

Enantioselective [2+2] Cycloaddition of Unactivated Alkenes with α -Acyloxyacroleins Catalyzed by Chiral Organoammonium Salts

Kazuaki Ishihara* and Kazuhiko Nakano

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

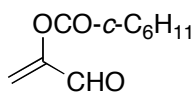
General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^1H NMR spectra were measured on Varian Gemini-2000 (300 MHz) or VXR 500 (500 MHz) spectrometers at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Gemini-2000 (75 MHz), VXR 500 (125 MHz), or Varian INOVA (175 MHz) spectrometers. ^{19}F NMR spectra were measured on Varian INOVA (282 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuteriochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm \times 25 cm), Daicel CHIRALPAK AS-H (4.6 mm \times 25 cm), or Daicel CHIRALPAK AD-H (4.6 mm \times 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. GC analysis was performed with Shimadzu 17A instruments with a flame-ionization detector and a capillary column of PEG-HT Bonded (25 m \times 0.25 mm) using nitrogen as carrier gas. Melting points were determined using a Yanaco MP-J3. The [2+2] cycloaddition reaction was carried out under an atmosphere of air. The others were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm or silica gel NH_2 F254S 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex[®] NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether, *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from TCI or Wako as the “anhydrous” and stored over 4A molecular sieves. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of α -Acyloxyacroleins (3). General Procedure for Preparing **3** were described in

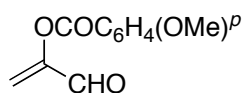
Funk's and our previous literatures.^{1,2}



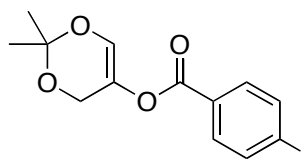
α -(Benzoyloxy)acrolein (3a): Spectral and analytical data were described in the previous literatures.^{1,2}



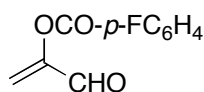
α -(Cyclohexanecarbonyloxy)acrolein (3b): Spectral and analytical data were described in the previous literatures.³



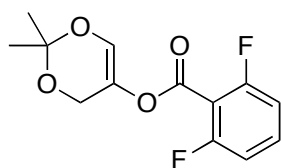
α -(*p*-Methoxybenzoyloxy)acrolein (3c): Spectral and analytical data were described in the previous literatures.²



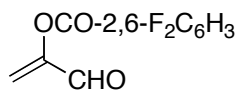
2,2-Dimethyl-4*H*-1,3-dioxin-5-yl 4-fluorobenzoate: ¹H NMR (300 MHz, CDCl₃) δ 1.58 (s, 6H), 4.38 (d, 2H, J = 1.5 Hz), 6.63 (c, 1H, J = 1.8 Hz), 7.11–7.20 (m, 2H), 8.07–8.11 (m, 2H).



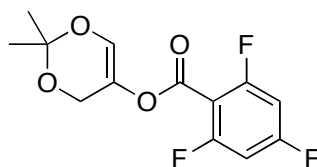
α -(*p*-Fluorobenzoyloxy)acrolein (3d): White solid; IR (KBr) 3116, 2869, 2362, 1746, 1693, 1645, 1603, 1508, 1417, 1256, 1156, 1074, 1015 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.06 (d, 1H, J = 2.4 Hz), 6.23 (d, 1H, J = 2.4 Hz), 7.10–7.24 (m, 2H), 8.10–8.18 (m, 2H), 9.49 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 115.8 (d, 2C, J = 2.2 Hz), 121.7, 124.5 (d, 1C, J_{CF} = 3 Hz), 133.0 (d, 2C, J_{CF} = 9 Hz), 152.7, 162.9, 160.3 (d, 1C, J_{CF} = 254 Hz), 185.1. HRMS(FAB) m/z calcd for C₁₀H₈O₃F [M+H]⁺ 195.0457, found: 195.0455.



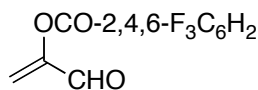
2,2-Dimethyl-4*H*-1,3-dioxin-5-yl 2,6-difluorobenzoate: ¹H NMR (300 MHz, CDCl₃) δ 1.57 (s, 6H), 4.40 (dd, 2H, J = 0.6, 1.5 Hz), 6.68 (s, 1H), 6.99 (t, 2H, J = 8.4 Hz), 7.48 (tt, 1H, J = 6.0, 8.4 Hz).



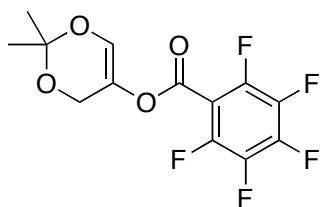
α -(2,6-Difluorobenzoyloxy)acrolein (3e): White solid; IR (KBr) 3118, 2883, 2361, 1750, 1689, 1646, 1624, 1571, 1470, 1285, 1093, 1063, 1019 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.09 (d, 1H, J = 2.7 Hz), 6.25 (d, 1H, J = 2.7 Hz), 7.02 (t, 2H, J = 8.7 Hz), 7.52 (tt, 1H, J = 6.0, 7.8 Hz), 9.49 (s, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ -109.0 (t, 2F, J = 6.2 Hz). HRMS(FAB) m/z calcd for C₁₀H₆O₃F₂Na [M+Na]⁺ 235.0183, found: 275.0176.



2,2-Dimethyl-4H-1,3-dioxin-5-yl 2,4,6-trifluorobenzoate: White solid; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.56 (s, 6H), 4.38 (d, 2H, $J = 1.5$ Hz), 6.67 (t, 1H, $J = 1.5$ Hz), 6.76 (t, 2H, $J = 8.1$ Hz).

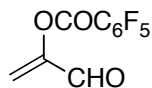


α -(2,4,6-Trifluorobenzoyloxy)acrolein (3f): 89% yield; white solid; IR (KBr) 3102, 2873, 1747, 1705, 1622, 1523, 1447, 1350, 1250, 1177, 1136, 1089, 1051, 1007 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.08 (d, 1H, $J = 2.7$ Hz), 6.24 (d, 1H, $J = 2.7$ Hz), 6.74 (t, 2H, $J = 8.4$ Hz), 9.48 (s, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 101.4 (m, 1C), 105.7 (dt, 2C, $J_{\text{CF}} = 4, 14$ Hz), 121.6 (d, $J_{\text{CF}} = 11$ Hz), 152.3, 157.6, 162.2 (ddd, 2C, $J_{\text{CF}} = 8, 16, 261$ Hz), 165.2 (td, 1C, $J_{\text{CF}} = 16, 256$ Hz), 184.2. HRMS (FAB) calcd for $\text{C}_{10}\text{H}_6\text{O}_3\text{F}_3$ $[\text{M}+\text{H}]^+$ 231.6269, found 231.0293.



2,2-Dimethyl-4H-1,3-dioxin-5-yl 2,3,4,5,6-pentafluorobenzoate:

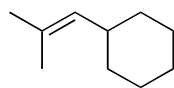
White solid; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.56 (s, 6H), 4.38 (d, 2H, $J = 1.5$ Hz), 6.70 (s, 1H).



α -(Pentafluorobenzoyloxy)acrolein (3g): White solid; IR (KBr) 1760, 1707, 1655, 1506, 1426, 1335, 1281, 1209, 1007 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.12 (d, 1H, $J = 2.7$ Hz), 6.28 (d, 1H, $J = 2.7$ Hz), 9.48 (s, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 106.2 (t, 1C, $J_{\text{CF}} = 14$ Hz), 122.1, 137.8 (dtd, 2C, $J_{\text{CF}} = 6, 16, 252$ Hz), 144.1 (m, 1C), 146.1 (m, 2C), 152.1, 156.1, 183.7; $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ -160.8– -160.6 (m, 2F), -146.9 (tt, 1F, $J = 5.9, 21.1$ Hz), -136.9– -136.8 (m, 2F). HRMS(FAB) m/z calcd for $\text{C}_{10}\text{H}_3\text{O}_3\text{F}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 288.9900, found: 288.9902.

2,4-Dimethyl-3-pentene (4a), 2,5-Dimethyl-2-hexene (4b), 2,4,4-Trimethyl-2-pentene (4d), and α -Methylstyrene (4g): Purchased from TCI, Japan.

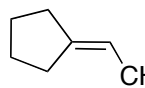
Preparation of (2-Methylprop-1-enyl)cyclohexene (4c). **4c** was prepared by Wittig reaction between cyclohexanecarboxaldehyde and triphenylphosphonium isopropylide which was prepared from isopropyltriphenylphosphonium iodide and BuLi in THF in situ.



4c:⁴ Colorless oil (bp. 57 $^{\circ}\text{C}$, 2.0 torr); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 0.92–1.35

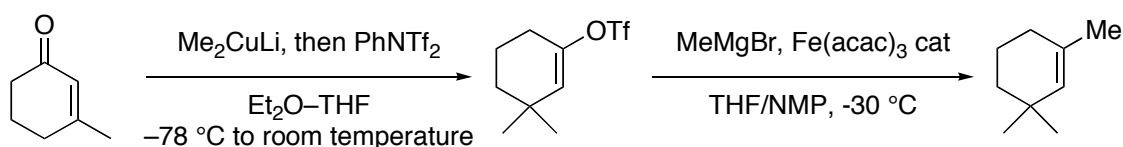
(m, 6H), 1.54–1.72 (m, 4H), 1.61 (s, 3H), 1.67 (s, 3H), 2.05–2.20 (m, 1H), 4.95 (quintetd, 1H, $J = 1.2, 8.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 17.8, 25.8, 26.1 (2C), 33.4 (2C), 37.0, 129.5, 131.2.

Preparation of (2-Ethylbutylidene)cyclopentane (4f). **4f** was prepared by Wittig reaction between 2-ethylbutanal and triphenylphosphonium cyclopentylide which was prepared from cyclopentyltriphenylphosphonium bromide and BuLi in THF in situ.



4f: Colorless oil; IR (film) 2956, 2871, 2360, 1455, 1376, 1334, 1038 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.82 (t, 6H, $J = 7.5$ Hz), 1.07–1.22 (m, 2H), 1.32–1.45 (m, 2H), 1.53–1.69 (m, 4H), 1.89 (tt, 1H, $J = 4.5, 13.8$ Hz), 2.16 (t, 2H, $J = 7.2$ Hz), 2.24 (t, 2H, $J = 7.2$ Hz), 4.92 (td, 1H, $J = 2.4, 9.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 11.9, 26.41, 26.43, 28.4, 29.0, 33.6, 43.3, 124.9, 142.8. HRMS(EI) m/z calcd for $\text{C}_{11}\text{H}_{20}$ $[\text{M}]^+$ 152.1565, found: 152.1576.

Preparation of 1,3,3-trimethylcyclohex-1-ene (4e).



3,3-Dimethylcyclohex-1-enyl trifloromethyl sulfate was prepared according to the procedure of Stoltz *et al.*⁵ To a stirring suspension of copper(I) iodide (9.52 g, 50.0 mmol) in Et_2O (50 mL) at 0 °C was added methyllithium (88.5 mL, 1.13 M in Et_2O , 100 mmol) dropwise over 10 min. The pale yellow solution was stirred for 30min, then cooled to -78 °C. 3-Methylcyclohexenone (5.67 mL, 50.0 mmol) in THF (50 mL) was added dropwise over 30min, and the resulting solution was stirred at -78 °C for 2 h and 0 °C for 2 h. PhNTf_2 (18.76 g, 52.5 mmol) in THF (105 mL) was added via cannula, and the reaction mixture was stirred at 0 °C for 3 h, then at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl aqueous solution (100 mL), and eluted with pentane (150 mL). The phases were separated, and the aqueous phase was extracted with pentane. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and, concentrated under reduce pressure. Purification by flash chromatography (pentane eluent) afforded vinyl triflate (9.17 g, 71% yield) as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 1.06 (s, 6H), 1.93 (m, 2H), 1.79 (tt, 2H, $J = 6.0, 6.3$ Hz), 2.28 (dt, 2H, $J = 1.5, 6.3$ Hz), 5.51 (brs, 1H).

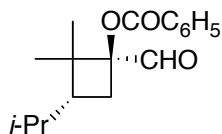
Iron-catalyzed cross-coupling reaction was carried out according to the procedure of Furstner *et al.*⁶ A solution of MeMgBr (13.5 mL, 3.0 M in Et_2O , 40.6 mmol) was rapidly added to a solution of vinyl triflate (8.73 g, 33.8 mmol) and $\text{Fe}(\text{acac})_3$ (596.9 mg, 1.69 mmol) in THF (70 mL) and NMP (6.44 mL) at -30 °C under N_2 . The mixture was stirred at -30 °C for 1 h before the reaction was quenched with saturated NH_4Cl aqueous solution (80 mL), and eluted with pentane (80 mL).

The aqueous phase was extracted with pentane. The combined organic layers were washed with brine and H₂O, dried over MgSO₄, filtered and, concentrated under reduce pressure. The residue was distilled (30–35 °C/50 torr) yielding **4e** (3.13g, 75% yield) as a colorless oil.

4e:⁷ Bp. 30 °C/50 torr; IR (film) 2928, 2865, 1455, 1360, 1208, 1016 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.99 (s, 6H), 1.34–1.38 (m, 2H), 1.59–1.64 (m, 2H), 1.62 (s, 3H), 1.83 (t, 2H, *J* = 5.7 Hz), 5.11 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 19.9, 23.8, 30.1, 30.1 (2C), 31.6, 37.0, 131.6, 132.0.

Representative Procedure for the Enantioselective [2+2] Cycloaddition of **4** with **3** Catalyzed by **1•2.6HNTf₂**.

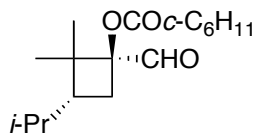
To a solution of **1** (15.2 mg, 0.050 mmol) and trifluoromethanesulfonimide (36.5 mg, 0.130 mmol) in 0.25 mL of nitroethane or nitropropane was added **3** (0.5 mmol). After cooling to –20 °C, **4** (1.0 mmol) was added to the solution, and the reaction mixture was stirred at –20 °C for several hours. Upon consumption of **3**, the reaction was quenched with NaHCO₃ and the reaction mixture was diluted with ethyl acetate and washed with brine and H₂O. The combined organic layer was dried over MgSO₄, filtered and, concentrated under reduce pressure. The crude product was purified by silica gel chromatography using hexane–EtOAc as the eluent.



(1S,3R)-1-Benzoyloxy-2,2-dimethyl-3-isopropylcyclobutane-

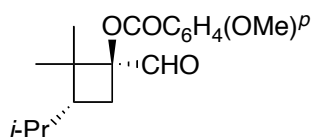
carboxaldehyde (5aa, anti-isomer): Colorless oil; $[\alpha]_D^{22.3} = 39.2$ (c 1.06, CHCl₃) for 73% ee; IR (CHCl₃) 2959, 2871, 2816, 2719, 1716, 1602, 1585, 1491, 1466, 1452, 1387, 1368, 1316, 1285, 1175, 1148, 1125, 1108, 1069, 1026 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.78 (d, 3H, *J* = 7.0 Hz), 0.87 (d, 3H, *J* = 6.0 Hz), 1.08 (s, 3H), 1.44 (s, 3H), 1.60–1.72 (m, 1H), 1.86 (dt, *J* = 9.0, 11.0 Hz), 2.08 (dd, 1H, *J* = 9.0, 13.5 Hz), 2.53 (dd, 1H, *J* = 10.5, 13.5 Hz), 7.49 (t, 2H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 8.12 (dd, 2H, *J* = 1.0, 8.0 Hz), 9.53 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 18.7, 19.8, 21.8, 25.6, 28.7, 28.9, 33.0, 46.3, 48.2, 86.9, 128.5 (2C), 129.5, 129.8 (2C), 133.6. HRMS(FAB) *m/z* calcd for C₁₇H₂₃O₃ [M+H]⁺ 275.1647, found: 275.1645. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.53 (s, 1H, *anti*-isomer) and δ 9.73 (s, 1H, *syn*-isomer). The ee was determined by HPLC analysis (two linear Daicel Chiralcel OD-H columns, hexane–*i*-PrOH = 40 : 1; flow rate = 0.5 mL/ min) after conversion to (1-hydroxy-3-isopropyl-2,2-dimethylcyclobutyl)methyl benzoate by reducing with LiAlH₄ (2 equiv) in THF at room temperature and the subsequent selective benzylation of primary hydroxy group of the corresponding 1,2-diol with benzoyl chloride (1.3 equiv) in the presence of *N,N*-diisopropylethylamine (2 equiv) in dichloromethane at –78 °C⁸: *t_R* = 53.5 ((1*R*,3*S*)-enantiomer)

and 90.2 ((1*S*,3*R*)-enantiomer) min.



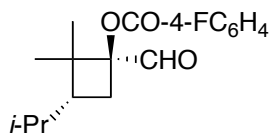
(1*S*,3*R*)-1-Cyclohexanecarboxyloxy-2,2-dimethyl-3-isopropyl-

cyclobutanecarboxaldehyde (5ba, *anti*-isomer): Colorless oil; $[\alpha]^{22.7}_D = 39.6$ ($c = 0.20$, CHCl_3) for 78% ee; IR (CHCl_3) 2934, 2857, 1738, 1712, 1466, 1451, 1420, 1386, 1364, 1298, 1249, 1160, 1134, 1086, 1051, 1021 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.77 (d, 3H, $J = 6.6$ Hz), 0.83 (d, 3H, $J = 6.3$ Hz), 1.00 (s, 3H), 1.24–1.84 (m, 10H), 1.26 (s, 3H), 1.89 (dd, 1H, $J = 8.7, 13.2$ Hz), 1.86–2.04 (m, 2H), 2.40 (dd, 1H, $J = 10.2, 13.2$ Hz), 2.34–2.52 (m, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 18.7, 19.8, 21.7, 25.25, 25.30, 25.31, 25.7, 28.7, 28.76, 28.84 (2C), 42.8, 46.0, 48.0, 85.8, 175.7, 197.9. HRMS(FAB) m/z calcd for $\text{C}_{17}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$ 281.2117, found: 281.2111. The *syn/anti* ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.38 (s, 1H, *anti*-isomer) and δ 9.59 (s, 1H, *syn*-isomer). The ee was determined by the same method with that of **5aa**.



(1*S*,3*R*)-2,2-Dimethyl-3-isopropyl-1-(4-methoxybenzyloxy)-

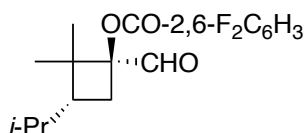
cyclobutanecarboxaldehyde (5ca, *anti*-isomer): Colorless oil; $[\alpha]^{22.3}_D = 28.6$ (c 0.52, CHCl_3) for 75% ee; IR (KBr) 2958, 2870, 2842, 2715, 1710, 1606, 1580, 1512, 1465, 1421, 1386, 1368, 1318, 1288, 1259, 1198, 1169, 1148, 1125, 1099, 1071, 1029 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.77 (d, 3H, $J = 6.6$ Hz), 0.86 (d, 3H, $J = 6.3$ Hz), 1.07 (s, 3H), 1.43 (s, 3H), 1.59–1.70 (m, 1H), 1.85 (dt, 1H, $J = 8.7, 10.8$ Hz), 2.05 (dd, 1H, $J = 9.0, 13.2$ Hz), 2.51 (dd, 1H, $J = 10.5, 13.2$ Hz), 3.89 (s, 3H), 6.97 (td, 2H, $J = 1.8, 9.0$ Hz), 8.07 (td, 2H, $J = 1.8, 8.7$ Hz), 9.51 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 18.8, 19.8, 21.8, 25.6, 28.6, 28.9, 46.2, 48.1, 55.5, 86.6, 113.8, 121.8, 131.9, 163.8, 165.9, 197.8. HRMS(FAB) m/z calcd for $\text{C}_{18}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$ 305.1753, found: 305.1755. The *syn/anti* ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.51 (s, 1H, *anti*-isomer) and δ 9.72 (s, 1H, *syn*-isomer). The ee was determined by the same method with that of **5aa**.



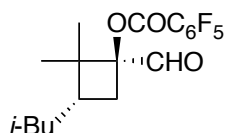
(1*S*,3*R*)-1-(4-Fluorobenzoyloxy)-2,2-dimethyl-3-isopropylcyclobutanecarb

oxaldehyde (5da, *anti*-isomer): Colorless oil; $[\alpha]^{22.5}_D = 33.3$ ($c = 1.15$, CHCl_3) for 71% ee; IR (CHCl_3) 2962, 2871, 1718, 1604, 1508, 1466, 1420, 1388, 1369, 1288, 1239, 1153, 1129, 1111, 1092, 1014 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.78 (d, 3H, $J = 6.5$ Hz), 0.87 (d, 3H, $J = 6.0$ Hz), 1.09 (s, 3H), 1.43 (s, 3H), 1.58–1.73 (m, 1H), 1.86 (dt, 1H, $J = 8.5, 11.0$ Hz), 2.08 (dd, 1H, $J = 8.5, 13.5$ Hz), 2.53 (dd, 1H, $J = 10.5, 13.5$ Hz), 7.14–7.18 (m, 2H), 8.11–8.15 (m, 2H), 9.53 (s, 1H); ^{13}C

NMR (125 MHz, CDCl₃) δ 18.7, 19.8, 21.7, 25.6, 28.7, 28.9, 46.3, 48.2, 87.0, 115.7 (d, 2C, $J_{CF} = 22$ Hz), 125.8 (d, 1C, $J_{CF} = 3$ Hz), 132.4 (d, 2C, $J_{CF} = 9$ Hz), 165.1, 167.1, 197.5; ¹⁹F NMR (282 MHz, CDCl₃) δ -105.5– -105.3 (m, 1F). HRMS(FAB) m/z calcd for C₁₇H₂₁O₃FNa [M+Na]⁺ 315.1372, found: 315.1364. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.53 (s, 1H, *anti*-isomer) and δ 9.73 (s, 1H, *syn*-isomer). The ee was determined by the same method with that of **5aa**.

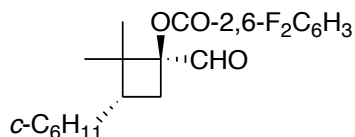


(1S,3R)-1-(2,6-Difluorobenzoyloxy)-2,2-dimethyl-3-isopropylcyclobutanecarboxaldehyde (5ea, *anti*-isomer): Colorless oil; $[\alpha]_D^{22.7} = 42.0$ ($c = 0.72$, CHCl₃) for 84% ee; IR (neat) 2959, 2871, 2812, 2715, 1732, 1625, 1591, 1471, 1387, 1370, 1304, 1267, 1237, 1147, 1109, 1072, 1058, 1015 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.80 (d, 3H, $J = 6.6$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz), 1.06 (s, 3H), 1.31 (s, 3H), 1.54–1.72 (m, 1H), 1.88 (dt, 1H, $J = 8.7, 10.5$ Hz), 2.14 (dd, 1H, $J = 8.7, 13.5$ Hz), 2.53 (dd, 1H, $J = 10.5, 13.5$ Hz), 7.01 (t, 2H, $J = 8.4$ Hz), 7.49 (tt, 1H, $J = 6.0, 8.7$ Hz), 9.56 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 18.7, 19.8, 21.7, 25.3, 28.7, 28.8, 46.4, 47.9, 88.6, 110.1, 112.3 (d, 2C, $J_{CF} = 26$ Hz), 133.5 (t, 1C, $J_{CF} = 11$ Hz), 161.2, 161.3 (dd, 2C, $J_{CF} = 5, 256$ Hz), 197.2. HRMS(FAB) m/z calcd for C₁₇H₂₀O₃F₂Na [M+Na]⁺ 333.1278, found: 333.1268. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.56 (s, 1H, *anti*-isomer) and δ 9.79 (s, 1H, *syn*-isomer). The ee was determined by the same method with that of **5aa**.

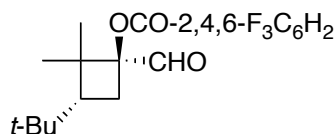


(+)-1-(Pentafluorobenzoyloxy)-2,2-dimethyl-3-isobutylcyclobutanecarboxaldehyde (5gb, *anti*-isomer): Colorless oil; $[\alpha]_D^{22.8} = 38.8$ ($c = 1.02$, CHCl₃) for 81% ee; IR (film) 2959, 2932, 2872, 2720, 1738, 1652, 1524, 1505, 1469, 1422, 1388, 1370, 1335, 1231, 1148, 1129, 1101, 1049, 1006 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.69 (d, 3H, $J = 6.6$ Hz), 0.73 (d, 3H, $J = 6.6$ Hz), 0.85 (s, 3H), 1.10 (s, 3H), 1.07–1.14 (m, 2H), 1.29–1.40 (m, 1H), 2.02–2.16 (m, 2H), 2.34–2.42 (m, 1H), 9.42 (s, 1H); ¹³C NMR (175 MHz, CDCl₃) δ 18.9, 22.6, 23.0, 25.2, 26.5, 30.9, 38.0, 38.6, 45.9, 89.5, 107.3, 137.8 (dm, 2C, $J_{CF} = 253$ Hz), 143.6 (dm, 1C, $J_{CF} = 258$ Hz), 145.9 (dm, 2C, $J_{CF} = 260$ Hz), 158.5, 190.6; ¹⁹F NMR (282 MHz, CDCl₃) δ -160.8– -160.6 (m, 2F), -148.0 (dt, 1F, $J = 5.9, 24.5$ Hz), -138.2– -138.1 (m, 2F). HRMS (FAB) calcd for C₁₈H₂₀O₃F₅ [M+H]⁺ 379.1333, found 379.1346. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.42 (s, 1H, *anti*-isomer) and δ 9.58 (s, 1H, *syn*-isomer). The ee was determined by chiral HPLC (three linear Daicel Chiralpak AS-H columns, hexane : *i*-PrOH = 800 : 1, flow rate 0.4 mL/min) $t_R = 51.6$ (major) and 55.4 (minor) min. The absolute configuration was

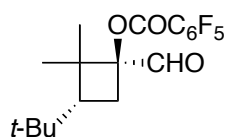
not established.



(+)-1-(2,6-Difluorobenzoyloxy)-2,2-dimethyl-3-cyclohexylcyclobutanecarboxaldehyde (5ec, *anti*-isomer): Colorless oil; $[\alpha]_D^{22.3} = 41.6$ (*c* 1.01, CHCl₃) for 85% ee; IR (film) 3442, 2925, 2851, 2713, 2360, 1733, 1625, 1592, 1471, 1449, 1389, 1370, 1305, 1268, 1237, 1207, 1184, 1149, 1109, 1014 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.68–0.95 (m, 2H), 1.06 (s, 3H), 1.14–1.38 (m, 4H), 1.30 (s, 3H), 1.52–1.78 (m, 5H), 1.96 (dd, 1H, *J* = 8.7, 10.8 Hz), 2.11 (dd, 1H, *J* = 8.7, 13.2 Hz), 2.52 (dd, 1H, *J* = 10.5, 13.2 Hz), 7.01 (t, 2H, *J* = 8.7 Hz), 7.49 (tt, 1H, *J* = 6.3, 8.4 Hz), 9.55 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 18.8, 25.4, 25.6, 25.9, 26.5, 28.1, 32.7, 38.4, 46.0, 46.5, 88.7, 110.0 (t, 1C, *J*_{CF} = 17 Hz), 112.2 (dd, 2C, *J*_{CF} = 3, 22 Hz), 133.6 (t, 1C, *J*_{CF} = 11 Hz), 161.2 (dd, 2C, *J*_{CF} = 6, 257 Hz), 161.2, 197.1; ¹⁹F NMR (282 MHz, CDCl₃) δ -110.2 (t, 2F, *J* = 5.9 Hz). HRMS(FAB) *m/z* calcd for C₂₀H₂₄O₃F₂ [M+H]⁺ 373.1591, found: 373.1599. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.55 (s, 1H, *anti*-isomer) and δ 9.76 (s, 1H, *syn*-isomer). The ee was determined by chiral HPLC (Daicel Chiralpak AS-H column, hexane–ethanol = 200 : 1, flow rate = 0.8 mL/min) *t*_R = 8.8 (major enantiomer) and 14.9 (minor enantiomer) min. The absolute configuration was not established.

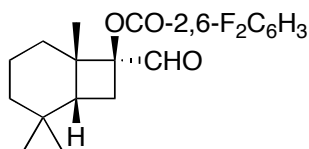


(+)-1-(2,4,6-Trifluorobenzoyloxy)-2,2-dimethyl-3-cyclohexylcyclobutanecarboxaldehyde (5fd, *anti*-isomer): Colorless oil; $[\alpha]_D^{22.5} = 40.7$ (*c* 1.20, CHCl₃) for 84% ee; IR (film) 3106, 2955, 2870, 1715, 1735, 1643, 1619, 1471, 1445, 1390, 1364, 1277, 1217, 1200, 1174, 1150, 1130, 1101 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (s, 9H), 1.15 (s, 3H), 1.32 (s, 3H), 1.99 (dd, 1H, *J* = 8.4, 12.6 Hz), 2.14 (dd, 1H, *J* = 8.4, 12.3 Hz), 2.77 (t, 1H, *J* = 12.6 Hz), 9.54 (s, 1H); ¹³C NMR (175 MHz, CDCl₃) δ 20.5, 25.8, 26.4, 28.2 (3C), 32.6, 49.2, 50.7, 89.1, 101.4, (dt, 1C, *J*_{CF} = 5, 25 Hz), 106.7 (dt, 2C, *J*_{CF} = 5, 17 Hz), 160.4 (ddd, 2C, *J*_{CF} = 8, 15, 258 Hz), 164.8 (td, 2C, *J* = 15, 255 Hz), 146.9; ¹⁹F NMR (282 MHz, CDCl₃) δ -105.7 (t, 2F, *J* = 9.0 Hz), -101.2 (quintet, 1F, *J* = 9.0 Hz). HRMS(FAB) *m/z* calcd for C₁₈H₂₂O₃F₃ [M+H]⁺ 343.1521, found: 343.1521. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.54 (s, 1H, *anti*-isomer) and δ 9.75 (s, 1H, *syn*-isomer). The ee was determined by chiral HPLC (two linear Daicel Chiralpak AS-H columns, hexane–*i*-PrOH = 400 : 1, flow rate = 0.5 mL/min) *t*_R = 59.4 (major enantiomer) and 67.4 (minor enantiomer) min. The absolute configuration was not established.



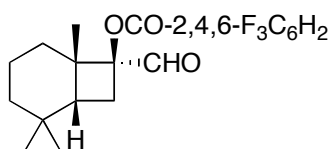
(+)-1-(Pentafluorobenzoyloxy)-2,2-dimethyl-3-cyclohexylcyclobutane-

carboxaldehyde (5gd, *anti*-isomer): White solid; $[\alpha]_{\text{D}}^{22.5} = 42.4$ (c 0.83, CHCl_3) for 87% ee; IR (film) 2957, 2716, 1734, 1652, 1525, 1504, 1471, 1422, 1391, 1370, 1335, 1236, 1149, 1131, 1104, 1077, 1060, 1007 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.93 (s, 9H), 1.18 (s, 3H), 1.31 (s, 3H), 2.02 (dd, 1H, $J = 8.7, 12.9$ Hz), 2.20 (dd, 1H, $J = 8.7, 12.3$ Hz), 2.79 (t, 1H, $J = 12.6$ Hz), 9.55 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.5, 25.9, 26.4, 28.2 (3C), 32.6, 49.4, 50.4, 89.9, 107.3, (dt, 1C, $J_{\text{CF}} = 4, 14$ Hz), 137.8 (dm, 2C, $J_{\text{CF}} = 255$ Hz), 143.7 (dm, 1C, $J_{\text{CF}} = 259$ Hz), 146.0 (dm, 2C, $J = 264$ Hz), 158.7; ^{19}F NMR (282 MHz, CDCl_3) δ -160.8–-160.6 (m, 2F), -147.8 (dt, 1F, $J = 5.1, 21.4$ Hz), -138.1–-137.9 (m, 2F). HRMS(FAB) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{F}_5$ $[\text{M}+\text{H}]^+$ 379.1333, found: 379.1346. The *syn/anti* ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.55 (s, 1H, *anti*-isomer) and δ 9.76 (s, 1H, *syn*-isomer). The ee was determined by chiral HPLC (Daicel Chiralpak AS-H column, hexane-*i*-PrOH = 400 : 1, flow rate = 0.2 mL/min) $t_{\text{R}} = 35.5$ (major enantiomer) and 40.5 (minor enantiomer) min. The absolute configuration was not established.



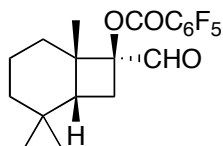
(1R,6S,7S)-7-Formyl-2,2,6-trimethylbicyclo[4.2.0]octan-7-yl

2,6-difluorobenzoate (5ee, *anti*-isomer): Colorless oil; $[\alpha]_{\text{D}}^{23.4} = 29.4$ ($c = 0.46, \text{CHCl}_3$) for 83% ee; IR (film) 2955, 2868, 2713, 1733, 1625, 1591, 1471, 1377, 1363, 1304, 1270, 1236, 1198, 1146, 1134, 1110, 1059 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.77 (s, 3H), 0.93 (s, 3H), 1.12–1.36 (m, 2H), 1.32 (s, 3H), 1.36–1.54 (m, 1H), 1.70–1.82 (m, 1H), 1.92 (dd, 1H, $J = 8.1, 12.6$ Hz), 2.10 (dd, 1H, $J = 8.1, 11.4$ Hz), 2.67 (t, 1H, $J = 12.3$ Hz), 7.02 (t, 2H, $J = 8.4$ Hz), 7.50 (tt, 1H, $J = 6.0, 8.4$ Hz), 9.56 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 18.0, 22.5, 26.3, 27.7, 28.5, 29.2, 9.6, 35.3, 46.0, 47.0, 89.1, 110.0 (t, 1C, $J = 16$ Hz), 112.3 (dd, 2C, $J = 4, 21$ Hz), 133.6 (t, 1C, $J = 10$ Hz), 161.3 (dd, 2C, $J = 5, 257$ Hz), 161.5, 196.6; ^{19}F NMR (282 MHz, CDCl_3) δ -110.1–-109.9 (m, 2F). HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{23}\text{O}_3\text{F}_2$ $[\text{M}+\text{H}]^+$ 337.1615, found 337.1605. The ee was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane-*i*-PrOH = 400 : 1; flow rate = 1.0 mL/min): $t_{\text{R}} = 18.7$ ((1R,6S,7S)-enantiomer) and 35.8 ((1S,6R,7R)-enantiomer) min. The *syn/anti* ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.56 (s, 1H, *anti*-isomer) and δ 9.79 (s, 1H, *syn*-isomer).



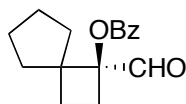
(1R,6S,7S)-7-Formyl-2,2,6-trimethylbicyclo[4.2.0]octan-7-yl

2,6-trifluorobenzoate (5fe, anti-isomer): Colorless oil; $[\alpha]_D^{22.8} = 38.0$ (*c* 0.70, CHCl₃) for 85% ee; IR (KBr) 3440, 3106, 2955, 2869, 2816, 2716, 1734, 1643, 1620, 1600, 1494, 1446, 1377, 1363, 1281, 1260, 1231, 1198, 1174, 1130, 1107, 1050, 1002 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.76 (s, 3H), 0.93 (s, 3H), 1.16–1.54 (m, 5H), 1.31 (s, 3H), 1.75 (dt, 1H, *J* = 4.8, 12.6 Hz), 1.91 (dd, 1H, *J* = 8.4, 12.6 Hz), 2.08 (dd, 1H, *J* = 8.4, 11.7 Hz), 2.67 (dd, *J* = 11.7, 12.3 Hz), 6.78 (t, 2H, *J* = 8.1 Hz), 9.54 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 22.5, 26.3, 27.7, 28.5, 29.2, 29.6, 35.2, 46.0, 47.0, 89.1, 101.4 (dt, 2C, *J*_{CF} = 4, 26 Hz), 106.7, 160.8, 162.3 (ddd, 2C, *J*_{CF} = 8, 15, 259 Hz), 164.8 (td, 1C, *J*_{CF} = 15, 255 Hz), 196.6; ¹⁹F NMR (282 MHz, CDCl₃) δ -105.6 (t, 2F, *J* = 9.0 Hz), -101.2 (quintet, 1F, *J* = 9.0 Hz). HRMS (FAB) calcd for C₁₉H₂₂O₃F₃ [M+H]⁺ 355.1521, found 355.1527. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.54 (s, 1H, *anti*-isomer) and δ 9.77 (s, 1H, *syn*-isomer). The ee was determined by HPLC analysis (Daicel Chiralpak AS-H column, hexane-*i*-PrOH = 400 : 1; flow rate = 1.0 mL/min): *t*_R = 21.9 (major *anti*-enantiomer), 30.3 (minor *anti*-enantiomer) min.



(1R,6S,7S)-7-Formyl-2,2,6-trimethylbicyclo[4.2.0]octan-7-yl

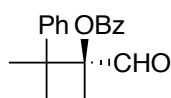
2,6-trifluorobenzoate (5ge, anti-isomer): White solid; $[\alpha]_D^{23.2} = 41.9$ (*c* 0.87, CHCl₃) for 80% ee; IR (KBr) 3448, 2954, 2871, 1733, 1651, 1505, 1470, 1419, 1379, 1334, 1239, 1146, 1099, 1009 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.77 (s, 3H), 0.94 (s, 3H), 1.16–1.36 (m, 3H), 1.30 (s, 3H), 1.36–1.54 (m, 2H), 1.75 (dt, 1H, *J* = 5.1, 13.2 Hz), 1.93 (dd, 1H, *J* = 8.1, 12.6 Hz), 2.08 (dd, 1H, *J* = 8.4, 11.7 Hz), 2.70 (dd, 1H, *J* = 11.7, 12.6 Hz), 9.56 (s, 1H); ¹³C NMR (175 MHz, CDCl₃) δ 17.9, 22.5, 26.4, 27.6, 28.5, 29.3, 29.6, 35.2, 46.2, 47.3, 90.0, 107.2 (dt, 1C, *J*_{CF} = 4, 15 Hz), 137.8 (dm, 2C, *J*_{CF} = 252 Hz), 143.7 (dm, 1C, *J*_{CF} = 260 Hz), 146.0 (dm 2C, *J*_{CF} = 259 Hz), 159.0, 196.0; ¹⁹F NMR (282 MHz, CDCl₃) δ -160.3– -160.0 (m, 2F), -160.0 (m, 2F), -147.2 (tt, 1F, *J* = 6.2, 21.4 Hz), -137.5– -137.3 (m, 2F). HRMS (FAB) calcd for C₁₉H₂₀O₃F₅ [M+H]⁺ 391.1333, found 391.1341. The *syn/anti* ratio was determined by ¹H NMR analysis of the formyl proton: δ 9.56 (s, 1H, *anti*-isomer) and δ 9.78 (s, 1H, *syn*-isomer). The ee was determined by HPLC analysis (Daicel Chiralpak AS-H column; hexane-*i*-PrOH = 800 : 1; flow rate = 0.5 mL/min): *t*_R = 12.1 ((1R,6S,7S)-enantiomer) and 14.3 ((1S,6R,7R)-enantiomer) min.



(+)-1-(2,6-Difluorobenzyloxy)-3-ethylpropyl-1-formylspiro[3.4]octane (5ef,

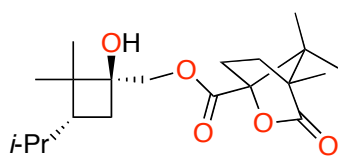
anti-isomer): Colorless oil; $[\alpha]_D^{23.4} = 45.8$ (*c* 0.36, CHCl₃) for 83% ee; IR (KBr) 2962, 2874, 2809, 2713, 1732, 1625, 1592, 1471, 1382, 1303, 1269, 1237, 1204, 1177, 1134, 1108, 1059, 1016 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.79 (t, 3H, *J* = 7.5 Hz), 0.83 (t, 3H, *J* = 7.5 Hz), 1.10–1.91 (m, 12H),

2.10 (dd, 1H, $J = 7.8, 12.6$ Hz), 2.32–2.42 (m, 2H), 2.52 (dd, 1H, $J = 1.08, 12.6$ Hz), 7.01 (t, 2H, $J = 8.1$ Hz), 7.44 (tt, 1H, $J = 6.3, 8.7$ Hz), 9.48 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 9.5, 9.9, 20.8, 22.6, 23.2, 23.5, 26.7, 29.0, 33.7, 39.0, 40.6, 59.4, 89.0, 110.1 (t, $J = 17$ Hz), 112.3 (dd, 2C, $J = 4, 21$ Hz), 133.5 (t, 1C, $J = 10$ Hz), 161.2, (dd, $J = 6, 257$ Hz), 161.4, 195.9; ^{19}F NMR (282 MHz, CDCl_3) δ -110.3 (t, 2F, $J = 6.2$ Hz). HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{22}\text{O}_3\text{F}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 359.1435, found 359.1408. The *syn/anti* ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.48 (s, 1H, *anti*-isomer) and 9.75 (s, 1H, *syn*-isomer). The ee was determined by HPLC analysis (Daicel Chiralcel OD-H column; hexane–EtOH = 400 : 1; flow rate = 1.0 mL/min): $t_{\text{R}} = 13.5$ (major enantiomer) and 50.0 (minor enantiomer) min. The absolute configuration was not established.



1-(Benzoyloxy)-2-methyl-2-phenylcyclobutanecarboxaldehyde (5ag):

Colorless oil; $[\alpha]_{\text{D}}^{22.0} = 44.5$ (c 0.25, CHCl_3) for 80% ee; IR (CHCl_3) 3060, 3026, 2965, 2870, 2814, 2717, 1714, 1602, 1583, 1496, 1451, 1379, 1316, 1282, 1207, 1178, 1107, 1070, 1057, 1027, 1002 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.49 (s, 3H), 1.97–2.14 (m, 2H), 2.77–2.88 (m, 1H), 3.12 (td, $J = 9.0, 12.9$ Hz), 7.25–7.35 (m, 5H), 7.40–7.58 (m, 5H), 9.78 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.1, 26.3, 27.8, 51.9, 87.9, 125.6, 126.4, 126.6 (2C), 128.2 (2C), 128.3 (2C), 129.7 (2C), 133.4, 143.6, 165.7, 197.3. HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$ 295.1334, found 295.1337. The diastereomeric ratio was determined by ^1H NMR analysis of the formyl proton: δ 9.78 (s, 1H, major diastereomer) and 9.43 (s, 1H, minor diastereomer). The ee was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*-PrOH = 400 : 1; flow rate = 1.0 mL/min): $t_{\text{R}} = 28.3$ (major enantiomer) and 48.7 (minor enantiomer) min. The absolute and relative configurations were not established.



((1S,3R)-1-Hydroxy-3-isopropyl-2,2-dimethylcyclobutyl)methyl

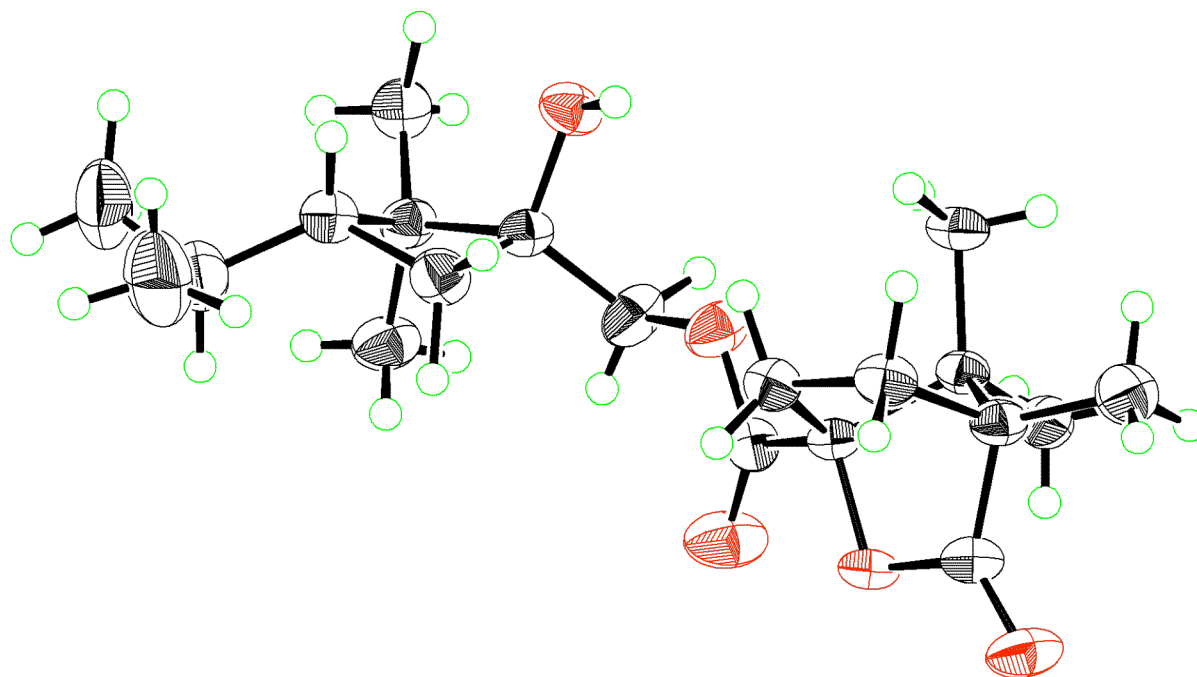
4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylate (8). To a solution of (1S,3R)-1-formyl-3-isopropyl-2,2-dimethylcyclobutyl benzoate (82.3 mg, 0.30 mmol) in THF (1.0 mL), was added LiAlH_4 (22.8 mg, 0.60 mmol) at 0 °C. After stirring at 0 °C for 8 h, the reaction was quenched with Na_2SO_4 (26.4 mg) and water (0.069 mL) with vigorous stirring at 0 °C. The white-gray suspension was filtered and concentrated. Purification by flash chromatography (eluent: hexane–EtOAc) afforded the corresponding diol as a colorless oil.

Esterification was carried out according to the reported procedure.⁸ To the crude product in dichloromethane (1 mL), was added *N,N*-diisopropylethylamine (87.8 mL, 0.504 mmol), DMAP

(1.8 mg, 0.015 mmol) and (1*S*)-camphanic chloride (65.5 mg, 0.302 mmol) at -78 °C. After stirring at -78 °C for 10 min, the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated water and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and, concentrated under reduce pressure. Purification by flash chromatography (eluent: hexane–EtOAc) afforded the corresponding ester (54.7 mg, 52% yield) as a white solid.

X-ray Crystallographic Analysis of 8: The white solid of **8** was recrystallized from Et_2O –hexane to obtain a colorless crystal at room temperature. Crystal data: $\text{C}_{20}\text{H}_{32}\text{O}_5$, $M = 352.46$, crystal dimensions $0.20 \times 0.20 \times 0.20$ mm³, monoclinic, space group $P21$, $a = 6.1108(15)$, $b = 25.720(6)$, $c = 7.225(2)$ Å, $V = 1029.2(5)$ Å³, $Z = 2$, $D_c = 1.137$ g/cm³, $\mu = 0.080$ mm⁻¹, $T = 223$ K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å). The structure was solved by direct methods and expanded using Fourier techniques. 4522 reflections were independent and unique, and 349 with $I > 2\sigma(I)$ ($2\theta_{\text{max}} = 29.21^\circ$) were used for the solution of the structure. $R = 0.0591$ and $R_w = 0.1648$.

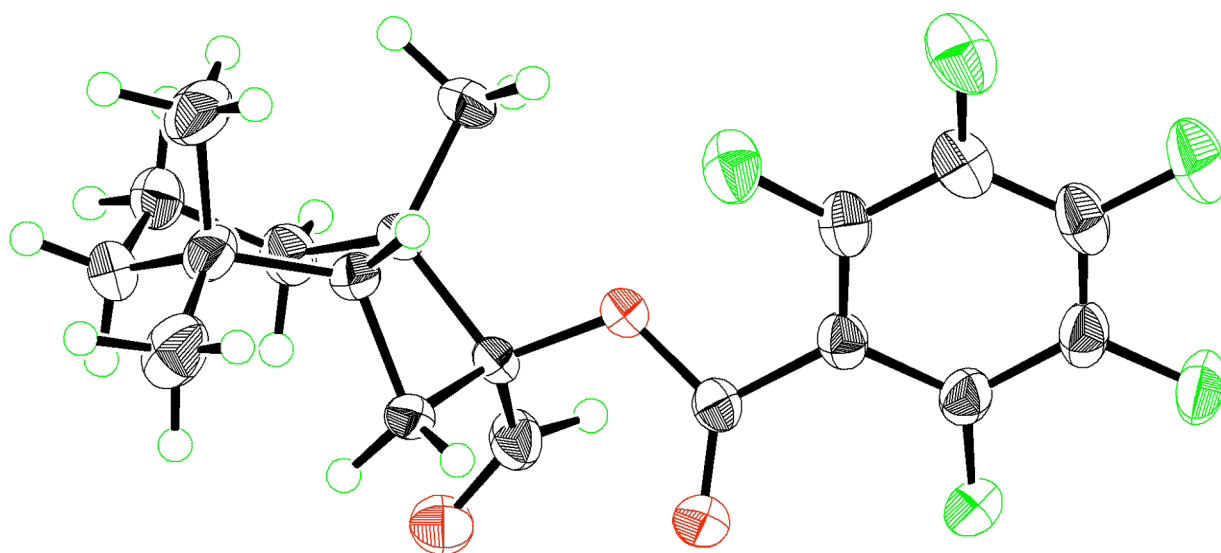
Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-644902. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).



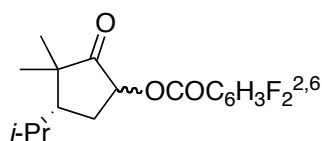
X-ray Crystallographic Analysis of 5ge: The white solid of **5ge** was recrystallized from *i*-PrOH–hexane to obtain a colorless crystal at -20 °C. Crystal data: $\text{C}_{19}\text{H}_{19}\text{O}_3\text{F}_5$, $M = 390.34$,

crystal dimensions $0.30 \times 0.20 \times 0.20 \text{ mm}^3$, monoclinic, space group $P21$, $a = 11.979(3)$, $b = 6.7154(17)$, $c = 12.222(3) \text{ \AA}$, $V = 907.5(4) \text{ \AA}^3$, $Z = 2$, $D_c = 1.428 \text{ g/cm}^3$, $\mu = 0.129 \text{ mm}^{-1}$, $T = 173 \text{ K}$. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct methods and expanded using Fourier techniques. 3823 reflections were independent and unique, and 320 with $I > 2\sigma(I)$ ($2\theta_{\text{max}} = 29.21^\circ$) were used for the solution of the structure. $R = 0.0358$ and $R_w = 0.0924$. Flack x parameter = 0.2618.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-644901. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).



Semi-Pinacol Rearrangement of **5ea** with AlCl_3 .

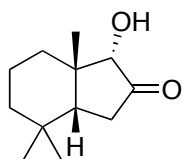


(*R*)-4-Isopropyl-3,3-dimethyl-2-oxocyclopentyl

2,6-Difluorobenzoate (7ea): Aluminum chloride (118 mg, 0.089 mmol) was added in one portion to a stirred solution of substrate **5ea** (23.0 mg, 0.074 mmol) in dry CH_2Cl_2 (0.37 mL) at 0°C and the reaction mixture was then stirred for 9 h. The reaction was then quenched with saturated NaHCO_3 and extracted with ether. The combined extracts were washed with water and brine, dried over MgSO_4 , filtered and, concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane–EtOAc as the eluent to give **7ea** in 61% yield as white solid. IR (KBr) 2926, 1759, 1737, 1626, 1471, 1287, 1263, 1121, 1076, 1012 cm^{-1} ; $^1\text{H NMR}$ (300

MHz, CDCl₃) δ 1.00 (d, 3H, *J* = 6.6 Hz), 1.05 (s, 3H), 1.06 (d, 3H, *J* = 6.6 Hz), 1.23 (s, 3H), 1.54–1.66 (m, 2H), 1.70–1.80 (m, 1H), 2.62–2.70 (m, 1H), 5.40–5.47 (m, 1H), 6.96 (t, 2H, *J* = 8.1 Hz), 7.43 (tt, 1H, *J* = 6.0, 8.7 Hz); ¹³C NMR (175 MHz, CDCl₃) δ 18.9, 21.6, 22.9, 26.3, 29.2, 30.8, 46.7, 49.2, 76.2, 110.4 (t, 1C, *J*_{CF} = 17 Hz), 112.1 (dd, 2C, *J*_{CF} = 4, 22 Hz), 133.1 (t, 1C, *J*_{CF} = 10 Hz), 160.8, 160.9 (dd, 2C, *J*_{CF} = 5, 256 Hz), 216.1; ¹⁹F NMR (282 MHz, CDCl₃) δ –110.4– –110.5 (m, 2F). HRMS (FAB) calcd for C₁₇H₂₁O₃F₂ [M+H]⁺ 311.1459, found 311.1447.

Semi-Pinacol Rearrangement of **6gd** with Bu₄NF•3H₂O.



(3aR,7aS)-1-Hydroxy-4,4,7a-trimethyl-hexahydro-1H-inden-2(3H)-one (6e):

To a solution of **5ge** (21 mg, 0.060 mmol) in THF (0.60 mL), was added TBAF (0.6 mL, 0.2 M in THF, 0.12 mmol) dropwise at –78 °C. After stirring at –78 °C for 5 min, the cooling bath was removed and the mixture was stirred at room temperature for 9.5 h. The mixture was quenched with saturated NH₄Cl aqueous solution, and eluted with Et₂O. The mixture was extracted with Et₂O. The combined organic layers were washed with brine and water, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane–EtOAc as eluent) afforded **6e** (11.2 g, 95% yield) with 64% ds as a colorless oil. The relative stereochemistry of **6e** was determined by X-ray crystal analysis of its major diastereomer.

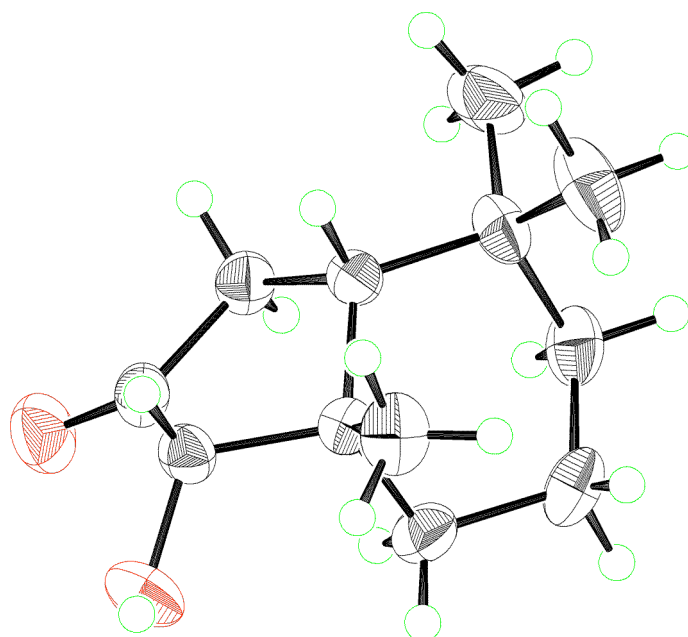
(1S)-Diastereomer (major diastereomer): Colorless oil; [α]^{22.0}_D = 81.9 (*c*, 0.40, CHCl₃) for 91% ee; TLC (hexane–EtOAc = 4:1) *R*_f = 0.17; IR (film) 2926, 2853, 1758, 1739, 1625, 1591, 1470, 1410, 1388, 1362, 1344, 1290, 1263, 1236, 1116, 1076, 1058, 1014 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.75 (dt, *J* = 4.0, 13.5 Hz), 0.85 (s, 3H), 1.15 (s, 3H), 1.20–1.33 (m, 1H), 1.37 (s, 3H), 1.45–1.50 (m, 1H), 1.54–1.63 (m, 1H), 1.77 (t, 1H, *J* = 10.5 Hz), 2.09 (dd, 1H, *J* = 11.0, 20.0 Hz), 2.33 (ddd, 1H, *J* = 4.0, 9.5, 20.0 Hz), 2.50 (brs, 1H), 3.81 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 17.7, 24.7, 26.2, 28.6, 30.6, 31.9, 33.6, 35.5, 42.1, 46.4, 86.3, 216.8.

(1R)-Diastereomer (minor diastereomer): Colorless oil; TLC (hexane–EtOAc = 4:1) *R*_f = 0.22; ¹H NMR (500 MHz, CDCl₃) δ 0.89 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.21–1.33 (m, 4H), 1.47–1.51 (m, 1H), 1.54–1.60 (m, 1H), 1.77 (dd, 1H, *J* = 3.5, 9.0 Hz), 2.27 (d, 1H, *J* = 1.8 Hz), 2.30 (ddd, 1H, *J* = 1.5, 4.0, 20.0 Hz), 2.39 (dd, 1H, *J* = 9.5, 20.0 Hz), 4.04 (brs, 1H). HRMS (FAB) calcd for C₁₂H₂₀O₂ [M+H]⁺ 196.1463, found 196.1468.

X-ray Crystallographic Analysis of (1S,3aR,7aS)-6e: The white solid of **6e** was recrystallized from EtOAc–hexane to obtain a colorless crystal at –20 °C. Crystal data: C₁₂H₂₀O₂, *M* = 196.28, crystal dimensions 0.30 × 0.20 × 0.20 mm³, orthorhombic, space group

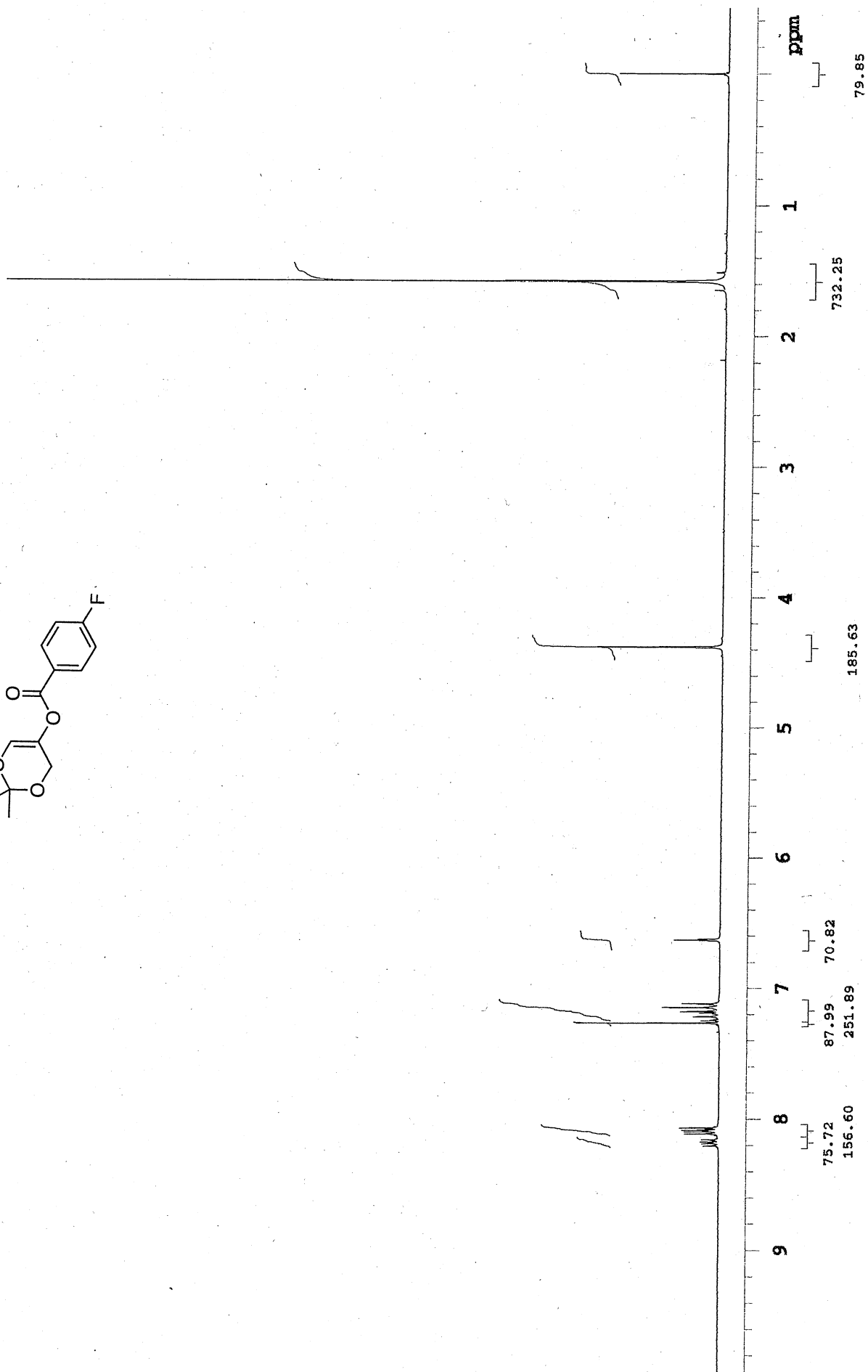
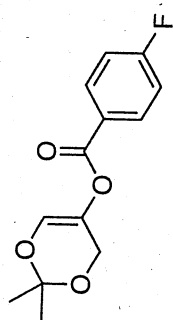
P212121, $a = 6.3260(18)$, $b = 13.085(4)$, $c = 13.589(4)$ Å, $V = 1124.8(6)$ Å³, $Z = 2$, $D_c = 0.580$ g/cm³, $\mu = 0.038$ mm⁻¹, $T = 223$ K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoK α radiation, $\lambda = 0.71073$ Å). The structure was solved by direct methods and expanded using Fourier techniques. 2805 reflections were independent and unique, and 207 with $I > 2\sigma(I)$ ($2\theta_{\max} = 29.21^\circ$) were used for the solution of the structure. $R = 0.0392$ and $R_w = 0.1013$.

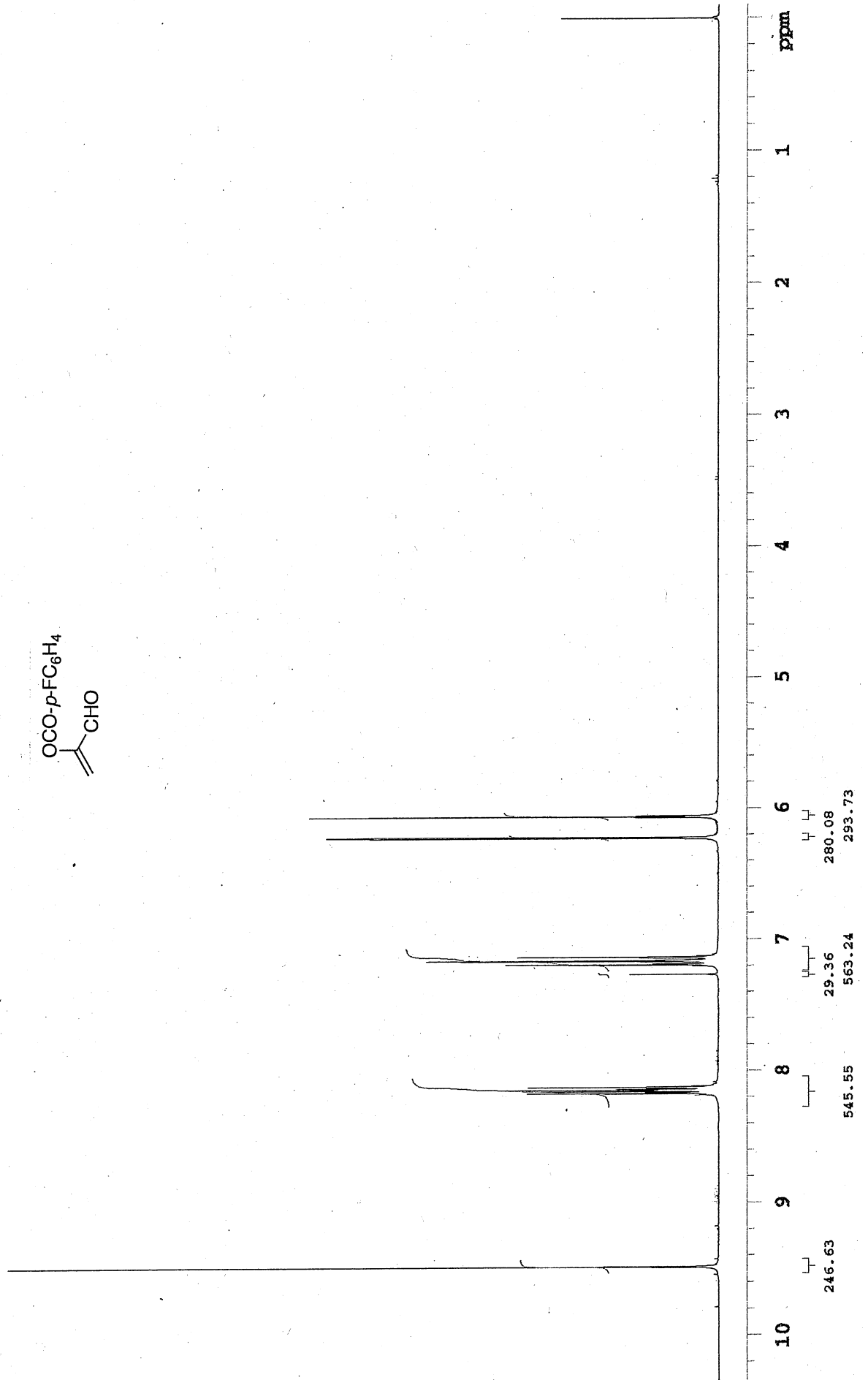
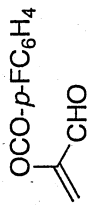
Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-650717. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

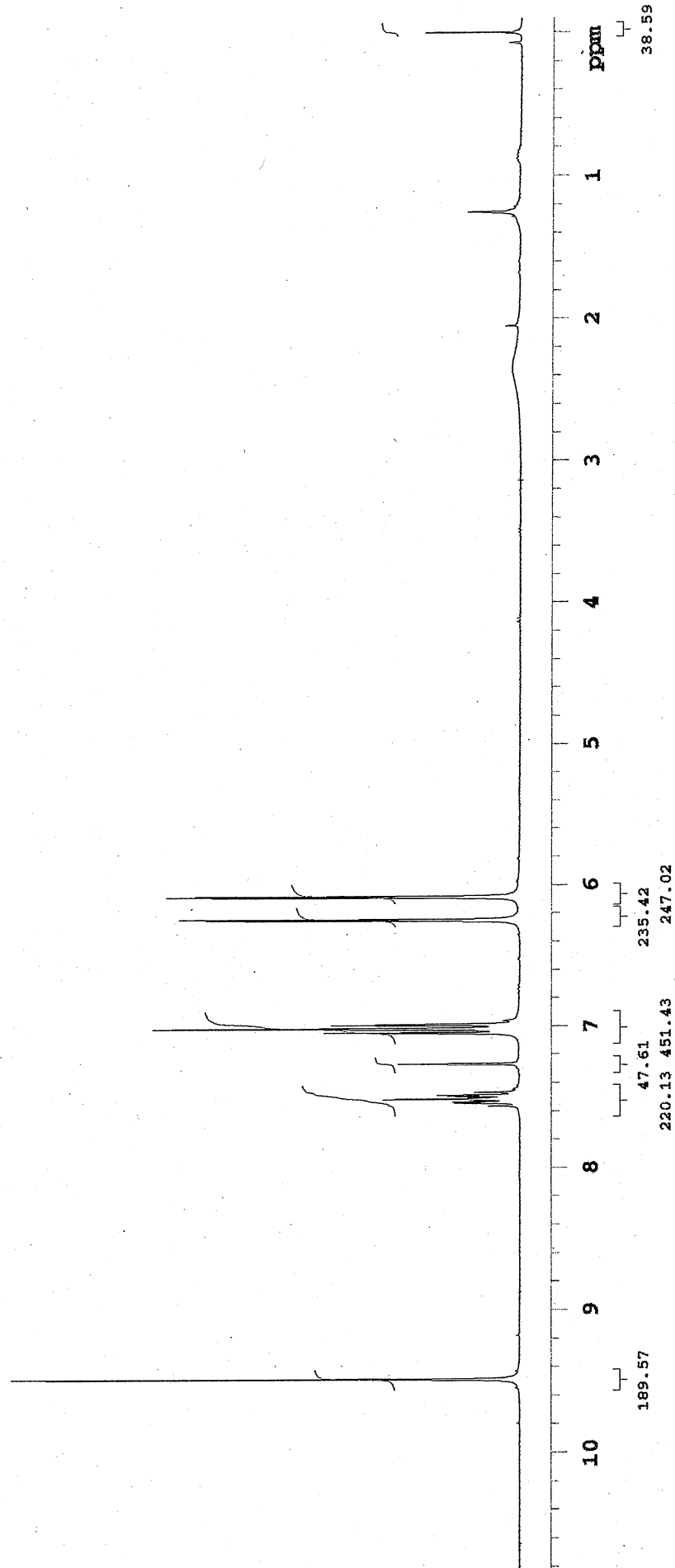
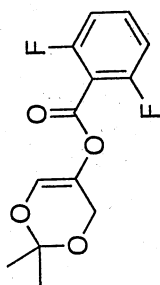


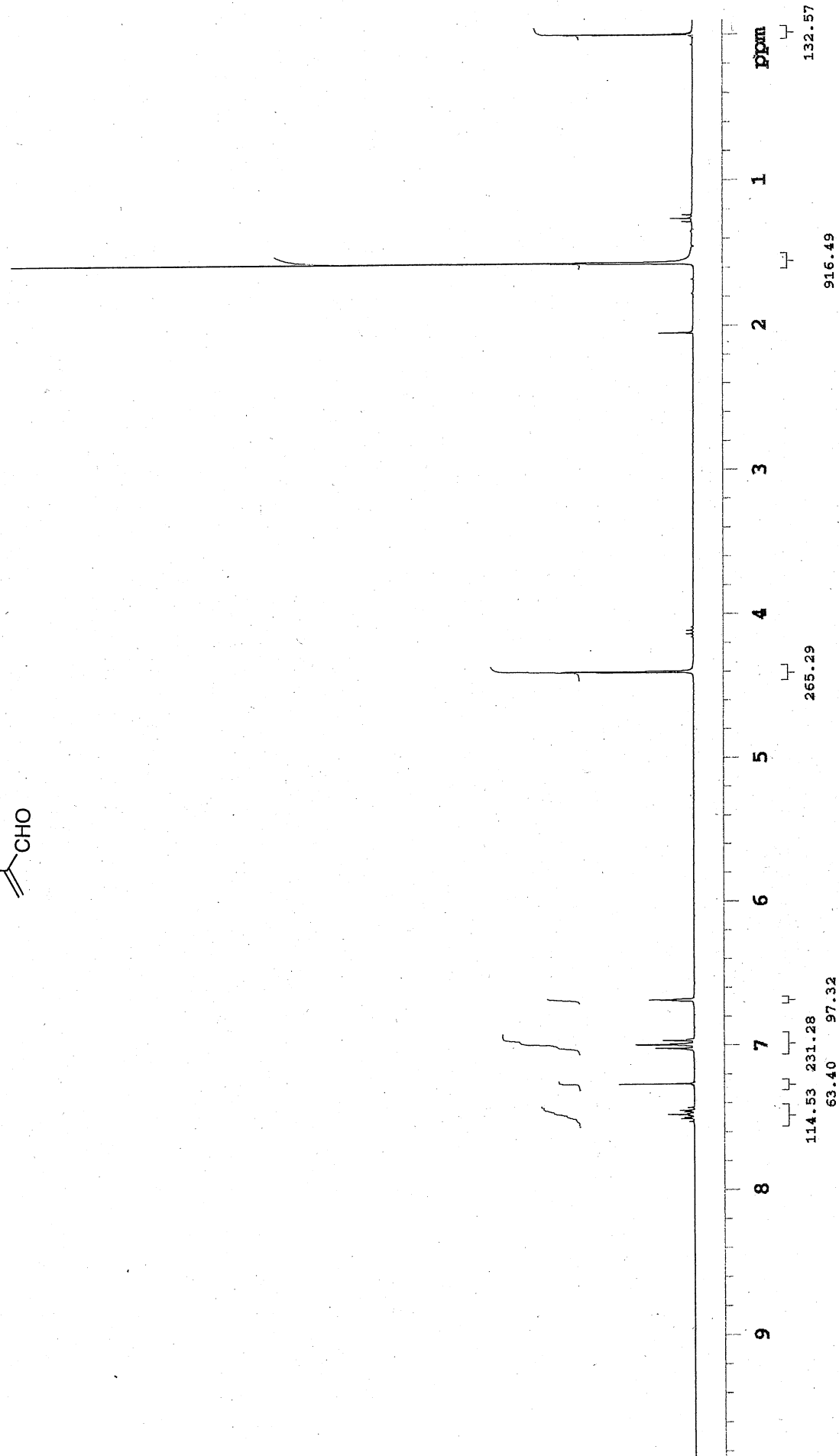
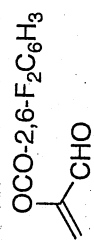
References

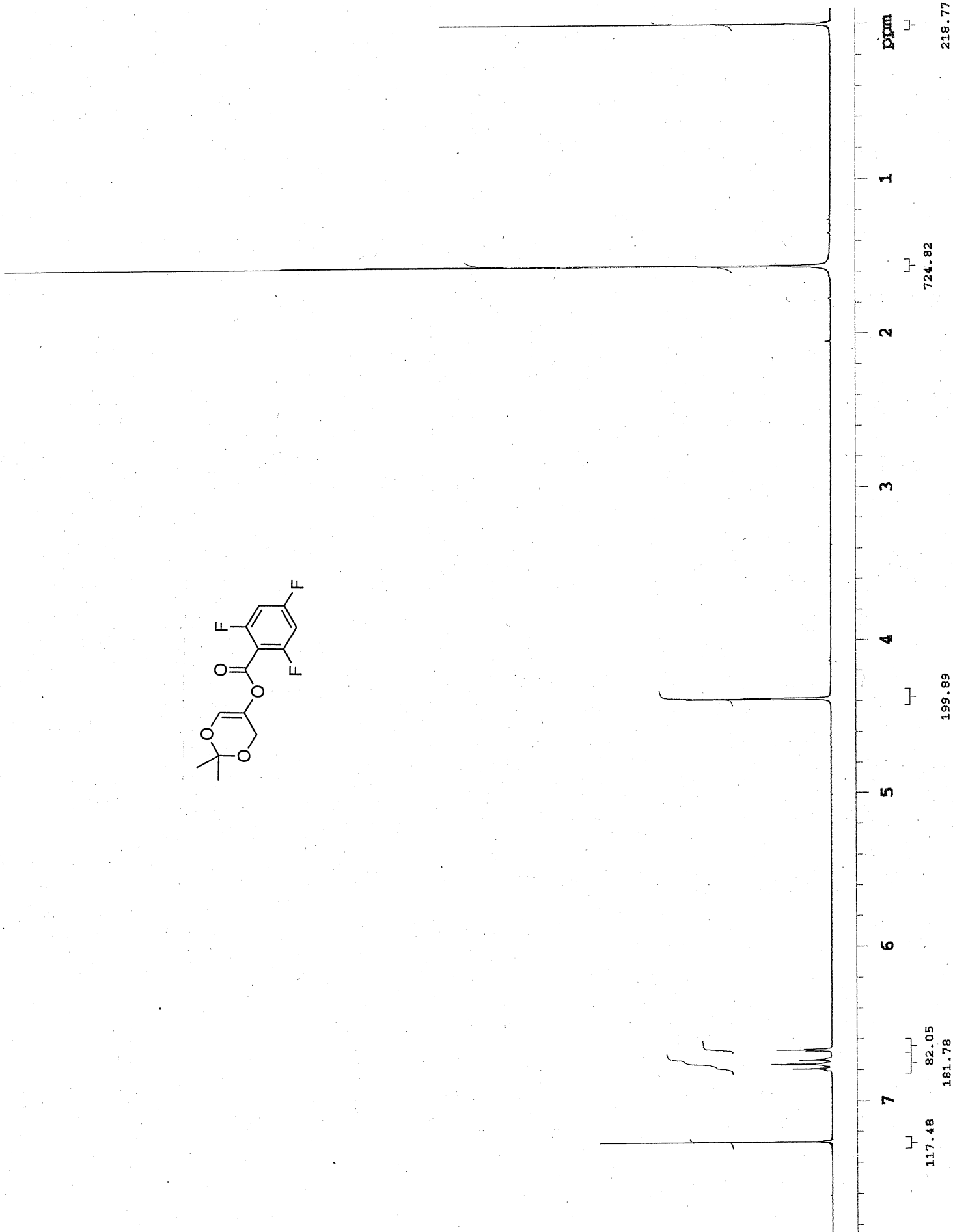
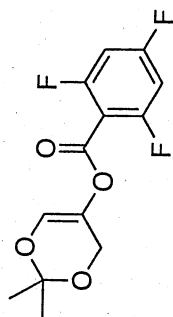
- (1) Funk, R. L.; Yost, K. J., III *J. Org. Chem.* **1996**, *61*, 2598.
- (2) Ishihara, K. Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505, 13079 (additions and corrections).
- (3) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229–2232.
- (4) Farkas, J.; Novak, J. J. K. *Collect. Czech. Chem. Commun.* **1960**, *25*, 1815–1823.
- (5) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726.
- (6) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A *J. Org. Chem.* **2004**, *69*, 3943–3949.
- (7) Crossley, A. W.; Gilling, C. *J. Chem. Soc., Trans.* **1910**, *97*, 2218–2223.
- (8) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791–3793.

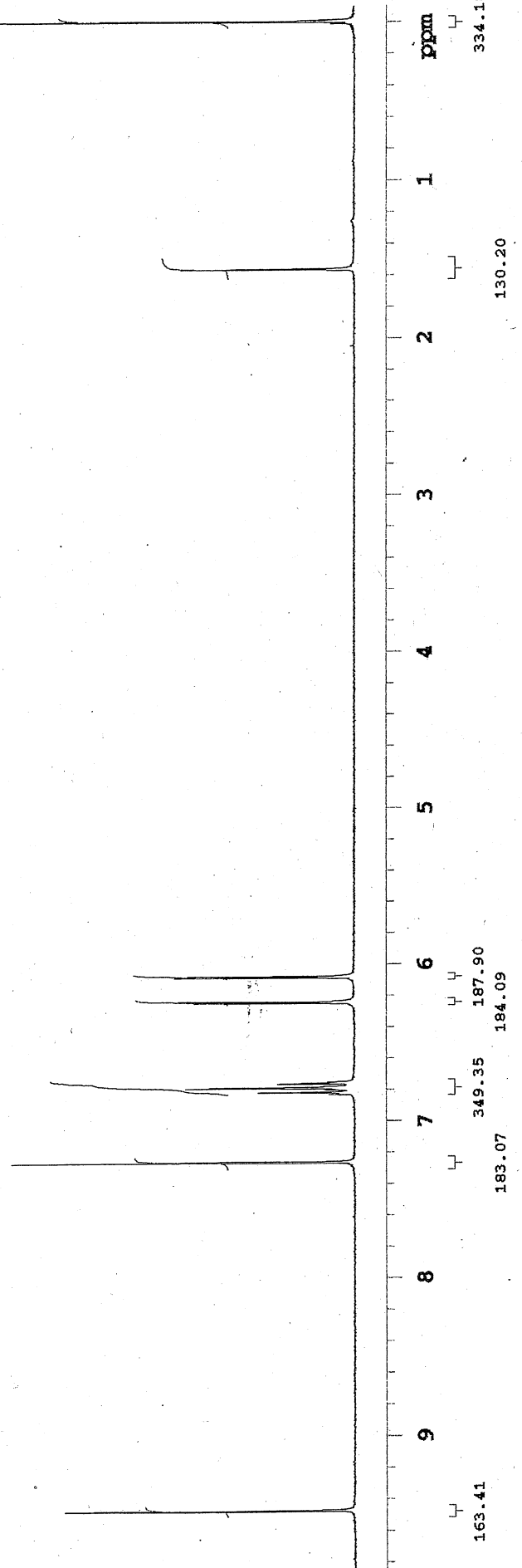
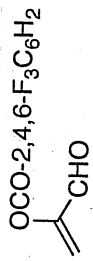


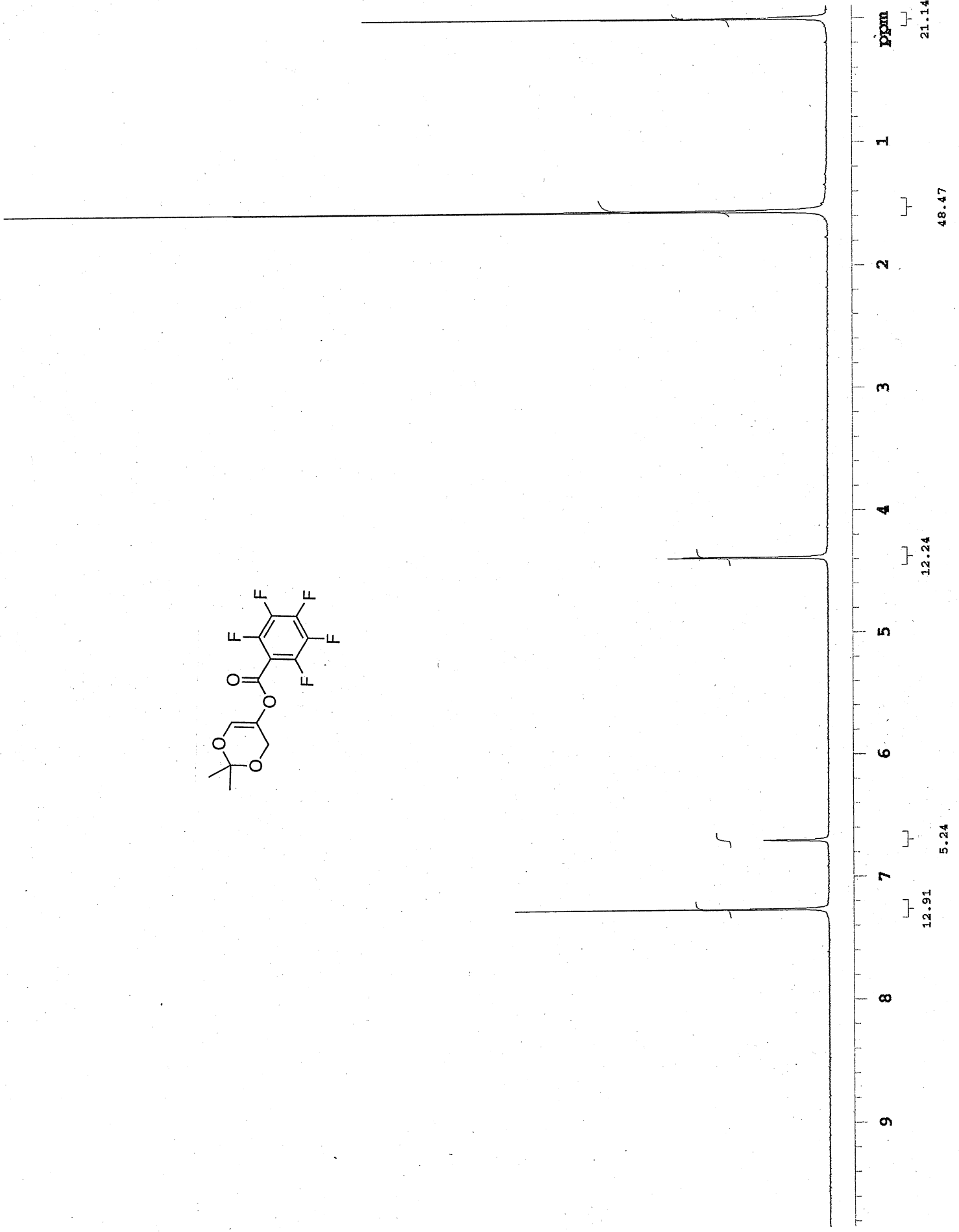
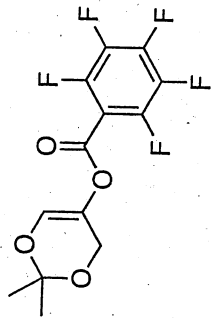


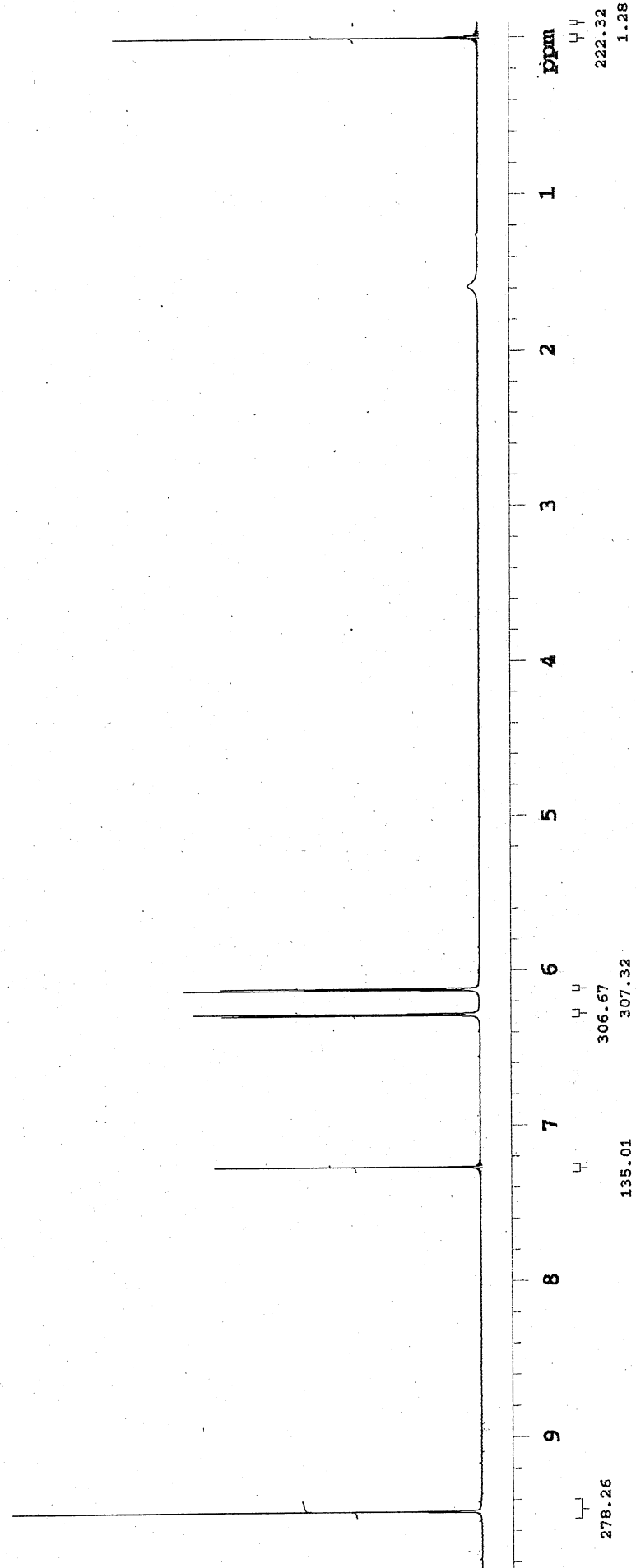
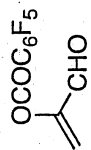


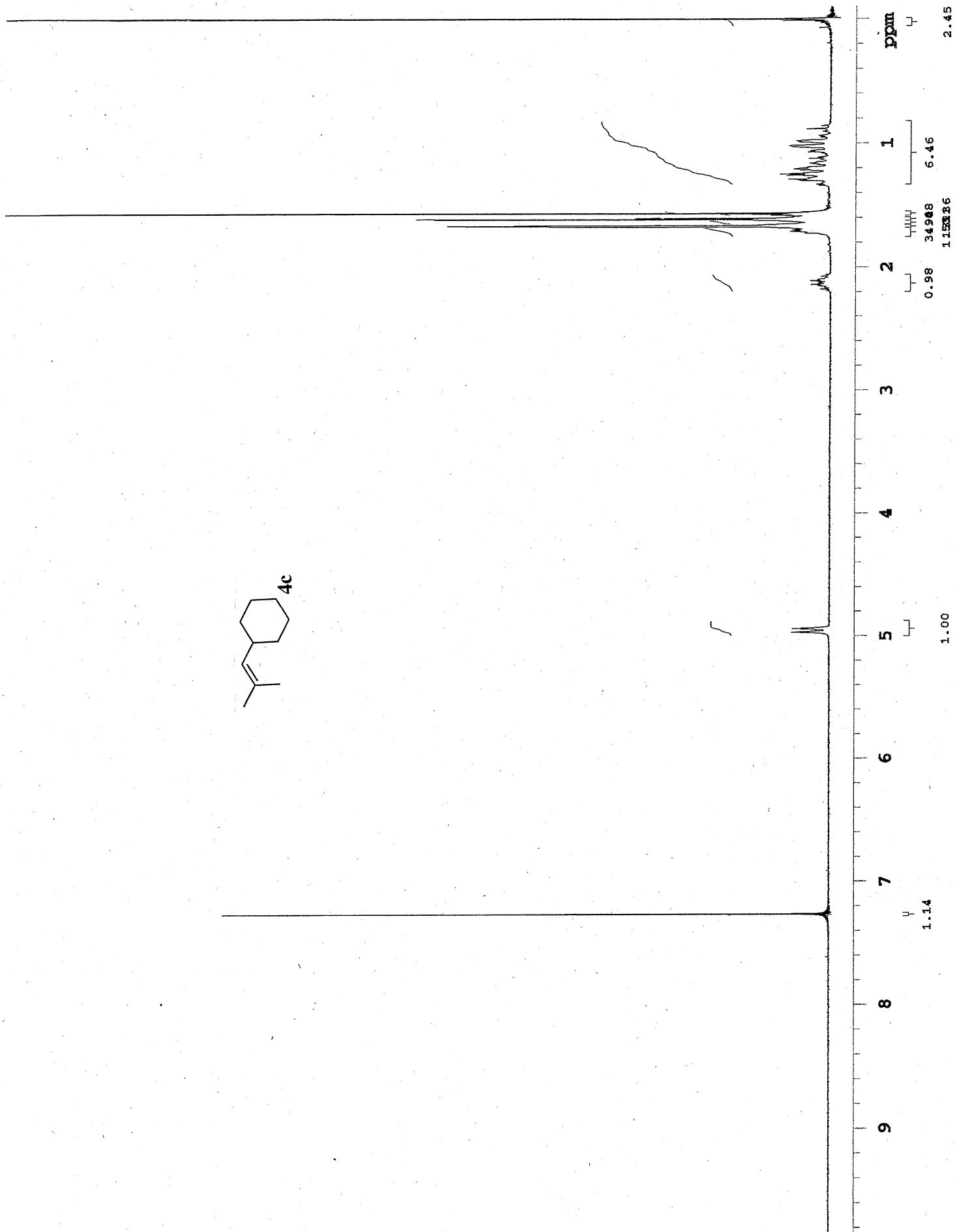
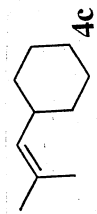


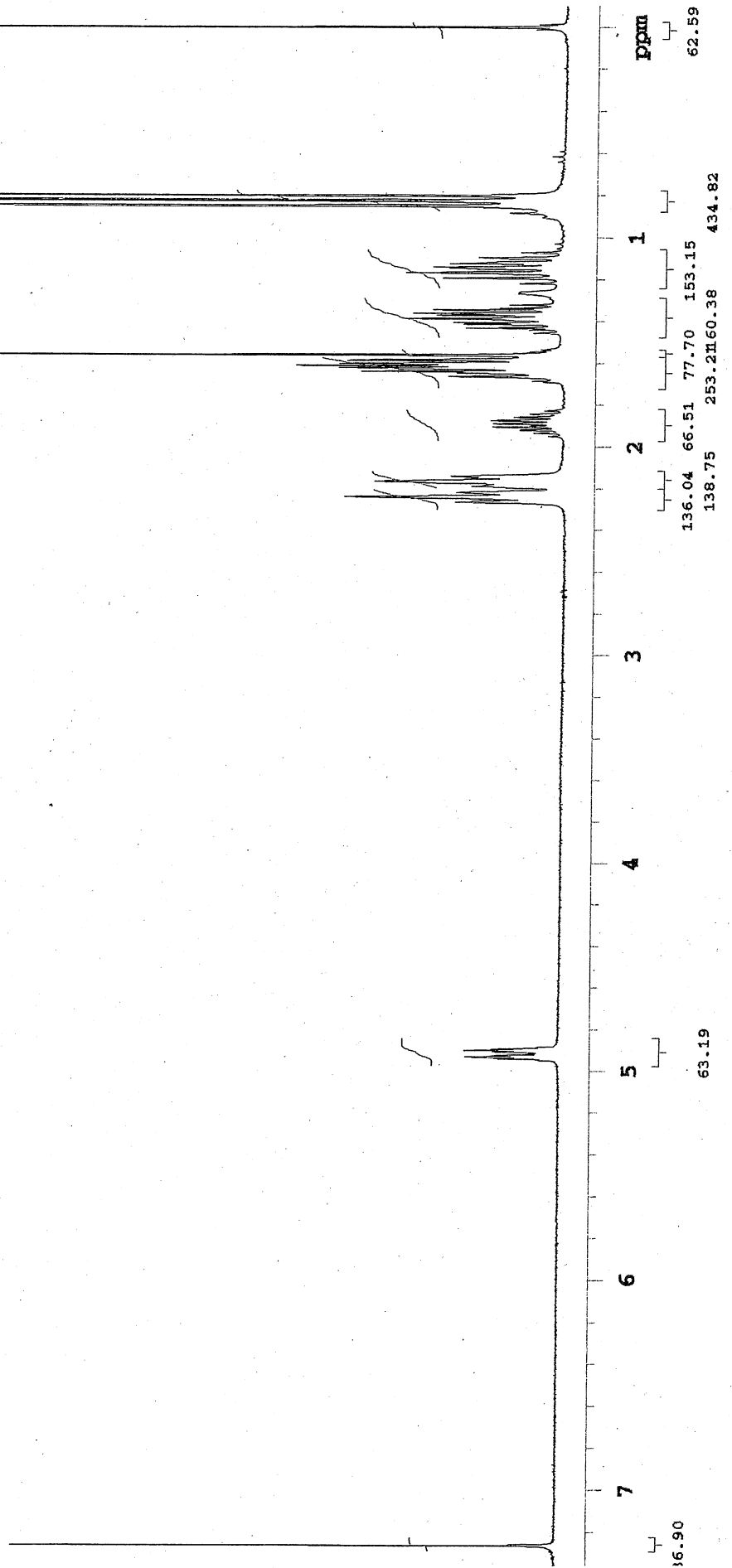
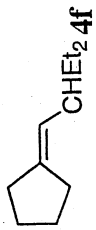


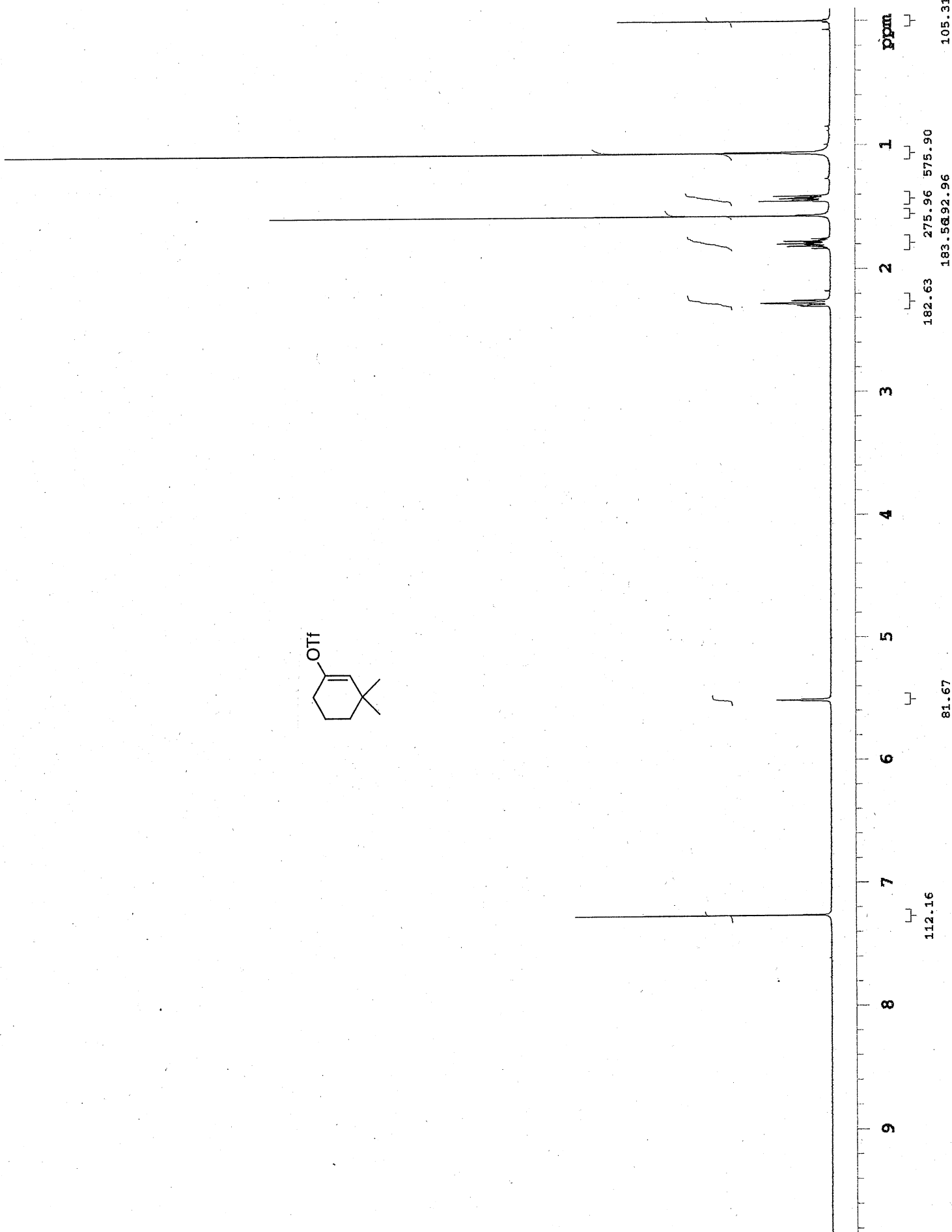
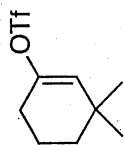


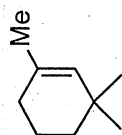




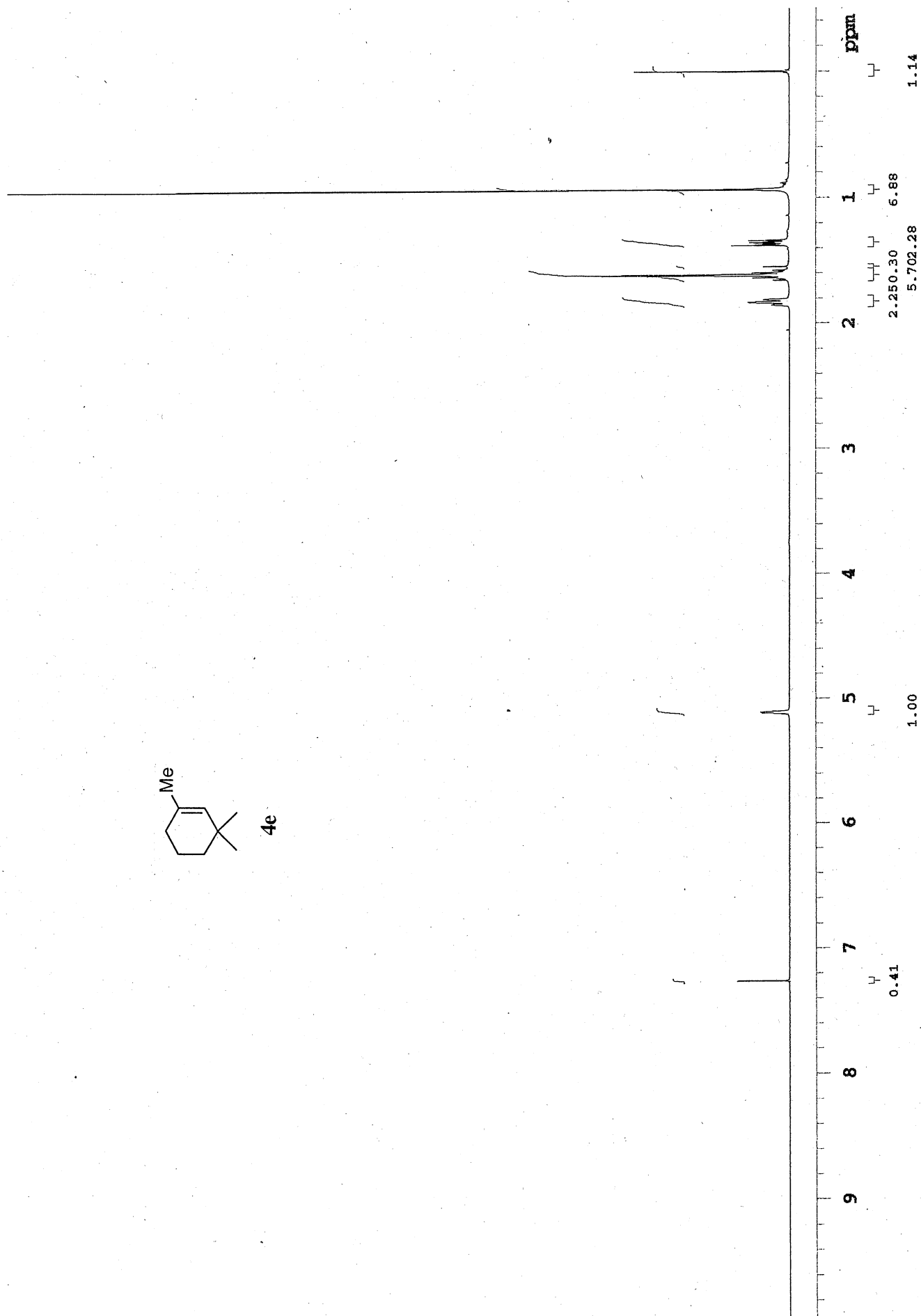


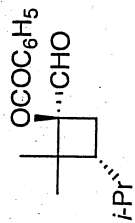




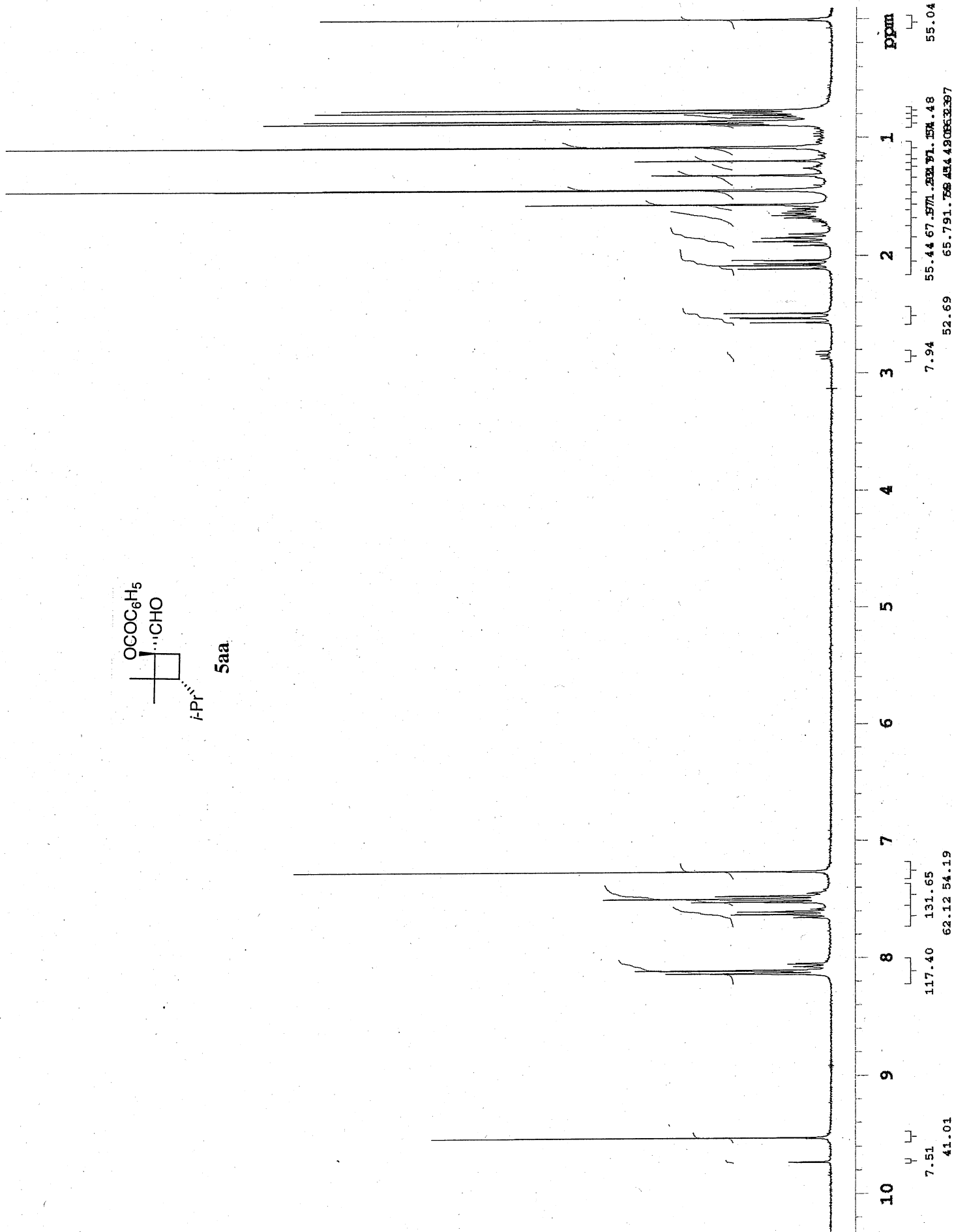


4e

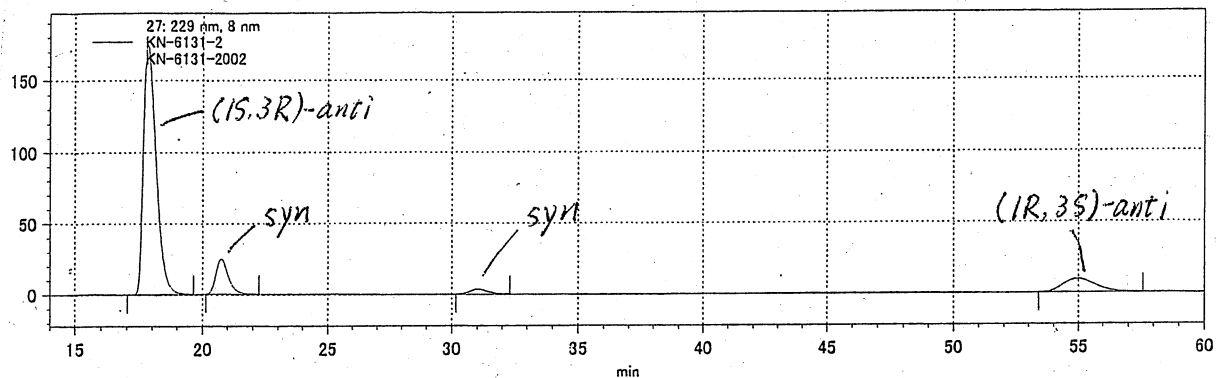




5aa



HPLC of optically active 5aa

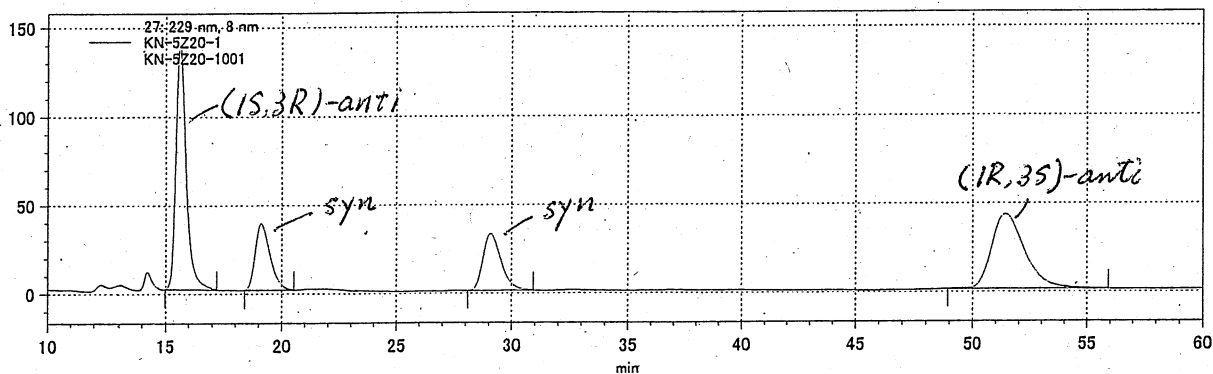


27: 229
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	27: 229 nm, 8 nm	17.825	0.99918	0.99841	0.99996	174712	82.26	6011570	75.89
2	27: 229 nm, 8 nm	20.741	0.99984	0.99990	0.99979	24722	11.64	859285	10.85
3	27: 229 nm, 8 nm	31.017	0.99752	0.99556	0.99949	3514	1.65	184716	2.33
4	27: 229 nm, 8 nm	54.971	0.99987	0.99985	0.99988	9431	4.44	866060	10.93

Total						212379	100.0 0	7921632	100.00
-------	--	--	--	--	--	--------	------------	---------	--------

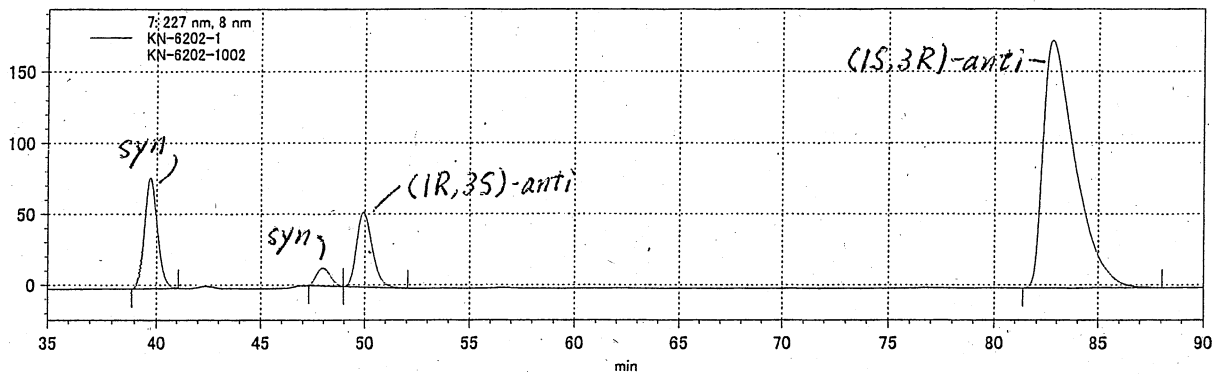
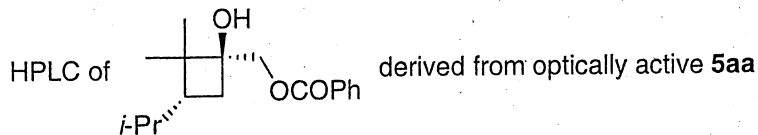
HPLC of (±)-5aa



27: 229
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	27: 229 nm, 8 nm	15.623	0.99595	0.99400	0.99791	137690	55.19	4289075	36.00
2	27: 229 nm, 8 nm	19.115	0.99990	0.99991	0.99989	37624	15.08	1697179	14.24
3	27: 229 nm, 8 nm	29.065	0.99976	0.99974	0.99978	32104	12.87	1743426	14.63
4	27: 229 nm, 8 nm	51.404	0.98954	0.97949	0.99959	42068	16.86	4184797	35.12

Total						249486	100.0 0	11914477	100.00
-------	--	--	--	--	--	--------	------------	----------	--------



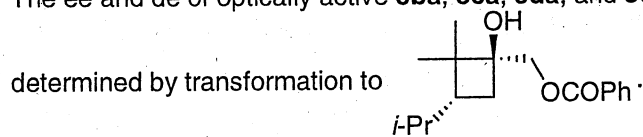
7: 227

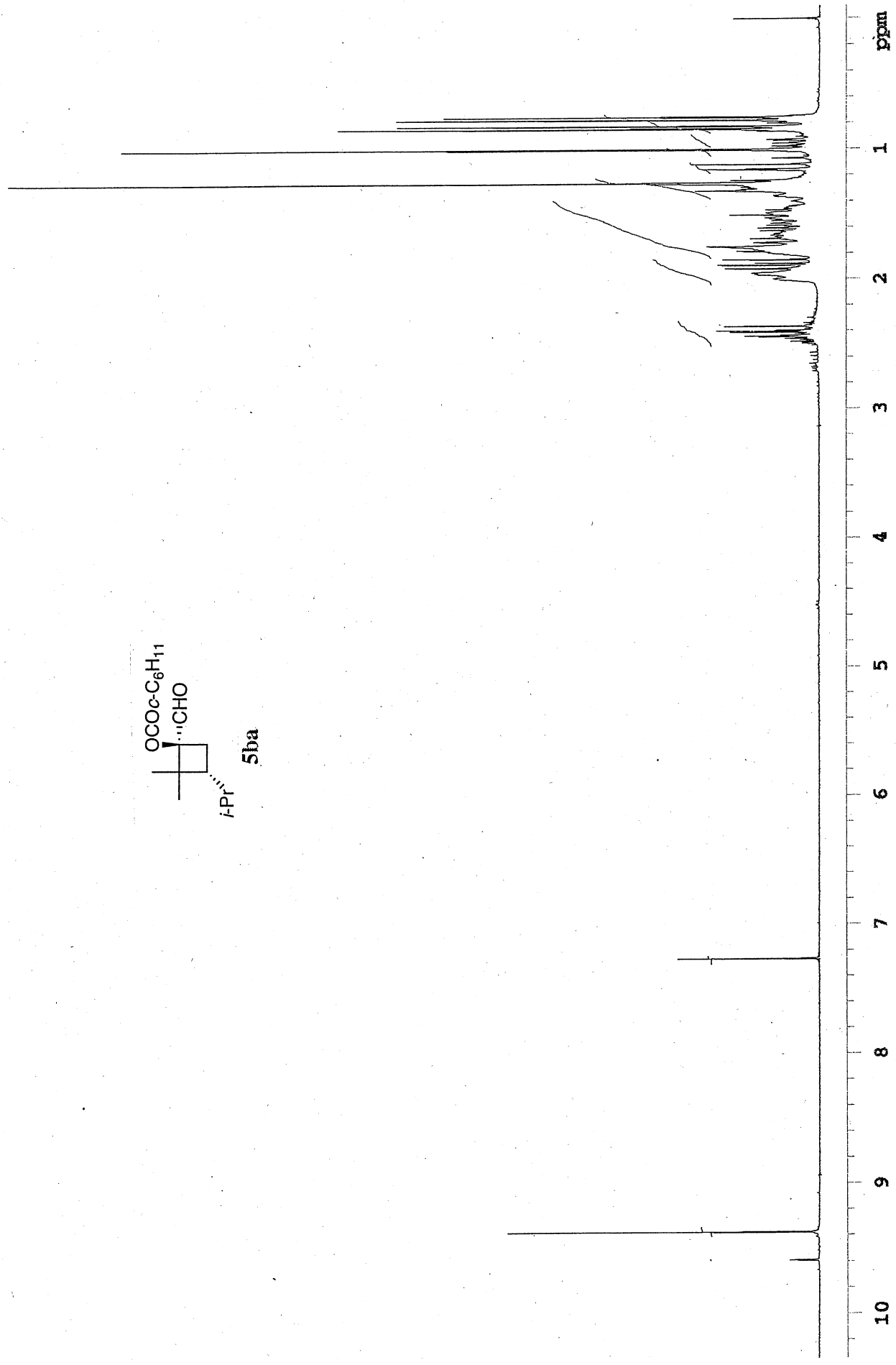
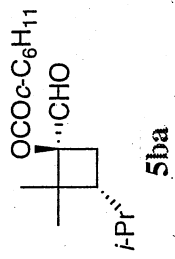
nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティ	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	7: 227 nm, 8 nm	39.686	0.99999	0.99999	1.00000	78100	24.62	3352929	13.06
2	7: 227 nm, 8 nm	47.942	0.99949	0.99906	0.99992	12489	3.94	571949	2.23
3	7: 227 nm, 8 nm	49.922	0.99998	0.99999	0.99997	52903	16.67	2809273	10.94
4	7: 227 nm, 8 nm	82.759	1.00000	1.00000	0.99999	173791	54.77	18941506	73.77

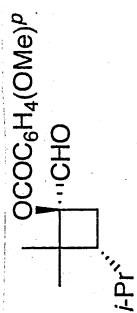
Total						317283	100.0 0	25675657	100.00
-------	--	--	--	--	--	--------	------------	----------	--------

The ee and de of optically active **5ba**, **5ca**, **5da**, and **5ea** were also

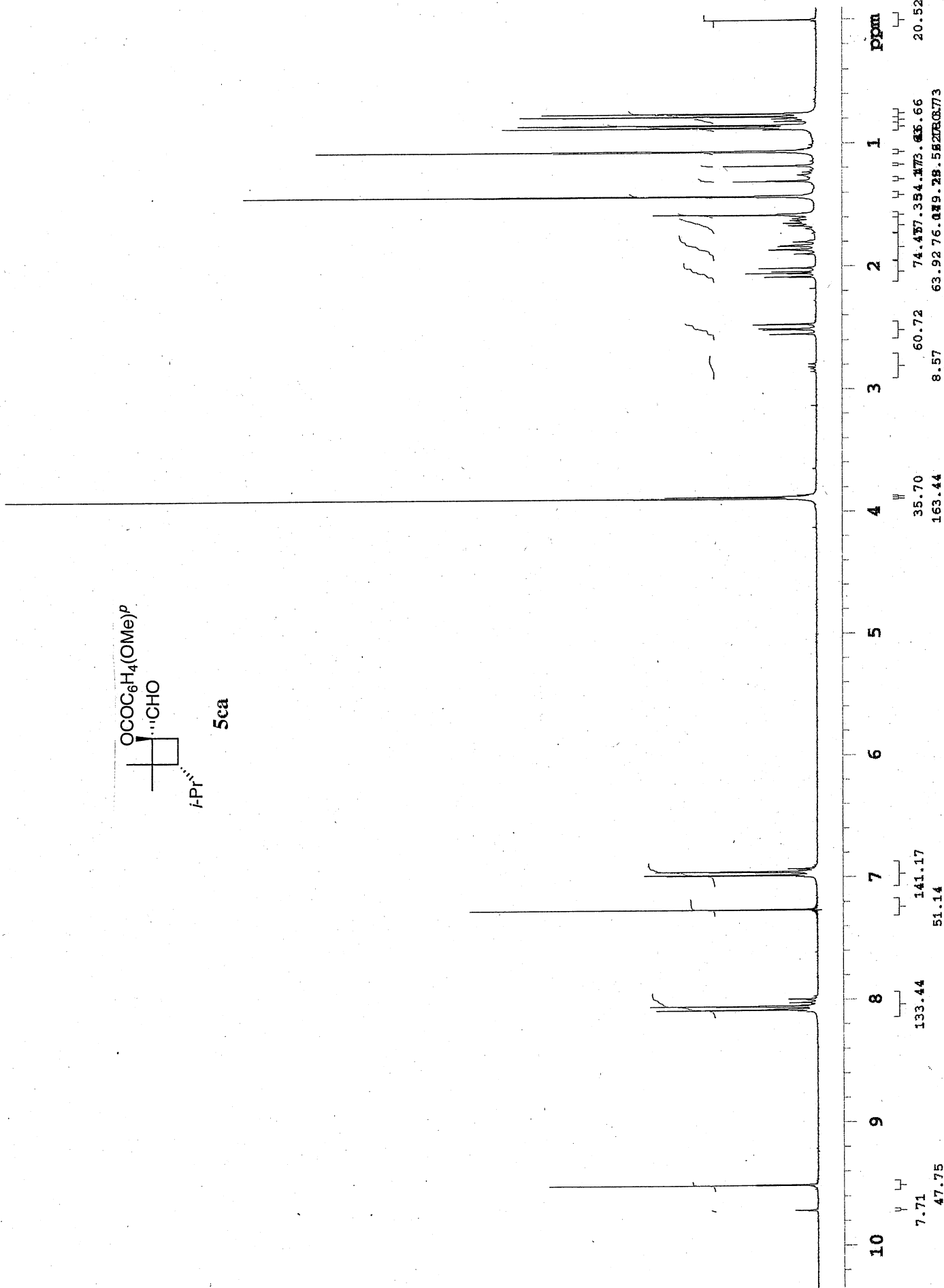


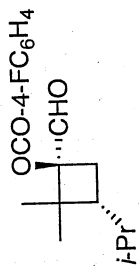


Chemical Shift (ppm)
195.38
386.35
361.57
528.24
71.88
71.61
107.83
10.28
4.88
33.47

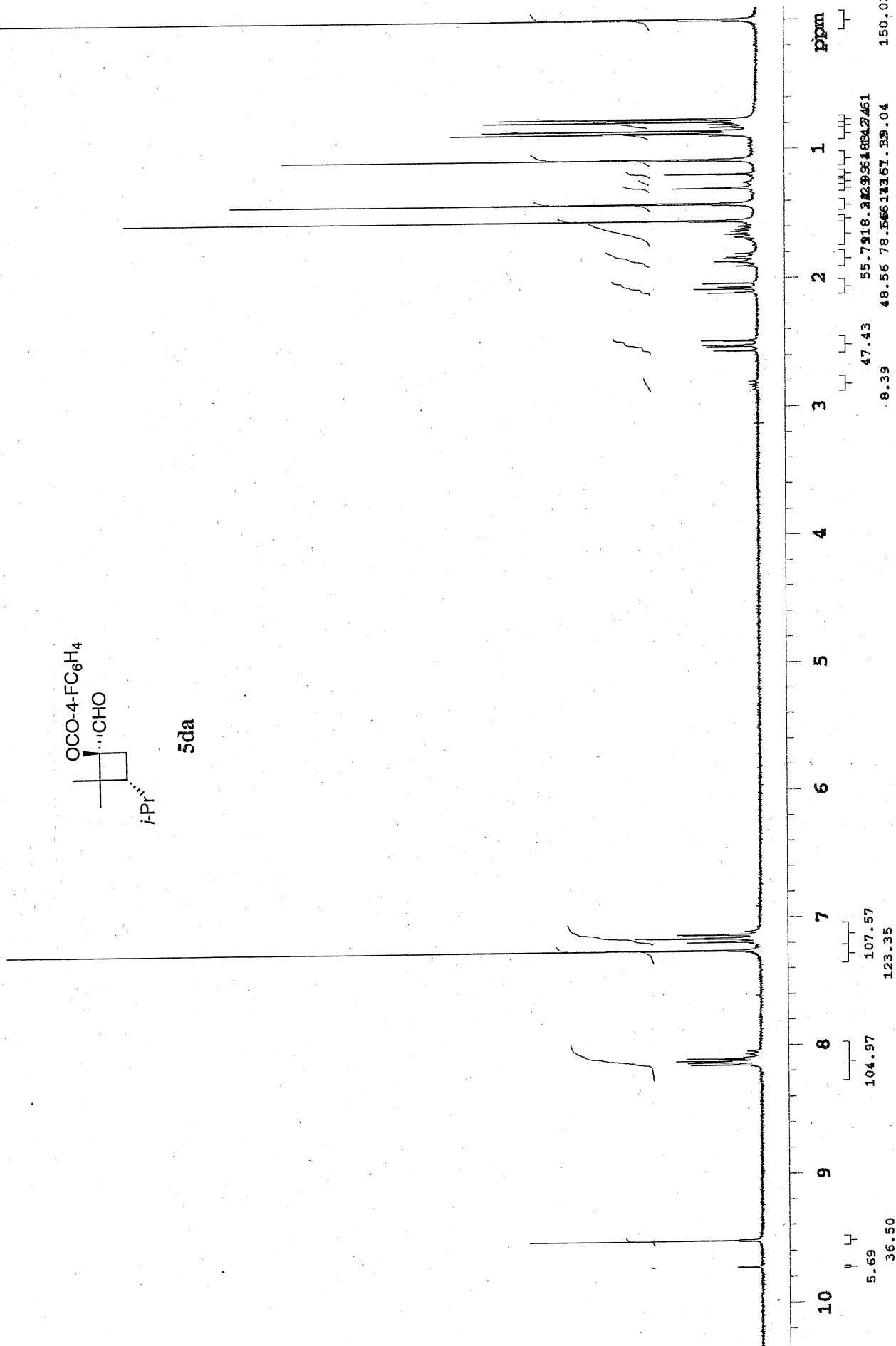


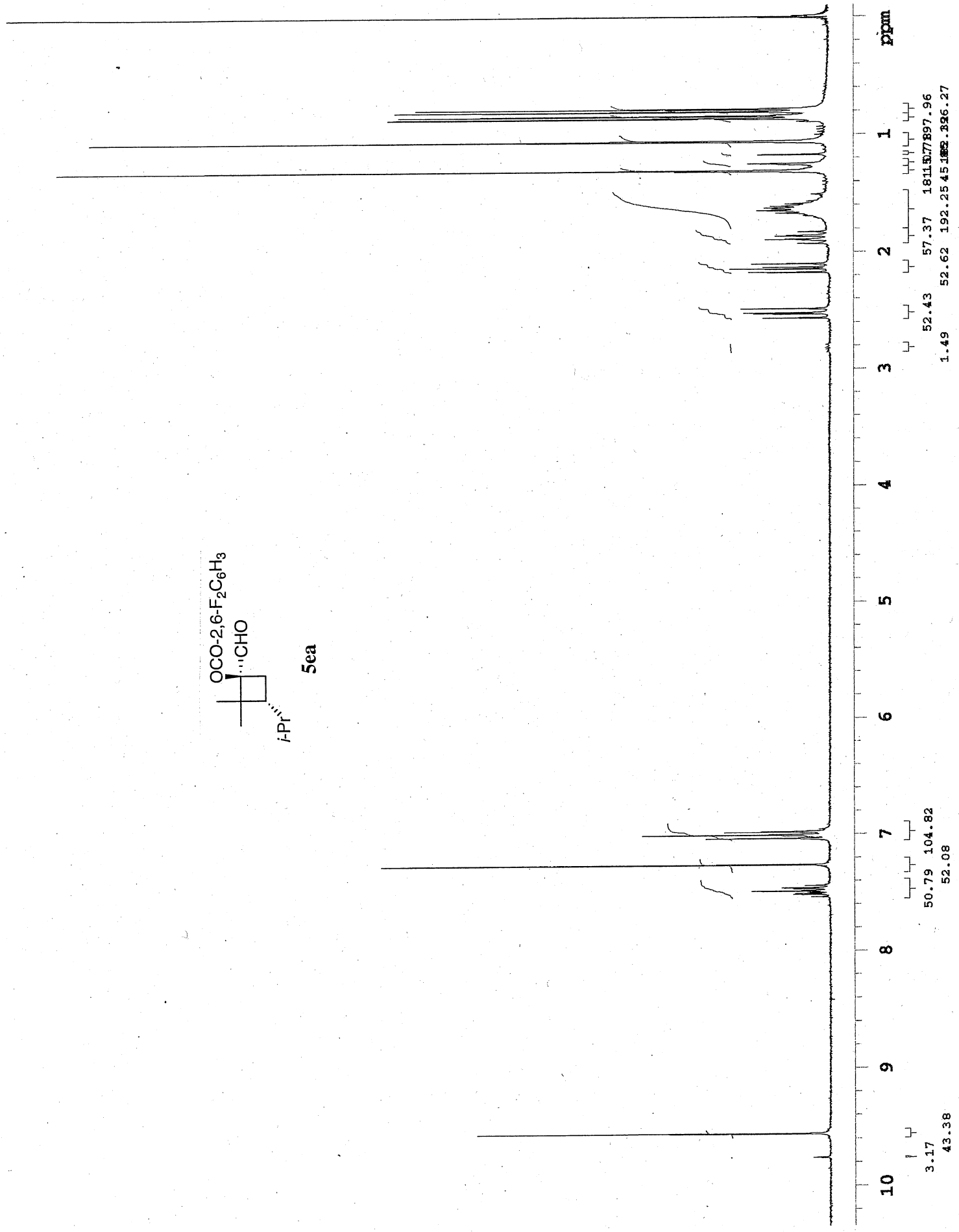
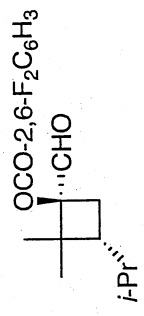
5ca

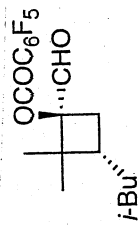




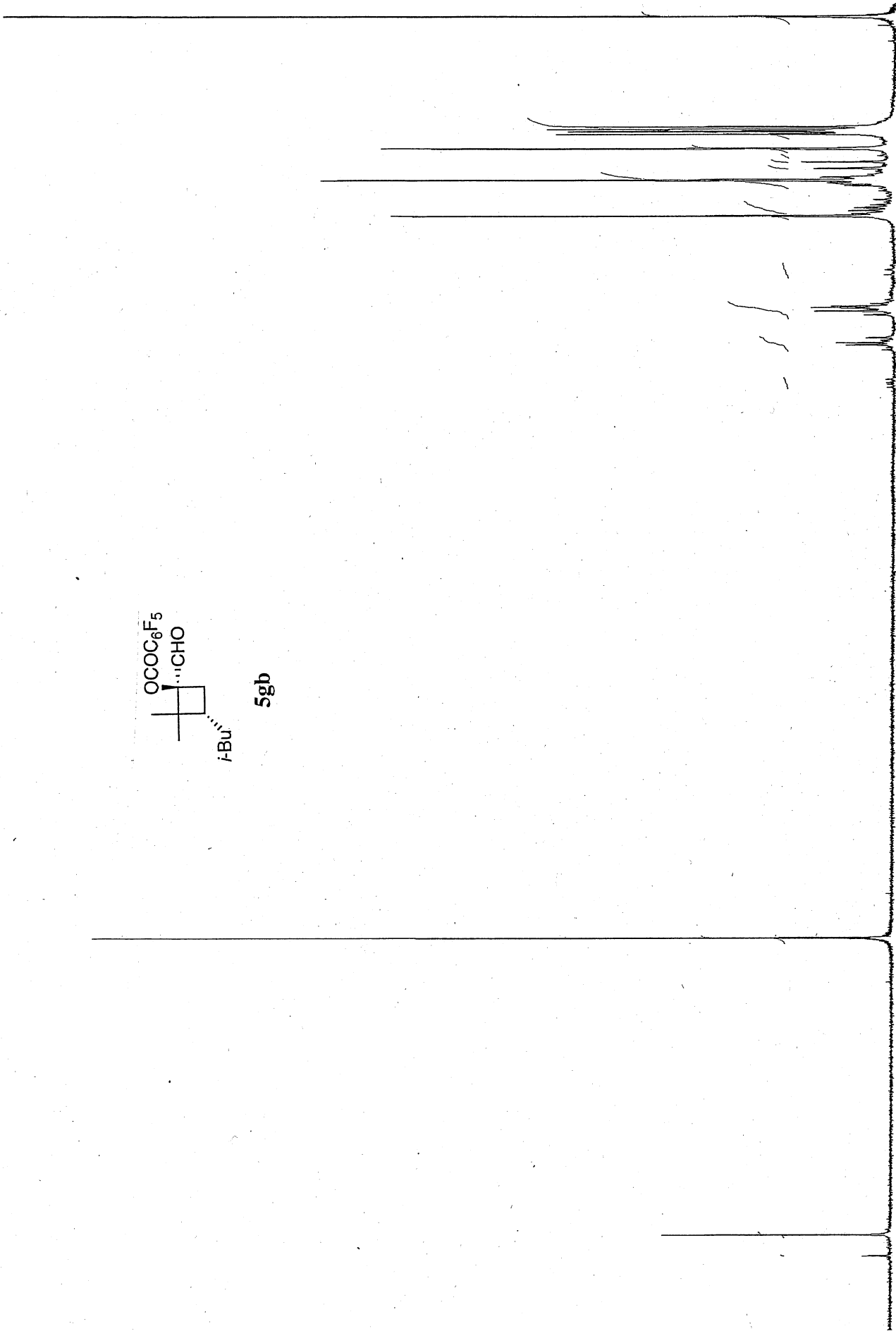
5da





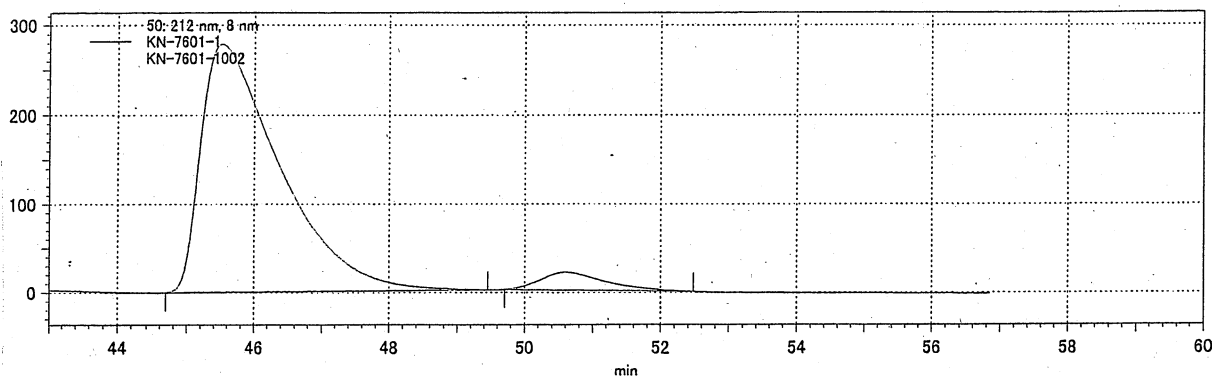


5gb



Peak #	Chemical Shift (ppm)
1	179.98
2	104.73
3	101.74
4	73.49
5	6.71
6	4.21
7	31.28
8	31.28
9	31.28
10	31.28

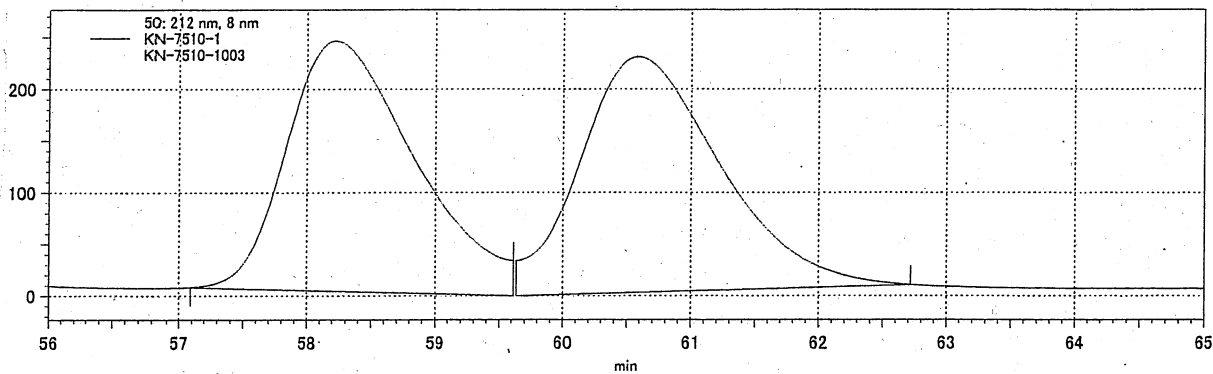
HPLC of optically active 5gb



50: 212
nm, 8 nm
成分名

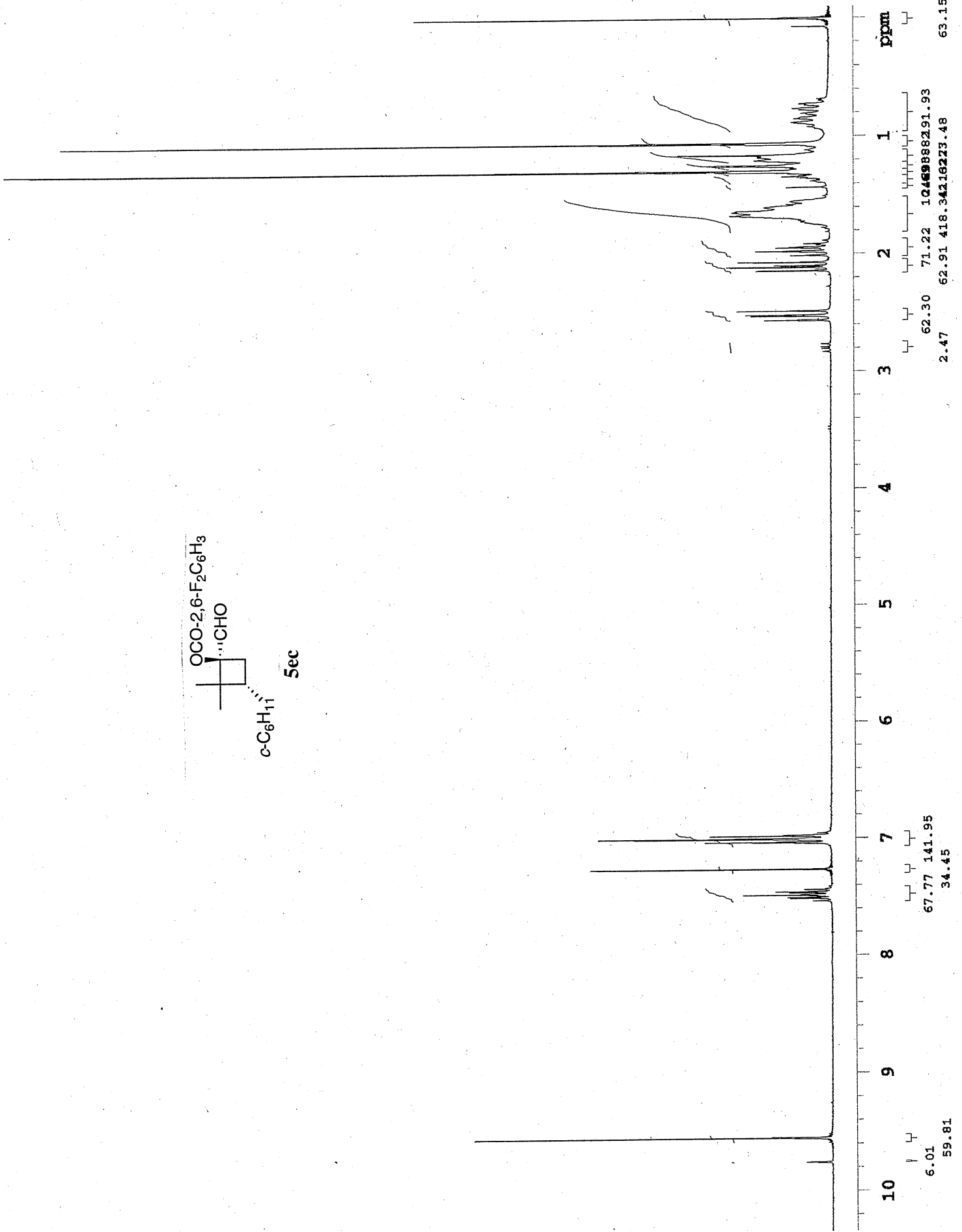
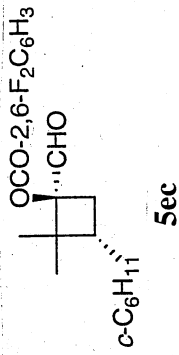
チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	45.513	0.99996	0.99997	0.99995	278370	93.21	22815936	94.47
2	50.585	0.99934	0.99941	0.99928	20276	6.79	1336304	5.53
Total					298645	100.00	24152240	100.00

HPLC of (±)-5gb

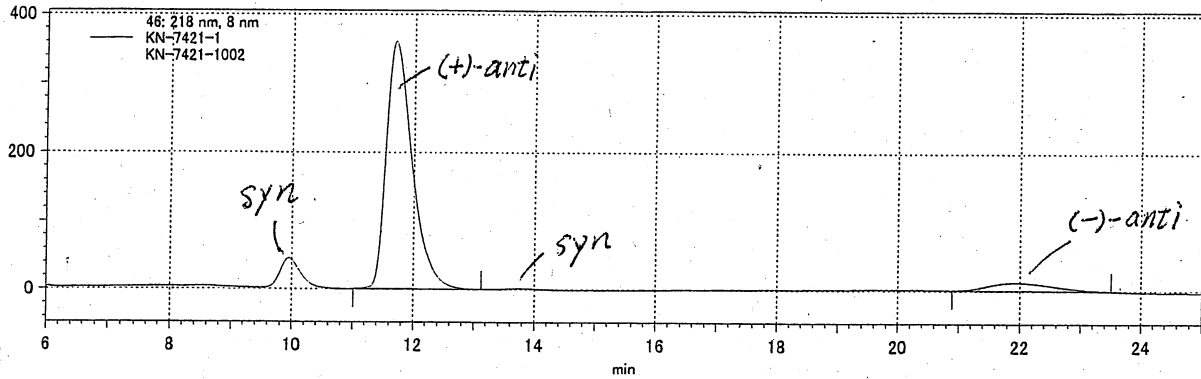


50: 212
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	58.217	0.99996	0.99993	0.99999	241922	51.49	16838637	49.21
2	60.580	0.99998	0.99998	0.99998	227961	48.51	17379071	50.79
Total					469882	100.00	34217708	100.00



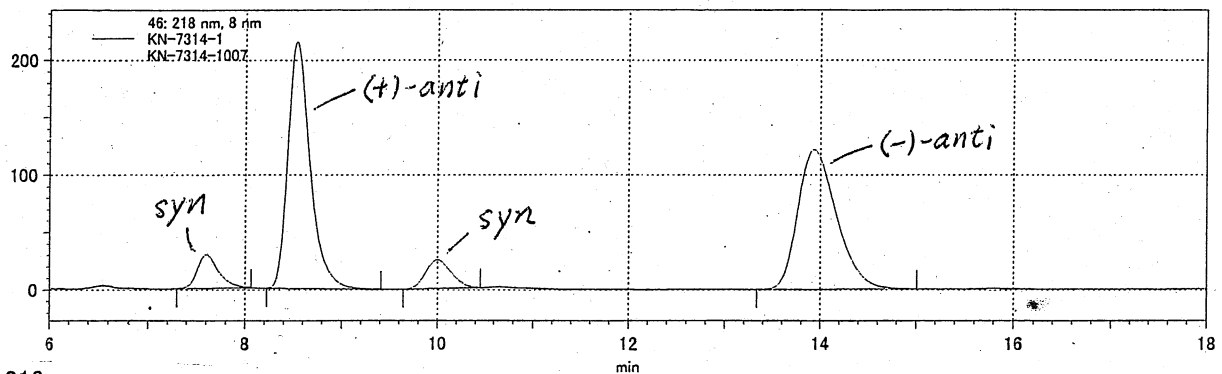
HPLC of optically active 5ec



46: 218
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	46: 218 nm, 8 nm	11.682	0.99835	0.99713	0.99958	360157	96.81	10721044	92.49
2	46: 218 nm, 8 nm	21.901	0.99905	0.99874	0.99935	11869	3.19	870817	7.51
Total					372025	100.0 0	11591861	100.00	

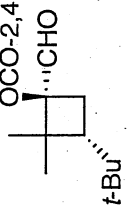
HPLC of (±)-5ec



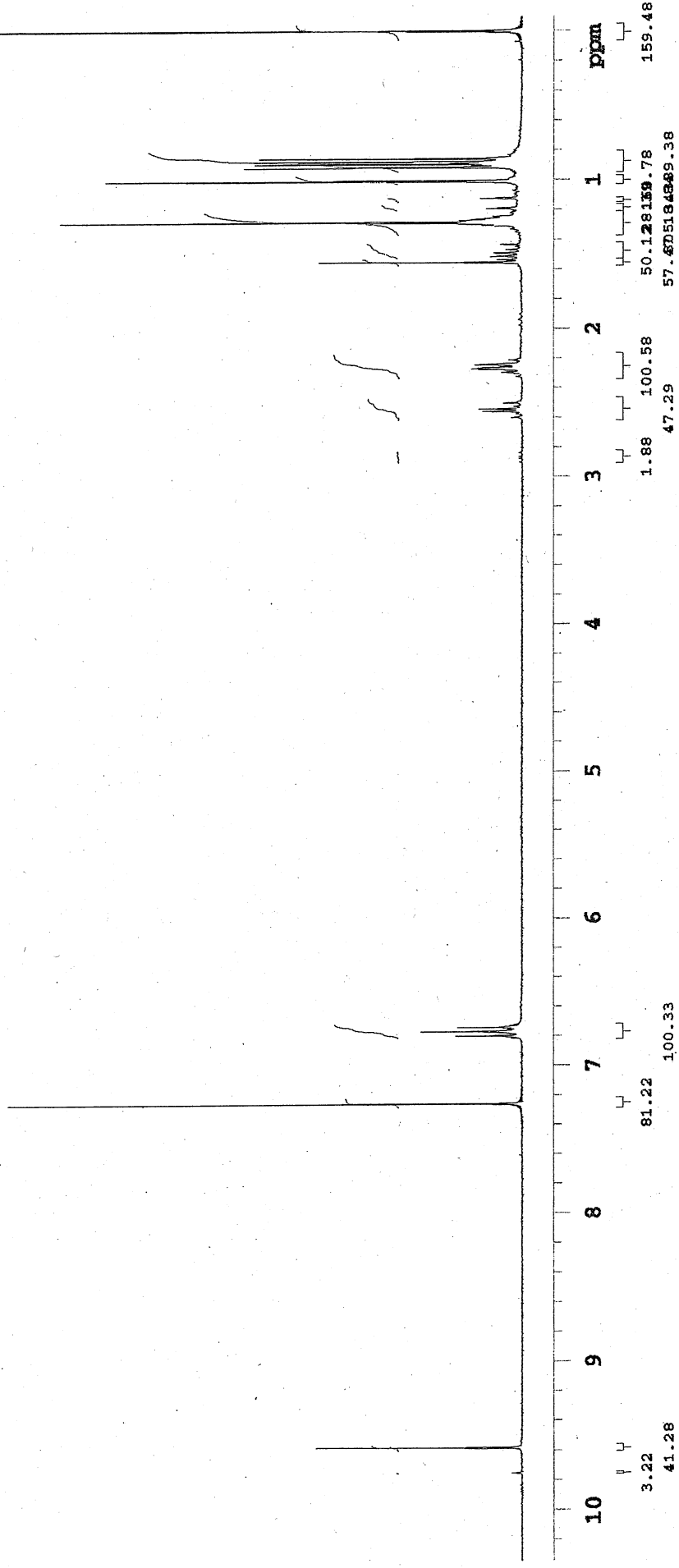
46: 218
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	46: 218 nm, 8 nm	7.594	0.99805	0.99642	0.99968	29432	7.53	447473	5.75
2	46: 218 nm, 8 nm	8.528	0.99986	0.99988	0.99983	214965	55.00	3425698	44.04
3	46: 218 nm, 8 nm	9.991	0.99943	0.99889	0.99998	24968	6.39	469422	6.04
4	46: 218 nm, 8 nm	13.926	0.99983	0.99973	0.99993	121454	31.08	3435409	44.17
Total					390819	100.0 0	7778002	100.00	

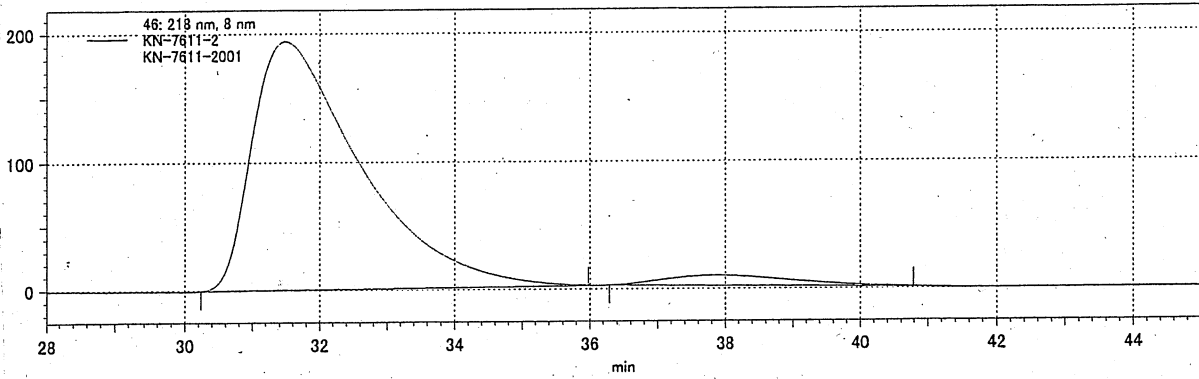
OCO-2,4,6-F₃C₆H₂



5fd



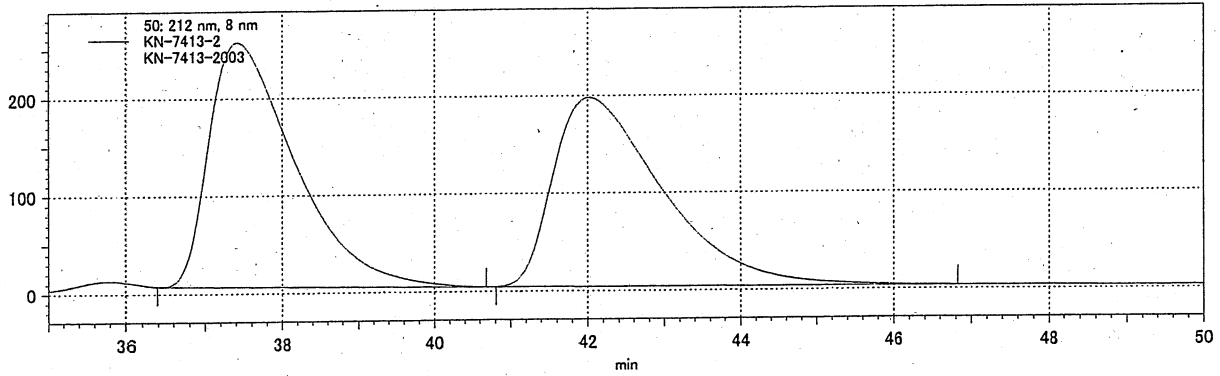
HPLC of optically active 5fd



46: 218
nm, 8 nm
成分名

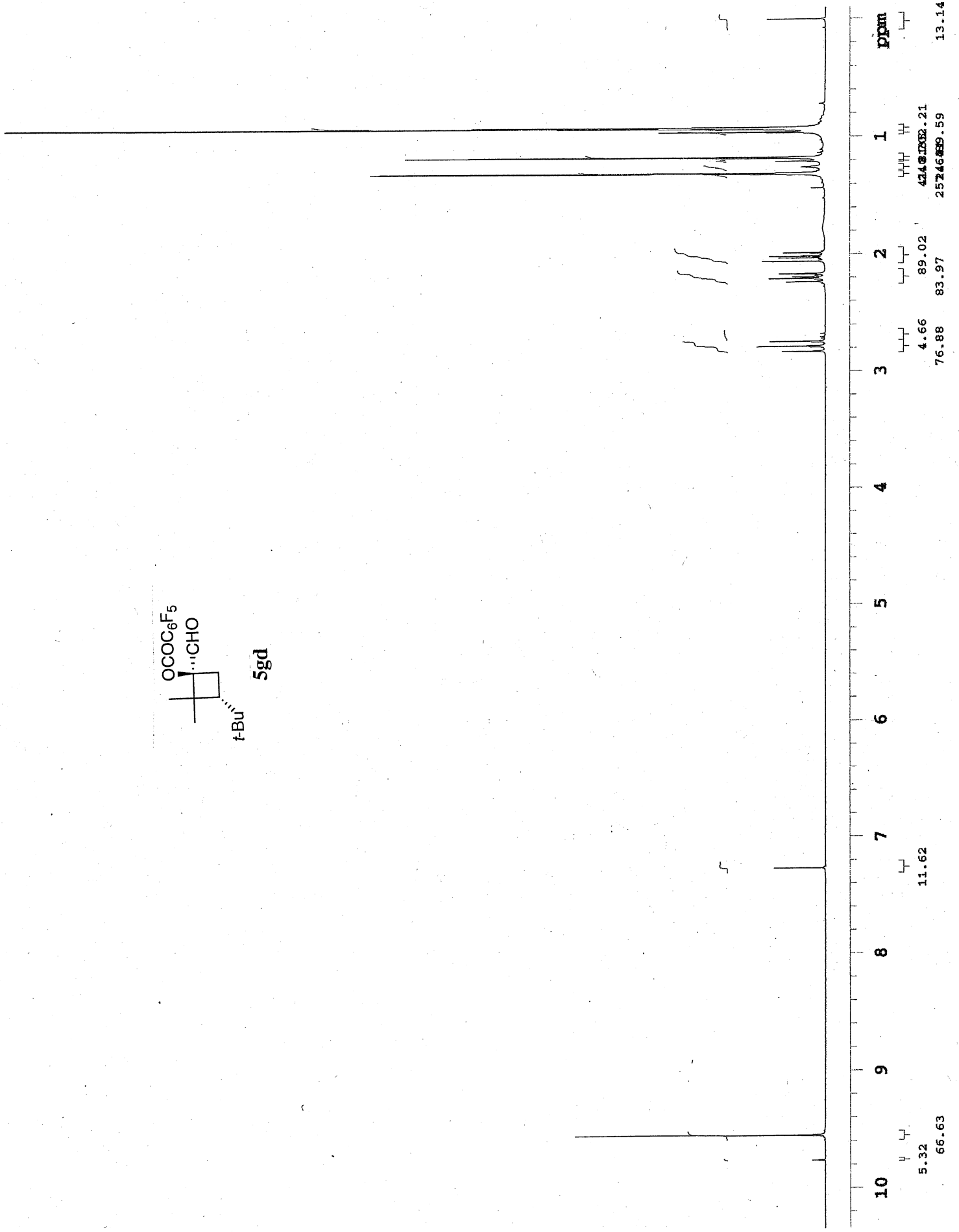
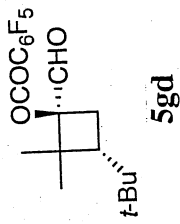
成分名	チャンネル	保持時間	3点ピーク ヒュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	46: 218 nm, 8 nm	31.483	0.99921	0.99930	0.99912	193716	96.02	21777302	95.41
2	46: 218 nm, 8 nm	37.831	0.99888	0.99857	0.99918	8024	3.98	1046531	4.59
Total						201740	100.00	22823832	100.00

HPLC of (±)-5fd

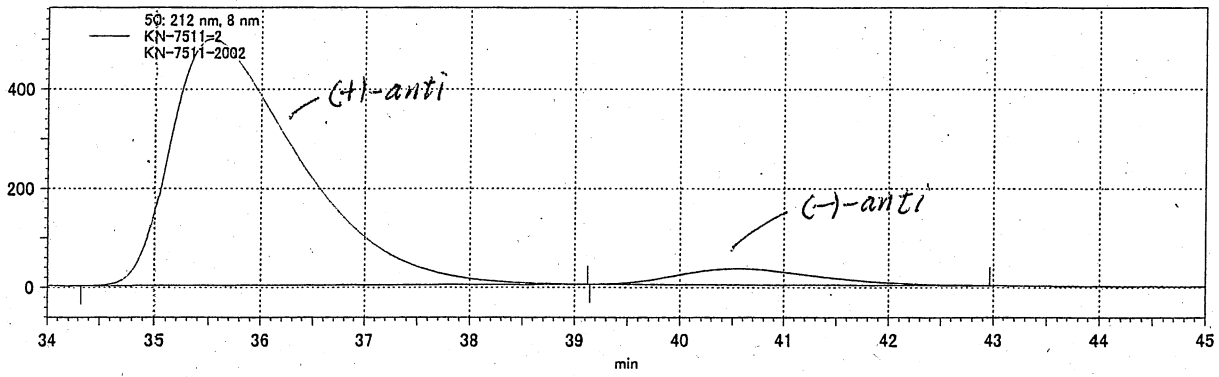


50: 212
nm, 8 nm
成分名

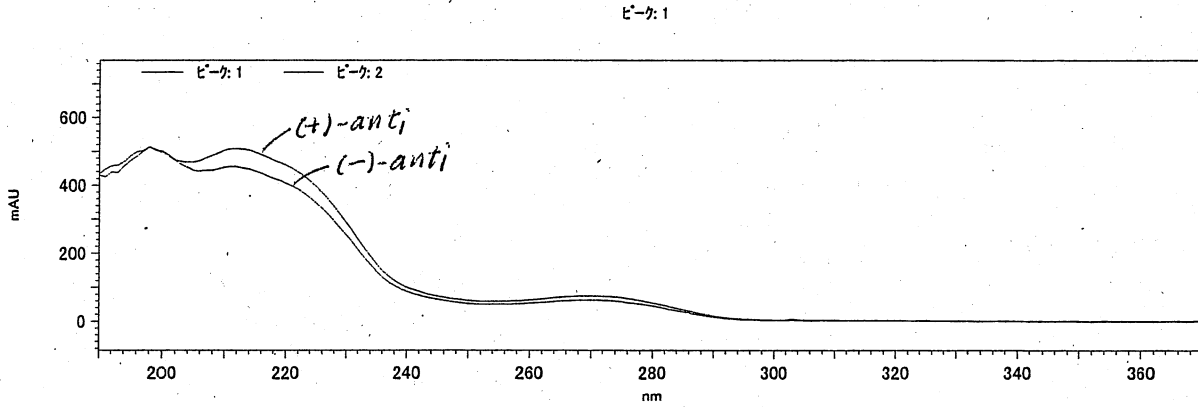
成分名	チャンネル	保持時間	3点ピーク ヒュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	50: 212 nm, 8 nm	37.411	0.99998	0.99998	0.99999	250450	56.42	19493246	50.58
2	50: 212 nm, 8 nm	42.010	0.99996	0.99998	0.99993	193418	43.58	19047482	49.42
Total						443868	100.00	38540729	100.00



HPLC of optically active 5gd

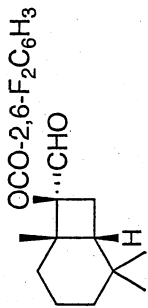


UV spectra of 5gd (enantiomers)

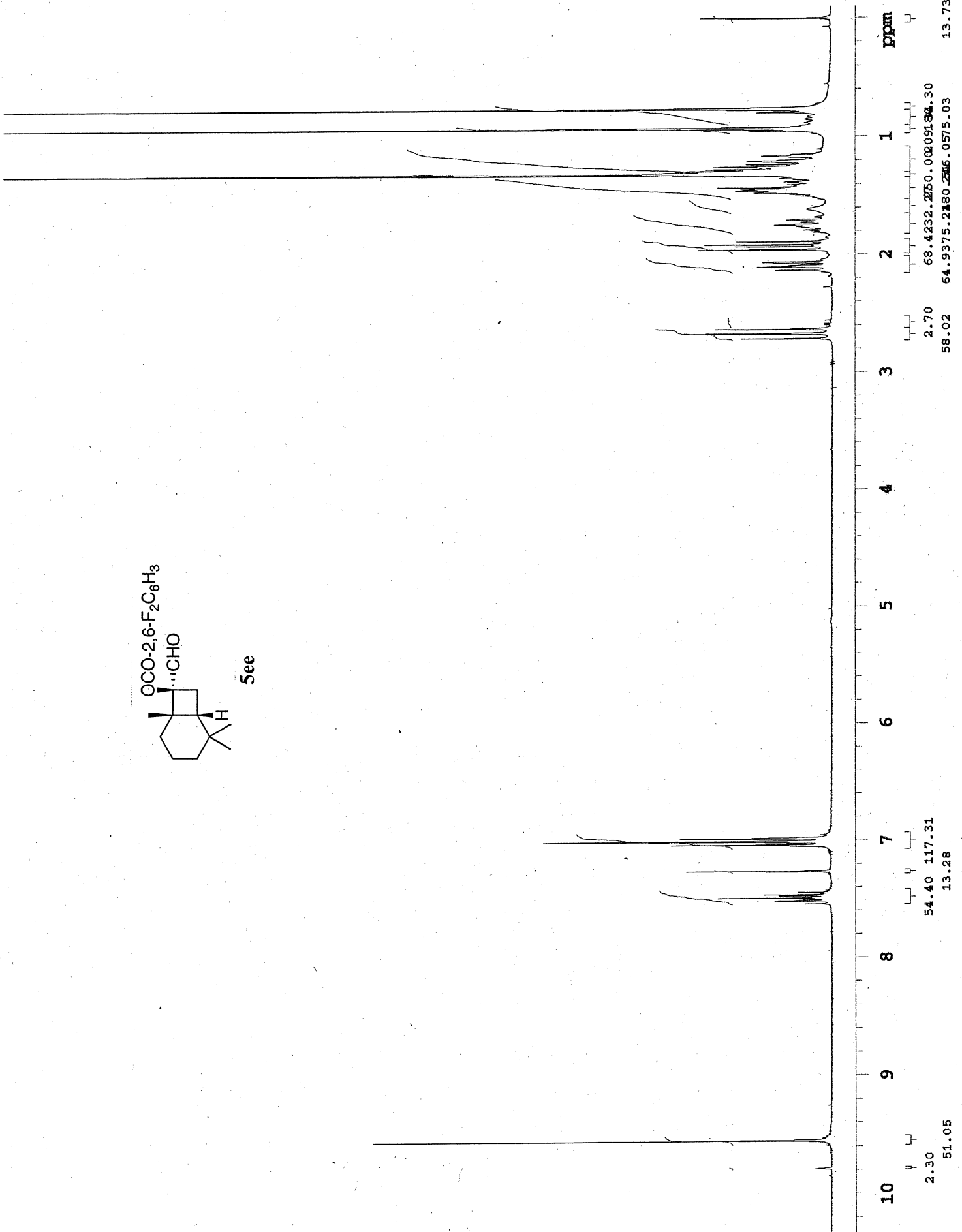


50: 212
nm, 8 nm
成分名

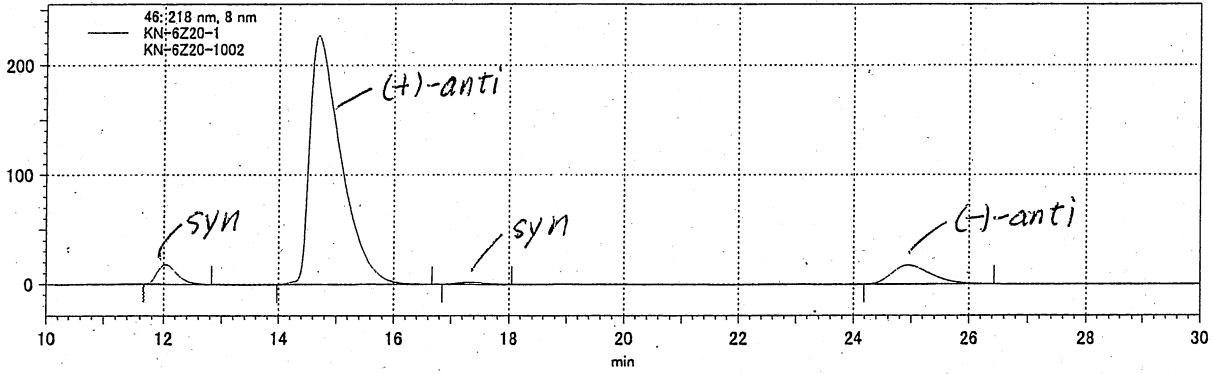
成分名	チャンネル	保持時間	3点ピーク ピュリティー	アッスローフ 類似度	ダウンスローフ 類似度	高さ	高さ %	面積	面積%
1	50: 212 nm, 8 nm	35.520	0.99995	0.99994	0.99997	496727	93.82	41991661	93.28
2	50: 212 nm, 8 nm	40.538	0.99990	0.99993	0.99987	32705	6.18	3024034	6.72
Total						529432	100.00	45015695	100.00



See



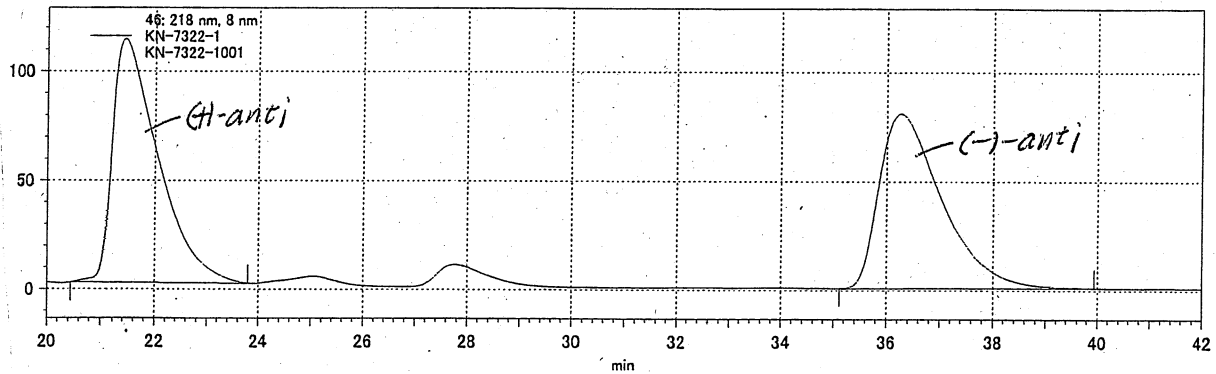
HPLC of optically active 5ee



46: 218
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	46: 218 nm, 8 nm	12.025	0.99965	0.99958	0.99973	18041	6.81	429451	4.34
2	46: 218 nm, 8 nm	14.688	0.99069	0.98159	0.99980	227381	85.84	8555191	86.52
3	46: 218 nm, 8 nm	17.305	0.98136	0.98645	0.97628	1947	0.74	63610	0.64
4	46: 218 nm, 8 nm	24.938	0.99935	0.99906	0.99963	17509	6.61	839969	8.49
Total					264878	100.0 0	9888220	100.00	

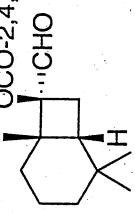
HPLC of (±)-5ee



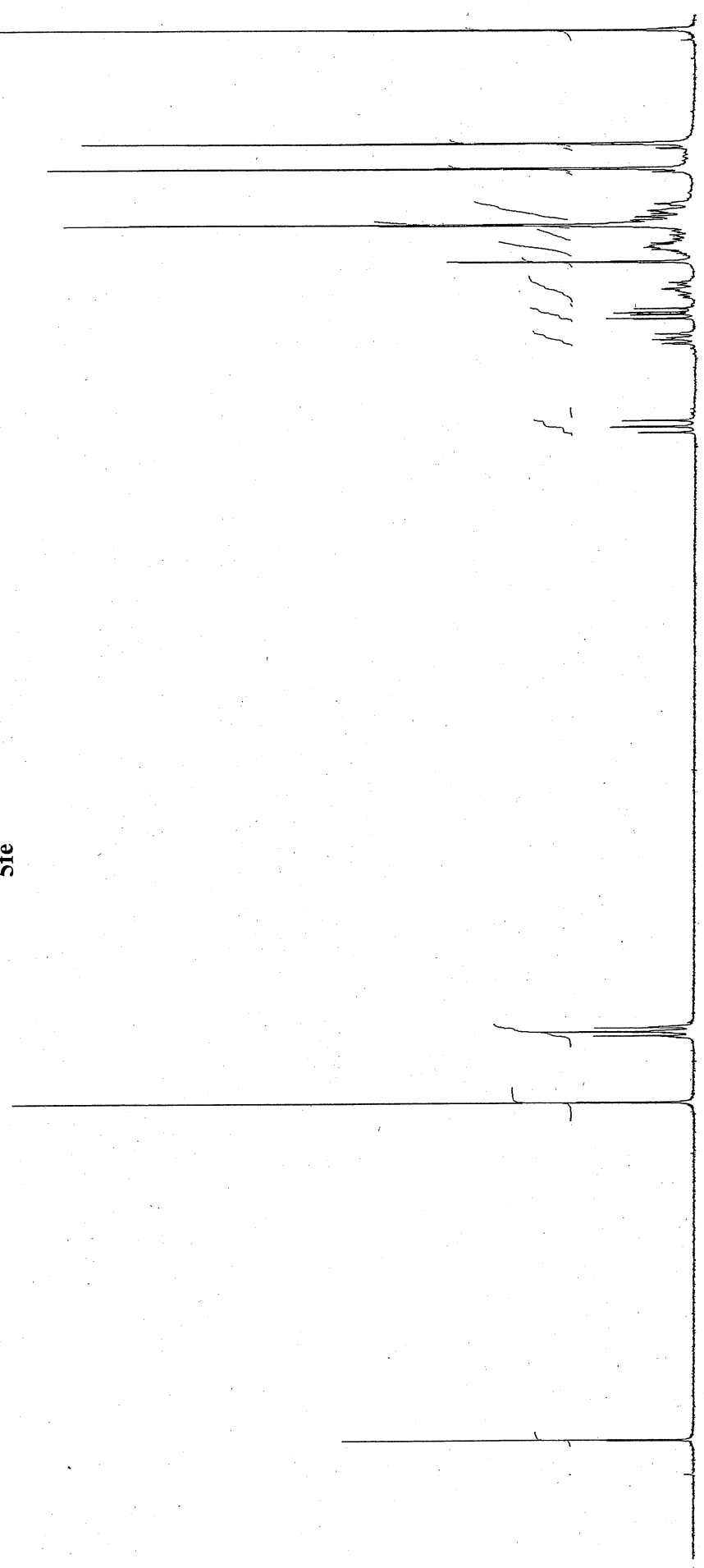
46: 218
nm, 8 nm
成分名

チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%	
1	46: 218 nm, 8 nm	21.422	0.99908	0.99835	0.99981	111919	58.27	6757533	50.71
2	46: 218 nm, 8 nm	36.253	0.99986	0.99985	0.99987	80137	41.73	6568145	49.29
Total					192056	100.0 0	13325678	100.00	

OCO-2,4,6-F₃C₆H₂

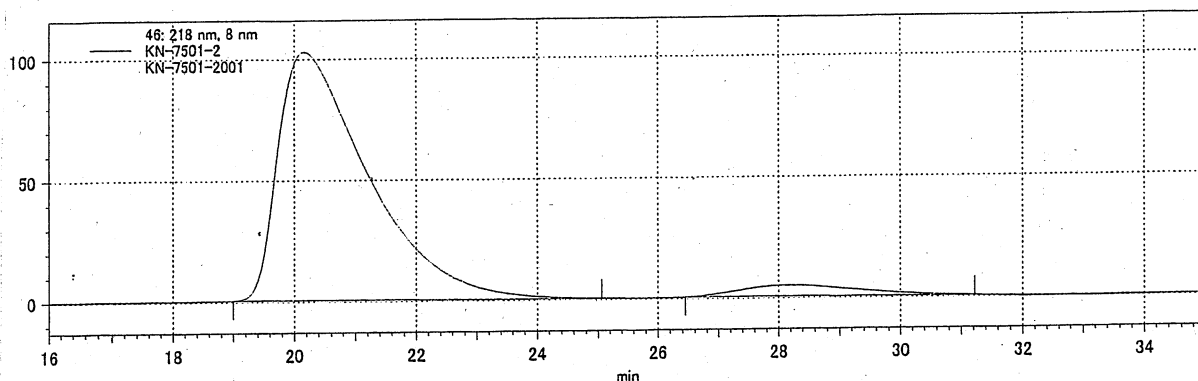


5fe



ppm	Integration
162.98	1.83
116.40	1.83
89.14	1.83
58.32	1.83
54.30	1.83
2.33	1.83

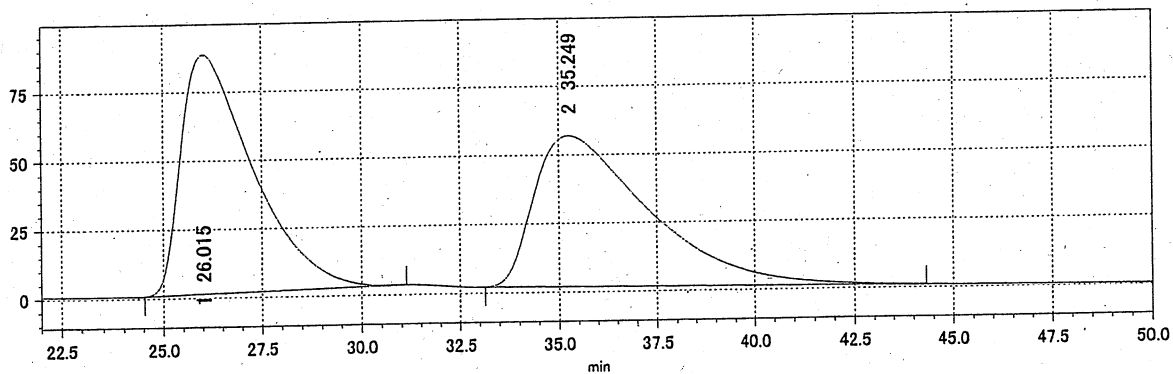
HPLC of optically active 5fe



46: 218 nm, 8 nm
成分名

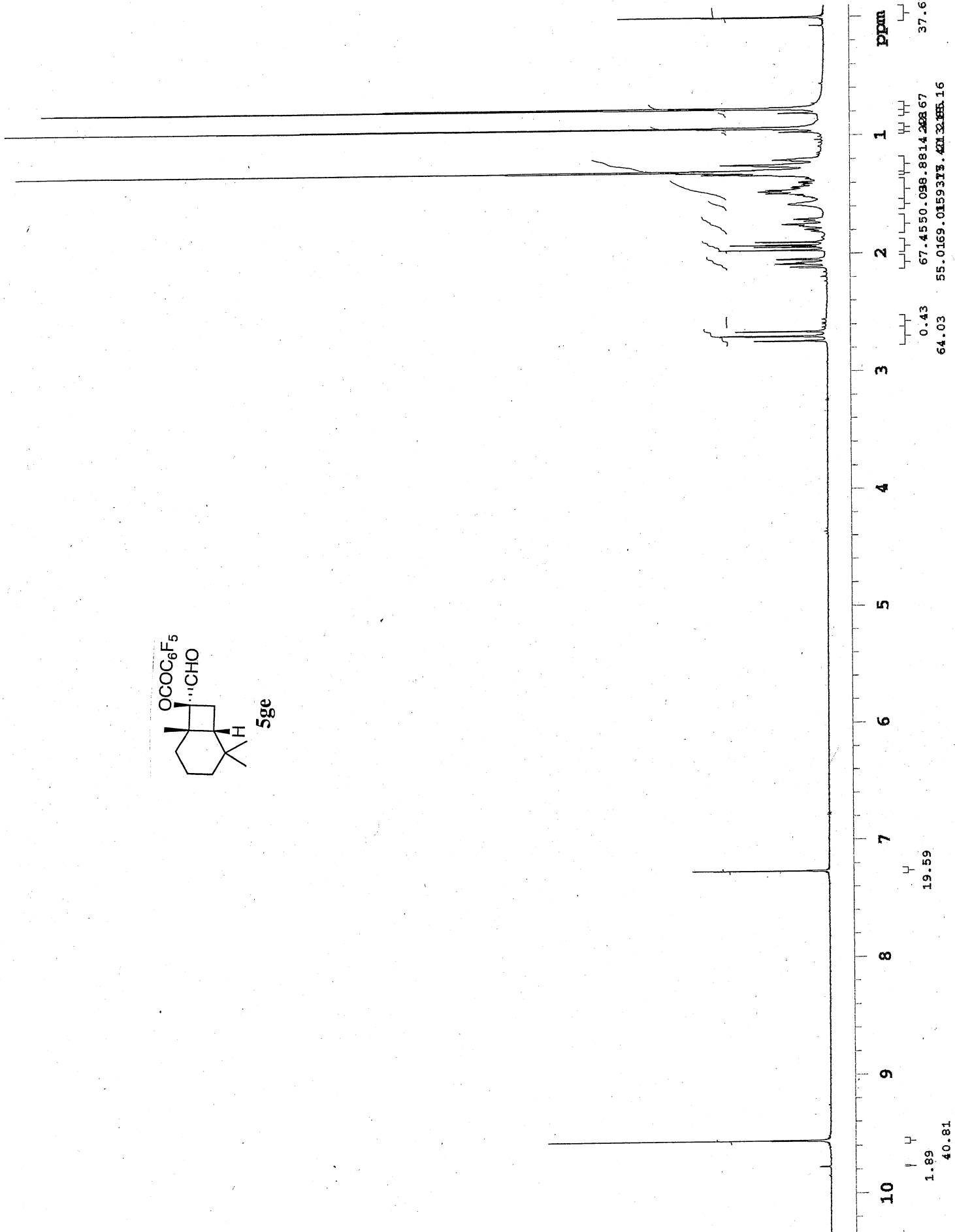
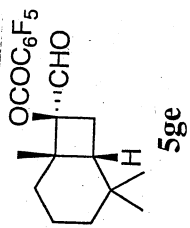
成分名	チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	46: 218 nm, 8 nm	20.158	0.99958	0.99964	0.99953	102354	95.73	10521761	94.48
2	46: 218 nm, 8 nm	28.197	0.99119	0.98863	0.99374	4569	4.27	615140	5.52
Total						106922	100.00	11136902	100.00

HPLC of (±)-5fe

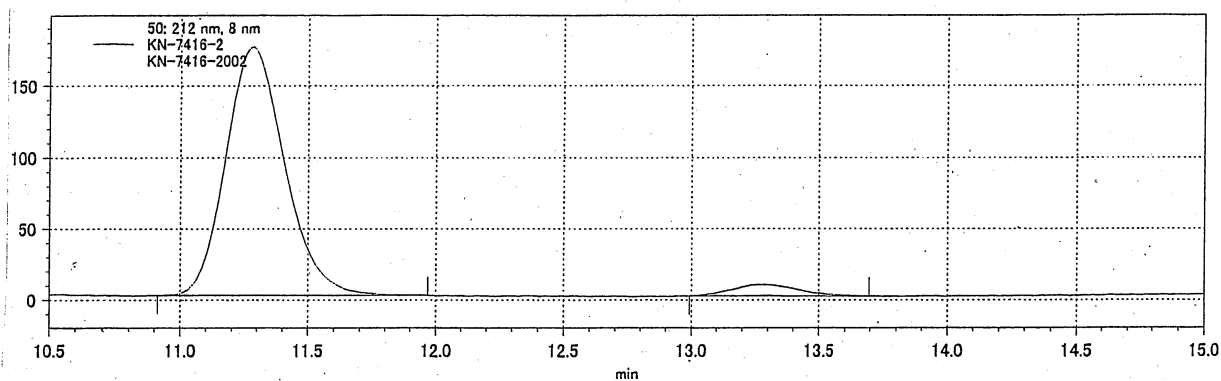


54: 218 nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ%	面積	面積%
1	54: 218 nm, 8 nm	26.015	0.99967	0.99961	0.99973	87238	61.29	11071486	49.82
2	54: 218 nm, 8 nm	35.249	0.99973	0.99994	0.99952	55089	38.71	11151101	50.18
Total						142326	100.00	22222586	100.00



HPLC of optically active 5ge

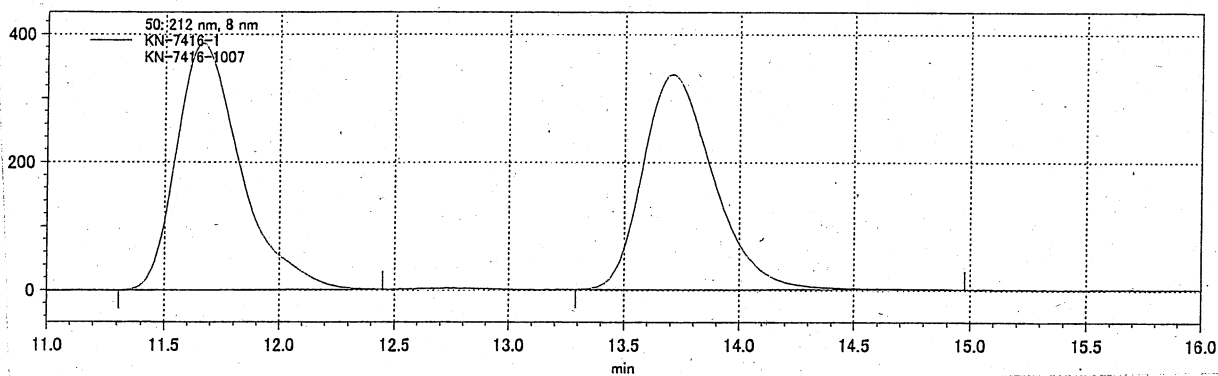


50: 212
nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティ	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	50: 212 nm, 8 nm	11.274	0.99863	0.99902	0.99824	173834	95.61	2810519	95.16
2	50: 212 nm, 8 nm	13.271	0.93058	0.90025	0.96090	7983	4.39	143051	4.84

Total						181817	100.0 0	2953570	100.00

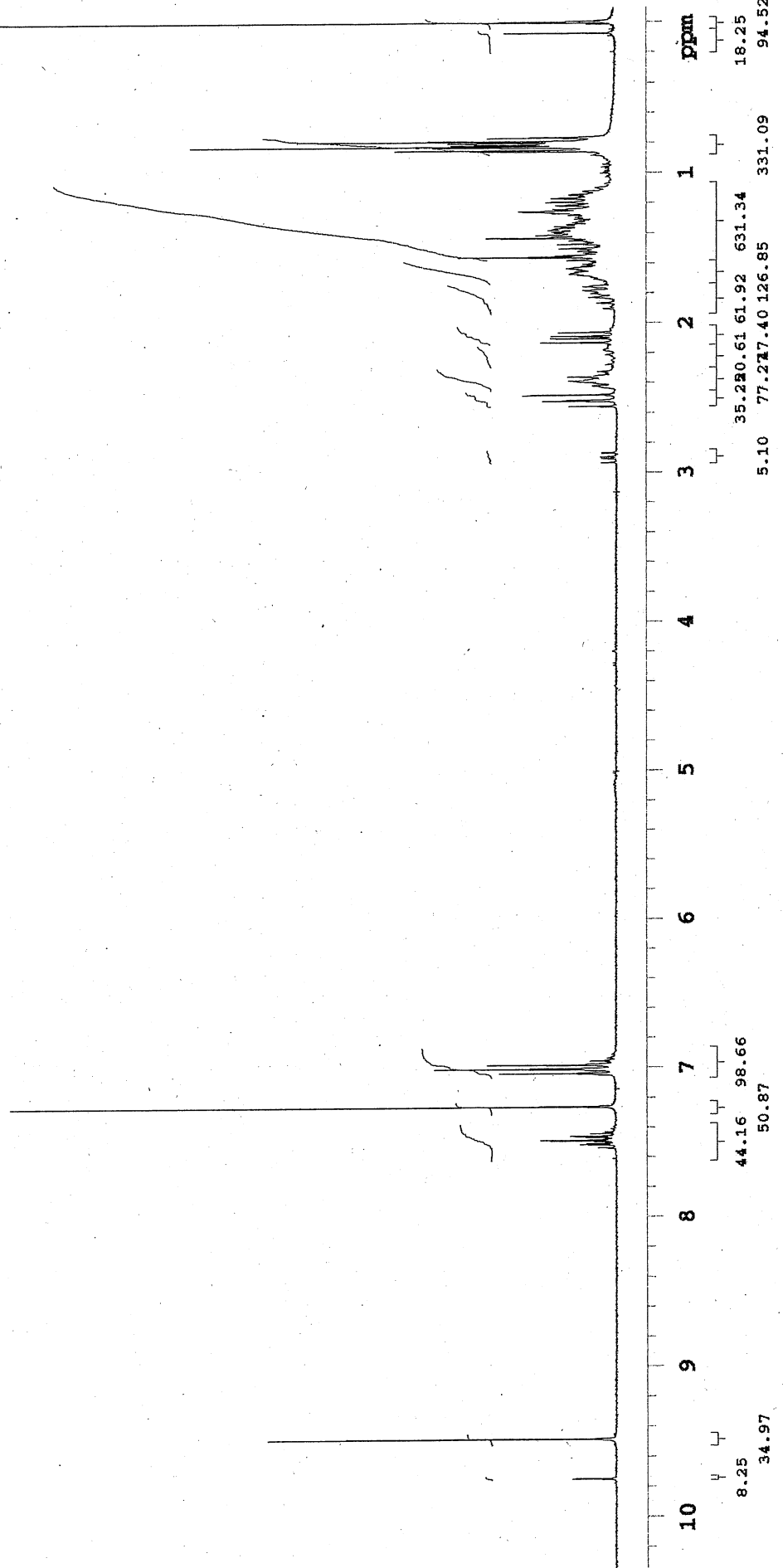
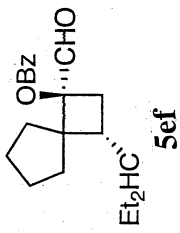
HPLC of (±)-5ge



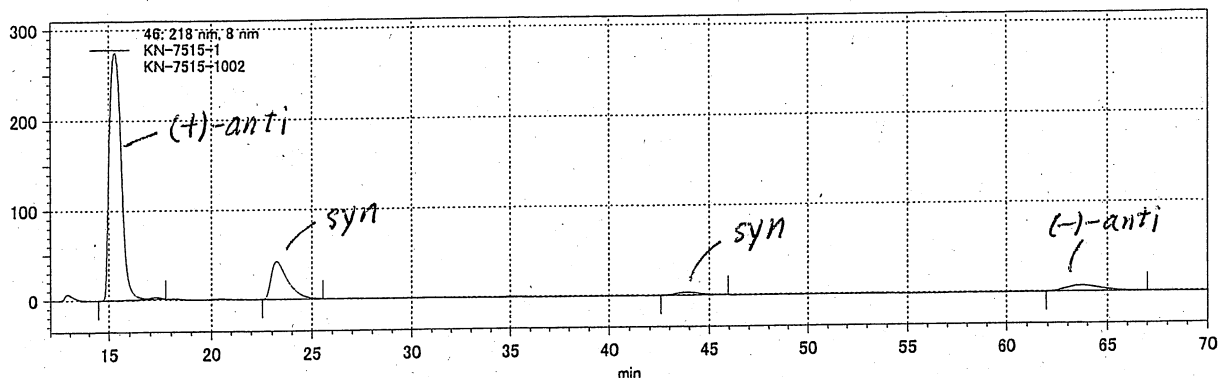
50: 212
nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティ	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	50: 212 nm, 8 nm	11.657	0.99932	0.99938	0.99925	385452	53.43	7481155	51.04
2	50: 212 nm, 8 nm	13.700	0.99820	0.99918	0.99723	335950	46.57	7174947	48.96

Total						721401	100.0 0	14656102	100.00

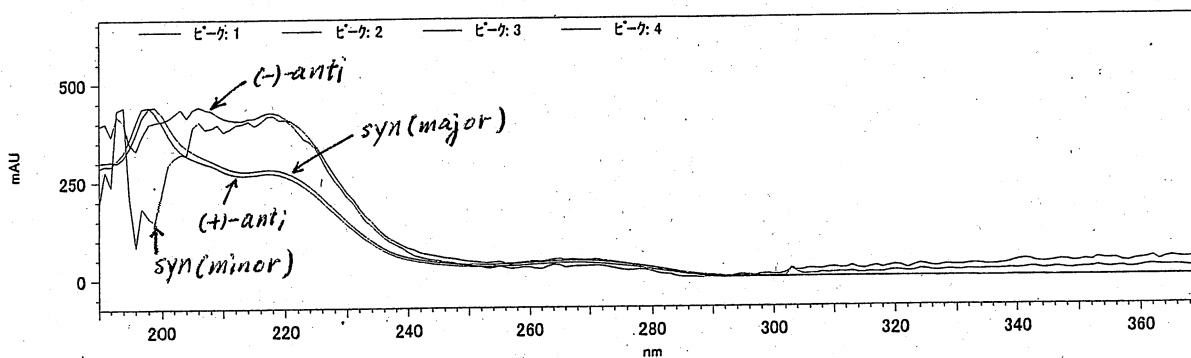


HPLC of optically active **5ef**



UV spectra of **5ef** (enantiomers, diastereomers)

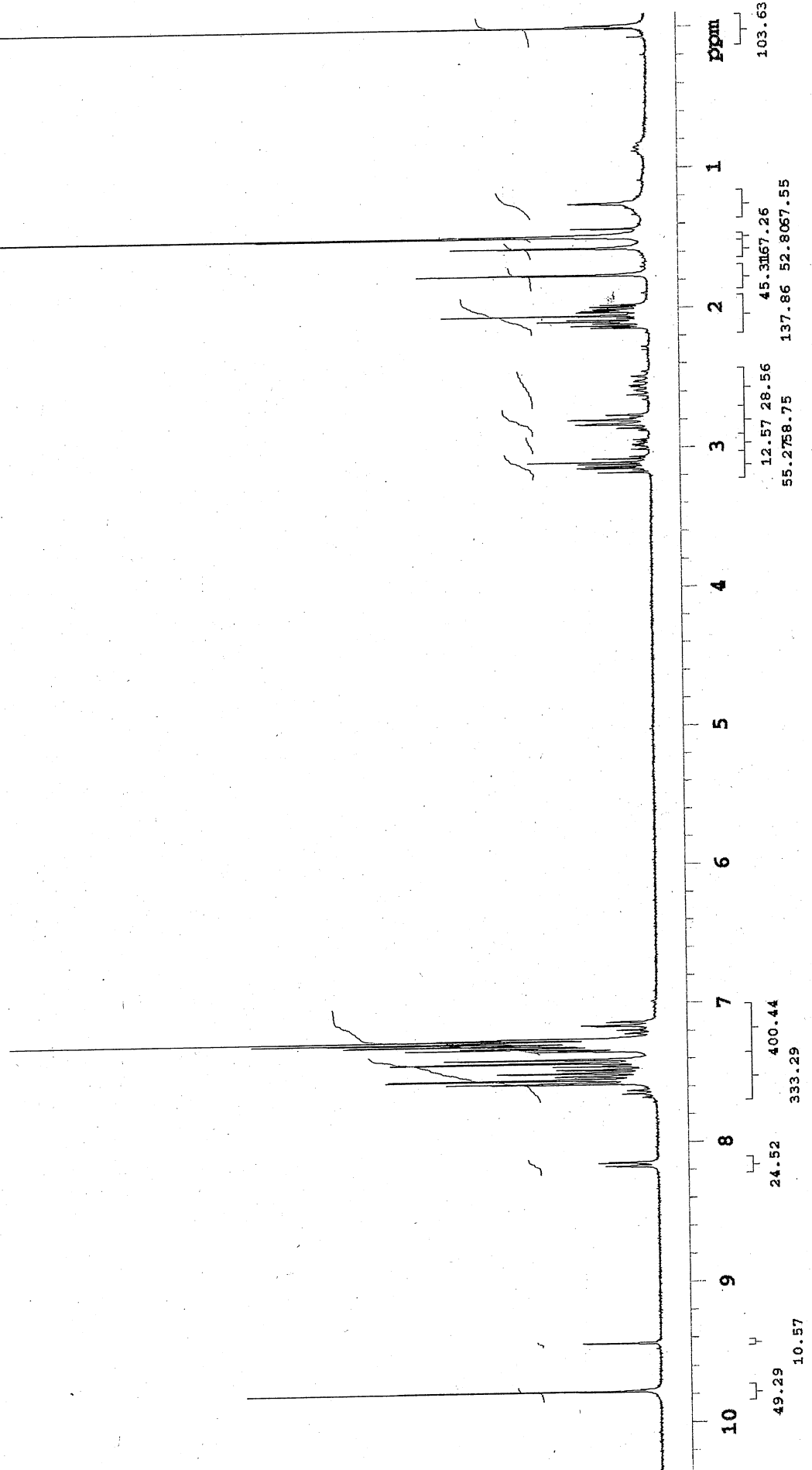
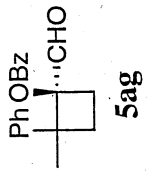
ピーク: 1



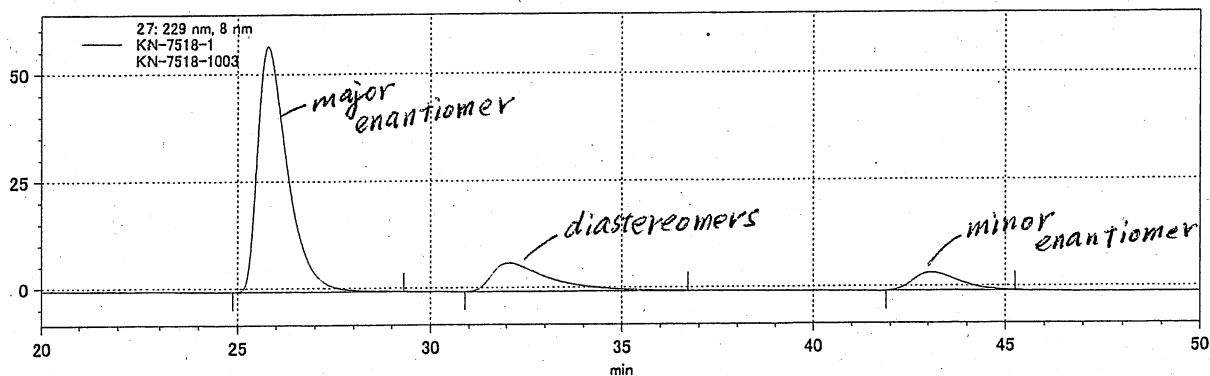
46: 218 nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	46: 218 nm, 8 nm	15.292	0.99101	0.99512	0.98690	274660	84.06	11319319	76.11
2	46: 218 nm, 8 nm	23.234	0.99983	0.99986	0.99979	42319	12.95	2465013	16.57
3	46: 218 nm, 8 nm	43.832	0.99408	0.99289	0.99527	3122	0.96	267171	1.80
4	46: 218 nm, 8 nm	63.678	0.98633	0.99869	0.97397	6638	2.03	820552	5.52

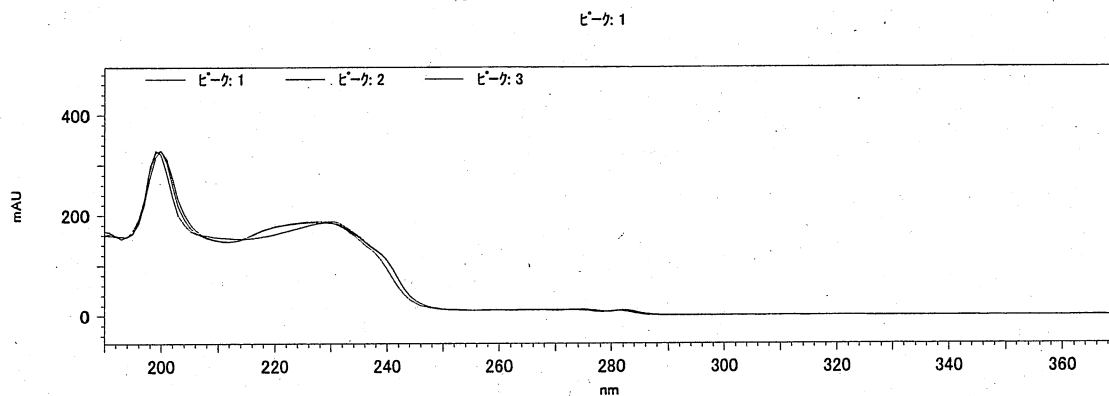
Total						326739	100.00	14872054	100.00
-------	--	--	--	--	--	--------	--------	----------	--------



HPLC of optically active 5ag

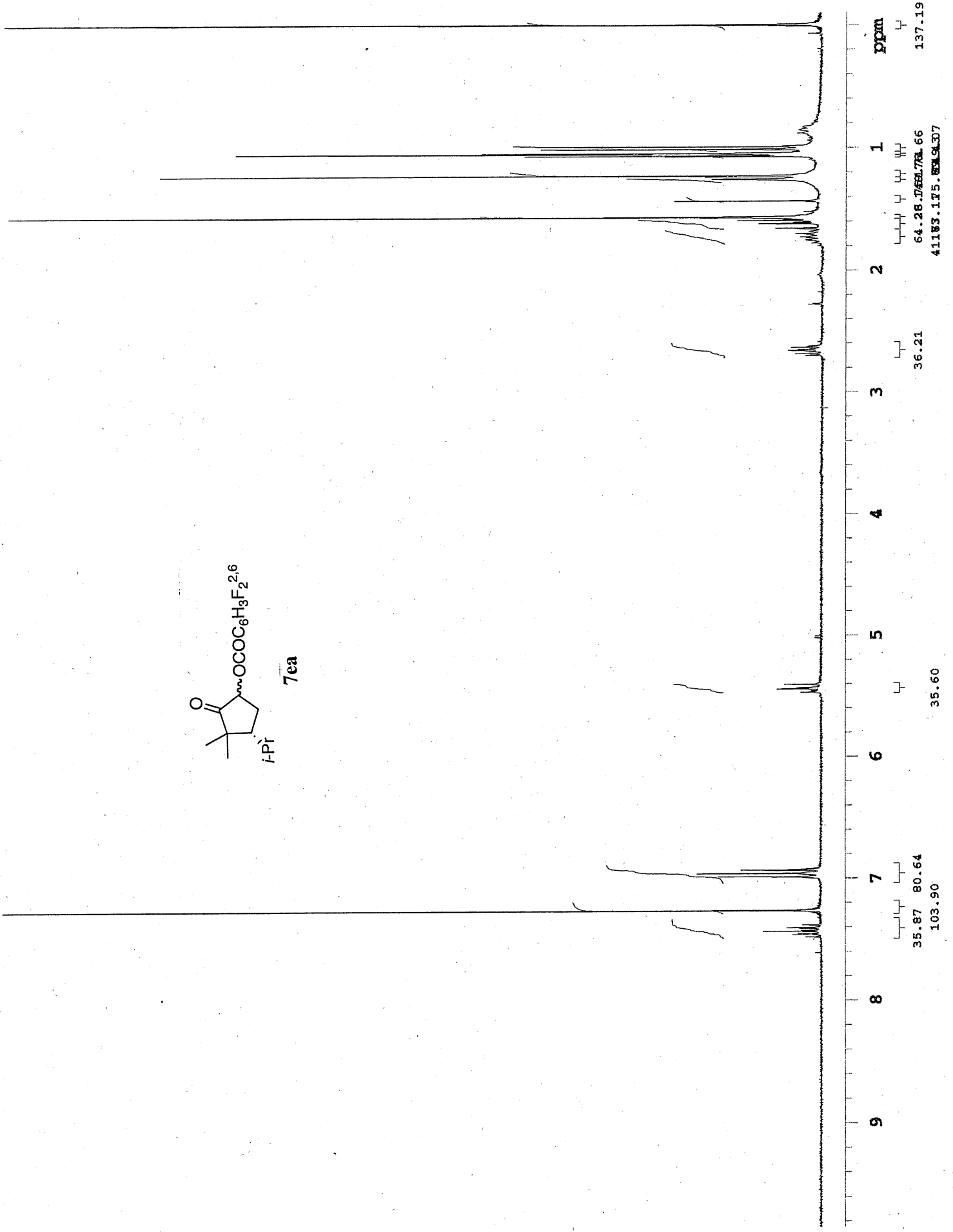
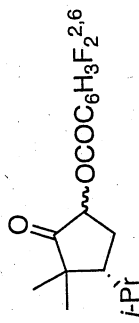


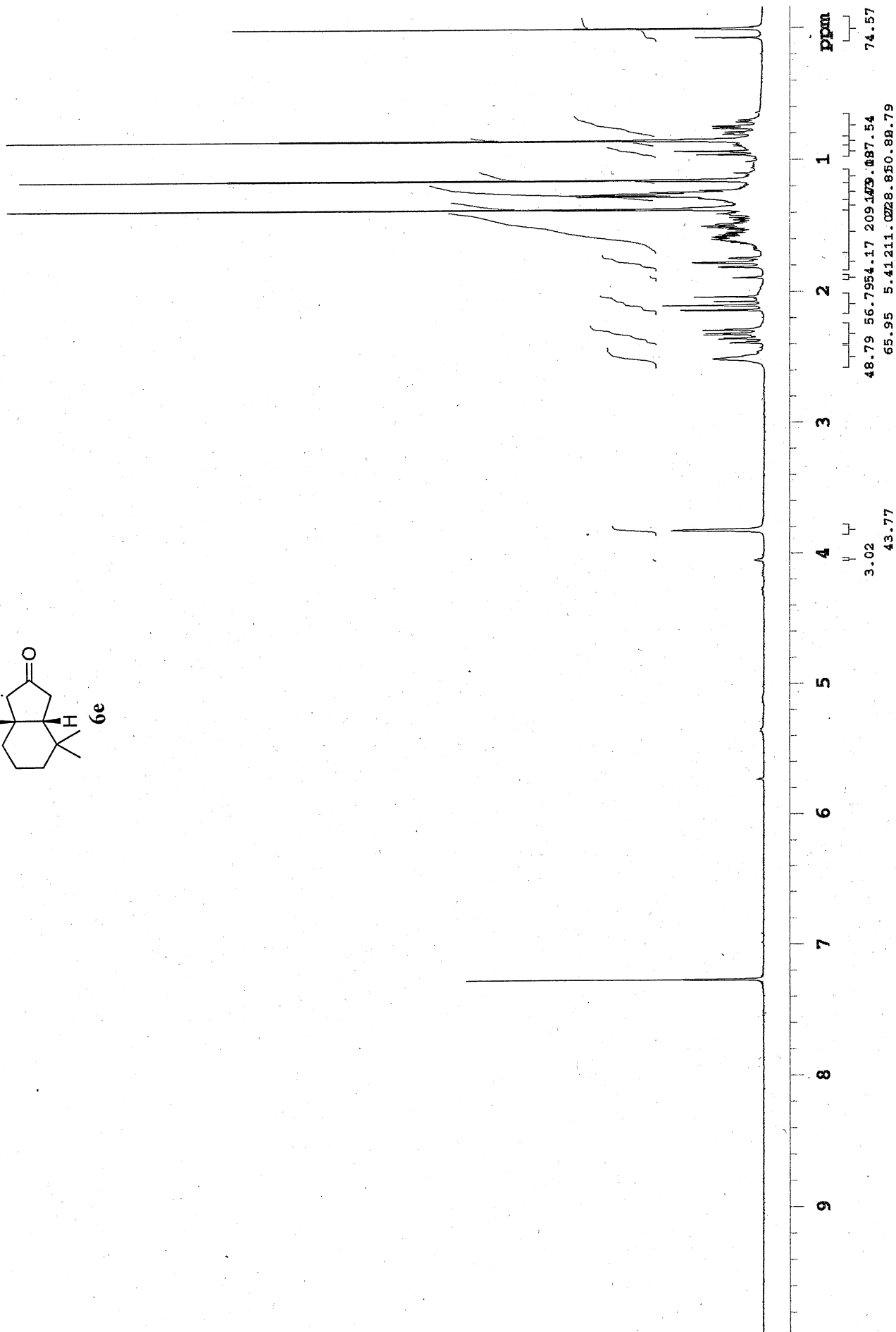
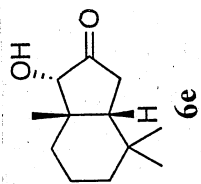
UV spectra of 5ag (enantiomers, diastereomers)

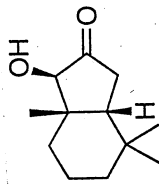


27: 229
nm, 8 nm
成分名

成分名	チャンネル	保持時間	3点ピーク ピュリティー	アップスロープ 類似度	ダウンスロープ 類似度	高さ	高さ %	面積	面積%
1	27: 229 nm, 8 nm	25.782	0.99784	0.99891	0.99678	57214	84.04	3089752	74.70
2	27: 229 nm, 8 nm	32.062	0.99345	0.99389	0.99300	6627	9.73	694498	16.79
3	27: 229 nm, 8 nm	43.110	0.99539	0.99553	0.99525	4240	6.23	351843	8.51
Total						68081	100.00	4136093	100.00







minor diastereomer of **6e**

