Indium-Mediated Reductive Cyclizations of Optically Active Iodoalkynes: Synthesis and Biological Evaluation for HIV-Protease Inhibitors

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General. All reactions were carried out under a positive pressure of argon or nitrogen. ^{1}H NMR spectra were recorded on a JEOL JNM-EX-270 or JEOL JNM-LA-500 spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 (67.8 MHz) or JEOL JNM-LA-500 (125.0 MHz) spectrometer spectrometer. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-HX/HX-110A instrument. Metallic indium was purchased from Kojundo Chemical Laboratory Co., Ltd. For flash chromatography, silica gel FL60D (Fuji Silysia Chemical Ltd.) and silica gel 60N (Kanto Chemical Co. Inco.) were employed.

Preparation of 2-butynyloxy-3-iodo-tetrahydropyran (2)

To a stirred, ice-cold suspension of 2.410 g (10.71 mmol) of *N*-iodosuccinimide in 2.5 ml of dichloromethane was added a mixture of 3,4-dihydro-2*H*-pyran (600 mg, 7.14 mmol) and 2-butyn-1-ol (525 mg, 7.50 mmol) in 2.5 ml of dichloromethane over 5 min. After warming to room temperature with stirring over 2 h, 5 ml of water was added, and the stirring was continued for 1 h. The layers were separated and aqueous layer was extracted with 2 x 60 ml of ethyl acetate. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ (2 x 10 ml) and brine solution, dried over anhydrous K_2CO_3, filtered, and concentrated. Chromatography over silica gel using 9% diethyl ether in hexane afforded the title iodo ether **2** (1.786 g, 89%) as an yellow oil.

2: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.54–1.57 (m, 1H), 1.83–1.88 (m, 1H), 1.86 (s, 3H), 1.98–2.03 (m, 1H), 2.32–2.36 (m, 1H), 3.59–3.63 (m, 1H), 3.93–3.95 (m, 1H), 4.12–4.20 (m, 1H), 4.22 (d, J = 15.2 Hz, 1H), 4.28 (d, J = 15.2 Hz, 1H), 4.87 (d, J = 4.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 3.7, 24.7, 28.7, 31.7, 55.4, 62.9, 74.2, 83.1, 100.1; LRMS (EI) *m/z* 280 (M^+); HRMS *m/z* calcd for $C_9H_{13}O_2I$ 279.9962, found 279.9960; IR ($CHCl_3$, cm^{-1}) 2952, 2858, 1439, 1375.

Preparation of 3-(1-iodo-ethylidene)-hexahydro-furo[2,3-b]-pyran (2a (*E*) and 2a (*Z*))

To a solution of **2** (140 mg, 0.50 mmol) in dry methanol (1.5 ml) was added indium (0) (57 mg, 0.50 mmol) and iodine (63 mg, 0.25 mmol). The mixture was stirred for 5 h at room temperature under argon atmosphere. The mixture was evaporated, filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane :

ethyl acetate = 9 : 1) to give unseparable mixture (84 mg) of **2a** (*E*) (47%) and **2a** (*Z*) (13%).

2a (*E* and *Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.30–1.64 (m, 3H), 1.78–1.83 (m, 1H), 2.42 (s, 3H), 2.64–2.67 (m, 1H), 3.64 (d, 1H, *J* = 11.0 Hz), 3.75–3.84 (m, 1H), 3.99 (d, 1H, *J* = 14.3 Hz), 4.29 (d, 1H, *J* = 14.3 Hz), 5.19 (d, 1H, *J* = 3.0 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 22.3, 22.5, 28.9, 45.9, 61.1, 65.7, 85.1, 99.48, 146.3; LRMS (EI), *m/z* 280 (M^+); HRMS *m/z* calcd for $C_9H_{13}O_2I$ 279.9962, found 279.9961; IR ($CHCl_3$, cm^{-1}) 3011, 2947, 1214, 1149, 1083, 1017.

3-Ethylidene-hexahydro-furo[2,3-*b*]pyran (2b (*E*) and **2b (*Z*))**

2b (*E*) ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.51–1.61 (m, 3H), 1.67 (d, 3H, *J* = 6.75 Hz), 1.85–1.87 (m, 1H), 2.65 (s, 1H), 3.68 (dd, 1H, *J* = 3.7, 9.5 Hz), 3.85 (t, 1H, *J* = 9.5 Hz), 4.22 (d, 1H, *J* = 12.5 Hz), 4.53 (d, 1H, *J* = 12.5 Hz), 5.19 (d, 1H, *J* = 3.7 H), 5.27 (d, 1H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 14.1, 22.6, 23.7, 37.3, 61.3, 68.4, 100.8, 115.1, 140.3; LRMS (EI) *m/z* 154 (M^+); HRMS, *m/z* calcd for $C_9H_{14}O_2$: 154.0994, found 154.0993; IR ($CHCl_3$, cm^{-1}) 3025, 2948, 1618, 1453, 1377, 1231, 1165, 1080, 1040.

2b (*Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.26–1.30 (m, 1H), 1.60–1.62 (m, 4H), 1.83–1.90 (m, 1H), 2.60 (d, 1H, *J* = 3.7 Hz), 3.44 (dt, 1H, *J* = 2.1, 5.5 Hz), 3.84–3.86 (m, 1H), 4.45 (d, 1H, *J* = 12.8 Hz), 4.61 (d, 1H, *J* = 12.8 Hz), 5.13 (d, 1H, *J* = 3.7 Hz), 5.27–5.32 (m, 1H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 14.4, 20.4, 22.6, 41.8, 64.5, 69.2, 101.6, 114.0, 137.7; LRMS (EI) *m/z* 154 (M^+); HRMS *m/z* calcd for $C_9H_{14}O_2$ 154.0994, found 154.0996; IR ($CHCl_3$, cm^{-1}) 3023, 2938, 1603, 1455, 1377, 1230, 1172, 1074, 1038.

Preparation of 3-iodo-2-(3-phenylprop-2-ynyloxy)tetrahydropyran (3)

To a stirred, ice cold suspension of 3.375 g (15.00 mmol) of *N*-iodosuccinimide in 2.5 ml of dichloromethane was added a mixture of 3,4-dihydro-2*H*-pyran (840 mg, 10.00 mmol) and 1-phenyl-1-propyn-3-ol (1.386 g, 10.50 mmol) in 2.5 ml of dichloromethane over 5 min. After warming to room temperature with stirring over 2 h, 5 ml of water was added, and the stirring was continued for 1 h. The layers were separated and aqueous layer was extracted with 2 x 60 ml of ethyl acetate. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ (2 x 10 ml) and brine solution, dried over anhydrous K_2CO_3, filtered, and concentrated. Chromatography over silica gel using 9 % diethyl ether in hexane afforded the title iodo ether **3** (2.820 g, 83%) as a

colorless oil.

3: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ1.57–1.60 (m, 1H), 1.85–1.86 (m, 1H), 2.02–2.07 (m, 1H), 2.36–2.39 (m, 1H), 3.63–3.66 (m, 1H), 4.00–4.01 (m, 1H), 4.18 (d, 1H, *J* = 4.6 Hz), 4.50 (d, 1H, *J* = 15.7 Hz), 4.55 (d, 1H, *J* = 15.7 Hz), 4.96 (d, 1H, *J* = 4.6 Hz), 7.31–7.35 (m, 3H), 7.45–7.48 (m, 2H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 24.9, 28.5, 31.9, 55.5, 63.2, 84.2, 86.6, 100.4, 122.5, 128.3, 128.5, 131.8; Anal. calcd. for $C_{14}H_{15}O_2I$, H 4.58; C 47.27; I 38.45, found H 4.34; C 47.35; I 38.61; IR ($CHCl_3$, cm^{-1}) 2233, 1125, 1070, 1026, 776, 738.

Preparation of 3-benzylidene-hexahydrofuro[2,3-b]-pyran (3b (*E*) and **3b (*Z*))**

To a solution of **3b** (855 mg, 2.50 mmol) in dry methanol (10 ml) was added indium (0) (290 mg, 2.52 mmol) and iodine (318 mg, 1.25 mmol). The mixture was stirred for 3 h at room temperature under argon atmosphere. The mixture was evaporated, filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane : ethyl acetate = 9 : 1) to give **3b** (*E*) (351 mg, 65%) and **3b** (*Z*) (97 mg, 18%).

3b (*E*)**:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ1.30 (d, 1H, *J* = 13.5 Hz), 1.63 (d, 1H, *J* = 11.5 Hz), 1.93–1.97 (m, 1H), 2.10 (d, 1H, *J* = 13.5 Hz), 2.77 (d, 1H, *J* = 3.7 Hz), 3.43 (t, 1H, *J* = 11.0 Hz), 3.81 (d, 1H, *J* = 11.0 Hz), 4.78 (dd, 2H, *J* = 14.1, 50.8 Hz), 5.13 (d, 1H, *J* = 3.7 Hz), 6.22 (s, 1H), 7.08–7.29 (m, 5H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 20.4, 22.9, 43.4, 60.2, 64.3, 100.4, 120.4, 126.5, 127.8, 128.4, 136.9, 139.8; LRMS (EI) *m/z* 216 (M^+); HRMS, *m/z* calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1156; IR ($CHCl_3$, cm^{-1}) 3029, 1718, 1176, 1111, 766, 747.

3b (*Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.57–1.64 (m, 3H), 1.98–2.04 (m, 1H), 2.97(s, 1H), 3.68 (d, 1H, *J* = 9.5 Hz), 3.89 (d, 1H, *J* = 9.5 Hz), 4.44 (d, 1H, *J* = 13.0 Hz), 4.74 (d, 1H, *J* = 13.0 Hz), 5.25 (s, 1H), 6.30 (s, 1H), 7.23–7.33 (m, 5H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 22.5, 23.2, 38.2, 61.4, 69.8, 101.2, 121.5, 126.9, 127.8, 128.4, 136.7, 141.8; LRMS (EI) *m/z* 216 (M^+); Anal. Calc. for $C_{14}H_{16}O_2$: H 7.46; C 77.74, found: H 7.48; C 77.41; IR ($CHCl_3$, cm^{-1}) 3009, 1602, 1244, 1176, 769, 747.

Preparation of 4-iodomethylene-2-(4-methoxy-phenyl)-tetrahydrofuran (4a (*E*) and **(*Z*))**

Indium (0) (171 mg, 1.49 mmol) and iodine (189 mg, 0.74 mmol) were added to the solution of 1-(2-iodo-1-prop-2-ynyloxy-ethyl)-4-methoxy-benzene **4** (470 mg, 1.49 mmol) in dry methanol (3

ml). The mixture was stirred for 18 h at room temperature under argon atmosphere. The mixture was extracted with 2 x 60 ml diethyl ether. The combined organic extracts were washed with brine solution, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Chromatography over silica gel using 10% diethyl ether in hexane afforded the title product **4a** (*E*) (137 mg, 29%) and **4a** (*Z*) (179 mg, 38%) respectively as a colorless oil.

4a (*E*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.50 (dd, 1H, *J* = 9.2, 16.8 Hz), 2.94 (dd, 1H, *J* = 4.9, 16.8 Hz), 3.80 (s, 3H), 4.35 (d, 1H, *J* = 12.8 Hz), 4.55 (d, 1H, *J* = 12.8 Hz), 4.98 (t, 1H, *J* = 9.2 Hz), 6.04 (s, 1H), 6.88 (dd, 2H, *J* = 2.2, 6.7 Hz), 7.29 (dd, 2H, *J* = 2.2, 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 45.5, 55.3, 67.3, 71.4, 80.1, 113.9, 127.3, 132.8, 152.4, 159.3; LRMS (FAB$^+$) *m/z* 317 (MH^+); HRMS calcd for $C_{12}H_{14}O_2I$ 317.0040, found: 317.0027; IR ($CHCl_3$, cm^{-1}) 3009, 2959, 2936, 2911, 2839, 1640, 1250, 1177, 1035.

4a (*Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.56 (dt, 1H, *J* = 8.5, 9.8 Hz), 2.94 (dd, 1H, *J* = 4.9, 9.8 Hz), 3.79 (s, 3H), 4.27 (d, 1H, *J* = 14.5 Hz), 4.50 (d, 1H, *J* = 14.5 Hz), 5.00 (t, 1H, *J* = 9.8 Hz), 6.01 (s, 1H), 6.88 (dd, 2H, *J* = 1.8, 6.7 Hz), 7.29 (dd, 2H, *J* = 1.8, 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 43.1, 55.2, 66.8, 75.5, 82.1, 113.7, 113.8, 127.2, 132.8, 151.4, 159.3; LRMS (FAB$^+$) *m/z* 317 (MH^+); HRMS calcd for $C_{12}H_{14}O_2I$ 317.0040, found: 317.0027; IR ($CHCl_3$, cm^{-1}) 3009, 2960, 2936, 2910, 2839, 1642, 1250, 1176, 1036.

Preparation of *N*-[2-iodo-1-(4-methoxy-phenyl)-ethyl]-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (5)

To a stirred, ice cold suspension of 586 mg (2.62 mmol) of *N*-iodosuccinimide in 2.5 ml of dichloromethane was added a mixture of 4-vinylanisole (320 mg, 2.39 mmol) and *N*-*p*-toluenesulfonyl propargylamine (500.0 mg, 2.39 mmol) in 2.2 ml of dichloromethane over 5 min. After warming to room temperature with stirring over 2 h, 4.7 ml of water was added, and the stirring was continued for 1 h. The layers were separated and aqueous layer was extracted with 2 x 60 ml of ethyl acetate. The combined organic extracts were washed with 10 % aqueous $Na_2S_2O_3$ (2 x 10 ml) and brine solution, dried over anhydrous K_2CO_3, filtered, and concentrated. Chromatography over silica gel using 13% diethyl ether in hexane afforded the title iodo ether **5** (785 mg, 70%) as a white solid.

5: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 1H), 2.45 (s, 3H), 3.45 (dd, 1H, *J* = 2.4, 18.9 Hz), 3.55

(dd, 1H, *J* = 4.3, 10.0 Hz), 3.80 (s, 3H), 3.86 (t, 1H, *J* = 11.3 Hz), 4.20 (dd, 1H, *J* = 2.4, 18.6 Hz), 5.25 (dd, 1H, *J* = 3.9, 11.6 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 7.14 (d, 2H, *J* = 8.5 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 7.78 (d, 2H, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 14.1, 21.5, 32.7, 55.1, 62.1, 73.1, 79.9, 113.9, 126.2, 127.3, 129.5, 129.6, 129.8, 137.3, 143.7, 159.6; Anal. calcd. for $C_{19}H_{20}NO_3SI$; H 4.26; C 48.61; I 27.08; N 2.99; O 10.23; found H 4.24; C 48.65; I 26.85; N 2.80; O 10.01; IR ($CHCl_3$, cm^{-1}): 3305, 3030, 3006, 2962, 2933, 2839, 1461, 1335, 1305, 1159, 1123.

Preparation of 4-iodomethylene-2-(4-methoxy-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine (5a (*E*) and 5a (*Z*))

To a solution of *N*-[2-Iodo-1-(4-methoxy-phenyl)-ethyl]-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide **5** (235 mg, 0.50 mmol) in dry methanol (1.0 ml) was added indium(0) (58 mg, 0.50 mmol) and iodine (64 mg, 0.25 mmol). The mixture was stirred for 18 h at room temperature under argon atmosphere. The mixture was extracted with 2 x 60 ml diethyl ether. The combined organic extracts were washed with brine solution, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography over silica gel using 20 % ethyl acetate in hexane afforded the title product **5a** (*E*) (131 mg, 28%) and **5a** (*Z*) (197 mg, 42%) as a colorless and unseparable oil and **5b** (14 mg, 8%) as an yellow solid.

5a (*E*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.40 (s, 3H), 2.52–2.59 (m, 2H), 3.79 (s, 3H), 4.10 (s, 1H), 4.86–4.88 (m, 2H), 6.12 (s, 1H), 6.80 (d, 2H, *J* = 8.9 Hz), 7.11 (d, 2H, *J* = 8.9 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.53 (d, 2H, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 21.3, 44.6, 52.2, 56.5, 61.8, 71.1, 113.5, 127.1, 127.2, 127.4, 127.5, 134.9, 143.3, 146.9, 158.6; LRMS (FAB^+) *m/z* 470 (MH^+); HRMS calcd for $C_{19}H_{21}NO_3SI$ 470.0289, found 470.0296; IR ($CHCl_3$, cm^{-1}) 2956, 2932, 2838, 1644, 1461, 1346, 1159, 1035.

5a (*Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.40 (s, 3H), 2.72 – 2.78 (m, 2H), 3.78 (s, 3H), 4.07 (s, 1H), 4.99–5.01 (m, 2H), 6.02 (s, 1H), 6.78 (d, 2H, *J* = 8.9 Hz), 7.16 (d, 2H, *J* = 8.9 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.53 (d, 2H, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 21.3, 42.3, 52.8, 55.1, 63.5, 70.3, 113.7, 127.1, 127.2, 127.4, 127.5, 132.7, 143.4, 147.0, 158.9; LRMS (FAB^+) *m/z* 470 (MH^+); HRMS calcd for $C_{19}H_{21}NO_3SI$ 470.0289, found 470.0296; IR ($CHCl_3$, cm^{-1}) 2956, 2932, 2838, 1644, 1461, 1346, 1159, 1035.

Preparation of [3-(2-iodo-cyclohexyloxy)-prop-1-ynyl]-benzene (7)

To a stirred, ice cold suspension of 2.250 g (10.00 mmol) of *N*-iodosuccinimide in 5 ml of dichloromethane was added a mixture of cyclohexene (840 mg, 10.00 mmol) and 1-phenyl-1-propyn-3-ol (1.320 g, 10.00 mmol) in 5 ml of dichloromethane over 5 min. After warming to room temperature with stirring over 2 h, 5 ml of water was added, and the stirring was continued for 1 h. The layers were separated and aqueous layer was extracted with 2 x 60 ml of ethyl acetate. The combined organic extracts were washed with 10 % aqueous $Na_2S_2O_3$ (2 x 10 ml) and brine solution, dried over anhydrous K_2CO_3, filtered, and concentrated. Chromatography over silica gel using 9 % diethyl ether in hexane afforded the title iodo ether **7** (1.171 g, 34%) as an yellow oil.

7: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.26–1.35 (m, 2H), 1.39–1.41 (m, 2H), 1.83 (m, 1H), 2.00 (dq, 1H, *J* = 3.7, 10.7 Hz), 2.26–2.29 (m, 1H), 2.40–2.42 (m, 1H), 3.66 (dt, 1H, *J* = 4.5, 8.6 Hz), 4.14 (dt, 1H, *J* = 4.5, 9.8 Hz), 4.50 (d, 2H, *J* = 6.4 Hz), 7.31–7.32 (m, 3H), 7.44–7.46 (m, 2H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 19.1, 23.4, 25.4, 34.8, 57.5, 81.7, 85.4, 86.0, 128.2, 128.3, 131.7; LRMS (FAB^+) *m/z* 341 (MH^+); HRMS calcd for $C_{15}H_{18}OI$ 341.0404, found 341.0407. IR ($CHCl_3$, cm^{-1}) 3690, 3006, 1448, 1228, 1168, 1083, 775, 743.

Preparation of 3-benzylidene-octahydro-benzofuran (7b (*E*) and 7b (*Z*))

To a solution of **7** (510 mg, 1.50 mmol) in dry methanol (3 ml) was added indium (0) (172 mg, 1.50 mmol) and iodine (191 mg, 0.75 mmol). The mixture was stirred for 30 h at room temperature under argon atmosphere. The mixture was evaporated, washed with diethyl ether, filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane: ethyl acetate = 9 : 1) to give **7b** (*E*) (122 mg, 38%) and **7b** (*Z*) (61 mg, 19%).

7b (*E*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.53–1.59 (m, 6H), 1.85–1.88 (m, 1H), 2.07–2.09 (m, 1H), 2.67 (m, 1H), 3.97–4.00 (m, 1H), 4.58–4.61 (dd, 1H, *J* = 1.9, 13.3 Hz), 4.80 (dd, 1H, *J* = 1.9, 13.3 Hz), 6.30 (m, 1H), 7.12–7.14 (m, 2H), 7.25–7.26 (m, 3H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ21.0, 23.3, 27.5, 27.6, 44.9, 68.8, 78.2, 120.0, 126.3, 127.8, 128.4, 137.3, 146.8; LRMS (EI) *m/z* 214 (M^+); HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1357. IR ($CHCl_3$, cm^{-1}) 3008, 1446, 1244, 1182, 1094, 741, 697.

7b (*Z*): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.53–1.59 (m, 6H), 1.85–1.88 (m, 1H), 2.07–2.09 (m, 1H),

2.88–2.91 (m, 1H), 3.92–3.93 (m, 1H), 4.40 (dd, 1H, *J* = 1.9, 13.4 Hz), 4.68 (dd, 1H, *J* = 1.9, 13.4 Hz), 6.18 (m, 1H), 7.18–7.22 (m, 2H), 7.32–7.33 (m, 3H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 20.1, 24.4, 25.8, 27.7, 41.0, 71.6, 78.2, 119.0, 126.5, 127.7, 128.4, 137.3, 146.8; LRMS (EI) *m/z* 214 (M^+); HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1358. IR ($CHCl_3$, cm^{-1}) 3008, 1446, 1244, 1182, 1094, 741, 697.

Preparation of 4-(tetrahydro-furo[2,3-b]pyran-3-ylidene)-butyronitrile (10a(Z)) and 3-(2-prop-2-ynyloxytetrahydro-pyran-3-yl)propionitrile (10b)

To a solution of **1** (50 mg, 0.19 mmol) in dry methanol (1 ml) was added indium (0) (22 mg, 0.19 mmol), iodine (24 mg, 0.09 mmol), and acrylonitrile (16 mg, 0.39 mmol). The mixture was stirred for 17 h at room temperature under argon atmosphere. The mixture was evaporated, washed with diethyl ether, filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane: ethyl acetate = 10 : 1) to give **10a** (*Z* and *E*) (24 mg, 65%), **10b** (3 mg, 7%), and **1a** (4 mg, 8%) respectively.

10a (*Z*)**:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.30–1.33 (m, 1H), 1.57–1.64 (m, 1H), 1.87–1.95 (m, 1H), 1.97–2.03 (m, 1H), 2.33 (ddd, 2H, *J* = 6.4, 7.0, 7.3 Hz), 2.44 (ddd, 2H, *J* = 6.4, 7.0, 7.3 Hz), 2.62–2.74 (m, 1H), 3.45 (dd, 1H, *J* = 7.2, 11.5 Hz), 3.86 (d, 1H, *J* = 11.5 Hz), 4.50 (d, 1H, *J* = 13.3 Hz), 4.63 (d, 1H, *J* = 13.3 Hz), 5.15 (d, 1H, *J* = 3.7 Hz), 5.29 (ddd, 1H, *J* = 2.1, 5.1, 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 17.3, 20.3, 22.6, 25.2, 42.1, 64.5, 68.8, 101.4, 115.3, 119.1, 141.5; LRMS (FAB^+) *m/z* 194 (MH^+); HRMS calcd for $C_{11}H_{16}NO_2$ 194.1182, found 194.1172. IR ($CHCl_3$, cm^{-1}) 3020, 2946, 2250, 1215, 1036.

10b: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.21 (m, 1H), 1.51–1.67 (m, 4H), 1.87–1.97 (m, 2H), 2.44 (s, 1H), 2.43–2.50 (m, 2H), 3.44–3.50 (m, 1H), 3.94–3.98 (m, 1H), 4.32 (d, 2H, *J* = 2.1 Hz), 4.36 (d, 1H, *J* = 6.1 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 15.3, 23.9, 26.8, 27.3, 38.8, 54.6, 64.6, 74.4, 79.2, 102.0, 119.8; Anal. calc. for $C_{11}H_{15}NO_2$: H 7.82; C 68.37; N 7.25; found H 7.99; C 68.54; N 7.25; LRMS (FAB^+) *m/z* 194 (MH^+); HRMS calcd for $C_{11}H_{16}NO_2$ 194.1182, found 194.1187. IR ($CHCl_3$, cm^{-1}) 3306, 3019, 2941, 2250, 2119, 1229, 1041, 635.

Preparation of 4-(tetrahydro-furo[2,3-b]pyran-3-ylidene)-butyric acid ethyl ester (11a (*Z*)).

To a solution of **1** (133 mg, 0.50 mmol) in dry DMF (0.5 ml) was added indium (0) (115 mg, 1.00

mmol), iodine (127 mg, 0.50 mmol), and acrylic acid ethyl ester (250 mg, 2.50 mmol). The mixture was stirred for 17 h at room temperature under argon atmosphere. The mixture was evaporated, washed with diethylether, filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, Hexane : AcOEt = 10 : 1) to give **11a** (*Z* and *E*) (42 mg, 35%), **1a** (48 mg, 36%), **1b** (7 mg, 5%), and **1c** (6 mg, 8%).

11a (*Z*)**:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, 3H, *J* = 7.0 Hz), 1.25–1.28 (m, 1H), 1.57–1.59 (m, 1H), 1.78–1.89 (m, 1H), 1.96–1.99 (m, 1H), 2.22–2.26 (m, 2H), 2.30 (q, 2H, *J* = 5.8 Hz), 2.60 (m, 1H), 3.42 (d, 1H, *J* = 9.2 Hz), 3.48 (q, 2H, *J* = 7.0 Hz), 3.84 (d, 1H, *J* = 9.2 Hz), 4.48 (d, 1H, *J* = 13.1 Hz), 4.63 (d, 1H, *J* = 13.1 Hz), 5.13 (d, 1H, *J* = 4.0 Hz), 5.21 (m, 1H); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 14.1, 20.2, 22.5, 24.7, 33.9, 41.8, 60.3, 64.4, 68.9, 101, 117, 143.0, 171.0; LRMS (FAB^+) *m/z* 240 (M^+); HRMS calcd for $C_{13}H_{20}O_4$ 240.1361, found: 240.11359; IR ($CHCl_3$, cm^{-1}) 3156, 2985, 2942, 2869, 1725, 1463, 1267, 1180, 1095, 1033.

Preparation of (2*R* , 3*S*)- and (2*S*, 3*R*)-3-Iodo-2-{(*S*)-1-methyl-prop-2-ynyloxy}-tetrahydropyran (12 and 13)

To a stirred, ice cold suspension of 4.012 g (17.83 mmol) of *N*-iodosuccinimide in 15 ml of dichloromethane was added a mixture of 3,4-dihydro-2*H*-pyran (1.000 g, 11.89 mmol) and (*S*)-(-)-3-butyn-2-ol (917 mg, 13.07 mmol) in 10 ml of dichloromethane over 5 min. After warming to room temperature with stirring over 2 h, 15 ml of water was added, and the stirring was continued for 1 h. The layers were separated and aqueous layer extracted with 2 x 60 ml of ethyl acetate. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ (2 x 10 ml) and brine solution, dried over anhydrous K_2CO_3, filtrated, and concentrated. Chromatography over silica gel using 9% diethyl ether in hexane afforded the title iodo ethers **12** (1.493 g, 45%) and **13** (1.243 g, 37%) respectively as colorless oil.

12: ^{1}H NMR (CDCl3, 500 MHz) δ 1.48 (d, 3H, *J* = 6.7 Hz), 1.57–1.62 (m, 1H), 1.76–1.78 (m, 1H), 2.00–2.04 (m, 1H), 2.36–2.39 (m, 1H), 2.47 (d, 1H, *J* = 2.2 Hz), 3.58–3.62 (m, 1H), 4.07–4.12 (m, 2H), 4.47 (dq, 1H, *J* = 2.2, 6.7 Hz), 4.79 (d, 1H, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 21.8, 25.3, 29.3, 32.6, 63.8, 64.2, 72.7, 83.7, 101.6; $[\alpha]_D^{26}$= + 24.1 (*c* 1.15, $CHCl_3$); Anal. calcd for $C_9H_{13}O_2I$: H, 4.68; C, 38.57; I, 45.32, found: H, 4.50; C, 38.67; I, 45.48; LRMS (EI) *m/z* 280 (M^+); HRMS (EI) calcd for $C_9H_{13}O_2I$ (M^+) 279.9962, found 279.9951; IR (cm^{-1}, $CHCl_3$) 3307, 2952, 2857,

1439, 1375, 1121, 1095, 1067.

13: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (dd, 3H, *J* = 2.2, 6.7 Hz), 1.55–1.58 (m, 1H), 1.81–1.82 (m, 1H), 2.02–2.05 (m, 1H), 2.34–2.37 (m, 1H), 2.44 (d, 1H, *J* = 2.2 Hz), 3.60–3.63 (m, 1H), 3.90–3.93 (m, 1H), 4.08–4.11 (m, 1H), 4.55 (dq, 1H, *J* = 2.2, 6.7 Hz), 4.99–5.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 21.9, 25.1, 28.6, 32.1, 61.6, 63.3, 73.5, 82.7, 99.3; $[\alpha]_D^{28}$= -127.6 (*c* 1.12, $CHCl_3$); Anal. calcd. for $C_9H_{13}O_2I$: H, 4.68; C, 38.57; I, 45.32, found H, 4.50; C, 38.67; I, 45.48; IR (cm^{-1}, $CHCl_3$) 3306, 2949, 2857, 1438, 1374, 1120, 1094, 1066.

(*2S, 3R*)-3-Iodo-2-{(*R*)-1-methyl-prop-2-ynyloxy}-tetrahydropyran (14)

From (*R*)-(+)-3-butyn-2-ol using the procedure substantially as described above for preparation of compound **14** and **15** were obtained 47% and 46% yields respectively as colorless oil.

14: $[\alpha]_D^{28}$= -24.1 (*c* 1.42, $CHCl_3$); LRMS (EI) *m/z* 280 (M^+); HRMS (EI) calcd for $C_9H_{13}O_2I$ (M^+) 279.9962, found 279.9958. Other spectral data of compounds **14** were in accordance with those of **12**.

(*2R, 3S*)-3-Iodo-2-{(*R*)-1-methyl-prop-2-ynyloxy}-tetrahydropyran (15)

15: $[\alpha]_D^{30}$= +131.0° (*c* 1.06, $CHCl_3$); LRMS (EI) *m/z* 280 (M^+); HRMS (EI) calcd for $C_9H_{13}O_2I$ (M^+) 279.9962, found 279.9956. Other spectral data of compounds **15** were in accordance with those of **13**.

(2*S*, 3a*S*, 7a*R*)-2-Methyl-3-methylene-hexahydro-furo[2,3-b]pyran (12a)

To solution of **12** (1.278 g, 4.57 mmol) in dry methanol (3 ml) was added indium(0) (525 mg, 4.57 mmol) and iodine (580 mg, 2.285 mmol). The mixture was stirred for 30 h at room temperature under argon atmosphere. The mixture was evaporated, washed by diethyl ether, filtrated by celite pad (diethyl ether as eluent), and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, hexane : diethylether = 9 : 1) to give **12a** (352 mg, 50%) as colorless oil.

12a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (d, 1H, *J* = 1.8, 13.5 Hz), 1.33 (d, 3H, *J* = 6.7 Hz), 1.57–1.67 (m, 1H), 1.86–1.93 (m, 1H), 2.01 (d, 1H, *J* = 11.6 Hz), 2.72 (d, *J* = 3.7 Hz), 3.42 (dt, 1H, *J* = 1.8, 11.6 Hz), 3.86 (d, 1H, *J* = 9.6 Hz), 4.76–4.78 (m,1H), 4.92 (m, 1H), 5.00 (m, 1H), 5.14 (d, 1H, *J* = 3.7 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 20.2, 21.6, 22.6, 42.0, 64.6, 77.7, 100.8, 103.9,

152.1; LRMS (EI) *m/z* 154 (M^+); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0991; $[\alpha]_D^{26}$= -120.4 (*c* 1.02, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3011, 2931, 1453, 1370, 1119, 1075, 1033.

(2*S*, 3a*R*, 7a*S*)-2-Methyl-3-methylene-hexahydro-furo[2,3-b]pyran (13a)

13a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29–1.33 (m, 1H), 1.42 (d, 1H, *J* = 6.4 Hz), 1.56–1.65 (m, 1H), 1.85–1.93 (m, 1H), 1.97–2.00 (m, 1H), 2.71 (s, 1H), 3.43 (dt, 1H, *J* = 2.5, 10.5 Hz), 3.84 (d, 1H, *J* = 11.6 Hz), 4.64 (m, 1H), 4.96 (dt, 2H, *J* = 2.5, 10.5 Hz), 5.09 (d, 1H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 20.6, 22.1, 22.5, 42.7, 64.2, 77.7, 100.5, 103.9, 151.9; Anal. calcd. for $C_9H_{14}O_2$: H, 9.16; C, 70.08, found H, 9.39; C, 69.87; $[\alpha]_D^{22}$= +26.3 (*c* 1.09, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3012, 2946, 1453, 1371, 1117, 1074, 1036.

(*2R, 3aR, 7aS*)-2-Methyl-3-methylene-hexahydro-furo[2,3-b]pyran (14a)

From **14** and **15** using the procedure substantially as described above for preparation of compound **14a** and **15a** were obtained 66% and 62% yields respectively as colorless oil.

14a: LRMS (EI) *m/z* 154 (M^+); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0995 $[\alpha]_D^{29}$= +123.9 (*c* 1.37, $CHCl_3$). Other spectral data of **14a** were in accordance with those of **12a**.

(*2R, 3aS, 7aR*)-2-Methyl-3-methylene-hexahydro-furo[2,3-b]pyran (15a)

15a: LRMS (EI) *m/z* 154 (M^+); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found: 154.0989 $[\alpha]_D^{30}$= -27.0 (*c* 1.05, $CHCl_3$). Other spectral data of **15a** were in accordance with those of **13a**.

(*2S, 3R, 3aS, 7aR*)-2-Methyl-hexahydro-furo[2,3-*b*]pyran-3-ol (12b)

A stream of ozone was dispersed into solution of **12a** (409 mg, 2.66 mmol) in methanol(3 ml) at -78 °C for 30 min. The resulting blue solution was purged with oxygene until the solution was clear, then to the solution sodium borohydride (58 mg, 1.81 mmol) was added. The reaction mixture was stirred for an additional 15 min at 0 °C, and then the reaction was quenched with 10% aqueous citric acid (1.5 ml). The resulting mixture was concentrated under reduced pressure, and the residue was partitioned between diethyl ether and brine. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 60 ml). The combined organic layers were dried over anhydrous K_2CO_3 and concentrated carefully under reduced pressure. The resulting residue was chromatographed over silica gel using 25% hexane in diethyl ether as the eluent to furnish the title

alcohol **12b** (326 mg, 77%) as yellow oil.

12b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (dd, 3H, *J* = 2.2, 6.4 Hz), 1.45–1.48 (m, 1H), 1.83–1.95 (m, 2H), 2.11 (m, 2H), 2.36 (s, 1H), 3.50 (dt, 1H, *J* = 2.2, 11.3 Hz), 3.87 (s, 1H), 3.94 (d, 1H, *J* = 11.7 Hz), 4.33 (q, 1H, *J* = 6.4 Hz), 5.07 (d, 1H, *J* = 3.4 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 20.1, 20.2, 22.7, 39.7, 64.0, 79.4, 84.4, 102.3; LRMS (EI) *m/z* 159 (MH^+), HRMS (EI) calcd for $C_8H_{15}O_3$ (MH^+) 159.1021, found 159.1022; $[\alpha]_D^{28}$= -14.5 (*c* 1.06, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3542, 3014, 2971, 1450, 1375, 1121, 1096, 1040.

(*2S, 3S, 3aR, 7aS*)-2-Methyl-hexahydro-furo[2,3-*b*]pyran-3-ol (13b)

From **13a** (385 mg, 2.50 mmol) using the procedure substantially as described above for preparation of compound **13b** was obtained as yellow oil (262 mg, 66%).

13b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (d, 3H, *J* = 6.4 Hz), 1.44–1.46 (m, 1H), 1.91–1.96 (m, 1H), 2.06 (d, 1H, *J* = 3.7 Hz), 2.22–2.28 (m, 2H), 3.44–3.48 (m, 1H), 3.94–3.95 (m, 2H), 4.14–4.16 (m, 1H), 4.98 (d, 1H, *J* = 3.7 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.9, 21.1, 22.8, 42.2, 64.4, 76.1, 80.9, 102.7; LRMS (FAB) *m/z* 159 (MH^+), HRMS (FAB) calcd for $C_8H_{15}O_3$ (MH^+) 159.1021, found 159.1024; $[\alpha]_D^{25}$=+15.3 (*c* 1.09, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3531, 3016, 2959, 1446, 1383, 1121, 1075, 1041.

(*2R, 3S, 3aR, 7aS*)-2-Methyl-hexahydro-furo[2,3-*b*]pyran-3-ol (14b) and (15b)

From **14a** and **15a** using the procedure substantially as described above for preparation of compound **14b** and **15b** were obtained 88% and 64% respectively as colorless oil.

14b: LRMS (EI) *m/z* 159 (MH^+), HRMS (EI) calcd for $C_8H_{15}O_3$ (MH^+) 159.1021, found 159.1026, $[\alpha]_D^{20}$=+14.1 (*c* 1.00, $CHCl_3$). Other spectral data of compound **14b** was in accordance with those of **12b**.

(*2R, 3R, 3aS, 7aR*)-2-Methyl-hexahydro-furo[2,3-*b*]pyran-3-ol (15b)

15b: LRMS (EI) *m/z* 159 (MH^+), HRMS (EI) calcd for $C_8H_{15}O_3$ (MH^+) 159.1021, found 159.1018, $[\alpha]_D^{30}$= -15.7 (*c* 1.23, $CHCl_3$). Other spectral data of compound **15b** was in accordance with those of **13b**.

[(*1S, 2R*)-1-Benzyl-3-(3-*tert*-butylcarbamoyl-octahydro-isoquinolin-2-yl)-2-hydroxypropyl]-

carbamic acid (*2S, 3R, 3aS, 7aR*)-2-methyl-hexahydro-furo[2,3-*b*]pyran-3-yl ester (12d)

To the solution of **12b** (57 mg, 0.38 mmol) in dry dichloromethane (1.4 ml) was added 4-nitrophenyl- chloroformate (108 mg, 0.54 mmol) and triethylamine (108 mg, 1.07 mmol). The mixture was stirred for 22 h at room temperature. The mixture was diluted with ethyl acetate, extracted with satd. aqueous $NaHCO_3$ (10 x 5 ml) and washed with brine. The organic layer was dried with anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was chromatographed over silica gel using 50% ethyl acetate in hexane as the eluent to furnish (100 mg, 87%) the activated alcohol **12c** as an yellow oil. To the solution of the activated alcohol **12c** (29 mg, 0.09 mmol) in dichloromethane (0.4 ml) was added amine **16** (30 mg, 0.075 mmol) and triethylamine (23 mg, 0.22 mmol). The mixture was stirred for 22 h at room temperature. The mixture was concentrated under reduced pressure, diluted with ethyl acetate, extracted with saturated aqueous $NaHCO_3$ (10 x 5 ml) and washed with brine. The organic layer was dried with anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was chromatographed over silica gel using 50% hexane in ethyl acetate as the eluent to furnish **12d** (29 mg, 67%) the title product as white powder.

12d: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12–1.51 (m, 26H), 1.66–2.17 (m, 7H), 2.57–2.65 (m, 2H), 2.90–3.09 (m, 3H), 3.27–3.46 (m, 2H), 3.75–3.78 (m, 1H), 3.90 (s, 1H), 4.76–4.77 (m, 1H), 5.10 (m, 1H), 5.49–5.51 (m, 1H), 5.89 (s, 1H), 7.17–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 19.7, 19.7, 20.6, 22.2, 25.9, 26.1, 28.7, 30.7, 33.4, 35.5, 35.9, 39.4, 51.0,56.2, 58.8, 59.4, 63.4, 70.5, 71.3, 79.5, 100.8, 126.2, 128.3, 129.2, 138.3, 156.4, 173.6; LRMS (FAB) *m/z* 586 (MH^+); HRMS (FAB) calcd for $C_{33}H_{52}N_3O_6$ (MH^+) 586.3855, found 586.3843; $[\alpha]_D^{28}$= -88.3 (*c* 1.05, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3430, 3008, 2928, 2859, 1712, 1670, 1244, 1094, 1052, 768, 736, 660.

[(*1S, 2R*)-1-Benzyl-3-(3-*tert*-butylcarbamoyl-octahydro-isoquinolin-2-yl)-2-hydroxy-propyl]-carbamic acid (*2S, 3S, 3aR, 7aS*)-2-methyl-hexahydro-furo[2,3-*b*]pyran-3-yl ester (13d)

Dry toluene (1.8 ml), **13b** (30 mg, 0.19 mmol), KOH (0.5 mg, 0.01 mmol), and 1,1'-carbonyl diimidazole (184 mg, 1.13 mmol) were added to a 10 ml round-bottomed flask fitted with a dry argon inlet and magnet stirrer and heated to 60 °C with stirring for 3 h. Amine **16** (15 mg, 0.038 mmol), DMAP (0.9 mg, 0.007 mmol), and triethylamine (12 mg, 0.112 mmol) was added. The solution was left to stir at 110 °C for a further 18 h. The clear mixture was left to cool. The

reaction was concentrated *in vacuo*, dissolved in ethyl acetate (60 ml), and washed with saturated aqueous $NaHCO_3$ (5 x 10 ml). The solution was dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was chromatographed over silica gel using 33% hexane in diethyl ether as the eluent to furnish **13d** (13 mg, 50%) the title carbamate as white powder.

13d: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00–1.52 (m, 26H), 1.60–2.18 (m, 7H), 2.25–2.30 (m, 1H), 2.30–2.42 (m, 1H), 2.64–2.72 (m, 1H), 2.78–3.02 (m, 2H), 3.32–3.91 (m, 1H), 3.76–3.88 (m, 1H), 3.90–4.00 (brs, 1H), 4.18–4.24 (m, 1H), 4.96 (d, 1H, *J* = 2.1 Hz), 5.17 (d, 1H, *J* = 3.7 Hz), 5.22 (t, 1H, *J* = 1.8 Hz), 5.88 (s, 1H), 7.18–7.39 (m, 5H); LRMS (FAB) *m/z* 586 (MH^+); HRMS (FAB) calcd for $C_{33}H_{52}N_3O_6$ (MH^+) 586.3855, found 586.3849. The other spectral data could not be measured because of the low yield of the product **13d**.

[(*1S, 2R*)-1-Benzyl-3-(3-*tert*-butylcarbamoyl-octahydro-isoquinolin-2-yl)-2-hydroxy-propyl]-carbamic acid (*2R, 3S, 3aR, 7aS*)-2-methyl-hexahydro-furo[2,3-*b*]pyran-3-yl ester (14d)

14d: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12–1.51 (m, 26H), 1.66–1.81 (m, 4H), 2.25–2.38 (m, 3H), 2.55–2.70 (m, 2H), 2.90–2.99 (m, 3H), 3.38–3.49 (m, 2H), 3.83 (s, 1H), 3.93 (s, 1H), 4.73 (s, 1H), 5.09 (s, 2H), 5.86 (s, 1H), 7.23–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 19.7, 20.1, 20.7, 22.5, 25.9, 26.0, 28.7, 30.7, 30.8, 33.3, 35.5, 35.8, 39.0, 56.1,58.9, 59.9, 63.2, 70.4, 71.1, 79.6, 79.8, 100.7, 126.4, 128.5, 129.4, 138.3, 156.4, 169.0; LRMS (FAB) *m/z* 586 (MH^+); HRMS (FAB) calcd for $C_{33}H_{52}N_3O_6$ (MH^+) 586.3856, found 586.3870; $[\alpha]_D^{29}$= -40.3 (*c* 1.00, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3430, 3008, 2929, 2859, 1723, 1670, 1249, 1094, 1052, 766, 748, 650.

{(*1S,2R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid (*2S, 3R, 3aS, 7aR*)-2-methyl-hexahydro-furo[2,3-b]pyran-3-yl ester (12e)

To the solution of the activated alcohol **12c** (30 mg, 0.09 mmol) in CH_2Cl_2 (0.4 ml) was added amine **17** (30 mg, 0.077 mmol) and triethylamine (23 mg, 0.23 mmol). The mixture was stirred for 37 h at room temperature. The mixture was concentrated under reduced pressure, diluted with ethyl acetate, extracted with saturated aqueous $NaHCO_3$ (10 x 5 ml) and washed with brine. The organic layer was dried with anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was chromatographed over silica gel using 25% hexane in ethyl acetate as the eluent to furnish **12e** (18 mg, 42%) as yellow oil.

12e: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87–0.92 (m, 9H), 1.24 (s, 4H), 1.46 (s, 1H), 1.54 (s, 1H), 1.82 (s, 1H), 2.20 (s, 1H), 2.80–3.11 (m, 6H), 3.41–3.47 (m, 1H), 3.72–3.87 (m, 4H), 4.18 (s, 2H), 4.73 (s, 1H), 4.96 (s, 1H), 5.05 (s, 1H), 6.68 (d, 2H, *J* = 8.5 Hz), 7.22–7.26 (m, 5H), 7.54 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 19.7, 19.7, 20.1, 22.3, 27.2, 35.6, 39.1, 53.8, 54.8, 58.8, 63.3, 72.7, 79.9, 100.9, 114.0, 126.0, 126.4, 128.4, 129.3, 129.5, 133.7, 137.5, 150.7; LRMS (FAB) *m/z*: 576 (MH^+); HRMS (FAB) calcd for $C_{29}H_{42}N_3O_7S$ (MH^+) 576.2743, found 576.2725; $[\alpha]_D^{24}$ = -1.5 (*c* 1.11, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3417, 1715, 1338, 1234, 1151, 1093, 765, 744, 668.

{(*1S,2R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid (*2R, 3S, 3aR, 7aS*)-2-methyl-hexahydro-furo[2,3-*b*]pyran-3-yl ester (14e)

14e: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84–0.92 (m, 9H), 1.07–1.40 (m, 4H), 1.55–1.57 (brs, 1H), 1.58–1.90 (m, 2H), 2.25–2.31 (brs, 1H), 2.75–3.21 (m, 6H), 3.44 (t, 1H, *J* = 9.7 Hz), 3.81–3.94 (m, 4H), 4.13–4.18 (m, 2H), 4.75–4.78 (brs, 1H), 5.05 (s, 1H), 6.68 (d, 2H, *J* = 8.5 Hz), 7.21–7.26 (m, 5H), 7.54 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 19.7, 19.7, 20.1, 22.3, 27.2, 35.5, 39.0, 53.8, 54.7, 58.8, 63.1, 72.3, 80.2, 100.4, 107.8, 112.6, 116.6, 128.4, 129.4, 129.5, 136.7, 138.9, 154.7; LRMS (FAB) *m/z* 576 (MH^+); HRMS (FAB) calcd for $C_{29}H_{42}N_3O_7S$ (MH^+) 576.2743, found 576.2761; $[\alpha]_D^{31}$ = +13.5 (*c* 1.00, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3417, 1715, 1336, 1231, 1151, 1092, 765, 744, 668.

Cells and viruses

MT-2 cells were grown in an RPMI 1640-based culture medium supplemented with 15% fetal calf serum (FCS, HyClone Laboratories, Logan, Utah, USA) plus 50 U of penicillin and 50 μg of streptomycin per mL. The following HIV-1 strains were used for the drug susceptibility assay: HIV-1_{LAI}, a clinical HIV-1 strain isolated from a drug-naive patient with AIDS, HIV-$1_{ERSI04pre}$, and three HIV-1 clinical isolates that were originally isolated from heavily pretreated patients, HIV-l_{TM}, HIV-l_{MM} and HIV-1_{JSL}, which were genotypically and phenotypically characterized as multi-drug-resistant HIV-1 variants. Amino acid substitutions identified in the protease-encoding region are as follows:

HIV-1_{I04pre} L63P

HIV-l_{TM} L10I/K14R/R41K/M46I/I54V/L63P/A71V/V82A/L90M/I93L

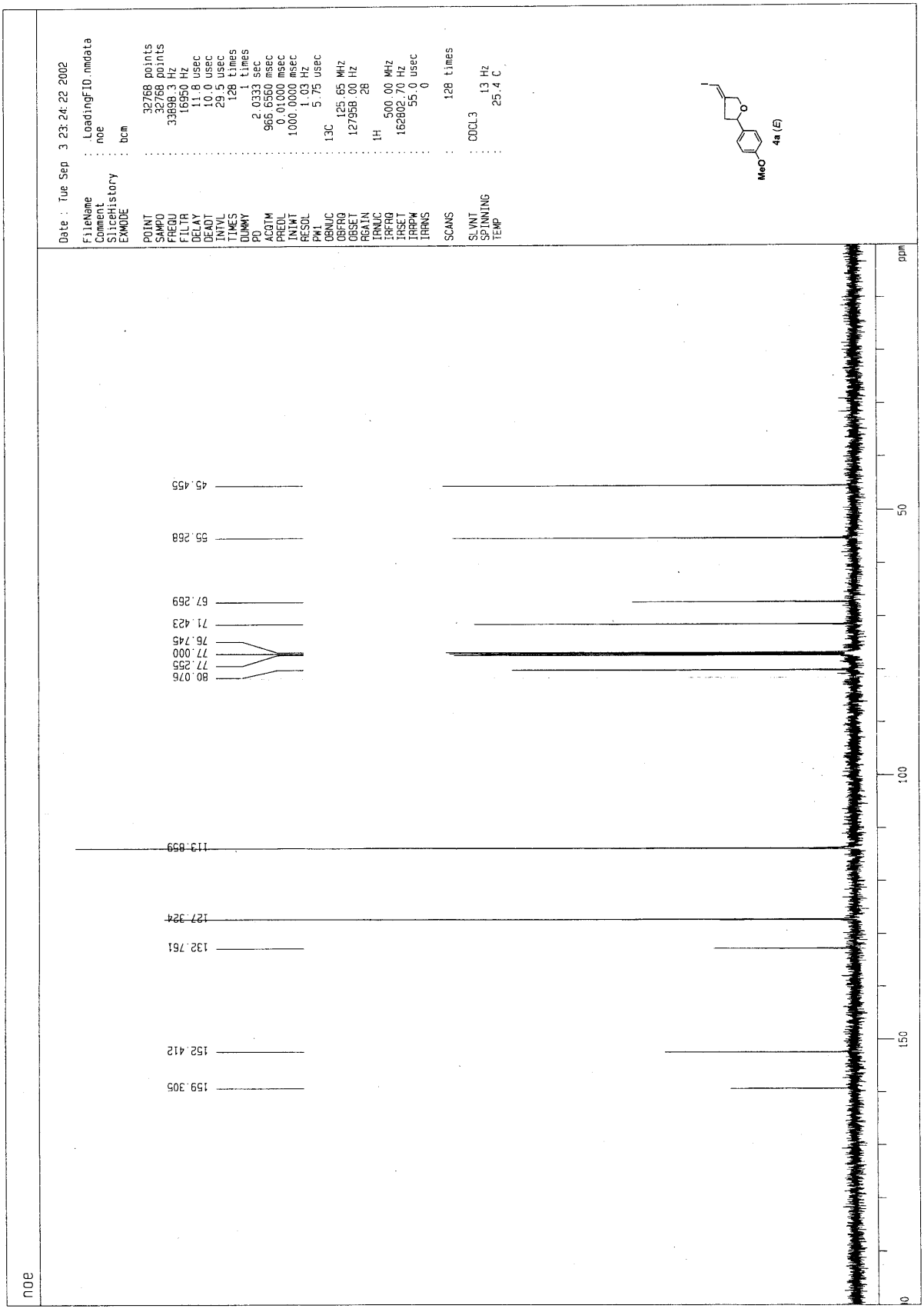
HIV-l_{MM} L10I/K43T/M46I/I54V/L63P/A71V/V82A/L90M/Q92K

HIV-1_{JSL} L10I/L24I/L33F/E35D/M36I/N37S/M46I/I54V/R57K/I62V/L63P/A71V/G73S/V82A

Anti-HIV assay

The sensitivity of HIV-1_{LAI} against various agents was determined as previously described (ref. Koh, Y. et al., *Antimicrob. Agents Chemother.* **2003**, *47*: 3123–3129). Briefly, MT-2 cells (2 x 10^3/well) were exposed to 100 50% tissue culture infective doses ($TCID_{50}$) of HIV-1_{LAI} in the presence of various concentrations of a test compound in 96-well microculture plates and incubated at 37°C for 7 days (final volume: 200 μL/well). After 100 μL of the medium was removed from each well, 10 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (7.5 mg/mL) in PBS was added to each well in the plate, followed by incubation at 37°C for 2 h. After incubation, to dissolve the formazan crystals, 100 μL of acidified isopropanol containing 4% (v/v) Triton X-100 was added to each well, the optical density (OD570) was measured in a microplate reader (V_{max}; Molecular Devices, Sunnyvale, Calif.). All assays were performed in at least triplicate.

Phytohemagglutinin (PHA)-treated peripheral blood mononuclear cells (PBMC) (1 x 10^5/well) were exposed to 50 $TCID_{50}$ of each HIV-1 clinical isolate in the presence or absence of various concentrations of a test compound in 96-well microculture plates (final volume: 200 μL/well). The amounts of p24 antigen produced by the cells were determined on day 7 in culture using a fully automated chemiluminescent enzyme immunoassay system (Lumipulse F; Fujirebio Inc, Tokyo, Japan) (Cite Koh et al., Ref. 35). Drug concentrations that resulted in 50% inhibition (IC_{50}) of p24 antigen production were determined by comparison with the p24 production level in drug-free control cell cultures. All assays were performed in triplicate or greater replicates.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DUMMY 1 times
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ACQTM 965.6560 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 1.03 Hz
PW1 5.75 usec
13C
OBNUC 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 28
OBGAIN
1H
IRNUC 500.00 MHz
IRFRQ 162802.70 Hz
IRSET 55.0 usec
IRRPW 0
IRRNS
SCANS 128 times
SLVNT CDCL3
SPINNING 13 Hz
TEMP 25.4 C
MeO
4a (E)
45.455
55.268
67.269
71.423
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150
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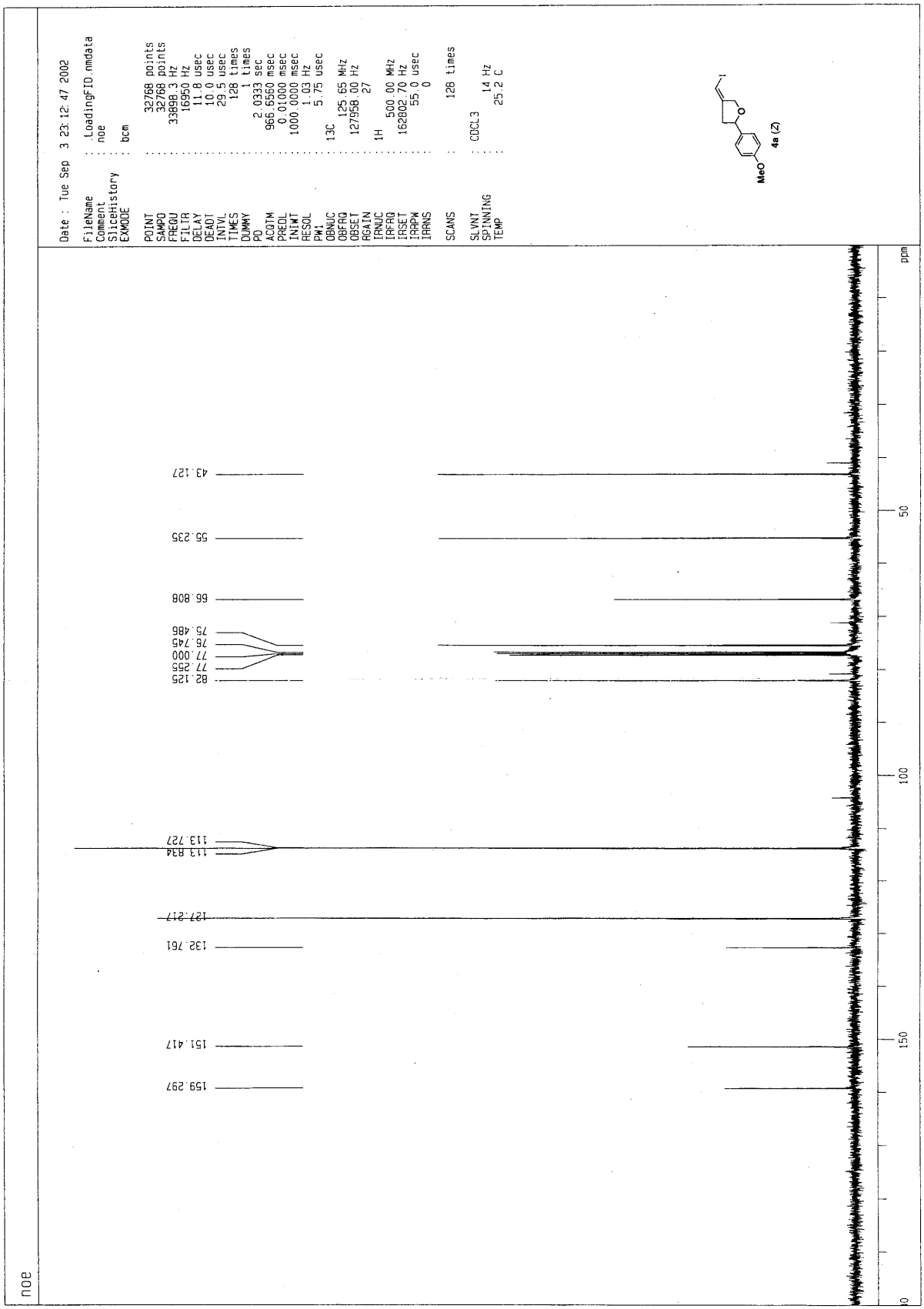
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INTVL 29.5 usec
TIMES 128 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 965.6560 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 1.03 Hz
PW1 5.75 usec
OBNUC 13C
OBFRQ 125.65 MHz
OBSET 127958.00 Hz
AGAIN 27
IRNUC 1H
IRFRQ 500.00 MHz
IRSET 162802.70 Hz
IRRPW 55.0 usec
IRRNS 0
SCANS 128 times
SLVNT CDCL3
SPINNING 14 Hz
TEMP 25.2 C
4a (Z)
MeO
43.127
55.235
66.808
75.486
76.745
77.000
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132.761
151.417
159.297
ppm
50
100
150
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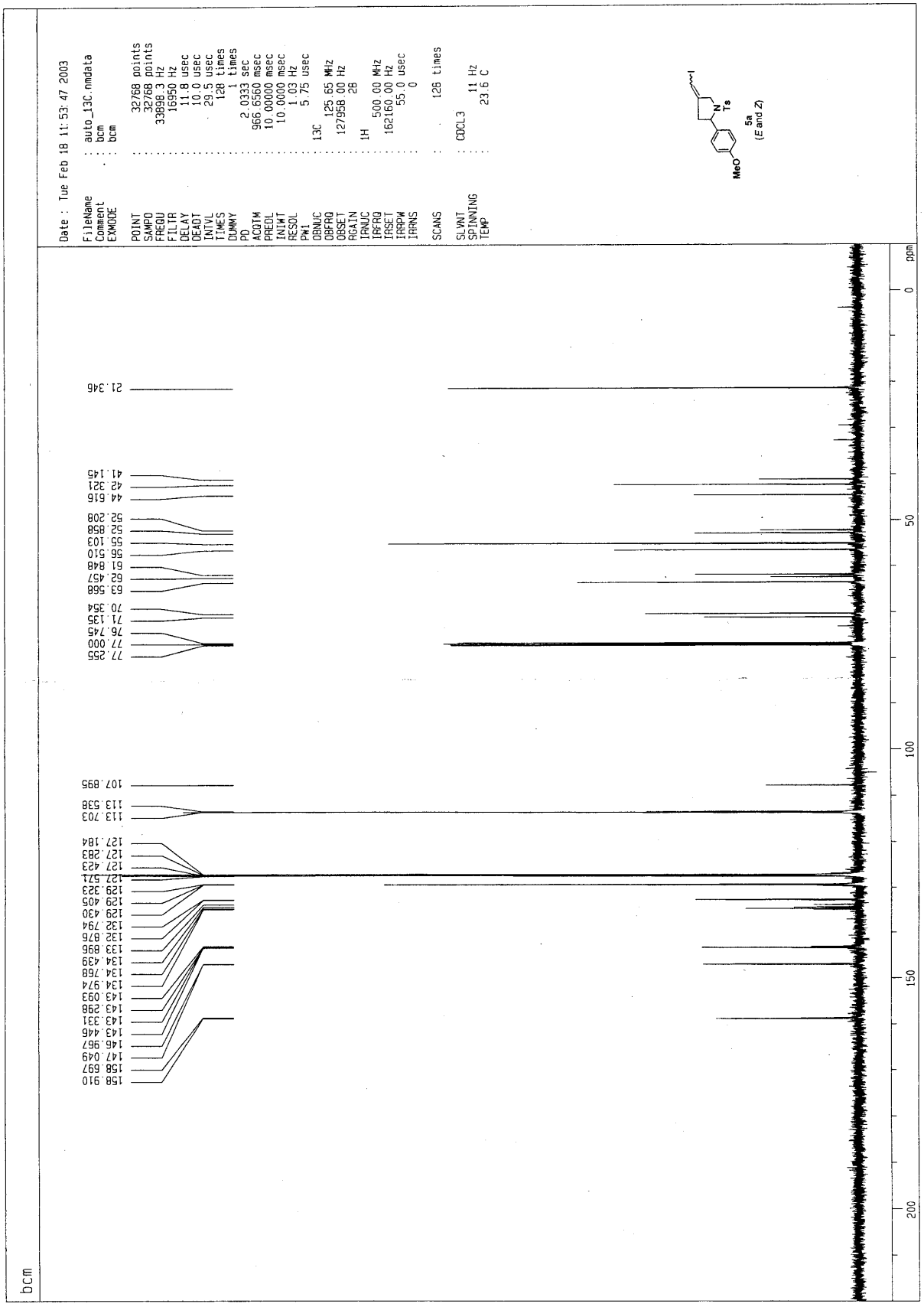
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INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
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ACQTM : 966.6560 msec
PREDL : 10.00000 msec
INIWT : 10.0000 msec
RESOL : 1.03 Hz
PW1 : 5.75 usec
OBNUC : 13C
OBFRQ : 125.65 MHz
OBSET : 12795.00 Hz
RGAIN : 28
IRNUC : 1H
IRFRQ : 500.00 MHz
IRSET : 162160.00 Hz
IRPPW : 55.0 usec
IRPNS : 0
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 11 Hz
TEMP : 23.6 C
5a
(E and Z)
MeO
Ts
N
21.346
41.145
42.321
44.616
52.208
52.858
55.103
56.510
61.848
62.457
63.568
70.354
71.135
76.745
77.000
77.255
107.895
113.538
113.703
127.184
127.283
127.423
127.571
129.323
129.405
129.430
132.794
132.876
133.896
134.439
134.768
134.974
143.093
143.298
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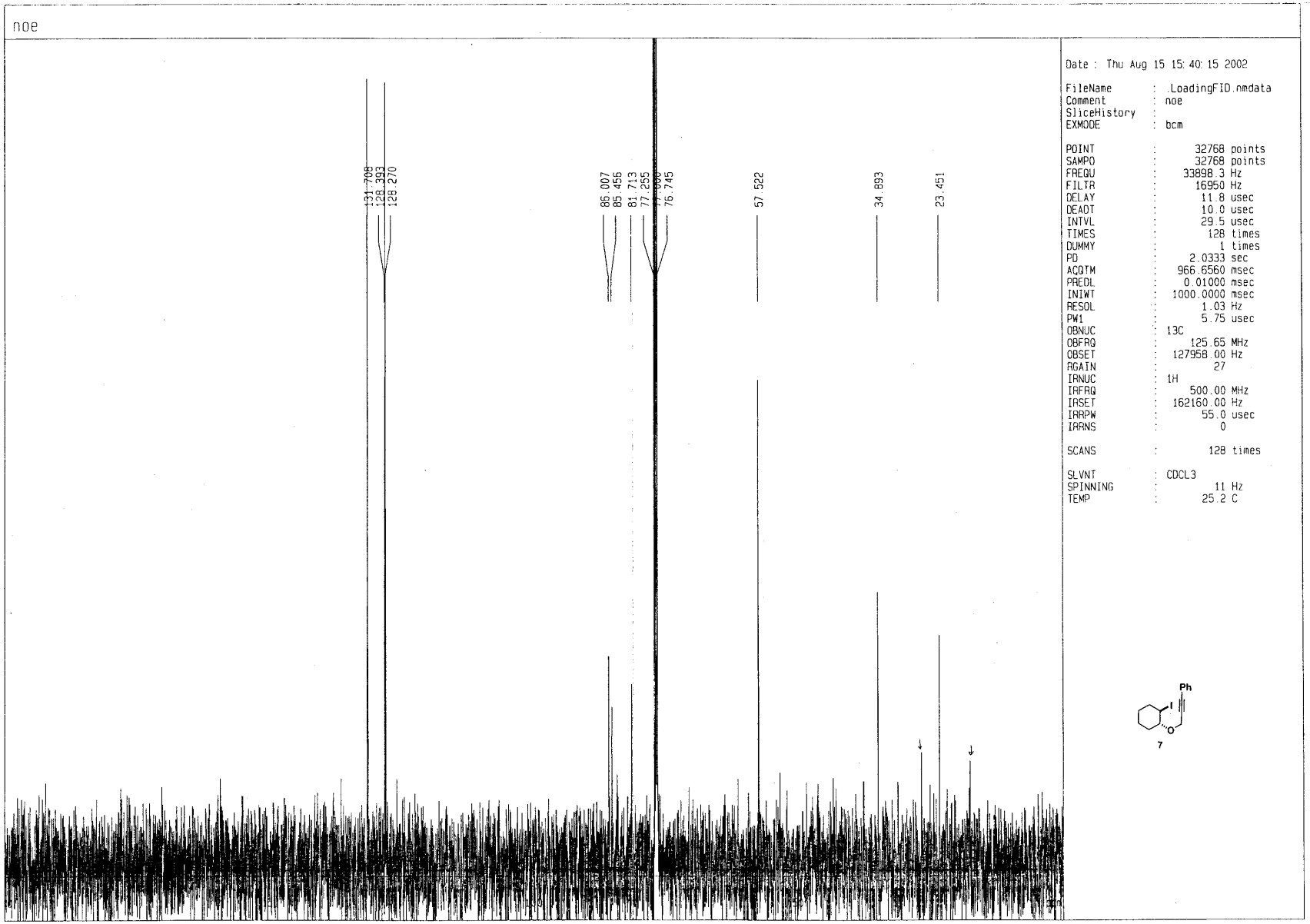
143.446
146.967
147.049
158.697
158.910
bcm
ppm
0
50
100
150
200


noe
131.708
128.393
128.270
86.007
85.456
81.713
77.255
76.745
57.522
34.893
23.451
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INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 0.01000 msec
INIWT : 1000.0000 msec
RESOL : 1.03 Hz
PW1 : 5.75 usec
OBNUC : 13C
OBFRQ : 125.65 MHz
OBSET : 127958.00 Hz
RGAIN : 27
IRNUC : 1H
IRFRQ : 500.00 MHz
IRSET : 162160.00 Hz
IRRPW : 55.0 usec
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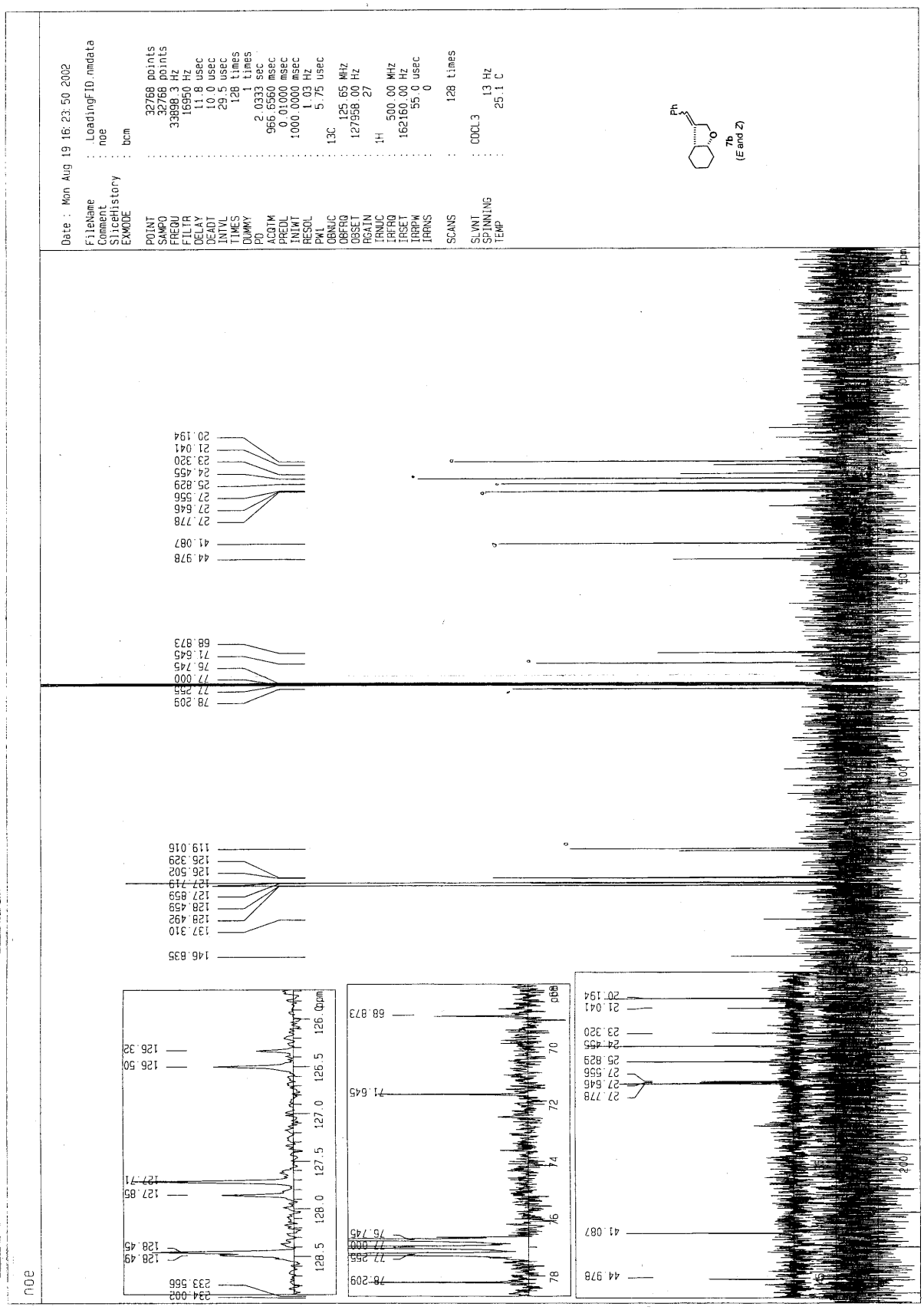
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 11 Hz
TEMP : 25.2 C
Ph
I
O
7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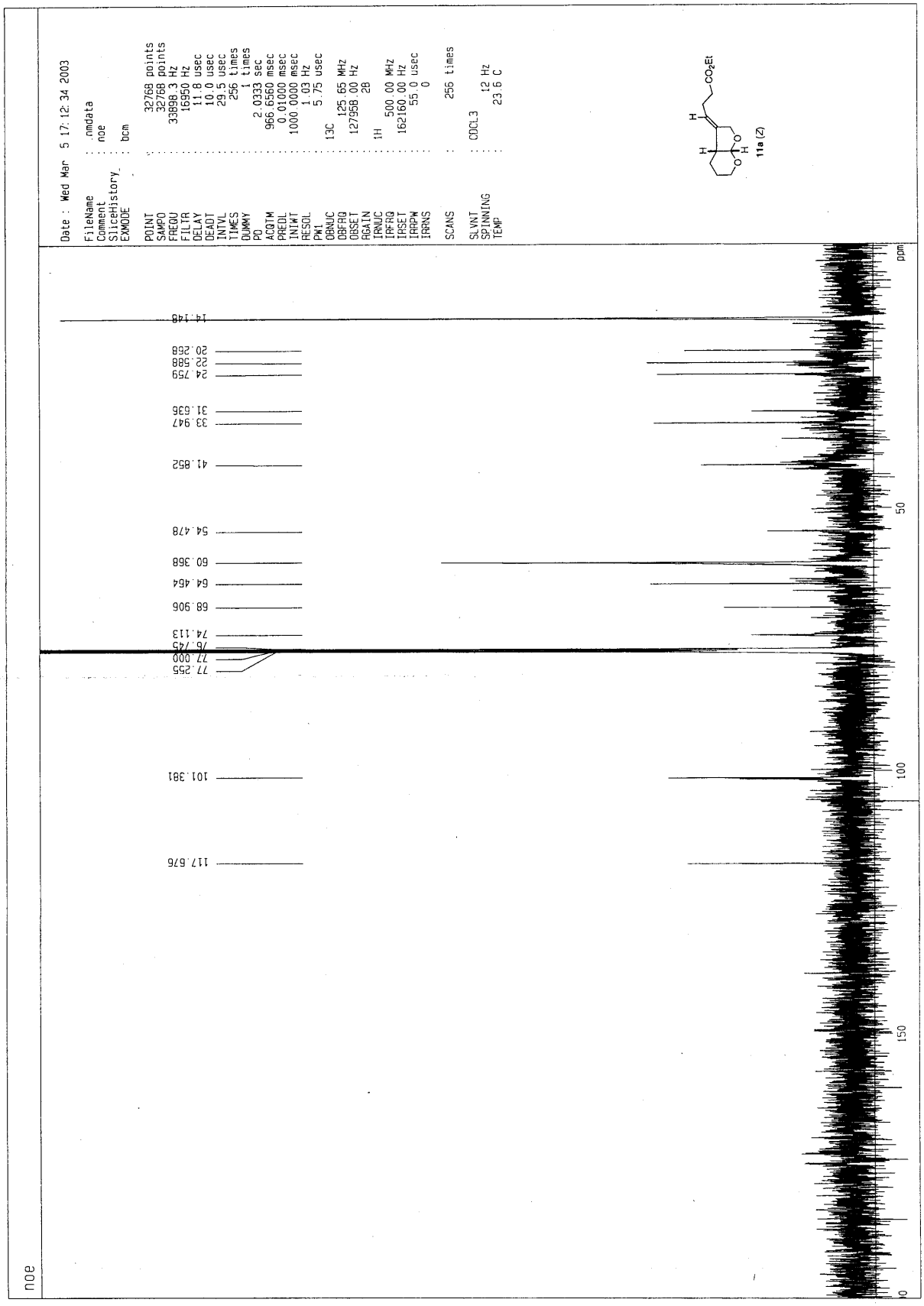
DELAY : 11.8 usec
DEADT : 10.0 usec
INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 0.01000 msec
INIWT : 1000.0000 msec
RESOL : 1.03 Hz
PW1 : 5.75 usec
OBNUC : 13C 125.65 MHz
OBFRQ : 127958.00 Hz
OBSET : 27
AGAIN :
1H
TANUC : 500.00 MHz
IAFRQ : 162160.00 Hz
IASET : 55.0 usec
IARPW : 0
IARNS :
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 13 Hz
TEMP : 25.1 C
Ph
O
O
7b
(E and Z)
ppm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DEADT : 10.0 usec
INTVL : 29.5 usec
TIMES : 256 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 0.01000 msec
INIWT : 1000.0000 msec
RESOL : 1.03 Hz
PW1 : 5.75 usec
OBNUC : 13C
OBFRQ : 125.65 MHz
OBSET : 12795B.00 Hz
AGAIN : 28
IRNUC : 1H
IRFRQ : 500.00 MHz
IRSET : 162160.00 Hz
IRADW : 55.0 usec
IRPWR : 0
SCANS : 256 times
SLVNT : CDCL3
SPINNING : 12 Hz
TEMP : 23.6 C
11a (Z)
14.148
20.268
22.588
24.759
31.636
33.947
41.852
54.478
60.368
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68.906
74.113
76.745
77.000
77.255
101.381
117.676
ppm
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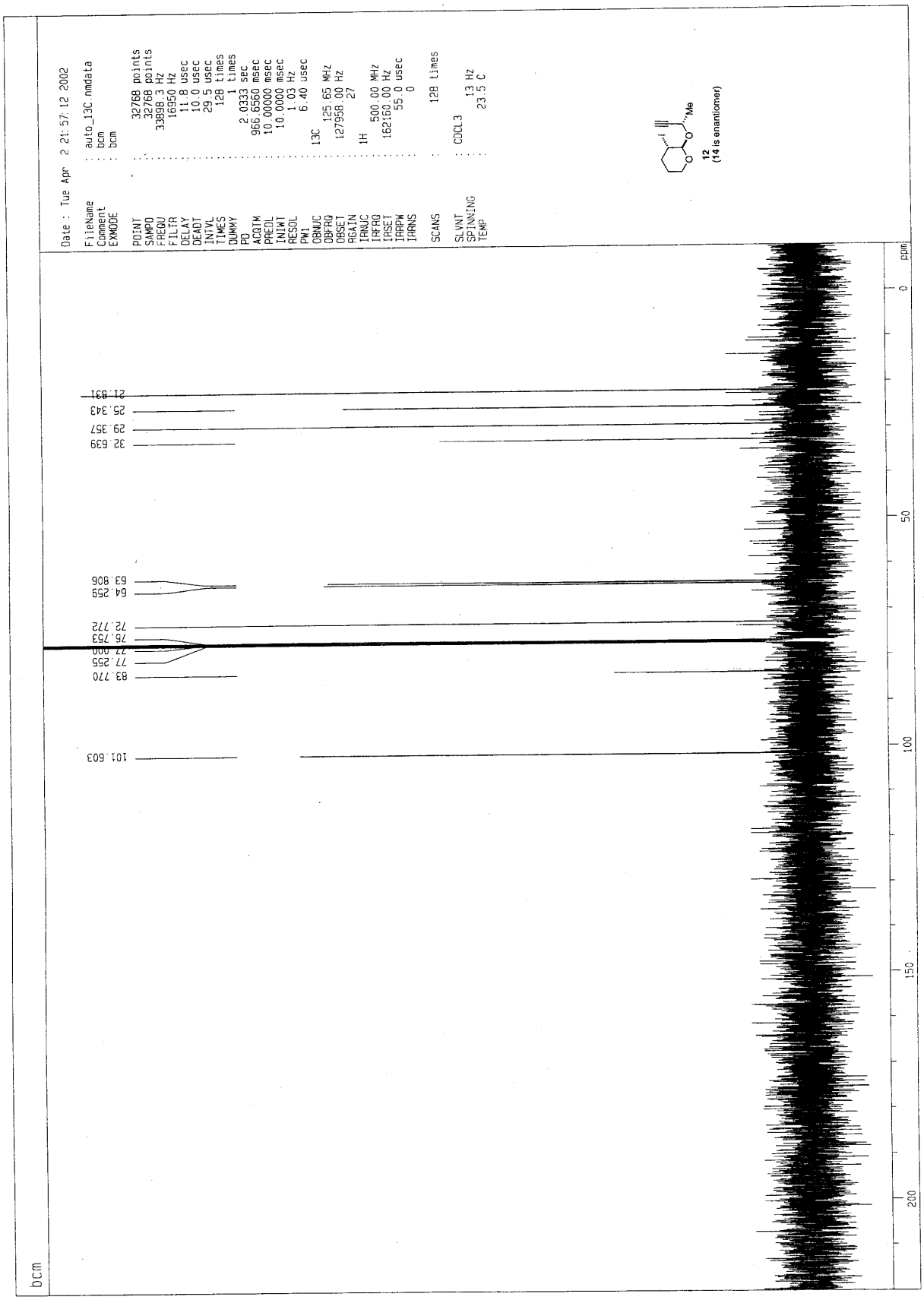
50
100
150
noe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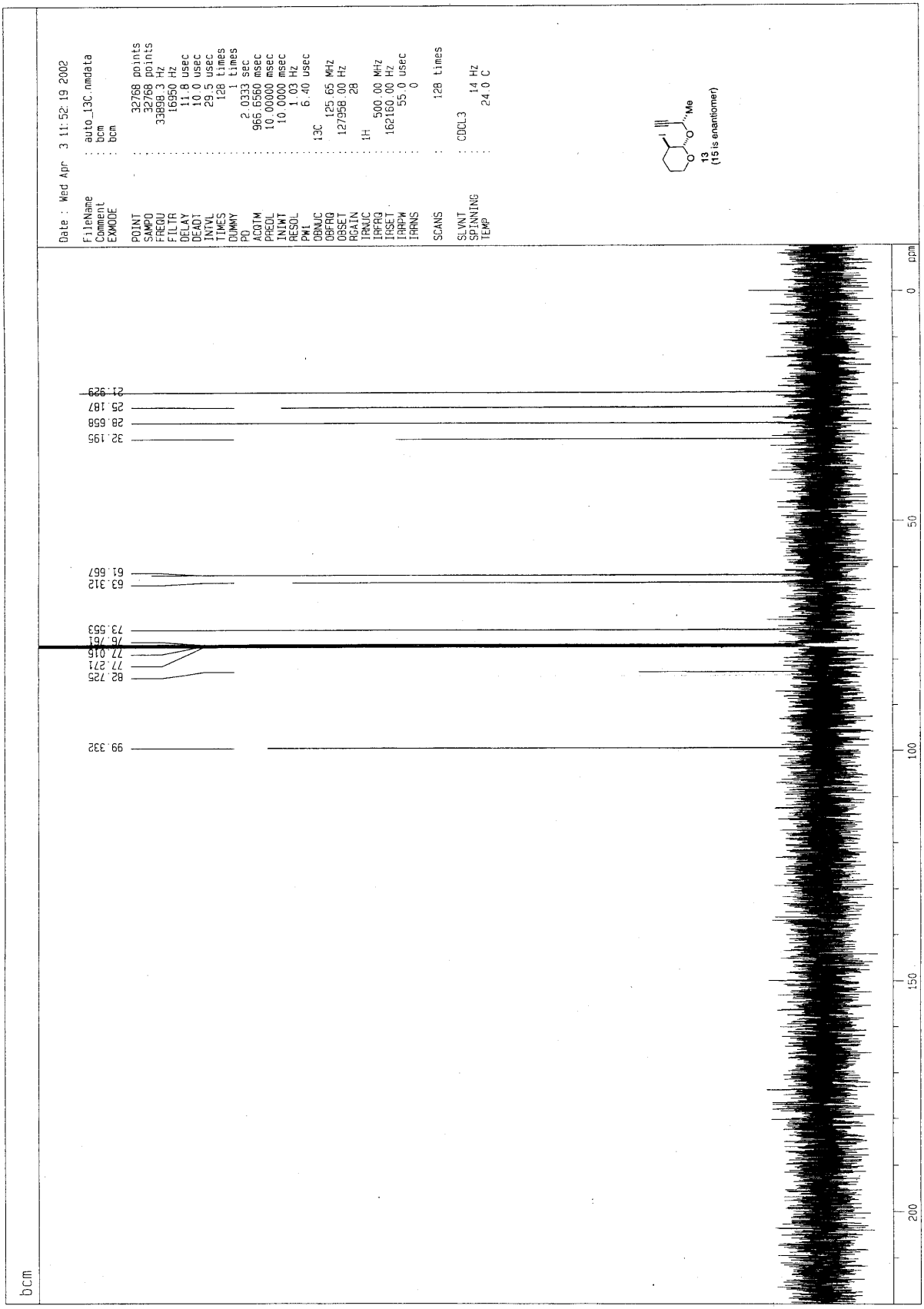
DEADT 10.0 usec
INIVL 29.5 usec
TIMES 128 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 10.00000 msec
INIWT 1.03 Hz
RESOL 6.40 usec
PW1
OBNUC 13C 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 27
AGAIN
IRNUC 1H 500.00 MHz
IRFRQ 162160.00 Hz
IRSET 55.0 usec
IRPPW 0
IRNNS
SCANS 128 times
SLVNT CDCL3
SPINNING 13 Hz
TEMP 23.5 C
12
(14 is enantiomer)
Me
21.831
25.343
29.357
32.639
63.806
64.259
72.772
76.753
77.000
77.255
83.770
101.603
ppm
0
50
100
150
200
bcm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DEADI : 10.0 usec
INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 10.00000 msec
INIWT : 10.0000 msec
RESOL : 1.03 Hz
PW1 : 6.40 usec
OBNUC : 13C
OBFRQ : 125.65 MHz
OBSET : 127958.00 Hz
OBSET : 28
RGAIN :
IRNUC : 1H
IRFRQ : 500.00 MHz
IRSET : 162160.00 Hz
IRPW : 55.0 usec
IRNS : 0
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 14 Hz
TEMP : 24.0 C
Me
13
(1S is enantiomer)
21.929
25.187
28.658
32.195
61.667
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76.761
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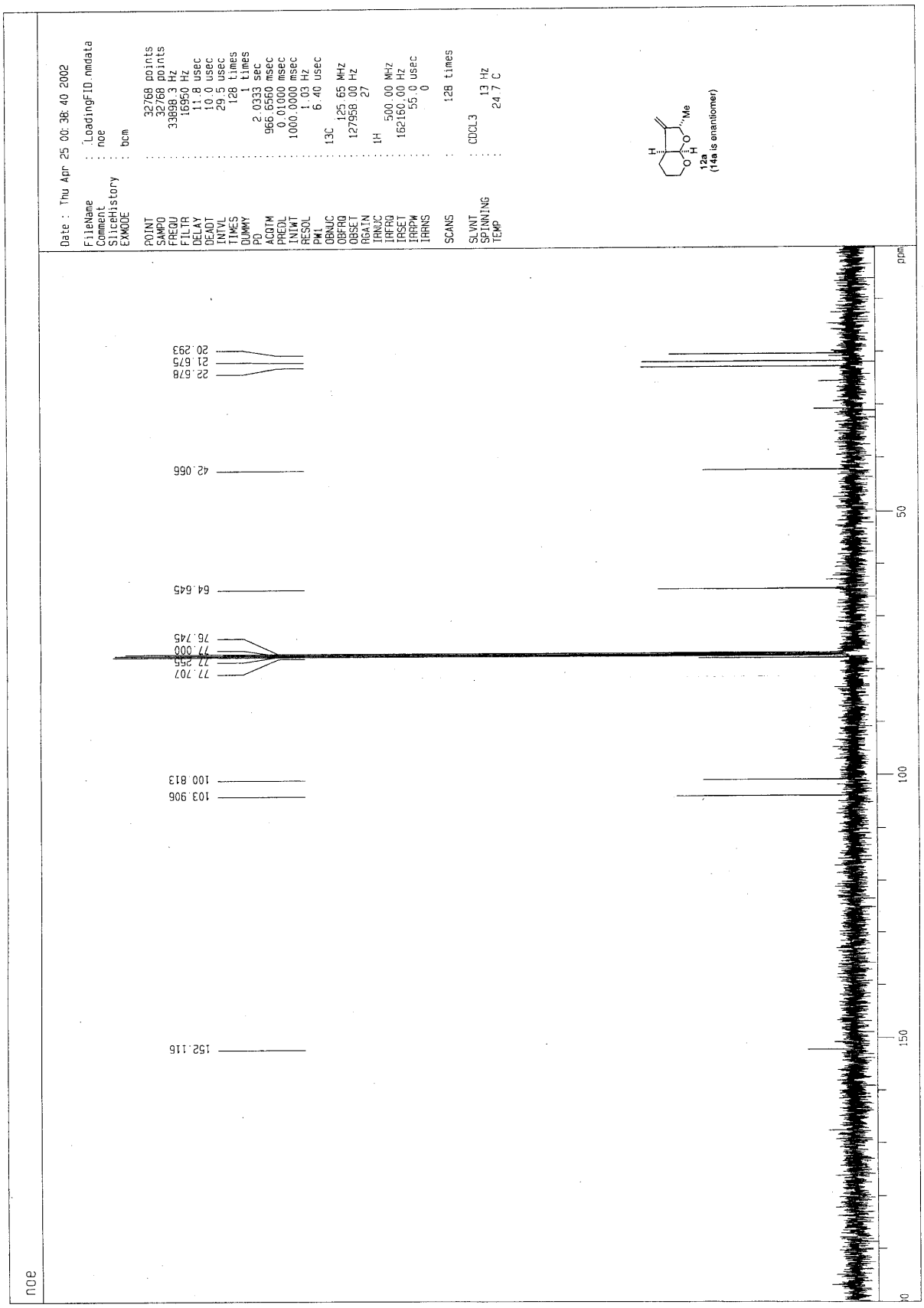
77.271
82.725
99.332
bcm
ppm
0
50
100
150
200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INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 0.01000 msec
INIWT : 1000.0000 msec
RESOL : 1.03 Hz
PW1 : 6.40 usec
OBNUC : 13C
OBFRQ : 125.65 MHz
OBSET : 127958.00 Hz
RGAIN : 27
1H
TRNUC : 500.00 MHz
TRFRQ : 162160.00 Hz
TRSET : 55.0 usec
TRPPW : 0
TRANS :
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 13 Hz
TEMP : 24.7 C
12a
(14a is enantiomer)
Me
H
H
O
O
20.293
21.675
22.678
42.066
64.645
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77.000
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77.707
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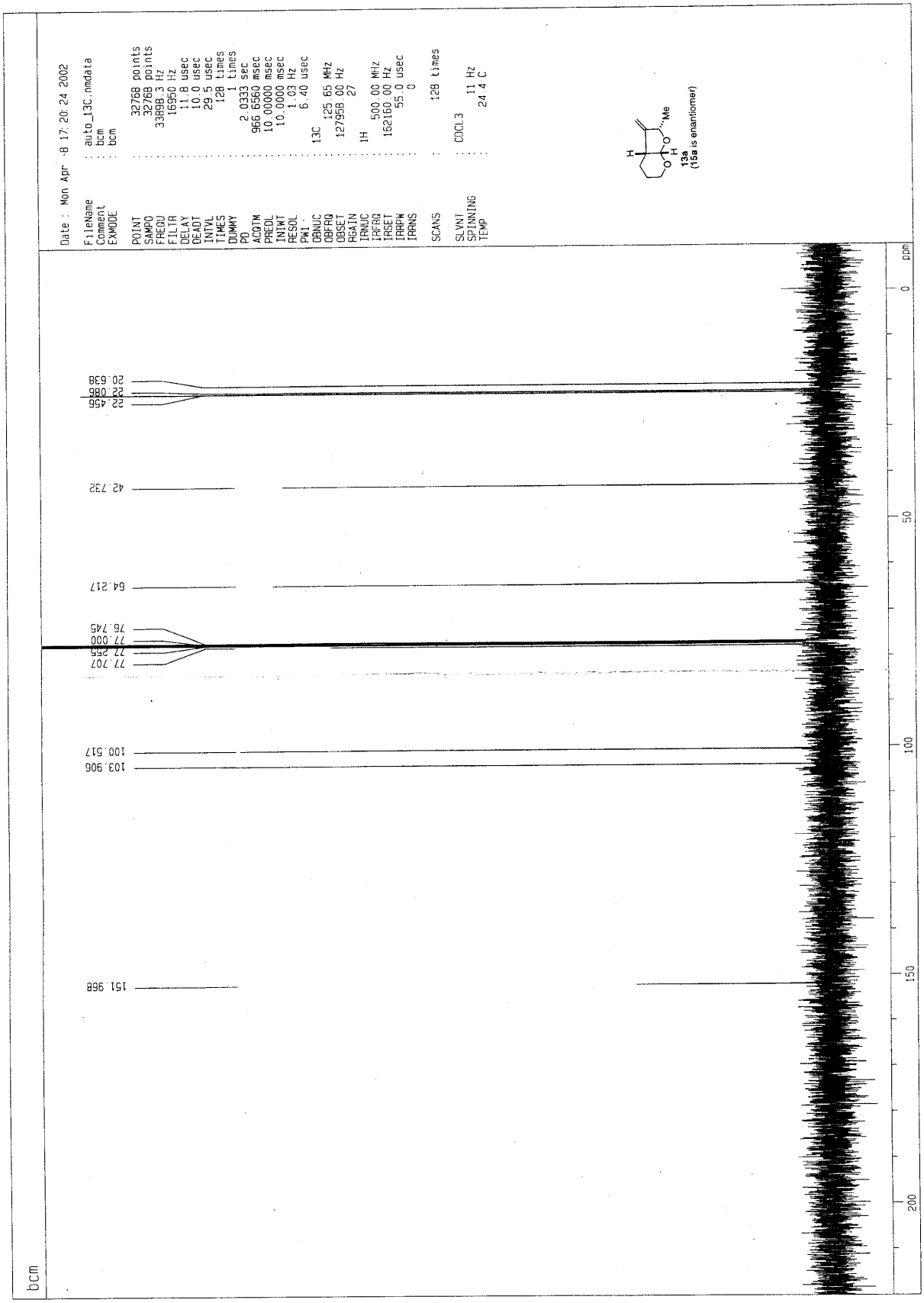
ppm
50
100
150
noe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INTVL 29.5 usec
TIMES 128 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 10.00000 msec
INIWT 1.03 Hz
RESOL 6.40 usec
PW1 .
13C
OBNUC 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 27
AGAIN
1H
IRNUC 500.00 MHz
IRFRQ 162160.00 Hz
IRSET 55.0 usec
IRRPW 0
IRRNS
SCANS 128 times
SLVNT CDCL3
SPINNING 11 Hz
TEMP 24.4 C
Me
13a
(15a is enantiomer)
20.638
22.086
22.456
42.732
64.217
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ppm
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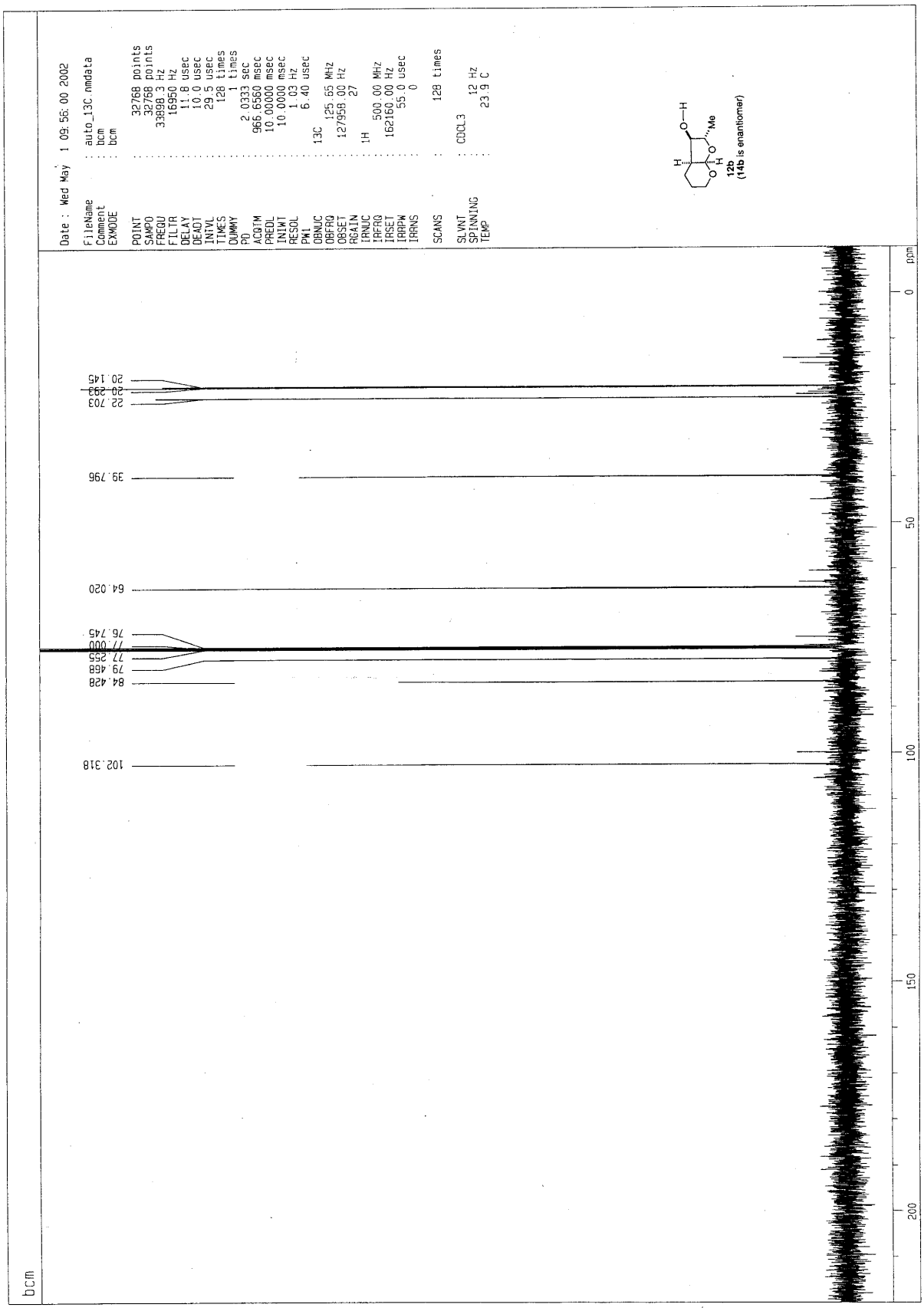
50
100
150
200
bcm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DEADT : 10.0 usec
INIVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 10.00000 msec
INIWT : 10.0000 msec
RESOL : 1.03 Hz
PW1 : 6.40 usec
OBNUC : 13C 125.65 MHz
OBFRQ : 127959.00 Hz
OBSET : 27
AGAIN :
IRNUC : 1H 500.00 MHz
IRFRQ : 162160.00 Hz
IRSET : 55.0 usec
IRAPW : 0
IRANS :
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 12 Hz
TEMP : 23.9 C
12b
(14b is enantiomer)
20.145
20.293
22.703
39.796
64.020
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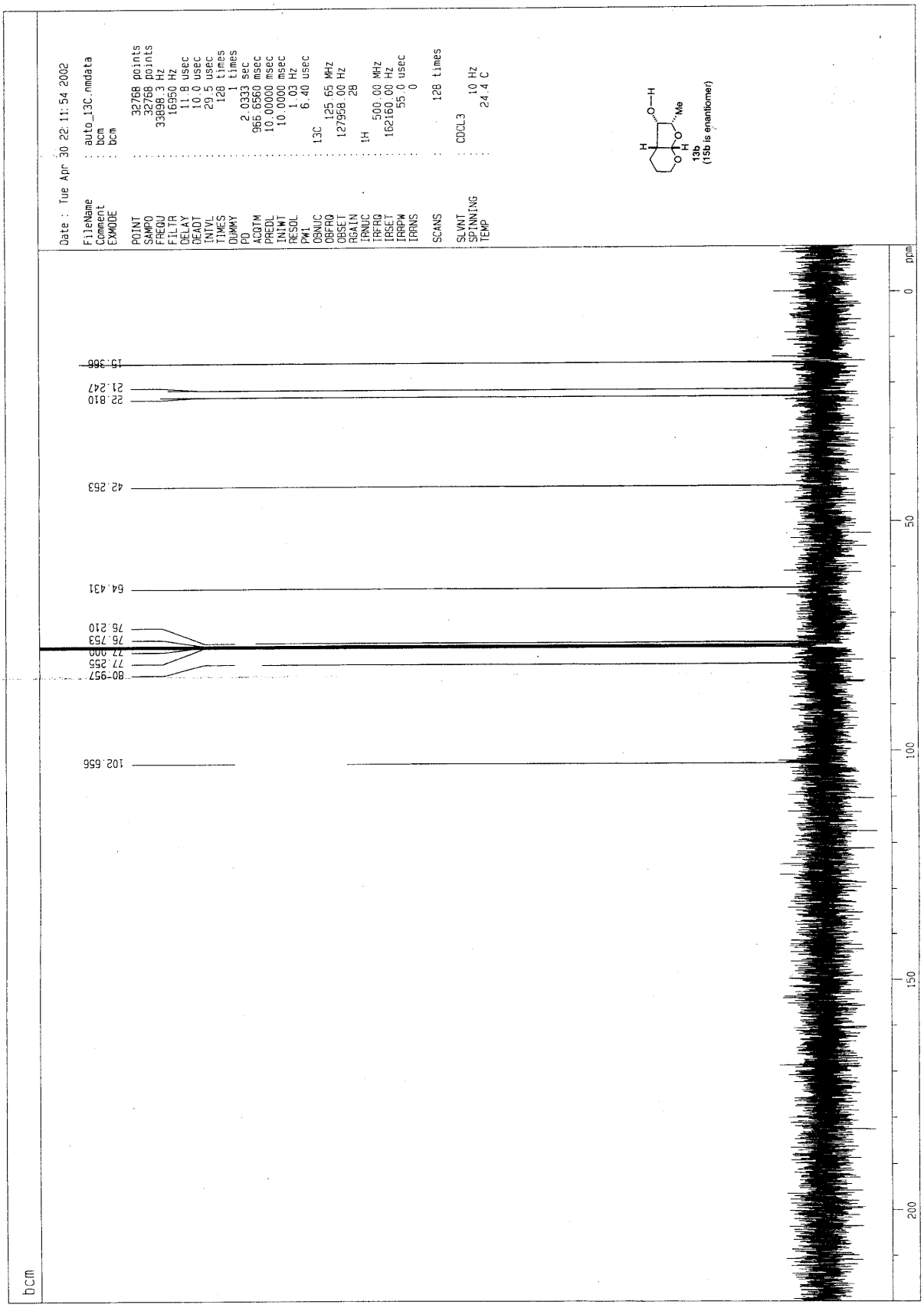
77.000
77.255
79.468
84.428
102.318
bcm
ppm
0
50
100
150
200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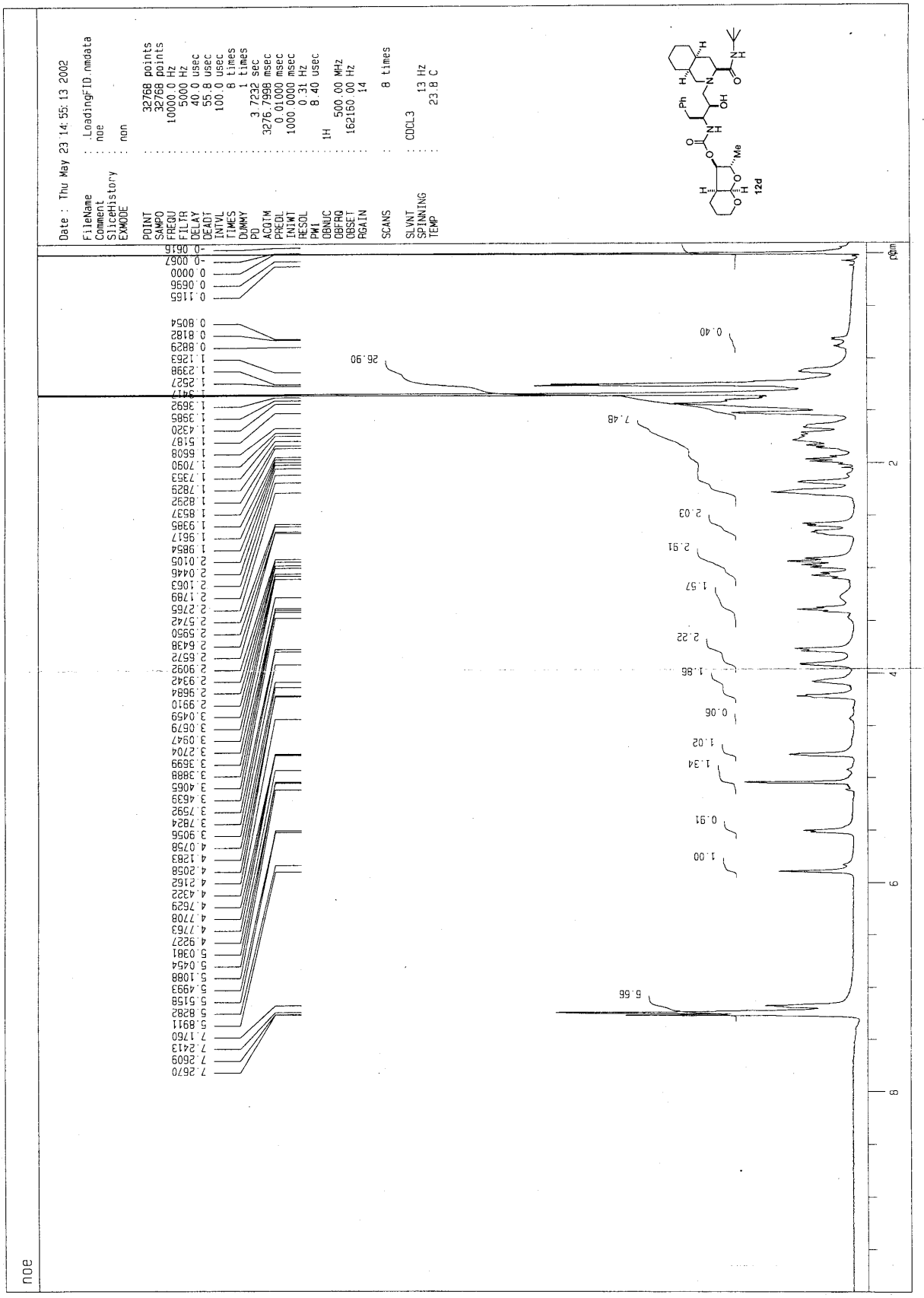
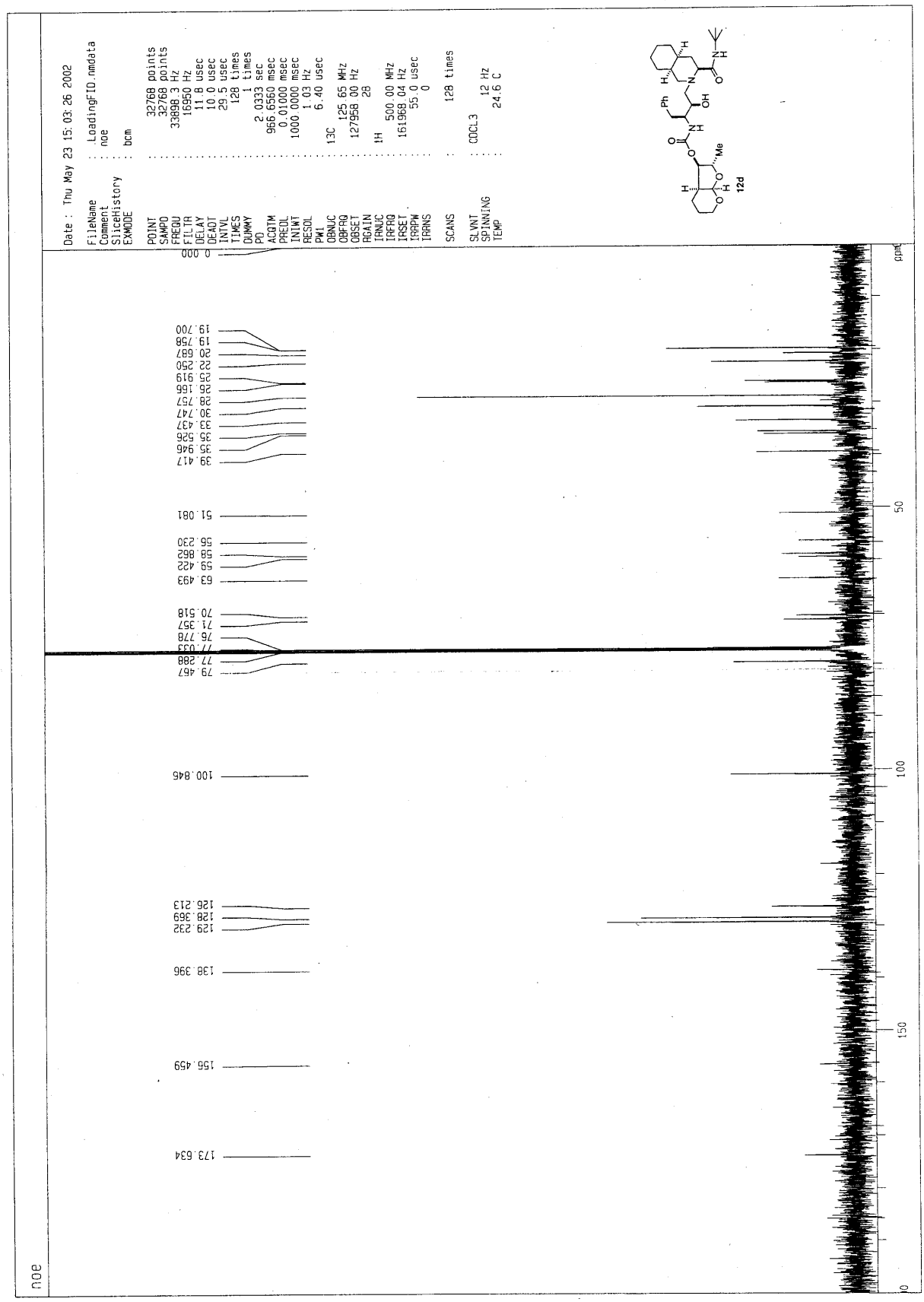
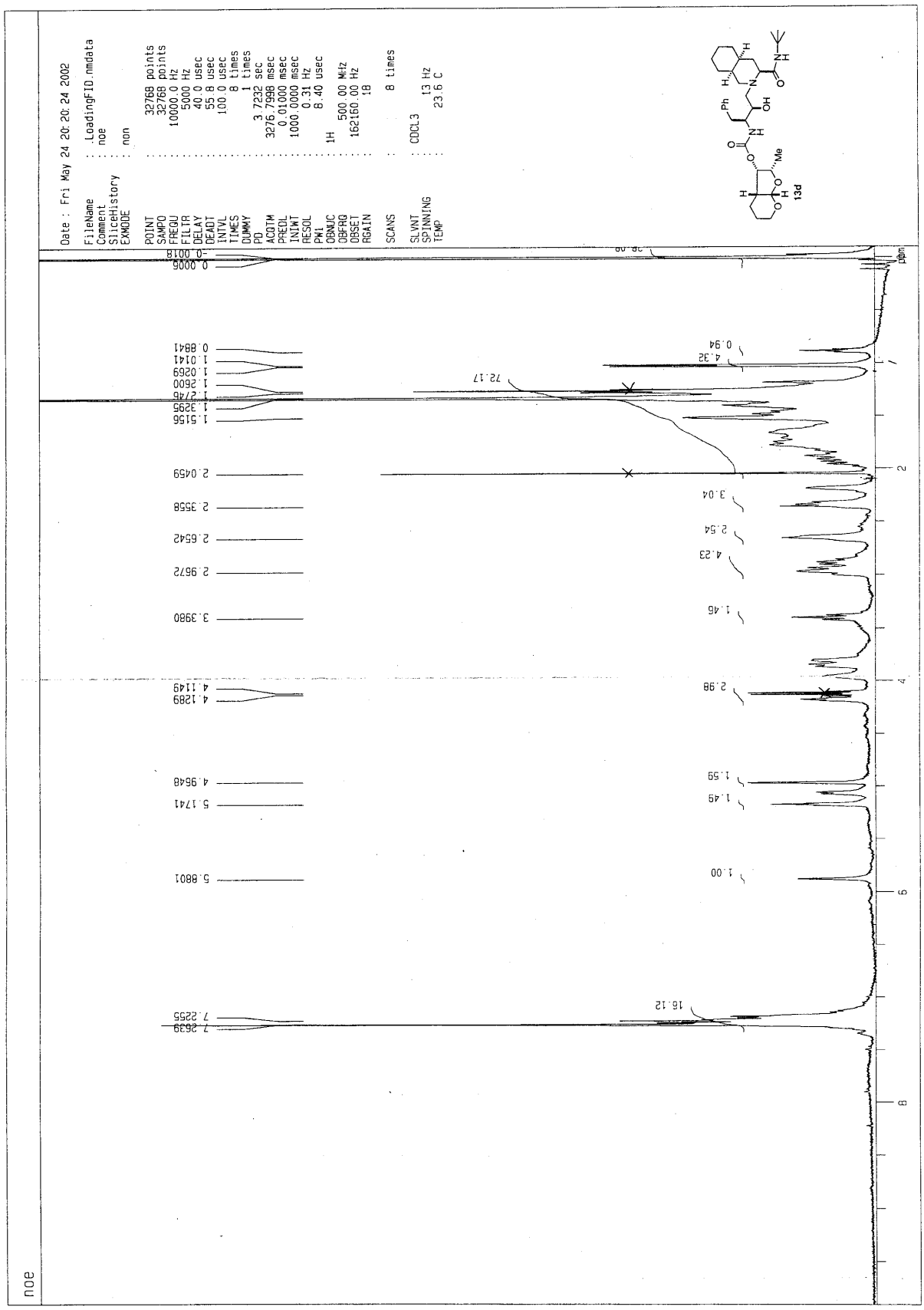
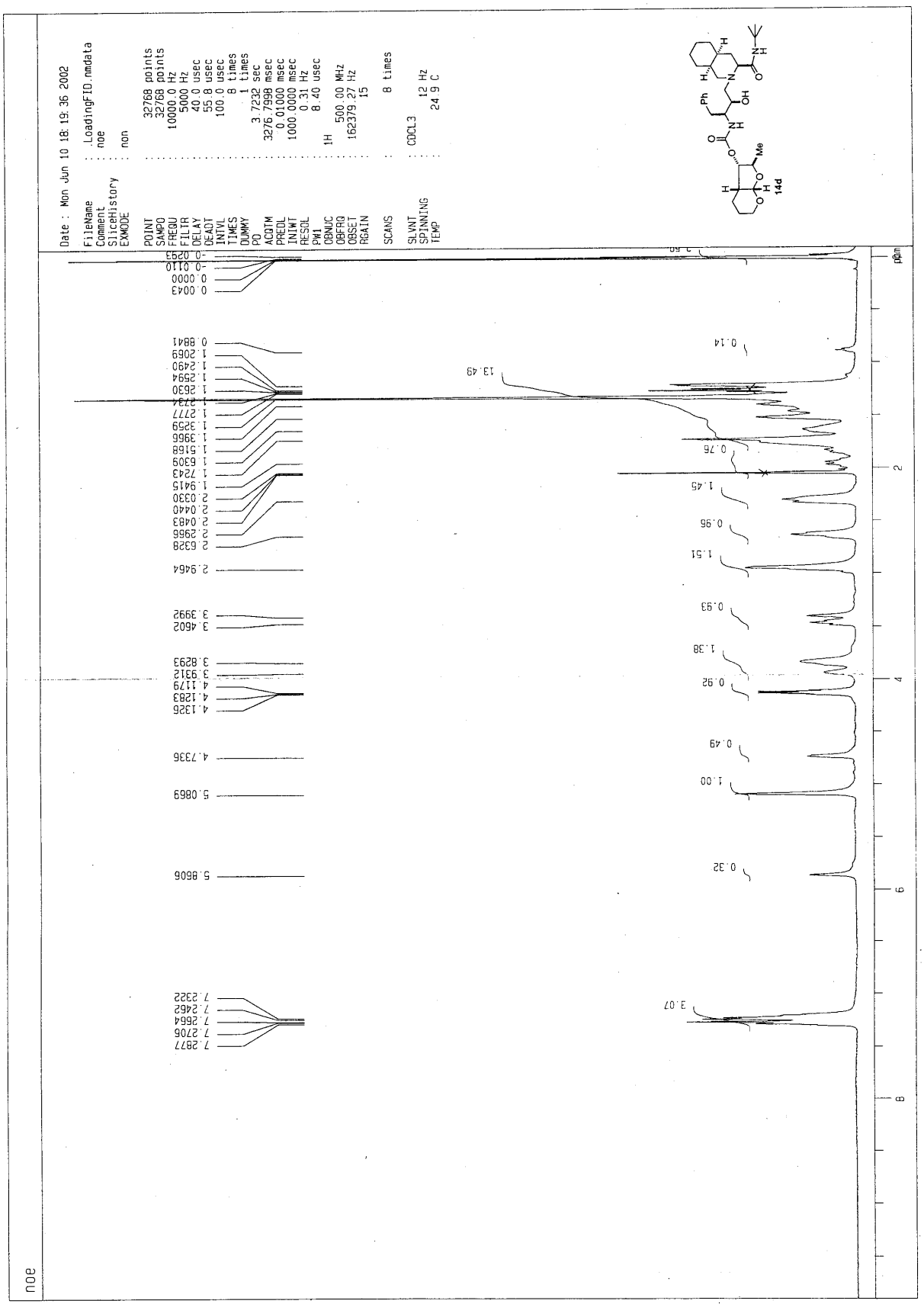
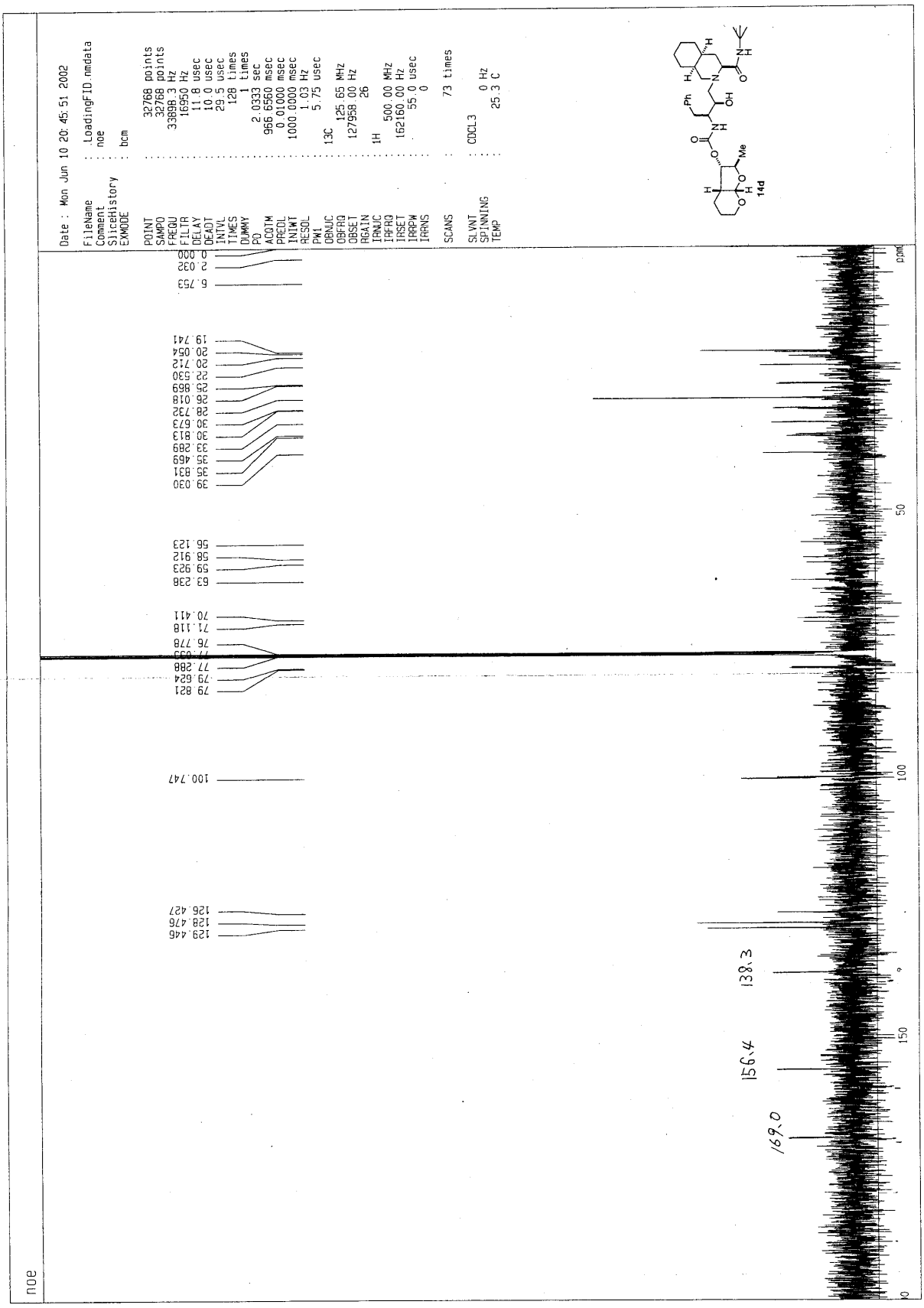
DEADT : 10.0 usec
INTVL : 29.5 usec
TIMES : 128 times
DUMMY : 1 times
PD : 2.0333 sec
ACQTM : 966.6560 msec
PREDL : 10.00000 msec
INIWT : 10.0000 msec
RESOL : 1.03 Hz
PW1 : 6.40 usec
OBNUC : 13C 125.65 MHz
OBFRQ : 127958.00 Hz
OBSET : 28
RGAIN :
IRNUC : 1H 500.00 MHz
IRFRQ : 162160.00 Hz
IRSET : 55.0 usec
IRAPW : 0
IRPWS :
SCANS : 128 times
SLVNT : CDCL3
SPINNING : 10 Hz
TEMP : 24.4 C
13b
(15b is enantiomer)
15.366
21.247
22.810
42.263
64.431
76.210
76.753
77.000
77.255
80.957
102.656
ppm
0
50
100
150
200
bcm

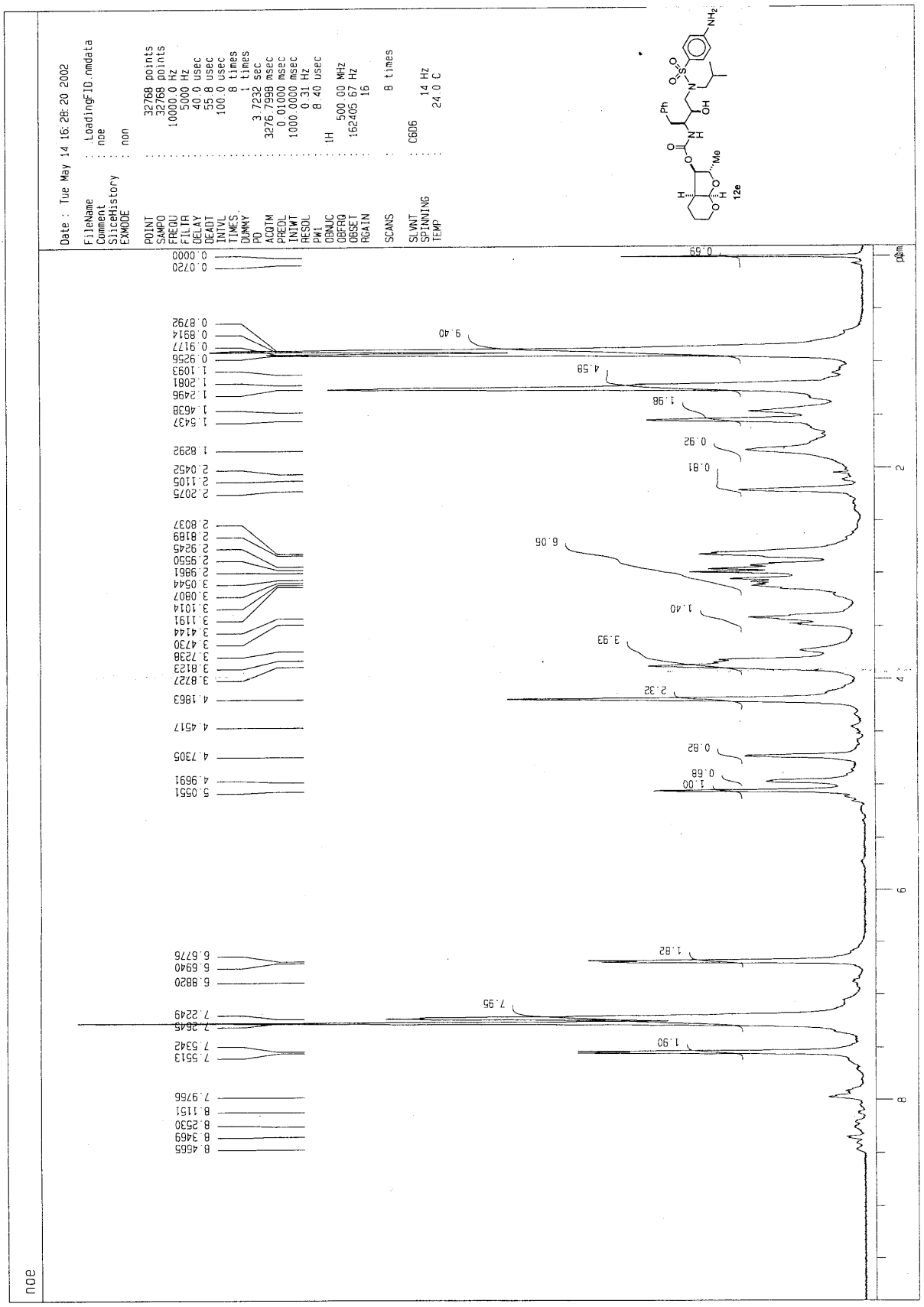

Date : Thu May 23 14:55:13 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory :
EXMODE : non
POINT 32768 points
SAMPO 32768 points
FREQU 10000.0 Hz
FILTR 5000 Hz
DELAY 40.0 usec
DEADT 55.8 usec
INTVL 100.0 usec
TIMES 8 times
DUMMY 1 times
PD 3.7232 sec
ACQTM 3276.7998 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 0.31 Hz
PW1 8.40 usec
1H
OBNUC
OBFRQ 500.00 MHz
OBSET 162160.00 Hz
AGAIN 14
SCANS 8 times
SLVNT CDCL3
SPINNING 13 Hz
TEMP 23.8 C
12d
noe
ppm
26.90
7.48
5.66
2.03
2.91
1.57
2.22
1.86
0.40
0.06
1.02
1.34
0.91
1.00

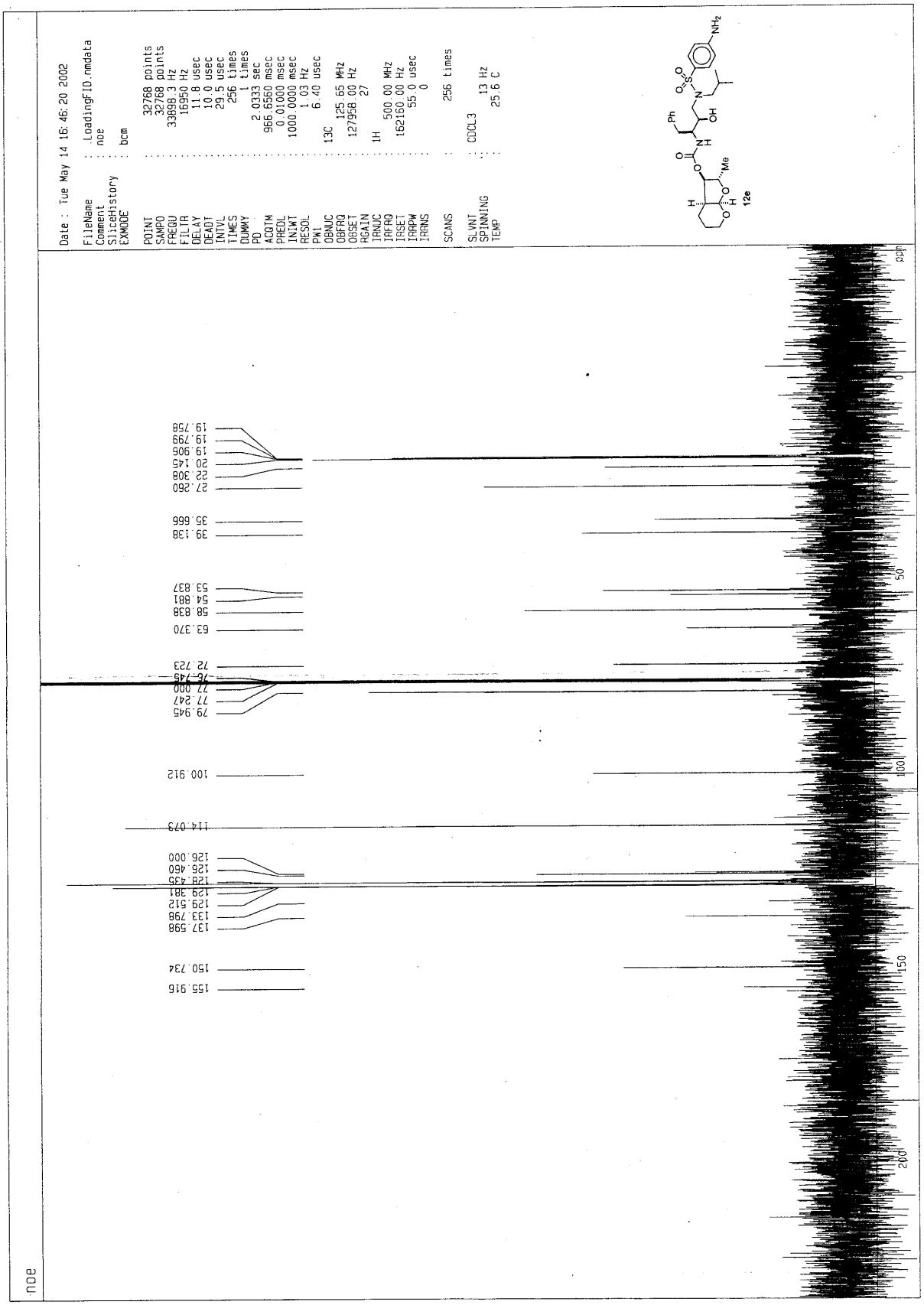

noe
Date : Thu May 23 15:03:26 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory : bcm
EXMODE :
POINT 32768 points
SAMPO 32768 points
FREQU 33898.3 Hz
FILTR 16950 Hz
DELAY 11.8 usec
DEADT 10.0 usec
INTVL 29.5 usec
TIMES 128 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 0.01000 msec
INTWT 1000.0000 msec
RESOL 1.03 Hz
PW1 6.40 usec
OBNUC 13C
OBFRQ 125.65 MHz
OBSET 127958.00 Hz
AGAIN 28
IFNUC 1H
IRFRQ 500.00 MHz
IRSET 161968.04 Hz
IRPW 55.0 usec
IRNS 0
SCANS 128 times
SLVNT CDCL3
SPINNING 12 Hz
TEMP 24.6 C
12d
ppm
19.700
19.758
20.687
22.250
25.919
26.166
28.757
30.747
33.437
35.926
35.946
39.417
51.081
56.230
58.862
59.422
63.493
70.518
71.357
76.778
77.033
77.288
79.467
100.846
126.213
128.369
129.232
138.396
156.459
173.634

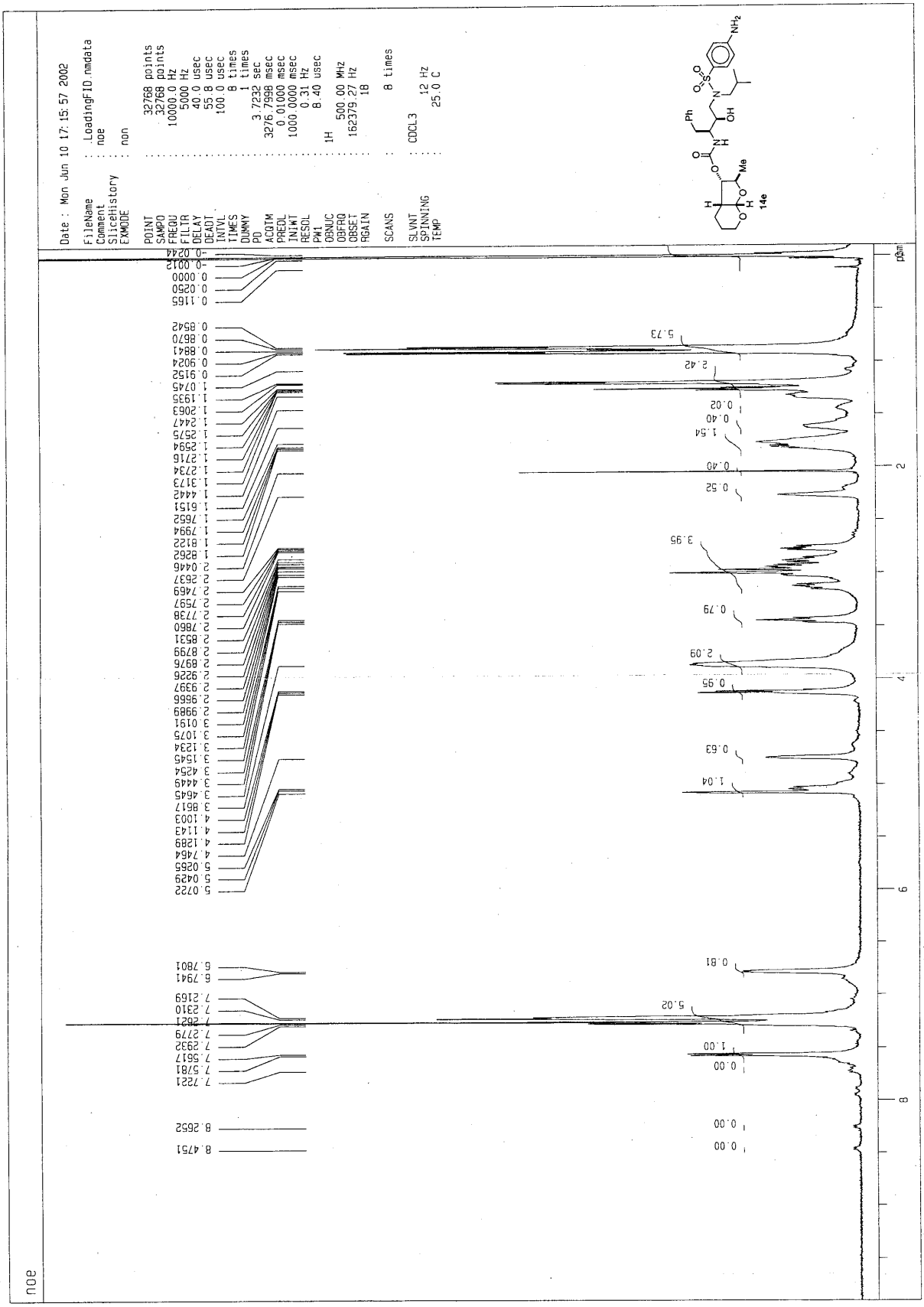

Date : Fri May 24 20:20:24 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory : ...
EXMODE : non
POINT 32768 points
SAMPO 32768 points
FREQU 10000.0 Hz
FILTR 5000 Hz
DELAY 40.0 usec
DEADT 55.8 usec
INTVL 100.0 usec
TIMES 8 times
DUMMY 1 times
PD 3.7232 sec
ACQTM 3276.7998 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 0.31 Hz
PWI 8.40 usec
OBNUC 1H
OBFRQ 500.00 MHz
OBSET 162160.00 Hz
RGAIN 18
SCANS 8 times
SLVNT CDCL3
SPINNING 13 Hz
TEMP 23.6 C
Ph
OH
Me
13d
noe
ppm
0.9006
0.8841
1.0141
1.0269
1.2600
1.2746
1.3295
1.5156
2.0459
2.3558
2.6542
2.9572
3.3980
4.1149
4.1289
4.9548
5.1741
5.8801
7.2539
7.2255
72.17
18.12
0.94
4.32
3.04
2.54
4.23
1.46
2.98
1.59
1.49
1.00

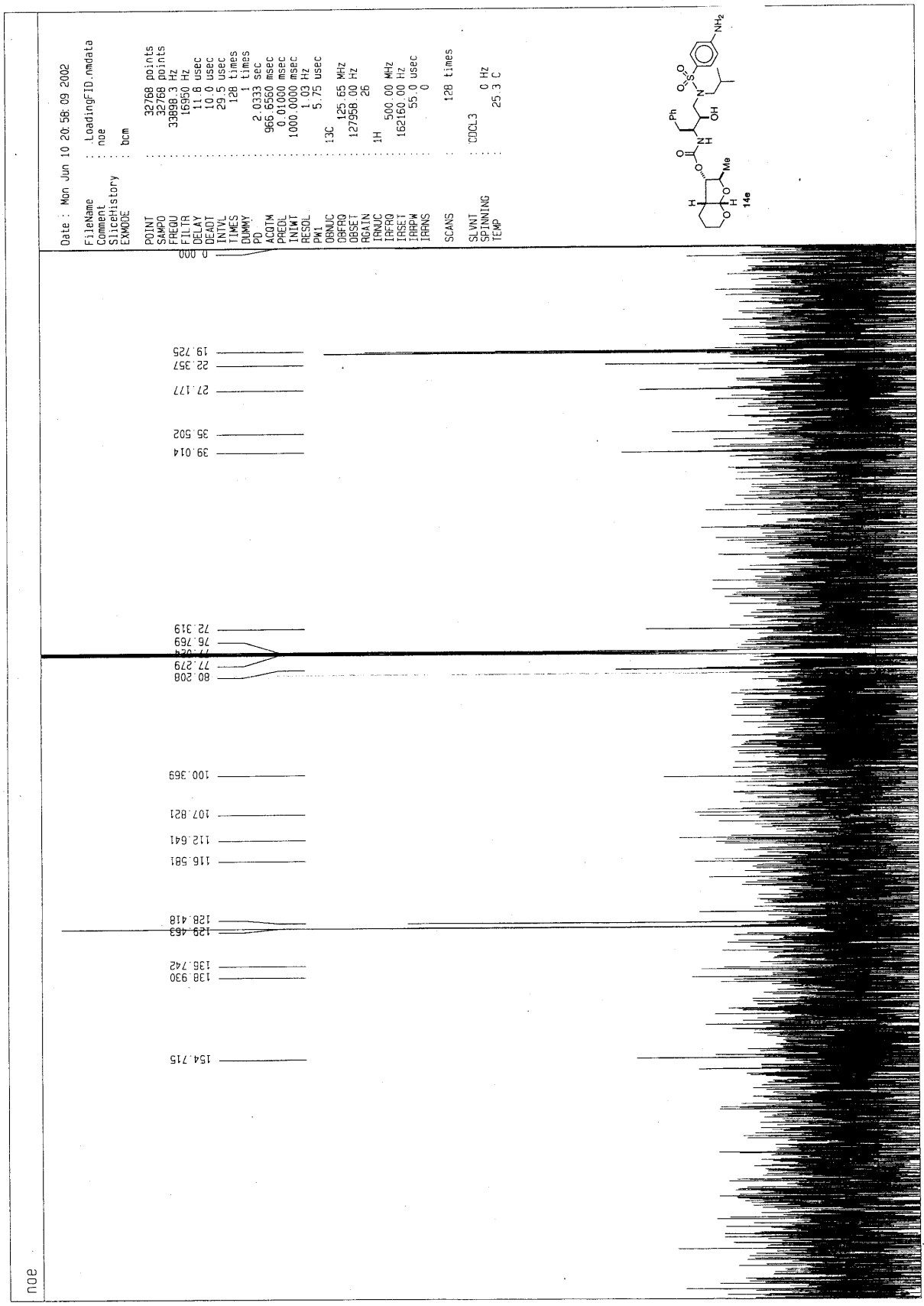

Date : Mon Jun 10 18:19:36 2002
FileName : LoadingFID.nmrdata
Comment : noe
SliceHistory : non
EXMODE
POINT 32768 points
SAMPO 32768 points
FREQU 10000.0 Hz
FILTR 5000 Hz
DELAY 40.0 usec
DEADT 55.8 usec
INTVL 100.0 usec
TIMES 8 times
DUMMY 1 times
PD 3.7232 sec
ACQTM 3276.7998 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 0.31 Hz
PW1 8.40 usec
1H
OBNUC 500.00 MHz
OBFRQ 162379.27 Hz
OBSET 15
RGAIN
SCANS 8 times
SLVNT CDCl3
SPINNING 12 Hz
TEMP 24.9 C
14d
noe
ppm


noe
Date : Mon Jun 10 20:45:51 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory : : : bcm
EXMODE
POINT 32768 points
SAMPO 32768 points
FREQU 33898.3 Hz
FILTR 16950 Hz
DELAY 11.8 usec
DEADT 10.0 usec
DEAVT 29.5 usec
INIVL 128 times
TIMES 1 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 0.01000 msec
INIMT 1000.0000 msec
RESOL 1.03 Hz
PW1 5.75 usec
OBNUC 13C 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 26
AGAIN
IANUC 1H
IAFRQ 500.00 MHz
IASET 162160.00 Hz
IARPW 55.0 usec
IARNS 0
SCANS 73 times
SLVNT CDCL3
SPINNING 0 Hz
TEMP 25.3 C
0.000
2.032
6.753
19.741
20.054
20.712
22.530
25.869
26.018
28.732
30.673
30.813
33.289
35.469
35.831
39.030
56.123
58.912
59.923
63.238
70.411
71.118
76.778
77.288
79.624
79.821
100.747
126.427
128.476
129.446
138.3
156.4
169.0
14d
ppm


Date : Tue May 14 16:28:20 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory :
EXMODE : non
POINT 32768 points
SAMPO 32768 points
FREQU 10000.0 Hz
FILTR 5000 Hz
DELAY 40.0 usec
DEADT 55.8 usec
INTVL 100.0 usec
TIMES 8 times
DUMMY 1 times
PD 3.7232 sec
ACQTM 3276.7998 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 0.31 Hz
PW1 8.40 usec
1H
OBNUC 500.00 MHz
OBFRQ 162405.67 Hz
OBSET 16
RGAIN
SCANS 8 times
SLVNT C6D6
SPINNING 14 Hz
TEMP 24.0 C
12e
noe
ppm


Date : Tue May 14 16:46:20 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory :
EXMODE : bcm
POINT 32768 points
SAMPO 32768 points
FREQU 33898.3 Hz
FILTR 16950 Hz
DELAY 11.8 usec
DEADT 10.0 usec
INTVL 29.5 usec
TIMES 256 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 1.03 Hz
PW1 6.40 usec
13C
OBNUC 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 27
PGAIN
1H 500.00 MHz
IRNUC 162150.00 Hz
IRFRQ 55.0 usec
IRSET 0
IRAPW
IRPNS
SCANS 256 times
SLVNT CDCL3
SPINNING 13 Hz
TEMP 25.6 C
12e
noe
ppm
19.758
19.799
19.906
20.145
22.308
27.260
35.666
39.138
53.837
54.881
58.838
63.370
72.723
76.745
77.000
77.247
79.945
100.912
114.073
126.000
126.460
128.435
129.381
129.512
133.798
137.598
150.734
155.916


Date : Mon Jun 10 17:15:57 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory : ...
EXMODE : non
POINT 32768 points
SAMPO 32768 points
FREQU 10000.0 Hz
FILTR 5000 Hz
DELAY 40.0 usec
DEADT 55.8 usec
INTVL 100.0 usec
TIMES 8 times
DUMMY 1 times
PD 3.7232 sec
ACQTM 3276.7998 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 0.31 Hz
PW1 8.40 usec
1H
OBNUC 500.00 MHz
OBFRQ 162379.27 Hz
OBSET 1B
RGAIN
SCANS 8 times
SLVNT CDCL3
SPINNING 12 Hz
TEMP 25.0 C
14e
noe
ppm


Date : Mon Jun 10 20:58:09 2002
FileName : LoadingFID.nmdata
Comment : noe
SliceHistory :
EXMODE : bcm
POINT 32768 points
SAMPO 32768 points
FREQU 33898.3 Hz
FILTR 16950 Hz
DELAY 11.8 usec
DEADT 10.0 usec
INTVL 29.5 usec
TIMES 128 times
DUMMY 1 times
PD 2.0333 sec
ACQTM 966.6560 msec
PREDL 0.01000 msec
INIWT 1000.0000 msec
RESOL 1.03 Hz
PW1 5.75 usec
OBNUC 13C 125.65 MHz
OBFRQ 127958.00 Hz
OBSET 26
RGAIN
IRNUC 1H 500.00 MHz
IRFRQ 162160.00 Hz
IRSET 55.0 usec
IRAPW 0
IRANS
SCANS 128 times
SLVNT CDCL3 0 Hz
SPINNING 25.3 C
TEMP
19.725
22.357
27.177
35.502
39.014
72.319
76.769
77.279
80.208
100.369
107.821
112.641
116.581
128.418
129.483
135.742
138.930
154.715
noe
14e