Supplementary Information

A novel total synthesis of aculeatin A via a stepwise approach

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1. Experimental section

Synthetic general method

All reactions were carried out under N_2 atmosphere with dry solvents unless otherwise noted and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254). Silica gel (200-300 mesh) supplied by Qingdao Marine chemical factory in China was used for flash column chromatography. Anhydrous THF was distilled from sodium-benzophenone. CH_2Cl_2 and DMF were distilled from CaH_2. Other solvents or reagents weren't purified. Yield refers to chromatographically and spectroscopically (^1H, ^{13}C NMR), unless otherwise stated. NMR spectra were recorded on either a 400 MHz spectrometers (^1H: 400 MHz, ^{13}C: 100 MHz) or 500MHz (^1H: 500 MHz, ^{13}C: 125 MHz). High-resolution mass spectra were obtained from a MALDI-TOF Mass Spectrometer. IR spectra were recorded on a shimadzu FT-IR spectrophotometer. Optical rotations were measured on a digital polarimeter in $CHCl_3$ at 25 ^oC.

(*R*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhexadecan-1-one (7)

To a stirred solution of compound **5** (4.00 g, 15.91 mmol, 1.0 equiv.) in dry CH_2Cl_2 (150 mL) was added dropwise $TiCl_4$ (16.70 mL, 16.70 mmol, 1 M in CH_2Cl_2, 1.05 equiv.) at 0°C under N_2. After 15 min, DIPEA (2.26 g, 17.50 mmol, 1.1 equiv.) was added to the solution slowly. After another 40 min, the solution was treated with NMP (3.10 mL, 31.82 mmol, 2.0 equiv.) at the same temperature. 10 minutes later, aldehyde **6** (3.70 g, 17.50 mmol, 1.1 equiv.) in dry CH_2Cl_2 (10 mL) was added to the solution via a cannula. The solution was stirred for 2 h at 0°C and then quenched with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted by CH_2Cl_2 (100 mL × 3). The combined organic solution was washed with sat. NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through flash chromatography (Hexane/EtOAc = 20:1) to yield the product **7** (4.46g) and its diastereoisomer (0.18g) as colorless oils (65%, dr = 93:7). **7**: $[\alpha]_D^{25}$ = 204.4 (c 2.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 3H), 5.43-5.38 (m, 1H), 4.19-4.11 (m, 1H), 3.64 (d, *J* = 17.5 Hz, 1H), 3.41 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.23 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.14 (dd, *J* = 17.5, 9.5 Hz, 1H), 3.05 (t, *J* = 11.8 Hz, 1H), 2.89 (d, *J* = 11.5 Hz, 1H), 2.64 (br, 1H, OH), 1.59-1.56 (m, 1H), 1.50-1.48 (m, 1H), 1.29-1.21 (m, 22H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 173.2, 136.3, 129.3, 128.8, 127.2, 68.2, 67.8, 45.8, 36.7, 36.3, 32.0, 31.8, 29.6-29.5 (br, 7C), 29.3, 25.5, 22.6, 14.1; IR (film): 3427, 2924, 2853, 1695, 1455, 1363, 1343, 1292, 1262, 1192, 1164, 1138, 1044, 746, 701 cm^{-1};

HRMS (ESI): m/z calcd. for $C_{26}H_{42}NO_2S_2$ $[M+H]^+$ 464.2651, found 464.2650.

Diastereoisomer of **7**: $[\alpha]_D^{25}$ = 98.8 (c 2.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H), 7.30-7.27 (m, 3H), 5.44-5.40 (m, 1H), 4.08-4.06 (m, 1H), 3.46 (d, *J* = 17.5, 9.3 Hz 1H), 3.41 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.35 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.24 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.05 (dd, *J* = 13.0, 10.5 Hz, 1H), 2.91 (d, *J* = 11.5 Hz, 1H), 2.73 (br, 1H, OH), 1.60-1.58 (m, 1H), 1.51-1.47 (m, 1H), 1.32-1.27 (m, 22H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 173.8, 136.3, 129.4, 128.9, 127.2, 68.4, 68.2, 45.5, 36.7, 36.6, 32.0, 31.9, 29.6-29.5 (br, 7C), 29.3, 25.4, 22.6, 14.1; IR (film): 3427, 2924, 2853, 1699, 1683, 1496, 1467, 1455, 1343, 1294, 1262, 1164, 1138, 1040, 773,

701 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{26}H_{42}NO_2S_2$ $[M+H]^+$ 464.2651, found 464.2650.

(*R*)-3-hydroxy-N-methoxy-N-methylhexadecanamide (8)

At 0°C, to a solution of compound **7** (0.16 g, 0.35 mmol, 1.0 equiv.) in anhydrous DCM (1.7 mL) was added MeONHMe▪HCl (0.14g, 1.38 mmol, 4.0 equiv.) and imidazole (0.12 g, 1.73 mmol, 5.0 equiv.). Then the resultant mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (5 mL × 3). The combined organic solution was washed with sat. aq. NaCl, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified with flash chromatography (Hexane/EtOAc = 8:1) to provide compound **8** (0.087 g, 80%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.02-3.98 (m, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.64 (d, *J* = 16.4 Hz, 1H), 2.43 (dd, *J* = 16.6, 9.4 Hz, 1H), 1.57-1.53 (m, 1H), 1.43-1.41 (m, 1H), 1.29-1.21 (m, 22H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 67.8, 61.2, 38.1, 36.5, 31.8, 31.8, 29.6-29.5 (br, 7C), 29.3, 25.5, 22.6, 14.0; IR (film): 3439, 2924, 2854, 2361, 1648, 1466, 1276, 1180, 999, 749 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{18}H_{38}NO_3^+$ $[M+H]^+$: 316.2846, found 316.2850.

(*R*)-3-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylhexadecanamide (9)

At 0°C, to a solution of compound **8** (87 mg, 0.28 mmol, 1.0 equiv.) and imidazole (75 mg, 1.10 mmol, 4.0 equiv.) in anhydrous DCM (1.7 mL) was added slowly the solution of TBSCl (95mg, 0.63mmol, 2.3equiv) in DCM. The mixture was then stirred overnight at room temperature. When TLC monitor indicated compound **8** was consumed, the reaction was quenched with sat. NH_4Cl solution and extracted with DCM (5 mL × 3). The combined organic layer was washed with sat. NaCl solution, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified with flash chromatography (Hexane/EtOAc = 25:1) to give the desired product **9** as a colorless oil (98mg, 83%). ^1H NMR (400 MHz, $CDCl_3$): 4.24-4.18 (m, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 2.70 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.37 (dd, *J* = 14.6, 5.2 Hz, 1H), 1.49-1.45 (m, 2H), 1.30-1.21 (m, 22H), 0,87 (t, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6,

69.5, 61.2, 39.6, 37.9, 31.9, 29.7-29.6 (br, 7C), 29.3, 25.8, 25.0, 22.6, 18.0, 14.0, -4.7, -4.7; IR (film): 2927, 2855, 2360, 1676, 1462, 1388, 1256, 1096, 1005, 836, 776, 749 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{24}H_{52}NO_3Si^+$ $[M+H]^+$: 430.3711, found 430.3711.

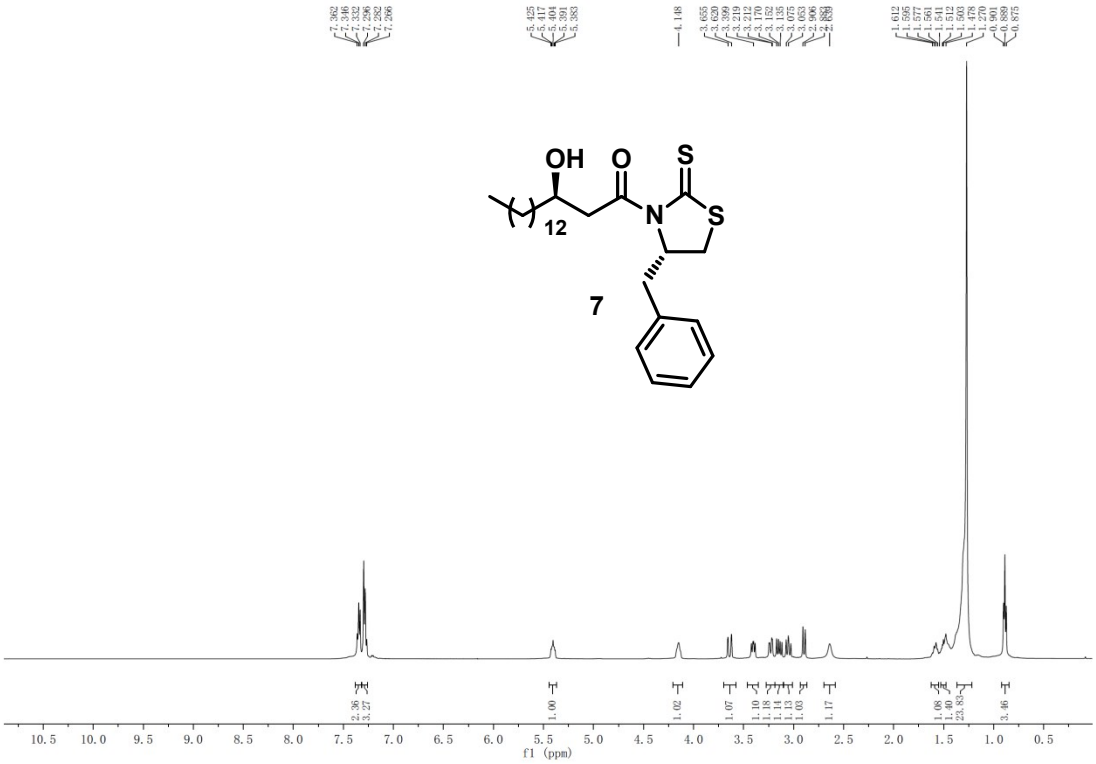
(*R*)-3-hydroxyhexadecanoic acid (11)

The preparation of acid **11** was following that of compound **14**. Yield: 70%.

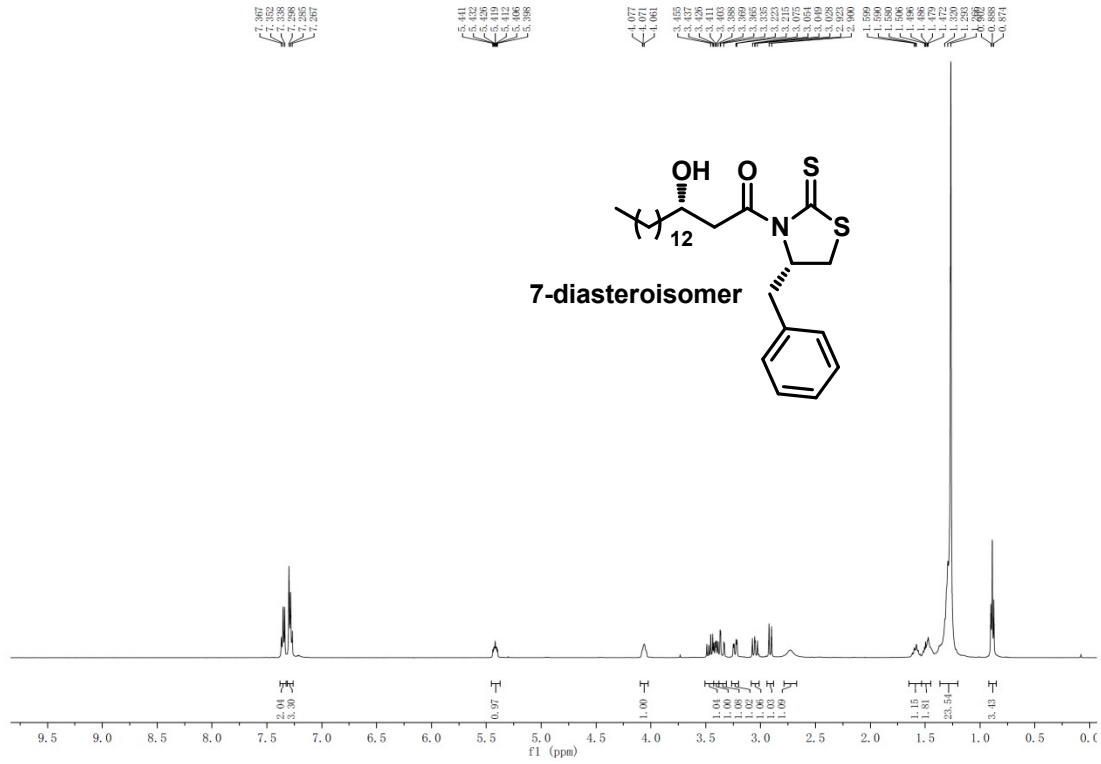
^1H NMR (500 MHz, $CDCl_3$): δ 4.09-4.01 (m, 1H), 2.58 (dd, *J* = 16.6, 2.7 Hz, 1H), 2.48 (dd, *J* = 16.6, 9.0 Hz, 1H), 1.57-1.55 (m, 1H), 1.48-1.45 (m, 2H), 1.29-1.21 (m, 21H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 177.0, 68.1, 41.0, 36.6, 31.9, 29.70-29.50 (br, 7C), 29.3, 25.4, 22.7, 14.1; IR (film): 2913, 2847, 1681, 1470, 1411, 1392, 1223, 1074, 1018, 874, 719, 547 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{16}H_{32}O_3Na^+$ $[M+Na]^+$: 295.2244, found 295.2230.

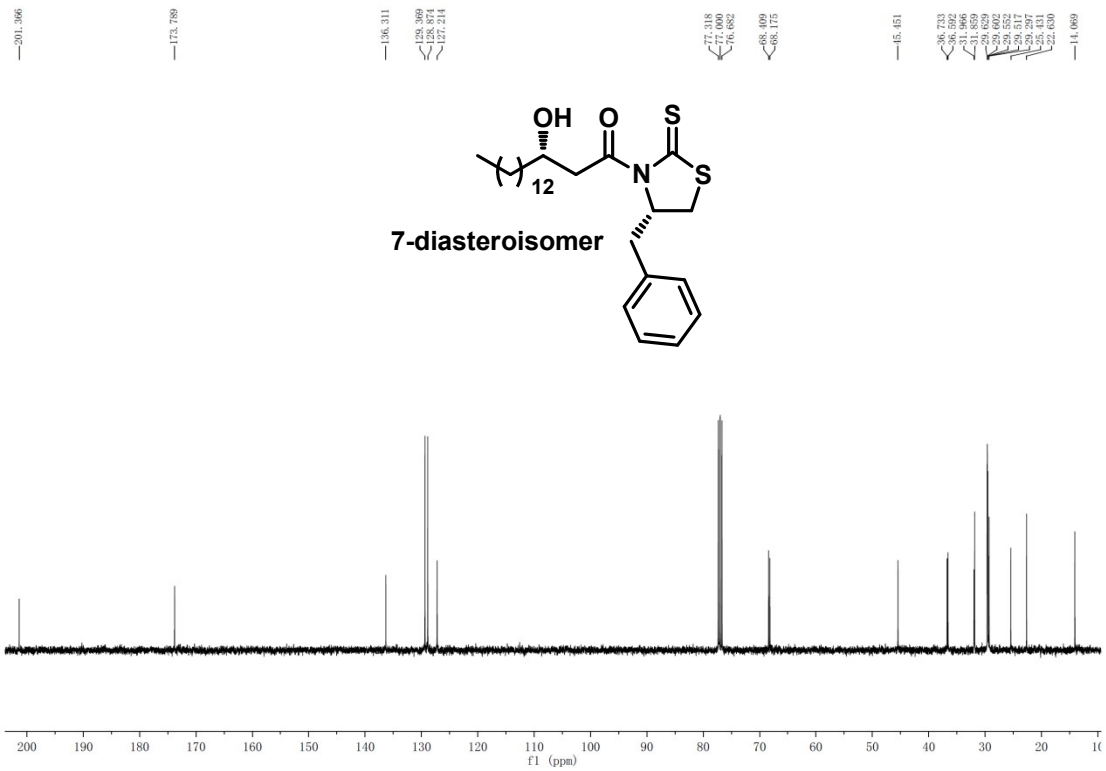
NMR spectra:

Compound **7**:

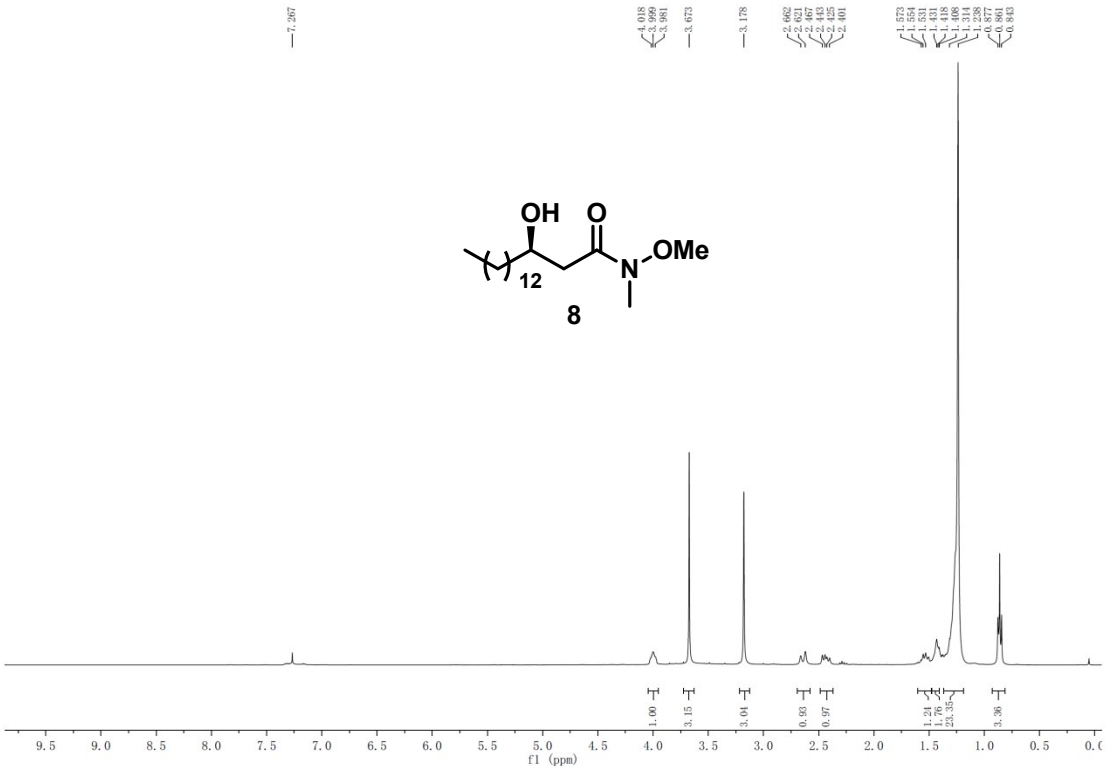


Compound 7-diastereoisomer:




201.366
173.789
136.311
129.369
128.874
127.214
77.318
77.000
76.682
68.409
68.175
45.451
36.733
36.592
31.966
31.659
29.629
29.602
29.552
29.517
29.297
25.431
22.630
14.069
OH
O
S
N
S
12
7-diasteroisomer
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

Compound 8: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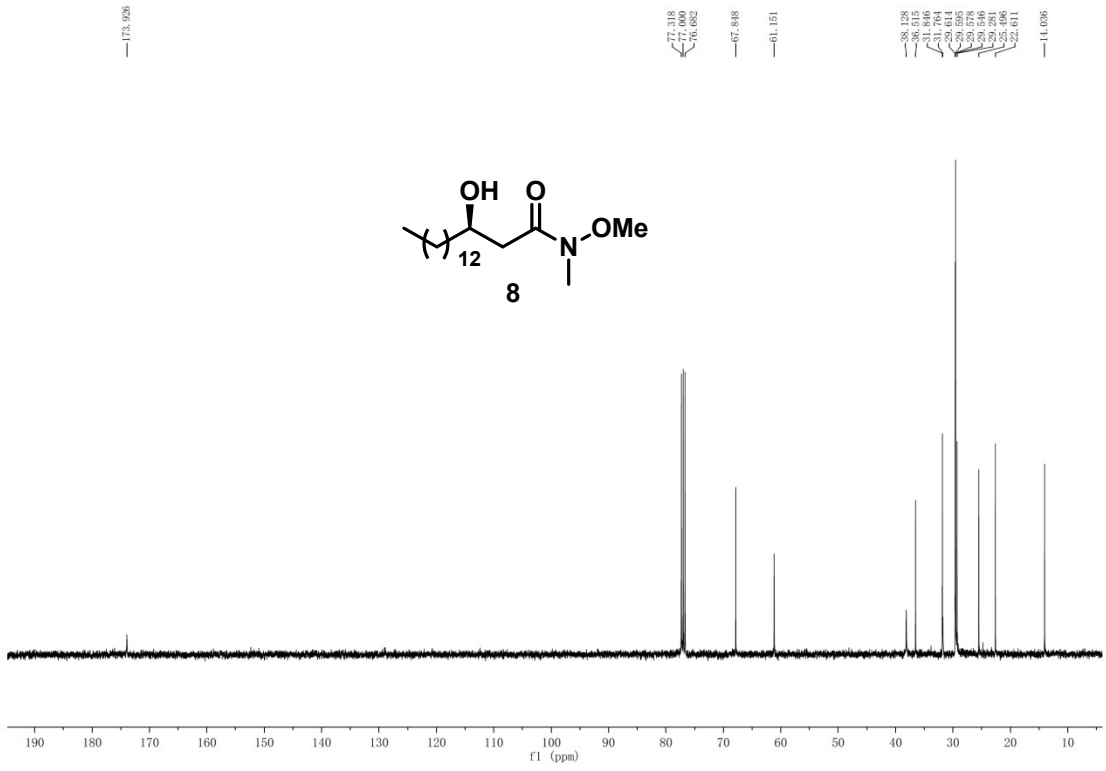
4.018
3.999
3.981
3.673
3.178
2.662
2.621
2.467
2.445
2.125
2.401
1.573
1.554
1.531
1.511
1.418
1.408
1.314
1.298
0.877
0.861
0.843
OH
O
OMe
N
12
8
1.00
3.15
3.04
0.93
0.97
1.24
1.76
23.35
3.36
f1 (ppm)


173.926
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67.848
61.151
38.128
36.515
31.846
31.764
30.614
29.595
29.578
29.546
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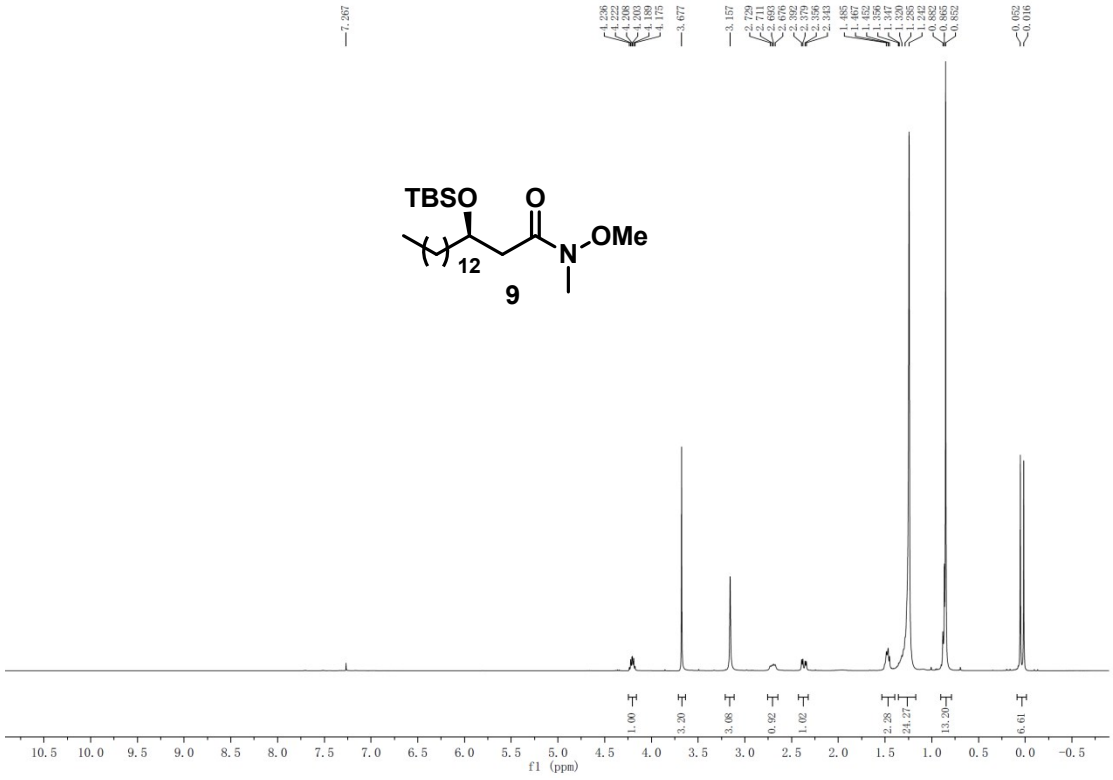
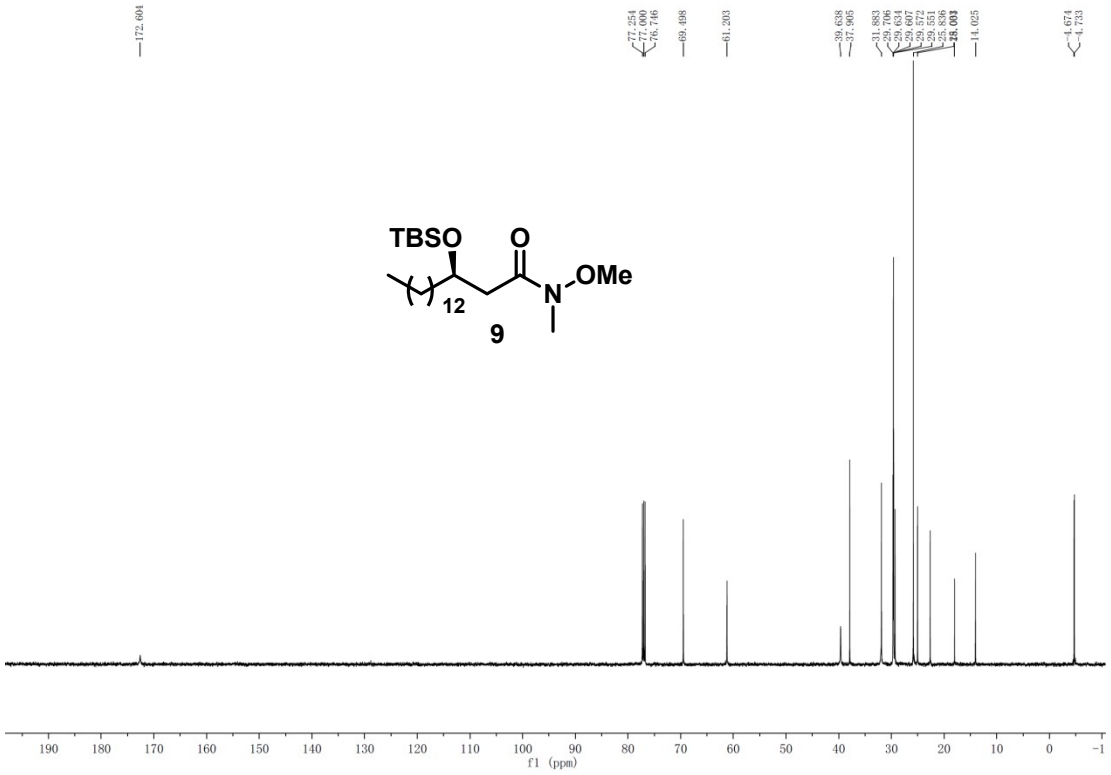
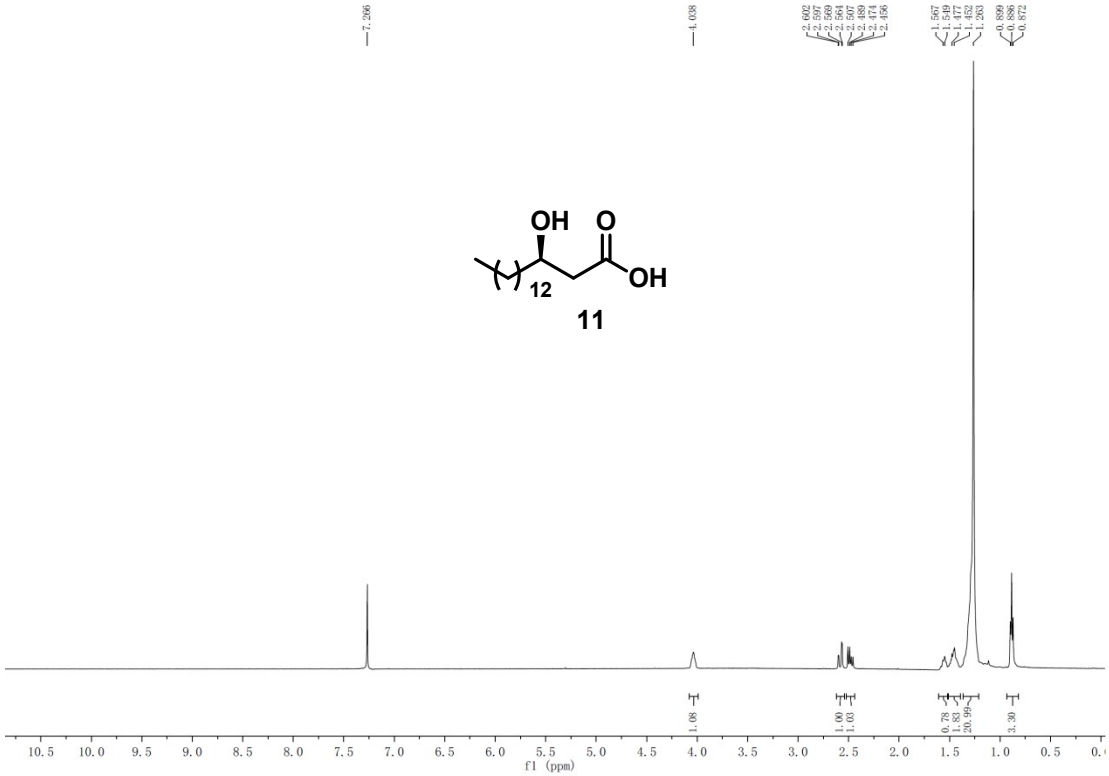
25.698
22.611
14.036
OH
O
OMe
N
12
8
f1 (ppm)

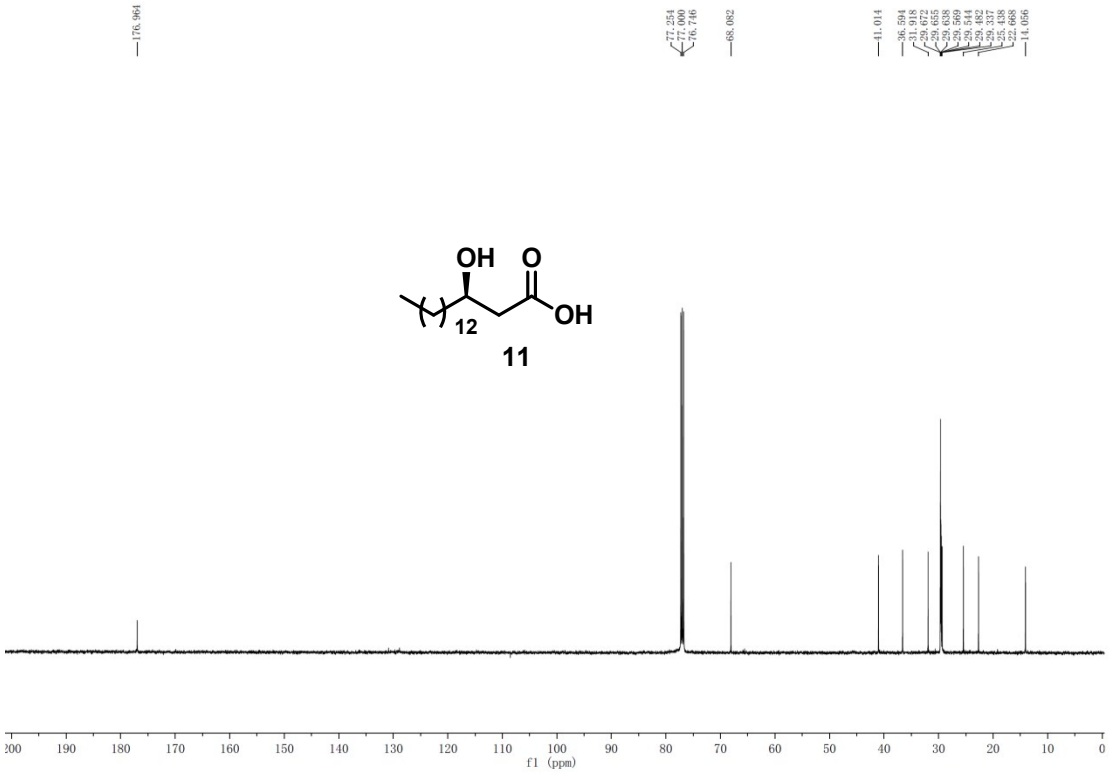
Compound 9:




172.604
77.254
77.000
76.746
69.498
61.203
39.638
37.905
31.883
29.706
29.634
29.497
29.372
29.551
25.836
18.003
14.025
-4.674
-4.733
TBSO
O
OMe
N
12
9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

Compound 11:


7.266
4.038
2.602
2.597
2.569
2.564
2.505
2.489
2.474
2.436
1.567
1.549
1.477
1.432
1.263
0.899
0.886
0.872
OH
O
OH
12
11
1.08
1.00
1.03
0.78
1.83
20.99
3.30
f1 (ppm)


176.964
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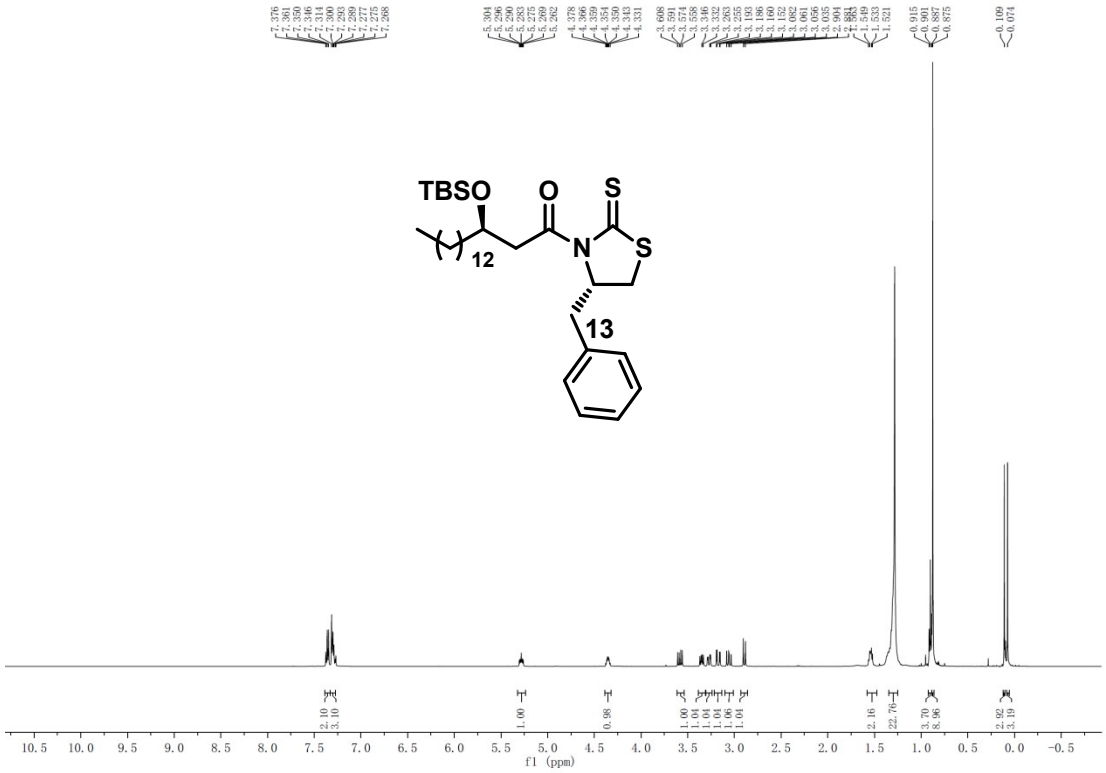
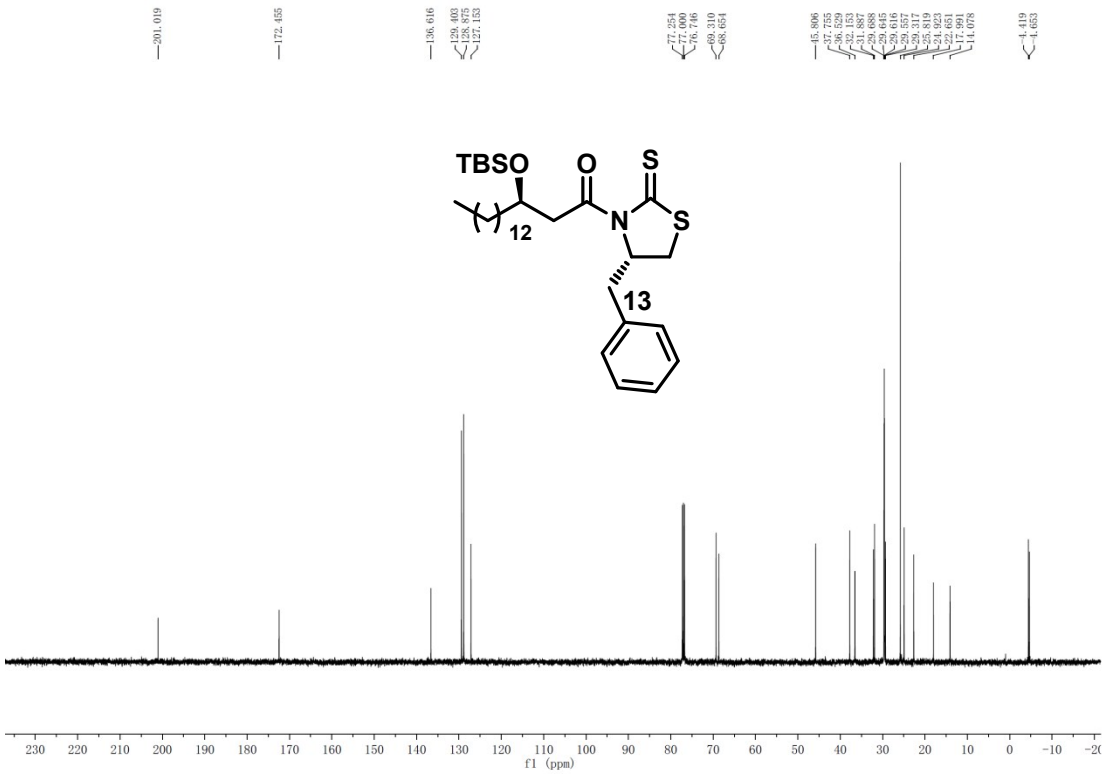
77.000
76.746
68.082
41.014
36.594
31.918
29.672
29.665
29.638
29.569
29.544
29.482
29.337
25.438
22.668
14.056
OH
O
OH
12
11
f1 (ppm)

Compound 13:





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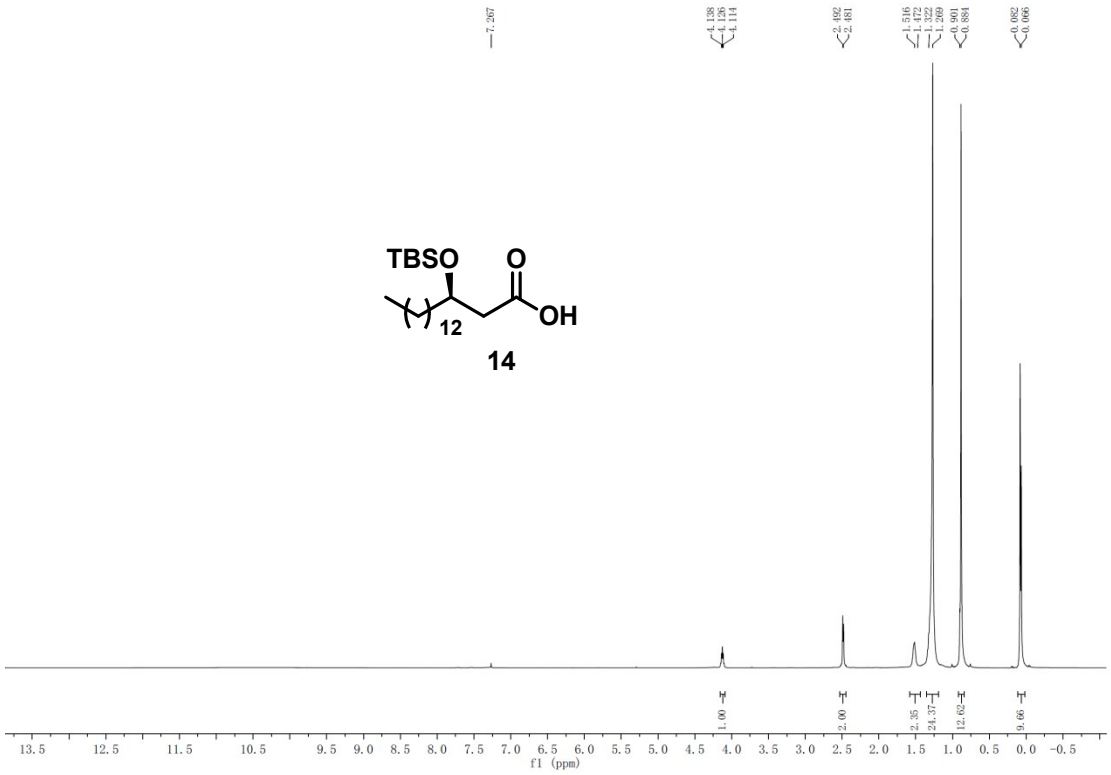
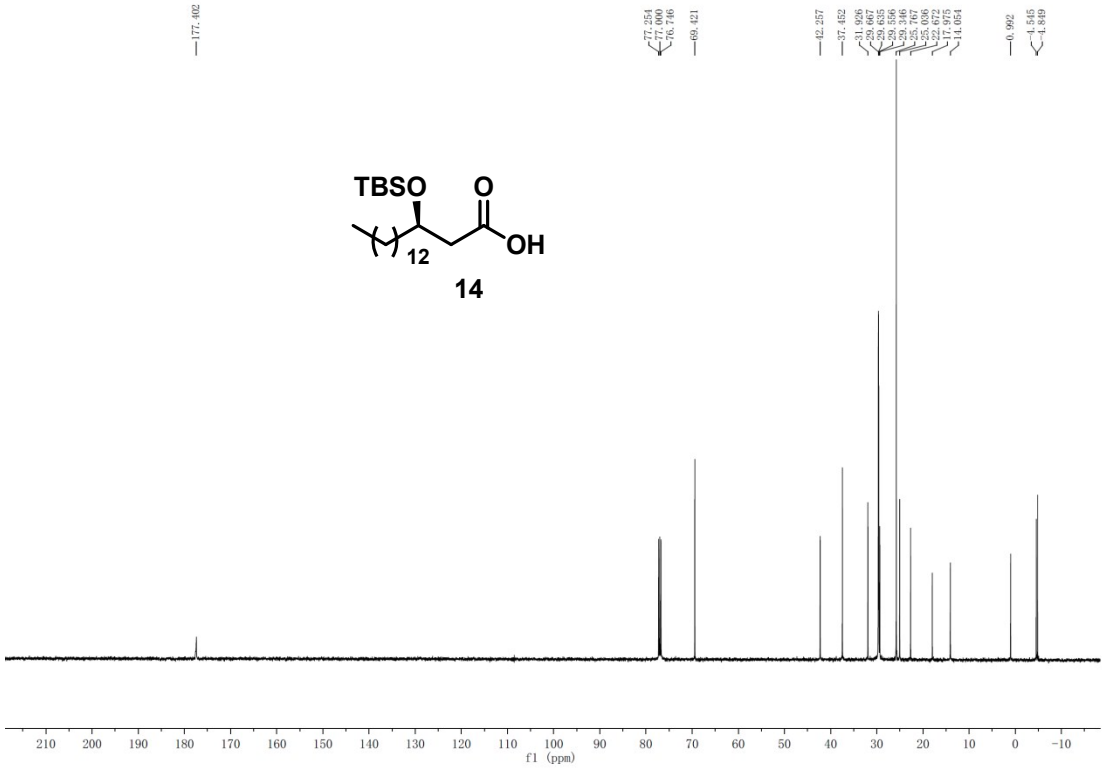

7.267
4.138
4.126
4.114
2.492
2.481
1.516
1.472
1.322
1.269
0.901
0.884
0.082
0.066
TBSO
O
OH
12
14
1.00
2.00
2.35
24.37
12.62
9.66
f1 (ppm)


177.402
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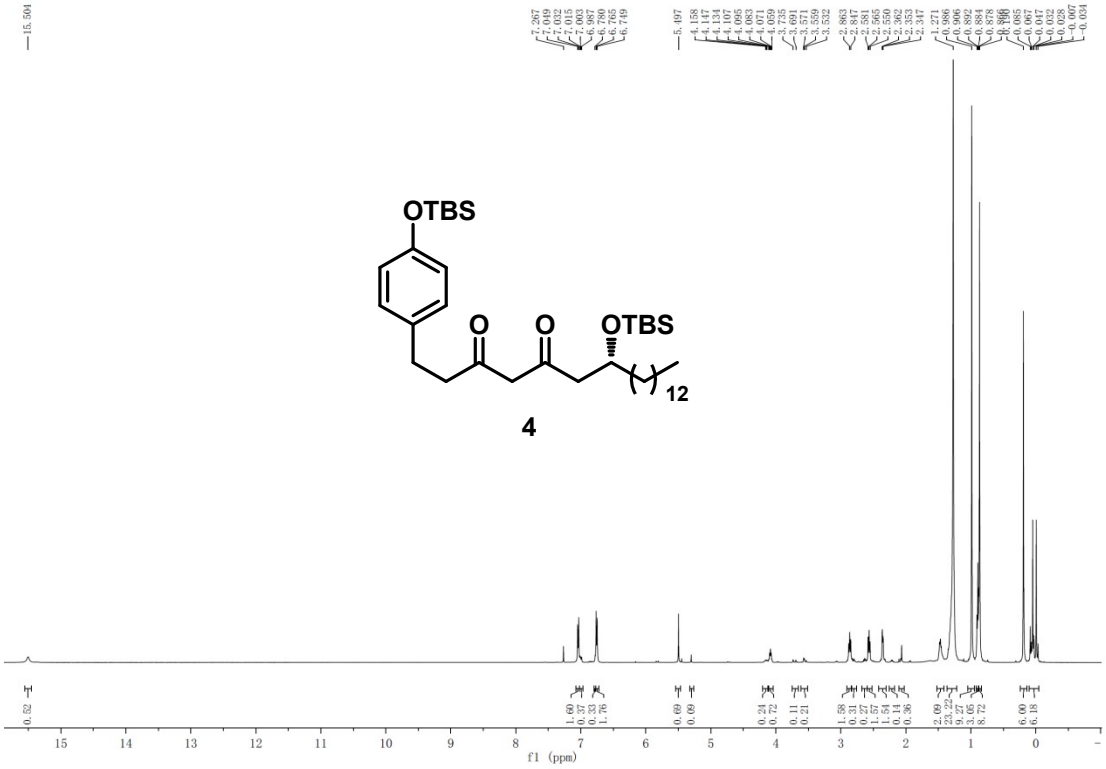
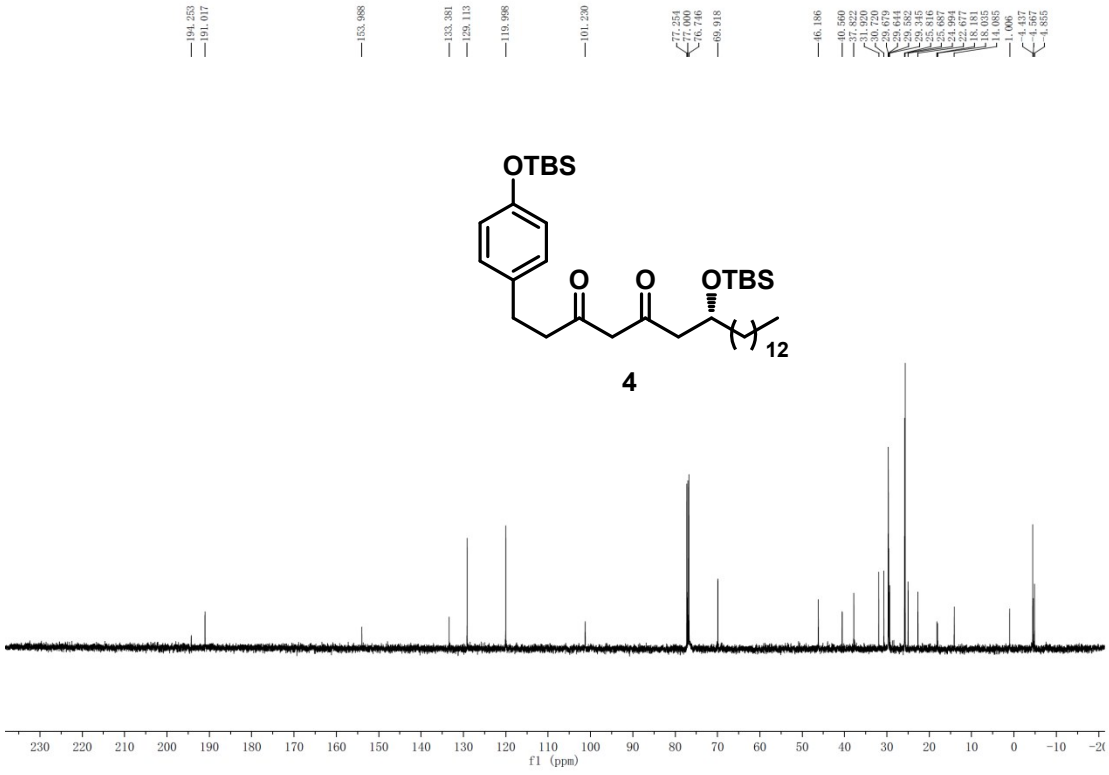
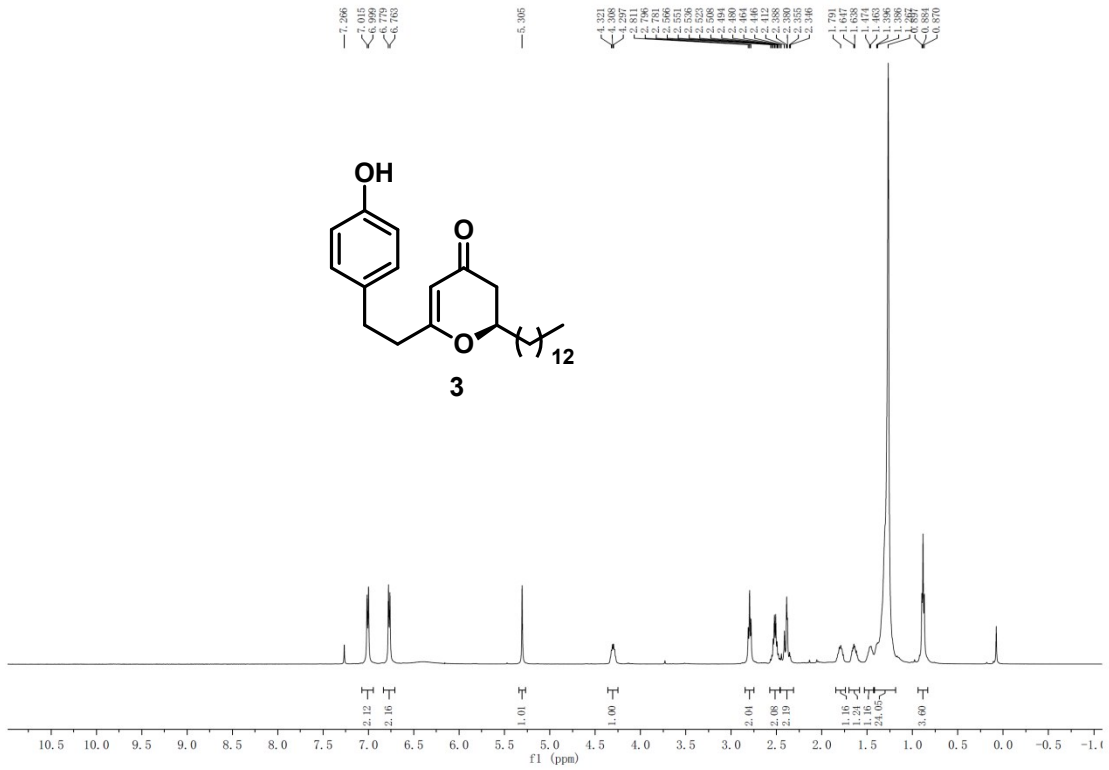
77.000
76.746
69.421
42.257
37.452
31.926
29.667
29.655
29.556
29.346
25.767
25.036
22.672
17.975
14.054
0.992
-4.545
-4.849
TBSO
O
OH
12
14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

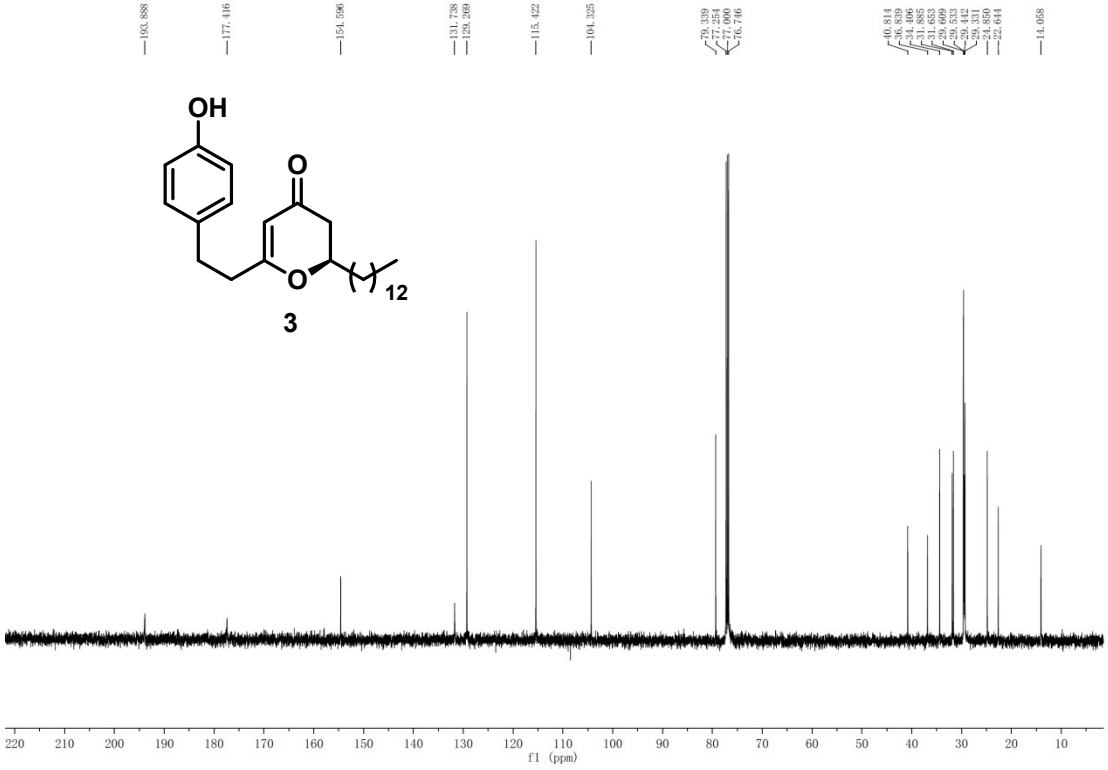
Compound 4:


OTBS
O
O
OTBS
12
4
f1 (ppm)


OTBS
O
O
OTBS
12
4
f1 (ppm)

Compound 3:

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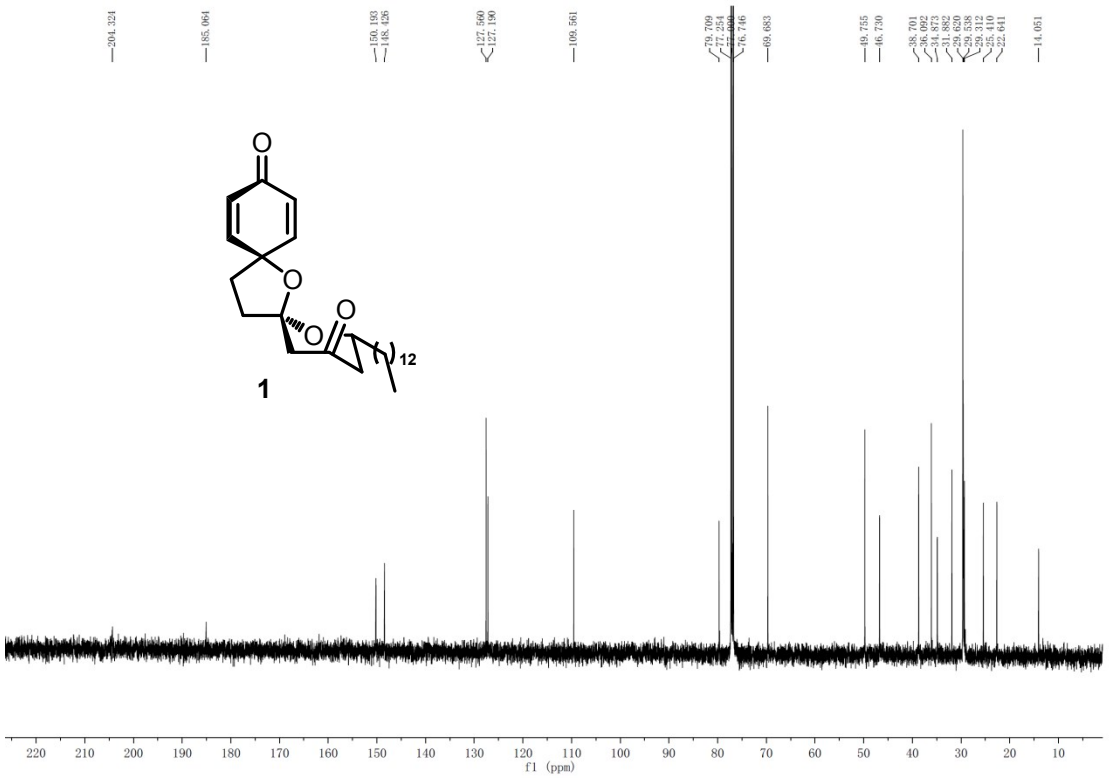
154.596
131.738
129.269
115.422
104.325
79.339
77.254
77.000
76.746
40.814
36.839
34.496
31.885
31.653
29.609
29.533
29.447
29.311
24.850
22.644
14.058
OH
O
O
12
3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Compound 1:


7.268
6.157
6.152
6.138
6.103
6.098
4.167
4.160
4.150
4.141
4.132
4.125
4.120
4.113
2.785
2.748
2.575
2.571
2.535
2.438
2.435
2.419
2.409
2.404
2.398
2.249
2.240
2.103
2.085
1.649
1.566
1.534
1.357
1.298
0.885
0.868
O
O
O
O
12
1
2.09
1.76
1.00
1.12
1.18
1.35
1.30
1.39
2.22
1.66
2.45
25.29
4.12
f1 (ppm)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150.193
148.436
127.560
127.190
109.561
79.709
77.254
76.746
69.683
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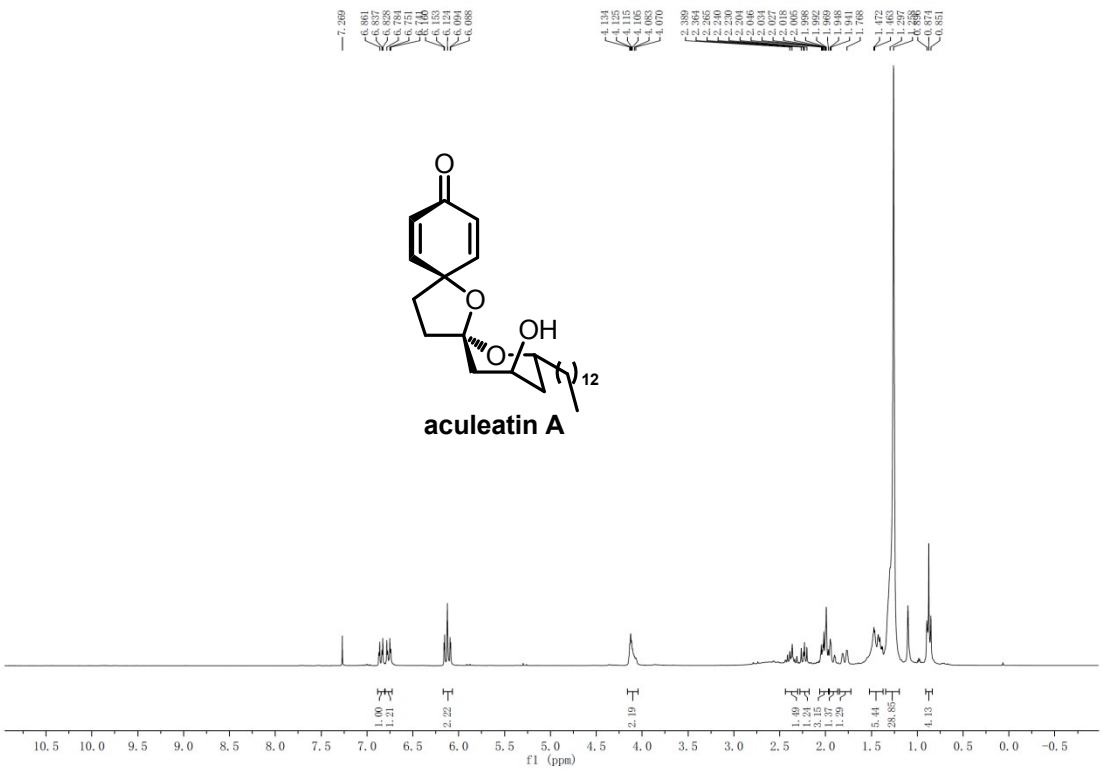
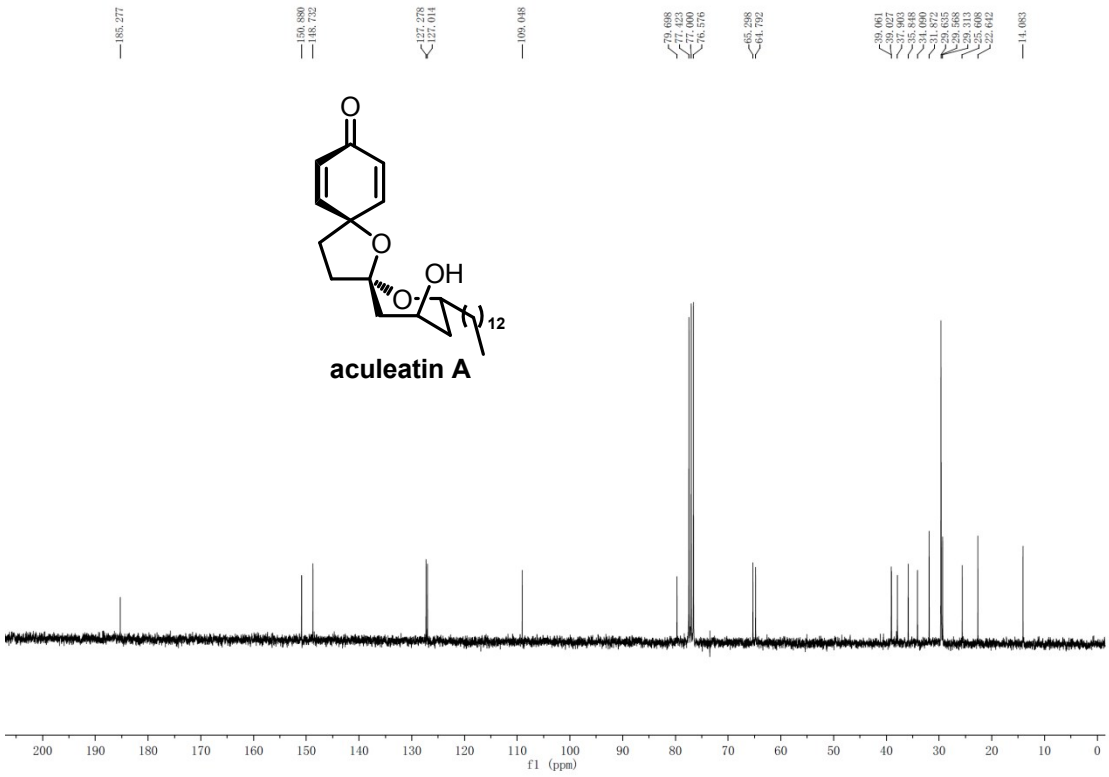
46.730
38.701
36.892
34.875
31.882
29.620
29.538
29.312
25.410
22.641
14.051
O
O
O
O
12
1
f1 (ppm)

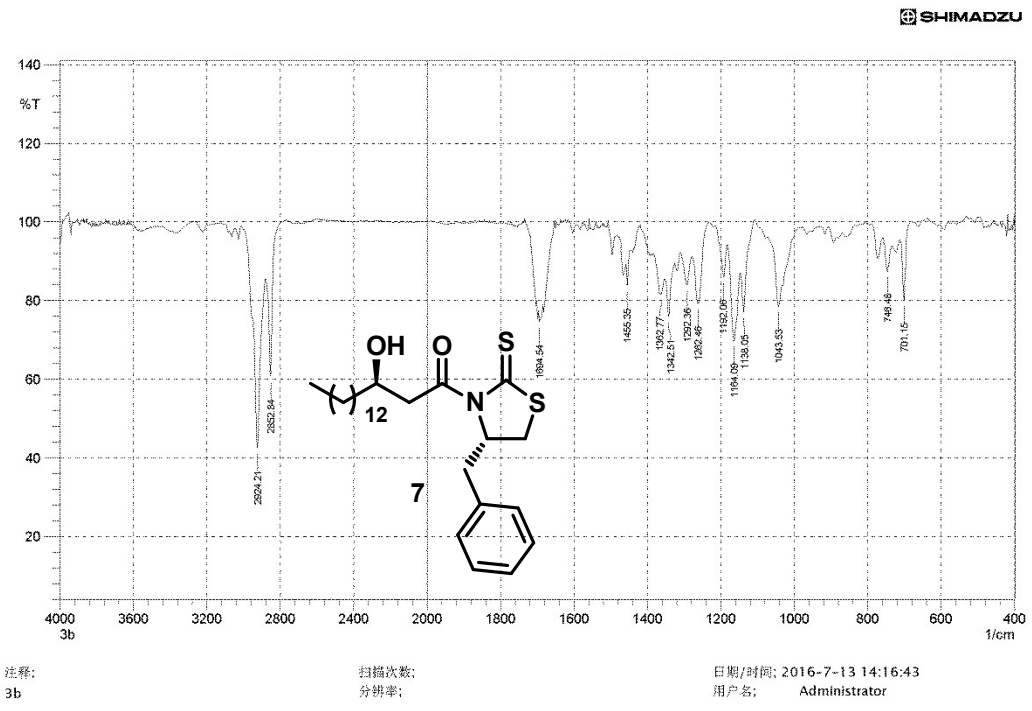
Aculeatin A:



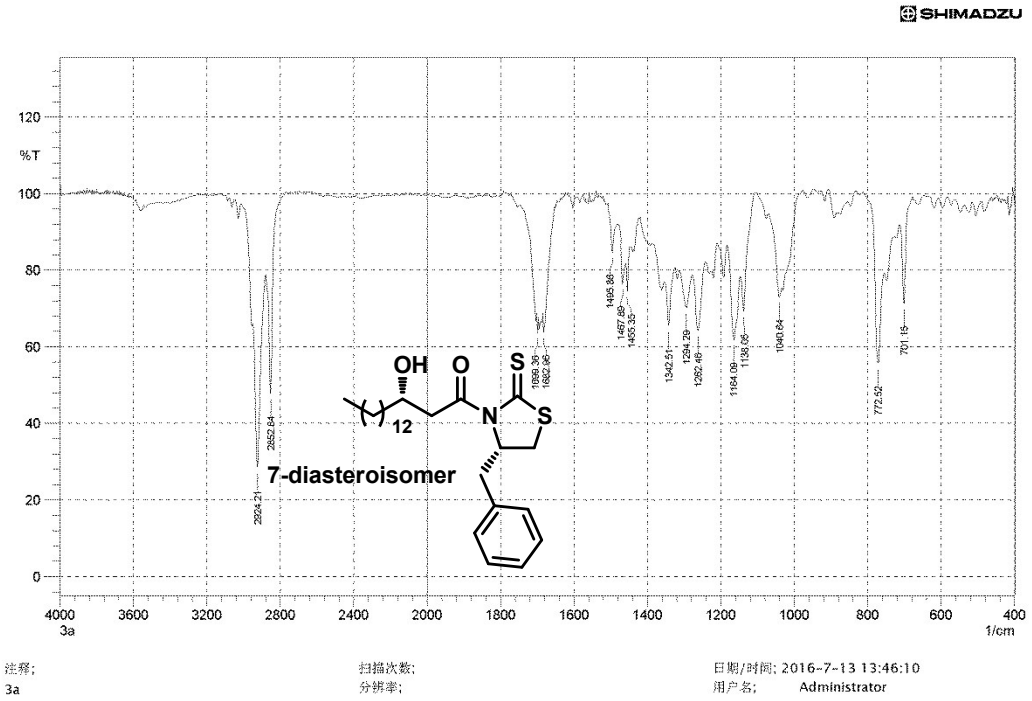


IR spectra:

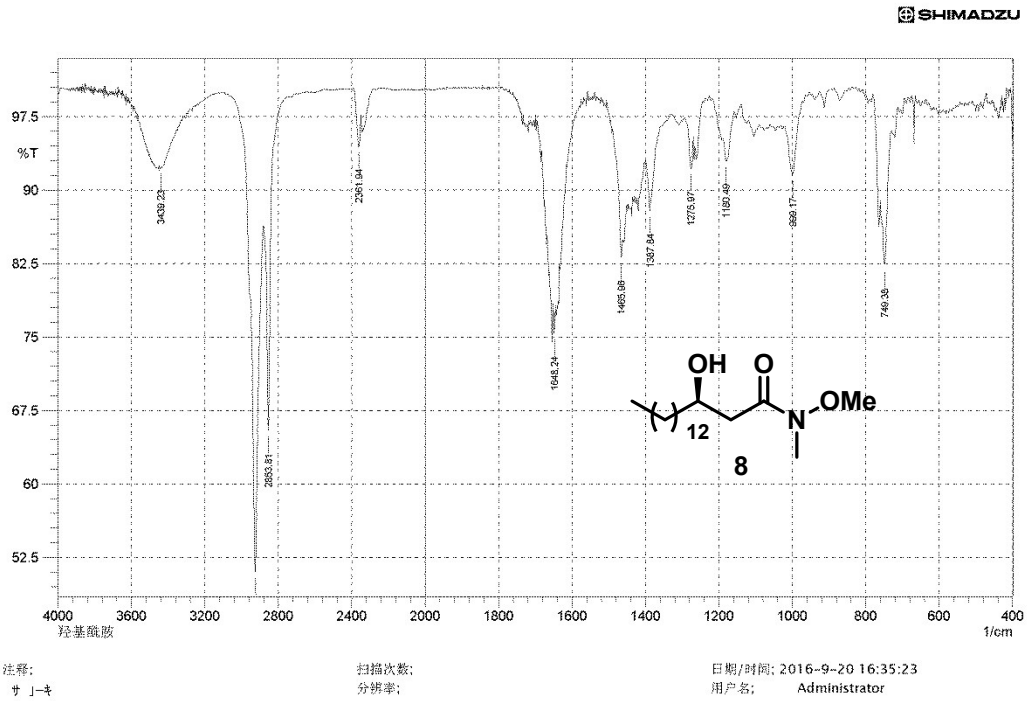
Compound 7:



Compound 7-diastereoisomer:



Compound 8:


SHIMADZU
%T
97.5
90
82.5
75
67.5
60
52.5
3439.23
2961.94
2853.81
1648.24
1465.98
1387.84
1275.97
1190.49
999.17
749.38
OH
O
OMe
N
12
8
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
1/cm
羟基酰胺
注释:
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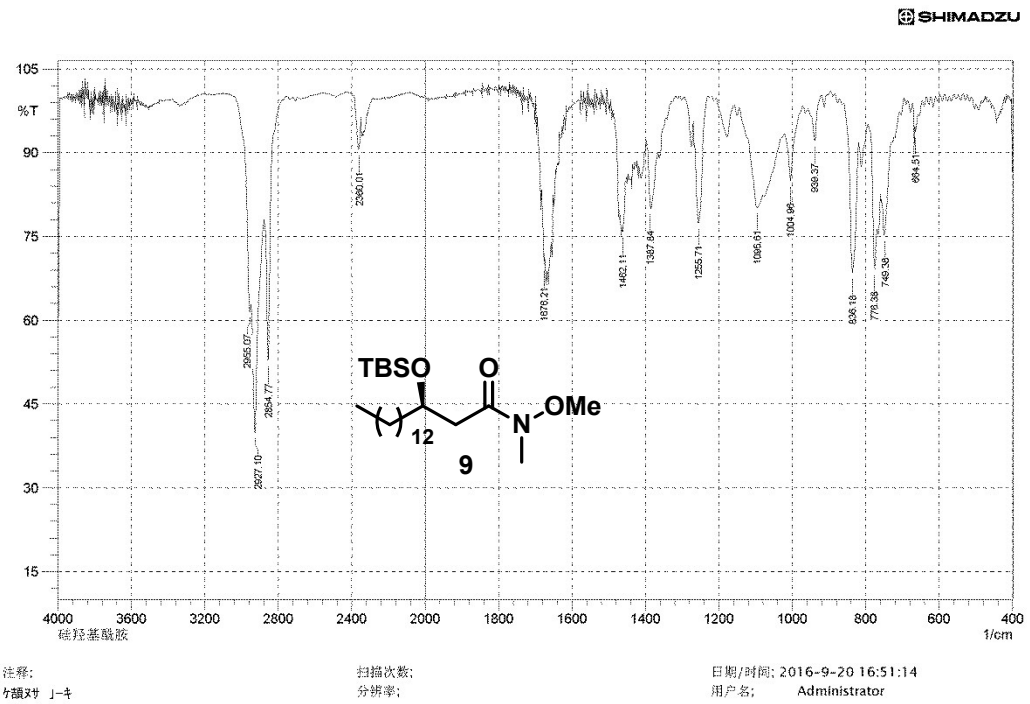
日期/时间; 2016-9-20 16:35:23
分辨率;
用户名; Administrator

Compound 9:


SHIMADZU
%T
105
90
75
60
45
30
15
2955.07
2927.10
2854.77
2360.01
1878.21
1462.11
1387.84
1255.71
1096.51
1004.96
938.57
836.18
778.38
749.36
694.51
TBSO
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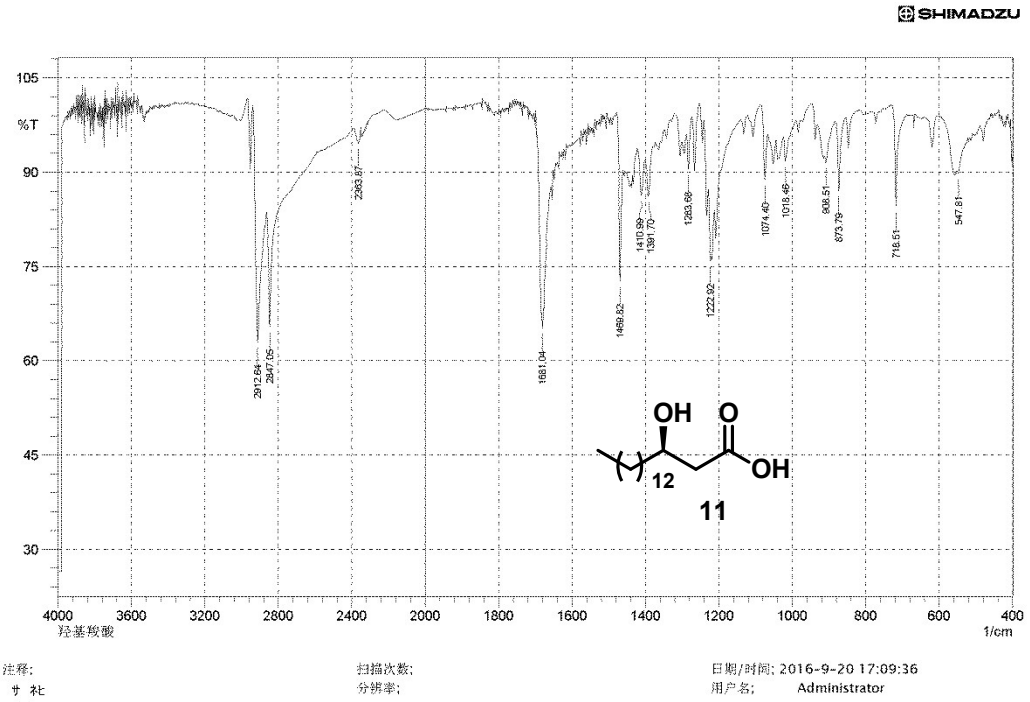
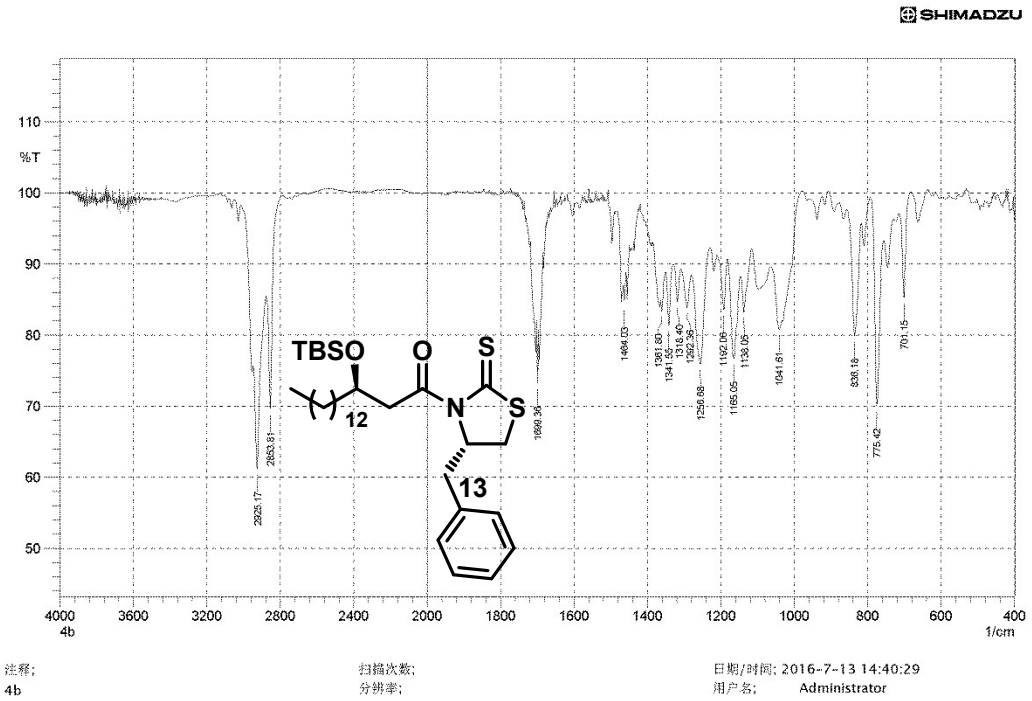
1/cm
硅羟基酰胺
注释:
扫描次数;
日期/时间; 2016-9-20 16:51:14
分辨率;
用户名; Administrator

Compound 11:



Compound 13:



注释;
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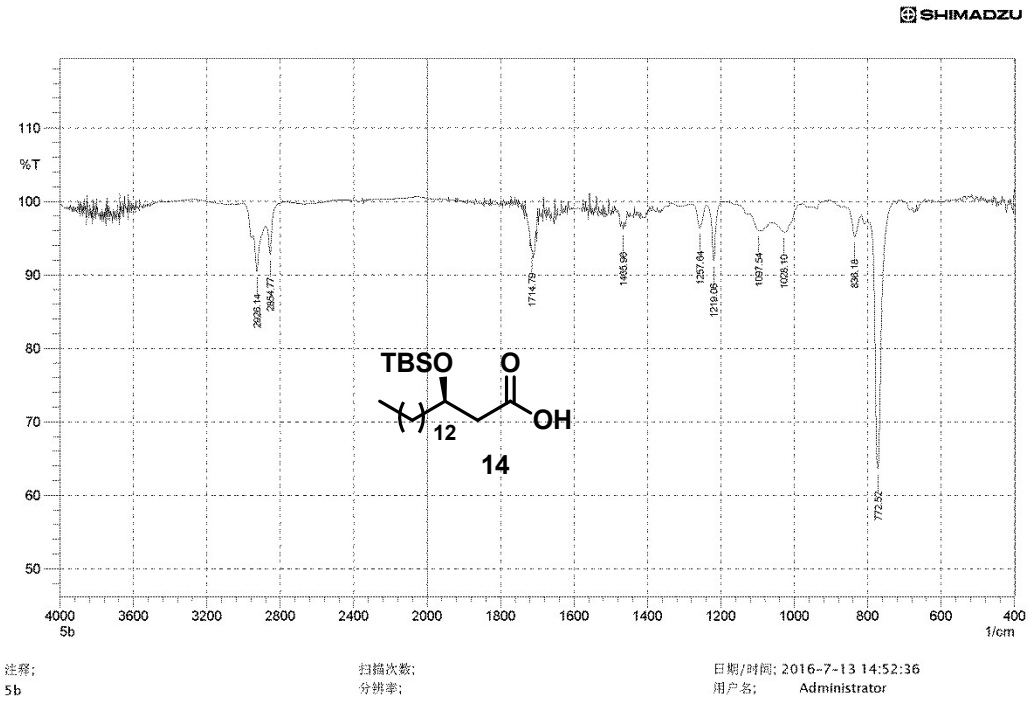
扫描次数;
分辨率;

日期/时间; 2016-7-13 14:40:29
用户名; Administrator

Compound 14:


SHIMADZU
%T
110
100
90
80
70
60
50
2925.14
2854.77
1714.79
1455.96
1257.84
1219.09
1097.54
1028.10
838.18
772.52
TBSO
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14
4000
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2400
2000
1800
1600
1400
1200
1000
800
600
400
1/cm
5b
注释;
5b
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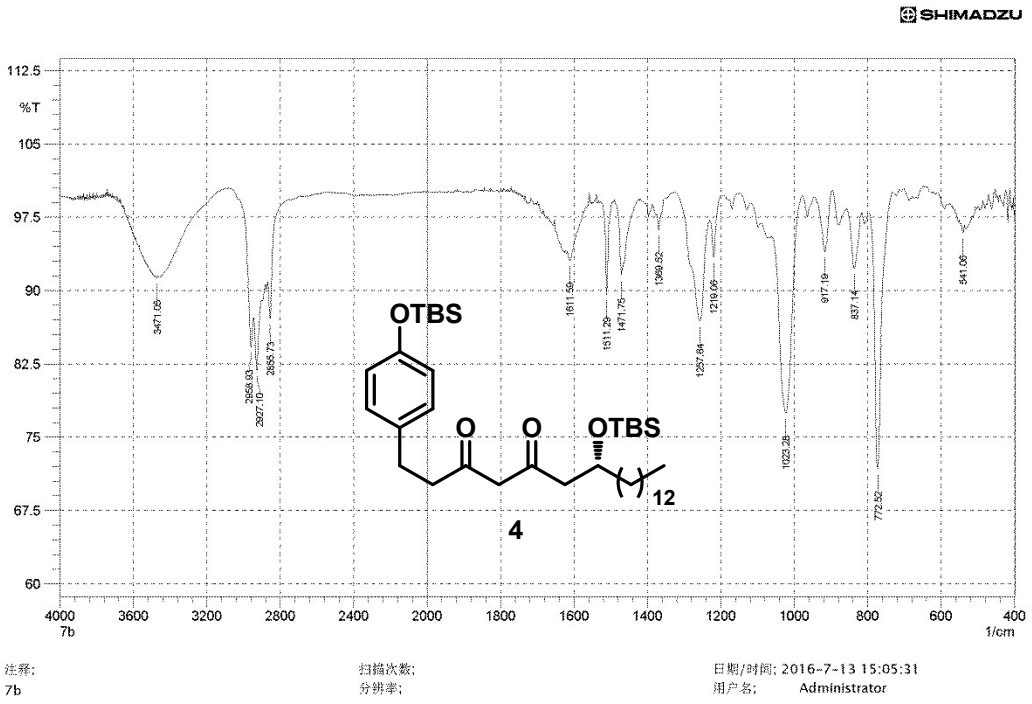
分辨率;
日期/时间; 2016-7-13 14:52:36
用户名; Administrator

Compound 4:


SHIMADZU
%T
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105
97.5
90
82.5
75
67.5
60
3471.08
2958.93
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2855.73
1611.56
1511.29
1471.75
1360.52
1257.84
1219.06
1022.28
917.19
857.14
772.32
541.08
OTBS
O
O
OTBS
12
4
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
1/cm
7b
注释;
7b
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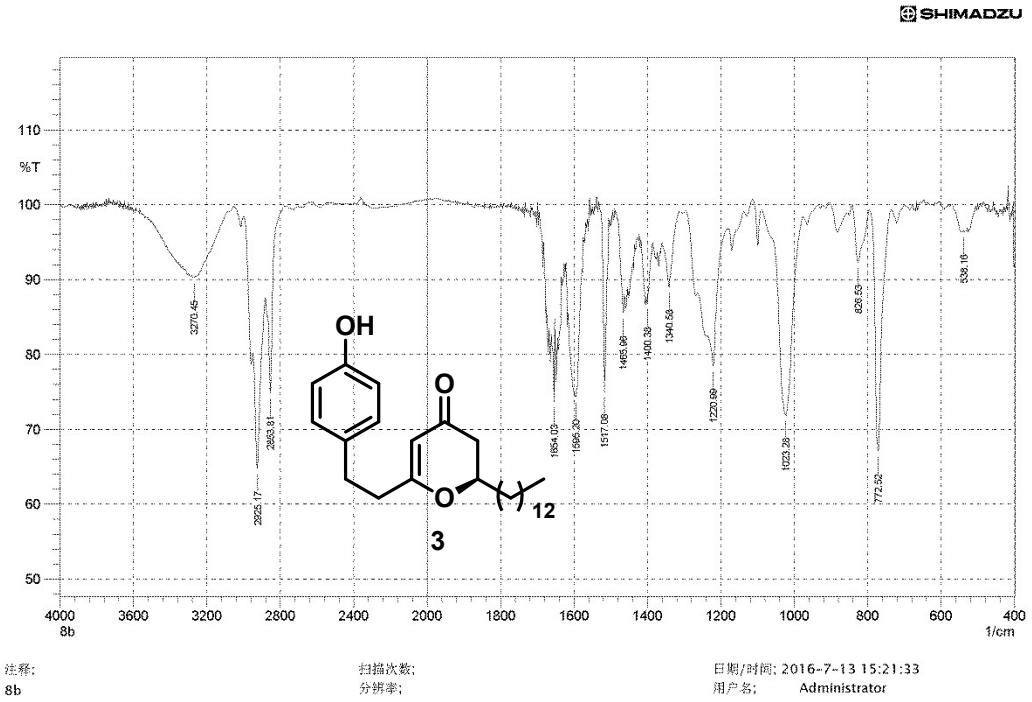
分辨率;
日期/时间; 2016-7-13 15:05:31
用户名; Administrator

Compound 3:



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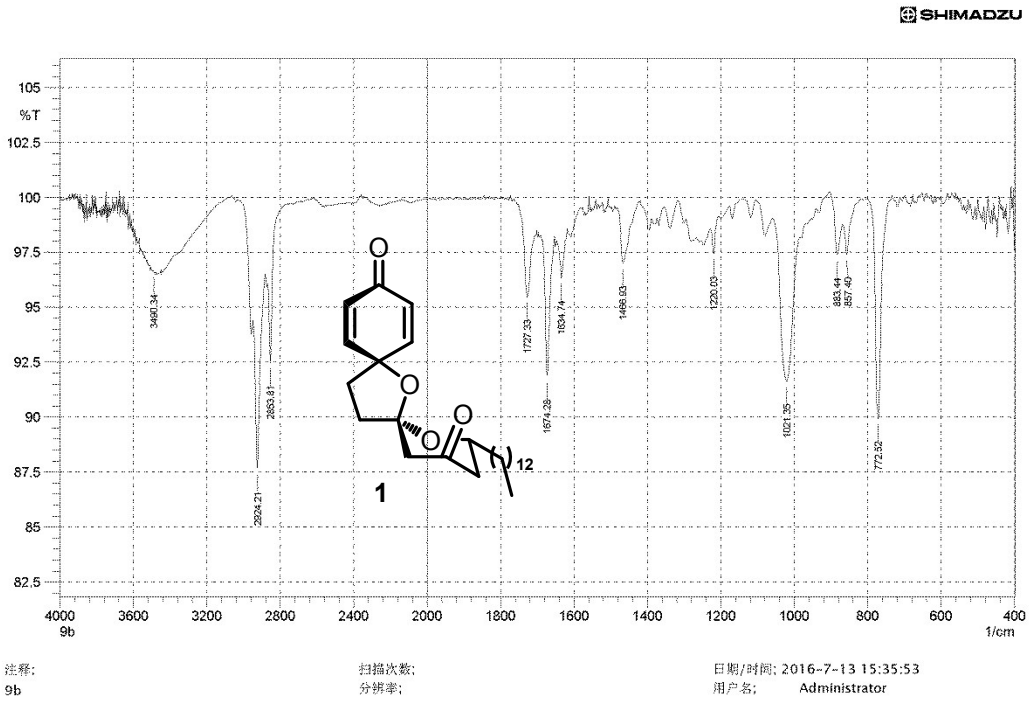
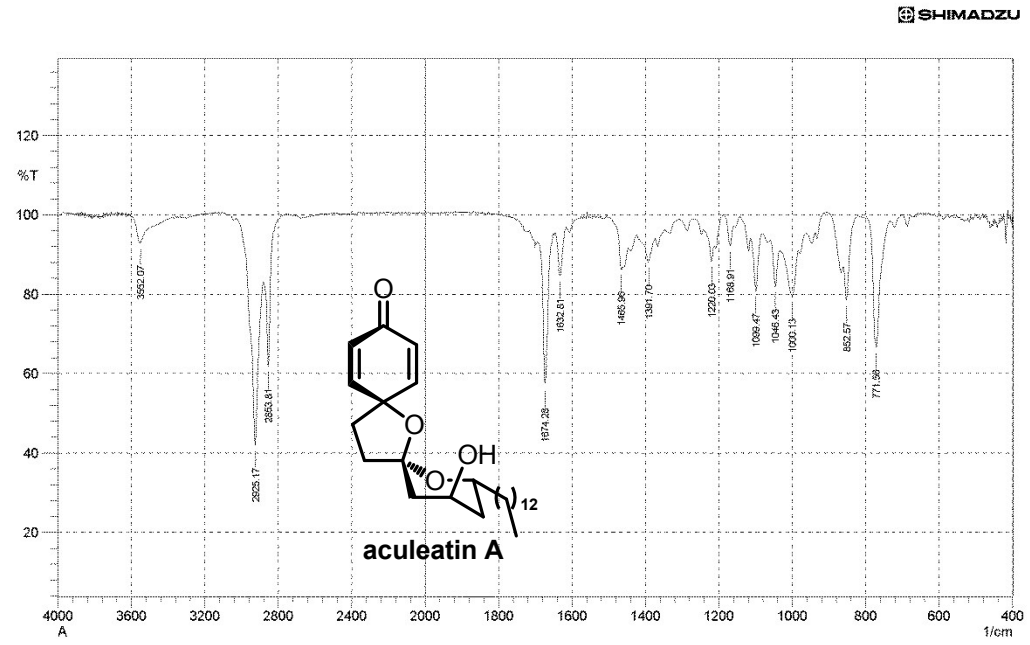


注释;
9b

扫描次数;
分辨率;

日期/时间; 2016-7-13 15:35:53
用户名; Administrator

Aculeatin A:



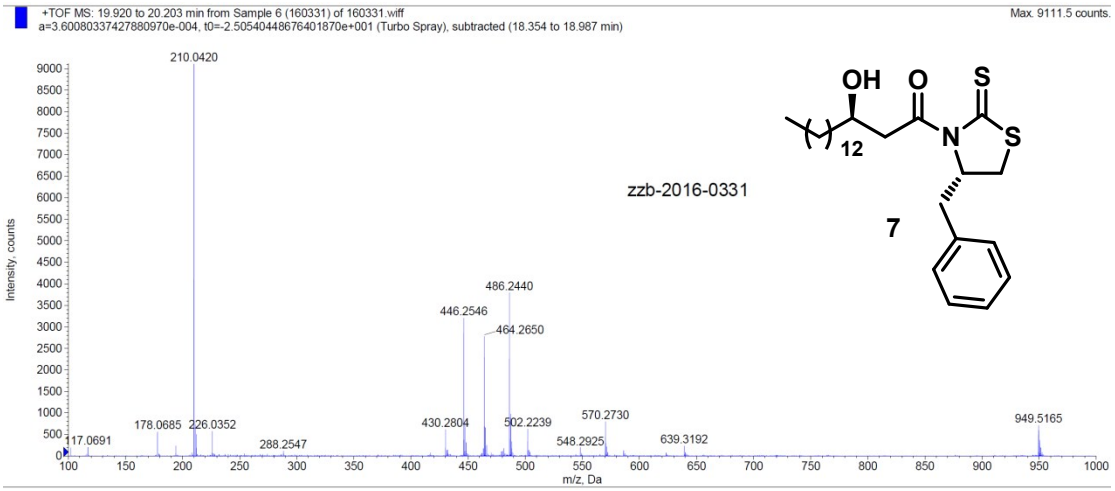
注释;
A

扫描次数;
分辨率;

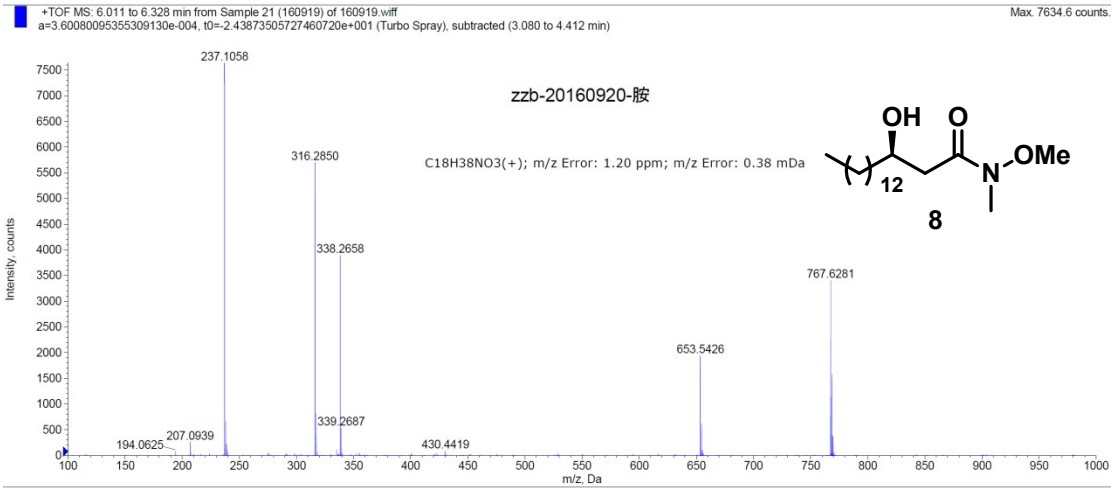
日期/时间; 2016-7-13 15:45:24
用户名; Administrator

HRMS spectra:

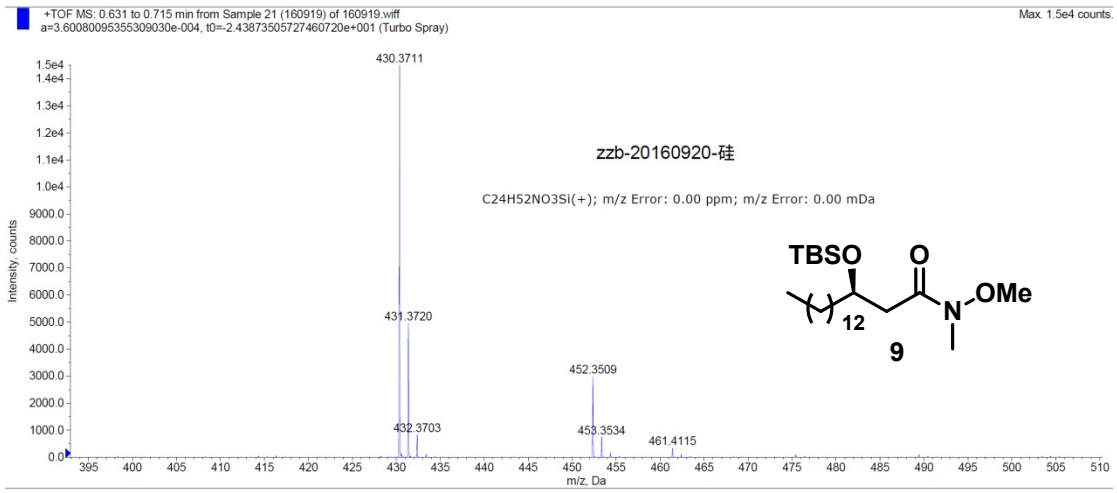
Compound 7:



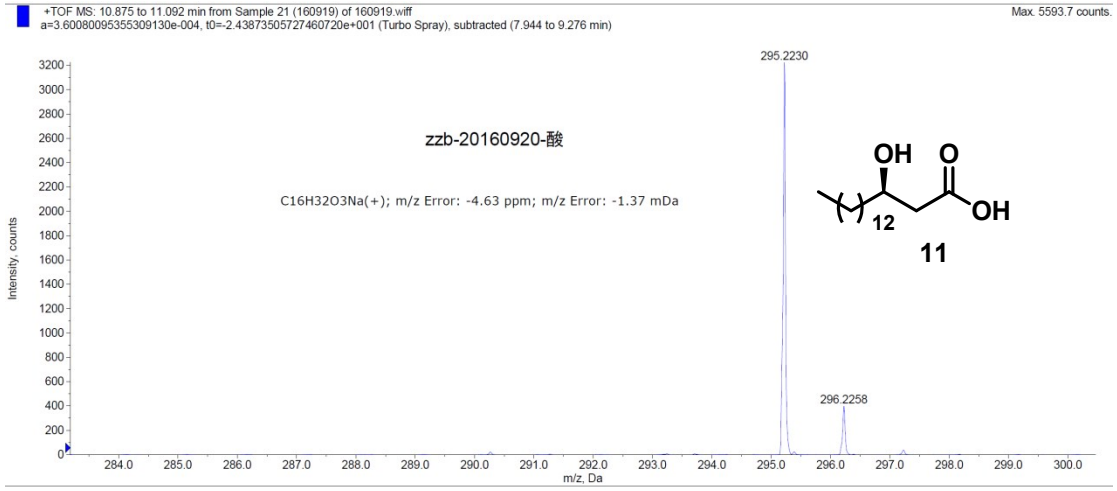
Compound 8:



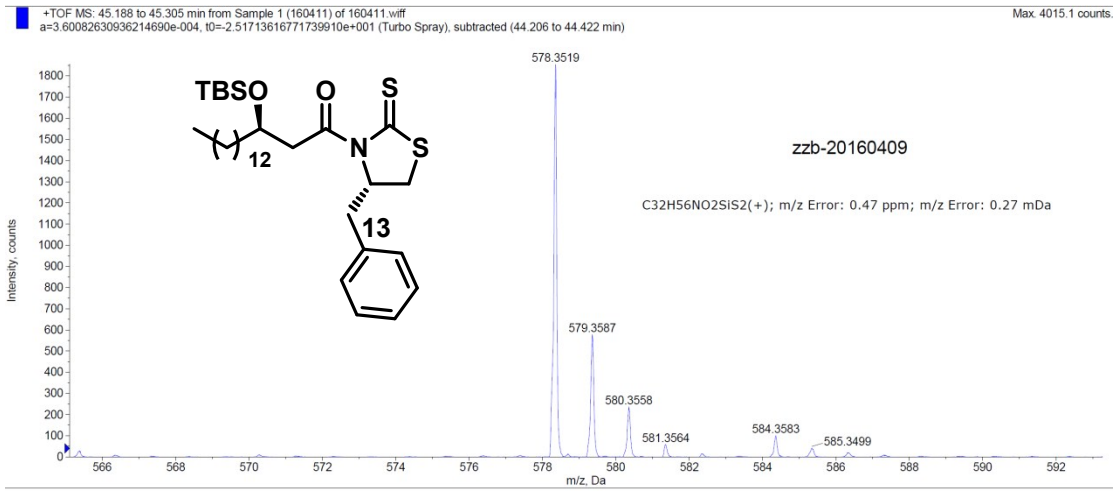
Compound 9:



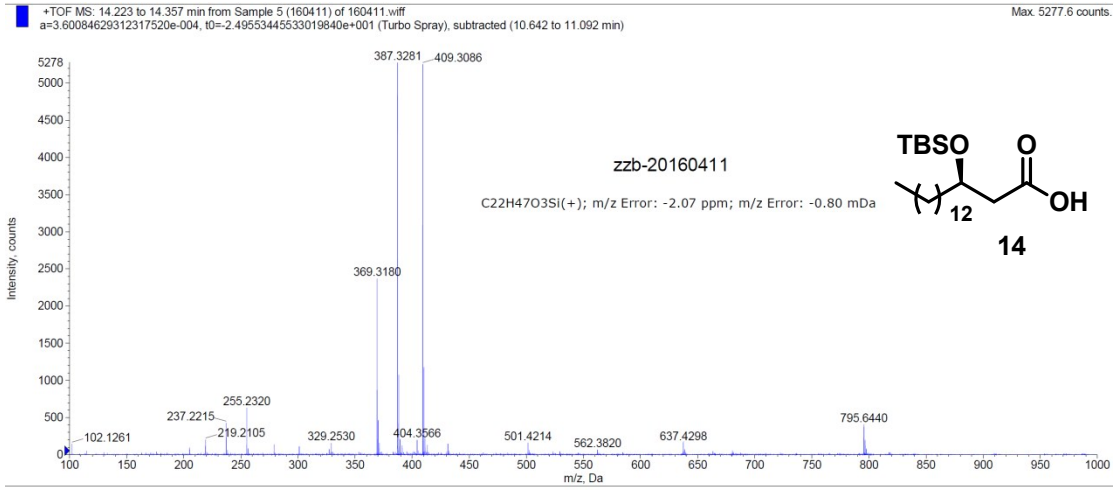
Compound 11:



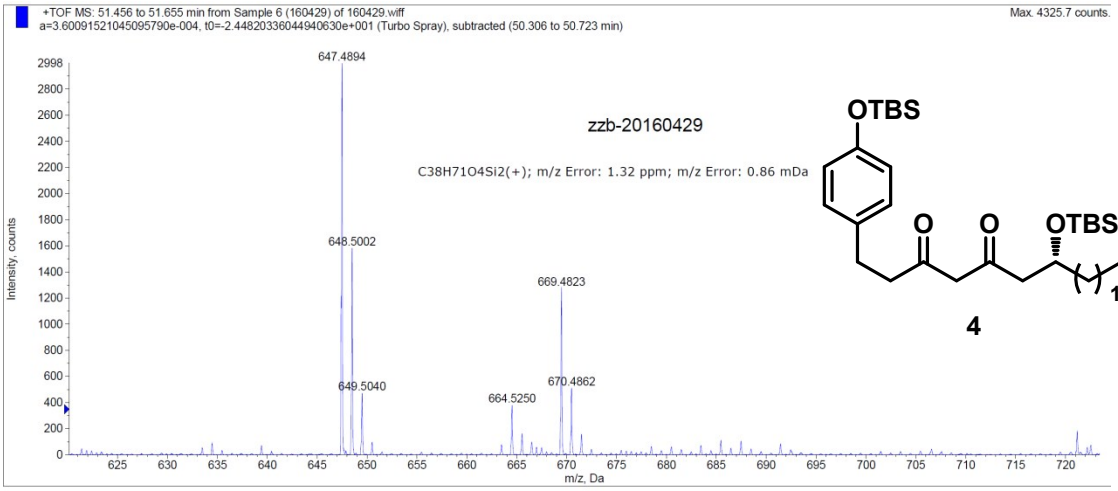
Compound 13:



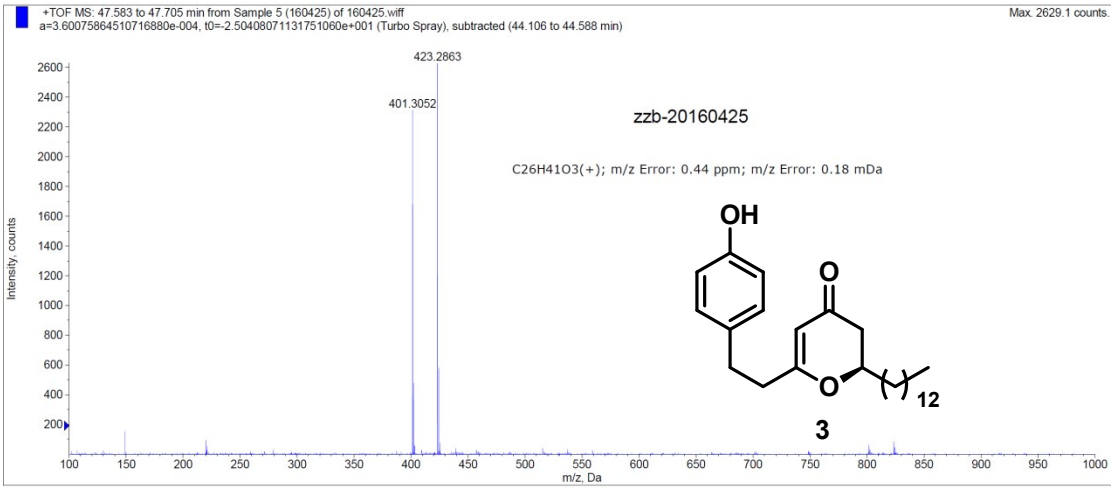
Compound 14:



Compound 4:



Compound 3:



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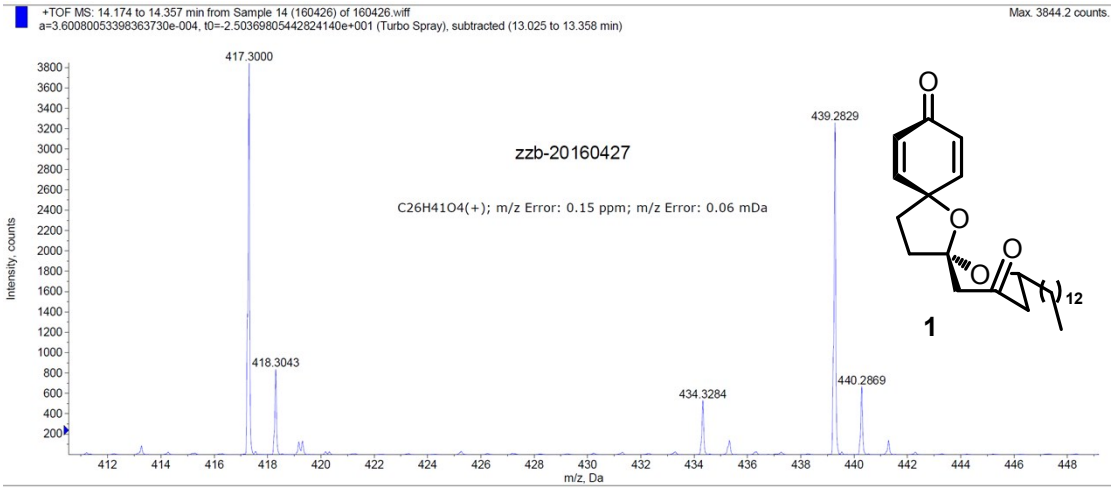
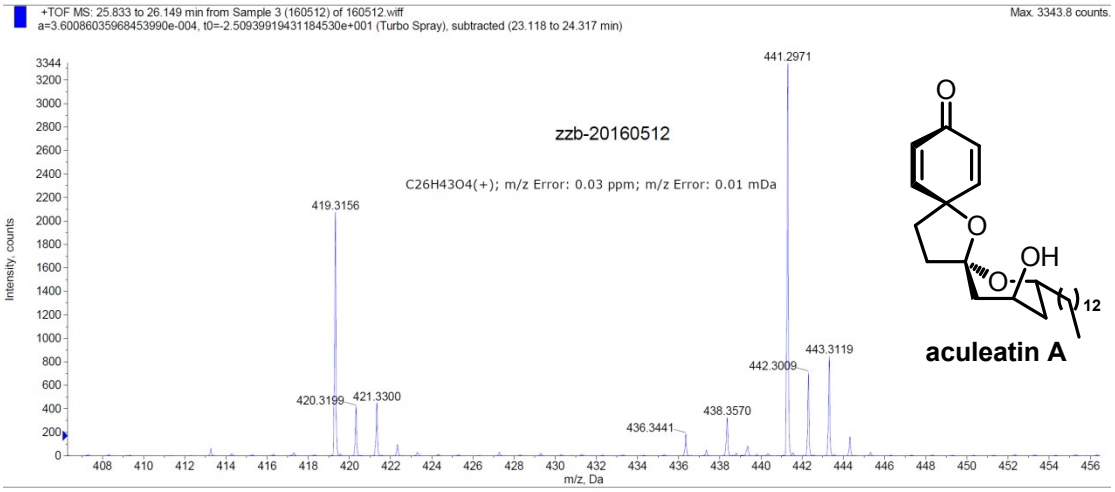


Aculeatin A:


+TOF MS: 25.833 to 26.149 min from Sample 3 (160512) of 160512.wiff
a=3.60086035968453990e-004, t0=-2.50939919431184530e+001 (Turbo Spray), subtracted (23.118 to 24.317 min)
Max. 3343.8 counts.
zzb-20160512
C26H43O4(+); m/z Error: 0.03 ppm; m/z Error: 0.01 mDa
441.2971
419.3156
443.3119
442.3009
420.3199
421.3300
438.3570
436.3441
Intensity, counts
m/z, Da
O
O
OH
O
12
aculeatin A