Supporting Information

Enantioselective Total Synthesis of Epothilone A and B Using Multifunctional Asymmetric Catalysis

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General. Optical rotations were measured on a JASCO P-1010 polarimeter. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 diffraction grating infrared spectrophotometer or a JASCO FT/IR-410 diffraction grating infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JMN-LA500 spectrometer and measured with $CDCl_3$ or C_6D_6 as solvents. Chemical shifts are reported in ppm on the δ scale relative to TMS (δ = 0.00 for ^{1}H NMR) or using residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR) or benzene (δ = 7.20 for ^{1}H NMR and δ = 128.0 for ^{13}C NMR) as an internal reference, rspectively. EI-Mass spectra were mesured on a JEOL JMS-BU20 instruments. All solvents used in the reactions were dried prior to use. All reagents were purified by standard methods. All experiments were performed under anhydrous conditions in an atmosphere of Ar, unless otherwise mentioned, and monitored with analytical TLC (Merck Art. No. 5715, silica gel 60·F_{254} plate). Flash column chromatography were carried out on Merck Art. No.9385, Silica gel 60 or on Wako, Aluminium Oxide (about 300 mesh ASTM). High performance liquid chromatography (HPLC) was carried out on a JASCO HPLC system consisting of the following equipments: pump, PU-980 intelligent HPLC pump; detector, UNIDEC-100IV or UV-970.

3-Benzyloxy-2,2-dimethyl-1-propanol (30): To a solution of neopentyl glycol **12** (550 mg, 5.28 mmol) in benzene (30 mL) were added benzaldehyde (644 μL, 6.34 mmol) and TsOH•H_2O (100 mg, 0.53 mmol) , and then the mixuture was heated at azeotropically reflux using Dean-Stark apparatus. After 5 h saturated aqueous $NaHCO_3$ (100 mL) was added to the mixture followed by the addition of AcOEt (100 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 50) to give acetal (914 mg, 4.75 mmol; 90%) as a colorless oil: IR (neat) 2952, 2857, 1455, 1384, 1104, 1025, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.36 (m, 3H), 5.40 (s, 1H), 3.79 (d, J = 11.0 Hz, 2H), 3.66 (d, J = 11.0 Hz, 2H), 1.31 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 129.2, 128.6, 126.5, 102.1, 78.0, 30.6, 23.4, 22.2; EI-MS *m/z* 192 (M^+); EI-HRMS Calcd for $C_{12}H_{16}O_2$ (M^+) : 192.1150, Found : 192.1150.

To a solution of acetal (895 mg, 4.66 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (12.25 mL, 0.95 M solution in hexane, 12.25 mmol) at 0 °C and the mixture was stirred at room temperature for 9 h. Saturated aqueous Rochelle salt solution (150 mL) and AcOEt (150 mL) were successively added, and the quenched mixture was stirred for 2 h. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (150 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 5) to give alcohol **30** (850 mg, 4.38 mmol; 94%) as a colorless oil: IR (neat) 3427, 2956, 2870, 1454, 1362, 1101, 1049, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.51 (s, 2H), 3.46 (d, J = 5.6 Hz, 2H), 3.33 (s, 2H), 2.57 (m, 1H), 0.94 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 129.0, 128.7, 128.1, 80.1, 74.1, 72.4, 36.8, 22.5; EI-MS *m/z* 194 (M^+); EI-HRMS Calcd for $C_{12}H_{18}O_2$ (M^+) : 194.1307, Found : 194.1307.

3-Benzyloxy-2,2-dimethyl-1-propanal (31): To a solution of alcohol **30** (838 mg, 4.31 mmol) in DMSO (10 mL) were added triethylamine (1.8 mL, 12.9 mmol), and then SO_3•Py complex (1.03 g, 6.47 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and then poured into ice-water (40 mL). AcOEt (40 mL) was added to the mixture and the organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give aldehyde **31** (746 mg, 3.88 mmol; 90%) as a colorless oil: IR (neat) 2969, 2858, 1732, 1455, 1362, 1099, 1028, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.30 (m, 5H), 4.51 (s, 2H), 3.46 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 138.7, 129.0, 128.2, 128.0, 75.7, 74.0, 47.7, 19.6; EI-MS *m/z* 192 (M^+); EI-HRMS Calcd for $C_{12}H_{16}O_2$ (M^+) : 192.1150, Found : 192.1156.

7-Benzyloxy-6,6-dimethyl-4-hepten-3-one (11): To a solution of *N,N*-diisopropylamine (638 μL, 4.55 mmol) in THF (20 mL) was added butyllithium (2.64 mL, 1.58 M hexane solution, 4.17 mmol) at -78 °C. The mixture was allowed to warm up to 0 °C, stirred for 40 min, and then cooled to -78 °C again. To the mixture was added 2-butanone (408 μL, 4.55 mmol). After 1 h aldehyde **31** (729 mg, 3.79 mmol) in THF (2 mL) was added to the mixture and the whole mixture was stirred for 1 h. Saturated aqueous NH_4Cl (40 mL) was added to the mixture followed by the addition of AcOEt (40 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was used for the next step without further purification.

To a crude mixture of hydroxyketone in CH_2Cl_2 (30 mL) were added TFAA (803 μL, 5.69 mmol) and DBU (1.7 mL, 11.4 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl (50 mL) was added to the mixture followed by the addition of AcOEt (50 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 25) to give enone **11** (765 mg, 3.07 mmol; 81% in 2 steps) as a colorless oil: IR (neat) 2967, 2871, 1698, 1674, 1627, 1455, 1361, 1200, 1099, 1029, 982, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.87 (d, J = 16.0 Hz, 1H), 6.07 (d, J = 16.0 Hz, 1H), 4.51 (s, 2H), 3.26 (s, 2H), 2.57 (q, J = 7.2 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H), 1.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ201.9, 153.7, 138.8, 128.7, 127.9, 127.8, 127.5, 78.7, 73.7, 38.5, 33.6, 24.3, 8.5; EI-MS *m/z* 246 (M^+); EI-HRMS Calcd for $C_{16}H_{22}O_2$ (M^+) : 246.1620, Found : 246.1624.

7-Benzyloxy-4,5-*trans*-epoxy-6,6-dimethyl-3-heptanone, a mixture of (4*S*,5*R*) and (4*R*,5*S*) isomers, (10): To a solution of enone **11** (5 g, 20.2 mmol) in MeOH (120 mL) were added 10% aqueous solution of NaOH (4 mL) and 30% aqueous solution of H_2O_2 (11.5mL) at 0 °C. The mixture was stirred for 13 h, and then saturated aqueous NH_4Cl (100 mL) and saturated aqueous $Na_2S_2O_3$ (50 mL) were added to the mixture. The solvent was removed under reduced pressure, and then AcOEt (100 mL) was added. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 25) to give epoxyketone **10** (3.51 g, 13.4 mmol; 66%) as a colorless oil: IR (neat) 2972, 2875, 1712, 1455, 1362, 1100, 883, 739, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.51 (s, 2H), 3.40 (d, J = 2.2 Hz, 1H), 3.30 (d, J = 8.8 Hz, 1H), 3.24 (d, J = 8.8 Hz, 1H), 3.03 (d, J = 2.2 Hz, 1H), 2.44 (dq, J = 7.2, 17.9 Hz, 1H), 2.33 (dq, J = 7.2, 17.9 Hz, 1H) 1.04 (dd, J = 7.2, 7.2 Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.8, 138.7, 128.7, 127.9, 127.8, 77.2, 73.7, 63.8, 59.9, 36.0, 31.1, 21.2, 20.7, 7.4; EI-MS *m/z* 262 (M^+); EI-HRMS Calcd for $C_{16}H_{22}O_3$ (M^+) : 262.1569, Found : 262.1571.

7-Benzyloxy-5-hydroxy-4,6,6-trimethyl-3-heptanone, a mixture of (4*S*,5*R*) and (4*R*,5*S*) isomers, (34): To a solution of epoxy ketone **10** (2.60 g, 9.91 mmol) in MeOH (40 mL) were added sodium acetate (2.44 g, 2.97 mmol) and methoxylamine hydrochloride (1.24 g, 1.49 mmol) at 0 °C. The mixture was stirred for 1 h, then saturated aqueous NH_4Cl (50 mL) was added to the mixture. The solvent was removed under reduced pressure, and then AcOEt (50 mL) was added. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (50 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated

to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 40) to give epoxy oxime **32** (2.40 g, 8.23 mmol; 83%) as a colorless oil.

To a suspension of CuCN (3.7 g, 41.4 mmol) in Et_2O (20 mL) was added MeLi (75 mL, 1.1 M Et_2O solution, 82.7 mmol) at -78 °C, and then the mixture was warmed up to 0 °C and stirred for 20 min. The mixture was cooled to -78 °C again and epoxy oxime **32** (2.41 g, 8.27 mmol) in Et_2O (2 mL) was added to the solution. After stirring for 20 h at the same temperature, saturated aqueous NH_4Cl (30 mL) and aqueous NH_3 (30 mL) were added to the mixture. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give hydroxyoxime **33** (1.53 g, 4.96 mmol; 60%) as a colorless oil.

Raney nickel (50% slurry in water, ca. 3 g, purchased from Aldrich) was washed with H_2O then with MeOH, and suspended in MeOH (7 mL), H_2O (1 mL) and acetone (1 mL). H_3BO_3 (1.5 g, 23.8 mmol) was added to a mixture, which was stirred for 1 h. Hydroxyoxime **33** (1.22 g, 4.0 mmol) in THF (7 mL) was added and the whole mixture was stirred under H_2 for 2 h at room temperature. The mixture was filtered through celite and the solvents were removed under reduced pressure. H_2O (30 mL) was added to the mixture followed by the addition of AcOEt (50 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give hydroxyketone **34** (862 mg, 3.1 mmol; 78%) as a colorless oil: IR (neat) 3461, 3030, 2971, 2936, 2875, 2360, 1693, 1455, 1411, 1378, 1259, 1207, 1102, 1050, 1027, 973, 801, 737, 698cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 5H), 4.39 (s, 2H), 3.40 (d, J = 2.8 Hz, 1H), 3.21 (d, J = 9.0 Hz, 1H), 3.19 (d, J = 9.0 Hz, 1H), 2.83 (dq, J = 2.8, 6.7 Hz, 1H), 2.45 (dq, J = 7.2, 18.3 Hz, 1H), 2.40 (dq, J = 7.2, 18.3 Hz, 1H) 1.21 (d, J = 6.7 Hz), 0.91 (dd, J = 7.2, 7.2 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ218.8, 138.6, 128.6, 127.9, 127.8, 82.0, 77.5, 73.5, 44.6, 40.2, 36.2, 23.2, 21.8, 18.3, 7.6; EI-MS *m/z* 279 (M^+); EI-HRMS Calcd for $C_{17}H_{27}O_3$ (M^+) : 279.1960, Found : 279.1952.

4-(1-Benzyloxy-2-methyl-2-propyl)-6-ethyl-2,2,5-trimethyl-1,3-dioxane, a mixture of (4*R*,5*R*,6*R*) and (4*S*,5*S*,6*S*) isomers, (35) and 4-(1-Benzyloxy-2-methyl-2-propyl)-6-ethyl-2,2,5-trimethyl-1,3-dioxane, a mixture of (4*R*,5*R*,6*S*) and (4*S*,5*S*,6*R*) isomers, (36): To a solution of hydroxyketone **34** (18.4 mg, 0.066 mmol) in MeOH (1 mL) was added $NaBH_4$ (5.5 mg, 0.145 mmol)and the mixture was stirred for 2 h. A saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the

aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 3) to give diol (9.6 mg, 0.034 mmol; 52%) and the isomeric diol (6.9 mg, 0.025 mmol; 37%) as a colorless oil.

To a solution of diol (9.6 mg, 0.034 mmol) in DMF (1 mL) were added 2,2-dimethoxypropane (11 μL, 0.0856 mmol) and small amounts of PPTS, and then the mixture was stirred for 24 h at 70 °C. H_2O (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 3) to give acetonide **35** (4.6 mg, 0.014mmol; 42%) and diol (5.0 mg, 0.0178 mmol; 52%) as a colorless oil: IR (neat) 2929, 2855, 1454, 1378, 1203, 1100, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.48 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 3.51 (d, J = 9.6 Hz, 1H), 3.41 (d, J = 8.3 Hz, 1H), 3.33 (m, 1H), 3.13 (d, J = 8.3 Hz, 1H), 1.69 (m, 1H), 1.52 (m, 1H) 1.40 (m, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.01 (s, 3H), 1.01 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR(125MHz,$CDCl_3$)δ 139.5, 128.5, 127.7, 127.6, 97.5, 77.6, 77.2, 76.2, 73.5, 39.7, 34.1, 30.5, 26.8, 24.0, 21.3, 20.2, 15.3, 10.0; EI-MS *m/z* 320 (M^+), 305 (M^+-Me); EI-HRMS Calcd for $C_{20}H_{32}O_3$ (M^+-Me) : 305.2117, Found : 305.2118.

To a solution of the isomeric diol (6.8 mg, 0.024 mmol) in DMF (1 mL) were added 2,2-dimethoxypropane (7.5 μL, 0.0606 mmol) and small amounts of PPTS, and then the mixture was stirred for 24 h at 70 °C. H_2O (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 3) to give acetonide **36** (5.7 mg, 0.0177 mmol; 73%) and the starting material (1.1 mg, 0.0039 mmol; 16%) as a colorless oil: IR (neat) 2964, 2869, 1462, 1378, 1227, 1091, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.49 (s, 2H), 3.57 (m, 1H), 3.31 (d, J = 8.3 Hz, 1H), 3.30 (d, J = 6.2 Hz, 1H), 3.19 (d, J = 8.3 Hz, 1H), 1.84 (m, 1H), 1.43 (m, 1H) 1.34 (m, 1H), 1.81 (s, 3H), 1.27 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 128.6, 127.7, 127.6, 100.1, 77.6, 77.2, 73.6, 71.7, 39.2, 34.4, 26.3, 24.1, 23.8, 21.5, 20.2, 13.7, 10.8; EI-MS *m/z* 320 (M^+); EI-HRMS Calcd for $C_{20}H_{32}O_3$ (M^+) : 320.2351, Found : 320.2354.

1-Benzyloxy-2,2,4,6-tetramethyl-8-nonen-3,5-diol, a mixture of (3*R*,4*R*,5*S*,6*S*) and (3*S*,4*S*,5*R*,6*R*) isomers, (38) and 1-Benzyloxy-2,2,4,6-tetramethyl-8-nonen-3,5-diol, a mixture

of (3*R*,4*R*,5*R*,6*S*) and (3*S*,4*S*,5*S*,6*R*) isomers, (39): Tetramethylammonium triacetoxyborohydride (337 mg, 1.28 mmol) was dissolved in MeCN (3.5 mL) and AcOH (2 mL) and the mixture was cooled to -40 °C. Ketone **37** (204 mg, 0.641 mmol) in MeCN (1 mL) was added to the mixture, which was then allowed to warm up to -20 °C. Then tetramethylammonium triacetoxyborohydride (337 mg, 1.28 mmol) was added portionwise for 5 times and stirred for 240 h at the same temperature. Then the mixture was poured into saturated aqueous $NaHCO_3$ (100 mL) at 0 °C and extracted with AcOEt (100 mL) for three times. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 30) to give diol **38** (162 mg, 0.506 mmol; 79%): IR (neat) 3441, 2967, 2923, 2883, 1639, 1455, 1379, 1078, 970, 909, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.80 (dddd, J = 6.8, 8.2, 10.4, 16.2 Hz, 1H), 5.01 (m, 2H), 4.51 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.72 (brs, 1H), 3.64 (dd, J = 1.6, 9.5 Hz, 1H), 3.53 (d, J = 2.8 Hz, 1H), 3.32 (d, J = 8.8 Hz, 1H), 3.30 (d, J = 8.8 Hz, 1H), 2.55 (m, 1H), 1.87 (m, 2H), 1.62 (m, 1H), 1.04 (s, 3H), 1.01 (d, J = 7.2 Hz), 0.88 (s, 3H), 0.76 (d, J =6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)
δ 138.0, 137.8, 128.9, 128.6, 128.0, 116.2, 85.0, 82.1, 75.5, 74.1, 39.5, 38.1, 36.0, 34.6, 23.0, 20.3, 15.6, 13.6; EI-MS *m/z* 321 (M^++1); EI-HRMS Calcd for $C_{20}H_{33}O_3$ (M^++1) : 321.2430, Found : 321.2432 and stereoisomer **39** (23 mg, 0.0705 mmol; 11%): IR (neat) 3410, 2967, 2936, 2871, 1455, 1096, 982, 910, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.75 (m, 1H), 4.96 (m, 1H), 4.91 (m, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 3.53 (dd, J = 2.5, 9.3 Hz, 1H), 3.45 (d, J = 5.4 Hz, 1H), 3.37 (d, J = 8.7 Hz, 1H), 3.22 (d, J = 8.7 Hz, 1H), 2.15 (m, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.61 (m, 1H), 0.97 (s, 3H), 0.78 (s, 3H), 0.75 (d, J = 9.3 Hz, 3H), 0.74 (d, J =9.1 Hz, 3H); ^{13}C NMR (125MHz,$CDCl_3$)δ 138.6, 137.7, 128.9, 128.3, 128.1, 115.9, 84.9, 81.1, 75.9, 74.2, 40.0, 39.5, 36.7, 34.9, 23.1, 19.1, 18.9, 11.9; EI-MS *m/z* 320 (M^+); EI-HRMS Calcd for $C_{20}H_{32}O_3$ (M^+) : 320.2351, Found : 320.2349.

4-(1-Benzyloxy-2-methyl-2-propyl)-6-(1-pente-4-yl)-2,2,5-trimethyl-1,3-dioxane, a mixture of (4*R*,5*R*,6*S*,4'*S*) and (4*S*,5*S*,6*R*,4'*R*) isomers, (40): To a solution of diol **38** (123 mg, 0.384 mmol) in DMF (2 mL) were added 2-methoxypropene (110 μL, 1.15 mmol) and small amounts of $TsOH•H_2O$, and then the mixture was stirred for 20 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 200) to

give acetonide **40** (133 mg, 0.368 mmol; 96%) as a colorless oil: IR (neat) 2977, 2933, 2874, 1639, 1455, 1378, 1228, 1099, 1000, 909, 734, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.20 (m, 2H), 5.73 (m, 1H), 4.95 (m, 2H), 4.42 (s, 2H), 3.26 (d, J = 8.4 Hz, 1H), 3.26 (d, J = 5.6 Hz, 1H), 3.21 (dd, J = 3.3, 10.3 Hz, 1H), 3.14 (d, J = 8.4 Hz, 1H), 2.45 (m, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 1.55 (m, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.72 (d, J =6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 137.6, 128.5, 127.7, 127.6, 116.3, 100.4, 78.2, 77.2, 73.8, 73.6, 39.2, 37.9, 32.9, 32.8, 26.3, 23.8, 21.4, 20.2, 14.7, 13.6; EI-MS *m/z* 360 (M^+); EI-HRMS Calcd for $C_{23}H_{36}O_3$ (M^+) : 360.2664, Found : 360.2663; $[\alpha]^{26}_D$ +18.1 (c 1.0, $CHCl_3$) (71% ee) for optically active **40**.

4-(1-Benzyloxy-2-methyl-2-propyl)-6-(1-pente-4-yl)-2,2,5-trimethyl-1,3-dioxane, a mixture of (4*R*,5*R*,6*R*,4'*S*) and (4*S*,5*S*,6*S*,4'*R*) isomers, (41): To a solution of diol **39** (19.8 mg, 0.0619 mmol) in DMF (1 mL) were added 2-methoxypropene (12 μL, 0.124 mmol) and small amount of $TsOH•H_2O$, and then the mixture was stirred for 20 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 200) to give acetonide **41** (16 mg, 0.0451 mmol; 73%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.27 (m, 2H), 5.75 (m, 1H), 5.01 (m, 2H), 4.48 (s, 2H), 3.49 (d, J = 9.7 Hz, 1H), 3.40 (d, J = 8.5 Hz, 1H), 3.39 (dd, J = 2.3, 9.7 Hz, 1H), 3.14 (d, J = 8.5 Hz, 1H), 2.12 (m, 1H), 2.00 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.82 (d, J =6.2 Hz, 3H); EI-MS *m/z* 345 (M^+-Me); EI-HRMS Calcd for $C_{22}H_{33}O_3$ (M^+-Me) : 345.243, Found : 345.2432.

2-Methyl-2-[2,2,5-trimethyl-6-(1-pente-4-yl)-1,3-dioxan-4-yl]-3-propanol, a mixture of (4'*R*,5'*R*,6'*S*,4''*S*) and (4'*S*,5'*S*,6'*R*,4''*R*) isomers, (43): Lithium (400 mg, 57.6 mmol) was dissolved in liq.NH_3 (ca. 30 mL) at -78 °C, and to the mixture were added *t*-BuOH (1 mL), and then acetonide **40** (540 mg, 1.5 mmol) in THF (6 mL). After 40 min MeOH (1 mL) was added to the mixture slowly, followed by the addition of saturated aqueous NH_4Cl (30 mL). AcOEt (30 mL) was added to the mixture, and then the organic layer was separated. The aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 7) to give alcohol **43** (405 mg, 1.5 mmol; quant) as a colorless oil. **43**: IR (neat) 3465, 3075, 2973, 2936, 2871, 1714, 1640, 1462, 1378, 1229, 997, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.02 (m, 2H), 3.52 (d, J = 10.9 Hz, 1H), 3.39 (d, J =

10.9 Hz, 1H), 3.31 (dd, J = 3.3, 10.5 Hz, 1H), 3.29 (d, J = 6.3 Hz, 1H), 2.49 (m, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.91 (d, J = 6.3 Hz, 3H), 0.81 (d, J =6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ137.1, 116.4, 100.6, 82.5, 73.6, 71.8, 38.8, 37.6, 33.1, 32.6, 26.1, 23.6, 22.0, 19.0, 14.5, 13.7; EI-MS *m/z* 271 (M^++1); EI-HRMS Calcd for $C_{16}H_{31}O_3$ (M^++1) : 271.2273, Found : 271.2266; $[\alpha]^{25}_D$ +29.9 (c 0.5, $CHCl_3$) (71% ee) for optically active **43**.

2-Methyl-2-[2,2,5-trimethyl-6-(1-pente-4-yl)-1,3-dioxan-4-yl]-3-propanal, a mixture of (4'*R*,5'*R*,6'*S*,4''*S*) and (4'*S*,5'*S*,6'*R*,4''*R*) isomers, (9): To a solution of alcohol **43** (384 mg, 1.42 mmol) in CH_2Cl_2 (9 mL) were added NMO (250 mg, 2.13 mmol) and MS4A (710 mg) then TPAP (32 mg, 0.071 mmol), and the mixture was allowed to stir for 1 h. The mixture was filtered through celite, and brine (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give aldehyde **9** (339 mg, 1.26 mmol; 89%) as a colorless oil: IR (neat) 3734, 3075, 2975, 2935, 2877, 2702, 2360, 2341, 1730, 1639, 1463, 1378, 1221, 1182, 1122, 1083, 1001, 912, 886, 812, 782, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 5.75 (m, 1H), 5.00 (m, 2H), 3.44 (d, J = 6.0 Hz, 1H), 3.27 (dd, J = 3.5, 10.5 Hz, 1H), 2.47 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.59 (m, 1H), 1.31 (s, 3H), 1.24 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.78 (d, J =6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ206.1, 137.2, 116.5, 100.9, 78.9, 73.5, 50.0, 37.7, 33.1, 32.7, 25.8, 23.6, 19.2, 16.6, 14.7, 13.8; EI-MS *m/z* 268 (M^+); EI-HRMS Calcd for $C_{16}H_{28}O_3$ (M^+) : 268.2038, Found : 268.2036; $[\alpha]^{24}_D$ +27.4 (c 0.9, $CHCl_3$) (71% ee) for optically active **9**.

3-(1-Benzyloxy-2,2-dimethyl-3-pentanol-4-yl)-4-methyl-tetrahydro-2-pyrone, a mixture of (3*S*,4*S*,3'*R*,4'*R*) and (3*R*,4*R*,3'*S*,4'*S*) isomers, (42): To a solution of acetonide **40** (36 mg, 0.1 mmol) in THF (1 mL) was added BH_3•THF complex (200 μL, 1.0 M THF solution, 0.2 mmol) at 0 °C, and the mixture was stirred for 4 h at room temperature. MeOH (0.2 mL) was added to the mixture slowly followed by 10% aqueous solution of NaOH (0.2 mL) and 30% aqueous solution of H_2O_2 (0.2 mL) at 0 °C, and the whole mixture was stirred for 2 h at room temperatue. A saturated aqueous NH_4Cl (30 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) were added to the mixture at 0 °C followed by the addition of AcOEt (50 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 2) to give alcohol (25 mg,

0.067 mmol; 67%).

To a mixture of alcohol (25 mg, 0.067 mmol) in DMF (2 mL) was added PDC (248 mg, 0.66 mmol), and the mixture was stirred for 36 h at room temperature. Brine (30 mL) was added to the mixture at 0 °C followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 1) to give the carboxylic acid (7.8 mg, 0.0198 mmol; 30%) as a colorless oil.

To a mixture of carboxylic acid (7.8 mg, 0.0198 mmol) in THF (1.5 mL) was added 1N. aqueous solution of HCl (1 mL), and the mixture was stirred for 48 h at 50 °C. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 2) to give lactone **42** (4.7 mg, 0.014 mmol; 70%): IR (neat) 3462, 2961, 2929, 2874, 1731, 1455, 1382, 1252, 1211, 1092, 1029, 996, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.58 (dd, J = 1.7, 10.2 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.58 (m, 1H), 3.38 (d, J = 8.8 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H), 3..8 (d, J = 4.5 Hz, 1H), 2.61 (ddd, J = 3.6, 6.6, 17.5 Hz, 1H), 2.44 (ddd, J = 6.9, 10.5, 17.5 Hz, 1H), 2.00 (m, 1H), 1.86 (m, 2H), 1.56 (m, 1H), , 0.99 (d, J = 6.7 Hz, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.94 (d, J = 6.2 Hz, 3H); ^{13}C NMR(125MHz,$CDCl_3$)δ 172.0, 138.5, 128.7, 128.0, 127.9, 86.5, 79.4, 78.6, 73.9, 39.9, 36.1, 30.1, 30.0, 28.5, 23.7, 20.5, 17.5, 12.8; EI-MS *m/z* 316 (M^+); EI-HRMS Calcd for $C_{20}H_{30}O_4$ (M^+) : 316.2038, Found : 316.2042.

(3*S*,5*S*,2'*S*,3'*R*,4'*R*)-5-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-3-(4-methyl-6-hepten-3-ol-2-yl)tetrahydro-2-pyrone (51): Into a flame dried flask, MS4A (9.7 mg) was put and dried at 180 °C for 12 h under the reduced pressure. Ligand **45** (1.6 mg, 0.00387 mmol) and K_2CO_3 (6.7 mg, 0.0484 mmol) were added, followed by CH_2Cl_2 (400 μL) under argon atmosphere. To the suspension were added $SnCl_4$ (4 μL, 0.00387 mmol, 1 M in CH_2Cl_2) and BTSP (206 μL, 0.194 mmol, 0.94 M in CH_2Cl_2) at 0 °C. After 10 min aldol **44** (19 mg, 0.0484 mmol) in CH_2Cl_2 (600 μL) was added to the mixture and the whole mixture was stirred for 10 h at the same temperature. Saturated aqueous $Na_2S_2O_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica

gel, AcOEt/hexane, 1 : 10) to give ester (11 mg, 0.0266 mmol; 55 %) as a colorless oil.

To a solution of ester (20 mg, 0.049 mmol) in CH_2Cl_2 (1.2 mL) were added diisopropylethylamine (26 μL, 0.15 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (17 μL, 0.074 mmol), and the mixture was stirred for 30 min. AcOEt (30 mL) was added to the mixture followed by the addition of saturated aqueous NH_4Cl (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give silyl-ether (22 mg, 0.424 mmol; 94%) as a colorless oil.

Silyl-ether (80 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was cooled to -78 °C. BCl_3 (96 μL, 0.0964 mmol, 1 M in CH_2Cl_2) was added to the solution, which was stirred at the same temperature for 20 min. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give lactone **51** (5.9 mg, 0.0154 mmol; 80%) as a colorless oil: $[\alpha]^{22}_D$ -12.1 (c 0.14, $CHCl_3$) (89% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.03 (m, 2H), 3.86 (d, J = 3.8 Hz, 1H), 3.69 (m, 1H), 3.64 (dd, J = 6.9, 9.6 Hz, 1H), 2.82 (dd, J = 6.9, 18.2 Hz, 1H), 2.58 (m, 1H), 2.48 (dd, J = 9.6, 18.2 Hz, 1H), 2.36 (d, J = 3.2 Hz, 1H), 2.20 (m, 1H), 1.90 (m, 1H), 1.67 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.84 (d, J = 7.2 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 137.8, 116.6, 89.6, 74.3, 72.7, 39.8, 38.1, 37.9, 36.0, 34.4, 26.0, 23.2, 18.3, 16.0, 13.6, 12.9, –3.9, –4.5; EI-MS *m/z* 327 (M^+-*t*-Bu); EI-HRMS Calcd for $C_{17}H_{31}O_4Si$ (M^+- *t*-Bu) : 327.1991, Found : 327.1991.

(*S*)-3-(4-*tert*-Butylphenylthio)-2-methyl-1-propanol (52): To a solution of **16** (2.75 g, 9.28 mmol) in Et_2O (30 mL) was added LAH (700 mg, 18.4 mmol) at room temperature and the mixture was stirred for 1 h. Saturated aqueous Na_2SO_4 (30 mL) was added to the mixture at 0 °C followed by the addition of AcOEt (30 mL) and the whole mixture was stirred for 6 h at room temperature. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give alcohol **52** (2.1 g, 8.82 mmol; 95%) as a colorless oil: $[\alpha]^{24}_D$ -9.38 (c 0.5, $CHCl_3$) (87% ee); IR (neat) 3346, 2961, 1497, 1460, 1362, 1268, 1120, 1035, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.30 (s, 4H), 3.62 (dd, J = 5.4, 10.7 Hz, 1H), 3.59 (dd, J = 5.8, 10.7 Hz, 1H), 3.03 (dd, J = 6.2, 12.7 Hz, 1H), 2.82 (dd, J = 6.9, 12.7 Hz, 1H), 1.95 (m, 1H), 1.78 (s, 1H), 1.31 (s 9H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 133.4, 129.6, 126.3, 67.2, 38.2, 35.8, 34.7, 31.6, 16.8; EI-MS *m/z* 238 (M^+); EI-HRMS Calcd for $C_{14}H_{22}OS(M^+)$: 238.1391, Found : 238.1392.

(*S*)-3-(4-*tert*-Butylphenylthio)-1-(4-methoxybenzyloxy)-2-methyl-propane (53): To a solution of **52** (2.1 g, 8.82 mmol) in DMF (30 mL) was added NaH (370 mg, 9.26 mmol) at 0 °C and the mixture was stirred for 30 min. Then 4-methoxybenzyl chloride (1.41 mL, 9.7 mmol) was added to the mixture, which was then stirred for 4 h at room temperature. Saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give ether **53** (3.1 g, 8.64 mmol; 98%) as a colorless oil: $[\alpha]^{24}_D$ +12.5 (c 0.9, $CHCl_3$) (87% ee); IR (neat) 2959, 1612, 1513, 1462, 1362, 1302, 1247, 1173, 1092, 1037, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 4H), 7.25 (m, 2H), 6.89 (m, 2H), 4.41 (s, 2H), 3.82 (s, 3H), 3.41 (d, J = 6.2 Hz, 1H), 3.13 (dd, J = 5.7, 12.6 Hz, 1H), 2.78 (dd, J = 5.6, 12.7 Hz, 1H), 2.07 (m, 1H), 1.31 (s 9H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 149.2, 133.9, 131.0, 129.4, 129.3, 126.2, 114.1, 74.1, 73.0, 55.6, 38.3, 34.7, 34.1, 31.6, 17.1; EI-MS *m/z* 358 (M^+); EI-HRMS Calcd for $C_{22}H_{30}O_2S(M^+)$: 358.1966, Found : 358.1967.

(*R*)-3-(4-Methoxybenzyloxy)-2-methyl-propanal (54): To a solution of **53** (3.1 g, 8.82 mmol) in CH_2Cl_2 (30 mL) was added mCPBA (2.17 g, 9.7 mmol) at -20 °C and the mixture was stirred for 30 min. Saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL) were added to the mixture. Then AcOEt (30 mL) was added and the organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 5) to give a diastereomixture of sulfoxides as a colorless oil.

To a solution of the diastereomixture of sulfoxides in CH_2Cl_2 (30 mL) was added pyridine (3.57 mL, 44 mmol) and trifluoroacetic anhydride (2.49 mL, 17.6 mmol) at 0 °C and the mixture was stirred for 30 min. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give aldehyde **50** (1.17 g, 5.62 mmol; 78%) as a colorless

oil: $[\alpha]^{22}_D$ -27.7 (c 0.4, $CHCl_3$) (87% ee); IR (neat) 2936, 2859, 2725, 1723, 1612, 1514, 1459, 1302, 1249, 1174, 1095, 1035, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, J = 1.5 Hz, 1H), 7.24 (m, 2H), 6.88 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.64 (dd, J = 6.6, 9.3 Hz, 1H), 2.78 (dd, J = 5.4, 9.3 Hz, 1H), 2.64 (m, 1H), 1.12 (d, J = 7.3 Hz, 3H);^{13}CNMR(125MHz,$CDCl_3$)δ204.2, 169.6, 130.3, 129.6, 114.1, 73.3, 70.1, 55.6, 47.1, 11.0; EI-MS *m/z* 208 (M^+); EI-HRMS Calcd for $C_{12}H_{16}O_3(M^+)$: 208.1099, Found : 208.1097.

(*S*)-3-(4-Methoxybenzyloxy)-2-methyl-1-propanol (55): To a solution of **54** (1.5 g, 7.21 mmol) in MeOH (10 mL) was added $NaBH_4$ (273 mg, 7.21 mmol) at 0 °C and the mixture was stirred for 10 min at room temperature. Saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give alcohol **55** (1.52 g, 7.21 mmol; 100%) as a colorless oil: $[\alpha]^{23}_D$ -14.7 (c 0.44, $CHCl_3$) (87% ee); IR (neat) 3420, 2872, 1613, 1514, 1464, 1302, 1248, 1173, 1092, 1037, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.88 (m, 2H), 4.45 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.60 (dd, J = 4.4, 10.5 Hz, 1H), 3.56 (dd, J = 7.9, 10.5 Hz, 1H), 3.51 (dd, J = 4.6, 9.0 Hz, 1H), 3.39 (dd, J = 7.8, 9.0 Hz, 1H), 2.61 (brs, 1H), 2.04 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 130.4, 129.5, 114.1, 75.4, 73.3, 38.1, 55.5, 35.8, 13.8; EI-MS *m/z* 210 (M^+); EI-HRMS Calcd for $C_{12}H_{18}O_3(M^+)$: 210.1256, Found : 210.1255.

(*R*)-3-Bromo-1-(4-methoxybenzyloxy)-2-methyl-1-propane (56): To a solution of **55** (995 mg, 4.73 mmol) in CH_2Cl_2 (30 mL) was added PPh_3 (2.48 g, 9.46 mmol) and CBr_4 (3.14 g, 9.46 mmol) at 0 °C and the mixture was stirred for 12 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give bromide **56** (1.29 g, 4.73 mmol; 100%) as a colorless oil: $[\alpha]^{22}_D$ -9.6 (c 0.47, $CHCl_3$) (87% ee); IR (neat) 2961, 2864, 1612, 1513, 1459, 1300, 1248, 1175, 1094, 1037, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.89 (m, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.51 (dd, J = 4.8, 9.7 Hz, 1H), 3.48 (dd, J = 5.7, 9.7 Hz, 1H), 3.40 (dd, J = 5.1, 9.0 Hz, 1H), 3.36 (dd, J = 6.9 9.0 Hz, 1H), 2.12 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 159.5, 130.8, 129.5, 114.1, 73.2, 72.8, 55.6, 38.6, 36.0, 16.2; EI-MS *m/z* 272 (M^+); EI-HRMS Calcd for $C_{12}H_{17}O_2Br(M^+)$: 272.0411, Found : 272.0411.

(*S*)-1-(4-methoxybenzyloxy)-2-methyl-4-pentene (57): To a suspension of CuCN (3.7 g, 41.4 mmol) in THF (20 mL) was added MeLi (75 mL, 1.1 M Et_2O solution, 82.7 mmol) at -78 °C then the mixture was warmed up to 0 °C and stirred for 20 min. The mixture was cooled to -78 °C again and tetravinyltin (2.41 g, 8.27 mmol) was added to the mixture, then the whole mixture was warmed up to room temperature and stirred for 90 min. The mixture was cooled to -78 °C again and **56** (2.26 g, 8.27 mmol) in THF (5 mL) was added to the mixture, which was then gradually warmed up to room temperature. After stirring for 20 h, saturated aqueous NH_4Cl (30 mL) and aqueous NH_3 (30 mL) were added to the mixture. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (50 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give alkene **57** (1.53 g, 4.96 mmol; 60%) as a colorless oil: $[\alpha]^{23}_D$ -2.4 (c 0.52, $CHCl_3$) (87% ee); IR (neat) 2956, 2857, 1613, 1514, 1463, 1302, 1248, 1173, 1093, 1038, 912, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.89 (m, 2H), 5.78 (m, 1H), 5.01 (m, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.31 (dd, J = 6.2, 8.8 Hz, 1H), 3.25 (dd, J = 5.8, 8.8 Hz, 1H), 2.22 (m, 1H), 1.89, (m, 2H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 137.3, 131.2, 129.4, 116.2, 114.0, 75.4, 73.0, 55.6, 38.4, 33.7, 17.1; EI-MS *m/z* 220 (M^+); EI-HRMS Calcd for $C_{14}H_{20}O_2$(M^+) : 220.1463, Found : 220.1464.

(4*R*,5*S*,6*S*)-1-Benzyloxy-5-*tert*-butyldimethylsilyloxy-2,2,4,6-tetramethyl-8-nonen-3-one (58): To a solution of aldol **13** (63 mg, 0.172 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (150 μL, 0.86 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (120 μL, 0.86 mmol), and the mixture was stirred for 30 min. AcOEt (30 mL) was added to the mixture followed by the addition of saturated aqueous NH_4Cl (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give silyl-ether **58** as a colorless oil: $[\alpha]^{22}_D$ -7.5 (c 0.79, $CHCl_3$) (71% ee); IR (neat) 2929, 1698, 1462, 1362, 1256, 1100, 1029, 837, 774, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.70 (m, 1H), 4.96 (m, 2H), 4.49 (s, 2H), 3.90 (dd, J = 1.8, 7.8 Hz, 1H), 3.46 (s, 2H), 3.23 (m, 1H), 2.22 (m, 1H), 1.82 (m, 1H), 1.46 (m, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 (s, 9H), 0.91 (d, J =6.7 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.2, 139.0, 138.3, 129.6, 127.9, 115.8, 78.0, 77.4, 73.6, 49.5, 45.2, 38.5, 35.7, 26.6, 23.1, 22.9, 18.9, 18.0, 16.4, −3.2, −3.4; EI-MS *m/z* 432 (M^+); EI-HRMS Calcd for $C_{26}H_{44}O_3Si$ (M^+) : 432.306, Found : 432.3059.

(4*R*,5*R*,6*S*,4'*S*)-4-(1-Benzyloxy-2-methyl-2-propyl)-6-(1-pente-4-yl)-2,2,5-trimethyl-1,3-

dioxane (40): Silyl-ether **58** (105 mg, 0.3 mmol) was dissolved in toluene (20 mL) and cooled to -78 °C. DIBAL (325 μL, 1 M solution in toluene, 0.32 mmol) was added dropwise to maintain the temperature at -78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature for 1 h. Saturated aqueous Rochelle salt solution (40 mL) and AcOEt (30 mL) were successively added, and the quenched mixture was allowed to warm to room temperature and stirred for 2 h. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give alcohol (86 mg, 0.28 mmol; 94%) as a colorless oil.

To a solution of the alcohol (123 mg, 0.384 mmol) in DMF (2 mL) were added 2-methoxypropene (110 μL, 1.15 mmol) and small amounts of $TsOH•H_2O$, and then the mixture was stirred for 20 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 200) to give acetonide **40** (133 mg, 0.368 mmol; 96%) as a colorless oil.

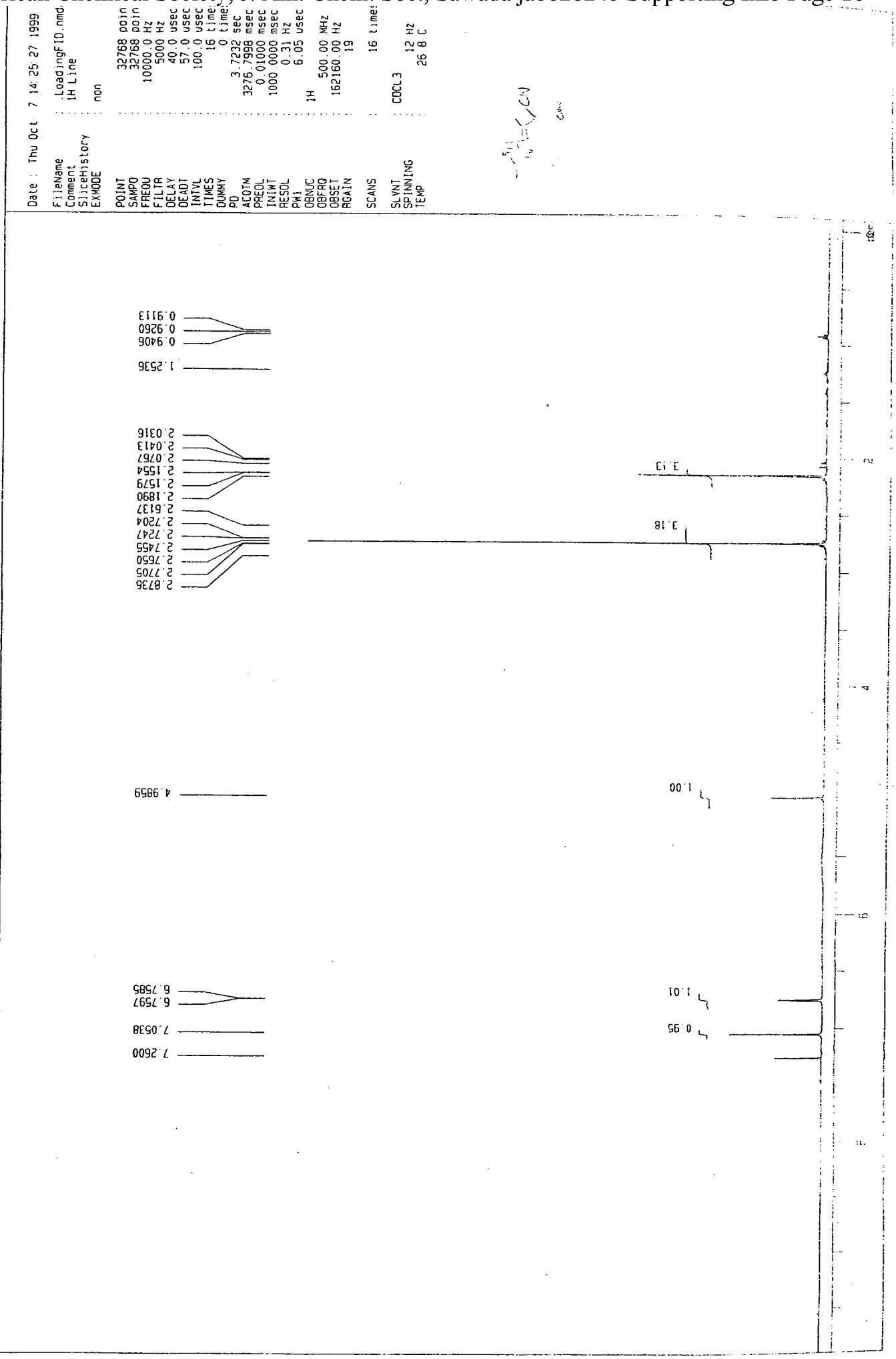
Epothilone A (1): To a mixture of lactone **60** (4.4 mg, 0.0062 mmol) in THF (1 mL) was added HF•Py (0.5 mL) at 0 °C and the mixture was stirred at room temperatuer for 12 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) at 0 °C carefully and extracted with AcOEt (20 mL) for three times. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 1) then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 1.5) to give epothilone C (**3**) (3.0 mg, 0.0062 mmol; 99%).To a solution of epothilone C (**3**) (3.0 mg, 0.0062 mmol) in CH_2Cl_2 (1 mL) was added freshly prepared 3,3-dimethyldioxirane (0.5 ml, ca.0.1 M in acetone) at -50 °C. The mixture was allowed to warm up to -30 °C and stirred for 2 h. A stream of argon was then bubbled through the solution to remove excess 3,3-dimethyldioxirane. The residue was purified by silica gel flash chromatography (AcOEt) then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 2 : 1) to give epothilone A (**1**). The spectral data of **1** thus obtained were identical with those of an authentic sample.[2h,2l]

Epothilone B (2): To a mixture of lactone **62** (3.4 mg, 0.00475 mmol) in THF (1 mL) was added HF•Py (0.5 mL) at 0°C and the mixture was stirred at room temperature for 12 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) at 0 °C and extracted with AcOEt (20

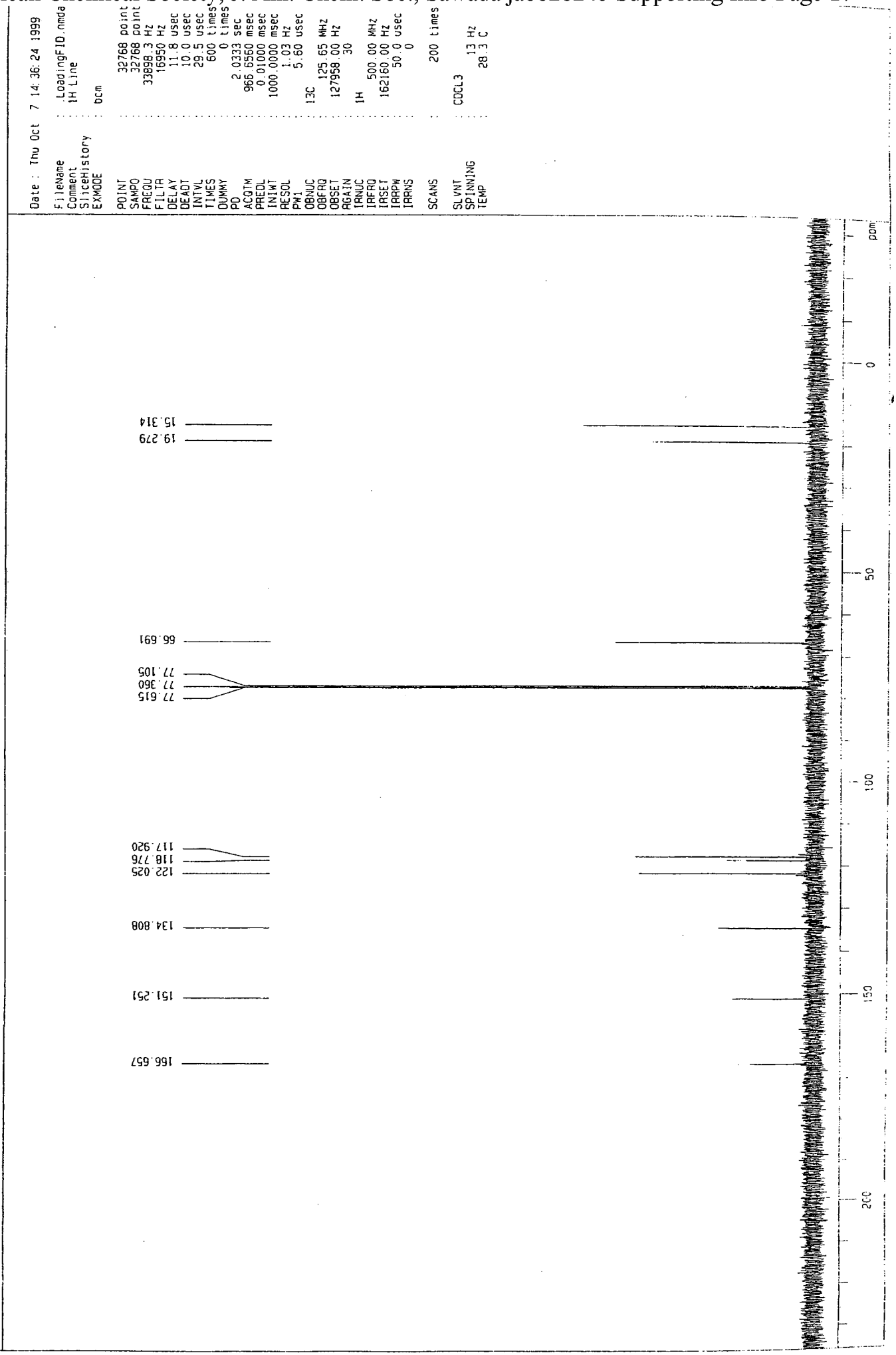
mL) for three times. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 1) then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1 : 1) to give epothilone D (**4**) (2.1 mg, 0.00434 mmol; 92%).

To a solution of epothilone D (**4**) (2.0 mg, 0.00407 mmol) in CH_2Cl_2 (1 mL) was added freshly prepared 3,3-dimethyldioxirane (0.5 ml, ca. 0.1M in acetone) at -78 °C. The mixture was allowed to warm up to -50 °C and stirred for 3 h. A stream of argon was then bubbled through the solution to remove excess 3,3-dimethyldioxirane. The residue was purified by silica gel flash chromatography (AcOEt/hexane, 2 : 1) then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 2 : 1) to give epothilone B (**2**) (2 mg, 0.00395 mmol; 97%). The spectral data of **2** thus obtained were identical with those of an authentic sample.[2h]

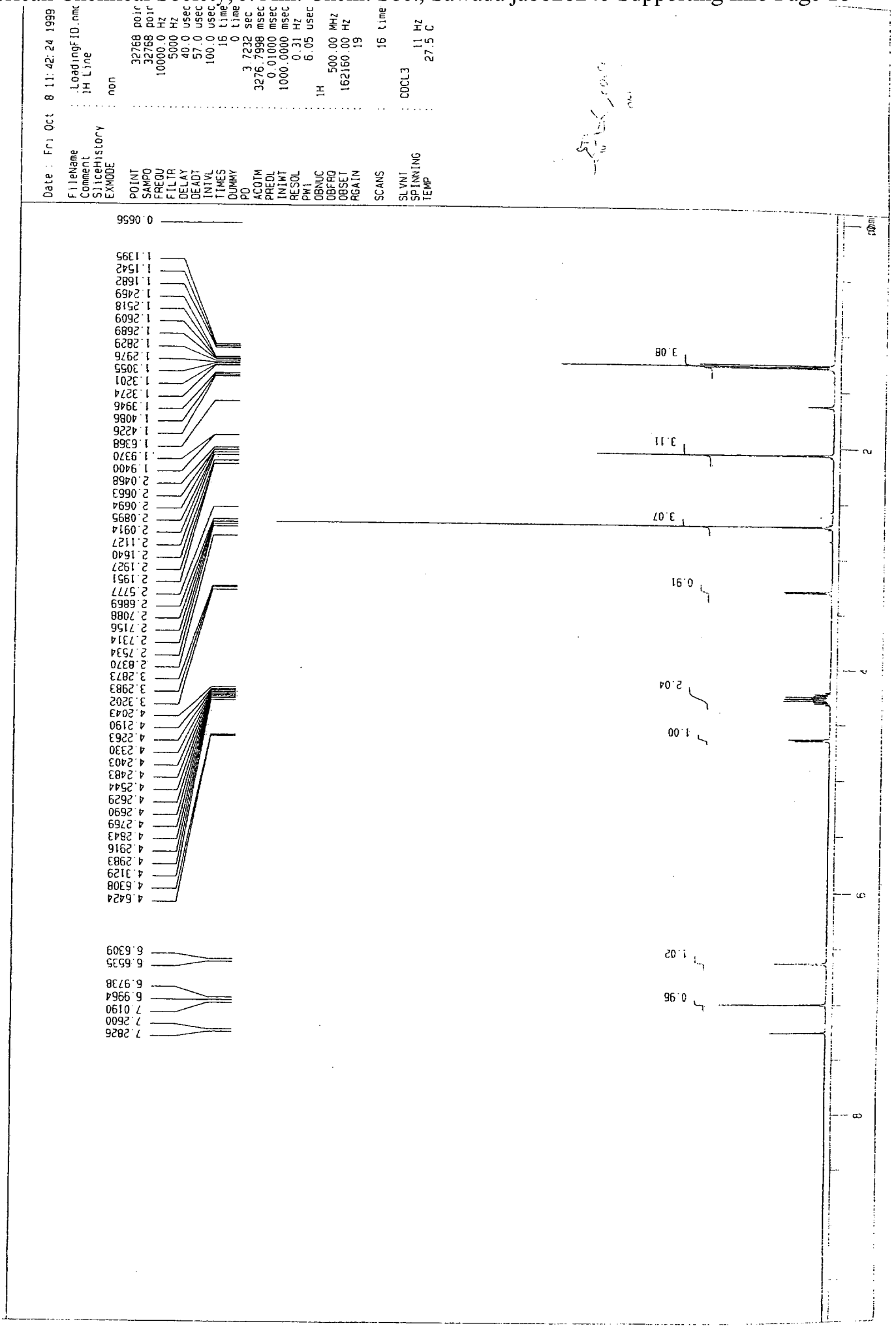
(2*R*,3*E*)-2-Hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenenitrile (6)

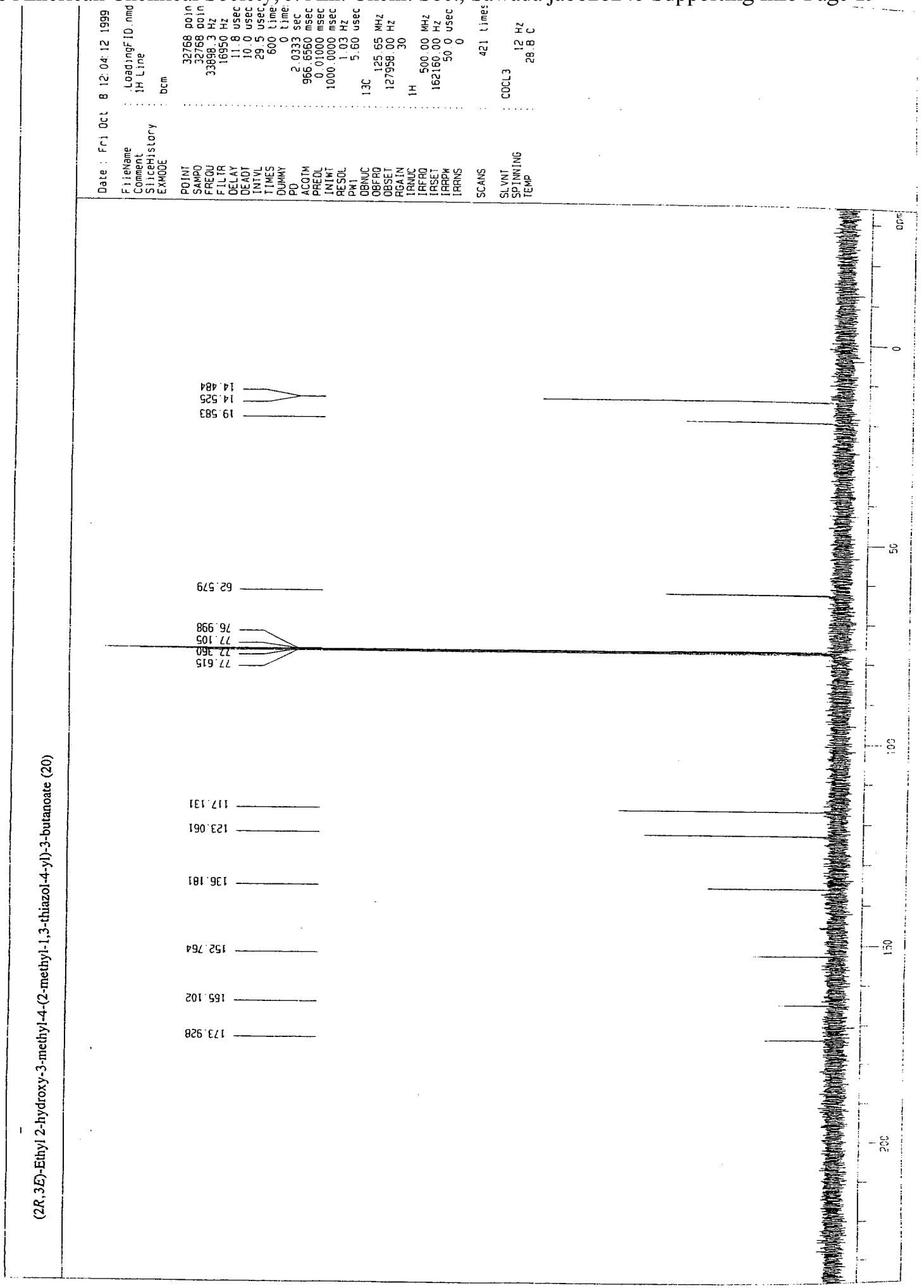


(2*R*,3*E*)-2-Hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenenitrile (6)

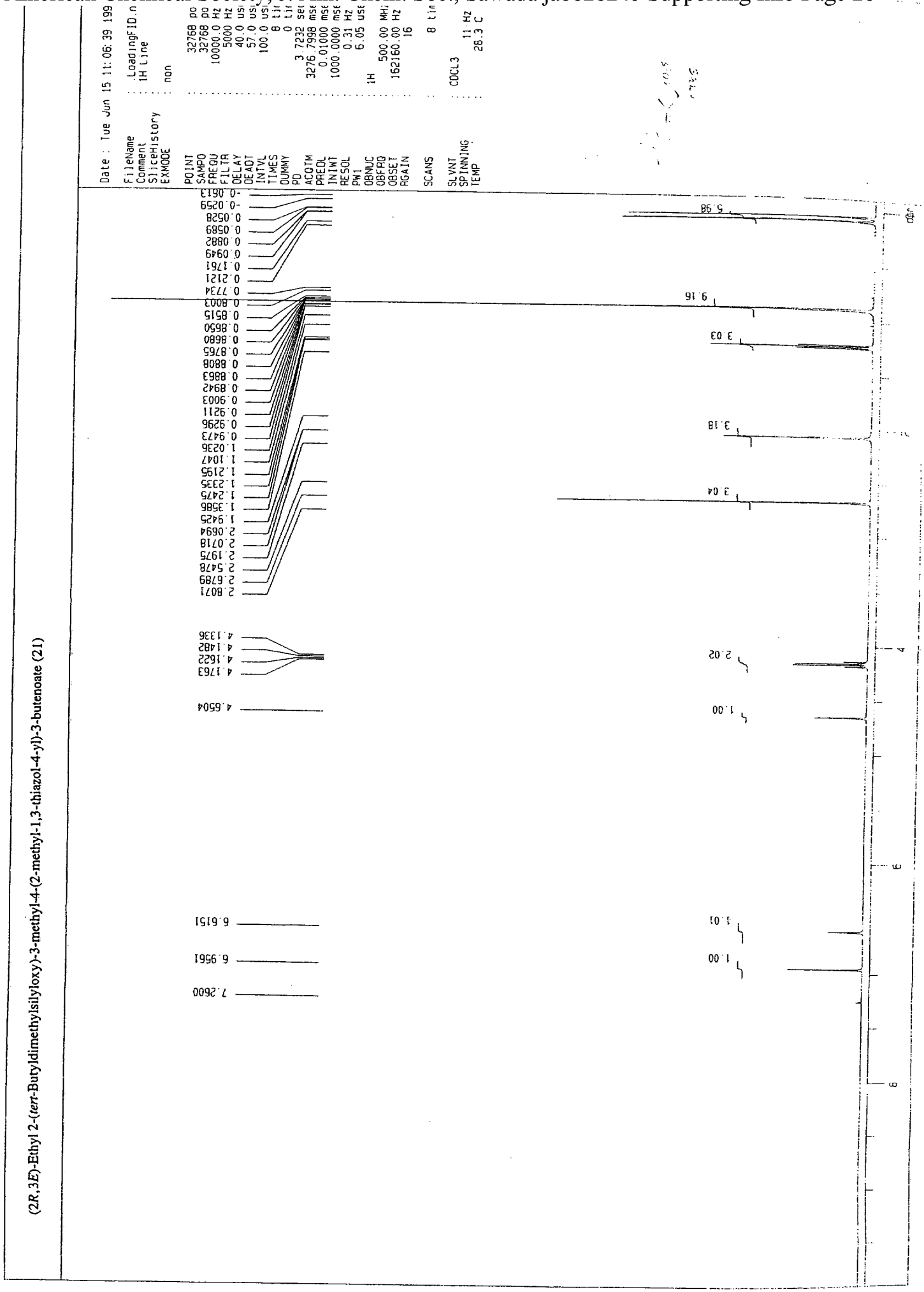


(2*R*,3*E*)-Ethyl 2-hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butanoate (20)

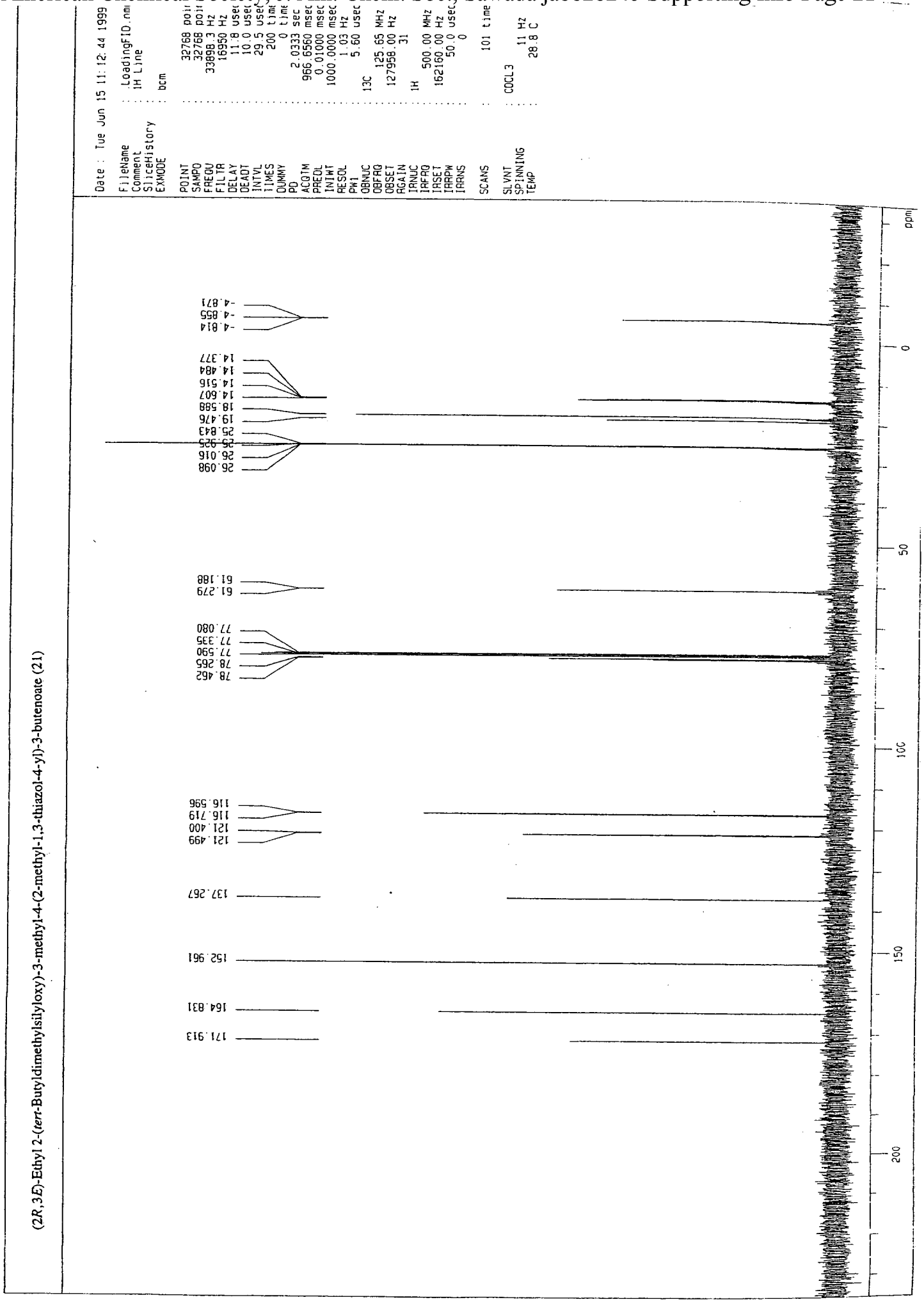




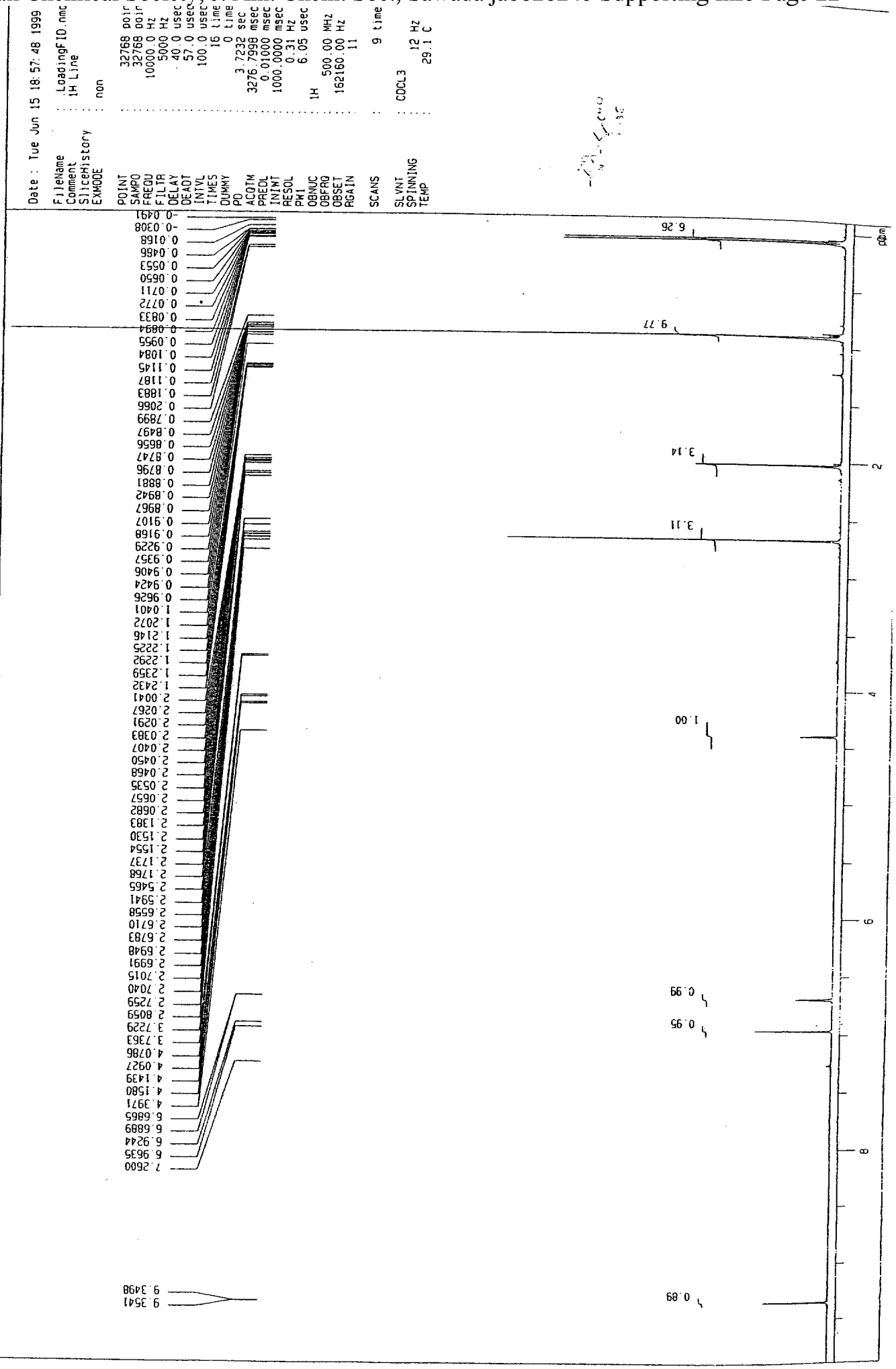
(2*R*,3*E*)-Ethyl 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenoate (21)



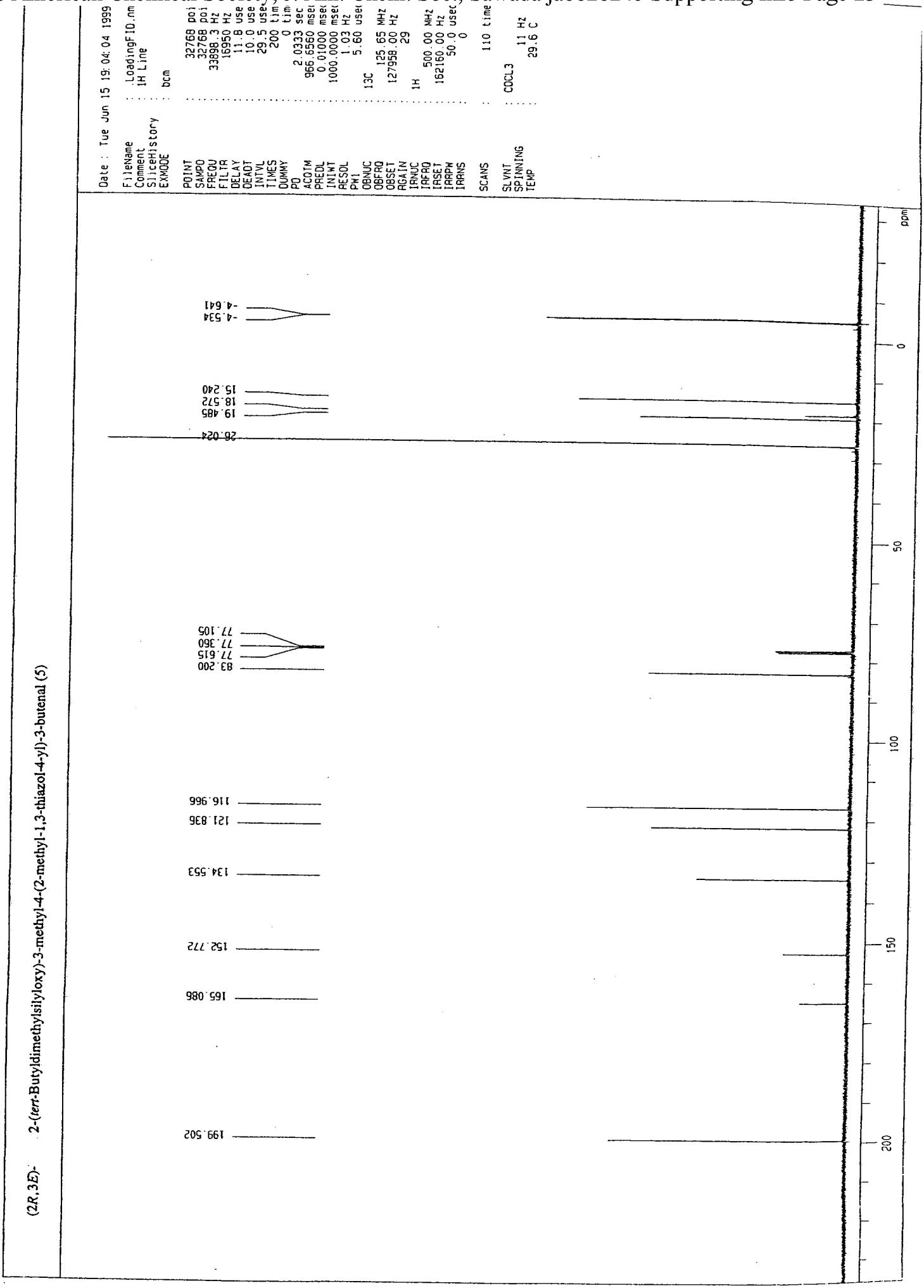
(2*R*,3*E*)-Ethyl 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenoate (21)

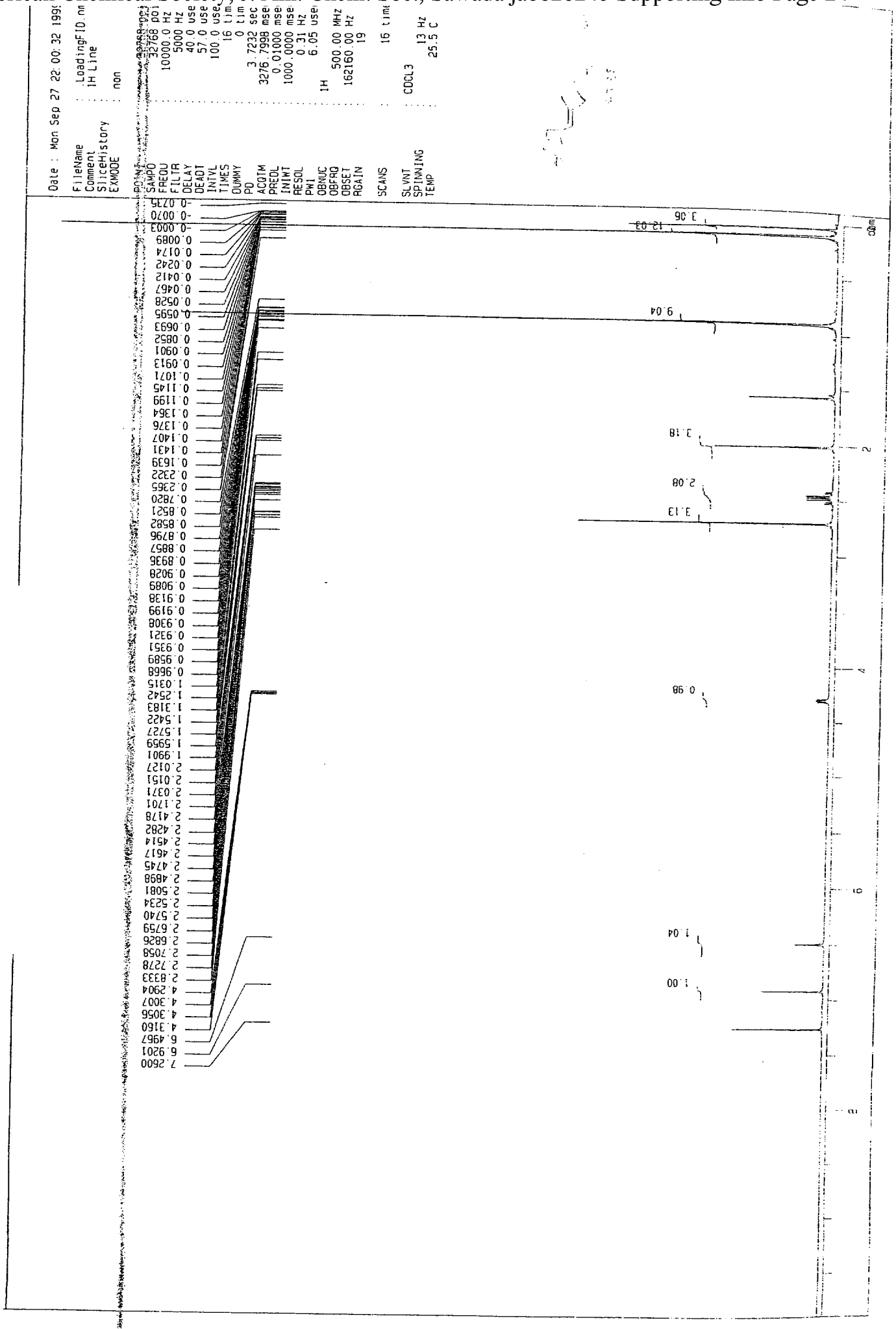


(2*R*,3*E*)- 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenal (5)



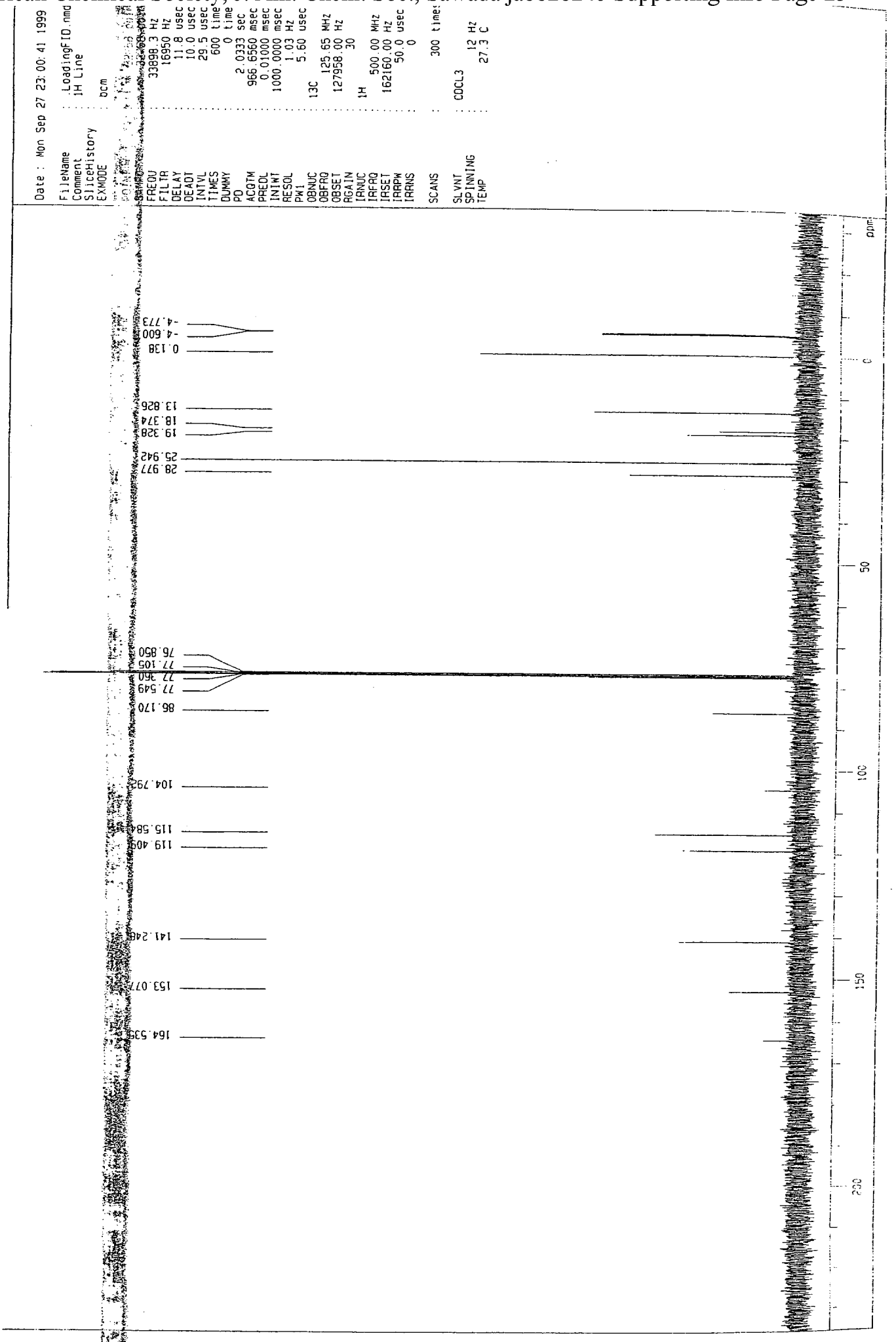
(2*R*,3*E*)- 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenal (5)

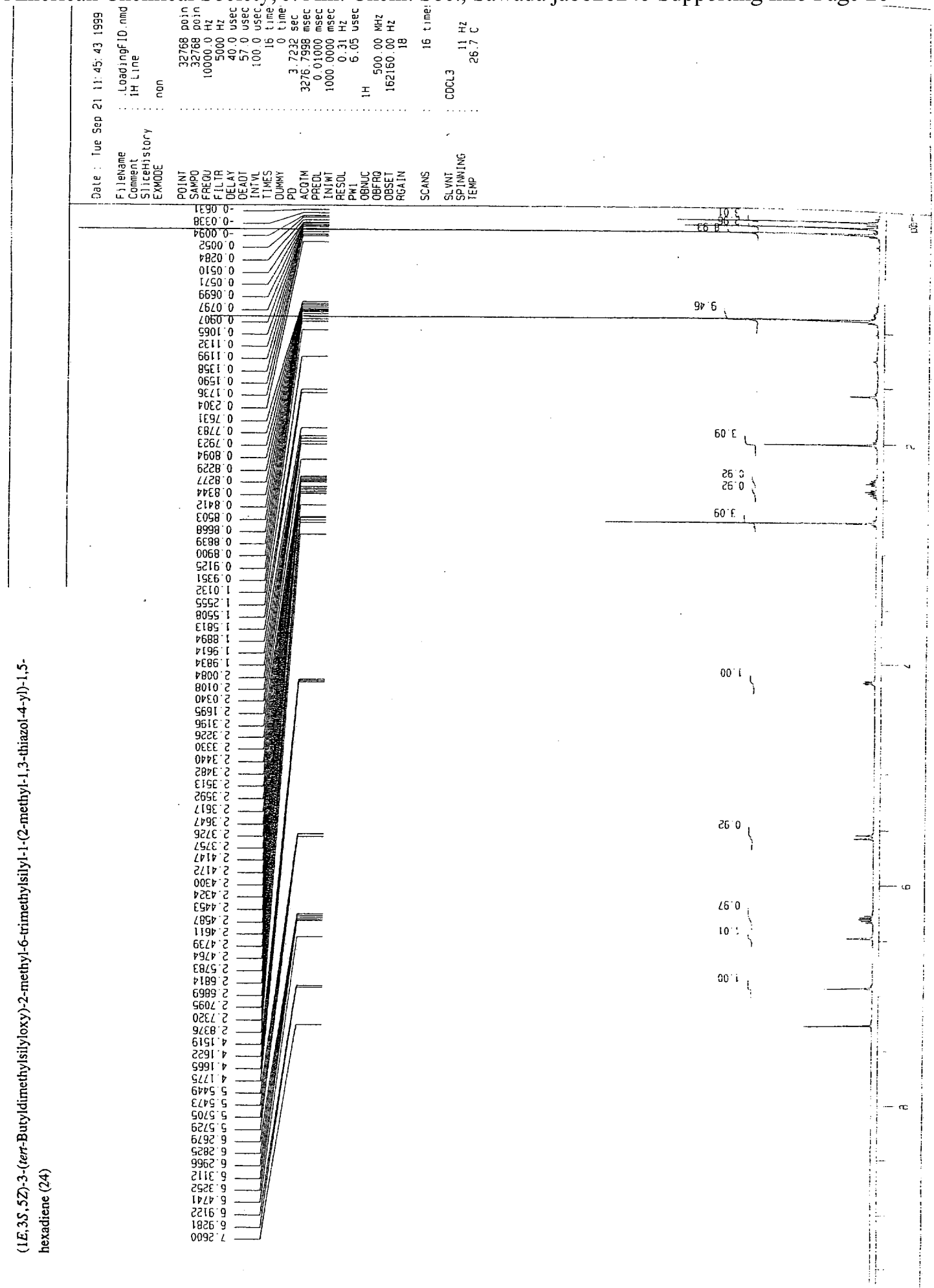




(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1-hexen-5-yne (23)

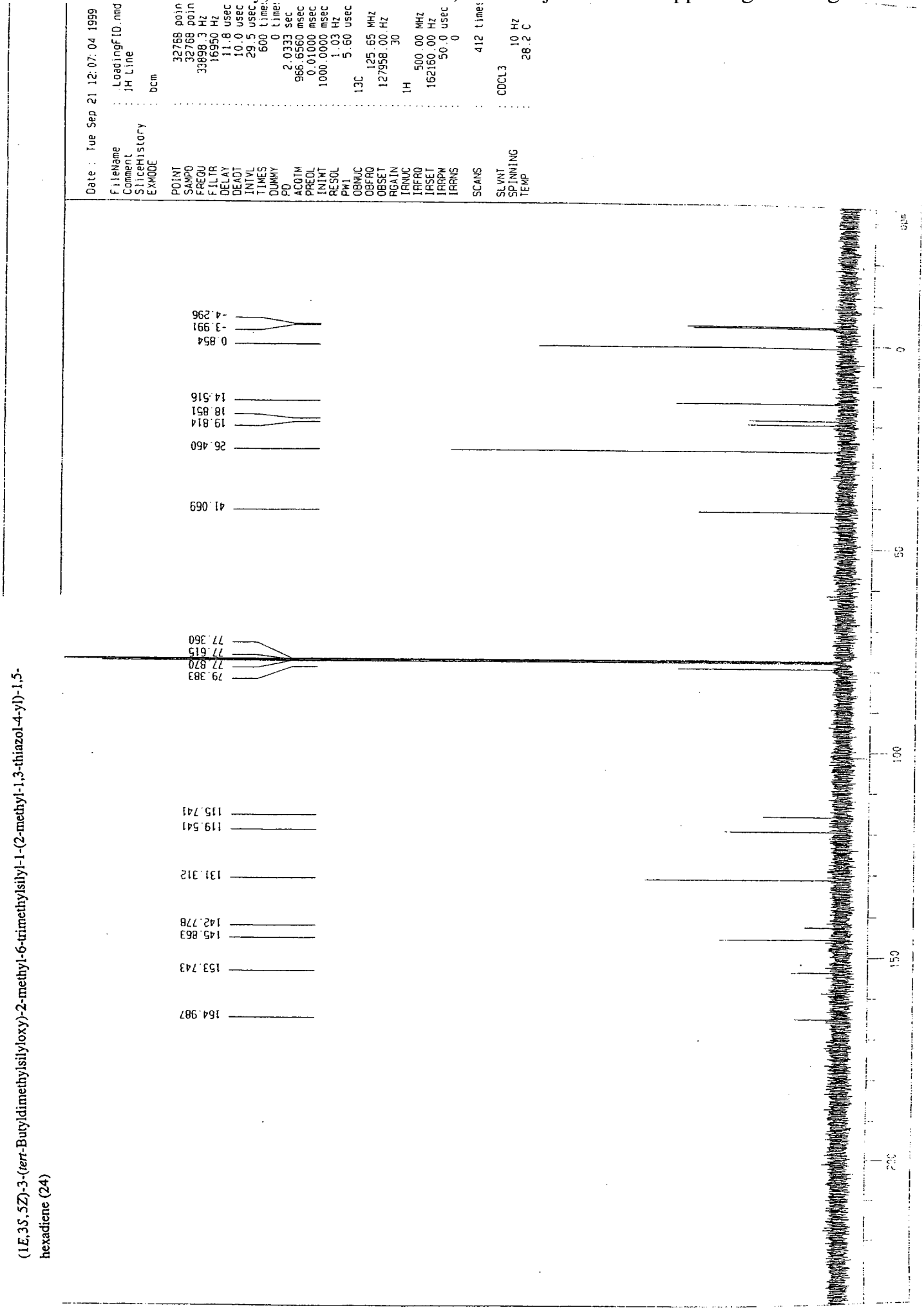
(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1-hexen-5-yne (23)



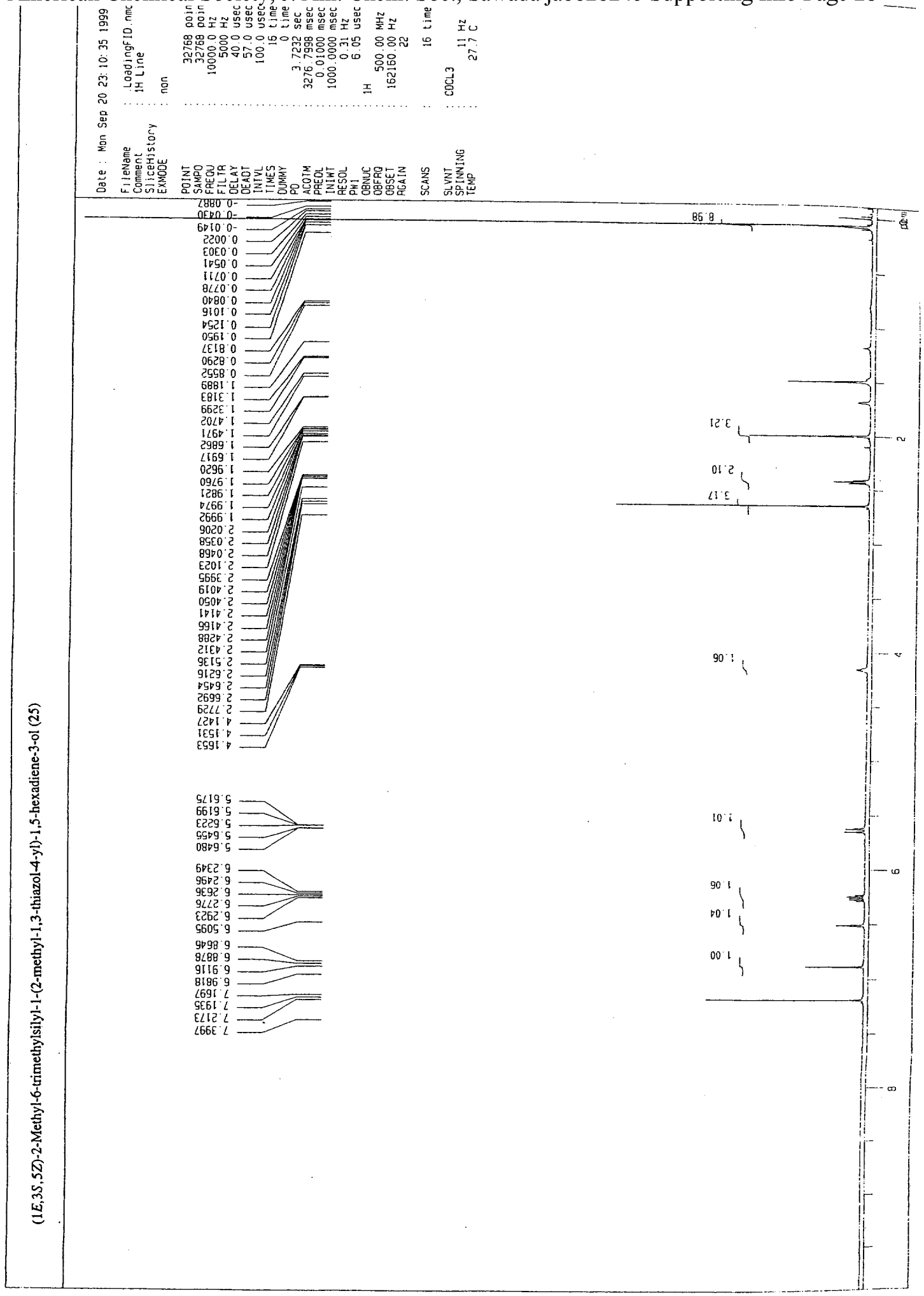


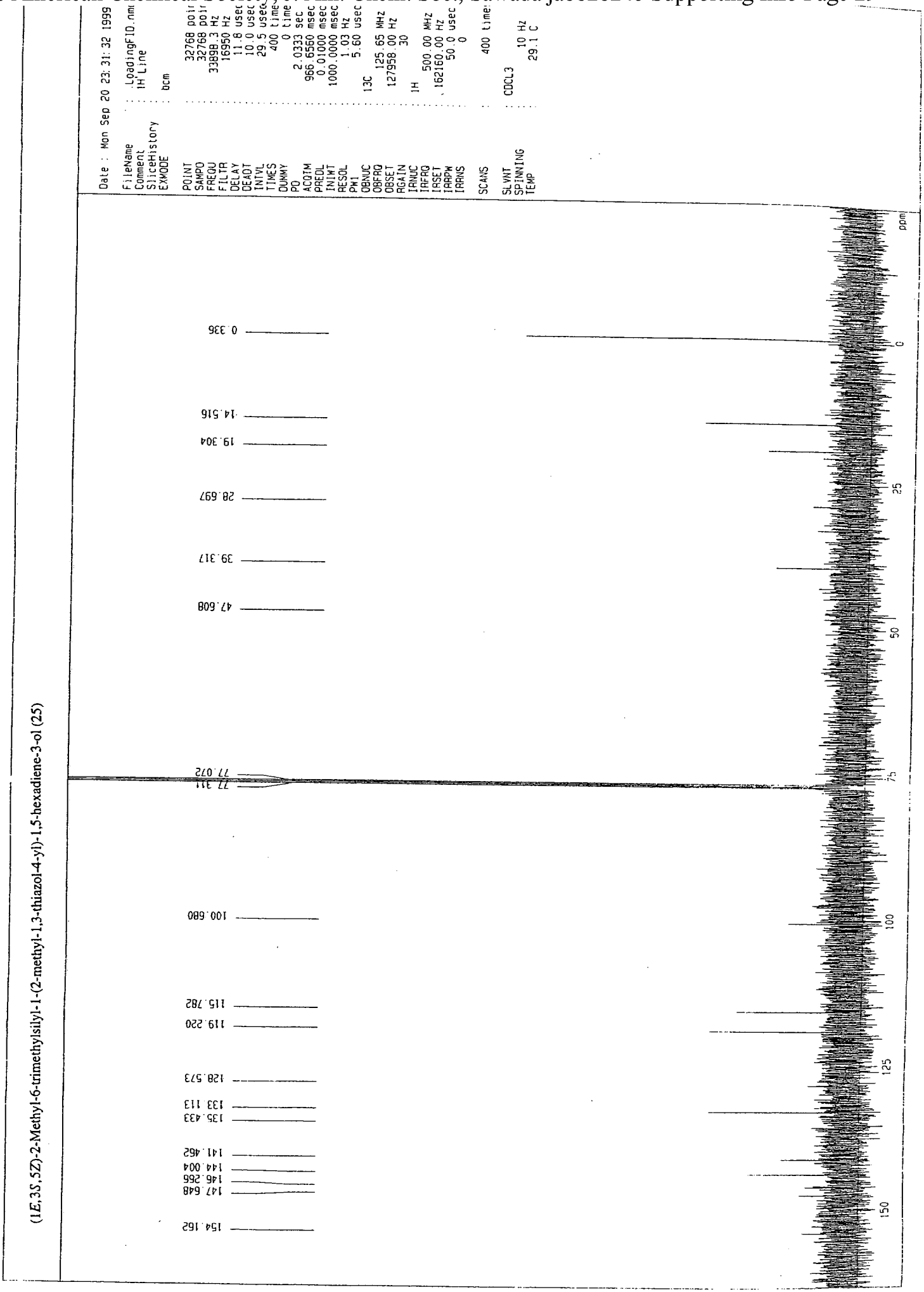
(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene (24)

(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene (24)

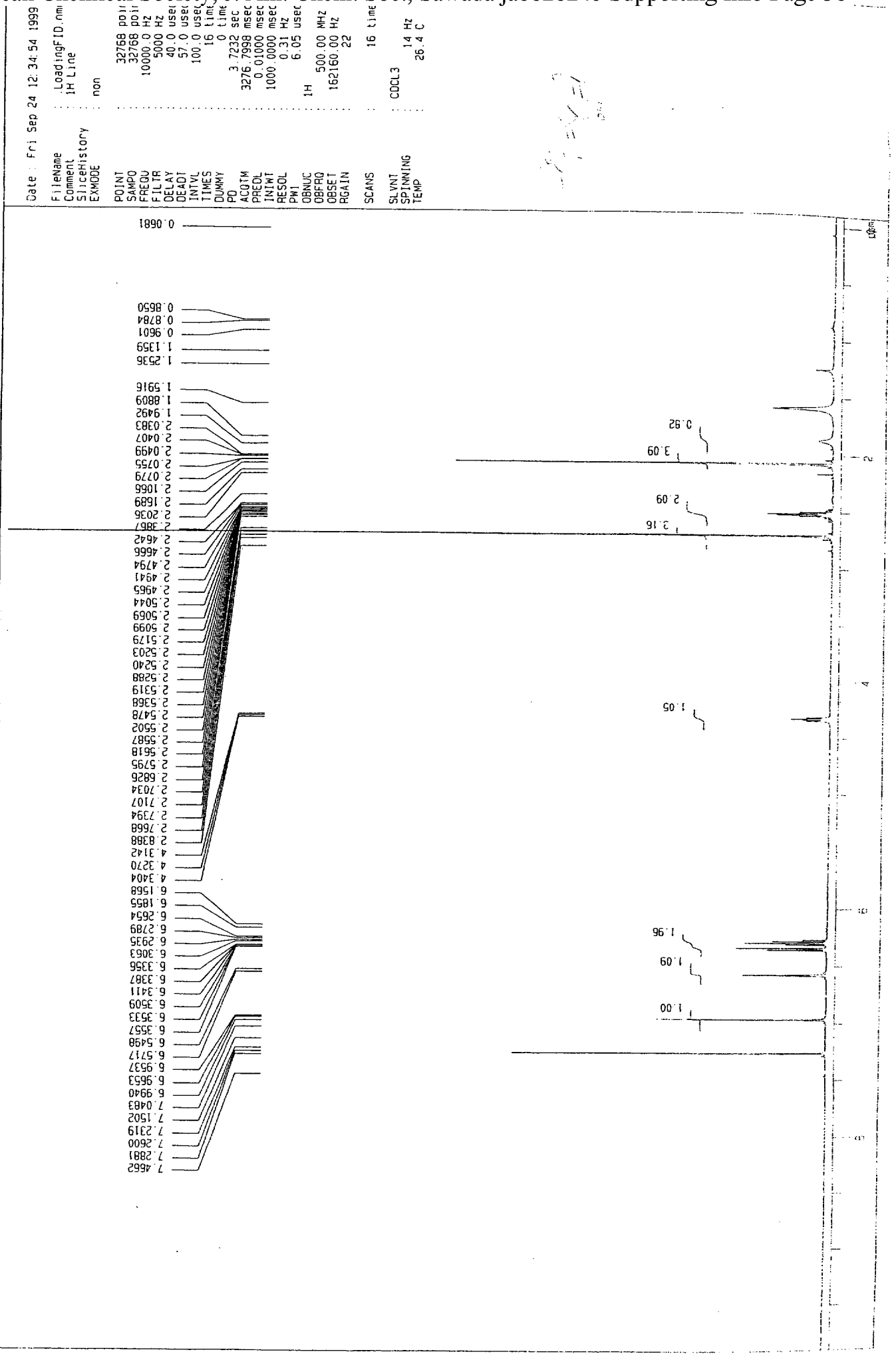


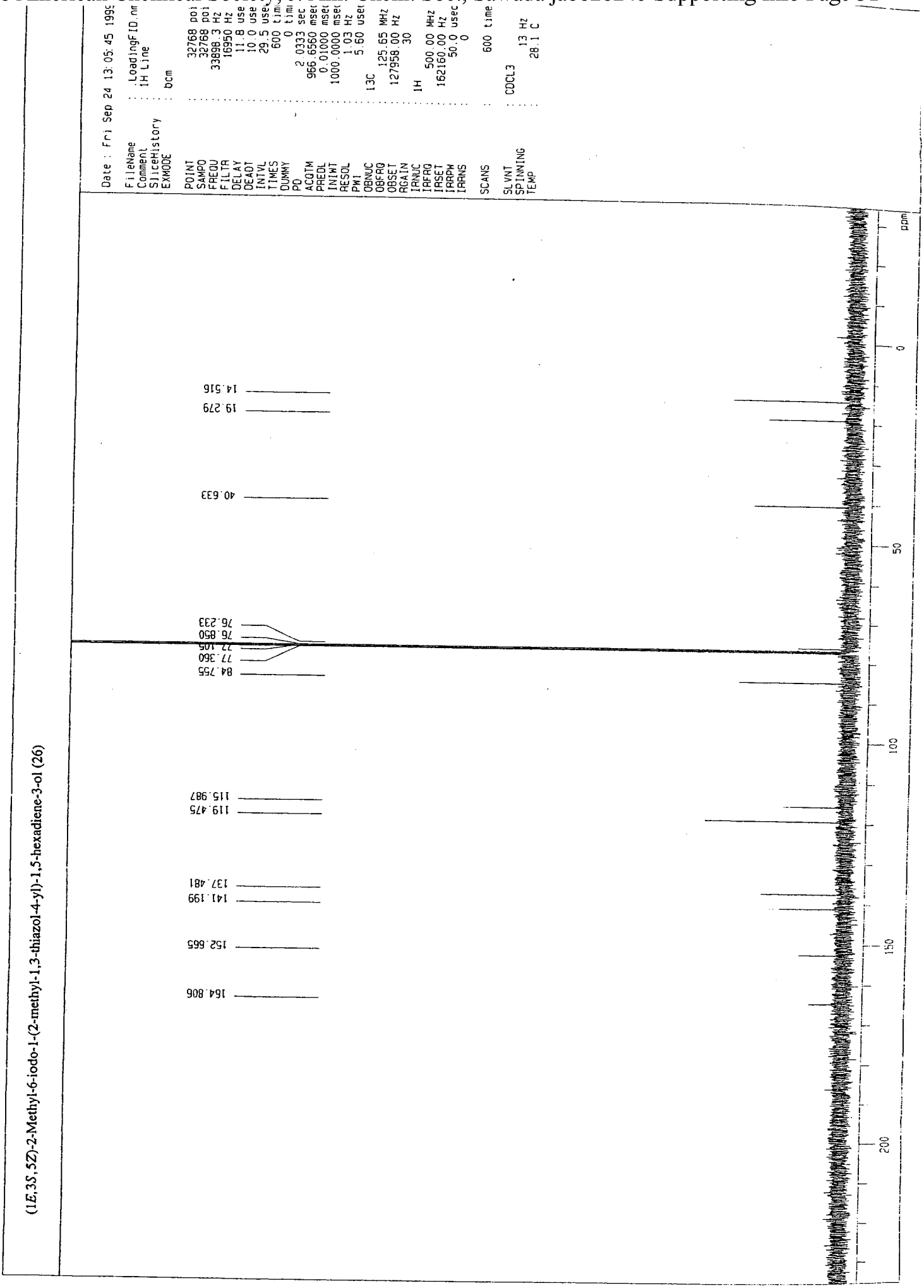
(1*E*,3*S*,5*Z*)-2-Methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene-3-ol (25)



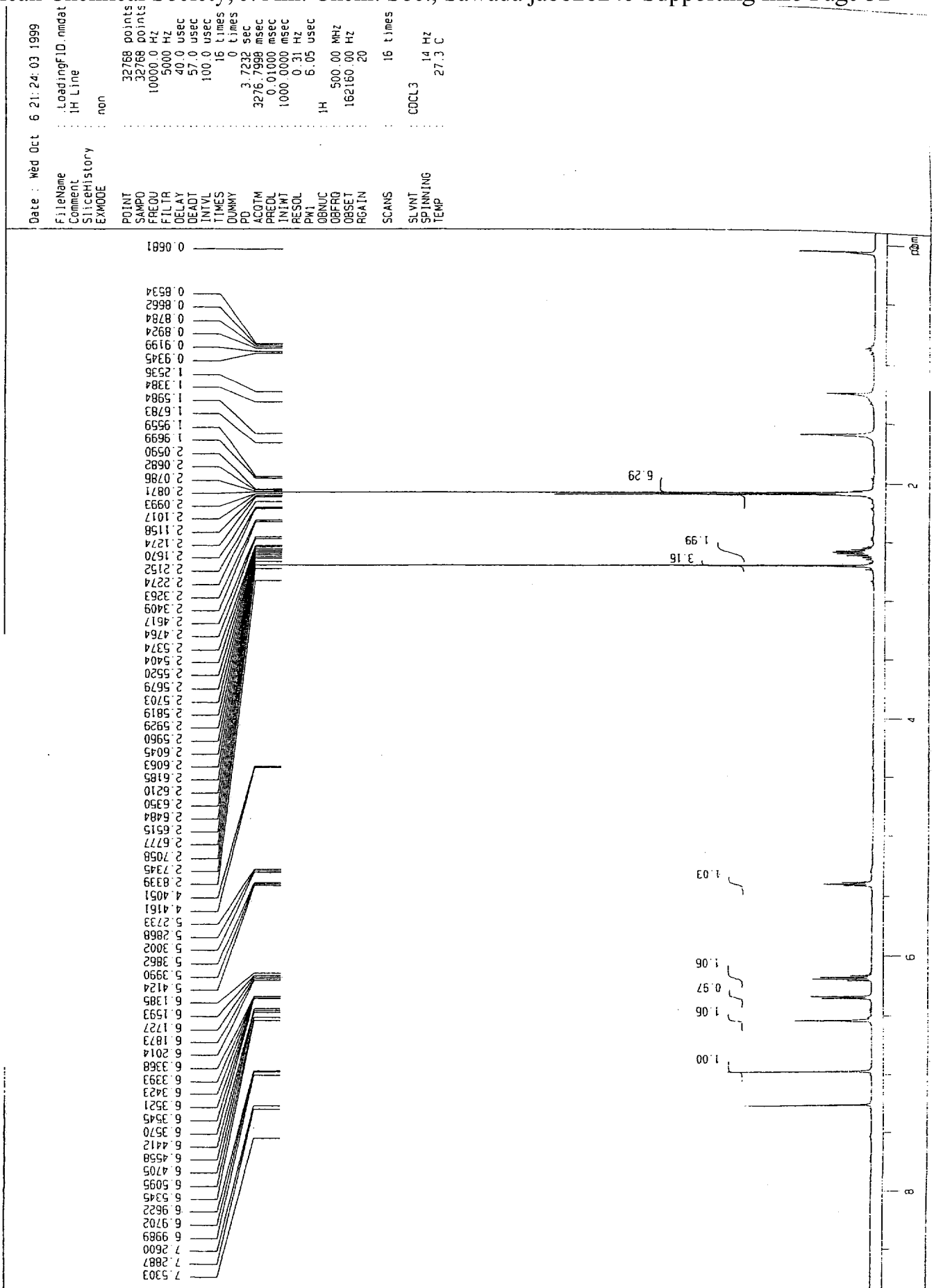


(1E,3S,5Z)-2-Methyl-6-iodo-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene-3-ol (26)

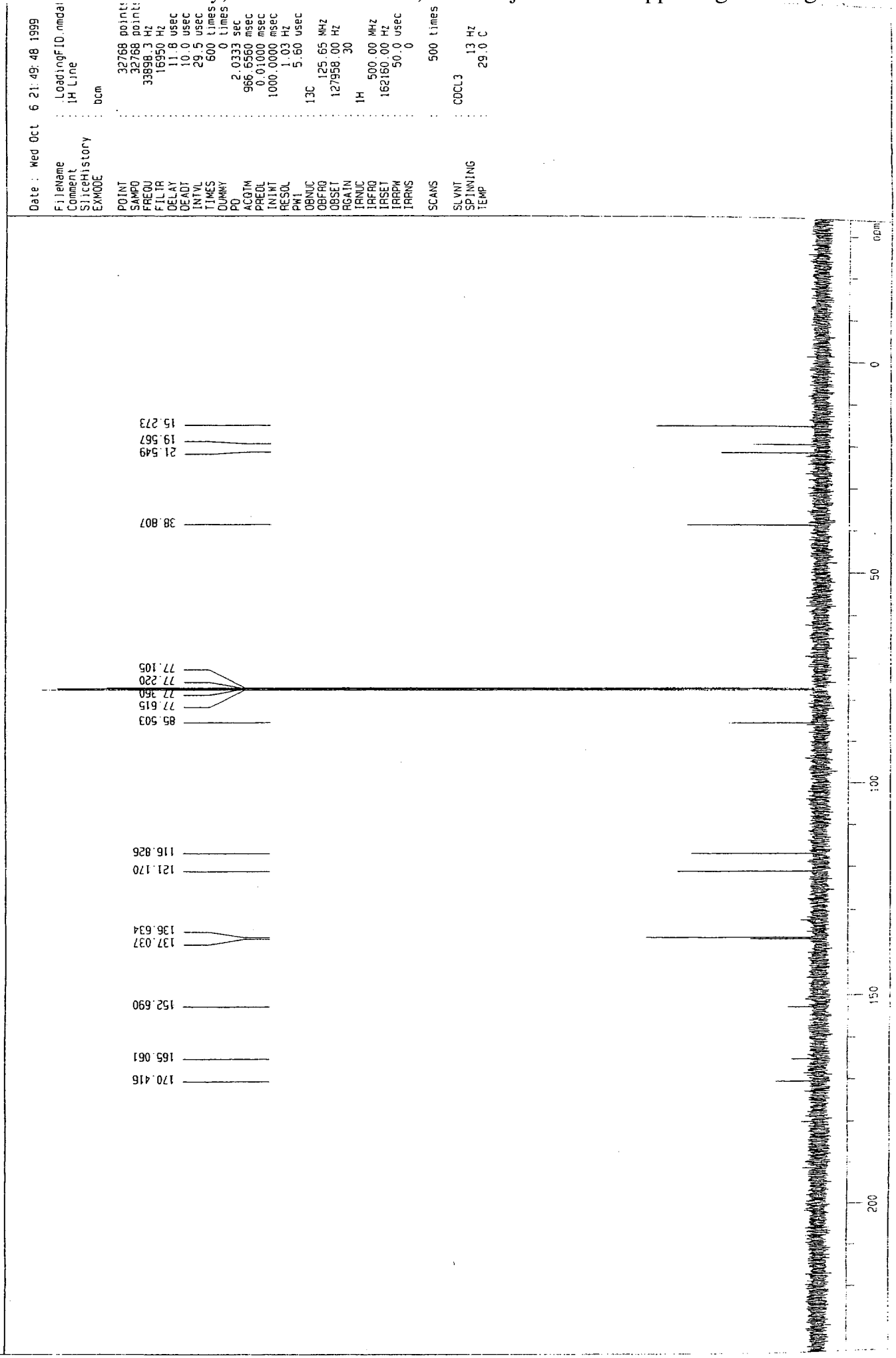




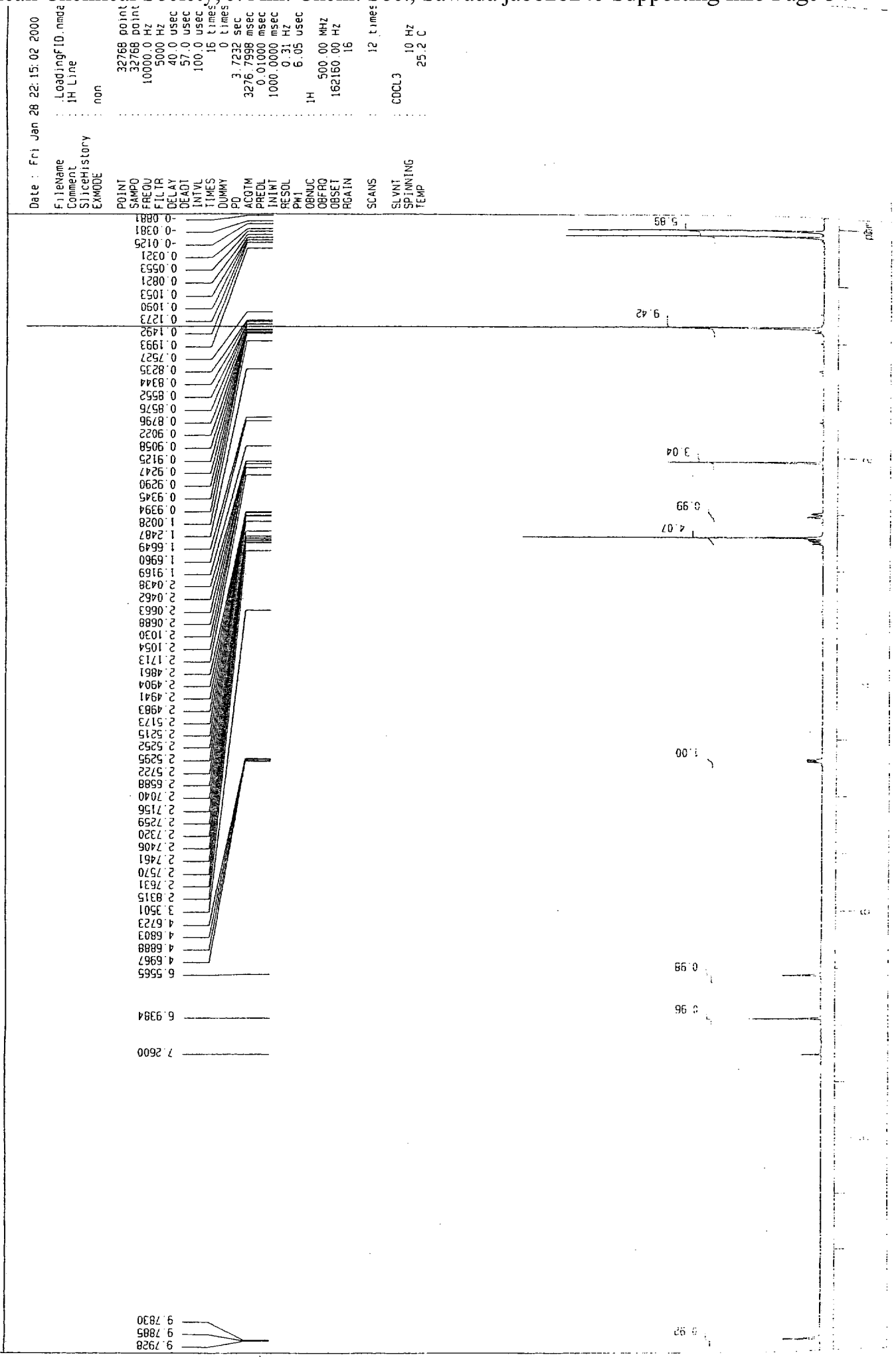
(1*E*,3*S*,5*Z*)-2-Methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene-3-yl acetate (Fragment A)



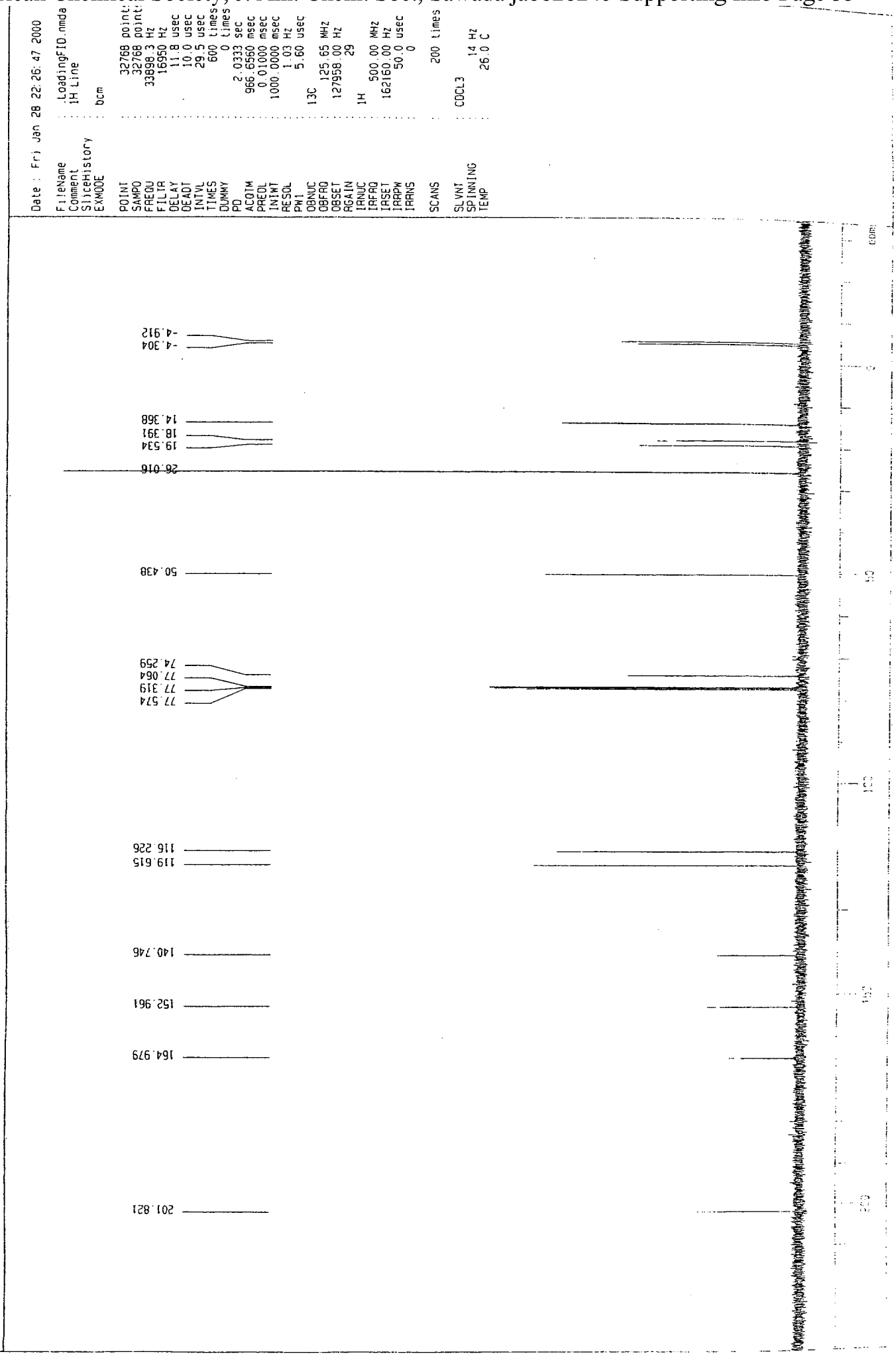
(1*E*,3*S*,5*Z*)-2-Methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene-3-yl acetate (Fragment A)



(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (27)

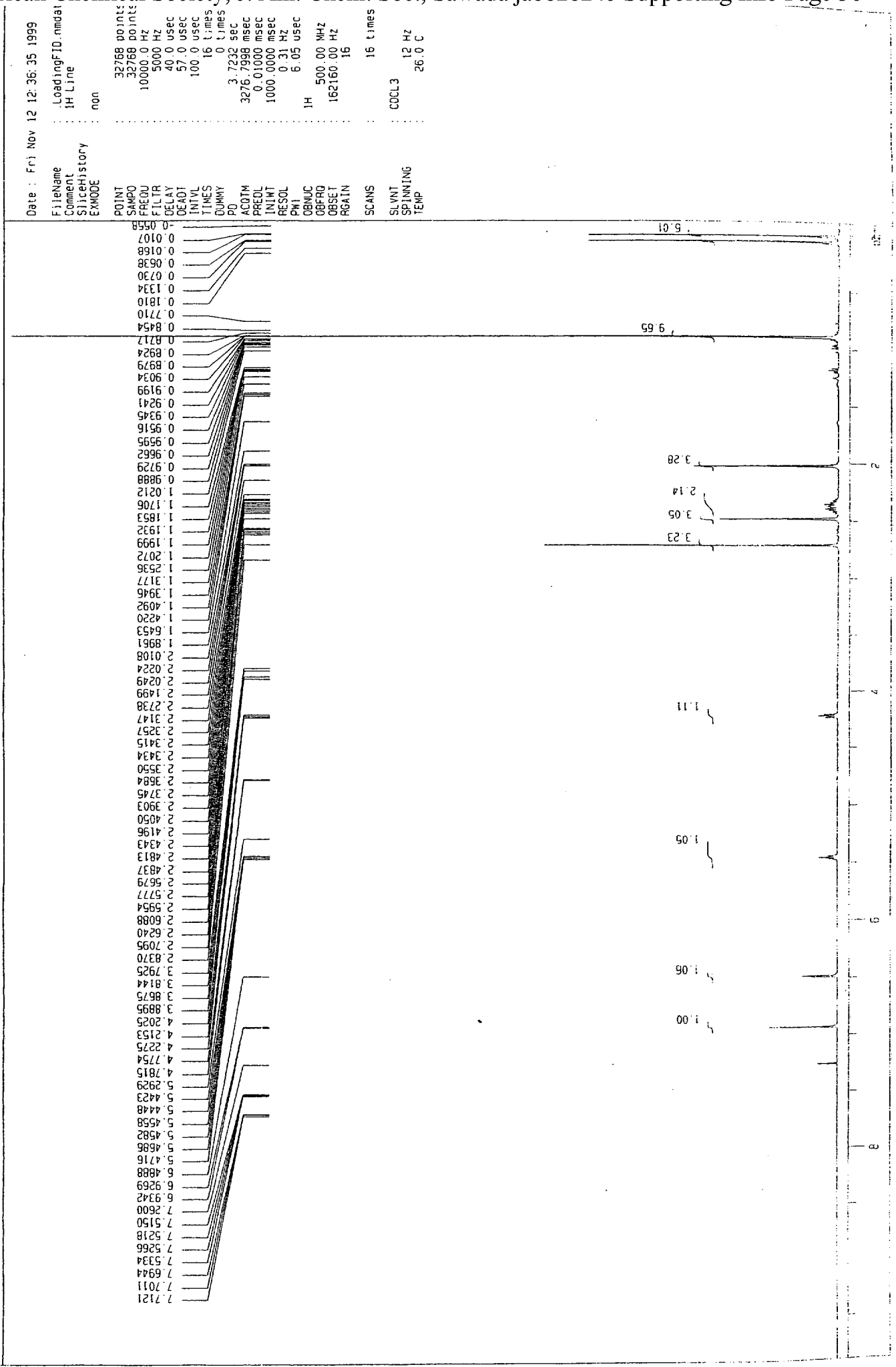


(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (27)



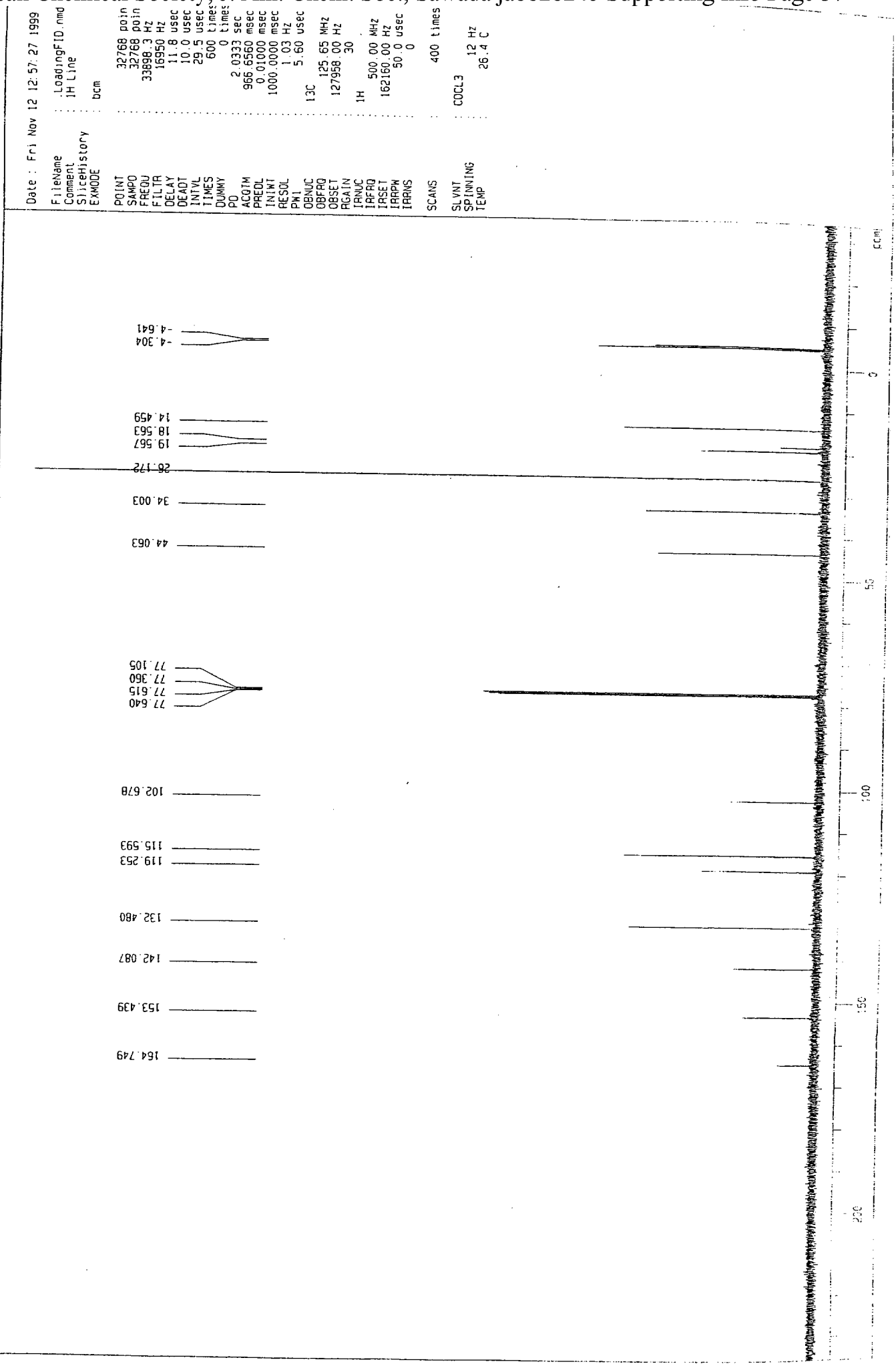
(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene

(28)

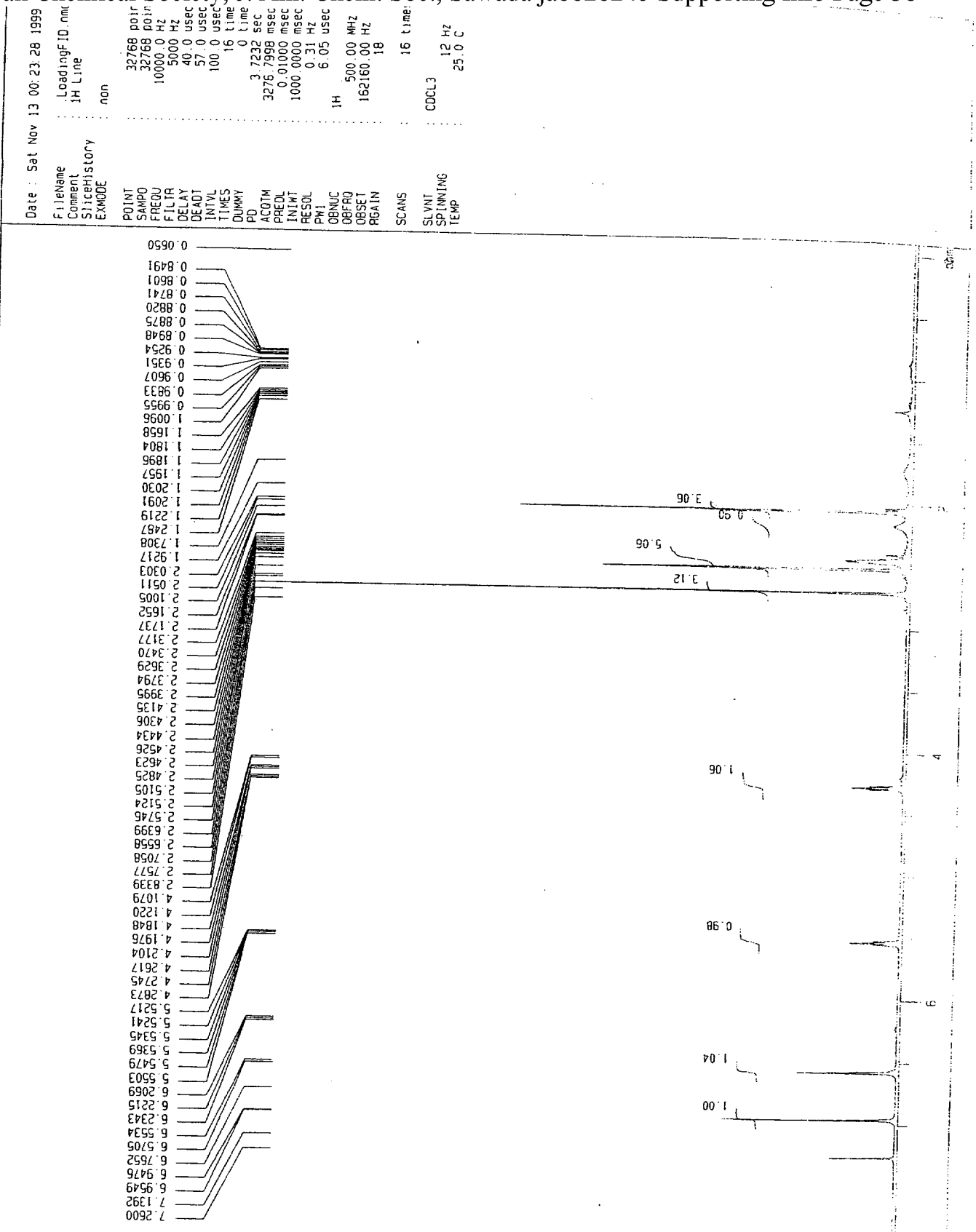


(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene

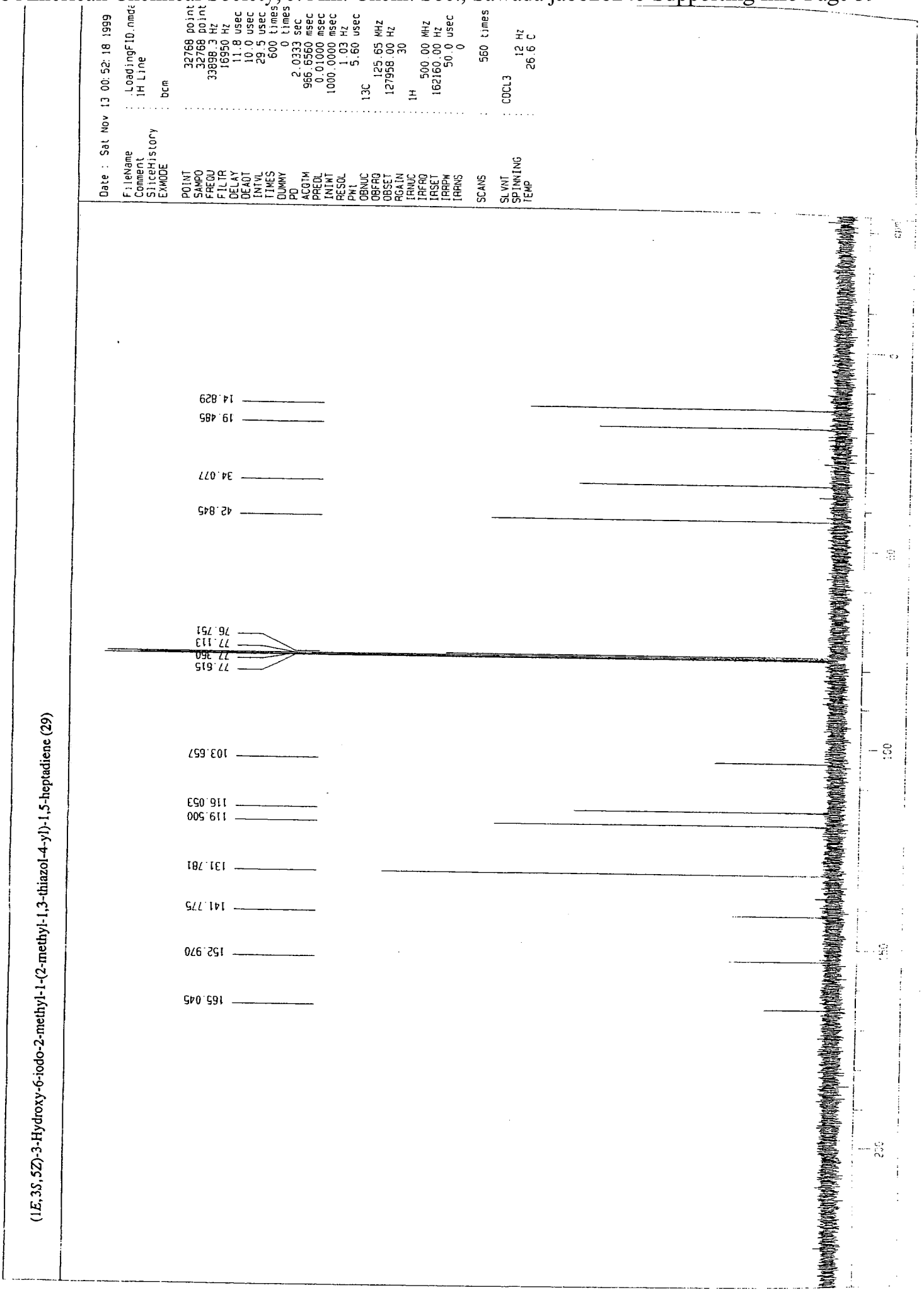
(28)



(1*E*,3*S*,5*Z*)-3-Hydroxy-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene (29)



(1*E*,3*S*,5*Z*)-3-Hydroxy-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene (29)



(1*E*,3*S*,5*Z*)-6-Iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene-3-yl acetate (Fragment B)