Supporting Information – Experimental Procedures

A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A and B

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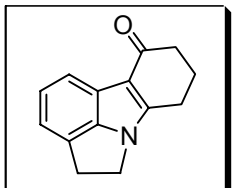
1. Materials and Methods.

Except as otherwise indicated, all reactions were carried out under an argon atmosphere in flame-dried glassware, and solvents were . The argon was deoxygenated and dried by passage through an OXICLEAR™ filter from Aldrich and Drierite tube, respectively. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium / benzophenone. Dichloromethane (CH_2Cl_2) and *N*-methyl pyrrolidinone (NMP) were distilled from calcium hydride. *s*-Butyllithium was purchased from Aldrich and titrated against *N*-benzylbenzamide prior to use. Except as indicated otherwise, all other reagents were purchased from Aldrich, Acros, or Strem chemicals and used as received. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Silica gel for flash chromatography (particle size 0.040-0.063 mm) was supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All melting points were determined on a Bristoline heated-stage microscope or Thomas Hoover apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer Model 283B, Perkin-Elmer Model 1600 FTIR, or Jasco FTIR-480plus spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported as δ values relative to internal $CDCl_3$ (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Optical rotations were obtained with a Perkin-Elmer polarimeter (model 241) in the solvent indicated. High resolution mass spectra were measured on either a VG Micromass 70/70H or VG ZAB-E spectrometer.

2. Detailed Experimental Procedures.

Preparation of 4,5,8,9-tetrahydropyrrolo[3,2,1-jk]carbazol-10(7H)-one (11).

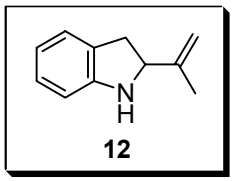


11

Compound **11** was prepared according to the procedure described by van Wijngaarden et al.[1] Since the authors did not supply full characterization data (^{1}H NMR, ^{13}C NMR, IR and HRMS data were not provided) we obtained the missing data.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 6.9 Hz, 1H), 4.48-4.41 (m, 2H), 3.87-3.73 (m, 2H), 2.91 (t, *J* = 6.2 Hz, 2H), 2.65-2.46 (m, 2H), 2.21 (td, *J* = 12.6, 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 149.5, 147.1, 124.5, 123.5, 119.5, 119.0, 117.4, 117.1, 47.6, 37.8, 33.9, 23.7, 22.9; IR (neat) 3040 (w), 2943 (w), 1636 (s), 1577 (w), 1489 (w), 1445 (s), 1427 (m), 1410 (m), 1394 (w), 1360 (w), 1344 (m), 1320 (w), 1182 (m), 1151 (w), 1120 (m), 1036 (w), 1015 (w), 969 (w), 922 (w), 894 (w), 809 (w), 775 (w), 725 (w). M.p. = 208-209 °C (lit. 208-210 °C). HRMS (CI-MS) calcd. for $C_{14}H_{13}NO$ [M^+] 211.0997, found 211.0996.

Preparation of 2-(prop-1-en-2-yl)indoline (12).



12

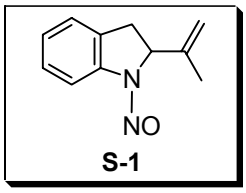
Compound **12** was prepared according to the procedure described by H.A. Dieck et al.[2] Since the authors did not supply full characterization data (^{13}C NMR, IR and HRMS data were not provided) we obtained the missing data.

(1) van Wijngaarden, I.; Hamminga, D.; van Hes, R.; Standaar, P. J.; Tipker, J.; Tulp, M. T. M.; Mol, F.; Olivier, B.; de Jonge, A. *J. Med. Chem.* **1993**, *36*, 3693-3699.

(2) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807-809.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.73 (dt, *J* = 7.4, 0.9 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 0.8 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 4.41 (t, *J* = 9.1 Hz, 1H), 3.88 (s, 1H), 3.23 (dd, *J* = 15.5, 9.2 Hz, 1H), 2.89 (dd, *J* = 15.5, 8.9 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 146.7, 128.1, 127.3, 124.5, 118.3, 110.4, 108.6, 64.8, 35.4, 18.3; IR (neat) 3371 (br, s), 3074 (m), 3051 (m), 3030 (m), 2969 (s), 2912 (s), 2847 (s), 1918 (w), 1875 (w), 1803 (w), 1651 (m), 1608 (s), 1484 (s), 1465 (s), 1439 (m), 1398 (m), 1320 (m), 1301 (w), 1246 (s), 1151 (w), 1104 (w), 1063 (w), 1046 (w), 1018 (m), 998 (w), 975 (w), 898 (s), 847 (w), 747 (s), 710 (m), 692 (m). HRMS (CI-MS) calcd. for $C_{11}H_{13}N$ [M^+] 159.1048, found 159.1037.

Preparation of 1-nitroso-2-(prop-1-en-2-yl)indoline (S-1).



S-1

A 10 mL round bottom flask was charged with 2-isopropenyl indoline **12** (1.35 g, 8.49 mmol, 1 equiv; FW = 159.10) followed by 10% aqueous HCl solution (3.90 mL, 11.03 mmol, 1.3 equiv). The resulting suspension was cooled to 0 °C using an ice/water bath.

In the meantime, $NaNO_2$ (644 mg, 1.1 equiv; FW = 68.99) was dissolved in deionized water (5.00 mL) and this solution was added dropwise to the vigorously stirred suspension of **12** and aqueous HCl over 3 minutes. After each drop of the $NaNO_2$ solution, the color of the reaction mixture turned dark brownish red and then faded. At the end of the addition the reaction mixture had a permanent brownish red color. It was then allowed to warm to room temperature and stirred for 2 hours. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 4 : 1 where the product had a R_f value of 0.6).

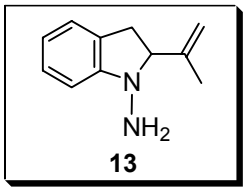
Workup: The reaction mixture was diluted with deionized water (20 mL) and extracted with chloroform (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL) then dried over $MgSO_4$ and the solvent was evaporated.

Purification: The crude product was isolated as brownish red oil: 1.59 g (96%). It was found to be sufficiently pure and was taken onto the next step without further purification.

Remarks: The product is not very stable. When a sample was subjected to column chromatography (Hexanes : EtOAc = 10 : 1) the dark color components could be temporarily removed (the product is a yellow oil), but upon standing, the dark color quickly returns. Interestingly, the NMR spectra of the crude product and the freshly purified sample do not differ much; the same contaminants are present in both.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.42-7.27 (m, 2H), 7.24 (ddd, *J* = 12.0, 6.2, 2.5 Hz, 1H), 5.18 (dd, *J* = 9.9, 3.5 Hz, 1H), 4.80 (s, 1H), 4.76 (s, 1H), 3.46 (dd, *J* = 16.6, 9.9 Hz, 1H), 2.91 (dd, *J* = 16.6, 3.5 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 130.4, 128.3, 126.9, 126.0, 114.4, 111.9, 111.3, 63.2, 34.1, 18.1; IR (neat) 3083 (m), 3051 (m), 2974 (m), 2937 (m), 2854 (w), 1654 (m), 1595 (m), 1485 (s), 1468 (s), 1426 (s), 1377 (m), 1363 (m), 1340 (m), 1293 (s), 1261 (s), 1223 (s), 1198 (s), 1167 (s), 1096 (m), 1048 (w), 1024 (w), 1015 (w), 995 (w), 941 (w), 900 (s), 873 (w), 815 (w), 784 (w), 754 (s), 705 (m), 694 (s). HRMS (CI-MS) calcd. for $C_{11}H_{13}N_2O$ $[(M+H)^+]$ 189.1028, found 189.1031.

Preparation of 2-(prop-1-en-2-yl)indolin-1-amine (13).



13

A 250 mL round bottom flask, equipped with a reflux condenser, was charged with $LiAlH_4$ (760 mg, 2 equiv; FW = 37.95) and then it was suspended in THF (80 mL). Next, the suspension was brought to reflux and a solution of **S-1** (1.88 g, 10 mmol, 1 equiv; FW = 188.22) in THF (20 mL) was added dropwise over 30 minutes. After the addition of **S-1** was complete, the reaction mixture was kept at reflux for 2 hours. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.55).

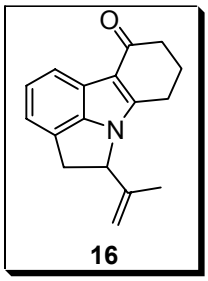
Workup: The reaction mixture was allowed to cool to room temperature and was carefully treated with the following substances/solutions: first, H_2O (1.0 mL) was added dropwise (Caution: gas evolution!), then aqueous 2N NaOH (2.0 mL) and finally again H_2O (1.0 mL), The resulting grayish/white suspension was heated to reflux for 15 minutes during which time a solution became pale yellow and a white precipitate formed. The reaction mixture was then filtered and the filtrate evaporated *in vacuo*.

Purification: The crude product was isolated as a yellow oil: 1.74 g (~100%). It was found to be sufficiently pure and it was taken onto the next step without further purification.

Remarks: The product is not very stable and has to be used immediately. The reaction was found to work best with new $LiAlH_4$.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.80 (dt, *J* = 7.4, 1.0 Hz, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 3.67 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.38 (s, 2H), 3.05 (dd, *J* = 15.3, 8.4 Hz, 1H), 2.81 (dd, *J* = 15.3, 11.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 152.7, 127.5, 127.1, 124.2, 119.9, 114.0, 110.0, 79.1, 33.6, 18.1; IR (neat) 3342 (br, w), 3073 (w), 3047 (w), 3026 (w), 2969 (w), 2946 (w), 2912 (w), 2844 (w), 1649 (w), 1644 (w), 1636 (w), 1624 (m), 1620 (m), 1615 (m), 1608 (m), 1595 (m), 1475 (s), 1460 (m), 1455 (m), 1440 (m), 1435 (m), 1357 (w), 1325 (w), 1300 (w), 1260 (w), 1238 (w), 1228 (w), 1185 (w), 1134 (w), 1078 (w), 1016 (w), 981 (w), 898 (m), 849 (w), 793 (w), 749 (s), 724 (w), 717 (w), 620 (w). HRMS (CI-MS) calcd. for $C_{11}H_{14}N_2$ [M^+] 174.1157, found 174.1155.

Preparation of 5-(prop-1-en-2-yl)-4,5,8,9-tetrahydropyrrolo[3,2,1-jk]carbazol-10(7H)-one (16).



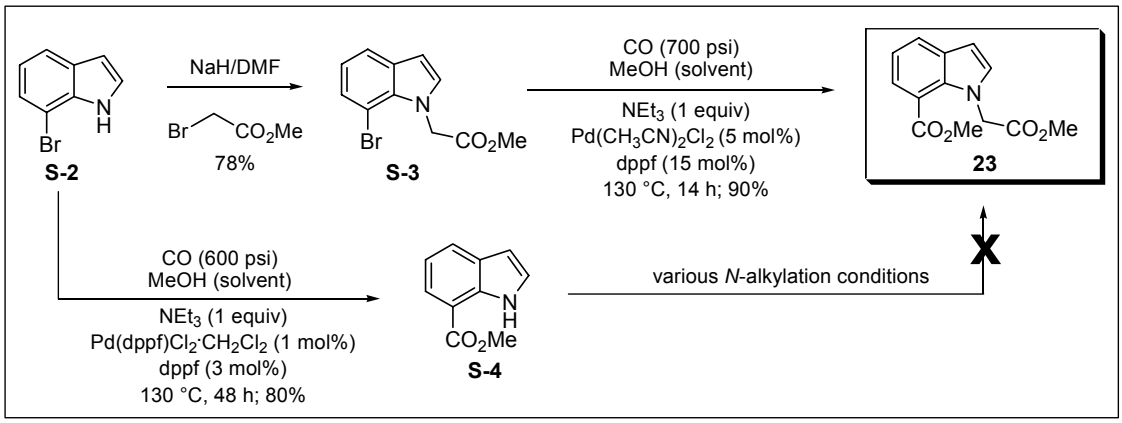
16

A 250 mL round bottom flask equipped with a reflux condenser was charged with the crude hydrazine **13** (1.74 g; ~10.00 mmol, 1 equiv; FW = 174.24), 200 proof EtOH (100 mL) and glacial acetic acid (11 mL). The resulting brownish yellow solution was then heated to reflux and kept at that temperature for 12 h. The solvent was then evaporated *in vacuo* and the crude product subjected to column chromatography (gradient elution with Hexanes : EtOAc = 12:1 to 8:1 to 4:1). Hydrazone **14** was obtained as an amorphous solid: 1358 mg (50%) along with some of the tetracyclic indole **16**: 234 mg (9%).

Next, hydrazone **14** was dissolved in glacial acetic acid (100 mL) and heated to reflux for 12 h. The solvent was then evaporated and the crude material subjected to column chromatography.

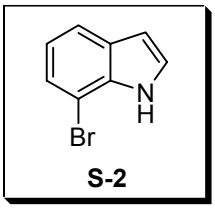
Purification: MeOH *:* $CHCl_3$ = 1 : 20. The tetracyclic indole product **16** was obtained as a white solid: 254 mg (20%) with a sharp melting point; M.p.=134-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 5.29 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.99 (s, 2H), 4.00 (dd, *J* = 16.3, 8.6 Hz, 1H), 3.52 (dd, *J* = 16.3, 4.4 Hz, 1H), 2.83 (dt, *J* = 6.0, 2.5 Hz, 2H), 2.54 (dd, *J* = 6.9, 5.7 Hz, 2H), 2.17 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 149.9, 147.0, 142.6, 124.5, 122.7, 119.0, 117.3, 117.2, 116.9, 113.7, 67.1, 41.3, 37.8, 23.7, 22.7, 16.9; IR (neat) 3063 (w), 2939 (w), 1645 (s), 1464 (m), 1456 (m), 1441 (s), 1436 (s), 1429 (s), 1419 (m), 1413 (m), 1387 (w), 1362 (w), 1331 (m), 1183 (m), 1118 (m), 1037 (w), 1015 (w), 911 (w), 761 (m); HRMS (CI-MS) calcd. for $C_{17}H_{17}NO$ [M^+] 251.1310, found 251.1304.



Preparation of diester 23 from S-2

Preparation of 7-bromo-1*H*-indole (S-2).[3, 4]



Remark: The literature described the preparation of this compound only on a 1 mmol scale using the Bartoli indole synthesis. We disclose the procedure on a 30 mmol scale which delivers substantial quantities of this very expensive material.

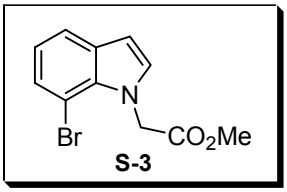
Large scale procedure: A 500 mL round bottom flask was charged with 1-bromo-2-nitrobenzene (6.00 g, 29.70 mmol, 1 equiv; FW = 202.01) and THF (180 mL). The resulting bright yellow solution was cooled to -45 °C. Then a 1.0 M THF solution of vinylmagnesium bromide (90 mL, 90 mmol, 3 equiv) was added over 10 minutes, while the internal temperature of the reaction mixture was carefully monitored. (Since the reaction is quite exothermic, the rate of addition has to be adjusted so that the internal temperature does not rise above -40 °C.) During the addition of the vinylmagnesium bromide, the color changed from bright yellow to orange. After the addition was complete, the reaction mixture was stirred at -45 °C for another 25 minutes.

(3) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989,** *30*, 2129-2132.
(4) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2757-2761.

Workup: The reaction mixture was poured into saturated aqueous NH_4Cl solution (200 mL) and extracted with Et_2O (5 x 75 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was subjected to column chromatography (Hexanes : EtOAc = 9 : 1) on a column having the following properties: diameter = 5.0 cm, packing length = 30 cm, fraction size = 45 mL. The product was obtained as light yellow crystals: 4.17 g (72%). M.p.= 43-44 °C (lit.[3] 43-44 °C).

Preparation of S-3 from S-2.



S-3

A 100 mL round bottom flask was sequentially charged with 95% NaH (386 mg, 15.30 mmol, 3 equiv; FW = 23.99) and dry DMF (30 mL). The resulting suspension was cooled to 0 °C with an ice/water bath.

In the meantime, 7-bromoindole **S-2** (1.00 g, 5.10 mmol, 1 equiv; FW = 196.04) was dissolved in dry DMF (5 mL) and the resulting solution was added to the cooled NaH/DMF suspension dropwise over 10 minutes. During the addition, the evolution of hydrogen gas (H_2) was observed. The reaction mixture was allowed to stir for 1 h at 0 °C. Next, a solution of methyl bromoacetate (1.17 g, 7.65 mmol, 1.5 equiv; FW = 152.97) in dry DMF (5 mL) was added over 5 minutes. The progress of the reaction was followed by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.65). The starting material was consumed in 15 minutes.

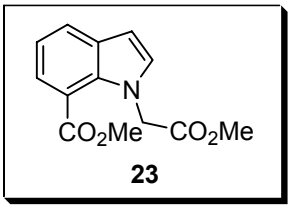
Workup: The reaction mixture was poured into a solution of brine (150 mL) and extracted with Et_2O (4 x 80 mL). The combined organic layers were then washed with brine (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was subjected to column chromatography (Hexanes : EtOAc = 10:1) on a column having the following properties: diameter = 3.5 cm, packing length = 33 cm,

fraction size = 45 mL. The product was obtained as a pale yellow solid: 1.07 g (78%). M.p. = 69-70 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 3.2 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 5.30 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 132.8, 131.8, 131.3, 127.1, 121.1, 120.6, 103.5, 102.8, 52.6, 49.9; IR (neat) 3104 (w), 3064 (w), 2999 (w), 1751 (s), 1559 (m), 1482 (m), 1436 (s), 1319 (s), 1273 (w), 1214 (s), 1176 (s), 1133 (w), 1099 (w), 1047 (w), 998 (w), 958 (w), 916 (w), 856 (w), 813 (w), 782 (m), 764 (w), 719 (m), 697 (w). HRMS (CI-MS) calcd. for $C_{11}H_{10}BrNO_2$ [M^+] 266.9895, found 266.9906.

Preparation of methyl 1-(2-methoxy-2-oxoethyl)-1H-indole-7-carboxylate (23).



23

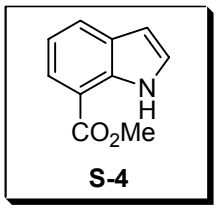
A 50 mL bomb (rated to withstand a pressure of 1000 psi) was charged with **S-3** (220 mg, 0.82 mmol, 1 equiv; FW = 268.11) and HPLC grade MeOH (5 mL). Next, $Pd(CH_3CN)_2Cl_2$ (10.64 mg, 0.041 mmol, 5 mol%; FW = 259.41), dppf (68.19 mg, 0.123 mmol, 15 mol%; FW = 554.39) and NEt_3 (114 μL, 0.82 mmol, 1 equiv; FW = 101.19) were added. The resulting solution was purged with a stream of carbon-monoxide gas for 1 minute and then the bomb pressurized to 700 psi with carbon-monoxide. The bomb was then immersed in an oil bath and heated to 130 °C for 14 h. After cooling the apparatus, the bomb was very slowly depressurized (caution: danger of spraying the contents of the bomb through the valve if one depressurizes too quickly). The status of the reaction was checked by TLC (Hexanes : EtOAc = 3 : 1 where the product had a R_f value of 0.6) and visualized using Ehrlich's reagent (product shows up as a red spot upon heating the TLC plate). The TLC showed spot to spot conversion of the starting material to the product.

Workup: The solvent was evaporated *in vacuo*.

Purification: The crude product was subjected to column chromatography (gradient elution with Hexanes : EtOAc = 12:1 to 8:1 to 5:1) on a column having the following properties: diameter = 2.5 cm, packing length = 20 cm, fraction size = 8 mL. The product was obtained as a thick, colorless oil: 182 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.6, 5.2 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 3.2 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 5.22 (s, 2H), 3.91 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 167.8, 133.8, 131.8, 131.5, 126.0, 119.5, 119.0, 115.9, 103.1, 52.1, 52.2, 51.7; IR (neat) 3001 (w), 2951 (w), 1750 (s), 1714 (s), 1528 (m), 1436 (s), 1318 (m), 1271 (s), 1207 (s), 1176 (m), 1137 (s), 1112 (w), 1067 (w), 1049 (w), 1020 (w), 961 (w), 923 (w), 843 (w), 811 (w), 779 (w), 756 (m), 722 (w), 667 (w). HRMS (CI-MS) calcd. for $C_{13}H_{13}NO_4$ [M^+] 247.0845, found 247.0840.

Preparation of methyl 1H-indole-7-carboxylate (S-4).[5]



S-4

A 50 mL bomb (rated to withstand a pressure of 1000 psi) was charged with 7-bromoindole **S-2** (4.00 g, 20.40 mmol, 1 equiv; FW = 196.04) and HPLC grade MeOH (15 mL). The resulting solution was purged with carbon monoxide gas for 10 minutes. Next, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (166 mg, 0.204 mmol, 1 mol%; FW = 816.68), dppf (339 mg, 0.612 mmol, 3 mol%; FW = 554.34) and NEt_3 (2.84 mL, 20.40 mmol, 1 equiv; FW = 101.19, d = 0.726) were added. The bomb was then sealed and pressurized to 600 psi with carbon monoxide. The bomb was immersed in an oil bath and heated to 130 °C for 48 h. After cooling the apparatus, the bomb was very slowly depressurized (caution: danger of spraying the contents of the bomb through the valve if one depressurizes too quickly). The status of the reaction was checked by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.8) and visualized using Ehrlich's reagent (product

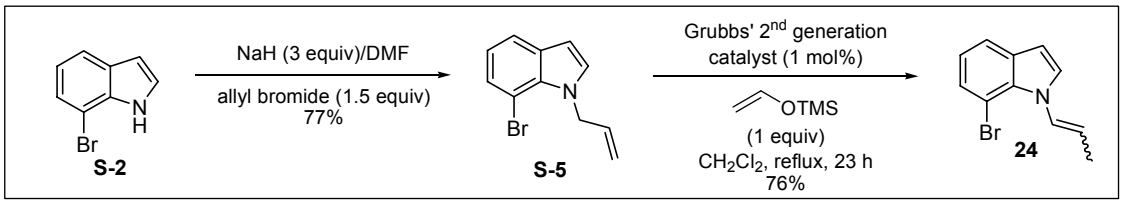
(5) This compound was prepared before using different methods: Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. *J. Heterocycl. Chem.* **1989**, *26*, 1405-1413, Soderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838-5845.

shows up as a red spot upon hearing the TLC plate). The TLC showed spot to spot conversion of the starting material to product.

Workup: The solvent was evaporated *in vacuo*.

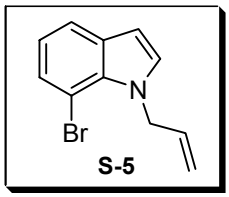
Purification: The crude product was subjected to column chromatography (gradient elution with Hexanes : EtOAc = 20:1 to 10:1) on a column having the following properties: diameter = 5.0 cm, packing length = 25 cm, fraction size = 45 mL. The product was obtained as a pale yellow solid: 2.85 g (80%). M.p. = 48-49 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.91 (dd, *J* = 19.3, 7.5 Hz, 2H), 7.32 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 4.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 135.7, 129.1, 126.4, 125.2, 124.2, 119.00, 112.4, 102.5, 51.8; HRMS (CI-MS) calcd. for $C_{10}H_9NO_2$ $[M^+]$ 175.0633, found 175.0630.



Preparation of compound 24 from S-2

Preparation of 1-allyl-7-bromo-1H-indole (S-5).[6]



A 250 mL round bottom flask was charged with 95% NaH (850 mg, 33.66 mmol, 3 equiv; FW = 23.99) and dry DMF (50 mL). The resulting suspension was cooled to 0 °C.

In the meantime, 7-bromoindole **S-2** (2.20 g, 11.22 mmol, 1 equiv; FW = 196.04) was dissolved in dry DMF (20 mL). The resulting solution was slowly added to the vigorously stirred suspension of NaH at 0 °C over 10 minutes. (Caution: hydrogen gas evolution!) The reaction mixture was stirred at 0 °C for 20 minutes and then allyl bromide (2.04 g, 16.83 mmol, 1.5 equiv; FW = 120.95, d = 1.398) was added at 0 °C over 5 minutes. The reaction mixture was then allowed to warm to room temperature. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.5).

Workup: The reaction mixture was quenched with brine (150 mL) and was extracted with Et_2O (5 x 50 mL). The combined organic layers were then washed with brine (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

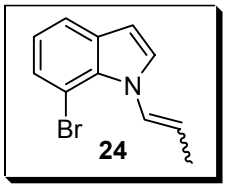
Purification: The crude product was subjected to column chromatography (Hexanes : EtOAc = 9:1) on a column having the following properties: diameter = 5.5 cm, packing length = 25 cm, fraction size = 45 mL. The product was obtained as a pale yellow oil: 2.05 g (77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.41 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 6.12 (tdd, *J* = 17.1, 10.3,

(6) This compound has been prepared before using a different method: Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5379-5382.

4.9 Hz, 1H), 5.22 (td, *J* = 4.9, 1.7 Hz, 2H), 4.96-4.84 (m, 1H), 5.19 (ddd, *J* = 10.3, 2.8, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 132.4, 131.8, 130.7, 126.9, 120.6, 120.4, 116.2, 103.6, 102.0, 50.2.

Preparation of 7-bromo-1-(prop-1-enyl)-1H-indole (24). (^{1}H NMR peaks are reported for the major E isomer while the ^{13}C NMR peaks are reported for the E/Z mixture):



24

A 500 mL round bottom flask, equipped with a reflux condenser, was charged with **S-5** (2.03 g, 8.59 mmol, 1 equiv; FW = 236.10) and CH_2Cl_2 (350 mL). Next, neat vinyloxytrimethylsilane (1.00 g, 8.59 mmol, 1 equiv; FW = 116.24, d = 0.779) was added. The reaction mixture was heated to reflux, then in one portion, Grubbs' second generation catalyst (73 mg, 0.086 mmol, 1 mol%; FW = 848.98) was added. The reaction was kept at reflux for 23 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 4:1 where the product had a R_f value of 0.75).

Workup: The solvent was evaporated *in vacuo*.

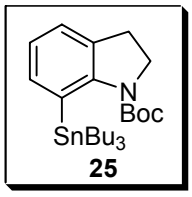
Purification: The crude product was purified using column chromatography (Hexanes : EtOAc = 24:1) and the product obtained as a pale yellow oil: 1.54 g (76%). The product is a 3:2 mixture of E/Z stereoisomers. Also, a small amount of starting material **S-5** was recovered: 308 mg (15%).

Remarks: The above procedure was based on the isomerization of *N*-allyl sulfonamides to the corresponding *N*-alkenyl sulfonamides reported by M. Arisawa.[7] The E/Z ratio changes with time during storage of the product. Also, depending on the acidity of the silica gel used for the purification, the E/Z ratio may increase. The use of 5 mol% catalyst increases the conversion to the product significantly. However, on large scale the use of no more than 1 mol% of catalyst is recommended.

(7) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4732-4734.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.38 (m, 2H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.58 (d, *J* = 3.2 Hz, 1H), 5.66 (qd, *J* = 14.1, 7.0 Hz, 1H), 1.75 (dd, *J* = 7.0, 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 132.1, 131.9, 131.2, 130.5, 128.2, 127.7, 127.5, 127.5, 126.9, 121.1, 121.0, 120.5, 120.4, 120.2, 115.2, 104.4, 104.0, 103.4, 102.6, 15.3, 12.5; IR (neat) 3104 (w), 3053 (w), 2973 (w), 2940 (w), 2916 (w), 2858 (w), 1659 (m), 1652 (m), 1557 (m), 1475 (s), 1427 (s), 1399 (m), 1363 (m), 1323 (s), 1276 (s), 1251 (w), 1191 (s), 1133 (m), 1097 (w), 1075 (w), 1051 (w), 1029 (w), 916 (m), 828 (w), 781 (s), 769 (w), 733 (m), 716 (s); HRMS (CI-MS) calcd. for $C_{11}H_{10}BrN$ [M^+] 234.9997, found 234.9999.

Preparation of 7-tributylstannanyl-2,3-dihydro-indole-1-carboxylic acid *tert*-butyl ester (25).



25

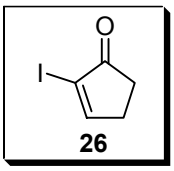
A 250 mL round bottom flask was charged with *N*-Boc indoline (4.30 g, 19.6 mmol, 1 equiv; FW: 219.28) and diethyl ether (100 mL) to make an approximately 0.2 M solution. (Note: a more concentrated solution results in the precipitation of the starting material at -78 °C.) Next, TMEDA was added (3.90 mL, 1.3 equiv) and the resulting solution cooled to -78 °C with an acetone/dry ice bath. Once the temperature was at equilibrium, *sec*-BuLi (19.61 mL, 1.3 equiv; 1.3 M in cyclohexane) was added slowly over 10 minutes. During the course of the addition, the initially pale yellow solution slowly turned into a strong orange color. After 1 hour at -78 °C, Bu_3SnCl (7.98 mL, 1.5 equiv; FW = 328.49; d = 1.207; 96%) was added *via* syringe over 3 minutes. The reaction mixture was then kept at -78 °C for another 30 minutes, and then allowed to warm to room temperature over an hour. The progress of the reaction was followed by TLC (Hexanes : EtOAc = 10:1) where the product had a R_f value of 0.35). Anisaldehyde stain was used to develop the chromatogram.

Workup: The reaction mixture was diluted with diethyl ether (100 mL) and slowly poured into 250 mL of deionized water with vigorous stirring. The aqueous layer was further extracted with diethyl ether (3 x 75 mL). The combined organic layers were then washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was preabsorbed onto silica gel (30 g) and purified *via* flash chromatography using Hexanes: EtOAc = 15:1 (diameter = 6.5 cm; packing length = 25 cm; fraction size = 45 mL). The product was obtained as a thick, colorless oil: 7.80g (78%). The various spectra of this product were in excellent agreement with those reported in the literature.[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 6.6 Hz, 1.2 Hz, 1H), 7.10 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 3.96 (t, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 8.4 Hz, 2H), 1.51 (s, 9H), 1.40-1.60 (m, 6H), 1.32 (sextet, *J* = 7.2 Hz, 6H), 0.97 (m, 6H), 0.87 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.2, 136.6, 131.5, 130.5, 124.5, 122.8, 80.7, 48.2, 29.6, 28.8, 28.2, 27.9, 14.0, 13.2; HRMS (CI-MS) calcd. for $C_{25}H_{43}NO_2SnNa$ [$(M+Na)^+$] 509.2316, found 532.2201.

Preparation of 2-iodo-2-cyclopentene-1-one (26).



26

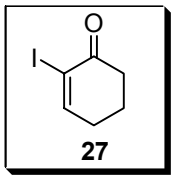
Compound **26** was prepared according to the procedure described by C.R. Johnson et al.[9]

M.p. = 70-71 °C (lit. 71 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dt, *J* = 2.9, 0.8 Hz, 1H), 2.75 (m, 2H), 2.47(m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 169.5, 102.7, 31.2, 30.8.

(8) Diep, V.; Dannenberg, J. J.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 7907-7910.
(9) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917-918.

Preparation of 2-iodo-2-cyclohexene-1-one (27).



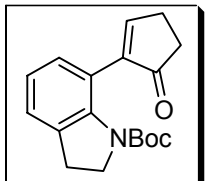
27

Compound **27** was prepared according to the procedure described by C.R. Johnson et al.[9]

M.p. = 49-50 °C (lit. 48.0-48.5 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (t, *J* = 4.4 Hz, 1H), 2.82-2.55 (m, 2H), 2.44 (dt, *J* = 5.9, 4.5 Hz, 2H), 2.09 (td, *J* = 13.3, 5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 159.3, 103.9, 37.2, 29.9, 22.8.

Preparation of arylated 2-cyclopentenone (28).



28

A 100 mL round bottom Schlenk flask was charged with 7-tributylstannyl-*N*-Boc indoline **25** (5.08 g, 10.00 mmol, 1.5 equiv; FW = 508.32) followed by dry NMP (35 mL). Next, $Pd_2(dba)_3{\cdot}CHCl_3$ (345 mg, 0.333 mmol, 5 mol%; FW = 1035.08) and P(2-furyl)$_3$ (310 mg, 1.334 mmol, 20 mol%; FW = 232.17) were added quickly. The resulting solution was purged with Ar for 15 minutes as the initially deep purple color turned into a dark, almost transparent, green color.

In the meantime, in a 20 mL round bottom flask, 2-iodo-2-cyclopentenone **26** (1.387 g, 6.67 mmol, 1 equiv; FW = 207.99) was dissolved in dry NMP and sealed. Also, CuI (1.27 g, 6.67 mmol, 1 equiv; FW = 190.44) was flame-dried in a 10 mL round bottom flask under vacuum and allowed to cool to room temperature.

Once the reaction mixture was purged for the designated 15 minutes, the NMP solution of the 2-iodo-2-cyclopentenone **26** was added *via* syringe followed by addition of the CuI in one portion. The reaction vessel was then equipped with a reflux condenser.

The flask was then heated to 120 °C for 50 minutes using a heating mantel. The color of the reaction mixture turned strongly yellow at around 50 °C and then became completely black once

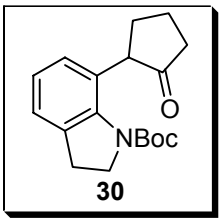
the temperature exceeded 100 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.3). The product **28** had almost the same R_f value as the starting material **26**, however, the product stained much faster with $Ce(SO_4)_2$ initially showing a red color when heated on the TLC plate.

Workup: The reaction mixture was slowly poured into a 500 mL Erlenmeyer flask containing saturated ammonium hydroxide (200 mL) and Et_2O (200 mL) with vigorous stirring. The ether layer became turbid yellow. The aqueous layer was then washed with Et_2O (3 x 200 mL) and EtOAc (1 x 100 mL). The combined organic layers were then washed with brine (4 x 75 mL), dried over $MgSO_4$, concentrated *in vacuo* and preabsorbed onto silica gel (25 g).

Purification: The crude product (now on silica gel) was purified using Hexanes : EtOAc = 4:1 on a column which had the following properties: diameter = 6.5 cm, packing length = 21 cm, fraction size = 45 mL. The product eluted after the residual tin starting material, by-products, as well as proto-destannylated starting material. The product was isolated as an off white powder: 1.488 g (75%). M.p. = 149-150 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (t, *J* = 2.7 Hz, 1H), 7.23-7.07 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.08 (t, *J* = 8.1 Hz, 2H), 3.03 (t, *J* = 8.1 Hz, 2H), 2.76-2.68 (m, 2H), 2.51 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 154.0, 152.5, 146.8, 140.4, 134.2, 128.7, 124.3, 123.3, 120.4, 80.1, 49.5, 34.4, 28.7, 28.2, 26.6; IR (neat) 2965 (br, m), 1702 (s), 1435 (m), 1386 (s), 1333 (m), 1244 (m), 1165 (m), 1012 (m), 761 (w), 736 (m); HRMS (CI-MS) calcd. for $C_{18}H_{21}NO_3$ [$(M)^+$] 299.1521, found 299.1527.

Preparation of *tert*-butyl 7-(2-oxocyclopentyl)indoline-1-carboxylate (30).



30

A 100 mL round bottom flask was was charged with the α,β-unsaturated ketone derivative **28** (600 mg, 2.00 mmol, 1 equiv; FW = 299.36) and THF (20 mL) and the resulting solution was cooled to -78 °C with an acetone/dry ice bath. Next, a 1.0 M L-Selectride solution in THF (2.20 mL, 2.2 mmol, 1.1 equiv; Aldrich metal cylinder) was added over 5 minutes. The color of the initial pale yellow solution turned darker by the end of addition. The cold bath was then removed and the reaction mixture allowed to warm to room temperature. The progress of the reaction was followed by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.45). The chromatogram was developed using $Ce(SO_4)_2$, and upon heating, the product turned deep blue while the starting material was brownish red.

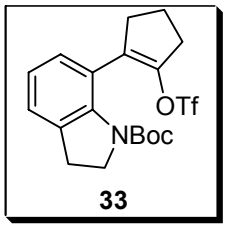
Workup: The reaction mixture was sequentially diluted with Et_2O (10 mL) and 2N NaOH (40 mL) with vigorous stirring. The aqueous layer was then extracted with Et_2O (3 x 40 mL) and EtOAc (2 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (10 g) and chromatographed with Hexanes : EtOAc = 4:1 on a flash column with the following specifications: diameter = 4.0 cm; packing length = 30 cm; fraction size = 45 mL. The product was obtained as a very thick (almost sappy) colorless oil which solidified upon standing over 3 days to give a white solid: 402 mg (67%). M.p. = 73-74 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.3, 1.05 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.15 (dddd, *J* = 10.9, 8.7, 4.5, 0.8 Hz, 1H), 3.96 (ddd, *J* = 11.2, 9.9, 8.8 Hz, 1H), 3.83 (dd, *J* = 12.0, 8.2 Hz, 1H), 3.15-2.95 (m, 1H), 2.93-2.82 (m, 1H), 2.78-2.65 (m, 1H), 2.44 (dd, *J* = 18.7, 8.3 Hz, 1H), 2.35-2.22 (m, 1H), 2.12 (dt, *J* = 14.7, 7.2 Hz, 1H), 2.08-1.99 (m, 1H), 1.96-1.83 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.7, 153.9, 142.1, 135.0, 129.0, 127.5, 124.8, 123.0, 80.5, 53.9, 50.7, 38.5, 31.8, 29.5, 28.3, 20.9; IR (neat) 2972 (m),

2359 (m), 2340 (m), 1740 (s), 1701 (s), 1597 (w), 1479 (w), 1449 (m), 1368 (s), 1333 (m), 1241 (m), 1158 (s), 1123 (m), 1052 (w), 1007 (w), 846 (w), 768 (w), 740 (w). HRMS (CI-MS) calcd. for $C_{18}H_{23}NO_3Na$ [$(M+Na)^+$] 324.1576, found 324.1561.

Preparation of *tert*-butyl 7-(2-(trifluoromethylsulfonyloxy)cyclopent-1-enyl)indoline-1-carboxylate (33).



33

A 25 mL round bottom flask was charged with α,β-unsaturated ketone **28** (300 mg, 1 mmol, 1 equiv; FW = 299.36) and THF (10 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M THF solution of L-Selectride (1.10 mL, 1.1 mmol; 1.1 equiv) was added over 3 minutes and stirring continued at -78 °C for an additional 10 minutes.

In the meantime, Comins' reagent (589 mg, 1.5 mmol, 1.5 equiv; FW = 392.68) was dissolved in THF (5 mL), and the resulting solution was added to the reaction mixture at -78 °C over 3 minutes. The reaction mixture was then allowed to stir at -78 °C for 30 minutes at which point the reaction was judged complete by TLC analysis (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.7).

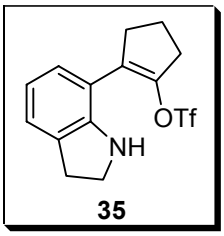
Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (10 g) and chromatographed with Hexanes : EtOAc = 20:1 on a flash column with the following specifications: diameter = 3.5 cm; packing length = 20 cm; fraction size = 45 mL. The product was obtained as a white solid: 380 mg (87%). M.p. = 104-105 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.1 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.02-6.98 (m, 1H), 4.05 (t, *J* = 8.0 Hz, 2H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.87-2.78 (m, 2H), 2.74-2.68 (m, 2H),

2.22-2.02 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 141.8, 140.3, 134.5, 130.5, 126.8, 124.3, 123.4, 122.1, 121.8, 119.5, 117.0, 114.4, 80.2, 49.5, 32.2, 31.3, 29.0, 28.2, 20.2 (the CF_3 group shows up as a quartet and all four of these peaks are reported) ; IR (neat) 2966 (m), 2929 (m), 2862 (w), 1701 (s), 1590 (w), 1478 (m), 1450 (s), 1418 (s), 1380 (s), 1331 (s), 1246 (s), 1197 (s), 1144 (s), 1097 (m), 1053 (w), 1034 (w), 1006 (m), 987 (m), 914 (w), 873 (s), 848 (s), 781 (w), 765 (m), 736 (w), 683 (w), 609 (s), 584 (w), 535 (w), 519 (w). HRMS (CI-MS) calcd. for $C_{19}H_{23}F_3NO_5S$ $[(M+H)^+]$ 434.1249 found 434.1267.

Preparation of 2-(indolin-7-yl)cyclopent-1-enyl trifluoromethanesulfonate (35).



35

A 25 mL round bottom flask was charged with *N*-Boc enol triflate **33** (343 mg, 1.00 mmol, 1 equiv; FW = 433.44) and CH_2Cl_2 (5 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, TMSI (400 mg, 285 μL, 2 mmol, 2 equiv; FW = 200.10, d = 1.4) was added over 2 minutes. The reaction mixture then was allowed to warm to room temperature at which point the reaction was complete (spot to spot conversion). The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.60).

Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*.

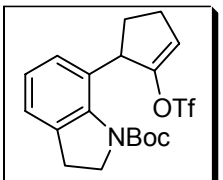
Purification: The crude product was preabsorbed onto silica gel (3 g) and chromatographed with Hexanes : EtOAc = 4:1 on a flash column with the following specifications: diameter = 2.5 cm; packing length = 20 cm; fraction size = 8 mL. The product was obtained as a yellow oil: 302 mg (90%).

Remarks: It is important to note that the crude product is usually very clean (depending on the quality of the TMSI) and no purification is necessary. We found that the yield of the Buchwald-

Hartwig coupling reaction (next step) was unaffected when using either the crude or purified material.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 3.59 (t, *J* = 8.5 Hz, 2H), 3.06 (t, *J* = 8.3 Hz, 2H), 2.78 (ttd, *J* = 10.0, 5.1, 2.4 Hz, 4H), 2.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 142.6, 130.1, 129.9, 126.4, 124.6, 122.1, 119.5, 118.4, 117.0, 114.1, 47.0, 32.6, 31.7, 29.8, 20.0 (the CF_3 group shows up as a quartet and all the peaks are reported); IR (neat) 3432 (br, m), 3059 (w), 2948 (m), 2857 (m), 2360 (w), 1727 (w), 1677 (w), 1597 (m), 1483 (m), 1451 (s), 1437 (s), 1419 (s), 1321 (m), 1282 (w), 1246 (s), 1212 (s), 1139 (s), 1097 (m), 1060 (w), 1031 (w), 992 (m), 982 (m), 950 (w), 915 (w), 875 (s), 851 (s), 767 (m), 743 (m), 679 (w), 609 (s), 515 (m). HRMS (CI-MS) calcd. for $C_{14}H_{14}F_3NO_3S$ [M^+] 333.0646., found 333.0644.

Preparation of *tert*-butyl 7-(2-(trifluoromethylsulfonyloxy)cyclopent-2-enyl)indoline-1-carboxylate (32).



32

A 50 mL round bottom flask was charged with THF (15 mL) and 1.0 M THF solution of LiHMDS (2.86 mL, 2.86 mmol, 2 equiv). The resulting solution was cooled to -78 °C using an acetone/dry ice bath.

In the meantime, ketone **30** (430 mg, 1.43 mmol, 1 equiv; FW = 301.38) was dissolved in THF (3 mL) and was added to the LiHMDS solution -78 °C over 2 minutes *via* syringe. The reaction mixture was then stirred at -78 °C for 10 minutes and then a solution of Comins' reagent (842 mg, 2.14 mmol, 1.5 equiv; FW = 392.68) in THF (5 mL) was added over 5 minutes *via* syringe. The reaction mixture was then allowed to stir at -78 °C for an additional 25 minutes. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.75).

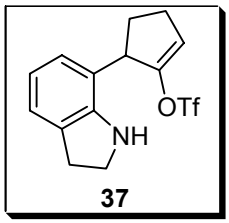
Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with Et_2O (4 x 20 mL). The ether was then evaporated *in vacuo*.

Purification: The crude product was preabsorbed onto silica gel (7 g) and chromatographed with Hexanes : EtOAc = 20:1 on a flash column with the following specifications: diameter = 4.0 cm; packing length = 25 cm; fraction size = 45 mL. The product was obtained as a white solid: 560 mg (90%). M.p. = 138-139 °C

Remarks: When the deprotonation was carried out by adding the LiHMDS solution to a -78 °C solution of **30**, and the resulting enolate was treated with Comins' reagent, a 6:1 mixture of regioisomeric enol triflates was formed (~15% of **33** was formed which could not be separated from **32**). Using the inverse addition procedure above, only the kinetic enol triflate **32** was formed.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.02 (m, 3H), 5.78 (dd, *J* = 4.4, 2.3 Hz, 1H), 4.40 (s, 1H), 4.24 (ddd, *J* = 12.0, 8.8, 3.4 Hz, 1H), 3.84 (dt, *J* = 10.0, 8.6 Hz, 1H), 3.08 (td, *J* = 15.3, 9.4 Hz, 1H), 2.90-2.74 (m, 2H), 2.52 (m, 2H), 2.09 (ddd, *J* = 14.5, 9.9, 5.3 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 151.6, 141.6, 134.9, 131.4, 125.9, 125.2, 123.1, 122.3, 119.7, 117.9, 117.2, 114.6, 80.6, 50.8, 45.4, 30.8, 29.7, 28.3, 26.9 (the CF_3 group shows up as a quartet and all the peaks are reported); IR (neat) 2973 (m), 2935 (w), 2903 (w), 1697 (s), 1657 (w), 1594 (w), 1477 (w), 1452 (m), 1432 (w), 1419 (s), 1401 (w), 1376 (s), 1333 (m), 1224 (m), 1205 (s), 1170 (m), 1137 (s), 1116 (s), 1009 (w), 985 (w), 946 (w), 922 (w), 886 (m), 843 (m), 770 (m), 743 (w), 610 (m), 571 (w), 519 (w). HRMS (ESI-MS) calcd. for $C_{19}H_{22}F_3NO_5SNa$ [$(M+Na)^+$] 456.1068, found 456.1056.

Preparation of 5-(indolin-7-yl)cyclopent-1-enyl trifluoromethanesulfonate (37).



37

A 10 mL round bottom flask was charged with enol triflate **32** (52 mg, 0.12 mmol, 1 equiv; FW = 433.44) and CH_2Cl_2 (3 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, TMSI (48 mg, 35 μL, 2 equiv; FW = 200.10, d = 1.4) was added in one portion. The reaction mixture was then allowed to warm to 0 °C over 1 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.60).

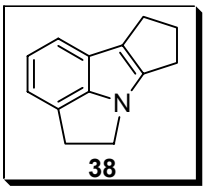
Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$.

Purification: The solvent was evaporated *in vacuo* affording the product as a pale yellow oil: 37 mg (93%).

Remark: The crude product was very clean (purity checked by ^{1}H- and ^{13}C-NMR) therefore no further purification was performed.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 7.2, 1.0 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 5.87 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.08-3.95 (m, 1H), 3.57 (dt, *J* = 8.7, 1.4 Hz, 2H), 3.43 (br, s, 1H), 3.05 (t, *J* = 8.4 Hz, 2H), 2.70-2.40 (m, 3H), 2.20-2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 149.5, 130.1, 126.0, 123.5, 121.4, 119.7, 119.2, 118.9, 117.2, 115.3, 114.1, 47.3, 45.6, 29.8, 29.1, 27.0 (the CF_3 group shows up as a quartet and all the peaks are reported) ; IR (neat): 3397 (br, m), 2948 (m), 2857 (m), 1656 (w), 1602 (w), 1480 (w), 1457 (m), 1421 (s), 1347 (w), 1328 (w), 1308 (w), 1280 (w), 1249 (m), 1211 (s), 1140 (s), 1118 (m), 1063 (w), 1034 (w), 987 (w), 947 (m), 920 (w), 882 (m), 844 (m), 767 (w), 749 (w), 608 (m), 512 (w). HRMS (CI-MS) calcd. for $C_{14}H_{14}F_3NO_3S$ $[M^+]$ 333.0646, found 333.0647.

Preparation of tetracyclic indole (38).



38

Procedure using enol triflate 37: A 10 mL round bottom flask, equipped with a reflux condenser, was charged with enol triflate **37** (30 mg, 0.09 mmol, 1 equiv; FW = 333.32) and THF (4 mL). Next, xantphos (3.9 mg, 0.0067 mmol, 7.5 mol%; FW = 578.63), $Pd_2(dba)_3 \cdot CHCl_3$ (2.4 mg, 0.0022 mmol, 2.5 mol%; FW = 1035.08) and Cs_2CO_3 (59 mg, 1.8 mmol, 2 equiv; FW = 325.82) were sequentially added and the reaction mixture brought to reflux for 1 h. As the reaction progressed, the color changed from deep red to canary yellow. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.7).

Workup: The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was loaded on a 500 μm preparative TLC plate and eluted using Hexanes : EtOAc = 3:1. The product was washed from the silica gel using $CHCl_3$: MeOH = 4:1 (10 mL) and the solvents were evaporated *in vacuo* to afford a white solid: 12 mg (72%). M.p.= 109-110 °C.

Remarks: When the reaction was repeated with 86 mg of **37**, 10 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 30 mol% of xantphos, the yield of **38** was 67%.

Procedure using enol triflate 35:

A 25 mL round bottom flask, equipped with a reflux condenser, was sequentially charged with Cs_2CO_3 (451 mg, 1.386 mmol, 2 equiv; FW = 325.82), THF (10 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (71 mg, 0.07 mmol, 10 mol%; FW = 1035.08) and xantphos (121 mg, 0.208 mmol, 30 mol%; FW = 578.63). The resulting solution was then stirred for 5 minutes before adding a solution of enol triflate **35** (231 mg, 0.693 mmol, 1 equiv; FW = 333.4419) in THF (2 mL) in one portion. The

reaction mixture was then brought to reflux for 2 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.7).

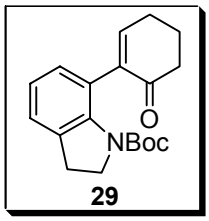
Workup: The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (3 g) and subjected to column chromatography using Hexanes : EtOAc = 30:1 on a flash column with the following specifications: diameter = 2.5 cm; packing length = 25 cm; fraction size = 8 mL. The product was obtained as a white solid: 69 mg (55%). M.p.= 109-110 °C.

Remarks: The more substituted enol triflate **35** required a four-fold increase in catalyst and ligand loading and twice as long reaction time to go to completion (2 h vs 1 h for **37**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.8 Hz, 1H), 6.97 (dd, *J* = 7.8, 6.8 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), 4.42-4.38 (m, 2H), 3.75 (t, *J* = 7.1 Hz, 2H), 2.84 (m, 4H), 2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 143.3, 124.6, 122.3, 121.0, 117.3, 115.8, 113.8, 48.6, 34.1, 28.8, 24.9, 24.7; IR (KBr pellet) 3047 (s), 3015 (w), 2956 (m), 2929 (m), 2901 (m) 2852 (s), 1646 (s), 1496 (s), 1478 (m), 1465 (s), 1456 (m), 1437 (s), 1379 (m), 1368 (m), 1338 (s), 1294 (m), 1269 (s), 1215 (w), 1174 (m), 1156 (w), 1096 (w), 1040 (w), 1012 (m), 951 (w), 822 (w), 752 (s), 743 (s), 617 (w), 588 (w), 517 (w). HRMS (CI-MS) calcd. for $C_{13}H_{13}N$ [M^+] 183.1048, found 183.1051.

Preparation of *tert*-butyl 7-(6-oxocyclohex-1-enyl)indoline-1-carboxylate (29).



29

A 100 mL round bottom flask, equipped with a reflux condenser, was charged with 7-tributylstannyl *N*-Boc indoline **25** (1.2 g, 2.352 mmol, 1.2 equiv; FW = 508.32) and NMP (20 mL). Next, $Pd_2(dba)_3 \cdot CHCl_3$ (203 mg, 0.196 mmol, 10 mol%; FW = 1035.08) and trifurylphosphine (182 mg, 0.784 mmol, 40 mol%; FW = 232.18) were added and the resulting solution was purged with Ar for 10 minutes.

In the meantime, 2-iodo-2-cyclohexene-1-one **27** (437 mg, 1.96 mmol, 1 equiv; FW = 222.13) was dissolved in NMP (5 mL) and added in one portion to the already prepared NMP solution of the tin coupling partner **25**, followed by flame dried CuI (373 mg, 1.96 mmol, 1 equiv; FW = 190.44). The reaction mixture was then heated to 120 °C with an oil bath for 1 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.51).

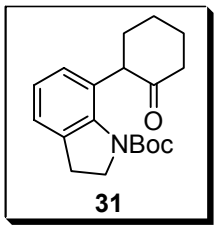
Workup: The reaction mixture was cooled to room temperature and poured into a vigorously stirring 1:1 mixture of saturated aqueous NH_4OH (75 mL) and Et_2O (75 mL). After 5 minutes, deionized water (30 mL) was also added. The aqueous phase was then extracted with Et_2O (3 x 25 mL) and EtOAc (2 x 15 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (5 g) and subjected to column chromatography with gradient elution using Hexanes : EtOAc = 9:1 to 5:1 to 4:1 on a flash column with the following specifications: diameter = 3.5 cm; packing length = 30 cm; fraction size = 45 mL. The product was obtained as an off white solid: 372 mg (61%). M.p.= 144-145 °C.

Remarks: The product **29** had the same R_f value as the vinyl iodide starting material **27**, however, they stained differently using $Ce(SO_4)_2$. The product stained grayish blue while the vinyl iodide stained purple.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (tdd, *J* = 4.9, 4.1, 1.0 Hz, 1H), 7.01-6.93 (m, 2H), 6.85 (t, *J* = 4.3 Hz, 1H), 4.02 (t, *J* = 8.2 Hz, 2H), 3.01 (t, *J* = 8.1 Hz, 2H), 2.55 (m, 2H), 2.50 (dt, *J* = 6.0, 4.4 Hz, 2H), 2.11 (td, *J* = 12.3, 6.1 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 152.3, 142.1, 142.0, 140.4, 133.7, 129.6, 124.8, 123.8, 123.3, 79.8, 49.4, 38.2, 28.6, 28.3, 26.3, 22.9; IR (neat) 2931 (br, m) 1703 (s), 1681 (s), 1477 (w), 1446 (m), 1433 (m), 1391 (s), 1366 (m), 1335 (m), 1244 (m), 1166 (s), 1137 (m), 1051 (w), 1010 (m), 917 (w), 847 (w), 765 (m), 739 (w), 603 (w), 565 (w), 525 (w); HRMS (CI-MS) calcd. for $C_{19}H_{23}NO_3$ [M^+] 313.1678, found 313.1686.

Preparation of *tert*-butyl 7-(2-oxocyclohexyl)indoline-1-carboxylate (31).



31

A 10 mL round bottom flask was charged with enone **29** (95 mg, 0.304 mmol, 1 equiv; FW = 313.39) and THF (3 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.33 mL, 0.33 mmol, 1.1 equiv; Aldrich metal cylinder) was added at -78 °C over 1 minute. The initial colorless solution turned yellow by the end of the addition. The cold bath was then removed and the reaction mixture was allowed to warm to room temperature. The progress of the reaction was followed by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.55). The chromatogram was developed using $Ce(SO_4)_2$, and upon heating, the product spot turned from red then into a deep grayish blue color.

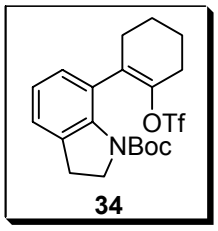
Workup: The reaction mixture was diluted with Et_2O (10 mL) and 2N NaOH (15 mL) with vigorous stirring. The aqueous layer was then extracted with Et_2O (3 x 10 mL) and EtOAc (2 x 5 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (3 g) and chromatographed with Hexanes : EtOAc = 5:1 on a flash column with the following specifications: diameter = 2.5

cm; packing length = 15 cm; fraction size = 8 mL. The product was obtained as a white solid: 73 mg (73%). M.p. = 120-121 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (m, 3H), 4.11 (dd, *J* = 12.8, 5.0 Hz, 1H), 4.02 (ddq, *J* = 11.2, 8.4, 7.1 Hz, 2H), 2.95 (m, 2H), 2.49 (m, 2H), 2.39-2.25 (m, 1H), 2.17 (dd, *J* = 8.1, 5.9 Hz, 1H), 2.06-1.96 (m, 1H), 1.96-1.89 (m, 1H), 1.87-1.69 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 153.9, 141.4, 134.5, 128.7, 127.8, 124.4, 122.8, 80.4, 54.0, 50.7, 42.9, 35.4, 29.6, 28.4, 28.3, 26.2. IR (neat) 3059 (w), 2933 (br, s), 2859 (m), 2247 (w), 1713 (s), 1597 (w), 1478 (m), 1448 (s), 1369 (s), 1336 (s), 1244 (s), 1161 (s), 1125 (s), 1051 (m), 1012 (s), 994 (m), 953 (w), 915 (m), 842 (m), 823 (w), 771 (s), 732 (s), 692 (w), 646 (w), 588 (w), 566 (w), 553 (w), 522 (w). HRMS (CI-MS) calcd. for $C_{19}H_{25}NO_3$ [M^+] 315.1834, found 315.1643

Preparation of *tert*-butyl 7-(2-(trifluoromethylsulfonyloxy)cyclohex-1-enyl)indoline-1-carboxylate (34).



34

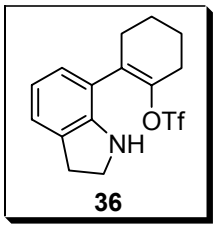
A 25 mL round bottom flask was charged with enone **29** (200 mg, 0.640 mmol, 1 equiv; FW = 313.39) and THF (6 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.7 mL, 0.700 mmol; 1.1 equiv) was added at -78 °C over 3 minutes. The resulting solution was then allowed to stir at -78 °C for 10 minutes before adding a solution of Comins' reagent (376 mg, 0.961 mmol, 1.5 equiv) in THF (4 mL) over 1 minute. The reaction mixture was then stirred at -78 °C for 25 minutes. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.70).

Workup: The -78 °C reaction mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (3 g) and chromatographed with Hexanes : EtOAc = 25:1 on a flash column with the following specifications: diameter = 2.5 cm; packing length = 22 cm; fraction size = 8 mL. The product was obtained as a white solid: 235 mg (82%). M.p. = 114-115 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 6.7 Hz, 1H), 7.00 (m, 2H), 4.17 (br, s, 1H), 3.84 (br, s, 1H), 3.14 (br, s, 1H), 2.85 (br, s, 1H), 2.73 (br, s, 1H), 2.57 (br, s, 1H), 2.34 (br, s, 2H), 1.86 (br, s, 3H), 1.72 (br, s, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 142.7, 140.2, 134.3, 130.1, 127.3, 125.3, 124.0, 123.4, 121.9, 119.4, 116.8, 114.3, 79.9, 49.4, 30.5, 29.1, 28.2, 27.8, 22.9, 22.3 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 2946 (br, m), 1707 (s), 1592 (w), 1477 (w), 1448 (m), 1437 (m), 1413 (s), 1390 (m), 1378 (s), 1338 (m), 1325 (w), 1243 (m), 1207 (s), 1198 (s), 1165 (m), 1145 (s), 1131 (s), 1082 (w), 1050 (w), 1026 (m), 1003 (m), 922 (m), 884 (m), 834 (m), 822 (m), 764 (m), 737 (w), 668 (w), 623 (m), 599 (m), 568 (w), 525 (w), 510 (w). HRMS (ESI-MS) calcd. for $C_{20}H_{24}F_3NO_5SNa$ [$(M+Na)^+$] 470.1225, found 470.1222.

Preparation of 2-(indolin-7-yl)cyclohex-1-enyl trifluoromethanesulfonate (36).



36

A 10 mL round bottom flask was charged with enol triflate **34** (132 mg, 0.295 mmol, 1 equiv; FW = 447.46) and CH_2Cl_2 (3 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, neat TMSI (118 mg, 84 μL, 2 equiv; FW = 200.10, d = 1.4) was added over 1 minute. The reaction mixture was then allowed to warm to 0 °C where it was stirred for an additional 30 minutes and quenched. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.50).

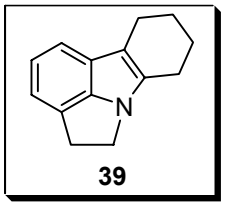
Workup: The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was shown to be sufficiently pure by ^1H- and ^{13}C-NMR analysis and was taken onto the next step (Buchwald-Hartwig coupling) without further purification. The product was a yellow oil: 99 mg (97%).

Remarks: The product was fairly unstable, it tended to undergo noticeable decomposition when subjected to column chromatography; therefore it was immediately used in the next step (Buchwald-Hartwig coupling).

^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 4.06 (br, s, 1H), 3.58 (t, *J* = 8.3 Hz, 2H), 3.07 (t, *J* = 8.3 Hz, 2H), 2.46 (m, 4H), 1.88 (m, 2H), 1.77 (ddd, *J* = 14.9, 7.5, 4.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 144.2, 130.3, 129.4, 126.7, 125.8, 124.3, 121.9, 119.6, 119.4, 119.1, 116.8, 114.3, 29.9, 29.9, 27.9, 23.0, 22.0 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 3391 (br, m), 2058 (w), 2943 (br, s), 2863 (br, s), 1726 (m), 1694 (m), 1598 (s), 1482 (m), 1452 (s), 1436 (s), 1414 (s), 1355 (m), 1342 (m), 1329 (m), 1310 (m), 1282 (m), 1244 (s), 1207 (br, s), 1140 (s), 1084 (m), 1058 (m), 1028 (s), 962 (w), 924 (s), 882 (s), 830 (s), 763 (m), 746 (m), 719 (w), 673 (w), 642 (w), 608 (br, s), 506 (m). HRMS (ESI-MS) calcd. for $C_{15}H_{17}F_3NO_5S$ $[(M+H)^+]$ 348.0881, found 348.0894.

Preparation of tetracyclic indole (39).



39

Procedure using compound 31: A 10 mL round bottom flask, equipped with a reflux condenser, was charged with ketone **31** (70 mg, 0.222 mmol, 1 equiv; FW = 315.40) and deoxygenated HPLC grade MeOH (2 mL).

In the meantime, acetyl chloride (174 mg, 2.22 mmol, 10 equiv; FW = 78.5) was carefully added to deoxygenated MeOH (2 mL) at 0 °C, to produce anhydrous HCl in MeOH. After 5 minutes, this freshly prepared MeOH/HCl solution was added in one portion to a solution of **31** in MeOH at room temperature. The reaction mixture was then heated to reflux for 15 minutes. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.7).

Workup: The solvent and the excess HCl were removed *in vacuo*.

Purification: The crude product was dissolved in $CHCl_3$ (1 mL) and loaded on a preparative TLC plate (1000 μm) and eluted using Hexanes: EtOAc = 3:1 (200 mL). The product was washed off the silica gel using $CHCl_3$: MeOH = 4:1. The product was obtained as a white solid after the removal of the solvents *in vacuo*: 31 mg (70%). M.p. = 149-150 °C.

Remarks: The identical treatment of ketone **30** did not result in the formation of the desired tetracyclic indole **38**. This cyclization (**30** to **38**) also failed when the MeOH was evaporated after the removal of the Boc group and the initially formed amine hydrochloride salt was taken up in benzene and heated to reflux for several hours; only decomposition occurred.

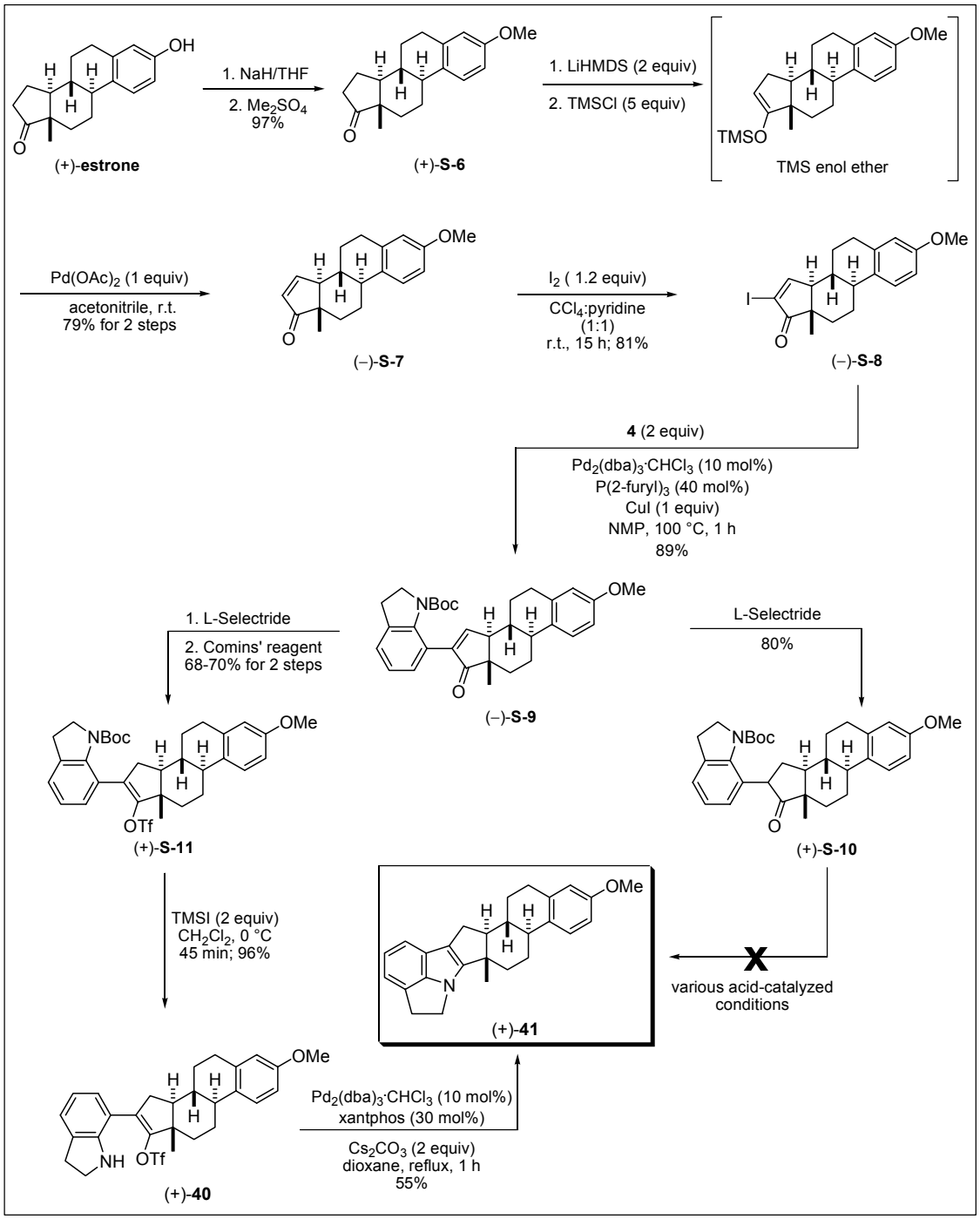
Procedure using compound 36: A 10 mL round bottom flask, equipped with a reflux condenser, was charged with enol triflate **36** (33 mg, 0.095 mmol, 1 equiv; FW = 347.35) and THF (4 mL). Next, Cs_2CO_3 (65 mg, 0.2 mmol, 2 equiv; FW = 325.82), $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mg, 0.0024 mmol, 2.5 mol%; FW = 1035.08) and xantphos (4.4 mg, 0.0071 mmol, 7.5 mol%; FW = 578.63) were added sequentially. The reaction mixture was then heated to reflux for 1 h. The

progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.7).

Workup: The reaction mixture was diluted with Et_2O (5 mL) and poured into saturated aqueous NH_4Cl (15 mL). The aqueous phase was then extracted with Et_2O (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

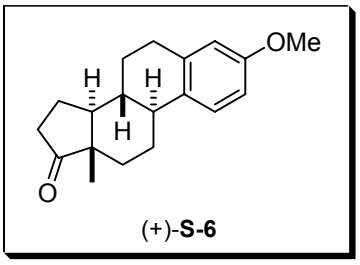
Purification: The crude product was dissolved in $CHCl_3$ (0.5 mL), loaded on a preparative TLC plate (1000 μm) and eluted using Hexanes: EtOAc = 3:1 (200 mL). The product was washed off the silica gel using $CHCl_3$: MeOH = 4:1. The product was obtained as a white solid after the removal of the solvents *in vacuo*: 11.4 mg (58%). M.p. = 149-150 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.7 Hz, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 6.7 Hz, 1H), 4.35 (t, *J* = 7.1 Hz, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.75 (m, 4H), 1.91 (m, 2H), 1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 134.8, 123.9, 120.7, 119.6, 115.6, 114.2, 113.4, 47.9, 34.0, 23.3, 23.0, 22.9, 22.6; IR (neat) 3046 (w), 2937 (s), 2912 (s), 2845 (s), 1651 (w), 1507 (w), 1418 (m), 1336 (w), 1309 (m), 1292 (s), 1193 (w), 743 (s), 582 (w). HRMS (CI-MS) calcd. for $C_{14}H_{15}N$ [M^+] 197.1204, found 197.1201.



Preparation of compound (+)-41 from (+)-estrone

Preparation of (+)-**S-6 from** (+)-**estrone.**



(+)-**S-6**

A 250 mL round bottom flask was charged with 95% NaH (500 mg, 20.35 mmol, 1.1 equiv) and THF (100 mL). The resulting suspension was cooled to 0 °C with an ice/water bath and stirred for 15 minutes. Next, (+)-estrone (5.00 g, 18.50 mmol, 1 equiv; FW = 270.26) was added to the NaH/THF suspension at 0 °C in three portions (as a solid) over 5 minutes. (Gas evolution occurred!) After stirring for 10 minutes at 0 °C, Me_2SO_4 (2.33 g, 1.75 mL, 18.50 mmol, 1 equiv; FW = 126.13, d = 1.333) was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1:1 where the product had a R_f value of 0.75).

Workup: The reaction mixture was diluted with Et_2O (100 mL) and 2 N NaOH (50 mL). The resulting biphasic reaction mixture was then vigorously stirred for 15 minutes. Next, the layers were separated and the organic layer was washed with brine (3 x 25 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

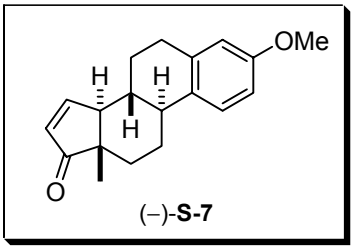
Purification: The crude product was recrystallized from EtOAc and the product was obtained as white crystals: 5.05 g (97%). M.p. = 168-169 °C (lit.[10] 167.5-168.5 °C). $[\alpha]_D^{20}$ = +148.50 (*c* 0.57, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 2.93-2.87 (m, 2H), 2.50 (dd, *J* = 19.0, 8.7 Hz, 1H), 2.43-2.36 (m, 1H), 2.26 (dt, *J* = 10.5, 4.0 Hz, 1H), 2.20-2.09 (m, 1H), 2.03 (m, 2H), 1.98-1.93 (m, 1H), 1.53 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.8, 157.6, 137.7, 132.0, 126.3, 113.9, 111.6,

(10) Curtis, J. M.; MacCorquodale, D. W.; Thayer, S. A.; Doisy, E. A. *Journal of Biological Chemistry* **1934**, *107*, 191-205.

55.2, 50.4, 48.0, 44.0, 38.4, 35.8, 31.6, 29.7, 26.5, 25.9, 21.6, 13.8. HRMS (ESI-MS) calcd. for $C_{19}H_{25}O_2$ [$(M+H)^+$] 285.1854, found 285.1855.

Preparation of (–)-**S-7.**



(–)-**S-7**

Preparation of TMS enol ether: A 100 mL round bottom flask was charged with (+)-**S-6** (1.00 g, 3.51 mmol, 1 equiv; FW = 284.39) and THF (20 mL). The resulting solution was cooled to 0 °C with an ice/water bath. (Part of the starting material precipitated at this temperature and made a solution cloudy.) Next, a 1.0 M THF solution of LiHMDS (7.02 mL, 2 equiv) was added at 0 °C over 3 minutes. (After the LiHMDS was added, the precipitate dissolved and a solution became clear.) The reaction mixture was stirred for 15 minutes at 0 °C and then TMSCl (1.91 g, 2.23 mL, 5 equiv; FW = 108.64, d = 0.856) was added over 2 minutes. The reaction mixture was then allowed to warm to room temperature and stir for 2 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3 : 1 where the TMS enol ether had a R_f value of 0.85).

Workup: The reaction was diluted with Et_2O (50 mL) and then poured into vigorously stirring saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (2 x 25 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude TMS enol ether was a yellow oil.

Purification: No purification was performed since the crude TMS enol ether was sufficiently pure to be used in the next step (Saegusa oxidation).

Remarks: We found that the cleanest conversion to the TMS enol ether was achieved by using a new bottle of LiHMDS and redistilled grade TMSCl. Using less than 5 equiv of TMSCl led to an incomplete conversion of the starting ketone.

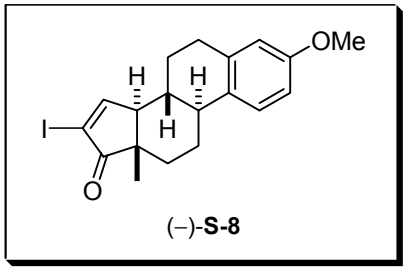
Saegusa oxidation: A 100 mL round bottom flask was charged with the crude TMS enol ether (~3.50 mmol) and HPLC grade acetonitrile (50 mL). Next, $Pd(OAc)_2$ (2.36 g, 3.50 mmol, 1 equiv; FW = 673.52) was added in one portion. The initial brownish yellow color of the reaction then darkened and eventually turned black. The reaction mixture was stirred for 25 minutes at room temperature. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.30).

Workup: The reaction mixture was filtered through a pad of Celite and evaporated *in vacuo*.

Purification: The crude product was loaded on a column (diameter = 3.0 cm, packing length = 25 cm) and eluted with Hexanes : EtOAc = 3:1. Fraction size = 45 mL. The product was obtained as a white crystalline solid: 785 mg (79%, 2 steps). M.p = 177-178 °C; $[\alpha]_D^{20}$ = -62.71 (*c* 0.59, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.0 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.74 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 6.09 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.79 (s, 3H), 2.96 (dd, *J* = 11.0, 4.6 Hz, 2H), 2.58-2.49 (m, 1H), 2.48-2.41 (m, 1H), 2.35 (dt, *J* = 10.8, 4.9 Hz, 1H), 2.24-2.15 (m, 1H), 2.06-1.97 (m, 1H), 1.82 (ddd, *J* = 22.0, 11.7, 2.7 Hz, 1H), 1.77-1.68 (m, 2H), 1.57 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 158.1, 157.7, 137.4, 131.9, 131.9, 126.0, 114.0, 111.5, 56.1, 55.2, 51.4, 45.1, 35.6, 29.3, 29.2, 26.7, 25.4, 20.9. HRMS (CI-MS) calcd. for $C_{19}H_{22}O_2$ [M^+] 282.1620, found 282.1622

Preparation of (–)-**S-8.**



(–)-**S-8**

A 100 mL round bottom flask was charged with (–)-**S-7** (500 mg, 1.77 mmol, 1 equiv; FW = 282.37), CCl_4 (5 mL) and pyridine (5 mL). The resulting solution was cooled to 0 °C using an ice/water bath.

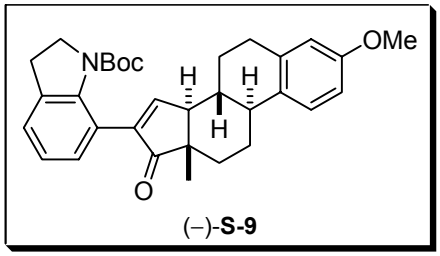
In the meantime, iodine (539 mg, 2.12 mmol, 1.2 equiv; FW = 253.81) was dissolved in the 1:1 mixture of CCl_4 : pyridine (30 mL), and the resulting dark brown solution was added to the solution of (–)-**S-7** over 2 minutes. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.35).

Workup: The reaction mixture was poured into a vigorously stirred mixture of Et_2O (100 mL) and 2N HCl (100 mL). The organic layer was washed with 2N HCl (2 x 100 mL), water (100 mL) and 10% aqueous $Na_2S_2O_3$ (3 x 50 mL) until the brownish color disappeared. The combined organic layers were then washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was loaded on a column (diameter = 5.0 cm, packing length = 25 cm) and eluted with Hexanes : EtOAc = 6:1. Fraction size = 45 mL. The product was obtained as a white crystalline solid: 581 mg (81%). M.p = 139-141 °C (decomp.); $[\alpha]_D^{20}$ = -61.10 (*c* 0.55, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 3.79 (s, 3H), 2.95 (dd, *J* = 9.00, 4.2 Hz, 2H), 2.54 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.44 (ddd, *J* = 8.9, 5.6, 2.7 Hz, 1H), 2.36 (dt, *J* = 10.7, 4.9 Hz, 1H), 2.21-2.13 (m, 1H), 2.09 (ddd, *J* = 11.9, 10.9, 6.0 Hz, 1H), 1.92-1.65 (m, 3H), 1.56 (ddd, *J* = 11.9, 10.9, 6.0 Hz, 1H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 163.8, 157.8, 137.3, 131.4, 125.9, 113.9, 111.6, 100.9, 58.5, 55.2, 49.7, 44.6, 35.6, 29.5, 29.1, 26.6, 25.3, 21.0; IR (neat) 2930 (br, m), 1717 (s), 1683 (w), 1653 (w), 1608 (w), 1558 (m), 1541 (m), 1521 (w), 1506 (s), 1457 (m), 1254 (m), 1233 (m), 1043 (w), 903 (w), 867 (w), 773 (w), 729 (w). HRMS (ESI-MS) calcd. for $C_{19}H_{21}IO_2Na$ [$(M+Na)^+$] 431.0484, found 431.0709.

Preparation of (–)-**S-9.**



(–)-**S-9**

A 50 mL round bottom Schlenk flask was charged with 7-tributylstannyl-*N*-Boc indoline substrate **25** (1.02 g, 2.00 mmol, 2 equiv; FW = 508.32) followed by NMP (20 mL). Next, $Pd_2(dba)_3 \cdot CHCl_3$ (104 mg, 0.100 mmol, 10 mol%; FW = 1035.08) and P(2-furyl)$_3$ (93 mg, 0.400 mmol, 40 mol%; FW = 232.17) were added quickly. The resulting solution was purged with deoxygenated Ar for 15 minutes.

In the meantime, in a 10 mL round bottom flask, (–)-**S-8** (409 mg, 1.00 mmol, 1 equiv; FW = 408.27) was dissolved in NMP (5 mL). Also, CuI (191 mg, 1.00 mmol, 1 equiv; FW = 190.44) was flame-dried in a 10 mL round bottom flask under vacuum and allowed to cool to room temperature.

Once the reaction mixture was purged for the designated 15 minutes, the NMP solution of (–)-**S-8** was added *via* syringe followed by the CuI in one portion. The reaction vessel then was equipped with a reflux condenser and heated to 100 °C for 1 h using a heating mantel. The color of the reaction mixture turned dark green at 100 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.52).

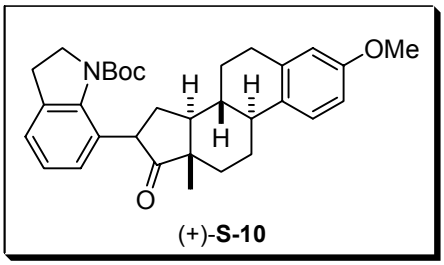
Workup: The reaction mixture was slowly poured into saturated NH_4OH (75 mL) and Et_2O (75 mL) with vigorous stirring. The ether layer became turbid yellow. The aqueous layer was then extracted with Et_2O (3 x 30 mL) and EtOAc (1 x 30 mL). The combined organic layers were then washed with brine (4 x 25 mL), dried over $MgSO_4$, concentrated in vacuo and preabsorbed onto silica gel (10 g).

Purification: The crude product (now on silica gel) was purified using Hexanes : EtOAc = 6:1 on a column which has the following properties: diameter = 5.0 cm, packing length = 25 cm,

fraction size = 45 mL. The product was obtained as an amorphous white solid: 445 mg (89%). M.p. = 164-165 °C. $[\alpha]_D^{20}$ = -39.25 (*c* 0.53, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.24 (dd, *J* = 7.9, 5.7 Hz, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 4.33-3.95 (m, 2H), 3.80 (s, 3H), 3.03 (t, *J* = 7.9 Hz, 2H), 3.00-2.94 (m, 2H), 2.69 (d, *J* = 11.5 Hz, 1H), 2.51-2.36 (m, 2H), 2.31-2.19 (m, 1H), 2.07 (d, *J* = 12.8 Hz, 1H), 1.93-1.68 (m, 3H), 1.66-1.55 (m, 1H), 1.46 (s, 9H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 157.6, 152.5, 149.6, 143.1, 140.6, 137.6, 134.4, 132.2, 128.4, 126.0, 124.1, 123.7, 121.9, 113.9, 111.5, 80.1, 55.2, 54.6, 51.5, 49.8, 45.2, 35.8, 29.8, 29.4, 29.0, 28.4, 26.8, 25.6, 21.1; IR (neat) 2929 (br, s), 2858 (m), 1711 (s), 1609 (m), 1576 (w), 1500 (s), 1447 (s), 1434 (s), 1389 (s), 1368 (s), 1336 (s), 1280 (m), 1244 (s), 1163 (s), 1135 (m), 1104 (w), 1075 (w), 1050 (m), 1007 (m), 983 (m), 910 (m), 869 (w), 821 (w), 799 (w), 767 (m), 734 (m), 647 (w), 592 (w). HRMS (ESI-MS) calcd. for $C_{32}H_{37}NO_4Na$ [$(M+Na)^+$] 522.2620, found 522.2591.

Preparation of (+)-**S-10.**



(+)-**S-10**

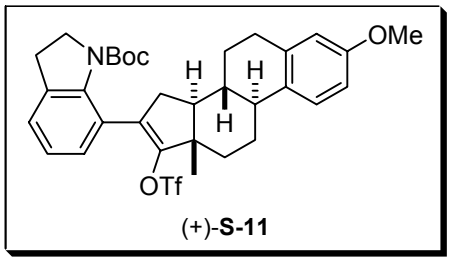
A 25 mL round bottom flask was charged with enone (–)-**S-9** (122 mg, 0.240 mmol, 1 equiv; FW = 499.64) and THF (10 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.27 mL, 0.27 mmol, 1.1 equiv; Aldrich metal cylinder) was added over 1 minute. The cold bath was then removed and the reaction mixture was allowed to warm to 0 °C and stirred at that temperature for 1 h. The progress of the reaction was followed by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.58).

Workup: The reaction mixture was quenched with 2N NaOH (10 mL) and then poured into a 100 mL separatory funnel containing Et_2O (15 mL). The organic layer was then washed with water (20 mL) and then brine (20 mL). The aqueous phase was extracted with EtOAc (2 x 15 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (3 g) and subjected to column chromatography using Hexanes : EtOAc = 5:1 as the eluent on a flash column with the following specifications: diameter = 2.0 cm; packing length = 15 cm; fraction size = 8 mL. The product was obtained as a white solid: 98 mg (80%). M.p. = 193-195 °C (browning). $[\alpha]_D^{20}$ = +170.00 (*c* 0.23, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 6.9 Hz, 1H), 7.02 (td, *J* = 14.8, 7.3 Hz, 2H), 6.73 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 4.23 (t, *J* = 8.6 Hz, 1H), 4.09 (dtd, *J* = 18.5, 11.2, 7.6 Hz, 2H), 3.79 (s, 3H), 3.05-2.93 (m, 2H), 2.91 (dd, *J* = 8.7, 3.9 Hz, 2H), 2.64 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.47-2.37 (m, 1H), 2.33 (s, 1H), 2.18-1.91 (m, 2H), 1.71-1.51 (m, 6H), 1.53 (s, 9H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 157.6, 153.6, 142.0, 137.8, 135.2, 132.2, 129.6, 126.2, 126.0, 124.8, 122.9, 113.9, 111.5, 80.7, 55.2, 52.8, 51.0, 48.9, 48.7, 44.1, 37.9, 32.1, 29.8, 29.6, 29.5, 28.4, 26.8, 26.0, 13.7; IR (neat) 2930 (br, s), 1736 (s), 1702 (s), 1641 (w), 1609 (m), 1549 (w), 1529 (w), 1500 (m), 1479 (w), 1449 (m), 1433 (m), 1369 (s), 1335 (m), 1281 (w), 1243 (m), 1160 (s), 1125 (m), 1053 (m), 1010 (w), 908 (m), 849 (w), 822 (w), 767 (w), 732 (s), 647 (w). HRMS (ESI-MS) calcd. for $C_{32}H_{40}NO_4$ [$(M+H)^+$] 502.2957, found 502.2953.

Preparation of (+)-**S-11.**



(+)-**S-11**

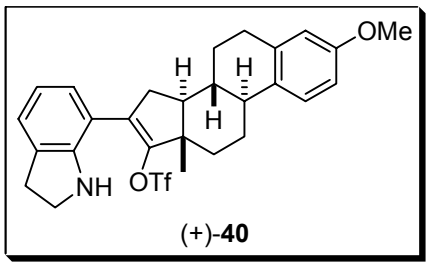
A 25 mL round bottom flask was charged with enone (–)-**S-9** (375 mg, 0.750 mmol, 1 equiv; FW = 499.64) and THF (10 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.83 mL, 0.830 mmol; 1.1 equiv) was added at -78 °C over 3 minutes. The resulting yellow solution was then stirred at -78 °C for 15 minutes before adding a solution of Comins' reagent (442 mg, 1.125 mmol, 1.5 equiv; FW = 392.68) in THF (4 mL) over 1 minute. The reaction mixture was then allowed to stir for 20 minutes at -78 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.60).

Workup: The -78 °C reaction mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 10 mL) and EtOAc (1 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (3 g) and chromatographed with Hexanes : EtOAc = 20:1 on a flash column with the following specifications: diameter = 4.0 cm; packing length = 25 cm; fraction size = 45 mL. The product was obtained as a thick, colorless oil which solidified upon standing to a white solid: 320 mg (67%). M.p. = 79-80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.04 (td, *J* = 14.5, 7.08 Hz, 2H), 6.73 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 4.13 (ddd, *J* = 11.0, 9.3, 6.0 Hz, 1H), 3.99 (ddd, *J* = 11.0, 9.3, 8.0 Hz, 1H), 3.79 (s, 3H), 3.20-2.83 (m, 5H), 2.78-2.58 (m, 2H), 2.37 (td, *J* = 10.8, 10.4 Hz, 2H), 2.11 (dt, *J* = 11.2, 7.06 Hz, 1H), 1.99 (m 1H), 1.93-1.86 (m, 1H), 1.78 (dt, *J* = 12.7, 3.84 Hz, 1H), 1.72-1.57 (m, 2H), 1.50 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 153.0, 151.0, 140.3, 137.8, 134.5, 132.4, 131.4, 127.4, 125.9, 124.2, 123.6, 122.6, 122.1, 119.6, 117.0, 114.5, 113.9, 111.5, 111.5, 80.2, 55.2, 52.9, 49.6, 46.1, 44.2,

36.8, 33.5, 29.6, 29.0, 28.5, 26.8, 26.0, 15.3 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 2976 (m), 2935 (s, br), 1709 (s), 1609 (m), 1575 (w), 1500 (m), 1478 (m), 1447 (m), 1435 (m), 1412 (s), 1378 (s), 1338 (m), 1281 (w), 1241 (s), 1210 (s), 1161 (s), 1140 (s), 1107 (w), 1059 (m), 1036 9m), 1010 (w), 957 (w), 911 (m), 858 (m), 846 (m), 813 (w), 768 (w), 735 9m0, 653 (w), 608 (m), 567 (w), 504 (w). HRMS (ESI-MS) calcd. for $C_{33}H_{38}F_3NO_6SNa$ [$(M+Na)^+$] 656.2270 found 656.2281. $[\alpha]_D^{20}$ = +46.59 (*c* 0.43, $CHCl_3$).

Preparation of enol triflate (+)-**40.**



(+)-**40**

A 10 mL round bottom flask was charged with (+)-**S-11** (203 mg, 0.321 mmol, 1 equiv; FW = 633.72) and CH_2Cl_2 (5 mL). The resulting solution was cooled to 0 °C using an ice/water bath. Next, TMSI (129 mg, 91 μL, 2 equiv; FW = 200.10, d = 1.4) was added at 0 °C over 1 minute. The reaction mixture was stirred for 45 minutes at 0 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2 : 1 where the product had a R_f value of 0.35).

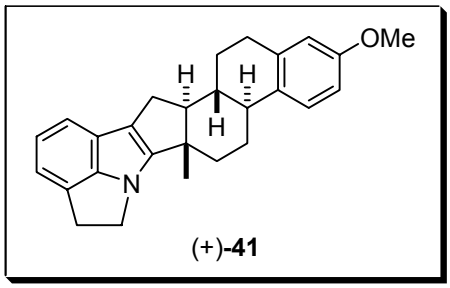
Workup: The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was shown to be sufficiently pure by ^1H- and ^{13}C-NMR analysis and was taken to the next step (Buchwald-Hartwig coupling) without further purification. The product was a yellow oil: 165 mg (96%). $[\alpha]_D^{20}$ = +27.72 (*c* 0.29, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.90 (dd, *J* = 7.7, 0.5 Hz, 1H), 6.73 (td, *J* = 15.0, 5.1 Hz, 2H), 6.66 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 3.59 (dt, *J* = 8.5, 1.25 Hz, 2H), 3.06 (t, *J* = 8.4 Hz, 1H), 2.92 (dd, *J* = 9.3, 6.5 Hz, 2H), 2.67 (dd, *J* =

14.9, 6.4 Hz, 1H), 2.48-2.40 (m, 3H), 2.37 (dd, *J* = 11.0, 4.3 Hz, 1H), 2.08-1.99 (m, 1H), 1.99-1.91 (m, 3H), 1.82 (dt, *J* = 12.7, 4.2 Hz, 1H), 1.63 (m, 2H), 1.48 (ddd, *J* = 23.2, 11.2, 7.4 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 153.0, 149.0, 137.7, 132.1, 130.0, 129.9, 126.7, 125.9, 124.6, 122.1, 119.6, 118.6, 117.0, 116.1, 114.6, 113.9, 111.5, 55.2, 52.6, 47.1, 46.1, 44.1, 36.7, 33.3, 33.3, 29.8, 29.4, 26.7, 25.9, 15.8 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 3328 (br, w), 2934 (br, s), 1608 (m), 1500 (m), 1452 (m), 1414 (s), 1282 (m), 1210 (s), 1139 (s), 1059 (m), 1036 (m), 911 (m), 847 (m), 735 (m), 650 (w), 608 (m). HRMS (ESI-MS) calcd. for $C_{28}H_{31}F_3NO_4S$ [$(M+H)^+$] 534.1926 found 534.1908.

Preparation of heptacyclic indole (+)-41 derived from estrone.



(+)-**41**

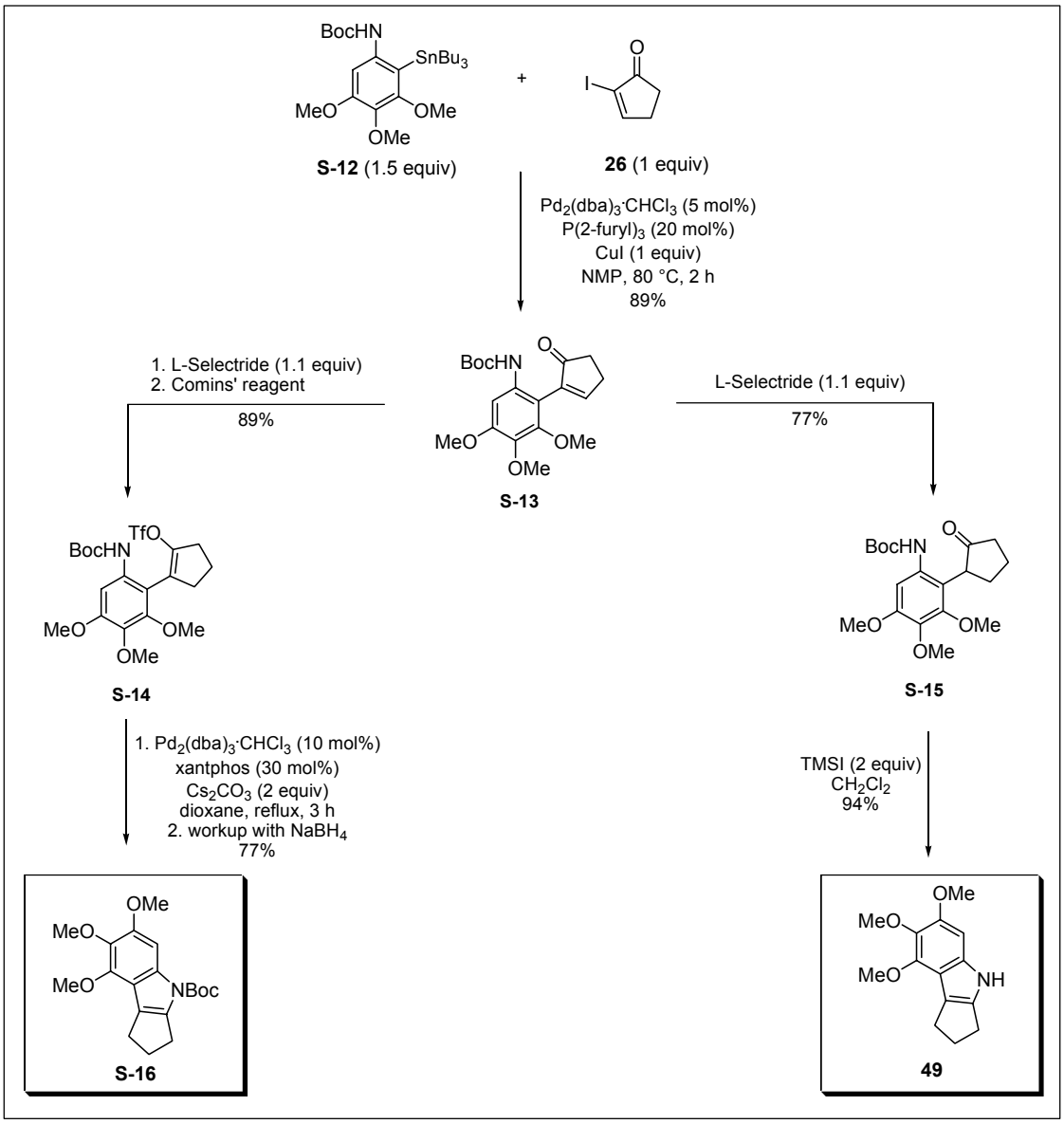
A 25 mL round bottom Schlenk flask was charged with Cs_2CO_3 (202 mg, 0.62 mmol, 2 equiv; FW = 325.82) and THF (8 mL). Next, xanthphos (54 mg, 0.09 mmol, 30 mol%; FW = 578.63) and $Pd_2(dba)_3{\cdot}CHCl_3$ (32 mg, 0.031 mmol, 10 mol%; FW = 1035.08) were added. Upon addition of the phosphine ligand the solution became deep brownish red. The resulting solution was stirred for 5 minutes before adding a solution of the enol triflate (+)-**40** (165 mg, 0.309 mmol, 1 equiv; FW = 533.6023) in THF (3 mL) in one portion. Next, the Schlenk flask was fitted with a reflux condenser and the reaction mixture was brought to reflux (oil bath, 100 °C). Once the oil bath's temperature reached 80 °C, the color of the reaction mixture turned dark brownish yellow. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2 : 1). (The best stain for visualizing the product was $Ce(SO_4)_2$ in H_2SO_4, which stained the product instantly at room temperature.) In 50 minutes all the starting material was consumed and the reaction was cooled to room temperature.

Workup: The reaction mixture was then poured into a mixture of Et_2O (20 mL) and saturated aqueous NH_4Cl (20 mL) with vigorous stirring. The aqueous layer was then washed with Et_2O (2 x 15 mL), the combined organic layers dried over $MgSO_4$, concentrated *in vacuo* and preabsorbed onto silica gel (2 g).

Purification: The crude product was loaded on a column (diameter = 2.5 cm, packing length = 30 cm) and eluted with Hexanes : EtOAc = 12:1; fraction size = 8 mL. The product was obtained as a white crystalline solid: 52.8 mg (45%). M.p = 204-205 °C (decomp.); $[\alpha]_D^{20}$ = +64.20 (*c* 0.26, $CHCl_3$).

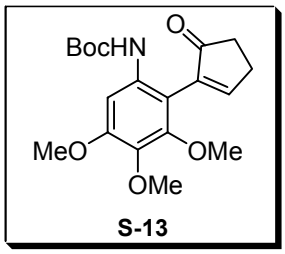
Remark: When the reaction was repeated using dioxane as the solvent, the yield increased to 55%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 7.8, 6.8 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 4.47 (dt, *J* = 9.3, 4.6 Hz, 1H), 4.39 (dt, *J* = 9.4, 5.9 Hz, 1H), 3.80 (s, 3H), 3.79 (m, 1H), 3.73 (dq, *J* = 8.9, 4.4 Hz, 1H), 3.09-2.87 (m, 2H), 2.81 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.43 (m, 3H), 2.26 (ddd, *J* = 10.6, 8.3, 4.7 Hz, 1H), 2.11-2.01 (m, 2H), 1.90 (dt, *J* = 12.7, 3.7 Hz, 1H), 1.77 (dtd, *J* = 16.2, 11.9, 3.4 Hz, 2H), 1.54 (dq, *J* = 12.0, 6.6 Hz, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 152.3, 151.6, 138.0, 132.7, 126.0, 124.6, 121.2, 119.7, 117.7, 115.9, 113.9, 113.7, 111.5, 60.1, 55.2, 48.3, 44.5, 41.7, 37.4, 34.7, 34.3, 29.8, 27.4, 26.3, 26.0, 17.9; IR (neat) 2947 (br, m), 1499 (m), 1497 (m), 1456 (m), 1447 (m), 1372 (w), 1362 (w), 1329 (w) 1280 (w), 1245 (m), 1182 (w), 1143 (w), 1046 (w), 909 (w), 732 (m). HRMS (ESI-MS) calcd. for $C_{27}H_{30}NO$ [$(M+H)^+$] 384.2327, found 384.2326.



Preparation of compound 49 from trimethoxyaniline derivative S-12

Preparation of enone (S-13).



S-13

A 100 mL round bottom Schlenk flask was charged with 2-tributylstannyl-*N*-Boc-3,4,5-trimethoxyaniline **S-12** (1.73 g, 3.03 mmol, 1.5 equiv; FW = 572.36) followed by NMP (30 mL). Next, $Pd_2(dba)_3 \cdot CHCl_3$ (104 mg, 0.101 mmol, 5 mol%; FW = 1035.08) and P(2-furyl)$_3$ (94 mg, 0.404 mmol, 20 mol%; FW = 232.17) were added quickly. The resulting solution was purged with Ar for 5 minutes.

In the meantime, in a 10 mL round bottom flask, 2-iodo-2-cyclopentenone **26** (420 mg, 2.02 mmol, 1 equiv; FW = 207.99) was dissolved in NMP (5 mL). Also, CuI (380 mg, 2.02 mmol, 1 equiv; FW = 190.44) was flame-dried in a 10 mL round bottom flask under vacuum and allowed to cool to room temperature.

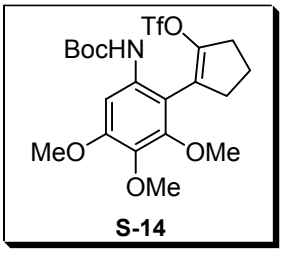
Once the reaction mixture was purged for the designated 5 minutes, the NMP solution of the 2-iodo-2-cyclopentenone was added *via* syringe followed by CuI in one portion. The reaction vessel then was equipped with a reflux condenser and heated to 80 °C for 2 h using a heating mantel. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1 : 1 where the product had a R_f value of 0.45).

Workup: After cooling to room temperature, the reaction mixture was slowly poured into saturated NH_4OH (50 mL) and Et_2O (150 mL) with vigorous stirring. The ether layer became turbid yellow. The aqueous layer was then washed with Et_2O (2 x 25 mL) and EtOAc (2 x 25 mL). The combined organic layers were then washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated *in vacuo* and preabsorbed onto silica gel (5 g).

Purification: The crude product (now on silica gel) was purified using Hexanes : EtOAc = 4:1 to 3:1 on a column which has the following properties: diameter = 4.0 cm, packing length = 25 cm, fraction size = 45 mL. The product was obtained as a thick, pale yellow oil: 649 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (t, *J* = 2.8 Hz, 1H), 7.27 (s, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 2.83 (dt, *J* = 4.7, 2.62 Hz, 2H), 2.66-2.54 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 165.2, 153.5, 153.2, 151.5, 139.5, 138.5, 132.2, 110.6, 102.2, 80.2, 61.1, 60.8, 55.9, 34.6, 28.3, 27.6; IR (neat) 3437 (w), 3333 (br, m), 2976 (m), 2936 (m), 1716 (s), 1699 (s), 1694 (s), 1599 (s), 1516 (s), 1454 (s), 1407 (s), 1367 (s), 1365 (s), 1304 (m), 1278 (m), 1232 (s), 1200 (m), 1161 (s), 1122 (s), 1040 (m), 1021 (m), 993 (m), 955 (w), 924 (w), 880 (w), 824 (w), 789 (w), 772 (w), 731 (m); HRMS (ESI-MS) calcd. for $C_{19}H_{25}NO_6Na$ [$(M+Na)^+$] 386.1579 found 386.1595.

Preparation of enol triflate S-14.



S-14

A 50 mL round bottom flask was charged with enone **S-13** (330 mg, 0.905 mmol, 1 equiv; FW = 363.40) and THF (15 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (1.00 mL, 1.00 mmol; 1.1 equiv) was added over 5 minutes. The resulting solution was then allowed to stir at -78 °C for 15 minutes before adding the solution of Comins' reagent (534 mg, 1.358 mmol; 1.5 equiv) in THF (5 mL) over 1 minute. The reaction mixture was then allowed to warm to room temperature. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1:1 where the product had a R_f value of 0.75).

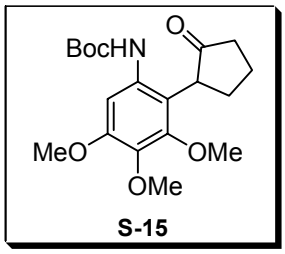
Workup: The reaction mixture was poured into saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was preabsorbed onto silica gel (5 g) and chromatographed with Hexanes : EtOAc = 20:1 on a flash column with the following specifications: diameter = 2.5

cm; packing length = 35 cm; fraction size = 8 mL. The product was obtained as a thick, colorless oil: 404 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.21 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 2.91-2.63 (m, 3H), 2.59-2.44 (m, 1H), 2.12 (dq, *J* = 8.5, 4.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 152.9, 151.1, 145.9, 138.1, 131.5, 126.0, 121.9, 119.4, 116.8, 114.3, 109.7, 100.8, 80.4, 61.0, 60.7, 55.8, 32.4, 31.0, 28.1, 20.2 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat): 3425 (br, m), 3347 (br, m), 3134 (w), 2977 (br, s), 2939 (s), 2864 (m), 1732 (s), 1603 (s), 1514 (s), 1454 (s), 1417 (s), 1368 (s), 1355 (s), 1324 (m), 1211 (s), 1159 (s), 1112 (s), 1042 (s), 991 (s), 954 (s), 926 (m), 856 (s), 794 (w), 768 (w), 734 (w), 607 (s), 574 (m). HRMS (ESI-MS) calcd. for $C_{20}H_{26}F_3NO_8SNa$ [$(M+Na)^+$] 520.1228 found 520.1206.

Preparation of ketone S-15.



S-15

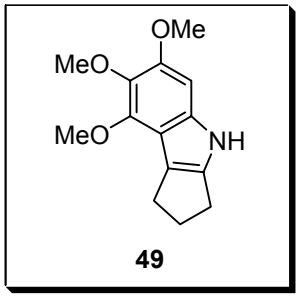
A 10 mL round bottom flask was charged with enone **S-13** (70 mg, 0.190 mmol, 1 equiv; FW = 363.40) and THF (3 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.21 mL, 0.21 mmol, 1.1 equiv; Aldrich metal cylinder) was added over 1 minute. The initial pale yellow solution turned colorless by the end of addition. The cold bath was then removed and the reaction mixture was allowed to warm to room temperature. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1 : 1 where the product had a R_f value of 0.55).

Workup: The reaction mixture was diluted with Et_2O (10 mL) and poured into saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was then extracted with Et_2O (3 x 5 mL) and EtOAc (2 x 5 mL). The combined organic layers were then washed with brine (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was purified on a 1000 μm preparative TLC plate (Hexanes : EtOAc = 2:1). The product was washed from the silica gel using $CHCl_3$: MeOH = 4:1 and obtained as a thick, colorless oil: 55 mg (77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 4.74 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.50 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.35 (br, s, 2H), 2.23 (br, s, 3H), 1.79 (td, *J* = 14.5, 7.3 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 149.5, 137.3, 116.4, 104.2, 95.1, 82.3, 61.0, 60.5, 56.0, 51.7, 50.6, 42.0, 33.6, 28.5, 25.5 (the C=O peak did not show up even at high concentrations); IR (neat) 3478 (br, m), 2970 (m), 2937 (m), 2869 (w), 1700 (s), 1680 (s), 1601 (m), 1486 (s), 1476 (s), 1449 (m), 1437 (w), 1393 (s), 1368 (s), 1336 (s), 1304 (w), 1241 (w), 1219 (w), 1196 (w), 1164 (s), 1138 (s), 1075 (m), 1059 (m), 1041 (m), 1020 (w), 1004 (w), 984 (w), 936 (w), 875 (w), 824 (w), 767 (w), 740 (w), 668 (w). HRMS (ESI-MS) calcd. for $C_{19}H_{27}NO_6Na$ [$(M+Na)^+$] 388.1736 found 388.1738.

Preparation of indole 49.



49

A 10 mL round bottom flask was charged with ketone **S-15** (50 mg, 0.137 mmol, 1 equiv; FW = 365.42) and CH_2Cl_2 (3 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath.

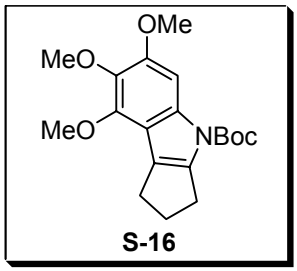
Next, TMSI (54 mg, 40 μL, 0.274 mmol, 2 equiv; FW = 200.1, d = 1.4) was added in one portion then the reaction mixture was allowed to warm to 0 °C over 1 h.

Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was purified on a 500 μm preparative TLC plate (Hexanes : EtOAc = 2:1). The product was washed off from the silica gel with $CHCl_3$: MeOH = 4:1 and the product was obtained as a thick, colorless oil: 32 mg (94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.60 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.93 (tdd, *J* = 7.2, 5.3, 1.5 Hz, 2H), 2.80 (ddd, *J* = 8.0, 3.0, 1.5 Hz, 2H), 2.59-2.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 145.3, 141.5, 137.6, 136.2, 118.0, 112.8, 91.1, 61.9, 61.5, 56.4, 28.7, 26.1, 25.7; IR (neat) 3358 (br, m), 2936 (br, m), 2850 (w), 1625 (w), 1560 (w), 1494 (w), 1466 (m), 1421 (w), 1369 (w), 1333 (w), 1278 (w), 1195 (w), 1152 (w), 1108 (m), 1052 (m), 1002 (w), 929 (w), 808 (w), 745 (w). HRMS (CI-MS) calcd. for $C_{14}H_{17}NO_3$ [M^+] 247.1208 found 247.1215.

Preparation of N-Boc protected indole S-16.



S-16

A 25 mL round bottom flask, equipped with a reflux condenser, was charged with Cs_2CO_3 (202 mg, 0.62 mmol, 2 equiv; FW = 325.82) and dioxane (8 mL). Next, xanthphos (54 mg, 0.09 mmol, 30 mol%; FW = 578.63) and $Pd_2(dba)_3{\cdot}CHCl_3$ (32 mg, 0.031 mmol, 10 mol%; FW = 1035.08) were added. The resulting solution was then allowed to stir for 5 minutes before adding a solution of enol triflate **S-14** (155 mg, 0.311 mmol, 1 equiv; FW = 497.48) in dioxane (3 mL) in one portion. Next, the reaction mixture was brought to reflux for 3 h. Once the oil bath temperature reached 80 °C, the color of the reaction mixture turned dark brownish yellow. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 2:1 where the product had a R_f value of 0.60). (The best stain for visualizing the product was anisaldehyde, which stained the product dark brown when heated.)

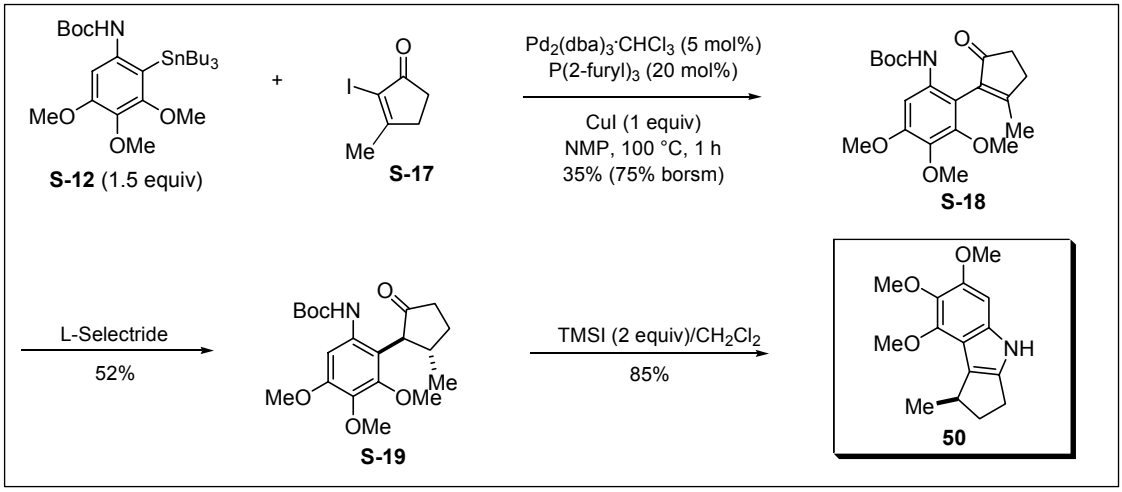
Workup: The reaction mixture was poured into a vigorously stirring mixture of Et_2O (20 mL) and saturated aqueous NH_4Cl (20 mL). The aqueous layer was washed with Et_2O (3 x 10 mL), the

combined organic layers were dried over $MgSO_4$ and concentarted *in vacuo*. The crude product was then dissolved in HPLC grade MeOH (3 mL) and $NaBH_4$ (12 mg, 0.311 mmol, 1 equiv; FW = 37.83) was added at room temperature. After 5 minutes, the reaction mixture was concentrated *in vacuo*.

Purification: The crude product was loaded on a column (diameter = 2.5 cm, packing length = 28 cm) and eluted with Hexanes : EtOAc = 15:1 to 10:1; fraction size = 8 mL. The product was obtained as a thick, pale yellow oil: 83 mg (77%).

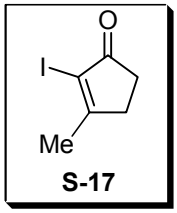
Remarks: The product co-eluted with the dba ligand, therefore treatment with $NaBH_4$ was necessary.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.07-2.94 (m, 2H), 2.92-2.81 (m, 2H), 2.53-2.33 (m, 2H), 1.63 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.0, 145.0, 141.6, 138.3, 136.5, 122.5, 114.7, 96.3, 82.9, 62.1, 61.3, 56.3, 29.0, 28.2, 27.5, 25.5; IR (neat) 2974 (m), 2937 (m), 2859 (w), 1728 (s), 1607 (w), 1574 (w), 1467 (s), 1441 (m), 1420 (m), 1405 (m), 1378 (s), 1340 (m), 1318 (m), 1302 (s), 1262 (m), 1229 (w), 1198 (m), 1157 (s), 1130 (s), 1111 (s), 1057 (m), 1020 (w), 994 (w), 958 (w), 916 (w), 861 (w), 833 (w), 765 (w), 732 (w). HRMS (CI-MS) calcd. for $C_{19}H_{25}NO_5$ [M^+] 347.1733 found 347.1736.



Preparation of compound 50 from trimethoxyaniline derivative S-12

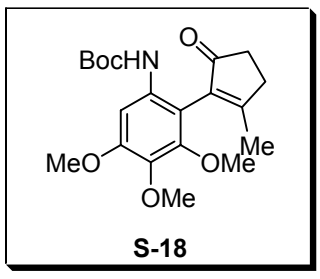
Preparation of 2-iodo-3-methyl-2-cyclopentene-1-one (S-17).



Compound **S-17** was prepared according to the procedure described by C.R. Johnson et al.[11]

The various spectra matched the reported values. M.p. = 92-94 °C (lit. 94 °C) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90-2.64 (m, 2H), 2.53 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 179.7, 102.4, 34.2, 33.0, 22.0.

Preparation of enone S-18.



A 25 mL round bottom flask, equipped with a reflux condenser, was charged with 2-tributylstannyl-*N*-Boc-3,4,5-trimethoxyaniline **S-12** (0.680 g, 1.19 mmol, 1.5 equiv; FW = 572.36) followed by NMP (15 mL). Next, $Pd_2(dba)_3·CHCl_3$ (41 mg, 0.025 mmol, 5

(11) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917-918.

mol%; FW = 1035.08) and P(2-furyl)$_3$ (46 mg, 0.01 mmol, 20 mol%; FW = 232.17) were added quickly. The resulting solution was purged with Ar for 5 minutes.

In the meantime, in a 5 mL round bottom flask, 2-iodo-3-methyl-2-cyclopentenone **S-17** (175 mg, 0.792 mmol, 1 equiv; FW = 222.02) was dissolved in NMP (2 mL). Also, CuI (151 mg, 0.792 mmol, 1 equiv; FW = 190.44) was flame-dried in a 5 mL round bottom flask under vacuum and allowed to cool to room temperature.

Once the reaction mixture was purged for the designated 5 minutes, the NMP solution of enone **S-17** was added *via* syringe followed by the CuI in one portion.

The flask was then heated to 100 °C for 1 h using a heating mantel. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1:1 where the product had a R_f value of 0.25).

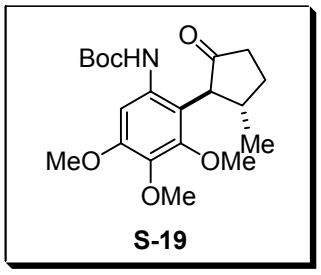
Workup: The reaction mixture was slowly poured into a vigorously stirring mixture of saturated NH_4OH (50 mL) and Et_2O (50 mL). The ether layer became turbid yellow. The aqueous layer was then extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, concentrated *in vacuo* and preabsorbed onto silica gel (3 g).

Purification: The crude product (now on silica gel) was purified using Hexanes : EtOAc = 2:1 to 1:1 on a column which has the following properties: diameter = 2.5 cm, packing length = 22 cm, fraction size = 8 mL. The product was obtained as a thick, pale yellow oil: 103 g (35%). Enone **S-17** was also recovered: 95 mg (54%), thus bringing the yield to 75% based on recovered starting material (borsm).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.26 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 2.80-2.70 (m, 2H), 2.62-2.54 (m, 2H), 1.98 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 177.3, 153.6, 153.1, 151.4, 138.3, 135.0, 132.4, 109.5, 101.6, 80.3, 61.1, 60.9, 55.9, 34.9, 32.2, 28.3, 18.7. IR (neat) 3433 (w), 3314 (br, m), 2976 (s), 2936 (s), 1738 (s), 1699 (s), 1643 (m), 1601 (s), 1514 (s), 1455 (s), 1406 (s), 1378 (m), 1366 (m), 1356 (m), 1328 (m), 1282 (w), 1233 (s), 1198 (m), 1160 (s), 1123 (s), 1041 (m), 1022 (m), 993 (m), 957 (w), 924 (w), 878

(w), 819 (w), 791 (w), 772 (w), 731 (m). HRMS (ESI-MS) calcd. for $C_{20}H_{27}NO_6Na$ [$(M+Na)^+$] 400.1736 found 400.1748.

Preparation of ketone S-19 (rotamers).



S-19

A 10 mL round bottom flask was charged with enone **S-18** (100 mg, 0.264 mmol, 1 equiv; FW = 377.43) and THF (5 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, a 1.0 M solution of L-Selectride in THF (0.29 mL, 0.29 mmol, 1.1 equiv; Aldrich metal cylinder) was added over 1 minute. The cold bath was then removed and the reaction mixture was allowed to warm to room temperature. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 1:1 where the product had a R_f value of 0.65).

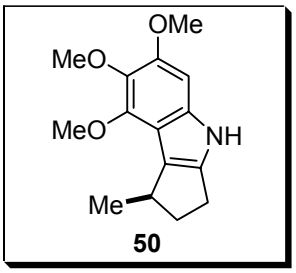
Workup: The reaction mixture was diluted with Et_2O (10 mL) and poured into saturated aqueous NH_4Cl (20 mL). The aqueous layer was then extracted with Et_2O (3 x 15 mL). The combined organic layers were then washed with brine (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude material was purified on a 1000 μm preparative TLC plate (Hexanes : EtOAc = 3:1). The product washed from the silica gel using $CHCl_3$:MeOH = 4:1 and obtained as thick, colorless oil: 52 mg (52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.63 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.08 (d, *J* = 7.2 Hz, 1H), 2.39 (s, 1H), 2.34 (s, 1H), 2.20-2.03 (m, 1H), 1.91 (s, 1H), 1.81 (s, 1H), 1.60 (s, 9H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 150.0, 137.4, 136.6, 104.4, 103.7, 95.2, 82.7, 82.2, 61.0, 60.4, 59.3, 58.3, 56.0, 42.7, 41.2, 38.6, 33.9, 30.3, 28.5, 28.3, 26.8, 19.9, 19.3, 17.5, 9.5 (all carbons of the rotameric mixture are reported; the C=O peak of the ketone does not show up); IR (neat) 3488 (br, m), 3133 (w), 2934 (br, s), 2871 (m),

2828 (w), 1682 (br, s), 1606 (m), 1485 (s), 1438 (m), 1394 (s), 1368 (s), 1335 (s), 1305 (m), 1290 (m), 1255 (m), 1239 (m), 1212 (m), 1198 (m), 1151 (s), 1138 (s), 1086 (m), 1065 (m), 1030 (m), 995 (m), 978 (m), 959 (w), 908 (w), 885 (w), 858 (w), 837 (w), 811 (w), 767 (m), 734 (m), 695 (w). HRMS (ESI-MS) calcd. for $C_{20}H_{29}NO_6Na$ [$(M+Na)^+$] 402.1894 found 402.1878.

Preparation of electron rich indole 50.



50

A 10 mL round bottom flask was charged with ketone **S-19** (45 mg, 0.119 mmol, 1 equiv; FW = 379.44) and CH_2Cl_2 (3 mL). The resulting solution was cooled to 0 °C using an ice/water bath.

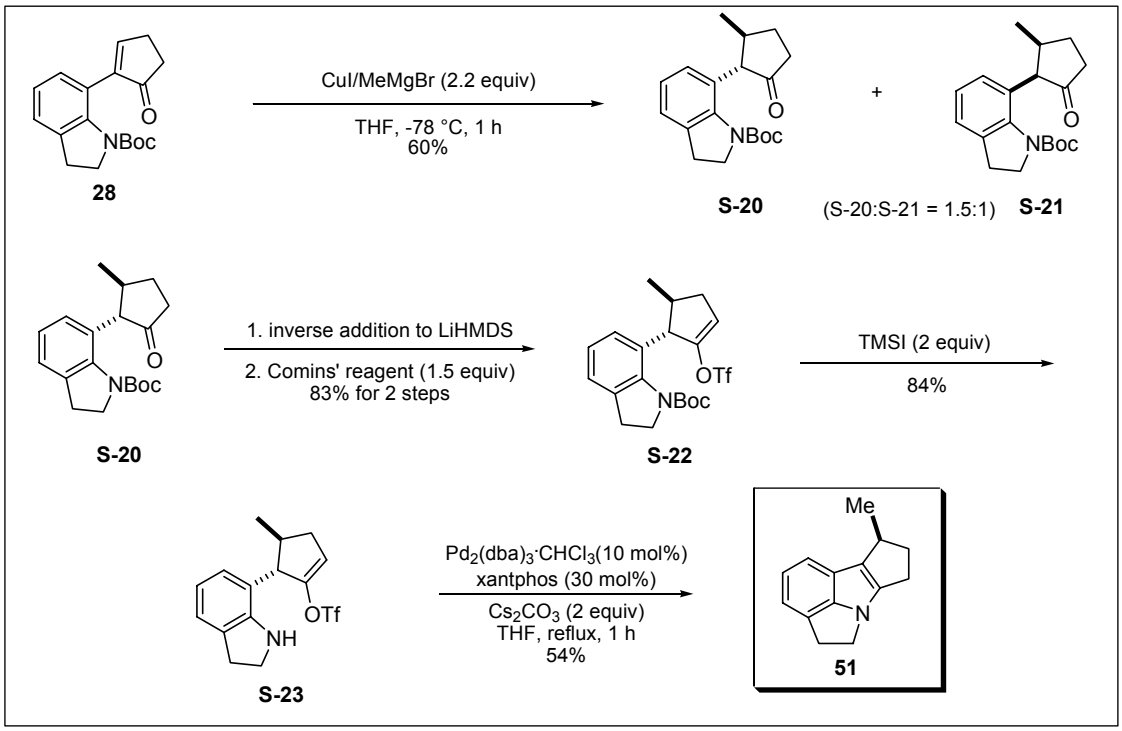
Next, TMSI (47 mg, 34 μL, 0.237 mmol, 2 equiv; FW = 200.1, d = 1.4) was added in one portion and the reaction mixture was stirred for 25 minutes at 0 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.30).

Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was purified on a 500 μm preparative TLC plate (Hexanes : EtOAc = 3:1). The product was washed from the silica gel with $CHCl_3$: MeOH = 4:1 and obtained as a thick, pale yellow oil: 26 mg (85%).

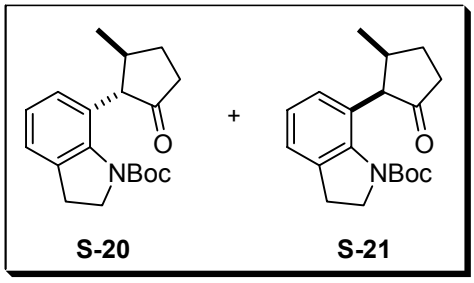
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.61 (s, 1H), 4.00 (d, *J* = 0.8 Hz, 3H), 3.88 (d, *J* = 0.8 Hz, 3H), 3.87 (d, *J* = 0.5 Hz, 3H), 3.33 (ddd, *J* = 8.8, 6.8, 2.7 Hz, 1H), 2.92-2.80 (m, 1H), 2.79-2.67 (m, 2H), 2.03 (tdd, *J* = 11.4, 10.1, 4.9 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 145.4, 140.7, 137.4, 136.5, 123.7, 112.9, 107.0, 91.2, 61.4, 56.5, 37.9, 34.0, 25.2, 22.3; IR (neat) 3365 (br, m), 2946 (br, m), 1627 (w), 1559 (w), 1495 (w), 1463 (m),

1420 (w), 1370 (w), 1314 (w), 1287 (w), 1195 (w), 1151 (w), 1111 (m), 1054 (w), 1001 (w), 925 (w), 821 (w). HRMS (ESI-MS) calcd. for $C_{15}H_{20}NO_3$ [$(M+H)^+$] 262.1443 found 262.1448.



Preparation of compound 51 from enone 28.

Preparation of ketones S-20 and S-21.

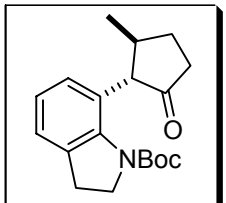


A 50 mL round bottom flask was charged with CuI (381 mg, 2.00 mmol, 1 equiv; FW = 190.45) and THF (10 mL). The resulting suspension was cooled to -78 °C with an acetone/dry ice bath and a 3.0 M solution of MeMgBr in THF (1.50 mL, 4.4 mmol, 2.2 equiv) was added. After 15 minutes, a white precipitate was formed.

In the meantime, enone **28** (600 mg, 2.00 mmol, 1 equiv; FW = 299.36) was dissolved in THF (10 mL) and added to the cuprate solution at -78 °C. The reaction mixture was stirred for 40 minutes at -78 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the two products had the following R_f values: 0.50 for **S-20** and 0.42 for **S-21**).

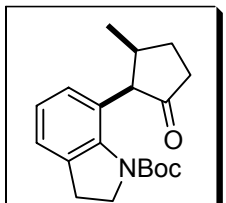
Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, concentrated in vacuo and preabsorbed onto silica gel (10 g).

Purification: The crude product (now on silica gel) was purified using Hexanes : EtOAc = 6:1 on a column which had the following properties: diameter = 4.5 cm, packing length = 28 cm, fraction size = 45 mL. The products **S-20** and **S-21** were initially obtained as thick, colorless oils (combined yield of 60%) which later solidified upon standing: 228 mg of **S-20** (36%) and 151 mg of **S-21** (24%). M.p. = 112-113 °C (for **S-20**) and 79-80 °C (for **S-21**).



S-20

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (ddd, *J* = 11.1, 7.6, 0.9 Hz, 1H), 7.04-6.99 (m, 2H), 4.30 (dd, *J* = 7.6, 0.9 Hz, 1H), 4.15 (ddd, *J* = 11.1, 8.6, 5.3 Hz, 1H), 3.91 (td, *J* = 11.1, 8.4 Hz, 1H), 3.02 (td, *J* = 16.4, 8.1 Hz, 1H), 2.97-2.83 (m, 2H), 2.48-2.20 (m, 2H), 2.15-1.98 (m, 1H), 1.79 (dddd, *J* = 12.8, 7.8, 3.7, 2.1 Hz, 1H), 1.51 (s, 9H), 0.73 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.1, 153.8, 142.4, 134.8, 128.8, 126.8, 124.2, 123.0, 80.7, 57.3, 51.2, 35.6, 34.3, 29.6, 28.3, 27.9, 16.2; IR (neat) 3059 (w), 2962 (s), 2931 (m), 2873 (m), 1739 (s), 1699 (s), 1592 (w), 1479 (m), 1447 (s), 1434 (s), 1370 (s), 1333 (s), 1292 (m), 1242 (s), 1210 (m), 1159 (s), 1124 (m), 1086 (w), 1069 (w), 1052 (m), 1038 (w), 1009 (m), 994 (m), 921 (w), 866 (w), 847 (m), 825 (w), 805 (w), 769 (m), 741 (m), 699 (w). HRMS (ESI-MS) calcd. for $C_{19}H_{25}NO_3Na$ [$(M+Na)^+$] 338.1732 found 338.1711.

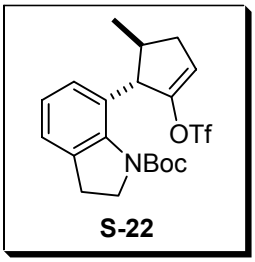


S-21

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.3 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 4.17 (ddd, *J* = 11.1, 8.7, 5.4 Hz, 1H), 3.92 (td, *J* = 11.1, 8.4 Hz, 1H), 3.73 (d, *J* = 11.9 Hz, 1H), 3.11-2.94 (m, 1H), 2.94-2.82 (m, 1H), 2.49 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.39-2.22 (m, 2H), 2.18 (ddd, *J* = 11.1, 7.5, 6.4 Hz, 1H), 1.56 (ddd, *J* = 21.6, 15.2, 8.4 Hz, 1H), 1.49 (s, 9H), 1.08 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 153.5, 142.5, 135.1,

128.0, 127.7, 124.7, 122.9, 80.5, 61.6, 50.8, 39.8, 38.5, 29.6, 29.3, 28.3, 19.1; IR (neat) 3055 (w), 2969 (br, s), 2927 (m), 2870 (m), 1740 (s), 1700 (s), 1594 (w), 1478 (m), 1447 (s), 1435 (s), 1369 (s), 1335 (s), 1289 (w), 1243 (s), 1211 (w), 1161 (s), 1126 (m), 1067 (w), 1051 (w), 1037 (w), 1008 (m), 949 (w), 867 (w), 848 (m), 824 (w), 799 (w), 769 (m), 737 (w), 694 (w), 583 (w). HRMS (CI-MS) calcd. for $C_{19}H_{25}NO_3$ [M^+] 315.1834 found 315.1842.

Preparation of enol triflate S-22.



S-22

A 25 mL round bottom flask was charged with THF (5 mL) and a 1.0 M THF solution of LiHMDS (0.82 mL, 0.82 mmol, 2 equiv). The resulting solution was cooled to -78 °C using an acetone/dry ice bath and then treated by a solution of ketone **S-20** (130 mg, 0.412 mmol, 1 equiv; FW = 315.41) in THF (3 mL) over 2 minutes. The reaction mixture was then allowed to stir at -78 °C for 20 minutes before adding a solution of Comins' reagent (247 mg, 0.618 mmol, 1.5 equiv; FW = 392.68) in THF (2 mL) over 1 minute. The reaction mixture was then allowed to stir for 25 more minutes at -78 °C. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.60).

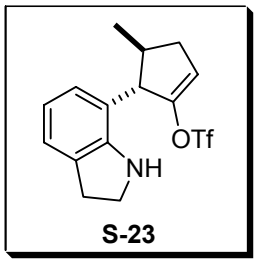
Workup: The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) then extracted with Et_2O (4 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was preabsorbed onto silica gel (3 g) and chromatographed with Hexanes : EtOAc = 9:1 on a flash column with the following specifications: diameter = 2.0 cm; packing length = 30 cm; fraction size = 8 mL. The product was obtained as a thick, colorless oil: 152 mg (83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 5.82 (d, *J* = 1.1 Hz, 1H), 4.53 (dd, *J* = 9.3, 2.7 Hz, 1H), 4.03 (t, *J* = 7.6 Hz, 2H),

3.05-2.84 (m, 3H), 2.62 (ddd, *J* = 16.2, 8.5, 2.9 Hz, 1H), 2.10 (dddd, *J* = 16.3, 7.7, 3.3, 2.4 Hz, 1H), 1.53 (s, 9H), 0.80 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 151.2, 142.6, 135.2, 127.6, 127.0, 124.3, 123.2, 122.3, 119.8, 117.7, 117.2, 114.7, 80.6, 51.0, 48.6, 35.8, 34.5, 29.7, 28.2, 17.0 (the CF_3 group shows up as a quartet and all four of these peaks are reported); IR (neat) 2976 (s), 2931 (s), 2852 (m), 1713 (s), 1657 (m), 1597 (m), 1478 (s), 1452 (s), 1418 (s), 1373 (s), 1335 (s), 1278 (m), 1204 (s), 1074 (m), 1052 (s), 1036 (m), 1008 (s), 915 (s), 896 (s), 869 (m), 845 (s), 769 (s), 740 (m), 700 (w), 668 (m), 607 (s), 567 (m), 517 (s). HRMS (ESI-MS) calcd. for $C_{20}H_{24}F_3NO_5SNa$ [$(M+Na)^+$] 470.1225 found 470.1216.

Preparation of enol triflate S-23.



S-23

A 10 mL round bottom flask was charged with *N*-Boc enol triflate **S-22** (147 mg, 0.330 mmol, 1 equiv; FW = 447.47) and CH_2Cl_2 (5 mL). The resulting solution was cooled to -78 °C using an acetone/dry ice bath. Next, TMSI (132 mg, 94 μL, 2 equiv; FW = 200.10, d = 1.4) was added over 1 minute. The reaction mixture was then allowed to warm to 0 °C in 1 h. The progress of the reaction was monitored by TLC (Hexanes : EtOAc = 3:1 where the product had a R_f value of 0.55).

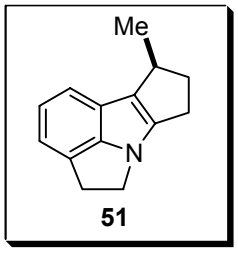
Workup: The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification: The crude product was shown to be sufficiently pure by ^{1}H- and ^{13}C-NMR analysis and was taken to the next step (Buchwald-Hartwig coupling) without further purification. The product was a yellow oil: 96 mg (84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.3 Hz, 1H), 6.89-6.63 (m, 2H), 5.90 (s, 1H), 4.55 (br s, 1H), 3.99 (d, *J* = 8.5 Hz, 1H), 3.59 (t, *J* = 7.9 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H), 2.90 (td, *J* =

15.6, 7.8 Hz, 1H), 2.63 (dd, *J* = 14.8, 6.6 Hz, 1H), 2.13 (s, 1H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 130.2, 128.8, 126.7, 126.0, 124.4, 123.5, 122.3, 119.5, 118.8, 118.2, 117.2, 47.9, 47.0, 35.5, 35.2, 30.0, 16.5 (the CF_3 group shows up as a quartet and all four of the peaks are reported); IR (neat) 3399 (br, m), 3053 (m), 3029 (m), 2962 (s), 2929 (s), 2852 (s), 1970 (w), 1903 (w), 1849 (w), 1726 (w), 1657 (s), 1603 (s), 1569 (w), 1481 (s), 1456 (s), 1418 (s), 1380 (m), 1349 (m), 1311 (s), 1277 (s), 1212 (s), 1140 (s), 1109 (s), 1063 (m), 1036 (m), 994 (m), 977 (m), 898 (s), 848 (s), 767 (s), 753 (s), 664 (m), 611 (s), 515 (s). HRMS (CI-MS) calcd. for $C_{15}H_{17}F_3NO_3$ [$(M+H)^+$] 348.0881 found 348.0885.

Preparation of tetracyclic indole 51.



51

A 25 mL round bottom flask, equipped with a reflux condenser, was charged with Cs_2CO_3 (169 mg, 0.52 mmol, 2 equiv; FW = 325.82) and THF (6 mL). Next, xanthphos (45 mg, 0.078 mmol, 30 mol%; FW = 578.63) and $Pd_2(dba)_3{\cdot}CHCl_3$ (27 mg, 0.026 mmol, 10 mol%; FW = 1035.08) were added. The resulting solution was then allowed to stir for 5 minutes before adding the solution of the enol triflate **S-23** (90 mg, 0.26 mmol, 1 equiv; FW = 347.35) in THF (1 mL) in one portion. The reaction mixture was then brought to reflux for 1 h.

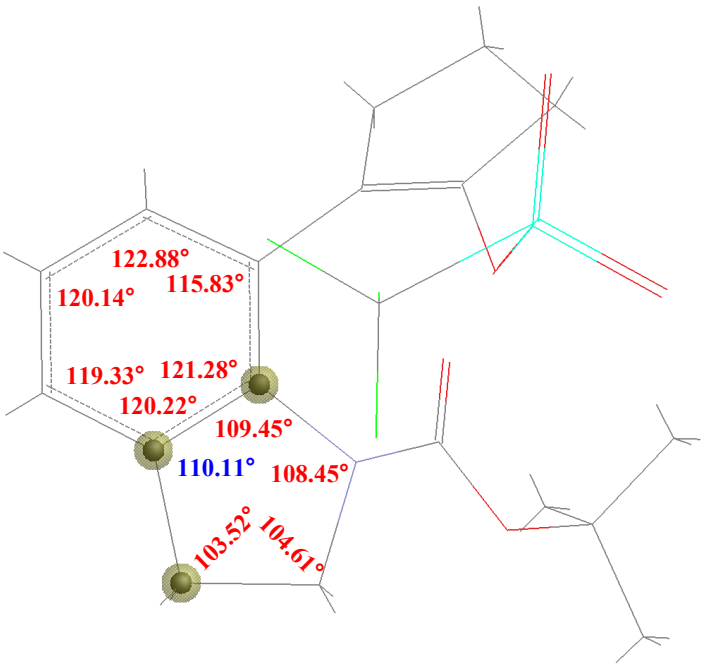
Workup: The reaction mixture was poured into a vigorously stirring mixture of Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL). The aqueous layer was then washed with Et_2O (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

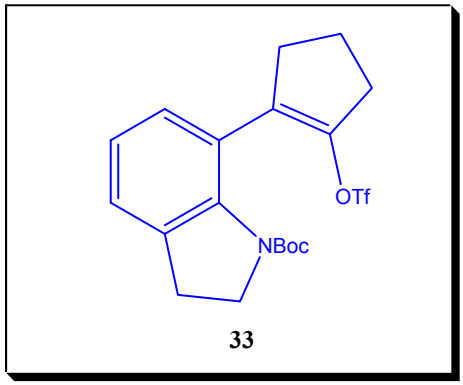
Purification: The crude product was loaded on a column (diameter = 2.0 cm, packing length = 28 cm) and eluted with Hexanes : EtOAc = 10 : 1; fraction size = 8 mL. The product was obtained as a white solid: 27 mg (54%). M.p. = 118-119 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 7.8, 6.8 Hz, 1H), 6.83 (d, *J* = 6.8 Hz, 1H), 4.66-4.07 (m, 2H), 3.87-3.62 (m, 2H), 3.39-3.23 (m, 1H), 2.81 (m, 2H), 2.70 (dddd,

J = 12.5, 8.3, 7.5, 4.0 Hz, 1H), 2.00 (ddt, *J* = 9.0, 7.6, 6.1 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 142.3, 127.8, 124.6, 120.9, 116.8, 115.5, 113.8, 48.5, 38.1, 34.2, 33.2, 24.4, 21.6; IR (KBr pellet) 3049 (s), 3015 (w), 2954 (m), 2929 (m), 2904 (m) 2852 (s), 1644 (s), 1496 (s), 1478 (m), 1465 (s), 1456 (m), 1437 (s), 1379 (m), 1368 (m), 1338 (s), 1294 (m), 1269 (s), 1210 (w), 1174 (m), 1150 (w), 1096 (w), 1040 (w), 1006 (m), 951 (w), 813 (w), 743 (s), 731 (s), 617 (w), 574 (w). HRMS (CI-MS) calcd. for $C_{14}H_{15}N$ $[M^+]$ 197.1204, found 197.1201.

BOND ANGLES IN ENOL TRIFLATE 33 (precursor to 38)





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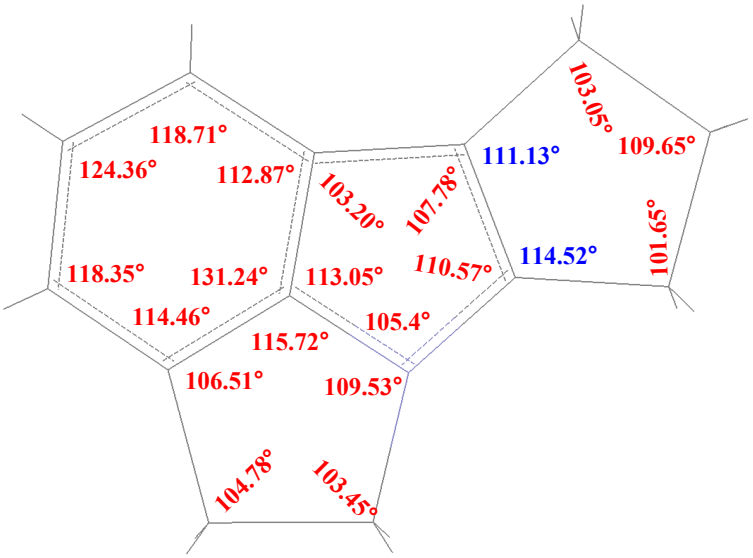
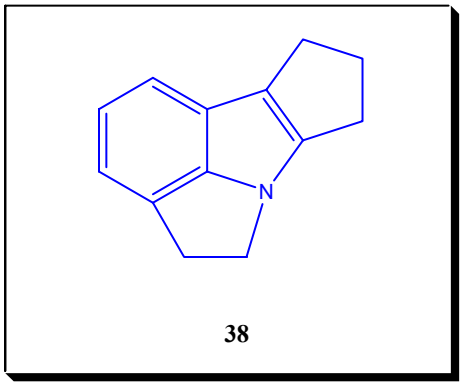
BOND ANGLES IN TETRACYCLIC INDOLE 38





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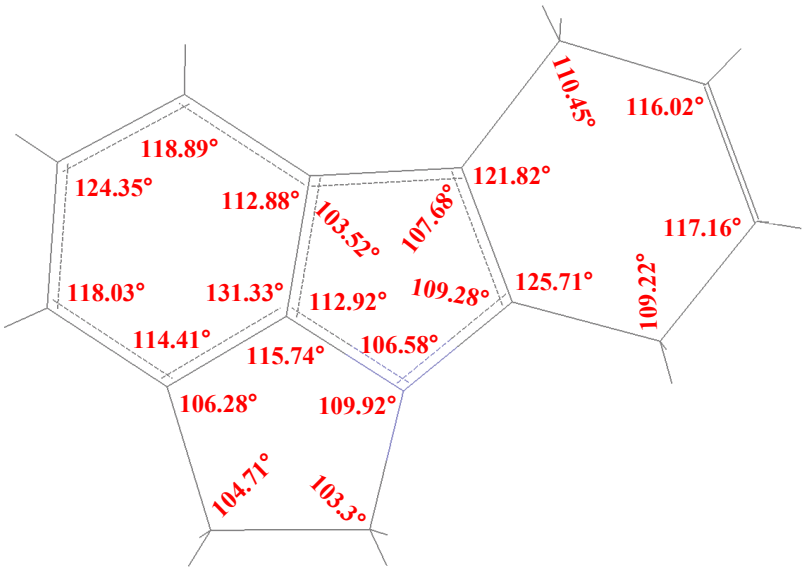
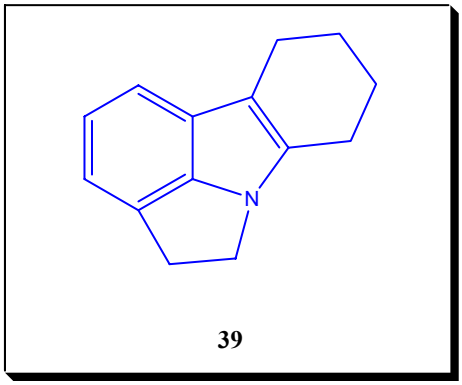
BOND ANGLES IN TETRACYCLIC INDOLE 39





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