A New and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Synthesis of (-)-Tubifoline by Palladium-Catalyzed Asymmetric Allylic Substitution

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Supporting Information

General. All manipulations were performed under an argon atmosphere unless otherwise mentioned. Solvents were distilled under an argon atmosphere from sodium-benzophenone (THF, Et_2O and toluene), CaH_2 (CH_2Cl_2, C_3H_7CN, DMF and DMSO), or sodium (EtOH). All other solvent, and reagent, were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70-230 or 230-400 mesh) using the indicated solvent.

1-*tert*-Butyldimethylsilanyloxymethyl-6-Vinyloxycarbonyloxy-1-cyclohexene (4h).

A toluene solution of DIBALH (1.01 M, 15 mL, 15.2 mmol) was added to a solution of **4a** (520 mg, 3.05 mmol) in toluene (25 mL) at -78 °C and the solution was stirred at room temperature for 3 h. The reaction was quenched by addition of MeOH (0.25 mL) and saturated Rochelle’s salt. Then AcOEt was added and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (1:2) gave 344.7 mg (2.69 mmol, 88%) of 2-hydroxymethyl-2-cyclohexenol as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 1.55-2.17 (m, 7 H), 2.32 (br s, 1 H), 4.21 (br s, 2 H), 4.33 (br s, 1 H), 5.83 (t, J = 3.7 Hz, 1 H); IR (neat) 3334, 2934, 1670 cm^{-1}. A solution of 2-

hydroxymethyl-2-cyclohexenol (7.8 g, 60.9 mmol), TBDMSCl (9.1 g, 60.9 mmol) and imidazole (12.4 g, 182.1 mmol) in DMF (100mL) was stirred at 0 °C for 1.5 h. Then AcOEt was added, the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 13.0 g (53.6 mmol, 88%) of 2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenol as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.92 (s, 9 H), 1.55-2.16 (m, 6 H), 2.90 (d, *J* = 3.3 Hz, 1 H), 4.17 (br d, *J* = 11.9 Hz, 1 H), 4.24 (br s, 2 H), 4.27(d, *J* = 11.9 Hz, 1 H), 5.76 (br t, *J* = 3.7 Hz, 1 H); IR (neat) 3384, 2930, 1256 cm^{-1}. To a solution of 2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenol (822 mg, 3.39 mmol) and pyridine (3 mL) in CH_2Cl_2 (10 mL) was added vinyl chloroformate (0.29 mL, 3.41 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexane gave 1.02 g (3.26 mmol, 96%) of **4h** as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$ δ 0.09 (s, 6 H), 0.87 (s, 9 H), 1.61-1.69 (m, 2 H), 1.70-1.81 (m, 1 H), 1.97-2.05 (m, 2 H), 2.10-2.14 (m, 1 H), 4.04 (d, *J* = 12.9 Hz, 1 H), 4.15 (d, *J* = 12.9 Hz, 1 H), 4.54 (d, *J* = 6.1 Hz, 1 H), 4.88 (d, *J* = 13.8 Hz, 1 H), 5.26 (s, 1 H), 5.98 (s, 1 H), 7.08 (dd, *J* = 13.8, 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.5, 17.7, 18.3, 24.7, 25.8, 28.2, 64.1, 71.6, 97.0, 128.7, 133.5, 142.1, 151.8; IR (neat) 2930, 2858, 1757, 1649 cm^{-1}; LR MS *m/z* 255 (M^+-^tBu), 225 (M^+-CH_2=$CHOCO_2$), 167, 145; HR MS calcd for $C_{12}H_{19}O_4Si$ 255.1057 (M^+-^tBu), found 255.1055.

General procedure for asymmetric allylic substitution. A THF or DMF solution of allyl carbonate **4** was added to a solution of $Pd_2dba_3 \cdot CHCl_3$ (2.6 mol %) and (*S*)-BINAPO (5.2 mol %) in THF or DMF. And then tosylamide **5** or **8** (1.1 equiv.) in THF or DMF was added, the mixture was stirred at appropriate temperature. Then AcOEt was added, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel.

(*S*)-*N*-Allyl-*N*-[(2-carboethoxy)-2-cyclohexenyl]-4-methylbenzenesulfonamide (9a). ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (t, *J* = 6.3 Hz, 3 H), 1.50-1.63 (m, 1 H), 1.72-1.92 (m, 2 H), 2.00-2.12 (m, 1 H), 2.18-2.24 (m, 2 H), 2.43 (s, 3 H), 3.75 (d, *J* = 6.3 Hz, 2 H), 3.90-4.10 (m, 2 H), 4.89 (br s, 1 H), 5.01 (d, *J* = 9.9 Hz, 1 H), 5.06 (d, *J* = 17.0 Hz, 1 H), 5.67 (ddt, *J* = 17.0, 9.9, 6.3 Hz, 1 H), 7.16 (m, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.79 (d, *J* = 8.3 Hz, 2 H); IR (neat) 3050, 2980, 2874, 1714, 1642, 1590 cm^{-1}; GC MS *m/z* 209 (M^+-Ts), 156 (Ts), 152 (M^+-CH_2=$CHCH_2NHTs$).

(*S*)-*N*-Allyl-*N*-[(2-benzyloxymethyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (9d). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.45-1.58 (m, 1 H), 1.61-1.68 (m, 1 H), 1.71-1.78 (m, 2 H), 2.00 (br s, 1 H), 2.39 (s, 1 H)< 3.63 (dd, *J* = 16.5, 6.6 Hz, 1 H), 3.64 (d, *J* = 12.7 Hz, 1 H), 3.72 (d, *J* = 12.2 Hz, 1 H), 3.82 (dd, *J* = 16.5, 6.6 Hz, 1 H), 4.35 (d, *J* = 11.9 Hz, 1 H), 4.40 (d, *J* = 11.9 Hz, 1 H), 4.53-4.60 (m, 1 H), 5.03 (d, *J* = 11.2 Hz, 1 H), 5.12 (d, *J* = 17.2 Hz, 1 H), 5.77 (ddt, *J* = 17.2, 11.2, 6.6 Hz, 1 H), 6.07 (s, 1 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 7.25-7.37 (m, 5 H), 7.72 (d, *J* = 7.9 Hz, 2 H); IR (neat) 3064, 3030, 2936, 2860, 1736, 1598 cm^{-1}; LR MS *m/z* 320 (M^+-Bn), 256 (M^+-Ts), 155, 91; ESI MS *m/z* 434 (M^++Na); HR MS calcd for $C_{17}H_{22}NO_3S$ 320.1320 (M^+-Bn), found 320.1329.

(*S*)-*N*-Allyl-*N*-[(2-*tert*-butyldimethylsilanyloxymethyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (9e). ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.04 (s, 6 H), 0.85 (s, 9 H), 1.45-1.58 (m, 1 H), 1.72-1.79 (m, 2 H), 2.00 (br s, 2 H), 2.41 (s, 3 H), 3.58 (dd, *J* = 16.2, 5.9 Hz, 1 H), 3.59 (d, *J* = 16.5 Hz, 1 H), 3.65 (d, *J* = 16.5 Hz, 1 H), 3.83 (dd, *J* = 16.2, 5.9 Hz, 1 H), 4.40-4.42 (m, 1 H), 5.07 (d, *J* = 10.3 Hz, 1 H), 5.17 (d, *J* = 17.0 Hz, 1 H), 5.85 (ddt, *J* = 17.0, 10.3, 5.9 Hz, 1 H), 6.03 (br s, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H); IR (neat) 2987, 2929, 1856, 1598 cm^{-1}; LR MS *m/z* 378 (M^+-^{t}Bu), 280 (M^+-Ts), 224, 167, 155, 91; HR MS calcd for $C_{19}H_{28}NO_3SSi$ 378.1559 (M^+-^{t}Bu), found 378.1551.

(*S*)-*N*-Allyl-*N*-[(2-triethylsilanyloxymethyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (9f). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.50 (q, *J* = 8.6 Hz, 6 H), 0.89 (t, *J* = 8.6 Hz, 9 H), 1.42-1.55 (m, 1 H), 1.58-1.67 (m, 1 H), 1.70-1.80 (m, 2 H), 1.97 (br s, 2 H), 2.39 (s, 3 H), 3.53 (dd, *J* = 16.5, 5.9 Hz, 1 H), 3.55 (d, *J* = 15.9 Hz, 1 H), 3.62 (d, *J* = 15.9 Hz, 1 H), 3.81 (dd, *J* = 16.5, 5.9 Hz, 1 H), 4.37-4.39 (m, 1

H), 5.06 (d, *J* = 11.2 Hz, 1 H), 5.13 (d, *J* = 17.3 Hz, 1 H), 5.84 (ddt, *J* = 17.3, 11.2, 5.9 Hz, 1 H), 6.03 (br s, 1 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H); 2954, 2876, 1592, 1340 cm^{-1}; GC MS *m/z* 406 (M$^+$-Et), 280 (M$^+$-Ts), 224 (M$^+$-CH$_2$=CHCH$_2$NHTs), 195, 91.

(*S*)-*N*-(2-Bromophenyl)-*N*-(2-[(2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenyl)-4-methylbenzenesulfonamide (6a). ^{1}H NMR (400 MHz, CDCl$_3$) δ -0.04 (d,*J* = 4.5 Hz, 4.8 H), 0.05 (d, *J* = 5.3 Hz, 1.2 H), 0.60-0.70 (m, 0.2 H), 0.90 (s, 7.2 H), 0.94 (s, 1.8 H), 1.05-1.10 (m, 0.8 H), 1.21-1.31 (m, 0.2 H), 1.44-1.50 (m, 0.8 H), 1.75-1.87 (m, 3 H), 2.04-2.09 (m, 0.2 H), 2.42 (s, 3 H), 2.55-2.62 (m, 0.8 H), 3.55 (br d, *J* = 14.5 HZ, 0.8 H), 3.62 (br d, *J* = 14.5 Hz, 0.8 H), 4.16 (br d, *J* = 15.2 Hz, 0.2 H), 4.49 (br d, *J* = 15.2 Hz, 0.2 H), 4.55 (br s, 0.8 H), 4.65 (br s, 0.2 H), 5.89 (br s, 1 H), 6.84 (d, *J* = 7.2 Hz, 0.8 H), 7.62-7.77 (m, 4.2 H), 7.57 (d, *J* = 7.2 Hz, 0.2 H), 7.65-7.70 (m, 2.8 H); IR (neat) 3071, 1598, 1470, 1350, 1160 cm^{-1}; LR MS *m/z* 535 (M$^+$-Me), 493 (M$^+$-^{t}Bu), 400 (M$^+$-Ts), 326 (BrC$_6$H$_4$NHTs), 225 (M$^+$- BrC$_6$H$_4$NHTs), 167, 155, 91; HR MS calcd for $C_{25}H_{33}NO_3SSiBr$ 534.1153 (M$^+$-Me), found 534.1113; $[\alpha]^{22}_D$ = +1.78 (*c* 3.00, CHCl$_3$).

(*S*)-*N*-[(2-*tert*-butyldimethylsilanyloxymethyl)-2-cyclohexenyl]-*N*-phenyl-4-methylbenzenesulfonamide (6b). ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.02 (s, 6 H), 0.78-0.91 (m, 1 H), 0.88 (s, 9 H), 1.21-1.30 (m, 1 H), 1.65-1.75 (m, 2 H), 1.77-1.85 (m, 2 H), 2.36 (s, 3 H), 4.02 (d, *J* = 14.5 Hz, 1 H), 4.16 (d, *J* = 14.5 Hz, 1 H), 4.77-4.83 (m, 1 H), 5.88 (br s, 1 H), 6.98 (d, *J* = 8.3 Hz, 2 H), 7.17-7.26 (m, 5 H), 7.57 (d, *J* = 8.3 Hz, 2 H); IR (neat) 3062, 2952, 2856, 1596 cm^{-1}; LR MS *m/z* 456 (M$^+$-Me), 414 (M$^+$-^{t}Bu), 247 (PhNHTs), 225 (M$^+$-PhNHTs), 167, 91; HR MS calcd for $C_{22}H_{28}NO_3SSi$ 414.1559 (M$^+$-^{t}Bu), found 414.1562.

(4a*S*,9a*S*)-4a-(*tert*-Butyldimethylsilanyloxymethyl)-9-(4-methylbenzenesulfonyl)-2,4a,9,9a-tetrahydro-1*H*-carbazole (10a). A solution of **6a** (763 mg, 1.39 mmol), Pd(OAc)$_2$ (15.6 mg, 69.3 μmol), Me$_2$PPh (20.0 μL, 139 μmol), and Ag$_2$CO$_3$ (382 mg, 1.39 mmol) in DMSO (14 mL) was heated at 120 °C for 24 h. After cooling to room temperature, the mixture was filtered through the pad of Celite. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/CH_2Cl_2 (1:1) gave 306.9 mg (653 μmol, 47%) of **10a** as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.24 (s, 3 H), -0.21 (s, 3 H), 0.80 (s, 9 H), 1.70-1.81 (m, 1 H), 2.00-2.06 (m, 2 H), 2.20-2.27 (m, 1 H), 2.35 (s, 3 H), 2.49 (d, *J* = 9.4 Hz, 1 H), 2.79 (d, *J* = 9.4 Hz, 1 H), 4.25 (dd, *J* = 10.8, 5.2 Hz, 1 H), 5.76 (d, *J* = 10.0 Hz, 1 H), 5.91-5.96 (m, 1 H), 6.98-7.02 (m, 2 H), 7.18-7.26 (m, 3 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, -5.3, 18.3, 21.6, 22.3, 25.8, 28.5, 50.9, 69.7, 115.9, 123.5, 124.1, 126.6, 127.3, 128.1, 129.3, 129.4, 135.4, 135.5, 139.5, 143.4; IR (neat) 2928, 2855, 1598, 1472, 1355 cm^{-1}; LR MS *m/z* 469 (M^+), 412 (M^+-^{t}Bu), 324 (M^+-TBSOCH_2), 314 (M^+-Ts), 168, 91; HR MS calcd for $C_{26}H_{35}NO_3SSi$ 469.2107, found 469.2124.

(*S*)-*N*-(2-Bromophenyl)-*N*-[(2-cyanomethyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (11).

An aqueous solution of HCl (4 N, 1 mL) was added to a solution of **6a** (133.0 mg, 241.5 μmol) in THF (2.4 mL), and the whole solution was stirred at room temperature for 1 h. Then AcOEt was added, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (1:1) gave 105.4 mg (241.5 μmol, quant.) of (*S*)-*N*-(2-Bromophenyl)-*N*-(2-hydroxymethyl-2-cyclohexenyl)-4-methylbenzenesulfonamide as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.25-0.42 (m, 0.42 H), 0.79-0.96 (m, 0.58 H), 1.20-1.30 (m, 0.42 H), 1.30-1.43 (m, 0.58 H), 1.60-1.90 (m, 3 H), 2.27-2.37 (m, 1 H), 2.44 (s, 1.74 H), 2.46 (s, 1.26 H), 2.69 (br t,*J* = 6.0 Hz, 0.58 H), 2.99 (br t, *J* =6.0 Hz, 0.42 H), 3.97 (br dd, *J* = 12.7, 6.0 Hz, 0.42 H), 4.06 (br dd, *J* = 12.7, 6.0 Hz, 0.42 H), 4.33 (br d, *J* = 12.7 Hz, 0.58 H), 4.94 (br s, 0.58 H), 4.97 (br s, 0.42 H), 5.02 (br d, *J* = 12.7 Hz, 0.58 H), 5.90 (br s, 0.42 H), 5.95 (br s, 0.58 H), 6.94-6.99 (m, 0.42 H), 7.09-7.30 (m, 4.58 H), 7.55-7.75 (m, 3 H); IR (neat) 3534, 2950, 2870, 1598 cm^{-1}; LR MS *m/z* 437 (M^+), 419 (M^+-H_2O), 327 (BrC_6H_4NHTs), 283 (M^+-Ts), 155, 93; HR MS calcd for

$C_{20}H_{22}NO_3S^{79}Br$ 435.0504, found 435.0502; $[\alpha]^{22}_{D}$ = +26.3 (*c* 1.13, $CHCl_3$). To a solution of (*S*)-*N*-(2-Bromophenyl)-*N*-(2-hydroxymethyl-2-cyclohexenyl)-4-methylbenzenesulfonamide (10.50 g, 24.1 mmol) in THF (40 mL) was added PBr_3 (0.85 mL (8.95 mmol), and the solution was stirred at 0 °C for 30min, then allowed to warm to room temperature for 1 h. Saturated $NaHCO_3$ was added at 0°C. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 10.80 g (21.63 mmol, 90%) of (*S*)-*N*-[(2-Bromomethyl)-2-cyclohexenyl]-*N*-(2-bromophenyl)-4-methylbenzenesulfonamide as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.30-0.42 (m, 0.47 H), 0.97-1.10 (m, 0.53 H), 1.12-1.20 (m, 0.47 H), 1.35-1.46 (m, 0.53 H), 1.65-1.80 (m, 3 H), 1.86-1.92 (m, 0.53 H), 2.44 (s, 1.59 H), 2.45 (s, 1.41 H), 2.53-2.60 (m, 0.47 H), 3.65 (d, *J* = 9.9 Hz, 0.53 H), 3.86 (d, *J* = 9.9 Hz, 0.53 H), 4.07 (d, *J* = 9.9 Hz, 0.47 H), 4.75 (d, *J* = 9.9 Hz, 0.47 H), 4.86 (br s, 0.53 H), 4.97 (br d, *J* = 5.9 Hz, 0.47 H), 6.06 (s, 0.53 H), 6.10 (s, 0.47 H), 6.81 (d, *J* = 8.6 Hz, 0.53 H), 7.08 (d, *J* = 8.6 Hz, 0.47 H), 7.15-7.32 (m, 3 H), 7.58-7.74 (m, 4 H); IR (neat) 2926, 1596, 1470, 1212 cm^{-1}; LR MS *m/z* 499 (M^+), 418 (M^+-HBr), 327 (BrC_6H_4NHTs), 262, 155, 91; HR MS calcd for $C_{20}H_{21}NO_2S^{79}Br^{81}Br$ 498.9591, found 498.9615; $[\alpha]^{22}_{D}$ = +9.65 (*c* 3.28, $CHCl_3$). To a solution of (*S*)-*N*-[(2-Bromomethyl)-2-cyclohexenyl]-*N*-(2-bromophenyl)-4-methylbenzenesulfonamide (900.0 mg, 1.80 mmol) in DMSO (9.0 mL) was added NaCN (181.3 mg, 3.70 mmol), and the solution was stirred at room temperature for 1 h. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (3:1) gave 761.0 mg (1.71 mmol, 95%) of **11** as a white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30-0.40 (m, 0.6 H), 1.05-1.15 (m, 0.4 H), 1.15-1.21 (m, 0.6 H), 1.37-1.43 (m, 0.4 H), 1.70-1.90 (m, 3.6 H), 2.35-2.43 (m, 0.4 H), 2.44 (s, 1.2 H), 2.46 (s, 1.8 H), 3.13 (br d, *J* = 18.2 Hz, 0.4 H), 3.29 (br d, *J* = 18.2 Hz, 0.4 H), 3.43 (dd, *J* = 18.9, 1.6 Hz, 0.6 H), 3.91 (dd, *J* = 18.9, 1.6 Hz, 0.6 H), 4.52 (br s, 0.4 H), 4.68 (br s, 0.6 H), 6.11-6.14 (m, 1 H), 6.94-6.96 (m, 0.6 H), 7.06-7.09 (m, 0.4 H), 7.17-7.33 (m, 4 H), 7.57-7.67 (m, 3 H); IR (nujol) 2932, 2868, 2246, 1654, 1596 cm^{-1}; LR MS *m/z* 445 (M^+), 327 (BrC_6H_4NHTs), 155, 91; HR MS calcd for $C_{21}H_{21}N_2O_2S^{81}Br$ 446.0530, found 446.0508; $[\alpha]^{22}_D$ = +18.1 (*c* 2.62, $CHCl_3$).

(4a*S*,9a*S*)-4a-Cyanomethyl-9-(4-methylbenzenesulfonyl)-2,4a,9,9a-tetrahydro-1*H*-carbazole (12). A solution of **11** (1.00 g, 2.25 mmol), $Pd(OAc)_2$ (10.1 mg, 45.0 μmol), Me_2PPh (13.0 μL, 91.3 μmol), and Ag_2CO_3 (620 mg, 2.25 mmol) in DMSO (4.5 mL) was heated at 90 °C for 17 h. After cooling to room temperature, the solution was filtered through the pad of Celite. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/CH_2Cl_2 (1:1) gave 714.2 mg (1.96 mmol, 87%) of **12** as a white solid; ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (d, *J* = 16.8 Hz, 1 H), 1.68-1.78 (m, 1 H), 1.82 (d, *J* = 16.8 Hz, 1 H), 2.08-2.19 (m, 2 H), 2.24-2.34 (m, 1 H), 2.39 (s, 3 H), 4.16 (dd, *J* = 11.2, 5.2 Hz, 1 H), 5.83 (br d, *J* = 9.2 Hz, 1 H), 6.09 (ddd, *J* = 9.2, 5.3, 3.6 Hz, 1 H), 7.07 (t, *J* = 7.9 Hz, 1 H), 7.09 (d, *J* = 7.9 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.30 (t, J = 7.9 Hz, 1 H), 7.70-7.74 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.5, 28.3, 31.1, 46.8, 66.6, 116.6, 116.9, 123.5, 124.9, 125.3, 126.9, 129.5, 130.1, 131.6, 135.3, 135.5, 138.9, 139.3; IR (nujol) 2244 cm^{-1}; LR MS *m/z* 364 (M^+), 324 (M^+-CH_2CN), 209 (M^+-Ts), 155, 91; HR MS calcd for $C_{21}H_{20}N_2O_2S$ 364.1245, found 364.1227; $[\alpha]^{22}_D$ = -35.5 (*c* 2.16, $CHCl_3$).

(4a*S*,9a*S*)-4a-[(2-*tert*-Butoxycarbonylamino)ethyl]-9-(4-methylbenzenesulfonyl)-2,4a,9,9a-tetrahydro-1*H*-carbazole (13). To a suspension of $LiAlH_4$ (1.19 g, 31.4 mmol) in THF (20 mL) was added a solution of **12** (3.79 g, 10.4 mmol) in THF (30 mL) at 0 °C, and the solution was stirred at room temperature for 1.5 h. To the solution was added water (1.2 mL), 4 N NaOH aq (1.2 mL), and water (3.6 mL). The solution was filtered and the filtrate was concentrated to give an oily product, which was dissolved in DMF (20 mL). To the DMF solution was added Boc_2O (4.8 mL, 20.9 mmol) and Et_3N (7.3 mL, 52.3 mmol). After stirring for 1h, AcOEt was added.

The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 3.22 g (6.87 mmol, 66%) of **13** as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.45-0.57 (m, 1 H), 1.14-1.24 (m, 1 H), 1.43 (s, 9 H), 1.73-1.84 (m, 1 H), 1.93-2.07 (m, 2 H), 2.10-2.25 (m, 1 H), 2.38 (s, 3 H), 2.66-2.76 (m, 1 H), 2.81-2.90 (m, 1 H), 3.88 (s, 1 H), 4.08 (dd, *J* = 9.9, 4.6 Hz, 1 H), 5.70 (d, *J* = 10.3 Hz, 1 H), 5.90 (ddd, *J* = 10.3, 4.4, 3.3 Hz, 1 H), 6.99 (dd, *J* =7.3, 2.0 Hz, 1 H), 7.02 (t, *J* = 7.3 Hz, 1 H), 7.21 (dt *J* = 2.0, 7.3 Hz, 1 H), 7.24 (*J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 7.3 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.9, 27.9, 28.5, 36.1, 41.3, 47.4, 65.3, 79.2, 116.4, 123.1, 124.3, 126.9, 128.0, 128.2, 128.9, 129.3, 129.6, 130.0, 131.4, 135.5, 138.9, 143.9, 155.3; IR (neat) 3410, 1710, 1648, 1600 cm^{-1}; LR MS *m/z* 468 (M^+), 395 (M^+-Me_3CO), 324 (M^+-CH_2CH_2NHBoc), 313 (M^+-Ts); HR MS calcd for $C_{28}H_{32}N_2O_4S$ 468.2083, found 468.2108; $[\alpha]^{22}_D$ = -40.4 (*c* 2.96, $CHCl_3$).

(3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-7-(4-methylbenzenesulfonyl)-1,2,3a,6,6a,7-hexahydropyrrolo[2,3-*d*]carbazole (14). A solution of $Pd(OAc)_2$ (81.4 mg, 363 μmol) and benzoquinone (157 mg, 1.45 mmol) in AcOH (11 mL) was stirred at room temperature for 15 min, and then MnO_2 (1.26 g, 14.5 mmol) was added. To the solution was added a solution of **13** (3.40 g, 7.26 mmol) in AcOH (15 mL), and the resulting solution was heated at 50 °C for 20 h. After cooling to room temperature, hexane/Et_2O (1:1) was added and the solution was filtered through the pad of Celite. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 2.60 g (5.57 mmol, 77%) of **14** as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75-0.79 (m, 1 H), 1.46 (s, 9 H), 2.04-2.18 (m, 1 H), 2.36 (s, 3 H), 2.69-2.82 (m, 1 H), 3.35 (br s, 1.4 H), 3.37 (br s, 0.6 H), 3.79 (dd, *J* = 10.4, 5.8 Hz, 1 H), 4.06 (br s, 0.7 H), 4.19 (br s, 0.3 H), 5.81-5.99 (m, 2 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 7.9 Hz, 2 H), 7.73 (d, *J* = 7.6 Hz, 1 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 21.7, 28.7, 39.2, 44.1, 60.4, 77.2, 80.0, 116.9, 122.9, 124.3, 125.2, 126.7, 128.7, 129.4, 132.7, 133.4, 134.4, 134.7, 137.6, 14.00, 143.9, 153.9; IR (CH_2Cl_2) 3046, 1696 cm^{-1}; LR MS *m/z* 466 (M^+), 366 (M^+-Boc), 168, 91, 57; HR MS calcd for $C_{26}H_{30}N_2O_4S$ 466.1926, found 466.1885; $[\alpha]^{22}_D$ = -60.2 (*c* 2.05, $CHCl_3$).

(3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-7-(4-methylbenzenesulfonyl)-5-oxo-1,2,3a,4,5,6,6a,7-octahydro[2,3-*d*]pyrrolocarbazole (15). To a solution of **14** (2.48 g, 5.31 mmol) in THF (20 mL) was added 9-BBN (0.5 M solution, 53.0 mL, 26.5 mmol) in THF and the resulting solution was warmed to 50 °C for 9 h. After cooling to 0 °C, 4 N NaOH aq. (20 mL) and 30% H_2O_2 (20 mL) were added and the solution was stirred at room temperature for 4 h. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (2:1) gave 2.06 g (4.25 mmol, 80%) of (3a*S*,5a*R*,6a*S*,11a*R*)- and (3a*S*,5a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-5-hydroxy-7-(4-methylbenzenesulfonyl)-1,2,3a,4,5,6,6a,7-octahydro[2,3-*d*]pyrrolocarbazole as an inseparable mixture. To a stirring solution of $(COCl)_2$ (0.74 mL, 8.48 mmol) in CH_2Cl_2 (22 mL) at –78 °C was added a solution of DMSO (1.2 mL, 16.9 mmol) in CH_2Cl_2 (1.0 mL). The resulting solution was stirred for 10 min and to this solution was added a solution of (3a*S*,5a*R*,6a*S*,11a*R*)- and (3a*S*,5a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-5-hydroxy-7-(4-methylbenzenesulfonyl)-1,2,3a,4,5,6,6a,7-octahydro[2,3-*d*]pyrrolocarbazole (2.06 g, 4.25 mmol) in CH_2Cl_2 (20 mL). After stirring at –78 °C for 40 min, Et_3N (10 mL) was added dropwise. After an additional 15 min at –78 °C, the solution was allowed to warm to room temperature. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (2:1) gave 1.78 g (3.69 mmol, 87%) of **15** as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91-0.98 (m, 1 H), 1.46 (s, 9 H), 1.58-1.69 (m, 1 H), 2.20 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.38 (s, 3 H), 2.58 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.86 (m, 2 H), 3.38 (br s, 2 H), 4.05 (br s, 0.7 H), 4.12 (br s, 0.3 H), 4.22 (dd, *J* = 11.2, 4.6 Hz, 1 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 7.12 (t, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 7.75 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 22.8, 28.6, 36.7, 44.4, 53.8, 59.2, 65.3, 80.7, 117.2, 122.9, 125.5, 126.7, 129.2, 129.6, 134.3, 136.5, 139.2, 144.3, 153.5; IR (neat) 3056, 2976, 1722, 1692, 1598 cm^{-1}; LR MS *m/z* 482 (M^+), 426 (M^+-*t*-Bu), 382 (M^+-Boc), 227; HR MS calcd for $C_{26}H_{30}N_2O_5S$ 482.1875, found 482.1891; $[\alpha]^{22}_D$ = -1.52 (*c* 2.45, $CHCl_3$).

(3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-7-(4-methylbenzenesulfonyl)-1,2,3a,4,6a,7-hexahydropyrrolo[2,3-*d*]carbazole (16). A solution of **15** (182.1 mg, 377 µmol) in THF (3.0 mL) was added dropwise to a solution of KHMDS (0.5M in toluene) (0.9 mL, 450 µmol) at –35 °C. To the solution was added a solution of *N*-phenyltriflimide (161 mg, 450 µmol) in THF (3 mL) and the solution allowed to stir at room temperature for 15 min. Then Et_2O was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 148.0 mg (241 µmol, 63%) of (3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-5-trifluoromethanesulfonyloxy-7-(4-methylbenzenesulfonyl)-1,2,3a,4,6a,7-hexahydropyrrolo[2,3-*d*]carbazole as a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80-0.92 (m, 1 H), 1.18-1.29 (m, 1 H), 1.46 (s, 9 H), 2.38 (s, 3 H), 2.71 (br s, 2 H), 3.34 (br s, 1 H), 3.49-3.59 (m, 1 H), 3.92 (br s, 0.4 H), 4.06 (br s, 0.6 H), 4.45 (s, 1 H), 6.16 (br s, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 7.09 (t, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 7.31 (t, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 2 H), 7.73 (d, *J* = 7.9 Hz, 1 H). To a solution of (3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-5-trifluoromethanesulfonyloxy-7-(4-methylbenzenesulfonyl)-1,2,3a,4,6a,7-hexahydropyrrolo[2,3-*d*]carbazole (148.0 mg, 241 µmol), $^iPr_2NEt$ (0.17 mL, 976 mmol), $Pd(OAc)_2$ (5.4 mg, 24.1 µmol) and PPh_3 (12.6 mg, 48.2 µmol) in DMF (2.0 mL) was added formic acid (99%, 36 µL, 954 µmol). The solution was stirred at 60 °C for 1 h. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 112.5 mg (241 μmol, quant.) of **15** as a colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ_1.02-1.08 (m, 1 H), 1.45 (s, 9 H), 1.50-1.65 (m, 1 H), 1.80-1.92 (m, 1 H), 2.37 (s, 3 H), 2.52-2.59 (m, 1 H), 3.30-3.44 (br s, 2 H), 3.53 (br s, 0.7 H), 3.73 (br s, 0.3 H), 4.27 (br s, 1 H), 5.80-5.90 (m, 1 H), 6.12 (br s, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.27 (t, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 28.6, 36.9 43.4, 53.0, 60.0, 66.1, 77.2, 79.8, 116.7, 122.8, 125.1, 125.9, 126.8, 128.1, 128.5, 129.4, 130.0, 133.7, 138.1, 140.0, 144.0, 154.2; LR MS *m/z* 466 (M+), 410 (M+-*t*-Bu), 366 (M+-Boc), 211 (M+-Boc-Ts); HR MS calcd for $C_{26}H_{30}N_2O_4S$ 466.1926, found 466.1930; $[\alpha]^{22}_D$ = -55.4 (*c* 2.08, CHCl$_3$).

(3a*S*,6a*S*,11a*R*)-3-(2-Iodo-2-butenyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole (17). To a solution of naphthalene (128.2 mg, 1.0 mmol) in THF (5 mL) was added sodium (23.1 mg, 1.0 mmol) and the solution was stirred at room temperature for 2 h to give sodium naphthalenide solution (0.2 M). To a solution of **16** (32.2 mg, 69.0 μmol) in THF (0.5 mL) was added 3.5 mL (700 μmol) of 0.2 M sodium naphthalenide in THF at –78 °C. After stirring at –78 °C for 15 min, the reaction solution was allowed to warm to 0 °C. Water was added and the organic layer was washed with brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (2:1) gave 19.2 mg (61.4 μmol, 89%) of (3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole as a colorless oil. To a solution of (3a*S*,6a*S*,11a*R*)-3-*tert*-Butoxycarbonyl-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole (169.7 mg, 543.2 μmol) in CH$_2$Cl$_2$ (6 mL) was added CF$_3$CO$_2$H (3 mL) at 0 °C and the solution was stirred for 30 min. The solvent was removed to give an oily product (251.2 mg), which was dissolved in DMF (3 mL). To the solution was added K$_2$CO$_3$ (75.1 mg, 5.43 mmol), Bu$_4$NCl (150.9 mg, 543.0 μmol) and then DMF solution of **18** (142.0 mg, 544.2 μmol/3 mL) was addedat 0 °C. After stirring at 0 °C for 2 h, Et$_2$O was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (3:1) gave 117.0 mg (298 μmol, 55%) of **17** as a colorless oil; ^{1}H NMR (400 MHz, CDCl3) δ 1.79 (d, *J* = 6.6 Hz, 3 H), 1.80-1.90 (m, 1 H), 2.08-2.20 (m, 3 H), 2.63-2.72 (m, 1 H), 3.05-3.15 (m, 2 H), 3.34 (d, *J* = 15.5 Hz, 1 H), 3.64 (d, *J* = 15.5 Hz, 1 H), 3.65-3.80 (m, 1 H), 3.99 (s, 1 H), 5.62 (d, *J* = 11.2 Hz, 1 H), 5.71 (br d, *J* = 11.2 Hz, 1 H), 5.90 (d, *J* = 6.6 Hz, 1 H), 6.63 (d, *J* = 7.3 Hz, 1 H), 6.74 (t, *J* = 7.3 Hz, 1 H), 7.04 (t, *J* = 7.3 Hz, 1 H), 7.13 (d, *J* = 7.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 24.5, 38.0, 50.4, 53.2, 62.1, 62.8, 65.5, 109.4, 109.8, 118.8, 123.2, 125.4, 127.5, 127.6, 130.3, 149.7; LR MS *m/z* 392 (M^+), 265 (M^+-I), 211 (M^+-CH_3CH=$CICH_2$), 182, 167, 144; HR MS calcd for $C_{18}H_{21}N_2I$ 392.0750, found 392.0742; $[\alpha]^{22}_D$ = -7.08 (*c* 2.72, $CHCl_3$).

(-)-Dehydrotubifoline. A solution of **17** (6.5 mg, 16.6 μmol), $Pd(OAc)_2$ (0.37 mg, 1.65 μmol), K_2CO_3 (11.5 mg, 83.2 μmol) and Bu_4NCl (4.7 mg, 16.9 μmol) in DMF (4.5 mL) was heated at 60 °C for 3 h. After cooling to room temperature Et_2O was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with Et_2O/Et_3N (95:5) gave 2.6 mg (9.85 μmol, 59%) of (-)-dehydrotubifoline; ^{1}H NMR (400 MHz, CDCl3) δ 1.12 (d, *J* = 14.1 Hz, 1 H), 1.68 (d, *J* = 6.4 Hz, 3 H), 1.82 (d, *J* = 14.1 Hz, 1 H), 2.10-2.30 (m, 2 H), 2.72 (d, *J* = 15.5 Hz, 1 H), 3.18 (d, *J* = 15.5 Hz, 1 H), 3.20-3.25 (m, 1 H), 3.28-3.50 (m, 3 H), 3.79 (d, *J* = 15.5 Hz, 1 H), 4.05 (s, 1 H), 5.42 (q, 6.4 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl3) d 13.0, 25.2, 31.8, 34.9, 36.1, 53.4, 55.1, 65.1, 66.1, 119.5, 121.0, 127.4, 153.8, 189.0; LR MS (*m/z*) 264 (M^+), 249 (M^+-CH_3), 233, 180, 158, 121, 93; HR MS calcd for $C_{18}H_{20}N_2$ 264.1626, found 264.1614; $[\alpha]^{22}_D$ = -272.4 (*c* 0.906, AcOEt).

(-)-Tubifoline. A solution of (-)-dehydrotubifoline (18.0 mg, 68.1 μmol) in EtOH (10 mL) was stirred in the presence of PtO_2 (6.0 mg, 26.4 μmol) under H_2 for 1 h. The catalyst removed by filtration through a Celite pad, and the filtrate was concentrated.

The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$/MeOH (10:1) gave 5.8 mg (21.8 μmol, 32%) of (-)-tubifoline; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3 H), 1.15-1.18 m, 1 H), 1.59-1.65 (m, 1 H), 1.92-1.97 (m, 1 H), 2.30-2.40 (m, 1 H), 2.55 (t, *J* = 12.5 Hz, 1 H), 2.59 (d, *J* = 14.6 Hz, 1 H), 2.73-2.88 (m, 2 H), 3.11-3.20 (m, 2 H), 3.22-3.30 (m, 1 H), 3.79 (s, 1 H), 7.18 (d, *J* = 8.1 Hz, 1 H), 7.29-7.34 (m, 2 H), 7.53 (d, *J* = 8.1 Hz, 1 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 25.3, 26.6, 28.6, 32.4, 33.2, 41.7, 50.7, 57.3, 65.5, 69.5, 120.0, 121.2, 125.6, 127.9, 145.0, 154.3, 190.0; LR MS (*m/z*) 266 (M^+), 223 (M^+-$CH_3CH_2CH_2$), 208, 182, 167, 158; HR MS calcd for $C_{18}H_{22}N_2$ 266.1783, found 266.1804. $[\alpha]^{22}_D$ = -311.0 (*c* 0.236, AcOEt).