Practical synthesis of 4,4,4-trifluorocrotonaldehyde: A versatile precursor for the enantioselective formation of trifluoromethylated stereogenic centers via organocatalytic 1,4-additions

Kazutaka Shibatomi, Akira Narayama, Yoshiyuki Abe, and Seiji Iwasa*

Department of Environmental and Life Sciences, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi 441-8580, Japan

shiba@ens.tut.ac.jp

Supplementary Information

Table of Contents

General

All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere and stirred via magnetic stir-plates. Thin-layer chromatography analyses were performed using Merck pre-coated silica gel plates with F-254 indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate, phosphomolybdic acid, or anisaldehyde. Flash column chromatography was performed using silica gel 60 (mesh 230-400) supplied by Kanto Chemical Co., Inc.

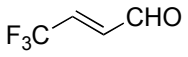
Instrumentation

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL JNM-ECX500 (500 MHz ^{1}H, 126 MHz ^{13}C, 470 MHz ^{19}F). Chemical shift values (δ) are reported in ppm (tetramethylsilane 0.00 ppm for ^{1}H; trichlorofluoromethane 0.00 ppm for ^{19}F; residual chloroform 77.0 ppm for ^{13}C). Infrared spectra were recorded as thin films on sodium chloride plates using a JASCO FTIR-230 spectrometer. Optical rotations were measured on a JASCO P-1030 digital polarimeter. GC analysis was performed with a Shimadzu model 2014 instrument using nitrogen as a carrier gas. Analytical HPLC was performed on a JASCO PU1586 with a UV-1575 UV/Vis detector using a chiral column.

Materials

Commercial grade reagents and solvents were used without further purification unless otherwise noted. Anhydrous toluene, diethyl ether, dimethylformamide (DMF), dichloromethane, and pyridine were purchased from Aldrich (packaged in Sure/Seal bottle) and used without further purification.

Synthesis of 4,4,4-trifluorocrotonaldehyde (1)



1

A solution of ethyl 4,4,4-trifluorocrotonate (**4**) (20 mmol) in anhydrous ether (10 mL) was added to a suspension of lithium aluminum hydride (30 mmol) and aluminum trichloride (15 mmol) in anhydrous ether (15 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Saturated $NaHCO_3$ was added to the mixture. The compound was extracted with ether, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was distilled under atmospheric pressure to give pure **3** in 61% yield. The spectral data were identical to those previously reported for this compound [N. Ishikawa, M. G. Koh, T. Kitazume, S. K. Choi, *J. Fluorine Chem*. 1984, **24**, 419.].

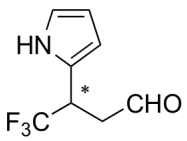
Manganese dioxide (320 mmol) was added to a solution of **3** (40 mmol) in mesitylene (30 mL), and the mixture was stirred for 24 h at 50 °C. The reaction mixture was filtrated thorough Celite. The filtrate was distilled under atmospheric pressure to give 4,4,4-trifluorocrotonaldehyde (**1**) in 47% yield as a nearly pure form (observed boiling point: 38 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (d, 1H, *J* = 5.2 Hz), 6.72-6.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.7, 136.5 (q, *J* = 35.5 Hz), 135.8 (q, *J* = 5.8 Hz), 122.0 (q, *J* = 270.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –66.2 (d, *J* = 1.5 Hz); FTIR (neat) υ_{max} 3505, 2919, 1604, 1129, 836, 685, 468 cm^{-1}.

General procedure for the enantioselective conjugate Friedel-Crafts arylation (Table 1):

Pyrroles or indoles (0.3 mmol) and **1** (0.2 mmol) were added successively to a solution of diarylprolinol silyl ethter **2** (0.02 mmol) in anhydrous toluene (2 mL). The mixture was stirred for 10–16 h at ambient temperature. The reaction mixture was directly subjected to silica gel column chromatography to give corresponding product **5** or **6** in high purity.

4,4,4-trifluoro-3-(1*H*-pyrrol-2-yl)butanal (5a)



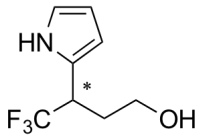
5a

The reaction mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 92% yield of **5a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.35 (brs, NH), 6.80-6.71 (m, 1H), 6.24-6.11 (m, 2H), 4.15-4.03 (m, 1H), 3.07 (d, 2H, *J* = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.9, 126.0 (q, *J* = 279.5 Hz), 123.6, 118.6, 108.7, 107.9, 42.9, 37.2 (q, *J*

= 28.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.1 (d, *J* = 8.9 Hz); $[\alpha]^{24}_D$ —22.4 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%) for $C_8H_9F_3NO$: C, 50.27; H, 4.22; N, 7.33. Found: C, 50.24; H, 4.22;N, 7.52.

The enantiomeric excess of **5a** was determined by HPLC after converted into **19a** (see below).

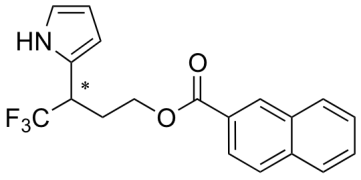
4,4,4-trifluoro-3-(1*H*-pyrrol-2-yl)butan-1-ol (18a)



18a

To a solution of sodium borohydride (0.2 mmol) in methanol (0.5 mL) was added a solution of **5a** (0.1 mmol) in dichloromethane (0.5 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C. Saturated aqueous NH_4Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give 81% yield of **18a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (brs, NH), 6.82-6.74 (m, 1H), 6.23-6.13 (m, 2H), 3.73 (ddd, 1H, *J* = 5.0, 5.4, 10.3 Hz), 3.70-3.60 (m, 1H), 3.50 (ddd, 1H, J = 4.2, 9.9, 9.9 Hz), 2.26-2.16 (m, 1H), 2.02-1.91 (m, 1H), 1.66 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 126.6 (q, *J* = 279.5 Hz), 123.8, 118.4, 108.6, 108.4, 59.3, 40.1 (d, *J* = 28.8 Hz), 31.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.9 (d, *J* = 9.4 Hz); $[\alpha]^{24}_D$ –21.6 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3432, 3132, 2963, 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_8H_{11}F_3NO$: C, 49.74; H, 5.22; N, 7.25. Found: C, 49.79; H, 5.31; N, 7.33.

4,4,4-trifluoro-3-(1*H*-pyrrol-2-yl)butyl 2-naphthoate (19a)



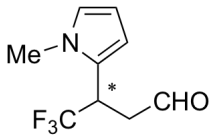
19a

To a solution of **18a** (0.08 mmol) in anhydrous dichloromethane (0.5 mL) were added triethylamine (0.16 mmol), DMAP (0.01 mmol), and 2-naphthoyl chloride (0.12 mmol) successively. The reaction mixture was stirred for 4 h at ambient temperature. Saturated $NaHCO_3$ was added to the mixture. The compound was extracted with dichloromethane, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 1 : 1) to give 80% yield of **19a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.32 (brs, NH), 8.03-7.94 (m, 2H), 7.89 (d, 2H, *J* = 8.6 Hz),

7.63-7.53 (m, 2H), 6.81-6.78 (m, 1H), 6.24-6.19 (m, 2H), 4.47-4.39 (m, 1H), 4.33-4.26 (m, 1H), 3.69-3.59 (m, 1H), 2.56-2.49 (m, 1H), 2.31-2.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.6, 135.6, 132.4, 131.1, 129.4, 128.4, 128.3, 127.8, 127.0, 126.8, 126.3 (q, J = 279.9 Hz), 125.1, 123.1, 118.7, 109.0, 108.9, 62.0, 40.8 (q, *J* = 28.8 Hz), 28.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.4 (d, *J* = 8.4 Hz); $[\alpha]^{24}_D$ –50.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3056, 2359, 1743, 1510, 1404, 1308, 1239, 1152, 1051, 1156, 784, 433 cm^{-1}; Anal. Calcd (%) for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.96; H, 4.62; N, 4.11.

The enantiomeric ratio was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 12.6 min and minor isomer 14.0 min.

4,4,4-trifluoro-3-(1-methyl-1*H*-pyrrol-2-yl)butanal (5b)

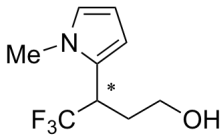


5b

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 96% yield of **5b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (brs, 1H), 6.61-6.57 (m, 1H), 6.14-6.04 (m, 2H), 4.20-4.02 (m, 1H), 3.69 (s, 3H), 3.25-3.03 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.2, 126.5, 126.0 (q, *J* = 279.5 Hz), 108.1, 107.2, 43.7, 35.0 (q, *J* = 30.0 Hz), 34.0, 30.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.9 (d, *J* = 9.4 Hz); $[\alpha]^{24}_D$ –19.3 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%) for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.83; H, 4.95; N, 6.65.

The enantiomeric excess of **5b** was determined by HPLC after converted into **19b** (see below).

4,4,4-trifluoro-3-(1-methyl-1*H*-pyrrol-2-yl)butan-1-ol (18b)

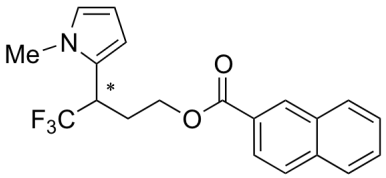


18b

The compound was synthesized according to a procedure similar to that employed for the synthesis of **18a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 81% yield of **18b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62-6.58 (m, 1H), 6.15-6.11 (m, 2H), 3.79-3.67 (m, 2H), 3.61 (s, 3H), 3.46 (ddd, 1H, J = 3.8, 3.8, 10.3 Hz), 2.30-2.20 (m, 1H), 2.06-1.97 (m, 1H), 1.37 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 126.6 (q, *J* = 279.5 Hz), 125.3, 122.9, 108.0, 107.2, 59.1, 37.3 (q, *J* = 27.6 Hz), 33.9, 31.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.2 (d, *J* = 8.0 Hz); $[\alpha]^{24}_D$ –20.5 (c = 0.2, $CHCl_3$); FTIR

(neat) υ_{max} 3420, 2872, 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_9H_{12}F_3NO$: C, 52.17; H, 5.84; N, 6.76. Found: C, 52.33; H, 5.90; N, 6.60.

4,4,4-trifluoro-3-(1-methyl-1*H*-pyrrol-2-yl)butyl 2-naphthoate (19b)

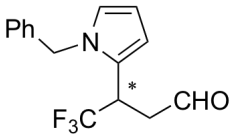


19b

The compound was synthesized according to a procedure similar to that employed for the synthesis of **19a**. The crude mixture was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 1 : 1) to give 80% yield of **19b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.00 (dd, 1H, *J* = 1.6, 8.6 Hz), 7.97 (d, 1H, *J* = 7.64 Hz), 7.89 (d, 2H, *J* = 8.41 Hz), 7.64-7.59 (m, 1H), 7.59-7.54 (m, 1H), 6.60 (dd, 1H, *J* = 1.9, 2.7 Hz), 6.23 (dd, 1H, *J* = 1.5, 3.4 Hz), 6.18 (dd, 1H, *J* = 2.7, 3.4 Hz), 4.48 (ddd, 1H, *J* = 5.4, 5.4, 10.7 Hz), 4.25 (ddd, 1H, *J* = 4.6, 9.6, 11.1 Hz), 3.72-3.62 (m, 1H), 3.56 (s, 3H), 2.61-2.52 (m, 1H), 2.37-2.27 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 135.6, 132.4, 131.1, 129.3, 128.4, 128.3, 127.8, 126.8, 126.2 (q, *J* = 280.8 Hz), 125.0, 123.3, 108.4, 107.5, 62.1, 38.3 (q, *J* = 28.8 Hz), 33.8, 28.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.4 (d, *J* = 8.4 Hz); $[\alpha]^{24}_D$ –50.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3056, 2359, 1743, 1510, 1404, 1308, 1239, 1152, 1051, 1156, 784, 433 cm^{-1}; Anal. Calcd (%) for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.96; H, 4.62; N, 4.11.

The enantiomeric ratio of **19b** was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 12.0 min, minor isomer 11.2 min (97% ee).

4,4,4-trifluoro-3-(1-benzyl-1*H*-pyrrol-2-yl)butanal (5c)



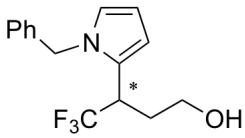
5c

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 85% yield of **5c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.39-7.24 (m, 3H), 7.07-7.03 (m, 2H), 6.71-6.67 (m, 1H), 6.22-6.16 (m, 2H), 5.19 (dd, 2H, *J* = 16.4, 36.8 Hz), 4.01-3.91 (m, 1H), 3.03-2.90 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.5, 137.4, 128.8, 127.8, 126.7, 125.8 (q, *J* = 275.9 Hz), 124.7, 123.3, 109.3, 107.9, 50.7, 43.5, 35.1 (q, *J* = 30.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.0 (d, *J* = 8.9 Hz); $[\alpha]^{24}_D$ +8.8 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%)

for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 64.22; H, 5.06; N, 5.31.

The enantiomeric excess of **5c** was determined by HPLC after converted into **18c** (see below).

4,4,4-trifluoro-3-(1-benzyl-1*H*-pyrrol-2-yl)butan-1-ol (18c)

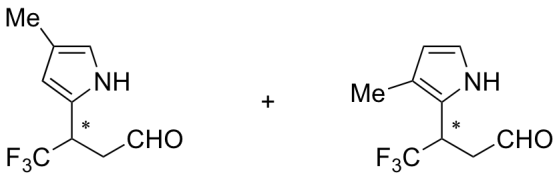


18c

The compound was synthesized according to a procedure similar to that employed for the synthesis of **18a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 85% yield of **18c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.25 (m, 3H), 7.09-7.00 (m, 2H), 6.82-6.76 (m, 1H), 6.29-6.17 (m, 2H), 5.17 (d, 1H, *J* = 16.4 Hz), 5.11 (d, 1H, *J* = 16.4 Hz), 3.54-3.43 (m, 2H), 3.18-3.08 (m, 1H), 2.14-2.03 (m, 1H), 1.95-1.85 (m, 1H), 0.53 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.5, 137.4, 128.8, 127.8, 126.7, 125.8 (q, *J* = 275.9 Hz), 124.7, 123.3, 109.3, 107.9, 50.7, 43.5, 35.1 (q, *J* = 30.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.0 (d, *J* = 8.9 Hz); $[\alpha]^{24}_D$ +3.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69; N, 4.94. Found: C, 63.57; H, 5.48; N, 5.06.

The enantiomeric ratio of **18c** was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 18.9 min, minor isomer 13.7 min (99% ee).

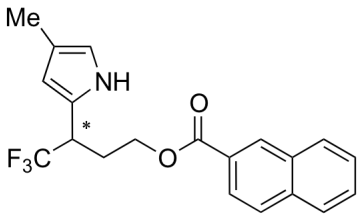
4,4,4-trifluoro-3-(4-methyl-1*H*-pyrrol-2-yl)butanal (5d)



5d (major) **5d'** (minor)

This compound was obtained together with 2,3-disubstituted form **5d'** which was inseparable by silica gel column chromatography. The isolation and determination of enantiomeric ratio were performed after converted into **19d** (see below).

4,4,4-trifluoro-3-(3-methyl-1*H*-pyrrol-2-yl)butyl 2-naphthoate (19d)

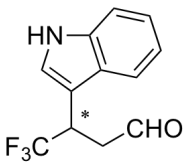


19d

The compound was synthesized according to procedures similar to those employed for the synthesis of **18a** and **19a**. The crude mixture was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 1 : 2) to give 81% yield of **19d**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.06 (brs, NH), 8.01 (d, 1H, *J* = 8.8 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.89 (d, 2H, *J* = 8.4 Hz), 7.61 (dd, 1H, *J* = 7.3, 7.3 Hz), 7.56 (dd, 1H, *J* = 7.3, 7.3 Hz), 6.74-6.71 (m, 1H), 6.04-6.01 (m, 1H), 4.40 (ddd, 1H, *J* = 5.4, 5.4, 11.1 Hz), 4.10 (ddd, 1H, *J* = 5.4, 9.6, 9.6 Hz), 3.85-3.69 (m, 1H), 2.60-2.45 (m, 1H), 2.26-2.11 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 135.6, 132.4, 131.1, 129.3, 128.4, 128.2, 127.8, 127.0 (q, *J* = 280.7 Hz), 126.7, 126.6, 125.0, 119.2, 118.7, 118.0, 110.3, 61.8, 38.3 (q, *J* = 28.8 Hz), 27.7, 10.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.5 (d, *J* = 9.4 Hz); $[\alpha]^{24}_D$ –35.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3056, 2359, 1743, 1510, 1404, 1308, 1239, 1152, 1051, 1156, 784, 433 cm^{-1}; Anal. Calcd (%) for $C_{20}H_{18}F_3NO_2$: C, 66.48; H, 5.02; N, 3.88. Found: C, 66.67; H, 5.31; N, 3.85.

The enantiomeric ratio of **19d** was determined by HPLC (hexane : 2-propanol = 50 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 21.7 min, minor isomer 19.4 min (80% ee).

4,4,4-trifluoro-3-(1*H*-indol-2-yl)butanal (6a)



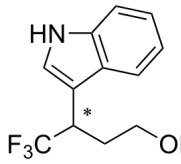
6a

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 98% yield of **6a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.63 (s, 1H), 8.25 (brs, NH), 7.67 (d, 1H, *J* = 7.6 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.25-7.20 (m, 1H), 7.20-7.15 (m, 1H), 7.11 (d, 1H, *J* = 2.7 Hz), 4.34 (qdd, 1H, *J* = 5.7, 8.8, 8.8 Hz), 3.18-3.07 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.3, 136.0, 126.8 (q, *J* = 279.5 Hz), 126.3, 123.7, 122.7, 120.2, 118.9, 111.5, 108.6, 42.9, 35.6 (q, *J* = 30.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.0 (d, *J* = 9.4 Hz); $[\alpha]^{24}_D$ –24.3 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%) for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.86; H,

4.20; N, 5.52.

The enantiomeric excess of **6a** was determined by HPLC after converted into **20a** (see below).

4,4,4-trifluoro-3-(1*H*-indol-2-yl)butan-1-ol (20a)

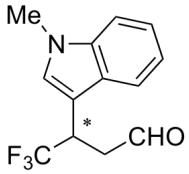


20a

The compound was synthesized according to a procedure similar to that employed for the synthesis of **18a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 92% yield of **20a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (brs, NH), 7.67 (d, 1H, *J* = 8.0 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 7.24 (ddd, 1H, *J* = 1.2, 6.9, 8.1 Hz), 7.20 (d, 1H, *J* = 2.3 Hz), 7.17 (ddd, 1H, *J* = 1.2, 6.9, 8.1 Hz), 3.91 (ddd, 1H, *J* = 3.8, 9.6, 9.9 Hz), 3.71 (ddd, 1H, *J* = 5.4, 5.4, 10.3 Hz), 3.50 (ddd, 1H, *J* = 5.0, 9.6, 9.6 Hz), 2.40-2.31 (m, 1H), 2.16 (dddd, 1H, *J* = 4.6, 4.6, 11.1, 13.8 Hz), 1.48 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.1, 127.5 (q, *J* = 279.5 Hz), 127.0, 123.4, 122.5, 120.1, 119.1, 111.4, 109.2, 59.6, 38.0 (q, *J* = 28.8 Hz), 31.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.7 (d, *J* = 9.9 Hz); $[\alpha]^{24}_{D}$ –8.4 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.05; H, 4.82; N, 5.94.

The enantiomeric ratio of **20a** was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 13.4 min, minor isomer 12.1 min (90% ee)

4,4,4-trifluoro-3-(1-methyl-1*H*-indol-2-yl)butanal (6b)



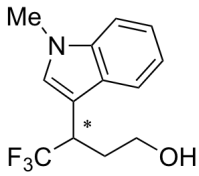
6b

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 83% yield of **6b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.66 (d, 1H, *J* = 8.0 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.27 (ddd, 1H, *J* = 1.2, 6.9, 8.0 Hz), 7.20 (d, 1H, *J* = 2.3 Hz), 7.18 (ddd, 1H, *J* = 1.2, 6.9, 8.0 Hz), 4.34 (qdd, 1H, *J* = 6.1, 9.2, 9.2 Hz), 3.77 (s, 3H), 3.18-3.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.2, 136.9, 128.2, 126.8, 126.8 (q, *J* = 283.1 Hz), 122.2, 119.8, 119.0, 109.6, 106.9, 43.0, 35.6 (q, *J* = 30.0 Hz), 32.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.0 (d, *J* = 9.4 Hz); $[\alpha]^{24}_{D}$ –37.3 (c = 0.1, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324,

1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%) for $C_{13}H_{12}F_3NO$: C, 61.17; H, 4.74; N, 5.49. Found: C, 61.46; H, 4.81; N, 3.85.

The enantiomeric excess of **6b** was determined by HPLC after converted into **20b** (see below).

4,4,4-trifluoro-3-(1-methyl-1*H*-indol-2-yl)butan-1-ol (20b)

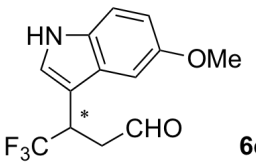


20b

The compound was synthesized according to a procedure similar to that employed for the synthesis of **18a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 97% yield of **20b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 8.4 Hz), 7.26 (ddd, 1H, *J* = 1.2, 6.9, 8.1 Hz), 7.15 (ddd, 1H, *J* = 1.2, 6.9, 8.1 Hz), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.69 (ddd, 1H, *J* = 5.4, 5.4, 10.3 Hz), 3.48 (ddd, 1H, *J* = 5.0, 9.6, 10.3 Hz), 2.38-2.29 (m, 1H), 2.18-2.08 (m, 1H), 1.44 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.8, 128.0, 127.6, 127.5 (q, *J* = 278.3 Hz), 122.0, 119.9, 119.1, 109.5, 107.3, 59.6, 37.9 (q, *J* = 28.8 Hz), 32.9, 31.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.8 (d, *J* = 9.9 Hz); $[\alpha]^{24}_D$ –27.2 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_{13}H_{14}F_3NO$: C, 60.70; H, 5.49; N, 5.44. Found: C, 61.01; H, 5.70; N, 5.72.

The enantiomeric ratio of **20b** was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 29.1 min, minor isomer 21.1 min (97% ee).

4,4,4-trifluoro-3-(5-methoxy-1*H*-indol-2-yl)butanal (6c)



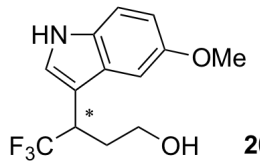
6c

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 71% yield of **6c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.21 (brs, NH), 7.26 (d, 1H, *J* = 8.8 Hz), 7.13 (d, 1H, *J* = 2.7 Hz), 7.09 (d, 1H, *J* = 2.3 Hz), 6.89 (dd, 1H, *J* = 2.3, 8.8 Hz), 4.31 (qdd, 1H, *J* = 5.4, 5.4, 9.2 Hz), 3.88 (s, 3H), 3.19-3.07 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.3, 131.1, 127.5, 127.5, (q, *J* = 280.7 Hz), 124.0, 112.7, 112.1, 108.8, 100.8, 59.6, 55.8, 37.9 (d, *J* = 28.8 Hz), 25.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.1 (d, *J* = 8.9 Hz);

$[\alpha]^{24}_{D}$ –35.4 (c = 0.1, $CHCl_3$); FTIR (neat) υ_{max} 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm^{-1}; Anal. Calcd (%) for $C_{13}H_{12}F_3NO_2$: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.55; H, 4.46; N, 5.44.

The enantiomeric excess of **6c** was determined by HPLC after converted into **20c** (see below).

4,4,4-trifluoro-3-(5-methoxy-1*H*-indol-2-yl)butan-1-ol (20c)



20c

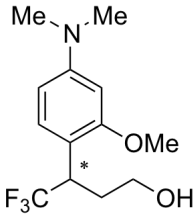
The compound was synthesized according to a procedure similar to that employed for the synthesis of **18a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give 94% yield of **20c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (brs, NH), 7.26 (d, 1H, *J* = 8.8 Hz), 7.13 (d, 1H, *J* = 2.7 Hz), 7.08 (d, 1H, *J* = 2.3 Hz), 7.15 (dd, 1H, *J* = 2.7, 8.8 Hz), 4.02 (qdd, 1H, J = 6.1, 6.1, 12.2 Hz), 3.85 (s, 3H), 3.70 (ddd, 1H, *J* = 5.0, 5.4, 10.3 Hz), 3.49 (ddd, 1H, *J* = 5.0, 9.6, 10.3 Hz), 2.37-2.29 (m, 1H), 2.17-2.08 (m, 1H), 1.53 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.3, 131.1, 127.5, 127.5 (q, *J* = 280.7 Hz), 124.0, 112.7, 112.1, 108.8, 100.8, 59.6, 55.8, 37.9 (d, *J* = 28.8 Hz), 25.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.7 (d, *J* = 9.9 Hz); $[\alpha]^{24}_{D}$ –10.8 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm^{-1}; Anal. Calcd (%) for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.11; H, 5.15; N, 5.38.

The enantiomeric ratio of **20c** was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 8.2 min, minor isomer 10.2 min (93% ee).

Experimental procedure and characterization of the products for Scheme 3:

Aromatic compounds (0.3 mmol) and **1** (0.2 mmol) were added successively to a solution of diarylprolinol silyl ethter **2** (0.06 mmol) in anhydrous toluene (2 mL). The mixture was stirred for 12–14 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 0.5 h at 0 °C. Saturated aqueous NH_4Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding adducts in high purity.

3-(4-(dimethylamino)-2-methoxyphenyl)-4,4,4-trifluorobutan-1-ol (7)

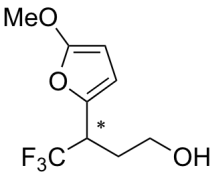


7

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 74% yield (99% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, 1H, *J* = 8.4 Hz), 6.35 (dd, 1H, *J* = 8.8, 2.3 Hz), 6.25 (d, 1H, *J* = 2.7 Hz), 4.12–4.01 (m, 1H), 3.85 (s, 3H), 3.64–3.55 (m, 1H), 3.43–3.34 (m, 1H), 2.97 (s, 6H), 2.30–2.20 (m, 1H), 1.96–1.85 (m, 1H), 1.78 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 151.4, 128.6, 127.6 (q, *J* = 279.5 Hz), 110.1, 105.2, 95.7, 59.7, 55.8, 40.4, 36.5 (q, *J* = 26.4 Hz), 31.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ –69.7 (d, *J* = 9.9 Hz); $[a]^{28}_{D}$ –20.4 (c = 0.95, $CHCl_3$); FTIR (neat) υ_{max} 3386, 2946, 1616, 1571, 1521, 1453, 1361, 1246, 1123, 1039, 813 cm^{-1}; Anal. Calcd (%) for $C_{13}H_{18}F_3NO_2$: C, 56.31; H, 6.54; N, 5.05. Found: C, 56.19; H, 6.67; N, 5.11.

The enantiomeric excess was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK IC column (0.46 cmϕ x 25 cm): major isomer 12.9 min and minor isomer 11.9 min.

4,4,4-trifluoro-3-(5-methoxyfuran-2-yl)butan-1-ol (8)



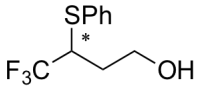
8

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 47% yield (70% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (d, 1H, *J* = 3.4 Hz), 5.11 (d, 1H, *J* = 3.4 Hz), 3.83 (s, 3H), 3.79–3.70 (m, 1H), 3.65–3.48 (m, 2H), 2.18–2.10 (m, 1H), 2.10–2.02 (m, 1H), 1.61 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 137.3, 125.8 (q, *J* = 279.5 Hz), 111.1, 80.0, 59.2, 57.7, 40.2 (q, *J* = 28.8 Hz), 29.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ –70.4 (d, *J* = 9.9 Hz); $[a]^{25}_{D}$ +43.1 (c = 0.45, $CHCl_3$); FTIR (neat) υ_{max} 3328, 2925, 1500, 1321, 1264, 1175, 1132, 1064, 916, 835, 737 cm^{-1}; Anal. Calcd (%) for $C_9H_{11}F_3O_3$: C, 48.22; H, 4.95. Found: C, 48.24; H, 4.97. The enantiomeric excess was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 16.7 min and minor isomer 15.1 min.

General procedure for the enantioselective Michael addition with alkylthiols (Table 2, Entries 1–6):

Alkylthiols (0.2 mmol) and **1** (0.3 mmol) were added successively to a solution of diarylprolinol silyl ethter **2** (0.02 mmol) and benzoic acid (0.02 mmol) in anhydrous toluene (0.5 mL). The mixture was stirred for 5 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 0.5 h at 0 °C. Saturated aqueous NH_4Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give corresponding thioethers **9** in high purity.

4,4,4-trifluoro-3-(phenylthio)butan-1-ol (9a)

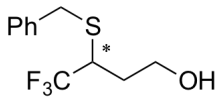


9a

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 97% yield of **9a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.47 (m, 2H), 7.40-7.27 (m, 3H), 4.11-3.98 (m, 1H), 3.98-3.89 (m, 1H), 3.74-3.64 (m, 1H), 2.25-2.12 (m, 1H), 1.85-1.69 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.1, 133.1, 129.2, 128.3, 126.8 (q, J = 278.0 Hz), 58.7, 49.1 (q, J = 29.7 Hz), 31.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.1 (d, J = 8.3 Hz); $[\alpha]^{22}_D$ –40.7 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 1983, 1822, 1737, 1366, 1280, 1161, 853, 714 cm^{-1}; Anal. Calcd (%) for $C_{10}H_{11}F_3OS$: C, 50.84; H, 4.69. Found: C, 50.86; H, 4.70.

The enantiomeric ratio of **9a** was determined by HPLC (hexane : 2-propanol = 99 : 1, 0.5 mL/min) using a CHIRALPAK IC column (0.46 cmϕ x 25 cm): major isomer 20.7 min, minor isomer 21.6 min (94% ee).

4,4,4-trifluoro-3-(benzylthio)butan-1-ol (9b)



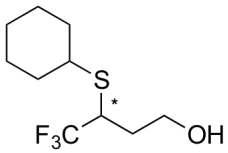
9b

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 98% yield of **9b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 3.83 (s, 2H), 3.60 (dd, 2H, J = 4.0, 7.6 Hz), 3.07 (qdd, 1H, J = 3.4, 8.5, 11.6 Hz), 2.07-1.95 (m, 2H), 1.53 (dddd, 1H, J = 4.0, 4.0, 11.6, 15.3 Hz), 1.25 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.2, 129.1, 127.6, 127.4 (q, J = 278.0 Hz), 58.6, 42.8 (q, J = 28.8 Hz), 30.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.3 (d, J = 8.0 Hz); $[\alpha]^{24}_D$ –147.7 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1764, 1735, 1456, 1394, 1326, 1281, 1212, 1121, 1025, 959, 864, 716 cm^{-1}; Anal. Calcd (%) for

$C_{11}H_{13}F_3OS$: C, 52.79; H, 5.24. Found: C, 52.62; H, 5.24.

The enantiomeric ratio of **9b** was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 8.1 min, minor isomer 10.1 min (95% ee).

4,4,4-trifluoro-3-(cyclohexylthio)butan-1-ol (9c)

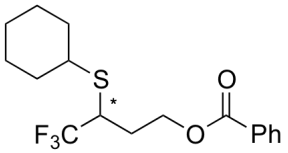


9c

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 99% yield of **9c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98-3.82 (m, 2H), 3.37 (qdd, 1H, *J* = 3.1, 8.5, 11.6 Hz), 2.91-2.80 (m, 1H), 2.19-2.04 (m, 2H), 2.01-1.90 (m, 1H), 1.84-1.71 (m, 2H), 1.71-1.58 (m, 3H), 1.41-1.19 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 127.2 (q, *J* = 278.0 Hz), 59.1, 44.8, 42.9 (q, *J* = 29.7 Hz), 33.8, 33.2, 31.3, 26.0, 25.8, 25.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.8 (d, *J* = 8.0 Hz); $[\alpha]^{24}_D$ –17.2 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1738, 1735, 1439, 1333, 1292, 1203, 1022, 959, 932, 794, 723 cm^{-1}; Anal. Calcd (%) for $C_{10}H_{17}F_3OS$: C, 49.57; H, 7.07. Found: C, 49.33; H, 7.02.

The enantiomeric excess of **9c** was determined by HPLC after converted into corresponding benzoate **21c** (see below).

4,4,4-trifluoro-3-(cyclohexylthio)butyl benzoate (21c)



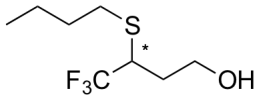
21c

To a solution of **9c** (0.1 mmol) in anhydrous dichloromethane (2 mL) were added triethylamine (0.3 mmol), DMAP (0.01 mmol), and benzoyl chloride (0.2 mmol) successively. The mixture was stirred for 6 h at ambient temperature. Saturated $NaHCO_3$ was added to the mixture. The compound was extracted with dichloromethane, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 2 : 1) to give 76% yield of **21c**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.00 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.43 (m, 2H), 4.63-4.53 (m, 2H), 3.38-3.25 (m, 1H), 2.90-2.77 (m, 1H), 2.49-2.36 (m, 1H), 2.02-1.89 (m, 2H), 1.89-1.78 (m, 1H), 1.78-1.64 (m, 2H), 1.64-1.51 (m, 1H), 1.40-1.15 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 133.1, 129.8, 129.5, 128.4, 127.0 (q, *J* = 278.3 Hz), 61.3, 44.7, 43.0 (q, *J* = 28.8 Hz), 33.5, 33.1, 28.2, 25.8, 25.6, 25.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.8 (d, *J* = 8.0 Hz); $[\alpha]^{24}_D$ –58.1 (c = 0.2, $CHCl_3$); FTIR (neat)

υ_{max} 2057, 1742, 1504, 1404, 1315, 1251, 1172, 1023, 960, 784, 740, 698 cm^{-1}; Anal. Calcd (%) for $C_{10}H_{17}F_3OS$: C, 58.94; H, 6.11. Found: C, 58.99; H, 6.12.

The enantiomeric ratio of **21c** was determined by HPLC (hexane : 2-propanol = 400 : 1, 0.2 mL/min) using a CHIRALPAK AS–H column (0.46 cmϕ x 25 cm): major isomer 27.7 min, minor isomer 33.7 min (96% ee)

4,4,4-trifluoro-3-(butylthio)butan-1-ol (9d)

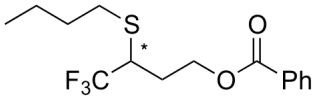


9d

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give 93% yield of **9d**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97-3.82 (m, 2H), 3.30 (qdd, 1H, *J* = 3.4, 8.5, 11.6 Hz), 2.75-2.62 (m, 2H), 2.19-2.08 (m, 1H), 1.76 (brs, OH), 1.73-1.58 (m, 3H), 1.49-1.35 (m, 2H), 0.92 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 127.3 (q, *J* = 279.5 Hz), 59.1, 44.7 (q, *J* = 28.8 Hz), 32.3, 31.3, 30.8, 21.8, 13.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.6 (d, *J* = 8.0 Hz); $[\alpha]^{24}_D$ –31.3 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1735, 1411, 1392, 1305, 1147, 1011, 912, 781, 714 cm^{-1}; Anal. Calcd (%) for $C_8H_{15}F_3OS$: C, 44.43; H, 6.99. Found: C, 44.07; H, 6.81.

The enantiomeric excess of **9d** was determined by HPLC after converted into corresponding benzoate **21d** (see below).

4,4,4-trifluoro-3-(butylthio)butyl benzoate (21d)



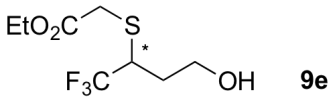
21d

The compound was synthesized according to a procedure similar to that employed for the synthesis of **21c**. The crude product was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 2 : 1) to give 92% yield of **21d**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09-7.99 (m, 2H), 7.62-7.54 (m, 1H), 7.50-7.42 (m, 2H), 4.64-4.52 (m, 2H), 3.24 (qdd, 1H, *J* = 3.4, 8.2, 11.6 Hz), 2.74-2.60 (m, 2H), 2.47-2.35 (m, 1H), 1.87 (dddd, 1H, J = 4.3, 4.6, 11.3, 15.6 Hz), 1.71-1.48 (m, 2H), 1.45-1.29 (m, 2H), 0.85 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 133.1, 129.8, 129.5, 128.4, 127.1 (q, *J* = 278.0 Hz), 61.2, 44.8 (q, *J* = 29.7 Hz), 32.3, 31.3, 27.8, 21.7, 13.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.7 (d, *J* = 8.3 Hz); $[\alpha]^{24}_D$ –29.5 (c = 0.9, $CHCl_3$); FTIR (neat) υ_{max} 2850, 1772, 1474, 1384, 1335, 1264, 1052, 1023, 960, 746, 678 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{19}F_3O_2S$: C, 56.24; H, 5.98. Found: C, 56.30; H, 6.02.

The enantiomeric ratio of **21d** was determined by HPLC (hexane : 2-propanol = 400 : 1, 0.3 mL/min) using a CHIRALPAK AS–H column (0.46 cmϕ x 25 cm): major isomer 17.7 min,

minor isomer 19.7 min (93% ee).

ethyl 2-(1,1,1-trifluoro-4-hydroxybutan-2-ylthio)acetate (9e)

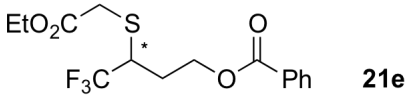


9e

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give 93% yield of **9e**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27-4.18 (m, 2H), 4.05 (ddd, 1H, *J* = 3.4, 11.0, 11.0 Hz), 3.85-3.77 (m, 2H), 3.65-3.52 (m, 1H), 3.58 (d, 1H, *J* = 16.8 Hz), 3.31 (d, 1H, *J* = 16.8 Hz), 2.33 (brs, OH), 2.24-2.14 (m, 1H), 1.55 (dddd, 1H, *J* = 3.1, 3.4, 12.2, 14.7 Hz), 1.31 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 127.2 (q, *J* = 278.0 Hz), 59.1, 42.9 (q, *J* = 29.7 Hz), 33.8, 26.0, 25.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.6 (d, *J* = 8.0 Hz); $[\alpha]^{22}_{D}$ –20.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1715, 1355, 1321, 1312, 1301, 1181, 931, 912, 773, 711 cm^{-1}; Anal. Calcd (%) for $C_8H_{13}F_3O_3S$: C, 39.02; H, 5.32. Found: C, 39.33; H, 5.12.

The enantiomeric excess of **9e** was determined by HPLC after converted into corresponding benzoate **21e** (see below).

3-((ethoxycarbonyl)methylthio)-4,4,4-trifluorobutyl benzoate (21e)



21e

The compound was synthesized according to a procedure similar to that employed for the synthesis of **21c**. The crude mixture was purified by silica gel column chromatography (hexane : CH_2Cl_2 = 2 : 1) to give 80% yield of **21e**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-8.01 (m, 2H), 7.63-7.54 (m, 1H), 7.50-7.42 (m, 2H), 4.63-4.50 (m, 2H), 4.16-4.07 (m, 2H), 3.64 (qdd, 1H, *J* = 3.4, 8.2, 11.6 Hz), 3.48 (d, 1H, *J* = 15.3 Hz), 3.28 (d, 1H, *J* = 15.3 Hz), 2.47-2.36 (m, 1H), 1.90 (dddd, 1H, J = 4.6, 4.6, 11.0, 15.6 Hz), 1.23 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 133.1, 129.8, 129.5, 128.4, 127.1 (q, *J* = 278.0 Hz), 61.2, 44.8 (q, *J* = 29.7 Hz), 32.3, 30.8, 21.7, 13.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –71.8 (d, *J* = 8.0 Hz); $[\alpha]^{24}_{D}$ –45.0 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 2822, 1832, 1829, 1474, 1371, 1321, 1184, 1062, 9540, 752, 669 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{17}F_3O_4S$: C, 51.42; H, 4.89. Found: C, 51.41; H, 4.89.

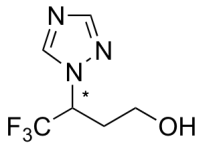
The enantiomeric ratio of **21e** was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 8.2 min, minor isomer 10.2 min (92% ee).

The enantioselective aza-Michael reaction with triazoles (Table 2, Entries 7 and 8)

Triazoles (0.2 mmol) and **1** (0.3 mmol) were added successively to a solution of diarylprolinol

silyl ethter **2** (0.04 mmol) and benzoic acid (0.04 mmol) in anhydrous toluene (5 mL) at –20 °C. The mixture was stirred for 40 h at –20 °C. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 1 h at ambient temperature. Saturated aqueous NH_4Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure.

4,4,4-trifluoro-3-(1*H*-1,2,4-triazol-1-yl)butan-1-ol (10a)

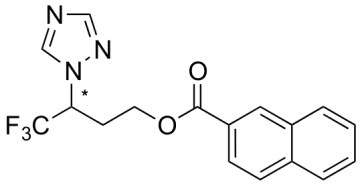


10a

The crude product was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give 77% yield of **10a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.04 (s, 1H), 5.24-5.13 (m, 1H), 3.87-3.78 (m, 1H), 3.31-3.21 (m, 1H), 2.52 (dddd, 1H, *J* = 3.4, 3.4, 11.5, 14.5 Hz), 2.42-2.32 (m, 1H), 1.96 (brs, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.4, 144.8, 123.6 (q, *J* = 280.7 Hz), 57.5 (q, *J* = 32.4 Hz), 56.4, 29.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ –74.7 (d, *J* = 7.0 Hz); $[\alpha]^{20}_D$ –31.5 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3349, 2895, 1512, 1439, 1273, 1199, 1135, 1065, 1008, 856, 680 cm^{-1}; Anal. Calcd (%) for $C_6H_8F_3N_3O$: C, 36.93; H, 4.13; N, 21.53. Found: C, 36.91; H, 4.13; N, 21.72.

The enantiomeric excess of **10a** was determined by HPLC after converted into corresponding 2-naphthoate **22a** (see below).

4,4,4-trifluoro-3-(1*H*-1,2,4-triazol-1-yl)butyl 2-naphthoate (22a)

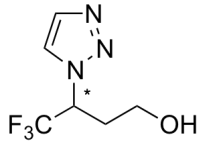


22a

The compound was synthesized according to a procedure similar to that employed for the synthesis of **19a**. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 acetone = 50 : 1) to give 96% yield of **22a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 8.01-7.94 (m, 2H), 7.93-7.88 (m, 2H), 7.66-7.55 (m, 2H), 5.12-5.03 (m, 1H), 4.55-4.48 (m, 1H), 4.22-4.14 (m, 1H), 2.90 (dddd, 1H, *J* = 4.6, 4.6, 11.1, 15.3 Hz), 2.72-2.62 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 152.8, 144.7, 135.7, 132.4, 131.2, 129.4, 128.6, 128.4, 127.8, 126.9, 126.4, 124.9, 123.2 (q, *J* = 281.9 Hz), 59.9, 58.5 (q, *J* = 32.4 Hz), 27.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ –75.0 (d, *J* = 7.0 Hz); $[\alpha]^{20}_D$ –69.6 (c = 0.2, $CHCl_3$); FTIR (neat)

υ_{max} 3123, 1715, 1633, 1511, 1466, 1384, 1278, 1195, 1136, 1098, 1005, 864, 679 cm^{-1}; Anal. Calcd (%) for $C_{17}H_{14}F_3N_3O_2$: C, 58.45; H, 4.04; N, 12.03. Found: C, 58.47; H, 4.33; N, 11.85. The enantiomeric ratio was determined by HPLC (hexane : 2-propanol = 10 : 1, 1.0 mL/min) using a CHIRALPAK AS-H column (0.46 cmϕ x 25 cm): major isomer 14.2 min, minor isomer 11.2 min (86% ee).

4,4,4-trifluoro-3-(1*H*-1,2,3-triazol-1-yl)butan-1-ol (10b)

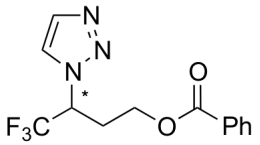


10b

The crude mixture was purified by silica gel column chromatography (dichloromethane : methanol = 15 : 1) to give 76% yield. ^{1}H NMR (500 MHz, CD_3OD): δ 8.21 (s, 1H), 7.83 (s, 1H), 5.70–5.60 (m, 1H), 3.67–3.59 (m, 1H), 3.21–3.12 (m, 1H), 2.61–2.51 (m, 1H), 2.42–2.32 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 134.3, 123.8, 123.6 (q, J = 281.9 Hz), 58.5 (q, J = 32.4 Hz), 56.5, 30.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –74.8 (d, J = 7.5 Hz); $[\alpha]^{24}_D$ –24.7 (c = 0.71, $CHCl_3$); FTIR (neat) υ_{max} 3393, 3123, 2959, 2893, 1650, 1452, 1389, 1267, 1195, 1132, 1065, 919, 853, 762, 700 cm^{-1}; Anal. Calcd (%) for $C_6H_8F_3N_3O$: C, 36.93; H, 4.13; N, 21.53. Found: C, 36.99; H, 4.20; N, 21.77.

The enantiomeric excess of **10b** was determined by HPLC after converted into corresponding 2-naphthoate **22b** (see below).

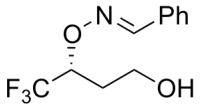
4,4,4-trifluoro-3-(1*H*-1,2,3-triazol-1-yl)butyl 2-benzoate (22b)



22b

The compound was synthesized according to a procedure similar to that employed for the synthesis of **21c**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 86% yield (84% ee). ^{1}H NMR (500 MHz, CD_3OD): δ 7.99–7.94 (m, 2H), 7.81 (s, 1H), 7.74 (s, 1H), 7.62–7.57 (m, 1H), 7.49–7.43 (m, 2H), 5.49–5.34 (m, 1H), 4.51–4.44 (m, 1H), 4.12–4.03 (m, 1H), 2.83–2.74 (m, 1H), 2.74–2.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 133.6, 133.5, 129.6, 129.2, 128.5, 123.5, 123.3 (q, J = 281.9 Hz), 59.5, 59.2 (q, J = 32.4 Hz), 27.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ –74.4 (d, J = 7.0 Hz). The enantiomeric excess was determined by HPLC (hexane : dichloromethane = 1 : 1, 1.0 mL/min) using a CHIRALPAK IE column (0.46 cmϕ x 25 cm): major isomer 17.5 min and minor isomer 18.8 min.

The enantioselective oxa-Michael reaction with aldoxime (Table 2, Entry 9): benzaldehyde *O*-(1,1,1-trifluoro-4-hydroxybutan-2-yl) oxime (11)

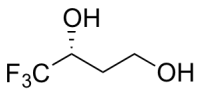


11

Benzaldehyde oxime (0.6 mmol) and **1** (0.2 mmol) were added to a solution of diarylprolinol silyl ether **2** (0.02 mmol) and benzoic acid (0.02 mmol) in toluene (0.5 mL). The mixture was stirred for 12 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 1 h at 0 °C. Saturated aqueous NH_4Cl solution was added to the reaction mixture. The compound was then extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 73% yield of **11**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.62-7.52 (m, 2H), 7.45-7.34 (m, 3H), 4.87-4.78 (m, 1H), 3.91-3.81 (m, 2H), 2.17-1.88 (m, 2H), 1.77 (brs, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.5, 131.0, 130.5, 128.8, 127.3, 124.6 (q, J = 238.1 Hz), 77.9 (q, J = 30.0 Hz), 57.8, 30.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –77.2 (d, J = 7.0 Hz); $[\alpha]^{25}_D$ +14.3 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 3368, 2963, 1277, 1172, 931, 763, 695, 453 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{12}F_3NO_2$: C, 53.34; H, 4.89; N, 5.67. Found: C, 53.46; H, 4.97; N, 5.81.

The enantiomeric ratio of **11** was determined by HPLC (hexane : 2-propanol = 50 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 18.8 min and minor isomer 13.5 min (95% ee).

Asymmetric synthesis of befloxatone (Scheme 4): (*R*)-4,4,4-trifluorobutane-1,3-diol (12)



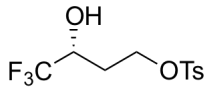
12

To a suspension of 20% $Pd(OH)_2/C$ (10 mg) in methanol (0.4 mL) was added a solution of **1** (0.15 mmol) in methanol (0.6 mL). The mixture was stirred for 3 h at ambient temperature under a hydrogen atmosphere. After the reaction mixture was filtered, the filtrate was concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 5 : 1) to give 91% yield of **12**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.87-4.78 (m, 1H), 3.91-3.81 (m, 2H), 2.17-1.88 (m, 2H); ^{13}C NMR (126 MHz,

$CDCl_3$): δ 124.9 (q, *J* = 281.9 Hz), 69.4 (q, *J* = 34.8 Hz), 59.8, 31.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ –80.4 (d, *J* = 7.0 Hz); $[\alpha]^{24}_D$ +7.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 3378, 2930, 1706, 1275, 1129, 413 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{12}F_3NO_2$: C, 33.34; H, 4.90. Found: C, 33.49; H, 5.02.

The absolute configuration of **12** was determined to be *R* by comparing the optical rotation with a reported value. [T. Yamazaki, N. Okamura, T. Kitazume, *Tetrahedron: Asymmetry* 1990, **1**, 521]

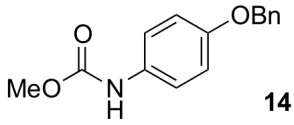
4,4,4-trifluoro-3-hydroxybutyl 4-methylbenzenesulfonate (13)



13

Tosyl chloride (0.33 mmol) was added to a solution of diol **12** (0.3 mmol) in pyridine (4.5 mmol). The mixture was stirred for 24 h at ambient temperature. Saturated $NaHCO_3$ was added to the mixture. The compound was extracted with dichloromethane, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 53% yield of **13**. ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 2H, *J* = 7.6 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 5.17-5.04 (m, 1H), 3.88-3.77 (m, 2H), 2.47 (s, 3H), 2.15-2.02 (m, 1H), 1.97-1.86 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 125.3 (q, *J* = 282.7 Hz), 71.1, 69.2 (q, *J* = 34.8 Hz), 59.8, 31.3, 29.7; $[\alpha]^{25}_D$ +24.7 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 3282, 1782, 1387, 1257, 1232, 1041, 1033, 417, 369 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{13}F_3O_4S$: C, 44.29; H, 4.39. Found: C, 44.22; H, 4.07.

methyl 4-(benzyloxy)phenylcarbamate (14)

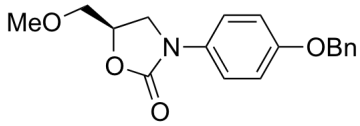


14

To a solution of 4-benzyloxyaniline hydrochloride (4 mmol) and triethylamine (4.4 mmol) in anhydrous dichloromethane (5 mL) was added methyl chloroformate (6 mmol). The mixture was stirred at ambient temperature for 8 h. Saturated $NaHCO_3$ was added to the mixture. The compound was extracted with dichloromethane, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used in the next step without further purification (90% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.49-7.18 (m, 7H), 6.98-6.87 (m, 2H), 6.48 (brs, NH), 5.04 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 154.3, 137.0, 131.1, 128.5, 127.9, 127.4, 120.5, 115.2, 70.2, 52.2; FTIR (neat) υ_{max} 3320, 1706, 1597, 1453, 1416, 1298, 1239, 1074, 733 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.04; H,

5.88; N, 5.43.

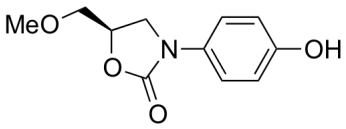
3-(4-(benzyloxy)phenyl)-5-(methoxymethyl)oxazolidin-2-one (16)



16

To a solution of **14** (3 mmol) and K_2CO_3 (6 mmol) in anhydrous DMF (6 mL) was added (*S*)-4-methoxymethyl-1,3-dioxolane-2-one (**15**) (3 mmol). The mixture was stirred for 3 h at 155 °C. After the mixture was diluted with water, the compound was extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 10 : 1) to give 83% yield of **16**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.28 (m, 7H), 6.99-6.95 (m, 2H), 5.05 (s, 2H), 4.77-4.70 (m, 1H), 4.02 (dd, 1H, *J* = 8.8, 8.8 Hz), 3.88 (dd, 1H, *J* = 6.5, 8.8 Hz), 3.64 (d, 2H, *J* = 4.6 Hz), 3.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.4, 136.8, 131.6, 128.6, 128.0, 127.4, 120.0, 115.2, 72.6, 71.1, 70.2, 59.6, 47.5; $[\alpha]^{26}_D$ –16.4 (c = 0.2, $CHCl_3$); FTIR (neat) υ_{max} 1745, 1510, 1229, 1132, 754 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{13}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.76; H, 5.97; N, 4.22.

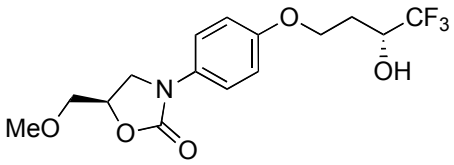
3-(4-hydroxyphenyl)-5-(methoxymethyl)oxazolidin-2-one (17)



17

A mixture of **16** (0.16 mmol) and 5% Pd/C (34 mg) dissolved in EtOH–CH_2Cl_2 (1:1) (1.6 mL) was stirred for 12 h at ambient temperature under hydrogen atmosphere. After the reaction mixture was filtered, the filtrate was concentrated at reduced pressure. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give 92% yield of **17**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, 2H, *J* = 8.0 Hz), 6.82 (d, 2H, *J* = 8.0 Hz), 4.81-4.69 (m, 1H), 4.01 (dd, 1H, *J* = 8.8, 8.8 Hz), 3.87 (dd, 1H, *J* = 6.5, 8.4 Hz), 3.64 (d, 2H, *J* = 4.2 Hz), 3.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.4, 153.3, 130.6, 120.9, 115.9, 72.6, 71.4, 59.6, 47.9; $[\alpha]^{25}_D$ –40.0 (c = 0.3, $CHCl_3$); FTIR (neat) υ_{max} 3248, 1717, 1515, 1427, 1236, 1134, 756 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.97; N, 6.21.

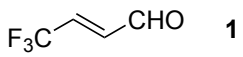
befloxatone



befloxatone

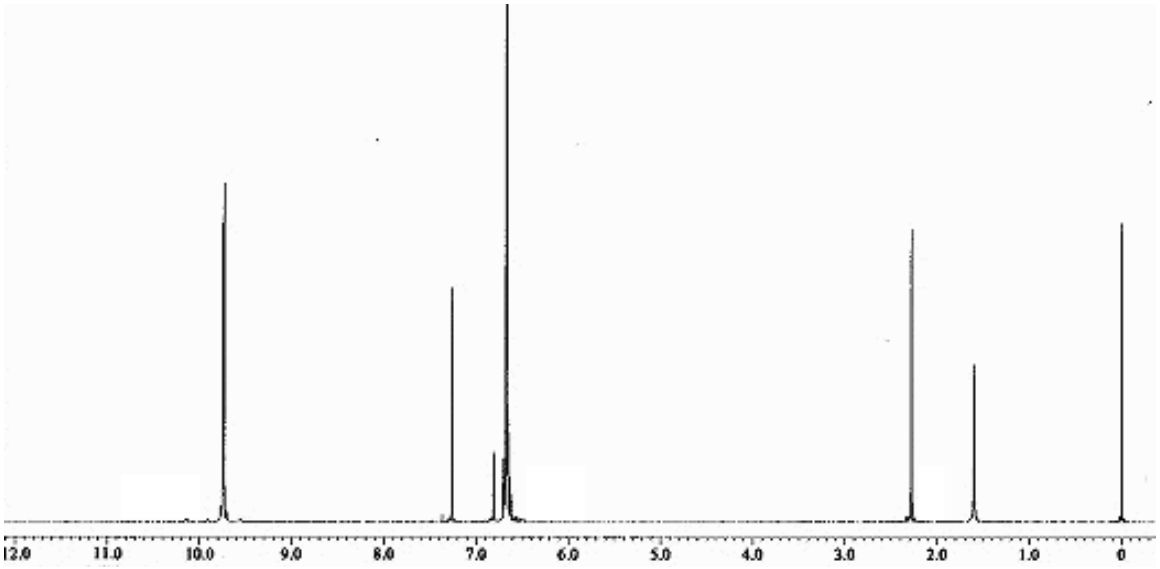
A mixture of **17** (0.1 mmol), **13** (0.15 mmol), and K_2CO_3 (0.2 mmol) dissolved in anhydrous DMF (0.5 mL) was stirred for 6 h at 85 °C. After the mixture was diluted with water, the compound was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 84% yield of befloxatone as a diastereomeric mixture (dr = 98 : 2). ^{1}H NMR (500 MHz, CD_3OD): δ 7.34-7.29 (m, 2H), 6.81-6.76 (m, 2H), 4.81-4.75 (m, 1H), 4.12-4.04 (m, 1H), 4.07 (dd, 1H, *J* = 8.8, 9.2 Hz), 3.84 (dd, 1H, *J* = 6.5, 8.6 Hz), 3.75-3.69 (m, 2H), 3.66 (dd, 1H, *J* = 3.4, 11.1 Hz), 3.59 (dd, 1H, *J* = 4.6, 11.1 Hz), 3.42 (s, 3H), 1.89-1.80 (m, 1H), 1.73-1.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.6, 153.2, 130.3, 124.9 (q, *J* = 281.9 Hz), 121.1, 115.8, 72.4, 71.5, 68.9 (q, *J* = 31.2 Hz), 59.5, 47.8, 31.0, 29.6; $[\alpha]^{26}_D$ +17.6 (c = 0.2, $CHCl_3$);FTIR (neat) υ_{max} 3368, 2933, 1726, 1516, 1131, 756, 416 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{18}F_3NO_5$: C, 51.58; H, 5.19; N, 4.01. Found: C, 51.66; H, 5.43; N, 4.33.

The diastereomeric ratio of befloxatone was confirmed by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 18.9 min, minor isomer 13.5 min (96% de)

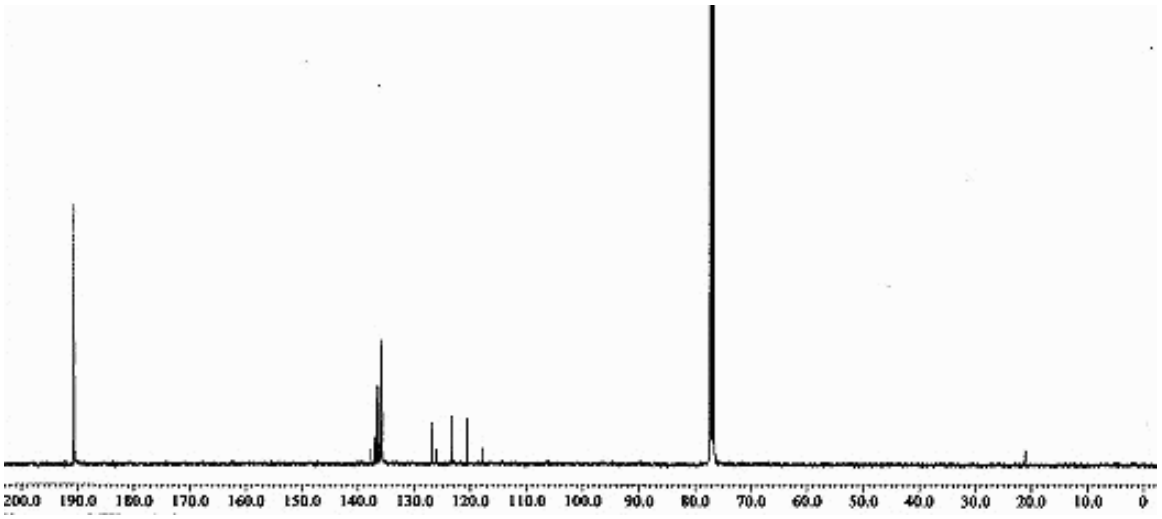


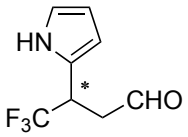
1

^{1}H NMR



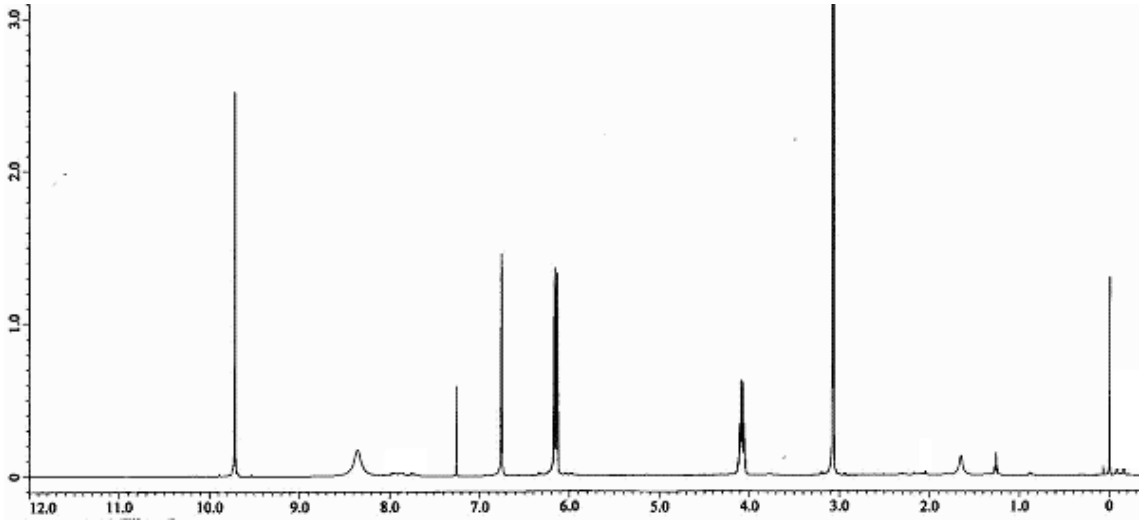
^{13}C NMR



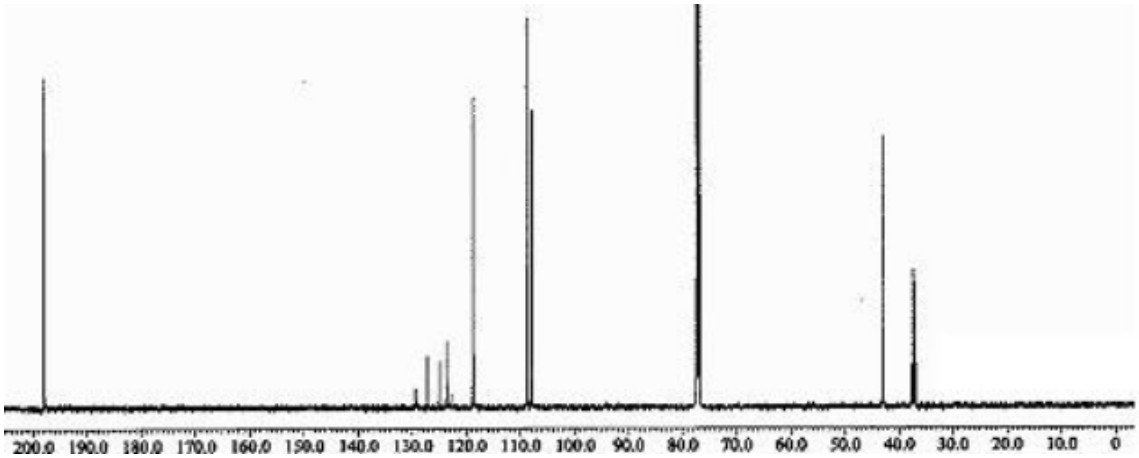


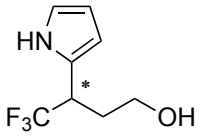
5a

^{1}H NMR



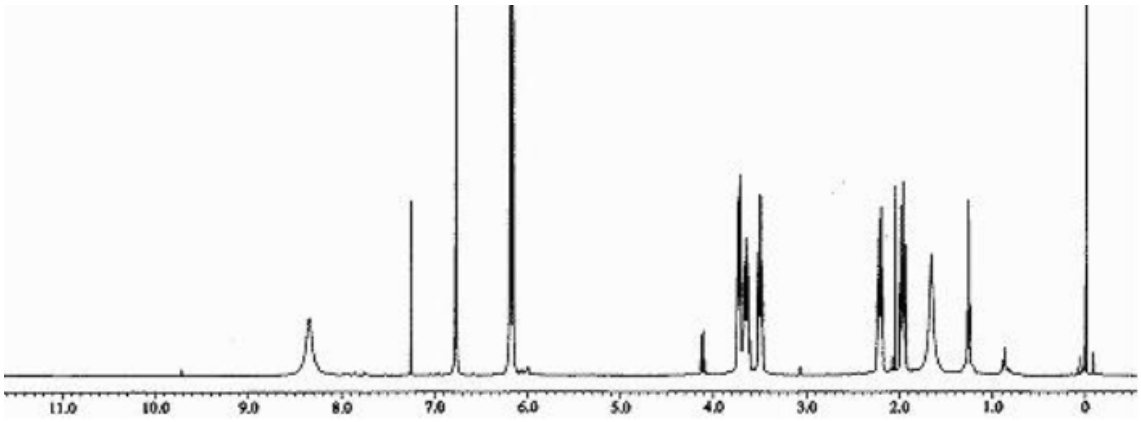
^{13}C NMR



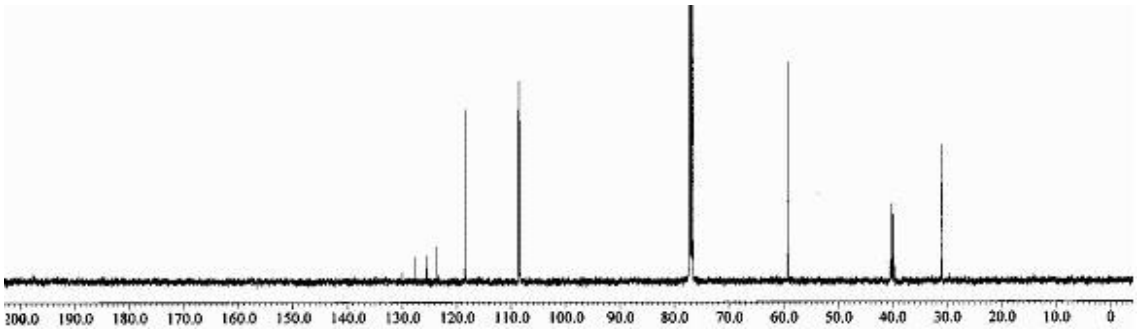


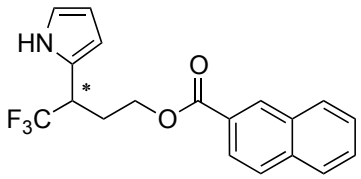
18a

^{1}H NMR



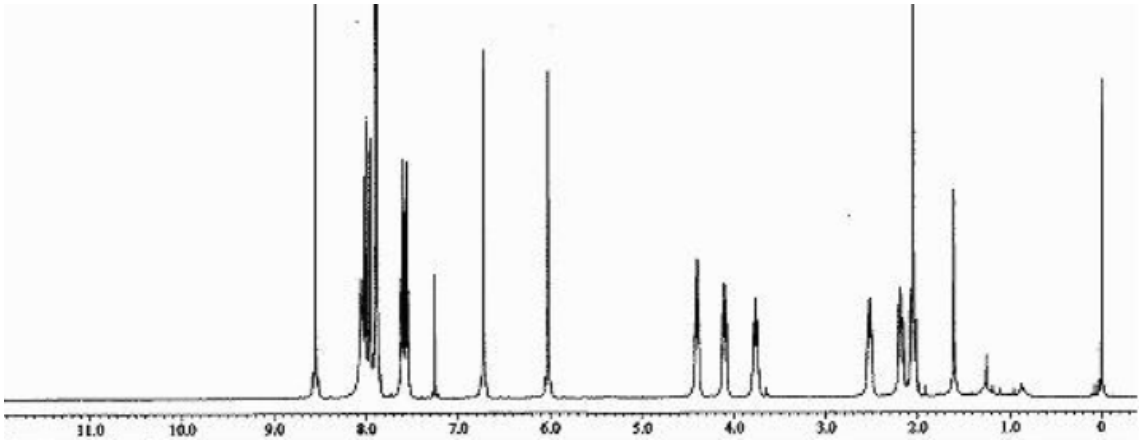
^{13}C NMR



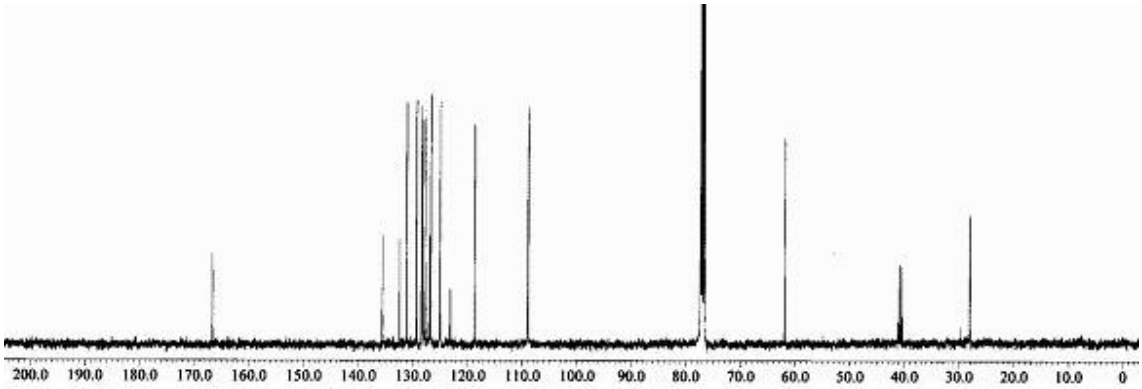


19a

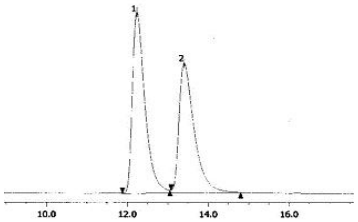
^{1}H NMR



^{13}C NMR



HPLC *racemic*



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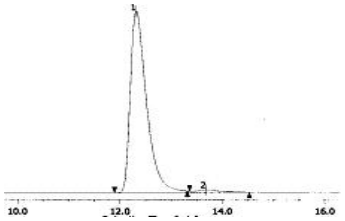
HPLC *optically active*



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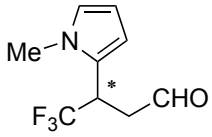
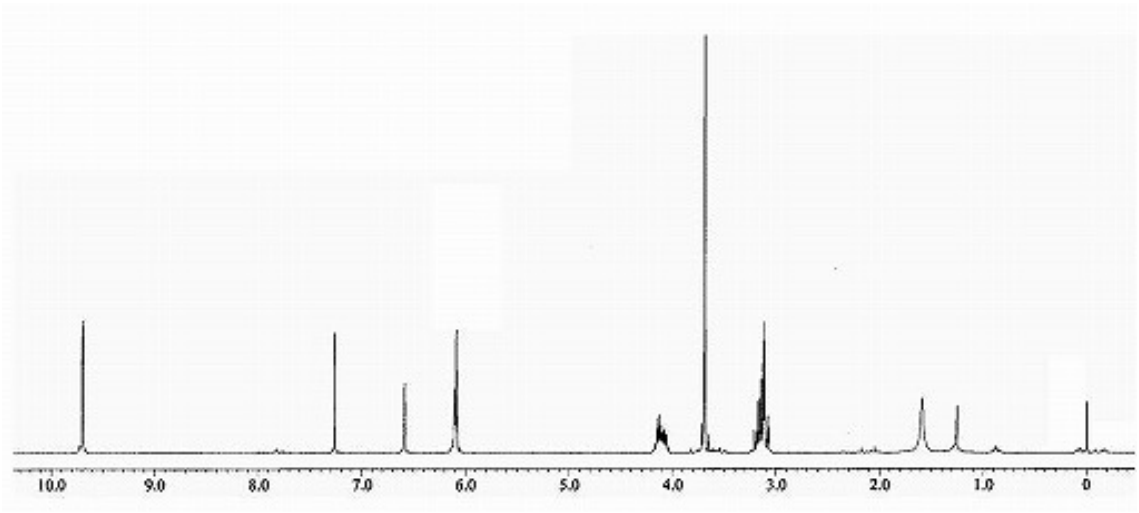
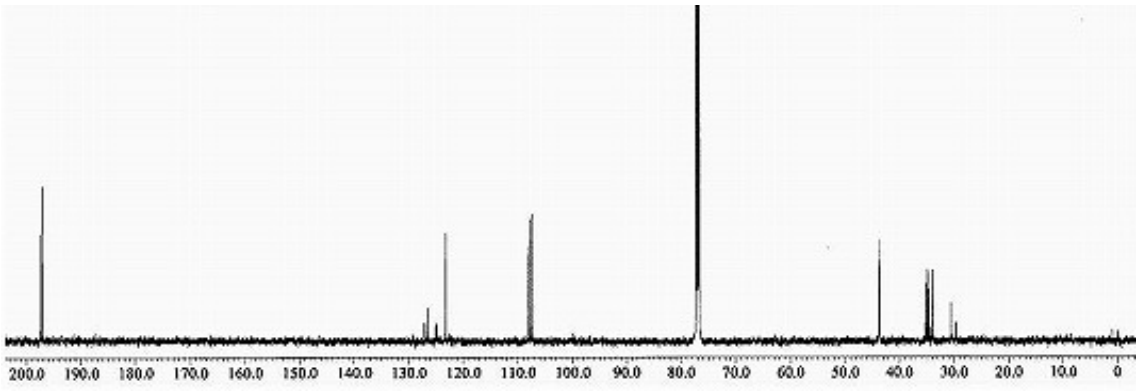


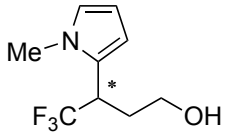
5b

^{1}H NMR



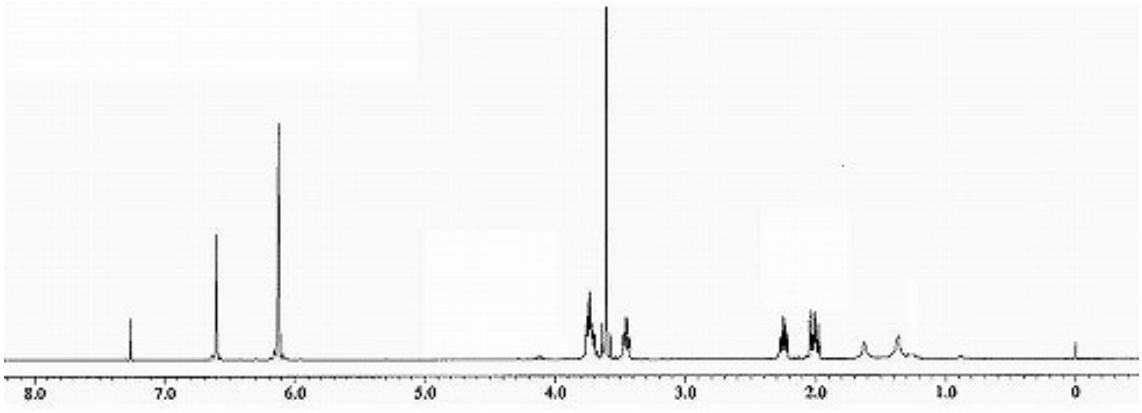
^{13}C NMR



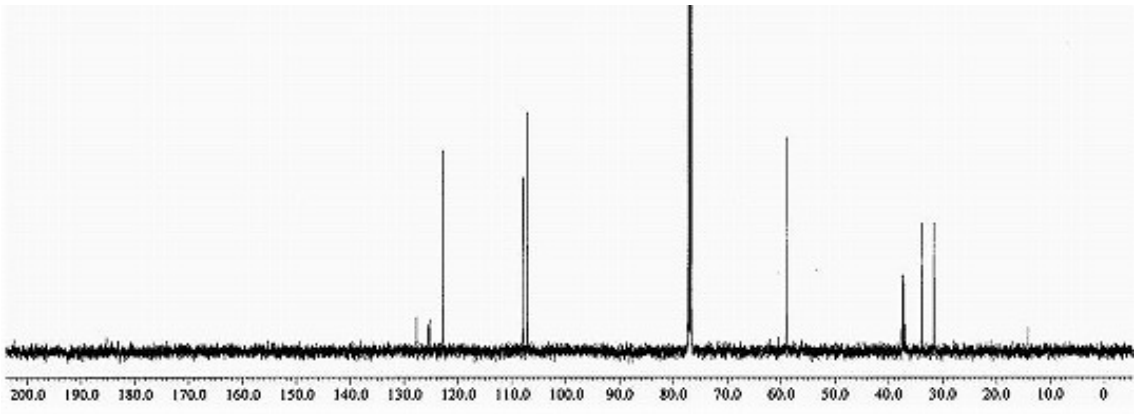


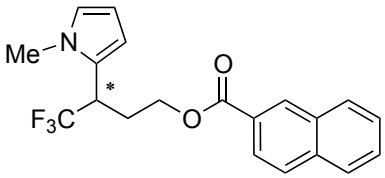
18b

^{1}H NMR



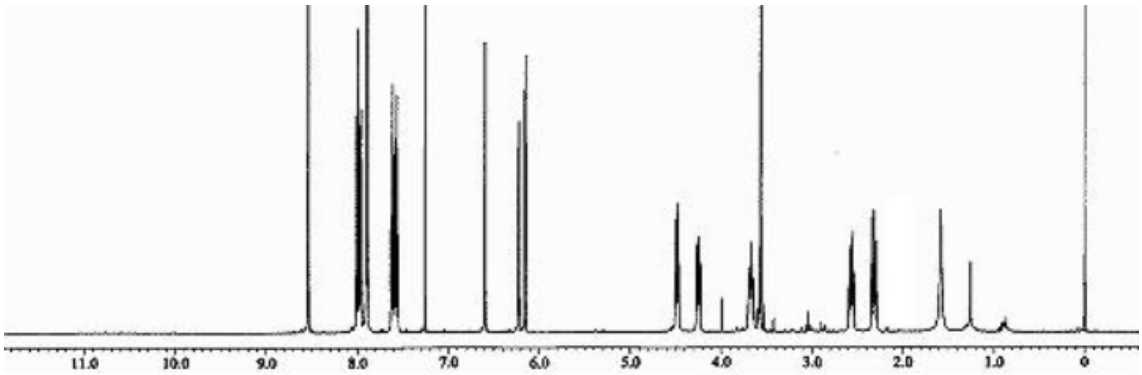
^{13}C NMR



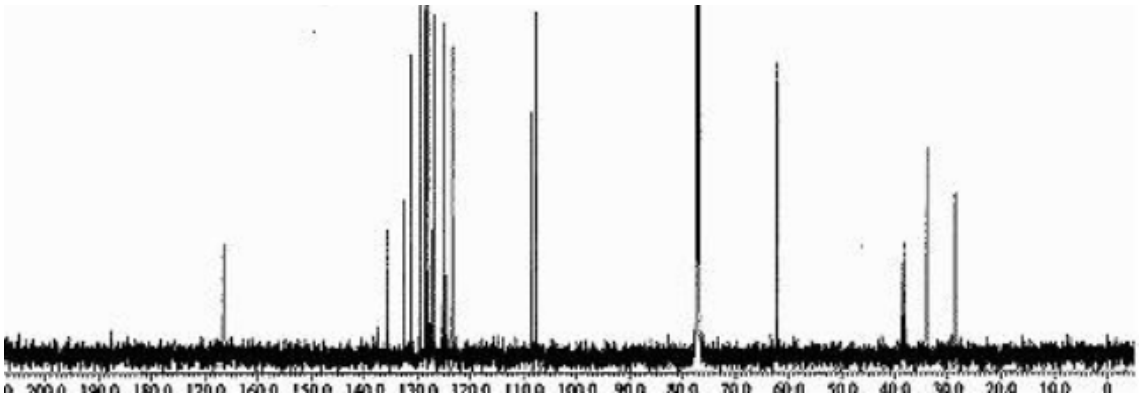


19b

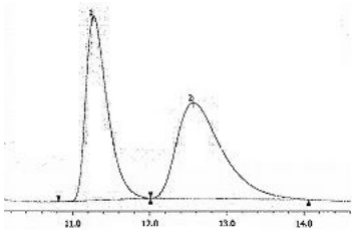
^{1}H NMR



^{13}C NMR



HPLC *racemic*



#	ピーク名	CH	tR[min]	面積[μV*sec]	高さ[μV]	面積%
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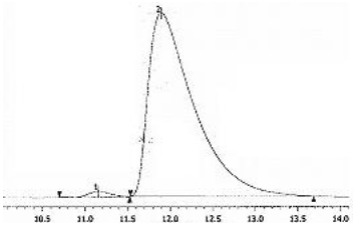
HPLC *optically active*



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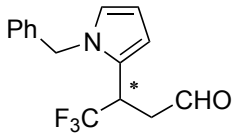
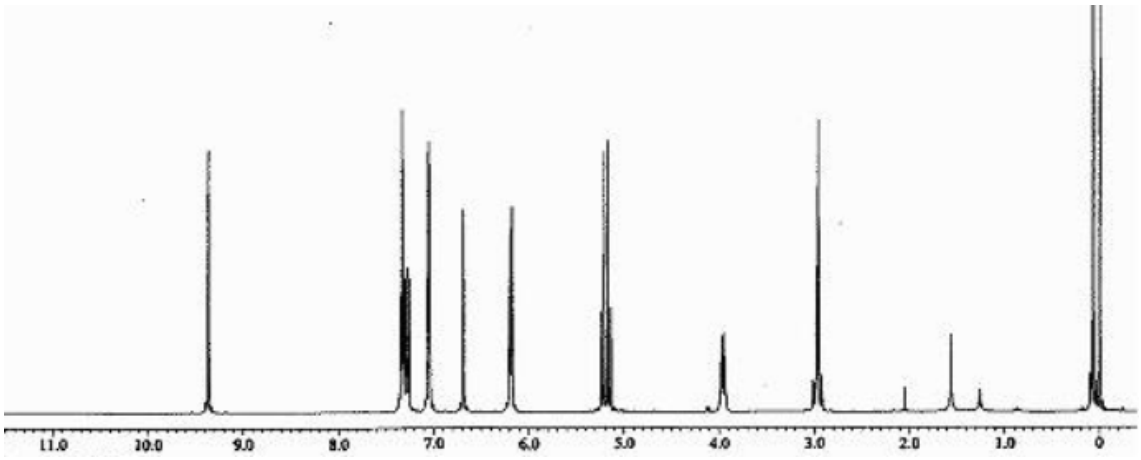


5c

^{1}H NMR



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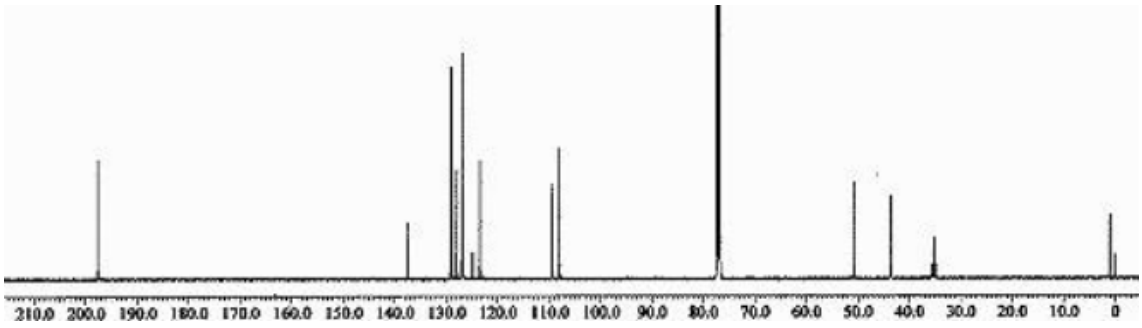
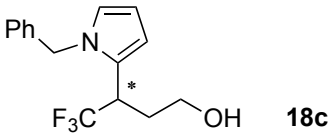
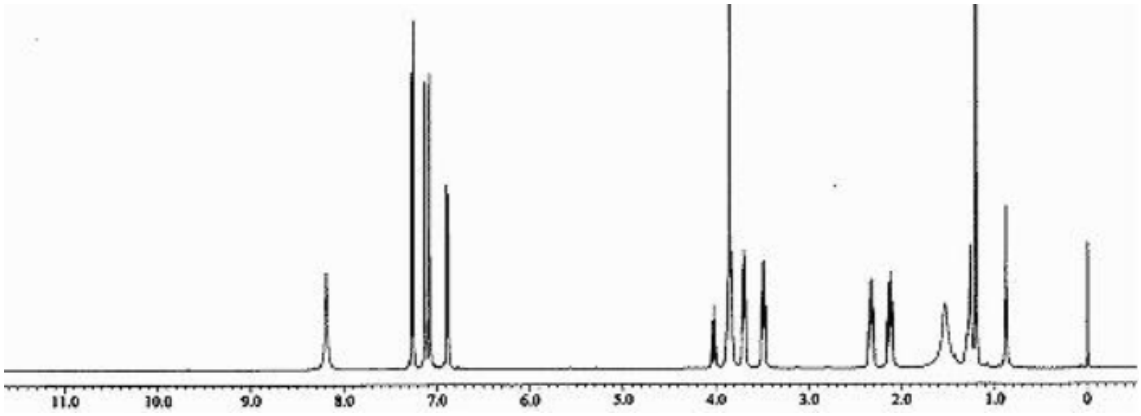


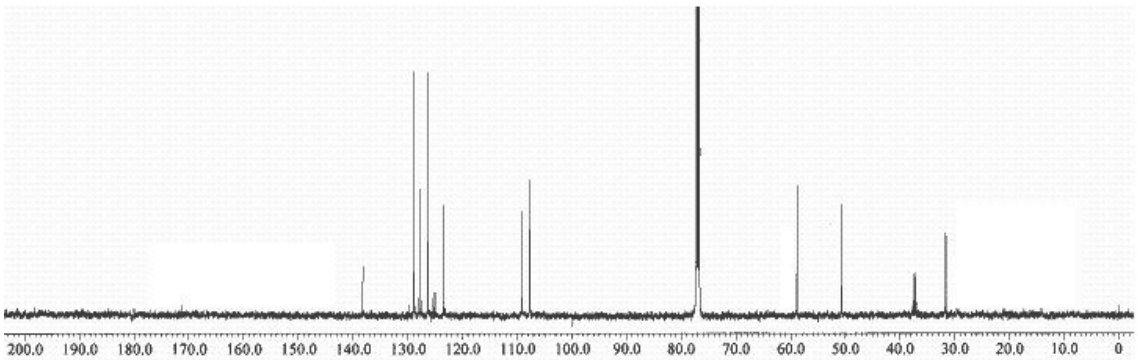


18c

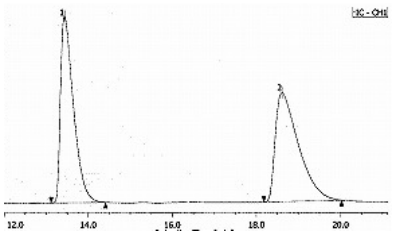
^{1}H NMR

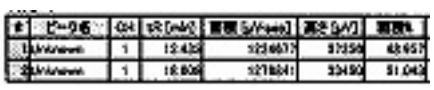


^{13}C NMR

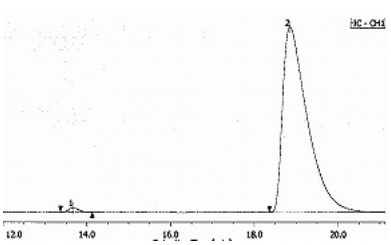


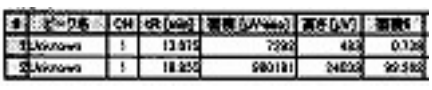
HPLC *racemic*

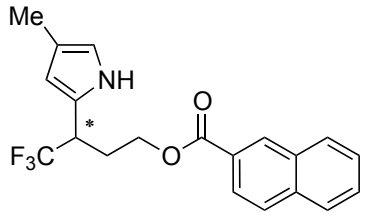




HPLC *optically active*

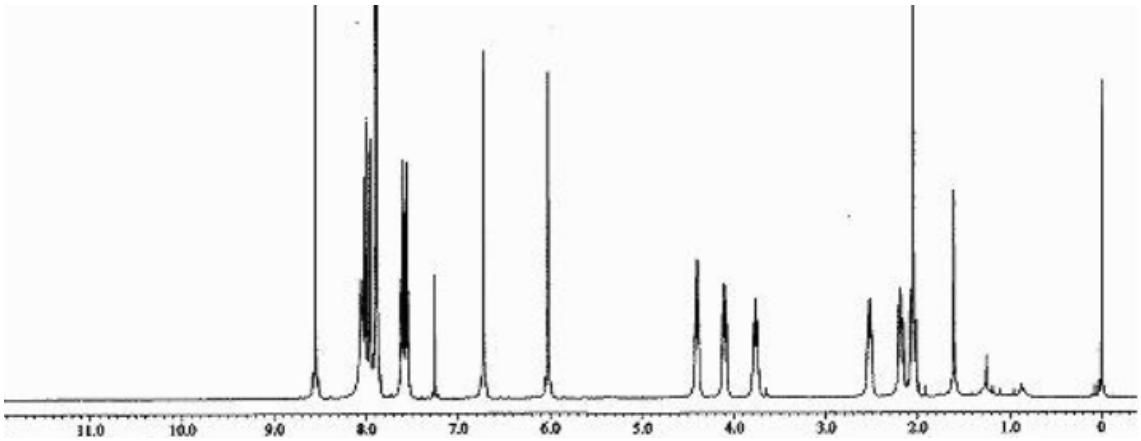




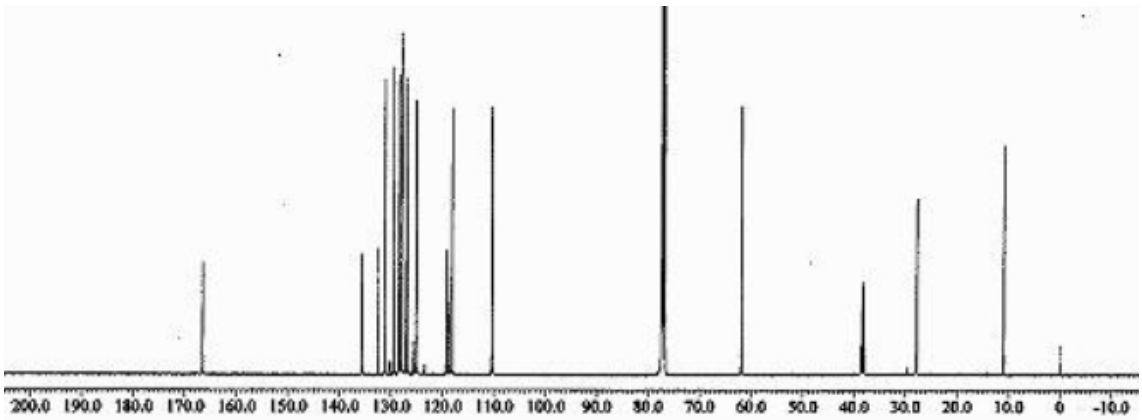


19d

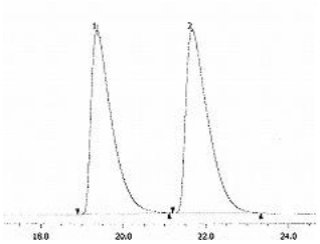
^{1}H NMR



^{13}C NMR

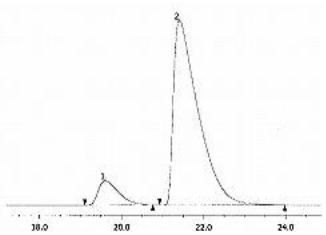


HPLC *racemic*

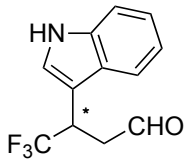


#	ピーク名	CH	保持時間 [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	19.208	10044574	254283	48.467
2	Unknown	1	21.667	10683661	253315	51.533

HPLC *optically active*

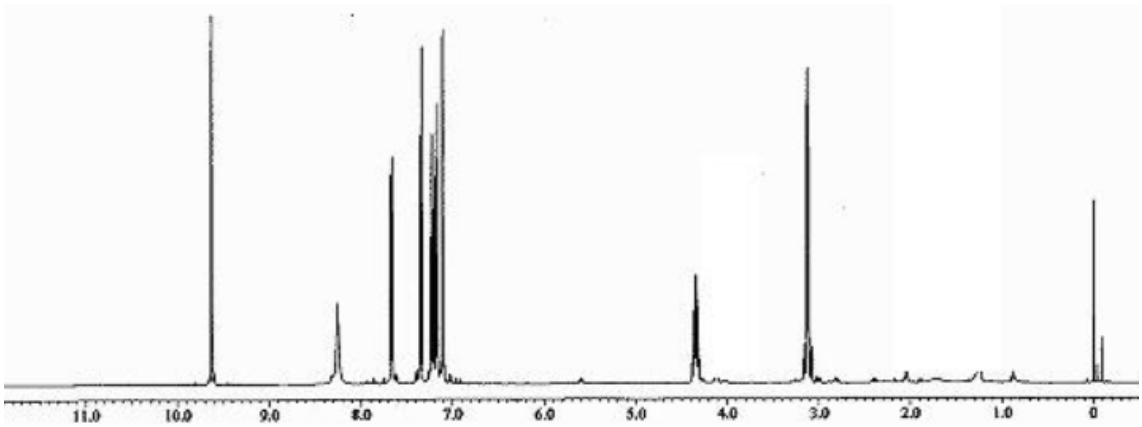


#	ピーク名	CH	保持時間 [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	19.500	2524126	68373	9.682
2	Unknown	1	21.400	23551142	521634	90.318

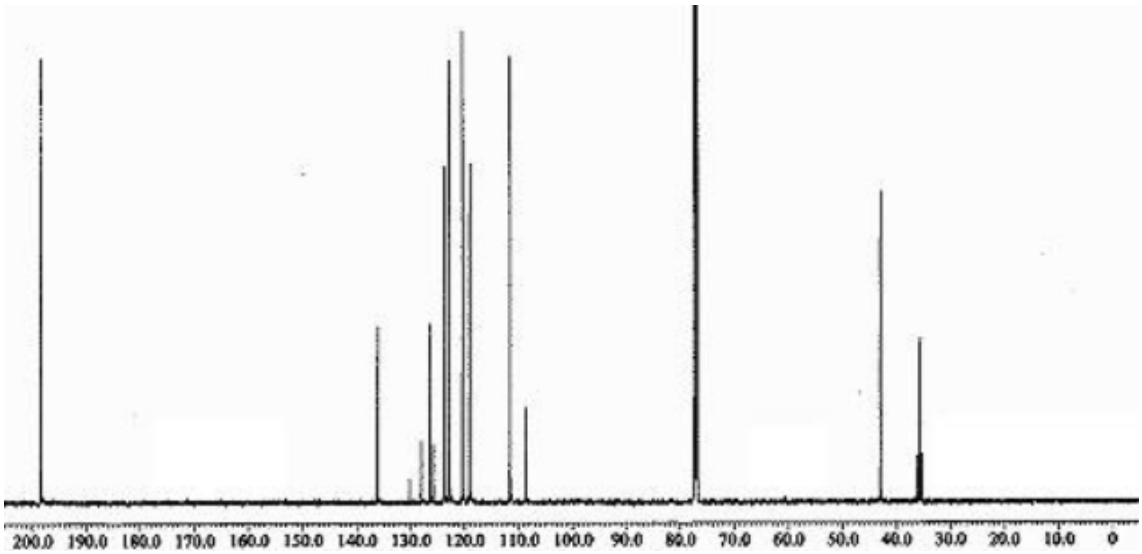


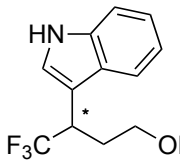
6a

^{1}H NMR



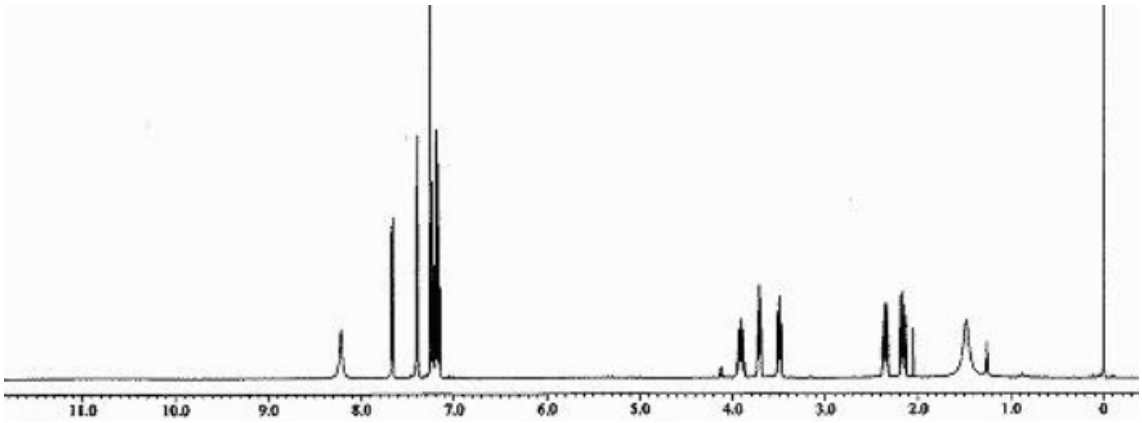
^{13}C NMR



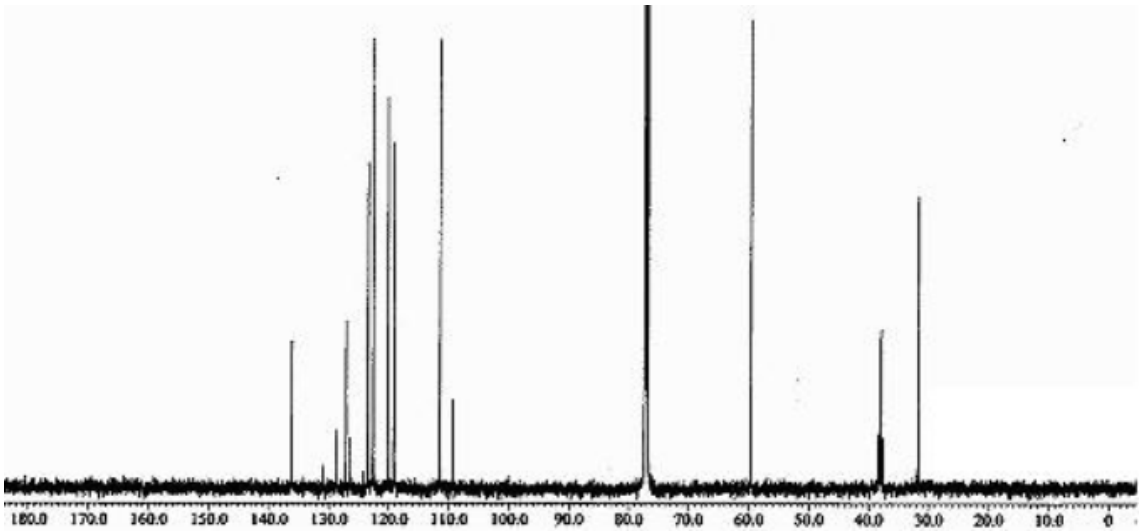


20a

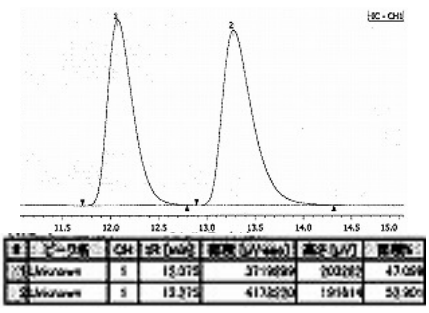
^{1}H NMR



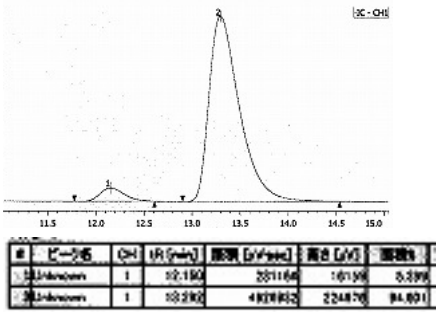
^{13}C NMR

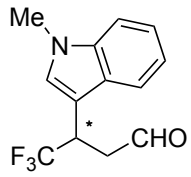


HPLC *racemic*



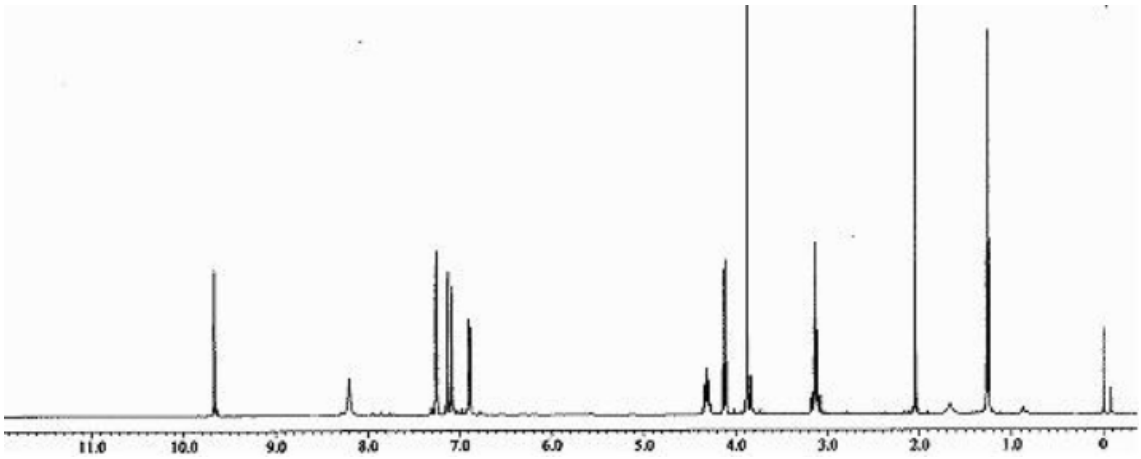
HPLC *optically active*



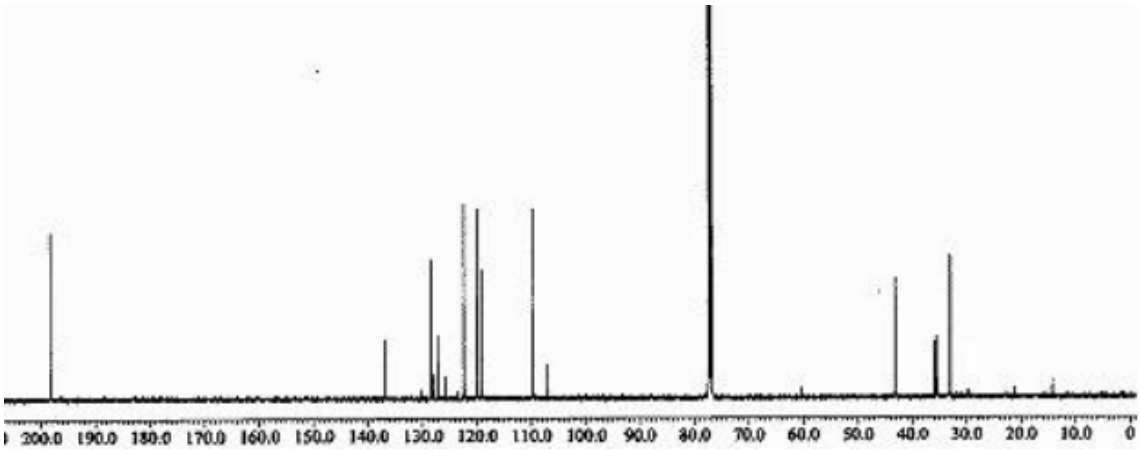


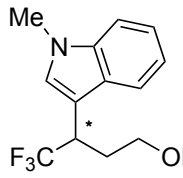
6b

^{1}H NMR



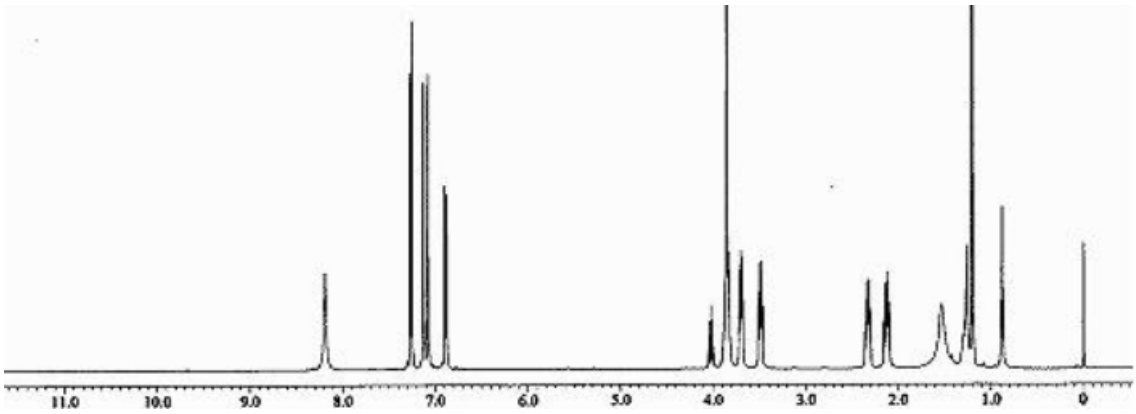
^{13}C NMR



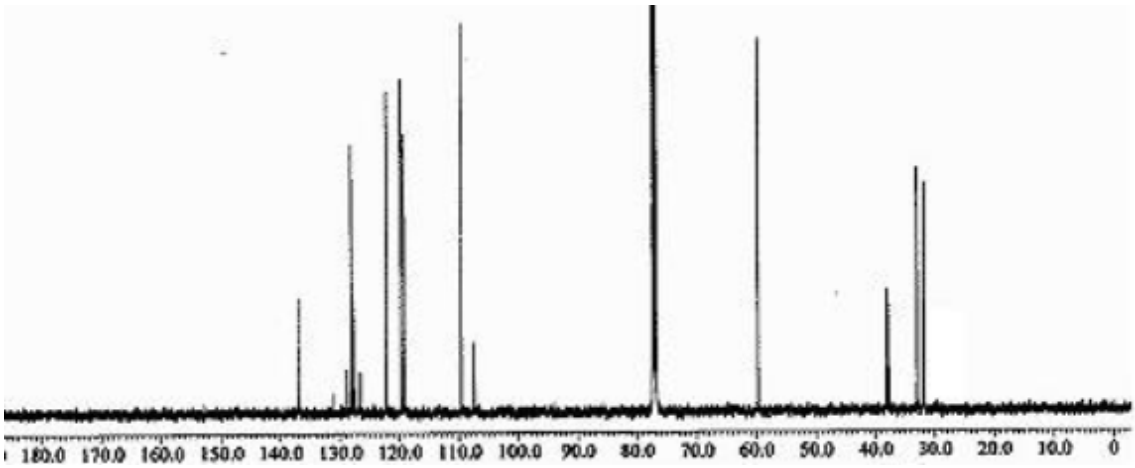


20b

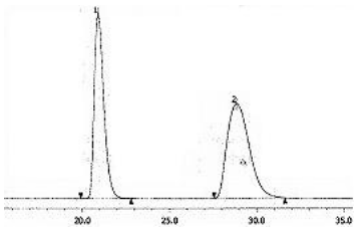
^{1}H NMR



^{13}C NMR

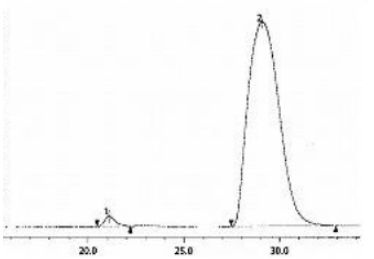


HPLC *racemic*

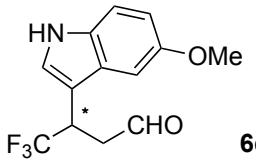


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	22.900	4276468	112038	45.942
2	Unknown	1	29.842	5031648	87201	54.057

HPLC *optically active*

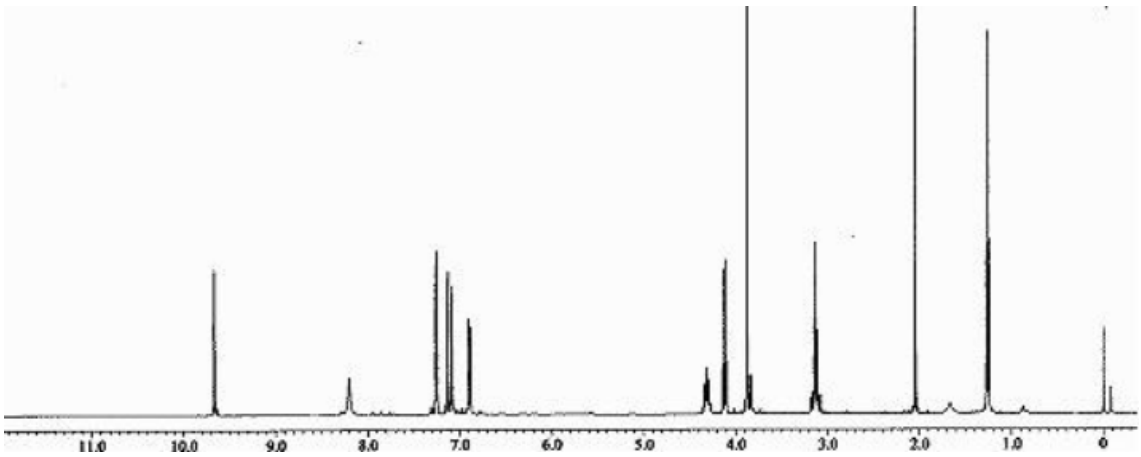


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	21.100	152963	3922	1.654
2	Unknown	1	25.108	9093485	80602	98.345

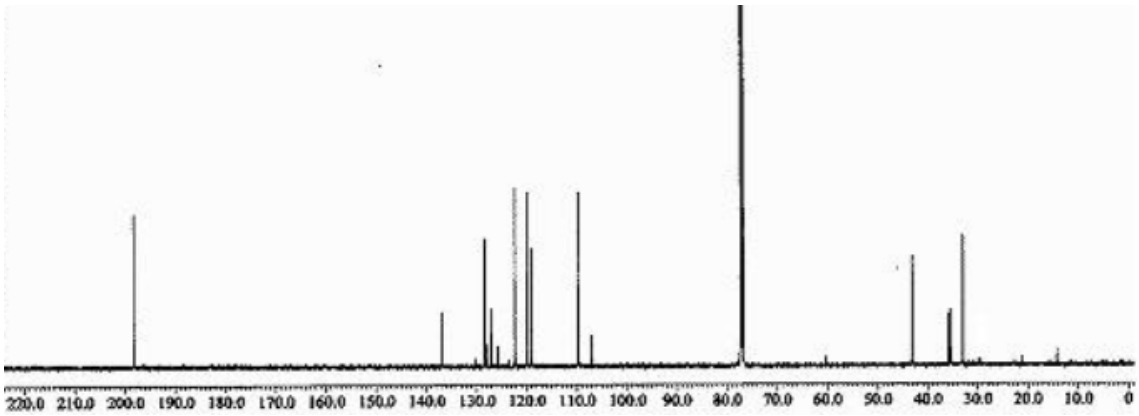


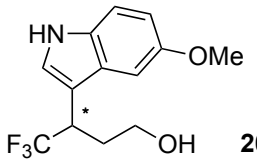
6c

^{1}H NMR



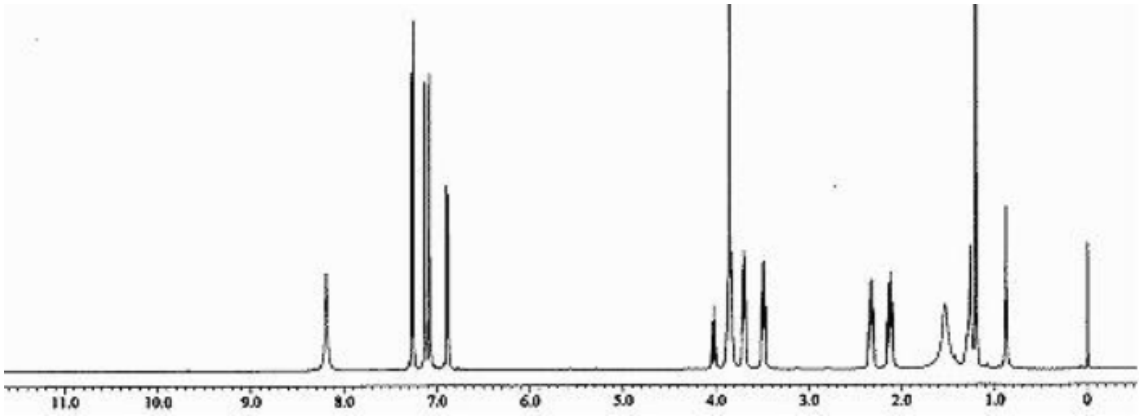
^{13}C NMR



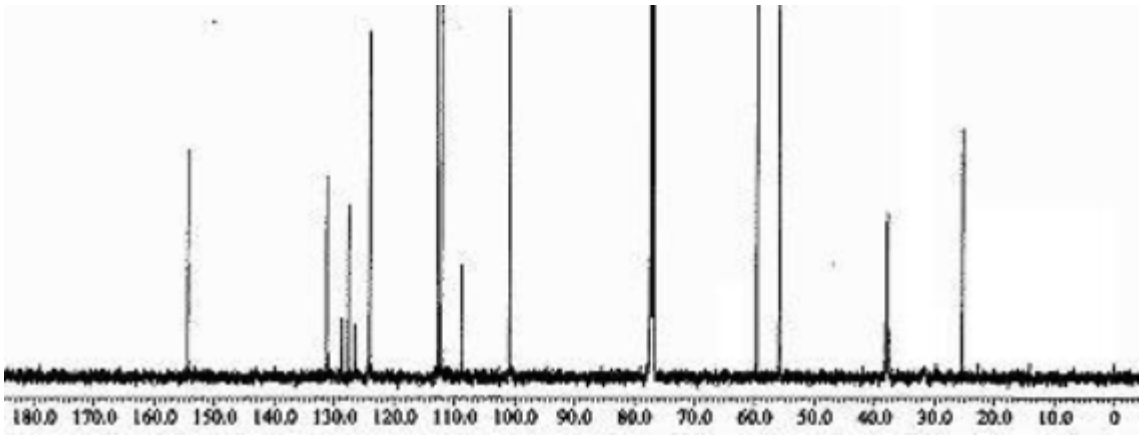


20c

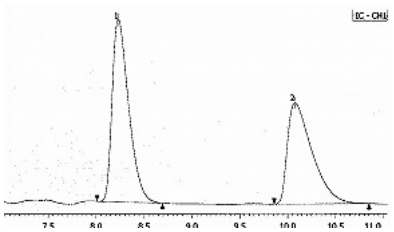
^{1}H NMR

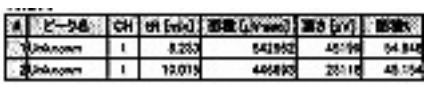


^{13}C NMR

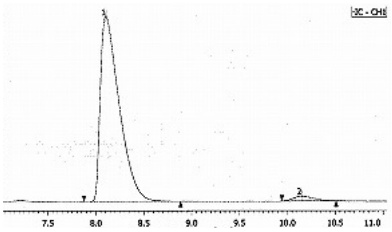


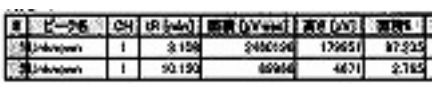
HPLC *racemic*

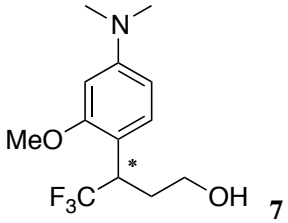




HPLC *optically active*

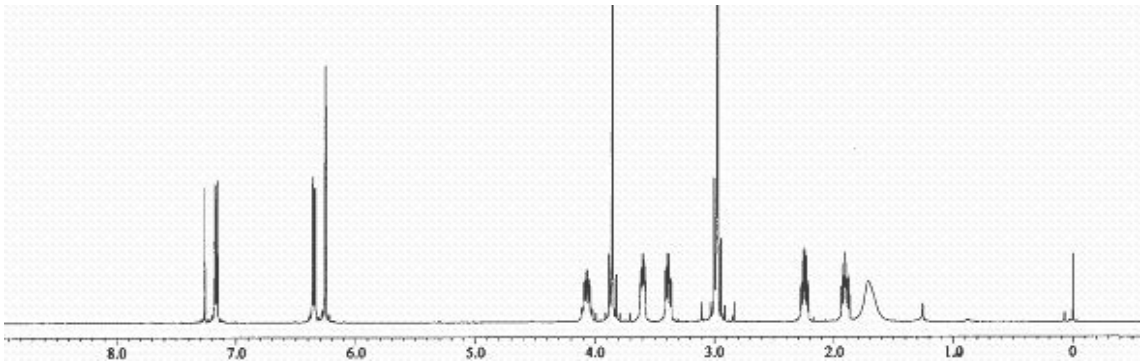




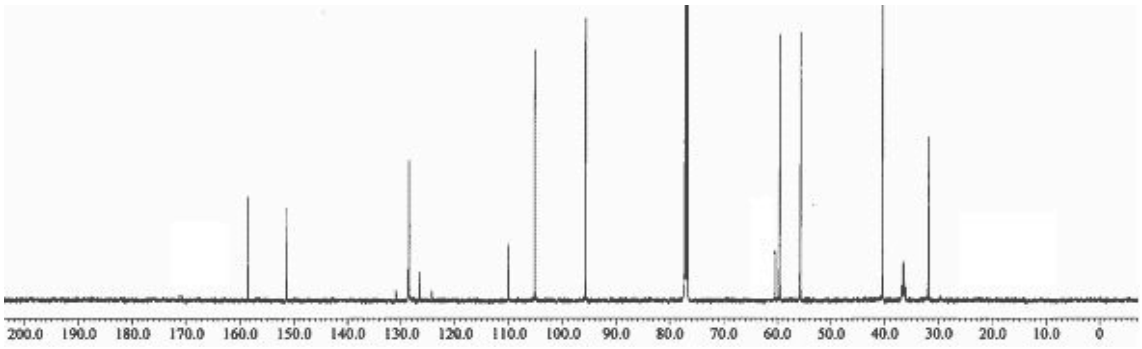


7

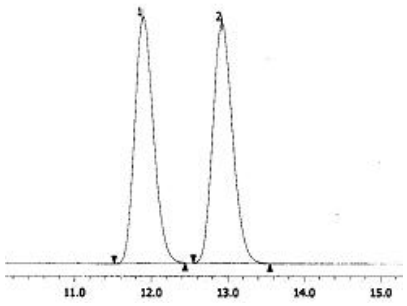
^{1}H NMR



^{13}C NMR

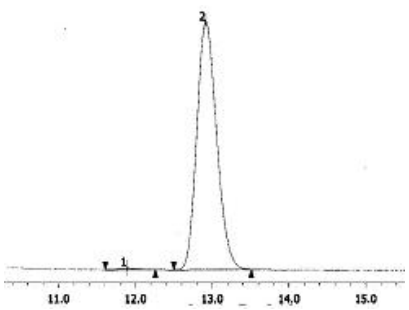


HPLC *racemic*

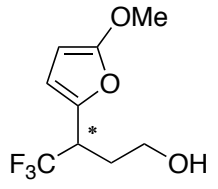


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	11.892	2981118	174004	49.319
2	Unknown	1	12.925	3042908	169303	50.681

HPLC *optically active*

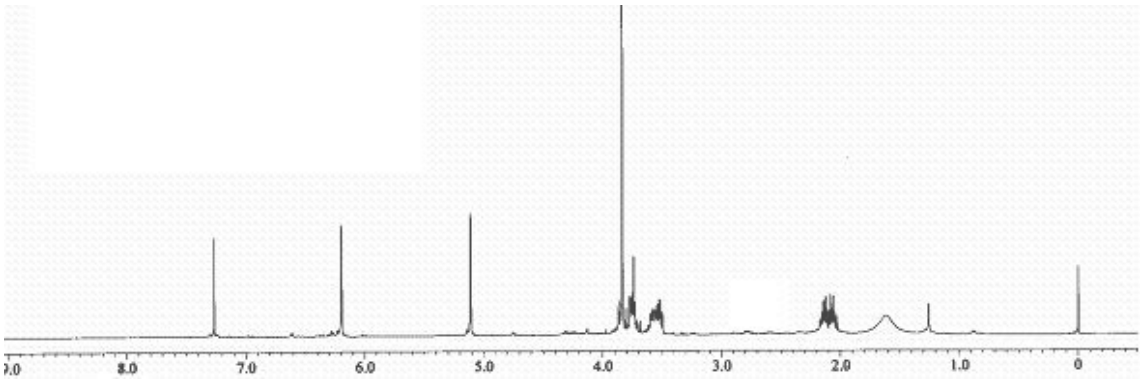


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	11.892	31581	1883	0.551
2	Unknown	1	12.917	5703556	318477	99.449

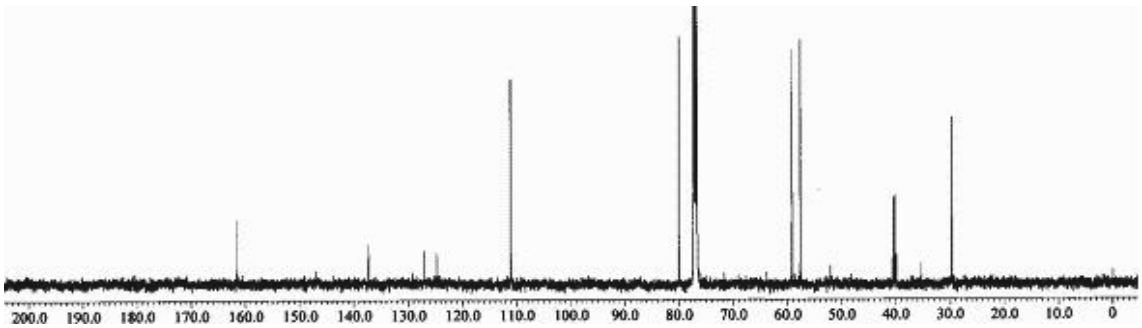


8

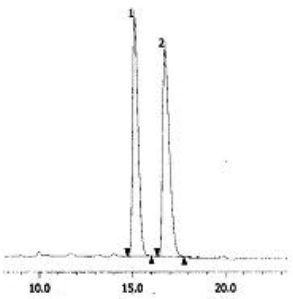
^{1}H NMR



^{13}C NMR

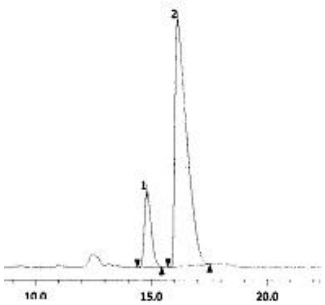


HPLC *racemic*

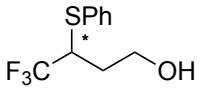


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	13.125	283809	13732	48.798
2	Unknown	1	16.750	297584	11843	51.202

HPLC *optically active*

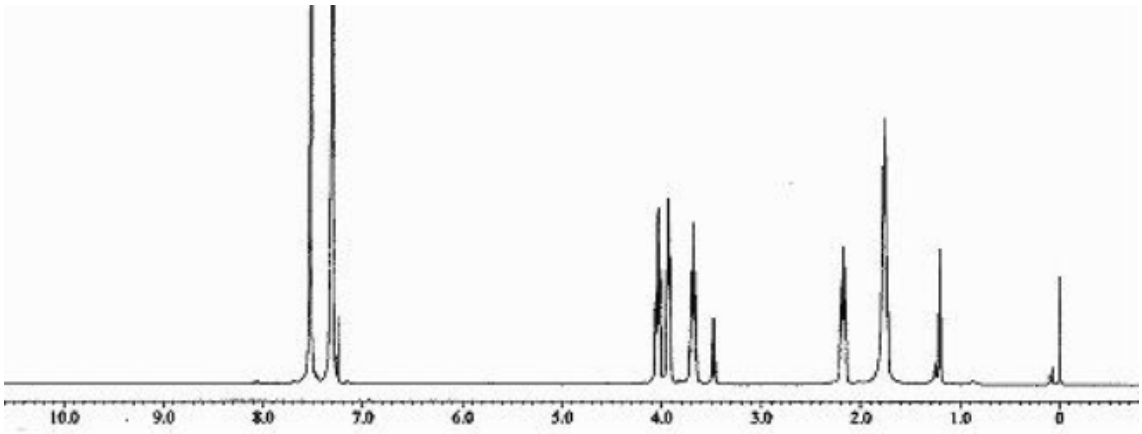


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	14.808	221578	10995	14.854
2	Unknown	1	16.117	1270143	36282	85.146

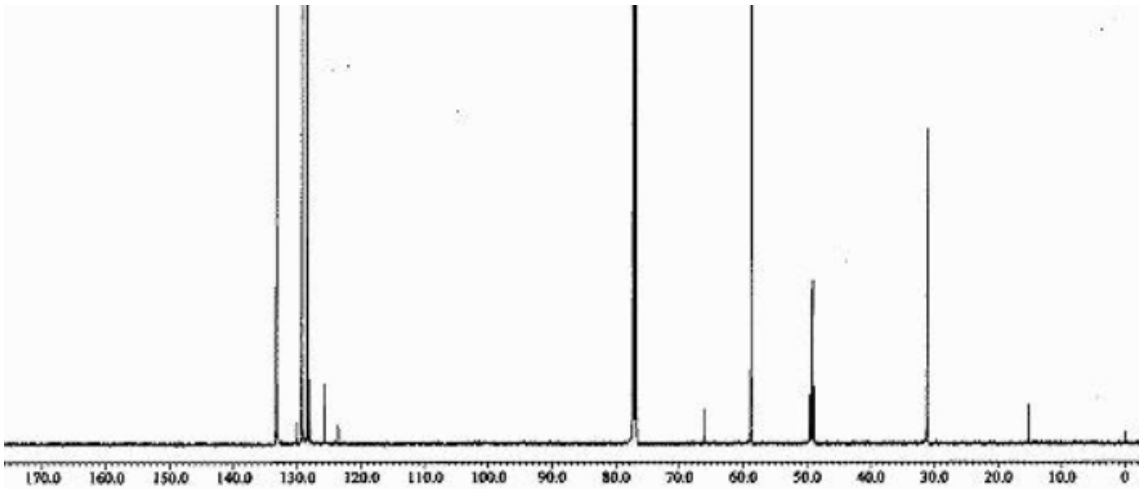


9a

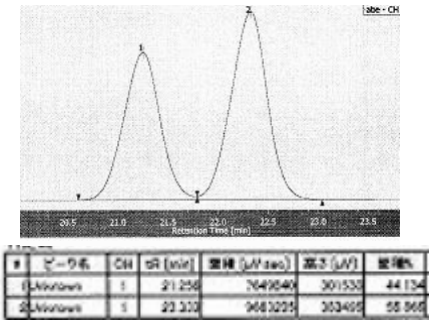
^{1}H NMR



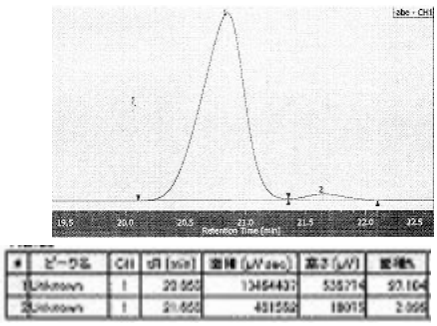
^{13}C NMR

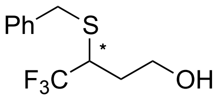


HPLC *racemic*



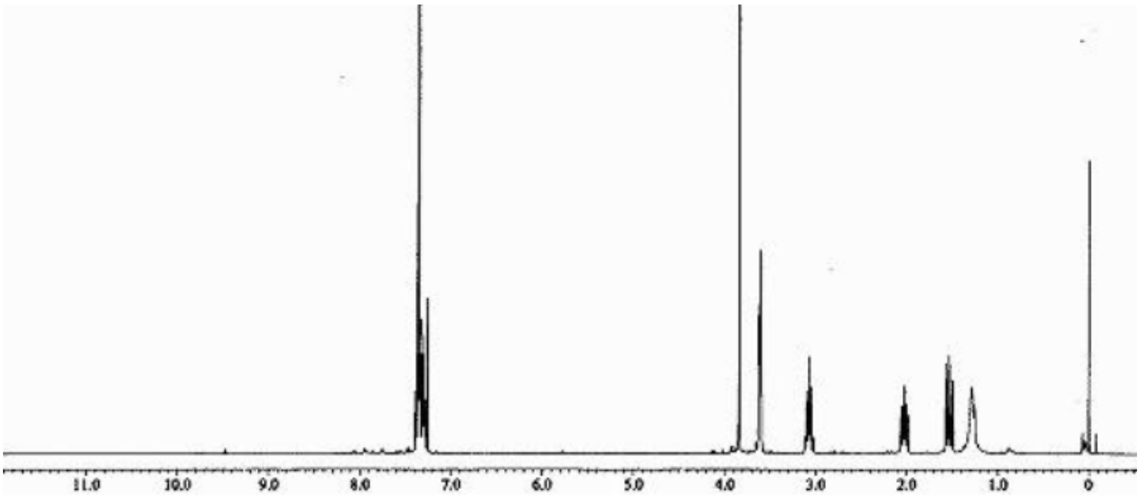
HPLC *optically active*



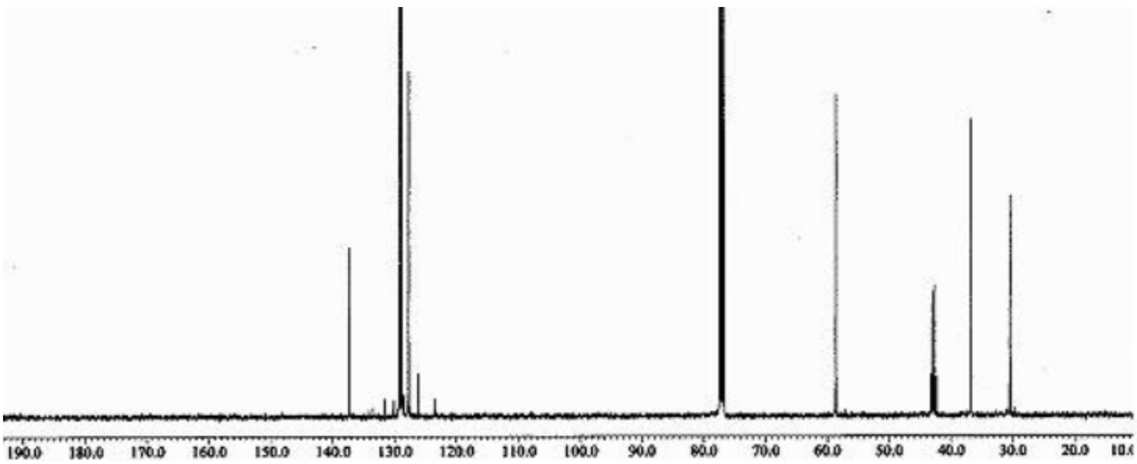


9b

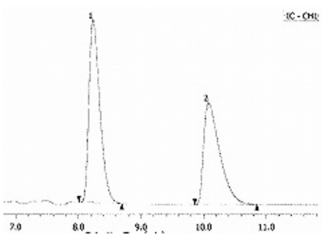
^{1}H NMR



^{13}C NMR

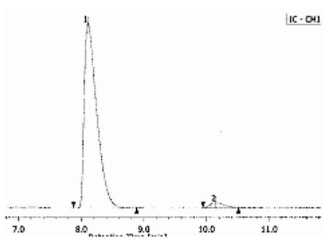


HPLC *racemic*

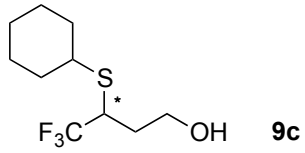


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	8.283	5423562	451095	54.846
2	Unknown	1	10.011	4466309	251118	45.154

HPLC *optically active*

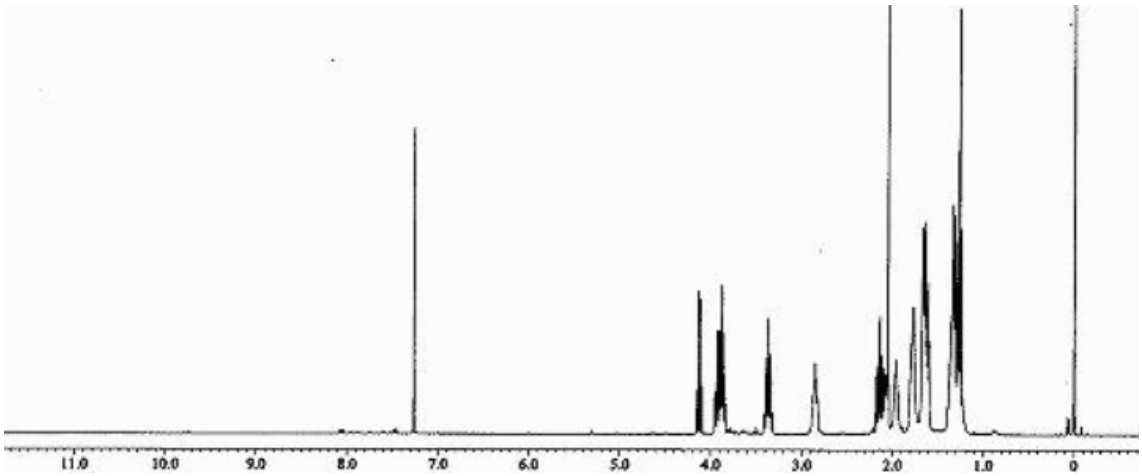


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%
1	Unknown	1	8.195	2466159	170951	97.235
2	Unknown	1	10.150	69968	4871	2.765

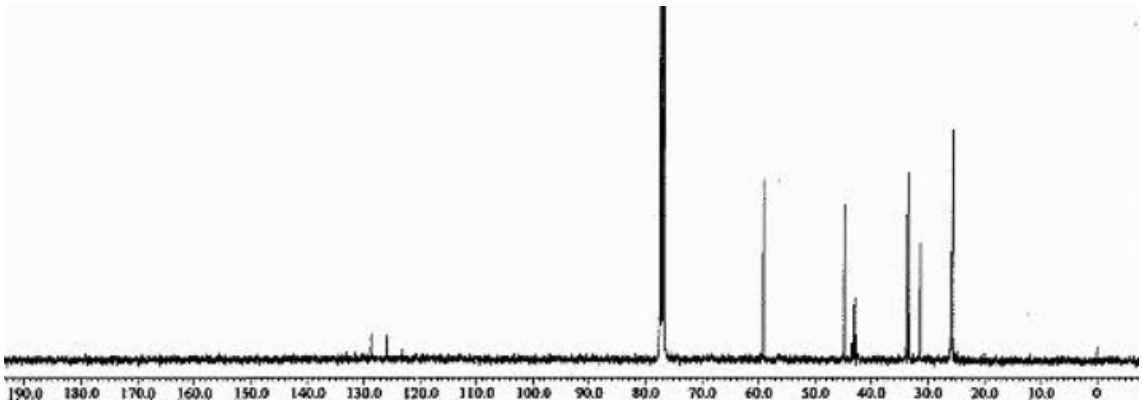


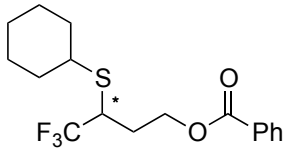
9c

^{1}H NMR



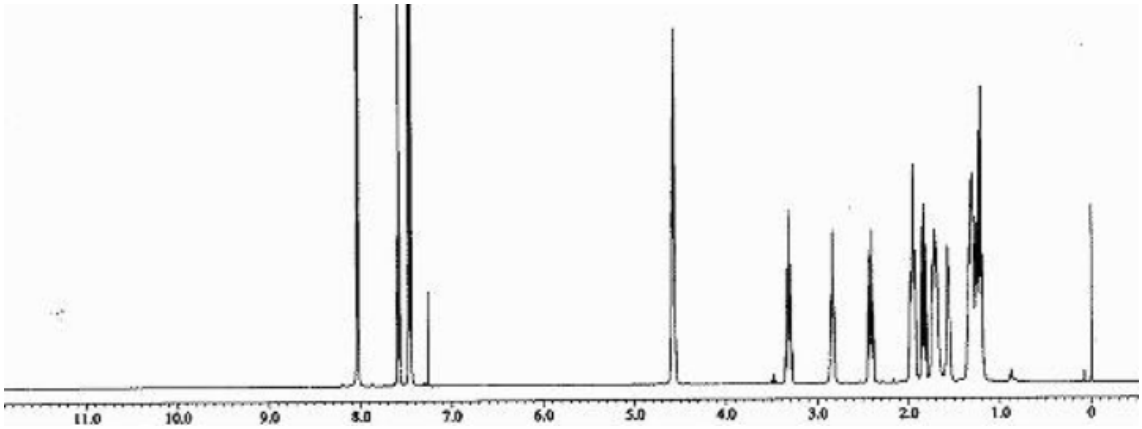
^{13}C NMR



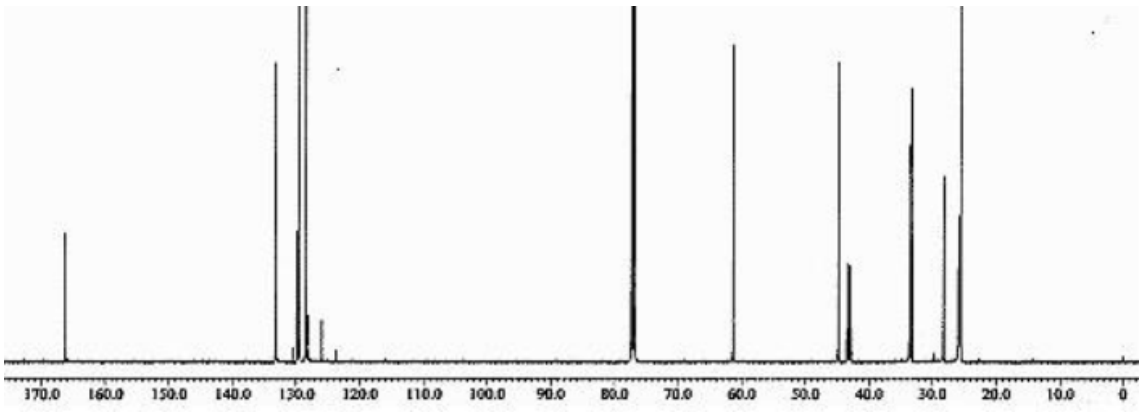


21c

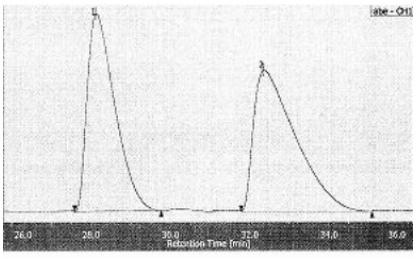
^{1}H NMR



^{13}C NMR

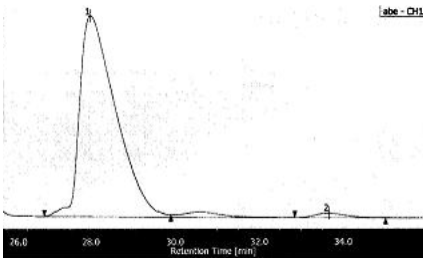


HPLC *racemic*

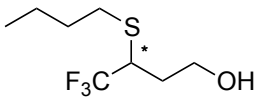


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	28.133	974810	20184	47.841
2	Unknown	1	32.858	1062318	14867	52.159

HPLC *optically active*

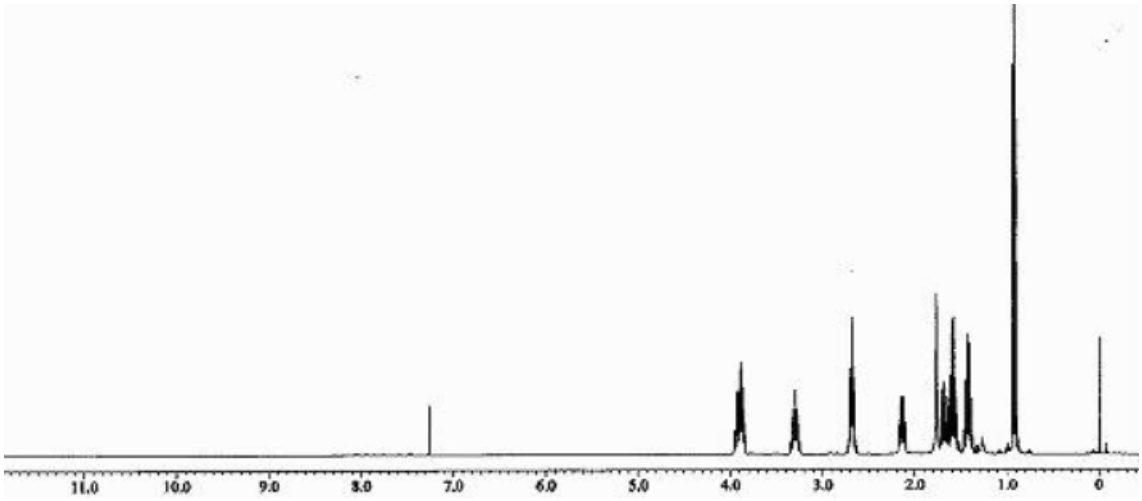


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	27.983	2173226	36604	98.081
2	Unknown	1	33.658	42511	843	1.919

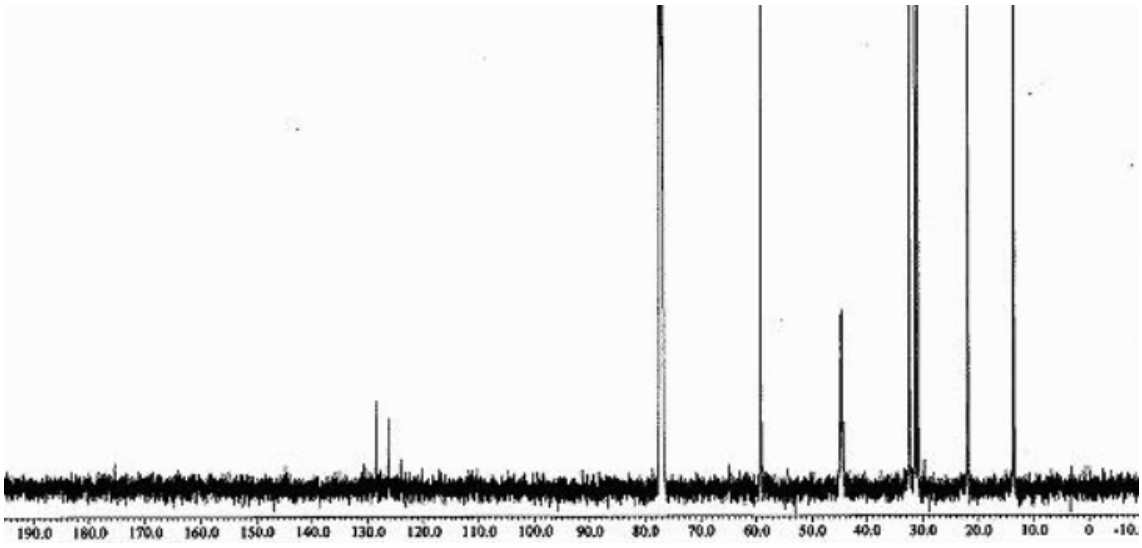


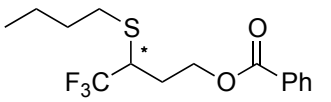
9d

^{1}H NMR



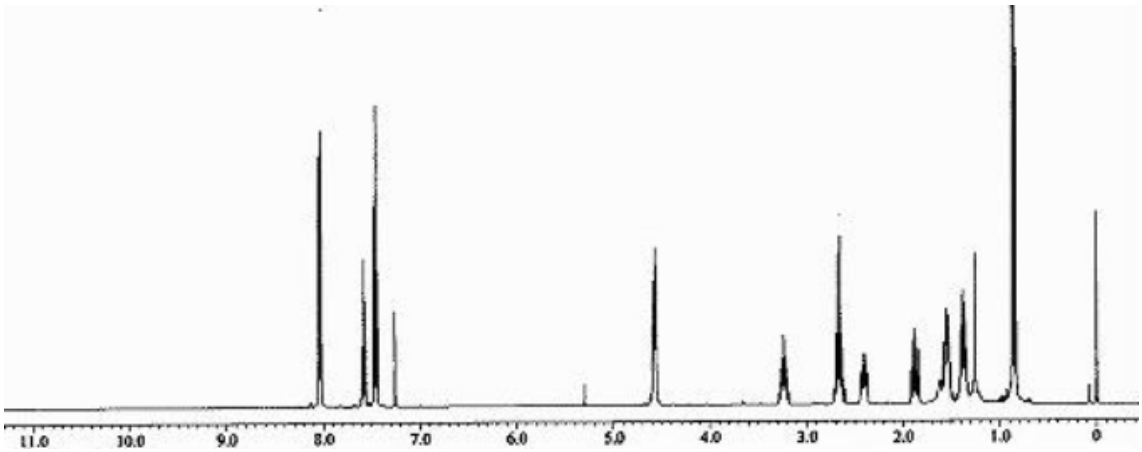
^{13}C NMR



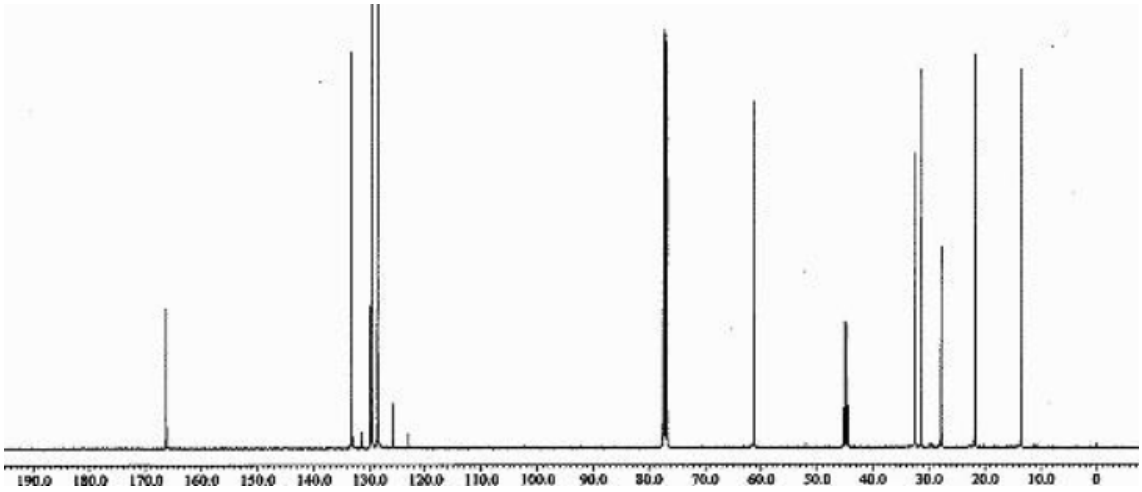


21d

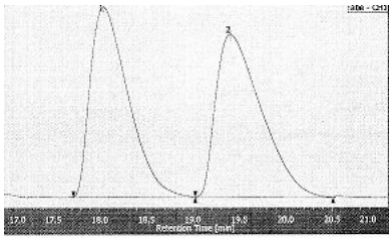
^{1}H NMR

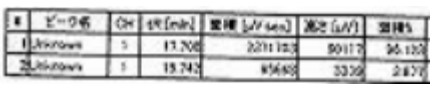


^{13}C NMR

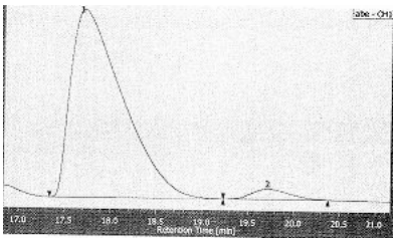


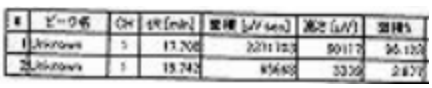
HPLC *racemic*

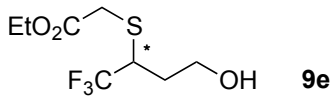




HPLC *optically active*

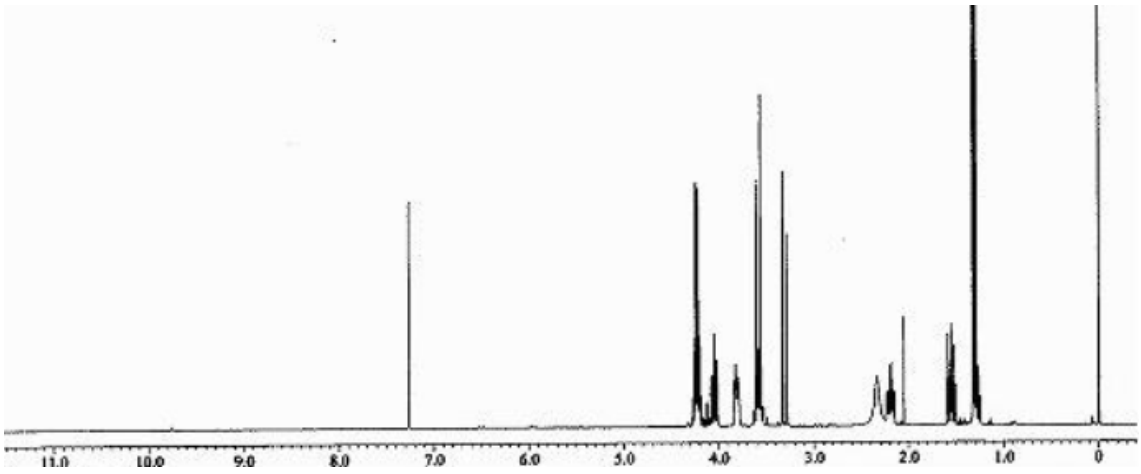




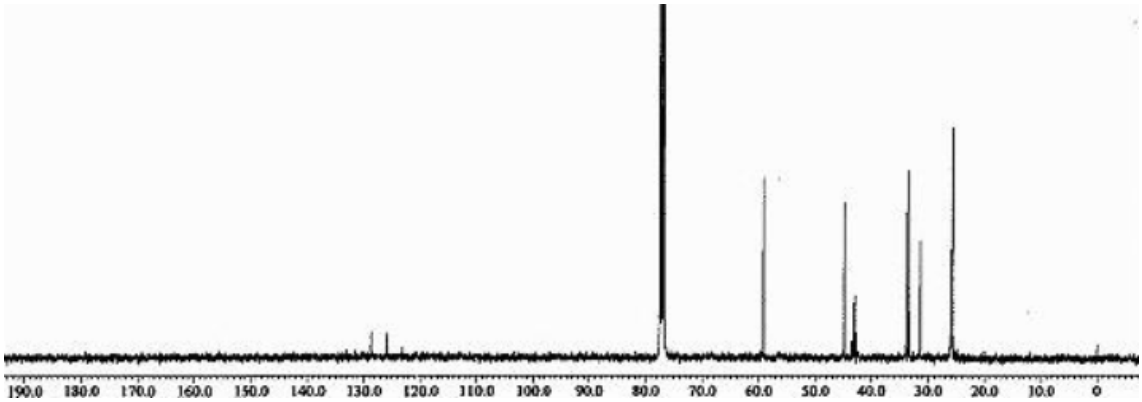


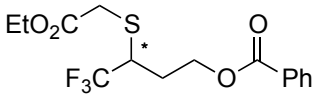
9e

^{1}H NMR



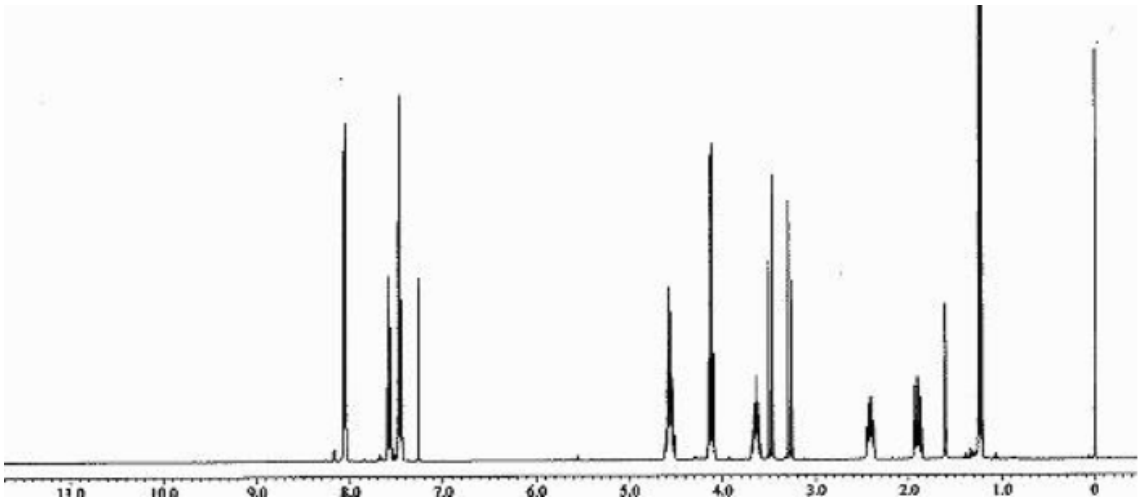
^{13}C NMR



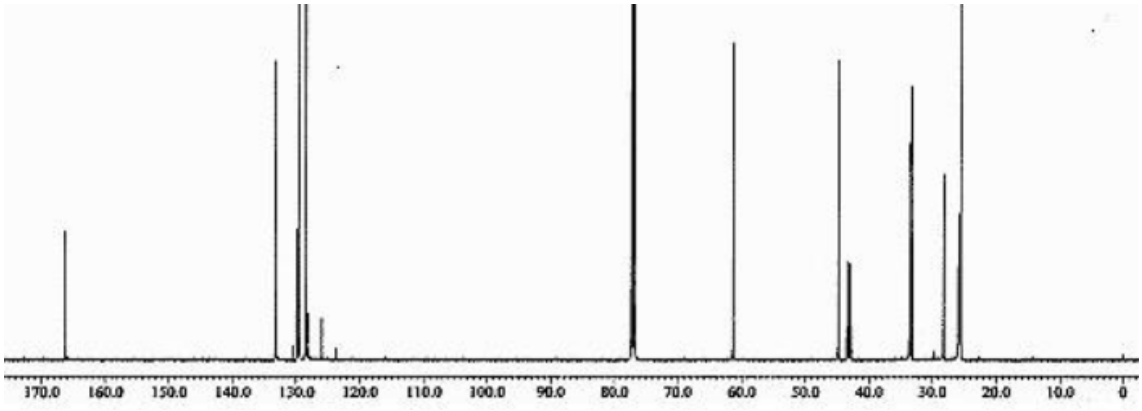


21e

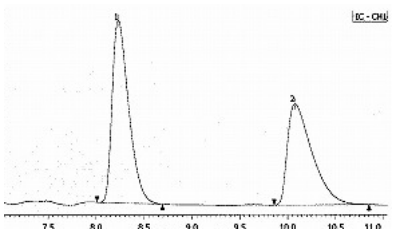
^{1}H NMR

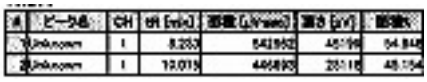


^{13}C NMR

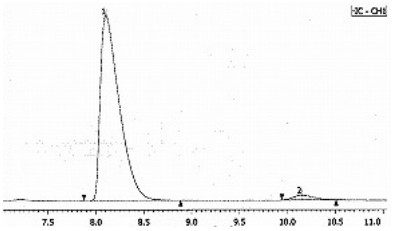


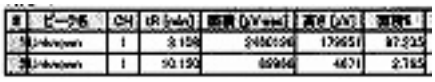
HPLC *racemic*

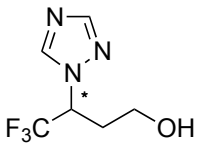




HPLC *optically active*

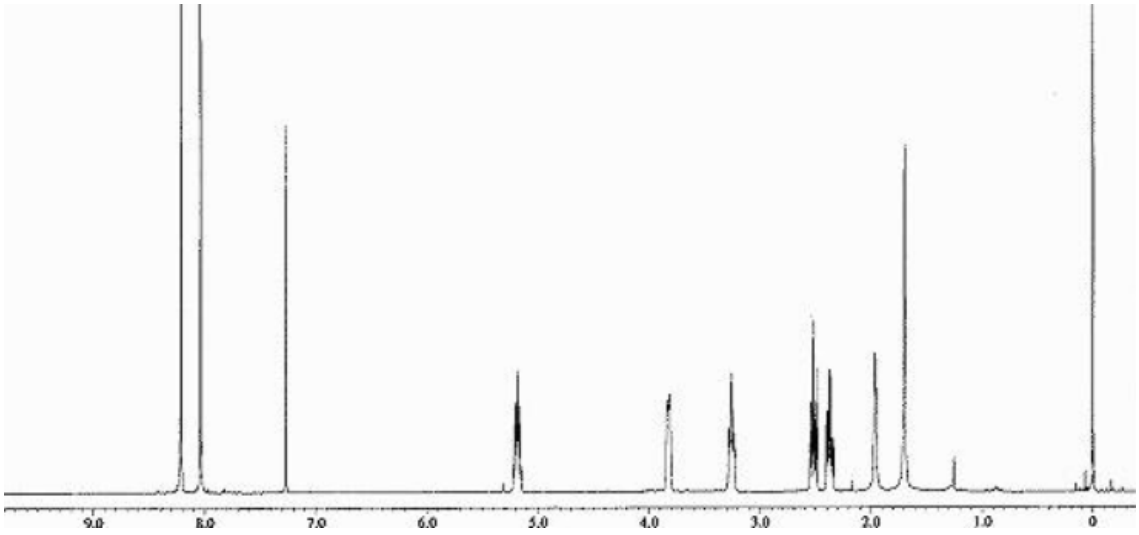




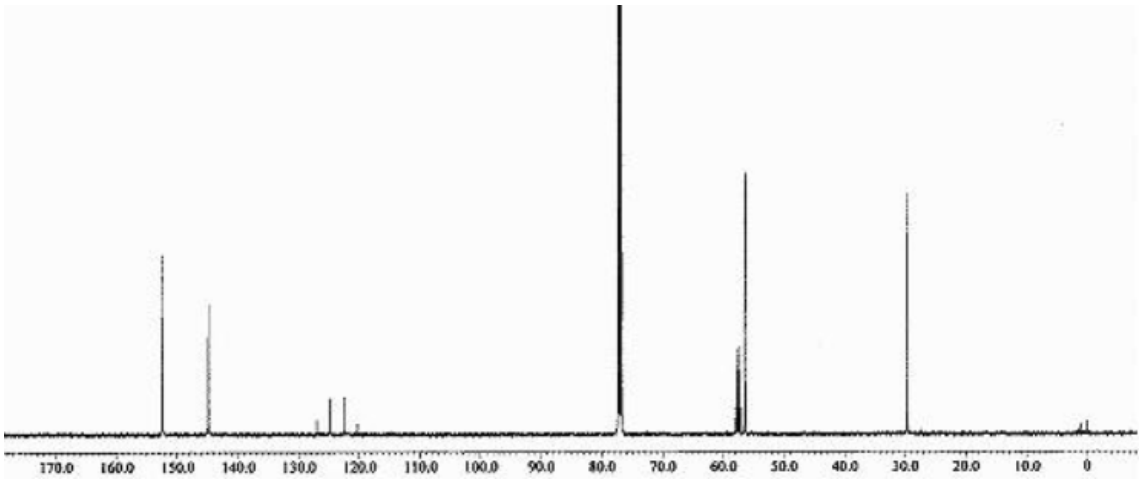


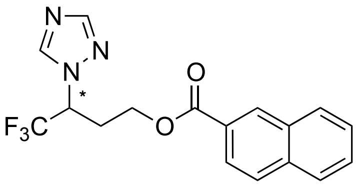
10a

^{1}H NMR



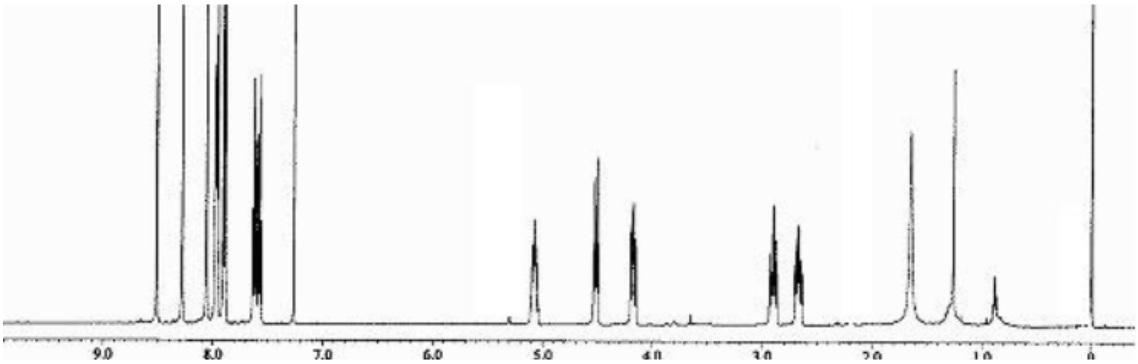
^{13}C NMR



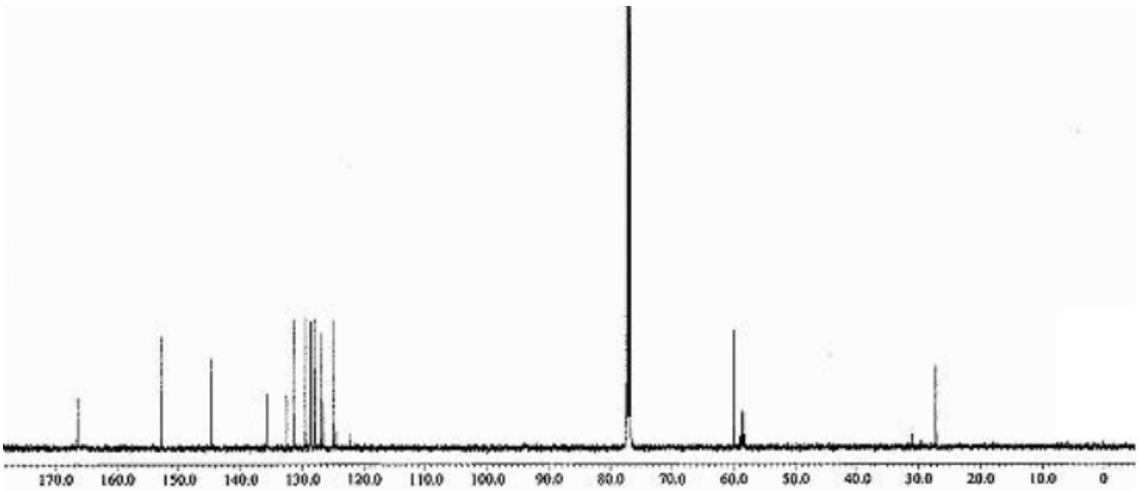


22a

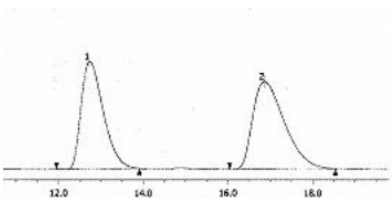
^{1}H NMR



^{13}C NMR

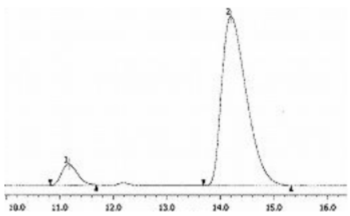


HPLC *racemic*

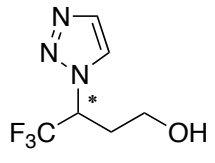


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	12.733	6221663	225671	46.350
2	Unknown	1	15.658	6511576	184506	53.650

HPLC *optically active*

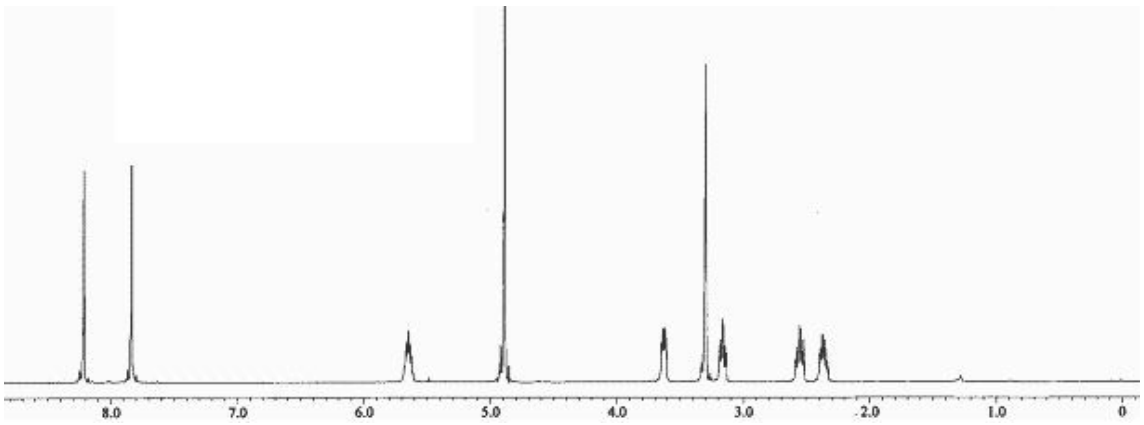


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	11.787	134328	8725	7.212
2	Unknown	1	14.182	1708261	84528	92.788

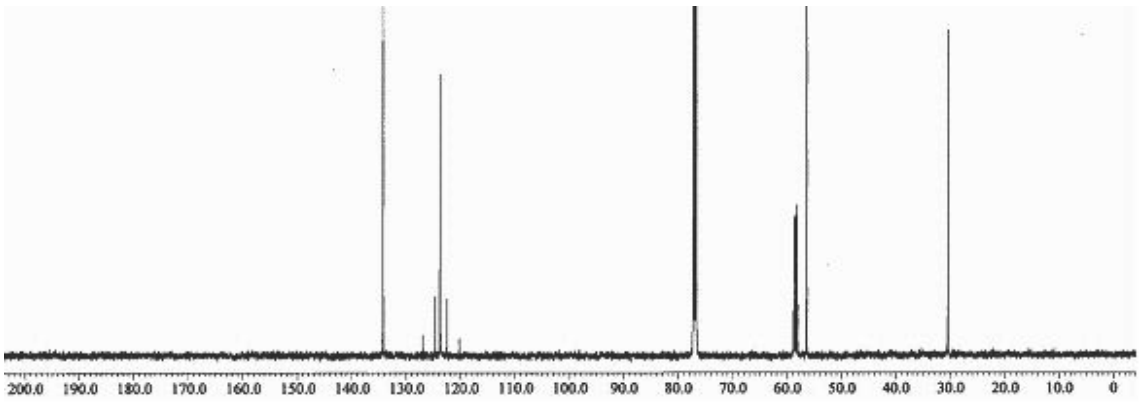


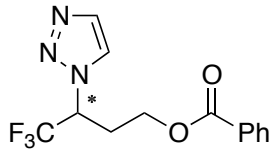
10b

^{1}H NMR



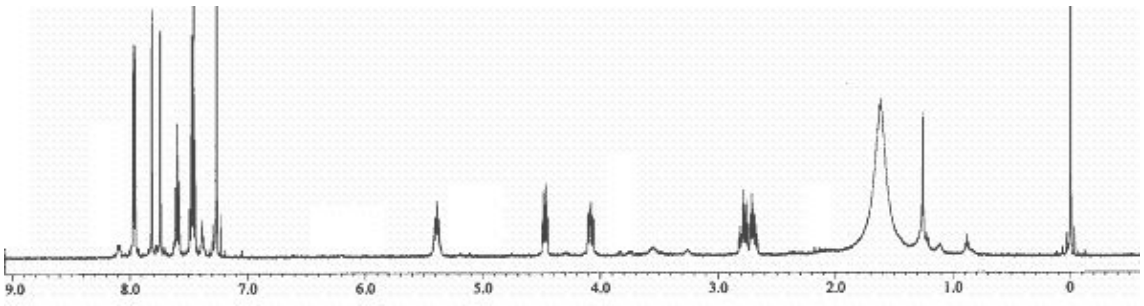
^{13}C NMR



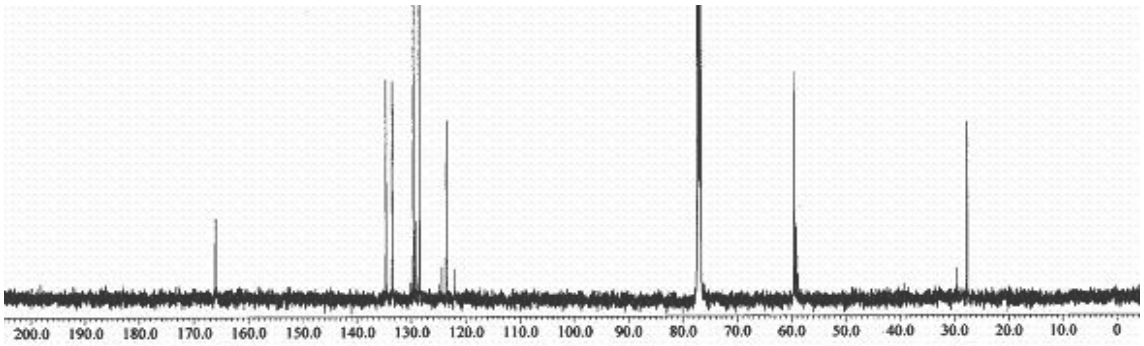


22b

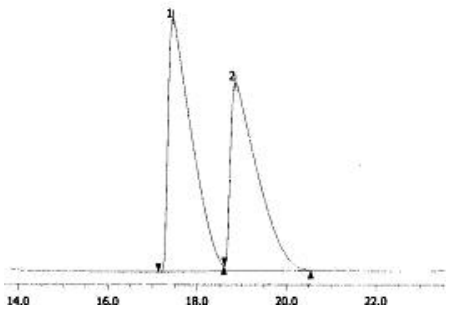
^{1}H NMR



^{13}C NMR

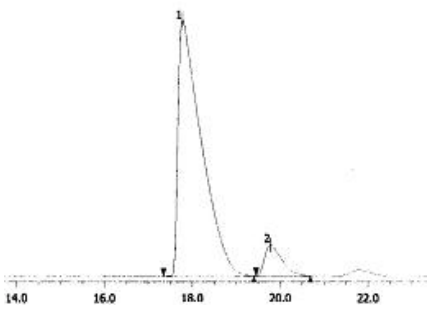


HPLC *racemic*

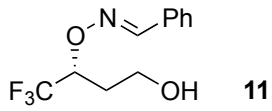


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	17.458	4144443	114013	53.011
2	Unknown	1	18.858	3543133	84788	46.088

HPLC *optically active*

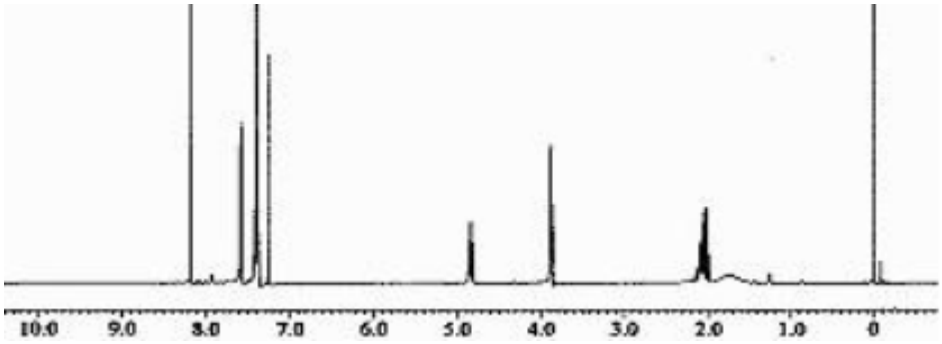


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	17.775	3148246	101366	91.882
2	Unknown	1	19.775	331187	12166	8.118

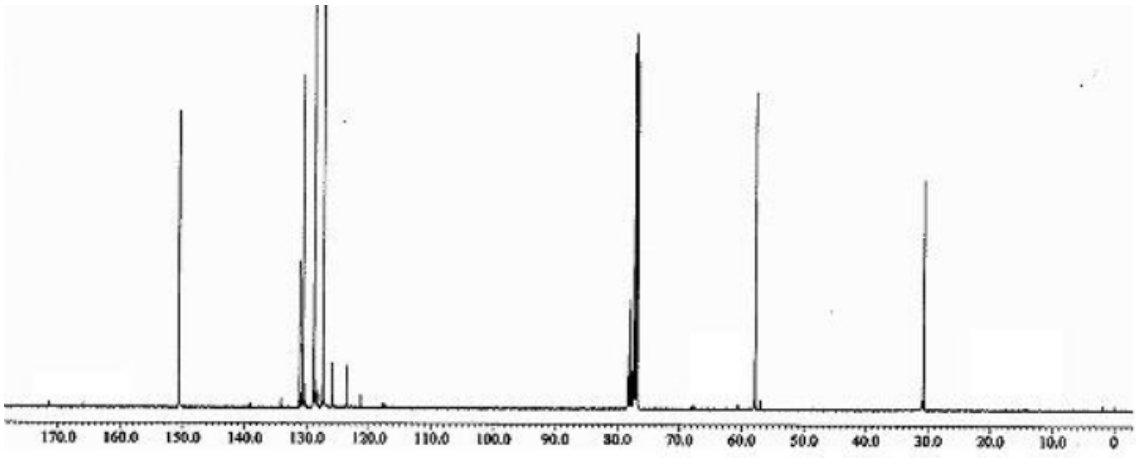


11

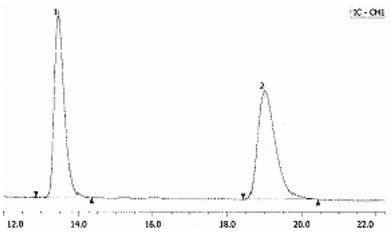
^{1}H NMR



^{13}C NMR

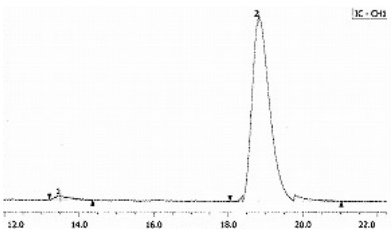


HPLC *racemic*

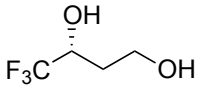


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	13.450	1715710	5129	48.89
2	Unknown	1	19.000	1792857	5445	51.10

HPLC *optically active*

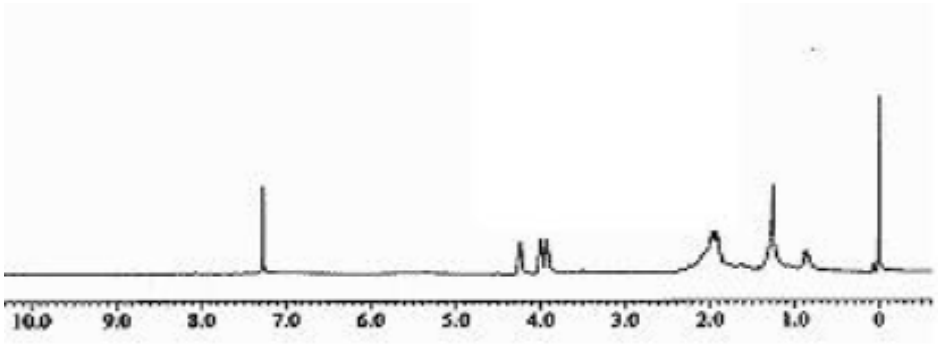


#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	13.500	2197	95	1.626
2	Unknown	1	18.917	132783	4035	98.373

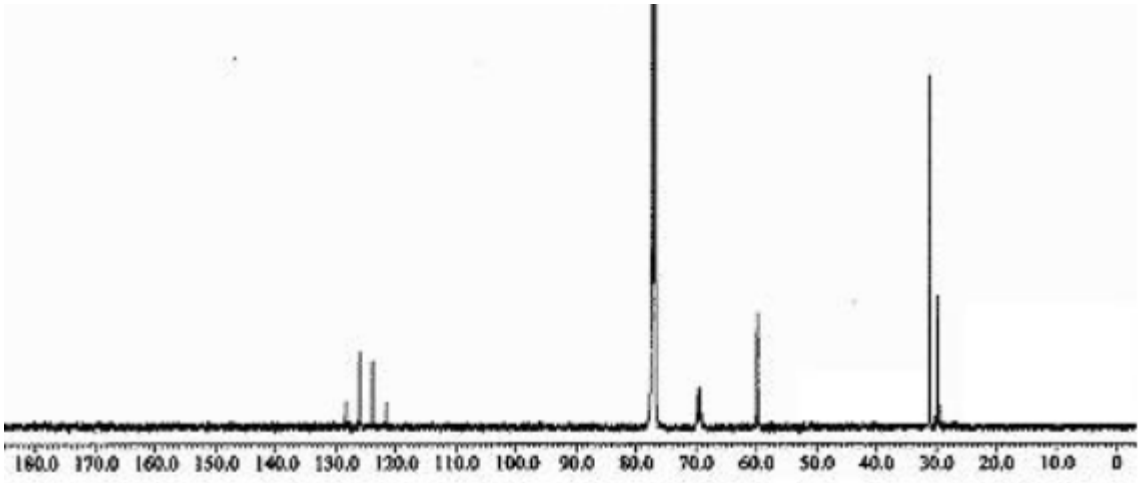


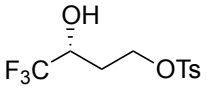
12

^{1}H NMR



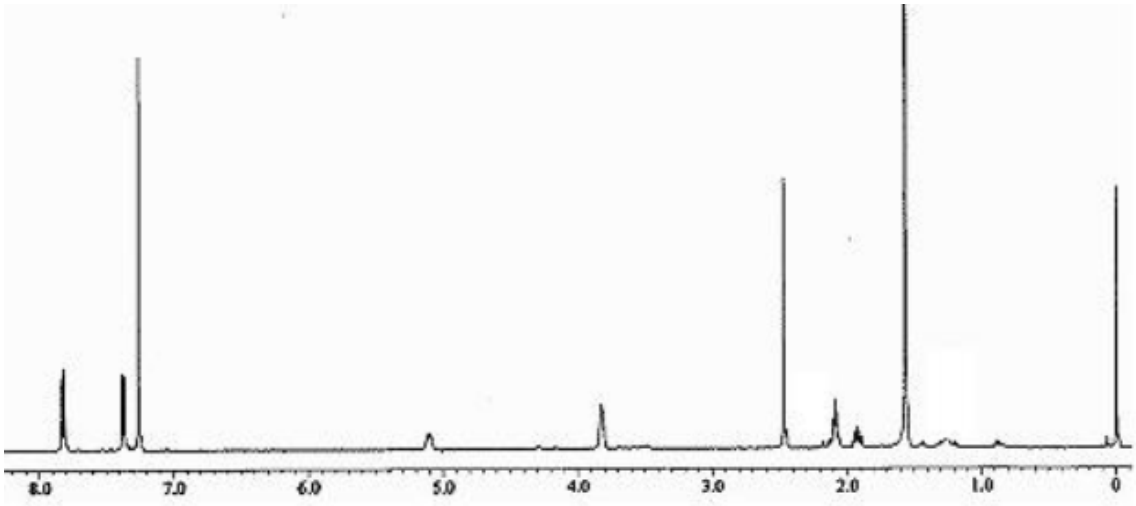
^{13}C NMR



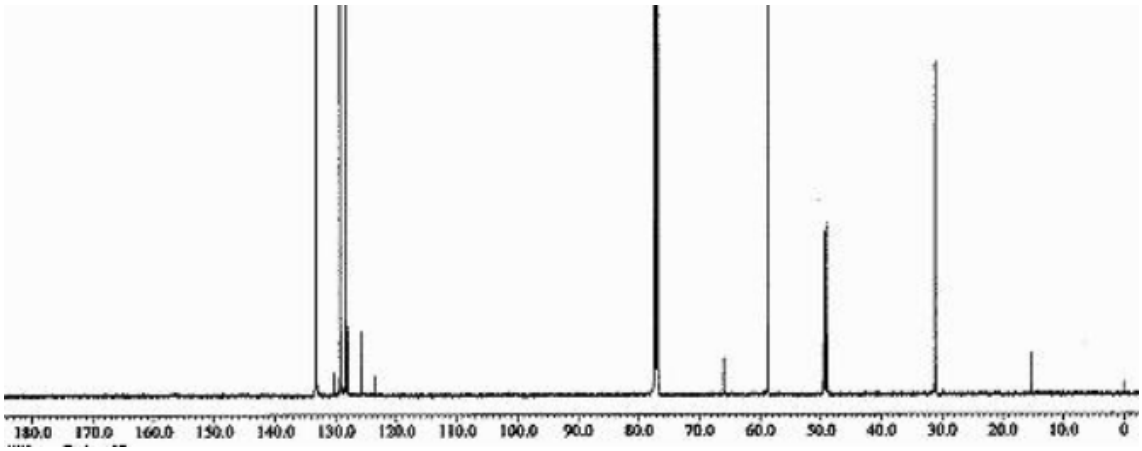


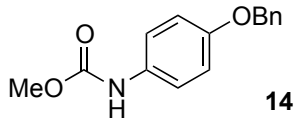
13

^{1}H NMR



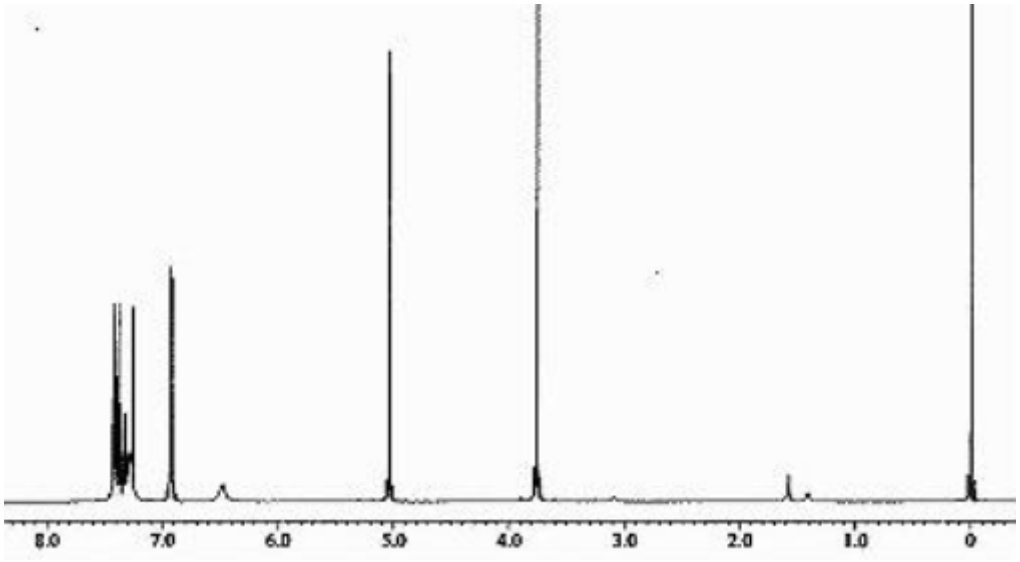
^{13}C NMR



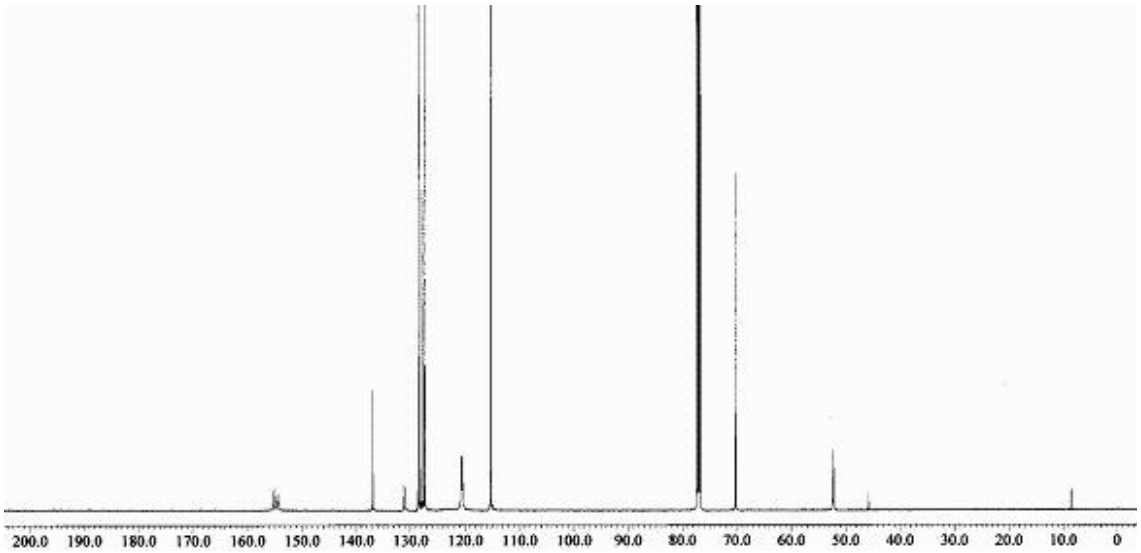


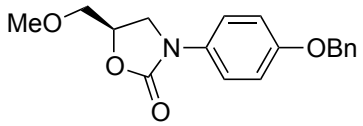
14

^{1}H NMR



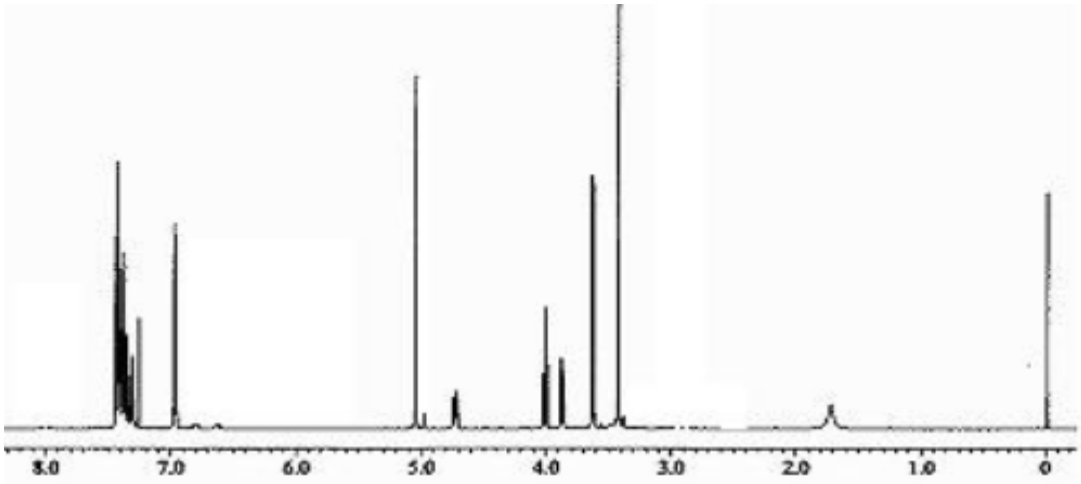
^{13}C NMR



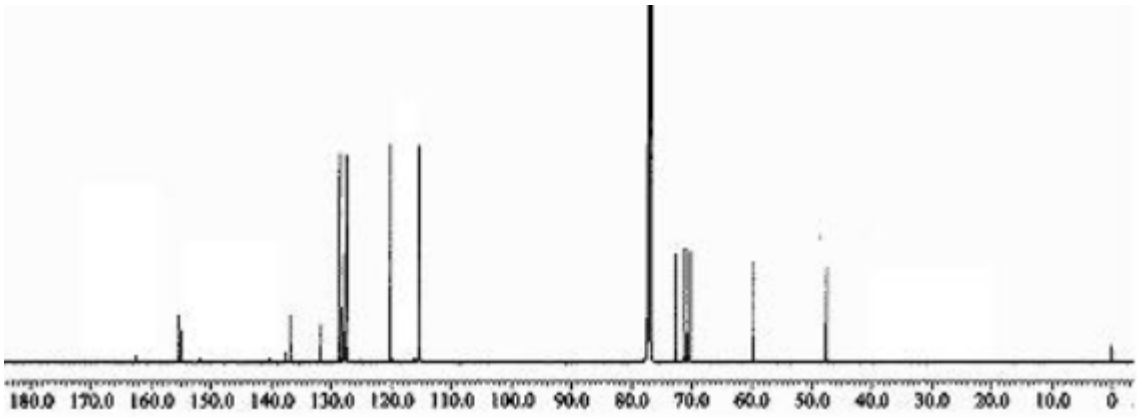


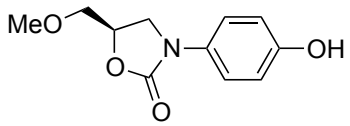
16

^{1}H NMR



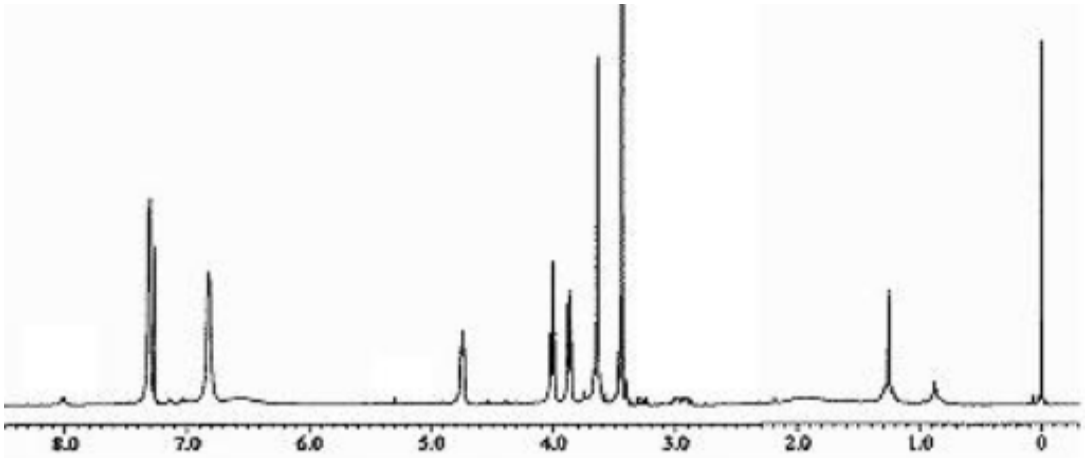
^{13}C NMR



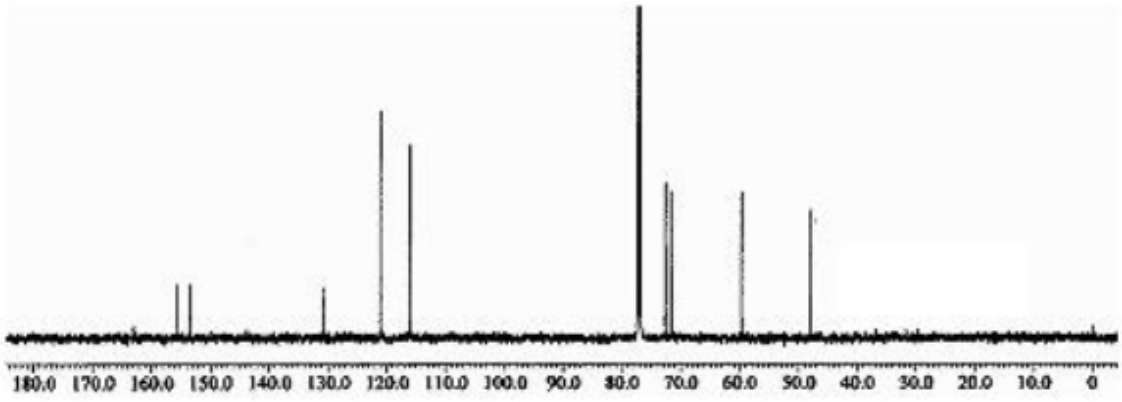


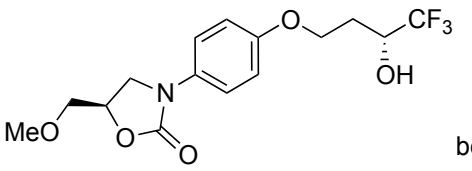
17

^{1}H NMR



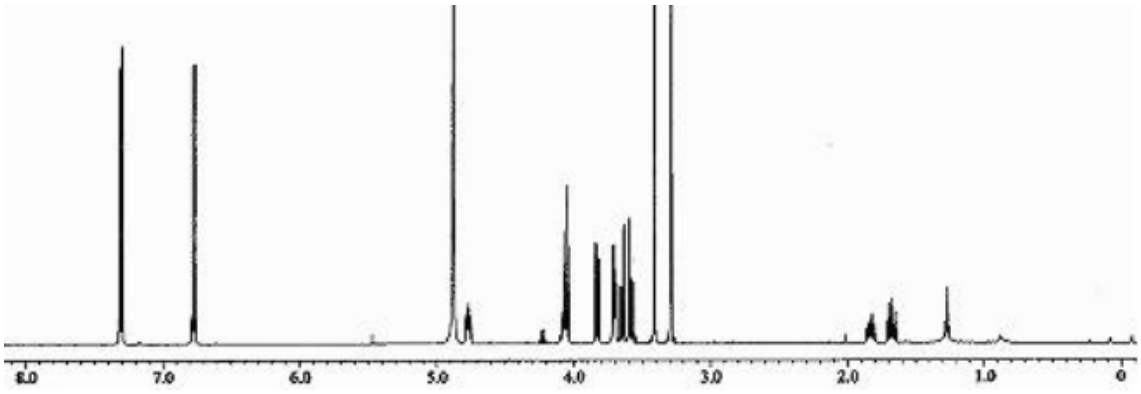
^{13}C NMR



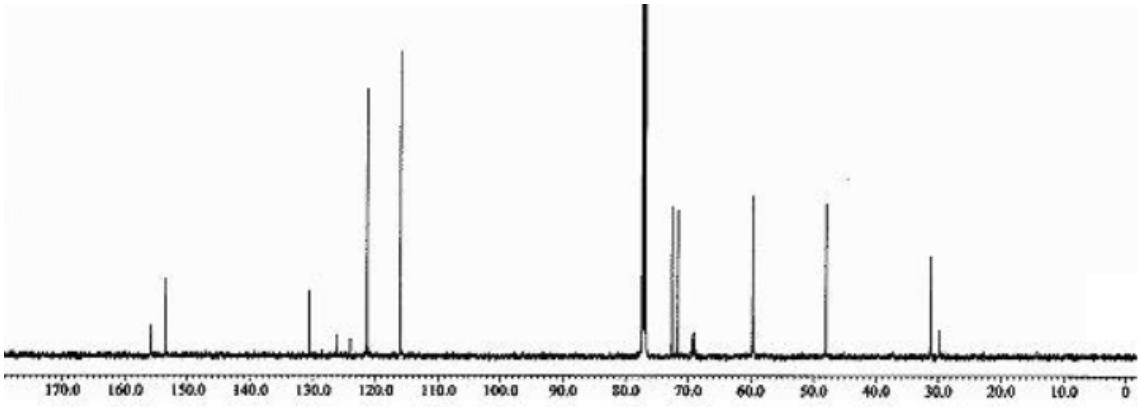


befloxatone

^{1}H NMR

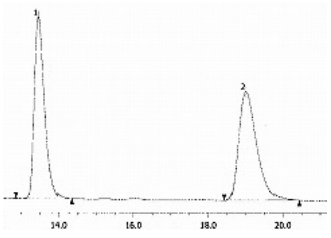


^{13}C NMR



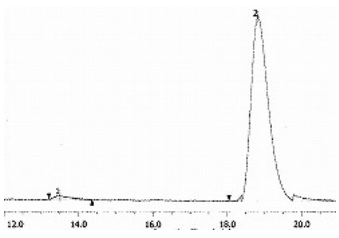
HPLC *diastereo mixture*

(major : minor = 1 : 1)



#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	12.450	171570	5129	48.897
2	Unknown	1	19.000	179355	5445	51.103

(major : minor = 98 : 2)



#	ピーク名	CH	tR [min]	面積 [μV*sec]	高さ [μV]	面積%
1	Unknown	1	12.500	2197	90	1.626
2	Unknown	1	18.917	132783	4605	98.374