N-Methoxy-N-Acylnitrenium Ions:
Application to the Formal Synthesis of (-)-TAN1251A

(Supporting Information)

Duncan J. Wardrop* and Arindrajit Basak

Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Chicago, Illinois 60607-7061,U.S.A

wardropd@uic.edu

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. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Methanol was dried from magnesium methoxide, prepared from magnesium turnings and iodine. Triethylamine, diisopropylamine and *N*-methylmorpholine were distilled from calcium hydride, under nitrogen, and stored over potassium hydroxide. Acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under nitrogen. *N,N*-dimethylformamide (DMF) was purchased from Aldrich and dried with freshly activated 4 Å molecular sieves prior to use. *Bis*(trifluoroacetoxy)iodobenzene, 1-bromo-3-methyl-2-butene, methyl chloroformate, benzyl chloroformate, methanesulfonyl chloride and aluminum trichloride were purchased from Aldrich and used without further purification. *t*-Butylithium (*t*-BuLi) was purchased from Aldrich and standardized by titration with diphenylacetic acid. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin-layer chromatography with Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light, potassium permanganate, phosphomolybdic acid, 2,4-dinitrophenylhydrazone or *p*-anisaldehyde 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. ^1H 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) and a Bruker AM-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. Chemical shift values (δ) are reported relative to internal tetramethylsilane (TMS) (δ 0.00 ppm), acetone (δ 2.05 ppm), chloroform (δ 7.27 ppm) for ^{1}H and acetone (δ 29.92 ppm) chloroform (δ 77.23 ppm) for ^{13}C. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter and reported as follows: $[\alpha]_{\text{wavelength}}^{\text{temperature}}$, concentration (*c* g/100 mL) and solvent. 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 analyses were performed by the Midwestern Microlab, Indianapolis, IN.

(*S*)-3-(4-Hydroxyphenyl)-2-methoxycarbonylamino-propionic acid. To a stirred solution of L-tyrosine (**12**) (5.00 g, 27.59 mmol) in 2 M aqueous NaOH (27 mL, 54.00 mmol) at 5 °C was added methyl chloroformate (4.5 mL, 58.24 mmol) and 4 M aqueous NaOH (15 mL, 60.00 mmol). After stirring for 1.5 h, the reaction mixture was filtered, the filtrate extracted with Et_2O (30 mL) and the organic extract discarded. To the aqueous phase, 4 M aqueous NaOH (10 mL, 40.00 mmol) was added and stirred for an additional 2 h at 0 °C. The reaction mixture was then acidified to pH 1-2 with 2 M aqueous HCl and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give the title compound (5.97 g, 90% yield): white solid; mp 89-90 °C, ($CHCl_3$); $[\alpha]^{30}_{D}$ +28.3° (*c* 0.72, MeOH); IR (film) 3400-3100, 1696, 1664, 1533 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.11 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 8.3 Hz, 2 H), 6.30 (d, *J* = 7.3 Hz, 1 H), 4.41-4.36 (m, 1 H), 3.53 (s, 3 H), 3.10 (dd, *J* = 14.0, 4.8 Hz, 1 H), 2.89 (dd, *J* = 14.0, 8.9 Hz, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 173.7, 157.5, 157.1, 131.2 (2 C), 128.9, 116.1 (2 C), 56.4, 52.1, 37.4; high-resolution mass spectrum (EI) *m/z* 239.0794 [(M^+); calcd for $C_{11}H_{13}NO_5$ 239.0794].

Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48. Found: C, 54.16; H, 5.49.

(*S*)-2-Methoxycarbonylamino-3-(4-methoxyphenyl)-propionic acid methyl ester (13). A mixture of (*S*)-3-(4-hydroxyphenyl)-2-methoxycarbonylamino-propionic acid (1.00 g, 4.18 mmol), dimethyl sulfate (990 μL, 10.46 mmol) and powdered anhydrous K_2CO_3 (1.73g, 12.52 mmol) in acetone (40 mL) was heated at reflux for 3 h, cooled to room temperature and filtered. The filtrate was concentrated and the resulting residue purified by flash column chromatography on silica gel (EtOAc/hexanes, 1:4) to afford **13** (940 mg, 84% yield): colorless crystals; mp 55-57 °C (Et_2O/hexanes, 1:1); $[\alpha]^{30}_{D}$ +60.8° (*c* 1.05, $CHCl_3$); R_f 0.60 (EtOAc/hexanes, 1:1); IR (film) 3342, 2953, 2838, 1723, 1612, 1513, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) two rotamers, major rotamer δ 7.03 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.14 (d, *J* = 7.6 Hz, 1 H), 4.63-4.59 (m, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 3.06-3.04 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 158.9, 156.5, 130.4 (2 C), 127.8, 114.2 (2 C), 55.4, 55.1, 52.53, 52.46, 37.6; high-resolution mass spectrum (EI) *m/z* 267.1113 [(M^+); calcd for $C_{13}H_{17}NO_5$ 267.1107].

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41. Found: C, 58.30; H, 6.35.

(*S*)-2-Methoxycarbonylamino-3-(4-methoxyphenyl)-propionic acid. A solution of **13** (15.06 g, 56.35 mmol) in 1,4-dioxane (70 mL) at 0 °C was treated with 1 M aqueous NaOH (70 mL, 70.00 mmol). The mixture was stirred for 30 min then washed with Et_2O (2 x 50 mL) and the organic extracts discarded. The aqueous phase was cooled to 0 °C, acidified to pH 1-2 with 1 M aqueous HCl and then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide the title compound (13.84 g, 97% yield): white solid; mp 90-92 °C (CH_2Cl_2/hexanes, 1:1); $[\alpha]^{30}_D$ +14.4° (*c* 1.92, MeOH); IR (film) 3360, 3323, 3001, 2954, 1719, 1612, 1513, 1248, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) two rotamers, major rotamer δ 10.44 (br, 1 H), 7.10 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.12 (d, *J* = 8.0 Hz, 1 H), 4.67-4.62 (m, 1 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.14 (dd, *J* = 14.0, 5.3 Hz, 1 H), 3.06 (dd, *J* = 14.0, 6.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 159.0, 156.8, 130.5 (2 C), 127.6, 114.3 (2 C), 55.4, 54.9, 52.7, 37.1; high-resolution mass spectrum (EI) *m/z* 253.0954 [(M^+); calcd for $C_{12}H_{15}NO_5$ 253.0950].

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97. Found: C, 56.73; H, 5.92.

(*S*)-[1-Methoxycarbamoyl-2-(4-methoxyphenyl)-ethyl]-carbamic acid methyl ester (11). A solution of (*S*)-2-methoxycarbonylamino-3-(4-methoxyphenyl)-propionic acid (1.50 g, 5.92 mmol) and 1-hydroxybenzotriazole hydrate (959 mg, 7.10 mmol) in CH_2Cl_2 (15 mL) and DMF (1 mL) was treated with a solution of 1,3-dicyclohexylcarbodiimide (1.34 g, 6.49 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 45 min and methoxylamine hydrochloride (1.48 g, 17.72 mmol) was added in one portion followed by *N*-methylmorpholine (4.27 mL, 38.84 mmol). After stirring for 24 h at room temperature the reaction mixture was filtered through a pad of Celite 521 and the filter cake washed with EtOAc (30 mL). The combined filtrates were then concentrated under reduced pressure and the residual solid 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 (2 x 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 3:2 then 4:1) to give a solid, which upon recrystallization ($CHCl_3$) provided **11** (1.25 g, 75% yield): white needles; mp 144-146 °C ($CHCl_3$); $[\alpha]^{30}_{D}$ +4.1° (*c* 1.92, $CHCl_3$); R_f 0.50 (EtOAc); IR (film) 3283, 3219, 3000, 2955, 1672, 1613, 1513, 1247, 1179, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.32 (d, *J* = 5.5 Hz, 1 H), 4.24-4.18 (m, 1 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.03-2.99 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 159.0, 156.9, 130.6 (2 C), 128.1, 114.4 (2 C), 64.6, 55.5, 54.4, 52.8, 37.6; high-resolution mass spectrum (EI) *m/z* 282.1219 [(M^+); calcd for $C_{13}H_{18}N_2O_5$ 282.1216].

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43. Found: C, 55.40; H, 6.40.

(*S*)-(1-Methoxy-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)-carbamic acid methyl ester (10). To a solution of **11** (1.138 g, 4.03 mmol) in anhydrous methanol (60 mL) at 0 °C was added *bis*(trifluoroacetoxy)iodobenzene (2.611 g, 6.07 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred for 10 min then water (15 mL) was added and the biphasic mixture stirred for an additional 5 min. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 3:1) to afford **10** (742 mg, 69% yield): white solid; mp 138-141°C (CH_2Cl_2/hexanes); $[\alpha]^{30}_D$ -60.3° (c 0.98, $CHCl_3$); R_f 0.44 (EtOAc); IR (film) 3322, 1715, 1671, 1631, 1541, 1271, 1254, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 9.4 Hz, 1 H), 6.83 (dd, *J* = 9.9, 3.0 Hz, 1 H), 6.42-6.37 (m, 2 H), 5.50 (s, 1 H), 4.36-4.31 (m, 1 H), 3.84 (s, 3 H), 3.71 (s, 3 H), 2.63 (dd, *J* = 13.1, 9.1 Hz, 1 H), 2.28 (dd, *J* = 13.1, 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 167.9, 156.8, 147.6, 146.3, 131.7, 131.2, 65.6, 60.2, 52.9, 48.6, 36.5; high-resolution mass spectrum (EI) *m/z* 266.0901 [$(M)^+$; calcd for $C_{12}H_{14}N_2O_5$ 266.0903].

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.44; H, 5.40; N, 10.52.

(*S*)-(1-Methoxy-2,8-dioxo-1-azaspiro[4,5]dec-3-yl)-carbamic acid methyl ester. To a solution of **10** (588 mg, 2.21 mmol) in EtOAc (25 mL) was added 10% Pd/C (12 mg). The resulting mixture was then placed under an atmosphere of H_2 (1 atm) and stirred at room temperature for 6 h. After flushing with N_2, the reaction mixture was filtered through a pad of Celite 521 and the filter cake washed with EtOAc (25mL) then methanol (25 mL). The combined filtrates were concentrated under reduced pressure and the resulting residue purified by flash chromatography on silica gel (MeOH/$CHCl_3$, 4:96) to afford the title compound (575 mg, 96% yield): white solid; mp 166-169 °C (EtOAc/CH_2Cl_2/petroleum ether, 5:1:2); $[\alpha]^{30}_D$ -31.3° (*c* 1.48, $CHCl_3$); R_f 0.25 (EtOAc);

IR (film) 3317, 2946, 1710, 1536, 1432, 1265, 1051, 1029 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.31 (br s, 1 H), 4.29-4.24 (m, 1 H), 3.94 (s, 3 H), 3.72 (s, 3 H), 2.97-2.92 (m, 1 H), 2.55- 2.39 (m, 5 H), 2.34-2.27 (m, 1 H), 1.98-1.91 (m, 2 H), 1.88-1.82 (m, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 208.1, 167.1, 157.1, 65.3, 60.9, 52.8, 48.9, 37.7, 37.3, 36.1, 35.3, 31.9; high-resolution mass spectrum (EI) *m/z* 270.1218 [(M$^+$); calcd for $C_{12}H_{18}N_2O_5$ 270.1216].

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71, N, 10.36. Found: C, 53.61; H, 6.85; N, 10.45.

(*S*)-(9-Methoxy-10-oxo-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-11-yl)-carbamic acid methyl ester (14). (*S*)-1-Methoxy-2,8-dioxo-1-azaspiro[4,5]dec-3-yl)-carbamic acid methyl ester (1.00 g, 3.70 mmol), ethylene glycol (920 mg, 14.82 mmol), pyridinium *p*-toluenesulfonate (93 mg, 0.37 mmol) and benzene (60 mL) were placed in a Dean-Stark apparatus and then heated at reflux for 3.5 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (50 mL) and washed with saturated aqueous NaHCO$_3$ and brine. The organic phase was dried (Na$_2$SO$_4$), filtered and the filtrate concentrated under reduced pressure. Flash column chromatography over silica gel (MeOH/CHCl$_3$, 3:97) afforded **14** (1.05 g, 90% yield): colorless needles; mp 198-200 °C (CH$_2$Cl$_2$/hexanes, 1:1); $[\alpha]^{30}_D$ -17.8° (*c* 1.35, CHCl$_3$); R_f 0.66 (MeOH/CHCl$_3$, 1:9); IR (film) 3304, 2944, 2890, 1711, 1538, 1445, 1266, 1104, 943, 752 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.40 (s, 1 H), 4.22-4.17 (m, 1 H), 3.98-3.94 (m, 4 H), 3.90 (s, 3 H), 3.68 (s, 3 H), 2.79 (dd, *J* = 12.2, 9.2 Hz, 1 H), 2.30 (td, *J* = 13.1, 4.0 Hz, 1 H), 2.13 (td, *J* = 13.4, 4.8 Hz, 1 H), 1.84-1.77 (m, 2 H), 1.73 (dd, *J* = 13.7, 4.4 Hz, 1 H), 1.70-1.65 (m, 2

H), 1.62-1.58 (m, 1 H), 1.51-1.47 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 157.1, 107.3, 65.2, 64.7, 64.6, 61.7, 52.6, 48.9, 35.7, 33.6, 31.9, 31.3, 29.9; high-resolution mass spectrum (EI) *m/z* 314.1461 [(M^+); calcd for $C_{14}H_{22}N_2O_6$ 314.1478].

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.27; H, 7.14; N, 8.86.

(*S*)-(9-Methoxy-1,4-dioxa-9-azadispiro[4.2.4.2] tetradec-11-yl)-methyl-amine (**15b**). To a stirred suspension of **14** (750 mg, 2.39 mmol) in THF (20 mL) at 0 °C was added lithium aluminum hydride (454 mg, 11.96 mmol) portionwise. After warming to room temperature, the reaction mixture was heated at reflux for 11 h. The gray reaction mixture was cooled to 0 °C, diluted with THF (10 mL), and then cautiously quenched with sufficient saturated aqueous Na_2SO_4 (~ 0.8 mL) to cause a white solid to precipitate. The resultant white suspension was filtered through a pad of Celite 521 and the filter cake washed with THF (15 mL) followed by CH_2Cl_2 (20 mL). The combined filtrates were concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (NH_3 in MeOH/CH_2Cl_2, 4:96) to provide **15b** (397 mg, 65% yield): colorless oil; $[\alpha]^{30}_D$ +6.9° (*c* 0.57, $CHCl_3$); R_f 0.50 (NH_3 in MeOH/CH_2Cl_2, 1:9); IR (film) 2935, 2879, 2803, 1444, 1373, 1267, 1133, 1037, 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81-3.79 (m, 4 H), 3.36 (s, 3 H), 3.19 (dd, *J* = 12.2, 7.4 Hz, 1H), 3.13-3.07 (m, 1 H), 2.89 (dd, *J* = 12.2, 4.1 Hz, 1H), 2.38 (s, 3 H), 1.92 (dd, *J* = 12.9, 8.6 Hz, 1 H), 1.88-1.81 (m, 1 H), 1.69-1.64 (m, 3 H), 1.52-1.29 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5, 68.2, 64.2, 64.1, 61.0, 59.0, 57.9, 40.4, 35.0, 32.0 (2 C), 31.7 (2 C); high-resolution mass spectrum (CI, NH_3) *m/z* 257.1854 [$(M+H)^+$; calcd for $C_{13}H_{25}N_2O_3$ 257.1865].

Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44. Found: C, 60.43; H, 9.31.

(*S*)-(9-Methoxy-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-11-yl)-methyl-carbamic acid benzyl ester. To a solution of **15b** (450 mg, 1.76 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added benzyl chloroformate (513 μL, 3.59 mmol) followed by Et_3N (1.46 mL, 10.47 mmol). The reaction was stirred for 2 h at 0 °C then 1 h at room temperature, poured into brine (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:4) affording the title compound (627 mg, 91% yield): colorless oil; $[\alpha]^{30}_D$ +3.3° (c 0.39, $CHCl_3$); R_f 0.50 (EtOAc/hexanes, 1:1); IR (film) 2940, 2888, 1701, 1325, 1151, 1039, 699 cm^{-1}; ^{1}NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5 H), 5.11 (s, 2 H), 4.97-4.92 (br, 1 H), 3.94-3.89 (m, 4 H), 3.50 (s, 3 H), 3.28 (br, 1 H), 3.07 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.88 (s, 3 H), 2.05-1.99 (br, 2 H), 1.81-1.77 (m, 3 H), 1.62-1.43 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 136.9, 128.5 (2 C), 128.0, 127.9 (2 C), 108.6, 67.9, 67.2, 64.3, 64.2, 61.3, 55.5, 52.9, 35.7, 32.4 (2 C), 31.6 (2 C), 28.9; high-resolution mass spectrum (EI) *m/z* 390.2131 [(M^+) calcd for $C_{21}H_{30}N_2O_5$ 390.2155].

Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74. Found: C, 64.36; H, 7.65.

(*S*)-(1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-11-yl)-methyl-carbamic acid benzyl ester. A mixture of (*S*)-(9-methoxy-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-11-yl)-

methyl-carbamic acid benzyl ester (627 mg, 1.61 mmol) and Zn dust (12.61 g, 192.9 mmol) in AcOH (30 mL) was heated at 75 °C for 5 h. After cooling to room temperature, the reaction was filtered, the filter cake washed with CH_2Cl_2 (50 mL) and the combined filtrates concentrated to dryness in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The remaining residue was purified by flash column chromatography on silica gel (NH_3 in MeOH/CH_2Cl_2, 3:97) to give the title compound (488 mg, 84% yield): colorless oil: $[\alpha]^{25}_{D}$ +10.4° (*c* 0.44, $CHCl_3$); R_f 0.58 (NH_3 in MeOH/CH_2Cl_2, 8:92); IR (film) 2945, 2869, 1697, 1442, 1342, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5 H), 5.13-5.08 (m, 2 H), 4.72 (br s, 1 H) 3.95-3.88 (m, 4 H), 3.14-3.12 (m, 1 H), 2.88 (dd, *J* = 11.4, 7.1, 1 H), 2.85 (s, 3 H), 1.97 (m, 1 H), 1.78-1.52 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.9, 128.6 (2 C), 128.1, 128.0 (2 C), 108.5, 67.3, 64.38, 64.36, 60.4, 56.5, 47.7, 39.4, 36.4, 34.6, 32.4, 32.0, 29.7; high resolution mass spectrum (EI) *m/z* 360.2042 [(M^+); calcd for $C_{20}H_{28}N_2O_4$ 360.2049].

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; O, 7.77. Found: C, 66.37; H, 7.81; O, 7.70.

(*S*)-[11-(Benzyloxycarbonyl-methyl-amino)-1,4-dioxa-9-azadispiro[4.2.4.2]tetradedecyl-9-yl]-acetic acid benzyl ester (**16**). A mixture of (*S*)-(1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-11-yl)-methyl-carbamic acid benzyl ester (238 mg, 0.660 mmol), benzyl bromoacetate (452 mg, 1.973 mmol) and powdered anhydrous

K_2CO_3 (273 mg, 1.975 mmol) in CH_3CN (15 mL) was heated at 35-40 °C for 15 h. The reaction mixture was cooled, filtered, and the filter cake washed with CH_2Cl_2 (20 mL). The combined filtrates were concentrated under reduced pressure and the residue purified by flash column chromatography over silica gel (NH_3 in MeOH/CH_2Cl_2, 1:99) to provide **16** (290 mg, 86% yield): colorless oil; $[\alpha]^{30}_{D}$ -21.1° (*c* 1.00, $CHCl_3$); R_f 0.65 (NH_3 in MeOH/CH_2Cl_2, 5:95); IR (film) 2939, 2875, 1748, 1697, 1496, 1453, 1326, 1157, 1105, 744, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) rotamers δ 7.41-7.31 (m, 10 H), 5.17-5.10 (m, 4 H), 4.91-4.76 (br, 1 H), 3.97-3.89 (m, 4 H), 3.60 (d, *J* = 15.7 Hz, 1 H), 3.15 (d, *J* = 8.5 Hz, 1 H), 3.07(d, *J* = 8.5 Hz, 1 H), 2.92 (s, 3H), 2.83-2.80 (m, 1 H), 2.38 (br, 1 H), 1.84-1.42 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 156.6, 137.2, 135.9, 128.8 (2 C), 128.7 (2 C), 128.5 (2 C), 128.4 (2 C), 128.1, 128.0, 108.4, 67.2, 66.6, 64.6, 64.4, 63.2, 54.6, 52.4, 49.8, 38.1, 33.4, 33.1, 32.4, 28.6, 25.1; high-resolution mass spectrum (EI) *m/z* 508.2566 [(M^+); calcd for $C_{29}H_{36}N_2O_6$ 508.2573].

(1*R*,5*S*)-4-Methyl-dispiro[1,4-diazabicyclo[3.2.1]octan-3-one-7,1'-cyclohexane-4',2"-[1,3]dioxolane] (**9**). To a solution of **16** (203 mg, 0.399 mmol) in MeOH (15 mL) was added 10% Pd/C (40 mg). The resulting mixture was then placed under an atmosphere of H_2 and stirred at room temperature for 30 min. After flushing with N_2, the reaction mixture was filtered through a pad of Celite 521 and the filter cake washed with MeOH (30 mL). The combined filtrates were concentrated to provide the amino acid (115 mg) as colorless solid. The amino acid was used immediately in the following procedure:

A mixture of the above amino acid (115 mg) and powdered anhydrous $NaHCO_3$ (84 mg, 1.00 mmol) in CH_2C1_2 (25 mL) and DMF (25 mL) at 0 °C was treated with diphenylphosphoryl azide (132 mg, 0.480 mmol). The reaction was stirred at 0 °C for 3 h and then for a further 84 h at room temperature. After this time, the reaction mixture was concentrated to dryness in vacuo and the residual solid partitioned between CH_2Cl_2 (25 mL) and water (25 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were then washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (NH_3 in MeOH/CH_2Cl_2, 2:98) furnishing **9** [60 mg, 57% yield from **16**: colorless oil**;** $[\alpha]^{30}_{D}$ +15.3° (*c* 0.29, $CHCl_3$); R_f 0.46 (NH_3 in MeOH/CH_2Cl_2, 8:92]; IR (film) 2935, 2892, 1639, 1490, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96-3.91 (m, 4 H), 3.61-3.60 (m, 1 H), 3.57 (d, *J* = 18.6 Hz, 1 H), 3.48 (d, *J* = 18.6 Hz, 1 H), 3.23 (dd, *J* = 12.3, 2.6 Hz, 1 H), 3.04 (d, *J* = 12.3 Hz, 1 H), 2.89 (s, 3 H), 1.88-1.82 (m, 3 H), 1.78-1.70 (m, 4 H), 1.65-1.58 (m, 2 H) 1.54-1.51 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 108.1, 64.50, 64.46, 64.3, 60.2, 56.5, 55.3, 45.3, 36.6, 33.6, 32.9, 32.8, 32.1; high-resolution mass spectrum (EI) *m*/*z* 266.1630 [(M^+); calcd for $C_{14}H_{22}N_2O_3$ 266.1630].

4-(3-Methyl-but-2-enyloxy)-benzaldehyde (**17**). A mixture of 4-hydroxybenzaldehyde (1.00 g, 8.19 mmol), 1-bromo-3-methyl-2-butene (1.34 g, 9.01 mmol) and powdered anhydrous K_2CO_3 (2.76 g, 19.97 mmol) in acetone (20 mL) was heated at reflux for 3.5 h. The mixture was cooled to room temperature, filtered and the filter cake washed with acetone (10 mL). The combined filtrates were concentrated and the resulting residue purified by flash column chromatography over silica gel (EtOAc/hexanes, 3:97) to yield **17** (1.34 g, 86% yield): colorless oil; R_f 0.60 (EtOAc/hexanes, 1:4); IR (film) 1690, 1601, 1576, 1508, 1247, 1154, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1 H), 7.84-7.81 (m, 2 H), 7.02-6.99 (m, 2 H), 5.50-5.47 (m, 1 H), 4.60 (d, *J* = 6.8 Hz, 2 H), 1.81 (s, 3H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 164.2, 139.3, 132.1 (2 C), 130.0, 118.9, 115.1 (2 C), 65.3, 26.0, 18.4; high-resolution mass spectrum (EI) *m/z* 190.0997 [(M^+); calcd for $C_{12}H_{14}O_2$ 190.0994].

(1*S*,2*S*,5*S*)-2-[Hydroxy-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-4-methyl-dispiro[1,4diazabicyclo[3.2.1]octan-3-one-7,1'-cyclohexane-4',2''-[1,3]dioxolane] (mixture of diastereomers) (**18**). To a stirred solution of **9** (67 mg, 0.252 mmol) in THF (2 mL) at 0 °C was added freshly prepared lithium diisopropylamide solution (1 M in pentane/THF, 550 μL, 0.55 mmol). After stirring for 25 minutes, the reaction mixture was cooled to –78 °C and a solution of **17** (96 mg, 0.505 mmol) in THF (2 mL) added dropwise over 5 minutes. This mixture was stirred for 1.5 h then quenched with saturated aqueous NH_4Cl (0.5 mL) followed by saturated aqueous $NaHCO_3$ (5 mL). After warming to room temperature, the biphasic mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were then washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography ($MeOH/CHCl_3$, 0:100 then 1:99) to provide **18** as an inseparable (1.2:1) mixture of diastereomers (92 mg, 80%): oily solid; $[\alpha]^{27}_D$ –5.0° (*c* 1.26, $CHCl_3$); R_f 0.60 ($MeOH/CHCl_3$, 1:9); IR (film) 3360, 2931, 2877, 1619, 1503, 1237, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33, 7.28 [diastereomers, (d, *J* = 8.7 Hz), (d, *J* = 8.6 Hz), 2 H], 6.88, 6.87 [diastereomers, (d, *J* = 8.7 Hz), (d, *J* = 8.6 Hz), 2 H], 5.52-5.48 (m, 1 H), 5.26, 5.00 (diastereomers, br, 1 H), 4.96, 4.76 [diastereomers, (dd, *J* = 7.9, 2.3 Hz), (d, *J*

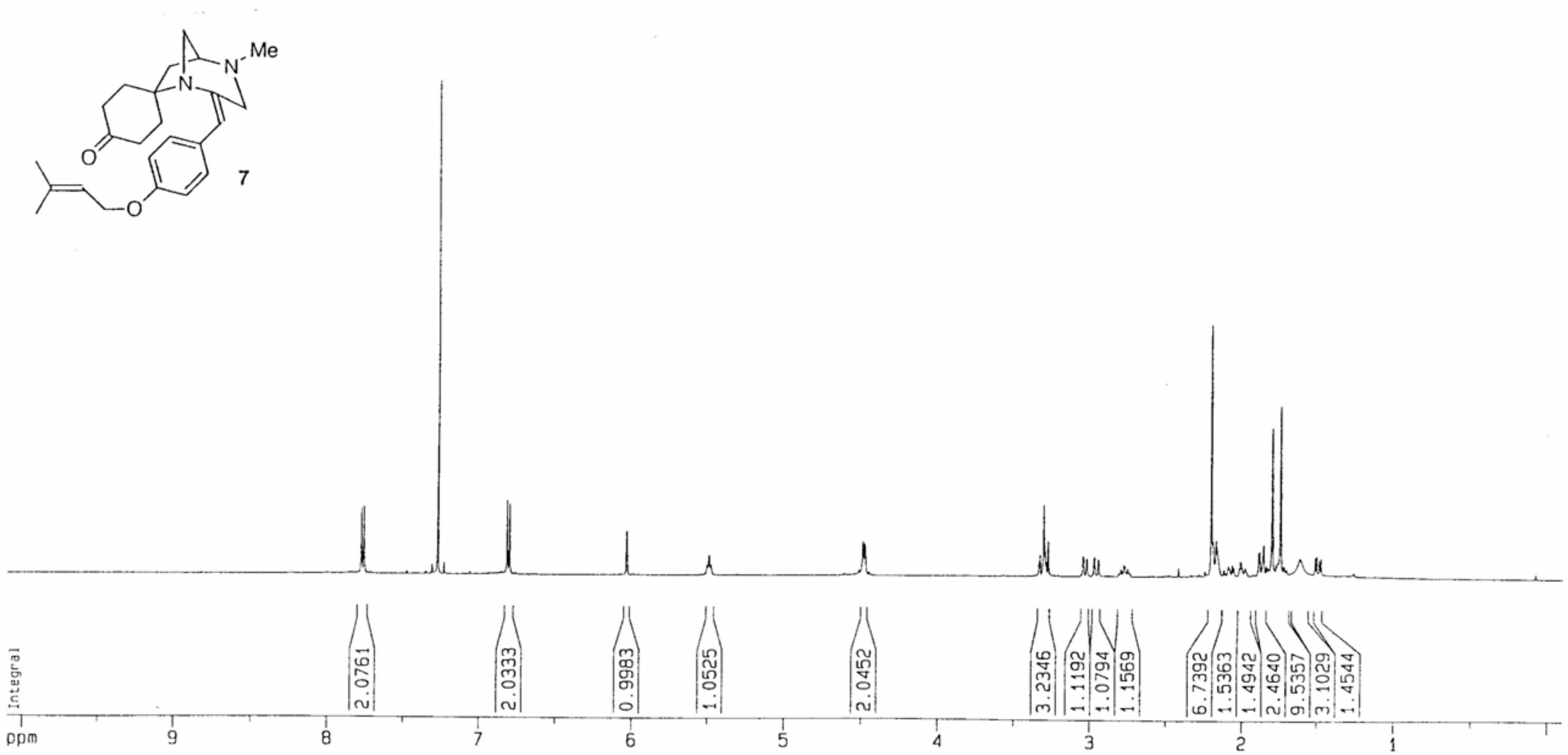
= 7.6 Hz), 1 H], 4.51-4.48 (m, 2 H), 3.96- 3.92, 3.86-3.81 (diastereomers, m, 4 H), 3.58-3.53 (m, 1 H), 3.57, 3.41 [diastereomers, (d, *J* = 7.6 Hz), (d, *J* = 7.9 Hz), 1 H], 3.28, 3.12 [diastereomers, (d, *J* = 12.5 Hz) (d, *J* = 12.4 Hz), 1 H], 2.93, 2.85 (diastereomers, s, 3 H), 2.83, 2.76 [diastereomers, (d, *J* = 12.5 Hz), 2.76 (d, *J* = 12.4 Hz), 1 H], 1.79, 1.78 (diastereomers, s, 3 H), 1.74, 1.73 (diastereomers, s, 3 H), 1.89-1.25 (complex series of m, 10 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 168.0, 158.7, 158.6, 138.1, 137.9 134.5, 134.2, 128.7, 128.1, 120.2, 120.1, 114.5, 114.3, 108.1, 108.0, 74.5, 73.9, 66.2, 65.8, 65.1, 64.9, 64.6, 64.54, 64.46, 64.3, 64.2, 60.5, 60.2, 52.7, 51.7, 45.9, 45.2, 36.4, 36.3, 33.8, 33.6, 32.61, 31.57, 32.5, 32.2, 32.0, 31.7, 29 9, 26.0, 8.4; high-resolution mass spectrum (EI) *m/z* 456.2633 [(M^+); calcd for $C_{26}H_{36}N_2O_5$ 456.2624].

(1*S*,2’*Z*,5*S*)-4-Methyl-2-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-dispiro[1,4diazabicyclo[3.2.1]octan-3-one-7,1’-cyclohexane-4’,2”-[1,3]dioxolane] (**19**). To a solution of **18** (40 mg, 0.088 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added triethylamine (73 μL, 0.526 mmol) and methanesulfonyl chloride (20 μL, 0.258 mmol). The mixture was stirred for 3 h and the solvent then removed under reduced pressure. The residue was dissolved in THF (8 mL), potassium *tert*-butoxide (147 mg, 1.31 mmol) was added and the mixture stirred at room temperature for 17 h. After this time, the mixture was concentrated to dryness in vacuo and the residue partitioned between saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (25 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography over silica gel (EtOAc/hexanes, 95:5) to afford **19** (29 mg, 75% yield): white solid; mp 141-143 °C (Et_2O/hexanes, 1:2); $[\alpha]^{27}_{D}$ -201.6° (*c* 0.35, $CHCl_3$); R_f 0.36 (EtOAc); IR (film) 2946, 2861, 1631, 1602, 1505, 1232, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2 H), 7.37 (s, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 5.53-5.48 (m, 1 H), 4.58-4.50 (m, 2 H), 3.89-3.82 (m, 4 H), 3.73 (m, 1 H), 3.30 (dd, *J* = 12.2, 2.2 Hz, 1 H), 3.13 (dd, *J* = 12.2, 2.3 Hz, 1 H), 3.03 (s, 3 H), 2.05-2.00 (m, 1 H), 1.94 (dd, *J* = 13.1, 2.0 Hz, 1 H), 1.86 (dd, *J* = 13.1, 4.4 Hz, 1 H), 1.82-1.56 (m, 6 H), 1.80 (s, 3 H), 1.76 (s, 3 H), 1.48-1.42 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 159.4, 138.5, 137.9, 132.9 (2 C), 129.5, 127.9, 119.7, 114.5 (2 C), 108.1, 66.6, 64.9, 64.5, 64.4, 61.0, 56.0, 42.8, 36.5, 34.3, 32.8, 32.7, 32.2, 26.1, 18.4; high-resolution mass spectrum (EI) *m/z* 438.2501 [(M^+); calcd for $C_{26}H_{34}N_2O_4$ 438.2519].

Preparation of alane (AlH_3) stock solution: To a stirred suspension of $LiAlH_4$ (38 mg, 1.001 mmol) in Et_2O (1 mL) at room temperature was added a solution of $AlCl_3$ (45 mg, 0.337 mmol) in Et_2O (3 mL). After stirring for 10 minutes this solution was immediately used for the following reaction:

(1*S*,2’*Z*,5*S*)-4-Methyl-2-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-dispiro[1,4diazabicyclo[3.2.1]octan-7,1’-cyclohexane-4’,2”-[1,3]dioxolane]. To a solution of **19** (20 mg, 0.046 mmol) in Et_2O (3 mL) at 0 °C was added alane (0.335 M in Et_2O, 410 μL, 0.137 mmol). The mixture was stirred at 0 °C for 1 h and then diluted with THF (5 mL) and quenched with saturated aqueous Na_2SO_4 (4-5 drops). The resultant white suspension was filtered through a plug of Celite 521 and the filter cake washed with THF (5 mL) followed by CH_2Cl_2 (20 mL). The combined filtrates were concentrated and the resulting residue purified by flash column chromatography on silica gel (NH_3 in $MeOH/CH_2Cl_2$, 2:98) to give the title compound (15 mg, 77 % yield): colorless oil; $[\alpha]^{27}_{D}$ -134.6° (*c* 0.15, $CHCl_3$); R_f 0.29 (NH_3 in $MeOH/CH_2Cl_2$, 5:95); IR (film) 2929, 2879, 1603, 1507, 1374, 1238, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.93 (s, 1 H), 5.52-5.49 (m, 1 H), 4.54-4.48 (m, 2 H), 3.92- 3.83 (m, 4 H), 3.24-3.19 (m, 3 H), 2.90-2.87 (m, 2 H), 2.17 (s, 3 H), 1.93-1.89 (m, 2 H), 1.84-1.50 (m, 7 H), 1.80 (s, 3 H), 1.74 (s, 3 H), 1.46 (dd, *J* = 13.9, 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 142.2, 138.2, 131.1 (2 C), 129.3, 122.5, 120.0, 114.2 (2 C), 108.9, 64.8, 64.6, 64.4, 64.3, 61.3, 58.5, 56.2, 42.7, 36.1, 33.8, 32.5, 32.2, 29.7, 26.1, 18.4; high-resolution mass spectrum (EI) *m/z* 424.2714 [(M^+); calcd for $C_{26}H_{36}N_2O_3$ 424.2726].

(1'*S*,2'*Z*,5'*S*)-4'-Methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan-4-one [7, (-)-TAN1251A]: A solution of the above enamine (9.5 mg, 0.022 mmol) and 1 M aqueous HCl (600 μL) in acetone (2 mL) was stirred at room temperature for 12 h. The reaction mixture was then quenched with saturated aqueous Na_2CO_3 (2 mL) and concentrated to dryness under reduced pressure. The residue was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous Na_2CO_3 (10 mL), the organic phase separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with saturated aqueous Na_2CO_3 (5 mL) then brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated and the resulting residue purified by flash column chromatography over silica gel (NH_3 in MeOH/CH_2Cl_2, 2:98) to afford (-)-**TAN1251A** (6.8 mg, 78% yield): white solid; mp 116-118 °C (lit.[9] 118.5-120 °C); $[\alpha]^{28}_{D}$ –10.1° (*c* 0.41, MeOH) (lit.[9] $[\alpha]_D$ –8.1° (*c* 0.42, MeOH)), R_f 0.29 (NH_3 in MeOH/CH_2Cl_2, 5:95); IR (film) 1715, 1603, 1507, 1238, 1173, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.03 (d, *J* = 1.3 Hz, 1 H), 5.50-5.47 (m, 1 H), 4.41-4.45 (m, 2 H), 3.33-3.27 (m, 3 H), 3.03 (dd, *J* = 11.6, 1.8 Hz, 1 H), 2.96 (d, *J* = 14.0, 1.3 Hz, 1 H), 2.81-2.73 (m, 1 H), 2.20 (s, 3 H); 2.19-2.16 (m, 3 H), 2.07 (dd, *J* = 12.4, 5.0 Hz, 1 H), 2.02-1.97 (m, 1 H), 1.87 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.86-1.70 (m, 2 H), 1.80 (s, 3 H), 1.74 (s, 3 H), 1.5 (dd, *J* = 14.0, 5.5 Hz, 1 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 158.2, 141.8, 138.3, 131.0 (2 C), 128.8, 123.2, 120.0, 114.4 (2 C), 64.9, 64.3, 61.5, 58.7, 55.9, 42.7, 38.9, 38.8, 38.5, 34.9, 32.5, 26.0, 18.4; high-resolution mass spectrum (FAB) *m*/*z* 381.2560 [$(M+H)^+$; calcd for $C_{24}H_{33}N_2O_2$ 381.2542].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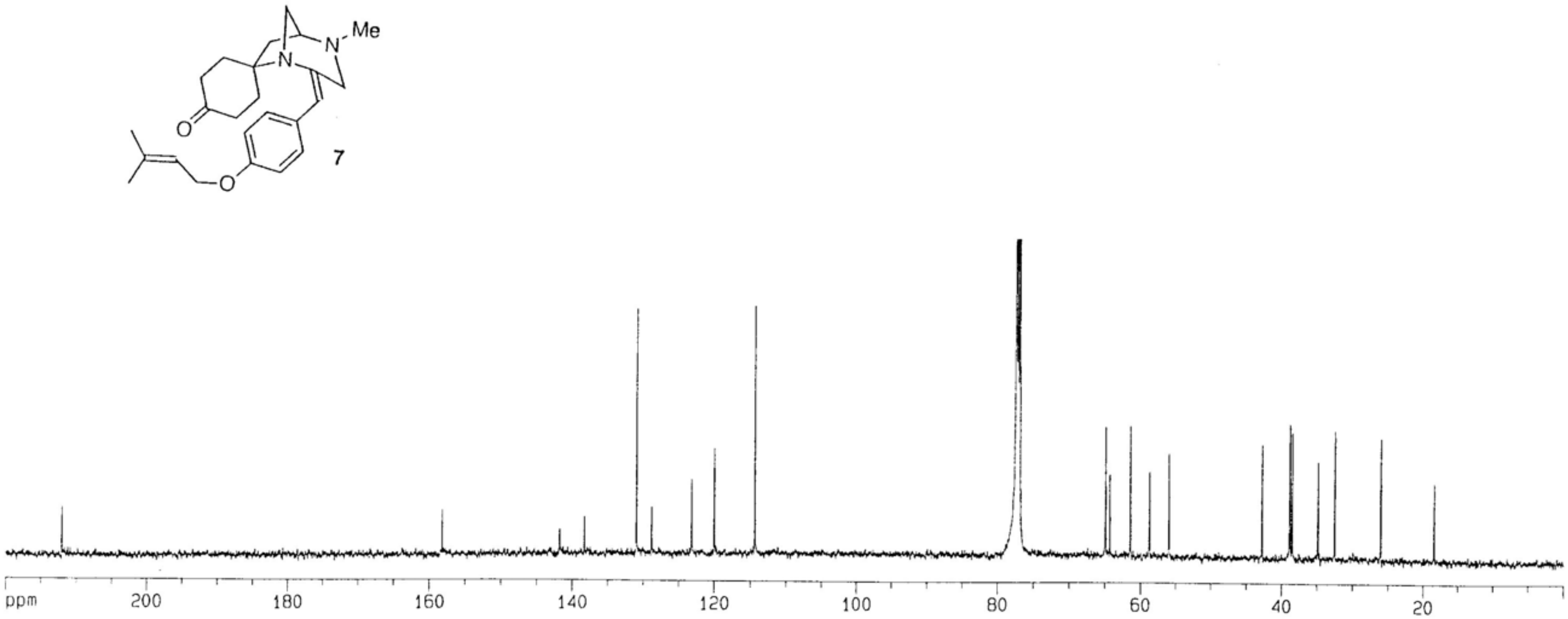

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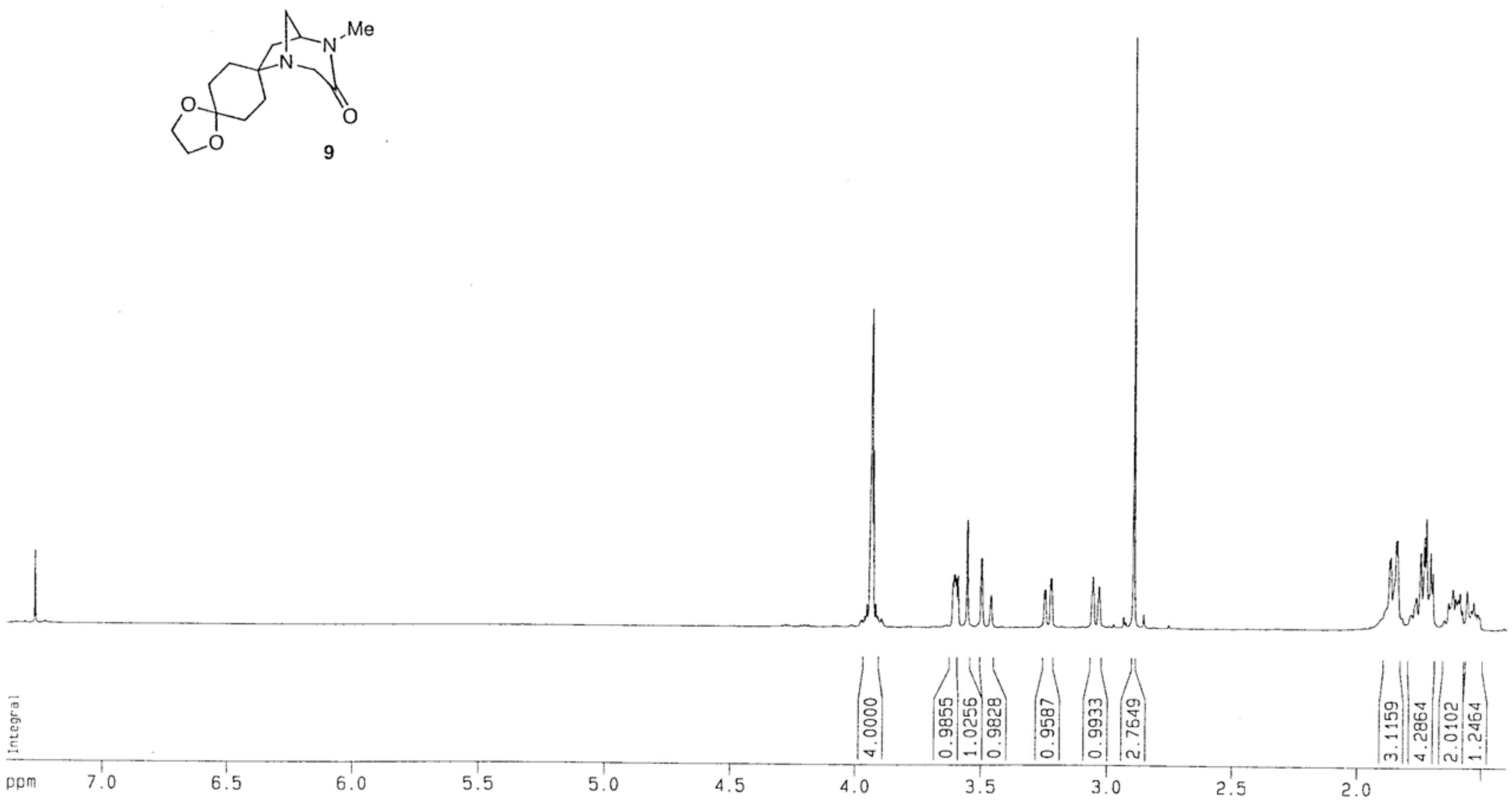
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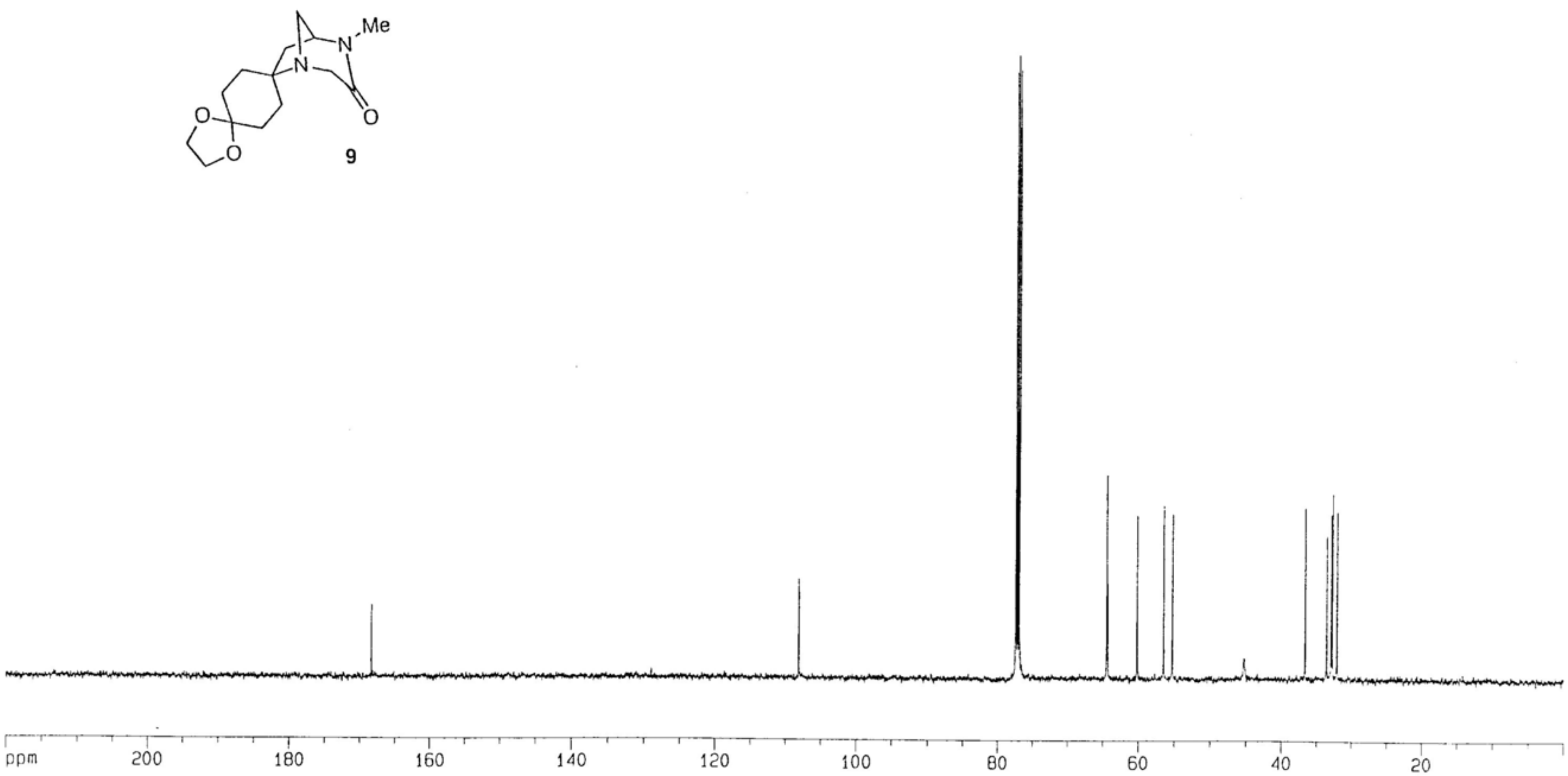
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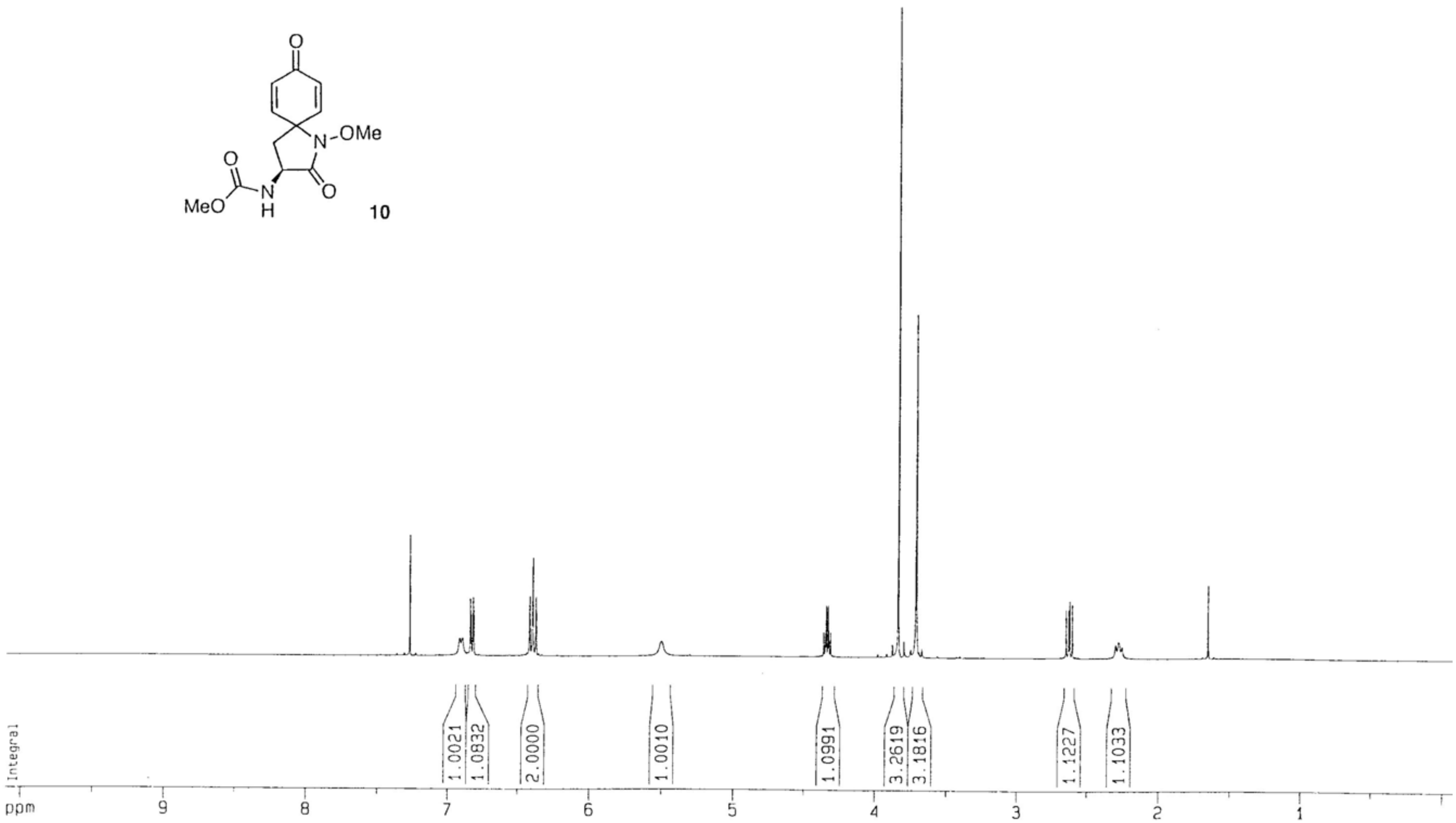

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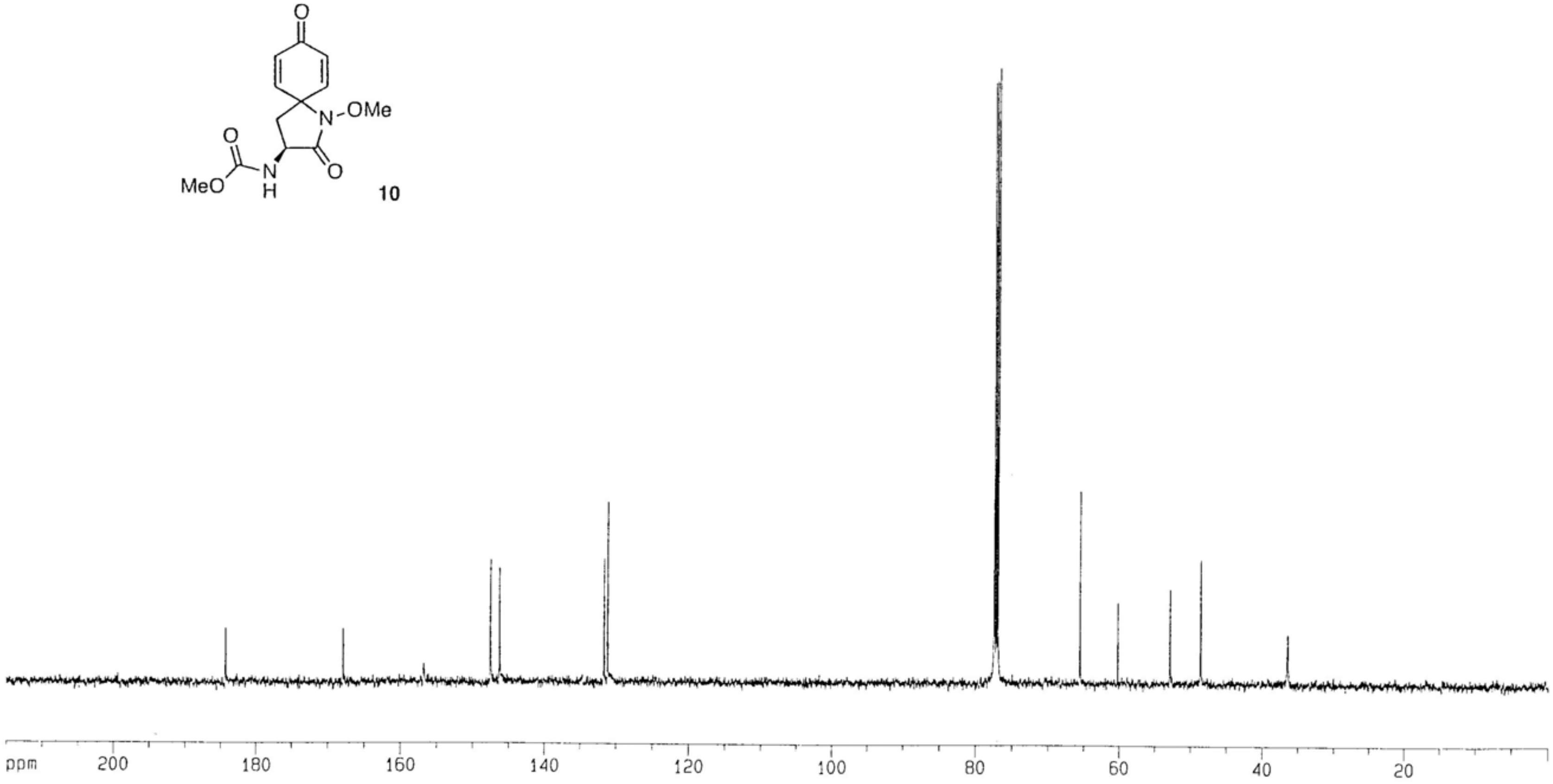
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