Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Chlorine, an atom economical auxiliary for asymmetric aldol reactions

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Supporting Information

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General Experimental Details

All reactions were performed under an atmosphere of dry nitrogen using oven dried glassware unless otherwise specified. THF was freshly distilled from sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2 prior to use. Commercial anhydrous EtOH (reagent grade) was used without further purification. Cold temperatures were maintained by use of the following reaction baths: 0 °C, ice-water; -78 °C, acetone-dry ice; temperatures between -78 °C and -0 °C required for longer reaction times were maintained with a Polyscience VLT-60A immersion chiller.

Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[1] Concentration and removal of trace solvents was carried out with a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on an Agilent 6890 gas chromatograph, equipped with a flame ionization detector and a custom-made chiral GC column coated with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-beta-cyclodextrin and OV-1701.[2] High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1100 HPLC, equipped with a variable wavelength UV-Vis detector and Chiralcel OD-H chiral column (0.46 cm x 25 cm).

NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent unless otherwise indicated. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR) Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), or Bruker 400 (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz), Varian Inova 500 (125 MHz), or Bruker 400 (100 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HMQC and nOe spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound. High resolution mass spectra (HRMS-ESI) were recorded on a Bruker micrOTOF II mass spectrometer. Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589nm.

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

2. Koenig, W.A.; Gehrke, B.; Icheln, D.; Evers, P.; Donnecke, J.; Wang, W. *J. High Resol. Chromatography* **1992**, *15*, 367.

The β-ketochlorohydrins **10, 12, 22** were all prepared according to previously described procedures without complication.[3]

General Procedure A: *dechlorination of β-ketochlorohydrins*

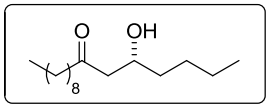
To a 0.1 M solution of β-ketochlorohydrin in toluene was added tris(trimethylsilyl)silane (5 equiv) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. Purification of the crude product was accomplished by flash chromatography as noted.

General Procedure B: *addition of acetonitrile to α-chloroaldehydes*

To a cold (-78 °C), stirred 0.2 M solution of diisopropylamine (1.1 equiv) in THF was added *n*-BuLi (1.1 equiv, 2.5 M in hexanes). This mixture was allowed to warm to 0 °C and was stirred at this temperature for 20 minutes prior to cooling to -78 °C, at which temperature a solution of acetonitrile (1.0 equiv) in THF (1 ml) was added. After an additional 30 minutes of stirring at -78 °C, a solution of the α-chloroaldehyde (1.3 equiv) in THF was slowly added to the reaction mixture. After a further 20 minutes stirring at -78 °C, the reaction mixture was treated with saturated aqueous NH_4Cl, diluted with EtOAc, the phases were separated, and the aqueous phase was washed with EtOAc (3 x 30 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to provide a crude oil. Purification of the crude product was carried out by flash chromatography as noted.

3. (a) Draper, J.; Britton, R. *Org. Lett.* **2010**, *12*, 4034. (b) Halperin, S. D.; Kang, B.; Britton, R. *Synthesis*, **2011**, 1946.

(*R*)-5-hydroxyhexadecan-7-one (24)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (*R*)-5-hydroxyhexadecan-7-one (**20**) (21 mg, 92%) as a white solid.

mp 41-44 °C

IR (neat): 3333, 2955, 2918, 2849, 1703, 1466, 1118, 720 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (m, 1H), 3.04 (d, *J* = 3.5 Hz, 1H), 2.60 (dd, *J* = 2.8, 17.5 Hz, 1H), 2.49 (dd, *J* = 9.2, 17.5 Hz, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.61-1.20 (m, 20H), 0.93-0.84 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.7, 67.7, 48.9, 43.7, 36.1, 31.9, 29.40, 29.38, 29.3, 29.2, 27.6, 23.6, 22.7, 22.6, 14.1, 14.0.

HRMS: *m/z* calc for $C_{16}H_{32}O_2$: 257.2481 (M+H); Found: 257.2477 (M+H).

$[\alpha]_D^{20}$ = + 29.1° (c 0.28, $CHCl_3$)

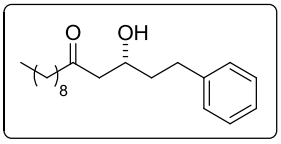
Determination of enantiomeric excess for 5-hydroxyhexadecan-7-one (**24**).

Samples of both 'racemic'[4,5] and optically enriched 5-hydroxyhexadecan-7-one (**24**) were converted into the corresponding benzoyl esters (5 equiv. benzoyl chloride, 10 equiv. pyridine, CH_2Cl_2, 14 h, room temperature). The corresponding enantiomeric benzoyl esters of 5-hydroxyhexadecan-7-one (**24**) were separable by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 95:5, detection at 230 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 5.18 min; the retention time of the (-)-enantiomer is 4.14 min (see chromatograms below).

4. 'Racemic' β-hydroxyketones were prepared in an identical manner to the optically enriched β-hydroxyketones except that the α-chloroaldehyde starting materials were prepared using proline catalysis. As reported by Jørgensen,[5] α-chloroaldehydes prepared in this way have an enantiomeric excess less 25% (enantiomeric ratio approximately 60:40). As a result, the chromatograms of 'racemic' β-hydroxyketones do not show an equal proportion of enantiomers and instead range from 0 to 25% enantiomeric excess.

5. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc*., **2004**, *126*, 4790.

(*R*)-3-hydroxy-1-phenyltetradecan-5-one (27)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (*R*)-3-hydroxy-1-phenyltetradecan-5-one (**27**) (18 mg, 85%) as a white solid.

mp 35-38 °C

IR (neat): 3372, 3273, 3027, 2953, 2917, 2850, 1704, 14468, 1453, 1110, 697 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 2H), 7.22-7.17 (m, 3H), 4.05 (m, 1H), 3.17 (d, *J* = 3.2 Hz, 1H), 2.82 (ddd, *J* = 5.4, 9.8, 14.2 Hz, 1H), 2.69 (ddd, *J* = 6.9, 9.8, 14.2 Hz, 1H), 2.60 (dd, *J* = 3.0, 17.7 Hz, 1H), 2.52 (dd, *J* = 8.9, 17.7 Hz, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.82 (m, 1H), 1.68 (m, 1H), 1.61-1.50 (m, 2H), 1.35-1.20 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.6, 141.9, 128.47, 128.41, 125.9, 66.9, 48.9, 43.7, 38.0, 31.9, 31.8, 29.4, 29.3, 29.2, 29.1, 23.6, 22.7, 14.1.

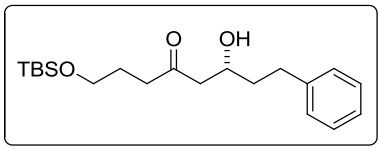
HRMS: *m/z* calcd for $C_{20}H_{32}O_2$: 305.2475 (M+H); Found: 305.2476 (M+H).

$[\alpha]_D^{20}$ = + 26.6° (c 0.15, $CHCl_3$)

Determination of enantiomeric excess for (*R*)-3-hydroxy-1-phenyltetradecan-5-one (**27**).

Samples of both 'racemic'[4,5] and optically enriched (*R*)-3-hydroxy-1-phenyltetradecan-5-one (**27**) were analyzed by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 20:1; detection at 205 nm; flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 12.13 min; the retention time of the (-)-enantiomer is 7.83 min. (see chromatograms below).

(*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (26)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 10:1) to afford (*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (**26**) (12 mg, 86%) as a colourless oil.

IR (neat): 3453, 3026, 3027, 2953, 2928, 2857, 1708, 1496, 1256, 1100, 1032, 836, 699 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.28 (m, 2H), 7.23-7.17 (m, 3H), 4.06 (m, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 3.19 (s, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.63 (dd, *J* = 2.7, 17.6 Hz, 1H), 2.55 (dd, *J* = 9.1, 17.6 Hz, 1H), 2.51 (t, *J* = 7.4 Hz, 2H), 1.88-1.76 (m, 3H), 1.69 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 141.9, 128.5, 128.4, 125.9, 66.9, 62.0, 49.1, 40.0, 38.1, 31.8, 26.6, 25.9, 25.9, 18.3, -5.4.

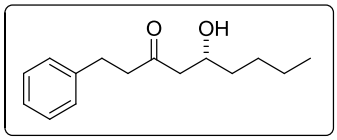
HRMS: *m/z* calcd for $C_{20}H_{34}O_3Si$: 351.2311 (M+H); Found: 351.2357 (M+H)

$[\alpha]_D^{20}$ = + 26.2° (c 0.11, $CHCl_3$)

Determination of enantiomeric excess for (*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (**26**).

Samples of both 'racemic'[4,5] and optically enriched (*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (**26**) were analyzed by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 95:5; detection at 205 nm; flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 18.06 min; the retention time of the (-)-enantiomer is 10.22 min (see chromatograms below).

(*R*)-5-hydroxy-1-phenylnonan-3-one (25)



Prepared following General Procedure A. The crude product was purified by flash chromatography hexanes-EtOAc 9:1) to afford (*R*)-5-hydroxy-1-phenylnonan-3-one (**25**) (16 mg, 92%) as a white solid.

mp 161-165 °C

IR (neat): 3454, 2955, 2928, 2857, 1711, 1604, 1454, 1260, 1032, 841 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.25 (m, 2H), 7.23-7.15 (m, 3H), 4.02 (m, 1H), 2.95-2.88 (m, 3H), 2.79-2.73 (m, 2H), 2.57 (dd, *J* = 3.0, 17.5 Hz, 1H), 2.49 (dd, *J* = 8.9, 17.5 Hz, 1H), 1.43-1.23 (m, 7H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 140.7, 128.5, 128.3, 126.2, 67.6, 49.3, 45.1, 36.1, 29.5, 27.6, 22.6, 14.0.

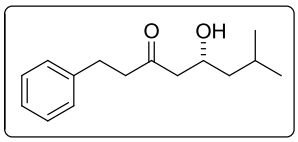
HRMS: *m/z* calcd for $C_{15}H_{23}O_2$: 235.1693 (M+H); Found: 235.1693 (M+H)

$[\alpha]_D^{20}$ = + 41.2° (c 0.27, $CHCl_3$)

Determination of enantiomeric excess for (*R*)-5-hydroxy-1-phenylnonan-3-one (**25**).

Samples of both 'racemic'[4,5] and optically enriched (*R*)-5-hydroxy-1-phenylnonan-3-one (**25**) were analyzed by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 20:1; detection at 210 nm; flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 12.25 min; the retention time of the (-)-enantiomer is 8.10 min. (see chromatograms below).

(*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (28)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (**28**) (20 mg, 95%) as a white solid.

mp 163-164 °C

IR (neat): 3442, 3027, 2955, 2928, 2869, 1707, 1496, 748, 699 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.26 (m, 2H), 7.23-7.16 (m, 3H), 4.12 (m, 1H), 2.95-2.87 (m, 3H), 2.80-2.75 (m, 2H), 2.56 (dd, *J* = 3.2, 17.4 Hz, 1H), 2.49 (dd, *J* = 8.6, 17.4 Hz, 1H), 1.78 (m, 1H), 1.46 (ddd, *J* = 5.5, 8.6, 13.9 Hz, 1H), 1.12 (dddd, *J* = 0.6, 4.5, 8.6, 13.9 Hz, 1H), 0.93 (d, *J* = 0.6 Hz, 3H), 0.91 (d, *J* = 0.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 140.7, 128.6, 128.3, 126.2, 65.7, 49.8, 45.6, 45.1, 29.5, 24.4, 23.3, 22.0.

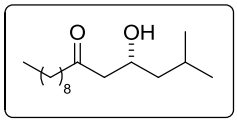
HRMS: *m/z* calcd for $C_{15}H_{23}O_2$: 235.1693 (M+H); Found: 235.1694 (M+H)

$[\alpha]_D^{20}$ = + 22.6° (c 0.53, $CHCl_3$)

Determination of enantiomeric excess for (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (**28**).

Samples of both 'racemic'[4,5] and optically enriched (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (**28**) were analyzed by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 20:1; detection at 205 nm; flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 10.21 min; the retention time of the (-)-enantiomer is 6.95 min. (see chromatograms below).

(*R*)-4-hydroxy-2-methylpentadecan-6-one (29)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (*R*)-4-hydroxy-2-methylpentadecan-6-one (**29**) (57 mg, 81%) as a colourless oil.

IR (neat): 3439, 2955, 2925, 2855, 1707, 1466, 1358, 840 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (m, 1H), 3.06 (d, *J* = 3.3 Hz, 1H), 2.58 (dd, *J* = 2.6, 17.6 Hz, 1H), 2.48 (dd, *J* = 9.1, 17.6 Hz, 1H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.79 (m, 1H), 1.61-1.52 (m, 2H) 1.46 (m, 1H), 1.30-1.20 (m, 12H), 1.11 (m, 1H), 0.91 (d, *J* = 1.8 Hz, 3H), 0.90 (d, *J* = 1.8 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.4, 66.5, 50.2, 46.3, 44.5, 31.6, 30.2, 30.1, 30.0, 29.9, 25.1, 24.4, 24.1, 23.4, 22.8

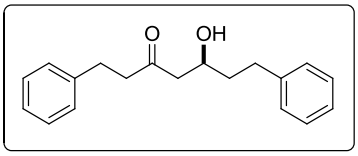
HRMS: *m/z* calcd for $C_{16}H_{32}O_2$: 257.2467 (M+H); Found: 257.2475 (M+H).

$[\alpha]_D^{20}$ = + 30.0° (c 0.3, $CHCl_3$)

Determination of enantiomeric excess for (*R*)-4-hydroxy-2-methylpentadecan-6-one (**29**).

Samples of both 'racemic'[4,5] and optically enriched (*R*)-4-hydroxy-2-methylpentadecan-6-one (**29**) were analyzed by chiral GC using an Agilent 6890 gas chromatograph, equipped with a flame ionization detector and a custom-made chiral GC column coated with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-beta-cyclodextrin and OV-1701. Temperature program: 140 °C isothermal, split injection. The retention time of the (+)-enantiomer is 89.7 min; the retention time of the (-)-enantiomer is 88.3 min.

(+)-Dihydroyashabushiketol (**32**)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (+)-dihydroyashabushiketol (**32**) (28 mg, 96%) as a white solid. The spectral data acquired on this material was in complete agreement with that reported.[6]

mp 62-65 °C

IR (neat): 3439, 3026, 2926, 2860, 1709, 1603, 1495, 1453, 1406, 1371, 1096, 748, 699 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (m, 4H), 7.26-7.19 (m, 6H), 4.10 (m, 1H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.89-2.67 (m, 5H), 2.60-2.56 (m, 2H), 1.89-1.80 (m, 1H), 1.77-1.67 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.1, 141.8, 140.7, 128.6, 128.5, 128.4, 128.3, 126.3, 125.9, 66.9, 49.3, 45.0, 38.0, 31.7, 29.5.

HRMS: *m/z* calcd for $C_{19}H_{22}O_2$: 305.1509 (M+Na); Found: 305.1512 (M+Na).

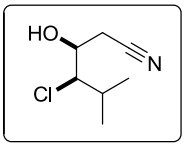
$[\alpha]_D^{20}$ = + 14.6° (c 0.75, $CHCl_3$)

Determination of enantiomeric excess for dihydroyashabushiketol (**32**).

Samples of both 'racemic'[4,5] and optically enriched dihydroyashabushiketol (**32**) were converted into the corresponding benzoyl esters (5 equiv. benzoyl chloride, 10 equiv. pyridine, CH_2Cl_2, 14 h, room temperature). The corresponding enantiomeric benzoyl esters of dihydroyashabushiketol (**32**) were separable by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 90:10; detection at 230 nm; flow rate = 1.5 mL/min. The retention time of the (+)-enantiomer is 8.39 min; the retention time of the (-)-enantiomer is 9.54 min. (see chromatograms below).

6. Romanski, J.; Nowak, P.; Chapuis, C., Jurczak, J. *Tetrahedron: Asymmetry*, **2011**, *22*, 787

(+/-)-(4*R*,3*S*)-4-chloro-3-hydroxy-5-methylhexanenitrile (14)



Prepared following General Procedure B. The crude product (4:1 d.r.) was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (+/-)-(4*R*,3*S*)-4-chloro-3-hydroxy-5-methylhexanenitrile (**14**) (121 mg, 54%, 8:1 *dr*) as a colourless oil.

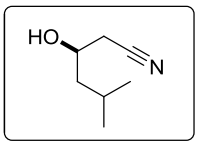
IR (neat): 3443, 2969, 2937, 2878, 2257, 1636, 1464, 1414, 1389, 1371, 1063, 821, 758, 739 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08 (dt, *J* = 7.3, 3.8 Hz, 1H), 3.84 (dd, J = 8.1, 4.1 Hz, 1H), 2.88 (dd, *J* = 16.7, 3.6 Hz, 1H), 2.77 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.31 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 117.2, 70.7, 69.1, 29.4, 23.9, 20.5, 16.1.

HRMS: *m/z* calcd for $C_7H_{12}ClNO$: 184.0500 (M+Na); Found: 184.0504 (M+Na).

(+/-)-(3*R*)-3-hydroxy-5-methylhexanenitrile (19)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 4:1) to afford (+/-)-(3*R*)-3-hydroxy-5-methylhexanenitrile (**19**) (33 mg, 70%) as a colourless oil.

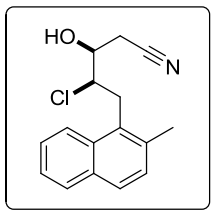
IR (neat): 3437, 2959, 2932, 2872, 2252, 1469, 1416, 1369, 1224, 1078, 1023, 612 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.02 (m, 1H), 2.57 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.47 (dd, *J* = 16.7, 6.3 Hz, 1H), 2.29 (s, 1H) 1.79 (m, 1H), 1.57 (m, 1H), 1.36 (m, 1H), 0.97-0.91 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 117.8, 65.9, 45.5, 26.6, 24.5, 23.1, 21.8.

HRMS: *m/z* calcd for $C_7H_{13}NO$: 150.0889 (M+Na); Found: 150.0893 (M+Na).

(+/-)-(4*R*,3*S*)-4-chloro-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile (11)



Prepared following General Procedure B. Analysis of the crude reaction product indicated that the ratio of diastereomeric chlorohydrins was 2:1. The major (1,2-*anti*) chlorohydrin was purified by flash chromatography (hexanes:EtOAc:CH_2Cl_2 9:1:1) to afford (+/-)-(4*R*,3*S*)-4-chloro-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile

(**11**) (378 mg, 53%, 12:1 d.r.) as white solid.

mp 132-136 °C.

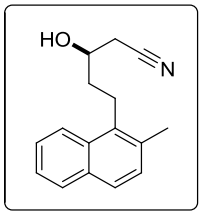
IR (neat): 3425, 3052, 2972, 2930, 2870, 2254, 2211, 1729, 1709, 1624, 1599, 1512, 1265, 1076, 955 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.44 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.4 (m, 1H), 4.27 (m, 1H), 3.84 (dd, *J* = 15.0, 4.4 Hz, 1H), 3.51 (dd, *J* = 15.0, 9.7 Hz, 1H), 2.91 (dd, *J* = 16.9, 4.0 Hz, 1H), 2.79 (dd, *J* = 16.9, 8.0 Hz, 1H), 2.75 (d, *J* = 6.1 Hz, 1H), 2.58 (s, 3H),

^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9, 132.7, 132.1, 129.8, 129.3, 129.0, 127.7, 126.6, 124.9, 123.1, 117.1, 71.6, 64.9, 32.6, 23.5, 21.0.

HRMS: *m/z* calcd for $C_{16}H_{16}ClNO$: 274.0993 (M+H); Found: 274.0998 (M+H).

(+/-)-(3*R*)-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile (16)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes:EtOAc 4:1) to afford (+/-)-(3*R*)-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile (**16**) (113 mg, 88%) as a colourless oil.

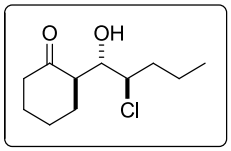
IR (neat): 3453, 3050, 2955, 2924, 2251, 1730, 1707, 1597, 1511, 1414, 1265, 1087, 813 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.52 (dt, *J* = 7.24, 1.15 Hz, 1H), 7.43 (t, *J* = 7.24 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 4.11 (m, 1H), 3.31 (m, 1H), 3.16 (m, 1H), 2.60-2.55 (m, 2H), 2.53 (s, 3H), 1.94-1.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.0, 133.2, 132.8, 132.06, 129.4, 126.7, 126.3, 124.8, 123.3, 117.7, 67.9, 60.6, 36.6, 26.5, 24.4, 20.3.

HRMS: *m/z* calcd for $C_{16}H_{17}NO$: 240.1383 (M+H); Found: 240.1355 (M+H).

(+/-)-(2*R*)-2-((1'*S*,2'*R*)-2'-chloro-1'-hydroxypentyl)cyclohexanone (12)



To a cold (-78 °C), stirred 0.2 M solution of diisopropylamine (1.1 equiv) in THF was added *n*-BuLi (1.1 equiv, 2.5 M in hexanes). This mixture was allowed to warm to 0 °C and was stirred at this temperature for 20 minutes prior to cooling to -78 °C, at which temperature a solution of cyclohexanone (1.0 equiv) in THF (1 ml) was added. After an additional 30 minutes of stirring at -78 °C, a solution of the 2-chloropentanal (1.3 equiv) in THF was slowly added to the reaction mixture. After a further 20 minutes stirring at -78 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, diluted with EtOAc, the phases were separated, and the aqueous phase was washed with EtOAc (3 x 30 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to provide a crude oil. Purification of the crude product was carried out by flash chromatography (hexanes-CH_2Cl_2-EtOAc 9:2:1) to afford (+/-)-(2*R*)-2-((1'*S*,2'*R*)-2'-chloro-1'-hydroxypentyl)cyclohexanone (**12**) (56%, 9:1 d.r.) as a colourless oil.

IR (neat): 3508, 2959, 2938, 2870, 1696, 1450, 1312, 1132, 1082, 974 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ: 4.09 (dt, *J* = 8.7, 2.5 Hz, 1H), 3.43 (m, 1H), 3.36 (d, *J* = 10.1 Hz, 1H), 3.01 (ddd, *J* = 12.4, 5.4, 3.1 Hz, 1H), 2.40-2.33 (m, 2H), 2.14-2.0 (m, 3H), 1.96-1.55 (m, 6H), 1.41 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 216.3, 77.1, 64.5, 51.4, 43.1, 36.0, 33.0, 28.5, 25.6, 19.7, 13.6

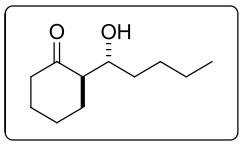
HRMS: *m/z* calcd for $C_{11}H_{19}ClO_2$: 219.1146 (M+H); Found: 219.1138 (M+H).

Proof of the relative stereochemistry of **12** was accomplished as follows.

A purified sample of **12** was reduced (catecholborane (1.2 eq.), THF) and subsequently converted to the corresponding epoxide (2M NaOH (1.2 eq), EtOH). Analysis of the ^1H NMR spectrum recorded on the epoxide revealed that the two epoxide protons resonated at 2.94 and 2.82 ppm, and shared a coupling constant of 2.5 Hz, typical of a *trans* epoxide. Additionally, irradiation of either proton resonance did not result in an enhancement of the other proton resonance in nOe experiments. These results confirm the *anti* stereochemistry of the chlorohydrin function in **12**.

As described below, reduction of the chloromethine function in **12** afforded the β-hydroxyketone **17**. The spectral data recorded on **17** was consistent with that reported for structurally related *anti*-aldol adducts of cyclohexanone (see below for details).

(+/-)-(2*R*)-2-(1'*R*)-(1'-hydroxypentyl)cyclohexanone (17)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (+/-)-(*R*)-2-(1'*R*)-(1'-hydroxypentyl)cyclohexanone (**17**) (74%) as a colourless oil. The spectral data derived from compound **17** matched closely to that reported for (2*R*)-2-(1'*R*)-(1'-hydroxydecyl)cyclohexanone.[7] Based on these spectral similarities, the relative stereochemistry for compound **17** was assigned as depicted above and in the manuscript.

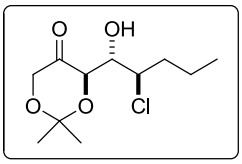
IR (neat): 3528, 2936, 2861, 1697, 1449, 1403, 1312, 969 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73 (m, 1H), 3.42 (d, *J* = 4.3 Hz, 1H), 2.44-2.26 (m, 3H), 2.14-2.05 (m, 2H), 1.91 (m, 1H), 1.74-1.61 (m, 2H), 1.56-1.24 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.9, 71.5, 55.9, 42.9, 33.3, 30.8, 27.8, 27.4, 25.0, 22.8, 14.1.

HRMS: *m/z* calcd for $C_{11}H_{20}O_2$: 185.1497 (M+H); Found: 185.1536 (M+H).

(+/-)-(4*R*)-4-((1'*S*,2'*R*)-2'-chloro-1'-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (13)



To a cold (-78 °C), stirred solution of diisopropylamine (0.065 ml, 1.1 equiv) in THF (5 ml) was added *n*-BuLi (0.18 ml, 1.1 equiv, 2.5 M in hexanes). This mixture was allowed to warm to 0 °C and was stirred at this temperature for 20 minutes prior to cooling to -78 °C, at which temperature a solution of 2,2-dimethyl-1,3-dioxan-5-one (0.046 ml, 1.0 equiv) in THF (1 ml) was added. After an additional 5 minutes of stirring at -78 °C, a solution of 2-chloropentanal (0.082 g, 1.5 equiv) in THF was slowly added to the reaction mixture. After a further 15 minutes stirring at -78 °C, the reaction mixture was quenched by the slow addition of water (5 ml), diluted with EtOAc, the phases were separated, and the aqueous phase was washed with EtOAc (3 x 10 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to provide a crude oil. Purification of the crude product was carried out by flash chromatography (hexanes-

7. The protons H-1' and OH in the 1,2-*anti*-diastereomer of 2-(1'-hydroxydecyl)cyclohexanone resonate at δ 3.72 (m) and 3.41 (d, J = 4.0 Hz) ppm, respectively, which is consistent with the spectral data for compound **17**. The proton H-1' in the *syn*-diastereomer of 2-(1'-hydroxydecyl)cyclohexanone resonates at 4.15 ppm. For details, see: Estevez, R. E.; Paradas, M.; Millan, A.; Jimenez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2008**, *73*, 1616.

CH_2Cl_2-EtOAc 9:2:1) to afford (+/-)-(4*R*)-4-((1'*S*,2'*R*)-2'-chloro-1'-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (**13**) (0.051 g, 54%) as a colourless oil.

IR (neat) 3512, 2964, 1749, 1374, 1226, 1100, 864 cm^{-1}

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 4.46 (dd, *J* = 6.7, 1.4 Hz, 1H), 4.30 (dd, *J* = 17.4, 1.4 Hz, 1H), 4.27-4.21 (m, 1H,), 4.10-4.05 (m, 1H), 4.06 (d, *J* =17.4 Hz, 1H), 3.08 (d, *J* = 4.0 Hz, 1H), 1.83-1.77 (m, 2H), 1.70-1.59 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 0.95 (t, *J* = 7.3 Hz, 3H)

^{13}C-NMR: (150 MHz, $CDCl_3$): δ 210.1, 101.4, 74.1, 66.9, 62.7, 34.9, 24.0, 23.9, 19.8, 13.6

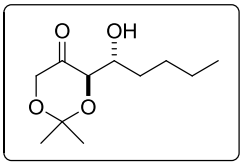
HRMS: *m/z* calcd for $C_{11}H_{19}ClO_4$: 251.1045 (M+H); Found: 251.1036 (M+H).

Proof of the relative stereochemistry of **13** was accomplished as follows.

A purified sample of **13** was reduced (catecholborane (1.2 eq.), THF) and subsequently converted into the corresponding epoxide (2M NaOH (1.2 eq), EtOH). Analysis of the ^{1}H NMR spectrum recorded on the epoxide revealed that the two epoxide protons resonated at 2.96 and 2.93 ppm, and shared a coupling constant of 2.2 Hz, typical of a *trans* epoxide. Additionally, irradiation of either proton resonance did not result in an enhancement of the other proton resonance in nOe experiments. These results confirm the *anti* stereochemistry of the chlorohydrin function in **13**.

As described below, reduction of the chloromethine function in **13** afforded the β-hydroxyketone **18**. The spectral data recorded on **18** was consistent with that reported for structurally related *anti*-aldol adducts of 2,2-dimethyl-1,3-dioxan-5-one (see below for details)

(+/-)-(4*R*)-4-(1'*R*)-1'-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (18)



Prepared following General Procedure A. The crude product was purified by flash chromatography (hexanes-EtOAc 9:1) to afford (+/-)-(4*R*)-4-((1'*R**)-1'-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (**18**) (24 mg, 74%) as a colourless oil. The spectral data derived from compound **18** matched closely to that reported for (4*R*)-4-((1'*R**)-1'-

hydroxybutyl)-2,2-dimethyl-1,3-dioxan-5-one.[8] Based on these spectral similarities, the relative stereochemistry for compound **18** was assigned as depicted above and in the manuscript.

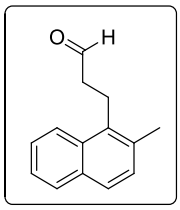
IR (neat): 3524, 2988, 2957, 2936, 2873, 1742, 1376, 1093, 862 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.26 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.09 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.02 (d, *J* = 17.2 Hz, 1H), 3.89 (m, 1H), 2.94 (d, *J* = 3.9 Hz, 1H), 1.64 (m, 1H), 1.54-1.51 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41-1.30 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.5, 100.9, 75.9, 70.9, 66.8, 31.9, 27.4, 24.0, 23.5, 22.6, 14.4

HRMS: m/z calcd for C11H20O4: 217.1434 (M+H); found: 217.1430 (M+H).

3-(2-methylnaphthalen-1-yl)propanal (34)

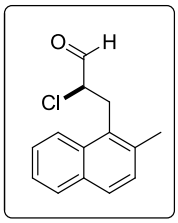


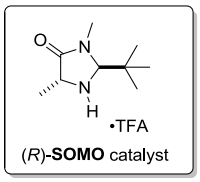
1-bromo-2-methylnaphthalene (0.2 ml, 1.3 mmol), allyl alcohol (0.13 ml, 1.9 mmol), and sodium bicarbonate (130 mg, 1.5 mmol) were added to *N*-methylpyrrolidinone (2.5 ml) and the suspension was sparged with N_2 for 20 minutes. $Pd(PPh_3)_2Cl_2$ (89 mg, 0.13 mmol) was then added and the solution was sparged with N_2 for a further 5 minutes. The nitrogen inlet was removed and the reaction vial was sealed and heated at 140 °C for 4.5 hours. The reaction vessel was then cooled to room temperature and the reaction mixture was filtered through a pad of Celite®, the organic layer extracted with ethyl acetate (2 x 15 ml), and the combined extracts were washed with brine (3 x 20 ml), dried ($MgSO_4$), and concentrated via rotary evaporator to yield an orange oil. Purification of the crude product by column chromatography (hexanes-ethyl acetate 20:1) gave the aldehyde **34** as a colorless oil (251 mg, 89%). The spectral data recorded for this material was in complete agreement with that reported.[9]

8. The protons H-4, H6a, H6b, and H1' in the 1,2-*anti*-diastereomer of 4-(1'-hydroxybutyl)-2,2-dimethyl-1,3-dioxan-5-one resonate at δ 4.08, 4.25, 4.01, and 3.89 ppm, respectively, which is consistent with the spectral data for compound **18** (comparison: δ 4.09, 4.26, 4.02, and 3.89 ppm). Likewise, the carbons C4 and C1' resonate at δ 76.07 and 70.34 ppm, respectively in the ^{13}C NMR spectrum of 4-(1'-hydroxybutyl)-2,2-dimethyl-1,3-dioxan-5-one, which compare well with compound **18** (δ 75.9 and 70.9). For details, see: Enders, D.; Prokopenko, O. F.; Raabe, G.; Runsink, J. *Synthesis*, **1996**, 1095.

9. Binder, J. T.; Kirsch, S. F. *Chem. Comm.* **2007**, 4164.

(2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal (36)





To a cold (-30 °C), stirred solution of (*R*)-SOMO catalyst[10] (42 mg, 0.20 mmol), $Cu(TFA)_2$ (89 mg, 0.49 mmol), LiCl (63 mg, 1.5 mmol), and $Na_2S_2O_8$ (215 mg, 0.98 mmol) in CH_3CN (10 ml) and H_2O (0.03 ml, 1.9 mmol) was added a solution of the aldehyde **34** (148 mg, 0.747 mmol) in CH_3CN (1 ml), and the resultant green-yellow mixture was stirred at -30 °C for 4 days. The reaction mixture was then diluted with H_2O (1 mL), the organic layer extracted with ethyl acetate (3 x 10 ml) and the combined extracts washed with brine (1 x 20 ml), dried ($MgSO_4$) and concentrated to yield an orange oil. Purification of the crude product by column chromatography (hexanes-ethyl acetate 4:1) gave (2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal (**36**) (82 mg, 47%, 66% based on recovered starting material), as a yellow oil. The enantiomeric excess of this material was determined to be ≥ 94% following its conversion to (+)-solistatin (see below).

IR (neat): 3051, 2958, 2929, 2870, 1731, 1623, 1598, 1512, 1443, 1265, 1067, 811, 741 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ: 9.63 (d, *J* = 2.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.45 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.58 (dt, *J* = 7.6, 2.2 Hz, 1H), 3.89 (dd, *J* = 15.0, 6.2 Hz, 1H), 3.62 (dd, *J* = 15.0, 8.2 Hz, 1H), 2.56 (s, 3H).

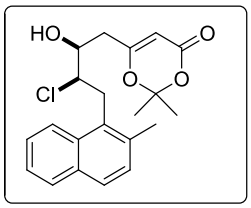
^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 135.2, 132.8, 132.1, 129.4, 129.2, 128.6, 126.8, 125.1, 122.9, 63.8, 31.4, 21.0.

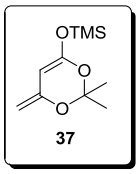
HRMS: *m/z* calcd for $C_{14}H_{13}ClO$: 255.0547 (M+Na); Found: 255.0545 (M+Na).

$[\alpha]_D^{20}$ = + 32.4° (c 0.34, $CHCl_3$)

10. Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121. For preparation of the SOMO catalyst, see: Graham, T. H.; Horning, B. D.; MacMillan, D. W. C. *Org. Synth.* **2011**, *88*, 42.

Chlorohydrin 38





To cold (-60 °C), stirred a solution of (2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal (**36**) (76 mg, 0.33 mmol, 1 equiv) in dry CH_2Cl_2 (3 ml) was added BF_3•OEt_2 (0.12 ml, 0.95 mmol) and the resultant orange solution was stirred for 10 minutes. Silyl enol ether **37**[11] was then added neat (140 mg, 0.66 mmol), and the resulting colourless solution was stirred at -60 °C for 18 hours. H_2O (5 ml) was then added, and the reaction mixture was allowed to slowly warm to room temperature. The phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 x 10 ml), and the combined organic washes were extracted with brine (1 x 10 ml), dried ($MgSO_4$), and concentrated to provide a crude 2:1 mixture of 1,2-*anti* and 1,2-*syn* chlorohydrins. Purification of the of the crude products by flash chromatography (hexanes-CH_2Cl_2-EtOAc 9:2:1; 2 columns required to completely separate diastereomers) afforded chlorohydrin **38** as a white solid (78 mg, 63 %).

mp 32-35 °C

IR (neat): 3413, 3057, 2992, 2948, 1709, 1634, 1511, 1391, 1378, 1275, 1203, 1015, 810, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.39 (s, 1H), 4.44 (m, 1H), 4.22 (m, 1H), 3.76 (dd, *J* = 14.9, 4.5 Hz, 1H), 3.54 (dd, *J* = 9.5, 14.9 Hz, 1H), 2.80 (dd, *J* = 14.9, 2.7 Hz, 2H), 2.66-2.57 (m, 2H), 2.59 (s, 3H), 1.72 (s, 3H), 1.71 (s, 3H).

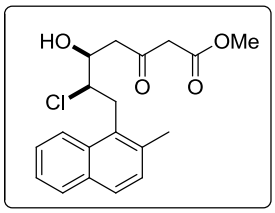
^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 160.9, 134.9, 132.7, 132.1, 130.3, 129.3, 129.0, 127.5, 126.4, 124.8, 123.1, 106.9, 95.8, 72.0, 66.8, 37.6, 32.3, 25.5, 24.7.

HRMS: *m/z* calcd for $C_{21}H_{23}ClO_4$: 375.1358 (M+H); Found: 3375.1391 (M+H).

$[\alpha]_D^{20}$ = - 43.3° (c 0.06, $CHCl_3$)

11. Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274

Methyl (5*S*,6*R*)-6-chloro-5-hydroxy-7-(2-methylnaphthalen-1-yl)-3-oxoheptanoate (41)



To a stirred solution of anhydrous methanol (0.034 ml, 4 eq.) in toluene (3 ml, 0.07 M) at room temperature was added chlorohydrin **38** (79 mg, 0.21 mmol) and the reaction vessel was sealed and heated to 65 °C in an oil bath and maintained at this temperature for 18 h. Concentration of the crude reaction mixture and purification of the crude product by silica gel chromatography (hexanes-ethyl acetate 4:1) gave methyl (5*S*,6*R*)-6-chloro-5-hydroxy-7-(2-methylnaphthalen-1-yl)-3-oxoheptanoate (**41**) as a colourless oil (61 mg, 83%).

IR (neat): 3477, 3050, 3003, 2955, 2925, 1747, 1713, 1654, 1512, 1437, 1363, 1223, 1092, 814, 531 cm^{-1}

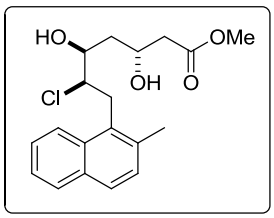
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.41-4.30 (m, 2H), 3.91 (dd, *J* = 15.2, 3.5 Hz, 1H), 3.77 (s, 3H), 3.54 (d, *J* = 2.0 Hz, 2H), 3.45 (dd, *J* =15.2, 9.8 Hz, 1H), 3.18 (dd, *J* = 17.8, 2.1 Hz, 1H), 2.97 (dd, *J* = 17.8, 8.5 Hz, 1H), 2.58 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 167.2, 134.9, 132.6, 132.2, 130.7, 129.3, 128.8, 127.3, 126.2, 124.7, 123.5, 71.4, 65.6, 52.6, 49.6, 46.2, 32.7, 21.0.

HRMS: *m/z* calcd for $C_{19}H_{21}ClO_4$: 349.1201(M+H); Found: 349.1196 (M+H).

$[\alpha]_D^{20}$ = - 22.6° (c 0.15, $CHCl_3$)

Methyl (3*R*,5*S*,6*R*)-6-chloro-3,5-dihydroxy-7-(2-methylnaphthalen-1-yl)heptanoate (39)



To a stirred solution of triethylborane (0.17 ml, 1.0 M in THF) in THF (5 ml) at room temperature was added methanol (0.4 ml). The resulting solution was stirred for 20 minutes and then cooled to -78 °C. A solution of methyl (5*S*,6*R*)-6-chloro-5-hydroxy-7-(2-methylnaphthalen-1-yl)-3-oxoheptanoate (51 mg, 0.15 mmol) in THF (1 ml) was then added slowly, and the resultant yellow solution was stirred for one hour. Sodium borohydride (11 mg, 0.3 mmol) was then added, and the reaction mixture was stirred for one hour at -78 °C. The reaction mixture was then treated with glacial acetic acid (0.2 ml), followed by water (6 ml), and slowly warmed to room temperature. The phases were separated and the aqueous layer was extracted with ethyl acetate (4 x 15 ml). The combined organic extracts were washed

with saturated aqueous $NaHCO_3$ (2 x 10 ml) and brine (1 x 10 ml), then dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in methanol and concentrated (5 x 10 mL) repeatedly [to ensure complete removal of boron reagents via formation and evaporation of trimethylborate] to give the crude diol **39** as a single diastereomer. Purification of the crude product by column chromatography (hexanes-ethyl acetate 3:1) gave methyl (3*R*,5*S*,6*R*)-6-chloro-3,5-dihydroxy-7-(2-methylnaphthalen-1-yl)heptanoate (**39**) as a colourless oil (39 mg, 77%).

IR (neat): 3437, 3051, 2953, 2924, 2853, 1732, 1512, 1438, 1375, 1250, 1072, 1050, 813 cm^{-1}

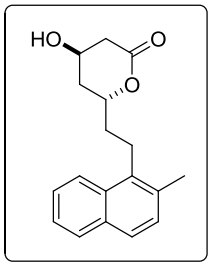
^1H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 4.37 (m, 1H) 4.28 (m, 1H), 4.15 (m, 1H) 4.11 (d, *J* = 2.1 Hz, 1H)), 3.89 (dd, *J* = 15.0, 3.6 Hz, 1H), 3.82 (m, 1H), 3.75 (s, 3H) 3.45 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.58 (s, 3H), 2.56 (d, *J* = 1.68 Hz, 1H) 2.10 (m, 1H), 1.78 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 134.9, 132.6, 132.3, 131.2, 129.3, 128.8, 127.2, 126.2, 124.6, 123.6, 75.6, 68.9, 67.0, 52.0, 41.2, 38.5, 29.7, 21.0.

HRMS: *m/z* calcd for $C_{19}H_{23}ClO_4$: 351.1358 (M+H); Found: 351.1361 (M+H).

$[\alpha]_D^{20}$ = - 26.9° (c 0.13, $CHCl_3$)

(+)-Solistatin (40)



Prepared following General Procedure A. The crude product was flushed through a short plug of silica gel (hexanes-EtOAc 2:1) to provide a mixture of diol (14 mg) and solistatin (6 mg), which was immediately dissolved in CH_2Cl_2 (2 ml), treated with a catalytic amount of *p*-TsOH and stirred for 4 hours at room temperature. The resulting solution was then treated with saturated $NaHCO_3$ (3 ml), extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (hexanes:EtOAc 2:1) to provide (+)-solistatin (**40**) (18 mg, 57% yield over 2 steps) as a colourless oil. The spectral data acquired on this material was in complete agreement with that reported for the natural product.[12]

12. Sorensen, D., Larsen, T. O., Christophersen, C., Nielsen, P. H., Anthoni, U., *Phytochem.* **1999**, *51*, 1027.

IR (neat): 3422, 3049, 2956, 2922, 2851, 1709, 1511, 1388, 1256, 1056, 1069, 811, 743 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.5 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.3 (d, *J* = 8.3 Hz, 1H),4.85 (m, 1H), 4.42 (m, 1H), 3.41 (m, 1H), 3.19 (m, 1H), 2.80 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.67 (ddd, *J* = 17.0, 3.6, 1.6 Hz, 1H), 2.52 (s, 3H), 2.03-1.98 (m, 2H), 1.93 (m, 1H), 1.86 (dt, *J* = 12.9, 3.3 Hz, 1H)

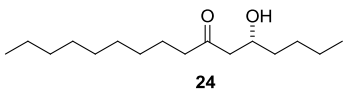
^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 134.2, 133.2, 132.6, 132.0, 129.3, 128.7, 126.5, 126.2, 124.6, 123.4, 75.5, 63.0, 38.8, 36.2, 35.7, 24.1, 20.2

HRMS: *m/z* calcd for $C_{18}H_{20}O_3$: 307.1305 (M+Na); Found: 307.1309 (M+Na).

$[\alpha]_D^{20}$ = + 29.1° (c 0.17, $CHCl_3$)

Determination of enantiomeric excess for (+)-solistatin (**40**).

Samples of both 'racemic'[4,5] and optically enriched (+)-solistatin (**40**) were analyzed by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes-IPA 92:8; detection at 227 nm; flow rate = 1.5 mL/min. The retention time of the (+)-enantiomer is 15.19 min; the retention time of the (-)-enantiomer is 14.01 min (see chromatogram below).



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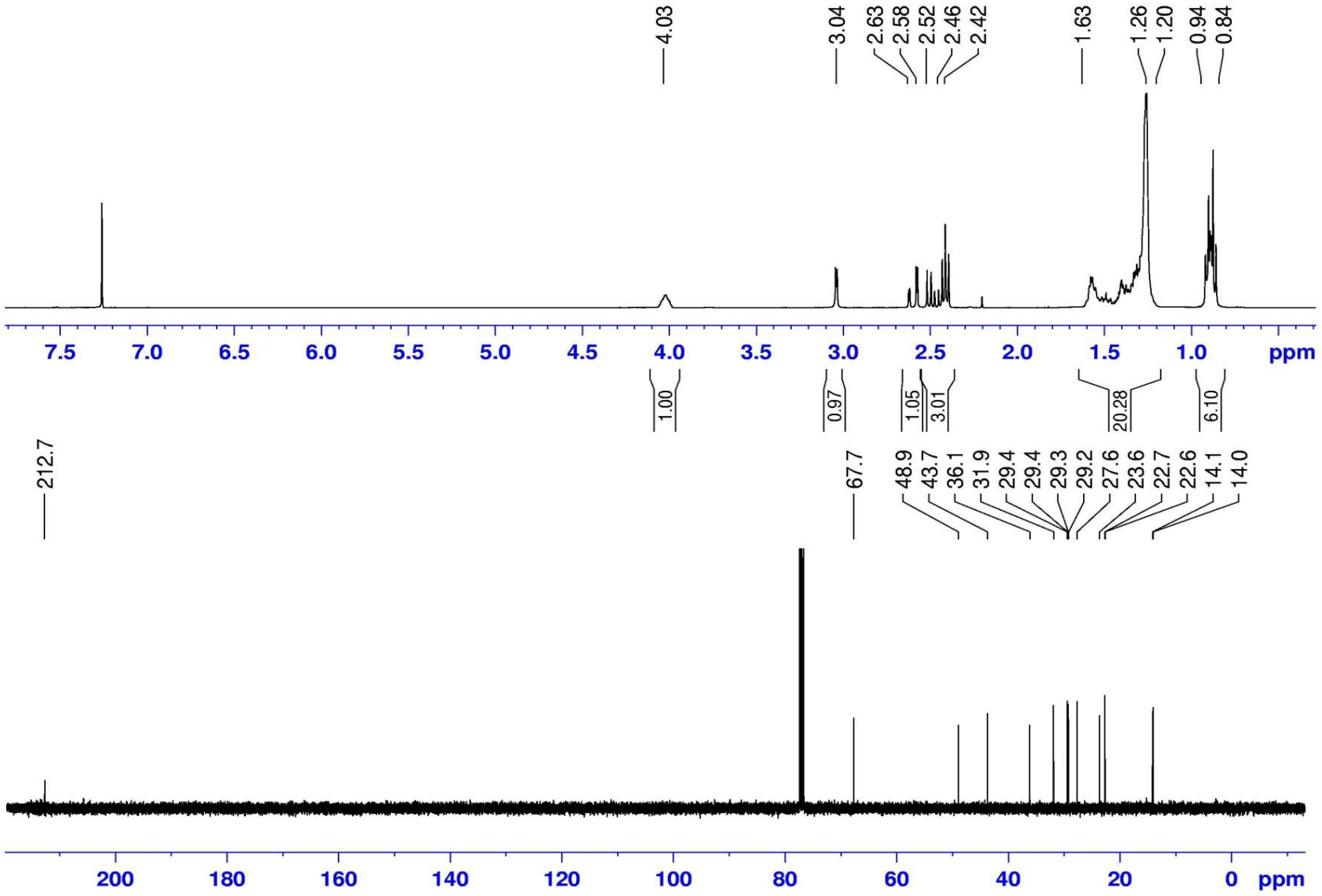

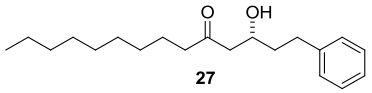

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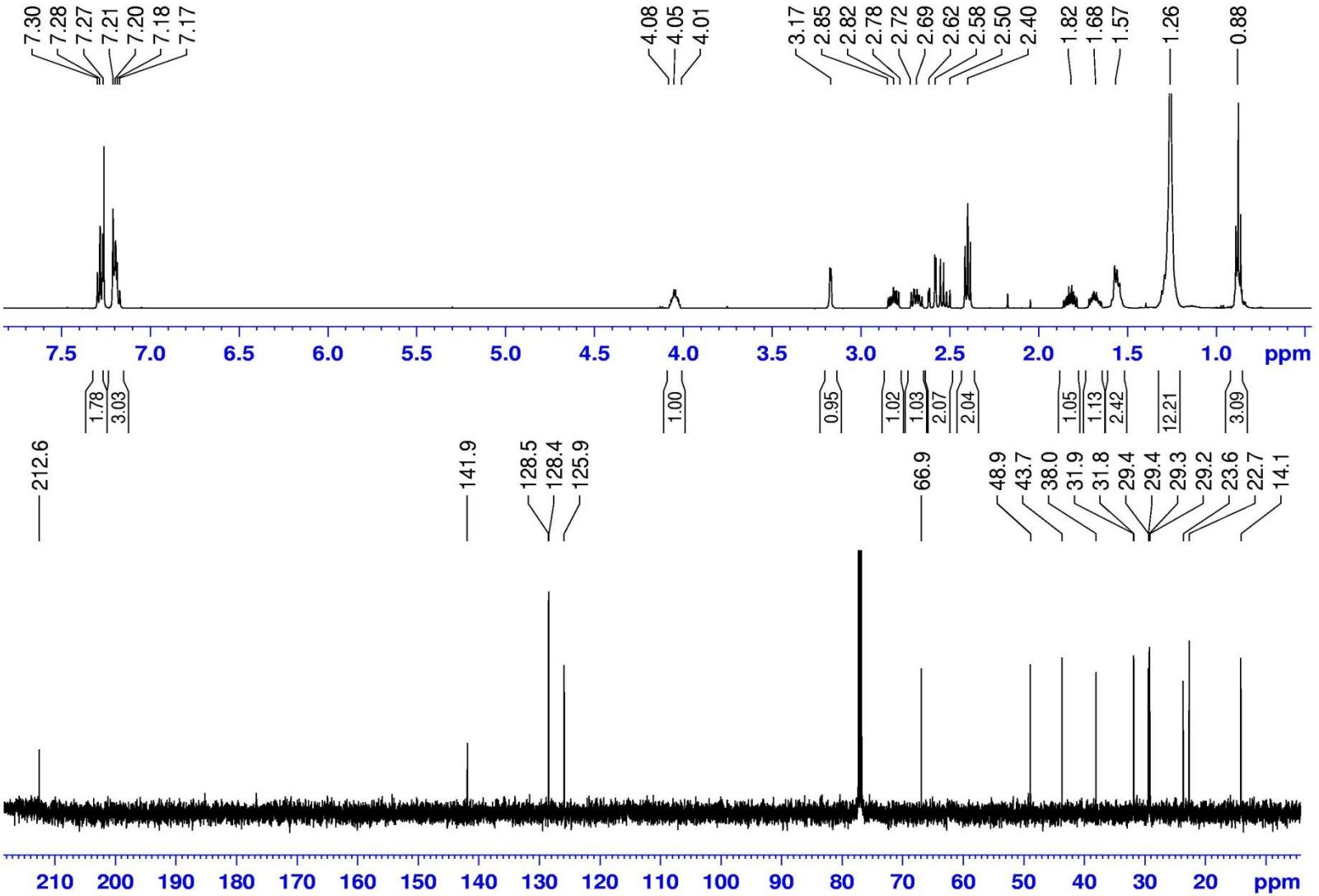

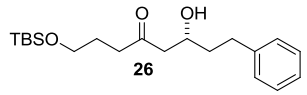

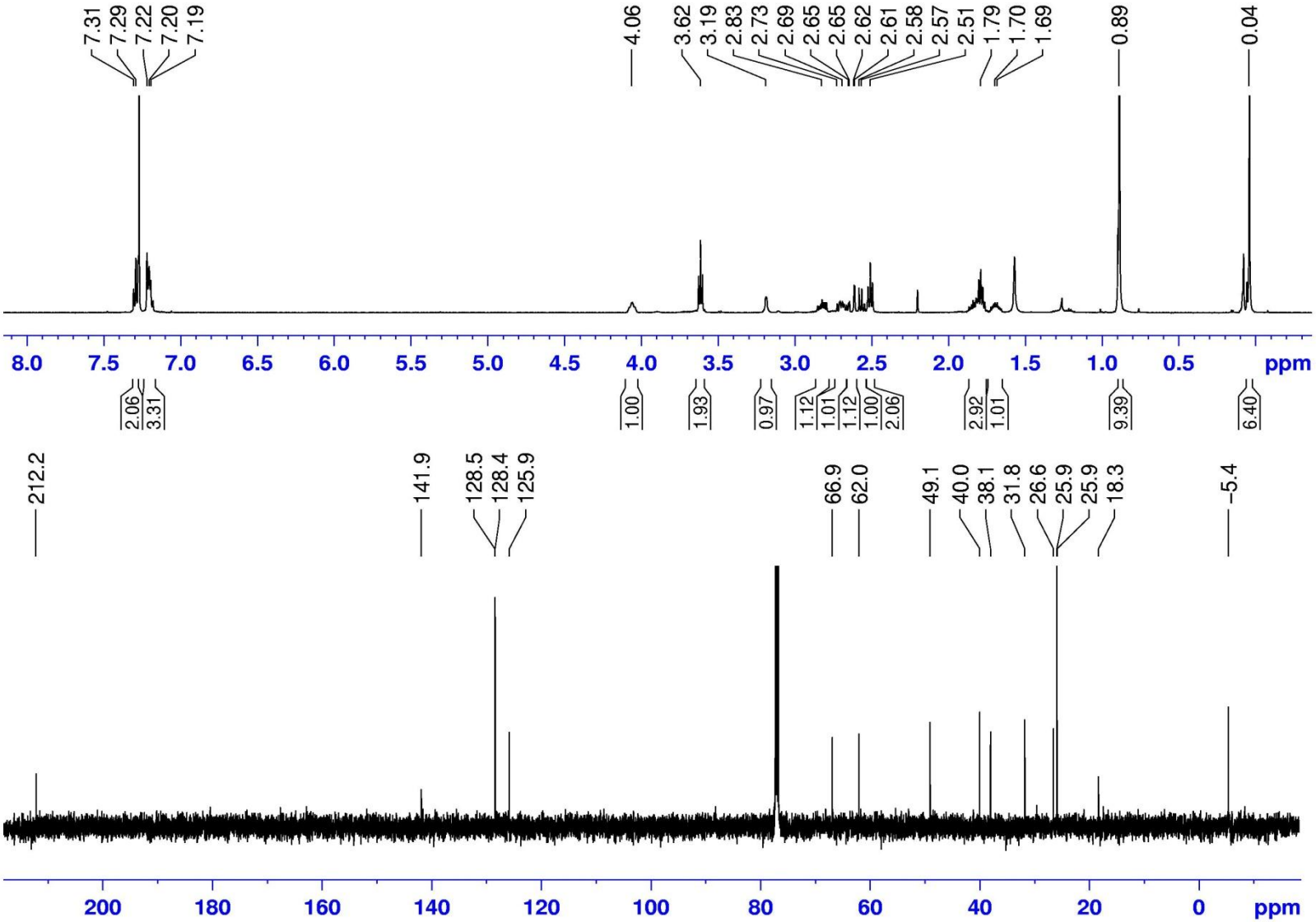

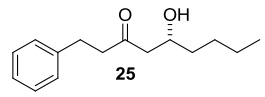

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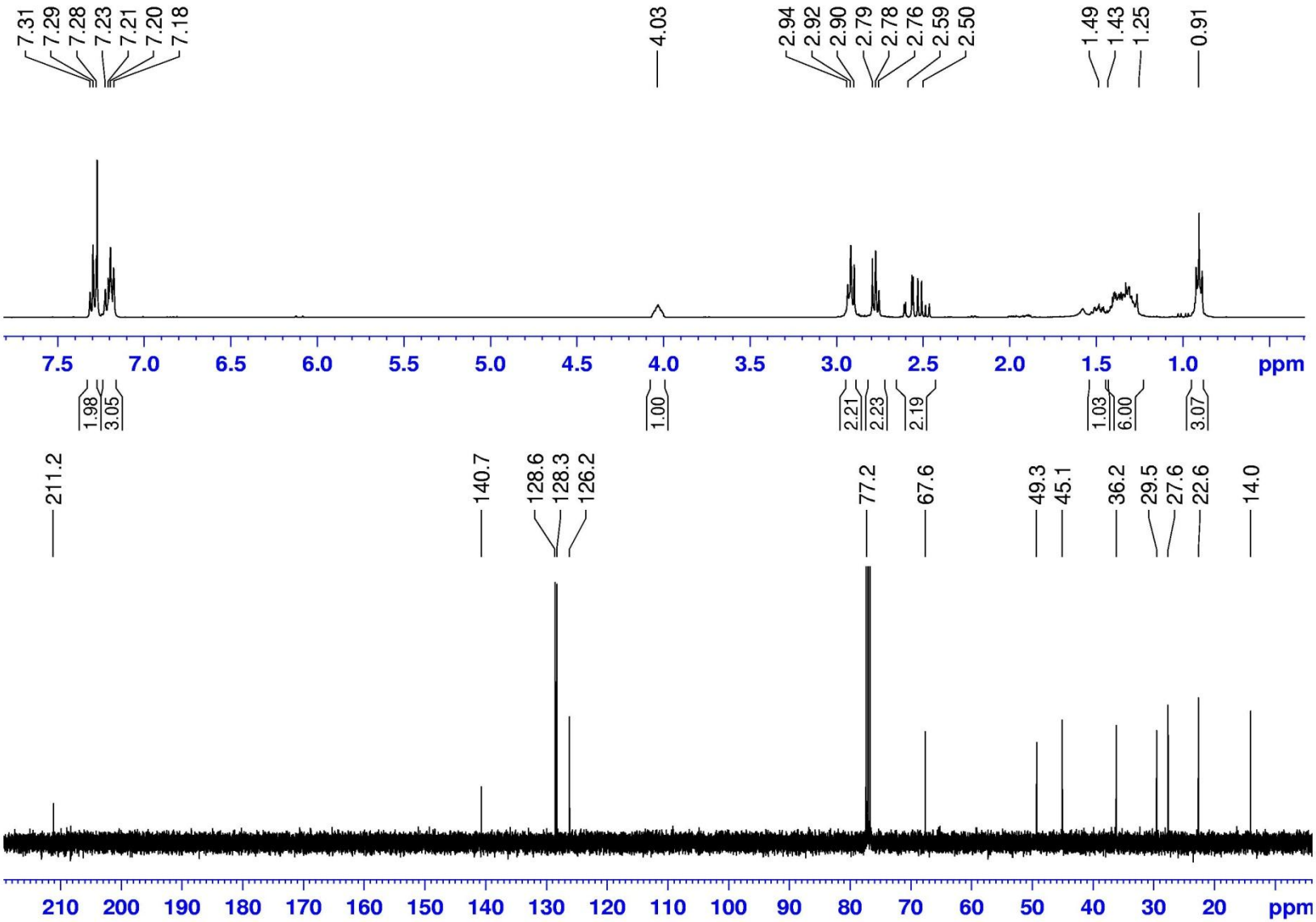

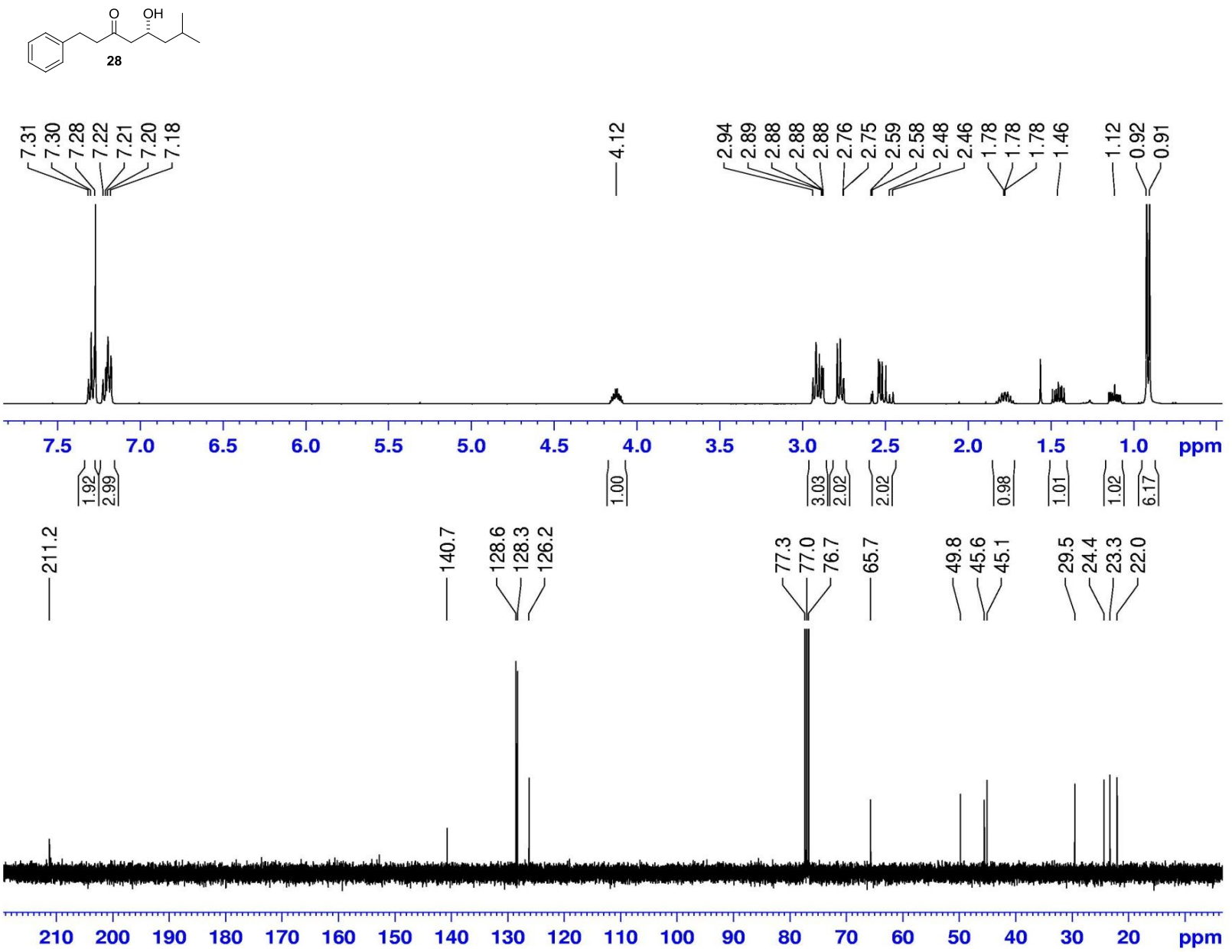

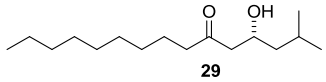

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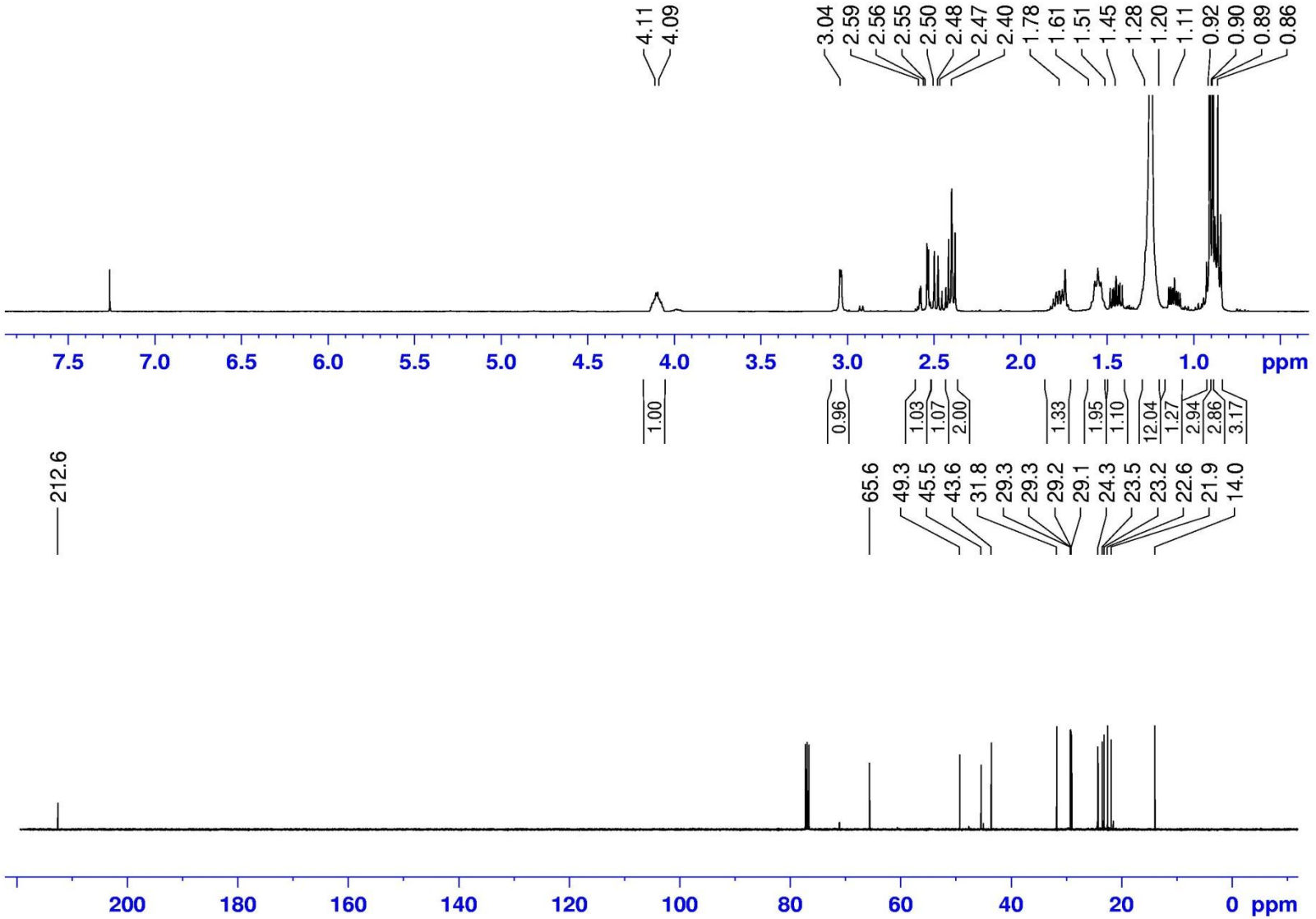

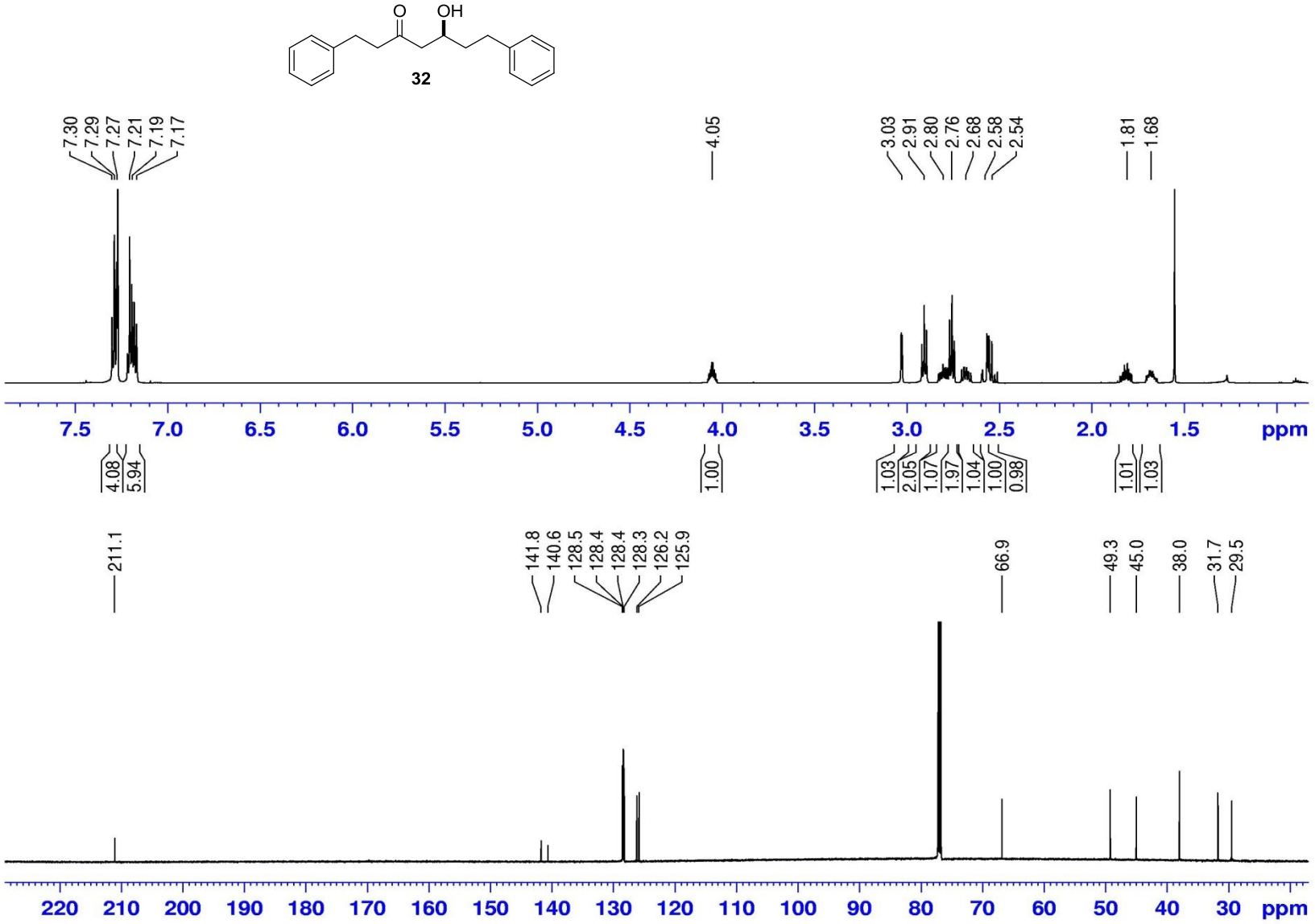

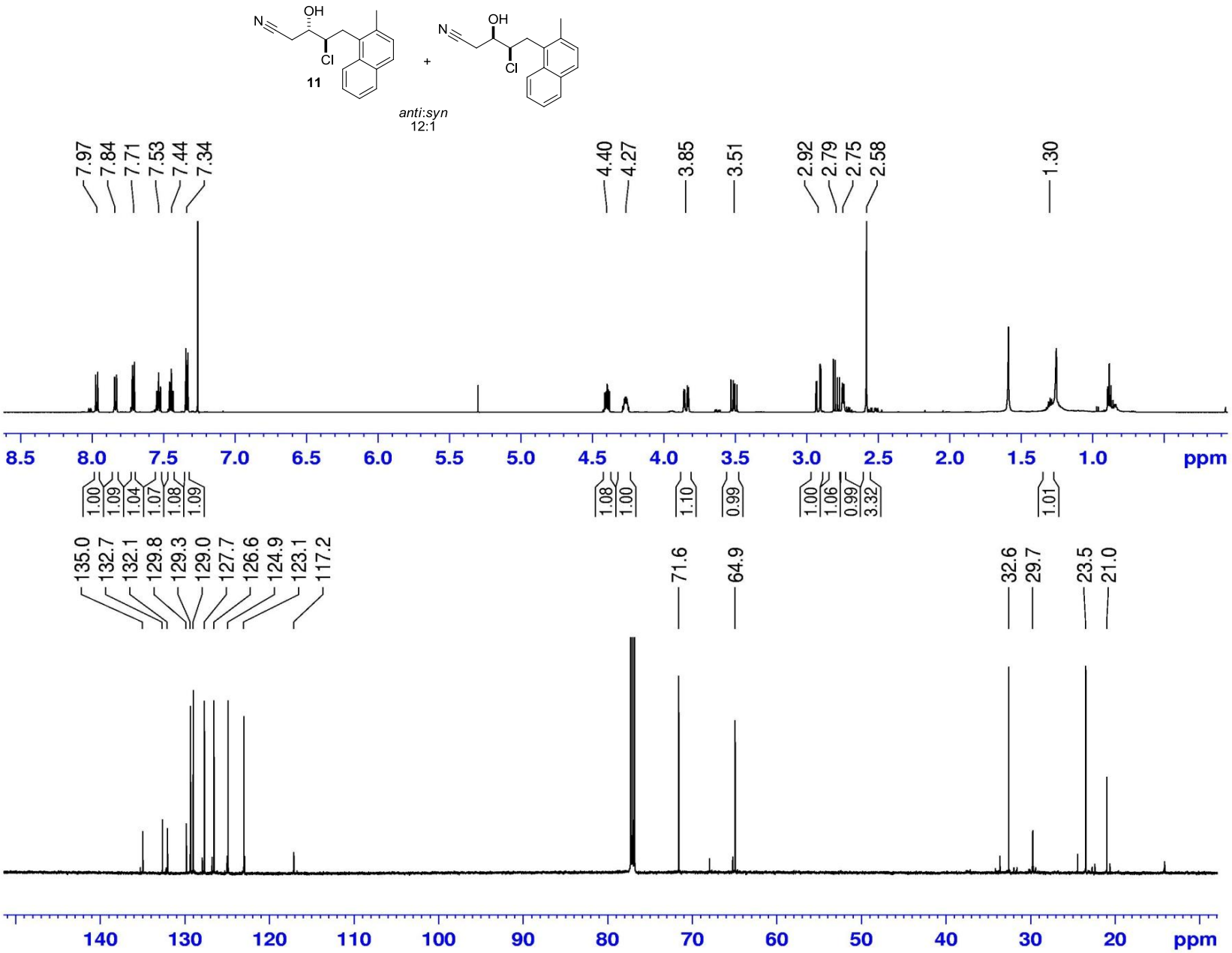

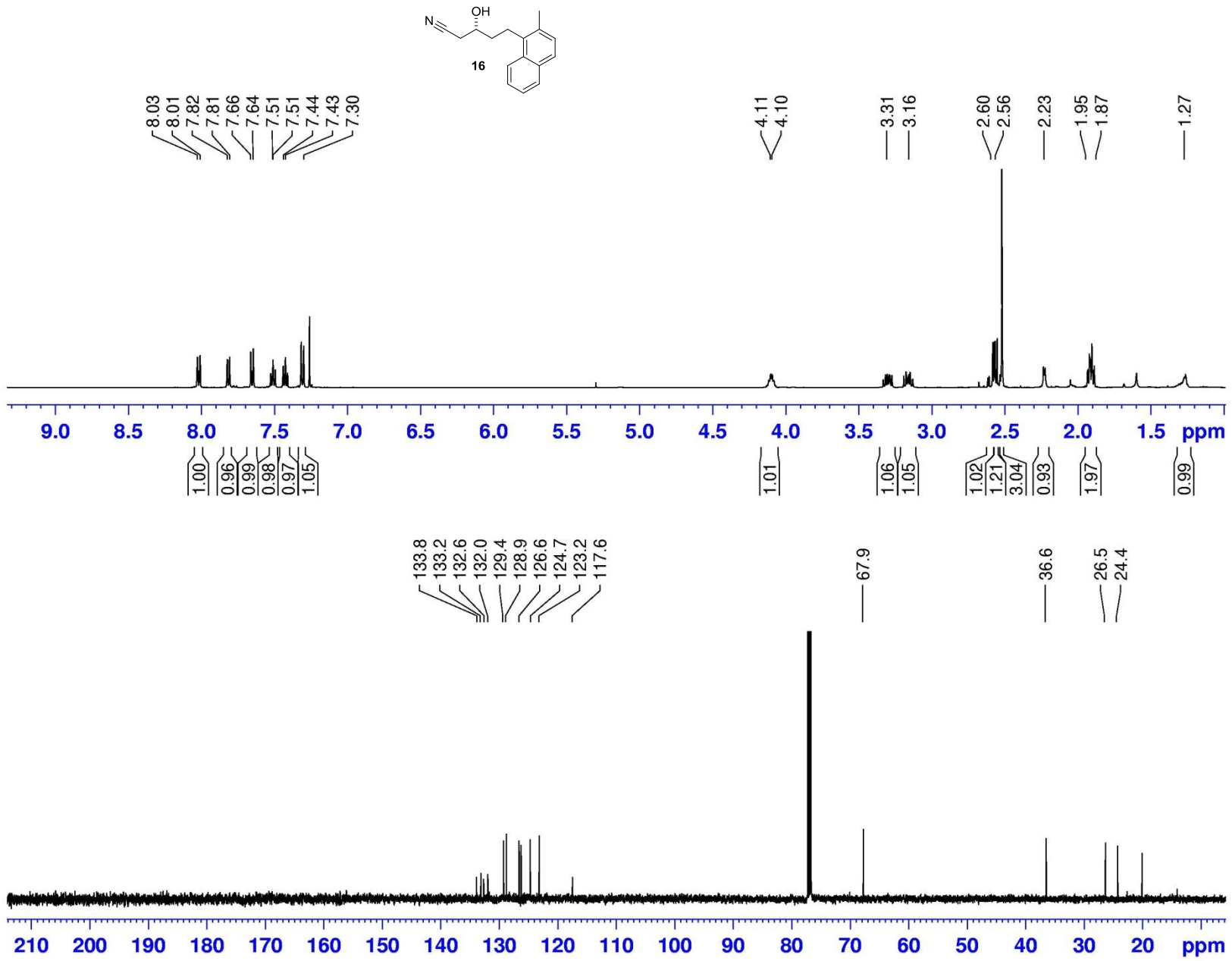

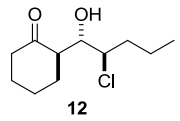

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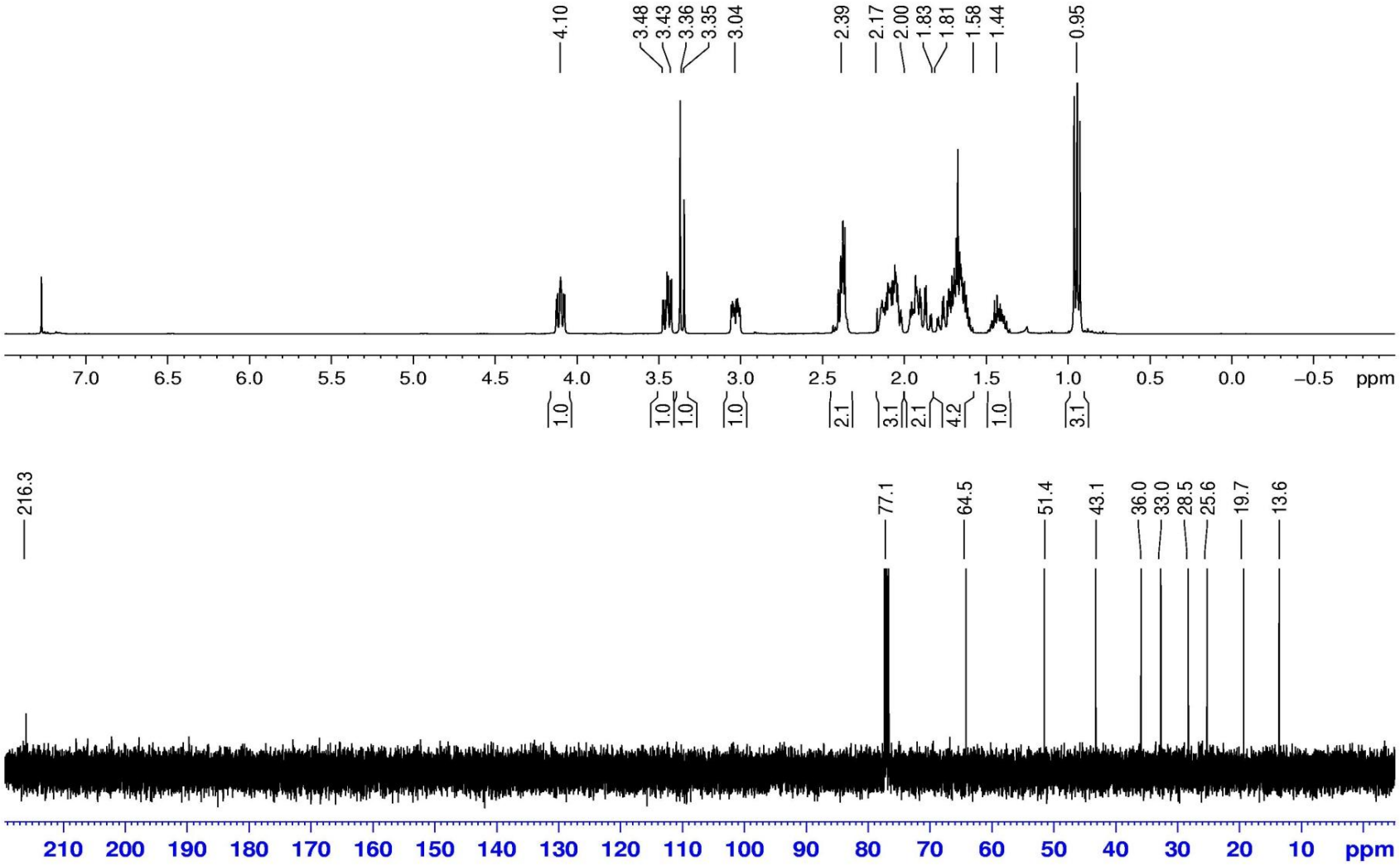

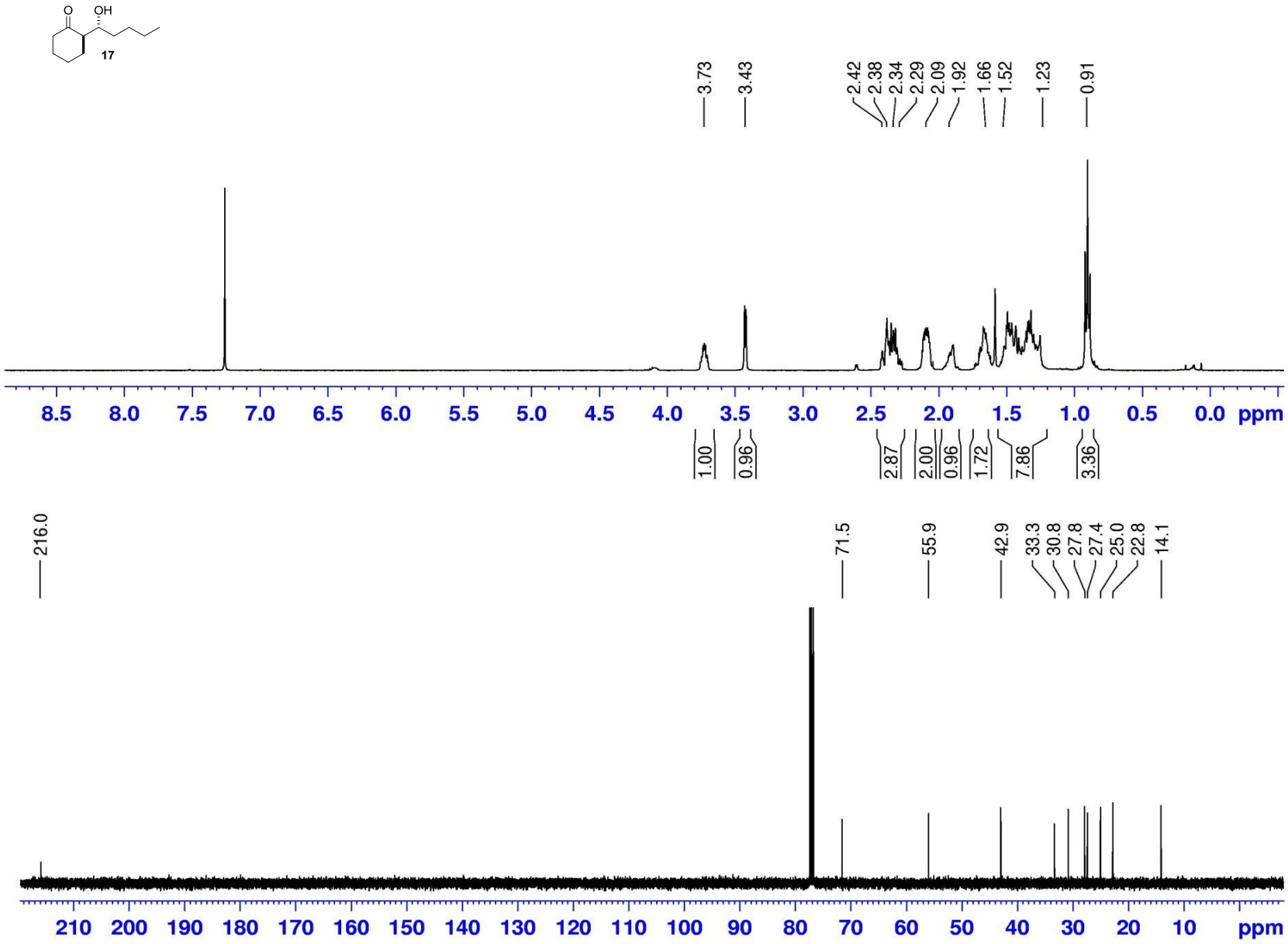

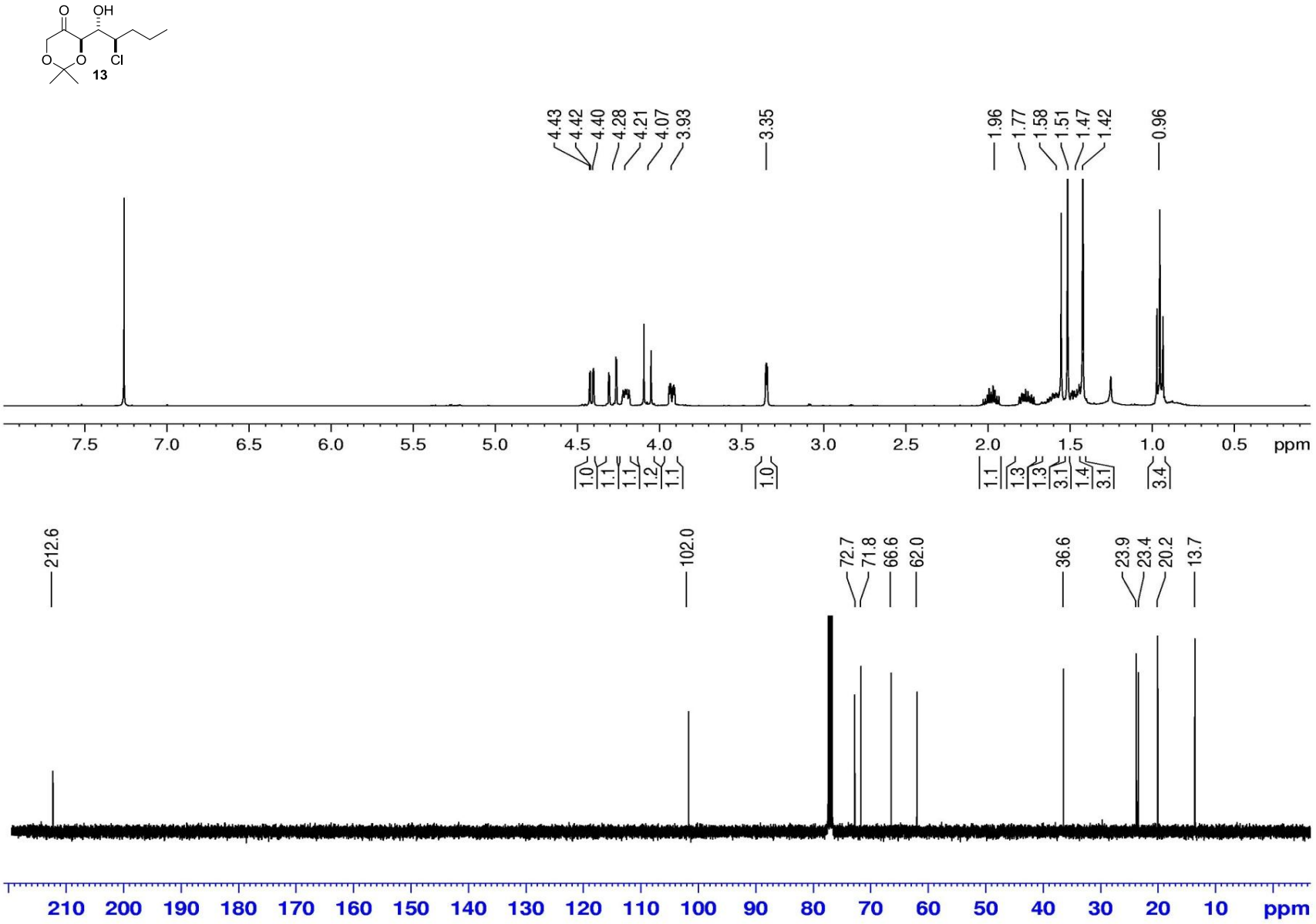

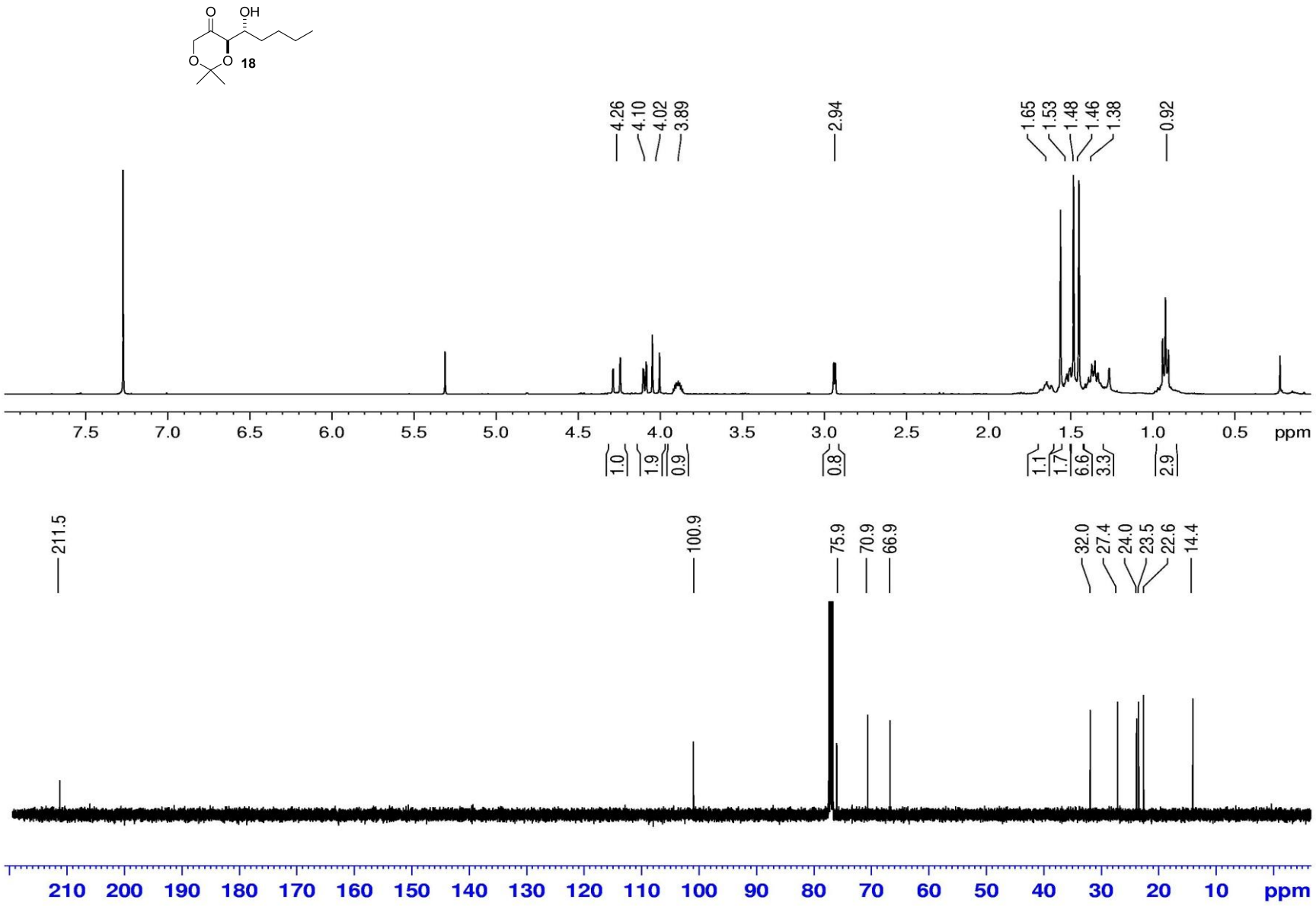

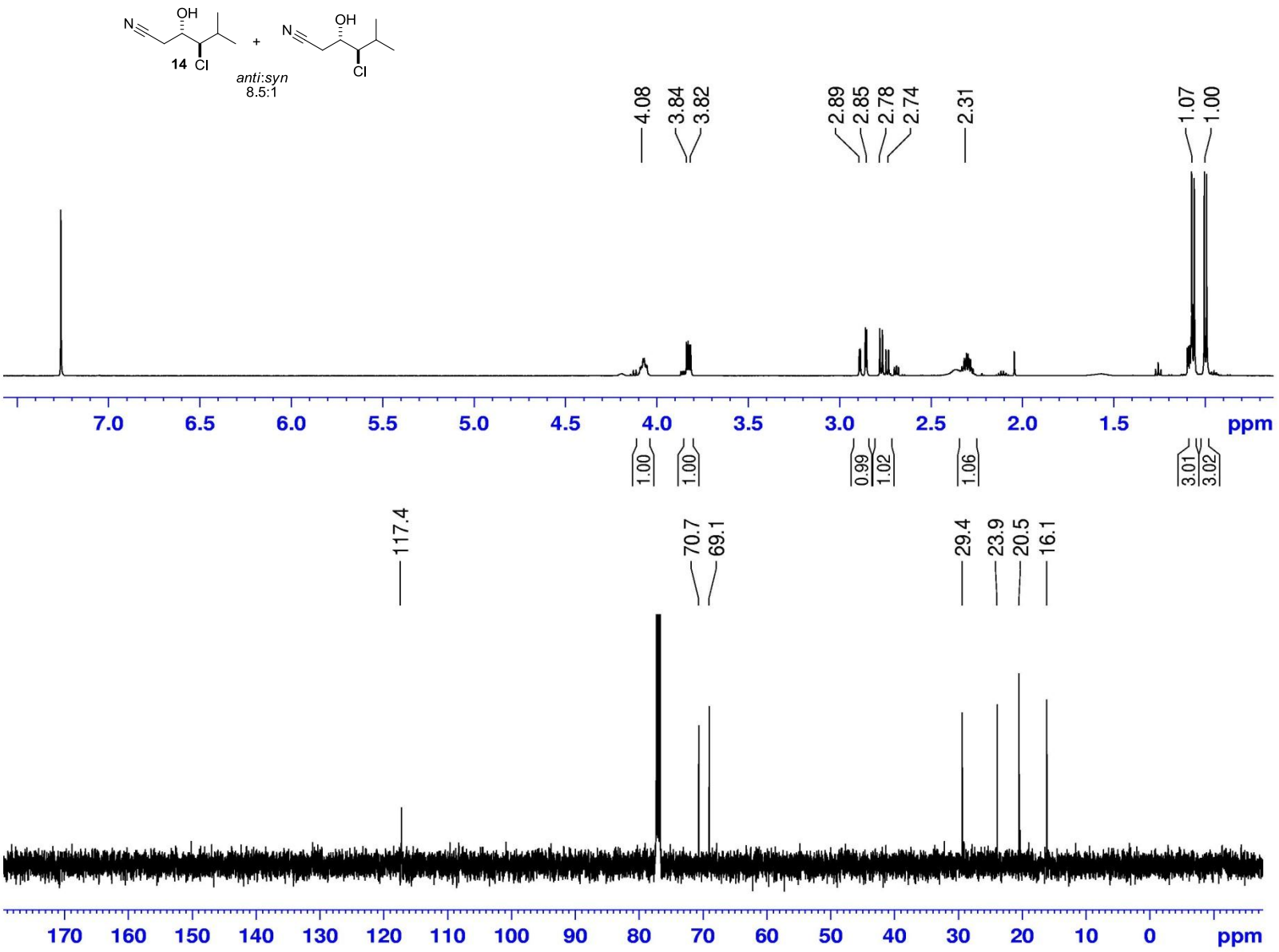

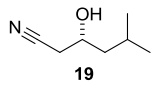

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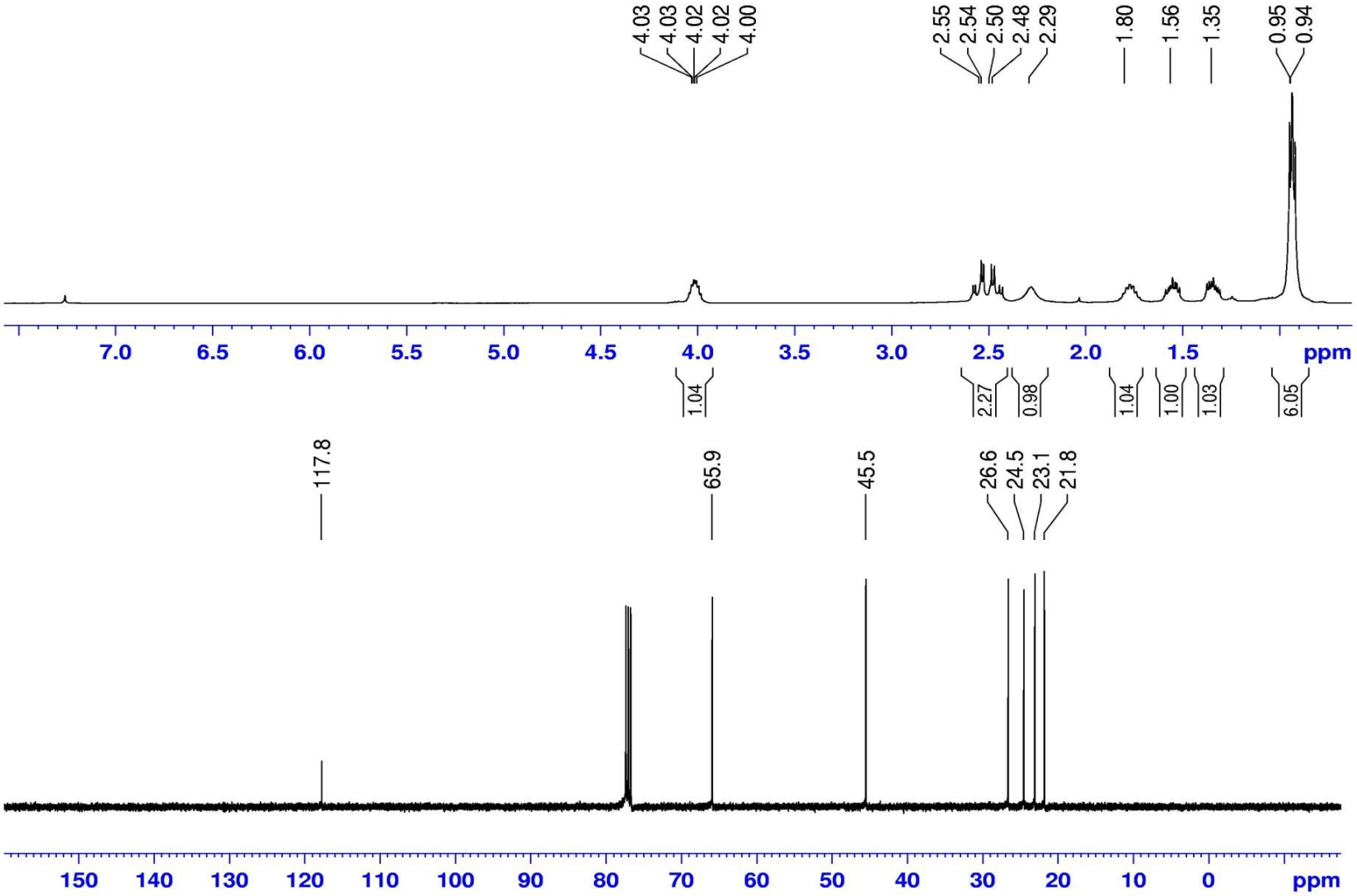

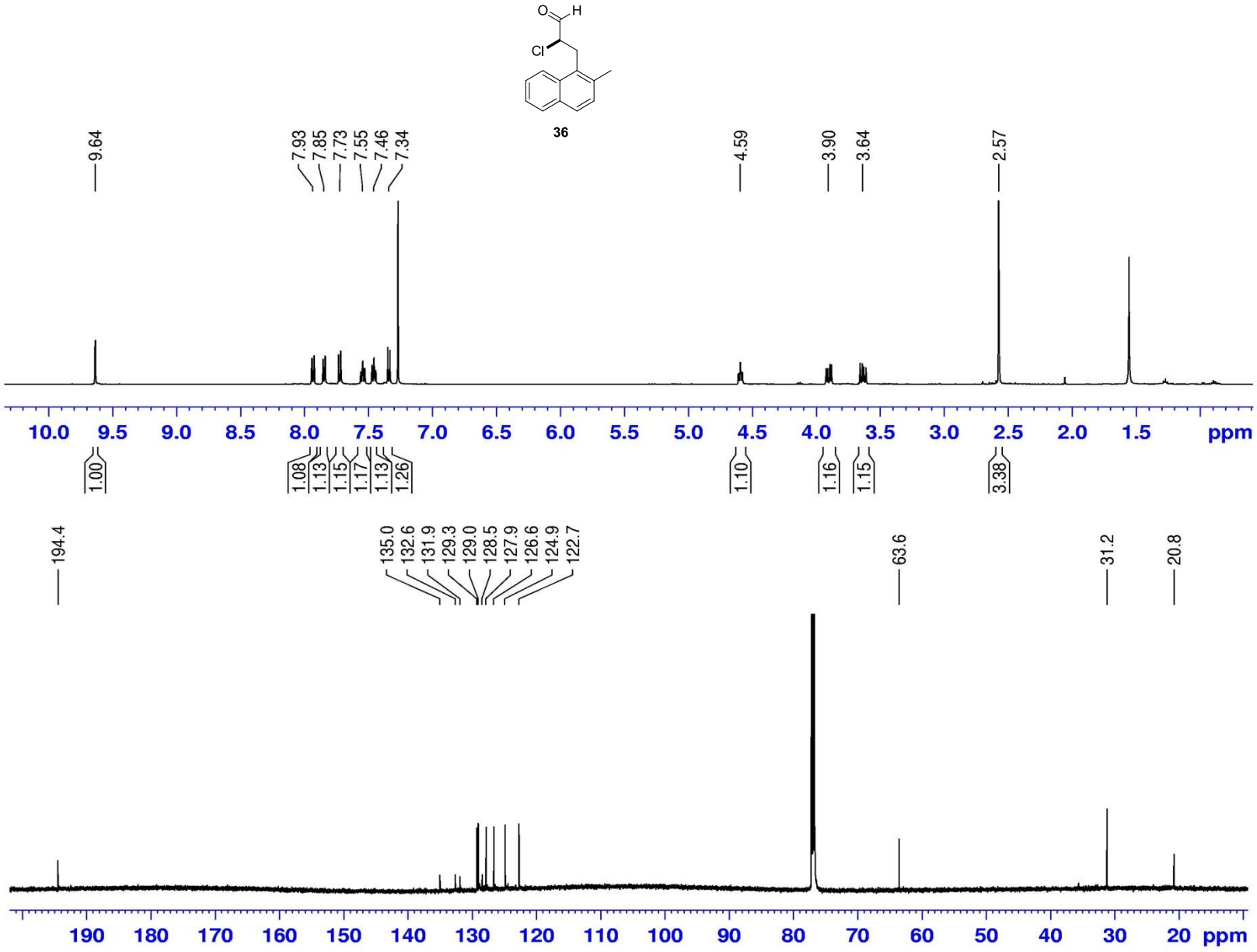

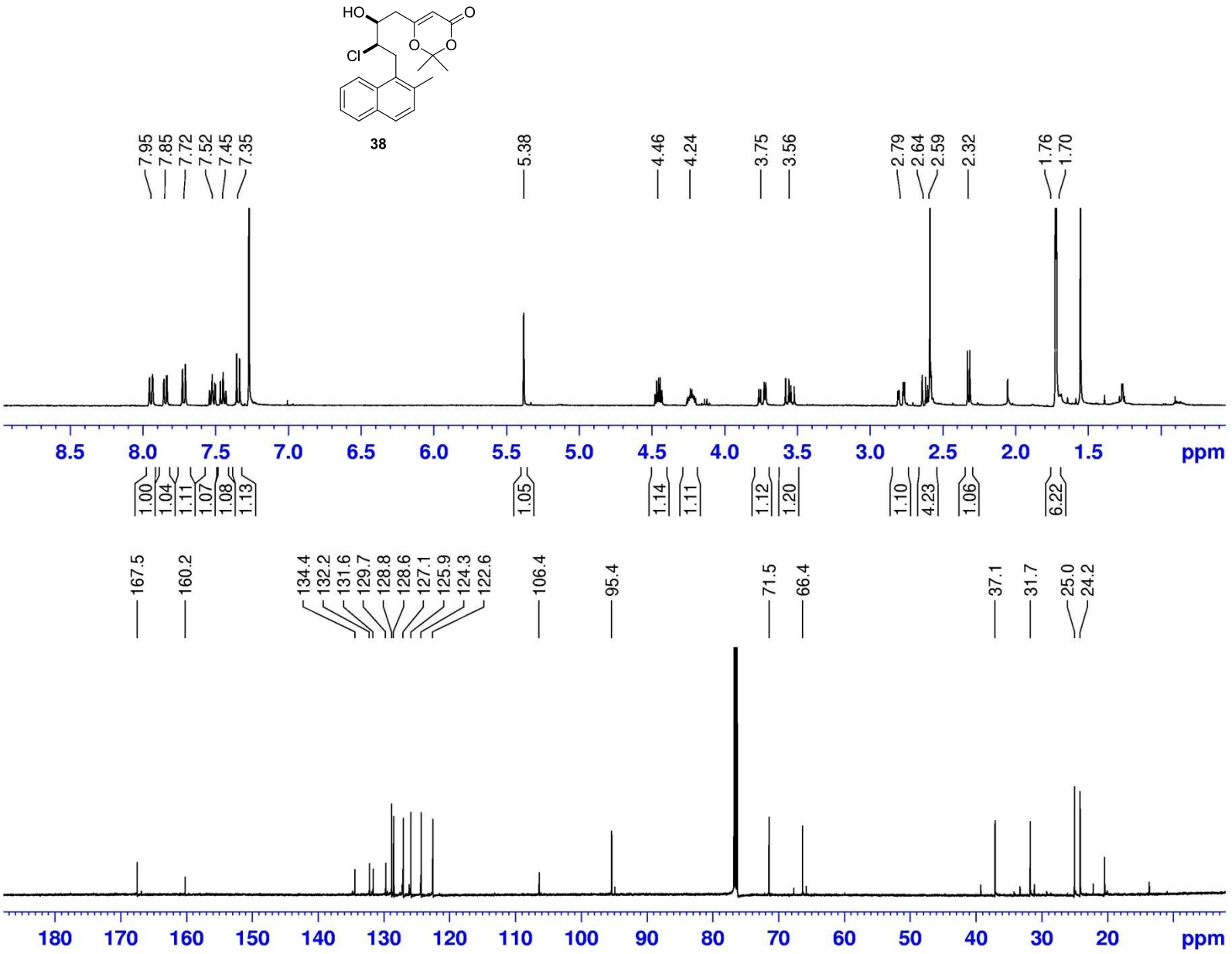

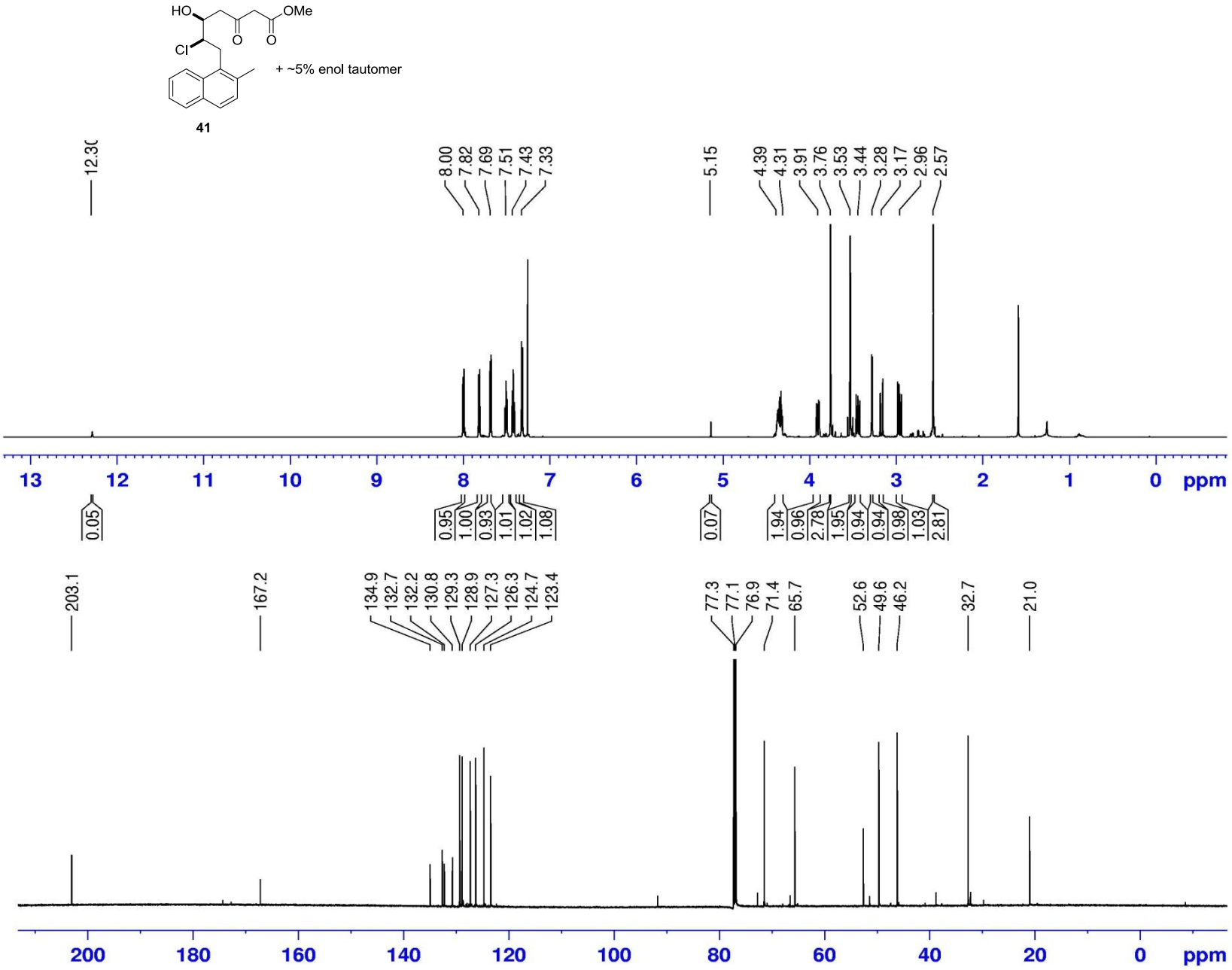

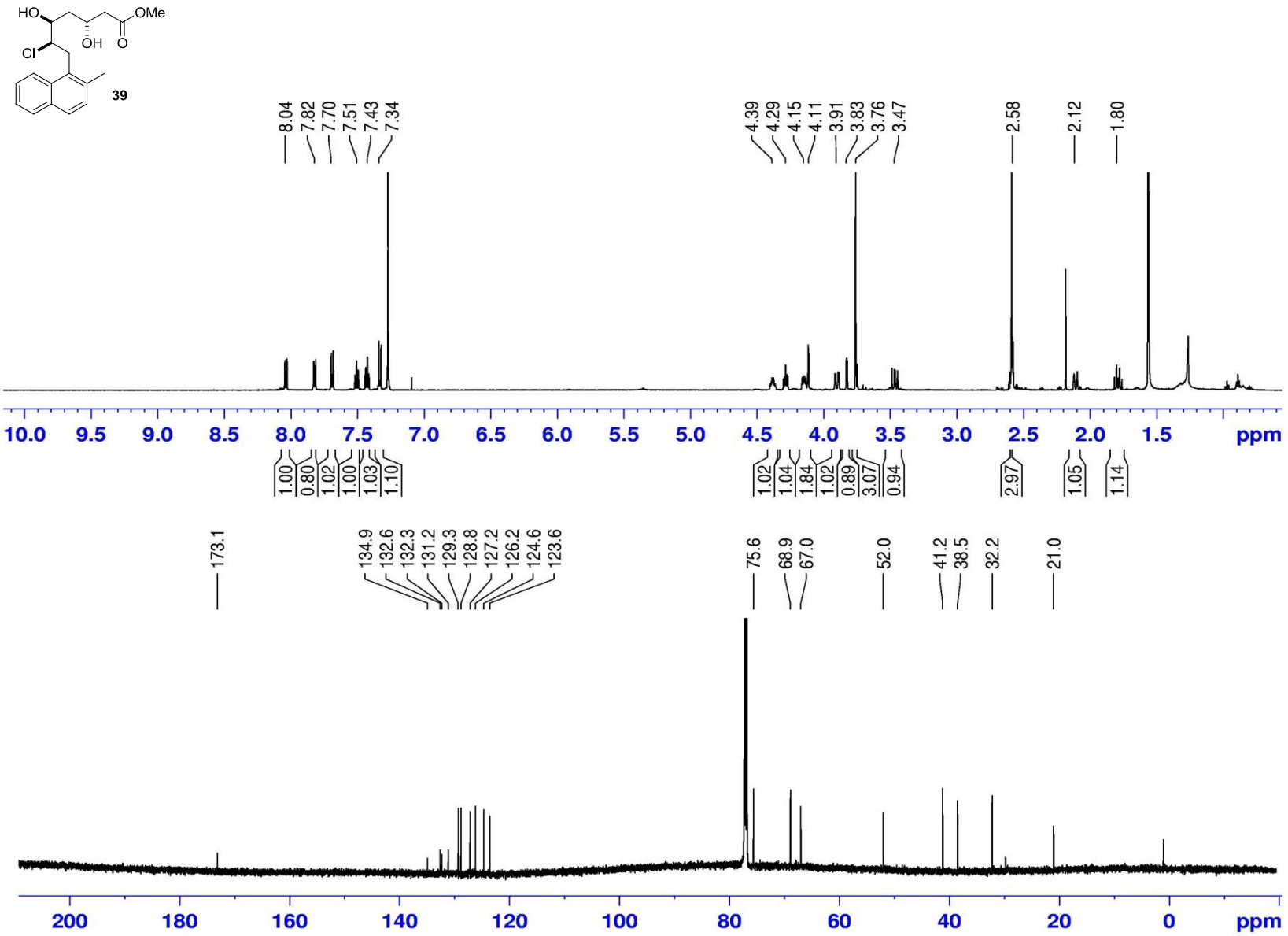

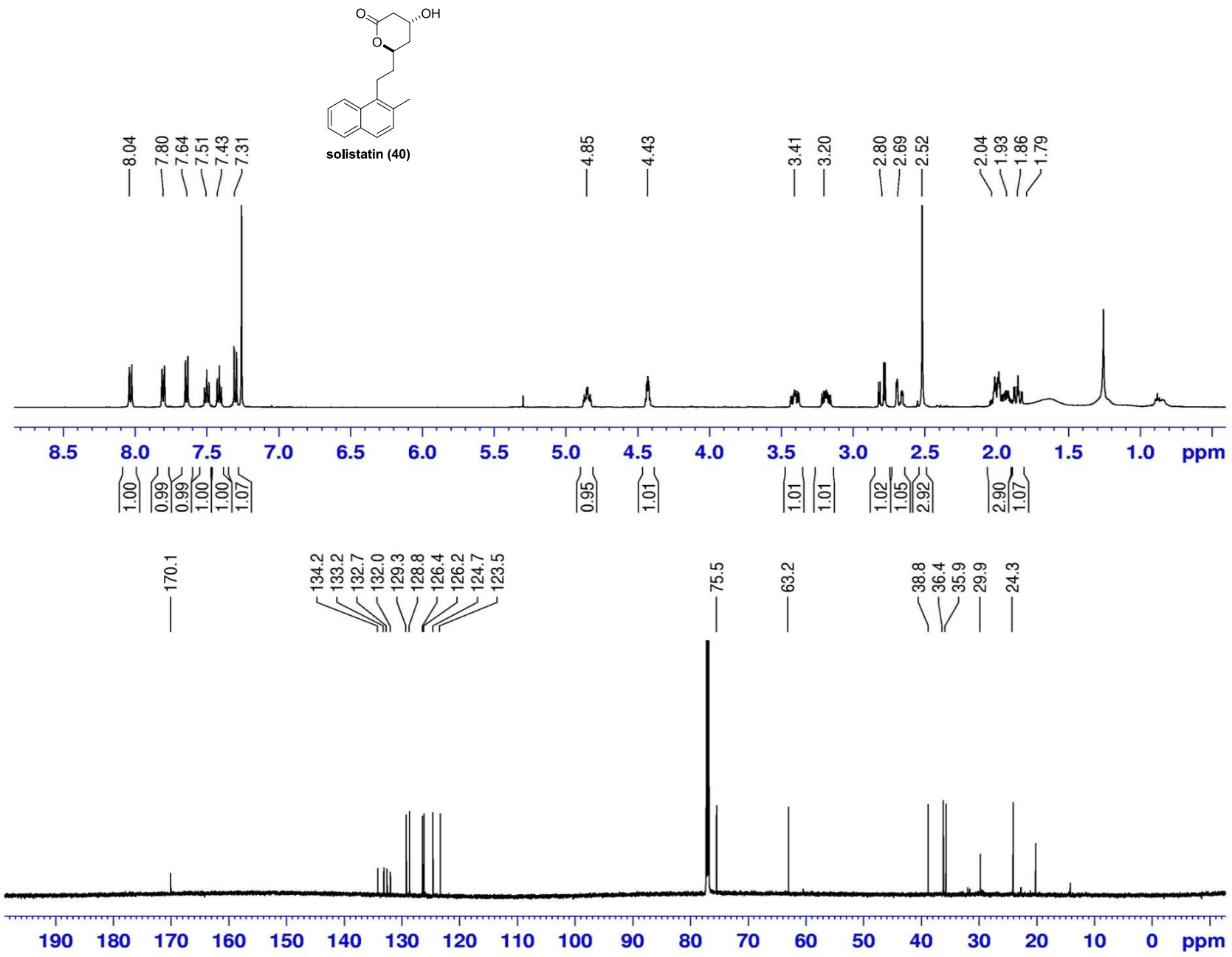

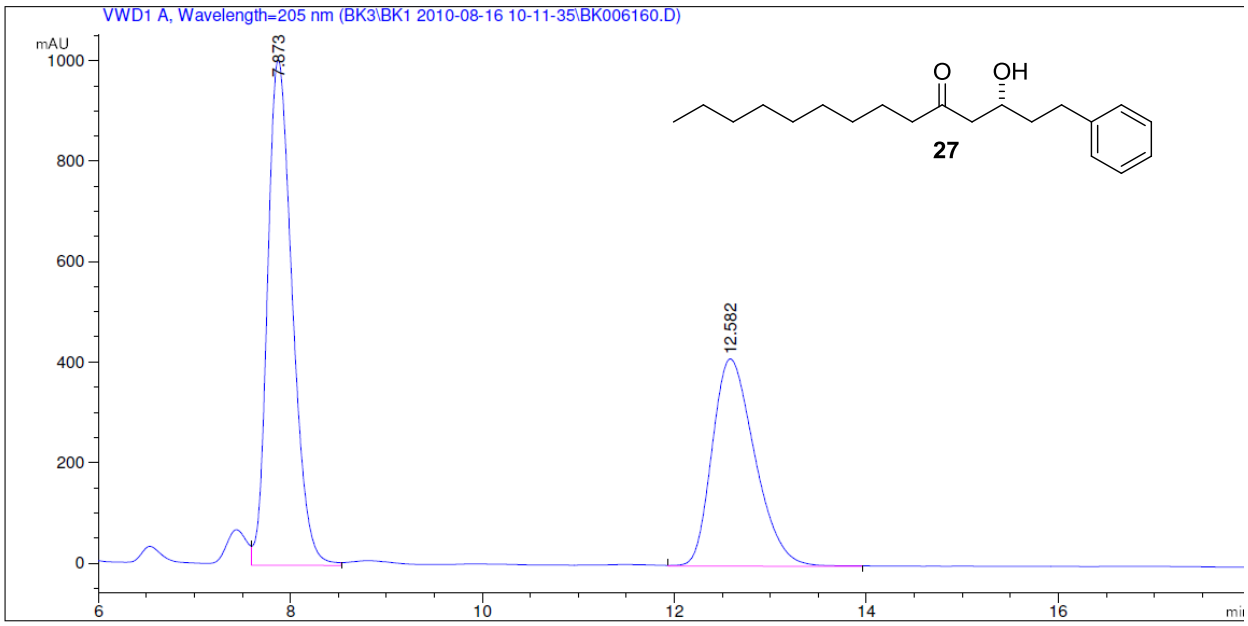

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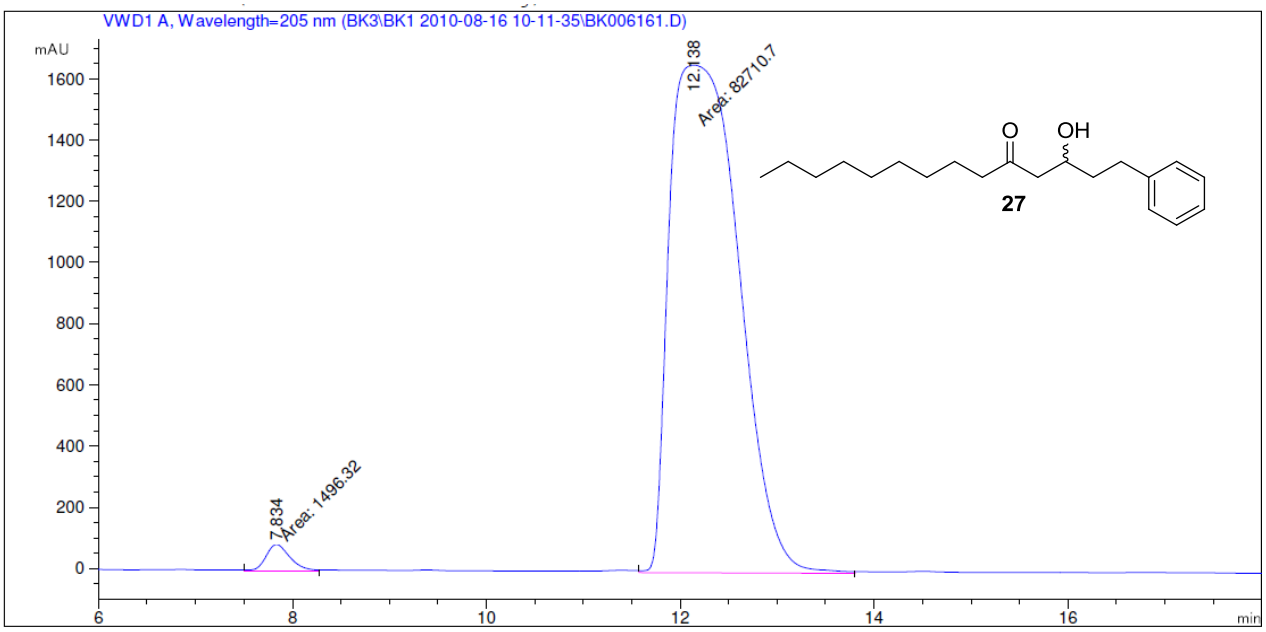

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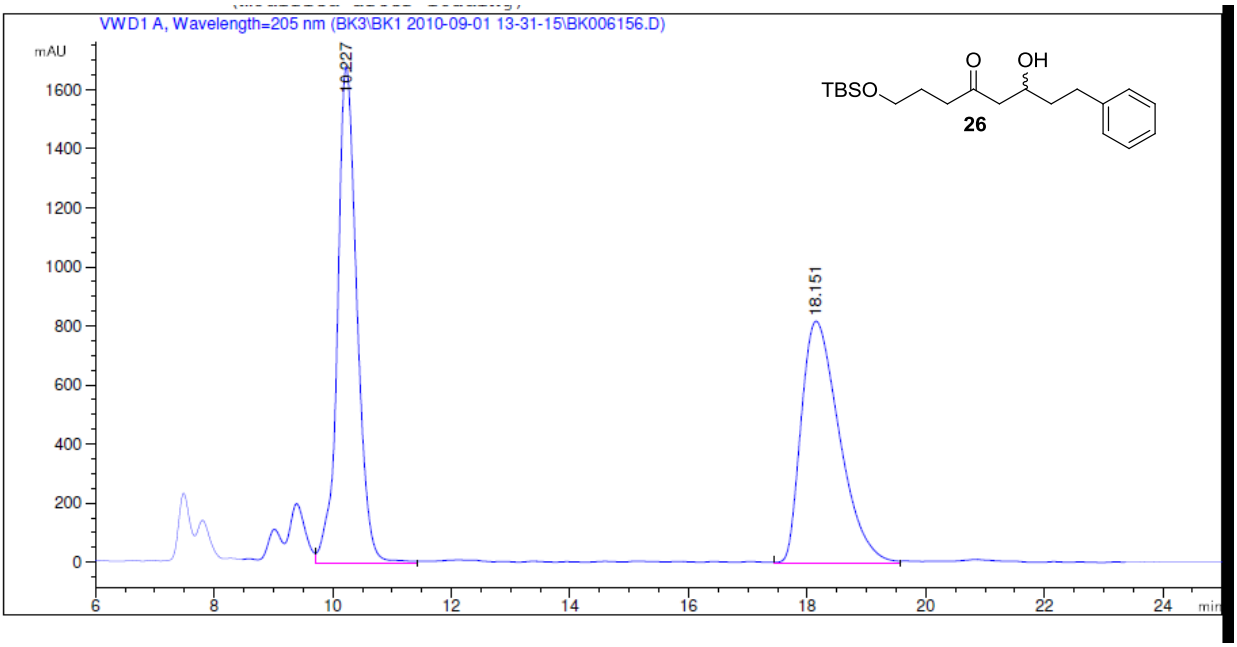

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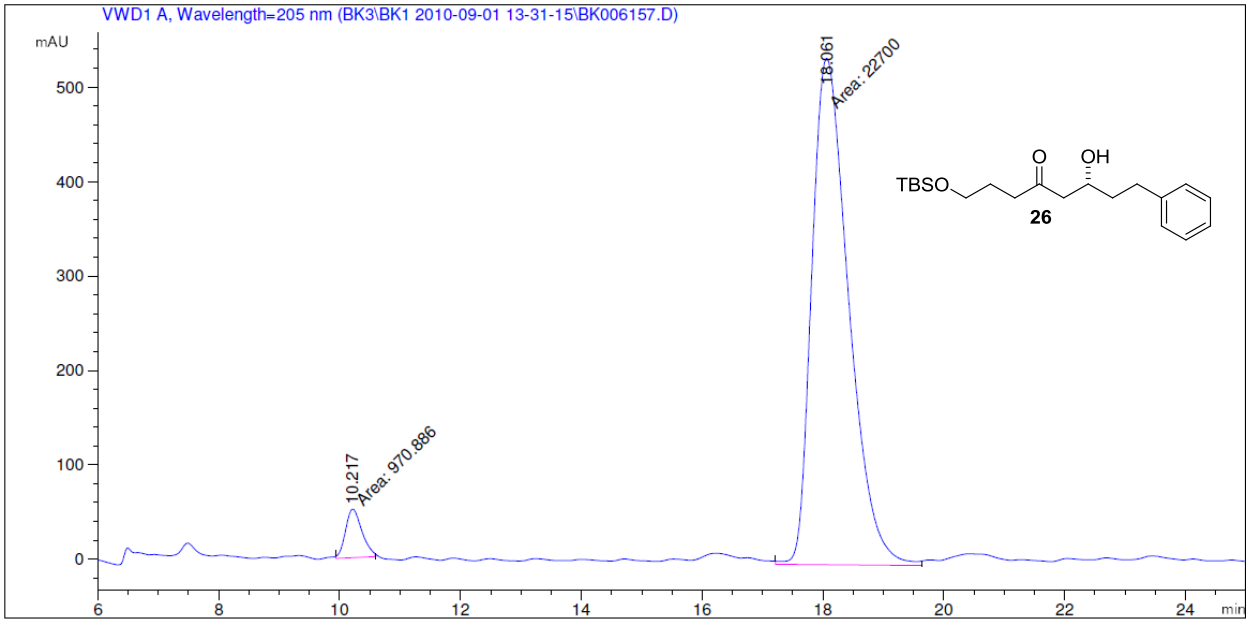

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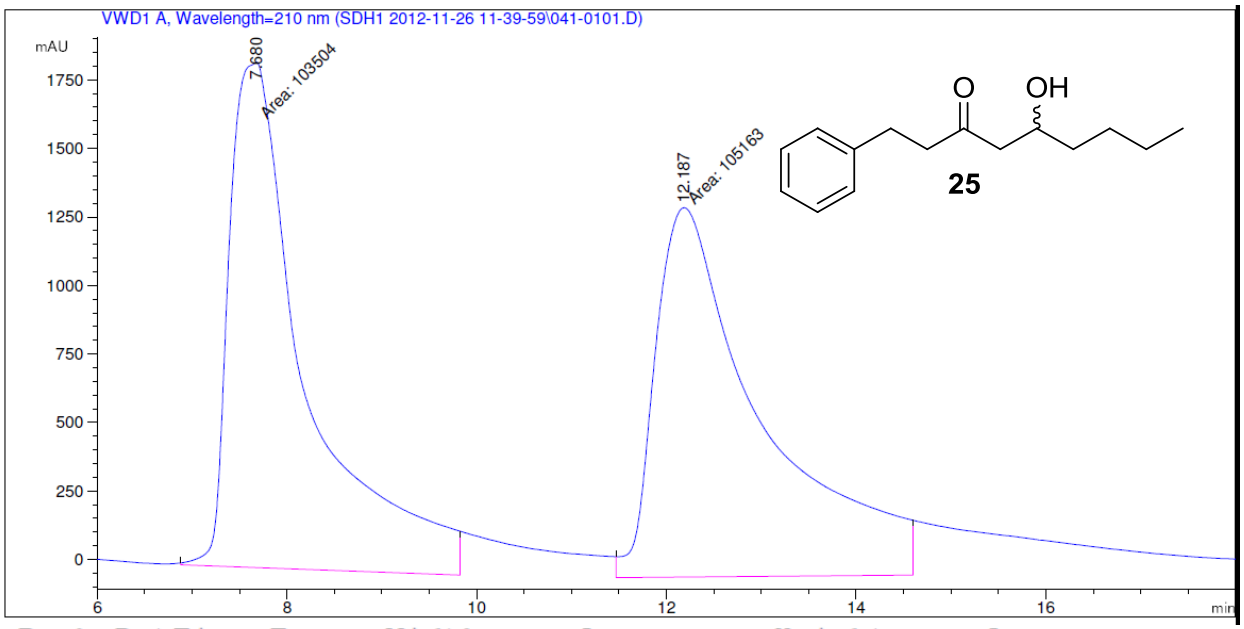

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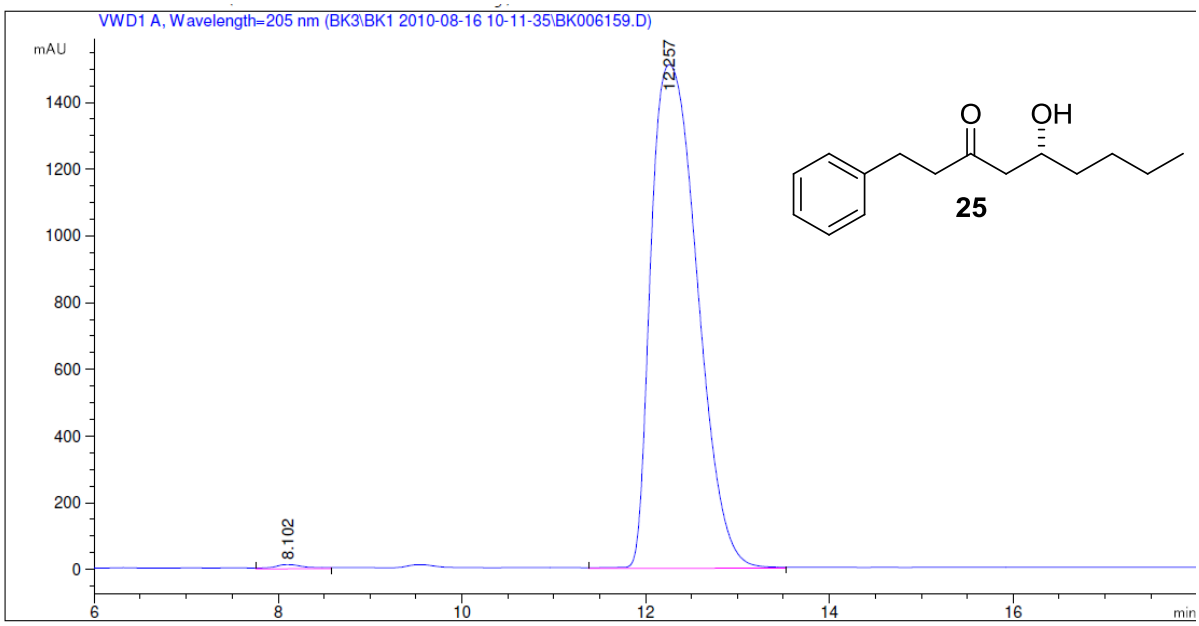

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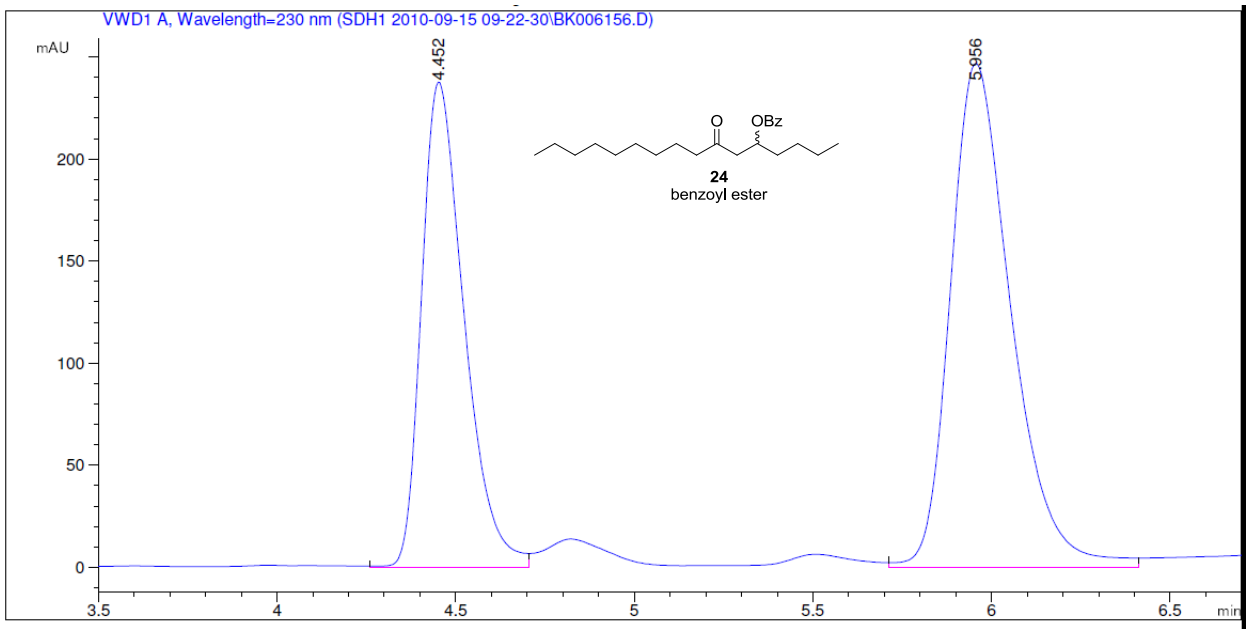

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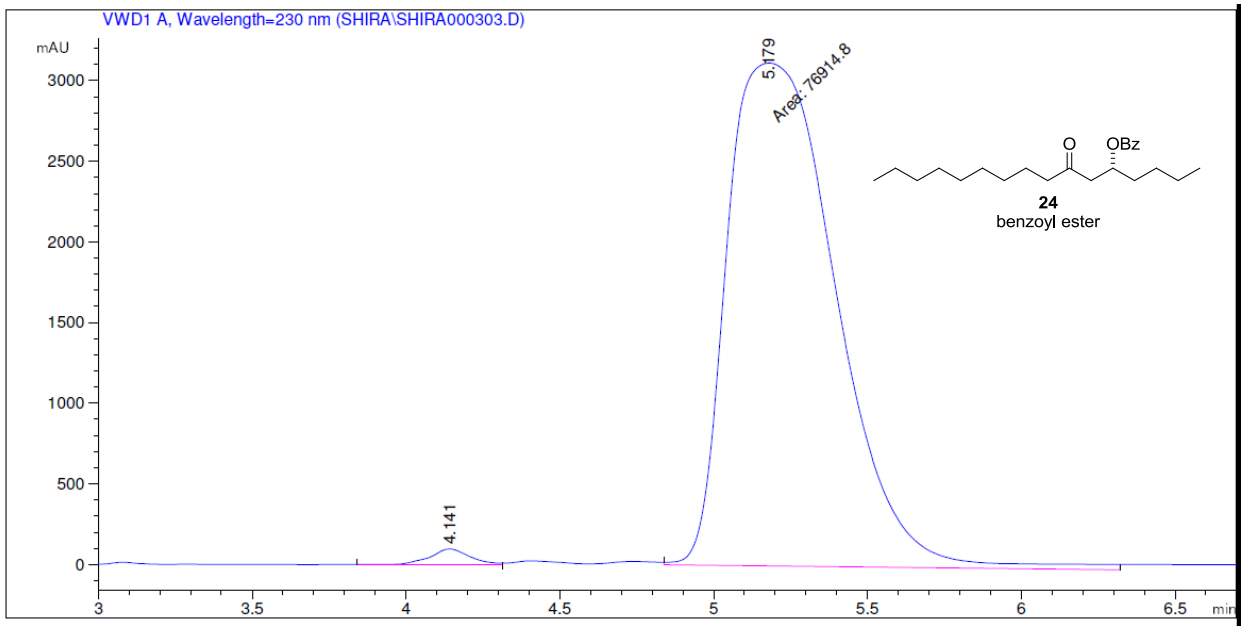
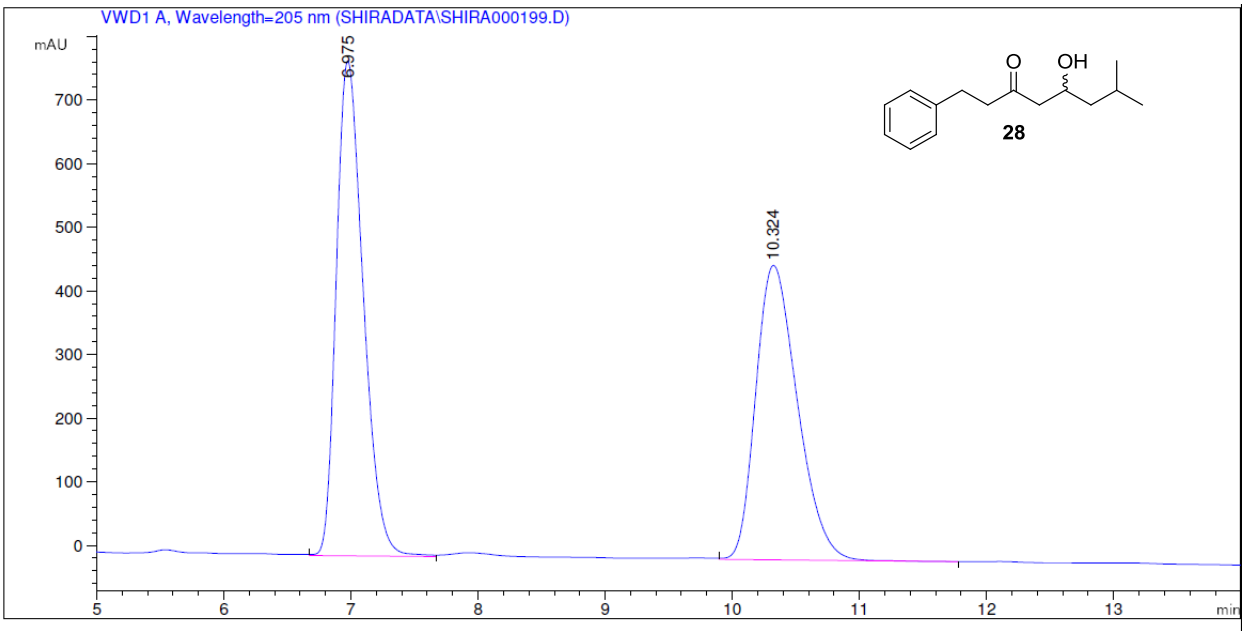
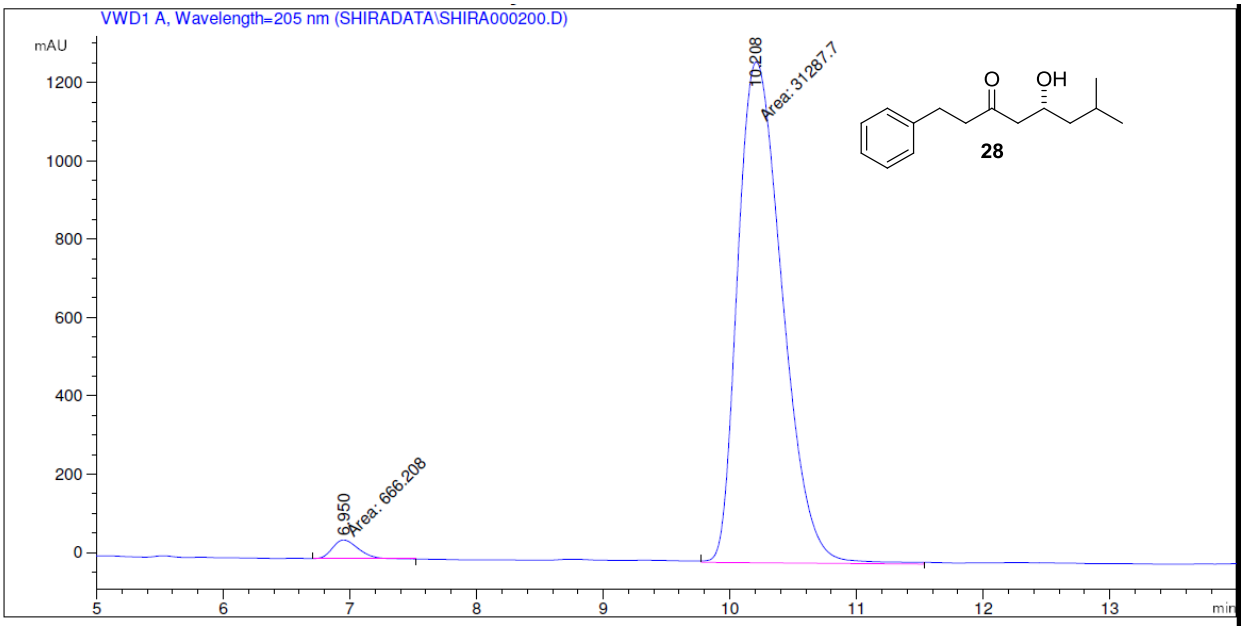
2	5.956	VV	0.1806	2927.96362	246.86720	59.7620



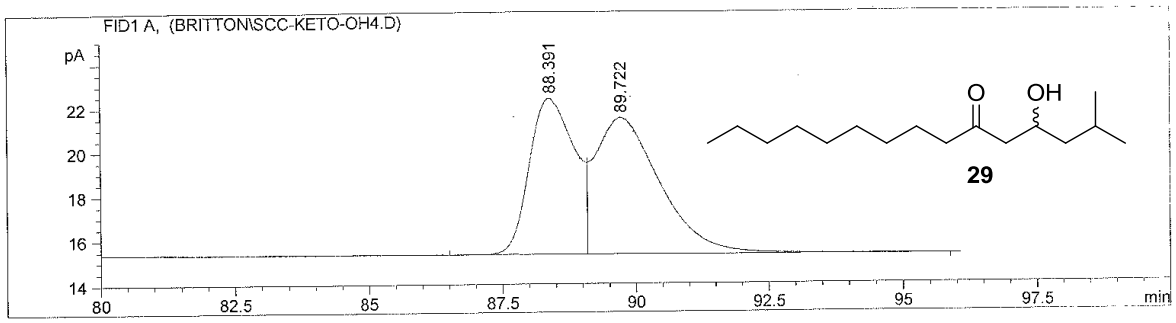
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.141	VV	0.1305	881.31396	97.26041	1.1541
2	5.179	VB	0.3836	7.54797e4	3110.52026	98.8459



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.975	MM	0.2445	1.14400e4	779.66901	52.5809
2	10.324	MM	0.3738	1.03169e4	460.00323	47.4191



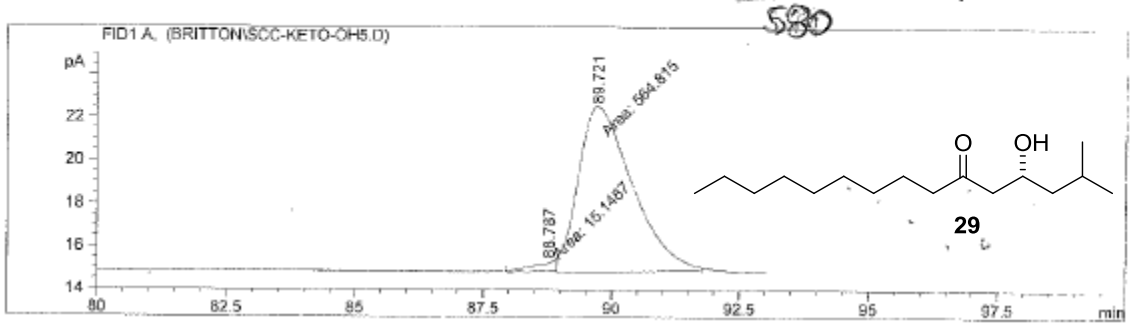
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.950	MM	0.2294	649.61737	47.19313	2.0484
2	10.208	MM	0.4052	3.10637e4	1277.60266	97.9516



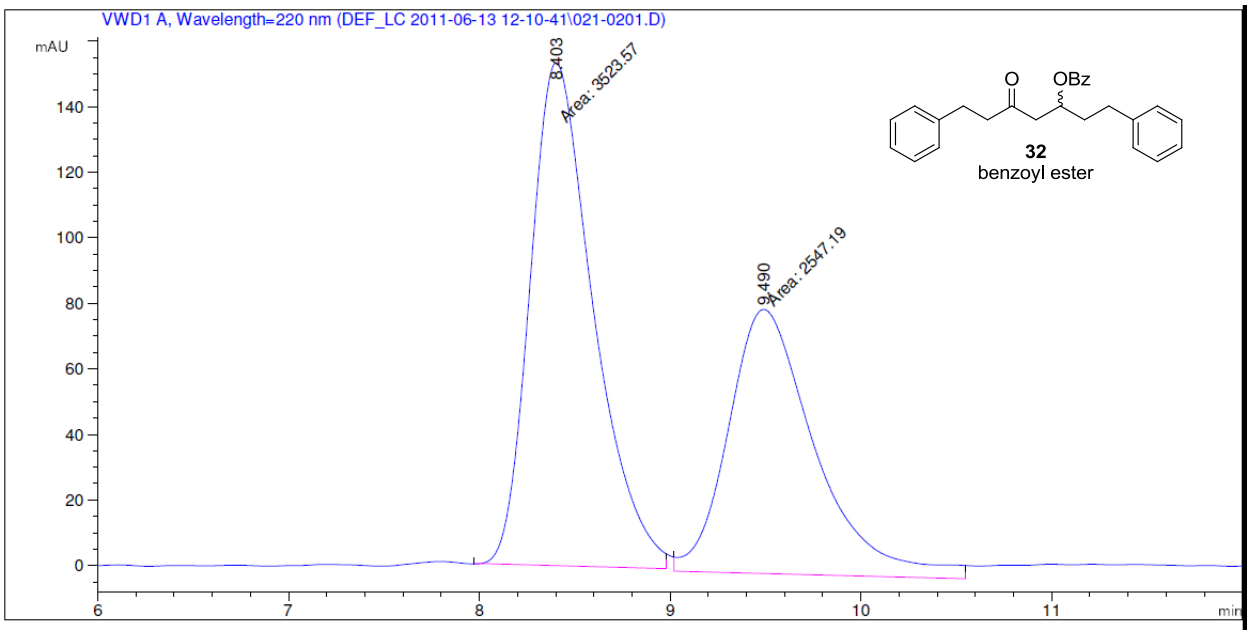
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	39.963	VV	0.4322	41.15893	1.49949	4.21302
2	88.391	VV	0.8940	415.05957	7.05911	42.48537
3	89.722	VV	1.2395	520.72864	6.17689	53.30162

Analysis Method : C:\CHEM32\1\METHODS\FFAP.M
Last changed : 09/08/2012 2:08:27 PM by Regine
(modified after loading)
Sample Info : 100(0)10-140, chiral material!

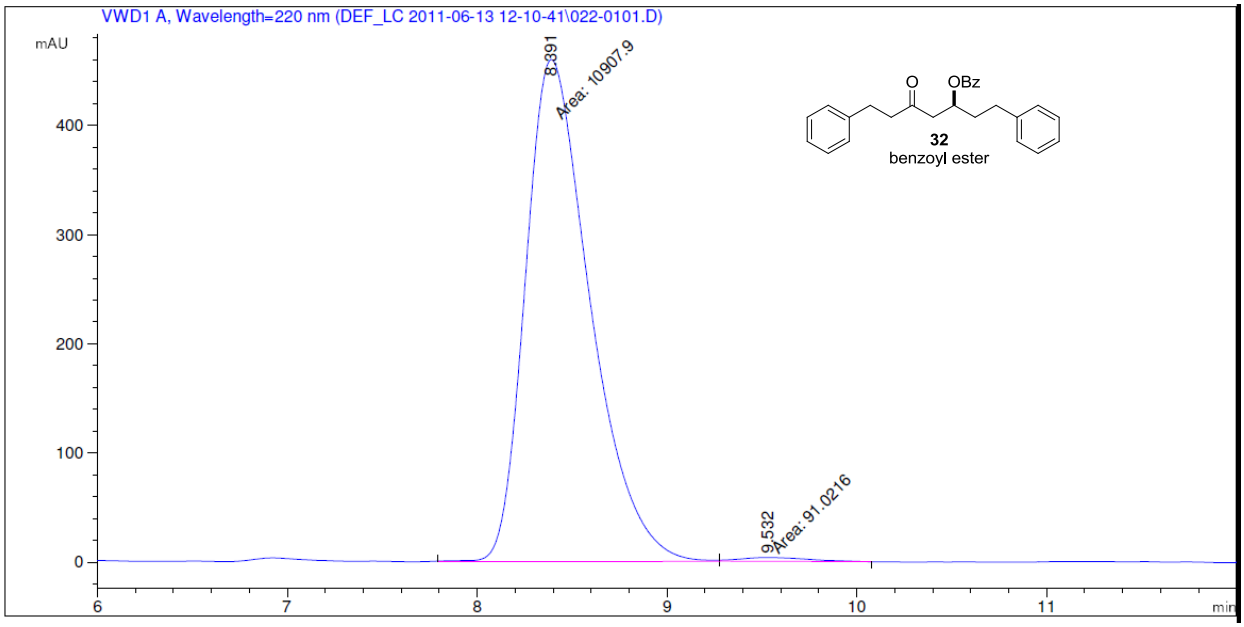
$\frac{550}{580} = 95\%$



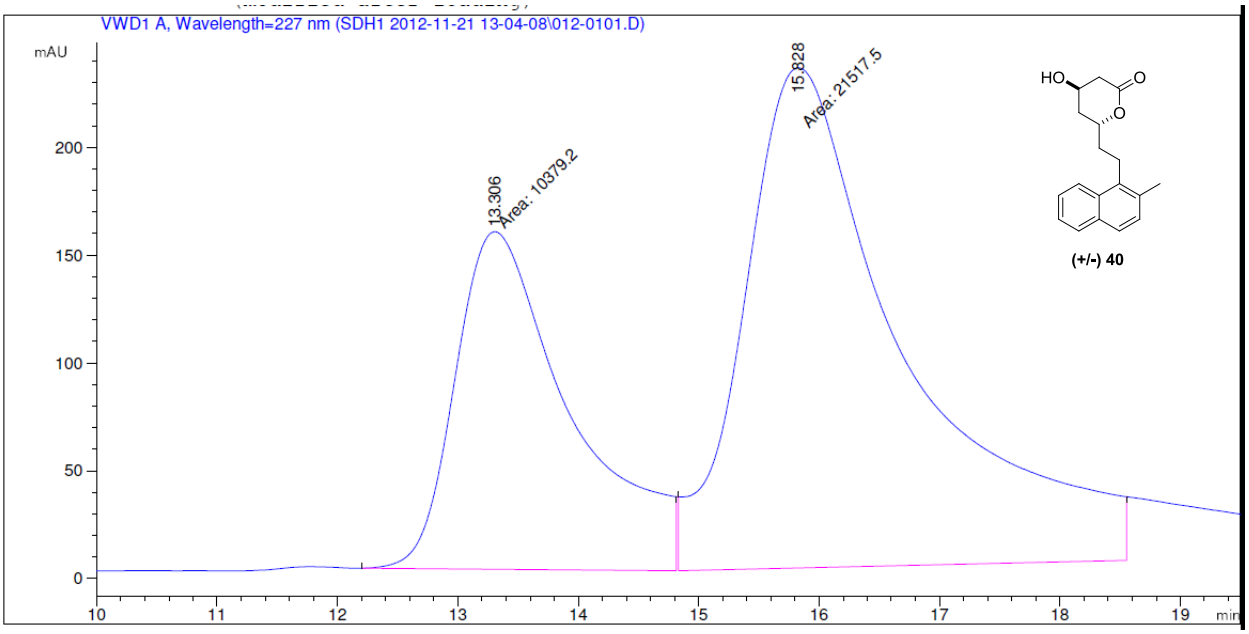
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.137	BV	0.4077	12.16436	7.72565e-1	1.84717
2	7.628	VV	3.5795	61.98114	2.09506e-1	9.41190
3	39.978	VV	0.6314	4.43102	1.09652e-1	0.67286
4	88.787	MM	0.6199	15.14868	4.07288e-1	2.30034
5	89.721	MM	1.2195	564.81488	7.71907	85.76773



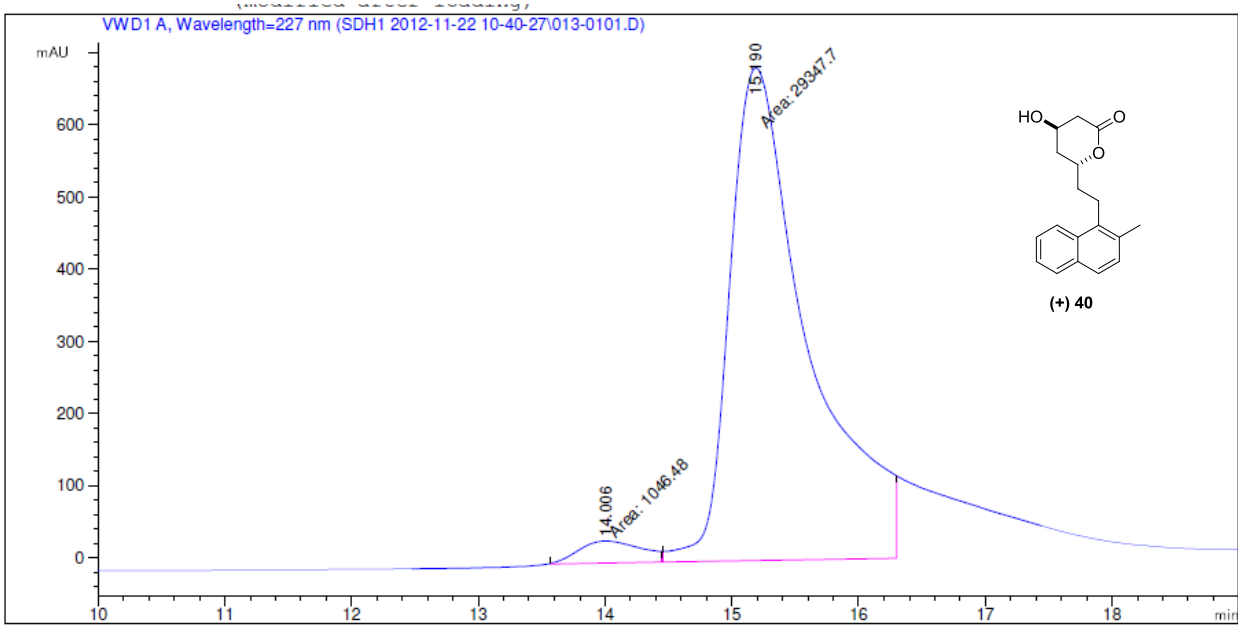
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.403	VV	0.3491	3546.01221	153.76456	60.6862
2	9.490	VB	0.4469	2297.18335	78.35359	39.3138



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.391	MM	0.3954	1.09079e4	459.75327	99.1724
2	9.532	MM	0.4221	91.02157	3.59410	0.8276



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.306	MM	1.1379	1.07567e4	157.54660	32.1620
2	15.828	MM	1.6209	2.26888e4	233.29745	67.8380



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.006	MM	0.6682	1482.08887	36.96630	3.4584
2	15.190	MM	0.9960	4.13725e4	692.29071	96.5416