Supplementary Material for "Application of Reactive Enols in Synthesis: A Versatile, Efficient and Stereoselective Construction of the Welwitindolinone Carbon Skeleton"

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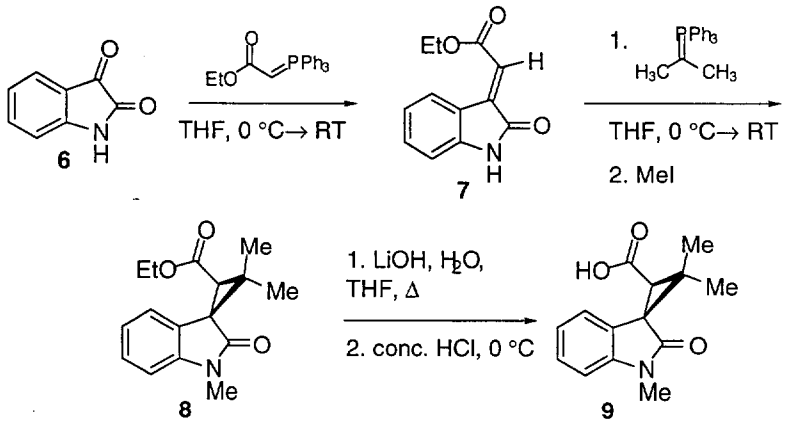
Materials and Methods

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. All melting points were obtained on a Gallenkamp variable temperature melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer. High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainen Dynamax SD-200 system with a Rainen Microsorb 80-120-C5 column. Single crystal X-ray analyses were performed by Susan DeGala (Yale University).

Preparation of enoate 7, ester 8 and acid 9.



All solvents used in this procedure were used as received. To a solution of ethyl triphenylphosphoranylidene acetate (74.6 g, 214 mmol, 1.05 equiv) in THF (244 mL) at 0 °C in a one-neck, 1L flask equipped with an addition funnel was added isatin (**6**) (30.0 g, 204 mmol) in THF (232 mL) rapidly via an addition funnel. The ice bath was removed and the solution was stirred until all starting material had been consumed and a new higher R_f spot appeared by TLC (ca. 30 min). In a separate 3-neck flask equipped with a mechanical stirrer and addition funnel was introduced isopropyl triphenylphosphonium iodide (212 g, 490 mmol, 2.4 equiv) and THF (613 mL). This suspension was cooled to 0 °C and was treated slowly via syringe with a 2.33 M solution of *n*-BuLi in hexanes (228 mL, 531 mmol, 2.6 equiv). After stirring at 0 °C for 30 min the derived red mixture was treated with the entire crude reaction containing enoate **7** (dropwise via addition funnel). The resultant mixture was stirred for 2.5 h (0 °C - rt) and then excess iodomethane (63.6 mL, 1.02 mol, 5 equiv) was added. After stirring for 1.5 h at rt, the reaction was vacuum filtered to separate the methyl triphenylphosphonium iodide salt and the solid was washed with 1 L diethyl ether. The filtrate was concentrated under reduced pressure to yield the cyclopropyl ester **8**. Crude ester **8** was dissolved in THF (577 mL) and placed into a 2L, one-necked flask equipped with a condenser. To this solution was added 4.6N LiOH (577 mL, 2.65 mol, 13 equiv) and the two-phased reaction was heated to reflux overnight. After cooling, the THF was removed under reduced pressure and the aqueous layer was washed with CH_2Cl_2 (2 x 200 mL). After removing any remaining traces of CH_2Cl_2 in vacuo, the aqueous layer was acidified with conc. HCl at 0 °C to afford, after vacuum filtering and azeotropic drying with benzene, acid **9** (38.8 g, 79% yield, 4 steps) as a tan

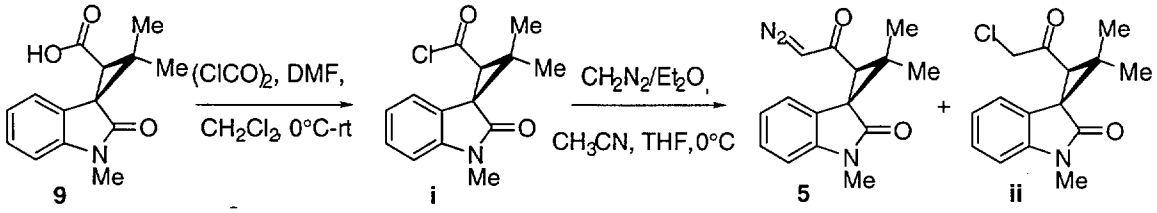
solid.

Although generally carried directly through to acid **9**, several intermediates were isolated and characterized. Thus, an analytical sample of enoate **7** can be obtained by purifying via silica gel flash chromatography (hexanes:EtOAc, 3:2) followed by recrystallization from EtOH. Enoate **7** was identical in all respects to data reported in the literature.

An analytically pure sample of ester **8** can be obtained by subjecting to silica gel chromatography (4:1 hexanes:EtOAc eluent). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.29 (td, *J* = 1.2, 7.7 Hz,. 1H), 7.05 (td, *J* = 1.0, 7.7 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.13 (m, 2H), 3.27 (s, 3H), 2.77 (s, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.8, 168.7, 144.2, 127.0, 125.6, 124.9, 121.4, 107.7, 60.5, 41.7, 40.9, 34.8, 26.4, 20.5, 16.9, 14.1; **IR** (thin film/NaCl) 2945 (br w), 1708 (s), 1606 (m), 1465 (m), 1351 (m), 1263 (w), 1166 (m), 1102 (m), 1003 (w), 751 (m) cm^{-1}; **HRMS** (CI) *m/z* found: 274.1443, [calc'd for $C_{16}H_{19}NO_3$ (M+H): 274.1443]; **m.p.** 91-92° C.

To obtain an analytical sample of acid **9**, the dry solid can be recrystallized from MeOH to yield white needles. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 3.18 (s, 3H), 2.52 (s, 1H), 1.48 (s, 3H), 1.45 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 173.1, 169.2, 144.0, 127.0, 124.7, 124.6, 121.1, 108.3, 40.7, 40.6, 34.0, 26.4, 20.1, 16.8; **IR** (KBr pellet) 2932 (br m), 2673 (w), 1753 (s), 1661 (s), 1602 (s), 1418 (m), 1364 (s), 1191 (s), 1103 (s), 1094 (m), 755 (s), 697 (s) cm^{-1}; **HRMS** (CI) *m/z* found: 246.1129, [calc'd for $C_{14}H_{15}NO_3$ (M+H): 246.1130]; **m.p.** 168-169° C.

Preparation of α-diazo ketone 5.



To a 500 mL round bottom flask was added recrystallized acid **9** (9.00 g, 36.7 mmol) and CH_2Cl_2 (200 mL). The resulting white slurry was cooled to 0 °C and stirred. Oxalyl chloride (4.66 g, 38.5 mmol, 1.05 equiv) was added neat via syringe followed by DMF (100 μL, 1.3 mmol, 0.04 equiv). The ice bath was removed after 1 h and stirring continued for 90 min, at which time gas evolution had ceased and a clear, pale yellow solution remained. The solution was concentrated and azeotroped (3x) with benzene under reduced pressure to give acid chloride **i** as a yellow solid. The solid was then dried in vacuo for 45 min and used crude in the next step.

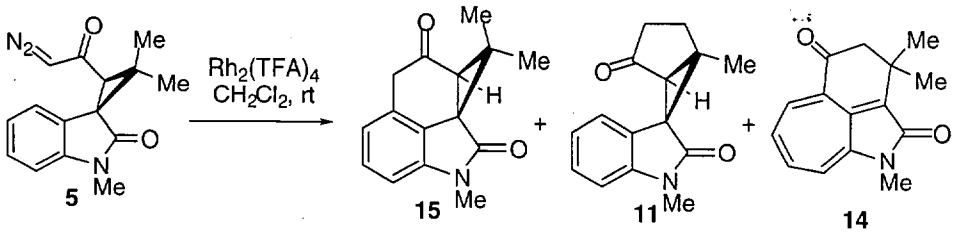
To a scratch-free 2L round bottom flask equipped with a 250 mL addition funnel was added triethylamine (4.36 g, 43.0 mmol, 1.2 equiv) and acetonitrile (25 mL) and the solution was cooled to 0 °C. Ethereal diazomethane (450 mL, prepared from 32.2 g Diazald) was added to the flask through a plastic funnel. Dried acid chloride **i** was dissolved in THF (200 mL), transferred to the addition funnel via cannula, and added dropwise over 30-40 min to the diazomethane solution. The funnel was rinsed with THF (10 mL) and the resulting heterogeneous mixture was stirred for 1 h after which time 400 mL of 0.1N acetic acid was added slowly. After gas evolution ceased, the biphasic mixture was transferred to a separatory funnel. The aqueous layer was removed and washed with ethyl ether (100 mL). The combined organic layers were concentrated under reduced pressure to give a yellow oil which solidified upon cooling. The solid was purified via silica gel flash chromatography, eluting with a gradient of hexanes:EtOAc (1:4-1:1) to afford α-chloro ketone **ii** as a yellow solid (0.99 g, 9.7%) and α-diazo ketone **5** (8.36 g, 84% yield from acid **9**) as a light yellow solid.

The first compound to elute was α-chloro ketone **ii**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.89 (d, J =

7.8 Hz, 1H), 4.21 (d, J = 15.5 Hz, 1H), 4.09 (d, J = 15.5 Hz, 1H), 3.27 (s, 3H), 3.08 (s, 1H), 1.64 (s, 3H), 1.56 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.3, 173.4, 144.0, 127.4, 126.0, 124.2, 121.9, 107.9, 49.9, 45.0, 44.8, 37.6, 26.6, 20.6, 16.7; **IR** (thin film/NaCl) 2932 (b rw), 1702 (s), 1609 (m), 1468 (m), 1375 (m), 1349 (m), 1266 (w), 1141 (w), 1091 (m), 1024 (w), 753 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 277.0867, [calc'd for $C_{15}H_{16}ClNO_2$ (M+): 277.0870]; **m.p.** >135° C (dec).

The second compound to elute was the desired α-diazo ketone **5**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.29 (td, J = 1.57, 7.7 Hz, 1H), 7.06 (t, J = 6.7 Hz, 1H), 6.90 (dd, J = 1.3, 7.6 Hz, 1H), 5.37 (s, 1H), 3.27 (s, 3H), 2.67 (s, 1H), 1.63 (s, 3H), 1.59 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.2, 174.0, 144.0, 127.0, 126.0, 125.0, 121.7, 107.7, 57.1, 46.2, 36.9, 26.5, 20.8, 17.0; **IR** (thin film, NaCl) 3080 (b rw), 2934 (br w), 2101 (s), 1702 (s), 1636 (m), 1469 (m), 1415 (m), 1348 (s), 1266 (m), 1146 (m), 1094 (s), 1029 (w), 753 (m), 695 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 269.1167, [calc'd for $C_{15}H_{15}N_3O_2$ (M+): 269.1164]; **m.p.** >133° C (dec).

Preparation of ketone 15, spirocycle 11, and heterocycle 14.



To a stirred solution of diazo ketone **5** (100 mg, 0.37 mmol) in CH_2Cl_2 (4 mL) at rt was added rhodium trifluoroacetate (1 mg, 0.002 mmol, 0.4 mol %). After 20 min, nitrogen evolution ceased and the reaction turned from yellow to red. The reaction was adsorbed onto silica gel and purified via flash chromatography (4:1-2:1 hexanes:EtOAc) to provide ketone **15** (14 mg, 15% yield) as a yellow solid, spirocycle **11** (1mg, 1% yield) as an off-white solid, and heterocycle **14** (14 mg, 15% yield) as a red solid.

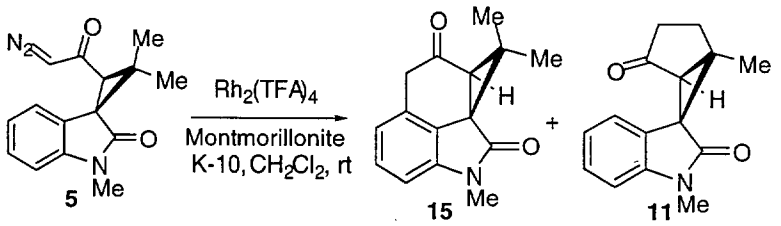
The first compond to elute was ketone **15**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (t, J = 7.8Hz, 1H), 6.77 (d, J = 7.7 Hz, 2H), 3.51 (d, J = 21.5 Hz, 1H), 3.42 (d, J = 21.7 Hz, 1H), 3.26 (s, 3H), 2.76 (s, 1H), 1.62 (s, 3H), 1.37 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.4, 173.7, 142.2, 129.6, 127.9, 124.1, 120.4, 106.0, 44.9, 43.2, 42.7,

36.5, 26.6, 21.4, 18.7 ; **IR** (thin film/NaCl) 2931 (br w), 1706 (s), 1615 (m), 1468 (m), 1377 (w), 1330 (w), 1279 (w), 1224 (w), 1104 (w), 1033 (m), 870 (w), 766 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 241.1102, [calc'd for $C_{15}H_{15}NO_2$ (M+): 241.1103]; **m.p.** 139-140° C.

The second compond to elute was spirocycle **11**. The solid was recrystallized from ethyl acetate/hexanes to provide white crystals suitable for X-ray analysis (see Appendix for X-ray structure report). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 3.27 (s, 3H), 3.25-2.30 (comp m, 4H), 2.82 (s, 1H), 1.70 (s, 3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 211.3, 172.3, 144.9, 127.7, 125.0, 122.0, 121.3, 108.5, 48.9, 44.1, 41.0, 40.3, 27.8, 26.6, 15.6 ; **IR** (thin film/NaCl) 2934 (w), 1716 (s), 1605 (w), 1482 (m), 1462 (w), 1378 (m), 1255 (w), 1136 (m), 1067 (m), 750 (m), 624 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 241.1104, [calc'd for $C_{15}H_{15}NO_2$ (M+): 241.1103]; **m.p.** 182-183° C.

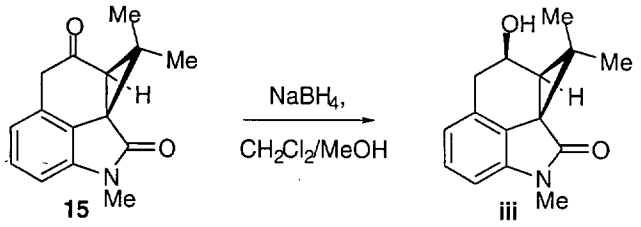
The final compound to elute was ketone **14**. An analytically pure sample of **14** was obtained via HPLC purification (5%.MeOH/CH_2Cl_2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9.0 Hz, 1H), 7.15 (t, *J* = 10.0 Hz, 1H), 6.86 (t, *J* = 9.5 Hz, 1H), 6.78 (d, *J* = 9.2 Hz, 1H), 3.56 (s, 3H), 2.71 (s, 2H), 1.44 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.7, 166.3, 146.4, 139.0, 134.5, 129.7, 126.6, 119.0, 109.9, 53.6, 33.9, 27.4, 26.2; **IR** (thin film/NaCl) 2956 (w), 1664 (s), 1615 (m), 1591 (m), 1548 (m), 1475 (m), 1456 (m), 1414 (w), 1361 (w), 1270 (w), 1201 (m), 1088 (w), 830 (w), 757 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 241.1107, [calc'd for $C_{15}H_{15}NO_2$ (M+): 241.1103]; **m.p.** 193-198° C.

Preparation of ketone 15 and spirocycle 11: An improved aryl C-H insertion reaction.



Montmorillonite K-10 (10 g) was flamed dried under vacuum for 10 min, cooled to rt and then suspended in CH_2Cl_2 (100 mL). The vigorously stirred suspension was treated with $Rh_2(TFA)_4$ (10 mg, 0.02 mmol, 0.4 mol %) followed by a solution of α-diazo ketone **5** (1.0 g, 3.7 mmol) in CH_2Cl_2 (40 mL) (added over a 45 min period via an addition funnel). Immediately after addition, the reaction mixture was filtered through a pad of celite topped with a thin layer of silica gel. The filter pad was washed with EtOAc (500 mL) and MeOH (50 mL). The filtrate was concentrated and the crude material purified by silica gel column chromatography (hexane:EtOAc, 3:1) to afford cyclohexanone **15** (512 mg, 57% yield) as a yellow solid and spirocycle **11** (45 mg, 5% yield) as an off-white solid.

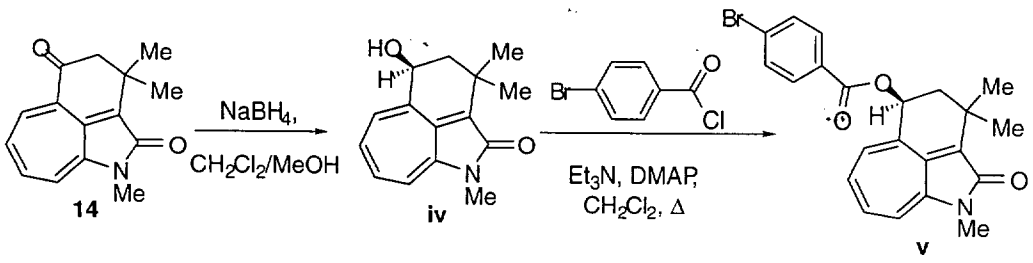
Preparation of alcohol iii: Confirmation of the aryl C-H insertion event via X-ray analysis.



To a solution of ketone **15** (30 mg, 0.12 mmol) in CH_2Cl_2/MeOH (8 mL, 1:1) was added $NaBH_4$ (15 mg, 0.40 mmol, 3.3 equiv). The reaction was stirred for 30 min in the open air, after which time the solvents were removed under reduced pressure. The flask was cooled to 0 °C, and the residue was treated with 1N HCl (5 mL). After stirring at 0 °C for 0.5 h, the reaction was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The product was purified via silica

gel flash chromatography (1:1 hexanes:EtOAc) to afford alcohol **iii** (28 mg, 93% yield) as a white solid. The solid was recrystallized from CH_2Cl_2/Et_2O/hexanes to provide white crystals suitable for X-ray analysis (see Appendix for X-ray structure report). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 3.78 (m, 1H), 3.26 (s, 3H), 3.03 (dd, *J* = 7.3, 16.4 Hz, 1H), 2.80 (dd, *J* = 10.2, 16.4 Hz, 1H), 1.59 (s, 3H), 1.31 (s, 3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.1, 142.2, 130.1, 126.7, 125.8, 120.9, 105.6, 67.9, 40.2, 39.2, 38.0, 35.7, 26.6, 23.4, 19.1 ; **IR** (thin film/NaCl) 3054 (w), 2999 (w), 2936 (br m), 2880 (w), 2244 (w), 1688 (s), 1611 (s), 1469 (m), 1378 (m), 1339 (m), 1287 (m), 1175 (m), 1102 (m), 1041 (m), 961 (w), 914 (w), 760 (m), 732 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 243.1261, [calc'd for $C_{15}H_{17}NO_2$ (M+): 243.1259]; **m.p.** 166-168° C.

Preparation of alcohol iv and ester v: Confirmation of the structure of ketone 14 via X-ray analysis.



To a solution of **14** (100 mg, 0.41 mmol) in CH_2Cl_2/MeOH (15 mL, 1:1) was added $NaBH_4$ (51 mg, 1.35 mmol, 3.3 equiv). After stirring for 45 min in the open air, the yellow reaction was concentrated, cooled to 0 °C and treated with 1N HCl (5 mL). After stirring at 0 °C for 20 min, the reaction was extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The product was purified via silica gel flash chromatography using 3:2 hexanes:EtOAc to afford alcohol **iv** (73 mg, 73% yield) as a yellow solid.

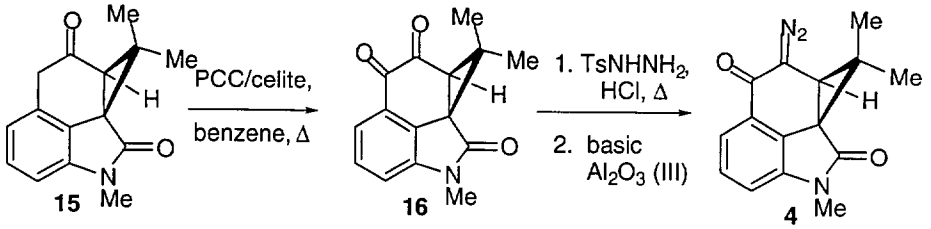
To alcohol **iv** (52 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) was added 4-bromobenzoyl chloride (52 mg, 0.24 mmol, 1.1 equiv), triethylamine (45μL, 0.32 mmol, 1.5 equiv), and finally DMAP (1 mg, 0.008 mmol, 0.04 equiv). The resulting solution was heated to reflux for 30 min. After cooling to rt, the reaction was cooled, adsorbed onto SiO_2 and

chromatographed using hexanes:EtOAc (4:1). The derived benzoate **v** (60 mg, 67% yield) was recrystallized from ethyl acetate to furnish yellow crystals suitable for X-ray analysis (see Appendix for X-ray structure report).

Data for alcohol **iv**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 1H), 6.93 (t, *J* = 9.5 Hz, 1H), 6.84 (t, *J* = 9.9 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.84 (dd, *J* = 4.3, 11.2 Hz, 1H), 3.51 (s, 3H), 2.17 (d, *J* = 5.6 Hz, 1H), 2.08 (dd, *J* = 4.4, 8.0 Hz), 1.86 (t, *J* = 11.9 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 142.4, 141.5, 137.3, 128.4, 127.4, 125.0, 120.7, 110.3, 68.8, 47.2, 31.9, 27.8, 27.4, 26.0; **IR** (thin film/NaCl) 3371 (br m), 2952 (w), 2862 (w), 2240 (w), 1646 (s), 1590 (m), 1546 (m), 1513 (m), 1446 (m), 1408 (m), 1358 (w), 1271 (w), 1188 (w), 1088 (m), 1035 (w), 915 (w), 732 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 243.1265, [calc'd for $C_{15}H_{17}NO_2$ (M+): 243.1259]; **m.p.** 187-192° C.

Data for benzoate **v**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.96 (t, *J* = 10.0 Hz, 1H), 6.76 (m, 2H), 6.30 (t, *J* = 6.3 Hz, 1H), 3.55 (s, 3H), 2.12 (d, *J* = 6.7 Hz, 2H), 1.55 (s, 3H), 1.5 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 165.3, 143.0, 137.2, 135.7, 131.9, 131.3, 129.5, 128.9, 128.5, 127.4, 126.9, 121.0, 110.0, 72.4, 42.8, 31.4, 27.9, 27.4, 26.1; **IR** (thin film/NaCl) 2957 (w), 2930 (w), 2865 (w), 2242 (w), 1719 (m), 1669 (s), 1591 (m), 1551 (w), 1516 (w), 1480 (w), 1443 (w), 1418 (w), 1362 (w), 1267 (s), 1192 (w), 1098 (m), 1011 (m), 920 (w), 849 (w), 753 (m), 733 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 425.0625, [calc'd for $C_{22}H_{20}NO_3Br$ (M+): 425.0627]; **m.p.** 177-178° C.

Preparation of diketone 16 and α-diazo ketone 4.



15 16 4

To a solution of ketone **15** (1.5 g, 6.2 mmol) in benzene (100 mL) was added celite (15 g) and pyridinium chlorochromate (PCC) (6.7 g, 31 mmol, 5 equiv). The reaction mixture was heated to reflux for 1 h. After this time, isopropyl alcohol (approx. 50 mL) was added and heating was continued for an additional 0.5 h. After cooling to rt, the mixture was filtered through a pad of celite topped with a thin layer of silica gel and $MgSO_4$. The filter pad was washed with Et_2O and EtOAc (500 mL each). The filtrate was concentrated in vacuo and the resulting brown residue **16** was then dissolved in THF (60 mL). This solution was treated with *p*-toluenesulfonhydrazide (1.0 g, 5.6 mmol, 0.9 equiv) followed by a catalytic amount of conc. HCl (4 drops). The reaction was heated to reflux for 1 h and concentrated in vacuo. To a stirring solution of the crude mixture in $CHCl_3$ (150 mL) was added basic alumina (III) (200 mg). The reaction mixture was then directly placed onto a flash column containing basic alumina (III) (450 g) and eluted with $CHCl_3$ to furnish a brown solid. Trituration of the brown solid with cold Et_2O afforded α-diazo ketone **4** (978 mg, 59% yield, 2 steps) as a yellow solid.

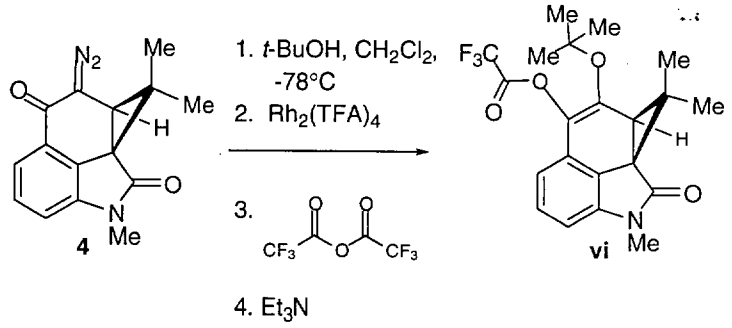
Although used crude in this reaction, diketone **16** can be purified via silica gel flash chromatography to obtain an analytically pure sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 1H), 1.69 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.2, 178.6, 171.9, 142.9, 132.9, 129.0, 128.6, 119.3, 112.6, 43.6, 42.9, 40.4, 27.1, 21.2, 17.0; **IR** (thin film/NaCl) 3025 (w), 2959 (w), 1704 (s), 1604 (m), 1485 (m), 1416 (m), 1380 (m), 1330 (m), 1264 (m), 1127 (w), 1100 (m), 1058 (w), 1035 (m), 1015 (m), 948 (w), 863 (w), 786 (m), 765 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 255.0895, [calc'd for $C_{15}H_{15}NO_3$ (M+): 255.0895]; **m.p.** >150° C(dec).

Data for α-diazo ketone **4**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H),

7.37 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 3.29 (s, 3H), 3.20 (s, 1H), 1.65 (s, 3H), 1.07 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 181.4, 174.6, 143.1, 129.2, 128.3, 127.6, 117.5, 111.0, 36.4, 32.7, 31.9, 26.8, 19.4, 16.7; **IR** (thin film/NaCl) 2928 (w), 2247 (w), 2089 (s), 1711 (s), 1632 (m), 1602 (s), 1478 (m), 1419 (m), 1374 (m), 1339 (m), 1305 (m), 1244 (m), 1225 (w), 1192 (w), 1137 (m), 1104 (w), 1034 (m), 996 (m), 913 (w), 858 (w), 794 (m), 732 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 267.1009, [calc'd for $C_{15}H_{13}N_3O_2$ (M+): 267.1008]; **m.p.** >134° C(dec).

Preparation of trifluoroacetate vi.

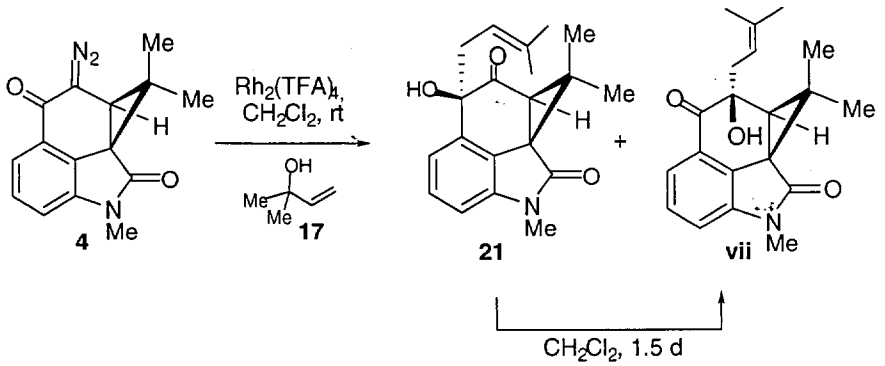
The following experiment was performed to support the intermediacy of an enol in the reactions of diazo ketone **4** with alcohols. Although enols derived from the coupling of tertiary allylic alcohols with diazo ketone **4** can be trapped, the derived products are difficult to handle due to rapid Claisen rearrangement (e.g., reaction of diazo ketone **4** with 2-methyl-3-buten-2-ol; see below). The experiment using *t*-butanol (illustrated below) was performed since trapping of the derived enol affords a stable product.



A solution of α-diazo ketone **4** (50 mg, 0.19 mmol) and *t*-butanol (54 μL, 0.56 mmol, 3.0 equiv) in CH_2Cl_2 (10 mL) was cooled to -78 °C and treated with $Rh_2(TFA)_4$ (1.2 mg, 0.002 mmol, 1 mol %). The cold bath was removed and the reaction was allowed to warm slightly (approx. 3 min) until nitrogen evolution commenced and the reaction turned brown. Immediately after gas evolution ceased (ca. 1 min), trifluoroacetic anyhdride (134 μL, 0.95 mmol, 5 equiv) and Et_3N (132 μL, 0.95 mmol, 5 equiv) were added rapidly. The resulting yellow reaction was allowed to warm to rt at which time it was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel using hexanes:EtOAc (3:1) to provide enol ether **vi** (20 mg, 27% yield) as a white solid, and

diazo ketone **4** (30 mg). The yield of the desired trapped product was 90% based on recovered starting material. Data for trifluoroacetate **vi**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.27 (s, 3H), 3.06 (s, 1H), 1.71 (br s, 3H), 1.42 (s, 9H), 0.97 (br s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.4, 154.9 (q, J_{CF}= 42.6 Hz), 142.7, 141.6, 132.2, 127.7, 126.0, 120.0, 114.7 (q, J_{CF}= 285.6 Hz), 112.8, 106.7, 82.2, 43.4, 42.7, 29.4, 26.6 (3), 20.9, 19.7 (br), 16.2 (br); **IR** (thin film, NaCl) 2697 (m), 2929 (m), 1800 (w), 1712 (s), 1656 (m), 1606 (m), 1466 (m), 1367 (m), 1341 (m), 1298 (m), 1172 (m), 1148 (m), 1021 (m), 770 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 409.1496, [calc'd for $C_{21}H_{22}F_3NO_4$(M+): 409.1501]; **m.p.** 156-159° C.

Preparation of α-hydroxy ketones 21 and vii: Reaction of α-diazo ketone 4 with a tertiary allylic alcohol.



To α-diazo ketone **4** (100 mg, 0.37 mmol) and 2-methyl-3-buten-2-ol (43 μL, 0.41 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL) at rt was added $Rh_2(TFA)_4$ (2.4 mg, 0.004 mmol, 1 mol %). Gas evolution was noted and appeared to cease at which time the reaction was concentrated. NMR analysis of crude material indicated the presence of one compound, alcohol **21**. The reaction was chromatographed on silica gel (5:1 hexanes:EtOAc) to yield alcohol **21** (99 mg, 81% yield) as a yellow residue, which now contained a trace of regioisomer **vii**. Upon stirring in CH_2Cl_2 for 1.5 d or standing in CDCl3, alcohol **21** was completely converted to regioisomer **vii** (98mg, 99% yield), a clear, pale yellow oil.

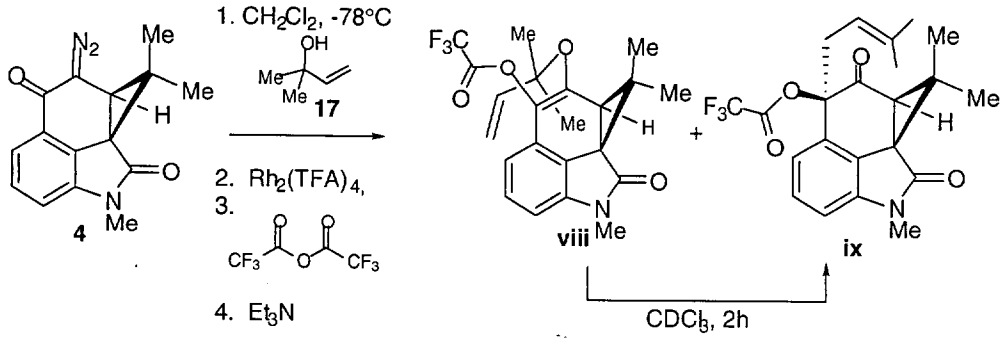
Alcohol **21** was triturated from Et_2O to furnish white crystals suitable for X-ray analysis (see Appendix for X-ray structure report). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.37 (m, 1H), 3.45

(s, 1H), 3.30 (s, 3H), 3.02 (s, 1H), 2.51 (dd, J = 9.0, 13.3 Hz, 1H), 2.30 (dd, J = 6.7, 13.3 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.11 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.6, 173.7, 141.6, 137.2, 133.9, 128.2, 123.5, 119.1, 115.3, 106.3, 77.7, 45.5, 45.1, 38.7, 37.9, 26.8, 22.6, 20.8, 18.3, 14.1; **IR** (thin film, NaCl) 3442 (br w), 2961 (w), 2932 (w), 2885 (w), 1703 (s), 1617 (m), 1478 (m), 1388 (m), 1338 (w), 1289 (m), 1080 (m), 1037 (m), 854 (w), 790 (m), 725 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 325.1674, [calc'd for $C_{20}H_{23}NO_3$(M+): 325.1678]; **m.p.** 120-123° C.

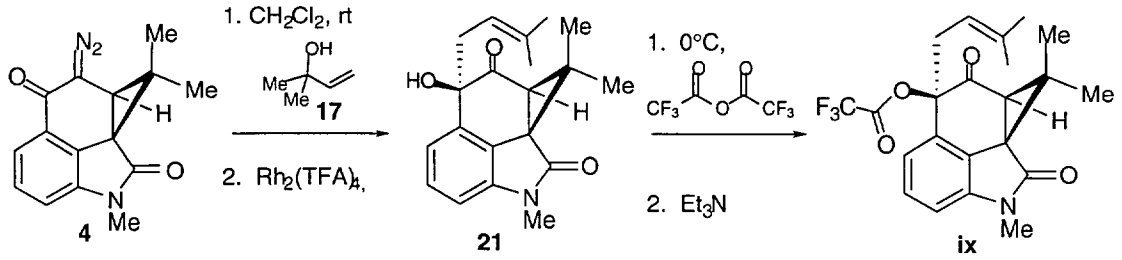
Data for alcohol **vii**: **^{11}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 4.76 (m, 1H), 3.85 (br s, 1H), 3.30 (s, 3H), 2.60 (s, 1H), 2.11 (dd, J = 8.3, 14.2 Hz, 1H), 1.98 (dd, J = 7.4, 14.2 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H), 1.30 (s, 3H), 1.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.1, 174.4, 142.5, 136.5, 133.2, 127.1, 125.4, 117.1, 116.1, 111.5, 77.6, 40.7, 39.0, 38.8, 36.5, 26.7, 25.7, 21.2, 17.7, 16.4; **IR** (thin film, NaCl) 2924 (br w), 1702 (s), 1613 (m), 1478 (w), 1377 (w), 1341 (w), 1285 (m), 1106 (w), 1027 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 325.1680, [calc'd for $C_{20}H_{23}NO_3$(M+): 325.1678].

Preparation of trifluoroacetate ix.

Due to the propensity of α-hydroxy ketone **21** to rearrange to **vii**, alcohol **21** was protected as the trifluoroacetate **ix**. Described below are two ways to access trifluoroacetate **ix**; first, by trapping the intermediate enol followed by Claisen rearrangement (Method A) and second by trapping alcohol **21** after Claisen rearrangement but prior to α-ketol rearrangement (Method B).



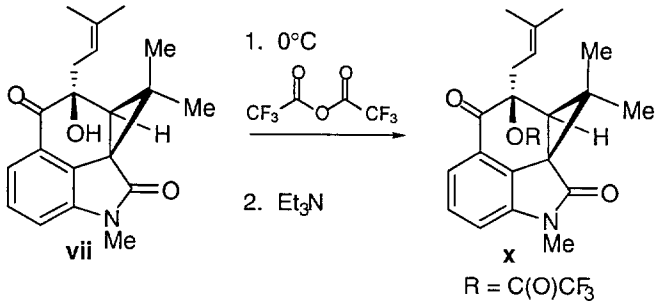
Method A: A solution of α-diazo ketone **4** (50 mg, 0.19 mmol) and 2-methyl-3-buten-2-ol (22 μL, 0.21 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) was cooled to -78 °C and treated with $Rh_2(TFA)_4$ (1.2 mg, 0.002 mmol, 1 mol %). The cold bath was removed and the reaction was allowed to warm slightly (approx. 3 min) until nitrogen evolution commenced and the reaction turned brown. Immediately after gas evolution ceased, trifluoroacetic anyhdride (134 μL, 0.95 mmol, 5 equiv) followed by Et_3N (132 μL, 0.95 mmol, 5 equiv) were added rapidly. The resulting yellow reaction was allowed to warm to rt at which time it was concentrated and chromatographed on silica gel using hexanes:EtOAc (3:1) to yield an inseparable mixture of enol ether **viii** (assigned via NMR analysis) and ketone **ix**. Upon standing for 2 h in $CDCl_3$, the mixture of compounds undergoes complete conversion to ketone **ix** (55 mg, 69% yield) which can be isolated as a white solid.



Method B: A solution of α-diazo ketone **4** (50 mg, 0.19 mmol) and 2-methyl-3-buten-2-ol (22 μL, 0.21 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) at rt was treated with $Rh_2(TFA)_4$ (1.2 mg, 0.002 mmol, 1 mol %). After N_2 evolution ceased, the reaction was cooled to 0 °C and trifluoroacetic anhydride (134 μL, 0.95 mmol, 5 equiv) was added followed by the addition of triethylamine (132 μL, 0.95 mmol, 5 equiv). The reaction was stirred for 0.5 h (0 °C to rt) then concentrated in vacuo and subjected to silica gel chromatography (3:1 hexanes:EtOAc) to provide the protected alcohol **ix** (60 mg, 75% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.59 (tt, *J* = 1.3, 7.9 Hz, 1H), 3.28 (s, 3H), 3.12 (s, 1H), 2.57 (dd, *J* = 7.8, 13.9 Hz, 1H), 2.50 (dd, *J* = 8.0, 13.9 Hz, 1H), 1.56 (s, 3H), 1.53 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.3, 173.8, 154.9 (q, J_{CF} = 43.0), 142.9, 138.9, 131.4, 128.6, 124.6, 117.0, 116.6 (q, J_{CF} = 285.6), 113.9, 107.1, 87.7, 46.9, 41.4, 40.9, 38.7, 26.8, 25.8, 21.9, 18.8, 17.4; **IR** (thin film, NaCl) 2924 (w), 1794 (m), 1717 (s), 1616 (w), 1462 (w), 1372 (w), 1280 (w), 1223 (m), 1161 (m), 1046 (w), 983 (w), 777 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 421.1505, [calc'd for $C_{22}H_{22}F_3NO_4$(M+): 421.1501]; **m.p.** 89-94° C.

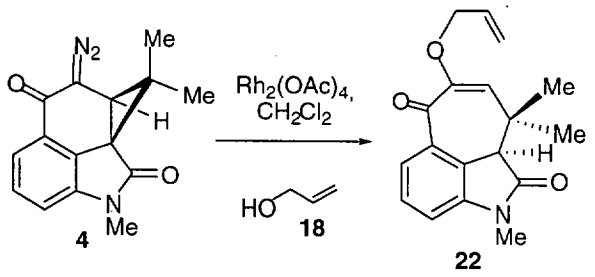
Preparation of trifluoroacetate x.

Given the possibility that **21** could undergo isomerization to **vii** prior to acylation (to furnish **x** instead of the desired **ix**), an authentic sample of the potential end product **x** was prepared. Comparison of the data obtained for **ix** and **x** clearly indicated they are different.



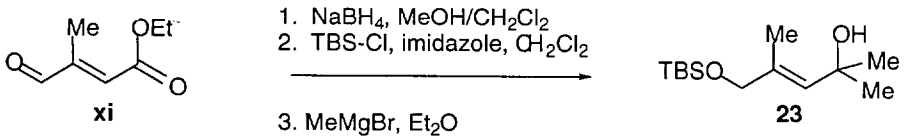
A solution of alcohol **vii** (30 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with trifluoroacetic anhydride (65 μL, 0.46 mmol, 5 equiv) and triethylamine (64 μL, 0.46 mmol, 5 equiv). The reaction was stirred for 0.5 h (0 °C to rt) and then concentrated in vacuo and chromatographed (3:1 hexanes:EtOAc) to provide ketone **x** (35 mg, 92% yield) as a clear colorless oil which solidified upon cooling. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 1H), 7.37 (m, J = 7.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 4.61 (t, J = 7.7 Hz, 1H), 3.32 (s, 3H), 3.14 (s, 1H), 2.70 (d, J = 7.8 Hz, 2H), 1.57 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.12 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.5, 173.6, 155.9 (q, J_{CF}= 42.2 Hz), 142.5, 138.0, 131.7, 127.7, 126.1, 117.9, 114.4 (q, J_{CF}= 286.6 Hz), 114.2, 111.7, 89.2, 38.1, 37.5, 36.9, 36.4, 26.9, 25.5, 20.7, 17.7, 16.9; **IR** (thin film, NaCl) 2933 (br w), 1787 (m), 1713 (s), 1603 (m), 1358 (w), 1337 (m), 1159 (s), 1038 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 421.1503, [calc'd for $C_{22}H_{22}F_3NO_4$(M+): 421.1501]; **m.p.** 64-68° C.

Reaction of α-diazo ketone 4 with a primary allylic alcohol: Preparation of ring-opened allylic enol ether 22.



To a solution of diazo ketone **4** (2.2 g, 8.2 mmol) and allyl alcohol (2.8 mL, 41.2 mmol, 5 equiv) in CH_2Cl_2 (82 mL) at rt was added $Rh_2(OAc)_4$ (40 mg, 0.09 mmol, 1 mol %). The solution was stirred for 5 min and then concentrated under reduced pressure. The resulting residue was chromatographed (2:1 hexanes:EtOAc) to afford **22** (2.3 g, 95% yield) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.07-5.99 (comp m, 1H), 5.78 (s, 1H), 5.38 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.23 (dd, *J* = 1.3, 10.4 Hz, 1H), 4.37 (dd, *J* = 1.3, 5.5 Hz, 2H), 3.74 (s, 1H), 3.25 (s, 3H), 1.73 (s, 3H), 0.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 184.7, 173.9, 148.8, 143.7, 133.3, 133.2, 133.1, 128.5, 126.6, 122.3, 117.9, 111.2, 70.7, 52.7, 37.9, 28.7, 26.4, 21.8; **IR** (thin film/NaCl) 2943 (w), 2872 (w), 1706 (s), 1689 (m), 1650 (s), 1462 (m), 1341 (m), 1299 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 297.1371, [calc'd for $C_{18}H_{19}NO_3$ (M+): 297.1365]; **m.p.** 140-142° C.

Preparation of allylic alcohol 23.



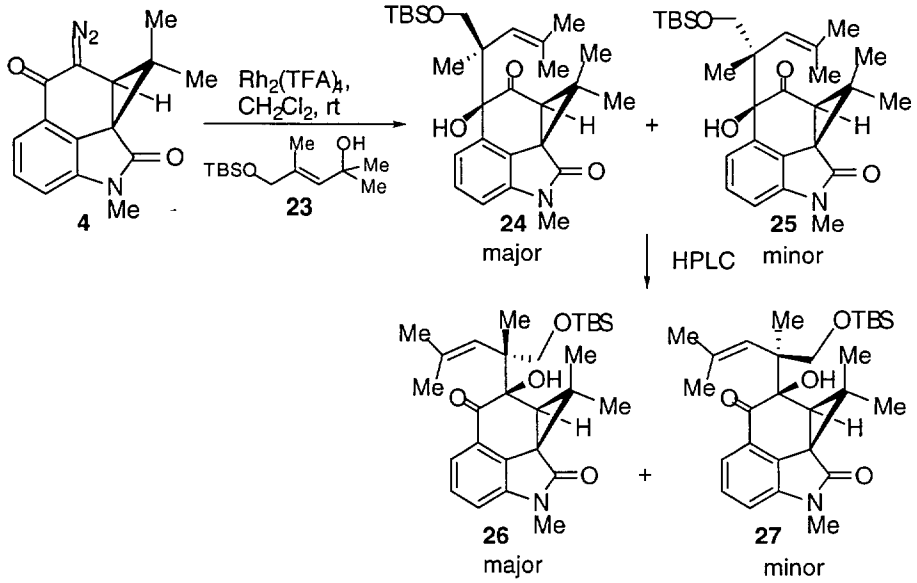
To ethyl-3-methyl-4-oxocrotonate (**xi**) (1 g, 7.0 mmol) in CH_2Cl_2 and MeOH (70 mL, 1:1) was added $NaBH_4$ (530 mg, 14.0 mmol, 2 equiv). After stirring for 5 min, the solvents were removed in vacuo and the derived residue was cooled to 0 °C and treated with 1N HCl (50 mL). The reaction was stirred for 15 min and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, then

concentrated to yield an oil which was used in the next step without further purification.

A solution of the derived alcohol in CH_2Cl_2 (70 mL) was treated with TBSCl (1.1 g, 7.4 mmol, 1.1 equiv) and imidazole (572 mg, 8.4 mmol, 1.2 equiv). A white precipitate rapidly formed and the reaction was stirred for 20 min. After this time, 1N HCl (50 mL) was added and the layers were separated. The organic layer was washed with 1N HCl (3 x 50 mL) then brine (3 x 50 mL). Drying (K_2CO_3), filtering, and concentrating afforded an oil which was used crude in the next step.

To a 1.4 M solution of methylmagnesium bromide in toluene/THF (25 mL, 35 mmol, 5 equiv) and ether (35 mL) was added a solution of the crude TBS-protected alcohol in ether (35 mL). After 5 minutes, the reaction was quenched with ice (750 mg). Extracting with ether (3 x 100 mL), drying (Na_2SO_4) and concentrating provided an oil which was subjected to silica gel chromatography (5:1 pentane:Et_2O) to yield tertiary alcohol **23** (1.1 g, 64% overall yield) as a clear, colorless oil . **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.51 (m, 1H), 3.89 (s, 2H), 2.00 (br s, 1H), 1.75 (s, 3H), 1.30 (m, 6H), 0.85 (s, 9H), .005 (s, 3H), 0.002 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.5, 131.1, 70.7, 68.7, 30.9, 25.8, 18.2, 13.9, -4.75; **IR** (thin film, NaCl) 3432 (br w), 2959 (s), 2934 (s), 2864 (s), 1693 (w), 1476 (m), 1463 (m), 1377 (m), 1358 (m), 1254 (s), 1144 (m), 1093 (s), 1008 (w), 843 (s), 774 (s) cm^{-1}; **HRMS** (EI) *m/z* found: 243.1774, [calc'd for $C_{13}H_{27}SiO_2$(M–H): 243.1780].

Preparation of diastereomeric alcohols 26 and 27.



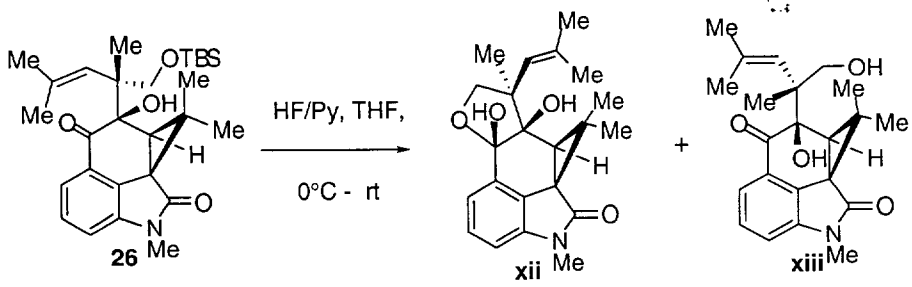
To a solution of α-diazo ketone **4** (50 mg, 0.19 mmol) and alcohol **23** (46 mg, 0.19 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at rt was added $Rh_2(TFA)_4$ (1.2 mg, 0.002 mmol, 1 mol %). After 5 min, the reaction was concentrated under reduced pressure and chromatographed (10:1 hexanes:EtOAc) to yield a residue (75 mg) which contained a mixture of diastereomeric alcohols **24** and **25** (2:1, **24**:**25**, 70% yield based on NMR integrations). Efforts to obtain analytically pure samples of **24** and **25** using HPLC (3:1 hexanes:EtOAc) resulted in the isolation of diastereomeric alcohols **26** and **27** (2:1 ratio, **26**:**27**), which arise via α-ketol rearrangement of alcohols **24** and **25**, respectively.

The first compound to elute was alcohol **26**, the α-ketol rearrangement product of **24**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 5.20 (s, 1H), 4.95 (s, 1H), 3.50 (d, J = 10.1 Hz, 1H), 3.46 (d, J = 9.9 Hz, 1H), 3.31 (s, 3H), 2.91 (s, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.09 (s, 3H), 0.91 (s, 9H), 0.62 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.8, 174.6, 142.4, 134.0, 133.8, 128.5, 127.0, 124.8, 116.7, 110.8, 81.7, 69.2, 48.6, 38.8, 37.6, 37.5, 29.1, 26.8, 25.8, 21.9, 19.3, 18.3, 17.0, -4.3, -4.4; **IR** (thin film, NaCl) 3470 (br w), 2942 (m), 2870 (m), 2248 (w), 1704 (s), 1617 (m), 1474 (m), 1387 (w), 1346 (. m), 1270 (m), 1072 (m), 1022 (m), 922 (w), 846 (m), 783 (m),

763 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 483.2797, [calc'd for $C_{28}H_{41}NO_4Si$(M+): 483.2805].

The second compound to elute was alcohol **27**, the α-ketol rearrangement product of **25**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 3.74 (s, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.28 (s, 3H), 3.13 (d, *J* = 10.0 Hz, 1H), 2.78 (s, 1H), 1.62 (s, 3H), 1.54 (s, 3H), 1.39 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.2, 174.7, 142.4, 133.9, 133.7, 128.6, 126.9, 124.5, 116.4, 110.7, 82.4, 69.8, 48.6, 38.2, 37.6, 37.2, 28.7, 26.7, 25.8, 21.8, 19.3, 18.3, 18.2, 17.0, -4.2, -4.4; **IR** (thin film, NaCl) 3472 (br m), 2936 (m), 2851 (m), 1709 (s), 1687 (s), 1611 (m), 1468 (m), 1335 (m), 1284 (m), 1254 (m), 1069 (m), 1009 (m), 845 (m), 780 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 483.2808, [calc'd for $C_{28}H_{41}NO_4Si$(M+): 483.2805].

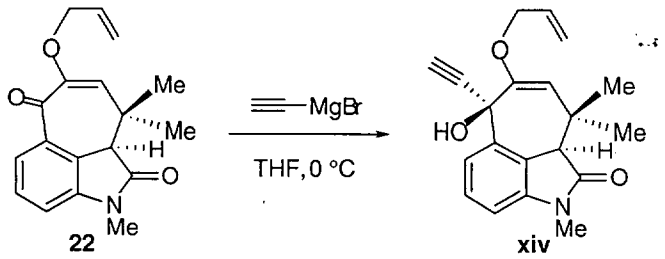
Preparation of hemi-acetal xii alcohol xiii: Confirmation of the [3,3]/[1,2] event via X-ray analysis.



To a solution of TBS-alcohol **26** (246 mg, 0.51 mmol) in THF (5 mL) at 0 °C was slowly added excess HF/Py (~5 mL of a 23% HF/Py solution). After stirring for 3 h and warming from 0 °C to rt, a saturated aqueous solution of $NaHCO_3$ was added until CO_2 evolution ceased (~250 mL). The reaction was extracted with EtOAc (10 x 50 mL) and the combined organic layers were washed with $CuSO_4$ solution (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated. The derived oil was purified via silica gel chromatography (3:1 hexanes:EtOAc) to yield a white solid (114 mg, 61% yield) which was recrystallized from methanol to provide white crystals suitable for X-ray analysis (see Appendix for X-ray structure report). Although recrystallization provided hemiacetal **xii** for X-ray analysis, both **xii** and **xiii** were observed in the ^{1}H and ^{13}C NMR spectra in a 1:1.5 ratio. **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 7.39-7.25 (comp m, 4H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 7.3 Hz, 1H), 5.42 (s, 1H), 4.95 (br s, 1H), 4.56 (s, 1H), 4.40 (br s, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 3.95 (d, *J* = 8.1 Hz, 1H), 3.88 (d, *J* = 11.4 Hz, 1H), 3.45 (d, *J* = 11.4 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.95 (br s, 1H), 2.87 (s, 1H), 2.43 (s, 1H), 1.81 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3), 1.26 (s, 1H), 1.06 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.8, 175.1, 174.4, 142.5, 141.6, 136.7, 135.2, 134.3, 134.2, 127.7, 127.5, 127.2, 124.3, 124.0, 123.5, 117.7, 116.7, 111.3, 106.6, 102.5, 83.8, 82.3, 75.2, 68.2, 53.8, 49.4, 38.9, 38.6, 37.8, 37.6, 36.5, 36.4, 29.0, 27.9, 26.8, 26.6, 22.8, 21.9, 21.1, 19.5, 19.1, 18.6, 18.4, 16.8; **IR** (thin film, NaCl) 3398 (br w), 2930 (br w), 2248 (w), 1689 (s), 1611 (m), 1470 (m), 1378 (m), 1340 (m), 1288 (m), 1058 (m), 1039 (m), 976 (w), 914 (m), 783 (m), 732 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 369.1945, [calc'd for $C_{22}H_{27}NO_4$(M+): 369.1940]; **m.p.** 151-153° C(dec).

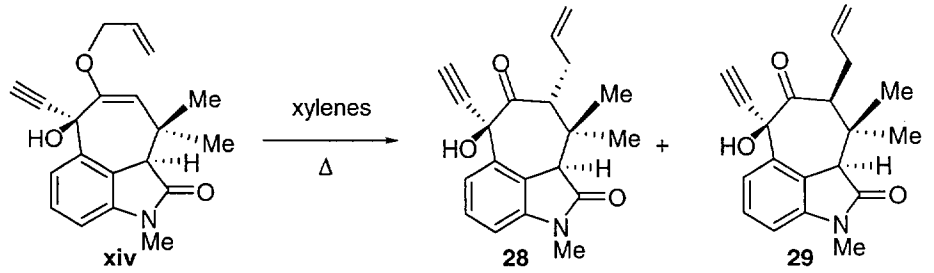
Preparation of alcohol xiv.



To a stirred solution of ketone **22** (1.92 g, 6.5 mmol) in benzene (64 mL) at 0 °C was added 16.2 mL of a 1.0 M solution of ethynyl Grignard in THF (16.2 mmol, 2.5 equiv). After stirring for 10 minutes, the reaction was diluted with H_2O (250 mL) and extracted with ethyl acetate (4 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4), concentrated and chromatographed (3:1 hexanes:EtOAc) to provide **xiv** (1.9 g, 91% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.06-5.99 (comp m, 1H), 5.39 (dq, *J* = 1.4, 17.3 Hz, 1H), 5.31 (dq, *J* = 1.2, 10.4 Hz, 1H), 4.53 (s, 1H), 4.46 (s, 1H), 4.40 (dd, *J* = 5.6, 12.2 Hz, 1H), 4.31 (dd, *J* = 5.6, 12.2 Hz, 1H), 3.97 (s, 1H), 3.22 (s, 3H), 2.51 (s, 1H), 1.6 (s, 3H), 0.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.8, 148.4, 144.1, 138.0, 132.4, 128.4, 124.2, 118.4, 117.5, 113.2,

107.3, 86.1, 71.0, 69.9, 67.6, 51.7, 37.8, 29.1, 26.2, 23.5; **IR** (thin film/NaCl) 3488 (bw), 3253 (w), 1691 (s), 1608 (w), 1469 (s), 1355 (w), 1140 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 323.1514, [calc'd for $C_{20}H_{21}NO_3$ (M+): 323.1521]; **m.p.** 183-185° C.

Preparation of alcohols 28 and 29.



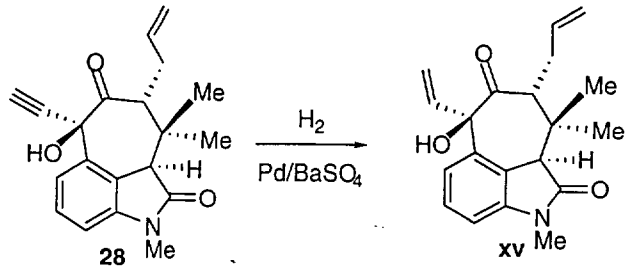
A solution of enol ether **xiv** (900 mg, 2.8 mmol) in xylenes (50 mL) was submersed into an oil bath that had been preheated to 145 °C. The solution was refluxed for 10 minutes, cooled, and concentrated. The resulting residue was chromatographed (2:1 hexanes:EtOAc) to afford ketone **28** (860 mg, 96% yield) and ketone **29** (25 mg, 2% yield) as white solids.

The first compound to elute was ketone **28**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 5.69-5.61 (comp m, 1H), 5.07 (dd, *J* = 1.2, 17.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 3.26 (s, 1H), 3.20 (s, 3H), 3.03 (dd, *J* = 2.7. 11.6 Hz, 1H), 2.78 (s, 1H), 2.73 (q, *J* = 12.1 Hz, 1H), 2.19 (dd, *J* = 4.9, 12.4 Hz, 1H), 1.43 (s, 3H), 0.78 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.3, 175.1, 144.1, 135.9, 135.7, 129.5, 122.1, 120.0, 117.1, 108.0, 81.1, 78.1, 76.4, 55.1, 51.8, 41.0, 31.2, 26.2, 21.8, 20.6; **IR** (thin film, NaCl) 2972 (bw), 2936 (w), 1693 (s), 1609 (s), 1467 (s), 1347 (m), 1310. w, 915 (w), 732 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 323.1526, [calc'd for $C_{20}H_{21}NO_3$ (M+): 323.1521]; **m.p.** 194-196° C(dec).

The second compound to elute was ketone **29**. The solid was recrystallized from CH_2Cl_2/hexanes to furnish crystals suitable for X-ray analysis (see Appendix for X-ray structure report). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.74-5.68 (comp m, 1H), 5.12 (dd, *J* = 1.2,

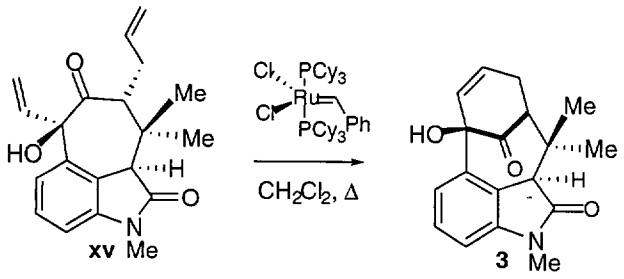
17.1 Hz, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.40 (s, 1H), 4.12 (dd, J = 2.7, 11.1 Hz, 1H), 3.82 (s, 1H), 3.20 (s, 3H), 2.80 (s, 1H), 2.65-2.59 (comp m, 1H), 2.49-2.44 (comp m, 1H), 1.72 (s, 3H), 0.47 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.4, 174.5, 144.3, 135.8, 135.4, 129.4, 123.2, 117.0, 116.8, 108.0, 81.2, 76.8, 76.2, 58.4, 55.4, 44.4, 29.8, 26.4, 24.3, 16.4; **IR** (thin film/NaCl) 2973 (w), 1702 (s), 1604 (m), 1468 (m), 1340 (m), 765 (s) cm-1; **HRMS** (EI) *m/z* found: 323.1521, [calc'd for $C_{20}H_{23}NO_3$ (M+): 323.1521]; **m.p.** 189-192° C.

Preparation of diene xv.



To a solution of acetylene **28** (500 mg, 1.5 mmol) in EtOAc (30 mL) was added Lindlar's catalyst (100 mg) and the mixture was placed under 1 atmosphere of H_2. The reaction was carefully monitored by TLC (3:1 hexanes:EtOAc) and upon completion (ca. 15 min) was filtered through celite. The filtrate was evaporated and the residue purified by silica gel chromatography (3:1 hexanes:EtOAc) to afford diene **xv** (495 mg, 99% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.20 (dd, J = 10.8, 17.2 Hz, 1H), 5.71-5.63 (comp m, 1H), 5.29 (d, J = 10.8 Hz, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.12 (dd, J = 1.1, 16.9 Hz, 1H), 4.98 (d, J = 10.0 Hz, 1H), 3.20 (s, 3H), 3.13 (brs, 1H), 3.08 (dd, J = 2.4, 11.6 Hz, 1H), 2.68-2.61 (compm, 1H), 2.14-2.13 (br s, 1H), 1.41 (s, 3H), 0.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.1, 175.3, 144.1, 138.1, 136.5, 136.4, 129.2, 122.6, 120.3, 116.9, 115.3, 107.3, 82.1, 52.1, 41.1, 30.9, 29.7, 26.1, 21.7, 20.5; **IR** (thin film/NaCl) 2969 (w), 2242 (w), 1717 (s), 1691 (s), 1614 (s), 1464 (m), 1335 (m), 908 (m), 738 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 325.1677, [calc'd for $C_{20}H_{23}NO_3$ (M+): 325.1678]; **m.p.** 148-149° C.

Preparation of olefin 3.

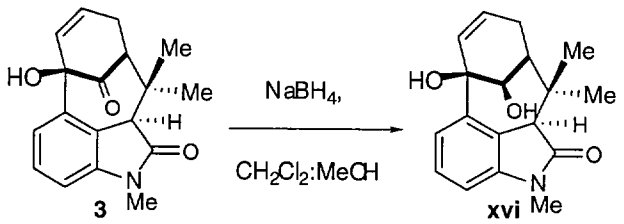


To a solution of diene **xv** (25 mg, 0.08 mmol) in CH_2Cl_2 (30 mL) was added Grubbs' catalyst (13 mg, 0.015 mmol, 20 mol %). The resulting solution was refluxed for 24 h, cooled and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (2:1 hexanes:EtOAc) to afford recovered diene **xv** (5.2 mg, 21%) and the desired olefin **3** (12.9 mg, 56% yield) as a white solid (71% yield based on recovered starting material).

The first compound to elute was diene **xv**.

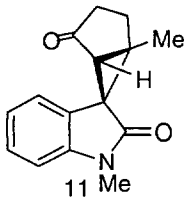
The second compound to elute was olefin **3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.94-5.91 (comp m, 1H), 5.61 (dd, J = 2.6, 9.7 Hz, 1H), 4.24 (s, 1H), 3.78 (s, 1H), 3.20 (s, 3H), 3.03-2.98 (comp m, 1H), 2.80-2.74 (comp m, 2H), 1.56 (s, 3H), 0.62 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.6, 175.2, 144.1, 135.8, 130.0, 129.0, 126.3, 123.9, 117.9, 107.6, 77.2, 61.1, 49.7, 40.8, 29.5, 26.3, 26.2, 22.8; **IR** (thin film/NaCl) 3032 (w), 2930 (w), 2248 (w), 1708 (2), 1597 (m), 1471 (m), 1340 (m), 1146 (m), 725 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 197.1362, [calc'd for $C_{18}H_{19}NO_3$ (M+): 297.1365]; **m.p.** >235° C(dec).

Preparation of diol xvi: Confirmation of the structure of olefin 3 via X-ray analysis.



A solution of olefin **3** (16 mg, 0.05 mmol) in methanol and CH_2Cl_2 (1 mL, 1:1) was treated with sodium borohydride (1.9 mg, 0.08 mmol, 1.7 equiv) at 0 °C. The resulting slurry was stirred for 10 min when the reaction was quenched by the addition of silica gel (ca. 100 mg). The mixture was concentrated under reduced pressure and chromatographed (EtOAc) to yield alcohol **xvi** (15.2 mg, 95% yield) as a white crystalline solid. Recrystallization from Et_2O/hexanes provided crystals suitable for single crystal X-ray analysis (see Appendix for X-ray structure report). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 5.86 (ddd, *J* = 9.8, 5.4, 2.0 Hz, 1H), 5.42 (dd, *J* = 2.8, 9.9 Hz, 1H), 4.31 (t, *J* = 4.0 Hz, 1H), 3.60 (s, 1H), 3.18 (s, 3H), 2.74 (dd, *J* = 5.4, 19.2 Hz, 1H), 2.57 (s, 1H), 2.55-2.49 (comp m, 1H), 2.16 (t, *J* = 5.7 Hz, 1H), 2.10 (d, *J* = 4.0 Hz, 1H), 1.47 (s, 3H), 0.86 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.3, 144.0, 138.5, 128.5, 128.1, 127.3, 124.8, 119.4, 107.0, 80.0, 75.3, 51.4, 49.8, 37.1, 29.1, 28.3, 26.2, 24.6; **IR** (thin film/NaCl) 3413 (bw), 2969 (w), 1682 (s), 1598 (m), 1469 (m), 1351 (m), 1036 (w) cm-1; **HRMS** (EI) *m/z* found: 299.1508, [calc'd for $C_{18}H_{21}NO_3$ (M+): 299.1521]; **m.p.** >235° C(dec).

APPENDIX



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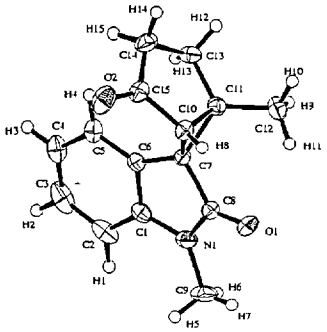


X-RAY STRUCTURE REPORT

Data Collection

A colorless prism crystal of $C_{15}H_{15}NO_2$ having approximate dimensions of 0.21 x 0.38 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using ten (1° in ω, 10s exposure, de-zingered) data frames, corresponded to a primitive monoclinic cell with dimensions: a = 7.282(1) Å, b = 16.256(1) Å, β = 91.46(1)°, c = 10.196(1) Å, V = 1206.6(2) Å3. For Z = 4 and F.W. = 241.29, the calculated density is 1.33 g/cm^3. The systematic absences of: h0l: l = 2n+1; 0k0: k = 2n+1, uniquely determine the space group to be:
$P2_1/c$ (#14).

The data were collected at a temperature of 23 ± 1° C to a maximum 2θ value of 52.7°. One phi scan consisting of 163 data frames and one omega scan consisting of 85 data frames, respectively, were collected with a scan width of 1° and a detector-to-crystal distance, Dx, of 35mm. Each frame was exposed twice (for the purpose of de-zingering) for 60s. The data frames were processed and scaled using the DENZO software package. (Z. Otwinowski and W. Minor, "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," Methods in Enzymology, vol. 276: Macromolecular Crystallography,

part A, 307-326, 1997, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press).

Data Reduction

A total of 2439 reflections was collected. No decay correction was applied. The linear absorption coefficient, μ, for Mo-Kα radiation is 0.9 cm^{-1} and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. In the case of the methyl group hydrogen atoms, one hydrogen was located in the difference map and included at an idealized distance to set the orientation of the other two hydrogen atoms. The final cycle of full-matrix least-squares refinement[3] was based on 1988 observed reflections ($I > 3.00\sigma(I)$) and 163 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.044$

$Rw = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo2)]^{1/2} = 0.068$

The standard deviation of an observation of unit weight[4] was 4.05. The weighting scheme was based on counting statistics and included a factor ($p = 0.010$) to downweight the intense reflections. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.21 and -0.15 e-/Å3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G.; *J. Appl. Cryst.*, 27, 435-336, (1994).

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized $\Sigma w(|Fo|-|Fc|)^2$

where $w = 4Fo^2/\sigma^2(Fo^2)$

and $\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$

S = Scan rate
C = Total integrated peak count
R = Ratio of scan time to background counting time
B = Total background count
Lp = Lorentz-polarization factor
p = p-factor

(4) Standard deviation of an observation of unit weight:

$[\Sigma w(|Fo|-|Fc|)^2/(No-Nv)]^{1/2}$

where No = number of observations
Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; *Acta Crystallogr.*, 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

Experimental Details

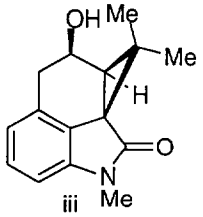
A. Crystal Data	
Empirical Formula	$C_{15}H_{15}NO_2$
Formula Weight	241.29
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.21 X 0.38 X 0.40 mm
Crystal System	monoclinic
Lattice Parameters	a = 7.282(1)Å
	b = 16.256(1) Å
	c = 10.196(1) Å
	β = 91.46(1)o
	V = 1206.6(2) Å3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.328 g/cm^3
F000	512.00
μ(MoKα)	0.88 cm^{-1}
B. Intensity Measurements	
Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Type	ω
Scan Rate	60s/frame
Scan Width	1°/frame
2θmax	52.7°
No. of Reflections Measured	Total: 2439
Corrections	Lorentz-polarization
C. Structure Solution and Refinement	
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares

Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1988
No. Variables	163
Reflection/Parameter Ratio	12.20
Residuals: R; Rw	0.044 ; 0.068
Goodness of Fit Indicator	4.05
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.21 e-/Å3
Minimum peak in Final Diff. Map	-0.15 e-/Å3

Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	Beq
O(1)	0.2481(1)	-0.19964(6)	0.49693(8)	3.49(2)
O(2)	0.6122(1)	-0.11788(7)	0.0967(1)	4.23(3)
N(1)	0.2374(1)	-0.06022(7)	0.5318(1)	2.68(2)
C(1)	0.2605(2)	0.01112(8)	0.4567(1)	2.51(3)
C(2)	0.2722(2)	0.09138(9)	0.5008(2)	3.52(3)
C(3)	0.3000(2)	0.15271(9)	0.4083(2)	4.10(4)
C(4)	0.3146(2)	0.13388(8)	0.2770(2)	3.57(3)
C(5)	0.3038(2)	0.05275(7)	0.2339(1)	2.73(3)
C(6)	0.2774(1)	-0.00961(7)	0.3240(1)	2.19(2)
C(7)	0.2595(2)	-0.10055(7)	0.3155(1)	2.11(2)
C(8)	0.2476(2)	-0.12924(8)	0.4559(1)	2.45(3)
C(9)	0.2169(2)	-0.0622(1)	0.6727(1)	3.82(4)
C(10)	0.3580(2)	-0.16107(7)	0.2261(1)	2.31(3)
C(11)	0.1545(2)	-0.15079(7)	0.2095(1)	2.32(3)
C(12)	0.0158(2)	-0.21498(8)	0.2453(1)	3.04(3)
C(13)	0.1165(2)	-0.10457(9)	0.0815(1)	3.04(3)
C(14)	0.3007(2)	-0.09830(9)	0.0117(1)	3.24(3)

C(15)	0.4482(2)	-0.12383(8)	0.1106(1)	2.76(3)
H(1)	0.2615	0.1042	0.5912	4.2264
H(2)	0.3091	0.2084	0.4360	4.9256
H(3)	0.3323	0.1768	0.2153	4.2832
H(4)	0.3144	0.0402	0.1434	3.2819
H(5)	0.3121	-0.0309	0.7139	4.5815
H(6)	0.1011	-0.0396	0.6941	4.5815
H(7)	0.2238	-0.1175	0.7026	4.5815
H(8)	0.4054	-0.2109	0.2621	2.7779
H(9)	-0.1010	-0.1898	0.2542	3.6446
H(10)	0.0084	-0.2556	0.1783	3.6446
H(11)	0.0522	-0.2401	0.3259	3.6446
H(12)	0.0297	-0.1339	0.0283	3.6492
H(13)	0.0704	-0.0512	0.0992	3.6492
H(14)	0.3009	-0.1340	-0.0621	3.8831
H(15)	0.3210	-0.0434	-0.0163	3.8831



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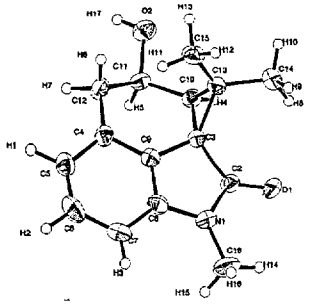


X-RAY STRUCTURE REPORT

Data Collection

A colorless prism crystal of $C_{15}H_{17}NO_2$ having approximate dimensions of 0.21 X 0.39 X 0.48 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Mo Kα radiation.

Cell constants and an orientation matrix for data collection obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $5.81 < 2\theta < 20.97°$ corresponded to a monoclinic cell with dimensions: a = 8.849 (3)Å, b = 16.577 (3)Å, c = 9.522 (2)Å, β= 115.34 (2)° , and V = 1262 (1)Å^3. For Z = 4 and F.W. = 243.30 the calculated density is 1.280 g/cm^3. Based on the systematic absences of: h0l: l = 2n+1; 0k0: k = 2n+1; and the successful solution and refinement of the structure the space group was determined to be: $P2_1/c$ (#14).

The data were collected at a temperature of 23 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections made prior to data collection had an average width at half-height of 0.19° with a take-off angle of 6.0° . Scans of (1.57 + 0.30 tan θ)° were made at a speed of 8.0° /min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 285.0 mm.

Data Reduction

Of the 2478 reflections which were collected 2323 were unique (R_{int} = .031). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Mo Kα is 0.8 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1]. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located in subsequent difference maps and refined isotropically. The final cycle of full-matrix least-squares refinement[2] was based on 1023 observed reflections ($I > 3.00\sigma(I)$) and 231 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.038$$

$$Rw = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.040$$

The standard deviation of an observation of unit weight[3] was 1.39. The weighting scheme was based on counting statistics and included a factor (p = 0.02) to downweight the intense reflections. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.15 and -0.14 e-/$Å^3$ respectively.

Neutral atom scattering factors were taken from Cromer and Waber[4]. Anomalous dispersion effects were included in Fcalc[5]; the values for Δf' and Δf" were those of Cromer[6]. All calculations were performed using the TEXSAN[7] crystallographic software package of Molecular Structure Corporation.

References

(1) Structure Solution Methods:
MITHRIL
Gilmore C.J.; MITHRIL - an integrated direct methods computer program, *J. Appl. Cryst.*, 17, 42-46, University of Glasgow, Scotland (1984).

(2) Least-Squares:

Function minimized: $\Sigma w (|Fo| - |Fc|)^2$

where: $w = 4Fo^2/\sigma^2(Fo^2)$

$\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$

S = Scan rate
C = Total Integrated Peak Count
R = Ratio of Scan Time to background counting time
B = Total Background Count
Lp = Lorentz-polarization factor
p = p-factor

(3) Standard deviation of an observation of unit weight:

$[\Sigma w(|Fo| - |Fc|)^2/(No - Nv)]^{1/2}$

where: No = number of observations Nv = number of variables

(4) Cromer D.T. & Waber J.T.; "International Tables for X-ray Crystallography," Vol. IV, The Kynoch Press, Birmingham England, Table 2.2 A (1974).

(5) Ibers J.A. & Hamilton W.C.; *Acta Crystallogr.*, 17, 781 (1964).

(6) Cromer D.T.; "International Tables for X-ray Crystallography," Vol. IV, The Kynoch Press, Birmingham England, Table 2.3.1 (1974).

(7) TEXSAN - TEXRAY Structure Analysis Package Molecular Structure Corporation (1989).

Experimental Details

A. Crystal Data	
Empirical Formula	$C_{15}H_{17}NO_2$
Formula Weight	243.30
Crystal Color/Habit	colorless prisms
Crystal Dimensions (mm)	0.21 X 0.39 X 0.48
Crystal System	monoclinic
No. Reflections Used for Unit Cell Determination (2θ range)	25(5.8 - 21.0°)
Omega Scan Peak Width at Half-height	0.19
Lattice Parameters:	a = 8.849 (3)Å b = 16.577 (3)Å c = 9.522 (2)Å β = 115.34 (2)° V = 1262 (1)Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.280 g/cm^3
F000	520
μ(MoKα)	0.79 cm-1
B. Intensity Measurements	
Diffractometer	Rigaku AFC5S
Radiation	MoKα(λ = 0.71069 Å)
Temperature	23° C
Attenuator	Zr foil (factors: 2.3, 5.2, 11.7)
Take-off Angle	6.0°
Detector Aperture	6.0 mm hor./6.0 mm vert.
Crystal to Detector Distance	285 mm
Scan Type	ω-2θ

Scan Rate	8.0° /min (in omega) (2 rescans)
Scan Width	(1.57 + 0.30 tanθ)°
2θmax	50.0°
No. of Reflections Measured	Total: 2478
Unique:	2323 (R_{int} = 0.031)
Corrections	Lorentz-polarizatin

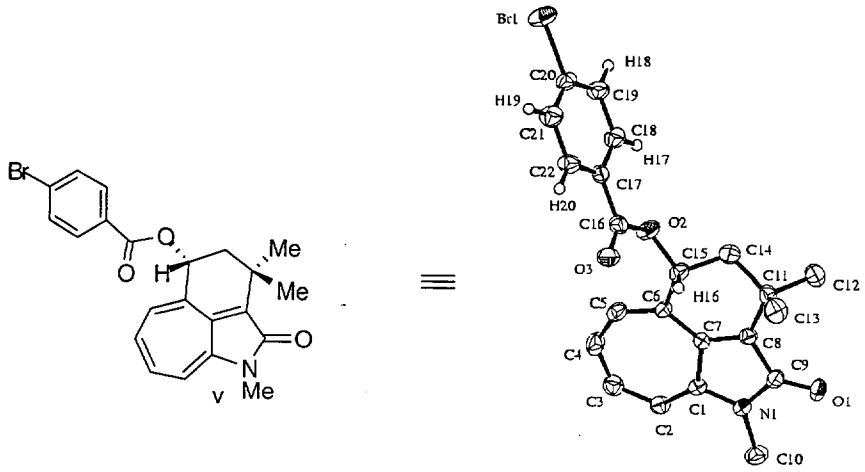
C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.02
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1023
No. Variables	231
Reflection/Parameter Ratio	4.43
Residuals:	R; Rw 0.038; 0.040
Goodness of Fit Indicator	1.39
Max Shift/Error in Final Cycle	0.00
Maximum Peak in Final Diff. Map	0.15 e-/Å^3
Minimum Peak in Final Diff. Map	-0.14 e-/Å^3

Positional parameters and $B_{(eq)}$

atom	x	y	z	B(eq)
O1	0.6720(3)	0.2045(2)	0.3462(3)	4.8(1)
O2	-0.0150(3)	0.2267(2)	-0.0505(3)	4.7(1)
N1	0.5892(3)	0.1282(2)	0.5035(3)	3.5(1)
C2	0.5629(4)	0.1688(2)	0.3685(4)	3.4(2)
C3	0.3822(4)	0.1562(2)	0.2597(3)	2.8(1)
C4	0.1435(4)	0.1136(2)	0.3272(4)	3.4(2)
C5	0.1084(5)	0.0818(2)	0.4464(5)	4.4(2)

C6	0.2358(6)	0.0590(3)	0.5855(5)	4.9(2)
C7	0.4042(6)	0.0693(2)	0.6183(5)	4.3(2)
C8	0.4385(4)	0.1007(2)	0.5015(4)	3.2(2)
C9	0.3103(4)	0.1184(2)	0.3561(4)	2.8(1)
C10	0.2644(4)	0.2075(2)	0.1270(4)	3.0(1)
C11	0.0872(4)	0.2172(2)	0.1113(4)	3.4(2)
C12	0.0172(4)	0.1485(3)	0.1768(5)	4.0(2)
C13	0.3298(4)	0.1324(2)	0.0867(4)	3.1(1)
C14	0.4583(6)	0.1452(3)	0.0234(5)	4.8(2)
C15	0.2252(6)	0.0575(3)	0.0229(5)	4.2(2)
C16	0.7499(5)	0.1245(3)	0.6388(5)	5.2(2)
H1	-0.014(4)	0.080(2)	0.428(4)	5.4(9)
H2	0.210(4)	0.037(2)	0.666(4)	4.6(8)
H3	0.494(4)	0.056(2)	0.718(4)	4.7(8)
H4	0.306(4)	0.259(2)	0.104(3)	4.4(8)
H5	0.090(3)	0.271(2)	0.178(3)	2.9(7)
H6	-0.030(4)	0.108(2)	0.094(3)	3.8(8)
H7	-0.079(4)	0.170(2)	0.196(3)	4.1(7)
H8	0.533(4)	0.192(2)	0.066(4)	6(1)
H9	0.536(4)	0.099(2)	0.048(4)	6(1)
H10	0.396(4)	0.149(2)	-0.092(4)	5.6(9)
H11	0.176(4)	0.034(2)	0.086(4)	6(1)
H12	0.294(4)	0.015(2)	0.010(4)	6(1)
H13	0.136(5)	0.066(2)	-0.084(4)	7(1)
H14	0.830(6)	0.147(3)	0.611(5)	10(1)
H15	0.737(5)	0.144(2)	0.725(5)	7(1)
H16	0.792(6)	0.068(3)	0.664(5)	9(1
H17	-0.117(5)	0.245(3)	-0.067(4)	7(1)



X-RAY STRUCTURE REPORT

Data Collection

An orange prism crystal of $C_{22}H_{20}NO_3Br$ having approximate dimensions of 0.15 x 0.23 x 0.29 mm was mounted on a glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using ten (1° in ω, 10s exposure, de-zingered) data frames, corresponded to a primitive triclinic cell with dimensions:

a = 8.1052(3) Å	α = 101.220(2)°
b = 9.4180(2) Å	β = 107.306(2)°
c = 13.4027(4) Å	γ = 97.417(2)
V = 938.82(6) Å3	

For Z = 2 and F.W. = 426.31, the calculated density is 1.51 g/cm^3. Based on a statistical analysis of intensity distribution,and the successful solution and refinement of the structure, the space group was determined to be: P_{-1} (#2).

The data were collected at a temperature of 23 ± 1° C to a maximum 2θ value of

61.0°. One phi scan consisting of 183 data frames and one omega scan consisting of 120 data frames were collected with a scan width of 1° and a detector-to-crystal distance, Dx, of 35 mm. Each frame was exposed twice (for the purpose of de-zingering) for 20s. The data frames were processed and scaled using the DENZO software package. (Z. Otwinowski and W. Minor, "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," Methods in Enzymology, vol. 276: Macromolecular Crystallography, part A, 307-326, 1997, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press).

Data Reduction

Of the 9204 reflections which were collected, 5071 were unique (R_{int} = 0.035). No decay correction was applied. The linear absorption coefficient, μ, for Mo-Kα radiation is 22.2 cm^{-1} and a SORTAV absorption correction was applied. (MaXus: Mackay, S., Edwards, C., Henderson, A., Gilmore, C., Stewart, N., Shankland, K. and Donald, A. (1998) Chemistry Department, The University of Glasgow, Scotland.). The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

In the case of the methyl group hydrogen atoms, one hydrogen was located in the difference map and included at an idealized distance to set the orientation of the other two hydrogen atoms. The final cycle of full-matrix least-squares refinement[3] was based on 1978 observed reflections ($I > 3.00\sigma(I)$) and 244 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.035$$

$$Rw = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.031$$

The standard deviation of an observation of unit weight[4] was 1.57. The weighting scheme was based on counting statistics and included a factor (p = 0.020) to downweight

the intense reflections. Plots of Σ w (|Fo| - |Fc|)^2 versus |Fo|, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.32 and -0.31 e-/Å3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G.; *J. Appl. Cryst.*, 27, 435-436 (1994).

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized $\Sigma w(|Fo|-|Fc|)^2$

where $w = 4Fo^2/\sigma^2(Fo^2)$

and $\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$

S = Scan rate
C = Total integrated peak count
R = Ratio of scan time to background counting time
B = Total background count
Lp = Lorentz-polarization factor
p = p-factor

(4) Standard deviation of an observation of unit weight:

$[\Sigma w(|Fo|-|Fc|)^2/(No-Nv)]^{1/2}$

where No = number of observations
Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; *Acta Crystallogr.*, 17, 781 (1964).