Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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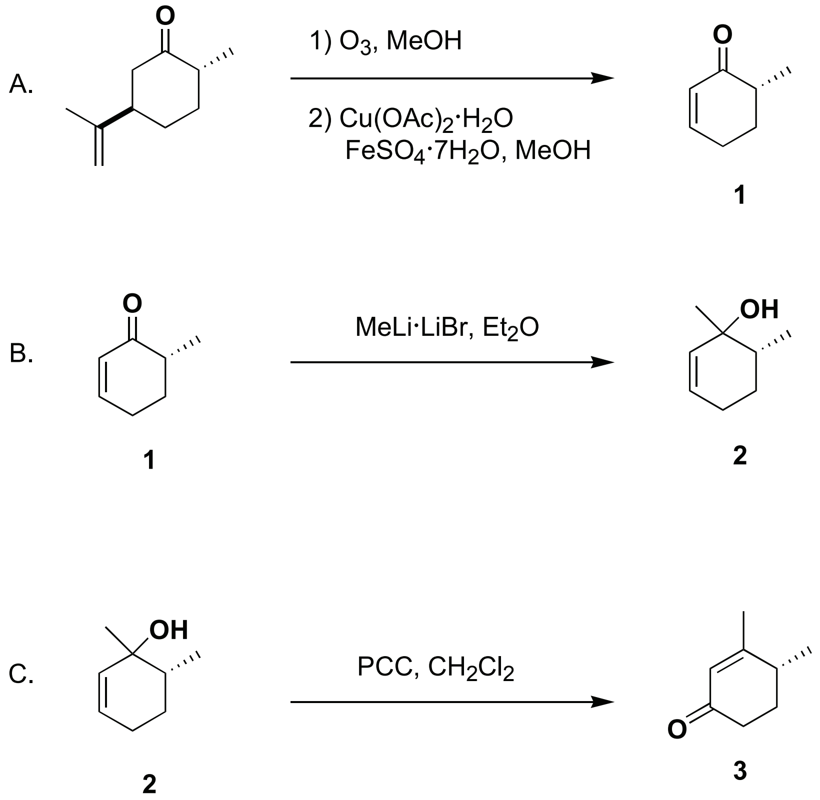
(*R*)-(+)-3,4-DIMETHYLCYCLOHEX-2-EN-1-ONE
((*R*)-(+)-3,4-Dimethyl-2-cyclohexen-1-one)



Submitted by James D. White, Uwe M. Grether, and Chang-Sun Lee.[1]
Checked by Rick L. Danheiser and Charnsak Thongsornkleeb.

1. Procedure

Caution! Ozone is extremely toxic and can react explosively with certain oxidizable substances. Ozone also reacts with some compounds to form explosive and shock-sensitive products. Ozone should only be handled by individuals trained in its proper and safe use and all operations should be carried out in a well-ventilated fume hood behind a protective safety shield. [Note added September 2009].

A. (R)-(+)-6-Methylcyclohex-2-en-1-one (**1**). A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, thermometer, and a disposable pipette attached via tygon tubing to an ozone generator (Note 1). The flask is charged with (2*R*,5*R*)-(+)-*trans*-dihydrocarvone (10.4 g, 68 mmol) (Note 2) and 200 mL of methanol (Note 3). The solution is cooled to –30 °C in a dry ice-acetone bath and ozone is passed through the solution until TLC analysis shows that no dihydrocarvone remains (Note 4).

The reaction mixture is flushed with argon for 7 min and then allowed to warm to –20 °C. Copper(II) acetate monohydrate (27.2 g,136 mmol) (Note 5) is added in one portion. The resulting suspension is stirred for 15 min, and ferrous sulfate heptahydrate (22.7 g, 82 mmol) (Note 5) is added in 1 g portions over a 20 min period. The dark green suspension is stirred at –20 °C for 7 hr and then at ambient temperature for 3 hr. Water (200 mL) is added and the resulting mixture is extracted with six 125-mL portions of diethyl ether. The combined organic layers are washed with 100 mL of saturated aq sodium hydrogen carbonate (Note 6) and 50 mL of brine, and dried over anhydrous magnesium sulfate. The solvent is removed by rotary evaporation at ambient temperature (50 mmHg) and the residue is purified by column chromatography on 350 g of silica (elution with 6:1 to 4:1 pentane/diethyl ether) (Notes 7, 8) to give 4.26 g (57%) of (*R*)-(+)-6-methylcyclohex-2-en-1-one as a colorless oil (Notes 9, 10).

B. (6R)-(+)-1,6-Dimethylcyclohex-2-en-1-ol (**2**). A flame-dried, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, rubber septum, glass stopper, and an argon inlet. The flask is charged with a solution of (*R*)-(+)-6-methylcyclohex-2-en-1-one (4.16 g, 38 mmol) in 70 mL of diethyl ether (Note 3) and cooled at -78 ºC. A solution of methyllithium-lithium bromide complex in diethyl ether (27.4 mL, 1.5M, 41 mmol) (Note 5) is then added via syringe during 20 min. The cooling bath is removed and the resulting solution is stirred for 3 hr at ambient temperature. After 3 hr, the reaction mixture is cooled at 0 ºC and 40 mL of water is very slowly added to the yellow solution (Note 11). The aqueous phase is separated and extracted with two 40-mL portions of diethyl ether. The combined organic layers are washed with 40 mL of water, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation at room temperature (50 mmHg) to afford 4.79 g (100%) of crude (6*R*)-(+)-1,6-dimethylcyclohex-2-en-1-ol (**2**) as a yellow oil which is used in the next step without further purification (Note 12).

C. (R)-(+)-3,4-Dimethylcyclohex-2-en-1-one (**3**). A flame-dried, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, rubber septum, glass stopper, and an argon inlet. The flask is charged with pyridinium chlorochromate (16.4 g, 76 mmol) (Note 5) and 75 mL of dichloromethane (Note 3). A solution of crude (6*R*)-(+)-1,6-dimethylcyclohex-2-en-1-ol (4.79 g, 38 mmol)prepared as described above in 25 mL of dichloromethane (Note 3) is transferred into the reaction mixture via cannula over 5 min, and the resulting mixture is stirred at ambient temperature for 3 hr. The reaction mixture is then diluted with 120 mL of diethyl ether (Note 7), the solution is decanted, and the remaining black resinous polymer is thoroughly washed with three 50-mL portions of diethyl ether. The combined dark brown/black ether solution is washed successively with two 100-mL portions of 5% aqueous sodium hydroxide solution, 100 mL of 5% aqueous hydrochloric acid, and two 50-mL portions of saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation at room temperature (50 mmHg) to give 4.42 g of the crude product as a yellow oil. Purification by column chromatography (Note 13) yields 3.71-3.85 g (79-82% overall from **1**) of (*R*)-(+)-3,4-dimethylcyclohex-2-en-1-one (**3**) as a colorless oil (Note 14).[4]

2. Notes

1. The checkers used a Welsbach model T-816 ozone generator and introduced the ozone via a disposable pipette in an open neck of the flask fitted with a reducing adapter. The submitters vented the reaction flask through a trap filled with 40% aqueous sodium bisulfite solution.

2. (+)-Dihydrocarvone was purchased from Aldrich Chemical Company, Inc. as a ca. 80:20 mixture of *(*2*R,*5*R*)-(+)-*trans*-dihydrocarvone and (2*S*,5*R*)-(+)-*cis*-dihydrocarvone. Prior to use, this material (23 ml, 21 g, 136 mmol) was purified by column chromatography on 450 g of silica (elution with 8:1 to 6:1 hexane/diethyl ether) to afford 13.9 g (91 mmol) of pure (2*R*,5*R*)-(+)-*trans*-dihydrocarvone.

3. The submitters purchased absolute methanol from J. T. Baker, Inc. and used it without further purification. Anhydrous methanol was purchased by the checkers from Mallinckrodt Chemical Company, Inc., and used as received. The submitters freshly distilled dichloromethane from calcium hydride under argon before use and distilled diethyl ether from sodium and benzophenone under argon. Dichloromethane and diethyl ether were purified by the checkers by pressure filtration through activated alumina .

4. TLC analysis is carried out on silica gel (elution with 50% ethyl acetate-hexane, visualization with $KMnO_4$). Dihydrocarvone exhibits R_f = 0.67. The reaction mixture is a pale blue color after ozonolysis is complete.

5. Copper(ll) acetate monohydrate (≥ 99.0%) and ferrous sulfate heptahydrate (≥ 99.5%) were purchased from Fluka Chemical Company,

Inc., and were used without further purification. Methyllithium, as a complex with lithium bromide, and pyridinium chlorochromate (98%) were purchased from Aldrich Chemical Company, Inc., and were used without further purification.

6. Caution: a large amount of carbon dioxide is liberated!

7. The crude product consists of a mixture of αβ and βγ enone isomers in a ratio of 74:26. The isomers have R_f values of 0.60 and 0.70, respectively (silica gel TLC, elution with 50% ethyl acetate-hexane and visualization with $KMnO_4$). For purification, the product is charged on a column (24 x 50 cm) of 350 g of silica gel (Sorbent Technologies, 32-63 μm) and eluted with 500 mL of 6:1 pentane-ethyl ether. At that point, fraction collection (30-mL fractions) is begun, and elution is continued with 1500 mL of 6:1 pentane-ethyl ether, 1500 mL of 5:1 pentane-ether, and then 1500 mL of 4:1 pentane-ether. The desired product is obtained in fractions 63-116 and the corresponding β,γ-unsaturated isomer is obtained in fractions 38-55 (17% yield). Pentane, purchased from J.T. Baker, and diethyl ether, purchased from Mallinckrodt Chemical Company, Inc. (certified ACS), were used without further purification.

8. The fractions containing the product were concentrated by careful fractional distillation at room temperature and atmospheric pressure through a 10-inch Vigreux column to a volume of ca. 40-50 mL. This step is necessary to avoid loss of the relatively volatile product. Further concentration was conducted by rotary evaporation at room temperature at 50 mmHg.

9. In other runs the product was obtained in 48-63% yield.

10. (*R*)-(+)-6-Methylcyclohex-2-en-1-one has the following physical properties: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, *J* = 7 Hz, 3 H), 1.70-1.79 (m, 1 H), 2.05-2.11 (m, 1 H), 2.37-2.45 (m, 3 H), 5.99 (td, *J* = 10 Hz, 3 Hz, 1 H), 6.92-6.96 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.2, 25.7, 31.0, 41.8, 129.6, 149.9, 202.6; IR (neat) cm^{-1}: 3033, 2964, 2932, 1682, 1389, 1215; $[\alpha]_D^{20}$ + 83 (*c* 1.31, MeOH); + 86 (*c* 1.46, $CHCl_3$); lit[2] + 91 (*c* 1.1 $CHCl_3$); lit[3] + 70 (*c* 3.0, $CHCl_3$)); Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.13; H, 9.13. Enantiomeric excess of the product was determined by the Submitters to be >99:1 (OD column, 92:8 Hexane/*i*-PrOH, 0.6 mL/min).

11. Water is carefully added dropwise from a disposable pipette. Addition of the first ca. 5 mL is accompanied by violent bubbling.

12. (6*R*)-(+)-1,6-Dimethylcyclohex-2-en-1-ol (**2**) is a pungent liquid. ^{1}H NMR analysis of the crude product indicated that it consists of a 67:33 mixture of diastereomers (the configuration of the isomers was not assigned.)

13. The product is charged on a column (19 x 43 cm) of 150 g of silica gel (Sorbent Technologies, 32-63 μm) and eluted with 300 mL of 6:1 pentane-ether. At that point, fraction collection (30-mL fractions) is begun, and elution is continued with 1200 mL of 6:1 pentane-ether, 500 mL of 4:1 pentane-ether, 500 mL of 2:1 pentane-ether, and then 700 mL of 1:1 pentane-ether. The desired product is obtained in fractions 38-72 and has R_f = 0.47 (silica gel TLC, elution with 50% ethyl acetate-hexane, visualization with *p*-anisaldehyde).

14. The product has the following physical properties: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (d, *J* = 7 Hz, 3 H), 1.73-1.80 (m, 1 H), 1.96 (s, 3 H), 2.09-2.15 (m, 1 H), 2.32 (ddd, *J* = 5, 8, 17 Hz, 1 H), 2.38-2.50 (m, 2 H), 5.83 (app s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.9, 22.9, 30.5, 34.5, 34.7, 126.5, 166.8, 199.8; IR (neat) cm^{-1}: 3028, 2966, 2877, 1671, 1626, 1378, 1255; $[\alpha]_D^{20}$ + 108 (*c* 1.28, $CHCl_3$; lit[4] + 111 (*c* 1.06)). The purity of the product was determined to be 95% by GC analysis. The enantiomeric excess of the product was determined by the submitters to be 100% (OD column, 95:5 hexane/*i*-PrOH, 0.6 mL/min; OJ Column, 97:3 Hexane/*i*-PrOH, 0.6 mL/min).

Safety and Waste Disposal Information

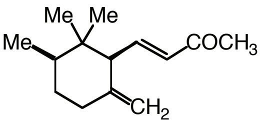
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

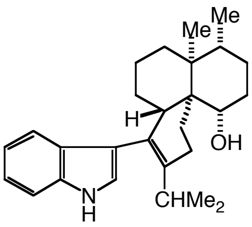
The method described for the preparation of (*R*)-(+)-6-methylcyclohex-2-en-1-one (**1**) was first reported by Schreiber[5] and was improved by Solladié and Hutt.[3] An alternative approach to (*R*)-(+)-6-methylcyclohex-2-en-1-one (**1**) commences from cyclohex-2-en-1-one using Enders' methodology.[2,6] This route delivers **1** via a four-step sequence and in an overall yield of 46%, including two steps for attachment and removal of the chiral auxiliary, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP).[6] Since (+)-dihydrocarvone is inexpensive and the *trans*- and *cis*- isomers are conveniently separated by either column chromatography on silica[7] or on 100 g scale by fractional crystallization of the corresponding oximes,[8] the route to **1** from (+)-dihydrocarvone is superior for the large scale preparation of (*R*)-(+)-6-methylcyclohex-2-en-1-one (**1**).

The transformation of (*R*)-(+)-6-methylcyclohex-2-en-1-one (**1**) to (*R*)-(+)-3,4-dimethylcyclohex-2-en-1-one (**3**) via (6*R*)-(+)-1,6-dimethylcyclohex-2-en-1-ol (**2**) was first reported by Tokoroyama *et al*[2] and is based upon a procedure by Dauben and Michno.[9] The optical purity of **3** derived from the Tokoroyama synthesis ($[\alpha]_D^{20}$ + 111 (c 1.06, $CHCl_3$))[2] is comparable to that of the present route starting from (+)-dihydrocarvone ($[\alpha]_D^{20}$ + 104 (c 1.04, $CHCl_3$)). Alternatively, **3** can be prepared via a five-step sequence starting from comparatively expensive (*R*)-(+)-pulegone.[4,10-12]

(*R*)-(+)-3,4-Dimethylcyclohex-2-en-1-one (**3**) is a valuable starting material for the asymmetric synthesis of a variety of natural products and their analogues, many of which possess important properties. Examples include irones, e.g. (2*R*,6*S*)-(+)-*cis*-γ-irone (**4**),[7] which are constituents of essential oils that are highly prized ingredients of certain perfumes; the epiaflavinine derivative 3-demethylaflavinine (**5**);[12] the sponge metabolite (+)-agelasimine A (**6**);[8] the clerodane diterpenoid (-)-methyl kolavenate (**7**);[2] and the antiviral antibiotic (-)-ascochlorin (**8**).[4]



(2*R*,6*S*)-(+)-cis-γ-Irone (**4**)



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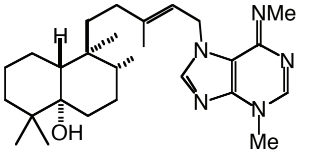
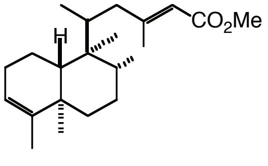
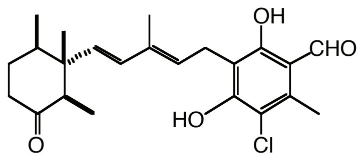


(+)-Agelasimine A (**6**)



(-)-Methyl Kolavenate (**7**)



(-)-Ascochlorin (**8**)

1. Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(2*R*,5*R*)-(+)-*trans*-dihydrocarvone: (2*R*,5*R*)-2-Methyl-5-(1-methylethenyl)-cyclohexanone; (5948-04-9)

Copper(II) acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate; (6046-93-1)

Ferrous sulfate heptahydrate: Sulfuric acid, iron(2+) salt (1:1), heptahydrate; (7782-63-0)

(*R*)-(+)-6-Methylcyclohex-2-en-1-one: (6*R*)-6-Methyl-2-cyclohexen-1-one; (62392-84-1)

Methyllithium-lithium bromide; (332360-06-2)

(6*R*)-(+)-1,6-Dimethylcyclohex-2-en-1-ol: *trans*-1,6-Dimethyl-2-Cyclohexen-1-ol; (114644-29-0), *cis*-1,6-Dimethyl-2-Cyclohexen-1-ol; (114644-28-9)

Pyridinium chlorochromate; (26299-14-9)

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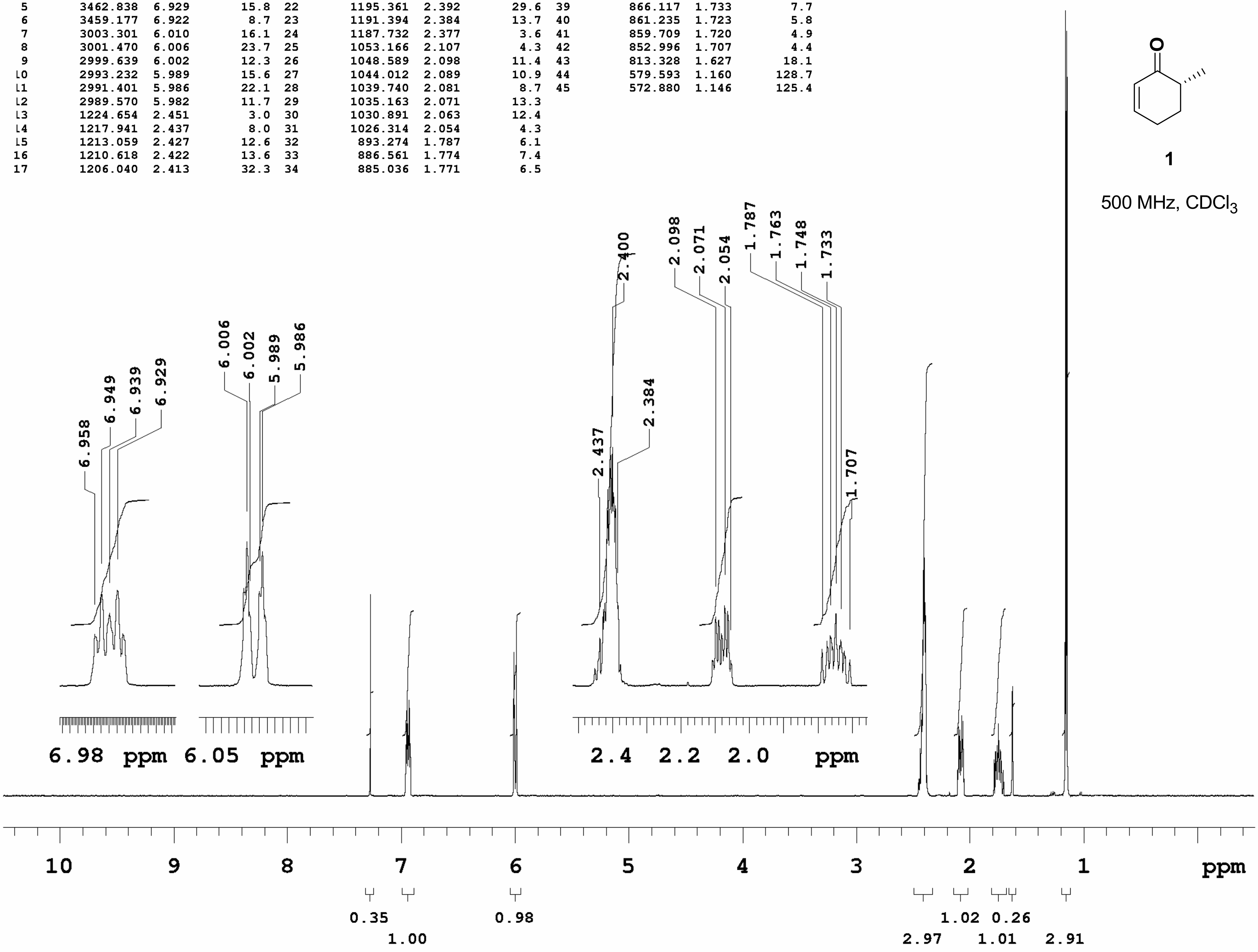
3	3472.908	6.949	15.2	20	1199.327	2.400	39.1	37	873.440	1.748	12.0
4	3467.721	6.939	12.1	21	1197.497	2.396	31.7	38	867.948	1.737	6.8
5	3462.838	6.929	15.8	22	1195.361	2.392	29.6	39	866.117	1.733	7.7
6	3459.177	6.922	8.7	23	1191.394	2.384	13.7	40	861.235	1.723	5.8
7	3003.301	6.010	16.1	24	1187.732	2.377	3.6	41	859.709	1.720	4.9
8	3001.470	6.006	23.7	25	1053.166	2.107	4.3	42	852.996	1.707	4.4
9	2999.639	6.002	12.3	26	1048.589	2.098	11.4	43	813.328	1.627	18.1
10	2993.232	5.989	15.6	27	1044.012	2.089	10.9	44	579.593	1.160	128.7
11	2991.401	5.986	22.1	28	1039.740	2.081	8.7	45	572.880	1.146	125.4
12	2989.570	5.982	11.7	29	1035.163	2.071	13.3				
13	1224.654	2.451	3.0	30	1030.891	2.063	12.4				
14	1217.941	2.437	8.0	31	1026.314	2.054	4.3				
15	1213.059	2.427	12.6	32	893.274	1.787	6.1				
16	1210.618	2.422	13.6	33	886.561	1.774	7.4				
17	1206.040	2.413	32.3	34	885.036	1.771	6.5				



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  3        1249.370  2.500        6.0  20        1156.608  2.314         6.3  37         887.477  1.776          7.1
  4        1244.793  2.491        6.3  21        1151.726  2.305         7.3  38         885.036  1.771         10.3
  5        1239.911  2.481        6.8  22        1148.980  2.299         7.0  39         879.848  1.761         10.3
  6        1235.029  2.471        8.4  23        1144.097  2.289         7.1  40         877.102  1.755          5.7
  7        1232.587  2.466       10.0  24        1076.357  2.154         4.7  41         874.051  1.749          5.8
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  9        1222.823  2.447       11.7  26        1066.593  2.134         8.2  43         866.422  1.734          4.0
 10        1217.941  2.437       12.1  27        1062.015  2.125         9.5  44         823.093  1.647          8.3
 11        1214.584  2.430        5.4  28        1058.049  2.117        11.2  45         603.394  1.207        101.0
 12        1207.871  2.417        9.6  29        1053.166  2.107         9.2  46         596.375  1.193        102.1
 13        1201.769  2.405       12.1  30        1048.589  2.098         8.7  47         587.221  1.175          2.4
 14        1195.361  2.392        5.8  31        1043.707  2.088         4.2
 15        1188.953  2.379        1.6  32         978.408  1.958       128.7
 16        1173.696  2.349        9.5  33         898.462  1.798         4.8
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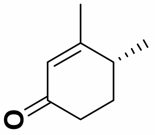

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