Supporting Information

Novel Acetoxylation and C–C Coupling Reactions at Unactivated Positions in α-Amino Acid Derivatives

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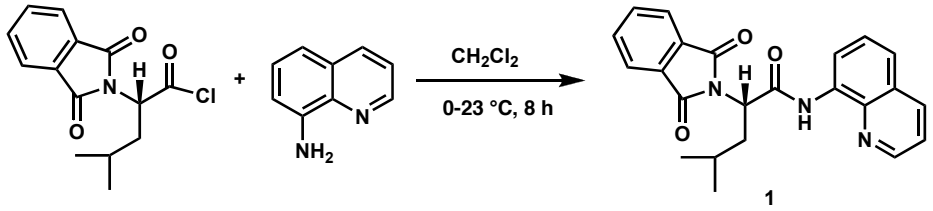
Experimental

General. All moisture sensitive reactions were performed under nitrogen gas in flame-dried glassware with magnetic stirring. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) was freshly distilled from the sodium complex of benzophenone before use. Hexanes, pyridine, triethylamine, pentane and dichloromethane were freshly distilled from CaH_2 before use. Toluene was distilled from sodium. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μm particle size). All compounds were judged pure by TLC analysis (single spot/ two solvent systems) using a UV lamp or CAM or PMA or anisaldehyde or basic $KMnO_4$ for detection purposes. NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz and 600 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard. High-resolution mass spectral analyses were performed at Harvard University Mass Spectrometry Center.

Preparation of *N*-Phthaloyl α-Amino Acid 8-Aminoquinoline Amides.

General Procedure: (GP1): To a stirred solution of 8-aminoquinoline (1.44 g, 10 mmol), and triethylamine (1.67 mL, 12 mmol) in dichloromethane (20 mL) was added the acid chloride drop wise (10 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature for 8.0 h and then diluted with water (20 mL) and extracted twice with dichloromethane (2x15 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification on silica gel afforded pure 8-aminoquinoline amide.

***N*-Phthaloylleucine 8-Aminoquinoline Amide (1).**

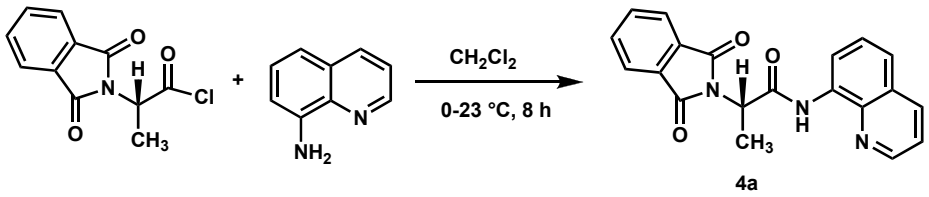


1

Following the general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloylleucine acid chloride (2.79 g, 10 mmol) gave 3.09 g (80%) of the pure amide **1** as a colorless solid, mp 105-106 °C. $[\alpha]_D^{25}$ = +1.5° (*c* 1.8, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3344, 2960, 2931, 2873, 1777, 1713, 1690, 1530, 1488, 1426, 1383, 1328, 1262, 1173, 1154, 1075, 1061, 941, 879, 825, 791, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (brs, 1H, NH), 8.70 (m, 2H), 8.13 (dd, J = 1.0 Hz & 8.0 Hz, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.49 (m, 2H), 7.40 (dd, J = 4.5 Hz & 8.5 Hz, 1H), 5.23 (dd, J = 5.5 Hz & 11.5 Hz, 1H), 2.65 (m, 1H), 2.12 (m, 1H), 1.64 (m, 1H), 1.06 (d, J = 6.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

168.40, 167.57, 148.58, 138.73, 136.51, 134.45, 134.17, 132.11, 128.07, 127.52, 123.83, 122.11, 121.85, 116.90, 53.85, 37.62, 25.80, 23.49, 21.54. HRMS (EI) Calcd for $C_{23}H_{21}N_3O_3$ [M+1]: 388.1661, Found 388.1653.

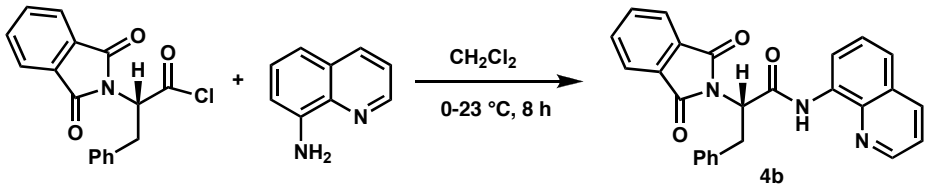
***N*-Phthaloylalanine 8-Aminoquinoline Amide (4a).**



4a

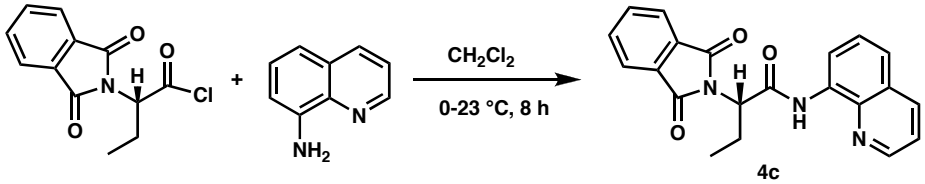
Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloylalanine acid chloride (2.37 g, 10 mmol) gave 2.93 g (85%) of the amide **4a** as a brown solid, mp 190-193 °C, $[\alpha]_D^{25}$ **=** +1.05° (*c* 1.7, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3342, 2983, 2923, 2852, 1777, 1713, 1524, 1478, 1385, 1358, 1318, 1144, 1084, 1052, 1019, 937, 879, 787, 719. ^1H NMR (500 MHz, $CDCl_3$) δ 10.31 (brs, 1H, NH), 8.71 (m, 1H), 8.66 (m, 1H), 8.10 (m, 1H), 7.87 (m, 2H), 7.73 (m, 2H), 7.48 (m, 2H), 7.40 (m, 1H), 5.23 (q, J = 7.5 Hz, 1H), 1.98 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.06, 167.45, 148.54, 138.68, 136.52, 134.43, 134.09, 132.20, 128.06, 127.51, 123.78, 122.15, 121.87, 116.82, 50.32, 15.63. HRMS (EI) Calcd for $C_{20}H_{15}N_3O_3$ [M+1]: 346.1191, Found 346.1204.

***N*-Phthaloylphenylalanine 8-Aminoquinoline Amide (4b).**



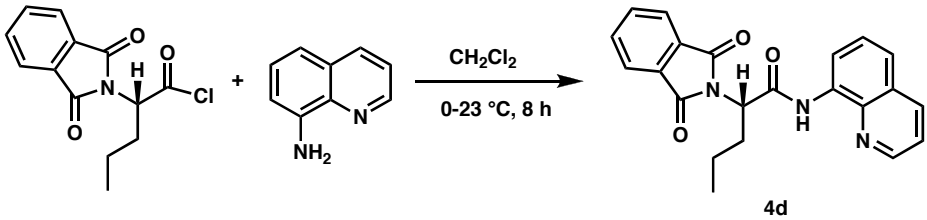
Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloylphenylalanine acid chloride (3.13 g, 10 mmol) gave 3.66 g, (87%) of the amide **4b** as a colorless solid, mp 120-122 °C, $[\alpha]_D^{25}$ **=** -61.1° (*c* 0.8, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 3062, 3029, 2925, 1715, 1692, 1530, 1488, 1385, 1328, 1171, 1102, 955, 877, 825, 791, 719. ^{1}HNMR (500 MHz, $CDCl_3$) δ 10.35 (brs, 1H, NH), 8.75 (dd, J = 2 Hz & 6.5 Hz, 1H), 8.60 (dd, J = 1.5 Hz & 4.5 Hz, 1H), 8.12 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.50 (m, 2H), 7.39 (dd, J = 3.5 Hz & 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 2H), 7.22 (t, J = 7.0 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 5.47 (dd, J = 6.5 Hz & 10 Hz, 1H), 3.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.12, 166.68, 148.42, 138.57, 136.95, 136.65, 134.40, 134.01, 131.85, 129.26, 128.92, 128.09, 127.58, 127.19, 123.77, 122.26, 121.84, 117.18, 56.46, 34.98. HRMS (EI) Calcd for $C_{26}H_{19}N_3O_3$ [M+1]: 422.1504, Found 422.1488.

***N*-Phthaloyl-β-methylalanine 8-Aminoquinoline Amide (4c).**



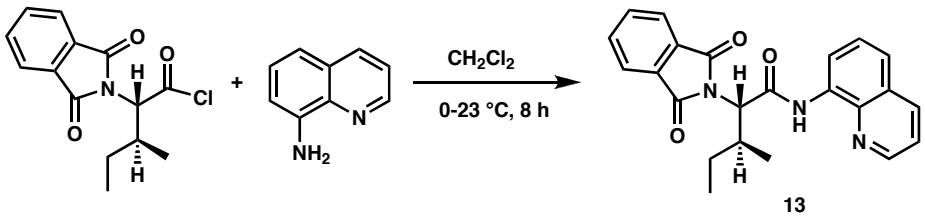
Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloyl-β-methylalanine acid chloride (2.51 g, 10 mmol) gave 2.94 g, (82%) of the amide **4c** as a colorless solid, mp 95-97 °C, $[\alpha]_D^{25}$ = +3.7° (*c* 3.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3346, 2973, 2935, 2879, 1775, 1713, 1686, 1528, 1486, 1426, 1382, 1328, 1264, 1173, 1150, 1069, 1057, 1038, 964, 901, 825, 791, 717. ^1H NMR (500 MHz, $CDCl_3$) δ 10.34 (brs, 1H, NH), 8.70 (m, 2H), 8.14 (m, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.50 (m, 2H), 7.41 (m, 1H), 5.06 (dd, J = 5 Hz & 10.5 Hz, 1H), 2.59 (m, 1H), 2.48 (m, 1H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.40, 167.17, 148.55, 138.73, 136.54, 134.45, 134.16, 132.07, 128.09, 127.54, 123.83, 122.14, 121.86, 116.97, 57.00, 22.42, 11.43. HRMS (EI) Calcd for $C_{21}H_{17}N_3O_3$ [M+1]: 360.1348, Found 360.1349.

***N*-Phthaloyl-β-ethylalanine 8-Aminoquinoline Amide (4d).**



Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloyl-β-ethylalanine acid chloride (2.65 g, 10 mmol) gave 3.2 g, (86%) of amide **4d** as a colorless solid, mp 155-157 °C, $[\alpha]_D^{25}$ **=** +4.0° (*c* 3.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3344, 3058, 2964, 2933, 2875, 1775, 1713, 1690, 1611, 1528, 1486, 1426, 1382, 1328, 1246, 1177, 1150, 1086, 1075, 1052, 887, 825, 791, 717. ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (brs, 1H, NH), 8.70 (m, 2H), 8.14 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.89 (m, 2H), 7.74 (m, 2H), 7.49 (m, 2H), 7.40 (dd, J = 4.5 Hz & 8.0 Hz, 1H), 5.17 (dd, J = 5.0 Hz & 10.5 Hz, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 1.47 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.38, 167.34, 148.56, 138.71, 136.53, 134.45, 134.15, 132.06, 128.07, 127.52, 123.82, 122.14, 121.86, 116.94, 55.19, 30.90, 20.14, 13.75. HRMS (EI) Calcd for $C_{22}H_{19}N_3O_3$ [M+1]: 374.1504, Found 374.1517.

***N*-Phthaloylisoleucine 8-Aminoquinoline Amide (13).**

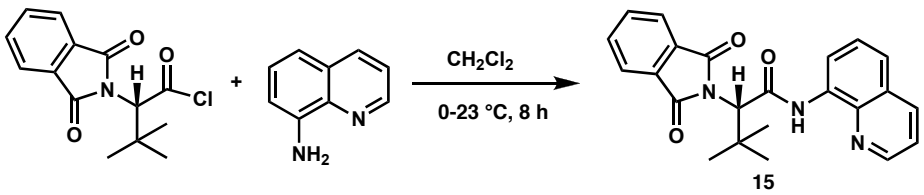


13

Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 mL, 12 mmol) and *N*-phthaloylisoleucine acid chloride (2.79 g, 10 mmol) gave 3.14 g (81%) of the amide **13** as a pale yellow solid, mp 140-142 °C. $[\alpha]_D^{25}$ **=** -30.6° (*c* 1.3, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 2968, 2933, 2877, 1773, 1713, 1684, 1526, 1486, 1468, 1426, 1382, 1353, 1326, 1264, 1173, 1148, 1071, 908, 879, 827, 791, 754,

719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (brs, 1H, NH), 8.86 (m, 1H), 8.76 (m, 1H), 8.14 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 7.88 (m, 2H), 7.72 (m, 2H), 7.49 (d, J = 4 Hz, 2H), 7.44 (dd, J = 4 Hz & 7.5 Hz, 1H), 4.79 (d, J = 11.0 Hz, 1H), 3.07 (m, 1H), 1.53 (m, 1H), 1.19 (d, J = 6.5, 3H), 1.16 (m, 1H), 0.934 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.41, 167.23, 148.77, 138.94, 136.41, 134.47, 131.85, 128.13, 127.46, 123.88, 122.20, 121.85, 117.24, 62.29, 33.00, 25.89, 16.60, 10.56. HRMS (EI) Calcd for $C_{23}H_{21}N_3O_3$ [M+1]: 388.1661, Found 388.1662.

_N_-Phthaloyl-_tert_-leucine 8-Aminoquinoline Amide (15).

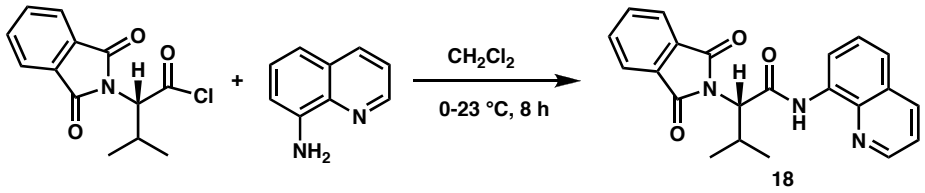


15

Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloyl-*tert*-leucine acid chloride (2.79 g, 10 mmol) gave 3.01 g, (78%) of the amide **15** as a pale yellow solid, mp 165-167 °C, $[\alpha]_D^{25}$ = -39.6° (*c* 2.4, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3342, 2964, 2910, 2873, 1773, 1715, 1526, 1486, 1426, 1378, 1326, 1254, 1160, 1100, 1086, 1034, 901, 825, 791, 754, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (brs, 1H, NH), 8.73 (d, J = 7.5 Hz, 1H), 8.62 (m, 1H), 8.09 (m, 1H), 7.89 (m, 2H), 7.74 (m, 2H), 7.50 (m, 2H), 7.35 (m, 1H), 5.01 (s, 1H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.68, 166.26, 148.52, 138.92,

136.39, 134.53, 131.87, 128.10, 127.51, 123.90, 122.01, 121.75, 117.19, 63.97, 36.32, 28.72. HRMS (EI) Calcd for $C_{23}H_{21}N_3O_3$ [M+1]: 388.1661, Found 388.1656.

***N*-Phthaloylvaline 8-Aminoquinoline Amide (18).**

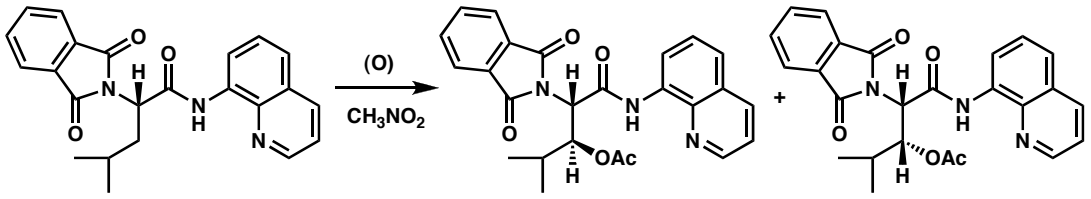


Following general procedure (GP-1), the reaction of 8-aminoquinoline (1.44 g, 10 mmol) with NEt_3 (1.67 ml, 12 mmol) and *N*-phthaloylvaline acid chloride (2.65 g, 10 mmol) gave 3.10 g, (83%) of the amide **18** as a colorless solid, mp 110-112 °C, $[\alpha]_D^{25}$ **=** -43.9° (*c* 2.5, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 3016, 2968, 2933, 2875, 1769, 1713, 1686, 1526, 1486, 1468, 1426, 1382, 1326, 1262, 1192, 1173, 1152, 1071, 991, 914, 889, 827, 791, 754, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 (brs, 1H, NH), 8.83 (dd, J = 1.5 Hz & 4.0 Hz, 1H), 8.76 (m, 1H), 8.13 (dd, J = 2.0 Hz & J = 8.5 Hz, 1H), 7.87 (m, 2H), 7.72 (m, 2H), 7.50 (m, 2H), 7.43 (dd, J = 3.5 Hz & 7.5 Hz, 1H), 4.70 (d, J = 10.5 Hz, 1H), 3.24 (m, 1H), 1.23 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.38, 167.06, 148.75, 138.92, 136.42, 134.49, 131.83, 128.12, 127.46, 123.88, 122.20, 121.85, 117.22, 63.44, 27.55, 20.69, 19.83. HRMS (EI) Calcd for $C_{22}H_{19}N_3O_3$ [M+1]: 374.1504, Found 374.1509.

β-Acetoxylation of 1 and 4a - 4d.

General Procedure: (GP2): A mixture of the phthaloylamino acid 8-aminoquinoline amide (1 mmol), $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) was stirred at 80 °C over 8 to 48 h under an air atmosphere. Upon completion of the reaction as indicated by TLC analysis, the mixture was filtered and washed with dichloromethane (2x 15 mL). Removal of solvent followed by purification on silica gel afforded the pure β-acetoxyated amino acid. This procedure was used for the synthesis of **2** and **5a - 5d**.

β-Acetoxylation of *N*-Phthaloylleucine 8-Aminoquinoline (1) to Form 2.



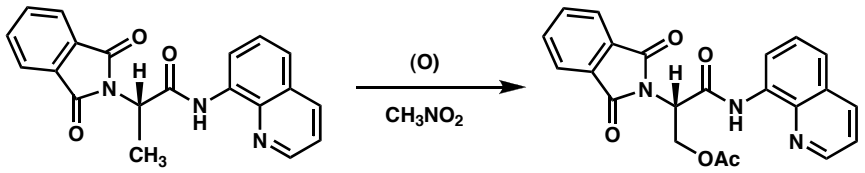
1 2 3

Following general procedure (GP-2), the reaction of **1** (0.387 g, 1 mmol) with $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) at 80 °C for 22 h under an air atmosphere afforded pure β-acetoxy derivatives **2** and **3** in 64.3% combined yield. The mixture was separated by chromatography on silica gel to give pure **2** and **3**. Major diastereomer (**2**, 266 mg, 59.8%): mp 148-150 °C, $[\alpha]_D^{25}$ = -8.0° (*c* 0.5, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1})

3334, 2968, 2933, 2879, 1779, 1750, 1719, 1530, 1488, 1426, 1383, 1326, 1223, 1123, 1075, 1021, 879, 827, 793, 721. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (brs, 1H, NH), 8.82 (dd, J = 1.5 Hz, 1H), 8.71 (dd, J = 1.5 Hz & 6.5 Hz, 1H), 8.17 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.47 (m, 3H), 6.15 (dd, J = 4.0 Hz & 9.5 Hz, 1H), 5.28 (d, J = 8.5 Hz 1H), 2.19 (s, 3H), 2.04 (m, 1H), 1.64 (m, 1H), 1.02 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.40, 168.15, 165.24, 148.39, 138.69, 136.62, 134.60, 134.27, 132.03, 128.17, 127.62, 124.02, 122.33, 121.93, 117.41, 74.27, 56.22, 30.38, 21.34, 19.99, 15.90. HRMS (EI) Calcd for $C_{25}H_{23}N_3O_5$ [M+1]: 446.1716, Found 446.1712.

Minor diastereomer (**3,** 20 mg, 4.5%): mp 60-62 °C, $[\alpha]_D^{25}$ **=** -45.4° (*c* 0.6, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3332, 2966, 2931, 2879, 1781, 1744, 1717, 1528, 1488, 1426, 1370, 1326, 1227, 1173, 1106, 1081, 1023, 941, 881, 827, 791, 760. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (brs, 1H, NH), 8.71 (m, 2H), 8.12 (dd, J = 2.5 Hz & 13.5 Hz, 1H), 7.91 (m, 2H), 7.76 (m, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.40 (dd, J = 7.0 Hz & 13.5 Hz, 1H), 6.00 (dd, J = 7.5 Hz & 14 Hz, 1H), 5.33 (d, J = 14 Hz 1H), 2.29 (m, 1H), 1.89 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.24, 167.85, 164.73, 148.69, 138.86, 136.39, 134.64, 134.20, 131.79, 128.10, 127.43, 124.00, 122.40, 121.84, 117.41, 74.08, 56.55, 30.25, 20.78, 20.06, 16.37. HRMS (EI) Calcd for $C_{25}H_{23}N_3O_5$ [M+1]: 446.1716, Found 446.1723.

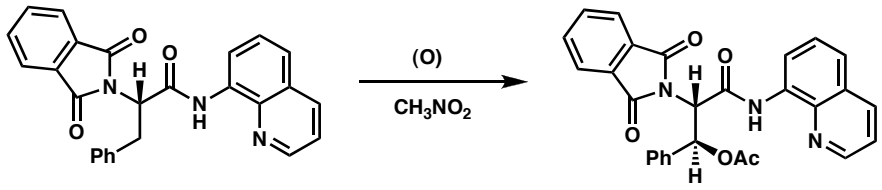
β-Acetoxylation of *N*-phthaloyl Alanine 8-Aminoquinoline Amide (4a) to Form 5a.



Following general procedure (GP-2), the reaction of **4a** (0.345 g, 1 mmol) with $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) at 80 °C for 48 h under an air atmosphere afforded pure β-acetoxy derivative **5a** (210 mg) in 52% yield.

Data for **5a**: Solid, mp 182-185 °C, $[\alpha]_D^{25}$ = +8.2° (*c* 1.7, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3321, 2960, 2925, 2854, 1779, 1719, 1536, 1468, 1385, 1264, 1237, 1082, 1067, 1046, 1025, 879, 827, 791, 719. ^1H NMR (500 MHz, $CDCl_3$) δ 10.53 (brs, 1H, NH), 8.68 (m, 2H), 8.14 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 7.91 (m, 2H), 7.77 (m, 2H), 7.51 (m, 2H), 7.48 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 5.39 (t, J = 7.0 Hz, 1H), 5.15 (dd, J = 8 Hz & 12 Hz, 1H), 4.78 (d, J = 7 Hz & 12 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.45, 167.93, 164.71, 148.48, 138.69, 136.61, 134.66, 134.05, 132.04, 128.13, 127.53, 124.04, 122.45, 121.92, 117.25, 62.07, 53.18, 21.02. HRMS (EI) Calcd for $C_{22}H_{17}N_3O_5$ [M+1]: 404.1246, Found 404.1240.

β-Acetoxylation of 4b to Form 5b.

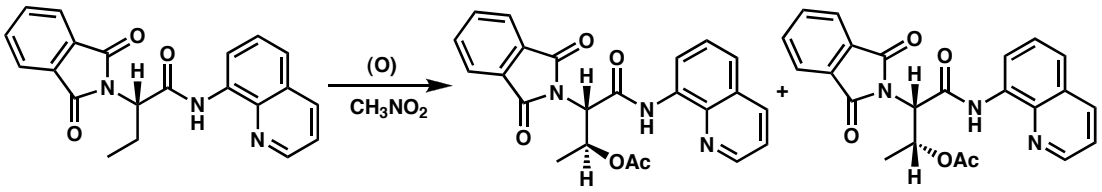


4b 5b

Following general procedure (GP-2), the reaction of **4b** (0.421 g, 1 mmol) with $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) at 80 °C over 8 h (air atmosphere) afforded pure β-acetoxy derivative **5b** (308 mg) in 63% yield.

Data for **5b**. Solid, mp 198-200 °C, $[\alpha]_D^{25}$ **=** -3.0° (*c* 1.2, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3330, 3066, 2962, 2925, 1754, 1719, 1692, 1532, 1488, 1426, 1387, 1326, 1206, 1019, 887, 827, 791, 721. ^1H NMR (500 MHz, $CDCl_3$) δ 10.75 (brs, 1H, NH), 8.80 (dd, J = 1.5 Hz & 4 Hz, 1H), 8.76 (dd, J = 1.5 Hz & 7.5 Hz, 1H), 8.19 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.75 (m, 2H), 7.64 (m, 2H), 7.50 (m, 2H), 7.48 (m, 3H), 7.23 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 10.5 Hz, 1H), 5.66 (d, J = 10.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.42, 167.59, 164.55, 148.35, 138.58, 136.87, 136.76, 134.32, 131.68, 129.13, 128.69, 128.23, 127.84, 127.66, 123.78, 122.46, 121.95, 117.56, 74.08, 56.90, 21.65. HRMS (EI) Calcd for $C_{28}H_{21}N_3O_5$ [M+1]: 480.1559, Found 480.1544.

β-Acetoxylation of of 4c to Form 5c.



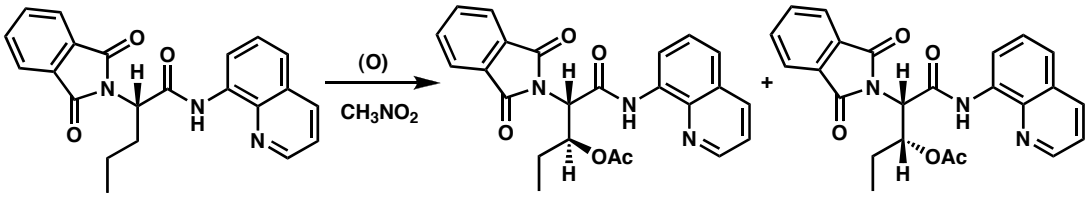
4c 5c

Following general procedure (GP-2), the reaction of **4c** (0.359 g, 1 mmol) with $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) at 80 °C for 24 h in air afforded a mixture of the β-acetoxy derivative **5c** and a minor amount of the C(3)-diastereomer (255 mg) in 61% yield.

Major diastereomer (**5c):** 213 mg, 51%): Solid, mp 60-62 °C, $[\alpha]_D^{25}$ **=** -7.8° (*c* 1.1, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3332, 3060, 2933, 2925, 2854, 1777, 1748, 1717, 1688, 1528, 1488, 1426, 1383, 1326, 1221, 1111, 1057, 1017, 943, 903, 827, 791, 719. ^1H NMR (500 MHz, $CDCl_3$) δ 10.56 (brs, 1H, NH), 8.79 (dd, J = 2.0 Hz & 3.5 Hz, 1H), 8.75 (d, J = 6.5 Hz, 1H), 8.20 (d, J = 7 Hz, 1H), 7.96 (m, 2H), 7.81 (m, 2H), 7.55 (m, 2H), 7.49 (dd, J = 3.5 Hz & 7 Hz, 1H), 6.09 (m, 1H), 5.29 (d, J = 7.5 Hz, (1H), 2.31 (s, 3H), 1.38 (d, J = 6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.09, 168.14, 164.78, 148.31, 138.71, 136.70, 134.64, 134.22, 132.03, 128.18, 127.58, 124.06, 122.39, 121.92, 117.42, 69.48, 57.50, 21.73, 18.34. HRMS (EI) Calcd for $C_{23}H_{19}N_3O_5$ [M+1]: 418.1403, Found 418.1405.

Minor diastereomer: (42 mg, 10%): Solid, mp 57-59 °C, $[\alpha]_D^{25}$ = +13.8° (*c* 0.9, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3334, 2962, 2925, 2854, 1777, 1744, 1717, 1692, 1530, 1488, 1426, 1380, 1326, 1229, 1063, 1019, 827, 793, 756, 719. ^1H NMR (500 MHz, $CDCl_3$) δ 10.61 (brs, 1H, NH), 8.79 (d, J = 4.2 Hz, 1H), 8.76 (m, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.95 (m, 2H), 7.80 (m, 2H), 7.56 (m, 2H), 7.46 (dd, J = 4.2 Hz & 8.4 Hz, 1H), 6.01 (m, 1H), 5.23 (d, J = 7.2 Hz, (1H), 2.04 (s, 3H), 1.62 (d, J = 6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.09, 168.14, 164.78, 148.31, 138.71, 136.70, 134.64, 134.22, 132.03, 128.18, 127.58, 124.06, 122.39, 121.92, 117.42, 69.48, 57.50, 21.73, 18.34. HRMS (EI) Calcd for $C_{23}H_{19}N_3O_5$ [M+1]: 418.1403, Found 418.1401.

β-Acetoxylation of of 4d to Form 5d.



4d 5d

Following general procedure (GP-2), the reaction of *N*-phthaloyl-β-ethylalanine 8-aminoquinoline amide (0.373 g, 1 mmol) with $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Mn(OAc)_2$ (207 mg, 1.2 mmol), Oxone® (3.07 g, 5 mmol), and Ac_2O (1.02 mL, 10 mmol) in CH_3NO_2 (20 mL) at 80 °C for 24 h in air afforded the β-acetoxy derivative **5d** and the β-diastereomer (272 mg) in 63% yield.

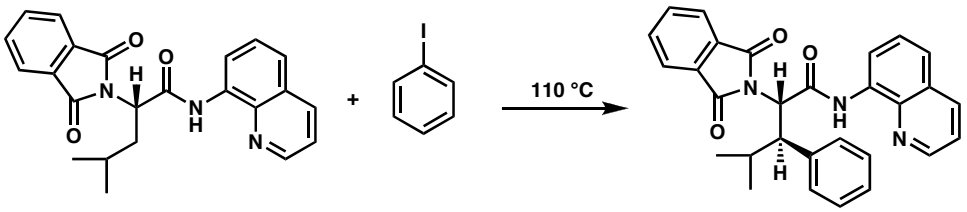
Major diastereomer (**5d):** 240 mg, 55.5%): Solid, mp 120-122 °C, $[\alpha]_D^{25}$ = -10.3° (*c* 1.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3336, 3060, 2975, 2939, 2883, 1777, 1746, 1717, 1690, 1530, 1488, 1426, 1382, 1326, 1221, 1115, 1073, 1019, 960, 885, 827, 791, 756, 721. ^1H NMR (500 MHz, $CDCl_3$) δ 10.47 (brs, 1H, NH), 8.75 (dd, J = 1.0 Hz & 2.5 Hz, 1H), 8.69 (dd, J = 1.0 Hz & 7.0 Hz, 1H), 8.20 (dd, J = 1.0 Hz & 8.5 Hz, 1H), 7.90 (m, 2H), 7.76 (m, 2H), 7.49 (m, 2H), 7.44 (dd, J = 4.5 Hz & 8.0 Hz, 1H), 6.07 (m, 1H), 5.32 (d, J = 6.5 Hz, (1H), 2.27 (s, 3H), 2.03 (m, 1H), 1.61 (m, 1H), 0.96 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.31, 168.18, 165.02, 148.34, 138.70, 136.65, 134.62, 134.21, 132.03, 128.16, 127.58, 124.04, 122.35, 121.91, 117.40, 72.74, 55.98, 24.62, 21.52, 8.48. HRMS (EI) Calcd for $C_{24}H_{21}N_3O_5$ [M+1]: 432.1559, Found 432.1540.

Minor diastereomer: (32 mg, 7.5%): Solid, mp 115-118 °C, $[\alpha]_D^{25}$ = +4.5° (*c* 1.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3338, 3058, 2966, 2935, 2877, 1777, 1744, 1715, 1528, 1488, 1426, 1378, 1328, 1229, 1073, 1036, 966, 885, 827, 791, 756, 719. ^1H NMR (500 MHz, $CDCl_3$) δ 10.53 (brs, 1H, NH), 8.72 (m, 2H), 8.13 (d, J = 8.5 Hz, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.50 (m, 2H), 7.40 (dd, J = 4.5 Hz & 8.5 Hz, 1H), 5.93 (m, 1H), 5.24 (d, J = 7.0 Hz, 1H), 2.07 (m, 1H), 1.98 (s, 3H), 1.83 (m, 1H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.24, 167.89, 164.62, 148.66, 138.79, 136.48, 134.66, 134.15, 131.80, 128.11, 127.47, 124.02, 122.44, 121.90, 117.38, 72.18, 57.77, 25.67, 21.05, 9.76. HRMS (EI) Calcd for $C_{24}H_{21}N_3O_5$ [M+1]: 432.1559, Found 432.1545.

General Procedure For β-Arylation. A mixture of 8-aminoquinoline amide (1 mmol), $Pd(OAc)_2$ (44 mg, 0.2 mmol), AgOAc (250 mg, 1.5 mmol) or $(CuOAc)_2$ (272 mg, 1.5

mmol) and iodoarene (4 mmol) was heated at 110 °C over 30 min to 14 h under N_2. Upon completion of the reaction as indicated by TLC analysis, the mixture was dissolved in dichloromethane (30 mL) and then filtered under vacuo. Removal of sovent followed by purification on silica gel gave pure β-arylated α-amino acid derivatives.

β-Phenylation of 1 to Form 10 a.



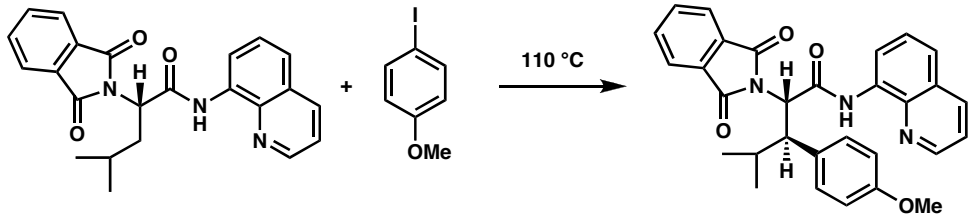
1 10a

Following general procedure (GP-3), treatment **1** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and iodobenzene (0.816 g, 4 mmol) at 110 °C for 12 h under solvent-free conditions gave the β-phenylleucine derivative **10a,** 398 mg, in 86% yield.

Data for **10a**. Solid, mp 191-193 °C, $[\alpha]_D^{25}$ **=** -33.4° (*c* 3.2, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3290, 3029, 2964, 2931, 2877, 1777, 1713, 1679, 1526, 1488, 1426, 1385, 1326, 1260, 1127, 1111, 1079, 941, 881, 825, 791, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (brs, 1H, NH), 8.66 (dd, J = 1.0 Hz & 4.0 Hz, 1H), 8.53 (dd, J = 1.5 Hz & 7.0 Hz, 1H), 8.01 (d, J = 1.0 Hz & 8.0 Hz, 1H), 7.90 (m, 2H), 7.72 (m, 2H), 7.50 (d, J = 7.5 Hz 2H), 7.35 (m, 5H), 7.28 (t, J = 7.0 Hz, 1H), 5.68 (d, J = 12.5 Hz, 1H), 4.27 (dd, J = 3.5 Hz & 12.5 Hz, 1H), 2.02 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.74, 166.49, 148.16, 138.72, 136.70, 136.14, 134.51, 134.39, 132.06, 130.32, 128.65, 127.88, 127.56, 127.27, 123.93, 121.97, 121.66, 117.03, 58.18, 48.75,

29.34, 21.82, 16.60. HRMS (EI) Calcd for $C_{29}H_{25}N_3O_3$ [M+1]: 464.1974, Found 464.1960.

β-Arylation of 1 to Form 6.

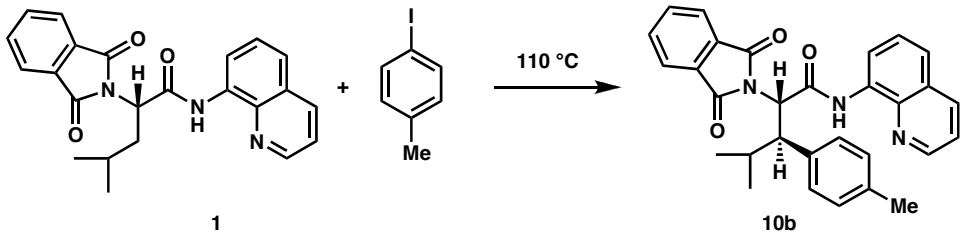


1 6

Treatment of **1** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole(0.936 g, 4 mmol) at 110 °C for 30 min under solvent-free conditions **6,** 468 mg, in 95% yield.

Data for **6**: colorless solid, mp 210-212 °C, $[\alpha]_D^{25}$ **=** -8.2° (*c* 0.9, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3286, 2962, 2933, 2836, 1777, 1713, 1679, 1611, 1524, 1513, 1488, 1466, 1426, 1383, 1326, 1248, 1183, 1129, 1079, 1034, 941, 881, 827, 791, 717. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (brs, 1H, NH), 8.70 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 7.0 Hz, 1H), 7.95 (m, 2H), 7.79 (m, 2H), 7.40 (m, 5H), 5.66 (d, J = 10 Hz, 1H), 4.24 (dd, J = 2.5 Hz & 10.5 Hz, 1H), 3.81 (s, 3H), 2.01 (m, 1H), 0.85 (d, J = 6.0 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.78, 166.63, 159.15, 148.08, 138.77, 136.12, 134.46, 132.13, 131.33, 128.60, 127.90, 127.32, 123.93, 121.93, 121.67, 117.09, 114.13, 58.29, 55.36, 48.00, 29.39, 21.78, 16.48. HRMS (EI) Calcd for $C_{30}H_{27}N_3O_4$ [M+1]: 494.2080, Found 494.2061.

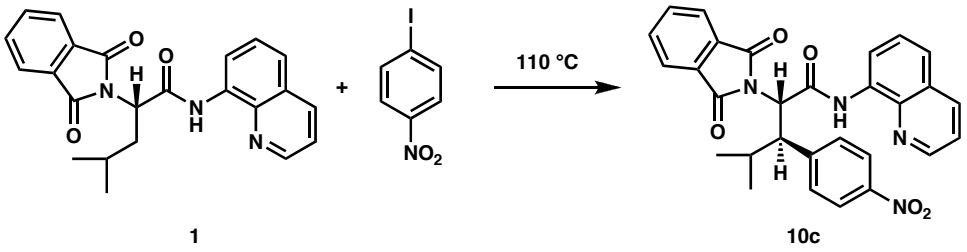
Conversion of 1 to 10b.



Treatment of **1** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodotoluene (0.872 g, 4 mmol) at 110 °C for 3 h under solvent-free conditions gave **10b,** 443 mg, in 93% yield.

Data for **10b:** solid, mp 198-200 °C**,** $[\alpha]_D^{25}$ **=** -32.0° (*c* 3.2, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3288, 3024, 2964, 2931, 2875, 1777, 1713, 1681, 1524, 1488, 1426, 1383, 1326, 1260, 1129, 1079, 941, 881, 825, 754, 717. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (brs, 1H, NH), 8.67 (dd, J = 1.0 Hz & 3.5 Hz, 1H), 8.55 (d, J = 7.0 Hz, 1H), 8.05 (dd, J = 8.5 Hz, 1H), 7.92 (m, 2H), 7.75 (m, 2H), 7.35 (m, 5H), 7.17 (d, J = 7.5 Hz, 2H), 5.66 (d, J = 12.0 Hz, 1H), 4.23 (dd, J = 3.5 Hz & 12.0 Hz, 1H), 2.30 (s, 3H), 1.99 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.73, 166.60, 148.03, 138.78, 137.01, 136.12, 134.52, 134.44, 133.54, 132.12, 130.15, 129.36, 127.90, 127.31, 123.92, 121.88, 121.61, 117.11, 58.26, 48.33, 29.29, 21.79, 21.36, 16.56. HRMS (EI) Calcd for $C_{30}H_{27}N_3O_3$ [M+1]: 478.2130, Found 478.2135.

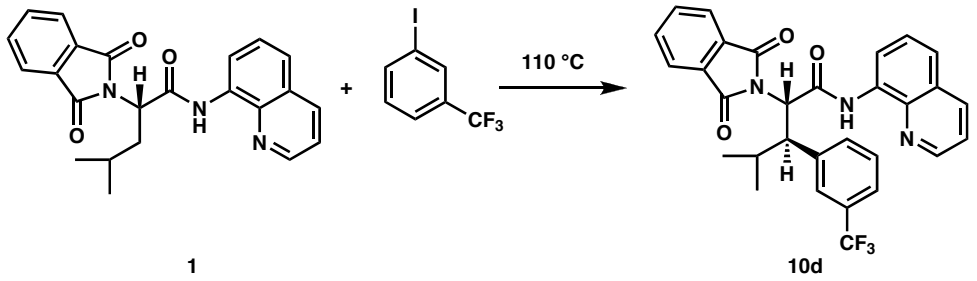
Conversion of 1 to 10c.



Treatment of **1** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodo-nitrobenzene (0.996 g, 4 mmol) at 110 °C for 14 h under solvent-free conditions gave **10c,** 401 mg, in 79% yield.

Data for **10c:** solid, mp 249-251 °C**,** $[\alpha]_D^{25}$ **=** -34.0° (*c* 0.5, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3298, 2966, 2929, 2854, 1775, 1715, 1605, 1524, 1488, 1426, 1385, 1343, 1328, 1260, 1131, 1079, 883, 827, 791, 721. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (brs, 1H, NH), 8.67 (dd, J = 1.5 Hz & 4.0 Hz, 1H), 8.46 (dd, J = 1.0 Hz & 7.5 Hz, 1H), 8.20 (d, J = 9.0 Hz, 2H), 8.07 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.94 (m, 2H), 7.78 (m, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.40 (m, 3H), 5.67 (d, J = 12.5 Hz, 1H), 4.45 (dd, J = 4.0 Hz & 12.5 Hz, 1H), 2.06 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.41, 165.57, 148.36, 147.44, 145.36, 138.58, 136.40, 134.74, 133.93, 131.86, 130.93, 127.97, 127.31, 124.13, 123.71, 122.33, 121.88, 117.14, 57.78, 48.69, 29.11, 21.66, 16.70. HRMS (EI) Calcd for $C_{29}H_{24}N_4O_5$ [M+1]: 509.1825, Found 509.1804.

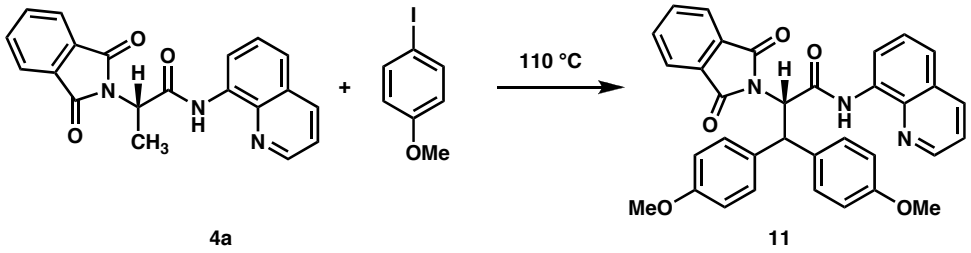
Conversion of 1 to 10d.



Treatment of **1** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *3*-iodo-benzotrifluoride (1.08 g, 4 mmol) at 110 °C for 3.5 h under solvent-free conditions gave **10d,** 483 mg, in 91% yield.

Data for **10d:** solid, mp 156-158 °C**,** $[\alpha]_D^{25}$ **=** -28.6° (*c* 1.5, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3309, 3024, 2966, 2935, 2879, 1775, 1715, 1683, 1526, 1488, 1426, 1383, 1326, 1260, 1165, 1125, 1077, 891, 827, 791, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (brs, 1H, NH), 8.67 (dd, J = 1.5 Hz & 4.0 Hz, 1H), 8.50 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 8.00 (dd, J = 1.0 Hz & 8.0 Hz, 1H), 7.90 (m, 2H), 7.72 (m, 3H), 7.67 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.35 (m, 3H), 5.68 (d, J = 12.5 Hz, 1H), 4.40 (dd, J = 3.5 Hz & 12.5 Hz, 1H), 2.05 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.55, 165.89, 148.41, 138.62, 138.19, 136.23, 134.64, 134.03, 131.91, 130.91, 130.66, 129.06, 127.90, 127.17, 124.47, 124.44, 124.01, 122.20, 121.76, 117.00, 57.98, 48.71, 29.14, 21.65, 16.62. HRMS (EI) Calcd for $C_{30}H_{24}F_3N_3O_3$ [M+1]: 532.1848, Found 532.1835.

Synthesis of 11.

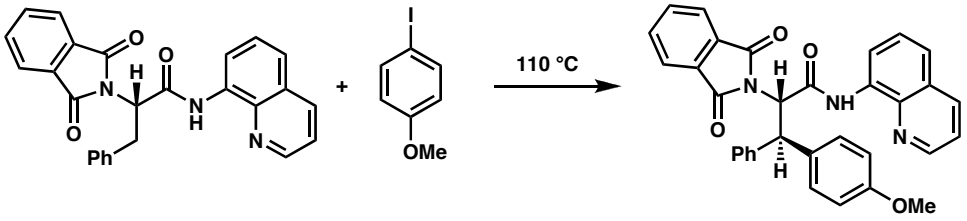


4a 11

Treatment of **4a** (0.345 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodo-anisole (0.936 g, 4 mmol) at 110 °C for 1.5 h under solvent-free conditions gave the β,β′-di-*p*-methoxyphenyl alanine derivative **11,** 512 mg, in 92% yield.

Data for **11:** solid, mp 233-235 °C**,** $[\alpha]_D^{25}$ **=** -5.5° (*c* 0.6, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3282, 3060, 3000, 2956, 2935, 2836, 1777, 1713, 1683, 1609, 1526, 1511, 1478, 1382, 1326, 1248, 1179, 1123, 1032, 885, 825, 793, 717. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (brs, 1H, NH), 8.70 (d, J = 3.5 Hz, 1H), 8.68 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 6.5 Hz, 1H), 7.79 (m, 2H), 7.66 (m, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.47 (m, 2H), 7.42 (m, 1H), 7.31 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.0 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 5.93 (d, J = 10.5 Hz, 1H), 5.56 (d, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.17, 166.07, 158.98, 158.40, 148.24, 138.73, 136.19, 134.36, 134.22, 133.63, 133.26, 131.72, 129.34, 128.89, 127.94, 127.38, 123.69, 122.08, 121.72, 117.12, 114.89, 114.25, 59.23, 55.36, 55.31, 49.07. HRMS (EI) Calcd for $C_{34}H_{27}N_3O_5$ [M+1]: 558.2029, Found 558.2009.

Conversion of 4b to 12a.

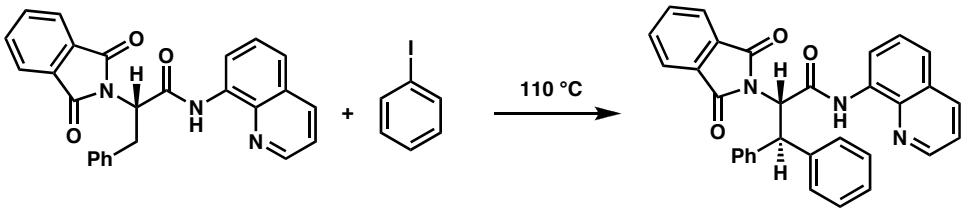


4b 12a

Treatment of **4b** (0.421 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole (0.936 g, 4 mmol) at 110 °C for 1 h under solvent-free conditions gave **12a,** 479 mg, in 91% yield.

Data for **12a:** solid, mp 228-230 °C, $[\alpha]_D^{25}$ **=** -1.5° (*c* 2.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3284, 2960, 2923, 2852, 1777, 1713, 1684, 1611, 1526, 1513, 1488, 1383, 1326, 1260, 1179, 1084, 1032, 883, 789, 750, 717. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (brs, 1H, NH), 8.65 (m, 2H), 8.60 (d, J = 8.5 Hz, 1H), 7.74 (m, 2H), 7.61 (m, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.43 (m, 2H), 7.40 (m, 1H), 7.35 (d, J = 7.5 Hz, 2H), 7.15 (t, J = 8.0 Hz, 2H), 7.03 (t, J = 7.0 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 5.95 (d, J = 12.5 Hz, 1H), 5.58 (d, J = 13 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.14, 166.00, 159.06, 148.24, 141.42, 138.71, 136.21, 134.34, 134.22, 132.88, 131.67, 129.47, 128.86, 127.90, 127.39, 127.01, 123.65, 122.11, 121.73, 117.14, 114.91, 59.04, 55.35, 49.88, 29.94. HRMS (EI) Calcd for $C_{33}H_{25}N_3O_4$ [M+1]: 528.1923, Found 528.1908.

Conversion of 4b to 12b.

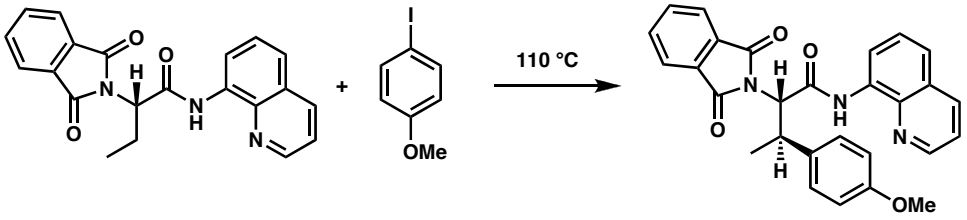


4b 12b

Treatment of **4b** (0.421 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and iodobenzene (0.816 g, 4 mmol) at 110 °C for 8 h under solvent-free conditions gave **12b,** 442 mg, in 89% yield.

Data for **12b:** solid, mp 223-225 °C**,** $[\alpha]_D^{25}$ **=** -6.0° (*c* 1.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3284, 2958, 2923, 2854, 1777, 1715, 1683, 1526, 1478, 1383, 1326, 1262, 1169, 1111, 1084, 1032, 883, 827, 793, 717. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (brs, 1H, NH), 8.66 (dd, J = 1.5 Hz & 4.0 Hz, 1H), 8.63 (dd, J = 2.0 Hz & 6.5 Hz, 1H), 8.08 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.75 (m, 2H), 7.63 (m, 4H), 7.43 (m, 2H), 7.40 (m, 3H), 7.31 (t, J = 7.0 Hz, 2H), 7.16 (m, 3H), 7.03 (t, J = 7.0 Hz, 1H), 6.01 (d, J = 12.5 Hz, 1H), 5.63 (d, J = 12.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.10, 165.83, 158.35, 148.29, 140.77, 136.21, 134.24, 129.45, 128.86, 128.39, 128.05, 127.54, 127.37, 127.11, 123.68, 122.11, 121.71, 117.12, 116.82, 58.81, 50.60. HRMS (EI) Calcd for $C_{32}H_{23}N_3O_3$ [M+1]: 498.1817, Found 498.1831.

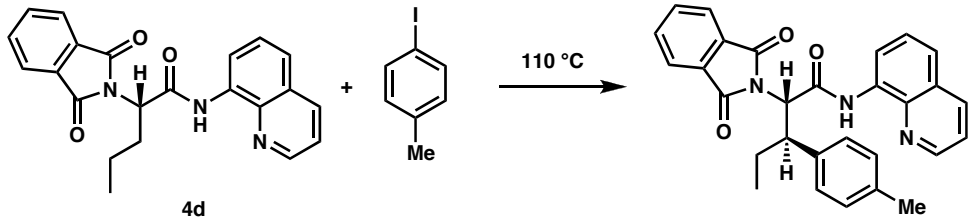
β-Anisylation of 4c.



4c

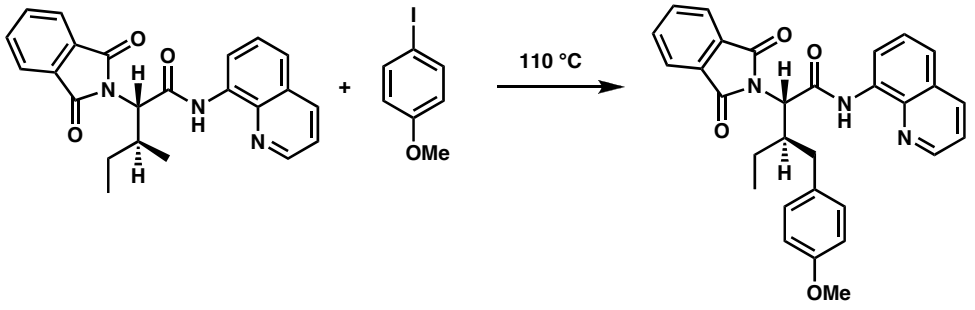
Reaction of **4c** (0.359 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole (0.936 g, 4 mmol) at 110 °C for 30 min under solvent-free conditions gave β-*p*-anisyl derivative 418 mg, in 90% yield as a colorless solid, mp 180-182 °C, $[\alpha]_D^{25}$ = +2.5° (*c* 2.4, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3288, 3016, 2968, 2933, 2836, 1773, 1713, 1683, 1611, 1326, 1486, 1383, 1326, 1246, 1179, 1129, 1081, 1036, 906, 876, 827, 791, 715. ^1H NMR (500 MHz, $CDCl_3$) δ 9.92 (brs, 1H, NH), 8.64 (dd, J = 1.5 Hz & 4.5 Hz, 1H), 8.59 (dd, J = 2.0 Hz & 6.5 Hz, 1H), 8.05 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 7.92 (m, 2H), 7.75 (m, 2H), 7.44 (d, J = 9.0 Hz, 2H), 7.42 (m, 2H), 7.38 (m, 1H), 6.86 (d, J = 9.0 Hz, 2H), 5.27 (d, J = 6.0 Hz, 1H), 4.30 (m, 1H), 3.70 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.59, 166.32, 159.03, 148.14, 138.65, 136.17, 134.83, 134.49, 134.30, 132.02, 129.09, 127.91, 127.37, 123.92, 121.97, 121.68, 116.99, 114.81, 61.84, 55.36, 38.30, 20.93. HRMS (EI) Calcd for $C_{28}H_{23}N_3O_4$ [M+1]: 466.1767, Found 466.1765.

β-Arylation of 4d.



Reaction of **4d** (0.373 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodotoluene (0.872 g, 4 mmol) at 110 °C for 2.5 h under solvent-free conditions gave β-*p*-tolyl derivative, 402 mg, in 87% yield as a colorless solid, mp 58-60 °C, $[\alpha]_D^{25}$ = -32° (*c* 3.0, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3392, 3022, 2966, 2931, 2875, 1777, 1713, 1683, 1526, 1488, 1426, 1383, 1328, 1262, 1169, 1127, 1081, 984, 937, 881, 825, 791, 717. ^1H NMR (500 MHz, $CDCl_3$) δ 9.99 (brs, 1H, NH), 8.67 (dd, J = 1.5 Hz & 4.5 Hz, 1H), 8.56 (dd, J = 2.5 Hz & 7.0 Hz, 1H), 8.04 (d, J = 1.5 Hz & 8.5 Hz, 1H), 7.90 (m, 2H), 7.72 (m, 2H), 7.36 (m, 5H), 7.12 (d, J = 7.5 Hz, 2H), 5.37 (d, J = 12.5 Hz, 1H),), 4.07 (m, 1H), 2.23 (s, 3H), 1.73 (m, 1H), 1.58 (m, 1H), 0.75 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.60, 166.37, 148.10, 138.68, 137.25, 136.98, 136.18, 134.47, 134.39, 132.01, 129.96, 128.79, 127.91, 127.33, 123.88, 121.93, 121.65, 117.00, 61.27, 45.51, 26.56, 21.33, 11.43. HRMS (EI) Calcd for $C_{29}H_{25}N_3O_3$ [M+1]: 464.1974, Found 464.1964.

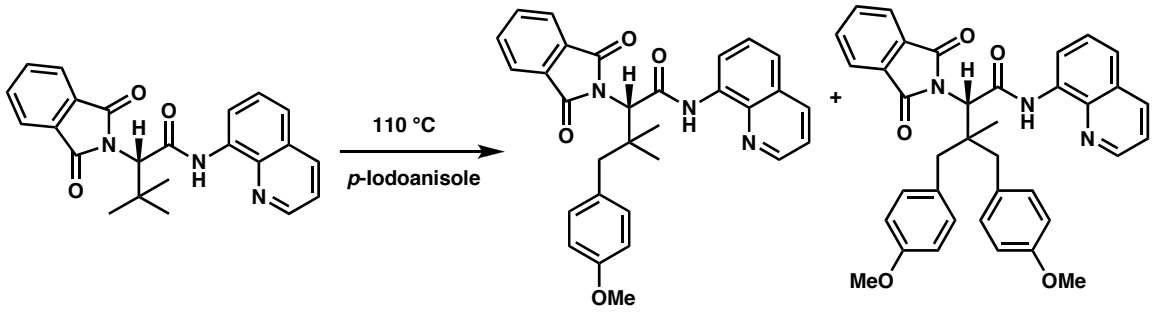
Conversion of 13 to 14.



13 14

Reaction of **13** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole (0.936 g, 4 mmol) at 110 °C for 2.5 h under solvent-free conditions gave **14,** 428 mg, in 87% yield as a colorless solid, mp 63-65 °C, $[\alpha]_D^{25}$ **=** -30.7° (*c* 2.7, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 3014, 2964, 2933, 1775, 1713, 1683, 1613, 1526, 1488, 1426, 1382, 1326, 1246, 1177, 1081, 1036, 865, 791, 752, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.69 (brs, 1H, NH), 8.88 (dd, J = 1.5 Hz & 4.5 Hz, 1H), 8.73 (t, J = 4.5 Hz, 1H), 8.13 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 7.86 (m, 2H), 7.70 (m, 2H), 7.49 (d, J = 5.0 Hz, 2H), 7.44 (dd, J = 4.0 Hz & 8.5 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 4.79 (d, J = 11.5 Hz, 1H), 3.70 (s, 3H), 3.40 (m, 1H), 2.93 (dd, J = 4.5 Hz & 13.5 Hz, 1H), 2.67 (dd, J = 9.0 Hz & 13.5 Hz, 1H),1.47 (m, 1H), 1.28 (m, 1H), 0.885 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.34, 167.00, 158.11, 148.75, 139.01, 136.38, 134.51, 134.45, 131.84, 131.78, 130.39, 128.13, 127.42, 123.90, 122.23, 121.87, 117.35, 113.85, 59.68, 55.36, 39.29, 35.19, 21.42, 9.16. HRMS (EI) Calcd for $C_{30}H_{27}N_3O_4$ [M+1]: 494.2080, Found 494.2073.

Conversion of 15 to 16 and 17.



15 16 17

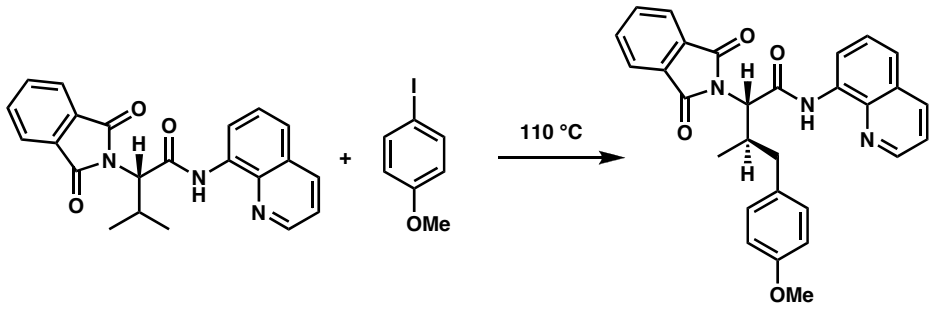
Reaction of **15** (0.387 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole (0.936 g, 4 mmol) at 110 °C for 3.5 h under solvent-free conditions gave **16** (197 mg, 40%) and **17** (239 mg, 40%) (1:1), in 80% yield.

Data for **16**: mp 78-80 °C, $[\alpha]_D^{25}$ **=** -12.6° (*c* 1.3, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 3047, 2964, 2933, 2856, 1769, 1717, 1611, 1526, 1511, 1486, 1426, 1378, 1326, 1260, 1245, 1177, 1104, 1079, 1034, 889, 825, 793, 758, 721. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (brs, 1H, NH), 8.76 (dd, J = 1.5 Hz & 7.5 Hz, 1H), 8.59 (dd, J = 1.5 Hz & 3.5 Hz, 1H), 8.10 (dd, J = 1.5 Hz & 8.5 Hz, 1H), 7.90 (m, 2H), 7.76 (m, 2H), 7.50 (m, 2H), 7.37 (dd, J = 4.5 Hz & 8.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.11 (s, 1H), 3.78 (s, 3H), 3.16 (d, J = 13.5 Hz, 1H), 2.97 (d, J = 13.5 Hz, 1H), 1.24 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.73, 166.34, 158.33, 148.50, 138.92, 136.42, 134.58, 134.44, 132.21, 131.86, 130.21, 128.11, 127.54, 123.95, 122.06, 121.78, 117.22, 113.48, 63.01, 55.40, 45.06, 39.99, 25.42, 25.26. HRMS (EI) Calcd for $C_{30}H_{27}N_3O_4$ [M+1]: 494.2080, Found 494.2066.

Data for **17**: solid, mp 108-110 °C**,** $[\alpha]_D^{25}$ **=** -14.0° (*c* 1.8, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 2995, 2964, 2933, 2836, 1771, 1717, 1611, 1526, 1511, 1486, 1426, 1378, 1326,

1246, 1179, 1073, 889, 825, 791, 754, 721. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (brs, 1H, NH), 8.80 (dd, J = 1.0 Hz & 8.0 Hz, 1H), 8.45 (dd, J = 1.5 Hz & 4.0 Hz, 1H), 8.10 (dd, J = 1.5 Hz & 8.0 Hz, 1H), 7.87 (m, 2H), 7.75 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.49 (dd, J = 1.0 Hz & 8.5 Hz, 1H), 7.32 (dd, J = 4.5 Hz & 8.5 Hz, 1H), 7.20 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.16 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.67 (d, J = 13.0 Hz, 1H), 3.64 (d, J = 12.5 Hz, 1H), 3.24 (d, J = 13.5 Hz, 1H), 2.65 (d, J = 13.5 Hz, 1H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.72, 166.75, 158.41, 158.21, 148.38, 138.84, 136.42, 134.56, 134.33, 132.53, 132.06, 131.86, 130.55, 130.06, 128.10, 127.56, 123.91, 122.05, 121.76, 117.09, 113.80, 113.38, 59.49, 55.40, 55.34, 43.37, 42.77, 42.43, 23.26. HRMS (EI) Calcd for $C_{37}H_{33}N_3O_5$ [M+1]: 600.2498, Found 600.2513.

Conversion of 18 to 19.



18 19

Reaction of **18** (0.373 g, 1 mmol) with AgOAc (250 mg, 1.5 mmol) and *p*-iodoanisole (0.936 g, 4 mmol) at 110 °C for 3.5 h under solvent-free conditions gave **19,** 407 mg, in 85% yield.

Data for **19**: solid, mp 60-62 °C, $[\alpha]_D^{25}$ **=** -40° (*c* 1.8, $CHCl_3$). FTIR (film) $\sqrt{}_{max}$ (cm^{-1}) 3340, 2964, 2923, 2852, 1773, 1713, 1611, 1528, 1513, 1426, 1382, 1326, 1246, 1177, 1086, 1077, 1034, 879, 825, 791, 719. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.66 (brs, 1H, NH), 8.85 (dd, J = 1.5 Hz & 4.5 Hz, 1H), 8.76 (t, J = 4.5 Hz, 1H), 8.14 (dd, J = 1.5 Hz & J = 8.5 Hz, 1H), 7.88 (m, 2H), 7.52 (m, 2H), 7.45 (dd, J = 4.0 Hz & 8.5 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 4.87 (d, J = 10.5 Hz, 1H), 3.75 (m, 3H), 3.35 (m, 1H), 3.16 (dd, J = 3.5 Hz & J = 13.5 Hz, 1H), 2.39 (dd, J = 9.5 Hz & J = 13.0 Hz, 1H), 0.877 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.28, 166.75, 158.23, 148.76, 138.98, 136.45, 134.54, 134.39, 131.80, 131.76, 130.59, 128.16, 127.48, 123.93, 122.28, 121.90, 117.31, 113.88, 61.70, 55.43, 39.91, 34.67, 15.97. HRMS (EI) Calcd for $C_{30}H_{27}N_3O_4$ [M+1]: 480.1923, Found 480.1941.