Supporting Information for

**Copper-Catalyzed Multicomponent Cascade Process for the Synthesis
of Hexahydro-1*H*-Isoindolones**

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General Experimental

Unless otherwise indicated, all NMR data were collected at room temperature in CDCl₃ with internal CHCl₃ as the reference (δ 7.26 ppm for ¹H and 77.00 ppm for ¹³C). IR spectra were measured as thin films on salt (NaCl) plates. Melting points are uncorrected and were taken in open capillary tubes. MS were measured under electrospray ionization (ES⁺) conditions. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 250 μ m thickness, with fluorescent indicator (F-254) or stained with aqueous KMnO₄ solution. Column chromatography was performed with 32-63 μ m silica gel (Sorbent). Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. 1,2-Dichloroethane, methylene chloride, DMF, MeCN, and toluene were kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon; other solvents were used as received. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140 °C) glassware. Dienylstannanes **III** were prepared according to a modified literature protocols.¹ All imines were prepared according to a modified literature procedure² by condensation of a 1 : 1 mixture of aldehyde and amine in benzene (65 °C) in the presence of activated 3Å (8-12 mesh) molecular sieves (4-6 h, monitored by GC) followed by filtration through Celite and removal of solvent under vacuum to afford pure imines that were used immediately. Other materials were used as received from commercial suppliers. For ¹³C NMR data, peaks of major isomers are printed in **bold**, and peaks of the third isomers (trace amount) are printed in *italic* if identifiable.

General Procedure for Pd-Catalyzed 3-Component-Coupling Reactions (3CR, Method A). A solution of the imine (0.5 mmol, 1.0 equiv) and benzoyl chloride (0.5 mmol, 1.0 equiv) in acetonitrile (6 mL) was stirred for 1 h. Pd₂(dba)₃ (0.012 mmol, 2.5 mol%) and a solution of the tributylvinyltin (0.5 mmol, 1.0 equiv) in dichloromethane (6 mL) were added, and the resulting solution was stirred at ambient temperature for 24 h. The solvent was removed in *vacuo*, and the residue was dissolved in ethyl acetate (50 mL) and a saturated KF solution (15 mL) was added. The resulting white precipitate was filtered off through Celite, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (MgSO₄), solvent was removed in *vacuo*, and the crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1: 9 followed by 1: 4) to afford the corresponding amides.

General Procedure for Cu-Catalyzed 3-Component-Coupling Reactions (3CR, Method B). A solution of the imine (0.5 mmol, 1.0 equiv) and benzoyl chloride (0.65 mmol, 1.3 equiv) in acetonitrile (3 mL) was added to a solution of CuCl (5.0 mg, 0.05 mmol, 10 mol%) in acetonitrile (1 mL). A solution of tributylvinyltin (0.5 mmol, 1.0 equiv) in methylene chloride (3 mL) was added, and the reaction mixture was heated to 45 °C overnight. The reaction mixture was then concentrated in *vacuo* and re-dissolved in ethyl acetate (50 mL). Saturated KF solution (15 mL) was added, the mixture was stirred for 2 h, and the resulting white solid was filtered off through Celite. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (MgSO₄), solvents were removed in *vacuo*, and the

crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1: 9 followed by 1: 4) to afford the corresponding amides.

***N*-[1-(2-Bromophenyl)-2-propenyl]-*N*-phenylmethyl-benzamide (2a).** According to the general Method A or B described above, benzamide **2a** was isolated as a colorless oil (Method A: 0.033 g, 16%; Method B: 0.156 g, 77%): $R_f = 0.32$ (EtOAc/hexane 1 : 4); ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.42 (m, 2 H), 7.34-7.24 (m, 5 H), 7.16 (t, $J = 7.5$ Hz, 1 H), 7.08-7.00 (m, 3 H), 7.00-6.88 (m, 3 H), 5.94 (ddd, $J = 16.2$ Hz, 10.4 Hz, 5.4 Hz, 1 H), 5.80-5.38 (m, 2 H), 5.21 (d, $J = 17.1$ Hz, 1 H), 5.00-4.70 (m, 1 H), 4.39 (d, $J = 10.8$, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.9, 137.8, 137.4, 136.6, 135.8, 133.2 (2 C), 130.8 (2 C), 129.6, 128.1, 127.9, 127.3, 127.2, 126.8 (3 C), 126.6, 125.6, 118.5, 118.3, 64.4, 47.0; IR (neat, cm^{-1}) 1636 (s); HRMS (ES^+) calcd for $\text{C}_{23}\text{H}_{21}\text{BrNO}$ ($\text{M}+\text{H}^+$), 406.0807, found 406.0812.

***N*-[1-(3-Bromophenyl)-2-propenyl]-*N*-phenylmethyl- benzamide (2b).** According to the general Method A or B described above, benzamide **2b** was isolated as a colorless oil (Method A: 0.040 g, 20%; Method B: 0.148 g, 73%): $R_f = 0.44$ (EtOAc/hexane 1 : 4); ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.05 (m, 14 H), 6.20-5.90 (m, 1 H), 5.75-5.50 (m, 1 H), 5.39 (d, $J = 10.3$ Hz, 1 H), 5.35-5.18 (m, 1 H), 4.95-4.46 (m, 1 H), 4.46 (d, $J = 15.8$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.8, 141.0, 138.0, 136.4, 134.4, 130.9 (2 C), 130.1, 129.8, 128.6, 128.3 (2 C), 127.2, 126.9, 126.5 (3 C), 126.4, 122.8, 119.9, 119.6, 64.8, 46.6; IR (neat, cm^{-1}) 1642 (s); HRMS (ES^+) calcd for $\text{C}_{23}\text{H}_{21}\text{BrNO}$ ($\text{M}+\text{H}^+$), 406.0807, found 406.0812.

Compound 4.

(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(3-bromophenyl)-2-(phenylmethyl)-1*H*-isoindol-1-one (exo) and 2,3,3*a*,6,7,7*a*-Hexahydro-3-(3-bromophenyl)-2-(phenylmethyl)-1*H*-isoindol-1-one. According to the general Method C described in the main text, isoindolone **4** was isolated as a pale yellow oil (0.143 g, 75%) as a mixture of major (exo) : minor diastereomers in 2.6 : 1 ratio (containing trace amount of a third diastereomer detected by GC-MS): R_f = 0.37 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3): δ 7.48 (t, J = 7.7 Hz, 1 H), 7.36-6.90 (m, 8 H), 5.91 (dtd, J = 10.0 Hz, 4.0 Hz, 1.8 Hz, 0.72 H), 5.70-5.45 (m, 1.28 H), 5.27 (d, J = 14.8 Hz, 0.28 H), 5.22 (d, J = 15.0 Hz, 0.72 H), 4.49 (d, J = 7.6 Hz, 0.28 H, H_3), 3.97 (d, J = 4.4 Hz, 0.72 H, H_3), 3.66 (d, J = 14.8 Hz, 0.28 H), 3.54 (d, J = 15.0 Hz, 0.72 H), 2.90 (td, J = 7.2 Hz, 4.8 Hz, 0.72 H, H_{7a}), 2.88-2.82 (m, 0.28 H, H_{3a}), 2.72-2.65 (m, 0.72 H, H_{3a}), 2.43 (td, J = 12.7 Hz, 2.8 Hz, 0.28 H, H_{7a}), 2.38-1.60 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ **176.4** (C), 175.7 (C), 175.5 (C), **142.1** (C), 139.9 (C), 137.8 (C), **136.5** (C), 136.3 (C), 135.9 (C), 131.6 (CH), **131.2** (CH), 131.1 (CH), 130.8 (CH), **130.6** (CH), 130.5 (CH), 130.1 (CH), **130.0** (CH), 129.8 (CH), **129.5** (CH), 128.7 (2 CH), **128.6** (2 CH), 128.5 (2 CH), 128.2 (2 CH), **128.1** (2 CH), 127.7 (CH), **127.5** (CH), 125.6 (CH), **125.5** (CH), 125.2 (CH), **124.0** (CH), 123.8 (CH), **123.2** (C), 123.0 (C), **65.7** (CH), 64.3 (CH), 61.2 (CH),

48.6 (CH), 46.2 (CH), 44.7 (CH₂), **44.4** (CH₂), 44.2 (CH₂), 43.9 (CH), **42.0** (CH), 41.3 (CH), **39.1** (CH), 29.7 (CH₂), 26.2 (CH₂), 25.8 (CH₂), 22.3 (CH₂), **22.1** (CH₂), **20.7** (CH₂); IR (neat, cm⁻¹) 1695 (s); HRMS (ES⁺) calcd for C₂₁H₂₁BrNO (M+H⁺), 382.0807, found 382.0808.

Compound 5.

(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-2-(phenylmethyl)-3-(3-tolyl)-1*H*-isoindol-1-one (exo) and 2,3,3*a*,6,7,7*a*-Hexahydro-2-(phenylmethyl)-3-(3-tolyl)-1*H*-isoindol-1-one. According to the general Method C described in the main text, isoindolone **5** was isolated as a pale yellow oil (0.112 g, 71%) as a mixture of major (exo) : minor diastereomers in 2.3 : 1 ratio (containing trace amount of a third diastereomer detected by GC-MS): *R*_f = 0.34 (EtOAc/hexane 1 : 4); ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.12 (m, 6 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.97 (s, 1 H), 6.96-6.89 (m, 1 H), 5.89 (dtd, *J* = 10.0 Hz, 4.0 Hz, 1.8 Hz, 0.7 H), 5.58 (ddt, *J* = 10.0 Hz, 3.5 Hz, 1.8 Hz, 1 H), 5.48 (ddt, *J* = 10.0 Hz, 6.4 Hz, 3.2 Hz, 0.3 H), 5.27 (d, *J* = 14.9 Hz, 0.3 H), 5.21 (d, *J* = 14.8 Hz, 0.7 H), 4.51 (d, *J* = 7.5 Hz, 0.3 H, *H*3), 4.00 (d, *J* = 4.5 Hz, 0.7 H, *H*3), 3.65 (d, *J* = 14.9 Hz, 0.3 H), 3.53 (d, *J* = 14.8 Hz, 0.7 H), 2.91 (td, *J* = 7.4 Hz, 5.1 Hz, 0.7 H, *H*7*a*), 2.89-2.81 (m, 0.3 H,

H3a), 2.73-2.67 (m, 0.7 H, *H3a*), 2.48 (td, *J* = 12.5 Hz, 2.9 Hz, 0.3 H, *H7a*), 2.37 (s, 3 H), 2.30-1.50 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) & DEPT δ **176.2** (C), **175.47** (C), 175.3 (C), **139.2** (C), **138.3** (C), 138.2 (C), 138.0 (C), 136.8 (C), 136.5 (C), 136.4 (C), **135.9** (C), 134.7 (C), 129.2 (CH), 129.2 (CH), **129.2** (CH), 128.8 (CH), **128.4** (CH), **128.9** (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), **128.0** (2 CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), **127.7** (2 CH), 127.0 (CH), 126.9 (CH), **126.9** (CH), 126.8 (CH), **126.7** (CH), **125.6** (CH), 124.7 (CH), 124.2 (CH), 124.0 (CH), 123.7 (CH), **123.3** (CH), **65.8** (CH), 64.4 (CH), 61.2 (CH), 48.1 (CH), 45.8 (CH), 44.1 (CH₂), **43.8** (CH₂), 43.6 (CH₂), 43.6 (CH), **41.6** (CH), 40.9 (CH), **38.8** (CH), 25.8 (CH₂), 25.5 (CH₂), 22.0 (CH₂), **21.7** (CH₂), 21.6 (CH₂), 21.1 (CH₃), **21.1** (CH₃), 21.0 (CH₃), **20.4** (CH₂); IR (neat, cm⁻¹) 1695 (s); HRMS (ES⁺) calcd for C₂₂H₂₄NO (M+H⁺), 318.1858, found 318.1853.

Compound 6.

(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-2-allyl-3-(3-tolyl)-1*H*-isoindol-1-one (*exo*) and 2,3,3*a*,6,7,7*a*-Hexahydro-2-allyl-3-(3-tolyl)-1*H*-isoindol-1-one. According to the general Method C described in the main text, isoindolone **6** was isolated as a colorless oil (0.090 g, 68%) as a mixture of major (*exo*) : minor diastereomers in 2 : 1 ratio (containing trace amount of a third diastereomer detected by GC-MS): *R*_f = 0.37

(EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.24 (m, 1 H), 7.20-7.10 (m, 1 H), 7.07-6.90 (m, 2 H), 5.92 (dtd, $J = 10.0$ Hz, 3.8 Hz, 1.9 Hz, 0.66 H), 5.81-5.56 (m, 2 H), 5.50 (ddt, $J = 10.0$ Hz, 6.3 Hz, 3.2 Hz, 0.34 H), 5.16 (dq, $J = 10.1$ Hz, 0.9 Hz, 0.34 H), 5.10 (dm, $J = 10.8$ Hz, 0.66 H), 5.10-5.06 (m, 0.34 H), 5.02 (dm, $J = 17.2$ Hz, 0.66 H), 4.70 (d, $J = 7.5$ Hz, 0.34 H, *H3*), 4.57 (ddt, $J = 15.4$ Hz, 4.4 Hz, 1.9 Hz, 0.34 H), 4.49 (ddt, $J = 15.5$ Hz, 4.3 Hz, 1.9 Hz, 0.66 H), 4.24 (d, $J = 4.1$ Hz, 0.66 H, *H3*), 3.23 (ddm, $J = 15.5$ Hz, 7.5 Hz, 0.34 H), 3.09 (ddm, $J = 15.6$ Hz, 7.2 Hz, 0.66 H), 2.99-2.90 (m, 0.34 H, *H3a*), 2.87 (td, $J = 7.2$ Hz, 6.0 Hz, 0.66 H, *H7a*), 2.75-2.68 (m, 0.66 H, *H3a*), 2.43 (td, $J = 12.5$ Hz, 2.4 Hz, 0.34 H, *H7a*), 2.37 (s, 3 H), 2.35-1.58 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ **175.3** (C), 174.6 (C), 174.58 (C), **138.8** (C), **137.7** (C), 137.5 (C), 137.3 (C), 136.2 (C), 134.3 (C), 131.7 (CH), 131.1 (CH), **130.9** (CH), **128.7** (CH), 128.6 (CH), 128.1 (CH), **127.8** (CH), **127.7** (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.3 (CH), **125.9** (CH), **125.2** (CH), 124.0 (CH), 123.6 (CH), 123.4 (CH), 123.0 (CH), **122.5** (CH), 116.7 (CH_2), 116.6 (CH_2), **116.3** (CH_2), **65.5** (CH), 64.2 (CH), 60.9 (CH), 47.6 (CH), 44.9 (CH), 42.9 (CH), 42.4 (CH_2), **41.9** (CH_2), 41.7 (CH_2), **41.0** (CH), 40.4 (CH), **38.1** (CH), 28.6 (CH_2), 25.2 (CH_2), **24.8** (CH_2), 21.3 (CH_2), 21.0 (CH_2), **20.9** (CH_2), 20.5 (CH_3), 20.4 (CH_3), **19.9** (CH_3); IR (neat, cm^{-1}) 1669 (s); HRMS (ES^+) calcd for $\text{C}_{18}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}^+$), 268.1708, found 268.1685.

Compound 11.

(±)-(3*R*,3*aR*,7*aR*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-7*a*-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one (exo, major) and 2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-7*a*-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one (minor). According to the general Method C described in the main text, isoindolone **11** was isolated as a white solid (0.130 g, 66%) as a mixture of titled diastereomers in 7 : 1 ratio (containing trace amount of a third diastereomer detected by GC-MS): R_f = 0.38 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.60 (dd, J = 8.0 Hz, 1.0 Hz, 1 H), 7.42 (t, J = 7.8 Hz, 1 H), 7.35-7.10 (m, 5 H), 6.98-6.93 (m, 2 H), 5.96 (dq, J = 9.8 Hz, 2.3 Hz, 0.12 H), 5.67 (dq, J = 9.8 Hz, 2.0 Hz, 0.88 H), 5.59 (dq, J = 9.8 Hz, 3.2 Hz, 0.88 H), 5.56-5.52 (m, 0.12 H), 5.29 (d, J = 14.6 Hz, 0.12 H, CH_2Ph), 5.14 (d, J = 14.1 Hz, 0.88 H, CH_2Ph), 4.91 (d, J = 8.6 Hz, 0.12 H, $H3$), 4.58 (d, J = 10.6 Hz, 0.88 H, $H3$), 3.68 (d, J = 14.1 Hz, 0.12 H, CH_2Ph), 3.46 (d, J = 14.1 Hz, 0.88 H, CH_2Ph), 3.16 (dq, J = 8.6 Hz, 2.9 Hz, 0.12 H, $H3a$), 2.56 (dq, J = 10.6 Hz, 2.7 Hz, 0.88 H, $H3a$), 2.28-2.20 (m, 2 H), 2.03 (ddd, J = 13.0 Hz, 6.2 Hz, 2.5 Hz, 1 H), 1.83 (dt, J = 13.0 Hz, 9.3 Hz, 1 H), 0.97 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, CDCl_3) δ **180.0**, **137.0**, **135.9**, 133.7, **133.2**, **129.5**, 129.3, **129.0** (2 C), **128.8**, 128.7, **128.6** (3 C), 128.4, **128.2**, 128.0, **127.6**, 127.2, 126.3, **124.4**, 123.7, **121.78**, 60.6, **59.9**, **52.8**, 46.5, 44.6, **44.2**, 43.2, **43.0**, 32.0, **29.0**, **23.5**, 17.8, **14.0**; IR (neat, cm^{-1})

1700 (s); LRMS (EI, m/z) 397/395 (M^+), 316 ($M^+ - Br$), 174, 91, 69, 41.

(±)-(3*R*,3*aR*,7*aR*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-7*a*-methyl-2-

(phenylmethyl)-1*H*-isoindol-1-one (exo, major). Isolated as a colorless crystal by recrystallization with dichloromethane/pentane: mp 138-140 °C; R_f = 0.38 (EtOAc/hexane 1 : 4); 1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.0 Hz, 1.0 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.31-7.26 (m, 4 H), 7.23 (td, J = 7.6 Hz, 1.7 Hz, 1 H), 6.98-6.93 (m, 2 H), 5.67 (dq, J = 9.8 Hz, 2.0 Hz, 1 H), 5.59 (dq, J = 9.8 Hz, 3.2 Hz, 1 H), 5.14 (d, J = 14.1 Hz, 1 H, CH_2Ph), 4.58 (d, J = 10.6 Hz, 1 H, H_3), 3.46 (d, J = 14.1 Hz, 1 H, CH_2Ph), 2.56 (dq, J = 10.6 Hz, 2.7 Hz, 1 H, H_{3a}), 2.28-2.20 (m, 2 H), 2.03 (ddd, J = 13.0 Hz, 6.2 Hz, 2.5 Hz, 1 H), 1.83 (dt, J = 13.0 Hz, 9.3 Hz, 1 H), 0.97 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) & DEPT δ 179.9 (C), 136.9 (C), 135.8 (C), 133.1 (CH), 129.4 (CH), 128.9 (2 CH), 128.7 (CH), 128.6 (3 CH), 128.2 (CH), 127.6 (CH), 124.4 (C), 121.7 (CH), 59.9 (CH), 52.7 (CH), 44.2 (CH_2), 43.0 (C), 29.0 (CH_2), 23.5 (CH_2), 13.9 (CH_3); IR (neat, cm^{-1}) 1700 (s); HRMS (ES^+) calcd for $C_{22}H_{23}BrNO$ ($M+H^+$), 396.0963, found 396.0964.

General Procedure for Two-Step Synthesis of Isoindolones. Method E (two-pot/two-step): The reaction was run as described in Method C, heating the reaction mixture at 45°C overnight. The reaction was worked up according to the procedure described in Method B to afford the corresponding α -substituted amides. The amides were dissolved in toluene (10 mL), and the reaction mixture was refluxed overnight. The solvent was removed in vacuo providing the crude product, which was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1: 4) as to afford the corresponding isoindolones. The yields of isoindolones were calculated per 1 mol of

isolated amides **8**.

Compounds **7.1** and **7.2**.

According to the general Method D described in the main text, isoindolones **7.1** and **7.2** were isolated as colorless oils. **(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-2-(*p*-methoxyphenyl)-1*H*-isoindol-1-one (7.1, *exo*):** 0.103 g, 52% yield; R_f = 0.42 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, J = 8.1 Hz, 1 H), 7.44 (d, J = 9.2 Hz, 2 H), 7.24 (d, J = 7.5 Hz, 1 H), 7.18 (t, J = 7.5 Hz, 2 H), 6.82 (d, J = 9.2 Hz, 2 H), 5.99 (br s, 2 H), 5.15 (br s, 1 H, H_3), 3.78 (s, 3 H), 2.98 (dt, J = 7.2 Hz, 3.8 Hz, 1 H, H_{7a}), 2.86 (dm, J = 7.2 Hz, 1 H, H_{3a}), 2.28 (dm, J = 13.5 Hz, 1 H), 2.24-2.12 (m, 1 H), 2.02 (dm, J = 17.9 Hz, 1 H), 1.71-1.61 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ 175.4 (C), 156.4 (C), 138.9 (C), 133.5 (CH), 131.9 (C), 130.7 (CH), 129.2 (CH), 127.8 (CH), 126.7 (CH), 126.6 (CH), 122.6 (C), 122.2 (2 CH), 114.0 (2 CH), 67.8 (CH), 55.4 (CH_3), 40.5 (CH), 39.0 (CH), 21.0 (CH_2), 20.1 (CH_2); IR (neat, cm^{-1}) 1699 (s); HRMS (ES^+) calcd for $\text{C}_{21}\text{H}_{21}\text{BrNO}_2$ ($\text{M}+\text{H}^+$), 398.0756, found 398.0741.

2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-2-(*p*-methoxyphenyl)-1*H*-isoindol-1-one (7.2): 0.010 g, 5% yield; R_f = 0.36 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 2 H), 7.28 (d, J = 7.5 Hz, 1 H), 7.18 (t, J = 7.5 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 5.97 (dm, J = 10.0 Hz, 1 H), 5.72 (d, J = 7.6 Hz, 1

H, *H*3), 5.56 (ddt, *J* = 10.0 Hz, 6.4 Hz, 3.2 Hz, 1 H), 3.74 (s, 3 H), 3.25-3.15 (m, 1 H, *H*3*a*), 2.64 (td, *J* = 12.7 Hz, 2.8 Hz, 1 H, *H*7*a*), 2.37 (ddd, *J* = 12.8 Hz, 7.5 Hz, 2.7 Hz, 1 H), 2.27 (dm, *J* = 18.8 Hz, 1 H), 2.20-2.10 (m, 1 H), 1.72 (tdd, *J* = 12.5 Hz, 10.7 Hz, 7.3 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) & DEPT δ 173.9 (C), 155.2 (C), 133.9 (C), 132.5 (CH), 131.0 (C), 129.5 (CH), 128.5 (CH), 126.8 (CH), 126.6 (CH), 123.6 (CH), 122.2 (C), 120.7 (2 CH), 113.0 (2 CH), 63.5 (CH), 54.3 (CH₃), 42.5 (CH), 41.5 (CH), 24.8 (CH₂), 21.3 (CH₂); IR (neat, cm⁻¹) 1705 (s); HRMS (ES⁺) calcd for C₂₁H₂₁BrNO₂ (M+H⁺), 398.0756, found 398.0748.

Compound 9.

According to the general Method E described above, amide **8a** was isolated as a pale yellow oil (0.160 g, 81%): *R*_f = 0.46; ¹H NMR (400 MHz, CDCl₃): δ 7.50-6.90 (m, 10 H), 6.80-6.30 (m, 3 H), 6.05 (br s, 1 H), 5.80-5.60 (m, 2 H), 5.55 (br s, 1 H), 4.80-4.25 (m, 2 H), 1.71 (dd, *J* = 7.1 Hz, 0.7 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 176.0, 168.4 (E), 166.8 (Z); 138.5, 138.0, 137.5, 133.2 (2 C), 130.6 (Z), 130.2 (E), 130.0 (Z), 129.5 (E), 129.3 (E), 129.1 (Z), 128.3 (3 C), 128.1, 127.7 (Z), 127.5 (Z), 127.3 (E), 127.1 (E), 126.4 (Z), 126.1 (Z), 125.6 (E), 125.5 (E), 124.0 (E), 123.9 (Z), 62.7 (E), 60.2 (Z), 48.5 (Z), 47.0 (E), 13.6; IR (neat, cm⁻¹) 1653 (s); HRMS (ES⁺) calcd for C₂₂H₂₃NOBr (M+H⁺),

396.0963, found 396.0948.

As described in Method E, amide **8a** (0.086 mg, 0.217 mmol) was heated in toluene (10 mL) overnight at 110 °C. Isoindolones **9.1** and **9.2** were isolated as pale yellow oils.

(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-6-methyl-2-

(phenylmethyl)-1*H*-isoindol-1-one (9.1, *exo*): 0.060 g, 69% (containing trace amount of an additional diastereomer detected by GC-MS); R_f = 0.31 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3): δ 7.60 (d, J = 7.9 Hz, 1 H), 7.35-7.22 (m, 5 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 2 H), 5.72 (br s, 2 H), 5.26 (d, J = 15.0 Hz, 1 H), 4.41 (br s, 1 H, H_3), 3.57 (d, J = 15.0 Hz, 1 H), 2.85 (dt, J = 7.0 Hz, 3.6 Hz, 1 H, H_{7a}), 2.67 (d, J = 7.0 Hz, 1 H, H_{3a}), 2.37-2.22 (m, 2 H), 1.30-1.19 (m, 1 H), 1.03 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ 176.51 (C), 138.7 (C), 136.4 (CH), 135.9 (C), 133.7 (CH), 129.1 (CH), 128.5 (2 CH), 127.8 (2 CH), 127.7 (CH), 127.4 (CH), 126.1 (CH), 123.9 (C), 123.2 (CH), 64.8 (CH), 44.7 (CH_2), 40.5 (CH), 37.9 (CH), 29.0 (CH_2), 26.2 (CH), 21.4 (CH_3); IR (neat, cm^{-1}) 1695 (s); HRMS (ES^+) calcd for $\text{C}_{22}\text{H}_{23}\text{NOBr}$ ($\text{M}+\text{H}^+$), 396.0963, found 396.0965.

2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-6-methyl-2-(phenylmethyl)-1*H*-

isoindol-1-one (9.2): 0.009 g, 11%; R_f = 0.19 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3): δ 7.57 (d, J = 7.9 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.30-7.22 (m, 4 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.05-7.00 (m, 2 H), 5.67 (d, J = 10.0 Hz, 1 H), 5.62 (dt, J = 10.0 Hz, 2.7 Hz, 1 H), 5.15 (d, J = 14.4 Hz, 1 H), 4.58 (d, J = 7.0 Hz, 1 H, H_3), 3.43 (d, J = 14.4 Hz, 1 H), 2.78 (ddd, J = 10.6 Hz, 8.3 Hz, 5.3 Hz, 1 H, H_{7a}), 2.66-2.58 (m, 1 H, H_{3a}), 2.30-2.18 (m, 1 H), 2.07 (dt, J = 13.1 Hz, 5.1 Hz, 1 H), 1.37-1.25 (m, 1 H), 1.05 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ 177.4 (C), 138.6 (C), 135.7 (C), 135.6 (CH),

133.3 (CH), 129.3 (CH), 128.6 (2 CH), 128.5 (2 CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 123.9 (C), 123.9 (CH), 64.1 (CH), 44.4 (CH₂), 42.5 (CH), 40.2 (CH), 29.6 (CH₂), 28.9 (CH), 21.3 (CH₃); IR (neat, cm⁻¹) 1695 (s); HRMS (ES⁺) calcd for C₂₂H₂₃NOBr (M+H⁺), 396.0963, found 396.0948.

Compound 10.

(±)-(3*R*,3*aS*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-6-methyl-2-(phenylmethyl)-3-(3-tolyl)-1*H*-isoindol-1-one (exo) and 2,3,3*a*,6,7,7*a*-Hexahydro-6-methyl-2-(phenylmethyl)-3-(3-tolyl)-1*H*-isoindol-1-one. According to the general Method E described above, amide **8c** was isolated as a pale yellow oil (0.132 g, 80%): *R*_f = 0.46 (EtOAc/hexane 1 : 4); ¹H NMR (400 MHz, CDCl₃): δ 7.50-6.90 (m, 10 H), 6.70-6.25 (m, 3 H), 5.96 (t, *J* = 10.6 Hz, 1 H), 5.80 (dd, *J* = 15.0 Hz, 7.9 Hz, 1 H), 5.67 (d, *J* = 11.5 Hz, 1 H), 5.59-5.50 (m, 1 H), 4.80-4.60 (m, 1 H), 4.50 (d, *J* = 17.6 Hz, 1 H), 2.32 (s, 3 H), 1.74-1.70 (m, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 176.3 (E), 176.2 (Z), 167.7 (E), 166.9 (Z), 139.5 (Z), 139.1 (E), 138.5, 138.2, 138.1, 129.8 (Z), 129.6 (E), 129.3 (Z), 129.0 (E), 128.9 (E), 128.8 (Z), 128.5 (3 C), 128.3, 128.2 (2 C), 127.7, 127.1 (Z), 126.9 (E), 126.2, 124.8 (Z), 124.5 (E), 63.3 (E), 59.7 (Z), 48.4 (Z), 44.3 (E), 21.5, 13.6; IR (neat, cm⁻¹) 1655 (s); HRMS (ES⁺)

calcd for $C_{23}H_{26}NO$ ($M+H^+$), 332.2015, found 332.2014.

As described in Method E, amide **8c** (0.070 mg, 0.211 mmol) was heated in toluene (10 mL) overnight at 110 °C. Isoindolone **10** was isolated as a pale yellow oil (0.058 g, 83 %) as a mixture of major (exo) : minor diastereomers in 2 : 1 ratio (containing trace amount of two additional diastereomers detected by GC-MS): R_f = 0.30 (EtOAc/hexane 1 : 4); 1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 5 H), 7.15 (d, J = 7.4 Hz, 1 H), 7.07 (d, J = 7.8 Hz, 1 H), 7.00-6.88 (m, 2 H), 5.74 (dm, J = 10.0 Hz, 0.66 H), 5.56 (dt, J = 10.0 Hz, 2.9 Hz, 0.66 H), 5.54-5.51 (m, 0.34 H), 5.40 (dt, J = 10.0 Hz, 3.2 Hz, 0.34 H), 5.27 (d, J = 14.9 Hz, 0.34 H), 5.24 (d, J = 14.7 Hz, 0.66 H), 4.51 (d, J = 7.6 Hz, 0.34 H, *H3*), 4.02 (d, J = 2.3 Hz, 0.66 H, *H3*), 3.65 (d, J = 14.9 Hz, 0.34 H), 3.55 (d, J = 14.7 Hz, 0.66 H), 3.03 (dt, J = 7.6 Hz, 4.2 Hz, 0.66 H, *H7a*), 2.83-2.74 (m, 0.34 H, *H3a*), 2.71-2.66 (m, 0.66 H, *H3a*), 2.46 (td, J = 12.2 Hz, 2.9 Hz, 0.34 H, *H7a*), 2.37 (s, 3 H), 2.35-2.00 (m, 2 H), 1.93-1.82 (m, 0.34 H), 1.36 (ddd, J = 13.0 Hz, 8.8 Hz, 4.3 Hz, 0.66 H), 1.06 (d, J = 7.3 Hz, 1.98 H), 0.94 (d, J = 7.3 Hz, 1.02 H); ^{13}C NMR (125 MHz, $CDCl_3$, *major*) & DEPT δ 176.3 (C), 140.0 (C), 138.8 (C), 136.3 (C), 135.9 (CH), 128.9 (CH), 128.7 (CH), 128.5 (2 CH), 127.8 (2 CH), 127.3 (CH), 126.7 (CH), 125.9 (CH), 123.3 (CH), 66.0 (CH), 44.2 (CH₂), 41.7 (CH), 38.1 (CH), 29.1 (CH₂), 26.5 (CH), 21.5 (CH₃), 21.2 (CH₃); IR (neat, cm^{-1}) 1695 (s); HRMS (ES^+) calcd for $C_{23}H_{26}NO$ ($M+H^+$), 332.2015, found 332.1989.

Compound 12.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-7-methyl-2-(phenylmethyl)-3-(3-tolyl)-1*H*-isoindol-1-one. According to the general Method D described in the main text, isoindolone **12** was isolated as a colorless oil (0.115 g, 70%): R_f = 0.45 (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.24 (m, 4 H), 7.16 (d, J = 7.5 Hz, 1 H), 7.05 (d, J = 7.1 Hz, 2 H), 6.97 (s, 1 H), 6.96 (d, J = 8.0 Hz, 1 H), 5.80 (dtd, J = 10.0 Hz, 3.8 Hz, 1.7 Hz, 1 H, H_5), 5.55 (ddt, J = 10.0, 3.4, 1.8 Hz, 1 H, H_4), 5.22 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.01 (d, J = 4.0 Hz, 1 H, H_3), 3.54 (d, J = 14.8 Hz, 1 H, CH_2Ph), 2.74-2.66 (m, 1 H, H_{3a}), 2.60 (t, J = 7.0 Hz, 1 H, H_{7a}), 2.38 (s, 3 H), 2.28 (dm, J = 17.5 Hz, 1 H, $H_{6\alpha}$), 2.22 (heptet, J = 6.0 Hz, 1 H, H_7), 1.80 (dm, J = 16.9 Hz, 1 H, $H_{6\beta}$), 1.15 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, CDCl_3) & DEPT δ 176.0 (C), 139.5 (C), 138.7 (C), 136.5 (C), 128.8 (CH), 128.7 (CH), 128.4 (2 CH), 128.0 (2 CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 125.4 (CH), 123.8 (CH), 66.3 (CH), 45.4 (CH), 44.1 (CH_2), 41.5 (CH), 30.2 (CH_2), 26.1 (CH), 21.5 (CH_3), 19.2 (CH_3); IR (neat, cm^{-1}) 1689 (s); HRMS (ES^+) calcd for $\text{C}_{23}\text{H}_{26}\text{NO}$ ($\text{M}+\text{H}^+$), 332.2015, found 332.2014.

Compound 14.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-bromophenyl)-7-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one According to the general Method D described in the main text, isoindolone **14** was isolated as a white solid (0.130 g, 66%): mp 90-92 °C (CH₂Cl₂/pentane); *R*_f = 0.34 (EtOAc/hexane 1 : 4); ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.32-7.25 (m, 3 H), 7.22 (td, *J* = 7.5 Hz, 1.4 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 3 H), 5.81 (dm, *J* = 10.0 Hz, 1 H, *H*5), 5.74 (dm, *J* = 10.0 Hz, 1 H, *H*4), 5.27 (d, *J* = 15.0 Hz, 1 H, CH₂Ph), 4.47 (br s, 1 H, *H*3), 3.59 (d, *J* = 15.0 Hz, 1 H, CH₂Ph), 2.72-2.66 (m, 1 H, *H*3*a*), 2.57 (dd, *J* = 7.1 Hz, 3.8 Hz, 1 H, *H*7*a*), 2.55-2.46 (m, 1 H, *H*7), 2.35 (dm, *J* = 17.8 Hz, 1 H, *H*6*α*), 1.80 (dm, *J* = 17.5 Hz, 1 H, *H*6*β*), 1.05 (d, *J* = 6.8 Hz, 3 H, CH₃); ¹³C NMR (125 MHz, CDCl₃) & DEPT δ 176.3 (C), 138.5 (C), 135.9 (C), 133.7 (CH), 129.2 (CH), 128.5 (2 CH), 127.8 (2 CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.3 (CH), 125.8 (CH), 123.4 (C), 64.8 (CH), 44.6 (CH₂), 44.0 (CH), 39.0 (CH), 29.7 (CH₂), 25.1 (CH), 19.0 (CH₃); IR (neat, cm⁻¹) 1693 (s); HRMS (ES⁺) calcd for C₂₂H₂₃BrNO (M+H⁺), 396.0963, found 396.0959.

Compound 16.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(3-*trans*-methoxycarbonylvinyl-phenyl)-7-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one. To a solution of

isoindolone **13** (0.040 g, 0.100 mmol) in DMF were added sodium carbonate (0.011 g, 0.100 mmol), tetrabutylammonium chloride (0.028 g, 0.100 mmol) and methyl acrylate (0.018 g, 0.210 mmol), and the reaction mixture was stirred for 2 min. Palladium(II) acetate (0.001 g, 0.005 mmol) was added, the flask was flushed with Ar, sealed and the reaction mixture was allowed to stir at 80 °C for 24 h. The resulting mixture was poured into water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford the crude product, which was purified by flash chromatography over silica eluting with ethyl acetate/hexane (1: 4) to afford isoindolone **16** as a colorless oil (0.028 g, 70%): *R*_f = 0.20 (EtOAc/hexane 1 : 4); ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 16.0 Hz, 1 H, CH=CHCO₂Me), 7.52 (d, *J* = 7.7 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.30-7.25 (m, 4 H), 7.19 (d, *J* = 7.7 Hz, 1 H), 7.04-7.00 (m, 2 H), 6.45 (d, *J* = 16.0 Hz, 1 H, CH=CHCO₂Me), 5.82 (dtd, *J* = 10.0 Hz, 3.9 Hz, 1.7 Hz, 1 H, *H*5), 5.53 (ddt, *J* = 10.0 Hz, 3.4 Hz, 1.8 Hz, 1 H, *H*4), 5.22 (d, *J* = 14.8 Hz, 1 H, CH₂Ph), 4.03 (d, *J* = 4.8 Hz, 1 H, *H*3), 3.84 (s, 3 H, CO₂CH₃), 3.53 (d, *J* = 14.8 Hz, 1 H, CH₂Ph), 2.71-2.65 (m, 1 H, *H*3*a*), 2.57 (t, *J* = 7.3 Hz, 1 H, *H*7*a*), 2.27 (dm,

$J = 17.6$ Hz, 1 H, $H6\alpha$), 2.17 (heptet, $J = 6.3$ Hz, 1 H, $H7$), 1.80 (dm, $J = 17.6$ Hz, 1 H, $H6\beta$), 1.17 (d, $J = 6.8$ Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) & DEPT δ 175.9 (C), 167.1 (C), 144.1 (CH), 140.5 (C), 136.2 (C), 135.2 (C), 129.6 (CH), 128.5 (2 CH), 128.4 (CH), 128.3 (CH), 128.1 (2 CH), 127.7 (CH), 127.5 (CH), 126.3 (CH), 124.9 (CH), 118.7 (C), 66.2 (CH), 51.7 (CH_3), 45.5 (CH), 44.3 (CH_2), 41.7 (CH), 30.4 (CH_2), 26.1 (CH), 19.2 (CH_3); IR (neat, cm^{-1}) 1722 (s), 1690 (s); HRMS (ES^+) calcd for $C_{26}H_{28}NO_3$ ($M+H^+$), 402.2069, found 402.2058.

Compound 17.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-7-methyl-3-(3-phenylacetylene-phenyl)-2-(phenylmethyl)-1*H*-isoindol-1-one. To a solution of isoindolone **13** (0.080 g, 0.200 mmol) in diethylamine (1 mL) were sequentially added palladium(II) chloride (0.007 g, 0.040 mol), triphenylphosphine (0.021 g, 0.080 mol), phenylacetylene (0.031 g, 0.300 mmol) and cuprous iodide (0.015 g, 0.080 mol). The flask was flushed with Ar, sealed and the reaction mixture was allowed to stir at 50 °C for 48 h. Solvent was removed in vacuo, the residue was extracted with hexanes (20 mL) and the hexane

extract was filtered through Celite. The solution was concentrated in *vacuo* and the crude product was purified by flash chromatography over silica eluting with ethyl acetate: hexanes (1:9) to afford **17** as a pale yellow oil (0.079 g, 95%): $R_f = 0.36$ (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.55 (m, 2 H), 7.53 (dt, $J = 7.7$ Hz, 1.2 Hz, 1 H), 7.42-7.34 (m, 5 H), 7.32-7.26 (m, 3 H), 7.12 (d, $J = 7.7$ Hz, 1 H), 7.08-7.03 (m, 2 H), 5.82 (dtd, $J = 10.0$ Hz, 3.8 Hz, 1.5 Hz, 1 H, H_5), 5.56 (ddt, $J = 10.0$ Hz, 3.7 Hz, 1.8 Hz, 1 H, H_4), 5.26 (d, $J = 14.9$ Hz, 1 H, CH_2Ph), 4.04 (d, $J = 4.5$ Hz, 1 H, H_3), 3.56 (d, $J = 14.9$ Hz, 1 H, CH_2Ph), 2.74-2.66 (m, 1 H, H_{3a}), 2.61 (t, $J = 7.1$ Hz, 1 H, H_{7a}), 2.28 (dm, $J = 17.5$ Hz, 1 H, $H_{6\alpha}$), 2.22 (hept, $J = 6.0$ Hz, 1 H, H_7), 1.82 (dm, $J = 17.5$ Hz, 1 H, $H_{6\beta}$), 1.16 (d, $J = 6.8$ Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ 176.1, 139.9, 136.2, 135.1, 131.7 (2 CH), 131.3, 129.5, 129.1, 128.6 (2 CH), 128.5, 128.4 (2 CH), 128.1, 128.0 (2 CH), 127.4, 126.6, 125.1, 124.1, 122.9, 90.1, 88.8, 45.3, 44.2, 41.5, 30.2, 26.0, 19.2; IR (neat, cm^{-1}) 1690 (s); HRMS (ES^+) calcd for $\text{C}_{30}\text{H}_{28}\text{NO}$ ($\text{M}+\text{H}^+$), 418.2171, found 418.2172.

Compound 18.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2,3,3*a*,6,7,7*a*-Hexahydro-3-(2-*para*-methoxyphenyl-phenyl)-2-

(phenylmethyl)-7-methyl-1*H*-isoindol-1-one. According to Conditions A described in the main text, compound **18** was isolated as a colorless oil (0.037 g, 88%): $R_f = 0.33$ (EtOAc/hexane 1 : 4); ^1H NMR (400 MHz, CDCl_3) δ 7.39 (td, $J = 7.3$ Hz, 1.5 Hz, 1 H), 7.35 (td, $J = 7.3$ Hz, 1.5 Hz, 1 H), 7.27-7.22 (m, 4 H), 7.20 (td, $J = 7.5$ Hz, 1.5 Hz, 1 H), 7.01-6.96 (m, 2 H), 6.87 (d, $J = 8.4$ Hz, 2 H), 6.79 (d, $J = 8.8$ Hz, 2 H), 5.62-5.55 (m, 1 H, $H5$), 5.22 (d, $J = 14.9$ Hz, 1 H, CH_2Ph), 4.90 (dm, $J = 10.0$ Hz, 1 H, $H4$), 4.24 (d, $J = 2.0$ Hz, 1 H, $H3$), 3.83 (s, 3 H), 3.59 (d, $J = 14.9$ Hz, 1 H, CH_2Ph), 2.68 (dd, $J = 7.4$ Hz, 4.4 Hz, 1 H, $H3a$), 2.58-2.51 (m, 1 H, $H7a$), 2.47-2.40 (m, 1 H, $H7$), 2.24 (dm, $J = 17.8$ Hz, 1 H, $H6\alpha$), 1.71 (dm, $J = 17.8$ Hz, 1 H, $H6\beta$), 1.03 (d, $J = 7.1$ Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ 176.0, 158.6, 141.7, 137.4, 136.2, 132.5, 130.8, 130.0 (2 CH), 128.4 (2 CH), 127.9 (2 CH), 127.7 (CH), 127.3, 127.2, 127.1, 125.4, 124.7, 113.5 (2 CH), 62.2, 55.2, 44.5, 44.4, 39.7, 28.6, 25.3, 19.1; IR (neat, cm^{-1}) 1686 (s); HRMS (ES^+) calcd for $\text{C}_{29}\text{H}_{30}\text{NO}_2$ ($\text{M}+\text{H}^+$), 424.2277, found 424.2262.

Assignment of Relative Stereochemistry

In an effort to assign the relative stereochemistry for the diastereomers of isoindolones, several series of selective NOE experiments were recorded for compounds **11.1**, **13**, **14**, **7.1**, **7.2**, **9.1** and **9.2**. Furthermore, the key coupling constants between protons H3, H3a, H7a and H7, e.g. $J(\text{H3}, \text{H3a})$ and $J(\text{H3a}, \text{H7a})$ were tabulated (Table S-1) and the data was compared to the structures of **11.1** and **13** established by X-ray crystallography. The following observations could be made:

- (1) Unexpectedly, NOE correlation observed between H3a and CH₃ group at C7 in compound **13** did NOT correspond to *cis* configuration of these substituents (compare NOE and X-ray data for **13**).
- (2) The information about the relative configurations at carbons C3a and C7a could not be obtained from the NOE experiments due to the difficulties in selectively irradiating protons with close chemical shifts. Furthermore, the difference in the coupling constants $J(\text{H3a}, \text{H7a})$ observed for the major and minor diastereomers, e.g. 7-7.6 Hz (major) vs 12.2-12.7 (minor) (see Table S-1) was not sufficient to unequivocally assign the relative stereochemistry.
- (3) The relatively small differences in the key coupling constants between major and minor diastereomers, as well as insufficient information from the NOE experiments on the minor diastereomers **7.2** and **9.2** did not allow us to assign the relative stereochemistry in the minor diastereomers of the isoindolones.
- (4) As stated in the text of the manuscript, the relative stereochemistry of the major diastereomers of isoindolones **3-7**, **9-10** and **12-14** was assigned on the basis of X-ray data for isoindolone **13**, and the analogous values of the key coupling constants (see

Table S-1).

Table S-1. Characteristics of ^1H NMR spectra for Compounds **3-7** and **9-14**

Cmpd #	$\delta(\text{H3})$ <i>ppm</i>	$\delta(\text{H3a})$ <i>ppm</i>	$\delta(\text{H7a})$ <i>ppm</i>	$\delta(\text{H7})$ <i>ppm</i>	$J(\text{H3},\text{H3a})$ <i>Hz</i>	$J(\text{H3a},\text{H7a})$ <i>Hz</i>
3-major	4.45	2.73	2.84	-	0	7.2
3-minor	5.02	2.92	2.47	-	7.7	12.5
3-trace	4.62	-	-	-	9.9	-
4-major	3.97	2.68	2.90	-	4.4	7.2
4-minor	4.49	2.85	2.43	-	7.6	12.7
4-trace	3.89	-	-	-	10.1	-
5-major	4.00	2.70	2.91	-	4.5	7.4
5-minor	4.51	2.85	2.48	-	7.5	12.5
5-trace	3.92	-	-	-	10.1	-
6-major	4.24	2.71	2.87	-	4.1	7.2
6-minor	4.70	2.71	2.43	-	7.5	12.5
6-trace	4.15	-	-	-	10.1	-
7.1	5.15	2.86	2.98	-	0	7.2
7.2	5.72	3.20	2.64	-	7.6	12.7
9.1	4.41	2.67	2.85	-	0	7.0
9.2	4.58	2.60	2.78	-	7.0	10.6
10-major	4.02	2.68	3.03	-	2.3	7.6
10-minor	4.51	2.78	2.46	-	7.6	12.2
11.1	4.58	2.56	-	-	10.6	-
11.2	4.91	3.16	-	-	8.6	-
12	4.01	2.68	2.60	2.22	4.0	7.0
13	3.98	2.66	2.57	2.19	4.5	7.1
14	4.47	2.68	2.57	2.51	0	7.1

Note: The assignment of chemical shifts of H3, H3a, H7 and H7a are based on 2D-NMR spectra (e.g. COSY, HMQC).

13

13: δ (ppm) and J (Hz)

H3: 3.98 (d, $J = 4.5$)

H3a: 2.70-2.63 (m)

H4: 5.52 (ddt, $J = 10.0, 3.4, 1.8$)

H7: 2.19 (heptet, $J = 6.0$)

CH₃: 1.15 (d, $J = 6.8$)

H7a: 2.57 (t, $J = 7.1$)

14

14: δ (ppm) and J (Hz)

H3: 4.47 (d, $J = 0$)

H3a: 2.72-2.66 (m)

H4: 5.74 (dm, $J = 10.0$)

H7: 2.55-2.46 (m)

CH₃: 1.05 (d, $J = 6.8$)

H7a: 2.57 (dd, $J = 7.1, 3.8$)

7.1

7.1: δ (ppm) and J (Hz)

H3: 5.15 (br s)

H3a: 2.86 (dm, $J = 7.2$)

H4: 5.99 (br s)

H7a: 2.98 (dt, $J = 7.2, 3.8$)

7.2

7.2: δ (ppm) and J (Hz)

H3: 5.72 (d, $J = 7.6$)

H3a: 3.25-3.15 (m)

H7a: 2.64 (td, $J = 12.7, 2.8$)

9.1

9.1: δ (ppm) and J (Hz)

H3: 4.41 (br s)

H3a: 2.67 (d, $J = 7.0$)

H4: 5.72 (br s)

H6: 2.37-2.22 (m, overlapping with H7)

CH₃: 1.03 (d, $J = 6.8$)

H7a: 2.85 (dt, $J = 7.0, 3.6$)

9.2

9.2: δ (ppm) and J (Hz)

H3: 4.58 (d, $J = 7.0$)

H3a: 2.66-2.58 (m)

H6: 2.30-2.18 (m)

CH₃: 1.05 (d, $J = 7.2$)

H7a: 2.78 (ddd, $J = 10.6, 8.3, 5.3$)

11.1

11.1: δ (ppm) and J (Hz)

H3: 4.58 (d, $J = 10.6$)

H3a: 2.56 (dq, $J = 10.6, 2.7$)

Thermal ellipsoid diagrams for isoindolones **11.1** and **13** are drawn at the 50% probability level.

13

NOE (500 MHz, CDCl₃)

Ar/H-H

13

NOE (500 MHz, CDCl₃)

14

NOE (500 MHz, CDCl₃)

14

NOE (500 MHz, CDCl₃)

7.1

NOE (500 MHz, CDCl₃)

7.2

NOE (500 MHz, CDCl₃)

Aryl-H

H3a

H3

9.1

NOE (500 MHz, CDCl₃)

9.1

NOE (500 MHz, CDCl₃)

11.1

NOE (500 MHz, CDCl₃)

11.1
NOE (500 MHz, CDCl₃)

References

1. For synthesis of (E)-3-(Tributylstannyl)acrolein, see: Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555-4556; for synthesis of dienylstannanes through Wittig reaction, see: Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*(23), 3967.
2. Iovel, I.; Golomba, L.; Fleisher, M.; Popelis, J.; Grinberga, S.; Lukevics, E. *Chemistry of Heterocyclic Compound* **2004**, *40*, 701.

2a

^1H NMR (500 MHz, CDCl_3)

2a

^{13}C NMR (125 MHz, CDCl_3)

2b

^1H NMR (500 MHz, CDCl_3)

2b

^{13}C NMR (125 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

GC: 3 peaks
MS: 381/383 (M^+)

3

^{13}C NMR (125 MHz, CDCl_3)

4

^1H NMR (400 MHz, CDCl_3)

4

^{13}C NMR (125 MHz, CDCl_3)

5

^1H NMR (400 MHz, CDCl_3)

5

^{13}C NMR (125 MHz, CDCl_3)

6

^1H NMR (400 MHz, CDCl_3)

GC: 3 peaks
MS: 267 (M^+)

6

^{13}C NMR (125 MHz, CDCl_3)

7.1

^1H NMR (400 MHz, CDCl_3)

7.1

^{13}C NMR (125 MHz, CDCl_3)

7.2

^1H NMR (400 MHz, CDCl_3)

7.2

^{13}C NMR (125 MHz, CDCl_3)

8a

^1H NMR (400 MHz, CDCl_3)

8a

^{13}C NMR (125 MHz, CDCl_3)

8c

^1H NMR (400 MHz, CDCl_3)

8c

^{13}C NMR (125 MHz, CDCl_3)

9.1

¹H NMR (400 MHz, CDCl₃)

S-59

9.1

^{13}C NMR (125 MHz, CDCl_3)

9.2

¹H NMR (400 MHz, CDCl₃)

9.2

^{13}C NMR (125 MHz, CDCl_3)

10

^1H NMR (400 MHz, CDCl_3)

10

^{13}C NMR (125 MHz, CDCl_3)

11

¹H NMR (400 MHz, CDCl₃)

GC: 3 peaks
MS: 395/397 (M⁺)

11

^{13}C NMR (125 MHz, CDCl_3)

11.1

^1H NMR (400 MHz, CDCl_3)

11.1

^{13}C NMR (125 MHz, CDCl_3)

12

^1H NMR (400 MHz, CDCl_3)

12

^{13}C NMR (125 MHz, CDCl_3)

13

^1H NMR (400 MHz, CDCl_3)

13

^{13}C NMR (125 MHz, CDCl_3)

14

^1H NMR (400 MHz, CDCl_3)

14

^{13}C NMR (125 MHz, CDCl_3)

15

^1H NMR (400 MHz, CDCl_3)

15

^{13}C NMR (125 MHz, CDCl_3)

16

^1H NMR (400 MHz, CDCl_3)

16

¹³C NMR (125 MHz, CDCl₃)

17

^1H NMR (400 MHz, CDCl_3)

17

^{13}C NMR (125 MHz, CDCl_3)

18

^1H NMR (400 MHz, CDCl_3)

18

^{13}C NMR (125 MHz, CDCl_3)