Highly Stereoselective $TiCl_4$-Catalyzed Evans-Aldol and Et_3Al-Mediated Reformatsky Reactions. Efficient Accesses to Optically Active syn- or anti- α-Trifluoromethyl-β-hydroxy Carboxylic Acid Derivatives

Taichi Shimada, Masamitsu Yoshioka, Tsutomu Konno, and Takashi Ishihara*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

ishihara@kit.ac.jp

SUPPORTING INFORMATION

CONTENTS

I. General Experimental

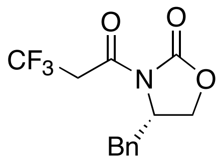
Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. ^1H NMR spectra were measured with a Bruker DRX 500 (500.13 MHz) in a chloroform-*d* ($CDCl_3$) solution using tetramethylsylane (Me_4Si) as internal standard. ^{13}C NMR spectra were measured with a Bruker DRX (125.75 MHz) in a ($CDCl_3$) solution with chloroform ($CHCl_3$) as internal reference. ^{19}F NMR spectra were measured with JEOR JNM-EX 90A (84.10 MHz) and ECA 500 (470.62 MHz) in a $CDCl_3$ solution. Trichlorofluoromethane ($CFCl_3$) was used as an internal standard for ^{19}F NMR. All reactions were routinely monitored by ^{19}F NMR spectroscopy or TLC. High resolution mass spectra (HRMS) were taken on a JEOL JMS-700 mass spectrometer by FAB method.

Anhydrous tetrahydrofuran (THF) was purchased from Wako Chemical Co. and used without any purification. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates, and column chromatography was carried out with Wako gel C-200. All reactions were carried out under an atmosphere of argon.

II. Synthetic Chemistry

Preparation of (4*S*)-Benzyl-3-(3,3,3-trifluoro-propanoyl)-oxazolidin-2-one (3)

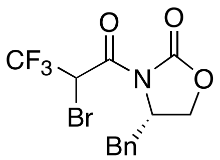
To a dry three-necked flask under argon was added a solution of 3,3,3-trifluoropropanoic acid (2.561 g, 20.0 mmol) in THF (100 mL). To the mixture was added trimethylacethyl chloride (*t*-BuCOCl, 2.653 g, 22.0 mmol) and triethylamine (Et_3N, 2.226 g, 22.0 mmol) at –78 °C. The reaction was allowed to stir at –78 °C for 15-min prior to warming to –15 °C and strring for 45-min. Then the solution was cooled to –78 °C, 40.0 mmol of lithiated oxazolidinone was added. After stirring at 0 °C for 1 h, the reaction was quenched with saturated aqueous ammonium chloride (40 mL). The bulk of the THF was removed on a rotary evaporator at a bath temperature of 30 °C, and the resulting mixture was extracted with ethyl acetate (40 mL x 2), saturated sodium hydrogencarbonate (40 mL). Combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to afford pure product **3** (0.293 g, 10.2 mmol, 51 % yield).



IR (neat) 1790, 1715, 1454, 1410, 1393, 1244, 1144 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.81 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.32 (dd, *J* = 3.2, 13.4 Hz, 1H), 3.81 – 3.98 (m, 1H), 4.23 – 4.29 (m, 2H), 4.69 – 4.45 (m, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.27 – 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 37.5, 39.7 (q, *J* = 29.9 Hz), 55.2, 66.6, 123.5 (q, *J* = 276.6 Hz), 127.6, 129.1, 129.4, 134.6, 153.1, 163.3 (q, *J* = 3.4 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.3 (t, *J* = 9.0 Hz, 3F); HRMS (FAB^+) Found: *m/z* 288.0849, Calcd for (M+H) $C_{13}H_{13}F_3NO_3$: 288.0848.

Preparation of (4*S*)-Benzyl-3-(2-bromo-3,3,3-trifluoro-propanoyl)-oxazolidin-2-one (4)

Under an argon atmosphere, to a solution of imide 1 (0.287 g, 1.00 mmol) in CH_2Cl_2 (5.0 mL) was gradually added trimethylsilyltrifluoromethanesulfonate (TMSOTf, 0.333 g, 1.50 mmol) at –20 °C. To the mixture was added triethylamine (Et_3N, 0.152 g 1.50 mmol). After stirring at the reflux temperature for 0.5 h, the solution was cooled –78 °C, then a solution of bromine (0.208 g, 1.30 mmol) in CH_2Cl_2 (8.0 mL) was added. After stirring at that temperature for 0.5 h, the reaction was quenched with ice water (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL x 4), and the extracts were washed with saturated aqueous sodium sulfite (20 mL) and brine (20 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to afford pure product **4** (0.297 g, 0.811 mmol, 81 % yield).



IR (neat) 3011, 1771, 1705, 1456, 995, 874, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.84 (dd, J = 9.4, 13.9 Hz, 1H, for one isomer), 2.87 (dd, J = 9.4, 14.6 Hz, 1H, for another isomer), 3.30 (dd, J = 2.1, 13.5 Hz, 1H), 4.26 – 4.35 (m, 1H), 4.70 – 4.76 (m, 1H, for one isomer), 4.75 – 4.76 (m, 1H, for another isomer), 6.17 (q, J = 6.3 Hz, 1H, for one isomer), 6.21 (q, J = 6.3 Hz, 1H, for another isomer), 7.18 – 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 36.8 (for one isomer),37.4 (for another isomer), 37.1 (q, J = 34.7 Hz, for one isomer), 37.3 (q, J = 34.5 Hz, for another isomer), 55.2 (for one isomer), 55.7 (for another isomer), 66.5 (for one isomer), 66.6 (for another isomer), 121.9 (q, J = 278.3 Hz, for one isomer), 121.9 (q, J = 278.7 Hz, for another isomer), 127.7 (for another isomer), 127.7 (for another isomer), 129.1, 129.3, 129.4, 134.1 (for another isomer), 134.2 (for another isomer), 152.3, 162.1; ^{19}F NMR ($CDCl_3$) δ = -68.6 (d, J = 4.4 Hz, 3F); HRMS (FAB^+) Found: m/z 365.9954, Calcd for (M+H) $C_{13}H_{12}BrF_3NO_3$: 365.9953.

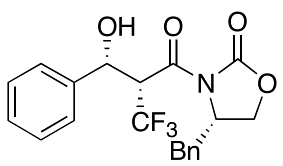
General procedure for synthesis of α-trifluoromethyl-β-hydroxyimides 1 by *syn*-selective Evans-aldol reaction

To a dried three-necked flask was added imide **3** (0.287 g, 1.00 mmol) in CH_2Cl_2 (5.0 mL) under argon. To the mixture were added trimethylsilyltrifluoromethanesluflonate (TMSOTf, 0.333 g, 1.50 mmol) and triethylamine (Et_3N, 0.152 g, 1.50 mmol) at –20 °C. After stirring at reflux temperature for 0.5 h, the solution was cooled to 0 °C. Then benzaldehyde (0.127 g, 1.20 mmol) and titanium tetrachloride (0.057 g, 0.3 mmol) were added to it. After stirring at that temperature for 4 h, the solution was poured into cooled water. The mixture was extracted with CH_2Cl_2 (20 mL x 4). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (benzene/ethyl acetate = 95/5) to afford pure product **1a** (0.248 g, 0.63 mmol, 63 % yield).

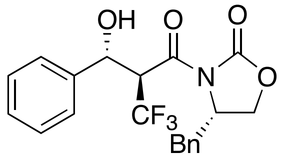
General procedure for synthesis of α-trifluoromethyl-β-hydroxyimides 1 by *anti*-selective Reformatsky reaction

To a suspension of zinc (0.078 g, 1.20 mmol) and benzaldehyde (0.053 g, 0.5 mmol) in THF (2 mL) and triethylaluminum in hexane solution (0.53 mL) was added a solution of (4*S*)-benzyl-3-(2-bromo-3,3,3-trifluoro-propanoyl)-oxazolidin-2-one **4** (0.366 g, 1.0 mmol) in THF (1 mL) at -40 °C under an argon atmosphere. After stirring at the same temperature for 3 h, the reaction was quenched with saturated aqueous ammonium chloride (25 mL) and acidified by the addition of 1N hydrochloric acid solution. The resulting mixture was extracted with ethyl acetate (25 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (benzene/ethyl acetate 95/5) to afford pure product **1a** (0.169 g, 0.430 mmol, 86%).

(4*S*)-Benzyl-3-[3-hydroxy-3-phenyl-2-(trifluoromethyl)propanoyl]-oxazolidin-2-one (1a)

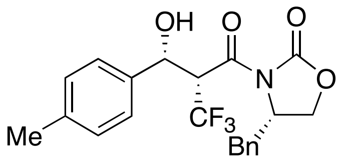


***syn*-(2*R*,3*S*)** : IR (KBr) 1778, 1763, 1705, 1682, 1369, 1161, 700, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.80 (dd, *J* = 10.1, 13.5 Hz, 1H), 2.44 (d, *J* = 3.7 Hz, 1H), 2.57 (dd, *J* = 3.3, 13.5 Hz, 1H), 3.95 (dd, *J* = 2.7, 9.2 Hz, 1H), 4.07 (dd, *J* = 8.2, 9.2 Hz, 1H), 4.49 – 4.55 (m, 1H), 5.39 (dd, *J* = 3.7, 9.1 Hz, 1H), 5.66 (dq, *J* = 9.1, 7.7 Hz, 1H), 6.91 – 6.93 (m, 2H), 7.20 – 7.28 (m, 3H), 7.31 – 7.40 (m, 3H), 7.47 – 7.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 36.6, 53.2 (q, *J* = 25.5 Hz), 54.9, 65.7, 72.8 (q, *J* = 1.3 Hz), 124.1 (q, *J* = 281.8 Hz), 127.4, 127.6, 128.8, 129.0, 129.1, 129.2, 134.7, 139.1, 152.6, 164.9 (q, *J* = 3.1 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.4 (d, *J* = 7.7 Hz, 3F); HRMS (FAB$^+$) Found: *m*/*z* 394.1266, Calcd for (M+H) $C_{20}H_{19}F_3NO_4$: 394.1266.

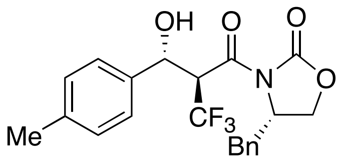


***anti*-(2*S*,3*S*)** : IR (KBr) 3499, 1786, 1709, 1456, 1391, 1211, 1078, 955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.79 (br, 1H), 2.79 (dd, *J* = 9.5 Hz, 13.5 Hz, 1H), 3.30 (dd, *J* = 3.4, 13.5 Hz, 1H), 4.06 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.16 (dd, J = 2.7, 9.0 Hz, 1H), 4.64 – 4.69 (m, 1H), 5.31 (d, *J* = 7.4 Hz, 1H), 5.55 (dq, *J* = 7.8, 7.8 Hz, 1H), 7.20 – 7.21 (m, 2H), 7.27 – 7.34 (m, 3H), 7.35 – 7.40 (m, 3H), 7.42 – 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 37.6, 53.7 (q, *J* = 25.4 Hz), 55.4, 66.1, 72.0 (q, *J* = 1.6 Hz), 123.3 (q, *J* = 281.3 Hz), 126.4, 127.5, 128.7, 128.8, 129.0, 129.3, 134.6, 139.7, 153.1, 166.3 (q, *J* = 2.5 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.88 (d, *J* = 8.5 Hz, 3F); HRMS (FAB$^+$) Found: *m*/*z* 394.1267, Calcd for (M+H) $C_{20}H_{19}F_3NO_4$: 394.1266.

(4*S*)-Benzyl-3-[3-hydroxy-3-(4-methylphenyl)-2-(trifluoromethyl)propanoyl]-oxazolidin-2-one (1b)

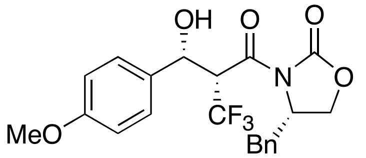


***syn*-(2*R*,3*S*)** : IR (KBr) 3452, 1780, 1684, 1163, 1113, 1001, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.84 (dd, *J* = 9.8, 13.6 Hz, 1H), 2.30 (s, 3H), 2.45 (br s, 1H), 2.59 (dd, *J* = 3.3, 13.6 Hz, 1H), 3.95 (dd *J* = 2.6, 9.2 Hz, 1H), 4.05 – 4.09 (m, 1H), 4.51 – 4.57 (m, 1H), 5.35 (d, *J* = 9.3 Hz, 1H), 5.55 – 5.65 (m, 1H), 6.88 – 6.90 (m, 2H), 7.17 – 7.38 (m, 7H); ^{13}C NMR ($CDCl_3$) δ = 21.1, 36.6, 53.1 (q, *J* = 25.4 Hz), 54.8, 65.6, 72.6 (q, *J* = 1.5 Hz), 124.1 (q, *J* = 282.1 Hz), 127.4, 127.5, 128.9, 129.1, 129.4, 134.7, 136.2, 139.1, 152.6, 165.0 (q, *J* = 3.3 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.6 (d, *J* = 6.6 Hz, 3F); HRMS (FAB$^+$) Found: *m*/*z* 407.1346, Calcd for (M+) $C_{21}H_{20}F_3NO_4$: 407.1344.

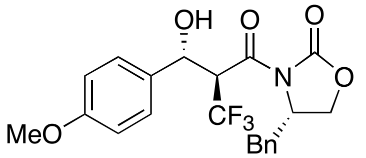


***anti*-(2*S*,3*S*)** : m.p. 42 - 44 ºC; IR (KBr) 3445, 2924, 1786, 1456, 1393, 1254, 1111, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.35 (s, 3H), 2.68 (br s, 1H), 2.79 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.30 (dd, *J* = 2.8, 9.1 Hz, 1H), 4.65 – 4.71 (m, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 5.54 (dq, *J* = 7.9, 7.9 Hz, 1H), 7.18 – 7.21 (m, 4H), 7.29 – 7.35 (m, 5H); ^{13}C NMR (125.75 MHz, $CDCl_3$, TMS) δ = 21.1, 37.6, 52.8 (q, *J* = 25.2 Hz), 55.4, 66.1, 72.0, 123.4 (q, *J* = 281.1 Hz), 126.4, 127.4, 129.0, 129.4, 129.4, 134.7, 136.8, 138.7, 153.2, 166.4 (q, *J* = 2.6 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.8 (d, *J* = 8.5 Hz, 3F); HRMS (FAB$^+$) Found: *m*/*z* 407.1349, Calcd for (M+) $C_{21}H_{20}F_3NO_4$: 407.1344.

(4*S*)-Benzyl-3-[3-hydroxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)propanoyl]-oxazolidin-2-one (1c)

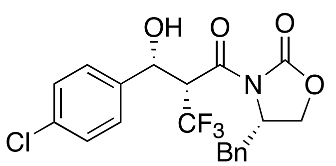


***syn*-(2*R*,3*S*)** : IR (KBr) 3449, 2927, 1778, 1682, 1377, 1362, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.89 (dd, *J* = 10.0, 13.6 Hz, 1H), 2.41 (br s, 1H), 2.63 (dd, *J* = 3.3, 13.6 Hz, 1H), 3.75 (s, 1H), 3.96 (dd *J* = 2.7, 9.2 Hz, 1H), 4.08 (dd *J* = 8.2, 9.2 Hz, 1H), 4.52 – 4.58 (m, 1H), 5.34 (d, *J* = 9.4 Hz, 1H), 5.60 (dd *J* = 9.0, 7.9 Hz, 1H), 6.87 – 6.93 (m, 2H), 7.22 – 7.42 (m, 7H); ^{13}C NMR ($CDCl_3$) δ = 27.0, 36.7, 53.2 (q, *J* = 25.5 Hz), 54.9, 55.3, 65.7, 72.4 (q, *J* = 1.4 Hz), 114.1, 124.1 (q, *J* = 281.9 Hz), 127.4, 128.9, 121.0, 129.1, 131.2, 134.7, 152.6, 160.2; ^{19}F NMR ($CDCl_3$) δ = -63.7 (d, *J* = 8.8 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 423.1294, Calcd for (M+H) $C_{21}H_{21}F_3NO_5$: 423.1294.

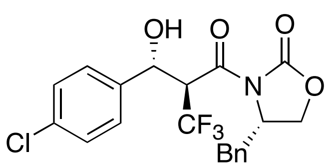


***anti*-(2*S*,3*S*)** : m.p. 114 - 116 ºC; IR (KBr) 3531, 2926, 1782, 1713, 1516, 1352, 1254, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.61 (br s, 1H), 2.80 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.80 (s, 3H), 4.13 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.17 (dd, *J* = 2.9, 9.0 Hz, 1H), 4.69 – 4.73 (m, 1H), 5.24 (d, *J* = 8.1 Hz, 1H), 5,52 (dq, *J* = 8.0, 8.0 Hz, 1H), 6.89 – 6.92 (m, 2H), 7.20 – 7.21 (m, 2H), 7.27 – 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 37.7, 52.9 (q, *J* = 25.0 Hz), 55.3, 55.4, 66.1, 71.8 (q, *J* = 1.5 Hz), 114.1, 123.4 (q, *J* = 281.6 Hz), 127.5, 127.8, 129.0, 129.4, 131.8, 134.7, 153.2, 160.0, 166.5 (q, *J* = 2.7 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.8 (d, *J* = 8.2 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 423.1302, Calcd for (M+H) $C_{21}H_{21}F_3NO_5$: 423.1294.

(4*S*)-Benzyl-3-[3-(4-chloro-phenyl)-3-hydroxy-2-(trifluoromethyl)propanoyl]-oxazolidin-2-one (1d)

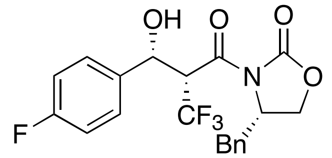


***syn*-(2*R*,3*S*)** : IR (KBr) 3443, 1778, 1682, 1194, 1165, 822, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.79 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.23 (d, *J* = 5.5 Hz, 1H), 3.28 (dd, *J* = 3.2, 13.5 Hz, 1H), 4.12 (dd *J* = 8.0, 9.1 Hz, 1H), 4.17 (dd *J* = 2.9, 9.1 Hz, 1H), 4.65 – 4.73 (m, 1H), 5.25 – 5.28 (m, 1H), 5.49 – 5.56 (m, 1H), 7.18 – 7.21 (m, 2H), 7.26 – 7.38 (m, 7H); ^{13}C NMR ($CDCl_3$) δ = 21.1, 36.6, 53.1 (q, *J* = 25.4 Hz), 37.5, 52.7 (q, *J* = 25.3 Hz), 66.1, 71.3 (q, *J* = 1.3 Hz), 123.2 (q, *J* = 281.1 Hz), 127.5, 128.0, 128.3, 128.9, 129.0, 129.3, 134.6 (q, *J* = 13.5 Hz), 138.3, 153.12, 166.1 (q, *J* = 2.6 Hz); ^{19}F NMR (84.10 MHz, $CDCl_3$, $CFCl_3$) δ = -63.6 (d, *J* = 6.6 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 428.0880, Calcd for (M+H) $C_{20}H_{18}ClF_3NO_4$: 428.0876.



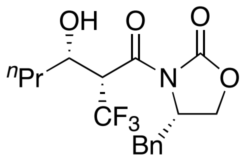
***anti*-(2*S*,3*S*)** : IR (neat) 3468, 2924, 1784, 1391, 1352, 1252, 1211, 1169, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.78 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.29 (dd, *J* = 3.4, 13.5 Hz, 1H), 4.12 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.18 (dd, *J* = 3.0, 9.1 Hz, 1H), 4.67 – 4. 71 (m, 1H), 5.27 (d, *J* = 7.9 Hz, 1H), 5,52 (dq, *J* = 7.9, 7.9 Hz, 1H), 7.19 – 7.20 (m, 2H), 7.27 – 7.30 (m, 2H), 7.32 – 7.34 (m, 2H), 7.35 – 7.38 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 37.6, 52.7 (q, *J* = 25.4 Hz), 55.4, 66.2, 71.4 (q, *J* = 1.5 Hz), 123.2 (q, *J* = 280.9 Hz), 127.5, 127.9, 129.0, 129.0, 139.3, 134.5, 134.7, 138.3, 153.2, 166.2 (q, *J* = 2.6 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.7 (d, *J* = 8.8 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 427.0804, Calcd for (M+) $C_{20}H_{17}ClF_3NO_4$: 427.0798.

(4*S*)-Benzyl-3-[3-(4-fluoro-phenyl)-3-hydroxy-2-(trifluoromethyl)propanoyl]-oxazolidin-2-one (1e)

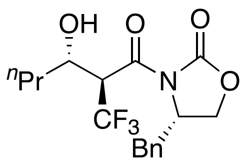


***syn*-(2*R*,3*S*)** : IR (KBr) 3485, 1784, 1607, 1393, 1227, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.95 (dd, *J* = 10.0, 13.5 Hz, 1H), 2.57 (br s, 1H), 2.68 (dd, *J* = 3.2, 13.5 Hz, 1H), 4.00 (dd, *J* = 1.7, 9.2 Hz, 1H), 4.09 (dd, *J* = 0.8, 9.2 Hz, 1H), 4.53 – 4.58 (m, 1H), 5.38 (d, *J* = 4.6 Hz, 1H), 5.57 (dq, *J* = 0.8, 8.8 Hz, 1H), 6.94 – 6.96 (m, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 7.22 – 7.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 36.8, 53.2 (q, *J* = 25.4 Hz), 55.0, 65.8, 72.0 (d, *J* = 1.3 Hz), 115.7 (d, *J* = 21.8 Hz), 124.0 (q, *J* = 281.8 Hz), 127.5, 129.0, 129.1, 129.4 (d, *J* = 8.2 Hz), 134.5, 135.0 (d, *J* = 2.6 Hz), 152.6, 163.0 (d, *J* = 248.6 Hz), 165.0 (q, *J* = 3.0 Hz); ^{19}F NMR ($CDCl_3$) δ = -63.5 (d, *J* = 8.8 Hz, 3F), -112.3 – -112.8 (m, 1F); HRMS (FAB^+) Found: *m*/*z* 412.1175, Calcd for (M+H) $C_{20}H_{18}F_4NO_4$: 412.1172.

(4*S*)-Benzyl-3-[3-hydroxy-2-(trifluoromethyl)hexanoyl]-oxazolidin-2-one (1f)

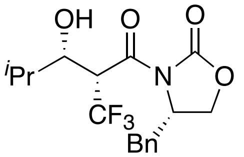


***syn*-(2*R*,3*S*)** : IR (neat) 3512, 2963, 1782, 1705, 1388, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.96 (t, *J* = 7.0 Hz, 3H), 1.40 – 1.47 (m, 1H), 1.53 – 1.69 (m, 3H), 2.35 (br s, 1H), 2.76 (dd, *J* = 9.9, 13.3 Hz, 1H), 3.34 (dd, *J* = 3.3, 13.3 Hz, 1H), 4.20 – 4.30 (m, 3H), 4.75 – 4.80 (m, 1H), 5.00 – 5.08 (m, 1H), 7.22 – 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 13.7, 18.8, 36.5, 37.6, 51.9 (q, *J* = 24.6 Hz), 55.5, 66.3, 69.7, 124.2 (q, *J* = 281.7 Hz), 127.5, 129.0, 129.3, 134.6, 153.2, 166.0 (q, *J* = 3.3 Hz); ^{19}F NMR ($CDCl_3$) δ = -62.5 (d, *J* = 8.7 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 360.1430, Calcd for (M+H) $C_{17}H_{21}F_3NO_4$: 360.1422.

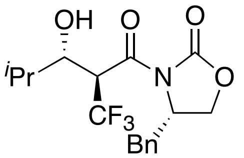


***anti*-(2*S*,3*S*)** : IR (neat) 3479, 2964, 1784, 1709, 1391, 1254, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.96 (t, *J* = 7.3 Hz, 3H), 1.37 – 1.47 (m, 1H), 2.32 (br s, 1H), 2.78 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.32 (dd, J = 3.3, 13.5 Hz, 1H), 4.20 (dd, *J* = 3.3, 9.1 Hz, 1H), 4.23 – 4.26 (m, 2H), 4.76 – 4.81 (m, 1H), 5.104 (dq, *J* = 8.1, 8.1 Hz, 1H), 7.20 – 7.22 (m, 2H), 7.28 –7.30 (m, 1H), 7.32 – 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 13.6, 18.2, 37.3, 37.6, 51.9 (q, *J* = 25.3 Hz), 55.4, 66.2, 69.4, 123.8 (q, *J* = 281.1 Hz), 127.5, 129.0, 129.3, 134.7, 153.4, 166.9 (q, *J* = 3.1 Hz); ^{19}F NMR ($CDCl_3$) δ = -64.0 (d, *J* = 8.2 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 360.1424, Calcd for (M+H) $C_{17}H_{21}F_3NO_4$: 360.1422.

(4*S*)-Benzyl-3-[3-hydroxy-4-methyl-2-(trifluoromethyl)pentanoyl]-oxazolidin-2-one (1g)

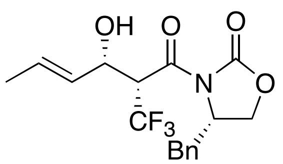


***syn*-(2*R*,3*S*)** : IR (KBr) 3464, 2970, 2343, 1757, 1705, 1394, 1213 cm^{-1}; H NMR ($CDCl_3$) δ = 1.03 (dd, *J* = 6.7, 10.6 Hz, 6H), 1.77 – 1.84 (m, 1H), 2.16 (br s, 1H), 2.75 (dd, *J* = 9.8, 13.3 Hz, 1H), 3.31 (dd, *J* = 3.4, 13.3 Hz, 1H), 4.03 – 4.10 (m, 1H), 4.20 – 4.28 (m, 2H), 4.75 – 4.81 (m, 1H), 5.16 – 5.23 (m, 5H), 7.21 – 7.23 (m, 2H), 7.27 – 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 16.7, 19.6, 31.4, 37.8, 49.6 (q, *J* = 24.2 Hz), 55.3, 66.3, 74.6, 124.4 (q, *J* = 281.9 Hz), 127.6, 129.1, 129.3, 134.6, 152.8, 166.4 (q, *J* = 3.4 Hz); ^{19}F NMR ($CDCl_3$) δ = -62.2 (d, *J* = 8.7 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 360.1430, Calcd for (M+H) $C_{17}H_{21}F_3NO_4$: 360.1422.

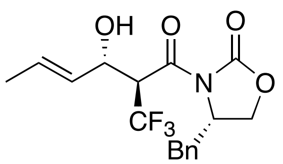


***anti*-(2*S*,3*S*)** : IR (neat) 3503, 2970, 1786, 1709, 1391, 1352, 1213, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.99 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.89 – 1.94 (m, 1H), 2.33 (br s, 1H), 2.78 (dd, *J* = 9.6, 13.5 Hz, 1H), 3.32 (dd, J = 3.4, 13.5 Hz, 1H), 4.06 (dd, *J* = 4.0, 7.7 Hz, 1H), 4.22 – 4.26 (m, 2H), 4.75 – 4.80 (m, 1H), 5.27 (dq, *J* = 8.0, 8.0 Hz, 1H), 7.20 – 7.2 2 (m, 2H), 7.28 – 7.30 (m, 1H), 7.32 – 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 15.1, 19.6, 31.0, 37.5, 49.4 (q, *J* = 25.5 Hz), 55.4, 66.2, 74.2, 123.8 (q, *J* = 281.2 Hz), 127.5, 129.0, 129.3, 134.7, 153.3, 167.3 (q, *J* = 3.5 Hz); ^{19}F NMR ($CDCl_3$) δ = -64.1 (d, *J* = 8.8 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 360.1424, Calcd for (M+H) $C_{17}H_{21}F_3NO_4$: 360.1422.

(4*S*)-Benzyl-3-[3-hydroxy-2-(trifluoromethyl)hex-4-enoyl]-oxazolidin-2-one (1h)

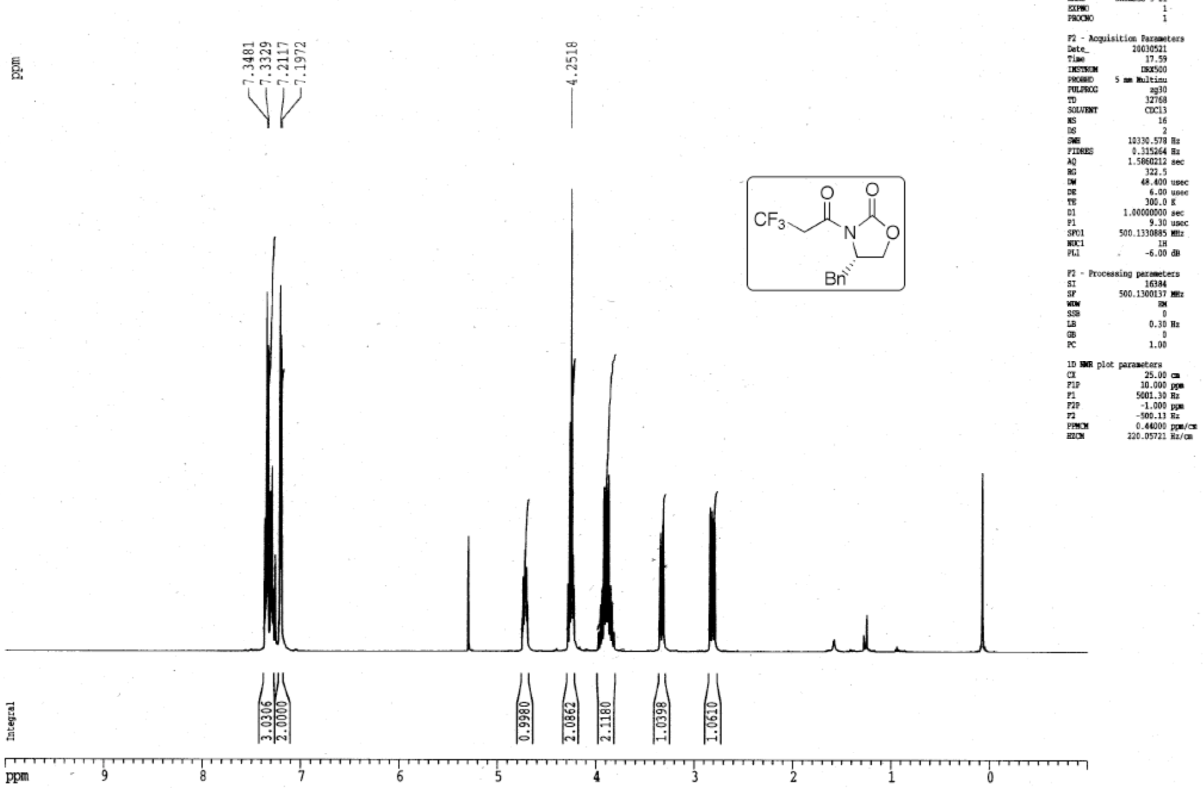


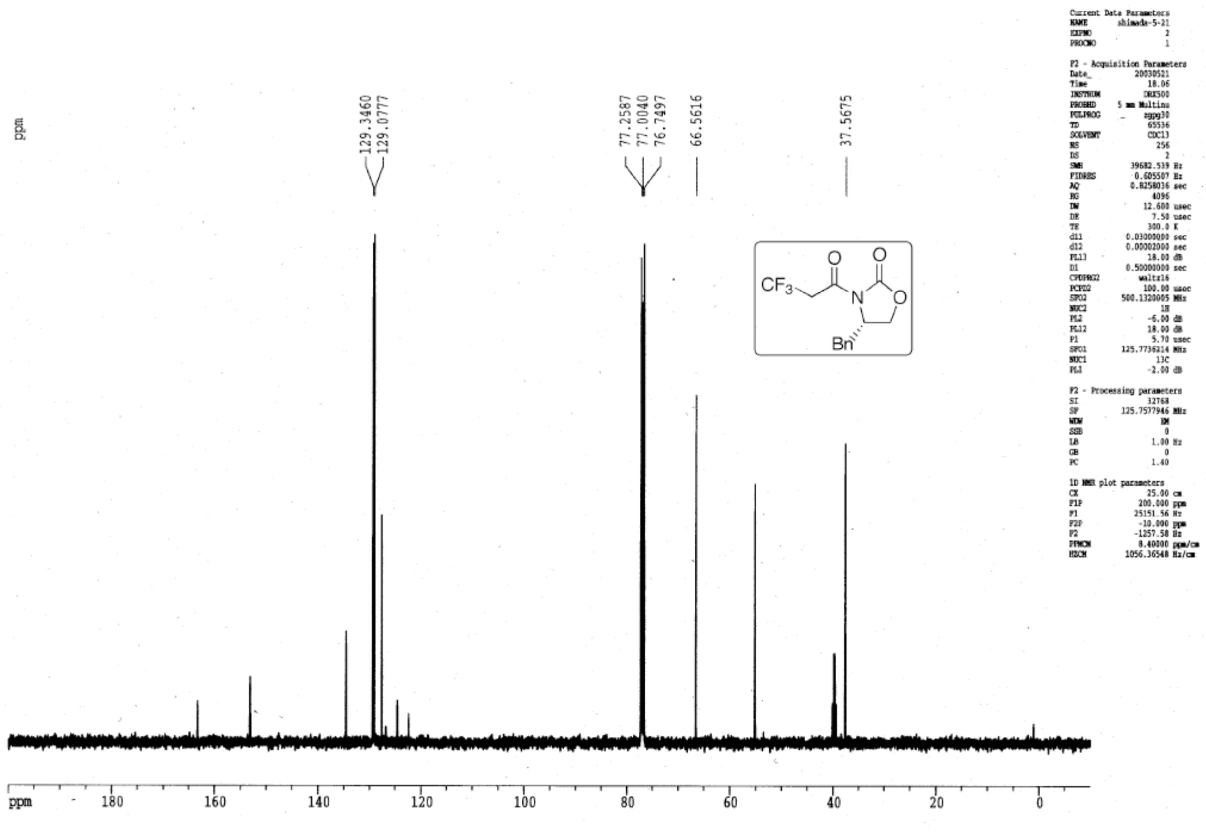
***syn*-(2*R*,3*S*)** : IR (neat) 3501, 3030, 1778, 1705, 1355, 1256, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.72 (dd, *J* = 1.4, 6.5 Hz, 3H), 2.22 (br s, 1H), 2.58 (dd, *J* = 10.2, 13.3 Hz, 1H), 3.27 (dd, *J* = 3.3, 13.3 Hz, 1H), 4.70 – 4.77 (m, 2H), 5.15 – 5.22 (m, 1H), 5.62 (dd, *J* = 8.1, 15.3 Hz, 1H), 5.85 (qd, *J* = 15.3, 6.6 Hz, 1H), 7.21 – 7.23 (m, 2H), 7.27 – 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 17.7, 37.5, 52.1 (q, *J* = 25.1 Hz), 55.5, 66.0, 71.4, 123.9 (q, *J* = 281.3 Hz), 127.5, 128.7, 129.1, 129.3, 131.6, 134.8, 153.1, 165.2 (q, *J* = 2.9 Hz); ^{19}F NMR ($CDCl_3$) δ = -62.2 (d, *J* = 8.7 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 358.1270, Calcd for (M+H) $C_{17}H_{19}$ F_3NO_4: 358.1266.



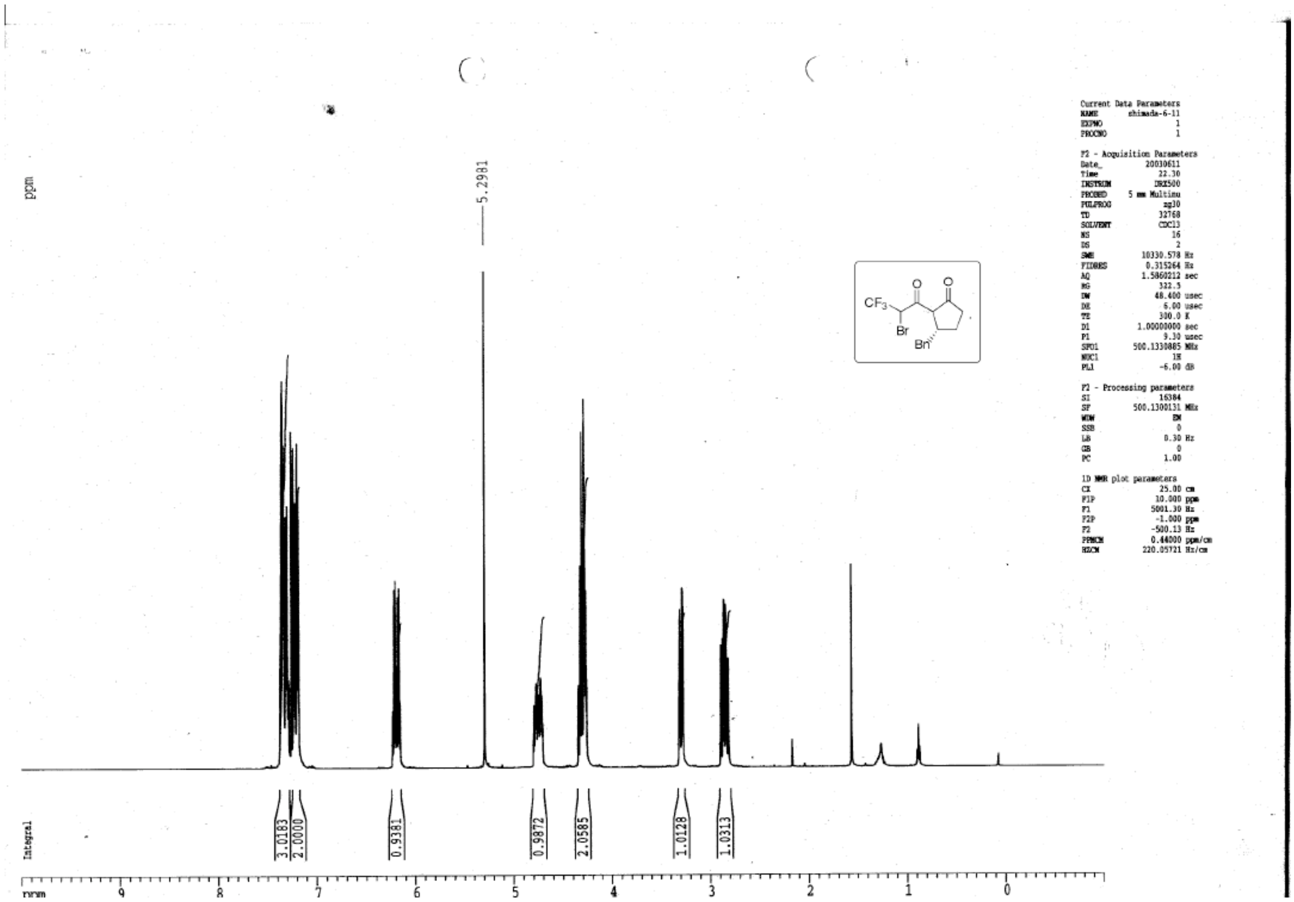
***anti*-(2*S*,3*S*)** : IR (neat) 3468, 3032, 1786, 1707, 1391, 1354, 1167, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.74 (d, *J* = 6.5 Hz, 3H), 2.24 (br s, 1H), 2.79 (dd, *J* = 9.6, 13.5 Hz, 1H), 3.31 (dd, J = 3.2, 13.5 Hz, 1H), 4.18 – 4.24 (m, 2H), 4.68 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.74 – 4.79 (m, 1H), 5.15 (dq, *J* = 8.2, 8.2 Hz, 1H), 5.56 (dd, *J* = 7.5, 15.2 Hz, 1H), 5.88 (dq, *J* = 6.6, 15.2 Hz, 1H), 7.20 – 7.22 (m, 2H), 7.28 – 7.29 (m, 1H), 7.31 – 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 17.6, 37.6, 52.1 (q, *J* = 25.0 Hz), 55.4, 66.1, 70.7, 123.4 (q, *J* = 280.7 Hz), 127.4, 129.0, 129.4, 129.4, 130.8, 134.7, 153.3, 166.4; ^{19}F NMR ($CDCl_3$) δ = -63.8 (d, *J* = 8.7 Hz, 3F); HRMS (FAB^+) Found: *m*/*z* 357.1272, Calcd for (M+H) $C_{17}H_{19}F_3NO_4$: 358.1266.

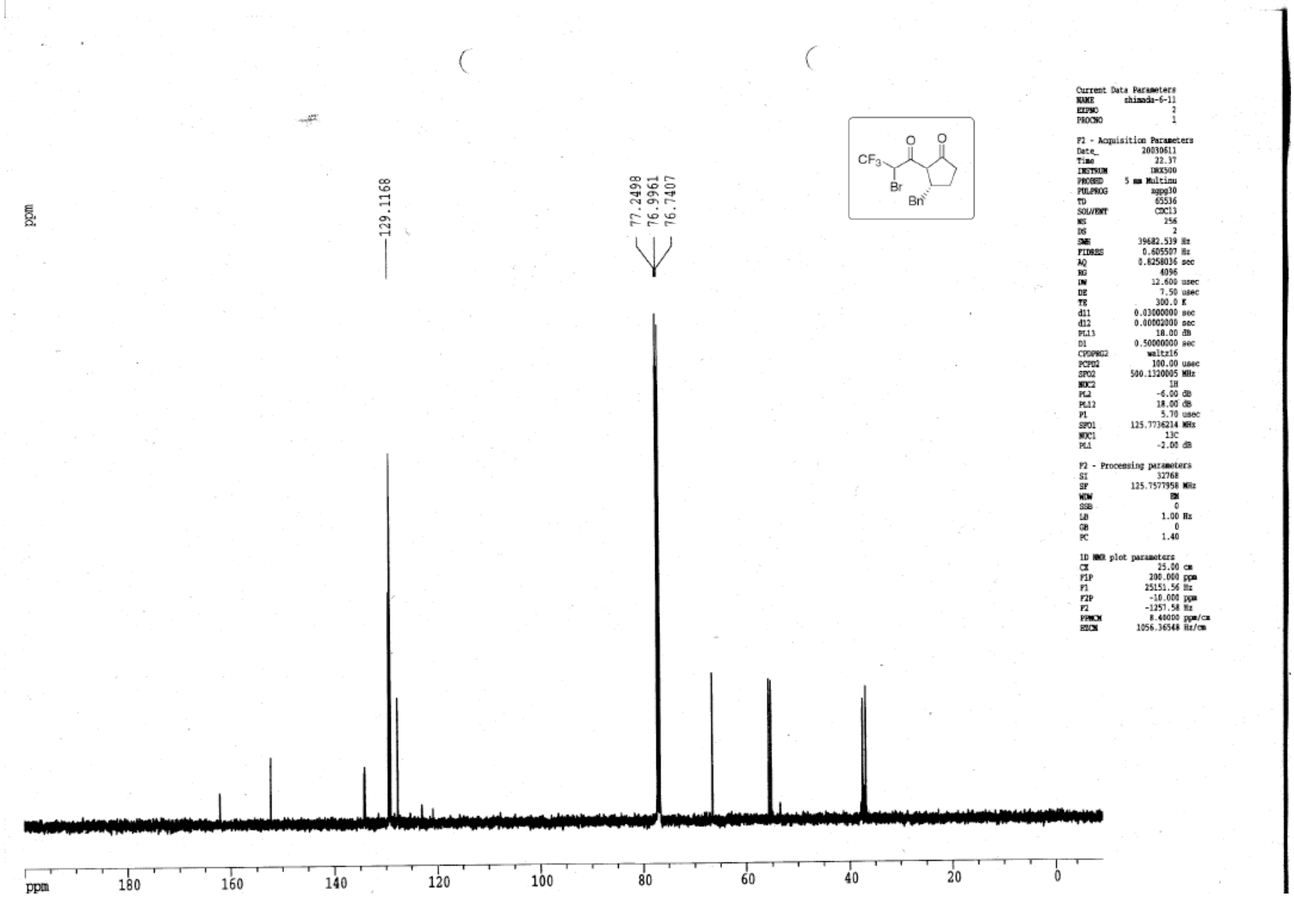
(4*S*)-Benzyl-3-(3,3,3-trifluoro-propanoyl)-oxazolidin-2-one **(3)**



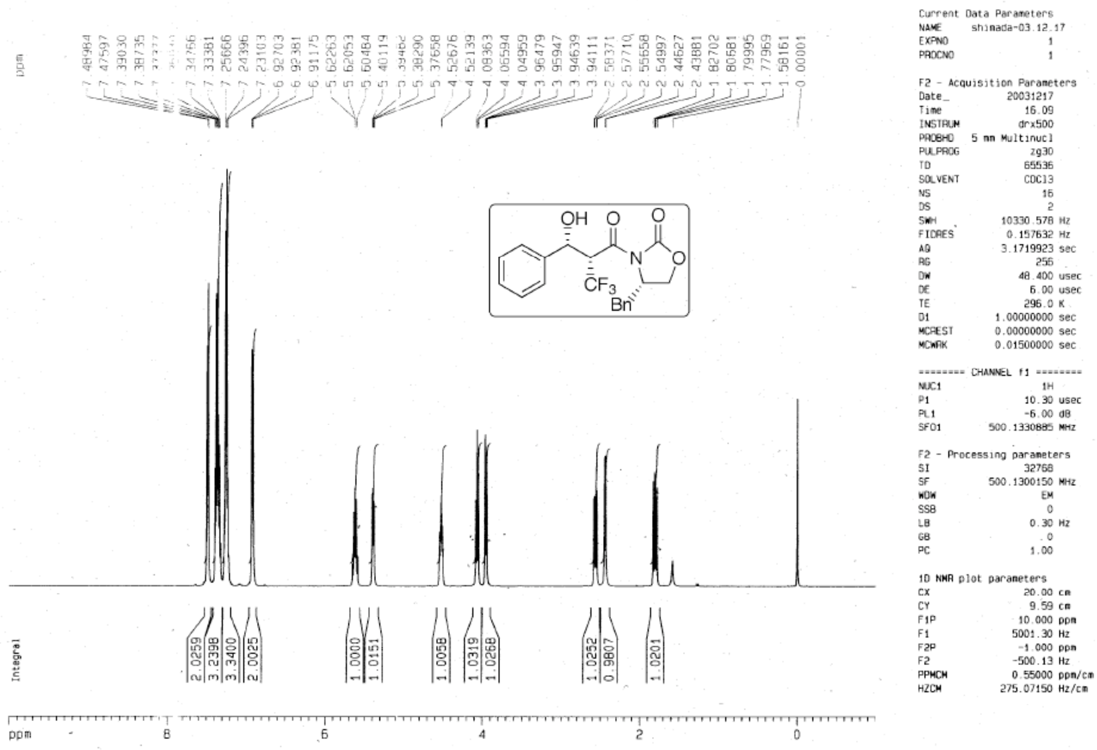


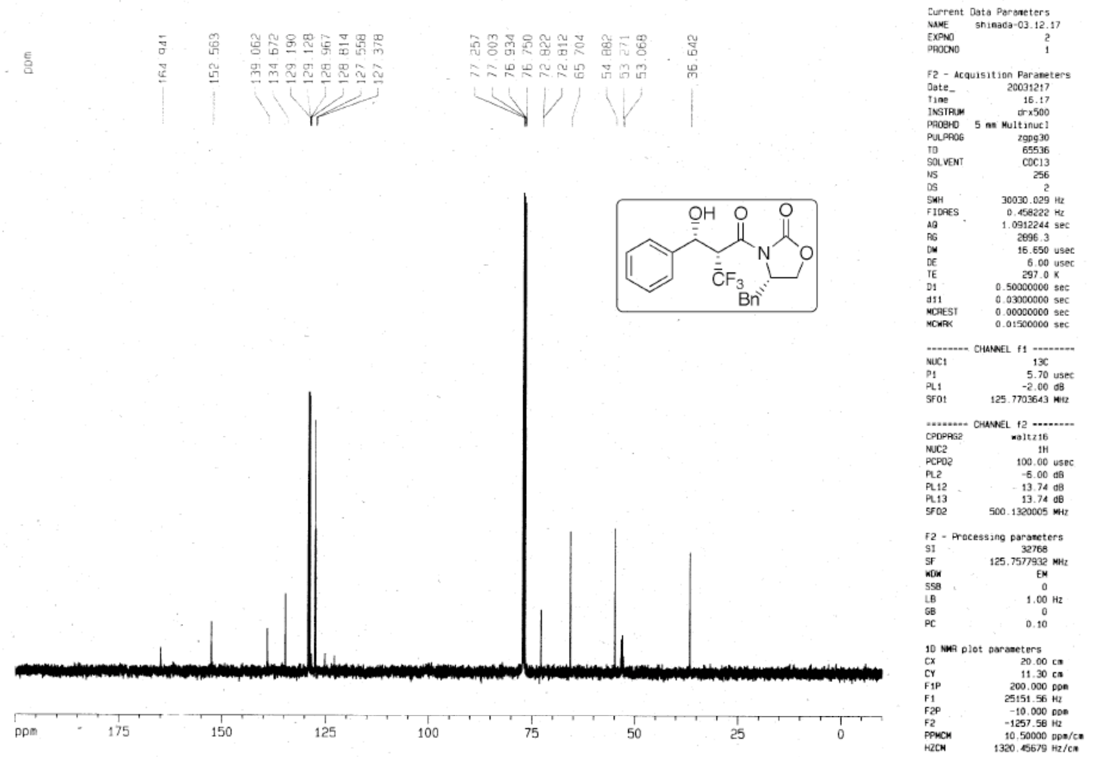
(4*S*)-Benzyl-3-(2-bromo-3,3-trifluoro-propanoyl)-oxazolidin-2-one **(4)**



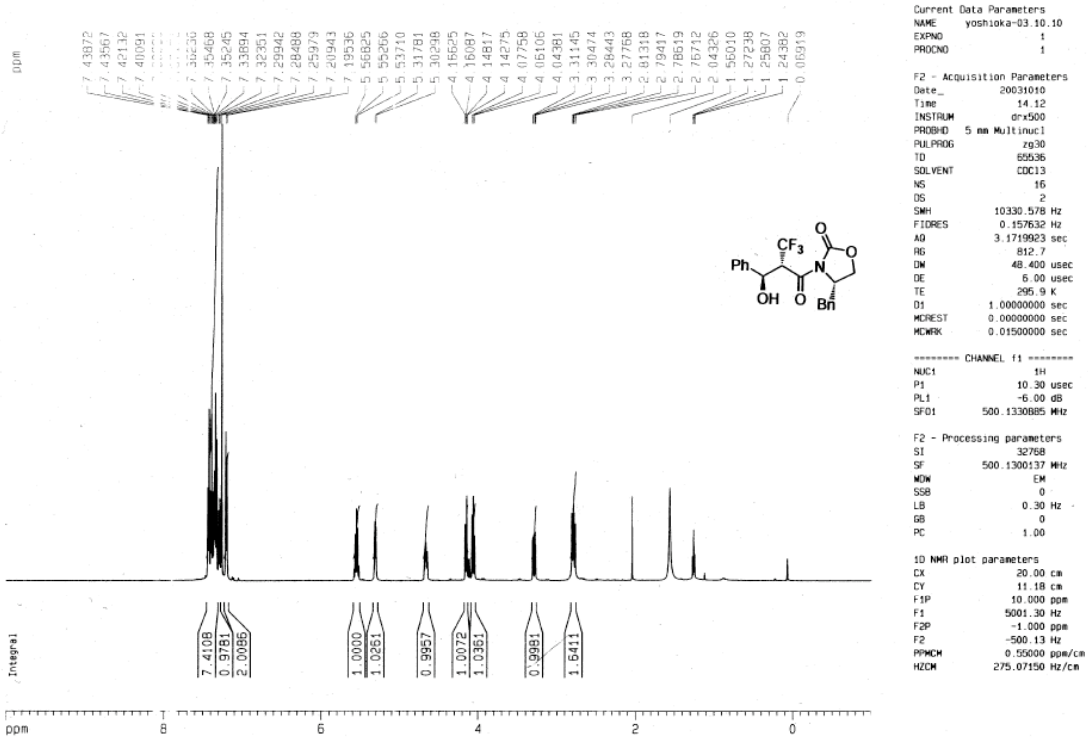


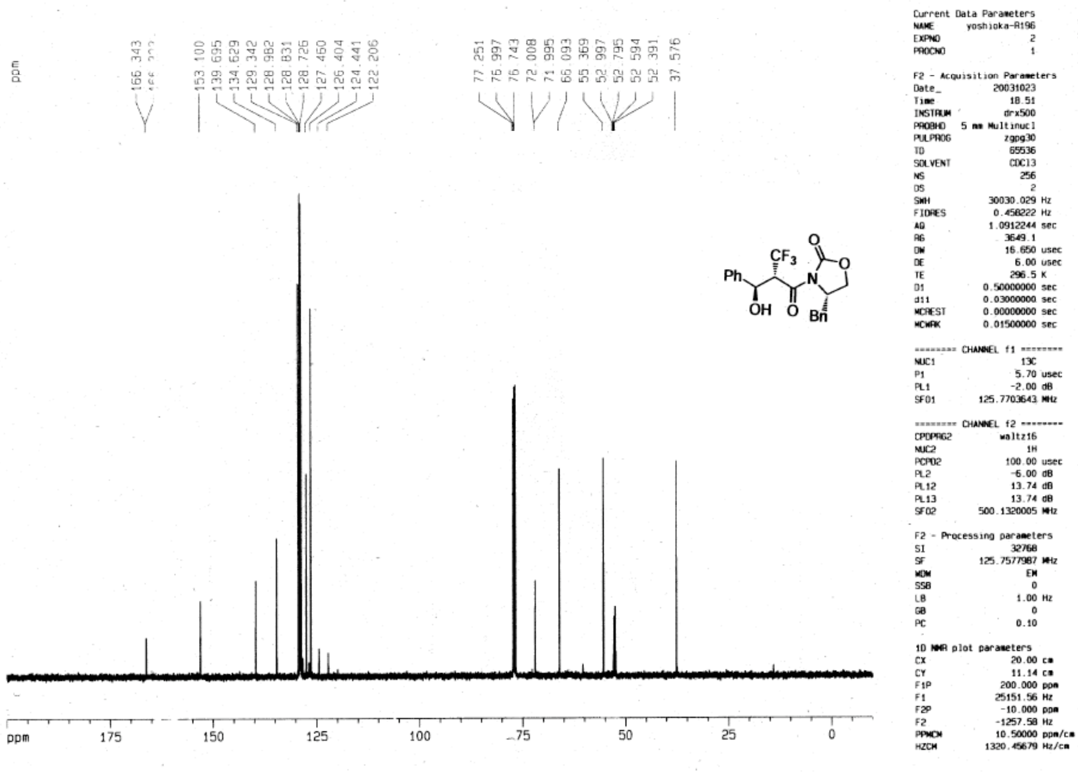
***syn*-(2*R*,3*S*) (1a)**



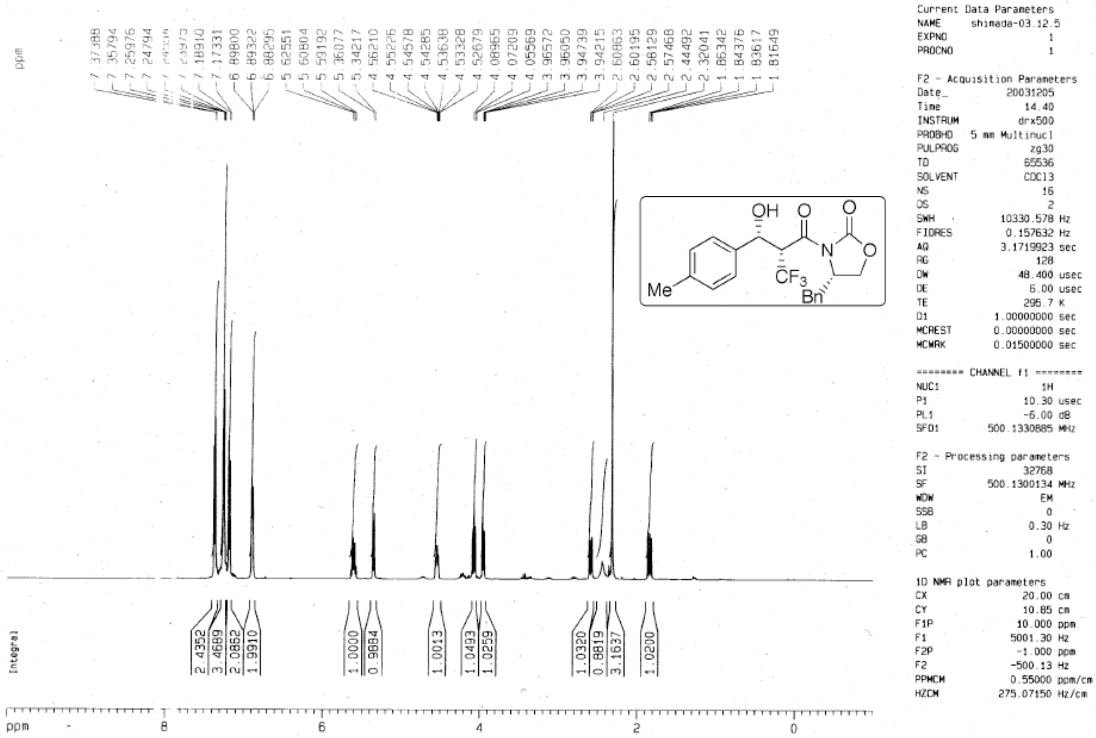


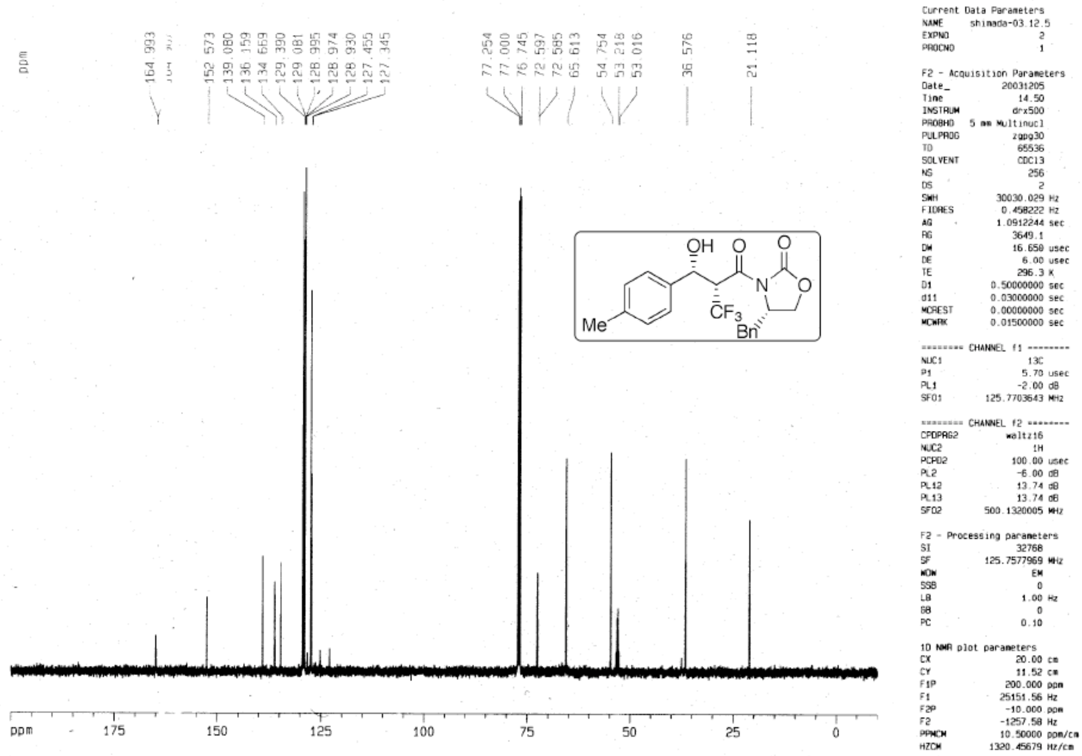
***anti*-(2*S*,3*S*) (1a)**


Current Data Parameters
NAME yoshioka-03.10.10
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20031010
Time 14.12
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 812.7
DW 48.400 usec
DE 6.00 usec
TE 295.9 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.30 usec
PL1 -6.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300137 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 11.18 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -1.000 ppm
F2 -500.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07150 Hz/cm
Ph
CF3
OH
O
N
O
O
Bn
Integral
ppm

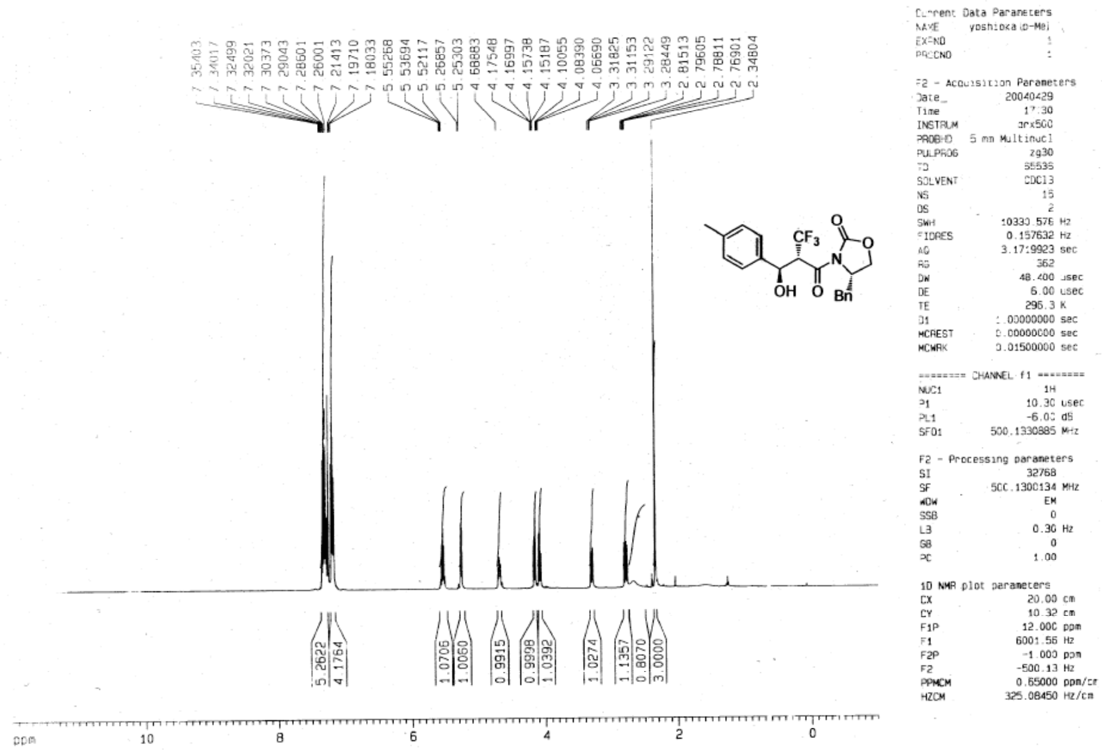

166.343
153.100
139.695
134.629
129.342
128.982
128.831
128.726
127.460
126.404
124.441
122.206
77.251
76.997
76.743
72.008
71.995
66.093
55.369
52.997
52.795
52.594
52.391
37.576
Current Data Parameters
NAME yoshioka-R196
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20031023
Time 18.51
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 3649.1
DW 16.650 usec
DE 6.00 usec
TE 296.5 K
D1 0.50000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 5.70 usec
PL1 -2.00 dB
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.74 dB
PL13 13.74 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7577987 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.10
1D NMR plot parameters
CX 20.00 cm
CY 11.14 cm
F1P 200.000 ppm
F1 25151.56 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 10.50000 ppm/cm
HZCM 1320.45679 Hz/cm
Ph
CF3
OH
O
N
O
O
Bn
ppm

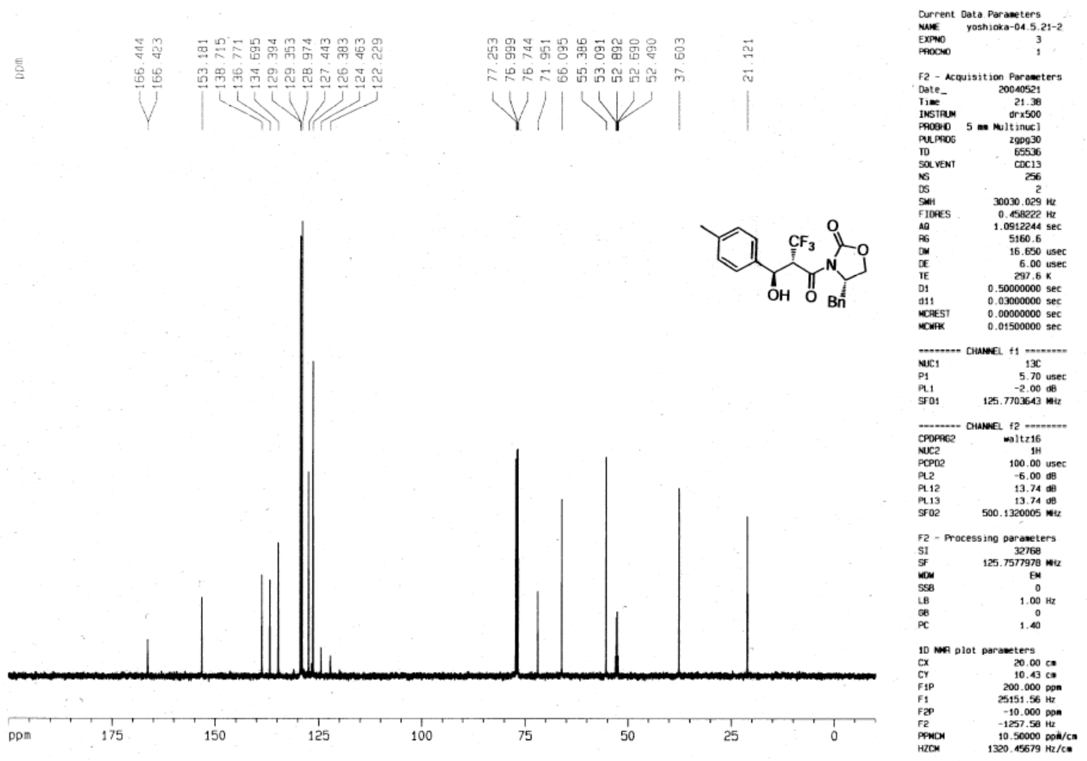
***syn*-(2*R*,3*S*) (1b)**



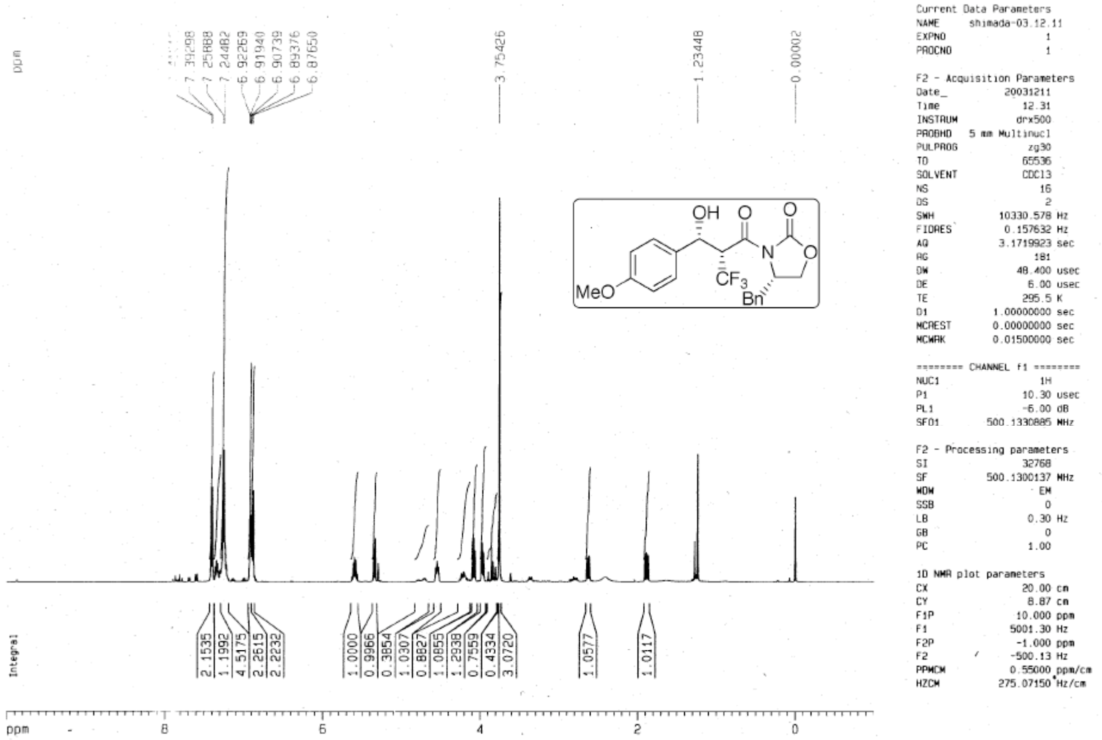


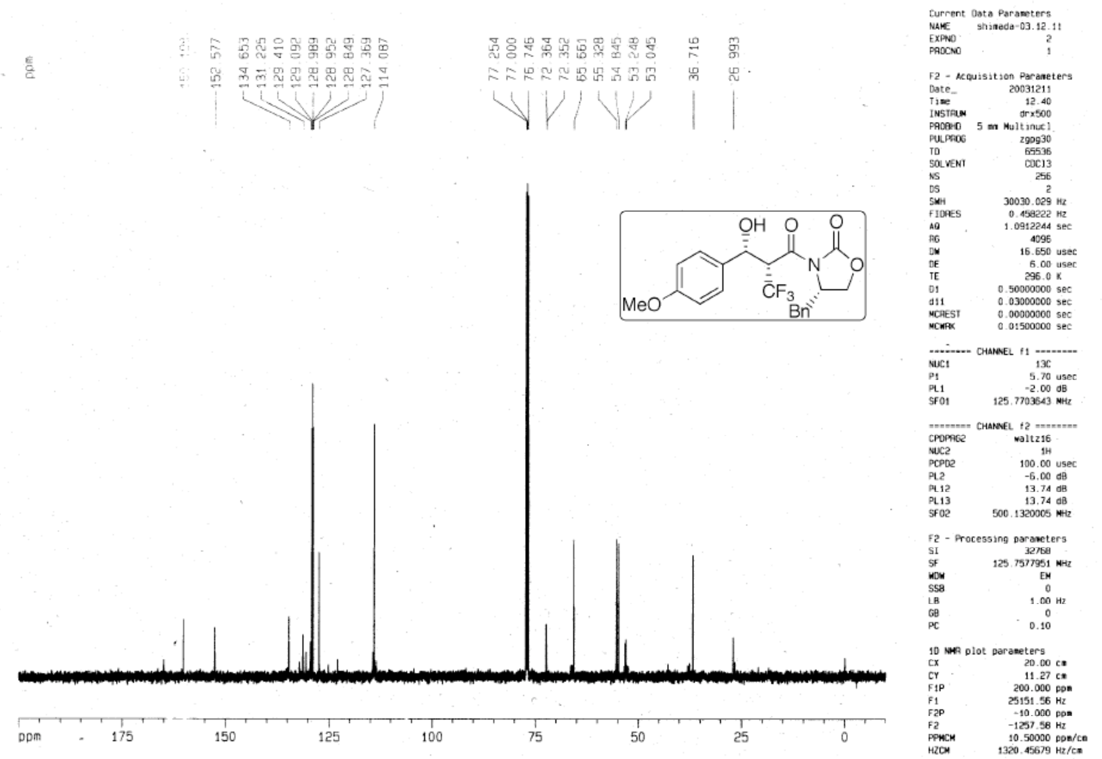
***anti*-(2*S*,3*S*) (1b)**



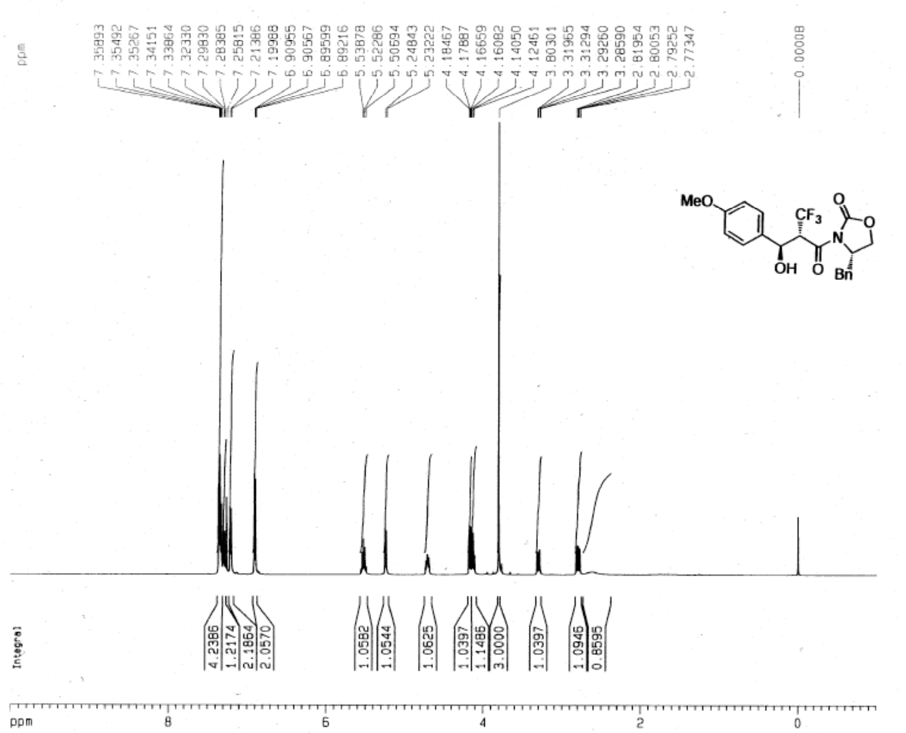


syn-(2*R*,3*S*) (1c)





***anti*-(2*S*,3*S*) (1c)**



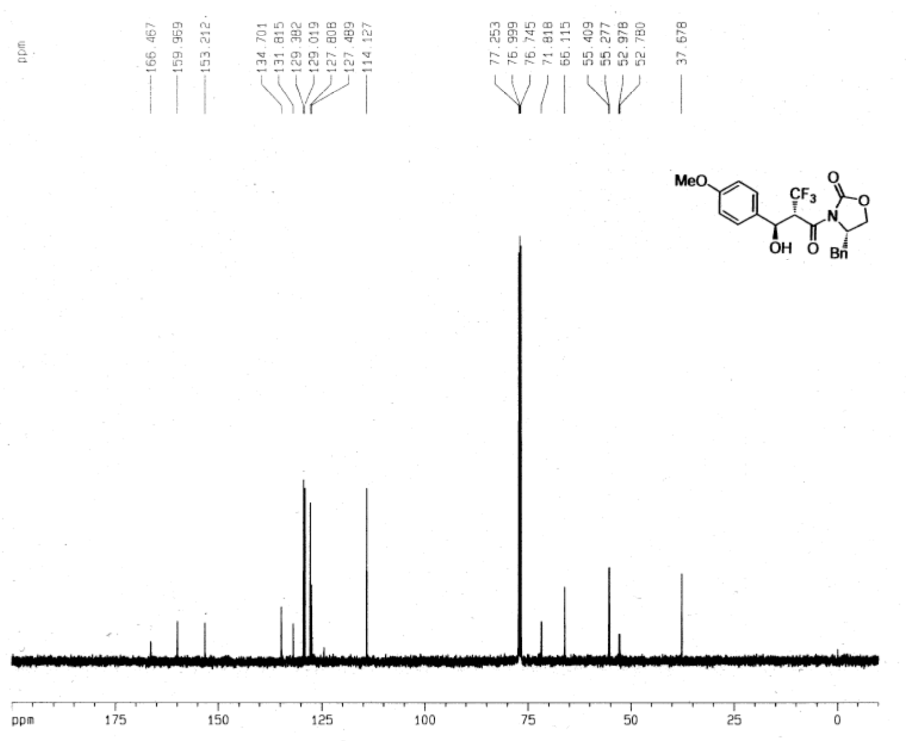
Current Data Parameters
NAME yoshioka-04.5.21
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040521
Time 11.56
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 287.4
DW 48.400 usec
DE 6.00 usec
TE 296.6 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 10.30 usec
PL1 -6.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.39 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -1.000 ppm
F2 -500.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07150 Hz/cm



Current Data Parameters
NAME yoshioka-04.5.21
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040521
Time 12.05
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 1625.5
DW 16.650 usec
DE 6.00 usec
TE 297.5 K
D1 0.50000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

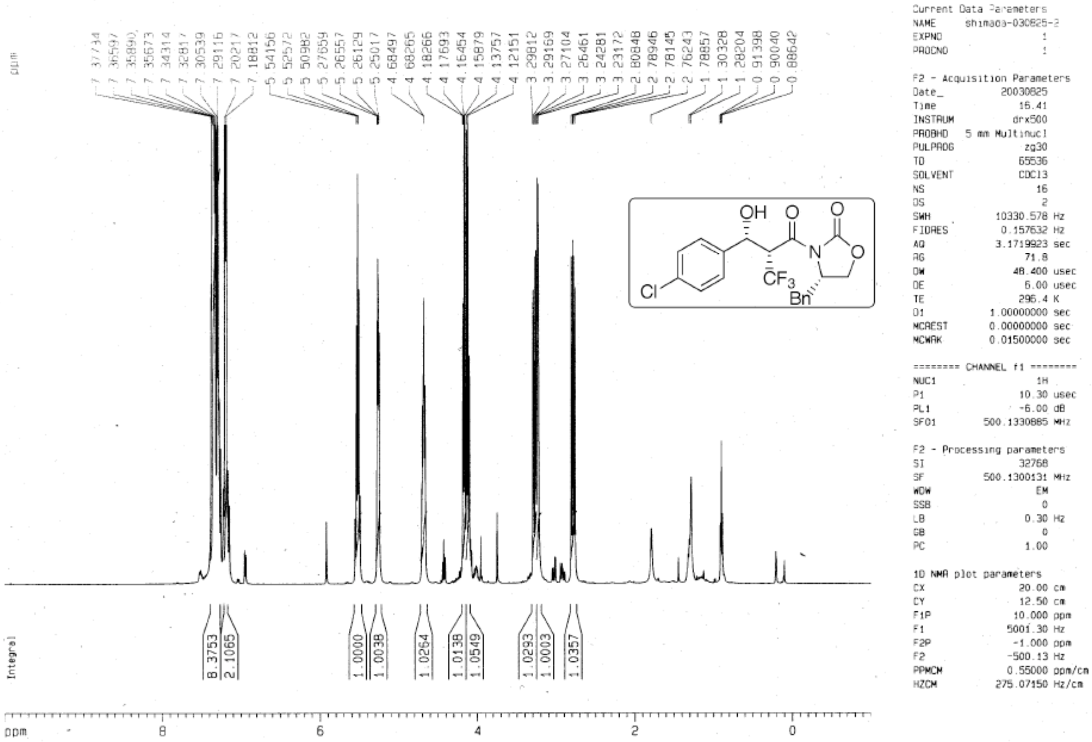
======== CHANNEL f1 ========
NUC1 13C
P1 5.70 usec
PL1 -2.00 dB
SFO1 125.7703643 MHz

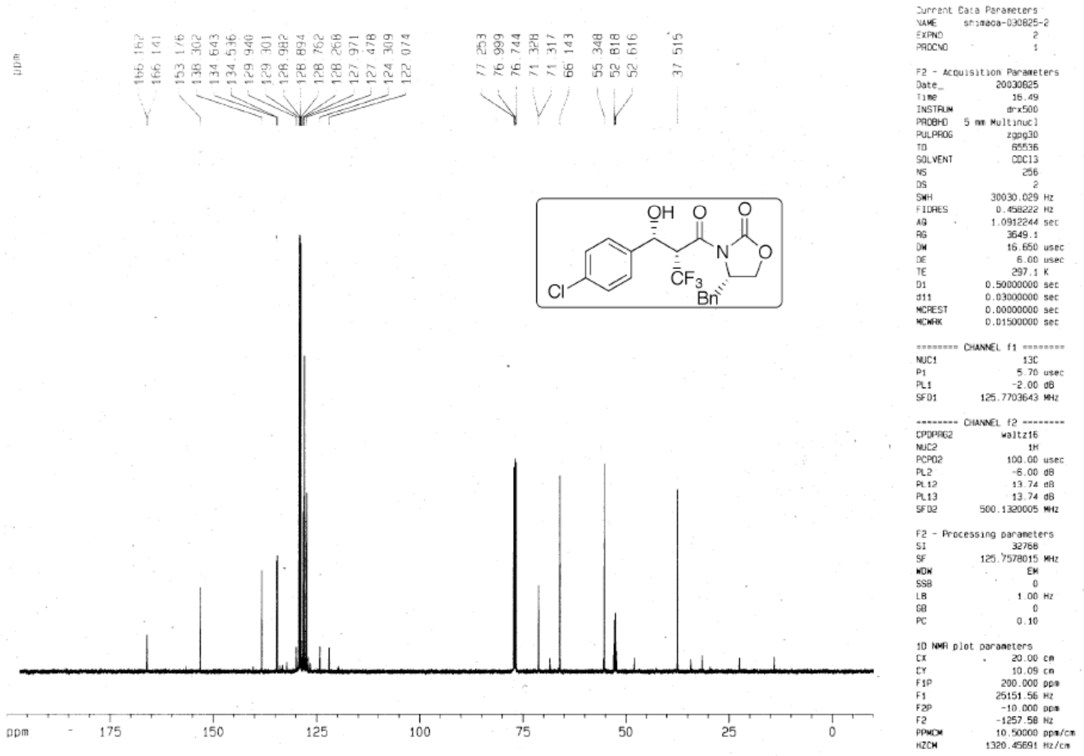
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.74 dB
PL13 13.74 dB
SFO2 500.1320005 MHz

F2 - Processing parameters
SI 32768
SF 125.7577932 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

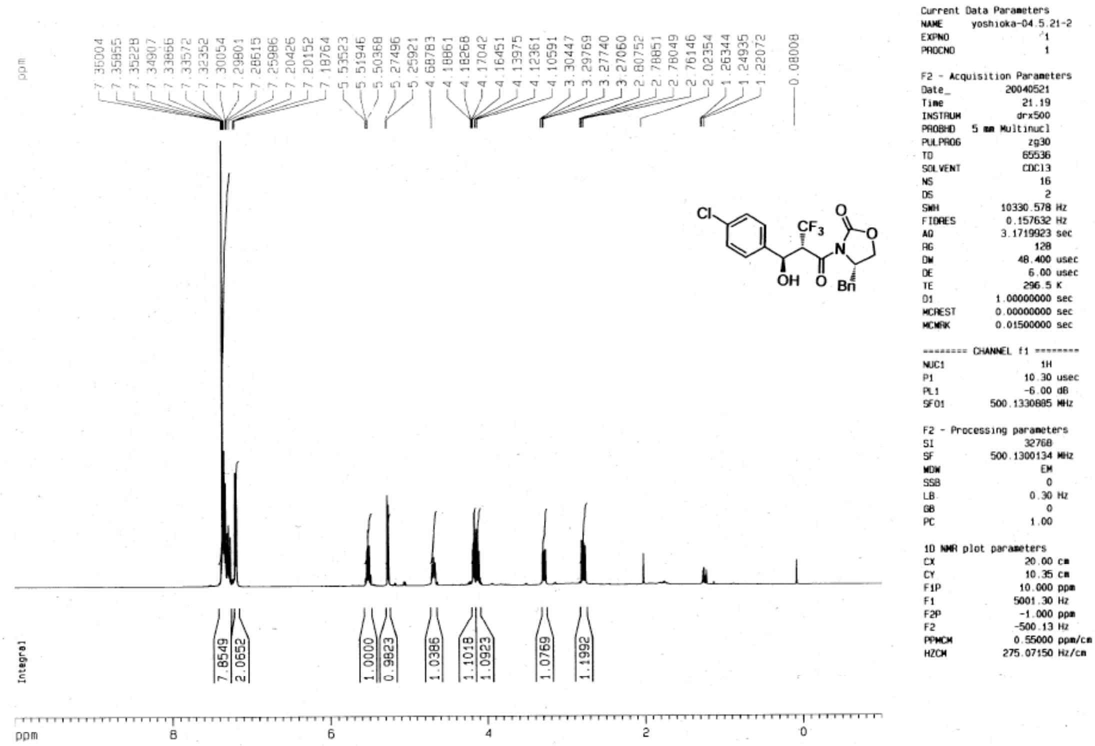
1D NMR plot parameters
CX 20.00 cm
CY 9.72 cm
F1P 200.000 ppm
F1 25151.56 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 10.50000 ppm/cm
HZCM 1320.45679 Hz/cm

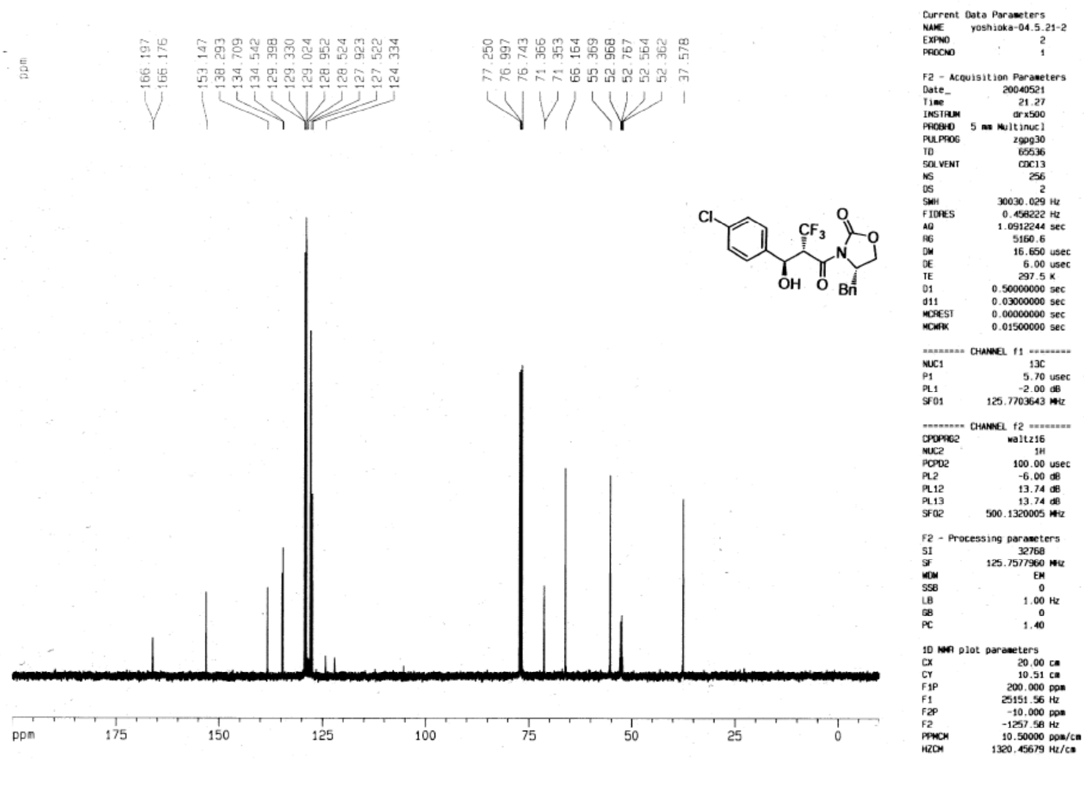
***syn*-(2*R*,3*S*) (1d)**


Current Data Parameters
NAME shimada-030825-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030825
Time 16.41
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 71.8
DW 48.400 usec
DE 6.00 usec
TE 295.4 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.30 usec
PL1 -6.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300131 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -1.000 ppm
F2 -500.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07150 Hz/cm
Integral
8.3753
2.1065
1.0000
1.0038
1.0264
1.0138
1.0549
1.0293
1.0003
1.0357
ppm

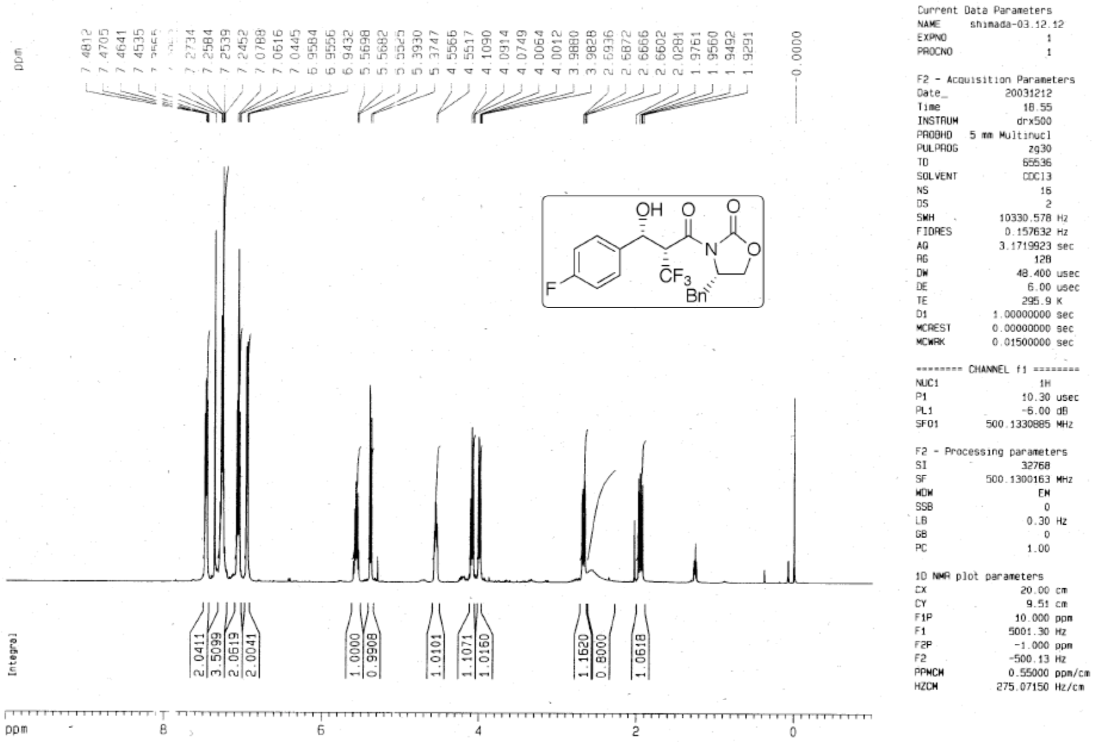

Current Data Parameters
NAME shimada-030825-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030825
Time 16.49
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 3649.1
DW 16.650 usec
DE 6.00 usec
TE 297.1 K
D1 0.50000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 5.70 usec
PL1 -2.00 dB
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.74 dB
PL13 13.74 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578015 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.10
1D NMR plot parameters
CX 20.00 cm
CY 10.09 cm
F1P 200.000 ppm
F1 25151.56 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 10.50000 ppm/cm
HZCM 1320.45691 Hz/cm
ppm

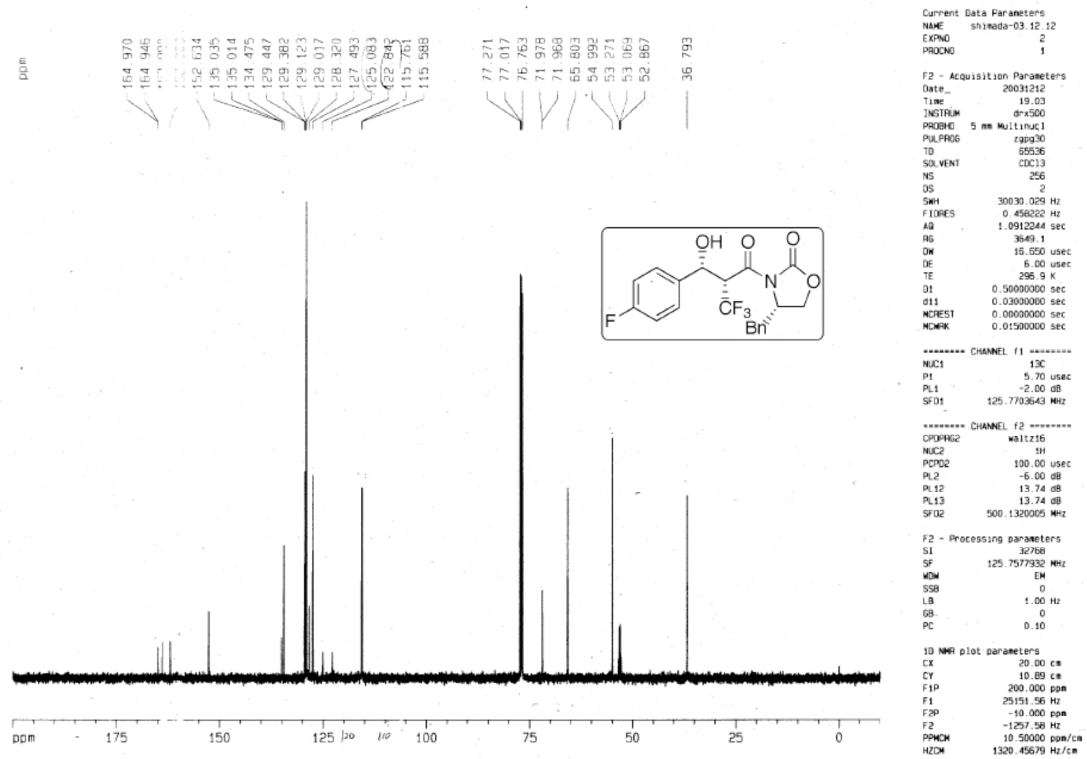
***anti*-(2*S*,3*S*) (1d)**


Current Data Parameters
NAME yoshioka-04.5.21-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040521
Time 21.19
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 128
DW 48.400 usec
DE 6.00 usec
TE 296.5 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.30 usec
PL1 -6.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300134 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 10.35 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -1.000 ppm
F2 -500.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07150 Hz/cm
Cl
CF3
O
N
OH
Bn
ppm
Integral
7.8549
2.0652
1.0000
0.9823
1.0386
1.1018
1.0923
1.0769
1.1992
ppm
8
6
4
2
0

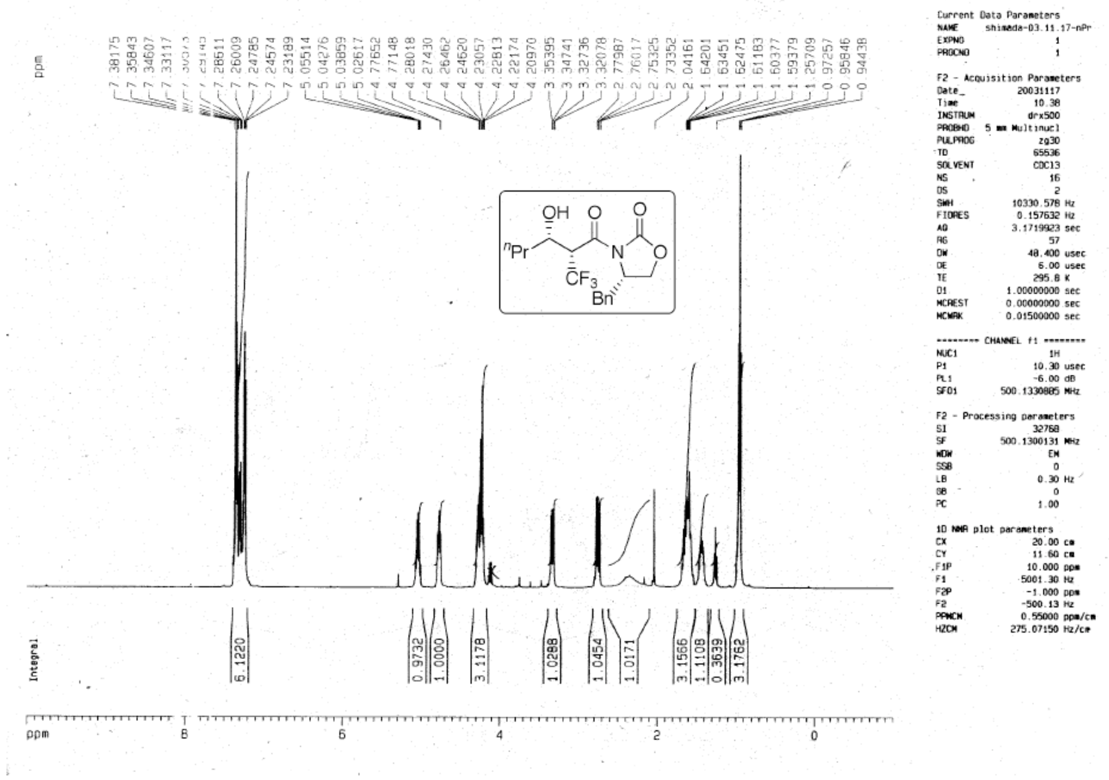

Current Data Parameters
NAME yoshioka-04.5.21-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040521
Time 21.27
INSTRUM drx500
PROBHD 5 mm Multinucl
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 5160.6
DW 16.650 usec
DE 6.00 usec
TE 297.5 K
D1 0.50000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 5.70 usec
PL1 -2.00 dB
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.74 dB
PL13 13.74 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7577960 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 10.51 cm
F1P 200.000 ppm
F1 25151.56 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 10.50000 ppm/cm
HZCM 1320.45679 Hz/cm
Cl
CF3
O
N
OH
Bn
ppm
166.197
166.176
153.147
138.293
134.709
134.542
129.398
129.330
129.024
128.952
128.524
127.923
127.522
124.334
77.250
76.997
76.743
71.366
71.353
66.164
55.369
52.968
52.767
52.564
52.362
37.578
ppm
175
150
125
100
75
50
25
0

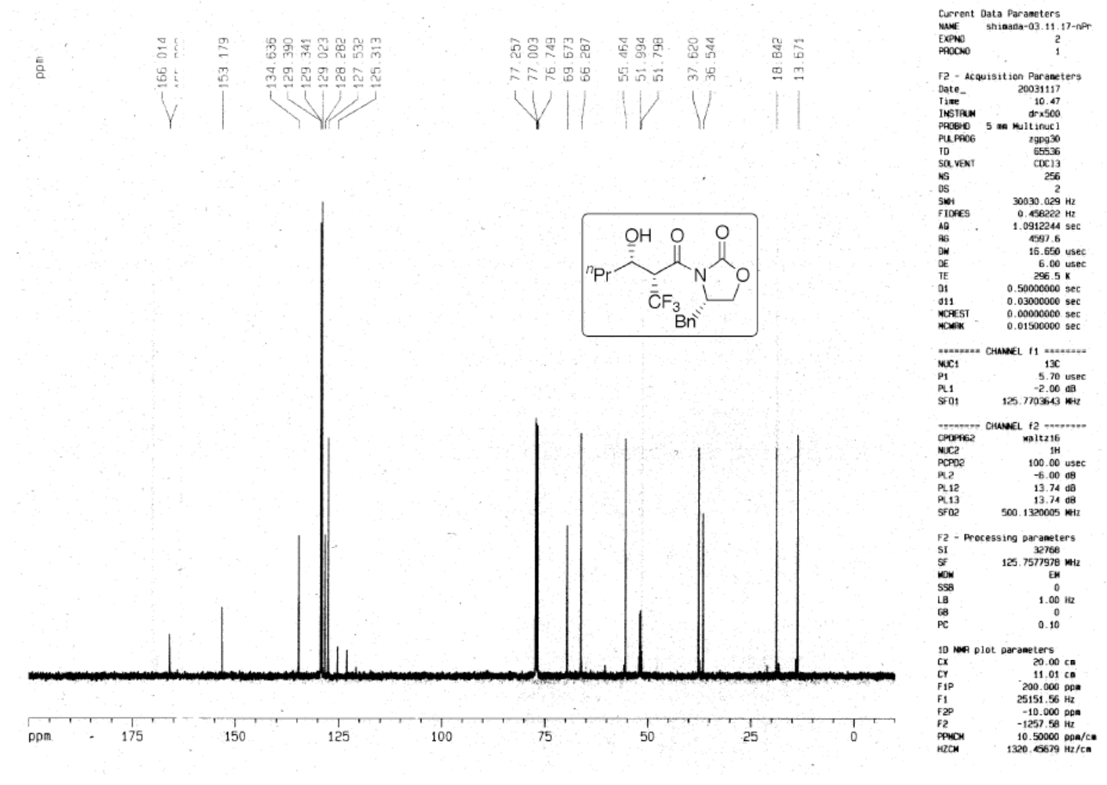
***syn*-(2*R*,3*S*) (1e)**



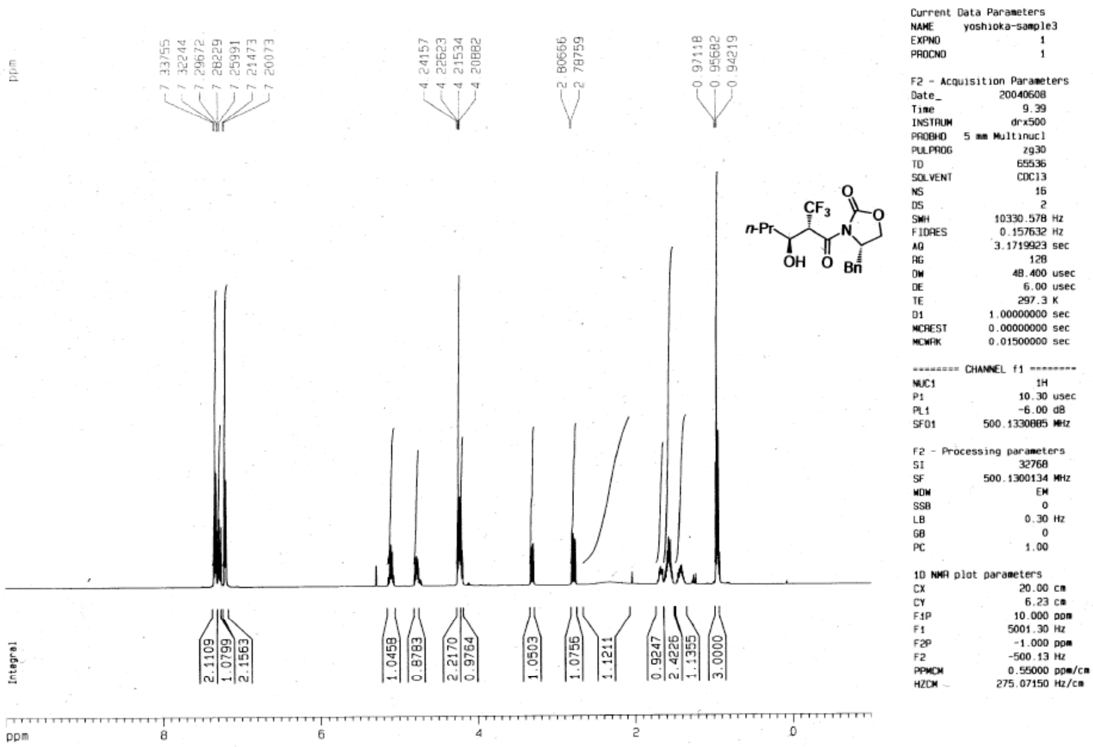


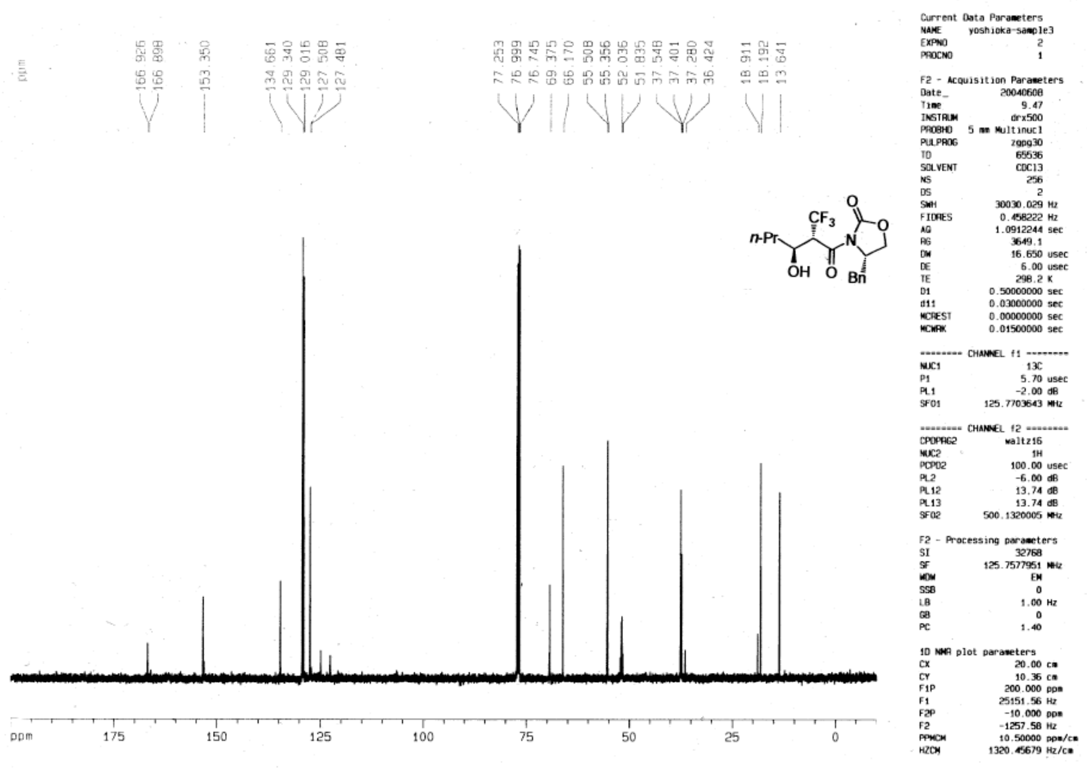
***syn*-(2*R*,3*S*) (1f)**



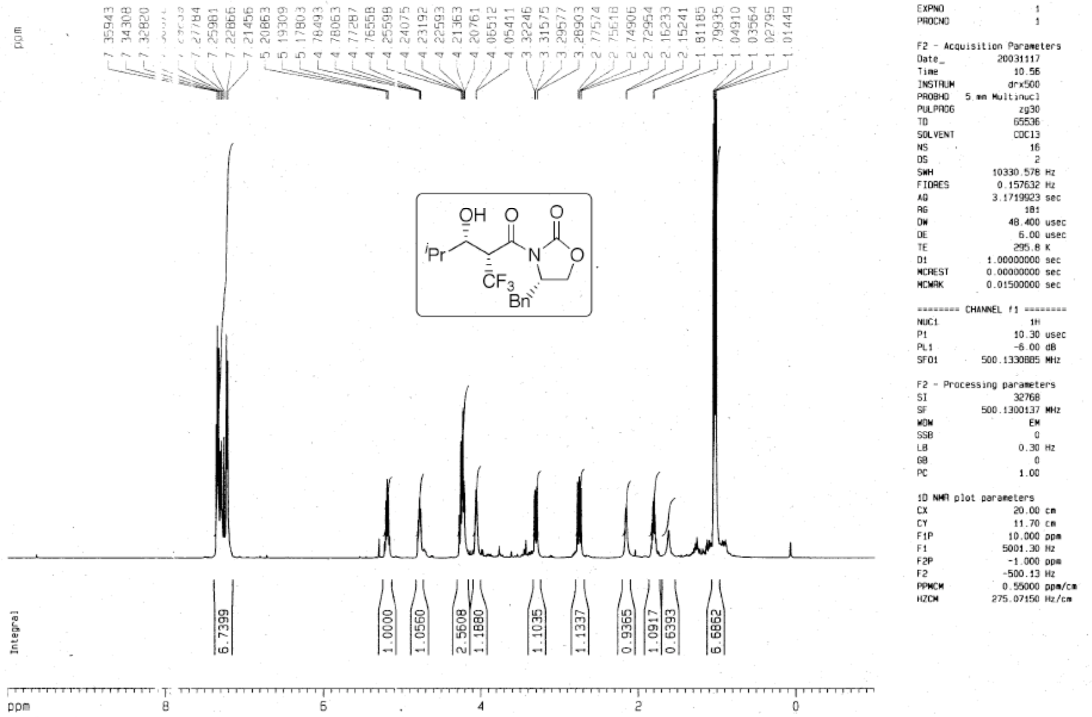


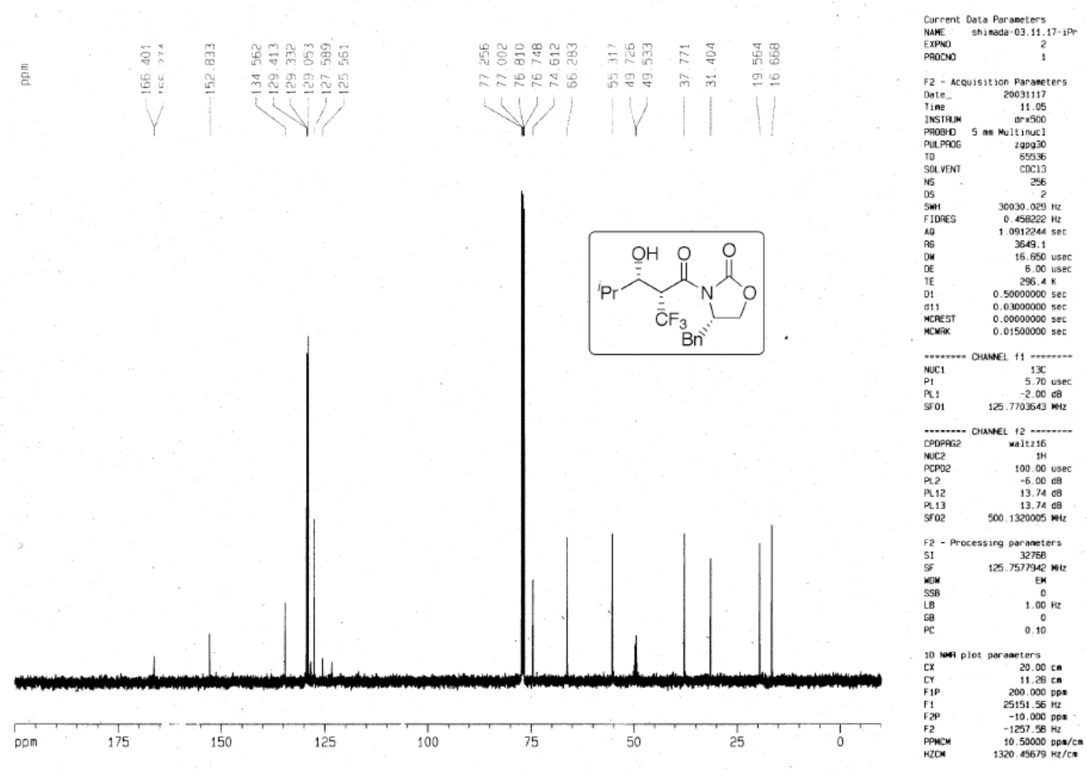
***anti*-(2*S*,3*S*) (1f)**



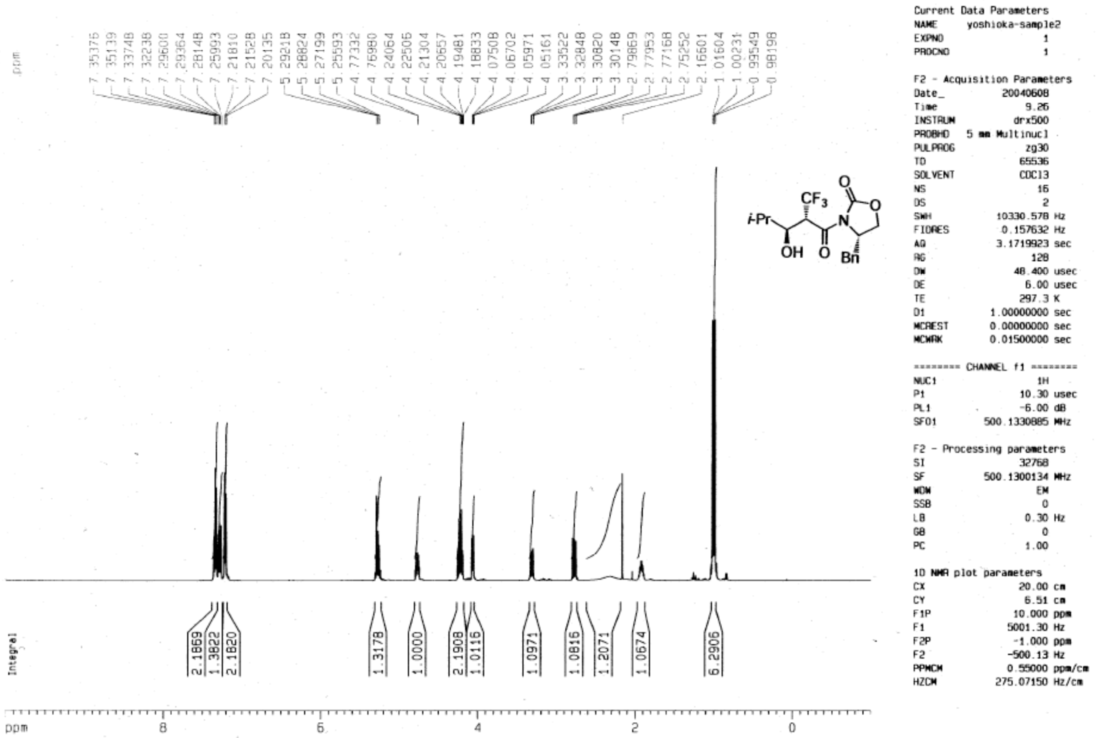


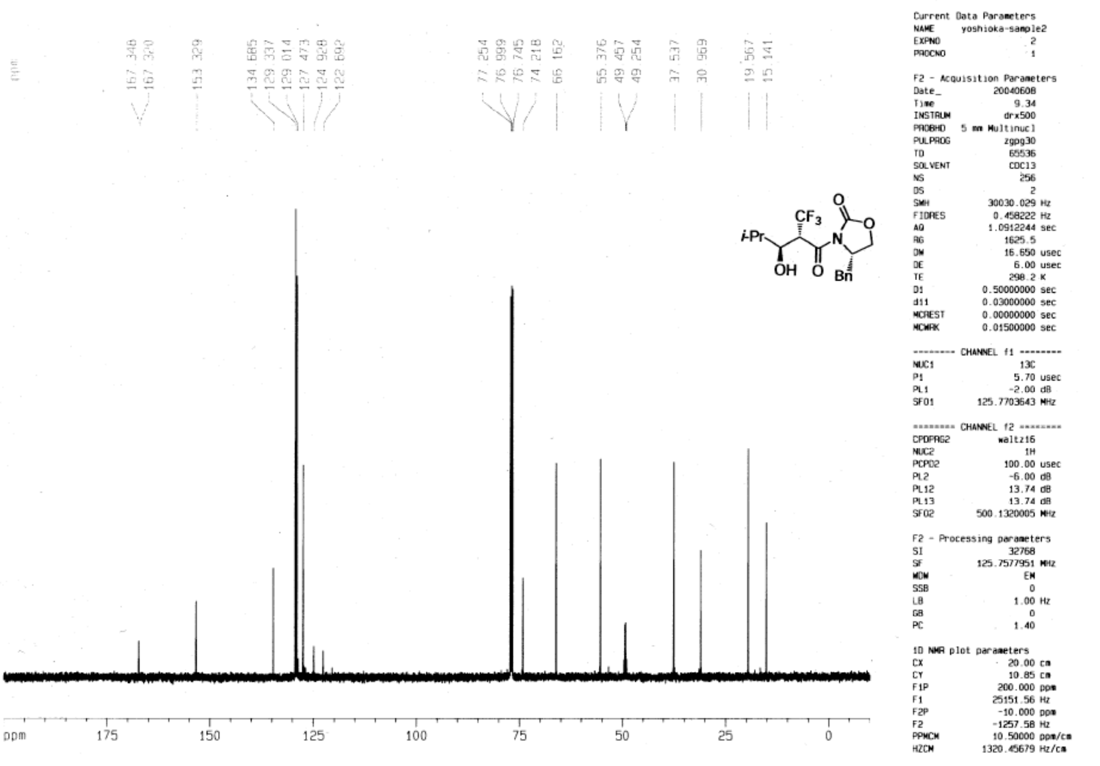
***syn*-(2*R*,3*S*) (1g)**



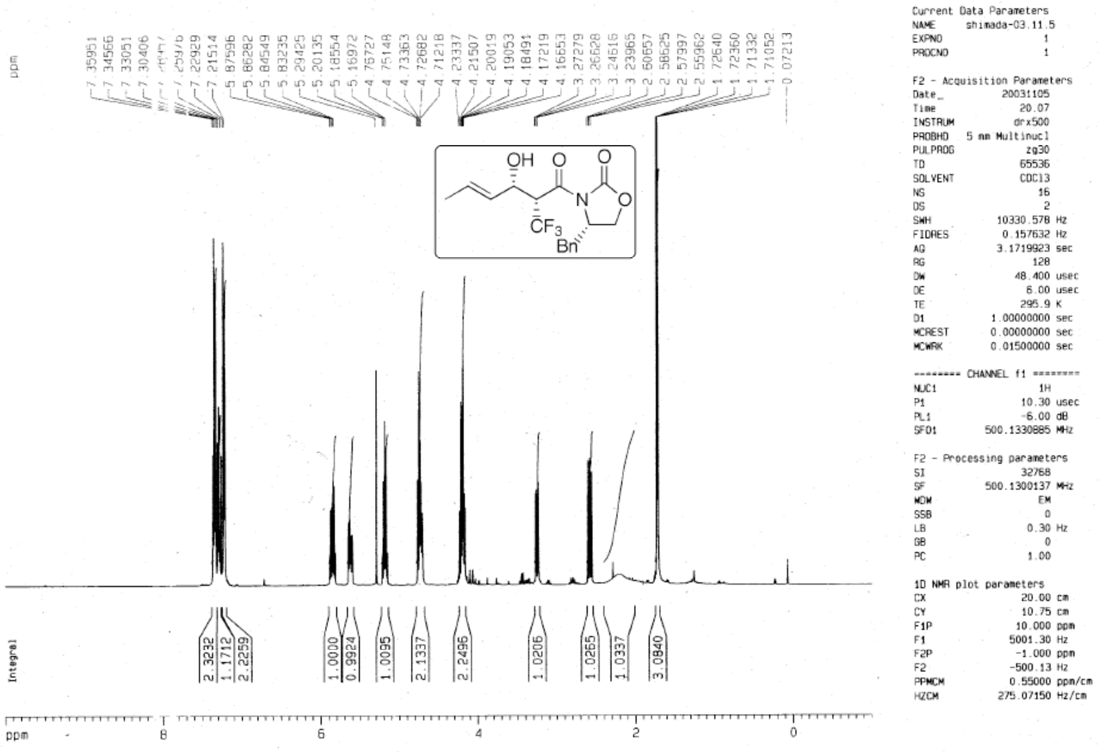


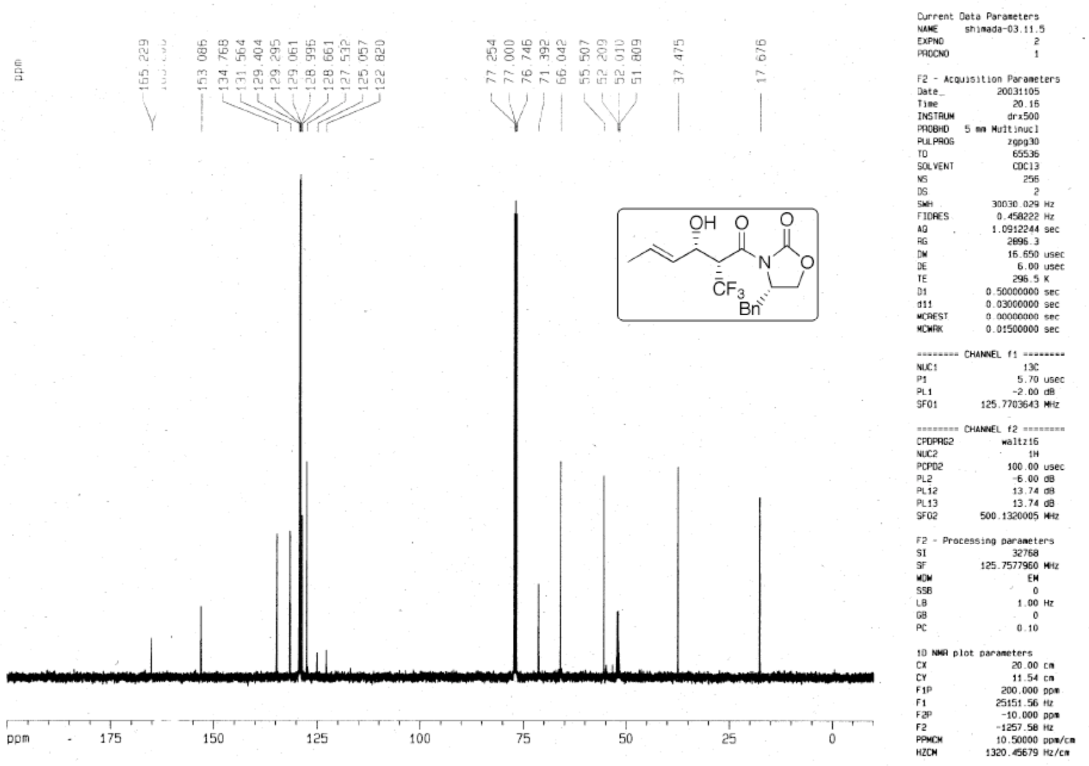
***anti*-(2*S*,3*S*) (1g)**



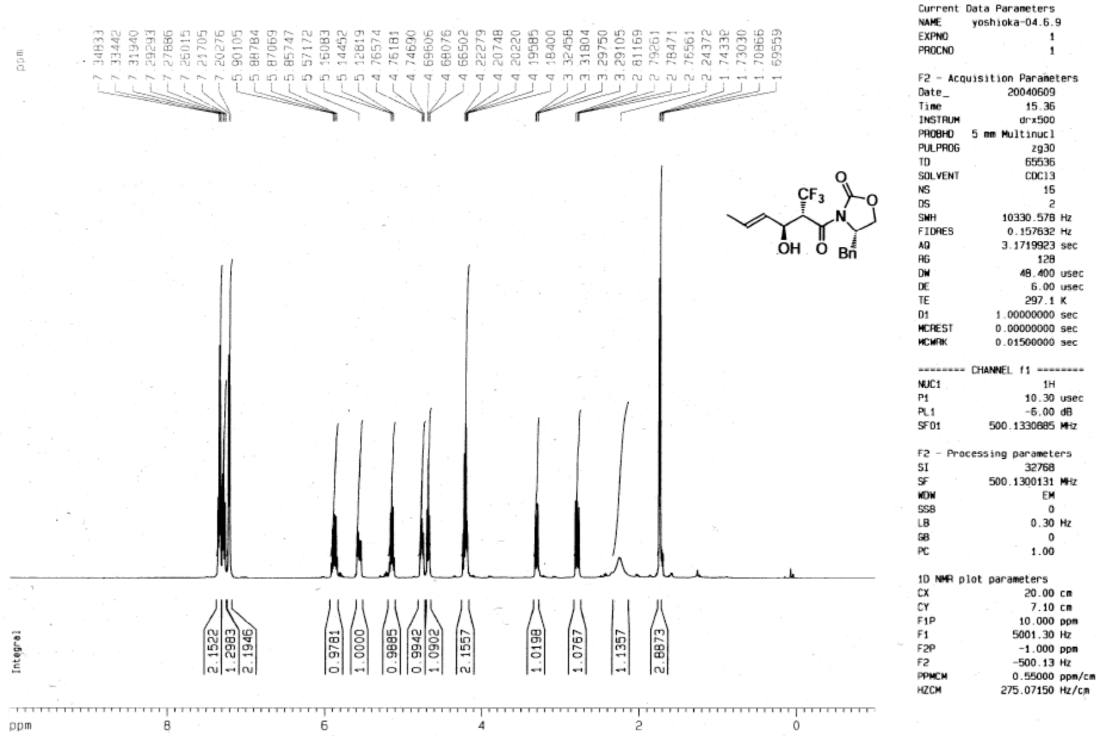


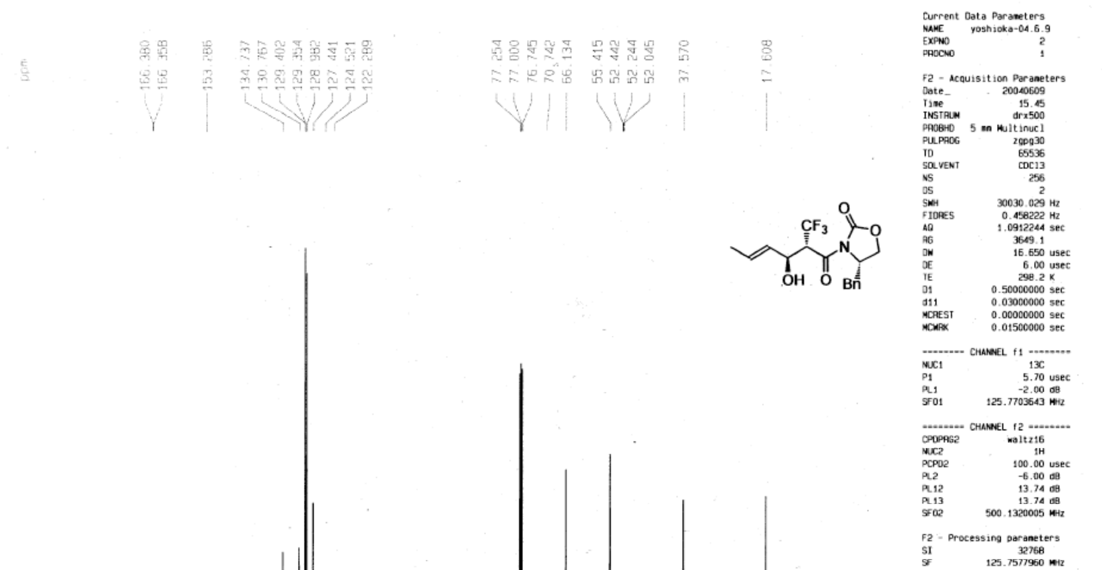
syn-(2*R*,3*S*) (1h)





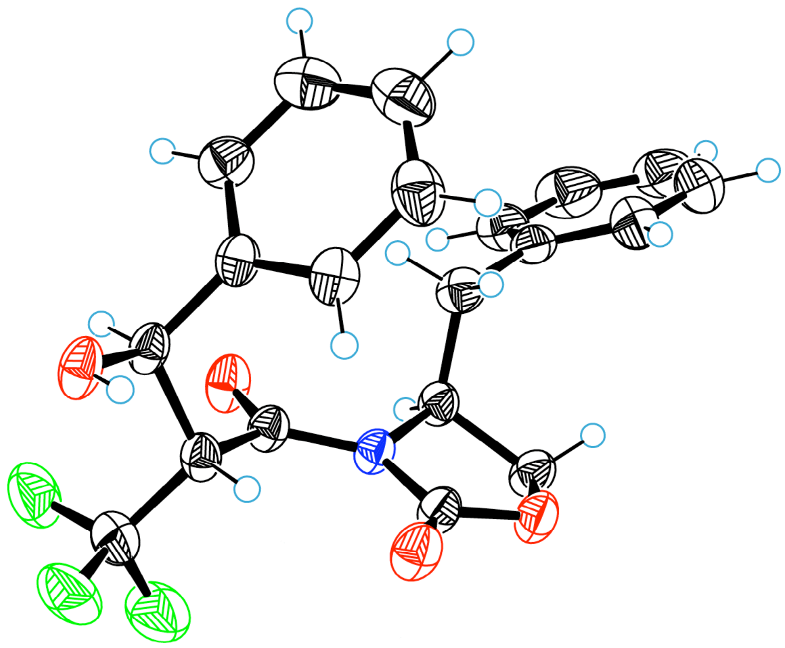
***anti*-(2*S*,3*S*) (1h)**





IV. ORTEP drawing

non-Evans *syn* (**1a**)



Evans *anti* (**1c**)