Molybdenum Catalyzed Asymmetric Allylation of 3-alkyl oxindoles: Application to the formal total synthesis of (-) physostigmine

Barry M. Trost,* and Yong Zhang

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Experimental section

All reactions were carried out in oven-dried flasks or pyrex test tubes under a positive pressure of nitrogen, argon for Mo-catalyzed AAA. Anhydrous solvents were obtained from elution through alumina column, except for THF, which was distilled from Na-benzophenone ketyl. All reagents were purchased commercially and used without further purification unless stated otherwise. TLC was performed on precoated glass plates (Merck), flash chromatography with silica gel 60, 230-400 mesh. Enantiomeric excesses were determined by HPLC on Tsp Spectra series P100/UV100 apparatus with a chiral stationary phase (see details where applies). Melting points (uncorrected) were determined in open capillary tubes using a Thomas-Hoover apparatus. ¹H-NMR (0 ppm as internal standard) and ¹³C-NMR (77 ppm as internal standard) spectra were recorded on Varian Mercury 400 (400 MHz for ¹H-NMR) and on Unity Inova 500 (500 MHz for ¹H-NMR). IR spectra (cm⁻¹) were obtained with a Perkin-Elmer FT-IR Paragon 500 spectrometer, either using neat sample on NaCl pad (for oils and liquids), or preparing a KBr pellet.

General procedure for preparing oxindoles 8a, 8b, 8c, 8d, 14, 16, 18a, 18b, 18c, and 20 .

N-protected oxindole (3 mmol)¹ was dissolved in THF (25 mL) and HMPA (5mL), and to this solution was added dropwise a solution of Lithium bis(trimethylsilyl)amide (3 mmol) in THF (3.5 mL) at -78 °C under N₂. The resulting solution was stirred at -78 °C for 1h, and then the appropriate electrophile (4.5 mmol) was added dropwise with stirring. The reaction was quenched after 1h with acetic acid (1mL, 5% in THF) and submitted to aqueous work-up and column chromatography to give pure mono-alkylated oxindole in 50-65% yield.

General procedure for preparing oxindoles 4, 6a, 6b, 10a, 10b, and 22

Commercially available indole was N-alkylated using Heaney's method (KOH, DMSO),² and then oxidized to the corresponding oxindole (DMSO, conc. HCl).³

3-allyl-3-benzyl-1-methylindolin-2-one(8a)

Isolated as white solid identical with previously reported material.⁵

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3057, 2925, 1713, 1612, 1494, 1469, 1375, 1349, 1253, 1127, 1089, 750, 700; ^1H NMR (500 MHz, CDCl_3): δ 7.28–7.14 (m, 6H), 6.90(t, $J=7.5$, 1H), 6.76–6.70(m,

2H), 3.70 (dd, $J=4.8$, 1H), 3.49(dd, $J=4$, 14, 1H) 3.15 (s, 3H), 2.87 (dd, $J=8$, 14, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 177.0, 144.1, 137.9, 129.3, 128.3, 128.2, 127.9, 126.6, 124.5, 121.9, 107.8, 47.0, 36.8, 26.1;

3-benzyl-1-methoxymethyl-1,3-dihydro-indol-2-one(8b)

Isolated as white solid. Mp: 67–69°C

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3050, 2926, 1721, 1613, 1487, 1467, 1348, 1232, 1188, 1120, 1090, 914, 752; ^1H NMR (500 MHz, CDCl_3): δ 7.25–7.17(m, 4H), 7.13–7.09(m, 2H), 6.98(dt, $J=1.7.5$,

1H), 6.93(d, $J=7.5$, 1H), 6.90(d, $J=7.5$, 1H), 5.08(d, $J=11$, 1H), 5.00(d, $J=11$, 1H), 3.81(dd, $J=4.8$, 1H), 3.47(dd, $J=4$, 14, 1H), 3.07(s, 3H), 3.03(dd, $J=8$, 14, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 142.4, 137.3, 129.4, 128.2, 128.0, 127.6, 126.6, 124.5, 122.5, 109.3, 71.1, 55.8, 47.2, 36.5; HRMS—EI (m/z): calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$: 267.1259; found: 267.1256

1,3-dibenzyl-1,3-dihydro-indol-2-one (8c)

Isolated as white solid. Mp: 95-96°C

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3060, 3030, 2922, 1712, 1613, 1488, 1466, 1361, 1186, 751, 698; ^1H NMR (500 MHz, CDCl_3): δ = 7.23-7.18(m, 6H), 6.96-6.91(m, 3H), 6.96-6.91(m, 4H), 6.54 (d, J = 7.5, 1H), 5.03 (d, J = 16, 1H), 4.63 (d, J = 16, 1H), 3.85 (dd, J = 4, 8, 1H), 3.50(dd, J = 4, 14, 1H), 3.13 (dd, J = 8, 14, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ = 176.9, 143.3, 137.3, 135.5, 129.6, 128.6, 128.2, 128.1, 127.9, 127.3, 126.9, 126.6, 124.4, 122.1, 109.0, 47.0, 43.5, 36.4; Anal calcd for $\text{C}_{22}\text{H}_{19}\text{NO}$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.14; H, 6.13; N, 4.32.

3-isopropyl-1-methylindolin-2-one(10a)

Isolated as yellow oil

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3081, 2921, 2251, 1715, 1612, 1489, 1467, 1436, 1365, 1210, 1178, ; ^1H NMR (500 MHz, CDCl_3): 7.27 (dt, J = 7.5, 1.5, 1H), 7.21 (dd, J = 7.5, 1.5, 1H), 7.05 (dt, J = 7.5, 1, 1H), 6.81 (d, J = 7.5, 1H), 3.18 (s, 3H), 2.67-2.58 (m, 2H), 2.20(sept, J = 7, 1H), 0.98(d, J = 7, 3H), 0.73(d, J = 7, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 179.4, 144.2, 132.9, 130.8, 127.6, 123.7, 122.0, 118.2, 107.5, 56.3, 39.6, 34.7, 25.8, 17.4, 17.2,; HRMS—EI (m/z): calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: 229.1467; found: 229.1476

(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetonitrile(12a)

Isolated as white solid identical with previously reported material. ⁴

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2918, 1713, 1612, 1469, 1374, 1347 1089; ^1H NMR (400 MHz, CDCl_3): δ = 7.53 (dd, J = 7.5, 1.5, 1H), 7.37 (dt, J = 7.5, 1.5, 1H), 7.14 (dt, J = 7.5, 1, 1H), 6.89 (d, J = 7.5, 1H), 3.68(dd, J = 5, 9, 1H), 3.21(s, 3H), 3.15 (dd, J = 5, 16, 1H), 2.69(dd, J = 10, 16, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 174.2, 144.2, 129.4, 125.7 124.2, 123.2, 117.2, 108.6, 41.3, 26.5, 19.0

2-(1-allyl-2-oxoindolin-3-yl)acetonitrile(12b)

Isolated as yellow oil.

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3059, 2927, 1713, 1613, 1489, 1467, 1362, 1204, 1171, 1101, 928, 752 ;

^1H NMR (400 MHz, CDCl_3): 7.51 (dd, $J = 7.5, 1.5$, 1H), 7.31 (dt, $J = 7.5, 1.5$, 1H), 7.13 (dt, $J = 7.5$, 1, 1H), 6.88 (d, $J = 7.5$, 1H), 5.88- 5.77 (m, 1H), 5.28- 5.22 (m, 2H), 4.38-4.34(m, 2H), 3.71 (dd, $J = 4.5$, 9, 1H), 3.14 (dd, $J = 4.5$, 9, 1H), 2.74(dd, $J = 9, 17$, 1H); ^{13}C NMR (125 MHz,

CDCl_3) $\delta = 174.0$, 143.3, 130.7, 129.3, 125.6, 124.2, 123.1, 117.9, 117.1, 109.5, 42.341.3, 19.1; HRMS—EI (m/z): calcd for $\text{C}_{13}\text{H}_{12}\text{NO}$: 212.0950; found: 212.0952

3-(but-2-ynyl)-1-methylindolin-2-one(18a)

Isolated as yellow solid. Mp:52-53°C

IR (film) $\nu_{\max}/\text{cm}^{-1}$:3054, 2918, 1714, 1613, 1494, 1469, 1375, 1352, 1250, 1088, 1019, 751;

^1H NMR (500 MHz, CDCl_3) : $\delta = 7.52$ (dd, $J = 7.5, 1.5$, 1H), 7.31 (dt, $J = 7.5, 1.5$, 1H), 7.27 (dt, $J = 7.5$, 1, 1H), 6.85 (d, $J = 7.5$, 1H), 3.50(dd, $J = 4.5$, 9.5, 1H), 3.21 (s, 3H), 2.92(qdd, $J = 2.5$, 9.5, 16, 1H), 2.48(qdd, $J = 2.5$, 4.5, 16, 1H), 1.76 (t, $J = 2.5$, 3H); ^{13}C NMR (125 MHz, CDCl_3)

$\delta = 176.3$, 144.2, 128.7, 128.4, 124.6, 122.4, 107.9, 77.5, 75.4, 44.6, 26.2, 20.8, 3.5 HRMS—EI (m/z): calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$: 199.0998; found: 199.0991

3-(but-2-ynyl)-1-(methoxymethyl)indolin-2-one(18b)

Isolated as yellow solid. Mp:67-69°C

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2926, 1722, 1621, 1482, 1467, 1347, 1300, 1238, 1067; ^1H NMR (500

MHz, CDCl_3): $\delta = 7.49$ (dd, $J = 7.5, 1.5$, 1H), 7.33 (dt, $J = 7.5, 1.5$, 1H), 7.14 (dt, $J = 7.5$, 1, 1H), 7.06 (d, $J = 7.5$, 1H), 5.21 (d, $J = 11$, 1H), 5.12(d, $J = 11$, 1H), 3.61(dd, $J = 4.5$, 8, 1H), 3.36

(s, 3H), 2.95(qdd, $J = 2.5$, 4.5, 16.5, 1H), 2.68 (qdd, $J = 2.5$, 8, 16.5, 1H), 1.73(t, $J = 2.5$, 3H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 177.0$, 142.5, 128.3, 127.7, 124.3, 123.0, 109.4, 77.6 77.6, 74.9, 71.2, 56.0, 44.9, 20.8, 3.5; HRMS—EI (m/z): calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$: 229.1103; found: 229.1102

1-benzyl-3-(but-2-ynyl)indolin-2-one(18c)

Isolated as white solid. Mp: 112-113 °C

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3028, 2917, 1711, 1613, 1488, 146, 1361, 1167, 750; ^1H NMR (500 MHz, CDCl_3): δ = 7.45 (dd, J = 7.5, 1.5, 1H), 7.33-7.24 (m, 5H), 7.17 (dt, J = 7.5, 1.5, 1H), 7.04 (dt, J = 7.5, 1, 1H), 6.69 (d, J = 7.5, 1H), 5.07 (d, J = 15.8, 1H), 4.67 (d, J = 15.8, 1H),

3.60 (dd, J = 4.5, 8, 1H), 3.36 (s, 3H), 2.95 (qdd, J = 2.5, 4.5, 16.5, 1H), 2.71 (qdd, J = 2.5, 8, 16.5, 1H), 1.73 (t, J = 2.5, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 176.5, 143.5, 135.8, 128.7, 128.2, 128.1, 127.5, 127.2, 124.2, 122.4, 108.9, 77.5, 75.0, 44.6, 43.7, 20.8, 3.5; HRMS—EI (m/z): calcd for $\text{C}_{19}\text{H}_{17}\text{NO}$: 275.1310; found: 275.1317

1-methyl-3-(3-(trimethylsilyl)prop-2-ynyl)indolin-2-one(20)

Isolated as yellow oil

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2958, 2177, 1710, 1614, 1494, 1470, 1422, 1375, 1351, 1250, 1126, 1089, 843, 750 ^1H NMR (400 MHz, CDCl_3): δ = 7.51 (dd, J = 7.5, 1.5, 1H), 7.26 (dt, J = 7.5, 1.5, 1H), 7.05 (dt, J = 7.5, 1, 1H), 6.80 (d, J = 7.5, 1H), 3.52 (dd, J = 4.5, 9, 1H), 3.19 (s, 3H), 2.98 (dd, J = 4.5, 17, 1H), 2.52 (dd, J = 9, 17, 1H), 0.57 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ = 176.1, 144.3, 128.3, 128.1, 124.4, 122.4, 107.9, 103.2, 86.9, 44.2, 26.2, 22.0, -0.1; HRMS—EI (m/z): calcd for $\text{C}_{15}\text{H}_{19}\text{NOSi}$: 257.1235; found: 257.1225

3-(2-(tert-butyldimethylsilyloxy)ethyl)-1-methylindolin-2-one(22)

Isolated as pale yellow oil

IR (film) $\nu_{\max}/\text{cm}^{-1}$: ^1H NMR (500 MHz, CDCl_3): δ = 7.79-7.24 (m, 2H), 7.04 (dt, J = 7.5, 1.5, 1H), 6.80 (d, J = 7.5, 1H), 3.88-3.76 (m, 2H), 3.64 (t, J = 8, 1H), 3.19 (s, 3H), 2.19 (qd, J = 8, 17, 1H), 2.04 (qd, J = 8, 17, 1H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 178.1, 144.2, 129.1, 127.7, 124.0, 122.1, 107.8, 59.8, 42.2, 33.4, 26.1, 25.9, 25.6, 18.2, -5.4, -5.5; HRMS—EI (m/z): calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_2\text{Si}$: 345.2124; found: 345.2141

General procedure for Mo catalyzed AAA reactions.

Preparation of the active catalyst solution

A solution of freshly distilled and degassed THF (0.3 mL) of (*R,R*) ligand **2** (2.4 mg, 0.015 mmol) and $[(\eta^3\text{-C}_7\text{H}_8)\text{Mo}(\text{CO})_3]$ (1.4mg, 0.01 mmol) was stirred at 60 °C in a sealed pyrex test tube under Ar atmosphere. The solution turned deep purple after 3-5 min, indicating successful generation of the active catalyst. Further heating causes black precipitation and decomposition. The active catalyst is very sensitive to oxygen and moisture and should be used immediately after generation.

Preparation of nucleophile

A pyrex test tube containing 0.1 mmol of oxindole was transferred to the dry box and to it 0.2mmol of LiOtBu was added. The test tube was sealed, taken out of the dry box, and to it was added 0.7 mL of degassed THF. The resulting solution was stirred for 5 min before a solution of the active catalyst solution was added via cannula, followed by the addition of allyl *tert*-Butyl carbonate (0.12 mmol) via syringe. The resulting solution was stirred at r.t. under Ar for 3-6 h until TLC indicates complete consumption of the starting oxindole. The reaction mixture was then concentrated and purified through silica gel to give the desired product.

3-Allyl-1,3-dimethyl-1,3-dihydro-indol-2-one (5)

Isolated as colorless oil identical to previously reported material.⁶

Chiral HPLC, OJ-column, flow rate 1.0 mL/min, 90/10 heptane / *i*-PrOH,

t_A (major) = 9.70 min, t_B (minor) = 10.90min; $[\alpha]_D^{24} = -33.3^\circ$ (c 1.0, CHCl_3);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3077, 2929, 2835, 1715, 1643, 1600, 1504, 1470, 1373, 1291, 1235, 1204, 1177, 1122, 1037, 920, 741; ^1H NMR (400 MHz, CDCl_3): δ = 6.92 – 6.72 (m, 3H), 5.50 – 5.40 (m, 1H), 5.02 – 4.91 (m, 2H), 3.80 (s, 3H), 3.17 (s, 3H), 2.54 – 2.44 (m, 2H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 180.1, 156.2, 136.9, 135.2, 132.8, 118.9, 111.8, 110.9, 108.3, 56.0, 48.9, 42.6, 26.4, 23.0.

3-Allyl-1,3-dimethyl-1,3-dihydro-indol-2-one(7a)

Isolated as colorless oil identical to previously reported material.⁷

Chiral HPLC, AD-column, flow rate 1.0 mL/min, 96/4 heptane / *i*-PrOH, t_A (major)

= 8.7 min, t_B (minor) = 9.4 min; $[\alpha]_D^{24} = -9.7^\circ$ (c 0.9, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3046, 2974, 2924, 1717, 1614, 1486, 1460, 1405, 1305, 1240; ^1H NMR (500 MHz, CDCl_3): δ = 7.27 (dt, $J = 7.5, 1.5$, 1H), 7.20 (dd, $J = 7.5, 1.5$, 1H), 7.06 (dt, $J = 7.5$, 1, 1H), 6.83 (d, $J = 7.5$, 1H), 5.41- 5.49 (m, 1H), 4.99 (dm, $J = 16$, 1H), 4.92 (dm, $J = 16$, 1H), 3.20 (s, 3H), 2.54-2.49 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 180.2, 143.1, 133.6, 132.5, 127.7, 122.8, 122.3, 118.6, 107.9, 48.2, 42.4, 26.1, 22.7;

3-Allyl-1-benzyl-3-methyl-1,3-dihydro-indol-2-one(7b)

Isolated as colorless oil

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3058, 2967, 1711, 1607, 1486, 1451, 1350, 1179; $[\alpha]_D^{24} = -26.9$ (c 1.5, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ = 7.34-7.19 (m, 6H), 7.13 (dt, $J = 7.5, 1.5$, 1H), 7.02 (dt, $J = 7.5, 1.5$, 1H), 6.74 (d, $J = 7.5$, 1H), 5.41-5.51 (m, 1H), 4.92-5.06 (m, 3H), 4.81 (d, $J = 15$, 1H), 2.54-2.64 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 180.5, 142.5, 136.2, 133.8, 132.9, 128.9, 127.9, 127.7, 127.5, 123.2, 122.6, 119.1, 109.3, 48.6, 43.9, 42.8, 23.4; HRMS—EI (m/z): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}$: 277.1467; found: 277.1473

3-allyl-3-benzyl-1-methylindolin-2-one(9a)

Isolated as white solid. Mp: 48-50°C

Chiral HPLC, OD-column, flow rate 0.8 mL/min, 98:2 heptane / *i*-PrOH, t_A (major) = 6.58 min, t_B (minor) = 7.06 min] $[\alpha]_D^{24} = 22.7^\circ$ (c 2.5, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3058, 2916, 1711, 1612, 1494, 1470, 1377, 1356, 1251; ^1H NMR (500 MHz, CDCl_3): δ = 7.19 – 7.55 (m, 2H), 7.06-7.00 (m, 4H), 6.85-6.82 (m, 2H), 6.58 (d, $J = 7.5$, 1H), 5.48-5.38 (m, 1H), 5.03 (dm, $J = 16$, 1H), 4.91 (dm, $J = 16$, 1H), 3.15 (d, $J = 13$, 1H), 3.04 (d, $J = 13$, 1H), 2.95 (s, 3H), 2.73 (dd, $J = 9, 7.5$, 1H), 2.64 (dd, $J = 9, 7.5$, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ = 178.6, 143.7, 135.8, 132.4, 130.7, 129.9, 127.8, 127.5, 126.4, 123.8, 122.0, 118.7, 107.6, 54.4, 43.3, 41.2, 25.8;

3-Allyl-3-benzyl-1-methoxymethyl-1,3-dihydro-indol-2-one(9b)

Isolated as colorless oil

Chiral HPLC, OD-H-column, flow rate 0.6 mL/min, 97/3 heptane / *i*-PrOH, t_A (major) = 10.85 min, t_B (minor) = 11.67 min; $[\alpha]_D^{24} = 35.2^\circ$ (*c* 1.5, CHCl₃); IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3030, 2935, 1719, 1612, 1488, 1467, 1352, 1090; ¹H NMR (400 MHz, CDCl₃): δ = 7.27 – 7.25 (d, *J* = 7.5, 1H), 7.20 (t, *J* = 7.5, 1H), 7.11 (t, *J* = 7.5, 1H), 7.05–6.99 (m, 3H), 6.85–6.82 (m, 3H), 5.48–5.38 (m, 1H), 5.04 (dd, *J* = 17.2, 1H), 4.92 (dd, *J* = 10.1, 1H), 4.89 (s, 3H), 3.17 (d, *J* = 13, 1H), 3.11 (d, *J* = 13, 1H), 2.85 (s, 3H), 2.74–2.67 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 179.0, 142.0, 135.8, 132.2, 130.3, 129.9, 128.0, 127.7, 126.6, 123.9, 122.5, 119.0, 109.3, 71.1, 55.6, 55.0, 43.2, 42.0; HRMS—EI (*m/z*): calcd for C₂₀H₂₁NO: 307.1572; found: 307.1568

3-Allyl-1,3-dibenzyl-1,3-dihydro-indol-2-one (9c)

Isolated as colorless oil

Chiral HPLC, OD-H-column, flow rate 1 mL/min, 90/10 heptane / *i*-PrOH, t_A (major) = 9.31 min, t_B (minor) = 10.12 min; $[\alpha]_D^{24} = 53.4^\circ$ (*c* 2.7, CHCl₃); IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3030, 2918, 1711, 1612, 1488, 1466, 1364, 1170; ¹H NMR (500 MHz, CDCl₃): δ = 7.30 – 7.28 (m, 1H), 7.15 – 7.10 (m, 5H), 7.07 – 7.03 (m, 5H), 6.88 (d, *J* = 8.0, 1H), 6.67 (d, *J* = 7.5, 1H), 6.39 – 6.36 (m, 1H), 5.52 – 5.43 (m, 1H), 5.06 (dd, *J* = 18, 1.5, 1H), 4.95 (dd, *J* = 10, 2, 1H), 4.89 (d, *J* = 16.0, 1H), 4.52 (d, *J* = 16.0, 1H), 3.24 (d, *J* = 13.0, 1H), 3.15 (d, *J* = 13.0, 1H), 2.81 – 2.69 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 178.4, 142.9, 135.9, 135.3, 136.2, 132.3, 130.7, 130.1, 128.5, 127.7, 127.0, 126.6, 126.5, 123.7, 122.0, 119.0, 109.0, 54.6, 43.3, 43.0, 42.2; HRMS—EI (*m/z*): calcd for C₂₅H₂₃NO: 353.1780; found: 353.1778

3-allyl-3-isopropyl-1-methylindolin-2-one (11a)

Isolated as colorless oil

Chiral HPLC, AD-column, flow rate 1.0 mL/min, 95:5 heptane / *i*-PrOH, t_A (major) = 8.30 min, t_B (minor) = 9.14 min; $[\alpha]_D^{24} = -57.7^\circ$ (*c* 2.0, CHCl₃); IR (film) $\nu_{\max}/\text{cm}^{-1}$: 3081, 2921, 2251, 1715, 1612, 1489, 1467, 1436, 1365, 1210, 1178; ¹H NMR (500 MHz, CDCl₃): 7.27 (dt, *J* = 7.5, 1.5, 1H), 7.21 (dd, *J* = 7.5, 1.5, 1H), 7.05 (dt, *J* = 7.5, 1, 1H), 6.81 (d, *J* = 7.5, 1H), 5.35–5.26 (m, 1H), 4.95 (dm, *J* = 15, 1H), 4.82 (dm, *J* = 10, 1H), 3.18 (s, 3H), 2.67–2.58 (m, 2H), 2.20 (sept, *J* = 7, 1H), 0.98 (d, *J* = 7, 3H),

0.73(d, $J=7$, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 179.4, 144.2, 132.9, 130.8, 127.6, 123.7, 122.0, 118.2, 107.5, 56.3, 39.6, 34.7, 25.8, 17.4, 17.2,;

3-allyl-1-benzyl-3-isopropylindolin-2-one(11b)

Isolated as colorless oil

Chiral HPLC, AD-column, flow rate 1.0 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) = 6.15min, t_B (minor) = 6.91 min] $[\alpha]_D^{24} = -69.7^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3062, 2965, 1710, 1611, 1488, 1466, 1360, 1176, ; ^1H NMR (500 MHz, CDCl_3): 7.30-7.20(m, 6H), 7.14 (dt, $J=1$, 7.5, 1H), 7.01(dt, $J=1$, 7.5, 1H), 6.69 (d, $J=7.5$, 1H), 5.38-5.28 (m, 1H), 4.99 (dm, $J=10$, 1H), 4.94 (d, $J=15$, 1H), 4.88 – 4.83 (m, 2H), 2.71–2.64(m, 2H), 2.25 (sept, $J=7$, 1H), 1.00(d, $J=7$, 3H), 0.79(d, $J=7$, 3H) ; ^{13}C NMR (125 MHz, CDCl_3) δ = 179.4, 143.4, 136.1, 132.9, 130.8, 128.6, 127.6, 127.5, 127.4, 123.8, 122.0, 118.5, 108.7, 56.2, 43.6, 39.8, 34.9, 17.5, 17.4,; HRMS—EI (m/z): calcd for $\text{C}_{21}\text{H}_{23}\text{NO}$: 305.1780; found: 305.1793

(3-Allyl-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetonitrile(13a)

Isolated as colorless oil identical to previously reported material.⁸

Chiral HPLC, AD-column, flow rate 1 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) = 8.88 min, t_B (minor) = 9.83 min]: $[\alpha]_D^{24} = -40.9^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2922, 1713, 1612, 1493, 1470, 1376, 1087; ^1H NMR (400 MHz, CDCl_3): δ = 7.43 (dd, $J=7.5, 1.5$, 1H), 7.33 (dt, $J=7.5, 1.5$, 1H), 7.13 (dt, $J=7.5$, 1, 1H), 6.87 (d, $J=7.5$, 1H), 5.46-5.34 (m, 1H), 5.07 (dm, $J=16$, 1H), 4.98(dm, $J=7$, 1H), 3.21(s, 3H), 2.85 (d, $J=7$, 1H), 2.68-2.57 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 176.3, 143.3, 130.5, 129.3, 128.8, 123.5, 123.2, 120.3, 116.4, 108.6, 48.7, 40.2, 26.4, 25.0

2-(1,3-diallyl-2-oxoindolin-3-yl)acetonitrile(13b)

Isolated as colorless oil

Chiral HPLC, AD-column, flow rate 1.0 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) = 8.26 min, t_B (minor) = 9.10 min] $[\alpha]_D^{24} = -57.7^\circ$ (c 2.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$:

3081,2921, 2251,1715, 1612, 1489, 1467, 1436, 1365, 1210, 1178, ; ^1H NMR (400 MHz, CDCl_3): 7.45 (dd, $J = 7.5, 1.5$, 1H), 7.32 (dt, $J = 7.5, 1.5$, 1H), 7.13 (dt, $J = 7.5$, 1, 1H), 6.87 (d, $J = 7.5$, 1H), 5.85- 5.75 (m, 1H), 5.48- 5.36 (m, 1H), 5.24 (dm, $J = 9$, 1H), 5.21 (t, $J = 2$, 1H), 5.10 (dm, $J = 15$, 1H), 5.01(dm, $J = 10$, 1H), 4.41 (tdd, $J = 2, 5, 16$, 1H), 4.29 (tdd, $J = 2, 5, 16$, 1H), 2.86(d, $J = 16$, 1H), 2.76-2.61 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 176.1, 142.5, 130.8, 130.5, 129.2, 128.7, 123.5, 123.0, 120.5, 117.8, 116.3, 109.5, 48.8, 42.4, 40.4, 25.1$; HRMS—EI (m/z): calcd for $\text{C}_{16}\text{H}_{16}\text{NO}$: 252.1263; found: 252.1261

***tert*-butyl 2-((3-allyl-1-methyl-2-oxoindolin-3-yl)methyl)phenylcarbamate(15)**

Isolated as white solid. Mp:157-161°C

Chiral HPLC, AD-column, flow rate 1 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) = 6.06 min, t_B (minor) = 7.88 min $[\alpha]_D^{24} = 144.5^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$:; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.54$ (s, b, 1H), 7.47(d, $J = 7$, 1H), 7.36(d, $J = 7$, 1H), 7.24(t, $J = 7.5$, 1H), 7.14(t, $J = 7.5$, 1H), 7.05(t, $J = 7$, 1H), 6.68-6.63(m, 2H), 6.49(d, $J = 7.5$, 1H), 5.47-5.38(m, 1H), 5.04(dm, $J = 16$, 1H), 4.93(dm, $J = 10$, 1H), 3.33(d, $J = 14$, 1H), 2.99(d, $J = 14$, 1H), 2.94(s, 3H), 2.78- 2.69 (m, 2H), 1.57 (s, 9H); ^{13}C NMR (125MHz, CDCl_3) $\delta = 179.9, 154.1, 143.6, 136.2, 131.9, 130.7, 128.2, 127.1, 124.7, 123.6, 123.5, 122.6, 119.1, 108.2, 79.8, 54.7, 42.2, 37.4, 28.4, 26.0$;

3-Allyl-1-benzyl-3-(3-methyl-but-2-enyl)-1,3-dihydro-indol-2-one(17)

Isolated as colorless oil

$[\alpha]_D^{24} = 29.9^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3059, 2976, 2913, 1713, 1612, 1488, 1466, 1352, 1168, 994, 919, 750; ^1H NMR (500 MHz, d_6 -PhH): $\delta = 7.16 - 6.79$ (m, 8H), 6.40 (d, $J = 11$, 1H), 5.59 – 5.48 (m, 1H), 5.05 – 4.84 (m, 4H), 4.44 (d, $J = 19$, 1H), 2.85 – 2.69 (m, 2H), 2.52 – 2.42 (m, 2H), 1.51 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, d_6 -PhH) $\delta = 178.7, 143.6, 136.7, 135.0, 133.0, 131.8, 128.7, 127.7, 127.4, 123.3, 121.9, 118.7, 118.6, 108.8, 52.9, 43.4, 41.9, 36.3, 25.8, 18.0$; HRMS—EI (m/z): calcd for $\text{C}_{23}\text{H}_{25}\text{NO}$: 277.1936; found: 331.1947

1-Benzyl-3-(3-hydroxypropyl)-3-(3-methylbut-2-enyl)indolin-2-one

Oxindole **17** (21 mg, 63 μmol) was dissolved in anhydrous THF (0.18 mL). The reaction mixture was stirred at room temperature when 9-BBN (0.14 mL, 70 μmol , 0.5 M solution in THF). The solution so obtained was stirred at 50°C overnight. After cooling to 0°C, 3M aqueous NaOH (0.15 mL) was added followed by the careful addition of 30% aqueous H_2O_2 (0.15 mL). The resultant solution was stirred at ambient temperature (8 h) whereupon it was poured into brine (10 mL), and EtOAc (5 mL). The layers were separated and the aqueous phase was extracted further with EtOAc (2 x 5 mL). The combined organic portions were dried (MgSO_4), filtered and concentrated. Chromatography on silica (10% EtOAc / hexane) revealed pure alcohol **184** as a colorless oil. Isolated as colorless oil (11.5 mg, 33 μmol , 88%). Chiral HPLC, OD-H-column, flow rate 0.8 mL/min, 90/10 heptane / *i*-PrOH, t_{A} (major) = 11.70 min, t_{B} (minor) = 13.57 min]: $[\alpha]_{\text{D}}^{24} = 48.8^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3402, 3061, 2936, 2828, 1602, 1540, 1495, 1486, 1445, 1423, 1266, 1212, 1132, 1091, 1033; ^1H NMR (400 MHz, CDCl_3): δ = 7.31 – 7.01 (m, 8H), 6.66 (d, J = 6.4, 1H), 5.13 (d, J = 12.4, 1H), 4.79 – 4.78 (m, 2H), 4.66 (d, J = 12.4, 1H), 3.51 – 3.46 (m, 2H), 2.67 – 2.63 (m, 1H), 2.52 – 2.48 (m, 1H), 2.09 – 2.03 (m, 1H), 1.95 – 1.90 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.34 (bs, 1H), 1.31 – 1.25 (m, 1H), 1.18 – 1.13 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 180.2, 143.3, 136.3, 135.6, 132.2, 128.9, 127.9, 127.7, 127.5, 123.3, 122.6, 118.2, 109.2, 62.9, 53.1, 43.9, 37.1, 33.6, 27.9, 26.1, 18.3; Anal calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2$: C, 79.05; H, 7.70; N, 4.07. Found: C, 79.06; H, 7.57; N, 4.07.

3-allyl-3-(but-2-ynyl)-1-methylindolin-2-one(19a)

Isolated as colorless oil
Chiral HPLC, AD-column, flow rate 1.0 mL/min, 90:10 heptane / *i*-PrOH, t_{A} (major) = 5.20 min, t_{B} (minor) = 6.48 min $[\alpha]_{\text{D}}^{24} = -88.5^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3072, 2910, 1713, 1613, 1493, 1470, 1375, 1352, 1251, 1080, ; ^1H NMR (500 MHz, CDCl_3): δ = 7.40 (dd, J = 7.5, 1.5, 1H), 7.27 (dt, J = 7.5, 1.5, 1H), 7.08 (dt, J = 7.5, 1, 1H), 6.83 (d, J = 7.5, 1H),

5.41- 5.31 (m, 1H), 5.00 (dm, $J=16$, 1H), 4.88 (dm, $J=16$, 1H), 3.20(s, 3H), 2.73 (tdd, $J=1,7,14$, 1H), 2.67 (qd, $J=2.5$, 16, 1H), 2.60 (tdd, $J=1,7,14$, 1H), 2.44 (qd, $J=2.5$, 16, 1H), 1.73(t, $J=2.5$, 3H) ; ^{13}C NMR (125 MHz, CDCl_3) $\delta=178.5$, 143.6, 132.2, 131.2, 128.1, 123.6, 122.3, 118.8, 107.7, 78.2, 74.1, 51.2, 40.0, 27.1, 26.1, 3.5; HRMS—EI (m/z): calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$: 239.1310; found: 239.1305

3-allyl-3-(but-2-ynyl)-1-(methoxymethyl)indolin-2-one(19b)

Isolated as colorless oil

Chiral HPLC, AD-column, flow rate 1.0 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) =

5.43min, t_B (minor) = 7.24 min $[\alpha]_D^{24} = -83.6^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3061,

2929, 1720, 1613, 1487, 1467, 1352, 1299, 1240, 1183, 1090 ; ^1H NMR (500 MHz,

CDCl_3): $\delta=7.38$ (dd, $J=7.5,1.5$, 1H), 7.28 (dt, $J=7.5,1.5$, 1H), 7.11 (dt, $J=7.5$, 1, 1H), 7.03 (d, $J=7.5$, 1H),

5.41- 5.31 (m, 1H), 5.12 (d, $J=2$, 2H), 5.02 (dm, $J=16$, 1H), 4.90 (dm, $J=16$, 1H), 3.31(s, 3H), 2.74-2.51(m,

4H), 1.67(t, $J=2.5$, 3H) ; ^{13}C NMR (125 MHz, CDCl_3) $\delta=179.2$, 141.9, 132.2, 130.7, 128.3, 123.7, 122.9, 119.2,

109.4, 78.4, 74.0, 71.3, 56.2, 52.1, 40.5, 27.5, 3.5; HRMS—EI (m/z): calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_2$: 269.1416; found:

269.1414

3-allyl-1-benzyl-3-(but-2-ynyl)indolin-2-one(19c)

Isolated as colorless oil

Chiral HPLC, OD-column, flow rate 0.8 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) =

7.84min, t_B (minor) = 8.95 min $[\alpha]_D^{24} = -41.3^\circ$ (c 1.0, CHCl_3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3060,

2918, 1714, 1613, 1488, 1466, 1364, 1173, 751; ^1H NMR (500 MHz, CDCl_3): $\delta=7.37$ (d,

$J=7.5$, 1H), 7.32-7.13 (m, 5H), 7.15 (t, $J=7.5$, 1H), 7.04 (t, $J=7.5$, 1H), 6.68 (d, $J=7.5$, 1H), 5.46- 5.35 (m,

1H), 5.05(d, $J=16$, 1H), 4.97 (d, $J=16$, 1H), 4.92 (d, $J=10$, 1H), 4.86 (d, $J=16$, 1H), 2.76-2.69(m, 2H), 2.67-

2.56(m, 2H), 1.67(t, $J=2.5$, 3H) ; ^{13}C NMR (125 MHz, CDCl_3) $\delta=178.5$, 142.8, 135.8, 132.3, 131.2, 128.7,

128.0, 127.4, 127.3, 123.5, 122.4, 119.0, 108.9, 78.2, 74.1, 51.5, 43.7, 40.5, 27.2, 3.5; HRMS—EI (m/z): calcd

for $\text{C}_{22}\text{H}_{21}\text{NO}$: 315.1623; found: 315.1609

3-allyl-1-methyl-3-(3-(trimethylsilyl)prop-2-ynyl)indolin-2-one(21)

isolated as colorless oil

Chiral HPLC, AD-column, flow rate 0.6 mL/min, 90:10 heptane / *i*-PrOH, t_A (major) =

6.55 min, t_B (minor) = 7.22 min [$[\alpha]_D^{24} = -78.8^\circ$ (*c* 2.1, CHCl₃); IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2958,

2178, 171, 1613 493, 1469, 1376, 1250, 842; ¹H NMR (400 MHz, CDCl₃): δ = 7.41 (dd, *J* = 7.5, 1.5, 1H), 7.28 (dt, *J* = 7.5, 1.5, 1H), 7.07 (dt, *J* = 7.5, 1, 1H), 6.82 (d, *J* = 7.5, 1H), 5.45- 5.31 (m, 1H), 5.02 (dm, *J* = 16, 1H), 4.90 (dm, *J* = 16, 1H), 3.20(s, 3H), 2.77-2.70 (m, 2H), 2.61(dd, *J* = 7, 16, 1H), 2.52 (d, *J* = 16, 1H), 0.57(s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ = 178.5, 143.6, 132.2, 131.2, 128.1, 123.6, 122.3, 118.8, 107.7, 78.2, 74.1, 51.2, 40.0, 27.1, 26.1, 3.5; HRMS—EI (*m/z*): calcd for C₁₈H₂₃NOSi: 297.1549; found: 297.1559

3-allyl-3-(2-(tert-butyldimethylsilyloxy)ethyl)-1-methylindolin-2-one(23)

Isolated as colorless oil

Chiral HPLC, AD-column, flow rate 0.5 mL/min, 97:3 heptane / *i*-PrOH, t_A (minor) =

9.75 min, t_B (minor) = 10.49 min [$[\alpha]_D^{24} = 12.49^\circ$ (*c* 2.0, CHCl₃); IR (film) $\nu_{\max}/\text{cm}^{-1}$: ¹H

NMR (500 MHz, CDCl₃): δ = 7.26 (dt, *J* = 7.5, 1.5, 1H), 7.16 (dd, *J* = 7.5, 1.5, 1H), 7.04 (dt,

J = 7.5, 1, 1H), 6.80 (d, *J* = 7.5, 1H), 5.45- 5.35 (m, 1H), 4.96 (dm, *J* = 16, 1H), 4.90 (dm, *J* = 16, 1H), 3.36- 3.30(m, 2H), 3.17(s, 3H), 2.51 (d, *J* = 7, 2H), 2.29-2.21(m, 1H), 2.04-1.98(m, 1H), 0.76(s, 9H), -0.15(s, 3H), 0.14 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 179.1, 143.8, 132.2, 131.2, 127.7, 123.3, 122.0, 118.8, 107.7, 59.3, 50.8, 42.8, 38.9, 26.1, 25.8, 18.2, -5.6, -5.7, HRMS—EI (*m/z*): calcd for C₂₀H₃₁NO₂Si: 345.2124; found: 345.2141

(S)-2-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetaldehyde

Oxindole **5** (231 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL).

NMO (300 mg, 2.55 mmol) was added followed by osmium tetroxide (120

μL , 4% solution in water). The reaction mixture was stirred vigorously at r.t. for 1h, whereupon the reaction was quenched with saturated aqueous Na_2SO_3 solution. The layers were separated and the aqueous phase was further extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated to reveal the diol as white solid, which was dissolved in acetone (5 mL) and water (1 mL). Solid sodium periodate (400 mg, 1.85 mmol) was added and the reaction was stirred at room temperature until deemed complete by TLC (1 - 3 h). The reaction was poured into water (20 mL) and diethyl ether (30 mL). The layers were separated and the aqueous phase was further extracted with diethyl ether (3 x 20 mL), washed with brine, dried (MgSO_4), filtered and concentrated. The residue was chromatographed (50% EtOAc / hexane) to reveal the known aldehyde **24** as a white powder (215 mg, 92 %), identical to previously described material⁹: mp 115 – 117°C (lit 116 – 117°C EtOAc / hexane); $[\alpha]_{\text{D}}^{24} = 33.3^\circ$ (c 1.0, C_6H_6); ^1H NMR (400 MHz, CDCl_3): $\delta = 9.52$ (s, 1H), 6.81 – 6.79 (m, 3H), 3.79 (s, 3H), 3.24 (s, 3H), 2.96 (dd, $J = 17.2, 1.2$, 2H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 198.7, 179.1, 156.1, 136.7, 134.1, 112.1, 110.3, 108.6, 55.8, 50.6, 45.4, 26.5, 24.0$; IR ν_{max} (cm^{-1}) (film) 2924, 2872, 2821, 1701, 1604, 1557, 1501, 1465, 1434, 1378, 1290, 1234, 1218, 1039, 869, 807. Recrystallization from isopropyl alcohol-cyclohexane provided enantiopure (*S*)-**24** in 72% yield. $[\alpha]_{\text{D}}^{24} = 49.5^\circ$ (c 1.0, CHCl_3)

(-)-Esermethole

Overman's procedure⁹ was followed to give pure (-)-esermethole: enantiopure aldehyde **24** (46 mg, 0.2 mmol), $\text{MeNH}_2 \cdot \text{HCl}$ (140 mg, 2 mmol), MgSO_4 (140 mg), triethylamine (0.29 mL, 2 mmol) was dissolved in anhydrous THF (5 mL) and stirred at ambient temperature overnight, whereupon solid LAH (77 mg, 2 mmol) was added and the resultant suspension was stirred at reflux (2 h). After returning to room temperature ethyl acetate (20 mL) was added followed by saturated aqueous NaHCO_3 (10 mL). The layers were separated and the aqueous phase was extracted further with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO_4), filtered, concentrated and chromatographed on silica (3% MeOH / CH_2Cl_2) to reveal pure esermethole as a slightly yellow solid : $[\alpha]_{\text{D}}^{24} = -140.1^\circ$ (c 1.0, C_6H_6); IR ν_{max} (cm^{-1}) (film) 2944, 2854, 2791, 1592, 1493, 1461, 1258, 1214, 1112, 1053, 1031, 802; ^1H NMR (400 MHz, CDCl_3): $\delta = 6.67 - 6.63$ (m, 2H), 6.35 (d, $J = 8.4$, 1H), 4.07 (s, 1H), 3.75 (s, 3H), 2.89 (s, 3H), 2.76 – 2.60 (m, 2H), 2.54 (s, 3H), 1.97 – 1.93 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 153.0, 146.5, 138.2, 112.2, 109.8, 107.5, 98.2, 56.0, 53.1, 52.7, 40.8, 38.1, 37.9, 27.4$.

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