Do Shapeshifters Racemize? Synthesis and Study of a Chiral Bullvalene

Maggie He and Jeffrey W. Bode*

Laboratorium für Organische Chemie, ETH-Zürich

8093 Zürich, Switzerland

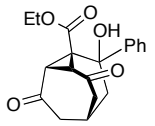
bode@org.chem.ethz.ch

Contents

I. General Procedures

All reactions were carried out in dried glassware and under an atmosphere of dry N_2. CH_2Cl_2 was distilled over CaH_2. THF was distilled over Na/benzophenone. Pyridine was distilled over KOH. *N,N*-Diisopropylethylamine was distilled over CaH_2. Isobutyl chloroformate was distilled over $CaCl_2$. Flash column chromatography was performed on EMD silica gel 60 (230-400 Mesh) using a force flow of 0.5-1.0 bar. ^1H, ^{13}C and 2D-NMR spectra were measured on Bruker 400, 500 or 600 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported as Hertz (Hz). NMR splitting parameter are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. Infrared Spectra were recorded on a JASCO FT/IR-4100 spectrometer and are reported in wavenumber (cm^{-1}). Optical rotations were measured in a Jasco P-2000 polarimeter with a 100 mm path length cell operating at the sodium D line and recorded as $[\alpha]^D_{25}$ = (concentration (g/100 mL), solvent). CD spectra were recorded with a Jasco J-715 spectrometer with a 1.0 mm path length cell. Prior to each use, the CD spectrometer was purged with nitrogen and lamp was allowed to warm up for 1 h. Spectra were collected at 25 °C with standard sensitivity (100 mdeg), 1 nm data pitch, continuous scanning mode, 200 nm/sec scanning speed, 5 nm bandwidth and 5 accumulations.

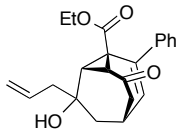
II. Experimental Procedures and Spectral Data



S1

Tertiary alcohol S1. A solution of triketone **2** (500 mg, 2.00 mmol) in CH_2Cl_2 (200 mL) was cooled −78 °C. After 15 min, a solution of phenylmagnesium bromide (2.8 M in diethyl ether, 1.8 mL, 5.0 mmol) was added to the cooled triketone solution. After 65 min, the reaction was quenched with 50 mL saturated NH_4Cl(aq) at −78 °C. The quenched reaction mixture was diluted with 75 mL water, extracted with CH_2Cl_2 (90 mL x 3), washed with brine and dried over

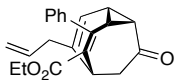
Na_2SO_4. The solvent was removed under reduced pressure. Purification by column chromatography (EtOAc:Hex 1:2) furnished **S1** as the major phenylation product as a white solid (402 mg, 65%). Also a minor regioisomeric phenylation product (99 mg, 16%) and starting triketone **2** (94.5 mg, 19%) were recovered. Major phenylation product **S1**: mp: 142-143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.37 (m, 2H), 7.31 (t, 2H, *J* = 7.5 Hz), 7.23-7.20 (m, 1H), 4.19 (d, 1H, *J* = 2.5 Hz), 3.89-3.82 (m, 2H), 3.57-3.54 (m, 2H), 2.92 (dd, 1H, *J* = 7.0 Hz, *J* = 17.0 Hz), 2.71 (dd, 1H, *J* = 5.5 Hz, *J* = 18.5 Hz), 2.58 (d, 1H, *J* = 17.0 Hz), 2.44 (d, 1H, *J* = 9.5 Hz), 2.40-2.32 (m, 2H), 1.80 (d, 1H, *J* = 14.5 Hz), 0.83 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.3, 204.1, 169.9, 149.1, 128.8, 127.5, 123.9, 79.4, 62.6, 50.0, 48.0, 46.2, 45.5, 43.2, 40.9, 23.8, 13.5. IR (thin film): ν_{max} = 3506, 3059, 3026, 2981, 2928, 1733, 1687, 1492, 1347, 1296, 1239, 1204 cm^{-1}. HRMS (ESI) calc for $C_{19}H_{20}O_5Na^+$ $[M+Na]^+$ 351.1208, found 351.1203



S2

Monoallylated alcohol S2. *Elimination*: A solution of pyridine (0.27 mL, 3.3 mmol) in CH_2Cl_2 (4.5 mL) was cooled to −78 °C. After 10 min, thionyl chloride (0.21 mL, 2.9 mmol) was added dropwise. After another 10 min, a solution of tertiary alcohol **S1** (157 mg, 0.478 mmol) in CH_2Cl_2 (42 mL) was added slowly at −78 °C. After 1 h, the reaction was quenched with saturated NH_4Cl(aq) (7.5 mL) at −78 °C, diluted with water and immediately extracted with CH_2Cl_2 (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. Because product was unstable to silica gel, it was used without further purification. *Allylation*: The crude product from elimination step was dissolved in CH_2Cl_2 (50 mL) and cooled to −78 °C. After 15 min, a solution of allylmagnesium bromide (1M in diethyl ether, 0.67 mL, 0.48 mmol) was added at −78 °C dropwise. The reaction was quenched after 40 min with saturated NH_4Cl(aq) (15 mL) at −78 °C, diluted with water, and extracted with CH_2Cl_2 (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. Purification by column chromatography (EtOAc:Hex 1:2) provided the desired monoallylation product **S2** (49 mg, 29%) as a white solid. We noted that **S2** is unstable to prolonged exposure to silica gel. mp: 98-100

°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.21 (m, 3H), 7.18-7.16 (m, 2H), 6.07 (d, 1H, *J* = 9.0 Hz), 6.04-5.98 (m, 1H), 5.29 (d, 1H, *J* = 10 Hz), 5.23 (d, 1H, *J* = 17.0 Hz), 3.67-3.64 (m, 2H), 3.04-3.00 (m, 1H), 2.84 (d, 1H, *J* = 10.0 Hz), 2.70-2.59 (m, 3H), 2.43 (dd, 1H, *J* = 8.0 Hz, *J* = 13.5 Hz), 2.33 (d, 1H, *J* = 10.5 Hz), 2.23-2.20 (m, 1H) 2.17-2.16 (m, 1H), 1.95 (dd, 1H, *J* = 4.5 Hz, *J* = 15.0 Hz), 0.67 (t, 3H, 7.0 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.8, 171.1, 143.9, 138.8, 133.4, 132.5, 128.3, 127.0, 126.6, 120.9, 74.9, 61.6, 50.1, 46.8, 42.0, 41.3, 40.6, 39.6, 28.3, 13.3. IR (thin film): ν_{max} = br 3439, 2979, 2926, 1728, 1680, 1256, 1225 cm^{-1}. HRMS (ESI) calc for $C_{22}H_{24}O_4Na^+$ $[M+Na]^+$ 375.1572, found 375.1573.



3

Chiral bullvalone 3. *N,N*-Diisopropylethylamine (23 μL, 1.5 mmol) was dissolved in CH_2Cl_2 (1.3 mL) and cooled to −78°C. After 10 min, thionyl chloride (71 μL, 0.97 mmol) was added dropwise. After another 10 min, a solution of **S2** (49 mg, 0.14 mmol) in CH_2Cl_2 (13.4 mL) was added at −78°C slowly. The reaction mixture was stirred at −78°C for 30 min before pyridine (58 μL, 0.72 mmol) was added dropwise to the reaction. After stirring at −78°C for 1 h, the reaction was quenched with saturated NH_4Cl(aq) (5 mL), diluted with water and extracted with CH_2Cl_2 (20 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. The crude was allowed to stand at rt overnight and purified by column chromatography (PhMe:EtOAc 15:1). Further purification by preparative HPLC on Alltima Silica column (250 × 22 mm ID, IPA:Hex 2:98, 10 mL/min flow rate, 286 nm detection) provided the racemic bullvalone (±)-**3** (13.4 mg, 27%) as a light yellow liquid (Figure **S1**, **A**). Bullvalone **3** was not stable when stored as a neat sample and was frozen in benzene at −20 °C. The enantiomers of **3** were separated by preparative HPLC (Figure **S1**, **B**) on a Chiralpak IA column (250 × 22 mm ID, IPA:Hex 1:20, flow rate 10 mL/min, 286 nm detection, RT = 14.5 – 15.4 min). The ee of the separated enantiomers were checked by analytical HPLC on a Chiralpak IA column (250 × 4.6 mm ID, IPA:Hex 1:20, flow rate 1.0 mL/min, 286 nm detection). First eluted fraction: 98.5% ee, $[\alpha]^{D}_{25}$ = +50.2 (c = 0.775, CH_2Cl_2). Second eluted fraction: 98.5% ee, $[\alpha]^{D}_{25}$ = −51.2 (c = 1.00, CH_2Cl_2). The CD spectra of the two

enantiomers were recorded in CH_2Cl_2 and CH_3CN (Figure **S1**, **C** and **D**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.28 (m, 3H), 7.19-7.18 (m, 2H), 5.83 (d, 1H, J = 7.0 Hz), 5.81-5.74 (m, 1H), 5.15 (d, 1H, J = 17.0 Hz), 5.09 (d, 1H, J = 10.0 Hz), 3.83 (q, 2H, J = 7.5 Hz), 3.27-3.26 (m, 1H), 3.02-2.92 (m, 2H), 2.87 (t, 1H, J = 9.0 Hz), 2.64 (dd, 1H, J = 4.0 Hz, J = 19.0 Hz), 2.55-2.47 (m, 3H), 0.79 (t, 3H, J = 7.0 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.9, 169.5, 144.6, 144.2, 141.3, 135.5, 130.0, 128.4, 127.6, 127.5, 120.3, 117.7, 60.8, 44.9, 43.9, 37.7, 35.7, 30.9, 25.8, 13.6. IR (thin film): ν_{max} = 3055, 2960, 2925, 2854, 1681, 1491, 1443, 1366, 1257 cm^{-1}. HRMS (ESI) calc for $C_{22}H_{23}O_3^+$ $[M+H]^+$ 335.1647, found 335.1630.

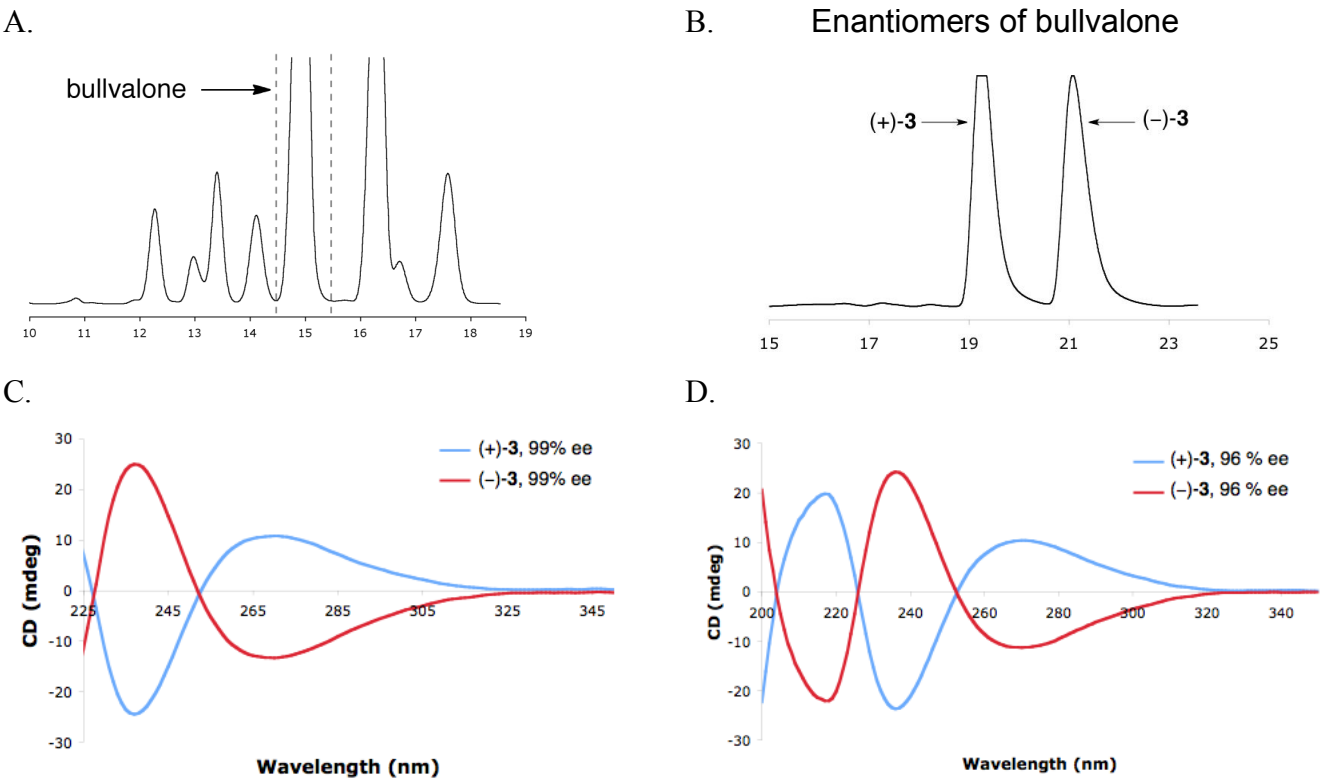
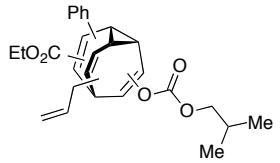


Figure S1. (**A**) Preparative HPLC trace for isolation of racemic bullvalone (±)-**3**. (**B**) Preparative HPLC trace for separation of bullvalone enantiomers on a chiral column. (**C**) CD spectra of (+)-**3** and (–)-**3** in CH_2Cl_2. (**D**) CD Spectra of (+)-**3** and (–)-**3** in CH_3CN.



5

Bullvalene 5. The detailed procedure for preparation of bullvalene **5** is given in the Method section of the paper. Purification of the crude reaction mixture by flash column chromatography (EtOAc:Hex 1:9) obtained bullvalene **5** (6.2 mg, 40%). Also 6 mg (50%) of starting bullvalone (+)-**3** was recovered. ^{13}C NMR (600 MHz, $CDCl_3$)* δ 165.7, 165.4, 153.9, 153.5, 146.2, 145.9, 142.6, 142.6, 142.4, 142.4, 141.7, 141.2, 139.3, 139.3, 138.5, 138.3, 138.1, 138.1, 138.0, 137.9, 136.0, 135.9, 135.8, 135.7, 135.6, 135.5, 135.3, 135.3, 135.2, 135.1, 135.0, 135.0, 134.9, 134.8, 134.6, 134.2, 131.1, 130.6, 129.0, 128.9, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.2, 127.2, 127.1, 127.1, 127.1, 126.9, 126.6, 126.4, 126.3, 126.2, 126.2, 126.0, 124.8, 124.6, 124.3, 124.2, 123.9, 123.4, 122.8, 122.5, 122.5, 122.0, 121.8, 121.8, 120.4, 120.0, 119.6, 119.5, 117.9, 117.7, 117.6, 117.5, 117.5, 117.3, 117.2, 117.2, 117.1, 117.1, 117.0, 116.9, 116.8, 116.6, 116.3, 112.8, 111.3, 74.8, 74.8, 74.7, 74.7, 74.7, 74.7, 74.6, 74.6, 65.7, 61.9, 61.9, 61.8, 61.3, 61.2, 61.2, 61.1, 61.1, 61.0, 61.0, 61.0, 45.9, 45.7, 45.4, 45.1, 45.0, 45.0, 44.6, 44.5, 44.4, 43.9, 43.8, 39.2, 38.9, 38.9, 38.8, 37.6, 37.6, 37.5, 37.0, 36.4, 36.3, 32.1, 32.0, 31.8, 31.3, 30.9, 30.7, 30.3, 30.2, 30.1, 30.1, 29.9, 29.8, 29.5, 29.4, 28.9, 28.8, 28.0, 27.9, 27.9, 27.9, 27.8, 26.5, 26.4, 25.9, 23.3, 23.0, 22.8, 22.0, 21.1, 20.4, 19.3, 19.3, 19.2, 19.0, 19.0, 18.9, 18.8, 14.4, 14.3, 13.9. IR (thin film): ν_{max} = 2924, 2853, 1757, 1704, 1635, 1469, 1378, 1237 cm^{-1}. HRMS (ESI) calc for $C_{27}H_{30}O_5Na^+$ $[M+Na]^+$ 457.1991, found 457.1972.

* Only major peaks are reported.

III. Racemization Experiment HPLC and CD Spectra

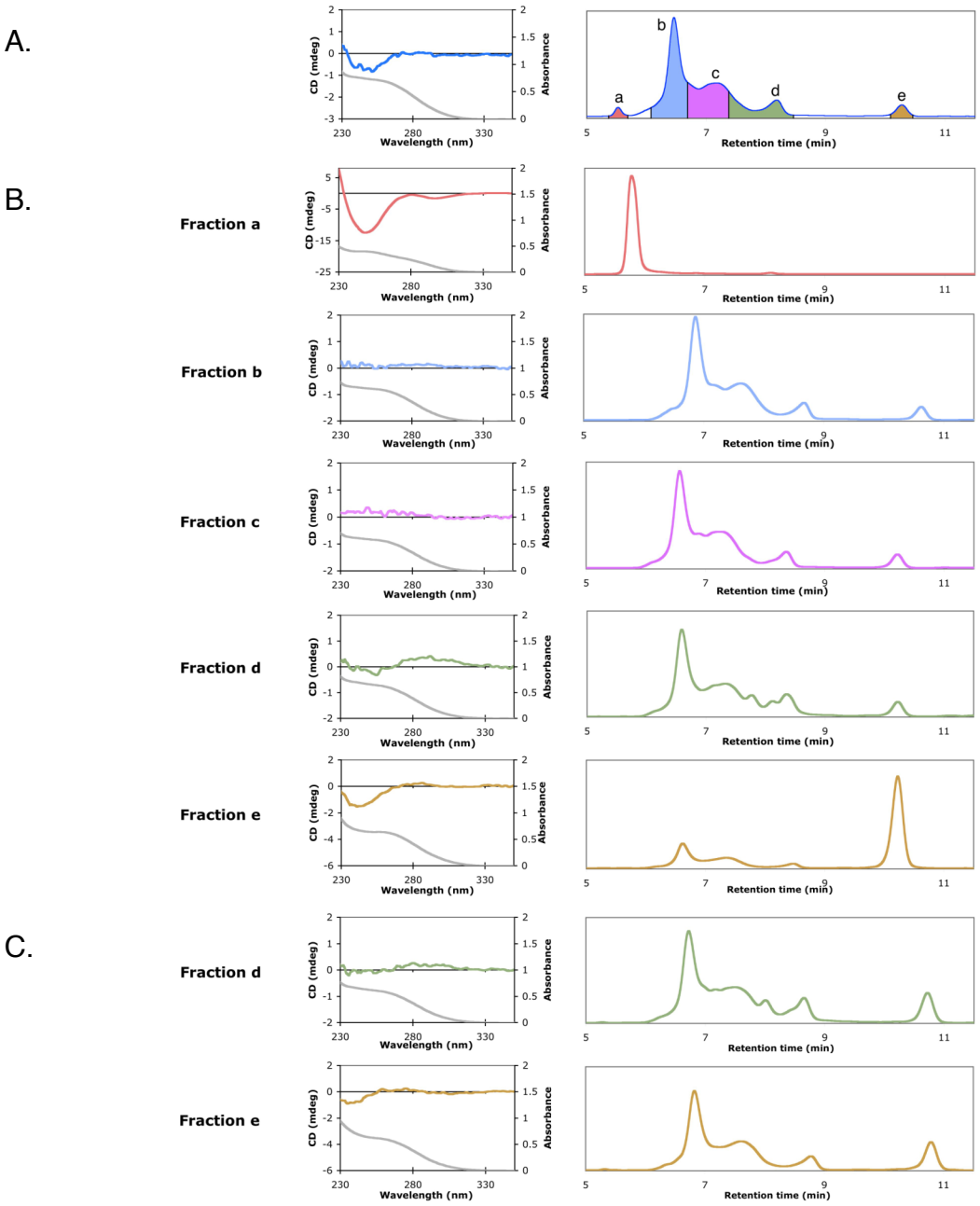


Figure S2. Racemization experiment. (A) CD Spectrum (left) and HPLC trace (right) of column chromatography purified bullvalene **5**. Different colors represent fractions collected from Prep HPLC separation. (B) CD spectra and reinjection HPLC traces of fractions a-e 10-12 h after racemization experiment. (C) CD spectra and reinjection HPLC traces of fractions d and e 24 h and 31 h after racemization experiment respectively. Gray color graph under each CD spectrum are the UV spectra of corresponding CD samples.

IV. Reinjection of Fraction e onto Achiral HPLC Column

Bullvalene **5** was introduced onto an analytical HPLC (Alltima Silica column, EtOAc:Hex 1:9 eluent, detection 286 nm); the last fraction (fraction e, Figure S3) was collected and immediately reinjected onto the same HPLC column. Equilibration of fraction e to the other isomeric bullvalene fractions (fraction b-d, Figure 3 B) was not observed within this short time frame, and thus the appearance of HPLC peaks b-d are not induced by the HPLC column.

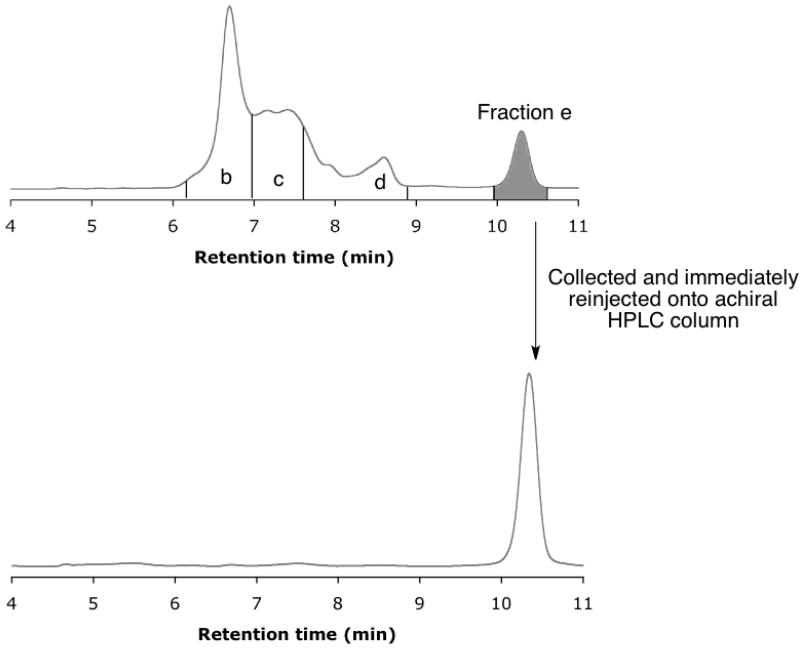


Figure S3. HPLC experiment showing that the equilibration of bullvalene fraction b-d was not induced by HPLC column.

V. Enantioresolution of Fraction e by Chiral HPLC Column

Racemic fraction e that was collected from an achiral HPLC column (Figure S4 A) was immediately reinjected onto a Chiralpak IA HPLC column. Fraction e was resolved into two equal peaks (Figure S4 B). These two peaks were verified to be enantiomers by parallel HPLC-UV (254 nm) and CD (237 nm) detection, i.e., the two peaks observed in the UV channel gave opposite CD signals (Note: there was a ca. 15 second delay the UV detector and CD detector). Consistent with other HPLC experiments on fraction e, these two enantiomeric fraction e peaks slowly reequilibrated to the bullvalene mixture upon collection and reinjection onto an achiral column one day later (Figure S4 C).

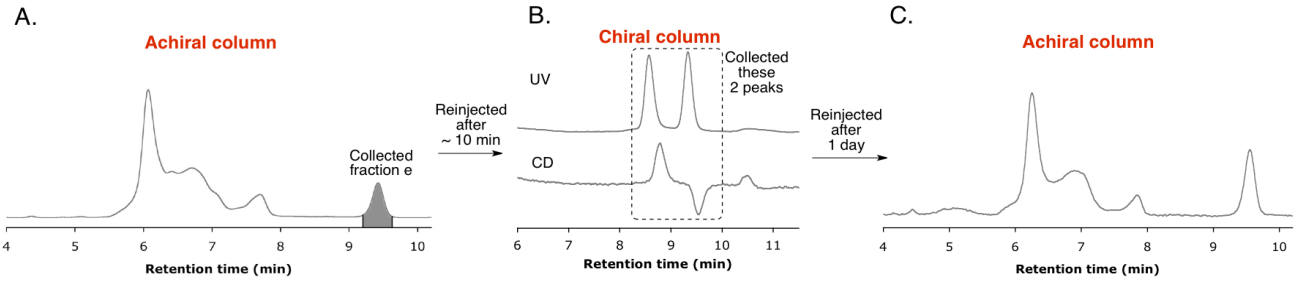


Figure S4. Resolution of fraction e by chiral HPLC revealed two enantiomeric peaks.

VI. Additional Evidence for the Racemization of Fraction e

When we monitored the racemization of fraction e by CD spectroscopy, we observed the CD activity decrease gradually; however, we did not observe a completely flat line in the CD spectrum. Because the source of this very slight CD activity could not be definitively attributed to either incomplete racemization, a chiral impurity, or the detection limits of the CD spectrometer, we sought to further analyze the racemization of fraction e. To this end, chiral bullvalene **5** was freshly synthesized from (–)-**3** and immediately subjected to achiral preparative HPLC separation. Fraction e was collected and immediately reinjected onto a chiral analytical HPLC column. Two enantiomeric peaks which integrated to a 57:43 ratio were observed. These two peaks correspond to an enantioenriched bullvalene, is consistent with the small residual CD signal that is routinely observed upon timely analysis of fraction e. In an analogous experiment, isolated fraction e, which possessed a residual CD signal upon immediate analysis, was re-analyzed by chiral HPLC after a period of 3 weeks of storage at 5 °C and 2 hours at 90 °C. At

this time, the two enantiomeric peaks were observed in an equal 50:50 ratio (Figure S5 B). This data provides further support of the racemization of fraction e.

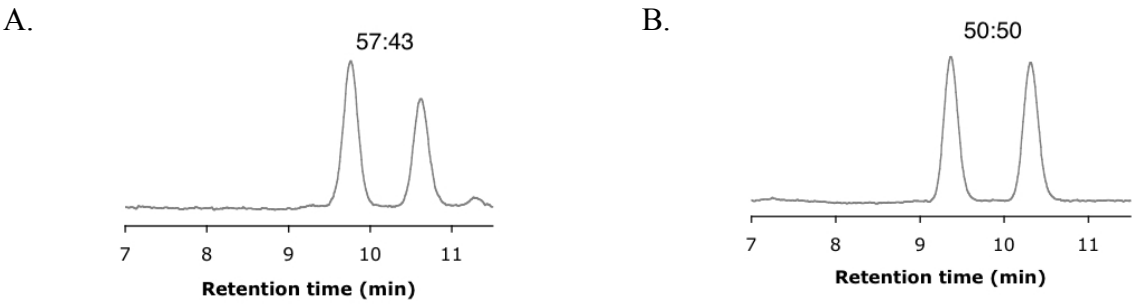


Figure S5. (A) Chiral HPLC trace of enantioenriched fraction e immediately after bullvalene synthesis. (B) Chiral HPLC trace of racemic fraction e upon heating and standing.

VI. Rearrangement Network of Bullvalene 5

A binary tree diagram representing a subset of rearrangements of the initially formed chiral bullvalene from bullvalone **3** is shown in Figure S6. The numbers 3, 6, 9 and 0 are used to represent the attachments of allyl, isobutylcarbonate, phenyl and ethyl ester substituents, respectively. Four generations of rearrangements from the initially formed chiral bullvalene isomer are shown. Degenerate isomers within this subset are shown in colors. The complete reaction graph of bullvalene **5** is much larger (contains 1680 constitutional isomers) and has thousands of additional rearrangements. The fewest number of rearrangements required for the interconversion of any one isomer to its enantiomeric partner is unknown, however, no enantiomeric pairs are found in this subset of five generations.

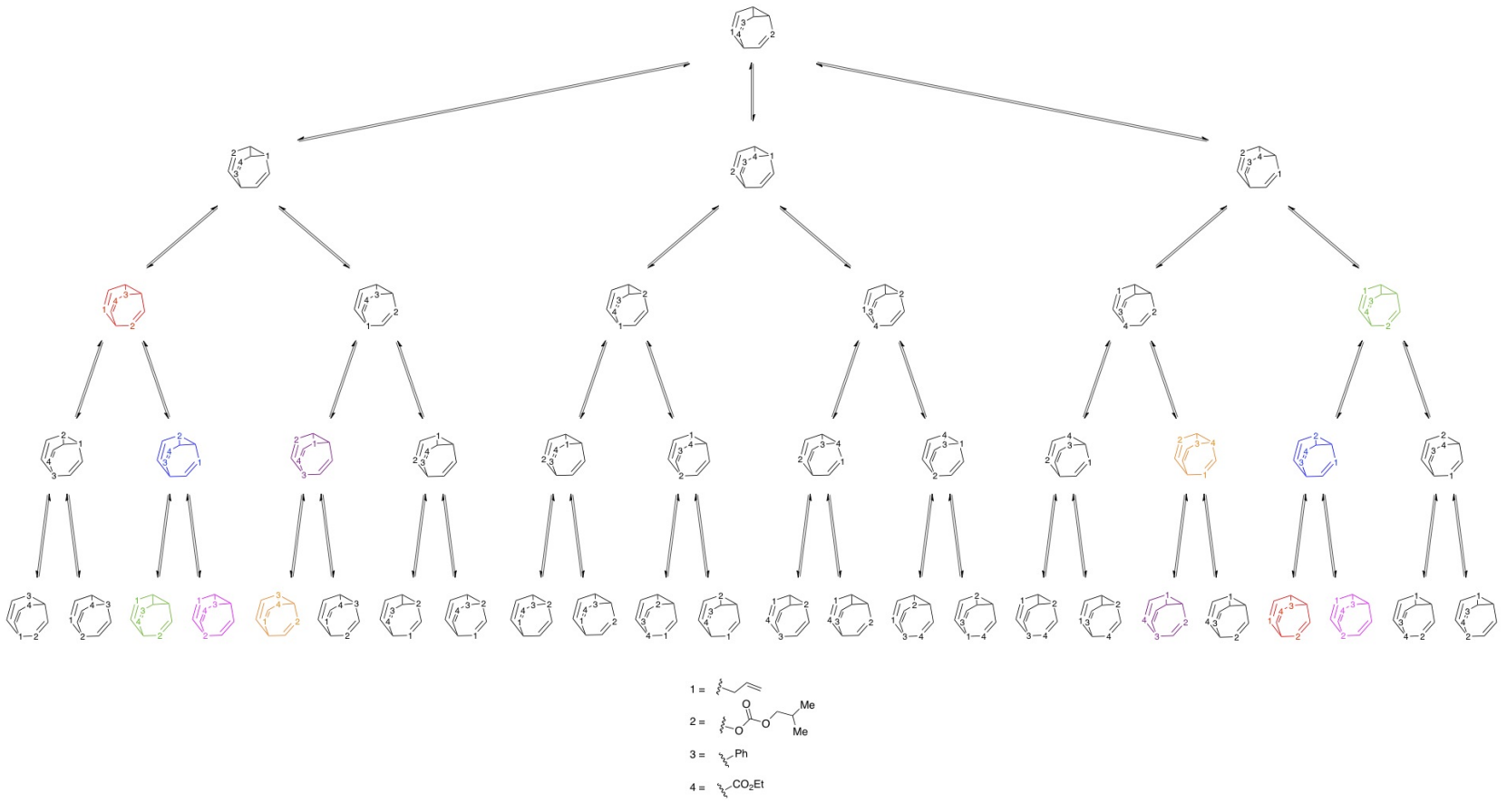


Figure S6. Binary tree diagram representing the first four generations of rearrangements of the initially formed chiral bullvalene **5** from bullvalone **3**

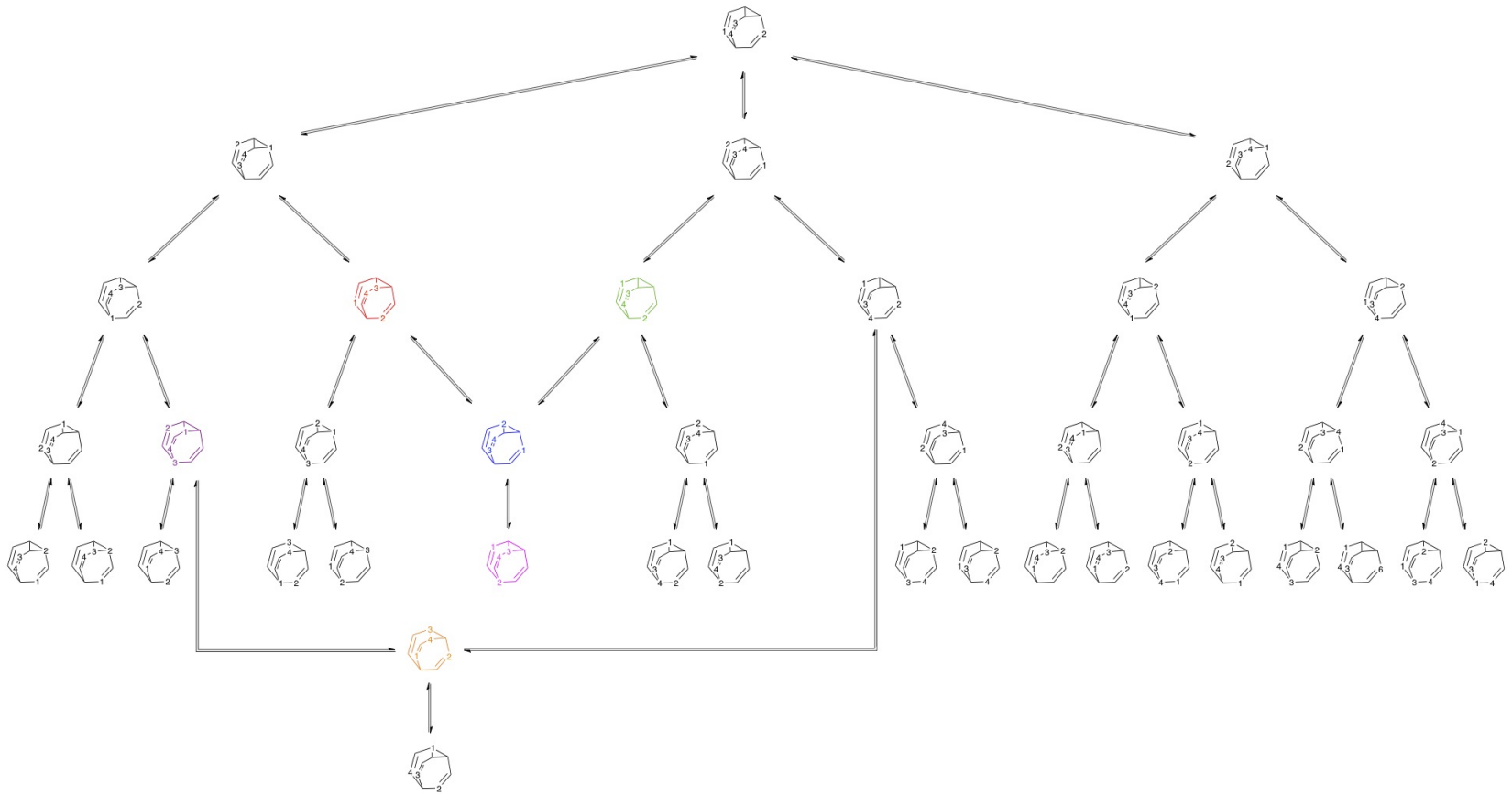


Figure S7. Reorganized binary tree diagram after removal of degenerate isomers.

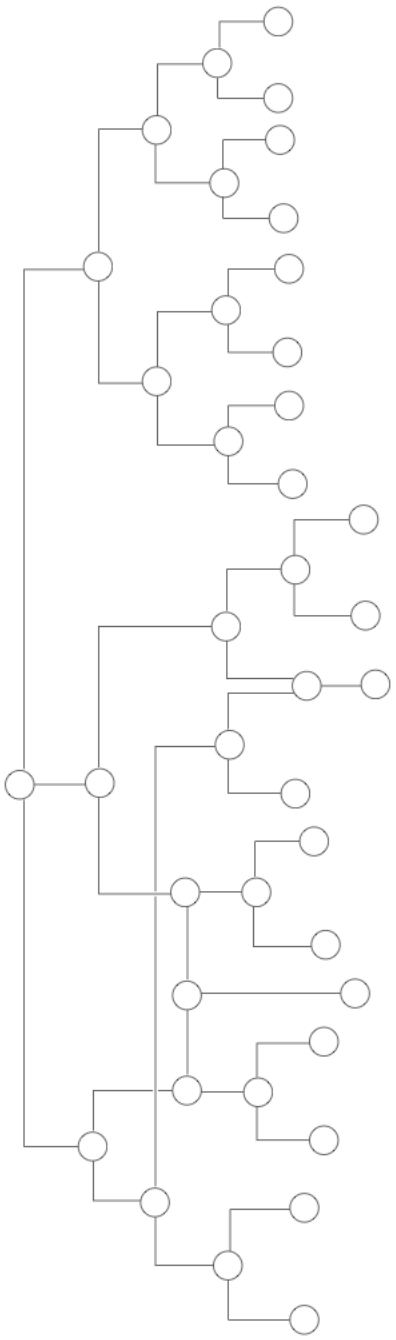
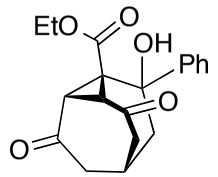


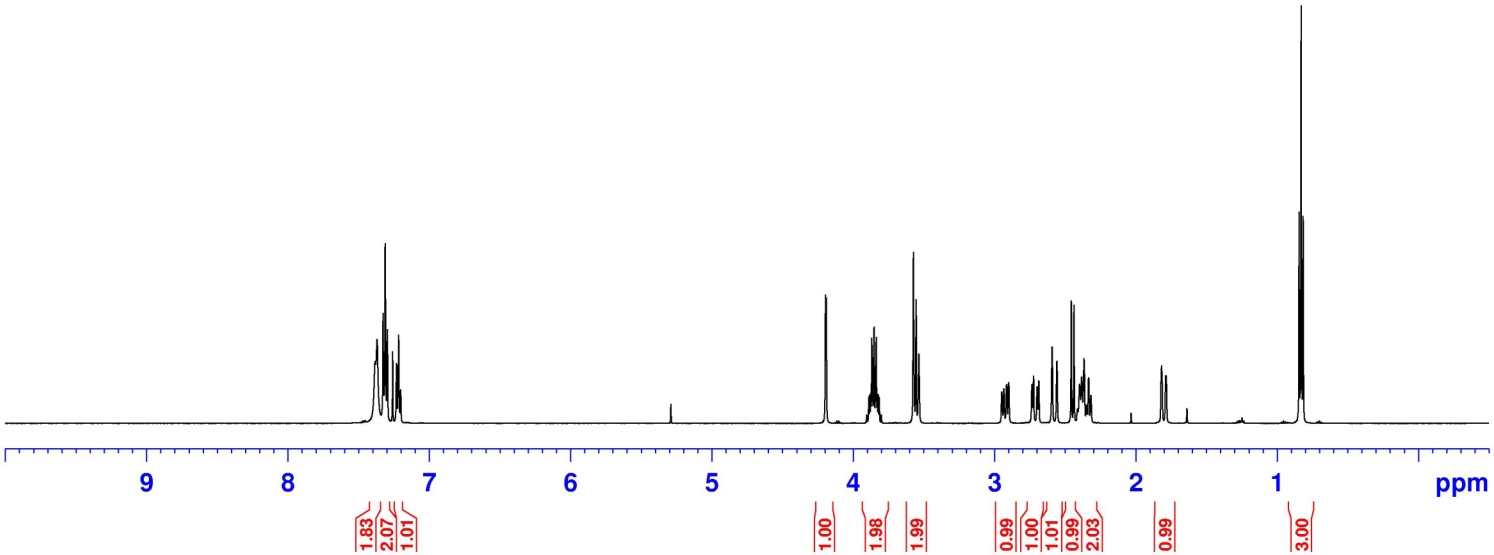
Figure S8. A simplified version of the rearrangement network. Circles represent structurally distinct bullvalene isomers. Lines connecting the circles represent Cope rearrangements.

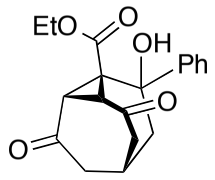
VIII. NMR Spectra



S1

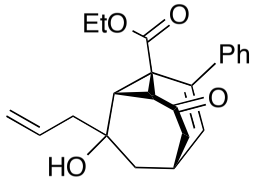
(500 MHz, $CDCl_3$)





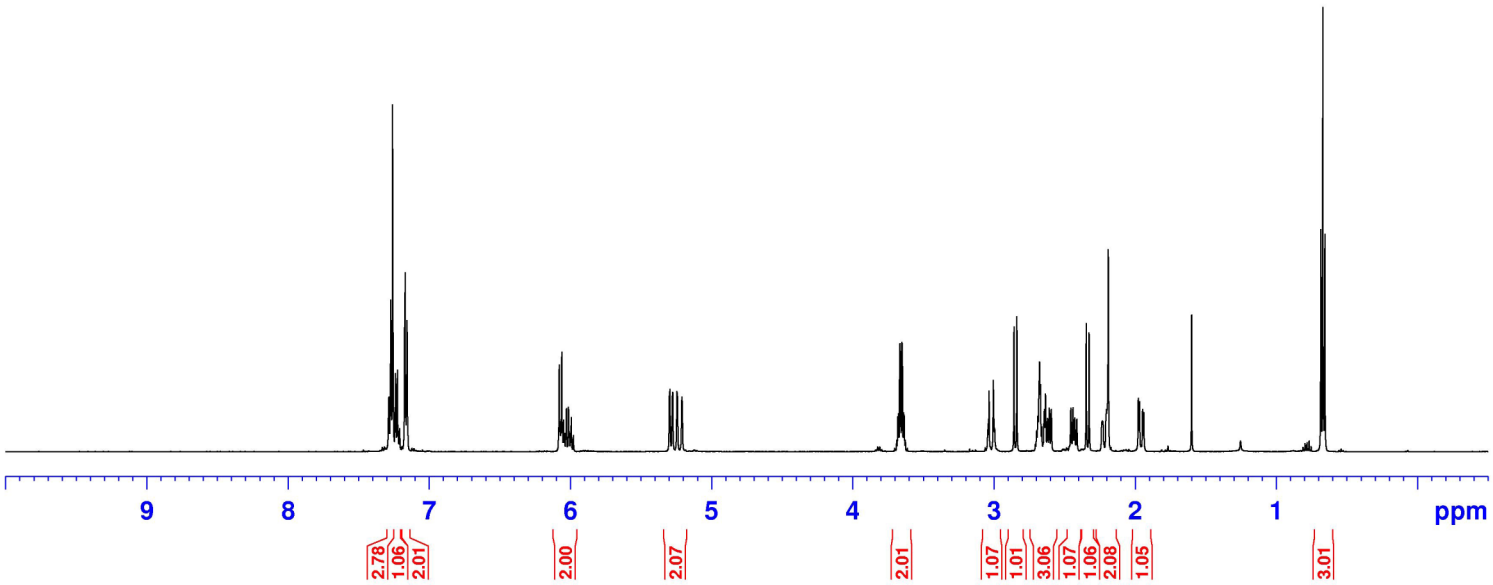
S1

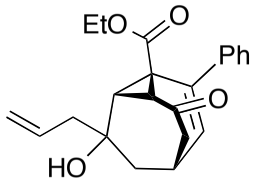
(500 MHz, $CDCl_3$)



S2

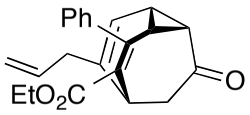
(500 MHz, $CDCl_3$)





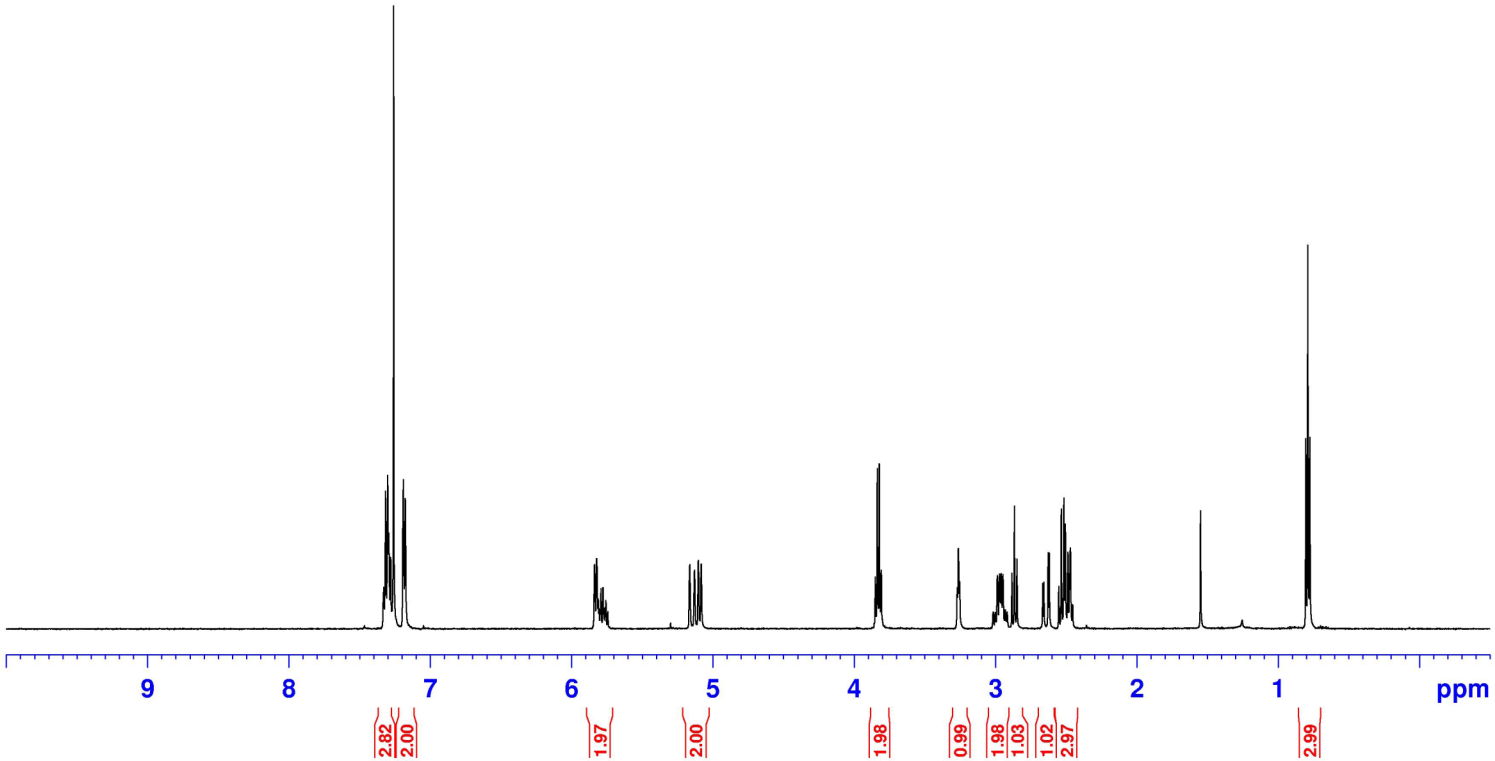
S2

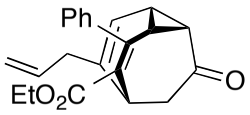
(500 MHz, $CDCl_3$)



3

(500 MHz, $CDCl_3$)





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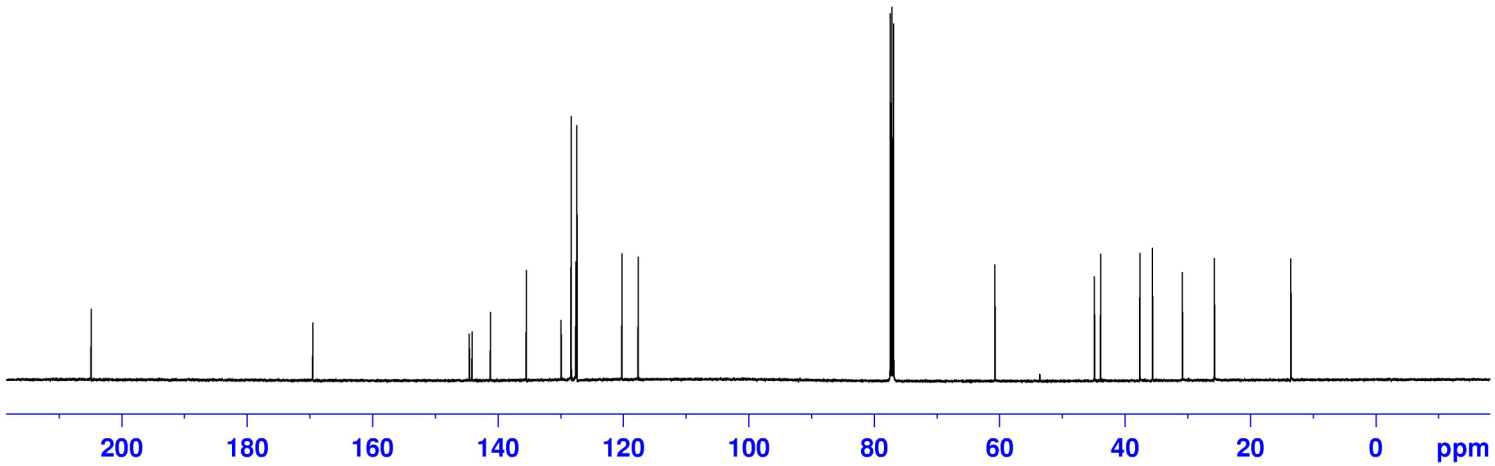
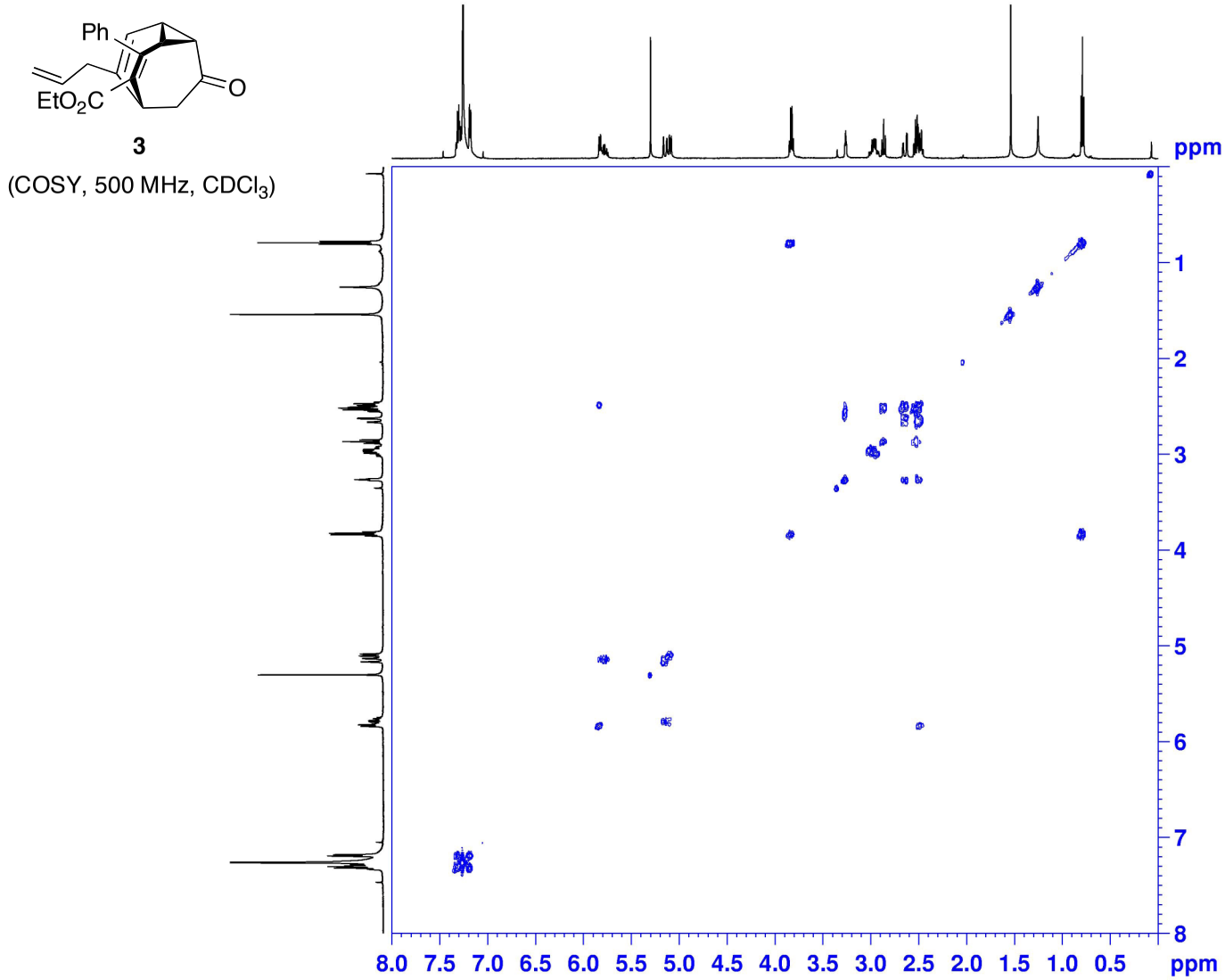
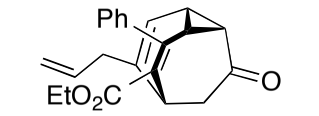
(500 MHz, $CDCl_3$)

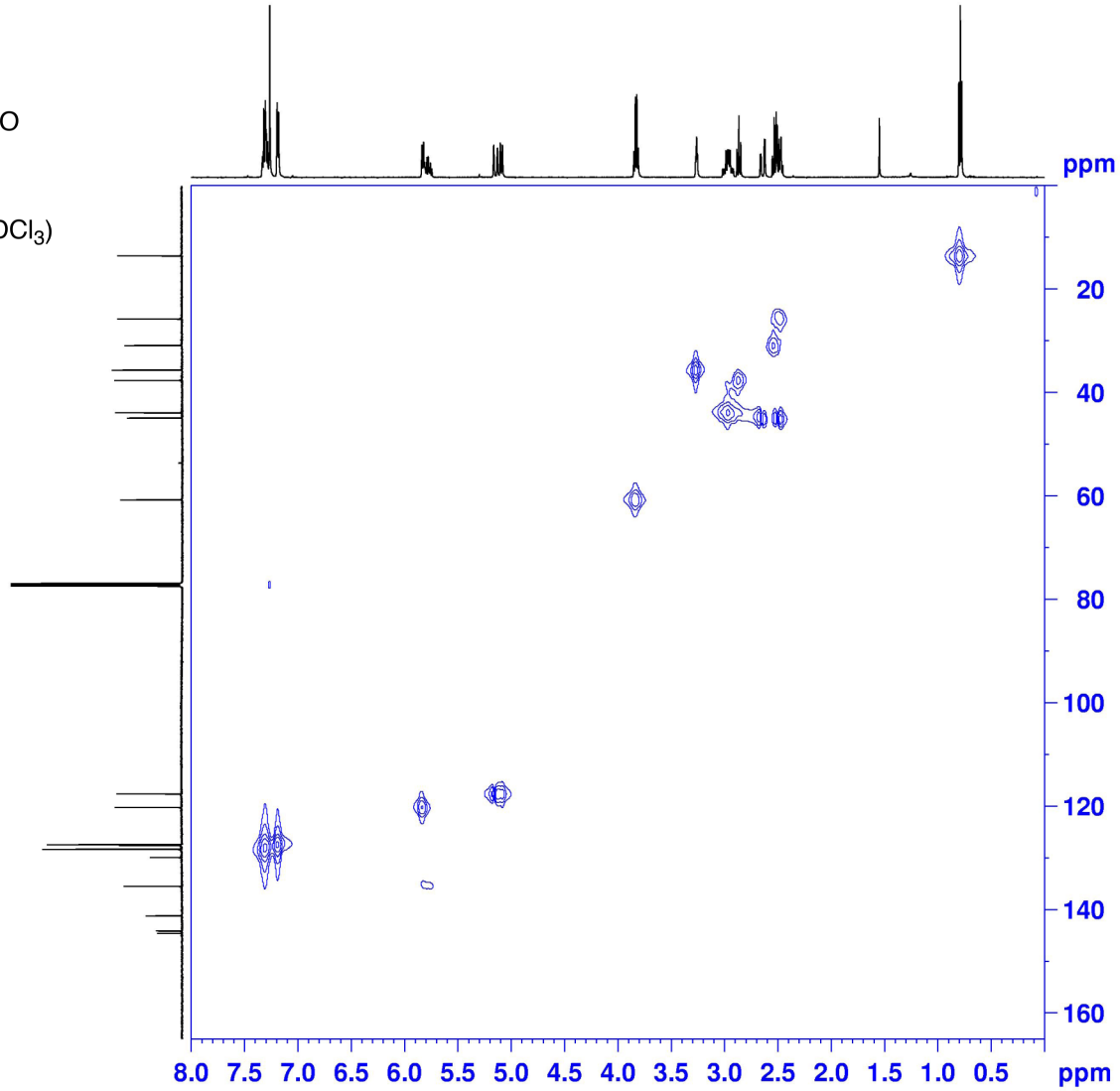


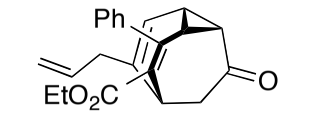

Ph
EtO2C
O
3
(COSY, 500 MHz, CDCl3)
ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm



3

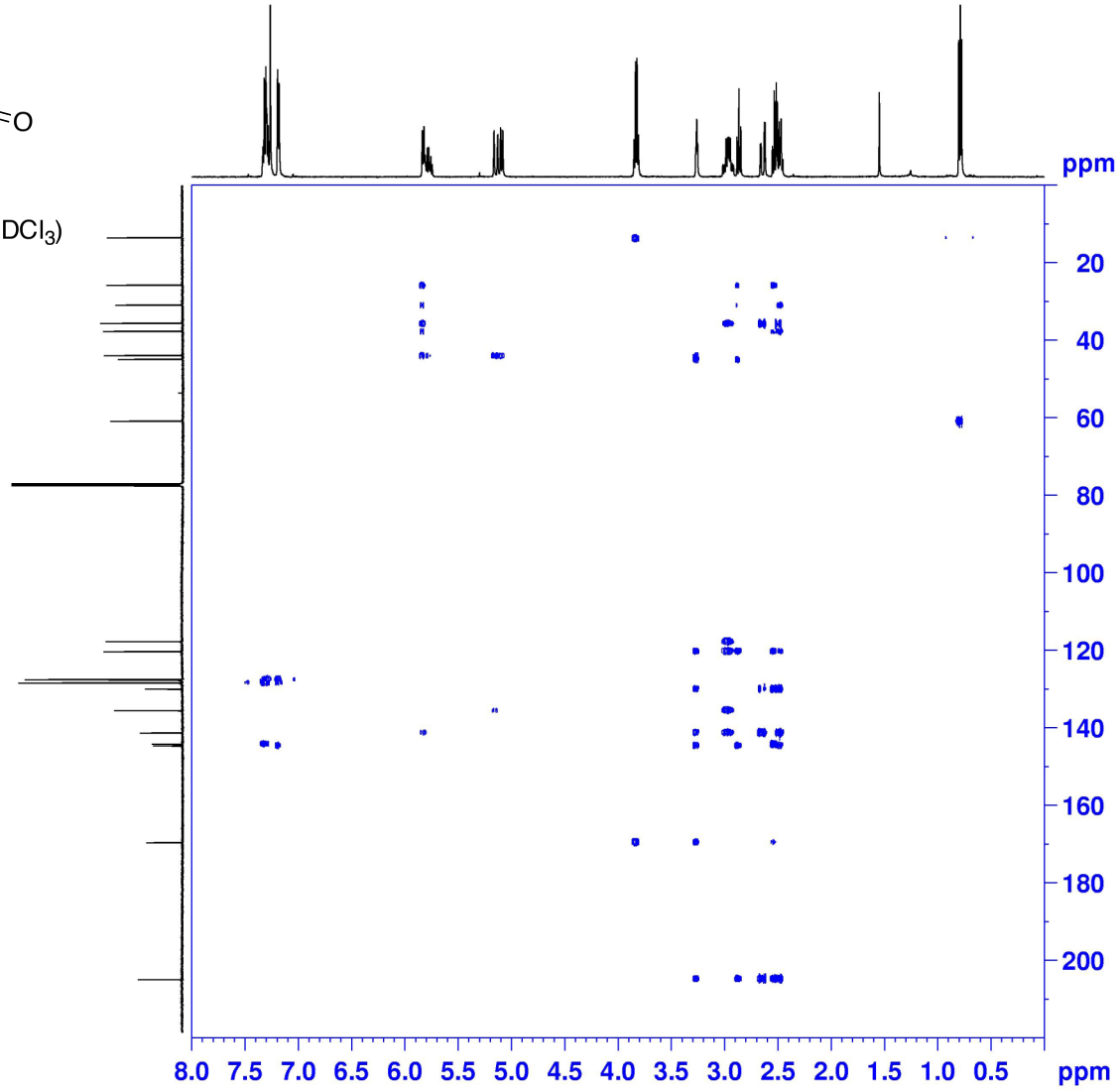
(HMQC, 500 MHz, $CDCl_3$)

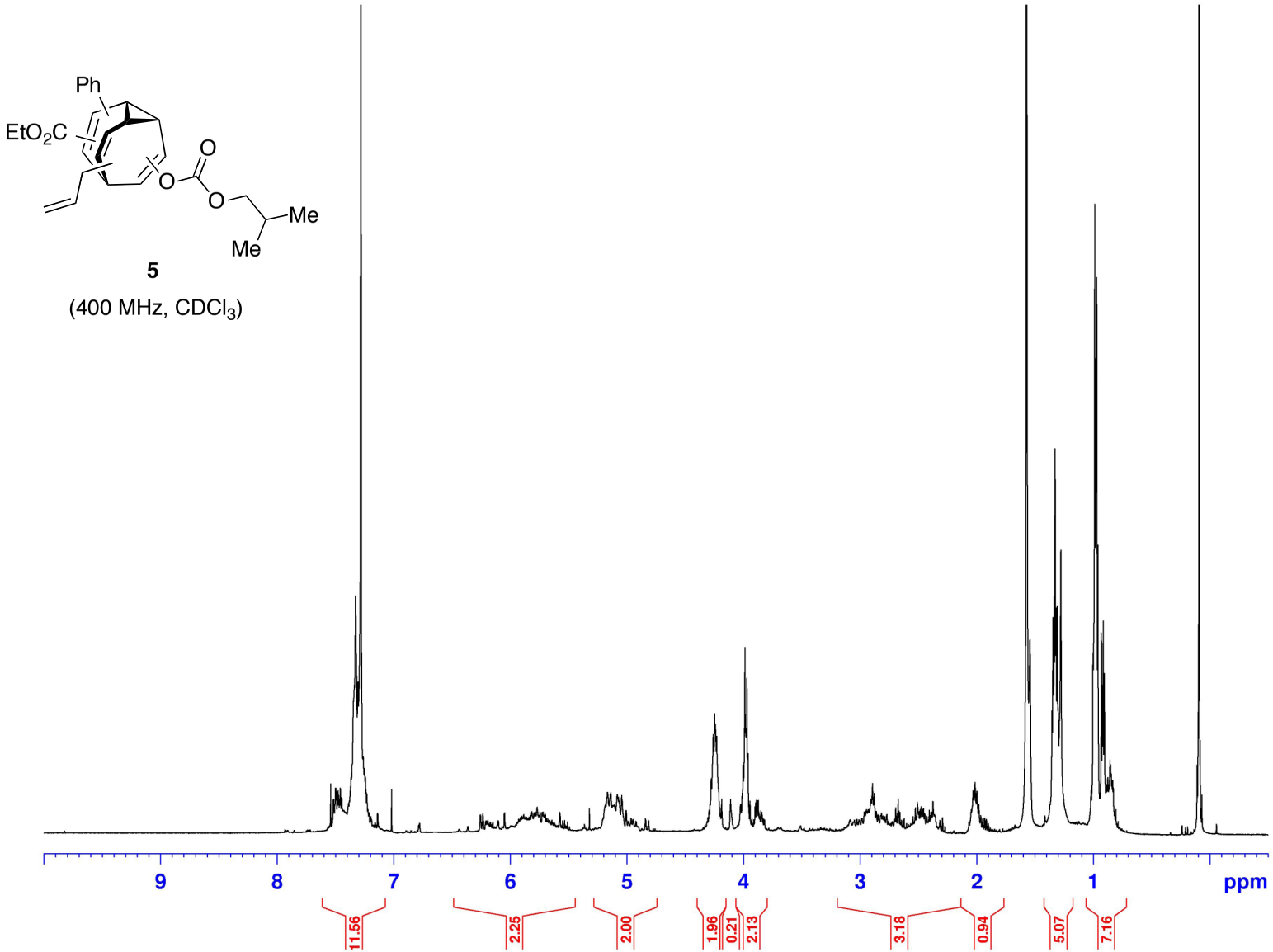


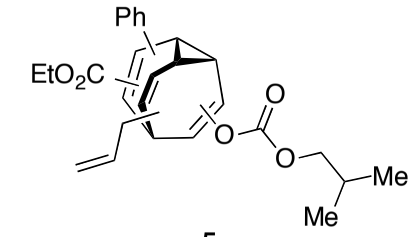


3

(HMBC, 500 MHz, $CDCl_3$)

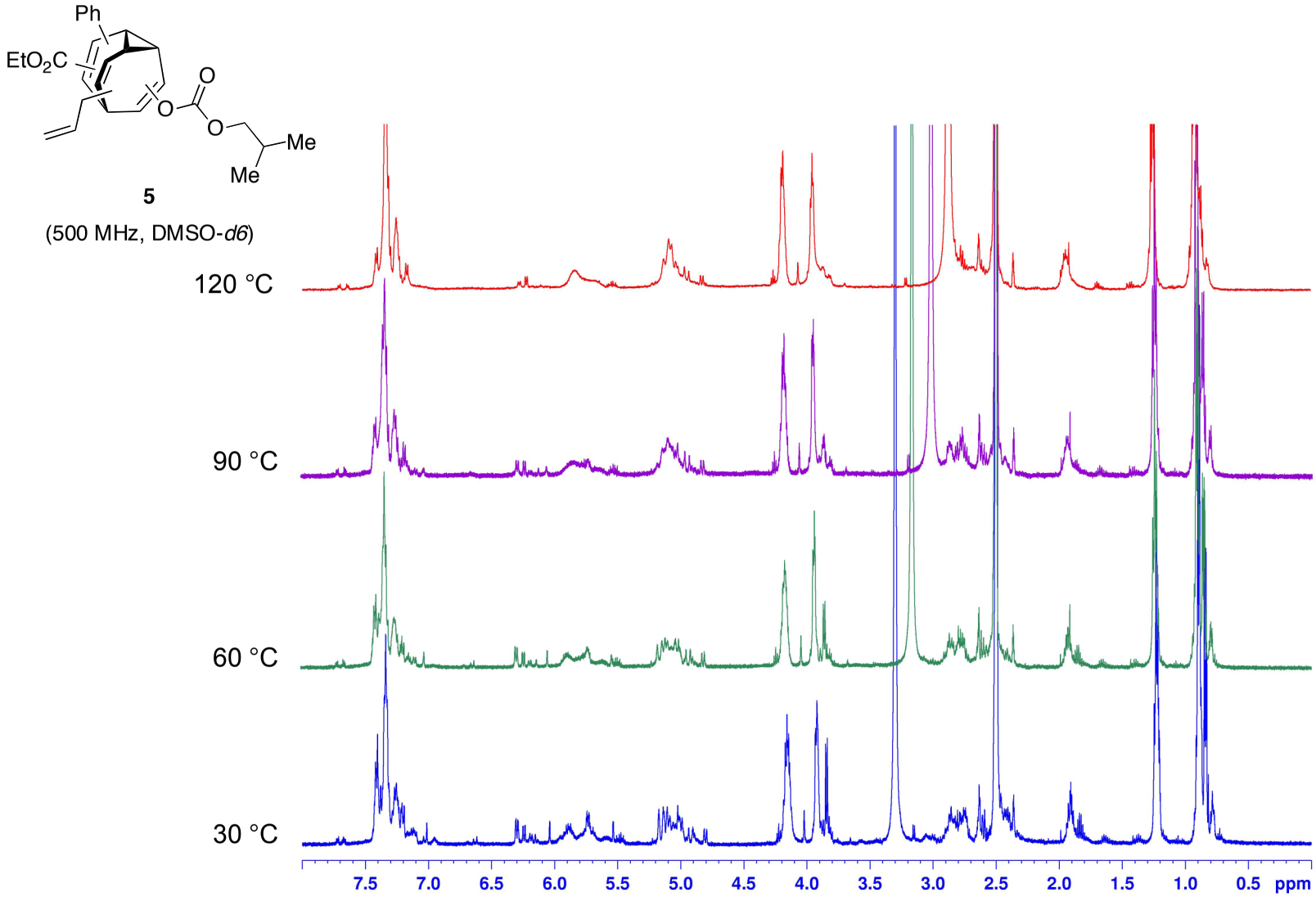


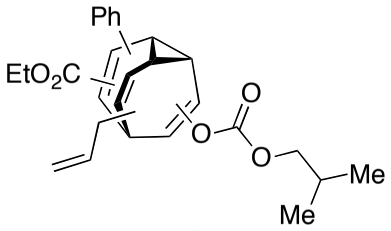

Ph
EtO2C
O
O
O
Me
Me
5
(400 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
ppm
11.56
2.25
2.00
1.96
0.21
2.13
3.18
0.94
5.07
7.16



5

(600 MHz, $CDCl_3$)


Ph
EtO2C
O
O
O
Me
Me
5
(500 MHz, DMSO-d6)
120 °C
90 °C
60 °C
30 °C
7.5
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
ppm



5

(2D-EXSY, 500 MHz, $CDCl_3$)