N-Methoxy-*N*-Acylnitrenium Ions: Application to the Formal Synthesis of (±)-Desmethylamino FR901483

(Supporting Information)

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Materials and General Procedures: All reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. Methanol (MeOH) was dried from magnesium methoxide, prepared from magnesium turnings and iodine. Benzene (PhH), toluene ($PhCH_3$) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Acetonitrile (MeCN) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride, under nitrogen, immediately prior to use. *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich and dried with freshly activated 4 Å molecular sieves prior to use. Triethylamine was distilled from calcium hydride, under nitrogen, and stored over potassium hydroxide. Triethylsilyl chloride was distilled from calcium hydride, under nitrogen prior to use. Samarium diiodide (SmI_2) was prepared by the method of Imamoto.[i] *p*-Methoxybenzyl bromide was freshly prepared from the corresponding alcohol by the method of Rader.[ii] bis(Trifluoroacetoxy)iodobenzene, tributylstannane (Bu_3SnH), trimethylsilyl iodide (TMSI), *tert*-butyl methyl ether (TBME) and zinc chloride etherate solution ($ZnCl_2 \bullet Et_2O$, 1 M in Et_2O) were purchased from Aldrich and used without further purification. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin-layer chromatography with Merck precoated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light or potassium permanganate solution. Flash column chromatography was performed using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise stated. All melting points were obtained on a Thomas Hoover capillary melting point apparatus or Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson genesis series FTIR

spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz, ^{13}C). Chemical shift values (δ) are reported relative to internal tetramethylsilane (TMS) (δ 0.00 ppm) or chloroform (δ 7.27 ppm) for ^{1}H and chloroform (δ 77.23 ppm) for ^{13}C. High-resolution electron impact (EI) mass spectra were obtained on a Kratos Concept 1H spectrometer at the University of Illinois Research Resources Center with a typical ionization voltage of 70 eV. High-resolution chemical ionization (CI) mass spectra were obtained on a FINNIGAN MAT 95 and high-resolution fast atom bombardment (FAB) spectra were obtained on a VG 7070-HF at the Mass Spectrometry Service Laboratory, University of Minnesota. Elemental analysis was performed by Midwestern Microlab, Indianapolis, IN.

***N*-Methoxy-3-(4-methoxy-phenyl)-propionamide** (**10**): A solution of methoxylamine-hydrochloride (1.02 g, 12.21 mmol), Et_3N (1.74 mL, 12.43 mmol) and DCC (2.40 g, 11.66 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and 3-(4-methoxylphenyl)-propionic acid (**9**) (2.00 g, 11.10 mmol) added. The reaction mixture was stirred for 3 h at 0 °C then 18 h at room temperature before being filtered through Celite 521. The filter cake was washed with EtOAc (100 mL) and the combined filtrates concentrated to provide a residue, which was partitioned between EtOAc (40 mL) and 0.5 M aqueous HCl (40 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 x 40 mL). The combined organic extracts were then washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (MeOH/$CHCl_3$, 1:99 then 6:94) to provide **10** (2.13 g, 92% yield): white solid; mp 72-73 °C (CH_2Cl_2/hexanes, 1:1); R_f 0.37 (EtOAc/hexanes,

1:1); IR (film) 3330-2817, 1641, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (bs, 1H), 7.09 (d, *J* = 8.2 Hz, 2 H), 6.79 (d, *J* = 8.2 Hz, 2 H), 3.75 (s, 3 H), 3.65 (s, 3 H), 2.89 (t, *J* = 7.4 Hz 2 H), 2.35 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 158.2, 132.6 (2 C), 129.5, 114.0 (2 C), 64.3, 55.4, 35.4, 30.7; high-resolution mass spectrum (EI) *m/z* 209.1064 [(M^+); calcd for $C_{11}H_{15}NO_3$ 209.1052].

1-Methoxy-1-aza-spiro[4.5]deca-6,9-diene-2,8-dione (**7**): To a solution of **10** (2.90 g, 13.86 mmol) in anhydrous methanol (60 mL) at 0 °C was rapidly added a solution of bis(trifluoroacetoxy)iodobenzene (8.94 g, 20.79 mmol) in CH_2Cl_2 (60 mL). The resulting mixture was stirred for 15 sec, then water (15 mL) was added and the biphasic mixture stirred for 5 min before saturated aqueous $NaHCO_3$ (45 mL) was added. The reaction mixture was then poured into and extracted with CH_2Cl_2 (10 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash chromatography over silica gel (MeOH/CH_2Cl_2, 2:98) to afford **7** (1.93 g, 72% yield): white; mp 127-128 °C (MTBE); R_f 0.30 (EtOAc); IR (film) 3045, 1726, 1706, 1673, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10.0 Hz, 2 H), 6.31 (d, *J* = 10.0 Hz, 2 H), 3.72 (s, 3 H), 2.49 (t, *J* = 7.7 Hz, 2 H), 2.13 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 171.8, 147.4 (2 C), 131.1 (2 C), 65.3, 62.0, 27.5, 26.0; high-resolution mass spectrum (EI) *m/z* 193.0732 [(M^+); calcd for $C_{10}H_{11}NO_3$ 193.0739].

1,4-Dioxa-9-aza-dispiro[4.2.4.2]tetradecan-10-one (11): To a solution of **7** (5.87 g, 30.38 mmol) in EtOAc (300 mL) was added 10% Pd/C (250 mg). The resulting mixture was then placed under an atmosphere of H_2 (1 atm) and stirred at room temperature for 20 h. After flushing with N_2, the reaction mixture was filtered through a pad of Celite

521 and the filter cake washed with EtOAc (3 × 25 mL). The combined filtrates were then concentrated under reduced pressure and the resulting residue used in the following procedure without further purification:

A mixture of the above ketone, ethylene glycol (6.55 g, 105.53 mmol), pyridinium *p*-toluenesulfonate (PPTS) (660 mg, 2.63 mmol) and benzene (60 mL) were placed in a Dean-Stark apparatus and heated at reflux for 3.5 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, and the aqueous wash extracted with EtOAc (5 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure. The resulting residue was submitted to the following procedure without further purification:

A solution of the above acetal in THF (10 mL) was added slowly to a mixture of Na (1.62 g, 70.43 mmol) in freshly distilled ammonia (60 mL) cooled to -78 °C in a flask fitted with a dry ice condensor. The resulting mixture was stirred at this temperature for 30 min, quenched with solid NH_4Cl (4.20 g, 78.50 mmol) and allowed to warm to room temperature over 3 h. The reaction mixture was then filtered, the filter cake washed with EtOAc (3 x 20 mL) and the combined filtrates concentrated under reduced pressure. The resulting residue was purified by flash column chromatography over silica gel (MeOH/$CHCl_3$, 1.5:98.5) to afford **11** (5.18 g, 81% yield over 3 steps): white needles; sublimed ~150 °C (CH_2Cl_2/hexanes, 2:1); R_f 0.37 (MeOH/$CHCl_3$, 1:9); IR (film) 3072, 1694, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 3.94-3.93 (m, 4 H), 2.39 (t, J = 8.0 Hz, 2 H), 1.95 (t, J = 8.0 Hz, 2 H), 1.77-1.68 (m, 8 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 177.4, 107.9, 64.5 (2 C), 58.5, 35.6 (2 C), 32.3, 31.8 (2 C), 30.1; high-resolution mass spectrum (EI) *m/z* 211.1218 [(M^+); calcd for $C_{11}H_{17}NO_3$ 211.1208].

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.16; N, 6.70.

1-Prop-2-ynyl-1-aza-spiro[4.5]decane-2,8-dione (**12**): A solution of **11** (124.2 mg, 0.59 mmol) in anhydrous DMF (4 mL) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 51.7 mg, 1.29 mmol) added portionwise. After stirring for 3 h at 0 °C, propargyl bromide (130 μL, 1.76 mmol) was added and the mixture then stirred for a further 4 h. The reaction was quenched with saturated aqueous NH_4Cl (8 mL), and the aqueous phase was extracted with EtOAc (6 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was used directly in the following procedure:

A mixture of the above *N*-alkylation product, 0.5 M aqueous HCl (1.0 mL, 0.5 mmol), and acetone (1.5 mL) was stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc (6 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography over silica gel (EtOAc/hexanes, 90:10) to afford **12** (104.3 mg, 86% yield for 2 steps): pale yellow oil; R_f 0.38 (MeOH/$CHCl_3$, 1:9); IR (film) 3252, 3042, 2117, 1715, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (d, *J* = 2.5 Hz, 2 H), 2.57-2.43 (m, 6 H), 2.33 (dt, *J* = 13.3, 5.1 Hz, 2 H), 2.21 (t, *J* = 8.0 Hz, 2 H), 2.16 (t, *J* = 2.5 Hz 1 H), 1.91-1.85 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 173.9, 79.8, 71.4, 62.7, 37.7 (2 C), 33.9 (2 C),

29.1, 29.0, 28.2; high-resolution mass spectrum (CI) *m/z* 206.1190 [(MH^+); calcd for $C_{12}H_{16}NO_2$ 206.1181].

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.15; H, 7.53; N, 6.67.

(7b,8a,10ab)-Hexahydro-8-benzyloxy-6-triethylsilyloxy-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-5-ene (**6**): A solution of **12** (26.8 mg, 0.13 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (55.2 μL, 0.26 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred at room temperature for 30 min. The reaction mixture was then cooled to -20 °C and iodotrimethylsilane (29 μL, 0.20 mmol) added dropwise via a syringe. The mixture was stirred at -20 °C for 10 min, and then at room temperature for 2 h. After quenching with a mixture of saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), the mixture was extracted with EtOAc/hexanes (1:1, 5 × 4 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The resulting enol ether **6** was deemed by ^{1}H NMR spectroscopy to be of sufficient purity for use in the radical cyclization:

A solution of **6** in deoxygenated anhydrous benzene (1.0 mL) was heated to 80 °C and a solution of tributylstannane (*n*-Bu_3SnH) (42.2 μL, 0.157 mmol) and AIBN (2.1 mg, 15.7 μmol) in deoxygenated anhydrous benzene (700 μL) was then added via a syringe pump over 4 h. After stirring at 80 °C for a further 30 min, the mixture was concentrated and the residue taken up in 1 M aqueous HCl (1 mL) and MeOH (2 mL) and stirred for 2 h at room temperature. This mixture was then diluted with brine (3 mL) and extracted with EtOAc (6 × 3 mL). The combined organic phases were dried (Na_2SO_4), filtered and

concentrated. The resulting residue was purified by flash column chromatography over silica gel (EtOAc/hexanes, 50:50 to 100:0) to afford three products:

(7β,8α,10αβ)-Octahydro-8-hydroxy-6-methylidene-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-3-one (**5**): (10.8 mg, 40% yield for three steps): colorless oil; R_f 0.31 (MeOH/$CHCl_3$, 1:9); IR (film) 3659-3117 (b), 2932, 1652, 1418, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.14 (t, *J* = 1.1 Hz, 1 H), 5.02 (t, *J* = 1.1 Hz, 1 H), 4.54 (d, *J* = 18.0 Hz, 1 H), 3.96 (d, *J* = 18.0 Hz, 1 H), 3.89-3.83 (m, 1 H), 2.80-2.79 (m, 1 H), 2.54-2.46 (m, 1 H), 2.33 (ddd, *J* = 17.0, 9.7, 2.7 Hz, 1 H), 2.05-2.02 (m, 1 H), 2.00-1.96 (m, 1 H), 1.91-1.86 (m, 2 H), 1.84-1.79 (m, 2 H), 1.74 (dt, *J* = 13.0, 3.5 Hz, 1 H), 1.63 (td, *J* = 14.0, 5.6 Hz, 1 H), 1.46 (tdd, t, *J* = 13.8, 11.7, 5.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 138.8, 115.3, 70.4, 57.7, 46.4, 45.9, 39.6, 36.1, 33.0, 31.1, 29.8; high-resolution mass spectrum (CI) *m/z* 208.1344 [(MH^+); calcd for $C_{12}H_{18}NO_2$ 208.1338].

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.04; H, 8.24; N, 6.80.

(3β,4α,8α)–1-Aza-3-[tri-(*n*-butyl)-stannyl-methyl]-tricyclo[7.3.0.0]dodecane-6,12-dione (13): (29.2 mg, 45% yield for three steps): colorless oil; R_f 0.33 (EtOAc); IR (film) 2927, 1718, 1695, 1399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.29 (dd, *J* = 11.5, 8.7 Hz, 1 H), 3.02 (dd, *J* = 11.5, 8.7 Hz, 1 H), 2.82 (dt, *J* = 16.6, 10.2 Hz, 1 H), 2.56 (dd, *J* = 15.5, 7.1 Hz, 1 H), 2.49-2.46 (m, 1 H), 2.42-2.38 (m, 2 H), 2.29-2.25 (m, 3 H), 2.04 (t, *J* = 10.6 Hz, 1 H), 2.00-1.95 (m, 2 H), 1.73 (t, *J* = 8.5 Hz, 1 H), 1.42-1.38 (m, 6 H), 1.27-1.22 (m, 6 H), 1.07 (dd, *J* = 12.0, 3.4 Hz, 1 H), 0.85 (t, *J* = 7.4 Hz, 9 H), 0.78 (t, *J* = 8.1 Hz, 6 H), 0.56 (t, *J* = 12.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 174.3, 68.5, 56.8, 48.7, 44.6 39.0, 37.4, 33.5, 32.1, 31.9, 29.4 (3 C), 27.6 (3 C), 13.9 (3 C), 12.2, 9.6 (3 C); high-

resolution mass spectrum (FAB) *m/z* 520.2237 [(MNa^+); calcd for $C_{24}H_{43}NNaSnO_2$ 520.2213].

1-Allyl-1-aza-spiro[4.5]decane-2,8-dione (**14**): (0.5 mg, 2% yield for three steps): colorless oil; R_f 0.17 (EtOAc); IR (film) 2937, 1717, 1674, 1408, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.75 (m, 1 H), 5.18-5.09 (m, 2 H), 3.87-3.84 (m, 2 H), 2.70-2.45 (m, 6 H), 2.22-2.13 (m, 4 H), 1.84-1.82 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 174.0, 134.5, 116.7, 62.5, 41.9, 37.6 (2 C), 34.1 (2 C), 29.0, 28.8; high-resolution mass spectrum (CI) *m/z* 208.1342 [(MH^+); calcd for $C_{12}H_{18}NO_2$ 208.1338].

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 68.87; H, 8.14; N, 6.46.

(7α,8α,10αβ)-Octahydro-8-benzyloxy-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-3,6-dione (**17**): To a mixture of **5** (354.7 mg, 1.71 mmol) and tetra-*n*-butylammonium iodide (62.2 mg, 168 μmol) in anhydrous DMF (8 mL) was added NaH (60% dispersion in mineral oil, 205.3 mg, 5.13 mmol), followed by benzyl bromide (610 μL, 5.13 mmol). After stirred for 6 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (12 mL), and the aqueous phase was extracted with EtOAc (6 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was used directly in the following procedure:

A mixture of the above *O*-benzyl ether, pyridine (68.9 μL, 852 μmol), and OsO_4 (8.5 mL, 0.02 M in *t*-BuOH, 171 μmol) in THF (16 mL) and water H_2O (5 mL) was stirred at room temperature for 30 min. Solid $NaIO_4$ (2.19 g, 10.2 mmol) was added in three portions, over 6 h. The mixture was then filtered and concentrated and the resulting residue purified by flash column chromatography over silica gel (EtOAc/MeOH, 95:5) to afford

(**17**): (433.2 mg, 85% yield for 2 steps): white needles; m.p. 131-132 °C (MTBE); R_f 0.25 (MeOH/$CHCl_3$, 7:93); IR (film) 2940, 1722, 1690, 1641, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, *J* = 11.6 Hz, 1 H), 4.50 (d, *J* = 11.6 Hz, 1 H), 4.37 (d, *J* = 21.0 Hz, 1 H), 3.89 (d, *J* = 21.0 Hz, 1 H), 3.76-3.71 (m, 1 H), 3.24 (br s, 1 H), 2.66-2.59 (m, 1 H), 2.41 (qd, *J*= 9.6, 2.0 Hz, 1 H), 2.16-2.13 (m, 2 H), 2.03-1.92 (m, 4 H), 1.70-1.67 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 173.8, 137.9, 128.7 (2 C), 128.1, 128.0(2 C), 76.3, 70.3, 58.0, 53.4, 48.0, 36.6, 35.9, 33.1, 30.4, 28.4; high-resolution mass spectrum (FAB) *m/z* 300.1591 [(MH^+); calcd for $C_{18}H_{22}NO_3$ 300.1600].

(5β,7β,8α,10αβ)-Octahydro-8-benzyloxy-5-[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-3,6-dione (**19**): To a stirring solution of KHMDS (19.2 mg, 92 μmol) in anhydrous THF (500 μL), at -50 °C, was slowly added a solution of ketone **17** (21.1 mg, 70.4 μmol) in anhydrous THF (1.0 mL). After stirring for a further 15 min, the mixture was cooled to -78 °C, and TESCl (29.6 μL, 176 μmol) rapidly added via syringe. After 40 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the aqueous phase extracted with EtOAc (3 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide **18** which was immediately used in the following alkylation:

To a solution of **18** in anhydrous CH_2Cl_2 (1 mL), at -78 °C, was added *p*-methoxybenzyl bromide (14 μL, 105 μmol). After stirring for 5 min, $ZnCl_2$•Et_2O (105 μL, 1.0 M solution in Et_2O, 105 μmol) was added via syringe and the mixture stirred at -25 °C for 16 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (2 mL), and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting

residue was purified by flash column chromatography over silica gel (EtOAc/hexanes, 60:40) to afford **19** (20.1 mg, 68% yield over 2 steps): white solid; m.p. 74-75 °C; R_f 0.33 (EtOAc); IR (film) 2935, 1714, 1683, 1511, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 4.87 (d, *J* = 11.5 Hz, 1 H), 4.52 (br s, 1 H), 4.45 (d, *J* = 11.5 Hz, 1 H), 3.86 (dd, J = 13.5, 5.4 Hz, 1 H), 3.79 (s, 3 H), 3.51 (dt, *J* = 12.0, 4.6 Hz, 1 H), 3.23 (dd, *J* = 13.5, 2.6 Hz, 1 H), 2.80 (br s, 1 H), 2.66-2.60 (m, 1 H), 2.47-2.42 (m, 1 H), 2.04-1.97 (m, 2 H), 1.76-1.72 (m, 1 H), 1.56-1.51 (m, 1 H), 1.43-1.25 (m, 3 H), 0.49 (dt, *J* =13.6, 3.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 174.9, 159.1, 138.3, 131.5 (2 C), 129.6 , 128.9 (2 C), 128.7, 128.3 (2 C), 114.1 (2 C), 77.9, 70.3, 65.5, 59.0, 55.7, 46.8, 35.7, 35.3, 33.7, 32.6, 31.5, 28.5; high-resolution mass spectrum (FAB) *m/z* 420.2176 [(MH^+); calcd for $C_{26}H_{30}NO_4$ 420.2175].

(5β,6β,7β,8α,10αβ)-Octahydro-8-benzyloxy-6-hydroxy-5-[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-3-one (**20**): To a mixture of ketone **19** (9.55 mg, 1.71 mmol) and water (13.5 μL, 168 μmol) in freshly distilled THF (500 μL) was added a solution of SmI_2 (0.1 M in THF, 500 μL, 50 μmol). After stirring for 5 min at room temperature, the reaction mixture was concentrated, and the resulting residue was purified by flash column chromatography over silica gel (MeOH/$CHCl_3$, 1:49) to afford **20** (8.2 mg, 85% yield): colorless oil; R_f 0.16 (EtOAc); IR (film) 3384, 2935, 1662, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 6.85 (d, *J* = 8.1 Hz, 2 H), 4.53-4.42 (m, 3 H), 4.24-4.19 (m, 1 H), 3.86-3.85 (br s, 1 H), 3.80 (s, 3 H), 3.72-3.66 (m, 1 H), 2.92 (dd, *J* = 14.0, 10.7 Hz, 1 H), 2.49-2.44 (m, 1 H), 2.42-2.31 (m, 2 H), 2.16 (dt, *J* = 14.0, 3.5 Hz, 1 H), 2.09 (t, *J* = 7.1 Hz, 1 H),

2.05-1.99 (m, 1 H), 1.80-1.73 (m, 3 H), 1.49 (td, *J* = 13.7, 6.8 Hz, 1 H), 1.40 (dd, *J* = 13.1, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 158.2, 138.6, 131.3, 130.1 (2 C), 128.5 (2 C), 127.7, 127.5 (2 C), 114.3 (2 C), 75.6, 70.0, 64.6, 60.6, 59.6, 55.4, 39.4, 35.6, 33.7, 33.1, 32.9, 30.9, 28.2; high-resolution mass spectrum (FAB) *m/z* 444.2171 [(MNa^+); calcd for $C_{26}H_{31}NO_4Na$ 444.2151].

Reduction of Pyrrolidone 20: To a solution of **20** (12.2 mg, 28.8 μmol) in anhydrous THF (500 μL) at -78 °C was added $LiAlH_4$ (2.3 mg, 57.6 μmol) in a single portion. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature over 22 h then carefully quenched with sufficient saturated aqueous Na_2SO_4, to cause a white solid to precipitate. The reaction mixture was then filtrated, the filtrate concentrated and purified by flash column chromatography over silica gel (MeOH saturated with NH_3/CH_2Cl_2, 1:49) to afford two products:

(5β,6β,7β,8α,10αβ)-Octahydro-8-benzyloxy-5-[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-6-ol (**21**): (3.3 mg, 28% yield): colorless oil; R_f 0.26 (MeOH saturated with NH_3/CH_2Cl_2, 1:19); IR (film) 3480, 2923, 1512, 1246, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 6.85 (d, *J* = 8.1 Hz, 2 H), 4.54 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 3.81 (s, 3 H), 3.73-3.67 (m, 2 H), 3.45 (m, 1 H), 3.24 (m, 1 H), 2.91 (dd, *J* = 13.2, 4.7 Hz, 1 H), 2.75 (t, *J* = 11.4 Hz, 1 H), 2.63-2.58 (m, 1 H), 2.51 (br s, 1 H), 2.12-2.09 (m, 1 H), 2.02-1.95 (m, 2 H), 1.81-1.72 (m, 2 H), 1.63 (s, 1 H (OH)), 1.58-1.43 (m, 3 H), 1.26-1.20 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 139.2, 131.7, 130.7 (2 C), 128.7 (2 C), 127.7 (3 C), 114.2 (2 C), 76.9, 69.8, 65.6,, 62.8, 59.1, 55.6, 48.0, 40.1, 39.1, 36.9, 33.9, 29.6, 28.7,

20.2; high-resolution mass spectrum (FAB) *m/z* 408.2556 [(MH^+); calcd for $C_{26}H_{34}NO_3$ 408.2539].

(5β,6β,7β,8α,10αβ)-Octahydro-5-[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-6,8-diol (**4**): (3.6 mg, 39% yield): crystalline solid; mp >175 °C (decomp); R_f 0.11 (MeOH saturated with NH_3/CH_2Cl_2, 1:19); IR (film) 3359, 2954, 1512 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.28 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 3.96 (ddd, *J* = 12.5, 6.8, 4.4 Hz, 1 H), 3.80 (s, 3 H), 3.75 (br s, 1 H), 3.45-3.42 (m, 1 H), 3.40 (m, 1 H), 3.00 (dd, *J* = 13.0, 10.0 Hz, 1 H), 2.86-2.76 (m, 2 H), 2.23 (m, 1 H), 2.16 (app dt, *J* = 12.5, 3.6 Hz, 1 H), 2.08-2.05 (m, 1 H), 1.81-1.39 (m, 6 H), 1.35 (d, *J* = 11.6 Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 159.4, 132.4, 131.4, (2 C), 114.5 (2 C), 71.3, 65.2, 64.2, 61.2, 55.5, 47.2, 45.4, 39.1, 36.7, 32.0, 31.6, 31.0, 20.3; high-resolution mass spectrum (FAB) *m/z* 318.20717 [(MH^+); calcd for $C_{19}H_{28}NO_3$ 318.20692]. See attached ^1H and ^{13}C NMR spectra.

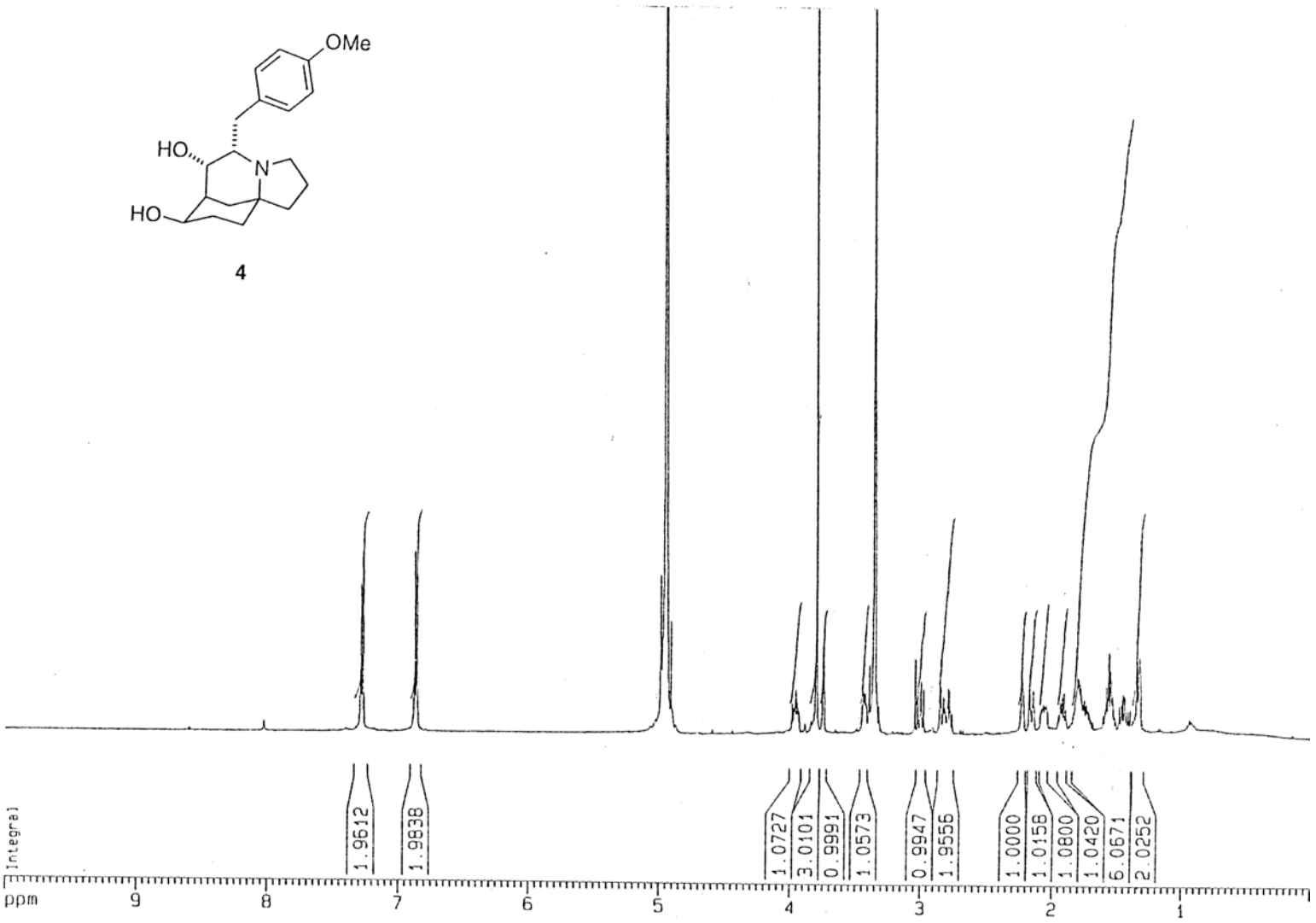
Physical and Spectroscopic Data for 4, as reported by Snider:[iii]

Mp >175 °C (decomp); IR (film) 3383, 2936, 1513 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) 7.24 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 3.92 (ddd, *J* = 11.6, 6.8, 4.4 Hz, 1 H), 3.76 (s, 3 H), 3.75 (br s, 1 H), 3.46 (m, 1 H), 3.40 (m, 1 H), 3.00 (dd, *J* = 13.2, 10.0 Hz, 1 H), 2.87 (m, 1 H), 2.82 (dd, *J* = 13.2, 4.8 Hz, 1 H), 2.19 (m, 1 H), 2.17 (ddd, *J* = 11.6, 3.6, 2.8 Hz, 1 H), 2.04 (ddd, *J* = 14.8, 6.8, 2.8 Hz, 1 H), 1.95-1.45 (m, 7 H), 1.34 (d, *J* = 11.6 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.7, 132.5, 131.6 (2 C), 114.9 (2 C), 71.2, 65.1, 64.1, 61.1, 55.8, 47.2, 45.4, 39.0, 36.7, 31.8, 31.6, 31.2, 20.4.

(5β,6β,7β,8α,10αβ)-Octahydro-5-[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-6,8-diol (**4) (via hydrogenolysis of 21)**: To a solution of

21 (3.3 mg, 8.1 μmol) in MeOH (3 mL) was added 20% $Pd(OH)_2/C$ (5 mg). The resulting mixture was then placed under an atmosphere of H_2 (1 atm) and stirred at room temperature for 3 h. After flushing with N_2, the reaction mixture was filtered through a pad of Celite 521 and the filter cake washed with MeOH (3 × 2 mL). The filtrate was concentrated and purified by flash column chromatography over silica gel (MeOH saturated with NH_3/CH_2Cl_2, 1:19) to afford **4** (2.8 mg, 99% yield): data as described above.

(5αβ,7β,8α,10αβ)-Octahydro-8-benzyloxy-5,5-di[(4-methoxy-phenyl)methyl]-1*H*-7,10a-methanopyrrolo[1,2-a]azocine-3,6-dione (product of α–dialkylation of ketone 17: not shown in text): colorless oil; R_f 0.49 (EtOAc); IR (film) 2935, 1706, 1675, 1610, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.73 (d, *J* = 8.5 Hz, 2 H), 4.77 (d, *J* = 11.7 Hz, 1 H), 4.34 (d, *J* = 11.7 Hz, 1 H), 4.02 (d, *J* = 13.6 Hz, 1 H), 3.93 (d, *J* = 13.2 Hz, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.62 (d, *J* = 13.6 Hz, 1 H), 3.31-3.26 (m, 1 H), 2.97 (d, *J* = 13.2 Hz, 1 H), 2.77-2.69 (m, 1 H), 2.58 (br s, 1 H), 2.47-2.40 (m, 1 H), 1.74-1.52 (m, 3 H), 1.29-1.14 (m, 2 H), 1.01-0.97 (m, 1 H), 0.22-0.12 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 176.2, 159.1, 158.8, 138.8, 132.7 (2 C), 131.5 (2 C), 130.0, 129.6, 128.5 (2 C), 128.4, 127.5 (2 C), 114.1 (2 C), 113.6 (2 C), 78.9, 75.9, 69.4, 60.1, 55.5, 55.4, 46.5, 43.6, 40.7, 35.9, 34.7, 32.8, 31.9, 25.0; high-resolution mass spectrum (FAB) *m/z* 562.2532 [(MNa^+); calcd for $C_{34}H_{37}NO_5Na$ 562.2570].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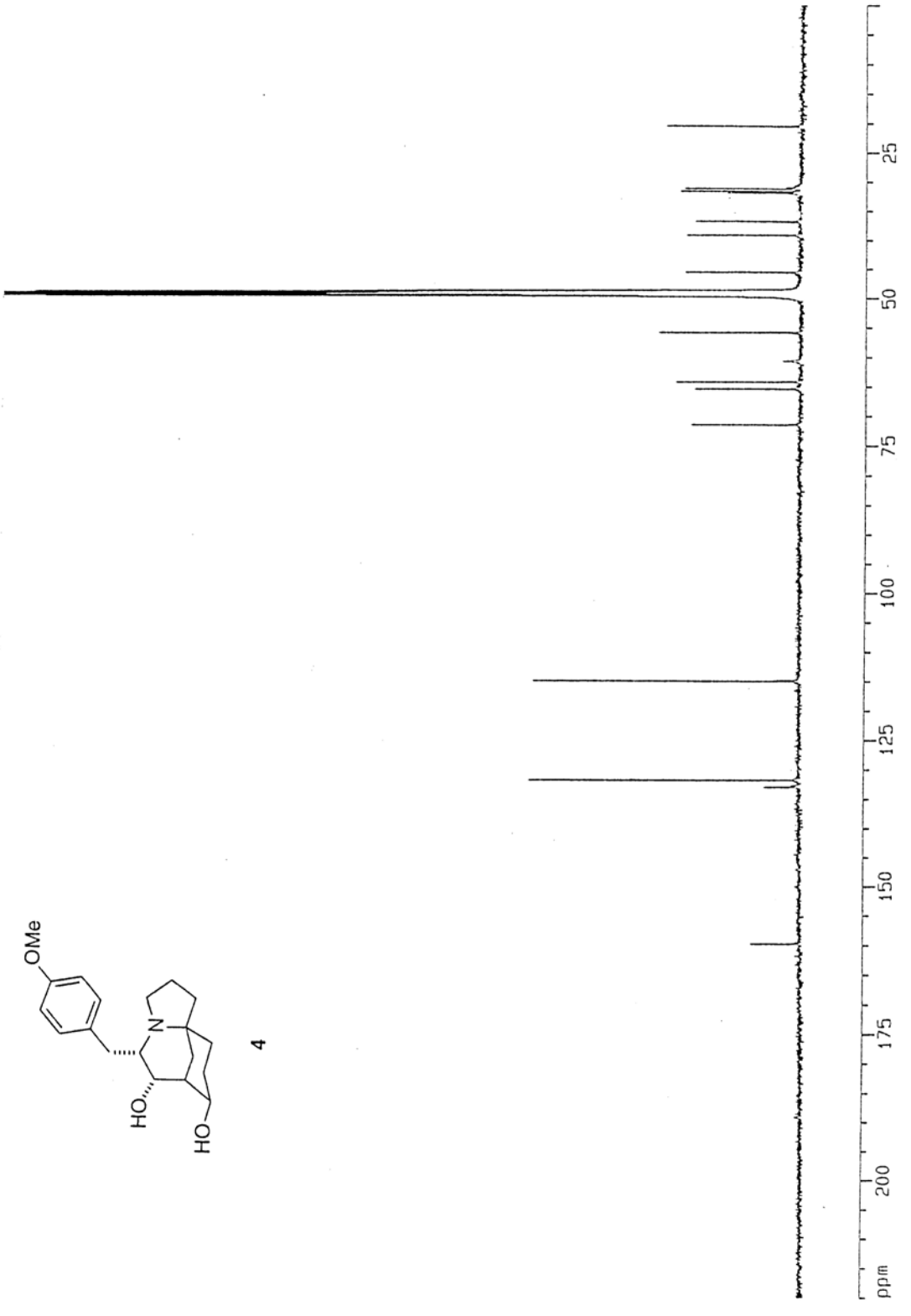

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