Complete Facial Selectivity in the Diels-Alder Reaction of a 5-amino-5-carboxycyclopentadiene derivative

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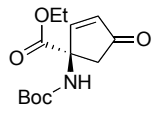
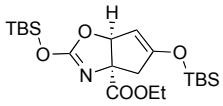
A. Experimental Protocols.

Melting points are uncorrected. Unless otherwise indicated, ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature from $CDCl_3$ solutions. Chemical shifts are reported as ppm on the δ scale and coupling constants, *J*, are in Hz. Multiplicities are described as s (singlet), d / dd / dt (doublet / doublet of doublets / doublet of triplets), t (triplet), q (quartet), m (multiplet). Low- and high resolution mass spectra were obtained in the ESI mode. Infrared (IR) spectra (cm^{-1}) were recorded on a Fourier transform spectrometer from films deposited on NaCl plates or on a Universal Sampling Accessory. Elemental analyses were performed by the UBC Microanalysis laboratory. Chromatographic separations were effected over silica gel 60. Tetrahydrofuran was freshly distilled from Na/benzophenone and $CH_2C;_2$ freshly distilled from CaH_2. All other commercial reagents and solvents were used without purification. All reactions were performed under argon in flasks equipped with stirring bars and fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.

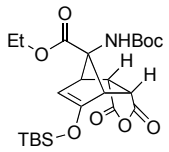


Ethyl 1-(*tert*-butoxycarbonylamino)-4-oxocyclopent-2-enecarboxylate, 15. A solution of the known (Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815) epoxide **13** (141 mg, 518 mmol) in THF (2.5 mL) was added dropwise to a cold (0°C), stirred solution of LDA (3 equiv), prepared just before use by addition of BuLi (1.6 M in hexanes, 1.0 mL, 1.6 mmol) to a solution of diisopropylamine (230 μL, 1.7 mmol) in THF (2.5 mL). The reaction mixture was stirred at 0°C for 40 min, and then it was poured into sat. aq. NH_4Cl (12 mL). The solution was extracted with EtOAc (3x15mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. To the orange oily residue was dissolved in CH_2Cl_2 (4.5 mL) and treated with Dess-Martin reagent (404 mg, 953 μmol). The mixture was stirred at RT for 3 hr, then it was washed with an aqueous solution composed of a 1:1 mixture of sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaS_2O_3 (15 mL). The aqueous phase was back-extracted with CH_2Cl_2 (2 x 20mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo,* and the residue was flash chromatographed (1:4 EtOAc:hex) to furnish **15** (96 mg, 69%) as an off-white solid, m.p. 84-86 °C. **^{1}H**: 7.44 (d, 1H, *J* = 5.1), 6.34 (d, 1H, *J* = 5.6), 5.68 (s, 1H), 4.21 (q, 2H, *J* = 7.1), 3.09 - 2.50 (AB, 2H), 1.41 (s, 9H), 1.24 (t, 3H, *J* = 7.1). **^{13}C**: 205.3, 170.8, 159.7, 154.4, 135.8, 80.8, 65.1, 62.9, 46.0, 28.3, 14.0. **IR**: 3346, 2980, 1727, 1506, 1368, 1288, 1255, 1166, 1044, 817, 788. **MS**: 292.4 $[M+Na]^+$. **HRMS**: calcd for $C_{13}H_{19}NO_5Na$ $[M+Na]^+$ 292.1161; found: 292.1166.

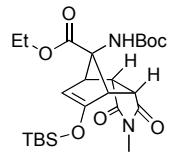


Ethyl 2,5-bis(*tert*-butyldimethylsilyloxy)-4,6a-dihydro-3a*H*-cyclopenta [d]oxazole-3a-carboxylate, 17. Neat TBSOTf (90 μL, 400 μmol) was added

dropwise to a cold (–78 °C), well stirred solution of **15** (54 mg, 200 μmol) and Hunig's base (100 μL, 570 μmol), in CH_2Cl_2 (1 mL), and then the solution was allowed to warm to RT. After stirring for 4 hr of, the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 6mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was flash chromatographed (1:19 to 1:5, EtOAc:hexanes) on neutral alumina (Bockman grade I) to furnish **17** (29 mg, 33%) as a pale yellow oil. **^{1}H**: 5.31 (t, 1H, *J* = 1.8), 4.82 (q, 1H, *J* = 1.8), 4.29 (q, 2H, *J* = 7.1), 3.36 (dd, 1H, *J* = 16.85, 1.8), 2.57 (dt, 1H, *J* = 16.9, 1.8), 1.00 (s, 9H), 0.95 (s, 9), 0.40 (s, 3H), 0.22 - 0.29 (overlapping s, 6H), 0.13 (s, 3H). **^{13}C**: 173.1, 161.7, 159.7, 100.9, 88.0, 70.5, 63.3, 45.7, 28.0, 26.0, 19.6, 18.8, 14.5, -4.2, -4.4, -4.5, -4.7. **IR**: 2932, 2859, 1749, 1646, 1338, 1354, 1201, 1056, 1022, 953, 839, 785. **MS**: 464.4 $[M+Na]^+$. **HRMS**: calcd for $C_{21}H_{40}NO_5SiNa$ $[M+Na]^+$: 464.2445; found: 464.2304.

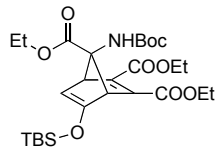


Diels-Alder adduct 19. Neat TBS-OTf (100 μL, 440 μmol) was added dropwise to a cold (–78 °C), well stirred solution of **15** (55 mg, 204 μmol) and Et_3N (100 μL, 780 μmol), in CH_2Cl_2 (1 mL). The solution was then warmed to rt, and after 15 min it was adsorbed directly unto neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) to afford 70 mg of a 1:1 mixture (^{1}H NMR) of **16** (32 mg, 42%, NMR) and **17** (38 mg, 42%, NMR) as a clear oil. A solution of this mixture and maleic anhydride (25 mg, 180 μmol) in CH_2Cl_2 (1 mL) was stirred at RT for 1.5 hr, and then the solvent was removed *in vacuo*. The oily residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) to provide **19** (25 mg, 62% from **16**, 26% over two steps) as a white solid, m.p. 159-162°C. **^{1}H (acetone-*d*$_6$):** 6.86 (br s, 1H), 4.87 (d, 1H, *J* = 2.0), 4.12 (q, 2H, *J* = 7.1), 4.02 (dd, 1H, *J* = 7.8, 4.6), 3.86 (dd, 1H, *J* = 7.7, 4.7), 3.70 (br s, 1H), 3.59 (br s, 1H), 1.40 (s, 9H), 1.22 (t, 3H, 7.1), 0.92 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H). **^{13}C (acetone-*d*$_6$):** 171.7, 170.8, 169.1, 158.8, 154.1, 97.6, 79.3, 78.8, 60.6, 54.0, 48.8, 48.4, 44.7, 27.4, 24.7, 17.5, 13.5, -6.0, -6.2. **IR:** 1781, 1735. **MS (negative ion mode):** 480.2 [M-1]. **HRMS (negative ion mode):** calcd for $C_{23}H_{34}NO_8Si$ [M-1]: 480.2054; found: 480.2050.

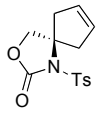


Diels-Alder adduct 20. Neat TBSOTf (85 μL, 370 μmol) was added dropwise to a cold (–78 °C), well-stirred solution of **15** (50 mg, 186 μmol) and Et_3N (85 μL, 650 μmol) in CH_2Cl_2 (1 mL), and the mixture was then warmed to rt. After 15 min at rt the mixture was adsorbed directly unto neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) to afford 62 mg of a 1.2:1 mixture (^{1}H NMR) of **16** (32 mg, 44%, NMR) and **17** (30 mg, 37%) as a clear oil. A solution of this material and N-methylmaleimide (17 mg, 176 μmol) in CH_2Cl_2 (1 mL) was stirred at rt for 2 hr, then the solvent was removed *in vacuo*. The oily residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) yielding **30** (38 mg, 92% from **16**, 41% over two steps) as a white solid, m.p. 161-

165°C. **^{1}H (benzene-d_6):** 4.44 (dd, 1H, J = 3.5, 1.4), 3.84 - 4.01 (m, 2H), 3.79 (br s, 1H), 3.39 (br s, 1H), 2.98 - 2.91 (m, 1H), 2.88, (br s, 1H), 2.71 (s, 3H), 1.37 (s, 9H), 0.96 (t, 3H, J = 7.1), 0.06 (s, 3H), -0.01 (s, 3H). **^{13}C (benzene-d_6):** 176.5, 175.4, 170.2, 158.7, 154.4, 97.52, 78.76, 61.1, 53.9, 48.6, 47.1, 43.5,30.2, 28.3, 25.5, 24.5, 18.1, 14.2, -5.1 (2 overlapping peaks). **IR:** 3337, 1705, 1618. **MS:** 517.3 $[M+Na]^+$. **HRMS:** calcd for $C_{24}H_{38}N_2O_7SiNa$ $[M+Na]^+$ 517.2346; found 517.2344. **EA:** calcd for $C_{24}H_{38}N_2O_7Si$ N 5.66%, C 58.27%, H 7.74%, found: N 5.51%, C 58.57%, H 7.80%.

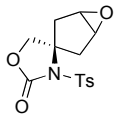


Diels-Alder adduct 21. Neat TBS-OTf (70 μL, 300 μmol) was added dropwise to a cold (–78 °C), well stirred solution of **15** (42 mg, 156 μmol) and Et_3N (70 μL, 500 μmol) in CH_2Cl_2 (750 μL). The mixture was then warmed to rt, and after 15 min at rt it was applied directly to a column of neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) to give 58 mg of a 1:1 mixture (^{1}H NMR) of **16** (27 mg, 45%, NMR) and **17** (31 mg, 45%, NMR) as a clear oil. A solution of this material and diethyl but-2-ynedioate (40 μL, 200 μmol) in CH_2Cl_2 (1mL) was stirred at RT for 15 hr, then the solvent was removed *in vacuo*. The residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) to afford 33 mg of **21** (86% from **16**, 39% over two steps) as a pale yellow oil. **^{1}H (benzene-d_6):** 5.33 (s, 1H), 5.13 (dd, 1H, J = 3.7, 1.4), 4.50 (br s, 1H), 4.33 (br s, 1H), 4.23 - 3.70 (m, 6H), 1.34 (s, 9H), 0.94 - 1.05 (m, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). **^{13}C (benzene-d_6):** 169.9, 169.8, 164.8, 164.3, 154.4, 151.2, 146.6, 103.9, 91.7, 79.9, 62.3, 61.0 (3 overlapping peaks), 56.9, 30.2, 28.2, 25.7, 18.3, 14.1(2 overlapping peaks), -4.8 (2 overlapping peaks). **IR:** 3350, 1716, 1618. **MS:** 576.5 $[M+Na]^+$. **HRMS:** calcd for $C_{27}H_{43}NO_9SiNa$ 576.2608 $[M+Na]^+$; found: 576.2605. **EA:** calcd for $C_{27}H_{43}NO_9Si$ C 58.86%, H 7.91%, N 2.67%; found: C 58.57%, H 7.83%, N 2.53%.

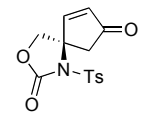


3'-tosyl-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazolidin]-2'-one, 25. Commercial $LiBH_4$ in THF (2M, 16.1 mL, 32.2 mmol) was added to a cold (0 °C), stirred solution of the known [(a) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J., *Tetrahedron* **1999,** *55*, 10815. (b) Varie, D. L.; Beck, C.; Borders, S. K.; Brady, M. D.; Cronin, J. S.; Ditsworth, T. K.; Hay, D. A.; Hoard, D. W.; Hoying, R. C.; Linder, R. J.; Miller, R. D.; Moher, E. D.; Remacle, J. R.; Rieck, J. A.; Anderson, D. D.; Dodson, P. N.; Forst, M. B.; Pierson, D. A.; Turpin, J. A., *Org. Proc. Res. Dev.* **2007,** *11*, 546) cyclopentene **12** (5.2 g, 20.3 mmol) in THF (200 mL). After 15 min at 0°C, the mixture was warmed to rt and stirred for an additional 24 hr, then it was cooled back to 0°C and carefully quenched with sat. aq. NH_4Cl (100 mL; **CAUTION**: evolution of flammable H_2 gas) followed by deionized water (100 mL). The mixture was then extracted with CH_2Cl_2 (1 x 200 mL, 2 x 150 mL) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (100 mL), cooled to 0°C and carefully treated with NaH (60% oil dispersion, 2.5 g, 63 mmol; **CAUTION**:

evolution of flammable H_2 gas), added portionwise with good stirring. The mixture was warmed to rt and stirred for 19 hr, then it was again cooled to 0 °C and solid TsCl (9.0 g, 46 mmol) was added as a single portion. The mixture was warmed to rt and stirred for 15 hr, then it was cooled back to 0°C and carefully poured into sat. aq. NH_4Cl (100 mL; **CAUTION**: vigorous reaction, evolution of flammable H_2 gas). The aqueous mixture was extracted with EtOAc (3x100 mL) and the combined extracts were evaporated *in vacuo* to yield a brown residue, which was flash chromatographed (2:8 to 1:1, EtOAc:hex) to fusnish the title compound (2.8 g, 47%) as a white solid, m.p. 131-134 °C. **^{1}H**: 7.96 (d, 2H, *J* = 8.4), 7.34 (d, 2H, *J* = 8.5), 5.73 (s, 2H), 4.19 (s, 2 H), 3.49 (d, 2H, *J* = 15.3), 2.52 (d, 2H, *J* = 15.0), 2.44 (s, 3H). **^{13}C**: 152.8, 145.6, 135.8, 129.7, 128.9, 128.3, 79.1, 70.7, 43.9, 21.8. **IR**: 1785, 1596, 1363, 1285. **MS**: 294.3 $[M+H]^+$. **HRMS**: calcd for $C_{14}H_{16}NO_4S$ $[M+H]^+$: 294.0800; found: 294.0793 $[M+H]^+$.

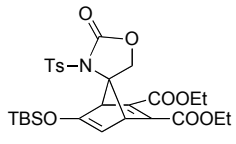


3'-Tosyl-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazolidin]-2'-one, 26. A solution of **25** (770 mg, 2.6 mmol) and *m*CPBA (70%, 830 mg, 3.1 mmol) in CH_2Cl_2 (12 mL) containing suspended $NaHCO_3$ (534 mg, 6.4 mmol) was stirred at RT for 24 hr, then it was diluted with CH_2Cl_2 (18 mL) and washed with sat. aq. $NaHSO_3$ (100 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with H_2O (2x30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield epoxide **26** (784 mg, 97%) as a white solid. **^{1}H**: 7.90 (d, 2H, *J* = 8.3), 7.33 (d, 2H, *J* = 8.1), 4.03 (s, 2 H), 3.61 (s, 2 H), 3.03 (d, 2H, *J* = 14.1), 2.43 (s, 3H), 2.25 (d, 2H, *J* = 14.1). **^{13}C**: 152.2, 145.7, 129.7, 128.8, 79.5, 66.8, 54.6, 38.7, 21.8. **IR**: 1758, 1364. **MS**: 332.3 $[M+Na]^+$. **HRMS**: calcd for $C_{14}H_{15}NO_5SNa$ $[M+Na]^+$ 332.0569; found 332.0577 $[M+Na]^+$.

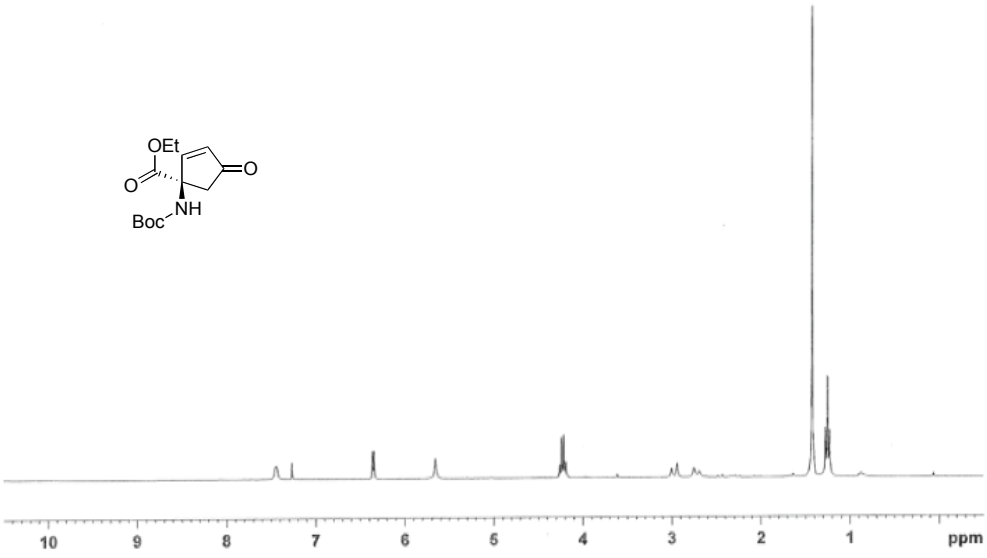


1-Tosyl-3-oxa-1-azaspiro[4.4]non-8-ene-2,7-dione, 28. Neat TMS-OTf (1.1 mL, 6.0 mmol) was added dropwise at rt to a stirred solution of **26** (1.2 g, 4.0 mmol) and TEA (2.2 mL,1.6 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred at RT for 1.5 hr, and then DBU (3 mL, 20 mmol) was added dropwise. The mixture was stirred for an additional 6 hr, then it was diluted with CH_2Cl_2 (30 mL) and poured into sat. aq. NH_4Cl (30mL). The organic phase was separated and the aqueous phase was extracted with more CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with H_2O (3 x 50mL), dried ($MgSO_4$) and concentrated *in vacuo* to furnish a dark oily residue. A solution of this material in a CH_2Cl_2 (12 mL) containing PCC (2.5 g, 11.6 mmol) was stirred at rt for 4 hr, then it was filtered over florisil and concentrated *in vacuo.* The residue was flash chromatographed (1:9 to 1:2 to 1:0 EtOAc:hex) to yielding **28** (838 mg, 68%) as a white solid, m.p. 203-205°C. **^{1}H (dichloromethane-d_2)**: 7.91 (d, 2H, *J* = 8.4), 7.47 (d, 1H, *J* = 5.6), 7.42 (d, 2H, *J* = 8.2), 6.45 (d, 1H, *J* = 5.6), 4.33 (d, 2H, *J* = 8.5), 3.30 (d, 1H, *J* = 18.4), 2.64 (d, 1H, *J* = 18.4), 2.49 (s, 3 H). **^{13}C (dichloromethane-d_2)**: 202.4, 157.6, 151.6, 146.5, 136.8, 134.8, 129.9, 128.9, 72.3, 69.3,

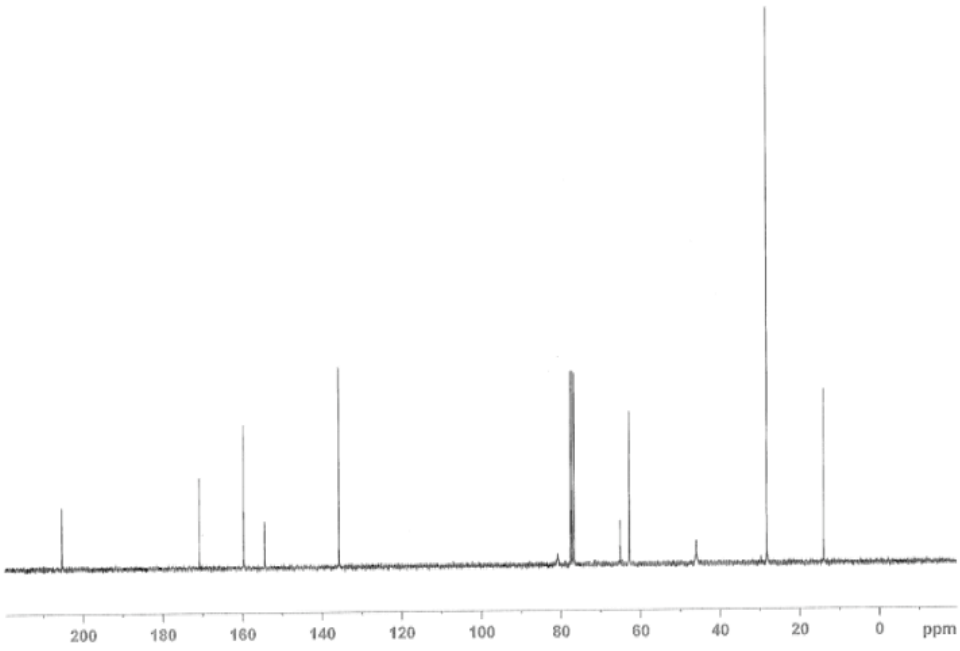
53.52 (CD_2Cl_2), 45.9, 21.6. **IR**: 1770, 1716, 1364. **MS**: 330.3 $[M+Na]^+$. **HRMS**: calcd for $C_{14}H_{13}NO_5Na$ $[M+Na]^+$ 330.0412; found 330.0418 $[M+Na]^+$.



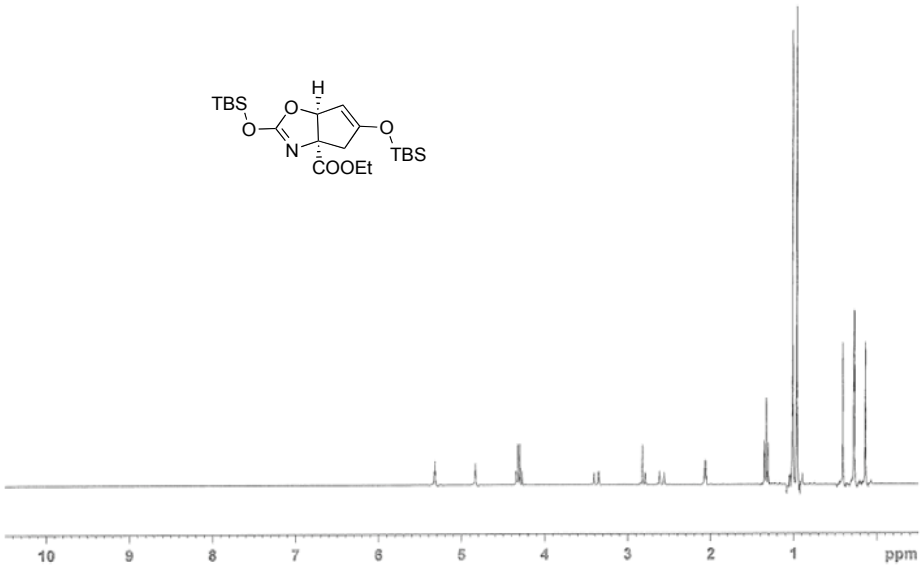
Diels-Alder adduct 29. Neat TBS-OTf (110 μL, 480 μmol) was added dropwise to a cold (–78 °C), well-stirred solution of **28** (80 mg, 261 μmol) and Et_3N (110 μL, 790 μmol) in CH_2Cl_2 (7 mL), then the mixture was warmed to rt. After stirring at rt for 1.5 hr, MeOH (0.5 mL) was added, and then the mixture was concentrated *in vacuo*. The residue was dissolved in diethyl acetylene dicarboxylate (1.5 mL, 12 mmol) and the solution was stirred at 60 °C (bath temperature) for 6 hr. The resulting orange oil was flash chromatographed (1:9 to 2:8, EtOAc:hex) to give **29** (71 mg, 46%) as a yellow oil. **^{1}H (acetone-d_6)**: 7.97 (d, 2H, *J* =8.4), 7.44 (d, 2H, *J* = 8.1), 4.90 (dd, 1H, *J* = 3.5, 1.0), 4.40 (d, 2H, *J* = 4.6), 4.18 - 4.27 (m, 4 H), 3.96 (t, 1H, *J* = 3.4), 3.85 (dd, 1H, *J* = 3.2, 1.1), 2.45 (s, 3 H), 1.27 (td, 6H, *J* = 7.1, 2.9), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.09 (s, 3 H). **^{13}C-APT (benzene-d_6)**: 169.0, 164.3, 163.2, 154.5, 152.9, 144.5, 144.2, 138.2, 129.3, 128.4, 104.7, 97.8, 70.5, 61.4, 61.3, 59.6, 57.8, 25.7, 21.3, 18.3, 14.1, 14.0, -3.91, -4.88**.** **IR**: 1798, 1714, 1621. **MS**: 614.4 $[M+Na]^+$. **HRMS**: calcd for $C_{28}H_{37}NO_9SSiNa$ $[M+Na]^+$ 614.1856; found 614.1851.



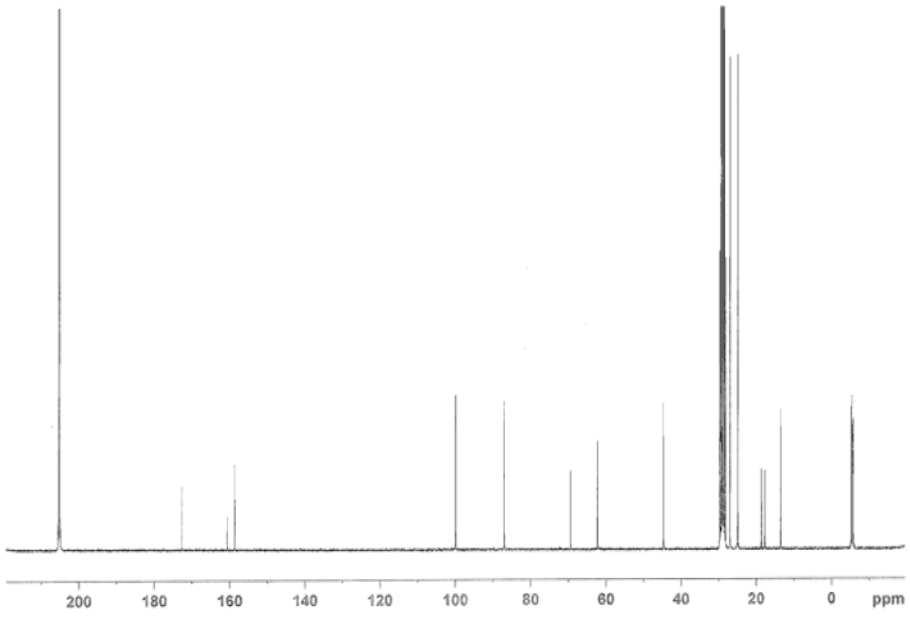
^{1}H NMR Spectrum of Compound **15**



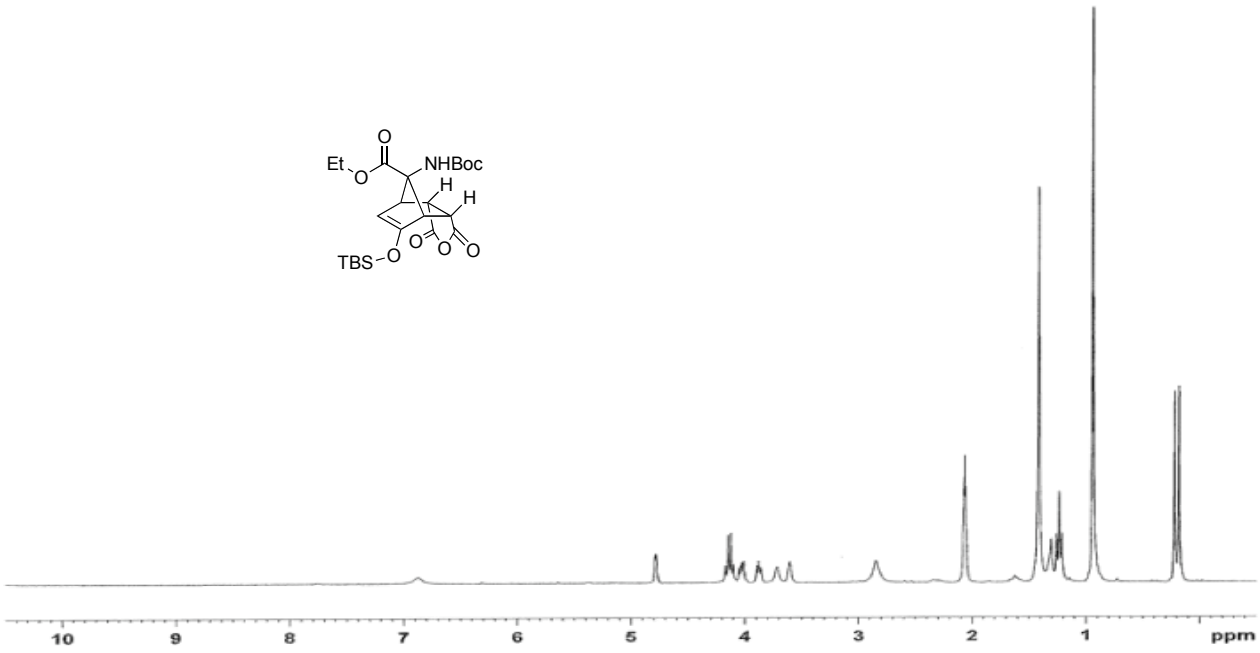
^{13}C NMR Spectrum of Compound **15**



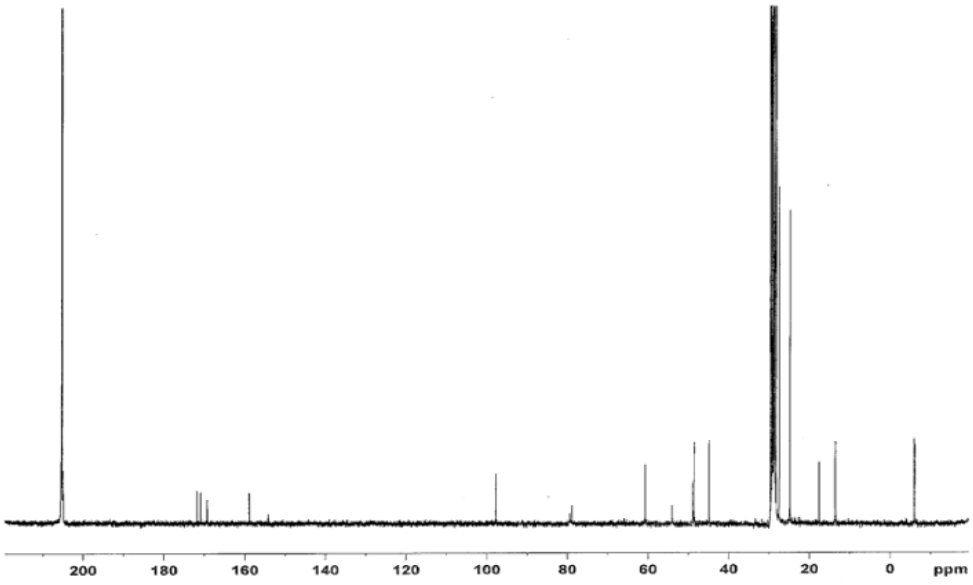
^{1}H NMR Spectrum of Compound **17**



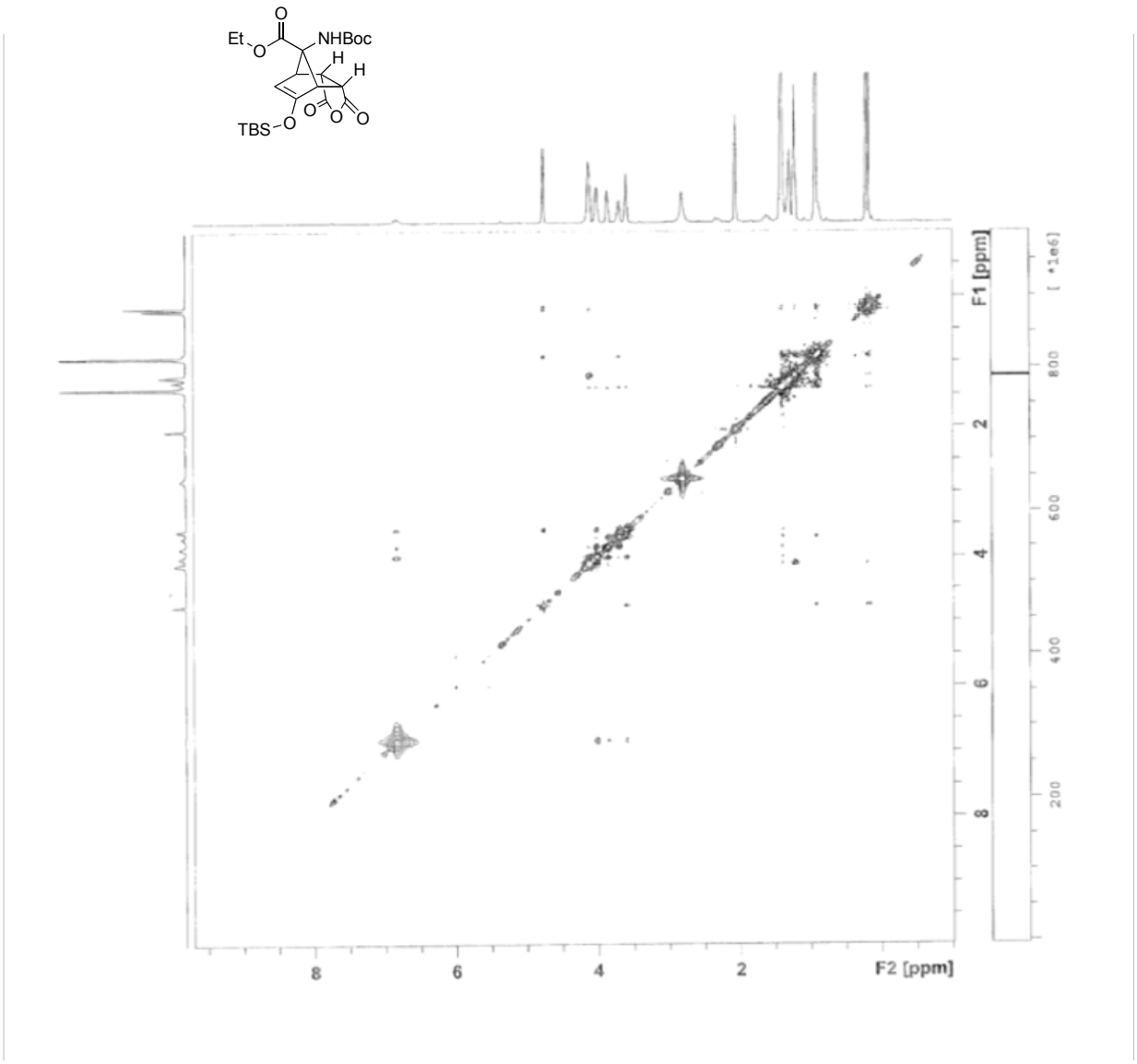
^{13}C NMR Spectrum of Compound **17**



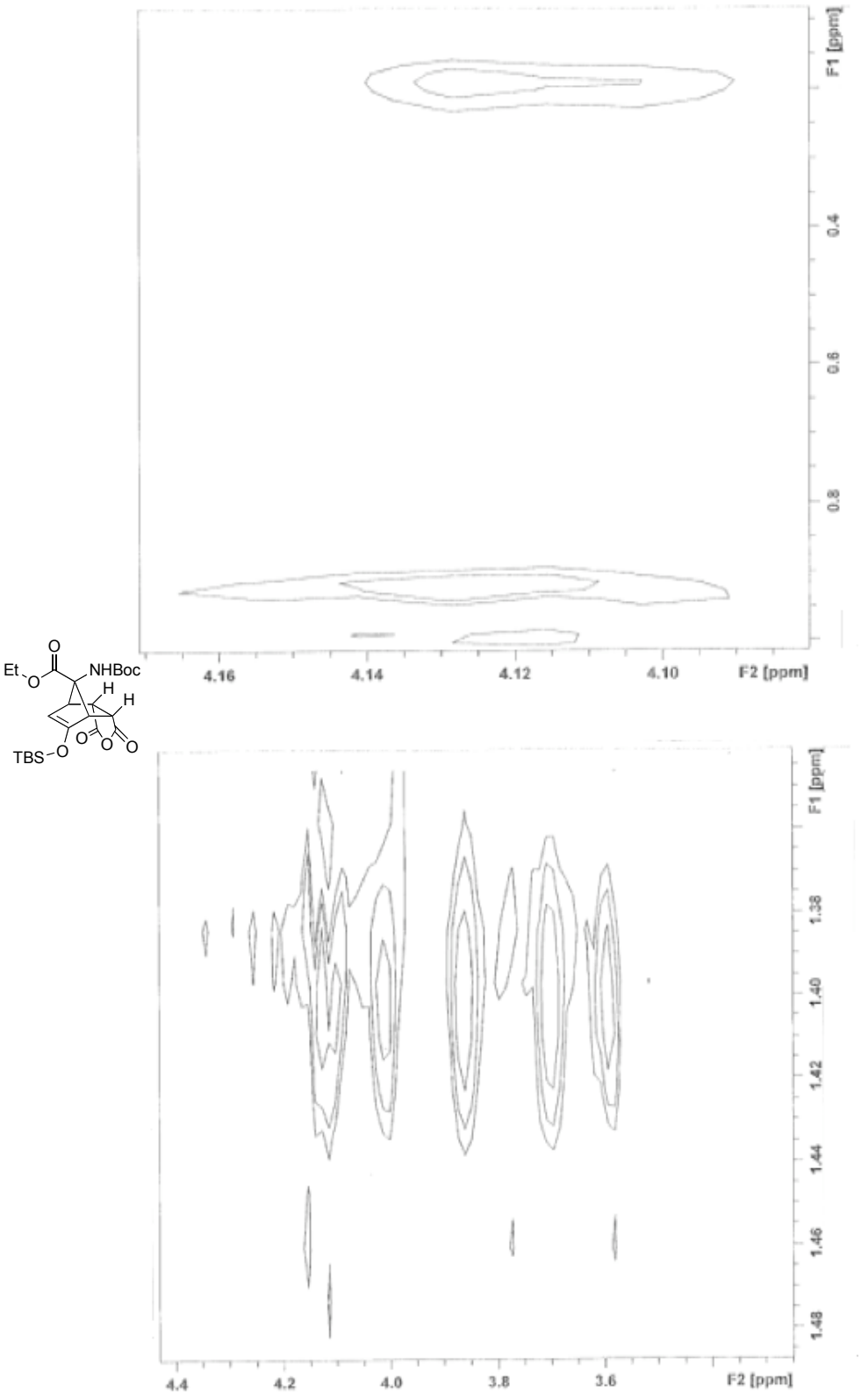
^{1}H NMR Spectrum of Compound **19**



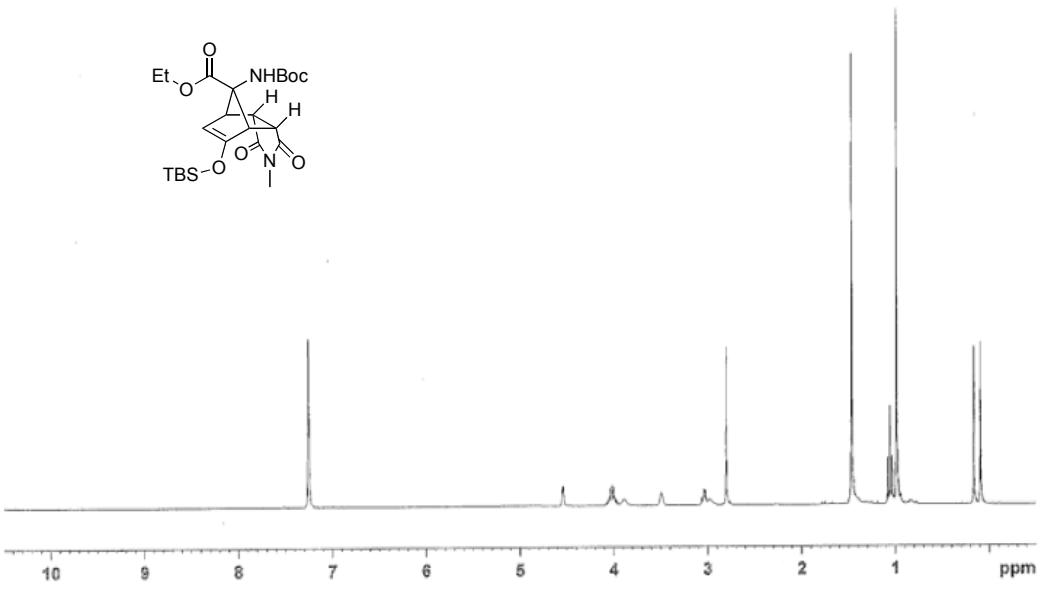
^{13}C NMR Spectrum of Compound **19**



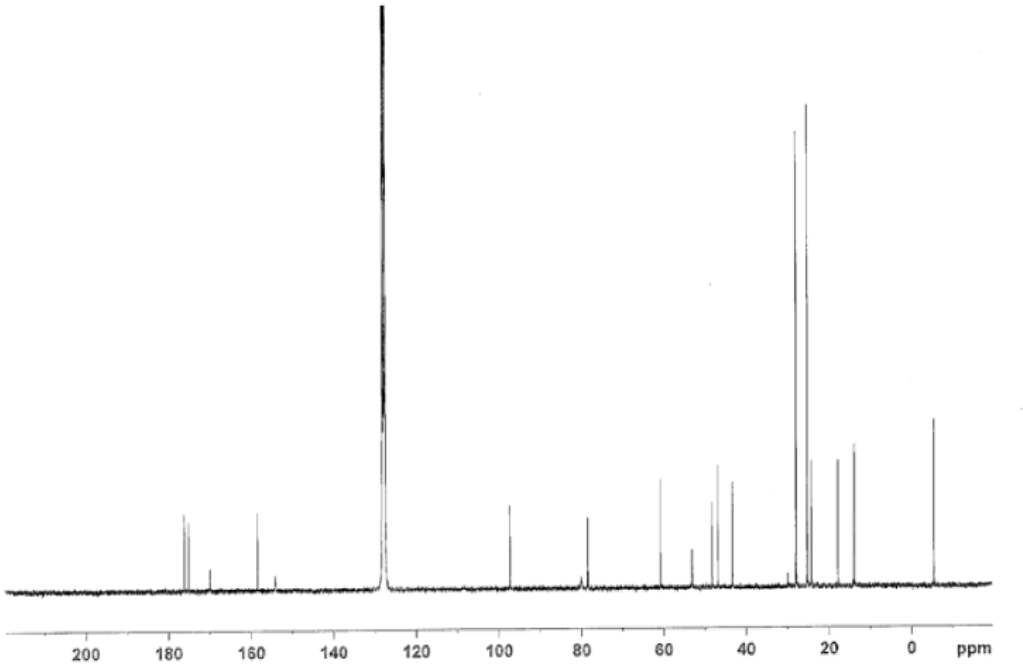
Full 2D-NOESY NMR Spectrum of Compound **19**



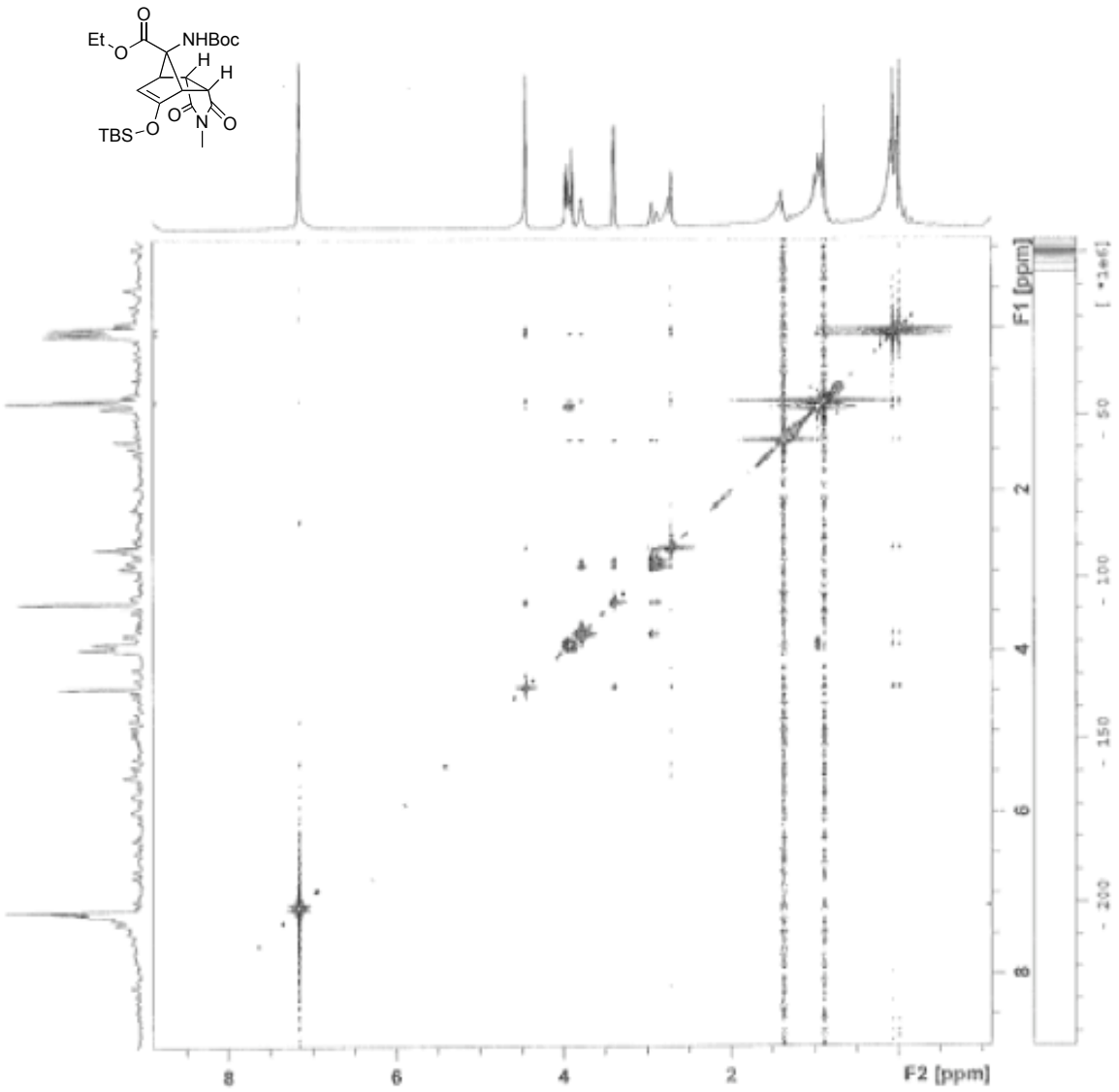
Expansions of the 2D-NOESY NMR Spectrum of Compound **19**



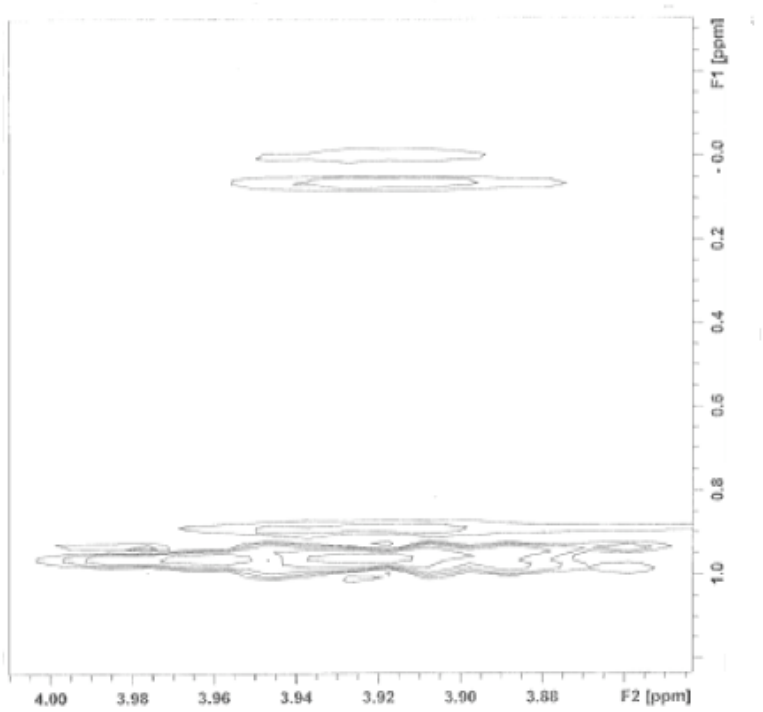
^{1}H NMR Spectrum of Compound **20**

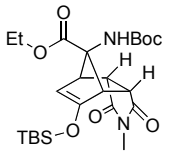


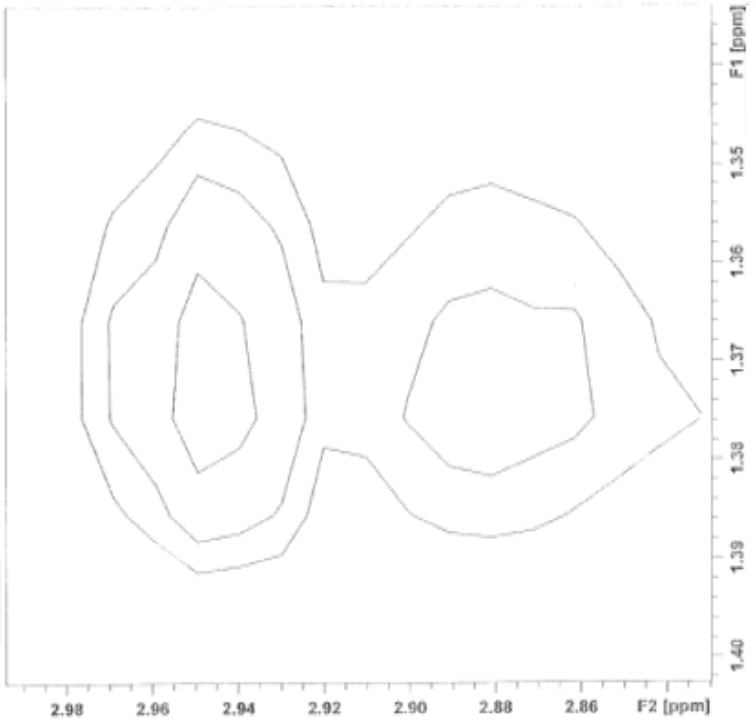
^{13}C NMR Spectrum of Compound **20**



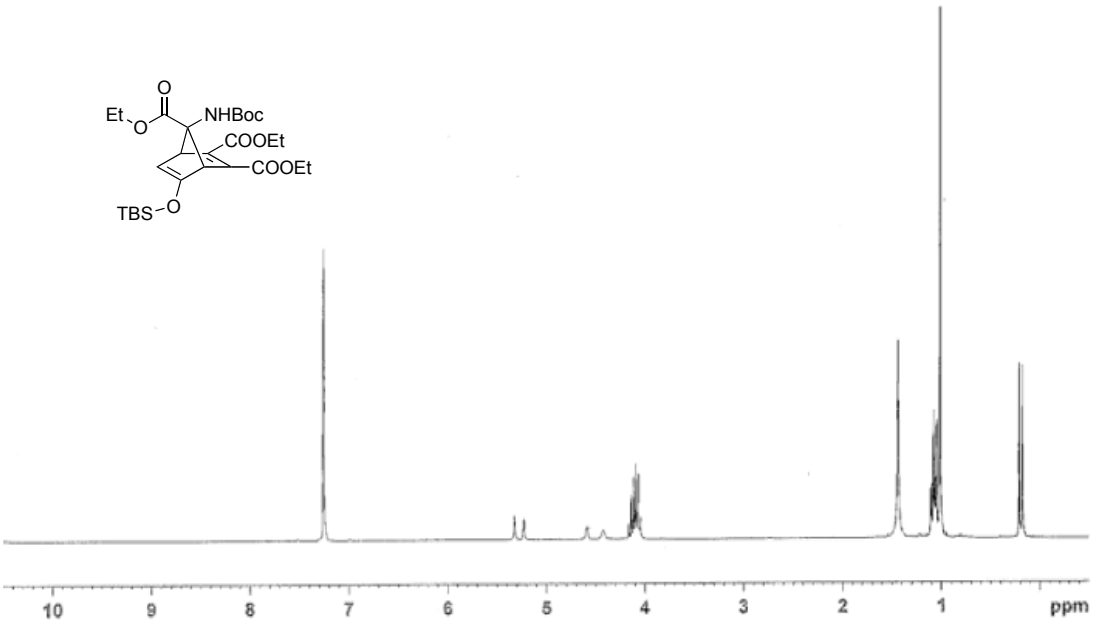
Full 2D-NOESY NMR Spectrum of Compound **20**



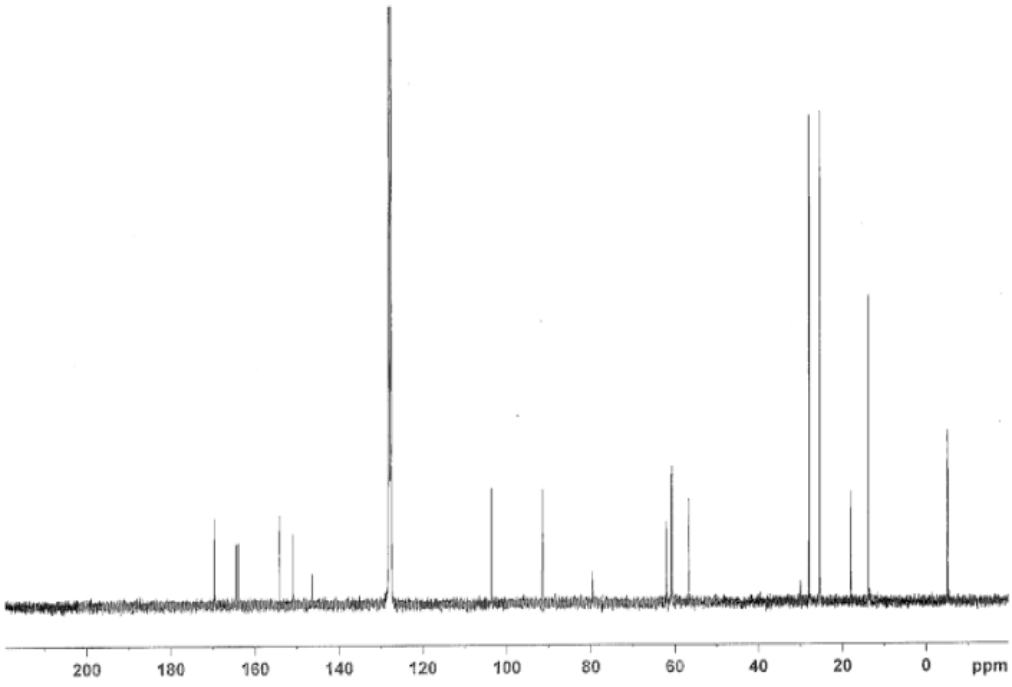




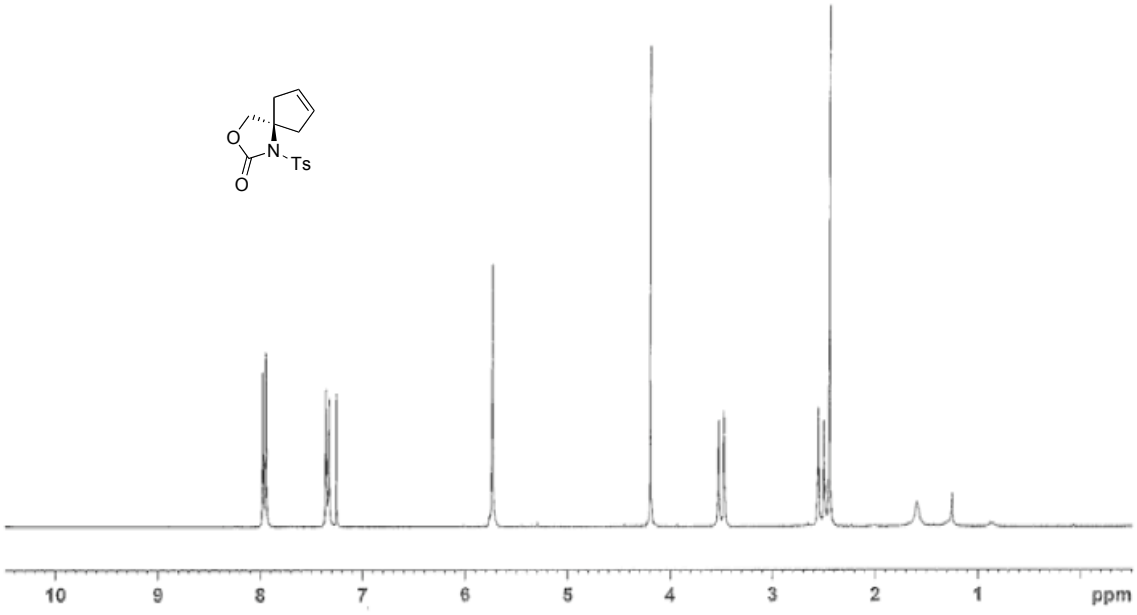
Expansions of the 2D-NOESY NMR Spectrum of Compound **20**



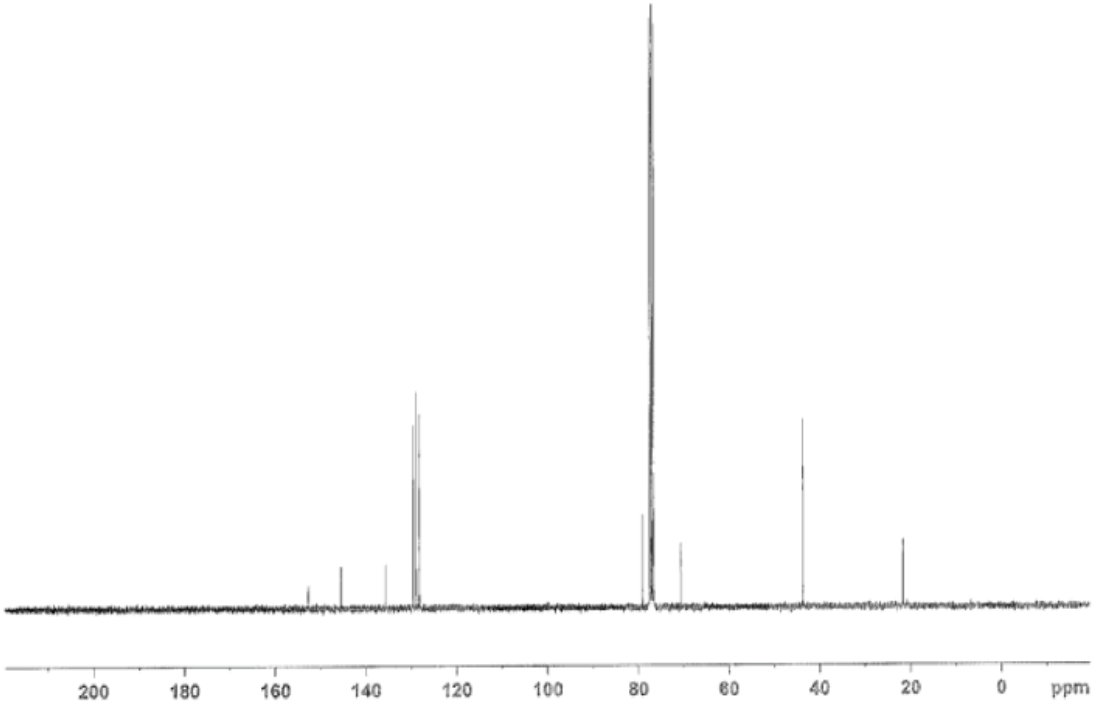
^{1}H NMR Spectrum of Compound **21**



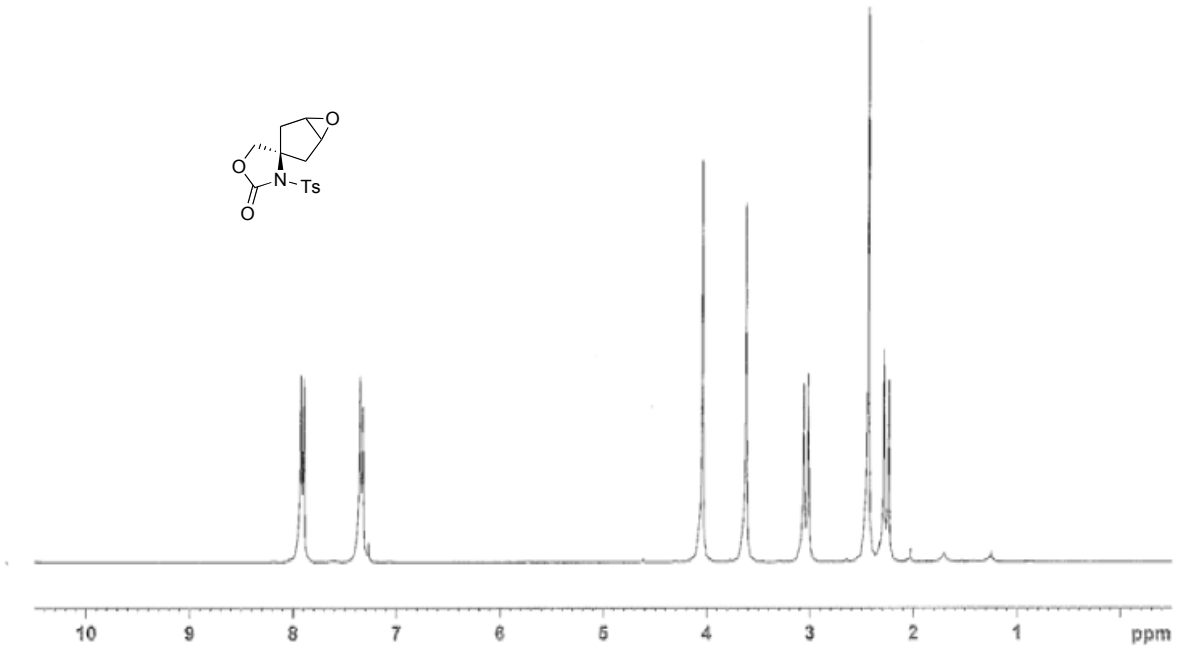
^{13}C NMR Spectrum of Compound **21**



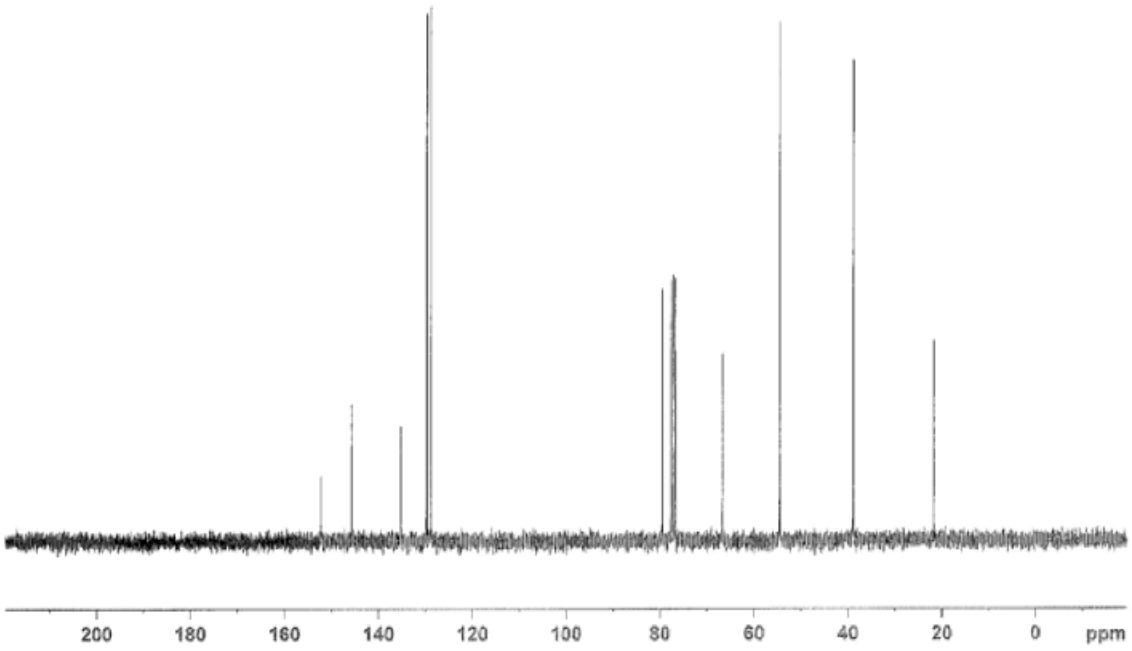
^{1}H NMR Spectrum of Compound **25**



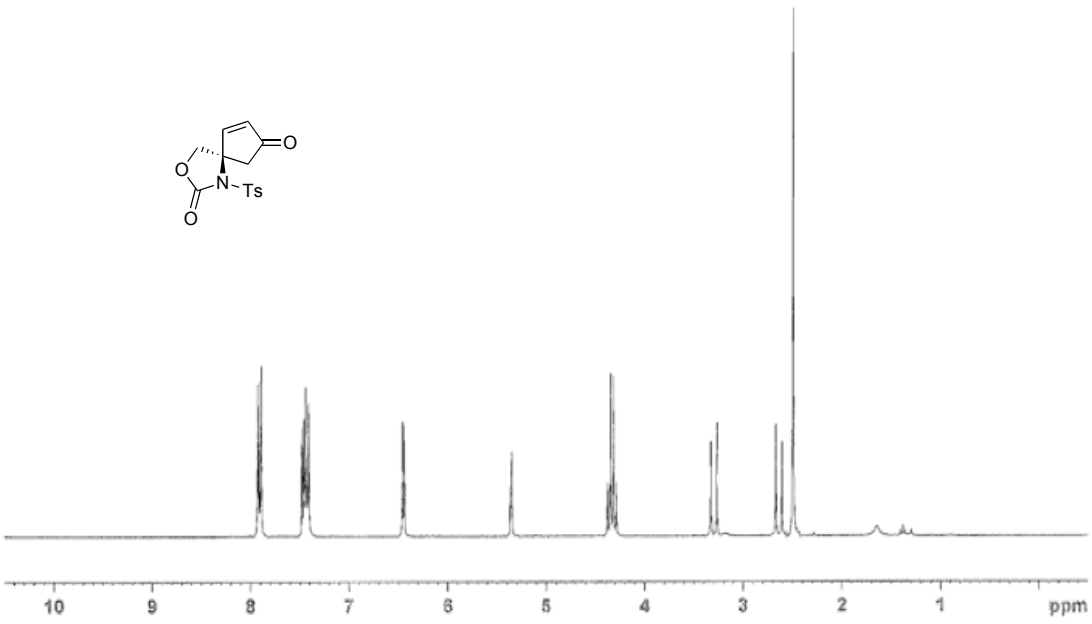
^{13}C NMR Spectrum of Compound **25**



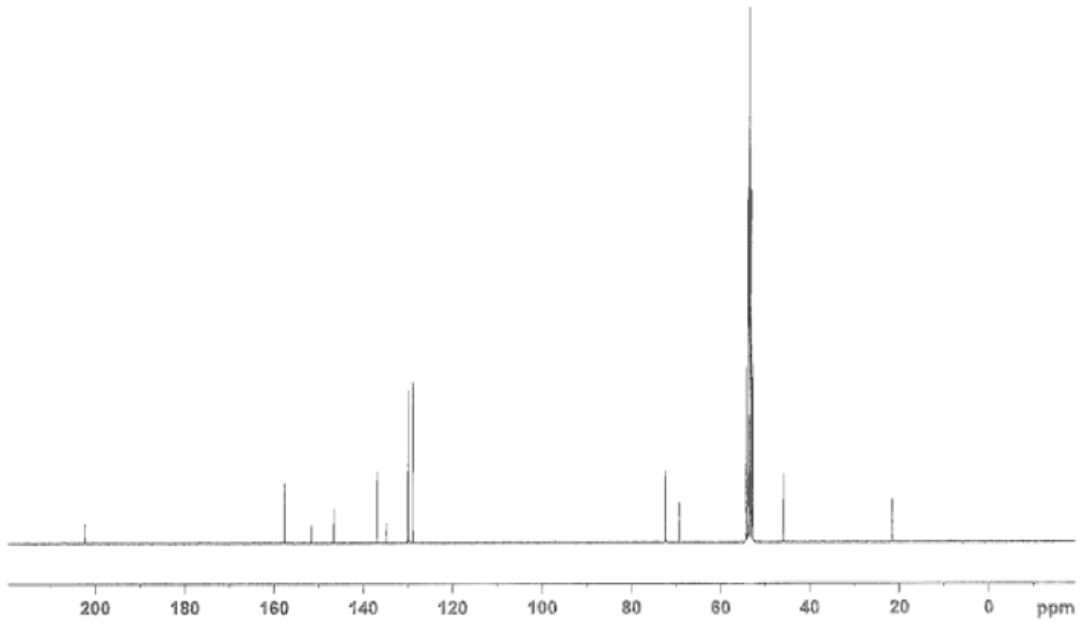
^{1}H NMR Spectrum of Compound **26**



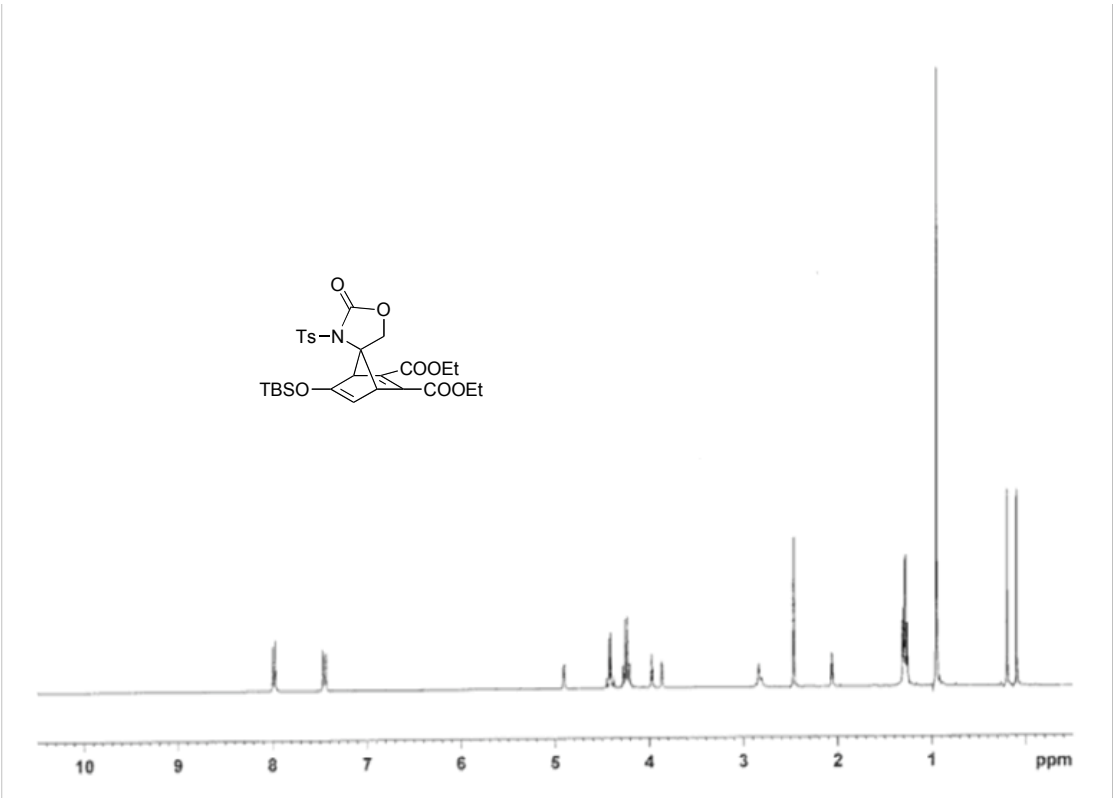
^{13}C NMR Spectrum of Compound **26**



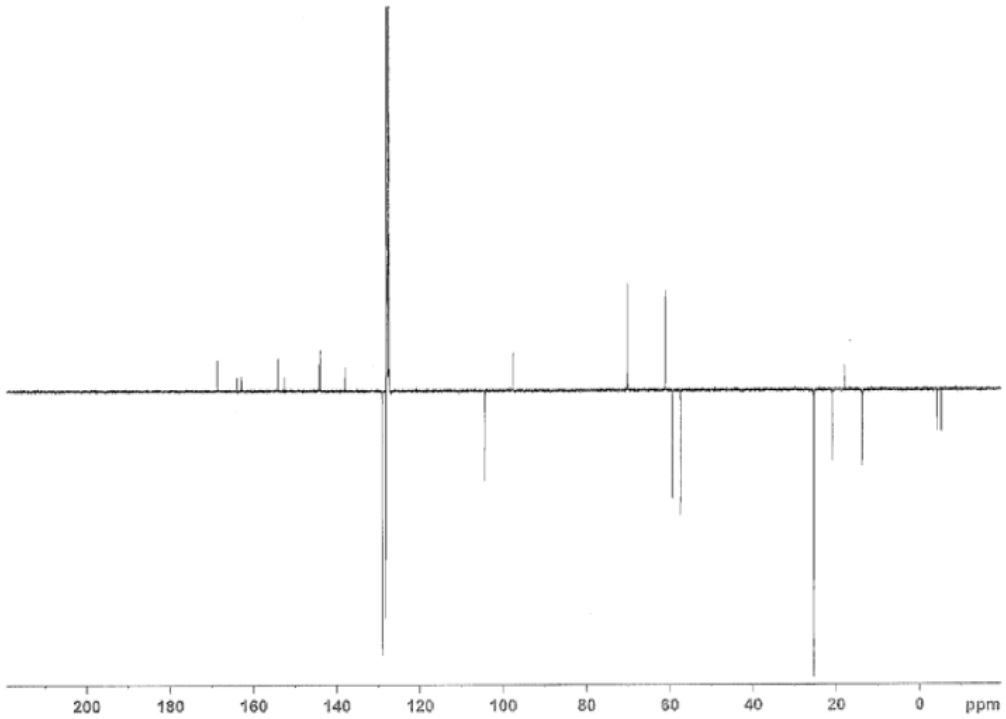
^{1}H NMR Spectrum of Compound **28**



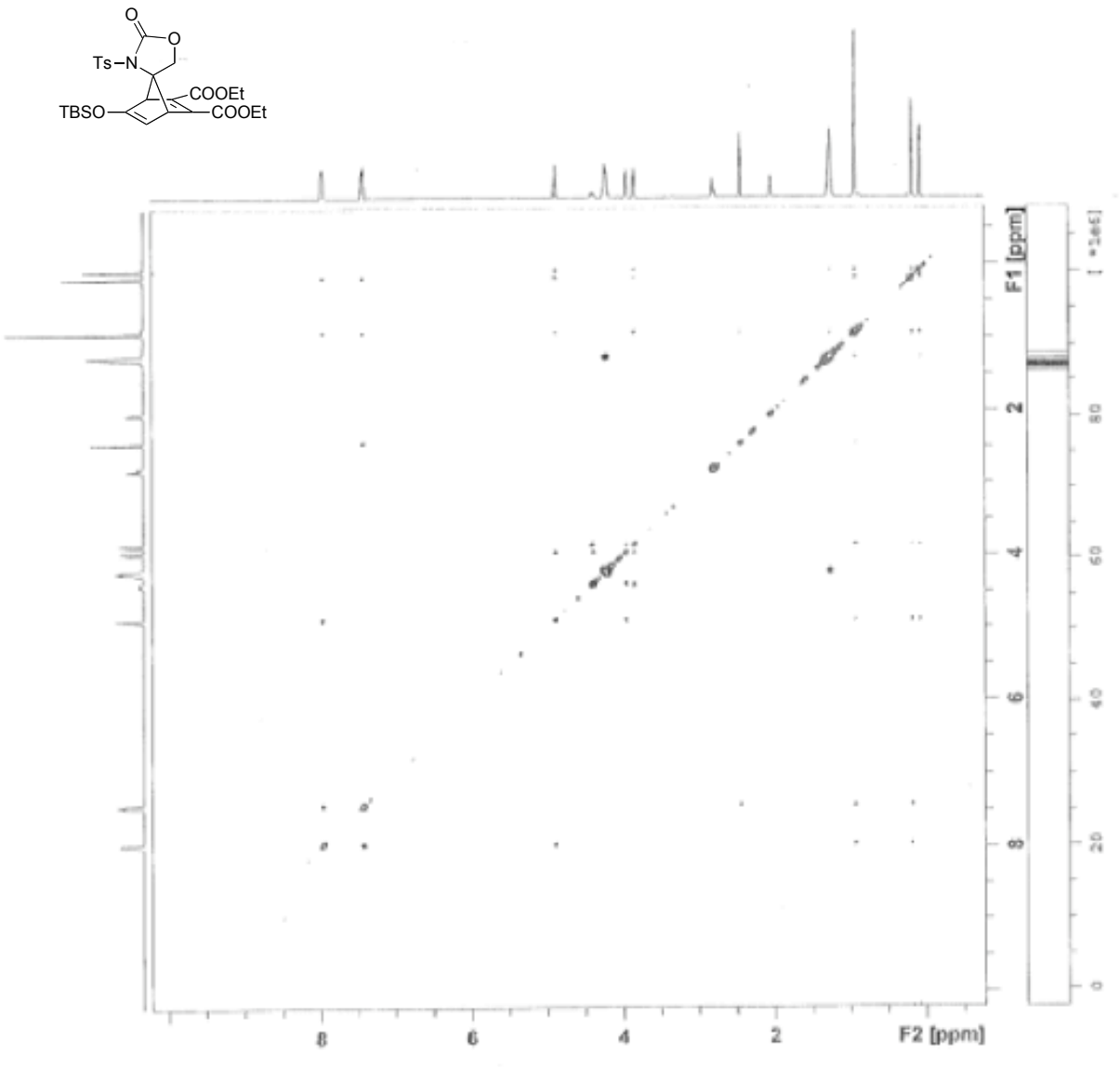
^{13}C NMR Spectrum of Compound **28**



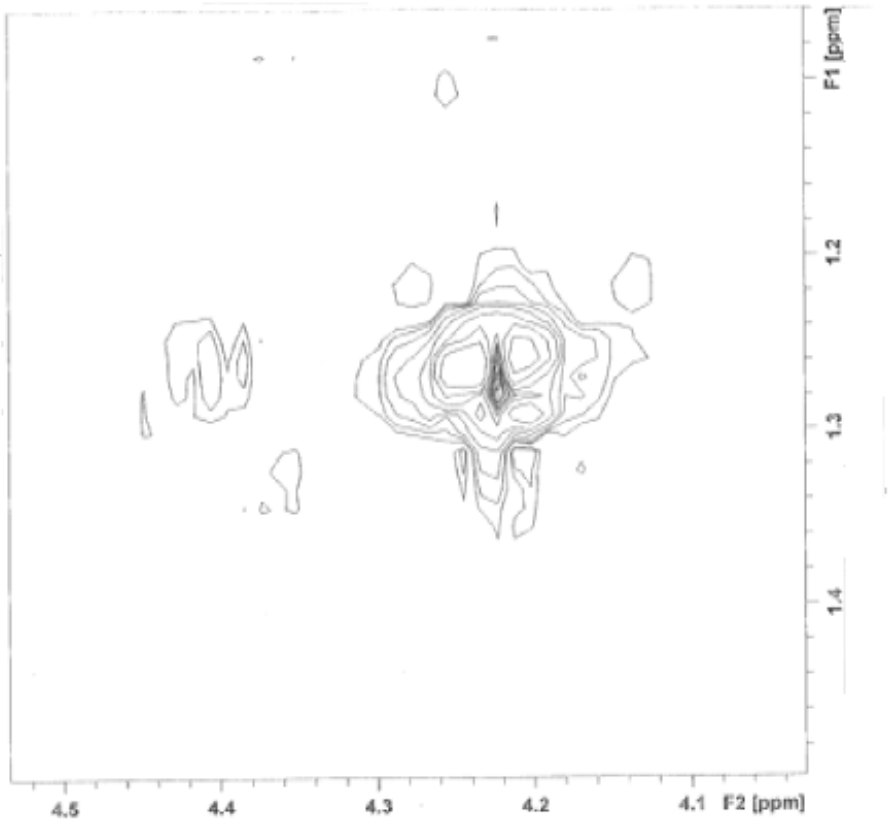
^{1}H NMR Spectrum of Compound **29**

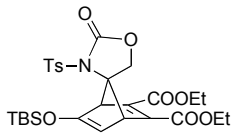


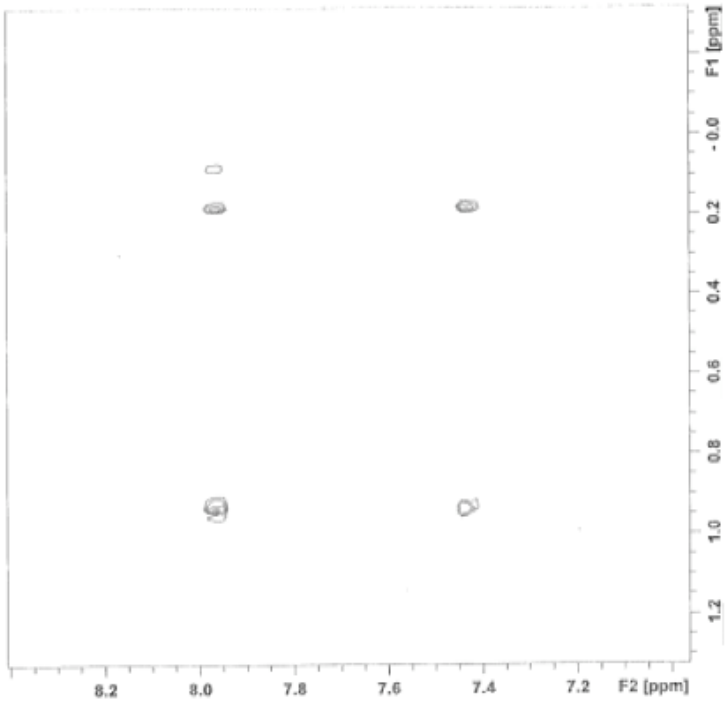
^{13}C-APT NMR Spectrum of Compound **29**



Full 2D-NOESY NMR Spectrum of Compound **29**







Expansions of the 2D-NOESY NMR Spectrum of Compound **29**