

Supporting Information

Regioselectivity switch in chiral amine-catalysed asymmetric addition of aldehydes to reactive enals

Taichi Kano, Hiroki Maruyama, Ryu Sakamoto and Keiji Maruoka*

*Department of Chemistry, Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan*

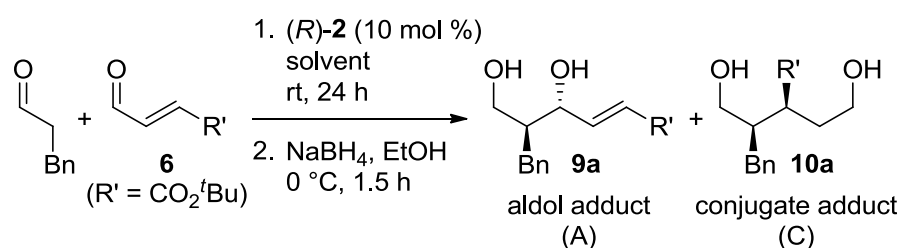
General Information: Infrared (IR) spectra were recorded on a Thermo SCIENTIFIC Nicolet iS5 spectrometer. ¹H NMR spectra were measured on JEOL JNM-FX400 (400 MHz) and JEOL JNM-ECA500 (500 MHz) spectrometers. Chemical shifts were reported in ppm from tetramethylsilane (in the case of CDCl₃) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ¹³C NMR spectra were recorded on JEOL JNM-FX400 (100 MHz) and JEOL JNM-ECA500 (125 MHz) spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel CHIRALPAK OD-3, IA, IA-3, IB-3, IC-3, IE and IF 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used. The products were purified by flash column chromatography on neutral silica gel 60N (Kanto Chemical Co. Inc., 40-50 μm). For purification with preparative thin layer chromatography (PLC), Merck precoated PLC plates (silica gel 60 GF₂₅₄, 0.5 mm) were used. Ethanol, acetonitrile, Dimethyl sulfoxide and aliphatic aldehydes were purchased from Wako Pure Chemical Industries, Ltd. Acetonitrile were stored over molecular sieve 4A. Amine catalysts (*R*)-**1** and (*R*)-**2** were purchased from Sigma-Aldrich Japan, co. Amine catalysts (*R*)-**3** was purchased from Wako Pure Chemical Industries, Ltd. Amine catalysts (*R*)-**4**¹, (*S*)-**5**², were synthesized according to the literature procedures.

Synthesis of *t*-butyl 4-oxo-2-butenate (**6**)

To a stirred solution of *t*-butyl diethylphosphonoacetate (15 mmol) and potassium carbonate (15 mmol) in toluene (45 mL) was added 2,2-dimethoxyacetaldehyde (15 mmol) at room temperature. After stirring for 1.5 h under reflux, the mixture was cooled to room temperature, quenched with H₂O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was roughly purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 20/1). The obtained *t*-butyl 4,4-dimethoxy-2-butenate (8.0 mmol) was dissolved in water (32 ml) and formic acid (16 ml). After stirring for 4 h at 40 °C, the mixture was cooled to room temperature,

quenched with saturated NaHCO₃ aq. and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 20/1) to give *t*-butyl 4-oxo-2-butenoate (**6**) in 53 % yield (2 steps); ¹H NMR (400 MHz, CDCl₃) δ 9.75 (1H, d, *J* = 7.6), 6.89 (1H, dd, *J* = 16.1, 7.8 Hz), 6.65 (1H, d, *J* = 16.2 Hz), 1.53 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 192.7, 164.0, 141.5, 139.6, 82.5, 27.9; IR (neat) 2980, 1717, 1700, 1311, 1256, 1154 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₉H₁₆NaO₄ (methanol adduct): 211.0941 ([M + MeOH + Na]⁺), Found: 211.0937 ([M + MeOH + Na]⁺).

Table S1. Solvent Screening for the Asymmetric Aldol Reaction^a



entry	solvent	yield (%) ^b	A/C ^c	<i>anti/syn</i> ^d	ee (%) ^e
1 ^f	MeCN	12	>20/1	2.5/1	93
2	MeCN	49	>20/1	2.5/1	89
3	CH ₂ Cl ₂	40	>20/1	1.6/1	87
4	THF	56	>20/1	3.0/1	85
5	dioxane	31	>20/1	3.5/1	89
6	MeOH	34	>20/1	2.9/1	74
7	DMSO	28	>20/1	6.2/1	96
8 ^g	DMSO	76	>20/1	7.3/1	97

^aThe reaction of 3-phenylpropanal (0.1 mmol) with **6** (0.3 mmol) was carried out in the presence of **(R)-2** (0.01 mmol) in a solvent (0.1 mL) at room temperature for 24 h. ^bIsolated yield. ^cDetermined by ¹H-NMR.

^dThe diastereoselectivity of **9a** was determined by ¹H-NMR. ^eThe enantioselectivity of *anti-9a* was determined by HPLC using chiral column. ^fPerformed at 0 °C for 6 days. ^gUse of 5 equiv of H₂O as additive.

General Procedure for the Asymmetric Aldol Reaction

To a stirred solution of catalyst **(R)-2** (0.01 mmol) and water (0.5 mmol) in dimethyl sulfoxide (100 μL) were added an aliphatic aldehyde (0.1 mmol) and **6** (0.3 mmol) at room temperature. The mixture was stirred for 24 h. To the reaction mixture were then added EtOH (1.0 mL) and NaBH₄ (15 mg, 0.4 mmol) at 0 °C. After 30 min of stirring at 0 °C, the reaction mixture was quenched with 1N HCl aq. and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel to afford the corresponding aldol product. All products showed a single spot on TLC and were obtained as a diastereomeric mixture.

t-Butyl (4*R*,5*S*,2*E*)-5-benzyl-4,6-dihydroxy-2-hexenoate (Table 2, entry 2)

¹H NMR (400 MHz, CDCl₃) δ 7.32-7.20 (5H, m), 6.90 (1H, dd, *J* = 15.9, 4.6 Hz), 6.05 (1H, dd, *J* = 15.8, 1.8 Hz), 4.39 (1H, app s), 3.88 (1H, app d, *J* = 10.7 Hz), 3.62 (1H, app d, *J* = 10.8 Hz), 2.94 (1H, dd, *J* = 13.9, 7.3 Hz), 2.93 (1H, br), 2.83 (1H, dd, *J* = 13.9, 8.5 Hz), 2.02 (1H, br), 1.94 (1H, m), 1.51 (9H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 148.2, 139.7, 129.1, 128.5, 126.3, 123.2, 80.6, 73.7, 62.9, 46.0, 34.6, 28.1; IR (neat) 3373, 2961, 1723, 1367, 1149, 1050 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₇H₂₄NaO₄: 315.1567 ([M + Na]⁺), Found: 315.1573([M + Na]⁺); Daicel Chiralpak IB-3, hexane/ethanol = 20/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 17.3 min (major) and 18.3 min.

***t*-Butyl (4*R*,5*S*,2*E*)-4,6-dihydroxy-5-methyl-2-hexenoate (Table 2, entry 3)**

¹H NMR (400 MHz, CDCl₃) δ 6.86 (1H, dd, 15.6, 5.6 Hz), 5.99 (1H, dd, *J* = 15.9, 1.5 Hz), 4.24-4.21 (1H, m, HOCH), 3.80 (1H, dd, *J* = 11.0, 3.7 Hz), 3.64 (1H, dd, *J* = 11.0, 6.8 Hz), 3.41 (1H, br), 2.78 (1H, br), 1.90-1.80 (1H, m), 1.49 (9H, s), 0.96 (3H, d, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 147.4, 123.3, 80.6, 76.1, 66.8, 39.9, 28.1, 13.5; IR (neat) 3366, 2977, 1693, 1311, 1150 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₁H₂₀NaO₄: 239.1254 ([M + Na]⁺), Found: 239.1251 ([M + Na]⁺); Daicel Chiralpak IF, hexane/ethanol = 20/1, flow rate 0.75 mL/min, λ = 206 nm, retention time: 36.8 min (major) and 52.0 min.

***t*-Butyl (4*R*,5*S*,2*E*)-4-hydroxy-5-(hydroxymethyl)-2,7-octadienoate (Table 2, entry 4)**

¹H NMR (400 MHz, CDCl₃) δ 6.89 (1H, dd, *J* = 15.9, 4.9 Hz), 6.05 (1H, dd, *J* = 15.9, 1.7 Hz), 5.86-5.78 (2H, m), 5.15-5.07 (2H, m), 4.41 (1H, app d, *J* = 3.9 Hz), 3.90 (1H, app d, *J* = 11.0 Hz), 3.70 (1H, d, *J* = 6.4 Hz), 2.92 (1H, app d, *J* = 4.9 Hz), 2.38-2.21 (2H, m), 2.13 (1H, br), 1.78-1.71 (1H, m), 1.49 (9H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 147.9, 136.0, 123.3, 117.3, 80.6, 63.5, 44.1, 32.8, 28.1; IR (neat) 3400, 2978, 1694, 1314, 1153 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₃H₂₂NaO₄: 265.1410 ([M + Na]⁺), Found: 265.1410 ([M + Na]⁺); Daicel Chiralpak IF-OD-3 (connected two columns), hexane/2-propanol = 20/1, flow rate 0.75 mL/min, λ = 208 nm, retention time: 39.9 min (major) and 42.2 min.

***t*-Butyl (4*R*,5*S*,2*E*)-4-hydroxy-5-(hydroxymethyl)-6-methyl-2-heptenoate (Table 2, entry 5)**

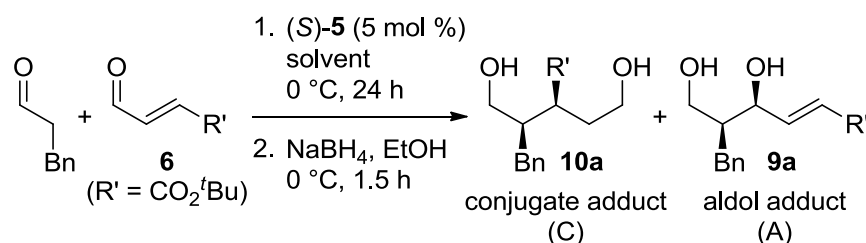
¹H NMR (400 MHz, CDCl₃) δ 6.89 (1H, dd, 15.8, 4.8 Hz), 6.07 (1H, dd, *J* = 15.9, 1.7 Hz), 4.58 (1H, app s), 3.91-3.85 (2H, m), 3.19 (1H, br), 2.31 (1H, br), 2.10-2.02 (1H, m), 1.49 (9H, s), 1.33-1.29 (1H, m), 1.05 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 165.8, 149.0, 122.8, 80.5, 73.4, 61.8, 50.2, 28.1, 25.5, 21.2, 19.7; IR (neat) 3391, 2966, 1712, 1518, 1280, 1152 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₃H₂₄NaO₄: 267.1567 ([M + Na]⁺), Found: 267.1560 ([M + Na]⁺); Daicel Chiralpak IC-3, hexane/2-propanol = 10/1, flow rate 0.6 mL/min, λ = 208 nm, retention time: 31.3 min (major) and 33.0 min.

***t*-Butyl (4*R*,5*S*,*E*)-5-(((benzyloxy)carbonyl)amino)-4,6-dihydroxy-2-hexenoate (Table 2, entry 6)**

¹H NMR (400 MHz, CDCl₃) δ 7.37-7.30 (5H, m), 6.88 (1H, dd, *J* = 15.7, 4.0 Hz), 6.10 (1H, dd, *J* = 15.7, 1.3 Hz), 5.64 (1H, br), 5.12 (2H, s), 4.60 (1H, br), 3.93 (1H, d, *J* = 8.8 Hz), 3.77-3.74 (2H, m), 3.08 (1H, br), 2.35 (1H, br), 1.49 (9H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.5, 156.5, 145.0, 136.1, 128.6, 128.3, 128.1,

124.1, 80.9, 73.3, 67.1, 62.3, 54.9, 28.1; IR (neat) 3391, 2977, 1694, 1530, 1255, 1152, 1055 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{18}\text{H}_{25}\text{NNaO}_6$: 374.1574 ($[\text{M} + \text{Na}]^+$), Found: 374.1573 ($[\text{M} + \text{Na}]^+$); Daicel Chiralpak IB-3, hexane/ethanol = 20/1, flow rate 0.75 mL/min, $\lambda = 206$ nm, retention time: 35.6 min (major) and 40.9 min.

Table S2. Solvent Screening for the Asymmetric Conjugate Addition^a



entry	solvent	yield (%) ^b	C/A ^c	<i>syn/anti</i> ^d	ee (%) ^e
1	toluene	65	2.1/1	5.0/1	96
2	CH_2Cl_2	46	3.1/1	3.2/1	95
3	THF	44	2.6/1	5.7/1	97
4	DMF	19	>20/1	12/1	96
5	MeCN	62	6.6/1	16/1	98
6 ^f	MeCN	68	8.2/1	14/1	97
7 ^{f,g}	MeCN	79	8.6/1	15/1	97

^aThe reaction of 3-phenylpropanal (0.1 mmol) with **6** (0.3 mmol) was carried out in the presence of (*S*)-**5** (0.005 mmol) and H_2O (0.5 mmol) in a solvent (0.1 mL) at 0 °C for 24 h. ^bIsolated yield. ^cDetermined by $^1\text{H-NMR}$. ^dThe diastereoselectivity of **10a** was determined by $^1\text{H-NMR}$. ^eThe enantioselectivity of *syn*-**10a** was determined by HPLC using chiral column. ^fUse of 5 equiv of H_2O as additive. ^gPerformed for 36 h.

General Procedure for the Asymmetric Conjugate Addition

To a stirred solution of catalyst (*S*)-**5** (0.005 mmol) and water (0.5 mmol) in acetonitrile (100 μL) were added an aliphatic aldehyde (0.1 mmol) and **6** (0.3 mmol) at 0 °C. The mixture was stirred for 36 h. To the reaction mixture were then added EtOH (1.0 mL) and NaBH_4 (15 mg, 0.4 mmol) at 0 °C. After 30 min of stirring at 0 °C, the reaction mixture was quenched with 1N HCl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to afford the corresponding conjugate adduct. All products showed a single spot on TLC and were obtained as a diastereomeric mixture.

t-Butyl (2*S*,3*R*)-3-benzyl-4-hydroxy-2-(2-hydroxyethyl)butanoate (Table 3, entry 3)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.31-7.27 (2H, m), 7.22-7.18 (3H, m), 3.73-3.51 (4H, m), 2.73-2.65 (2H, m), 2.58 (1H, dd, $J = 13.9, 10.0$ Hz), 2.17-2.12 (1H, m), 2.04-1.94 (2H, m), 1.85-1.77 (2H, m), 1.50 (9H, s); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 175.2, 140.1, 129.0, 128.5, 126.2, 81.2, 62.1, 61.4, 44.8, 44.2, 35.0, 31.9, 28.1; IR (neat) 3367, 2932, 1720, 1703, 1367, 1149, 1052 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{17}\text{H}_{26}\text{NaO}_4$:

317.1723 ($[M + Na]^+$), Found: 317.1728 ($[M + Na]^+$); Daicel Chiralpak IE, hexane/ethanol = 30/1, flow rate 1.0 mL/min, $\lambda = 209$ nm, retention time: 31.8 min and 36.4 min (major).

***t*-Butyl (2*S*,3*R*)-4-hydroxy-2-(2-hydroxyethyl)-3-methylbutanoate (Table 3, entry 4)**

1H NMR (400 MHz, $CDCl_3$) δ 3.71-3.63 (2H, m), 3.60-3.57 (2H, m), 2.61-2.56 (1H, m), 2.04-1.93 (2H, m), 1.73-1.65 (1H, m), 1.47 (9H, s), 0.93 (3H, d, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 81.1, 65.9, 61.3, 44.8, 38.0, 32.4, 28.1, 13.8; IR (neat) 3365, 2968, 1723, 1705, 1368, 1153, 1044 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NaO_4$: 241.1410 ($[M + Na]^+$), Found: 241.1409 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA-3, hexane/ethyl acetate = 7/3, flow rate 0.75 mL/min, $\lambda = 252$ nm, retention time: 30.5 min and 31.8 min (major).

***t*-Butyl (2*S*,3*R*)-2-(2-hydroxyethyl)-3-(hydroxymethyl)heptanoate (Table 3, entry 5)**

1H NMR (400 MHz, $CDCl_3$) δ 3.74-3.57 (4H, m), 2.65-2.60 (1H, m), 2.01-1.93 (2H, m), 1.87 (2H, br d, $J = 14.9$ Hz, water overlapped) 1.73-1.63 (1H, m), 1.47 (9H, s), 1.35-1.24 (6H, m), 0.90 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 81.1, 63.3, 61.4, 44.3, 42.8, 31.7, 29.7, 28.3, 28.1, 22.8, 14.0; IR (neat) 3365, 2931, 1723, 1367, 1152, 1051 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{14}H_{28}NaO_4$: 283.1880 ($[M + Na]^+$), Found: 283.1884 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA-IF (connected two columns), ethylacetate/hexane = 3/7, flow rate 1.0 mL/min, $\lambda = 251$ nm, retention time: 22.1 min and 24.9 min (major).

***t*-Butyl (2*S*,3*R*)-2-(2-hydroxyethyl)-3-(hydroxymethyl)hex-5-enoate (Table 3, entry 6)**

$[\alpha]_D^{24} = 10.7$ (c 0.79, $CHCl_3$; 94% ee); 1H NMR (400 MHz, $CDCl_3$) δ 5.85-5.75 (1H, m), 5.10-5.04 (2H, m), 3.73-3.60 (4H, m), 2.67-2.62 (1H, m), 2.17-2.03 (2H, m), 1.96-1.90 (4H, m), 1.77-1.70 (1H, m), 1.47 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 136.6, 116.8, 81.2, 62.8, 61.2, 43.9, 42.5, 33.5, 31.7, 28.1; IR (neat) 3362, 2931, 1722, 1703, 1367, 1151, 1050 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{13}H_{24}NaO_4$: 267.1567 ($[M + Na]^+$), Found: 267.1558 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA3, hexane/ethanol/ethylacetate = 4/0.15/1, flow rate 1.0 mL/min, $\lambda = 250$ nm, retention time: 24.1 min and 27.9 min (major).

***t*-Butyl (2*S*,3*R*)-2-(2-hydroxyethyl)-3-(hydroxymethyl)-4-methylpentanoate (Table 3, entry 7)**

$[\alpha]_D^{27} = 18.8$ (c 0.31, $CHCl_3$; 95% ee); 1H NMR (400 MHz, $CDCl_3$) δ 3.76-3.62 (4H, m), 2.71-2.66 (1H, m), 2.08 (2H, br), 2.02-1.93 (1H, m), 1.83-1.68 (3H, m), 1.46 (9H, s), 0.98 (3H, d, $J = 6.6$ Hz), 0.95 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 81.0, 61.6, 61.4, 48.5, 43.6, 31.3, 28.2, 28.0, 21.6, 19.5; IR (neat) 3373, 2961, 1723, 1367, 1149, 1050 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{13}H_{26}NaO_4$: 269.1723 ($[M + Na]^+$), Found: 269.1717 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA-3, hexane/ethyl acetate = 7/3, flow rate

0.75 mL/min, $\lambda = 251$ nm, retention time: 17.7 min and 20.9 min(major).

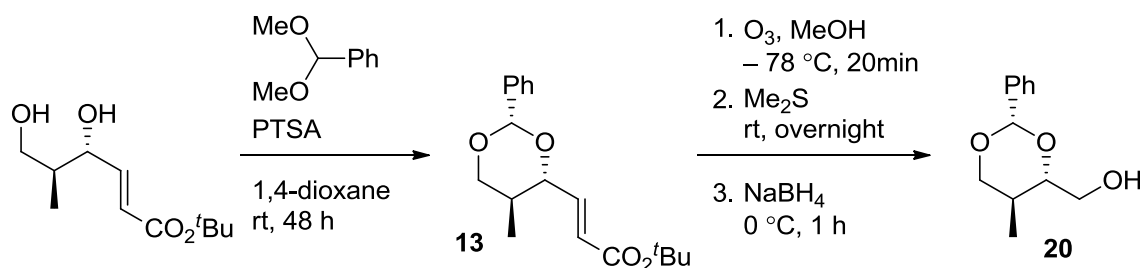
(2S,3R,4E)-2-Methyl-5-(4-nitrophenyl)pent-4-ene-1,3-diol (11)

^1H NMR (400 MHz, CDCl_3) δ 8.19 (2H, d, $J = 9.0$ Hz), 7.52 (2H, d, $J = 8.8$ Hz), 6.71 (1H, d, $J = 16.4$ Hz), 6.45 (1H, dd, $J = 16.1, 6.6$ Hz), 4.30 (1H, app t, $J = 7.1$ Hz), 3.86 (1H, app d, $J = 10.6$ Hz), 3.72 (1H, app t, $J = 8.9$ Hz), 2.97 (1H, br), 2.31 (1H, br), 1.97-1.90 (1H, m), 0.96 (3H, d, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 147.1, 143.1, 136.0, 129.1, 127.0, 124.0, 77.8, 67.3, 40.4, 13.6; IR (neat) 3359, 2926, 2360, 1515, 1343 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{12}\text{H}_{15}\text{NNaO}_4$: 260.0893 ($[\text{M} + \text{Na}]^+$), Found: 260.0889 ($[\text{M} + \text{Na}]^+$); Daicel Chiralpak IF, hexane/ethanol = 10/1, flow rate 1.0 mL/min, $\lambda = 305$ nm, retention time: 47.2 min and 50.4 min (major).

(2R,3S)-2-Benzyl-3-(4-nitrophenyl)pentane-1,5-diol (12)

^1H NMR (400 MHz, CDCl_3) δ 8.21 (2H, d, $J = 8.8$ Hz), 7.43 (2H, d, $J = 8.8$ Hz), 7.24-7.22 (2H, m), 7.19-7.16 (1H, m), 7.05-7.03 (2H, m), 3.76-3.72 (1H, m), 3.61-3.56 (1H, m), 3.46-3.39 (2H, m), 3.26-3.21 (1H, m), 2.50 (1H, dd, $J = 13.9, 4.2$ Hz), 2.36 (1H, dd, $J = 13.9, 10.8$ Hz), 2.29-2.20 (1H, m), 2.10-2.02 (1H, m), 1.99-1.91 (1H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 151.4, 146.7, 140.2, 129.4, 128.9, 128.5, 126.2, 123.7, 60.8, 60.7, 47.6, 42.5, 35.3, 35.0; IR (neat) 3345, 2928, 1515, 1345, 1050 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{18}\text{H}_{21}\text{NNaO}_4$: 338.1363 ($[\text{M} + \text{Na}]^+$), Found: 338.1363 ($[\text{M} + \text{Na}]^+$); Daicel Chiralpak IA, hexane/ethanol = 5/1, flow rate 1.0 mL/min, $\lambda = 273$ nm, retention time: 9.4min (major) and 22.7 min.

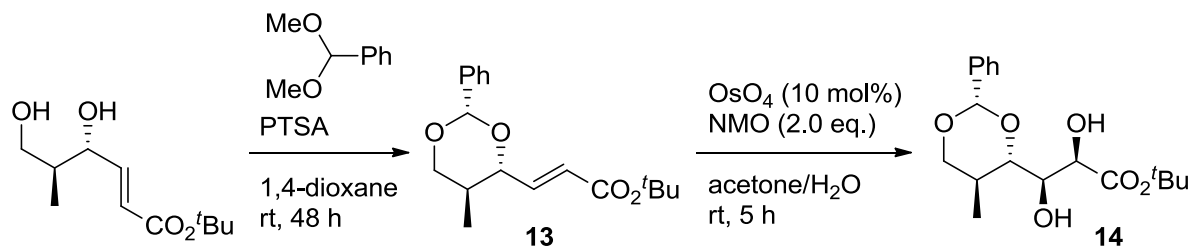
Determination of Relative and Absolute Configuration of the Aldol Product



To a stirred solution of *t*-butyl (4*R*,5*S*,2*E*)-4,6-dihydroxy-5-methyl-2-hexenoate (11.4mg, 0.52 mmol) and PTSA (4.9 mg, 0.025 mmol) in dioxane (2.5 mL) was added benzaldehyde dimethyl acetal (0.155 mL, 1.0 mmol) at room temperature. After stirring for 48 h, the reaction mixture was quenched with saturated NaHCO_3 aq. and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was roughly purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 10/1) to give *t*-butyl 3-(5-methyl-2-phenyl-1,3-dioxan-4-yl)acrylate (**13**) in 91 % yield (137 mg, 0.47 mmol). To a precooled solution of **13** (34.2 mg, 0.12 mmol) in MeOH (6 mL) at -78 °C, ozone was bubbled for 20 minutes. Methyl sulfide was then added to the reaction mixture. After stirring at room temperature overnight, the reaction mixture was cooled to 0 °C, and added an excess amount of NaBH_4 . After stirring for 1 h at 0 °C, the mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate =

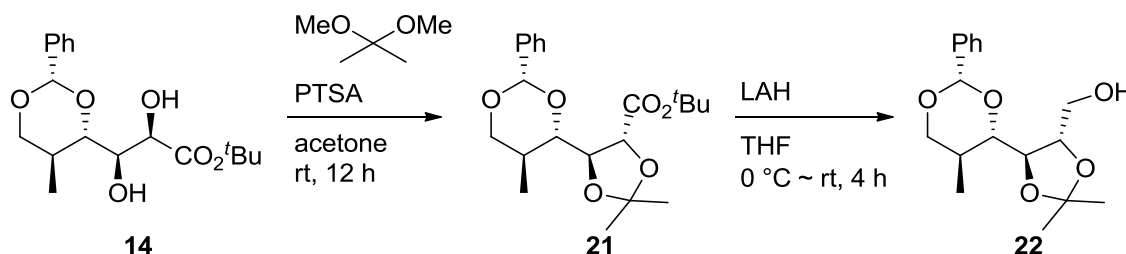
5/1) to give ((4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl)methanol (**20**) in 59 % yield (14.4 mg, 0.069 mmol). $[\alpha]_D^{24} = 11.4$. (c 0.83, CHCl₃) The relative and absolute configuration was determined by comparison with ¹H NMR spectra and optical rotation of the literature data (lit $[\alpha]_D^{25} = 13.1$ (c 0.69, CHCl₃)).³

t-Butyl-(2*R*,3*R*)-2,3-dihydroxy-3-((2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl)propanoate (**14**)



Diol **13** was prepared by the procedure described above. To a solution of **13** (13.0 mg, 0.043 mmol) and *N*-methylmorpholine *N*-oxide (10 mg, 0.086 mmol) in acetone (100 μ L) and water (10 μ L) was added 4% osmium tetroxide solution in water (27 μ L) at room temperature. After stirring at room temperature for 5 h, the reaction mixture was quenched with K₂S₂O₅ (22 mg 0.1 mmol). After stirring for 20 min, the reaction mixture was added water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 3/1) to give *t*-butyl-(2*R*,3*R*)-2,3-dihydroxy-3-((2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl)propanoate (**14**) and the inseparable diastereomer (d.r. = 2.9 :1) in 95% yield (13.8 mg, 0.041 mmol). ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.44 (2H, m), 7.38-7.31 (3H, m), 5.49 (1H, s), 4.50 (1H, dd, *J* = 3.6, 1.2 Hz), 4.13 (1H, dd, *J* = 11.4, 4.8 Hz), 4.05 (1H, ddd, *J* = 11.3, 6.9, 1.1 Hz), 3.64 (1H, dd, *J* = 9.9, 6.8 Hz), 3.53 (1H, app t, *J* = 11.2 Hz), 3.23 (1H, d, *J* = 3.4 Hz), 2.49 (1H, d, *J* = 11.4 Hz), 2.14-2.03 (1H, m), 1.49 (9H, s), 0.98 (3H, d, *J* = 6.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 172.7, 138.1, 128.9, 128.2, 126.0, 101.0, 83.1, 82.5, 74.1, 73.1, 70.1, 33.2, 28.0, 13.0; IR (neat) 3475, 2976, 1728, 1369, 1290, 1143, 1120, 1072 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₈H₂₆O₆Na: 361.1622 ([M + Na]⁺), Found: 316.1621 ([M + Na]⁺).

Determination of Relative Configuration of **14**



To a stirred solution of **14** (17.0 mg, 0.05 mmol) and PTSA (1 mg, 5 μ mol) in acetone (580 μ L) was added 2,2-dimethoxypropane (184 μ L, 1.5 mmol) at room temperature. After stirring for 12 h, the reaction mixture was quenched with saturated NaHCO₃ aq. and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was roughly purified by PLC

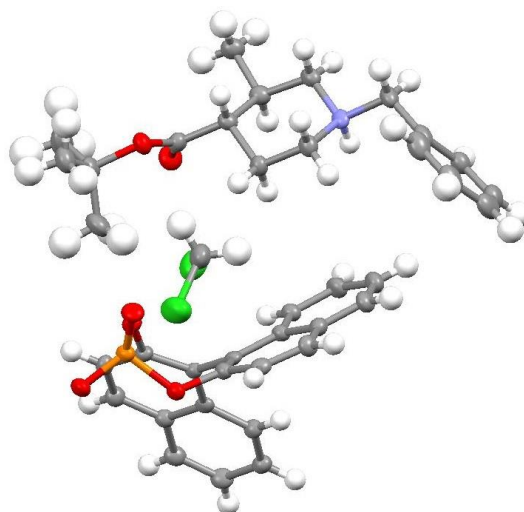
(hexane/ethyl acetate = 10/1) to give the protected tetraol **21**. To a precooled solution of **21** (12.2 mg, 0.033 mmol) in THF (260 μ L) at 0 °C, lithium aluminium hydride was added. After stirring for 1 h, the reaction mixture was warmed up to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C, and quenched with saturated potassium sodium tartrate aq. After stirring for 20 min at room temperature, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give the protected pentaol **22** quantitatively. The relative configuration of **14** was determined by comparison of ¹H NMR spectra of **22** with the literature data.⁴

***t*-Butyl (3*R*,4*S*)-1-benzyl-3-methylpiperidine-4-carboxylate (16)**

To a stirred solution of *t*-butyl (2*S*,3*R*)-3-methyl-4-oxo-2-(2-oxoethyl)butanoate (**15**) (13.8 mg, 0.065 mmol) and AcOH (7.2 μ L, 0.012 mmol) in methanol (4 mL) were added benzylamine (110 μ L, 0.12 mmol) and sodium cyanoborohydride (25 mg, 0.4 mmol) at room temperature. After stirring at room temperature for 25 h, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 10/1) to give *t*-butyl (3*R*,4*S*)-1-benzyl-3-methylpiperidine-4-carboxylate (**16**) in 64 % yield (12.0 mg, 0.041 mmol). [α]_D²⁴ = 7.8 (*c* 0.77, CHCl₃; 91% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.22 (5H, m), 3.48 (2H, s), 2.90 (1H, dd, *J* = 11.2, 1.6 Hz), 2.82 (1H, ddd, *J* = 11.4, 3.8, 1.4 Hz), 1.93-1.87 (2H, m), 1.82-1.75 (3H, m), 1.60 (1H, app t, *J* = 11.1 Hz), 1.44 (9H, s), 0.85 (3H, d, *J* = 6.6 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 174.7, 138.3, 129.1, 128.2, 126.9, 80.0, 63.1, 60.6, 52.9, 50.8, 33.1, 29.1, 28.1, 17.5; IR (neat) 2930, 2801, 1725, 1366, 1278, 1152 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₈H₂₈NO₂: 290.2115 ([M + Na]⁺), Found: 290.2117 ([M + H]⁺); Daicel Chiralpak IF, hexane/ethanol = 200/3, flow rate 1.0 mL/min, λ = 209 nm, retention time: 7.2 min (major) and 9.0 min.

Crystal Structure Analysis of 16·(S)-Binaphthyl Phosphoric Acid Salt

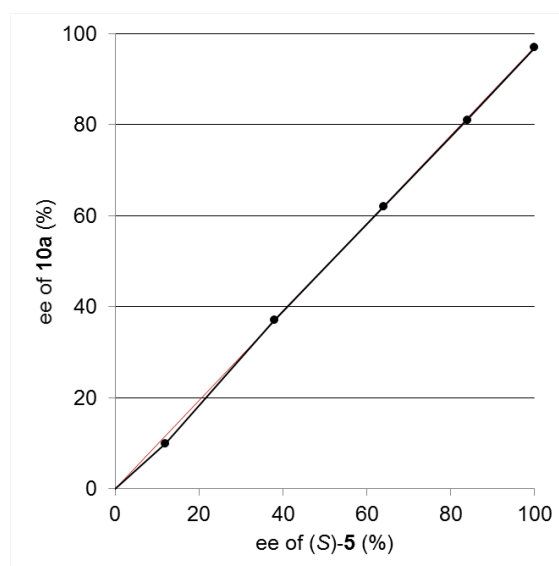
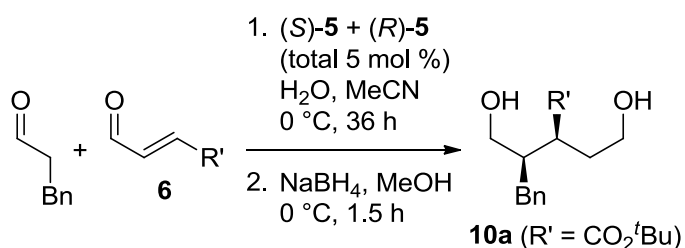
Single crystals of **16**·(S)-binaphthyl phosphoric acid Salt for X-ray diffraction experiments were grown from CH₂Cl₂, ethyl acetate and diethyl ether at room temperature. The data were collected at -150 °C on a Rigaku R-AXIS RAPID IP diffractometer with graphite-monochromated Cu K α radiation (λ = 1.5419 Å). The crystal structure was solved by direct methods using SIR97⁵ and refined in SHELXL-97⁶ by full matrix least-squares using anisotropic thermal displacement parameters for all non-hydrogen atoms. Crystallographic data for **16**·(S)-binaphthyl phosphoric acid Salt: C₁₈H₂₈NO₂ + C₂₀H₁₂O₄P + CH₂Cl₂, colorless prisms, 0.08×0.04×0.01 mm³, monoclinic, *P*2₁, *a* = 9.921(3), *b* = 16.320(4), *c* = 11.549(3) Å, *V* = 1854.5(9) Å³, ρ_{calcd} = 1.294 gcm⁻³, *Z* = 2, $2\theta_{\text{max}}$ = 136.64°, μ = 2.361 mm⁻¹. A total of 14750 reflections were measured. *R* = 0.0518, and *R*_w = 0.1233 for 6264 observed reflections with *I* > 2.0 σ (*I*). CCDC-990981 (**16**·(S)-binaphthyl phosphoric acid Salt) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



ORTEP diagram of **16**·(*S*)-binaphthyl phosphoric acid Salt

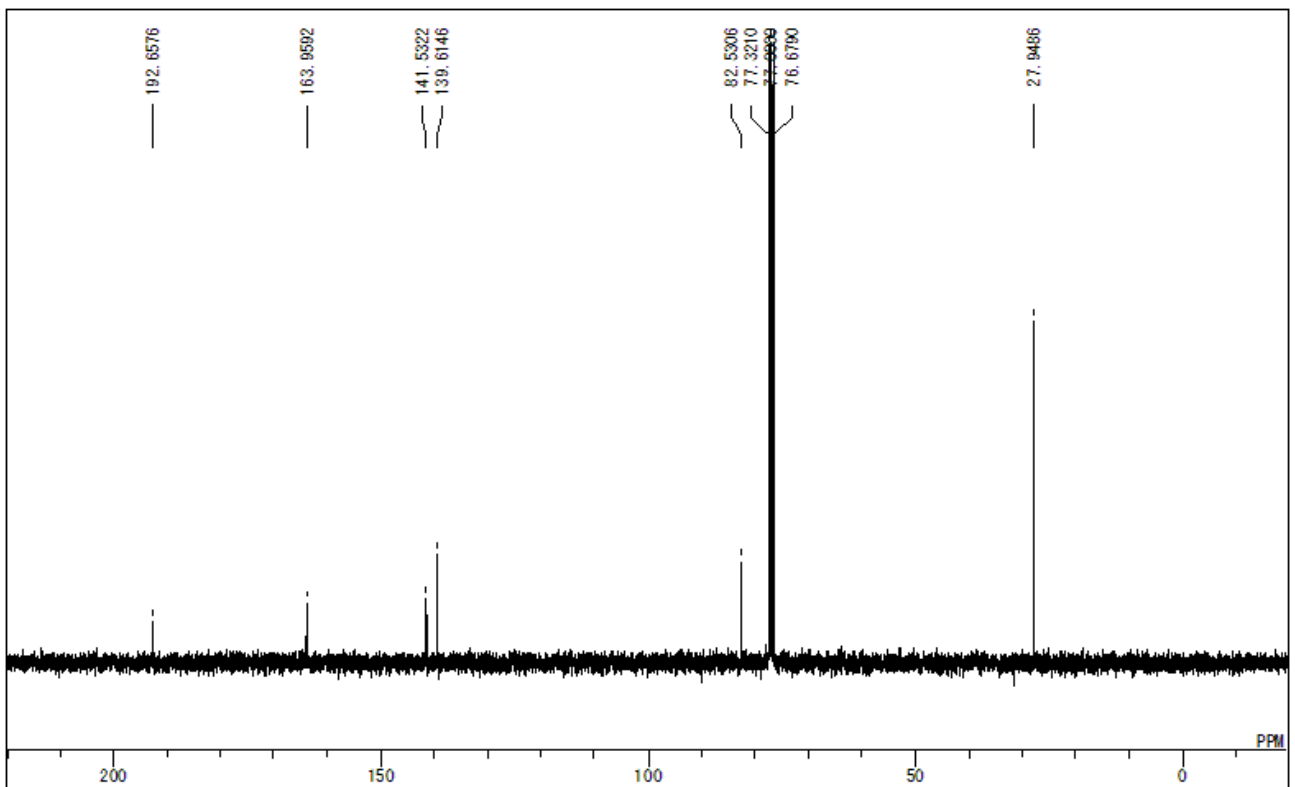
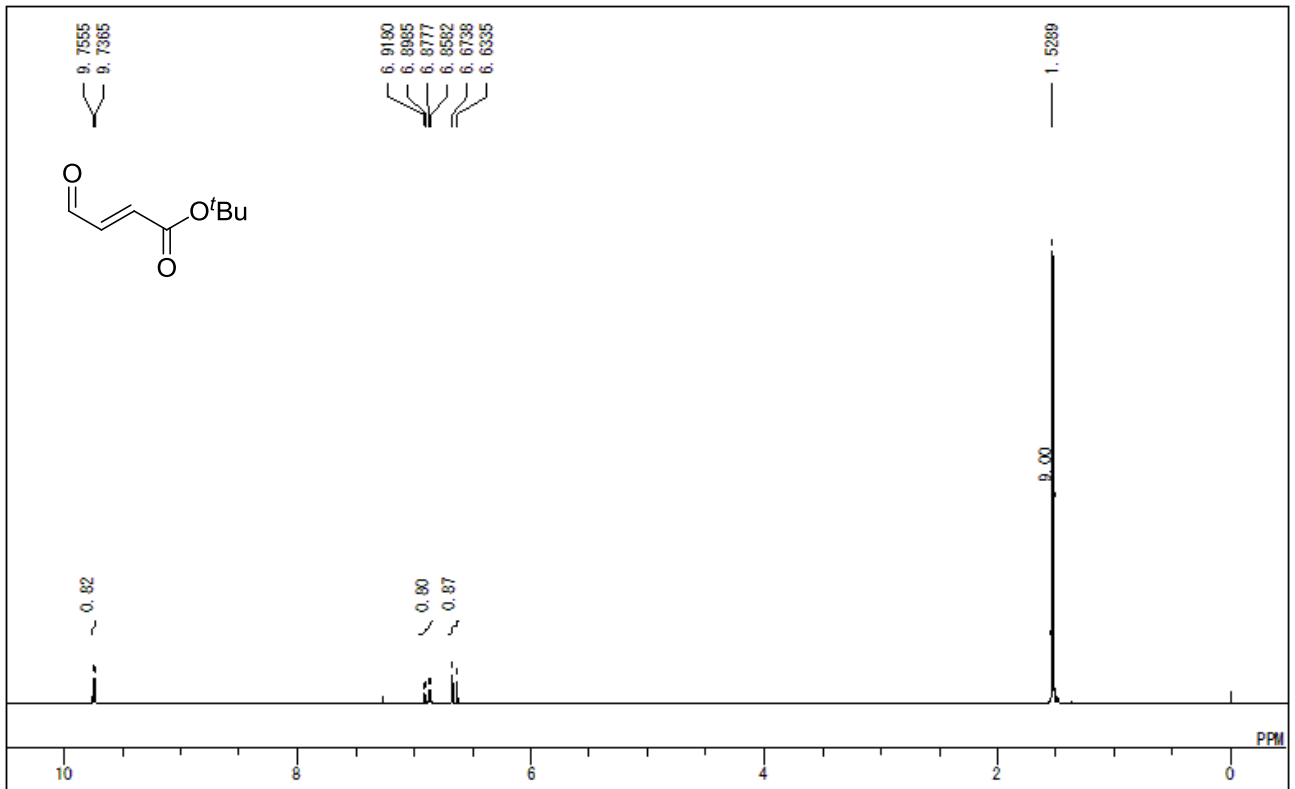
A Study of Non-linear Effect in the Asymmetric Conjugate Addition

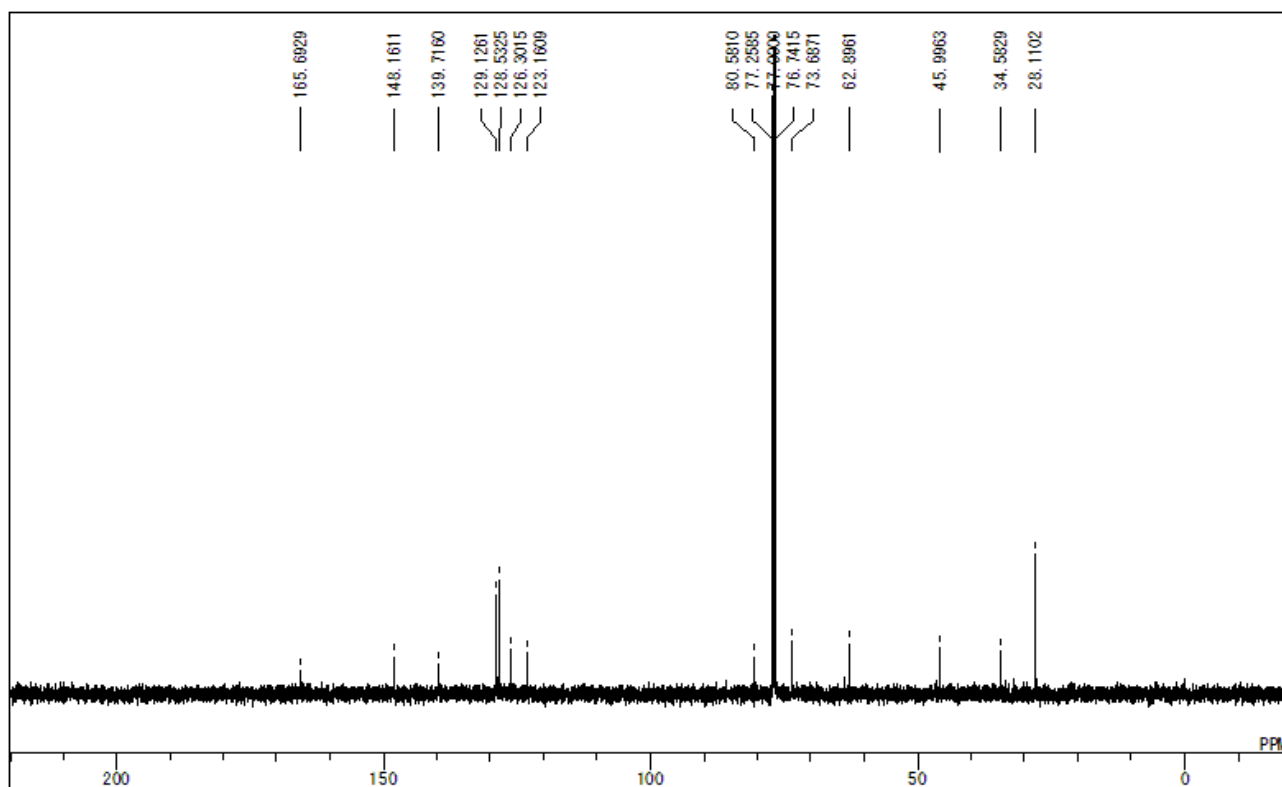
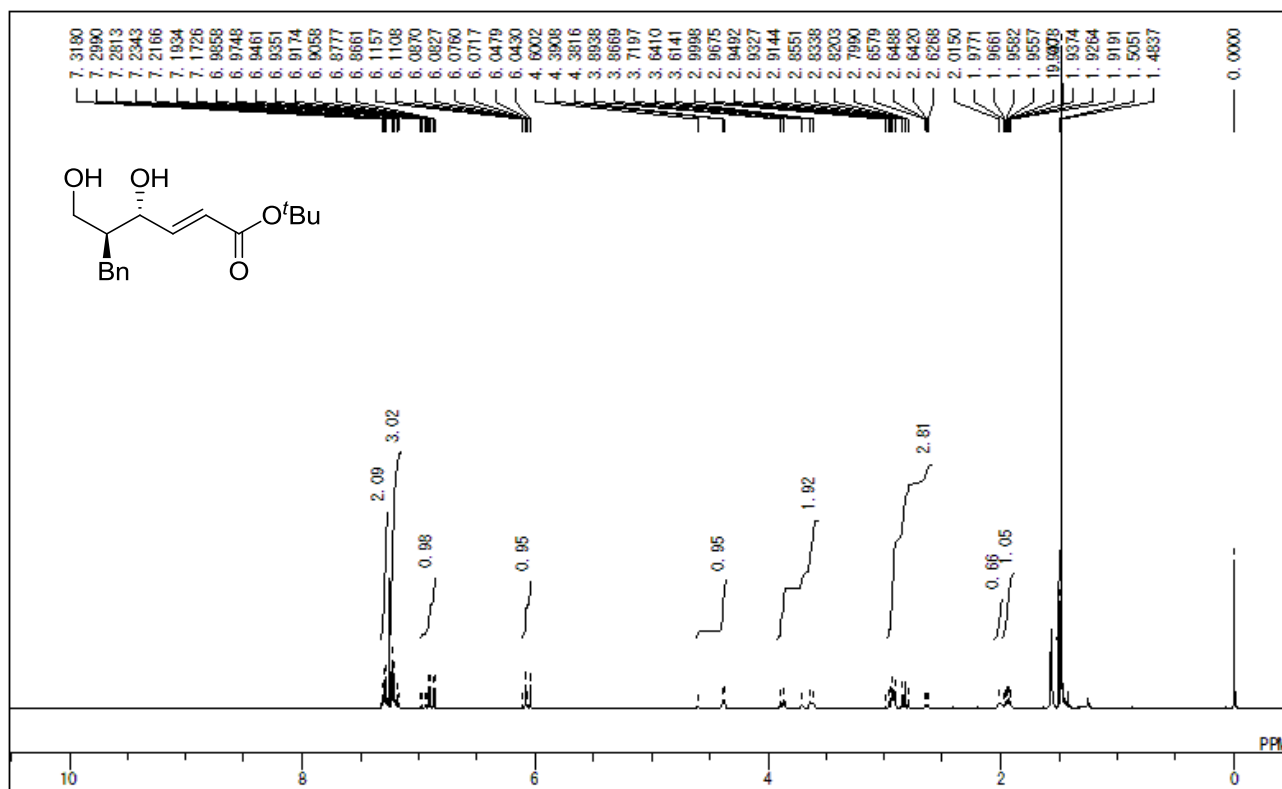
The ee value of the conjugate adduct **10a** correlated linearly with that of the catalyst **5** and the present conjugate addition did not exhibit a non-linear effect.

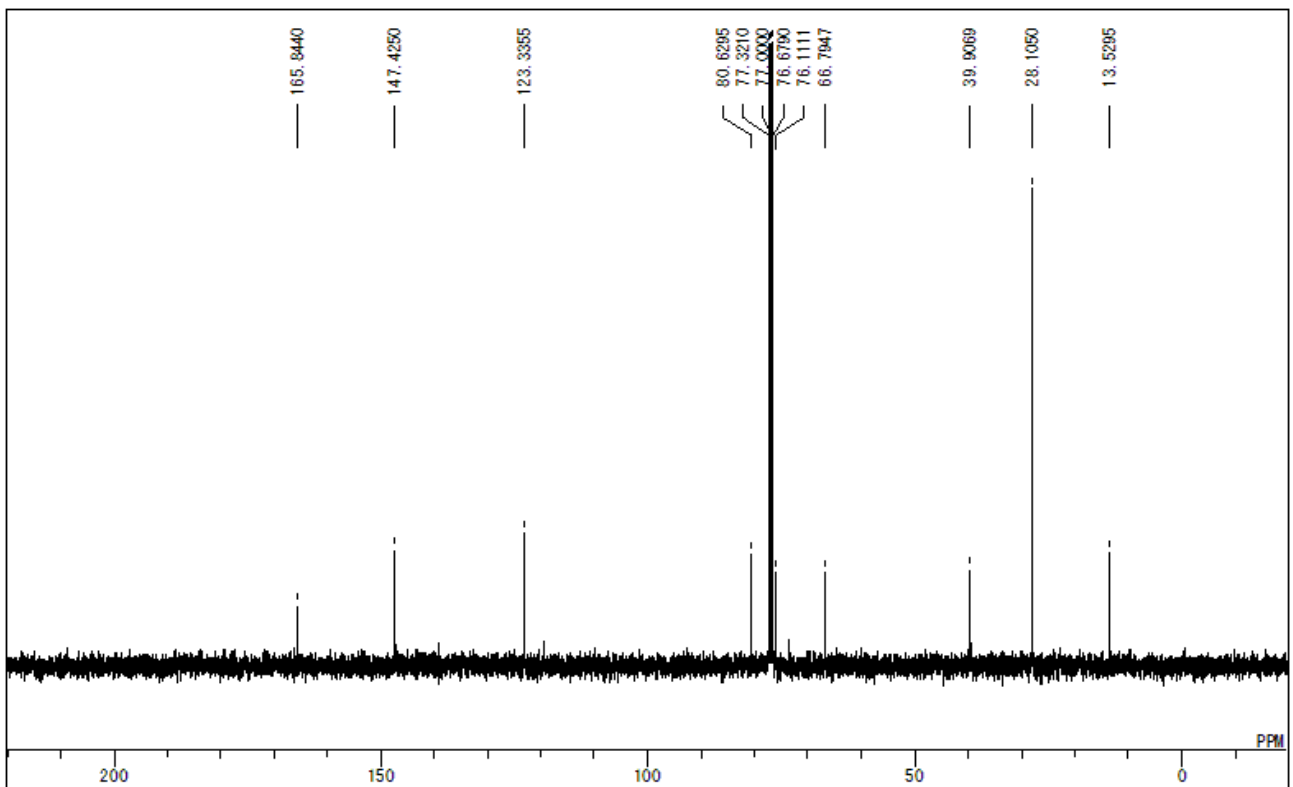
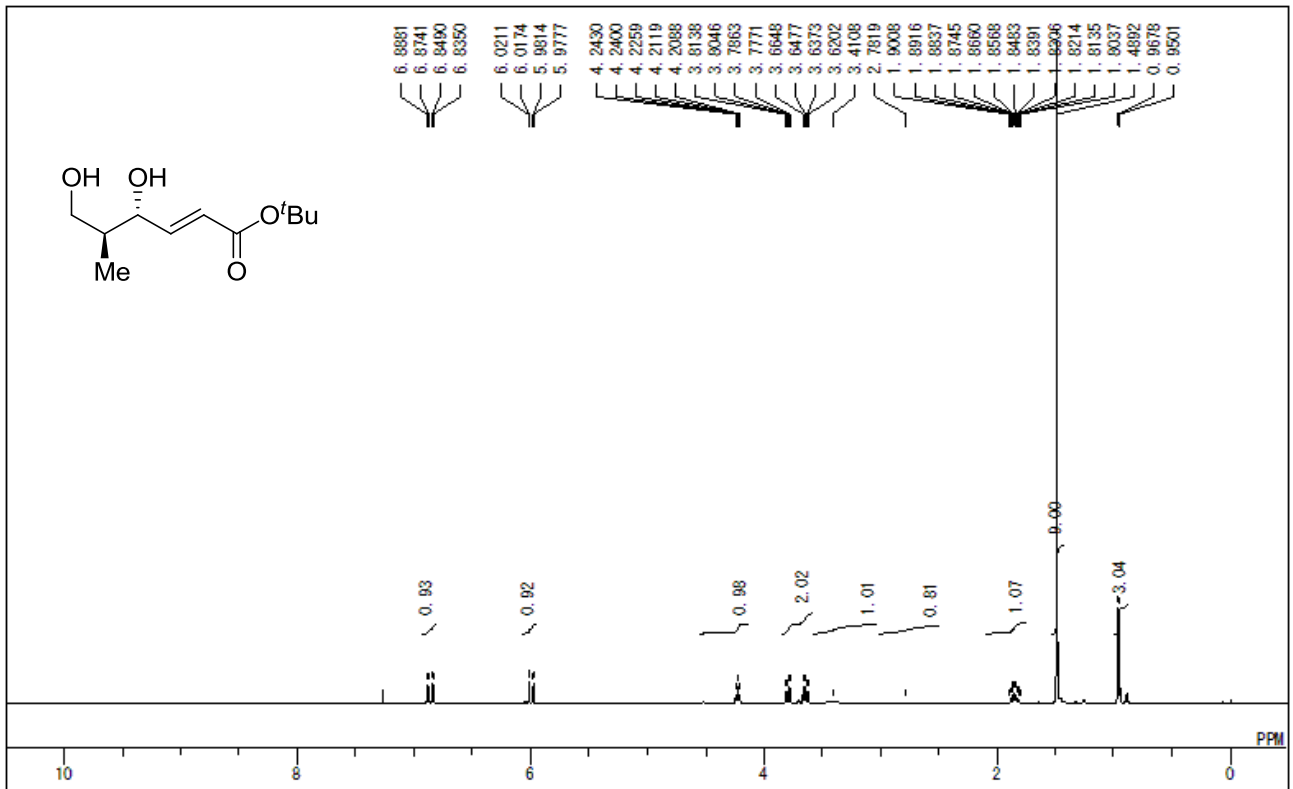


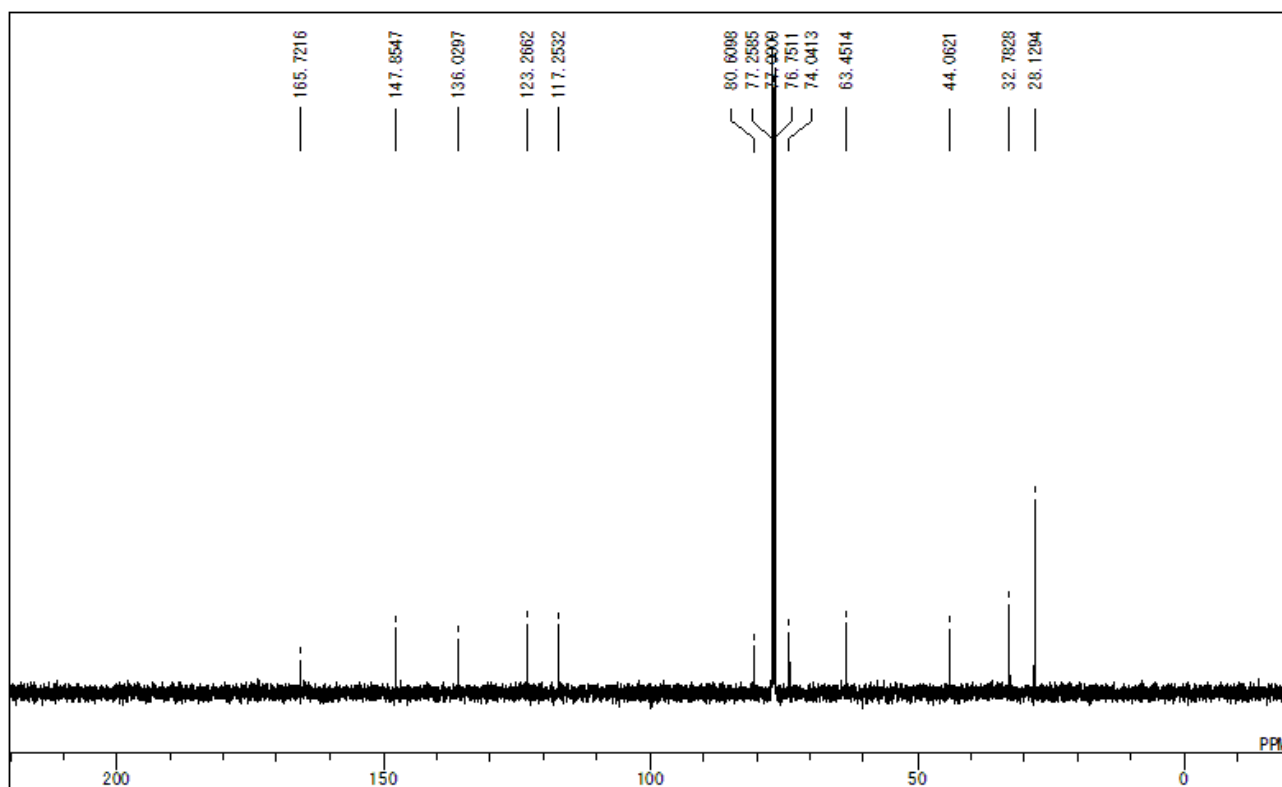
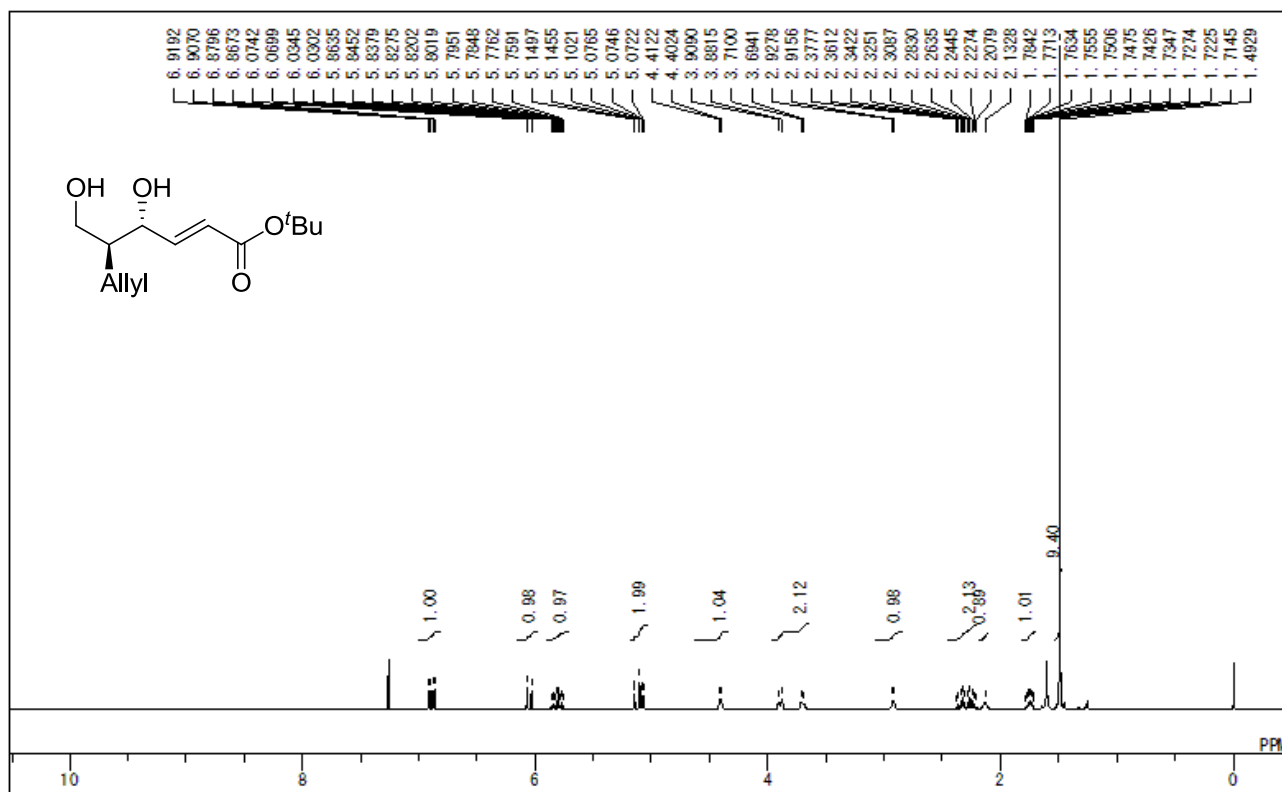
References

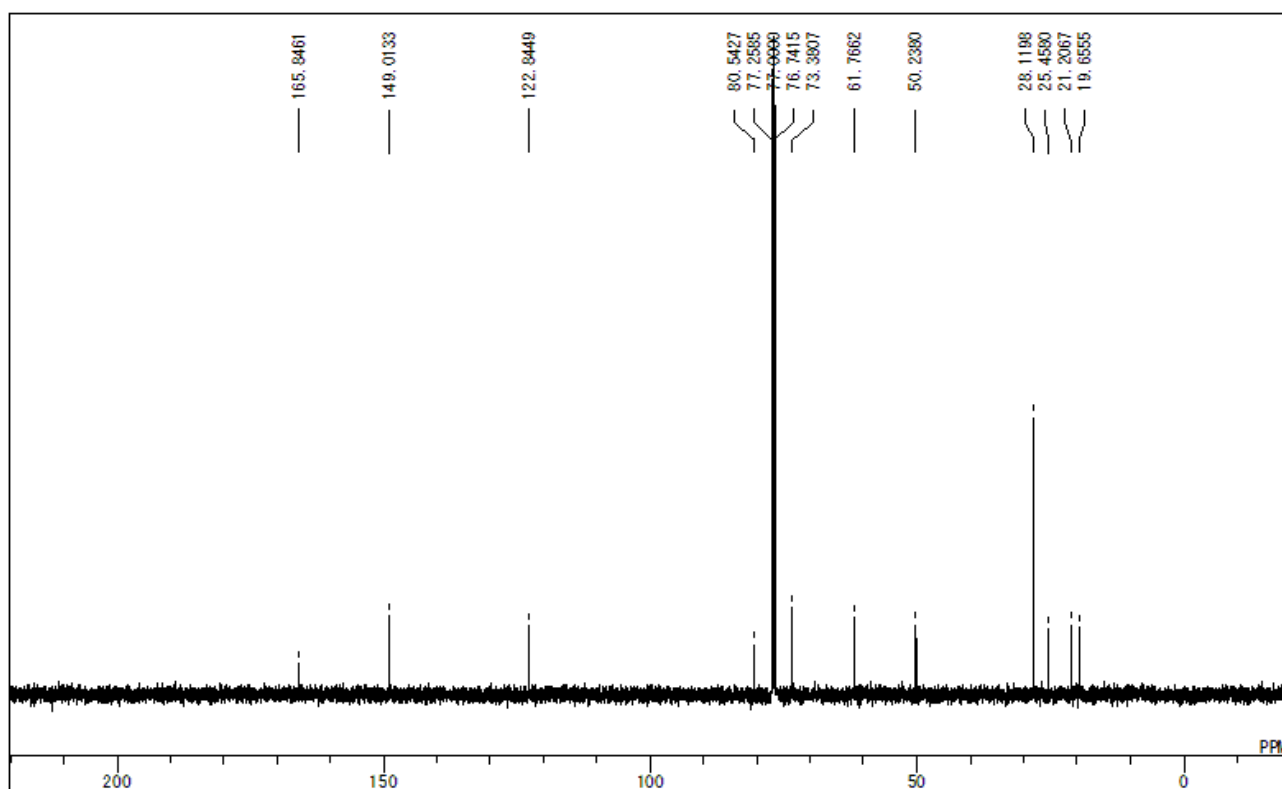
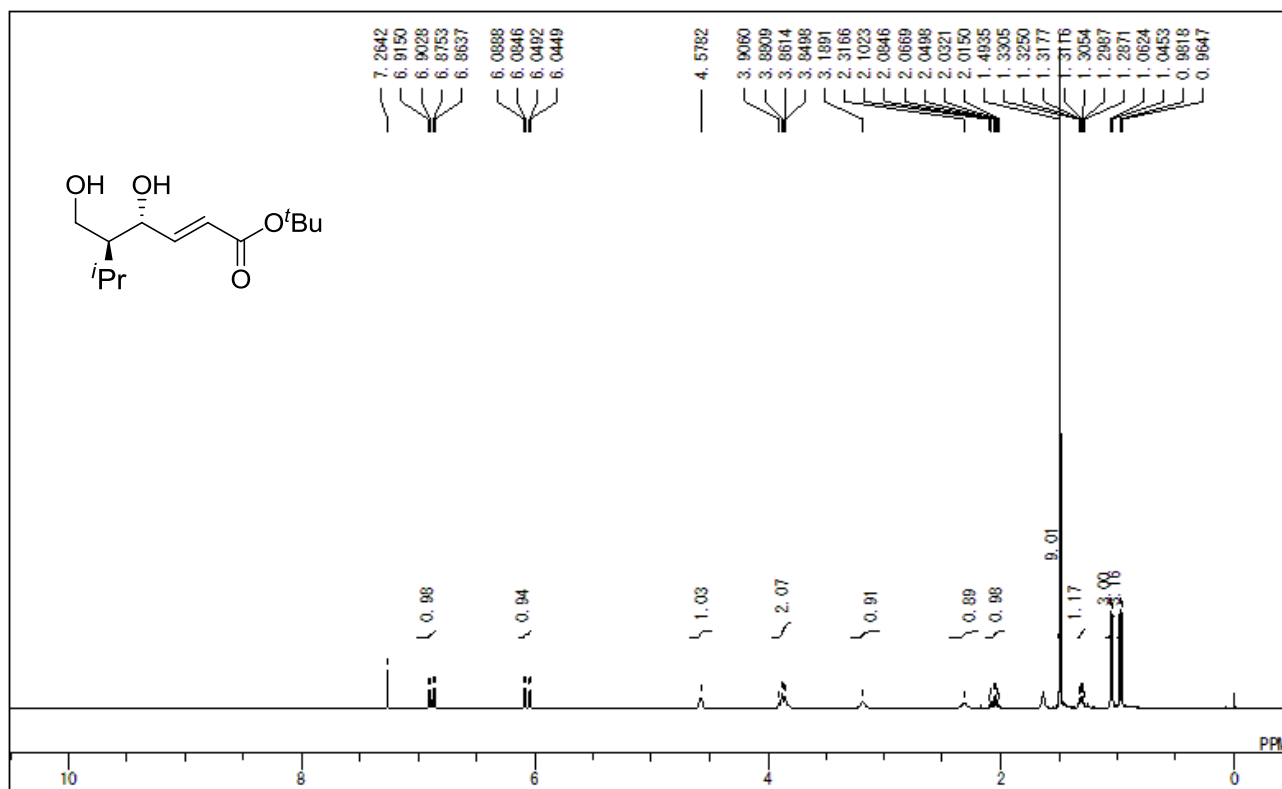
1. T.Kano, Y. Hato, A. Yamamoto and K. Maruoka, *Tetrahedron*, 2008, **64**, 1197.
2. (a) T. Kano, Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408; (b) T. Kano, Y. Yamaguchi and K. Maruoka, *Chem. Eur. J.*, 2009, **15**, 6678.
3. Y. Mori, M. Asai, A. Okumura and H. Furukawa, *Tetrahedron*, 1995, **51**, 5299.
4. G. Sabitha, A. S. Rao and J. S. Yadav, *Org. Biomol. Chem.*, 2013, **11**, 7218.
5. SIR97, Program for the solution of crystal structures: A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.
6. G. M. Sheldrick, *SHELXL-97*, Program for Crystal Structure Refinement; University of Göttingen: Göttingen, Germany, 1997.

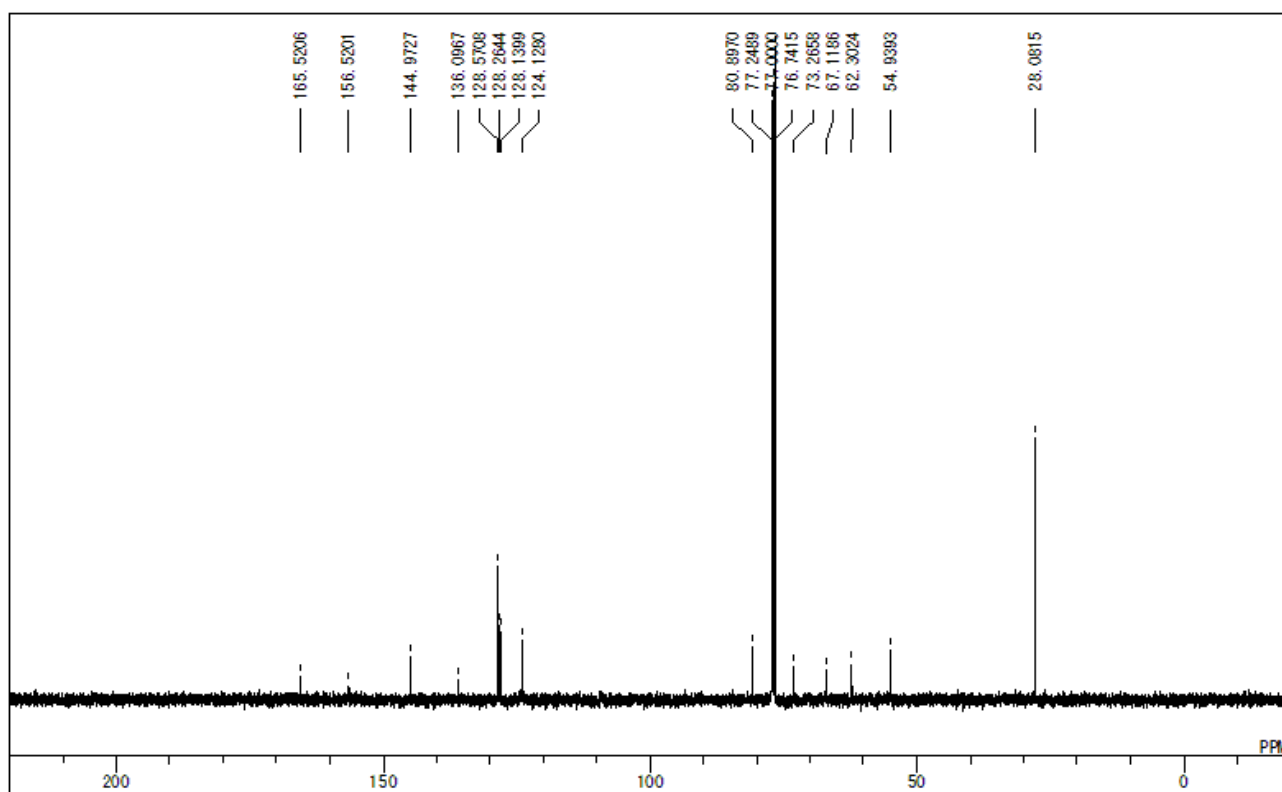
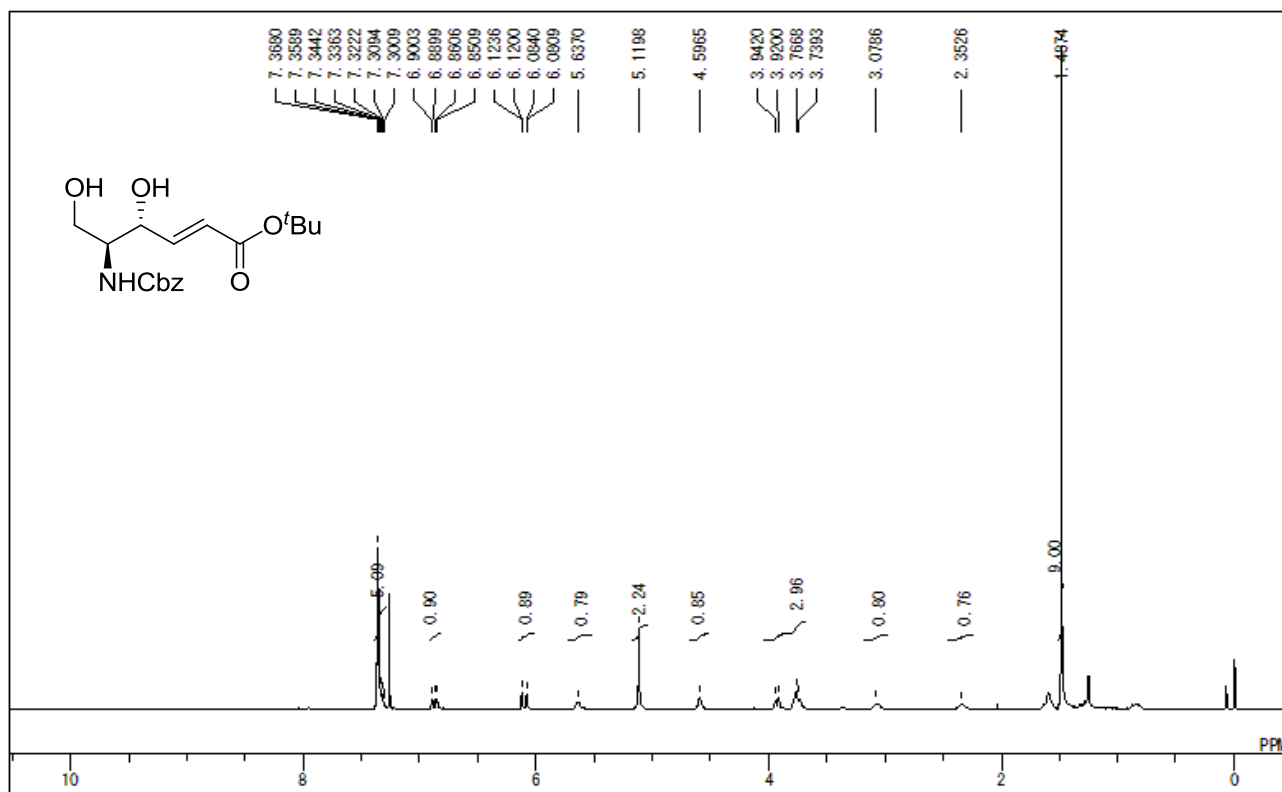


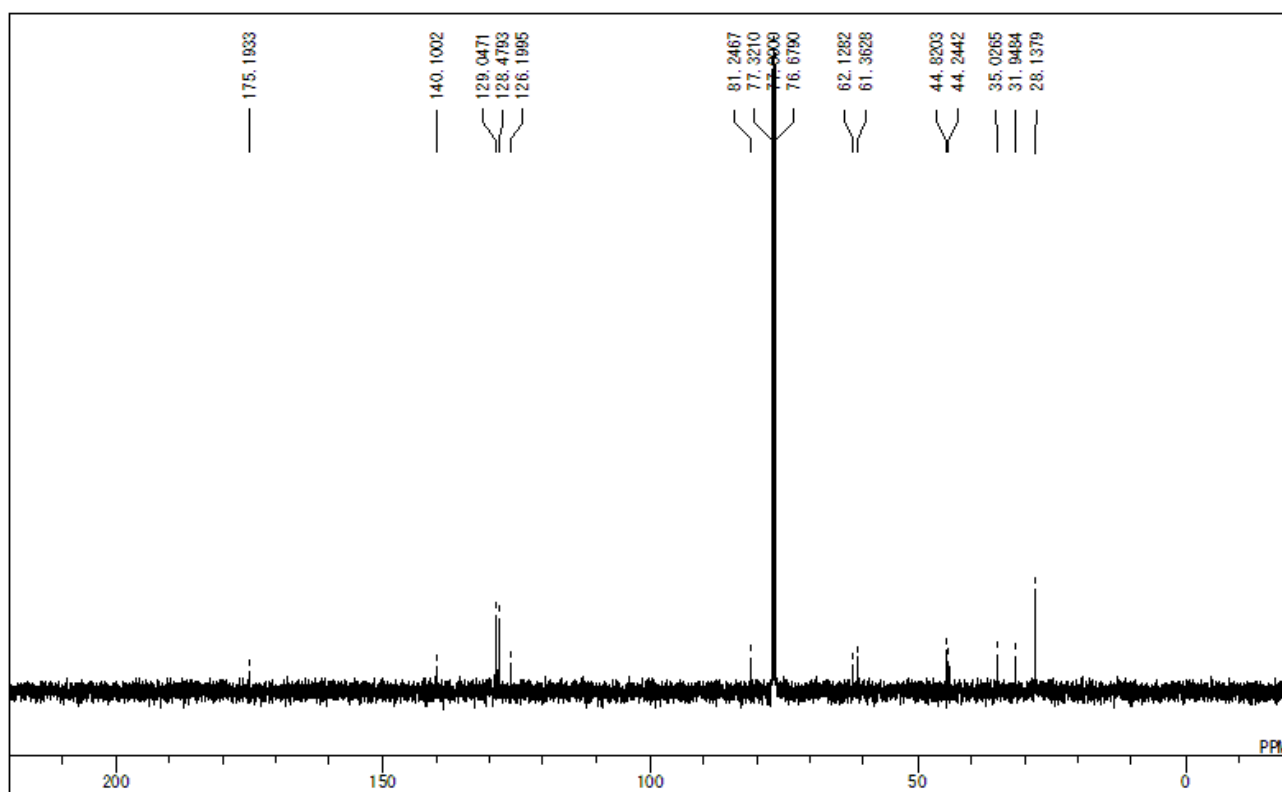
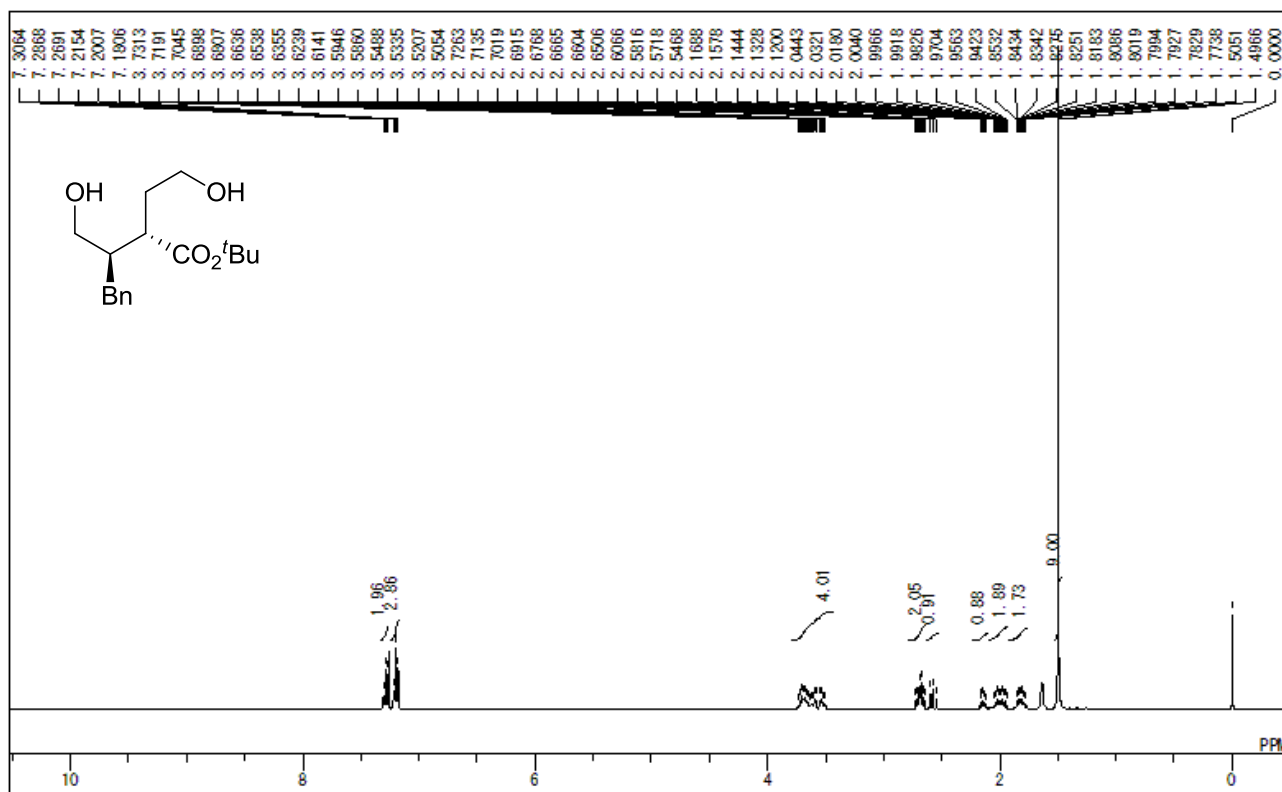


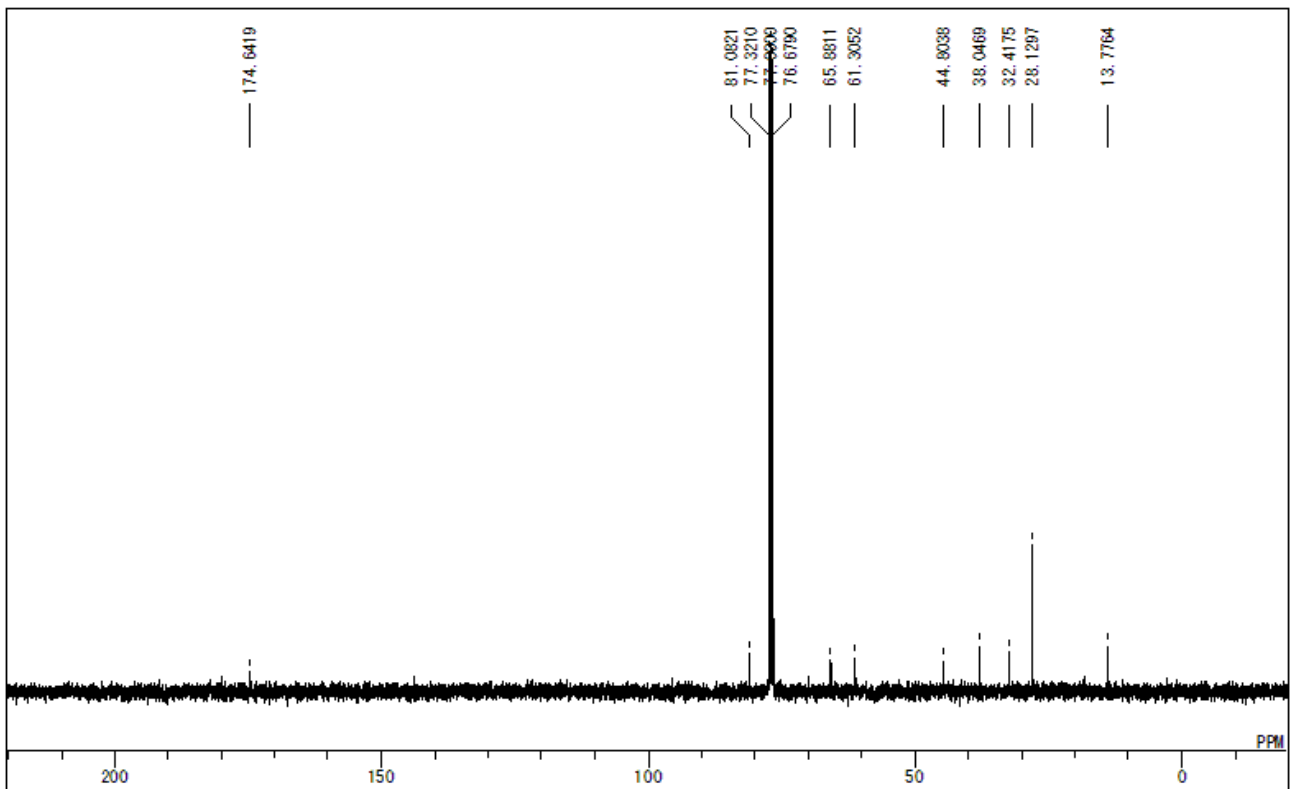
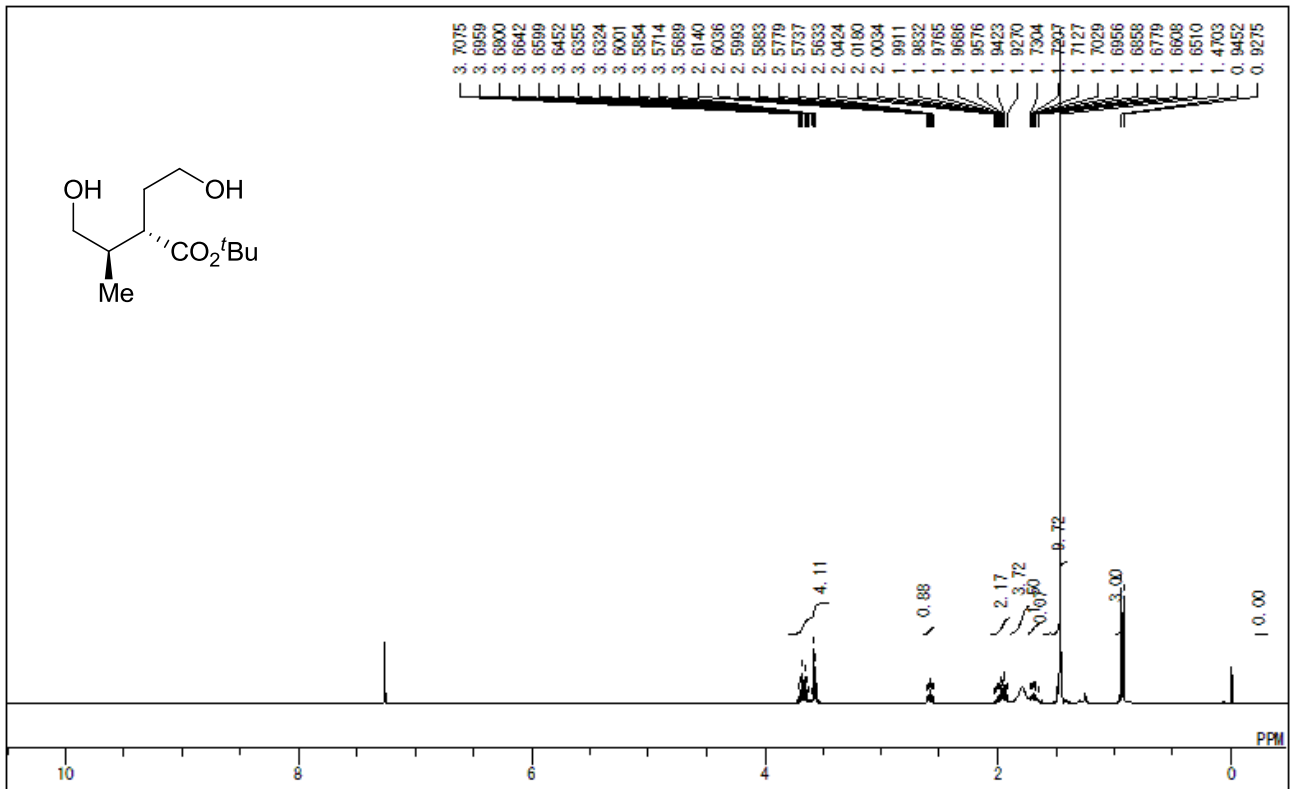


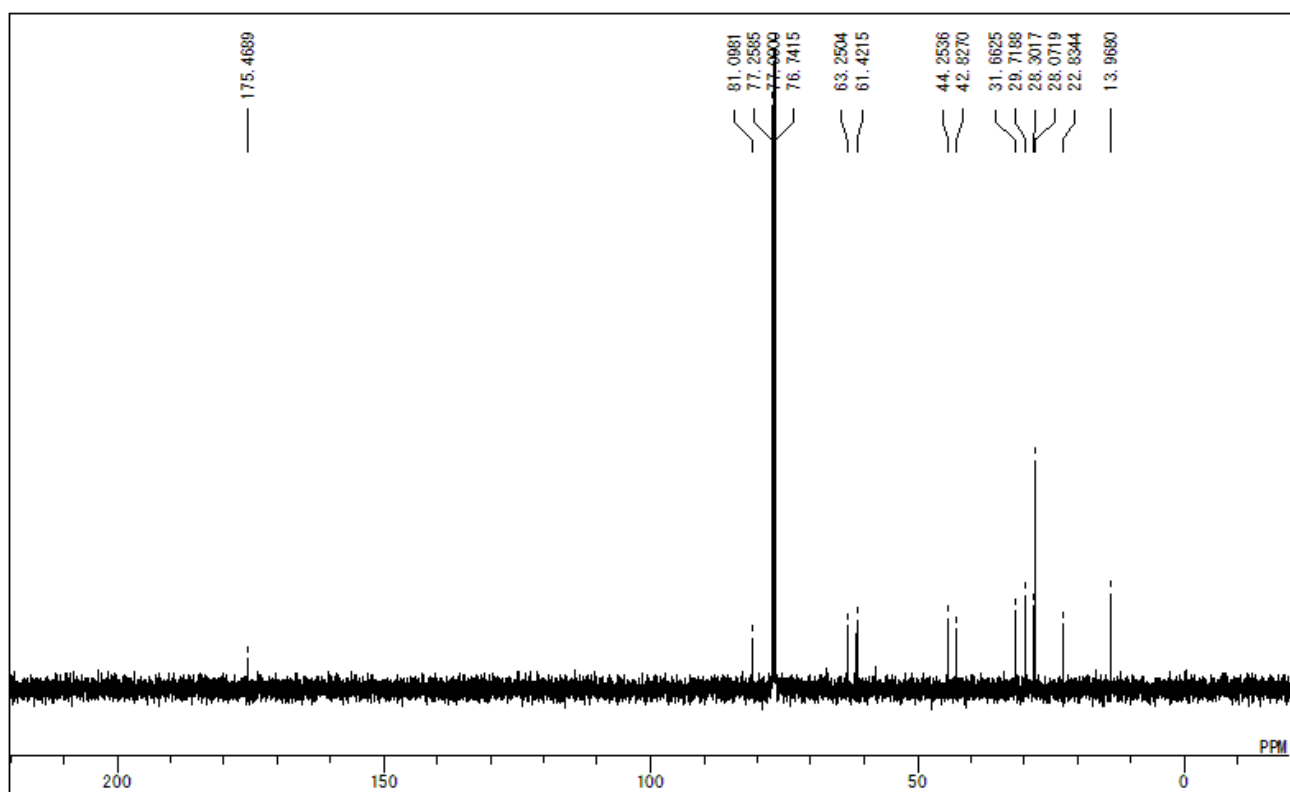
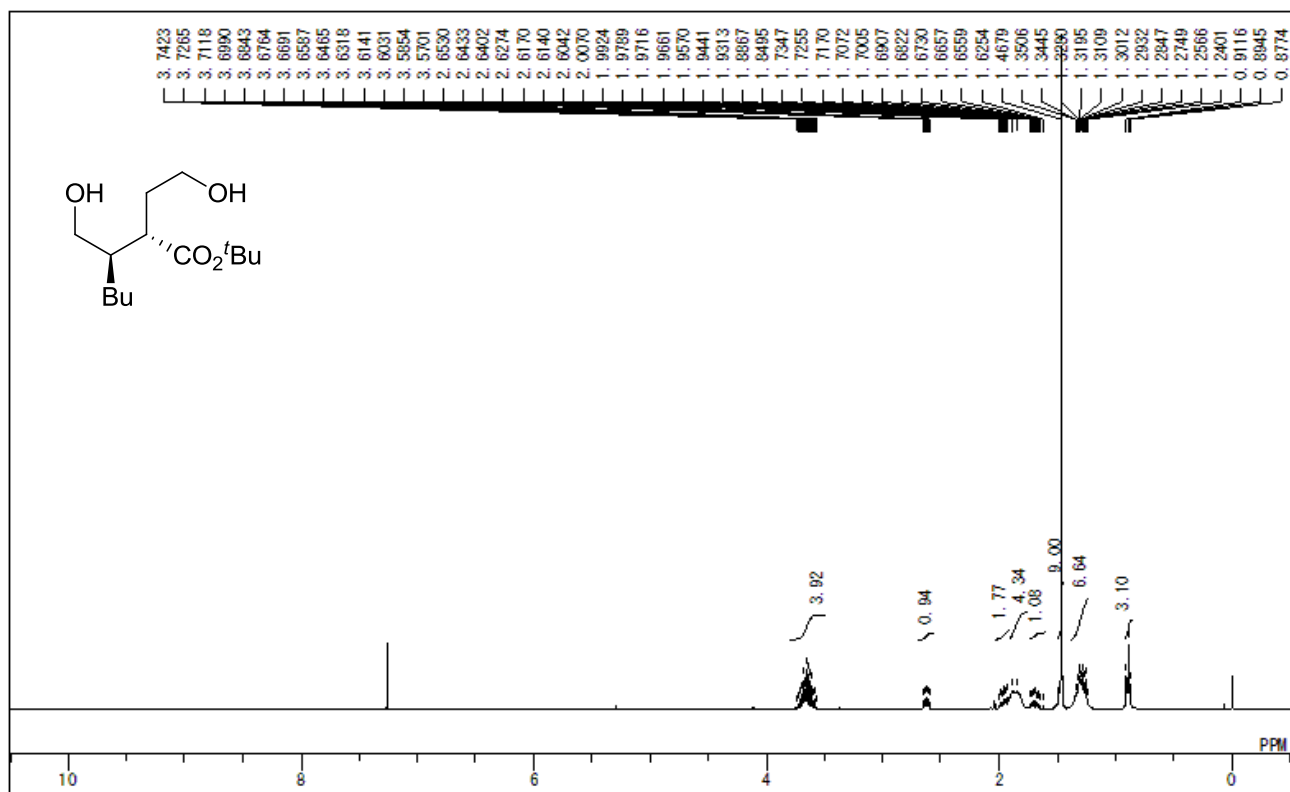


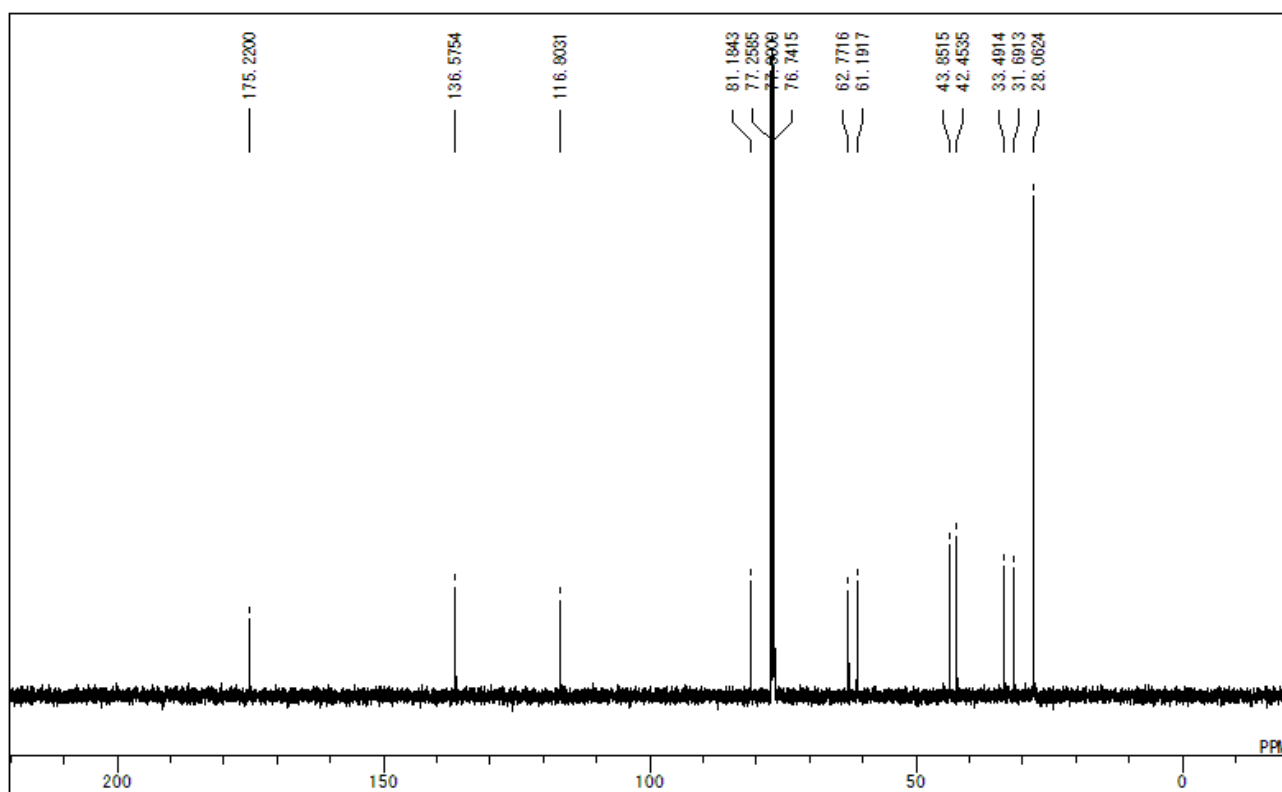
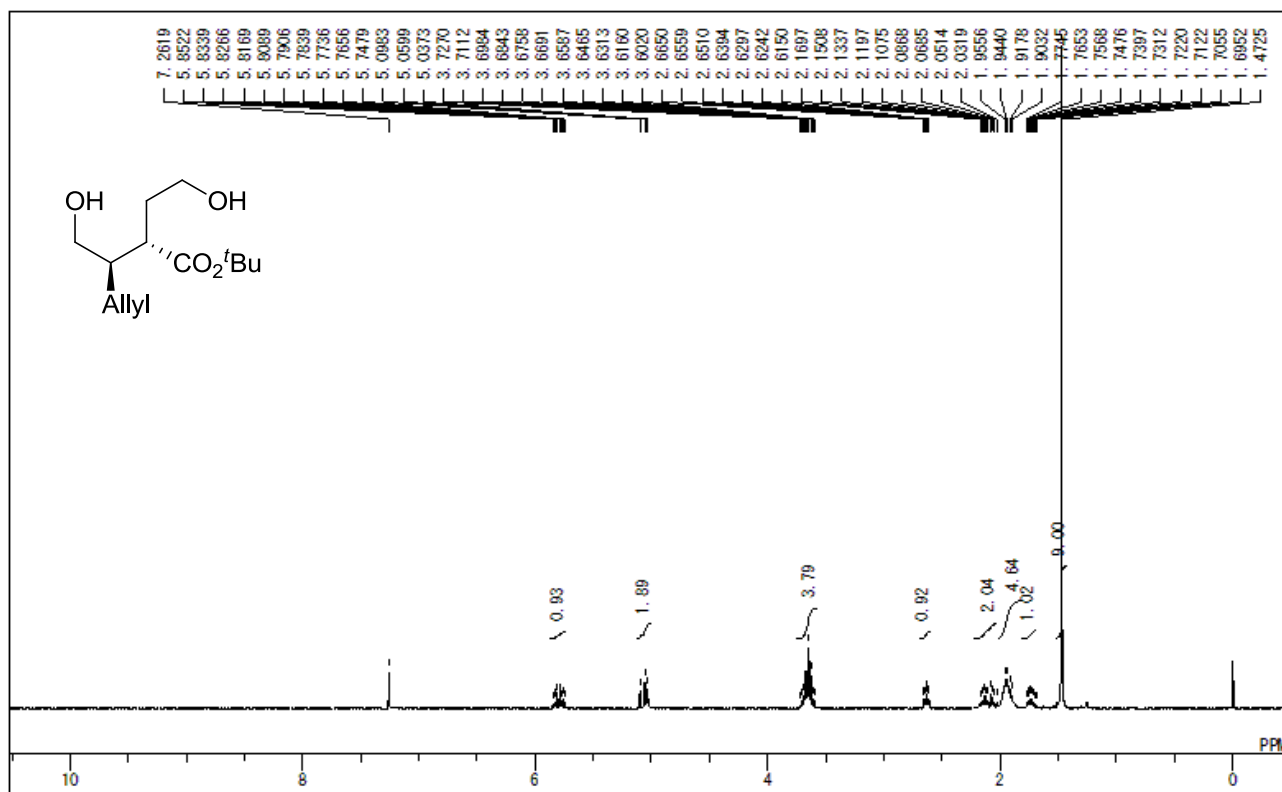


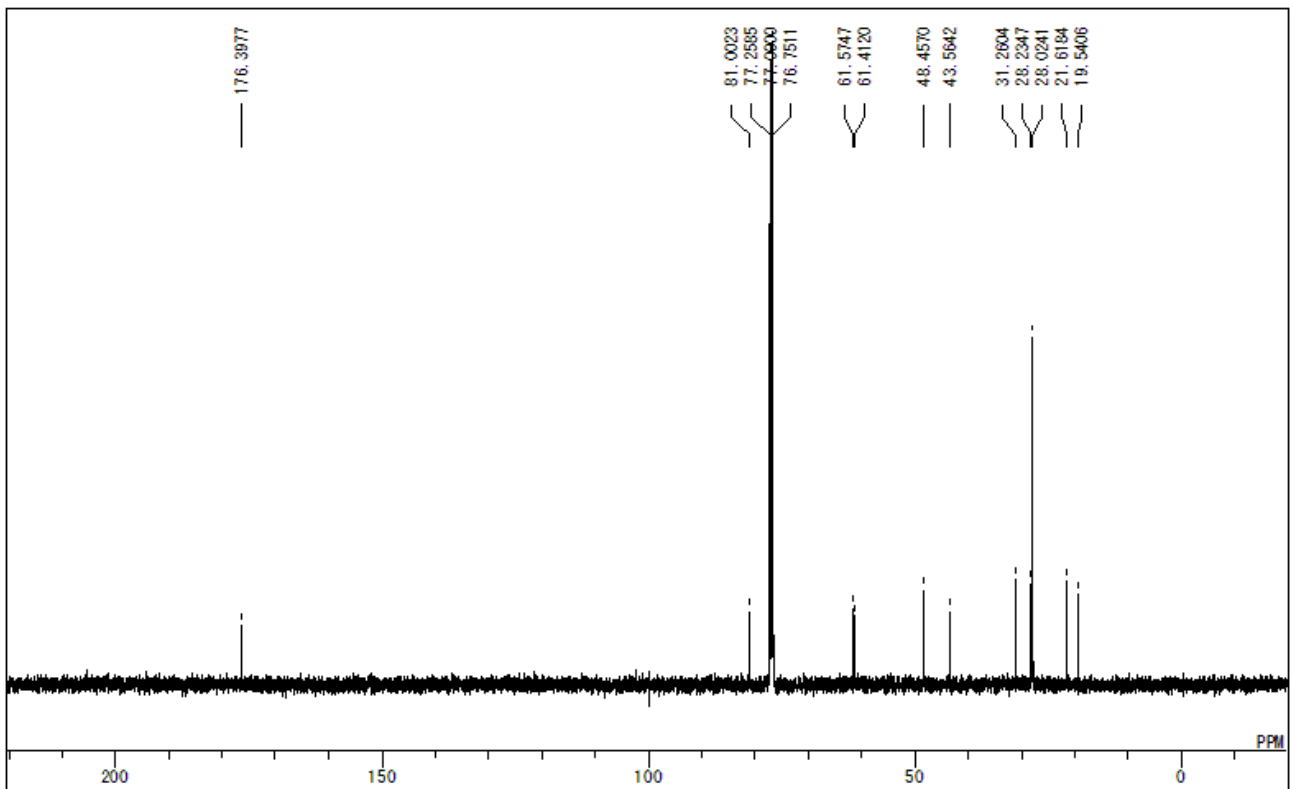
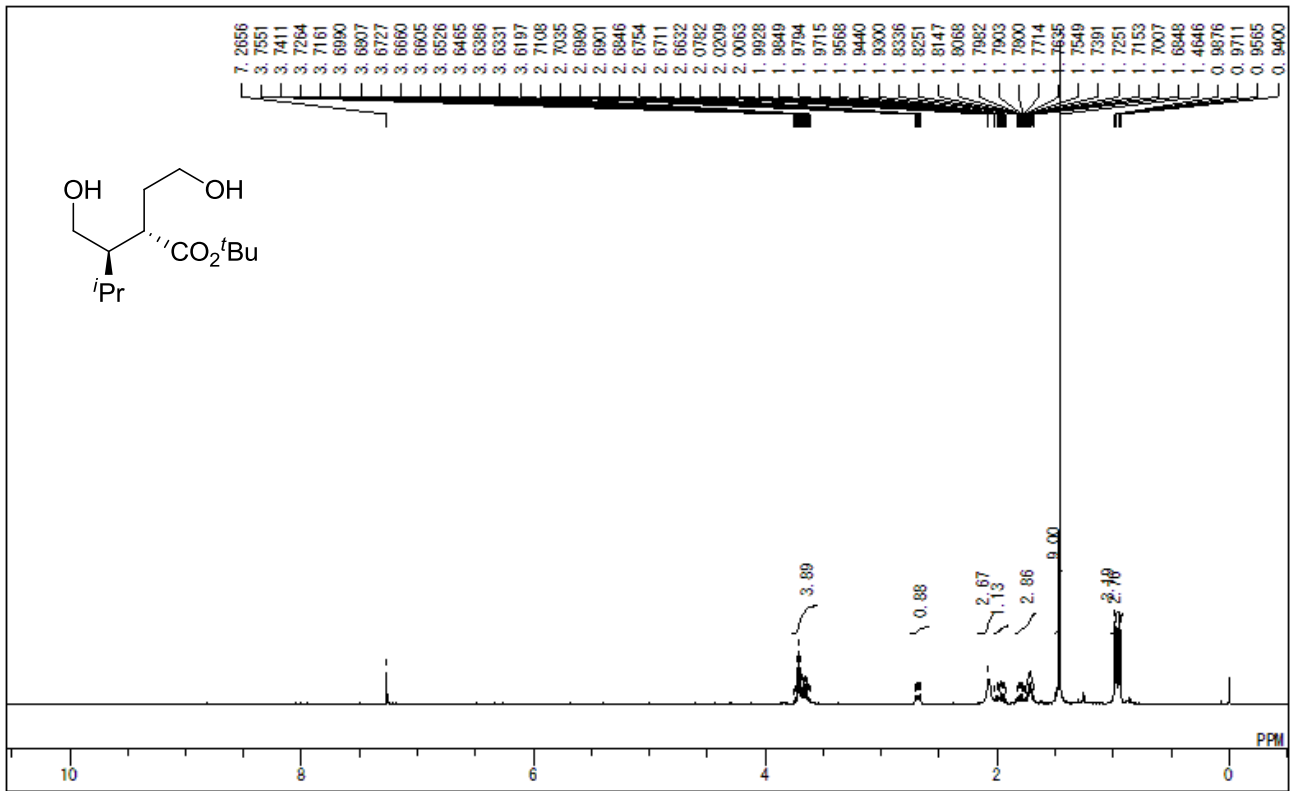


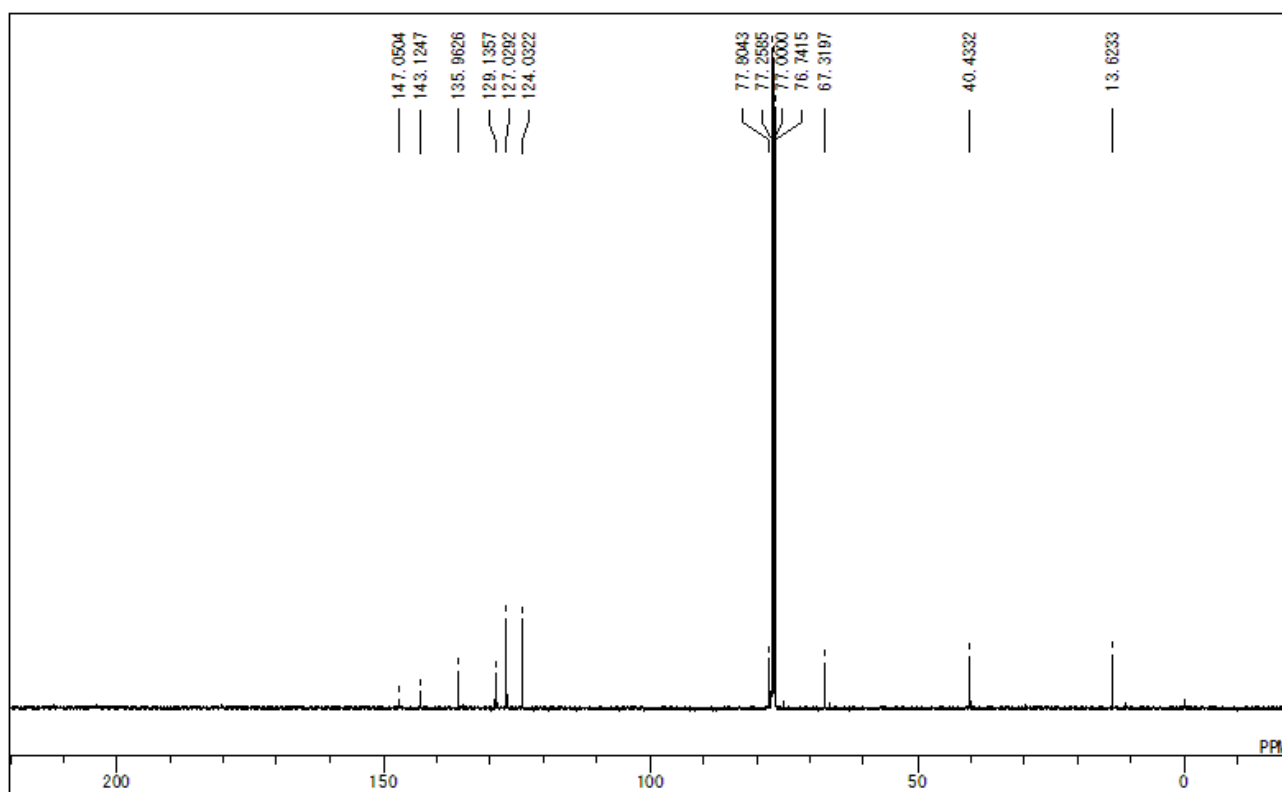
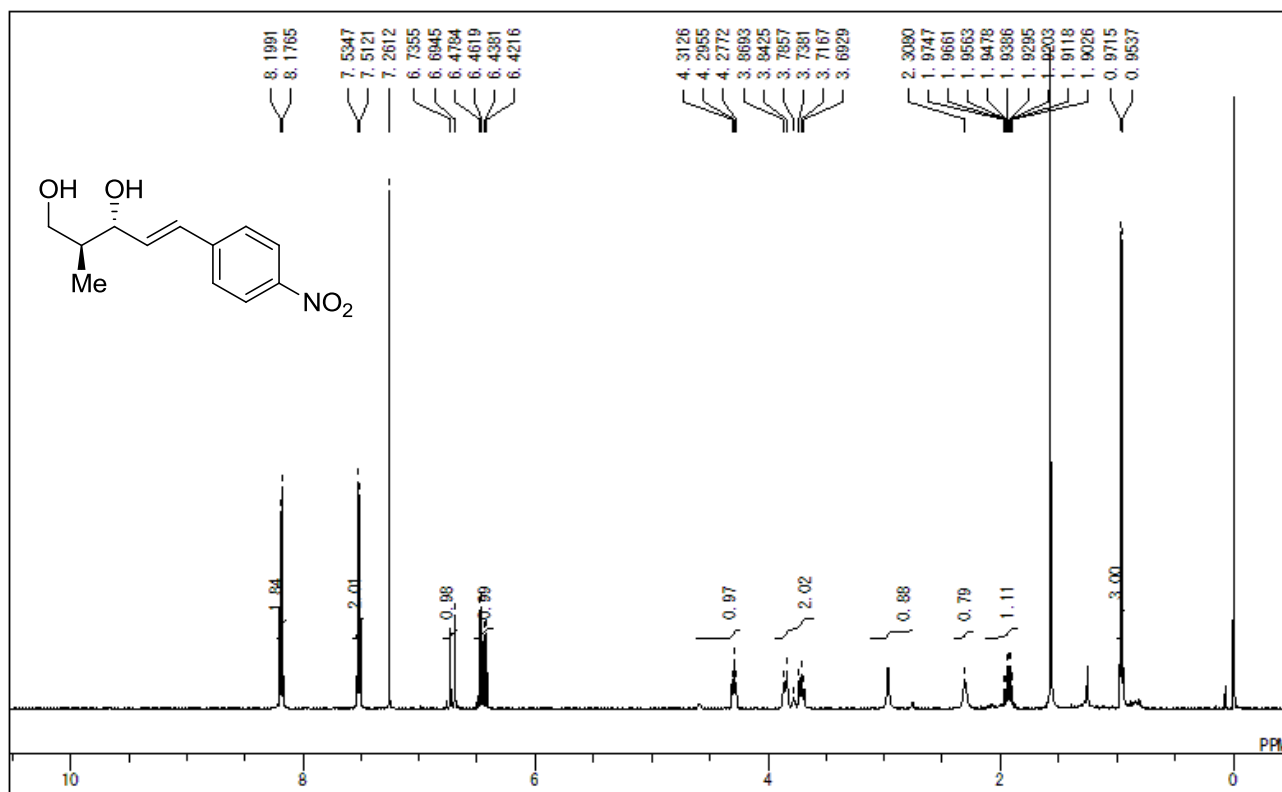


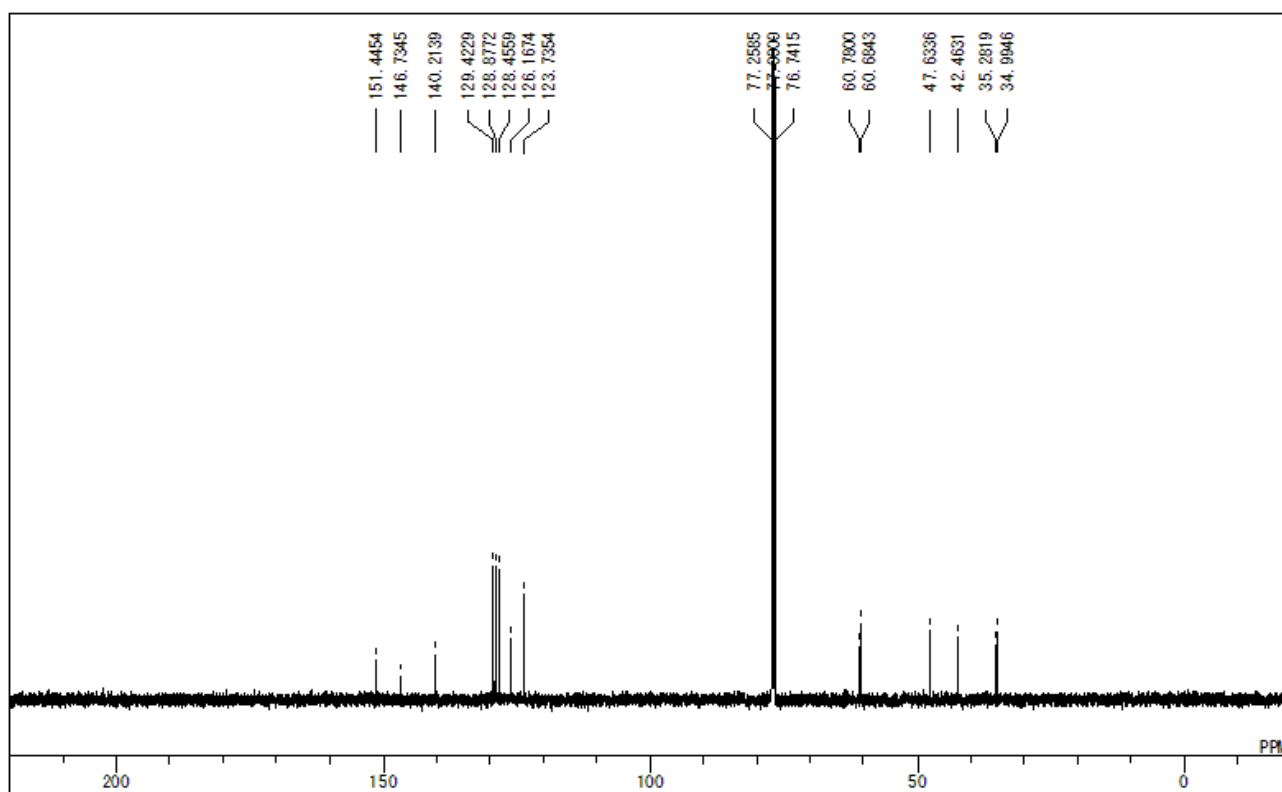
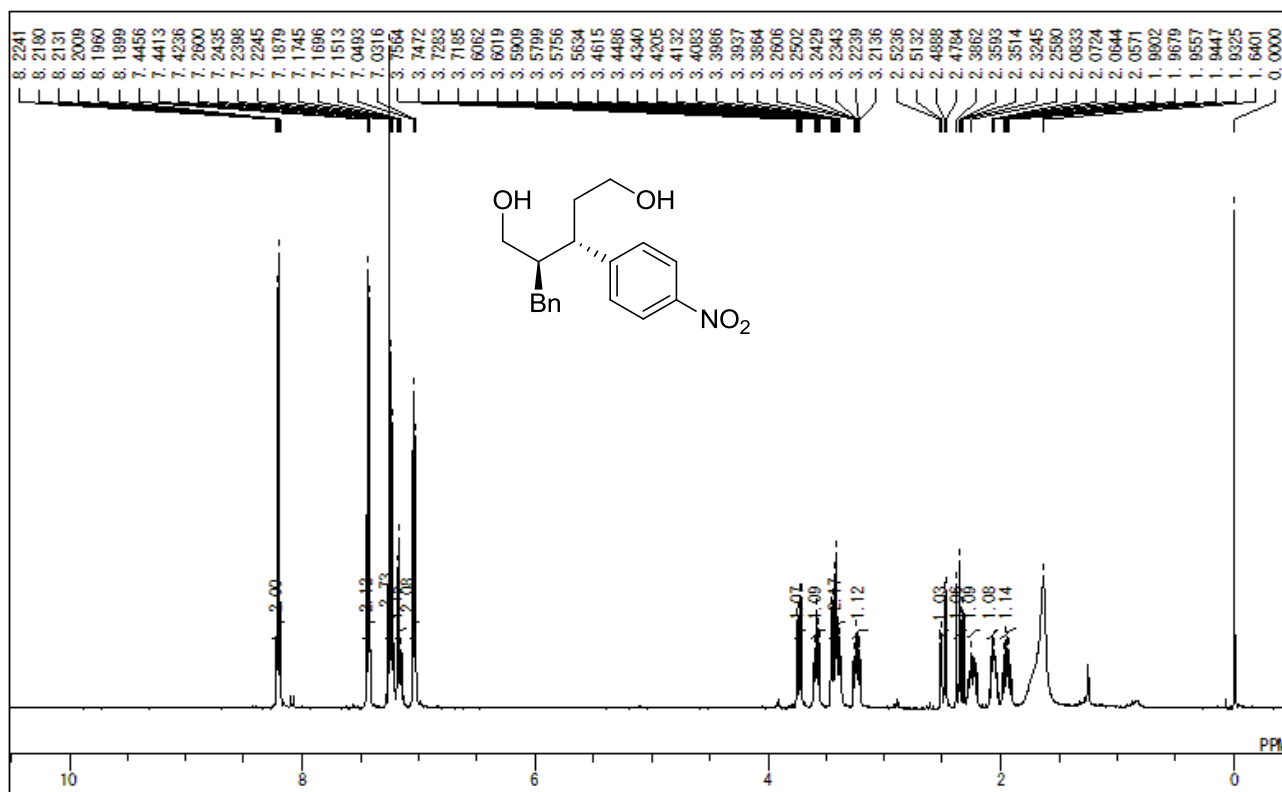


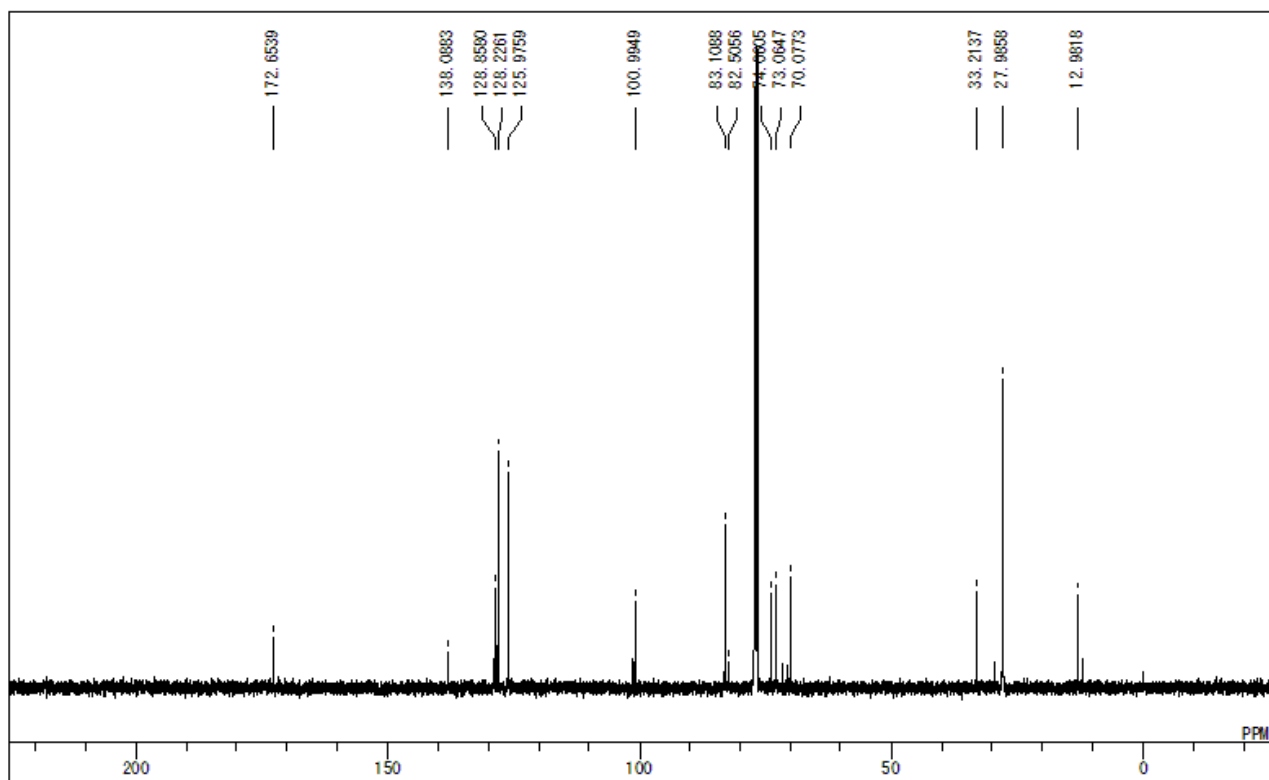
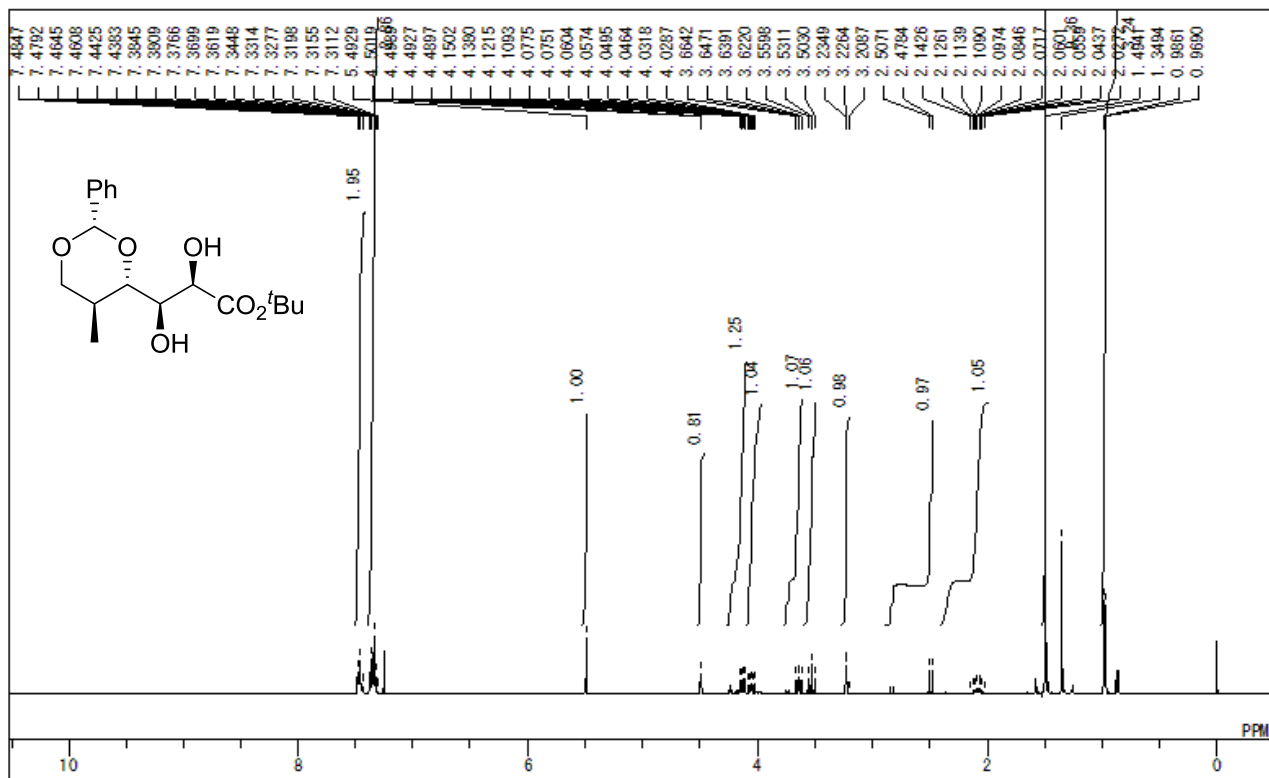


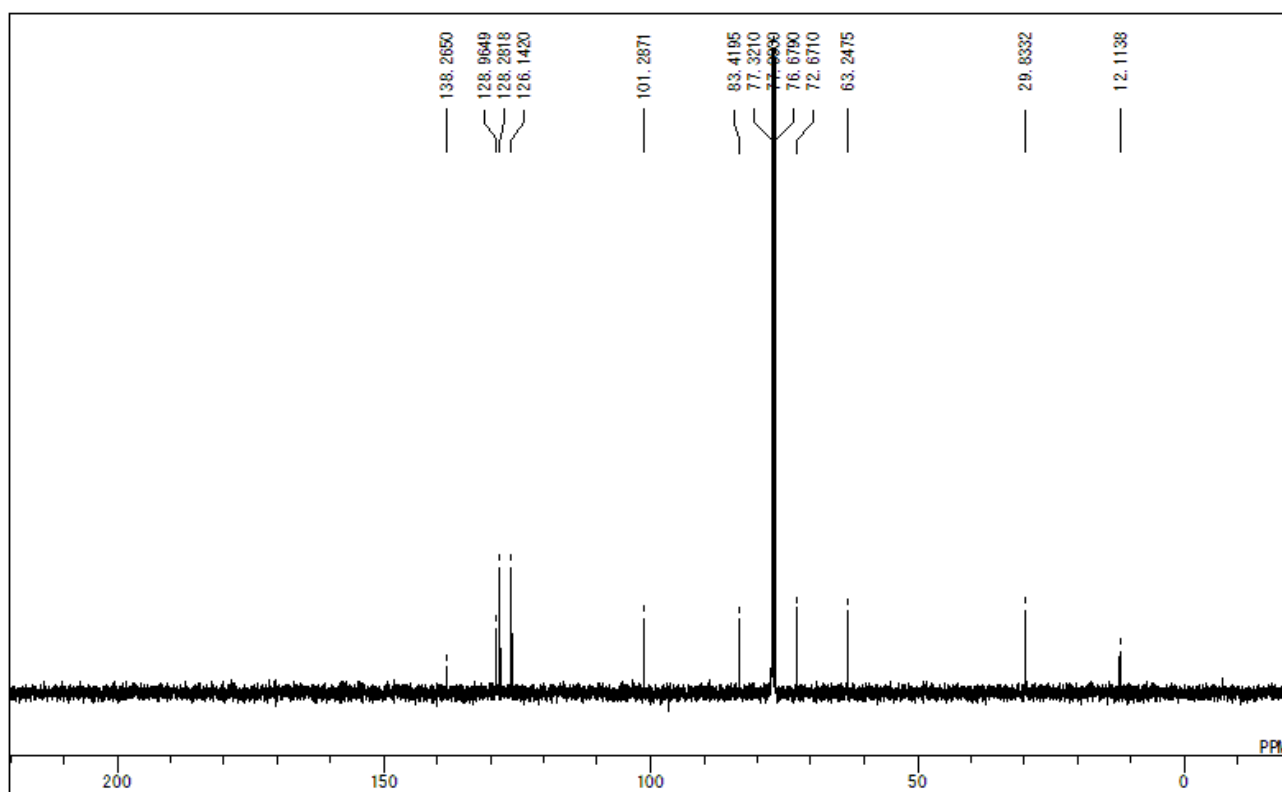
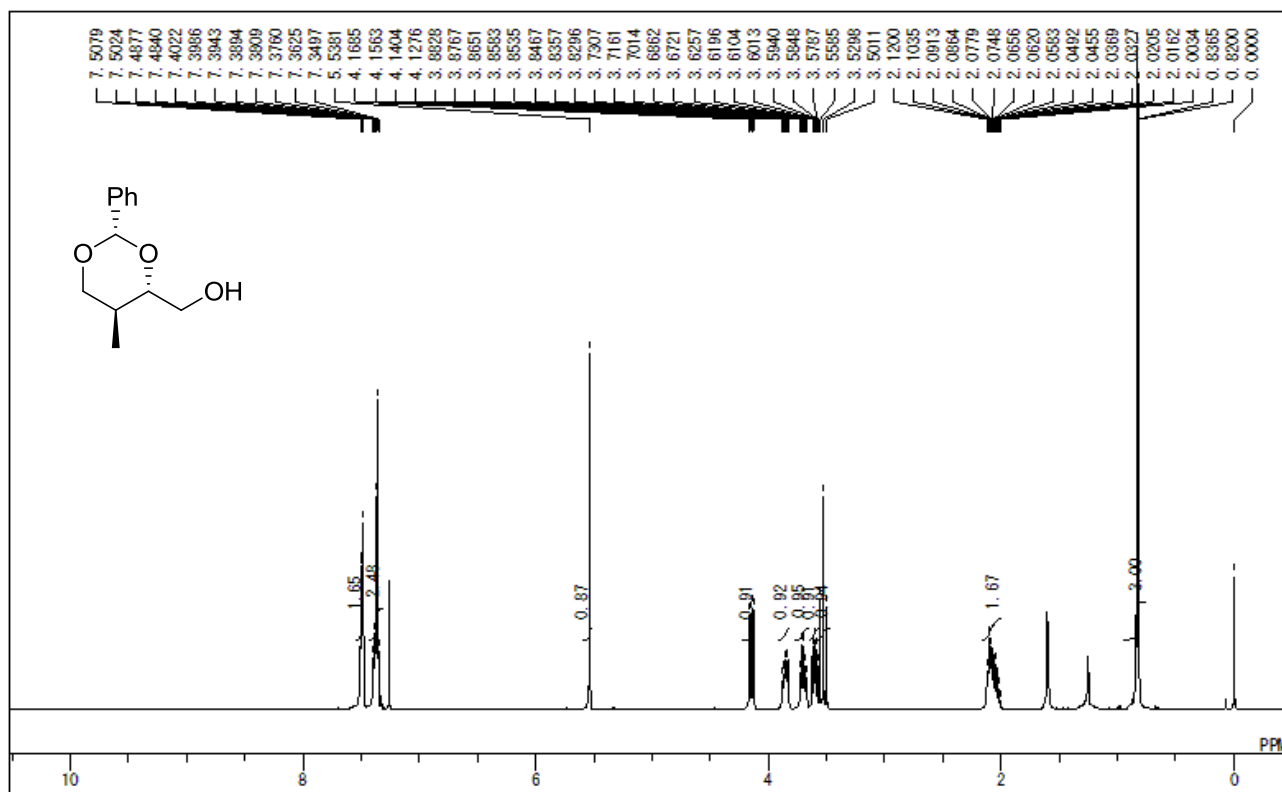


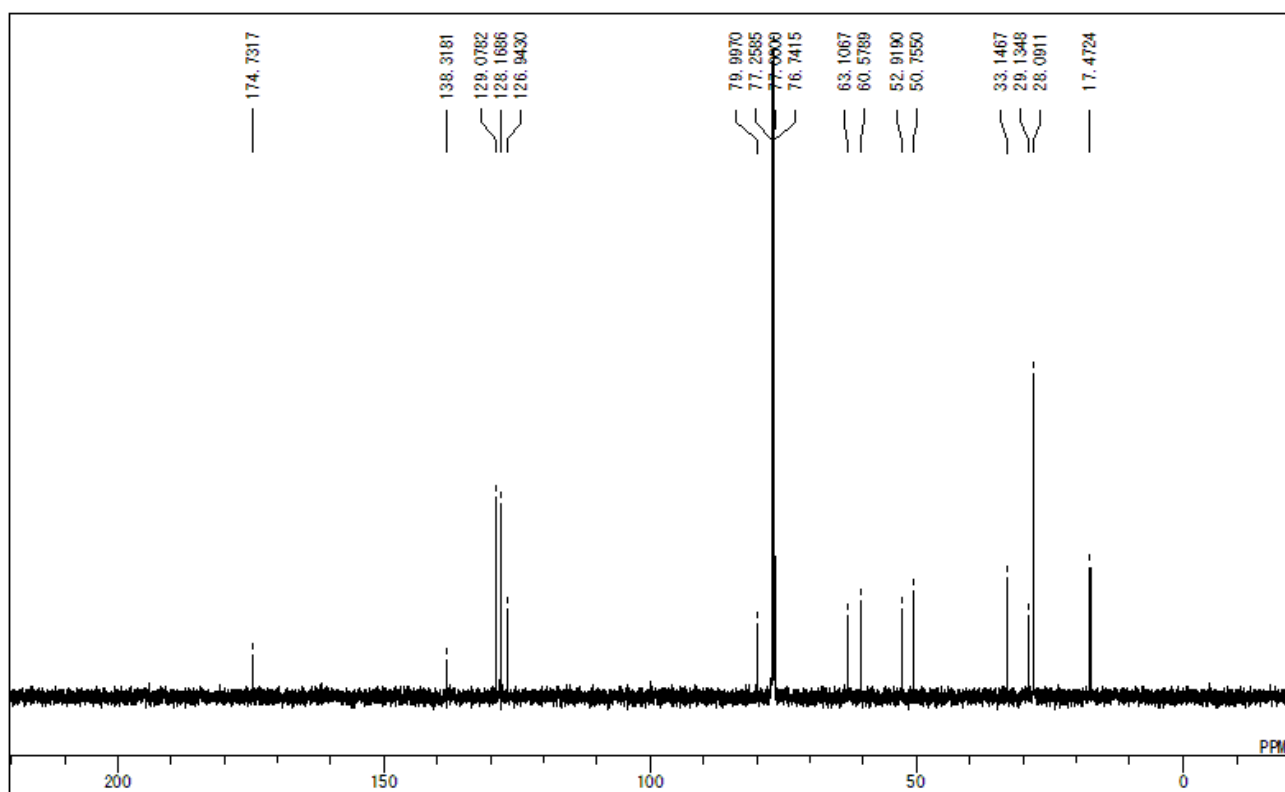
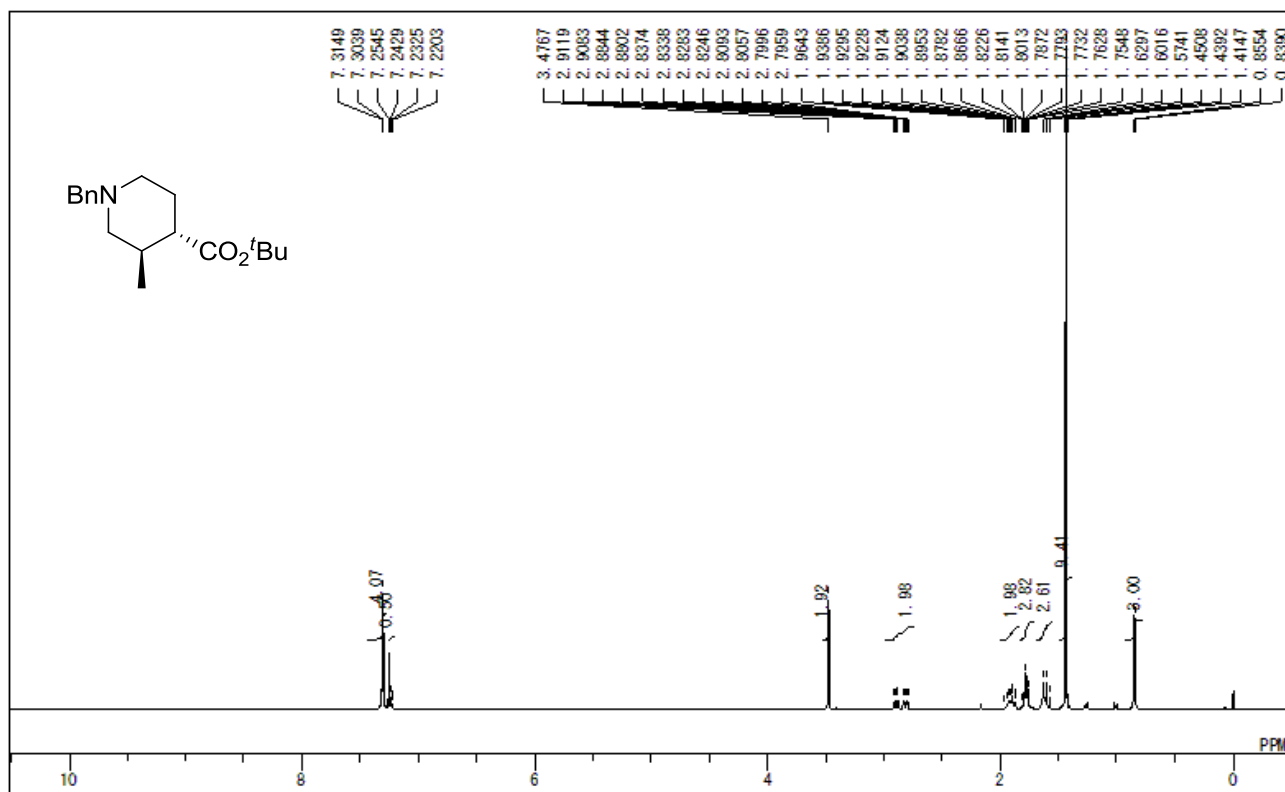




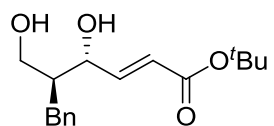




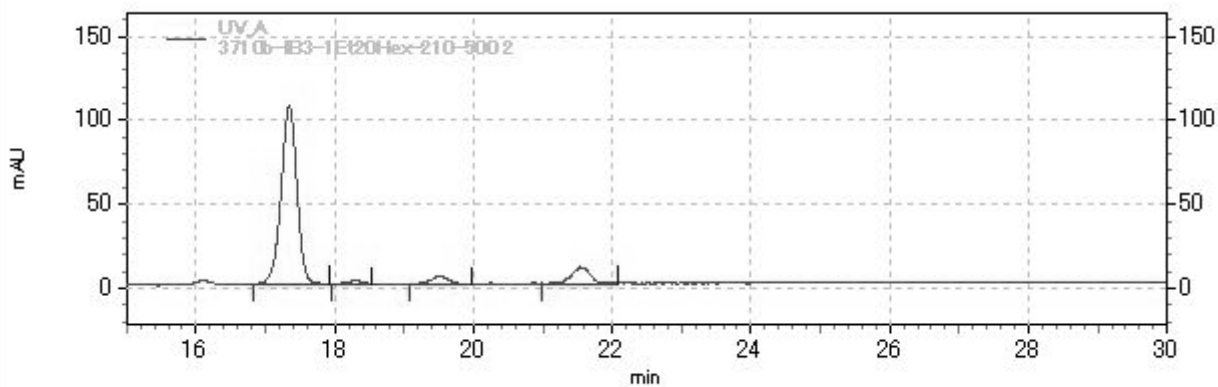
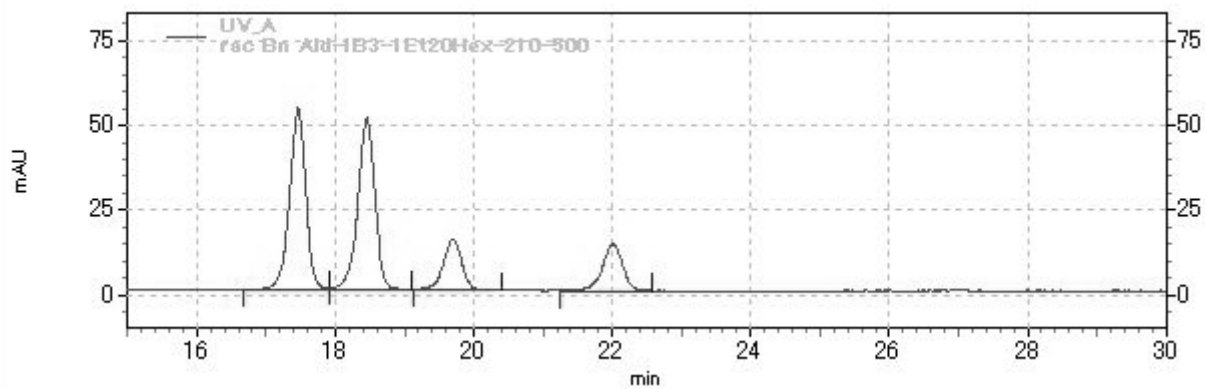


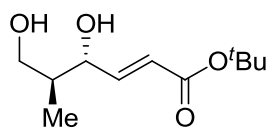


Chiral HPLC Chart

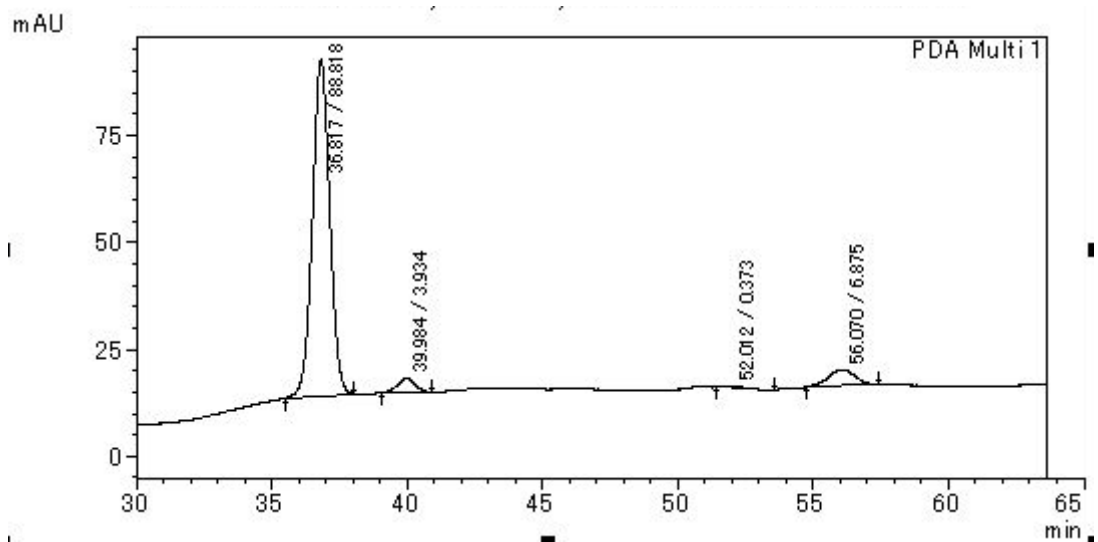
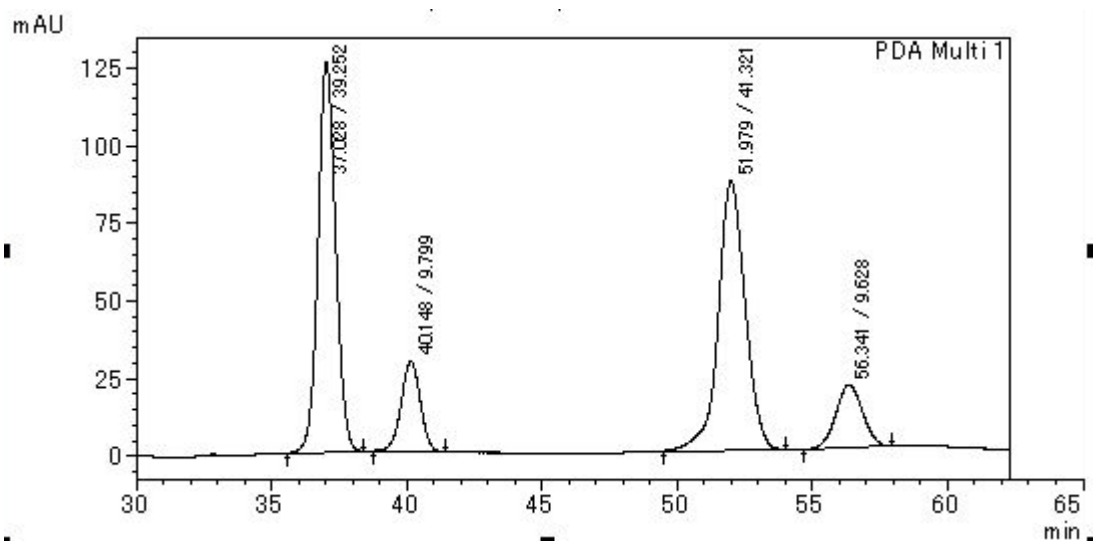


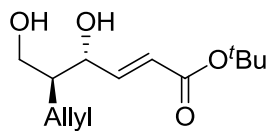
Daicel Chiralpak IB-3, hexane/ethanol = 20/1, flow rate 0.5 mL/min, $\lambda = 210$ nm, retention time: 17.3 min (major) and 18.3 min.



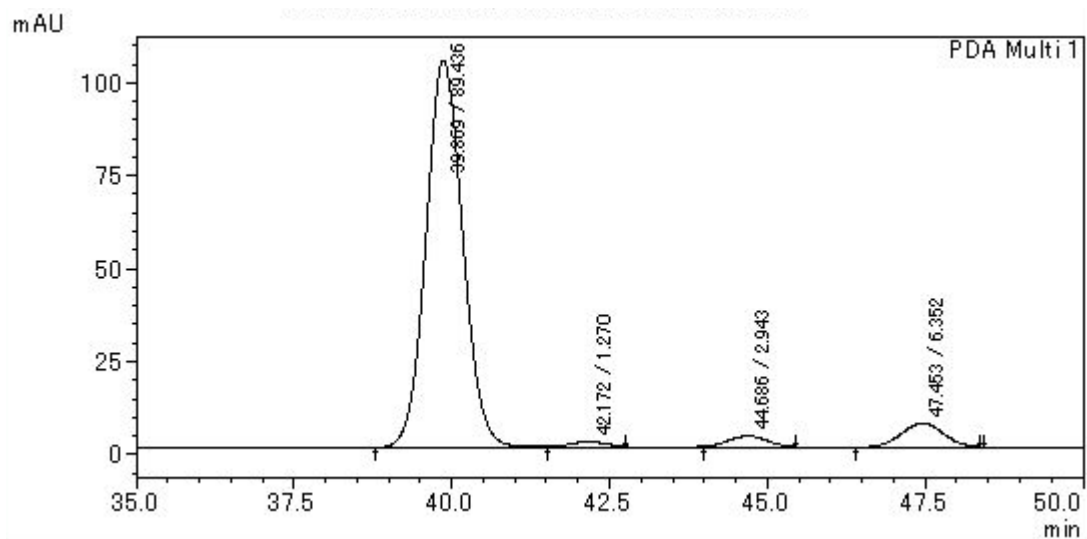
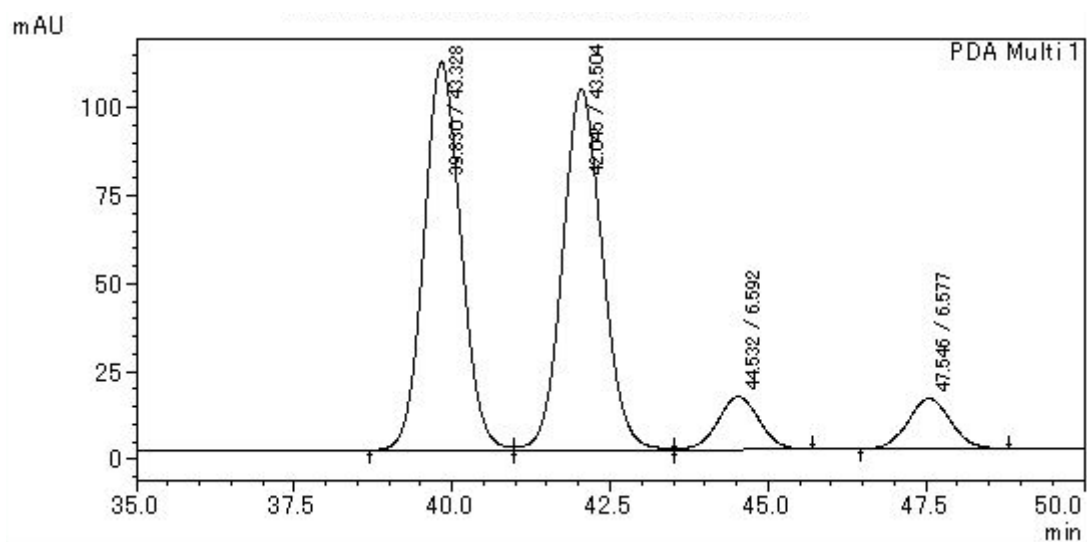


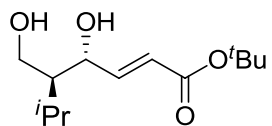
Daicel Chiralpak IF, hexane/ethanol = 20/1, flow rate 0.75 mL/min, $\lambda = 206$ nm, retention time: 36.8 min (major) and 52.0 min.



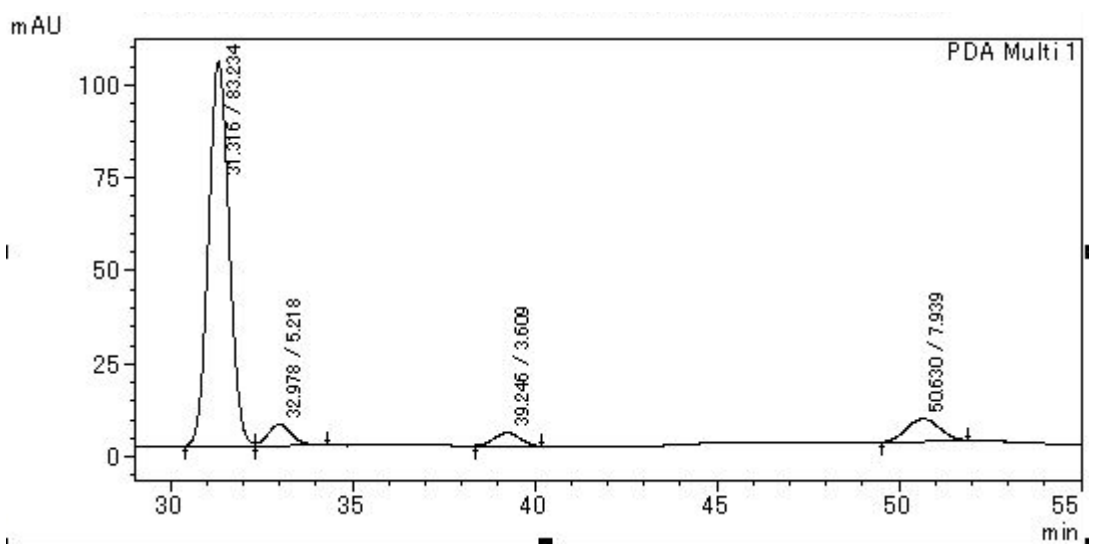
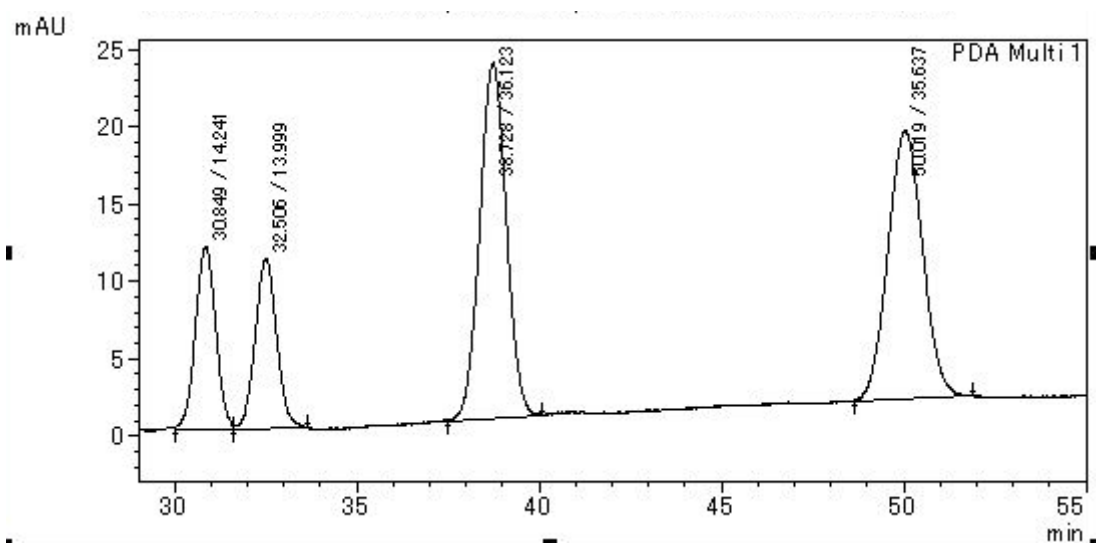


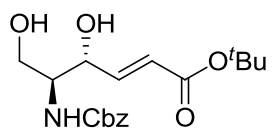
IF-OD-3 (connected two columns), hexane/2-propanol = 20/1, flow rate 0.75 mL/min, $\lambda = 208$ nm, retention time: 39.9 min (major) and 42.2 min.



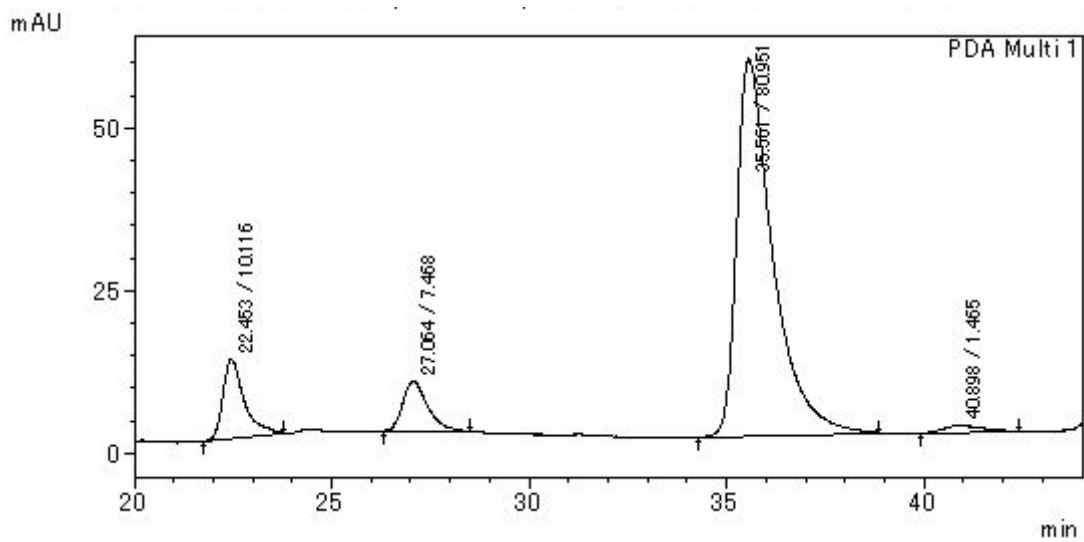
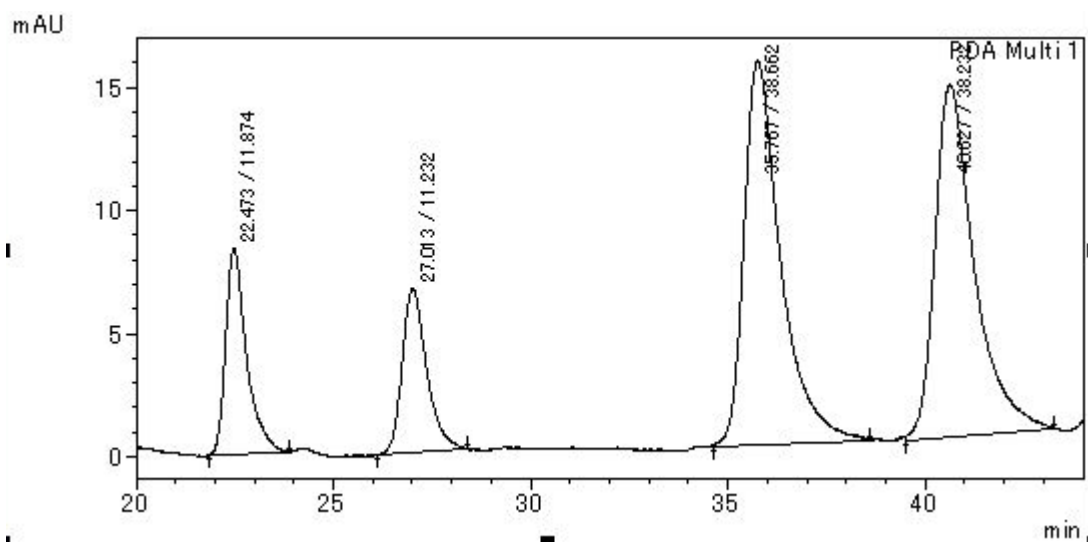


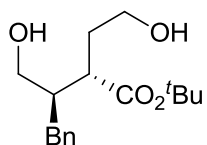
Daicel Chiralpak IC-3, hexane/2-propanol = 10/1, flow rate 0.6 mL/min, $\lambda = 208$ nm, retention time: 31.3 min (major) and 33.0 min.



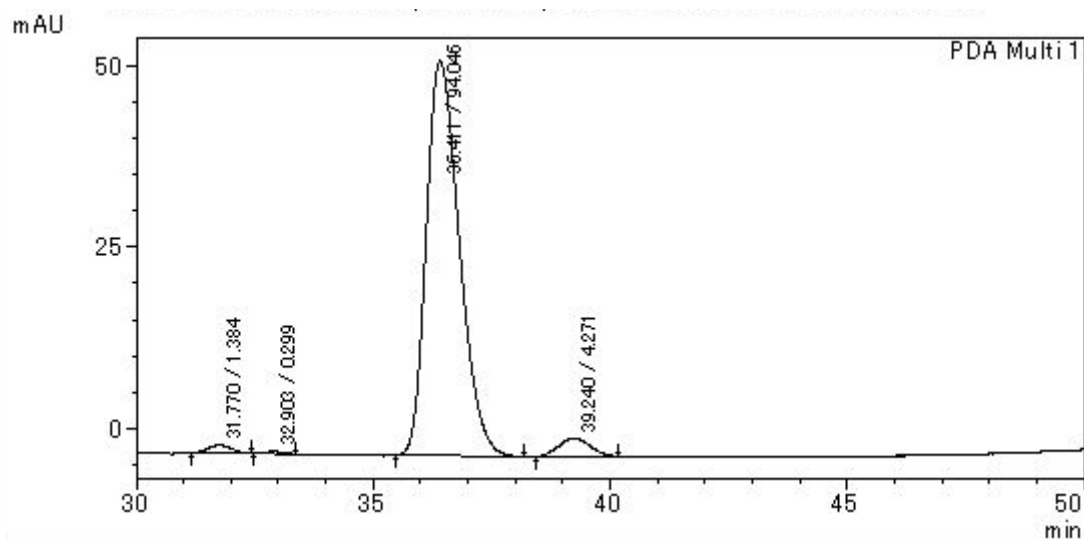
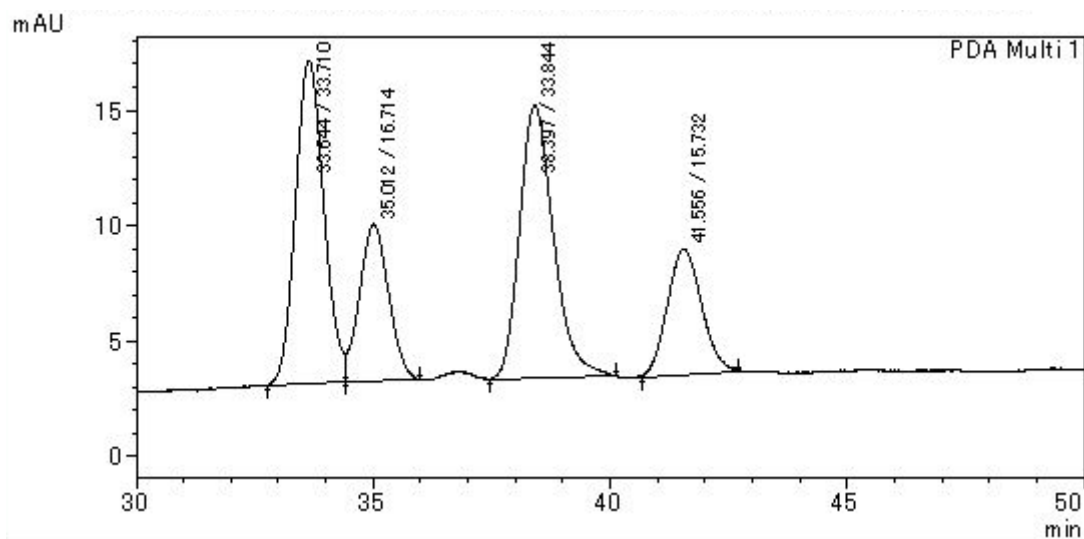


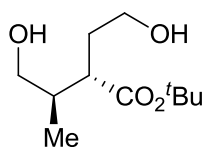
Daicel Chiralpak IB-3, hexane/ethanol = 20/1, flow rate 0.75 mL/min, $\lambda = 206$ nm, retention time: 35.6 min (major) and 40.9 min.





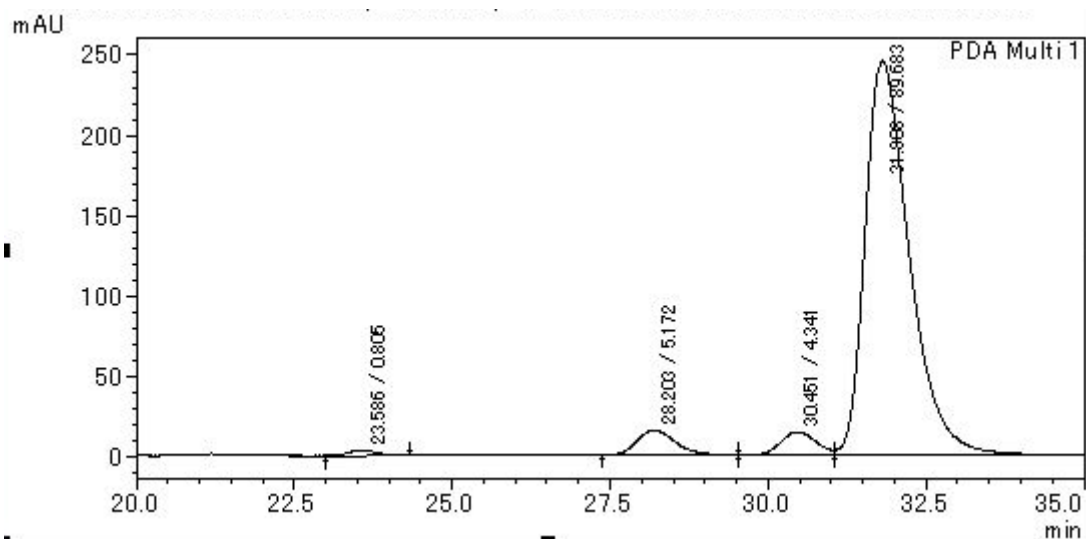
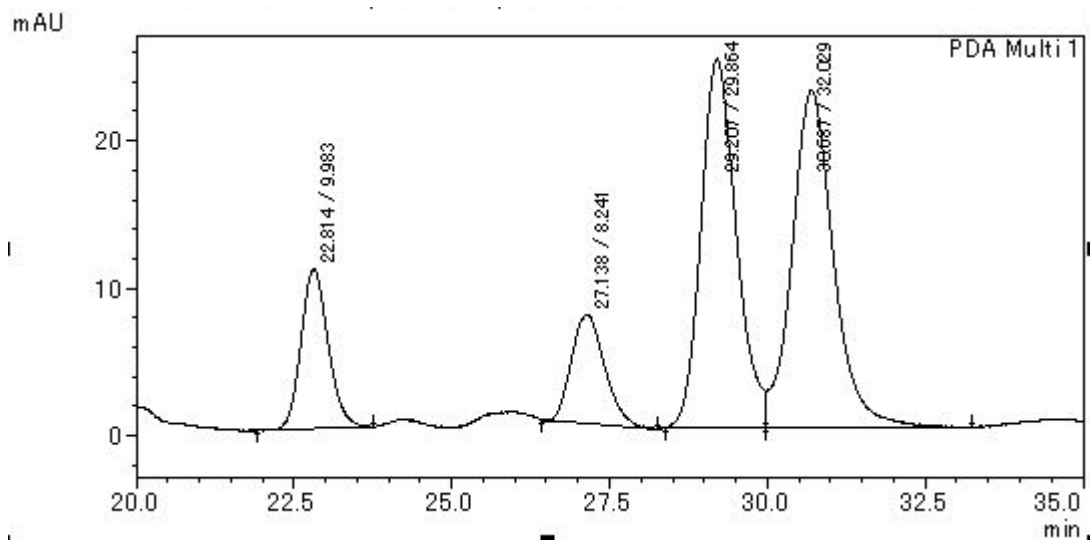
Daicel Chiralpak IE, hexane/ethanol = 30/1, flow rate 1.0 mL/min, $\lambda = 209$ nm, retention time: 31.8 min and 36.4 min (major).

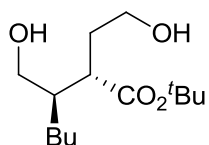




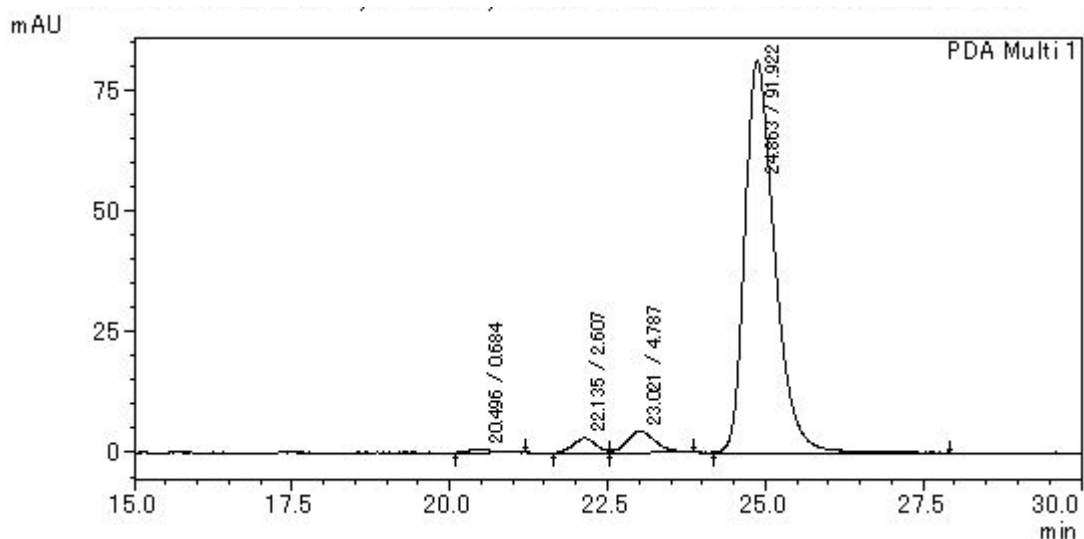
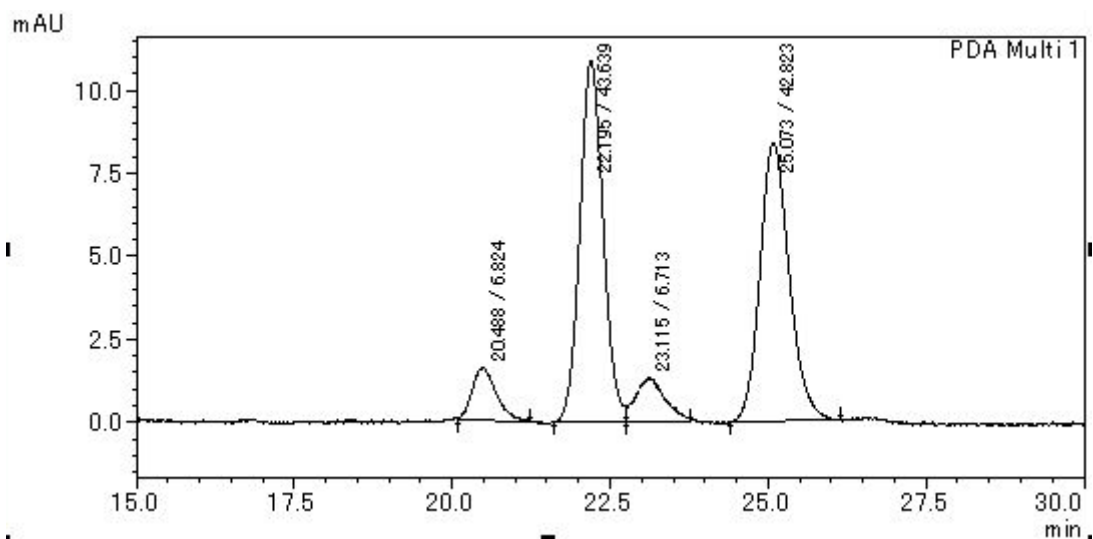
The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester.

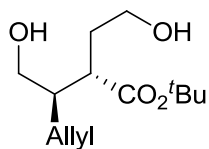
Daicel Chiralpak IA-3, hexane/ethyl acetate = 7/3, flow rate 0.75 mL/min, $\lambda = 252$ nm, retention time: 30.5 min and 31.8 min (major).



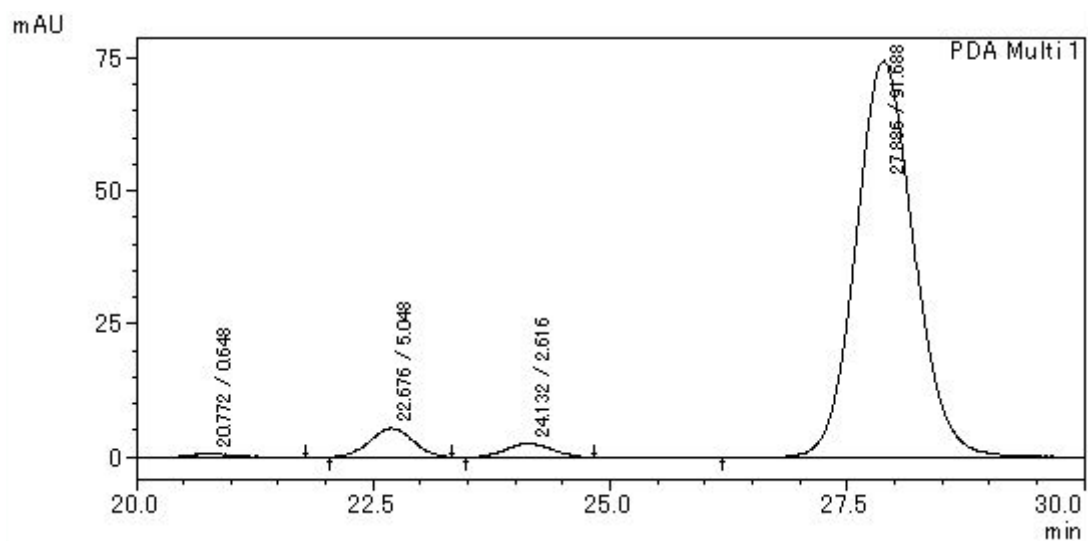
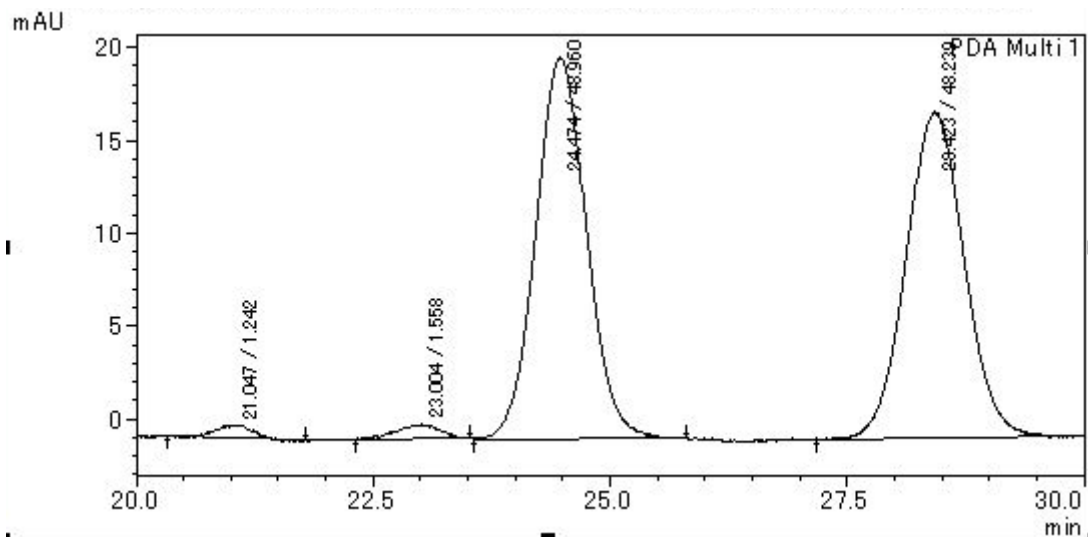


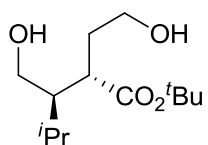
The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA-IF (connected two columns), ethylacetate/ hexane = 3/7, flow rate 1.0 mL/min, $\lambda = 251$ nm, retention time: 22.1 min and 24.9 min (major).



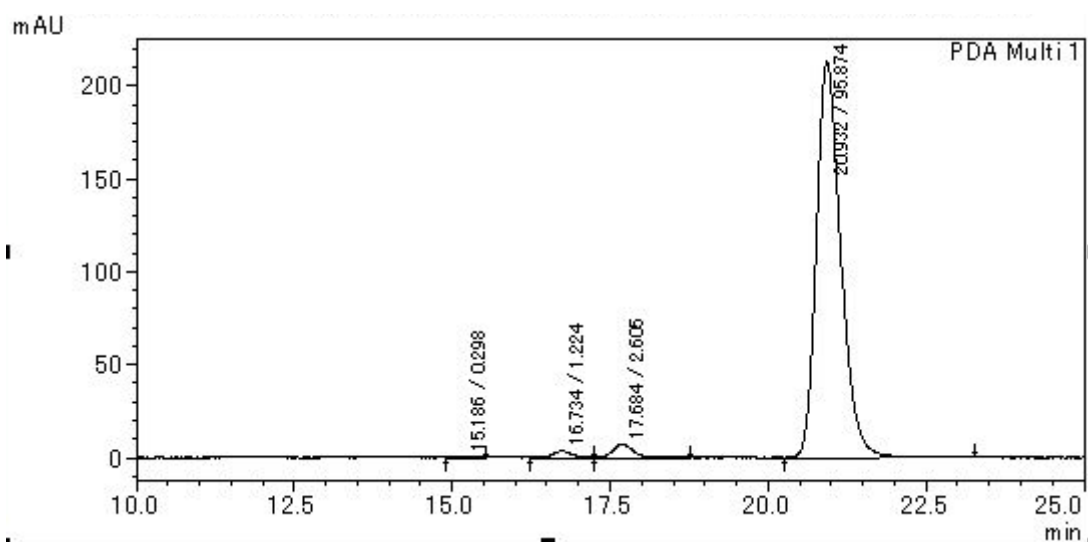
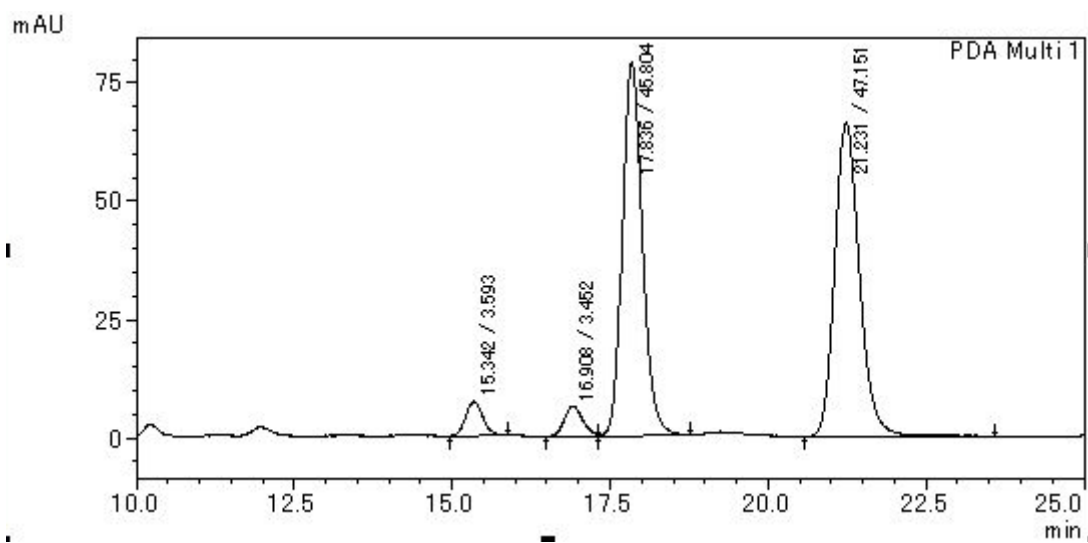


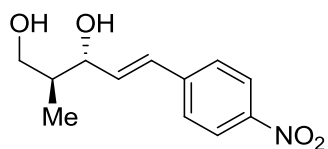
The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA3, hexane/ethanol/ethylacetate = 4/0.15/1, flow rate 1.0 mL/min, $\lambda = 250$ nm, retention time: 24.1 min and 27.9 min (major).



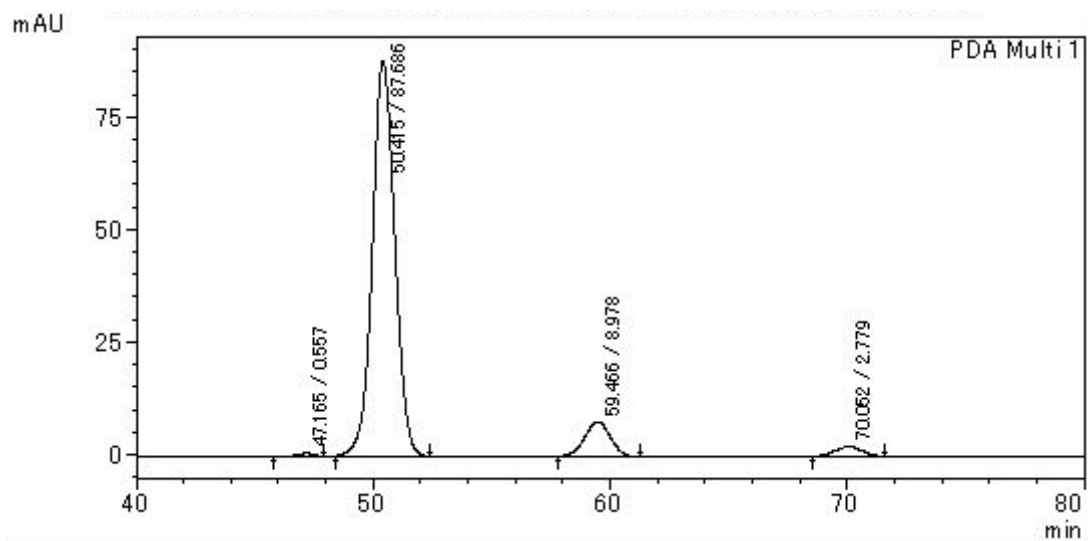
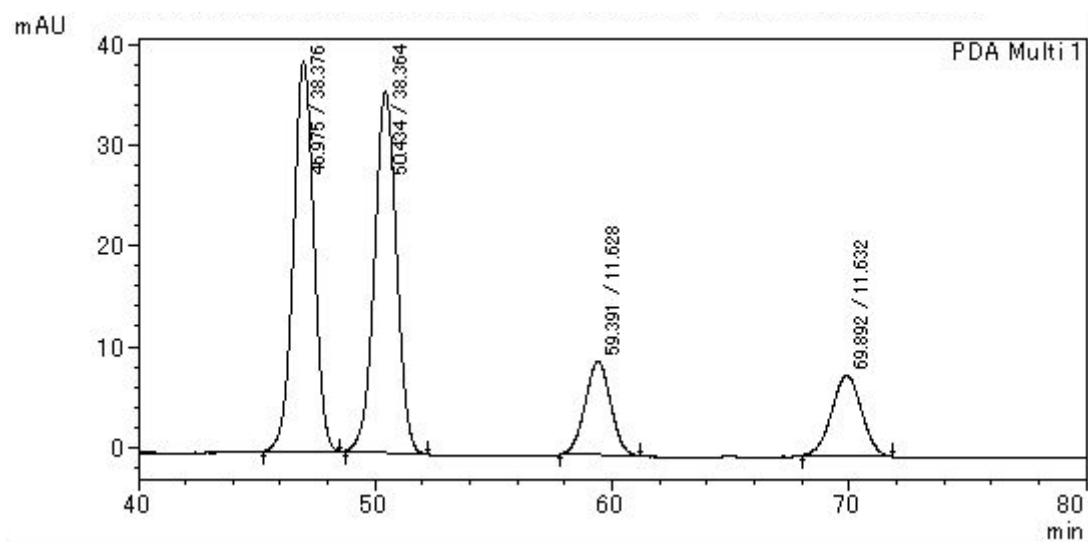


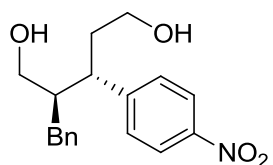
The enantiomeric excess was determined by HPLC after conversion to the corresponding 3,5-dinitrobenzoate ester. Daicel Chiralpak IA-3, hexane/ethyl acetate = 7/3, flow rate 0.75 mL/min, $\lambda = 251$ nm, retention time: 17.7 min and 20.9 min(major).



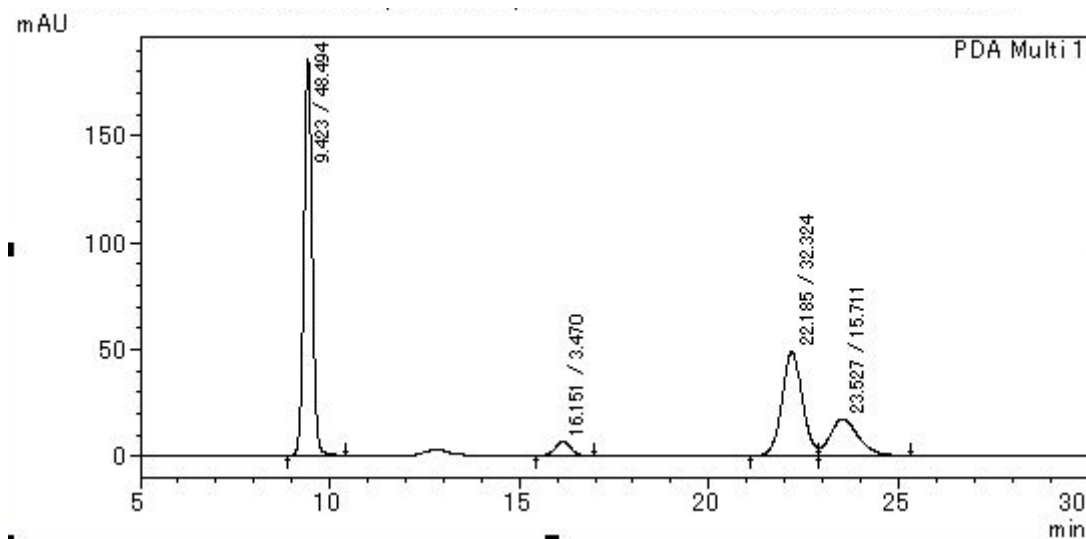
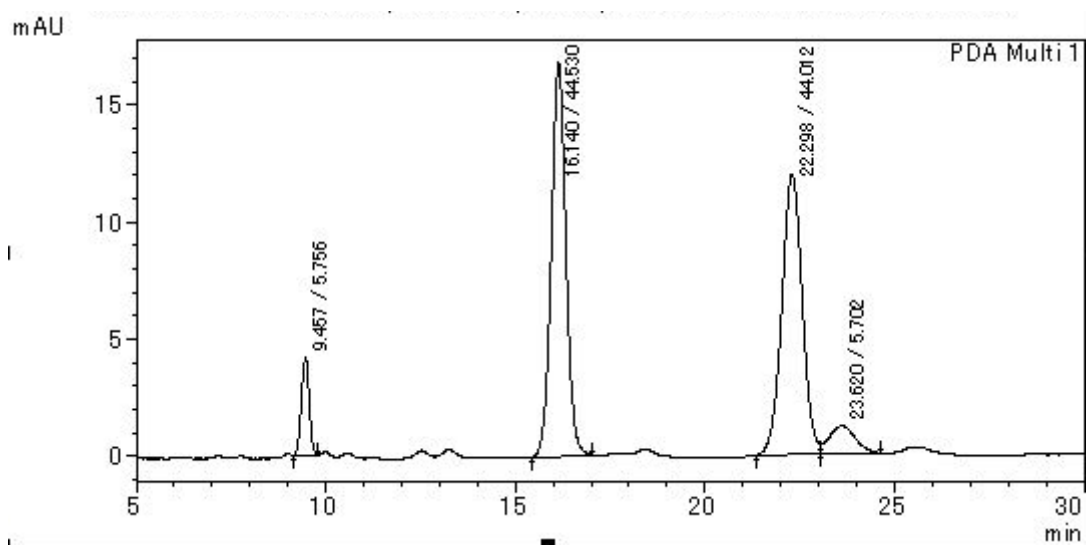


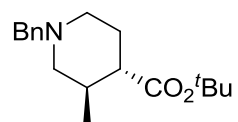
Daicel Chiralpak IF, hexane/ethanol = 10/1, flow rate 1.0 mL/min, $\lambda = 305$ nm, retention time: 47.2 min and 50.4 min (major).





Daicel Chiralpak IA, hexane/ethanol = 5/1, flow rate 1.0 mL/min, $\lambda = 273$ nm, retention time: 9.4min (major) and 22.7 min.





Daicel Chiralpak IF, hexane/ethanol = 200/3, flow rate 1.0 mL/min, $\lambda = 209$ nm, retention time: 7.2 min (major) and 9.0 min.

