Total Synthesis of (−)-Horsfiline via Asymmetric Nitroolefination

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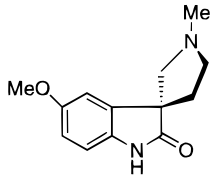
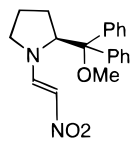
Introduction

(−)-Horsfiline (**1**) is an oxindole alkaloid isolated by Bodo and co-workers in 1991 from the Malaysian medicinal plant *Horsfildea superba*.[1] Several synthetic approaches are available in the literature for the synthesis of both racemic and enantiomeric horsfiline. In 1992 Jones et al. reported the synthesis of racemic **1** via radical cyclization.[2] Later, two strategies for the synthesis of racemic **1** were reported, both involving oxidative rearrangement of a tetrahydrocarboline derivative and spirocyclization of 2-oxo-5-methoxytryptamine with formaldehyde.[3] Recently, two groups disclosed new synthetic routes for the synthesis of enantiomeric **1** via rearrangement of a tetrahydrocarboline derivative and 1,3-dipolar cycloaddition of thermally generated *N*-azomethine ylide, respectively.[4] Herein, we report a highly enantioselective total synthesis of (−)-horsfiline via asymmetric nitroolefination using chiral nitroenamine **2**.



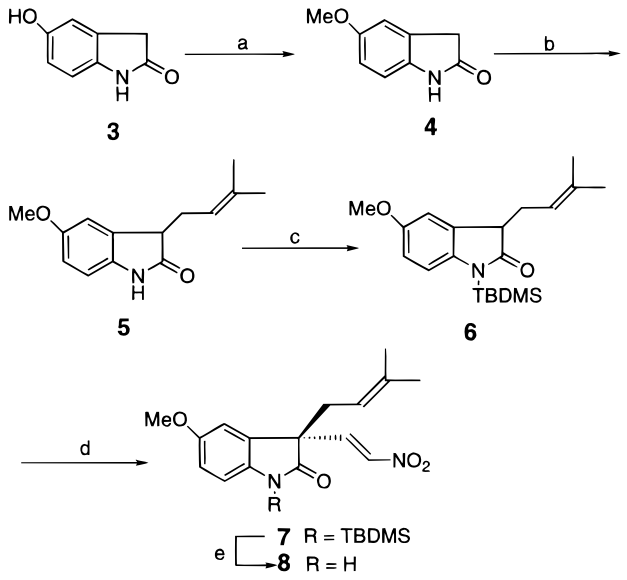
1



2

We have developed a methodology for the creation of chiral quaternary carbon centers via an addition−elimination process,[5b] and the resulting optically active nitroalkenes have been used as precursors for the synthesis of natural products such as aspidosperma and huntarian alkaloids.[5a,c] More recently, we reported an efficient asymmetric nitroolefination of oxindole derivatives using chiral nitroenamine **2** and its application to the synthesis of (−)-pseudophrynaminol and (−)-esermethole.[6] A similar strategy involving asymmetric nitroolefination of **6** (Scheme 1) was expected to be well suited to the synthesis of **1**.

Scheme 1[a]



[a] (a) KOH, $(CH_3)_2SO_4$, 73%; (b) *n*-BuLi/THF, $BrCH_2CH{=}C(CH_3)_2$, 79%; (c) 2,6-lutidine, TBDMSOTf, CH_2Cl_2, 95%; (d) *n*-BuLi/toluene: ether (4:1), **2**, 84%; (e) 1 M HCl/MeOH, 95%.

Results and Discussion

The oxindole **6** was prepared starting from **3**, which was readily available from *p*-anisidine through steps described in the literature.[7] Selective O-methylation of **3** was achieved by using dimethyl sulfate in the presence of potassium hydroxide to afford **4** in 73% yield. A prenyl group was introduced into **4** by treating it with 1-bromo-3-methyl-2-butene to furnish **5**. After the amide nitrogen was protected with TBDMS, the oxindole **6** was treated with *n*-BuLi/THF followed by chiral nitroenamine **2** at −78 °C to give **7** in 38% ee. Then we began screening solvents such as ether, toluene, and a toluene−ether mixture. Among these, the toluene−ether (4:1) mixture gave the highest enantioselectivity (97% ee) and a good yield (84%). The enhanced enantioselectivity could be rationalized by the tight coordination of the lithium enolate of **6** with **2** at the cyclic transition state[5b] in the less coordinating solvents such as toluene−ether. The TBDMS group of **7** was removed by treating **7** with HCl to give **8**.

With compound **8** of high enantiomeric excess in hand, we started to construct the spiropyrrolidine ring system (Scheme 2). The nitroolefin was reduced with $NaBH_4$ to give **9** in high yield. Attempted conversion of the nitro group of **9** into a carboxyl group using $DMSO/NaNO_2/CH_3COOH$ conditions[8] instead resulted in several byproducts. It was suspected that the free amide hydrogen might be causing trouble. Therefore, the amide was protected with a benzyl group in 42% yield and recovery of **9**. Further extending the reaction time resulted in benzylation α to the nitro group. Conversion of nitroal-

(1) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
(2) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767.
(3) Bascop, S.-I.; Sapi, J.; Laronze, J.-Y.; Levy, J. *Heterocycles* **1994**, *38*, 725.
(4) (a) Pelligrine, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (b) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1.
(5) (a) Node, M.; Nagasawa, Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (b) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921. (c) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517
(6) (a) Fuji, K.; Kawabata, T.; Ohmori, T.; Node, M. *Synlett* **1995**, 367. (b) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951.
(7) Giovannini, E.; Portmann, P. *Helv. Chim. Acta* **1948**, *31* (5), 1381.
(8) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234.

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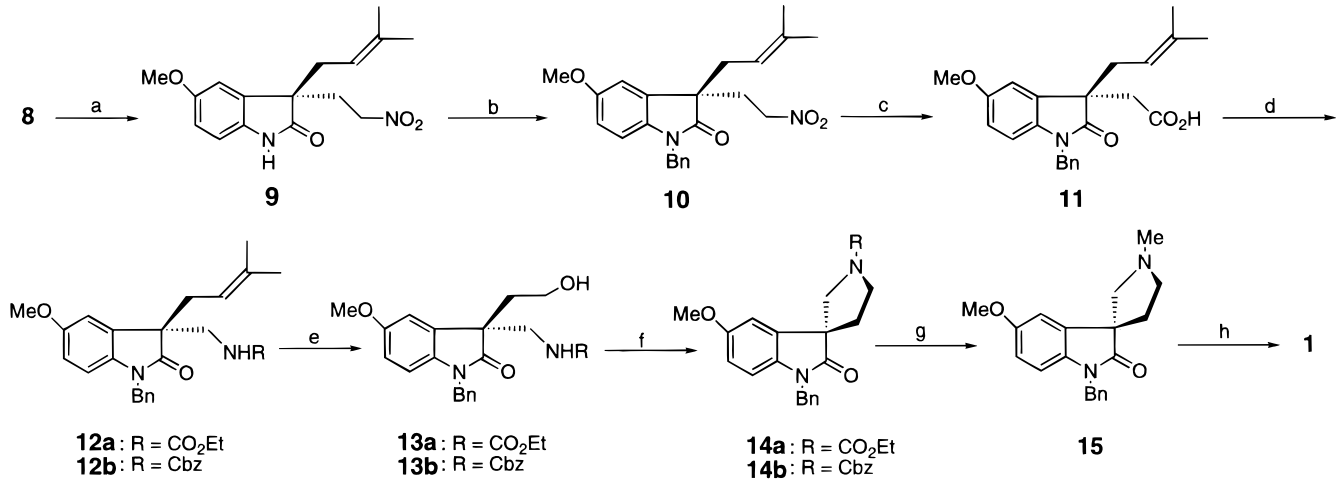
Scheme 2[a]



[a] (a) $NaBH_4$, dioxane/MeOH, 97%; (b) NaH, DMF, $PhCH_2Cl$, 42%; (c) $NaNO_2$, CH_3COOH, DMSO, 80%; (d) (for **12a**) Et_3N/DPPA, EtOH 71%; (for **12b**) Et_3N/DPPA, toluene/$PhCH_2OH$, 81%; (e) (i) O_3, ethanol, −78 °C, Me_2S, (ii) $NaBH_4$, MeOH, **13a** (89%), **13b** (81%); (f) (i) Et_3N/MsCl, CH_2Cl_2, (ii) NaH, THF, **14a** (85%), **14b** (94%); (g) from **14a** (i) KOH, NH_2NH_2, $HOCH_2CH_2OH$, (ii) HCOOH/HCHO 87%; from **14b** (i) Pd/C, H_2, MeOH, (ii) HCHO, $NaCNBH_3$, AcOH, 85%; (h) Li/NH_3, 83%.

kane **10** into the carboxylic acid was successful, affording **11** in 80% yield. Thermal Curtius rearrangement of **11** in ethanol furnished the corresponding ethoxy carbamate **12a** in 71% yield. Ozonolysis of **12a** followed by reduction of the resulting aldehyde with $NaBH_4$ produced alcohol **13a** in 89% yield. The hydroxy group of **13a** was mesylated, and the crude residue was directly treated with NaH/THF at room temperature to afford spiropyrrolidine **14a** in high yield. Carbamate **14a** was deprotected under basic conditions (KOH, hydrazine, ethylene glycol, 100 °C) to give a free amine, which was N-methylated under Eschweiler−Clarke conditions (HCOOH/HCHO, reflux) to produce **15**. Unfortunately, **15** did not show any rotation.[9] Compound **15** on debenzylation gave racemic horsfiline, which was identical with the authentic sample, mp 152−154 °C (lit.[1] mp 156−157 °C).

It was suspected that acidic conditions for methylation and/or strongly basic conditions for deprotection of carbamate might cause racemization.[9] Therefore, an alternative route was chosen, which involved protection of amine with a Cbz group. Carbamate **12b** was readily obtained in 81% yield under Curtius rearrangement of **11** using benzyl alcohol. Spiropyrrolidine **14b** was obtained from **12b** by the same procedure as that for the conversion of **12a** to **14a**. To confirm that no racemization occurred until this stage, the ee of **14b** was determined by HPLC analysis to be 97% ee (Chiralpak AD, 2-propanol−hexane = 10:90). Then the Cbz group was deprotected under neutral conditions (Pd−C, H_2, MeOH) at room temperature to yield the free amine. Without purification, it was methylated using formaldehyde and $NaCNBH_3$ at room temperature to furnish **15**, which showed an optical rotation of $[\alpha]^{20}_D$ −2.7 (*c* 1.3, $CHCl_3$). Finally, debenzylation was achieved by using Li/NH_3 to give **1** whose optical rotation and melting point were identical with those of natural (*R*)-(−)-horsfiline.[1]

Next, we investigated another route to **1**, which involved hydroxylation of the indole ring at the final step, since the expected starting material, isatin, is readily available and very cheap. Oxindole **16** was prepared from isatin by the known method.[11] The hydroxylation of the indole ring system at the 5-position is well-known in biological or chemical synthesis of various indole alkaloids.[10] We suspected that spiropyrrolidine **24** (Scheme 3) is quite suitable for the hydroxylation at the 5-position, since it does not have any other carbon centers prone to oxidation. Introduction of a prenyl group into **16**, followed by asymmetric nitroolefination using chiral nitroenamine **2**, afforded **18** in 65% yield with >99% ee (Scheme 3).

Compound **18** was converted into Cbz-protected amine **21** by methods similar to those described above. Ozonolysis of **21** followed by reduction with $NaBH_4$ afforded primary alcohol **22** and cyclic secondary alcohol **23** in 70% and 14% yields, respectively. Mesylation of **22** followed by base treatment afforded spiropyrrolidine **24**, while reduction of **23** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ gave **24**. Regioselective oxidation of **24** at the 5-position was achieved by treatment with $Pb(CF_3CO_2)_4$ in TFA[12] to give a crude phenolic compound which, upon O-methylation, gave **14b** in 61% yield. The product thus obtained was identical with **14b** obtained previously (Scheme 2) in its ^1H NMR and optical rotation.

In conclusion, we have developed two synthetic routes to (−)-horsfiline using asymmetric nitroolefination as the key step.

Experimental Section

TLC analyses and preparative TLC were performed on commercial glass plates bearing a 0.25-mm layer and a 0.5-mm layer of Merck Kieselgel 60 F_{254}, respectively. Silica gel column chromatography was carried out with Wakogel C-200, Fuji Silysia BW-1277H, or Nacalai tesque silica gel 60 (150−325 mesh). Tetrahydrofuran (THF), ether, and toluene were distilled

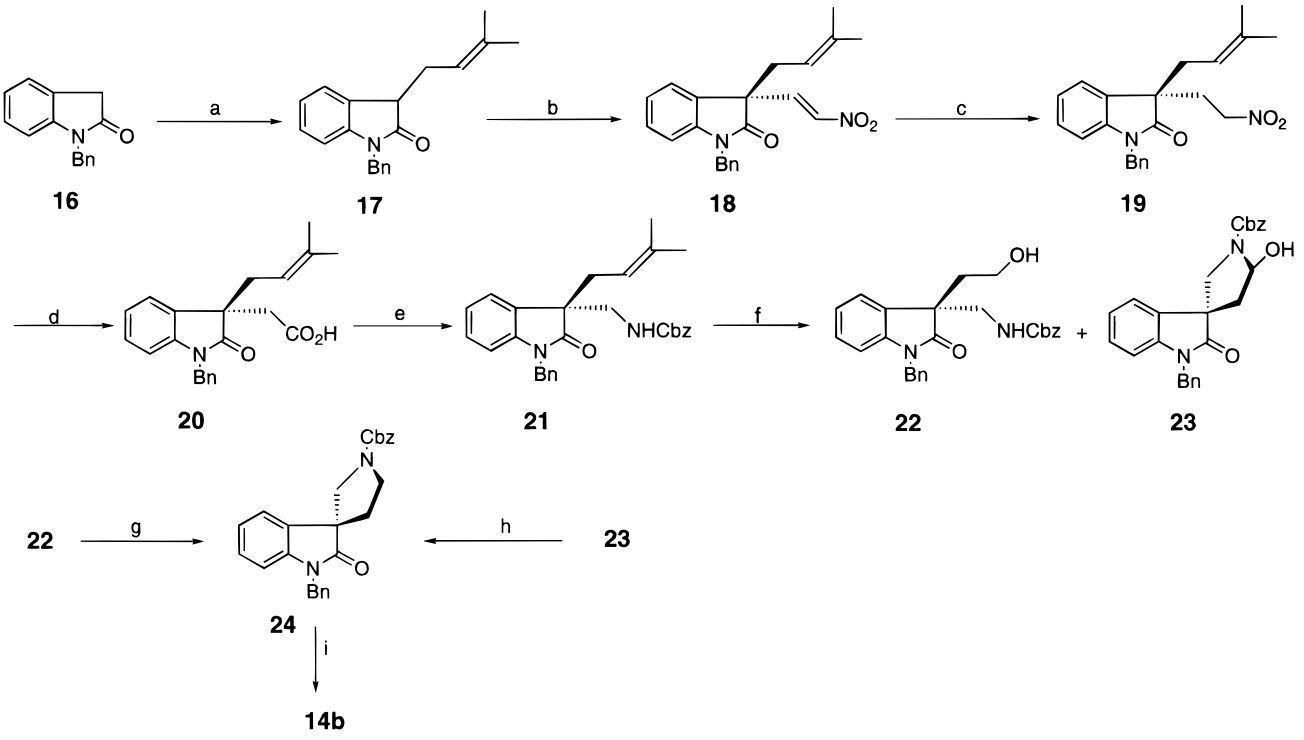
(9) The possible mechanism of racemization of the quaternary carbon center involves the bond fission−cyclization process as shown in Scheme 4. For racemization in the related system, see: Wenkert, E.; Udelhofen, J. H.; Bhattacharyya, N. K. *J. Am. Chem. Soc.* **1959**, *81*, 3763. For a review, see: Bindra, J. S. *Oxindole Alkaloids in The Alkaloids-Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. XIV, pp 83−121.

(10) Taniguchi, M.; Anjiki, T.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 2544 and references therein.

(11) Hirose, S.; Sohda, S.; Toyoshima, S. *Yakugaku Zasshi* **1971**, 1323.

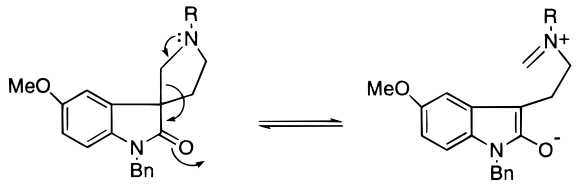
(12) Partch, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 3662.

Scheme 3[a]



[a] (a) *n*-BuLi, THF, $BrCH_2CH{=}C(CH_3)_2$, 60%; (b) *n*-BuLi, ether, **2**, 65%; (c) $NaBH_4$, dioxane/MeOH, 97%; (d) $NaNO_2$, CH_3COOH/DMSO, 87%; (e) Et_3N, DPPA, toluene, BnOH, 83%; (f) (i) O_3/EtOH, −78 °C, Me_2S, (ii) $NaBH_4$, MeOH, **22** (70%), **23** (14%); (g) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaH, THF, 96%; (h) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 86%; (i) (i) $Pb(CF_3CO_2)_4$, CF_3CO_2H, (ii) NaH, THF, MeI, 61%.

Scheme 4



over benzophenone ketyl before each use. Dichloromethane was distilled from calcium hydride.

5-Methoxy-2-oxindole (4). Dimethyl sulfate (2.1 mL, 22.1 mmol) was added to an aqueous KOH solution (22.1 mL, 1.00 M, 22.1 mmol) of 5-hydroxy-2-oxindole (**3**) (3.00 g, 20.1 mmol) at 0 °C. The resulting solution was stirred for 2 h, diluted with water, and extracted with EtOAc (3 × 50 mL). The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel flash chromatograpy (ethyl acetate−hexane = 5:5) to give colorless needles **4** (2.40 g, 73%): mp 148−151 °C (actone−hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.53 (s, 2H), 3.77 (s, 3H), 6.76−6.85 (m, 3H), 8.47 (s, br 1H, NH); IR ($CHCl_3$) 3420, 3200, 1750, 1710, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 163 (M^+, 70), 58 (100). Anal. Calcd for $C_9H_9NO_2$: C, 66.26; H, 5.52; N, 8.58. Found: C, 66.21; H, 5.52; N, 8.54.

5-Methoxy-3-(3-methylbut-2-enyl)-2-oxindole (5). A solution of **4** (2.52 g, 15.4 mmol) in THF (60 mL) was treated with *n*-BuLi (1.42 M in hexane, 21.9 mL, 30.8 mmol) at −78 °C under argon for 1 h followed by 1-bromo-3-methyl-2-butene (2.30 mL, 19.3 mmol). The reaction mixture was slowly warmed to −30 °C during a period of 2 h and then quenched with saturated NH_4-Cl. The mixture was extracted with EtOAc (3 × 90 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate−hexane = 5:5) to afford compound **5** (2.80 g, 79%) as pale yellow crystals: mp 96−98 °C (hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.59 (s, 3H), 1.68 (s, 3H), 2.50−2.80 (m, 2H), 3.44 (dd, J = 7.7, 4.8 Hz, 1H), 3.77 (s, 3H), 5.13 (t, J = 6.6 Hz, 1H), 6.71−6.87 (m, 3H), 8.28 (s, br, 1H, NH); IR ($CHCl_3$) 3420, 3010, 1710, 1605 cm^{-1}; MS *m*/*z* (rel intensity) 231 (M^+, 29), 163 (100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.42; H, 7.32; N, 5. 98.

1-*tert*-Butyldimethylsilyl-3-(3-methylbut-2-enyl)-5-methoxy-2-oxindole (6). A solution of **5** (1.50 g, 6.50 mmol) in dichloromethane was treated with 2,6-lutidine (6.80 mL, 58.5 mmol) and TBDMS triflate (8.96 mL, 39.0 mmol) at 0 °C. The resulting solution was stirred for 2 h at room tempertaure and poured into a saturated $NaHCO_3$ (100 mL) solution. The aqueous layer was extracted with ether (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane−acetone = 9:1) to give **6** as a yellow oil (2.12 g, 95%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.49 (d, J = 6.8 Hz, 6H), 0.97 (s, 9H), 1.57 (s, 3H), 1.62 (s, 3H), 2.62 (t, J = 6.8 Hz, 2H), 3.41 (t, J = 5.8 Hz, 1H), 3.78 (s, 3H), 4.95−5.06 (m, 1H), 6.70 (dd, J = 8.8, 2.5 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H); IR ($CHCl_3$) 1700, 1590 cm^{-1}; MS *m*/*z* (rel intensity) 345 (M^+, 100); exact MS calcd for $C_{20}H_{31}O_2NSi$ M^+ 345.2125, found *m*/*z* 345.2111.

(*S*)-1-*tert*-Butyldimethylsilyl-3-(3-methylbut-2-enyl)-5-methoxy-3-(2-nitrovinyl)-2-oxindole (7) and (*S*)-3-(3-Methylbut-2-enyl)-5-methoxy-3-(2-nitrovinyl)-2-oxindole (8). A solution of **6** (2.50 g, 7.10 mmol) in toluene−ether (4:1, 60 mL) was treated with *n*-BuLi (1.59 M in hexane, 4.68 mL, 7.10 mmol) at −78 °C. The reaction mixture was warmed to 0 °C and stirred for 30 min. The resulting enolate solution was transferred to a suspension of chiral nitroenamine **2** (600 mg, 1.80 mmol) in toluene (12 mL) at −78 °C. The reaction mixture was warmed immediately to −30 °C and then slowly warmed to −10 °C, and the stirring was continued for an additional 3 h. The mixture was poured into ice-cooled aqueous HCl (2.5 M, 40 mL) and stirred for 10 min. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, hexane−acetone = 9:1) to afford **7** (617 mg, 84%) as a pale yellow viscous oil. The ee was determined to be 97% ee after conversion of **7** into **8** (95% yield) by treatment with methanolic HCl. HPLC conditions: Daicel

Chiralpak AD, 2-propanol−hexane = 3:97, flow 1 mL/min, t_R = 36.9 min (*R*) and 50.3 min (*S*). **(*S*)-7**: $[\alpha]^{20}_D$ −15.4 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.51 (d, *J* = 2.7 Hz, 6H), 0.97 (s, 9H), 1.53 (s, 3H), 1.56 (s, 3H), 2.51−2.84 (m, 2H), 3.81 (s, 3H), 4.75 (t, *J* = 7.5 Hz, 1H), 6.75−6.96 (m, 3H), 7.02, 7.36 (ABq, *J* = 13.6 Hz, 2H); IR ($CHCl_3$) 1710, 1530 cm^{-1}; MS *m*/*z* (rel intensity) 416 (M^+, 67), 301 (100); exact MS calcd for $C_{22}H_{32}N_2O_4Si$ M^+ 416.2132, found *m*/*z* 416.2108. **(*S*)-8**: a pale yellow oil; $[\alpha]^{20}_D$ −24.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.64 (s, 3H), 2.70 (d, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.91 (t, *J* = 7.5 Hz, 1H), 6.80−6.92 (m, 3H), 7.03, 7.39 (ABq, *J* = 13.6 Hz, 2H), 8.50 (s, br, 1H, NH); IR ($CHCl_3$) 3200, 1710, 1610, 1530 cm^{-1}; MS *m*/*z* (rel intensity) 302 (M^+, 5), 58 (100). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.58; H, 5.96; N, 9.27. Found: C, 63.34; H, 5.99; N, 9.14.

(*S*)-3-(3-Methylbut-2-enyl)-5-methoxy-3-(2-nitroethyl)-2-oxindole (9). $NaBH_4$ (347 mg, 9.20 mmol) was added portionwise to a solution of **8** (1.90 g, 6.12 mmol) in dioxane−methanol (3:1, 100 mL) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with ether (3 × 100 mL). The organic phase was washed with saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatoghaphy (silica gel, ethyl acetate−hexane = 7:3) to give **9** (1.80 g, 97%) as a pale yellow oil: $[\alpha]^{20}_D$ +41.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.53 (s, 3H), 1.61 (s, 3H), 2.45−2.64 (m, 4H), 3.80 (s, 3H), 3.95−4.10 (m, 1H), 4.15−4.30 (m, 1H), 4.88 (t, *J* = 7.5 Hz, 1H) 6.75−6.87 (m, 3H), 8.25 (s, br, 1H, NH); IR ($CHCl_3$) 3420, 3200, 1710, 1560, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 304 (M^+, 28), 175 (100). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 63.16; H, 6.57; N, 9.21. Found: C, 63.02; H, 6.68; N, 9.07.

(*S*)-1-Benzyl-3-(3-methylbut-2-enyl)-5-methoxy-3-(2-nitroethyl)-2-oxindole (10). A suspension of NaH (473 mg, 60% in oil, 11.8 mmol) in DMF (4 mL) was treated with **9** (3.00 g, 9.90 mmol) in DMF (6 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 30 min and treated with benzyl chloride (1.20 mL, 9.90 mmol) at 0 °C. After being stirred at the same temperature for 5 h, the mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, ethyl acetate−hexane = 3:7) to give **10** (1.62 g, 42%) as a colorless oil. The remaining starting material **9** was recovered quantitatively. **10**:$[\alpha]^{20}_D$ +79.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.57 (s, 3H), 2.45−2.74 (m, 4H), 3.76 (s, 3H), 3.92−4.10 (m, 1H), 4.12−4.29 (m, 1H), 4.63 and 5.13 (ABq *J* = 15.8 Hz, 2H), 4.78 (t, *J* = 6.9 Hz, 1H), 6.62 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 7.20−7.35 (m, 5H); IR ($CHCl_3$) 1710, 1555, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 394 (M^+, 50), 91 (100). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.05; H, 6.59; N, 7.10. Found: C, 70.01; H, 6.71; N, 6.97.

(*S*)-3-[1-Benzyl-3-(3-methylbut-2-enyl)-5-methoxy-2-oxindolyl]acetic Acid (11). A solution containing **10** (190 mg, 0.48 mmol), sodium nitrite (100 mg, 1.50 mmol), and acetic acid (0.28 mL, 4.82 mmol) in DMSO (1.0 mL) was stirred for 8 h at 37 °C. The reaction mixture was diluted with water (20 mL), acidified with 10% aqueous HCl, and extracted with ether (5 × 120 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate−hexane = 4:5) to yield pure **11** (146 mg, 80%) as a yellow amorphous solid: $[\alpha]^{20}_D$ +34.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3H), 1.57 (s, 3H), 2.44−2.63 (m, 2H), 2.86 & 3.06 (ABq, *J* = 16.8 Hz, 2H), 3.73 (s, 3H), 4.73, 5.00 (ABq, *J* = 15.8 Hz, 2H), 4.80 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 6.66 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 7.26 (s, 5H); IR ($CHCl_3$) 1710, 1605, 1495 cm^{-1}; MS *m*/*z* (rel intensity) 379 (M^+, 40), 91 (100); exact MS calcd for $C_{23}H_{25}NO_4$ M^+ 379.1784, found *m*/*z* 379.1810.

(*R*)-1-Benzyl-3-(3-methylbut-2-enyl)-3-(ethoxycarbonylaminomethyl)-5-methoxy-2-oxindole (12a). A solution of **11** (115 mg, 0.30 mmol) in ethanol (8.0 mL) was treated with triethylamine (84 μL, 0.61 mmol) and diphenylphosphoryl azide (DPPA) (131 μL, 0.61 mmol) at room temperature under argon. The resulting mixture was refluxed for 48 h. After removal of the solvent in vacuo, the residue was purified by preparative TLC (silica gel, ethyl acetate−hexane = 2:8) to afford **12a** (91 mg, 71%) as a viscous oil: $[\alpha]^{20}_D$ +44.8 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.52 (s, 3H), 1.56 (s, 3H), 2.45−2.80 (m, 2H), 3.30−3.40 (m, 1H), 3.76 (s, 3H), 3.80−3.90 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.68, 5.08 (ABq, *J* = 15.8 Hz, 2H), 4.78 (t, *J* = 8.0 Hz, 1H), 5.25 (s, br, 1H, NH), 6.55 (d, *J* = 8.4 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.87 (br s, 1H), 7.16−7.36 (m, 5H); IR ($CHCl_3$) 3420, 1710, 1520, 1495 cm^{-1}; MS *m*/*z* (rel intensity) 422 (M^+, 36), 91 (100); exact MS calcd for $C_{25}H_{30}N_2O_4$ M^+ 422.2206, found *m*/*z* 422.2186.

(*R*)-1-Benzyl-3-(3-methylbut-2-enyl)-3-(benzyloxycarbonylaminomethyl)-5-methoxy-2-oxindole (12b). To a solution of **11** (300 mg, 0.79 mmol) in toluene (15 mL) were added triethylamine (183 μL, 1.60 mmol) and DPPA (220 μL, 1.60 mmol) at room temperature under argon. The resulting mixture was refluxed for 2 h, and benzyl alcohol (0.30 mL, 2.80 mmol) was added. After refluxing for another 12 h, solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate−hexane = 2:8) to afford **12b** in 81% yield (310 mg) as a viscous oil: $[\alpha]^{20}_D$ +44.5 (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H), 1.65 (s, 3H), 2.41−2.79 (m, 2H), 3.39 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.76 (s, 3H), 3.78−3.91 (m, 1H), 4.65 (d, *J* = 16.1 Hz, 1H), 4.73−4.8 (m, 1H), 4.99−5.12 (m, 3H), 5.34 (m, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.89 (br s, 1H), 7.15−7.40 (m, 10 H); IR ($CHCl_3$) 3420, 1710, 1605, 1515, 1495 cm^{-1}; MS *m*/*z* (rel intesity) 484 (M^+, 20), 91 (100). Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.38; H, 6.61; N, 5.78. Found: C, 74.08; H, 6.63; N, 5.74.

(*R*)-1-Benzyl-3-(2-hydroxyethyl)-3-(ethoxycarbonylaminomethyl)-5-methoxy-2-oxindole (13a). A solution of **12a** (60 mg, 0.14 mmol) in ethanol (12 mL) was cooled to −78 °C and treated with ozone until the starting material disappeared. Excess ozone was removed by bubbling nitrogen, and dimethyl sulfide (0.30 mL) was added. The resulting mixture was allowed to warm to room temperature, and stirring was continued overnight. After removal of the solvent under vacuo, the crude product was dissolved in methanol (2.5 mL) and treated with $NaBH_4$ (30 mg, 0.70 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with saturated NH_4Cl. After removing methanol under vacuo, the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by preparative TLC (silica gel, ethyl acetate−hexane = 7:3) to give **13a** (50 mg, 89%) as a colorless oil: $[\alpha]^{20}_D$ −6.02 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (t, *J* = 7.0 Hz, 3H), 2.03−2.41 (m, 2H), 3.29−3.65 (m, 3H), 3.76 (s, 3H), 3.70−3.90 (m, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.88 (s, 2H), 5.25 (br, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.88 (s, 1H), 7.20−7.40 (m, 5H); IR ($CHCl_3$) 3450, 1700, 1520, 1495 cm^{-1}; MS *m*/*z* (rel intensity) 398 (M^+, 23), 297 (100); exact MS calcd for $C_{22}H_{26}N_2O_5$ M^+ 398.1843, found *m*/*z* 398.1864.

(*R*)-1-Benzyl-3-(2-hydroxyethyl)-3-(benzyloxycarbonylaminomethyl)-5-methoxy-2-oxindole (13b). **13b** was obtained from **12b** in 81% yield through a procedure similar to that for the conversion of **12a** into **13a**. **13b:** $[\alpha]^{20}_D$ −14.6 (c 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.00−2.05 (m, 1H), 2.25−2.40 (m, 1H), 3.32−3.60 (m, 3H), 3.74 (s, 3H), 3.80−3.90 (m, 1H), 4.86 (s, 2H), 5.01, 5.10 (ABq, *J* = 12.1 Hz, 2H), 5.30 (s, br, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 7.20−7.40 (m, 10H); IR ($CHCl_3$) 3450, 1710, 1600, 1515, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 460 (M^+, 10), 91 (100); exact MS calcd for $C_{27}H_{28}N_2O_5$ M^+ 460.1984, found *m*/*z* 460.1999.

(*R*)-1-Benzyl-1′-ethoxycarbonyl-5-methoxy-2-oxospiro-(3*H*-indole-3,3′-pyrrolidine) (14a). A solution of **13a** (40 mg, 0.10 mmol) in CH_2Cl_2 (4 mL) was treated with Et_3N (20 μL, 0.14 mmol) and methane sulfonyl chloride (9.3 μL, 0.12 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, quenched with water (2 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuo. The crude product was used for the next step without purification. The residue was dissolved in THF (2 mL) and treated with an NaH (10 mg, 60% in oil, 0.19 mmol) suspension in THF (0.5 mL) at 0 °C. The reaction mixture was stirred for 10 h at room temperature, quenched with saturated NH_4Cl, and extracted with

EtOAc (3 × 25 mL). The combined oganic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, ethyl acetate−hexane, 4:6) to give amorphous **14a** (32 mg, 85%): $[\alpha]^{20}_D$ −28.4 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20−1.38 (m, 3H), 2.02−2.66 (m, 2H), 3.50−3.70 (m, 2H), 3.76 (s, 3H), 3.78−3.88 (m, 2H), 4.10−4.26 (m, 2H), 4.90 (s, 2H), 6.60−6.72 (m, 2H), 6.80 (m, 1H), 7.20−7.32 (m, 5H); IR ($CHCl_3$) 1700, 1495 cm^{-1}; MS *m*/z (rel intensity) 380 (M^+, 60), 265 (100); exact MS calcd for $C_{22}H_{24}N_2O_4$ M^+ 380.1736, found *m*/*z* 380.1737.

(*R*)-1-Benzyl-1′-benzyloxycarbonyl-5-methoxy-2-oxospiro-(3*H*-indole-3,3′-pyrrolidine) (14b). 14b was obtained from **13b** in 94% yield by a procedure similar to that for the conversion of **13a** into **14a**. **14b**: $[\alpha]^{20}_D$ −36.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.02−2.20 (m, 1H), 2.40−2.60 (m, 1H), 3.61−3.70 (m, 1H), 3.73 (s, 3H), 3.80−4.0 (m, 3H), 4.89 (s, 2H), 5.21, 5.17 (two s, ratio = 3:4, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.80 (t, *J* = 2.8 Hz, 1H), 7.20−7.45 (m, 10 H); IR ($CHCl_3$) 1705, 1600, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 442 (M^+, 25), 91 (100). Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.30; H, 6.11; N, 6.33. Found: C, 73.05; H, 5.94; N, 6.15.

(*R*)-1-Benzyl-1′-methyl-5-methoxy-2-oxospiro(3*H*-indole-3,3′-pyrrolidine) (15). (A) From 14a. A solution of **14a** (24 mg, 0.06 mmol), KOH (53 mg, 0.94 mmol), and NH_2NH_2 (10 μL, 0.32 mmol) in ethylene glycol (1 mL) was heated at 100 °C for 10 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude free amine was refluxed in HCO_2H (1 mL) and HCHO (47 μL, 0.58 mmol, 37% in water) for 1 h. The reaction mixture was cooled to room temperature, diluted with water, basified with saturated $NaHCO_3$, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by preparative TLC (methanol−dichloromethane = 1:9) to give **15** (18 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05−2.22 (m, 1H), 2.31−2.47 (m, 1H), 2.50 (s, 3H), 2.81 (t, *J* = 8.2, Hz 1H), 2.90 (d, *J* = 9.5 Hz, 1H), 3.01 (d, *J* = 9.5 Hz, 1H), 3.15 (ddd, *J* = 11.5, 8.2, 3.9 Hz, 1H), 3.77 (s, 3H), 4.88 (s, 2H), 6.57 (d, *J* = 8.5 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.24−7.35 (m, 5H); IR ($CHCl_3$) 1705, 1490 cm^{-1}; MS *m*/*z* (rel intensity) 322 (M^+, 29), 265 (100); exact MS calcd for $C_{20}H_{22}N_2O_2$ M^+ 322.1681, found *m*/*z* 322.1700.

(B) From 14b. A solution of **14b** (50 mg, 0.11 mmol) and Pd/C (10 mg) in methanol (5 mL) was stirred under atmospheric hydrogen at room temperature for 8 h. The catalyst was filtered and washed with methanol. The combined filtrate was concentrated under reduced pressure to give crude free amine. The crude amine was dissolved in CH_3CN (1.5 mL) and treated with HCHO (49 μL, 0.60 mmol, 37% in water) and $NaCNBH_3$ (12.8 mg, 0.20 mmol) at room temperature. The mixture was stirred for 15 min and neutralized with acetic acid. After stirring was continued for a further 1 h, the mixture was basified with ammonia solution. Solvent was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated under vacuo. The crude product was purified by preparative TLC (silica gel, methanol−dichloromethane = 1:9) to give **15** (31 mg, 85%) as a colorless oil: $[\alpha]^{20}_D$ −2.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR and mass spectra were identical with those of **15** obtained from **14a**.

(−)-Horsfiline (1). A solution **15** (obtained from **14b**, 15 mg, 0.05 mmol) in THF−*t*-BuOH (1.1 mL, 10:1) was added dropwise to a dark blue solution of lithium (5.0 mg) in liquid ammonia (ca 5 mL) at −78 °C. The resulting solution was stirred for 6 min and then quenched with 35 mg of NH_4Cl. Ammonia was allowed to evaporate, and the remaining solvent was removed under vaccum. The crude material was treated with water (2.0 mL) and extracted with EtOAC (3 × 35 mL). The organic phase was washed with saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, methanol−dichloromethane = 1:9) to give **1** (9.2 mg, 83%) as colorless crystals: $[\alpha]^{20}_D$ −7.0 (*c* 0.32, MeOH) {lit.[1] $[\alpha]^{20}_D$ −7.2 (*c* 1.0, MeOH)}, mp 120−122 °C (acetone) {lit.[1] mp 124−126 °C (acetone)}. The spectral data (^{1}H NMR, mass, C^{13} NMR, and HRMS) were identical with those reported.[1]

1-Benzyl-3-(3-methylbut-2-enyl)-2-oxindole (17). 17 was obtained from **16** in 60% yield by a procedure similiar to that for the conversion of **4** into **5**: a yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H), 1.59 (s, 3H), 2.74 (br t, *J* = 6.6, Hz, 2H), 3.57 (t, *J* = 6.6 Hz, 1H), 4.73, 5.10 (ABq, *J* = 15.7 Hz, 2H), 5.03−5.10 (m, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.7, 7.4 Hz, 1H), 7.11−7.36 (m, 7H); IR (neat) 1713, 1613, 1488 cm^{-1}; MS *m*/*z* (rel intensity) 291 (M^+, 22), 223 (100); exact MS calcd for $C_{20}H_{21}NO$ M^+ 291.1624, found *m*/*z* 291.1598.

(*S*)-1-Benzyl-3-(3-methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindole (18). A solution of **17** (10.1 g, 34.6 mmol) in dry ether (90 mL) was treated with *n*-BuLi (1.59 M solution in hexane, 21.8 mL, 34.6 mmol) at −78 °C under argon. The reaction mixture was warmed to 0 °C and stirred for 30 min. The resulting enolate solution was transferred to a suspension of **2** (3.9 g, 11.5 mmol) in ether (30 mL) at −78 °C via cannula. The mixture was warmed rapidly to −50 °C and then slowly allowed to warm to 0 °C, and stirring was continued for 3 h. The reaction mixture was poured into an HCl solution (2.50 M, 150 mL) and stirred for 30 min. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate−hexane = 1: 9) to afford **18** (2.7 g, 65%) as pale yellow crystals, mp 122−124 °C (ethyl acetate−hexane). The ee was determined to be >99% by HPLC with CHIRALPAK AS (5% 2-propanol−hexane, flow 1.0 mL/min, t_R =21.8 min (*S*) and 26.0 min (*R*). **18**: $[\alpha]^{20}_D$ +13.6 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.55 (s, 3H), 1.59 (s, 3H), 2.68−2.92 (m, 2H), 4.69, 5.15 (ABq, *J* = 15.9 Hz, 2H), 4.81 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 7.06, 7.46 (ABq, *J* = 13.6 Hz, 2H), 7.07−7.36 (m, 8H); IR (KBr) 1717, 1612, 1512 cm^{-1}; MS *m*/*z* (rel intensity) 362 (M^+, 25), 247 (100). Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.05; N, 7.73. Found: C, 72.65; H, 6.14; N, 7.48.

(*S*)-1-Benzyl-3-(3-methylbut-2-enyl)-3-(2-nitroethyl)-2-oxindole (19). 19 was obtained from **18** in 97% yield by a procedure similar to that for the conversion of **8** into **9**. **19**: colorless crystals (benzene−heptane), mp 99−100 °C; $[\alpha]^{20}_D$ +55.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (s, 3H), 1.57 (s, 3H), 2.49−2.79 (m, 4H), 3.93−4.28 (m, 2H), 4.67, 5.16 (ABq, *J* = 15.7 Hz, 2H), 4.77 (t, *J* =6.7 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 7.02−7.36 (m, 8H); IR (KBr) 1717, 1610, 1550 cm^{-1}; MS *m*/*z* (rel intensity) 364 (M^+, 18), (100); exact MS calcd for $C_{22}H_{24}N_2O_3$ M^+ 364.1788, found *m*/*z* 364.1782.

(*S*)-3-[1-Benzyl-3-(3-methylbut-2-enyl)-2-oxindolyl)]acetic Acid (20). 20 was obtained from **19** in 87% yield by a procedure similar to that for the conversion of **10** into **11**. **20**: a yellow oil; $[\alpha]^{20}_D$ +1.9 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3H), 1.57 (s, 3H), 2.56 (d, *J* = 8.1 Hz, 2H), 2.92, 3.13 (ABq, *J* = 16.7 Hz, 2H), 4.77, 5.08 (ABq, *J* = 15.9 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.98−7.29 (m, 8H); IR (neat) 1714, 1613, 1489 cm^{-1}; MS *m*/*z* (rel intensity) 349 (M^+, 26), 235 (100); exact MS calcd for $C_{22}H_{23}NO_3$ M^+ 349.1679, found *m*/*z* 349.1669.

(*S*)-1-Benzyl-3-(3-methylbut-2-enyl)-3-(benzyloxycarbonylaminomethyl)-2-oxindole (21). 21 was obtained from **20** in 83% yield as a yellow oil by a procedure similar to that for the conversion of **11** into **12b**. **21**: $[\alpha]^{20}_D$ −33.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H), 1.55 (s, 3H), 2.45−2.57 (m, 1H), 2.67−2.78 (m, 1H), 3.40−3.51 (m, 1H), 3.78−3.89 (m, 1H), 4.63−4.81 (m, 2H), 4.98−5.14 (m, 2H), 5.24−5.30 (m, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 7.0−7.40 (m, 13 H); IR (KBr) 3326, 1712, 1612, 1488 cm^{-1}; MS *m*/*z* (rel intensity) 454 (M^+, 12), 91(100); exact MS calcd for $C_{29}H_{30}N_2O_3$ M^+ 454.2258, found *m*/*z* 454.2224.

(*R*)-1-Benzyl-3-(hydroxymethyl)-3-(3-benzyloxycarbonylaminomethyl)-2-oxindole (22) and (3*R*)-1-Benzyl-1′-benzyloxycarbonyl-2′-hydroxy-2-oxospiro(3*H*-indole-3,4′-pyrrolidine) (23). A solution of **21** (347 mg, 0.76 mmol) in ethanol (30 mL) was treated with ozone at −78 °C until starting material was disappeared. Excess ozone was removed by bubbling nitrogen, and dimethyl sulfide (1.0 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 24 h. After removal of solvent under reduced pressure, the crude aldehyde was dissolved in methanol (10 mL) and treated with $NaBH_4$ (144 mg, 3.82 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with

saturated NH_4Cl. Methanol was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, ethyl acetate−hexane = 4:6) to afford **22** (230 mg, 70%) as a colorless oil and **23** (2:1 diastereomeric mixture, 47 mg, 14%) as a colorless oil. **22:** $[\alpha]^{20}_D$ +8.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (2.07−2.16 (m, 1H), 2.26−2.50 (m, 1H), 3.39−360 (m, 3H), 3.80−3.91 (m, 1H), 4.90 (s, 2H), 5.01, 5.09 (ABq, J = 12.3, Hz, 2H), 5.17−5.28 (m, 1H), 6.74 (d, J = 7.6 Hz, 1H), 7.0−7.37 (m, 13 H); IR (KBr) 3331, 1694, 1612, 1488 cm^{-1}; MS *m*/*z* (rel intensity) 430 (M^+, 2), 91 (100); exact MS calcd for $C_{26}H_{26}N_2O_4$ M^+ 430.1894, found *m*/*z* 430.1915. **23**: $[\alpha]^{20}_D$ −13.4 (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15−2.37 (m, 1H), 2.48−2.80 (m, 1H), 3.65−4.05 (m, 2H), 4.91 (s, 2H), 5.15−5.40 (m, 2H), 5.69−6.10 (m, 1H), 6.73, 6.78 (two d, J = 8.6, 8.6 Hz, ratio = 2:1, 1H), 7.00−7.74 (m, 13H); IR (neat) 3404, 1612, 1488 cm^{-1}, MS *m*/*z* (rel intensity) 428 (M^+, 3), 91 (100); exact MS calcd for $C_{26}H_{24}N_2O_4$ M^+ 428.1737, found 428.1764.

(*R*)-1-Benzyl-1′-benzyloxycarbonyl-2-oxospiro(3*H*-indole-3,3′-pyrrolidine) (24). (A) From 23. A solution of **23** (47 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was treated with triethylsilane (18 μL, 0.11 mmol) and boron trifluoride etherate (14 μL, 0.11 mmol) at −78 °C. After 30 min, additional triethylsilane (18 μL, 0.11 mmol) and boron trifluoride etherate (14 μL, 0.11 mmol) were added and stirring was continued for another 3 h at −78 °C. The reaction mixture was quenched with saturated NaCl and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate−hexane = 3:7) to afford **24** (39 mg, 86%) as a colorless oil: $[\alpha]^{20}_D$ −18.7(*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.04−2.20 (m, 1H), 2.40−2.60 (m, 1H), 3.65−4.0 (m, 4H), 4.92 (s, 2H), 5.21, 5.17 (two s, ratio = 2:3, 2H), 6.47 (d, J = 4.0 Hz, 1H), 7.02 (t, J = 9.2 Hz, 1H), 7.49−7.41 (m, 12H); IR (neat) 1713, 1613, 1487 cm^{-1}; MS *m*/*z* (rel intensity) 412 (M^+, 33), 91 (100); exact MS calcd for $C_{26}H_{24}N_2O_3$ M^+ 412.1788, found *m*/*z* 412.1773.

(B) From 22. 24 was obtained from **22** in 96% yield by a procedure similar to that for the conversion of **13b** into **14b**. The spectral data and the optical rotation of **24** thus obtained were identical with those of **24** obtained from **23**.

Preparation of 14b from 24. To a solution of lead tetrakis(trifluoroacetate) (736 mg, 1.12 mmol) in trifluoroacetic acid (4 mL) was added a solution of **24** (92 mg, 0.22 mmol) in trifluoroacetic acid (4 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and then quenched with saturated aqueous K_2CO_3, and stirring was continued for 30 min. The mixture was extracted with ether (3 × 40 mL). The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude material was dissolved in THF (2.0 mL) and added to a NaH (53 mg, 1.32 mmol, 60% in oil) suspension in THF (1.0 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and treated with MeI (0.5 mL), and stirring was continued for 30 min at room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate−hexane = 4:6) to afford **14b** (60 mg, 61%) as a colorless oil. Spectral data (^1H NMR, mass, IR, and optical rotaion) were identical with those of **14b** obtained from **13b**.

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