

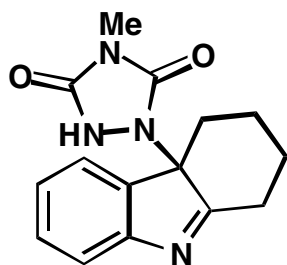
## The First Method for Protection-Deprotection of the Indole 2,3- $\pi$ Bond

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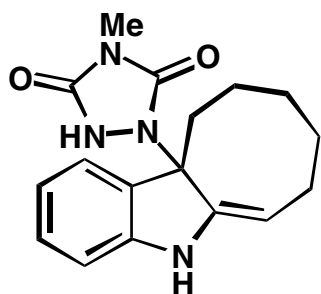
### Supporting Information

**General Techniques.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. 4-Methyl-1,2,4-triazoline-3,5-dione (MTAD) was purchased from Aldrich, Inc. and used without further purification. Dry methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) was obtained by drying over  $\text{CaH}_2$ . Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an acidic mixture of phosphomolybdic acid/cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Mass spectrometric data were collected by the Harvard University Department of Chemistry Mass Spectrometry Facility. ApCI mass spectra were obtained by using a Platform II mass spectrometer (Micromass Inc. (Beverly, MA)). NMR spectra were recorded on Innova-500 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Thermo Nicolet Avatar 360 series FT-IR spectrometer.



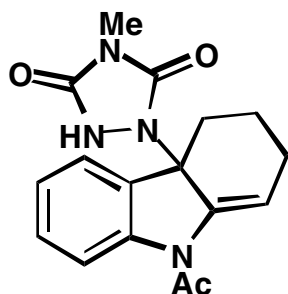
**MTAD adduct 4:** To a solution of 1,2,3,4-tetrahydrocarbazole (86 mg, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added MTAD (57 mg, 0.5 mmol) in one portion. Once the reaction was complete (about one minute according to TLC analysis) the solvent was removed in vacuo and the residue was chromatographed through a short silica gel plug (hexanes/EtOAc 2:1 to 1:2 to 100% EtOAc) to furnish 142 mg (100% yield) of **4** which crystallized upon standing in the column fractions as short white needles. **MTAD adduct 4:** mp, 99-100 (dec, red liquid),  $R_f = 0.55$  (silica gel,  $\text{CH}_2\text{Cl}_2$ :MeOH 5:1); IR (neat)  $\nu_{\text{max}}$  2942, 1773,

1696, 1595, 1474, 1398, 1286, 1019, 911, 730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (bs, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.58 (d,  $J = 8.0$  Hz, 1 H), 7.46 (d,  $J = 7.5$  Hz, 1 H), 7.39 (t,  $J = 8.0$  Hz, 1 H), 7.17 (t,  $J = 7.5$  Hz, 1 H), 3.04 (dd,  $J = 15.0, 2.0$  Hz, 2 H), 2.96 (s, 3 H) 2.82 – 2.73 (m, 1 H), 2.30 – 2.22 (m, 1 H), 1.95 – 1.83 (m, 1 H), 1.82 – 1.75 (m, 1 H), 1.62 – 1.51 (m, 1 H), 1.34 – 1.24 (m, 1 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 156.1, 155.0, 154.0, 137.3, 129.7, 125.8, 122.0, 120.7, 73.1, 36.9, 30.1, 28.6, 25.1, 20.5; MS (APCI+) 285.0 ( $\text{M} + \text{H}^+$ ).



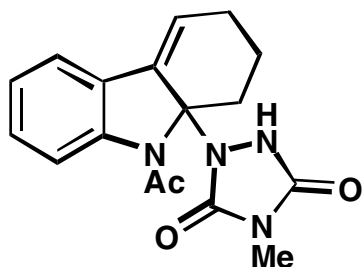
**MTAD adduct 7:** To a solution of indolo(2,3-b)cyclooctene (100 mg, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added MTAD (57 mg, 0.5 mmol). Once the reaction was complete (about 15 minutes according to TLC analysis) the solvent was removed in vacuo and the residue was purified by recrystallization from methanol to furnish 125 mg (80% yield) of **6** as a semi-crystalline white solid. **MTAD adduct 7:**

mp, 189-191 (dec, yellow liquid),  $R_f = 0.84$  (silica gel,  $\text{CH}_2\text{Cl}_2:\text{MeOH}$  5:1); IR (neat)  $\nu_{\text{max}}$  2924, 1683, 1487, 1457, 1238, 996, 781;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  10.52 (s, 1 H,  $\text{D}_2\text{O}$  exchangeable), 10.35 (s, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.44 (d,  $J = 7.5$  Hz, 1 H), 7.30 (d,  $J = 7.5$  Hz, 1 H), 7.03 (t,  $J = 7.5$  Hz, 1 H), 6.94 (t,  $J = 7.5$  Hz, 1 H), 5.33 (dd,  $J = 12.5, 3.5$  Hz, 1 H), 3.10 – 3.00 (m, 1 H), 2.91 (s, 3 H), 2.85 – 2.78 (m, 1 H), 2.47 – 2.35 (m, 1 H), 1.90 – 1.80 (m, 1 H), 1.68 – 1.54 (m, 3 H), 1.48 – 1.29 (m, 3 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  155.0, 154.5, 136.5, 132.3, 128.3, 121.7, 119.0, 118.3, 112.5, 112.0, 54.4, 31.3, 29.4, 25.4, 25.3, 25.0, 22.3; MS (APCI-) 311.0 ( $\text{M} - \text{H}^+$ ).



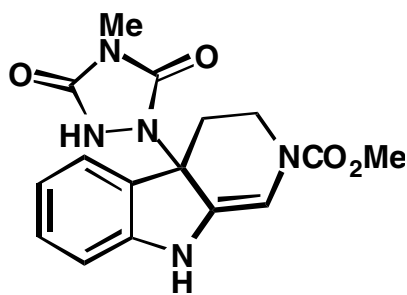
**MTAD adduct 9:** To a solution of *N*-acetyl-1,2,3,4-tetrahydrocarbazole (21.3 mg, 0.1 mmol) in  $\text{CH}_2\text{Cl}_2$  at 0 °C was added MTAD (14.8 mg, 0.13 mmol). The reaction mixture was allowed to warm to room temperature; all starting material was consumed after 4 h. The solvent was then removed in vacuo and the residue was passed through a short silica gel plug using EtOAc to furnish 27.3 mg (84% yield) of **9** as a white powder. **MTAD adduct 9:**  $R_f = 0.25$  (silica gel, EtOAc); IR (neat)  $\nu_{\text{max}}$  2944, 1763, 1683, 1609, 1475, 1455, 1397, 1300, 1223, 1026, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (d,  $J = 8.5$  Hz, 1 H), 7.51 (d,  $J = 7.5$  Hz, 1 H), 7.32 (t,  $J = 8.5$  Hz, 1 H), 7.25 (t,  $J = 7.5$  Hz, 1 H), 6.87

(bs, 1 H, D<sub>2</sub>O exchangeable), 5.55 (t,  $J = 5.0$  Hz, 1 H), 3.12 (s, 3 H), 3.09 – 3.01 (m, 1 H), 3.00 – 2.93 (m, 1 H), 2.59 (s, 3 H), 2.19 – 2.09 (m, 2 H), 2.02 – 1.95 (m, 1 H), 1.94 – 1.85 (m, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.0, 154.8, 154.3, 139.9, 135.8, 127.8, 124.7, 123.9, 118.6, 115.5, 113.2, 50.8, 27.1, 26.0, 25.7, 25.3, 21.1; MS (APCI<sup>-</sup>) 324.9 (M – H<sup>+</sup>).



**Procedure using BF<sub>3</sub>-OEt<sub>2</sub> :** To a solution of *N*-acetyl-1,2,3,4-tetrahydrocarbazole (21.3 mg, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added BF<sub>3</sub>-OEt<sub>2</sub> (0.013 mL, 0.02 mmol) followed by MTAD (14.8 mg, 0.13 mmol). The reaction was instantly complete. The solvent was then removed in vacuo and the residue was passed through a

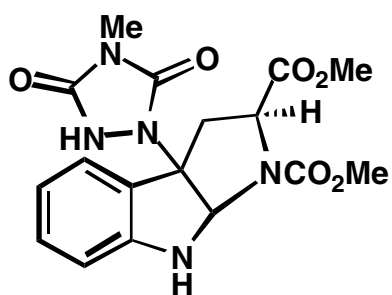
short silica gel plug using EtOAc to furnish 25.0 mg (75% yield) of the C(2) regioisomer of **9** as a white powder.  $R_f = 0.25$  (silica gel, EtOAc); IR (neat)  $\nu_{\max}$  2942, 1761, 1684, 1477, 1458, 1399, 1347, 1220, 1032, 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (d,  $J = 10.5$  Hz, 1 H), 7.52 (d,  $J = 10.5$  Hz, 1 H), 7.36 (td,  $J = 9.5, 1.5$  Hz, 1 H), 7.28 (td,  $J = 9.5, 1.5$  Hz, 1 H), 5.72 (t,  $J = 4.5$  Hz, 1 H), 2.97 (s, 3 H), 2.88 (ddd,  $J = 21, 6.0, 3.5$  Hz, 1 H), 2.72 (3 H), 2.67 – 2.59 (m, 1 H), 2.29 – 2.23 (m, 1 H), 2.04 – 1.82 (3 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  169.4, 155.1, 154.6, 135.8, 129.9, 129.3, 125.5, 123.5, 123.1, 119.4, 114.5, 52.4, 30.3, 27.2, 25.0, 20.7, 18.1; MS (APCI<sup>-</sup>) 325.0 (M – H<sup>+</sup>).



**MTAD adduct 11:** A solution of indole **10** (115 mg, 0.5 mmol) was prepared by heating to boiling in methanol (5 mL) using a heat gun. MTAD (57 mg, 0.5 mmol) was then added immediately to the warm solution. TLC analysis indicated that starting material remained after 30 minutes so additional MTAD (28 mg, 0.25 mmol) was added to the solution. After one hour,

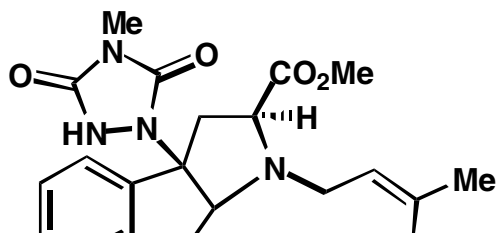
TLC analysis indicated the presence of starting material so additional MTAD was added (28 mg, 0.25 mmol); the reaction went to completion after a total of 2 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1 to 2:1) to furnish 151 mg (88 % yield) of MTAD adduct **11** as a fine white solid. **MTAD adduct 11:**  $R_f = 0.78$  (silica gel, CH<sub>2</sub>Cl<sub>2</sub>:MeOH 5:1); IR (neat)  $\nu_{\max}$  1791, 1684, 1472, 1398,

1737, 1232, 771, 669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, 1:1 mixture of rotomers acetone- $\text{d}_6$ )  $\delta$  10.20 (brs, 1 H), 9.5 – 8.5 (brs, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.59 – 7.38 (m, 2.5 H), 7.25 (t,  $J = 7.5$  Hz, 0.5 H), 7.16 (t,  $J = 7.5$  Hz, 0.5 H), 7.06 (t,  $J = 7.5$  Hz, 0.5 H), 5.22 (brs, 0.5 H), 4.51 (brs, 0.5 H), 4.11 (brs, 1 H), 3.72 (s, 1.5 H), 3.67 (s, 1.5 H), 3.51 (brs, 1 H), 3.11 – 3.05 (m, 1 H), 2.99 (s, 1.5 H), 2.90 – 2.72 (m, 1 H), 2.82 (s, 1.5 H);  $^{13}\text{C}$  NMR (100 MHz, acetone- $\text{d}_6$ )  $\delta$  175.4, 170.3, 155.7, 137.0, 130.1, 126.6, 122.9, 121.5, 119.4, 118.8, 111.9, 59.9, 52.5, 24.1, 20.2, 13.8; MS (APCI+) 343.9 ( $\text{M} + \text{H}^+$ ).



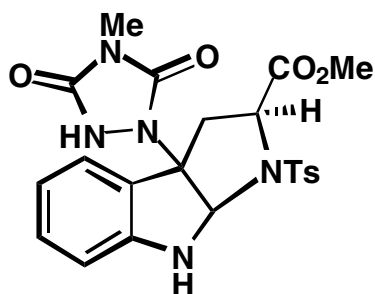
**MTAD adduct 14:** To a solution of *N*-carbomethoxy-*L*-tryptophan methyl ester (498 mg, 1.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (18 mL) at  $0^\circ\text{C}$  was added MTAD (204 mg, 1.80 mmol). Once the reaction was complete (about ten minutes according to TLC analysis) the solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:1 to

1:4) to furnish 433 mg (62%) of MTAD adduct **14** as a 1:1 mixture of diastereomers (stereochemistry not determined). **MTAD adduct 14:** white foam,  $R_f = 0.83$  (silica gel,  $\text{CH}_2\text{Cl}_2$ :MeOH 5:1); IR (neat)  $\nu_{\text{max}}$  2954, 1694, 1609, 1449, 1382, 1315, 1206, 1046, 772, 731  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, spectra complex due to 1:1 mixture of diastereomers and rotomers or each diastereomer, acetone- $\text{d}_6$ )  $\delta$  8.91 (bs, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.28 (d,  $J = 7.0$  Hz, 0.5 H), 7.18 (d,  $J = 8.0$  Hz, 0.5 H), 7.13 (dd,  $J = 15.0, 7.5$  Hz, 0.5 H), 7.08 (d,  $J = 7.0$  Hz, 0.5 H), 6.71 (dd,  $J = 15.0, 8.0$  Hz, 1 H), 6.61 (dd, 15.0, 7.5 Hz, 1 H), 6.31 (s, 0.5 H), 6.15 (s, 0.5 H), 5.99 (s, 0.5 H), 5.94 (s, 0.5 H), 5.84 (s, 0.5 H), 5.81 (s, 0.5 H), 4.71 (d,  $J = 9.0$  Hz, 1 H), 4.23 (t,  $J = 7.5$  Hz, 0.5 H), 4.11 ( $J = 7.5$  Hz, 0.5 H), 3.73 (s, 1.5 H), 3.72 (s, 1.5 H), 3.71 (s, 1.5 H), 3.62 (s, 1.5 H), 3.31 – 3.02 (m, 2 H), 3.18 (s, 1.5 H), 2.93 (s, 1.5 H);  $^{13}\text{C}$  NMR (100 MHz, acetone- $\text{d}_6$ )  $\delta$  172.0, 171.4, 170.8, 156.5, 155.2, 155.0, 154.7, 152.0, 150.6, 131.0, 125.9, 124.7, 124.0, 119.0, 118.3, 110.4, 110.0, 109.8, 80.9, 80.0, 79.5, 76.5, 75.3, 59.9, 59.5, 59.2, 52.4, 51.9, 51.6, 39.0, 38.4, 24.5, 20.2, 13.9; MS (APCI+) 391.0 ( $\text{M} + \text{H}^+$ ).



**MTAD adduct 16:** To a solution of *N*-prenyl-*L*-tryptophan methyl ester (286 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$

(10 mL) at 0 °C was added MTAD (113 mg, 1.0 mmol). Once the reaction was complete (about ten minutes according to TLC analysis) the solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:1 to 1:4) to furnish 319 mg (80%) of MTAD adduct **16** as a 1:1 mixture of diastereomers (stereo-configurations not determined). **MTAD adduct 16**: white foam;  $R_f = 0.61$  (silica gel,  $\text{CH}_2\text{Cl}_2$ :MeOH 5:1); IR (neat)  $\nu_{\text{max}}$  3336, 2949, 1734, 1689, 1457, 1199, 1174, 1010, 912, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, data for both isomers given,  $\text{CDCl}_3$ )  $\delta$  8.24 (bs, 0.5 H,  $\text{D}_2\text{O}$  exchangeable), 8.18 (bs, 0.5 H,  $\text{D}_2\text{O}$  exchangeable), 7.62 (dd,  $J = 8.0, 3.5$  Hz, 1 H), 7.34 (dd,  $J = 8.5, 6.0$  Hz, 1 H), 7.17 (dd,  $J = 16.0, 7.5$  Hz, 0.5 H), 7.10 (td,  $J = 11.0, 7.5, 3.5$  Hz, 0.5 H), 7.06 (d,  $J = 7.0$  Hz, 1 H), 5.00 (t,  $J = 7.5$  Hz, 0.5 H), 4.80 (t,  $J = 7.5$  Hz, 0.5 H), 4.36 (dd,  $J = 8.5, 5.0$  Hz, 0.5 H), 4.23 (dd,  $J = 7.0$  Hz, 5.0 Hz, 0.5 H), 3.76 (s, 1.5 H), 3.68 (s, 1.5 H), 3.31 (dd,  $J = 14.5, 4.0$  Hz, 0.5 H), 3.24 (dd,  $J = 14.5, 4$  Hz, x H), 3.11 (dd,  $J = 14.5, 9.0$  Hz, 1 H), 2.97 (s, 1.5 H), 2.95 (s, 1.5 H), 2.46 (dd,  $J = 11.0, 7.0$  Hz, 0.5 H), 2.36 (dd,  $J = 13.0, 6.5$  Hz, 0.5 H), 1.97 (dd,  $J = 13.5, 7.0$  Hz, 0.5 H), 1.55 (s, 1.5 H), 1.45 (s, 1.5 H), 1.24 (s, 1.5 H), 1.19 (s, 1.5 H);  $^{13}\text{C}$  NMR (100 MHz, data for both isomers given,  $\text{CDCl}_3$ )  $\delta$  174.9, 174.5, 153.8, 153.1, 136.2, 136.1, 127.7, 127.4, 122.8 (2 C), 122.2, 121.9, 119.5 (2 C), 119.3, 119.1, 118.8 (2 C), 111.4, 111.2, 111.0, 110.6, 70.2, 68.7, 61.7, 61.3, 59.2, 58.1, 52.1 (2 C), 49.9, 49.8, 29.6, 29.0, 26.8 (2 C), 25.2, 25.1, 22.8, 22.6; MS (APCI+) 399.9 ( $\text{M} + \text{H}^+$ ).



**MTAD adduct 18**: To a solution of *N*-tosyl-*l*-tryptophan methyl ester (186 mg, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added MTAD (57 mg, 0.5 mmol). The reaction was allowed to warm to room temperature; the starting material was completely consumed after about 1 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1 to 1:1) to furnish 141 mg (58% yield) of **18** as a white foam (2:1 mixture of diastereomers). **MTAD adduct 18**:  $R_f = 0.83$  (silica gel,  $\text{CH}_2\text{Cl}_2$ : MeOH 5:1); IR (neat)  $\nu_{\text{max}}$  1699, 1609, 1472, 1339, 1158, 1037, 909, 728, 668;  $^1\text{H}$  NMR (500 MHz, 2:1 mixture of diastereomers,  $\text{CDCl}_3$ )  $\delta$  8.10 (brs, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.80 (d,  $J = 7.5$  Hz, 0.33 H), 7.74 (d,  $J = 8.5$  Hz, 0.67 H), 7.34 (d,  $J = 8.5$  Hz, 0.33 H), 7.23 (d,  $J = 8.0$  Hz, 0.67 H), 7.19 – 7.14 (m, 4 H) 7.10 (t,  $J = 8.0$ , 1 H), 6.75 (d,  $J = 7.5$  Hz, 1 H), 6.72 (d,  $J = 7.5$  Hz, 1 H), 6.52 (d,  $J = 7.5$

Hz, 1 H), 6.12 (s, 0.67 H), 5.8 (s, 0.33 H), 4.47 (dd,  $J = 9.0, 1.5$  Hz, 0.33 H), 4.14 (t,  $J = 7.0$  Hz, 0.67 H), 3.70 (s, 3 H), 3.31 (dd,  $J = 14.0, 7.0$  Hz, 1 H), 2.97 (s, 2 H), 2.94 (s, 1 H), 2.91 (dd,  $J = 14.0, 7.0$  Hz, 1 H), 2.44 (s, 1 H), 2.37 (s, 2 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  171.7, 155.6, 149.1, 143.9, 137.1, 131.2, 130.3, 129.6, 127.8, 126.1, 123.6, 120.5, 111.1, 82.8, 76.5, 60.7, 53.1, 39.4, 25.5, 21.8; MS (APCI+) 486.0 ( $\text{M} + \text{H}^+$ ).

**Thermolysis Procedure:** Lindberg (Watertown, Wisconsin) tube furnace apparatus, type 55035  
General thermolysis procedure: A 5 mL flask was charged with the MTAD adduct. This was fitted with a 20 cm Pyrex tube (14/20 joints on each end, one of which was connected to a vacuum line). The assembly was horizontally inserted into the preheated tube furnace approximately half way (about 20 cm). The progress of the reaction was monitored visually by the condensation that took place in the Pyrex receiver. Once this process ceased, the assembly was pulled out and allowed to cool. The reaction products could be collected merely by rinsing sections of the tube with an organic solvent. Total process times varied between 5-30 minutes; yields of products are given in Table 1.

**Acid-Catalyzed Conversion of **11** to **10**:** To a solution of MTAD adduct **11** (5 mg, 0.0146 mmol) at 0 °C in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added  $\text{MeSO}_3\text{H}$  (0.0002 mL, 0.0031 mmol). After two hours the ice bath was removed and the reaction allowed to reach room temperature. After a total of 30 hours, solid  $\text{NaHCO}_3$  (10 mg) was added to the reaction mixture and it was allowed to stir for 15 minutes. The solvent was evaporated in vacuo and the crude residue was passed through a  $\text{MgSO}_4$ /silica gel plug using a solution of  $\text{CH}_2\text{Cl}_2$ /MeOH (4:1). The solvent mixture was removed in vacuo and the residue purified by flash column chromatography (silica gel, hexanes:EtOAc 1:1 to 3:1 to 100% EtOAc) to furnish 0.5 mg (of **11**) and 3.9 mg of indole **10** (68% based on recovered starting material), identical with an authentic sample.