1) (Typical Proce-

dure). Zinc powder (8.0 g, 122.3 mmol) was added to a stirred solution of 3-(2-nitroethyl)indole (4.0 g, 21.3 mmol) and NH_4Cl (2.3 g, 42.9 mmol) in THF (100 mL)−H_2O (40 mL) at room temperature over a period of 10 min. After being stirred at room temperature for 1.3 h, the mixture was filtered through a Celite pad. The organic layer was separated, washed with brine (40 mL), and dried over Na_2SO_4. Evaporation of the solvent gave crude hydroxytryptamine as a yellow solid, which was used for the next reaction without further purification. Benzaldehyde (3.2 mL, 31.4 mmol) was added to a stirred solution of the hydroxytryptamine (21.3 mmol) in dry THF (40 mL) at room temperature over a period of 5 min under an argon atmosphere. The whole was stirred at room temperature for 3 h and then concentrated. The resulting brown oil was chromatographed on silica gel with AcOEt/*n*-hexane (1/1−4/1) to give **1** as a yellow solid. Recrystallization from benzene gave nitrone **1** (3.4 g, 61% yield) as yellow prisms: mp 128−129 °C (benzene). This compound was spectroscopically identical to the authentic sample.[3d]

***N*-(4-Methoxybenzylidene)-*N*-[2-(3-indolyl)ethyl]amine oxide (2):** yield 69% (rt, 0.5 h); colorless needles; mp 157.5−158.0 °C (AcOEt/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 3.47 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 4.15 (t, J = 6.8 Hz, 2H), 6.90 (dt, J = 2.4, 9.9 Hz, 2H), 7.01 (s, 1H), 7.03 (d, J = 2.2 Hz, 1H), 7.13 (ddd, J = 0.9, 7.0, 7.9 Hz, 1H), 7.20 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 8.05 (brs, 1H), 8.14 (dt, J = 2.3, 9.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.71, 55.26, 67.09, 111.30, 111.36, 113.73, 118.28, 119.34, 121.95, 122.96, 123.28, 126.86, 130.52, 134.52, 136.26, 160.94; LRFABMS m/z 295 (M^+ + H). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.09; N, 9.54.

***N*-(4-Nitrobenzylidene)-*N*-[2-(3-indolyl)ethyl]amine oxide (3):** yield 68% (rt, 0.5 h); orange prisms; mp 196.0−197.0 °C (AcOEt/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 3.49 (t, J = 6.4 Hz, 2H), 4.25 (t, J = 6.7 Hz, 2H), 7.04 (d, J = 2.2 Hz, 1H), 7.12 (ddd, J = 0.9, 7.0, 7.9 Hz, 1H), 7.16 (s, 1H), 7.21 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 8.00 (brs, 1H), 8.21 (dt, J = 2.0, 9.1 Hz, 2H), 8.27 (dt, J = 2.0, 8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 23.44, 67.42, 110.11, 110.37, 118.20, 118.36, 121.04, 123.15, 123.70, 127.00, 128.47, 132.43, 136.10, 136.75, 146.84; LRFABMS m/z 310 (M^+ + H). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.06; H, 4.73; N, 13.71.

***N*-[(1-Naphthyl)methylidene]-*N*-[2-(3-indolyl)ethyl]amine oxide (4):** yield 72% (rt, 1.7 h); colorless prisms; mp 156.0−156.5 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 3.50 (t, J = 6.6 Hz, 2H), 4.34 (t, J = 6.6 Hz, 2H), 6.98 (d, J = 2.1 Hz, 1H), 7.16−7.26 (m, 3H), 7.31−7.45 (m, 3H), 7.52 (t, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.69−7.85 (m, 3H), 8.07 (brs, 1H), 9.39 (d, J = 9.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 23.66, 67.15, 110.42, 111.37, 118.37, 118.41, 121.02, 122.64, 123.19, 125.33, 125.43, 125.93, 126.23, 126.59, 127.09, 128.79, 129.60, 130.02, 130.13, 133.04, 136.18; LREIMS m/z 314 (M^+). Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.13; H, 5.75; N, 8.66.

***N*-Ethylidene-*N*-[2-(3-indolyl)ethyl]amine oxide (5):** yield 96% (rt, 0.1 h); brown amorphous solid; ^{1}H NMR ($CDCl_3$) δ 1.90 (d, J = 5.8 Hz, 3H), 3.39 (t, J = 6.7 Hz, 2H), 4.03 (t, J = 6.7 Hz, 2H), 6.46 (q, J = 5.8 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.13 (ddd, J = 1.1, 7.1, 8.2 Hz, 1H), 7.21 (ddd, J = 1.3, 7.0, 8.3 Hz, 1H), 7.38 (dd, J = 1.0, 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 8.25 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.47, 23.38, 65.64, 110.57, 111.42, 118.00, 118.96, 121.62, 122.96, 126.76, 135.95, 136.27; LRFABMS m/z 203 (M^+ + H); HRFABMS calcd for $C_{12}H_{14}N_2O$ + H 203.1184, found 203.1189.

***N*-(3-Methylbutylidene)-*N*-[2-(3-indolyl)ethyl]amine oxide (6):** yield 86% (rt, 0.4 h); brown oil. This compound was spectroscopically identical to the authentic sample.[3d]

Synthesis of (±)-2-Hydroxy-1-substituted-1,2,3,4-tetrahydro-*β*-carbolines. Synthesis of (±)-2-Hydroxy-1-(1-naphthyl)-1,2,3,4-tetrahydro-*β*-carboline ((±)-17) (Typical Procedure). Trifluoroacetic acid (0.12 mL, 1.5 mmol) was added dropwise to a stirred solution of nitrone **4** (171.9 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, and the reaction was quenched with saturated $NaHCO_3$ (10 mL) at 0 °C. The mixture was diluted with $CHCl_3$ (10 mL), and the organic layer was separated, washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent gave a yellow solid, which was recrystallized from AcOEt/*n*-hexane to give the hydroxytetrahydro-*β*-carboline (±)-**17** (130.7 mg, 76% yield) as colorless prisms: mp 160.0−161.0 °C (AcOEt/*n*-hexane); HPLC (eluent; *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min) t_R (min) 25.06 (*S*), 30.75 (*R*); ^{1}H NMR ($CDCl_3$) δ 3.02 (d, J = 5.1 Hz, 1H), 3.17 (brs, 1H), 3.30 (m, 1H), 3.61 (brs, 1H), 5.36 (m, 2H), 7.07−7.21 (m, 3H), 7.24 (m, 1H), 7.43−7.54 (m, 5H), 7.88 (m, 2H), 8.22 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 19.25, 79.19, 106.86, 111.19, 117.68, 118.33, 120.50, 125.21, 125.38, 125.53, 126.25, 128.24, 131.97, 133.78, 136.14, 136.53; LREIMS m/z 314 (M^+). Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.09; H, 6.07; N, 8.60.

(±)-2-Hydroxy-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline ((±)-9): yield 83% (rt, 2 h). This compound was spectroscopically identical to the authentic sample:[3d] HPLC (eluent; *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min) t_R (min) 12.48 (*S*), 22.60 (*R*).

(±)-2-Hydroxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-*β*-carboline ((±)-15): yield 54% (rt, 1 h); colorless prisms; mp 202.0−203.0 °C (AcOEt/*n*-hexane); HPLC (eluent; *n*-hexane/2-propanol/Et_2NH = 800/200/0.1, flow rate 0.5 mL/min) t_R (min) 21.46 (*S*), 38.27 (*R*); ^{1}H NMR ($CDCl_3$) δ 2.93 (m, 1H), 3.08 (m, 1H), 3.21 (m, 1H), 3.52 (m, 1H), 3.80 (s, 3H), 4.82 (brs, 1H), 6.10 (brs, 1H), 6.88 (m, 2H), 7.07−7.14 (m, 2H), 7.17 (m, 1H), 7.23 (m, 2H), 7.32 (brs, 1H), 7.50 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 20.03, 54.70, 55.07, 68.43, 106.76, 111.24, 113.37, 117.64, 118.34, 120.52, 126.12, 130.49, 133.02, 134.48, 136.67, 158.69; LRFABMS m/z 295 (M^+ + H). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.17; H, 6.08; N, 9.39.

(±)-2-Hydroxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydro-*β*-carboline ((±)-16): yield 45% (rt, 3 h); colorless prisms; mp 184.0−185.0 °C (AcOEt/*n*-hexane); HPLC (eluent; *n*-hexane/2-propanol/Et_2NH = 800/200/0.1, flow rate 1.0 mL/min) t_R (min) 11.28 (*S*), 25.59 (*R*); ^{1}H NMR (CD_3OD) δ 2.92 (m, 1H), 3.09 (m, 1H), 3.20 (m, 1H), 3.56 (m, 1H), 4.99 (brs, 1H), 6.98 (dt, J = 1.2, 7.3 Hz, 1H), 7.02 (dt, J = 1.4, 7.5 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.61 (dt, J = 2.2, 9.3 Hz, 2H), 8.23 (dt, J = 2.2, 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 20.34, 55.42, 59.75, 68.53, 107.14, 111.28, 117.86, 118.57, 120.90, 123.17, 125.88, 130.69, 133.11, 136.85, 146.99, 148.90; LRFABMS m/z 310 (M^+ + H). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.86; H, 4.71; N, 13.69.

(±)-2-Hydroxy-1-methyl-1,2,3,4-tetrahydro-*β*-carboline ((±)-18): yield 54% (rt, 0.5 h); colorless prisms; mp 191.0−192.0 °C (AcOEt/*n*-hexane); HPLC (eluent; *n*-hexane/2-propanol = 95/5, flow rate 1.2 mL/min) t_R (min) 52.67 (*S*), 61.42 (*R*); ^{1}H NMR ($CDCl_3$) δ 1.58 (d, J = 6.6 Hz, 3H), 2.88 (m, 2H), 3.17 (m, 1H), 3.58 (m, 1H), 3.98 (m, 1H), 6.30 (brs, 1H), 7.10 (t, J = 7.3 Hz, 1H), 7.16 (t, J = 7.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.71 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 18.01, 20.23, 55.43, 59.91, 105.63, 110.94, 117.50, 118.31, 120.33, 126.25, 136.01, 136.31; LRFABMS m/z 203 (M^+ + H). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.97; H, 7.03; N, 13.63.

(±)-2-Hydroxy-1-isobutyl-1,2,3,4-tetrahydro-*β*-carboline ((±)-19): yield 89% (rt, 0.4 h). This product was spectroscopically identical to the authentic sample:[3d] HPLC (eluent; *n*-hexane/2-propanol = 95/5, flow rate 1.0 mL/min) t_R (min) 32.27 (*S*), 66.54 (*R*).

Asymmetric Pictet−Spengler Reaction of Nitrones with Diisopinocampheylchloroborane. Synthesis of 2-Hydroxy-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline (9) (Typical Procedure: Table 1, Entry 4). A solution of (+)-Ipc_2BCl (259.4 mg, 0.8 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of nitrone **1** (110.5 mg, 0.41 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C under an argon atmosphere over a period of 10 min. The reaction mixture was stirred at −78 °C for 6 h, and the reaction was then quenched with saturated $NaHCO_3$ (10 mL). The mixture was diluted

with $CHCl_3$ (10 mL), and the organic layer was separated, washed with brine (10 mL), and dried over Na_2SO_4. After removal of the solvent, the resulting yellow oil was subjected to column chromatography on silica gel with AcOEt/*n*-hexane (1/8−1/2). Eluted product was further purified with silica gel preparative TLC with $Et_2O/CHCl_3$ (1/2) to give **9** (101.1 mg, 92% yield) as a colorless solid. The enantiomeric excess of this compound was determined to be 75% ee (*S*) by HPLC analysis. This product was spectroscopically identical to racemic **9**. Recrystallization from AcOEt/*n*-hexane gave (*S*)-**9** (100% ee) as colorless prisms. Optically pure (*S*)-**9**: mp 191.5−192.5 °C (AcOEt/*n*-hexane); $[\alpha]^{25}_D$ +49.5 (*c* 0.25, $CHCl_3$); CD (91% ee (*S*), MeOH, 4.1×10^{-4} M, 28 °C, 0.2 cm) λ ($\Delta\epsilon$) 206.6 (7.89), 215.8 (0), 227.8 (−12.41), 252.9 (0), 272.0 (2.68), 286.0 (1.85), 292.1 (1.16), 295.4 (1.29) nm; CD (83% ee (*R*), prepared in Table 1, entry 6, MeOH, 1.13×10^{-4} M, 26 °C, 0.1 cm) λ ($\Delta\epsilon$) 205.4 (−17.20), 215.1 (0), 227.6 (29.62), 254.4 (0), 270.6 (−5.48), 288.0 (−3.26), 292.1 (−1.99), 296.2 (−2.60) nm.

Asymmetric Pictet−Spengler Reaction of Nitrones with Chiral Brønsted Acid-Assisted Lewis Acid. Synthesis of 2-Hydroxy-1-phenyl-1,2,3,4-tetrahydro-β-carboline (9) (Typical Procedure: Table 3, Entry 7). A solution of $(PhO)_3B$ (232.4 mg, 0.8 mmol) in dry CH_2Cl_2 (5 mL) was added to a stirred suspension of (*S*)-**22** (458.4 mg, 1.6 mmol) and powdered MS-4A (2.0 g) in dry CH_2Cl_2 (15 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h, and the resulting suspension was used as Brønsted acid-assisted chiral Lewis acid (*S*)-**24** (0.8 mmol). A solution of nitrone **1** (104.3 mg, 0.39 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred suspension of Brønsted acid-assisted chiral Lewis acid (*S*)-**24** (0.8 mmol) and the mixture was stirred at room temperature for 48 h. The mixture was filtered through a Celite pad, and the filtrate was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a yellow solid, which was chromatographed on silica gel with AcOEt/*n*-hexane (1/6−1/2−1/0) to give the hydroxytetrahydro-β-carboline **9** (85.7 mg, 82%) as a colorless solid. This product was spectroscopically identical to racemic **9**. Binaphthol (*S*)-**22** (436.0 mg) and nitrone **1** (6.8 mg, 7%) were recovered. The enantiomeric excess of **9** (78% ee, *R*) was determined by a chiral HPLC analysis.

2-Hydroxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-β-carboline (15): yield 65%, 90% ee (*S*) (with (+)-Ipc_2BCl, −78 °C, 3 h), 39%, 91% ee (*S*) (with (*R*)-**24**). This product was spectroscopically identical to racemic **15**. After removal of racemic crystals by crystallization of **15** (80% ee) from AcOEt as the first and second crop, enantiomerically pure **15** was obtained from the third crop and its mother liquor. Recrystallization from AcOEt gave (*S*)-**15** (100% ee) as colorless prisms: mp 186.0−186.5 °C (AcOEt); $[\alpha]^{27.5}_D$ +33.6 (*c* 1.04, THF) for 100% ee (*S*); CD (100% ee (*S*), MeOH, 1.7×10^{-4} M, 26 °C, 0.1 cm) λ ($\Delta\epsilon$) 209.6 (22.42), 220.4 (44.02), 225.1 (0), 233.2 (−116.88), 252.3 (0), 285.2 (12.49), 295.4 (6.72) nm.

2-Hydroxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydro-β-carboline (16): yield 81%, 0.6% ee (with (+)-Ipc_2BCl, −78 °C, 1 h), 75%, 74% ee (*S*) (with (*R*)-**24**). This product was spectroscopically identical to racemic **16**: CD (71% ee (*S*), MeOH, 3.2×10^{-4} M, 22 °C, 0.2 cm) λ ($\Delta\epsilon$) 205.2 (3.00), 210.2 (0), 217.4 (−4.77), 220.1 (0), 227.6 (15.04), 239.4 (−7.27), 252.8 (−7.52), 268.5 (0), 281.8 (5.80), 301.0 (0), 309.8 (−0.69) nm.

2-Hydroxy-1-(1-naphthyl)-1,2,3,4-tetrahydro-β-carboline (17): yield 94%, 86% ee (*S*) (with (+)-Ipc_2BCl, −78 °C, 1 h), 59%, 31% ee (*S*) (with (*R*)-**24**). This product was spectroscopically identical to racemic **17**: $[\alpha]^{23}_D$ +62.6 (*c* 1.20, $CHCl_3$) for 86% ee (*S*); CD (86% ee (*S*), MeOH, 2.86×10^{-4} M, 20 °C, 0.1 cm) λ ($\Delta\epsilon$) 213.4 (7.01), 210.6 (0), 224.8 (−11.95), 227.9 (0), 230.8 (7.26), 233.2 (0), 236.6 (−2.87), 242,4 (−1.58), 245.3 (−1.70), 267.9 (0), 283.0 (2.14), 292.1 (0.92), 297.2 (1.44) nm.

2-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (18): yield 91%, 43% ee (*S*) (with (+)-Ipc_2BCl, −78 °C, 3 h), 94%, 15% ee (*R*) (with (*R*)-**24**). This product was spectroscopically identical to racemic **18**: CD (15% ee (*R*), MeOH, 1.98×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 202.2 (−1.54), 207.5 (0), 209.0 (0.07), 209.7 (0), 214.2 (−1.52), 221.6 (0), 230.0 (1.14), 239.5 (0), 253.0 (−0.19), 259.0 (0), 263.6 (0.18), 279.2 (0.13) nm.

2-Hydroxy-1-isobutyl-1,2,3,4-tetrahydro-β-carboline (19): yield 75%, 35% ee (*S*) (with (+)-Ipc_2BCl, −78 °C, 4 h), 68%, 50% ee (*S*) (with (*R*)-**24**). This product was spectroscopically identical to racemic **19**: CD (25% ee (*R*), MeOH, 2.86×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 212.8 (1.35), 217.9 (0), 224.8 (−2.63), 229.1 (0), 235.6 (4.06), 258.8 (0), 272.8 (−0.35), 277.5 (−0.26), 284.8 (−0.37), 291.6 (−0.26) nm.

Preparation of Chiral Dialkylchloroboranes. Preparation of 11 (Typical procedure).[15] Monochloroborane−dimethyl sulfide complex (0.10 mL, 0.96 mmol) was added dropwise to a stirred solution of **13** (331 mg, 2.20 mmol) in dry *n*-hexane (0.25 mL) at −10 °C under an argon atmosphere. After being stirred at 30 °C for 3 h, the resulting mixture was used as **11** (0.96 mmol) without further purification.

Synthesis of 1-Phenyl-1,2,3,4-tetrahydro-β-carboline (10). A mixture of **9** (70.1 mg, 0.26 mmol, 83% ee (*R*)) and $AcONH_4$ (50.0 mg) in aqueous 28% ammonia (2 mL), methanol (10 mL), and H_2O (5 mL) was heated at reflux temperature. Zinc powder (300.0 mg) was added to the refluxing mixture, and the mixture was refluxed for 0.5 h. Zinc powder (300.0 mg) was added to the reaction mixture, and the whole was refluxed for an additional 3.5 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was diluted with AcOEt (20 mL), and 3 N sodium hydroxide was added (∼pH 10). The organic layer was separated, washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was chromatographed on silica gel with AcOEt/*n*-hexane (1/1)−AcOEt to give the tetrahydro-β-carboline **10** (52.5 mg, 80%) as a colorless solid. This product was spectroscopically identical to known **10**.[3d,19] The enantiomeric excess of this compound was determined by measuring the optical rotation, which indicated 66% ee (*R*). Compound **10**: $[\alpha]^{20}_D$ +10.9 (*c* 0.53, EtOH), 66% ee (*R*); CD (66% ee (*R*), MeOH, 2.82×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 205.0 (−9.88), 213.6 (0), 229.2 (18.08), 253.6 (0), 271.6 (−4.84), 286.6 (−3.17), 292.2 (−1.40), 296.4 (−2.35) nm; CD (43% ee (*S*), MeOH, 2.82×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 206.8 (11.80), 215.1 (0), 229.0 (−18.90), 252,9 (0), 271.0 (4.15), 286.4 (3.15), 292.1 (1.89), 295.4 (2.28) nm.

Hydrogenolysis of 2-Hydroxytetrahydro-β-carboline. Synthesis of 1-Methyl-1,2,3,4-tetrahydro-β-carboline (20) (Typical Procedure). A mixture of **18** (54 mg, 0.26 mmol, 43% ee (*S*)) and 20% $Pd(OH)_2$ on carbon (16 mg) in methanol (5 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The catalyst was filtered through a Celite pad, and the pad was washed with AcOEt. The combined filtrate was concentrated under reduced pressure to give a residue, which was chromatographed on silica gel with AcOEt−AcOEt/methanol/Et_3N (20:2:1) to give **20** (46 mg, 93% yield) as a yellow solid. This product was spectroscopically identical to known **20**.[19] The enantiomeric excess of **20** was determined by measuring the optical rotation, which indicated 26% ee (*S*). Compound **20**: $[\alpha]^{24}_D$ −13.6 (*c* 0.46, EtOH), 26% ee (*S*); CD (50% ee (*S*), MeOH, 4.29×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 210.2 (−4.56), 212.6 (−4.35), 217.0 (−5.33), 219.4 (0), 232.6 (5.85), 243.2 (0), 246.6 (−0.13), 253.6 (0), 261.6 (0.31), 291.2 (0), 296.2 (0.25) nm.

1-Isobutyl-1,2,3,4-tetrahydro-β-carboline (21): yield 57%, 30% ee (*S*) from **18** of 34% ee (*S*) (rt, 38 h); $[\alpha]^{20}_D$ −16.6 (*c* 0.96, MeOH), 30% ee (*S*); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.62 (m, 2H), 1.87−2.04 (m, 2H), 2.74 (m, 2H), 3.03 (ddd, J = 5.4, 7.9, 13.3 Hz, 1H), 3.35 (dt, J = 4.6, 12.9 Hz, 1H), 4.11 (m, 1H), 7.09 (ddd, J = 1.1, 6.1, 8.3 Hz, 1H), 7.14 (ddd, J = 1.2, 7.6, 8.8 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.73 (brs, 1H); LREIMS *m*/*z* 228 (M^+); CD (30% ee (*S*), MeOH, 4.38×10^{-4} M, 25 °C, 0.2 cm) λ ($\Delta\epsilon$) 203.0 (−1.39), 205.2 (−1.09), 213.4 (−1.81), 215.6 (−1.52), 219.4 (−2.05), 226.8 (0), 231.2 (1.04), 241.7 (0), 245.4 (−0.11), 255.1 (0), 275.4 (0.22), 290.1 (0.05), 296.2 (0.17) nm.

(19) Nakagawa, M.; Kawate, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, *49*, 1739−1748.

Acknowledgment. This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Science, Education, Sports and Culture. Financial support from the Research Foundation of Optically Active Compounds, Japan Tabacco, Inc., and Toso Co., Inc., is gratefully acknowledged. The authors thank Dr. Hiroko Seki and Ms. Ritsuko Hara of the Chemical Analytical Center of Chiba University for performing the microanalyses and measuring mass spectra.

Supporting Information Available: Copies of the ^{1}H NMR spectra of compounds **1**−**6**, **9**, **10**, and **15**−**21**, copy of the ^{13}C NMR spectrum of **5**, IR and UV data for compounds **2**−**5**, (±)-**15**−**18**, and **21**, and X-ray material for (*S*)-**15** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980810H