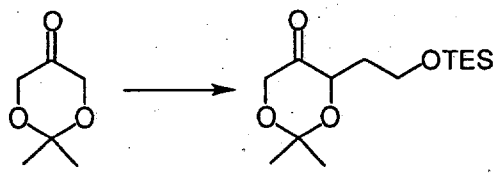
Synthesis of (*Z*)-2-Acyl-2-enals via Retrocycloadditions of 5-Acyl-4-alkyl-4*H*-1,3-dioxins: Application in the Total Synthesis of the Cytotoxin (+/-)-Euplotin A

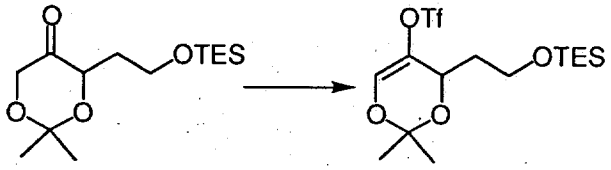
Ronald A. Aungst, Jr. and Raymond L. Funk*
Department of Chemistry, Pennsylvania State University, University Park, PA 16802



5

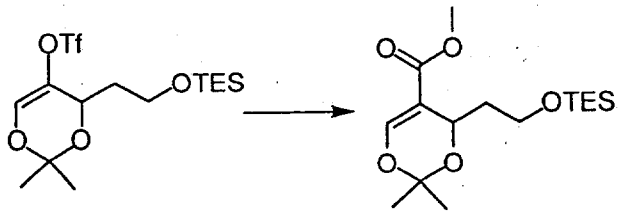
2,2-Dimethyl-4-[2-(triethylsilyloxy)-ethyl]-1,3-dioxan-5-one (5). To a solution of 2,2-dimethyl-1,3-dioxan-5-one (5.7 g, 43.6 mmol) in benzene (215 mL) were added molecular sieves (4Å, 6.0 g) and cyclohexylamine (10 mL, 87.0 mmol). The solution was stirred at rt overnight, filtered, and concentrated to yield the crude cyclohexylimine **4** (8.23 g). The imine was dissolved in THF (39 mL) and added dropwise to a solution of lithium diethylamide [formed by addition of n-BuLi (2.5 M in hexane, 14.6 mL, 36.5 mmol) to a solution of diethylamine (4.0 mL, 39.0 mmol) in THF (39 mL) at –35 C] at –78 °C. The solution was warmed to –35 °C over 2 h, recooled to –78 °C and a solution of 1-iodo-2-(triethylsilyloxy)ethane (6.97 g, 24.4 mmol) was added. The resultant mixture was warmed to rt over 2 h and quenched with saturated aqueous NH_4Cl. This mixture was stirred at rt overnight and extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 32) gave a colorless oil (6.12 g, 87%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.58 (qd, J = 2.3, 7.4 Hz, 6 H), 0.95 (t, J = 7.4 Hz, 9 H), 1.42 (s, 3 H) 1.45 (s, 3 H), 1.68 (ddt, J = 4.8, 8.8, 9.5 Hz, 1 H), 2.10 (dddd, J = 1.3, 3.9, 4.8, 9.5 Hz, 1 H), 3.70 (dd, J = 1.3, 4.8 Hz, 1 H), 3.74 (d, J = 4.8 Hz, 1 H), 3.98 (d, J = 16.9

^{13}C NMR (50 MHz, $CDCl_3$) δ 4.4, 6.8, 23.5, 24.1, 31.8, 57.9, 66.6, 71.3, 100.7, 209.9; IR (neat) 2935, 1749 cm^{-1}; HRMS (MNa^+) calcd for $C_{14}H_{28}O_4SNa$ 311.1655, found 311.1651.



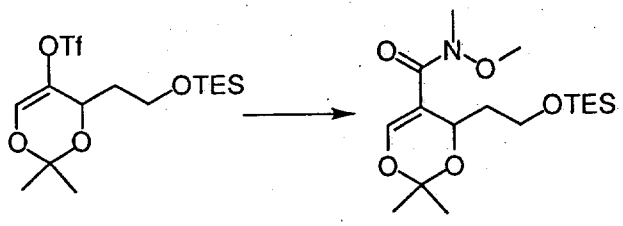
5

Trifluoromethane sulfonic acid 2,2-dimethyl-4-[2-(triethylsilyloxyl-ethyl]-4*H*-[1,3]dioxin-5-yl ester. A solution of ketone **5** (1.00 g, 3.47 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.61 g, 4.51 mmol) in THF (17 mL) was added dropwise over 1 h to a solution of NaHMDS (1.0 M in THF, 4.51 mL, 4.51 mmol) in THF (15 mL) at −78 °C. The mixture was warmed slowly over 2 h to rt and poured onto saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane and the combined extracts were washed with saturated aqueous Na_2CO_3, dried (Na_2SO_4), and concentrated. The crude material was purified by florisil chromatography (hexane, florisil deactivated with 10% triethylamine by slurrying the support in the solvent and adding 10% v/v of Et_3N) to give a colorless oil (1.24 g, 93%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.58 (qd, *J* = 1.3, 7.6 Hz, 6 H), 0.95 (t, *J* = 7.6 Hz, 9 H), 1.49 (s, 3 H), 1.52 (s, 3 H), 1.73 (ddt, *J* = 4.8, 9.5, 14.0 Hz, 1 H), 2.08 (dtd, *J* = 2.8, 9.5, 14.0 Hz, 1 H), 3.76 (m, 2 H), 4.62 (dt, *J* = 1.6, 9.5 Hz, 1 H), 6.71 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (50 MHz, C_6D_6) δ 4.7, 6.9, 20.5, 27.1, 34.3, 57.8, 65.5, 101.4, 120.0 (q, *J* = 240 Hz), 132.2, 137.6; IR (neat) 1680, 2957 cm^{-1}; HRMS (MNa^+) calcd for $C_{15}H_{27}O_6SSiF_3Na$ 443.1147, found 443.1168.



6a

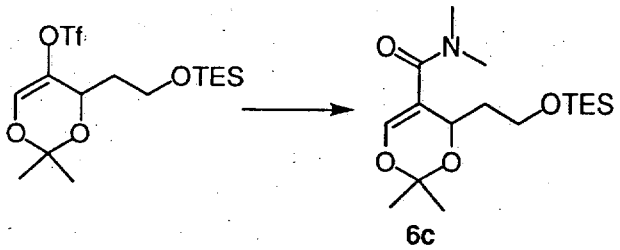
2,2-Dimethyl-4-[2-(triethylsilyloxy)-ethyl]-4*H*-[1,3]dioxine-5-carboxylic acid methyl ester (6a). To a solution of the triflate (2.00 g, 5.2 mmol) in methanol (8.5 mL) and THF (173 mL) were added dppp (161 mg, 0.39 mmol), diisopropylethylamine (2.0 mL, 11.4 mmol), and K_2CO_3 (3.60 g, 26.0 mmol) followed by palladium (II) acetate (88 mg, 0.39 mmol). The solution was placed under a CO atmosphere (balloon pressure) and stirred at rt overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexanes, 1 : 32, silica-gel deactivated with 10% triethylamine) gave a colorless oil (1.48 g, 86%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.55 (qd, J = 1.3, 7.9 Hz, 6 H), 0.92 (t, J = 7.9 Hz, 9 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.78 (tdd, J = 5.0, 6.4, 8.1 Hz, 1 H), 2.28 (dtd, J = 2.7, 6.4, 7.6 Hz, 1 H), 3.53-3.80 (m, 2 H), 3.65 (s, 3 H), 4.58 (ddd, J = 1.0, 2.7, 8.1 Hz, 1 H), 7.47 (d, J = 1.0 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.3, 6.6, 21.5, 27.4, 35.6, 50.8, 58.7, 65.3, 100.9, 107.8, 152.8, 165.8; IR (neat) 1631, 1713 cm^{-1}; HRMS (MNa^+) calcd for $C_{16}H_{30}O_5SiNa$ 353.1760, found 353.1768.



6b

2,2-Dimethyl-4-[2-(triethylsilyloxy)-ethyl]-4*H*-[1,3]-dioxine-5-carboxylic acid methoxy-methylamide (6b). To a solution of the triflate (370 mg, 0.096 mmol) in DMF (19 mL) were added dppp (79 mg, 0.19 mmol), N,O-dimethylhydroxylamine (712 mg, 19.2 mmol) and Et_3N (54 mL, 0.384 mmol) followed by palladium (II) acetate (43 mg, 0.19 mmol). The solution was placed under a CO atmosphere (balloon pressure)

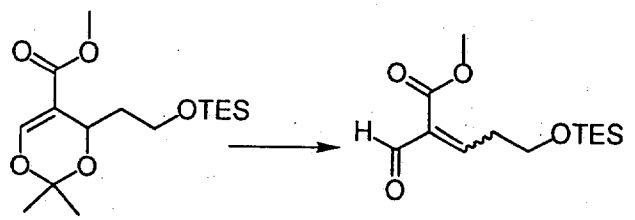
and stirred at rt overnight. The mixture was poured onto a saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by florisil chromatography (ethyl acetate-hexanes, 1 : 3, florisil deactivated with 10% triethylamine) gave a colorless oil (280 mg, 81%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.58 (qd, J = 1.3, 7.9 Hz, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 1.47 (s, 3 H), 1.48 (s, 3 H), 1.65 (tdd, J = 4.3, 8.5, 11.5 Hz, 1 H), 2.00 (dtd, J = 2.6, 7.9, 11.5 Hz, 1 H), 3.22 (s, 3 H), 3.65 (s, 3 H) 3.67-3.81 (m, 2 H), 4.74 (ddd, J = 1.4, 2.6, 8.5 Hz, 1 H), 7.22 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.3, 6.7, 21.5, 27.6, 32.6, 35.9, 58.8, 60.9, 65.4, 100.2, 110.9, 148.2, 167.0; IR (neat) 1651, 1615 cm^{-1}; HRMS (MNa^+) calcd for $C_{17}H_{33}O_5NSiNa$ 382.2026, found 382.2016.



6c

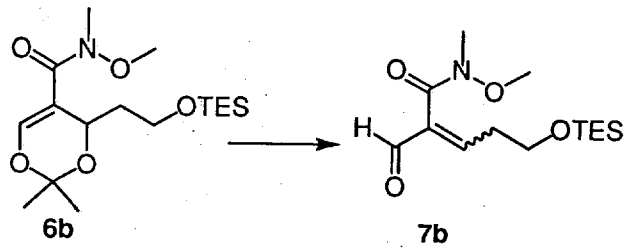
2,2-Dimethyl-4-[2-(triethylsilyloxy)-ethyl]-4*H*-[1,3]dioxine-5-carboxylic acid dimethylamide (6c). To a solution of the triflate (852 mg, 2.22 mmol) in THF (74 mL) were added dppp (68 mg, 0.17 mmol), dimethylamine (2.0 M in THF, 11 mL,), and diisopropylethylamine (850 mL, 4.88 mmol) followed by palladium (II) acetate (37 mg, 0.17 mmol). The solution was placed under a CO atmosphere (balloon pressure) and stirred at rt overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude material was purified by silica-gel chromatography (ethyl acetate-hexanes, 1 : 3, silica-gel deactivated with 10% triethylamine) to give a colorless oil (763 mg, 90%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.53 (q, J = 7.6 Hz, 6 H), 0.89 (t, J = 7.6 Hz, 9 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.63 (tdd, J = 4.5, 6.5, 9.2 Hz, 1 H), 1.85 (dtd, J = 2.6, 7.9, 9.2 Hz, 1 H), 2.97 (s, 6 H), 3.57-3.77 (m, 2 H), 4.66 (ddd, J = 1.3, 2.6, 9.2 Hz, 1 H), 6.62 (d, J = 1.3 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.3, 6.6,

21.8, 27.6, 35.6, 36.9, 58.7, 65.5, 100.1, 111.6, 143.6, 168.1; IR (neat) 1649, 1622 cm^{-1}.



6a 7a

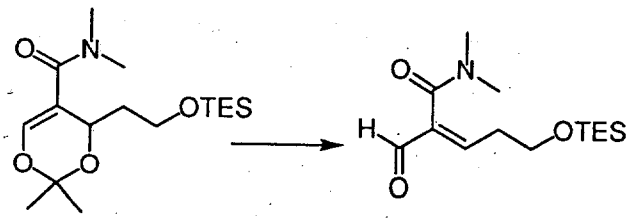
2-Formyl-5-(triethylsilyloxy)-pent-2-enoic acid methyl ester (7a). A solution of ester **6a** (85 mg, 0.26 mmol) in $CDCl_3$ (1 mL) was heated at 50 °C for 36 h and concentrated to give a colorless oil (70 mg, 99%) as an inseparable mixture of stereoisomers (*Z* : *E*, 72 : 28); ^1H NMR (200 MHz, $CDCl_3$) δ 0.60 (q, *J* = 8.1 Hz, 6 H), 0.92 (t, *J* = 8.1 Hz, 9 H), major 2.81 (q, *J* = 7.5 Hz, 2 H), minor 2.94 (q, *J* = 7.1 Hz, 2 H), 3.65-3.88 (m, 2 H), minor 3.82 (s, 3 H), major 3.83 (s, 3 H), major 7.22 (t, *J* = 7.5 Hz, 1 H), minor 7.54 (td, *J* = 2.7, 7.1 Hz, 1 H), major 9.65 (s, 1 H), minor 10.08 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ 4.3, 6.6, 33.7, 52.0, 60.8, 134.6, 157.0, 189.1; minor isomer: 4.3, 6.6, 33.0, 52.1, 61.0, 130.0, 157.3, 190.8; IR (neat) 1703, 1720 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{25}O_4Si$; 273.1522, found 273.1533.



6b 7b

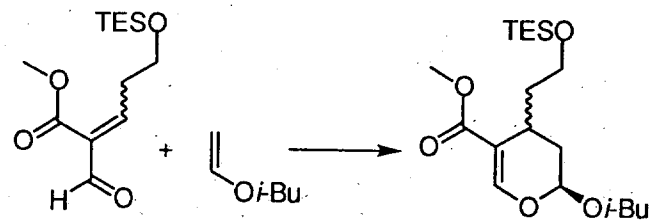
2-Formyl-5-(triethylsilyloxy)-pent-2-enoic acid methoxy-methylamide (7b). A solution of methoxy-methyl amide **6b** (690 mg, 1.92 mmol) in toluene (19 mL) was heated at 100 °C for 2 h. The solution was concentrated and the crude material was purified by silica-gel chromatography (ethyl acetate-hexane, 1 : 3) to give a colorless oil (533 mg, 93%) as an inseparable mixture of stereoisomers(*Z* : *E*, 97 : 3); ^1H NMR (200 MHz, $CDCl_3$) δ 0.61 (qd, *J* = 1.3, 7.4 Hz, 6 H), 0.95 (t, *J* = 7.4 Hz, 9 H), major 2.61 (q, *J* = 6.2 Hz, 2 H), minor 2.88 (q, *J* = 6.3 Hz, 2 H), 3.24 (d, *J* =

15.8 Hz, 3 H), 3.60 (d, J = 15.8 Hz, 3 H), 3.79 (t, J = 6.2 Hz, 2 H), 6.88 (t, J = 6.2 Hz, 1 H), major 9.44 (s, 1 H), minor 9.91 (d, J = 0.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 4.1, 6.5, 31.6, 33.6, 60.6, 61.5, 141.3, 152.6, 189.5; IR (neat) 1694, 1659 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{28}O_4NSi$ 302.1788, found 302.1779.



6c **7c**

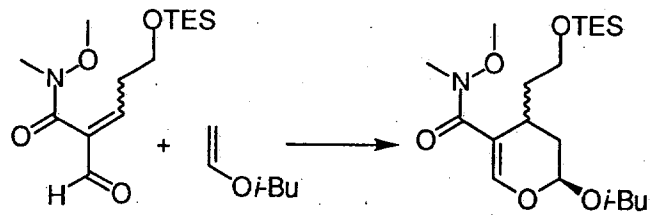
(Z)-2-Formyl-5-(triethylsilyloxy)-pent-2-enoic acid dimethylamide (7c). A solution of amide **6c** (200 mg, 0.58 mmol) in toluene (4 mL) was heated at 100 °C for 1 h and then concentrated to give a colorless oil (158 mg, 85%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.54 (q, J = 8.0 Hz, 6 H), 0.88 (t, J = 8.0 Hz, 9 H), 2.51 (q, J = 6.1 Hz, 2 H), 2.82 (s, 3 H), 2.99 (s, 3 H), 3.74 (t, J = 6.1 Hz, 2 H), 6.80 (t, J = 6.1 Hz, 1 H), 9.39 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 4.6, 7.0, 34.2, 34.7, 38.1, 61.1, 143.0, 153.9, 165.8, 190.6; IR (neat) 1692, 1643 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{28}O_3NSi$ 286.1838, found 286.1857.



7a **8a**

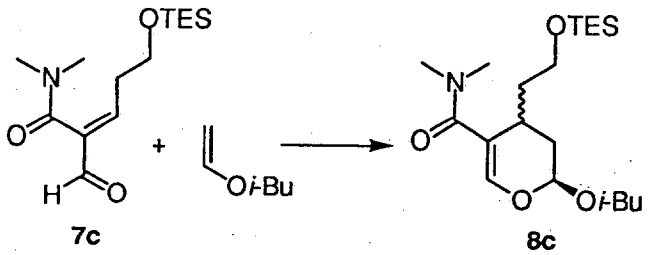
6-Isobutoxy-4-[2-(triethylsilyloxy)-ethyl]-5,6-dihydro-4*H*-pyran-3-carboxylic acid methyl ester (8a). To a solution of esters **7a** (101 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added isobutyl vinyl ether (242 mL, 1.86 mmol) and the mixture was stirred at rt for 24 h. The solution was concentrated and the crude material was purified by silica-gel chromatography (ethyl acetate-hexanes, 1 : 32, silica-gel deactivated with 10% triethylamine) to afford a colorless oil (112 mg, 81%) as an

inseperable mixture of diastereomers (*cis : trans*, 74 : 26): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.0 Hz, 6 H), major 0.85 (dd, *J* = 1.4, 6.7 Hz, 6 H), minor 0.89 (d, *J* = 2.3 Hz, 6 H), 0.94 (t, *J* = 8.0 Hz, 9 H), minor 1.18 (dt, *J* = 7.9, 11.8 Hz, 1 H), minor (ddd, *J* = 6.4, 9.7, 11.8 Hz, 1 H), 1.74-1.94 (m, 4 H), minor 2.06 (dt, *J* = 1.9, 12.0 Hz, 1 H), major (dt, *J* = 2.7, 14.3 Hz, 1 H), 2.61-2.73 (m, 1 H), major (dd , *J* = 6.4, 9.1 Hz, 1 H), minor 3.27 (dd , *J* = 6.9, 9.3 Hz, 1 H), major 3.55 (dd , *J* = 6.6, 9.1 Hz, 1 H), 3.62-3.75 (m, 1 H), minor 3.68 (s, 3 H), major 3.69 (s, 3 H), minor 4.97 (dd, *J*=2.3, 8.9 Hz, 1 H), major 5.08 (t, *J*=2.7 Hz, 1 H), 7.45 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ 4.4, 6.7, 19.2, 24.9, 28.4, 28.8, 35.7, 51.0, 61.1, 75.9, 98.6, 110.8, 151.8, 167.9; minor isomer: d 4.3, 6.7, 19.1, 27.3, 28.4, 31.2, 37.7, 51.0, 61.2, 76.2, 98.7, 109.9, 153.1, 167.7; IR (neat) 1712, 1635 cm^{-1}; HRMS (M+Na$^+$) calcd for $C_{19}H_{36}O_5SiNa$ 395.2229, found 395.2286.



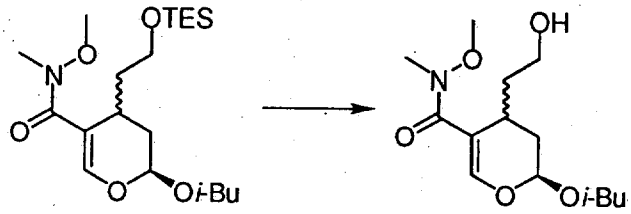
7b **8b**

6-Isobutoxy-4-[2-(triethylsilyloxy)-ethyl]-5,6-dihydro-4*H*-pyran-3-carboxylic acid methoxy-methylamide (8b). To a solution of amides **7b** (394 mg, 1.31 mmol) in CH_2Cl_2 (3 mL) was added isobutyl vinyl ether (0.852 mL, 6.54 mmol) and the solution subjected to high pressure (12 kbar) overnight. The solution was then concentrated and the crude material was purified by silica-gel chromatography (ethyl acetate-hexanes, 1 : 9) to give a colorless oil (369 mg, 71%) as an inseparable mixture of diastereomers (*cis : trans*, 92 : 8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (q, *J* = 7.8 Hz, 6 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 1.75 (h, *J* = 6.7 Hz, 1 H), 1.82-1.93 (m, 3 H), 2.08-2.19 (m, 1 H), minor 3.97 (s, 3 H), major 3.98 (s, 3 H), 3.03 (dd , *J* = 6.2, 9.1 Hz, 1 H), 3.17 (s, 3 H), 3.53 (dd, *J* = 6.7, 9.1 Hz, 1 H), 3.75 (dd, *J* = 6.1, 6.7 Hz, 2 H), major 4.74 (dd, *J* = 3.1, 4.4 Hz, 1 H), minor 4.89 (dd, *J* = 2.5, 5.2 Hz, 1 H), 7.29 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 4.8, 7.2, 19.7, 27.6, 28.9, 31.8, 34.3, 36.9, 61.1, 61.3, 76.3, 113.6, 147.2, 169.6; IR (neat) 2956, 1645 cm^{-1}; HRMS (MH$^+$) calcd for $C_{20}H_{40}O_5NSi$ 402.2676, found 402.2709.



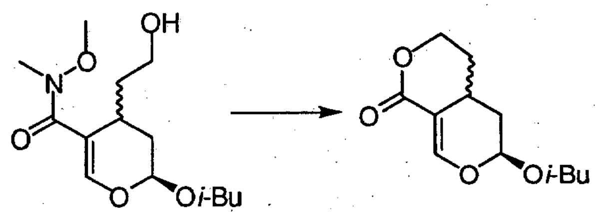
7c 8c

6-Isobutoxy-4-[2-(triethylsilyloxy)-ethyl]-5,6-dihydro-4*H*-pyran-3-carboxylic acid dimethylamide (8c). To a solution of amide 7c (157 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was added isobutyl vinyl ether (360 mL, 2.75 mmol) and the solution was subjected to high pressure (12 kbar) overnight. The mixture was then concentrated to give a colorless oil (180 mg, 85%) as a mixture of diastereomers (*cis* : *trans*, 93 : 7); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.50 (q, J = 7.9 Hz, 6 H), 0.84 (d, J = 6.6 Hz, 6 H), 0.87 (t, J = 7.9 Hz, 9 H), 1.52-1.74 (m, 2 H), 1.75-1.86 (m, 2 H), 1.98 (ddd, J = 2.5, 6.8, 13.6 Hz, 1 H), 2.75 (dt, J = 5.1, 14.5 Hz, 1 H), minor 2.92 (s, 6 H), major 2.95 (s, 6 H), 3.18 (dd, J = 6.4, 9.1 Hz, 1 H), 3.46-3.61 (m, 3 H), 4.91 (dd, J = 2.6, 5.6 Hz, 1 H), major 6.39 (d, J = 0.6 Hz, 1 H) minor 6.43 (d, J = 0.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ 4.2, 6.6, 19.1, 27.6, 28.33, 31.5, 36.2, 60.7, 75.6, 98.7, 113.9, 142.4, 170.3 minor isomer: δ 3.9, 4.6, 19.1, 25.8, 28.3, 32.1, 37.1, 60.3, 75.1, 96.8, 114.9, 142.5, 169.9; IR (neat) 2955, 1650cm^{-1}; HRMS (MH$^+$) calcd for $C_{20}H_{40}O_4NSi$ 386.2727, found 386.2723.

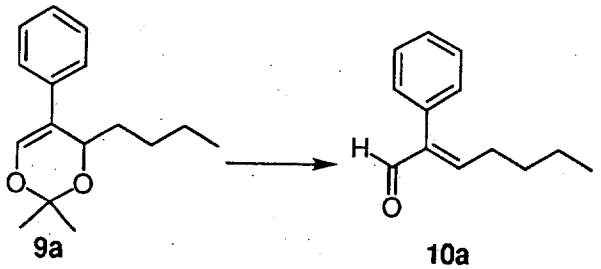


6-Isobutoxy-4-[(2-hydroxy)-ethyl]-5,6-dihydro-4*H*-pyran-3-carboxylic acid methoxy-methyl amide. To the mixture of dihydropyans **8b** (266 mg, 0.66 mmol) in THF (3 mL) was added TBAF (1.0 M in THF, 0.795 mL) at 0 °C. The solution was stirred for 2 h and poured onto saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow oil (190 mg, 99%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.87 (d, J = 6.7 Hz, 6 H), 1.71 (h, J = 6.7 Hz,

1 H), 1.80-1.97 (m, 4 H), 2.79-2.91 (m, 1 H), 2.92-3.03 (m, 1 H), minor 3.22 (s, 3 H), major 3.23 (s, 3 H), 3.27 (dd , *J* = 6.2, 9.1 Hz, 1 H), 3.49-3.61 (m, 2 H), 3.53 (dd , *J* = 6.8, 9.1 Hz, 1 H), 3.6 (s, 3 H), minor 4.99 (dd, *J* = 2.5, 6.8 Hz, 1 H), major 5.06 (t, *J* = 3.2 Hz, 1 H), minor 7.21 (d, *J* = 0.8 Hz, 1 H), major 7.22 (d, *J* = 0.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.2, 24.9, 28.4, 31.3, 34.1, 37.8, 60.1, 60.4, 75.8, 98.2, 111.4, 148.9, 169.4; IR (neat) 3427, 1643cm^{-1}; HRMS (MH+) calcd for $C_{14}H_{26}O_5N$ 288.1811, found 288.1787.

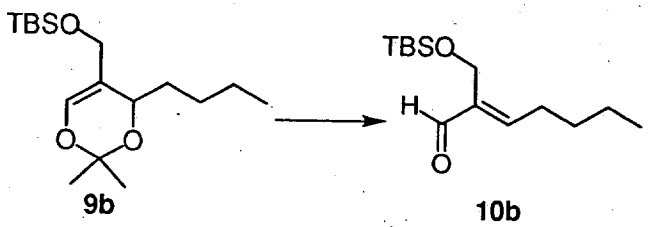


6-Isobutoxy-4,4a,5,6-tetrahydro-3*H*-pyrano[3,4-c]pyran-1-one. To a solution of the above alcohols (41 mg, 0.14 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil, 6 mg, 0.16 mmol). The solution was stirred at rt for 48 h and poured onto brine, extracted with Et_2O, washed with brine, dried (Na_2SO_4) and concentrated to give a colorless oil (27 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ minor 0.81 (d, *J* = 6.7 Hz, 3 H), minor 0.83 (d, *J* = 6.7 Hz, 3 H), major 0.86 (d, *J* = 6.7 Hz, 3 H), major 0.87 (d, *J* = 6.7 Hz, 3 H), 1.42-1.64 (m, 2 H), 1.83 (h, *J* = 6.7 Hz, 1 H), 1.90 (ddt, *J* = 2.3, 4.4, 13.6 Hz, 1 H), minor 2.01 (ddd, *J* = 1.5, 5.0, 13.0 Hz, 1 H), major 2.13 (ddd, *J* = 2.3, 5.0, 13.1 Hz, 1 H), 2.69 (ttd, *J* = 2.2, 4.9, 12.1 Hz, 1 H), major 3.31 (dd, *J* = 6.8, 9.2 Hz, 1 H), minor 3.32 (dd, *J* = 6.7, 9.2 Hz, 1 H), minor 3.56 (dd, *J* = 6.7, 9.2 Hz, 1 H), major 3.73 (dd, *J* = 6.5, 9.2 Hz, 1 H), 4.28 (ddd, *J* = 2.5, 11.4, 12.7 Hz, 1 H), 4.45 (ddd, *J* = 2.0, 4.4, 11.4 Hz, 1 H), major 5.09 (dd, *J* = 2.3, 9.8 Hz, 1 H), minor 5.22 (t, *J* = 1.9 Hz, 1 H), minor 7.62 (d, *J* = 2.2 Hz, 1 H), major 7.65 (d, *J* =2 .0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 19.2, , 21.4, 29.2, 29.7, 33.5, 68.2, 76.4, 101.6, 104.1, 155.4; IR (neat) 1705, 1616 cm^{-1}; HRMS (MNa+) calcd for $C_{12}H_{18}O_4Na$ 249.1103, found 249.1098.



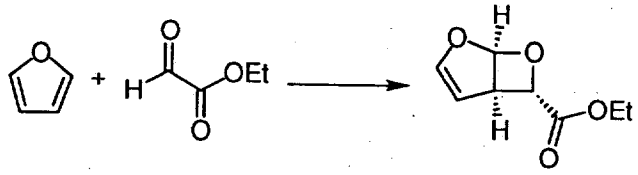
9a 10a

(*E*)-2-Phenyl-hept-2-enal (10a). A solution of dioxin **9a** (20 mg, 0.081 mmol) in d^8-toluene (1 mL) was heated at 110 °C for 8 h and then concentrated to give a colorless oil (15 mg, >99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.40 (h, J = 7.3 Hz, 2 H), 1.48 (p, J = 7.3 Hz, 2 H), 2.37 (q, J = 7.2 Hz, 2 H), 6.72 (t, J = 7.2 Hz, 1 H), 9.61 (s, 1 H).



9b 10b

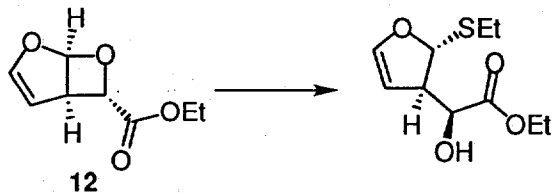
(*E*)-2-(*tert*-Butyldimethylsilyloxymethyl)-hept-2-enal (10b). A solution of dioxin **9b** (13 mg, 0.041 mmol) in d^8-toluene (1 mL) was heated at 95 °C for 2 h and then concentrated to give a colorless oil (10 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 0.93 (t, J = 7.3 Hz, 3 H), 1.35-1.53 (m, 4 H), 2.52 (q, J = 7.2 Hz, 2 H),4.36 (s, 2 H), 6.62 (t, J = 7.2 Hz, 1 H), 9.38 (s, 1 H).



12

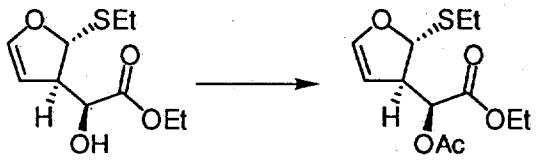
6-Carboethoxy-2,7-dioxabicyclo[3.2.0]hept-3-ene (12). A solution of ethyl glyoxylate (33.9 g, 0.332 mol) in furan (330 mL) at 0 °C was irradiated with a 550 W high-pressure mercury lamp under argon in a Pyrex filtered photochemical reactor. After 28 h the furan was distilled off and the residue purified by silica-gel flash chromatography (ethyl acetate-hexane, 1 : 4) to give a white solid (36.5 g, 65%): mp 35-36 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2Hz, 3 H), 3.76 (dddd, J = 1.0, 2.9, 3.0, 4.1 Hz, 1

H) 4.27 (q, J = 7.2 Hz, 2 H), 4.88 (d, J = 3.0 Hz, 1 H), 5.43 (t, J = 2.9 Hz, 1 H), 6.47 (d, J = 4.1 Hz, 1 H), 6.66 (dd, J = 1.0, 2.9 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 49.1, 61.5, 86.1, 103.4, 108.7, 148.9, 170.5; IR (neat) 1748, 1606 cm^{-1}; HRMS (MH^+) calcd for $C_8H_{11}O_4$ 171.0657, found 171.0642.



12

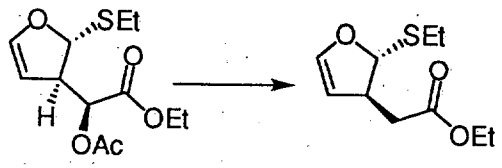
***trans*-(2-Ethylsulfanyl-2,3-dihydrofuran-3-yl)-hydroxyacetic acid ethyl ester.** To a solution of oxetane **12** (3.00 g, 17.6 mmol) and ethanethiol (6.50 mL, 88.2 mmol) in CH_3CN (18 mL) was added $BF_3 \cdot OEt_2$ (223 mL, 1.76 mmol) dropwise at –40 °C. The reaction mixture was stirred at –40 °C for 5 min and quenched with saturated aqueous Na_2CO_3, extracted with Et_2O, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (Et_2O-CH_2Cl_2-hexane, 0.7 : 4 : 5) gave a colorless oil (2.86 g, 70%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H), 1.25 (t, J = 7.4 Hz, 3 H), 2.61 (dq, J = 7.4, 12.9 Hz, 1 H), 2.72 (dq , J = 7.4, 12.9 Hz, 1 H), 3.09 (d, J = 5.6 Hz, 1 H), 3.08-3.14 (m, 1 H), 4.09 (t, J = 5.6 Hz, 1 H), 4.18 (qd, J = 2.8, 7.1 Hz, 1 H), 4.25 (qd, J = 2.8, 7.1 Hz, 1 H) 4.95 (t, J = 2.7 Hz, 1 H), 5.61 (d, J = 5.2 Hz, 1 H), 6.32 (dd, J = 2.0, 2.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 14.7, 24.9, 50.5, 54.0, 61.9, 71.0, 85.7, 89.5, 100.3, 101.3, 145.9, 172.9; IR (neat) 3477, 1731, 1620 cm^{-1}.



13

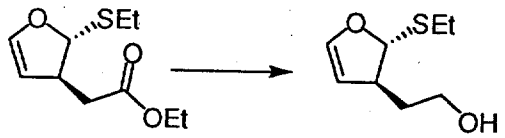
***trans*-Acetoxy-(2-ethylsulfanyl-2,3-dihydrofuran-3-yl) acetic acid ethyl ester (13).** To a solution of the above alcohol (3.62 g, 15.6 mmol) in CH_2Cl_2 (63 mL) were added pyridine (3.78 mL, 46.8 mmol), acetic anhydride (2.21 mL, 23.4 mmol), and 4-(dimethylamino)-pyridine (190 mg, 1.56 mmol) at 0 °C. The mixture was stirred 2 h at 0 °C and then was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 and the

combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification by silica-gel flash chromatography (ethyl acetate-hexanes, 1 : 19) gave a colorless oil (3.81 g, 89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 1.27 (t, J = 7.4 Hz, 3 H), 2.10 (s, 3 H), 2.63 (dq, J = 7.4, 12.8 Hz, 1 H), 2.74 (dq, J = 7.4, 12.8 Hz, 1 H), 3.26 (dddd, J = 1.9, 2.8, 4.4, 5.1 Hz, 1 H), 4.19 (qd, J = 3.0, 7.2 Hz, 2 H), 4.90 (t, J = 2.8 Hz, 1 H), 4.95 (d, J = 4.4 Hz, 1 H) 5.63 (d, J = 5.1 Hz, 1 H), 6.31 (dd, J = 1.9, 2.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 14.8, 20.4, 25.0, 51.5, 61.5, 72.1, 85.9, 99.7, 146.3, 168.0, 170.1; IR (neat) 1748, 1621 cm^{-1}; HRMS (MNa^+) calcd for $C_{12}H_{18}O_5SNa$ 297.0773, found 297.0788.

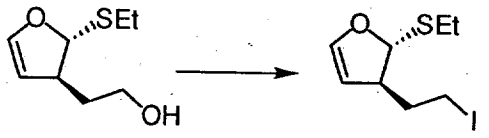


13

***trans*-(2-Ethylsulfanyl-2,3-dihydrofuran-3-yl) acetic acid ethyl ester (17).** To a solution of acetate **13** (3.81 g, 13.9 mmol) in HMPA (23 mL) was added ethanol (956 mL, 16.6 mmol) followed by SmI_2 (0.1 M in THF, 347 mL). The purple solution was stirred 10 min and quenched with 0.1 N HCl. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Purification by silia-gel flash chromatography (Et_2O-hexane, 1 : 12) gave a colorless oil (2.53 g, 84%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 1.22 (t, J = 7.4 Hz, 3 H), 2.30 (dd, J = 7.4, 15.4 Hz, 1 H), 2.40 (dd, J = 7.4, 15.4 Hz, 1 H), 2.58 (dq, J = 7.4, 12.8 Hz, 1 H), 2.68 (dq, J = 7.4, 12.8 Hz, 1 H), 3.02 (tddd, J = 1.7, 2.7, 4.6, 7.4 Hz, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 4.99 (t, J = 2.7 Hz, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 6.19 (dd, J = 1.7, 2.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 14.7, 24.8, 39.0, 45.8, 60.3, 89.7, 104.0, 144.5, 170.9; IR (neat) 1732, 1617 cm^{-1}; HRMS (MH^+) calcd for $C_{10}H_{17}O_3S$ 217.0898, found 217.0896.



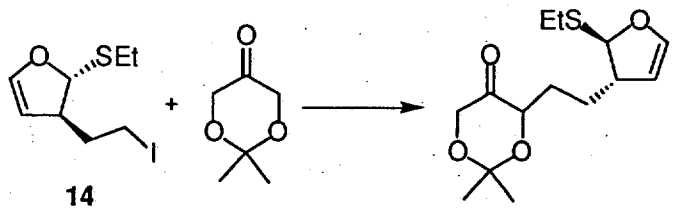
***trans*-2-(2-Ethylsulfanyl-2,3-dihydrofuran-3-yl)-ethanol.** To a solution of the above ester (2.53 g, 11.7 mmol) in Et_2O (46 mL) was added $LiAlH_4$ (444 mg, 11.7 mmol) at 0 °C. The mixture was stirred for 40 min at 0 °C then EtOAc (2 mL) was added dropwise at 0 °C. Saturated aqueous Rochelle's salt was added dropwise until H_2 evolution ceased. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with saturated aqueous Rochelle's salt and brine, dried (Na_2SO_4), and concentrated. Purification by silica-gel flash chromatography (Et_2O-CH_2Cl_2, 1 : 9) gave a colorless oil (1.98 g, 97%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.4 Hz, 3 H), 1.66 (q, J = 6.6 Hz, 2 H), 2.41 (s, 1H), 2.63 (dq, J = 7.4, 12.8 Hz, 1 H), 2.71 (dq, J = 7.4, 12.8 Hz, 1 H), 2.78-2.89 (m, 1 H), 3.62 (t, J = 6.6 Hz, 2 H), 5.00 (t, J = 2.8 Hz, 1 H), 5.35 (d, J = 5.2 Hz, 1 H), 6.22 (dd, J = 1.9, 2.8 Hz, 1 H); ^{13}C NMR (50 MHZ, $CDCl_3$) δ 14.8, 25.0, 37.4, 46.6, 60.2, 90.5, 104.8, 143.8; IR (neat) 3356, 1619 cm^{-1}; HRMS (M-OH$^+$) calcd for $C_8H_{13}OS$ 157.0687, found 157.0688.



14

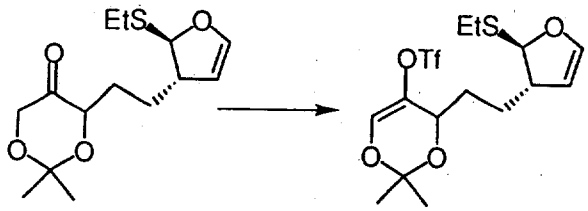
***trans*-2-Ethlysulfanyl-3-(2-iodoethyl)-2,3-dihydrofuran (14).** To a solution of the above alcohol (1.40 g, 8.04 mmol) in benzene (133 mL) was added imidazole (657 mg, 9.65 mmol), triphenylphosphine (2.53 g, 9.65 mmol), and iodine (2.24 g, 8.84 mmol). The mixture was stirred 10 min at rt and poured onto a 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in THF (25 mL) and iodomethane was added (2.50 mL, 40.2 mmol) and the mixture was stirred 2 h, filtered and concentrated. Purification by silica-gel flash chromatography (hexane, silica-gel deactivated with 10% triethylamine) gave a colorless oil (1.78 g, 78%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, J = 7.4 Hz, 3 H), 2.00 (dtd, J = 7.1, 7.4, 10.9 Hz, 2 H), 2.67 (dq, J = 7.4, 12.8 Hz, 1 H), 2.74 (dq, J = 7.4, 12.8 Hz, 1 H),

2.79-2.91 (m, 1 H), 3.15 (td, J = 1.4, 7.4 Hz, 2 H), 5.04 (t, J = 2.7 Hz, 1 H), 5.32 (d, J = 4.9 Hz, 1 H), 6.29 (dd, J = 1.8, 2.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.7, 14.9, 25.2, 38.8, 50.3, 89.9, 103.5, 144.7; IR (neat) 1618, 1446 cm^{-1}; HRMS ($M\text{-}I^+$) calcd for $C_8H_{13}OS$ 157.0687, found 157.0676.



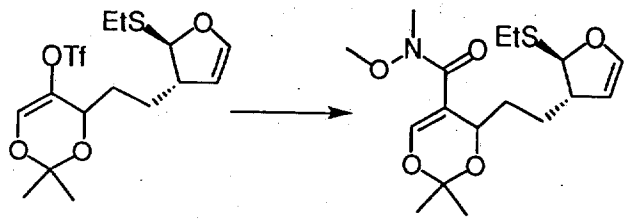
14 15

4-[2-(2-Ethylsulfanyl-2,3-dihydrofuran-3-yl)-ethyl]-2,2-dimethyl-1,3-dioxan-5-one (15). To a solution of 2,2-dimethyl-1,3-dioxan-5-one (419 mg, 3.22 mmol) in benzene (20 mL) was added molecular sieves (4Å, 420 mg) and cyclohexylamine (737 mL, 6.44 mmol). The mixture was stirred at rt overnight, filtered and concentrated. The crude imine **4** was dissolved in anhydrous THF (6.5 mL) and added dropwise to a solution of lithium diethylamide [formed by addition of butyllithium (2.5 M in hexane, 1.21 mL) to a solution of diethylamine (333 mL, 3.22 mmol) in THF (3.5 mL) at –30 °C] at –78 °C. The solution was warmed over 2 h to –25 °C and recooled to –78 °C. Iodide **14** (571 mg, 2.01 mmol) in THF (4 mL) was added dropwise and the solution was warmed to rt overnight. The resultant mixture was hydrolyzed by addition of saturated aqueous NH_4Cl (10 mL) followed by stirring at rt for 6h. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with the saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Purification by silica-gel flash chromatography (ethyl acetate-hexane, 1 : 32, silica-gel deactivated with 10% triethylamine) gave a colorless oil (0.360 g, 62%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.28 (t, J = 7.4 Hz, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.50-1.59 (m, 3 H), 1.83-1.93 (m, 1 H), 2.66 (dq, J = 7.4, 12.8 Hz, 1 H), 2.68-2.73 (m, 1 H), 2.73 (dq, J = 7.4, 12.8 Hz, 1 H), 3.95 (d, J = 16.9 Hz, 1 H), 4.11-4.18 (m, 1 H), 4.21 (dd, J = 1.4, 16.9 Hz, 1 H), 5.00 (t, J = 2.7 Hz, 1 H), 5.30 (d, J = 4.9 Hz, 1 H), 6.23 (dd, J = 1.9, 2.7 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.8, 23.5, 23.8, 25.0, 25.5, 30.0, 49.1, 66.5, 74.1, 90.3, 100.7, 104.5, 143.9; IR (neat) 1746, 1618 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{23}O_4S$ 287.1317, found 287.1314.



15

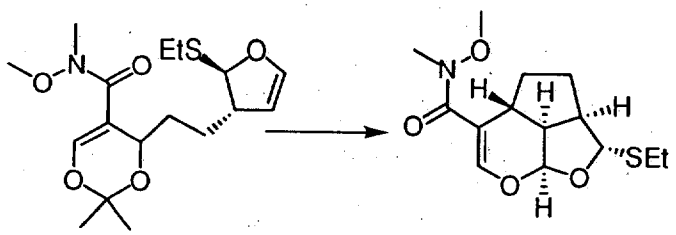
Trifluoromethanesulfonic acid 4-[2-(2-ethylsulfanyl-2,3-dihydroforan-3-yl-ethyl]-2,2-dimethyl-4H-[1,3]dioxin-5-yl ester. A solution of ketone **15** (358 mg, 1.25 mmol) and N-phenyltrifluoromethanesulfonimide (625 mg, 1.75 mmol) in THF (12 mL) was added to NaHMDS (1.0 M in THF, 1.75 mL) in THF (9 mL) at –78 °C over 2 h. The solution was warmed to rt over 2 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combine organic layers were washed with saturated aqueous Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. Purification by florisil flash chromatography (hexane, florisil deactivated with 10% triethylamine) gave a colorless oil (0.445 g, 85%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.32 (t, J = 7.5 Hz, 3 H), 1.48 (s, 3 H), 1.51 (s, 3 H), 1.51-1.69 (m, 3 H), 1.78-1.88 (m, 1 H), 2.67 (dq, J = 7.5, 12.8 Hz, 1 H), 2.73-2.78 (m, 1 H), 2.78 (dq, J = 7.5, 12.8 Hz, 1 H), 4.46-4.48 (m, 1 H), 5.04 (t, J = 2.7 Hz, 1 H), 5.31 (d, J = 4.8 Hz, 1 H), 6.26 (dd, J = 1.8, 2.7 Hz, 1 H), 6.72 (d, J = 1.1 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.3, 21.1, 25.5, 27.6, 27.7, 29.4, 49.5, 68.5, 90.8, 101.8, 104.9, 118.9 (q, J = 319 Hz), 131.4, 138.1, 144.5; IR (neat) 1679, 1619 cm^{-1}; HRMS (MH^+) calcd for $C_{15}H_{22}O_6S_2F_5$ 419.0810, found 419.0800.



16

4-[2-[2-Ethylsulfanyl-2,3-dihydrofuran-3-yl)-ethyl]-2,2-dimethyl-4*H*-[1,3]dioxine-5-carboxylic acid methoxy-methylamide (16). A solution of the above triflate (29 mg, 0.069 mmol), N,O-dimethyl hydroxylamine (103 mg, 2.77 mmol), dppp (7 mg, 0.017 mmol), triethylamine (5 mL, 0.035 mmol), and palladium (II) acetate (4

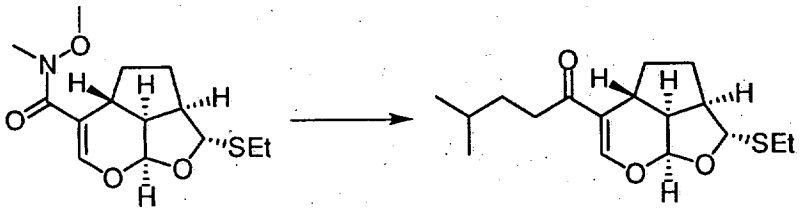
mg, 0.017 mmol) in DMF (2 mL) was placed under an atmosphere of CO (balloon pressure) and stirred 10 h at rt. The solution was poured onto saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Purification by silica-gel flash chromatography (ethyl acetate-hexane, 1 : 19, silica-gel deactivated with 10% triethylamine) gave a colorless oil (22 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.5 Hz, 3 H), 1.41 (s, 6 H), 1.44-1.58 (m, 3 H), 1.62-1.74 (m, 1 H), 2.59 (dq, J = 7.5, 13.0 Hz, 1 H), 2.61-2.68 (m, 1 H), 2.69 (dq, J = 7.5, 13.0 Hz, 1 H), 3.16 (s, 3 H), 3.59 (s, 3 H), 4.53-4.55 (m, 1 H), 4.97 (t, J = 2.7 Hz, 1 H), 5.23 (d, J = 4.8 Hz, 1 H), 6.17 (dd, J = 1.7, 2.7 Hz, 1 H), 7.21 (d, J = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 22.1, 25.4, 28.1, 30.1, 30.4, 33.5, 49.6, 61.3, 68.5, 91.0, 100.7, 105.4, 110.8, 144.1, 149.2, 167.3; IR (neat) 1650, 1614 cm^{-1}.



16 17

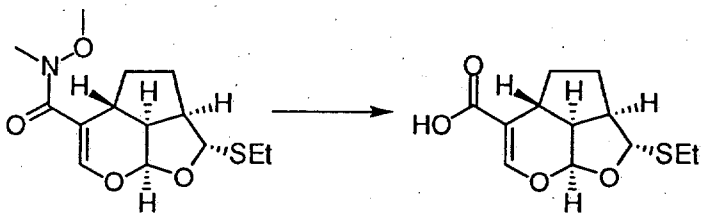
2-Ethylsulfanyl-2a, 3, 4, 4a, 7a, 7b-hexahydro-2*H*-1,7-dioxa-cyclopenta[cd]indene-5-carboxylic acid methoxy-methyl amide (17). A solution of amide **16** (237 mg, 0.68 mmol) in toluene (13 mL) was heated at 110 °C for 1h. The solution was cooled and concentrated. Recrystallization from hexanes gave the pure 2,6-*trans* cycloadduct **17**. Concentration and further purification by silica-gel flash chromatography (Et_2O-benzene, 3 : 22) of the filtrate gave **17** (2,6-*trans* : 2,6-*cis*, 4.5 : 1) as a white solid (151 mg, 72%): major isomer mp 72-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 1.52 (tdd, J = 9.0, 11.6, 13.1 Hz, 1 H), 1.77 (tdd, J = 3.0, 7.3, 13.1 Hz, 1 H), 1.96 (ddd, J = 3.6, 7.1, 11.3 Hz, 1 H), 2.18 (ddd, J = 2.6, 5.0, 11.3 Hz, 1 H), 2.19-2.32 (m, 2 H), 2.48 (dddd, J = 3.0, 5.7, 7.1, 9.3 Hz, 1 H), 2.62 (dq, J = 7.5, 12.8 Hz, 1 H), 2.70 (dq, J = 7.5, 12.8 Hz, 1 H), 3.16 (s, 3 H), 3.54 (s, 3 H), 5.12 (d, J = 5.7 Hz, 1 H), 5.73 (d, J = 3.6 Hz, 1 H), 7.12 (d, J = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 26.0, 28.6, 31.8, 33.1, 36.7, 46.3, 51.1, 60.6, 91.2, 103.2, 115.9, 149.9, 166.8; IR (neat) 1633, 1599 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{22}O_4NS$ 300.1270, found

300.1288. minor isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.4 Hz, 3 H), 1.69 (dtd, J = 6.3, 12.8, 19.1 Hz, 1 H), 1.70-1.75 (m, 1 H), 2.07 (dtd, J = 1.7, 5.8, 12.1 Hz, 1 H), 2.58 (dq, J = 7.4, 12.8 Hz, 1 H), 2.57-2.62 (m, 1H), 2.68 (dq, J = 7.4, 12.8 Hz, 1 H), 2.69-2.75 (m, 1 H), 2.88 (td, J = 7.1, 10.5 Hz, 1 H), 3.20 (s, 3 H), 3.56 (s, 3 H), 4.89 (d, J = 5.1 Hz, 1 H), 5.68 (d, J = 3.7 Hz, 1 H), 7.25 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 25.5, 31.3, 33.0, 33.3, 34.1, 40.6, 51.3, 60.8, 87.9, 99.2, 112.1, 146.5, 168.5; IR (neat) 1648, 1449 cm^{-1}, HRMS (MH^+) calcd for $C_{14}H_{22}O_4NS$ 300.1270, found 300.1293.



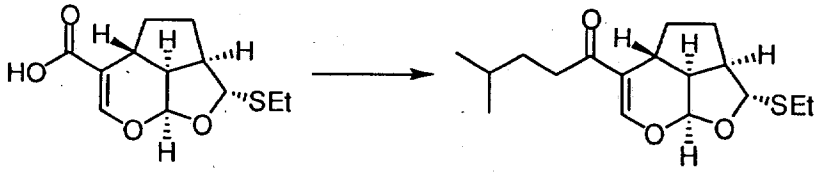
17

1-(2-Ethylsulfanyl-2a,3,4,4a,7a,7b-hexahydro-2*H*-1,7-dioxacyclopenta[cd]inden-5-yl)-4-methyl-pentan-1-one. To a solution of amide **17** (41 mg, 0.13 mmol) in a 1 : 1 pentane / ether solution (2 mL) was added isopentyllithium (0.08 M in 3:2 pentane / ether, 3.50 mL) at –40 °C. The solution was stirred 30 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by florisil flash chromatography (ethyl acetate-hexane, 1 : 19, florisil deactivated with 10% triethylamine) gave ketone (16.5 mg, 39%)[16] as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.2 Hz, 6 H) 1.24 (t, J = 7.4 Hz, 3 H), 1.39-1.55 (m, 3 H), 1.57-1.69 (m, 1 H) 1.74 (tdd, J = 3.6, 6.9, 10.3 Hz, 1H), 1.87 (ddd, J = 3.5, 6.9, 11.7 Hz, 1 H), 2.01 (dddd, J = 2.5, 4.7, 10.3, 11.7 Hz, 1 H), 2.24 (dt, J = 8.5, 14.1 Hz, 1 H), 2.39-2.55 (m, 4 H), 2.61 (dq, J = 7.4, 12.8 Hz, 1 H), 2.68 (dq, J = 7.4, 12.8 Hz, 1 H), 5.09 (d, J = 5.7 Hz, 1 H), 5.76 (d, J = 3.5 Hz, 1 H), 7.39 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 22.3, 22.4, 26.1, 27.8, 29.1, 32.2, 33.7, 35.6, 35.7, 46.1, 50.9, 91.5, 103.6, 122.9, 155.3, 198.0; IR (neat) 1658, 1591 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_{27}O_3S$ 311.1681, found 311.1667.



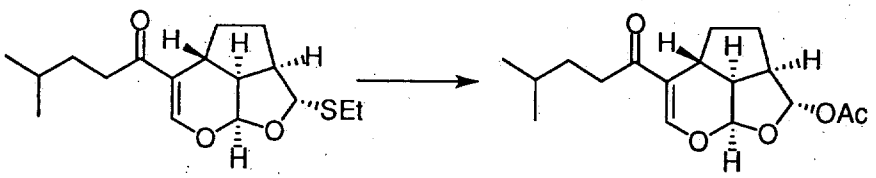
17

2-Ethylsulfanyl-2a, 3, 4, 4a, 7a, 7b-hexahydro-2*H*-1,7-dioxa-cyclopenta[cd]indene-5-carboxylic acid. To a solution of amide **17** (155 mg, 0.52 mmol) in Et_2O (5.2 mL) was added potassium *tert*-butoxide (384 mg, 3.42 mmol) and H_2O (31 μL, 1.71 mmol). The solution was stirred at rt overnight then poured onto saturated aqueous KH_2PO_4. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to give a white solid (130 mg, 98%): mp 118-120 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.4 Hz, 3 H), 1.63 (tdd, *J* = 8.5, 11.7, 13.2 Hz, 1 H), 1.83 (tdd, *J* = 2.7, 7.0, 9.8 Hz, 1 H), 1.98 (ddd, *J* = 3.6, 7.0, 11.7 Hz, 1 H), 2.15 (tdd, *J* = 2.7, 5.0, 13.2 Hz, 1 H), 2.31 (dt, *J* = 8.5, 17.2 Hz, 1 H), 2.37-2.56 (m, 2 H), 2.68 (dq, *J* = 7.4, 12.8 Hz, 1 H), 2.76 (dq, *J* = 7.4, 12.8 Hz, 1 H), 5.17 (d, *J* = 5.6 Hz, 1 H), 5.82 (d, *J* = 3.6 Hz, 1 H) 7.58 (d , *J* = 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 26.1, 29.0, 29.7, 32.0, 33.3, 35.0, 46.2, 50.7, 51.1, 91.4, 103.6, 112.2, 156.9, 171.3; IR (neat) 2929, 1662 cm^{-1}; HRMS (M-H$^+$) calcd for $C_{12}H_{15}O_4S$ 255.0691, found 255.0688.



1-(2-Ethylsulfanyl-2a,3,4,4a,7a,7b-hexahydro-2*H*-1,7-dioxacyclopenta[cd]inden-5-yl)-4-methyl-pentan-1-one. To a solution of the above carboxylic acid (10 mg, 0.039 mmol) in THF (580 mL) was added isopentyllithium (0.34 M in 3 : 2 pentane / ether, 580 mL) dropwise at 0 °C. The solution was stirred overnight at 0 °C and acetone (29 mL, 0.39 mmol) was added at 0 °C. The solution was stirred 5 min at 0 °C and poured onto saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by silica-gel chromatography (ethyl acetate-hexanes, 1 : 9, silica-gel deactivated with

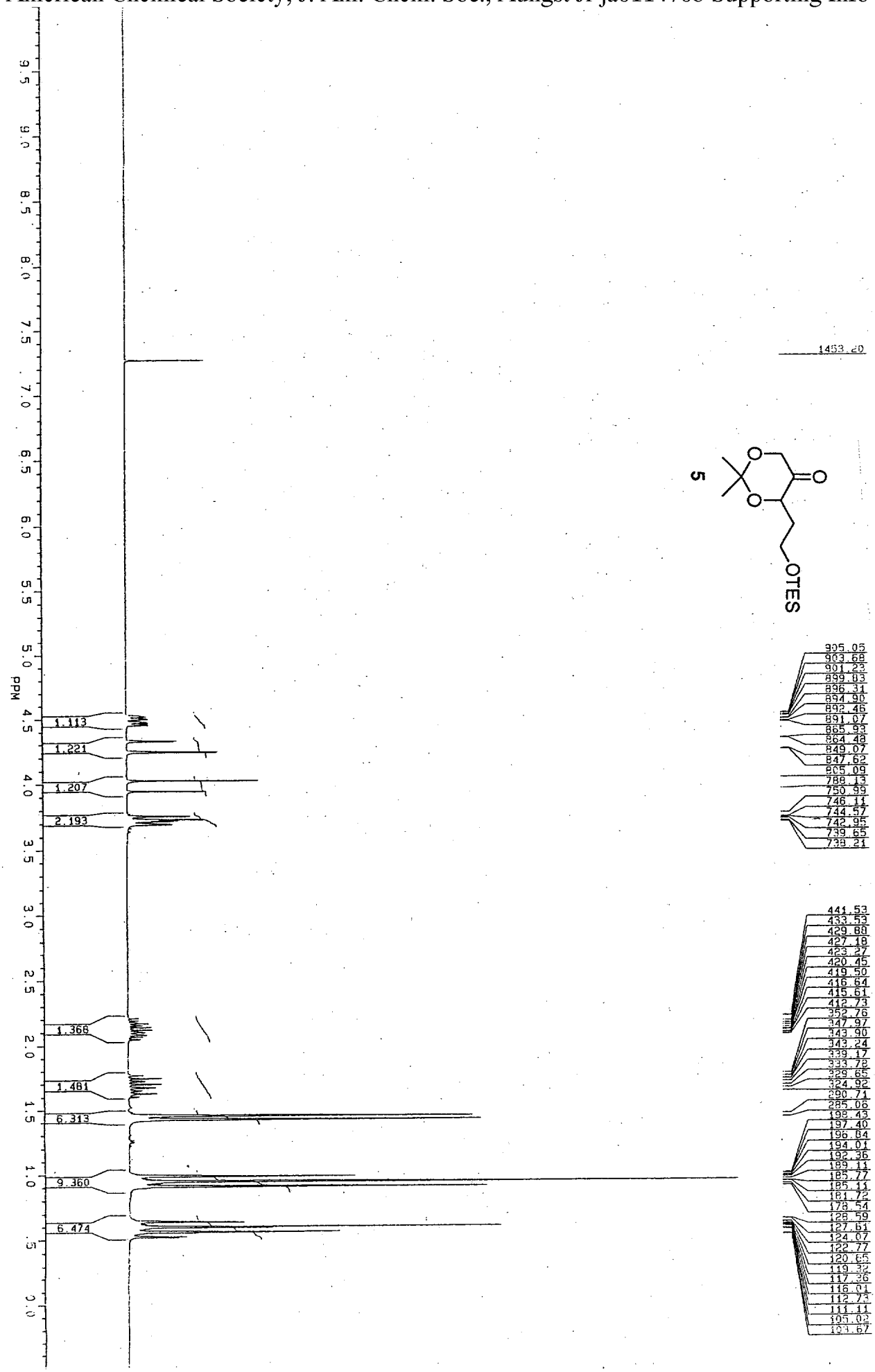
10% triethylamine) to give a colorless oil (9 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.2 Hz, 6 H) 1.24 (t, J = 7.4 Hz, 3 H), 1.39-1.55 (m, 3 H), 1.57-1.69 (m, 1 H) 1.74 (tdd, J = 3.6, 6.9, 10.3 Hz, 1H), 1.87 (ddd, J = 3.5, 6.9, 11.7 Hz, 1 H), 2.01 (dddd, J = 2.5, 4.7, 10.3, 11.7 Hz, 1 H) 2.24 (dt, J = 8.5, 14.1 Hz, 1 H), 2.39-2.55 (m, 4 H), 2.61 (dq, J = 7.4, 12.8 Hz, 1 H), 2.68 (dq, J = 7.4, 12.8 Hz, 1 H) 5.09 (d, J = 5.7 Hz, 1 H), 5.76 (d, J = 3.5 Hz, 1 H), 7.39 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 22.3, 22.4, 26.1, 27.8, 29.1, 32.2, 33.7, 35.6, 35.7, 46.1, 50.9, 91.5, 103.6, 122.9, 155.3, 198.0; IR (neat) 1658, 1591 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_{27}O_3S$ 311.1681, found 311.1667.

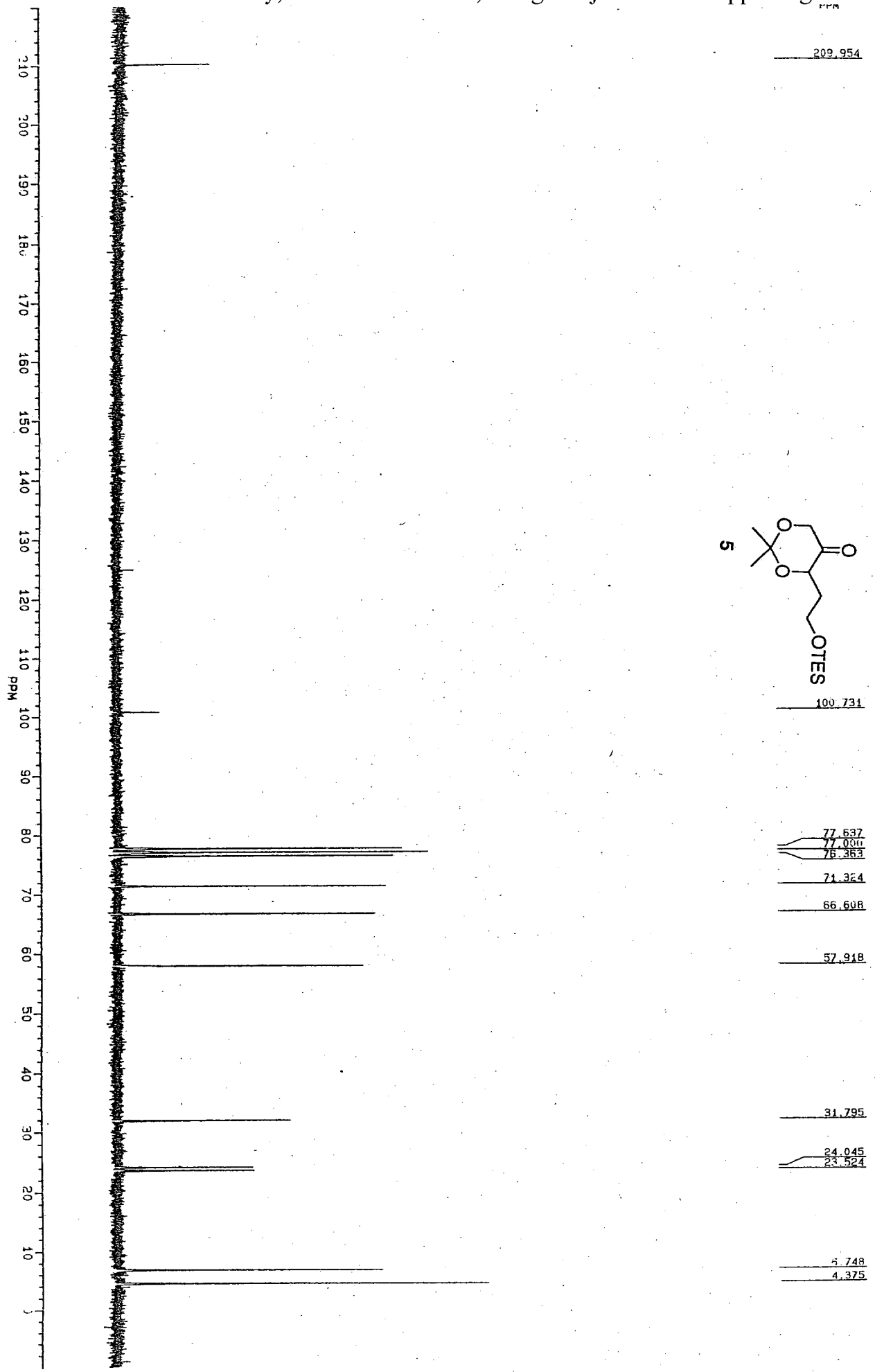


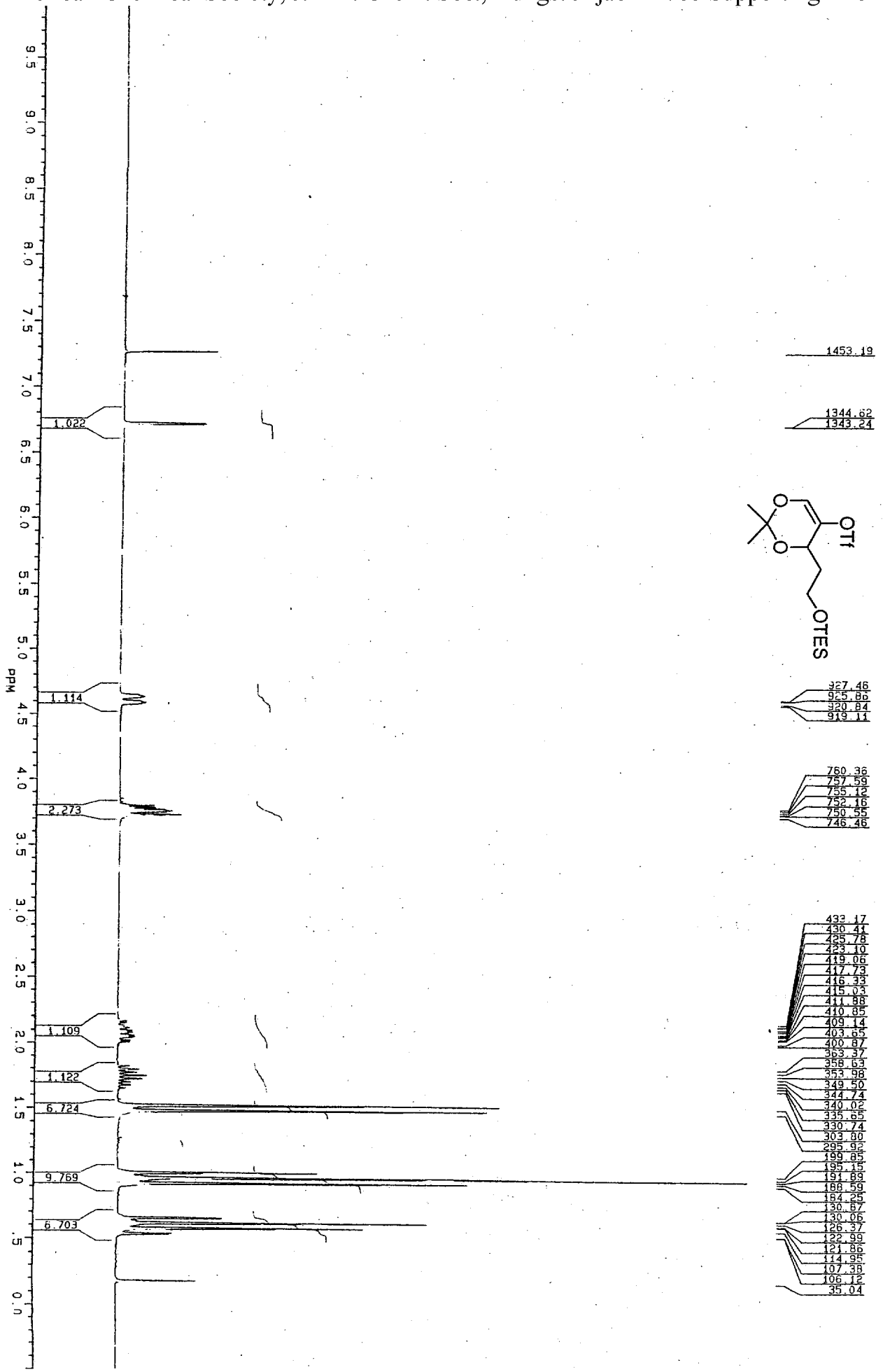
1

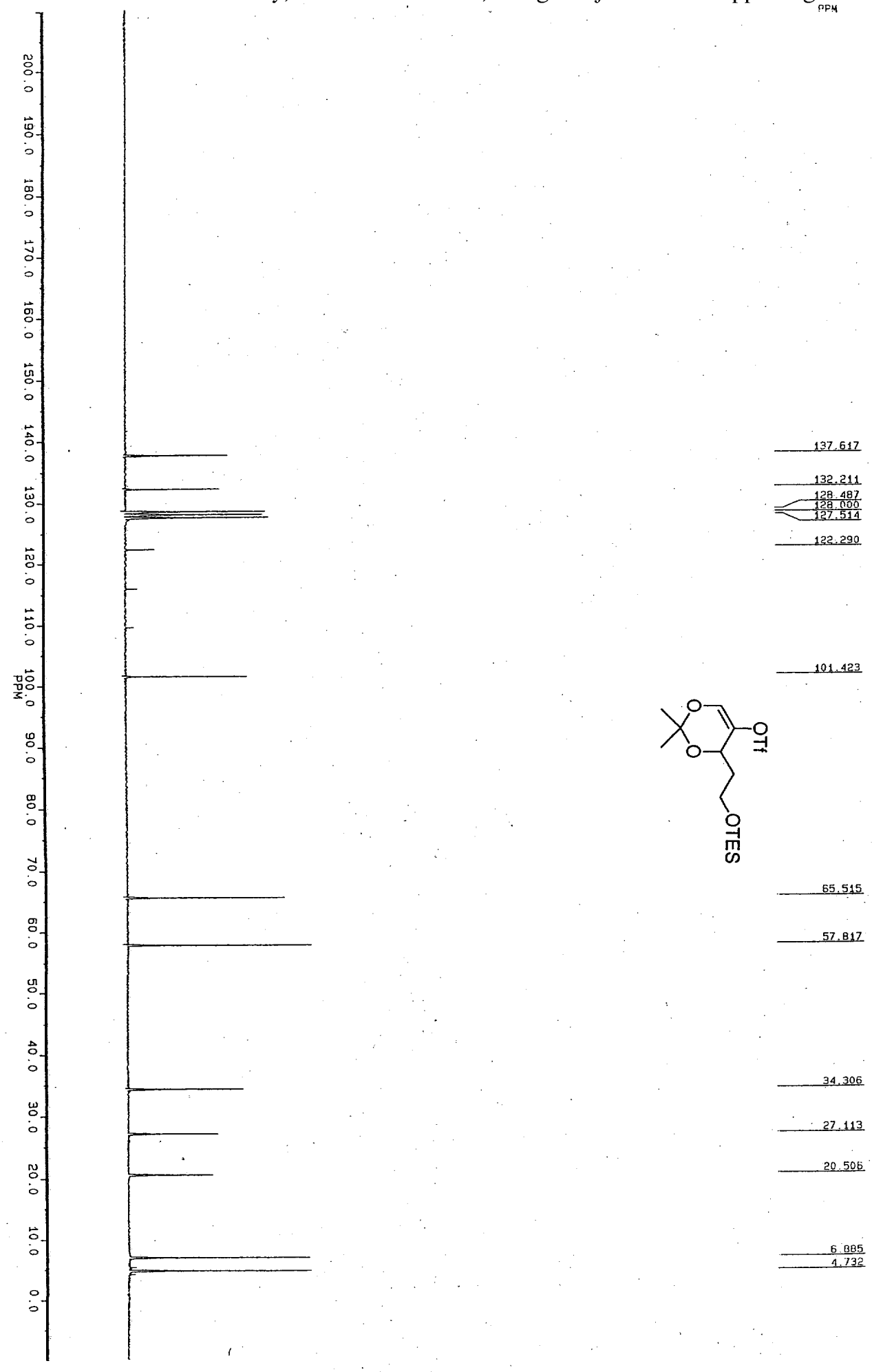
Euplotin A (1). To a solution of the above ketone (23 mg, 0.074 mmol) in CH_3CN (2 mL) was added mercuric acetate (47 mg, 0.15 mmol). The solution was stirred for 1.5 h at rt and poured onto CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated to give a mixture of diastereomers (α : β, 5.5 : 1). Purification by silica-gel flash chromatography (ethyl acetate-hexanes, 1 : 9) gave **1** as a colorless oil (15 mg, 67%): major isomer: ^{1}H NMR (610 MHz, $CDCl_3$) δ 0.88 (d, J = 6.4 Hz, 6 H), 1.49-1.61 (m, 3 H), 1.71 (dddd, J = 8.5, 10.6, 11.8, 12.2 Hz, 1 H), 1.93 (dddd, J = 3.1, 7.2, 10.6, 13.9 Hz, 1 H), 1.98 (dddd, J = 2.4, 4.8, 11.8, 11.8 Hz, 1 H), 2.03 (ddd, J = 3.3, 6.9, 11.8 Hz, 1 H), 2.11 (s, 3 H), 2.35 (dt, J = 8.5, 13.9 Hz, 1 H), 2.54 (td, J = 3.8, 7.2 Hz, 2 H), 2.61 (ddd, J = 4.8, 6.9, 12.2 Hz, 1 H), 2.70 (ddd, J = 3.1, 6.9, 9.5 Hz, 1 H), 5.92 (d, J = 3.3 Hz, 1 H), 6.06 (d, J = 3.1 Hz, 1 H), 7.47 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.3, 22.4, 27.8, 29.3, 30.9, 33.6, 35.7, 36.2, 45.9, 50.2, 103.8, 104.6, 122.9, 155.1, 169.9, 197.8; IR (neat) 1749, 1658, 1592 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{25}O_5$ 309.1706, found 309.1702. minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.2 Hz, 6 H), 1.44 - 1.61 (m, 3 H), 1.76 (ddd, J = 9.5, 12.1, 13.2 Hz, 1 H), 1.89 - 2.06 (m, 3 H), 2.10 (s, 3 H), 2.26 (ddd, J = 2.6, 5.3, 10.6 Hz, 1 H), 2.51 (td, J = 2.1, 7.2 Hz, 2 H), 2.57 (m, J = 6.5 Hz, 1 H), 2.94 (ddd, J = 3.1, 7.2, 15.4 Hz, 1

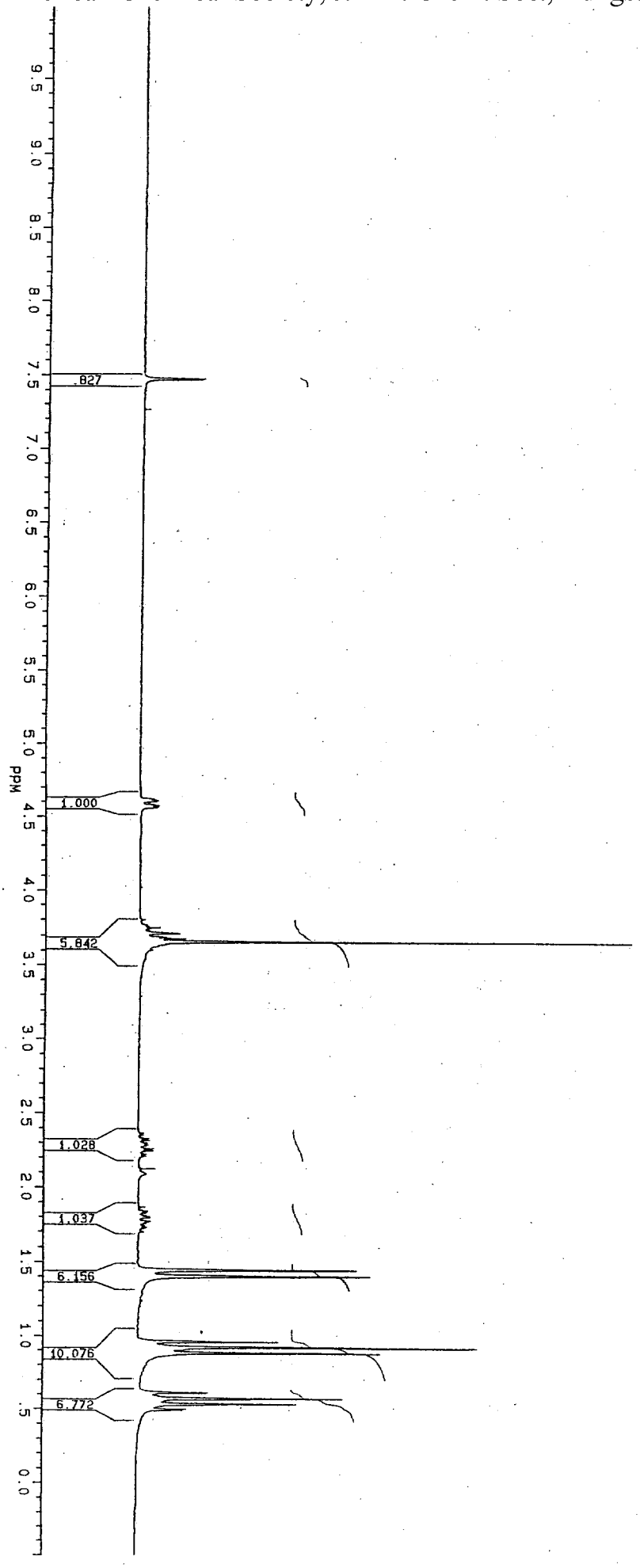
H), 5.66 (d, J = 4.4 Hz, 1 H), 6.25 (d, J = 7.2 Hz, 1 H), 7.46 (d, J = 2.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.3, 22.4, 25.8, 27.8, 28.8, 33.7, 35.3, 35.7, 42.8, 50.3, 96.9, 103.4, 123.6, 155.5, 169.5, 198.0; IR (neat) 1751, 1643 cm^{-1}; HRMS ($M+Na^+$) calcd for $C_{17}H_{24}O_5Na$ 331.1521, found 331.1494.

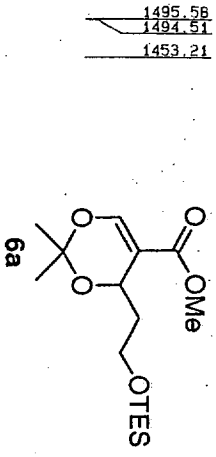


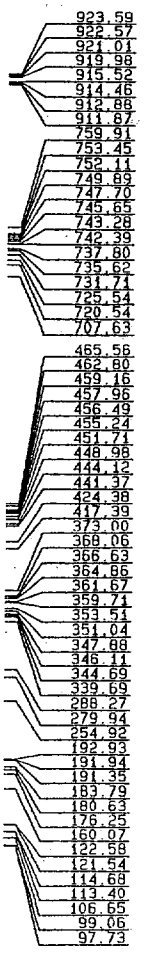


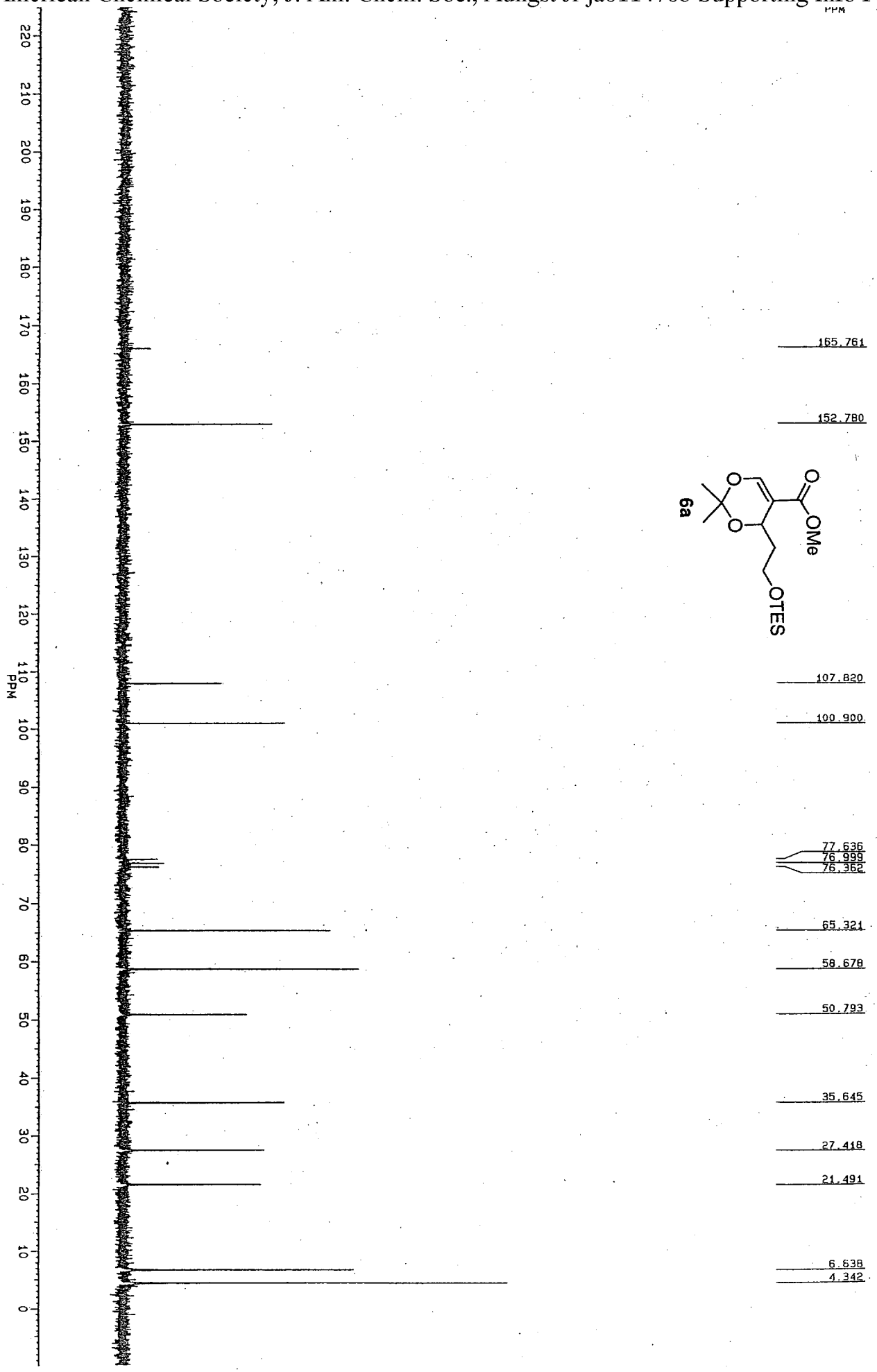


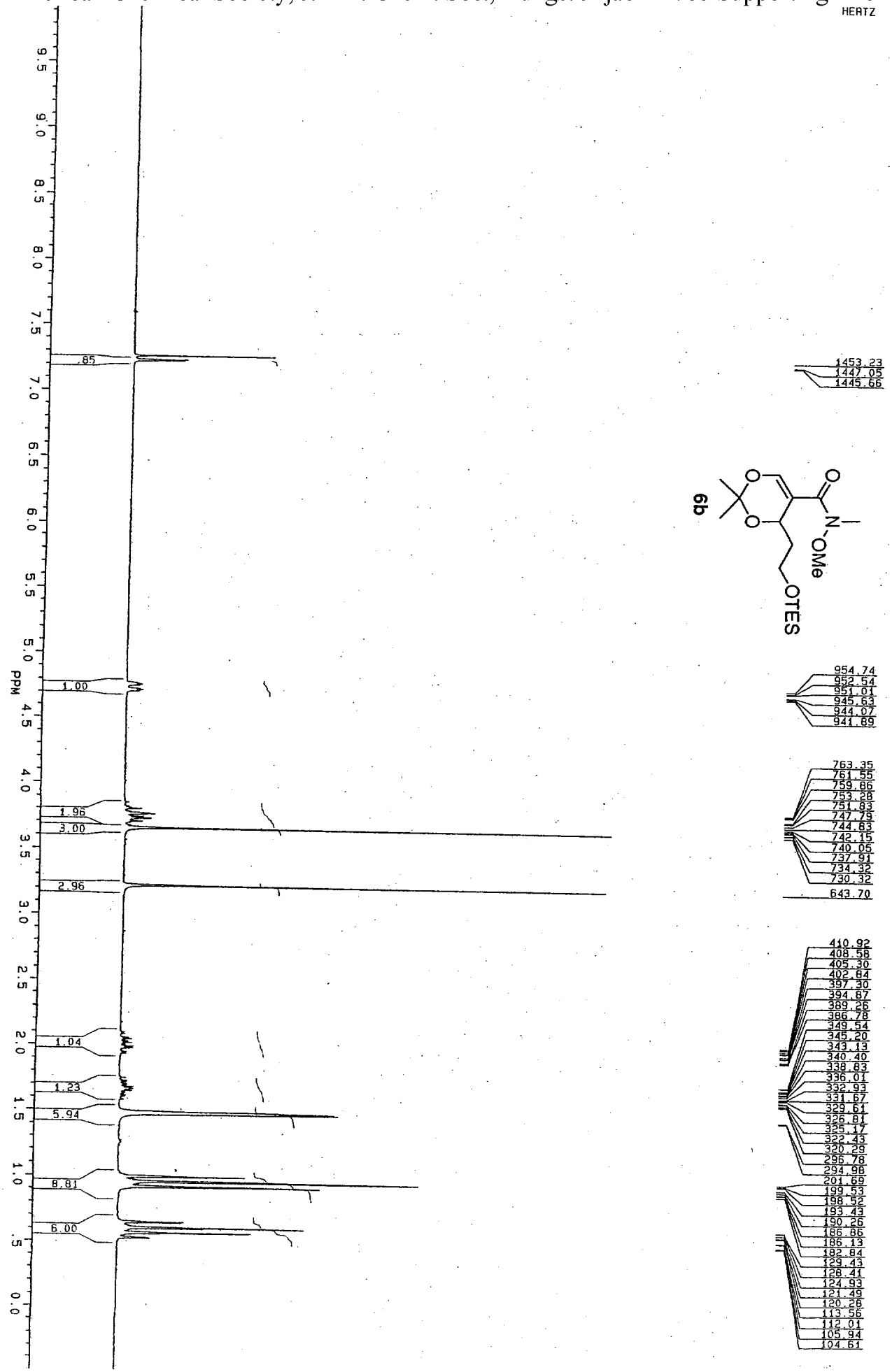


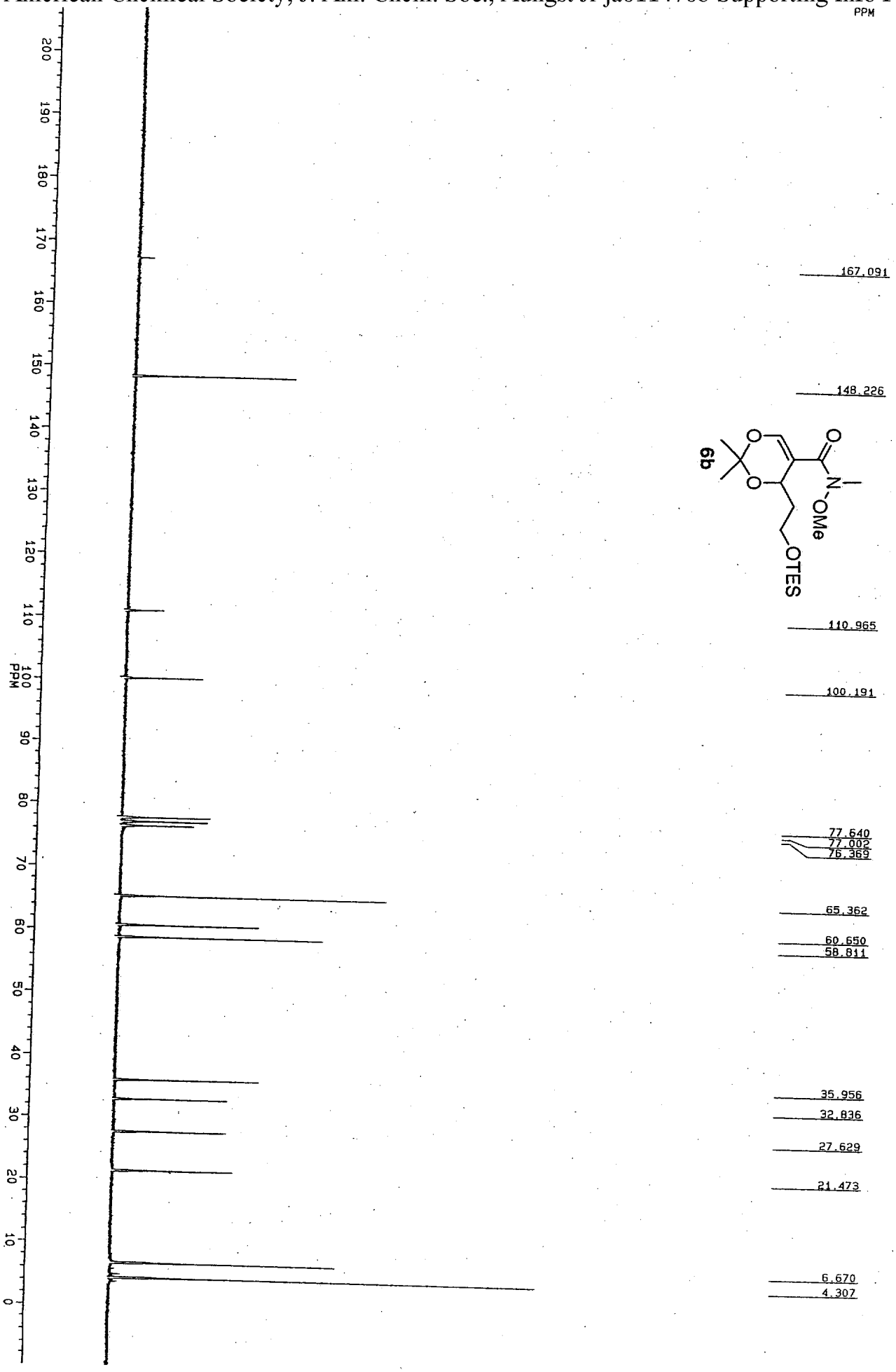


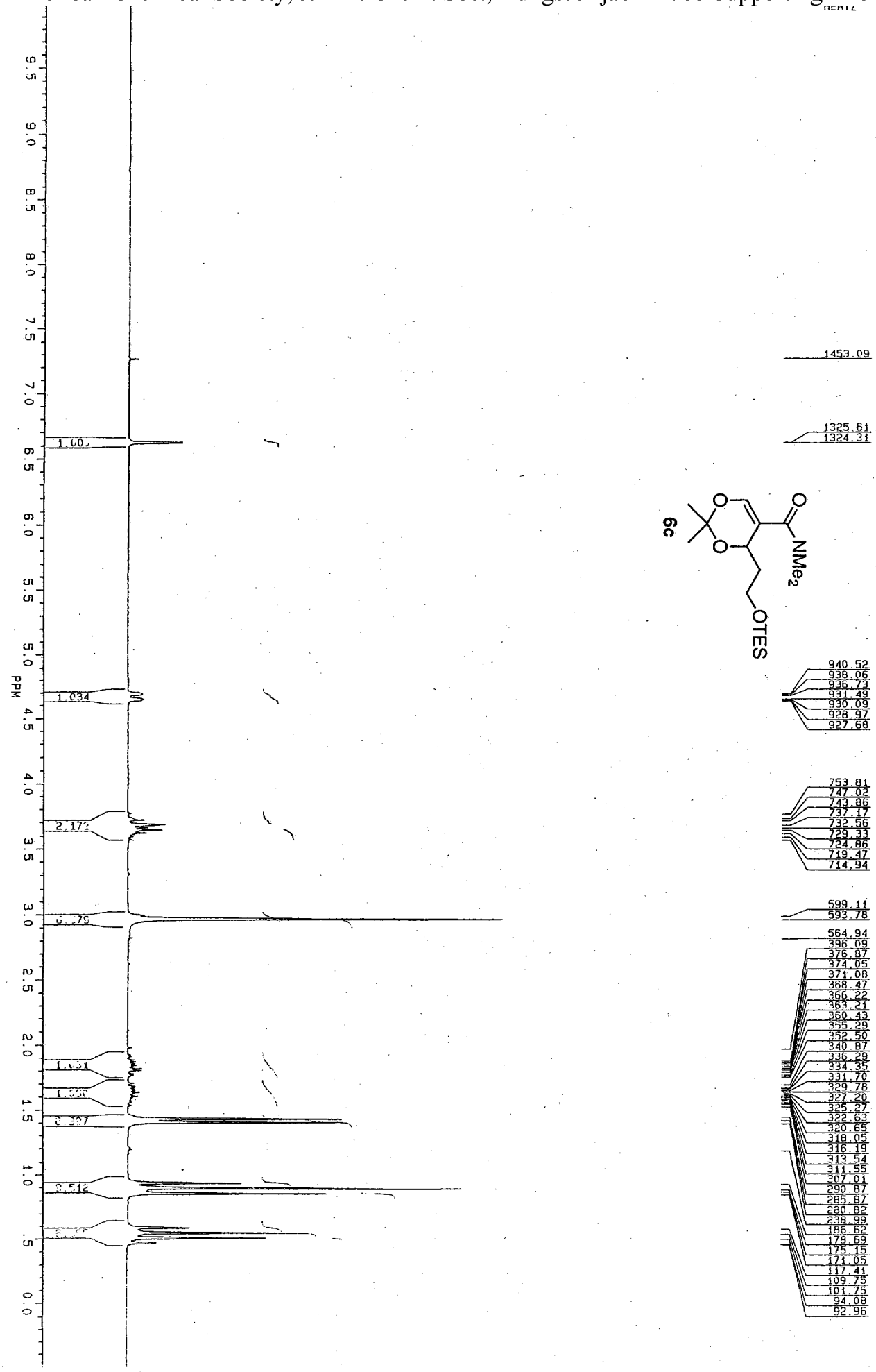


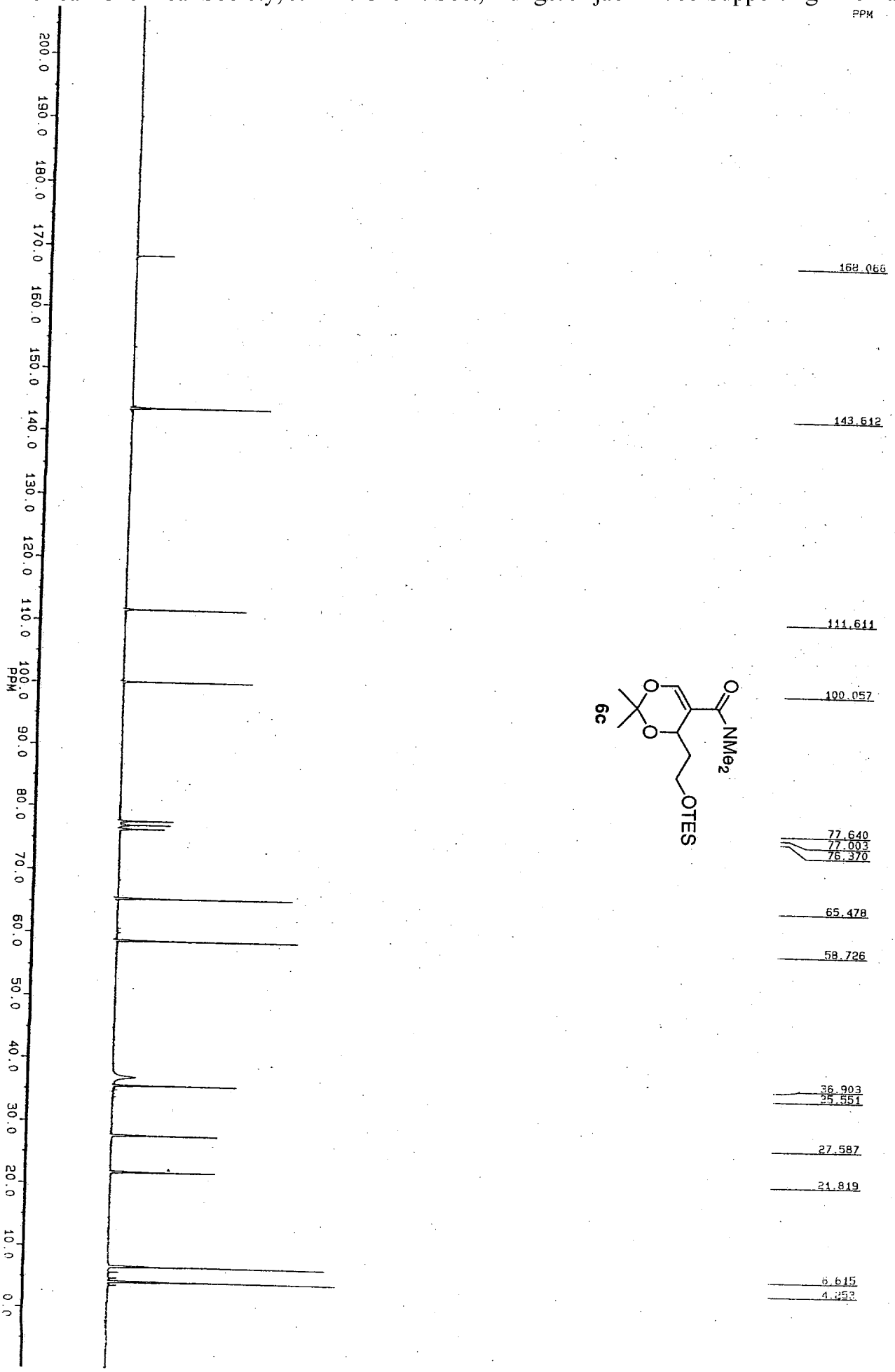


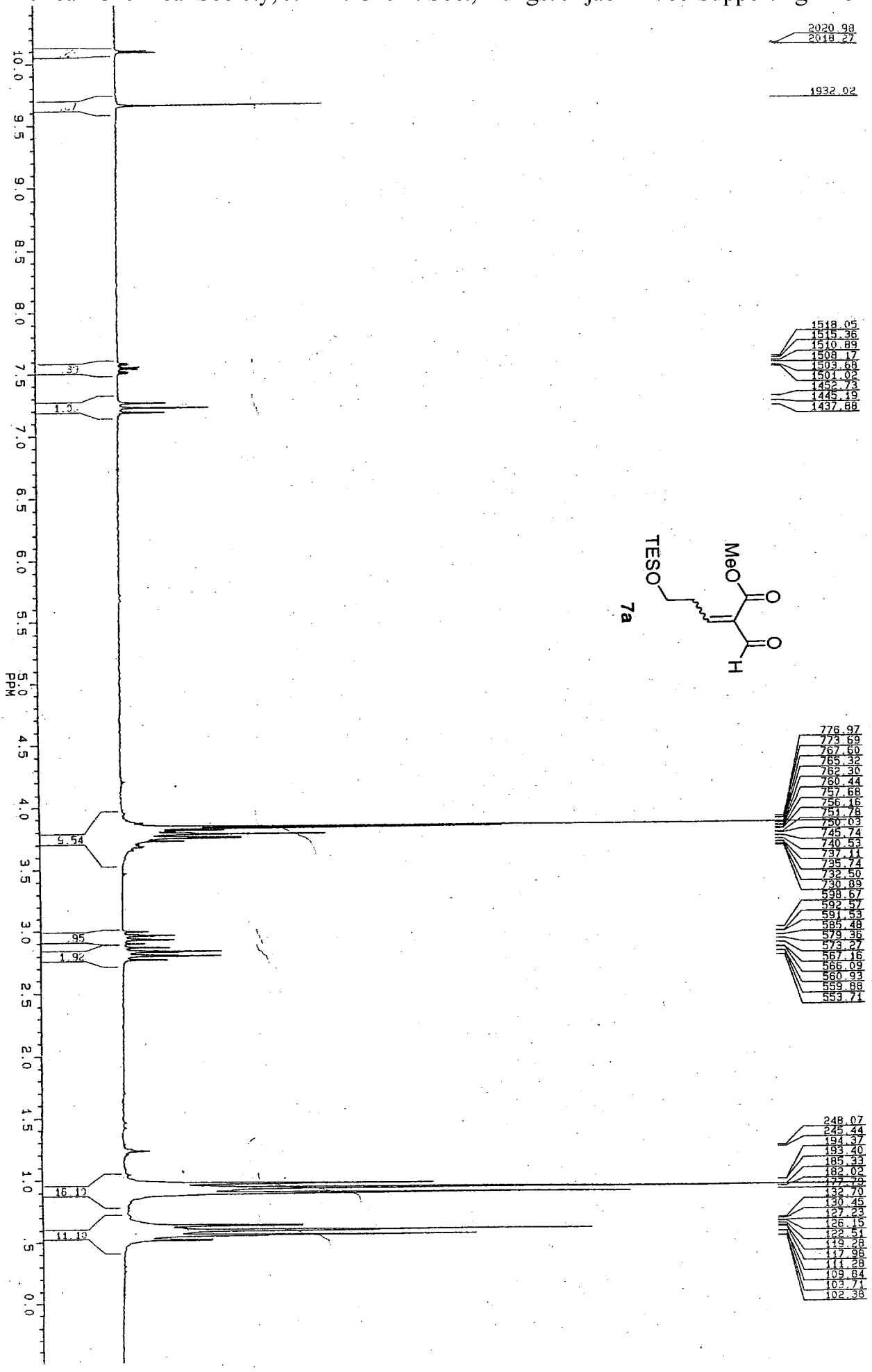


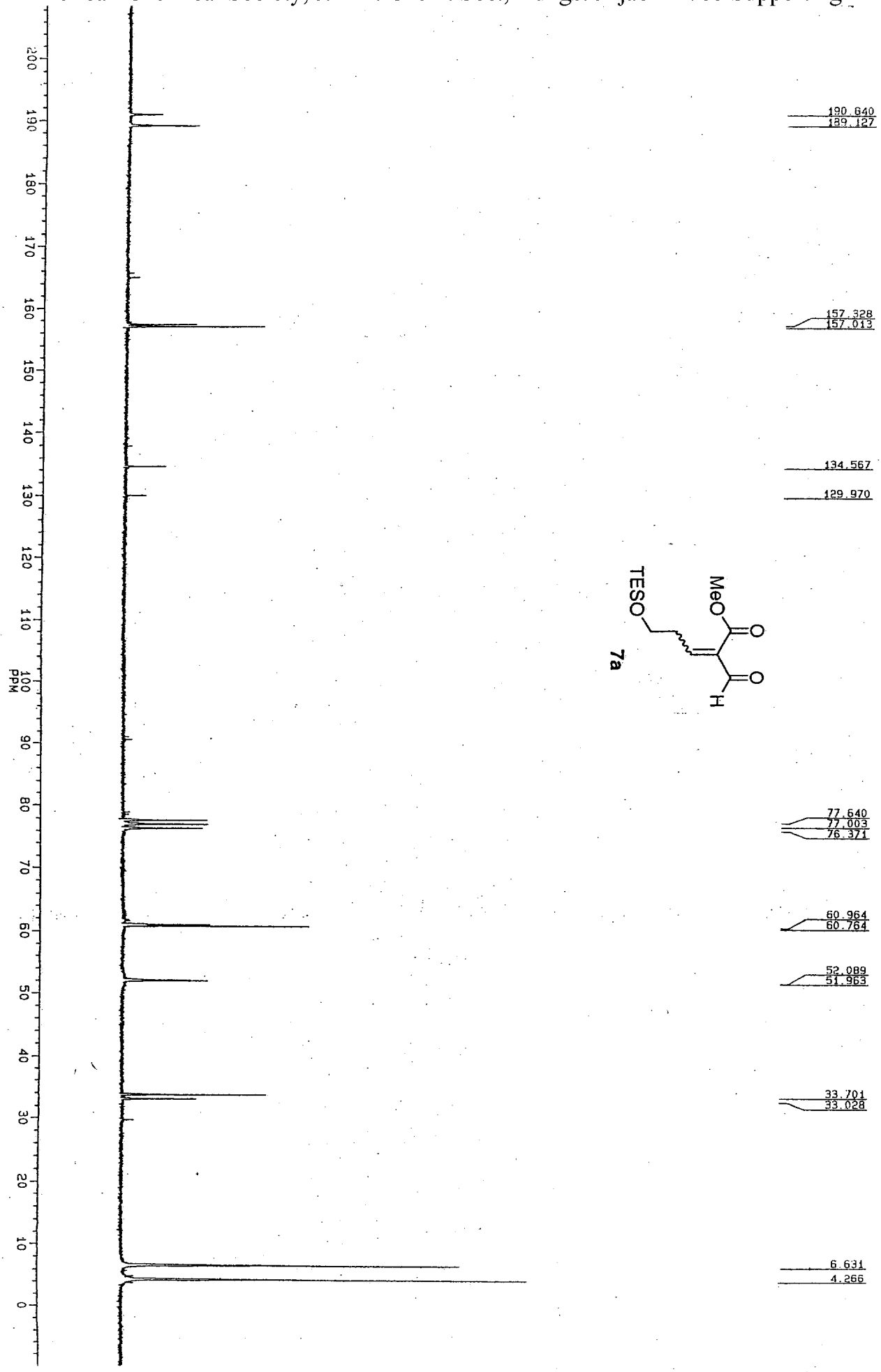


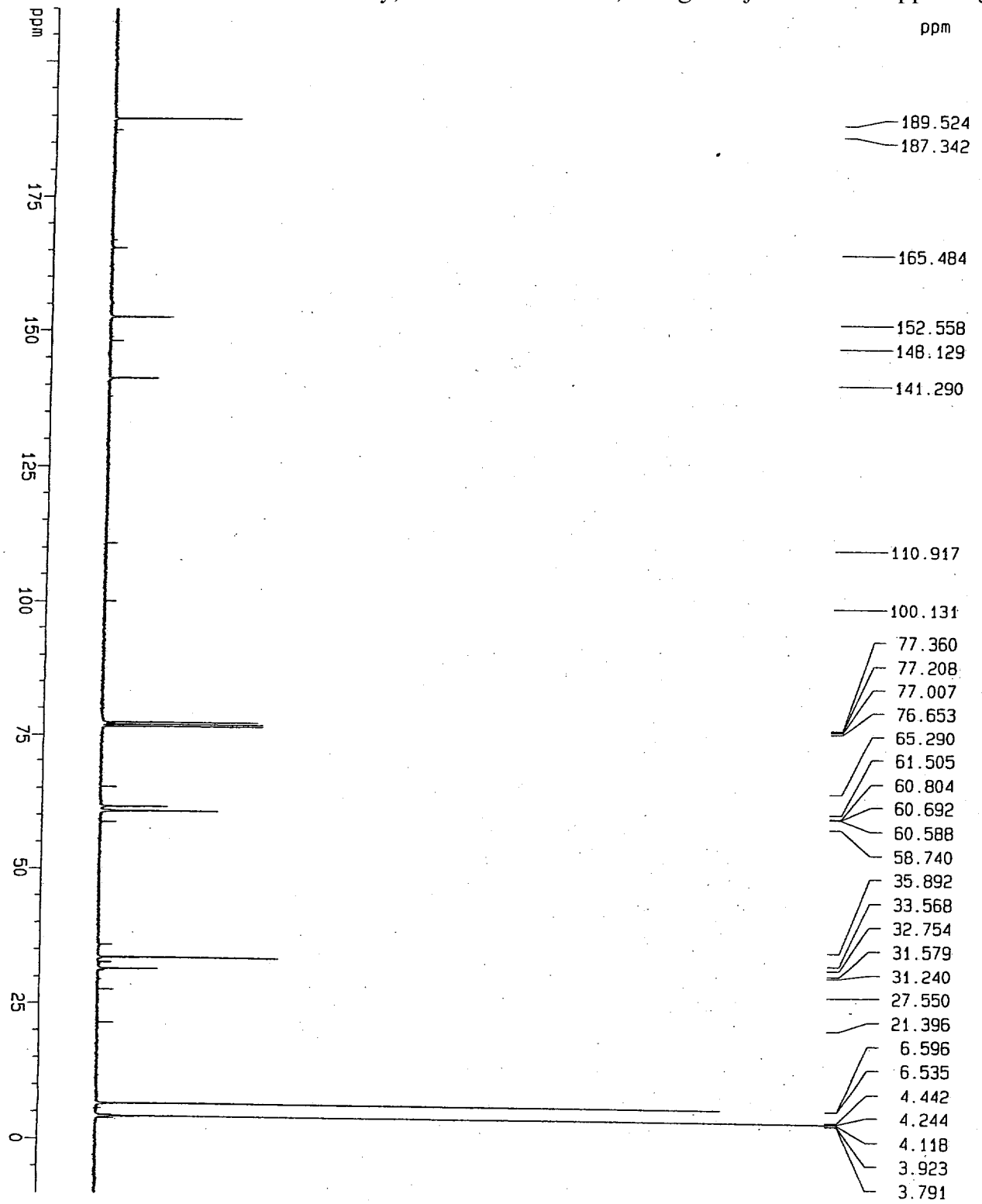







2020.98
2018.27
1932.02
1518.05
1515.36
1510.89
1508.17
1503.68
1501.02
1452.73
1445.19
1437.68
TESO
MeO
O
O
H
7a
776.97
773.69
767.60
765.32
762.30
760.44
757.68
756.16
751.78
750.03
745.74
740.53
737.11
735.74
732.50
730.89
598.67
592.57
591.53
585.48
579.36
573.27
567.16
566.09
560.93
559.88
553.71
248.07
245.44
194.37
193.40
185.33
182.02
177.79
132.70
130.45
127.23
126.15
122.51
119.28
117.96
111.28
109.84
103.71
102.38
9.54
.95
1.92
16.13
11.13
1.0
.39
PPM



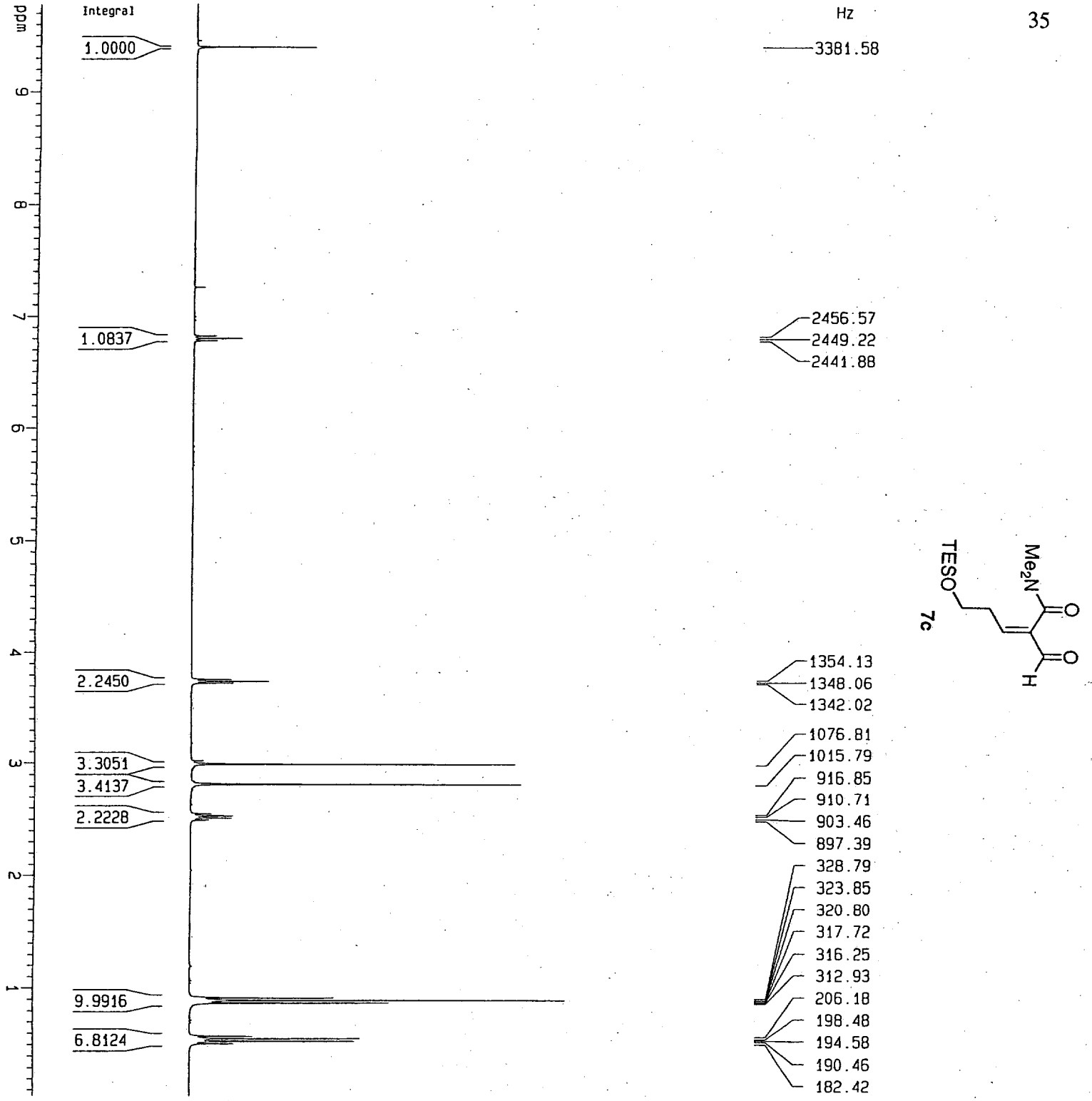


Current Data Parameters
NAME Jan27-00-Funk
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20000127
Time 16.21
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 29411.766 Hz
FIDRES 0.448788 Hz
AQ 1.1141620 sec
RG 32768
DW 17.000 usec
DE 24.29 usec
TE 300.0 K
HL1 0 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 106.00 usec
S4 30 dB
D11 0.03000000 sec
S2 30 dB
P1 8.50 usec
SFO1 90.5638242 MHz
NUCLEUS 13C

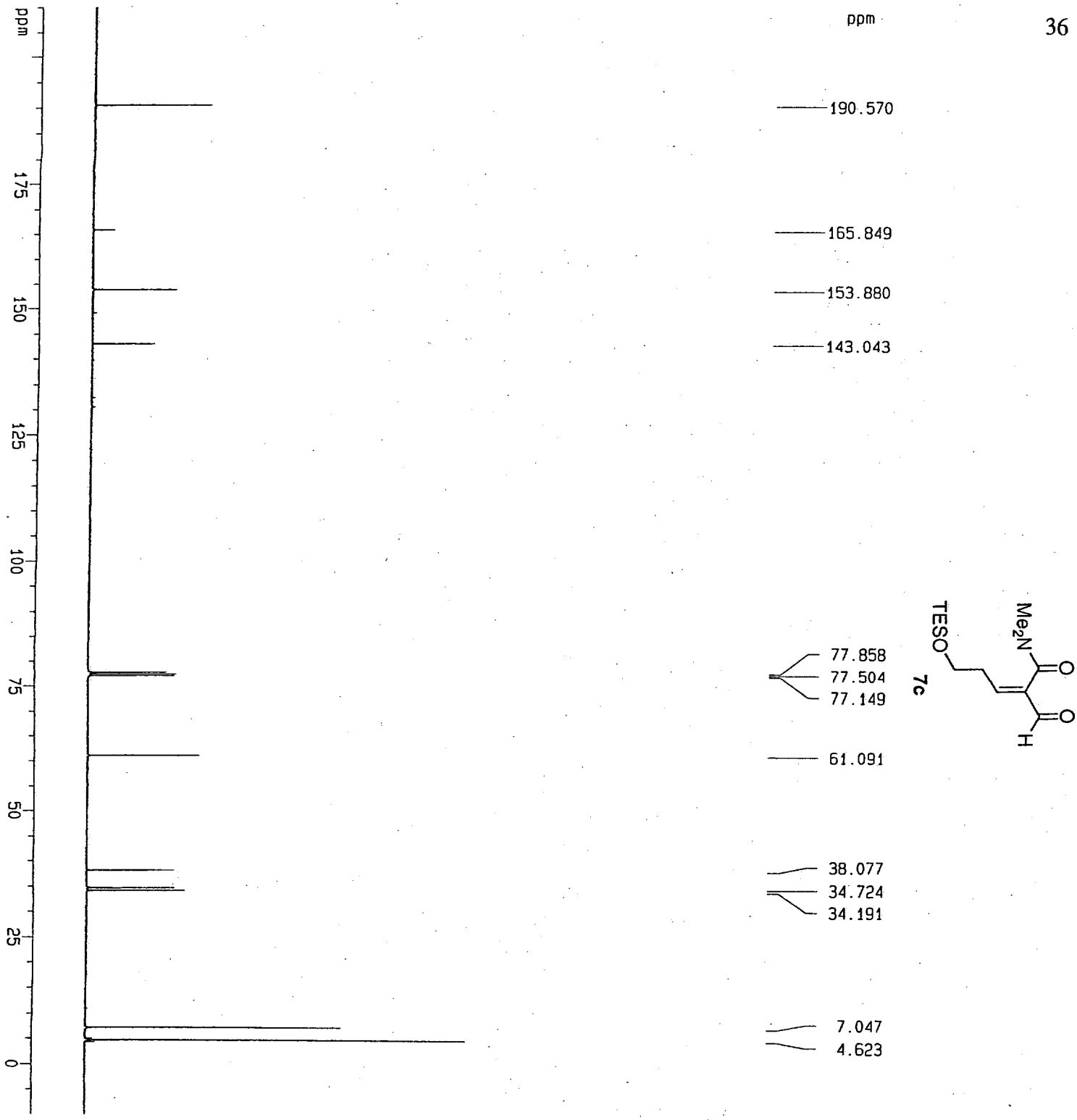
F2 - Processing parameters
SI 32768
SF 90.5557694 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 210.000 ppm
F1 19016.71 Hz
F2P -10.000 ppm
F2 -905.56 Hz
PPMCM 11.00000 ppm/cm
HZCM 996.11346 Hz/cm



7c

```
Current Data Parameters
NAME                  Jan25-00-Funk
EXPNO                           10
PROCNO                           1

F2 - Acquisition Parameters
Date_                     20000125
Time                         16.48
INSTRUM                      spect
PROBHD          5 mm QNP 1H
PULPROG                      zg30
TD                           32768
SOLVENT                      CDCl3
NS                              16
DS                               2
SWH                       7462.687 Hz
FIDRES                    0.227743 Hz
AQ                        2.1955061 sec
RG                             128
DW                        67.000 usec
DE                        95.71 usec
TE                        300.0 K
HL1                          0 dB
D1                        1.00000000 sec
P1                        12.60 usec
SFO1                      360.1361940 MHz
NUCLEUS                      1H

F2 - Processing parameters
SI                            16384
SF                        360.1339834 MHz
WDW                              EM
SSB                               0
LB                            0.30 Hz
GB                                0
PC                             1.00

1D NMR plot parameters
CX                           20.00 cm
F1P                          9.781 ppm
F1                           3522.45 Hz
F2P                          0.044 ppm
F2                           15.89 Hz
PPMCM                        0.48684 ppm/cm
HZCM                         175.32817 Hz/cm
```

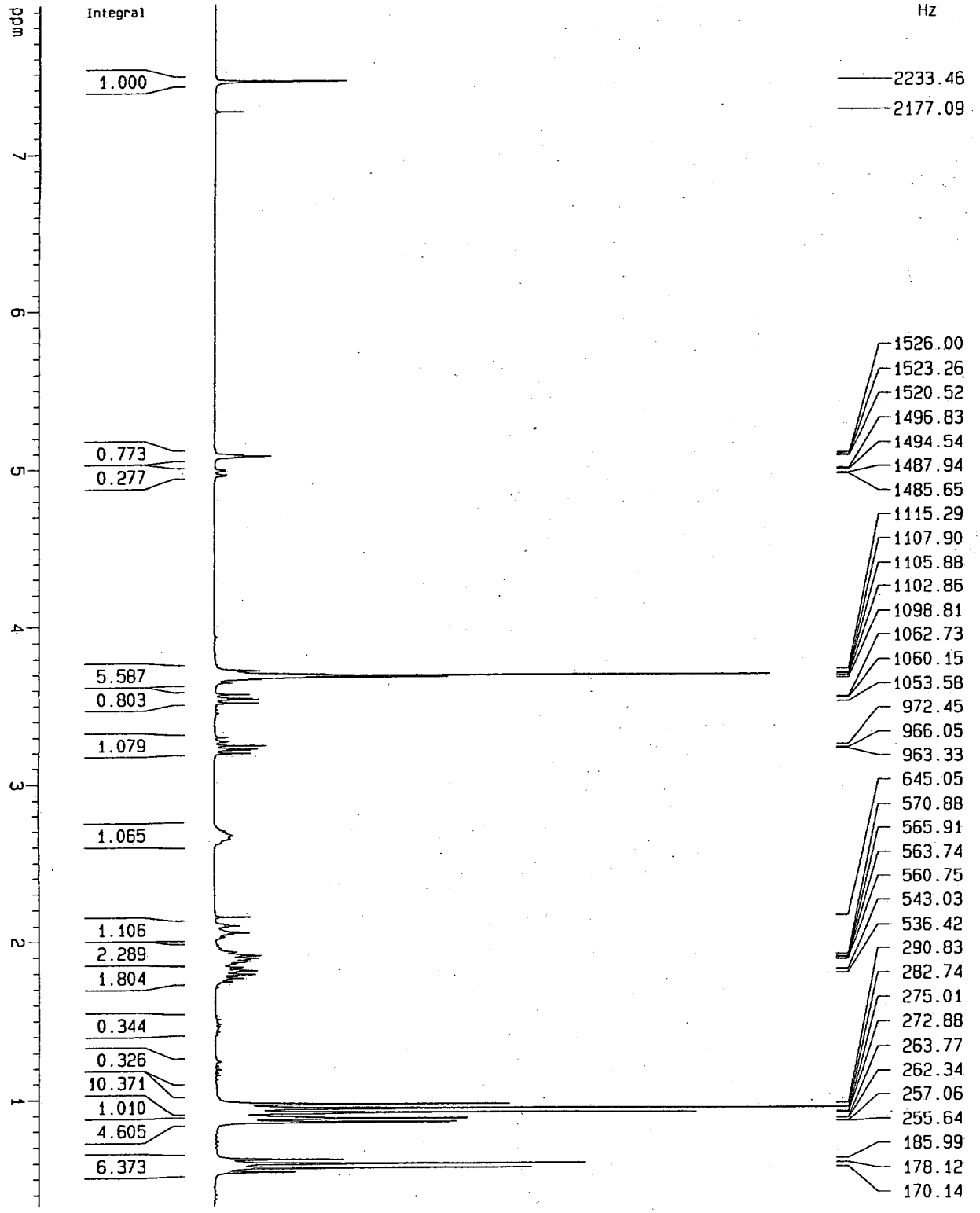


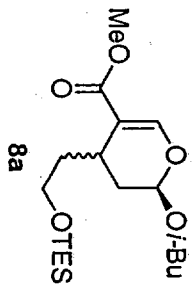
Current Data Parameters
NAME Jan25-00-Funk
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20000125
Time 17.10
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 29411.766 Hz
FIDRES 0.448788 Hz
AQ 1.1141620 sec
RG 32768
DW 17.000 usec
DE 24.29 usec
TE 300.0 K
HL1 0 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 106.00 usec
S4 30 dB
D11 0.03000000 sec
S2 30 dB
P1 8.50 usec
SFO1 90.5638242 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 32768
SF 90.5557236 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

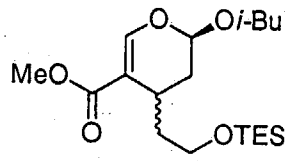
1D NMR plot parameters
CX 20.00 cm
F1P 210.000 ppm
F1 19016.70 Hz
F2P -10.000 ppm
F2 -905.56 Hz
PPMCM 11.00000 ppm/cm
HZCM 996.11298 Hz/cm



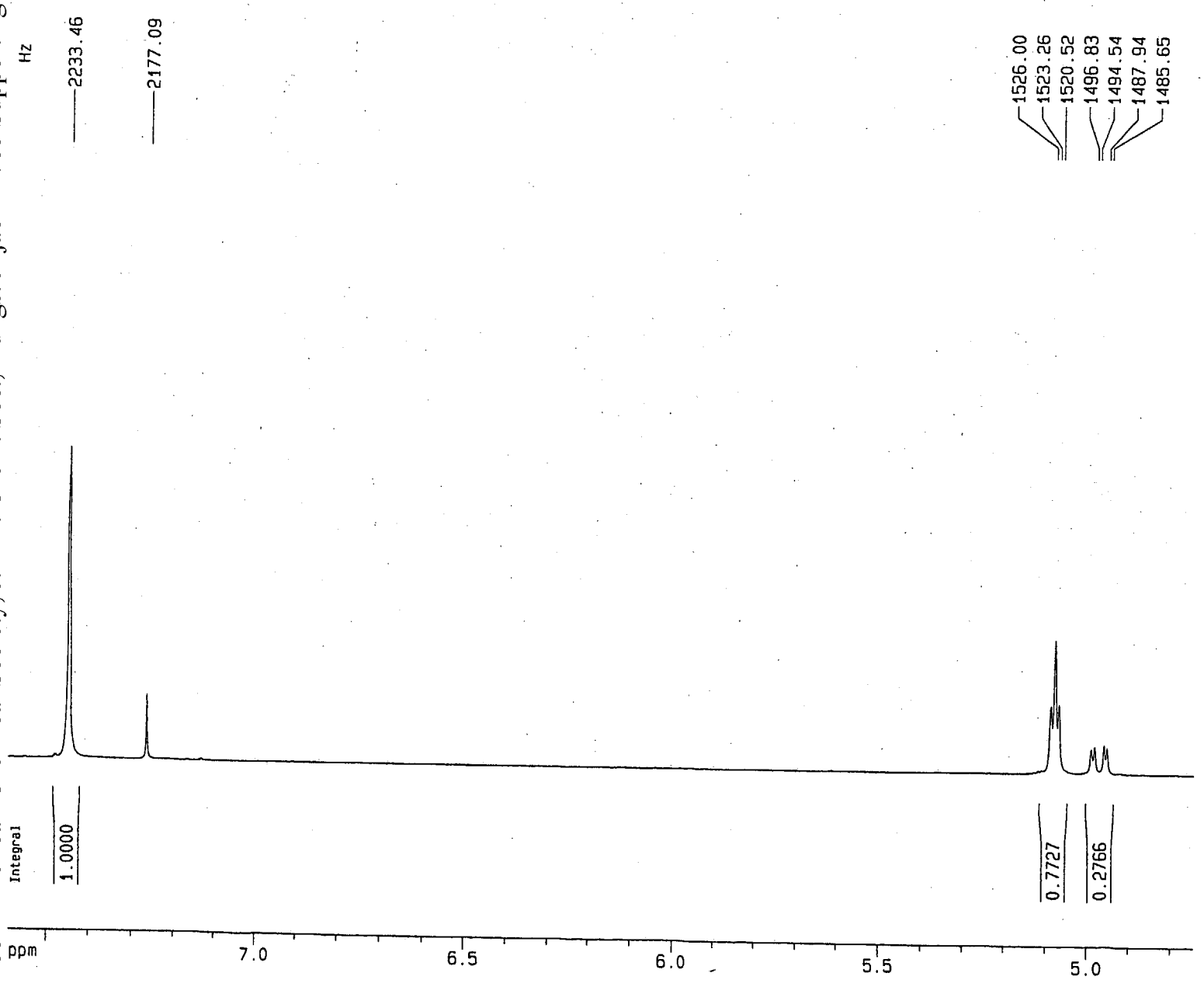


8a

```
Current Data Parameters
NAME                  Nov29-2000-Funk
EXPNO                              10
PROCNO                              1

F2 - Acquisition Parameters
Date_                        20001129
Time                            18.05
INSTRUM                          spect
PROBHD     5 mm QNP 1H/1
PULPROG                          zg30
TD                              65536
SOLVENT                         CDCl3
NS                                 16
DS                                  2
SWH                       6172.839 Hz
FIDRES                     0.094190 Hz
AQ                        5.3084660 sec
RG                                 57
DW                          81.000 usec
DE                           6.00 usec
TE                            300.0 K
D1                    1.00000000 sec

========== CHANNEL f1 ==========
NUC1                              1H
P1                           11.70 usec
PL1                           0.00 dB
SFO1                299.8718518 MHz

F2 - Processing parameters
SI                               32768
SF                    299.8700099 MHz
WDW                                EM
SSB                                 0
LB                           0.30 Hz
GB                                  0
PC                              1.00

1D NMR plot parameters
CX                             20.00 cm
F1P                          7.944 ppm
F1                         2382.05 Hz
F2P                          0.327 ppm
F2                          98.10 Hz
PPMCM                     0.38082 ppm/cm
HZCM                    114.19753 Hz/cm
```



8a



Current Data Parameters

NAME	Nov29-2000-Funk
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20001129
Time	18.05
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	57
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ========

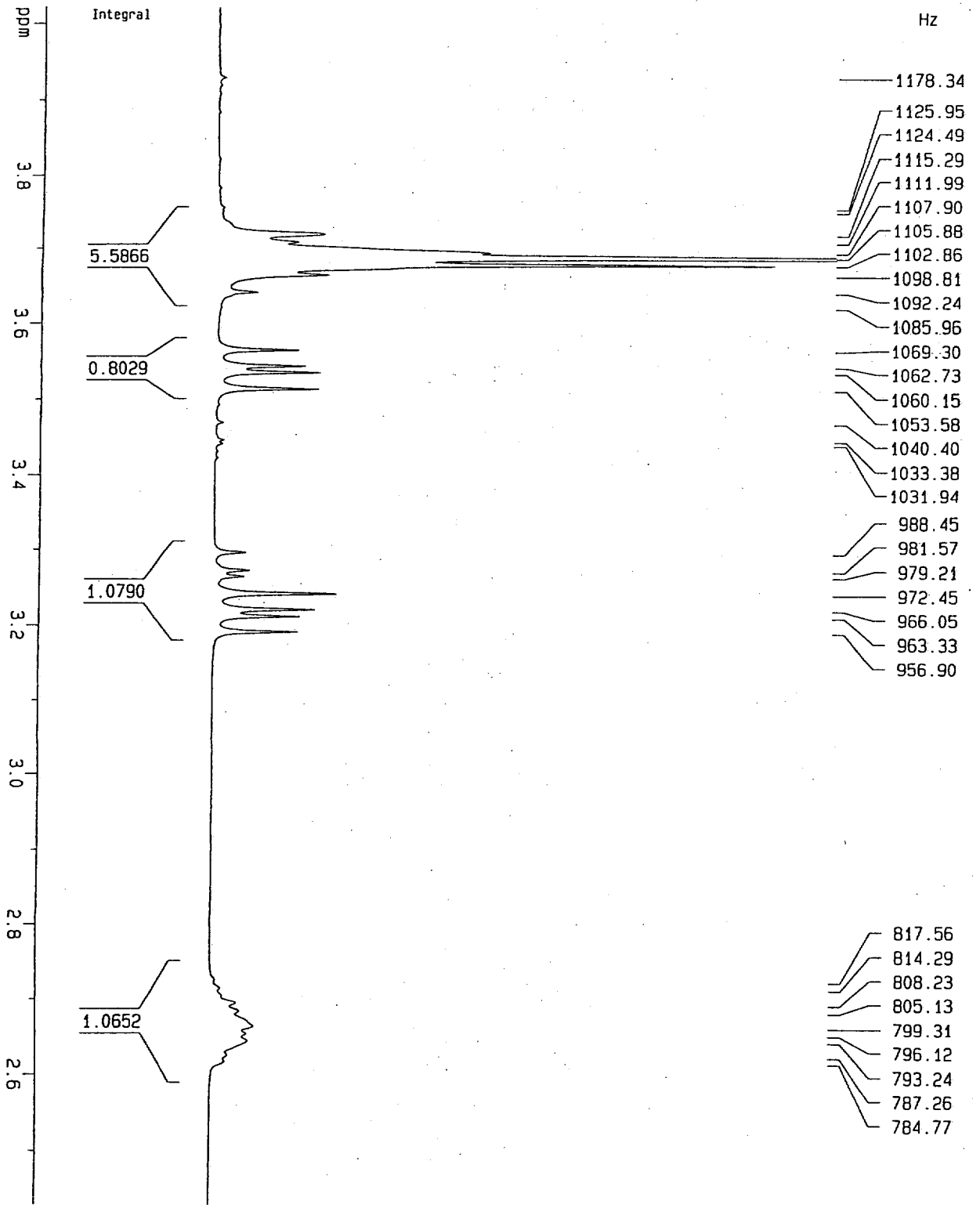
NUC1	1H
P1	11.70 usec
PL1	0.00 dB
SFO1	299.8718518 MHz

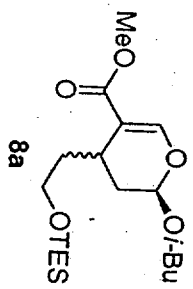
F2 - Processing parameters

SI	32768
SF	299.8700099 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

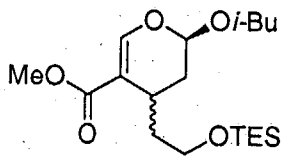
CX	20.00 cm
F1P	7.591 ppm
F1	2276.42 Hz
F2P	4.745 ppm
F2	1422.79 Hz
PPMCM	0.14233 ppm/cm
HZCM	42.68133 Hz/cm



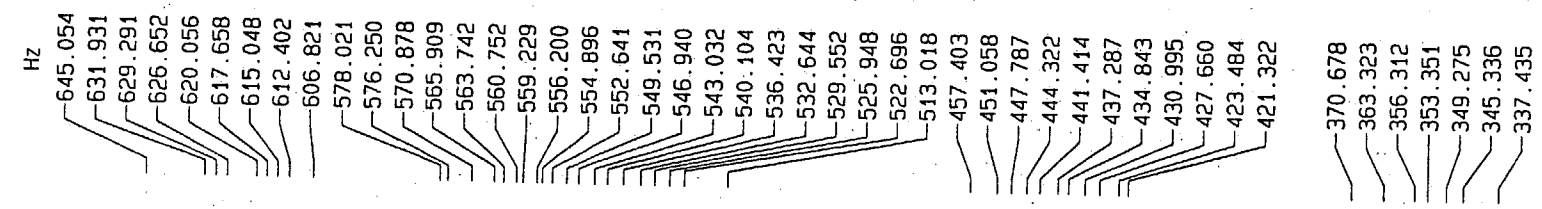


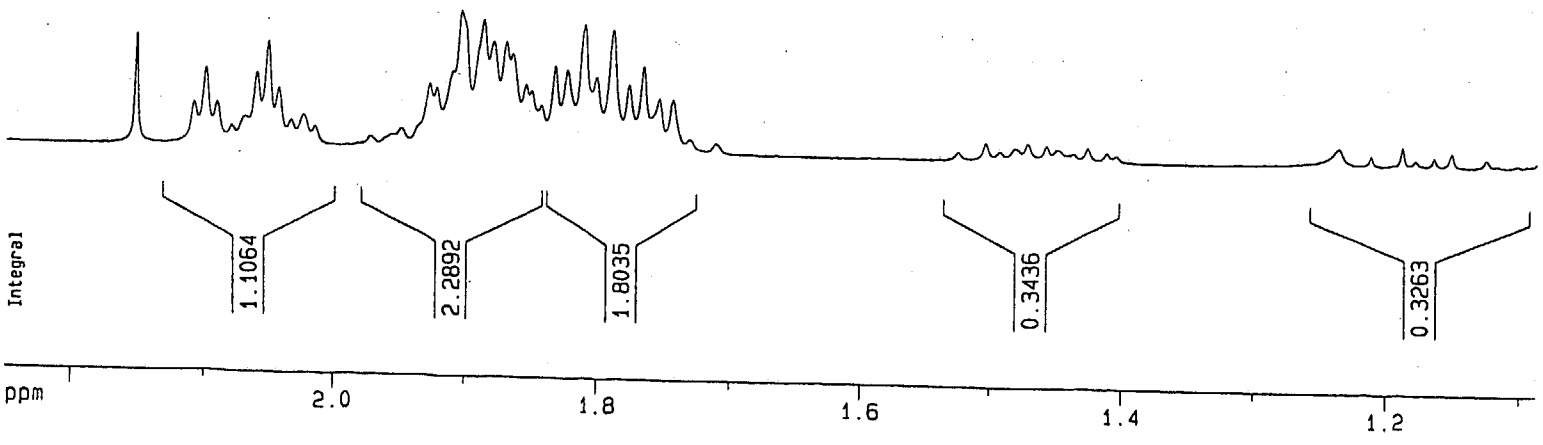
8a

```
Current Data Parameters
NAME                  Nov29-2000-Funk
EXPNO                             10
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20001129
Time                           18.05
INSTRUM                         spect
PROBHD     5 mm QNP 1H/1
PULPROG                         zg30
TD                             65536
SOLVENT                        CDCl3
NS                                16
DS                                 2
SWH                        6172.839 Hz
FIDRES                     0.094190 Hz
AQ                         5.3084660 sec
RG                                57
DW                             81.000 usec
DE                              6.00 usec
TE                             300.0 K
D1                         1.00000000 sec

========== CHANNEL f1 ==========
NUC1                              1H
P1                             11.70 usec
PL1                             0.00 dB
SFO1                   299.8718518 MHz

F2 - Processing parameters
SI                             32768
SF                     299.8700099 MHz
WDW                               EM
SSB                                0
LB                              0.30 Hz
GB                                 0
PC                              1.00

1D NMR plot parameters
CX                             20.00 cm
F1P                             4.022 ppm
F1                          1206.18 Hz
F2P                             2.428 ppm
F2                            728.15 Hz
PPMCM                       0.07971 ppm/cm
HZCM                       23.90154 Hz/cm
```



8a





Current Data Parameters

NAME	Nov29-2000-Funk
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20001129
Time	18.05
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	57
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ========

NUC1	1H
P1	11.70 usec
PL1	0.00 dB
SFO1	299.8718518 MHz

F2 - Processing parameters

SI	32768
SF	299.8700099 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	2.249 ppm
F1	674.38 Hz
F2P	1.087 ppm
F2	326.01 Hz
PPMCM	0.05809 ppm/cm
HZCM	17.41825 Hz/cm