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SUPPORTING INFORMATION

A three-step enantioselective synthesis of (+)- and (−)-α-thujone

Kellie L. Weeks,[†] Jack D. Williams[‡] and Gregory R. Boyce*[†]

[†] Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965, United States
[‡] Department of Chemistry, Mercyhurst University, Erie, Pennsylvania 16546, United States

Tel: 239-590-1471, Fax: 239-590-7200, E-mail: gboyce@fgcu.edu

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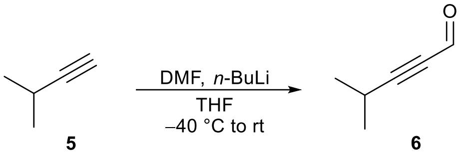
General Experimental Procedures. All reagents and solvents were used as received from Fisher Scientific or other commercial sources. *cis*-2-Butene was purchased from Synquest Laboratories. Triphenylphosphine gold(I) bis(trifluoromethanesulfonyl) imidate (866395-16-6) was purchased from Strem Chemical Inc. Reactions were monitored by thin-layer chromatography (TLC) carried out on commercial silica gel plates (F254) with visualization accomplished with UV light and aqueous potassium permanganate ($KMnO_4$). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables and schemes, which are averages of at least two experiments.

Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded at 400 and 100 MHz, respectively, with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Specific rotations were measured on a Autopol IV polarimeter with a 1 dm cuvette and are stated in ° mL dm^{-1} g^{-1} (c in g/100 mL).

GC-MS Procedures: For thujone (**1**, **3**), enantiomeric excess was determined by chiral GC-MS analysis using an Agilent 7890A instrument equipped with a Restek Rt®-βDEXsa capillary column (0.25 mm x 30 m, 0.25 µm phase), attached to an Agilent 5975C mass spectrometer detector (EI mode, ionization energy 70 eV; source 230 °C, quad 150 °C). All GC-MS data was collected and analyzed using Agilent ChemStation software and a NIST-17 mass spectral database. Helium (99.995% purity) was used as the carrier gas at 1.0 mL/min (constant flow) with a split ratio of 20/1. Complete stereoisomer separation occurred within 12 minutes using an oven temperature of 120 °C.

For 3,7-dimethyloct-1-en-5-yn-4-ol (**7**, **S1**), enantiomeric excess was determined by chiral GC-MS analysis using an Agilent 7890A gas chromatograph equipped with an Agilent CycloSil B column (0.25 mm x 30 m, 0.25 µm phase) attached to an Agilent flame ionization detector (250 °C). Helium (99.995% purity) was used as the carrier gas at 1.0 mL/min (constant flow) with a split ratio of 20/1. All four stereoisomers separated within 10 minutes using an oven temperature of 125 °C.

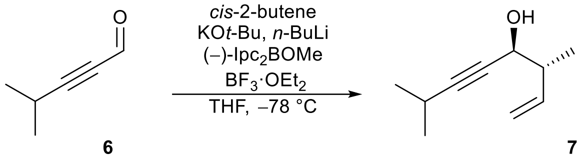
II. EXPERIMENTAL PROCEDURES



5 **6**

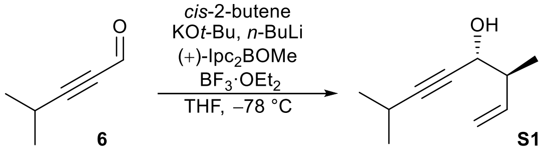
4-Methylpent-2-ynal (6): A solution of 3-methyl-1-butyne **5** (3.0 mL, 29.4 mmol, 1.0 equiv) was added to a flame-dried flask, purged with nitrogen, and cooled to –40 °C. A 2.5 M solution of *n*-butyl lithium in hexanes (13 mL, 32.3 mmol, 1.1 equiv) was added dropwise over 5 minutes and stirred for 30 minutes. Anhydrous DMF (3.4 mL, 44.0 mmol, 1.5 equiv) was then added to the reaction flask in one portion and the ice bath was removed. The reaction was allowed to warm to room temperature and then stirred for an additional 2 hours. The reaction was quenched by slowly adding the reaction mixture to a vigorously stirred solution of aqueous 0.6 M KH_2PO_4 (145 mL) and Et_2O (90 mL) at 0 °C. After stirring for 10 min, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The organic extracts were combined and washed 3 times with water (20 mL) and then with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. Due to volatility of the product, the solvent was removed *in vacuo* while in an ice bath to afford 2.09 g of **6** as a yellow oil in 74% yield. The product was taken on crude to the next step. Spectral data matched those reported for the title compound.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.18 (s, 1H), 2.83–2.71 (m, 1H), 1.25 (d, *J* = 8.9 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.6, 104.0, 80.9, 21.9. 21.0.
TLC (10% EtOAc/hexanes): R_f = 0.68. ($KMnO_4$)

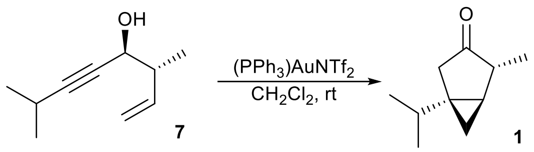


(3*R*,4*S*)-3,7-Dimethyloct-1-en-5-yn-4-ol (7): A mixture of 1.6 M *t*-BuOK in THF was added to a flame dried round bottom flask and stirred at −78 °C. After storing for 12 hours in the freezer, the liquid *cis*-2-butene (1.4 mL, 51.1 mmol, 5.2 equiv) was poured into a graduated cylinder which was cooled with dry ice and then immediately added to the round bottom flask. The round bottom flask was then equipped with a rubber seal and purged with nitrogen. 2.5 M *n*-Butyl lithium in hexanes (7.8 mL, 19.6 mmol, 2 equiv) was added to the mixture dropwise before the −78 °C bath was removed and replaced with a −40 °C bath and allowed to stir for 30 min. The solution was then re-cooled to −78 °C and (–)-β-methoxydiisopinocamphenylborane (5.0 g, 15.8 mmol, 1.6 equiv) was added to the reaction mixture followed by $BF_3 \cdot Et_2O$ (ca 46%, 4.0 mL, 15.1 mmol, 1.54 equiv). After 30 minutes, a 2.5 M solution of 4-methylpent-2-ynal **6** (942 mg, 9.80 mmol, 1.0 equiv) in anhydrous THF was added slowly at −78 °C and allowed to stir for 1 hour. 1 M NaOH (15 mL) was added slowly followed by 30% H_2O_2 (15 mL) at −78 °C. The resulting mixture was warmed to room temperature and extracted with ether. The organic phase was washed with saturated aqueous $Na_2S_2O_3$ brine, dried with $MgSO_4$, and concentrated *in vacuo* to afford the crude alcohol. Purification by flash chromatography (10% EtOAc/hexanes) yielded 1212 mg of **2** as a colorless oil in 81% yield. Spectral data matched those reported for the title compound.[1b] Chiral GC-MS analysis provided a 91% ee for the product.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.89–5.80 (m, 1H), 5.16–5.13 (m, 2H), 4.24 (dd, *J* = 4.8, 1.8 Hz, 1H), 2.65–2.34 (m, 2H), 1.74 (br. s, 1H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.09 (d, *J* = 6.8 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.2, 117.1, 92.3, 78.3, 66.3, 44.6, 23.1, 20.6, 15.8.
TLC (10% EtOAc/hexanes): R_f = 0.33. ($KMnO_4$)
$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{23}}$= −13.00 (c = 1.00, $CHCl_3$, 91% ee)



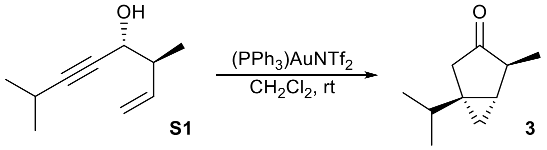
(3*S*,4*R*)-3,7-Dimethyloct-1-en-5-yn-4-ol (S1): The reaction procedure above was performed with antipode of the borane reagent, (+)-β-methoxydiisopinocamphenylborane and with 1.0 g of the 4-methylpent-2-ynal **6** to provide 1150 mg of **S1** as a colorless oil in 76% yield.
$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{23}}$= +12.99 (c = 1.07, $CHCl_3$, 92% ee)



(–)-α-Thujone (1): The crotyl alcohol **7** (100 mg, 0.66 mmol, 1.0 equiv) and dichloromethane (0.3 M, 2.2 mL, 3.3 mmol) were added to a flame dried vial under an atmosphere of air.

Triphenylphosphine gold(I) bis(trifluoromethanesulfonyl) imidate (24 mg, 0.033 mmol, 0.05 equiv) was added to the solution at room temperature. The reaction was stirred for 1 hour and ran through a silica plug. The solvent was carefully removed *in vacuo*. Purification by flash chromatography (2% Et_2O/pentanes) yielded 59 mg of **1** as a volatile yellow oil in 59% yield in a 10:1 ratio of α:β thujone. Spectral data matched those reported for the title compound.[1b-3] Chiral GC-MS analysis provided an 88% ee for the product.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.60 – 2.48 (m, 1H), 2.21 (q, *J* = 7.4 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.34 (heptet, *J* = 6.8 Hz, 1H), 1.15 (d, *J* = 7.5 Hz, 3H), 1.07 (dd, *J* = 8.1, 4.0 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 4H), 0.75 (ddd, *J* = 8.1, 5.6, 2.5 Hz, 1H), 0.11 (dd, *J* = 5.7, 3.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 221.7, 47.5, 39.8, 33.1, 29.8, 25.7, 20.2, 19.9, 18.9, 18.4.
TLC (5% EtOAc/hexanes): R_f = 0.47. ($KMnO_4$)
$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{23}}$= –10.10 (c = 1.00, $CHCl_3$, 88% ee, 10:1 α/β)
Note: The sign matches the literature value of (–)-α-thujone $[a]_D^{23}$= –20.5 (c = 1.0, $CHCl_3$, 99% ee)[2]; however, the optical rotation is shifted due to the presence of a 10:1 mixture of the α:β isomers. (+)-β-thujone has an optical rotation of $[a]_D^{23}$= +72.46[4] so small amounts significantly alter the observed rotation. The chiral GC-MS traces below unequivocally confirm that the (–)-α-thujone and the (+)-β-thujone are the major products of the reaction as well as the enantiomeric excess and the diastereomeric ratio.



(+)-α-Thujone (3): The reaction procedure above was performed with crotyl alcohol **S1** instead of **7**. The reaction was run on a 73 mg scale to provide 46 mg of **3** in a 63% yield in a 10:1 ratio of α:β thujone. Spectral data matched those reported for the title compound.[1b-3] Chiral GC-MS analysis provided an 88% ee for the product.
$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{23}}$= +10.30 (c = 1.00, $CHCl_3$, 88% ee, 10:1 α/β)

III. REFERENCES

1. (a) M. Journet, D. Cai, L. M. DiMichele and R. D. Larsen, *Tetrahedron Lett.*, 1998, **39**, 6427. (b) J. D. Williams, J. A. Yazarians, C. C. Almeyda, K. A. Anderson and G. R. Boyce, *J. Agric. Food Chem.*, 2016, **64**, 4319.
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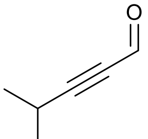
IV. ^{1}H AND ^{13}C SPECTRA OF COMPOUNDS



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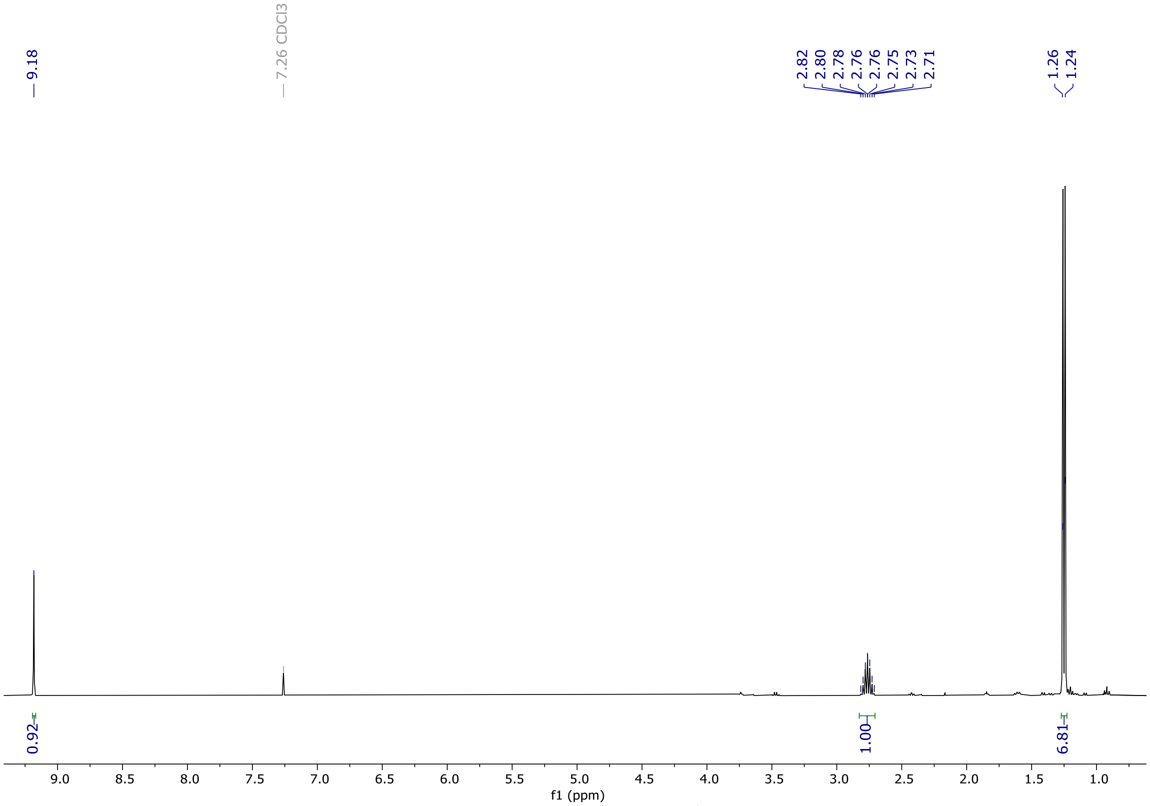

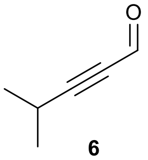

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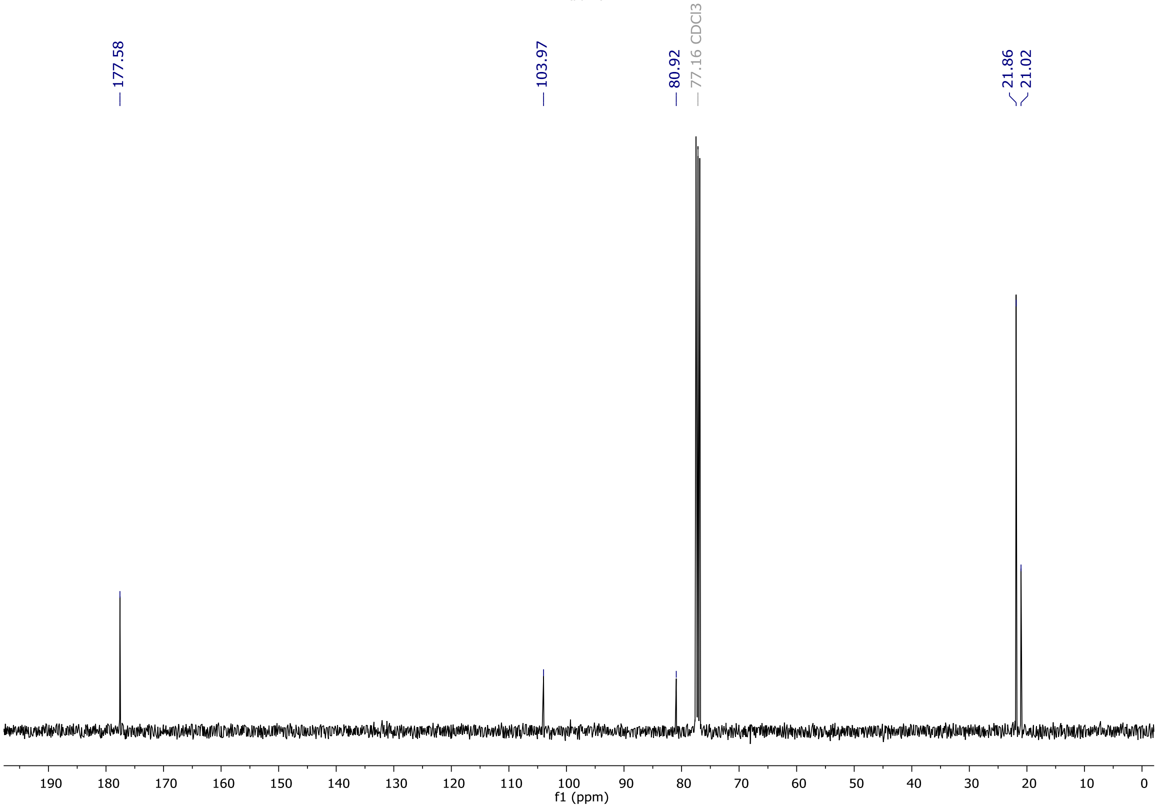
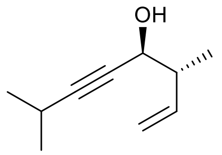
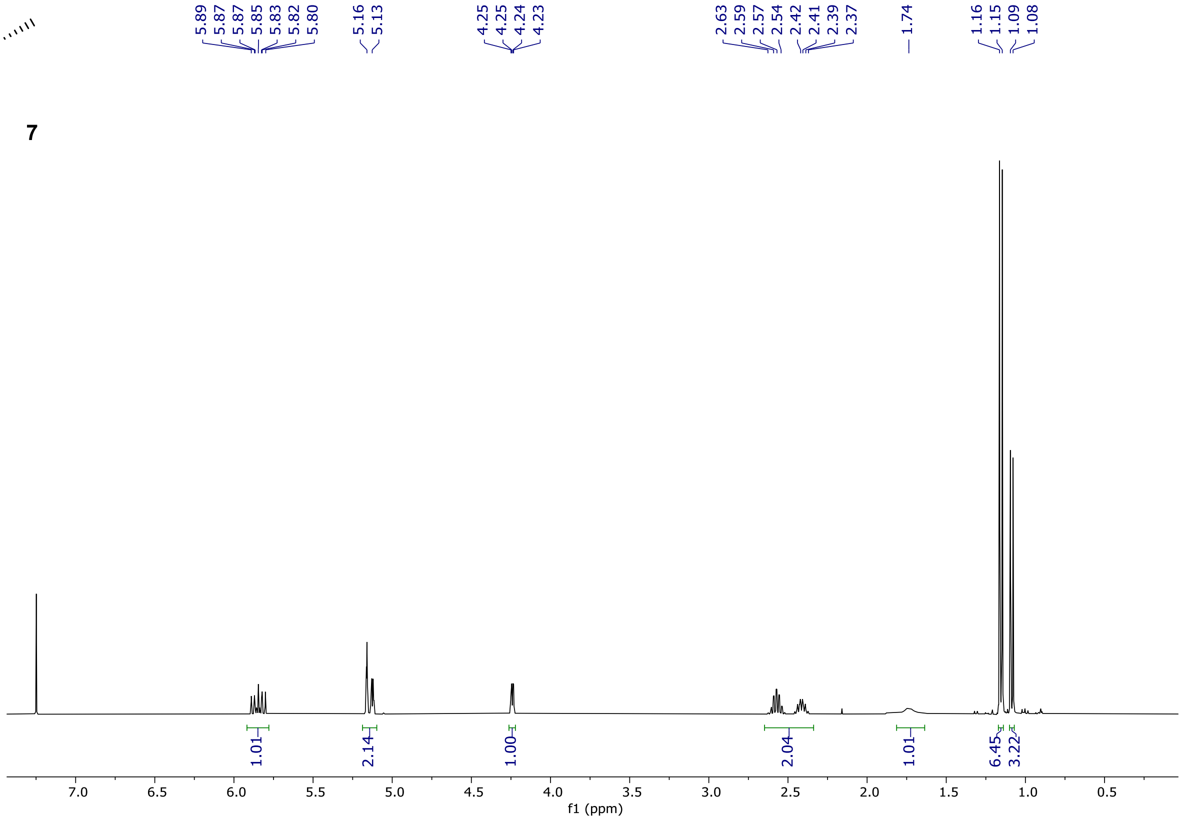
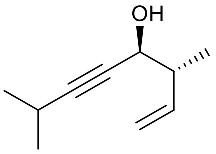


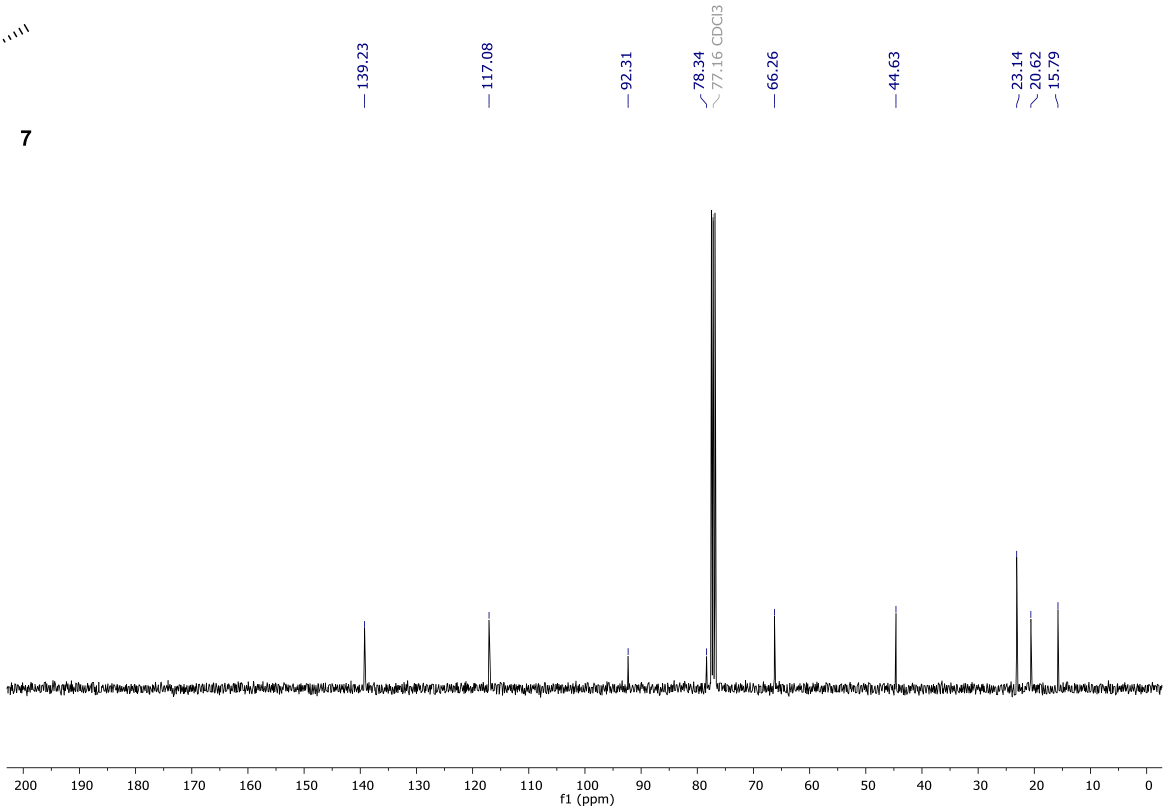

OH

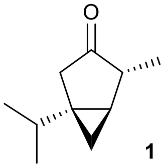
7


5.89
5.87
5.87
5.85
5.83
5.82
5.80
5.16
5.13
4.25
4.25
4.24
4.23
2.63
2.59
2.57
2.54
2.42
2.41
2.39
2.37
1.74
1.16
1.15
1.09
1.08
1.01
2.14
1.00
2.04
1.01
6.45
3.22
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

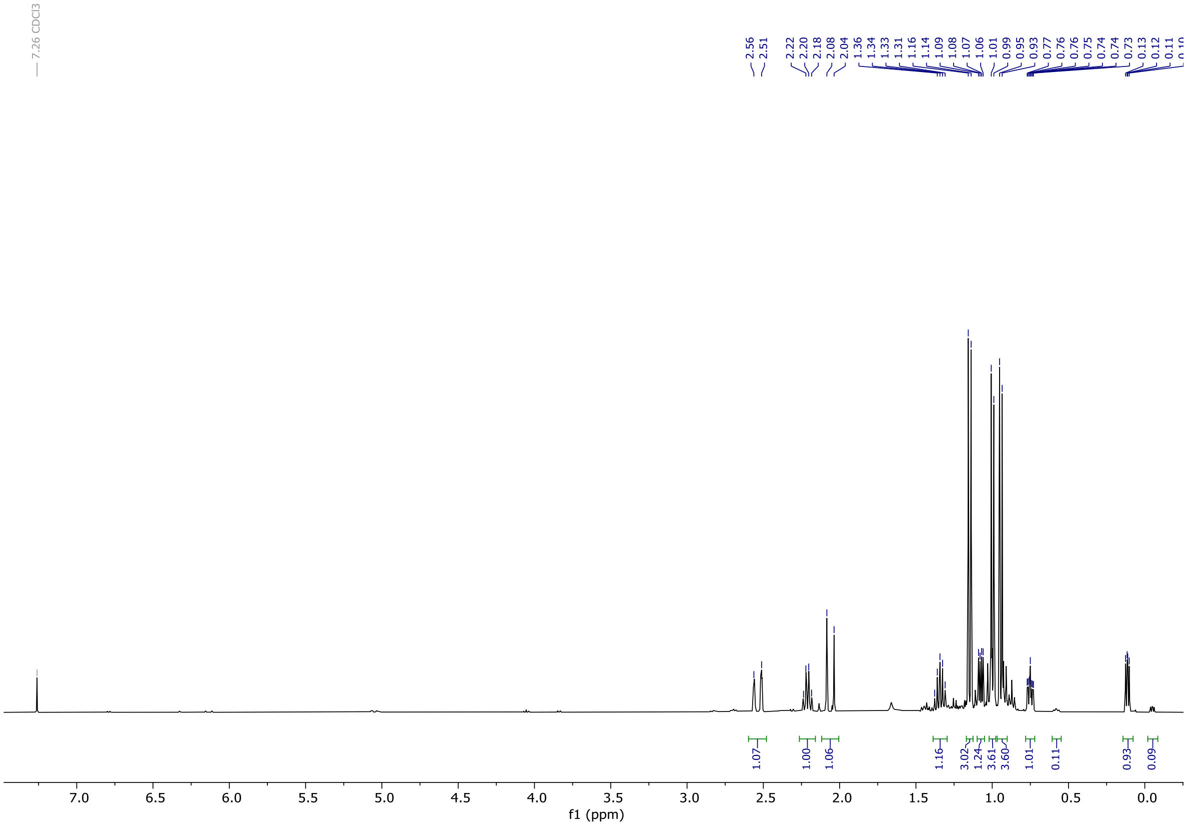

OH

7


139.23
117.08
92.31
78.34
77.16 CDCl3
66.26
44.63
23.14
20.62
15.79
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



1



7.26 CDCl3
2.56
2.51
2.22
2.20
2.18
2.08
2.04
1.36
1.34
1.33
1.31
1.16
1.14
1.09
1.08
1.07
1.06
1.01
0.99
0.95
0.93
0.77
0.76
0.76
0.75
0.74
0.74
0.73
0.13
0.12
0.11
1.07
1.00
1.06
1.16
3.02
1.24
3.61
3.60
1.01
0.11
0.93
0.09
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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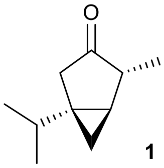
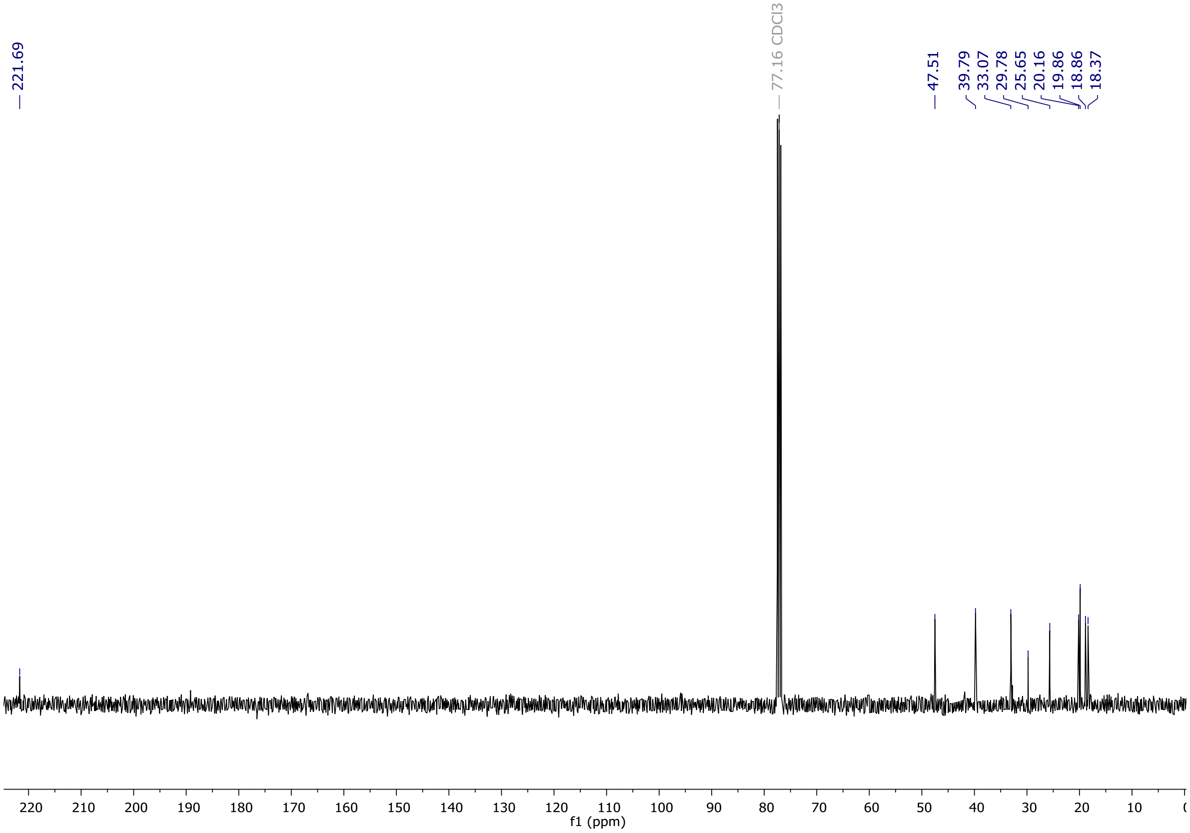
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



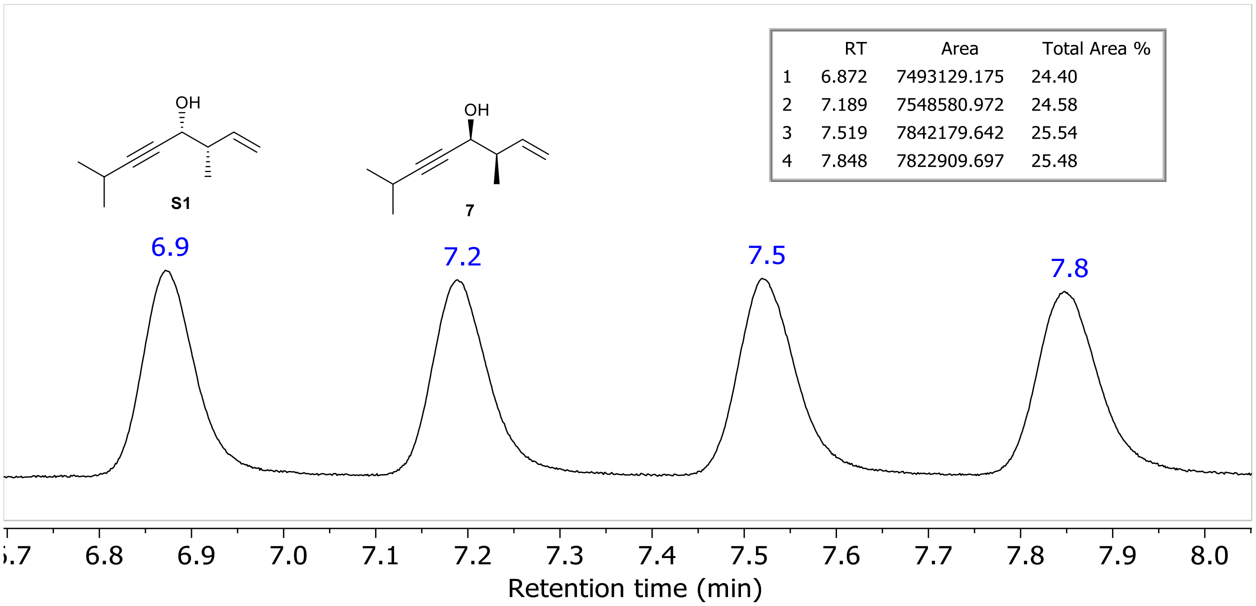
1



221.69
77.16 CDCl3
47.51
39.79
33.07
29.78
25.65
20.16
19.86
18.86
18.37
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

V. CHIRAL GC SPECTRA OF COMPOUNDS

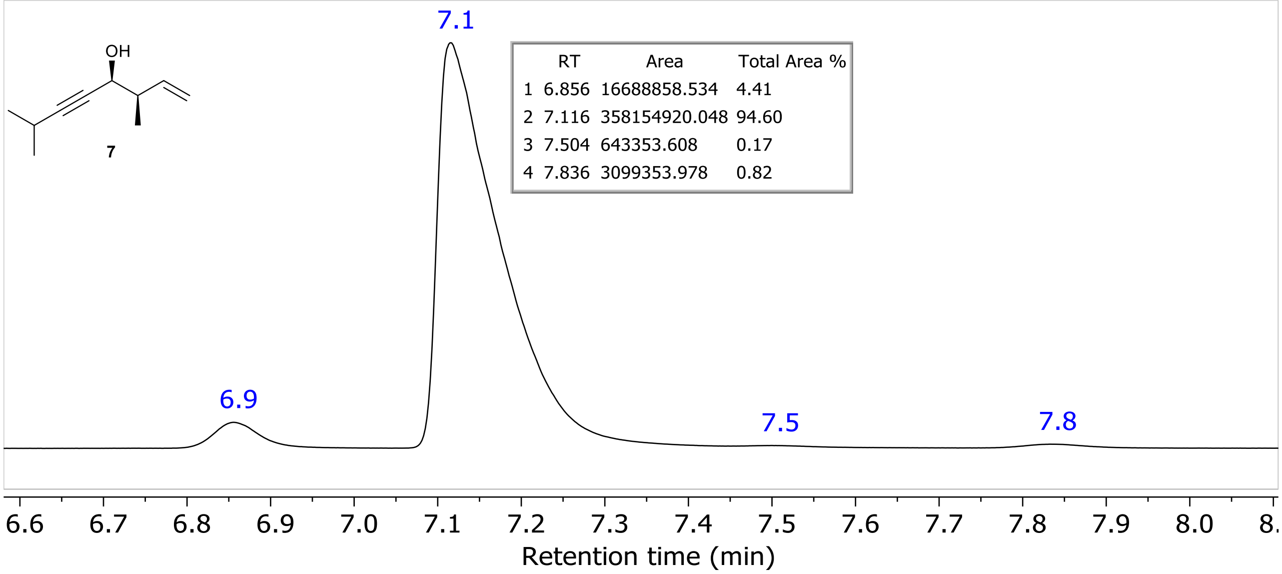
Racemic alcohol



	RT	Area	Total Area %
1	6.872	7493129.175	24.40
2	7.189	7548580.972	24.58
3	7.519	7842179.642	25.54
4	7.848	7822909.697	25.48

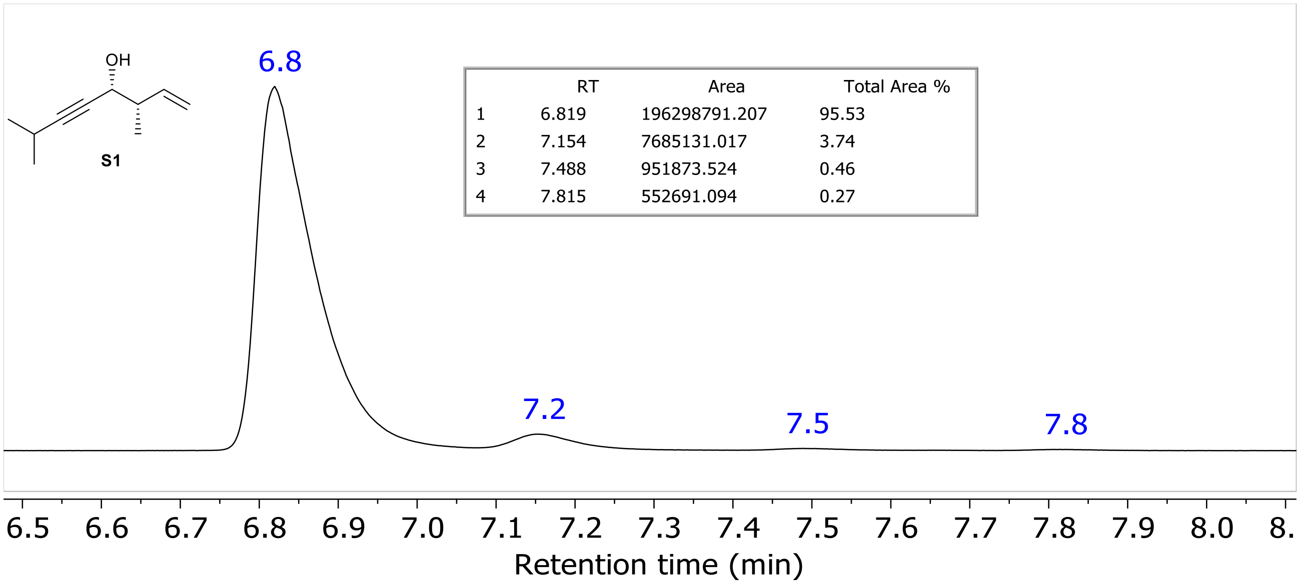
The unlabeled peaks at 7.5 and 7.8 min are the *trans*-isomers where the absolute configuration of each peak was not determined.

Enantioenriched alcohol (–)-7



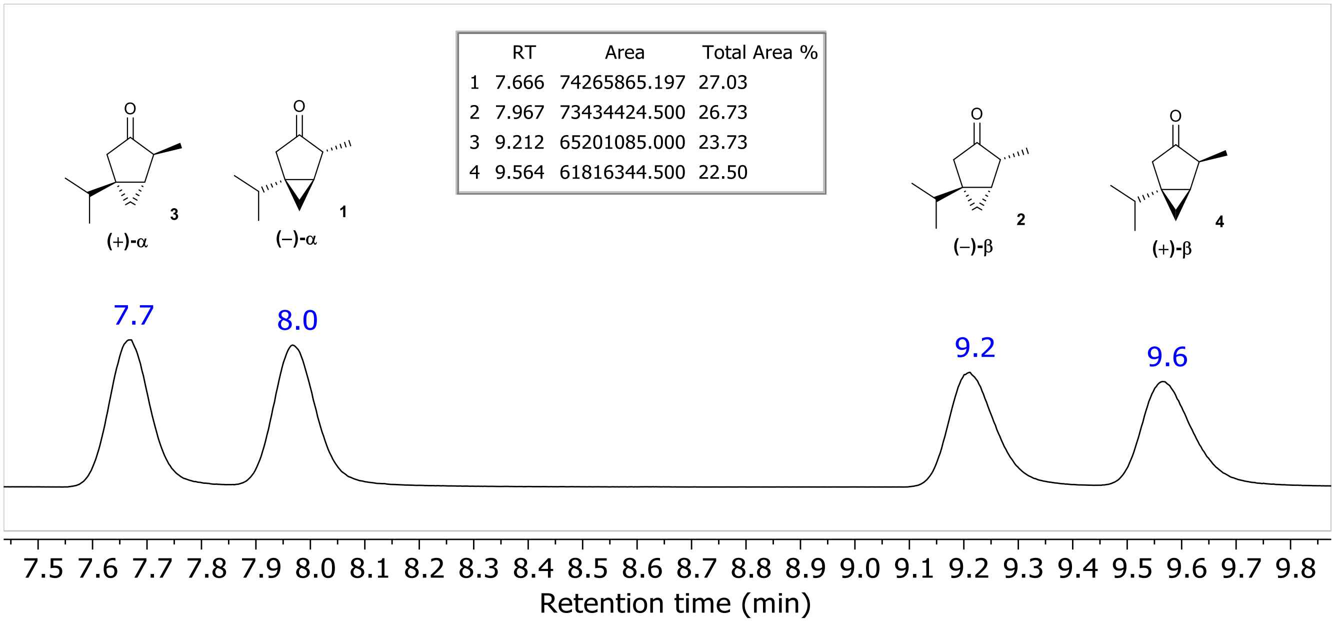
	RT	Area	Total Area %
1	6.856	16688858.534	4.41
2	7.116	358154920.048	94.60
3	7.504	643353.608	0.17
4	7.836	3099353.978	0.82

Enantioenriched alcohol (+)-S1



	RT	Area	Total Area %
1	6.819	196298791.207	95.53
2	7.154	7685131.017	3.74
3	7.488	951873.524	0.46
4	7.815	552691.094	0.27

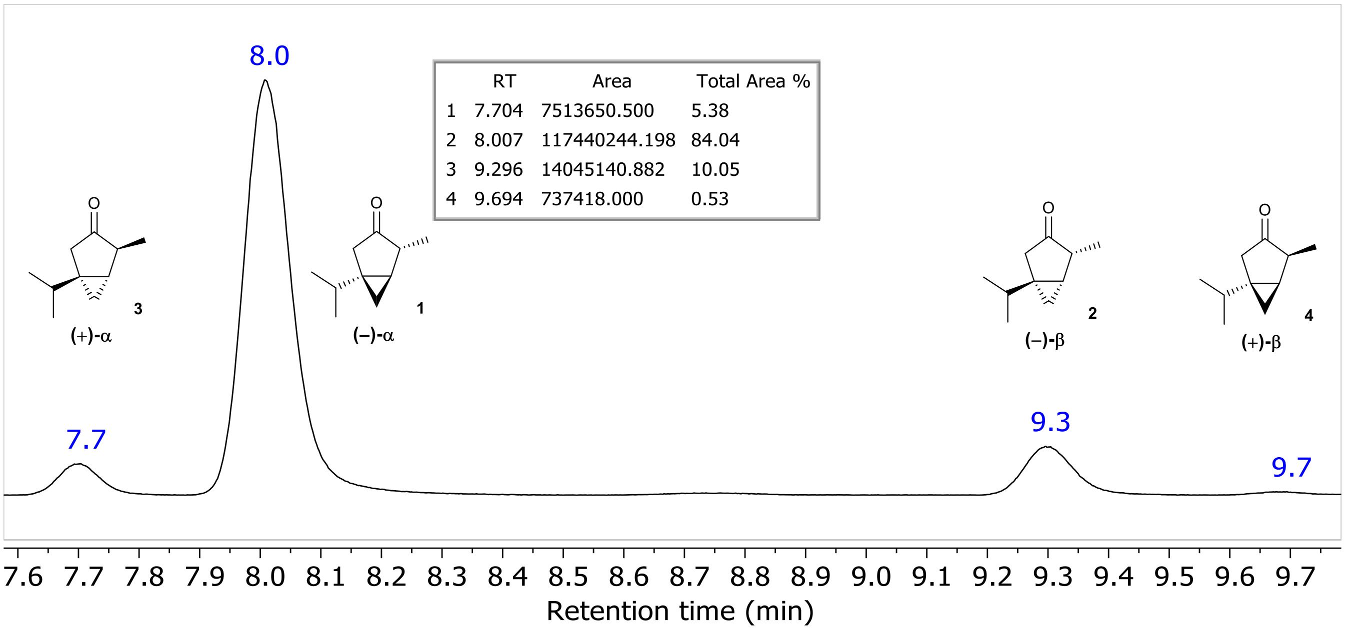
Racemic Thujone



	RT	Area	Total Area %
1	7.666	74265865.197	27.03
2	7.967	73434424.500	26.73
3	9.212	65201085.000	23.73
4	9.564	61816344.500	22.50

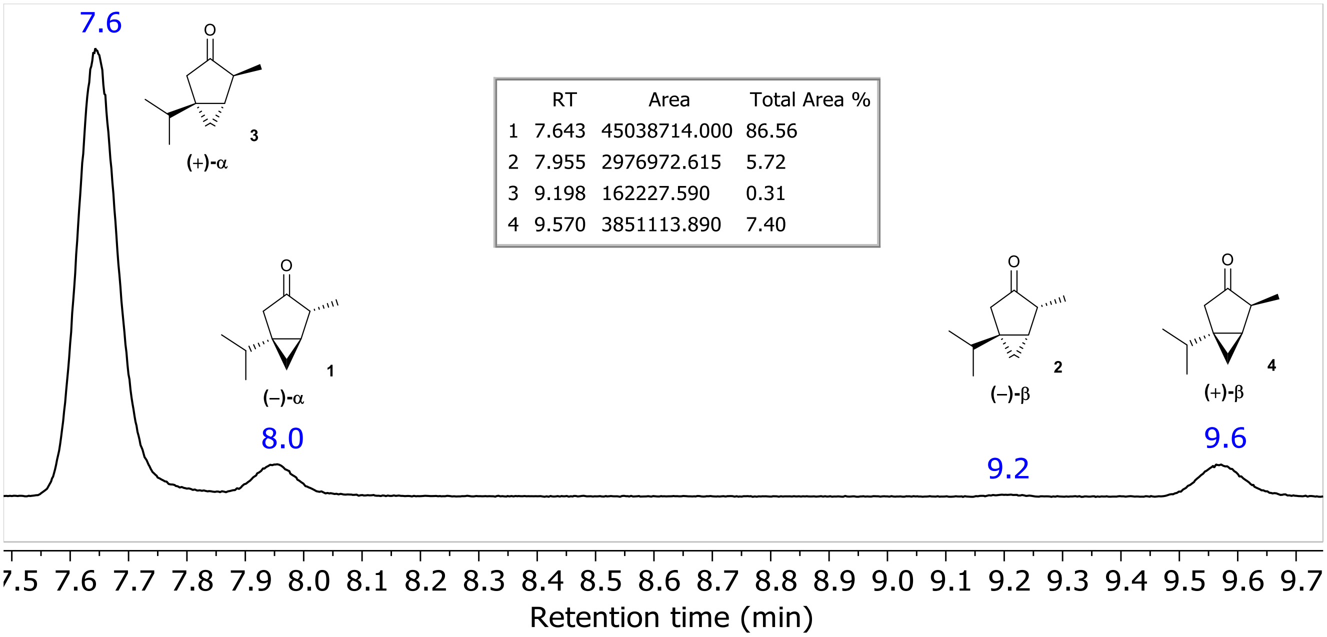
The identity of each peak was previously determined.[1b]

(–)-α-Thujone



	RT	Area	Total Area %
1	7.704	7513650.500	5.38
2	8.007	117440244.198	84.04
3	9.296	14045140.882	10.05
4	9.694	737418.000	0.53

(+)-α-Thujone



	RT	Area	Total Area %
1	7.643	45038714.000	86.56
2	7.955	2976972.615	5.72
3	9.198	162227.590	0.31
4	9.570	3851113.890	7.40