Supporting Information for "Efficient Syntheses of Novel C2'-Alkylated (±)-K252a Analogs"

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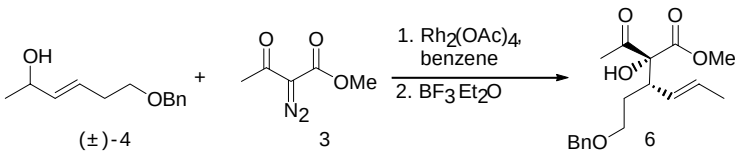
Material and Methods

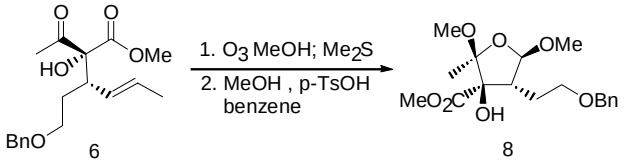
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), and benzene were distilled from calcium hydride. All other commercially obtained reagents were used 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 was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. Preparative TLC was was performed with the indicated solvents using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm), acetone (^{1}H, δ 2.04 ppm, ^{13}C, δ 206.0 ppm), or dimethyl sulfoxide (^{1}H, δ 2.49 ppm, ^{13}C, δ 39.5 ppm). Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

Preparation of ketone 6.



A stirred solution of methyl 2-diazo-3-oxobutanoate **3** (9.50 g, 63.1 mmol), allyl alcohol (±)-**4** (3.00g, 63.1 mmol), and $Rh_2(OAc)_4$ (95mg, 0.44 mmol) in benzene 300 mL was immersed into a preheated (100-110 °C) oil bath. The mixture was heated at reflux for 45 min, cooled to room temperature, treated with BF_3•OEt_2 (9.60 ml, 75.8 mmol), and stirred for 3.5 h at 25°C. The reaction mixture was washed with H_2O (300 mL), and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with H_2O (150 mL), brine (150 mL), dried over Na_2SO_4, and evaporated to a residue. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded alcohol **6** (7.61 g, 38% yield) as a colorless oil: IR (thin film/NaCl) 3485 (m), 3030 (w), 2953 (s), 2923 (s), 2857 (s), 1724 (s), 1604 (w), 1586 (w), 1453 (m), 1437 (m), 1364 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.55 (dq, *J*=15.1, 6.4 Hz, 1H), 5.26 (ddd, *J*=1.5, 9.6, 15.1 Hz, 1H), 4.51 (d, *J*=11.9 Hz, 1H), 4.42 (d, *J*=11.9 Hz, 1H), 4.25 (s, 1H), 3.74 (s, 3H), 3.44 (ddd, *J*=4.0, 5.5, 9.4 Hz, 1H), 3.36 (dt, *J*=9.4 Hz, 5.1H), 3.22 (m, 1H), 2.39 (s, 3H), 1.63 (dd, *J*=1.5, 6.4 Hz, 3H), 1.55 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 170.4, 138.4, 130.1, 128.2, 127.6, 127.5, 127.4, 88.1, 72.8, 67.2, 53.1, 45.5, 28.9, 25.5, 18.0; HRMS (FAB) *m/z* 320.1614 [calc'd for $C_{18}H_{24}O_5$ (M) 320.1624].

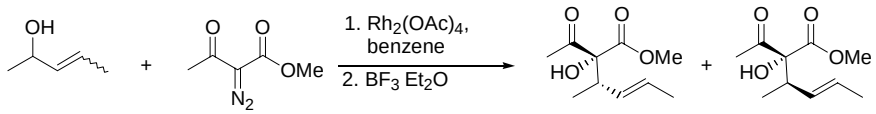
Preparation of benzyl ether 8.



A solution of alcohol **6** (6.50 g, 20.3 mmol) and trace of Sudan red 7B dye in MeOH (125 mL) was cooled to -78 °C and treated with O_3 until the dye was completely discolored (about 7 min). The mixture was purged with nitrogen for 10 min at -78 °C and dimethyl sulfide (20 mL) was added at that temperature. The dry ice bath was replaced with an ice bath and the mixture was stirred for 1 h at 0 °C. The solvent was removed *in vacuo* and the crude product was dissolved in

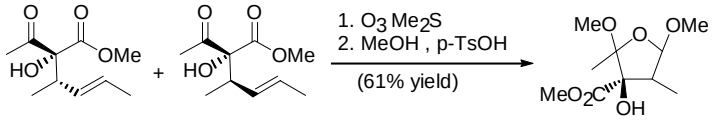
benzene (125 mL). To the solution MeOH (19.0 mL) and p-toluenesulfonic acid (58 mg, 3.1 mmol) were added and the mixture was stirred at 25 °C for 16 h. After evaporation of the solvent *in vacuo*, flash chromatography (6:1 hexanes/EtOAc eluent) provided benzyl ether **8** (3.65 g, 51% yield) as a pale yellow oil: IR (thin film/ NaCl) 3501 (m), 2993 (m), 2951 (s), 1732 (s), 1603 (w), 1586 (w), 1496 (m), 1454 (m), 1379 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.85 (d, *J*=5.1 Hz, 1H), 4.50 (s, 2H), 3.78 (s, 3H), 3.72 (br s, 1H), 3.57-3.49 (m, 2H), 3.46 (s, 3H), 3.37 (s, 3H), 2.60 (m, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 137.9, 128.3, 127.7, 127.6, 108.5, 104.4, 87.0, 73.0, 68.7, 56.4, 52.5, 50.5, 48.8, 26.8, 16.3; HRMS (EI) *m/z* 323.1503 [calc'd for $C_{17}H_{23}O_6$ (M-CH_3OH+H) 323.1495].

Preparation of ketone 5a and 5b.



The procedure for providing **6** was followed using (±)-3-pentene-2-ol (**2**) (*E*:*Z*=23:1 mixture) (1.00 g, 11.6 mmol) and methyl 2-diazo-3-oxo-butanoate (1.50 g, 10.6 mmol) to afford a mixture of diastereomers **5a**/**5b** (ca.7:1) (1.53 g, 66% yield) as a pale yellow oil. These diastereomers were difficult to separate, thus characterization was carried out as mixture: IR (thin film/NaCl) 3488 (br m), 3028 (m), 2971 (m), 2938 (m), 2880 (m), 2857 (m), 1722 (s), 1670 (w), 1451 (m), 1437 (m), 1356 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59-5.47 (m, 1H), 5.32 (m, 0.88H), 5.22 (m, 0.12H), 4.22 (br s, 0.12H), 4.09 (br s, 0.88H), 3.78 (s, 0.36H), 3.73 (s, 2.64H), 3.19-3.10 (m, 1H), 2.32 (s, 2.64H), 2.27 (s, 0.36H), 1.61 (dd, *J*=1.4, 6.5 Hz, 2.64H), 1.59 (dd, *J*=1.5, 6.6 Hz, 0.36H), 1.01 (d, *J*=6.4 Hz, 0.36H), 0.87 (d, *J*=7.1 Hz, 2.64H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3/204.9, 170.8/170.7, 129.8/129.2, 127.6/127.8, 87.7/87.5, 53.2, 42.9/43.0, 25.5/25.0, 17.9/17.9, 14.3/15.7 ; HRMS (EI) *m/z* 201.1132 [calc'd for $C_{10}H_{17}O_4$ (M+H) 201.1127].

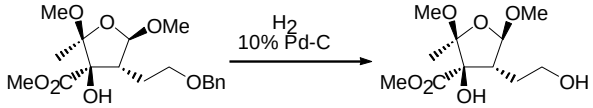
Preparation of alcohol 7.



5a ca 7 : 1 5b 7

The procedure for providing **8** was followed using diastereomeric mixture of alcohols **5a**/**5b** (ca.7:1)(6.55 g, 37.9 mmol) to afford a diastereomeric mixture of alcohols (5.58 g, 61% yield) as a colorless oil. A major single diastereomer **7** (2.42g, 27% yield) was isolated by flash chromatography (1:1 pentane/Et_2O) as a pale yellow oil: IR (thin film/NaCl) 3503 (s), 2990, (s), 2952 (s), 2913 (s), 2835 (m), 1756 (s), 1732 (s), 1462 (s), 1391 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, *J*=6.5 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 3H), 3.36 (s, 3H), 2.54 (app p, *J*=6.6 Hz, 1H), 1.26 (s, 3H), 1.05 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 109.2, 104.1, 87.4, 56.5, 52.4, 48.7, 47.2, 16.3, 9.7; HRMS (CI) *m/z* 203.0918 [calc'd for $C_9H_{15}O_5$ (M-CH_3OH+H) 203.0919] This major diastereomer was used for next step.

Preparation of alcohol 9.

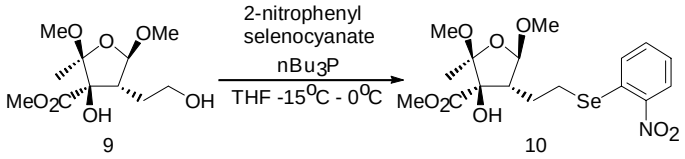


8 9

A mixture of benzyl ether **9** (3.12 g, 8.81 mmol) and 10% Pd-C (600 mg) in MeOH (80 mL) was stirred for 7 h under H_2 atmosphere. The mixture was filtered through Celite and the filtrate was evaporated to give a white solid. Crystallization from hexanes/EtOAc provided alcohol **9** (1.83 g, 79% yield) as colorless crystals.

Crystals suitable for X-ray analysis were obtained by recrystallization from hexanes/EtOAc: mp 116-117 °C (dec); IR (thin film/NaCl) 3436 (br s), 3281 (br m), 2949 (s), 2896 (m), 2838 (m), 1744 (s), 1443 (m), 1391 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, *J*=6.2 Hz, 1H), 3.81 (s, 3H), 3.79 (br s, 1H), 3.70-3.59 (m, 2H), 3.47 (s, 3H), 3.34 (s, 3H), 2.79-2.61 (br, 1H), 2.56 (app q, *J*=6.6 Hz, 1H), 1.78-1.63 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 108.1, 104.3, 86.8, 61.5, 56.4, 52.6, 51.1, 48.8, 29.1, 16.3; HRMS (EI) *m/z* 201.0765 [calc'd for $C_9H_{13}O_5$ (M-2x(CH_3OH)+H) 201.0763].

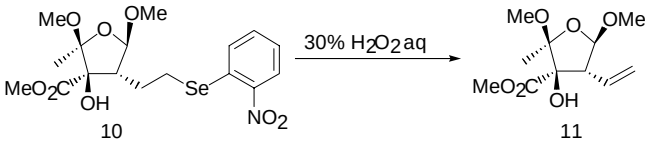
Preparation of selenyl compound 10.



9 10

To a stirred solution of alcohol **9** (150 mg, 0.568 mmol) and 2-nitrophenyl selenocyanate (155 mg, 0.683 mmol) at -15 °C in THF (6.5 mL) was added tri-*n*-butylphosphine (0.170 mL, 0.682 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C over 2.5 h. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (2:1 then 1:1 hexanes/EtOAc eluent) to provide selenyl compound **10** (252 mg, 99% yield) as a yellow solid. Crystallization from hexanes/EtOAc/CH_2Cl_2 afforded **10** as yellow crystals: mp 108-109°; IR (thin film/NaCl) 3501 (m), 2992 (m), 2948 (m), 2835 (m), 1732 (s), 1590 (m), 1566 (m), 1513 (s), 1451 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J*=1.5, 8.6 Hz, 1H), 7.52 (m, 1H), 7.45 (dd, *J*=1.3, 8.0 Hz, 1H), 7.30 (m, 1H), 4.86 (d, *J*=6.3 Hz, 1H), 3.83 (s, 3H), 3.49 (s, 3H), 3.46 (br s, 1H), 3.37 (s, 3H), 3.02-2.88 (m, 2H), 2.67 (m, 1H), 1.99-1.86 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 146.7, 133.6, 133.0, 128.7, 126.3, 125.3, 108.0, 104.3, 87.1, 56.4, 52.9, 52.8, 48.9, 25.9, 23.5, 16.1; HRMS (FAB) *m/z* 449.0588 [calc'd for $C_{17}H_{23}NO_8{}^{80}Se$ (M) 449.0589].

Preparation of olefin 11.

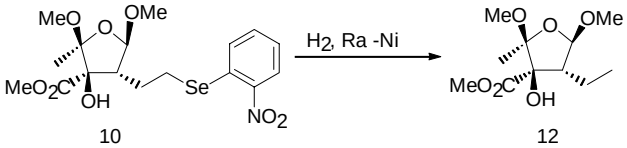


10 11

To a stirred ice-cooled solution of **10** (97.1 mg, 0.217 mmol) in THF (4.0 mL) was added a 30% H_2O_2 solution (0.50 mL). After 1 h stirring, the mixture was warmed to 35 °C and the stirring was continued another 4 h at that temperature. The mixture was cooled to 0 °C and saturated aqueous $Na_2S_2O_3$ solution was added. The mixture was extracted with EtOAc (3 x 12 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided olefin **11** (35.4 mg, 66% yield) as a pale yellow oil: IR (thin film/NaCl) 3501 (s), 3084 (w), 2993 (s), 2952 (s), 2836 (m), 1757 (s), 1732 (s), 1642 (w), 1445 (s), 1383 (s) cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 5.69 (m, 1H), 5.28 (dd, *J*=1.0, 17.2 Hz, 1H), 5.20 (dd, *J*=1.0, 10.0 Hz, 1H), 4.98 (d, *J*=5.9 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.46 (br s, 1H), 3.35 (s, 3H), 3.12 (app t, *J*=7.1 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 131.0, 120.8, 107.1, 104.3, 87.6, 57.0, 56.6, 52.7, 48.8, 16.1; HRMS (CI) *m/z* 215.0919 [calc'd for $C_{10}H_{15}O_5$ (M-CH_3OH+H) 215.0919].

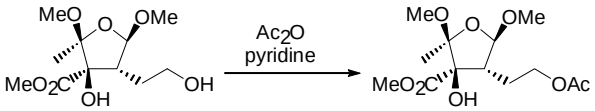
Preparation of alcohol 12.



10 12

A mixture of **10** (1.18 g, 2.63 mmol) and Ra-Ni (6 g) (washed by decantation with H_2O (15 times) and THF (5 times)) in THF (45 mL) was stirred for 2 h under H_2 atmosphere. The mixture was filtered through Celite and the filtrate was evaporated to a residue. Purification by flash chromatography (4:1 then 3:1 hexanes/EtOAc eluent) provided alcohol **12** (546 mg, 84% yield) as a colorless oil: IR (thin film/NaCl) 3502 (m), 2963 (m), 2878 (m), 1756 (m), 1732 (s), 1463 (m), 1443 (m), 1382 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J*=6.3 Hz, 1H), 3.81 (s, 3H), 3.46 (s, 3H), 3.38 (br s, 1H), 3.34 (s, 3H), 2.37 (dt, *J*=9.4, 6.3 Hz, 1H), 1.52 (m, 1H), 1.41 (m, 1H), 1.23 (s, 3H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 108.9, 104.2, 87.3, 56.3, 53.9, 52.5, 48.7, 19.7, 16.0, 12.3; HRMS (CI) *m/z* 217.1066 [calc'd for $C_{10}H_{17}O_5$ (M-CH_3OH+H) 217.1076].

Preparation of acetate 13.

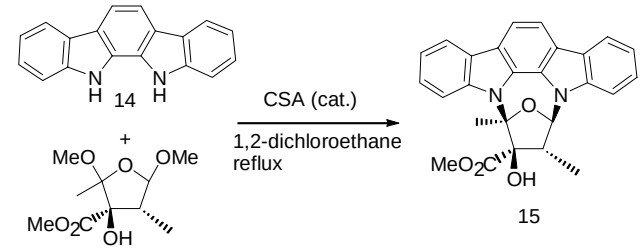


9 13

A mixture of alcohol **9** (360 mg, 1.36 mmol), pyridine (1.0 mL), and Ac_2O (1.0 mL) was kept at 25 °C for 3 h. Toluene (5 mL) was added and the mixture was evaporated (repeated 3 times) to a residue. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided acetate **13** (405 mg, 97% yield) as a colorless oil: IR (thin film/NaCl) 3493 (br m), 2992 (m), 2953 (m), 2836 (m), 1738 (s), 1443 (m), 1369 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 d, *J*=6.4, 1H),

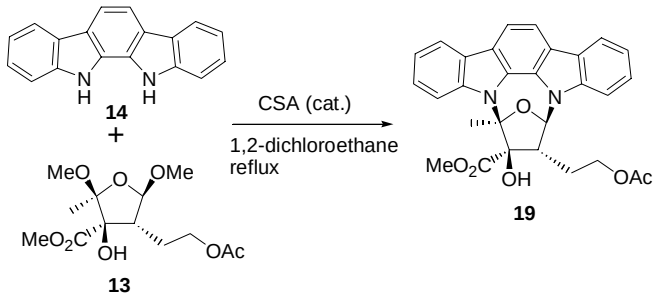
4.15-3.99 (m, 2H), 3.83 (s, 3H), 3.45 (s, 3H), 3.41 (br s, 1H), 3.34 (s, 3H), 2.55 (dt, *J*=9.0, 6.4 Hz, 1H), 2.02 (s, 3H), 1.89-1.69 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.8, 108.2, 104.2, 87.0, 62.4, 56.4, 52.7, 49.7, 48.8, 25.7, 20.9, 16.2; HRMS (CI) *m/z* 275.1134 [calc'd for $C_{12}H_{19}O_7$ (M-CH_3OH+H) 275.1131].

Preparation of alcohol 15.



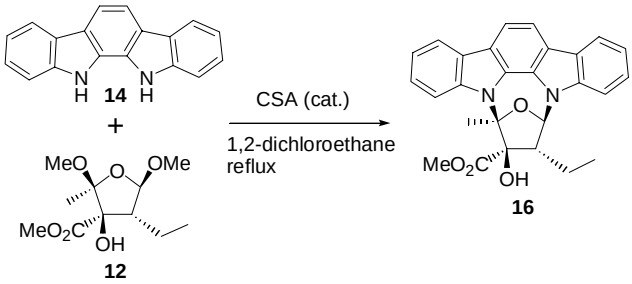
A stirred solution of indolocarbazole **14** (128 mg, 0.500 mmol) and camphorsulfonic acid (27 mg, 0.12 mmol) in 1,2-dichloroethane (20 mL) was heated at reflux and treated over 16 h with a solution of **7** (400 mg, 1.71 mmol) in 1,2-dichloroethane (5.0 mL). After an additional 24 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (8 mL), and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (3:1 hexanes/EtOAc eluent) provided alcohol **15** (188 mg, 89% yield). Crystals suitable for X-ray analysis were obtained by recrystallization from pentane/EtOAc: **15**: mp 229-231°C; IR (thin film/NaCl) 3497 (s), 3049 (s), 2955 (s), 1727 (s), 1639 (s), 1569 (s), 1457 (s), 1440 (s), 1393 (s), 1312 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 7.98 (s, 2H), 7.72 (d, *J*=10.9 Hz, 1H), 7.53-7.45 (m, 2H), 7.41 (app t, *J*=9.2 Hz, 1H), 7.33-7.27 (m, 2H), 6.43 (d, *J*=8.0 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 1H), 2.82 (app q, *J*=7.5 Hz, 1H), 2.19 (s, 3H), 1.21 (d, *J*=8.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.5, 137.4, 126.9, 126.3, 124.9, 124.9, 124.7, 121.0, 120.8, 120.1, 119.8, 119.5, 113.5, 112.5, 112.2, 107.6, 98.2, 90.3, 88.3, 53.5, 48.0, 22.2,10.9; HRMS (FAB) *m/z* 426.1571 [calc'd for $C_{26}H_{22}N_2O_4$ (M) 426.1566].

Preparation of acetate 19.



To a stirred suspension of indolocarbazole **14** (157 mg, 0.613 mmol) and acetate **13** (376 mg, 1.23 mmol) in 1,2-dichloroethane (20 mL) was added camphorsulfonic acid (14.2 mg, 0.0611 mmol). After heating at reflux for 36 h, the reaction mixture was allowed to cool to room temperature, and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 7 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (3:1 then 2:1 hexanes/EtOAc eluent) provided acetate **19** (252 mg, 83% yield) as a pale yellow powder: IR (thin film/NaCl) 3479 (br m), 3051 (m), 3003 (m), 2955 (m), 1732 (s), 1639 (m), 1569 (m), 1458 (m), 1440 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21-8.14 (m, 2H), 8.03-7.95 (m, 2H), 7.73 (d, *J*=8.2 Hz, 1H), 7.54-7.47 (m, 3H), 7.30 (app t, *J*=7.3 Hz, 2H), 6.50 (d, *J*=6.2 Hz, 1H), 4.13 (s, 3H), 4.01 (m, 1H), 3.92 (s, 1H), 3.71 (m, 1H), 2.88 (m, 1H), 2.18 (s, 3H), 2.13 (m, 1H), 2.03 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.4, 139.5, 137.0, 126.8, 126.3, 125.0, 124.8, 124.7, 124.7, 121.1, 120.9, 120.8, 120.2, 120.0, 119.7, 113.5, 112.6, 112.4, 107.7, 98.5, 89.4, 87.7, 61.9, 53.7, 50.7, 26.8, 22.2, 20.4; HRMS (FAB) *m/z* 498.1791 [calc'd for $C_{29}H_{26}N_2O_6$ (M) 498.1791].

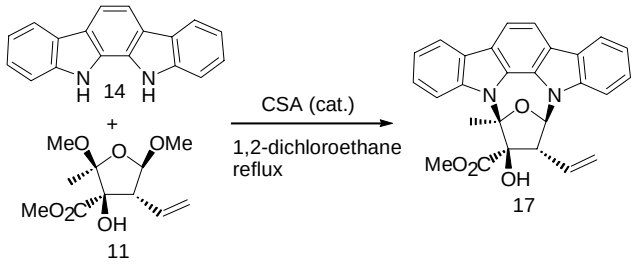
Preparation of alcohol 16.



The procedure for providing acetate **19** was followed using indolocarbazole **14** (103 mg, 0.402 mmol) and alcohol **12** (200 mg, 0.806 mmol) to afford alcohol **16** (167 mg, 94% yield) as a

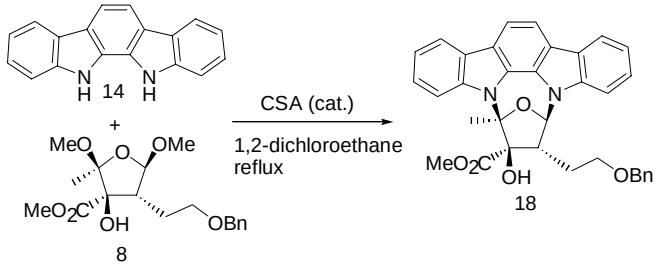
white solid. Crystals of **16** suitable for X-ray analysis were obtained by recrystallization from pentane/EtOAc: m.p. 230-231°C; IR (thin film/NaCl) 3495 (s), 3048 (m), 2966 (m), 1727 (s), 1639 (m), 1569 (m), 1458 (s), 1440 (s), 1387 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22-8.17 (m, 2H), 8.04-7.98 (m, 2H), 7.72 (d, *J*=8.4 Hz, 1H), 7.53-7.45 (m, 2H), 7.42 (app t, *J*=8.3 Hz, 1H), 7.35-7.27 (m, 2H), 6.45 (d, *J*=6.0 Hz, 1H), 4.12 (s, 3H), 3.89 (s, 1H), 2.72 (app q, *J*=7.5 Hz, 1H), 2.17 (s, 3H), 1.82-1.69 (m, 2H), 0.78 (t, *J*=7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 139.5, 136.8, 126.9, 126.3, 124.9, 124.8, 124.7, 124.7, 121.0, 120.8, 120.8, 120.1, 119.8, 119.4, 113.6, 112.5, 112.2, 108.0, 98.3, 89.9, 88.1, 54.7, 53.6, 22.1, 20.9, 12.4; HRMS (FAB) *m/z* 440.1734 [calc'd for $C_{27}H_{24}N_2O_4$ (M) 440.1736].

Preparation of benzyl olefin 17.



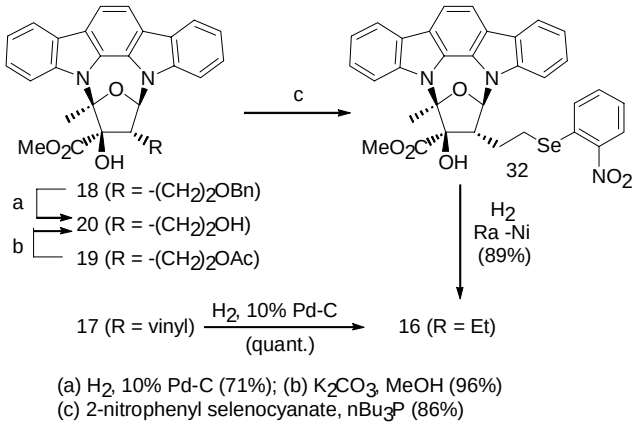
The procedure for providing acetate **19** was followed using indolocarbazole **14** (20.0 mg, 0.0781 mmol) and olefin **11** (38.8 mg, 0.158 mmol) to afford olefin **17** (18.7 mg, 55% yield) as a pale yellow powder: IR (thin film/NaCl) 3488 (m), 3048 (m), 2953 (m), 2925 (m), 1730 (s), 1639 (m), 1569 (m), 1458 (s), 1441 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21-8.14 (m, 2H), 8.03-7.97 (m, 2H), 7.73 (d, *J*=8.6 Hz, 1H), 7.50-7.38 (m, 3H), 7.35-7.25 (m, 2H), 6.68 (d, *J*=5.5 Hz, 1H), 5.96 (ddd, *J*=8.0, 10.4, 16.8 Hz, 1H), 5.21 (app d, *J*=10.4 Hz, 1H), 5.05 (app d, *J*=16.8 Hz, 1H), 4.11 (s, 3H), 3.94 (s, 1H), 3.41 (dd, *J*=5.5, 8.0 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 139.5, 137.3, 130.1, 126.7, 126.3, 124.9, 124.8, 124.7, 122.5, 121.1, 120.9, 120.7, 120.2, 119.9, 119.6, 113.5, 112.6, 112.3, 107.9, 98.2, 88.6, 88.5, 57.6, 53.7, 22.2; HRMS (FAB) *m/z* 438.1578 [calc'd for $C_{27}H_{22}N_2O_4$ (M) 438.1580].

Preparation of benzyl ether 18.

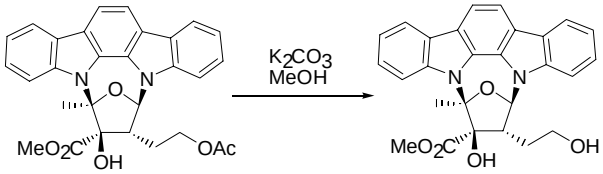


The procedure for providing acetate **19** was followed using indolocarbazole **14** (109 mg, 0.426 mmol) and benzyl ether **8** (302 mg, 0.853 mmol) to afford benzyl ether **18** (105 mg, 45% yield) as a pale yellow powder: IR (thin film/NaCl) 3484 (br m), 3056 (m), 2951 (m), 2867 (m), 1731 (s), 1638 (m), 1569 (m), 1493 (s), 1457 (s), 1440 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J*=4.8 Hz, 1H), 8.16 (d, *J*=4.8 Hz, 1H), 8.04-7.95 (m, 2H), 7.79 (d, *J*=8.6 Hz, 1H), 7.53-7.38 (m, 3H), 7.35-7.21 (m, 5H), 7.12-7.03 (m, 2H), 6.53 (d, *J*=6.1 Hz, 1H), 4.35 (s, 1H), 4.21 (d, *J*=11.8 Hz, 1H), 4.15 (d, *J*=11.8 Hz, 1H), 3.95 (s, 3H), 3.40 (m, 1H), 3.19 (m, 1H), 2.85 (m, 1H), 2.26 (m, 1H), 2.13 (s, 3H), 1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 139.6, 137.3, 136.9, 128.3, 127.8, 127.7, 127.0, 126.2, 124.9, 124.8, 124.7, 121.0, 120.8, 120.7, 120.0, 119.8, 119.5, 113.9, 112.5, 112.3, 107.8, 99.0, 89.9, 87.8, 73.1, 68.5, 53.1, 52.9, 27.7, 22.4; HRMS (FAB) *m/z* 546.2157 [calc'd for $C_{34}H_{30}N_2O_5$ (M) (FAB) 546.2155].

Chemical correlation of 16 - 20.

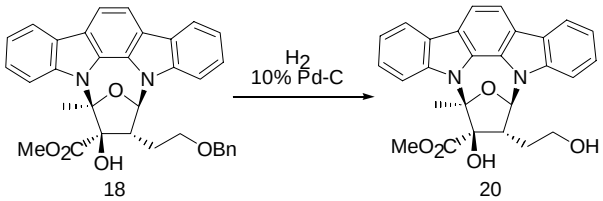


Preparation of alcohol 20.



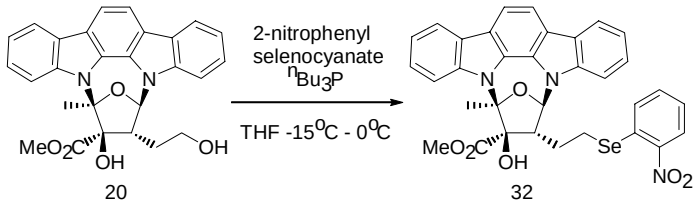
A solution of acetate **19** (248 mg, 0.498 mmol) in MeOH (13 mL) was treated with K_2CO_3 (103 mg, 0.745 mmol) at 25 °C. After 40 min stirring, the mixture was concentrated under reduced pressure to half of the original volume. The mixture was poured into EtOAc (30 mL) and washed with H_2O (20 mL) then the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with H_2O (20 mL), brine (30 mL), dried over Na_2SO_4, and evaporated to a residue. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) afforded alcohol **20** (217 mg, 96% yield) as a white powder: IR (thin film/NaCl) 3476 (br m), 3049 (m), 2952 (m), 1730 (s), 1638 (m), 1569 (m), 1492 (m), 1458 (s), 1440 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18-8.11 (m, 2H), 8.01-7.93 (m, 2H), 7.77 (d, *J*=8.7 Hz, 1H), 7.53-7.36 (m, 3H), 7.32-7.23 (m, 2H), 6.53 (d, *J*=6.2 Hz, 1H), 4.58 (s, 1H), 4.07 (s, 3H), 3.62 (m, 1H), 3.31 (m, 1H), 2.85 (m, 1H), 2.19 (s, 3H), 2.14 (m, 1H), 1.93 (m, 1H), 1.67 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.5, 137.2, 126.9, 126.2, 124.9, 124.8, 124.7, 124.6, 120.9, 120.7, 120.7, 120.0, 119.8, 119.5, 113.7, 112.5, 112.2, 107.7, 98.9, 89.7, 87.6, 60.5, 53.0, 52.5, 29.6, 22.3; HRMS (FAB) *m/z* 456.1686 [calc'd for $C_{27}H_{24}N_2O_5$ (M) 456.1685].

Preparation of alcohol 20.



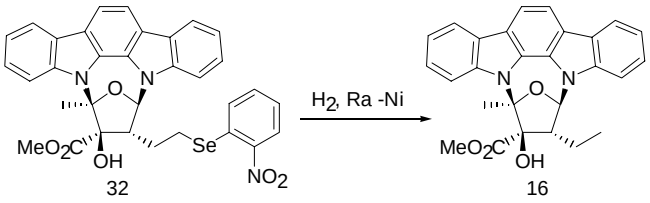
A mixture of benzyl ether **18** (28.1 mg, 0.0515 mmol) and 10% Pd-C (6 mg) in MeOH (2.5 mL) was stirred under H_2 atmosphere. Additional 10% Pd-C (5 mg) was added every 2 days and stirring was continued for 10 days. The mixture was filtered through Celite and the filtrate was evaporated, purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford alcohol **20** (16.7 mg, 71% yield) as a white powder.

Preparation of selenyl compound 32.



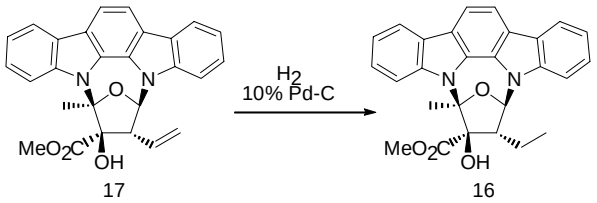
The procedure for providing selenyl compound **10** was followed using **20** (70.8 mg, 0.155 mmol) to afford selenyl compound **32** (85.3 mg, 86% yield) as a yellow solid. Crystals for data analysis were obtained by recrystallization from hexanes/EtOAc: m.p. >235 °C (dec); IR (thin film/NaCl) 3485 (m), 3055 (w), 2953 (w), 1727 (s), 1638 (w), 1590 (m), 1567 (m), 1510 (s), 1457 (m), 1439 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.16 (m, 3H), 8.03 (d, *J*=8.3 Hz, 1H), 7.95 (d, *J*=8.3 Hz, 1H), 7.71 (d, *J*=8.1 Hz, 1H), 7.50-7.38 (m, 3H), 7.36-7.21 (m, 4H), 6.95-6.88 (m, 1H), 6.50 (d, *J*=6.1 Hz, 1H), 4.12 (s, 3H), 3.96 (s, 1H), 2.92 (m, 1H), 2.73 (dt, *J*=11.8, 5.2 Hz, 1H), 2.48 (dt, *J*=11.8, 6.1 Hz, 1H), 2.19 (s, 3H), 2.19-2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 146.4, 139.4, 136.7, 133.6, 132.3, 128.5, 126.8, 126.3, 126.3, 125.4, 125.0, 124.9, 124.7, 121.2, 121.0, 120.9, 120.2, 120.0, 119.7, 113.4, 112.6, 112.5, 107.8, 98.2, 89.1, 87.8, 53.9, 53.9, 26.2, 23.2, 22.1; HRMS (FAB) *m/z* 641.1068 [calc'd for $C_{33}H_{27}N_3O_6{}^{80}Se$ (M) 641.1065].

Preparation of alcohol 16.



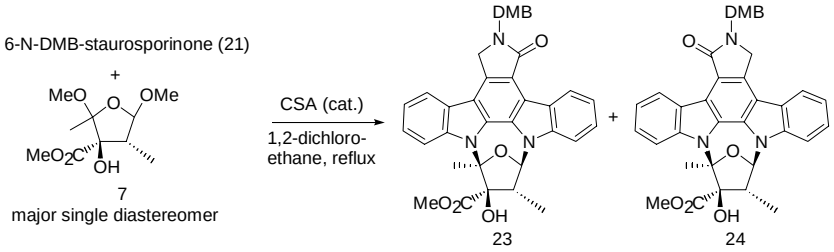
The procedure for providing alcohol **12** was followed using selenyl compond **32** (64.9 mg, 0.101 mmol) to afford alcohol **16** (39.5 mg, 89% yield) as a white solid.

Preparation of alcohol 16.



The procedure for providing alcohol **9** was followed using olefin **17** (7.8 mg, 0.018 mmol) and 10% Pd-C (1.5 mg) to afford alcohol **16** (7.8 mg, quant.) as a white solid.

Preparation of indolocarbazole 23 and 24.



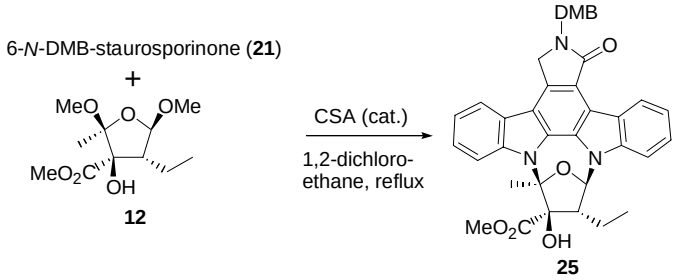
A stirred solution of 6-*N*-DMB-staurosporinone (**21**) (75.0 mg, 0.163 mmol) and camphorsulfonic acid (3.8 mg, 0.0164 mmol) in 1,2-dichloroethane (5.4 mL) was heated at reflux and treated over 24 h with a solution of alcohol **7** (84.0 mg, 0.359 mmol) in 1,2-dichloroethane (3.6 mL) using a syringe pump. After an additional 48 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (8 mL), and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (40:1 (70%CH_2Cl_2/hexanes)/MeOH eluent) followed by preparative TLC (60:1 (70%CH_2Cl_2/hexanes)/MeOH 10 elutions) provided indolocarbazole **23** (40.6 mg, 40% yield) and **24** (9.6 mg, 9.4% yield). Crystals of **23** suitable for X-ray analysis were obtained by recrystallization from acetone-d_6.

23: mp 270-272 °C (dec); IR (thin film/NaCl) 3485 (br m), 3303 (br m), 3052 (m), 2998 (m), 2953 (m), 2835 (m), 1731 (s), 1673 (s), 1649 (s), 1590 (m), 1515 (s), 1459 (s), 1397 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.38 (d, *J*=8.0 Hz, 1H), 7.98 (d, *J*=8.2 Hz, 1H), 7.93 (d, *J*=7.5 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 1H), 7.44 (app t, *J*=7.6 Hz, 1H), 7.41 (app t, *J*=6.7 Hz, 1H), 7.33-7.20 (m, 2H), 7.03 (d, *J*=1.1 Hz, 1H), 6.97-6.84 (m, 2H), 6.74 (d, *J*=6.1 Hz, 1H), 5.44 (s, 1H), 4.94 (d, *J*=17.4 Hz, 1H), 4.89 (d, *J*=17.4 Hz, 1H), 4.82 (d, *J*=14.6 Hz, 1H), 4.72 (d, *J*=14.6 Hz,

1H), 4.04 (s, 3H), 3.75 (s, 3H), 3.75 (s, 3H), 2.87 (m, 1H), 2.18 (s, 3H), 1.31 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.2, 169.7, 150.3, 149.5, 141.0, 138.5, 131.5, 131.1, 129.7, 127.0, 126.4, 125.6, 125.5, 125.3, 123.9, 121.8, 121.1, 120.8, 120.4, 120.2, 117.2, 115.6, 115.5, 112.5, 112.5, 108.6, 100.2, 91.0, 89.4, 55.8, 55.8, 53.0, 50.2, 49.6, 46.2, 22.7, 11.1; HRMS (FAB) *m/z* 632.2398 [calc'd for $C_{37}H_{34}N_3O_7$ (M+H) 632.2397].

24: IR (thin film/NaCl) 3484 (br m), 3322 (br m), 3051 (m), 2954 (m), 2836 (m), 1732 (s), 1673 (s), 1591 (m), 1515 (s), 1455 (s), 1403 (s), 1349 (s) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.70 (d, *J*=7.6 Hz, 1H), 8.01 (d, *J*=7.9 Hz, 1H), 7.94 (d, *J*=8.8 Hz, 1H), 7.87 (d, *J*=8.8 Hz, 1H), 7.51 (app t, *J*=7.5 Hz, 1H), 7.42 (app t, *J*=7.6 Hz, 1H), 7.30 (app t, *J*=7.5 Hz, 1H), 7.29 (app t, *J*=7.3 Hz, 1H), 7.07 (d, *J*=1.8 Hz, 1H), 6.99 (dd, *J*=1.8, 8.1 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 1H), 6.74 (d, *J*=6.2 Hz, 1H), 5.36 (s, 1H), 5.01-4.92 (AB-q, 2H), 4.91-4.83 (AB-q, 2H), 4.04 (s, 3H), 3.77 (s, 6H), 2.85 (m, 1H), 2.19 (s, 3H), 1.29 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.1, 170.0, 150.3, 149.5, 140.8, 138.6, 131.6, 131.6, 127.7, 127.6, 126.9, 126.2, 125.8, 125.8, 123.5, 122.4, 121.0, 120.9, 120.8, 120.3, 118.0, 115.2, 114.9, 112.5, 112.5, 109.3, 100.1, 90.9, 89.6, 55.8, 55.8, 53.0, 49.7, 49.7, 46.3, 22.8, 11.0; HRMS (FAB) *m/z* 631.2319 [calc'd for $C_{37}H_{33}N_3O_7$ (M) 631.2319].

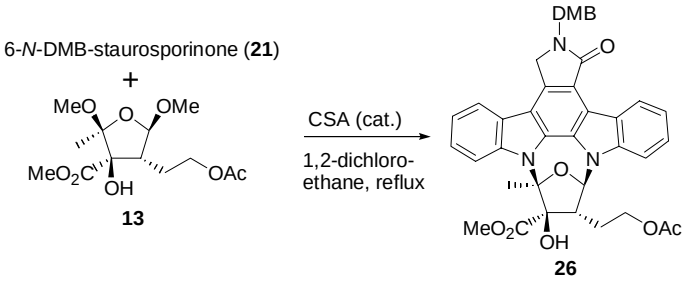
Preparation of indolocarbazole 25.



The procedure for providing indolocarbazole **23**/**24** was followed using **21** (100 mg, 0.217 mmol) and alcohol **12** (119 mg, 0.480 mmol) to afford indolocarbazole **25** (30.4 mg, 22% yield) as a pale yellow powder: IR (thin film/NaCl) 3485 (br m), 3390 (m), 3051 (m), 2960 (m), 2928 (m), 2853 (m), 1731 (s), 1673 (s), 1591 (m), 1514 (s), 1459 (s) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.45 (d, *J*=7.8 Hz, 1H), 7.98 (d, *J*=8.5 Hz, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 7.82 (d, *J*=8.4 Hz, 1H), 7.51 (app t, *J*=8.1 Hz, 1H), 7.41 (app t, *J*=7.4 Hz, 1H), 7.29 (app t, *J*=7.7 Hz, 1H), 7.26 (app t, *J*=7.9 Hz, 1H), 7.06 (d, *J*=1.6 Hz, 1H), 6.97 (dd, *J*=1.6, 8.3 Hz, 1H), 6.91 (d,

J=8.3 Hz, 1H), 6.78 (d, *J*=6.0 Hz, 1H), 5.37 (s, 1H), 4.97-4.93 (AB-q, 2H), 4.85 (br s, 2H), 4.04 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.69 (m, 1H), 2.17 (s, 3H), 1.89-1.62 (m, 2H), 0.77 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.3, 169.8, 150.3, 149.5, 141.0, 137.9, 131.6, 131.1, 129.7, 127.2, 126.2, 125.6, 125.5, 125.3, 124.1, 121.8, 121.1, 120.8, 120.5, 120.2, 117.3, 115.7, 115.6, 112.5, 112.5, 109.1, 100.1, 90.5, 89.3, 56.4, 55.9, 55.8, 53.1, 50.2, 46.3, 22.5, 21.1, 12.8; HRMS (FAB) *m/z* 646.2552 [calc'd for $C_{38}H_{36}N_3O_3$ (M+H) 646.2553].

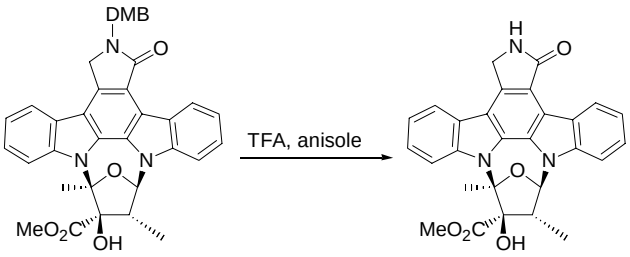
Preparation of indolocarbazole 26.



A stirred solution of 6-*N*-DMB-staurosporinone (**21**) (73.0 mg, 0.158 mmol) and camphorsulfonic acid (3.7 mg, 0.016 mmol) in 1,2-dichloroethane (5.3 mL) was heated at reflux and treated over 24 h with a solution of acetate **13** (169 mg, 0.552 mmol) in 1,2-dichloroethane (5.5 mL) by using syringe pump. After an additional 65 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (8 mL), and washed with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (50:1 (70%CH_2Cl_2/hexanes)/ MeOH eluent) followed by preparative TLC (40:1 (70%CH_2Cl_2/hexanes)/MeOH 8 elutions) provided indolocarbazole **26** (20.8 mg, 19% yield): IR (thin film/NaCl) 3475 (br m), 3052 (m), 2999 (m), 2954 (m), 2836 (m), 1738 (s), 1674 (s), 1652 (s), 1591 (m), 1515 (s), 1459 (s), 1396 (m) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.46 (d, *J*=7.5 Hz, 1H), 8.02-7.96 (m, 2H), 7.86 (d, *J*=8.6 Hz, 1H), 7.51 (app t, *J*=7.7 Hz, 1H), 7.43 (app t, *J*=7.8 Hz, 1H), 7.31 (app t, *J*=7.4 Hz, 1H), 7.30 (app t, *J*=7.2 Hz, 1H), 7.09 (d, *J*=1.8 Hz, 1H), 7.00 (dd, *J*=2.0, 8.2 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 6.81 (d, *J*=5.9 Hz, 1H), 5.39 (s, 1H), 5.11-4.93 (AB-q, 2H), 4.90 (br s, 2H), 4.07 (s, 3H), 3.98 (m, 1H), 3.83 (m, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 2.95 (m, 1H), 2.23-2.12 (m, 2H), 2.18 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.5, 169.6, 149.3, 148.4, 140.0, 137.2, 130.1, 130.1, 128.9, 126.6, 125.9, 125.2, 124.8,

124.5, 123.3, 121.1, 120.8, 120.2, 120.1, 119.7, 117.1, 114.9, 114.4, 111.0, 110.9, 107.1, 99.1, 89.5, 88.0, 61.8, 55.9, 55.8, 53.7, 51.0, 49.6, 46.0, 27.1, 22.5, 20.5; HRMS (FAB) *m/z* 704.2614 [calc'd for $C_{40}H_{38}N_3O_9$ (M+H) 704.2608].

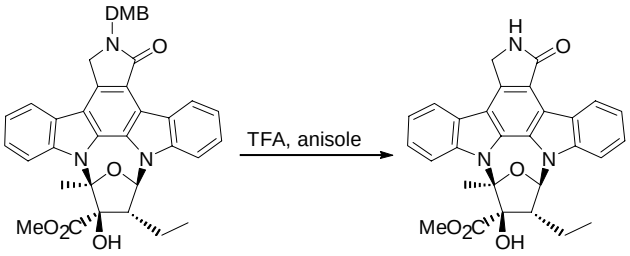
Preparation of C2'-methyl-K252a (29).



23 **29**

To a stirred solution of indolocarbazole **23** (23.9 mg, 0.0379 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C was added anisole (0.206 mL, 1.90 mmol) followed by 2,2,2-trifluoroacetic acid (2.0 mL). After 7.5 h stirring, the reaction mixture was cooled in ice bath, diluted with CH_2Cl_2 (15 mL), and saturated aqueous $NaHCO_3$ (15 mL) was added carefully. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Purification by preparative TLC (60:1 (70%CH_2Cl_2/hexanes)/MeOH 10 elutions) afforded C2'-methyl-K252a (**29**) (11.6 mg, 64% yield) as a pale yellow powder: IR (thin film/NaCl) 3399 (br m), 2957 (m), 2929 (m), 2880 (w), 1734 (s), 1670 (s), 1588 (w), 1458 (s), 1395 (m) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.38 (d, *J*=8.6 Hz, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 8.01 (d, *J*=8.9 Hz, 1H), 7.81 (d, *J*=8.3 Hz, 1H), 7.61 (br s, 1H), 7.49 (app t, *J*=7.8 Hz, 1H), 7.45 (app t, *J*=7.8 Hz, 1H), 7.34 (app t, *J*=7.6 Hz, 1H), 7.28 (app t, *J*=7.5 Hz, 1H), 6.75 (d, *J*=5.8 Hz, 1H), 5.41 (s, 1H), 5.10 (br s, 2H), 4.05 (s, 3H), 2.83 (m, 1H), 2.20 (s, 3H), 1.29 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.7, 172.2, 140.9, 138.5, 133.9, 133.9, 129.9, 127.1, 126.3, 125.6, 125.5, 124.1, 121.9, 121.2, 120.6, 120.2, 117.3, 115.8, 115.6, 108.6, 100.2, 91.0, 89.3, 53.0, 49.6, 46.3, 22.7, 11.0; HRMS (FAB) *m/z* 482.1717 [calc'd for $C_{28}H_{24}N_3O_5$ (M+H) 482.1716].

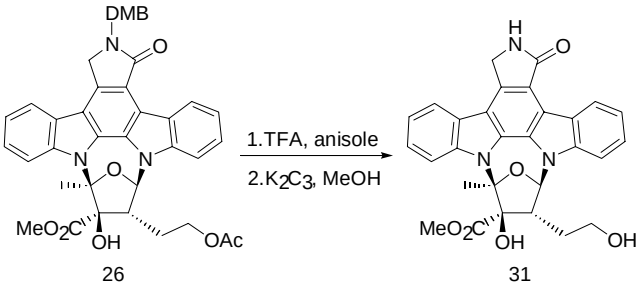
Preparation of C2'-ethyl-K252a (30).



25 30

To a stirred solution of indolocarbazole **25** (25.0 mg, 0.0388 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C was added anisole (0.422 mL, 3.88 mmol) followed by 2,2,2-trifluoroacetic acid (2.0 mL). After 7.5 h stirring, the reaction mixture was cooled in ice bath, diluted with CH_2Cl_2 (15 mL), and saturated aqueous $NaHCO_3$ (15 mL) was added carefully. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. Purification by preparative TLC (60:1 (70%CH_2Cl_2/hexanes)/MeOH 10 elutions) afforded C2'-ethyl-K252a (**30**) (12.1 mg, 63% yield) as a pale yellow powder: IR (KBr pellet) 3426 (br m), 3216 (br m), 3051 (m), 2961 (m), 2927 (m), 2874 (m), 1732 (s), 1668 (s), 1632 (s), 1590 (m), 1458 (m) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.40 (d, *J*=7.5 Hz, 1H), 8.05 (d, *J*=8.0 Hz, 1H), 8.01 (d, *J*=8.4 Hz, 1H), 7.82 (d, *J*=8.1 Hz, 1H), 7.60 (br s, 1H), 7.51 (app t, *J*=7.8 Hz, 1H), 7.45 (app t, *J*=7.2 Hz, 1H), 7.34 (app t, *J*=7.6 Hz, 1H), 7.28 (app t, *J*=7.2 Hz, 1H), 6.78 (d, *J*=6.1 Hz, 1H), 5.34 (s, 1H), 5.10 (br s, 2H), 4.05 (s, 3H), 2.67 (m, 1H), 2.19 (s, 3H), 1.88 (m, 1H), 1.79 (m, 1H), 0.76 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 171.2, 139.9, 136.6, 133.1, 128.7, 125.8, 125.5, 125.1, 124.3, 124.2, 122.6, 121.3, 120.5, 119.6, 119.5, 115.8, 115.2, 114.6, 109.2, 99.6, 89.5, 88.3, 55.7, 52.5, 45.6, 22.2, 20.0, 12.7; HRMS (FAB) *m/z* 496.1874 [calc'd for $C_{29}H_{26}N_3O_5$ (M+H) 496.1872].

Preparation of C2'-(2-hydroxyethyl)-K252a (31).



26 31

To a stirred solution of indolocarbazole **26** (11.4 mg, 0.0162 mmol) in CH_2Cl_2 (0.80 mL) at 25 °C was added anisole (0.176 mL, 1.62 mmol) followed by 2,2,2-trifluoroacetic acid (0.80 mL). After 10 h stirring, the reaction mixture was cooled in ice bath, diluted with CH_2Cl_2 (10 mL), and saturated aqueous $NaHCO_3$ (10 mL) was added carefully. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to afford a slightly brown solid. The solid was dissolved in MeOH (2.0 mL) and CH_2Cl_2 (1.0 mL) followed by treatment with K_2CO_3 (3.5 mg, 0.0253 mmol, 1.6 eq) at 25 °C. After 3 h stirring, the mixture was poured into brine (5.0 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over Na_2SO_4, evaporated and purified by preparative TLC (20:1 (70%CH_2Cl_2/hexanes)/MeOH 5 elutions) to provide C2'-(2-hydroxyethyl)-K252a (**31**) (5.1 mg, 62% yield in 2 steps): IR (KBr pellet) 3322 (br m), 3051 (m), 2951 (m), 2869 (m), 1731 (m), 1661 (m), 1590 (m), 1460 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.20 (d, *J*=7.8 Hz, 1H), 8.64 (s, 1H), 8.04 (d, *J*=7.7 Hz, 1H), 7.97 (d, *J*=8.5 Hz, 1H), 7.93 (d, *J*=8.4 Hz, 1H), 7.48 (app t, *J*=8.5 Hz, 1H), 7.46 (app t, *J*=8.6 Hz, 1H), 7.35 (app t, *J*=7.4 Hz, 1H), 7.27 (app t, *J*=7.5 Hz, 1H), 6.82 (d, *J*=5.8 Hz, 1H), 6.37 (s, 1H), 5.05-4.95 (AB-q, 2H), 4.34 (m, 1H), 3.94 (s, 3H), 3.28 (m, 1H), 2.99 (m, 1H), 2.64 (m, 1H), 2.09 (s, 3H), 1.89 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 171.3, 139.9, 136.9, 133.1, 128.7, 125.8, 125.5, 125.1, 124.3, 124.2, 122.6, 121.3, 120.5, 119.7, 119.5, 115.9, 115.2, 114.6, 109.1, 99.4, 89.4, 88.3, 58.9, 52.6, 50.9, 45.6, 30.4, 22.3; HRMS (FAB) *m/z* 512.1828 [calc'd for $C_{29}H_{26}N_3O_6$ (M+H) 512.1822].

***In vitro* Kinase Assay**

To determine the IC_{50} of K252a and its derivatives for PAK and a few other kinases, the assay was conducted at 25°C in the presence of 100 uM peptide substrate(s) and 10 uM ATP, and at

various concentrations of each test compound. PAK assay was performed, using the GST-PAK3 fusion protein purified from E. coli which is constitutively activated, and its specific peptide substrate PC9 as previously described[1]. PKA (c-AMP-dependent kinase) assay was carried out, using the purified catalytic subunit of PKA (Sigma Chemicals) and its specific substrate "kemptide" (Sigma Chemicals) as described previously[2,3]. PKC (Ca/phospholipid/TPA-dependent kinase) assay was conducted, using purified rat brain PKC (a gift of Drs. Belinda Michell and Bruce Kemp) and its specific peptide substrate derived from EGF receptor (Sigma Chemicals) in the presence of its activators, i.e., 0.1 mM Ca, 20 ug/ml phophatidylserine (PS) and 10 ng/ml TPA as described previously[4].

References (*In vitro* Kinase Assay)

1. Brzeska, H., Lynch, T., Martin, B., Corigliano-Murphy, A. & Korn, E. D. *J. Biol. Chem.* 265, 16138-16144 (1990).

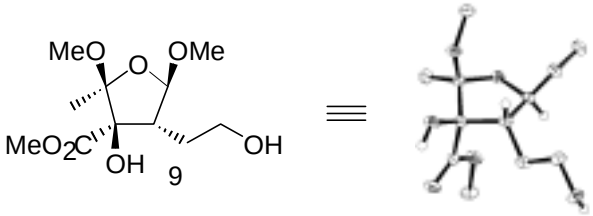
2. a) Maroney, A., Glicksman, M., Basma, A., Walton, K. et al *J. Neurosci.* 18, 104-111 (1998).

b) Kitagawa, M., Okabe, T., Ogino, H. et al *Oncogene* 8, 425-2432 (1993).

3. Kase, H., Iwahashi, K., Nakanishi, S., Matsuda, Y., Yamada, K., Tkahashi, M., Murakata, C., Sato, A. & Kaneko, M. Biochem. *Biophys. Res. Comm.* 142, 436-440 (1987).

4. Castagna, M., Takai, Y., Kaibuchi, K., Sano, K., Kikkawa, U. & Nishizuka, Y. *J. Biol. Chem.* 257, 7847-7851 (1982).

Appendix



X-ray Structure report

Data Collection

A colorless prism crystal of $C_{11}H_{20}O_7$ having approximate dimensions of 0.20 x 0.24 x 0.24 mm was mounted on a glass fiber. All measurements were made on an 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^o in ω, 10s exposure, de-zingered) data frames, corresponded to a primitive triclinic cell with dimensions:

a = 7.1314(2) Å α = 82.269(2)°
b = 8.0930(2) Å β = 78.113(2)°
c = 11.6224(3) Å γ = 73.421(2)
V = 627.05(3) Å^3

For Z = 2 and F.W. = 264.27, the calculated density is 1.40 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 -90 ± 1°C to a maximum 2θ value of 54.9°. Six omega scans consisting of 55, 51, 33, 51, 55 and 55 data frames, respectively, were collected with a scan width of 2.0° and a detector-to-crystal distance, Dx, of 33mm. Each frame was exposed twice (for the purpose of de-zingering) for 40s. 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 5346 reflections which were collected, 2869 were unique (R_{int} = 0.016); equivalent reflections were merged. No decay correction was applied. The linear absorption coefficient, μ, for Mo-Kα radiation is 1.2 cm^{-1} and no absorption correction was applied.

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 refined isotropically. The final cycle of full-matrix least-squares refinement[3] was based on 2064 observed reflections (I > 5.00σ(I)) and 243 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.036$$

$$R_W = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.044$$

The standard deviation of an observation of unit weight[4] was 2.33. 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 θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.23 and -0.28 e$^-$/Å^3, 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.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula $C_{11}H_{20}O_7$

Formula Weight	264.27
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.20 X 0.24 X 0.24 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 7.1314(2)Å b = 8.0930(2) Å c = 11.6224(3) Å α = 82.269(2)° β = 78.113(2)° γ = 73.421(2)° V = 627.05(3) Å^3
Space Group	P_{-1} (#2)
Z value	2
D_{calc}	1.400 g/cm^3
F000	284.00
μ(MoKα)	1.17 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	33 mm
Temperature	-90.0°C
Scan Rate	40s/frame
Scan Width	2°/frame
2θmax	54.9°
No. of Reflections Measured	Total: 5346 Unique: 2869 (R_{int} = 0.016)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

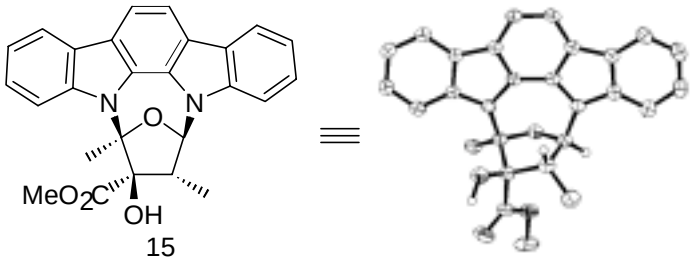
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	1/σ^2(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	2064
No. Variables	243
Reflection/Parameter Ratio	8.49
Residuals: R; Rw	0.036 ; 0.044
Goodness of Fit Indicator	2.33

Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.23 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.28 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.7177(1)	0.1222(1)	0.37658(8)	1.72(2)
O(2)	0.9322(1)	0.3014(1)	0.31919(8)	2.04(2)
O(3)	0.7797(2)	0.1140(1)	0.00198(9)	2.53(3)
O(4)	0.6795(2)	-0.0223(1)	0.17492(9)	2.34(2)
O(5)	0.8763(1)	0.3434(1)	0.10272(10)	2.26(2)
O(6)	0.0758(1)	0.5774(1)	0.14022(10)	2.41(2)
O(7)	0.4505(1)	0.3521(1)	0.44663(8)	2.01(2)
C(1)	0.8719(2)	0.1614(2)	0.2888(1)	1.71(3)
C(2)	0.7714(2)	0.2376(2)	0.1801(1)	1.68(3)
C(3)	0.5646(2)	0.3400(2)	0.2403(1)	1.67(3)
C(4)	0.5285(2)	0.2375(2)	0.3587(1)	1.66(3)
C(5)	1.0451(2)	0.0029(2)	0.2719(2)	2.35(4)
C(6)	0.9591(3)	0.2880(3)	0.4391(1)	2.47(4)
C(7)	0.7486(2)	0.1022(2)	0.1076(1)	1.75(3)
C(8)	0.6490(3)	-0.1544(2)	0.1133(2)	2.50(4)
C(9)	0.3978(2)	0.3817(2)	0.1676(1)	2.00(3)
C(10)	0.2335(2)	0.5398(2)	0.2057(1)	2.07(3)
C(11)	0.4067(3)	0.2699(2)	0.5619(1)	2.41(4)
H(1)	0.583(2)	0.449(2)	0.257(1)	1.6(3)
H(2)	0.437(2)	0.162(2)	0.362(1)	1.2(3)
H(3)	1.003(2)	-0.095(2)	0.260(1)	2.9(4)
H(4)	1.139(2)	0.029(2)	0.205(2)	3.4(4)
H(5)	1.115(2)	-0.026(2)	0.342(1)	3.1(4)
H(6)	1.037(2)	0.369(2)	0.442(1)	2.6(3)
H(7)	0.835(3)	0.312(2)	0.490(2)	3.7(4)
H(8)	1.042(3)	0.170(3)	0.461(2)	3.6(4)
H(9)	0.756(3)	-0.180(3)	0.042(2)	4.8(5)
H(10)	0.521(3)	-0.112(3)	0.085(2)	5.0(5)
H(11)	0.643(3)	-0.256(3)	0.170(2)	5.8(5)
H(12)	0.871(4)	0.354(4)	0.027(3)	10.7(9)
H(13)	0.451(2)	0.405(2)	0.087(2)	2.5(3)
H(14)	0.340(2)	0.280(2)	0.176(1)	2.4(3)
H(15)	0.281(2)	0.644(2)	0.194(1)	2.4(3)
H(16)	0.179(2)	0.530(2)	0.295(2)	2.7(3)
H(17)	0.027(5)	0.488(5)	0.146(3)	12(1)
H(18)	0.326(3)	0.363(2)	0.617(2)	4.1(4)
H(19)	0.331(3)	0.184(3)	0.562(2)	3.9(4)
H(20)	0.527(3)	0.208(2)	0.595(2)	4.3(4)

$Beq = 8/3\ \pi^2(U11(aa^*)^2 + U22(bb^*)^2 + U33(cc^*)^2 + 2U12(aa^*bb^*)\cos\gamma + 2U13(aa^*cc^*)\cos\beta + 2U23(bb^*cc^*)\cos\alpha)$



15

X-ray Structure report

Data Collection

A colorless prism crystal of $C_{26}H_{22}N_2O_4$ having approximate dimensions of 0.12 x 0.20 x 0.25 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^o in ω, 10s exposure, de-zingered) data frames, corresponded to a primitive monoclinic cell with dimensions: a = 9.2658(3) Å, b = 20.771(1) Å, β = 93.659(2)^o, c = 10.8824(4) Å, V = 2090.2(1) Å^3. For Z = 4 and F.W. = 426.47, the calculated density is 1.36 g/cm^3. The systematic absences of: h0l: h = 2n+1, 0k0: k = 2n+1; uniquely determine the space group to be:
$P2_1/a$ (#14).

The data were collected at a temperature of -90 ± 1^{o}C to a maximum 2θ value of 55.1^o. Four omega scans consisting of 82, 74, 74 and 82 data frames, respectively, were collected with a scan width of 1.4^o and a detector-to-crystal distance, Dx, of 35mm. Each frame was exposed twice (for the purpose of de-zingering) for 28s. 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 4925 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 refined isotropically. The final cycle of full-matrix least-squares refinement[3] was based on 2850 observed reflections ($I > 3.00\sigma(I)$) and 377 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma\ ||Fo| - |Fc|| / \Sigma\ |Fo| = 0.043$$

$$R_W = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.044$$

The standard deviation of an observation of unit weight[4] was 2.07. The weighting scheme was based on counting statistics and included a factor (p = 0.020) 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 0.25 and -0.19 $e^-/Å^3$, 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.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{26}H_{22}N_2O_4$
Formula Weight	426.47
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.12 X 0.20 X 0.25 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.2658(3)Å b = 20.771(1) Å c = 10.8824(4) Å β = 93.659(2)° V = 2090.2(1) $Å^3$
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.355 g/cm^3
F000	896.00
μ(MoKα)	0.92 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0°C
Scan Type	ω
Scan Rate	28s/frame
Scan Width	1.4°
2θmax	55.1°

No. of Reflections Measured	Total: 4925
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

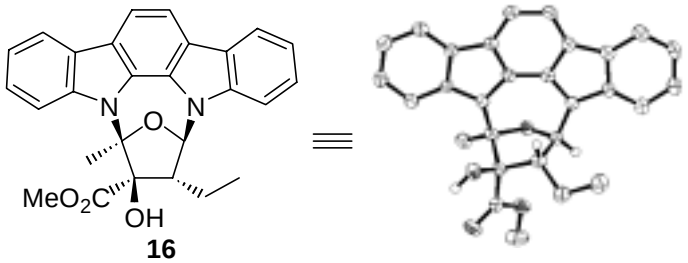
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2850
No. Variables	377
Reflection/Parameter Ratio	7.56
Residuals: R; Rw	0.043 ; 0.044
Goodness of Fit Indicator	2.07
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.19 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	Beq
O(1)	0.8274(1)	0.35796(5)	0.6880(1)	2.68(3)
O(2)	0.8012(2)	0.50039(7)	0.5064(1)	3.54(3)
O(3)	0.5836(2)	0.52924(7)	0.6381(1)	4.88(4)
O(4)	0.6335(1)	0.45231(6)	0.7774(1)	3.54(3)
N(1)	0.8764(2)	0.37325(6)	0.4807(1)	2.54(4)
N(2)	1.0745(2)	0.36424(7)	0.7318(1)	2.75(4)
C(1)	0.8414(2)	0.36510(8)	0.3543(2)	2.55(4)
C(2)	0.7217(2)	0.38491(10)	0.2809(2)	3.35(5)
C(3)	0.7152(2)	0.36926(10)	0.1574(2)	3.77(6)
C(4)	0.8256(2)	0.33505(10)	0.1051(2)	3.63(5)
C(5)	0.9467(2)	0.31730(9)	0.1764(2)	3.01(5)
C(6)	0.9571(2)	0.33305(8)	0.3015(2)	2.42(4)
C(7)	1.0693(2)	0.32342(8)	0.3976(2)	2.41(4)
C(8)	1.0154(2)	0.34849(8)	0.5052(2)	2.36(4)
C(9)	1.2079(2)	0.29531(8)	0.3988(2)	2.60(5)
C(10)	1.2917(2)	0.29093(8)	0.5066(2)	2.79(5)
C(11)	1.2397(2)	0.31500(8)	0.6163(2)	2.66(4)
C(12)	1.1029(2)	0.34451(8)	0.6144(2)	2.51(4)
C(13)	1.2955(2)	0.31643(8)	0.7437(2)	2.75(4)
C(14)	1.4221(2)	0.29366(9)	0.8054(2)	3.23(5)
C(15)	1.4420(3)	0.30189(9)	0.9309(2)	3.70(6)
C(16)	1.3372(2)	0.33255(10)	0.9967(2)	3.81(6)
C(17)	1.2108(2)	0.35607(10)	0.9390(2)	3.37(5)
C(18)	1.1905(2)	0.34725(8)	0.8121(2)	2.77(4)

C(19)	0.9385(2)	0.39499(8)	0.7523(2)	2.72(4)
C(20)	0.9281(2)	0.46358(9)	0.6991(2)	3.06(5)
C(21)	0.7900(2)	0.46224(8)	0.6125(2)	2.80(4)
C(22)	0.7768(2)	0.38953(8)	0.5781(2)	2.63(4)
C(23)	0.9383(3)	0.5157(1)	0.7969(2)	4.28(6)
C(24)	0.6573(2)	0.48494(9)	0.6762(2)	3.23(5)
C(25)	0.5047(3)	0.4701(1)	0.8378(3)	4.97(7)
C(26)	0.6245(2)	0.3657(1)	0.5462(2)	3.17(5)
H(1)	0.644(2)	0.4088(8)	0.313(2)	3.2(4)
H(2)	0.633(2)	0.3814(8)	0.108(2)	3.8(5)
H(3)	0.814(2)	0.3232(9)	0.017(2)	4.2(5)
H(4)	1.026(2)	0.2940(8)	0.142(2)	2.9(4)
H(5)	1.242(2)	0.2791(8)	0.327(1)	2.4(4)
H(6)	1.383(2)	0.2709(8)	0.508(1)	2.7(4)
H(7)	1.498(2)	0.2745(8)	0.759(1)	3.1(4)
H(8)	1.532(2)	0.2853(8)	0.974(2)	4.0(5)
H(9)	1.358(2)	0.3390(8)	1.085(2)	3.6(4)
H(10)	1.137(2)	0.3771(8)	0.981(2)	3.1(4)
H(11)	0.923(2)	0.3914(7)	0.844(2)	2.8(4)
H(12)	1.007(2)	0.4693(7)	0.646(1)	2.7(4)
H(13)	0.853(3)	0.508(1)	0.862(2)	6.2(6)
H(14)	1.036(3)	0.5160(10)	0.830(2)	4.8(5)
H(15)	0.915(2)	0.557(1)	0.759(2)	6.4(6)
H(16)	0.726(2)	0.532(1)	0.516(2)	5.3(5)
H(17)	0.500(3)	0.440(1)	0.903(2)	6.6(6)
H(18)	0.519(3)	0.515(1)	0.867(2)	6.5(6)
H(19)	0.418(3)	0.467(1)	0.776(2)	9.2(9)
H(20)	0.564(2)	0.3988(9)	0.494(2)	4.2(4)
H(21)	0.573(2)	0.3617(8)	0.626(2)	3.7(4)
H(22)	0.627(2)	0.3224(10)	0.505(2)	4.9(5)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$



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X-ray Structure report

Data Collection

A colorless plate crystal of $C_{27}H_{24}N_2O_4$ having approximate dimensions of 0.12 x 0.21 x 0.25 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^o in ω, 10s exposure, de-zingered) data frames, corresponded to a primitive monoclinic cell with dimensions: a = 9.2213(3) Å, b = 21.886(1) Å, β = 92.073(2)^o, c = 10.7661(4) Å, and V = 2171.3(1) Å^3. For Z = 4 and F.W. = 440.50, the calculated density is 1.35 g/cm^3. The systematic absences of: h0l: h = 2n+1, 0k0: k = 2n+1; uniquely determine the space group to be:
$P2_1/a$ (#14).

The data were collected at a temperature of -90 ± 1^{o}C to a maximum 2θ value of 54.9^o. Three omega scans consisting of 69, 64 and 69 data frames, respectively, were collected with a scan width of 1.6^o and a detector-to-crystal distance, Dx, of 33mm. Each frame was exposed twice (for the purpose of de-zingering) for 16s. 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 5088 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. Some hydrogen atoms were refined isotropically, the rest were included in fixed positions. 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 2338 observed reflections (I > 3.00σ(I)) and 302 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.045$$

$$R_W = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.042$$

The standard deviation of an observation of unit weight[4] was 1.75. The weighting scheme was based on counting statistics and included a factor (p = 0.020) 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 0.22 and -0.24 e$^-$/Å^3, 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.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{27}H_{24}N_2O_4$
Formula Weight	440.50
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.12 X 0.21 X 0.25 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.2213(3)Å b = 21.886(1) Å c = 10.7661(4) Å β = 92.073(2)° V = 2171.3(1) Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.347 g/cm^3
F000	928.00
μ(MoKα)	0.91 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	33 mm
Temperature	-90.0°C
Scan Rate	16s/frame
Scan Width	1.6°/frame
2θmax	54.9°
No. of Reflections Measured	Total: 5088
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/σ ^{2}(Fo)
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2338

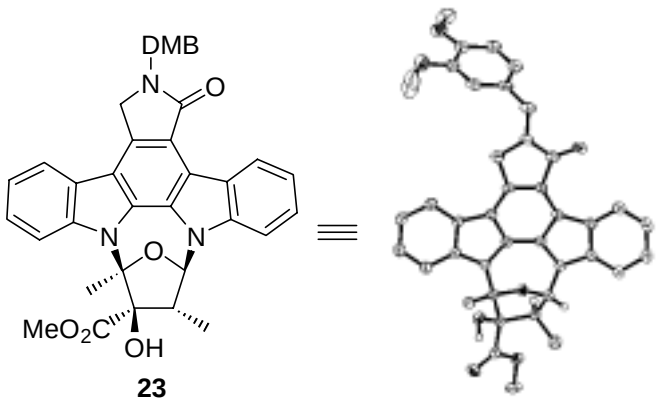
No. Variables	302
Reflection/Parameter Ratio	7.74
Residuals: R; Rw	0.045 ; 0.042
Goodness of Fit Indicator	1.75
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.22 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.24 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	Beq
O(1)	-0.2985(2)	-0.14364(7)	-0.1815(1)	2.17(4)
O(2)	-0.2709(2)	-0.00966(8)	0.0085(2)	2.90(5)
O(3)	-0.0448(2)	0.01271(10)	-0.1306(2)	4.36(5)
O(4)	-0.1191(2)	-0.05212(8)	-0.2798(2)	3.00(4)
N(1)	-0.5467(2)	-0.13898(9)	-0.2169(2)	2.20(5)
N(2)	-0.3439(2)	-0.13238(9)	0.0309(2)	2.03(5)
C(1)	-0.6610(2)	-0.1570(1)	-0.2957(2)	2.20(6)
C(2)	-0.6806(3)	-0.1496(1)	-0.4237(2)	2.62(7)
C(3)	-0.8056(3)	-0.1734(1)	-0.4790(2)	2.97(7)
C(4)	-0.9099(3)	-0.2032(1)	-0.4101(2)	2.92(7)
C(5)	-0.8902(3)	-0.2108(1)	-0.2834(2)	2.64(7)
C(6)	-0.7650(2)	-0.1873(1)	-0.2236(2)	2.21(6)
C(7)	-0.7090(2)	-0.1880(1)	-0.0959(2)	2.13(6)
C(8)	-0.7605(2)	-0.2115(1)	0.0158(2)	2.35(6)
C(9)	-0.6763(2)	-0.2064(1)	0.1230(2)	2.31(6)
C(10)	-0.5384(2)	-0.1786(1)	0.1209(2)	1.97(6)
C(11)	-0.4248(2)	-0.1702(1)	0.2145(2)	1.97(6)
C(12)	-0.4135(3)	-0.1862(1)	0.3393(2)	2.49(6)
C(13)	-0.2880(3)	-0.1722(1)	0.4077(2)	2.86(7)
C(14)	-0.1753(3)	-0.1419(1)	0.3511(2)	2.82(7)
C(15)	-0.1828(3)	-0.1258(1)	0.2273(2)	2.51(6)
C(16)	-0.3078(2)	-0.1413(1)	0.1578(2)	2.03(6)
C(17)	-0.4858(2)	-0.1549(1)	0.0106(2)	1.97(6)
C(18)	-0.5740(2)	-0.1585(1)	-0.0974(2)	1.98(6)
C(19)	-0.4125(2)	-0.1073(1)	-0.2392(2)	2.19(6)
C(20)	-0.4045(2)	-0.0439(1)	-0.1772(2)	2.37(6)
C(21)	-0.2614(2)	-0.0457(1)	-0.0998(2)	2.21(6)
C(22)	-0.2467(2)	-0.1154(1)	-0.0699(2)	2.14(6)
C(23)	-0.4254(3)	0.0100(1)	-0.2662(2)	3.04(7)
C(24)	-0.5752(3)	0.0109(1)	-0.3297(2)	3.68(7)
C(25)	-0.1310(3)	-0.0242(1)	-0.1709(2)	2.66(7)
C(26)	0.0128(3)	-0.0395(1)	-0.3449(3)	4.53(8)
C(27)	-0.0928(2)	-0.1379(1)	-0.0456(2)	2.62(6)
H(1)	-0.6106	-0.1291	-0.4711	3.1482
H(2)	-0.8212	-0.1693	-0.5663	3.5669
H(3)	-0.9955	-0.2184	-0.4511	3.5086

H(4)	-0.9608	-0.2318	-0.2374	3.1636
H(5)	-0.8527	-0.2307	0.0171	2.8213
H(6)	-0.7109	-0.2217	0.1989	2.7764
H(7)	-0.4913	-0.2065	0.3774	2.9838
H(8)	-0.2787	-0.1833	0.4929	3.4364
H(9)	-0.0904	-0.1319	0.3994	3.3830
H(10)	-0.1050	-0.1049	0.1904	3.0072
H(11)	-0.3988	-0.1038	-0.3259	2.6290
H(12)	-0.4808	-0.0420	-0.1202	2.8496
H(13)	-0.3548	0.0074	-0.3281	3.6474
H(14)	-0.4120	0.0469	-0.2206	3.6474
H(15)	-0.5868	-0.0241	-0.3813	4.4196
H(16)	-0.5855	0.0468	-0.3790	4.4196
H(17)	-0.6470	0.0107	-0.2686	4.4196
H(18)	0.0167	0.0028	-0.3649	5.4383
H(19)	0.0134	-0.0629	-0.4192	5.4383
H(20)	0.0947	-0.0500	-0.2933	5.4383
H(21)	-0.179(4)	0.006(2)	0.025(3)	11(1)
H(22)	-0.0408	-0.1092	0.0049	3.1450
H(23)	-0.0949	-0.1762	-0.0042	3.1450
H(24)	-0.0463	-0.1424	-0.1224	3.1450

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$



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DMB = 3,4-dimethoxybenzyl

X-ray Structure report

Data Collection

A pale yellow prism crystal of $C_{37}H_{33}N_3O_7 \cdot C_{1.5}O_{0.5}$ having approximate dimensions of 0.12 x 0.12 x 0.15 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^o in ω, 10s exposure, de-zingered) data frames, corresponded to a

primitive monoclinic cell with dimensions: a = 8.6682(2) Å, b = 22.6193(5) Å, β = 96.219(1)°, c = 17.3278(4) Å, and V = 3377.4(1) Å^3. For Z = 4 and F.W. = 657.70, the calculated density is 1.29 g/cm^3. The systematic absences of: h0l: h+l = 2n+1, 0k0: k = 2n+1; uniquely determine the space group to be: $P2_1/n$ (#14).

The data were collected at a temperature of -90 ± 1°C to a maximum 2θ value of 55.0°. Three omega scans consisting of 69, 69 and 77 data frames, respectively, were collected with a scan width of 1.5° 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 7880 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 refined isotropically. There is one disordered, 50% occupancy acetone solvent molecule in the asymmetric unit. The solvent is present in two overlapping (C38 is the overlapping carbon atom) orientations of 25% occupancy each. The final cycle of full-matrix least-squares refinement[3] was based on 4027 observed reflections ($I > 5.00\sigma(I)$) and 619 variable parameters and converged (largest parameter shift was 0.10 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.048$$

$$R_W = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.059$$

The standard deviation of an observation of unit weight[4] was 2.92. The weighting scheme was based on counting statistics and included a factor (p = 0.025) 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 0.42 and -0.21 e$^-$/Å^3, 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.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula $C_{37}H_{33}N_3O_7 \cdot C_{1.5}O_{0.5}$

Formula Weight	657.70
Crystal Color, Habit	pale yellow, prism
Crystal Dimensions	0.12 X 0.12 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.6682(2)Å b = 22.6193(5) Å c = 17.3278(4) Å β = 96.219(1)° V = 3377.4(1) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
Dcalc	1.293 g/cm^3
F000	1380.00
μ(MoKα)	0.91 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0°C
Scan Rate	60s/frame
Scan Width	1.5°/frame
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 7880
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)
p-factor	0.0250
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	4027
No. Variables	619
Reflection/Parameter Ratio	6.51
Residuals: R; Rw	0.048 ; 0.059
Goodness of Fit Indicator	2.92
Max Shift/Error in Final Cycle	0.10
Maximum peak in Final Diff. Map	0.42 e$^-$/Å^3

Minimum peak in Final Diff. Map -0.21 $e^-/Å^3$

Table 1. Atomic coordinates and Biso/Beq

atom	x	y	z	Beq
O(1)	0.3063(2)	0.34711(8)	0.16700(9)	3.13(5)
O(2)	-0.2276(2)	0.10552(9)	-0.0710(1)	3.98(5)
O(3)	-0.2825(3)	0.09911(10)	0.0722(1)	5.16(6)
O(4)	0.9200(2)	0.16184(7)	0.34442(9)	2.32(4)
O(5)	0.7485(2)	0.12267(7)	0.5134(1)	2.78(4)
O(6)	1.0317(2)	0.07579(8)	0.5574(1)	3.53(5)
O(7)	1.1453(2)	0.13565(8)	0.4775(1)	3.05(4)
O(8)	0.278(3)	0.0607(7)	0.1120(7)	9.9(5)
O(9)	0.142(2)	0.0681(5)	0.1098(7)	5.4(3)
N(1)	0.6707(2)	0.12604(8)	0.3592(1)	2.13(5)
N(2)	0.8071(3)	0.25391(9)	0.3336(1)	2.54(5)
N(3)	0.1703(3)	0.26060(10)	0.1785(1)	2.93(5)
C(1)	0.5567(3)	0.0812(1)	0.3574(1)	2.22(6)
C(2)	0.5605(4)	0.0262(1)	0.3934(2)	2.79(7)
C(3)	0.4311(3)	-0.0093(1)	0.3805(2)	3.09(7)
C(4)	0.2986(4)	0.0086(1)	0.3336(2)	3.18(7)
C(5)	0.2915(4)	0.0641(1)	0.3006(2)	2.81(7)
C(6)	0.4204(3)	0.1015(1)	0.3133(1)	2.26(6)
C(7)	0.4484(3)	0.1615(1)	0.2907(1)	2.28(6)
C(8)	0.3590(3)	0.2049(1)	0.2491(1)	2.38(6)
C(9)	0.4198(3)	0.2603(1)	0.2358(1)	2.31(6)
C(10)	0.5733(3)	0.2750(1)	0.2652(1)	2.33(6)
C(11)	0.6715(3)	0.3269(1)	0.2660(1)	2.40(6)
C(12)	0.6537(4)	0.3833(1)	0.2333(2)	3.22(7)
C(13)	0.7768(4)	0.4224(1)	0.2457(2)	4.07(8)
C(14)	0.9136(4)	0.4078(1)	0.2907(2)	4.07(8)
C(15)	0.9342(4)	0.3527(1)	0.3240(2)	3.35(8)
C(16)	0.8127(3)	0.3126(1)	0.3100(1)	2.56(6)
C(17)	0.6621(3)	0.2314(1)	0.3077(1)	2.27(6)
C(18)	0.6030(3)	0.1747(1)	0.3201(1)	2.16(6)
C(19)	0.1946(3)	0.2016(1)	0.2130(2)	2.87(7)
C(20)	0.2978(3)	0.2954(1)	0.1907(1)	2.52(6)
C(21)	0.0192(4)	0.2805(1)	0.1410(2)	3.42(7)
C(22)	-0.0524(3)	0.2369(1)	0.0823(1)	3.00(7)
C(23)	-0.0310(4)	0.2418(1)	0.0047(2)	3.47(8)
C(24)	-0.0900(4)	0.1987(1)	-0.0485(2)	3.62(8)
C(25)	-0.1708(3)	0.1508(1)	-0.0245(1)	3.15(7)
C(26)	-0.1979(3)	0.1472(1)	0.0540(2)	3.27(7)
C(27)	-0.1403(3)	0.1896(1)	0.1055(2)	3.27(7)
C(28)	-0.1715(5)	0.1014(2)	-0.1463(2)	5.0(1)
C(29)	-0.300(1)	0.0921(3)	0.1528(3)	11.6(2)
C(30)	0.9202(3)	0.2188(1)	0.3804(1)	2.34(6)

C(31)	0.8807(3)	0.2095(1)	0.4639(1)	2.28(6)
C(32)	0.8717(3)	0.1416(1)	0.4727(1)	2.20(6)
C(33)	0.8387(3)	0.1205(1)	0.3867(1)	2.15(6)
C(34)	0.9867(4)	0.2440(1)	0.5238(2)	3.40(8)
C(35)	1.0233(3)	0.1137(1)	0.5084(1)	2.48(6)
C(36)	1.2949(4)	0.1096(2)	0.5048(2)	3.76(8)
C(37)	0.9012(4)	0.0600(1)	0.3695(2)	2.63(7)
C(38)	0.413(2)	0.0183(7)	0.019(1)	7.3(5)
C(39)	0.290(3)	0.0609(7)	0.0540(9)	4.3(4)
C(40)	0.251(1)	0.1003(8)	-0.0009(9)	15.2(5)
C(41)	0.176(3)	0.0607(7)	0.053(1)	4.1(4)
C(42)	0.078(3)	0.0238(8)	0.003(1)	13.1(8)
H(1)	0.650(3)	0.015(1)	0.428(1)	2.5(6)
H(2)	0.430(3)	-0.049(1)	0.406(1)	3.1(6)
H(3)	0.207(3)	-0.018(1)	0.324(1)	2.8(5)
H(4)	0.199(3)	0.079(1)	0.269(1)	2.9(6)
H(5)	0.557(4)	0.394(1)	0.200(2)	4.3(7)
H(6)	0.767(3)	0.462(1)	0.224(1)	3.8(6)
H(7)	1.002(4)	0.436(1)	0.298(2)	5.1(8)
H(8)	1.029(3)	0.344(1)	0.357(2)	3.3(6)
H(9)	0.128(3)	0.193(1)	0.252(2)	3.4(6)
H(10)	0.180(3)	0.170(1)	0.172(1)	2.6(5)
H(11)	-0.056(3)	0.284(1)	0.186(2)	4.4(6)
H(12)	0.037(3)	0.321(1)	0.116(2)	4.7(7)
H(13)	0.027(3)	0.276(1)	-0.013(1)	4.1(7)
H(14)	-0.073(3)	0.201(1)	-0.105(2)	4.1(6)
H(15)	-0.158(3)	0.188(1)	0.160(1)	3.0(6)
H(16)	-0.204(4)	0.060(2)	-0.161(2)	5.6(9)
H(17)	-0.219(4)	0.140(2)	-0.180(2)	6.8(9)
H(18)	-0.046(5)	0.102(1)	-0.141(2)	5.9(8)
H(19)	-0.350(9)	0.120(3)	0.179(5)	17(2)
H(20)	-0.364(6)	0.063(2)	0.151(3)	9(1)
H(21)	-0.16(1)	0.091(4)	0.169(5)	22(2)
H(22)	1.017(3)	0.2362(9)	0.378(1)	1.0(5)
H(23)	0.773(3)	0.2240(9)	0.467(1)	2.0(5)
H(24)	0.972(4)	0.284(1)	0.517(2)	5.1(8)
H(25)	0.964(4)	0.235(1)	0.578(2)	5.1(7)
H(26)	1.102(4)	0.236(1)	0.517(2)	4.6(7)
H(27)	1.387(4)	0.133(1)	0.478(2)	6.5(9)
H(28)	1.303(3)	0.065(1)	0.488(2)	5.5(8)
H(29)	1.310(3)	0.115(1)	0.560(2)	4.5(7)
H(30)	0.865(3)	0.047(1)	0.319(2)	4.0(7)
H(31)	0.873(3)	0.030(1)	0.405(1)	3.0(6)
H(32)	1.018(4)	0.062(1)	0.377(1)	3.5(6)
H(33)	0.780(5)	0.127(2)	0.569(2)	8(1)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

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3. Least-Squares:

Function minimized $Sw(|F_o|-|F_c|)^2$

where $w = 4F_o^2/2(F_o^2)$

and $s^2(F_o^2) = [S^2(C+R^2B) + (pF_o^2)^2]/Lp^2$

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:

$[Sw(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$

where N_o = number of observations and N_v = number of variables

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