

Supporting Information for

Stereocontrolled Total Synthesis of (\pm)-Catharanthine via Radical-Mediated Indole Formation

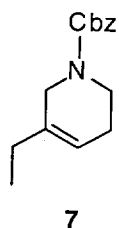
Matthew T. Reding and Tohru Fukuyama*
*Graduate School of Pharmaceutical Sciences, The University of Tokyo,
CREST, The Japan Science and Technology Corporation (JST),
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan*

General:

All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise stated. Reagents were either commercially available and used as obtained, or were prepared as noted or according to published methods. Benzene, toluene, and dichloromethane were distilled from CaH₂ and stored over activated molecular sieves (4Å). THF, ether, and acetonitrile, methanol, and ethanol were purchased anhydrous and stored over molecular sieves (4Å) under argon. t-Butanol and 1-propanol were 99%+ reagent grade and used as received. 'Workup', unless otherwise noted, refers to partitioning the reaction mixture between the indicated aqueous and organic phases, followed by separation and extraction of the aqueous phase and washing of the combined organic phases as indicated. Organic solutions were dried with powdered anhydrous magnesium sulfate. Preparative flash column chromatography was performed using a quantity of silica gel (Merck Silica gel 60, 230-400 mesh) equal to 30 to 50 times sample weight, with gradient elution over the indicated range of solvent mixtures. Preparative thin layer chromatography (pTLC) was carried out on 200 x 65 x 0.5 mm precoated glass plates (Merck Silica gel 60 F₂₅₄). Yields, unless otherwise stated, refer to isolated yields of compounds judged greater than 95% pure by ¹H NMR. Previously reported compounds were identified on the basis of their ¹H NMR spectra, while new compounds were further characterized by ¹³C NMR and IR, and gave satisfactory high

resolution mass spectrographic analyses, unless noted otherwise. NMR spectra were obtained in CDCl_3 on a JEOL LA-400 400 MHz spectrometer. All ^1H NMR spectra are reported in ppm downfield from tetramethylsilane as an internal standard. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for CDCl_3 at 77 ppm. IR spectra were recorded on a JASCO FT/IR-410, and absorptions are reported in cm^{-1} . High resolution mass spectra were obtained on a JEOL JMS-GCmate MS-DIP20 quadrupole at 70 eV, using direct probe insertion at temperatures of 70 to 330 °C.

Experimental.



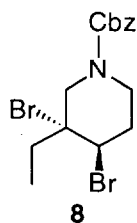
1-Benzylloxycarbonyl-3-ethyl-3,4-dehydropiperidine, 7.¹ 3-Ethylpyridine (17.1 mL, 150 mmol) was cooled to 0 °C in an ice bath. Benzyl bromide (17.8 mL, 150 mmol) was added dropwise with stirring over several minutes. The reaction mixture evolved heat and turned yellow; after ca. 20 min, the reaction mixture grew viscous and rapidly solidified to a yellow glass. This was allowed to warm to room temperature and was left to stand overnight. The resulting opaque yellow-white solid was broken up with a spatula and ground in a mortar to produce a coarse, off-white powder. This was washed with several portions of ether and dried under vacuum to afford 1-benzyl-3-ethylpyridinium bromide as an off-white solid (41.58 g, 99.6%).

The pyridinium salt (6.00 g, 21.6 mmol) was dissolved in ethanol (35 mL) in an addition funnel, and added dropwise over 15 minutes to a stirred suspension of NaBH_4 (3.22g, 86.3 mmol) in ethanol (60 mL) cooled to 0 °C on

¹ Szántay, C.; Bölcskei, H.; Gács-Baitz, E. *Tetrahedron* **1990**, *46*, 1711.

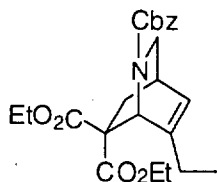
an ice bath. Hydrogen evolved steadily during the addition. The resulting bright-yellow mixture was allowed to warm slowly to room temperature overnight with stirring. The solvent was then removed under vacuum and the residue was worked up between water and dichloromethane (3x50 mL, brine) and dried. Concentration by rotary evaporation afforded crude 1-benzyl-3,4-dehydro-3-ethylpiperidine as an orange oil, 4.58 g.

The crude dehydropiperidine was dissolved in benzene. Benzyl chloroformate (6.17 mL, 43.2 mmol) was added in one portion via syringe. A slight exotherm was noted. The reaction mixture was heated at reflux for 4 h, at which time TLC analysis indicated complete conversion of the starting material. The solvent was removed under vacuum and the residue was purified by flash column chromatography (hexanes/ethyl acetate 15:1-5:1) to afford 1-benzyloxycarbonyl-3,4-dehydro-3-ethylpiperidine, **7**, as a colorless oil (3.28 g, 62% from the pyridinium salt). $^1\text{H NMR}$: 1.03 (t, $J=7.3$ Hz, 3H); 1.92 (br s, 2H); 2.13 (br s, 2 H); 3.52 (t, $J=5.6$ Hz, 2H); 3.86 (br s, 2H); 5.22 (s, 2H); 5.52 (br s, 1H); 7.35 (m, 5H).



1-Benzyloxycarbonyl-3,4-*trans*-dibromo-3-ethylpiperidine, 8.¹ The Cbz-protected dehydropiperidine **7** (3.28 g, 13.4 mmol) was dissolved in reagent-grade dichloromethane (50 mL). Bromine (ca. 0.69 mL, 13.4 mmol) was added dropwise until the red color persisted. The mixture was stirred an additional 5 min., then decolorized with aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was worked up with brine (1x20ml CH_2Cl_2) and dried. Concentration afforded a slightly yellow oil, 1-benzyloxycarbonyl-3,4-dibromo-3-ethylpiperidine, **8**,

(5.33 g, 98%). $^1\text{H NMR}$: 1.14 (m, 3H); 2.02 (m, 3H); 2.78 (m, 1H); 3.33 (m, 2H); 4.19 (m, 2H); 4.62 (s, 1H); 5.17 (br s, 2H); 7.37 (m, 5H).



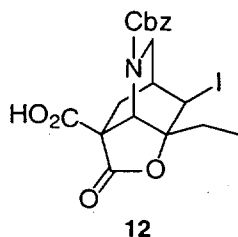
11

2-Carboxybenzyloxy-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7,7-dicarboxylic acid diethyl ester, 11. Palladium on carbon (1.0 g, 10 % Pd) was suspended in reagent grade EtOAc (150 mL) and cooled to 0 °C on an ice bath with stirring. The mixture was then purged with hydrogen gas for 10 min. Diethyl ethoxymethylenemalonate (10.7 g, 49.4 mmol) was then added via syringe in one portion. The reaction mixture was allowed to warm to room temperature. After 2 h, TLC analysis indicated the the starting material had been consumed. The reaction mixture was purged with bubbling argon, then filtered through a pad of Celite, and rinsed with CH_2Cl_2 . Removal of the solvent under vacuum afforded diethyl ethoxymethylmalonate as a clear, colorless oil (11.0g, 100%). $^1\text{H NMR}$ also indicated the presence of ca. 9% diethyl methylmalonate. The mixture was used as obtained in the following step.

Dibromo compound **8** (5.33 g, 13.2 mmol) and DABCO (5.13 g, 45.7 mmol) were dissolved in acetonitrile (100 mL). The solution was heated to reflux; a white precipitate formed rapidly. After ca. 2 h, TLC analysis showed that the starting material had been consumed. The mixture was cooled to room temperature (under argon) and the supernatant was decanted. The precipitate was rinsed (2x20 mL CH_2Cl_2) and the combined organic solutions were worked up between CH_2Cl_2 and water (2x20 mL CH_2Cl_2 , brine), dried, and concentrated under vacuum to afford an orange, slightly cloudy oil (3.03

g, 94% crude yield). Although the ^1H NMR spectrum of this oil was consistent with structure **9**, generally this material was not characterized but immediately used in the next step.

Crude dihydropyridine **9** and diethyl ethoxymethylmalonate were mixed and pump/purged with argon (3x). The slightly cloudy orange mixture was heated with stirring under argon under with a condenser at 100 °C overnight. The mixture was then cooled, and the volatiles were removed under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate 10:1-2:1) to afford 2-carboxybenzyloxy-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7,7-dicarboxylic acid diethyl ester, **11**, as a clear, slightly yellow oil (6.95g, >100%). The ^1H NMR of this material was consistent with the desired structure; the presence of polymeric ethyl esters was also revealed by the presence of broad multiplets near 1 and 4 ppm. The compound was used as obtained from the initial chromatography. ^1H NMR: the compound was found to exist as a mixture of rotamers that gave a complex spectrum; please see attached. Variable temperature NMR experiments supported the assignment as rotamers and *not* a mixture of regioisomers (T_c of dimethyl ester derivative in $\text{DMF}-d_6$ 90 °C). IR (cm^{-1}): 858, 1021, 1108, 1149, 1245, 1412, 1704, 1735, 2879, 2980. HRMS: calc'd for $\text{C}_{23}\text{H}_{29}\text{NO}_6$: 415.1995; found: 415.2009.

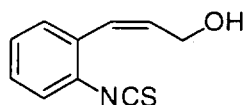


Iodolactone of 2-carboxybenzyloxy-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7,7-dicarboxylic acid, 12. The once-chromatographed diester **11** (6.95 g, ca. 13.2 mmol) was dissolved in reagent-grade ethanol (50 mL). An aqueous KOH solution (5 M, 50 mL) was added to give a homogenous yellow

solution which grew warm to the touch. This mixture was refluxed under argon with stirring for 2 h, until TLC analysis (4:1:1 toluene/formic acid/ethyl formate eluant) showed complete conversion of the starting material. The reaction mixture was cooled to room temperature and diluted with water (20 mL). The mixture was cooled to 0 °C on an ice bath, and acidified with 4 N HCl (ca. 90 mL) with stirring. The acidification was judged complete when the solution tested below pH 1 according to universal indicating paper, and a cloudy mixture was obtained. The mixture was extracted with ether (50 mL) and the layers separated. The aqueous layer was saturated with NaCl, and extracted with ether (5x30 mL). The combined extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation (bath temperature less than 30 °C) and exposure to vacuum to afford a viscous yellow oil. ¹H NMR indicated the presence of the desired diacid, along with appreciable quantities of ether and ethanol.

The crude diacid obtained above was dissolved in saturated aqueous NaHCO₃ (150 mL) to afford a cloudy white solution. Iodine (3.35 g, 13.2 mmol) was added and the mixture was stirred vigorously. The iodine slowly dissolved to afford a deep brown/purple solution. After stirring overnight, TLC (4:1:1 toluene/formic acid/ethyl formate eluant) showed complete consumption of the starting material. The mixture was carefully acidified with 4 N HCl (**CAUTION!** Vigorous bubbling!) until the pH was below 1 according to universal paper. The mixture was extracted with ether (100 mL). The aqueous layer was saturated with NaCl and extract with ether (5x30 mL). The combined organic layers were then decolorized with a small amount of saturated aqueous Na₂S₂O₃ solution, and washed with brine (10 mL). The solution was dried and concentrated by rotary evaporation; the last traces of solvent were removed by prolonged exposure to vacuum to afford iodolactone **12** as a pale yellow foam (4.26 g, 67% over the four steps from dibromide **8**).

^1H NMR: the compound was found to exist as a mixture of rotamers that gave a complex spectrum; please see attached. IR (cm^{-1}): 734, 930, 964, 1078, 1118, 1176, 1308, 1346, 1422, 1709, 1794, 2944, 2974.

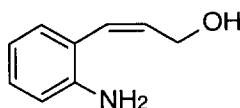


14

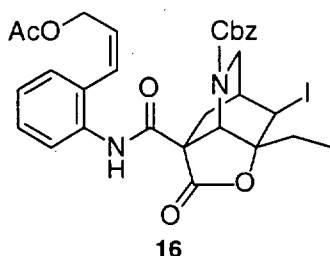
2-(*cis*-3'-hydroxyprop-1-enyl)phenylisothiocyanate, 14.² (Note: Failure to maintain the temperature of the initially obtained *cis* aldehyde at or below 0 °C prior to reduction results in the formation of appreciable amounts of the undesired *trans* isomer.) Quinoline (11.82 mL, 100 mmol) and BaCO₃ (29.6 g, 150 mmol) were suspended in water (150 mL) and reagent-grade CH₂Cl₂ (150 mL) with rapid stirring at 0 °C in a ice bath. Thiophosgene (7.62 mL, 100 mmol) was added dropwise over 15 minutes. After 35 min, TLC indicated complete consumption of the quinoline. The reaction mixture was filtered through a pad of Celite 545 with suction into an ice-cooled receiver, and the Celite was rinsed with small portions of ice-cold CH₂Cl₂. The mixture was partitioned between ice-cold brine and ice-cold CH₂Cl₂, and the layers were separated. The aqueous layer was washed (2x20 mL ice-cold CH₂Cl₂ and the combined deep-orange organic layers were diluted with ice-cold methanol (300 mL) and stirred rapidly at -15 °C in a methanol/ice bath. To this solution was added in small portions NaBH₄ (1.89g, 50 mmol; **CAUTION!** Vigorous bubbling!) to afford a bright yellow solution. Immediately after adding the reductant, TLC indicated complete consumption of the aldehyde. The reaction was quenched with 1 M HCl (100 mL) and the layers separated. The organic layer was worked up between saturated NaHCO₃ and CH₂Cl₂ (1x20ml CH₂Cl₂, brine) and dried. Concentration afforded a bad-smelling

²) Tokuyama, H; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791.

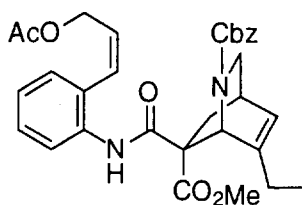
deep orange oil, 19.27 g. This was recrystallized from hot CHCl_3 /hexanes to afford one crop of fine needles (7.94 g) and the mother liquor was then concentrated and chromatographed (hexanes/EtOAc 10:1-1:2) to afford another portion of product (3.42 g). The title alcohol **14** was thus obtained as orange needles (11.36 g total, 60%) as a single *cis* diastereomer. ^1H NMR: 1.56 (s, 1H); 4.32 (br s, 2H); 6.08 (narrow quintet, 1H); 6.65 (t, $J=11.6$ Hz, 1H); 7.25 (m, 4H).

**15**

2-(*cis*-3'-hydroxyprop-1-enyl)aniline, 15.² Isothiocyanate **14** (3.83 g, 20 mmol) was dissolved in *t*-BuOH (75 mL). An aqueous KOH solution (5 M, 75 mL) was added. The mixture was stirred vigorously under argon at reflux for 2 h, until TLC indicated both the starting material and the presumed cyclothiocarbamate intermediate had been consumed. The reaction was cooled to room temperature, and worked up with saturated aqueous NH_4Cl solution (2x30 mL Et_2O , brine) and dried. Concentration afforded a sticky yellow solid, which was purified by flash column chromatography (hexanes/ethyl acetate 2:1-1:3 + 0.5% NEt_3) to afford the title aniline **15** as an off-white solid (2.12 g, 71%). ^1H NMR: 2.05 (s, 1H); 3.70 (br s, 2H); 4.23 (d, $J=6.8$ Hz, 2H); 6.01 (m, 1 H); 6.47 (d, $J=11.6$ Hz, 1 H); 6.95 (d, $J=8.0$ Hz, 1H); 6.75 (m, 2H); 7.10 (t, $J=6.8$ Hz, 1H).

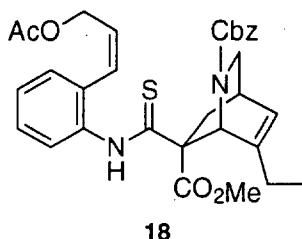


2-alkenyl anilide 16. Iodolactone acid **12** (3.9 g, 8.04 mmol), aniline **15** (1.00 g, 6.74 mmol), and water-soluble carbodiimide (1.7 g, 8.75 mmol) were dissolved in CH₂Cl₂ (25 mL) under argon. NEt₃ (1.4 mL, 10.11 mmol) was added via syringe and the mixture was stirred at room temperature until TLC indicated complete consumption of the aniline (1.5 h). The reaction mixture was partitioned between 1 N HCl and CH₂Cl₂ (50 mL each); the layers were separated and the organic layers were washed (1x 50 mL each 1 N HCl, sat'd NaHCO₃, brine), dried, and concentrated to afford the desired crude anilide as a white foam (4.55 g). The crude material was immediately dissolved in a mixture of Ac₂O (5 mL, 53 mmol) and pyridine (5 mL, 62 mmol) and stirred for 2 h at room temperature. The mixture was then partitioned between ether and 1 N HCl; the layers were separated and the organic layers were washed (2 x 20 mL sat'd NaHCO₃, 1 x 20 mL brine), dried, and concentrated to afford a viscous orange-brown oil (4.95 g), which was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc + 0.5% NEt₃) to afford the anilide **16** as a colorless foam (3.29 g, 74 %). ¹H and ¹³C NMR: the compound was found to exist as a mixture of rotamers that gave complex spectra; please see attached. IR (cm⁻¹): 764, 963, 1234, 1305, 1420, 1535, 1708, 1737, 1764, 2943, 2975, 3325. HRMS: calc'd for C₃₀H₃₁N₂O₇: 658.1176; found: 658.1197.

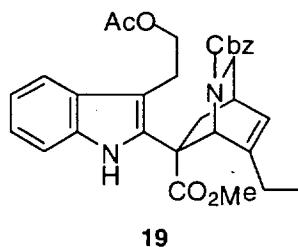


17

De-iodolactonized methyl ester anilide 17. Anilide **16** (3.29 g, 5.00 mmol) was dissolved in CH₂Cl₂ (25 mL) under argon. Powdered zinc (3.3 g, 50 mmol) was added, followed by glacial acetic acid (5.7 mL, 100 mmol) with rapid stirring. The reaction mixture warmed slightly, and was stirred at room temperature until TLC indicated complete consumption of the starting material (30 min). The reaction mixture was passed through Celite to remove excess zinc; the Celite pad was rinsed with several portions each of CH₂Cl₂ and ether. The filtrate was washed (3 x 20 mL 1 N HCl), dried, and filtered. The solution volume was reduced to ca. 100 mL. To this gently swirled solution was added an ethereal solution of diazomethane (generated at 0 °C from *N*-methyl-*N*-nitrosourea using 50% aqueous NaOH). The diazomethane solution was added at room temperature until the bright yellow color persisted for 2-3 min. The yellow solution was quenched with a small amount of AcOH, and then stirred with sat'd NaHCO₃. The layers were separated and the organic layer was washed (brine), dried, and concentrated to afford a bright yellow oil (3.02 g). This was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc + 0.5% NEt₃) to afford the desired methyl ester **17** as a clear, viscous, nearly colorless oil (2.26 g, 83%). ¹H and ¹³C NMR: the compound was found to exist as a mixture of rotamers that gave complex spectra; please see attached. IR (cm⁻¹): 760, 1030, 1250, 1451, 1526, 1581, 1702, 1740, 2962, 3382. HRMS: calc'd for C₃₁H₃₄N₂O₇: 546.2366; found: 546.2363.

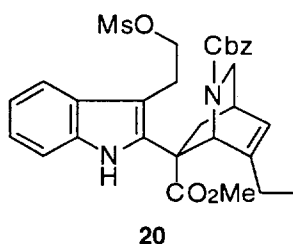


Thioanilide 18. Anilide **17** (2.26 g, 4.13 mmol) was dissolved in toluene (50 mL) under argon. Lawesson's reagent (5.02 g, 12.4 mmol) was added, followed by pyridine (0.17 mL, 2.1 mmol). The mixture was stirred at reflux under a condenser and argon balloon overnight, after which time TLC showed complete consumption of the starting material. The mixture was cooled to room temperature, and worked up (sat'd NaHCO₃/ether, brine), dried, and concentrated. The resulting bad-smelling bright-yellow oil was purified by flash column chromatography (5:1-1:5 hexanes/CH₂Cl₂ + 1% MeOH) to afford thioanilide **18** as a nearly odorless, pale-yellow foam (2.00 g, 86%). ¹H and ¹³C NMR: the compound was found to exist as a mixture of rotamers that gave complex spectra; please see attached. IR (cm⁻¹): 761, 1101, 1238, 1370, 1417, 1507, 1699, 1739, 2962. HRMS: calc'd for C₃₁H₃₄N₂O₆S: 562.2138; found: 562.2125.



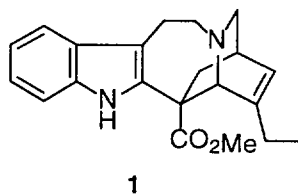
Indole 19. Thioanilide **18** (414 mg, 0.74 mmol) was dissolved in 1-propanol (5 mL) under argon along with AIBN (133 mg, 0.81 mmol), hypophosphorous acid (30% aqueous solution, 1.4 mL, 7.4 mmol), and NEt₃ (1.55 mL, 11.1 mmol). The mixture warmed slightly, and was stirred in a 90 °C oil bath under a reflux condenser and argon balloon. After 45 min, TLC indicated complete consumption of the starting material. The mixture was cooled to RT and

diluted with ether (20 mL). Workup (1 N HCl, 1 N NaOH, brine), drying, and concentration afforded a yellow oil, which was purified by flash column chromatography (10:1-5:1 hexanes/EtOAc + 0.5% NEt₃) to give the desired indole **19** as a clear, faintly yellow oil (198 mg, 50%). ¹H NMR: 1.06 (t, *J*=7.6 Hz, 3H); 1.91 (d, *J*=10.8 Hz, 1H); 2.04 (s, 3H); 2.18 (m, 2H); 2.9-3.2 (m, 5H); 3.54 (s, 3H); 3.60 (m, 1H); 4.14 (m, 1H); 4.25 (m, 1H); 5.12 (q, *J*=15.6, 10.8 Hz, 2H); 5.48 (s, 1H); 6.11 (d, *J*=5.6 Hz, 1H); 7.09 (t, *J*=8.0 Hz, 1H); 7.17 (t, *J*=7.2 Hz, 1H); 7.38 (d, *J*=8.0 Hz, 1H); 7.60 (d, *J*=8.0 Hz, 1H); 9.96 (s, 1H). ¹³C NMR: 11.4, 21.1, 23.4, 24.3, 25.1, 26.5, 30.8, 34.9, 48.4, 52.6, 53.5, 63.8, 67.6, 108.4, 111.6, 118.5, 119.3, 121.8, 126.7, 127.7, 128.1, 128.5, 128.7, 135.2, 135.5, 136.1, 144.5, 156.9, 171.0, 171.4, (1 obscured peak). IR (cm⁻¹): 737, 1083, 1244, 1419, 1457, 1672, 1698, 1738, 2962, 3298. HRMS: calc'd for C₃₁H₃₄N₂O₆: 530.2417; found: 530.2406.



Mesylate 20. Acetate-indole **19** (166 mg, 0.29 mmol) was dissolved in dry methanol (5 mL) under argon. K₂CO₃ (powdered anhydrous, 200 mg, 1.45 mmol) was added and the mixture was stirred vigorously for 30 min at room temperature, at which time TLC analysis showed complete consumption of the starting material. The mixture was partitioned between ether and water, and worked up (ether, brine), dried, and concentrated to afford a white foam (152 mg). The crude material was immediately dissolved in dry CH₂Cl₂ (2 mL) and treated with mesyl chloride (27 μL, 0.35 mmol) and NEt₃ (53 μL, 0.38 mmol). The mixture was stirred for 20 minutes at room temperature, at which time TLC analysis indicated complete consumption of the free primary alcohol. The

mixture was partitioned between 1 N HCl and ether, and worked up (ether, NaHCO₃, brine), dried, and concentrated to afford the crude product as a yellow oil (176 mg). This material was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc + 0.5% NEt₃) to afford the desired mesylate **20** as a white foam (135 mg, 82%). ¹H NMR: 1.06 (t, *J*=6.8 Hz, 3H); 1.88 (d, *J*=12.8 Hz, 1H); 2.17 (m, 2H); 2.78 (s, 3H); 2.93 (m, 2H); 3.21 (m, 5H); 3.57 (s, 3H); 4.25 (m, 1H); 4.35 (m, 1H); 5.17 (s, 2H); 5.62 (s, 1H); 6.12 (br d, *J*=6.0 Hz, 1H); 7.11 (t, *J*=7.6 Hz, 1H); 7.21 (t, *J*=7.6 Hz, 1H); 7.38 (d, *J*=7.6 Hz, 1H); 7.52 (d, *J*=7.6 Hz, 1H); 10.06 (s, 1H). ¹³C NMR: 11.3, 24.9, 26.5, 30.7, 34.9, 37.2, 48.4, 52.7, 53.4, 53.5, 67.6, 68.9, 106.6, 111.8, 118.0, 119.6, 122.0, 126.8, 127.7, 128.1, 128.3, 128.4, 135.1, 136.0, 136.1, 144.4, 157.0, 171.5 (2 obscured peaks). IR (cm⁻¹): 737, 952, 1174, 1355, 1421, 1458, 1671, 1735, 2962, 3296.. HRMS: calc'd for C₃₀H₃₄N₂O₆S: 566.2087; found: 566.2088.



(±)-Catharanthine, **1**.³ Mesylate **20** (82 mg, 0.14 mmol) was dissolved in EtOAc (passed through Al₂O₃, 0.5 mL) along with Pd(OAc)₂ (11 mg, 0.05 mmol) under argon. Dry ethanol (0.5 mL) was added and the mixture was stirred at room temperature for 3 min (orange solution slowly turned red/brown). Triethylsilane (50 μL, 0.29 mmol) was added via syringe, and the mixture bubbled, warmed, and rapidly turned black. NEt₃ (20 μL, 0.14 mmol) was added immediately. The mixture was stirred at room temperature for 15 min, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was diluted with CH₂Cl₂, and filtered through Celite to remove the precipitated palladium. The filtrate was worked

³Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913.

up (CH₂Cl₂, NaHCO₃), dried, and concentrated. The crude material was purified by pTLC (two 200 x 65 x 0.5 mm plates, double elution with 1:1 hexanes/EtOAc + 0.5% NEt₃) to afford (±)-catharanthine, **1**, as a white powder (45 mg, 96%). ¹H NMR: 1.07 (t, *J*=6.8 Hz, 3H); 1.77 (dd, *J*=13.6, 3.6 Hz, 1H); 2.09 (m, 1H); 2.31 (m, 1H); 2.72 (br d, *J*=6.8 Hz, 1H); 2.81-2.94 (m, 3H); 3.25-3.40 (m, 3H); 3.56 (m, 1H); 3.73 (s, 3H); 4.17 (s, 1H); 5.92 (dm, 1H); 7.08-7.16 (overlapping triplets, 2H); 7.23 (d, *J*=7.6 Hz, 1H); 7.48 (d, *J*=7.6 Hz, 1H); 7.68 (s, 1H). ¹³C NMR: 10.6, 21.4, 28.2, 30.7, 38.7, 49.3, 52.3, 53.0, 55.4, 61.9, 110.4, 110.7, 118.2, 119.4, 121.8, 123.5, 129.0, 134.9, 136.4, 149.4, 174.2. IR (cm⁻¹): 741, 909, 1078, 1267, 1460, 1713, 2844, 2961, 3375. HRMS: calc'd for C₂₁H₂₄N₂O₂: 336.1838; found: 336.1846. The structure was further confirmed by ¹H-¹H COSY, DEPT, and HMQC (¹H-¹³C correlation) NMR measurements (data not shown).

Spectral Data Section:

The ¹H NMR, ¹³C NMR, and IR spectra for selected compounds are reproduced on the following pages.

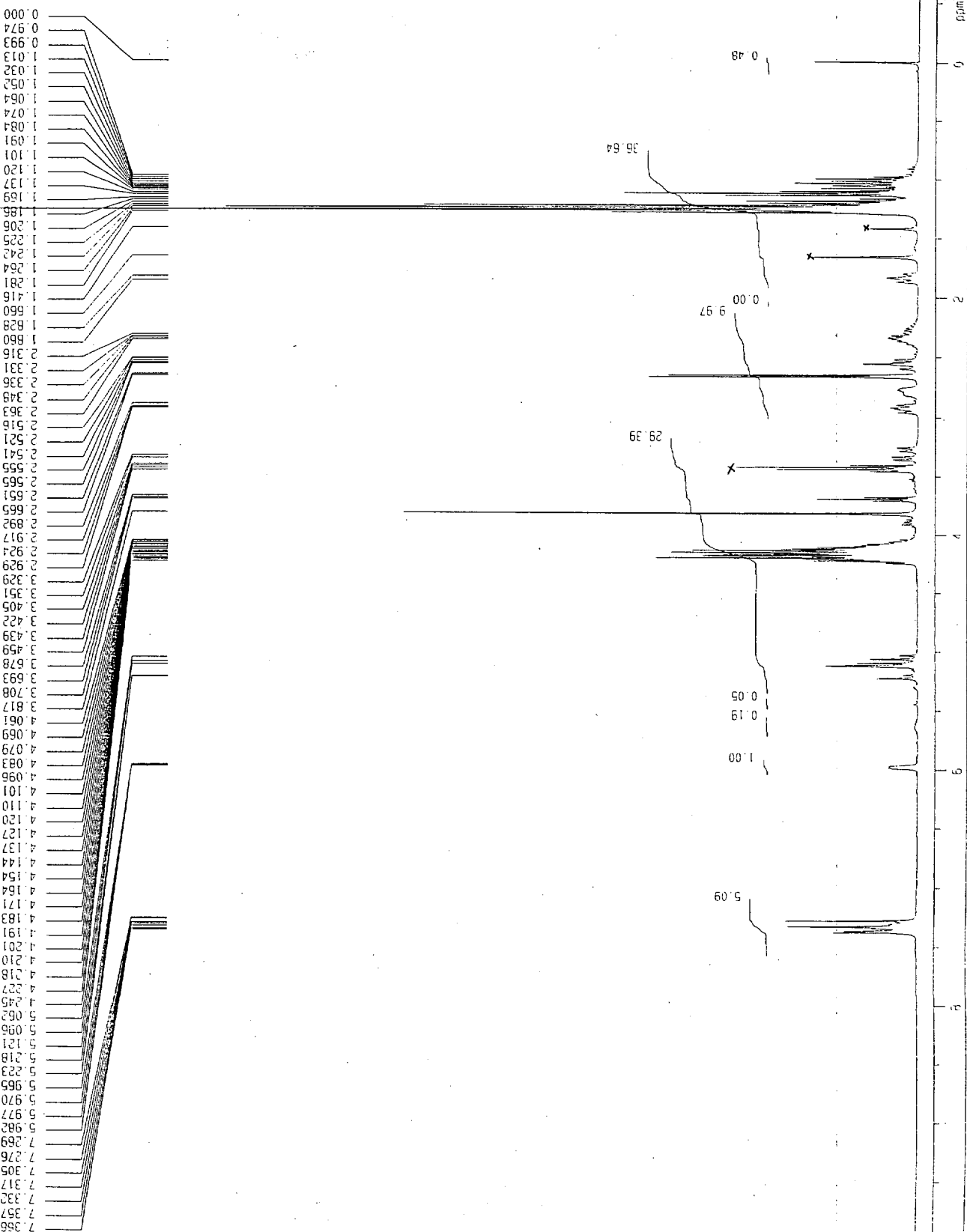
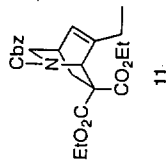
MR03090P

Date : Fri Jun 11 00:21:28 1999

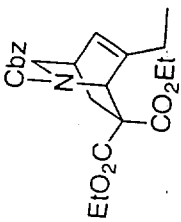
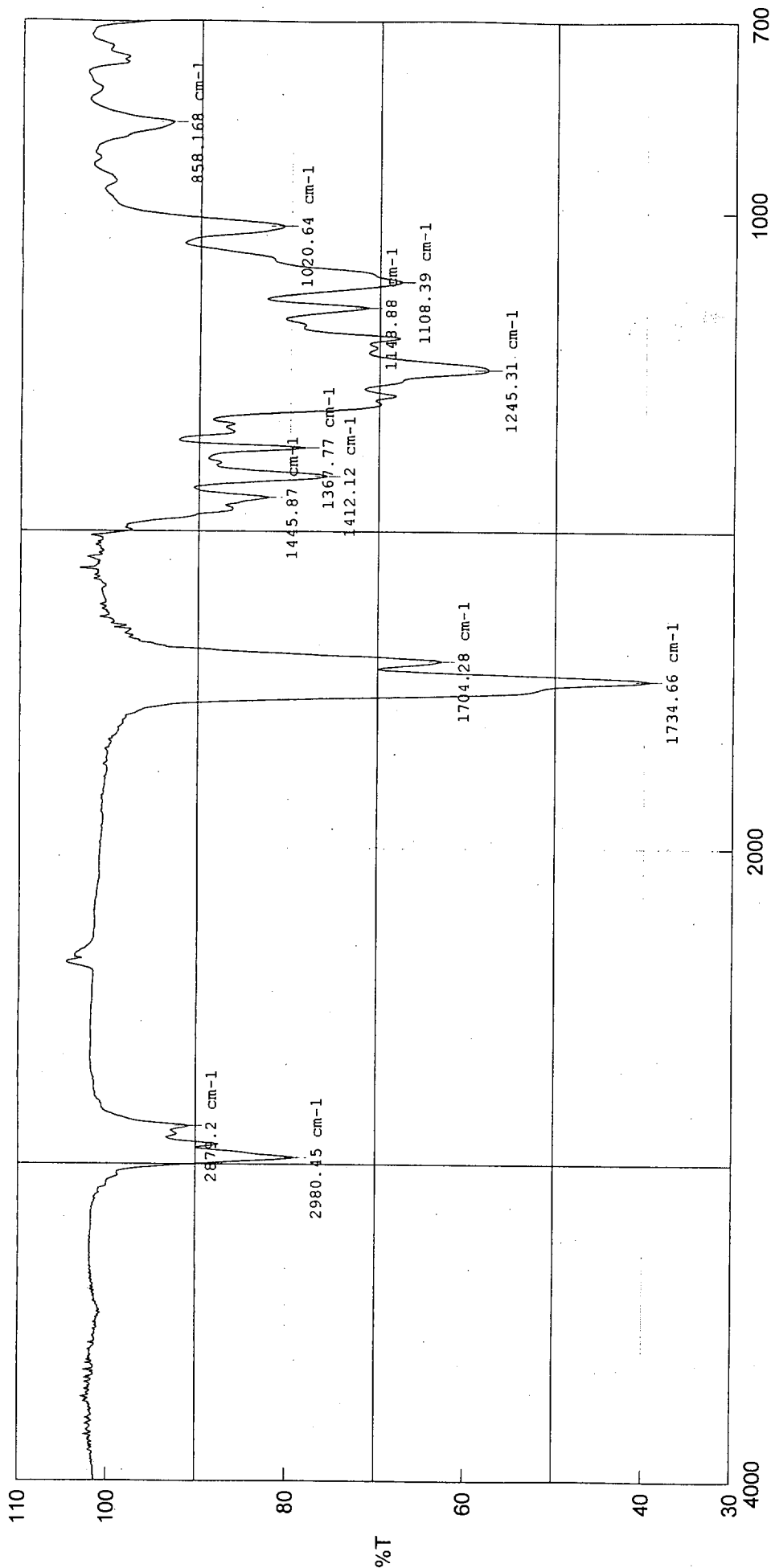
Filename : MR03090P.nmdata
 Comment : MR03090P
 EXAMODE : non

POINT 8152 points
 SAMPO 8192 points
 FREQD 7993.5 Hz
 FILTR 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INITL 125.1 usec
 TIMES 64 times
 DUMMY 0 times
 PD 0.0300 sec
 ACOVM 1024.8152 msec
 PREOL 10.00000 msec
 INITR 0.5000 msec
 RESOL 0.98 Hz
 PWT 5.75 usec
 1H 399.65 MHz
 134300.00 Hz
 17
 SCANS 64 times

SLVNT CDCL3
 SPINNING 13 Hz
 TEMP 22.2 C



MR03090

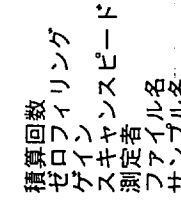


128
ON
1
2 mm/sec
オペレータ
Mr03090.jws
コメント

分解
アポダイゼーション
アパーチャー
日時

2 cm-1
Cosine
-0.001 mm
99/06/11 15:04

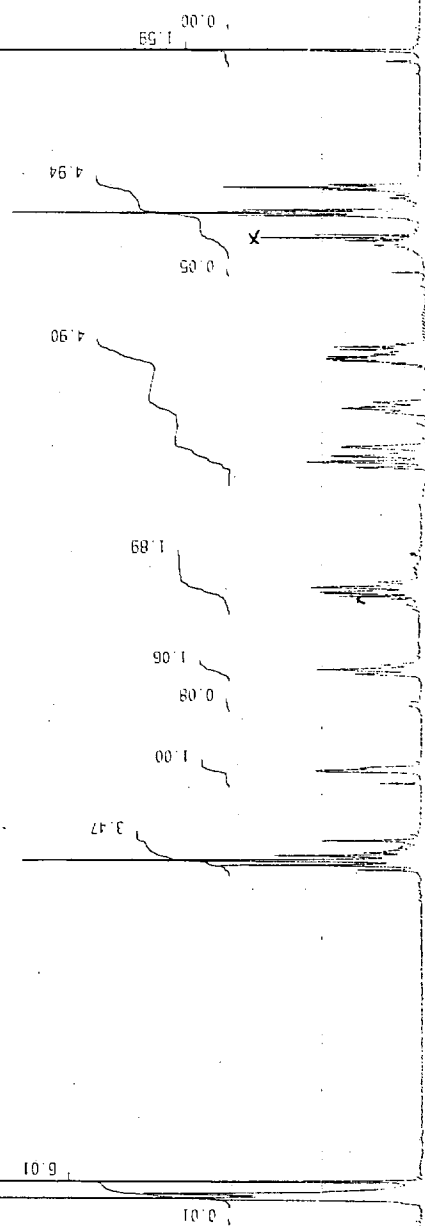
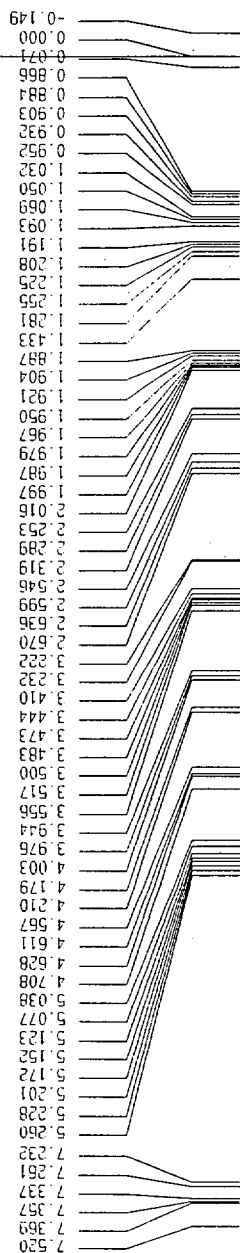
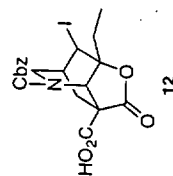
11



MP02198

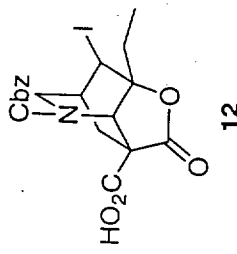
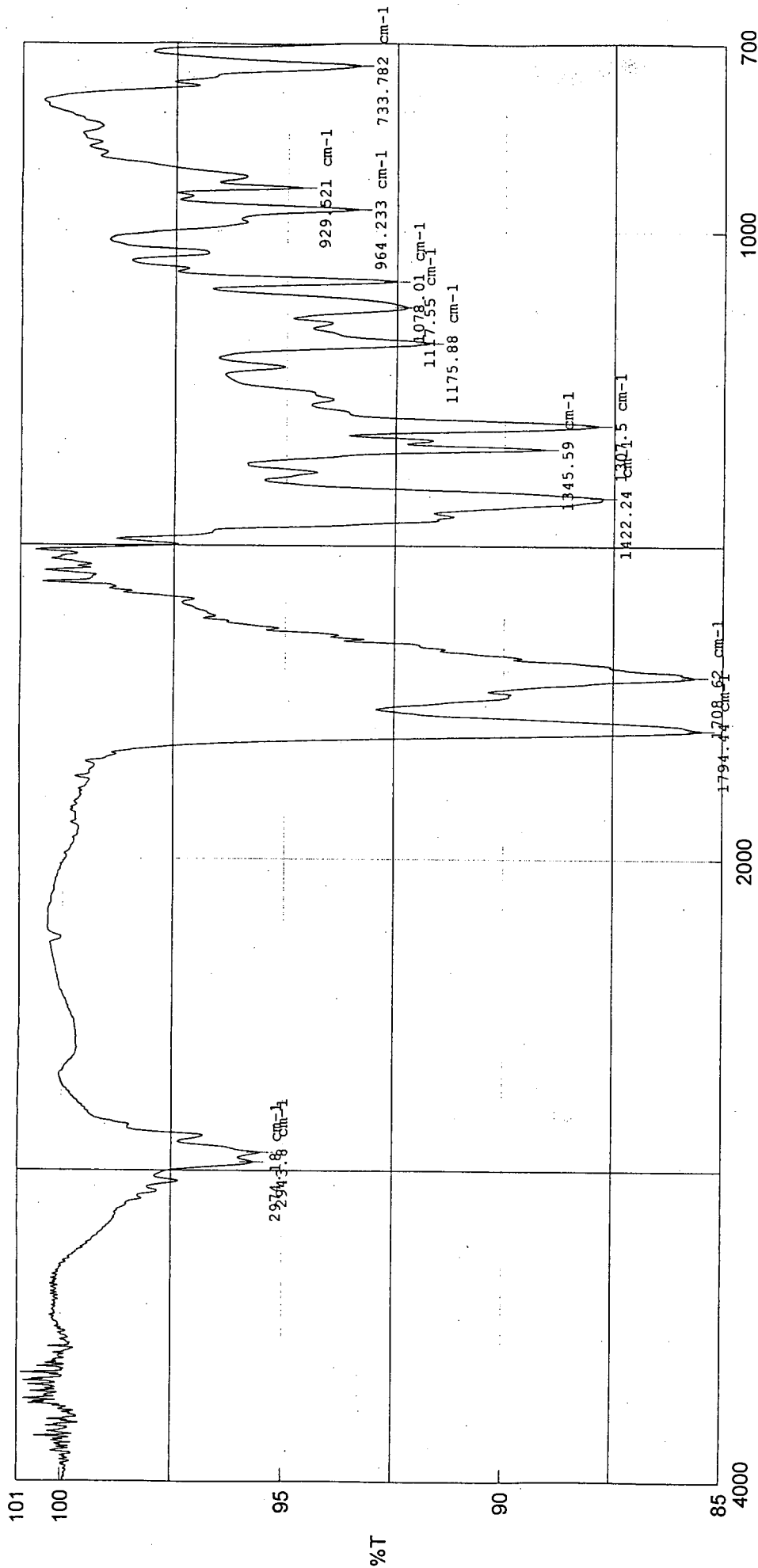
Date : Thu Oct 15 17:33:08 1998
 Filename : MP02198.nmrdata
 Comment : MP02198
 EXMODE : nor

POINT 8192 points
 SAMPO 8192 points
 FREQ0 7993.16 Hz
 FILTR 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INTRVL 125.1 usec
 TIMES 16 times
 DUMMY 0 times
 PD 0.0300 sec
 ACOVM 1024.8192 msec
 PREOL 10.00000 msec
 INTRM 0.5000 msec
 RESOL 0.98 Hz
 PW1 5.75 usec
 OBNUC 1H
 OBFRQ 399.65 MHz
 OBSET 134300.00 Hz
 RGAIN 23
 SCANS 16 times
 SLVMT CDCL3
 SPINNING 11 Hz
 TEMP 23.0 C



7.520 7.369 7.357 7.337 7.261 7.232 5.260 5.228 5.201 5.172 5.152 5.123 5.077 5.038 4.708 4.628 4.611 4.567 4.210 4.179 4.003 3.976 3.944 3.556 3.517 3.500 3.483 3.444 3.410 3.232 3.222 2.670 2.636 2.599 2.546 2.319 2.289 2.253 2.016 1.997 1.987 1.979 1.967 1.950 1.921 1.904 1.887 1.433 1.281 1.255 1.225 1.208 1.191 1.093 1.069 1.050 1.032 0.952 0.932 0.903 0.884 0.866 0.871 0.000 -0.149

MR03093



2 cm-1
Cosine
-0.001 mm
99/06/11 14:46

128 ON
2 2 mm/sec
オベレータ
Mr03093. jws

積分回数
ゼロフライング
ゲイン
スキヤンスピード
測定者
ファイル名
サンプル名
コメント

分解
アボダイゼーション
アパーチャー
日時

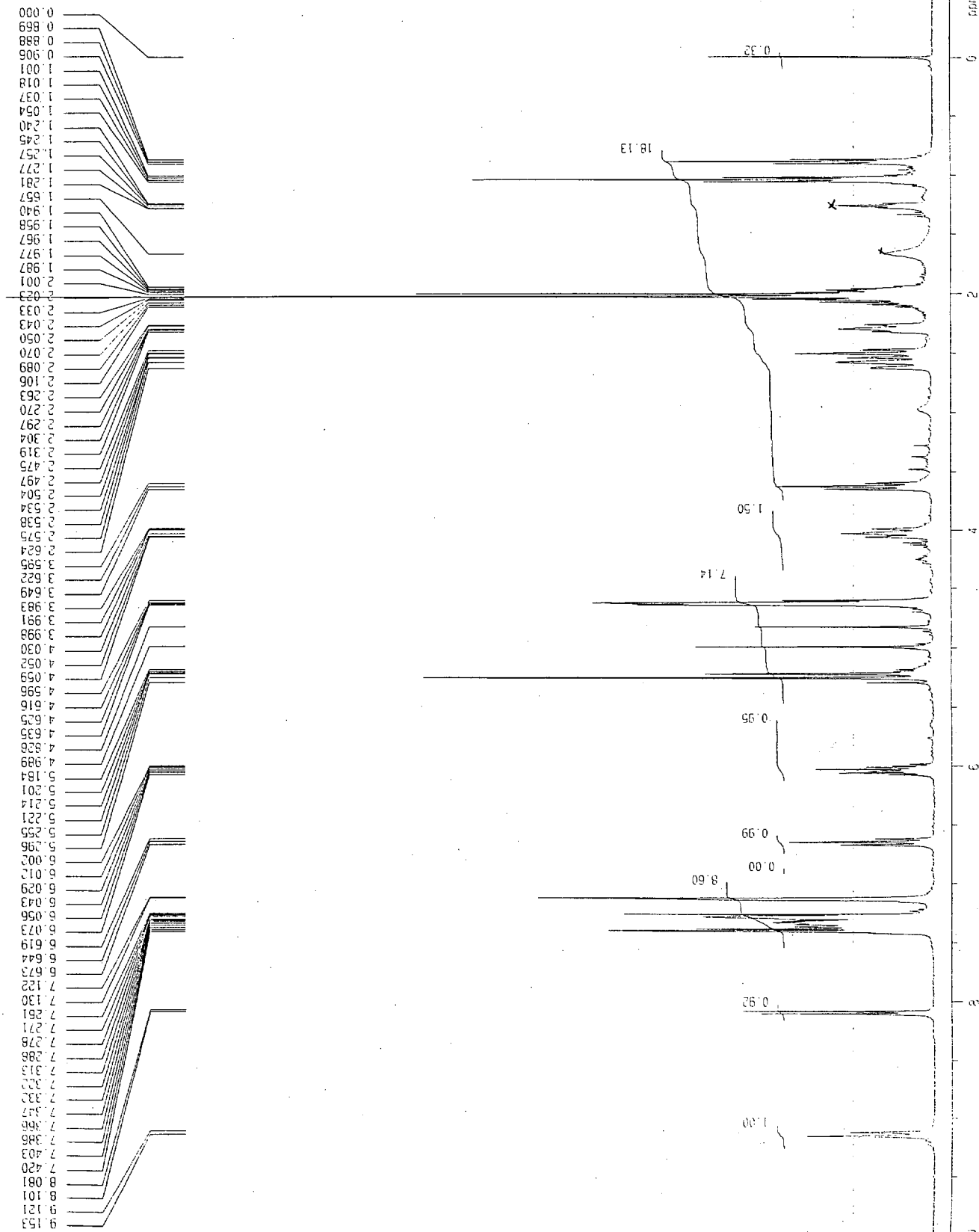
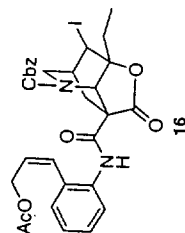
コメント

MR03094P

Date : Thu Jun 10 19:06:06 1999

File Name : MR03094P.nmdata
 Comment : MR03094P
 EXMODE : non

POINT 8192 points
 SAMPO 8192 points
 FREQ0 7993.6 Hz
 FILTR 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INIYL 125.1 usec
 TIMES 8 times
 DUMMY 0 times
 PU 0.0300 sec
 ACOIM 1024.8192 msec
 PREDL 10.000000 msec
 INIWT 0.5000 msec
 RESOL 0.98 Hz
 PWT 5.75 usec
 OBTNUC 1H
 OBTFRQ 399.65 MHz
 OBTSET 134300.00 Hz
 RGAIN 18
 SCANS 8 times
 SLVIT COOL3
 SPINLING 13 Hz
 TEMP 22.2 C



MF03094CP

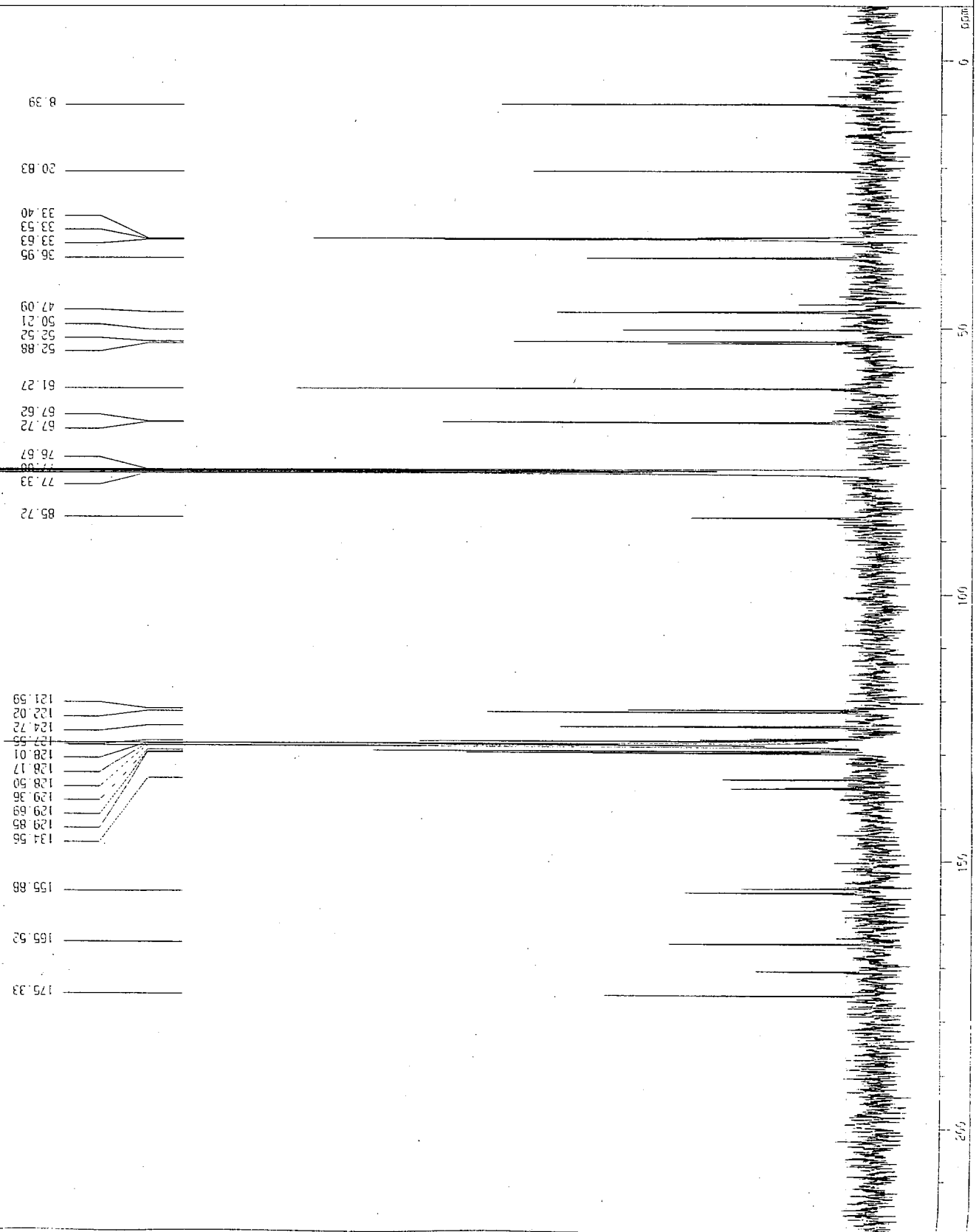
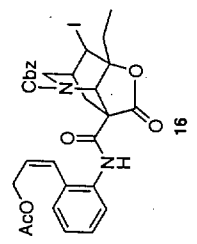
Date : Thu Jun 16 23:52:23 1999
 FileName : MF03094CP.nmrdata
 Comment : MF03094CP
 EXMODE : bcm

POINT 8192 points
 SAMPO 8192 points
 FREQ0 27100.3 Hz
 FILTR 13550 Hz
 DELAY 14.8 usec
 DEACT 19.7 usec
 INIYL 36.9 usec
 TIMES 1024 times
 DUMY 1 times

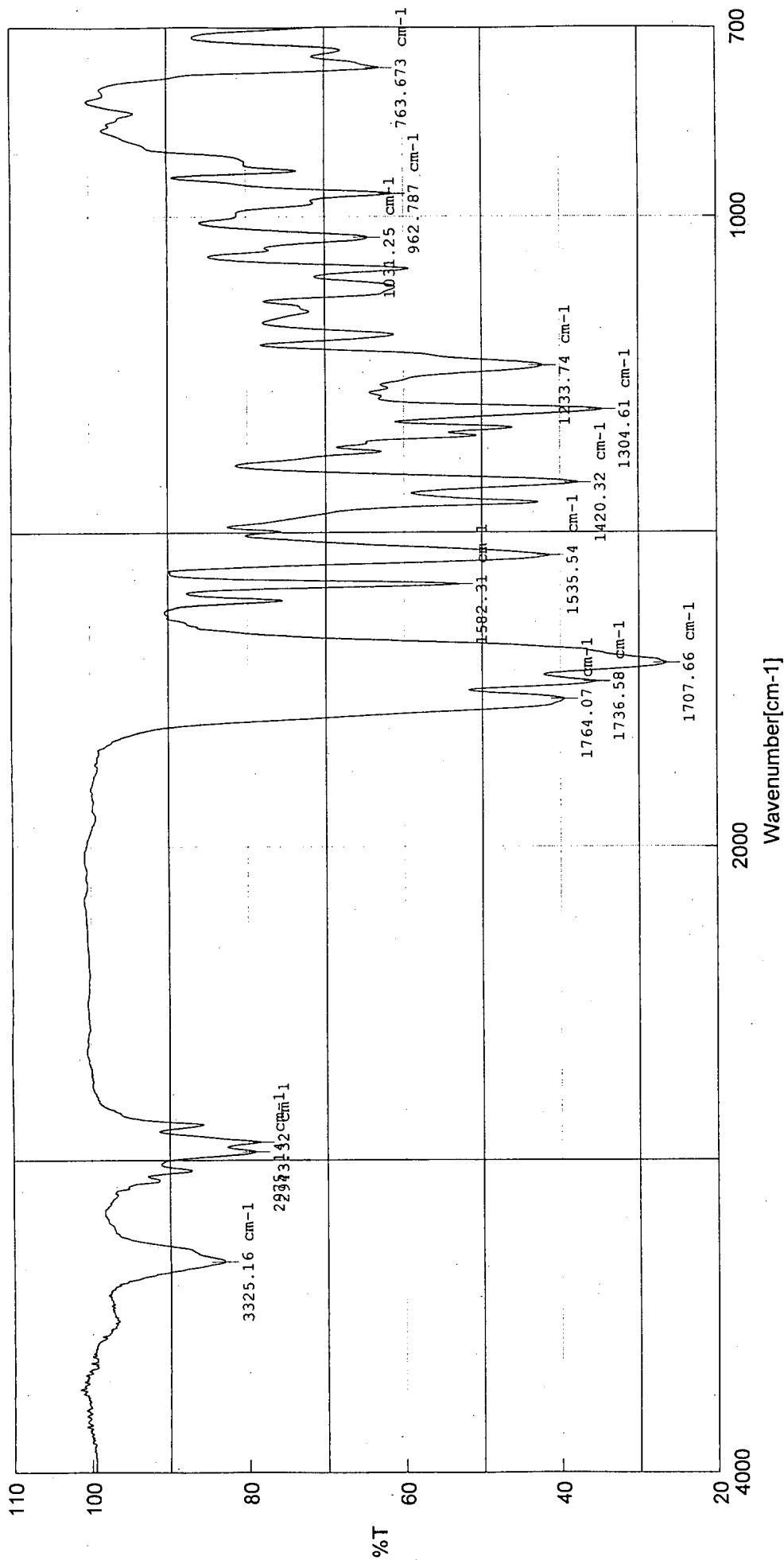
PD 2.6977 sec
 ACQIM 302.2848 msec
 PREDL 10.00000 msec
 INIWT 10.0000 msec
 RESOL 2.31 Hz
 PWT 4.60 usec

13C 100.46 MHz
 DEFRQ 135500.60 Hz
 RGAIN 26
 IRMUC 1H 399.65 MHz
 IRFRO 134300.60 Hz
 IRPFW 55.0 usec
 IPRIS 0

SCANS 1024 times
 SLVNT CDCL3
 SPINRG 13 Hz
 TEMP 23.4 C



MR03094

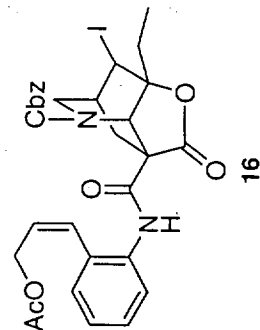


積算回数
ゼロファイリング
ゲイン
スキヤンスピード
測定者
ファイル名
サンプル名
コメント

128
ON
2
2 mm/sec
オベレータ
Mr03094.jws
コメント

分解
アポダイゼーション
アパーチャー
日時

2 cm-1
Cosine
-0.001 mm
99/06/11 14:23

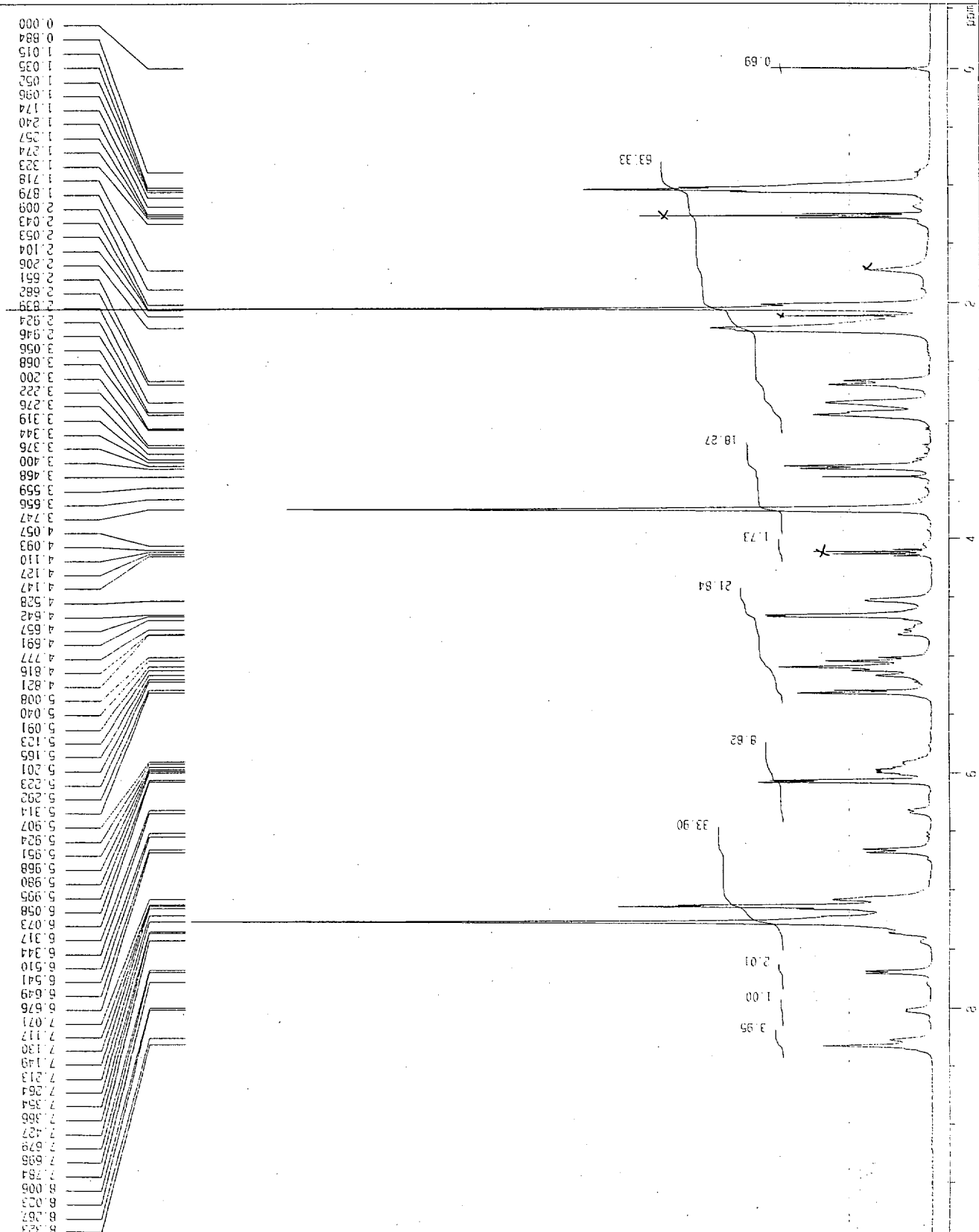
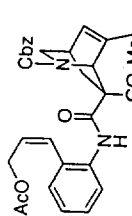


MP03100P

Date : Thu Jun 16 19:19:06 1999

Filename : MP03100P.nmdata
 Comment : MP03100P
 EXMODE : non

POINT 8192 points
 SAMP0 8192 points
 FREQ0 7993.6 Hz
 FILTR 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INTVL 125.1 usec
 TIMES 8 times
 DUMMY 0 times
 PD 0.0300 sec
 ACQTM 1024.8192 msec
 PREDL 10.00000 msec
 INIWT 0.5000 msec
 RESOL 0.98 Hz
 PWT 5.75 usec
 1H 399.65 MHz
 13C 125.00 MHz
 17 17
 SCANS 8 times
 SLVHT COLL3
 SPINNING 16 Hz
 TEMP 23.1 C



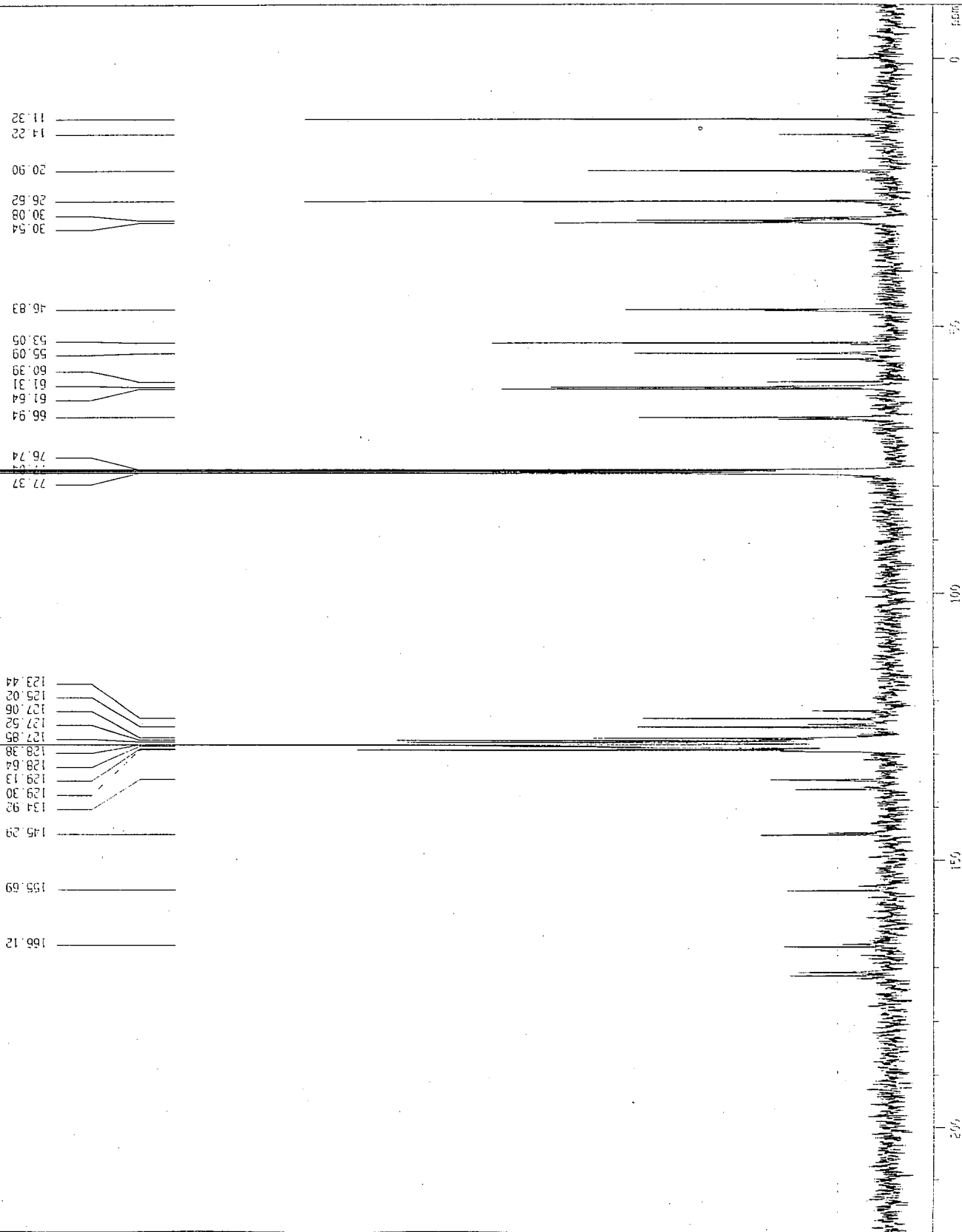
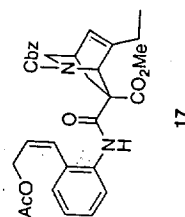
MR03100CP

Date : Fri Jun 11 01:51:07 1999
 FileName : MR03100CP.rmdata
 Comment : MR03100CP
 EXAMODE : bcm

POINT : 8192 points
 SAMP0 : 8192 points
 FREQ0 : 27100.3 Hz
 FILTR : 13550 Hz
 DELAY : 14.8 usec
 DEADT : 19.7 usec
 INIYL : 36.9 usec
 TIMES : 1024 times
 DUMMY : 1 times
 PD : 2.6977 sec
 ACOTM : 302.2848 msec
 PREDL : 10.00000 msec
 INIWT : 10.0660 msec
 RESOL : 3.31 Hz
 PWT : 4.60 usec

13C : 100.40 MHz
 135500.00 Hz
 1H : 399.65 MHz
 134300.00 Hz
 55.0 usec
 0

SCANS : 1024 times
 SOLVNT : CDCL3
 SPLITTING : 10 Hz
 TEMP : 23.3 C

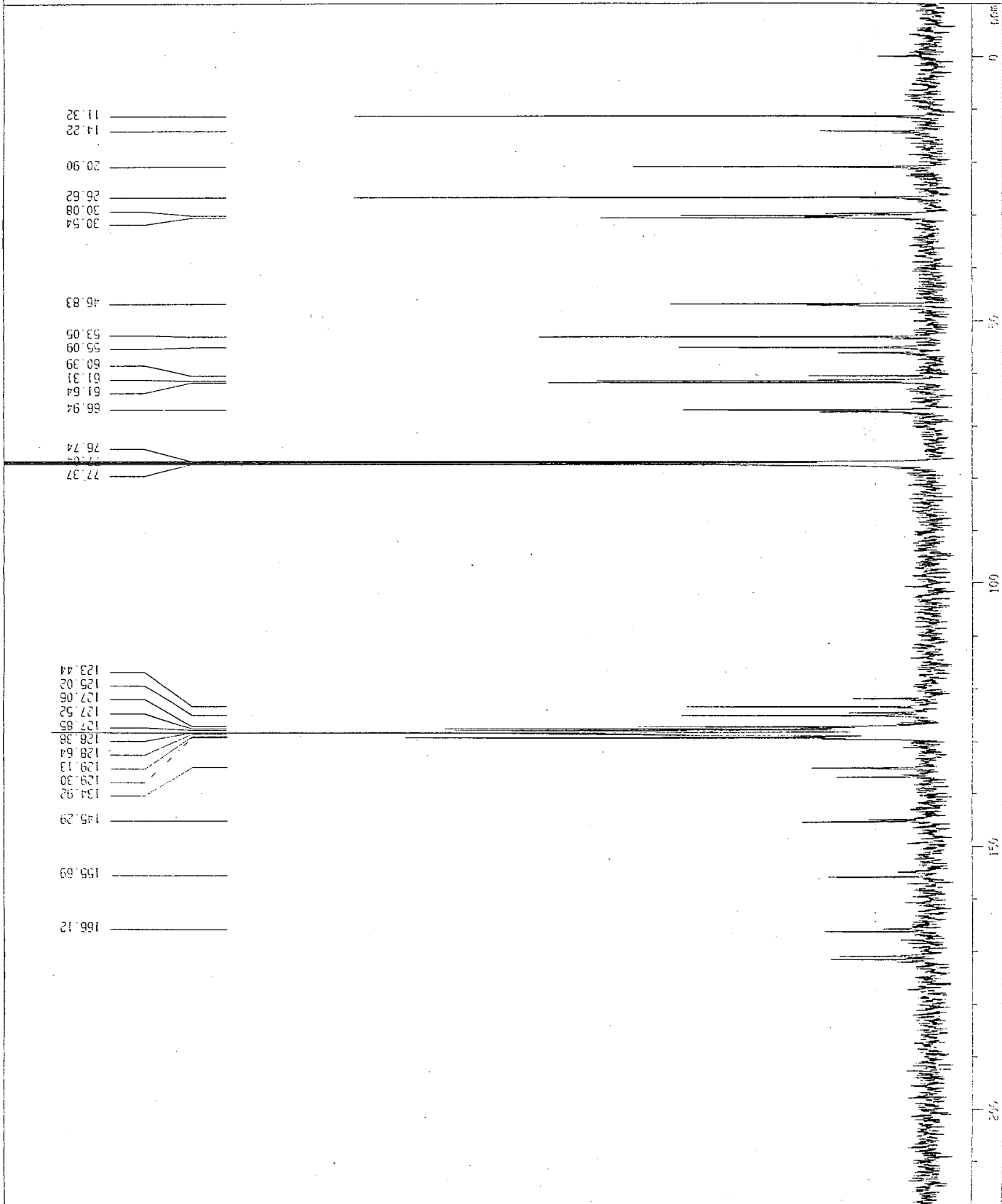
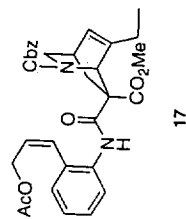


14R03100CP

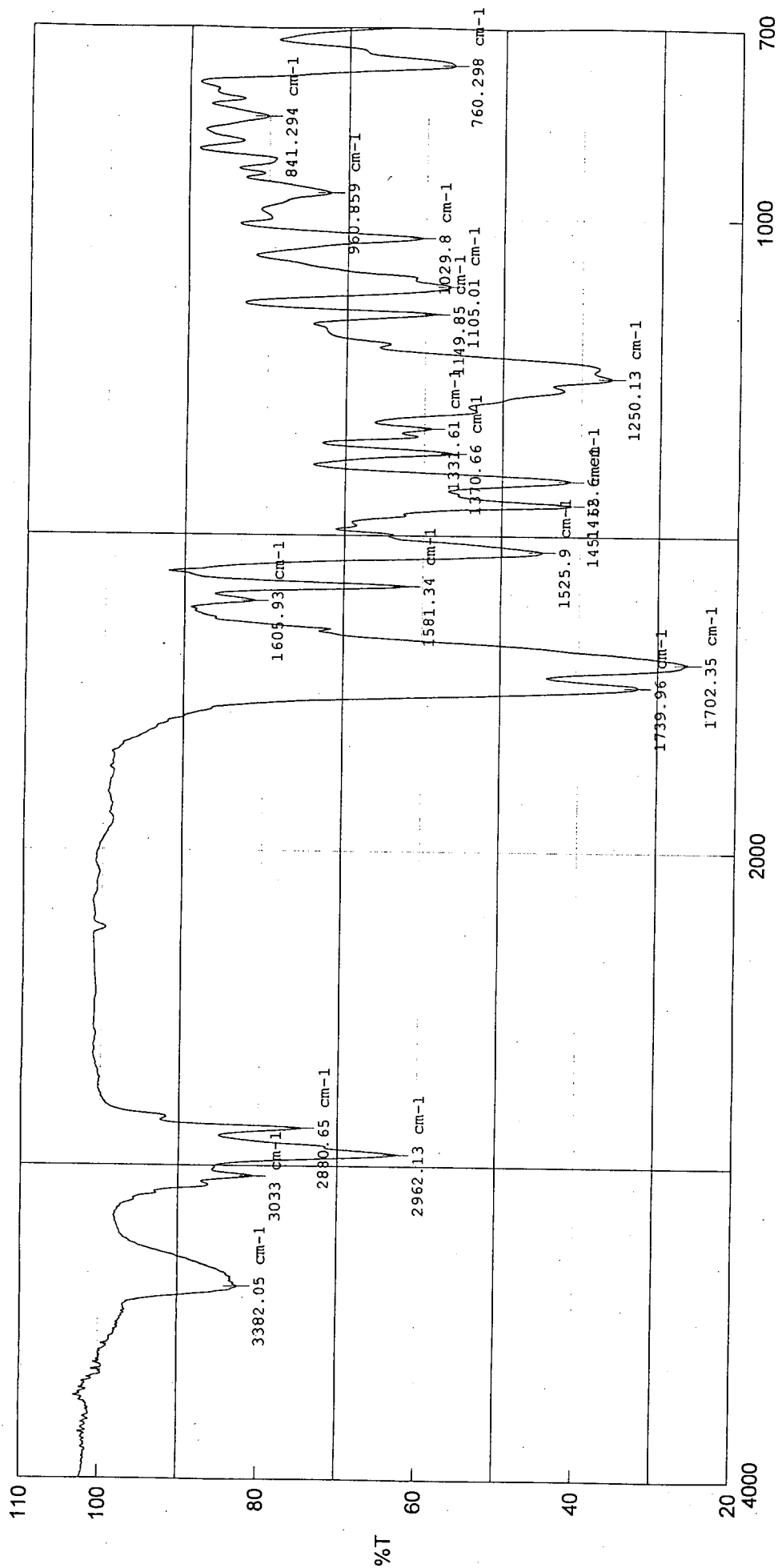
Date : Fri Jun 11 01:51:07 1999
 Filename : 14R03100CP.imdata
 Comment : 14R03100CP
 EXNGDE : bcm

POINT 8192 points
 SAMPD 8192.00mls
 FREQD 27100.3 Hz
 FILTR 13550 Hz
 DELAY 14.8 usec
 DEADF 19.7 usec
 INTVL 36.9 usec
 TIMES 1024 times
 DUMPRY 1 times
 PD 2.6977 sec
 ACOIM 302.2848 msec
 PREDL 10.00000 msec
 INTWT 10.00660 msec
 RESOL 3.31 Hz
 PRT 4.60 usec
 GENUC 13C
 OFPRO 100.40 MHz
 CSECT 135500.00 Hz
 PGMIN 28
 IPRUC 1H
 IPRRO 399.85 MHz
 IACET 134300.69 Hz
 IRRPW 55.0 usec
 IRRIS 0

SCANS 1024 times
 SLVNT CDCL3
 SPINNING 10 Hz
 TEMP 23.3 C



MR03100

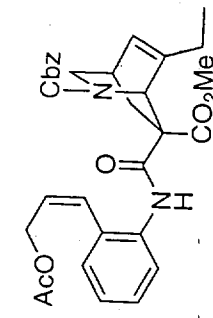


積算回数
ゼロファイリング
ケイマン
スキヤンスピード
測定者
ファイル名
サンプル名
コメント

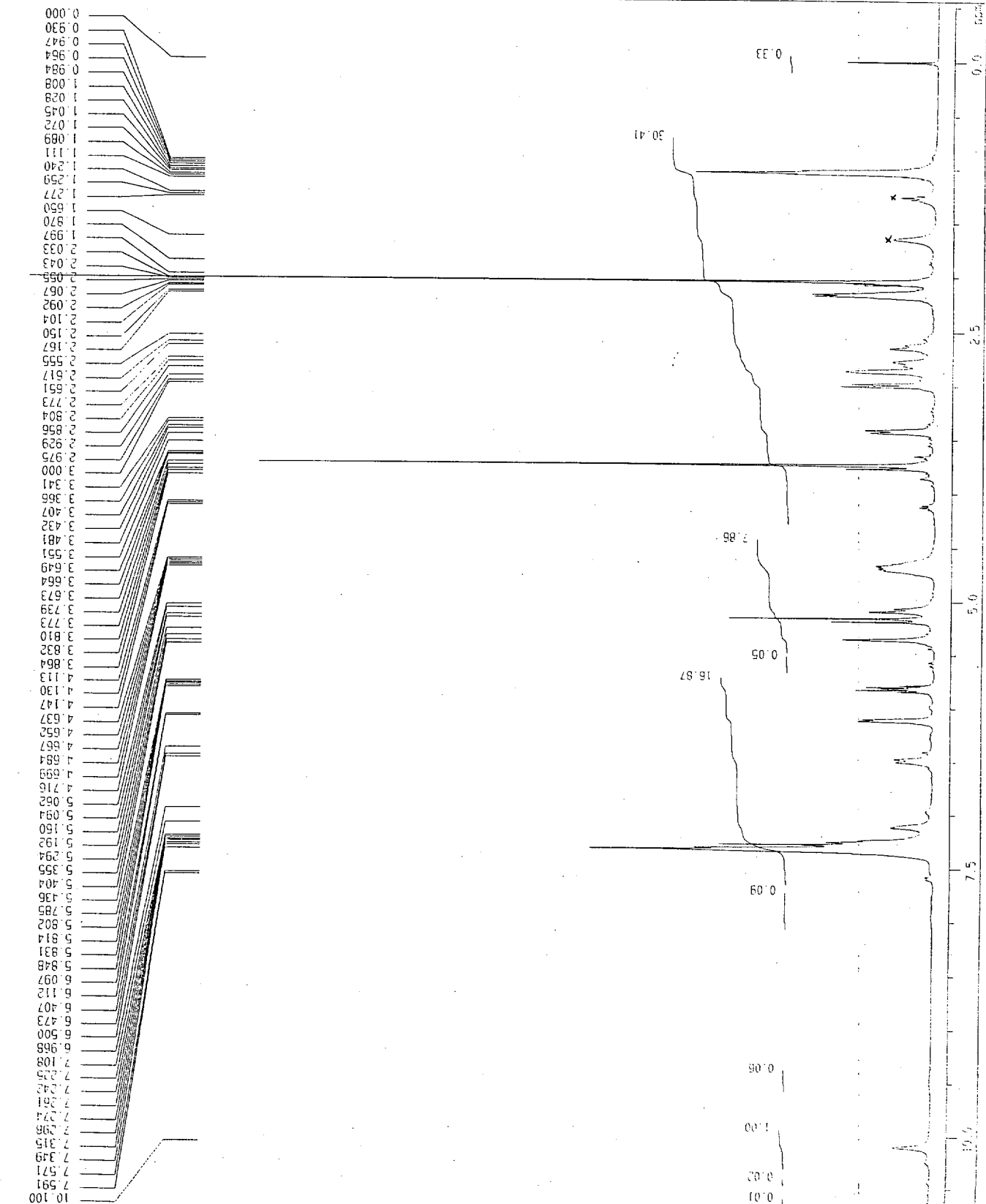
128
ON
2
2 mm/sec
オベレータ
Mr-03100.jws
コメント

分解
アボダイゼーション
アパーチャ
日時

2 cm-1
Cosine
-0.001 mm
99/06/11 13:35



MR03102F

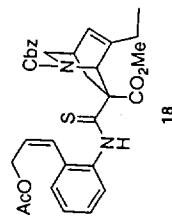


Date : Fri Jun 11 02:55:31 1995
 Filename : MR03102P.mrd
 Comment : MR03102P
 EXAMNO : non

POINTS 8192
 POINTS 8192
 FREQ 7993.6 Hz
 FILTR 4000 Hz
 DELAY 50.0 USEC
 DEAD1 72.1 USEC
 INITVL 125.1 USEC
 TIMES 64 Times
 DURMY 0 Times

PD 0.0300 sec
 ACOIM 1024.8192 msec
 PREOL 10.00000 msec
 INITI 0.5000 msec
 RESOL 0.98 Hz
 P41 5.75 USEC
 OFINDC
 OFFO 399.65 MHz
 OFSET 134300.00 Hz
 RGAIN 17

SCANS 64 Times
 SOLVT COCL3
 SPINNG 13 Hz
 TEMP 22.5 C

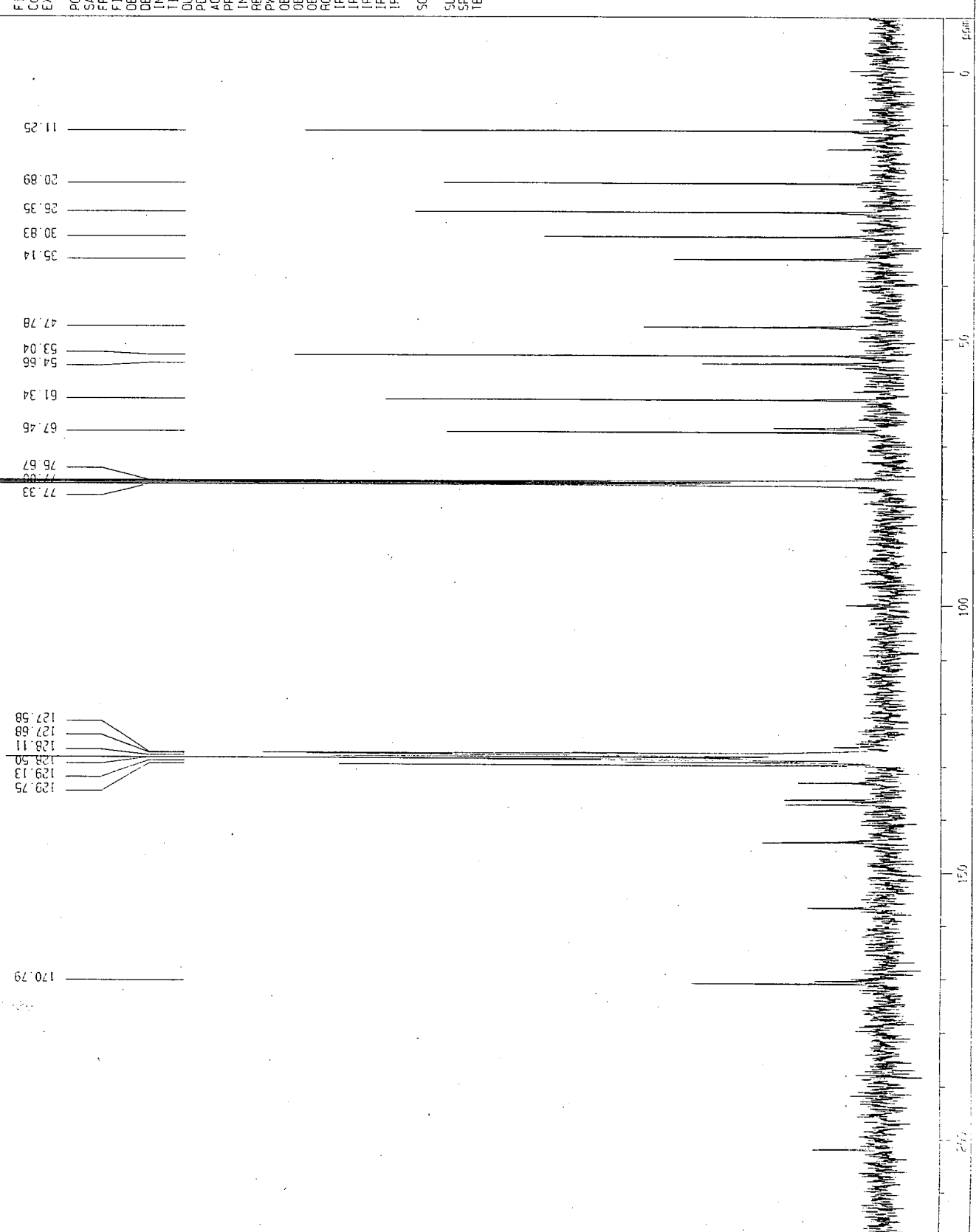
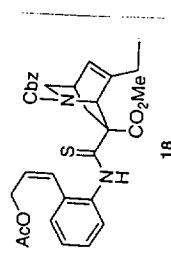


MR03102CP

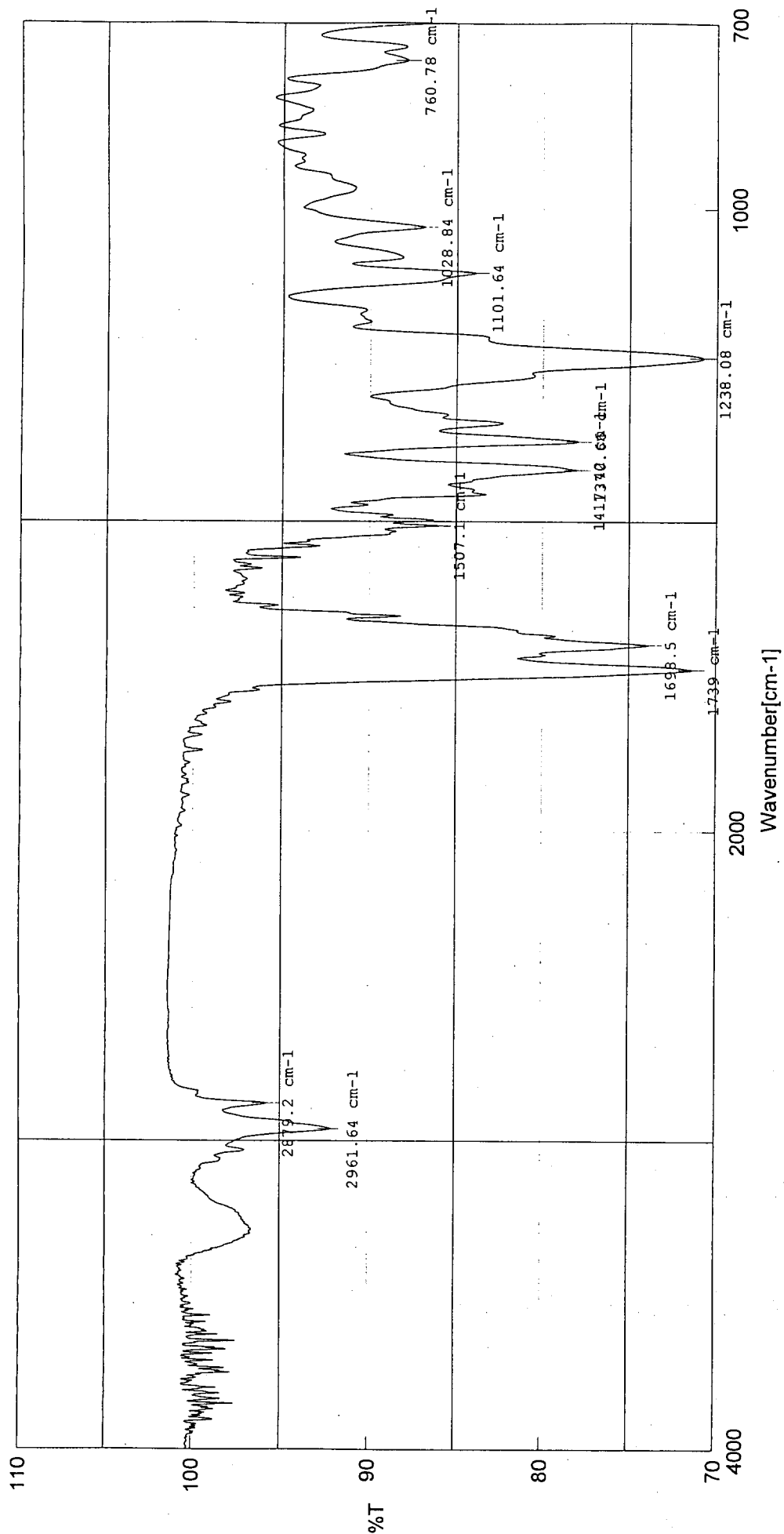
Date : Fri Jun 11 03:47:55 1999
 Filename : MR03102CP.nmdata
 Comment : MR03102CP
 EXMODE : bcm

POINT 8192 points
 SAMP0 8192 points
 FREQ0 27100.3 HZ
 F1LFR 13550 HZ
 DELAY 14.8 usec
 DEAD0 19.7 usec
 DEATH 36.9 usec
 IN1VL 1024 times
 TIMES 1024 times
 DUMMY 1 times
 PD 2.6977 sec
 ACQTM 302.2848 msec
 PREDL 10.00000 msec
 IN1NT 10.0000 msec
 RESOL 3.31 HZ
 PW1 4.60 usec
 OFAUC 13C
 OFFR0 100.40 MHZ
 OFSET 135500.00 HZ
 RGATH 30
 IRRUC 1H
 IRRFR 399.65 MHZ
 IRRST 134300.00 HZ
 IRRPW 55.0 usec
 IRRIS 0

SCANS 1024 times
 SLYHT COCL3
 SPIRIT 11 HZ
 TEMP 23.7 C



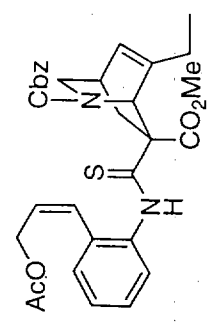
MR03102



積算回数 128
 セロフィン ON
 ゲスキャン 2
 スキヤンスピード 2 mm/sec
 測定者 オペレータ
 ファイル名 Mr03102.jws
 サンプル名 コメント

分解 アボダイゼーション
 アパーチャー
 日時 99/06/11 13:19

2 cm-1
 Cosine
 -0.001 mm
 99/06/11 13:19



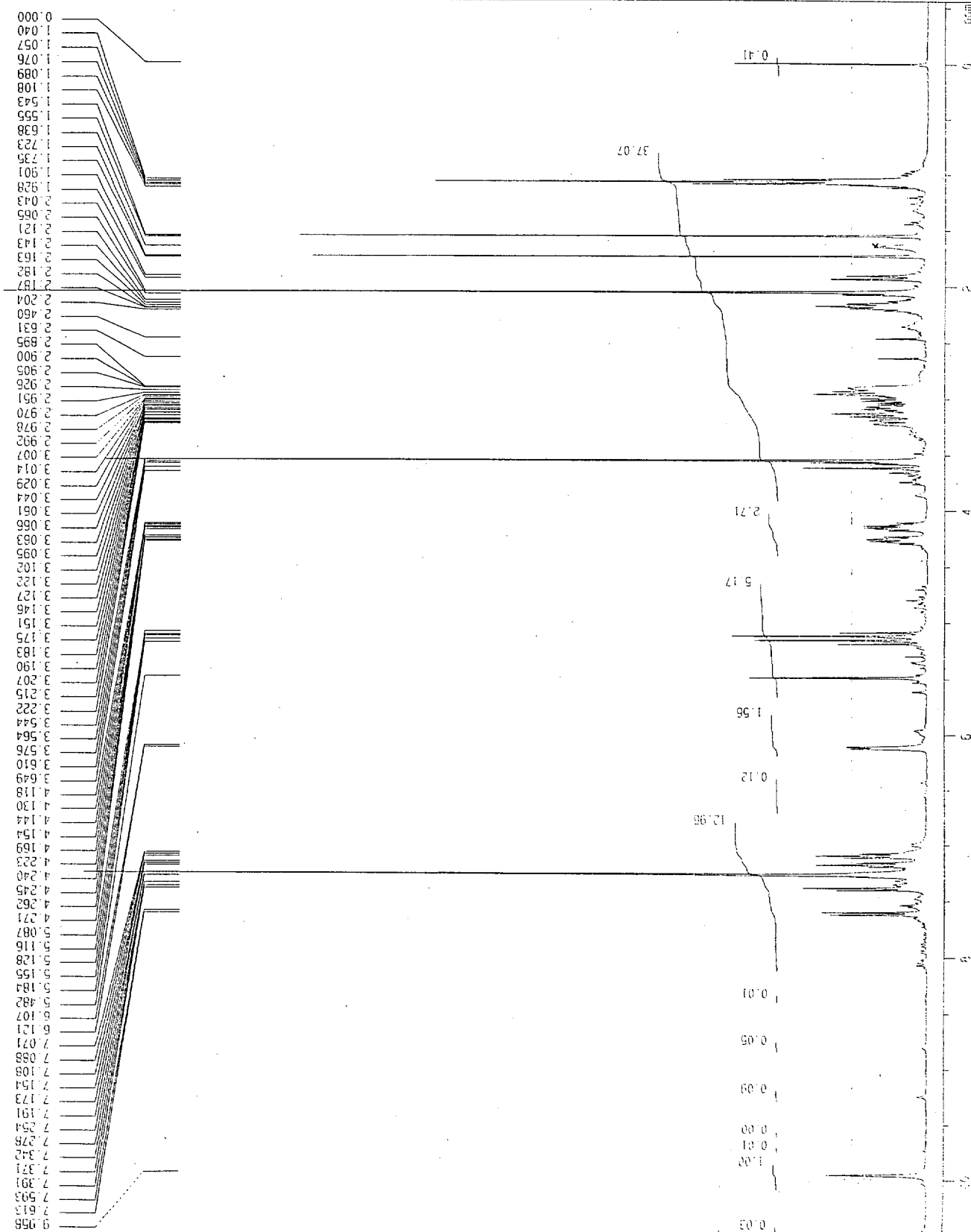
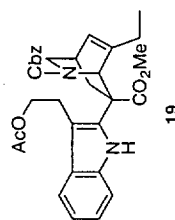
18

MR03103P

Date : Fri Jun 11 02:53:33 1999

Filename : MR03103P.mrd
 Comment : MR03103P
 EXMODE : non

POINT : 8192 points
 SAMPO : 8192 points
 FREQU : 7993.6 Hz
 FILTR : 4000 Hz
 DELAY : 50.0 usec
 DEACT : 72.1 usec
 INTRV : 125.1 usec
 TIMES : 64 times
 DUMPR : 0 times
 PO : 0.0300 sec
 ACQTM : 1024.8192 msec
 PREDL : 10.00000 msec
 INTRT : 0.5000 msec
 RESOL : 0.98 Hz
 PWL : 5.75 usec
 OBRUC : 0
 OBFRO : 399.65 MHz
 OBFSE : 134390.99 Hz
 RGAIN : 12
 SCANS : 54 times
 SLVRT : CDCL3
 SPTING : 13 Hz
 TEMP : 22.8 C



MR03103CP

Date : Fri Jun 11 04:45:39 1999
 Filename : MR03103CP.ncdata
 Comment : MR03103CP
 EXMODE : bcm

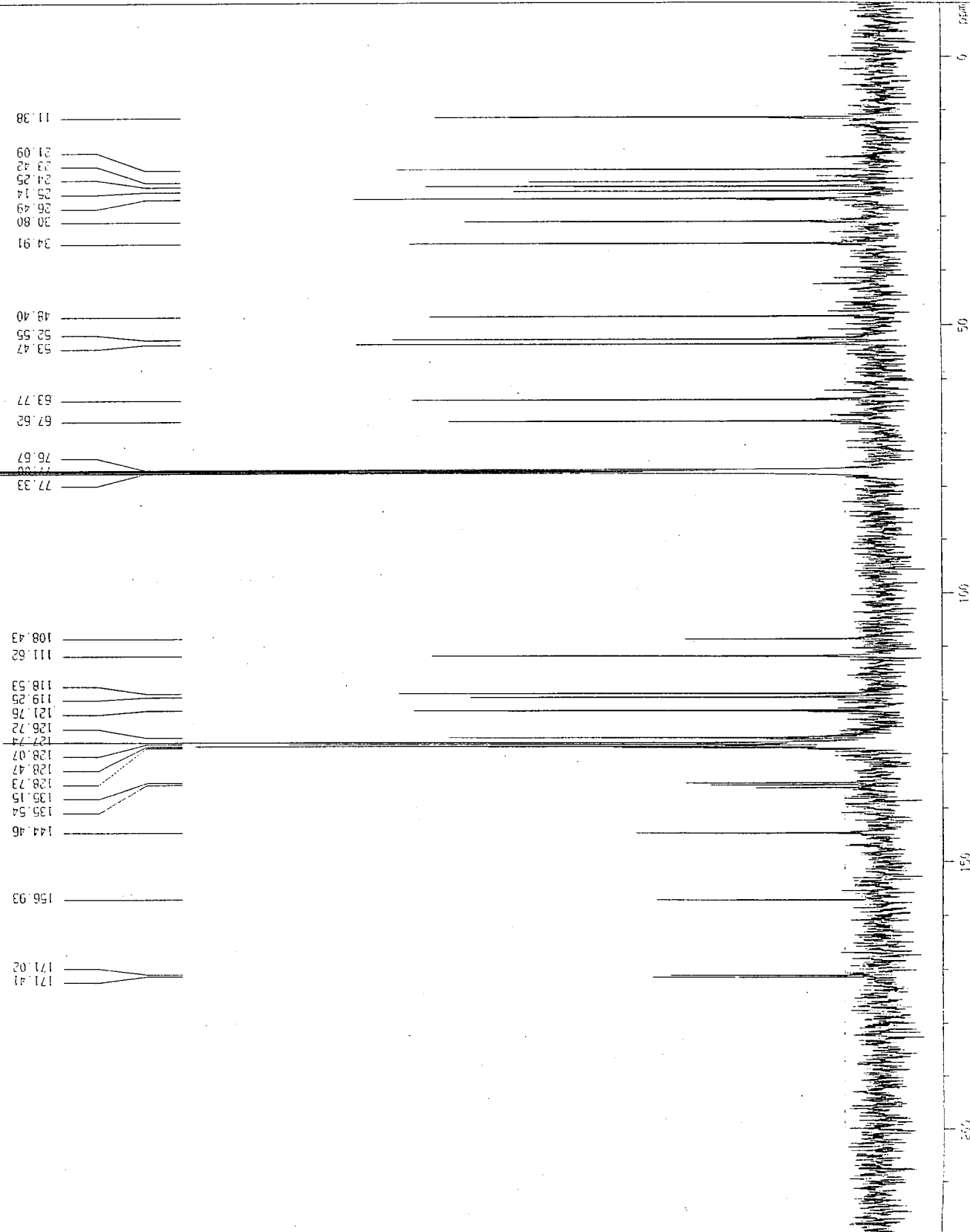
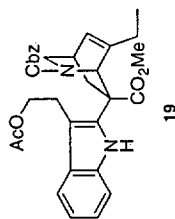
POINT 8192 points
 SAMPO 8192 points
 FREQ0 27100.3 HZ
 FILTR 13550 HZ
 DELAY 14.8 USEC
 DEADT 19.7 USEC
 TRIVL 36.9 USEC
 TIMES 1024 times
 DUMMY 1 times

PD 2.6977 sec
 ACQTM 302.2848 msec
 PREOL 10.00000 msec
 INHWT 10.00000 msec
 RESOL 3.31 HZ
 PHL 4.60 USEC

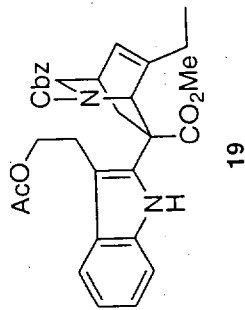
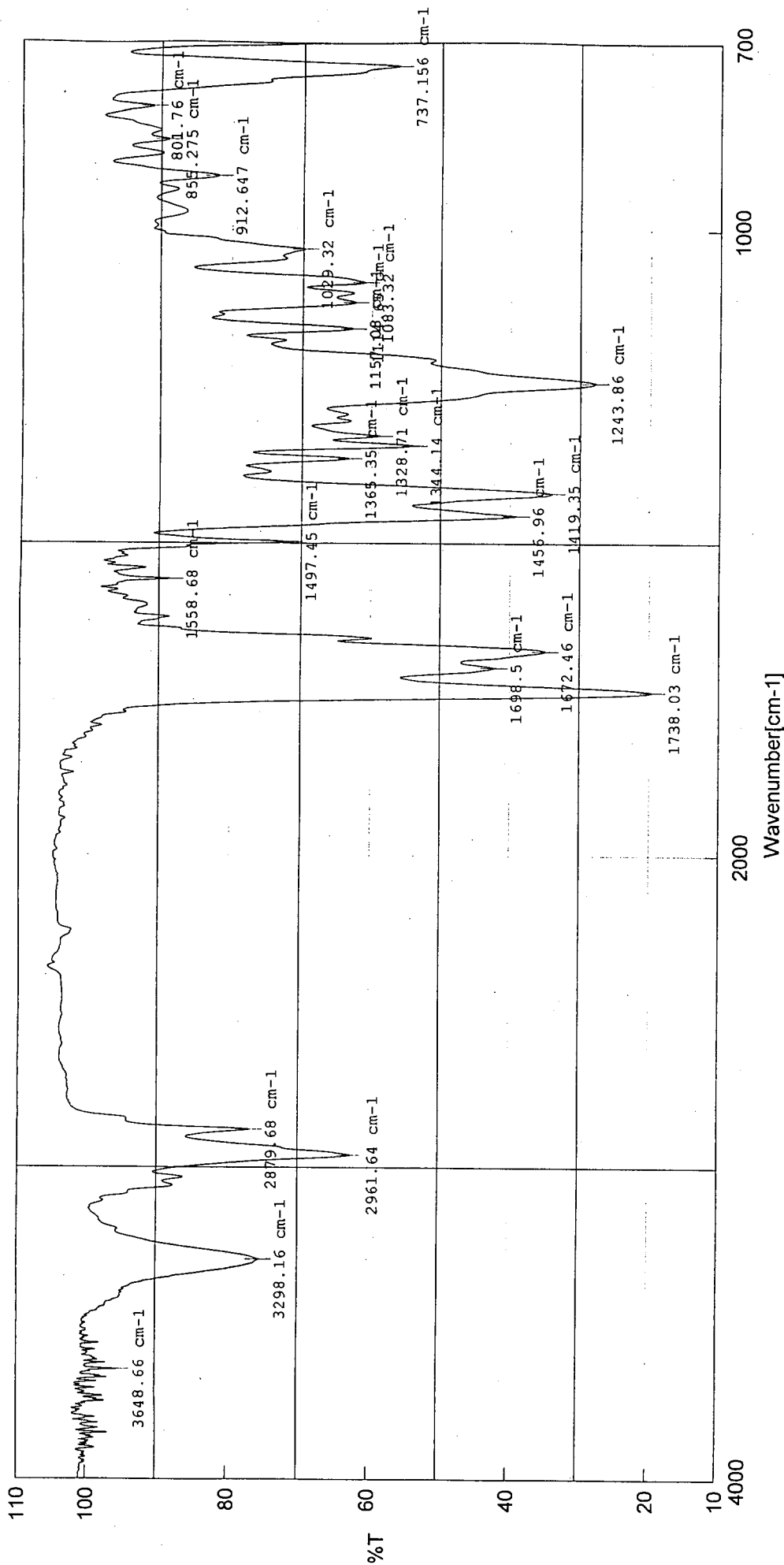
13C 100.49 MHz
 OBFRO 135500.00 HZ
 OBSET 25

1H 399.65 MHz
 134300.00 HZ
 55.0 usec
 0

SCANS 1024 times
 SOLVT CDCL3
 SPINNING 12 Hz
 TEMP 23.5 C



MR03103



2 cm-1
Cosine
-0.001 mm
99/06/11 13:04

分解
アポダイゼーション
アバーチャヤ
日時

64
ON
2
2 mm/sec
オペレータ
Mr03103.jws
コメント

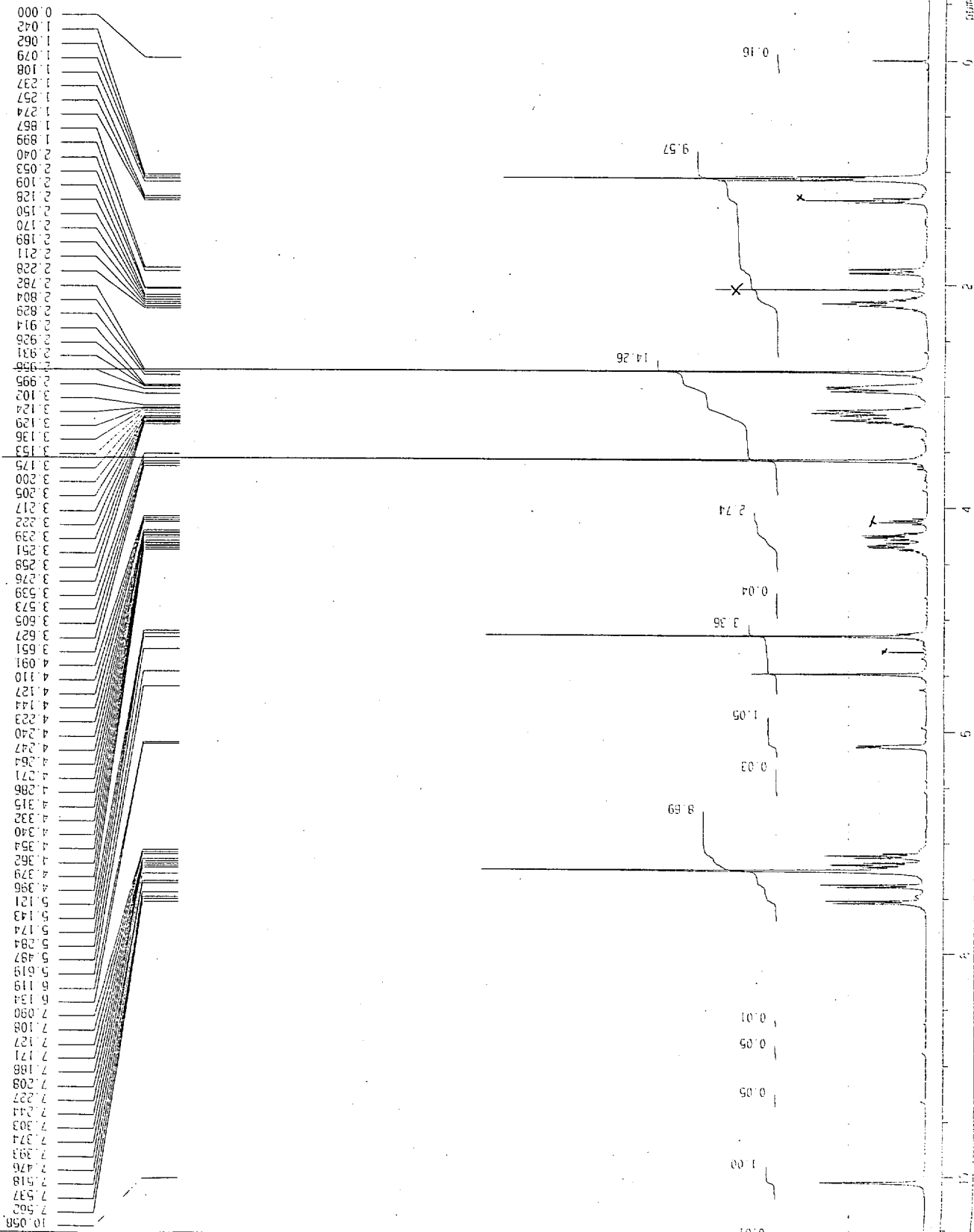
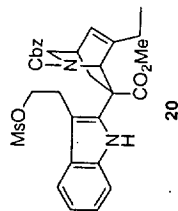
積算回数
ゼロフイルタ
ゲイ
スキャンスピード
測定者
ファイル名
サンプル名
コメント

MR03064P

Date: Fri Jun 11 01:57:13 1999

F1: Name: MR03064P.nmdata
 Comment: MR03064P
 EX: MODE: non

POINT 8192 points
 SAMPO 8192 points
 FREQD 7993.5 Hz
 F1: F1R 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INTVL 125.1 usec
 TIMES 64 Times
 DUMMY 0 Times
 PD 0.0300 sec
 ACQTM 1024.8192 msec
 PREOL 10.00000 msec
 TUNNT 0.5000 msec
 RESOL 0.98 Hz
 PWT 5.75 usec
 GBRJC 399.65 MHz
 GBFRG 134360.66 Hz
 OBSFT 15
 RGAIN 15
 SCANS 64 Times
 SLVNT CDCl3
 SPINNING 13 Hz
 TEMP 23.0 C



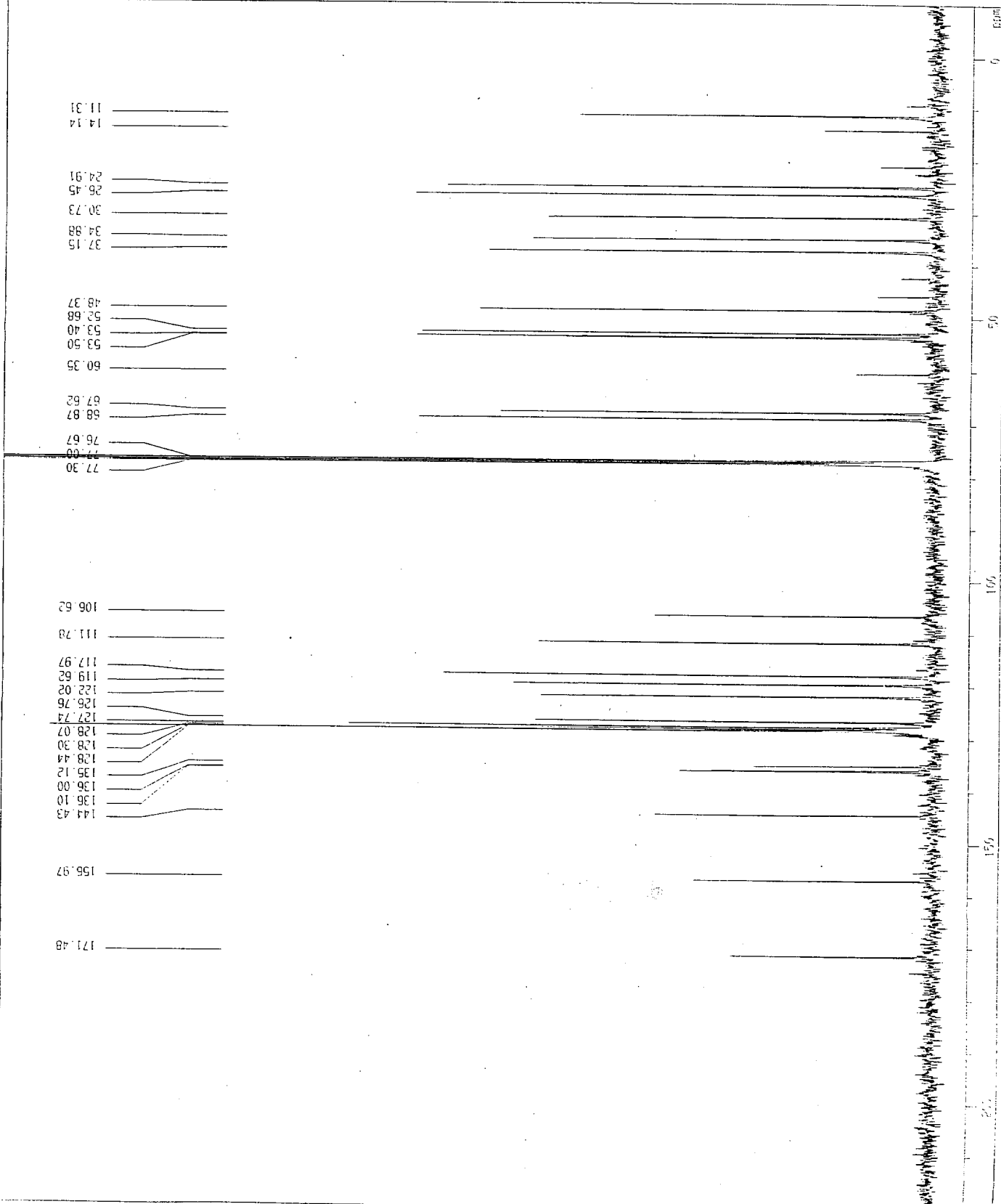
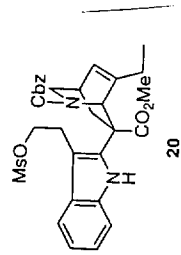
MR03064CP

Date : Fri Jun 11 02:49:53 1999
 FileName : MR03064CP.rmdata
 Comment : MR03064CP
 EXMODE : bcm

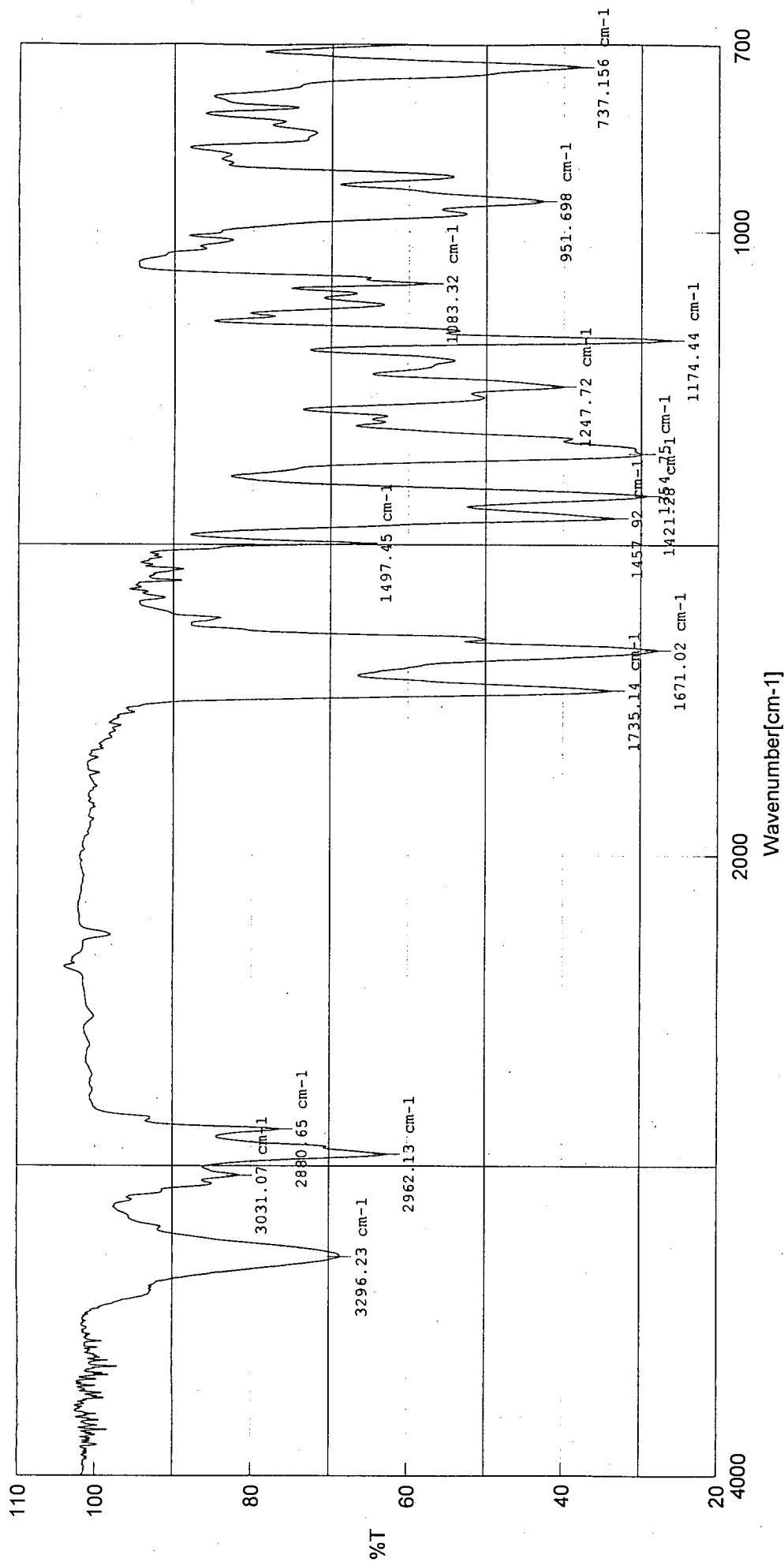
POINT 8192 points
 SAMPD 8192 points
 FREQU 27100.3 Hz
 FFLTR 13550 Hz
 DELAY 14.8 usec
 DEADT 19.7 usec
 INIYL 36.9 usec
 TIMES 1024 times
 DUMMY 1 times
 PD 2.6977 sec
 ACQTM 302.2648 msec
 PREDL 10.00965 msec
 ININT 10.07955 msec
 RESOL 3.33 Hz
 PW1 4.89 usec

13C 13C 100.49 MHz
 CBFR0 135500.00 Hz
 OBSST 30
 RGAIN 30
 IRRUC 399.83 MHz
 IFRRO 134300.00 Hz
 IRSET 55.0 usec
 IRRPW 9
 IRRNS 9

SCANS 1024 times
 SLVNT CDCL3
 SPINNING 15 Hz
 TEMP 23.5 C



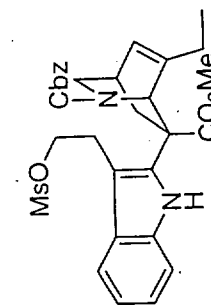
MR03064



積算回数 128
 セロフイン ON
 ゲスキャン 2
 スキヤンスピード 2 mm/sec
 測定者 オペレータ
 ファイル名 Mr03064.jws
 サンプル名
 コメント

分解 アポダイゼーション
 アパーチャー
 日時

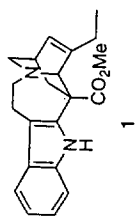
2 cm-1
 Cosine
 -0.001 mm
 99/06/11 12:45



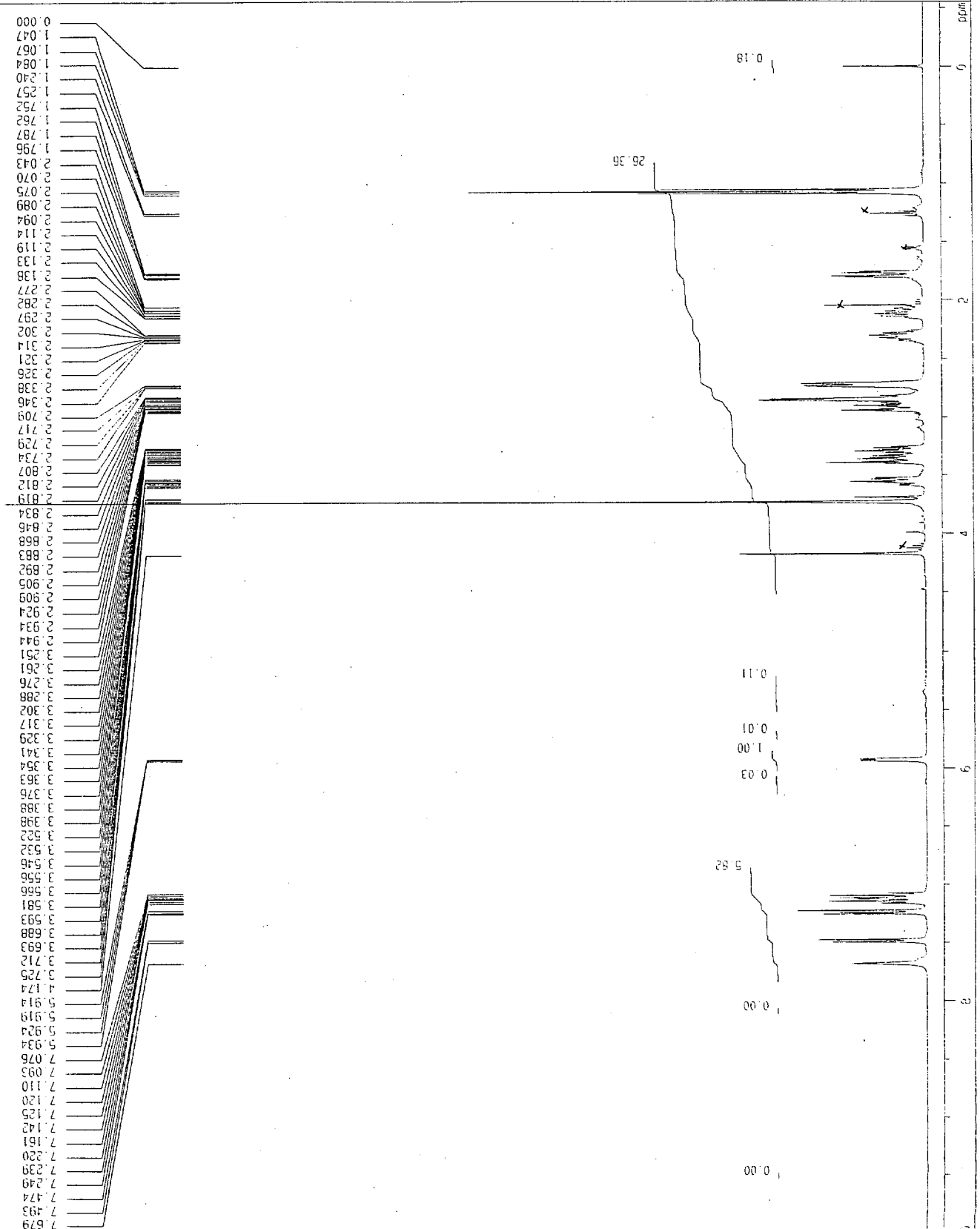
Date : Fri Jun 11 14:52:04 1999

File Name : MR03105P.nmdata
 Comment : MR03105P
 EXMODE : non

POINT 8192 points
 SAMPO 8192 points
 FREQ 7993.6 Hz
 FILTR 4000 Hz
 DELAY 50.0 usec
 DEADT 72.1 usec
 INI VL 125.1 usec
 TIMES 64 times
 DUMMY 0 times
 PC 0.0300 sec
 ACOIM 1024.8192 msec
 PREOL 10.00000 msec
 INI VL 0.5000 msec
 RESOL 0.96 Hz
 PW1 5.75 usec
 OBNUC 1H
 OBFRQ 359.65 MHz
 OBSET 134300.00 Hz
 RGAIN 17
 SCANS 64 times
 SLVNT CDCL3
 SPINNING 12 Hz
 TEMP 23.2 C



MR03105P



MR03105CP

Date : Fri Jun 11 05:44:16 1999
 File Name : MR03105CP.rmdata
 Comment : MR03105CP
 EXMODE : bcm.

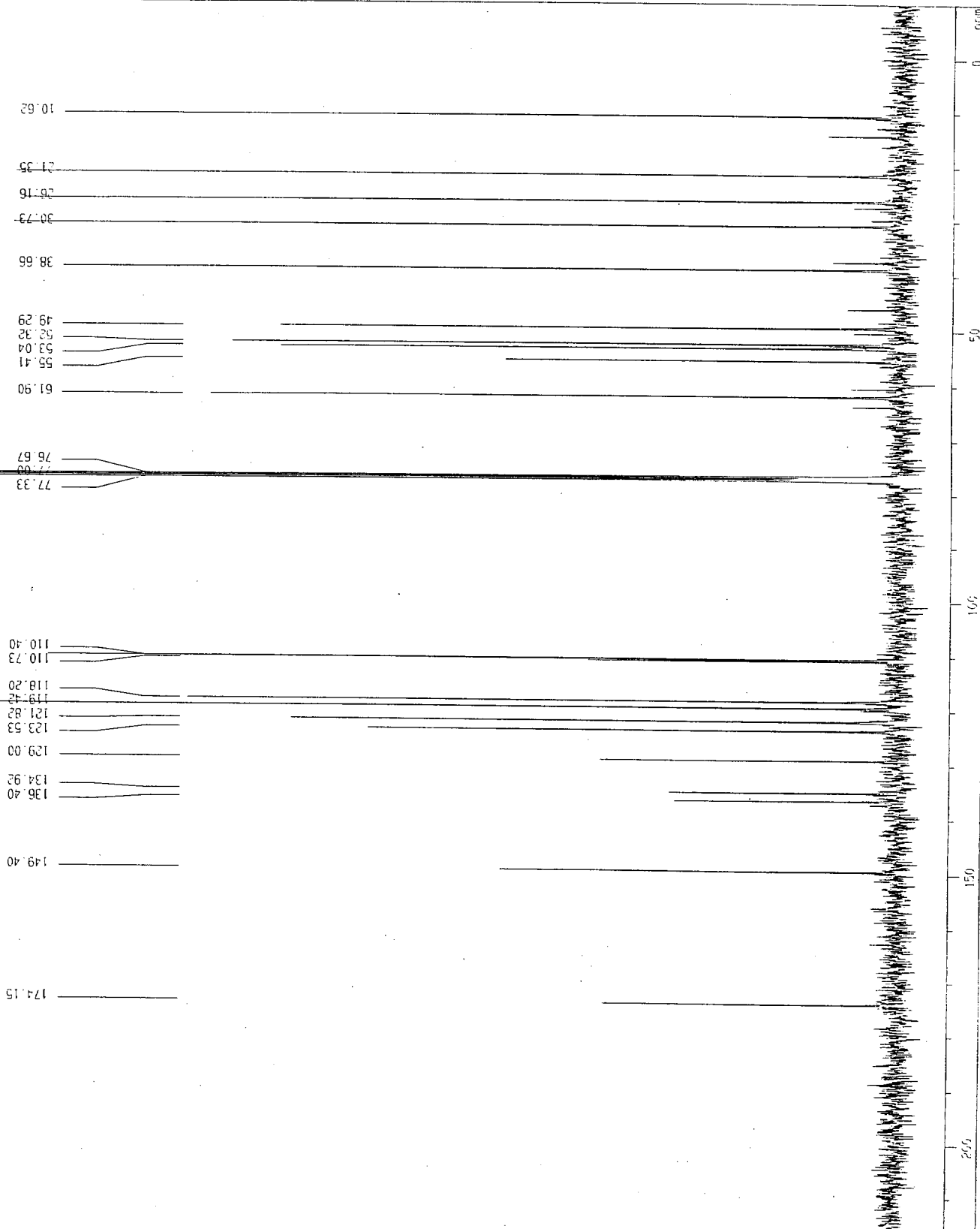
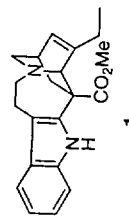
8192 points
 8192 points
 27100.3 Hz
 13550 Hz
 14.8 usec
 19.7 usec
 36.9 usec
 1024 times
 1 times
 2.5977 sec
 302.2848 msec
 10.00000 msec
 10.00000 msec
 3.31 Hz
 4.60 usec

13C
 100.46 MHz
 135500.00 Hz
 30

1H
 399.65 MHz
 134300.00 Hz
 55.0 usec
 0

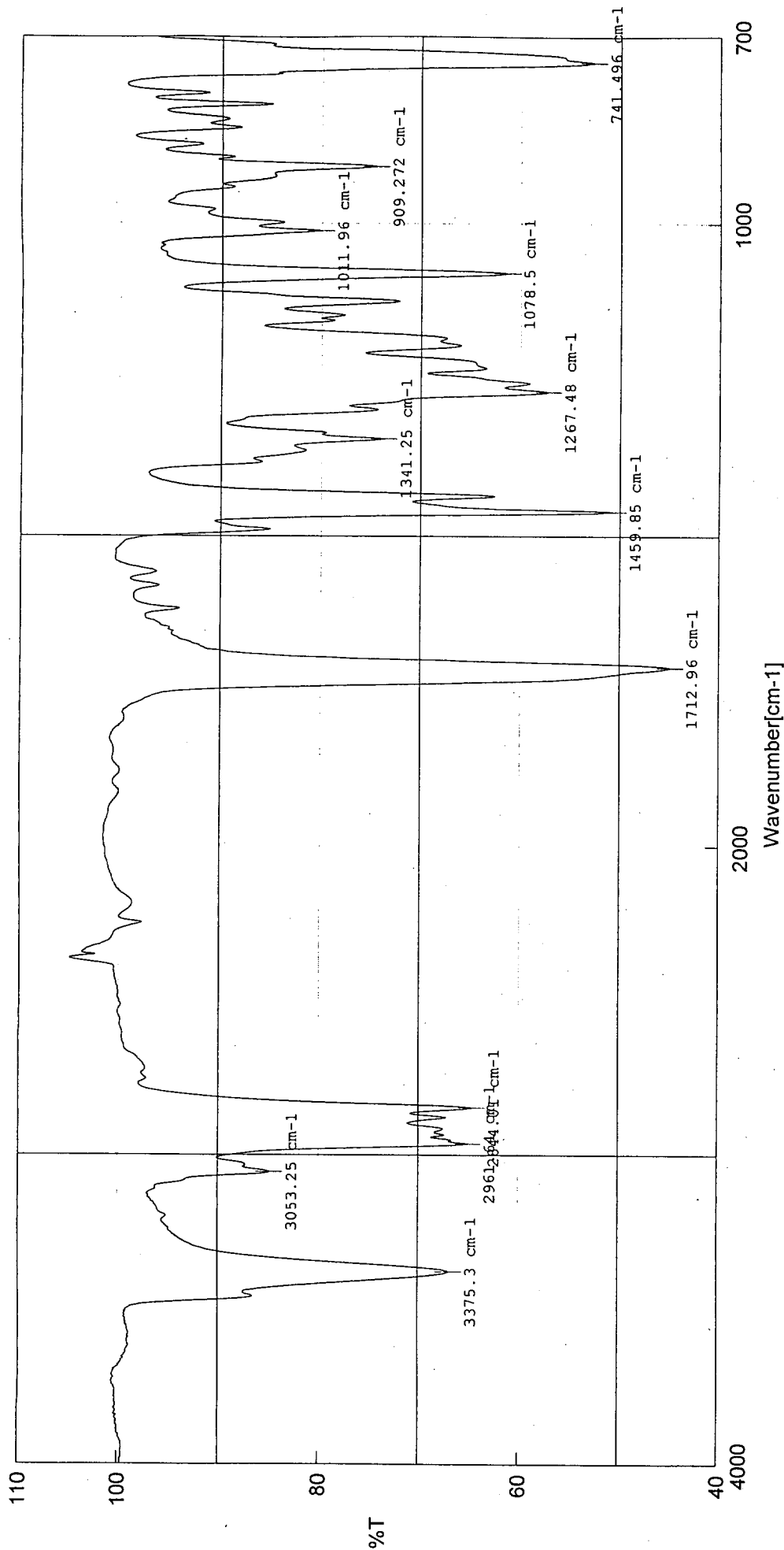
1024 times

CDCL3
 11 Hz
 23.5 C



100 150 200 ppm

MTR03105



積算回数 128
 セロフィン ON
 ケスキャンスピード 2
 測定者 2 mm/sec
 ファイル名 オペレータ
 サンプル名 Mr03105.jws
 コメント

分解 アボダイゼンシオン
 アパーチャ
 日時 99/06/11 12:01

2 cm-1
 Cosine
 -0.001 mm
 99/06/11 12:01

