Supporting Information

Diastereoselective Synthesis of 3,3-Disubstituted Oxindoles from N-Aryl-3-Chlorooxindoles bearing C-N Axial Chirality via Nucleophilic Substitution

Atsuo Nakazaki*, Keitaro Miyagawa and Toshio Nishikawa

Graduate School of Bioagricultural Sciences, Nagoya University
Furo-cho, Chikusa, Nagoya 464-8601, Japan

Contents:

General Techniques 2

Experimental Section 3-18

$^1$H and $^{13}$C NMR Spectra of New Compounds 19-54
General Techniques

Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 spectrophotometer and are reported in wave number (cm\(^{-1}\)). Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded on a Bruker AVANCE-400 (400 MHz). NMR samples were dissolved in CDCl\(_3\), and chemical shifts are reported in ppm relative to the residual undeuterated solvent (CDCl\(_3\) as \(\delta = 7.26\)). \(^1\)H NMR data are reported as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constant and assignment. Carbon nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded on a Bruker AVANCE-400 (100 MHz) spectrometer. NMR samples were dissolved in CDCl\(_3\), and chemical shifts are reported in ppm relative to the solvent (CDCl\(_3\) as \(\delta = 77.0\)). \(^1\)H NMR and \(^{13}\)C NMR spectra were measured at 300 K unless otherwise noted. Melting points (mp) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. High resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner Biospectrometry ESI-TOF and are reported in \(m/z\). Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate 60 F\(_{254}\) (Merck, # 1.05715). Visualization was achieved by using UV light and appropriate reagent (7% ethanolic phosphomolybdic acid or p-anisaldehyde solution), followed by heating. Silica gel 60 N (spherical, neutral, particle size 63-210 \(\mu\)m, Kanto Chemical Co., Inc., #37565-79) was used for open-column chromatography. Silica gel 60 N (spherical, neutral, particle size 40-50 \(\mu\)m, Kanto Chemical Co., Inc., #37563-79) was used for flash column chromatography. Unless otherwise noted, reactions sensitive to oxygen or moisture were carried out in oven-dried (120 °C) or flame-dried glassware under N\(_2\) or argon atmosphere. Dry THF, dry Et\(_2\)O and dry CH\(_2\)Cl\(_2\) were purchased from Kanto Chemical Co., Inc. Thionyl chloride was distilled. All other commercially available reagents were used as received.
3-Chlorooxindole 2a: To a solution of alcohol 1a (70.0 mg, 0.168 mmol) in dry Et₂O (1.6 mL) were added 2,4,6-collidine (0.44 mL, 3.4 mmol) and thionyl chloride (0.122 mL, 1.67 mmol) at −78 °C under nitrogen. After stirring at −78 °C for 1 h 20 min, the reaction was quenched with a saturated aqueous solution of NaHCO₃ at −78 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with EtOAc (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 6:1) to afford 3-chlorooxindole 2a (59.0 mg, 81%, a 71:29 mixture of diastereomers determined by ¹H NMR analysis) as a yellow solid.

mp 65-70 °C. IR (KBr) \( \nu_{\text{max}} \) 1735, 1611, 1496, 1466, 1068, 1019 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C_{26}H_{26}NO₃NaCl, 458.14934; found, 458.14934. ¹H NMR (CDCl₃, 400 MHz) \( \delta \) 1.42 (0.87H, s, -CH₃), 1.44 (0.87H, s, -CH₃), 1.44 (2.13H, s, -CH₃), 1.52 (2.13H, s, -CH₃), 1.99 (0.87H, s, -CH₃), 2.00 (2.13H, s, -CH₃), 3.01 (0.87H, s, -OCH₃), 3.05 (2.13H, s, -OCH₃), 5.128 (0.58H, s, -CH₂ of Bn), 5.132 (1.42H, s, -CH₂ of Bn), 6.40 (0.29H, d, \( J = 8 \) Hz, oxindole H-7), 6.42 (0.71H, d, \( J = 8 \) Hz, oxindole H-7), 6.98-7.04 (1.71H, m, aromatic), 7.07-7.16 (0.58H, m, aromatic), 7.13 (0.71H, ddd, \( J = 8, 8, 1 \) Hz, oxindole H-5), 7.20-7.28 (0.29H, m, aromatic), 7.25 (0.71H, ddd, \( J = 8, 8, 1 \) Hz, oxindole H-6), 7.31-7.51 (7H, m, aromatic). ¹³C NMR (CDCl₃, 100 MHz) \( \delta \) 25.8, 26.2, 27.4, 27.8, 28.0, 28.1, 50.8, 51.1, 61.6, 62.5, 70.27, 70.30, 77.1, 77.3, 110.65, 110.70, 115.0, 115.2, 115.4, 115.8, 123.3, 123.4, 123.79, 123.84, 124.4, 124.8, 127.55, 127.58, 128.1, 128.2, 128.7, 129.9, 130.2, 130.7, 131.0, 131.7, 132.0, 136.5, 136.6, 144.2, 144.3, 146.5, 147.2, 159.46, 159.54, 174.2, 174.8.
3-Chlorooxindole 2b: To a solution of alcohol 1b (41.4 mg, 0.0933 mmol) in dry Et₂O (1.5 mL) were added 2,4,6-collidine (0.25 mL, 1.9 mmol) and thionyl chloride (0.068 mL, 0.93 mmol) at –78 °C under nitrogen. After stirring at –78 °C for 30 min, the reaction was quenched with H₂O at –78 °C. The resulting mixture was allowed to warm to room temperature and aqueous layer was extracted with EtOAc (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 6:1) to afford 3-chlorooxindole (24.0 mg, 56%, a 50:50 mixture of diastereomers determined by 1H NMR analysis) as an orange oil.

IR (KBr) νmax 1735, 1610, 1496, 1068, 1024 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₂₈H₂₈NO₃NaCl, 484.16499; found, 484.16300. ¹H NMR (CDCl₃, 400 MHz) δ 1.42 (1.5H, s, -CH₃), 1.42 (1.5H, s, -CH₃), 1.45 (1.5H, s, -CH₃), 1.51 (1.5H, s, -CH₃), 2.94 (0.5H, dd, J = 14, 8 Hz, -CH₃H₅CH=CH₂), 3.03 (1.5H, s, -OCH₃), 3.04 (1.5H, s, -OCH₃), 3.07-3.14 (1.5H, m, -CH₃H₅CH=CH₂, -CH₂H₂CH=CH₂), 5.12 (2H, s, -CH₂ of Bn), 5.12-5.25 (2H, m, -CH=CH₂), 5.54 (0.5H, dddd, J = 17, 14, 10, 8 Hz, -CH=CH₂), 5.94 (0.5H, dddd, J = 17, 14, 10, 8 Hz, -CH=CH₂), 6.39 (1H, dd, J = 8, 1 Hz, oxindole H-7), 6.89 (0.5H, d, J = 8 Hz, aryl H-6), 6.95-7.02 (1H, m, aryl H-5), 7.05 (0.5H, d, J = 8 Hz, aryl H-6), 7.09 (0.5H, dd, J = 8, 8 Hz, oxindole H-5), 7.12 (0.5H, dd, J = 8, 8 Hz, oxindole H-5), 7.19-7.51 (8H, m, aryl H-3, oxindole H-4, oxindole H-6, Ph of Bn). ¹³C NMR (CDCl₃, 100 MHz) δ 27.4, 27.5, 28.1, 28.5, 43.0, 43.2, 50.8, 51.1, 63.7, 64.8, 70.25, 70.29, 76.9, 110.5, 110.9, 114.9, 115.3, 115.4, 115.7, 121.0, 121.3, 123.1, 123.3, 124.4, 124.5, 124.9, 125.2, 127.5, 127.6, 128.1, 128.2, 128.6, 128.7, 129.2, 129.9, 130.2, 130.3, 130.6, 131.8, 132.0, 136.5, 136.6, 144.9, 145.0, 146.7, 147.1, 159.4, 159.6, 173.3, 174.4.
Experiment of entry 4 in Table 1: To a mixture of 3-chlorooxindole 2a (18.0 mg, 0.0413 mmol), MS 4A (ca. 18 mg) and prenyltributylstannane (0.02 mL, 0.06 mmol) in dry CH₂Cl₂ (1.0 mL) was added AgBF₄ (24.1 mg, 0.124 mmol) at −40 °C. The mixture was stirred at −40 °C for 3 h, the reaction was quenched with H₂O at −40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH₂Cl₂ (2x). The organic layer was washed with brine and concentrated. The residue was purified by silica gel with 10% KF of silica gel flash column chromatography (hexane → hexane:AcOEt = 20:1) to afford oxindole 3a as an inseparable mixture of anti and syn isomers (11.2 mg, 62%, a anti :syn = 70:30 mixture of diastereomers determined by ¹H NMR analysis) as a colorless clear oil and oxindole 4 (1.9 mg, 10%, a dr = 60:40 mixture of diastereomers determined by ¹H NMR analysis) as a colorless clear oil. Relative stereochemistry of anti-3a was determined by NOESY correlation.

Oxindole 3a: IR (KBr) νmax 1710, 1608, 1496, 1463, 1068, 1023 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₃₁H₃₅NO₃Na, 492.25092; found, 492.24872. ¹H NMR (CDCl₃, 400 MHz) δ 1.16 (2.1H, s, -C₃H₃), 1.18 (0.9H, s, -C₃H₃), 1.25 (2.1H, s, -CH₃), 1.30 (0.9H, s, -CH₃), 1.31 (2.1H, s, -CH₃), 1.41 (0.9H, s, -CH₃), 1.43 (2.1H, s, -CH₃), 1.44 (2.1H, s, -CH₃), 1.50 (0.9H, s, -CH₃), 1.57 (0.9H, s, -CH₃), 3.00 (2.1H, s, -OCH₃), 3.12 (0.9H, s, -OCH₃), 5.02 (0.7H, dd, J = 18, 1 Hz, -CH=CH₂H₆), 5.04 (0.3H, dd, J = 18, 1 Hz, -CH=CH₂H₆), 5.12 (0.3H, brd, J = 11 Hz, -CH=CH₂H₆), 5.12 (0.7H, brd, J = 11 Hz, -CH=CH₂H₆), 5.13 (0.6H, s, -CH₂ of Bn), 5.13 (1.4H, s, -CH₂ of Bn), 6.05 (0.7H, dd, J = 18, 11 Hz, -CH=CH₂H₆), 6.24 (0.3H, dd, J = 18, 11 Hz, -CH=CH₂H₆), 6.32 (0.3H, brd, J = 8 Hz, oxindole H-7), 6.35 (0.7H, brd, J = 8 Hz, oxindole H-7), 6.79 (0.3H, d, J = 8 Hz, aryl H-6), 6.94 (0.3H, dd, J = 8, 3 Hz, aryl H-5), 6.96-7.05 (1.7H, m, aryl H-3, oxindole H-5), 7.12 (0.3H, ddd, J = 8, 8, 1 Hz, oxindole H-6), 7.15 (0.7H, ddd, J = 8, 8, 1 Hz, oxindole H-6), 7.27 (0.3H, d, J = 3 Hz, aryl H-3), 7.29 (0.3H, dd, J = 8, 1 Hz, oxindole H-4), 7.29 (0.7H, dd, J = 8, 1 Hz, oxindole H-4), 7.30-7.50 (1.5H, m, Ph of
Bn), 7.30-7.50 (4.9H, m, aryl H-5, aryl H-6, Ph of Bn). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 17.8, 20.7, 21.6, 22.4, 22.7, 22.8, 25.9, 28.0, 28.1, 29.2, 30.9, 42.0, 42.2, 50.8, 51.2, 53.0, 53.5, 70.19, 70.23, 76.6, 77.5, 109.3, 110.6, 113.3, 113.7, 114.4, 115.3, 115.4, 115.8, 121.6, 121.7, 124.7, 125.2, 125.4, 127.4, 127.5, 127.6, 127.7, 127.8, 128.05, 128.11, 128.6, 131.6, 132.4, 132.5, 134.1, 136.6, 136.7, 143.6, 144.2, 145.5, 146.3, 146.6, 146.8, 158.7, 159.3, 179.8, 181.6.

**Oxindole 4:** IR (KBr) $v_{\text{max}}$ 2970, 2931, 1721, 1620, 1498, 1069, 1025 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for C$_{31}$H$_{35}$NO$_3$Na, 492.25092; found, 492.25219. $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.29 (3H, s, -CH$_3$), 1.30 (3H, s, -CH$_3$), 1.35 (1.2H, s, -CH$_3$), 1.36 (1.8H, s, -CH$_3$), 1.42 (1.2H, s, -CH$_3$), 1.44 (1.8H, s, -CH$_3$), 1.52-1.58 (2H, m, -CH$_2$), 3.02 (1.2H, s, -OCH$_3$), 3.03 (1.8H, s, -OCH$_3$), 3.52 (1H, m, oxindole H-3), 4.95 (1H, br d, $J = 11$ Hz, -CH=CH$_2$), 4.96 (1H, br d, $J = 18$ Hz, -CH=CH$_2$), 5.14 (2H, m, -CH$_2$ of Bn), 5.92 (1H, m, -CH=CH$_2$), 6.32 (1H, m, oxindole H-7), 6.96-7.07 (3H, m, aryl H-5, oxindole H-4, oxindole H-6), 7.20 (1H, m, oxindole H-5), 7.33-7.53 (7H, m, Ph of Bn, aryl H-3, aryl H-6). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 15.1, 27.5, 28.2, 28.26, 28.32, 40.4, 41.3, 51.0, 70.3, 77.2, 108.1, 110.9, 115.4, 115.5, 120.1, 123.1, 125.4, 127.6, 127.8, 128.1, 128.6, 132.0, 132.1, 136.7, 145.8, 146.4, 147.6, 149.0, 159.3, 179.8.

**Oxindole 5:** To a mixture of the 3-chlorooxindole 2a (43.6 mg, 0.10 mmol), MS 4A (ca. 40 mg) and allyltrimethylsilane (0.024 mL, 0.15 mmol) in dry CH$_2$Cl$_2$ (3 mL) was
added AgBF$_4$ (58.4 mg, 0.300 mmol) at $-40$ °C under nitrogen. After stirring at $-40$ °C for 20 min, the reaction was quenched with H$_2$O at $-40$ °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 9:1 → 6:1) to afford oxindole 5 (39.0 mg, 88 %, a 60:40 mixture of diastereomers determined by $^1$H NMR analysis) as an orange oil.

IR (KBr) $\nu_{\text{max}}$ 1720, 1610, 1496, 1464, 1069, 1021 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcld for C$_{29}$H$_{31}$NO$_3$Na, 464.21961; found, 464.21986. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.39 (1.8H, s, -C$_3$H$_3$), 1.442 (1.8H, s, -C$_3$H$_3$), 1.445 (1.2H, s, -CH$_3$), 1.46 (1.2H, s, -CH$_3$), 1.47 (1.8H, s, -CH$_3$), 2.51-2.72 (2H, m, -CH$_2$CH=CH$_2$), 3.03 (1.8H, s, -OC$_3$H$_3$), 3.06 (1.2H, s, -OC$_3$H$_3$), 4.96-5.16 (2H, m, -CH=CH$_2$), 5.13 (2H, s, -CH$_2$ of Bn), 5.48 (0.6H, dddd, $J$ = 17, 10.5, 8.5, 6.5 Hz, -CH=CH$_2$), 5.88 (0.4H, dddd, $J$ = 17.5, 10, 7.5, 7.5 Hz, -CH=CH$_2$), 6.37 (0.6H, d, $J$ = 8 Hz, oxindole H-7), 6.39 (0.4H, d, $J$ = 8 Hz, oxindole H-7), 6.92 (1H, m, aryl H-6), 6.97 (0.6H, d, $J$ = 3 Hz, aryl H-3), 6.99 (0.4H, d, $J$ = 3 Hz, aryl H-3), 7.04 (0.4H, ddd, $J$ = 8, 8, 1 Hz, oxindole H-5), 7.06 (0.6H, ddd, $J$ = 8, 8, 1 Hz, oxindole H-5), 7.15 (1H, ddd, $J$ = 8, 8, 1 Hz, oxindole H-6), 7.25 (1H, m, oxindole H-4), 7.31-7.50 (6H, m, aryl H-5, Ph of Bn). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 22.7, 22.9, 27.4, 28.0, 28.1, 29.6, 41.8, 42.9, 47.8, 48.4, 50.9, 51.0, 70.2, 77.1, 109.9, 110.3, 115.0, 115.26, 115.28, 115.4, 119.0, 119.1, 122.3, 122.4, 122.8, 123.3, 125.7, 126.1, 127.53, 127.55, 127.63, 127.7, 128.07, 128.08, 128.6, 132.10, 132.14, 132.7, 132.9, 133.1, 133.8, 136.68, 136.69, 145.2, 145.3, 146.6, 146.9, 159.1, 159.3, 180.3, 181.1.

Oxindole 6: To a suspension of the 3-chlorooxindole 2a (30.0 mg, 0.0688 mmol), MS 4A (ca. 30 mg) and silyl enol ether (0.21 mL, 0.69 mmol) in dry CH$_2$Cl$_2$ (2 mL) was added AgBF$_4$ (41.0 mg, 0.211 mmol) at $-40$ °C under nitrogen. After stirring at
–40 °C for 2 h, the reaction was quenched with H₂O at –40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH₂Cl₂ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:toluene:EtOAc = 6:6:1) to afford anti-6 (18.8 mg, 52%) as a colorless clear oil and syn-6 (10.3 mg, 29%) as a colorless clear oil. Relative stereochemistry of syn-6 was determined by NOESY correlation.

**major isomer:** IR (KBr) v max 1716, 1693, 1610, 1494, 1465, 1450, 1068, 1020 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₃₄H₃₃NO₄Na, 542.23018; found, 542.22768. ¹H NMR (CDCl₃, 400 MHz) δ 1.49 (3H, s, -C₆H₃), 1.52 (3H, s, -CH₃), 1.54 (3H, s, -CH₃), 3.10 (3H, s, -OCH₃), 3.77 (1H, d, J = 18 Hz, -CH₂CH₃COPh), 3.81 (1H, d, J = 18 Hz, -CH₃CH₆COPh), 5.14 (2H, s, -CH₂ of Bn), 6.45 (1H, brd, J = 8 Hz, oxindole H-7), 6.96 (1H, brdd, J = 8, 8 Hz, oxindole H-5), 7.12 (1H, brd, J = 8 Hz, oxindole H-4), 7.14 (1H, brdd, J = 8, 8 Hz, oxindole H-6), 7.31-7.57 (9H, m, acetophenone, Ph of Bn, aryl H-3), 7.60 (1H, d, J = 9 Hz, aryl H-6), 7.89 (2H, m, acetophenone). ¹³C NMR (CDCl₃, 100 MHz) δ 24.5, 26.9, 28.5, 44.1, 46.4, 51.0, 70.2, 77.2, 110.6, 115.0, 115.1, 122.5, 123.8, 126.0, 127.6, 127.7, 128.08, 128.12, 128.56, 128.64, 132.0, 133.2, 133.5, 136.7, 137.1, 145.3, 147.4, 159.2, 180.7, 196.4.

**minor isomer:** IR (KBr) v max 1717, 1688, 1611, 1496, 1068, 1020 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₃₄H₃₃NO₄Na, 542.23084; found, 542.23084. ¹H NMR (CDCl₃, 400 MHz) δ 1.50 (3H, s, -CH₃), 1.57 (3H, s, -CH₃), 1.61 (3H, s, -CH₃), 3.12 (3H, s, -OCH₃), 3.55 (1H, d, J = 18 Hz, -CH₂CH₃COPh), 3.69 (1H, d, J = 18 Hz, -CH₃CH₆COPh), 5.13 (2H, s, -CH₂ of Bn), 6.43 (1H, brd, J = 8 Hz, oxindole H-7), 6.95 (1H, d, J = 9 Hz, aryl H-6), 6.97 (1H, d, J = 3 Hz, aryl H-3), 7.00 (1H, brdd, J = 8, 8 Hz, oxindole H-5), 7.14 (1H, brdd, J = 8, 8 Hz, oxindole H-6), 7.31-7.58 (10H, m, acetophenone, aryl H-5, Ph of Bn, oxindole H-4), 7.93 (2H, m, acetophenone). ¹³C NMR (CDCl₃, 100 MHz) δ 24.5, 28.1, 28.3, 45.1, 46.7, 51.1, 70.2, 77.2, 110.3, 114.9, 115.4, 121.3, 122.1, 126.6, 127.6, 127.7, 128.0, 128.0, 128.02, 128.5, 128.6, 132.2, 133.1, 133.7, 136.4, 136.8, 146.37, 146.41, 159.1, 181.2, 196.0.
Oxindole 7: To a suspension of the 3-chlorooxindole 2a (75.0 mg, 0.172 mmol), MS 4A (ca. 75 mg) and thiophene (0.14 mL, 1.7 mmol) in dry CH$_2$Cl$_2$ (4.3 mL) was added AgBF$_4$ (100 mg, 0.516 mmol) at –40 °C under nitrogen. After stirring at –40 °C for 45 min, the reaction was quenched with H$_2$O at –40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 6:1 → 2:1) to afford oxindole 7 (53.8 mg, 65%, a 73:18:9 mixture of isomers determined by $^1$H NMR analysis) as a yellow solid. Major regioisomer was found to be 2-thienyl analogue, which was confirmed by the transformation of 7 into n-butyl analogue S3 under reductive desulfurization using Raney Ni (vide infra).

IR (KBr) $\nu_{\text{max}}$ 1719, 1610, 1496, 1465, 1019 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcld for C$_{30}$H$_{29}$NO$_3$NaS, 506.17604; found, 506.17364.

**major isomer:** $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.44 (3H, s, -CH$_3$), 1.49 (3H, s, -CH$_3$), 1.91 (3H, s, -CH$_3$), 3.04 (3H, s, -OCH$_3$), 5.12 (2H, s, -CH$_2$ of Bn), 6.45 (1H, d, $J = 8$ Hz, oxindole H-7), 6.93-7.04 (4H, m, aryl H-5, aryl H-6, thienyl H-3, thienyl H-4), 7.11 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-5), 7.22 (1H, dd, $J = 8$, 1 Hz, thienyl H-5), 7.23 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-6), 7.31-7.50 (7H, m, aryl H-3, oxindole H-4, Ph of Bn).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 25.2, 28.0, 28.1, 50.2, 51.1, 70.2, 77.3, 110.4, 115.2, 115.4, 122.9, 124.2, 124.9, 125.0, 125.4, 126.8, 127.6, 128.1, 128.5, 128.6, 132.1, 133.8,
136.6, 144.9, 145.2, 146.5, 159.3, 178.1.

**Oxindole 9:** To a suspension of the 3-chlorooxindole 2a (30.0 mg, 0.0688 mmol), MS 4A (ca. 30 mg) and phenol (19.5 mg, 0.207 mmol) in dry CH$_2$Cl$_2$ (1.7 mL) was added AgBF$_4$ (40.4 mg, 0.207 mmol) at −40 °C under nitrogen. After stirring at −40 °C for 16.5 h, the reaction was quenched with H$_2$O at −40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1 → 3:1) to afford oxindole 9 (28.9 mg, 85%, a anti: syn = 94:6 mixture of diastereomers determined by ¹H NMR analysis) as a colorless clear oil. Relative stereochemistry of 9 was determined by the comparison of ¹H NMR spectrum with that of 8 after Williamson methylation.

IR (KBr) 3394, 1715, 1609, 1514, 1496, 1465, 1067 cm$^{-1}$. HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{32}$H$_{31}$NO$_4$Na, 530.21453; found, 516.21636. ¹H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.46 (3H, s, -CH$_3$), 1.49 (3H, s, -CH$_3$), 1.84 (3H, s, -CH$_3$), 3.05 (3H, s, -OCH$_3$), 5.12 (2H, s, -CH$_2$ of Bn), 6.47 (1H, d, $J = 8$ Hz, oxindole H-7), 6.50-6.55 (2H, m, hydroxypheny H-3, hydroxypheny H-5), 6.97-7.04 (2H, m, hydroxypheny H-3, hydroxypheny H-5), 7.01 (1H, d, $J = 3$ Hz, aryl H-3), 7.06 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-5), 7.14 (1H, brd, $J = 8$ Hz, oxindole H-4), 7.19 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-6), 7.31-7.50 (7H, m, aryl H-5, aryl H-6, Ph of Bn). ¹³C NMR (CDCl$_3$, 100 MHz) $\delta$ 22.4, 27.9, 28.2, 51.1, 51.8, 70.3, 77.3, 110.4, 115.2, 115.5, 115.6, 123.2, 124.1, 125.4, 127.6, 127.8, 127.9, 128.1, 128.7, 131.9, 132.1, 135.5, 136.6, 145.0, 146.5, 155.5, 159.3, 181.1.
**Oxindole 10:** To a suspension of the 3-chlorooxindole 2a (30.2 mg, 0.0692 mmol), MS 4A (ca. 30 mg) and acetanilide (14.0 mg, 0.104 mmol) in dry CH$_2$Cl$_2$ (2.3 mL) was added AgBF$_4$ (40.4 mg, 0.208 mmol) at −40 °C under nitrogen. After stirring at −40 °C for <1 h, the reaction was quenched with H$_2$O at −40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The organic layer was with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1 → 1:1) to afford oxindole 10 (28.3 mg, 77%, a *anti*:syn = 94:6 mixture of diastereomers determined by $^1$H NMR analysis) as a white solid. Relative stereochemistry of oxindole 10 was determined by NOESY correlation. Spectral data are given in the main text.

![Diagnostic NOESY correlation of oxindole 10.](image-url)
Oxindole 11: To a suspension of the 3-chlorooxindole 2a (33.3 mg, 0.0763 mmol), MS 4A (ca. 30 mg) and 1,3-dimethoxybenzene (0.10 mL, 0.76 mmol) in dry CH$_2$Cl$_2$ (1.5 mL) was added AgBF$_4$ (44.6 mg, 0.228 mmol) at –40 °C under nitrogen. After stirring at –40 °C for <1 h, the reaction was quenched with H$_2$O at –40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 6:1 → 3:1) to afford oxindole 11 (33.6 mg, 82%, an $anti: syn = >95:<5$ mixture of diastereomers determined by $^1$H NMR analysis) as a yellow oil. Relative stereochemistry of oxindole 11 was confirmed by NOESY analysis of the corresponding phenol S2 after debenzylation.

IR (KBr) $\nu_{\text{max}}$ 1718, 1608, 1496, 1464, 1069, 1027 cm$^{-1}$. HRMS-ESI (m/z): [M + Na]$^+$ calc for C$_{34}$H$_{35}$NO$_5$Na, 560.24074; found, 560.24130. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.52 (3H, s, -CH$_3$), 1.53 (3H, s, -CH$_3$), 1.81 (3H, s, -CH$_3$), 3.08 (3H, s, -OCH$_3$), 3.50 (3H, s, -OCH$_3$ of 2,4-dimethoxyphenyl), 5.14 (2H, s, -CH$_2$ of Bn), 6.39 (1H, d, $J = 7$ Hz, oxindole H-7), 6.41 (1H, d, $J = 3$ Hz, 2,4-dimethoxyphenyl H-3), 6.58 (1H, dd, $J = 9$, 3 Hz, aryl H-5), 6.87 (1H, ddd, $J = 7$, 7, 1 Hz, oxindole H-5), 6.92 (1H, brd, $J = 7$ Hz, oxindole H-4), 7.04 (1H, dd, $J = 9$, 3 Hz, 2,4-dimethoxyphenyl H-5), 7.09 (1H, ddd, $J = 7$, 7, 1 Hz, oxindole H-6), 7.16 (1H, d, $J = 9$ Hz, 2,4-dimethoxyphenyl H-6), 7.32-7.55 (7H, m, aryl H-3, aryl H-6, Ph of Bn).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 22.9, 27.6, 28.6, 49.5, 51.2, 55.3, 56.0, 70.2, 77.2, 100.3, 104.4, 109.5, 114.8, 115.4, 121.97, 122.02, 122.4, 126.9, 127.0, 127.5, 128.1, 128.3, 128.6, 131.8, 136.2, 136.7, 145.7, 146.6, 158.1, 158.9, 160.4, 181.0.
Oxindole 12: To a suspension of the 3-chlorooxindole 2b (11.2 mg, 0.0243 mmol), MS 4A (ca. 10 mg) and anisole (0.026 mL, 0.24 mmol) in dry CH₂Cl₂ (0.7 mL) was added AgBF₄ (14.2 mg, 0.0731 mmol) at –40 °C under nitrogen. After stirring at –40 °C for <30 min, the reaction was quenched with H₂O at –40 °C. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with CH₂Cl₂ (2x). The organic layer was washed with brine (1x) and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 6:1) to afford oxindole 12 (9.8 mg, 75%, an anti:syn = >95:<5 mixture of diastereomers determined by ¹H NMR analysis) as a yellow oil. Relative stereochemistry of oxindole 12 was determined by NOESY correlation.

IR (KBr) νₘₐₓ 1719, 1608, 1509, 1495 1069, 1027 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₃₅H₃₅NO₄Na, 556.24583; found, 556.24602. ¹H NMR (CDCl₃, 400 MHz) δ 1.47 (3H, s, -CH₃), 1.49 (3H, s, -CH₃), 2.93 (1H, dd, J = 14, 8.5 Hz, -CH₂H₃CH=CH₂H₄), 3.07 (3H, s, -OCH₃), 3.20 (1H, dd, J = 14, 6.5 Hz, -CH₂H₃CH=CH₂H₄), 3.78 (3H, s, -OCH₃ of methoxyphenyl), 5.04 (1H, brd, J = 11 Hz, -CH₂H₃CH=CH₂H₄), 5.09 (2H, s, -CH₂ of Bn), 5.11 (1H, brd, J = 17 Hz, -CH₂H₃CH=CH₂H₄), 5.75 (1H, ddd, J = 17, 11, 8.5, 6.5 Hz, -CH₂H₃CH=CH₂H₄), 6.45 (1H, d, J = 8 Hz, oxindole H-7), 6.80 (1H, d, J = 9 Hz, aryl H-6), 6.82-6.88 (2H, m, methoxyphenyl H-3, methoxyphenyl H-5), 6.90 (1H, dd, J = 9, 3 Hz, aryl H-5), 7.10 (1H, brdd, J = 8, 8 Hz, oxindole H-5), 7.22 (1H, ddd, J = 8, 8, 1 Hz, oxindole H-6), 7.27-7.48 (9H, m, oxindole H-4, methoxyphenyl H-2, methoxyphenyl H-6, Ph of Bn, aryl H-3). ¹³C NMR (CDCl₃, 100 MHz) δ 27.6, 28.6, 41.6, 51.0, 55.2, 55.4, 70.2, 77.2, 110.6, 113.9, 115.1, 115.2, 119.3, 122.3, 125.7, 126.0, 127.6, 128.05, 128.08, 128.5, 128.6, 131.6, 131.7, 132.2, 133.1, 136.7, 145.9, 146.9, 158.8, 159.1, 178.8.
Diagnostic NOESY correlation of oxindole 12.

Phenol S1: A solution of oxindole 8 (44.2 mg, 0.0874 mmol) in MeOH (1.5 mL) was treated with 10% Pd/C (22.1 mg) and stirred under an atmosphere of hydrogen (1 atm). After being stirred for 5 h at room temperature, the reaction mixture was filtered through a pad of Super-Cel by washing with EtOAc and the filtrate was concentrated to afford phenol S1 (36.5 mg, quantitative yield, a anti: syn = >95:<5 mixture of diastereomers determined by ¹H NMR analysis) as a white solid. Relative stereochemistry of oxindole S1 was determined by NOESY correlation.

mp 160-165 °C. IR (KBr) \nu_{max} 3394, 1698, 1511, 1068, 1031 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calecd for C₂₆H₂₇NO₄Na, 440.18323; found, 440.18518. ¹H NMR (CDCl₃, 400 MHz) δ 1.44 (3H, s, -CH₃), 1.51 (3H, s, -CH₃), 1.87 (3H, s, -CH₃), 3.12 (3H, s, -OCH₃ of methoxyphenyl), 3.78 (3H, s, -OCH₃ of methoxyphenyl), 6.48 (1H, brd, J = 8 Hz, oxindole H-7), 6.67 (1H, dd, J = 8, 3 Hz, aryl H-5), 6.74 (1H, brs, -OH), 6.81 (1H, d, J = 8 Hz, aryl H-6), 6.83-6.90 (2H, m, methoxyphenyl H-3, methoxyphenyl H-5), 7.08 (1H, ddd, J = 8, 8, 1 Hz, oxindole H-5), 7.16-7.30 (5H, m, aryl H-3, methoxyphenyl H-2, methoxyphenyl H-6, oxindole H-4, oxindole H-6). ¹³C NMR (CDCl₃, 100 MHz) δ 23.1, 27.8, 28.2, 51.0, 51.7, 55.3, 77.7, 110.4, 114.0, 115.8, 116.4, 123.1, 124.2, 124.5, 127.9, 128.0, 132.2, 133.1, 134.9, 145.0, 146.0, 157.1, 158.8, 180.5.
Phenol S2: A solution of oxindole 11 (26.2 mg, 0.0495 mmol) in MeOH (1 mL) was treated with 10% Pd/C (52 mg) and stirred under an atmosphere of hydrogen (1 atm). After being stirred for 3 days at room temperature, the reaction mixture was filtered through a pad of SuperCel by washing with EtOAc and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1 → 1:1) to afford phenol S2 (19.1 mg, 87%, a syn:anti = >95:<5 mixture of diastereomers determined by $^1$H NMR analysis) as a colorless clear oil. Relative stereochemistry of oxindole S2 was determined by NOESY correlation.

IR (KBr) $\nu_{\text{max}}$ 3279, 1698, 1609, 1498, 1464, 1030 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for C$_{27}$H$_{29}$NO$_5$Na, 470.19379; found, 470.19606. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.49 (3H, s, -CH$_3$), 1.51 (3H, s, -CH$_3$), 1.83 (3H, s, -CH$_3$), 3.11 (3H, s, -OCH$_3$), 3.52 (3H, s, -OCH$_3$ of 2,4-dimethoxyphenyl), 3.81 (3H, s, -OCH$_3$ of 2,4-dimethoxyphenyl) 6.42 (1H, brd, $J = 8$ Hz, oxindole H-7), 6.43 (1H, $J = 2$ Hz, 2,4-dimethoxyphenyl H-3), 6.60 (1H, dd, $J = 9$, 2 Hz, 2,4-dimethoxyphenyl H-5), 6.61 (1H, dd, $J = 9$, 3 Hz, aryl H-5), 6.86 (1H, dd, $J = 8$, 1 Hz, oxindole H-4), 6.92 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-6), 6.93 (1H, d, $J = 9$ Hz, aryl H-6), 7.07 (1H, d, $J = 3$ Hz, aryl H-3), 7.09 (1H, ddd, $J = 8$, 8, 1 Hz, oxindole H-5), 7.54 (1H, d, $J = 9$ Hz, 2,4-dimethoxyphenyl H-6). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 22.8, 27.8, 28.3, 49.8, 51.2, 55.4, 55.9, 77.3, 100.1, 104.5,
Diagnostic NOESY correlation of S2.

**Oxindole 13:** Phenol S1 (12.4 mg, 0.0297 mmol) was dissolved in MeCN/H\(_2\)O (6:1, 0.7 mL), and the resulting solution was cooled to 0 °C. To the solution was added [bis(trifluoroacetoxy)iodo]benzene (14 mg, 0.033 mmol). After being stirred at 0 °C for 3.5 h, the reaction was quenched with H\(_2\)O at that temperature. The resulting mixture was allowed to warm to room temperature and aqueous layer was extracted with CHCl\(_3\)/2-PrOH (3:1). The organic layer was concentrated. The residue was purified by silica gel chromatography (hexane:EtOAc = 4:1 → 2:1) to afford oxindole 1 (5.4 mg, 71%) as a white solid. mp 100-105 °C. IR (KBr) \(\nu_{\text{max}}\) 3425, 1709, 1618, 1511, 1472, 1032 cm\(^{-1}\). HRMS-ESI (m/z): [M + Na]\(^+\) calcd for C\(_{16}\)H\(_{15}\)NO\(_2\)Na, 276.09950; found, 276.09897. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.79 (3H, s, -C\(_2\)H\(_3\)), 3.77 (3H, s, -OC\(_2\)H\(_3\) of methoxyphenyl), 6.84 (2H, m, methoxyphenyl H-3, methoxyphenyl H-5), 6.95 (1H, brd, \(J = 8\) Hz, oxindole H-7), 7.06 (1H, ddd, \(J = 8, 8, 1\) Hz, oxindole H-5), 7.14 (1H, brd, \(J = 8\) Hz, oxindole H-4), 7.23 (2H, m, methoxyphenyl H-2, methoxyphenyl H-6), 7.23 (1H, m, oxindole H-6), 8.09 (1H, brs, NH). \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 23.7, 51.9, 55.3,
Oxindole 14: Phenol S2 (12.3 mg, 0.0275 mmol) was dissolved in MeCN/H₂O (6:1, 1.2 mL), and the resulting solution was cooled to 0 °C. To the solution was added [bis(trifluoroacetoxy)iodo]benzene (13.2 mg, 0.0307 mmol). After being stirred at 0 °C for 14 h, the reaction was quenched with H₂O at that temperature. The resulting mixture was allowed to warm to room temperature and the aqueous layer was extracted with EtOAc (2x). The organic layer was washed with brine and concentrated. The residue was purified by preparative TLC (hexane:EtOAc = 1:1) to afford oxindole 14 (5.4 mg, 69%) as a white solid.

mp 115-120 °C  IR (KBr) νₘₐₓ 3437, 1716, 1615, 1506, 1471, 1098, 1030 cm⁻¹. HRMS-ESI (m/z): [M + Na]⁺ calcd for C₁₇H₁₇NO₃Na, 306.11006; found, 306.10951. ¹H NMR (CDCl₃, 400 MHz) δ 1.70 (3H, s, -CH₃), 3.44 (3H, s, -OCH₃), 3.79 (3H, s, -OCH₃), 6.36 (1H, d, J = 3 Hz, 2,4-dimethoxyphenyl H-3), 6.57 (1H, dd, J = 8, 3 Hz, 2,4-dimethoxyphenyl H-5), 6.82 (1H, brd, J = 8 Hz, oxindole H-7), 6.87 (1H, brd, J = 8 Hz, oxindole H-4), 6.90 (1H, ddd, J = 8, 8, 1 Hz, oxindole H-5), 7.14 (1H, ddd, J = 8, 8, 1 Hz, oxindole H-6), 7.47 (1H, d, J = 8 Hz, 2,4-dimethoxyphenyl H-6), 7.81 (1H, brs, NH). ¹³C NMR (CDCl₃, 100 MHz) δ 23.7, 49.8, 55.4, 55.5, 99.9, 104.5, 108.9, 121.8, 122.2, 122.5, 127.1, 128.1, 136.7, 140.3, 158.0, 160.6, 183.0.
**Oxindole S3:** To a solution of the oxindole 7 (13 mg, 0.027 mmol) in dry THF (1 mL) was added excess amount of Raney Ni under nitrogen. After being stirred for ca. 7 days at room temperature, the reaction mixture was filtered through a pad of Super-Cel by washing with EtOAc and the filtrate was concentrated to afford crude phenol without further purification.

The crude phenol was dissolved in MeCN/H2O (6:1, 0.65 mL), and the resulting solution was cooled to 0 °C. To the solution was added [bis(trifluoroacetoxy)iodo]benzene (9.3 mg, 0.022 mmol) at 0 °C. After being stirred at 0 °C for 3 h, the reaction was quenched with H2O at that temperature. The aqueous layer was extracted with EtOAc (3x). The organic layer was concentrated. The residue was purified by preparative TLC (hexane:EtOAc = 2:1) to afford oxindole S3 (2.0 mg, 54% in 2 steps) as a white solid.

IR (KBr) 3249, 1706, 1621, 1475 cm⁻¹. HRMS-ESI (m/z): [M + H]⁺ calcd for C₁₃H₁₈NO, 204.13829; found, 204.13831.

*major isomer:* ¹H NMR (CDCl₃, 400 MHz) δ 0.780 (3H, t, J = 7 Hz, -CH₃H₂CH₂CH₂CH₃), 0.829-1.12 (2H, m, -CH₃H₂CH₂CH₂CH₃), 1.12-1.28 (2H, m, -CH₃H₂CH₂CH₂CH₃), 1.37 (3H, s, -CH₃), 1.73 (1H, td, J = 14, 5 Hz, -CH₃H₂CH₂CH₂CH₃), 1.89 (1H, td, J = 14, 5 Hz, -CH₃H₂CH₂CH₂CH₃), 6.88 (1H, d, J = 8 Hz, oxindole H-7), 7.04 (1H, dd, J = 8, 8 Hz, oxindole H-5), 7.15 (1H, dd, J = 8 Hz, oxindole H-4), 7.20 (1H, dd, J = 8, 8 Hz, oxindole H-6), 7.81 (1H, brs, NH). ¹³C NMR (CDCl₃, 100 MHz) δ 13.8, 22.8, 23.9, 26.6, 38.3, 48.8, 109.4, 122.4, 122.9, 127.5, 134.7, 140.2, 182.8.
Current Data Parameters
NAME  miyagawa-n400-2
EXPNO  77
PROCNO  1

F2 - Acquisition Parameters
Date_  20131130
Time  9.04
INSTRUM  av400
PULPROG  zgpp30
TD  65536
SOLVENT  CDC13
NS  12000
DS  4
SWH  23980.814 Hz
FIDRES  0.365918 Hz
AQ  1.2664756 sec
RG  16384
DW  20.850 usec
DE  30.00 usec
TE  300.0 K
D1  2.00000000 sec
d11  0.03000000 sec
d12  0.00002000 sec

--------------- CHANNEL f1 ---------------
NUC1  13C
P1  9.00 usec
PL1  -3.00 dB
SF01  100.6228298 MHz

--------------- CHANNEL f2 ---------------
CPDPRG2  waltz16
NUC2  1H
PCPD2  80.00 usec
PL2  -4.00 dB
PL12  14.80 dB
PL13  14.80 dB
SF02  400.1316005 MHz

F2 - Processing parameters
SI  32768
SF  100.6127700 MHz
WDW  EM
SSB  0
LB  1.00 Hz
GB  0
PC  1.40

\[ \text{Chemical structure image} \]

OMe

MeO

OBn