Total Syntheses of β-Carboline Alkaloids, (*R*)-(−)-Pyridindolol K1, (*R*)-(−)-Pyridindolol K2, and (*R*)-(−)-Pyridindolol

Naoko Kanekiyo,[†] Takeshi Kuwada,[‡] Tominari Choshi,[†] Junko Nobuhiro,[†] and Satoshi Hibino*[,†]

Graduate School of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan, and Process Chemistry Laboratory, Medicinal Research Laboratory, Taisho Pharmaceutical Co. Ltd., 1−403 Yoshino-cho, Saitama, Saitama 330-8530, Japan

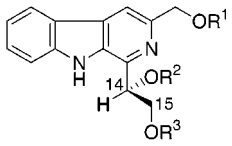
hibino@fupharm.fukuyama-u.ac.jp

Received June 4, 2001

The total syntheses of β-carboline alkaloids, (*R*)-(−)-pyridindolols (**1**, **5**, and **6**) are described. The two key steps involved are (1) a thermal electrocyclic reaction of the 3-alkenylindole-2-aldoxime **10** and (2) a thermal cyclization of 3-alkynylindole-2-aldoxime **11** to construct the β-carboline *N*-oxides **8**, which upon heating with acetic anhydride and sequential treatment with trifluoromethanesulfonic anhydride gave the triflates **18**. The Stille coupling reaction of **18** with vinylstannane, followed by cleavage of MOM ether, afforded the 1-ethenyl-3-hydroxymethyl-β-carboline (**7a**). Subsequent acetylation of **7a** yielded the acetate **7b**, which was subjected to the Sharpless asymmetric 1,2-dihydroxylation by AD-mix-β to produce (*R*)-(−)-pyridindolol K2 (**6**). Selective acetylation of **6** was effected by Ac_2O and collidine to form (*R*)-(−)-pyridindolol K1 (**5**). By contrast, hydrolysis of **6** provided (*R*)-(−)-pyridindolol (**1**).

Introduction

Pyridindolol (**1**) was isolated from *Streptomyces alboverticillatus* as a β-galactosidase inhibitor by Umezawa and co-workers in 1975.[1a] The structure has been elucidated by spectroscopic and X-ray crystallographic analyses to be 1-[1(*R*),2-dihydroxy]-3-hydroxymethyl-9*H*-pyrido-[3,4-*b*]indole.[1b] A structure−activity study has also been reported, with the data indicating that both hydroxy groups at C-14 and C-15 positions and the β-carboline nucleus are essential for the activity of pyridindolol in inhibiting β-galactosidase.[1c] In addition, three pyridindolol glucosides (**2**−**4**) have been isolated from *Streptomyces parvulus*, strain Tu2480 by Hagmann and co-workers.[2] Their structures were determined by spectroscopic investigations and degradation to pyridindolol and α,D-methylglucoside. Recently, the closely related pyridindolol K1 (**5**) and pyridindolol K2 (**6**) were isolated from *Streptomyces* sp. K93−0711 together with pyridindolol (**1**) by Omura and co-workers.[3] The conversion of pyridindolol K2 (**6**) to pyridindolol (**1**) has been carried out with sodium methoxide in methanol, with the absolute structures of **5** and **6** subsequently being determined to have the same stereochemistry as 14*R* of **1** by the CD spectrum. It has been also reported that pyridindolol K2 inhibits the adhesion of HL-60 cells to the LPS-activated HUVEC monolayer (IC_{50} = 75 μg/mL).



1 : R^1=R^2=R^3=H (pyridindolol)
2 : R^1=R^3=H, R^2=14β-D-glucoside
3 : R^1=R^2=H, R^3=15β-D-glucoside
4 : R^1=16β-D-glucoside, R^2=R^3=H
5 : R^1=R^3=Ac, R^2=H (pyridindolol K1)
6 : R^1=Ac, R^2=R^3=H (pyridindolol K2)

Two synthetic works regarding pyridindolol (**1**) have appeared. The first total synthesis of racemic pyridindolol (**1**) and (*S*)-(+)-pyridindolol (**1**) was reported by Cook and co-workers.[4] They employed Pictet−Spengler condensation of *dl*-tryptophan methyl ester with (*R*)-glyceraldehyde acetonide (60% optical purity) to produce the 1,2,3,4-tetrahydro-β-carboline acetonide as a mixture of diastereomers, enriched in the *S*-isomer ($[\alpha]^{23}_D$ −11°), which were subjected to aromatization with 5% Pd−C in refluxing cumene to provide the optically inactive β-carboline acetonide along with racemization. However, the optically active β-carboline acetonide with dextrorotatory direction ($[\alpha]^{23}_D$ +5.5°) was obtained by DDQ oxidation in benzene. Finally, total syntheses of racemic pyridindolol (**1**) and (*S*)-(+)-pyridoindolol (**1**) ($[\alpha]^{23}_D$ +7.7°) were established by two additional steps. At approximately the same time, Hamaguchi and Ohki[5] also reported that dehydrogena-

* To whom correspondence should be addressed. Fax: +81-849-36-2024.
[†] Fukuyama University.
[‡] Taisho Pharmaceutical Co. Ltd.

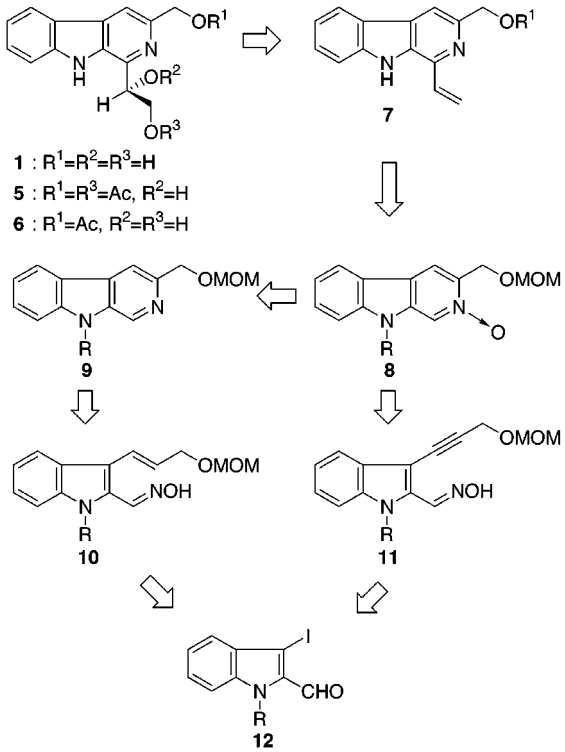
(1) (a) Aoyagi, T.; Kumagai, M.; Hazato, T.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1975**, *28*, 555−557. (b) Kumagai, M.; Naganawa, H.; Aoyagi, T.; Umezawa, H.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1975**, *28*, 876−880. (c) Kumagai, M.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 696−703.
(2) Hagemann, L.; Keller-Schierlein, W. *J. Antibiot.* **1988**, *41*, 289−295.
(3) Kim, Y.-P.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 189−193.
(4) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, F.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535−546.
(5) Hamaguchi, F.; Ohki, S. *Heterocycles* **1977**, *8*, 383−386.

10.1021/jo0105585 CCC: $20.00 © 2001 American Chemical Society
Published on Web 11/27/2001

tion of trihydroxy-1,2,3,4-tetrahydro-β-carboline, prepared from the condensation of tryptophanol and glyceraldehyde, with Pd/C does not lead to pyridindolol (**1**), and Cook[4] reported a similar failure for dihydroxy-1,2,3,4-tetrahydro-β-carboline.

In the course of our study, we have developed the syntheses of biologically active condensed heteroaromatic compounds, including natural products, based on a thermal electrocyclic reaction[6] of either hexatriene[7,8] or azahexatriene[7,9] systems incorporating a principal aromatic or heteroaromatic moiety. Recently, we communicated the first enantioselective total synthesis of (*R*)-(−)-pyridindolol K2 (**6**) and its enantiomer.[10] We here describe the details of the total synthesis of pyridindolol K2 (**6**) based on the construction of a β-carboline *N*-oxide framework **8** using two different ways of a thermal electrocyclic reaction of the 1-azahexatriene system **10** involving the indole 2,3-bond and a thermal cyclization of 3-alkynylindole-2-aldoxime **12** according to a modified Sakamoto's method,[11] followed by asymmetric 1,2-dihydroxylation of 1-ethenyl-β-carboline **7** as depicted in the retrosynthetic Scheme 1. In addition, we describe the total syntheses of (*R*)-(−)-pyridindolol K1 (**5**) and (*R*)-(−)-pyridindolol (**1**), starting from (*R*)-(−)-pyridindolol K2 (**6**), respectively.

Scheme 1



Results and Discussion

For the synthesis of β-carboline *N*-oxides **8** based on a thermal electrocyclic reaction of the 1-azahexatriene system **10**, we chose 3-iodoindole-2-carbaldehyde (**12a**)[8a] and *N*-methoxymethyl(MOM)-3-iodoindole-2-carbaldehyde (**12b**)[8a] as starting materials. The palladium-catalyzed cross-coupling reaction[12] of **12a** (or **12b**) with tributyl[3-(MOMoxy)prop-1-en-1-yl]stannane (**13**), prepared from 3-(MOMoxy)prop-1-yne[13] and tributyltin hydride, in the presence of $PdCl_2(PPh_3)_2$ and Et_4NCl in DMF gave the 3-alkenylindole **14a** (or **14b**) in a 83% (or 96%) yield. After the aldehyde **14a** (or **14b**) was converted to the oxime **10a** (or **10b**) as a 1-azahexatriene system, it was subjected to a thermal electrocyclic reaction in *o*-dichlorobenzene to produce the β-carboline **9a** (or **9b**) in 71% and 98% yields from **10a** and **10b**, respectively. Subsequent oxidation of **9a** (or **9b**) with *m*-chloroperbenzoic acid (*m*CPBA) afforded the β-carboline *N*-oxide **8a** (97%) [or **8b** (89%)]. By contrast, we utilized the same starting materials **12a** and **12b** for the synthesis of β-carboline *N*-oxides **8** based on thermal cyclization using a modified Sakamoto's method.[11] Specifically, the palladium-catalyzed cross-coupling reaction of **12a** (or **12b**) with tributyl[3-(MOMoxy)prop-1-yn-1-yl]stannane (**15**), prepared from 3-(MOMoxy)prop-1-yne[13] and tributyltin chloride with *n*-BuLi, in the presence of $PdCl_2(PPh_3)_2$ and Et_4NCl in DMF, gave the 3-alkynylindole **16a** (or **16b**) in a 48% (or 97%) yield. Treatment of **16a** (or **16b**) with hydroxylamine furnished the indole-3-aldoxime **11a** (42%) [or **11b** (93%)], which was then subjected to a thermal cyclization in *o*-dichlorobenzene to produce the β-carboline *N*-oxide **8a** (45%) [or **8b** (95%)] (Scheme 2). Two routes for the synthesis of β-carboline *N*-oxides **8** were established. The total yields of the former route in the four steps from **12a** or **12b** to **8a** or **8b** were 41.7% and 79.5%, respectively. In addition, the total yields of the latter route in the three steps from **12a** or **12b** to **8a** or **8b** were 9.1% and 85.7%, respectively. On the basis of these results, it is obvious that a protecting group of indole nitrogen atom is essential for both routes. Although the latter route resulted in a slightly better total

(6) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395−397. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; Chapter 5. (c) Freming, I. *Frontier Orbital and Organic Chemistry*; Wiley: London, 1976. (d) Marvel, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; Chapter 2. (e) Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 699−750.

(7) Hibino, S.; Sugino, E. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 1, pp 205−227.

(8) (a) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535−2543. (b) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Tetrahedron* **2000**, *56*, 5807−5811. (c) Hagiwara, H.; Choshi, T. Nobuhiro, J.; Fujimoto, Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881−886 and related references therein.

(9) (a) Choshi, T.; Yamada, S.; Sugino, S. Kuwada, T.; Hibino, S. *Synlett* **1995**, 147−148. (b) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899−5904. (c) Yoshioka, H.; Choshi, T.; Sugino, E.; Hibino, S. *Heterocycles* **1995**, *41*, 161−174. (d) Yoshioka, H.; Matsuya, Y.; Choshi, T.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1996**, *44*, 709−714. (e) Choshi, T.; Yamada, S.; Nobuhiro, J.; Mihara, Y.; Sugino, E.; Hibino, S. *Heterocycles* **1998**, *48*, 11−14. (f) Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1998**, *39*, 2341−2344. (g) Kuwabara, N.; Hayashi, H.; Hiramatsu, N.; Choshi, T.; E. Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1999**, *47*, 1805−1807. (h) Sugino, E.; Choshi, T.; Hibino, S. *Heterocycles* **1999**, *50*, 543−559. (i) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108−113.

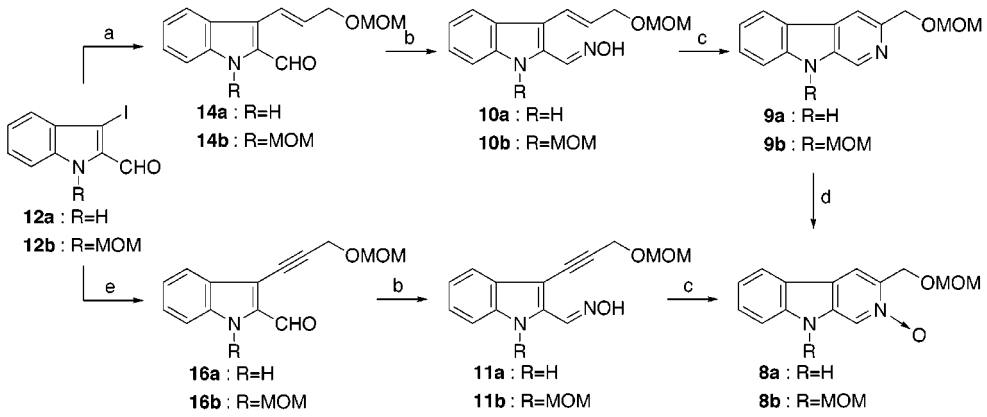
(10) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S. *Heterocycles* **2000**, *53*, 1877−1880.

(11) (a) Sakamoto, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311−2314. (b) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740−1743. (c) Sakamoto, T.; Numata, A.; Kondo, Y. *Chem. Pharm. Bull.* **2000**, *48*, 669−672.

(12) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040. (b) Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645−3648. (c) Niwa, H.; Watanabe, M.; Inagaki, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 7385−7400.

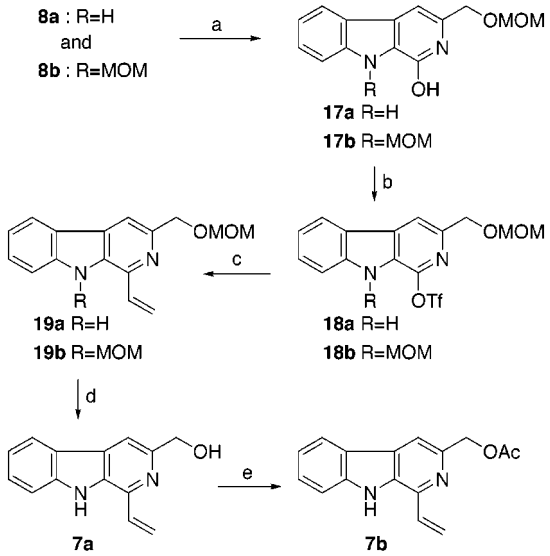
(13) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903−2910.

Scheme 2[a]



[a] Reagents and conditions: (a) $Bu_3Sn-CH=CH-CH_2OMOM$ **13**, $PdCl_2(PPh_3)_2$, DMF, 80 °C; (b) $NH_2OH\cdot HCl$, AcONa, EtOH, 80 °C; (c) *o*-dichlorobenzene, 180 °C; (d) *m*CPBA, CH_2Cl_2, rt; (e) $Bu_3Sn-C\equiv C-CH_2OMOM$ **15**, $PdCl_2(PPh_3)_2$, DMF, 80 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) Ac_2O, 110 °C; (b) Tf_2O, pyridine, CH_2Cl_2, rt; (c) $Bu_3Sn-CH=CH_2$, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 80 °C; (d) CF_3SO_3H, MeOH, $CH(OMe)_3$, CH_3NO_2, 100 °C; (e) Ac_2O, pyridine, rt.

yield than the former route, the two types of thermal ring closures for the construction of this fused pyridine ring system provided excellent results.

Next, the synthesis of 1-ethenyl-β-carboline **7** was attempted using the β-carboline *N*-oxides **8a** and **8b**. As shown in Scheme 3, heating of **8a** (or **8b**) with acetic anhydride at reflux temperature, followed by treatment of the resulting 1-hydroxy-β-carboline **17a** (67%) [or **17b** (90%)] with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine, afforded the triflates **18a** (93%) and **18b** (99%), respectively. The triflate **18a** (or **18b**) was subjected to the palladium-catalyzed cross-coupling reaction with ethenyl tributylstannane in the presence of $PdCl_2(PPh_3)_2$ and Et_4NCl in DMF to give the 1-ethenyl-β-carbolines **19a** (87%) and **19b** (72%). Synthesis of the 1,3-disubstituted β-carboline nucleus **19** was completed in a three-step sequence.

Finally, deprotection of **19b** with trifluoromethanesulfonic acid, MeOH, and trimethyl orthoformate in nitromethane at 100 °C[9i] yielded 1-ethenyl-3-hydroxymethyl-β-carboline (**7a**) (93%). The Sharpless asymmetric dihydroxylation reaction[14] of the resultant **7a** with AD-mix-α or AD-mix-β in a 1:1 mixture of *t*-BuOH and water did not give any pyridindolol (**1**), which may have been due to a problem with the solubility of **7a**. Thereupon, the alcohol **7a** was converted by the usual procedure to the acetate **7b** (98%).

The asymmetric 1,2-dihydroxylation of **7b** with AD-mix-α was carried out in a 1:1 mixture of *t*-BuOH and water to provide (*S*)-(+)-pyridindolol K2 (**6**) in a 66% yield (ee 99.2%). In contrast, the reaction of **7b** with AD-mix-β was carried out similarly to produce (*R*)-(−)-pyridindolol (**6**) in a 68% yield (ee 99.6%). In addition, the selective acetylation of **6** with acetyl chloride and collidine[15] at −78 °C for 5 h afforded (*R*)-(−)-pyridindolol K1 (**5**) (76%) together with (*R*)-(−)-pyridindolol triacetate (**20**) (15%). Furthermore, hydrolysis of the acetate **6** with 1 M K_2CO_3 in methanol according to the reported procedure[3] afforded (*R*)-(−)-pyridindolol (**1**) (93%) (Scheme 4). The synthetic (*R*)-(−)-pyridindolol K2 (**6**), (*R*)-(−)-pyridindolol K1 (**5**), and (*R*)-(−)-pyridindolol (**1**) were identical in all respects, including their specific rotation, to data[1,3] reported for the natural products.

Conclusions

The first enantioselective total synthesis of (*R*)-(−)-pyridindolol K2 (**6**) together with its enantiomer (*S*)-(+)-**6** was established in a nine-step or ten-step sequence based on the construction of β-carboline *N*-oxide (**8**) through the thermal electrocyclic reaction of a 1-azahexatriene system (**10**) involving the indole 2,3-bond or the thermal cyclization of 3-ethynylindole-2-carbaldehyde oxime (**11**), followed by the Sharpless asymmetric 1,2-dihydroxylation of **7b**. In addition, the asymmetric total syntheses of (*R*)-(−)-pyridindolol K1 (**5**) and (*R*)-(−)-pyridindolol (**1**) were also completed using **6** as a starting material.

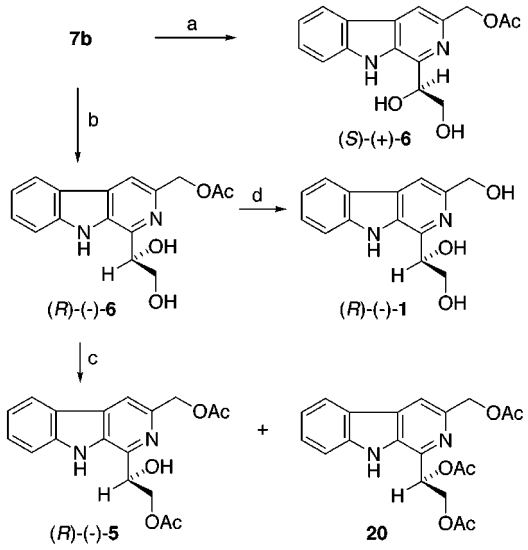
Experimental Section

General. Most reactions were conducted in flame-dried glassware under argon atmosphere. All air-sensitive reactions were run under argon atmosphere. THF was freshly distilled

(14) (a) Sharpless, K. B.; Amberg, W.; Bennami, Y. L.; Cripino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Sinha, S. C.; Sinha-Bagchi, A.; Keinami, E. *J. Org. Chem.* **1993**, *58*, 7789−7796.

(15) Ishikura, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791−3793.

Scheme 4[a]



[a] Reagents and conditions: (a) AD-mix-α, *t*-BuOH, H_2O, 0 °C; (b) AD-mix-*β*, *t*-BuOH, H_2O, 0 °C; (c) AcCl, collidine, CH_2Cl_2; (d) aq 1 M K_2CO_3, MeOH, rt.

from sodium benzophenone ketyl. DMF was freshly distilled under reduced pressure after drying over CaH_2. Silica gel (60−100 mesh, Merck Art 7734) was used for the column chromatography. Melting points are uncorrected. Enantiomeric excesses of chiral products were determined by high-performance liquid chromatography (HPLC) (CHIRALCEL OD: 250 mm × 4.6 mm *ϕ*) using 40% 2-propanol−hexane as an eluent (flow rate: 0.3 mL/min) along with UV detection at 245 nm. ^{1}H NMR (300 MHz) spectra were obtained in $CDCl_3$ using Me_4Si as an internal standard, unless otherwise stated. Low- and high-resolution mass spectra were measured at 70 eV (EI).

Tributyl[3-(methoxymethyloxy)prop-1-en-1-yl]stannane (13). A mixture of 3-(methoxymethyloxy)prop-1-yne[15] (10 g, 0.10 mol), tributyltin hydride (29.6 mL, 0.11 mol), and AIBN (328 mg, 2 mmol) were heated at 80 °C for 2 h. After being cooled to ambient temperature, the resultant was distilled under reduced pressure to give the alkenylstannane **13** (30 g, 84%). bp 153−156 °C/0.9 Torr; ^{1}H NMR ($CDCl_3$) *δ* 3.38 (s, 3H), 4.09 (dd, *J* = 1, 5 Hz, 2H), 4.65 (s, 2H), 6.06 (dd, *J* = 5, 19 Hz, 1H), 6.25 (dd, *J* = 1, 19 Hz, 1H).

3-[3-(Methoxymethyloxy)prop-1-en-1-yl]indole-2-carbaldehyde (14a). A mixture of 3-iodoindole **12a** (500 mg, 1.85 mmol), alkenylstannane **13** (1 g, 2.78 mmol), Et_4NCl (306 mg, 1.85 mmol), and $PdCl_2(PPh_3)_2$ (65 mg, 0.093 mmol) in dried DMF (20 mL) was heated at 80 °C for 40 min. After being cooled to ambient temperature, 30% aqueous KF solution (30 mL) was added to the reaction mixture and then stirred at room temperature for 30 min, which was filtered through the Celite pad. The filtrate was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc−hexane (3:17) as an eluent to give the oily 3-alkenylindole **14a** (375 mg, 83%). IR (neat) *ν*: 1610, 3200 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 3.45 (s, 3H), 3.60 (dd, *J* = 1, 6 Hz, 2H), 4.76 (s, 2H), 6.54 (dt, *J* = 6, 16 Hz, 1H), 7.22 (dd, *J* = 1, 16 Hz, 1H), 7.23 (m, 1H), 7.42 (m, 2H), 7.95 (d, *J* = 8 Hz, 1H), 8.93 (br s, 1H), 10.11 (s, 1H); MS *m*/*z*: 245 (M^+). HRMS (EI) calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1068.

3-[3-(Methoxymethyloxy)prop-1-en-1-yl]-*N*-(methoxymethyl)indole-2-carbaldehyde (14b). The same procedure as above was carried out using **12b** (2 g, 6.35 mmol) to give the oily 3-alkenylindole **14b** (96%). IR (neat) *ν*: 1670, 2990 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 3.30 (s, 3H), 3.34 (s, 3H), 4.35 (dd, *J* = 2, 6 Hz, 2H), 4.76 (s, 2H), 5.98 (s, 2H), 6.48 (td, *J* = 6, 16 Hz, 1H), 7.22 (td, *J* = 2, 16 Hz, 1H), 7.28 (td, *J* = 1, 7 Hz, 1H), 7.47 (td, *J* = 1, 8 Hz, 1H), 7.55 (d, *J* = 7 Hz, 1H), 7.95 (dd, *J* = 1, 8 Hz, 1H), 10.22 (s, 1H); MS *m*/*z*: 289 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1307.

3-[3-(Methoxymethyloxy)prop-1-en-1-yl]indole-2-carbaldehyde Oxime (10a). A suspension of 2-formylindole **14a** (100 mg, 0.41 mmol), NH_2OH·HCl (57 mg, 0.82 mmol), and AcONa (67 mg, 0.82 mmol) in EtOH (5 mL) was heated at 80 °C for 1 h. After being cooled to ambient temperature, the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc−hexane (1:4) as an eluent to give a syn-anti mixture of the oxime **10a** (80 mg, 73%). mp 154−165 °C (MeOH); IR (KBr) *ν*: 3250 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 3.30 (s, 12/5H), 3.31 (s, 3/5H), 4.19 (d, *J* = 6.6 Hz, 8/5H), 4.21 (d, *J* = 6.6 Hz, 2/5H), 6.24−6.28 (m, 1H), 7.02 (d, *J* = 15.4 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 4/5H), 7.60 (d, *J* = 8.1 Hz, 1/5H), 7.81 (d, *J* = 8.1 Hz, 1H), 8.39 (s, 1H), 11.36 (br s, 4/5H), 11.40 (br s, 1H), 12.06 (br s, 1/5H); MS *m*/*z*: 260 (M^+). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.79; H, 6.13; N, 10.90. Found: C, 64.83; H, 6.15; N, 11.01.

3-[3-(Methoxymethyloxy)prop-1-en-1-yl]-*N*-(methoxymethyl)indole-2-carbaldehyde Oxime (10b). The same procedure as above was carried out using **14b** (3 g, 10.38 mmol) to give the oxime **10b** (95%). mp 78−79 °C (Et_2O); IR (KBr) *ν*: 3250 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 3.28 (s, 3H), 3.45 (s, 3H), 4.33 (dd, *J* = 2, 6 Hz, 2H), 4.75 (s, 2H), 5.82 (s, 2H), 6.38 (td, *J* = 6, 16 Hz, 1H), 6.95 (td, *J* = 2, 16 Hz, 1H), 7.21 (td, *J* = 1, 8 Hz, 1H), 7.34 (td, *J* = 1, 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.87 (dd, *J* = 1, 8 Hz, 1H), 8.50 (s, 1H); MS *m*/*z*: 304 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.26; H, 6.69; N, 9.05.

3-(Methoxymethyloxy)methyl-9*H*-pyrido[3,4-*b*]indole (9a). A solution of the oxime **10a** (50 mg, 0.19 mmol) in *o*-dichlorobenzene (3 mL) was heated at 180 °C for 40 min. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (2:3) as an eluent to give the oily *β*-carboline **9a** (32 mg, 71%). ^{1}H NMR ($CDCl_3$) *δ* 3.84 (s, 3H), 4.85 (s, 2H), 4.90 (s, 2H), 7.31 (d, *J* = 7 Hz, 1H), 7.54 (m, 2H), 8.09 (s, 1H), 8.14 (d, *J* = 7 Hz, 1H), 8.38 (br s, 1H), 8.88 (s, 1H); MS *m*/*z*: 242 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 242.1055, found 242.1059.

3-(Methoxymethyloxy)methyl-*N*-methoxymethyl-9*H*-pyrido[3,4-*b*]indole (9b). The same procedure as above was carried out using **10b** (3 g, 9.86 mmol) to give the *β*-carboline **9b** (98%). mp 47−48 °C (Et_2O); ^{1}H NMR ($CDCl_3$) *δ* 3.30 (s, 3H), 3.48 (s, 3H), 4.86 (s, 2H), 4.91 (s, 2H), 5.75 (s, 2H), 7.34 (m, 1H), 7.62 (m, 2H), 8.09 (s, 1H), 8.15 (d, *J* = 8 Hz, 1H), 8.97 (s, 1H); MS *m*/*z*: 286 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.08; H, 6.49; N, 9.66.

3-(Methoxymethyl)methyl-9*H*-pyrido[3,4-*b*]indole *N*-Oxide (8a). *m*CPBA (43 mg, 0.248 mmol) was added to a solution of *β*-carboline **9a** (30 mg, 0.124 mmol) in CH_2Cl_2 (10 mL) under cooling with ice and then was stirred at r.t. for 2 h. The reaction mixture was quenched with H_2O and was extracted with MeOH−$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using MeOH−$CHCl_3$ (1:9) as an eluent to give the *β*-carboline *N*-oxide **8a** (31 mg, 97%). mp 200−203 °C ($CHCl_3$−hexane); ^{1}H NMR ($CDCl_3$) *δ* 3.48 (s, 3H), 4.90 (s, 2H), 5.05 (s, 2H), 7.30 (m, 2H), 7.54 (m, 2H), 8.05 (d, *J* = 8 Hz, 1H), 8.13 (s, 1H), 8.69 (br s, 1H); MS *m*/*z*: 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.98; H, 5.29; N, 10.91.

3-(Methoxymethyloxy)methyl-*N*-methoxymethyl-9*H*-pyrido[3,4-*b*]indole *N*-Oxide (8b). The same procedure as above was carried out using **9b** (820 mg, 2.86 mmol) to give the *β*-carboline *N*-oxide **8b** (89%). mp 153−154 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 3.31 (s, 3H), 3.48 (s, 3H), 4.91 (s, 2H), 5.03 (s, 2H), 5.62 (s, 2H), 7.37 (m, 1H), 7.55 (m, 2H) 8.06 (d, *J* = 8 Hz, 1H), 8.15 (s, 1H), 8.86 (s, 1H); MS *m*/*z*: 302 (M^+). Anal. Calcd

for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.74; H, 6.18; N, 9.33.

3-[3-(Methoxymethyloxy)prop-1-yn-1-yl]indole-2-carbaldehyde (16a). A mixture of 3-iodoindole **12a** (250 mg, 0.92 mmol), [(methoxymethyloxy)propynyl] tributyltin **15** (535 mg, 1.38 mmol), Et_4NCl (152 mg, 0.92 mmol), and $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol) in DMF (15 mL) was heated at 80 °C for 40 min. After being cooled to ambient temperature, 30% aqueous KF solution (10 mL) was added to the reaction mixture and then stirred at room temperature for 30 min, which was filtered through the Celite pad. The filtrate was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (1:9) as an eluent to give the oily 3-propynylindole **16a** (108 mg, 48%). IR (neat) ν: 1650, 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (s, 3H), 4.59 (s, 2H), 4.84 (s, 2H), 7.23 (m, 1H), 7.40−7.43 (m, 2H), 7.84 (d, J = 8 Hz, 1H), 8.88 (br s, 1H), 10.06 (s, 1H); MS m/z: 243 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 243.0895, found 243.0909.

3-[3-(Methoxymethyloxy)prop-1-yn-1-yl]-*N*-(methoxymethyl)indole-2-carbaldehyde (16b). The same procedure as above was carried out using **12b** (2 g, 6.35 mmol) to give the 3-propynylindole **16b** (97%). mp 70−70.5 °C (hexane); IR (KBr) ν: 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.45 (s, 3H), 4.59 (s, 2H), 4.38 (s, 2H), 5.89 (s, 2H), 7.30 (dd, J = 1, 8 Hz, 1H), 7.48 (td, J = 1, 8 Hz, 1H), 7.57 (dd, J = 1, 8 Hz, 1H), 7.48 (dd, J = 1, 8 Hz, 1H), 10.21 (s, 1H); MS m/z: 287 (M^+). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.03; H, 6.12; N, 4.83.

3-[3-(Methoxymethyloxy)prop-1-yn-1-yl]indole-2-carbaldehyde Oxime (11a). A suspention of 2-formylindole **16a** (100 mg, 0.41 mmol), $NH_2OH\cdot HCl$ (57 mg, 0.82 mmol), and AcONa (67 mg, 0.82 mmol) in EtOH (5 mL) was heated at 80 °C for 30 min. After being cooled to ambient temperature, the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (1:4) as an eluent to give the oily oxime **11a** (45 mg, 42%). IR (neat) ν: 1650, 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (s, 3H), 4.56 (s, 2H), 4.48 (s, 2H), 7.30 (m, 1H), 7.72 (m, 1H), 7.77 (d, J = 8 Hz, 1H), 7.82 (s, 1H), 8.37 (s, 1H), 8.68 (br s, 1H); MS m/z: 258 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 258.1004, found 258.1015.

3-[3-(Methoxymethyloxy)prop-1-yn-1yl]-*N*-(methoxymethyl)indole-2-carbaldehyde Oxime (11b). The same procedure as above was carried out using **16b** (6 g, 20.88 mmol) to give the oxime **11b** (93%). mp 79−80.5 °C (hexane); IR (KBr) ν: 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (s, 3H), 3.45 (s, 3H), 4.57 (s, 2H), 4.84 (s, 2H), 5.84 (s, 2H), 7.21 (td, J = 1, 8 Hz, 1H), 7.33 (td, J = 1, 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.71 (dd, J = 1, 8 Hz, 1H), 8.06 (br s, 1H), 8.55 (s, 1H); MS m/z: 302 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.46; H, 6.07; N, 9.38.

3-(Methoxymethyloxy)methyl-9*H*-pyrido[3,4-*b*]indole *N*-Oxide (8a) from 11a. A solution of the oxime **11a** (45 mg, 0.17 mmol) in *o*-dichlorobenzene (3 mL) was heated at 180 °C for 20 min. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using MeOH−$CHCl_3$ (1:9) as an eluent to give the β-carboline *N*-oxide **8a** (20 mg, 45%). The physical and spectral data of **8a** from **11a** were identical with those of **8a** obtained from **9a**.

3-(Methoxymethyloxy)methyl-*N*-methoxymethyl-9*H*-pyrido[3,4-*b*]indole *N*-Oxide (8b) from 11b. The same procedure as above was carried out using **11b** (805 mg, 2.67 mmol) to give the β-carboline *N*-oxide **8b** (95%). The physical and spectral data of **8b** from **11b** were identical with those of **8b** obtained from **9b**.

3-(Methoxymethyloxy)-9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one (17a). A solution of β-carboline *N*-oxide **8a** (36 mg, 0.14 mmol) in acetic anhydride (10 mL) was heated at 100 °C for 3 h. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc−hexane (2:3) as an eluent to give the oily pyridone **17a** (24 mg, 67%). IR (neat) ν: 1640, 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.46 (s, 3H), 4.64 (s, 2H), 4.76 (s, 2H), 6.92 (s, 1H), 7.31 (m, 1H), 7.46−7.61 (m, 1H), 7.94 (d, J = 8 Hz, 1H), 8.27 (s, 1H), 8.91 (br s, 1H); MS m/z: 258 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 258.1004, found 258.1021.

3-(Methoxymethyloxy)methyl-*N*-methoxymethyl-9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one (17b). The same procedure as above was carried out using **8b** (3.3 g, 10.93 mmol) to give the pyridone **17b** (90%). mp 214−216 °C (hexane); IR (KBr) ν: 1640, 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.36 (s, 3H), 3.47 (s, 3H), 4.16 (s, 2H), 4.76 (s, 2H), 6.25 (s, 2H), 6.86 (s, 1H), 7.31 (td, J = 1, 8 Hz, 1H), 7.53 (td, J = 1, 8 Hz, 1H), 7.65 (dd, J = 1, 8 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 9.82 (br s, 1H); MS m/z: 302 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 6.11; N, 9.15.

3-(Methoxymethyloxy)methyl-1-trifluoromethanesulfonyloxy-9*H*-pyrido[3,4-*b*]indole (18a). Tf_2O (20 μL, 0.12 mmol) was added to a stirred solution of the pyridone **17a** (20 mg, 0.078 mmol) and pyridine (19 μL, 0.23 mmol) in CH_2Cl_2 (5 mL) under cooling with ice. After stirring at room temperature for 10 min, the solution was treated with water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (1:4) as an eluent to give the oily triflate **18a** (28 mg, 93%). ^1H NMR ($CDCl_3$) δ 3.45 (s, 3H), 4.83 (s, 2H), 4.85 (s, 2H), 7.35 (td, J = 1, 7 Hz, 1H), 7.60 (m, 1H), 7.62 (dd, J = 1, 7 Hz, 1H), 8.12 (d, J = 7 Hz, 1H), 8.13 (s, 1H), 8.65 (br s, 1H); MS m/z: 390 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 390.0497, found 390.0502.

3-(Methoxymethyloxy)methyl-*N*-methoxymethyl-1-trifluoromethanesulfonyloxy-9*H*-pyrido[3,4-*b*]indole (18b). The same procedure as above was carried out using **17b** (1 g, 3.31 mmol) to give the triflate **18b** (99%). mp 50−52 °C (Et_2O); IR (KBr) ν: 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (s, 3H), 3.45 (s, 3H), 4.57 (s, 2H), 4.83 (s, 2H), 5.87 (s, 2H), 7.22 (td, J = 1, 8 Hz, 1H), 7.34 (td, J = 1, 7 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.73 (dd, J = 1, 7 Hz, 1H), 8.54 (s, 1H); MS m/z: 434 (M^+). Anal. Calcd for $C_{17}H_{17}F_3N_2O_6S$: C, 47.00; H, 3.94; N, 6.45. Found: C, 47.18; H, 4.10; N, 6.37.

1-Ethenyl-3-(methoxymethyloxy)methyl-9*H*-pyrido[3,4-*b*]indole (19a). A mixture of the triflate **18a** (25 mg, 0.064 mmol), vinyltributyltin (31 mg, 0.096 mmol), Et_4NCl (11 mg, 0.064 mmol), and $PdCl_2(PPh_3)_2$ (2 mg, 0.0032 mmol) in dried DMF (3 mL) was heated at 80 °C for 40 min. After being cooled to ambient temperature, 30% aqueous KF solution (5 mL) was added to the reaction mixture and then stirred at room temperature for 30 min, which was filtered through the Celite pad. The filtrate was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (1:9) as an eluent to give the oily 1-vinyl-β-carboline **19a** (12 mg, 87%). ^1H NMR ($CDCl_3$) δ 3.49 (s, 3H), 4.86 (s, 2H), 4.90 (s, 2H), 5.73 (dd, J = 2, 11 Hz, 1H), 6.36 (dd, J = 2, 17 Hz, 1H), 7.20 (dd, J = 11, 17 Hz, 1H), 7.30 (m, 1H), 7.55 (m, 2H), 8.01 (s, 1H), 8.13 (d, J = 8 Hz, 1H), 8.36 (br s, 1H); MS m/z: 268 (M^+). HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 268.1212, found 268.1198.

1-Ethenyl-3-(methoxymethyloxy)methyl-*N*-methoxymethyl-9*H*-pyrido[3,4-*b*]indole (19b). The same procedure as above was carried out using **18b** (2.3 g, 5.30 mmol) to give the 1-vinyl-β-carboline **19b** (72%). mp 84−86 °C (hexane); ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H), 3.49 (s, 3H), 4.87 (s, 2H), 4.93 (s, 2H), 5.64 (dd, J = 2, 11 Hz, 1H), 5.76 (s, 1H), 6.45 (dd, J = 2, 18 Hz, 1H), 7.31 (m, 1H), 7.59 (m, 1H), 7.65 (dd, J = 11, 18 Hz, 1H), 8.03 (s, 1H), 8.12 (d, J = 8 Hz, 1H); MS m/z: 312 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.45; H, 6.48; N, 8.69.

1-Ethenyl-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole (7a). Trifluoromethanesulfonic acid (1 mL, 11.52 mmol) was added to an ice-cooled mixture of *N*-MOM-β-carboline **19b** (1.2 g, 3.84 mmol), MeOH (1.56 mL, 38.40 mmol), and trimethyl orthoformate (4.2 mL, 38.40 mmol) in nitromethane (20 mL). The

resulting mixture was heated at 100 °C for 1 h. After being cooled to ambient temperature, the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc−hexane (1:4) as an eluent to give the *N*-deprotected *β*-carboline **7a** (800 mg, 93%). mp 115−117 °C (Et_2O); IR (KBr) *ν*: 3150 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 4.92 (s, 2H), 5.72 (dd, *J* = 2, 11 Hz, 1H), 6.43 (dd, *J* = 2, 17 Hz, 1H), 7.18 (dd, *J* = 11, 17 Hz, 1H), 7.29 (td, *J* = 1, 8 Hz, 1H), 7.51−7.59 (m, 2H), 7.79 (s, 1H), 8.10 (dd, *J* = 1, 8 Hz, 1H), 8.38 (br s, 1H); MS *m*/*z*: 224 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.21; H, 5.45; N, 12.31.

3-(Acetoxy)methyl-1-ethenyl-9*H*-pyrido[3,4-*b*]indole (7b). Acetic anhydide (0.51 mL, 5.76 mmol) was added dropwise to a solution of the *β*-carboline **7a** (645 mg, 2.88 mmol) in pyridine (20 mL) under cooled with ice, which was stirred at room temperature for 2 h. The resultant mixture was quenched with H_2O and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc−hexane (1:4) as an eluent to give the acetate **7b** (750 mg, 98%). mp 143−144 °C (hexane); IR (KBr) *ν*: 1690, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.18 (s, 3H), 5.40 (s, 2H), 5.75 (dd, *J* = 1, 11 Hz, 1H), 6.40 (dd, *J* = 1, 18 Hz, 1H), 7.18 (dd, *J* = 11, 18 Hz, 1H), 7.31 (td, *J* = 1, 7 Hz, 1H), 7.55 (m, 1H), 7.95 (s, 1H), 8.13 (dd, *J* = 1, 7 Hz, 1H), 8,35 (br s, 1H); MS *m*/*z*: 266 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.00; H, 5.24; N, 10.71.

(*S*)-(+)-Pyridindolol K2 (6). The acetate **7b** (100 mg, 0.45 mmol) was added to AD-mix-α (1.3 g, 2 eq) in *tert*-butyl alcohol−H_2O (1:1, 10 mL) at 0 °C. The mixture was stirred at the same temperature for 24 h. After addition of Na_2SO_3 (1.5 g), the mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was diluted with H_2O and extracted with MeOH−$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5 g) using MeOH−$CHCl_3$ (1:19) as an eluent to give the (*S*)-(+)-pyridindolol K2 (**6**) (30 mg, 66%). mp 122−124 °C ($CHCl_3$); $[\alpha]^{23}_D$ +33° (*c* = 0.212, MeOH); IR (KBr) *ν*: 1250, 1750, 3400 cm^{-1}; ^1H NMR (MeOH-d_4) *δ* 2.13 (s, 3H), 3.95 (m, 2H), 5.18 (m, 1H), 5.32 (s, 2H), 7.24 (td, *J* = 1, 8 Hz, 1H), 7.53 (td, *J* = 1, 8 Hz, 1H), 7.61 (dd, *J* = 1, 8 Hz, 1H), 8.06 (s, 1H), 8.16 (dd, *J* = 1, 8 Hz, 1H); ^{13}C NMR (MeOH-d_4) *δ* 20.9, 67.0, 68.4, 76.0, 113.0, 114.3, 120.7, 122.0, 122.5, 129.6, 131.6, 134.7, 142.8, 144.1, 145.7, 172.7; MS *m*/*z*: 300 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.12; H, 5.48; N, 9.27.

(*R*)-(−)-Pyridindolol K2 (6). The same procedure as above was carried out using **7b** (200 mg, 0.75 mmol) with AD-mix-*β* to give the (*R*)-(−)-pyridindolol K2 (**6**) (68%). mp 123−124 °C ($CHCl_3$)(lit. 123−124 °C); $[\alpha]^{23}_D$ −33° (*c* = 0.195, MeOH) (lit. $[\alpha]^{23}_D$ −35° (*c* = 0.400, MeOH)); IR (KBr) *ν*: 1250, 1748, 3400 cm^{-1}; ^1H NMR (MeOH-d_4) d: 2.13 (s, 3H), 3.95 (m, 2H), 5.20 (m, 1H), 5.33 (s, 2H), 7.24 (td, *J* = 1, 8 Hz, 1H), 7.54 (td, *J* = 1, 8 Hz, 1H), 7.60 (dd, *J* = 1, 8 Hz, 1H), 8.06 (s, 1H), 8.15 (dd, 1, *J* = 8 Hz, 1H); ^{13}C NMR (MeOH-d_4) *δ* 20.9, 67.0, 68.4, 76.1, 112.0, 113.0, 114.3, 120.7, 122.0, 122.5, 129.6, 131.6, 134.7, 142.8, 144.2, 145.7, 172.7; MS *m*/*z*: 300 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.08; H, 5.49; N, 9.19.

(*R*)-(−)-Pyridindolol (1). Aqueous K_2CO_3 solution (1 M, 0.3 mL) was added to a solution of (*R*)-(−)-pyridindolol K2 (**6**) (50 mg, 0.17 mmol) in MeOH (3 mL). After stirring at room temperature for 1 h, the reaction mixture was extracted with MeOH−$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC using MeOH−$CHCl_3$ (1:4) as an eluent to give the (*R*)-(−)-pyridindolol (**1**) (40 mg, 93%). mp 165−168 °C ($CHCl_3$) (lit. 167−168 °C); $[\alpha]^{25}_D$ −41° (*c* = 0.110, MeOH) (lit. $[\alpha]^{25}_D$ −49° (*c* = 0.100, MeOH)); IR (KBr) *ν*: 3400 cm^{-1}; ^1H NMR (MeOH-d_4) *δ* 3.95 (m, 2H), 4.96 (s, 2H), 5.19 (m, 1H), 7.22 (td, *J* = 1, 7 Hz, 1H), 7.52 (td, *J* = 1, 8 Hz, 1H), 7.63 (m, 1H), 8.07 (s, 1H), 8.15 (d, *J* = 8 Hz, 1H); ^{13}C NMR (MeOH-d_4) *δ* 64.5, 65.4, 74.4, 109.8, 112.2, 118.8, 120.4, 121.3, 127.7, 128.9, 132.3, 140.9, 144.6, 148.9; MS *m*/*z*: 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.27; H, 5.51; N, 10.64.

(*R*)-(−)-Pyridindolol K1 (5) and 3-Acetoxymethyl-1-(1,2-diacetoxy)ethyl-9*H*-pyrido[3,4-*b*]indole (20). Acetyl chloride (10 *μ*L, 0.15 mmol) was added to a solution of (*R*)-(−)-pyridindolol K2 (**6**) (30 mg, 0.10 mmol) and collidine (13.3 *μ*L, 0.1 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After stirring at the same temperature for 5 h, the mixture was allowed to warm to room temperature and stirred for further 1 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc−hexane (3:7) as an eluent to give the (*S*)-(+)-pyridindolol K2 (**5**) (16 mg, 76%) and the triacetate **20** (3 mg, 15%). **5**: mp 124−125 °C ($CHCl_3$); $[\alpha]^{25}_D$ −14° (*c* = 0.200 in MeOH) (lit. $[\alpha]^{25}_D$ −16° (*c* = 0.230 in MeOH)); IR (KBr) *ν*: 1650, 3380 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.18 (s, 3H), 2.24 (s, 3H), 4.14 (m, 1H), 4.90 (m, 1H), 5.38 (s, 2H), 5.40 (br d, 1H), 7.28 (m, 1H), 7.59 (m, 2H), 8.00 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H), 9.75 (br s, 1H); ^{13}C NMR ($CDCl_3$) *δ* 21.1, 21.2, 67.4, 70.5, 71.5, 112.0, 113.8, 120.3, 121.1, 121.7, 128.7, 130.3, 123.3, 140.0, 140.7, 143.2, 170.9, 173.0; MS *m*/*z*: 342 (M^+). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.20; H, 5.44; N, 8.07. **20**: mp 115−117 °C (hexane) (lit.116−119 °C); IR (KBr) *ν*: 1740, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.10 (s, 3H), 2.18 (s, 3H), 2.20 (s, 3H), 4.85 (m, 2H), 5.37 (s, 2H), 6.55 (m, 1H), 7.28 (m, 1H), 7.56 (m, 2H), 8.02 (s, 1H), 8.12 (d, *J* = 8 Hz, 1H), 9.20 (br s, 1H); MS *m*/*z*: 384 (M^+); $[\alpha]^{25}_D$ −19° (*c* = 0.195 in MeOH) (lit. $[\alpha]^{27}_D$ −27.5° (*c* = 0.125 MeOH)). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.54; H, 5.45; N, 7.11.

Acknowledgment. We thank Professor T. Sakamoto (Graduate School of Pharmaceutical Sciences, Tohoku University) for useful suggestions of the thermal ring closure of 3-alkynylindole-2-aldoxime. We thank the Ministry of Education, Science, Sports and Culture of Japan [Grant-in Aid for Scientific Research (11672131)] for support of this work.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds (*R*)-(−)-**5** (S1−5), (*R*)-(−)-**6** (S6−10), and (*R*)-(−)-**1** (S11−16). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0105585