Supplementary Information

Peptide-catalyzed consecutive 1,6- and 1,4-additions of thiols to α,β,γ,δ-unsaturated aldehydes

Kengo Akagawa, Nobuhiro Nishi, Jun Sen and Kazuaki Kudo

Institute of Industrial Science, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan
Tel.: +81 3 5452 6357; fax: +81 3 5452 6359; e-mail: kkudo@iis.u-tokyo.ac.jp

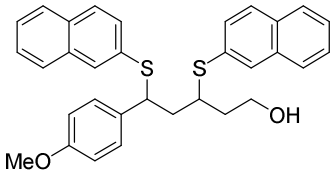
General information.

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively on a JEOL JNM-LA400 spectrometer, and chemical shifts were referenced to internal tetramethylsilane (TMS, $\delta = 0.0$ ppm) for ^{1}H and the central line of $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C. High-resolution FAB mass measurements were performed on a JEOL JMS-600H mass spectrometer in positive ionization mode using 3-nitrobenzyl alcohol as a matrix. Polyethylene glycol 400 was added to the matrix as an internal mass calibrant. HPLC traces were recorded on a Shimadzu CLASS-VP system using Chiralcel OD-H column (25 cm) and OD-H guard (1 cm), or Chiralpak AS-H column (25 cm) and AS-H guard (1 cm). The resin-supported peptide was synthesized according to our previous report using TentaGel S-NH_2 (AnaSpec, Inc., product number: 22798, 0.24 mmol/g amine loading) as a resin. To convert the supported peptide to an acid salt, the dried resin was soaked in trifluoroacetic acid, or dichloromethane (DCM) solution of benzoic acid or trichloroacetic acid for a few minutes. Then, the resin was washed successively with DCM, DMF, and DCM, and dried under reduced pressure.

Typical procedure for the peptide-catalyzed addition of a thiol to an α,β,γ,δ-unsaturated aldehyde.

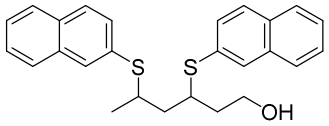
Water (334 μL) was slowly added with stirring to a round-bottom flask that contained an α,β,γ,δ-unsaturated aldehyde (0.025 mmol), a thiol (0.1 mmol of 2-naphthylthiol, or 0.125 mmol of benzenethiol), an acid salt of resin-supported peptide **4** (28 mg, 0.005 mmol of the terminal prolyl group), and methanol (167 μL) at lowered temperature. After stirring the mixture for 20 or 24 h, the peptide catalyst was filtered off and washed with chloroform. After removal of the solvent under reduced pressure, the ^{1}H NMR of the residue was measured to determine the product ratio. Product **3** was isolated as the corresponding alcohol form by the following procedure. The crude mixture was dissolved in ethanol (approximately 100 mM), and 3 equiv. of sodium borohydride was added. After the mixture had been stirred for 20 min, an aqueous saturated solution of ammonium chloride was added. The resulting solution was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (chloroform/methanol = 98:2 for **3a** and **3b**, hexanes/ethyl acetate = 3:2 for **3c**) to give a diastereomixture of the alcohol form of product **3**.

Spectroscopic data for the corresponding alcohols of products 3.



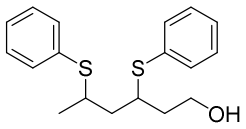
5-(4-Methoxyphenyl)-3,5-bis(2-naphthylthio)pentan-1-ol [diastereomeric mixture (ca. 6 : 4)]

^{1}H NMR ($CDCl_3$) δ = 7.82-7.09 (m, 16H), 6.79-6.72 (m, 2H), 4.79 (t, J = 7.6 Hz, 0.6H), 4.60 (t, J = 7.4 Hz, 0.4H), 3.90-3.67 (m, 2H), 3.77 (s, 3H), 3.63-3.54 (m, 0.4H), 3.14 (quin, J = 7.2 Hz, 0.6H), 2.32-2.17 (m, 2H), 2.02-1.92 (m, 0.4H), 1.85-1.74 (m, 1.6H). ^{13}C NMR ($CDCl_3$) δ = 158.87, 158.71, 133.73, 133.59, 133.55, 133.44, 132.37, 132.27, 132.25, 132.22, 132.17, 131.85, 131.82, 131.38, 131.36, 131.10, 130.85, 130.42, 129.82, 129.73, 129.61, 129.45, 129.14, 128.77, 128.46, 128.40, 128.27, 128.09, 127.65, 127.63, 127.61, 127.57, 127.46, 127.40, 127.32, 127.29, 126.49, 126.38, 126.26, 126.14, 126.05, 114.00, 113.85, 60.48, 60.34, 55.22, 50.57, 49.85, 44.26, 43.95, 42.24, 41.48, 38.37, 37.21. HRMS (FAB) *m/z*: calculated for $C_{32}H_{30}O_2S_2$ $[M]^+$: 510.1721, found 510.1707. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 90:10, 1.0 mL min^{-1}): for the major diastereomer, t_R = 19.0 min (minor), 23.7 min (major); for the minor diastereomer, t_R = 22.1 min (minor), 30.5 min (major).



3,5-bis(2-Naphthylthio)hexan-1-ol [diastereomeric mixture (ca. 5.5 : 4.5)]

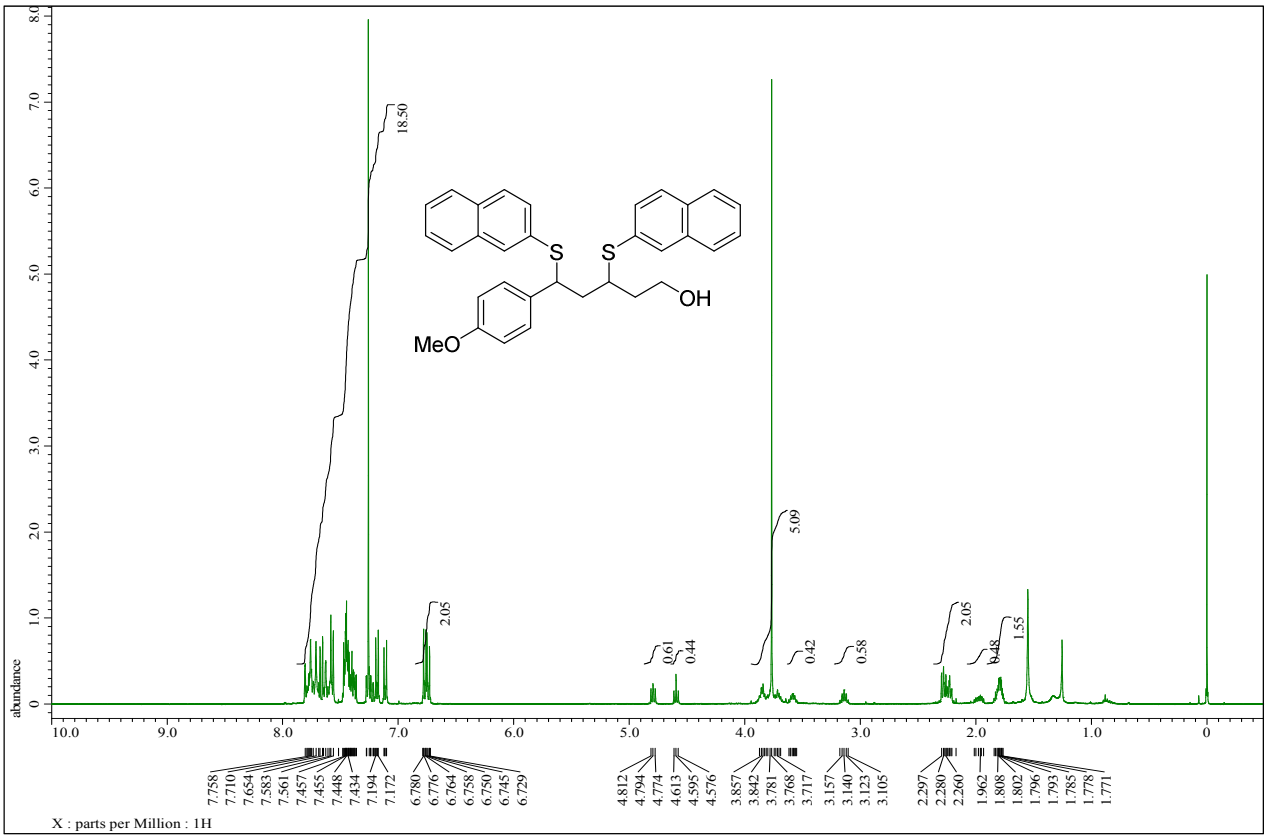
^{1}H NMR ($CDCl_3$) δ = 7.92-7.86 (m, 1.45H), 7.81-7.61 (m, 6.55H), 7.51-7.36 (m, 6H), 3.95-3.56 (m, 4H), 2.10-2.02 (m, 0.45H), 1.96-1.77 (m, 3.55H), 1.36 (d J = 6.8 Hz, 1.65H), 1.33 (d, J = 6.8 Hz, 1.35H). ^{13}C NMR ($CDCl_3$) δ = 133.65, 133.60, 133.58, 132.28, 132.22, 132.20, 132.03, 131.98, 131.93, 131.51, 131.01, 130.94, 130.79, 130.59, 129.86, 129.72, 129.61, 128.52, 128.48, 128.38, 128.26, 127.67, 127.63, 127.61, 127.39, 127.35, 127.31, 126.56, 126.49, 126.39, 126.18, 126.08, 126.02, 125.99, 60.45, 60.43, 44.49, 43.75, 42.72, 42.63, 41.81, 40.62, 38.44, 37.55, 22.63, 20.92. HRMS (FAB) *m/z*: calculated for $C_{26}H_{26}OS_2$ $[M]^+$: 418.1425, found 418.1419. Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 95:5, 1.0 mL min^{-1}): for the major diastereomer, t_R = 31.1 min (minor), 34.7 min (major); for the minor diastereomer, t_R = 24.3 min (minor), 27.8 min (major).

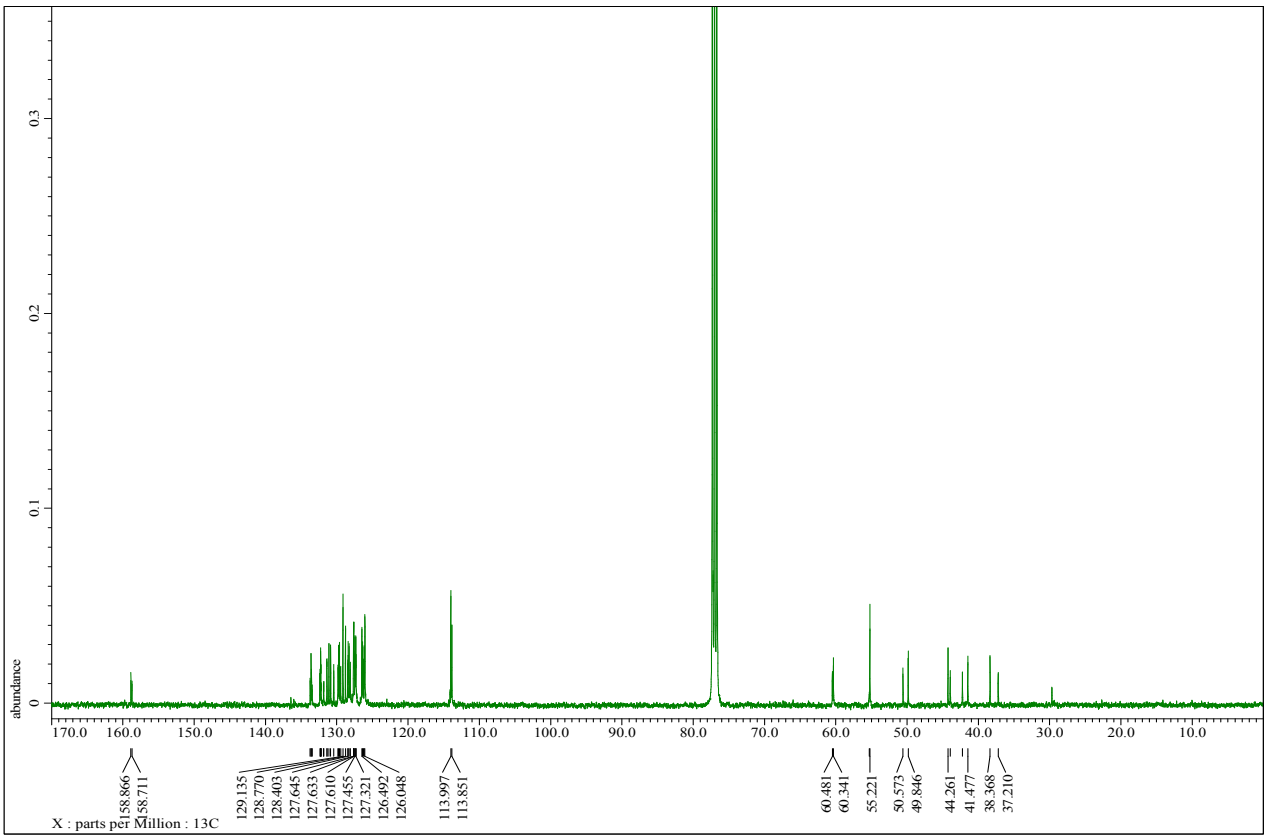


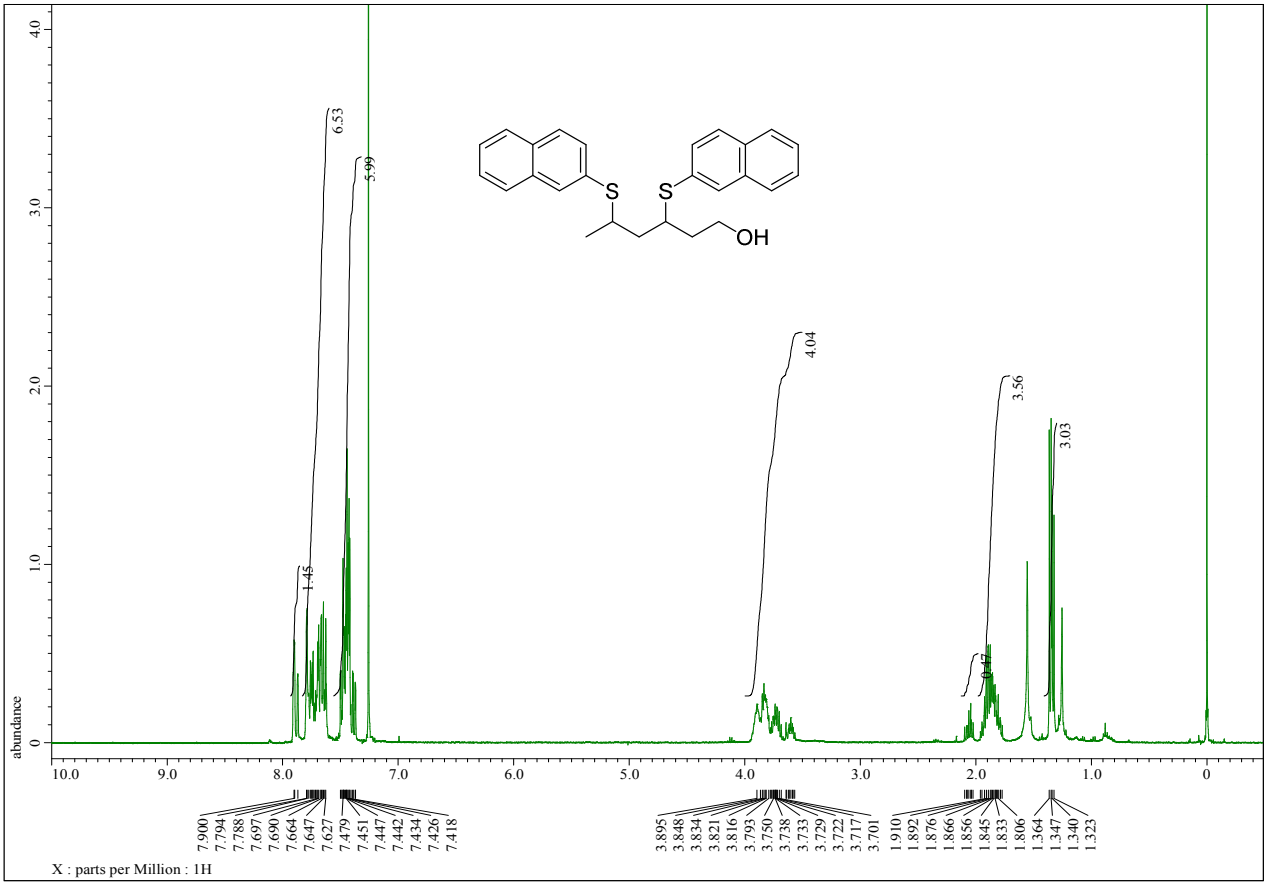
3,5-bis(Phenylthio)hexan-1-ol [diastereomeric mixture (ca. 5.5 : 4.5)]

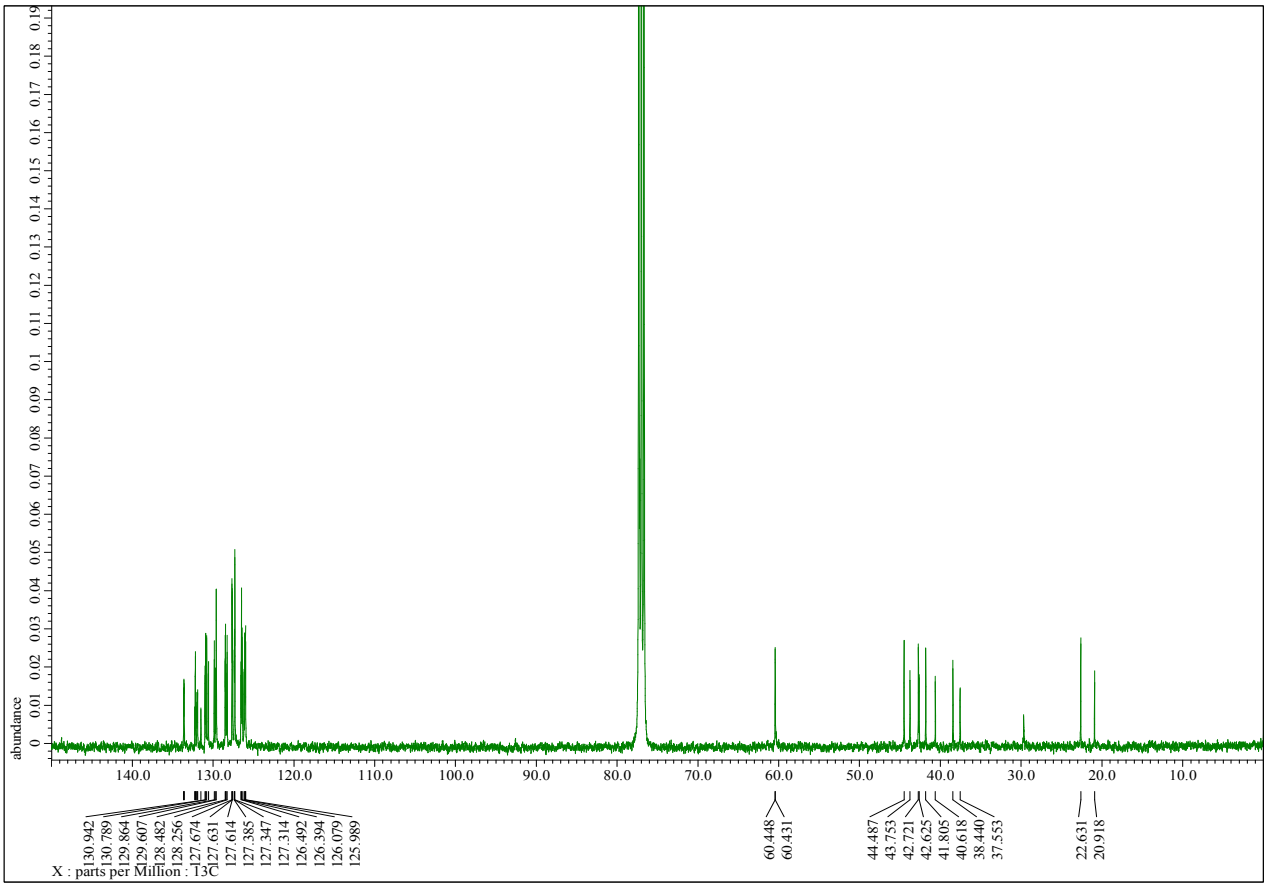
^{1}H NMR ($CDCl_3$) δ = 7.47-7.20 (m, 10H), 3.90-3.75 (m, 2H), 3.66-3.50 (m, 1.55H), 3.46-3.38 (m, 0.45H), 1.98-1.66 (m, 4H), 1.29 (d J = 6.8 Hz, 1.65H), 1.27 (d, J = 7.2 Hz, 1.35H). ^{13}C NMR ($CDCl_3$) δ = 134.41, 134.26, 134.16, 133.78, 132.73, 132.64, 132.60, 132.28, 128.96, 128.94, 128.86, 128.78, 127.26, 127.20, 127.10, 126.97, 60.38, 60.35, 44.50, 43.75, 42.36, 42.12, 41.77, 40.61, 38.18, 37.36, 22.44, 20.79. HRMS (FAB) *m/z*: calculated for $C_{18}H_{22}OS_2$ $[M]^+$: 318.1112, found 318.1104. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 98:2, 1.0 mL min^{-1}): for the major diastereomer, t_R = 34.3 min (major), 44.4 min (minor); for the minor diastereomer, t_R = 28.2 min (major), 39.4 min (minor).

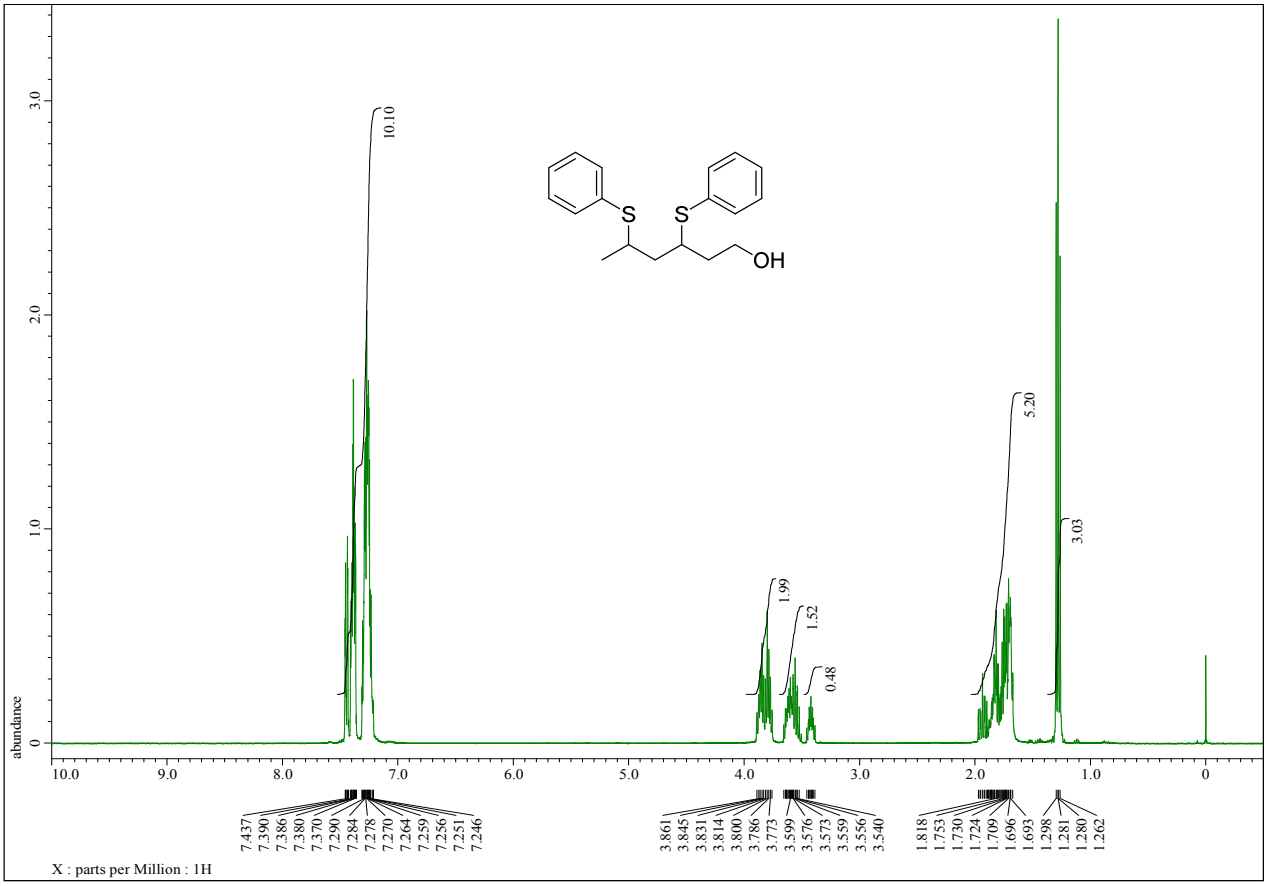
^{1}H and ^{13}C NMR spectra.

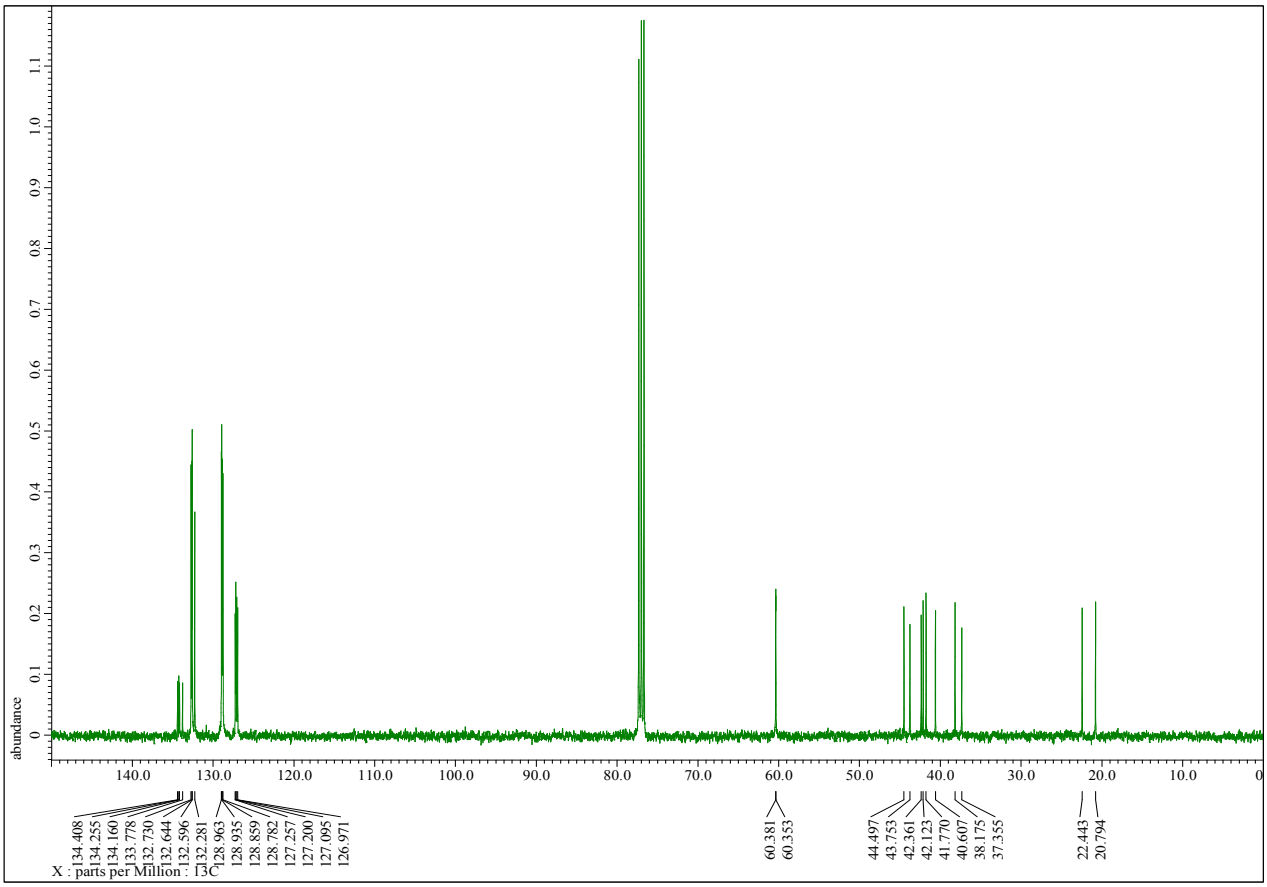





abundance
6.53
5.99
4.04
3.56
3.03
1.45
S
S
OH
7.900
7.794
7.788
7.697
7.690
7.664
7.647
7.627
7.479
7.451
7.447
7.442
7.434
7.426
7.418
3.895
3.848
3.834
3.821
3.816
3.793
3.750
3.738
3.733
3.729
3.722
3.717
3.701
1.910
1.892
1.876
1.866
1.856
1.845
1.833
1.806
1.364
1.347
1.340
1.323
X : parts per Million : 1H

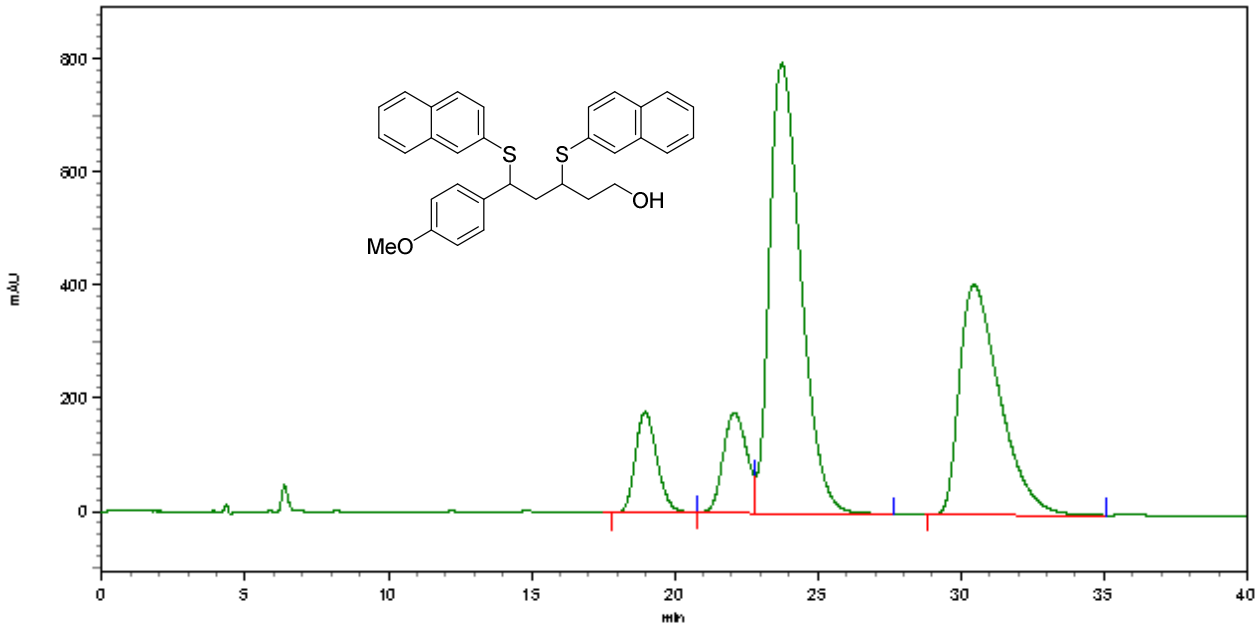

abundance
130.942
130.789
129.864
129.607
128.482
128.256
127.674
127.631
127.614
127.385
127.347
127.314
126.492
126.394
126.079
125.989
60.448
60.431
44.487
43.753
42.721
42.625
41.805
40.618
38.440
37.553
22.631
20.918
X : parts per Million : 13C


abundance
10.10
5.20
3.03
1.99
1.52
0.48
S
S
OH
X : parts per Million : 1H


abundance
X : parts per Million : 13C

HPLC traces.

Chiralcel OD-H, hexane/2-propanol = 90:10, 1.0 mL min^{-1}

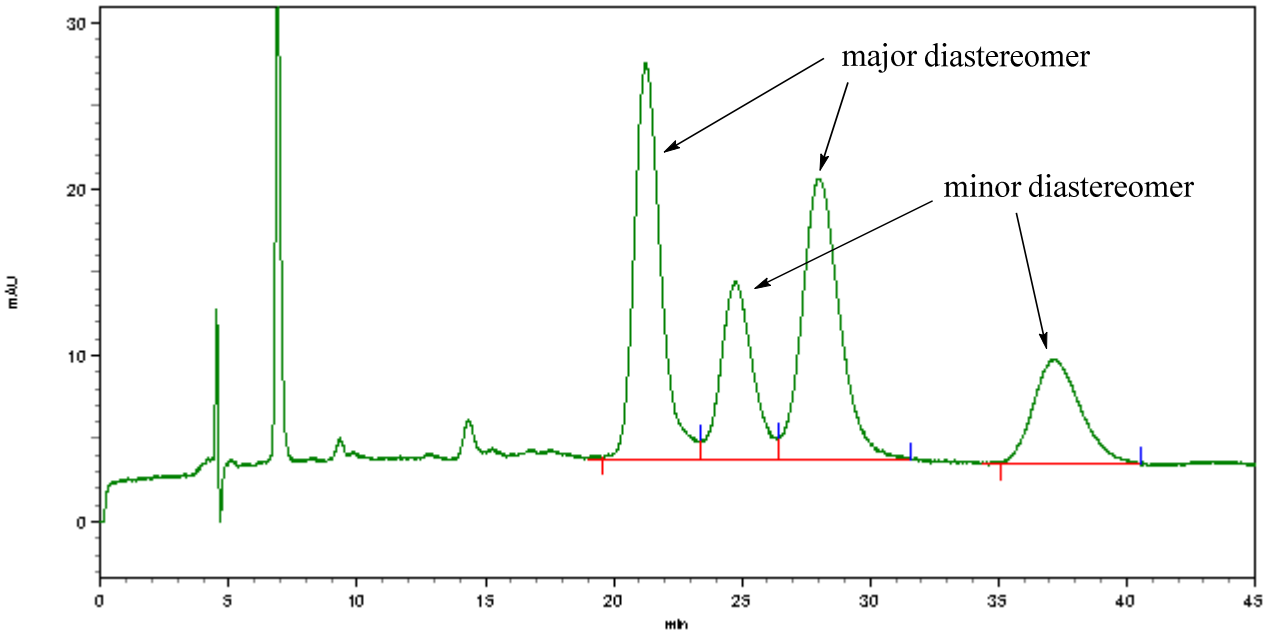


1: 254 nm, 8 nm

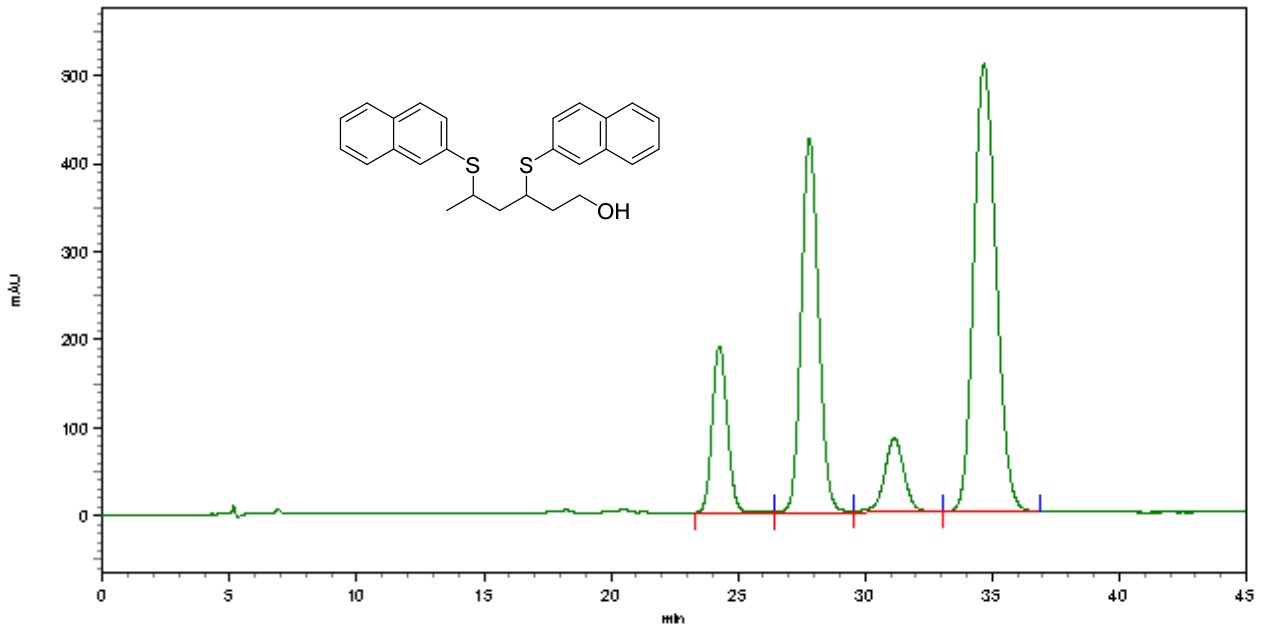
retention time	area	area%
18.997	9567522	7.93
22.091	10437395	8.65
23.748	60793371	50.40
30.496	39830560	33.02

Total	120628849	100.00

racemic sample



Chiralpak AS-H, hexane/2-propanol = 95:5, 1.0 mL min^{-1}

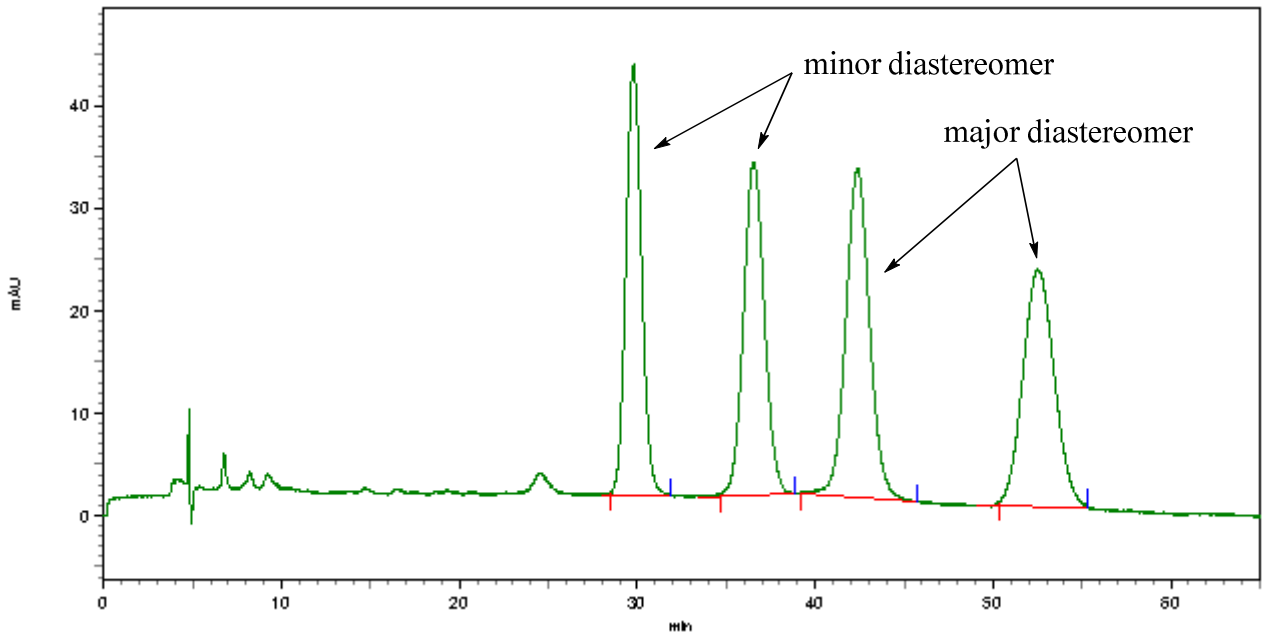


1: 254 nm, 8 nm

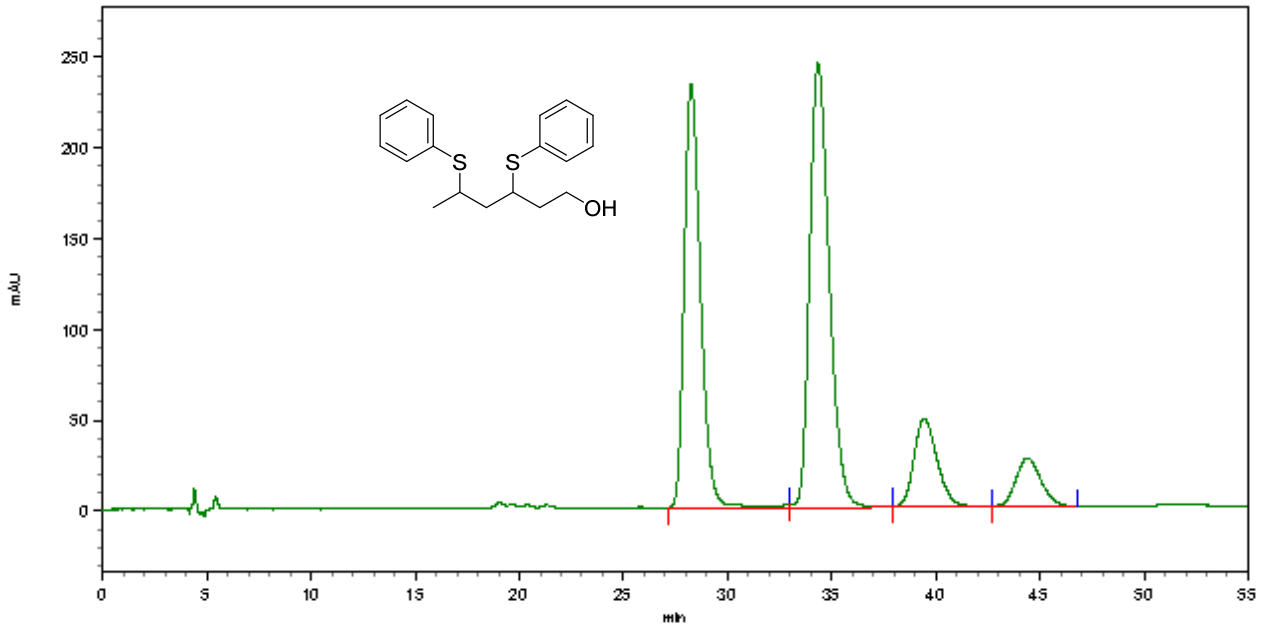
retention time	area	area%
24.265	7817712	12.29
27.806	20159819	31.70
31.145	4477215	7.04
34.671	31150018	48.97

Total	63604764	100.00

racemic sample



Chiralcel OD-H, hexane/2-propanol = 98:2, 1.0 mL min^{-1}



1: 254 nm, 8 nm

retention time	area	area%
28.247	12708950	36.64
34.341	15976867	46.06
39.438	3767440	10.86
44.401	2231936	6.43

Total	34685192	100.00

racemic sample