Access to a Welwitindolinone Core Using Sequential Cycloadditions

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Supporting Information

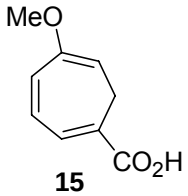
A. Materials and Methods:

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. Reaction solvents were dried using J. C. Meyer's Solvent Purification System passing through activated alumina prior to use. All other reagents were purchase from commercial sources and used without further purification, unless otherwise indicated.

Flash Chromatography was performed using SiliCycle SilicaFlash F 60 40-60 μm 60 Å silica gel. Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (E. Merck, DC-Glasfolien, Kieselgel 60 F254) and visualized with UV light and potassium permanganate stain. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) data were acquired on a Mercury 400 (400 MHz), a Varian 400 (400 MHz), or on a Varian Unity Inova-500 (500 MHz) spectrometer. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) data were acquired at 100 MHz on a Mercury 400 or at 125 MHz on a Varian Unity Inova 500 spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to deuterochloroform (7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C. Chiral HPLC analyses were performed on a Thermo Separation Products Spectra Series P-100 or P-200 and UV100 (254 nm or 220 nm) using Chiralcel columns (OB-H, OC, OD-H, OJ-H), or Chiralpak column (AD, AS, IA, IB, IC) eluting with the solvent mixtures indicated. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in dichloromethane. Infrared (IR) data were recorded as films on potassium bromide (KBr) pellets on a Thermo Scientific Nicolet IR 100 FT-IR spectrometer. High resolution mass spectra were obtained from Stanford University on a Micromass Q-Tof API US Mass Spectrometer using positive electrospray ionization (+ESI). Elemental analysis were conducted by M-H-W Laboratories, Pheonix, Az.

B. Procedures and Analytical Data

1. Preparation of the Tropone Intermediates

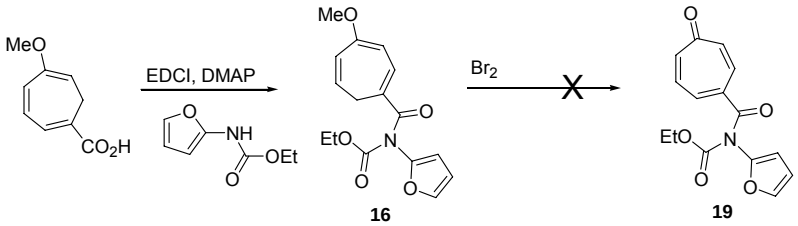


15

Carboxylic Acid **15**

A solution of cycloheptatriene **14**[1] (5.30 g, 27.3 mmole) and barium hydroxide (5.20 g, 16.4 mmole) in 65 mL methanol was heated to reflux temperature for 3 h. The reaction mixture was cooled, diluted with CH_2Cl_2 and acidified with saturated $NaHSO_4$. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4.02 g (89%) of the acid **15**. This material was used without further purification. m.p. = 144 °C, R_f = 0.4 (50% EtOAc/PE), ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 12.0 Hz, 1H), 6.61 (dd, *J* = 11.6, 6.8 Hz, 1H), 6.49 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.41 (d, *J* = 6.4 Hz), 3.61 (s, 3H), 2.62 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 151.4, 130.7, 130.6, 128.1, 121.4, 97.8, 56.4, 32.9; IR (film) 2968, 2836, 2658, 2534, 1684, 1622, 1605, 1537, 1449, 1412, 1359, 1282, 1264, 1197, 1167 cm $^{-1}$; Anal. calc'd for $C_9H_{10}O_3$: C, 65.05, H, 6.07. Found: C, 64.94, H, 5.96.

a. Attempted Preparation of Tropone **19**



16 **19**

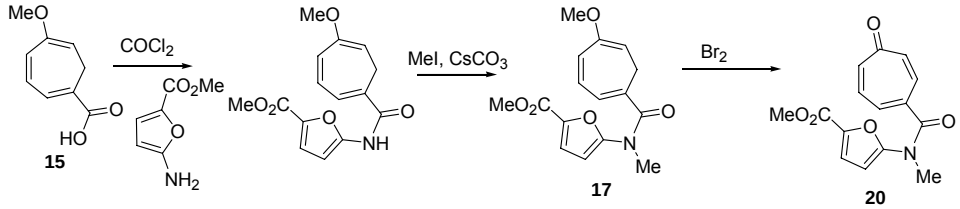
To a mixture of carboxylic acid **15** (0.299 g, 1.38 mmole), 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.302 g, 1.58 mmole), ethyl-2-furylcarbamte[2], and a catalytic amount of 4-dimethylaminopyridine was added 5 ml CH_2Cl_2. The resulting solution was stirred for 5 h at room temperature. The solvents were evaporated and the residue was purified by flash chromatography to give 0.209 g (50%) of the desired coupled product **16**. R_f = 0.15 (10% EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.52-

6.51 (band, 2H), 6.34 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.09 (dd, *J* = 3.2, 1.2 Hz, 1H), 5.86 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.33 (dd, *J* = 3.2, 1.2 Hz, 1H), 4.20 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 3.57 (s, 3H), 2.54 (d, *J* = 7.6 Hz, 2H), 1.21 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 153.3, 151.6, 143.8, 140.7, 136.1, 130.8, 122.7, 121.2, 111.5, 106.3, 97.5, 63.7, 56.4, 32.7, 14.1; IR (film) 2980, 2937, 1750, 1706, 1619, 1530, 1500, 1370, 1332, 1297, 1262, 1233, 1197, 1158 cm $^{-1}$.

Oxidation to Tropone **19**

Oxidation of cycloheptatriene **16** as described in the subsequent tropone synthesis using molecular bromine was unsuccessful in delivering tropone **19**.

b. Preparation of Tropone **20**



Amide Coupling

To a solution of carboxylic acid **15** (0.698 g, 4.20 mmole) in 30 ml CH_2Cl_2 under a nitrogen atmosphere was added oxalyl chloride (0.730 mL, 8.40 mmole). The resulting reaction mixture was stirred at room temperature for 4 h. After this time, the solvents were evaporated and the residue was redissolved in 5 mL CH_2Cl_2. Pyridine (0.453 mL, 5.60 mmole) was added, followed by the addition of 5-amino-2-furancarboxylic acid methyl ester[3] (0.395 g, 2.80 mmole). The reaction mixture was stirred for 1 h and quenched by the addition of saturated $NaHCO_3$. The organic layer was separated and the aqueous fraction extracted twice with CH_2Cl_2. The combined fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (30-40% EtOAc/PE) gave 0.710 g (88%) of the desired product as a 5:1 mixture of double bond isomers as a clear oil. Analysis of major isomer: R_f = 0.35 (35% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 3.8 Hz, 1H), 6.57 (d, *J* = 3.7 Hz, 1 H), 6.50 (d, *J* = 9.5 Hz, 1H), 5.53 (d, *J* = 7.3 Hz, 1H), 5.45 (ddd, *J* = 9.4, 7.3, 7.3 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.51 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.2, 157.3, 150.2, 136.4, 135.3, 127.7, 124.0, 121.5, 119.9, 97.3, 96.5, 57.0, 52.0, 33.4; IR (film) 3281, 1715, 1676, 1606, 1525, 1437, 1313, 1254, 1206, 1135 cm $^{-1}$.

Cycloheptatriene imide **17**

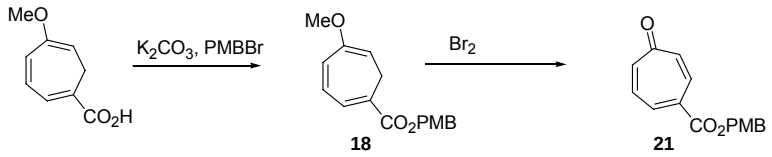
A mixture of the secondary amide prepared above (0.710 g, 2.45 mmole) and $CsCO_3$ (1.20 g, 3.68 mmole) was dissolved in 4 mL DMF and 1 mL THF.

Iodomethane (0.457 mL, 7.35 mmole) was added and the mixture was stirred for 4 h at room temperature. The reaction was diluted with water and ether. The organic layer was separated and the aqueous fraction extracted twice with ether. The combined fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (30-40% EtOAc/PE) gave 0.642 g (86%) of the desired product **17** as an off-white solid. R_f = 0.35 (35% EtOAc/PE); m.p = 88-90 ^oC (decomp); ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 3.6 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.12 (d, *J* = 9.3 Hz, 1H), 5.91 (d, *J* = 3.6 Hz, 1H), 5.32 (d, *J* = 7.2 Hz, 1H), 5.06 (ddd, *J* = 9.3, 7.1, 7.1 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 3.28 (s, 3H), 2.29 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.8, 155.0, 153.7, 139.7, 133.4, 130.1, 125.7, 119.7, 116.6, 104.2, 96.3, 56.6, 51.9, 36.4, 32.6; IR (film) 2951, 1727, 1665, 1606, 1532, 1435, 1373, 1308, 1263, 1212, 1161, 1137, 1019 cm $^{-1}$.

Oxidation to Tropone **20**

To a solution of the *N*-methylamide prepared above (0.642 g, 2.12 mmole) in 20 ml CH_2Cl_2 was added a solution of bromine (0.108 mL, 2.12 mmole) in 2 mL CH_2Cl_2. The resulting reaction mixture was immediately quenched with equal portions of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$. The organic layer was separated and the aqueous fraction extracted twice with CH_2Cl_2. The combined fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70-80% EtOAc/PE) gave 0.441 g (72%) of the desired tropone **20** as a clear oil. R_f = 0.15 (50% EtOAc/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 7.03-6.81 (band, 6H), 5.92 (bs, 1H), 3.81 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 169.2, 158.4, 151.4, 143.8, 141.5, 134.7, 134.3, 133.9, 119.4, 52.2, 36.2; IR (film) 3127, 2952, 1728, 1673, 1634, 1586, 1537, 1436, 1380, 1309, 1214, 1140 cm $^{-1}$; Anal. calc'd for $C_{15}H_{13}NO_5$: C, 62.72, H, 4.56, N, 4.88. Found: C, 62.61, N, 4.65, H, 5.00.

c. Preparation of Tropone **21**



18 **21**

Esterification to cycloheptatriene **18**

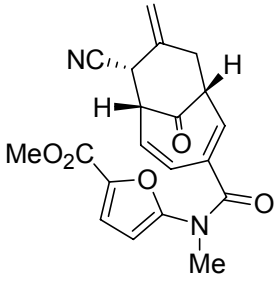
To a solution of the carboxylic acid **15** (1.0 g, 6.02 mmole) in 30 mL DMF was added K_2CO_3 (1.0 g, 7.22 mmole). The reaction mixture was cooled to 0 °C. Freshly prepared 4-methoxybenzyl bromide was added to the reaction mixture and the solution was stirred for 4 h at 0 °C. The reaction mixture was then diluted with water and ether. The organic layer was separated and the aqueous layer extracted twice with ether. The combined organic fractions were dried over

$MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (7-10% EtOAc/PE) gave 1.52 g (88%) of the PMB ester **18** as a clear oil. R_f = 0.25 (10% EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (band, 2H), 6.91-6.88 (band, 2H), 6.83 (dd, *J* = 11.2, 0.8 Hz, 1H), 6.58 (dd, *J* = 11.2, 6.4 Hz, 1H), 6.39 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 5.38 (d, *J* = 6.8 Hz, 1H), 5.15 (s, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 2.59 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 159.7, 151.6, 131.3, 130.4, 130.1, 128.4, 126.4, 121.8, 114.0, 97.5, 66.4, 56.4, 55.4, 32.8; IR (film) 2958, 2835, 1715, 1615, 1515, 1462, 1360, 1320, 1245, 1165, 1035 cm $^{-1}$; Anal. calc'd for $C_{17}H_{18}O_4$: C, 71.31, H, 6.34. Found: C, 71.23, H, 6.21.

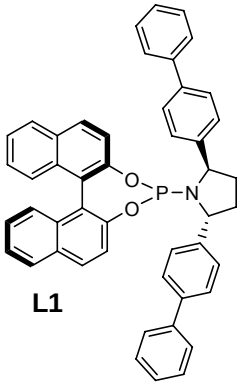
Oxidation to Tropone **21**

To a solution of triene **18** prepared above (5.83 g, 19.7 mmole) in 150 mL CH_2Cl_2 held at 0 °C was added bromine (1.01 mL, 19.7 mmole) in 20 mL CH_2Cl_2 dropwise over 10 min. The reaction mixture was immediately quenched with sat $NaHCO_3$ and sat $Na_2S_2O_3$. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (45-55% EtOAc/PE) gave 3.53 g (66%) of the desired tropone **21** as a brown solid. R_f = 0.55 (50% EtOAc/PE); m.p. = 52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.75 (ddd, *J* = 12.8, 1.6, 0.4 Hz, 1H), 7.34-7.31 (band, 2H), 7.14 (ddd, *J* = 12.0, 8.4, 0.4 Hz, 1H), 7.07 (ddd, *J* = 11.6, 2.4, 1.2 Hz, 1H), 6.99 (dd, *J* = 12.4, 2.8 Hz, 1H), 6.90-6.86 (band, 2H), 5.23 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 165.6, 160.0, 145.4, 141.1, 137.9, 135.5, 134.5, 134.2, 130.4, 127.2, 114.1, 67.9, 55.3; IR (film) 2938, 2837, 1717, 1636, 1589, 1515, 1455, 1374, 1262, 1214, 1176, 1081, 1030 cm $^{-1}$.

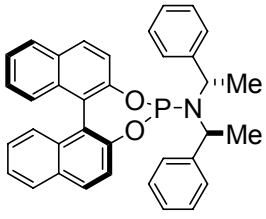
2. Enantioselective [6 + 3] Cycloadditions



22



L1

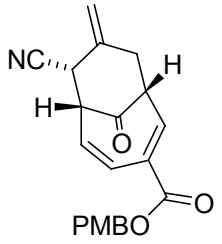


L2

TMM adduct **22**

A mixture of the tropone **20** (0.400 g, 1.39 mmole), $Pd(dba)_2$ (0.040 g, 0.070 mmole), and commercially available ligand **L2**[4] (0.075 g, (0.139 mmole) was purged with argon for 10 min. Anhydrous toluene (7 mL, 0.2 M) was added and the solution stirred at room temperature for 5 min. After cooling to 0 °C, the cyanoacetate donor **13**[5] (0.332 mL, 1.43 mmole) was added and the reaction mixture stirred for 15 h at 0-4 °C under an argon atmosphere. The reaction mixture was purified directly by flash chromatography (60-70% EtOAc/PE) to give 0.447 g (88%) of the desired adduct **22** as a single (>10:1) diastereomer. Chiral HPLC IC column, 70:30 EtOAc/Hexane, 1mL/min, 254 nm, 16.4 and 18.7 (major) min) gave an enantiomeric excess of 0%. R_f = 0.25 (60% EtOAc/PE); m.p. = 50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.6 Hz, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 5.98 (d, *J* = 11.9 Hz, 1H), 5.86 (d, *J* = 8.3 Hz, 1H), 5.63 (dd, *J* = 11.8, 7.6 Hz, 1H), 5.44 (s, 1H), 5.21 (s, 1H), 3.89 (s, 3H), 3.78 (d, *J* = 5.6 Hz, 1H), 3.63 (m, 1H), 3.40 (m, 1H), 3.31 (s, 3H), 2.64 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.54 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 170.2, 158.8, 152.0, 134.3, 133.1, 129.9, 126.9, 123.4, 119.7, 115.8, 54.1, 52.3, 40.7, 39.2, 36.2; IR (film) 2952, 1725, 1668, 1606, 1535, 1435, 1379, 1309, 1211, 1138 cm $^{-1}$; MS (HRMS) for $C_{20}H_{18}N_2O_5$ calc. [M + Na] 389.1114, found 389.1111.

Using ligand **L1**: The same procedure was applied using tropone **22** (0.025 g, 0.087 mmole), $Pd(dba)_2$ (0.0025 g, 0.0044 mmole), ligand **L1** (0.0060 g, 0.0087 mmole), and TMM donor **13** (0.031 mL, 0.139 mmole) held at 0-4 °C for 15 h to give 0.019 g (60%) of desired product as a single diastereomer. Chiral HPLC IC column, 70:30 EtOAc/Hexane, 1mL/min, 254 nm, 16.4 and 18.7 (major) min) gave an enantiomeric excess of 94%. $[\alpha]^{23}_D$ = –124.6 (*c* 1.8, CH_2Cl_2, 94% *ee*).



23

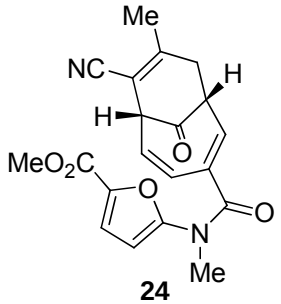
TMM adduct **23**

A mixture of the tropone **21** (1.85 g, 6.81 mmole), $Pd(dba)_2$ (0.196 g, 0.340 mmole), and ligand **L2** (0.334 g, (0.681 mmole) was purged with argon for 10 min. After which, 35 mL toluene were added and the solution was stirred at room temperature for 5 min. After cooling to 0 °C, the cyanoacetate donor **13** (1.65 mL, 7.11 mmole) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture purified directly by flash chromatography (30-40% EtOAc/PE) to give 1.83 g (77%) of the adduct **23** a

single diastereomer of the desired adduct as an amorphous solid. R_f = 0.25 (40% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (band, 2H), 6.92-6.88 (band, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 12.3 Hz, 1H), 5.75 (dd, *J* = 12.3, 7.9 Hz, 1H), 5.50 (s, 1H), 5.24 (s, 1H), 5.14 (AB, 2H, J_{AB} = 12.1 Hz, Δv_{AB} = 14.3 Hz), 3.81 (s, 3H), 3.83-3.80 (m, 1H), 3.69 (m, 1H), 3.56 (m, 1H), 2.73 (dd, *J* = 14.5, 6.3 Hz, 1H), 2.65 (dd, *J* = 14.5, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 166.0, 159.8, 135.7, 132.9, 130.3, 129.2, 127.6, 126.4, 122.9, 119.6, 115.9, 114.0, 67.3, 55.3, 54.0, 52.7, 40.6, 39.1; IR (film) 2856, 2838, 2246, 1714, 1613, 1515, 1462, 1375, 1304, 1238, 1176, 1091, 1042 cm $^{-1}$; MS (HRMS) for $C_{21}H_{19}NO_4$ calc. [M + Na] 372.1212, found 372.1210.

With Ligand **L1**; Procedure as above using tropone **21** (0.062 g, 0.229 mmole), $Pd(dba)_2$ (0.0079 g, 0.0138 mmole), ligand **L1** (0.016 g, 0.0275 mmole), and TMM donor **13** (0.077 mL, 0.330 mmole) held at 0-4 °C for 15 h to give 0.064 g (80%) of desired product as a single diastereomer. ee was determined after next step due to difficulties in chiral resolution. $[\alpha]^{23}_D$ = +86 (c 0.7, CH_2Cl_2, 94% ee).

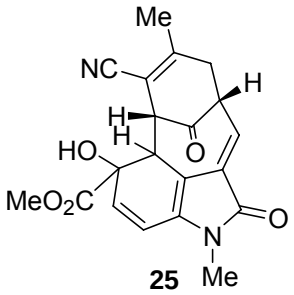
3. Completion of Core Structure From Adduct **22**



24

α, β-Unsaturated Nitrile **24**

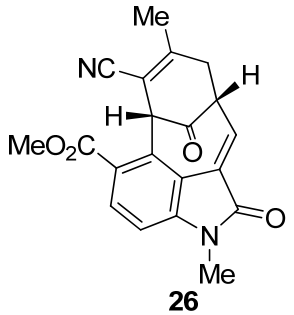
A mixture of the TMM adduct **22** (0.266 g, 0.726 mmole) and 4-dimethylamino pyridine (0.018 g, 0.145 mmole) was dissolved in dichloroethane (3.5 mL). The solution was heated to 50 °C for 15 h and purified directly using flash chromatography (60-70% EtOAc/PE) to give 0.244 g (92%) of the desired compound as a clear oil. R_f = 0.25 (60% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 3.5 Hz, 1H), 6.12 (d, *J* = 10.7 Hz, 1H), 5.98 (bs, 1H), 5.85 (dd, *J* = 10.0, 10.0 Hz, 1H), 5.79 (d, *J* = 5.4 Hz, 1H), 3.89 (s, 3H), 3.69 (d, *J* = 9.0 Hz, 1H), 3.44 (dd, *J* = 5.6, 5.6 Hz, 1H), 3.31 (s, 3H), 2.87 (dd, *J* = 18.7, 5.8 Hz, 1H), 2.43 (d, *J* = 18.8 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 169.8, 158.7, 151.9, 151.2, 140.8, 133.6, 131.8, 127.4, 123.3, 119.9, 116.3, 105.9, 52.3, 50.5, 50.3, 40.1, 36.2, 22.2; IR (film) 3131, 2951, 2214, 1731, 1671, 1606, 1536, 1435, 1379, 1308, 1212, 1138, 1018 cm $^{-1}$; MS (HRMS) for $C_{20}H_{18}N_2O_5$ calc. [M + Na] 389.1114, found 389.1109.



25

Diels Alder adduct **25**

A solution of the amidofuran **24** (0.302 g, 0.824 mmole) in toluene (5 mL) was heated in a microwave reactor at 150 °C for 6 h. The reaction mixture was purified directly using flash chromatography (70-90% EtOAc/PE) to give 0.081 g of recovered starting material and 0.127 g (42%, 57% brsm) of the desired alcohol as an unstable yellow solid. R_f = 0.20 (75% EtOAc/PE); ^{1}H NMR (400 MHz, C_6D_6) δ 6.31 (d, *J* = 7.3 Hz, 1H), 5.79 (d, *J* = 9.9 Hz, 1H), 5.51 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 1H), 3.72 (s, 3H), 3.64 (bs, 1H), 3.24 (bs, 1H), 2.94 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.40 (s, 3H), 1.64 (dd, *J* = 19.1, 7.4 Hz, 1H), 1.45 (d, *J* = 19.1 Hz, 1H), 1.35 (s, 3H).

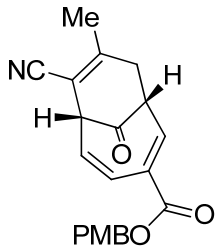


26

Oxindole **26**

A mixture of the alcohol **25** (0.036 g, 0.098 mmole) and Burgess reagent[6] (0.035 g, 0.147 mmole) was dissolved in toluene (1 mL). The solution was heated to 50 °C for 15 h and purified directly using flash chromatography (70% EtOAc/PE) to give 0.020 g (59%) of the desired oxindole as a yellow solid. R_f = 0.30 (60% EtOAc/PE); m.p. > 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 6.6 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.12 (bs, 1H), 3.93 (s, 3H), 3.75 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.26 (s, 3H), 3.09 (dd, *J* = 19.0, 6.8 Hz, 1H), 2.77 (d, *J* = 18.6 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 166.8, 166.7, 150.3, 147.1, 135.4, 133.9, 131.3, 129.1, 124.6, 122.5, 120.5, 109.3, 107.9, 52.6, 50.0, 49.4, 38.2, 26.6, 22.8; IR (film) 2952, 2210, 1710, 1599, 1478, 1267, 1150, 1130 cm^{-1}; MS (HRMS) for $C_{20}H_{16}N_2O_4$ calc. [M + Na] 371.1008, found 371.1010.

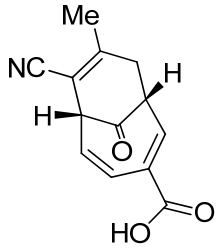
4. Completion of Core Structure From Adduct 23



27

α, β-Unsaturated Nitrile **27**

A mixture of the TMM adduct **23** (2.0 g, 5.73 mmole) and 4-dimethylamino pyridine (0.140 g, 1.15 mmole) was dissolved in dichloroethane (5 mL). The solution was heated to 50 °C for 15 h and purified directly using flash chromatography (40-50% EtOAc/PE) to give 2.0 g (quant.) of the desired compound as a clear oil. Chiral HPLC using IC column, 40% isopropanol/heptane, 0.8 mL/min, 254 nm, 24 (minor) and 45 (major) minutes gave an enantiomeric excess of -37% using ligand **L2** and 94% with ligand **L1**. R_f = 0.25 (40% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (band, 2H), 6.93-6.89 (band, 2H), 6.78 (d, *J* = 11.2 Hz,1H), 6.70 (d, *J* = 5.7 Hz, 1H), 6.01 (dd, *J* = 11.0, 9.6 Hz, 1H), 5.16 (AB, 2H, J_{AB} = 12.0 Hz, Δv_{AB} = 7.6 Hz), 3.82 (s, 3H), 3.79 (bs, 1H), 3.54 (m, 1H), 2.97 (dd, *J* = 18.4, 5.8 Hz, 1H), 2.64 (d, *J* = 18.3 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 165.8, 159.9, 151.0, 137.6, 130.5, 128.6, 127.5, 127.0, 123.8, 116.4, 114.1, 106.5, 67.5, 55.4, 50.7, 50.3, 39.8, 22.2; IR (film) 2957, 2213, 1715, 1612, 1515, 1442, 1377, 1319, 1241, 1175, 1110, 1031 cm^{-1}. $[\alpha]^{23}_D$ = –171.7 (c 0.8, CH_2Cl_2, >96% ee).

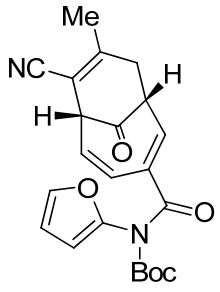


28

Carboxylic Acid **28**

To a solution of the PMB ester **27** (2.09 g, 5.30 mmole) in 14 mL CH_2Cl_2 under an argon atmosphere was added trifluoroacetic acid (1.18 mL, 15.9 mmole). The reaction mixture was stirred at room temperature for 15 h. The solution was slowly quenched using saturated $NaHCO_3$. The organic layer was separated and discarded. The aqueous layer was acidified using solid $NaHSO_4$ and extracted

twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4, filtered, and evaporated to give 1.24 g (quant.) of the desired acid as a white solid. R_f = 0.10 (50% EtOAc/PE); M.P. = 170-172°C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 5.5 Hz, 1H), 6.77 (d, *J* = 11.2 Hz, 1H), 6.07 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.29 (s, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.60 (dd, *J* = 5.6, 5.6 Hz, 1H), 3.02 (dd, *J* = 18.6, 5.6 Hz, 1H), 2.68 (d, *J* = 18.6 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 171.2, 151.1, 139.7, 128.0, 126.5, 124.4, 116.3, 106.6, 50.7, 50.5, 39.9, 22.2; IR (film) 3063 (br), 2216, 1721, 1428, 1270, 1230, 1108 cm $^{-1}$; $[\alpha]^{23}_D$ = –271.7 (c 0.8, CH_2Cl_2, 94% ee); MS (HRMS) for $C_{13}H_{10}NNaO_3$ calc. [M + Na] 274.0456, found 274.0455.

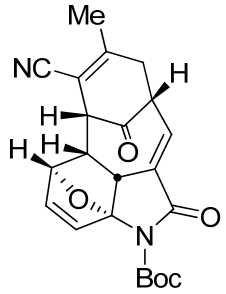


30

Imidofuran **30**

To a solution of the carboxylic acid **28** (0.861 g, 3.76 mmole) in 10 mL THF under an argon atmosphere was added triethylamine (0.576 mL, 4.13 mmole). The reaction mixture was cooled to 0 °C and isobutylchloroformate (0.536 mL, 4.13 mmole) was added dropwise. After stirring for 30 min at 0 °C, the solution was cooled to -78 °C. In a separated flask under an argon atmosphere was placed furan-2-ylcarbamic acid *tert*-butyl ester **29**[7] (0.895 g, 4.89 mmole) and 10 mL THF. The solution was cooled to -78 °C and *n*BuLi (2.22 mL, 4.89mmole, 2.2 M in hexanes) was added slowly. After stirring for 20 min the solution was transferred via cannula to the anhydride. The resulting mixture was stirred for 30 min at -78 °C and quenched with saturated $NaHCO_3$. After warming to room temperature, the organic layer was separated and the aqueous solution extracted twice with Et_2O. The combined organic fractions were dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (30-40% EtOAc/PE) gave 1.02 g (64%) of the desired imide **30** as a clear oil. Acidification of the aqueous layer followed by extraction with CH_2Cl_2 allowed for the recovery of 0.169 g starting acid (86% b.r.s.m). R_f = 0.55 (50% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 6.42 (m, 1H), 6.31 (d, *J* = 10.9, 1H), 6.12 (dd, *J* = 3.3, <1.0 Hz, 1H), 6.05 (d, *J* = 5.7 Hz, 1H), 5.97 (dd, *J* = 10.8, 9.6 Hz, 1H), 3.75 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.51 (dd, *J* = 5.8, 5.8 Hz, 1H), 2.94 (dd, *J* = 18.6, 6.0 Hz, 1H), 2.55 (d, *J* = 18.5 Hz, 1H), 2.06 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 170.4, 151.1, 150.8, 143.5, 140.9, 134.2, 133.2, 127.0, 123.9, 116.5, 111.9, 106.5, 84.8, 50.5, 40.1, 27.9, 22.3; IR (film) 2982, 2213, 1736,

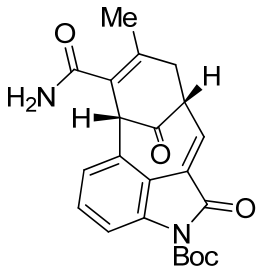
1705, 1607, 1500, 1432, 1370, 1341, 1254, 1149, 1113, 1072, 1007 cm $^{-}$1; $[\alpha]^{23}_{D}$ = –216.5 (c 1.3, CH_2Cl_2, 94% ee); MS (HRMS) for $C_{22}H_{22}N_2O_5$ calc. [M + Na] 417.1426, found 417.1432.



31

Diels-Alder adduct **31**

A solution of the imide **30** (0.0300 g, 0.0761 mmole) in 1.5 mL toluene was placed in a round bottom flask equipped with a reflux condenser. The reaction mixture was heated to 115 °C for 4 h. After cooling, the solution was directly purified by flash chromatography (1-2% MeOH/CH_2Cl_2) to give 0.0298 g (99%) of the intermediate Diels-Alder adduct **31** as a slightly yellow solid. R_f = 0.30 (50% EtOAc/PE); m.p. = >220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, *J* = 5.7 Hz, 1H), 6.55 (dd, *J* = 3.4, 3.4 Hz, 1H), 6.41 (dd, *J* = 5.8, 2.2 Hz, 1H), 5.70 (d, *J* = 2.2 Hz, 1H), 3.55 (m, 1H), 3.44 (m, 1H), 2.83 (ddd, *J* = 18.7, <1.0, <1.0 Hz, 1H), 2.75 (ddd, *J* = 8.4, 3.3, 3.3 Hz, 1H), 2.63 (d, *J* = 18.6 Hz, 1H), 2.46 (dd, *J* = 8.4, 7.0 Hz, 1H), 2.07 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 166.4, 152.6, 149.1, 135.6, 134.3, 133.4, 131.8, 117.9, 107.1, 99.3, 84.6, 78.0, 49.3, 48.6, 44.3, 43.9, 38.3, 28.1, 23.3; IR (film) 2981, 2209, 1786, 1731, 1682, 1356, 1305, 1258, 1156, 1074 cm $^{-1}$. $[\alpha]^{23}_{D}$ = –70.8 (c 1.2, CH_2Cl_2, 94% ee); MS (HRMS) for $C_{22}H_{22}N_2O_5$ calc. [M + Na] 417.1426, found 417.1413.

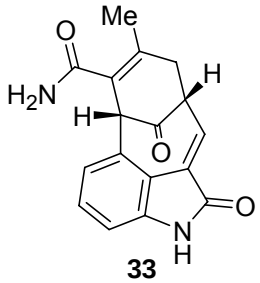


32

Oxindole **32**

To a solution of the Diels-Alder adduct **31** (0.003 g, 0.007 mmole) and 0.3 mL CH_2Cl_2 at 0 ºC was added ~0.010 mL anhydrous trifluoroacetic acid. The reaction

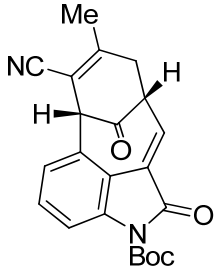
was monitored by TLC while allowing to warm to r.t. Upon consumption of the starting material, the mixture was quenched with saturated $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70-80% EtOAc/PE) gave ~ 0.001g of the *N*-Boc oxindole **32** as a yellow oil. R_f = 0.30 (75% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 1H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 6.7 Hz, 1H), 5.31 (bs, 1H), 4.97 (bs, 1H), 4.57 (s, 1H), 3.73 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.02 (dd, *J* = 17.9, 6.3 Hz, 1H), 2.66 (d, *J* = 18.0 Hz, 1H), 1.90 (s, 3H), 1.63 (s, 9H).



33

Oxindole **33**

A small amount of *N*-H oxindole **33** was isolated from the above reaction. R_f = 0.1 (75% EtOAc/PE); ^{1}H NMR (400 MHz, CD_3CN) δ 8.57 (bs, 1H), 7.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 6.6 Hz, 1H), 5.96 (bs, 1H), 5.69 (bs, 1H), 4.32 (d, *J* = 1.9 Hz, 1H), 3.66 (ddd, *J* = 6.9, 6.9, 1.3 Hz, 1H), 2.99 (dd, *J* = 18.1, 6.8 Hz, 1H), 2.68 (d, *J* = 18.1 Hz, 1H), 1.81 (s, 3H).

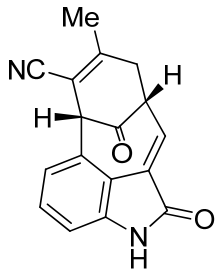


34

Oxindole **34**

A solution of the Diels-Alder adduct **31** (0.066 g, 0.167 mmole) and Burgess reagent[6] (0.142 g, 0.502 mmole) in 2 mL toluene was heated to 90 °C for 15 h. An additional 0.100 g Burgess reagent was added after this time to ensure complete dehydration. After stirring at 90 °C for an additional 4 h the mixture was cooled and diluted with saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined

organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (60% EtOAc/PE) gave 0.027 g (48%) of the *N*-Boc oxindole **34** as a yellow oil. R_f = 0.30 (50% EtOAc/PE); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0, <1.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.15 (d, *J* = 7.9, 1H), 6.84 (d, *J* = 6.7, 1H), 4.20 (m, 1H), 3.77 (dddd, *J* = 6.8, 6.8, 1.4, 1.4 Hz, 1H), 3.11 (dd, *J* = 18.8, 6.9 Hz, 1H), 2.80 (d, *J* = 18.8, 1H), 2.10 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 164.7, 150.8, 149.0, 140.2, 133.4, 132.0, 128.7, 128.3, 124.7, 119.0, 115.8, 115.6, 109.5, 84.9, 55.7, 49.8, 39.1, 28.3, 22.8; IR (film) 2981, 2211, 1785, 1732, 1599, 1447, 1369, 1336, 1305, 1282, 1254, 1207, 1153, 1097, 1074, 1046 cm^{-1}.



35

Oxindole **35**

A solution of the Diels-Alder adduct **31** (0.030 g, 0.076 mmole) and $Yb(OTf)_3$-H_2O (0.005 g, 0.0076 mmole) in 1 mL dichloroethane was heated to 50 °C for 45 min. The mixture was cooled and diluted with saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (70% EtOAc/PE) gave 0.0104 g (50%) of the oxindole **35** as a yellow solid. R_f = 0.15 (50% EtOAc/PE); m.p. = 150-160 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.31 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.01 (d, *J* = 7.8, 1H), 6.84 (dd, *J* = 7.9, <1.0 Hz, 1H), 6.79 (d, *J* = 6.8 Hz, 1H), 4.18 (m, 1H), 3.78 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.11 (dd, *J* = 18.9, 7.0 Hz, 1H), 2.81 (d, *J* = 18.8, 1H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 168.2, 150.8, 141.3, 132.7, 131.9, 129.6, 129.2, 122.6, 119.5, 116.0, 110.4, 109.6, 55.7, 49.9, 39.2, 22.9; IR (film) 3270 (b), 2212, 1714, 1656, 1614, 1453, 1306, 1241, 1152 cm^{-1}; $[\alpha]^{23}_D$ = –193.3 (c 1.0 CH_2Cl_2, 94% ee); MS (HRMS) for $C_{17}H_{12}N_2O_2$ calc. [M + Na] 299.0796, found 299.0785.

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[1] Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981,** *46*, 873-876.

[2] Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609-2617.

[3] Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088-4096.

[4] Aldrich Chemical Company. Catalog #665290

[5] Trost, B. M.; Cramer, N.; Silverman, S. M. J. Am Chem. Soc. 2007, 129, 12396-12397.

[6] Burgess, E. M.; Penton, H. R.; Taylor, E. A.; Williams, W. M., *Org. Synth.* **1988,** *50*, 788-791.

[7] Lynch, S. W.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643-4645.