Supplementary Information

"Asymmetric Total Synthesis of the Iridoid ß-Glucoside (+)-Geniposide *via* Phosphine Organocatalysis"

Regan A. Jones and Michael J. Krische*

University of Texas at Austin
Department of Chemistry and Biochemistry
Austin, TX 78712

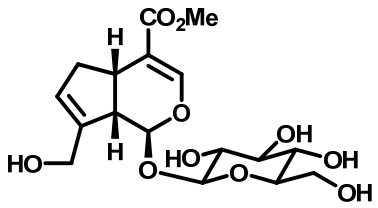
Table of Contents

Experimental Procedures

General

All reactions were run under an atmosphere of argon under anhydrous conditions unless otherwise indicated. Dichloromethane (DCM), dichloroethane (DCE), tetrahydrofuran (THF), and toluene (PhMe) were obtained from a Pure-Solv MD-5 Solvent Purification System (Innovative Technology, inc). Methanol (MeOH) was distilled from magnesium turnings and iodine. Pyridine was dried with and stored over sodium hydroxide pellets. Anhydrous solvents were transferred using oven-dried syringes. Thionyl Chloride ($SOCl_2$) was distilled from quinoline prior to use. Boron trifluoride diethyl etherate was distilled prior to use. *p*-Nitrobenzyl alcohol was recrystallized from DCM prior to use. Magnesium Sulfate ($MgSO_4$) was dried in an oven prior to use in the asymmetric kinetic resolution. All other commercial reagents were used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254). Visualization of the chromatograms was accomplished using UV light and vanillin, anisaldehyde, permanganate, or cerium molybdate stain with heating. Preparative column chromatography using silica gel was performed according to the method of Still.[1] Infrared spectra were recorded on a Nicolet 380 FTIR. High-resolution mass spectra (HRMS) were obtained on a Waters Micromass Autospec or a Varian FTICR as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M-1) or a suitable fragment ion. Melting points were obtained on a Thomas-Hoover Unimelt apparatus. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian (400 MHz) spectrometer and reported in parts per million (ppm) referenced to the residual protio solvent signal as an internal standards. Coupling constants are reported in hertz (Hz). Optical rotations were measured on a ATAGO AP-300 automatic polarimeter at a path length of 1 dm.

Detailed Procedure and Spectral Data for Compounds



7-Hydroxymethyl-1-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-4-carboxylic acid methyl ester (1)

A flask was charged with **10** (50 mg, 0.078 mmol), $LiOH \cdot H_2O$ (49 mg, 1.171 mmol, 1500 mol%), and a 7:3 mixture of CH_3CN:H_2O (1.56 mL, 0.05 M). The reaction was heated to 40 °C under a reflux condenser for 16.5 h and then quenched with AcOH (0.090 mL, 1.56 mmol, 2000 mol%). The resulting solution was passed through a column of Dowex®50WX8-200 ion-exchange resin with water and concentrated in *vacuo*. The crude material was dissolved in 1:1 MeOH:$CHCl_3$ (4 mL, 0.02 M) and a 2.0 M solution of TMS-diazomethane in hexane was added (0.078 mL 200 mol%) and the reaction was stirred at ambient temperature for 1h. After 1 h an additional portion of TMS-diazomethane in hexane was added (0.078 mL 200 mol%) and the reaction was deemed complete after another 30 minutes. The excess TMS-diazomethane was quenched with acetic acid and the resulting solution was concentrated in *vacuo* on to silica gel. The material was purified by flash column chromatography (SiO_2, 9:1 $CHCl_3$:MeOH to 4:1 $CHCl_3$:MeOH) and then ran through a column of Dowex®50WX8-200 ion-exchange resin with MeOH. The filtrate was concentrated to furnish (+)-geniposide as a white solid (18.4 mg 61%). The spectral data correspond to that of the previously reported material.[2,3]

^{1}H NMR: (400 MHz, CD_3OD): δ 7.51 (s, 1H), 5.79 (s, 1H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.70 (dd, *J* = 7.9, 2.1 Hz, 1H) 4.31 (d, *J* = 14.7, 1H), 4.18 (d, *J* = 14.4, 1H), 3.84 (d, *J* = 11.6, 1H), 3.70 (s, 3H), 3.63 (dd, *J* = 12.1, 5.2 Hz, 1H), 3.40-3.34 (m, 2H), 3.28-3.26 (m, 1H), 3.24-3.15 (m, 2H), 2.81 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.72 (t, *J* = 7.7 Hz, 1H), 2.12-2.06 (m, 1H).

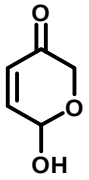
^{13}C NMR: (100 MHz, CD_3OD): δ 169.5, 153.3, 144.8, 128.3, 112.5, 100.3, 98.2, 78.4, 77.8, 74.9, 71.5, 62.7, 61.4, 51.7, 47.0, 39.7, 36.6.

HRMS: Calcd. For $C_{17}H_{23}O_{10}$ (M-1): 387.1293, Found: 387.1297.

FTIR: (neat): υ 3362, 2920, 2487, 1697, 1630, 1282, 1160, 1074, 1037, 942, 893, 822, 795, 767 cm^{-1}.

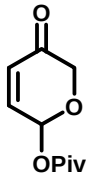
M.P.: 123-124 °C

$[\alpha]_D^{24}$ = +24.25 (C = 0.660, EtOH)



6-Hydroxy-6H-pyran-3-one (**3a**)

A flame-dried argon flask was charged with furfuryl alcohol (10g, 8.810 mL, 101.937 mmol) and DCM (510 mL, 0.2 M). The solution was cooled to 0 ºC and 70-75% *m*-chloroperoxybenzoic acid (37.693 g, 152.906 mmol, 150 mol%) was added portion-wise to the solution. The reaction was allowed to slowly warm to ambient temperature for 6 h during which time solid *m*-chlorobenzoic acid precipitated from the solution. The solution was cooled to -78 ºC for 15 minutes and the solid *m*-chlorobenzoic acid was filtered. The filtrate was concentrated in vacuo and purified by flash column chromatography, (SiO_2, 2:1 hexanes:EtOAc 1% acetic acid to 1:1 hexanes:EtOAc 1% acetic acid), to furnish the title compound as a light yellow solid (9.06 g, 78%). The spectral data correspond to that of the previously reported material.[4]



2,2-Dimethyl-propionic acid 5-oxo-5,6-dihydro-2H-pyran-2-yl ester (*rac*-3b)

A flame-dried argon flushed flask was charged with lactol **3a** (2.0g, 17.53 mmol), DCM (88 mL, 0.2M), 2,6-lutidine (4.08 mL, 35.06 mmol, 200 mol%) and DMAP (107 mg, 0.88 mmol, 5 mol%). The solution was cooled to 0 ºC and trimethylacetyl chloride (3.24 mL, 26.29 mmol, 150 mol%) was added. The reaction was slowly warmed to room temperature and stirred for 72 h. The reaction was diluted with Et_2O and washed with water, a saturated solution of $NaHCO_3$, a 5% solution of aqueous $CuSO_4$, and brine. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, (*Caution: compound **rac-3b** is volative under high vacuum*), and purified by flash column chromatography, (SiO_2, 8:1 pentane: Et_2O), to furnish the title compound as a white solid (2.78 g, 80%).

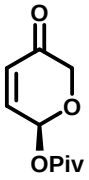
^{1}H NMR: (400 MHz, $CDCl_3$): δ 6.90 (dd, *J* = 10.4, 3.6 Hz, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 6.22 (d, *J* = 10.6, 1H), 4.43 (d, *J* = 16.8, 1H) 4.17 (d, *J* = 17.1, 1H), 1.21, (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 193.3, 176.7, 142.4, 128.5, 86.4, 67.1, 39.1, 26.8.

HRMS: Calcd. For $C_{10}H_{15}O_4$ (M+1): 199.0970, Found: 199.0974.

FTIR: (neat): υ 2956, 1731, 1699, 1686, 1281, 1264, 1132, 1102, 1026, 1006, 989, 912, 879, 865, 778 cm^{-1}.

MP: 45-46 ºC



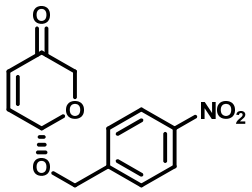
2,2-Dimethyl-propionic acid 5-oxo-5,6-dihydro-2H-pyran-2-yl ester ((*S*)-3b))

A flame dried argon flushed flask was charged with DCM (20 mL, 0.05 M), oven dried magnesium sulfate (400 mg, 200 wt %), recrystallized *p*-nitrobenzyl alcohol (85 mg, 0.554 mmol, 55 mol%), pivalate ***rac*-3b** (200 mg, 1.01 mmol, 100 mol%) and Trost ligand (21 mg, 0.030 mmol, 3 mol%), respectively. The solution was cooled to 4 ºC and allyl palladium chloride dimer (3.7 mg %, 0.010 mmol, 1.0 mol%) was added. The flask was sealed with a cap and parafilm and stirred for 48 hours at 4 ºC. The reaction was diluted with Et_2O, and washed with a saturated solution of aqueous $NaHCO_3$, and brine. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* (*Caution: compound* **(S)-3b** *is volative under high vacuum*), and purified by flash column chromatography (SiO_2, 5:1 pentane: Et_2O to 2:1 hexanes:EtOAc) to furnish the title compound as a white solid (70.5 mg, 70%, 92% ee) and the *p*-nitrobenzyl derivative **3c** as a light yellow solid (96 mg, 96%, 60% ee). Sixty-five milligrams of 92% ee compound (***S*)-3b** was recrystallized from pentanes twice to furnish 43 mg of the title compound in >99% ee (66% recovery).

$[\alpha]_D^{24}$ = +151.00 (c= 1.00, $CHCl_3$).

HPLC: (Chiralpak AD-H column, 2% i-PrOH/hexanes, 0.5 mL/min, 230 nm), t_{major} = 15.1 min, t_{minor} = 21.0 min; ee = 92%.

(Chiralpak AD-H column, 2% i-PrOH/hexanes, 0.5 mL/min, 230 nm), t_{major} = 15.7 m; ee = >99%.



6-(4-Nitro-benzyloxy)-6H-pyran-3-one (3c)

^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 8.9, 2H), 6.93, (dd, *J* = 10.4, 3.2 Hz, 1H), 6.21, (d, *J* = 10.3 Hz, 1H), 5.32 (dd, *J* = 3.4, 0.6, 1H), 4.97 (d, *J* = 13.0, 1H) 4.77 (d, *J* = 13.0, 1H), 4.45 (d, *J* = 16.8, 1H), 4.14 (d, *J* = 16.8, 1H).

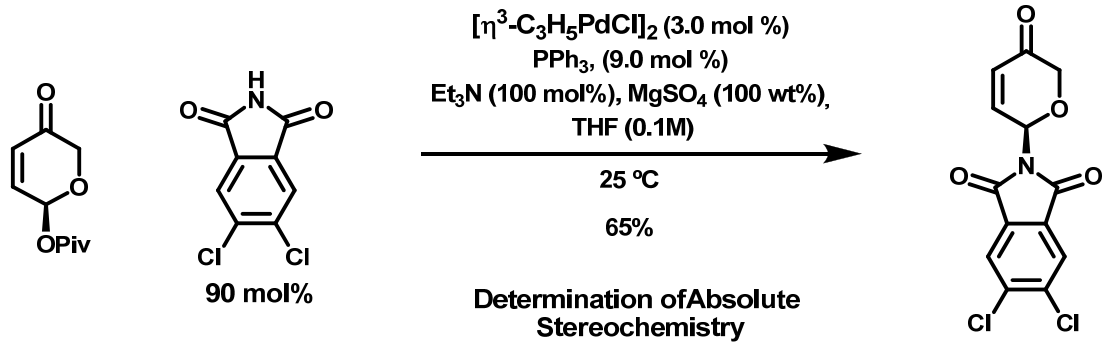
^{13}C NMR: (100 MHz, $CDCl_3$): δ 194.0, 147.5, 144.4, 143.5, 128.1, 128.0, 123.7, 92.7, 69.3, 66.3 ppm.

HRMS: Calcd. For $C_{12}H_{12}NO_5$ (M+1): 250.0719, Found: 250.0715

FTIR: (neat): 2916, 2853, 1483, 1516, 1346, 1334, 1106, 1054, 1034, 1005, 987, 976, 858, 832, 771, 735 cm^{-1}.

MP: 108-110 ºC

HPLC: (Chiralpak AD-H column, 2% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 47.1 min, t_{major} = 51.8 min; ee = 68%.



(*R*)-5,6-dichloro-2-(5-oxo-5,6-dihydro-2H-pyran-2-yl)isoindoline-1,3-dione

A flask was charged with THF, (2.5 mL, 0.1 M), >99% ee pivalate (***S*)-4.9**, (50 mg, 0.252 mmol), 4,5-dichlorophthalimide (49 mg, 0.227 mmol, 90 mol%), $MgSO_4$ (50 mg, 100 wt %), triphenylphosphine (6 mg, 0.023 mmol, 9 mol%), palladium allyl chloride dimer (3 mg, 0.008 mmol, 3 mol%), and Et_3N (0.035 mL, 0.252 mmol, 100 mol%). The reaction was then stirred at room temperature for 5 h. Afterwards, the reaction was diluted with EtOAc, and washed with a 5% solution of $CuSO_4$ and then brine. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 3:1 EtOAc: hexanes) to furnish the title compound as a white solid (46 mg, 65% based on 4,5-dichlorophthalimide).

^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.02 (dd, J = 10.5, 2.6 Hz, 1H), 6.42 (dd, J = 10.5, 2.3 Hz, 1H), 6.25 (m, 1H), 4.48 (d, J = 16.6 Hz, 1H), 4.31 (dd, J = 16.6, 1.2 Hz, 1H).

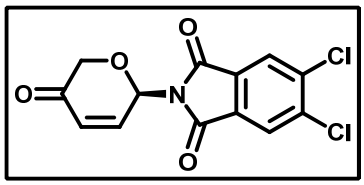
^{13}C NMR: (400 MHz, $CDCl_3$): δ 192.8, 165.1, 143.6, 140.0, 130.5, 129.5, 126.0, 72.6, 70.6.

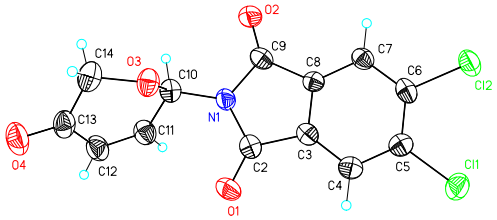
HRMS: Calcd. For $C_{13}H_7NO_4Cl_2Na^{+1}$: 333.9650, Found 333.9644.

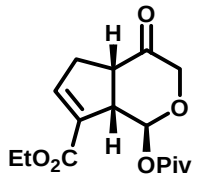
FTIR: (neat): υ 1725, 1703, 1380, 1361, 1341, 1124, 1082, 895, 754, 748, 741 cm^{-1}.

MP: 180 °C

$[\alpha]_D^{24}$ = +124.28 (c= 0.89, $CHCl_3$).







1-(2,2-Dimethyl-propionyloxy)-4-oxo-1,3,4,4a,5,7a-hexahydro-cyclopenta[c]pyran-7-carboxylic acid ethyl ester (4)

A flame-dried argon flushed flask was charged with PhMe (45mL, 0.2M with respect to ethyl butadienoate), and racemic pivalate **3b** (3.535g, 17.836 mmol, 200 mol %). The reaction vessel was heated to 110 °C and a catalytic amount of triphenylphosphine (234 mg, 0.892 mmol, 10 mol%) was added. Ethyl-2-butadienoate (1.035 mL, 9.918 mmol, 100 mol%) was added dropwise. The reaction was stirred for 0.5 h. The reaction mixture was cooled to ambient temperature and directly purified by flash column chromatography (SiO_2, 9:1 petroleum ether: Et_2O to 5:1 hexanes:ethyl acetate) to furnished the title compound as a white solid (1.732 g, 63%) and the unreacted pivalate **3b** as a white solid (1.695 g, 96% theoretical recovery). The reaction was also conducted using >99% ee (***S***)-**3b**.

^{1}H NMR: (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 2.1 Hz, 1H), 6.45 (d, *J* = 0.7 Hz, 1H), 4.27-4.14 (m, 2H), 4.18 (d, *J* = 18.1 Hz, 1H), 4.09 (d, *J* = 18.1 Hz, 1H), 3.47 (d, *J* = 8.9 Hz, 1H), 3.27 (dd, *J* = 15.6, 8.7 Hz, 1H), 2.90-2.78 (m, 2H), 1.28, (t, *J* = 7.2 Hz, 3H), 1.20, (s, 9H).

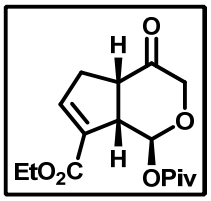
^{13}C NMR: (100 MHz, $CDCl_3$): δ 208.4, 175.9, 163.4, 144.7, 134.8, 90.5, 66.6, 60.7, 49.8, 46.0, 38.9, 36.3, 29.9, 14.1.

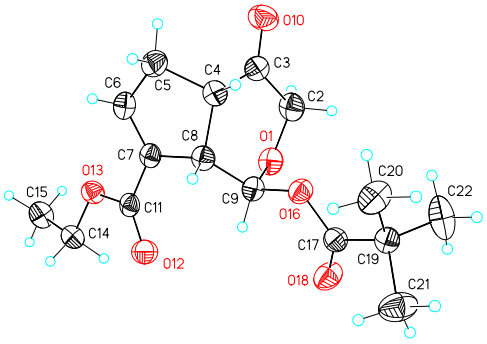
HRMS: Calcd. For $C_{16}H_{23}O_6$ (M+1): 311.1500, Found: 311.1495

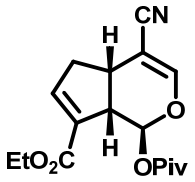
FTIR: (neat): 2976, 1735, 1717, 1702, 1257, 1161, 1149, 1130, 1104, 1077, 1025, 993, 944, 929, 848, 840, 761 cm^{-1}.

MP: 75-76 ºC

$[\alpha]_D^{24}$ = +72.00 (c= 1.00, $CHCl_3$).


O
H
O
H
EtO2C
OPiv


O10
C3
C4
C5
C6
C2
C8
O1
C7
O13
C15
C11
C9
O16
C20
C22
C14
C17
C19
O12
O18
C21



4-Cyano-1-(2,2-dimethyl-propionyloxy)-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-7-carboxylic acid ethyl ester (5)

A flame dried argon flushed flask was charged with enantiopure ketone **4** (446 mg, 1.437 mmol), ethanol (7.2 mL, 0.2 M), and potassium cyanide (468 mg, 7.185 mmol, 500 mol%). Acetic acid (0.411 mL, 7.185 mmol 500 mol%) was added dropwise to the solution and the reaction was stirred at ambient temperature for 5 hours. The solution was diluted with ether, and then washed with water, and brine. The combined organic layers were dried over Na_2SO_4, concentrated in *vacuo,* and taken on to the next step without further purification. To a flask charged with the crude cyanohydrin, was added DCE (14.4 mL, 0.1 M), pyridine (455 mg, 5.748 mmol, 400 mol%), and thionyl chloride (0.209 mL, 2.874 mmol, 200 mol%). The reaction was immediately immersed in an 80 ºC oil bath and stirred under a reflux condenser for 2.5 hours. The reaction was diluted with ether and then washed with water, a 5% aqueous solution of $CuSO_4$, and brine. The combined organic layers were dried over Na_2SO_4, concentrated in *vacuo*, and purified *twice* by flash column chromatographed (SiO_2, 3:1 hexanes: Et_2O) to furnish the title compound as an orange oil (277 mg, 60%).

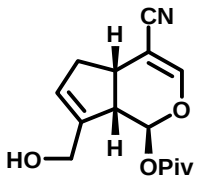
^{1}H NMR: (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 0.7 Hz, 1H), 6.92 (d, *J* = 5.0, 2.6 Hz, 1H), 6.85 (d, *J* = 3.1 Hz, 1H), 4.29-4.17 (m, 2H), 3.37-3.35, (m, 1H), 3.22 (t, *J* = 7.2 Hz, 1H), 2.89-2.81 (m, 1H), 2.71 (dd, *J* = 18.5, 2.4 Hz, 1H), 1.31 (t, *J* = 7.2, 3H), 1.21 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 176.0, 163.5, 153.6, 145.5, 132.9, 117.6, 93.8, 88.3, 60.8, 45.6, 38.8, 37.2, 32.7, 26.7, 14.1.

HRMS: Calcd. For $C_{17}H_{22}NO_5$ (M+1): 320.1503, Found: 320.1498

FTIR: (neat): 2974, 2217, 1737, 1701, 1642, 1269, 1103, 1021, 998, 922, 836, 771 cm^{-1}

$[\alpha]_D^{24}$ = +14.00 (c= 1.00, $CHCl_3$).



2,2-Dimethyl-propionic acid 4-cyano-7-hydroxymethyl-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-1-yl ester (6)

A flame-dried argon flushed flask was charged with racemic ester **5** (100 mg, 0.313 mmol) and THF (3.1 mL, 0.1M) and then cooled to -80 ºC. Reagent grade DIBAL-H (167 μL, 0.939 mmol, 300 mol%) was added and the reaction was stirred for 24h at -80 ºC. The reaction was quenched with acetic acid (0.090 μL, 1.565 mmol, 500 mol%) and partitioned between ethyl acetate and an aqueous solution of saturated Rochelle's salt. The biphasic solution was stirred vigorously for 1h until the aluminum salts precipitated into the aqueous layer. The salts were filtered, and the organic layer was washed with water and brine. The combined organic layers were dried over Na_2SO_4, concentrated in *vacuo,* and purified by flash column chromatography (SiO_2, 3:1 petroleum ether:Et_2O to 15:1 DCM:EtOAc) to furnish the title compound as a yellow oil (54mg, 62%). The reaction was also conducted using optically active **5**.

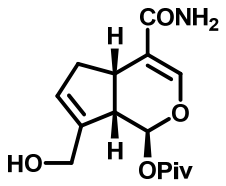
^{1}H NMR: (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 6.34 (d, *J* = 2.1, 1H), 5.81 (s, 1H), 4.27 (d, *J* = 13.7 Hz, 1H), 4.22 (d, *J* = 13.7, 1H), 3.12 (s, 2H), 2.75 (d, *J* = 16.8, 1H), 2.48 (d, *J* = 16.1, 1H), 1.22 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 176.4, 153.2, 140.2, 128.7, 117.9, 94.4, 89.1, 60.1, 46.0, 38.9, 36.9, 33.4, 26.8.

HRMS: Calcd. For $C_{15}H_{20}NO_4$ (M+1): 278.1392, Found: 278.1398.

FTIR: (neat): 3452, 2975, 2214, 1748, 1634, 1196, 1109, 1053, 1029, 982, 915, 824, 754 cm^{-1}.

$[\alpha]_D^{24}$ = -52.22 (c= 0.536, $CHCl_3$).



2,2-Dimethyl-propionic acid 4-carbamoyl-7-hydroxymethyl-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-1-yl ester (7)

A flask was charged with racemic nitrile **6** (130 mg, 0.469 mmol), 2:1 ethanol:water (2.4 mL, 0.2M) and the platinum catalyst (40 mg, 0.094 mmol, 20 mol%). The reaction was heated to 80 ºC under a reflux condenser and stirred for 3h. The solution was concentrated in *vacuo* and the crude material was chromatographed with (SiO_2, EtOAc) to furnish the title compound as a white solid (120 mg, 87%). The reaction was also conducted using optically active **6**.

^{1}H NMR: (400 MHz, d_6-DMSO): δ 7.17 (s, 1H), 7.16 (brs, 1H), 6.86 (brs, 1H), 5.80 (d, *J* = 6.5 Hz, 1H), 5.69 (d, *J* = 1.0 Hz, 1H), 4.84 (t, *J* = 5.3 Hz, 1H), 4.06-3.92 (m, 2H), 3.21 (dd, *J* = 14.7, 7.2 Hz, 1H), 2.82 (t, *J* = 7.2 Hz, 1H), 2.69 (dd, *J* =16.2, 8.4 Hz, 1H), 2.04-2.00 (m, 1H), 1.16 (s, 9H).

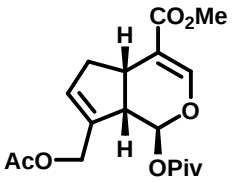
^{13}C NMR: (400 MHz, d_6-DMSO): δ 176.0, 167.7, 145.7, 142.9, 126.8, 115.2, 90.8, 59.0, 44.8, 38.3, 37.8, 33.8, 26.5.

HRMS: Calcd. For $C_{15}H_{22}NO_5$ (M+1): 296.1498, Found: 296.1498

FTIR: (neat): 3377, 3197, 1750, 1667, 1631, 1592, 1195, 1091, 1051, 1017, 985, 953, 829, 736.

MP: 154-155 ºC (decomp.)

$[\alpha]_D^{24}$ = +32.57 (c = 0.645, EtOH).



7-Acetoxymethyl-1-(2,2-dimethyl-propionyloxy)-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-4-carboxylic acid methyl ester (8)

A flame-dried argon flushed flask was charged with amide **7** (50 mg, 0.169 mmol), acetic anhydride (1.11 mL, 0.15 M), and Et_3N (0.047 mL, 0.338 mmol, 200 mol%) and the reaction was stirred for 1 h at 25 °C. The solution was cooled to 0-5 ºC and acetic acid (0.56 mL, 0.3 M) was added. Sodium nitrite (117 mg, 1.69 mmol, 1000 mol%) was added and the reaction was stirred at 0-5 ºC for 16.5 h. The reaction was quenched with water and ran through a column of Dowex®50WX8-200 ion-exchange resin with MeOH. The filtrate was concentrated in *vacuo* to provide the crude acid. The crude acid was dissolved in 1:1 MeOH:$CHCl_3$ (3.38 mL, 0.05 M) and cooled to 0 ºC. A 2.0 M solution of TMS-diazomethane in Et_2O was added in portions, (0.169 mL, 0.338 mmol, 200 mol%), at 15 minute time intervals until the reaction was deemed complete by TLC. The reaction was quenched with acetic acid, concentrated *in vacuo,* and purified by flash column chromatography (SiO_2, 5:1 hexane:Et_2O) to furnish the title compound as a white solid (44 mg, 74%). The reaction was also conducted using optically active **7.**

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 1.0 Hz, 1H), 5.92, (s, 1H), 5.88 (d, *J* = 7.2 Hz, 1H), 4.63 (s, 2H), 3.73 (s, 3H), 3.31-3.25 (m, 1H), 2.93-2.86 (m, 2H), 2.26-2.17 (m, 1H), 2.07 (s, 3H), 1.24 (s 9H).

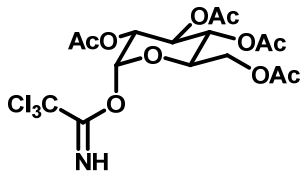
^{13}C NMR: (400 MHz, $CDCl_3$): δ 176.7, 170.6, 167.3, 151.6, 136.5, 132.6, 111.1, 91.7, 61.9, 51.3, 45.1, 38.8, 38.6, 34.7, 26.8, 20.8.

HRMS: Calcd. For $C_{18}H_{23}O_7$ (M-1): 351.1444, Found:351.1439.

FTIR: (neat): 2939, 1751, 1736, 1712, 1634, 1228, 1202, 1124, 1082, 1055, 1030, 970, 958, 765 cm^{-1}.

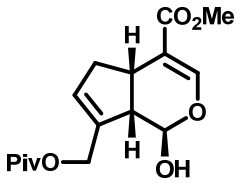
MP: 71-72 °C

$[\alpha]_D^{25}$ = +146.49 (c= 0.164, $CHCl_3$).



(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate

A flame-dried argon flushed flask was charged with tetraacetyl-glucose (200 mg, 0.574 mmol), DCM (5.7 mL, 0.1M), and cesium carbonate (37 mg, 0.115 mmol, 20 mol%) respectively. The reaction was stirred at ambient temperature for 3 h. The reaction was filtered through celite, concentrated in *vacuo*, and purified by flash column chromatography (SiO_2, 3:1 hexane:EtOAc 1% Et_3N) to furnish the title compound as a thick oil (237 mg, 84%). The spectral data for this compound has been previously reported.[5]



7-(2,2-Dimethyl-propionyloxymethyl)-1-hydroxy-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-4-carboxylic acid methyl ester (9)

An oven-dried sealed tube was charged with racemic acetate **8** (40 mg, 0.114 mmol), MeOH (1.14 mL, 0.1 M), and Otera's catalyst (10 mg, 0.011 mmol, 10 mol%) respectively. The reaction vessel was sealed and heated to 70 ºC for 20 h. The reaction vessel was then opened and PhMe (1.14 mL, 0.1 M) was added. The open reaction vessel was then heated to 85 °C for 0.5 h until the methanol fully evaporated from the solution. The reaction was then sealed and heated to 100 °C for an additional 1.5 h. The reaction was directly purified by flash column chromatographed (SiO_2, 5:1 hexane:ethyl acetate) to furnish the title compound as a white solid (25.6 mg, 73%). A similar reaction was also conducted with optically active **8**.

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 1.0 Hz, 1H), 5.92 (d, *J* = 1.0 Hz, 1H), 4.99-4.95 (m, 1H) 4.83-4.76 (m, 2H), 4.67 (d, *J* =13.3 Hz, 1H), 3.72 (s, 3H), 3.22-3.12 (m, 1H), 2.93-2.86 (m, 1H), 2.44 (dt, *J* = 8.0, 2.0 Hz, 1H) 2.09-2.01 (m, 1H), 2.21 (s, 9H).

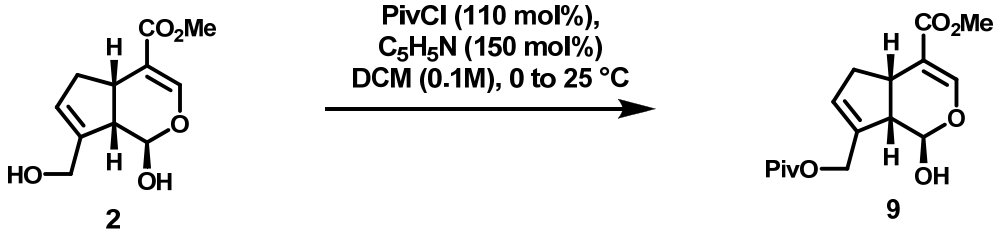
^{13}C NMR: (100 MHz, $CDCl_3$): δ 179.6, 167.8, 152.7, 138.4, 132.2, 110.5, 96.5, 63.2, 51.3, 46.9, 38.9, 38.8, 36.4, 27.1.

HRMS: Calcd. For $C_{16}H_{23}O_6$ (M+1): 311.1495, Found: 311.1493.

FTIR: (neat): 3551, 2966, 1708, 1629, 1284, 1191, 1163, 1142, 1131, 1100, 1085, 947, 928, 888, 832, 764 cm^{-1}.

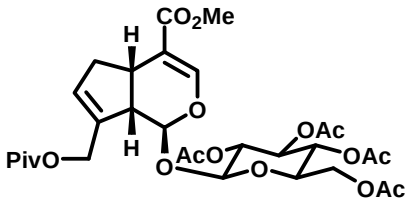
MP: 88-89 ºC

$[\alpha]_D^{25}$ = +80.84 (c= 1.064, $CHCl_3$).



7-(2,2-Dimethyl-propionyloxymethyl)-1-hydroxy-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-4-carboxylic acid methyl ester (9)

A flask was charged with commercially available (+)-genipin **2** (500 mg, 2.210 mmol), DCM (22 mL, 0.1M), and pyridine (0.267 mL, 3.315 mmol, 150 mol%). The reaction was cooled to 0 °C and trimethylacetylchloride (0.299 mL, 2.431 mmol, 110 mol%) was added and the reaction was allowed to warm to room temperature overnight under a balloon of argon. The reaction was diluted with Et_2O washed and then diluted with a saturated aqueous solution of NH_4Cl, a 5% aqueous solution of $CuSO_4$, and brine. The combined organic layers were concentrated *in vacuo*, and purified by flash column chromatographed (SiO_2, 4:1 hexane:ethyl acetate) to furnish the title compound as a white solid (555 mg, 81%)



7-(2,2-Dimethyl-propionyloxymethyl)-1-(3,4,5-triacetoxy-6-acetoxymethyl-tetrahydro-pyran-2-yloxy)-1,4a,5,7a-tetrahydro-cyclopenta[c]pyran-4-carboxylic acid methyl ester (10)

A flame-dried argon flushed flask was charged with the α-*O*-glycosyl-trichloroacetimidate (159 mg, 0.322 mmol 200 mol%), lactol **9** (50 mg, 0.161 mmol 100 mol %), and DCM (0.805 mL, 0.2 M). The solution was cooled to -20 ºC, and freshly distilled boron trifluoride diethyl etherate (0.010 mL, 0.081 mmol, 50 mol %) was added. The reaction was stirred at -20 ºC for 20 hours. The reaction was diluted with EtOAc and washed with saturate of $NaHCO_3$ and then brine. The organic solution was dried over magnesium sulfate, concentrated in *vacuo*, and purified 3 times by flash column chromatography (1^{st} columin: SiO_2, DCM to hexanes to 4:1 hexanes:EtOAc to 2:1 hexanes:EtOAc), (2^{nd} column: SiO_2 2:1 hexanes:EtOAc), (3^{rd} column, 15:1 DCM Et_2O to 9:1 DCM:Et_2O) to furnish the title compound as light yellow film (64.4 mg, 62% yield).

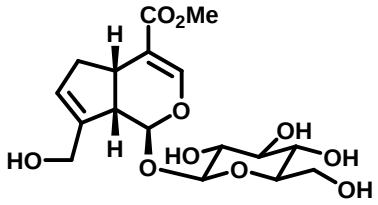
^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 1.2 Hz, 1H), 5.79 (d, *J* = 1.6 Hz, 1H), 5.23 (t, *J* = 9.5 Hz, 1H), 5.19 (d, *J* = 5.3 Hz, 1H), 5.12 (t, *J* = 9.6 Hz, 1H), 5.01 (dd, *J* = 9.7, 8.1 Hz, 1H), 4.86 (d, *J* = 8.0 Hz, 1H), 4.68 (s, 2H), 4.26 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.13, (dd, *J* = 12.4, 2.4 Hz, 1H), 3.74-3.69 (m, 1H), 3.712 (s, 3H), 3.23-3.18 (m, 1H), 2.94-2.91 (m, 1H), 2.84 (dd, *J* = 16.9, 7.9 Hz, 1H), 2.22-2.17 (m, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.21 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 177.9, 170.6, 170.2, 169.3, 169.0, 167.2, 150.8, 136.8, 130.4, 112.1, 96.5, 95.1, 72.4, 72.0, 70.6, 68.0, 61.7, 61.5, 51.2, 46.7, 38.8, 38.3, 33.1, 27.1, 20.6, 20.5, 20.5, 20.3.

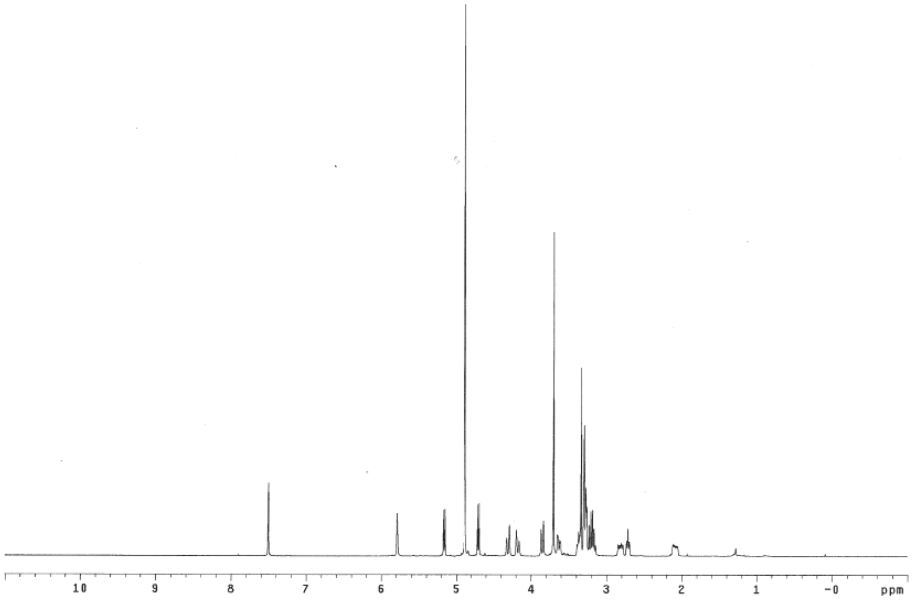
HRMS: Calcd. For$C_{30}H_{41}O_{15}$ (M+1): 641.2445, Found: 641.2446.

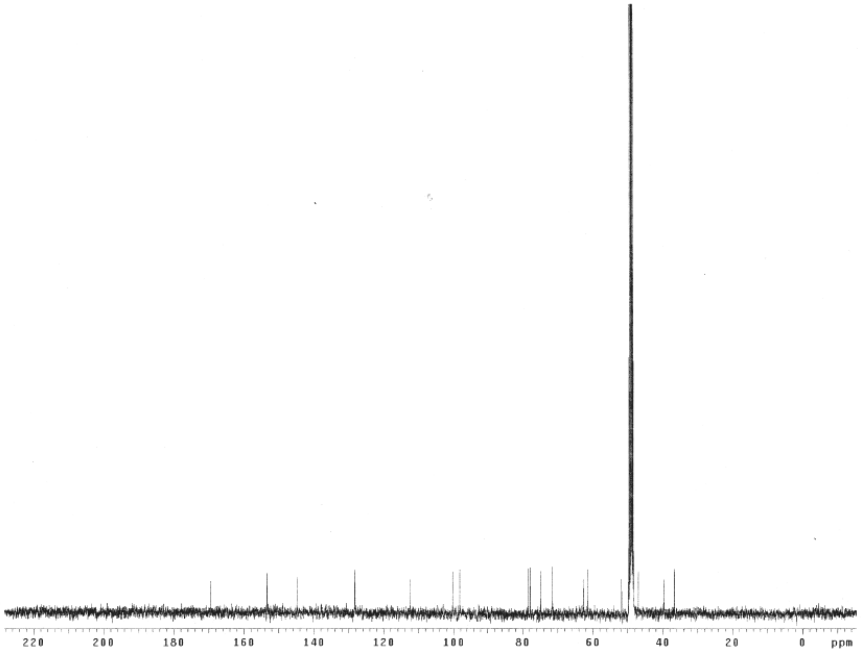
FTIR: (neat): 2958, 1746, 1367, 1278, 1214, 1152, 1077, 1036, 962, 903, 824 cm^{-1}.

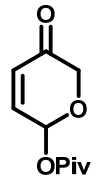
$[\alpha]_D^{25}$ = +25.84 (c= 1.006, $CHCl_3$).


CO2Me
H
H
O
HO
O
HO
O
OH
OH
OH

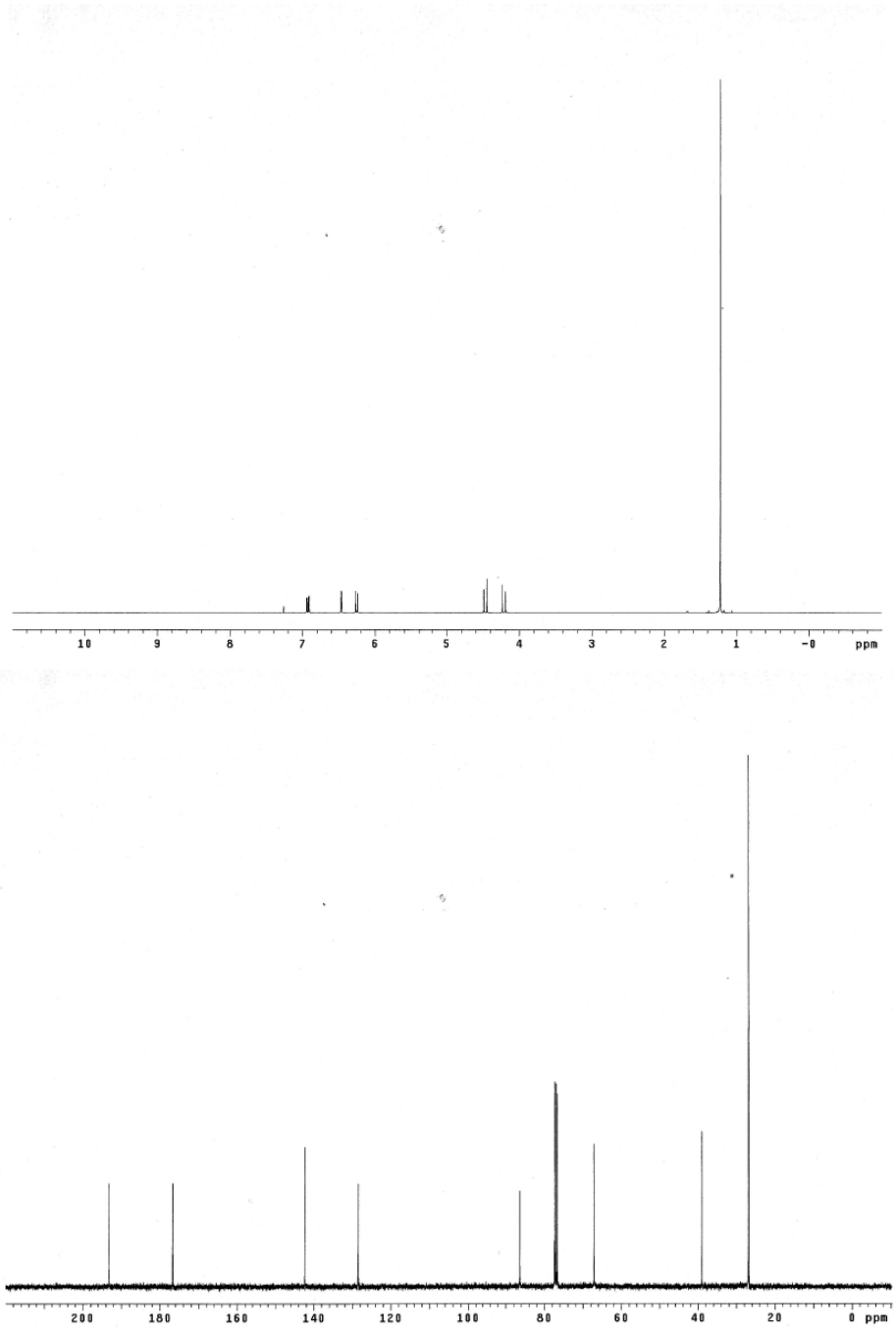
1

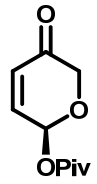

10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
OPiv

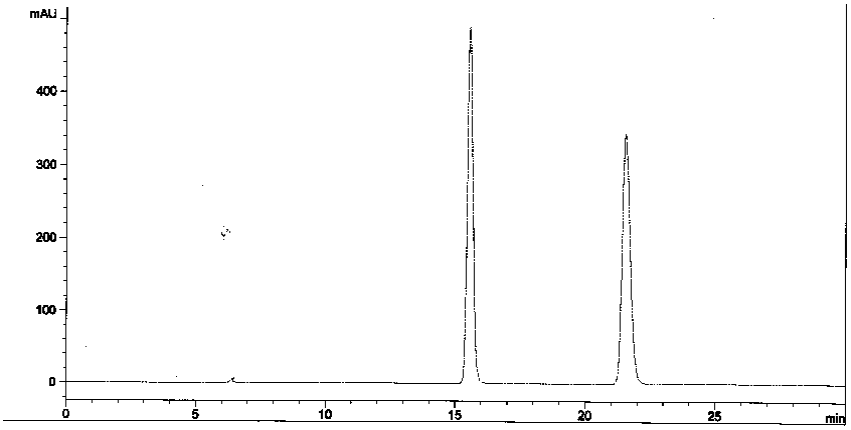
3b


10
9
8
7
6
5
4
3
2
1
-0
ppm
200
180
160
140
120
100
80
60
40
20
0 ppm



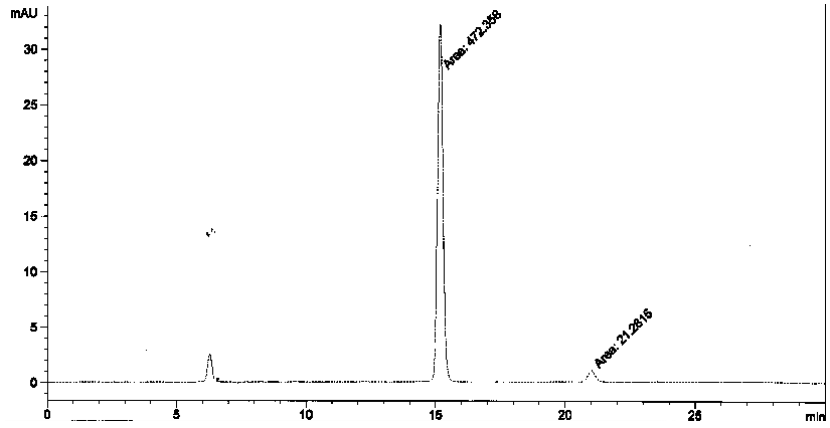
3b

Racemic



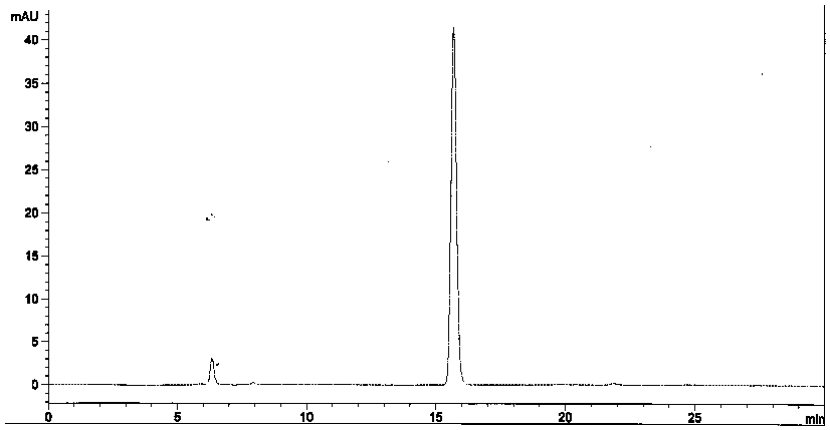
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.561	BB	0.2344	7429.66602	491.28580	49.9111
2	21.551	BB	0.3369	7456.13916	343.92117	50.0889

92% ee

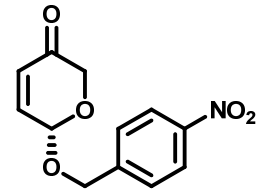


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.172	PM	0.2450	472.35770	32.13675	95.6889
2	21.000	MP	0.3434	21.28151	1.03282	4.3111

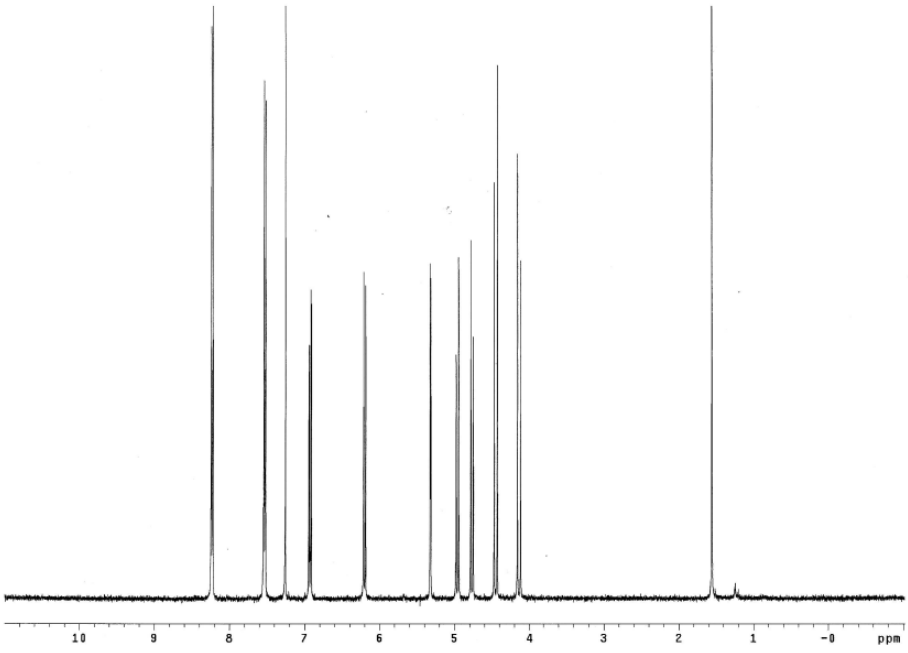
>99%ee

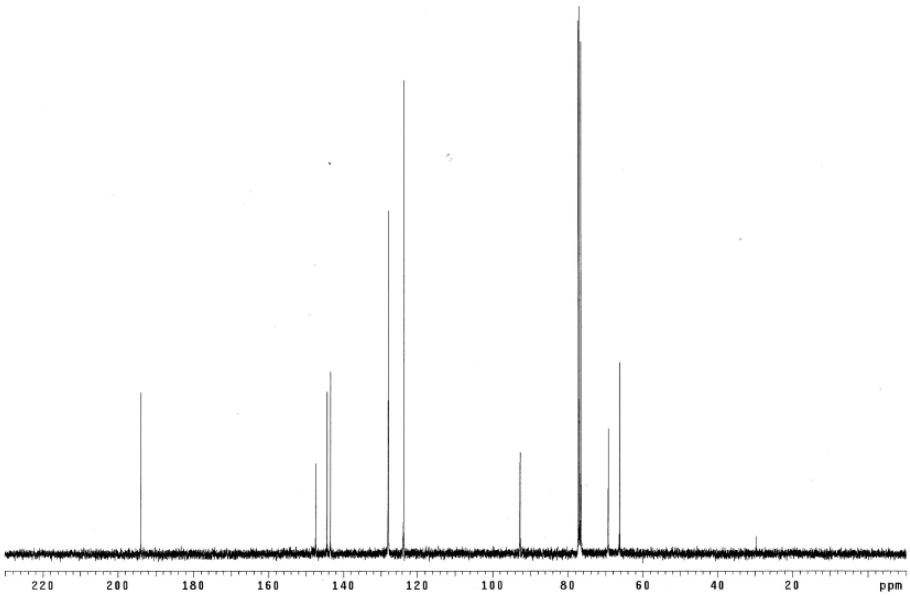


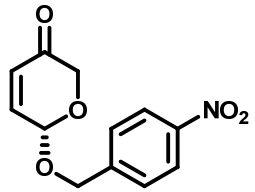
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.682	BB	0.2338	624.43903	41.44597	100.0000


O
O
O
NO2

3c

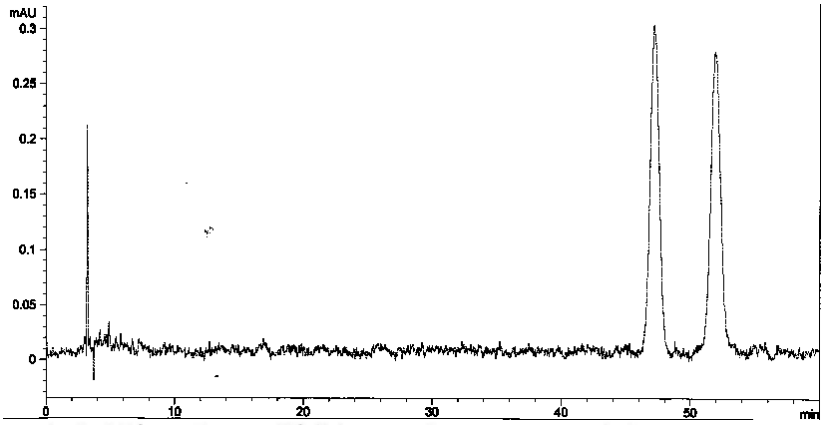

10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
ppm



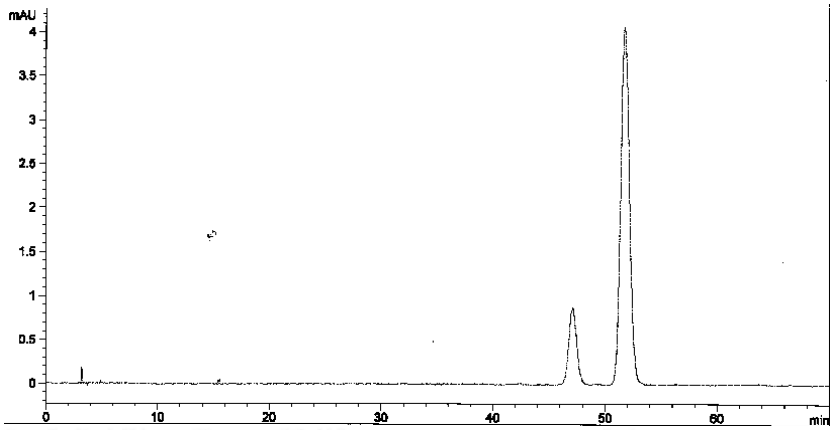
3c

Racemic

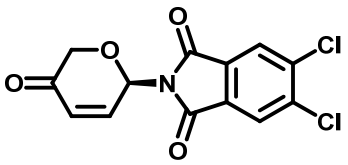


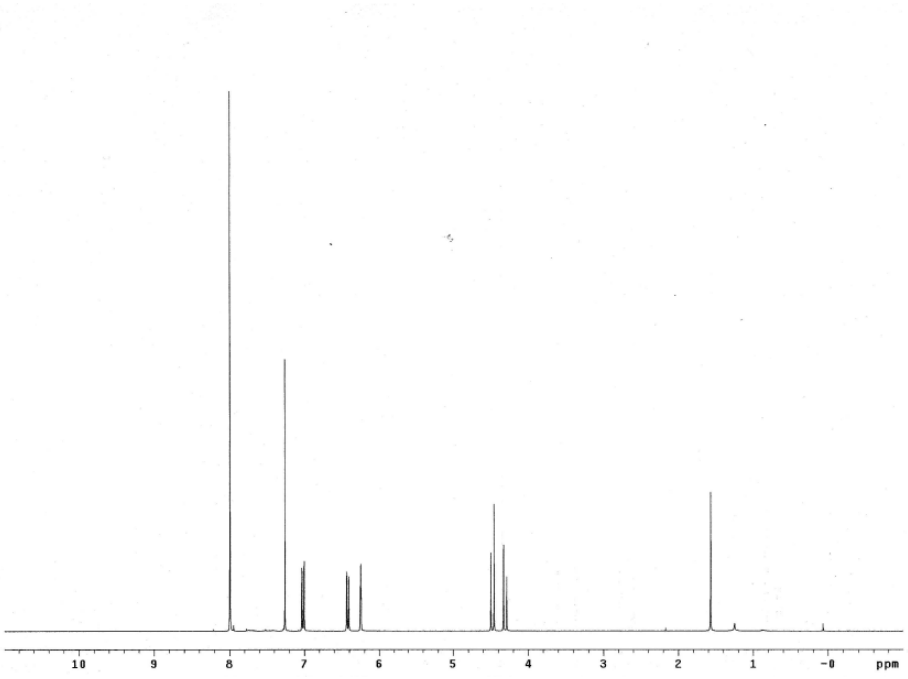
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.207	BB	0.5990	14.24622	2.95238e-1	51.8173
2	51.960	BB	0.5991	13.24696	2.62330e-1	48.1827

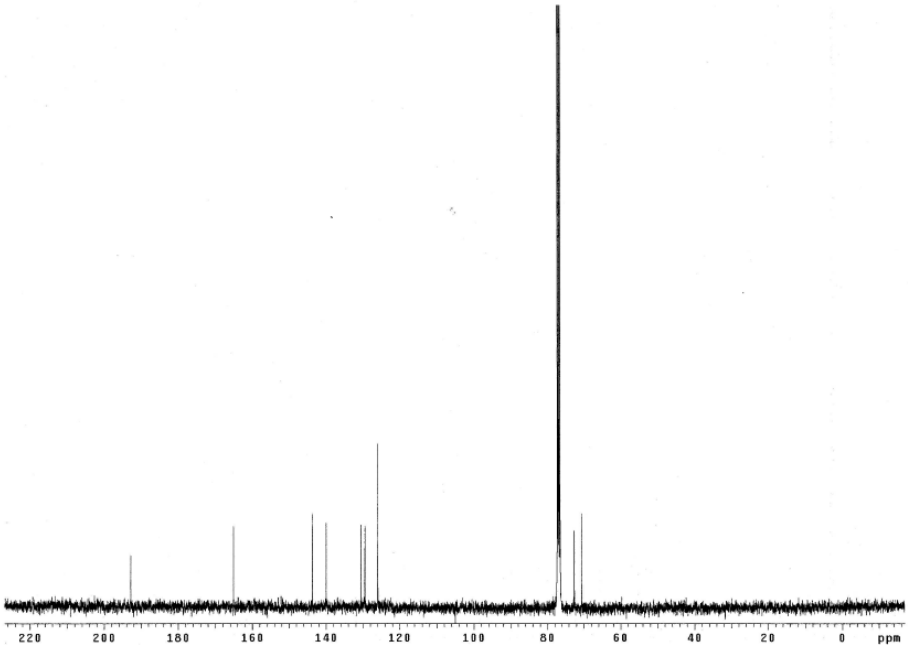
68% ee

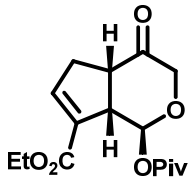


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.111	BB	0.6156	42.25035	8.68399e-1	16.1593
2	51.751	BB	0.7717	219.21112	4.06118	83.8407

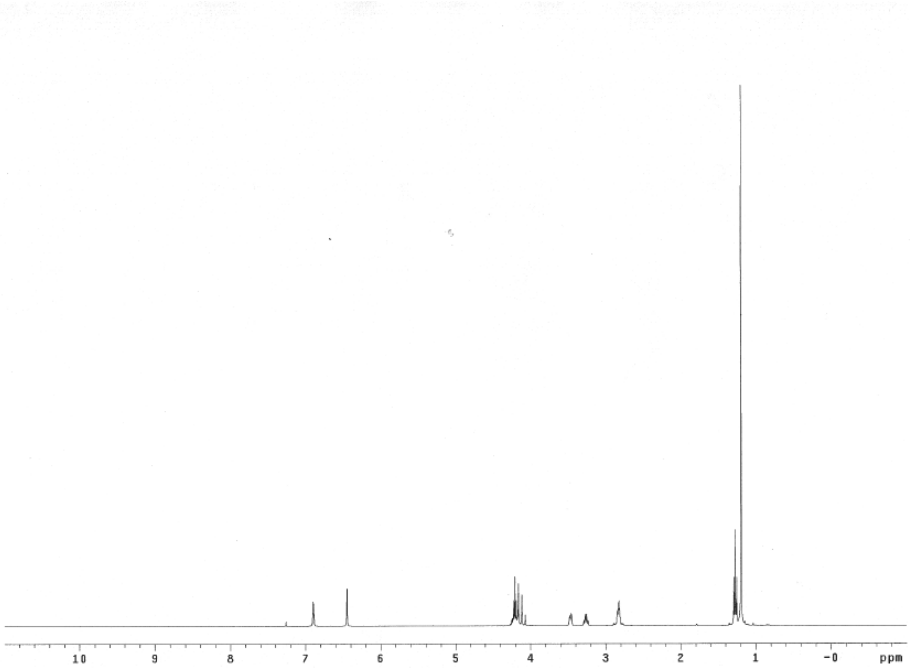

O
O
O
N
O
Cl
Cl

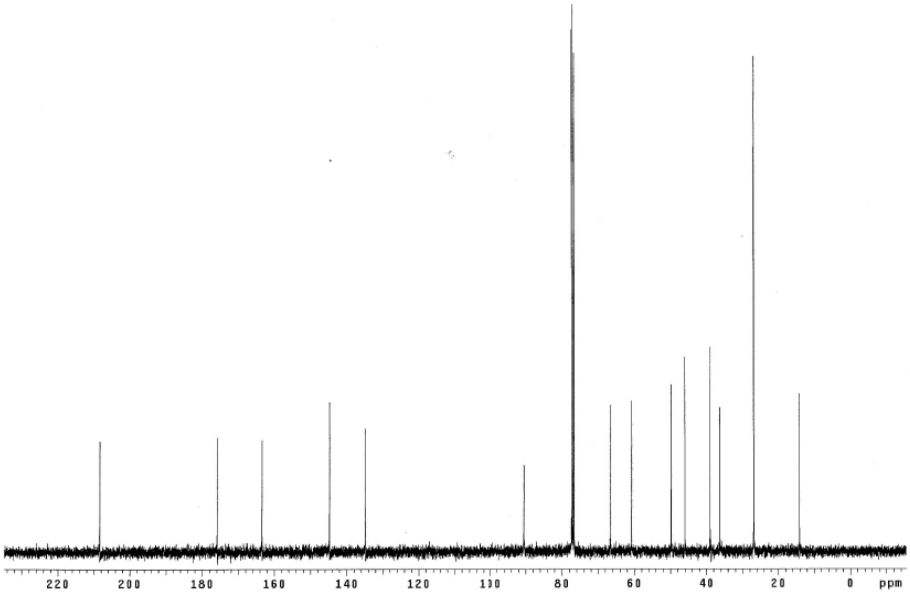

10
9
8
7
6
5
4
3
2
1
-0
ppm

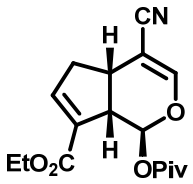

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H
O
H
EtO2C
OPiv

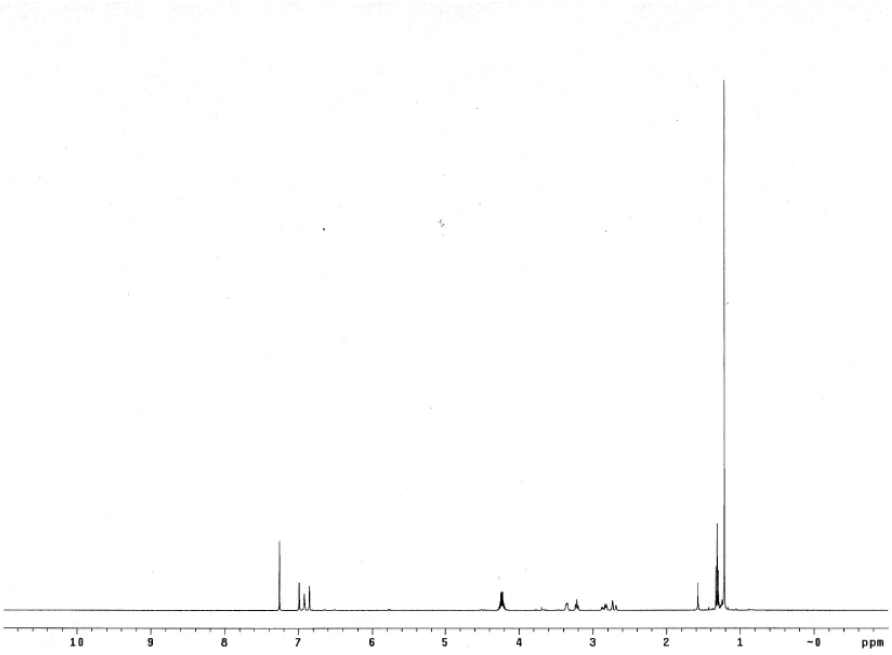
4

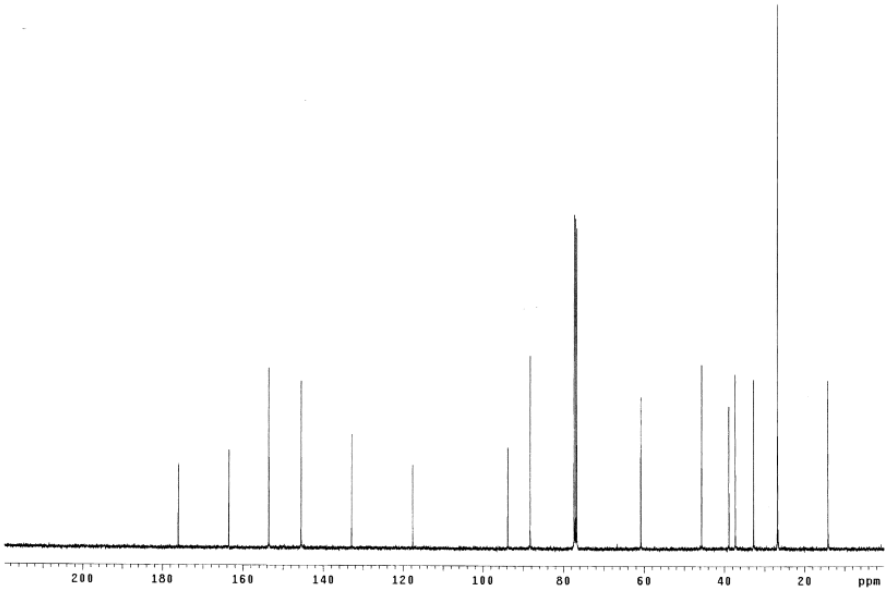

10
9
8
7
6
5
4
3
2
1
-0
ppm

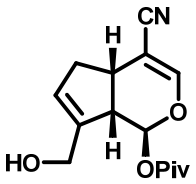

220
200
180
160
140
120
100
80
60
40
20
0
ppm


CN
H
O
H
EtO2C
OPiv

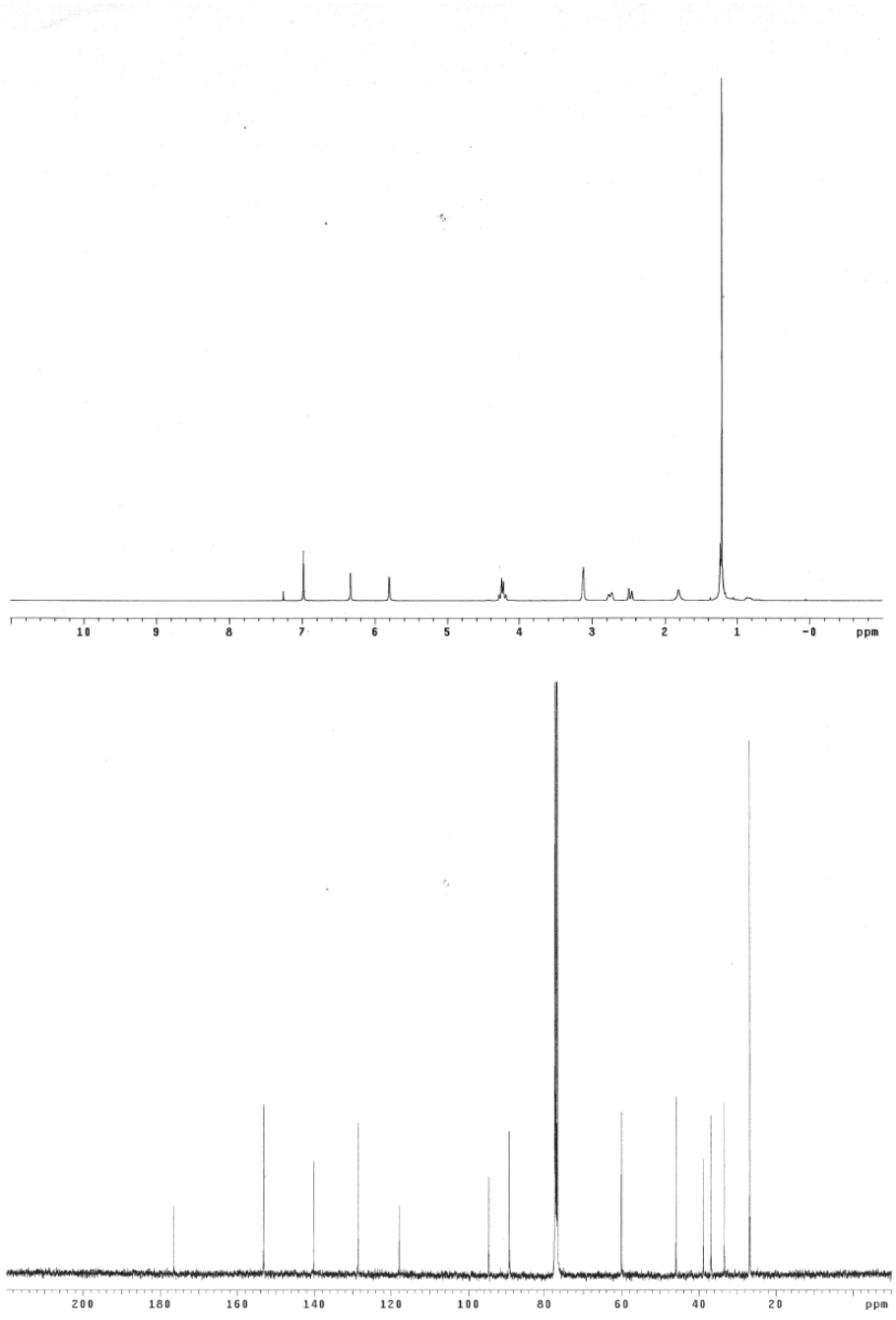
5

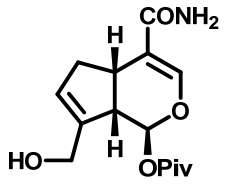

10
9
8
7
6
5
4
3
2
1
-0
ppm


200
180
160
140
120
100
80
60
40
20
ppm

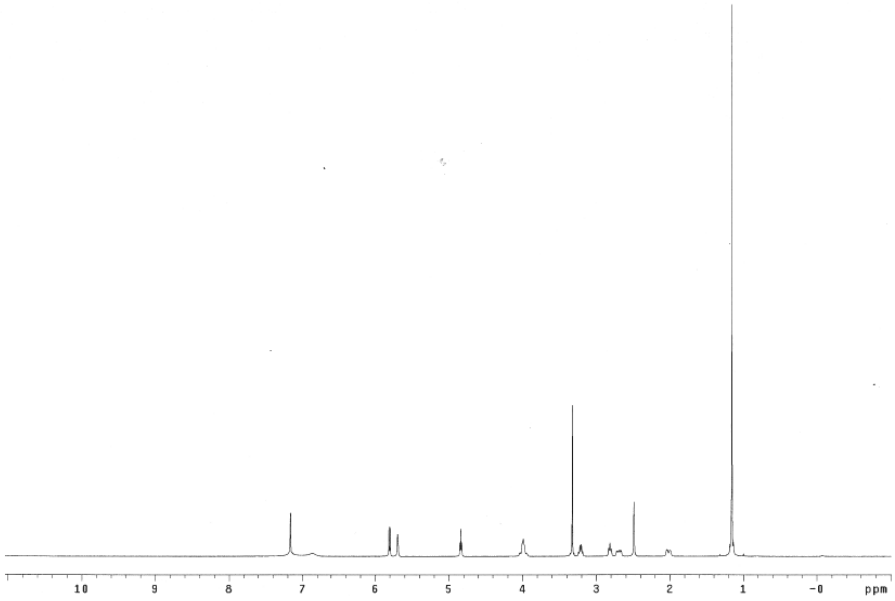

CN
H
O
H
HO
OPiv

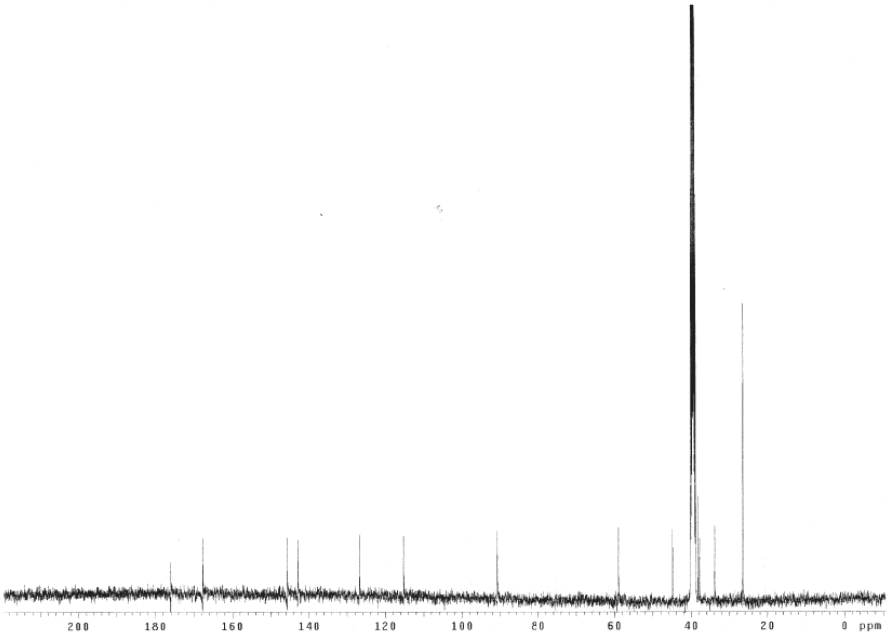
6

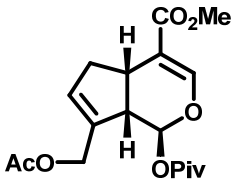

10
9
8
7
6
5
4
3
2
1
-0
ppm
200
180
160
140
120
100
80
60
40
20
ppm


CONH2
H
O
HO
H
OPiv

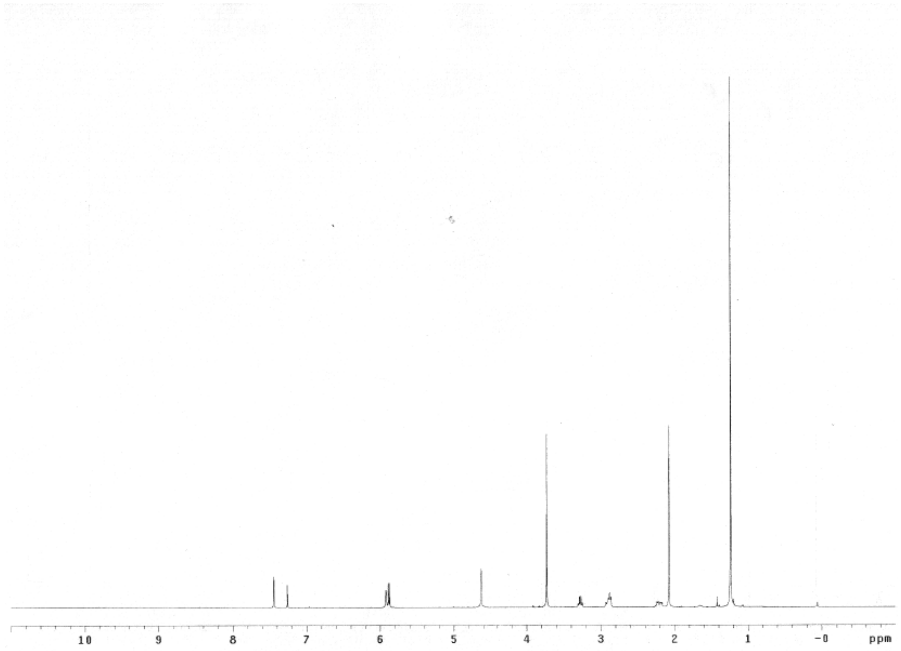
7

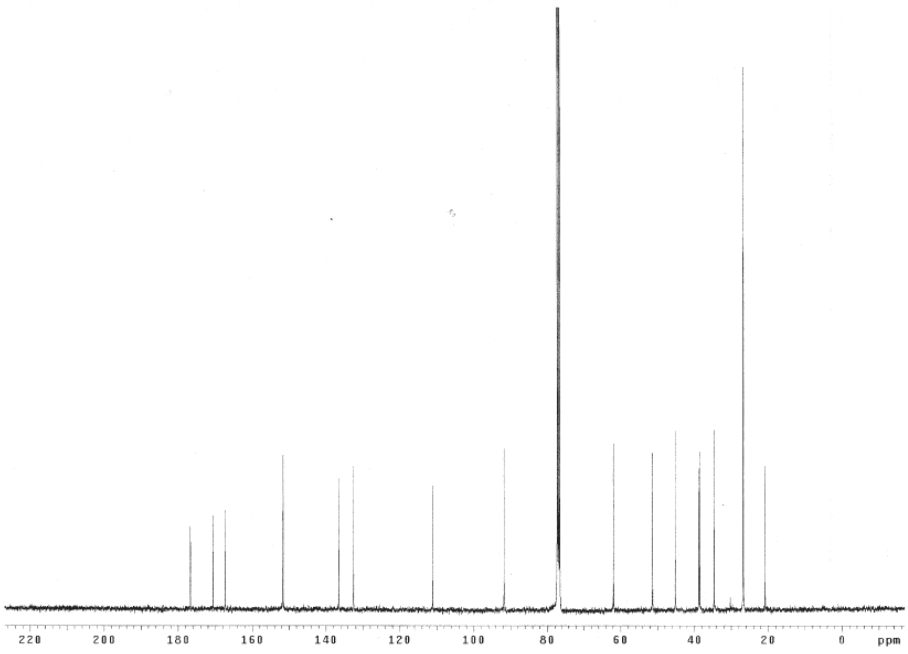

10
9
8
7
6
5
4
3
2
1
-0
ppm

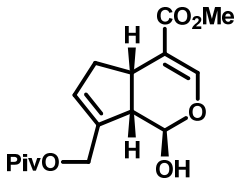

200
180
160
140
120
100
80
60
40
20
0 ppm


CO2Me
H
O
H
AcO
OPiv

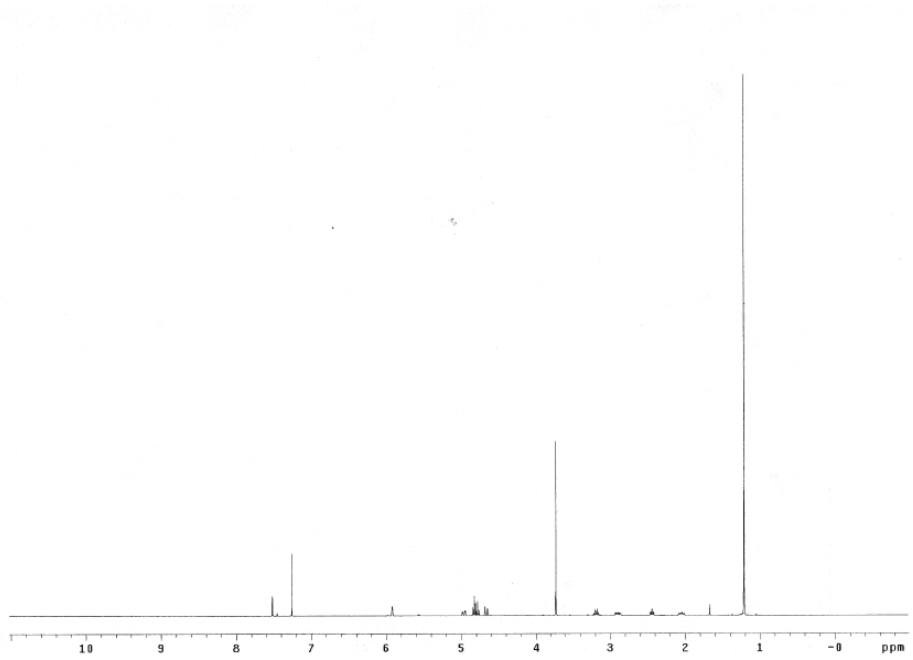
8

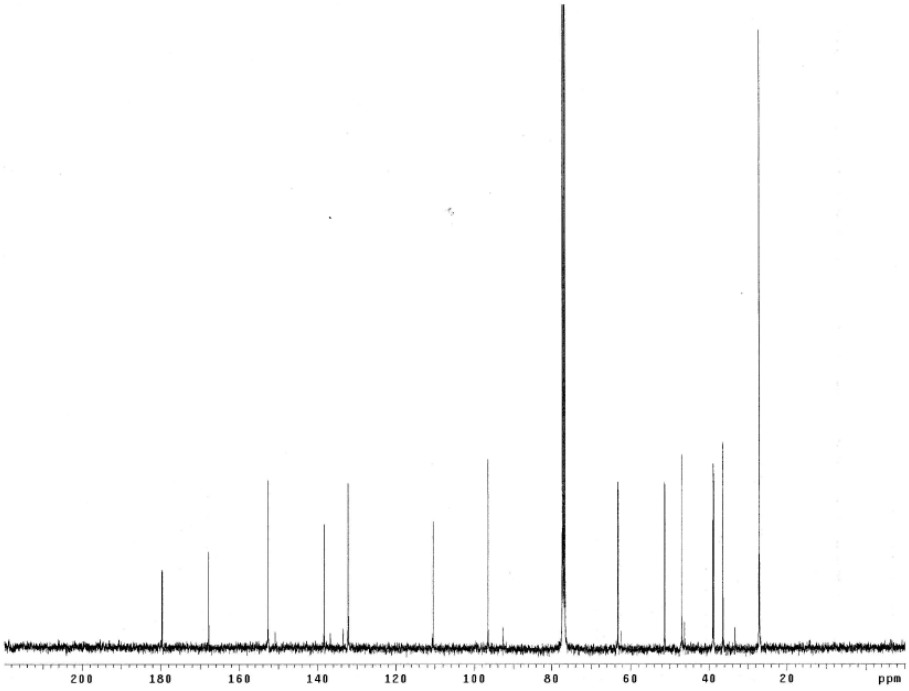

10
9
8
7
6
5
4
3
2
1
-0
ppm

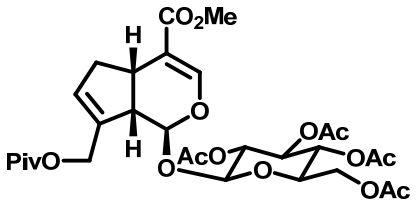

220
200
180
160
140
120
100
80
60
40
20
0
ppm


CO2Me
H
O
H
PivO
OH

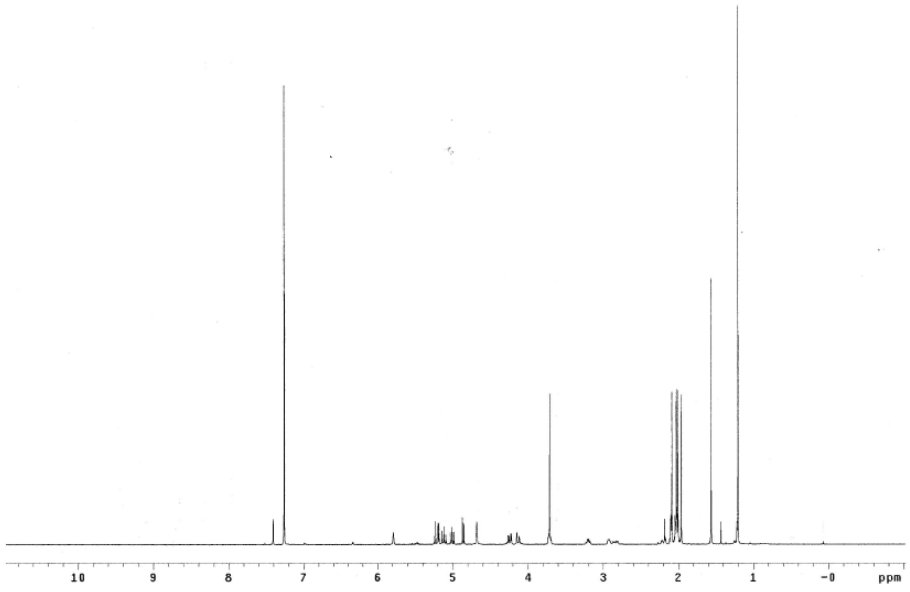
9

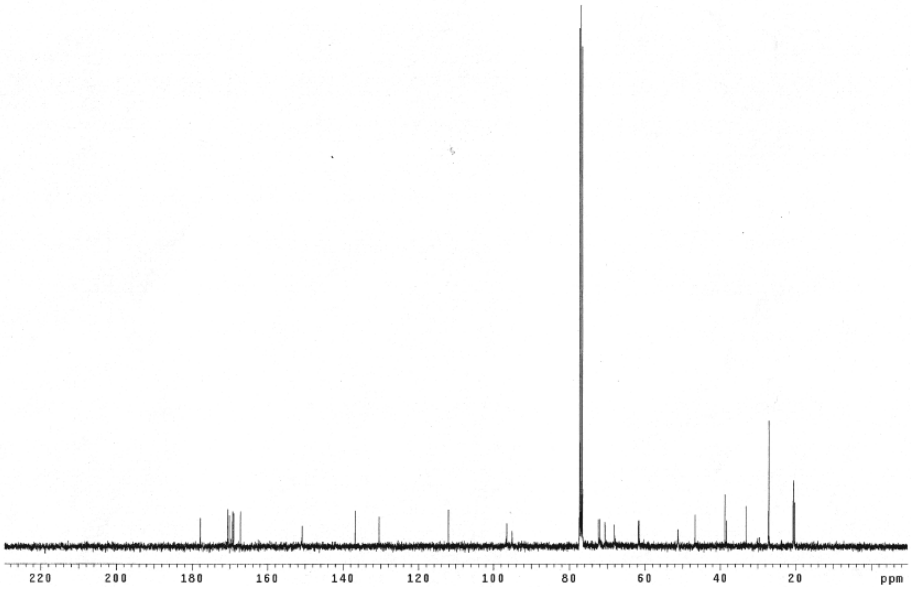

10
9
8
7
6
5
4
3
2
1
-0
ppm


200
180
160
140
120
100
80
60
40
20
ppm


CO2Me
H
H
O
PivO
AcO
O
O
OAc
OAc
OAc

10


10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
ppm

References

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

[2] Güvenalp, Z.; Kili□, N.; Kazaz, C.; Kaya, Y.; Demirezer, Ö. *Turk. J. Chem.* **2006**, *30*, 515.

[3] Morota, T.; Sasaki, H.; Nishimura, H.; Sugama, K.; Chin, M; Mitsuhashi, H. *Phytochemistry*, **1989**, *28*, 2149.

[4] Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B. Oehlerking, H. H. Prahst, G. W. *Tetrahedron*, **1993**, *49*, 8999.

[5] Kværnø, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4653.