Synthesis of Novel Heterocyclic Structures *via* Reaction of Isocyanides with *S-trans*-enones

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EXPERIMENTAL PROCEDURES

General Methods

All reactions were performed in oven- or flame-dried glassware under an argon atmosphere. Solvents used for the reactions (tetrahydrofuran and toluene) were passed through an activated alumina column.[1] Methylcyclohexane was distilled from calcium hydride. Except as otherwise noted, all other solvents and reagents were A. C. S.-, reagent-, or HPLC-grade (or better) and were used as received from commercial sources (Acros, Aldrich, Fluka, Fisher, TCI, or Strem) or were prepared according to literature procedures. Diethylaluminum chloride was purchased from Aldrich in a blue cylinder as a 1.0 M solution in hexanes. The gallium (III) chloride solution was either purchased from Aldrich as a 0.5M solution in pentane or prepared from solid gallium (III) chloride (5 g, Aldrich) and dissolved in methylcyclohexane (90 mL) to afford a 0.316 M solution and stored in a sure-seal bottle.

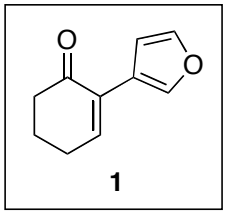
Merck precoated silica gel plates (250μm, K6F) were used for analytical TLC. The plates were visualized using 254 nm ultraviolet light and/or by treating the plates with potassium permanganate, ninhydrin, or anisaldehyde stains. Flash column chromatography was performed using silica gel (partical size 32-63 microns) purchased from Sorbent Technologies. Infrared spectra were acquired on a Perkin-Elmer 1600 series Fourier-transform spectrometer using the neat material on NaCl or KBr plates. Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. Bruker AM–500 or DRX–500 instruments were used to acquire ^{1}H and ^{13}C NMR spectra at 500 MHz and 125 MHz, repectively. The residual solvent peak of $CDCl_3$, unless otherwise noted, was used as the internal reference (δ 7.26 for ^{1}H, and δ 77.0 for ^{13}C). High-resolution mass spectra were recorded by Dr. Rakesh K. Kohli at the University of Pennsylvania Mass Spectrometry Service Center in positive ion mode using either chemical or electrospray ionization. X-ray crystallographic analyses were performed by Dr. Patrick J. Carroll at the University of Pennsylvania.

Abbreviations:

EA = ethyl acetate
HX = hexanes
DCM = dichloromethane
EE = diethyl ether
BRSM = based on recovered starting material

s = singlet
d = doublet
t = triplet
q = quartet
quint = quintet
m = multiplet
br = broad
app = apparent

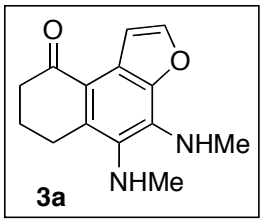
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.



1

2-Furan-3-yl-cyclohex-2-enone 1: To a solution of 2-bromo-cyclohex-2-enone[2] (1.42 g, 8.12 mmol) and tetrakis(triphenyl-phosphine)palladium (0) (Strem, 938 mg, 0.812 mmol) in toluene (80 mL) was added 2M Na_2CO_3 (8.1 mL, 16.24 mmol) and a solution of 3-furylboronic acid (Aldrich, 1.00 g, 8.94 mmol) in absolute ethanol (8.1 mL). The reaction mixture was heated to 100°C for 7.5 hours and then concentrated *in vacuo*. The resulting residue was partitioned between water and methylene chloride. The aqueous layer was extracted with methylene chloride and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% EA/HX to 10% EA/HX) afforded 2-furan-3-yl-cyclohex-2-enone **1** (847 mg, 64%) as a pale yellow liquid.

R_f = 0.40 (25% EA/HX); IR (film, cm^{-1}): 2926, 1675, 1159, 1037, 872, 791; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.36 (app t, J = 1.6 Hz, 1H), 7.12 (t, J = 4.5 Hz, 1H), 6.51 (dd, J = 0.6 Hz, J = 1.8 Hz, 1H), 2.55-2.49 (m, 4H), 2.06 (app quint, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.6, 144.4, 142.2, 131.4, 119.8, 107.9, 39.0, 26.3, 22.7; HRMS (CI) Calculated for $C_{10}H_{10}O_2$(M+): 162.0681, found: 162.0677.



3a

Benzofuran 3a: To a flask containing 2-furan-3-yl-cyclohex-2-enone **1** (64 mg, 0.395 mmol) was added methylisocyanide[3] from a 0.183 M stock solution in THF (1.94 mL, 0.356 mmol). Molecular sieves were added and the reaction mixture was cooled to 0°C. Diethylaluminum chloride (1.0 M solution in hexanes, 0.43 mL, 0.435 mmol) was added and the reaction was allowed to reach room temperature and stir at room temperature for 18 hours. The reaction mixture was then poured into an aqueous potassium carbonate solution (200 mg K_2CO_3 in 10 mL H_2O) and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (0% - 6% EE/DCM) afforded benzofuran **3a** (15.9 mg, 37%, 64% BRSM) as a yellow crystalline solid.

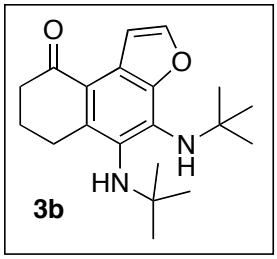
X-ray Structure shown on page 11.

m.p. = 97-98 °C; R_f = 0.23 (6% EE/DCM) and R_f = 0.33 (50% EA/HX); IR (film, cm^{-1}): 3354, 2938, 2869, 1646, 1602, 1570, 1534, 1388, 1306, 1185, 1133; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, J = 2.0, 1H), 7.64 (d, J = 2.0 Hz, 1H), 5.45 (br s, 1H, N*H*), 3.40 (s, 3H), 2.89 (t, J = 6.0 Hz, 2H), 2.62 (s, 3H), 2.59 (t, J = 6.2 Hz, 2H), 2.14 (quint, J = 6.2 Hz, 2H), 1.9-1.5 (br s, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.9, 146.2, 142.1, 137.2 (2 carbons accidentally equivalent), 127.0, 126.7, 114.0, 108.5, 38.9, 34.9, 32.4,

[2] Smith III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47(10)*, 1855-1869.

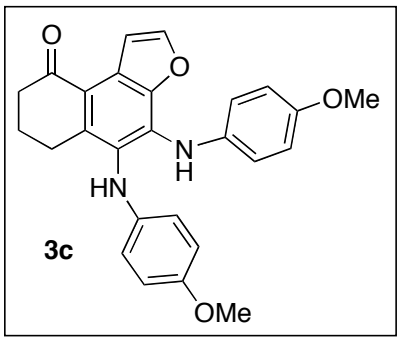
[3] Cappon, J. J.; Witters, K. D.; Baart, J.; Verdegem, P. J. E.; Hoek, A. C.; Luiten, R. J. H.; Raap, J.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 318-328.

25.1, 23.5; HRMS (CI) Calculated for $C_{14}H_{16}N_2O_2$ (M+): 244.1212, found: 244.1218.



Benzofuran 3b: To a solution of 2-furan-3-yl-cyclohex-2-enone **1** (50 mg, 0.27 mmol) in THF (3 mL) was added molecular sieves and *tert*-butyl isocyanide[4] (77 mg, 0.10 mL, 0.924 mmol). After stirring for 15 minutes, the solution was cooled to 0°C and diethylaluminum chloride (0.37 mL, 0.37 mmol) was added and the reaction was allowed to warm over 18 hours. The reaction mixture was poured into an aqueous K_2CO_3 solution (200 mg in 10 mL H_2O) and extracted with ethyl acetate several times. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-3% EE/DCM) to afford benzofuran **3b** (59 mg, 58%) as pale yellow oil.

R_f = 0.29 (6% EE/DCM); IR (film, cm^{-1}): 3316, 2966, 2868, 1639, 1595, 1570, 1531, 1386, 1364, 1354, 1290, 1223, 1207, 1183, 1138; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 6.53 (br s, 1H, N*H*), 2.86 (t, J = 5.8 Hz, 2H), 2.58 (t, J = 6.3 Hz, 2H), 2.44 (br s, 1H), 2.05 (quint, J = 6.4 Hz, 2H), 1.51 (s, 9H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.9, 145.9, 140.1, 139.5, 138.2, 127.3, 124.0, 113.3, 108.8, 55.0, 51.9, 39.0, 31.1, 30.9, 28.1, 23.7; HRMS (ES) Calculated for $C_{20}H_{28}N_2O_2$+Na: 351.2048, found: 351.2038.



Benzofuran 3c: 2-Furan-3-yl-cyclohex-2-enone **1** (50 mg, 0.308 mmol) and 4-methoxyphenyl isocyanide[5] (123 mg, 0.924 mmol) were azeotroped with benzene three times and further dried under vacuum for 5 minutes. THF (3 mL) was added and to this solution was added diethylaluminum chloride (1M in hexanes, 0.37 mL, 0.37 mmol) at 0 °C. The reaction was allowed to stir at 25 °C for 18 hours and was poured into aqueous potassium carbonate (200 mg in 10 mL water). The aqueous layer was washed with ethyl acetate several times. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (0-4% EE/DCM) to afford compound **3c** (56 mg, 43%, 46% BRSM) as yellow foam.

R_f = 0.30 (6% EE/DCM); IR (film, cm^{-1}): 3333, 2942, 1649, 1569, 1509, 1458, 1386, 1330, 1237, 1181, 1135, 1034, 912, 823, 730; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, J = 2.3 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H), 6.97 (m, 2H), 6.81 (m, 3H), 6.75 (m, 2H), 6.54 (m, 2H), 4.96 (s, 1H, N*H*), 3.80 (s, 3H), 3.73 (s, 3H), 2.81 (t, J = 7.0 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.04 (app quint, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.5, 156.2, 153.1, 146.8, 142.5, 141.3, 139.9, 134.3, 134.1, 127.6, 123.5, 121.9, 116.9, 115.0, 114.5,

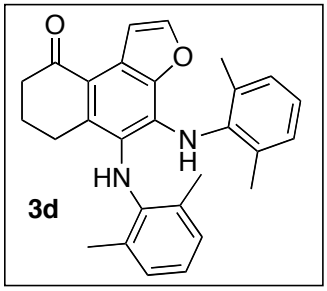
[4] Howell, B. A.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1975**, *97(8)*, 2136-2139.

[5] 4-Methoxyphenyl isocyanide is commercialy available from Aldrich, but was made instead by converting *p*-anisidine to *N*-(4-methoxyphenyl)formamide (59%) according to the general procedure in: Deetz, M. J.; Fahey, J . E.; Smith, B. D. *J. Phys. Org. Chem.* **2001**, *14(7)*, 463-467. *N*-(4-methoxyphenyl)formamide was then converted to 4-methoxyphenyl isocyanide using $POCl_3$ and triethylamine (81% yield).

113.8, 108.4, 55.6, 55.4, 38.9, 25.8, 23.2; HRMS (ES) Calculated for $C_{26}H_{24}N_2O_4$+H: 429.1814, found: 429.1806.

Preparation of compounds 3d and 4d using Et_2AlCl as the Lewis Acid: 2-Furan-3-yl-cyclohex-2-enone **1** (50 mg, 0.308 mmol) was azeotroped with benzene three times. The enone was taken up in THF (3 mL) and 2,6-dimethylphenyl isocyanide[6] (121 mg, 0.925 mmol) was added. The solution was cooled to 0 °C and diethylaluminum chloride (1M in hexanes, 0.37 mL, 0.37 mmol). The reaction was warmed to 25 °C and stirred for 18 hours. Additional diethylaluminum chloride (2 x 0.1 mL) was added in a 3- hour interval. It was later realized that the product and the starting material were cospotting on the TLC plate using 50%EA/HX as the eluent, so additional diethyl aluminum chloride may not have been necessary. The reaction mixture was poured into an aqueous solution of potassium carbonate (200 mg in 10 mL water). The aqueous layer was washed with ethyl acetate several times. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (100% DCM then 3-10% EE/DCM) to afford benzofuran **3d** (62 mg, 47%) as yellow solid and imine **4d** (13 mg, 14%) as a yellow film.

Preparation of Benzofuran 3d using $GaCl_3$ as the Lewis Acid: 2-Furan-3-yl-cyclohex-2-enone **1** (50 mg, 0.308 mmol) was azeotroped with benzene four times. The enone was taken up in toluene (1mL) and 2,6-dimethylphenyl isocyanide[6] (121 mg, 0.925 mmol) was added. To this mixture was added $GaCl_3$ (Aldrich, 0.5 M in pentane, 0.02 mL, 0.0154 mmol) and the reaction mixture was heated to 60°C for 18 hours. An additional amount of $GaCl_3$ (0.02 mL, 0.0154 mmol) was added and the reaction was heated for 60°C for an additional 18 hours. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography (0-2% EE/DCM) to afford benzofuran **3d** (100 mg, 77%) as yellow solid.



3d

Analytical data for 3d: m.p. = 128-130 °C; R_f = 0.42 (6% EE/DCM); IR (film, cm^{-1}): 3330, 2945, 1644, 1604, 1567, 1529, 1502, 1471, 1444, 1380, 1355, 1336, 1305, 1263, 1232, 1185, 1135, 1098, 1031, 910, 767, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.10 (m, 3H), 7.01 (d, J = 7.5 Hz, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.40 (s, 1H), 4.91 (s, 1H), 2.66 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.1 Hz, 2H), 2.13 (s, 6H), 2.10 (s, 6H), 2.03 (app quint, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.6, 146.9, 142.3, 141.4, 140.2, 138.2, 135.6, 134.6, 129.8, 127.9, 126.9, 126.1, 125.1, 121.3, 120.3, 114.6, 108.1, 38.8, 26.4, 23.3, 19.0, 18.5; HRMS (ES) Calculated for $C_{28}H_{28}N_2O_2$+H: 425.2229, found: 425.2210.

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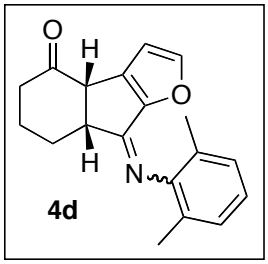
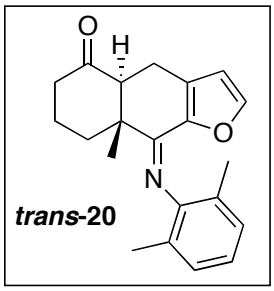
[6] The isocyanide is commercialy available from Aldrich, but was made instead by converting 2,6-dimethylaniline to *N*-(2,6-dimethylphenyl)formamide according to the procedure in: Deetz, M. J.; Fahey, J . E.; Smith, B. D. *J. Phys. Org. Chem.* **2001**, *14(7)*, 463-467. *N*-(2,6-dimethylphenyl)formamide was then converted to 2,6-dimethyl-phenylisocyanide using $POCl_3$ and triethylamine.



4d

Analytical data for imine 4d: R_f = 0.14 (6% EE/DCM); IR (film, cm^{-1}): 2943, 1709, 1661, 1591, 1472, 1431, 1202, 1134, 1092, 899, 765; (note: a small (~11%) amount of a geometric isomer is present, so only major isomer is listed in both the proton and carbon data; also, there is atropisomerism present, so each carbon and proton on aryl ring are chemically inequivalent); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 3.94 (app q, J = 6.7 Hz, 1H), 3.85 (d, J = 7.3 Hz, 1H), 2.49 (m, 2H), 2.28 (m, 2H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 208.9, 159.6, 153.5, 151.8, 151.1, 148.7, 143.3, 127.8, 127.7, 127.0, 123.2, 109.8, 50.8, 46.8, 39.6, 27.8, 20.5, 18.1, 17.9; HRMS (ES) Calculated for $C_{19}H_{19}NO_2$+H: 294.1494, found: 294.1491.

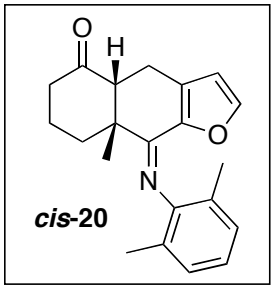
Preparation of compounds *trans*-20 and *cis*-20: Enone **18**[7] (50 mg, 0.263 mmol) and 2,6-dimethylphenyl isocyanide[6] (86 mg, 0.657 mmol) were azeotroped together with benzene three times. The mixture was taken up in THF (2.6 mL) and cooled to 0 °C. Diethylaluminum chloride (1M in hexanes, 0.32 mL, 0.32 mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction mixture was poured into aqueous potassium carbonate (200 mg in 10 ml in water) and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude ^{1}H NMR indicated 2:1 ratio of products. The residue was purified by silica gel chromatography (5-15% EA/HX) to give ***trans*-20** (54.5 mg), 6.8 mg of a mixture of the two products and the ***cis*-20** (34.7 mg). The *trans*- and the *cis*-products were each further purified by preparative thin layer chromatography (25% EA/HX) to afford the ***trans*-20** (39 mg) as light orange-yellow solid and the ***cis*-20** (20 mg) as yellow crystalline solid (71% total yield of both isomers). The stereochemistry of both isomers was determined by X-ray crystallographic analysis (see figures 2 and 3 on page 11 and 12, respectively).



***trans*-20**

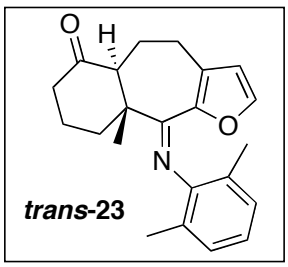
Analytical data for compound *trans*-20: m.p. = 126-127 °C; R_f = 0.38 (25% EA/HX); IR (film, cm^{-1}): 2962, 2938, 1712, 1640, 1592, 1467, 1432, 1373, 1269, 1216, 1185, 1161, 1090, 999, 892, 840, 765, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (s, 1H), 6.99 (m, 2H), 6.87 (t, J = 7.3 Hz, 1H), 6.25 (s, 1H), 2.95 (dd, J = 4.2 Hz, J = 11.2 Hz, 1H), 2.89 (dd, J = 11.4 Hz, J = 17.2 Hz, 1H), 2.74 (dd, J = 3.7 Hz, J = 17.7 Hz, 1H), 2.71 (d, J = 14.4 Hz, 1H), 2.48 (m, 1H), 2.41 (ddd, J = 13.3 Hz, J = 13.3 Hz, J = 6.7 Hz, 1H), 2.18 (m, 1H), 2.09 (app dt, J = 3.4 Hz, J = 14.3 Hz, 1H), 2.01-1.94 (m, 7H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.7, 158.5, 149.4, 145.9, 144.4, 128.6, 127.4, 127.3, 125.5, 124.7, 121.9, 110.7, 55.7, 47.8, 41.0, 34.1, 22.0, 19.9, 19.0, 17.9, 17.8; HRMS (ES) Calculated for $C_{21}H_{23}NO_2$+H: 322.1814, found: 322.1810.

[7] Chakraborty, A.; Kar, G. K.; Ray, J. K. *Tetrahedron* **1997**, *53*, 2989-2996.



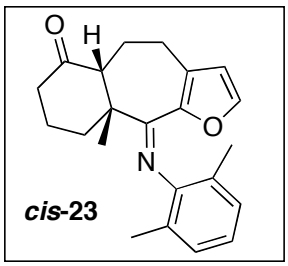
Analytical data for compound *cis*-20: m.p. = 178-179 °C; R_f = 0.26 (25% EA/HX); IR (film, cm^{-1}): 2940, 1712, 1647, 1590, 1462, 1435, 1374, 1349, 1324, 1264, 1204, 1161, 1091, 1035, 985, 898, 856, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (s, 1H), 6.97 (d, J = 7.4 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 6.27 (s, 1H), 3.25 (d, J = 16.9 Hz, 1H), 2.97 (d, J = 13.5 Hz, 1H), 2.86 (d, J = 4.9 Hz, 1H), 2.70 (dd, J = 5.2 Hz, J = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (ddd, J = 6.5 Hz, J = 13.7 Hz, J = 20.2 Hz, 1H), 2.21 (ddddd, J = 3.8 Hz, J = 3.8 Hz, J = 13.0 Hz, J = 13.0 Hz, J = 13.0 Hz, 1H), 2.03 (m, 1H), 1.94 (s, 3H), 1.91 (s, 3H), 1.76 (ddd, J = 3.9 Hz, J = 13.1 Hz, J = 13.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.7, 155.5, 149.7, 146.1, 144.5, 129.7, 127.6, 127.4, 125.3, 125.2, 122.0, 110.7, 56.1, 49.1, 41.2, 34.7, 29.2, 22.8, 19.0, 18.6, 18.0; HRMS (ES) Calculated for $C_{21}H_{23}NO_2$+H: 322.1807, found: 322.1821.

Preparation of imine tricycles *trans*-23 and *cis*-23: Compound **21**[8] (50 mg, 0.245 mmol) and 2,6-dimethylphenyl isocyanide[6] (80 mg, 0.612 mmol) were azeotroped together with benzene three times. The mixture was taken up in THF (2.0 mL) and cooled to 0°C. Diethylaluminum chloride (1M in hexanes, 0.29 mL, 0.29 mmol) was added and the reaction was stirred at room temperature for 48 hours. More isocyanide (80 mg) and diethylaluminum chloride (0.29 mL) were added and the reaction was allowed to stir an additional 48 hours. The reaction mixture was poured into aqueous potassium carbonate (200 mg in 10 ml in water) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude ^{1}H NMR indicated 1.2:1 ratio of geometric isomers. The crude residue was purified by preparative thin layer chromatography (20% EA/HX) to give ***trans*-23** (21 mg, 25%) as pale yellow solid, and an inseparable mixture of starting material and ***cis*-23** (24 mg, 18 mg ***cis*-23** and 6 mg recovered starting material **21** by ^{1}H NMR). The total yield by NMR was 47%. Compound ***trans*-23** was recrystallized from DCM/HX to obtain crystals for X-ray analysis (see figure 4 on page 12).



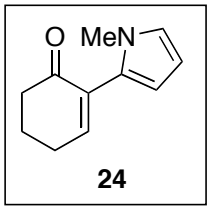
Analytical data for compound *trans*-23: m.p. = >175 °C decomp.; R_f = 0.35 (25% EA/HX); IR (film, cm^{-1}): 2940, 1712, 1625, 1465, 1375, 1232, 1154, 1089, 1002, 761; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.01 (d, J = 1.4 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 6.77 (t, J = 7.4 Hz, 1H), 6.11 (d, J = 1.3 Hz, 1H), 2.80 (d, J = 7.6 Hz, 1H), 2.76 (ddd, J = 2.8 Hz, J = 4.3 Hz, J = 17.5 Hz), 2.68 (br m, 1H), 2.51 (ddd, J = 5.5 Hz, J = 12.8 Hz, J = 17.9 Hz, 1H), 2.46 (br m, 1H), 2.35 (ddd, J = 7.5 Hz, J = J = 13.1 Hz, 1H), 2.25 (br m, 1H), 2.20 (ddd, J = 4.7 Hz, J = J = 13.3 Hz, 1H), 2.12 (s, 3H), 2.12-2.07 (m, 2H), 1.75 (s, 3H), 1.60 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.7, 164.3, 149.5, 144.6, 144.1, 127.2, 127.1, 126.3, 122.9, 121.7, 112.2, 56.5, 52.7, 40.8, 38.5, 25.8, 22.5, 20.0, 19.4, 18.2, 17.7; HRMS (ES) Calculated for $C_{22}H_{25}NO_2$+H: 336.1964, found: 336.1949.

[8] Mal, S. J.; Kar, G. K.; Ray, J. K. *Tetrahedron* **2004**, *60*, 2805-2811.



cis-23

Analytical data for compound *cis*-23: Compound *cis*-**23** could not be separated from the starting material, but had the following characteristics: R_f = 0.29 (25% EA/HX); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.77 (dd, J = 8.6 Hz, J = 8.6 Hz, 1H), 6.09 (s, 1H), 3.60 (dt, J = 20.4 Hz, J = 4.5 Hz, 1H), 3.39 (ddd, J = 6.4 Hz, J = 12.8 Hz, J = 19.7 Hz, 1H), 2.54-2.31 (m, 4H), 2.25 (m, 1H), 2.17-2.04 (m, 2H), 2.10 (s, 3H), 1.91 (m, 2H), 1.80 (s, 3H), 1.36 (s, 3H); HRMS (ES) Calculated for $C_{22}H_{25}NO_2$+H: 336.1964, found: 336.1952.

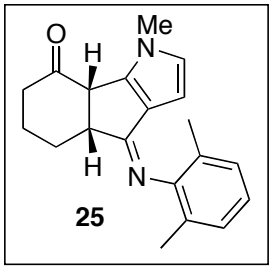


24

Enone 24: 2-Iodo-cyclohexen-2-one[9] (500 mg, 2.25 mmol) was azeotroped with benzene three times. The enone was taken up in THF (6 mL) and dichlorobis(triphenylphosphine)-palladium (II) (Aldrich, 79 mg, 0.113 mmol) and 1-methyl-2-tributylstannylpyrrole[10] were added. The reaction was refluxed for 18 hours. Once cooled to room temperature, the reaction mixture was diluted with diethyl ether and washed with water two times. The organic later was dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography afforded compound **24** (98 mg, 25%) as yellow-brown solid.
m.p. = 47-48 °C; R_f = 0.42 (100% DCM); IR (film, cm^{-1}): 2923, 2853, 1676, 1484, 1467, 1426, 1410, 1352, 1304, 1252, 1152, 1121, 1089, 1054, 966, 908, 814, 710; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.02 (t, J = 4.3 Hz, 1H), 6.64 (dd, J = 2.4 Hz, J = 2.4 Hz, 1H), 6.09 (dd, J = 2.8Hz, J = 3.5 Hz, 1H), 6.03 (dd, J = 1.8 Hz, J = 3.5 Hz, 1H), 3.43 (s, 3H), 2.57 (m, 2H), 2.52 (app dt, J = 4.5, J = 6.0 Hz, 2H), 2.11 (app quintet, J = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.9, 150.4, 133.6, 129.5, 123.2, 109.5, 107.2, 38.8, 34.8, 26.5, 22.8; HRMS Calculated for $C_{11}H_{13}NO^+$: 175.0997, found, 175.0992.

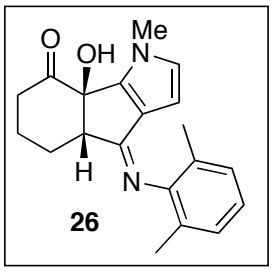
Preparation of imine 25 and α-hydroxyketone 26: Compound **24** (52 mg, 0.297 mmol) and 2,6-dimethylphenyl isocyanide[6] (97 mg, 0.743 mmol) were azeotroped together with benzene three times. The mixture was taken up in THF (3 mL) and diethylaluminum chloride (1M in hexanes, 0.52 mL, 0.52 mmol) was added. Reaction was stirred at room temperature for 18 hours and poured into an aqueous potassium carbonate solution (100 mg K_2CO_3 in 10 mL H_2O). The aqueous layer was extracted with methylene chloride several times. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated. Immediate purification was done by silica gel chromatography (10-50% EA/HX) to afford an inseparable mixture of **25** and oxidized product **26** (5:1 **25**:**26**, 53 mg, 57% yield of mixture) as yellow oil. (Exclusive formation of **26** occurs if crude mixture is exposed to air for a few hours prior to purification). X-ray data was obtained for **26** (see figure 5 on page 13).

[9] Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317-2323.
[10] (a) Peters, D.; Hörnfeldt, A.-B.; Bronowitz, S. *J. Heterocyclic Chem.* **1990**, *27*, 2165.
(b) Bailey, T. *Tetrahedron Lett.* **1986**, *27(37)*, 4407-4410.



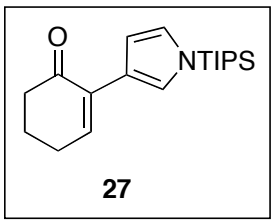
25

Analytical data for imine 25: R_f = 0.16 (50% EA/HX); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.01 (d, J = 7.1 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.90 (app t, J = 7.4 Hz, 1H), 6.39 (d, J = 2.8 Hz, 1H), 4.93 (d, J = 2.7 Hz, 1H), 3.94 (m, 2H), 3.63 (s, 3H), 2.48-2.41 (m, 3H), 2.16 (m, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.98 (m, 2H); HRMS (ES) Calculated for $C_{20}H_{22}N_2O$+H: 307.1760, found: 307.1816.



26

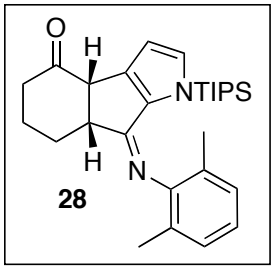
α-Hydroxyketone 26: m.p. = 140-142 °C; R_f = 0.38 (50% EA/HX); IR (film, cm^{-1}): 3349 (br), 2946, 2855, 1712, 1649, 1590, 1518, 1467, 1442, 1414, 1332, 1244, 1204, 1089, 1034, 767, 735; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.04 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.93 (app t, J = 7.4 Hz, 1H), 6.43 (d, J = 2.8 Hz, 1H), 4.96 (d, J = 2.8 Hz, 1H), 4.52 (br s, 1H), 3.68 (m, 1H), 3.40 (s, 3H), 2.55-2.51 (m, 2H), 2.46 (ddd, J = 3.2 Hz, J = 9.8 Hz, J = 17.4 Hz, 1H), 2.19-2.11 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.02-1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4, 166.4, 149.9, 144.9, 130.4, 128.1, 127.8, 127.5, 127.3, 127.0, 122.9, 103.8, 79.0, 63.2, 34.8, 33.6, 25.5, 20.1, 18.1, 17.9; HRMS (ES) Calculated for $C_{20}H_{22}N_2O_2$+H: 323.1760, found: 323.1756.



27

Enone 27: To a solution of 1-(triisopropylsilyl)-3-iodopyrrole[11] (1.91 g, 5.47 mmol) in THF (32 mL) was added *tert*-butyl lithium (1.7 M in pentane, 7.8 mL, 13.2 mmol) at –78 °C. After stirring for 25 minutes at –78 °C, zinc (II) chloride (Acros, 0.5 M in THF, 12.6 mL, 6.30 mmol) was added and the reaction was allowed to stir at 0 °C for 1 hour. The reaction was warmed to room temperature and Argon gas was bubbled through the solution for 15 minutes. Tetrakis(triphenylphosphine)palladium (242 mg, 0.21 mmol) and 2-iodo-cyclohex-2-enone[9] (932 mg, 4.20 mmol) were added. After stirring for 1.5 hours at room temperature, the reaction was poured into saturated NH_4Cl and extracted with ethyl ether a few times. The combined ether layers were dried over sodium sulfate, filtered, and concentrated. Purification was achieved by silica gel chromatography (0-10% EA/HX) to afford product **27** (345 mg, 26% yield) as off-white solid.
m.p. = 71-72 °C; R_f = 0.61 (25% EA/HX); IR (film, cm^{-1}): 2945, 2866, 1676, 1616, 1462, 1387, 1360, 1294, 1255, 1128, 1101, 1016, 883, 799; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (s, 1H), 7.11 (t, J = 4.5 Hz, 1H), 6.72 (dd, J = J = 2.3 Hz, 1H), 6.45 (m, 1H), 2.53 (t, J = 6.4 Hz, 2H), 2.48 (app q, J = 5.8 Hz, 2H), 2.03 (app quint, J = 6.1 Hz, 2H), 1.46 (septet, J = 7.5 Hz, 3H), 1.10 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.8, 141.7, 133.4, 124.4, 123.9, 120.3, 108.2, 39.5, 26.4, 22.9, 17.8, 11.6; HRMS (ES) Calculated for $C_{19}H_{31}NOSi$+H: 318.2253, found: 318.2242.

[11] Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E. *J. Org. Chem.* **1992**, *57*, 1653-1656.



28

Imine tricycle 28: Enone **27** (50 mg, 0.157 mmol) and 2,6-dimethylphenylisocyanide (31 mg, 0.236 mmol) were azeotroped with benzene three times. THF (1.6 mL) was added and the solution was cooled to 0 °C. Diethylaluminum chloride (1M in hexane, 0.19 mL, 0.19 mmol) was added and the reaction was stirred at room temperature for 8.5 hours. The reaction mixture was poured into aqueous potassium carbonate (200 mg in 10 ml in water) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Purification by thin layer preparative chromatography (40% EE/HX) provided compound **3.91** (39 mg, 55% yield) as a pale yellow oil. NOESY experiment was done to prove *cis*-stereochemistry at the ring-fusion.

R_f = 0.13 (30% EE/HX); IR (film, cm^{-1}): 2945, 2866, 1710, 1639, 1591, 1466, 1418, 1199, 1136, 1093, 1025, 882, 763; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.17 (d, J = 2.7 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 6.89 (app t, J = 7.4 Hz, 1H), 6.27 (d, J = 2.6 Hz, 1H), 3.83 (d, J = 6.9 Hz, 1H), 3.38 (app q, J = 6.5 Hz, 1H), 2.33 (m, 2H), 2.14 (s, 3H), 2.04 (s, 3H), 1.97 (septet, J = 7.6 Hz, 3H), 1.78 (m, 1H), 1.55 (m, 2H), 1.40 (m, 1H), 1.13 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.0, 164.5, 149.4, 144.1, 139.2, 136.0, 128.4, 127.7, 124.7, 122.2, 106.8, 49.8, 48.6, 38.6, 26.3, 21.2, 18.7, 18.3, 18.2, 12.9; HRMS (ES) Calculated for $C_{28}H_{40}N_2OSi$+H: 449.2988, found: 449.2977.

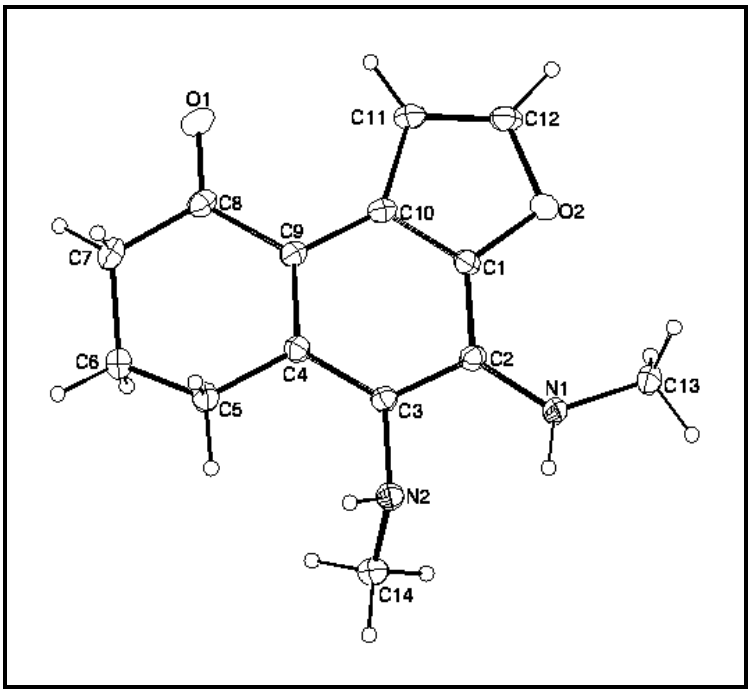


Figure 1. ORTEP drawing of 3a

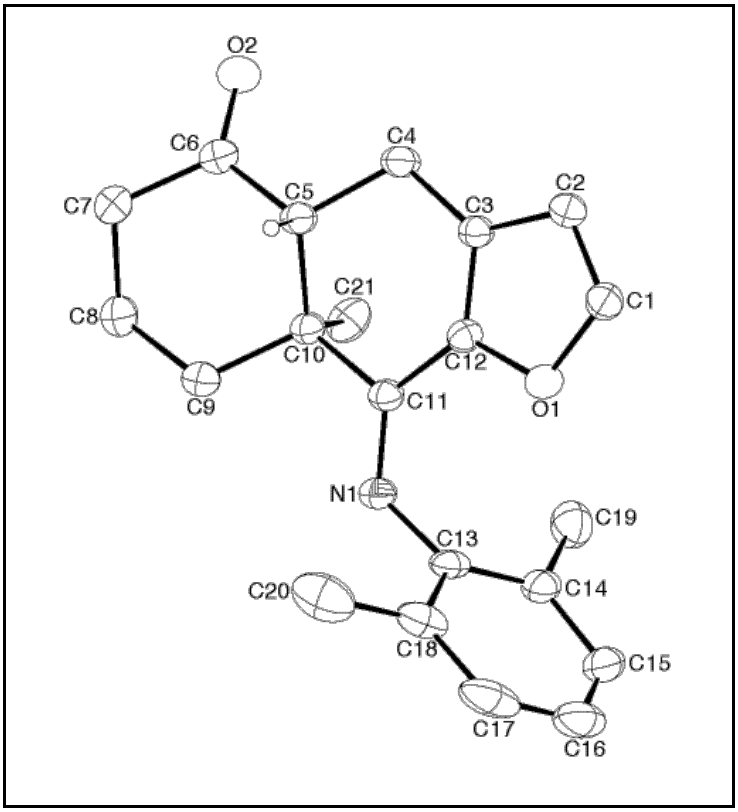


Figure 2. ORTEP drawing of ***trans*-20**

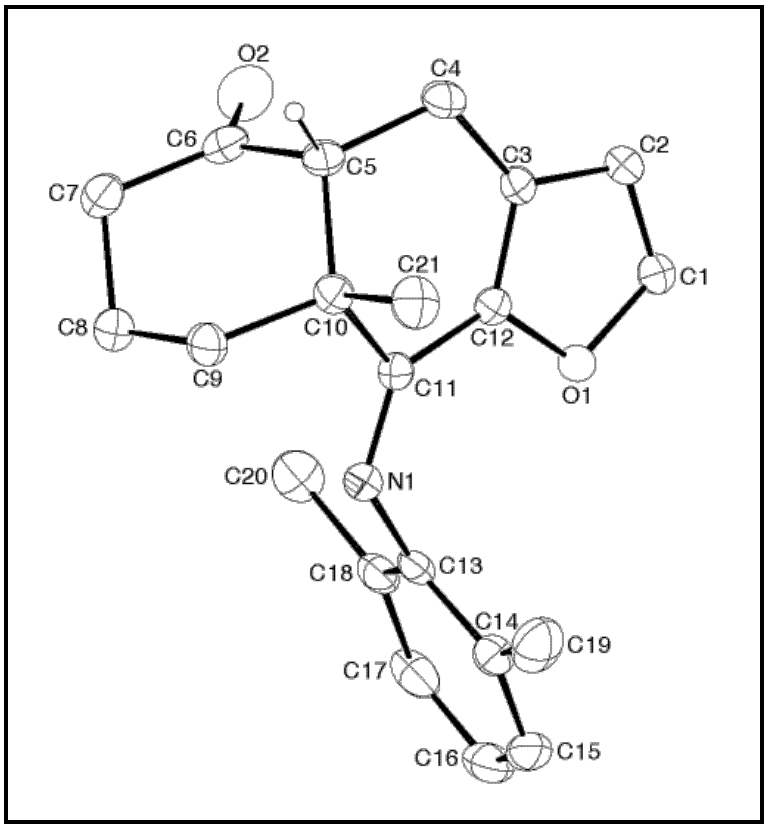


Figure 3. ORTEP drawing of ***cis*-20**

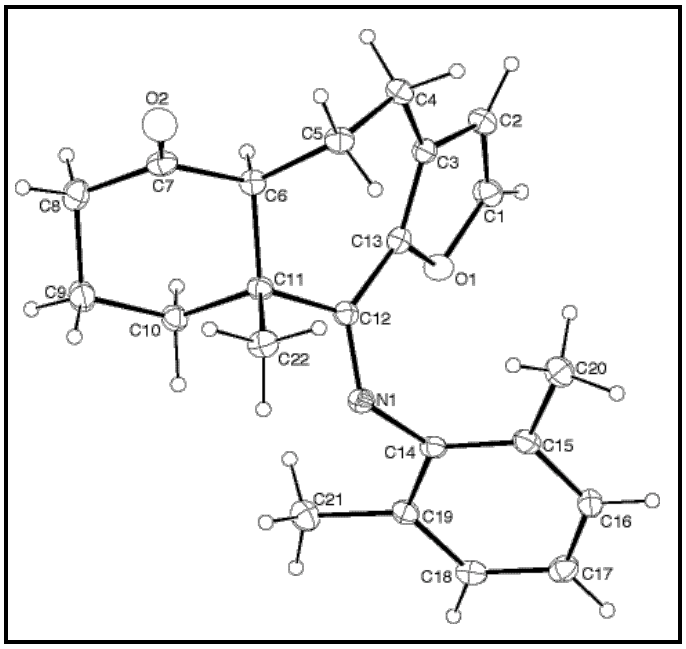


Figure 4. ORTEP drawing of ***trans*-23**

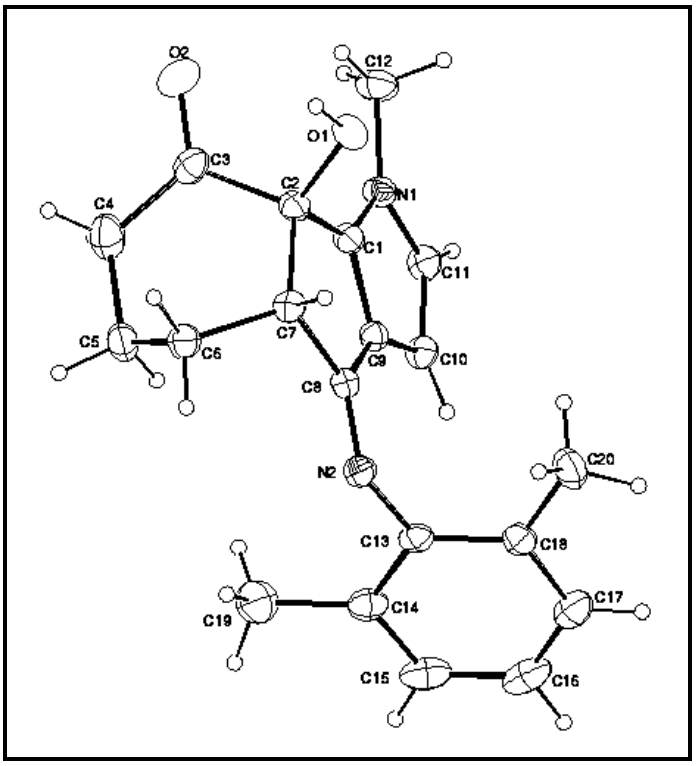


Figure 5. ORTEP drawing of **26**