Synthesis, Structural Analysis, and Reactivity of Bridged Orthoamides by Intramolecular Schmidt Reaction

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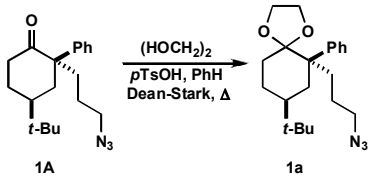
List of Known Compounds

The following compounds are known: azides **1A**, **1G**, **1H**, **1I**, **1J**, **1K**,[1,2] **1l**, **1M**,[3] **1n**,[4] 2-allyl-2-phenylcyclohexanone,[5] enamine **5**.[6] 2-Allyl-2-phenylcyclohexanone was prepared by alkylation of the commercially available 2-phenyl cyclohexanone with allyl bromide according to the reported procedure.[1]

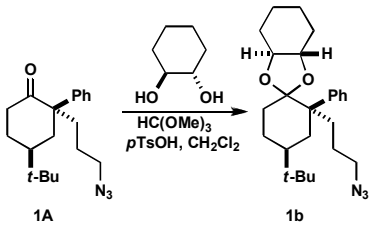
Preparation of Starting Materials

Scheme A. *Synthesis of azido ketal **1a** (Table 1)*



(6R,8S)-6-(3-Azidopropyl)-8-*tert*-butyl-6-phenyl-1,4-dioxaspiro[4.5]decane (1a). To a solution of azide **1A** (0.16 g, 0.50 mmol) in benzene (10 mL), ethylene glycol (2 mL) was added followed by *p*TsOH (5 mg, 0.05 mmol) and the resulting mixture was heated under Dean-Stark apparatus for 6 h. The reaction was cooled to rt, diluted with Et_2O (20 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL), extracted with Et_2O (3 x 30 mL), dried and concentrated. Chromatography (1/40 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.55, 1/10 EtOAc/hexanes). Yield 81% (0.14 g, 0.40 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.02-1.14 (m, 1H), 1.27-1.49 (m, 3H), 1.65-1.72 (m, 1H), 1.76-1.88 (m, 2H), 1.92-2.15 (m, 3H), 2.28 (td, *J* = 3.4, 13.1 Hz, 1H), 2.64 (qd, *J* = 1.0, 7.1 Hz, 1H), 3.16-3.28 (m, 2H), 3.51-3.56 (m, 1H), 3.58-3.63 (m, 1H), 3.75 (qd, *J* = 0.8, 7.2 Hz, 1H), 7.22 (tt, *J* = 1.0, 7.2 Hz, 1H), 7.28-7.34 (m, 2H), 7.54 (dd, *J* = 0.8, 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.6, 27.7, 29.3, 31.0, 32.5, 32.8, 41.3, 48.6, 52.1, 64.8, 65.1, 112.3, 126.0, 127.4, 128.6, 142.8; IR (neat) 2960, 2870, 2096, 1469, 1366, 1263, 1153, 1088, 1034, 950 cm^{-1}; HRMS calcd for $C_{21}H_{31}N_3O_2Na$ (M^+ + Na) 380.2314, found 380.2311.

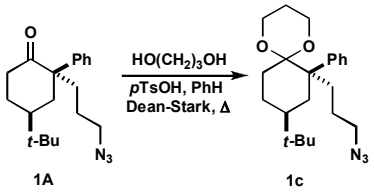
Scheme B. *Synthesis of azido ketal **1b** (Table 1)*



(2'R,3aS,4'S,7aS)-2'-(3-Azidopropyl)-4'-*tert*-butyl-2'-phenylhexahydrospiro [benzo[d][1,3]dioxole-2,1'-cyclohexane] (1b). To a solution of azide **1A** (0.0483 g, 0.15

mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) trans-1,2-cyclohexanediol (0.12 g, 1.05 mmol, 7.0 equiv) was added, followed by *p*TsOH (4 mg, 0.1 equiv) and trimethyl orthoformate (0.082 g, 0.75 mmol, 5.0 equiv). The resulting mixture was stirred at rt for 15 h, concentrated and purified directly by chromatography (1/100 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.44-0.46, 1/10 EtOAc/hexanes) as a mixture of two diastereoisomers (dr = 71:29, less polar:more polar). Further purification by PTLC (1/10 EtOAc/hexanes) afforded a sample consisting of 9:1 mixture of less polar:more polar diastereoisomer and a sample consisting of 1:5 mixture of less polar:more polar diastereoisomer. Less polar diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69-0.82 (m, 1H), 0.99 (s, 9H), 1.04-1.18 (m, 4H), 1.31-1.48 (m, 4H), 1.50-1.66 (m, 2H), 1.69-1.84 (m, 4H), 1.96-2.17 (m, 4H), 2.27 (td, *J* = 3.4, 13.5 Hz, 1H), 3.13-3.29 (m, 3H); 7.22 (tt, *J* = 2.0, 7.2 Hz, 1H), 7.27-7.33 (m, 2H), 7.53-7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.5, 23.6, 24.3, 27.7, 28.3, 29.0, 29.4, 31.1, 32.5, 34.0, 41.5, 48.7, 52.1, 79.9, 79.9, 111.4, 126.1, 127.0, 129.2, 142.3; IR (neat) 2945, 2869, 2095, 1445, 1365, 1262, 1216, 1184, 1115, 1068, 913 cm^{-1}; HRMS calcd for $C_{25}H_{38}NO_2$ ($M^+ + H - N_2$) 384.2903, found 384.2896. More polar diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (qd, *J* = 3.8, 11.8 Hz, 1H), 0.82-0.94 (m, 2H), 0.96 (s, 9H), 1.04-1.25 (m, 4H), 1.33-1.51 (m, 3H), 1.68-1.82 (m, 3H), 1.84-2.02 (m, 3H), 2.06-2.20 (m, 3H), 2.85 (td, *J* = 3.4, 15.0 Hz, 1H), 3.06-3.13 (m, 1H), 3.21-3.32 (m, 2H), 7.18-7.24 (m, 1H), 7.28-7.33 (m, 2H), 7.51-7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.5, 23.5, 24.7, 27.7, 28.3, 28.7, 29.4, 30.9, 32.5, 32.8, 40.9, 48.8, 52.1, 79.1, 80.5, 111.7, 126.0, 127.2, 129.1, 142.4; IR (neat) 2944, 2869, 2095, 1445, 1365, 1262, 1216, 1186, 1136, 1115, 913 cm^{-1}; HRMS calcd for $C_{25}H_{38}NO_2$ ($M^+ + H - N_2$) 384.2903, found 384.2875.

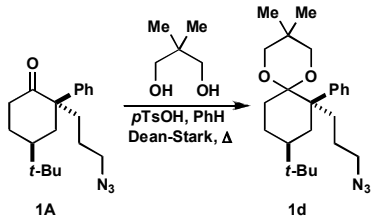
Scheme C. *Synthesis of azido ketal **1c** (Table 1)*



(7R,9S)-7-(3-Azidopropyl)-9-*tert*-butyl-7-phenyl-1,5-dioxaspiro[5.5]undecane (1c). According to the procedure described for **1a**, the reaction of **1A** (0.0508 g, 0.16 mmol), 1,3-propanediol (2 mL) and *p*TsOH (3 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 6 h afforded after chromatography (1/100 EtOAc/hexanes) the title compound as oil (R_f = 0.53, 1/10 EtOAc/hexanes). Yield 72% (0.0428 g, 0.12 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-0.95 (m, 1H), 0.98, (s, 9H), 1.11-1.25 (m, 2H), 1.29-1.45 (m, 2H), 1.49-1.63 (m, 2H), 1.67-1.73 (m, 1H), 1.79 (tt, *J* = 2.4, 13.0 Hz, 1H), 1.92-12.04 (m, 2H), 2.17 (td, *J* = 3.5, 13.0 Hz, 1H), 2.76 (tt, *J* = 3.4, 14.2 Hz, 1H), 2.09-3.23 (m, 2H), 3.47-3.53 (m, 1H), 3.76-3.84 (m 2H), 4.01 (td, *J* = 2.8, 11.8 Hz, 1H), 7.18-7.24 (m, 1H), 7.26-7.33 (m, 2H), 7.58-7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.1, 24.2, 25.1, 27.7, 29.6, 29.8, 32.5, 41.8, 49.4, 52.2, 58.8, 59.3, 100.5, 125.4, 126.9, 128.9, 144.3; IR (neat) 2961, 2867, 2095, 1467, 1366, 1245, 1179, 1139, 1115,

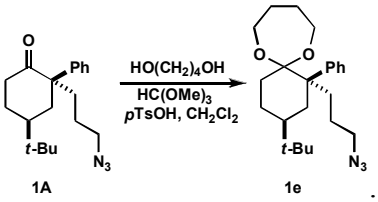
1098, 990, 913 cm^{-1}; HRMS calcd for $C_{22}H_{33}N_3O_2Na$ (M^+ + Na) 394.2470, found 394.2485.

Scheme D. *Synthesis of azido ketal* ***1d*** *(Table 1)*



((7R,9S)-7-(3-Azidopropyl)-9-*tert*-butyl-3,3-dimethyl-7-phenyl-1,5-dioxaspiro [5.5]undecane (1d). According to the procedure described for **1a**, the reaction of **1A** (0.0551 g, 0.175 mmol), neopentyl glycol (0.36 g, 3.5 mmol, 20 equiv) and *p*TsOH (3 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 12 h afforded after chromatography (1/100 EtOAc/hexanes) the title compound as oil (R_f = 0.55, 1/10 EtOAc/hexanes). Yield 60% (0.0418 g, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 3H), 0.60 (s, 3H), 0.97 (s, 9H), 0.99-1.10 (m, 1H), 1.21 (td, *J* = 4.1, 13.2 Hz, 1H), 1.27-1.54 (m, 3H), 1.66-1.78 (m, 2H), 1.99-2.14 (m, 2H), 2.27 (td, *J* = 3.5, 13.7 Hz, 1H), 2.72 (tt, *J* = 3.4, 14.1 Hz, 1H), 3.06 (dd, *J* = 2.5, 11.3 Hz, 1H), 3.14-3.29 (m, 3H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.68 (d, *J* = 11.2 Hz, 1H), 7.16-7.22 (m, 1H), 7.26-7.32 (m, 2H), 7.56-7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 22.4, 22.7, 23.0, 27.6, 28.8, 29.6, 29.7, 29.7, 32.5, 41.7, 49.3, 52.2, 69.5, 70.0, 100.1, 125.5, 126.8, 129.3, 143.2; IR (neat) 2955, 2867, 2095, 1471, 1394, 1365, 1262, 1179, 1115, 1095, 1039, 1020, 963, 912 cm^{-1}; HRMS calcd for $C_{24}H_{38}NO_2$ ($M^+ + H - N_2$) 372.2903, found 372.2904.

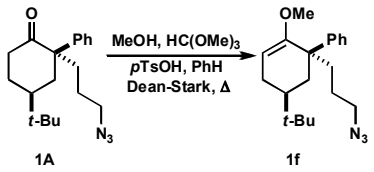
Scheme E. *Synthesis of azido ketal* ***1e*** *(Table 1)*



(1R,3S)-1-(3-Azidopropyl)-3-*tert*-butyl-1-phenyl-7,12-dioxaspiro[5.6] dodecane (1e). According to the procedure described for **1b**, the reaction of **1A** (0.0545 g, 0.17 mmol), 1,4-butanediol (0.15 g, 1.7 mmol, 10 equiv), trimethyl orthoformate (0.093 g, 0.85 mmol, 5.0 equiv) and *p*TsOH (3 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at rt for 20 h after chromatography (1/200-1/100 EtOAc/hexanes) the title compound as oil (R_f = 0.58, 1/10 EtOAc/hexanes). Yield 49% (0.0321 g, 0.083 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.03-1.14 (m, 1H), 1.18-1.42 (m, 6H), 1.58-1.66 (m, 2H), 1.72-1.81 (m, 2H), 1.98-2.13 (m, 3H), 2.32 (td, *J* = 3.2, 14.6 Hz, 1H), 2.49-2.57 (m, 1H), 3.15-3.27 (m, 3H), 3.42-3.49 (m, 1H), 3.59-3.68 (m, 1H), 7.19-7.25 (m, 1H), 7.26-7.33 (m, 2H), 7.58-7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.9, 27.6, 29.8, 30.0, 30.6,

31.2, 31.7, 32.5, 41.4, 49.5, 52.2, 63.5, 64.3, 103.9, 126.0, 127.2, 129.5, 143.3; IR (neat) 2957, 2094, 1467, 1365, 1235, 1186, 1140, 1095, 1069, 1004, 913 cm^{-1}; HRMS calcd for $C_{23}H_{36}NO_2$ ($M^+ + H - N_2$) 358.2746, found 358.2752. Note: the reaction of **1A** with (2*Z*)-2-butene-1,4-diol under identical reaction conditions afforded the corresponding ketal in 80% yield.

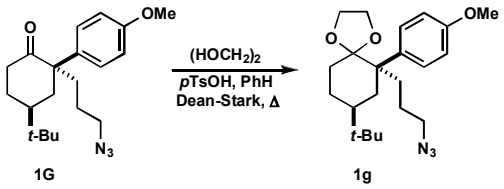
Scheme F. *Synthesis of enol ether **1f** (Table 1)*



1A 1f

((1R,5S)-1-(3-Azidopropyl)-5-*tert*-butyl-2-methoxycyclohex-2-enyl)benzene (1f). To a solution of **1A** (0.0959 g, 0.30 mmol) in methanol (5 mL), trimethyl orthoformate (0.33 mL, 3.0 mmol, 10 equiv) was added followed by *p*TsOH (3 mg, 0.1 mmol) and the resulting mixture was heated to reflux for 3 h. Work-up as described for **1a**, followed by chromatography (1/50 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.63, 1/10 EtOAc/hexanes). Yield 63% (0.0471 g, 0.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.47 (t, *J* = 13.0 Hz, 1H), 1.56-1.65 (m, 1H), 1.70-187 (m, 3H), 1.98 (ddd, *J* = 2.0, 11.2, 13.3 Hz, 1H), 2.08-2.25 (m, 3H), 3.24-3.36 (m, 2H), 3.47 (s, 3H), 4.92 (dd, *J* = 1.9, 6.2 Hz, 1H), 7.17-7.23 (m, 1H), 7.25-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.6, 27.3, 32.1, 35.5, 41.0, 43.7, 47.3, 52.4, 54.0, 96.6, 125.6, 126.6, 128.2, 147.9, 158.3; IR (neat) 2959, 2095, 1661, 1600, 1495, 1466, 1365, 1208, 1168, 1040, 912 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ ($M^+ + H - N_2$) 300.2327, found 300.2311.

Scheme G. *Synthesis of azido ketal **1g** (Table 2)*

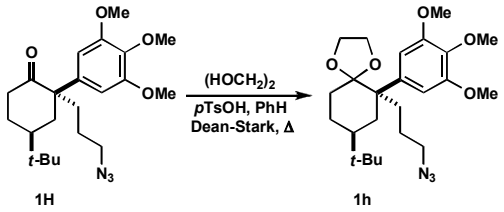


1G 1g

(6R,8S)-6-(3-Azidopropyl)-8-*tert*-butyl-6-(4-methoxyphenyl)-1,4-dioxaspiro [4.5]decane (1g). According to the procedure described for **1a**, the reaction of **1G** (0.105 g, 0.31 mmol), ethylene glycol (2 mL) and *p*TsOH (6 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 6 h afforded after chromatography (1/100-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.65, 1/4 EtOAc/hexanes). Yield 53% (0.0622 g, 0.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.02-1.15 (m, 1H), 1.26-1.45 (m, 3H), 1.63-1.71 (m, 1H), 1.73-1.84 (m, 2H), 1.91-2.12 (m, 3H), 2.22 (td, *J* = 3.5, 13.1 Hz, 1H), 2.69 (qd, *J* = 1.0, 7.2 Hz, 1H), 3.16-3.28 (m, 2H), 3.51-3.56 (m, 1H), 3.58-3.64 (m, 1H), 3.74 (q, *J* = 7.4 Hz, 1H), 3.82 (s, 3H), 6.83-6.88 (m, 2H), 7.41-7.46

(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.6, 27.7, 29.3, 31.2, 32.5, 32.8, 41.4, 48.0, 52.1, 55.1, 64.8, 65.1, 112.3, 112.7, 129.5, 134.8, 157.8; IR (neat) 2957, 2096, 1609, 1514, 1466, 1366, 1252, 1185, 1154, 1086, 1036, 950 cm^{-1}; HRMS calcd for $C_{22}H_{34}NO_3$ ($M^+ + H - N_2$) 360.2539, found 360.2544.

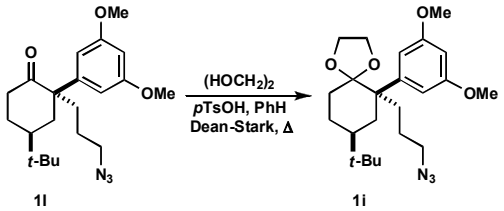
Scheme H. *Synthesis of azido ketal* ***1h*** *(Table 2)*



1H 1h

(6R,8S)-6-(3-Azidopropyl)-8-*tert*-butyl-6-(3,4,5-trimethoxyphenyl)-1,4-dioxaspiro[4.5]decane (1h). According to the procedure described for **1a**, the reaction of **1H** (0.108 g, 0.27 mmol), ethylene glycol (2 mL) and *p*TsOH (3 mg, 0.05 mmol) in benzene (10 mL) under Dean-Stark apparatus for 5 h afforded after chromatography (1/100-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.32, 1/4 EtOAc/hexanes). Yield 81% (0.0966 g, 0.22 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.02-1.14 (m, 1H), 1.2801.43 (m, 3H), 1.67 (tt, *J* = 2.4, 13.7 Hz, 1H), 1.72-1.81 (m, 2H), 1.86-1.98 (m, 2H), 2.01-2.11 (m, 1H), 2.18 (td, *J* = 3.5, 13.2 Hz, 1H), 2.82 (qd, *J* = 0.8, 7.6 Hz, 1H), 3.23 (t, *J* = 6.6 Hz, 2H), 3.58-3.68 (m, 2H), 3.77 (q, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 6H), 6.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.4, 27.7, 29.8, 31.2, 32.4, 32.9, 41.5, 48.7, 52.1, 56.3, 60.9, 64.9, 65.1, 106.6, 106.7, 112.3, 138.8, 152.1; IR (neat) 2956, 1095, 1585, 1512, 1465, 1411, 1326, 1248, 1183, 1126, 1012 cm^{-1}; HRMS calcd for $C_{24}H_{37}N_3O_5Na$ (M^+ + Na) 470.2631, found 470.2617.

Scheme I. *Synthesis of azido ketal* ***1i*** *(Table 2)*

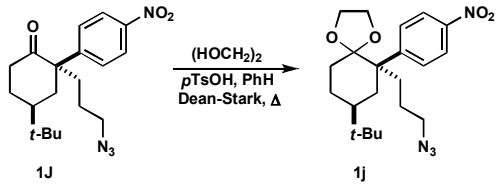


1I 1i

(6R,8S)-6-(3-Azidopropyl)-8-*tert*-butyl-6-(3,5-dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane (1i). According to the procedure described for **1a**, the reaction of **1I** (0.0972 g, 0.26 mmol), ethylene glycol (2 mL) and *p*TsOH (5 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 8 h afforded after chromatography (1/100-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.55, 1/4 EtOAc/hexanes). Yield 77% (0.0833 g, 0.20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.01-1.13 (m, 1H), 1.30-1.43 (m, 3H), 1.67 (tt, *J* = 3.9, 13.8 Hz, 1H), 1.72-1.78 (m, 1H), 1.82-1.98 (m, 3H), 2.02-2.11 (m, 1H), 2.17 (td, *J* = 3.7, 13.8 Hz, 1H), 2.89 (qd, *J* = 0.9, 7.4 Hz,

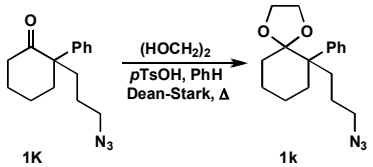
1H), 3.13-3.26 (m, 2H), 3.61-3.70 (m, 2H), 3.76-3.82 (m, 1H), 3.81 (s, 6H), 6.36 (t, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.4, 27.6, 29.9, 31.2, 32.5, 32.9, 41.4, 48.7, 52.1, 55.2, 64.9, 65.1, 97.3, 107.6, 112.4, 146.0, 159.9; IR (neat) 2956, 2095, 1595, 1455, 1421, 1289, 1205, 1156, 1081, 833 cm^{-1}; HRMS calcd for $C_{23}H_{36}NO_4$ ($M^+ + H - N_2$) 390.2644, found 390.2648.

Scheme J. *Synthesis of azido ketal **1j** (Table 2)*



(6R,8S)-6-(3-Azidopropyl)-8-*tert*-butyl-6-(4-nitrophenyl)-1,4-dioxaspiro [4.5]decane (1j). According to the procedure described for **1a**, the reaction of **1J** (0.102 g, 0.28 mmol), ethylene glycol (2 mL) and *p*TsOH (3 mg, 0.05 mmol) in benzene (10 mL) under Dean-Stark apparatus for 8 h afforded after chromatography (1/100-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.79, 1/4 EtOAc/hexanes). Yield 90% (0.101 g, 0.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-1.00 (m, 1H), 0.98 (s, 9H), 1.30-1.48 (m, 3H), 1.67-1.73 (m, 1H), 1.75-1.82 (m, 1H), 1.85-1.97 (m, 2H), 2.04 (t, *J* = 12.2 Hz, 1H), 2.16 (td, *J* = 5.1, 12.3 Hz, 1H), 2.28 (td, *J* = 3.6, 13.2 Hz, 1H), 2.79 (q, *J* = 7.0 Hz, 1H), 3.18-3.29 (m, 2H), 3.50-3.56 (m, 1H), 3.61-3.67 (m, 1H), 3.79 (q, *J* = 7.1 Hz, 1H), 7.68-7.74 (m, 2H), 8.12-8.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.3, 27.6, 29.4, 31.1, 32.2, 32.5, 41.3, 49.3, 51.8, 64.6, 64.9, 112.0, 122.3, 129.6, 146.3, 151.4; IR (neat) 2960, 2871, 2096, 1604, 1517, 1471, 1348, 1264, 1183, 1149, 1085, 1034, 948, 856 cm^{-1}; HRMS calcd for $C_{21}H_{31}N_2O_4$ ($M^+ + H - N_2$) 375.2284, found 375.2267.

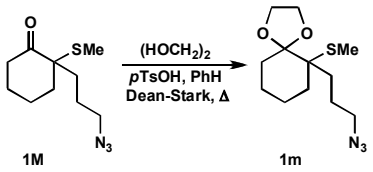
Scheme K. *Synthesis of azido ketal **1k** (Table 2)*



6-(3-Azidopropyl)-6-phenyl-1,4-dioxaspiro[4.5]decane (1k). According to the procedure described for **1a**, the reaction of **1K** (0.14 g, 0.55 mmol), ethylene glycol (2 mL) and *p*TsOH (5 mg, 0.05 mmol) in benzene (10 mL) under Dean-Stark apparatus for 8 h afforded after chromatography (1/100-1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.49, 1/10 EtOAc/hexanes). Yield 76% (0.126 g, 0.42 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04-1.15 (m, 1H), 1.26-1.42 (m, 1H), 1.51-1.69 (m, 4H), 1.72-1.79 (m, 1H), 1.81-1.93 (m, 2H), 1.97-2.07 (m, 1H), 2.20 (td, *J* = 4.0, 13.0 Hz, 1H), 2.33 (td, *J* = 3.4,

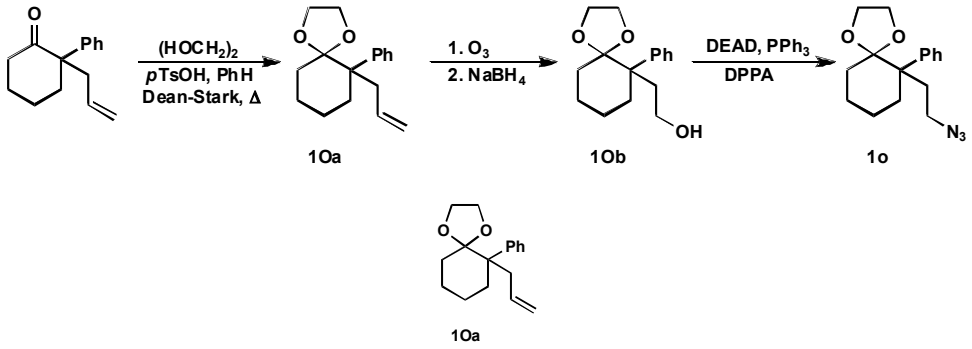
14.3 Hz, 1H), 2.90 (q, *J* = 6.8 Hz, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 3.54-3.61 (m, 1H), 3.65-3.71 (m, 1H), 3.78 (q, *J* = 7.0 Hz, 1H), 7.21 (tt, *J* = 1.1, 6.4 Hz, 1H), 7.27-7.33 (m, 2H), 7.53-7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 23.2, 23.6, 29.5, 30.1, 32.4, 49.0, 52.1, 64.8, 64.9, 112.5, 125.9, 127.5, 128.8, 142.5; IR (neat) 2950, 2869, 2096, 1499, 1446, 1350, 1266, 1177, 1152, 1093, 1033, 954, 872, 761 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_2$ ($M^+ + H - N_2$) 274.1807, found 274.1795.

Scheme L. *Synthesis of azido ketal **1m** (Table 2)*



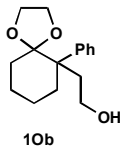
6-(3-Azidopropyl)-6-(methylthio)-1,4-dioxaspiro[4.5]decane (1m). According to the procedure described for **1a**, the reaction of **1M** (0.0445 g, 0.20 mmol), ethylene glycol (2 mL) and *p*TsOH (4 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 3 h afforded after chromatography (1/100-1/10 EtOAc/hexanes) the title compound as oil (R_f = 0.50, 1/10 EtOAc/hexanes). Yield 69% (0.0374 g, 0.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.48 (m, 1H), 1.53-1.91 (m, 10H), 2.09 (s, 3H), 2.11-2.20 (m, 1H), 3.33 (t, *J* = 6.3 Hz, 2H), 3.94-4.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 21.0, 23.3, 23.5, 28.6, 31.3, 33.5, 52.2, 54.9, 65.0, 65.3, 113.6; IR (neat) 2932, 2878, 2095, 1438, 1349, 1261, 1175, 1095, 1035, 948, 913, 866 cm^{-1}; HRMS calcd for $C_{12}H_{22}NO_2S$ ($M^+ + H - N_2$) 244.1371, found 244.1366.

Scheme M. *Synthesis of azido ketal **1o** (Table 2)*



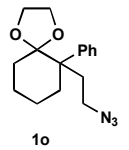
6-Allyl-6-phenyl-1,4-dioxaspiro[4.5]decane (1Oa). According to the procedure described for **1a**, the reaction of 2-allyl-2-phenylcyclohexanone (0.20 g, 0.92 mmol), ethylene glycol (2 mL) and *p*TsOH (20 mg, 0.1 mmol) in benzene (10 mL) under Dean-Stark apparatus for 5 h afforded after chromatography (1/100-1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.57, 1/10 EtOAc/hexanes). Yield 91% (0.216 g, 0.84 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56-1.68 (m, 4H), 1.72-1.81 (m, 1H), 1.84-1.92 (m, 2H), 2.27-2.34 (m, 1H), 2.71 (dd, *J* = 8.8, 14.4 Hz, 1H), 2.95 (q, *J* = 6.8 Hz, 1H), 2.98-3.05 (m, 1H), 3.57-3.63 (m, 1H), 3.68-3.73 (m, 1H), 3.80 (q, *J* = 7.0 Hz, 1H), 4.87-4.92 (m, 1H), 4.99-5.07 (m, 1H), 5.26-5.39 (m, 1H), 7.22 (tt, *J* = 1.2, 6.4 Hz, 1H), 7.28-7.35 (m, 2H), 7.57-7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 23.6, 30.3, 32.4, 37.2, 48.9, 64.8, 64.9, 112.4, 116.7, 125.8, 127.3, 129.1, 134.9, 142.6; IR (neat) 2949, 2868, 1498, 1445, 1175, 1146, 1085, 1040, 948, 912, 873 cm^{-1}; HRMS calcd for $C_{17}H_{26}NO_2$ (M^+ + NH_4) 276.1964, found 276.1965.



1Ob

2-(6-Phenyl-1,4-dioxaspiro[4.5]decan-6-yl)ethanol (1Ob). A solution of **1Oa** (0.21 g, 0.81 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (10 mL/20 mL) with Sudan III as indicator was ozonized at -78 °C until the color changed from light pink to transparent. The reaction mixture was purged with argon and $NaBH_4$ (0.30 g, 8.2 mmol, 10 equiv) was added in one portion. The reaction was warmed to rt and stirred for additional 2 h. The reaction was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 50 mL), dried and concentrated. Chromatography (1/4-1/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.48, 1/1 EtOAc/hexanes). Yield 85% (0.18 g, 0.69 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.63 (m, 4H), 1.67-1.76 (m, 1H), 1.81-1.89 (m, 3H), 2.12-2.19 (m, 1H), 2.24-2.33 (m, 1H), 2.38-2.46 (m, 1H), 3.05 (br, 1H), 3.18-3.25 (m, 1H), 3.36-3.43 (m, 1H), 3.59-3.65 (m, 1H), 3.69-3.75 (m, 1H), 3.80 (q, *J* = 6.7 Hz, 1H), 7.16-7.22 (m, 1H), 7.25-7.32 (m, 2H), 7.56-7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.6, 31.5, 32.1, 36.1, 48.4, 59.2, 64.6, 64.9, 112.4, 126.0, 127.6, 128.7, 142.6; IR (neat) 3368, 2948, 1445, 1177, 1147, 1092, 1032, 952, 913 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_3Na$ (M^+ + Na) 285.1467, found 285.1459.



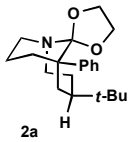
1o

6-(2-Azidoethyl)-6-phenyl-1,4-dioxaspiro[4.5]decane (1o). To a solution of **1Ob** (0.0875 g, 0.33 mmol, 1.0 equiv) in THF (10 mL) at 0 °C, PPh_3 (0.263 g, 1.0 mmol, 3.0 equiv) was added, followed by diethyl azodicarboxylate (40% in toluene, 0.45 mL, 1.0 mmol, 3.0 equiv) and diphenyl phosphoryl azide (0.22 mL, 1.0 mmol, 3.0 equiv). The reaction mixture was stirred at rt for 2 h, solvent was removed under reduced pressure and the residue was purified directly by chromatography (1/100 EtOAc/hexanes, followed by 1/100-1/50 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.42, 1/10 EtOAc/hexanes). Yield 96% (0.0826 g, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.66 (m, 4H), 1.71-1.77 (m, 1H), 1.79-1.88 (m, 2H), 2.17-2.25 (m, 1H), 2.29-2.38

(m, 1H), 2.42-2.51 (m, 1H), 2.83-3.03 (m, 3H), 3.61-3.67 (m, 1H), 3.71-3.76 (m, 1H), 3.82 (q, J = 7.0 Hz, 1H), 7.23 (tt, J = 1.2, 6.4 Hz, 1H), 7.29-7.35 (m, 2H), 7.55-7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 23.5, 30.7, 31.8, 32.2, 47.6, 48.4, 64.7, 64.9, 112.2, 126.3, 127.7, 128.7, 141.7; IR (neat) 2947, 2094, 1445, 1257, 1177, 1155, 1092, 1032, 956 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ ($M^+ + H - N_2$) 260.1651, found 260.1661.

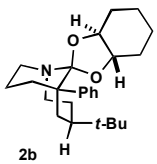
Synthesis of Bridged Orthoamides

General procedure for Schmidt Reaction. To a solution of azidoketal **1** (1.0 equiv) in CH_2Cl_2, Lewis or protic acid was added dropwise at specified temperature, the reaction was allowed to slowly warm to rt and was stirred at rt for a specified time. The reaction was cooled to 0 °C, quenched with sat. $NaHCO_3$ (10 mL), diluted with brine (10 mL), extracted with CH_2Cl_2 (4 x 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography afforded title α-amino ketals **2**. Note: due to unfavorable $N_{lp} \rightarrow \sigma^*_{C\text{-}O}$ arrangement the title products can be easily purified by traditional chromatography. By contrast, although fused amino ketals were sometimes observed by analysis of crude reaction mixtures by NMR, these compounds hydrolyze on silica gel.



2a

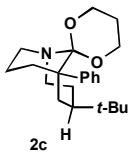
(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2a). According to the general procedure, the reaction of **1a** (0.0144 g, 0.040 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.16 mL, 0.20 mmol, 5.0 equiv) in CH_2Cl_2 (2.0 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.35, 1/4 EtOAc/hexanes). Yield 88% (0.0116 g, 0.35 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.48-1.56 (m, 1H), 1.68-1.86 (m, 3H), 1.89-2.01 (m, 2H), 2.09-2.21 (m, 2H), 2.55-2.66 (m, 2H), 2.68-2.76 (m, 1H), 3.39 (td, *J* = 4.5, 13.5 Hz, 1H), 3.45-3.56 (m, 2H), 3.87-3.96 (m, 2H), 4.03-4.11 (m, 1H), 7.17 (tt, *J* = 1.0, 6.6 Hz, 1H), 7.24-7.31 (m, 2H), 7.62-7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.7, 30.2, 33.8, 35.0, 43.8, 45.1, 46.2, 49.7, 51.2, 63.1, 64.6, 116.9, 125.2, 127.1, 127.4, 149.3; IR (neat) 2960, 2892, 2868, 1497, 1457, 1364, 1322, 1202, 1164, 1143, 1104, 1028, 950 cm^{-1}; HRMS calcd for $C_{21}H_{32}NO_2$ (M^+ + H) 330.2433, found 330.2406. Note: Analysis of the crude reaction mixture by NMR indicated the presence of **2a** as an exclusive compound in the crude reaction mixture. Note: the reaction of **1a** and TfOH afforded **2a** in 58%. The reaction of **1a** and $TiCl_4$ afforded **2a** in 84%. Interestingly, when **1a** was subjected to the reaction with TFA the formation of the bridged ketal was not observed. The influence of promoters on the selectivity of the Schmidt rearrangement is well-precedented.[2,3] Details of the current investigation will be reported in a full disclosure of this work.



2b

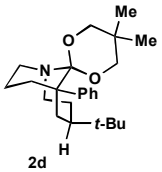
(3aS,4'R,6'R,7aS)-4'-*tert*-Butyl-6'-phenylhexahydro-1'-azaspiro[benzo[d][1,3]dioxole-2,10'-bicyclo[4.3.1]decane] (2b). According to the general procedure, the

reaction of **1b** (0.0270 g, 0.066 mmol, 1.0 equiv, 9:1 dr) and BF_3•CH_3CN (15.2% in CH_3CN, 0.27 mL, 0.33 mmol, 5.0 equiv) in CH_2Cl_2 (3.0 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/100-1/10 EtOAc/hexanes) the title compound as oil (R_f = 0.52, 1/4 EtOAc/hexanes). Yield 71% (0.0179 g, 0.047 mmol, single diastereoisomer, stereochemistry not determined). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.97 (m, 1H), 0.91 (s, 9H), 1.06 (tt, *J* = 3.9, 12.6 Hz, 1H), 1.18 (tt, *J* = 3.8, 13.3 Hz, 1H), 1.38 (qd, *J* = 3.8, 11.7 Hz, 1H), 1.47-1.55 (m, 1H), 1.57-1.69 (m, 2H), 1.72-1.98 (m, 6H), 2.02-2.08 (m, 1H), 2.09-2.18 (m, 1H), 2.20-2.27 (m, 1H), 2.61-2.69 (m, 2H), 2.77-2.88 (m, 2H), 3.49-3.66 (m, 3H), 7.14-7.19 (m, 1H), 7.25-7.31 (m, 2H), 7.63-7.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.7, 23.7, 27.7, 28.2, 29.7, 30.4, 34.1, 34.1, 42.3, 46.1, 46.1, 49.8, 51.7, 78.0, 82.1, 117.0, 125.2, 127.2, 128.1, 147.9; IR (neat) 2942, 1457, 1364, 1235, 1186, 1134, 1097 cm^{-1}; HRMS calcd for $C_{25}H_{38}NO_2$ (M^+ + H) 384.2903, found 384.2889.



2c

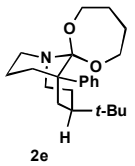
(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3] dioxane] (2c). According to the general procedure, the reaction of **1c** (0.0233 g, 0.063 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.15 mL, 0.19 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) for 5 h at -78 °C and 2 h at rt, afforded after chromatography (1/100-1/10 EtOAc/hexanes) the title compound as oil (R_f = 0.52, 1/10 EtOAc/hexanes). Yield 77% (0.0166 g, 0.048 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.26-1.36 (m, 1H), 1.44-1.57 (m, 2H), 1.69-1.88 (m, 4H), 1.94-2.20 (m, 3H), 2.42-2.52 (m, 1H), 2.61-2.75 (m, 2H), 3.13 (td, *J* = 4.2, 13.7 Hz, 1H), 3.44-3.51 (m, 1H), 3.52-3.58 (m, 1H), 3.87-3.93 (m, 1H), 4.02-4.11 (m, 1H), 4.13-4.22 (m, 1H), 7.16 (tt, *J* = 1.2, 6.8 Hz, 1H), 7.24-7.31 (m, 2H), 7.76-7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 24.6, 27.8, 30.4, 33.7, 33.9, 43.3, 46.2, 46.9, 48.9, 51.2, 57.8, 60.0, 107.0, 124.8, 127.2, 127.5, 150.6; IR (neat) 2958, 2871, 1465, 1365, 1321, 1247, 1170, 1135, 1103, 1025 cm^{-1}; HRMS calcd for $C_{22}H_{34}NO_2$ (M^+ + H) 344.2590, found 344.2583.



2d

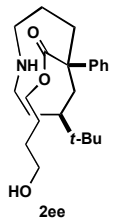
(4R,6R)-4-*tert*-Butyl-5',5'-dimethyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxane] (2d). According to the general procedure, the reaction of **1d** (0.0195 g, 0.049 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.12 mL, 0.15 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) for 5 h at -78 °C and 2 h at rt, afforded after chromatography (1/100-1/10 EtOAc/hexanes) the title compound as oil (R_f = 0.64, 1/10 EtOAc/hexanes). Yield 75% (0.0136 g, 0.037 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.76 (s,

3H), 0.87 (s, 9H), 1.48-1.61 (m, 2H), 1.71-1.86 (m, 3H), 1.90 (dd, *J* = 5.2, 13.2 Hz, 1H), 1.98-2.08 (m, 1H), 2.09-2.21 (m, 1H), 2.62-2.78 (m, 3H), 2.91 (dd, *J* = 2.5, 10.3 Hz, 1H), 3.11 (td, *J* = 4.2, 13.7 Hz, 1H), 3.33 (dd, *J* = 2.5, 10.4 Hz, 1H), 3.46-3.53 (m, 1H), 3.70 (d, *J* = 10.3 Hz, 1H), 3.80 (d, *J* = 10.4 Hz, 1H), 7.14-7.19 (m, 1H), 7.25-7.32 (m, 2H), 7.75-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 22.5, 23.3, 27.8, 29.0, 30.4, 33.2, 33.8, 42.6, 46.2, 46.6, 48.9, 51.2, 68.1, 70.7, 106.6, 125.0, 127.0, 128.0, 149.3; IR (neat) 2955, 2867, 1462, 1395, 1365, 1323, 1264, 1159, 1141, 1104, 1076, 1025, 907 cm^{-1}; HRMS calcd for $C_{24}H_{38}NO_2$ (M^+ + H) 372.2903, found 372.2894.



2e

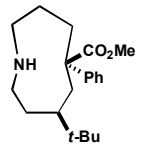
((4R,6R)-4-*tert*-Butyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3] dioxepane] (2e). According to the general procedure, **1e** (0.0165 g, 0.043 mmol, 1.0 equiv) was reacted with BF_3•CH_3CN (15.2% in CH_3CN, 0.11 mL, 0.13 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) for 5 h at -78 °C and 1 h at rt. After the usual work-up the reaction was analyzed by NMR. Yield 70% (vs. nitromethane as the internal standard). Note: the compound is unstable on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.37-1.91 (m, 10H), 2.05-2.21 (m, 2H), 2.62-276 (m, 3H), 2.93-2.99 (m, 1H), 3.31 (td, *J* = 4.5, 13.5 Hz, 1H), 3.47 (ddd, *J* = 3.1, 4.8, 12.0 Hz, 1H), 3.51-3.58 (m, 1H), 3.67-3.75 (m, 1H), 3.96-4.03 (m, 1H), 7.17 (tt, *J* = 1.1, 6.5 Hz, 1H), 7.23-7.31 (m, 2H), 7.73-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.8, 28.8, 28.8, 30.1, 33.9, 34.4, 42.6, 46.1, 47.4, 49.5, 51.4, 61.9, 63.0, 109.6, 125.2, 127.0, 128.5, 148.8; IR (neat) 2940, 1554, 1456, 1365, 1216, 1187, 1131, 1104, 1059, 1025, 913 cm^{-1}; HRMS calcd for $C_{23}H_{36}NO_2$ (M^+ + H) 358.2746, found 358.2743. Chromatography of the above reaction mixture (1/5/95-1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded the corresponding 9-membered amino ester **2ee** as oil (R_f = 0.21, 1/10/90 NH_4OH/MeOH/CH_2Cl_2) in 69% overall yield (0.0111 g, 0.030 mmol). As expected 1,3-dioxepane is more labile than 1,3-dioxolane or 1,3-dioxane derived ketals.[7] It is possible that in the case of bridged α-amino ketals the hydrolysis is facilitated by electron donation from the bridgehead nitrogen.



2ee

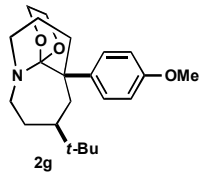
(5R,7R)-4-Hydroxybutyl 7-*tert*-butyl-5-phenylazonane-5-carboxylate (2ee). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 9H), 1.26-1.34 (m, 1H), 1.37-1.43 (m, 1H), 1.44-1.51 (m, 2H), 1.54-1.69 (m, 5H), 1.74-2.02 (m, 3H), 2.13-2.24 (m, 2H), 2.67-2.90 (m, 5H), 3.56 (t, *J* = 6.4 Hz, 2H), 4.06-4.17 (m, 2H), 7.17-7.24 (m, 1H), 7.26-7.32 (m,

4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.9, 25.3, 27.3, 29.2, 33.1, 34.0, 35.3, 37.7, 43.3, 46.5, 55.2, 62.2, 64.5, 126.6, 127.0, 128.2, 144.9, 177.1; IR (neat) 3369, 2948, 1722, 1555, 1446, 1366, 1216, 1186, 1048, 913 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO_3$ (M^+ + H) 376.2852, found 376.2831. Note: although all of the α-amino ketals are easily observed by thin layer chromatography methods (a result of unfavorable $N_{lp} \rightarrow \sigma^*_{C\text{-}O}$ overlap), **2e** could not be monitored by TLC, which is further consistent with its rapid hydrolysis. Interestingly, the reaction of the analogous azido ketal derived from (2*Z*)-2-butene-1,4-diol under identical reaction conditions afforded the corresponding α-amino ketal in 47% yield (NMR analysis). As expected, the allylic bond additionally facilitates the hydrolysis of this orthoamide.



2f

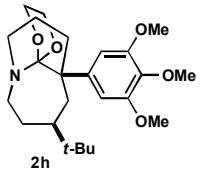
(7R)-Methyl 7-*tert*-butyl-5-phenylazonane-5-carboxylate (2f). According to the general procedure, the reaction of **1f** (0.0226 g, 0.069 mmol, 1.0 equiv) and TfOH (0.030 mL, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) for 0.5 h at 0 °C, afforded after chromatography (1/5/85-1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title product as oil (R_f = 0.32, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 64% (0.0140 g, 0.044 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 9H), 1.23-1.37 (m, 1H), 1.39-1.46 (m, 1H), 1.51-1.71 (m, 2H), 1.77-1.93 (m, 2H), 2.14-2.25 (m, 2H), 2.58-2.70 (m, 1H), 2.73-2.82 (m, 2H), 2.82-2.96 (m, 3H), 3.67 (s, 3H), 7.18-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 25.4, 27.3, 32.8, 34.0, 35.3, 37.7, 43.1, 46.3, 52.1, 55.2, 126.8, 126.9, 128.3, 144.8, 177.6; IR (neat) 2949, 2870, 1728, 1479, 1446, 1366, 1244, 1200, 1186, 1078, 910 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO_2$ (M^+ + H) 318.2433, found 318.2424. Note: in contrast to the Schmidt reaction of **2e**, the analysis of crude reaction mixture by NMR indicated the presence of the same species as after chromatographic purification. Attempted trapping of the oxonium ion generated from **1f** with external nucleophiles has not been successful so far.



2g

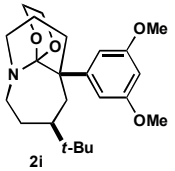
(4R,6R)-4-*tert*-Butyl-6-(4-methoxyphenyl)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2g). According to the general procedure, the reaction of **1g** (0.0201 g, 0.052 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.21 mL, 0.26 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/1 EtOAc/hexanes-EtOAc) the title compound as oil (R_f = 0.37, 1/1 EtOAc/hexanes). Yield 92% (0.0171 g, 0.48 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89

(s, 9H), 1.47-1.55 (m, 1H), 1.64-1.85 (m, 3H), 1.87-1.99 (m, 2H), 2.06-2.20 (m, 2H), 2.54-2.66 (m, 2H), 2.68-2.75 (m, 1H), 3.39 (td, *J* = 4.1, 13.2 Hz, 1H), 3.44-3.56 (m, 2H), 3.81 (s, 3H), 3.86-3.94 (m, 2H), 4.03-4.10 (m, 1H), 6.80-6.85 (m, 2H), 7.53-7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.7, 30.1, 33.8, 35.2, 43.9, 44.6, 46.2, 49.8, 51.3, 55.1, 63.1, 64.7, 112.6, 117.0, 128.1, 141.5, 157.0; IR (neat) 2958, 1610, 1512, 1464, 1365, 1323, 1253, 1189, 1105, 1038, 950, 914, 825 cm^{-1}; HRMS calcd for $C_{22}H_{34}NO_3$ (M^+ + H) 360.2539, found 360.2538. Note: Analysis of the crude reaction mixture by NMR indicated the presence of **2g** as an exclusive compound in the crude reaction mixture.



2h

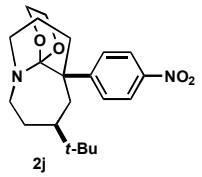
(4R,6R)-4-*tert*-Butyl-6-(3,4,5-trimethoxyphenyl)-1-azaspiro[bicyclo[4.3.1] decane-10,2'-[1,3]dioxolane] (2h). According to the general procedure, the reaction of **1h** (0.0212 g, 0.047 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.19 mL, 0.24 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (EtOAc) the title compound as oil (R_f = 0.38, EtOAc). Yield 86% (0.0169 g, 0.040 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.46-1.57 (m, 1H), 1.66-1.98 (m, 5H), 2.06-2.20 (m, 2H), 2.48-2.63 (m, 2H), 2.66-2.73 (m, 1H), 3.35 (td, *J* = 3.7, 13.6 Hz, 1H), 3.52 (dd, *J* = 3.9, 14.0 Hz, 1H), 3.59-3.66 (m, 1H), 3.86 (s, 3H), 3.88 (s, 6H), 3.92-4.01 (m, 2H), 4.08-4.17 (m, 1H), 6.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 27.7, 30.1, 33.8, 35.3, 44.2, 45.2, 46.2, 49.5, 51.2, 56.1, 60.7, 63.1, 64.6, 105.1, 117.1, 135.9, 145.4, 151.9; IR (neat) 2957, 1584, 1513, 1463, 1411, 1364, 1318, 1246, 1165, 1128, 1105, 1015, 950, 913 cm^{-1}; HRMS calcd for $C_{24}H_{38}NO_5$ (M^+ + H) 420.2750, found 420.2755. Note: Analysis of the crude reaction mixture by NMR indicated the presence of **2h** as an exclusive compound in the crude reaction mixture.



2i

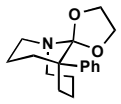
(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-1-azaspiro[bicyclo[4.3.1] decane-10,2'-[1,3]dioxolane] (2i). According to the general procedure, the reaction of **1i** (0.0270 g, 0.065 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.26 mL, 0.32 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.53, EtOAc). Yield 86% (0.0216 g, 0.056 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.47-1.54 (m, 1H), 1.64-1.82 (m, 3H), 1.86-1.99 (m, 2H), 2.05-2.18 (m, 2H), 2.48-2.62 (m, 2H), 2.69 (dd, *J* = 3.9, 12.6 Hz, 1H), 3.35 (td, *J* = 4.0, 13.8 Hz, 1H), 3.51 (ddd, *J* = 2.1,

5.6, 13.6 Hz, 1H), 3.61 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 6H), 3.90-4.02 (m, 2H), 4.09 (q, *J* = 6.8 Hz, 1H), 6.32 (t, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 27.7, 30.2, 33.8, 35.2, 44.0, 45.3, 46.2, 49.6, 51.2, 55.2, 63.1, 64.6, 96.9, 106.1, 116.9, 152.2, 159.8; IR (neat) 2957, 1595, 1456, 1421, 1324, 1203, 1150, 1103, 1028, 913, 842 cm^{-1}; HRMS calcd for $C_{23}H_{36}NO_4$ (M^+ + H) 390.2644, found 390.2635. Analysis of the crude reaction mixture by NMR indicated the presence of **2i** as an exclusive compound in the crude reaction mixture.



2j

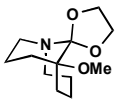
(4R,6R)-4-*tert*-Butyl-6-(4-nitrophenyl)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2j). According to the general procedure, the reaction of **1j** (0.0242 g, 0.060 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.25 mL, 0.30 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound as foam (R_f = 0.73, 1/1 EtOAc/hexanes). Yield 94% (0.0210 g, 0.056 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.52-1.59 (m, 1H), 1.66 (d, *J* = 13.0 Hz, 1H), 1.74-2.01 (m, 4H), 2.08-2.21 (m, 2H), 2.54-2.67 (m, 2H), 2.73 (dd, *J* = 4.7, 15.4 Hz, 1H), 3.36 (td, *J* = 3.8, 13.9 Hz, 1H), 3.47-3.55 (m, 2H), 3.87-3.97 (m, 2H), 4.06-4.17 (m, 1H), 7.78-7.84 (m, 2H), 8.08-8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 27.7, 30.1, 33.8, 35.1, 43.7, 45.7, 46.3, 49.5, 51.1, 62.9, 64.6, 116.4, 122.5, 128.1, 145.6, 157.1; IR (neat) 2961, 1593, 1617, 1469, 1344, 1263, 1144, 1163, 1107, 1028, 949, 912, 854, 822 cm^{-1}; HRMS calcd for $C_{21}H_{31}N_2O_4$ (M^+ + H) 375.2284, found 375.2274. Analysis of the crude reaction mixture by NMR indicated the presence of **2j** as an exclusive compound in the crude reaction mixture.



2k

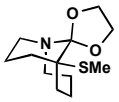
6-Phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2k). According to the general procedure, the reaction of **1k** (0.0185 g, 0.061 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.15 mL, 0.18 mmol, 3.0 equiv) in CH_2Cl_2 (3.0 mL) for 4 h at -78 °C and 2 h at rt, afforded after chromatography (1/1 EtOAc/hexanes-EtOAc) the title compound as oil (R_f = 0.46, 1/1 EtOAc/hexanes). Yield 59% (0.0098 g, 0.036 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.65 (m, 2H), 1.78-1.97 (m, 4H), 2.00-2.17 (m, 1H), 2.27-2.39 (m, 2H), 2.73 (td, *J* = 4.5, 13.0 Hz, 2H), 2.86 (dd, *J* = 5.3, 14.3 Hz, 1H), 3.15 (q, *J* = 7.0 Hz, 1H), 3.26-3.34 (m, 1H), 3.41 (td, *J* = 3.9, 13.9 Hz, 1H), 3.61 (q, *J* = 7.0 Hz, 1H), 3.75 (q, *J* = 7.0 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 1H), 7.12-7.18 (m, 1H), 7.23-7.29 (m, 2H), 7.53-7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 27.1, 32.8, 35.3, 40.6, 48.0, 49.0, 50.7, 62.5, 65.2, 116.7, 125.1, 126.9, 128.1, 149.5; IR (neat) 2919,

1496, 1450, 1359, 1265, 1201, 1157, 1105, 1024, 960, 913, 848 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_2$ (M^+ + H) 274.1807, found 274.1805.



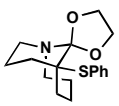
2l

6-Methoxy-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2l). According to the general procedure, the reaction of **1l** (0.0192 g, 0.075 mmol, 1.0 equiv) and TMSOTf (0.040 mL, 0.23 mmol, 3.0 equiv) in CH_2Cl_2 (3.0 mL) for 20 min at 0 °C and 20 min at rt, afforded after chromatography (1/1 EtOAc/hexanes-EtOAc) the title compound as oil (R_f = 0.30, EtOAc). Yield 52% (0.0088 g, 0.039 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.93 (m, 7H), 1.95-2.09 (m, 2H), 2.13-2.20 (m, 1H), 2.62-2.71 (m, 2H), 3.18-3.33 (m, 2H), 3.36 (s, 3H), 3.99-4.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.5, 30.4, 35.5, 36.4, 48.6, 50.5, 50.6, 62.4, 62.5, 77.4, 116.1; IR (neat) 2919, 1451, 1166, 1093, 1063, 1026, 913, 873 cm^{-1}; HRMS calcd for $C_{12}H_{22}NO_3$ (M^+ + H) 228.1600, found 228.1601.



2m

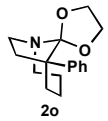
6-(Methylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2m). According to the general procedure, the reaction of **1m** (0.0185 g, 0.068 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.28 mL, 0.34 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL) for 2 h at 0 °C and 1 h at rt, afforded after chromatography (1/1 EtOAc/hexanes-EtOAc) the title compound as oil (R_f = 0.36, 1/1 EtOAc/hexanes). Yield 50% (0.0082 g, 0.034 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.48 (m, 1H), 1.58-2.04 (m, 7H), 2.14-2.23 (m, 1H), 2.16 (s, 3H), 2.30 (td, *J* = 4.6, 12.8 Hz, 1H), 2.61-2.68 (m, 1H), 2.73 (dd, *J* = 5.2, 14.2 Hz, 1H), 3.17-3.25 (m, 1H), 3.38 (td, *J* = 3.9, 13.8 Hz, 1H), 3.94-4.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.4, 26.1, 30.6, 37.5, 38.5, 49.1, 50.5, 52.7, 62.7, 65.3, 117.0; IR (neat) 2920, 1448, 1313, 1272, 1302, 1180, 1163, 1106, 1025, 950, 908, 890, 799, 774 cm^{-1}; HRMS calcd for $C_{12}H_{22}NO_2S$ (M^+ + H) 244.1371, found 244.1373.



2n

6-(Phenylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-[1,3]dioxolane] (2n). According to the general procedure, the reaction of **1n** (0.0274 g, 0.082 mmol, 1.0 equiv) and TMSOTf (0.045 mL, 0.25 mmol, 3.0 equiv) in CH_2Cl_2 (2.5 mL) for 20 min at 0 °C and 40 min at rt, afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound as yellowish solid (R_f = 0.66, EtOAc, Mp = 78-80 °C). Yield 78% (0.0194 g,

0.064 mmol). Recrystallization from EtOAc/CH_2Cl_2 afforded crystals suitable for X-ray analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29-1.36 (m, 1H), 1.52-1.64 (m, 3H), 1.68-1.78 (m, 2H), 1.79-1.89 (m, 2H), 2.10-2.17 (m, 1H), 2.34 (tdd, *J* = 1.1, 5.2, 13.5 Hz, 1H), 2.49-2.56 (m, 1H), 2.60 (dd, *J* = 5.2, 14.1 Hz, 1H), 3.13-3.20 (m, 1H), 3.30 (td, *J* = 4.0, 13.8 Hz, 1H), 3.91-3.96 (m, 2H), 3.99-4.03 (m, 1H), 4.07 (q, *J* = 7.0 Hz, 1H), 7.20-7.27 (m, 3H), 7.49-7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 25.8, 30.0, 38.7, 39.6, 49.3, 50.4, 57.6, 62.8, 65.5, 116.1, 128.2, 128.3, 133.2, 137.6; IR (neat) 2920, 2859, 1581, 1471, 1449, 1358, 1314, 1272, 1216, 1163, 1182, 1107, 1024, 952, 912, 887, 816, 799 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_2S$ (M^+ + H) 306.1528, found 306.1519. Note: the azide **1n** is known.[4] There is an error in reference 4; the single isomer obtained in the original report was incorrectly assigned as fused **16a** (in ref. 4). We now reassign this product as bridged **2n** based on 2D NMR experiments. In addition, we have been able to obtain x-ray of **2n**, thus unambiguously determining that **2n** contains a bridged structure.

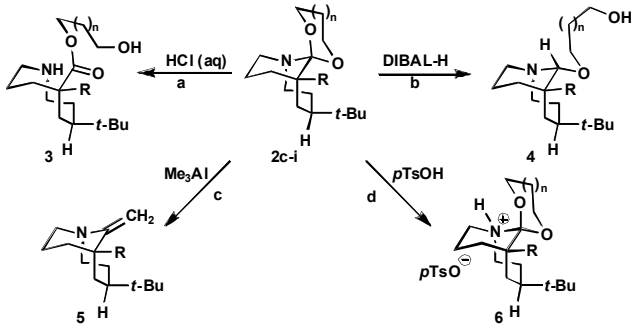


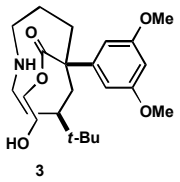
2o

6-Phenyl-1-azaspiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolane] (2o). According to the general procedure, the reaction of **1o** (0.0208 g, 0.072 mmol, 1.0 equiv) and BF_3•CH_3CN (15.2% in CH_3CN, 0.18 mL, 0.22 mmol, 3.0 equiv) in CH_2Cl_2 (3.0 mL) for 4 h at -78 °C and 2 h at rt, afforded after chromatography (EtOAc-1/4 MeOH/EtOAc) the title compound as oil (R_f = 0.28, 1/4 MeOH/EtOAc). Yield 92% (0.0170 g, 0.066 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.68 (m, 2H), 1.71-1.82 (m, 2H), 1.91-2.05 (m, 2H), 2.11-2.18 (m, 1H), 2.54-2.69 (m, 2H), 2.96-3.04 (m, 1H), 3.18 (dd, *J* = 7.3, 14.7 Hz, 1H), 3.45 (td, *J* = 3.4, 11.2 Hz, 1H), 3.70 (q, *J* = 6.7 Hz, 1H), 3.99 (qd, *J* = 1.2, 7.5 Hz, 1H), 4.12 (td, *J* = 2.1, 6.7 Hz, 2H), 7.19 (tt, *J* = 1.2, 6.6 Hz, 1H), 7.25-7.32 (m, 2H), 7.41-7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 29.0, 31.7, 42.3, 50.2, 50.5, 52.7, 62.5, 66.0, 123.3, 125.6, 126.4, 127.8, 146.6; IR (neat) 2929, 1602, 1554, 1493, 1445, 1314, 1246, 1194, 1163, 1070, 1044, 1032, 952, 851 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ (M^+ + H) 260.1651, found 260.1652. Analysis of the crude reaction mixture by NMR indicated the presence of **2o** as an exclusive compound in the crude reaction mixture. Note: we determined that the corresponding ketone also affords the bridged product as a single regioisomer, most likely due to strain involving a four-membered transition state. Details will be disclosed in a full account of this work.

Transformations of Bridged α-Amino Ketals

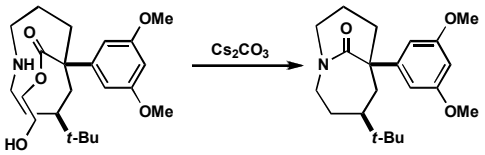
Scheme N. *Reactions of bridged a-amino ketals*





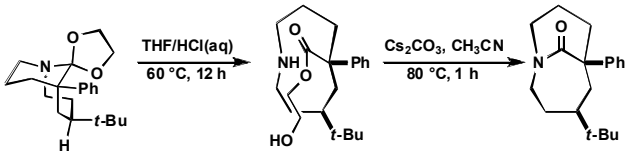
(5R,7R)-2-Hydroxyethyl 7-*tert*-butyl-5-(3,5-dimethoxyphenyl)azonane-5-carboxylate (3). To a solution of **2i** (0.0206 g, 0.053 mmol) in THF (2.0 mL), 5% $HCl_{(aq)}$ (2.0 mL) was added and the resulting mixture was stirred at 60 °C for 12 h. The reaction was concentrated under reduced pressure, the residue was taken in Et_2O (10 mL), sat. $NaHCO_3$ (10 mL) was added, the aqueous layer was extracted with Et_2O (3 x 30 mL) and CH_2Cl_2 (3 x 30 mL). Combined organic layers were dried and concentrated. Chromatography (1/10/90-1/20/80 NH_4OH/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.13, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 89% (0.0192 g, 0.047 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50 (s, 9H), 1.21-1.34 (m, 2H), 1.36-1.45 (m, 1H), 1.48-1.56 (m, 1H), 1.59-1.72 (m, 1H), 1.77-1.88 (m, 1H), 1.90-2.06 (m, 2H), 2.13 (dd, *J* = 4.6, 16.0 Hz, 1H), 2.27-2.35 (m, 1H), 2.58-2.66 (m, 1H), 2.93-3.16 (m, 3H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.79 (s, 6H), 4.19-4.31 (m, 2H), 4.42 (br, 1H), 6.33 (t, *J* = 2.0 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 25.8, 27.1, 30.6, 34.1, 34.7, 37.9, 42.1, 45.5, 55.2, 55.5, 61.5, 66.5, 98.9, 105.4, 146.4, 160.9, 176.8; IR (neat) 3392, 2953, 1723, 1596, 1457, 1426, 1205, 1155, 1066, 914 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO_5$ (M^+ + H) 408.2750, found 408.2764.

Note: the open-form 9-membered ring amino esters can be readily converted into the bridged lactams by treatment with base according to procedure described earlier.[11] The following examples illustrate the utility of bridged orthoamides in the synthesis of twisted lactams. To streamline the synthesis, the isolation of the amino esters is not necessary as exemplified by preparation of **8**.



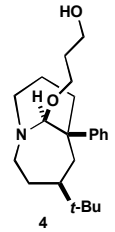
3 7

(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (7). To a solution of **3** (0.0152 g, 0.0375 mmol) in CH_3CN (6 mL), Cs_2CO_3 (0.061 g, 0.19 mmol, 5.0 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. The reaction was cooled to rt, solvent was removed under reduced pressure and the residue was purified directly by chromatography (1/1 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.82, EtOAc). Yield 86% (0.0111 g, 0.032 mmol). Spectroscopic properties matched those previously described.[6]



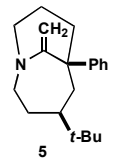
2a *not isolated* 8

(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-one (8). To a solution of **2a** (0.0116 g, 0.035 mmol) in THF (2.0 mL), 5% $HCl_{(aq)}$ (2.0 mL) was added and the resulting mixture was stirred at 60 °C for 12 h. The reaction was concentrated under reduced pressure, the residue was taken in Et_2O (10 mL), sat. $NaHCO_3$ (10 mL) was added, the aqueous layer was extracted with Et_2O (4 x 30 mL), dried and concentrated. The resulting residue was taken in CH_3CN (6 mL), Cs_2CO_3 (0.057 g, 0.18 mmol, 5.0 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. The reaction was cooled to rt, solvent was removed under reduced pressure and the residue was purified directly by chromatography (1/10-1.4 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.25, EtOAc/hexanes). Yield 72% (0.0072 g, 0.025 mmol). Spectroscopic properties matched those previously described.[1]



4

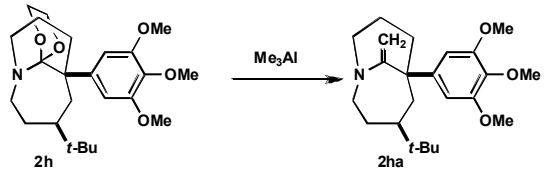
3-((4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yloxy)propan-1-ol (4). To a solution of **2c** (0.0200 g, 0.058 mmol) in benzene (6 mL), DIBAL-H (1.0 M in toluene, 0.29 mL, 0.29 mmol, 5 equiv) was added at rt, and the resulting mixture was heated at 80 °C for 15 h. The reaction was cooled to rt, quenched with sat. $NaHCO_3$ (10 mL) and brine (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried and concentrated. Chromatography (1/2/98-1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.48, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 67% (0.0135 g, 0.039 mmol). Single diastereoisomer. Stereochemistry determined by 2D NMR experiments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.38-1.44 (m, 1H), 1.61-1.89 (m, 6H), 1.91-2.09 (m, 4H), 2.16 (br, 1H), 2.69 (ddd, *J* = 5.3, 11.6, 13.8 Hz, 1H), 2.94-3.09 (m, 2H), 3.42-3.53 (m, 2H), 3.58-3.66 (m, 2H), 3.99-4.07 (m, 1H), 4.47 (s, 1H), 7.17-7.23 (m, 1H), 7.30-7.35 (m, 2H), 7.45-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 27.8, 30.0, 32.2, 34.0, 38.1, 38.6, 43.2, 46.0, 50.4, 53.0, 61.6, 67.3, 96.0, 125.6, 126.0, 128.0, 150.6; IR (neat) 3368, 2956, 2865, 1555, 1468, 1453, 1393, 1365, 1258, 1126, 1099 cm^{-1}; HRMS calcd for $C_{22}H_{35}NO_2Na$ (M^+ + Na) 368.2565, found 368.2565.



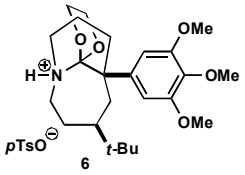
5

(4R,6R)-4-*tert*-Butyl-10-methylene-6-phenyl-1-azabicyclo[4.3.1]decane (5). To a solution of **2d** (0.0183 g, 0.049 mmol) in CH_2Cl_2 (10 mL), Me_3Al (2.0 M in toluene, 0.13 mL, 0.25 mmol, 5 equiv) was added at rt, and the resulting mixture was stirred at 40 °C for 15 h. The reaction was cooled to rt, quenched with sat. $NaHCO_3$ (10 mL) and brine (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried and concentrated. Chromatography (1/1 EtOAc/hexanes-EtOAc) afforded the title compound as oil (R_f = 0.20, 1/4 EtOAc/hexanes). Yield 56% (0.0078 g, 0.028 mmol). Spectroscopic properties matched those previously described.[6] In addition, the reaction of the orthoamide **2h** under the above reaction conditions afforded the corresponding bridged enamine **2ha** in 51% yield (Scheme O).

Scheme O. *Synthesis of bridged enamine from orthoamide* ***2h***



(4R,6R)-4-*tert*-Butyl-10-methylene-6-(3,4,5-trimethoxyphenyl)-1-azabicyclo [4.3.1]decane (2ha). To a solution of **2h** (0.0190 g, 0.045 mmol) in CH_2Cl_2 (10 mL), Me_3Al (2.0 M in toluene, 0.11 mL, 0.23 mmol, 5 equiv) was added at rt, and the resulting mixture was stirred at rt for 15 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) and brine (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried and concentrated. Chromatography (EtOAc-1/4 MeOH/EtOAc) afforded the title compound as oil (R_f = 0.48, 1/4 MeOH/EtOAc). Yield 51% (0.0086 g, 0.023 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.54-1.80 (m, 6H), 1.88-1.93 (m, 1H), 2.02-2.11 (m, 1H), 2.22-2.29 (m, 1H), 2.65 (td, *J* = 5.0, 12.7 Hz, 1H), 2.97-3.06 (m, 1H), 3.41-3.47 (m, 1H), 3.58 (dd, *J* = 3.7, 12.9 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 4.32 (s, 1H), 4.79 (s, 1H), 6.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.9, 28.0, 34.0, 39.9, 44.1, 44.9, 47.3, 54.6, 55.5, 56.3, 60.9, 105.1, 110.7, 136.2, 147.4, 152.2, 156.1; IR (neat) 2943, 2865, 1627, 1585, 1555, 1511, 1464, 1410, 1365, 1243, 1186, 1130, 1104, 1012, 913, 824, 864 cm^{-1}; HRMS calcd for $C_{23}H_{36}NO_3$ (M^+ + H) 374.2695, found 374.2693.



Salt 6. To a solution of α-amino ketal **2h** (0.0247 g, 0.059 mmol, 1.0 equiv) in acetone (2.0 mL), *p*TsOH (0.0112 g, 0.059 mmol, 1.0 equiv) was added in acetone (0.5 mL). Et_2O (2.5 mL) wad added and the reaction mixture was stirred at rt for 20 h. The solvent was removed to afford the title compound as white foam. Yield 96% (0.0345 g, 0.057 mmol). Note: the compound is unstable. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.68-1.78 (m, 2H), 1.92-2.04 (m, 2H), 2.06-2.20 (m, 3H), 2.25-2.38 (m, 1H), 2.35 (s, 3H), 2.70 (td, *J* = 4.6, 13.8 Hz, 1H), 2.97 (td, *J* = 3.7, 14.4 Hz, 1H), 3.25 (q, *J* = 7.6 Hz, 1H), 3.35 (d, *J* = 8.4 Hz, 1H), 3.78 (td, *J* = 4.0, 13.8 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 6H), 4.09-4.19 (m, 2H), 4.33-4.39 (m, 1H), 4.71 (q, *J* = 7.9 Hz, 1H), 6.74 (s, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, 2H), 10.80 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.3, 26.5, 27.4, 31.9, 34.1, 41.4, 45.7, 46.7, 51.3, 52.0, 56.4, 60.9, 66.9, 67.2, 105.0, 118.3, 125.9, 128.8, 137.3, 139.9, 140.1, 142.4, 152.3; IR (neat) 3467, 2963, 1586, 1514, 1461, 1413, 1319, 1231, 1165, 1122, 1034, 1010, 962, 914 cm^{-1}; HRMS calcd for $C_{24}H_{38}NO_5$ (M^+) 420.2750, found 420.2737.

References

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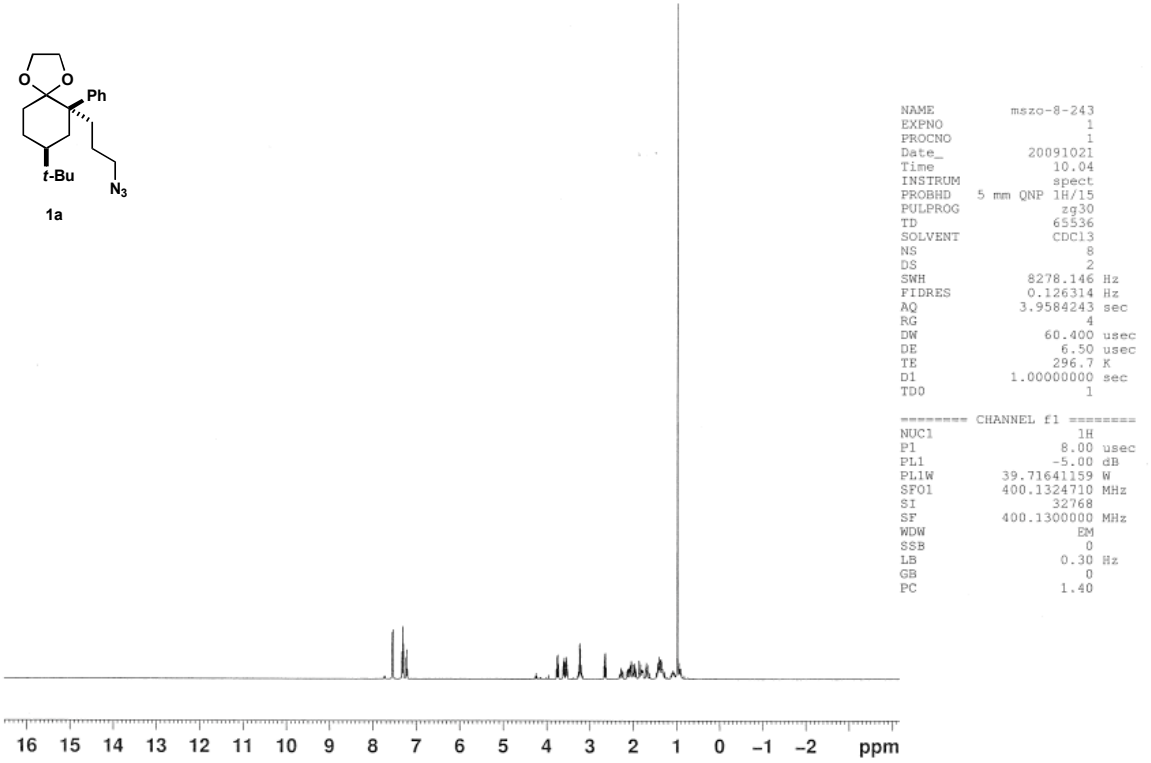
7. Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience; 4th edition, p. 448 and p. 471.
8. Szostak, M.; Aubé, J. *Org. Lett.*, **2009**, *11*, 3878-3881.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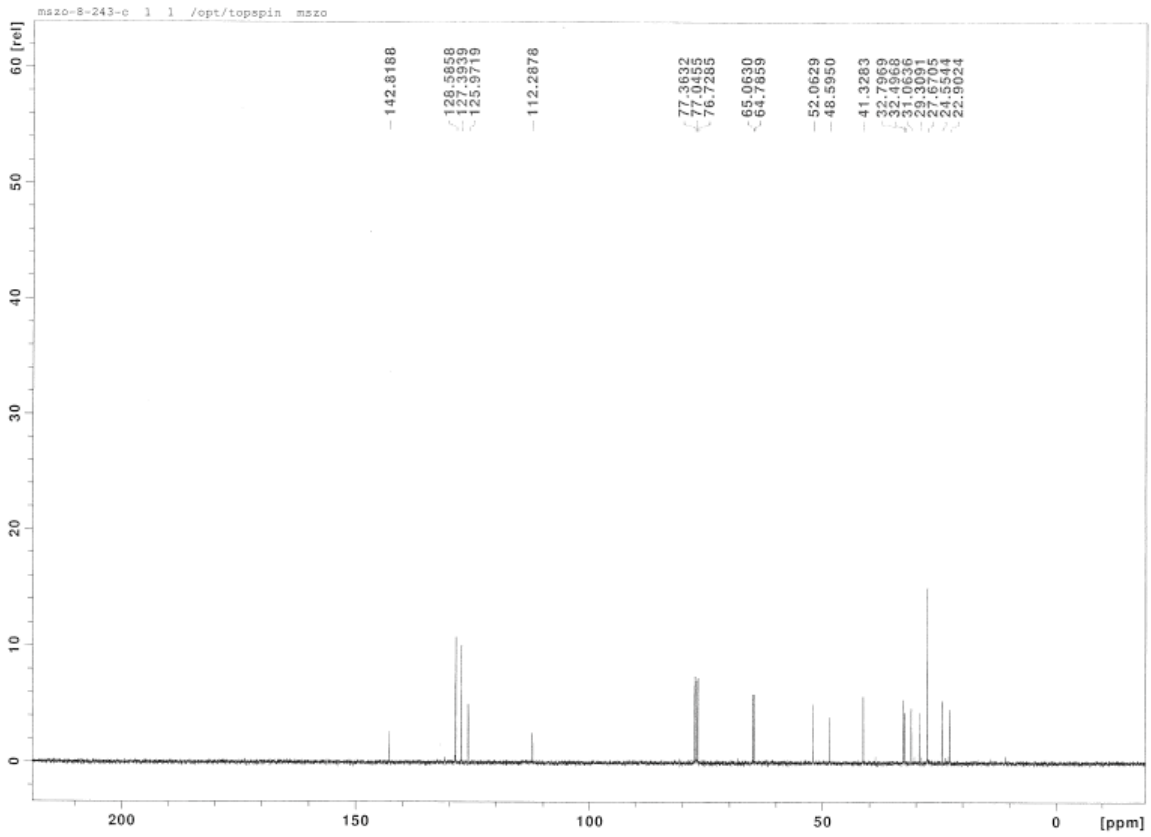
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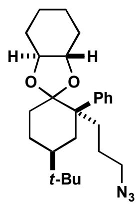

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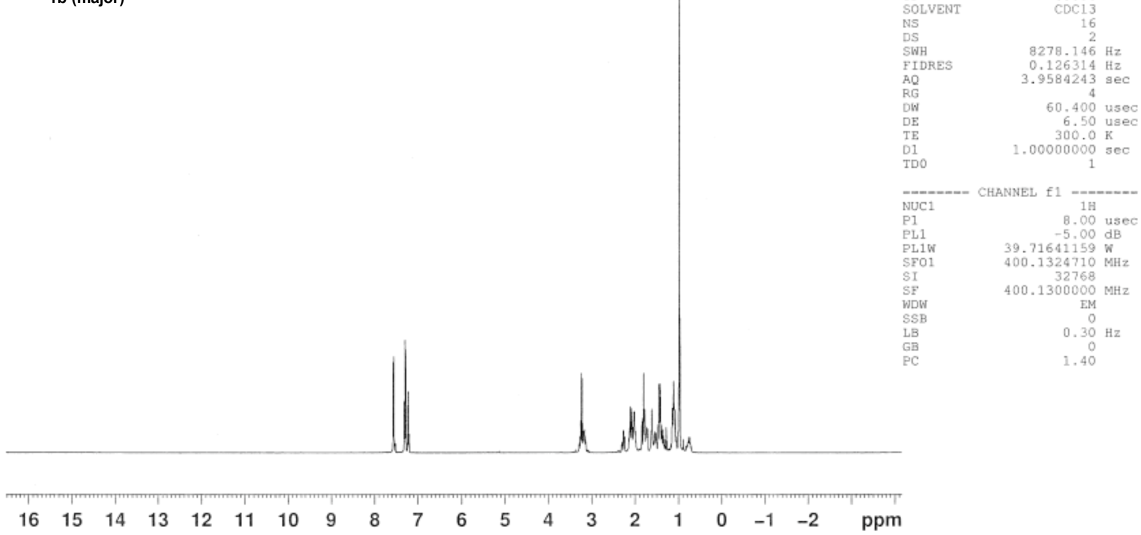
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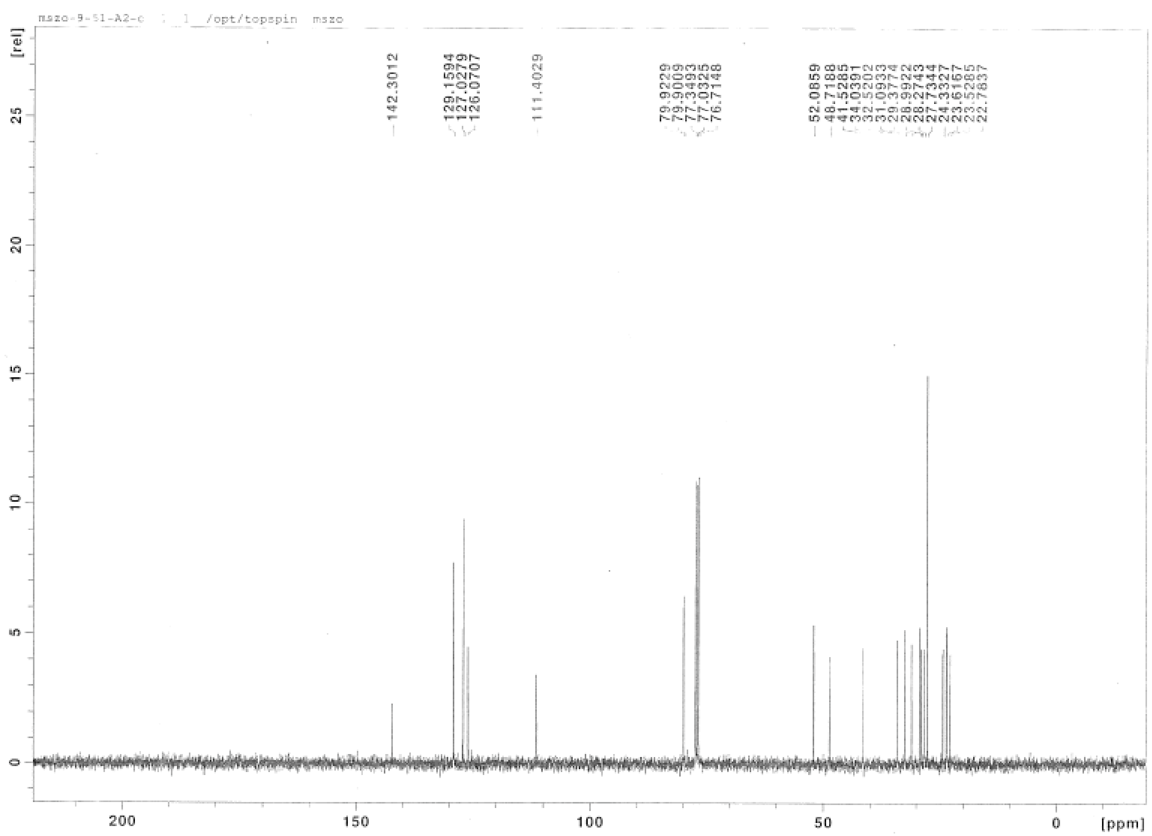
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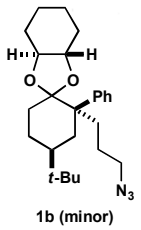
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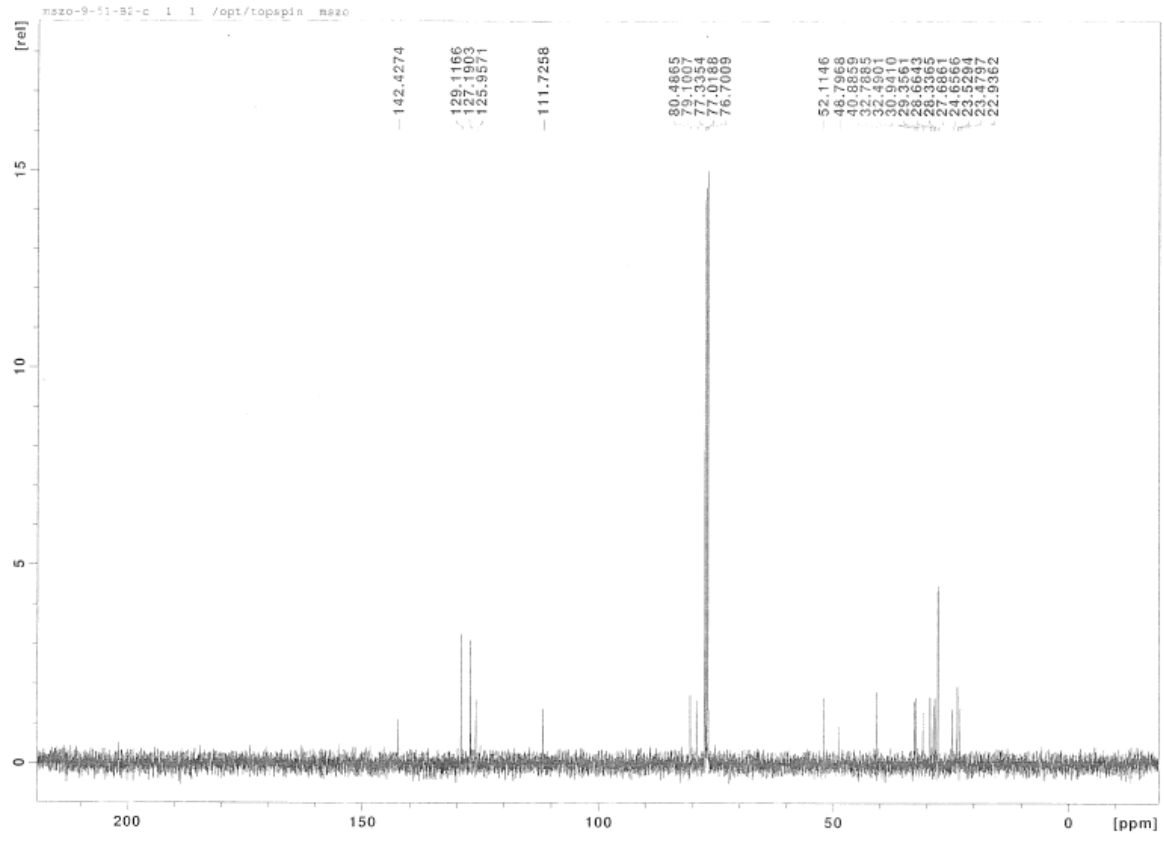
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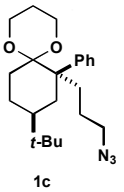

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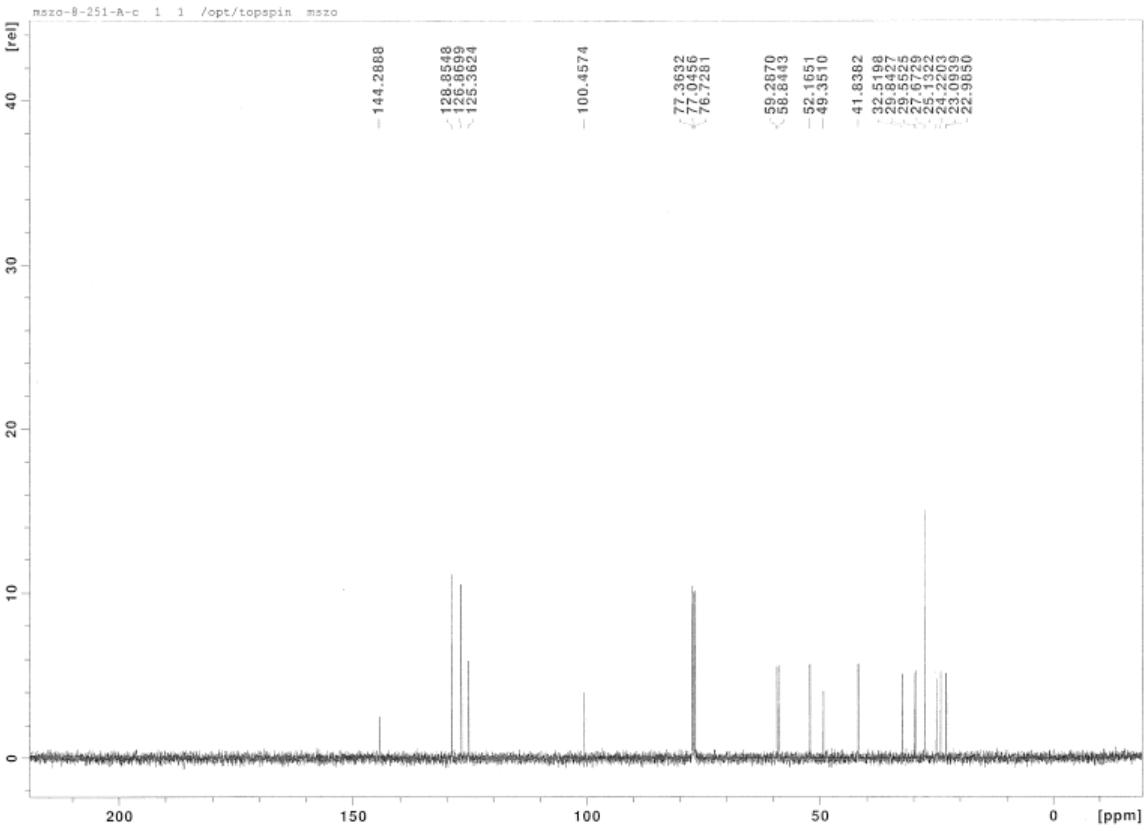
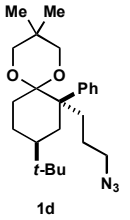
DE                   6.50 usec
TE                  296.6 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

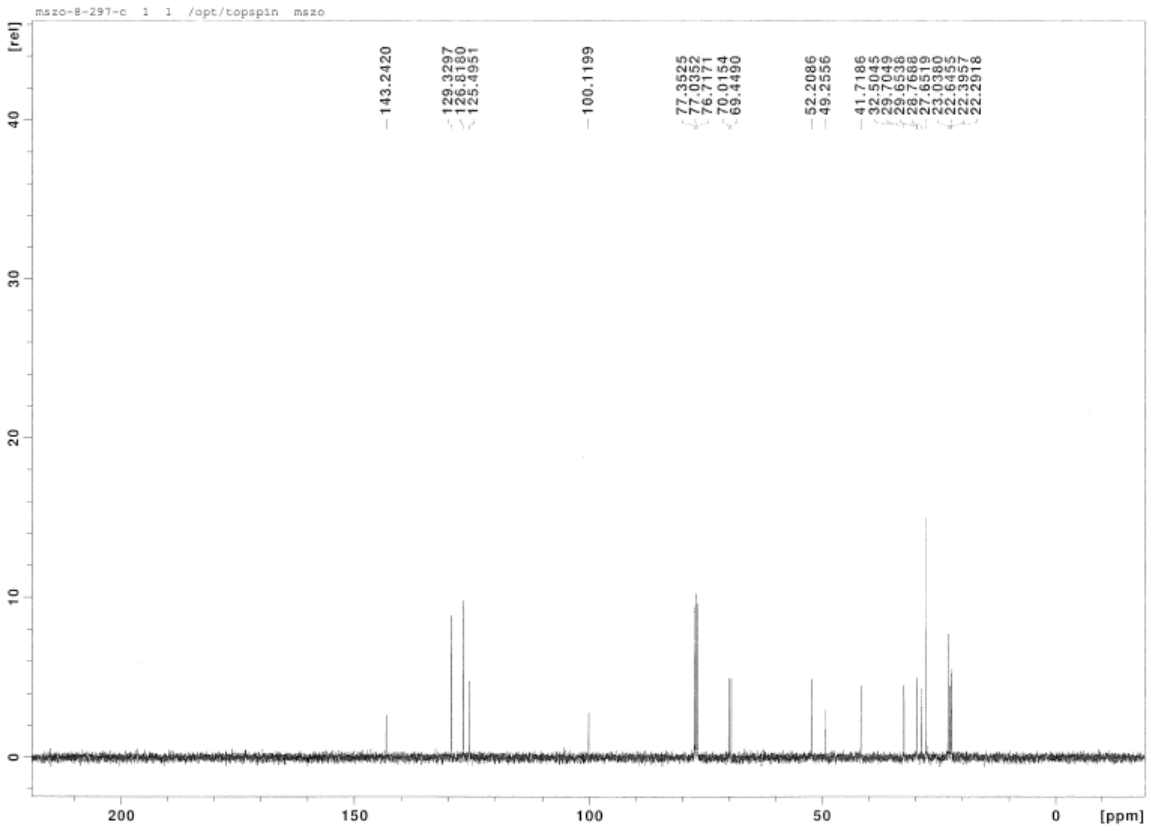


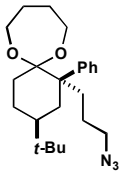


1d


```
NAME          mszo-8-297
EXPNO                  1
PROCNO                 1
Date_           20091113
Time               17.05
INSTRUM            spect
PROBHD   5 mm QNP 1H/15
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     9
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                     4
DW                60.400 usec
DE                 6.50 usec
TE                297.2 K
D1             1.00000000 sec
TD0                    1

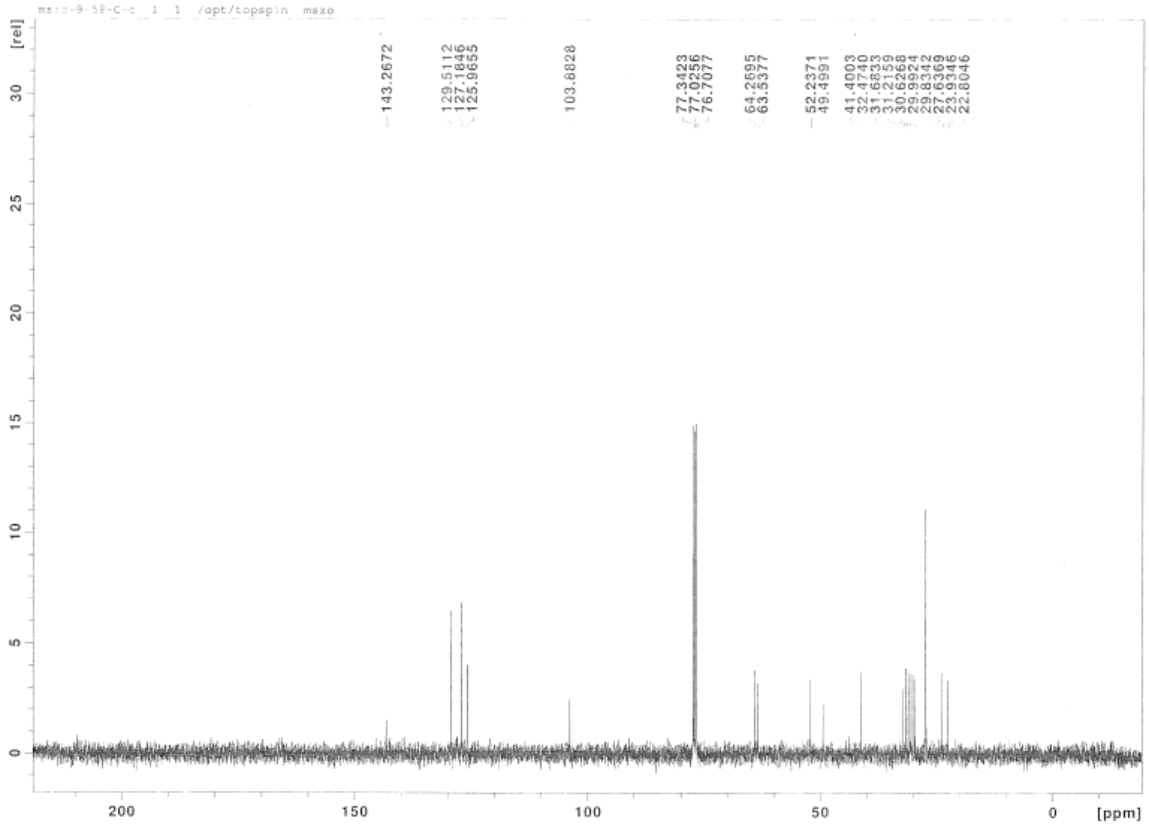
======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1               -5.00 dB
PL1W        39.71641159 W
SFO1       400.1324710 MHz
SI               32768
SF         400.1300000 MHz
WDW                 EM
SSB                 0
LB               0.30 Hz
GB                  0
PC               1.00
```

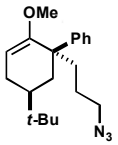



O
O
Ph
t-Bu
N3

1e

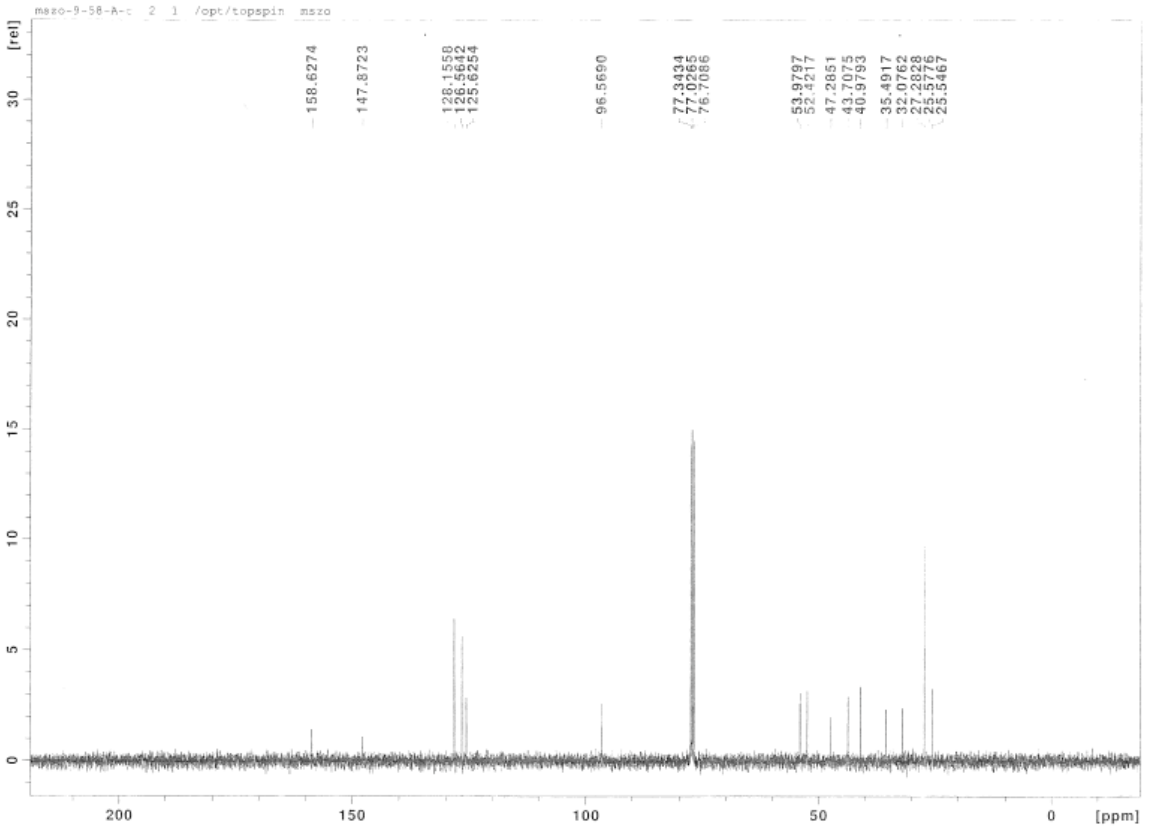
NAME mszo-9-58-C
EXPNO 1
PROCNO 1
Date_ 20091129
Time 22.01
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

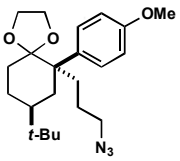

mszo-9-58-C-c 1 1 /opt/topspin mszo
[rel]
143.2672
129.5112
127.1846
125.9655
103.6828
77.3423
77.0256
76.7077
64.2695
63.5377
52.2371
49.4991
41.4003
32.4740
31.6033
31.2268
30.2656
29.9924
29.8442
27.6369
23.9346
22.8046
200 150 100 50 0 [ppm]


OMe
Ph
t-Bu
N3

1f

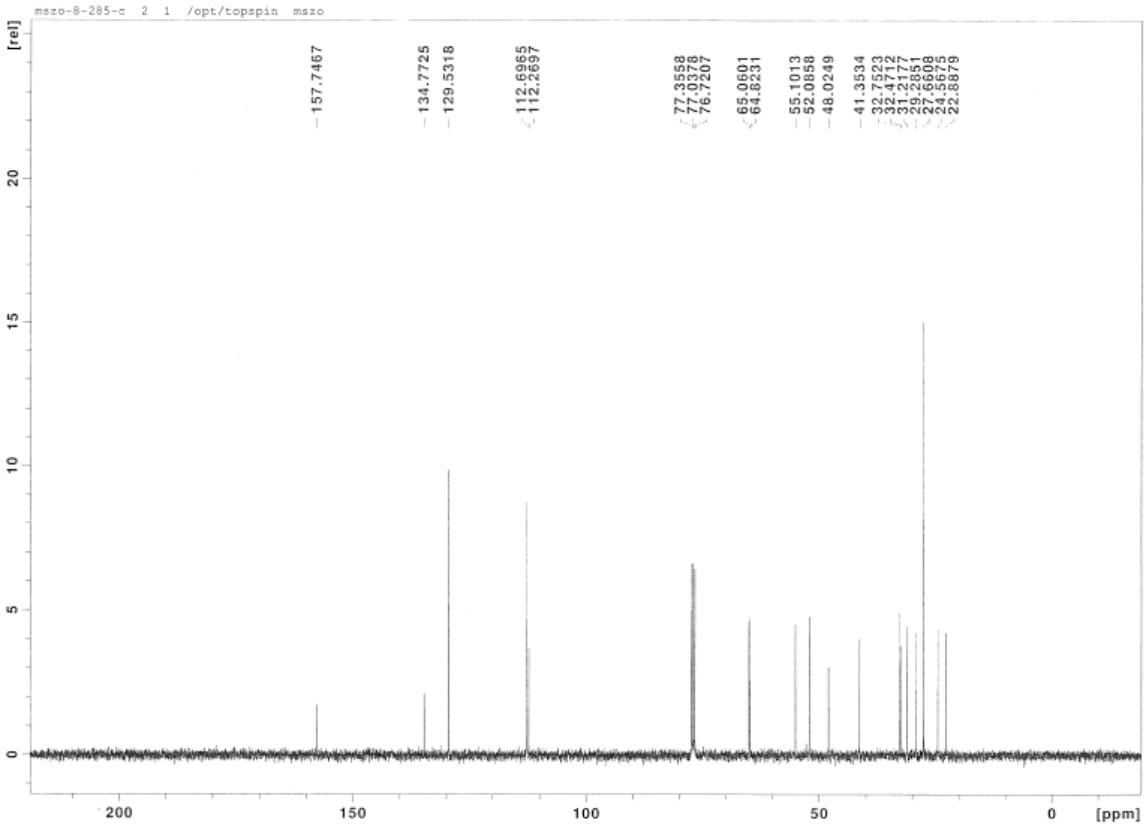
NAME mszo-9-58-A
EXPNO 2
PROCNO 1
Date_ 20091129
Time 18.10
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

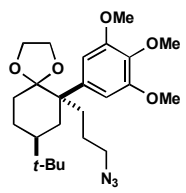

mszo-9-58-A-c 2 1 /opt/topspin mszo
[rel]
158.6274
147.8723
128.1558
126.5642
125.6254
96.5690
77.3434
77.0265
76.7086
53.9797
52.4217
47.2851
43.7075
40.9793
35.4917
32.0762
27.2828
25.5776
25.3467
200 150 100 50 0 [ppm]


OMe
O
O
t-Bu
N3

1g

NAME mszo-8-285
EXPNO 2
PROCNO 1
Date_ 20091111
Time 15.34
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

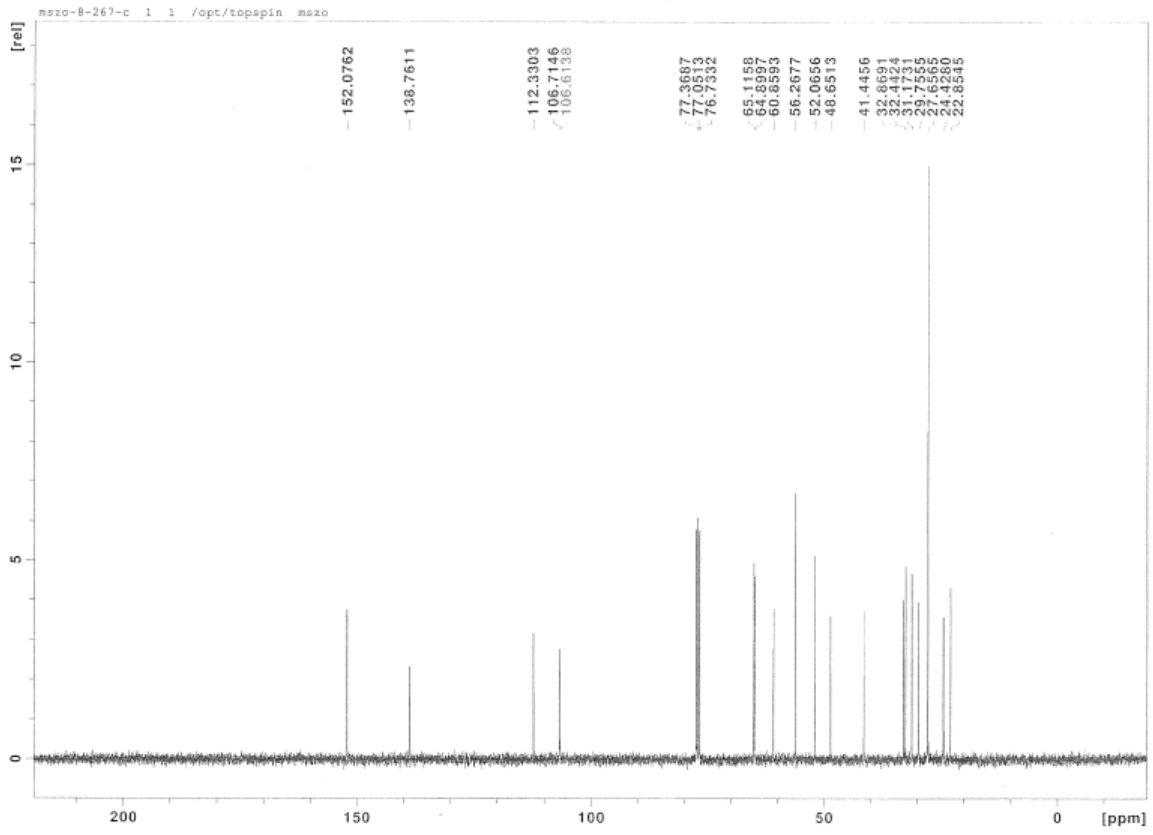

mszo-8-285-c 2 1 /opt/topspin mszo
[rel]
157.7467
134.7725
129.5318
112.6965
112.2697
77.3558
77.0378
76.7207
65.0601
64.8231
55.1013
52.0858
48.0249
41.3534
32.7523
32.4172
31.2177
29.2851
27.6608
24.5675
22.8879
0 5 10 15 20
200 150 100 50 0 [ppm]

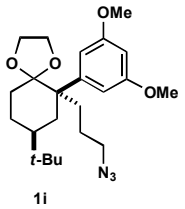


1h


```
NAME            mszo-8-267
EXPNO                    1
PROCNO                   1
Date_             20091106
Time                 19.18
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       9
DS                       2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  297.7 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W         39.71641159 W
SFO1         400.1324710 MHz
SI                   32768
SF           400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

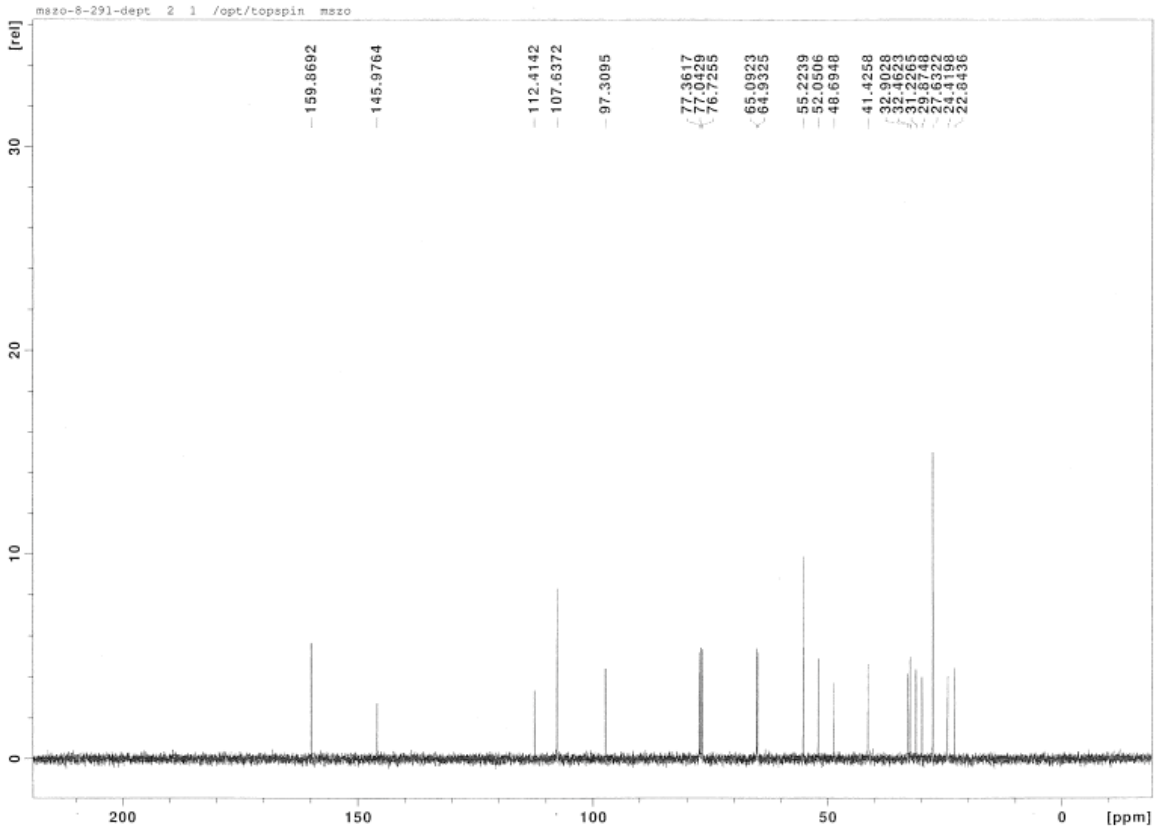


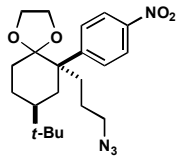


1i


```
NAME          mszo-8-291-A
EXPNO                    1
PROCNO                   1
Date_             20091112
Time                 21.25
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      16
DS                       2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  300.0 K
D1               1.00000000 sec
TD0                      1

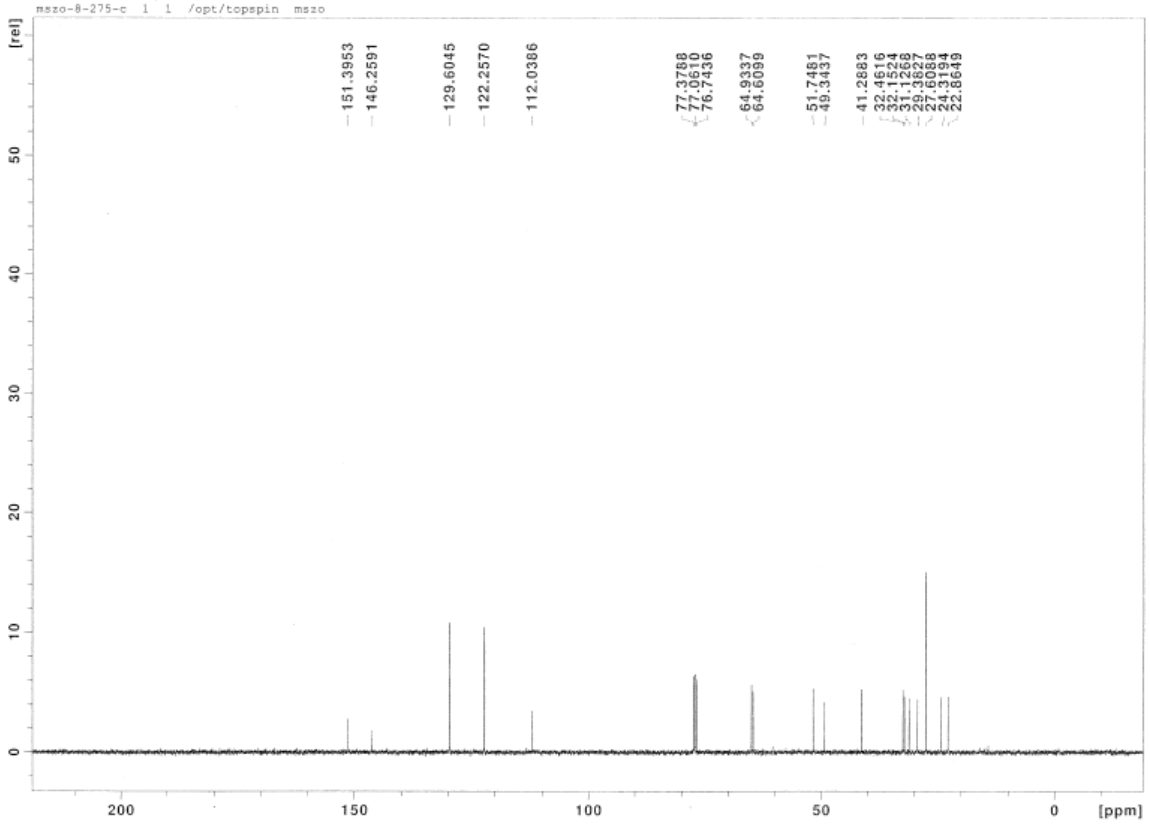
======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300000 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                    1.00
```

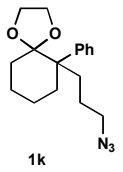



NO2
O
O
t-Bu
N3

1j

NAME mszo-8-275
EXPNO 2
PROCNO 1
Date_ 20091108
Time 18.24
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

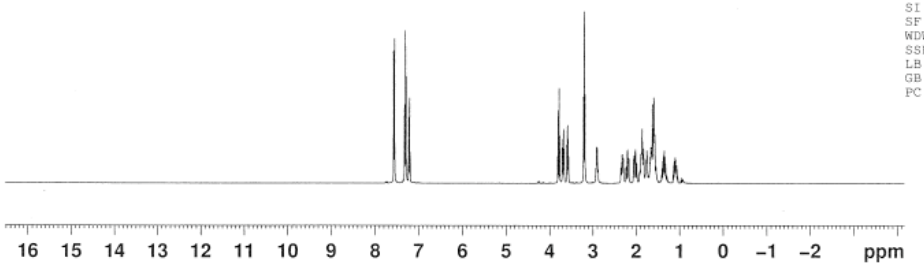

mszo-8-275-c 1 1 /opt/topspin mszo
[rel]
151.3953
146.2591
129.6045
122.2570
112.0386
77.3788
77.0610
76.7436
64.9337
64.6099
51.7481
49.3437
41.2883
32.4616
32.1524
31.1268
29.3627
27.6088
24.3194
22.8649
0 10 20 30 40 50
200 150 100 50 0 [ppm]

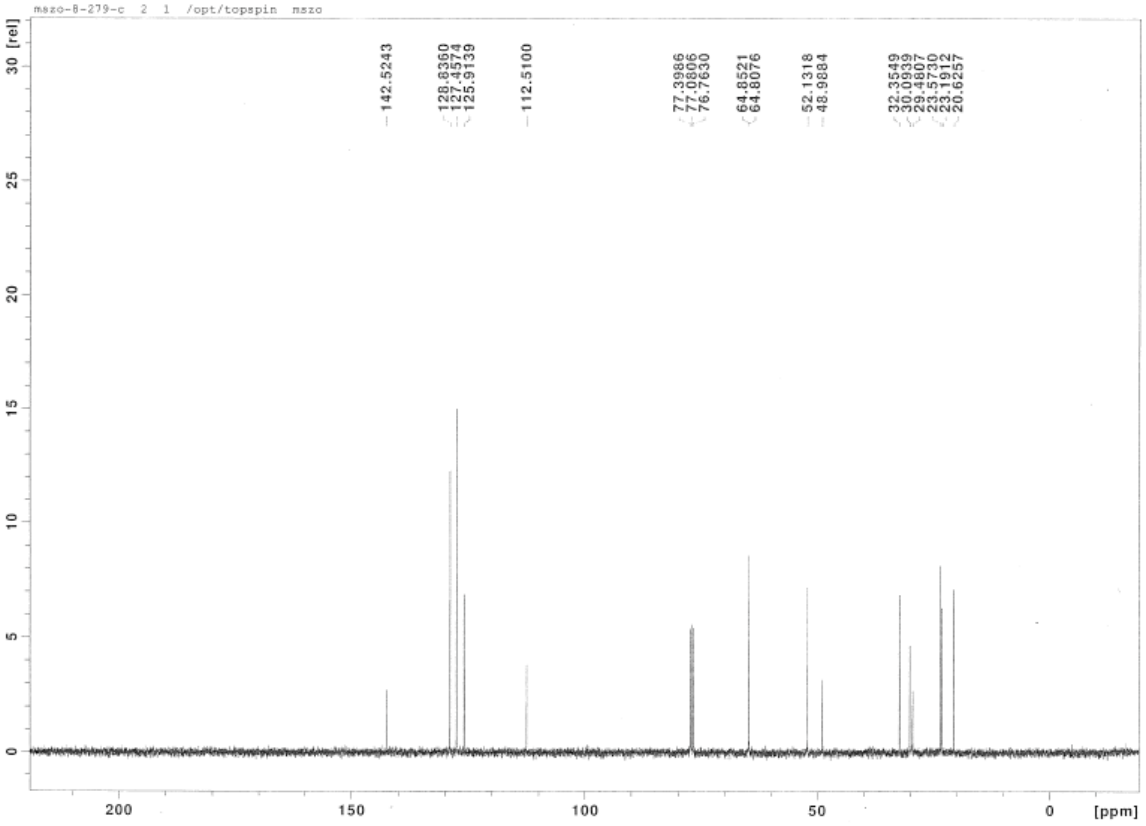


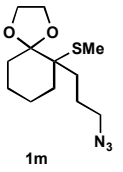
1k

```
NAME                mszo-8-279
EXPNO                        2
PROCNO                       1
Date_                 20091110
Time                     16.39
INSTRUM                  spect
PROBHD   5 mm QNP 1H/15
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8278.146 Hz
FIDRES                0.126314 Hz
AQ                    3.9584243 sec
RG                           4
DW                       60.400 usec
DE                        6.50 usec
TE                       296.9 K
D1                    1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       8.00 usec
PL1                     -5.00 dB
PL1W                39.71641159 W
SFO1                400.1324710 MHz
SI                       32768
SF                  400.1300000 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.40
```



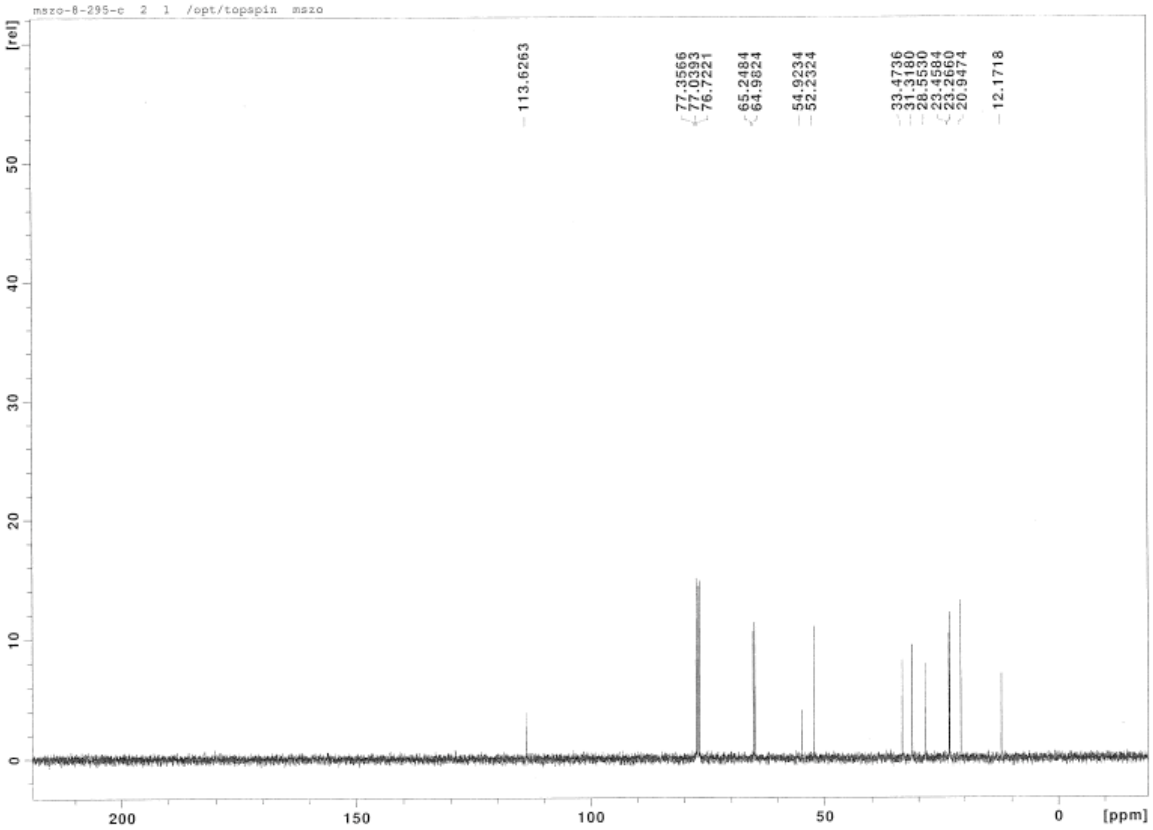


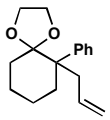


1m


```
NAME            mszo-8-295
EXPNO                    2
PROCNO                   1
Date_             20091112
Time                 21.35
INSTRUM              spect
PROBHD    5 mm QNP 1H/15
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  297.2 K
D1               1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

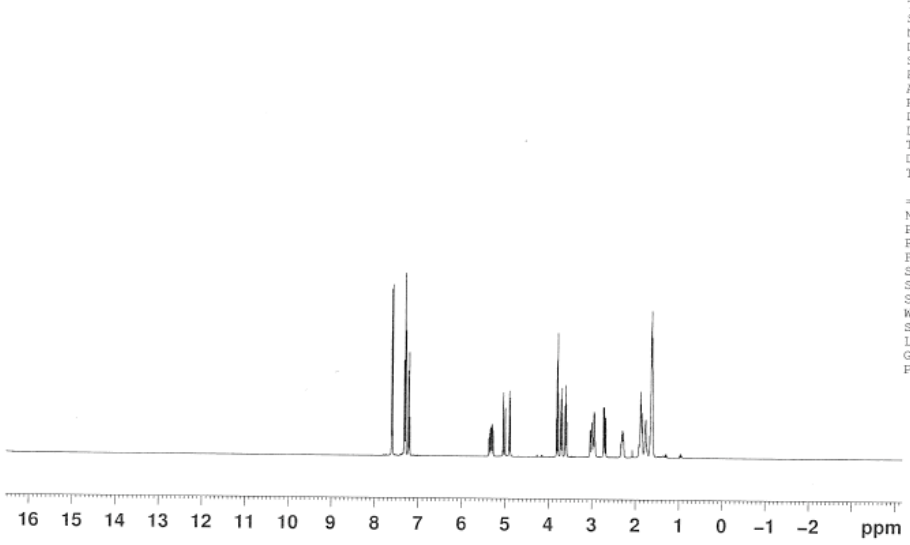


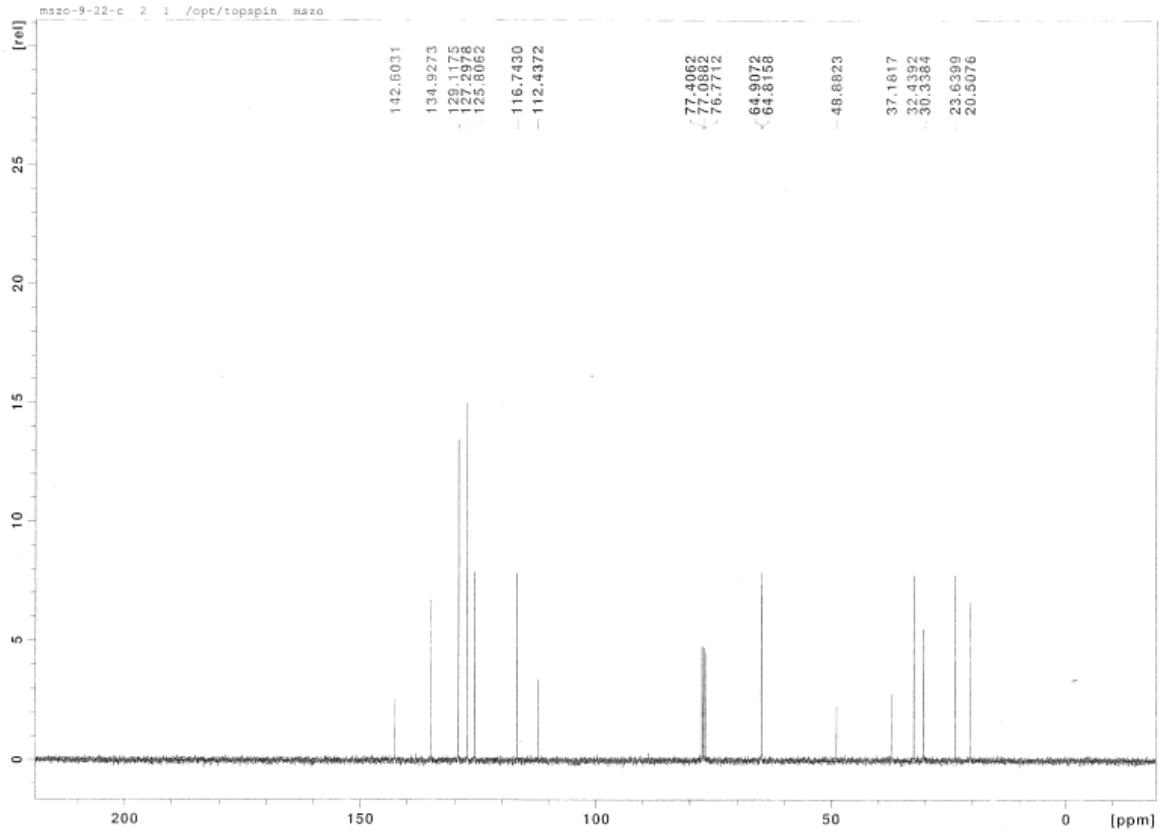


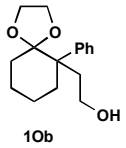
1Oa

```
NAME                mszo-9-22
EXPNO                       2
PROCNO                      1
Date_                20091119
Time                    20.13
INSTRUM                 spect
PROBHD   5 mm QNP 1H/15
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                         16
DS                          2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                          4
DW                    60.400 usec
DE                     6.50 usec
TE                    296.8 K
D1                 1.00000000 sec
TD0                         1

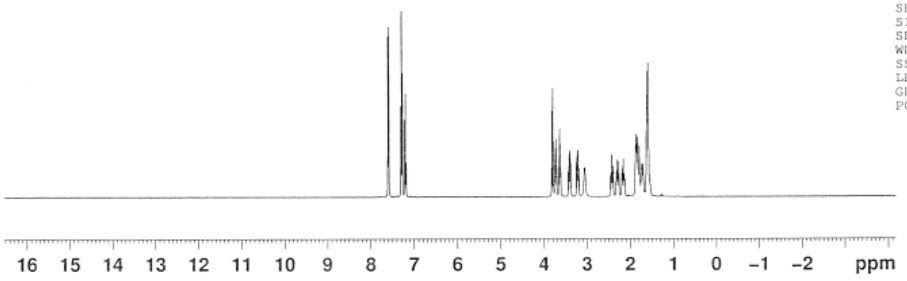
======== CHANNEL f1 ========
NUC1                       1H
P1                     8.00 usec
PL1                   -5.00 dB
PL1W              39.71641159 W
SFO1              400.1324710 MHz
SI                       32768
SF                400.1300000 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                     1.40
```



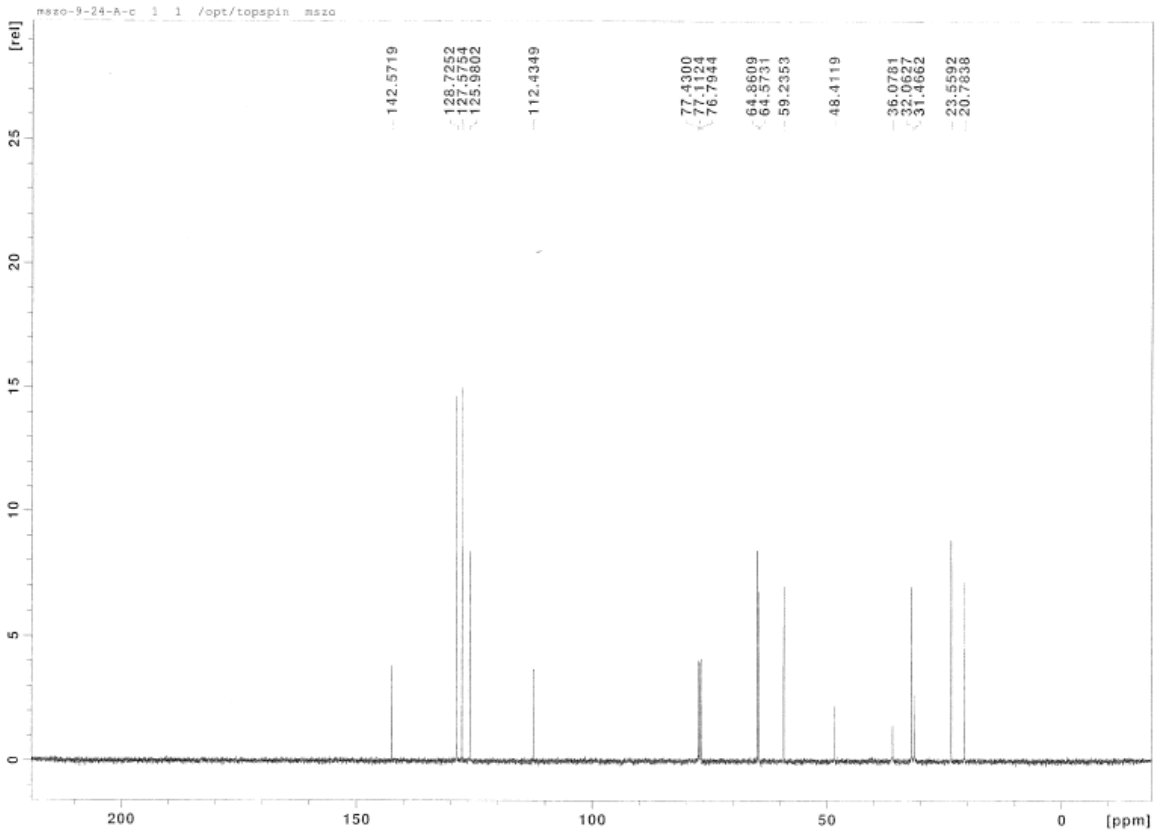


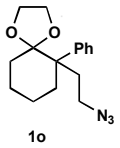


1Ob



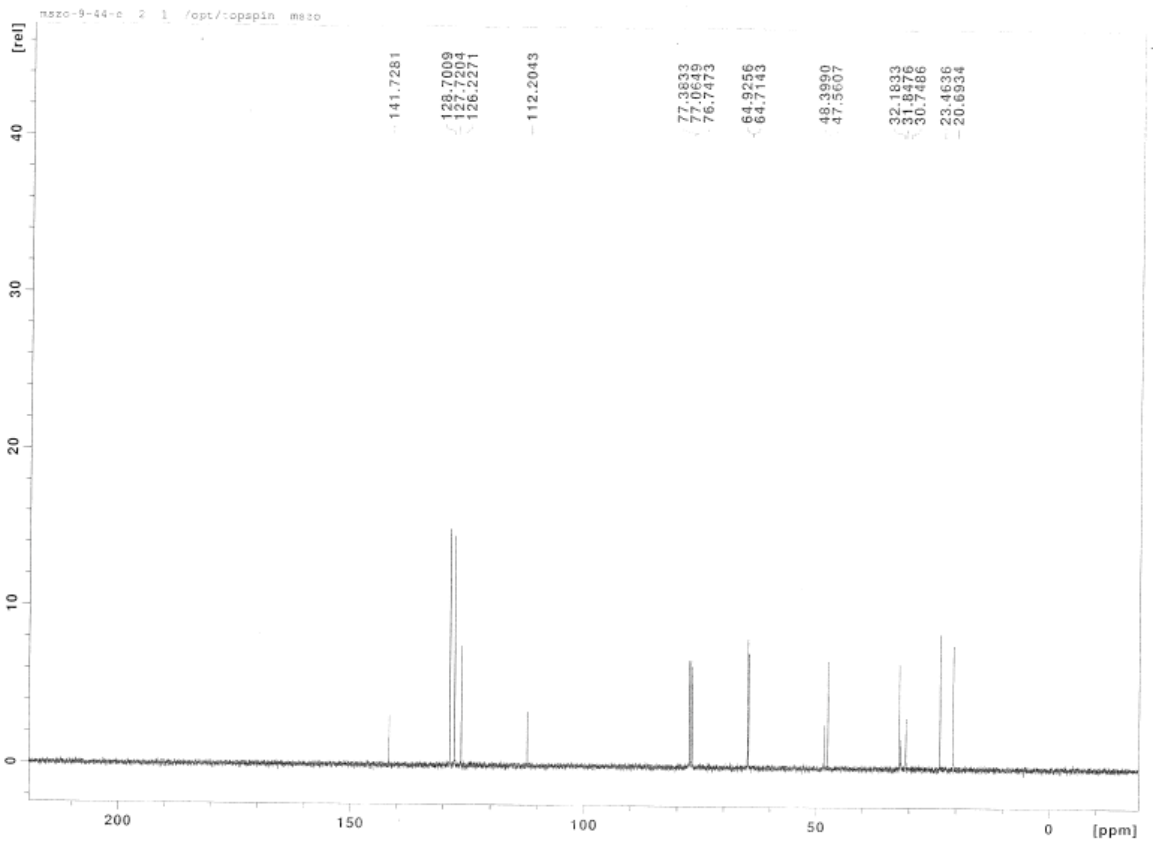
NAME	mszo-9-24-A
EXPNO	1
PROCNO	1
Date_	20091121
Time	10.10
INSTRUM	spect
PROBHD	5 mm QNP 1H/15
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	5
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	4
DW	60.400 usec
DE	6.50 usec
TE	296.8 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	8.00 usec
PL1	-5.00 dB
PL1W	39.71641159 W
SFO1	400.1324710 MHz
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

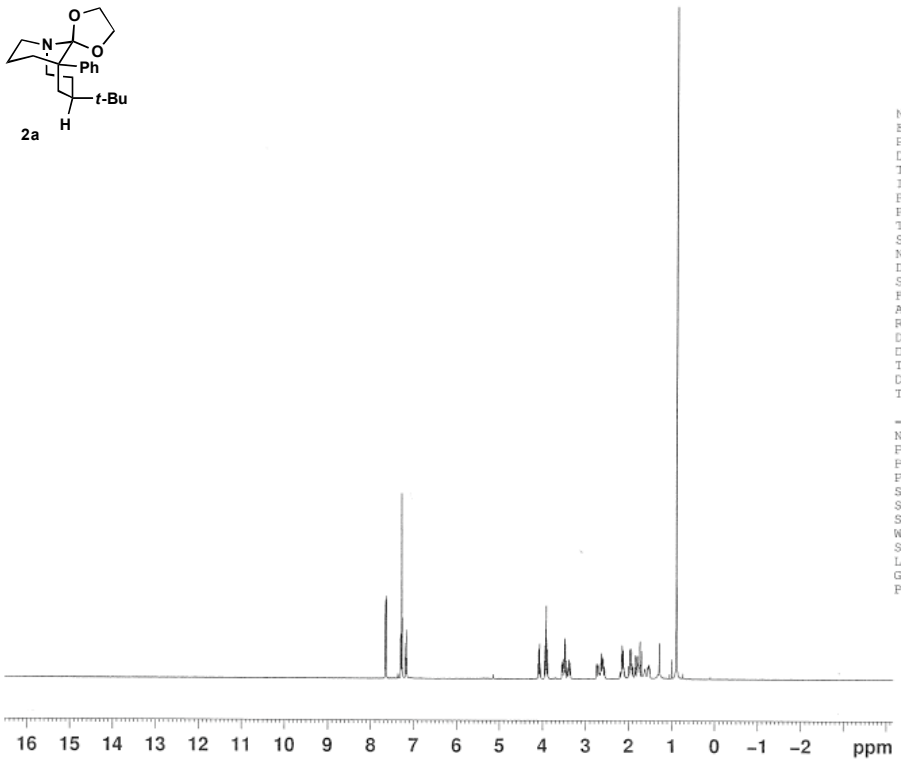


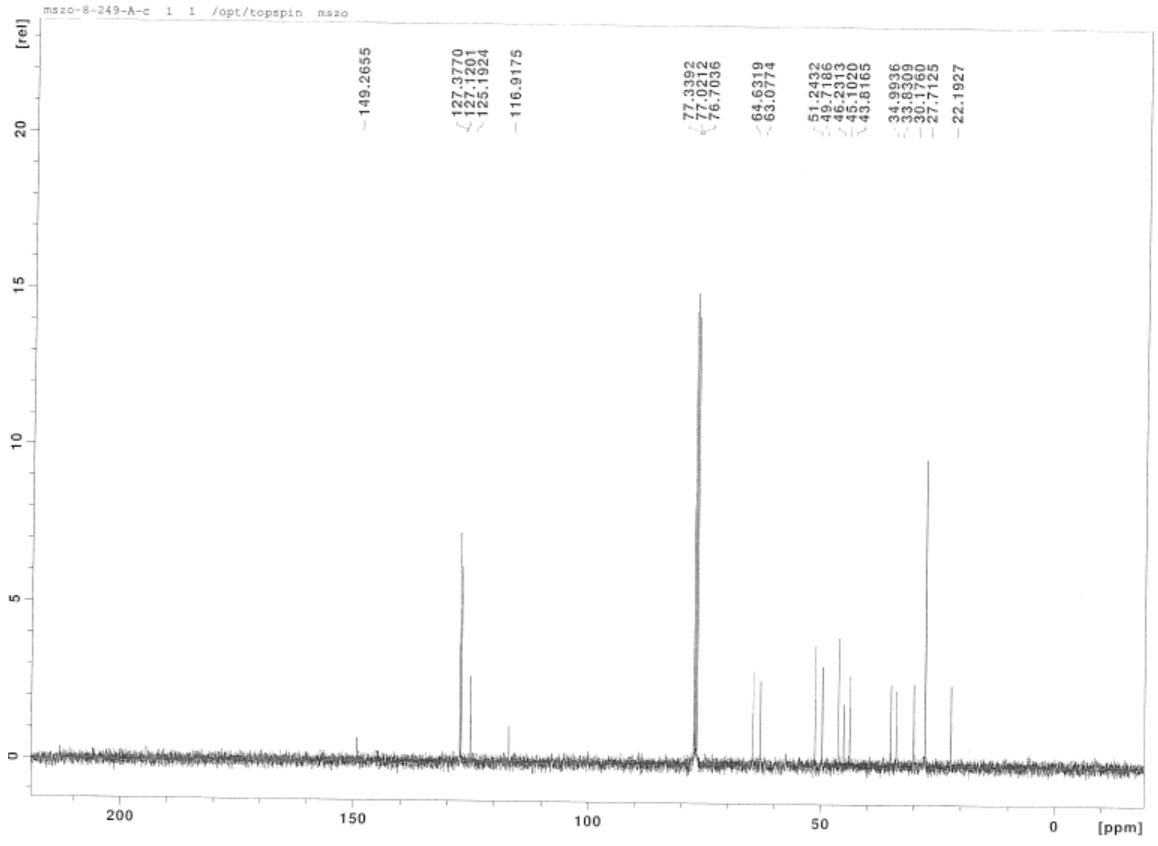

O
O
Ph
N3

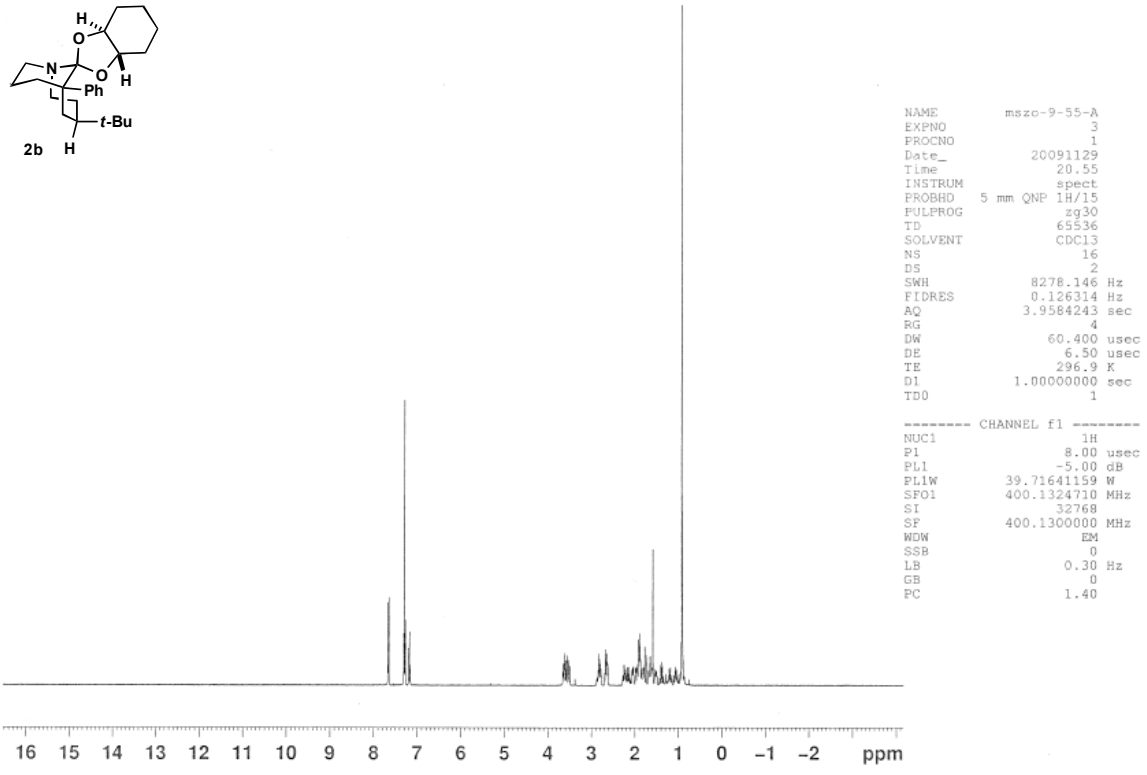
1o

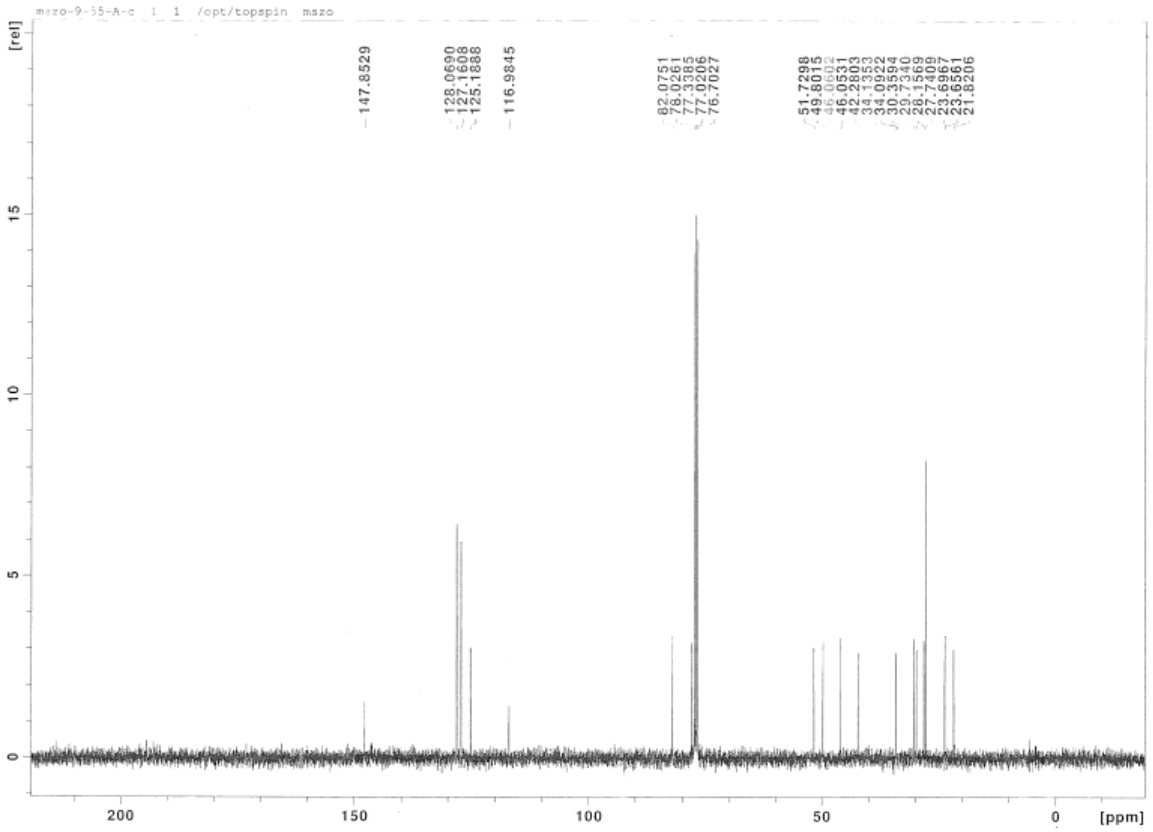
NAME mszo-9-44
EXPNO 2
PROCNO 1
Date_ 20091125
Time 12.30
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 6
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

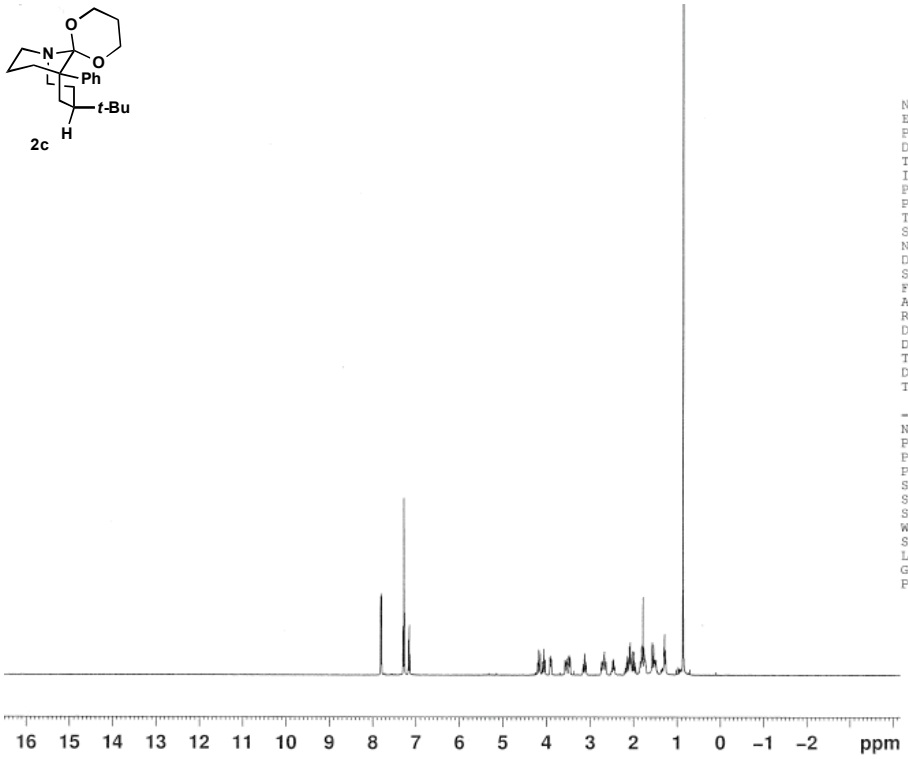

mszo-9-44-c 2 1 /opt/topspin mszo
[rel]
141.7281
128.7009
127.7204
126.2271
112.2043
77.3833
77.0649
76.7473
64.9256
64.7143
48.3990
47.5607
32.1833
31.8476
30.7486
23.4636
20.6934
0 10 20 30 40
200 150 100 50 0 [ppm]

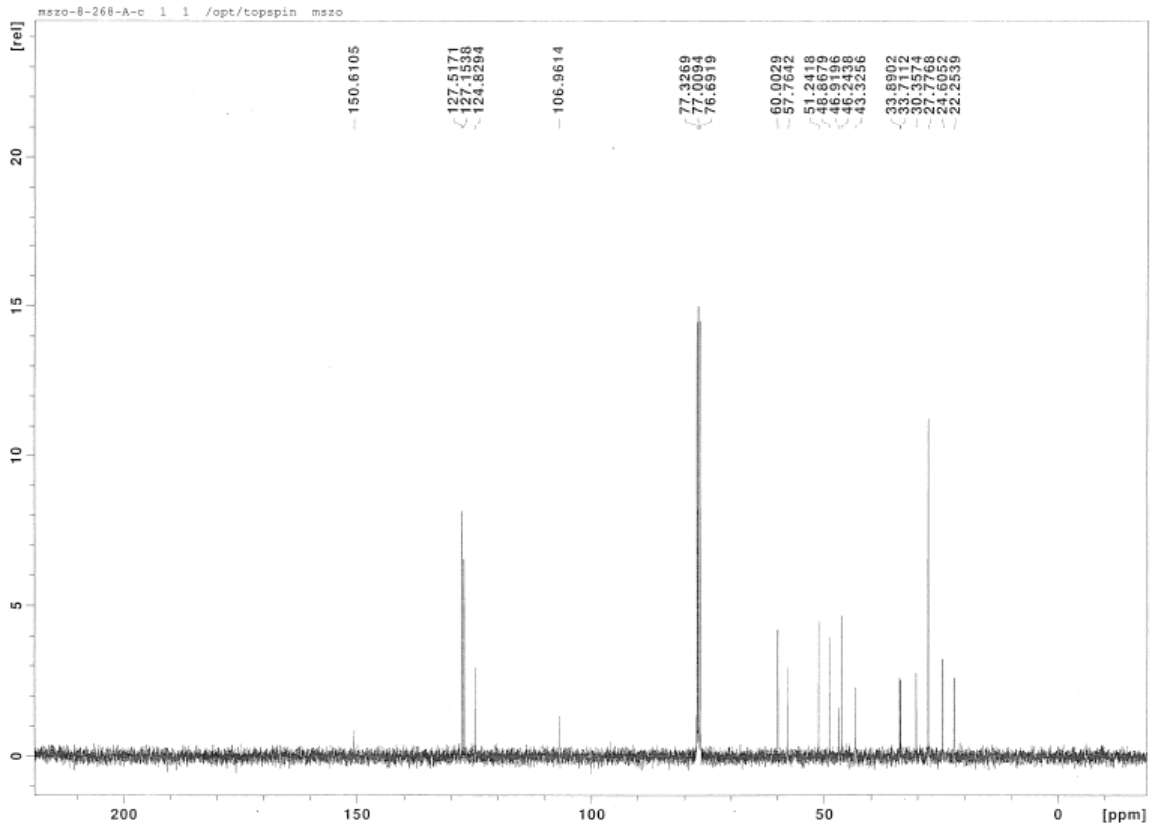

O
N
O
Ph
t-Bu
H
2a
NAME mszo-8-247-A
EXPNO 1
PROCNO 1
Date_ 20091027
Time 19.13
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

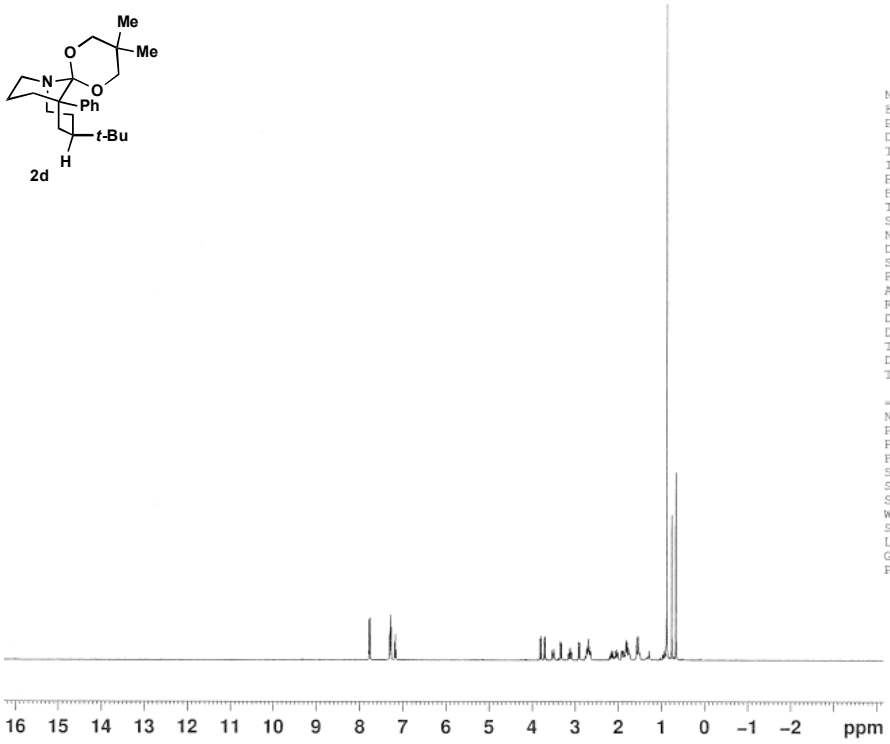

mszo-8-249-A-c 1 1 /opt/topspin mszo
[rel]
149.2655
127.3770
127.1601
125.1924
116.9175
77.3392
77.0212
76.7036
64.6319
63.0774
51.2432
49.7186
46.2313
45.1020
43.8165
34.9936
33.8309
30.1760
27.7125
22.1927
0 5 10 15 20
200 150 100 50 0 [ppm]

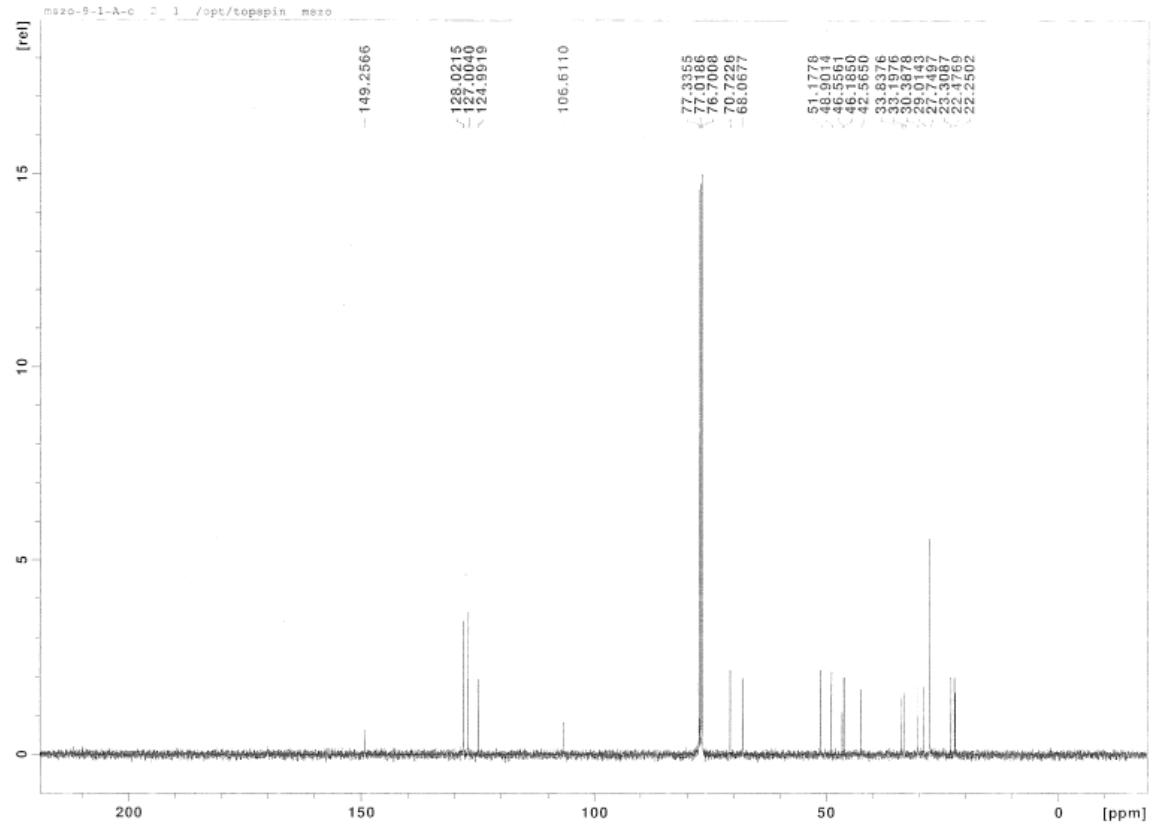

2b
NAME mszo-9-55-A
EXPNO 3
PROCNO 1
Date_ 20091129
Time 20.55
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

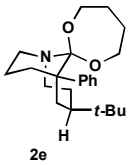

mszo-9-55-A-c 1 1 /opt/topspin mszo
[rel]
147.8529
128.0690
127.1608
125.1888
116.9845
82.0751
78.0261
77.3385
77.0206
76.7027
51.7298
49.8015
46.0531
42.2803
34.1523
30.3554
29.7340
28.1569
27.7409
23.6967
23.6561
21.8206
200 150 100 50 0 [ppm]


O
N
O
Ph
t-Bu
H
2c
NAME mszo-8-268-A
EXPNO 1
PROCNO 1
Date_ 20091107
Time 14.18
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm


mszo-8-268-A-c 1 1 /opt/topspin mszo
[rel]
150.6105
127.5171
127.1538
124.8294
106.9614
77.3269
77.0094
76.6919
60.0029
57.7642
51.2418
48.8679
46.9196
46.2438
43.3256
33.8902
33.7112
30.1374
24.6052
22.2539
0 5 10 15 20
200 150 100 50 0 [ppm]


Me
Me
O
N
O
Ph
t-Bu
H
2d
NAME mszo-9-16-A
EXPNO 2
PROCNO 1
Date_ 20091119
Time 20.04
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

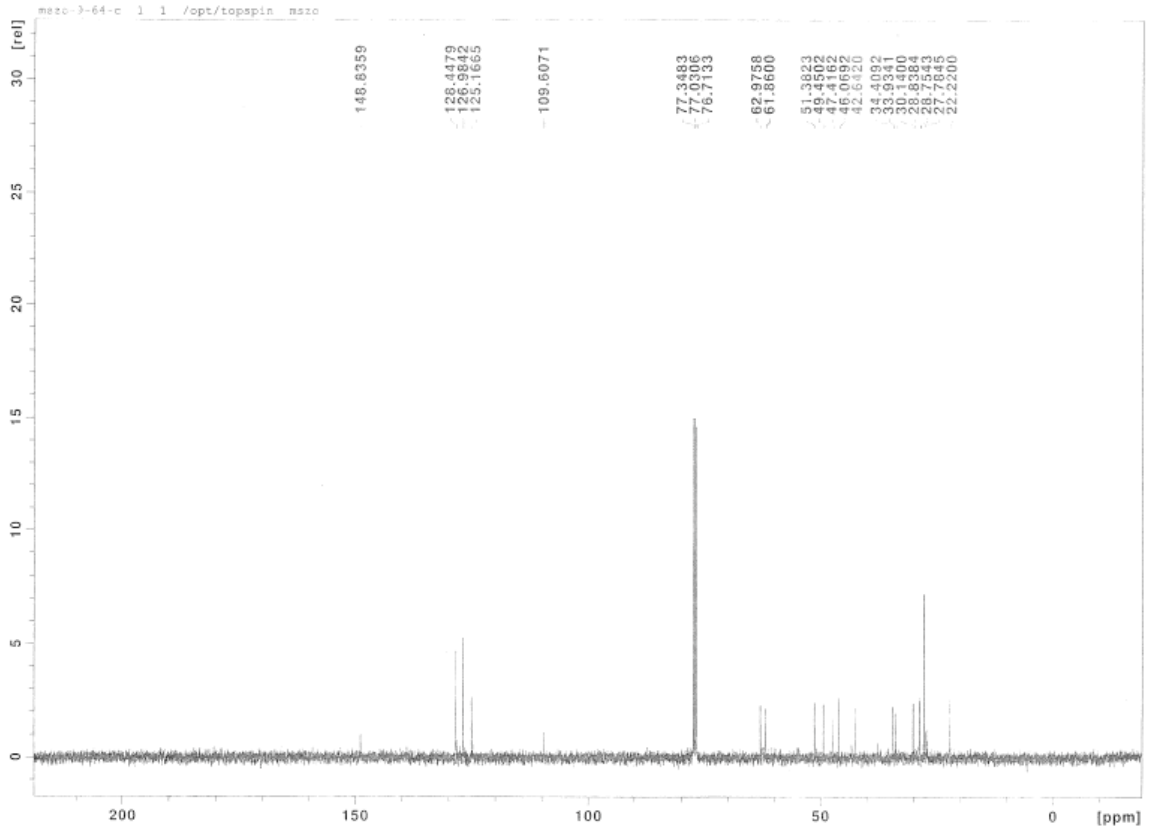

mszo-9-1-A-c 2 1 /opt/topspin mszo
[rel]
149.2566
128.0215
127.0040
124.9919
106.6110
77.3355
77.0186
76.7008
70.7226
68.0677
51.1778
48.9014
46.5561
46.1850
42.5650
33.8376
33.1576
30.3878
29.0143
27.7497
23.3087
22.4769
22.2502
0 5 10 15
200 150 100 50 0 [ppm]

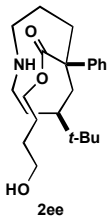


2e


```
NAME                mszo-9-64
EXPNO                       1
PROCNO                      1
Date_                20091130
Time                    17.10
INSTRUM                 spect
PROBHD   5 mm QNP 1H/15
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                         16
DS                          2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                  3.9584243 sec
RG                          4
DW                     60.400 usec
DE                      6.50 usec
TE                     296.7 K
D1                  1.00000000 sec
TD0                         1

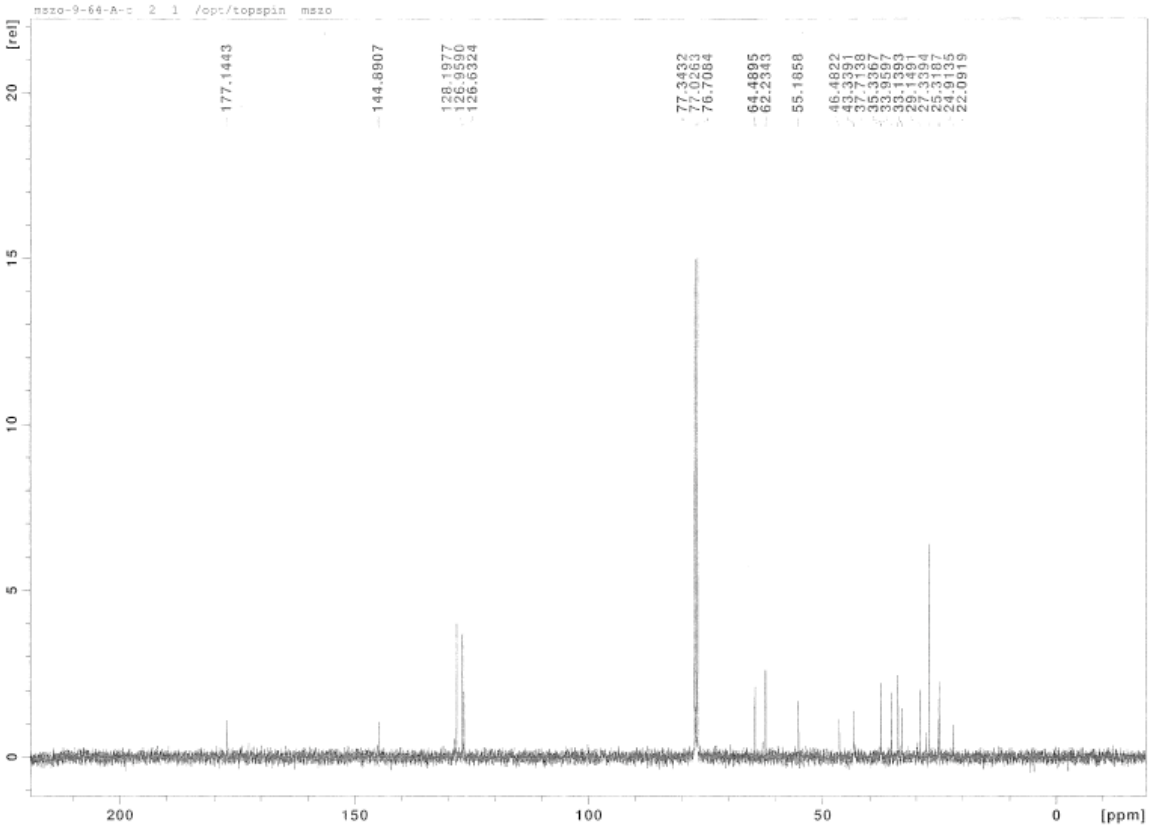
======== CHANNEL f1 ========
NUC1                       1H
P1                      8.00 usec
PL1                    -5.00 dB
PL1W             39.71641159 W
SFO1             400.1324710 MHz
SI                      32768
SF               400.1300000 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.40
```

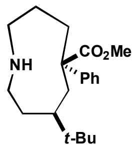



O
NH
O
Ph
t-Bu
HO

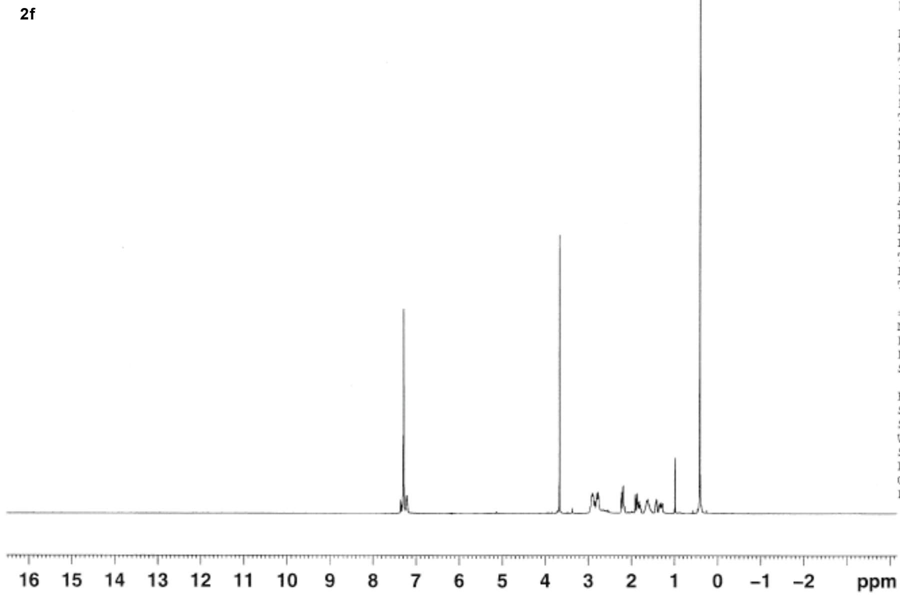
2ee

NAME mszo-9-64-A
EXPNO 2
PROCNO 1
Date_ 20091130
Time 19.56
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm


mszo-9-64-A-c 2 1 /opt/topspin mszo
[rel]
177.1443
144.8907
128.1977
126.9590
126.6324
77.3432
77.0263
76.7084
64.4895
62.2343
55.1858
46.4822
43.3391
37.7138
35.3667
33.9597
33.1493
30.1191
27.7394
25.3187
24.9135
22.0919
200 150 100 50 0 [ppm]



2f

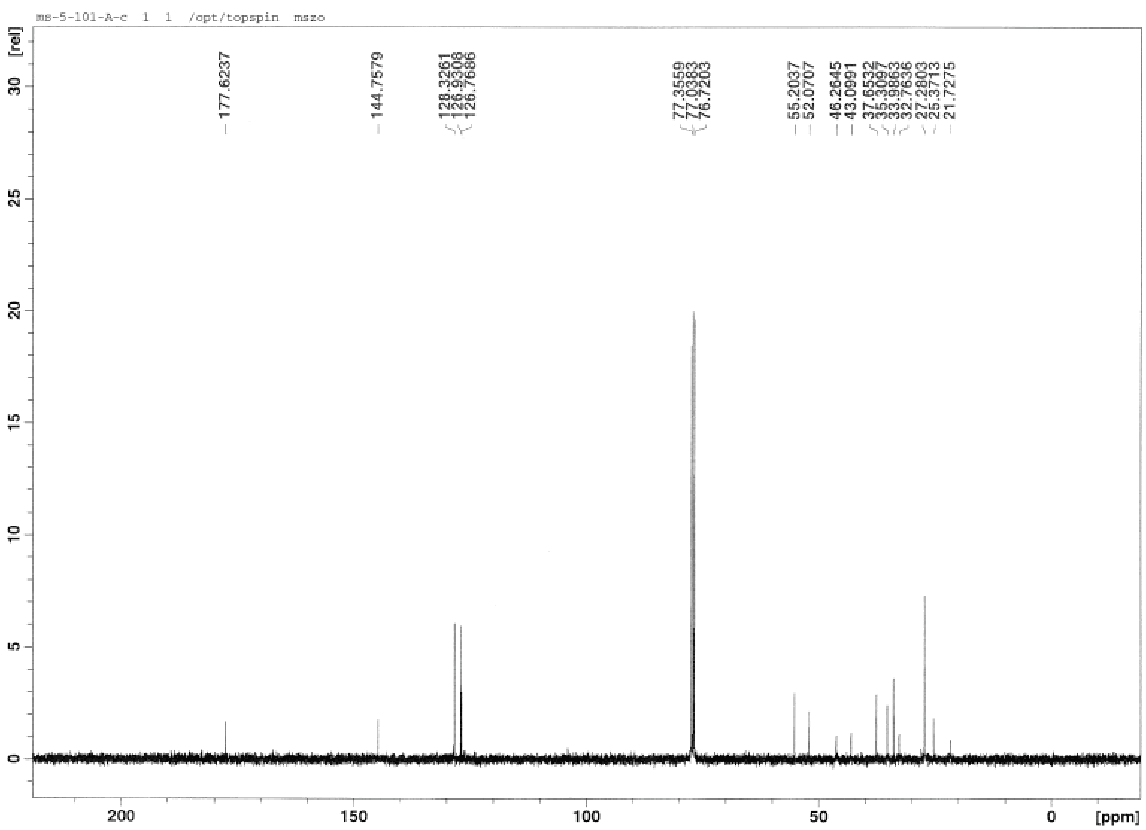


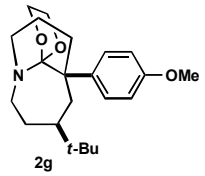

```
Current Data Parameters
NAME              ms-5-101-A
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20071110
Time                   17.17
INSTRUM               drx400
PROBHD   5 mm QNP 1H/13
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        32
DS                         2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                 3.9584243 sec
RG                         4
DW                    60.400 usec
DE                      6.00 usec
TE                     296.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     10.50 usec
PL1                    -5.00 dB
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                     32768
SF               400.1300000 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

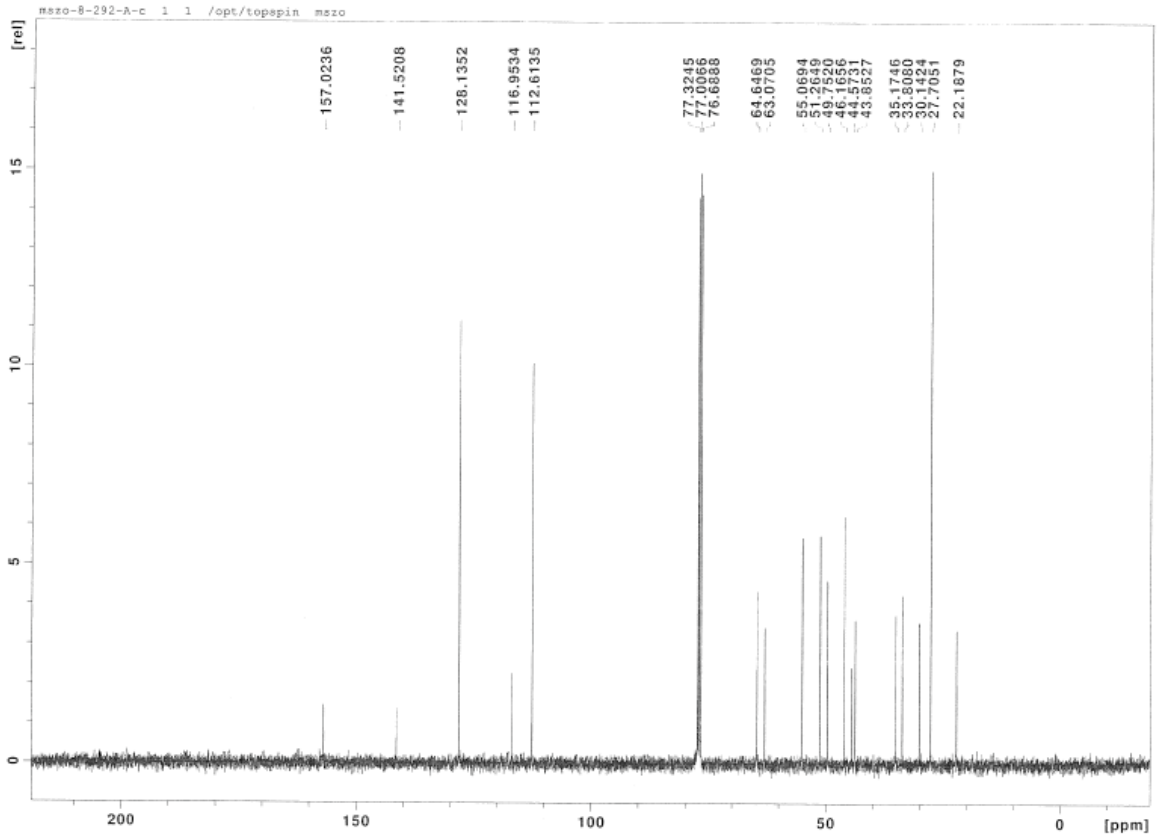


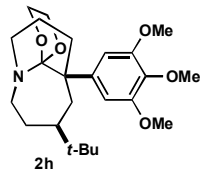


2g


```
NAME          mszo-8-292-A
EXPNO                    2
PROCNO                   1
Date_             20091113
Time                 16.58
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG               zg30
TD                   65536
SOLVENT              CDC13
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  297.2 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W           39.71641159 W
SFO1           400.1324710 MHz
SI                   32768
SF             400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

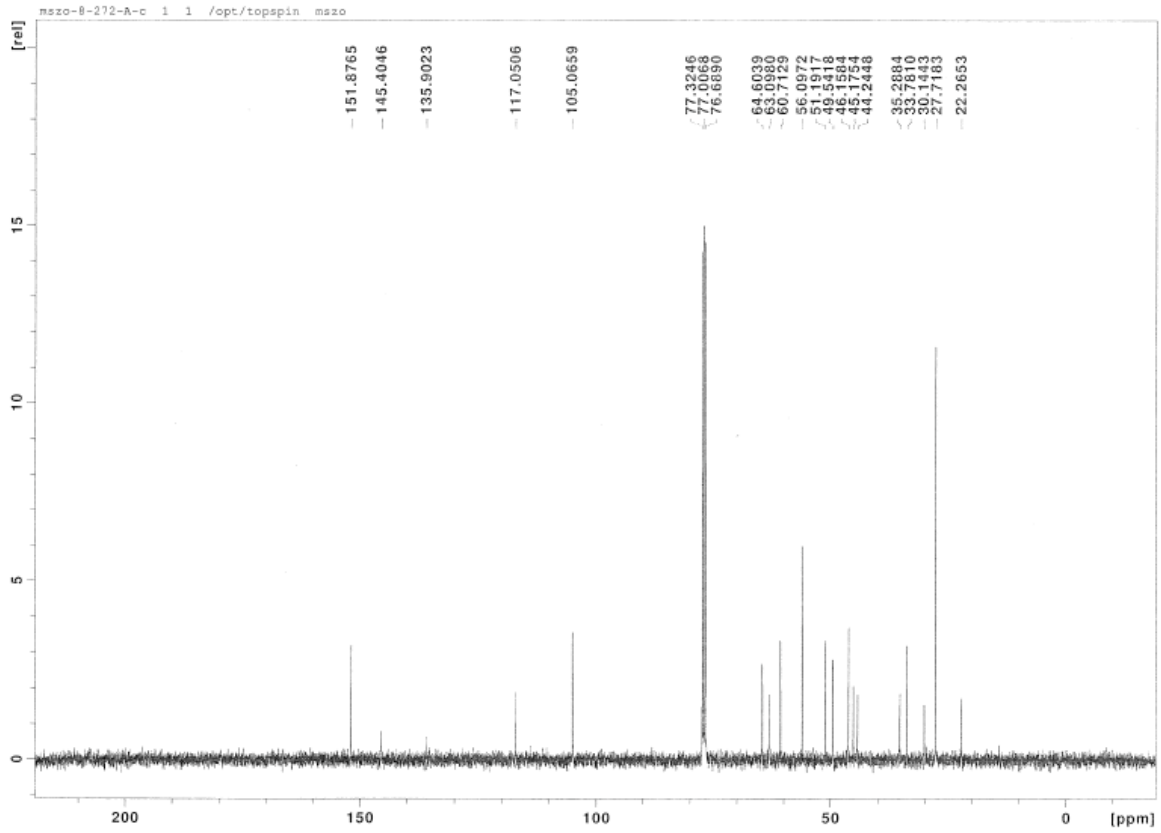


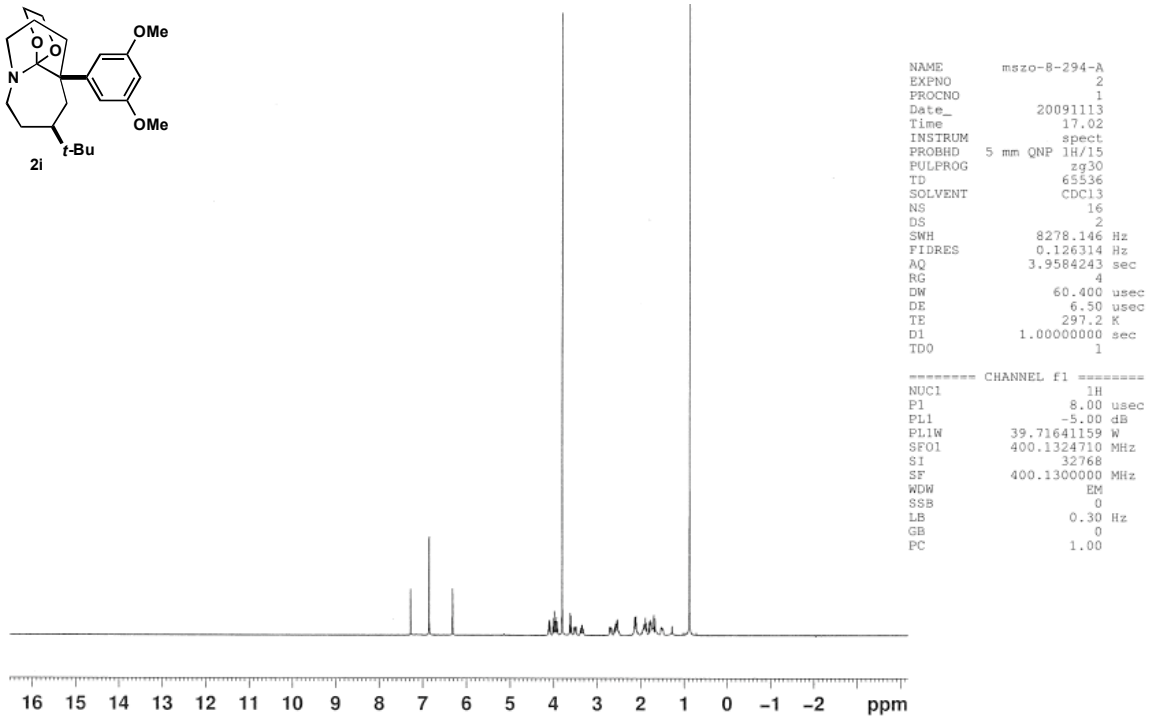


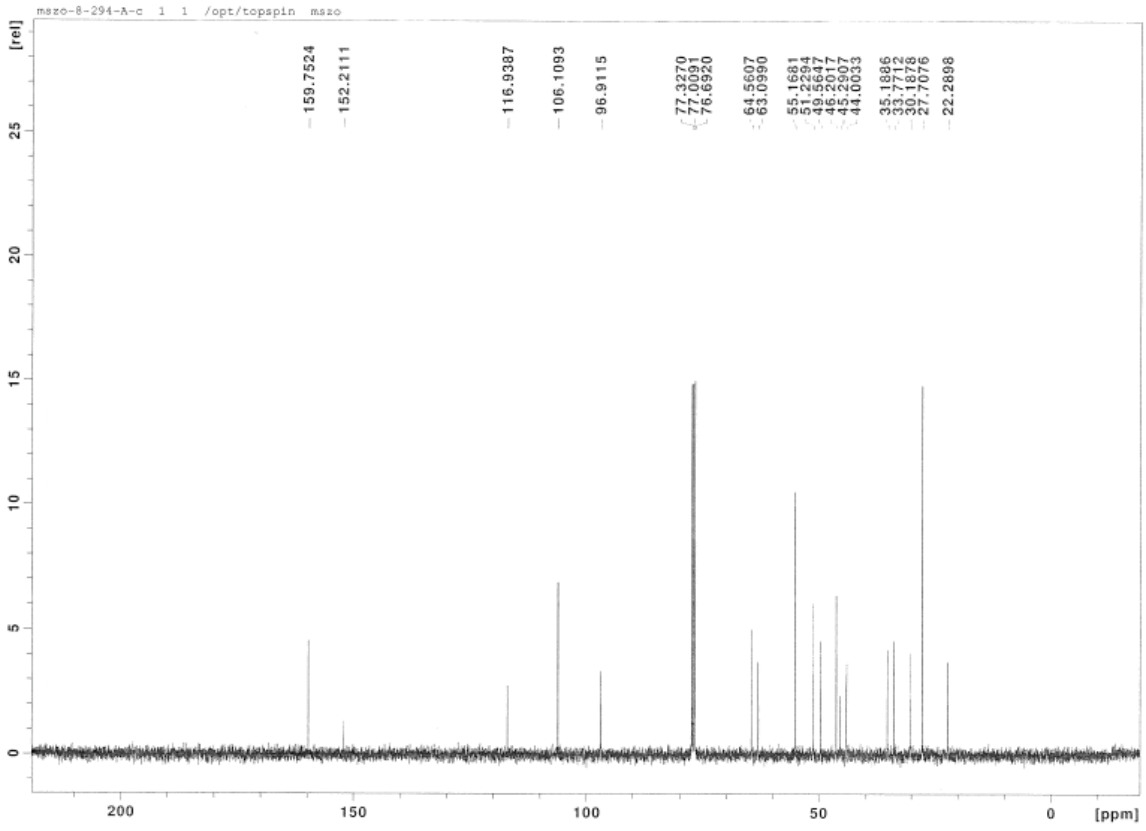
2h

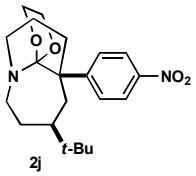

```
NAME          mszo-8-272-A
EXPNO                    2
PROCNO                   1
Date_             20091108
Time                 13.08
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      16
DS                       2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  297.0 K
D1               1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1         400.1324710 MHz
SI                   32768
SF           400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```




OMe
OMe
t-Bu
2i
NAME mszo-8-294-A
EXPNO 2
PROCNO 1
Date_ 20091113
Time 17.02
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

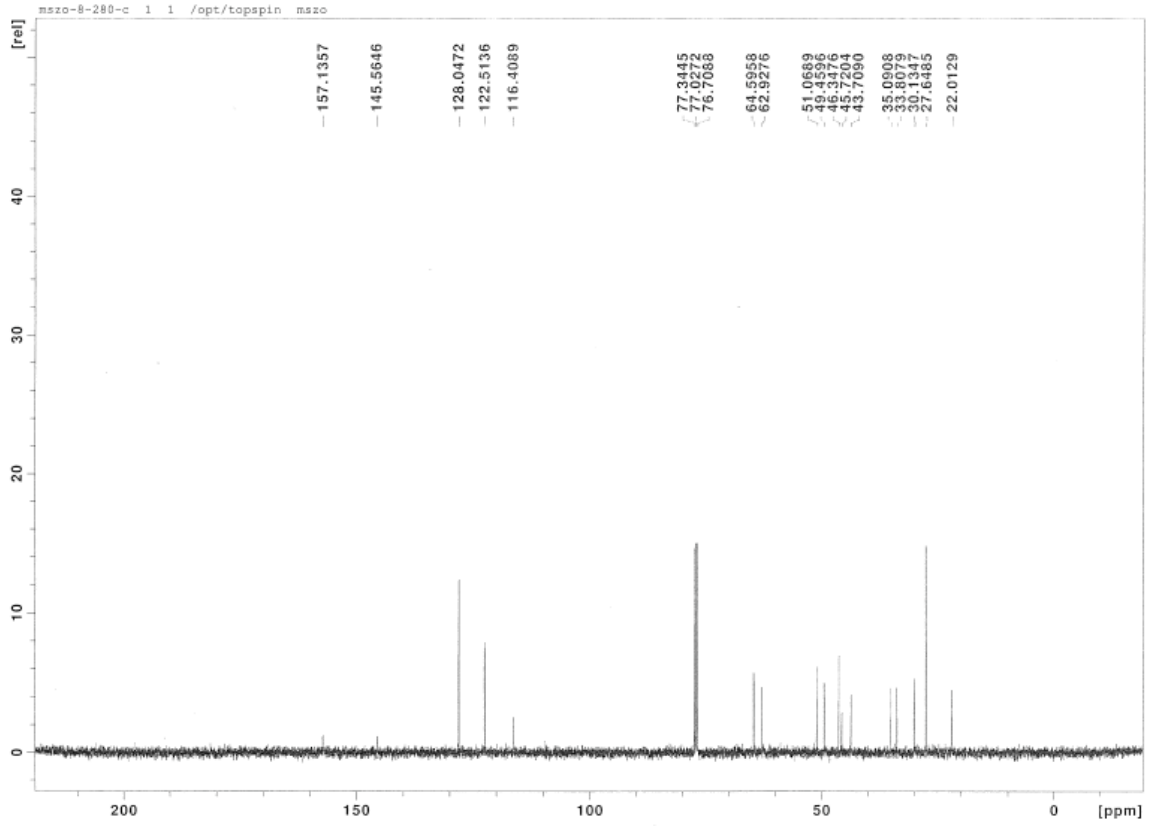

mszo-8-294-A-c 1 1 /opt/topspin mszo
[rel]
159.7524
152.2111
116.9387
106.1093
96.9115
77.3270
77.0091
76.6920
64.5607
63.0990
55.1681
55.0294
49.5647
46.2017
45.2907
44.0033
35.1886
33.7712
30.1878
27.7076
22.2898
0 5 10 15 20 25
200 150 100 50 0 [ppm]

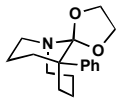


2j


```
NAME          mszo-8-280-A
EXPNO                    2
PROCNO                   1
Date_             20091110
Time                 16.34
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG               zg30
TD                   65536
SOLVENT              CDC13
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                  300.0 K
D1                1.00000000 sec
TD0                      1

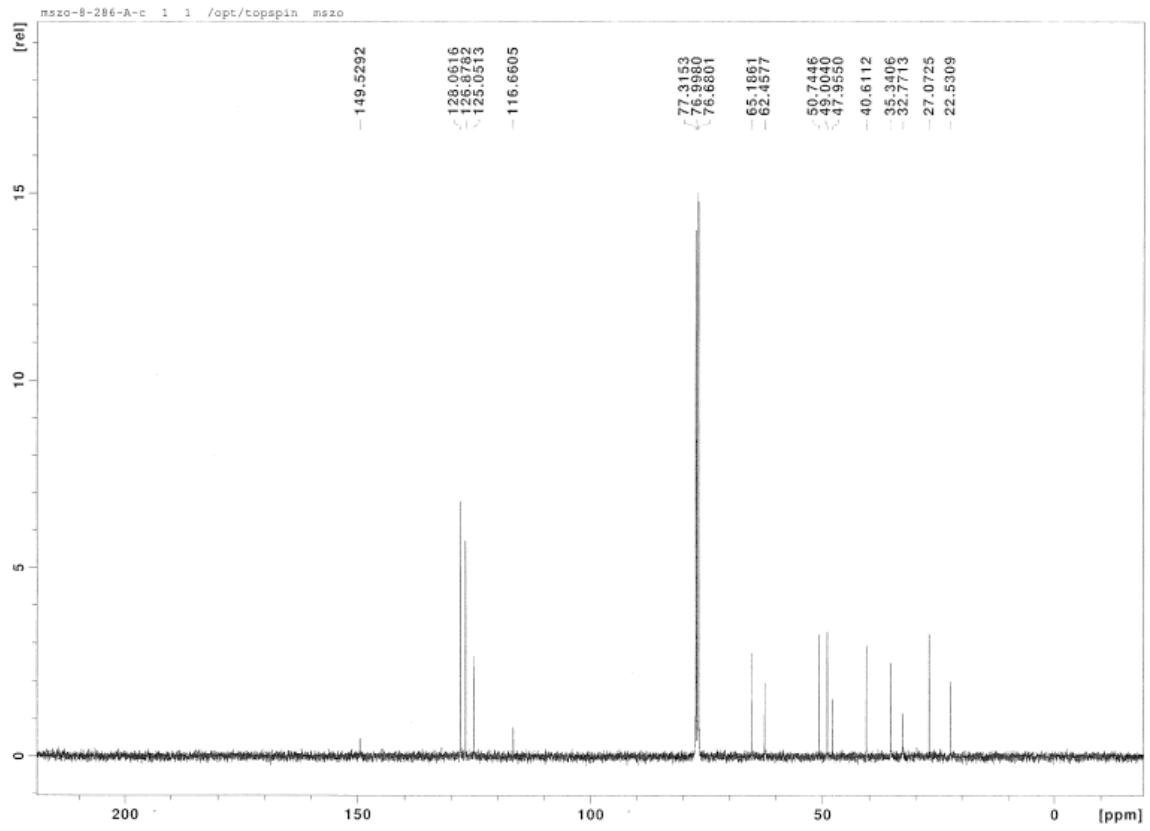
======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

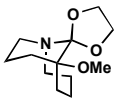



O
N
O
Ph

2k

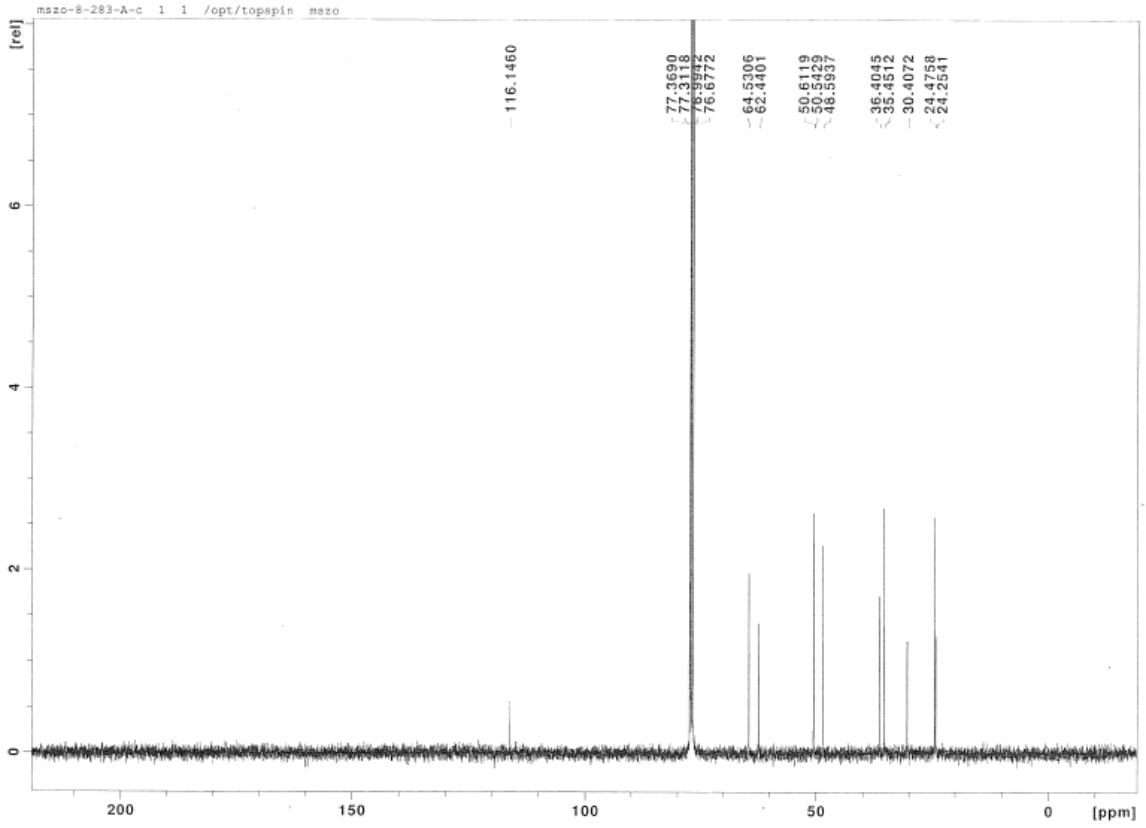
NAME mszo-9-12-A
EXPNO 2
PROCNO 1
Date_ 20091118
Time 21.07
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

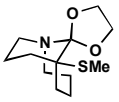

mszo-8-286-A-c 1 1 /opt/topspin mszo
[rel]
149.5292
128.0616
126.8782
125.0513
116.6605
77.3153
76.9980
76.6801
65.1861
62.4577
50.7446
49.0040
47.9550
40.6112
35.3406
32.7713
27.0725
22.5309
0 5 10 15
200 150 100 50 0 [ppm]


O
N
O
OMe

2l

NAME mszo-8-283-A
EXPNO 1
PROCNO 1
Date_ 20091109
Time 21.48
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 se
RG 4
DW 60.400 us
DE 6.50 us
TE 297.6 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 8.00 us
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MH
SI 32768
SF 400.1300000 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

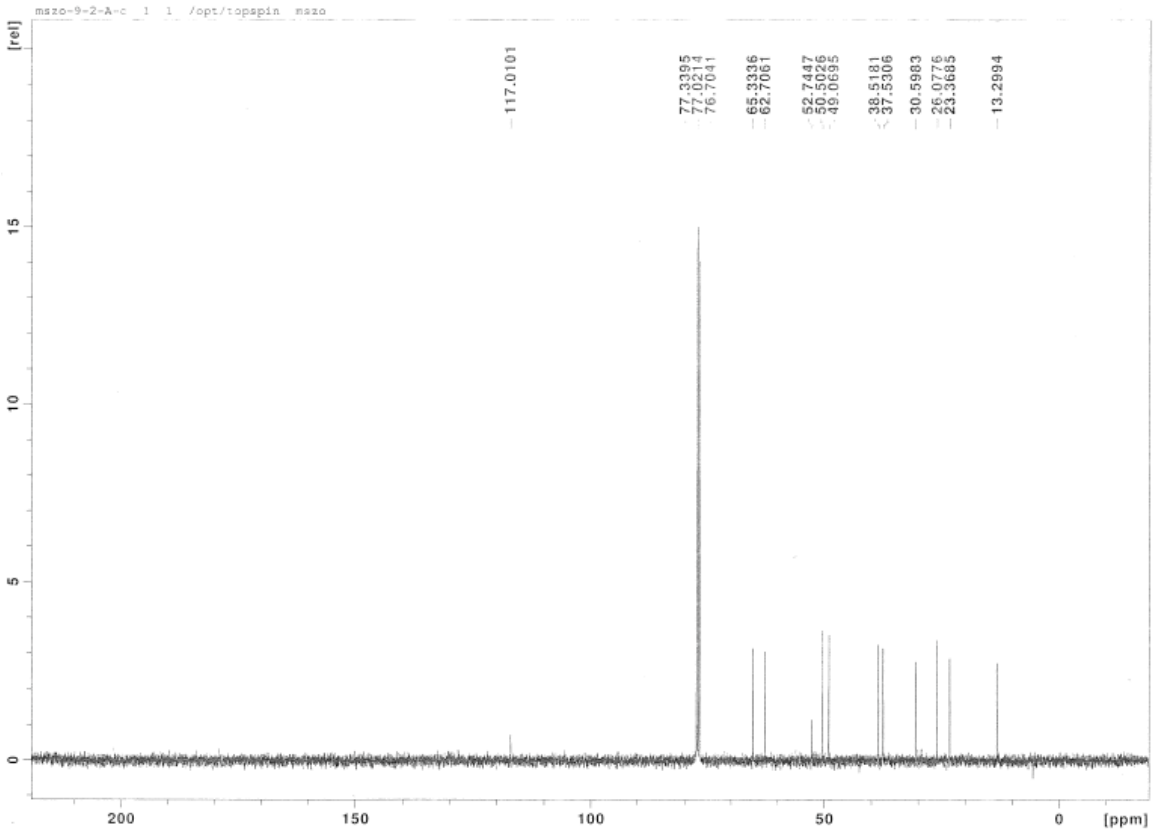

mszo-8-283-A-c 1 1 /opt/topspin mszo
[rel]
116.1460
77.3690
77.3118
76.9942
76.6772
64.5306
62.4401
50.6119
50.5429
48.5357
36.4045
35.4512
30.4072
24.4758
24.2541
0 2 4 6
200 150 100 50 0 [ppm]

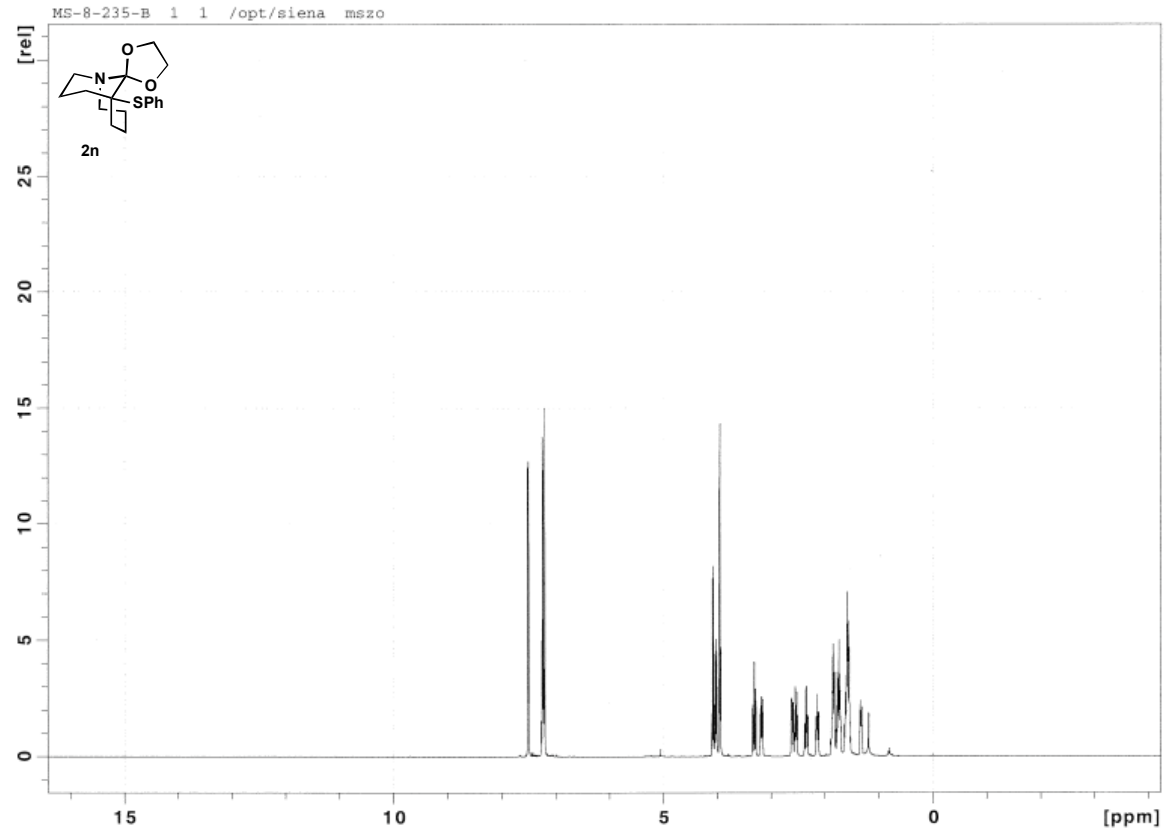


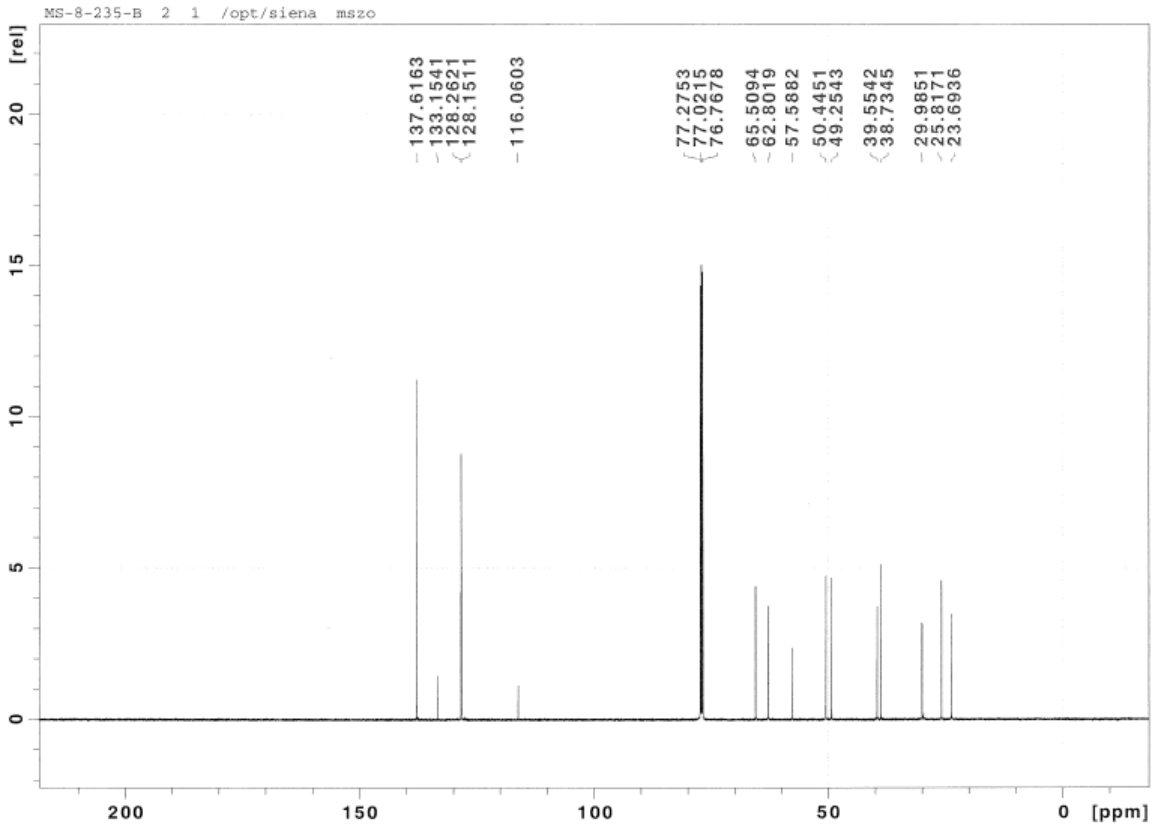
2m

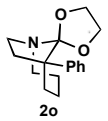

```
NAME            mszo-9-2-A
EXPNO                    1
PROCNO                   1
Date_             20091116
Time                 23.01
INSTRUM              spect
PROBHD   5 mm QNP 1H/15
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES           0.126314 Hz
AQ                3.9584243 sec
RG                       4
DW                  60.400 usec
DE                   6.50 usec
TE                   300.0 K
D1               1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W          39.71641159 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



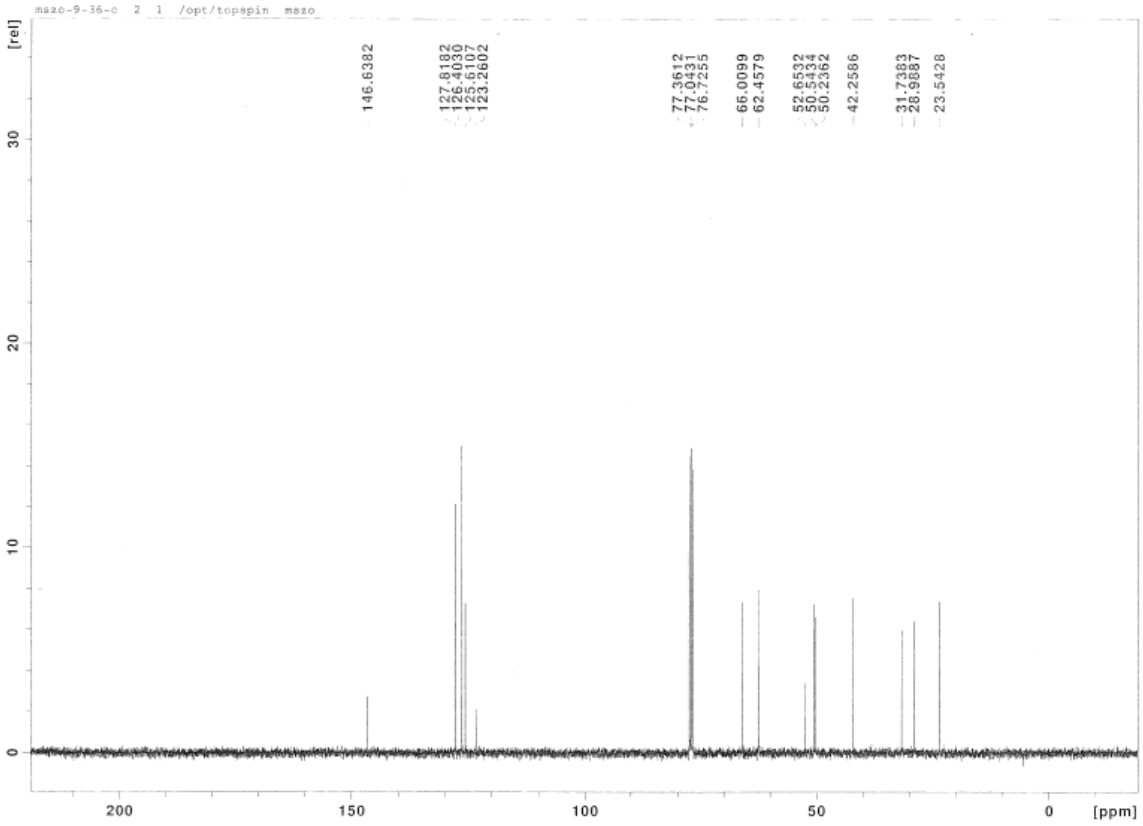

MS-8-235-B 1 1 /opt/siena mszo
[rel]
O
N
O
SPh
2n
0
5
10
15
20
25
15
10
5
0
[ppm]

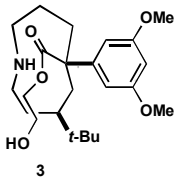

MS-8-235-B 2 1 /opt/siena mszo
[rel]
137.6163
133.1541
128.2621
128.1511
116.0603
77.2753
77.0215
76.7678
65.5094
62.8019
57.5882
50.4451
49.2543
39.5542
38.7345
29.9851
25.8171
23.6936
0
5
10
15
20
200
150
100
50
0
[ppm]


O
N
O
Ph

2o

NAME mazo-9-36-A
EXPNO 2
PROCNO 1
Date_ 20091122
Time 19.48
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

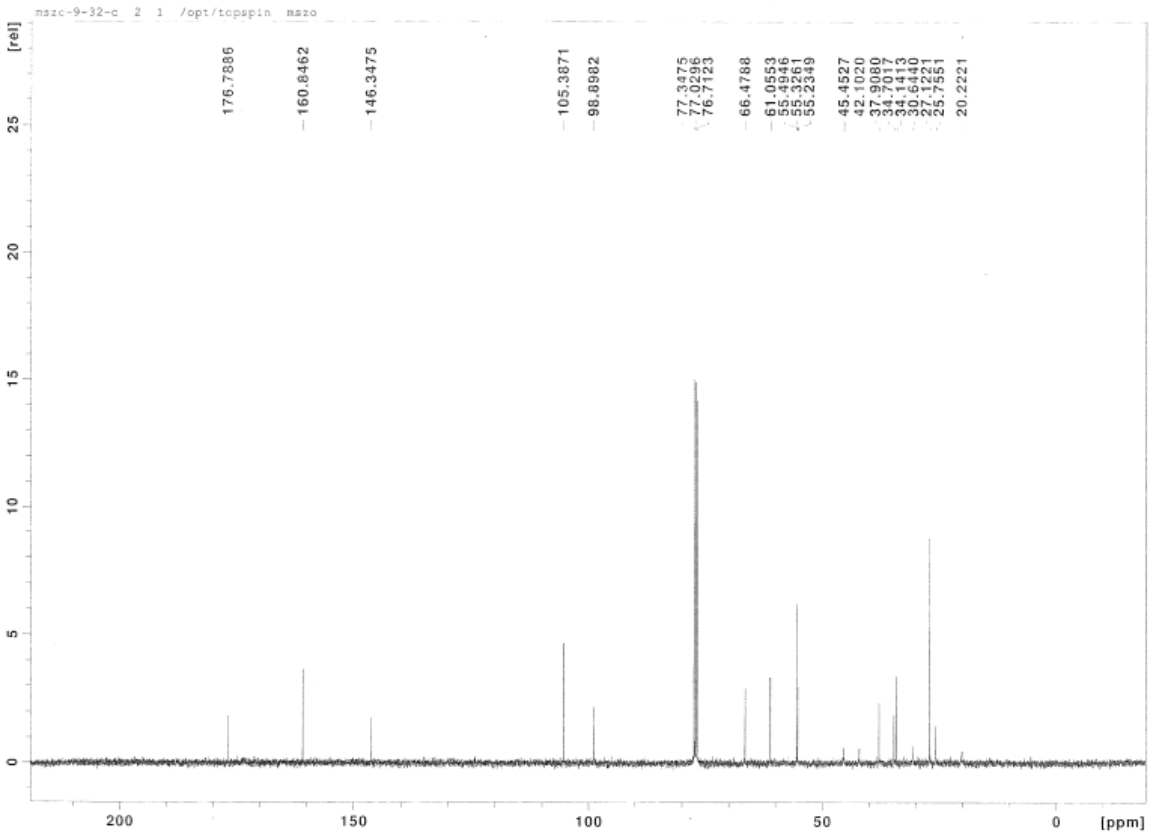

mazo-9-36-c 2 1 /opt/topspin mszo
[rel]
146.6382
127.8182
126.4030
125.1137
123.2602
77.3612
77.0431
76.7255
66.0099
62.4579
52.6532
50.5434
50.2362
42.2586
31.7383
28.9887
23.5428
0 10 20 30
200 150 100 50 0 [ppm]

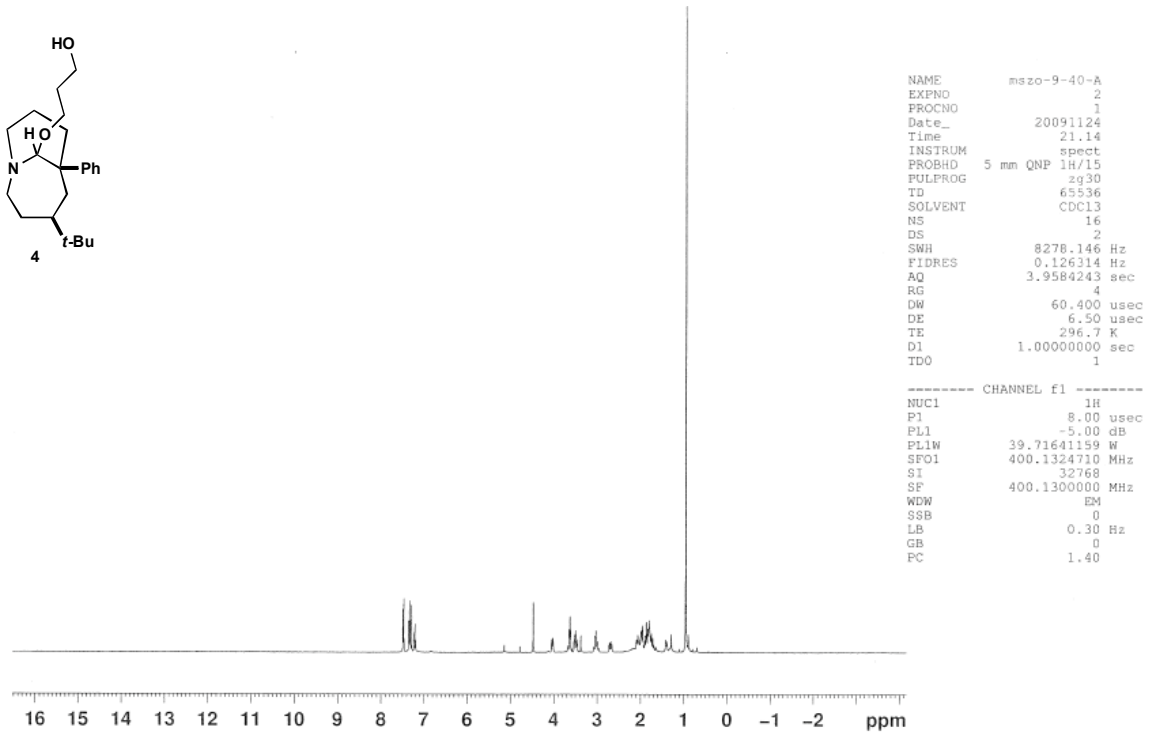


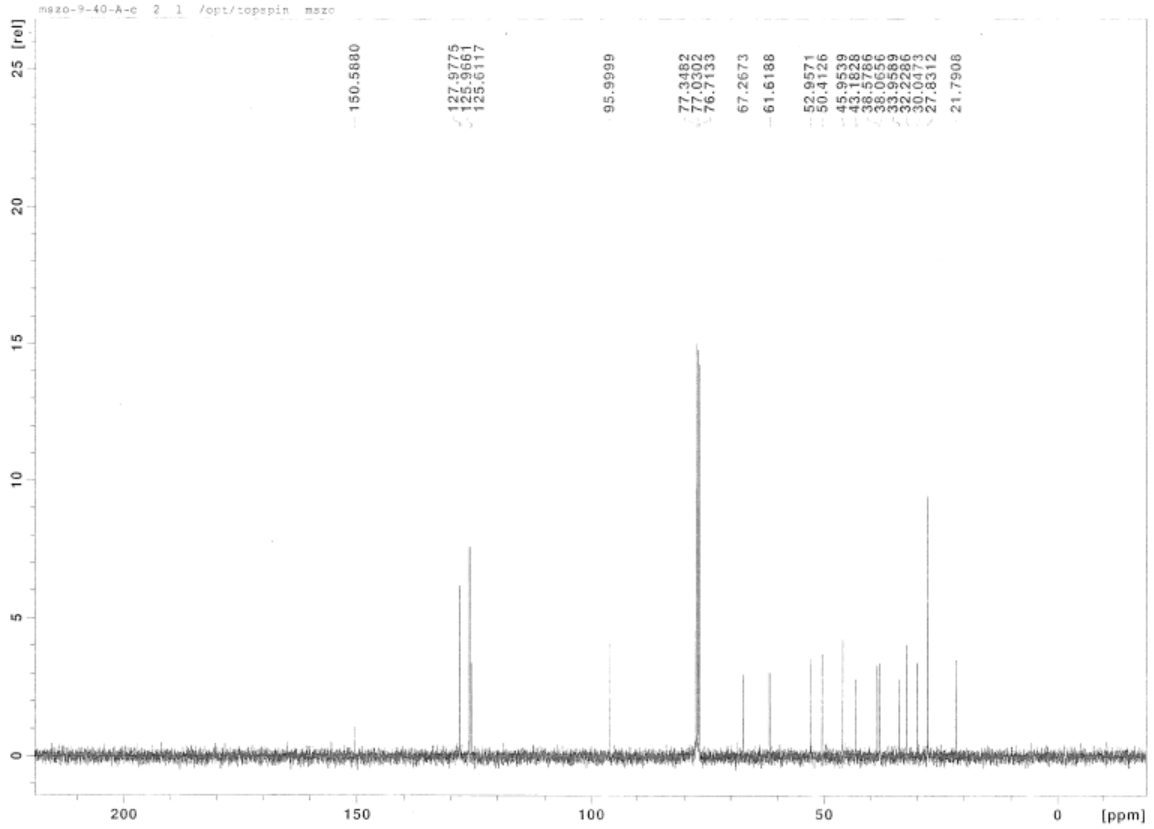
3

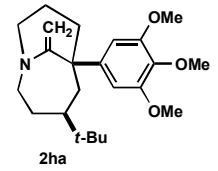

```
NAME                mszo-9-32
EXPNO                       2
PROCNO                      1
Date_                20091122
Time                    12.12
INSTRUM                  spect
PROBHD    5 mm QNP 1H/15
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                  8278.146 Hz
FIDRES               0.126314 Hz
AQ                   3.9584243 sec
RG                          4
DW                      60.400 usec
DE                       6.50 usec
TE                      296.7 K
D1                   1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       8.00 usec
PL1                     -5.00 dB
PL1W             39.71641159 W
SFO1             400.1324710 MHz
SI                      32768
SF               400.1300000 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00
```




HO
H
O
N
Ph
t-Bu
4
NAME mszo-9-40-A
EXPNO 2
PROCNO 1
Date_ 20091124
Time 21.14
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 4
DW 60.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 8.00 usec
PL1 -5.00 dB
PL1W 39.71641159 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm

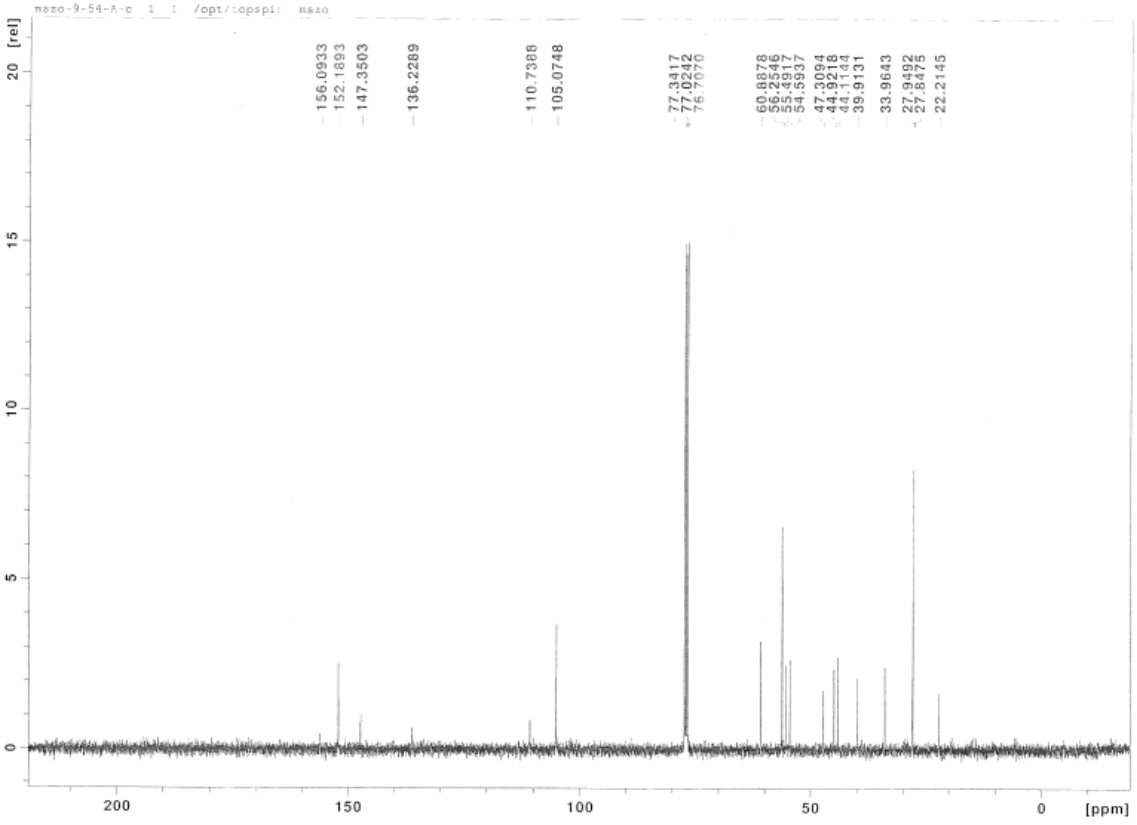

mszo-9-40-A-c 2 1 /opt/topspin mszc
25 [rel]
20
15
10
5
0
150.5880
127.9775
125.9661
125.6117
95.9999
77.3482
77.0302
76.7133
67.2673
61.6188
52.9571
50.4126
45.9539
43.1828
38.5766
38.0656
33.9589
32.2286
30.0473
27.8312
21.7908
200
150
100
50
0
[ppm]

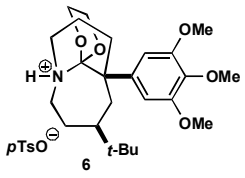


2ha


```
NAME          mszo-9-54-A
EXPNO                   1
PROCNO                  1
Date_            20091128
Time                18.16
INSTRUM             spect
PROBHD   5 mm QNP 1H/15
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                      4
DW                 60.400 usec
DE                  6.50 usec
TE                296.7 K
D1           1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.00 usec
PL1                 -5.00 dB
PL1W         39.71641159 W
SFO1         400.1324710 MHz
SI                  32768
SF           400.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40
```





6


```
NAME                mszo-9-56
EXPNO                       3
PROCNO                      1
Date_                20091129
Time                    21.56
INSTRUM                 spect
PROBHD   5 mm QNP 1H/15
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                         16
DS                          2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                          4
DW                    60.400 usec
DE                     6.50 usec
TE                    297.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      8.00 usec
PL1                    -5.00 dB
PL1W              39.71641159 W
SFO1              400.1324710 MHz
SI                      32768
SF                400.1300000 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.40
```