Rapid and scalable access into strained scaffolds through continuous flow photochemistry

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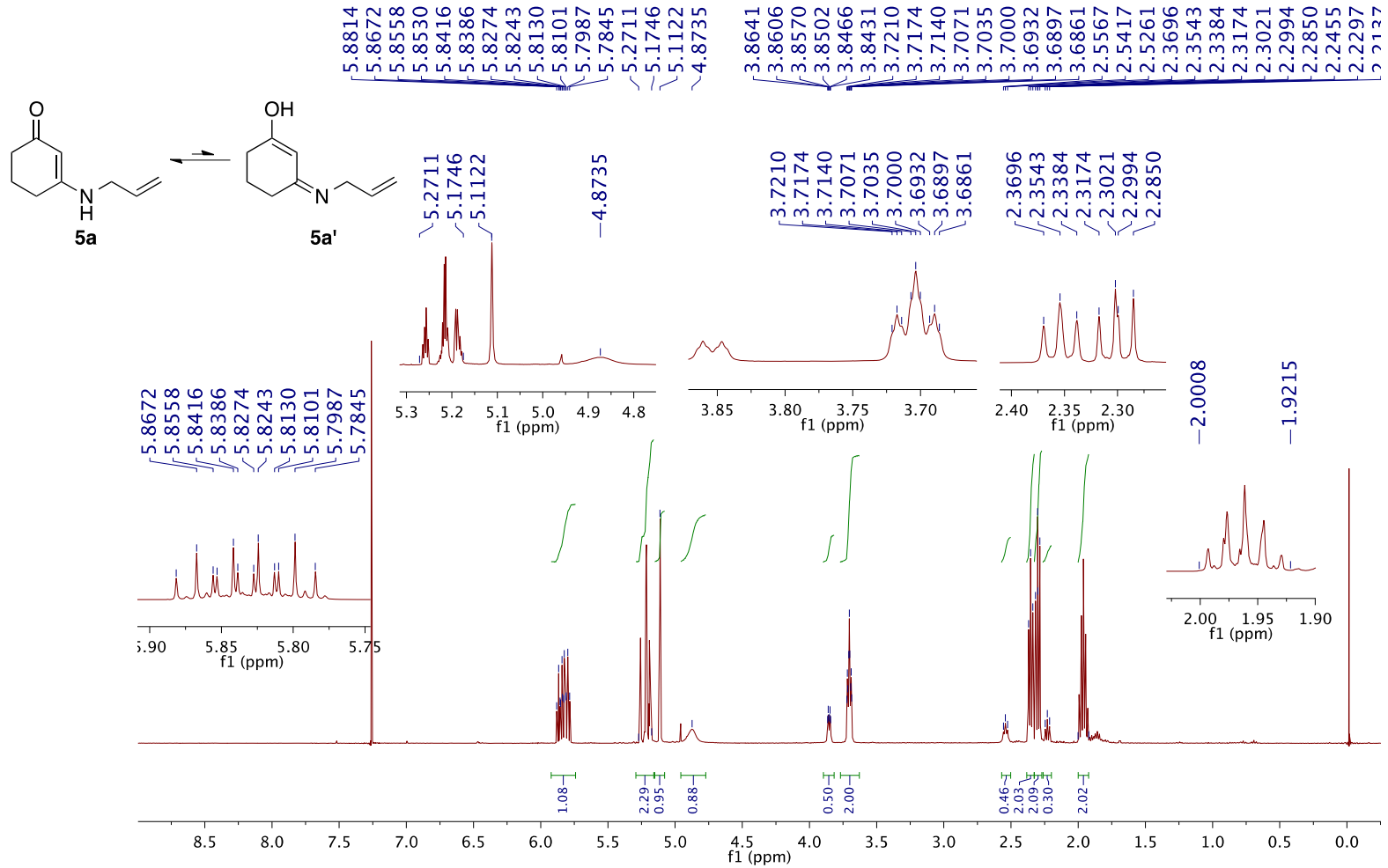
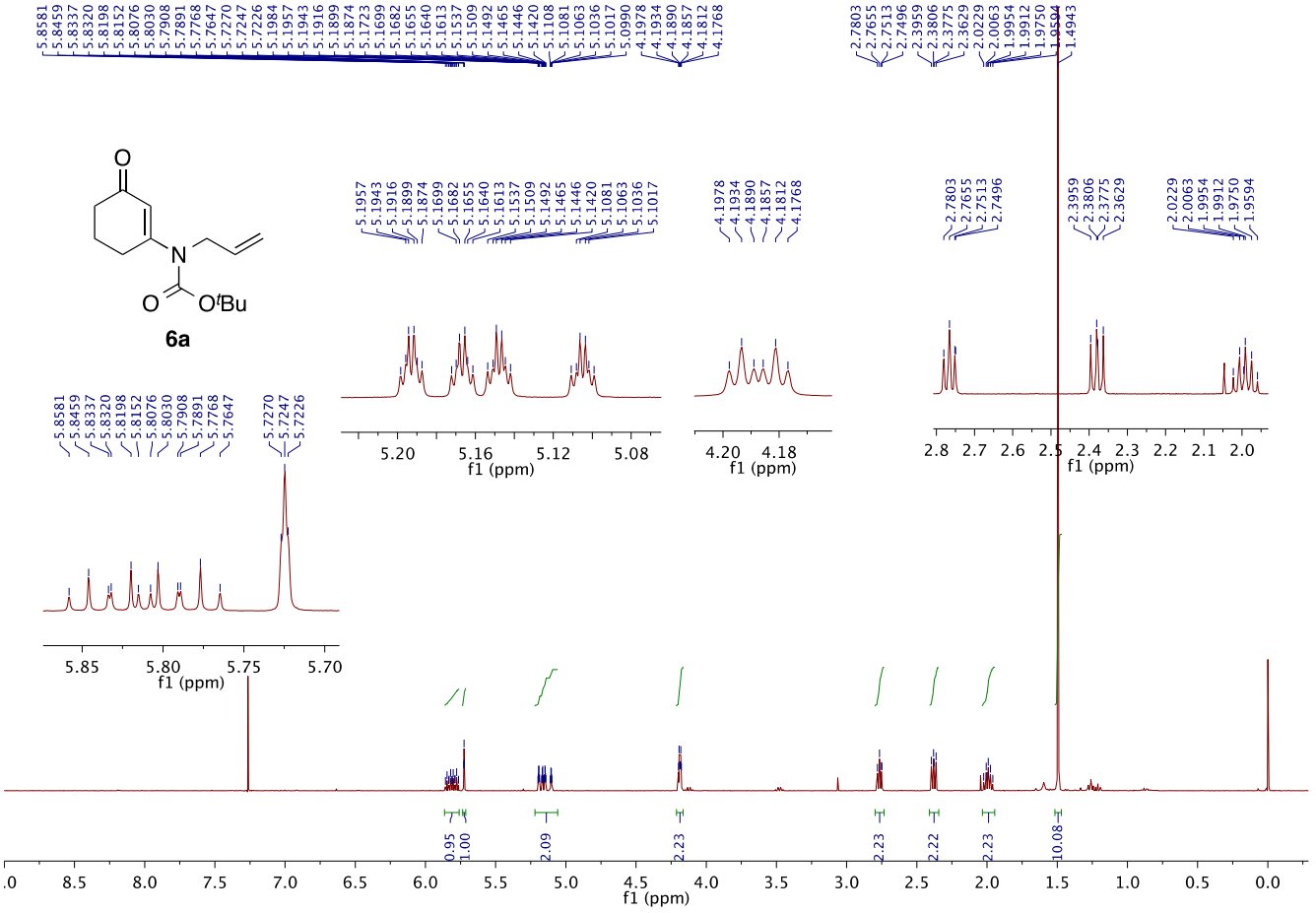
3-(allylamino)cyclohex-2-en-1-one (5a)

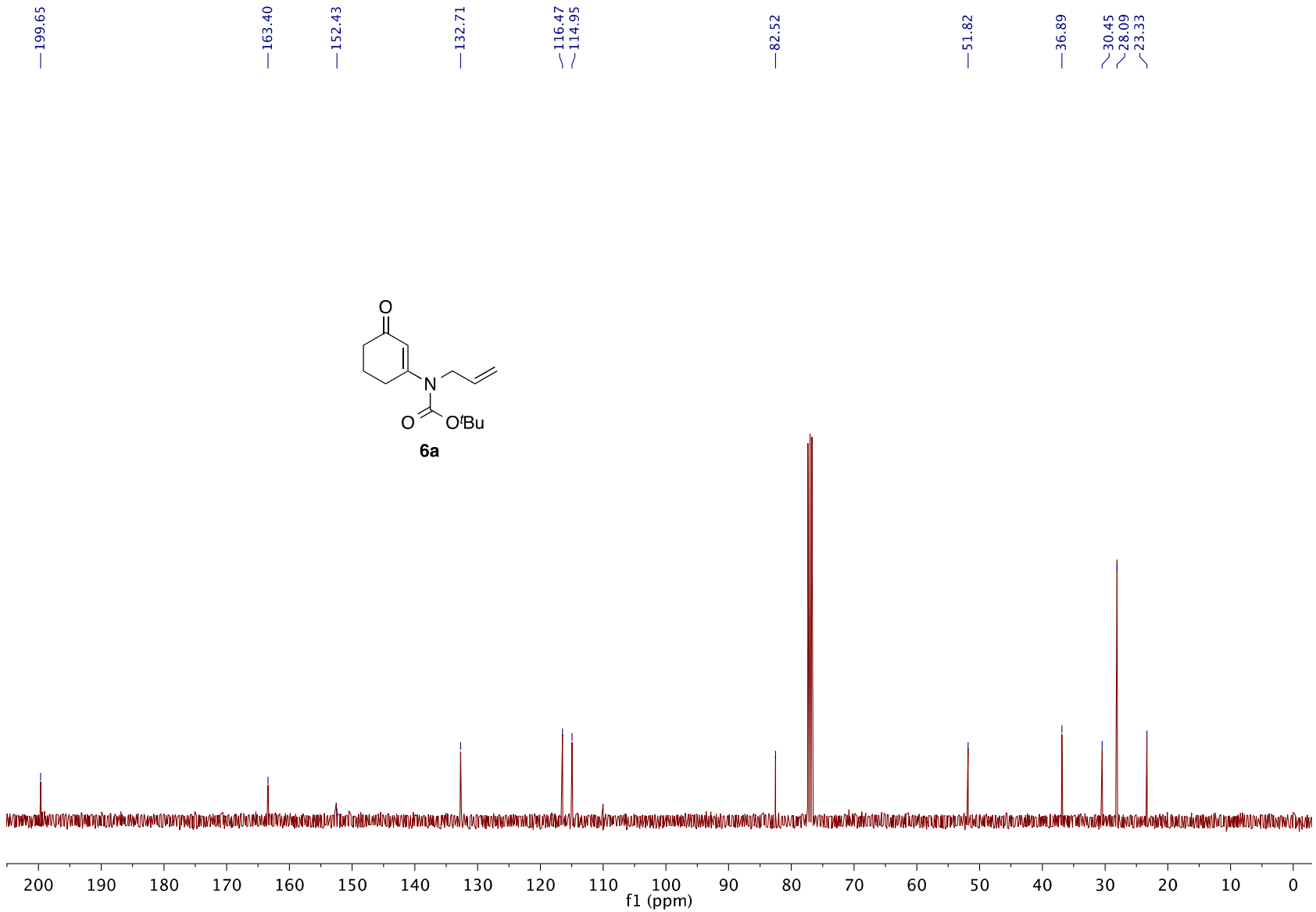
A solution of cyclohexa-1,3-dione (**4**, 10.0 g, 89.2 mmol) and allylamine (7.64 g, 134 mmol) in toluene (180 mL) was refluxed using a Dean–Stark apparatus. The reaction was monitored by TLC, and upon completion (5 h) the mixture was evaporated under reduced pressure to give enaminone **5a** (13.8 g, 88.3 mmol, 99%, 4:1 mixture of tautomers **5a**/**5a′**) as a colorless oil.



tert-Butyl allyl(3-oxocyclohex-1-en-1-yl)carbamate (6a)

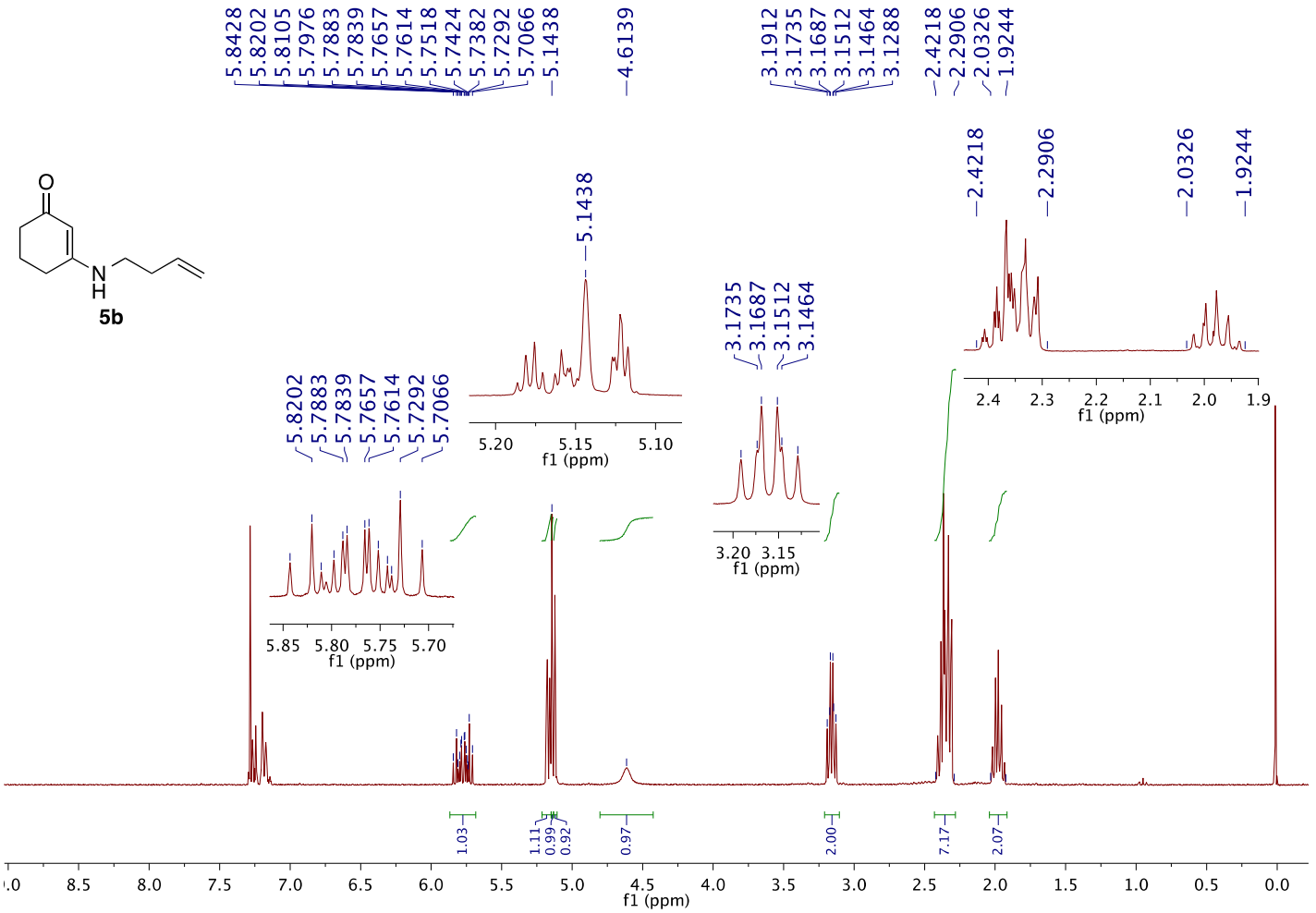
A solution of enaminone **5a** (1.00 g, 6.61 mmol) in CH_2Cl_2 (10 mL) was treated with Boc_2O (2.10 g, 9.92 mmol) and 4-(dimethylamino)pyridine (81 mg, 0.66 mmol) at 0 °C. After stirring for five minutes, the ice bath was removed and stirring was continued for 5 h at room temperature. The reaction mixture was diluted with water (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (1 × 20 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification with flash column chromatography (EtOAc/heptane 1:7→2:3), carbamate **6a** (992 mg, 3.95 mmol, 65%) was obtained as a colorless oil.




199.65
163.40
152.43
132.71
116.47
114.95
82.52
51.82
36.89
30.45
28.09
23.33
O
N
O
O
tBu
6a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

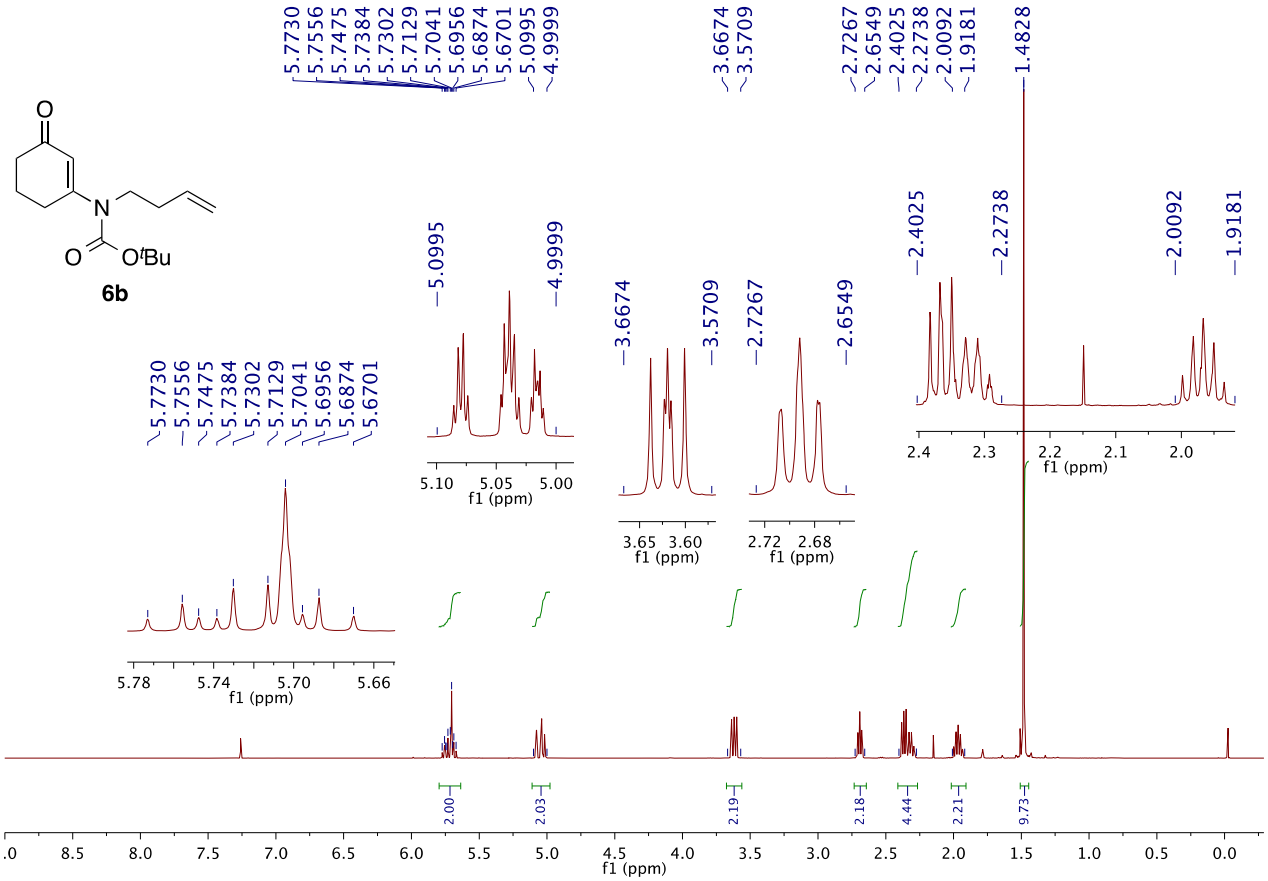
3-(But-3-en-1-ylamino)cyclohex-2-en-1-one (5b)

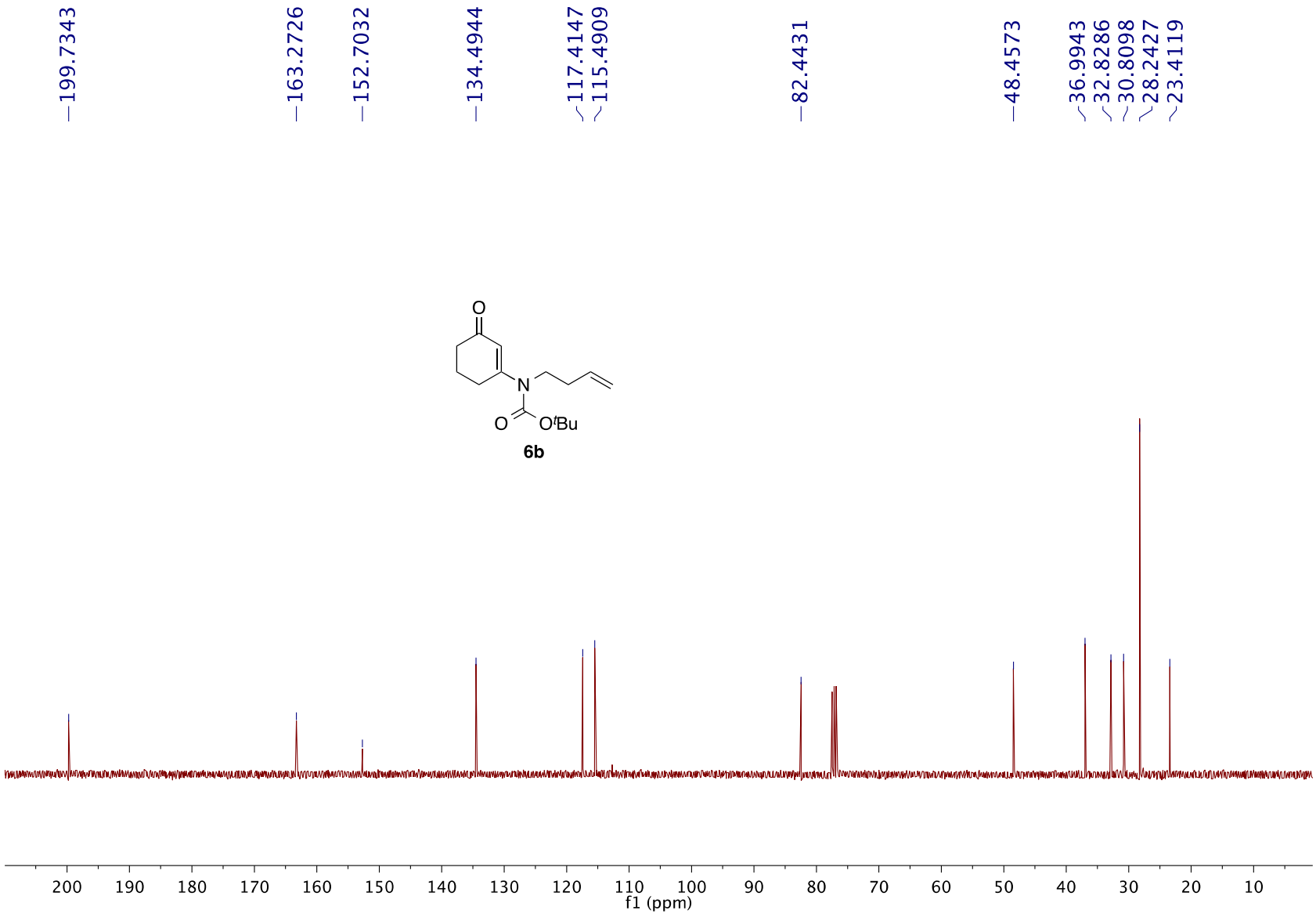
A solution of cyclohexane-1,3-dione (10.0 g, 89.2 mmol) and but-3-enylamine (9.51 g, 134 mmol) in toluene (180 mL) was refluxed using a Dean–Stark apparatus. The reaction was monitored by TLC, and upon completion (5 h) the mixture was evaporated under reduced pressure to give enaminone **5b** (14.6 g, 88.3 mmol, 99%) as a colorless oil.



tert-Butyl but-3-en-1-yl(3-oxocyclohex-1-en-1-yl)carbamate (6b)

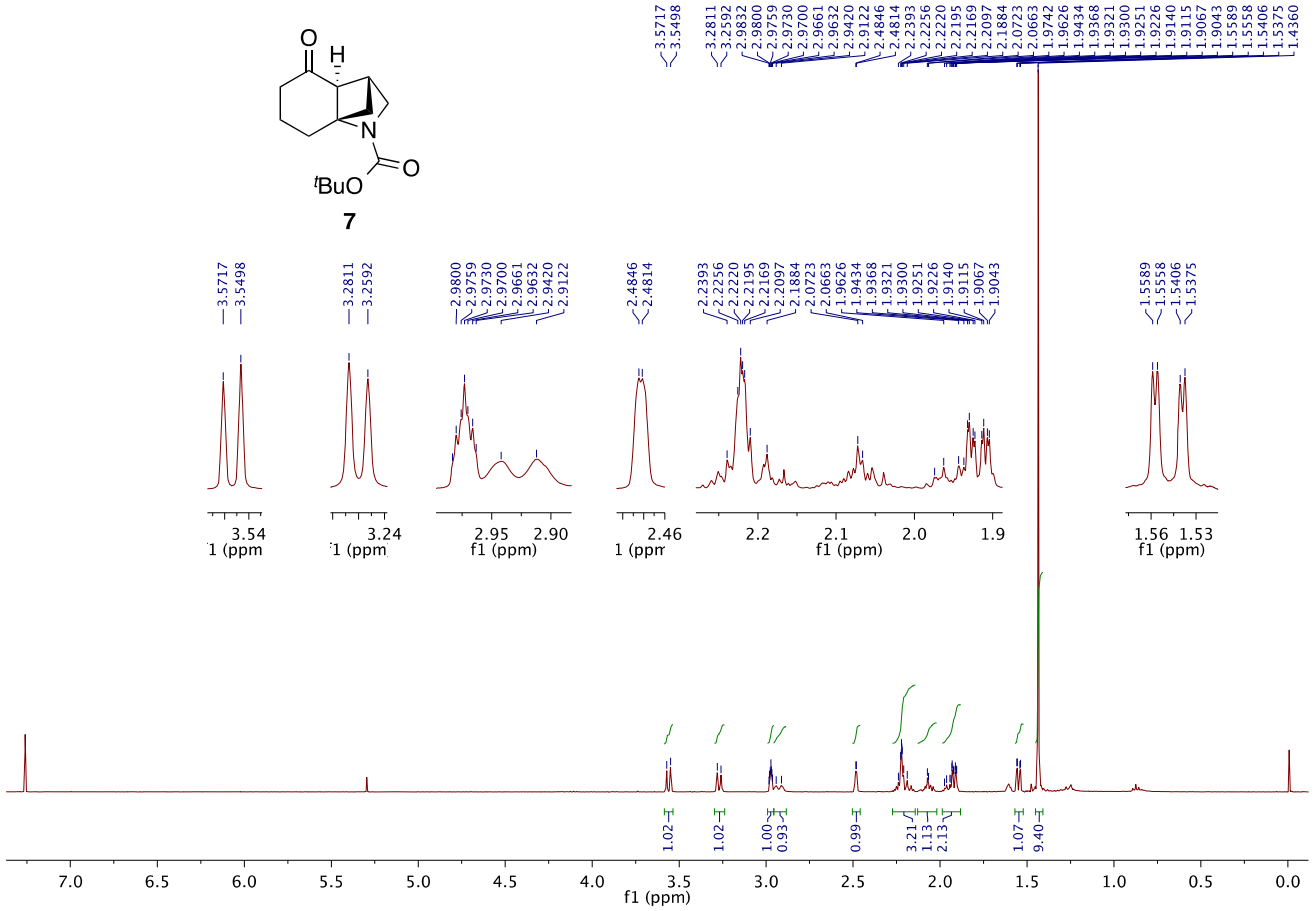
A solution of enaminone **5b** (1.55 g, 0.41 mmol) in CH_2Cl_2 (30 mL) was treated with Boc_2O (3.08 g, 14.1 mmol) and 4-(dimethylamino)pyridine (115 mg, 0.94 mmol) at 0 °C. After stirring for 15 minutes, the ice bath was removed and stirring was continued for 6 h at room temperature. The reaction mixture was diluted with water (20 mL), extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with brine (1 × 30 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification with flash column chromatography (15→25% EtOAc/heptane), carbamate **6b** (1.47 g, 5.55 mmol, 60% over two steps) was obtained as a colorless oil.

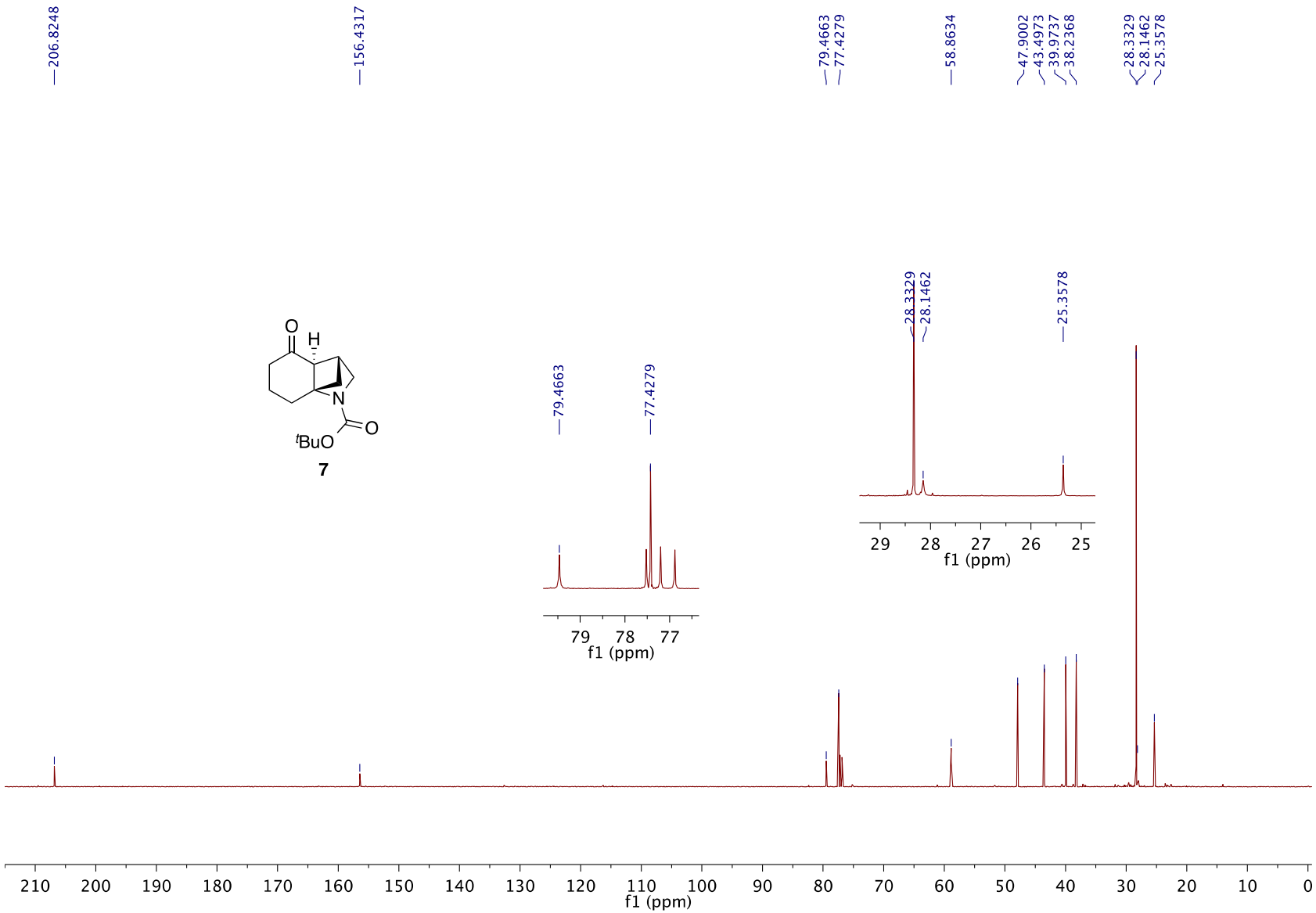



199.7343
163.2726
152.7032
134.4944
117.4147
115.4909
82.4431
48.4573
36.9943
32.8286
30.8098
28.2427
23.4119
O
N
O
O
tBu
6b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

A solution of enaminone **6a** (4.87 g, 19.4 mmol) in acetonitrile (485 mL, 40 mM) was pumped through FEP tubing (id: 2.7 mm, total volume 140 mL, irradiated volume 128 mL) at a flow of 3.5 mL/min, corresponding to a 36.7 min irradiation time using 254 nm UV light. After concentrating the reaction mixture in vacuo, a 4:1 mixture of compounds **7** and **8** (4.69 g, 18.7 mmol, 96% combined yield) was obtained after a first purification by column chromatography (EtOAc/heptane 1:7→1:4). A second purification over silica gel yielded **7** in pure form, along with a mixture of the two cycloadducts.

***tert*-Butyl (*rel*-3*R*,3a*S*,7a*S*)-4-oxohexahydro-3,7a-methanoindole-1(2*H*)-carboxylate (7)**

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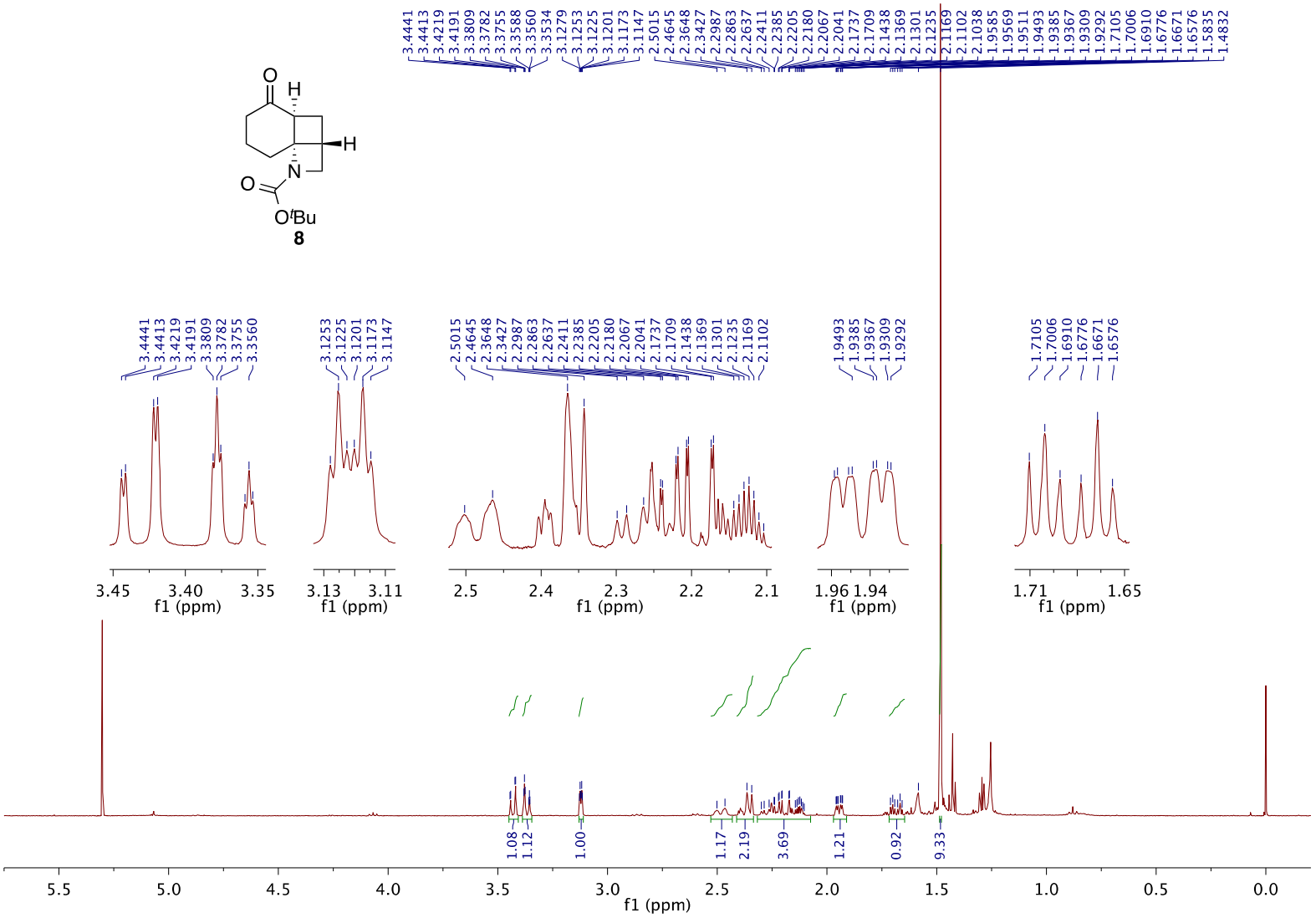
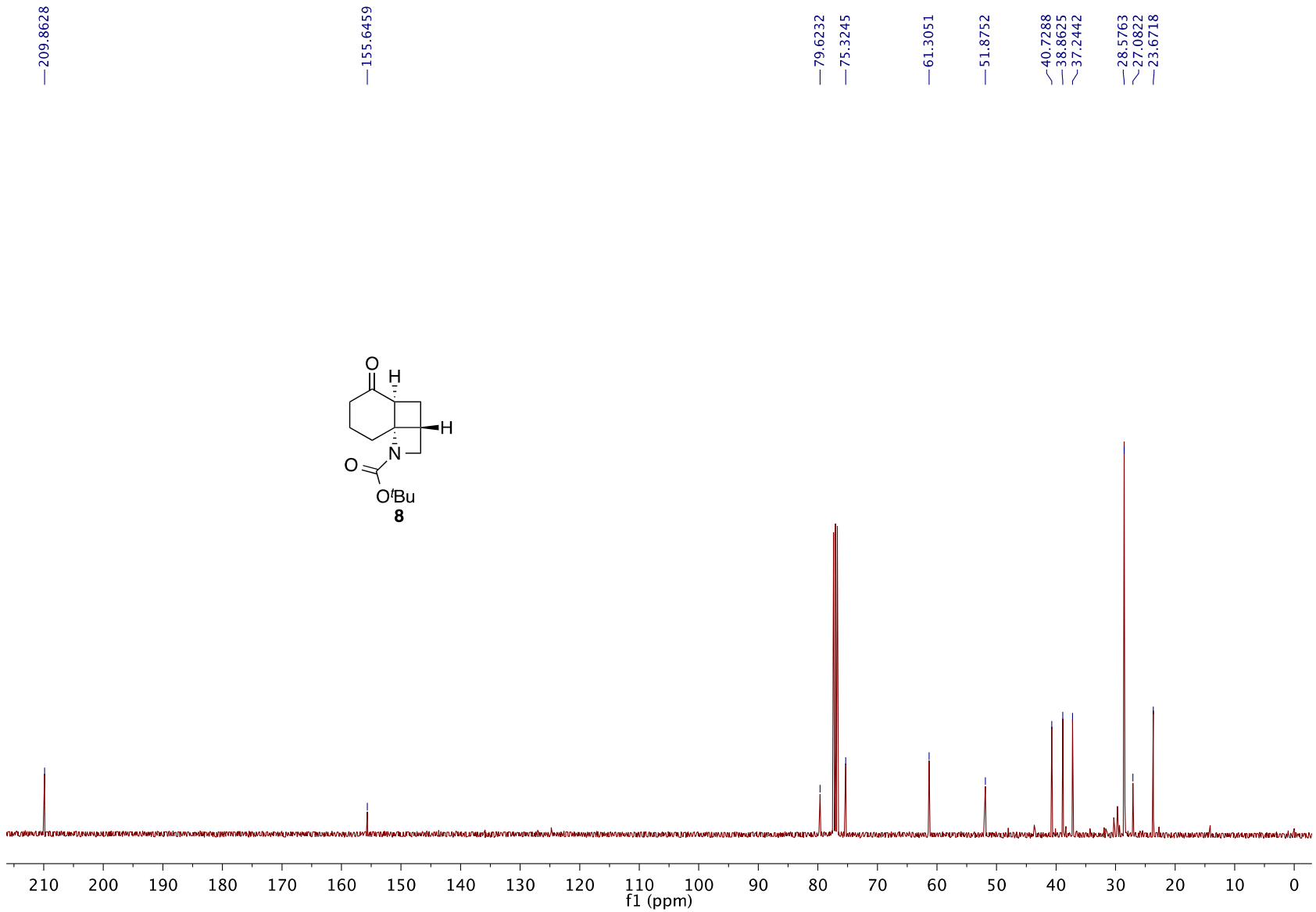
156.4317
79.4663
77.4279
58.8634
47.9002
43.4973
39.9737
38.2368
28.3329
28.1462
25.3578
O
H
N
O
tBuO
7
79.4663
77.4279
79 78 77
f1 (ppm)
28.3329
28.1462
25.3578
29 28 27 26 25
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

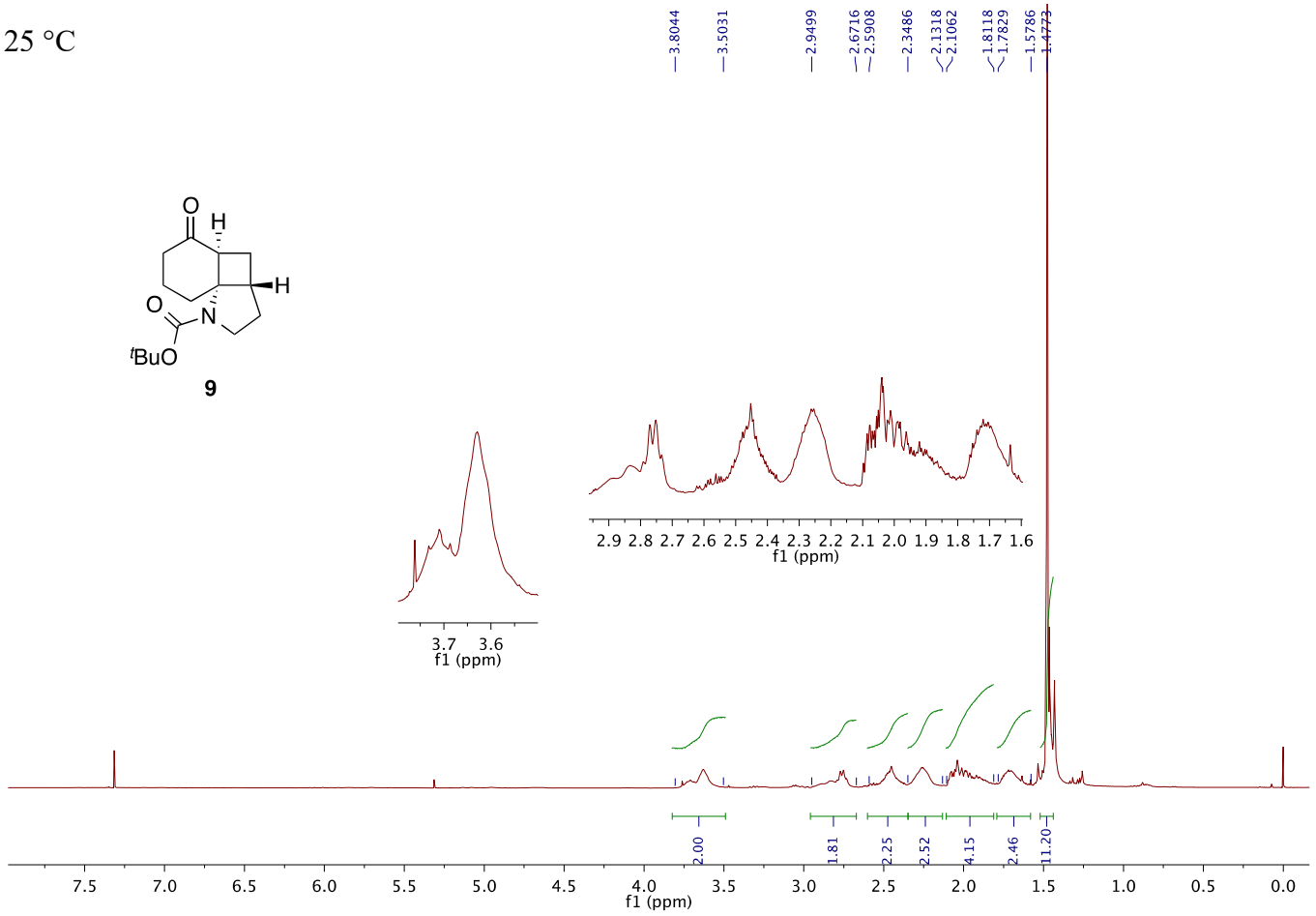
tert-Butyl (_rel_-1_S_,4_R_,6_S_)-7-oxo-2-azatricyclo[4.4.0.0^{1,4}]decane-2-carboxylate (8)



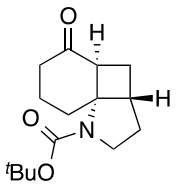

209.8628
155.6459
79.6232
75.3245
61.3051
51.8752
40.7288
38.8625
37.2442
28.5763
27.0822
23.6718
O
H
H
N
O
O
tBu
8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

tert-Butyl (_rel_-3a_R_,4a_S_,8a_S_)-5-oxooctahydrobenzo[1,4]cyclobuta[1,2-_b_]pyrrole-1(2_H_)-carboxylate (9)

A solution of enaminone **6b** (4.16 g, 15.7 mmol) in acetonitrile (530 mL, 30 mM) was pumped through FEP tubing at a flow rate of 2.88 mL/min, corresponding to a 40 min irradiation time using 254 nm UV light. After concentrating the reaction mixture in vacuo, cycloadduct **9** (3.95 g, 14.9 mmol, 95%, mixture of rotamers) was obtained as a colorless oil. Upon standing, even at low temperatures, the compound slowly decomposes. Therefore, follow-up reactions were carried out immediately after the photocycloaddition.

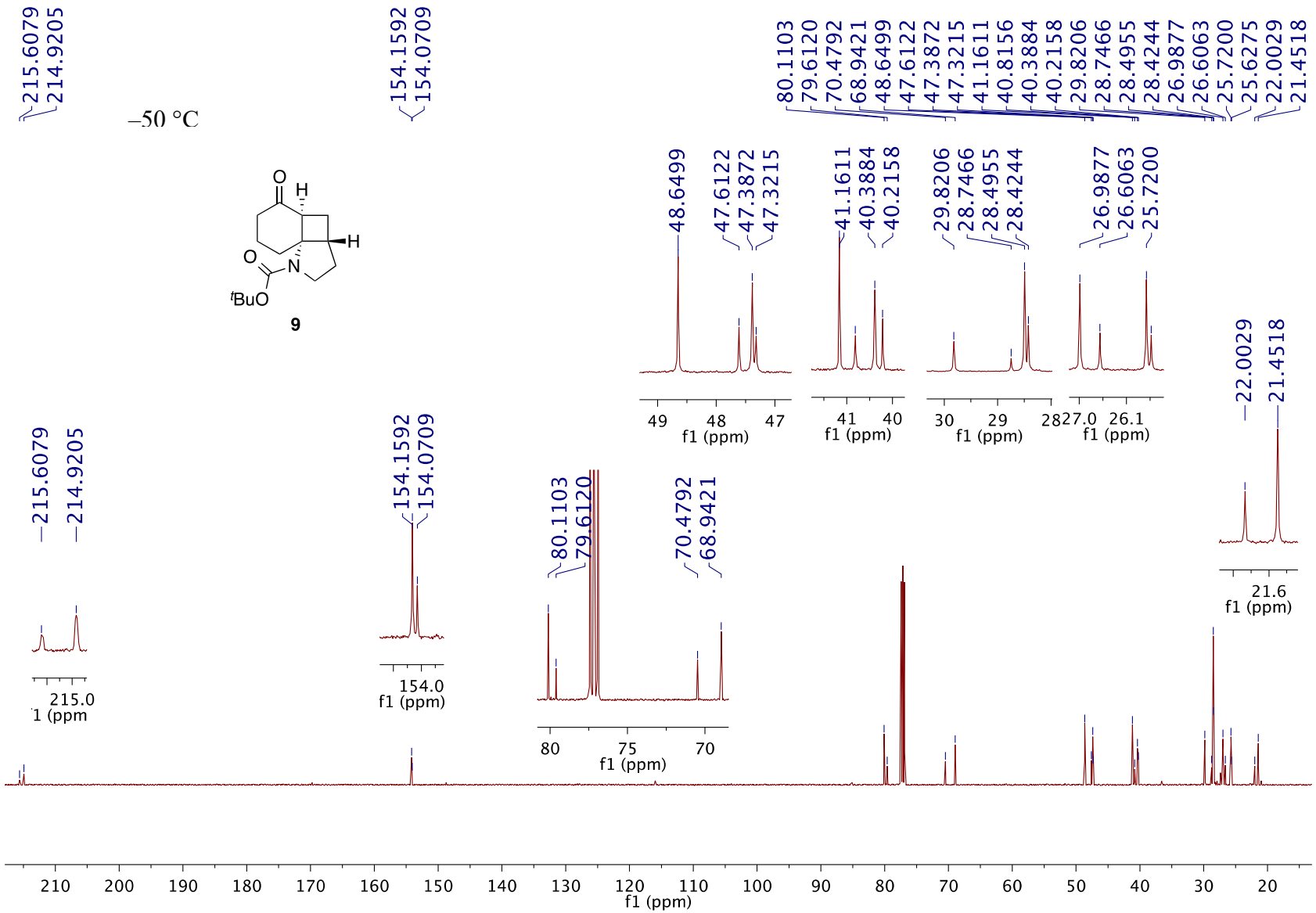


–50 °C


O
H
H
O
N
tBuO

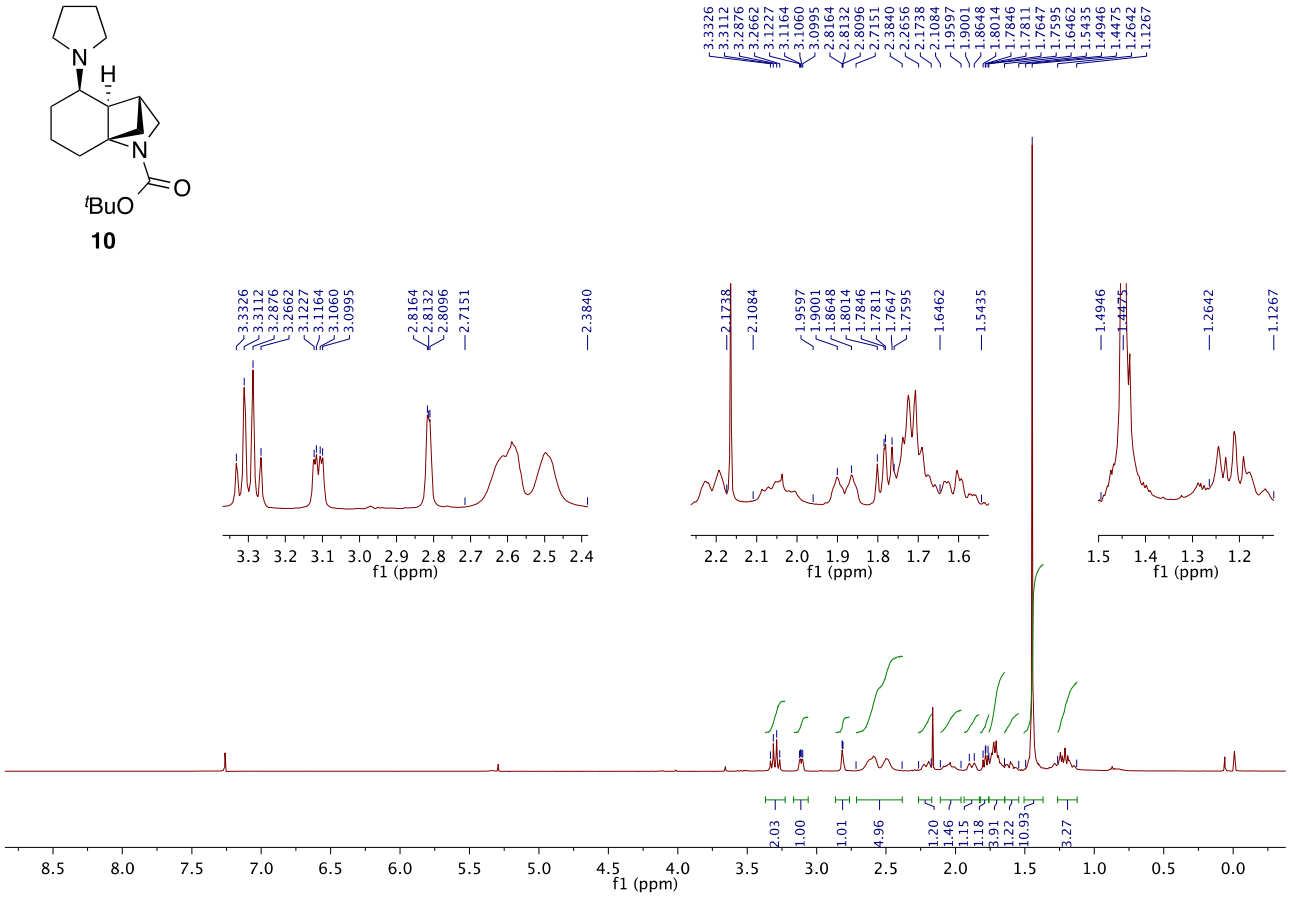
9

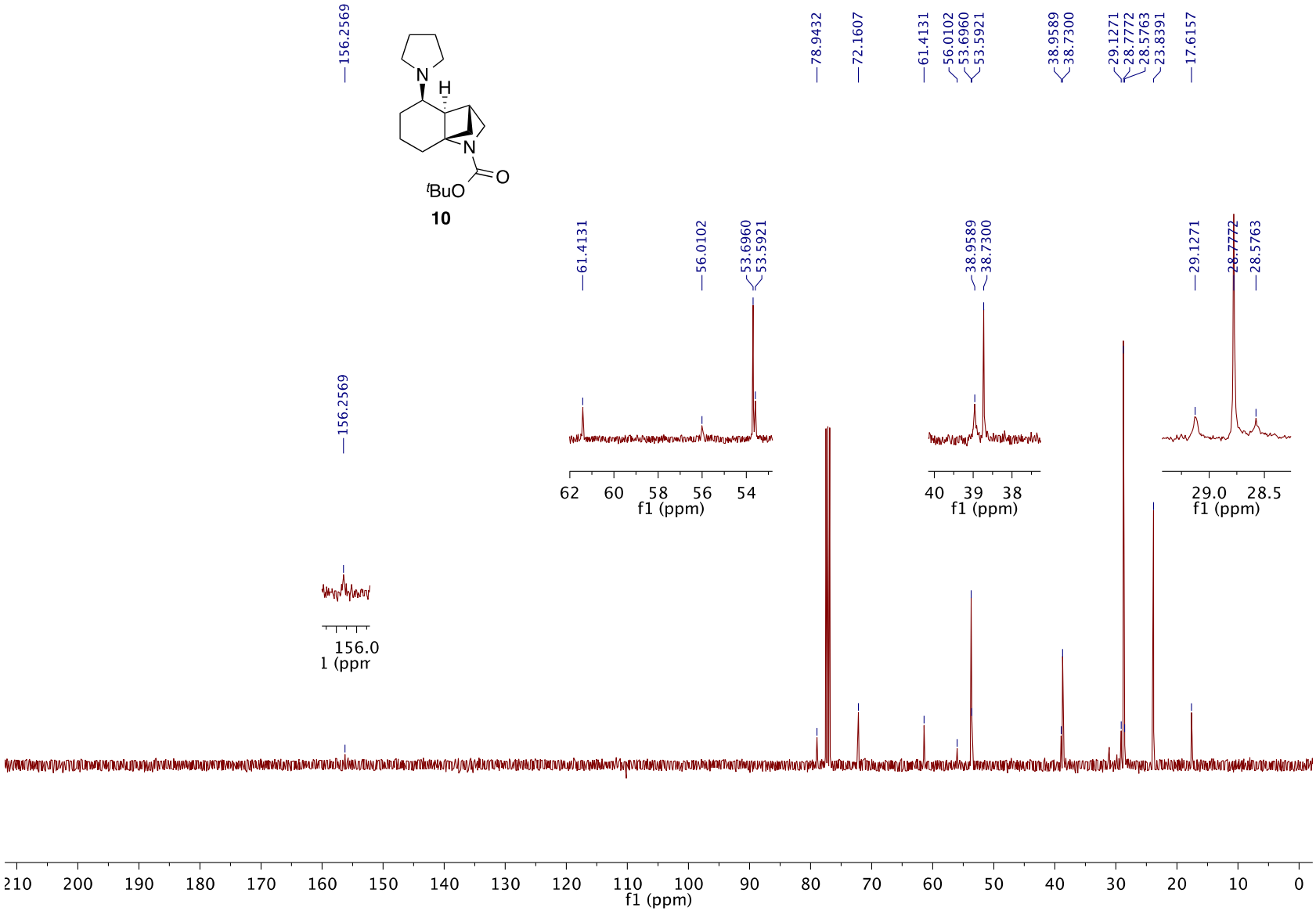
3.6860
3.4651
2.8770
2.6680
2.5577
2.3257
2.2734
2.1253
2.0764
1.9103
1.9053
1.7388
1.7284
1.5094
1.4161
f1 (ppm)
2.00
1.99
1.82
2.46
2.13
1.02
2.18
10.13


215.6079
214.9205
154.1592
154.0709
80.1103
79.6120
70.4792
68.9421
48.6499
47.6122
47.3872
47.3215
41.1611
40.8156
40.3884
40.2158
29.8206
28.7466
28.4955
28.4244
26.9877
26.6063
25.7200
25.6275
22.0029
21.4518
–50 °C
O
H
H
O
N
O
tBuO
9
f1 (ppm)

(*rel*-3*R*,3a*R*,4*R*,7a*S*)-*tert*-Butyl 4-(pyrrolidin-1-yl)hexahydro-3,7a-methanoindole-1(2*H*)-carboxylate (10)

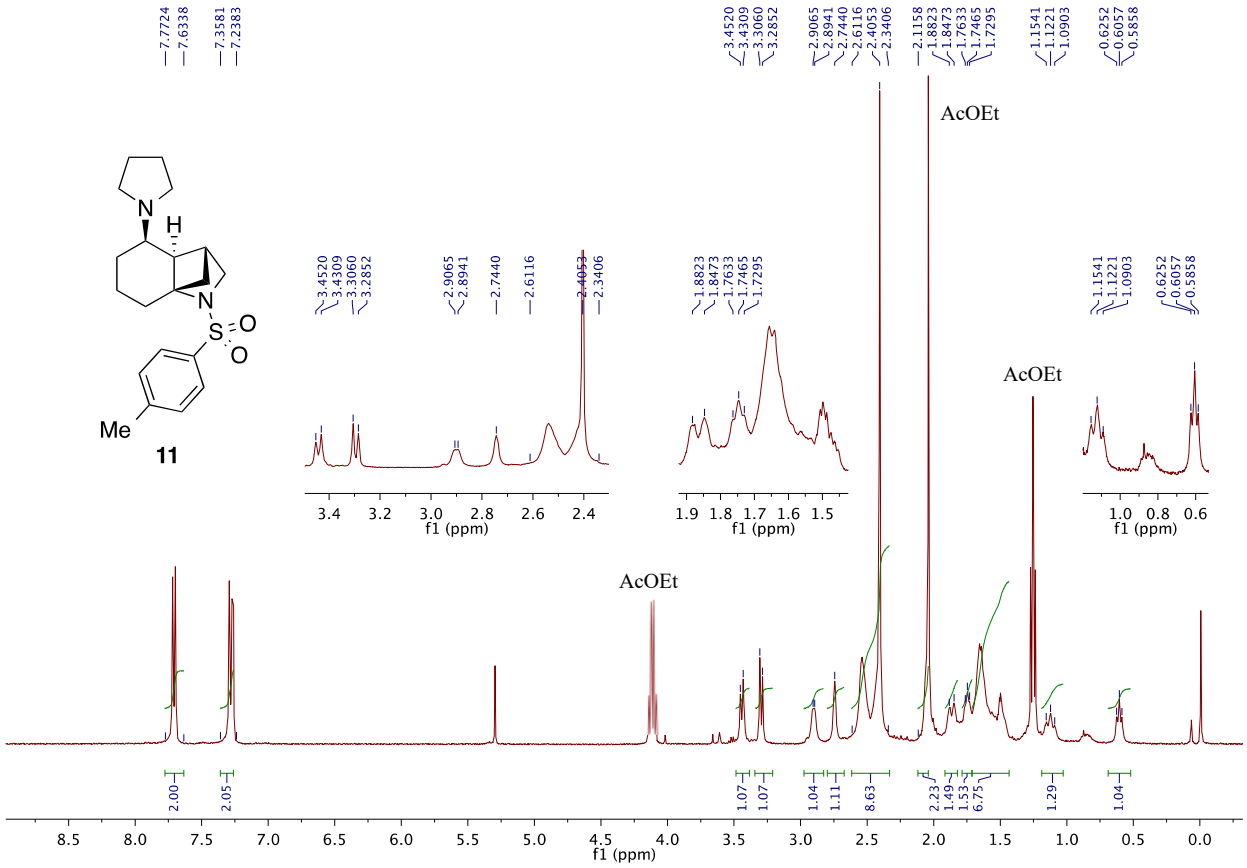
Acetic acid (24 mg, 0.40 mmol), pyrrolidine (28 mg, 0.40 mmol), $NaBH(OAc)_3$ (152 mg, 0.72 mmol) and molecular sieves (4Å), were added to a solution of ketone **7** (100 mg, 0.40 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at room temperature for 48 h (more pyrrolidine [28 mg, 0.40 mmol] was added after 24 h). The reaction was quenched with water (2 mL), extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification by column chromatography (EtOAc/heptane 4:1→1:0) compound **10** (45 mg, 0.15 mmol, 37%) was obtained as a colorless oil.

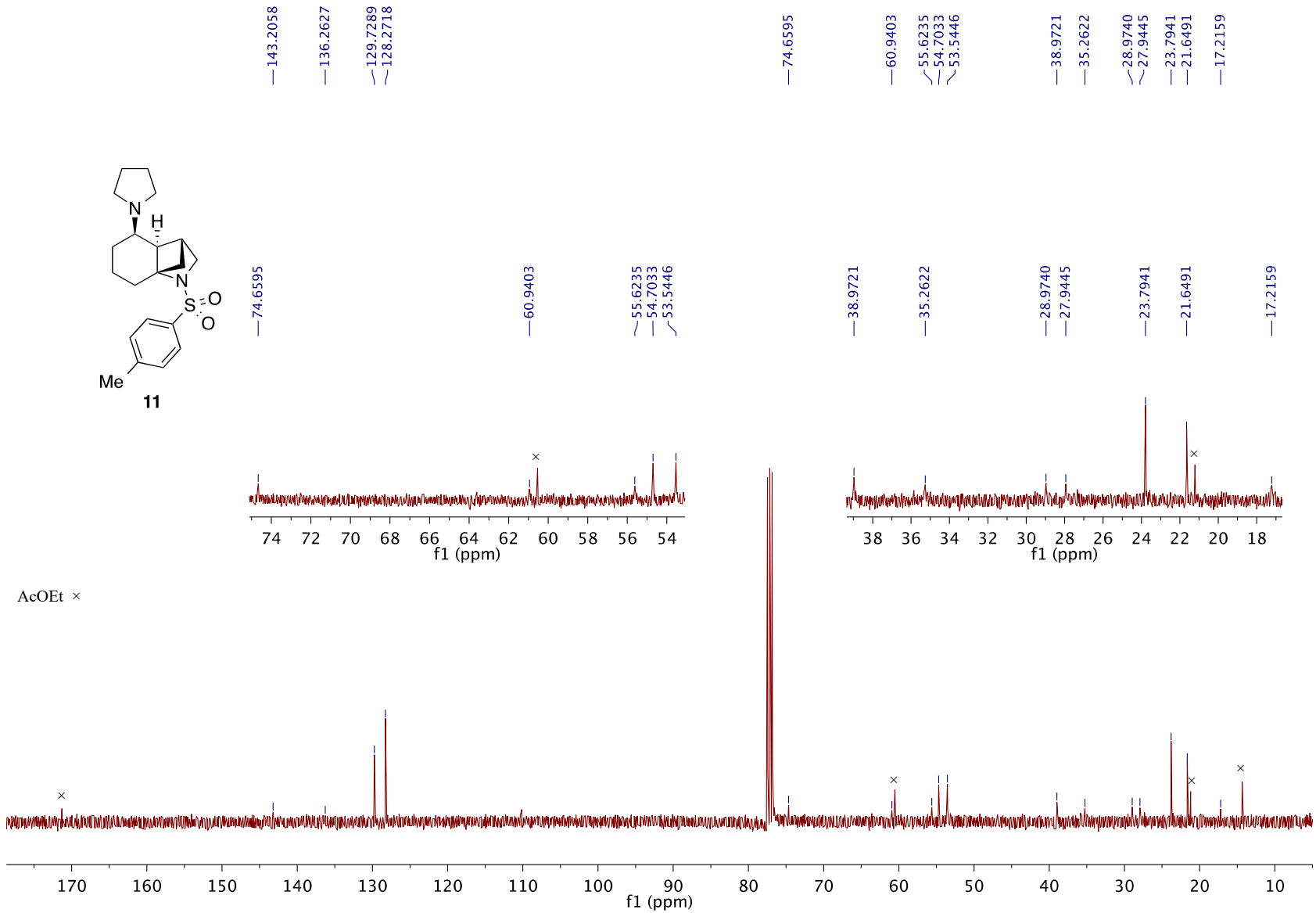



156.2569
78.9432
72.1607
61.4131
56.0102
53.6960
53.5921
38.9589
38.7300
29.1271
28.7772
28.5763
23.8391
17.6157
tBuO
10
f1 (ppm)

(*rel*-3*R*,3a*R*,4*R*,7a*S*)-4-(Pyrrolidin-1-yl)-1-tosyloctahydro-3,7a-methanoindole (11)

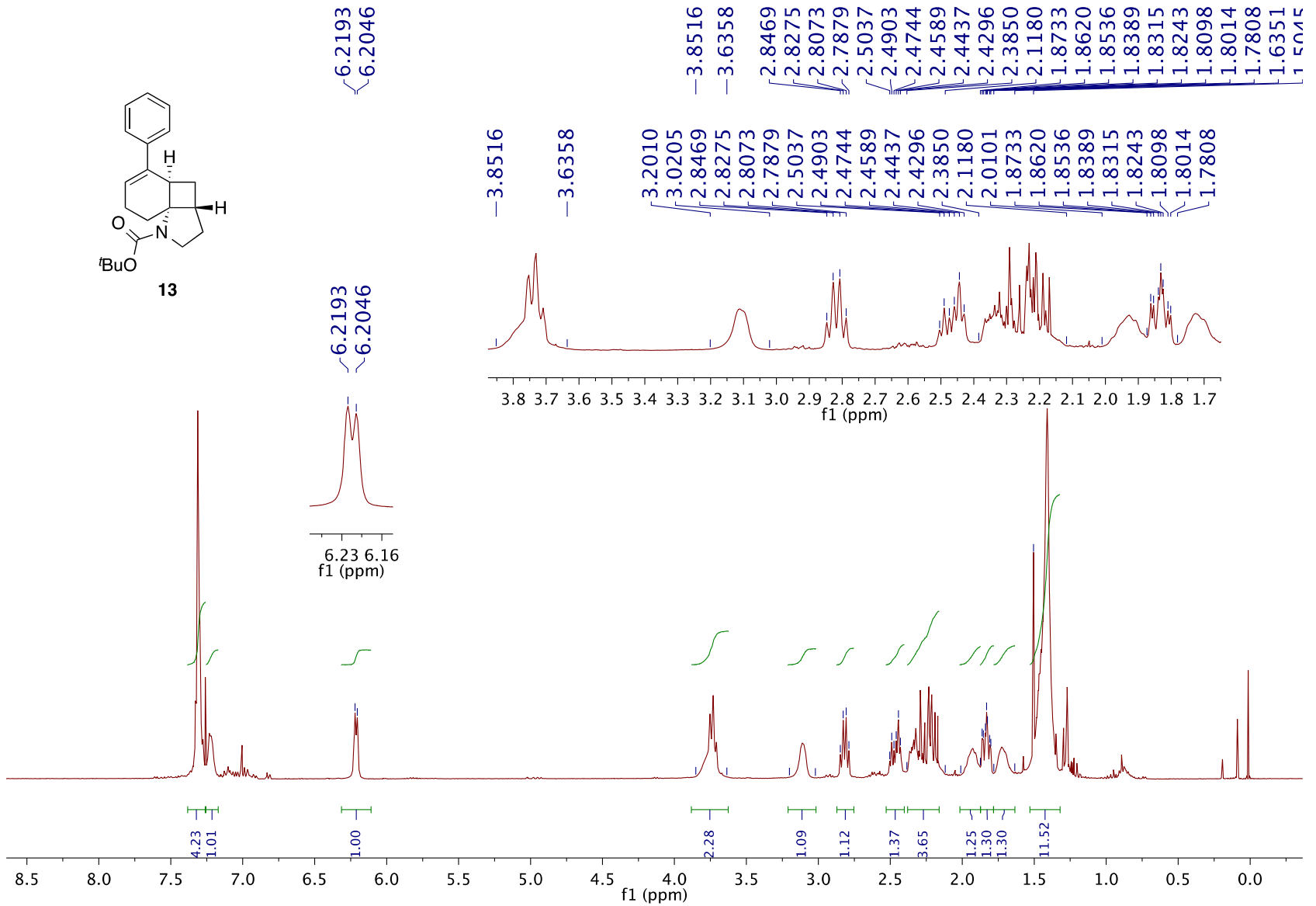
A solution of pyrrolidine **10** (17 mg, 0.055 mmol) was stirred at room temperature in a TFA/CH_2Cl_2 mixture (1:1) for 20 min. The mixture was concentrated, dissolved in CH_2Cl_2 (1 mL) and at 0 °C treated with triethylamine (17 mg, 0.17 mmol) and *p*-toluenesulfonyl chloride (11 mg, 0.055 mmol). After stirring for 2.5 h at room temperature, the reaction was quenched with water (1.5 mL), extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification by column chromatography (EtOAc/heptane 5→25%) sulfonamide **11** (14 mg, 0.039 mmol, 71% over two steps) was obtained as a colorless oil.




143.2058
136.2627
129.7289
128.2718
74.6595
60.9403
55.6235
54.7033
53.5446
38.9721
35.2622
28.9740
27.9445
23.7941
21.6491
17.2159
N
H
N
S
O
O
Me
11
AcOEt
f1 (ppm)

tert-Butyl (_rel_-3a_R_,4a_R_,8a_S_)-5-Phenyl-3,3a,4,4a,7,8-hexahydrobenzo[1,4]cyclobuta[1,2-_b_]pyrrole-1(2_H_)-carboxylate (13)

NaHMDS (643 µL of a 2 M solution in THF, 1.286 mmol) was added to a solution of compound **9** (310 mg, 1.168 mmol) in Et_2O (3 mL) at –20 °C, and after 20 min $PhNTf_2$ (417 mg, 1.168 mmol). After warming to room temperature, the mixture was stirred for 4 hours. Then, the temperature was lowered to –20 °C and NaHMDS (117 µL of a 2 M solution in THF, 0.117 mmol) was added and after 20 min $PhNTf_2$ (42 mg, 0.117 mmol). After 4 h, the same additions were performed. The reaction mixture was stirred for 10 h at room temperature, and then washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and water (5 mL). The combined aqueous phase was reextracted with Et_2O (2 × 12 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo to obtain vinyl triflate **12** (slightly contaminated with PhNHTf). The crude mixture was used for the Suzuki coupling reaction. A mixture of vinyl triflate **12**, $Pd(OAc)_2$ (38 mg, 0.17 mmol), PPh_3 (133 mg, 0.507 mmol) and 1.0 M aqueous sodium carbonate (2.34 mL) were dissolved in 1,4-dioxane (6.5 mL). The mixture was stirred for 30 minutes at room temperature. Then, phenylboronic acid (171 mg, 1.402 mmol) was added and the mixture was stirred for 20 hours. The reaction was quenched with water (4 mL) and extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with brine (8 mL), dried ($MgSO_4$), concentrated in vacuo and purified via silica column chromatography (EtOAc/heptane 0→7%) to yield compound **13** (156 mg, 0.480 mmol, 41% over two steps) as a white solid.


13
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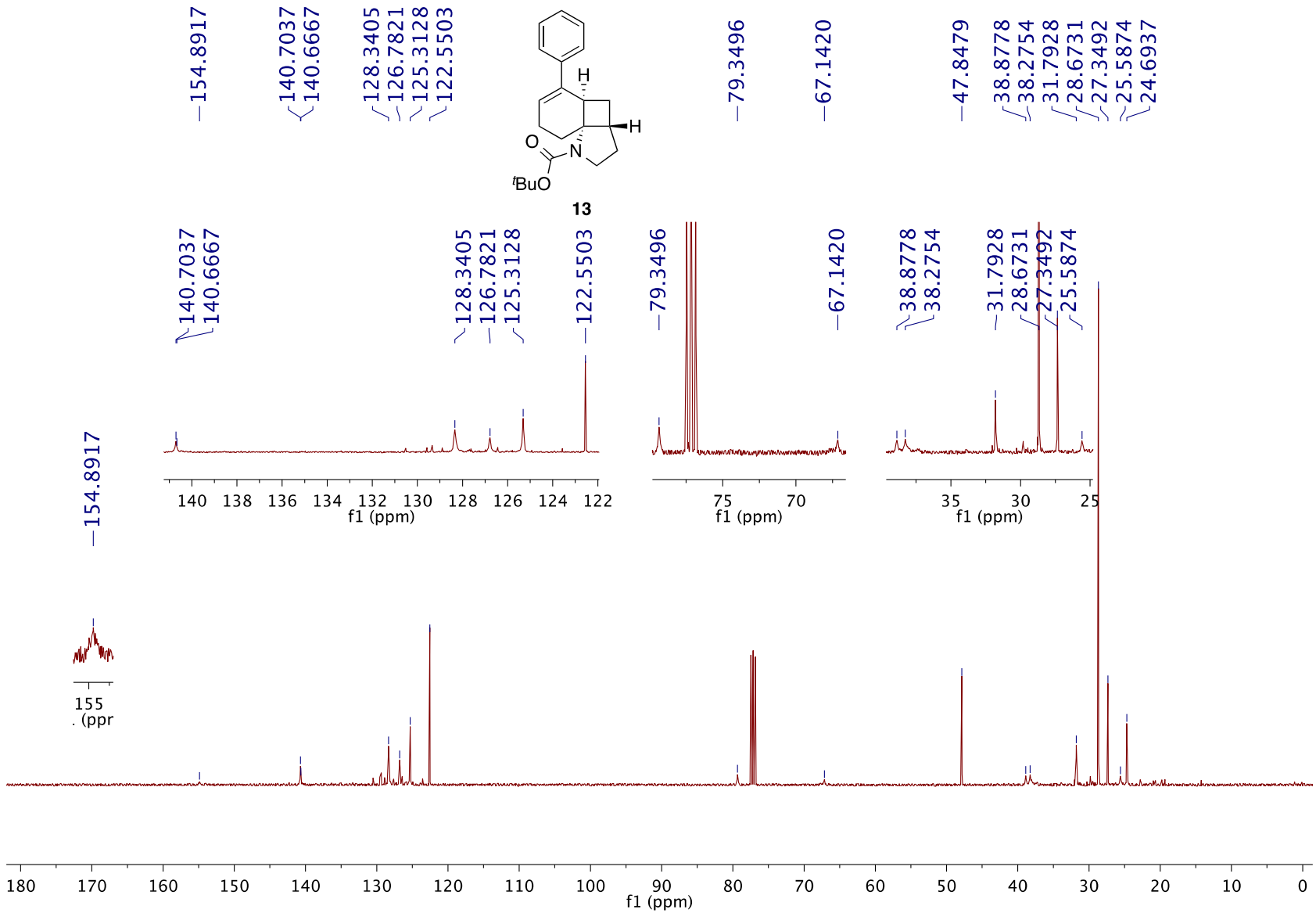
6.2046
3.8516
3.6358
2.8469
2.8275
2.8073
2.7879
2.5037
2.4903
2.4744
2.4589
2.4437
2.4296
2.3850
2.1180
1.8733
1.8620
1.8536
1.8389
1.8315
1.8243
1.8098
1.8014
1.7808
1.6351
3.2010
3.0205
2.0101
f1 (ppm)
4.23
1.01
1.00
2.28
1.09
1.12
1.37
3.65
1.25
1.30
1.30
11.52


154.8917
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140.6667
128.3405
126.7821
125.3128
122.5503
79.3496
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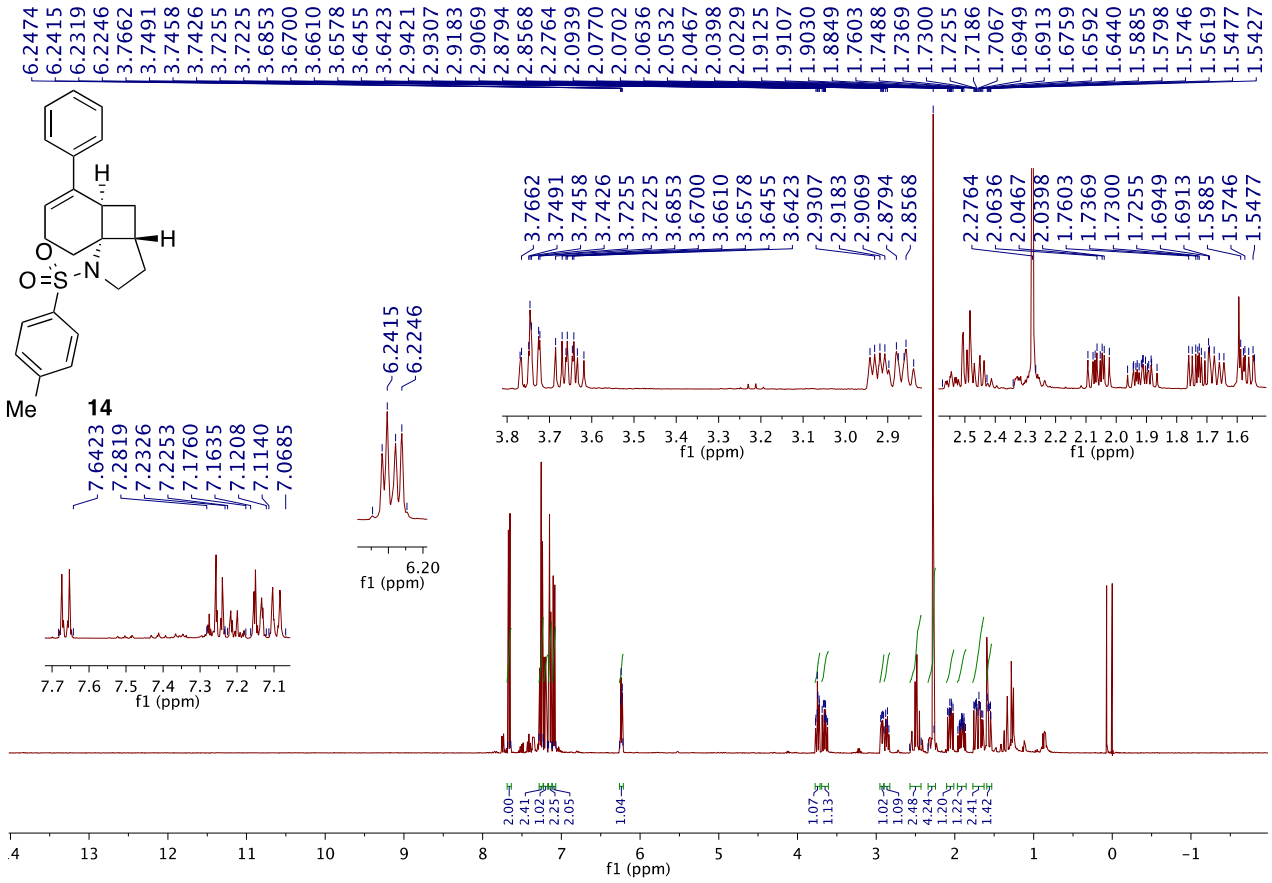
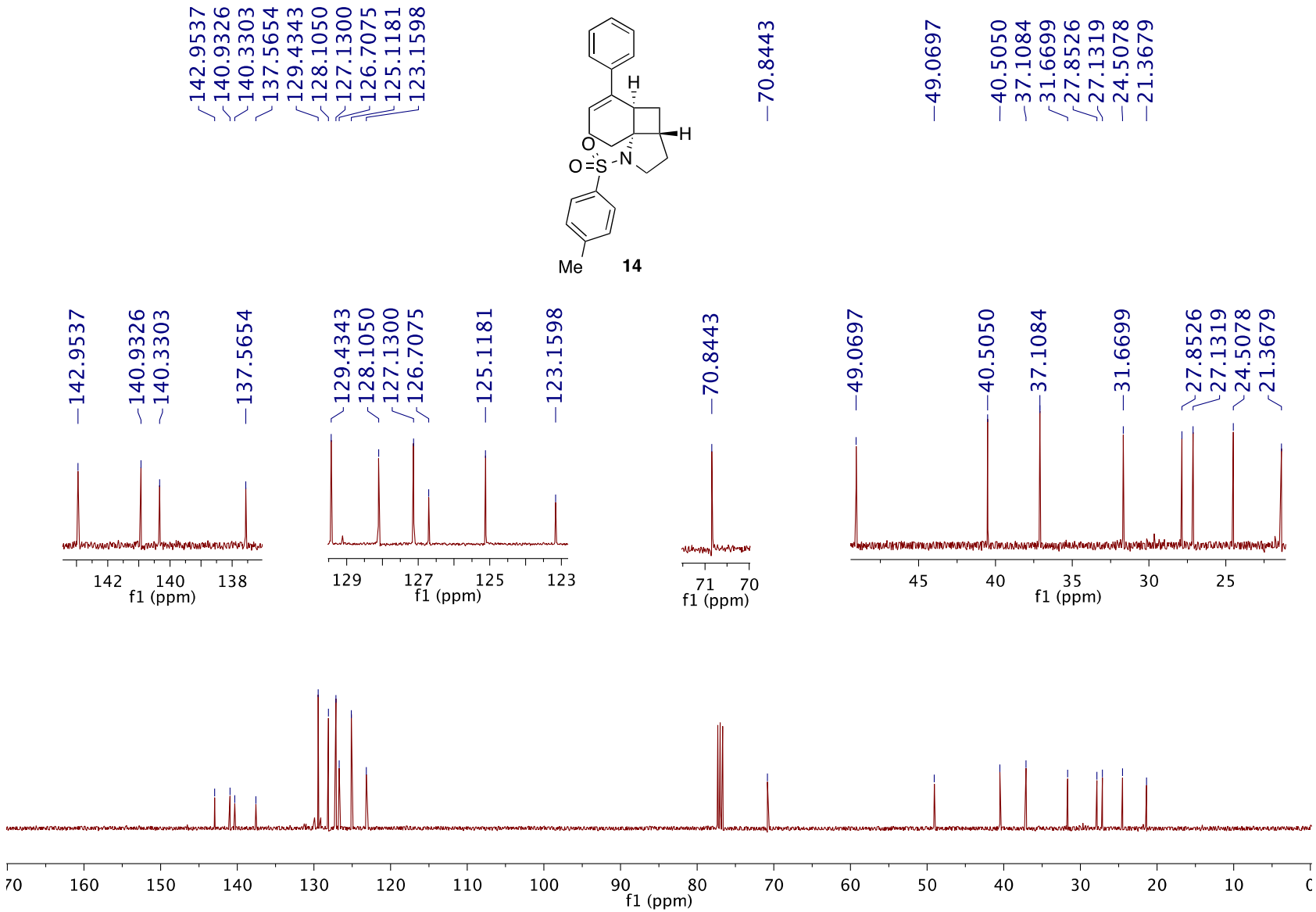
47.8479
38.8778
38.2754
31.7928
28.6731
27.3492
25.5874
24.6937
H
H
O
N
tBuO
13
f1 (ppm)

(*rel*-3a*R*,4a*R*,8a*S*)-5-Phenyl-1-tosyl-1,2,3,3a,4,4a,7,8-octahydrobenzo[1,4]cyclobuta[1,2-*b*]pyrrole (14)

A solution of Suzuki product **13** (27 mg, 0.083 mmol) was stirred at room temperature in a TFA/CH_2Cl_2 mixture (1:1, 2 mL) for 15 min. The mixture was concentrated, dissolved in CH_2Cl_2 (1 mL) and at 0 °C treated with triethylamine (21 mg, 0.207 mmol) and *p*-toluenesulfonyl chloride (16 mg, 0.084 mmol). After stirring for 2.5 h at room temperature, the reaction was quenched with a saturated solution of $NaHCO_3$ (1 mL), extracted with CH_2Cl_2 (3 × 2 mL), the combined organic layers were washed with brine (2 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification by column chromatography (EtOAc/heptane (1:5) sulfonamide **14** (29 mg, 0.079 mmol, 95% over two steps) was obtained as a white solid.

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137.5654
129.4343
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127.1300
126.7075
125.1181
123.1598
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49.0697
40.5050
37.1084
31.6699
27.8526
27.1319
24.5078
21.3679
H
H
O
O=S
N
Me
14
f1 (ppm)