Electronic Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

Copper-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Organolithium Reagents

*Pieter H. Bos, Alena Rudolph, Manuel Pérez, Martín Fañanás-Mastral, Syuzanna R. Harutyunyan and Ben L. Feringa**

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands.

General Procedures:

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector.

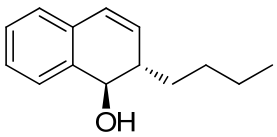
All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Dichloromethane was dried and distilled over calcium hydride; 1,2-dichloroethane was dried over molecular sieves (3Å). CuBr•SMe_2 was purchased from Aldrich, and used without further purification. Organolithium reagents **2** were purchased from Acros: *n*-BuLi (**2a**) (1.6 M in hexane), *i*-BuLi (**2d**) (1.6 M in hexane), $TMSCH_2Li$ (**2e**) (0.8 M in hexane), MeLi (**2f**) (1.6 M in diethyl ether) or Aldrich: EtLi (**2b**) (0.5 M in benzene/cyclohexane 9:1), *n*-HexLi (**2c**) (2.3 M in *n*-hexane), PhLi (**2g**) (1.8 M in dibutyl ether). Ligand **L1** was purchased from Aldrich. Phosphoramidite ligands **L2**, **L4**[1] and **L3**, **L5**[2] were prepared as reported in the literature.

Racemic products were synthesized by reaction of the oxabicyclic alkenes **1** with the corresponding organolithium reagent **2** at -80°C in dichloromethane in the presence of CuI (10 mol%) and PPh_3 (20 mol%).

[1] Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.
[2] Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586–2590.

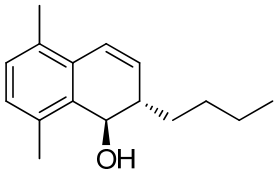
General procedure for the copper-catalyzed ring opening of oxabicyclic alkenes 1 with organolithium reagents 2

A Schlenk tube equipped with septum and stirring bar was charged with CuBr•SMe_2 (0.01 mmol, 2.06 mg, 5 mol%) and phosphoramidite ligand (*R*,*R*,*R*)-**L2** (0.012 mmol, 6.48 mg, 6 mol%). Dry dichloromethane (2 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, oxabicyclic alkene **1** (0.2 mmol) was added and the resulting solution was cooled to -80 °C. To the cooled mixture, BF_3•OEt_2 (28 μL, 0.22 mmol, 1.1 eq) was added with a microsyringe. In a separate Schlenk vessel, the corresponding organolithium reagent **2** (0.22 mmol, 1.1 eq) was diluted with dry hexane (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 2 hours using a syringe pump. Once the addition was complete, the mixture was stirred overnight at -80°C. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed up to room temperature, diluted with diethyl ether and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a gradient of *n*-pentane:Et_2O (15:1 – 9:1) as the eluent.



(+)-(1*R*,2*S*)-2-butyl-1,2-dihydronaphthalen-1-ol (3aa): Isolated as a white solid.
[84% yield, >99:1 anti:syn, 97% ee].
The physical data were identical in all respects to those previously reported.[3]
$[\alpha]_D^{20}$ = +230.0 (*c* = 1.0, $CHCl_3$), [lit.[3] (-)-(1*S*,2*R*)-**3aa** (92% ee): $[\alpha]_D^{20}$ = -233.0 (*c* = 0.94, $CHCl_3$)].
Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 98:2, 40 °C, 254 nm, retention times (min.): 23.1 (minor) and 26.5 (major).

[3] Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703-2705.



(+)-2-butyl-5,8-dimethyl-1,2-dihydronaphthalen-1-ol (3ba): Isolated as a pale yellow oil.

[82% yield, >99:1 anti:syn, 95% ee].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (q, *J* = 7.7 Hz, 2H), 6.71 (d, *J* = 9.9 Hz, 1H), 6.11 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.76 (s, 1H), 2.63 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.70 (bs, 1H), 1.43 – 1.10 (m, 6H), 0.87 (t, *J* = 7.1 Hz, 3H).

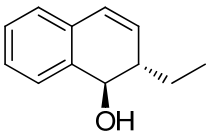
^{13}C NMR: (100 MHz, $CDCl_3$) δ 134.3, 132.7, 131.5, 130.4, 130.0, 129.9, 129.4, 122.6, 68.1, 42.1, 31.6, 29.9, 22.8, 18.9, 18.2, 14.0.

$[\alpha]_D^{20}$ = +357.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+, *m/z*): calcd for $C_{16}H_{23}O$ $[M+H]^+$: 231.17434; found: 231.17329.

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, 254 nm, retention times (min): 24.3 (minor) and 27.1 (major).

In accordance with the results obtained in the other ring opening reactions, the absolute configuration of this compound is assumed to be (1*R*, 2*S*), analogous to the other products.



(+)-(1*R*,2*S*)-2-ethyl-1,2-dihydronaphthalen-1-ol (3ab): Isolated as a white solid

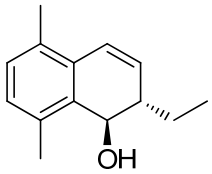
[80% yield, >99:1 anti:syn, 98% ee].

The physical data were identical in all respects to those previously reported. [3,4]

$[\alpha]_D^{20}$ = +245.0 (*c* = 1.0, $CHCl_3$).

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, 254 nm, retention times (min.): 44.9 (minor) and 51.9 (major).

[4] Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Chem. Commun.* **2001**, 2606-2607.

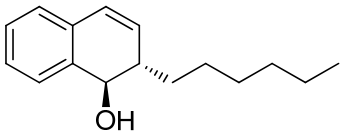


(+)-(1*R*,2*S*)-2-ethyl-5,8-dimethyl-1,2-dihydronaphthalen-1-ol (3bb): Isolated as a pale yellow oil. [71% yield, >99:1 anti:syn, 97% ee].

The physical data were identical in all respects to those previously reported.[3]

$[\alpha]_D^{20}$ = +250.6 (*c* = 0.53, $CHCl_3$), [lit.[3] (-)-(1*S*,2*R*)-**3bb** (99% ee): $[\alpha]_D^{20}$ = -256.16 (*c* = 2.66, $CHCl_3$)].

Enantiomeric excess was determined by chiral HPLC analysis, Chiralpak AD column, 1.0 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, 254 nm, retention times (min.): 14.2 (minor) and 15.8 (major).



(+)-2-hexyl-1,2-dihydronaphthalen-1-ol (3ac): Isolated as a white solid.

[81% yield, >99:1 anti:syn, 97% ee].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.25 (dqd, *J* = 14.4, 7.4, 1.5 Hz, 2H), 7.11 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.49 (d, *J* = 9.7 Hz, 1H), 6.02 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.52 (s, 1H), 2.70 – 2.45 (m, 1H), 1.79 (d, *J* = 5.2 Hz, 1H), 1.48 – 1.34 (m, 2H), 1.34 – 1.19 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H) .

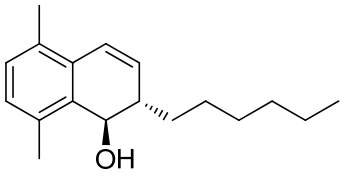
^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.7, 132.3, 131.1, 128.5, 127.8, 127.6, 126.4, 125.8, 72.4, 42.5, 31.7, 31.6, 29.4, 27.0, 22.6, 14.0.

$[\alpha]_D^{20}$ = +311.1 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+, *m/z*): calcd for $C_{16}H_{22}ONa$ $[M+Na]^+$: 253.15798; found: 253.15647.

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, 254 nm, retention times (min): 33.0 (minor) and 39.9 (major).

In accordance with the results obtained in the other ring opening reactions, the absolute configuration of this compound is assumed to be (1*R*, 2*S*), analogous to the other products.



(+)-2-hexyl-5,8-dimethyl-1,2-dihydronaphthalen-1-ol (3bc): Isolated as a pale yellow oil. [82% yield, >99:1 anti:syn, 93% ee].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (q, *J* = 7.7 Hz, 2H), 6.71 (d, *J* = 9.9 Hz, 1H), 6.10 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.76 (s, 1H), 2.63 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.72 (s, 1H), 1.48 – 1.32 (m, 2H), 1.32 – 1.12 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H).

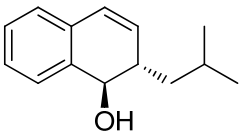
^{13}C NMR: (100 MHz, $CDCl_3$) δ 134.3, 132.7, 131.5, 130.4, 130.0, 129.9, 129.4, 122.5, 68.1, 42.1, 31.8, 31.7, 29.4, 27.6, 22.6, 18.9, 18.2, 14.0.

$[\alpha]_D^{20}$ = +272.8 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+, *m/z*): calcd for $C_{18}H_{27}O$ $[M+H]^+$: 259.20564; found: 259.20575.

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, 254 nm, retention times (min): 20.7 (minor) and 23.6 (major).

In accordance with the results obtained in the other ring opening reactions, the absolute configuration of this compound is assumed to be (1*R*, 2*S*), analogous to the other products.



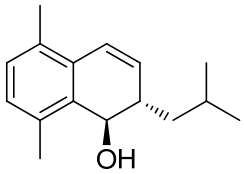
(+)-(1*R*,2*S*)-2-isobutyl-1,2-dihydronaphthalen-1-ol (3ad): Isolated as a white solid [86% yield, >99:1 anti:syn, 97% ee].

The physical data were identical in all respects to those previously reported.[5]

$[\alpha]_D^{20}$ = +270.6 (*c* = 1.0, $CHCl_3$), [lit.[5] (-)-(1*S*,2*R*)-**3ad** (94% ee): $[\alpha]_D^{20}$ = -345.9 (*c* = 0.66, $CHCl_3$)].

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 98:2, 40 °C, 254 nm, retention times (min.): 22.2 (minor) and 25.7 (major).

[5] Millet, R.; Gremaud, L.; Bernardez, T.; Palais, L.; Alexakis, A. *Synthesis* **2009**, 2101-2112.



(+)-2-isobutyl-5,8-dimethyl-1,2-dihydronaphthalen-1-ol (3bd): Isolated as a pale yellow oil. [96% yield, >99:1 anti:syn, 93% ee].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (q, *J* = 7.7 Hz, 2H), 6.71 (d, *J* = 9.9 Hz, 1H), 6.09 (dd, *J* = 9.8, 6.0 Hz, 1H), 4.72 (s, 1H), 2.74 (dd, *J* = 14.6, 6.9 Hz, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 1.86 – 1.60 (m, 2H), 1.15 – 1.00 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H).

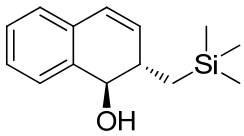
^{13}C NMR: (100 MHz, $CDCl_3$) δ 134.3, 132.6, 131.5, 130.4, 130.0, 129.9, 129.4, 122.6, 68.3, 40.8, 39.8, 25.8, 23.2, 22.3, 18.9, 18.2.

$[\alpha]_D^{20}$ = +345.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+, *m/z*): calcd for $C_{16}H_{23}O$ $[M+H]^+$: 231.17434; found: 231.17421.

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99.5:0.5, 40 °C, 254 nm, retention times (min): 40.2 (major) and 43.1 (minor).

In accordance with the results obtained in the other ring opening reactions, the absolute configuration of this compound is assumed to be (1*R*, 2*S*), analogous to the other products.



(+)-2-((trimethylsilyl)methyl)-1,2-dihydronaphthalen-1-ol (3ae): Isolated as a white solid. [65% yield, >99:1 anti:syn, 43% ee].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.26 (dt, *J* = 16.5, 7.3 Hz, 2H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 9.6 Hz, 1H), 6.02 (dd, *J* = 9.6, 5.1 Hz, 1H), 4.43 (s, 1H), 2.68 (td, *J* = 9.8, 5.0 Hz, 1H), 1.79 (s, 1H), 0.69 (dd, *J* = 14.4, 5.1 Hz, 1H), 0.50 (dd, *J* = 14.4, 10.3 Hz, 1H), 0.05 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.3, 132.7, 132.2, 128.6, 128.3, 127.6, 126.5, 125.0, 75.1, 38.9, 19.2, -0.6.

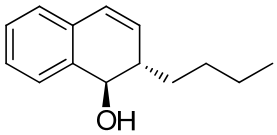
$[\alpha]_D^{20}$ = +84.7 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+, *m/z*): calcd for $C_{14}H_{21}OSi$ $[M+H]^+$: 233.13562; found: 233.13466.

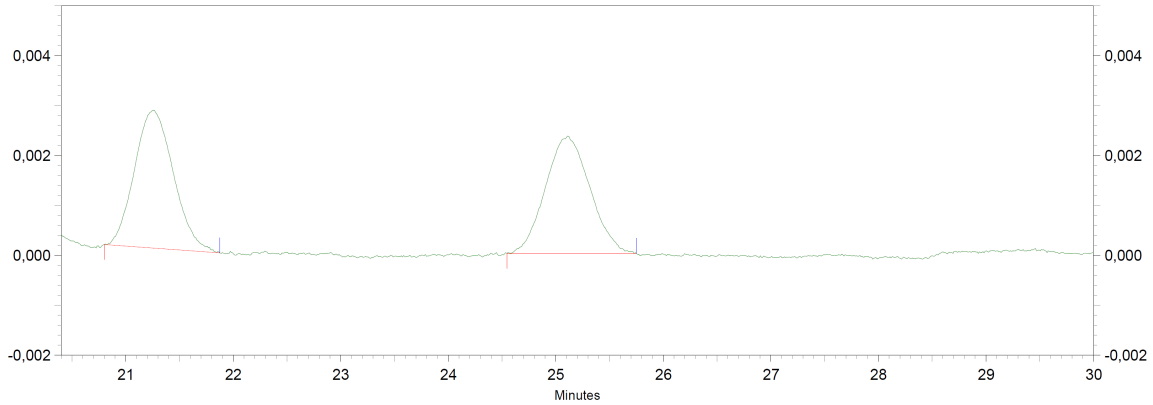
Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 98:2, 40 °C, 261 nm, retention times (min): 18.0 (minor) and 18.9 (major).

In accordance with the results obtained in the other ring opening reactions, the absolute configuration of this compound is assumed to be (1*R*, 2*S*), analogous to the other products.

HPLC traces of ringopened products

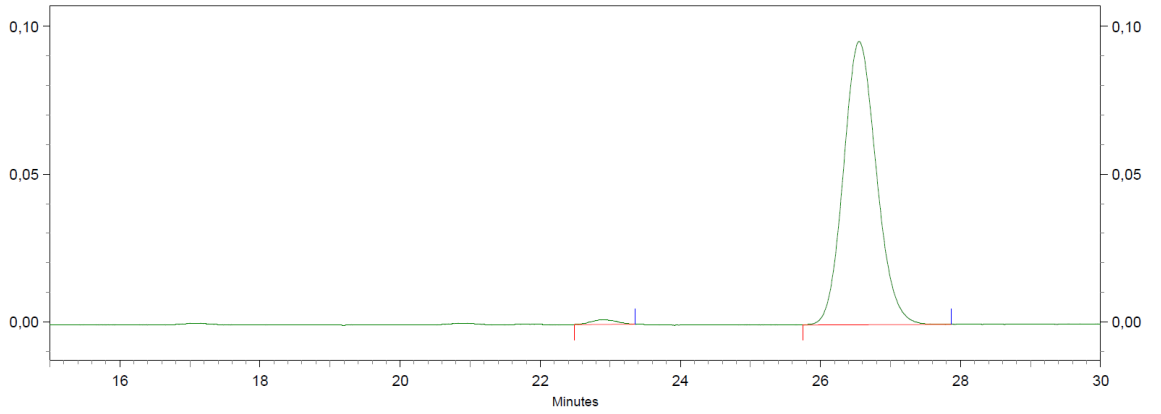


3aa



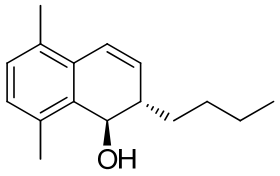
1: 265 nm, 8 nm Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 21,269 Minutes	21,269	69404	50,68
2	Peak @ 25,109 Minutes	25,109	67550	49,32
Totals			136954	100,00

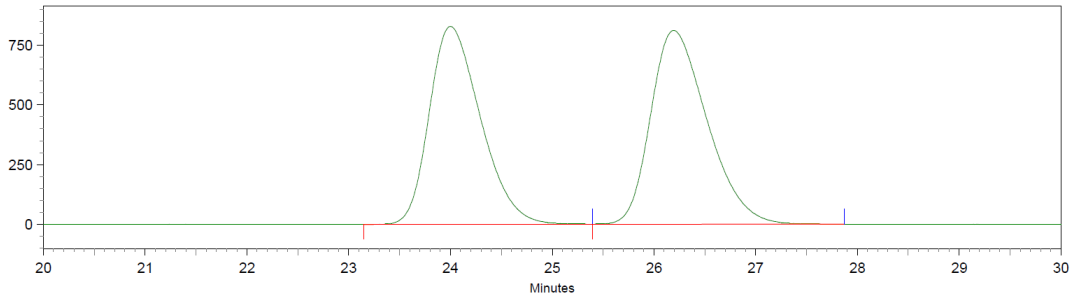


1: 265 nm, 8 nm Results

Pk #	Name	Retention Time	Area	Area Percent
1		22,891	40923	1,29
2		26,549	3130817	98,71
Totals			3171740	100,00

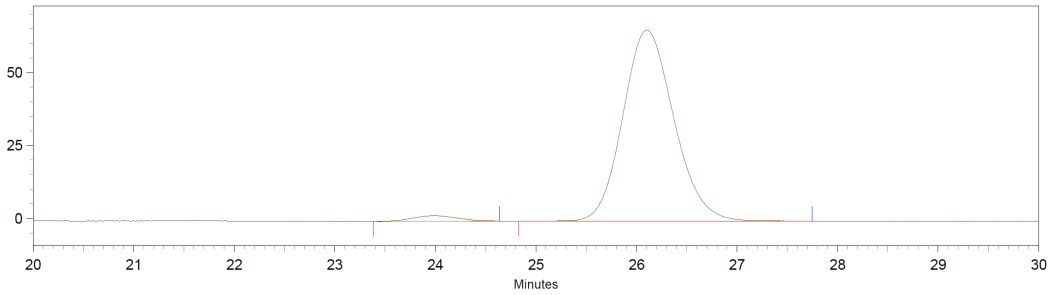


3ba



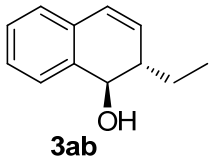
1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	24.000	29009088	48.13
2	2	26.197	31258306	51.87
Totals			60267394	100.00

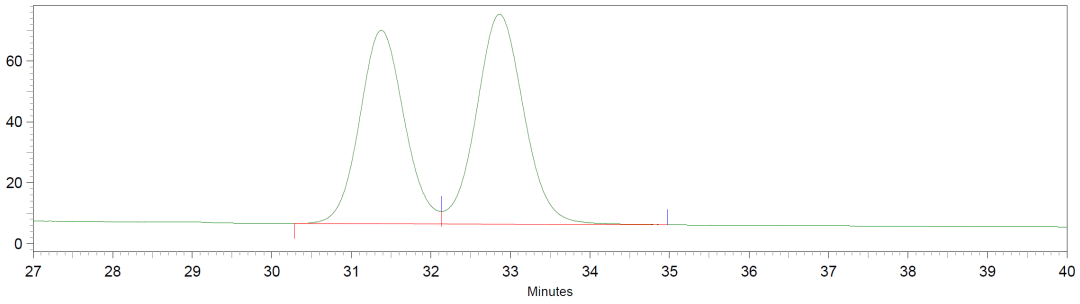


1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	23.968	58740	2.48
2	2	26.101	2311439	97.52
Totals			2370179	100.00

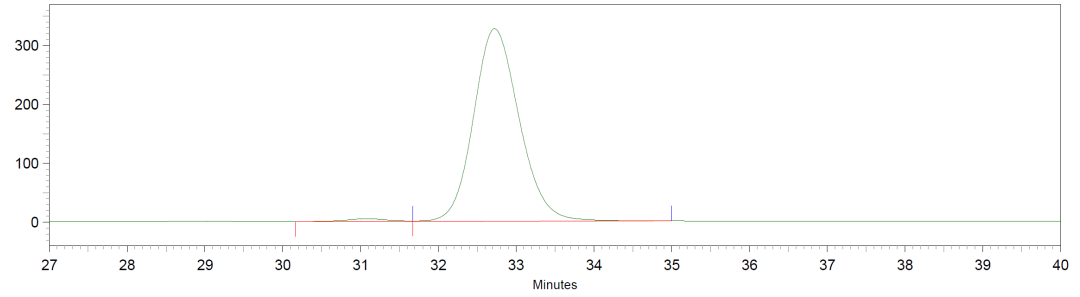


3ab



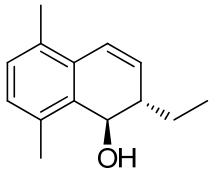
1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	31.381	2476813	46.45
2	2	32.864	2855639	53.55
Totals			5332452	100.00

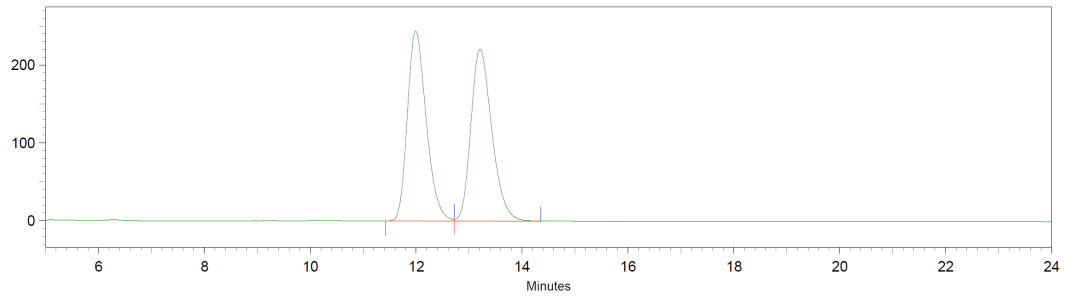


1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	31.072	164506	1.22
2	2	32.725	13329741	98.78
Totals			13494247	100.00

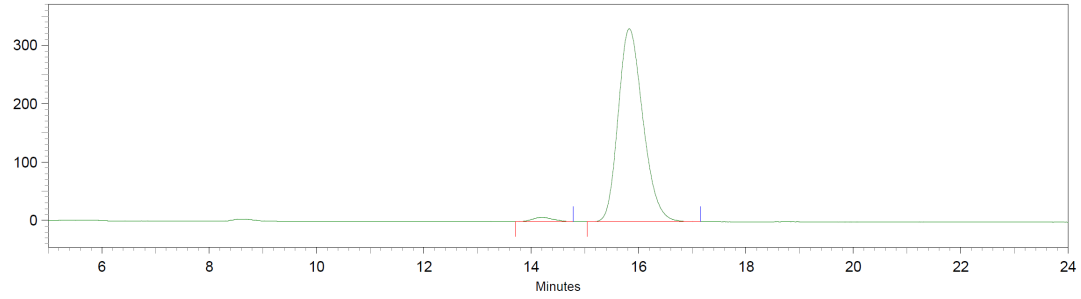


3bb



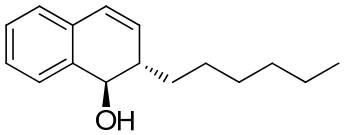
1: 230 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	11.989	6053272	49.89
2	2	13.205	6081121	50.11
Totals			12134393	100.00

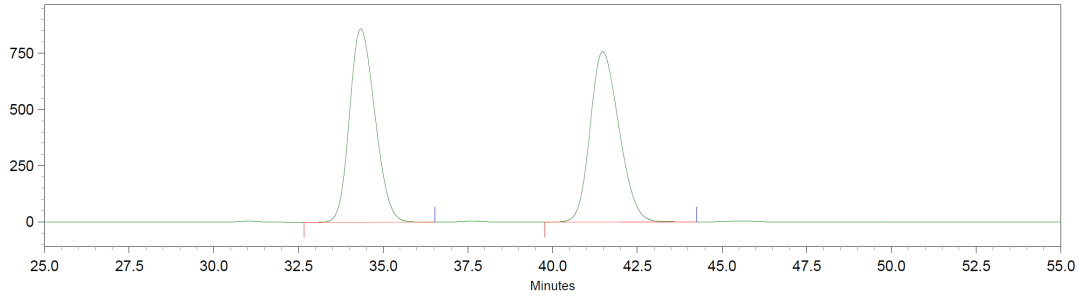


1: 230 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	14.208	192293	1.79
2	2	15.829	10565515	98.21
Totals			10757808	100.00



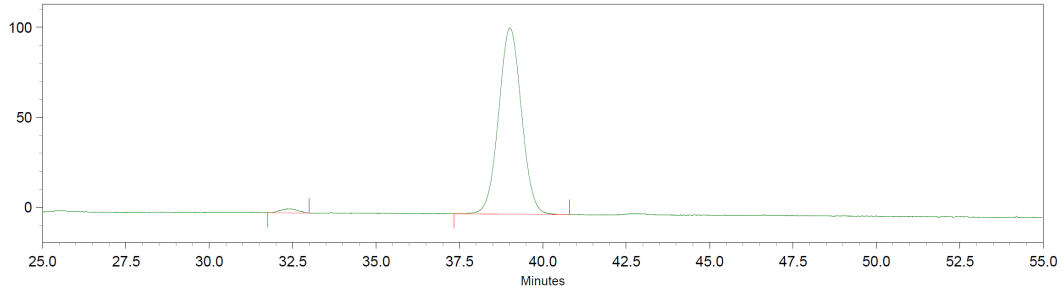
3ac



1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	34.336	44932466	49.91
2	2	41.483	45092999	50.09

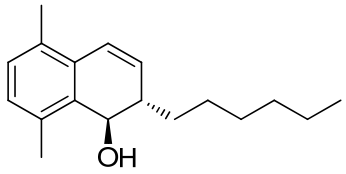
Totals			90025465	100.00



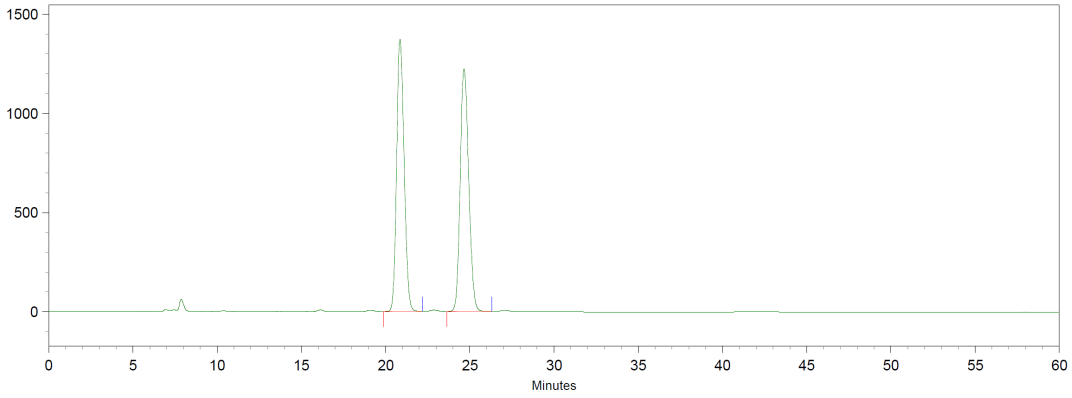
1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	32.331	79719	1.59
2	2	39.019	4923771	98.41

Totals			5003490	100.00

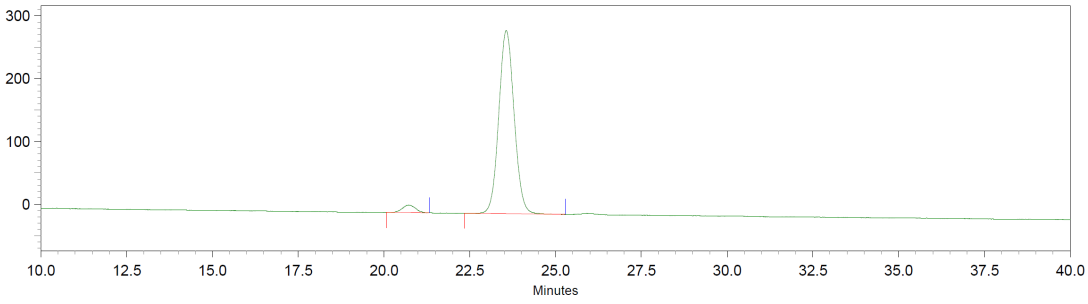


3bc



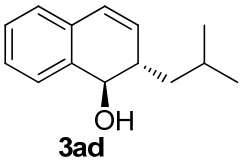
1: 265 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	20.853	42860165	49.79
2	2	24.661	43217369	50.21
Totals			86077534	100.00

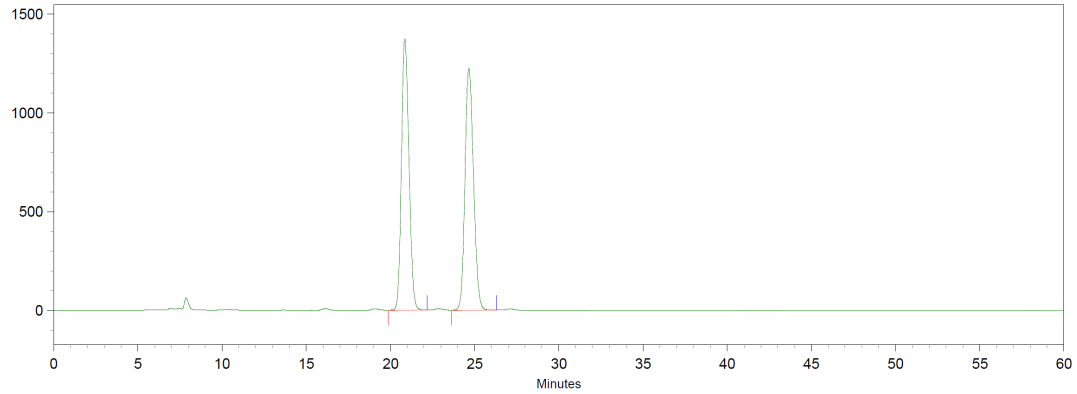


1: 254 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	20.725	332559	3.53
2	2	23.563	9075925	96.47
Totals			9408484	100.00

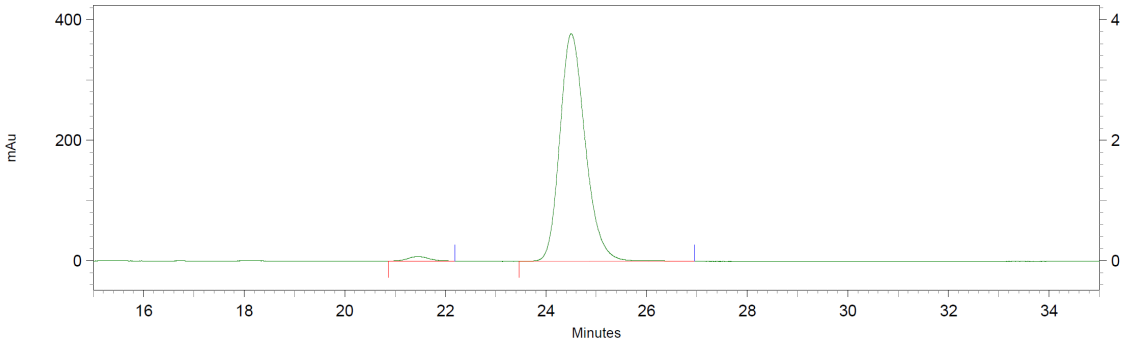


3ad



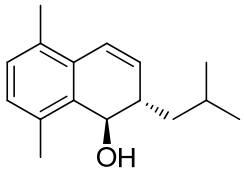
1: 265 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	20.853	42860165	49.79
2	2	24.661	43217369	50.21
Totals			86077534	100.00

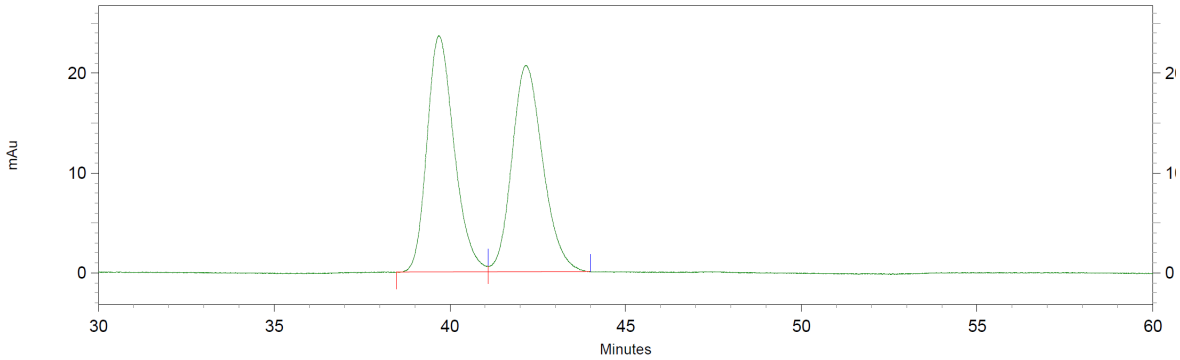


1: 254 nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 21,452 Minutes	21,452	231529	1,712
2	Peak @ 24,504 Minutes	24,504	13291143	98,288
Totals			13522672	100,000

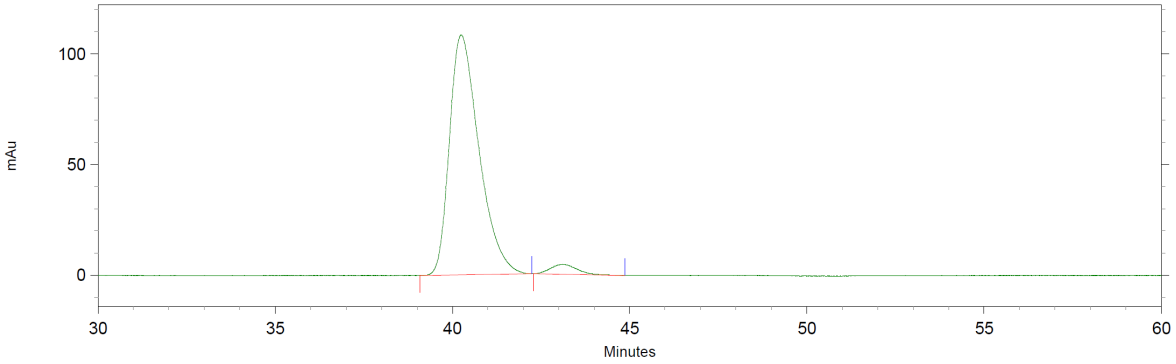


3bd



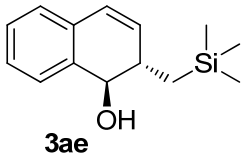
1: 254
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 39,692 Minutes	39,692	1272363	50,124
2	Peak @ 42,156 Minutes	42,156	1266073	49,876
Totals			2538436	100,000

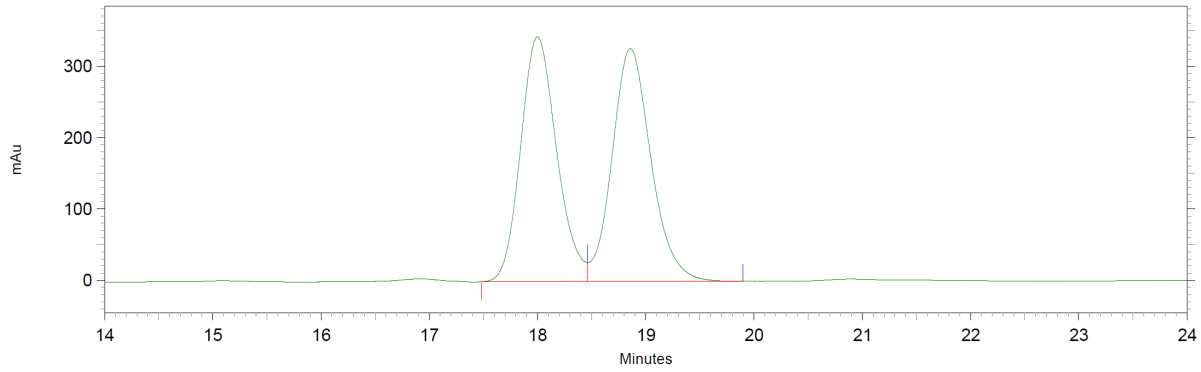


1: 254
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 40,248 Minutes	40,248	6286522	96,378
2	Peak @ 43,108 Minutes	43,108	236262	3,622
Totals			6522784	100,000

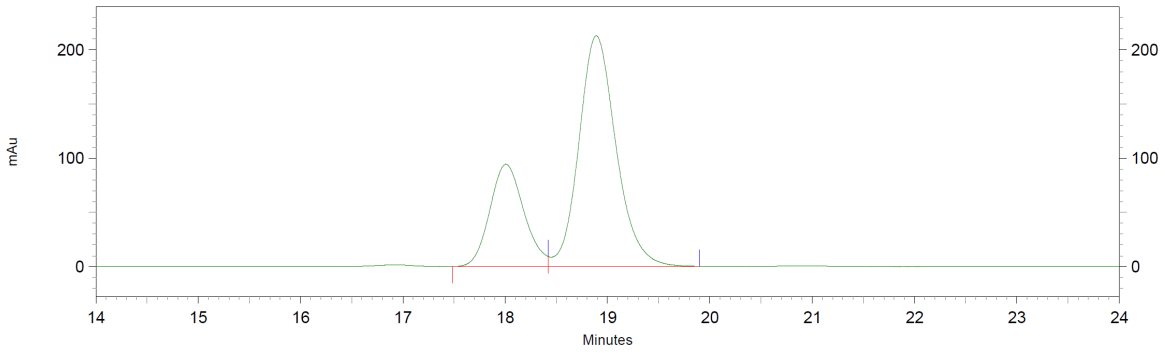


3ae



1: 215 nm,
2 nm Results

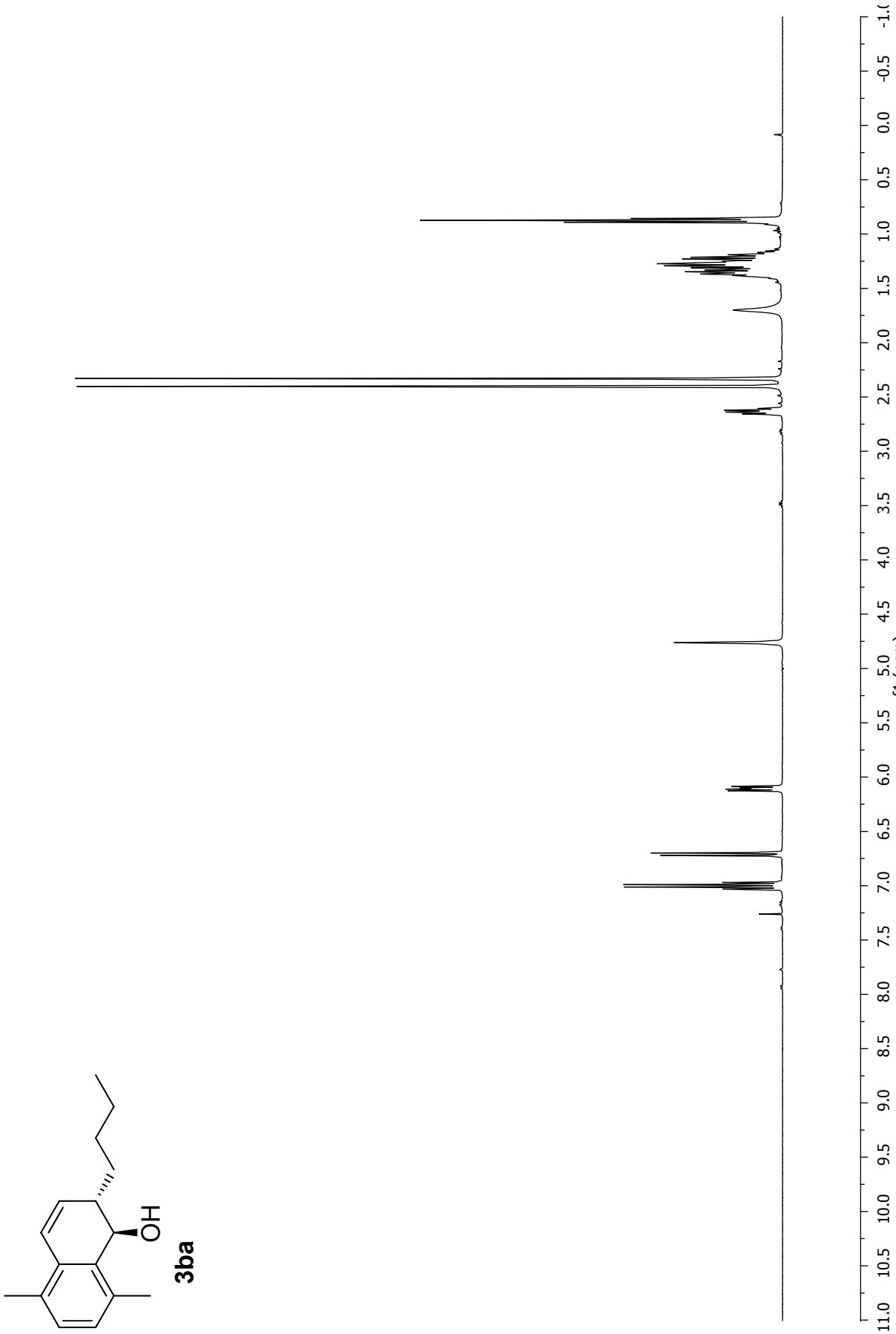
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 18,008 Minutes	18,000	7932686	49,281
2	Peak @ 18,888 Minutes	18,856	8164275	50,719
Totals			16096961	100,000

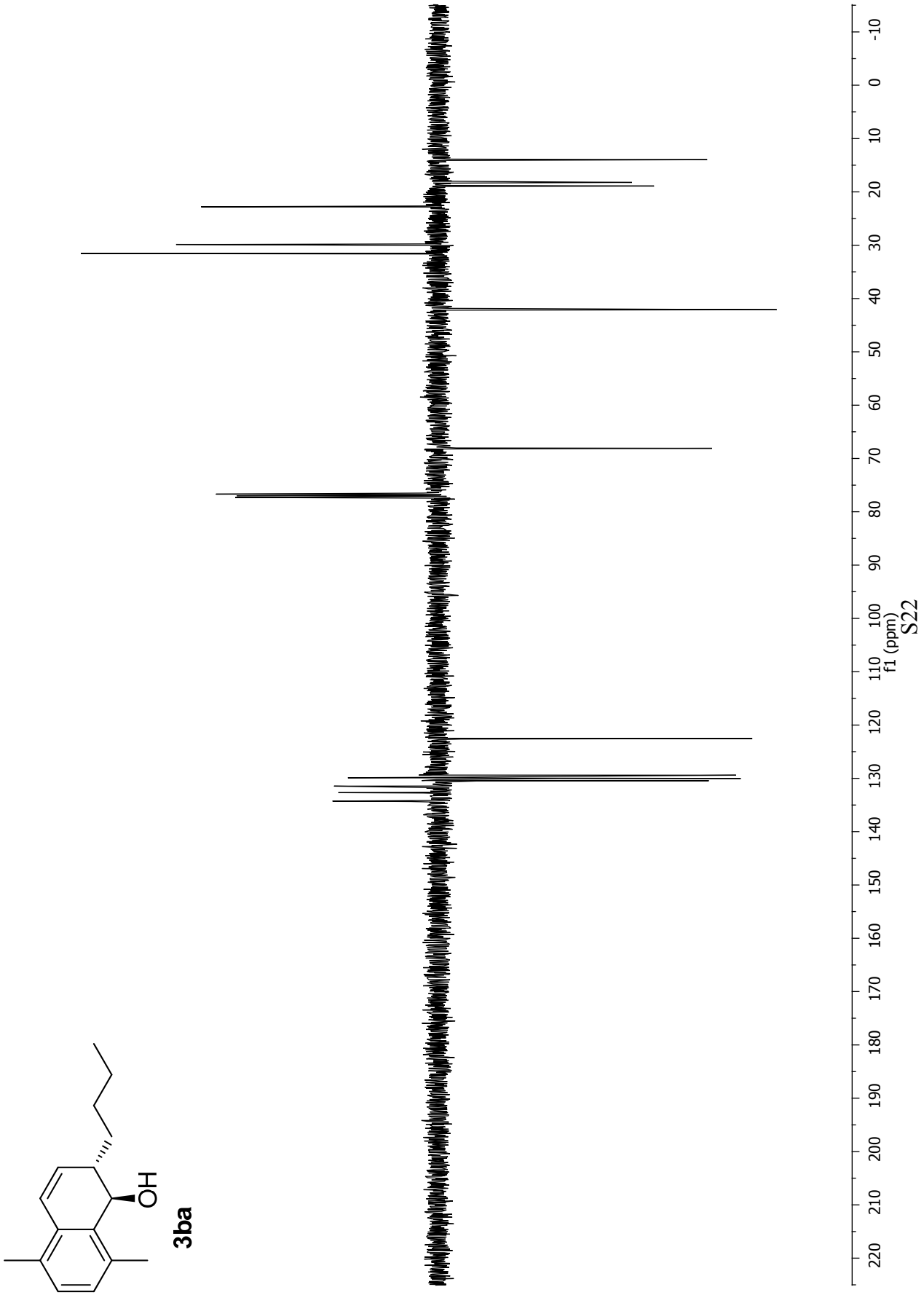


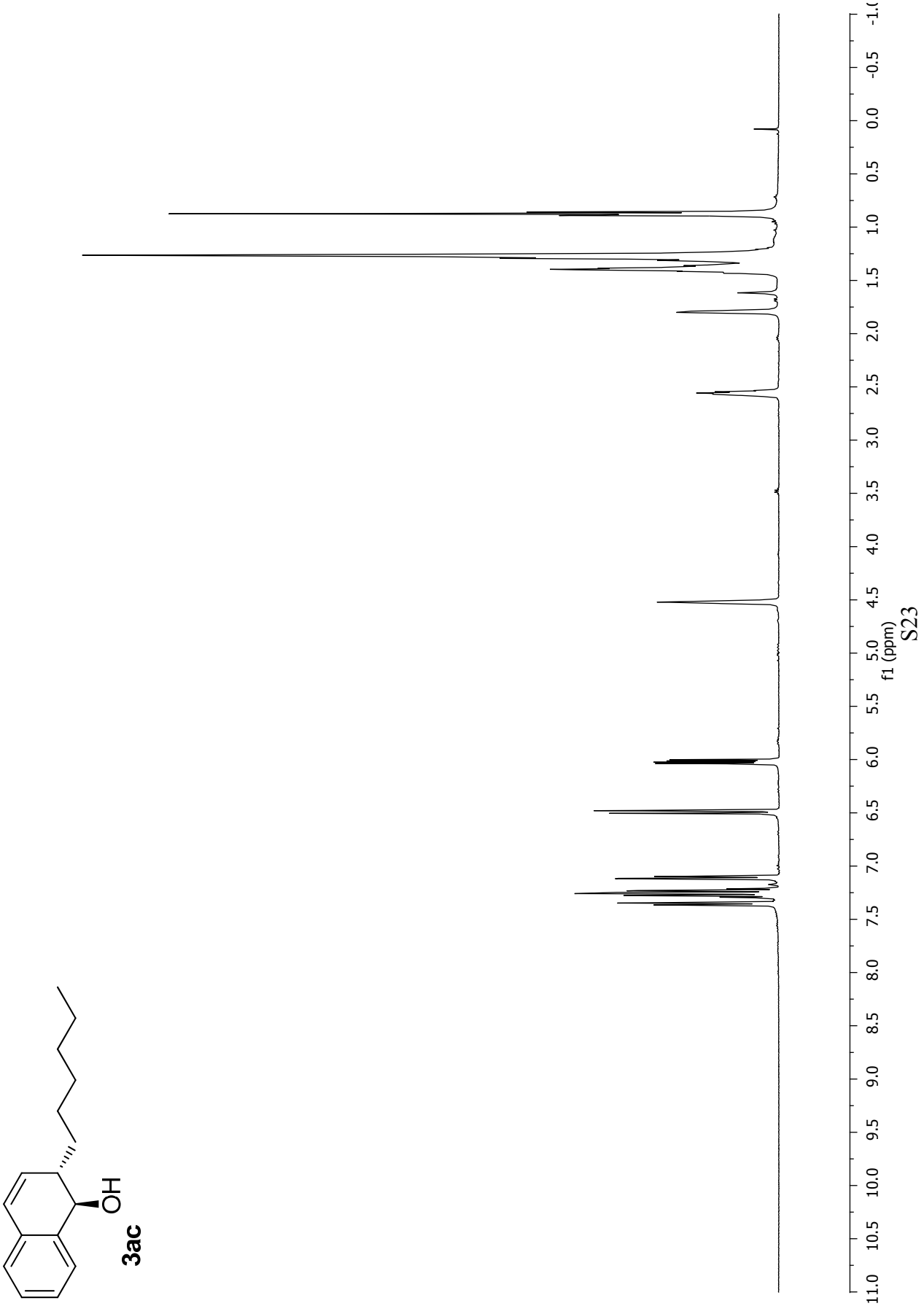
1: 215 nm,
2 nm Results

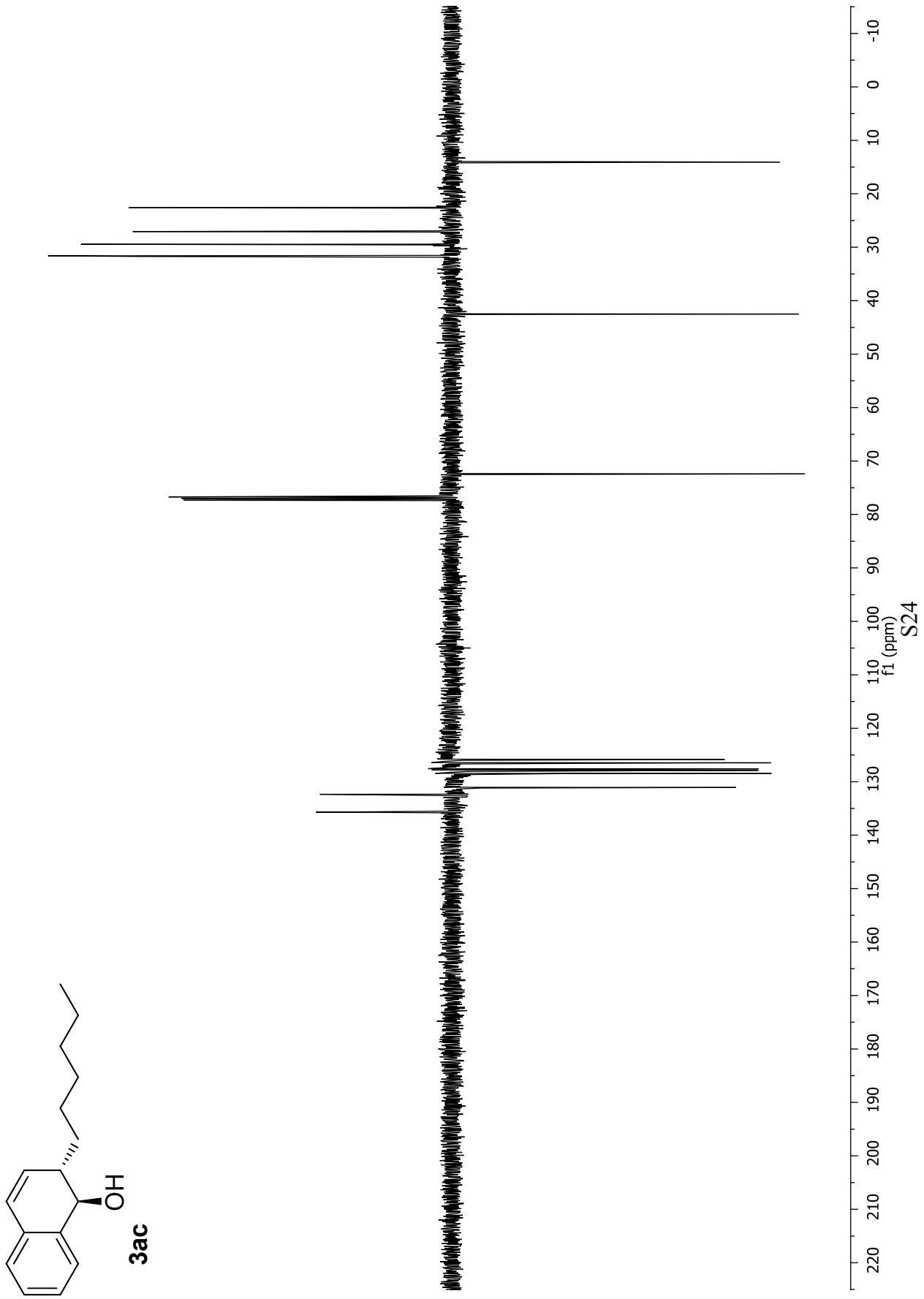
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 18,008 Minutes	18,008	2181610	28,852
2	Peak @ 18,888 Minutes	18,888	5379860	71,148
Totals			7561470	100,000

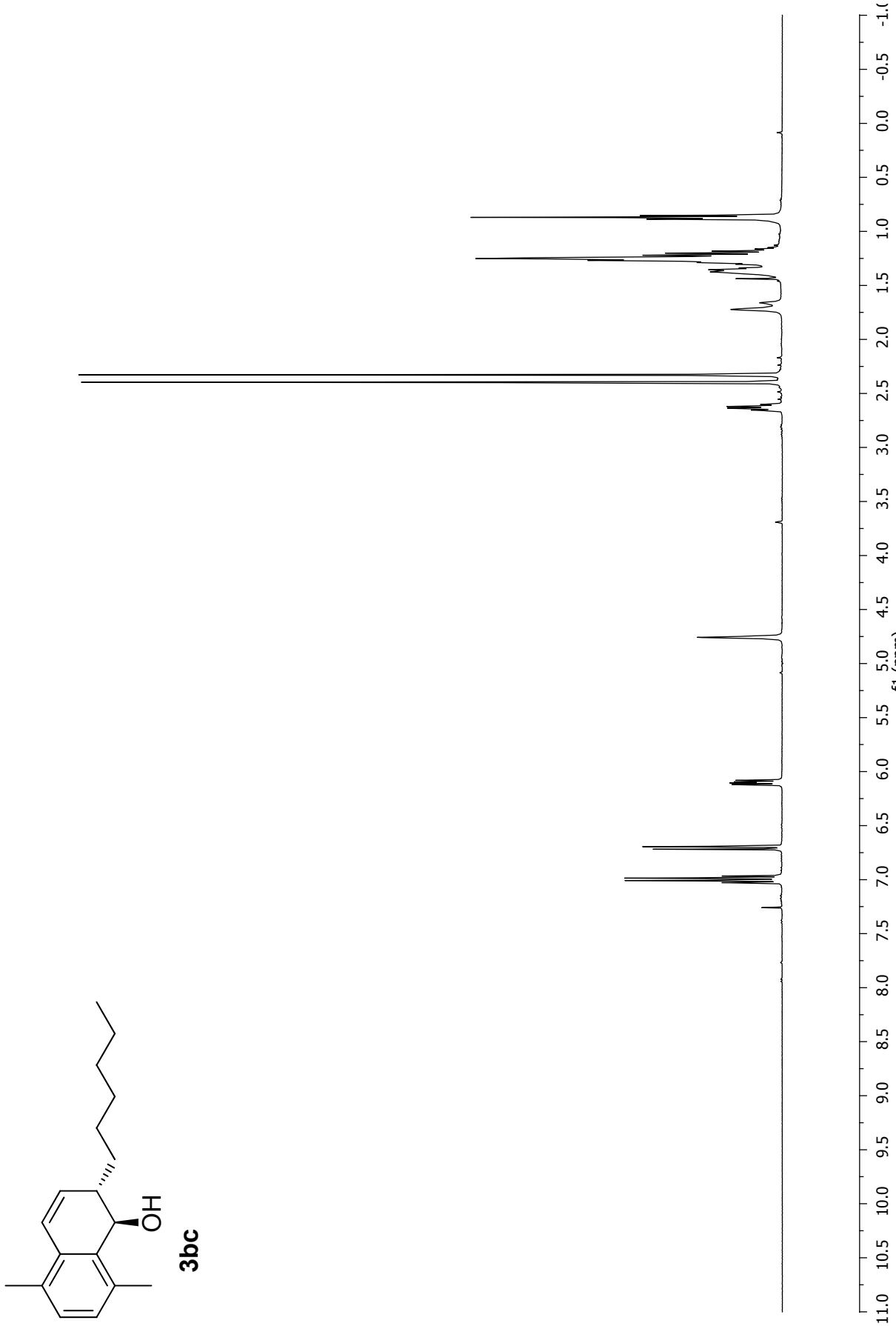
NMR spectra of new compounds

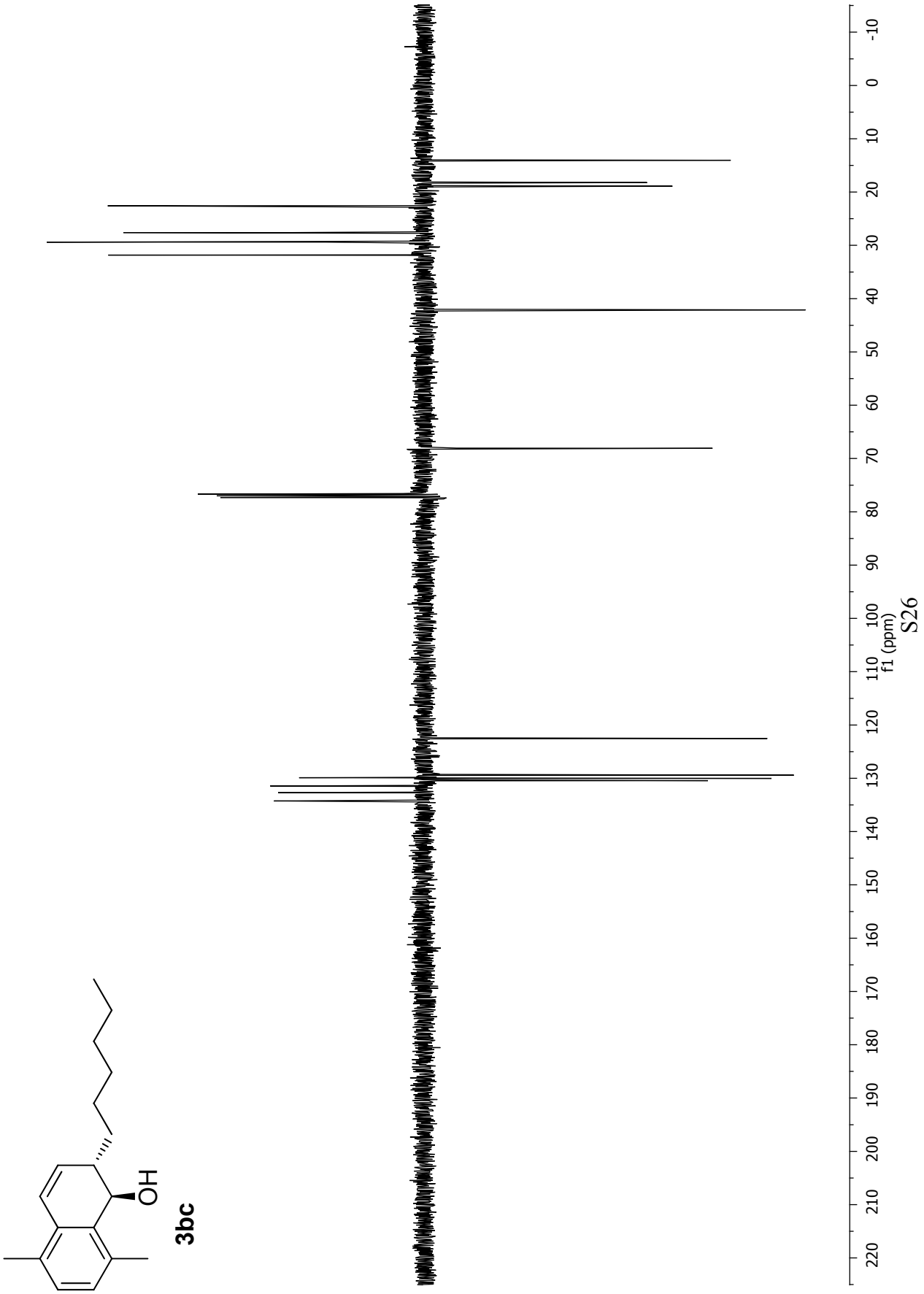


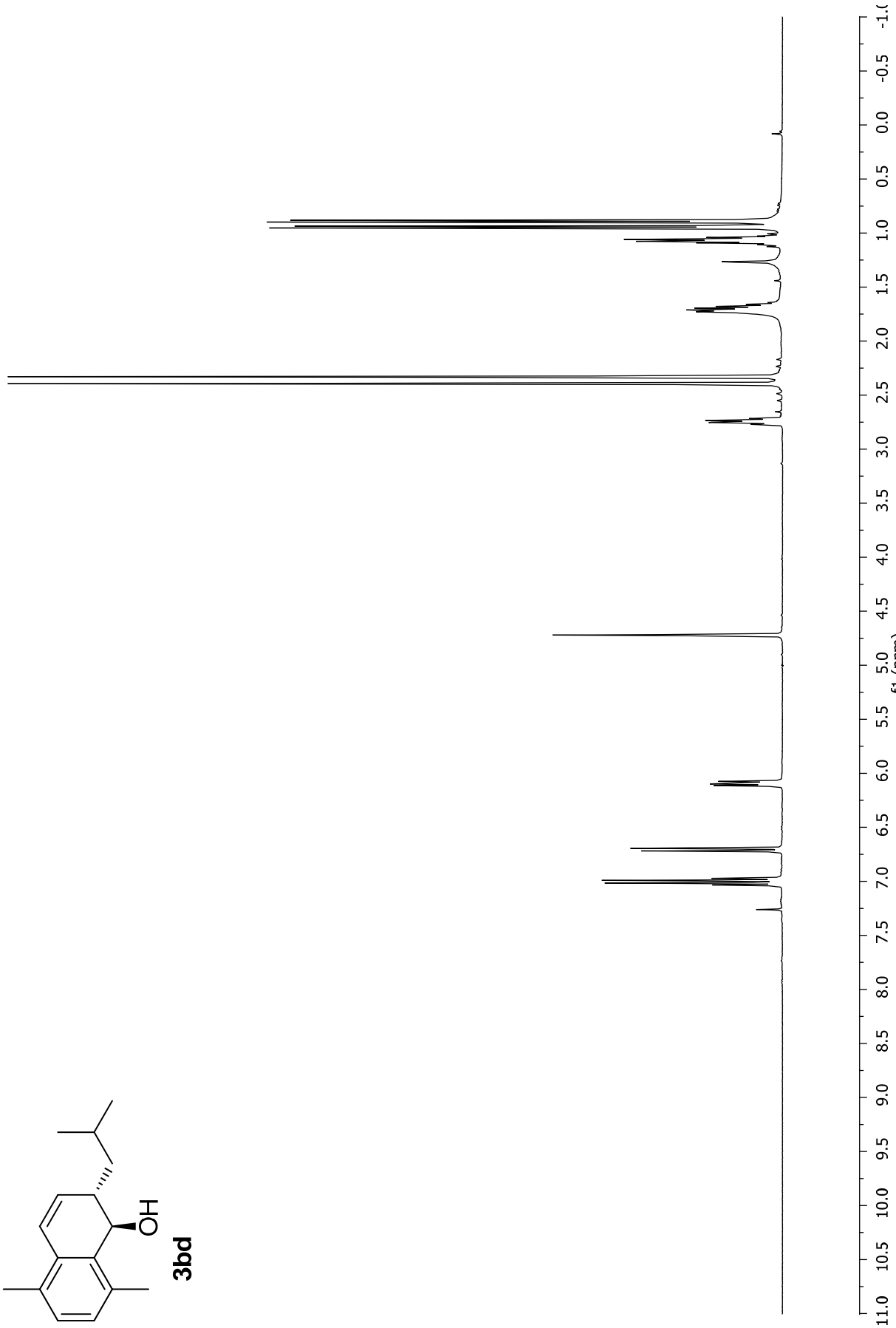


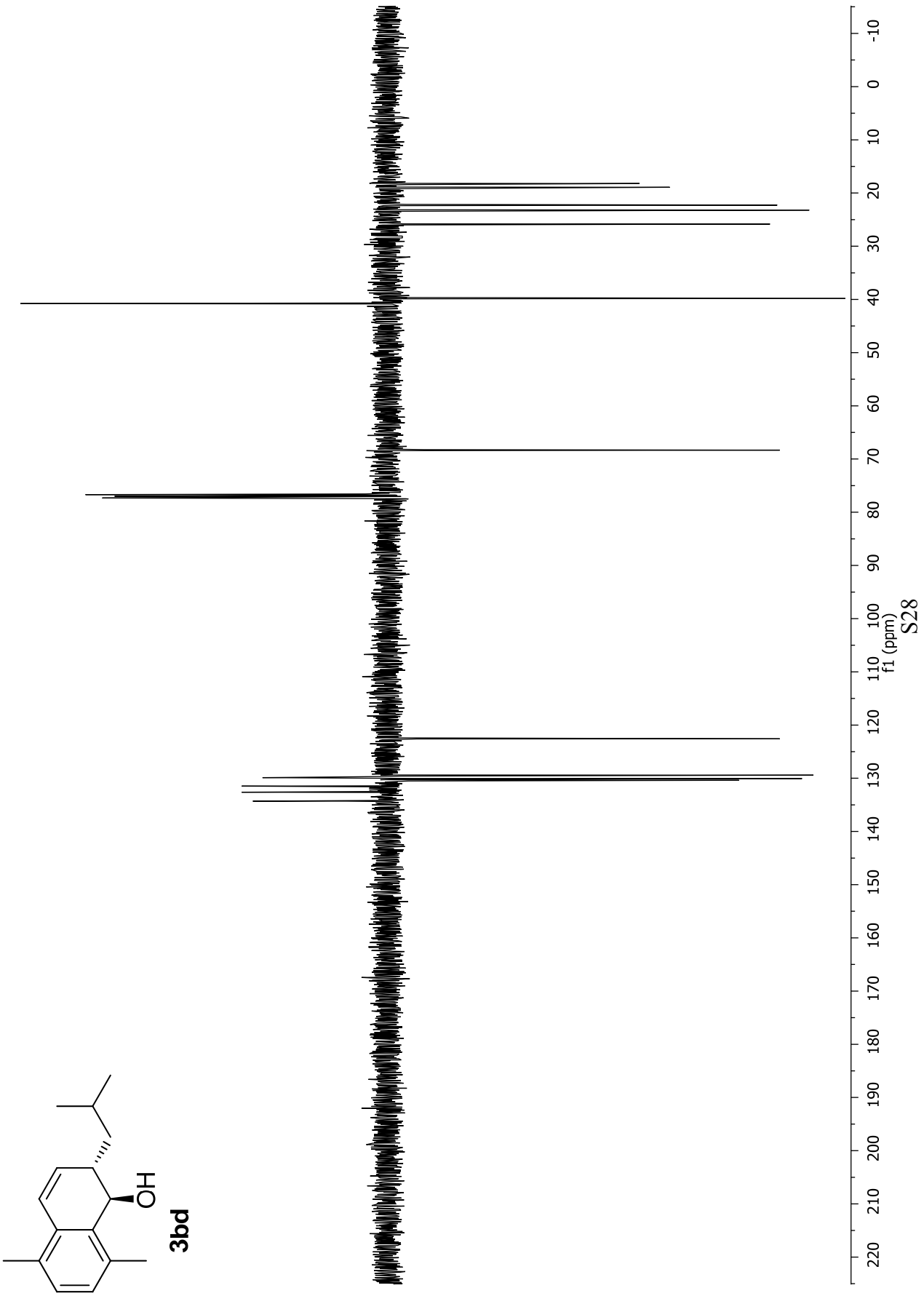


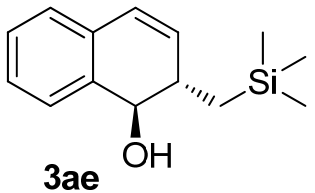












3ae