Supporting Information for

Aqueous organocatalyzed aldol reaction of glyoxylic acid for the enantioselective synthesis of α-hydroxy-γ-keto acids

Fernando J. N. Moles, Gabriela Guillena, Carmen Nájera**

Departamento de Química Orgánica e Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, Carretera de San Vicente s/n, E-03080-Alicante, Spain

Gabriela.guillena@ua.es, cnajera@ua.es

Table of Contents

General information: Catalysts **1** and **2** were prepared according to literature[1]. All the reagents were commercially available and used without further purification. ^{1}H NMR (300 MHz, 400 MHz) and ^{13}C NMR (75 MHz) spectra were obtained at 25 ºC using $CDCl_3$ as solvent and chemical shifts are reported as δ values relative to TMS as internal standard. IR spectra were obtained with Jasco 4100 LE (Pike Piracle ATR). High resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model Waters ACQUITY H CLASS. Optical rotations were measured on a Jasco P-1030 Polarimeter with a 5 cm cell (c given in g/100 mL). HPLC analyses were performed on equipped with a chiral column and automatic inyector, using mixtures of n-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 ºC. Analytical TLC was performed on silica gel plates and the spots were visualized using $KMnO_4$ solution as revelator. For flash chromatography we employed silica gel 60 (0.040-0.063 mm).

General procedures for the aldol reaction

General procedure for the aldehyde-ketone aldol reaction using glyoxylic acid monohydrate:

To a mixture of the glyoxylic acid monohydrate (0.25 mmol, 0.023 g), catalyst (10 mol%) and water (2.5 mmol, 0.045 mL) at the indicated temperature was added the corresponding ketone (0.5 mmol). The reaction was stirred until the glyoxylic acid was consumed (monitored by TLC). Then Me_3SiCHN_2 2 M in diethyl ether (1 mmol, 0.5 mL) was added at the crude product. The corresponding mixture was stirred for 1 h, and the solvents were evaporated in vacuo. The resulting residue was purified by chromatography (hexanes/AcOEt) to yield the pure aldol product. During purification the aldols **6c** and **6d** undergo an epimerisation and therefore the diastereoselectivities of the crude ^{1}H-RMN is different than the one showed in the HPLC or GC spectra.

General procedure for the aldehyde-ketone aldol reaction using glyoxylic acid 50%

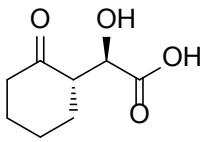
aqueous solution:

To a mixture of the glyoxylic acid 50% aqueous solution (0.25 mmol, 0.027 mL) and catalyst (10 mol%) at the indicated temperature was added the corresponding ketone (0.5 mmol). The reaction was stirred until the glyoxylic acid was consumed (monitored by TLC). Then, Me_3SiCHN_2 2 M in diethyl ether (1 mmol, 0.5 mL) was added at the crude product. The corresponding mixture was stirred for 1 h, and the solvents were evaporated in vacuo. The resulting residue was purified by chromatography (hexanes/AcOEt) to yield the pure aldol product. During purification the aldols **6c** and **6d** undergo an epimerisation and therefore the diastereoselectivities of the crude ^{1}H-RMN is different than the one showed in the HPLC or GC spectra.

Procedure for the α-hydroxy-γ-keto acids preparation:

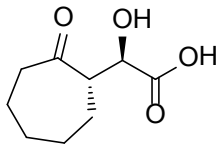
To a mixture of the glyoxylic acid monohydrate (0.25 mmol, 0.023 g) and catalyst **2a** (0.025 mmol, 0.013 g) at 0º C was added the corresponding ketone (0.5 mmol). The reaction was stirred until the glyoxylic acid was consumed (monitored by TLC). Then, ethyl acetate was added (10 mL), and the crude product was washed with H_2O (3x10 mL) the aqueous phase was evaporated to obtain the corresponding α-hydroxy-δ-keto acid with glyoxylic acid traces. The glyoxylic acid was precipitated using dioxane and the corresponding α-hydroxy-γ-keto acid was purified by passing it through a small silica gel pad and concentrated in vacuo.

Spectra data of aldol products



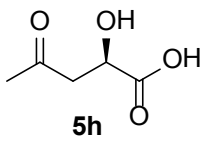
5a

(*R*)-2-Hydroxy-2-[(*S*)-oxocyclohexyl]acetic acid (5a).[2] Data for the major Isomer (2*S*, 2'*R*). Colorless oil (0.020 g, 71%); $[\alpha]^{26}_D$ = -10 (c = 0.9 in MeOH); R_f = 0.1 (EtOAc) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3421 (CO_2H), 1714 (CO), 1702 (CO). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.58 - 1.88 (3 H, m, H_{cyclo}), 1.90 - 2.05 (1 H, m, H_{cyclo}), 2.0.6 - 2.31 (2 H, m, H_{cyclo}), 2.31 - 2.56 (2 H, m, H_{cyclo}), 2.98 - 3.12 (1 H, m, CHCHOH), 4.18 (1 H, d, J = 3.1, CHOH). δ_C (75 MHz; $CDCl_3$; Me_4Si) 24.7 (CH_2), 27.2 (CH_2), 30.2 (CH_2), 42.0 (CH_2), 53.7 (CH), 70.4 (CH), 176.8 (C), 213.0 (C). *m/z* (IE) 172 (M^+,2%), 136 (10), 126 (100), 109 (95), 97 (18), 81 (51).



5f

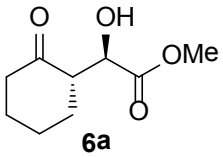
(*R*)-2-Hydroxy-2-[(*S*)-2-oxocycloheptyl]acetic acid (5f).[3] Data for the major Isomer (2*S*, 2'*R*). Colorless oil (0.012 g, 26%); $[\alpha]^{26}_D$ = -33 (c = 1.1 in MeOH); R_f= 0.1 (EtOAc) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3351 (CO_2H), 1745 (CO), 1701 (CO). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.19 - 1.36 (1 H, m, H_{cyclo}), 1.42 - 1.63 (2 H, m, H_{cyclo}), 1.71 - 1.74 (1 H, m, H_{cyclo}), 1.90 - 2.11 (4 H, m, H_{cyclo}), 2.46 - 2.79 (2 H, m, H_{cyclo}), 3.29 (1 H, d, J = 10.8, OH), 4.31 (1 H, d, J = 2.5, CHOH). δ_C (75 MHz; $CDCl_3$; Me_4Si) 23.1 (CH_2), 27.1 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 43.8 (CH_2), 54.5 (CH), 71.2 (CH), 174.8 (C), 219.4 (C). *m/z* (IE) 186 (M^+, 3%), 168 (20), 122 (100), 107 (74), 92 (18), 65 (48).



5h

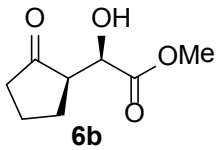
(*R*)-2-Hydroxy-4-oxopentanoic acid (5h).[2] Yellow oil (0.010 g, 30%); $[\alpha]^{26}_D$ = -10 (c = 0.5 in $CHCl_3$); R_f= 0.1 (EtOAc) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3359 (OH), 1742 (CO), 1714 (CO), 1219 (CHOHCO). δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.27 (3 H, s, CH_3), 3.01 (1 H, dd, J = 18.3, 6.5, CH_aH_b-CHOH), 3.10 (1 H, dd, J = 18.2, 4.4, CH_aH_b-CHOH), 4.54 (1 H, dd, J = 6.5, 4.5, CHOH). δ_C

(75 MHz; $CDCl_3$; Me_4Si) 30.4 (CH_3), 46.2 (CH_2), 66.6 (CH), 174.6 (C), 208.1 (C). *m/z* (IE) 132 (M^+, 3%), 114 (18), 103 (12), 96 (100), 68 (26), 55 (8).



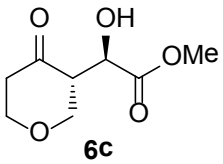
6a

(*R*)-Methyl 2-hydroxy-2-[(*S*)-2-oxocyclohexyl]acetate (6a).[4] Data for the major Isomer (2*S*, 2'*R*). Yellow oil. (0.036 g, 78%); $[\alpha]^{26}_D$ = -27 (c = 1.3 in $CHCl_3$); R_f = 0.23 (Hex/EtOAc; 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3507 (OH), 1734 (CO), 1707 (CO), 1239 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.62 - 1.80 (2 H, m, H_{cyclo}), 1.84 - 2.03 (2 H, m, H_{cyclo}), 2.03 - 2.20 (2 H, m, H_{cyclo}), 2.23 - 2.48 (2 H, m, H_{cyclo}), 2.97 (1 H, ddd, J = 12.8, 5.9, 3.3, CHCHOH), 3.78 (3 H, s, OCH_3), 4.04 (1 H, d, *J* = 3.3, CHOH). δ_C (75 MHz; $CDCl_3$; Me_4Si) 24.8 (CH_2), 26.9 (CH_2), 30.1 (CH_2), 42.0 (CH_2), 52.5 (CH), 53.6 (CH_3), 71.1 (CH), 173.8 (C), 211.3 (C). *m/z* (IE) 186 (M^+, 16%), 154 (19), 136 (17), 127 (100), 109 (20), 98 (36), 81 (81), 57 (30).



6b

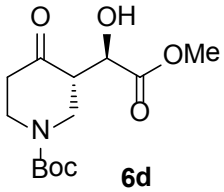
(*R*)-Methyl 2-hydroxy-2-[(*R*)-2-2oxocyclopentyl]acetate (6b).[2] As a diastereomer mixture (43:57, *anti:syn*). Yellow oil (0.036 g, 84%); $[\alpha]^{26}_D$ = +20 (c = 1.4 in $CHCl_3$); R_f = 0.25 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3453 (OH), 1735 (CO), 1722 (CO), 1243 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.86 - 1.72 (2 H, m, H_{cyclo}), 1.86 - 2.00 (4 H, m, H_{cyclo}), 2.00 - 2.14 (4 H, m, H_{cyclo}), 2.14 - 2.41 (4 H, m, H_{cyclo}), 2.51 - 2.62 (1 H, m, H_{cyclo}), 2.66 - 2.76 (1 H, m, H_{cyclo}), 3.81 (3 H, s, OCH_3, *syn*), 3.83 (3 H, s, OCH_3, *anti*), 4.34 (1 H, d, *J* = 3.4, *anti*), 4.73 (1 H, d, *J* = 2.5, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 20.5 (CH_2), 217.9 (C), 20.7 (CH_2), 22.4 (CH_2), 25.9 (CH_2), 38.4 (CH_2), 38.5 (CH_2), 51.6 (CH), 51.9 (CH), 52.8 (2xCH_3), 68.8 (CH), 69.6 (CH), 173.9 (C), 174.6 (C), 217.7 (C). *m/z* (IE) 172 (M^+, 3%), 154 (16), 140 (53), 122 (25), 113 (100), 95 (28), 85 (50), 67 (84), 57 (37).



6c

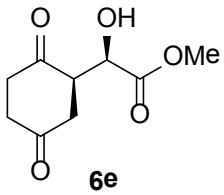
(*R*)-Methyl 2-hydroxy-2-[(*S*)-4-oxotetrahydro-2H-pyran-3-yl]acetate (6c). As a diastereomer mixture (89:11, *anti:syn*).Yellow oil (0.040 g, 86%); $[\alpha]^{26}_D$ = -23 (c = 1 in MeOH); R_f= 0.28

(Hex/EtOAc; 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3471 (OH), 1737 (CO), 1712 (CO), 1121 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si; diastereomer mixture (70:30)) 2.31 - 2.72 (4 H, m, H_{cyclo}), 3.00 (1 H, ddd, J = 9.8, 6.2, 3.6, CHCHOH, *syn*), 3.18 (1 H, ddd, J = 10.9, 6.7, 3.1, CHCHOH, *anti*), 3.67 - 3.95 (10 H, m), 4.07 (1 H, d, J = 3.1, CHOH, *anti*), 4.09 - 4.36 (4 H, m, H_{Cyclo}), 4.71 (1 H, d, J = 3.6, CHOH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 42.3 (2xCH_2), 52.8 (2xCH), 53.8 (CH_3), 54.4 (CH_3), 67.7 (CH_2), 67.8 (CH), 67.9 (CH), 68.0 (CH_2), 68.1 (CH_2), 69.8 (CH_2), 173.3 (C), 173.5 (C), 205.4 (C), 205.8 (C). HRMS (ESI) calculated for $C_8H_{12}O_5$: 188.0700 found: 189.0763 (M^+ + H, recalculated 189.0763).



6d

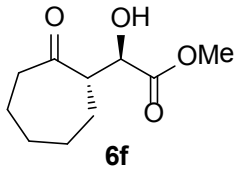
(*S*)-*tert*-Butyl 3-[(R)-1-hydroxy-2-methoxy-2-oxoethyl]-4-oxopiperidine-1-carboxylate (6d). As a diastereomer mixture (93:7, *anti:syn*).Yellow oil (0.038 g, 53%); $[\alpha]^{26}_D$ = -64 (c = 1.2 in MeOH); R_f = 0.18 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3463 (OH), 1741 (CO), 1687 (CO), 1156 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49 (9 H, s, C(CH_3)$_3$, *syn*), 1.50 (9 H, s, C(CH_3)$_3$, *anti*), 2.21 - 2.59 (4 H, m, H_{cyclo}), 2.80 - 3.58 (8 H, m, H_{cyclo}), 3.80 (3 H, s, OCH_3, *anti*), 3.82 (3 H, s, OCH_3, *syn*), 4.11 (1 H, dd, J = 6.2, 2.8, CHOH, *anti*), 4.70 (1 H, dd, J = 4.5, 3.4, CHOH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 28.3 (6xCH_3), 40.8 (CH_2), 40.9 (CH_2), 43.0 (2xCH_2), 45.2 (2xCH_2), 52.5 (2xCH_3), 52.8 (2xCH_3), 68.1 (CH), 68.7 (CH), 80.7 (2xC), 154.5 (2xC), 173.3 (C), 173.4 (C), 206.5 (C), 206.9 (C). HRMS (ESI) calculated for $C_{13}H_{21}NO_6$: 287.1369 found: 288.1446 (M^+ + H, recalculated 288.1447).



6e

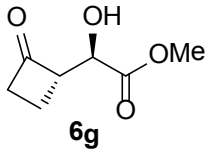
(*R*)-Methyl 2-[(*R*)-2,5-dioxocyclohexyl]-2-hydroxyacetate (6e). As a diastereomer mixture (40:60, *anti:syn*). Brown oil (0.035 g, 70%); $[\alpha]^{26}_D$ = -15 (c = 0.7 in MeOH); R_f = 0.35 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3503 (OH), 1730 (CO), 1705 (CO), 1267 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.49 - 3.19 (13 H, m, H_{cyclo}), 3.31 (1 H, ddd, J = 11.6, 6.2, 2.6, CHCHOH, *anti*), 3.83 (3 H, s, OCH_3, *syn*), 3.85 (3 H, s, OCH_3, *anti*), 4.15 (1 H, dd, J = 4.7, 2.6, CHOH, *anti*), 4.90 (1 H, dd, J = 3.9, 2.1, CHOH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 36.1 (CH_2), 36.3 (CH_2), 37.0 (CH_2), 37.5 (CH_2), 40.5 (2xCH_2), 48.8 (CH), 49.0 (CH), 53.0 (CH_3), 53.2 (CH_3), 69.8 (CH), 70.4 (CH), 173.2 (C),

173.4 (C), 207.2 (C), 207.3 (2xC), 207.4 (C). HRMS (ESI) calculated for $C_9H_{12}O_5$: 200.0685 found: 201.0753 (M^+ + H, recalculated 201.0763).



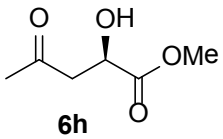
6f

(*R*)-Methyl 2-hydroxy-2-[(*S*))-2-oxocycloheptyl]acetate (6f). As a diastereomer mixture (94:6, *anti:syn*). Colorless oil (0.036 g, 84%); $[\alpha]^{26}_D$ = -62.7 (c = 1.2 in MeOH); R_f = 0.26 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3483 (OH), 1736 (CO), 1697 (CO), 1213 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 - 1.65 (6 H, m, H_{cyclo}), 1.73 - 2.08 (10 H, m, H_{cyclo}), 2.44 - 2.61 (4 H, m, H_{cyclo}), 2.96 (1 H, dt, *J* = 10.6, 3.4, CHCHOH, *syn*), 3.08 (1 H, dt, *J* = 10.8, 3.2, CHCHOH, *anti*), 3.18 (1 H, d, *J* = 4.6, OH, *syn*), 3.29 (1 H, d, *J* = 7.2, OH, *anti*), 3.80 (3 H, s, OCH_3, *anti*), 3.81 (3 H, s, OCH_3, *syn*), 4.23 (1 H, dd, *J* = 7.1, 3.4, CHOH, *anti*), 4.56 (1 H, dd, *J* = 4.5, 3.3, CHOH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 23.9 (CH_2), 24.1 (CH_2), 25.8 (CH_2), 28.2 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.8 (2xCH_2), 43.8 (CH_2), 44.1 (CH_2), 52.6 (2xCH), 55.0 (CH_3), 55.2 (CH_3), 72.1 (CH), 73.7 (CH), 173.9 (C), 174.0 (C), 214.5 (C), 215.1 (C). HRMS (ESI) calculated for $C_{10}H_{16}O_4$: 200.1049 found: 201.1126 (M^+ + H, recalculated 201.1127).



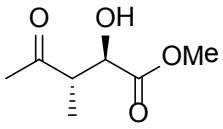
6g

(*R*)-Methyl 2-hydroxy-2-[(*S*)-2-oxocyclobutyl]acetate (6g). As a diastereomer mixture (76:24, *anti:syn*). Colorless oil (0.014 g, 35%); $[\alpha]^{26}_D$ = -16 (c = 0.8 in MeOH); R_f = 0.4 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3502 (OH), 1779 (CO), 1731 (CO), 1083 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si; diastereomer mixture (1:1)) 1.97 - 2.32 (4 H, m, H_{cyclo}), 2.93 - 3.13 (6 H, m, H_{cyclo}), 3.83 (3 H, s, OCH_3, *anti*), 3.86 (3 H, s, OCH_3, *anti*), 4.32 (1 H, dd, *J* = 4.4, 4.4, CHOH, *anti*), 4.63 (1 H, dd, *J* = 4.5, 2.9, CHOH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si; diastereomer mixture (1:1)) 11.0 (CH_2), 13.5 (CH_2), 46.0 (CH_2), 46.4 (CH_2), 53.0 (2xCH), 62.3 (2xCH_3), 67.6 (CH), 68.5 (CH), 173.2 (C), 173.6 (C), 207.7 (2xC). HRMS (ESI) calculated for $C_7H_{10}O_4$: 158.0600 found: 159.0654 (M^+ + H, recalculated 159.0657).



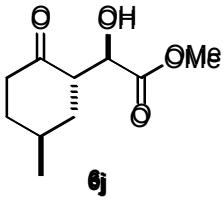
6h

***(R)*-Methyl 2-hydroxy-4-oxopentanoate (6h)**.[2] Yellow oil (0.018 g, 50%); $[\alpha]^{26}_{D}$ = -18 (c = 0.8 in $CHCl_3$); R_f = 0.3 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3311 (OH), 1735 (CO), 1717 (CO), 1237 (CHOHCO). δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.21 (3 H, s, $\underline{CH_3}$), 2.91 (1 H, dd, *J* = 17.6, 6.1, $CH_a\underline{H_b}$-CHOH), 3.00 (1 H, dd, *J* = 17.6, 4.0, $C\underline{H_a}H_b$-CHOH), 3.80 (3 H, s, $O\underline{CH_3}$), 4.49 (1 H, dd, *J* = 6.0, 4.0, $\underline{CH}$OH). δ_C (75 MHz; $CDCl_3$; Me_4Si) 30.5 (CH_3), 46.7 (CH_2), 52.7 (CH), 66.9 (CH_3), 174.0 (C), 206.2 (C). *m/z* (IE) 146 (M^+, 6%), 114 (13), 103 (12), 87 (100), 71 (15), 55 (12).



6i

(2*R*,3*S*)-Methyl 2-hydroxy-3-methyl-4-oxopentanoate (6i).[2] As a diastereomer mixture (90:10, *anti:syn*). Colorless oil (0.010 g, 22%); $[\alpha]^{26}_{D}$ = -27 (c = 1.2 in MeOH); R_f = 0.4 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3473 (OH), 1737 (CO), 1711 (CO), 1212 (OCH_3). δ_H (300 MHz; $CDCl_3$; Me_4Si; diastereomer mixture (40:60)) 1.18 (3 H, d, *J* = 7.2, $CH\underline{CH_3}$, *anti*), 1.31 (3 H, d, *J* = 7.4, $CH\underline{CH_3}$, *syn*), 2.21 (3 H, s, $CO\underline{CH_3}$, *syn*), 2.26 (3 H, s, $CO\underline{CH_3}$, *anti*), 2.89 - 3.12 (3 H, m), 3.20 (1 H, d, *J* = 7.6, OH, *anti*), 3.80 (3 H, s, $O\underline{CH_3}$, *syn*), 3.83 (3 H, s, $O\underline{CH_3}$, *anti*), 4.25 (1 H, dd, *J* = 6.7, 4.2, $\underline{CH}$OH, *anti*), 4.63 (1 H, dd, *J* = 3.6, 3.5, $\underline{CH}$OH, *syn*). δ_C (75 MHz; $CDCl_3$; Me_4Si; with traces of *iso* aldol) 10.5 (CH_3), 13.0 (CH_3), 28.3 (CH), 28.8 (CH_3), 49.9 (CH), 52.6 (CH), 52.7 (CH_3), 52.8 (CH_3), 71.0 (CH), 72.6 (CH), 173.7 (C), 174.1 (C), 209.2 (C), 210.5 (C). *m/z* (IE) 160 (M^+, 4%), 128 (7), 117 (18), 101 (78), 85 (43), 69 (100), 57 (36).

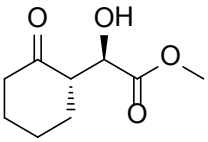


6j

(*R*)-methyl 2-hydroxy-2-((1*S*,5*S*)-5-methyl-2-oxocyclohexyl)acetate (6j)[5]. As a diastereomer mixture (84:12:2:2). Yellow oil. (0.040 g, 80%); $[\alpha]^{26}_{D}$ = -38 (c = 1.3 in MeOH); R_f = 0.33 (Hex/EtOAc 1:1) (revealed with $KMnO_4$). ν_{max}/cm^{-1} 3489.6 (OH), 1736.6 (C=O), 1707.7 (C=O), 1127.2 (OCH_3). Data for the major isomer (1*S*, 5*S*, 2'*R*). δ_H (300 MHz, $CDCl_3$) 1.20 (d, *J* = 7.0 Hz, 3 H, $CH\underline{CH_3}$), 1.68 – 2.09 (m, 3 H, H_{cyclo}), 2.09 – 2.54 (m, 4 H, H_{cyclo}), 3.02 - 3.12 (m, 2 H), 3.79 (s, 3 H, $O\underline{CH_3}$), 4.04 (dd, *J* = 7.5, 3.6 Hz, 1 H, $\underline{CH}$OH). δ_C (75 MHz, $CDCl_3$, with traces of minority aldol) 18.2 (CH_3), 26.7

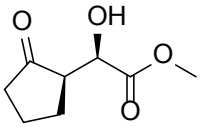
(CH), 32.2 (CH_2), 35.6 (CH_2), 37.7 (CH_2), 49.3 (CH), 52.6 (CH_3), 71.4 (CH), 173.8 (C), 211.7 (C). *m/z* (IE) 200 (M^+, 12), 168 (9), 141 (100), 123 (24), 112 (29), 95 (62), 55 (28).

HPLC data for aldol products



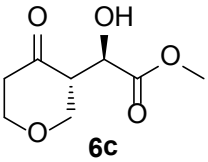
6a

The ee was determined by chiral GC analysis with a Cyclohexil-β column (130 ºC, 13.4 Psi,), R_t= 49.5 min (minor *anti*), R_t= 50.7 min (major *anti*), R_t= 68.2 min (minor *syn*), R_t= 69.5 min (major *syn*).



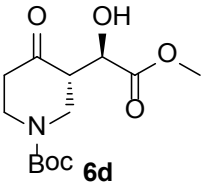
6b

The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (120 ºC, 13.4 Psi), R_t = 23.2 min (major *anti*), R_t = 25.2 min (minor *anti*), R_t = 38.7 min (major *syn*), R_t = 40.6 min (minor *syn*).



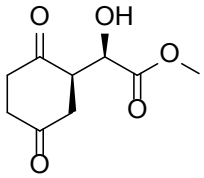
6c

The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (140 ºC, 13.4 Psi), R_t = 17.3 min (major *anti*), R_t = 18.0 min (minor *anti*), R_t = 22.5 min (minor *syn*), R_t = 24.0 min (major *syn*).



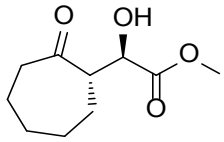
6d

The ee was determined by chiral HPLC on Chiralpak IA column (90% hexane, 10% EtOH, 25ºC, 1 mL/min, 210 nm, R_t= 15.5 min (major *anti*), R_t = 18.2 min (minor *syn*), R_t = 20.1 min (minor *syn*), R_t = 32.8 min (minor *anti*).



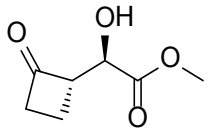
6e

The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (140 ºC, 13.4 Psi), R_t = 68.4 min (minor *syn*), R_t = 70.7 min (major *syn*), R_t = 80.5 min (major *anti*), R_t = 84.3 min (minor *anti*).



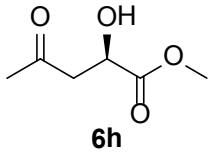
6f

The ee was determined by chiral GC analysis with a CYCLOHEXIL β column (150 ºC, 13.4 Psi), R_t = 32.3 min (minor *anti*), R_t = 32.9 min (major *anti*), R_t = 38.9 min (major *syn*), R_t = 40.5 min (minor *syn*).



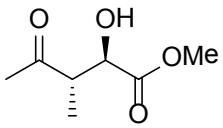
6g

The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (120 ºC, 13.4 Psi), R_t = 14.5 min (major *anti*), R_t = 15.5 min (minor *anti*), R_t = 25.4 min (*syn*).



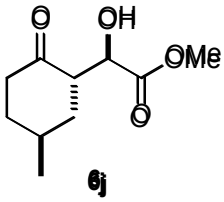
6h

The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (120 ºC, 13.4 Psi), R_t = 15.1 min (major), R_t = 15.4 min (minor).



6i

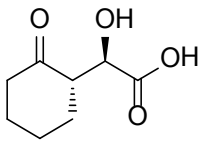
The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (100 ºC, 13.4 Psi), R_t = 27.1 min (minor *anti*), R_t = 28.8min (minor *syn*), R_t = 29.9 min (major *syn*), R_t = 32.1 min (major *anti*).



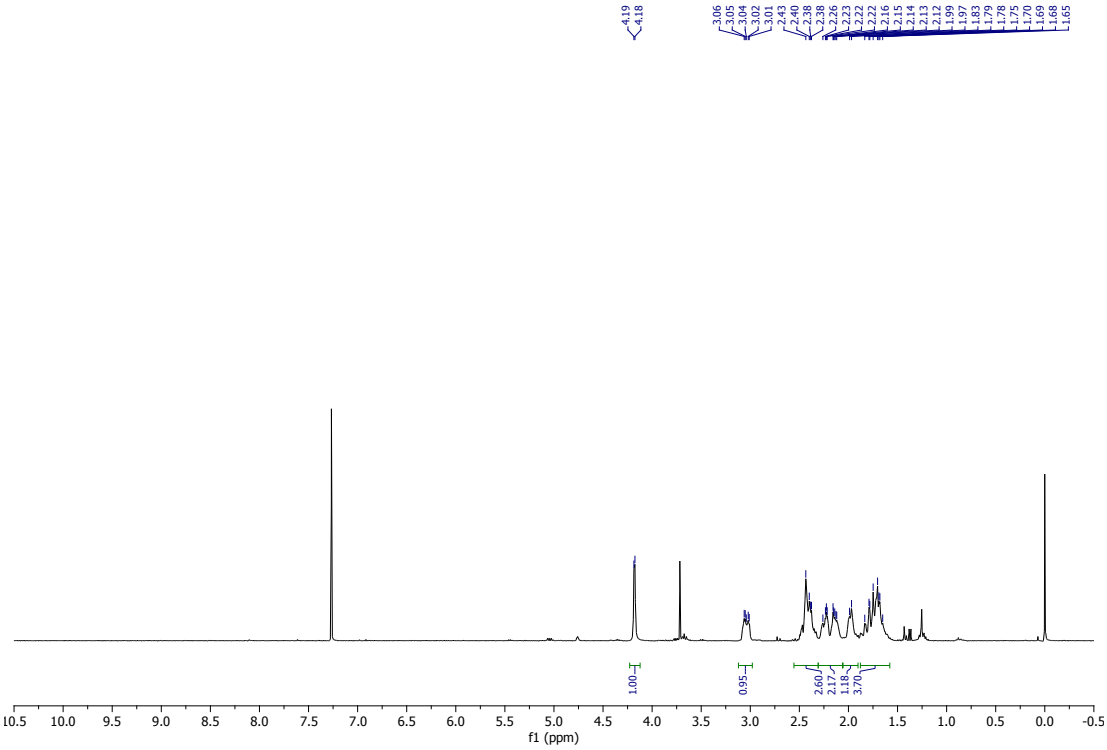
6j

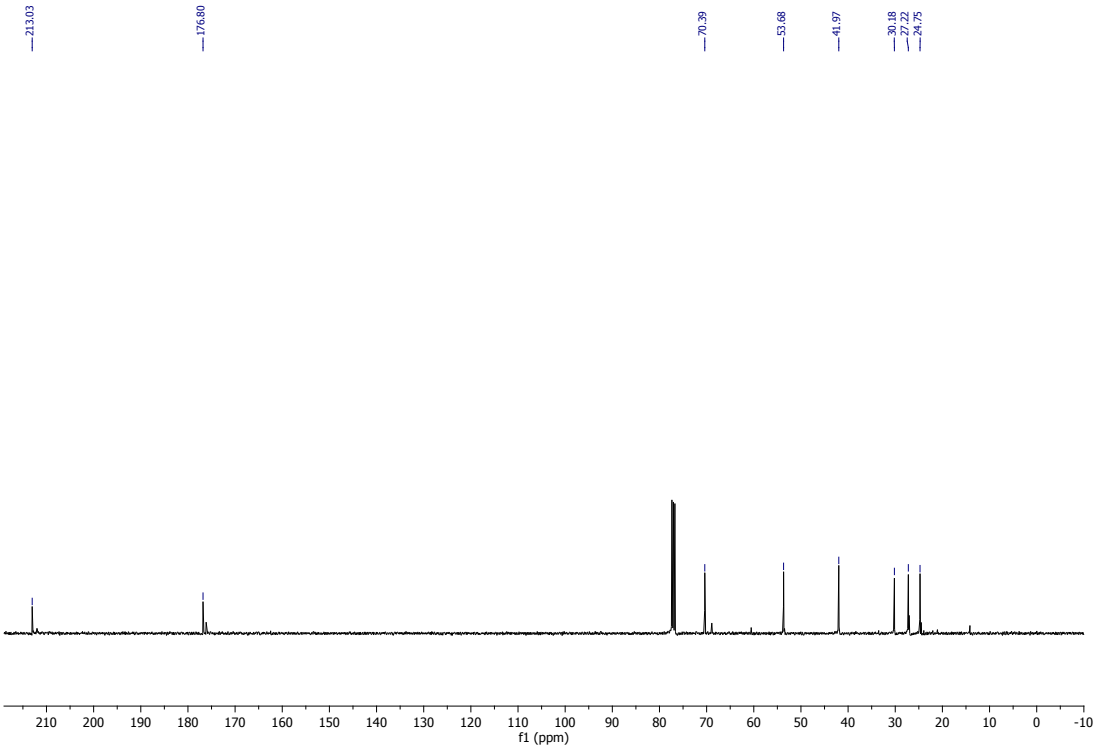
The ee was determined by chiral GC analysis with a CP CHIRALSIL DEX CB column (160 ºC, 13.4 Psi,), R_t= 64.1 min (mayor *anti*), R_t = 70.1 min (minor *anti*).

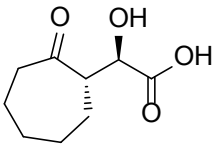
NMR spectra for aldol products



5a

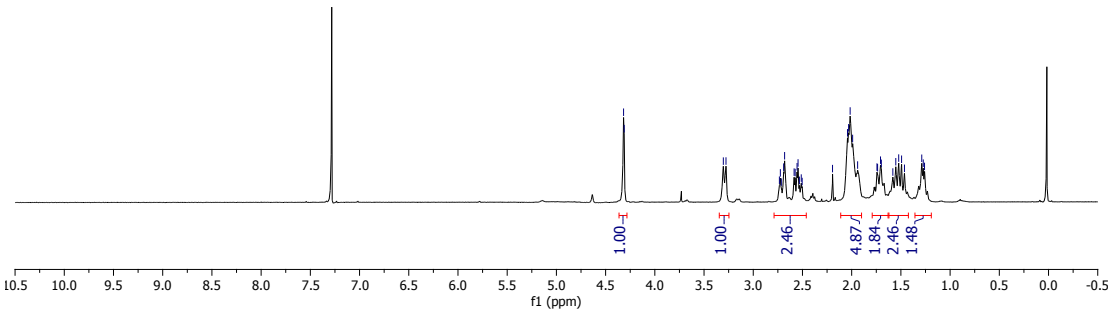


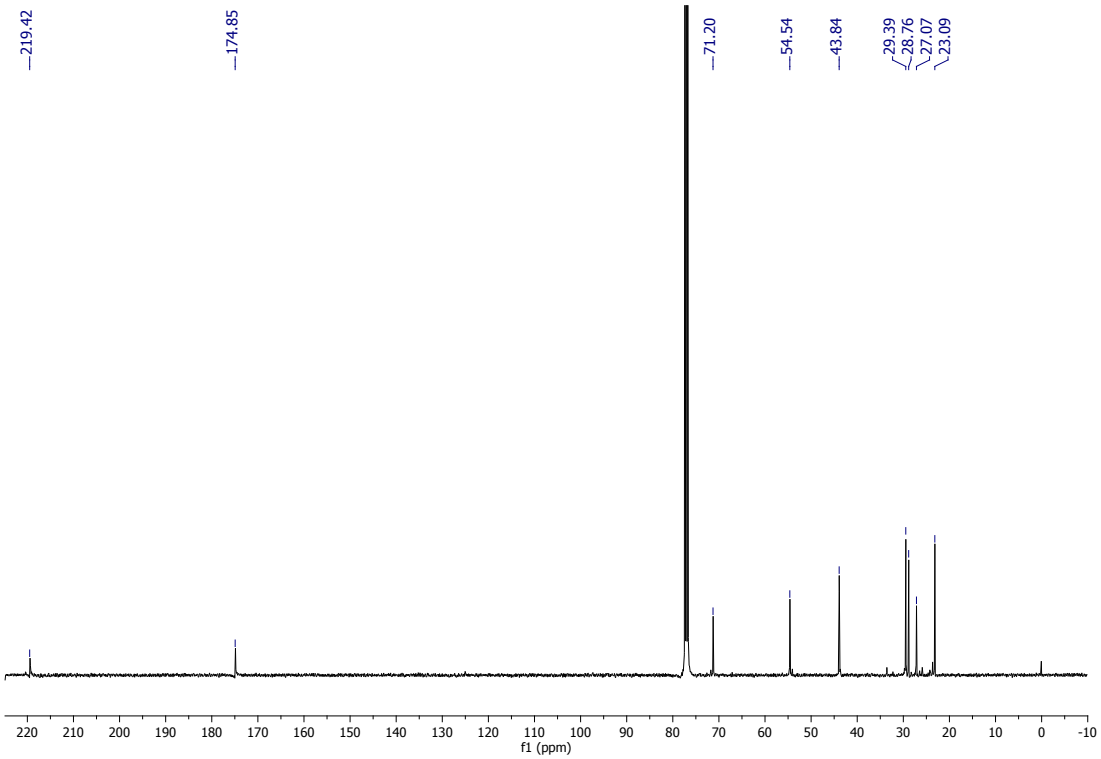

213.03
176.80
70.39
53.68
41.97
30.18
27.22
24.75
f1 (ppm)

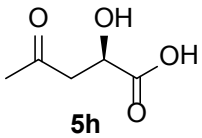

O
OH
OH
O

5f

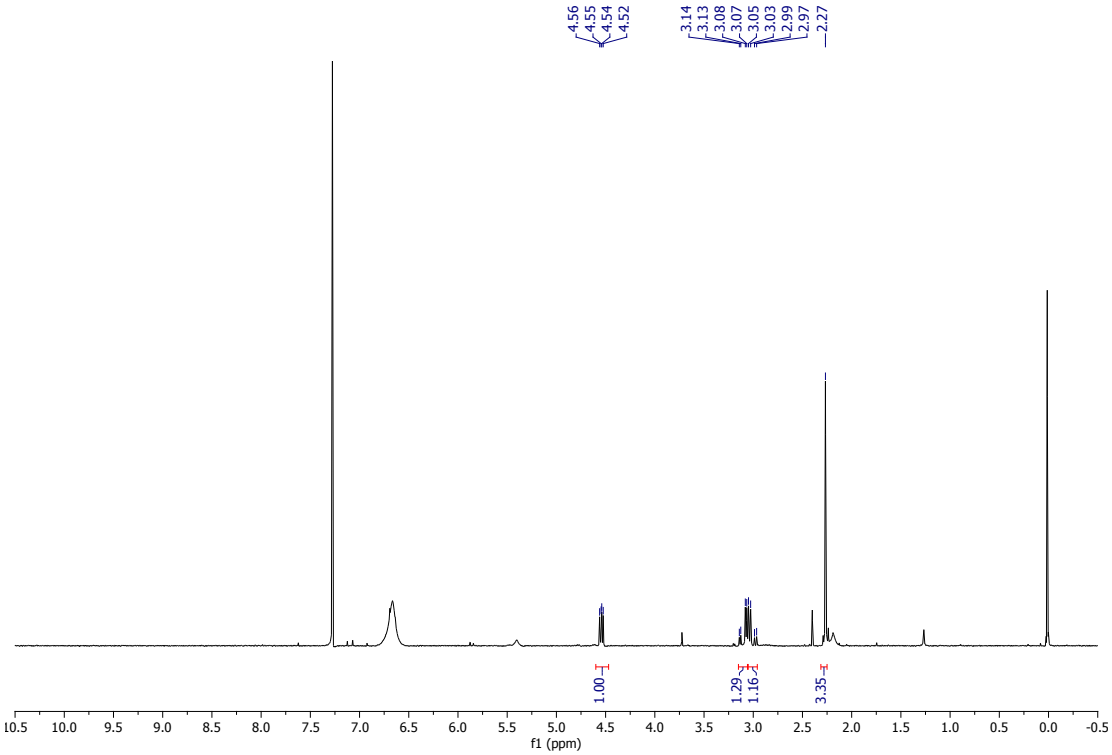

4.32
4.31
3.30
3.28
2.69
2.68
2.56
2.54
2.04
2.03
2.02
1.99
1.94
1.74
1.74
1.71
1.70
1.55
1.52
1.49
1.29
1.27
1.26

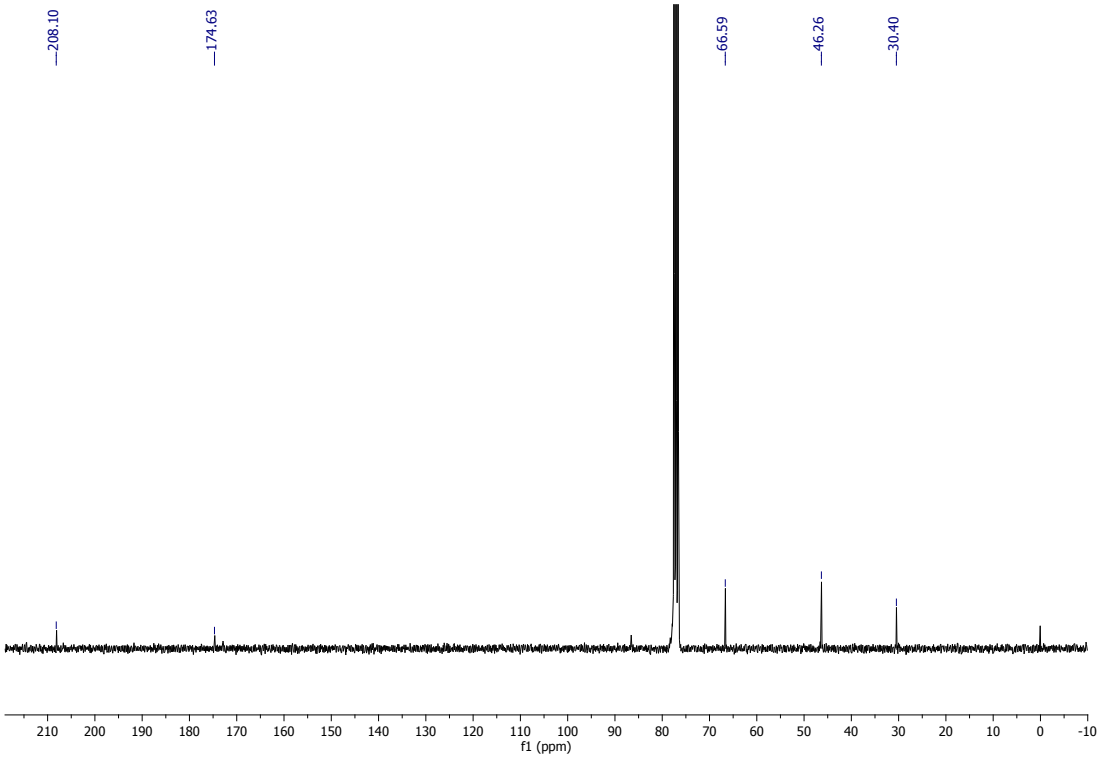

1.00
1.00
2.46
4.87
1.84
2.46
1.48
f1 (ppm)

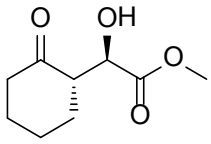




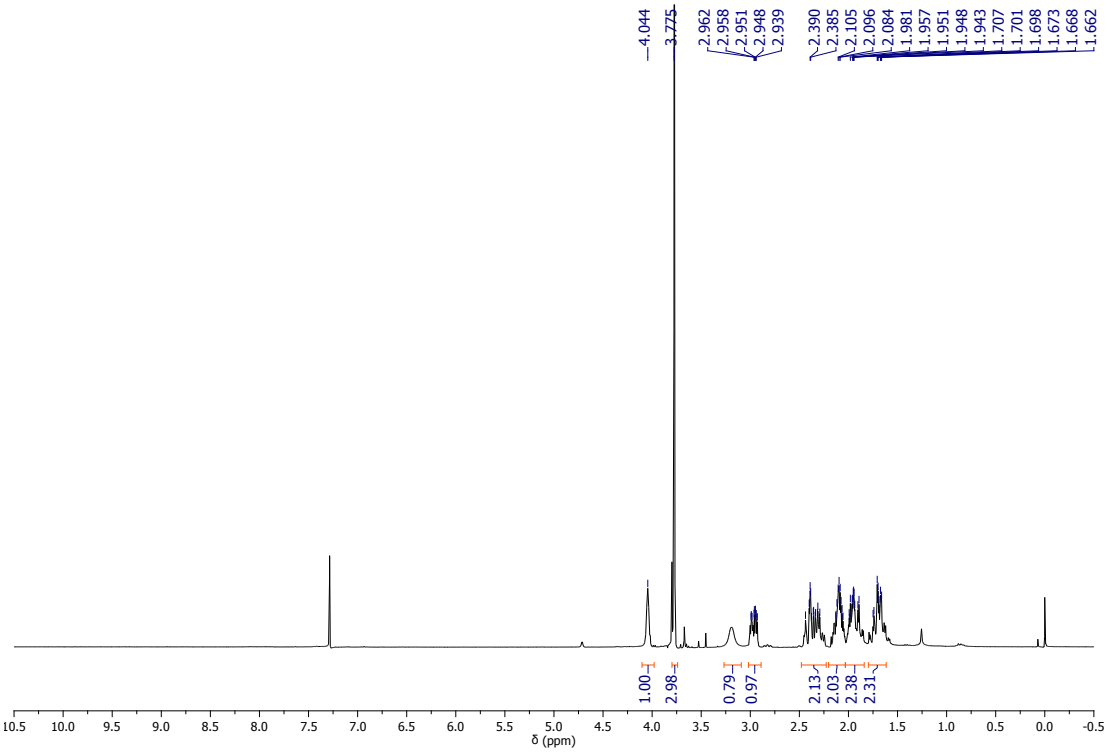
5h

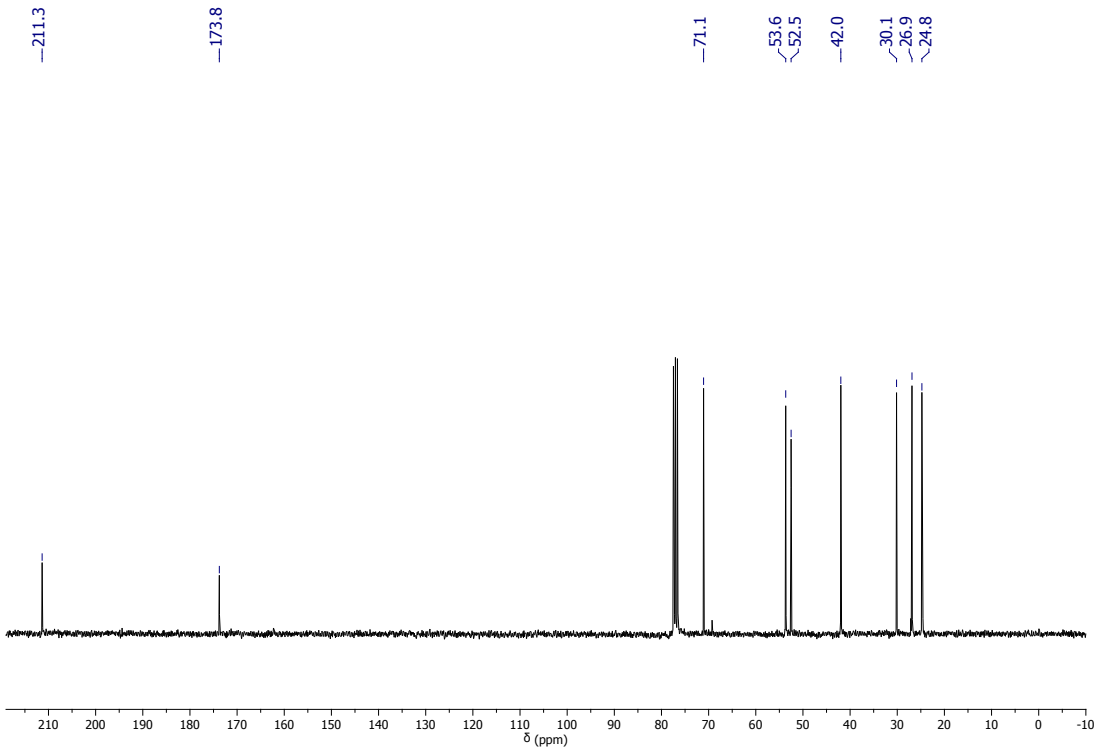


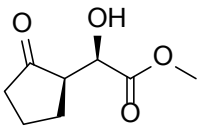

208.10
174.63
66.59
46.26
30.40
f1 (ppm)


O
OH
O
O

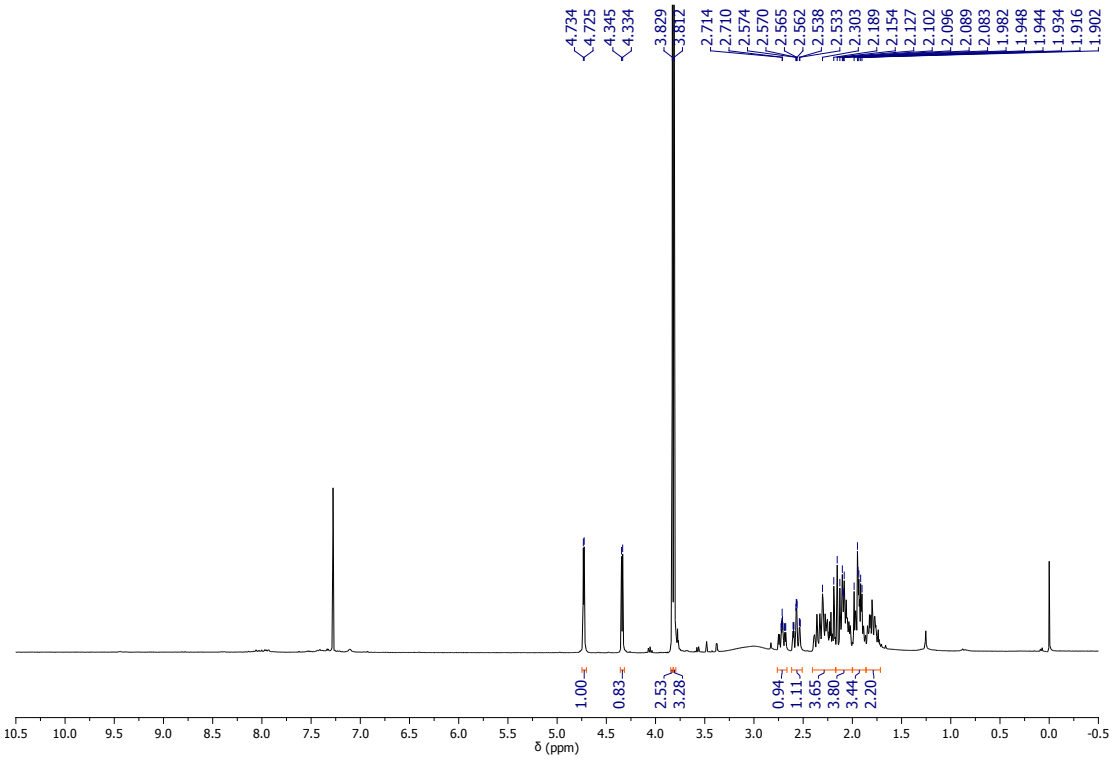
6a

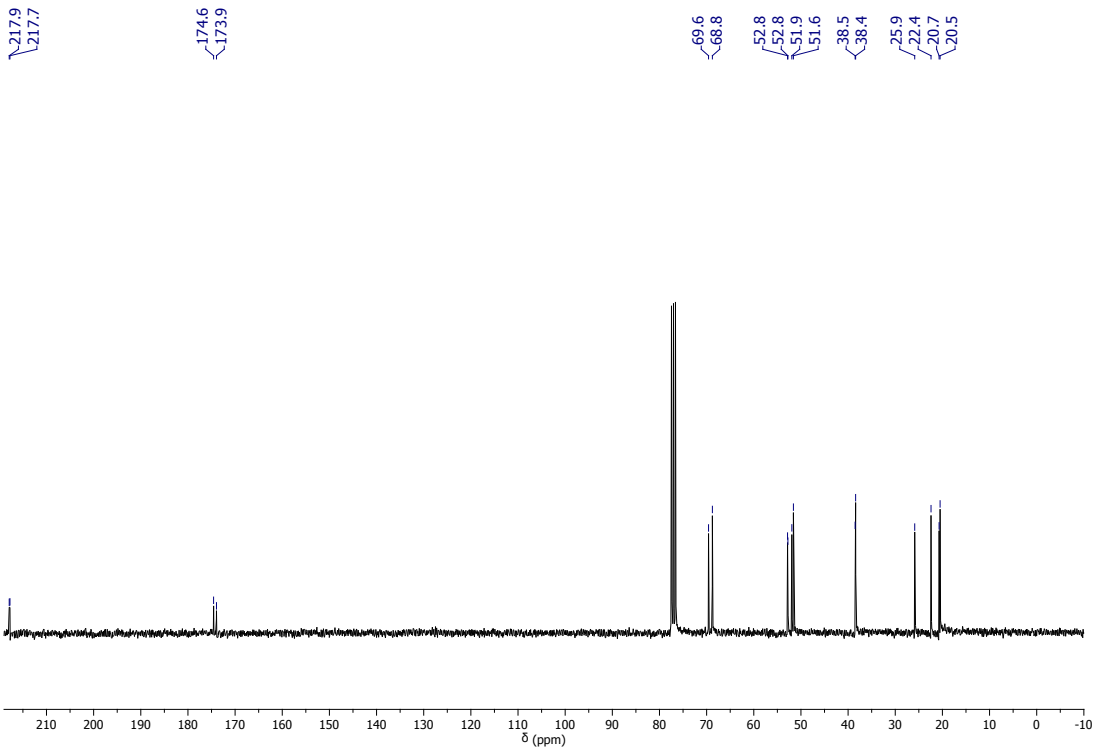

4.044
3.775
2.962
2.958
2.951
2.948
2.939
2.390
2.385
2.105
2.096
2.084
1.981
1.957
1.951
1.948
1.943
1.707
1.701
1.698
1.673
1.668
1.662
1.00
2.98
0.79
0.97
2.13
2.03
2.38
2.31
δ (ppm)

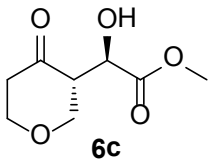

211.3
173.8
71.1
53.6
52.5
42.0
30.1
26.9
24.8
δ (ppm)


O
OH
O
O

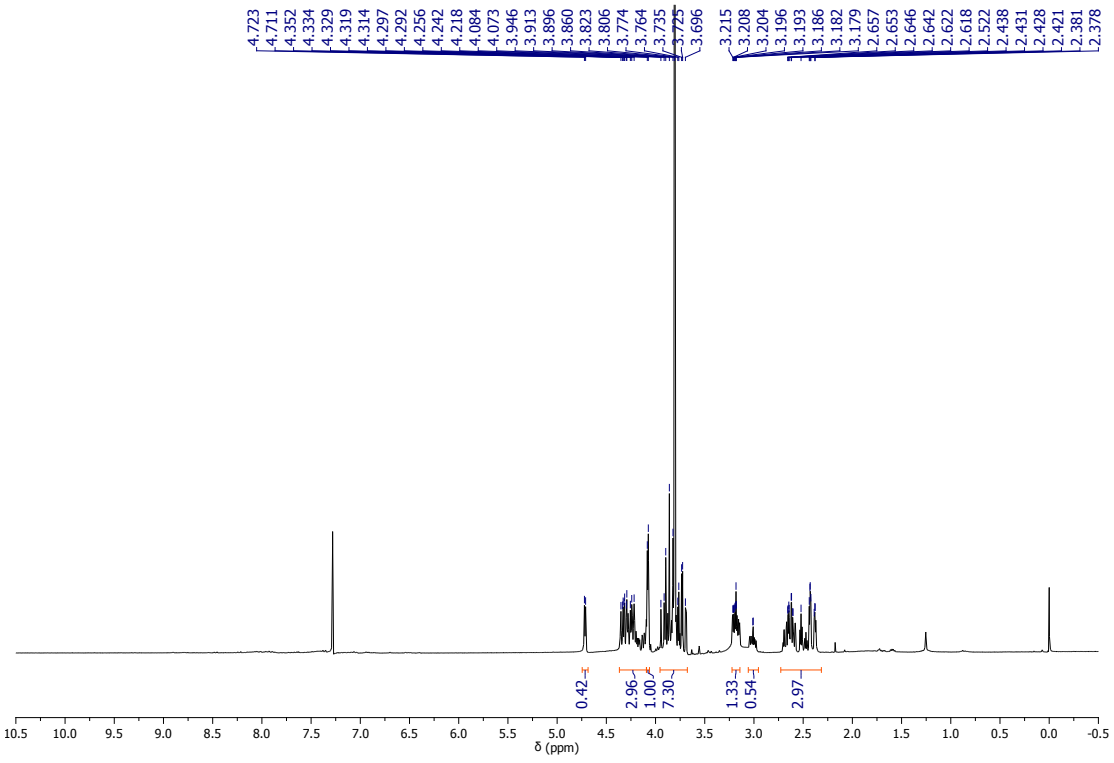
6b

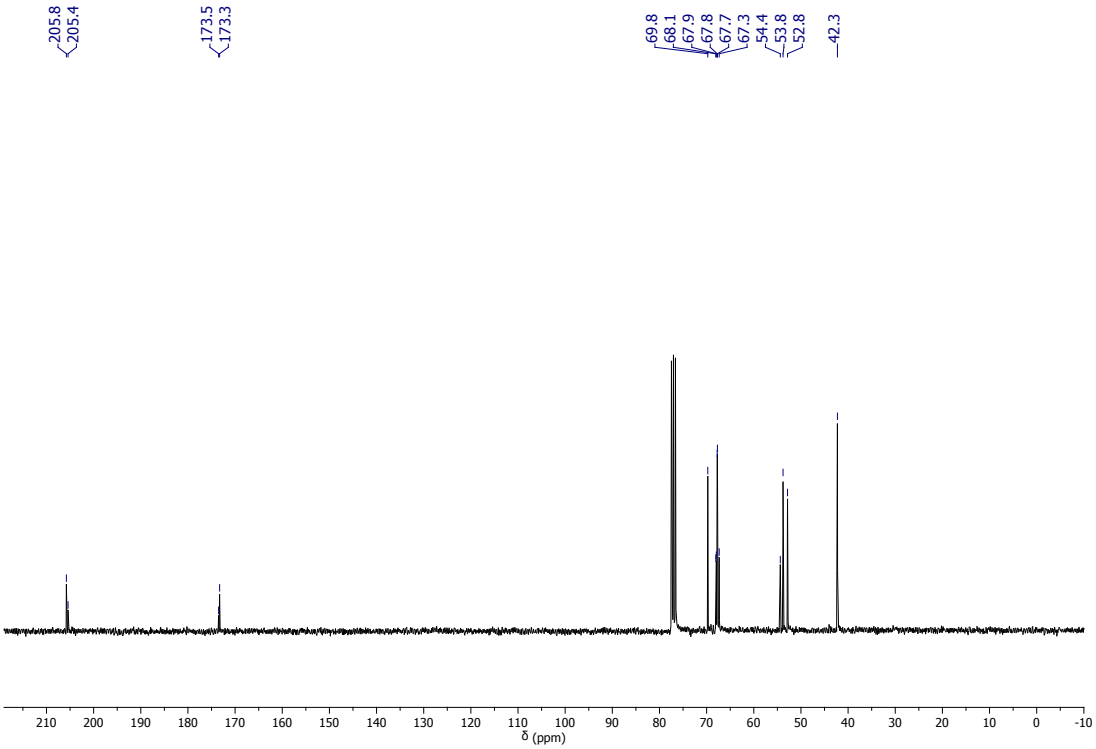

4.734
4.725
4.345
4.334
3.829
3.812
2.714
2.710
2.574
2.570
2.565
2.562
2.538
2.533
2.303
2.189
2.154
2.127
2.102
2.096
2.089
2.083
1.982
1.948
1.944
1.934
1.916
1.902
1.00
0.83
2.53
3.28
0.94
1.11
3.65
3.80
3.44
2.20
δ (ppm)

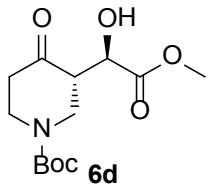

217.9
217.7
174.6
173.9
69.6
68.8
52.8
52.8
51.9
51.6
38.5
38.4
25.9
22.4
20.7
20.5
δ (ppm)


O
OH
O
O
O

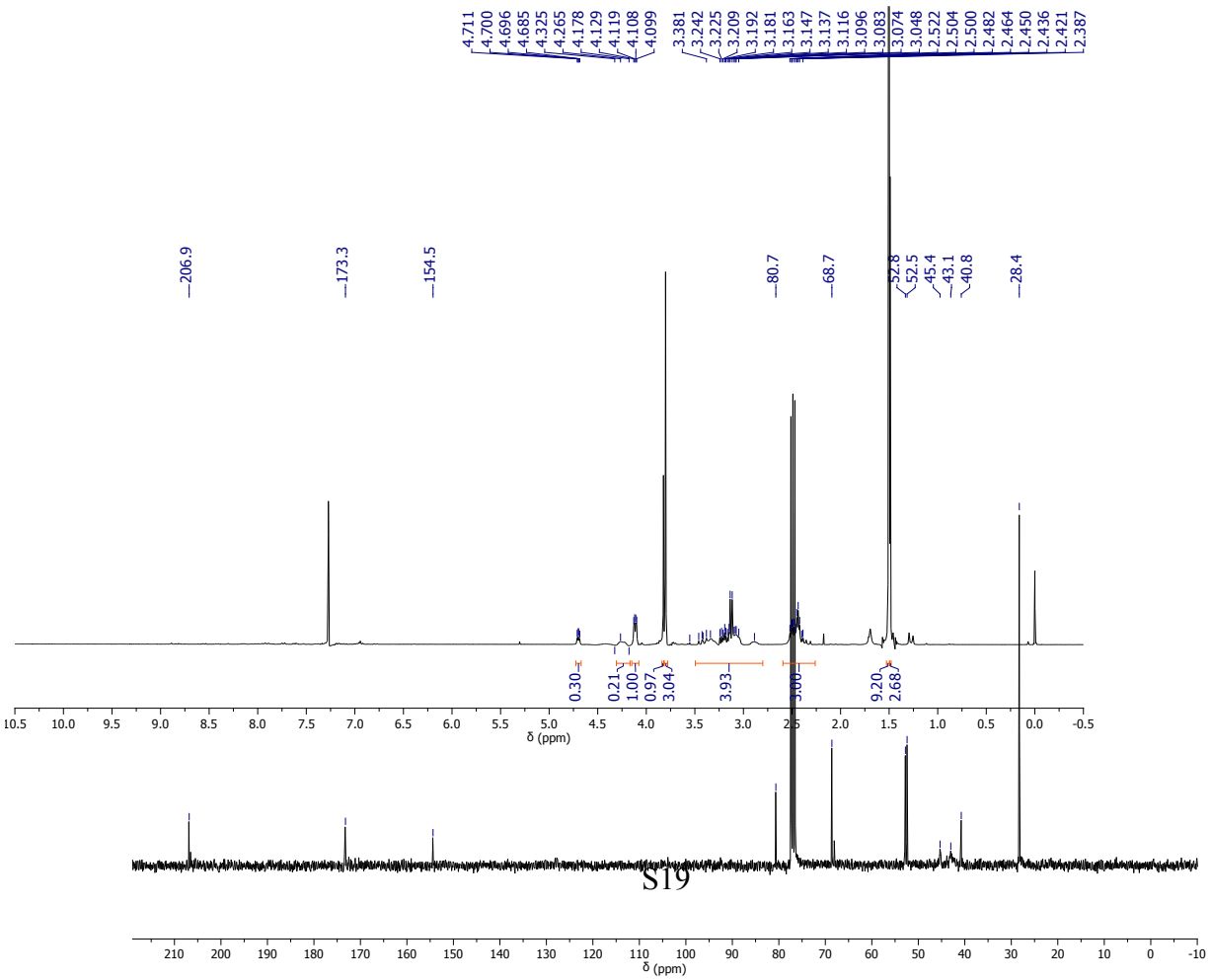
6c

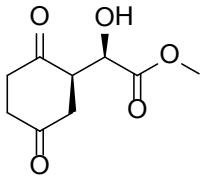

4.723
4.711
4.352
4.334
4.329
4.319
4.314
4.297
4.292
4.256
4.242
4.218
4.084
4.073
3.946
3.913
3.896
3.860
3.823
3.806
3.774
3.764
3.735
3.725
3.696
3.215
3.208
3.204
3.196
3.193
3.186
3.182
3.179
2.657
2.653
2.646
2.642
2.622
2.618
2.522
2.438
2.431
2.428
2.421
2.381
2.378
0.42
2.96
1.00
7.30
1.33
0.54
2.97
δ (ppm)


205.8
205.4
173.5
173.3
69.8
68.1
67.9
67.8
67.7
67.3
54.4
53.8
52.8
42.3
δ (ppm)

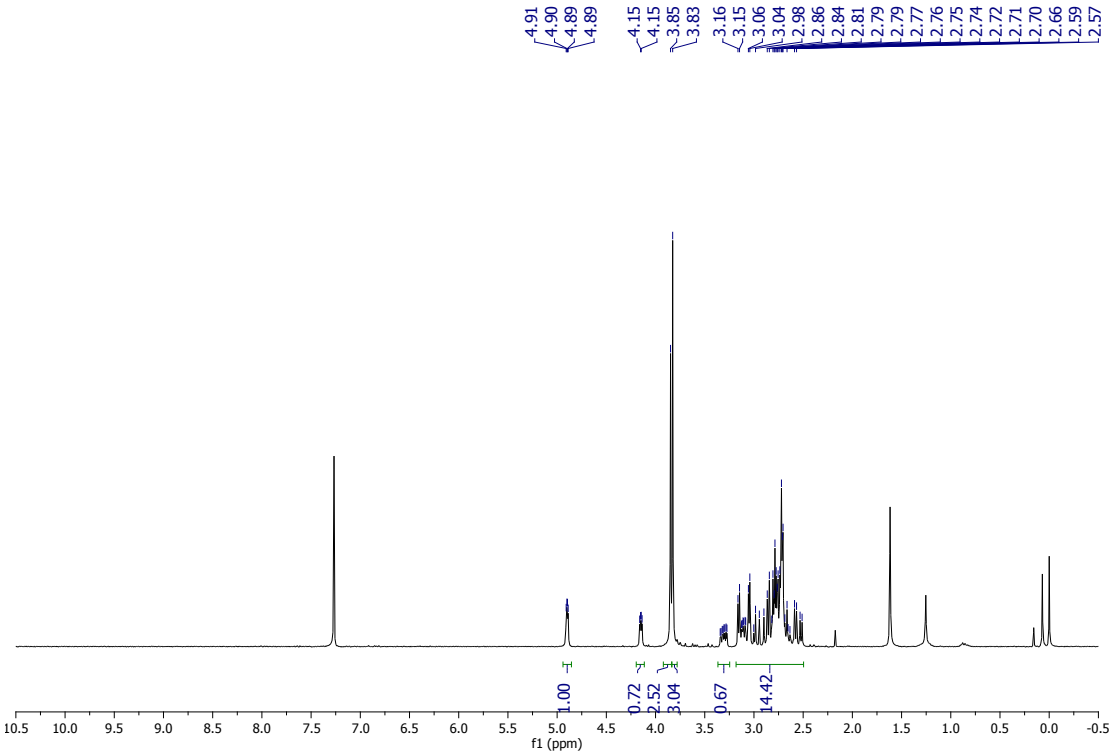

O
OH
O
O
N
Boc

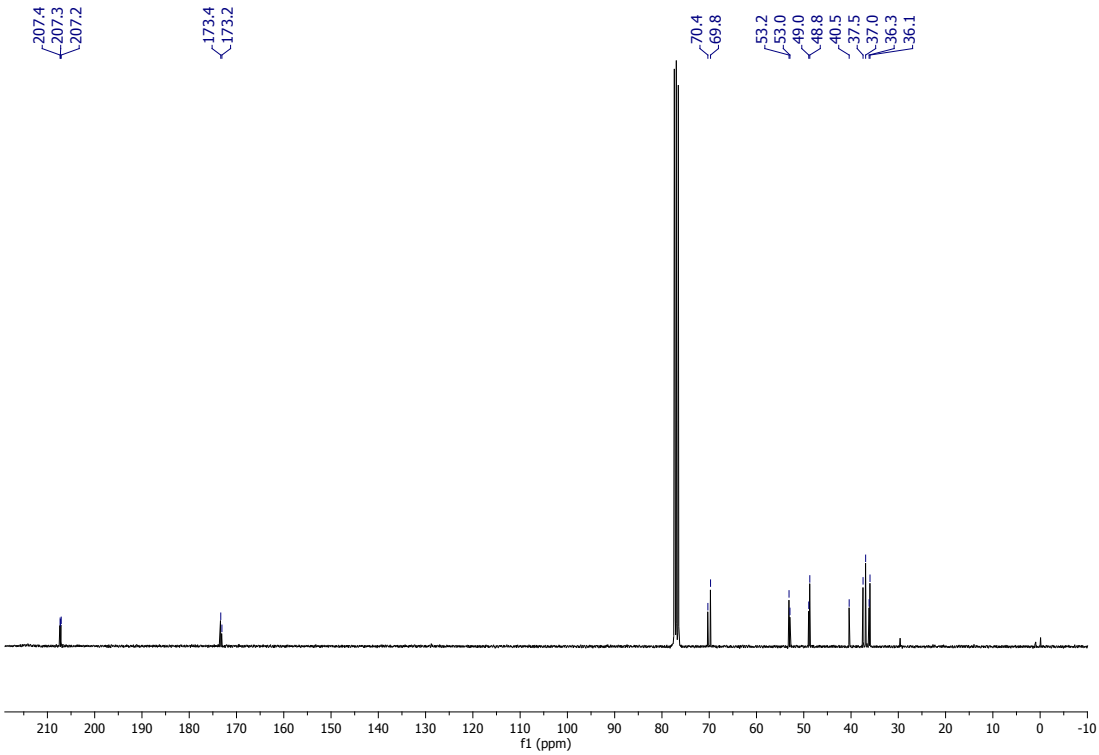
6d

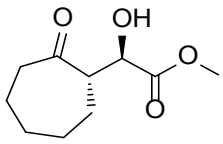

4.711
4.700
4.696
4.685
4.325
4.265
4.178
4.129
4.119
4.108
4.099
3.381
3.242
3.225
3.209
3.192
3.181
3.163
3.147
3.137
3.116
3.096
3.083
3.074
3.048
2.522
2.504
2.500
2.482
2.464
2.450
2.436
2.421
2.387
206.9
173.3
154.5
80.7
68.7
52.8
52.5
45.4
43.1
40.8
28.4
0.30
0.21
1.00
0.97
3.04
3.93
3.00
9.20
2.68
δ (ppm)


O
OH
O
O
O

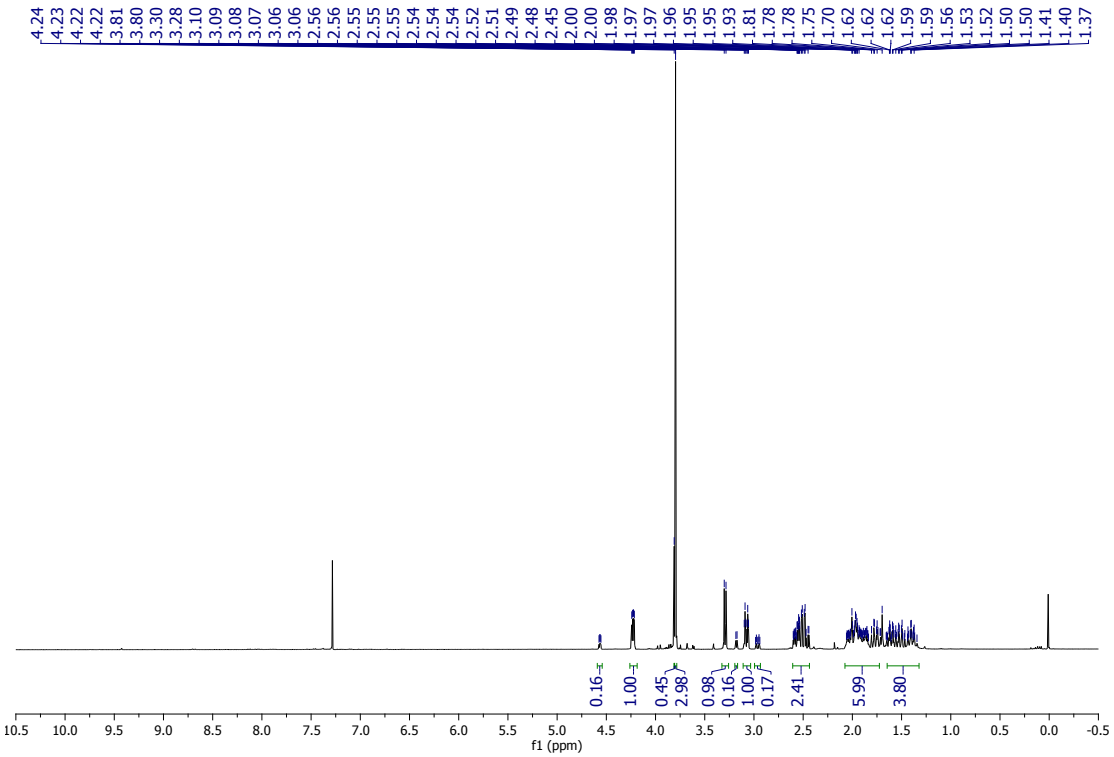
6e

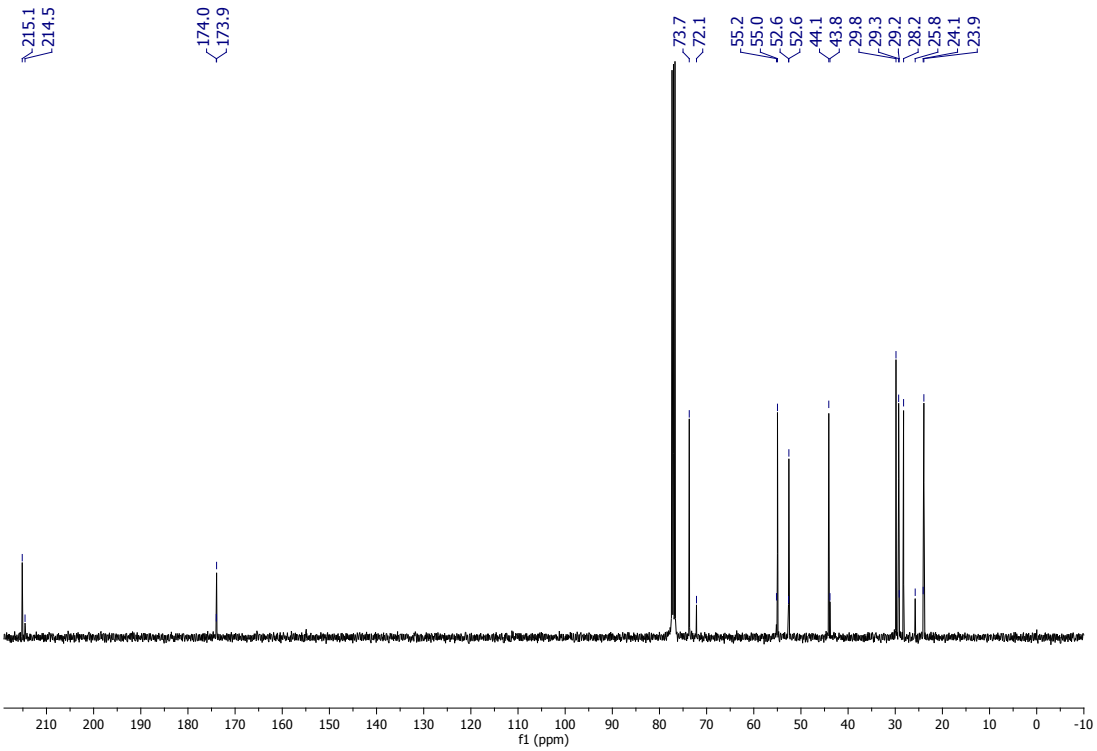

4.91
4.90
4.89
4.89
4.15
4.15
3.85
3.83
3.16
3.15
3.06
3.04
2.98
2.86
2.84
2.81
2.79
2.79
2.77
2.76
2.75
2.74
2.72
2.71
2.70
2.66
2.59
2.57
1.00
0.72
2.52
3.04
0.67
4.42
f1 (ppm)

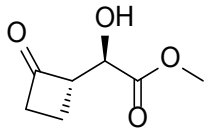

207.4
207.3
207.2
173.4
173.2
70.4
69.8
53.2
53.0
49.0
48.8
40.5
37.5
37.0
36.3
36.1
f1 (ppm)


O
OH
O
O

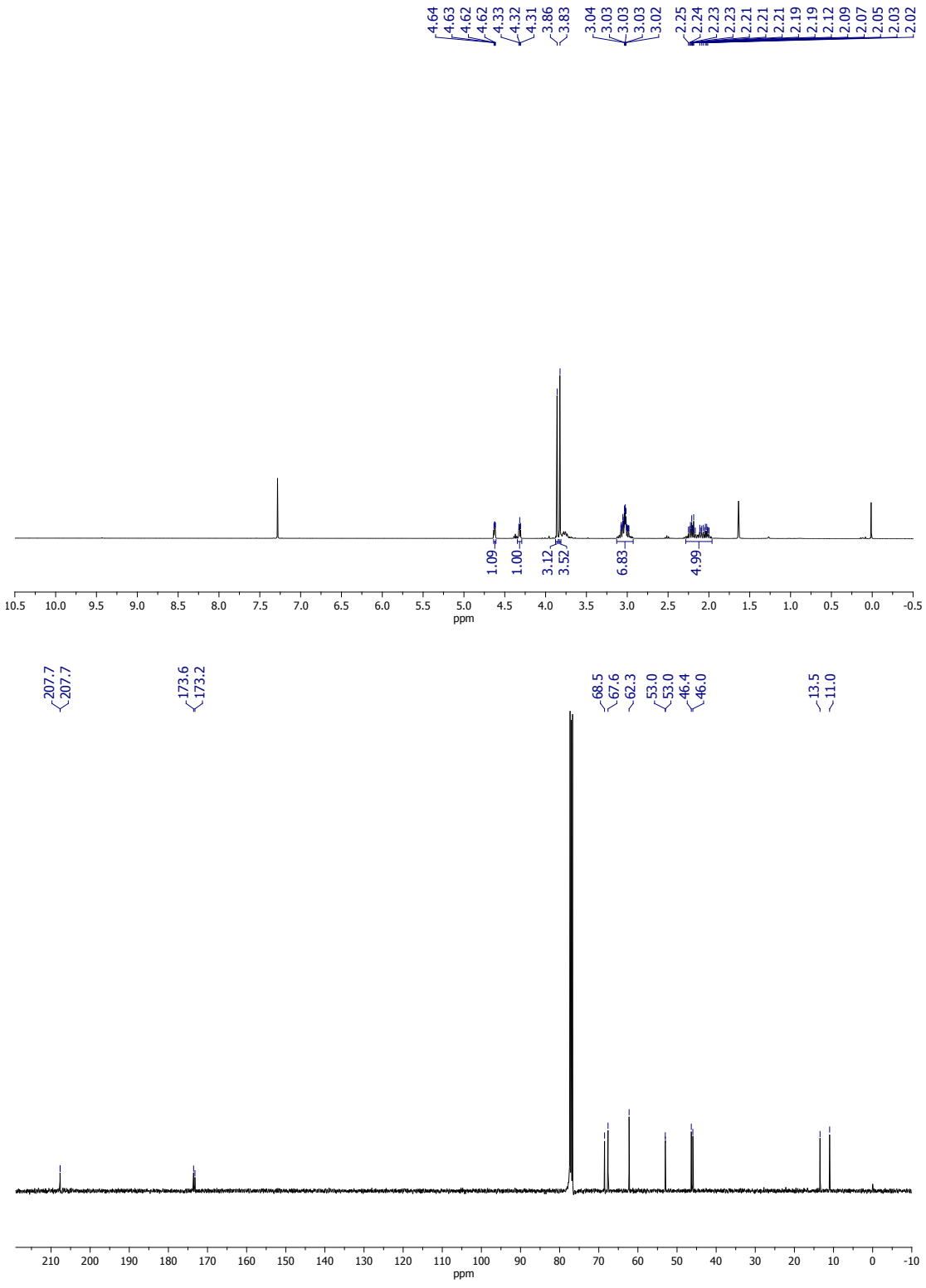
6f

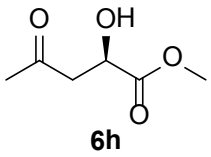

4.24
4.23
4.22
4.22
3.81
3.80
3.30
3.28
3.10
3.09
3.08
3.07
3.06
3.06
2.56
2.55
2.55
2.55
2.54
2.54
2.54
2.52
2.51
2.49
2.48
2.45
2.00
2.00
1.98
1.97
1.97
1.96
1.95
1.95
1.93
1.81
1.78
1.78
1.75
1.70
1.62
1.62
1.62
1.59
1.59
1.56
1.53
1.52
1.50
1.50
1.41
1.40
1.37
0.16
1.00
0.45
2.98
0.98
0.16
1.00
0.17
2.41
5.99
3.80
f1 (ppm)



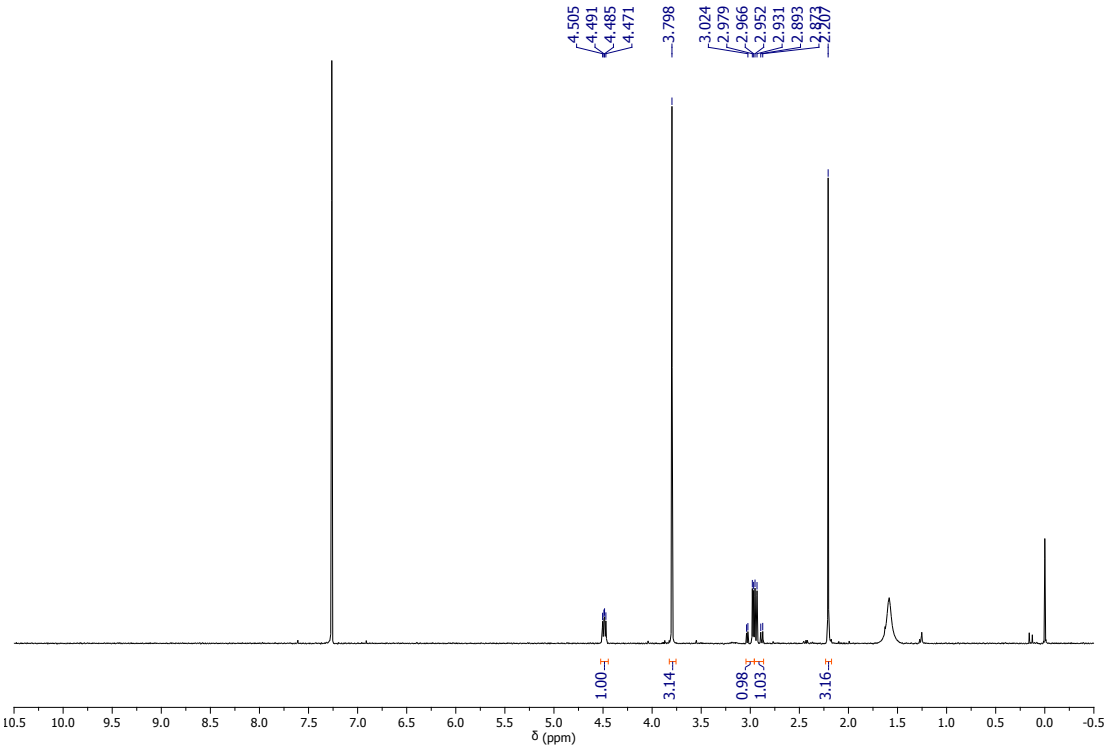


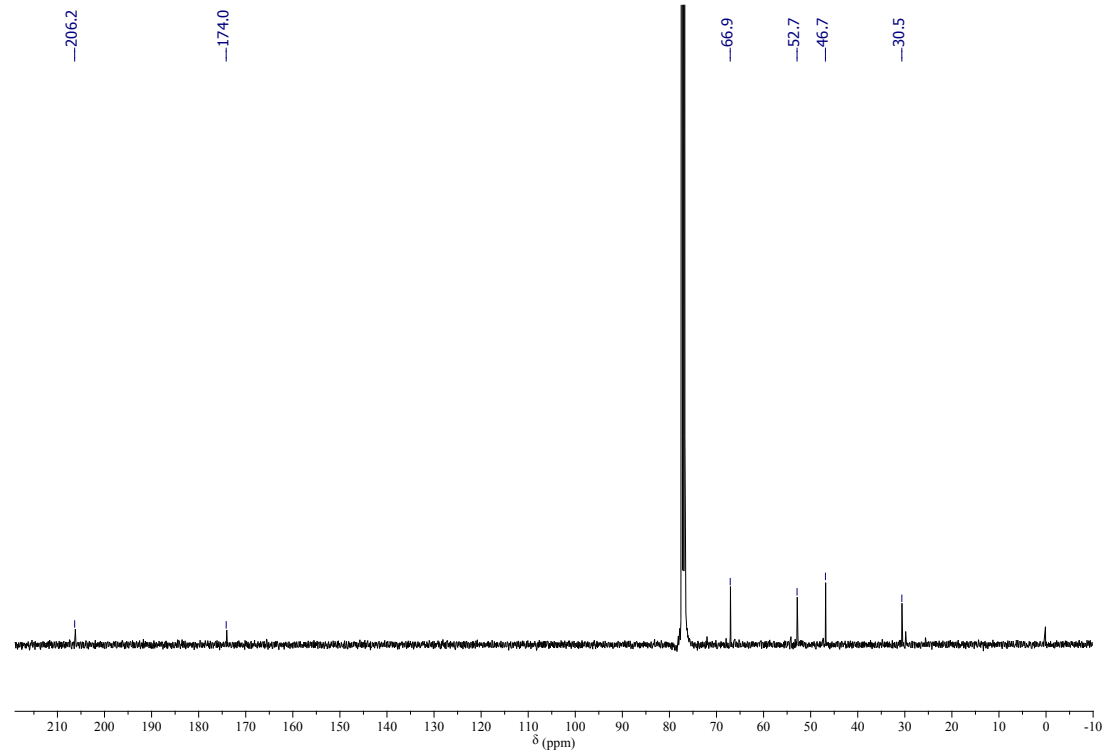
6g

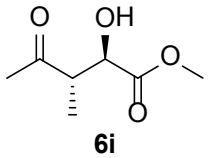

4.64
4.63
4.62
4.62
4.33
4.32
4.31
3.86
3.83
3.04
3.03
3.03
3.03
3.02
2.25
2.24
2.23
2.23
2.21
2.21
2.21
2.19
2.12
2.09
2.07
2.05
2.03
2.02
1.09
1.00
3.12
3.52
6.83
4.99
ppm
207.7
207.7
173.6
173.2
68.5
67.6
62.3
53.0
53.0
46.4
46.0
13.5
11.0
ppm


O
OH
O
O

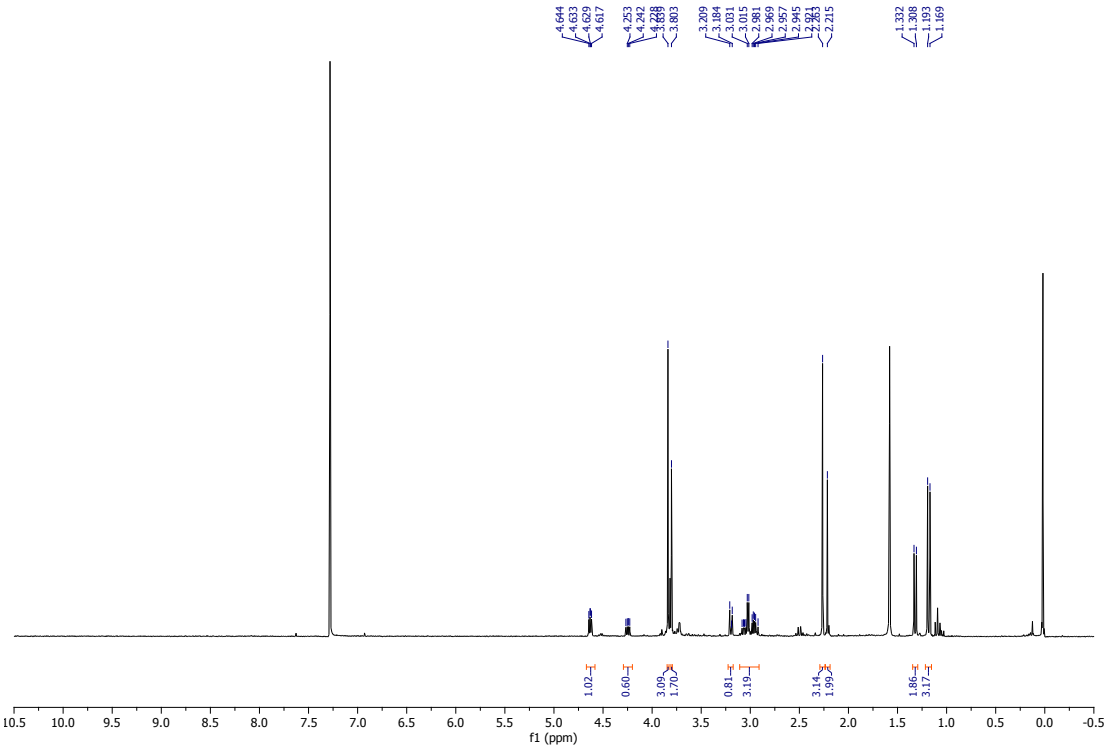
6h

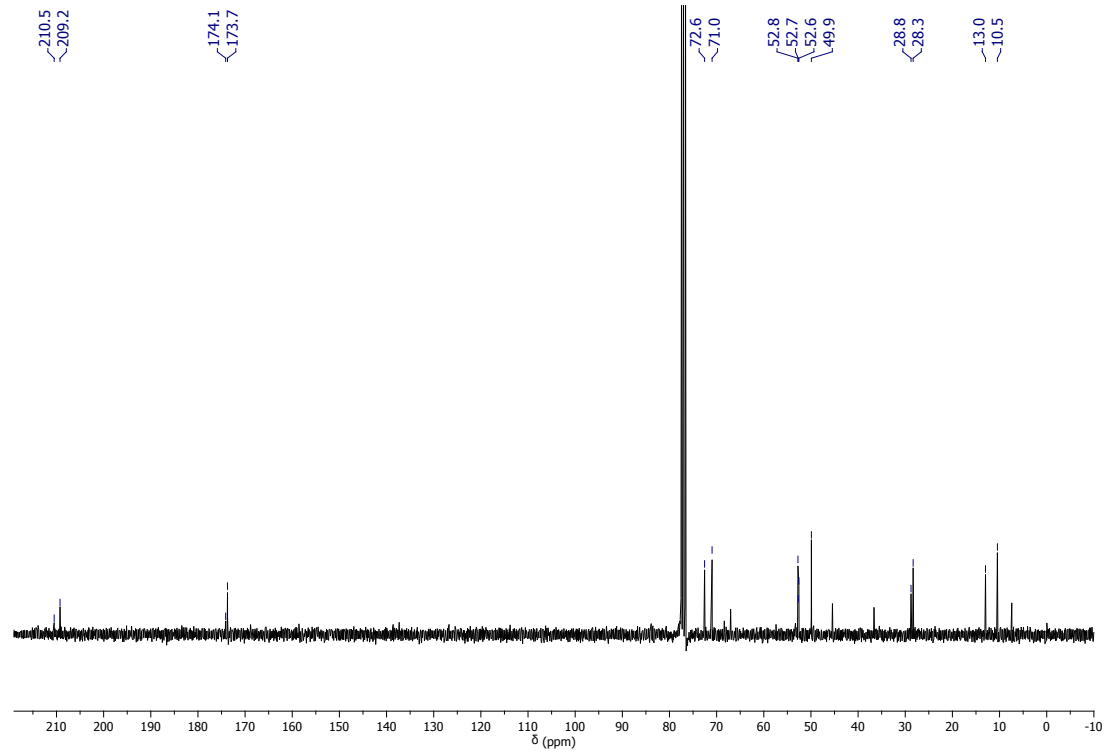

4.505
4.491
4.485
4.471
3.798
3.024
2.979
2.966
2.952
2.931
2.893
2.873
2.207
1.00
3.14
0.98
1.03
3.16
δ (ppm)

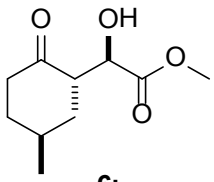

206.2
174.0
66.9
52.7
46.7
30.5
δ (ppm)


O
OH
O
O

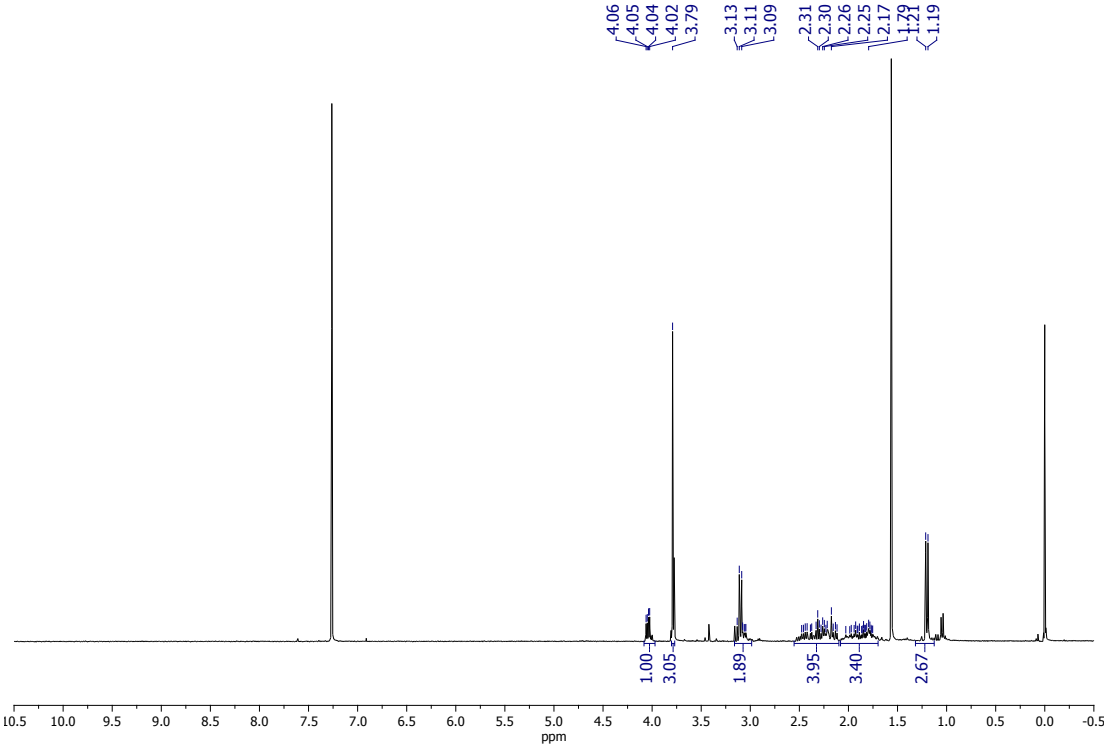
6i

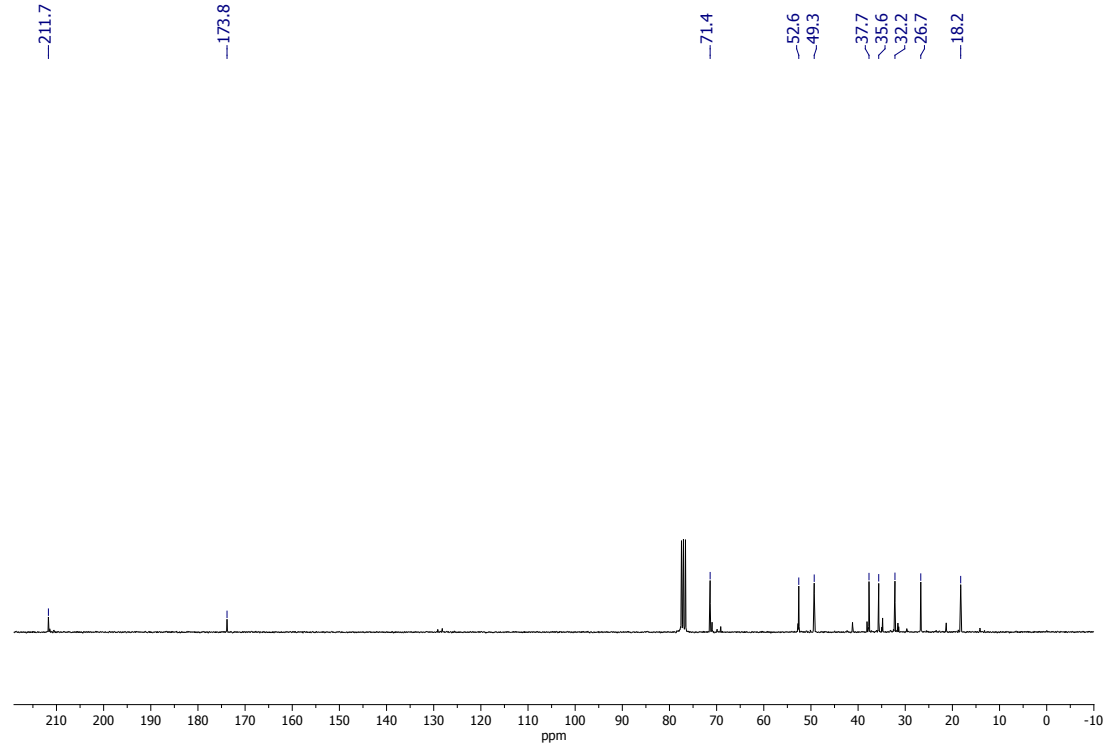




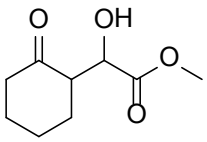


6j

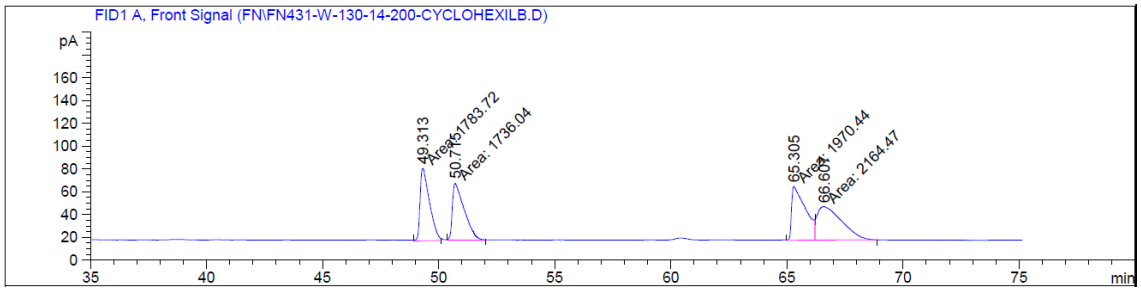




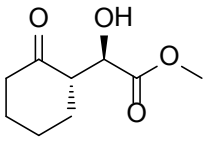
HPLC spectra for aldol products



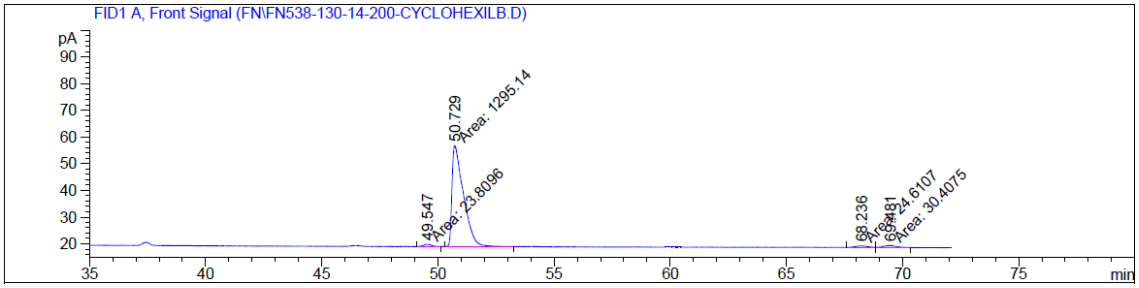
6a-*Rac*



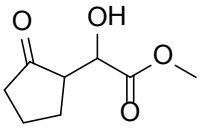
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	49.313	MM	0.4669	1783.72119	63.67047	23.30239
2	50.715	MM	0.5838	1736.03711	49.56264	22.67945
3	65.305	MF	0.6935	1970.44177	47.35276	25.74170
4	66.607	FM	1.2213	2164.46899	29.53866	28.27645



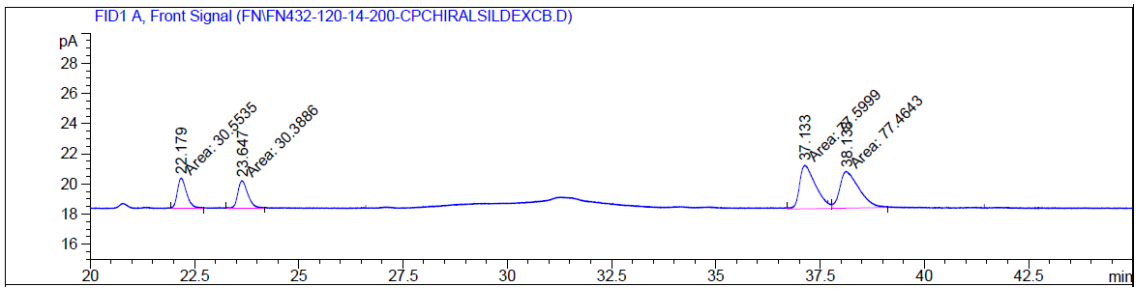
6a



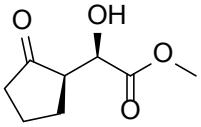
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	49.547	MM	0.4547	23.80962	8.72808e-1	1.73291
2	50.729	MM	0.5716	1295.14282	37.76358	94.26278
3	68.236	MF	0.6600	24.61066	6.21470e-1	1.79121
4	69.481	FM	0.6566	30.40747	7.71833e-1	2.21311



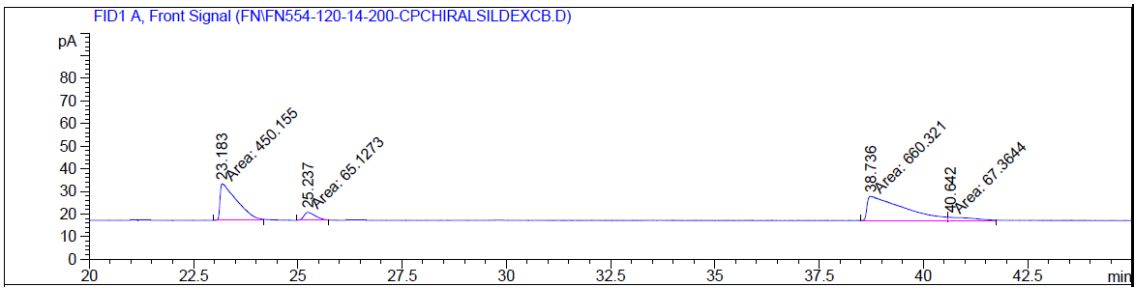
6b-*Rac*



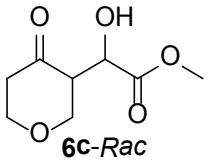
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.179	MM	0.2535	30.55349	2.00858	14.14472
2	23.647	MM	0.2768	30.38864	1.82959	14.06841
3	37.133	MF	0.4455	77.59990	2.90294	35.92483
4	38.138	FM	0.5303	77.46426	2.43467	35.86204



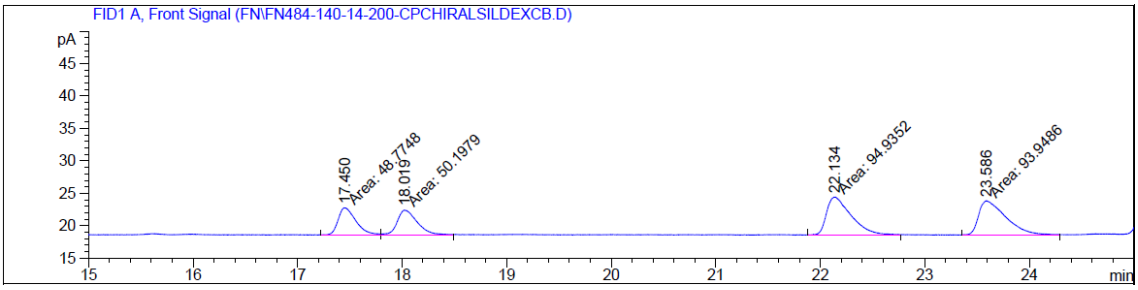
6b



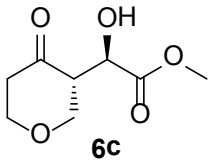
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.183	MM	0.4649	450.15494	16.13661	36.21613
2	25.237	MM	0.3096	65.12729	3.50576	5.23966
3	38.736	MF	1.0197	660.32147	10.79224	53.12457
4	40.642	FM	0.6878	67.36445	1.63227	5.41964



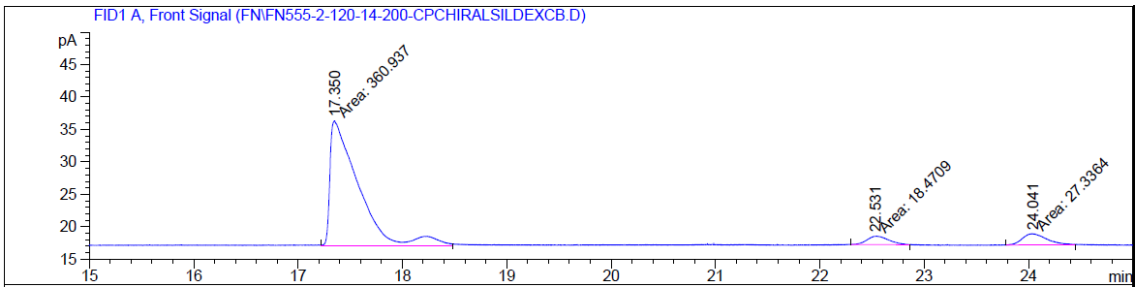
6c-*Rac*



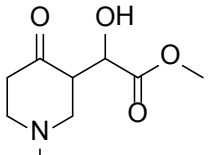
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	17.450	MF	0.1959	48.77477	4.14976	16.94413
2	18.019	FM	0.2183	50.19793	3.83328	17.43853
3	22.134	MM	0.2706	94.93517	5.84677	32.98004
4	23.586	MM	0.2979	93.94859	5.25650	32.63731



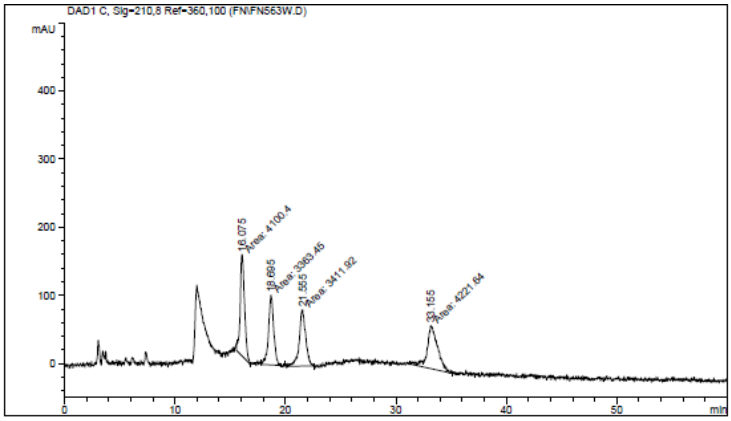
6c



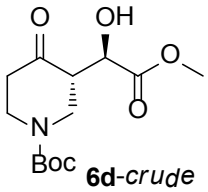
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	17.350	MM	0.3132	360.93735	19.21000	88.73807
2	22.531	MM	0.2376	18.47092	1.29574	4.54116
3	24.041	MM	0.2667	27.33636	1.70845	6.72077



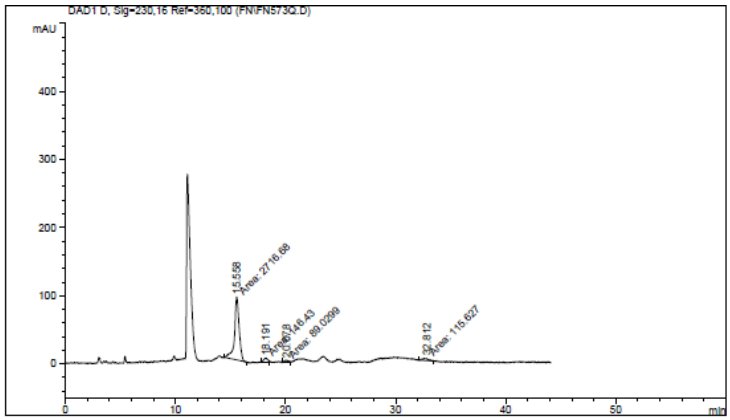
6d-*Rac*



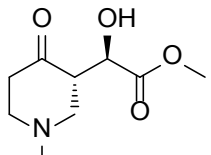
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.075	MM T	0.4707	4100.40381	149.05252	27.1596
2	18.695	MM T	0.5464	3363.45020	102.59899	22.2783
3	21.555	MM T	0.6857	3411.92383	82.93407	22.5994
4	33.155	MM T	1.1101	4221.64014	63.38070	27.9627



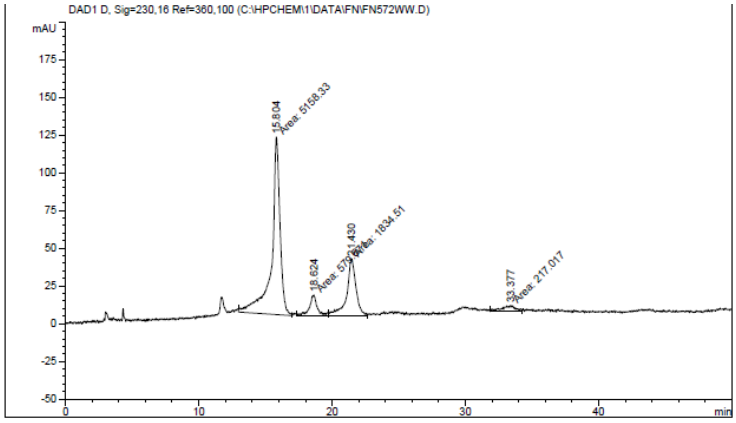
6d-*crude*



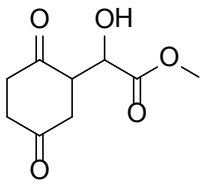
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.558	MM T	0.4899	2716.68042	92.41472	88.5556
2	18.191	MM T	0.4311	146.43019	5.67513	4.7732
3	20.078	MM T	0.4371	89.02989	3.39460	2.9021
4	32.812	MM T	0.5756	115.62706	3.34790	3.7691



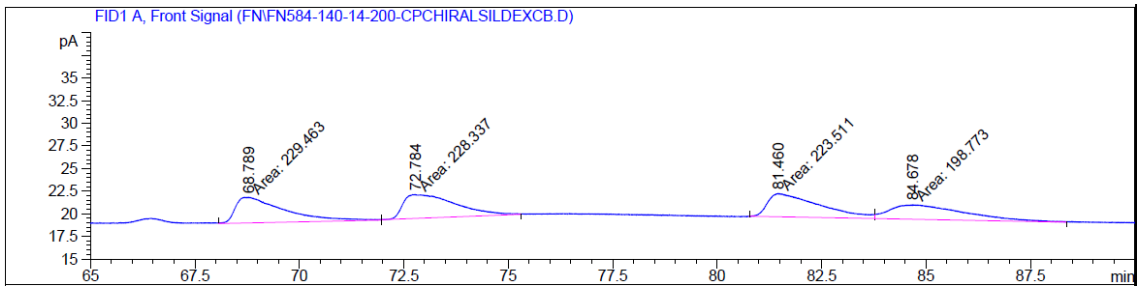
6d



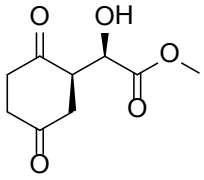
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.804	MM T	0.7303	5158.32666	117.71925	66.2222
2	18.624	MF T	0.6974	579.57056	13.85066	7.4405
3	21.430	FM T	0.8088	1834.50781	37.80505	23.5513
4	33.377	MM T	1.1991	217.01749	3.46340	2.7861



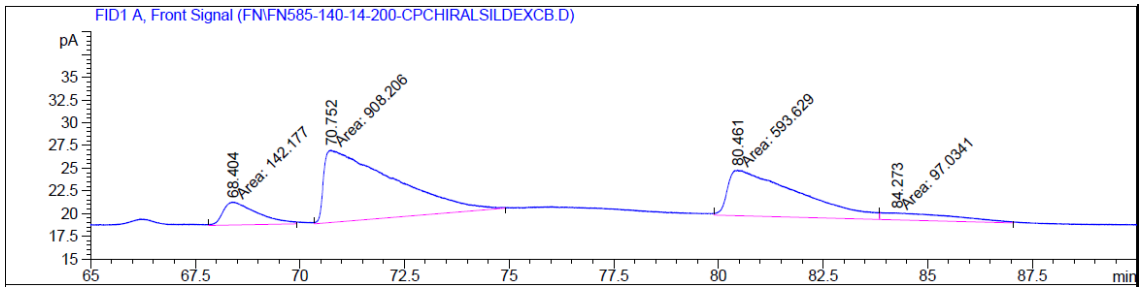
6e-*Rac*



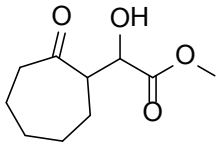
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	68.789	MM	1.3481	229.46333	2.83693	26.07290
2	72.784	MM	1.4405	228.33678	2.64180	25.94489
3	81.460	MF	1.4393	223.51067	2.58825	25.39652
4	84.678	FM	2.0267	198.77290	1.63458	22.58568



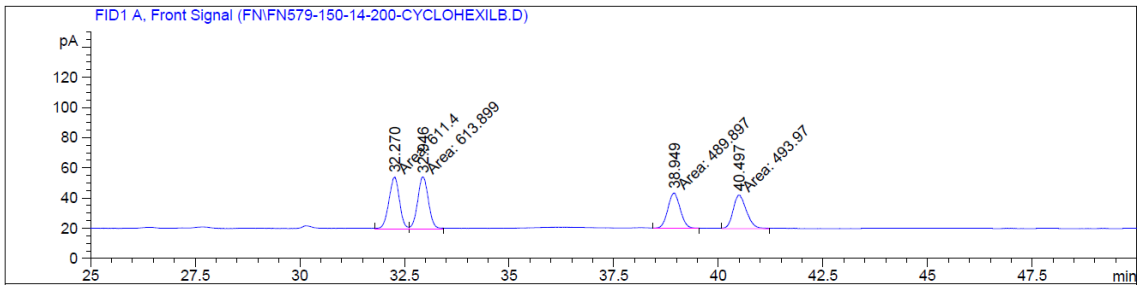
6e



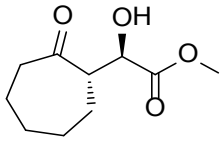
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	68.404	MM	0.9405	142.17714	2.51963	8.16619
2	70.752	MM	1.9030	908.20551	7.95434	52.16437
3	80.461	MF	1.9604	593.62891	5.04675	34.09611
4	84.273	FM	2.0733	97.03407	7.80025e-1	5.57332



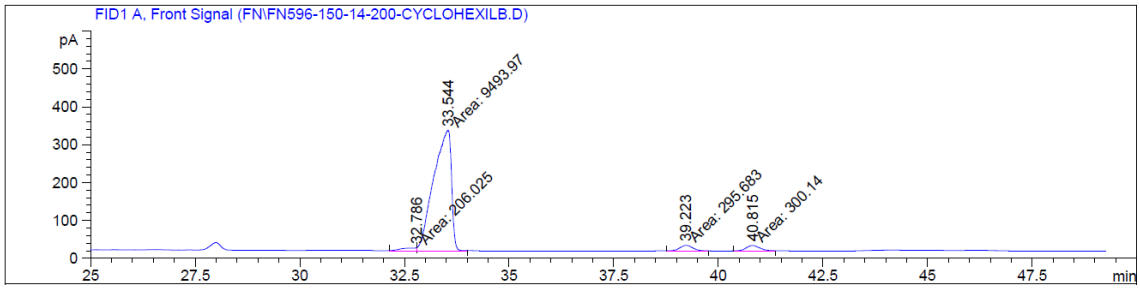
6f-*Rac*



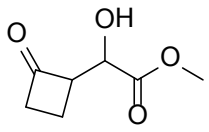
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.270	MF	0.2958	611.40002	34.44358	27.67560
2	32.946	FM	0.2977	613.89917	34.37333	27.78872
3	38.949	MM	0.3456	489.89716	23.62557	22.17565
4	40.497	MM	0.3711	493.97028	22.18338	22.36003



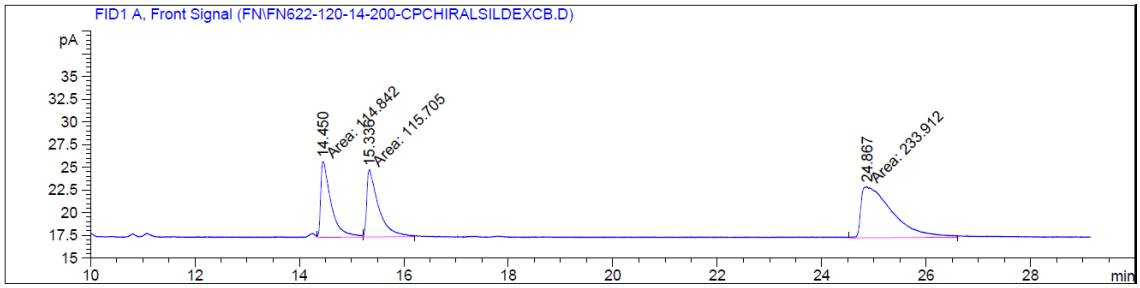
6f



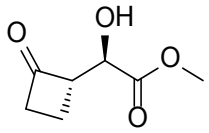
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.786	MF	0.3961	206.02478	8.66811	2.00105
2	33.544	FM	0.4963	9493.96777	318.84433	92.21191
3	39.223	MM	0.3455	295.68298	14.26475	2.87188
4	40.815	MM	0.3615	300.14005	13.83815	2.91517



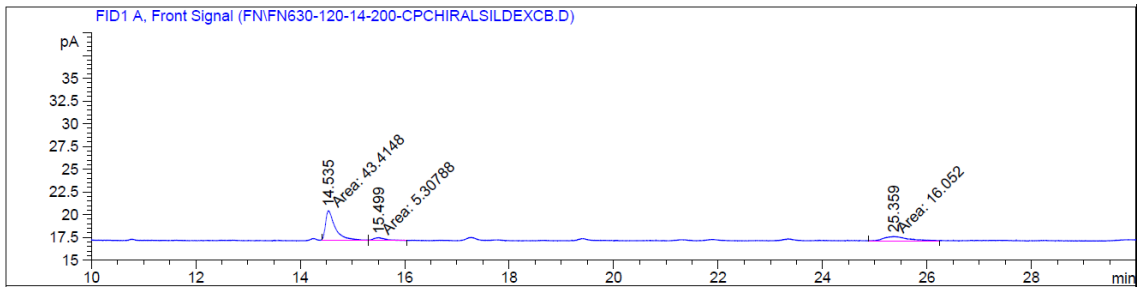
6g-*Rac*



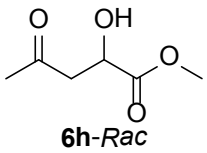
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.450	MF	0.2297	114.84156	8.33231	24.72589
2	15.336	FM	0.2604	115.70503	7.40444	24.91180
3	24.867	MM	0.6926	233.91209	5.62876	50.36230



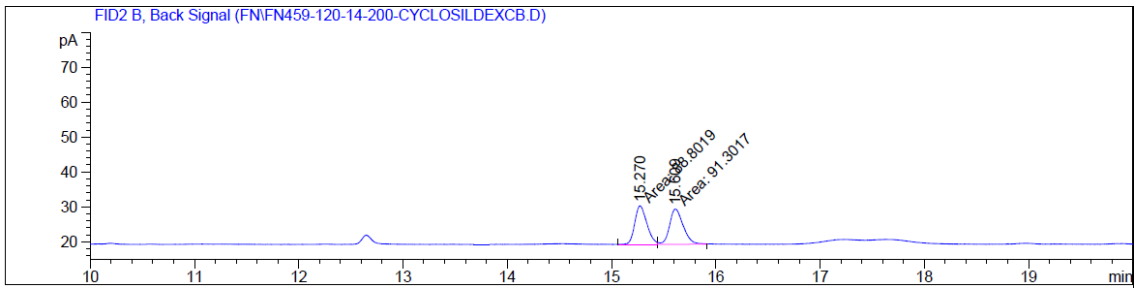
6g



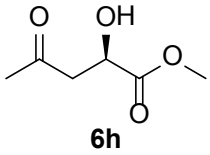
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.535	MF	0.2203	43.41481	3.28432	67.02438
2	15.499	FM	0.2729	5.30788	3.24186e-1	8.19437
3	25.359	MM	0.5212	16.05197	5.13341e-1	24.78125



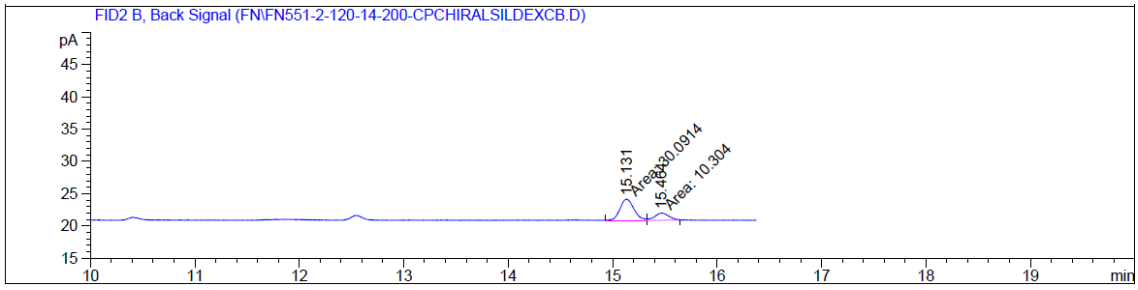
6h-*Rac*



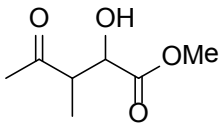
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	15.270	MF	0.1347	88.80193	10.99064	49.30601
2	15.609	FM	0.1510	91.30172	10.07436	50.69399



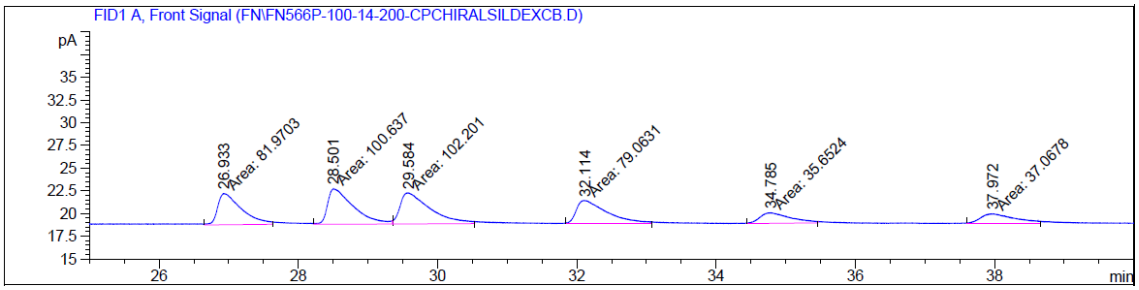
6h



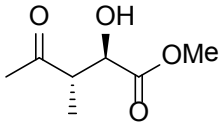
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	15.131	MF	0.1515	30.09142	3.30964	74.49210
2	15.464	FM	0.1553	10.30403	1.10585	25.50790



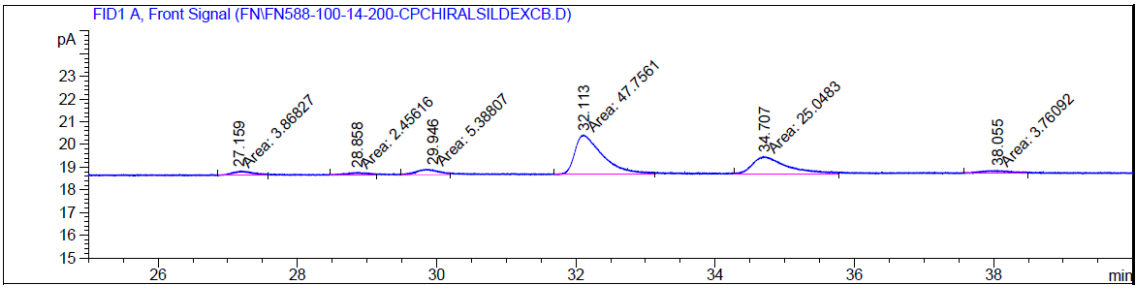
6i-*Rac*



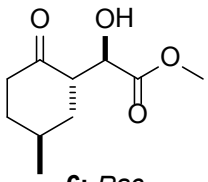
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	26.933	MM	0.3969	81.97029	3.44234	18.77503
2	28.501	MF	0.4293	100.63720	3.90686	23.05062
3	29.584	FM	0.4978	102.20137	3.42181	23.40889
4	32.114	MM	0.5180	79.06306	2.54395	18.10914
5	34.785	MM	0.5022	35.65242	1.18314	8.16607
6	37.972	MM	0.5772	37.06779	1.07034	8.49026



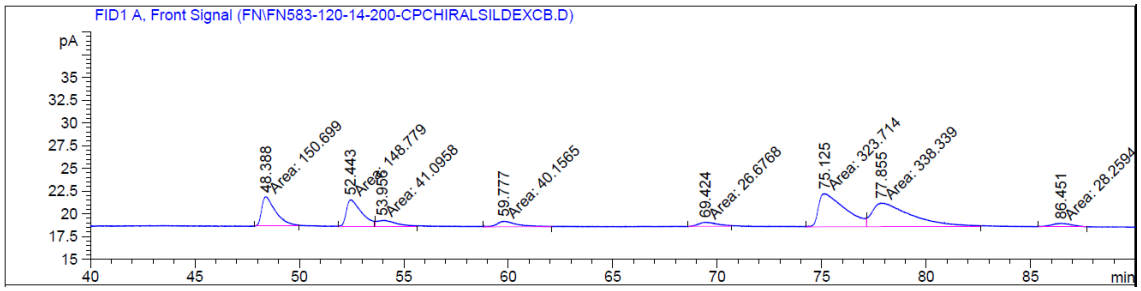
6i



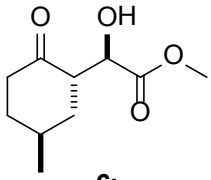
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.159	MM	0.3275	3.86827	1.96871e-1	4.38192
2	28.858	MM	0.3082	2.45616	1.32814e-1	2.78230
3	29.946	MM	0.3544	5.38807	2.53362e-1	6.10353
4	32.113	MM	0.4639	47.75608	1.71563	54.09748
5	34.707	MM	0.5555	25.04833	7.51521e-1	28.37443
6	38.055	MM	0.3740	3.76092	1.67589e-1	4.26033



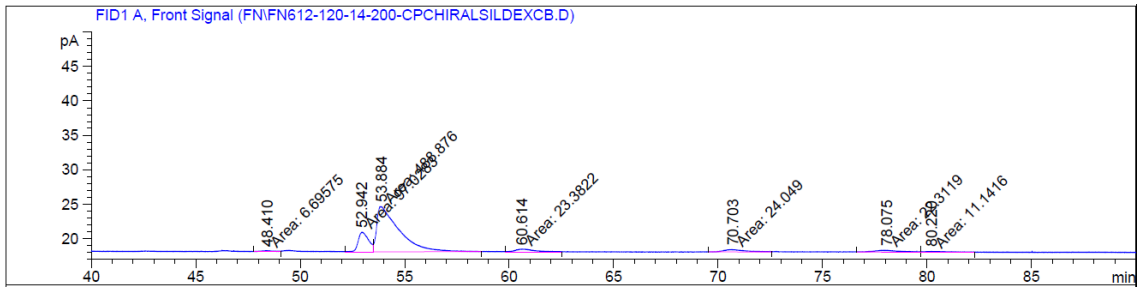
6j-*Rac*



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	48.388	MM	0.7735	150.69901	3.24710	13.72837
2	52.443	MM	0.8342	148.77864	2.97237	13.55343
3	53.956	FM	1.0429	41.09580	6.56759e-1	3.74374
4	59.777	MM	1.0613	40.15648	6.30612e-1	3.65817
5	69.424	MM	0.9790	26.67677	4.54170e-1	2.43020
6	75.125	MF	1.4607	323.71423	3.69350	29.48971
7	77.855	FM	2.1456	338.33914	2.62813	30.82200
8	86.451	MM	1.0884	28.25940	4.32753e-1	2.57437



6j



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	48.410	MM	0.6516	6.69575	1.71263e-1	0.99419
2	52.942	MF	0.5698	97.02833	2.83816	14.40690
3	53.884	FM	1.2407	488.87640	6.56746	72.58905
4	60.614	MM	0.9080	23.38215	4.29180e-1	3.47181
5	70.703	MM	1.1777	24.04897	3.40333e-1	3.57082
6	78.075	MF	1.2842	22.31186	2.89558e-1	3.31290
7	80.220	FM	1.2880	11.14160	1.44173e-1	1.65432

References

[1] a) G. Guillena, M. C. Hita, C. Nájera and S. F. Viozquez, *J. Org. Chem.* 2008, **73**, 5933. b) S. F. Viozquez, G. Guillena, C. Nájera, B. Bradshaw, G. Etxebarria-Jardi and J. Bonjoch, *Org. Synth.* 2011, **88**, 317.

[2] T. Loh, L. Feng and L. Wei, *Tetrahedron*, 2001, **57**, 4231.

[3] Supplier Name: FCH Group, Catalog Publication Date: 14 Sep 2012 Order Number: FCH1237125 CAS Registry Number: 1378713-26-8

[4] S. Tsuboi, E. Nishiyama, H. Furutani, M. Utakam and A.Takeda, *J. Org. Chem.* 1987, **52**, 1359.

[5] Stanek, M.; Hildebrand, P.; Zimmermann, C.; Castelijns, M. From PCT Int. Appl. (**2001**), WO 2001094329 A1 20011213