ABSTRACT

Total Synthesis of *ent*-Plagiochianin B and Development of a Metathesis Approach to Aleutianamine

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Isolated in 2018 from the Chinese liverwort *Plagiochila duthiana*, plagiochianin B features a novel 6/7/3 tricyclic core. The total synthesis of *ent*-plagiochianin B was achieved in 9 synthetic steps from a known cycloheptenone and 13 steps overall starting from (+)-3-carene. As anticipated, the inherent stereochemistry found in (+)-3-carene led to production of material that was enantiomeric to the natural product. Key features of the synthesis include the utilization of a 6π-azatriene electrocyclization and the subsequent discovery of a palladium catalyzed oxidative cleavage of a terminal olefin.

The strained and heavily bridged pyrroloiminoquinone alkaloid aleutianamine was isolated in 2019 from the North Pacific sponge *Latrunculia* (*Latrunculia*) *austini* Samaai, Kelly & Gibbons, 2006 and exhibits cytotoxicity against a number of cancer cell lines. Noteworthy is aleutianamine's IC_{50} value of 25 nM against pancreatic cancer. Synthetic challenges posed by this natural product include the pyrroloiminoquinone core, an *N*,*S*-acetal, vinyl bromide containing 1,3-diene, and an iminium ion. Efforts to provide synthetic access to this biologically interesting alkaloid have been fruitful and several key

checkpoints have been reached, including: the development of a scalable Larock-type indole synthesis for construction of the iminoquinone region, a model system study has validated the viability of a tandem metathesis reaction to forge a bromotetrahydrobenzo[*b*] thiophene moiety, and preparation of an intermediate that contains all necessary carbons for the natural product and is structurally poised for synthesis completion. The challenges, victories, and outlook of this synthetic campaign are herein described.

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TABLE OF CONTENTS

LIST OF FIGURES vii

LIST OF SCHEMES xiv

LIST OF TABLES xvi

LIST OF ABBREVIATIONS xvii

ACKNOWLEDGMENTS xix

RESPECTIVE CONTRIBUTIONS xxi

CHAPTER ONE 1

Total Synthesis of *ent*-Plagiochianin B 1
1.1 Isolation and Biological Activity of Plagiochianins A and B 1
1.2 The First Total Synthesis of ent-Plagiochianin B 3
1.3 Experimental 24
1.4 References and Notes 61

CHAPTER TWO 66

Aleutianamine: Isolation and Biological Activity and Model System Validation of Tandem Metathesis Approach 66
2.1 Aleutianamine Isolation and Biological Activity 66
2.2 Tandem Metathesis Model System 67
2.3 Conclusion 73
2.4 Experimental 74
2.5 References and Notes 83

CHAPTER THREE 85

Aleutianamine: First Directed *Ortho* Metalation Approach with an Indole 85
3.1 Retrosynthetic Analysis of Aleutianamine 85
3.2 Larock Indole Synthesis and Directed Ortho Metalation Approach to Aleutianamine 89

3.3 Experimental 96
3.4 References and Notes 111

CHAPTER Four 114

Aleutianamine: Pyrroloiminoquinone Synthesis and Total Synthesis of Makaluvamine A 114
4.1 The Total Synthesis of Makaluvamine A 114
4.2 Experimental 118
4.3 References and Notes 134

CHAPTER FIVE 135

Aleutianamine: Current Synthetic Approach, Outlook and Summary 135
5.1 Development of a Metathesis Approach to Aleutianamine 135
5.2 Experimental 144
5.3 References and Notes 169

APPENDICES 171

APPENDIX A 172

Spectra Relevant to Chapter One 172

APPENDIX B 261

Spectra Relevant to Chapter Two 261

APPENDIX C 288

Spectra Relevant to Chapter Three 288

APPENDIX D 322

Spectra Relevant to Chapter Four 322

APPENDIX E 357

Spectra Relevant to Chapter Five 357

COMPOUND NOTEBOOK CROSS REFERENCE 413

BIBLIOGRAPHY 415

ABOUT THE AUTHOR 420

LIST OF FIGURES

CHAPTER FIVE

Figure 5.1. Single Crystal XRD Analysis of **5.05a** allows for Assignment of Relative Stereochemistry 141
Figure 5.2 Key 2D NMR Analyses of **5.04a**, **5.18**, and **5.19** 143

APPENDIX A

Figure A.01. **^{1}H NMR** (600 MHz, $CDCl_3$) of Acetal **1.09** 173
Figure A.02. **^{1}H NMR** (600 MHz, $CDCl_3$) of Acetal **1.09** (5.0 – 0.0 ppm inset) 174
Figure A.03. **^{13}C NMR** (101 MHz, $CDCl_3$) of Acetal **1.09** 175
Figure A.04. **^{1}H NMR** (300 MHz, $CDCl_3$) of Crude TMS Silyl Enol Ether **1.10** 176
Figure A.05. **^{13}C NMR** (75 MHz, $CDCl_3$) of Crude TMS Silyl Enol Ether **1.10** 177
Figure A.06. **FTIR** (thin film) Crude TMS Silyl Enol Ether **1.10** 178
Figure A.07. **^{1}H NMR** (400 MHz, $CDCl_3$) of Ketone **1.12** 179
Figure A.08. **^{1}H NMR** (400 MHz, $CDCl_3$) of Ketone **1.12** (4.0 – 0.5 ppm inset) 180
Figure A.09. **^{13}C NMR** (101 MHz, $CDCl_3$) of Ketone **1.12** 181
Figure A.10. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** 182
Figure A.11. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** (7.5 – 5.5 ppm inset) 183
Figure A.12. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** (3.0 – 0.0 ppm inset) 184
Figure A.13. **^{13}C NMR** (101 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** 185
Figure A.14. **FTIR** (thin film) of Yamakawa's Enone **1.07** 186
Figure A.15. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13** 187
Figure A.16. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13** (7.0 – 5.0 ppm inset) 188
Figure A.17. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13** (3.0 – 0.5 ppm inset) 189
Figure A.18. **^{13}C NMR** (101 MHz, $CDCl_3$) of Triflate **1.13** 190
Figure A.19. **FTIR** (thin film) of Triflate **1.13** 191
Figure A.20. **^{1}H NMR** (400 MHz, $CDCl_3$) of Vinyl Nitrile **1.06** 192
Figure A.21. **^{13}C NMR** (101 MHz, $CDCl_3$) of Vinyl Nitrile **1.06** 193
Figure A.22. **FTIR** (thin film) of Vinyl Nitrile **1.06** 194
Figure A.23. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16** 195
Figure A.24. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16** (10.0 – 5.0 ppm inset) 196
Figure A.25. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16** (3.0 – 0.5 ppm inset) 197
Figure A.26. **^{13}C NMR** (101 MHz, $CDCl_3$) of Aldehyde **1.16** 198
Figure A.27. **FTIR** (thin film) of Aldehyde **1.16** 199
Figure A.28. **^{1}H NMR** (400 MHz, $CDCl_3$) of Pyridine **1.14** 200
Figure A.29. **^{1}H NMR** (400 MHz, $CDCl_3$) of Pyridine **1.14** (3.0 – 0.5 ppm inset) 201
Figure A.30. **^{13}C NMR** (101 MHz, $CDCl_3$) of Pyridine **1.14** 202
Figure A.31. **FTIR** (thin film) of Pyridine **1.14** 203

Figure A.32. **^{1}H NMR** (400 MHz, $CDCl_3$) of Enone **1.22** 204
Figure A.33. **^{1}H NMR** (300 MHz, $CDCl_3$) of Ketone **1.23**.....205
Figure A.34. **^{1}H NMR** (300 MHz, $CDCl_3$) of Ketone **1.23** (3.5 – 0.5 ppm inset) 206
Figure A.35. **^{13}C NMR** (101 MHz, $CDCl_3$) of Ketone **1.23**.....207
Figure A.36. **FTIR** (thin film) of Ketone **1.23** 208
Figure A.37. **^{1}H NMR** (400 MHz, $CDCl_3$) of Olefin **1.24** 209
Figure A.38. **^{1}H NMR** (400 MHz, $CDCl_3$) of Olefin **1.24** (3.0 – 0.5 ppm inset).....210
Figure A.39. **^{13}C NMR** (101 MHz, $CDCl_3$) of Olefin **1.24**.....211
Figure A.40. **FTIR** (thin film) Olefin **1.24**.....212
Figure A.41. **^{1}H NMR** (400 MHz, $CDCl_3$) of Tosylate **1.28**.....213
Figure A.42. **^{13}C NMR** (101 MHz, $CDCl_3$) of Tosylate **1.28** 214
Figure A.43. **^{1}H NMR** (400 MHz, $CDCl_3$) of Propargyl Alcohol **1.29**.....215
Figure A.44. **^{13}C NMR** (101 MHz, $CDCl_3$) of Propargyl Alcohol **1.29**.....216
Figure A.45. **^{1}H NMR** (400 MHz, $CDCl_3$) of Benzoate **1.30** 217
Figure A.46. **^{1}H NMR** (400 MHz, $CDCl_3$) of Crude **1.31**.....218
Figure A.47. **^{1}H NMR** (400 MHz, $CDCl_3$) of Terminal Olefin **1.26** 219
Figure A.48. **^{1}H NMR** (400 MHz, $CDCl_3$) of
Terminal Olefin **1.26** (10.0 – 4.0 ppm inset) 220
Figure A.49. **^{1}H NMR** (400 MHz, $CDCl_3$) of
Terminal Olefin **1.27** (3.0 – 0.5 ppm inset) 221
Figure A.50. **^{13}C NMR** (101 MHz, $CDCl_3$) of Terminal Olefin **1.26** 222
Figure A.51. **FTIR** (thin film) of Terminal Olefin **1.26**.....223
Figure A.52. **^{1}H NMR** (400 MHz, $CDCl_3$) of aldehyde **1.34**.....224
Figure A.53. **^{13}C NMR** (101 MHz, $CDCl_3$) of aldehyde **1.34**.....225
Figure A.54. **FTIR** (thin film) of aldehyde **1.34** 226
Figure A.55. **^{1}H NMR** (400 MHz, $CDCl_3$) of aldehyde **1.38**.....227
Figure A.56. **^{13}C NMR** (101 MHz, $CDCl_3$) of aldehyde **1.38**.....228
Figure A.57. **FTIR** (thin film) of aldehyde **1.38** 229
Figure A.58. **^{1}H NMR** (400 MHz, $CDCl_3$) Crude Acid **SI-1.05**.....230
Figure A.59. **^{13}C NMR** (101 MHz, $CDCl_3$) Crude Acid **SI-1.05**.....231
Figure A.60. **FTIR** (thin film) Crude Acid **SI-1.05** 232
Figure A.61. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05** 233
Figure A.62. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05** (9.5 – 5.5 ppm inset) 234
Figure A.63. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05** (3.0 – 0.5 ppm inset) 235
Figure A.64. **^{13}C NMR** (101 MHz, $CDCl_3$) Ester **1.05** 236
Figure A.65. **FTIR** (thin film) Ester **1.05**.....237
Figure A.66. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **1.39** 238
Figure A.67. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **1.39** (4.5 – 0.5 inset).....239
Figure A.68. **^{13}C NMR** (101 MHz, $CDCl_3$) Ketone **1.39**.....240
Figure A.69. **FTIR** (thin film) Ketone **1.39**.....241
Figure A.70. **^{1}H NMR** (400 MHz, $CDCl_3$) Benzylic Alcohols **1.40**.....242
Figure A.71. **^{13}C NMR** (101 MHz, $CDCl_3$) Benzylic Alcohols **1.40**.....243
Figure A.72. **FTIR** (thin film) Benzylic Alcohols **1.40** 244
Figure A.73. **^{1}H NMR** (400 MHz, $CDCl_3$) Olefin **1.25** 245
Figure A.74. **^{1}H NMR** (400 MHz, $CDCl_3$) Olefin **1.25** (3.0 – 0.5 ppm inset) 246
Figure A.75. **^{13}C NMR** (101 MHz, $CDCl_3$) Olefin **1.25** 247

Figure A.76. **FTIR** (thin film) Olefin **1.25** 248
Figure A.77. **^{1}H NMR** (600 MHz, Methanol-*d4*)
Diastereomer of *ent*-Plagiochianin B **1.41** 249
Figure A.78. **^{1}H NMR** (600 MHz, Methanol-*d4*)
Diastereomer of *ent*-Plagiochianin B **1.41** (5.0 – 0.0 ppm inset) 250
Figure A.79. **^{13}C NMR** (151 MHz, Methanol-*d4*)
Diastereomer of *ent*-Plagiochianin B **1.41** 251
Figure A.80. **FTIR** (thin film) Diastereomer of *ent*-Plagiochianin B **1.41** 252
Figure A.81. **^{1}H NMR** (600 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02** 253
Figure A.82. **^{1}H NMR** (600 MHz, Methanol-*d4*)
ent-Plagiochianin B **(-)-1.02** (4.5 – 0.5 ppm inset) 254
Figure A.83. **^{13}CNMR** (151 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02** 255
Figure A.84. **FTIR** (Thin film) *ent*-Plagiochianin B **(-)-1.02** 256
Figure A.85. **^{1}H NMR** (600 MHz, Methanol-*d4*) Overlay of Natural
Plagiochianin B **(+)-1.02** & Synthetic *ent*-Plagiochianin B **(-)-1.02** 257
Figure A.86. **^{13}C NMR** (151 MHz, Methanol-*d4*) Overlay of Natural
Plagiochianin B **(+)-1.02** & Synthetic *ent*-Plagiochianin B **(-)-1.02** 258
Figure A.87. **NOESY** (400 MHz, Methanol-*d4*)
Diastereomer of *ent*-Plagiochianin B **1.41** 259
Figure A.88. **NOESY** (600 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02** 260

APPENDIX B

Figure B.01. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **2.16** 262
Figure B.02. **^{13}C NMR** (126 MHz, $CDCl_3$) Ketone **2.16** 263
Figure B.03. **FTIR** (thin film) Ketone **2.16** 264
Figure B.04. **^{1}H NMR** (400 MHz, $CDCl_3$)
Major Diastereomer Tertiary Alcohol **2.17** 265
Figure B.05. **^{13}C NMR** (101 MHz, $CDCl_3$)
Major Diastereomer Tertiary Alcohol **2.17** 266
Figure B.06. **FTIR** (thin film) Major Diastereomer Tertiary Alcohol **2.17** 267
Figure B.07. **^{1}H NMR** (600 MHz, $CDCl_3$)
Minor Diastereomer Tertiary Alcohol **2.17** 268
Figure B.08. **^{13}C NMR** (151 MHz, $CDCl_3$)
Minor Diastereomer Tertiary Alcohol **2.17** 269
Figure B.09. **FTIR** (thin film) Minor Diastereomer Tertiary Alcohol **2.17** 270
Figure B.10. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **2.22** 271
Figure B.11. **^{13}C NMR** (101 MHz, $CDCl_3$) Tertiary Alcohol **2.22**
with DEPT 90 (middle) and DEPT 135 (top) overlayed 272
Figure B.12. **FTIR** (thin film) Tertiary Alcohol **2.22** 273
Figure B.13. **^{1}H NMR** (400 MHz, $CDCl_3$) Sulfide **2.19** 274
Figure B.14. **^{13}C NMR** (101 MHz, $CDCl_3$) Sulfide **2.19** with DEPT 90 (middle)
and DEPT 135 (top) overlayed 275
Figure B.15. **FTIR** (thin film) Sulfide **2.19** 276
Figure B.16. **^{1}H NMR** (500 MHz, $CDCl_3$) Major Diastereomer of Sulfide **2.20** 277
Figure B.17. **^{13}C NMR** (151 MHz, $CDCl_3$) Major Diastereomer of Sulfide **2.20** 278

Figure B.18. **FTIR** (thin film) Major Diastereomer of Sulfide **2.20** 279
Figure B.19. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer of Sulfide **2.20** 280
Figure B.20. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Sulfide **2.20**.....281
Figure B.21. **FTIR** (thin film) Minor Diastereomer Sulfide **2.20** 282
Figure B.22. **^{1}H NMR** (400 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21** 283
Figure B.23. **^{13}C NMR** (101 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21** with DEPT 90 (middle) and DEPT 135 (top) overlayed 284
Figure B.24. **FTIR** (thin film) Tetrahydrobenzo[*b*] thiophene **2.21**.....285
Figure B.25. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21** ..286
Figure B.26. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21**.....287

APPENDIX C

Figure C.01. **^{1}H NMR** (500 MHz, $CDCl_3$) Alkyne **3.08**.....289
Figure C.02. **^{13}C NMR** (126 MHz, $CDCl_3$) Alkyne **3.08**.....290
Figure C.03. **FTIR** (thin film) Alkyne **3.08**.....291
Figure C.04. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.07**.....292
Figure C.05. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.07**.....293
Figure C.06. **FTIR** (thin film) Indole **3.07** 294
Figure C.07. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.20**.....295
Figure C.08. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.20**.....296
Figure C.09. **FTIR** (thin film) Indole **3.20** 297
Figure C.10. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Indole **3.20**.....298
Figure C.11. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.21**.....299
Figure C.12. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.21**.....300
Figure C.13. **FTIR** (thin film) Indole **3.21** 301
Figure C.14. **^{1}H NMR** (300 MHz, $CDCl_3$) Terminal Olefin **3.24**.....302
Figure C.15. **^{1}H NMR** (600 MHz, $CDCl_3$) Aldehyde **3.25** 303
Figure C.16. **^{13}C NMR** (126 MHz, $CDCl_3$) Aldehyde **3.25** 304
Figure C.17. **FTIR** (thin film) Aldehyde **3.25**.....305
Figure C.18. **^{1}H NMR** (500 MHz, $CDCl_3$) Benzylic Alcohol **3.06**.....306
Figure C.19. **^{13}C NMR** (126 MHz, $CDCl_3$) Benzylic Alcohol **3.06**.....307
Figure C.20. **FTIR** (thin film) Benzylic Alcohol **3.06** 308
Figure C.21. **^{1}H-^{15}N HMBC** (400, 41 MHz, $CDCl_3$) Stannane **iii.21** 309
Figure C.22. **^{1}H NMR** (500 MHz, $CDCl_3$) Ketone **3.26** 310
Figure C.23. **^{13}C NMR** (126 MHz, $CDCl_3$) Ketone **3.26** 311
Figure C.24. **FTIR** (thin film) Ketone **3.26**.....312
Figure C.25. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **3.26**.....313
Figure C.26. **^{1}H NMR** (400 MHz, $CDCl_3$) Deuterium Incorporation Experiment with Tertiary Alcohol **3.26**.....314
Figure C.27. **^{13}C NMR** (151 MHz, $CDCl_3$) Tertiary Alcohol **3.27**.....315
Figure C.28. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30**.....316
Figure C.29. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30** (8.0 – 6.5 ppm inset) 317
Figure C.30. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30**

(6.0 – 3.6 ppm inset) 318
Figure C.31. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30**
(4.5 – 2.5 ppm inset) 319
Figure C.32. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30**
(2.0 – 0.0 ppm inset) 320
Figure C.33. **^{13}C NMR** (151 MHz, $CDCl_3$) Suspected Allene **3.30**
with DEPT 90 (middle) and DEPT 135 (top) overlayed 321

APPENDIX D

Figure D.01 **^{1}H NMR** (400 MHz, $CDCl_3$) Bis Phenol **4.06** 323
Figure D.02 **^{13}C NMR** (101 MHz, $CDCl_3$) Bis Phenol **4.06** 324
Figure D.03 **^{13}C NMR** (101 MHz, $CDCl_3$) Bis Phenol **4.06** 325
Figure D.04 **^{1}H NMR** (500 MHz, $CDCl_3$) Trimethoxy Nitro **4.07** 326
Figure D.05 **^{13}C NMR** (126 MHz, $CDCl_3$) Trimethoxy Nitro **4.07** 327
Figure D.06 **FTIR** (thin film) Trimethoxy Nitro **4.07** 328
Figure D.07 **^{1}H NMR** (400 MHz, $CDCl_3$) Iodine **4.08** 329
Figure D.08 **^{13}C NMR** (126 MHz, $CDCl_3$) Iodine **4.08** 330
Figure D.09 **FTIR** (thin film) Iodine **4.08** 331
Figure D.10 **^{1}H NMR** (300 MHz, $CDCl_3$) Aniline **4.04** 332
Figure D.11 **^{13}C NMR** (75 MHz, $CDCl_3$) Aniline **4.04** 333
Figure D.12 **FTIR** (thin film) Aniline **4.04** 334
Figure D.13 **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **4.02** 335
Figure D.14 **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **4.02** 336
Figure D.15 **FTIR** (thin film) Indole **4.02** 337
Figure D.16 **^{1}H NMR** (400 MHz, $CDCl_3$) Methyl Indole **4.09** 338
Figure D.17 **^{13}C NMR** (101 MHz, $CDCl_3$) Methyl Indole **4.09** 339
Figure D.18 **FTIR** (thin film) Methyl Indole **4.09** 340
Figure D.19 **^{1}H NMR** (300 MHz, $CDCl_3$) Crude Indoloquinone **SI-4.10** 341
Figure D.20 **^{1}H NMR** (300 MHz, $CDCl_3$) Tosylate **4.10** 342
Figure D.21 **^{13}C NMR** (126 MHz, $CDCl_3$) Tosylate **4.10** 343
Figure D.22 **FTIR** (thin film) Tosylate **4.10** 344
Figure D.23 **^{1}H NMR** (400 MHz, $CDCl_3$) Azide **4.11** 345
Figure D.24 **^{13}C NMR** (101 MHz, $CDCl_3$) Azide **4.11** 346
Figure D.25 **FTIR** (thin film) Azide **4.11** 347
Figure D.26 **^{1}H NMR** (400 MHz, $CDCl_3$) Pyrroloiminoquinone **4.12** 348
Figure D.27 **^{13}C NMR** (101 MHz, $CDCl_3$) Pyrroloiminoquinone **4.12** 349
Figure D.28 **FTIR** (thin film) Pyrroloiminoquinone **4.12** 350
Figure D.29 **^{1}H NMR** (600 MHz, Methanol-*d4*) Vinylogous Amidine **4.13** 351
Figure D.30 **^{13}C NMR** (151MHz, Methanol-*d4*) Vinylogous Amidine **4.13** 352
Figure D.31 **FTIR** (thin film) Vinylogous Amidine **4.13** 353
Figure D.32 **^{1}H NMR** (600 MHz, DMSO-*d6*) Makaluvamine A **4.01** 354
Figure D.33 **^{13}C NMR** (151 MHz, DMSO-*d6*) Makaluvamine A **4.01** 355
Figure D.34 **FTIR** (thin film) Makaluvamine A **4.01** 356

APPENDIX E

Figure E.01. **^{1}H NMR** (400 MHz, $CDCl_3$) MOM-Indole **5.08**.....358
Figure E.02. **^{13}C NMR** (101 MHz, $CDCl_3$) MOM-Indole **5.08** 359
Figure E.03. **FTIR** (thin film) MOM-Indole **5.08**.....360
Figure E.04. **^{1}H NMR** (400 MHz, $CDCl_3$) Benzylic Alcohol **5.09**.....361
Figure E.05. **^{13}C NMR** (101 MHz, $CDCl_3$) Benzylic Alcohol **5.09**.....362
Figure E.06. **FTIR** (thin film) Benzylic Alcohol **5.09** 363
Figure E.07. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **5.10**.....364
Figure E.08. **^{13}C NMR** (101 MHz, $CDCl_3$) Ketone **5.10** 365
Figure E.09. **FTIR** (thin film) Ketone **5.10**.....366
Figure E.10. **^{1}H NMR** (400 MHz, $CDCl_3$) β-Hydroxy Ketone **5.06**.....367
Figure E.11. **^{13}C NMR** (101 MHz, $CDCl_3$) β-Hydroxy Ketone **5.06**.....368
Figure E.12. **FTIR** (thin film) β-Hydroxy Ketone **5.06** 369
Figure E.13. **^{1}H NMR** (400 MHz, $CDCl_3$) 1,3-Diol **5.12**.....370
Figure E.14. **^{13}C NMR** (101 MHz, $CDCl_3$) 1,3-Diol **5.12**.....371
Figure E.15. **FTIR** (thin film) 1,3-Diol **5.12** 372
Figure E.16. **^{1}H NMR** (400 MHz, $CDCl_3$) E1$_{cB}$ Ketone **5.13**.....373
Figure E.17. **^{13}C NMR** (101 MHz, $CDCl_3$) E1$_{cB}$ Ketone **5.13**.....374
Figure E.18. **^{13}C NMR** (101 MHz, $CDCl_3$) E1$_{cB}$ Ketone **5.13**.....375
Figure E.19. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **5.14** 376
Figure E.20. **^{13}C NMR** (101 MHz, $CDCl_3$) Tertiary Alcohol **5.14** 377
Figure E.21. **FTIR** (thin film) Tertiary Alcohol **5.14**.....378
Figure E.22. **^{1}H NMR** (400 MHz, $CDCl_3$) 1,3-Diol **5.15**.....379
Figure E.23. **^{13}C NMR** (101 MHz, $CDCl_3$) 1,3-Diol **5.15**.....380
Figure E.24. **FTIR** (thin film) 1,3-Diol **5.15** 381
Figure E.25. **^{1}H NMR** (400 MHz, $CDCl_3$) Major Diastereomer Acetate **5.16a**.....382
Figure E.26. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Acetate **5.16a** 383
Figure E.27. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Acetate **5.16a** 384
Figure E.28. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer Acetate **5.16b** 385
Figure E.29. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Acetate **5.16b** 386
Figure E.30. **FTIR** (thin film) Minor Diastereomer Acetate **5.16b**.....387
Figure E.31. **^{1}H NMR** (400 MHz, $CDCl_3$) Major Diastereomer Silylene **5.05a**.....388
Figure E.32. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Silylene **5.05a**.....389
Figure E.33. **FTIR** (thin film) Major Diastereomer Silylene **5.05a** 390
Figure E.34. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer Silylene **5.05b** 391
Figure E.35. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Silylene **5.05b** 392
Figure E.36. **FTIR** (thin film) Minor Diastereomer Silylene **5.05b**.....393
Figure E.37. **^{1}H NMR** (400 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**.....394
Figure E.38. **^{13}C NMR** (101 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**
with DEPT 90 (middle) and DEPT 135 (top) overlayed 395
Figure E.39. **FTIR** (thin film) Tandem Metathesis Diol **5.04a** 396
Figure E.40. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**.....397
Figure E.41. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$)
Tandem Metathesis Diol **5.04a**.....398

Figure E.42. **^{1}H-^{13}C HSQC** (400, 101 MHz, $CDCl_3$)
Tandem Metathesis Diol **5.04a** 399
Figure E.43. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$)
Tandem Metathesis Diol **5.04a** 400
Figure E.44. **^{1}H NMR** (500 MHz, $CDCl_3$) Enyne Metathesis Product **5.18** 401
Figure E.45. **^{13}C NMR** (151 MHz, $CDCl_3$) Enyne Metathesis Product **5.18** 402
Figure E.46. **FTIR** (thin film) Enyne Metathesis Product **5.18** 403
Figure E.47. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.18** 404
Figure E.48. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.18** Inset 405
Figure E.49. **^{1}H NMR** (400 MHz, $CDCl_3$) Enyne Metathesis Product **5.19** 406
Figure E.50. **^{13}C NMR** (101 MHz, $CDCl_3$) Enyne Metathesis Product **5.19** 407
Figure E.51. **FTIR** (thin film) Enyne Metathesis Product **5.19** 408
Figure E.52. **^{1}H-^{1}H COSY** (400 MHz, $CDCl_3$) **5.19** 409
Figure E.53. **^{1}H-^{13}C HSQC** (400, 101 MHz, $CDCl_3$) **5.19** 410
Figure E.54. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.19** 411
Figure E.55. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.19** Inset 412

LIST OF SCHEMES

CHAPTER ONE

Scheme 1.1. Proposed Biosynthesis of **1.01** and **(+)-1.02** 2
Scheme 1.2. Initial Retrosynthetic analysis of *ent*-Plagiochianin B, **(-)-1.02**....3
Scheme 1.3. Access to Vinyl Triflate, **1.13**, and Synthesis of Vinyl Nitrile, **1.06** 4
Scheme 1.4. Revised Retrosynthetic Analysis of **(-)-1.02** 6
Scheme 1.5. Zhai's pyridine synthesis via 6π-azatriene electrocyclization 7
Scheme 1.6. Synthesis of methyl pyridine, **1.14**....8
Scheme 1.7. Newhouse's precedent regarding benzylic oxidations with Cr(V) and our application of this chemistry 9
Scheme 1.8 Challenging Methylation of **1.23** 12
Scheme 1.9. Final Retrosynthetic analysis of **(-)-1.02**....14
Scheme 1.10. Synthesis of **1.31** and application in 6π-azatriene electrocyclization with aldehyde **1.16** 15
Scheme 1.11. Discovery of a Regioselective Pd-mediated Oxidative Cleavage 16
Scheme 1.12 Precedent from Spencer and Mechanistic Investigation of Oxidative Cleavage Reaction on **1.26** 18
Scheme 1.13 Scheme 1.13. Synthesis of Ketone **1.39** and Isolation of Hydration Product **1.40** 22
Scheme 1.14. Final Reactions in the Total Synthesis of *ent*-Plagiochianin B **(-)-1.02** 23

CHAPTER TWO

Scheme 2.1. Retrosynthetic Analysis of Aleutianamine and representative Ruthenium Alkylidene complexes for Olefin Metathesis 68
Scheme 2.2. Honda's Tandem Metathesis Precedent 69
Scheme 2.3. Precedent for Ring-Closing Metathesis with Alkenyl Bromides 70
Scheme 2.4. Clayden's Synthesis of enantioenriched dihydrothiophenes via Olefin Metathesis of Allyl Sulfides....71
Scheme 2.5. Enyne/RCM Model System 72

CHAPTER THREE

Scheme 3.1. Retrosynthetic Analysis of Aleutianamine....86
Scheme 3.2. Key Precedent for D*o*M Strategy and Inspiration for Transition-metal Mediated Indole Synthesis 87
Scheme 3.3. Larock Indole Synthesis 89
Scheme 3.4. Aldehyde **3.25** Synthesis 90
Scheme 3.5. Synthesis of Tertiary Alcohol **3.27** 91
Scheme 3.6. Rationale for Cautious Assertion of Allene Synthesis 92

Scheme 3.7. Attempted Boronation Conditions 94

CHAPTER FOUR

Scheme 4.1. Retrosynthetic Analysis of Makaluvamine A 115
Scheme 4.2. New Larock Indole Synthesis 116
Scheme 4.3 Total Synthesis of Makaluvamine A **4.01**.....117

CHAPTER FIVE

Scheme 5.1. Retrosynthetic Analysis of Aleutianamine **5.01**.....136
Scheme 5.2. Synthesis of Aldol Product **5.06**.....137
Scheme 5.3. Synthesis of 1,3-Diol **5.12** and accompanying
Elimination Products **5.13** and **5.14**.....138
Scheme 5.4. Synthesis of Silylene **5.05** 140
Scheme 5.5. Synthesis of Desired Diol **5.04a** and Divergent Reactivity of the
Diastereomers **5.05a** and **5.05b** 142

LIST OF TABLES

CHAPTER ONE

Table 1.1. Advancing **1.23**: further attempts at benzylic oxidation.....11
Table 1.2 Further Investigation of Oxidative Cleavage Mechanism 20

CHAPTER FOUR

Table 4.1. Collation of **^{1}H NMR** (600 MHz, DMSO-*d6*)
data for Natural and Synthetic Makaluvamine A (**4.01**).....132
Table 4.2. Collation of **^{13}C NMR** (600 MHz, DMSO-*d6*)
data for Natural and Synthetic Makaluvamine A (**4.01**).....133

LIST OF ABBREVIATIONS

AcOH	acetic acid
Boc_2O	di-tert-butyl dicarbonate
Cat.	catalyst
$CDCl_3$	deuterochloroform
CH_2Cl_2	methylene chloride
Cl	chloride
CO	carbon monoxide
COSY	correlation spectroscopy
DCE	dicholorethane
DEPT	distortionless enhancement by polarization transfer
$(DHQD)_2AQN$	hydroquinidine (anthraquinone-1,4-diyl) diether
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
D*o*M	directed *ortho*-metalation
ECD	electronic circular dichroism
ent	enantiomer(ic)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FTIR	Fourier transform infrared spectroscopy
HMBC	heteronuclear multiple-bond correlation
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol
$K_2OsO_4 \cdot 2H_2O$	potassium osmate dihydrate
LDA	lithium diisopropylamine
LiHMDS	lithium bis(trimethylsilyl)amide
Methanol-*d4*	tetradeuteromehthanol
MeOH	methanol
MOM	methoxymethyl
Me	methyl
MeCN	acetonitrile
MS	molecular sieves
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p-TsOH	4-toluenesulfonic acid
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
rt	room temperature (usually 23 °C)
sat.	saturated
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	4-toluenesulfonyl
UPLC	ultra performance liquid chromatography
UV	ultraviolet
XRD	X-ray diffraction

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RESPECTIVE CONTRIBUTIONS

Chapter One

All reactions, spectra, and retrosynthetic analyses were performed by Richard K. Jackson, III. Prof. Yu-Wen Huang is graciously acknowledged for the laboratory training he so tirelessly gave to R. K. Jackson, III. R. K. Jackson, III is further indebted to Prof. Yu-Wen Huang and Prof. John L. Wood for listening to and critically examining the ideas of R. K. Jackson, III regarding a total synthesis of the title compound, until they finally produced the desired result.

Chapter Two

All reactions, spectra, and retrosynthetic analyses were performed by Richard K. Jackson, III. Prof. John L. Wood is credited with proposing the possibility of a tandem metathesis approach to aleutianamine.

Chapter Three

With the exception of the design of aniline **3.09** and the attempted boronations, all reactions, spectral data collection and tabulation, and retrosynthetic analyses were performed by Richard K. Jackson, III. R. K. Jackson, III is credited with proposing the Larock indole synthesis and Directed *ortho* Metalation approach to aleutianamine. Dr. Jason An is credited with synthetic design of aniline **3.09** and a scalable route to the aldehyde **3.25**. The indole synthesis described is the streamlined product of an expensive route designed by R. K. Jackson, III which was re-worked by Dr. Jason An.

Chapter Four

All reactions were run by Dr. Jason An. The Dakin oxidation, methylation of the indole, aryl oxidation, tosylation, and azide synthesis were repeated by Richard K. Jackson, III for the purposes of characterization. Spectral data collection and tabulation were performed by R. K. Jackson, III. The synthetic route was designed by Dr. Jason An with guidance from R. K. Jackson, III. In particular the highly efficient aniline synthesis is the streamlined product of an expensive route designed by R. K. Jackson, III which was re-worked by Dr. Jason An.

Chapter Five

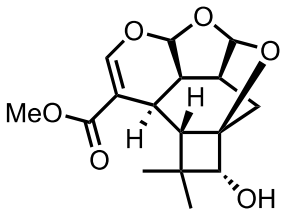
All reactions, spectral data collection and tabulation, and retrosyntheic analyses were performed by Richard K. Jackson, III and Dr. Jason An. In particular, Dr. Jason An performed the silylation reaction and enyne metathesis on the minor silylene diastereomer. The remaining reactions were performed by R. K. Jackson, III and repeated by Dr. Jason An. Joseph P. Tuccinardi is credited with proposing the idea of a tandem metathesis with labile silicon-based tether.

To my wife, Claire Alexis.

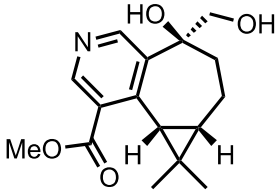
CHAPTER ONE

Total Synthesis of *ent*-Plagiochianin B

1.1 Isolation and Biological Activity of Plagiochianins A and B

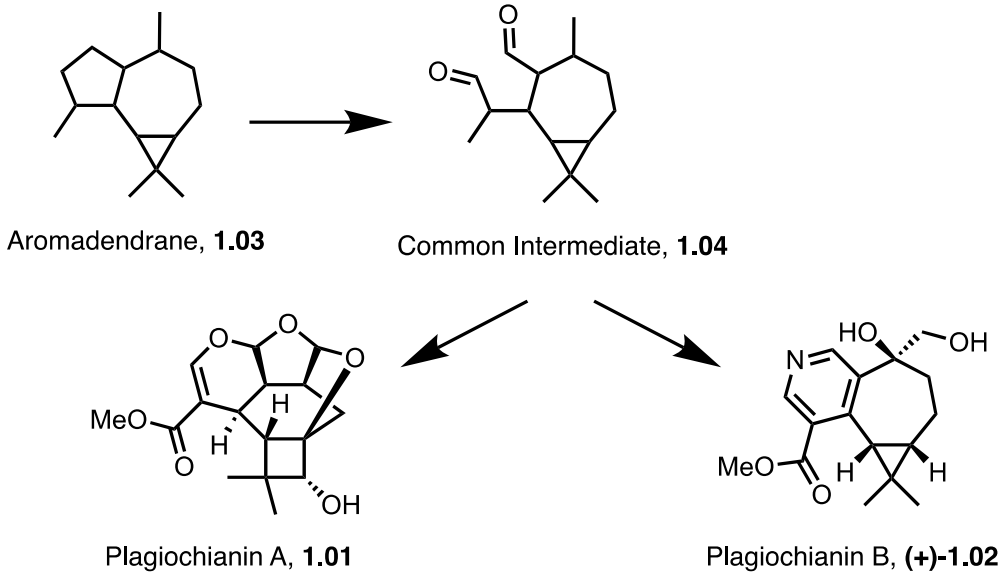


Plagiochianin A, **1.01**



Plagiochianin B, **(+)-1.02**

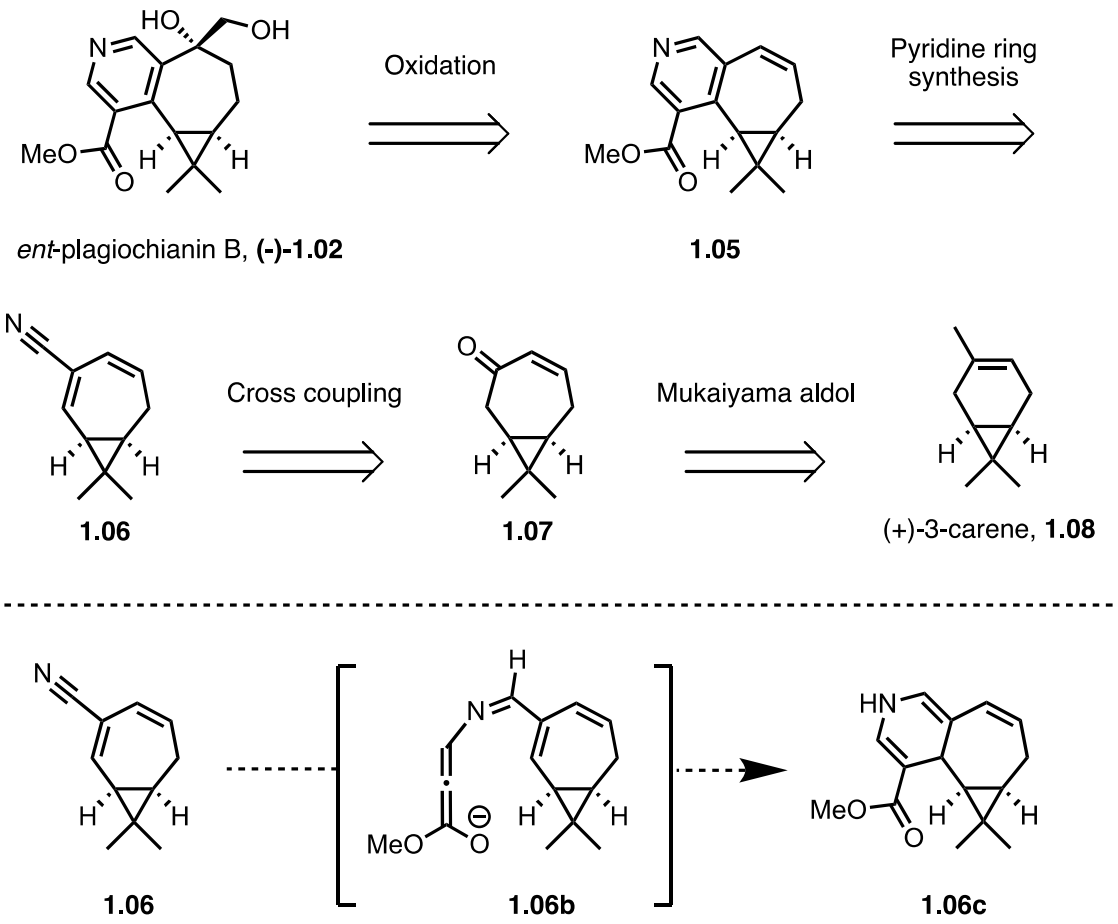
Plagiochianins A and B (**1.01** and **(+)-1.02** respectively) were isolated in 2018 from the Chinese liverwort *Plagiochila duthiana*.[1] The liverwort was collected in the North China province of Shanxi and was allowed to air-dry. The dried plant material (150 g) was then milled and extracted with ethanol. The crude ethanolic extracts were further purified by iterative chromatography (varying stationary phase), and finally HPLC (MeOH/H_2O) to yield 1.34 mg and 1.46 mg of **1.01** and **(+)-1.02**, respectively. The natural products were fully characterized and the relative and absolute stereochemistries of **1.01** were confirmed through single crystal XRD analysis. The relative stereochemistry of **(+)-1.02** was assigned via nOe correlations and the absolute configuration was determined by comparison of calculated and experimental ECD spectra. The minimal inhibitory detection of **1.01** against acetylcholinesterase was found to be 5 μg using galantamine (0.01 μg) as a positive control. Neither **1.01** nor **(+)-1.02** displayed significant activity against human non-small cell lung cancer A549 or antifungal activity (*Candida albicans* SC5314, DSY654, YEM13, and YEM15).



Scheme 1.1. Proposed Biosynthesis of **1.01** and **(+)-1.02**

In the same isolation paper,[1] the authors suggested a biosynthesis of **1.01** and **(+)-1.02** in which both natural products were derived from aromadendrane **1.03** through a common intermediate **1.04**. The hypothesis regarding a common intermediate such as **1.04** intrigued us, and indeed, at the conception of this synthetic adventure a divergent total synthesis towards both **1.01** and **(+)-1.02** was considered. Our first aim, however, was gaining access to **(+)-1.02**, the simpler of the two isolated natural products. We wanted our synthesis to draw from the chiral pool, and in particular, build upon a Mukaiyama aldol approach developed by Yamakawa which enables the synthesis of enone **1.07**.[2] Yamakawa's enone (**1.07**) is derived from commercially available (+)-3-carene, **1.08** (Scheme 1.2, *vide infra*), and due to the inherent stereochemistry found in **1.08**, we expected that employing this as a starting material would eventually lead us to the enantiomer of Plagiochianin B (*i.e.* **(-)-1.02**).[3]

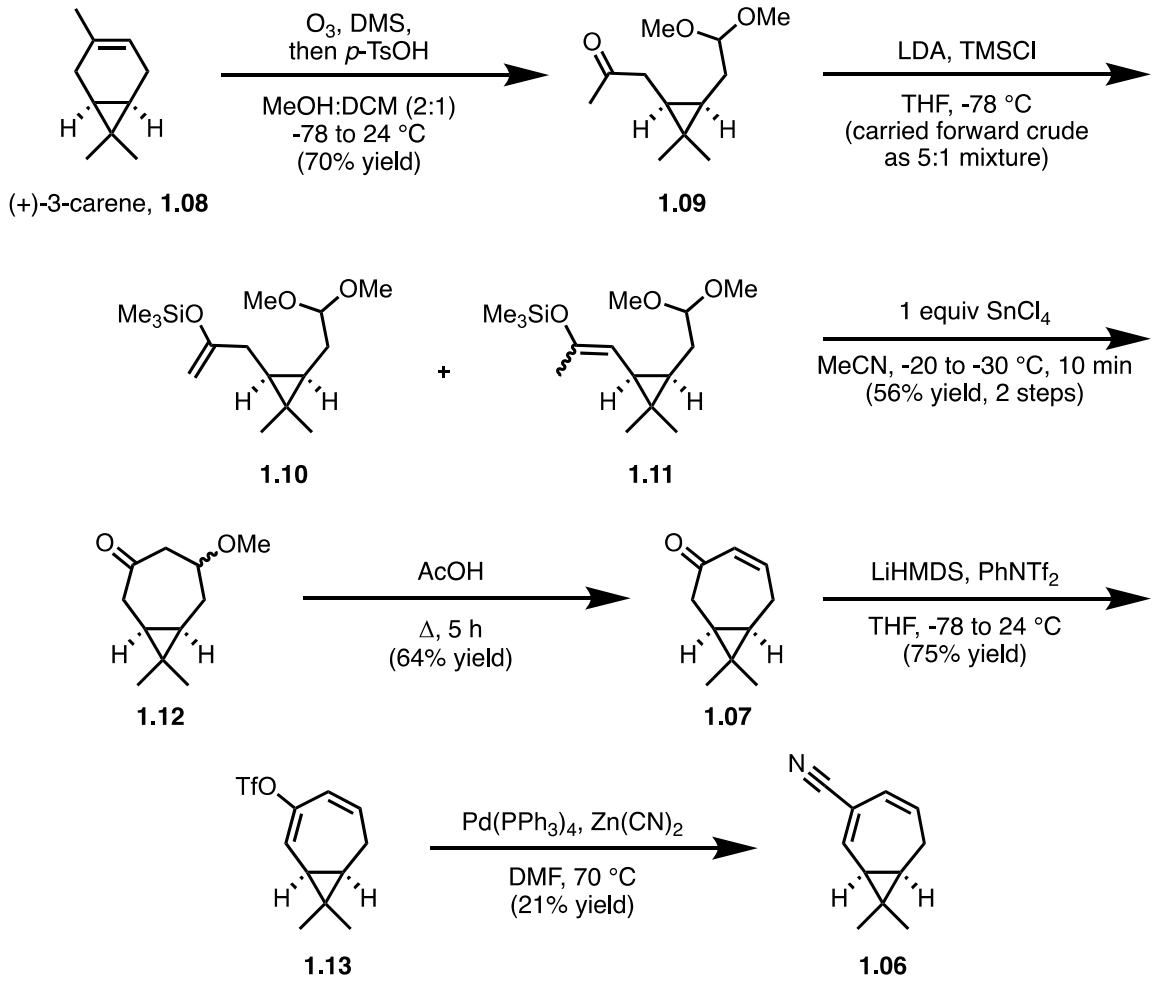
1.2 The First Total Synthesis of ent-*Plagiochianin B*



Scheme 1.2. Initial Retrosynthetic analysis of *ent*-Plagiochianin B, **(-)-1.02**

As shown in Scheme 1.2, our initial retrosynthetic analysis anticipated accessing *ent*-plagiochianin B (**(-)-1.02**) through late-stage oxidations of pyridine **1.05**. Although direct synthesis of a pyridine ring starting from a vinyl nitrile such as **1.06** was unprecedented, we became interested in developing such a method to gain access to **1.05** from **1.06**. This key reaction in our synthesis was envisioned as involving an anionic cyclization that was inspired by recent work from the Hsieh lab wherein the authors reduced nitriles with lithium triethylborohydride and captured the anionic intermediate intramolecularly through S_NAr producing a fused aryl ring.[4] We proposed *inter*molecular

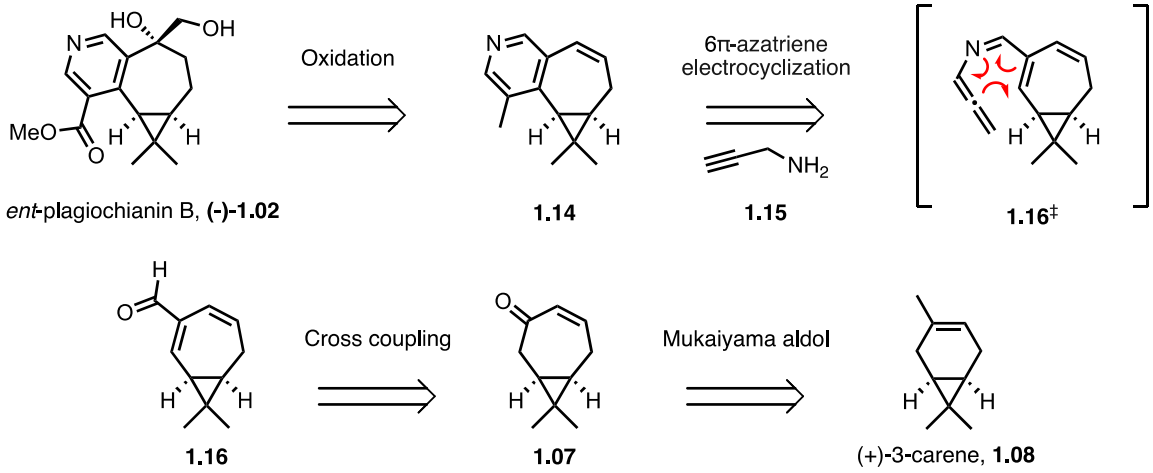
capture of an anionic intermediate with a Michael acceptor such as methyl propiolate, yielding **1.06b** (Scheme 1.2, bottom), which would further cyclize to form dihydropyridine (**1.06c**), a substrate that would be readily oxidized to the pyridine **1.05**. Nitrile **1.06** would be derived from a cross coupling reaction with an appropriate derivative of enone **1.07** which in turn would be prepared according to the Mukaiyama aldol approach detailed by Yamakawa.[2]



Scheme 1.3. Access to Vinyl Triflate, **1.13**, and Synthesis of Vinyl Nitrile, **1.06**

In a forward sense (Scheme 1.3), **1.08** was submitted to ozonolysis conditions employing a solvent containing MeOH which, following reductive work-up with DMS,

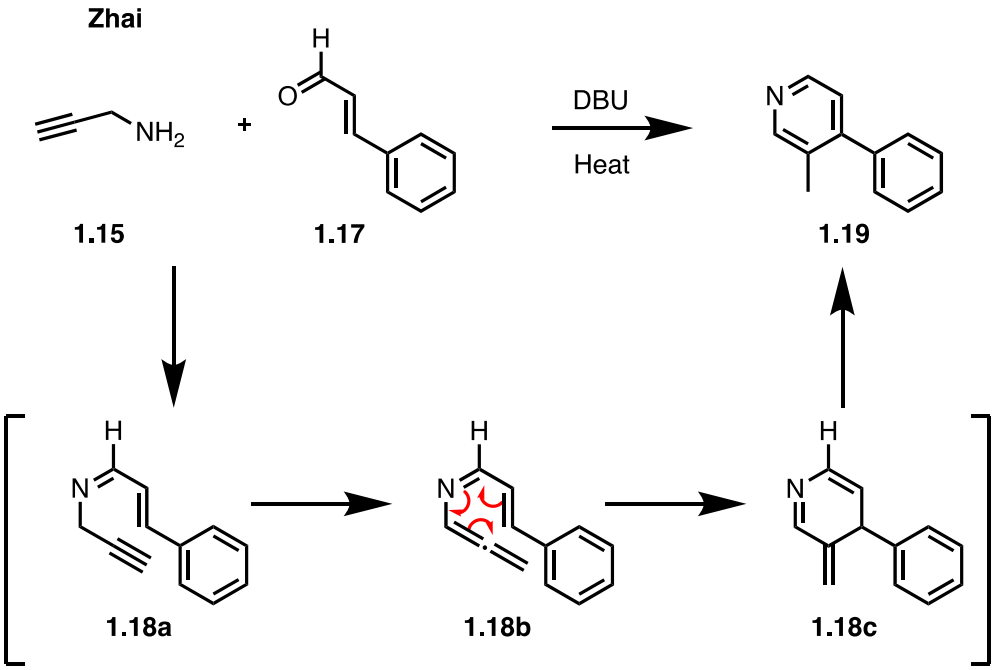
and treatment with a catalytic amount of *p*-TsOH enabled a single-pot transformation to acetal **1.09**.[5] It should be noted that in Yamakawa's original publication, the ozonolysis and acetal formation reactions were carried out over two steps whereas we were able to perform these two transformations in a single pot. Deprotonation of the ketone and trapping with TMSCl gave predominantly silyl enol ether **1.10** as a mixture with isomeric **1.11**; the selectivity in silyl enol ether formation was similar to that observed by Yamakawa. The mixture of **1.10** and **1.11** was taken forward together into the Mukaiyama aldol reaction from which desired β-methoxy ketone **1.12** was isolated in good synthetic yield.[6] The inconsequential mixture of diastereomers (**1.12**) was advanced by dissolving in AcOH and heating to reflux for 5 h to furnish Yamakawa's enone (**1.07**).[7] With **1.07** in hand, we looked toward preparing vinyl nitrile **1.06**. To this end, deprotonation with LiHMDS, at -78 °C in THF, was found to occur selectively at the α-position (as opposed to extended enolate formation) and the resulting enolate was trapped with *N*-phenyl-bistriflimide (McMurry's reagent) to provide enol triflate **1.13**. At this stage we found that conditions reported by Faber were capable of delivering the vinyl nitrile (**1.06**) albeit in modest yield.[8] Despite continued effort we could not access sufficient quantities of **1.06** to adequately explore the planned approach for introducing the pyridine ring. Nevertheless, access to the enol triflate (**1.13**) was quite efficient and **1.13** was a very versatile intermediate from which alternative approaches for pyridine synthesis could be envisioned. Thus, we decided to revise our retrosynthetic analysis.



Scheme 1.4. Revised Retrosynthetic Analysis of **(-)-1.02**

In our revised retrosynthetic analysis, summarized above in Scheme 1.4, we again imagined **(-)-1.02** as being accessed by late-stage oxidations, this time about the periphery of methyl pyridine **1.14**. In contrast to our previous plan, we now envisioned the pyridine ring of **1.14** as arising from a 6π-azatriene electrocyclization of intermediate **1.16**‡ which derives from aldehyde **1.16** after condensation with propargylamine (**1.15**). In taking advantage of chemistry developed thus far, the intermediate enal (**1.16**) would be accessed through a cross coupling reaction employing the vinyl triflate (**1.13**) that was previously prepared from enone **1.07**. As before, **1.07** is accessed from **1.08**. Precedent for the planned 6π-azatriene electrocyclization is found in recent work from Zhai who developed the method and applied it to the conversion of enals and enones into methyl pyridines.[9] As shown in Scheme 1.5, the nitrogen of the pyridine ring is derived from propargylamine **1.15** which first condenses onto **1.17** to yield imine **1.18a**. The addition of base (DBU) and heat drives an isomerization to allene **1.18b** which is capable of participating in an electrocyclization. The initially formed cyclic diene (**1.18c**) rapidly tautomerizes to give

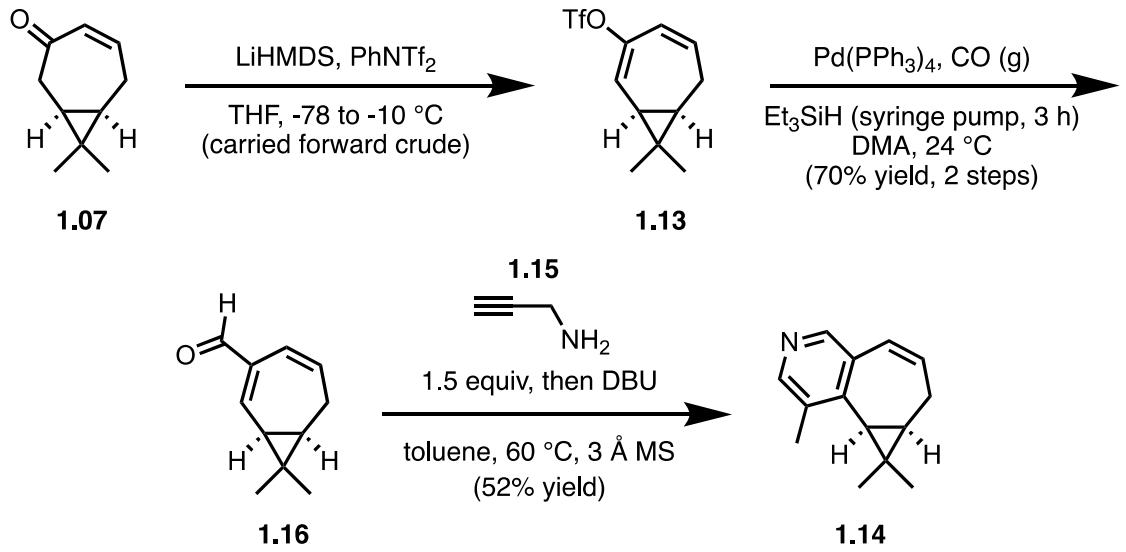
1.19. With solid precedent in hand, we turned toward preparing the requisite aldehyde (**1.16**).[9]



Scheme 1.5. Zhai's pyridine synthesis via 6π-azatriene electrocyclization

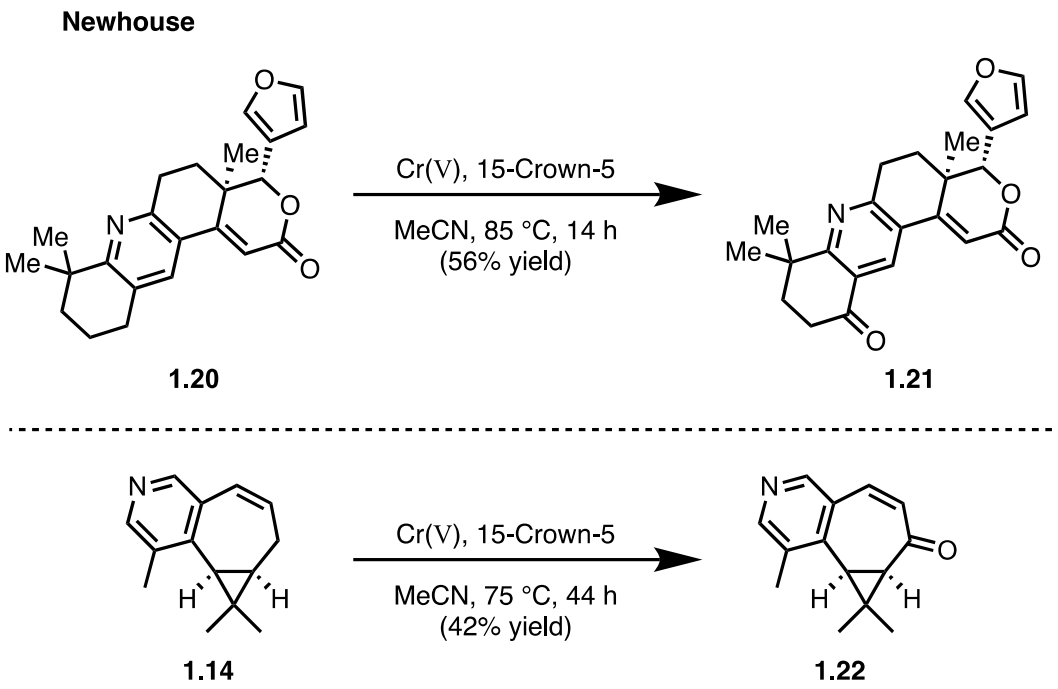
As detailed in Scheme 1.6 (*vide infra*), and in accord with our synthetic plan, the desired enal **1.16** was accessed through a one-step CO-insertion and reduction sequence employing conditions adapted from those reported by Stoltz.[10] Conveniently, **1.13** participated in the cross coupling as a crude product from the triflation step. Turning next to installation of the pyridine ring, **1.16** was combined with propargylamine **1.15** employing toluene as the solvent and 3 Å MS to promote dehydration. Gentle heating to 60 °C helped to drive the formation of the imine and upon complete conversion of **1.16**,[11] DBU was added to promote allene formation and heating was continued to induce electrocyclization. The power of this transformation lies in the fact that the derived pyridine ring is substituted at three positions (3,4, and 5) and is importantly *not* substituted at the 2

and 6 positions (typical sites of electrophilic functionalization of pyridine rings). Few conditions exist that would, in one step, forge a pyridine ring with this substitution pattern. Securing access to methyl pyridine **1.14** was an important step in the total synthesis. Nearly every carbon found in the natural product was present, two of the three stereocenters had been established, and what remained was largely functional group interconversion and oxidation about the periphery.



Scheme 1.6. Synthesis of Methyl Pyridine, **1.14**

In considering the steps required to complete the synthesis, we perceived that oxidation at the methyl group would be one of the most challenging due to the electron-withdrawing nature of the pyridine ring. Optimistically, we hoped that the *meta* position of the methyl group relative to the nitrogen of the pyridine ring would mitigate some of the challenges regarding its oxidation. Unfortunately, classic conditions such as the Jones oxidation decomposed **1.14** and conditions in which the pyridine nitrogen was intended to direct oxidation to the benzylic position ($Pd(OAc)_2$, PIDA, MeOH)[12] also failed.



Scheme 1.7. Newhouse's precedent regarding benzylic oxidations with Cr(V) and our application of this chemistry

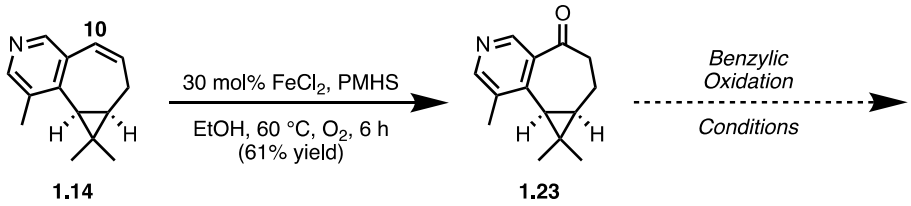
Turning to the literature, we were intrigued by a report from Newhouse describing conditions that proved effective for the oxidation at a benzylic position on a pyridine ring which was also *meta* relative to the nitrogen (see **1.20**→**1.21**, Scheme 1.7).[13] Although the carbon oxidized in this transformation is a methylene, as opposed to the methyl found in our substrate, we believed this was solid precedent for our desired transformation. In the event, treatment of **1.14** under the conditions reported by Newhouse indeed gave an oxidation product! Unfortunately, we believe oxidation took place at the undesired methylene giving **1.22**. Although the structure of **1.22** was never fully delineated, a ^{1}H NMR which contained three methyl groups at 2.38, 1.53, and 0.96 ppm, and apparent doublets at 6.89 and 6.19 ppm respectively, strongly suggested the formation of undesired enone **1.22** (see Appendix A for ^{1}H NMR). It is worth noting that our substrate (**1.14**) undergoes oxidation at a methylene located in a vinylogously benzylic *meta* position

relative to the pyridine nitrogen and thus the observed reactivity is analogous to that reported by Newhouse. Additionally, in **1.14**, the methylene is vicinal to a cyclopropane, a position with known proclivity toward oxidation.[14] Facing difficulties with the oxidation of the methyl group of **1.14**, we wondered if further elaboration of the seven-membered ring might produce a substrate more amendable toward oxidation at the pyridine methyl.

To complete the synthesis of **(-)-1.02**, the cycloheptenyl moiety would need to be functionalized at C-10 with a hydroxy methyl and tertiary alcohol (Plagiochianin B counting, Table 1.1). With regard to installing the additional carbon our plan was to first to oxidize the alkene to the corresponding benzylic ketone and further methylenate through a Wittig olefination. Dihydroxylation of the resulting exomethylene would then complete functionalization of the Eastern region of **(-)-1.02**. To this latter end we recognized that a Wacker-type oxidation would likely be the most expedient method for the alkene-to-ketone conversion (**1.14**→**1.23**). In the event however, traditional Wacker oxidation conditions proved incapable of converting our starting material (**1.14**).[16] In seeking alternatives we were intrigued by a method reported by Han wherein an iron catalyst is employed in the presence of polymethylhydrosiloxane (PMHS) under an atmosphere of air.[17] From a mechanistic perspective, Han had performed a radical trap experiment (galvinoxyl) which suggested that this particular Wacker-type oxidation proceeds via radical intermediates. Bearing these mechanistic considerations in mind, the concern arose with regard to our substrate that the presumed intermediate benzylic radical would be formed vinylogously adjacent to a dimethylcyclopropane making our substrate thereby prone to a deleterious ring opening event. Despite this potential pitfall the chemistry was attempted and we were delighted to observe consumption of starting material (**1.14**) and the formation of products

consistent with oxidation. In further studies, we found that sparging with and maintaining an atmosphere of pure O_2 improved the rate of the reaction without diminishing yields of desired benzylic ketone **1.23**. In retrospect, we are left to presume that the unfavorable disruption of pyridine ring aromaticity fortuitously prevents cyclopropyl opening.

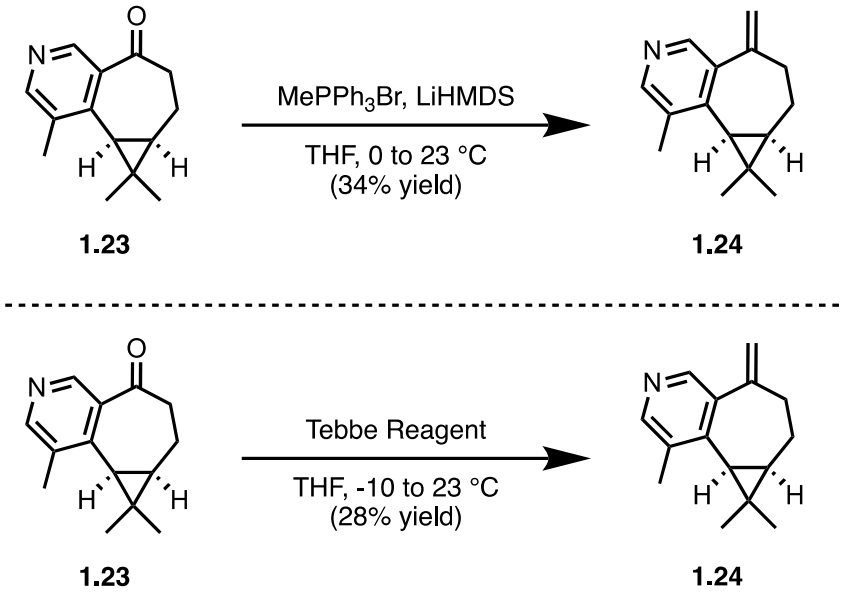
Table 1.1. Advancing **1.23**: further attempts at benzylic oxidation[15]



1.14 **1.23**

Condition	Result
SeO_2, Dioxane:H_2O, 80 °C, 9h	Returned Starting Material
IBX, DMSO, 23 °C, 32 h	Returned Starting Material
Bobbitt's Salt, MeCN:H_2O, 23 to 50 °C, 48 h	Returned Starting Material
TBHP, $Bi(OTf)_3$, picolinic acid, py, AcOH, 90 °C, 30 h	Returned Starting Material
NHPI, $Co(acac)_2$, O_2, AcOH, 100 °C, 24 h	Returned Starting Material
Cr(V), 15-Crown-5, MeCN, 75 °C	Returned Starting Material
CrO_3, DMA, O_2, AcOH, 90 °C, 24 h	Returned Starting Material
$Pd(OAc)_2$, PIDA, AcOH, 100 °C, 24 h	Decomposition
CrO_3, H_2SO_4, 80 °C, 24 h	Decomposition

With plentiful access to benzylic ketone **1.23**, we returned to investigations of the oxidation on this substrate's benzylic methyl group. We explored a litany of benzylic oxidation conditions, which are summarized in Table 1.1 (*vide supra*). Most conditions simply returned starting material whereas Jones oxidation and Sanford's heteroatom-directed oxidation conditions[12] led to decomposition of **1.23**. We hypothesized that the failure of these benzylic oxidation conditions could be attributed to the highly electron-withdrawn nature of the pyridine ring, which is heightened by the presence of a ketone, and so we carried functionalization of the Eastern region one step further.

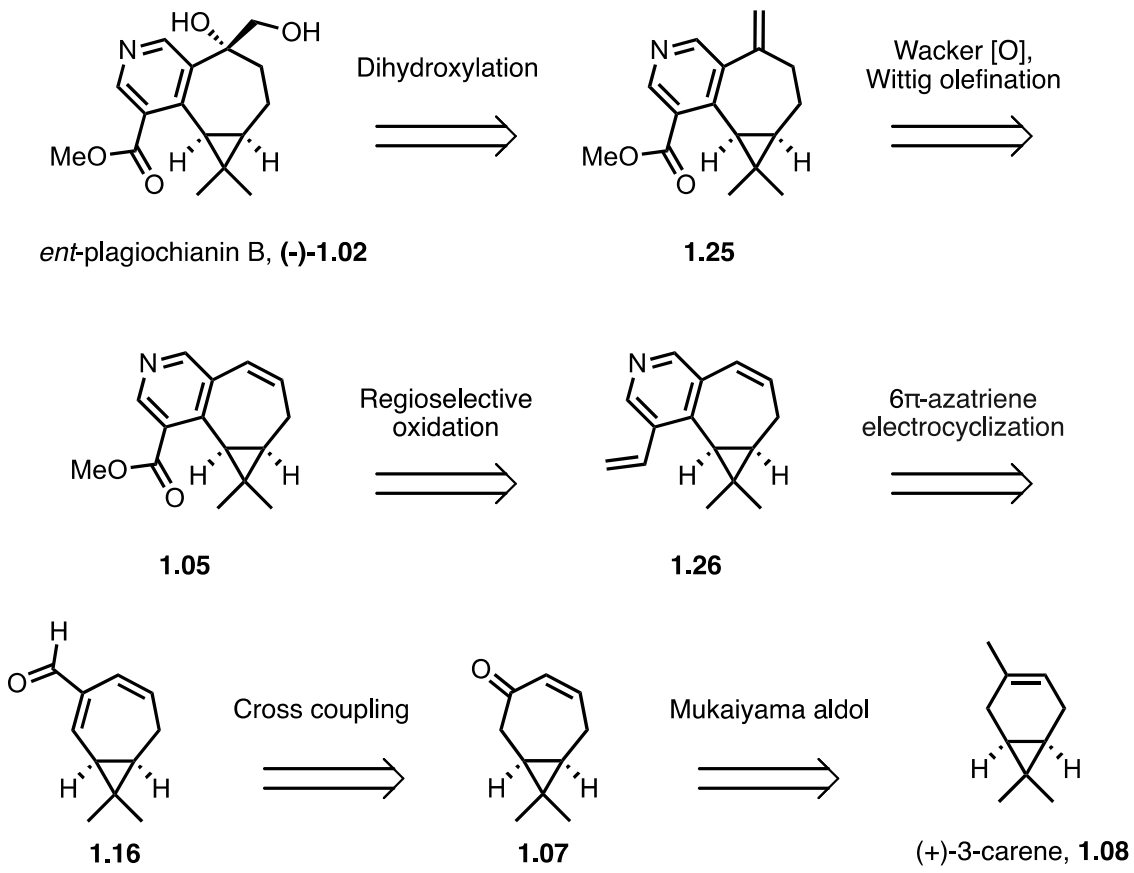


Scheme 1.8. Challenging Methylenation of **1.23**

In accord with the synthetic plan, we advanced ketone 1**.23** via methylenation chemistry. This could be done either with standard Wittig olefination conditions or the Tebbe reagent, as outlined in Scheme 1.8. Yields for the methylenation step at this point were quite low and so relatively few benzylic oxidation conditions were tried on derived exomethylene **1.24**. The Cr(V) conditions which had given the undesired oxidation of **1.14**

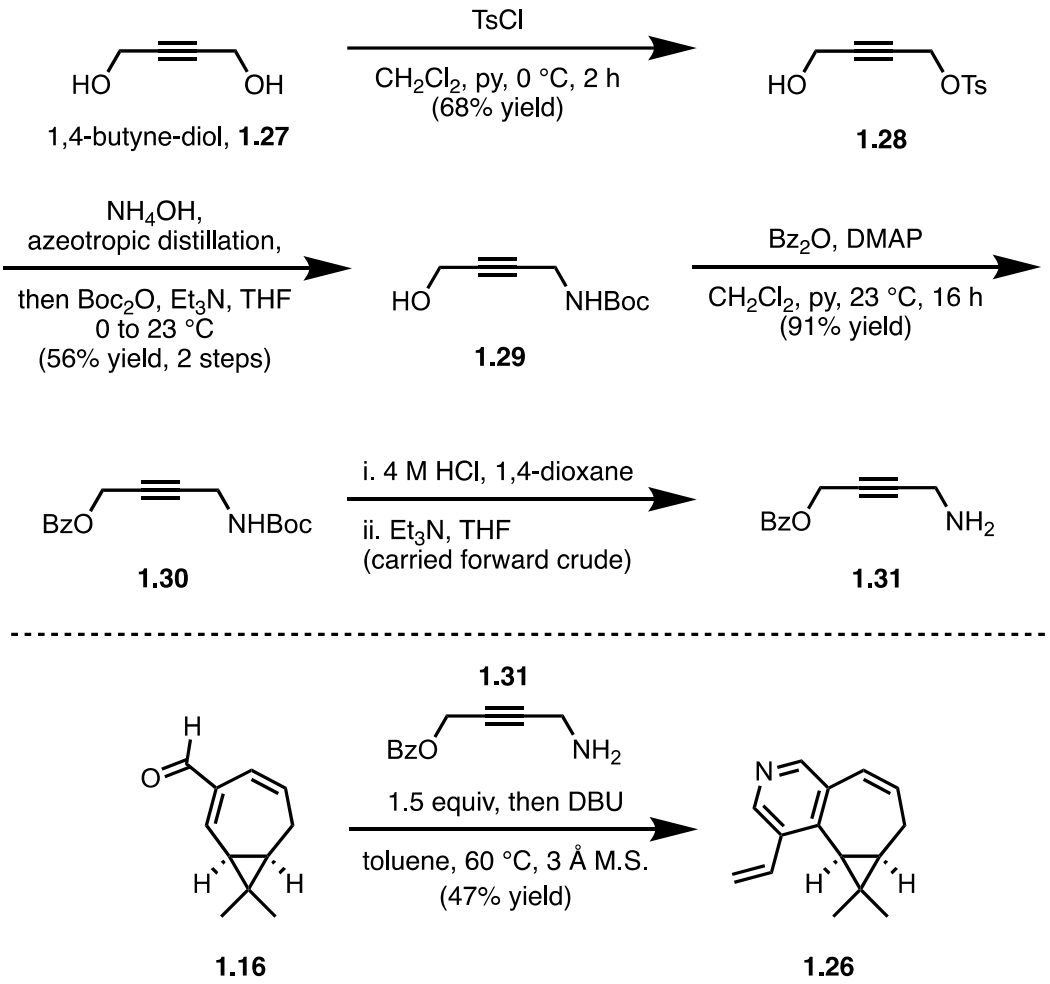
failed to oxidize **1.24**. Furthermore, aerobic oxidation of the methyl pyridine catalyzed by *N*-hydroxyphthalimide failed to deliver the desired oxidation products.[15e] Deprotonation of the benzylic methyl group of **1.24** and capture with camphorsulfonyl oxaziridine were also tried without success.[18]

The continuing difficulties surrounding oxidation of the benzylic methyl group of various substrates, led us to once again revise our synthetic plan. Although the methyl pyridine route had terminated short of the natural product, significant progress had been made in developing a route to the vicinal diol moiety.[19] A Wacker-type oxidation employing an iron catalyst had proven particularly efficacious in providing access to the desired ketone **1.23** and efforts to advance this material hinted at the remaining challenges regarding methylenation. Additionally, the effect of altering the substitution pattern resident in the Eastern region of the molecule had been briefly explored and these efforts further highlighted the difficulties associated with oxidation of the benzylic methyl group. In light of these considerations, we began to look for alternative approaches to the electrocyclization which would bring the benzylic carbon in at a higher oxidation state.[20]



Scheme 1.9. Final Retrosynthetic analysis of **(-)-1.02**

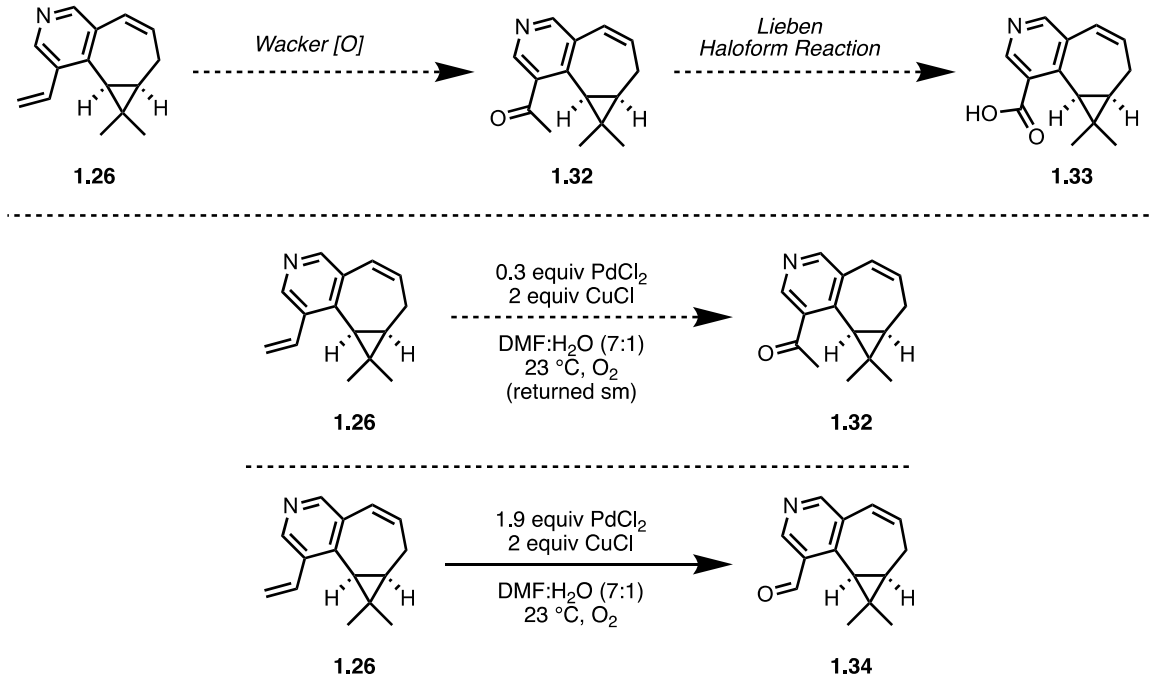
Our final retrosynthetic analysis, detailed in Scheme 1.9, illustrates **(-)-1.02** as arising through dihydroxylation of methylidene **1.25**. The 1,1-disubstituted olefin in **1.25** was expected to arise via application of the Wacker-type oxidation and Wittig olefination strategy, described above, to pyridine **1.05**. The methyl ester of **1.05** would be prepared by a regioselective oxidation of the terminal olefin found in **1.26** and subsequent functional group interconversions. Access to pyridine **1.26** would again be gained via 6π-azatriene electrocyclization this time, however, delivering a terminal olefin as opposed to a methyl group. The earlier stages of the retrosynthetic analysis would remain unchanged.



Scheme 1.10. Synthesis of **1.31** and application in 6π-azatriene electrocyclization with aldehyde **1.16**

Critical to our revised synthetic plan were further developments of the 6π-azatriene electrocyclization chemistry reported by Zhai and Li, wherein propargyl amines with functionalized alkynes had proven viable substrates for this transformation.[21] Implementation of this chemistry required synthetic access to propargylamine **1.31**, a substrate which was neither commercially available, nor, quite surprisingly, previously described in the literature. As illustrated in Scheme 1.10, we eventually pieced together a robust and scalable synthesis of **1.31** employing 1,4-butyne-diol (**1.27**) as our point of departure. In the event, by holding TsCl as the limiting reagent, and using pyridine as the

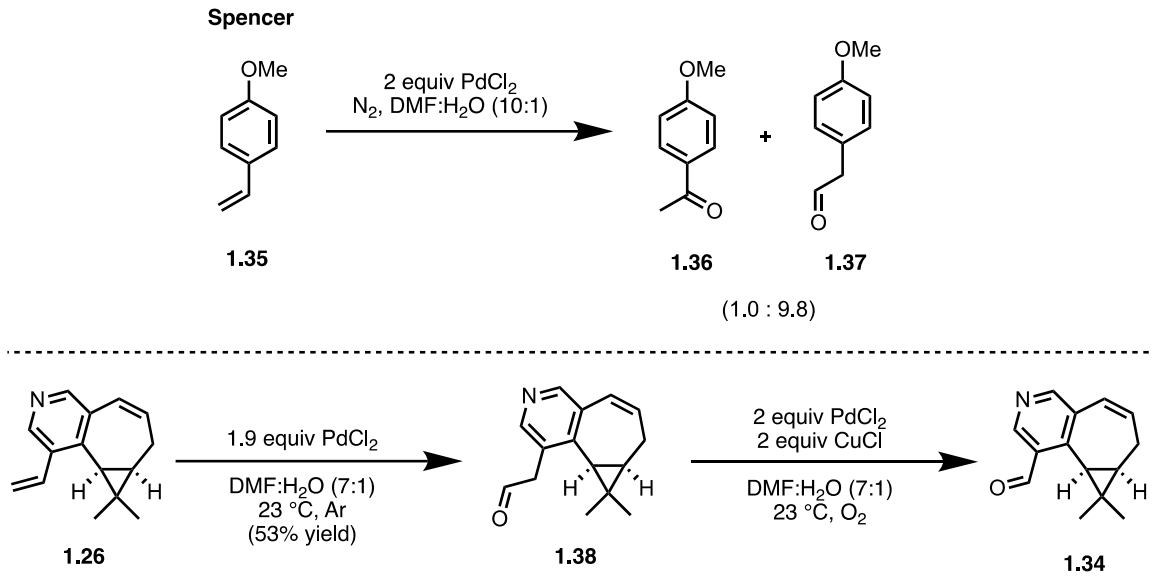
base, **1.27** could be advanced in good yield to mono-tosylate **1.28**.[22] The tosylate (**1.28**) was displaced with concentrated NH_4OH which, following azeotropic removal of water *in vacuo* with toluene (typically 3 x 50 mL), furnished a tosylate salt (not shown), that was free-based with Et_3N and protected with Boc_2O to furnish **1.29**.[22b] The propargylic alcohol of **1.29** was converted to benzoate **1.30** upon exposure to benzoyl anhydride in the presence of catalytic DMAP.[23] Finally, BOC-deprotection of **1.30** with anhydrous 4 M HCl, followed by free-basing the hydrochloride salt with Et_3N, gave the desired propargylamine **1.31**, which was carried forward crude into the key electrocyclization reaction (Scheme 1.10, bottom). Pleasingly, formation of the desired pyridine, **1.26**, was observed following treatment of **1.16** with **1.31** under the previously mentioned electrocyclization conditions.



Scheme 1.11. Discovery of a Regioselective Pd-mediated Oxidative Cleavage

With **1.26** in hand, a new challenge presented itself: regioselective oxidation of one olefin in the presence of the other. As had been seen earlier, typical Wacker oxidation

conditions failed to convert the internal olefin of **1.14** to benzylic ketone **1.23**. As summarized in Scheme 1.11, we wondered if we could leverage this observation by treating **1.26** with typical Wacker oxidation conditions and isolate a methyl ketone such as **1.32**. From there, a Lieben Haloform reaction might be expected to furnish the desired acid **1.33**. Much to our chagrin, catalytic quantities of $PdCl_2$ failed to deliver the desired ketone **1.32** and instead returned starting material. Determined to observe reactivity, in another experiment, **1.26** was treated with nearly 2 equiv $PdCl_2$ and 2 equiv CuCl in a DMF:H_2O solvent system under an O_2 atm. Indeed, under these latter conditions, **1.26** was consumed over a 24 h period. Remarkably, however, the desired methyl ketone (**1.32**) was not observed. Instead, ^{1}H NMR analysis clearly indicated that this transformation had produced an aldehyde which, upon further spectroscopic characterization was assigned as **1.34**! Clearly this result was unanticipated and thus we looked to the literature to see if any similar observations had been made. Eventually we found precedent in a paper published by Spencer which detailed synthetic efforts aimed at anti-Markovnikov selectivity in the Wacker oxidation (Scheme 1.12, top).[24] The authors found that treatment of styrene compounds such as **1.35**, with 2 equiv $PdCl_2$ in degassed DMF:H_2O solvents without oxidants such as CuCl or O_2, produced anti-Markovnikov aldehydes (**1.37**) selectively in preference to ketones (**1.36**, the typically observed product under traditional Wacker oxidation conditions). Furthermore, in an endnote, the authors stated that aldehyde products converted to analogous benzaldehydes in the presence of O_2. Intrigued by these reports we set out to perform a mechanistic investigation.

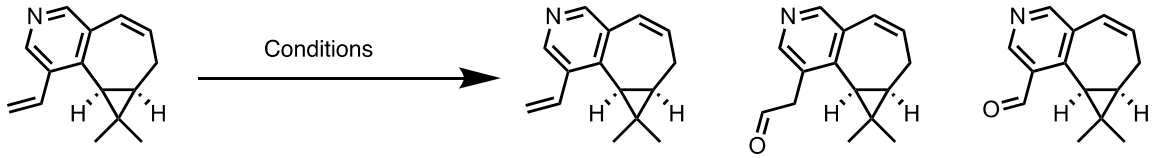


Scheme 1.12 Precedent from Spencer and Mechanistic Investigation of Oxidative Cleavage Reaction on **1.26**

As demonstrated in Scheme 1.12 (bottom), when **1.26** was exposed to 1.9 equiv of $PdCl_2$, under an inert atm in aqueous DMF, the expected aldehyde **1.38** was produced in good yield. Thereafter, **1.38** was exposed to the same Wacker-type oxidation conditions which had converted **1.26** directly to **1.34** (2 equiv $PdCl_2$, 2 equiv CuCl, DMF:H_2O, O_2), and **1.34** was again formed. Further probing of this reaction mechanism is summarized in Table 1.2. The necessity of superstoichiometric quantities of $PdCl_2$, without which no desired reactivity was observed, is demonstrated by entries 1 and 2. Curiously though, as shown in entries 2 and 3, small increases in Pd loading beyond 1 equiv could lead to significant conversion of starting material to the desired **1.34**. Reaction times for all of these entries were maintained below 24 h, and it is possible that given very extended reaction time periods, substoichiometric quantities of $PdCl_2$ may have given conversion of **1.26** to **1.34**. Nonetheless, from the experiments run, it seems as though stoichiometric $PdCl_2$ is necessary to observe desired reactivity. The role of oxygen and CuCl were tested

in entries 4-6. As suggested by Spencer, O_2 in conjunction with $PdCl_2$, without CuCl (entry 4), proved competent to convert aldehyde **1.38** to **1.34**, but, more intriguingly, CuCl seemed to play a role in the conversion of **1.38** to **1.34**. As shown in entries 5 and 6, holding other conditions equal, far greater conversion of **1.38** to **1.34** was observed when 2 equiv CuCl were present than when CuCl was withheld altogether. Lastly, when O_2 was rigorously excluded by a freeze-pump-thaw method, and CuCl was also excluded, incomplete conversion to **1.38** was observed. This suggests a potential catalytic function of O_2 in the formation of aldehyde **1.38**. Entry 8 contains a set of conditions which have previously delivered anti-Markovnikov selectivity in the Wacker oxidation.[25] As witnessed in previous reactions, catalytic amounts of $PdCl_2$, regardless of other additives, were incapable of converting the starting material, **1.26**. In practice, based on these studies and for the sake of material throughput in the conversion of **1.26** to **1.34**, 2 equiv $PdCl_2$ were utilized.

Table 1.2 Further Investigation of Oxidative Cleavage Mechanism



1.26 **1.26** **1.38** **1.34**

Entry	$PdCl_2$	CuCl	Solvent	Additive	atm	1.26	1.38	1.34
#	equiv	equiv	—	—	~ 1 atm	—	—	—
1	0.3	2	DMF : H_2O	—	O_2	1	—	—
2	1.1	2	DMF : H_2O	—	O_2	1	—	4.0
3	1.4	2	DMF : H_2O	—	O_2	1	—	5.7
4	1.9	0	DMF : H_2O	—	O_2	—	1	1
5	1.9	2	DMF : H_2O *	—	Ar	—	1	1.7
6	1.9	0	DMF : H_2O *	—	Ar	—	25	1
7	2.0	0	DMF : H_2O **	—	Ar	1.7	1	—
8	0.1	0.2 ***	*t*-BuOH : H_2O	BQ ****	O_2	1	—	—

* Solvent was degassed by 10 min sparge with Ar

** Solvent was rigorously degassed by freeze-pump-thaw

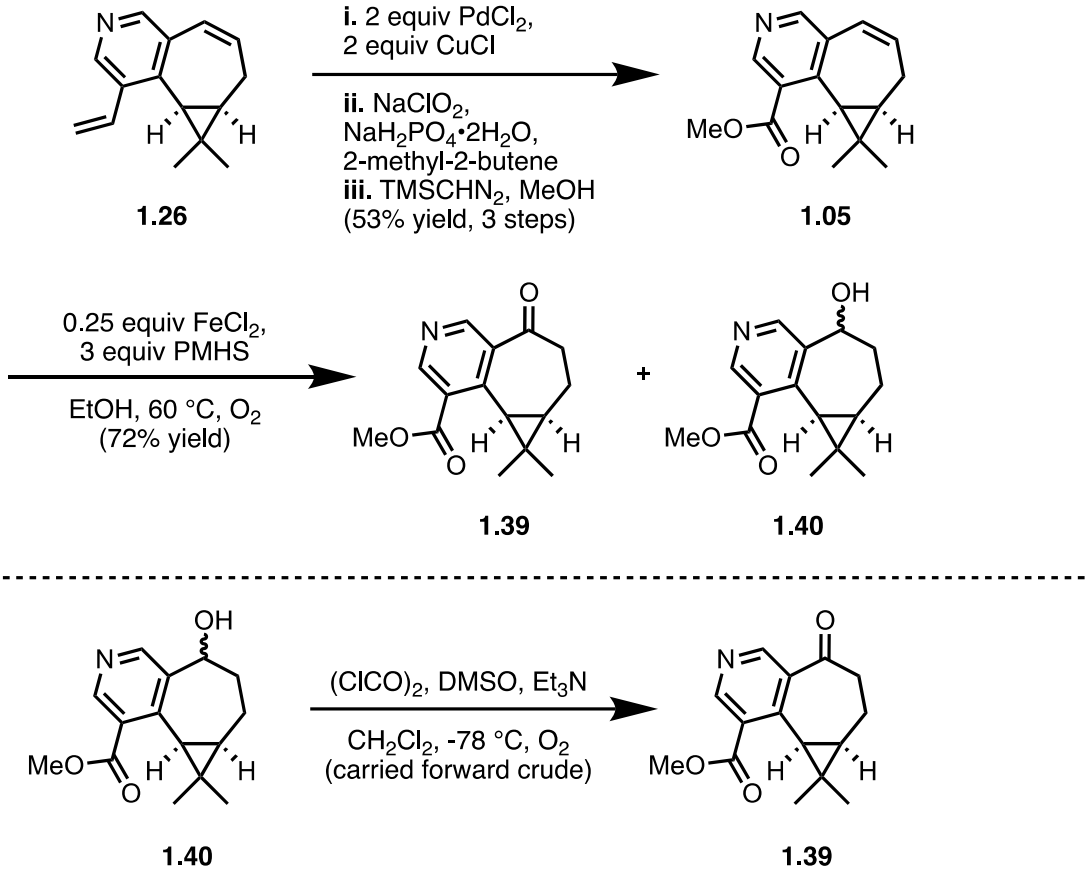
*** $CuCl_2$ was used intead of CuCl

**** BQ = 1,4-Benzoquinone

***** Entries 1-7 = 10 mg scale; reaction time = 19-22 h

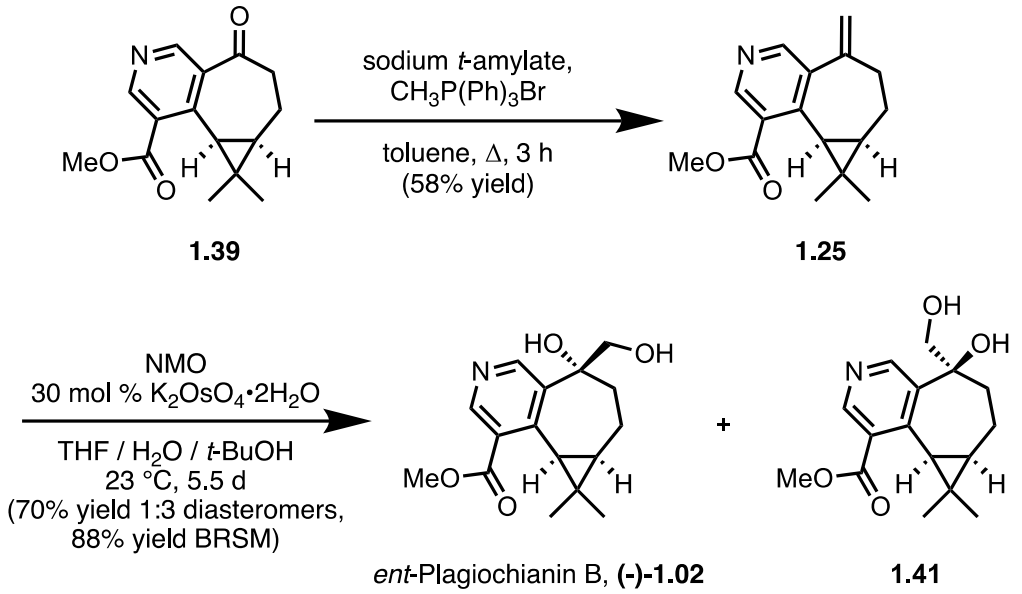
With a greater understanding of the remarkable transformation leading to **1.34**, we set out to complete our total synthesis. Fortunately, pyridine **1.34** indeed proved to be a malleable substrate for elaboration to methyl ester **1.05**. The best sequence of events to bring about this transformation, detailed in Scheme 1.13, was found to be first the oxidative cleavage reaction with 2 equiv $PdCl_2$ and 2 equiv CuCl, followed by a Pinnick oxidation which furnished an intermediate acid that was not isolated but converted to the methyl ester by treatment with $TMSCHN_2$ in MeOH.[26] Turning next to functionalization of the internal olefin, we drew upon our previous experiences and applied the same Wacker-type

oxidation conditions discussed previously (*i.e.* $FeCl_2$ and PMHS), which again delivered the desired ketone (**1.39**) accompanied by the corresponding hydration product (**1.40**).[27] Application of typical Swern conditions to **1.40** allowed for increased access to desired ketone **1.39**. At this point we needed to address the low-yielding methylenation step which had been problematic on the methyl pyridine series. In our previous studies, we attributed the incomplete conversion of ketone **1.23** to the acidity the ketone's α-protons and the propensity of this compound to undergo enolization instead of the desired methylenation. Fortunately, we were able to find conditions which have been employed to overcome this problem by establishing an equilibrium between base, enolate, and phosphonium ylid, which eventually funnels to the desired olefin.[28] Applying these sodium *t*-amylate conditions to ketone **1.39**,[28] we observed formation of the desired exocyclic olefin **1.25** in good yield.[29] For the final step in the total synthesis, dihydroxylation with catalytic amounts of $K_2OsO_4 \bullet 2H_2O$, with NMO as the stoichiometric oxidant, in a ternary solvent system (THF/H_2O/*t*-BuOH) gave **(-)-1.02** as a mixture favoring its diastereomer **1.41** (1:3).[30] Substrate control seemed to bias toward the undesired approach of the incipient osmium tetroxide. This likely arises due to a conformational preference in the seven-membered ring that is governed by the system avoiding a steric clash with the geminal dimethyl substituents on the cylopropane and leads to reaction at the most exposed β-diastereotopic face of the exocyclic olefin. Although attempts to reverse the observed selectivity employing chiral ligands failed, it is worth noting that $(DHQD)_2AQN$ improved the **(-)1.02**:**1.41** ratio from 1:3 to 1:1.6 respectively. Unfortunately, however, under these conditions, the already slow reaction was further lengthened to a half-life of 6 days!



Scheme 1.13. Synthesis of Ketone **1.39** and Isolation of Hydration Product **1.40**

A comparison of the experimental NOESY spectra of **(-)1.02** and **1.41** aided in confirmation of the relative stereochemistry proposed by the isolation chemists (see Appendix A). Furthermore, an optical rotation was taken of synthetic **(-)1.02**. From the outset we anticipated observing a negative optical rotation, and, indeed, we observed $[\alpha]_D^{23.7}$ = - 62.45 (c = 0.0427, MeOH). The isolation chemists reported an optical rotation for plagiochianin B (**(+)-1.02**) to be $[\alpha]_D^{20}$ = + 52.17 (c = 0.06, MeOH). The opposite sign of the optical rotation clearly indicates that, as expected, we had produced the enantiomer of plagiochianin B.



Scheme 1.14. Final Reactions in the Total Synthesis of *ent*-Plagiochianin B **(-)-1.02**

The first total synthesis of *ent*-Plagiochianin B **(-)-1.02** has been described. The asymmetric starting material, (+)-3-carene (**1.08**), allows for a single enantiomer to be delivered and due to the inherent stereochemistry found in **1.08**, the enantiomer of plagiochianin B was prepared. The route features an efficient construction of the carbocyclic core and pyridine ring through a 6π-azatriene electrocyclization and the selective oxidative cleavage of a terminal olefin, in the presence of an internal one, through a novel Pd-mediated transformation. Overall the route requires only nine synthetic steps from Yamakawa's enone (**1.07**) and thirteen from **1.08**. To date, no attempts have been made to diverge the synthesis to plagiochianin A (**1.01**). As will be documented in Chapters Two, Three, Four, and Five, the aleutianamine project became our main focus.

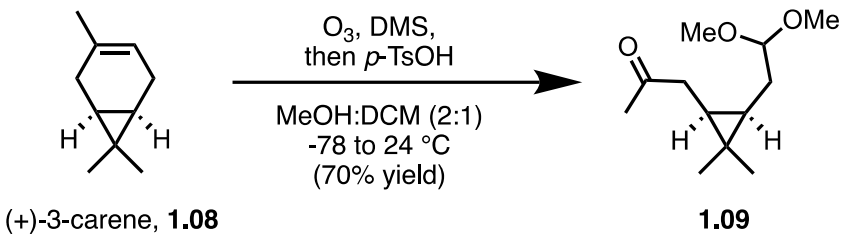
1.3 *Experimental*

1.3.1 General

Unless otherwise stated, all reactions were performed in flame- or oven-dried (~120 °C) glassware under a nitrogen (N_2) atmosphere, using reagents as received from the manufacturers. TMSCl was freshly distilled from CaH_2 prior to use. The 3 Å molecular sieves (MS) were activated in the following manner: MS were oven-dried (120 °C) overnight. The MS were then allowed to cool to room temperature (rt, usually 23°C) under a high vacuum (<1 Torr). The MS were then heated in a microwave oven for 1 min. Again, MS were allowed to cool to rt under a high vacuum. Lastly, the MS were flame-dried under vacuum and used once they had returned to rt. Abbreviations for common solvents are as follows: EtOAc = ethyl acetate, MeCN = acetonitrile, MeOH = methanol, EtOH = ethanol, *t*-BuOH = *tert*-butyl alcohol, THF = tetrahydrofuran, CH_2Cl_2 = methylene chloride Et_2O = diethyl ether. The argon (Ar) used was ultra-high purity (UHP, 99.999%) as was the oxygen (O_2, 99.993%). The reactions were monitored, and, where noted, analytical samples purified by, normal phase thin layer chromatography (TLC) using Millipore glass-backed 60 Å plates (indicator F-254, 250 μM). THF, CH_2Cl_2, MeCN, benzene, toluene, and Et_2O were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. MeOH was simply dried with activated 4 Å molecular sieves (MS), degassed, and held under Ar. Manual flash column chromatography was performed using the indicated solvent systems with Silicycle SiliaFlash P60® (230-400 mesh) silica gel as the stationary phase. All Medium Pressure Liquid Chromatography (MPLC) purifications were performed on either a Teledyne RF+ UV-Vis Ms Comp or a Teledyne CombiFlash NextGen 300+ RF using the indicated solvent systems and Teledyne RediSep® Rf normal phase disposable

columns. All Ultra-Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS) analyses were carried out on a Waters Acquity H UPLC Class system with a UPLC BEH C18 1.7 μm, 2.1 x 50 mm column using the indicated solvent systems as eluents. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300, Bruker AscendTM 400 autosampler or a Bruker AscendTM 600 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (*J*) are reported in hertz (Hz). NMR spectra were calibrated relative to their respective residual NMR solvent peaks; $CDCl_3$ = 7.26 ppm (^{1}H NMR) / 77.16 ppm (^{13}C NMR), MeOD-*d4* = 3.31 (^{1}H NMR) / 49.00 (^{13}C NMR). NMR peak pattern abbreviations are as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, dt = doublet of triplets, tt = triplet of triplets, q = quartet, m = multiplet. Infrared (IR) spectra were recorded on a Bruker Platinum-ATR IR spectrometer using a diamond window. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using + electrospray ionization (+ESI) and reported for the molecular ion ($[M+H]^+$, $[M+Na]^+$, or both). Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter using either Fisher Chemical Chloroform (HPLC grade; approx. 0.75% Ethanol as preservative) or Fisher Chemical Methanol (Optima® LC/MS). Melting points for the plagiochianin B project were taken on a Chemglass Life Sciences Afon Melting Point Device DMP100. Melting points for the aleutianamine project were taken on an Electrothermal Melting point measuring instrument 1101D Mel-Temp.

*Dimethoxy Acetal **1.09***



(+)-3-carene, **1.08** **1.09**

Note: undried CH_2Cl_2 and MeOH was acceptable to use for this transformation. This reaction was performed with the round-bottom flask open to ambient conditions.

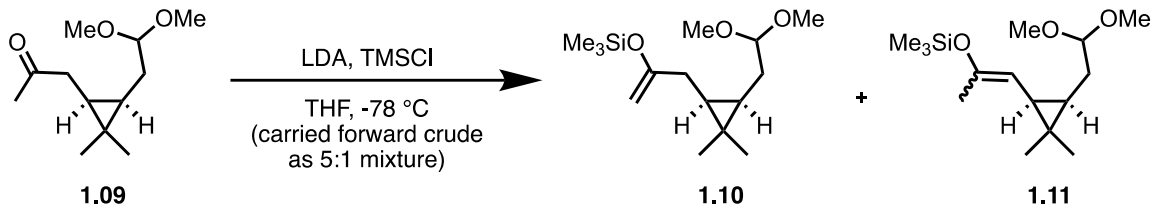
A 250 mL round-bottom flask, with stir bar, was charged with 21.176 g (+)-3-carene (**1.08**, 155 mmol, 1 equiv) and diluted with 40 mL CH_2Cl_2 and 70 mL MeOH. The solution was cooled to -78 °C in a dry ice/acetone bath for approximately 15 min. After cooling, O_3 was bubbled through the solution until consumption of starting material was observed by TLC analysis ($KMnO_4$); this process took approximately 3 hours but variation in the length of ozonolysis was observed from reaction to reaction. Thereafter, the ozone generator was turned off and O_2 was bubbled through the solution for 50 min. After the allotted time, 45 mL dimethyl sulfide (587 mmol, 4 equiv) and 0.253 g *p*-toluenesulfonic acid monohydrate (1.47 mmol, 0.01 equiv) were added to the solution which was then removed from the dry ice/acetone bath and stirred at ambient temperature for 15 h.

Warning: When scaling beyond this point, it is best to allow the reaction to slowly warm to room temperature instead of removing from the cooling bath. Before performing the aqueous work-up (vide infra), it is advisable to test for peroxides with either potassium iodide-starch test strips or MQuant peroxide colorimetric test strips from Merck.

After the allotted time, the solution was poured onto 100 mL 3 N HCl in a separatory funnel. The layers were mixed, allowed to separate and the organic layer was

separated. The aqueous layer was extracted with 75 mL CH_2Cl_2 twice. The combined organic extracts were washed with 150 mL DI water, 150 mL brine and then dried with Na_2SO_4. The heterogeneous solution was filtered, and concentrated *in vacuo* to afford 36.432 g crude product. The crude product was further purified by MPLC chromatography with the desired product eluting at 20% EtOAc/hexanes. The total yield for the reaction was 23.178 g **1.09** (108 mmol, 70% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 4.32 (t, *J* = 6.0 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 2.38 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.32 (dd, *J* = 18.0, 12.0 Hz, 1H), 2.16 (s, 3H), 1.56-1.51(m, 1H), 1.49-1.44 (m, 1H), 1.08 (s, 3H), 0.90 (s, 3H), 0.86 (apparent q, *J* = 12.0, 6.0 Hz, 1H), 0.66 (apparent q, *J* = 18.0, 6.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): 209.1, 105.3, 53.4, 53.4, 39.6, 29.8, 28.9, 28.4, 21.6, 21.2, 17.0, 15.3. **TLC**: R_f = 0.29 (25% EtOAc/hexanes). **Physical Appearance**: Yellow oil. Spectral data are consistent with reports from Yamakawa: *Chem. Pharm. Bull.* **1984**, *32*, 3452-3460.

*TMS Silyl Enol Ether **1.10***



1.09 **1.10** **1.11**

A 100 mL round-bottom flask, with stir bar, was charged with dimethoxy acetal starting material **1.09** (18.392 g, 85.8 mmol, 1 equiv) and the starting material was azeotropically dried once from benzene (~ 30 mL).

A separate 300 mL round-bottom flask, with stir bar, was charged with THF (38 mL) and diisopropylamine (18 mL, 0.129 mol, 1.5 equiv). The solution of diisopropylamine and THF was cooled to -78 °C in a dry ice / acetone bath for ~ 15 min.

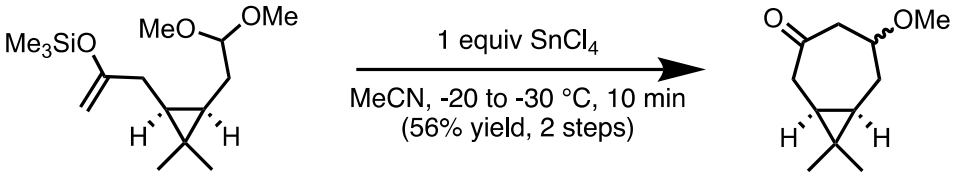
At this point, *n*-BuLi as a 2.5 M solution in hexanes (48 mL, 120 mmol, 1.3 equiv) was added dropwise to the cold 300 mL round-bottom flask. The resulting solution was allowed to stir at the same temperature for 30 min.

The starting material, **1.09**, was transferred dropwise to the cold solution of LDA in 10 mL THF followed by a 5 mL THF wash. The solution was allowed to stir at the same temperature for another 30 min at which point TMSCl, (22 mL, 173 mmol, 2 equiv) was added dropwise. The resulting solution was allowed to stir at the same temperature for 1 h at which point it was quenched with 40 mL $NaHCO_3$ (sat.).

The flask was removed from the dry ice / acetone bath and allowed to warm to room temperature for 5-10 min. The solution was quantitatively transferred to a separatory funnel with EtOAc and water. The layers were mixed and allowed to separate. The organic layer was removed and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 150 mL brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 20.0 g crude product **1.10** and **1.11**. The crude product was carried on to the next reaction without further purification. Analysis of the integration around the methoxy peaks suggested a 5:1 isomeric mixture which compares favorably to the ratio reported by Yamakawa. *Note: Only signals relating to the desired silyl enol ether **1.10** are tabulated below.* **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 4.37 (t, *J* = 5.9 Hz, 1H), 4.16 (apparent s, 1H), 4.09 (apparent s, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 2.04-1.97 (m, 1H), 1.89 (dd, *J* = 16.4, 7.8 Hz, 1H), 1.57-1.52 (m, 2H), 1.07 (s, 3H), 0.93 (s, 3H), 0.76-0.54 (m, 2H, 2 overlapping proton signals), 0.21 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): 160.0, 105.3, 90.0, 53.1, 53.1, 31.8, 29.2, 28.2, 23.8, 21.3, 17.0, 15.0, 0.3. **IR** (thin film): cm^{-1} 2954 (w), 1635 (w), 1377 (w), 1252 (m), 1223 (w), 1125 (m), 1054 (m), 1019 (m), 902 (w), 840 (s),

753 (w). **TLC**: R_f = 0.81 (25% EtOAc/hexanes). **Physical Appearance**: Yellow liquid. Spectral data are consistent with reports from Yamakawa: *Chem. Pharm. Bull.* **1984**, *32*, 3452-3460.

Ketone **1.12**



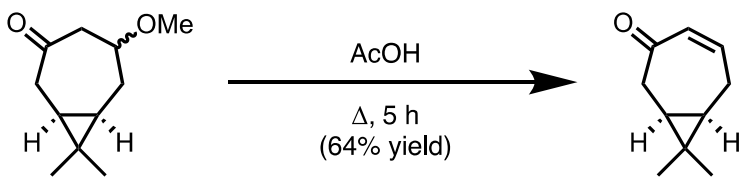
1.10 **1.12**

A 1 L round-bottom flask was charged with MeCN (390 mL, 0.13 M) and $SnCl_4$ as a 1 M solution in CH_2Cl_2 (52 mL, 52 mmol, 1 equiv). The resulting solution was cooled to -20 °C in a dry ice / acetone bath for ~ 10 min. Throughout the reaction, the temperature was maintained between -20 and -30 °C by adding small amounts of dry ice to the acetone bath. After the solution had cooled, the silyl enol ethers **1.10** and **1.11** (14.9 g, 52 mmol, 1 equiv) were added dropwise neat to the cold solution by syringe through the septum followed by a MeCN (10 mL) wash. The reaction was allowed to stir for 10 min and was monitored by TLC ($KMnO_4$).

Once complete consumption of starting material was observed by TLC (usually within 10 min) the reaction was quenched with $NaHCO_3$ (sat.). The flask was removed from the dry ice / acetone bath and allowed to warm to room temperature for 5-10 min. The solution was quantitatively transferred to a separatory funnel with EtOAc and water. The layers were mixed and allowed to separate. The organic layer was removed and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 150 mL brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford

the crude product. The crude product was further purified through MPLC: the crude product was dry loaded with 30 g silica gel onto a 220 g silica gel column. A linear ramp from 0 to 5% EtOAc/hexanes was applied for first 3 min, followed by isocratic hold for 5 min at 5% EtOAc/hexanes. Another 3 min linear ramp from 5 to 10% EtOAc/hexanes and then another isocratic hold for 10 min. The desired compound eluted in the isocratic hold at 10% EtOAc/hexanes. The yield for this reaction was 4.9 g ketone **1.12** (27 mmol, 56% yield). *Note: The below tabular data represents an inconsequential 2:1 mixture of diastereomers about the methoxy group.* **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 3.68-3.63 (m, 1H major diastereomer), 3.62-3.55 (m, 1H minor diastereomer), 3.34 (s, 3H major diastereomer), 3.32 (s, 1.35 H minor diastereomer), 3.07-3.00 (m, 1.45 H), 2.65 (dd, *J* = 16.2, 8.0 Hz, 1H major diastereomer), 2.57-2.51 (m, 1.49 H), 2.45 (dd, *J* = 12.0, 7.1 Hz, 0.51 H minor diastereomer), 2.34-2.26 (m, 1.54H), 2.19-2.09 (m, 1.57 H), 1.32-1.17 (m, 0.71H), 1.12-1.07 (m, 1H, overlaps with methyl groups from major and minor diastereomers), 1.09 (s, 3H), 1.07 (s, 1.61H minor diastereomer), 1.05 (s, 1.72H minor diastereomer), 1.00 (s, 3H major diastereomer), 0.99-0.92 (m,1H), 0.77 (q, *J* = 8.7 Hz, 1 H major diastereomer), 0.71-0.67 (m, 1 H). **^{13}C NMR** (101 MHz, $CDCl_3$): 209.7, 209.7, 78.6, 76.8, 56.6, 56.5, 49.3, 48.2, 39.7, 39.1, 29.9, 28.6, 28.5, 27.1, 22.7, 22.0, 21.2, 20.2, 20.1, 19.6, 15.2, 15.2. **TLC**: R_f = 0.29 (25% EtOAc/hexanes). **Physical Appearance**: Clear, slightly yellow oil. Spectral data are consistent with reports from Yamakawa: *Chem. Pharm. Bull.* **1984**, *32*, 3452-3460.

α,β-Unsaturated Ketone **1.07**



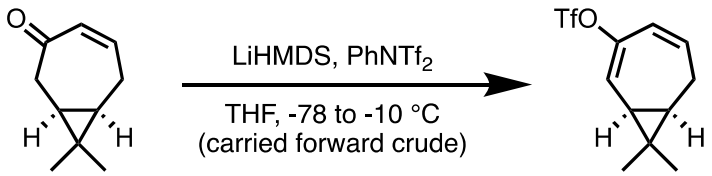
1.12 **1.07**

A 500 mL round-bottom flask, with stir bar, was charged with α,β-unsaturated ketone **1.12** (6.6 g, 36 mmol, 1 equiv). Thereafter, glacial acetic acid (231 mL, 0.16 M) was added and a reflux condenser was placed over the top of the round-bottom flask. The contents of the flask were heated to reflux and maintained at the same temperature for 5 h. The solution was then allowed to gradually cool to room temperature in the heating mantle over a 1-2 h period.

The contents of the round-bottom flask were quantitatively transferred to a separatory funnel with EtOAc. The organic layer was washed with 200 mL Na_2CO_3 (sat.). The layers were mixed, and the organic layer was separated. The aqueous layer was extracted with 100 mL EtOAc twice. The combined organic extracts were then washed with 150 mL $NaHCO_3$ (sat.) and 150 mL brine sequentially back-extracting with 150 mL EtOAc after each wash. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 5.8 g crude product. Further purification was achieved by flash with the desired product eluting at 10% EtOAc/hexanes. The yield for this reaction was 3.47 g α,β-unsaturated ketone (**1.07**) (23.1 mmol, 64% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.80 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H), 5.96 (apparent d, *J* = 12.0 Hz, 1H), 2.74 (apparent dd, *J* = 16.0, 4.0 Hz, 1H), 2.56 (ddd, *J* = 16.0, 8.0, 4.0 Hz, 1H), 2.30 (t, *J* = 12 Hz, 1H), 2.13-2.05 (m, 1H), 1.20-1.13 (m, 1H overlaps with methyl), 1.17 (s, 3H), 1.08 (s,

3H), 0.74-0.68 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): 201.6, 148.4, 133.8, 42.1, 31.4, 28.6, 25.7, 24.6, 23.0, 15.7. IR (thin film): cm-1 2945 (w), 1658 (s), 1455 (w), 1391 (w), 1287 (w), 1213 (w), 1184 (w), 947 (w), 838 (w), 807 (w), 750 (w), 608 (w), 515 (w), 449 (w). **TLC**: R_f = 0.44 (20% EtOAc/hexanes). α,β-unsaturated ketone (**1.07**); $KMnO_4$. **Physical Appearance**: Pale yellow crystals. Spectral data are consistent with reports from Yamakawa: *Chem. Pharm. Bull.* **1984**, *32*, 3452-3460.

*Enol Triflate **1.13***



1.07 **1.13**

This reaction was originally run with lithium diisopropylamide (LDA), however, conveniently, the reaction was found to work equally well with lithium (bistrimethylsilyl) amide (LiHMDS). For completeness, both methods are listed below.

A 100 mL round-bottom flask was charged with 500.7 mg enone **1.07** (3.333 mmol, 1 equiv). A white septum was placed over the top and vacuum was pulled for 1 min. The flask was backfilled with N_2 and this process was repeated twice.

LDA generation:

A separate 250 mL round-bottom flask, with stir bar, was charged with 28 mL THF (28 mL, 0.1 M) were added followed by 1 mL diisopropylamine (DIPA, 6.7 mmol, 2 equiv). The flask was placed in a dry ice/acetone bath for ~ 15 min and then 1.5 mL *n*-BuLi (2.55 M solution in THF, 3.7 mmol, 1.1 equiv) were added dropwise. The flask was stirred for 5 min in the dry ice/acetone bath and then transferred to an ice-water bath for ~

30 min. The yellow color of *n*-BuLi disappeared after ~ 15 min. After that time, the solution of LDA was returned to the dry ice/acetone bath and cooled for ~ 15 min.

The starting material (**1.07**) from the original flask was added dropwise to the LDA solution in 6 mL THF followed by a 5 mL wash with THF. Once all of **1.07** had been added, the solution was stirred for 1 h in the dry ice/acetone bath.

*Note: LiHMDS may be used instead of LDA; in the event, LiHMDS (1M in THF) is added to a cooled (dry ice/acetone bath, 15-20 min) solution of **1.07** in THF (0.2 M) and stirred for 1-3 hours at -78 °C. The rest of the experimental procedure is identical to what follows.*

During that hour of stirring in a dry ice/acetone bath:

A 30 mL round-bottom flask was charged with Ph*N*$(Tf)_2$ (1.33 g, 3.7 mmol, 1.1 equiv) were weighed out, placed into the flask, and a septum was placed over the top of the flask. Using the N_2-backfilling method previously described, the flask was placed under an inert atmosphere.

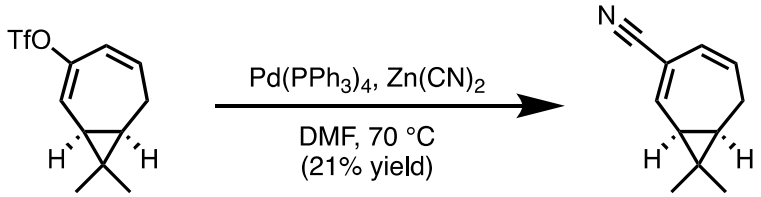
After the allotted time, the Ph*N*$(Tf)_2$ was added to the flask with **1.07** and LDA by syringe as a single portion in 10 mL THF followed by a 5 mL THF wash. The reaction flask was stirred in a dry ice/acetone bath for ~ 15 min and then transferred to a 0 °C bath, and held at this temperature for 17 h. The bath temperature could range from -10 to 4 °C without serious alteration in product yield.

When the reaction had gone to completion, as judged by TLC analysis, 6 mL $NaHCO_3$ (sat.) were added to the solution at 0 °C. The solution was transferred to a separatory funnel and washed with 75 mL DI water. The layers were separated and the aqueous layer was extracted with 50 mL EtOAc two times. The combined organic extracts were washed with 100 mL brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to

afford a crude enol triflate **1.13** which was carried on to the next step without further purification.

Diminished yields were observed when **1.13** was purified chromatographically. However, should further purification be desired, a good solvent system for isolation of the triflate through flash column chromatography is simply hexanes. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.32 (ddd, *J* = 12.0, 7.4, 4.0 Hz, 1H), 6.18-6.16 (m, 1H), 5.73 (apparent d, *J* = 12.0, Hz, 1H), 2.50 (dt, *J* = 16.0, 8.0 Hz, 1H), 2.30-2.22 (m, 1H), 1.32 (q, *J* = 8.0 Hz, 1H), 1.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 1.11 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.4, 139.5, 125.3, 123.2, 118.7 (q, $J_{C\text{-}F}$ = 323 Hz), 31.8, 27.9, 25.0, 24.3, 17.6, 15.9. **IR** (thin film): cm^{-1} 2950 (w), 1416 (s), 1246 (m), 1202 (s), 1140 (s), 1036 (m), 1013 (m), 887 (s), 800 (w), 749 (w), 614 (s), 512 (w). **HRMS** (ESI+): calculated for $C_{11}H_{13}F_3NaO_3S$ $[M+Na]^+$ 305.0430, found: 305.0434. **TLC**: R_f = 0.67 (15% EtOAc/hexanes). **Physical Appearance**: Clear liquid which darkens with exposure to light and air. **Optical Rotation**: $[\alpha]_D^{21.8}$: (c = 0.73, $CHCl_3$), + 109.59.

*Vinyl Nitrile **1.06***



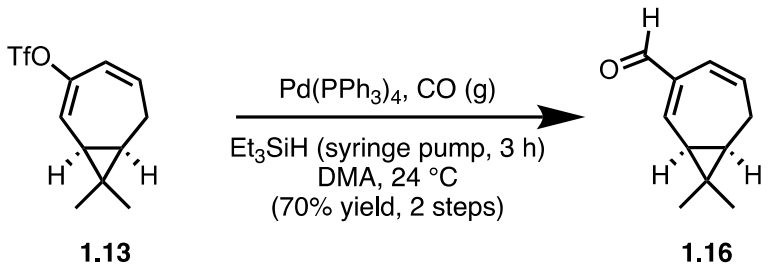
1.13 **1.06**

A 10 mL round-bottom flask, with stir bar, was charged with 96.4 mg **1.13** (0.342 mmol, 1 equiv) and was diluted with DMF (2 mL, 0.2 M). Thereafter, $Zn(CN)_2$ (26.9 mg, 0.229 mmol, 0.7 equiv) was added and the solution was sparged with Ar for approximately 10 min. Lastly, $Pd(PPh_3)_4$ (40.9 mg, 0.0354 mmol, 0.1 equiv) were added and the solution

was heated to 70 C in an oil bath. Heating was maintained at the same temperature for 24 h.

After the allotted time, the reaction was quenched with a 20% NH_4OH solution. The aqueous layer was extracted 3 x hexanes. The combined organic extracts were washed 2 x DI H_2O and 1 x brine. The organic was further dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product which was further purified by flash column chromatography eluting with a solvent system of 5% Et_2O/hexanes. The yield for this reaction was 11.7 mg vinyl nitrile (**1.06**) (0.073 mmol, 21% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.86 (d, *J* = 4.7 Hz, 1H), 6.08-6.04 (m, 1H), 5.70 (ddd, *J* = 11.6, 2.0, 1.0 Hz, 1H), 2.58 (dt, *J* = 18.2, 6.5 Hz, 1H), 2.40 (dtd, *J* = 18.1, 5.4, 2.2 Hz, 1H), 1.48-1.43 (m, 1H), 1.33 (dd, *J* = 7.9, 4.8 Hz, 1H), 1.16 (s, 3H), 1.02 (s, 3 H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.9, 137.3, 123.1, 120.5, 112.5, 33.9, 30.1, 28.5, 25.9, 24.6, 16.0. **IR** (thin film): cm^{-1} 2947 (s), 2866 (m), 2213 (m), 1604 (s), 1452 (w), 1416 (w), 1377 (w), 1239 (w), 1132 (w), 1055 (w), 993 (w), 880 (w), 831 (w), 742 (m), 601 (w), 574 (w), 469 (w). **HRMS** (ESI+): calculated for $C_{11}H_{13}NNa^+$ $[M+Na]^+$ 182.0940, found: 182.0940. Also observed **HRMS** (ESI+): calculated for $C_{11}H_{14}N^+$ $[M+H]^+$ 160.1121, found: 160.1119.

*Aldehyde **1.16***



1.13 **1.16**

Pd and LiCl sparged with CO solution:

A 300 mL round-bottom flask was charged with 1.5 g LiCl (3.5 equiv, 35.4 mmol). The flask was placed under a high vacuum (< 1 Torr) and the LiCl was flame-dried. Once the flask and its contents had returned to room temperature (rt, 23 °C), 1.17 g $Pd(PPh_3)_4$ (0.1 equiv, 1.0 mmol) were weighed out and added to the flask. A septum was placed over the flask and an atmosphere (atm) of CO (g) was introduced by a balloon with syringe. Thereafter, 30 mL DMA (Aldrich, SureSeal) were added by syringe and the heterogeneous mixture was sparged with stirring for 5 min.

Enol triflate **1.13** and triethylamine in DMA solution:

In a separate flask, enol triflate **1.13** was placed under an inert atm (either N_2 or Ar) and 5 mL triethylamine (TEA, freshly distilled, 3.55 equiv, 35.8 mmol) were added. The solution was then transferred dropwise by syringe to the original flask in 15 mL DMA, followed by a 15 mL wash. In total, the original flask contained 60 mL DMA (0.17 M triflate in DMA).

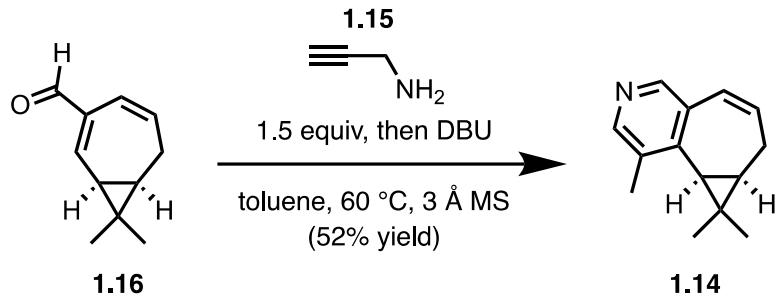
triethylsilane in DMA solution:

Note: on larger scale, it was found useful to sparge solution for approximately 10 min with Ar before addition into main reaction flask.

A 100 mL was charged with triethylsilane (TES-H, 1.94 mL, 1.2 equiv, 12.1 mmol). The TES-H was diluted in 61 mL DMA (0.2 M) and the solution was added to the original flask by syringe pump over a 3 h period.

When the reaction was complete as judged by TLC, the contents were slowly poured into a separatory funnel containing 200 mL NH_4Cl (sat.). The solution became warm to the touch. The aqueous and organic layers were separated and the aqueous layer was extracted two times with 100 mL EtOAc. The combined organic layers were washed successively with 250 mL DI water and 250 mL brine. The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude product which was later purified by MPLC (hexanes to 5% EtOAc/hexanes). The yield for this reaction was 421.3 mg aldehyde (**1.13**) (2.597 mmol, 78% yield of desired product over 2 steps; however this reaction was exceptional and the typical yield was 70%). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.30 (apparent s, 1H), 6.95 (apparent d, *J* = 4.6 Hz, 1H), 6.28-6.23 (m, 1H), 5.99 (dt, *J* = 16, 5.2 Hz, 1H), 2.76-2.67 (m, 1H), 2.54-2.46 (m, 1H), 1.59-1.52 (m, 2H, overlapped signals of 2 protons and water peak), 1.26 (s, 3H), 0.97 (s, 3 H). **^{13}C NMR** (MHz, $CDCl_3$): 194.3, 155.3, 137.7, 134.8, 119.5, 34.8, 31.2, 30.0, 29.2, 26.9, 16.0. **IR** (thin film): cm^{-1} 2944 (w), 1682 (s), 1621 (w), 1439 (w), 1375 (w), 1186 (w), 1153 (m), 1056 (w), 987 (w), 875 (w), 788 (w), 746 (w), 701 (w), 546 (w). **HRMS** (ESI+): calculated for $C_{11}H_{15}O$ $[M+H]^+$ 163.1117, found: 163.1117. **TLC**: R_f = 0.26 (5% EtOAc/hexanes). **Physical Appearance**: Orange-red liquid. **Optical Rotation**: $[\alpha]_D^{22.4}$: (c = 0.7952, $CHCl_3$), + 303.99.

*Methyl Pyridine **1.14***



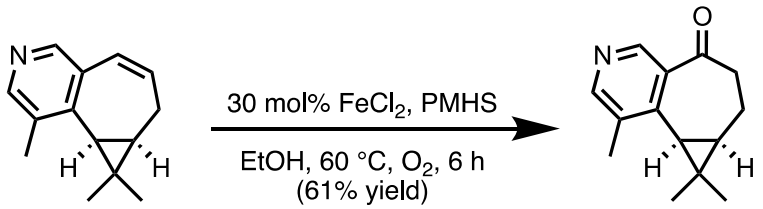
*Note: aldehyde (**1.16**) was azeotropically dried one time from benzene prior to running this reaction.*

A f20 mL scintillation vial, containing activated 3 Å M.S. and a stir bar, was charged with 152.9 mg aldehyde (**1.16**) (0.9425 mmol, 1 equiv) and toluene (6 mL, 0.2 M). Propargylamine (**1.15**, 90 μL, 1.405 mmol, 1.5 equiv) was added neat and the reaction was heated to 60 °C with stirring. After 3-7 hours, a small aliquot was taken by microsyringe and placed in a flame-dried 1 Dr vial. The aliquot was concentrated under a high vacuum (< 1 Torr) for 5-15 min and then a ^{1}H NMR was taken in benzene-*d6*. When the starting material (**1.16**) had disappeared by ^{1}H NMR, 200 μL DBU (1.34 mmol, 1.4 equiv) were added and the reaction was stirred with heating until the starting material disappeared by TLC. This reaction took anywhere from 2-5 days depending on the consistency of the heating.

The contents of the scintillation vial were filtered and washed with plenty of EtOAc. After removal of the volatiles, 368 mg of a crude product were obtained. The crude was further purified by MPLC with a linear gradient of 0 to 25% EtOAc/hexanes. The yield for this reaction was 98.5 mg methyl pyridine (**1.14**) (0.494 mmol, 52% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.10 (s, 1H), 6.32-6.25 (m, 2H overlapping olefin

protons), 2.45-2.37 (m, 1H), 2.25 (s, 3H), 2.05-1.98 (m, 1H), 1.54-1.48 (m, 2H 2 overlapping protons), 1.25 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 149.4, 147.7, 146.4, 135.3, 135.0, 133.2, 128.0, 31.0, 28.9, 27.9, 23.5, 17.4, 16.4, 14.6. **IR** (thin film): cm^{-1} 3023 (w), 2924 (m), 2861 (w), 1575 (m), 1440 (m), 1416 (w), 1395 (w), 1376 (m), 1278 (w), 1254 (w), 1241 (w), 1202 (w), 1180 (w), 1157 (w), 1136 (w), 995 (w), 916 (w), 887 (m), 841 (w), 822 (w), 765 (w), 737 (m), 712 (m), 674 (s), 524 (w). **HRMS** (ESI+): calculated for $C_{14}H_{18}N$ $[M+H]^+$ 200.1434, found: 200.1434. **Physical Appearance**: Orange oil.

*Ketone **1.23***



1.14 **1.23**

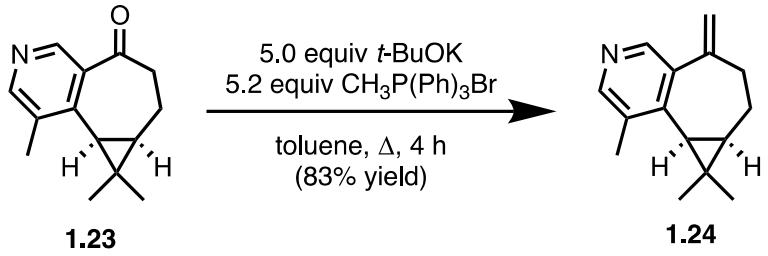
Note: for the following reaction, the flask did not need to be flame dried nor did the ethanol (EtOH) need to be absolute.

A 20 mL scintillation vial, with stir bar, was charged with 46.6 mg pyridine (**1.14**) (0.234 mmol, 1 equiv) and diluted with 1 mL EtOH (0.25 M). Thereafter, 170 μL polymethylhydrosiloxane (PMHS, 2.85 mmol, 12 equiv) and 8.3 mg $FeCl_2$ (0.066 mmol, 0.3 equiv) were added sequentially. The reaction flask was sealed with a septum and sparged with O_2 for 10 min. The scintillation vial was then heated to 60 °C in an aluminum block containing sand. The temperature was held between 60 and 70 °C for the duration of

the reaction. Occasionally sparging the solution with O_2 accelerated the rate of the reaction. The reaction was complete after approximately 6 h as judged by TLC.

Once the reaction was complete, silica gel was added to the reaction vial and the solvent was removed *in vacuo*. Once the crude had been adsorbed onto silica gel, the solid was loaded onto a saturated silica gel column and chromatographically isolated. The desired product eluted with an isocratic solvent system of 40% EtOAc/hexanes. The yield for this reaction was 30.9 mg (**1.23**) (0.234 mmol, 61% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.46 (s, 1H), 2.94-2.74 (m, 2H overlapping protons), 2.27 (s, 3H), 2.17-2.08 (m, 1H), 1.66 (d, *J* = 8.2 Hz, 1H), 1.49-1.27 (m, 2H, 3 overlapping proton signals which includes one of the methyl signals from dimethylcyclopropane and therefore integrates to 5), 1.31 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 206.2, 152.8, 148.7, 145.1, 135.9, 134.8, 42.5, 29.2, 28.2, 28.0, 22.5, 20.3, 17.0, 15.9. **IR** (thin film): cm^{-1} 2945 (w), 2868 (w), 1674 (s), 1576 (m), 1545 (w), 1454 (w), 1407 (w), 1378 (w), 1329 (w), 1283 (m), 1095 (m), 1016 (w), 943 (w), 899 (w), 858 (w), 796 (w), 689 (w). **HRMS** (ESI+): calculated for $C_{14}H_{18}NO$ $[M+H]^+$ 216.1383, found: 216.1383. Furthermore, the sodium adduct was also observed: calculated for $C_{14}H_{17}NNaO$ $[M+Na]^+$ 238.1202, found: 238.1201. **TLC**: R_f = 0.14 (40% EtOAc/hexanes). **Physical Appearance**: White Solid. **Melting Point**: 44-51 °C. **Optical Rotation**: $[\alpha]_D^{22.7}$: (c = 0.3403, $CHCl_3$), -245.66.

*Exomethylene **1.24***



1.23 **1.24**

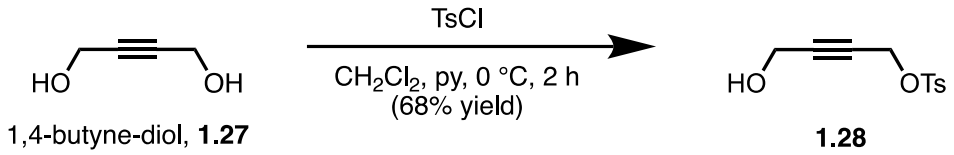
To a solution containing 129.8 mg *t*-BuOK (1.157 mmol, 5.0 equiv) and 7 mL toluene were added 429.5 mg methyltriphenylphosphonium bromide (1.202 mmol, 5.2 equiv) and the solution was heated to reflux and maintained at that temperature for 1 h.

After the allotted time, 50.0 mg ketone (**1.23**) were added to the solution in 3 mL toluene followed by 4 consecutive 3 mL washes with toluene. The resulting solution was maintained at reflux temperature for 4 h and was then allowed to cool to room temperature (rt, usually 23 °C).

The solution was quenched by pouring the contents of the scintillation vial into separatory funnel containing 20 mL DI H_2O. The scintillation vial was washed several times with EtOAc to aid in quantitative transfer to the separatory funnel. The layers of the separatory funnel were mixed, allowed to resolve and were separated. The aqueous layer was back-extracted with 10 mL EtOAc two times. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 309.9 mg crude product. Further purification was achieved by flash column chromatography employing an isocratic solvent system of 15% EtOAc/hexanes. The yield for the reaction was 41.2 mg **1.24** (0.193 mmol, 83% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.15 (s, 1H), 5.16 (apparent s, 1H), 4.91 (apparent s, 1H), 2.72-2.56 (m, 2H overlapping protons), 2.25 (s, 3H), 1.90-1.85 (m, 1H), 1.56 (d, *J* = 7.8 Hz, 1H), 1.23 (s, 3H), 1.04-0.91 (m, 2H, 2

overlapping protons), 0.87 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 149.7, 147.1, 146.5, 144.6, 138.8, 134.2, 117.1, 33.0, 28.2, 28.0, 26.1, 21.9, 20.3, 16.8, 16.2. **IR** (thin film): cm^{-1} 2951 (m), 2922 (m), 2863 (w), 1624 (w), 1574 (m), 1454 (m) 1433 (w), 1409 (m), 1376 (m), 1271 (w), 1242 (w), 1216 (w), 1168 (w), 1129 (m), 1027 (w), 1006 (w), 945 (w), 916 (w), 890 (s), 812 (m), 800 (w), 756, (w), 713 (w), 686 (w), 627 (w), 586 (m), 561 (w), 529 (w), 506 (w), 444 (w). **HRMS** (ESI+): calculated for $C_{15}H_{20}N$ $[M+H]^+$ 214.1590, found: 214.1590. **TLC**: R_f = 0.36 (30% EtOAc/hexanes). **Physical Appearance**: White Solid. **Melting Point**: 42-46 °C. **Optical Rotation**: $[\alpha]_D^{23.5}$: (c = 0.1552, $CHCl_3$), +24.91.

*Tosylate **1.28***

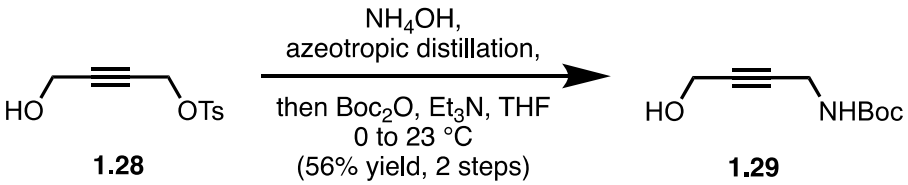


To a chilled (ice/water bath) solution of 1,4-butyne-diol **1.27** (55.1 g, 640 mmol, 5 equiv), pyridine (22 mL, 272 mmol, 2 equiv), and CH_2Cl_2 (300 mL, 0.4 M) was added tosyl chloride (24.9 g, 131 mmol, 1 equiv) in portions over a 10 min period. After 2 h, the reaction was complete as judged by TLC analysis.

The reaction was quenched with 250 mL 1 M HCl, washed with 250 mL deionized water, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 28.7 g crude product. Further purification was achieved with flash column chromatography using a step gradient of 30 to 40 to 50% EtOAc/hexanes. The yield for the reaction was 21.2 g **1.28** (88.2 mmol, 68% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.74-4.72 (m, 2H), 4.17-4.15 (m, 2H), 2.45 (s, 3H). **^{13}C NMR** (101 MHz,

$CDCl_3$): 145.4, 133.1, 130.0, 128.3, 87.7, 77.6, 58.0, 50.9, 21.8.**TLC**: R_f = 0.18 (40% EtOAc/hexanes).

*Propargylic Alcohol **1.29***



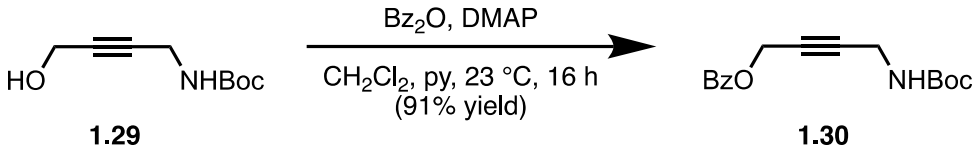
A 300 mL round-bottom flask, with stir bar, was charged with **1.28** (10.0 g, 41.6 mmol, 1 equiv). To the same flask, concentrated NH_4OH (79 mL) was added. With adequate stirring, the reaction was typically complete within 1-2 hours. The solvent and ammonia were removed by rotary evaporation employing toluene to azeotropically remove solvent; typically 3 cycles of 50-100 mL toluene were necessary to remove solvent. The crude material was carried forward without further purification.

The crude material was diluted with THF (163 mL) and Boc_2O (10.9 g, 50 mmol, 1.2 equiv) were added. The mixture was cooled in an ice/water bath for approximately 15 min and then triethylamine (7 mL, 50 mmol, 1.2 equiv) were added dropwise. After 30 min, the flask was removed from the ice/water bath and allowed to react at room temperature (rt, usually 23 °C) for 17 h.

The resulting solution was concentrated *in vacuo* and transferred to a separatory funnel with CH_2Cl_2. The organic layer was washed with 50 mL DI H_2O. The layers of the separatory funnel were mixed, allowed to resolve, and were separated. The aqueous layer was back-extracted with 50 mL CH_2Cl_2; this process was repeated twice. The combined organic extracts were washed with brine (100 mL), dried with Na_2SO_4, filtered, and

concentrated *in vacuo* to afford 7.9 g crude product. Further purification was achieved with flash column chromatography using a step gradient of 33 to 40 to 45% EtOAc/hexanes. The yield for the reaction was 4.3 g **1.29** (23 mmol, 56% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.24 (t, *J* = 1.9 Hz, 2H), 3.93 (d, *J* = 4.9 Hz, 2H), 2.48 (s, 1H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): 155.7, 81.9, 81.5, 80.3, 51.0, 30.7, 28.5. **TLC**: R_f = 0.2 (40% EtOAc/hexanes).

*Benzoate **1.30***



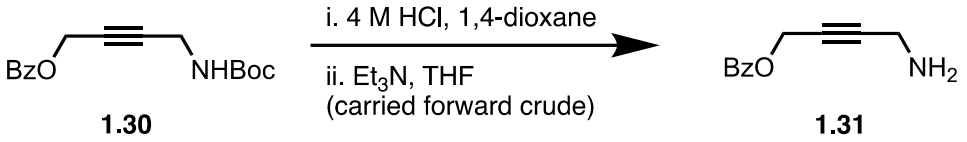
1.29 **1.30**

A 1000 mL round-bottom flask, with stir bar, was charged with **1.29** (4.0 g, 22 mmol, 1 equiv) and placed under an inert atmosphere of N_2 at room temperature (rt, usually 23 °C). Through a septum and *via* syringe, CH_2Cl_2 (20 mL) was added followed by pyridine (3.6 mL, 44 mmol, 2 equiv). The septum was momentarily opened in order to add benzoic anhydride (5.162 g, 22.8 mmol, 1 equiv) followed by DMAP (273 mg, 2.2 mmol, 0.1 equiv). Lastly, 24 mL CH_2Cl_2 were added (0.5 M). The reaction was allowed to continue for 16 h.

After the allotted time, the solution was transferred to a separatory funnel with CH_2Cl_2. The organic layer was washed with 50 mL $NaHCO_3$ (sat.). The layers of the separatory funnel were mixed, allowed to resolve, and were separated. The aqueous layer was back-extracted with 50 mL CH_2Cl_2 twice. The combined organic extracts were washed with 50 mL brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 7.4 g crude product. Further purification was achieved with flash column chromatography using

a step gradient of 0 to 20% EtOAc/hexanes. The yield for the reaction was 5.8 g **1.30** (20 mmol, 91% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.10-8.05 (m, 2H), 7.58 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.48-7.43 (m, 2H), 4.92 (t, *J* = 2.0 Hz, 2H), 4.74 (br. s, 1H), 3.99 (br. s, 2H), 1.45 (s, 9H). **TLC**: R_f = 0.27 (20% EtOAc/hexanes).

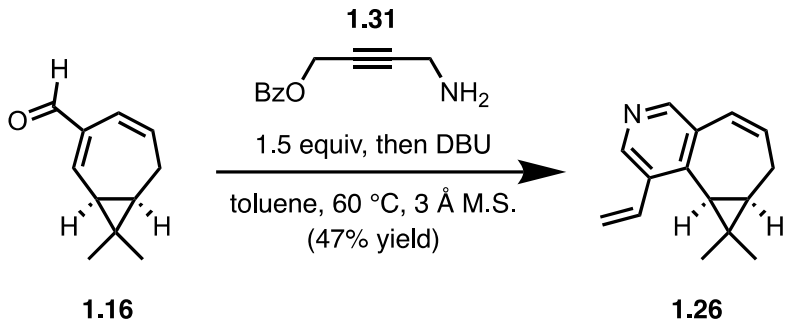
*Propargylamine **1.31***



A 300 mL round-bottom flask, with stir bar and **1.30** (2.287 g, 7.905 mmol, 1 equiv) was charged with 4 M HCl in 1,4-dioxane (56 mL, 224 mmol). The reaction was allowed to continue for 1 h at which point the solvent was removed *in vacuo*.

The resulting white solid was placed under an inert atmosphere of N_2 and diluted with 40 mL THF (0.2 M). Lastly, Et_3N (2.2 mL, 16 mmol, 2 equiv) were added and the reaction was allowed to stir for 1.5 h. The solvent was then removed *in vacuo* and the crude residue was washed with 25 mL diethyl ether. A white solid formed and the resulting mixture was filtered. The crude residue was washed and filtered in a similar way four more times. The diethyl ether was removed *in vacuo* to afford 1.160 g crude propargylamine (**1.31**), which was carried forward without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 4.94 (t, *J* = 2.0 Hz, 1H), 3.50 (t, *J* = 2.0 Hz, 1H). **HRMS** (ESI+): calculated for $C_{14}H_{16}NO_2$ $[M+H]^+$ 190.0863, found: 190.0865.

*Pyridine **1.26***



1.16 **1.26**

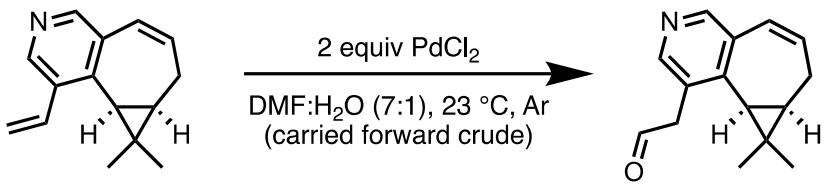
*Note: aldehyde (**1.16**) was was azeotropically dried one time from benzene prior to running this reaction.*

A flame-dried, 20 mL scintillation vial containing activated 3 Å M.S. and stir was charged with aldehyde **1.16** (32.3 mg, 0.199 mmol, 1 equiv) and diluted with toluene (2 mL, 0.1 M). Propargylamine (**1.31**, 52.4 mg, 0.277 mmol, 1.4 equiv) was added in toluene (2 mL) and the reaction was heated to 60 °C with stirring. After 3-7 hours, a small aliquot was taken by microsyringe and placed in a flame-dried 1 Dr vial. Solvent was removed under a high vacuum for about 5-15 min and then a ^{1}H NMR was taken in benzene-*d6*. When all starting material (**1.16**) had disappeared by ^{1}H NMR, 30 μL DBU (0.199 mmol, 1 equiv) were added and the reaction was stirred with heating until the starting material disappeared by TLC. This reaction took anywhere from 2-5 days depending on the consistency of the heating.

The contents of the scintillation vial were filtered and washed with plenty of EtOAc. The crude was then concentrated *in vacuo* to afford 113 mg crude. Further purification was achieved by flash column chromatography with a step gradient of 15 to 20% EtOAc/hexanes. The yield for this reaction was 19.6 mg pyridine (**1.26**) (0.093 mmol, 47% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.15 (s, 1H), 6.91 (dd, *J* = 17.6,

11.1 Hz, 1H), 6.36-6.28 (m, 2H, overlapping internal olefin protons), 5.74 (dd, *J* = 17.6, 1.2 Hz, 3H), 5.40 (dd, *J* = 11.1, 1.2 Hz, 1H), 2.44-2.36 (m, 1H), 2.03-1.96 (m, 1H), 1.58-1.51 (m, 2H, 2 overlapping protons), 1.25 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 150.1, 145.3, 144.1, 135.9, 135.5, 133.5, 133.4, 127.7, 117.0, 31.6, 27.8, 27.8, 23.5, 16.6, 15.0. **IR** (thin film): cm^{-1} 3025 (w), 2938 (m), 2861 (w), 1625 (w), 1568 (m), 1453 (m), 1414 (m) 1376 (w), 1202 (w), 1180 (w), 1161 (w), 1136 (w), 1041 (w), 989 (m), 915 (s), 898 (s), 841 (w), 769 (w), 737 (m), 719 (w), 691 (w), 656 (s), 621 (w). **HRMS** (ESI+): calculated for $C_{15}H_{18}N$ $[M+H]^+$ 212.1434, found: 212.1434. **TLC**: R_f = 0.33 (Developed 5% EtOAc/hexanes and a second time at 25% EtOAc/hexanes). **Physical Appearance**: Orange oil. **Optical Rotation**: $[\alpha]_D^{23.6}$: (c = 1.1707, $CHCl_3$), +138.38.

Aldehyde **1.26**

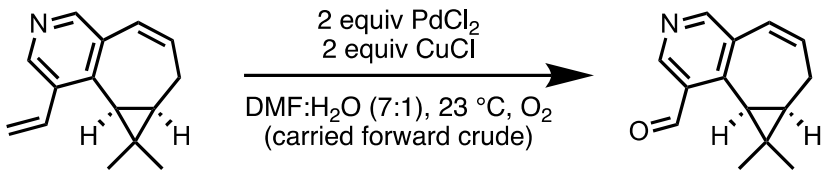


1.26 **1.38**

A 20 mL scintillation vial, with stir bar, was charged with $PdCl_2$ (17.7 mg, 0.100 mmol, 2.2 equiv) and was diluted with 0.3 mL DMF:H_2O (7:1). The resulting solution was sparged with Ar for 10 min. Thereafter, the contents of the flask were held under an Ar atmosphere for 40 min. Pyridine **1.26** (9.7 mg, 0.046 mmol, 1 equiv) was added by syringe in 2 portions of 0.2 mL DMF:H_2O (7:1); *note: the solution of vinyl pyridine in DMF:H_2O (7:1) was sparged with Ar for 10 min prior to transfer*. The reaction was stirred at room temperature (rt, usually 23 °C) for 19 h.

The contents of the rbf were filtered through a packed plug of Celite with EtOAc into a separatory funnel containing 50 mL NH_4Cl (sat.). The layers of the separatory funnel were mixed, allowed to resolve and were separated. The aqueous layer was back-extracted with 20 mL EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 18.3 mg crude product. Further purification was achieved by flash column chromatography employing a step gradient of 50% EtOAc/hexanes to 75% EtOAc/hexanes to 100% EtOAc. The yield for the reaction was 5.5 mg **1.38** (0.0242 mmol, 53% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.74 (apparent s, 1H), 8.40 (apparent s, 2H, protons on alpha to the pyridine ring nitrogen), 6.43-6.37 (m, 1H), 6.27 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.83-3.71 (m, 2H), 2.49-2.42 (m, 1H), 2.02-1.93 (m, 1H), 1.62-1.58 (m, 1H, overlaps with water peak), 1.48 (d, *J* = 8.2 Hz, 1H), 1.26 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 197.0, 153.8, 151.0, 150.3, 137.7, 135.9, 131.9, 126.2, 46.1, 31.6, 28.0, 27.7, 23.3, 16.8, 16.1. **IR** (thin film): cm^{-1} 2939 (m), 2863 (w), 1722 (s), 1599 (w), 1465 (w), 1432 (w), 1379 (w), 1321 (w), 1244 (w), 1185 (w), 1135 (w), 1071 (w), 1027 (w), 913 (w), 734 (m), 679 (w). **HRMS** (ESI+): calculated for $C_{15}H_{18}NO$ $[M+H]^+$ 228.1383, found: 228.1383. Also, when the compound was dissolved in methanol, the mass of the resulting hemiacetal was observed: calculated for $C_{16}H_{22}NO_2$ $[M+H]^+$ 260.1645, found: 260.1646. **TLC**: R_f = Compound streaked on TLC plate, however, rose to an Rf of 0.2-0.3 with 75% EtOAc/hexanes. **Physical Appearance**: Yellow amorphous solid. **Optical Rotation**: $[\alpha]_D^{23.6}$: (c = 0.0764, $CHCl_3$), + 274.00. Submission of aldehyde **1.38** to the oxygenated reaction conditions (see next experiment) gave **1.34** (*vide infra*).

*Aldehyde **1.34***



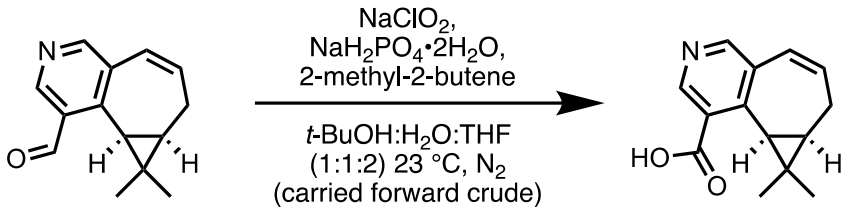
1.26 **1.34**

A 500 mL round-bottom flask, with stir bar, was charged with $PdCl_2$ (675.1 mg, 3.807 mmol, 2 equiv) and CuCl (378.4 mg, 3.822 mmol, 2 equiv). The flask was sealed with a septum and placed under an O_2 atmosphere. The reagents were diluted with 50 mL DMF:H_2O (7:1) and sparged with O_2 for 10 min. Thereafter, the contents of the flask were held under an O_2 atmosphere for 40 min. Pyridine (**1.26**) (393 mg, 1.86 mmol, 1 equiv) was added by syringe in 3 portions of 4 mL DMF:H_2O (7:1). The reaction was stirred at room temperature (rt, usually 23 °C) for 24 h.

The contents of the flask were filtered through a packed plug of Celite with EtOAc and concentrated *in vacuo*. After most of the EtOAc was removed, the solution was added to a separatory funnel containing 60 mL NH_4Cl (sat.). The layers of the separatory funnel were mixed, allowed to resolve and were separated. The aqueous layer was back-extracted with 20 mL EtOAc three times. The combined organic extracts were then washed 5 times with 100 mL deionized water and once with brine. The organic extracts were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford 517.1 mg crude aldehyde (**1.34**). The crude product was carried on to the next step without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 8.94 (s, 1H), 8.59 (s, 1H), 6.51 (ddd, *J* = 11.0, 7.9, 4.9 Hz, 1H), (dd, *J* = 11.0, 2.2 Hz, 1H), 2.54-2.46 (m, 1H), 2.05-1.97 (m, 1H), 1.94 (d, *J* = 8.3 Hz, 1H), 1.76 (ddd, *J* = 10.4, 8.2, 6.4 Hz 1H), 1.28 (s, 3H), 0.93 (s, 3H). **^{13}C NMR** (101 MHz,

$CDCl_3$): 189.4, 157.2, 152.9, 151.3, 139.1, 136.9, 133.3, 125.6, 32.7, 27.4, 26.5, 23.4, 17.2, 17.0. **IR** (thin film): cm^{-1} 3192 (m), 3052 (w), 2930 (w), 1697 (m), 1656 (s), 1595 (m), 1541 (w), 1463 (w), 1412 (m), 1388 (m), 1271 (w), 1253 (w), 1132 (m), 1101 (m), 916 (w), 847 (w), 771 (w), 736 (w), 664 (w), 574 (w), 522 (w). **HRMS** (ESI+): calculated for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1226, found: 214.1228.

Pinnick Oxidation Acid **SI-1.05**



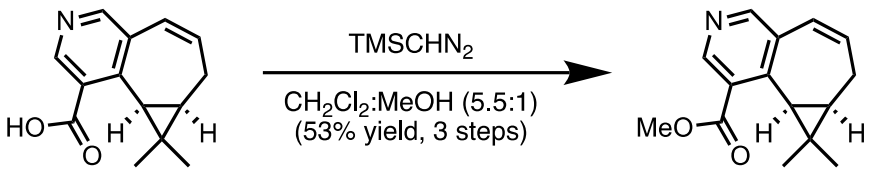
1.34 **SI-1.05**

A 100 mL round-bottom flask, with stir bar and crude (**1.34**), was charged with *t*-BuOH (6 mL). The reaction vessel was further diluted with THF (12 mL). Thereafter, 2-methyl-2-butene (2.1 mL, 20 mmol, 11 equiv) was added. Lastly, $NaH_2PO_4•2H_2O$ (781.6 mg, 5.664 mmol, 3 equiv) and $NaClO_2$ (634.6 mg, 5.613 mmol, 3 equiv) were dissolved in DI H_2O (6 mL) and were added dropwise to the reaction flask *via* Pasteur pipet. The reaction was monitored by UPLC-MS analysis. Occassionally, the reaction would cease prior to complete conversion of starting material. To drive the reaction to completion, an additional portion of 2-methyl-2-butene, $NaH_2PO_4•2H_2O$, and $NaClO_2$ were added in the same equivalency as above.

Once the reaction was complete, the contents of the flask were transferred to a separatory funnel, which contained 50 mL NH_4Cl (sat.), with 10 mL EtOAc used over 3 washes. The aqueous layer was further saturated with solid NaCl. The layers of the

separatory funnel were mixed, allowed to resolve and were separated. The aqueous layer was back-extracted with 20 mL EtOAc twice. The combined organic extracts were then washed once with an equal volume of brine. The organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford 638.5 mg crude product (**SI-1.05**), which was carried forward without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.55 (s, 1H), 6.52-6.46 (m, 1H), 6.29 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.46-2.39 (m, 1H), 2.12 (d, *J* = 8.2 Hz, 1H), 2.03-1.95 (m, 1H), 1.70-1.66 (m, 1H), 1.21 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 169.7, 156.5, 153.3, 151.6, 139.2, 136.8, 130.0, 125.5, 33.2, 28.8, 28.1, 23.2, 17.0, 16.9. **IR** (thin film): cm^{-1} 3088 (br), 2950 (m), 1708 (s), 1596 (w), 1542 (w), 1462 (w), 1426 (w), 1376 (w), 1245 (m), 1152 (m), 1133 (m), 1065 (w), 912 (w), 845 (w), 807 (w), 755 (s), 666 (w), 620 (w). **HRMS** (ESI+): calculated for $C_{14}H_{16}NO_2$ $[M+H]^+$ 230.1176, found: 230.1175. **Physical Appearance**: orange foam. **UPLC-MS Conditions**: (linear gradient 95% Water + 0.2% formic acid/MeCN – 10% Water + 0.2% formic acid/MeCN, 13 min).

*Methyl Ester **1.05***



SI-1.05 **1.05**

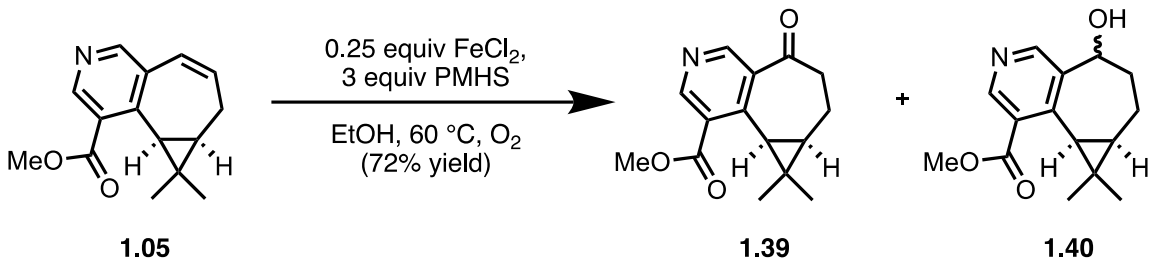
*Note: carboxylic acid (**SI-1.05**) was azeotropically dried one time from benzene prior to running this reaction.*

A 50 mL round-bottom flask, with stir bar and **SI-1.05** was diluted with 22 mL CH_2Cl_2 and 4 mL MeOH. $TMSCHN_2$ was then added until effervescence ceased, at which point glacial acetic acid was added, again, until effervescence ceased. The solution turned black upon addition of $TMSCHN_2$ and heat was given off on this scale (~1 mmol).

The solution was concentrated *in vacuo* to afford the crude product. The crude product was further purified with flash column chromatography with an isocratic solvent system of 25% EtOAc/hexanes. The product yield was 241.2 mg methyl ester (**1.05**) (0.9914 mmol, 53% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.32 (s, 1H), 6.40 (ddd, *J* = 10.9, 7.6, 4.8 Hz, 1H), 6.32 (apparent d, *J* = 10.9 Hz, 1H), 3.93 (s, 3H), 2.40-2.33 (m, 1 H), 2.07 (d, *J* = 8.5 Hz, 1H), 2.01-1.93 (m, 1H), 1.58 (ddd, *J* = 10.4, 8.5, 6.6 Hz 1H), 1.19 (s, 3H), 0.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 167.9, 153.5, 148.0, 147.9, 137.0, 134.3, 130.0, 127.1, 52.5, 33.0, 28.2, 28.1, 23.3, 16.8, 15.5. **IR** (thin film): cm^{-1} 2948 (w), 1730 (s), 1570 (w), 1545 (w), 1435 (m), 1375 (w), 1284 (s), 1240 (w), 1192 (m), 1140 (s), 1014 (w), 915 (w), 830 (w), 797 (w), 762 (w), 731 (w), 718 (w), 662 (w), 590 (w), 551 (w). **HRMS** (ESI+): calculated for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1332, found: 244.1337. **TLC**:

R_f = 0.32 (30% EtOAc/hexanes). **Physical Appearance**: amber oil. **Optical Rotation**: $[\alpha]_D^{21.9}$: (c = 0.559, $CHCl_3$), - 67.98.

*Ketone **1.39** and Benzylic Alcohol **1.40***



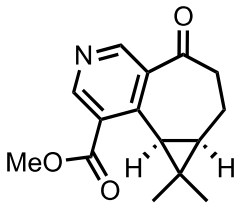
1.05 **1.39** **1.40**

Note: for the following reaction, the reaction flask did not need to be dried nor did the EtOH need to be absolute.

A 20 mL scintillation vial, with stir bar, was charged with methyl ester **1.05** (226.7 mg, 0.9318 mmol, 1 equiv) and diluted with 3.7 mL EtOH (0.25 M). Thereafter, polymethylhydrosiloxane (PMHS, 170 μL, 2.85 mmol, 3 equiv) and $FeCl_2$ (29.5 mg, 0.066 mmol, 0.3 equiv) were added sequentially. The reaction flask was sealed with a septum and sparged with O_2 for 20 min. The scintillation vial was then heated to 60 °C in an aluminum block containing sand. The temperature was raised to 60 °C and held at that same temperature for the duration of the reaction. Occasionally sparging the solution with O_2 accelerated the rate of the reaction. The reaction was complete after approximately 24 h.

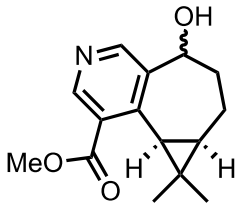
Once the reaction was judged complete by TLC analysis, the solution was filtered through a plug of Celite and concentrated *in vacuo* to afford 576 mg crude product. Further purification was achieved by flash column chromatography with a step gradient of 30 to 40% EtOAc/hexanes to elute the ketone. Once the ketone had eluted, the solvent system

was altered to 10% MeOH/CH_2Cl_2 and maintained until elution of alcohols. The yield of ketone (**1.39**) was 111.7 mg (0.431 mmol, 46% yield) and the yield of alcohols (**1.40**) was 61.6 mg (0.236 mmol, 25% yield). The isolated products accounted for 72% of the mass balance.



1.39

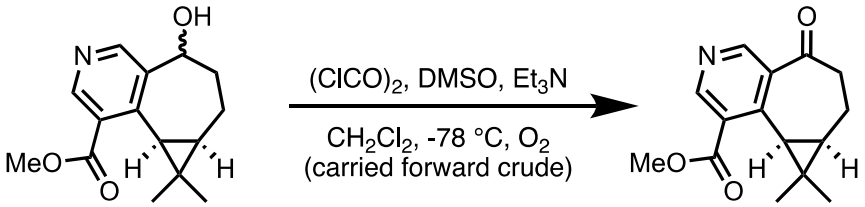
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.66 (s, 1H), 3.94 (s, 3H), 2.94-2.84 (m, 1H), 2.77 (dt, , *J* = 19, 3.3 Hz, 1H), 2.18 (d, *J* = 7.7 Hz, 1H), 2.15-2.06 (m, 1H), 1.37-1.28 (m, 2H, 2 overlapping proton signals), 1.25 (s, 3H), 0.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 206.2, 166.8, 153.0, 152.6, 146.3, 137.6, 129.3, 52.7, 42.2, 29.7, 28.3, 28.2, 23.4, 20.1, 16.4. **IR** (thin film): cm^{-1} 2951 (m), 2926 (m), 2868 (w), 1732 (s), 1683 (s), 1573 (w), 1547 (w), 1457 (w), 1436 (w), 1302 (m), 1277 (m), 1195 (m), 1155 (s), 1131 (w), 1080 (w). **HRMS** (ESI+): calculated for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1281, found: 260.1285. **TLC**: R_f = 0.19 (30% EtOAc/hexanes). **Physical Appearance**: White solid. **Melting Point**: 53-55 °C. **Optical Rotation**: $[\alpha]_D^{21.5}$: (c = 1.0175, $CHCl_3$), - 366.78.



1.40

Note: The below tabular data represents an inconsequential 4:1 mixture of diastereomers about the secondary alcohol.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.81 (s, 0.27H, minor diastereomer), 8.38 (s, 1H), 5.50 (dd, *J* = 9.9, 7.4 Hz, 0.27H, minor diastereomer), 4.96 (d, *J* = 5.1 Hz, 1H, major diastereomer), 3.93 (s, 3H, major diastereomer), 3.92 (s, 3H, methyl ester of minor diastereomer) 2.43-2.33 (m, 0.63H), 2.19 (d, *J* = 8.3 Hz, 1H, major diastereomer), 2.15-2.01 (m, 1H), 1.97 (d, *J* = 8.5 Hz, 0.35H, minor diastereomer) 1.90-1.82 (m, 2 H), 1.57-149 (m, 0.44H), 1.24 (s, 3H, major diastereomer), 1.23 (s, 1H, minor diastereomer methyl), 1.21-1.18 (m, 1H), 1.01 (ddd, *J* = 12.6, 8.5, 4.5 Hz 0.45H, minor diastereomer), 0.73 (s, 3H, major diastereomer methyl), 0.68 (s, 1H, minor diastereomer methy), 0.63-0.50 (m, 0.47H). **^{13}C NMR** (101 MHz, $CDCl_3$): 167.4, 151.9, 151.0, 150.0, 148.8, 148.4, 145,4, 138.3, 130.3, 73.2, 69.0, 52.6, 52.5, 33.2, 32.6, 29.8, 28.7, 28.4, 28.4, 27.8, 26.7, 25.6, 23.3, 21.5, 20.8, 20.8, 16.3, 16.2. **IR** (thin film): cm^{-1} 3347 (br), 2922 (w), 1722 (s), 1585 (w), 1553 (w), 1436 (w), 1291 (s), 1219 (w), 1192 (m), 1132 (s), 1084 (m), 1006 (w), 987 (w), 921 (w), 832 (w), 806 (w), 762 (w), 557 (w). **HRMS** (ESI+): calculated for $C_{15}H_{20}NO_3$ $[M+H]^+$ 262.1438, found: 262.1440. **TLC**: R_f = 0.39 (10% MeOH/CH_2Cl_2). **Physical Appearance**: yellow oil.

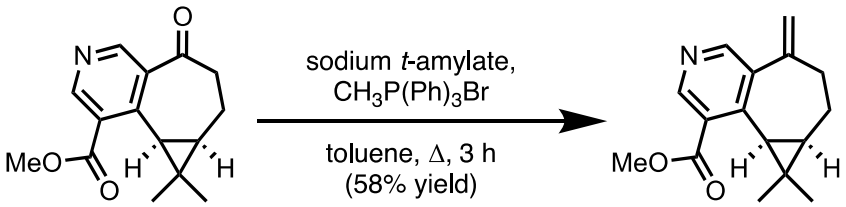


1.40 **1.39**

*Note: the starting Benzylic Alcohol (**1.40**) was azeotropically dried with benzene one time before addition into solution.*

A flame-dried 1 Dr vial, with stir bar, was charged with oxalyl chloride (8 μL, 0.093 mmol, 2.1 equiv) and CH_2Cl_2 (3 mL). The solution was cooled in a dry ice/acetone bath for 10 min. After the allotted time, dimethylsulfoxide (DMSO, 20 μL, 0.282 mmol, 6.3 equiv) were added to the vial by microsyringe and the solution was allowed to stir at the same temperature for 30 min. At this time, the diastereomeric mixture of alcohols (**1.40**) were added in 1.5 mL CH_2Cl_2 followed by a 1.5 mL wash with the same solvent. The solution was allowed to stir for an additional hour in the dry ice/acetone bath. Lastly, triethylamine (70 μL, 0.502 mmol, 11.3 equiv) was added and the reaction vial was removed from the cooling bath and allowed to warm to room temperature (rt, usually 23°C). After approximately 1 h stirring at rt, the reaction was quenched with DI water. The contents of the vial were transferred to a separatory funnel containing 10 mL deionized water and the aqueous layer was extracted with 10 mL CH_2Cl_2 three times. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford 10.5 mg desired ketone. The resulting ketone (**1.39**) could be carried forward without further purification.

*Olefin **1.25***



1.39 **1.25**

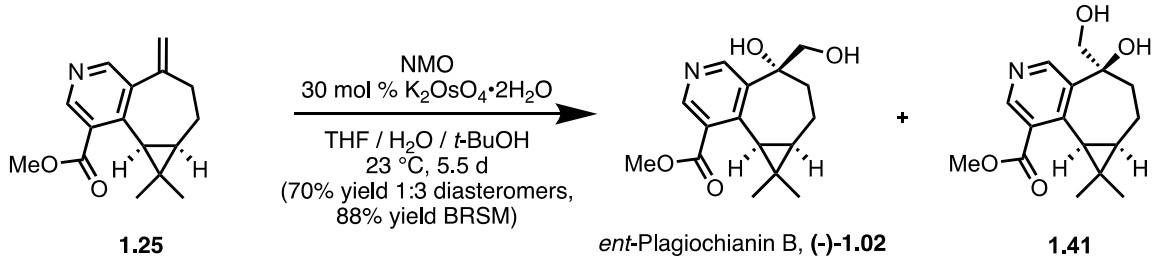
A 50 mL round-bottom flask, with stir bar, was charged with methyltriphenylphosphonium bromide (232.1 mg, 0.6497 mmol, 1.5 equiv). The reagent was azeotropically dried with ~10 mL benzene twice and then placed under an inert atmosphere of Ar by pulling a high vacuum (< 1 Torr) and then refilling with Ar three times. The seal over the reagent was broken and a reflux condenser was placed over the top. The refluxing apparatus was placed under Ar. Approximately 12 mL toluene were added by syringe through the top of the reflux condenser. Lastly, sodium *t*-amylate (65.9 mg, 0.598 mmol, 1.4 equiv) was added and the resulting yellow solution was heated to reflux and maintained at that temperature for 1 h.

In a separate vial, ketone (**1.39**) (111.7 mg, 0.4308 mmol, 1 equiv) was dried azeotropically with benzene twice and placed under an inert atmosphere in the same manner as described above. After the allotted hour, ketone (**1.39**) was added to the refluxing solution by syringe through the reflux condenser in 3 portions of 4 mL toluene. The solution was maintained at reflux for 3 h.

The solution was allowed to cool to room temperature (rt, usually 23 °C) and was poured into a separatory funnel containing 50 mL DI H_2O. The 50 mL flask was washed several times with EtOAc to aid in quantitative transfer to the separatory funnel. The layers of the separatory funnel were mixed, allowed to resolve, and were separated. The aqueous

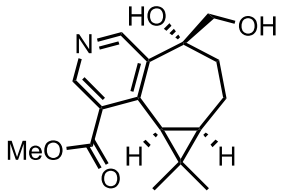
layer was back-extracted with 20 mL EtOAc twice. The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford 242.5 mg crude product. Further purification was achieved with flash column chromatography using a step gradient of 15-20% EtOAc/hexanes to elute the desired compound. The yield for this reaction was 64.5 mg olefin (**1.25**) (0.251 mmol, 58% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.41 (s, 1H), 5.24 (apparent s, 1H), 4.99 (apparent s, 1H), 3.93 (s, 3H), 2.72-2.63 (m, 1 H), 2.60-2.52 (m, 1H), 2.00 (d, *J* = 8.5 Hz, 1H), 1.90-1.84 (m, 1H), 1.21 (s, 3H), 1.03 (ddd, *J* = 12.4, 8.6, 4.4 Hz 1H), 0.90-0.77 (m, 1H), 0.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 167.6, 151.5, 150.2, 146.7, 146.3, 139.8, 128.9, 117.5, 52.5, 32.8, 28.7, 28.3, 27.0, 21.4, 21.2, 16.4. **IR** (thin film): cm^{-1} 2978 (w), 2950 (m), 2925 (m), 2862 (w), 1732 (s), 1572 (w), 1457 (w), 1435 (w), 1282 (m), 1242 (w), 1202 (m), 1155 (w), 1116 (w), 1103 (w), 1068 (w), 900 (w). **HRMS** (ESI+): calculated for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found: 258.1491. **TLC**: R_f = 0.22 (15% EtOAc/hexanes). **Physical Appearance**: White solid. **Melting Point**: 34-36 °C. **Optical Rotation**: $[\alpha]_D^{22.1}$: (c = 0.40, $CHCl_3$), - 161.00.

ent-*Plagiochianin B* ***(-)-1.02*** *and Diastereomer* ***1.41***



A 25 mL pear-shaped flask containing a stir bar and Olefin (**1.25**) (39.3 mg, 0.153 mmol, 1.0 equiv), was charged with THF/H_2O/*t*-BuOH (1:1:1, 10 mL), 4-

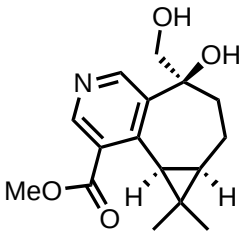
methylmorpholine N-oxide (NMO, 19.7 mg, 0.168 mmol, 1.1 equiv), methanesulfonamide (14.5 mg, 0.152 mmol, 1.0 equiv), and $K_2OsO_4 \bullet 2H_2O$ potassium osmate dihydrate (17.7 mg, 0.0480 mmol, 0.3 equiv). An additional 5 mL of the same solvent were used to wash down the walls of the flask. The contents of the flask were allowed to react for 5.5 days before quenching with 4 mL $Na_2S_2O_3$ (sat.). The flask was allowed to stir for an additional 15 min and then the contents were transferred to a separatory funnel which contained 10 mL $NaHCO_3$ (sat.). The layers of the separatory funnel were mixed, allowed to resolve, and were separated. The aqueous layer was back-extracted with 20 mL EtOAc five times. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford 57.9 mg crude product. Further purification was achieved with flash column chromatography using a step gradient of 30% EtOAc/hexanes (to remove remaining starting material) to 5% MeOH/CH_2Cl_2 to elute a mixture of diastereomers. The yield for the reaction was 31.3 mg **(-)-1.02** and **1.41** (0.107 mmol, 70% yield). Furthermore, 8 mg starting material (**1.25**) were recovered (88% yield by returned starting material [BRSM]). Separation of the diastereomers was achieved through preparative TLC by developing the same plate a minimum of five times in a solvent system of 5% MeOH/CH_2Cl_2; further developments were occasionally necessary to achieve adequate separation of the diastereomers.



ent-Plagiochianin B, **(-)-1.02**

ent-Plagiochianin B **(-)-1.02**:

^{1}H-NMR (600 MHz, Methanol-*d4*): δ 8.75 (s, 1H), 8.71 (s, 1H), 3.94 (d, *J* = 11.4 Hz, 1H, overlaps with methyl ester), 3.93 (s, 3H overlaps with diastereotopic proton from the hydroxyl-bearing methylene), 3.79 (d, *J* = 11.4 Hz, 1H), 2.26 (d, *J* = 8.9 Hz, 1H), 1.89-1.83 (m, 3H, 3 overlapping aliphatic proton signals), 1.23 (s, 3H), 1.22-1.19 (m, 1H, overlaps with a methyl from dimethylcyclopropane), 0.73-0.65 (m, 1H, overlaps with a methyl from dimethylcyclopropane) 0.70 (s, 3 H). **^{13}C NMR** (151 MHz, Methanol-*d4*): 168.9, 152.1, 151.0, 149.8, 141.1, 132.6, 77.0, 69.2, 53.0, 34.4, 31.5, 28.7, 27.7, 24.4, 22.6, 16.6. **IR** (thin film): cm^{-1} 3363 (br), 2923 (s), 1731 (s), 1585 (w), 1549 (w), 1456 (w), 1300 (s), 1196 (w), 1163 (m), 1102 (m), 845 (w), 820 (w), 776 (w), 560 (w), 421 (w). **HRMS** (ESI+): calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1543, found: 292.1546. Furthermore, the sodium adduct was also observed: calculated for $C_{16}H_{21}NNaO_4$ $[M+Na]^+$ 314.1363, found: 314.1364. **TLC**: R_f = 0.28 (5% MeOH/CH_2Cl_2). **Physical Appearance**: white powder. **Optical Rotation**: $[\alpha]_D^{23.7}$ = - 62.45 (c = 0.0427, MeOH). **Literature Value for Plagiochianin B: Optical Rotation**: $[\alpha]_D^{20}$ = + 52.17 (c = 0.06, MeOH). *Cf.* Han, J.-J.; Zhang, J.-Z.; Zhu, R.-X.; Li, Y.; Qiao, Y.-N.; Gao, Y.; Jin, X.-Y.; Chen, W.; Zhou, J.-C.; Lou, H.-X. *Org. Lett.* **2018**, *20*, 6550-6553.



1.41

Diastereomer of *ent*-Plagiochianin B (**1.41**):

^{1}H-NMR (600 MHz, Methanol-*d4*): δ 8.96 (s, 1H), 8.78 (s, 1H), 4.24 (d, *J* = 11.3 Hz, 1H), 3.93 (s, 3H), 3.84 (d, *J* = 11.4 Hz, 1H), 2.24 (td, *J* = 13.7, 4.9 Hz, 1H), 2.16 (d, *J* = 8.2 Hz 1H), 1.85-1.81 (m, 1H), 1.72 (ddd, *J* = 14.0, 5.3, 2.1 Hz, 1H), 1.24 (s, 3H), 1.07 (ddd, *J* = 12.1, 8.3, 4.6 Hz, 1H) 0.77 (ddd, *J* = 21.4, 13.1, 5.6 Hz, 1H), 0.69 (s, 3 H). **^{13}C NMR** (151 MHz, Methanol-*d4*): 168.8, 152.2, 150.0, 147.6, 141.3, 131.5, 78.2, 71.1, 53.0, 35.7, 30.7, 28.7, 27.7, 24.8, 22.4, 16.4. **IR** (thin film): cm^{-1} 3367 (br), 2950 (m), 1731 (s), 1582 (w), 1456 (w), 1297 (s), 1215 (w), 1153 (w), 1063 (w), 922 (w), 822 (w), 779 (w), 748 (w), 670 (w). **HRMS** (ESI+): calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1543, found: 292.1548. **TLC**: R_f = 0.28 (5% MeOH/CH_2Cl_2). **Physical Appearance**: white powder. **Optical Rotation**: $[\alpha]_D^{23.2}$: (c = 0.138, MeOH), -156.52.

1.4 References and Notes

[1] Han, J.-J.; Zhang, J.-Z.; Zhu, R.-X.; Li, Y.; Qiao, Y.-N.; Gao, Y.; Jin, X.-Y.; Chen, W.; Zhou, J.-C.; Lou, H.-X. *Org. Lett.* **2018**, *20*, 6550-6553.

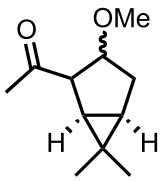
[2] Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3452-3460.

[3] To the best of our knowledge, (-)-3-carene is not commercially available, nor does a synthesis exist. A racemic synthesis of 3-carene has been reported through a Diels-Alder approach: Johnson, C. R.; Kadow, J. F. *J. Org. Chem.* **1987**, *52*, 1493-1500.

[4] Chen, W.-L.; Chen, C.-Y.; Chen, Y.-F.; Hsieh, J.-C. *Org. Lett.* **2015**, *17*, 1613-1616.

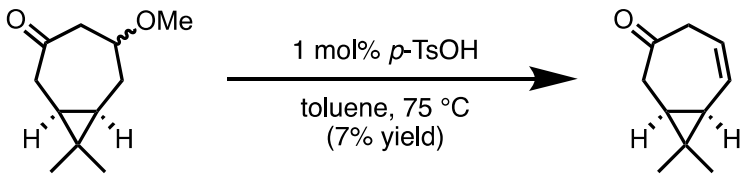
[5] Hudlicky, T.; Ranu, B. C.; Naqvi, S. M.; Srnak, A. *J. Org. Chem.* **1985**, *50*, 123-127.

[6] The 5-membered isomer (**i.12**) was also formed as a mixture of diastereomers in this reaction but was readily separable from **1.12** by flash column chromatography.



i.12

[7] Though not fully delineated, good evidence for the isomerization of the alkene *out of* conjugation with the ketone was observed when catalytic amounts of *p*-TsOH were used to promote the E1cB elimination (2 vinyl protons at 5.59 and 5.78 ppm respectively):



1.12 **i.07**

[8] Winkler, C. K.; Clay, D.; Davies, S.; O'Neill, P.; McDaid, P.; Debarge, S.; Steflik, J.; Karmilowicz, M.; Wong, J. W.; Faber, K. *J. Org. Chem.* **2013**, *78*, 1525-1533.

[9] Wei, H.; Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H. *Org. Lett.* **2015**, *17*, 5974-5977.

[10] Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4077-4080.

[11] Hydrolysis of the imine was invariably observed on typical SiO_2 TLC conditions even following treatment of the plate with Et_3N. The best way to monitor for imine formation was through ^1H NMR analysis of a small aliquot (concentrated *in vacuo* without aqueous work-up) in benzene-*d6*.

[12] Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300-2301.

[13] Schuppe, A. W.; Huang, D.; Chen, Y.; Newhouse, T. R. *J. Am. Chem. Soc.* **2018**, *140*, 2062-2066.

[14] Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362-3374.

[15] Oxidation conditions applied to ketone **1.23**: a) Riley [O]: Collman, J. P.; Decréau, R. A.; Costanzo, S. *Org. Lett.* **2004**, *6*, 1033-1036. b) IBX [O]: Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245-2258. c) Bobbitt Salt [O]: Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles*, **1990**, *30* 1131-1140. d) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. *Org. Lett.* **2005**, *7*, 4549-4552. e) NHPI and $Co(acac)_2$: Shibamoto, A.; Sakaguchi, S.; Ishii, Y. *Org. Proc. Res. Dev.* **2000**, *4*, 505-508. f) Jones [O]: Manzanaro, S.; Vicent, M. J.; Martín, M. J.; Salvador-Tormo, N.; Pérez, J. M.; del Mar Blanco, M. Avendaño, C.; Menéndez, J. C.; de la Fuente, J. A. *Bioorg. Med. Chem.* **2004**, 6505-6515. g) Review of Cr-catalyzed oxidations from which CrO_3/O_2 was taken: Muzart, J. *Chem. Rev.* **1992**, *92*, 113-140. CrO_3/O_2: Bae, S. K.; Lee, S. B.; Park, D. C.; Lee, K. *Taehan Hwahakhoe Chi*, **1989**, *33*, 106; *Chem. Abstr.* **1989**, *111*, 77606v.

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[17] Liu, B.; Jin, F.; Wang, T.; Yuan, X.; Han, W. *Angew. Chem. Int. Ed.* **2017**, *56*, 12712-12717.

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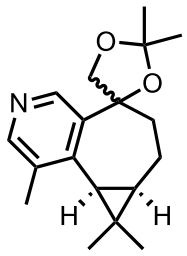
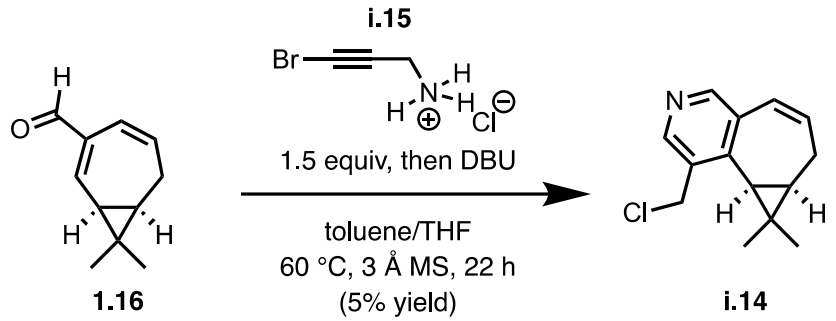
[19] Though not fully characterized, milligrams of cyclic ketal **i.24** were produced as a mixture of diastereomers. Unfortunately, the desired oxidation of the benzylic methyl group of **i.24** was not observed with Cr(V). Owing to a dearth of material, no other conditions were tried to oxidize **i.24**.



i.24

[20] A few conditions were tried to gain access to a pyridine containing a benzylic carbon was more amenable to oxidation to the acid. An interesting observation came when using the hydrochloride salt **i.15** (synthesis reported by Ovaa *J. Am. Chem. Soc.* **2019**, *141*, 3507-3514.) in the 6π-azatriene electrocyclization. A pyridine with a halogen at the benzylic position is indeed formed, however the halogen appeared to be chloride! Presumably small amounts of the expected benzylic bromide are formed followed by displacement by the chloride freed after treatment of **i.15** with DBU. This result was determined through ^{1}H and ^{13}C NMR analyses and the identity of the halogen was assigned through MS analysis which

showed the expected mass of **i.14** including the distinctive isotopes of chlorine. Yields for this reaction were unfortunately very low and **i.14** was never fully characterized. Nonetheless, the result stands as an interesting variant of the 6π-azatriene electrocyclization.



[21] Zhao, Z.; Wei, H.; Xiao, K.; Cheng, B.; Zhai H.; Li, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 1148-1152.

[22] a) Hori, H.; Arai, S. Nishida, A. *Adv. Synth. Catal.* **2017**, *359*, 1170-1176. b) de Bruin, G.; van Rooden, E. J.; Ward, D.; Wesseling, C.; van den Nieuwendijk, A. M. C. H.; van Boeckel, C. A. A.; Driessen, C.; Kisselev, A. F.; Florea, B. I.; van der Stelt, M.; Overkleeft, H. S. *Eur. J. Org. Chem.*, **2017**, 5921-5934.

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[24] Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem. Eur. J.* **2006**, *12*, 949-955.

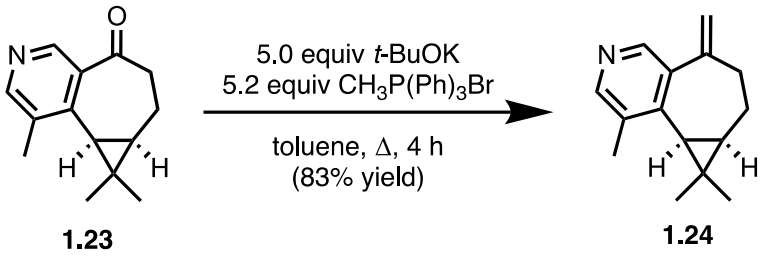
[25] Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science*, **2011**, *333*, 1609-1612.

[26] Pinnick [O]: Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 6084-6096. This standard sequence was not the only one we tested for advancing **1.26** to **1.05**. Another successful route involved oxidation of **1.34** with Bobbitt's salt in the presence of pyrazole and pyridine which gave an *N*-Acylpyrazole intermediate (Leadbeater *Org. Lett.* **2017**, *19*, 1286-1289.) that was quickly converted to the methyl ester **1.05** by treatment with NaOMe in MeOH at 0 °C. Higher yields were obtained with the chemistry described in the manuscript above.

[27] A similar side-product was observed on the earlier methyl pyridine sequence but was never isolated or characterized.

[28] a) Conia, J. M.; Limasset, J. C. *Bull Soc. Chim. Fr.* **1967**, *6*, 1936-1938. b) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103-1108. c) Short, R. P.; Revol, J. M. Ranu, B. C. Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453-4461.

[29] We tested similar conditions on the ketone **1.23** and observed very good yield for the desired **1.24**. For conditions see: Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511-6515.



1.23 **1.24**

[30] Jackson, III, R. K.; Wood, J. L. *Org. Lett.* **2021**, *23*, 1243-1246.

CHAPTER TWO

Aleutianamine: Isolation and Biological Activity and Model System Validation of Tandem Metathesis Approach

2.1 Aleutianamine Isolation and Biological Activity

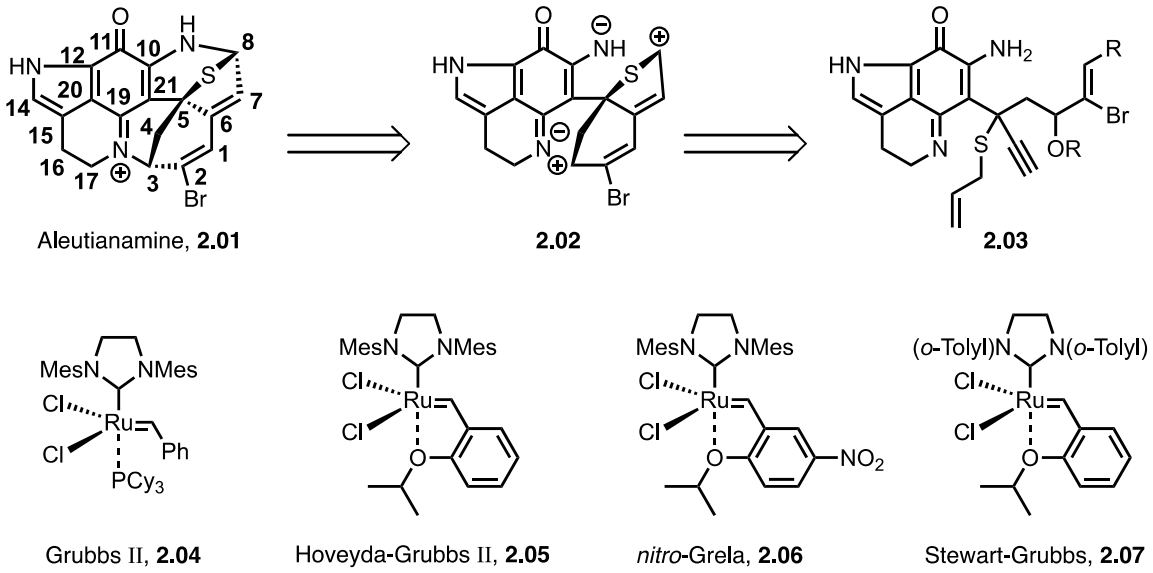
The isolation of aleutianamine (**2.01**) was reported in 2019.[1] The frozen sponge *Latrunculia* (*Latrunculia*) *austini* Samaai, Kelly & Gibbons, 2006 (4 kg) were cut into 1-2 cm^3 pieces and extracted with ethanol. The ethanolic extracts were then purified through iterations of chromatography altering both the mobile and stationary phases ultimately yielding 15 mg of **2.01**. An array of computational methods, mass spectroscopy, and NMR experiments were employed to characterize the structure of this compound including assignment of relative and absolute stereochemistry. In particular, MS fragmentation data, assessed as vector correlations and displayed as an MS/MS network identified a previously unreported brominated alkaloid for further analysis. Typical two-dimentional NMR analyses (^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{1}H-^{15}N HMBC) allowed for the connectivity of the molecule to be assigned. The relative stereochemistry was suggested by the tetrahedral geometry of carbons 3, 5, and 8 (aleutianamine numbering; see Scheme 2.1): the only stable configuration would feature a syn-periplanar alignment between the sulfur bridge between C-5 and C-8 and the C-4 methylene. Furthermore, ROESY signal intensities correlated to calculated proton distances aided in establishing relative stereochemistry. Lastly, the illustrated absolute stereochemistry (3*R*, 5*R*, 8*S*) was assigned via comparison of experimental and calculated ECD spectra.

Although the structural complexity of this highly strained, brominated, pyrroloiminoquinone natural product is truly astounding, perhaps more intriguing, and societally relevant, is the biological data obtained for **2.01** in several bioassays. Indeed, aleutianamine displayed selective cytotoxicity against murine colon cancer 38, human prostate cancer LNCaP, and **human pancreatic cancer PANC-1** relative to murine and human leukemia cells. Furthermore, **2.01** displayed IC_{50} values of 1 μM against human HCT-116 colon cancer cells and **25 nM against PANC-1 pancreatic cancer cells** signifying high potency. Lastly, clonogenic studies of **2.01** against HCT-116 were performed which yielded $_tS_{10}$ values in the low μM range (>5 to 0.1 μM). Though insufficient without pharmacokinetic and maximum tolerated dose studies, these clonogenic data suggest that **2.01** could serve as a chronic treatment for HCT-116. Clearly, a total synthesis of this intriguing natural product could have broad impact on efforts seeking novel therapeutics for the treatment of cancer, particularly pancreatic cancer.

2.2 Tandem Metathesis Model System

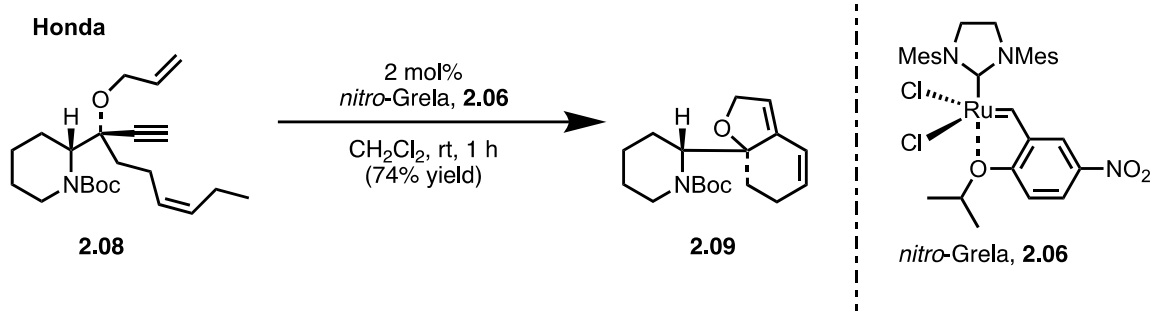
In considering possible synthetic routes to **2.01** we focused our retrosynthetic analysis on several key disconnections designed to divide the molecule roughly in half and allow for late-stage construction of what was perceived to be a sensitive sulfur-bridged bicycle. Accordingly, rupture of the two bridgehead carbon-nitrogen bonds revealed a bromotetrahydrobenzo[*b*] thiophene (**2.02**) wherein the imbedded 1,3-diene was envisioned as arising through a tandem enyne/ring-closing metathesis (referred to from now as either tandem metathesis or enyne/RCM; Scheme 2.1). This key reaction would deliver all components of the bridged heterocycle (dihydrothiophene, 1,3-diene, and vinyl

bromide) in a single step. Although no such reaction was found in the literature, precedent from related transformations gave some justification to the approach (*vide infra*).



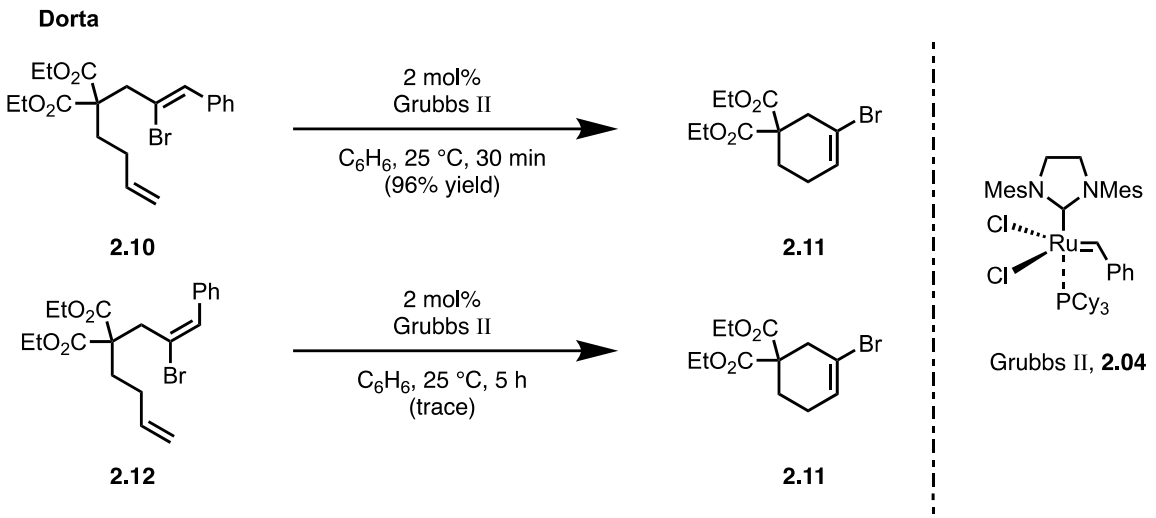
Scheme 2.1. Retrosynthetic Analysis of Aleutianamine and representative Ruthenium Alkylidene complexes for Olefin Metathesis

The possibility of forming a bridged heterocyclic ring system via enyne metathesis followed by ring-closing metathesis was found in the work of Honda and coworkers (Scheme 2.2).[2] By employing low catalyst loading of *nitro*-Grela (**2.06**), a Hoveyda-Grubbs-type ruthenium catalyst, the tandem metathesis proceeded in good synthetic yield to deliver the requisite tetrahydrobenzofuran, which upon oxidation to the butenolide, was carried on to the natural product securinine (not shown).



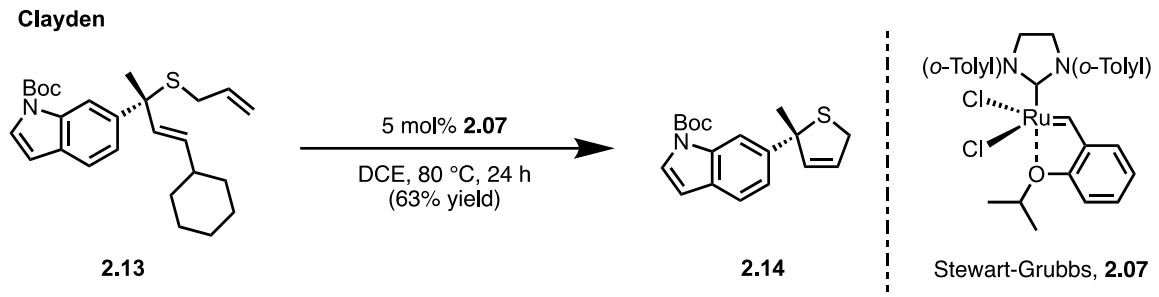
Scheme 2.2. Honda's Tandem Metathesis Precedent

Intriguingly, metatheses in the presence of vinyl halides, and in particular, vinyl bromides have proven to be difficult transformations.[3] Dorta and coworkers undertook a systematic investigation of ring-closing metatheses in the presence of vinyl bromides. Results in the Dorta lab suggested that the incipient ruthenium carbenoid, when brought in close proximity to the alkenyl halide, would initiate a decomposition pathway rendering alkenyl bromides poor substrates for metathesis. However, Dorta contended if a substrate could be constructed in such a way as to spatially distance the alkenyl bromide and ruthenium carbenoid, then efficient metathesis may be possible. Indeed, a number of substrates were prepared with the vinyl bromide as part of a styrene. As detailed in Scheme 2.3, the authors found that when the double bond geometry of the styrene was Z, with the bromine and phenyl ring on the same side, efficient metatheses took place (*e.g.* **2.10**→**2.11**). However, when the double bond geometry was E, the authors observed only trace conversion to the desired cyclohexene products (**2.12**→**2.11**). Such a result strongly suggests the Z-configured phenyl ring protects the ruthenium carbenoid from the vinyl bromide and allows for ring-closing metathesis.



Scheme 2.3. Precedent for Ring-Closing Metathesis with Alkenyl Bromides

Perhaps most interesting of all the precedents regarding our key enyne/RCM was a report from Davis who noted that allyl sulfides are excellent substrates for ring-closing metathesis.[4] A significant rate enhancement is observed when an allyl sulfide is used relative to allyl ethers or simple alkenes. In an attempt to rationalize such an observation, the Davis group has suggested that rapid binding between the ruthenium catalyst and the sulfur helps initiate the metathesis, however, because of the distance between sulfur and the resulting ruthenium carbenoid (4 atoms), a stable chelate is not formed and a metathesis may proceed as opposed to sequestration of the ruthenium carbenoid by sulfur. Synthetic advantage of this discovery has been taken in the laboratories of Jonathan Clayden wherein enantioenriched allyl sulfides were converted to dihydrothiophenes in useful yields (Scheme 2.4).[5] For our purposes especially, it was comforting to see the formation of dihydrothiophenes with α-quaternary centers in the presence of an indole ring.

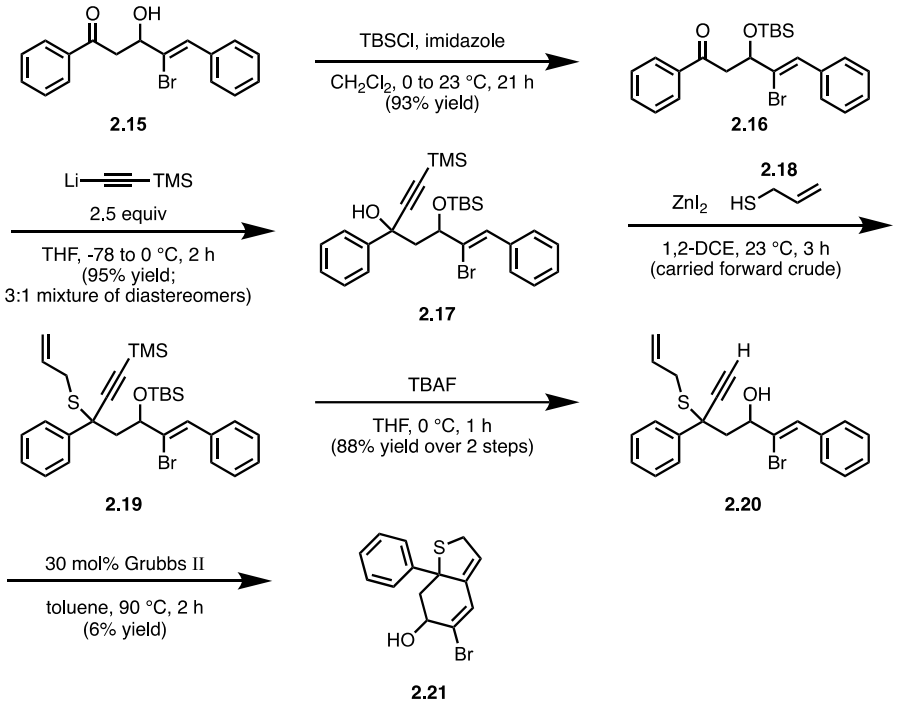


Scheme 2.4. Clayden's Synthesis of enantioenriched dihydrothiophenes via Olefin Metathesis of Allyl Sulfides

Given a reasonable level of literature precedent, we initiated a model study of the metathesis approach to **2.01**. Starting from the known β-hydroxy ketone **2.15**,[6] the alcohol was protected with TBSCl and imidazole in CH_2Cl_2 to yield silyl ether **2.16**. Acetylide addition to the derived ketone (**2.16**) furnished, in nearly quantitative yield, a 3:1 diastereomeric mixture of tertiary alcohols **2.17**.[7] Given the benzylic and allylic nature of the resultant tertiary alcohol, we opted to explore Lewis acid-mediated S_N1-type chemistry for installation of the sulfide. Using conditions found in a seminal report by Guindon and Frenette,[8] the alcohol (**2.17**) was converted to sulfide **2.19**, with catalytic amounts of ZnI_2 and an excess of allyl mercaptan (**2.18**). In practice, it was easiest to form **2.19** and carry the crude product immediately to the next step, global deprotection of the silyl groups with TBAF. With sulfide **2.20** in hand, we were in position to test the key tandem metathesis. Gratifyingly, 30 mol% Grubbs II catalyst in a solvent of toluene heated to 90 °C for 2 h produced the desired metathesis product **2.21** in 6% yield. Although the yield was low, the result was reproducible and gave validation to this key reaction and our approach to aleutianamine.

In further efforts, we attempted to separate the diastereomers formed during the ZnI_2-mediated reaction but could only isolate small quantities of the major diastereomer of

2.20 (< 5 mg). As such, an enyne/RCM was never run on diastereomerically pure sulfides **2.20**. Nonetheless, it is noteworthy that samples in which one diastereomer predominated gave divergent results. In a reaction whose starting material favored the minor diastereomer of **2.20** (2:1 by integration of ^{1}H NMR), trace quantities of **2.21** were observed by ^{1}H NMR of the crude. Conversely, in reactions where the starting material was enriched with the major diastereomer (3:1), **2.21** was obtained. Consistent with this result is the fact that, only one diastereomer of **2.21** was observed which suggests only a single diastereomer of **2.20** engages in the tandem metathesis. When considering future efforts on substrates suited for advancement in the synthesis, this result suggested that controlling the relative configuration might be an important step toward improving the efficiency of this transformation.



Scheme 2.5. Enyne/RCM Model System

2.3 Conclusion

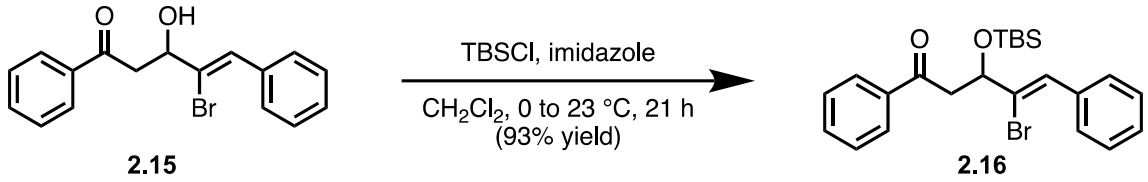
The first significant check point in the development of our metathesis approach to aleutianamine has been described. A model system study gave validation to the proposal that the bromotetrahydrobenzo[*b*] thiophene may be accessed via a tandem metathesis reaction. Moreover, a straightforward synthetic approach to the metathesis precursor, entailing simple and seemingly robust reactions (silyl protection, acetylide addition, sulfide formation with ZnI_2, deprotection), was developed. The remaining chapters will discuss the application of conditions to a variety of substrates suitable for advancement to the natural product.

2.4 Experimental

2.4.1 General

For general experimental information, see 1.2.1.

*Ketone **2.16***



2.15 **2.16**

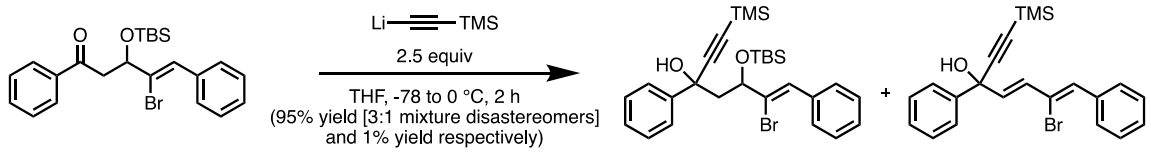
The starting material is a known compound which may be prepared through an aldol procedure described by Bressy and coworkers in *Angew. Chem. Int. Ed.* **2017**, *56*, 16052-16056.

The starting material (**2.15**, 6.5 g, 0.02 mol, 1 equiv) was dissolved in methylene chloride (CH_2Cl_2, 20 mL, 1 M). Imidazole (3.27 g, 0.0392 mol, 2 equiv) was added and the solution was cooled in an ice/water bath. The septum was broken momentarily as TBSCl (3.27 g, 0.0217 mol, 1.1 equiv) was added. After 10 min stirring on the ice/water bath, the solution was allowed to warm to room temperature (23 °C) and stirring was continued for 18 h.

After the allotted time, the solution was quenched by the addition of NH_4Cl (sat.) and the aqueous layer was extracted 3 x Et_2O. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo to afford a crude product which was purified by flash column chromatography eluting in a step gradient of pure hexanes to 3% EtOAc/hexanes. The yield for this reaction was 8.1 g (**2.16**) (0.018 mol, 93% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.02-8.00 (m, 2H), 7.63-7.60 (m, 1H), 7.59-

7.56 (m, 1H), 7.50-7.46 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 7.19 (s, 1H), 5.05-5.02 (m, 1H), 3.55 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.23 (dd, *J* = 15.6, 3.5 Hz, 1H), 0.84 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.0, 137.6, 135.3, 133.3, 129.9, 129.2, 128.7, 128.6, 128.3, 128.2, 128.0, 75.4, 46.1, 25.8, 18.2, -4.5, .5.0. **IR** (thin film): cm^{-1} 2954 (w), 2928 (w), 2886 (w), 2855 (w), 1686 (s), 1597 (w), 1580 (w), 1492 (w), 1471 (w), 1447 (m), 1390 (w), 1360 (m), 1285 (m), 1252 (s), 1180 (w), 1097 (s), 1020 (w), 1002 (w), 982 (w), 946 (s), 920 (m), 875 (w), 828 (s), 778 (s), 754 (s), 689 (s), 638 (w), 561 (w), 519 (w). **HRMS** (ESI+): calculated for $C_{23}H_{29}BrNaO_2Si^+$ $[M+Na]^+$ 467.1012, found: 467.1011. **TLC**: R_f = 0.42 (10% EtOAc/hexanes). **Physical Appearance**: Clear, pale yellow oil.

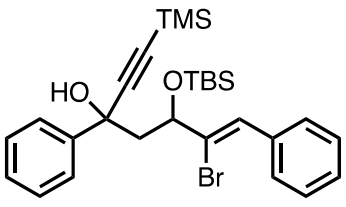
*Tertirary Alcohols **2.17** and **2.22***



2.16 **2.17** **2.22**

The starting material (**2.16**, 1.0519 g, 2.361 mmol, 1 equiv) was azeotropically dried one time with benzene and then held under high vacuum (< 1 Torr) for approximately 1 h. In a separate flask, THF (14 mL, 0.5 M) and TMS acetylene (1.0 mL, 7.1 mmol, 3 equiv) were added sequentially and the flask was cooled in a dry ice/acetone bath. A 2.5 M solution of *n*-BuLi in hexanes (2.4 mL, 5.9 mmol, 2.5 equiv) was added to the flask containing THF and TMS acetylene dropwise. After 15 min stirring in the dry ice/acetone bath, the solution was transferred to an ice/water bath and stirred at the same temperature for 30 min. After the allotted time, **2.16** was placed under an inert atmosphere and diluted with THF (12 mL, 0.2 M). Both solutions were cooled to in separate dry ice/acetone baths

and the lithium TMS acetylide was transferred via cannula onto the starting material (**2.16**). After 1 hour, the starting material solution was transferred to an ice/water bath and stirred for an additional hour. The reaction was monitored by TLC; multiple developments at 5% EtOAc/hexanes allowed for the observation that starting material was consumed. The solution was quenched by the addition of NH_4Cl (sat.) and the aqueous layer was extracted 3 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. Purification of the crude was achieved by flash column chromatography eluting over a gradient of 10% to 35% CH_2Cl_2/hexanes, increasing the polarity by 5% CH_2Cl_2, until both diastereomers had eluted. This gradient is capable of separating the diastereomers from one another and the eliminated product. To elute the eliminated product, the solvent system should be switched to 5-10% EtOAc/hexanes after the diastereomeric tertiary alcohols have been collected. The yield for this reaction was 0.8801 g major diastereomer, 0.2246 g minor diastereomer (collectively known as **2.17**) and 14.1 mg of the eliminated product (**2.22**) (2.24 mmol **2.17**, 95% yield, and 0.0343 mmol **2.22**, 1% yield). Based on analysis of the crude ^{1}H NMR, the dr for this reaction was judged to be 3:1.



2.17

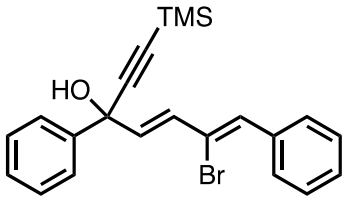
Major Diastereomer of **2.17**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70-7.67 (m, 2H), 7.58-7.55 (m, 2H), 7.38-7.24 (m, 6H; overlaps with $CHCl_3$ peak.), 7.07 (s, 1H), 5.18 (s, 1H), 5.17 (dd, *J* = 10.4, 2.2 Hz, 1H), 2.36

(dd, *J* = 14.4, 10.4 Hz, 1H), 2.06 (dd, *J* = 14.4, 2.2 Hz, 1H), 1.02 (s, 9H), 0.34 (s, 3H), 0.26 (s, 9H), 0.21 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 144.6, 135.0, 129.5, 129.1, 128.9, 128.5, 128.4, 128.3, 127.7, 125.5, 107.8, 91.0, 79.0, 72.8, 50.8, 26.0 18.2, 0.1, -3.7, -4.5. **IR** (thin film): cm^{-1} 3474 (br), 2957 (w), 2858 (w), 1493 (w), 1471 (w), 1448 (w), 1389 (w), 1363 (w), 1250 (m), 1191 (w), 1070 (m), 1030 (w), 983 (w), 918 (w), 898 (m), 837 (s) 809 (m) 780 (m), 760 (m), 731 (m), 694 (s), 639 (w), 610 (w), 559 (w), 522 (w). **HRMS** (ESI+): calculated for $C_{28}H_{39}BrNaO_2Si_2^+$ $[M+Na]^+$ 565.1564, found: 565.1564. **TLC**: R_f = 0.52 (10% EtOAc/hexanes). **Physical Appearance**: clear pale yellow oil.

Minor Diastereomer of **2.17**:

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.65-7.64 (m, 2H), 7.59-7.57 (m, 2H), 7.42-7.39 (m, 2H), 7.38-7.34 (m, 2H), 7.33-7.30 (m, 2H), 6.89 (s, 1H), 4.32-4.30 (m, 1H), 4.21 (s, 1H), 2.65 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.52 (dd, *J* = 14.8, 4.0 Hz, 1H), 0.93 (s, 9H), 0.15 (s, 9H), 0.03 (s, 3H), -0.03 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 144.1, 135.0, 129.9, 129.2, 128.8, 128.4, 128.4, 128.3, 127.7, 125.7, 108.3, 89.5, 76.8, 72.0, 49.6, 25.9, 18.1, 0.0, -3.9, -4.9. **IR** (thin film): cm^{-1} 3460 (br), 2956 (w), 2929 (w), 2857 (w), 1492 (w), 1471 (w), 1447 (w), 1389 (w), 1362 (w), 1250 (m), 1123 (w), 1074 (m), 1004 (w), 959 (w), 902 (m), 836 (s), 777 (m), 757 (m), 733 (m), 694 (s), 631 (w), 581 (w), 521 (w). **HRMS** (ESI+): calculated for $C_{28}H_{39}BrNaO_2Si_2^+$ $[M+Na]^+$ 565.1564, found: 565.1562. **TLC**: R_f = 0.41 (10% EtOAc/hexanes). **Physical Appearance**: clear pale yellow oil.

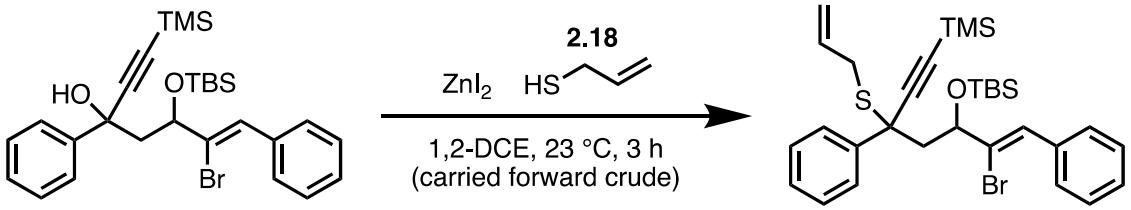


2.22

Tertiary Alcohol **2.22**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (m, 4H), 7.42-7.29 (m, 2H), 7.02 (s, 1H), 6.76 (apparent d, *J* = 14.5 Hz, 1H), 6.38 (apparent d, *J* = 14.4 Hz, 1H), 2.59 (s, 1H; alcohol peak confirmed by running ^{1}H NMR with the addition of D_2O), 0.26 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.0, 138.1, 135.7, 133.4, 130.2, 129.7, 128.6, 128.5, 128.3, 128.3, 126.0, 122.2, 105.9, 92.8, 72.8, 0.0. **IR** (thin film): cm^{-1} 3428 (br), 3059 (w), 2958 (w), 2168 (w), 1599 (w), 1490 (w), 1447 (w), 1283 (w), 1250 (m), 1055 (w), 1029 (w), 950 (m), 918 (w), 842 (s), 760 (m), 696 (m), 651 (w), 614 (w), 595 (w), 562 (w), 511 (w). **HRMS** (ESI+): calculated for $C_{22}H_{23}BrNaOSi^+$ $[M+Na]^+$ 433.0594, found: 433.0595. **TLC**: R_f = 0.31 (10% EtOAc/hexanes). **Physical Appearance**: Clear, pale yellow oil.

*Sulfide **2.19***



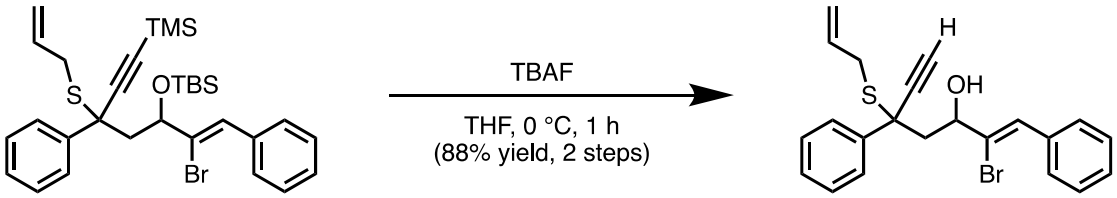
2.17 **2.19**

The starting material (**2.17**, 2.5 g, 0.0046 mol, 1 equiv) was dissolved in 1,2-DCE (23 mL, 0.2 M) and allyl mercaptan (**2.18**, technical purity ≥ 70%, 1.6 mL, 0.014 mol, 3 equiv) was added by syringe. The septum was momentarily broken for the addition of ZnI_2

(0.734 g, 0.0023 mol, 0.5 equiv). After complete consumption of starting material was observed by TLC analysis, the reaction was quenched by the addition of DI water and the aqueous layer was extracted 3 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. Typically, this crude material was carried on to the next step without chromatographic purification. Should greater purity be desired, flash column chromatography, eluting over a gradient of hexanes to 10% CH_2Cl_2/hexanes, followed by further purification by HPLC with the same solvent system at an isocratic polarity of 5% CH_2Cl_2/hexanes may be employed. Analysis of the crude ^{1}H NMR showed a diastereomeric ratio of 1.5:1. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.71-7.69 (m, 2H; major diastereomer), 7.66-7.64 (m, 0.8H; minor diastereomer), 7.37-7.19 (m, 8.38H; overlapping aryl peaks from both diastereomers and $CHCl_3$), 7.13-7.09 (m, 0.47 H; minor diastereomer) 6.70 (s, 1H; major diastereomer), 6.58 (s, 0.4; minor diastereomer), 5.76-5.64 (m, 1.42H; overlapping vinyl methine from the major and minor diastereomers), 5.09-5.03 (m, 1.43H; overlapping vinyl methylene peaks from the major and minor diastereomers), 4.98-4.94 (m, 1.43H; overlapping vinyl methylene peaks from the major and minor diastereomers), 4.65 (dd, J = 7.5, 4.2 Hz, 0.44H; minor diastereomer), 4.33 (apparent t, J = 5.8 Hz, 1H; major diastereomer), 3.33-3.23 (m, 1.50H; overlapping α-sulfur methylene peaks from the major and minor diastereomers), 3.08-3.02 (m, 1H; major diastereomer), 2.99-2.94 (m, 0.45H), 2.79 (dd, J = 14.0, 7.5 Hz, 0.4H; minor diastereomer that overlaps with the major diastereomer), 2.74 (dd, J = 14.2, 6.0 Hz, 1H; major diastereomer that overlaps with the minor diastereomer), 2.55 (dd, J = 14.1, 5.7 Hz, 1H; major diastereomer), 2.36 (dd, J = 14.0, 4.1 Hz, 0.45H; minor diastereomer), 0.92 (s, 3.49H; minor diastereomer), 0.73 (s, 9H; major diastereomer), 0.29 (s, 3.45H; minor

diastereomer), 0.16 (s, 9H; major diastereomer), 0.12 (s, 1.26H; minor diastereomer), 0.06 (s, 1.23H; minor diastereomer), -0.09 (s, 3H; major diastereomer), -0.20 (s, 3H; major diastereomer). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.5, 140.2, 135.5, 135.3, 133.9, 133.8, 131.2, 131.1, 129.3, 129.2, 129.1, 128.5, 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 127.7, 127.6, 127.5, 127.5, 117.7, 117.5, 105.8, 104.9, 93.5, 93.3, 76.7, 76.6, 49.8, 49.8, 48.2, 47.9, 34.8, 34.6, 26.0, 25.9, 18.3, 18.1, 0.3, 0.1, -4.2, -4.4, -4.4, -4.8. **IR** (thin film): cm^{-1} 2956 (w), 2928 (w), 2856 (w), 2160 (w), 1637 (w), 1599 (w), 1493 (w), 1471 (w), 1447 (w), 1362 (w), 1250 (m), 1217 (w), 1182 (w), 1075 (m), 1005 (w), 986 (w), 911 (w), 836 (s), 776 (m), 753 (s), 693 (s), 669 (w), 619 (w), 578 (w), 519 (w), 439 (w). **HRMS** (ESI+): calculated for $C_{31}H_{43}BrNaOSSi_2$ $[M+Na]^+$ 621.1649, found: 621.1649. **TLC**: R_f = 0.3 (5% CH_2Cl_2/hexanes then 10% CH_2Cl_2/hexanes). **Physical Appearance**: yellow oil.

*Sulfide **2.20***



2.19 **2.20**

Taking the theoretical yield from the preceding reaction, starting material (**2.19**, 4.6 mmol, 1 equiv) was dissolved in THF (23 mL, 0.2 M) and cooled in an ice/water bath. TBAF (18 mL, 1.0 M solution in THF, 18.0 mmol, 4 equiv) was added dropwise and an orange color change occurred. After TLC analysis had indicated complete consumption of starting material, the reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 3 x EtOAc. The combined organic was washed with brine,

dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product (2.8 g). The crude was further purified by flash column chromatography eluting over a gradient of hexanes to 10% to 20% EtOAc/hexanes. The yield for this reaction was 1.7 g Sulfide **2.20** (4.1 mmol, 89% yield of a mixture of diastereomers).

Major diastereomer of **2.20**:

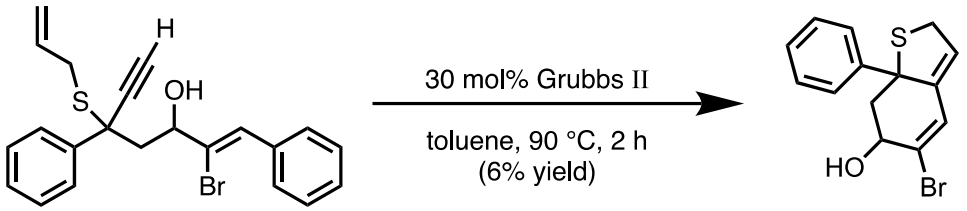
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.79-7.77 (m, 2H), 7.59-7.57 (m, 2H), 7.41-7.28 (m, 6H), 6.97 (s, 1H), 5.75-5.67 (m, 1H), 5.12-5.07 (m, 1H), 5.01-4.98 (m, 1H), 4.63-4.59 (m, 1H), 3.36-3.31 (m, 1H), 3.07-3.02 (m, 1H), 2.93 (s, 1H), 2.71 (dd, *J* = 14.4, 3.9 Hz, 1H), 2.51 (dd, *J* = 14.3, 7.5 Hz, 1H), 2.11 (d, *J* = 4.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 140.5, 135.2, 133.2, 129.2, 128.8, 128.7, 128.6, 128.3, 128.3, 128.1, 127.3, 118.2, 83.9, 77.0, 75.4, 49.3, 49.0, 34.4. **IR** (thin film): cm^{-1} 3298 (w), 2918 (w), 1636 (w), 1598 (w), 1490 (w), 1446 (w), 1260 (w), 1073 (w), 1029 (w), 907 (s), 863 (w), 802 (w), 729 (s), 694 (s), 647 (s), 595 (w), 516 (w). **HRMS** (ESI+): calculated for $C_{22}H_{21}BrNaOS^+$ $[M+Na]^+$ 435.0389, found: 435.0388. **TLC**: R_f = 0.39 (20% EtOAc/hexanes). **Physical Appearance**: orange oil.

Minor Diastereomer of **2.20**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2H), 7.48-7.44 (m, 2H), 7.37-7.28 (m, 6H), 6.95 (s, 1H), 5.75-5.65 (m, 1H), 5.12-5.07 (m, 1H), 5.01-4.98 (m, 1H), 4.47-4.45 (m, 1H), 3.37-3.32 (m, 1H), 3.08-3.03 (m, 1H), 3.00 (s, 1H), 2.90 (br s, 1H), 2.68 (dd, *J* = 14.4, 3.4 Hz, 1H), 2.53 (dd, *J* = 14.4, 7.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): Unambiguous assignment could not be made of all the carbons in this sample. An unmarked spectrum is attached in Appendix B to aid in comparison should this compound be made again. **IR** (thin film): cm^{-1} 3424 (br), 3292 (w), 3058 (w), 3024 (w), 2918 (w), 2849 (w), 1636 (w),

1598 (w), 1492 (m), 1447 (m), 1231 (w), 1074 (w), 1031 (w), 989 (w), 920 (w), 861 (w), 752 (s), 695 (s), 655 (w), 596 (w), 513 (w), 433 (w). **HRMS** (ESI+): calculated for $C_{22}H_{21}BrNaOS^+$ $[M+Na]^+$ 435.0389, found: 435.0388. **TLC**: R_f = 0.39 (20% EtOAc/hexanes). **Physical Appearance**: orange oil.

*Tetrahydrobenzo[*b*] thiophene **2.21***



2.20 **2.21**

A flame-dried 500 mL round-bottom flask was charged with **2.20** (192.3 mg, 0.46517 mmol, 1 equiv) and 94 mL toluene (0.005 M). The solution was sparged with argon for approximately 15 min and then Grubbs II was added (118.5 mg, 0.1396 mmol, 0.3 equiv). The solution was sparged with argon for 5 min and then heated to 90 °C for 2 hours. The solution was then allowed to cool to room temperature (23 °C) and the solution was exposed to air by removal of the septum. After stirring for 2 hours open to air, the toluene was removed in vacuo and the residue was passed through a silica gel plug with EtOAc. The EtOAc was removed *in vacuo* yielding a crude mass of 224.9 mg. The crude was further purified by flash column chromatography through a dry-loading process. The solvent system employed involved a step gradient of hexanes, 5% EtOAc/hexanes, 10% EtOAc/hexanes, and finishing at 20% EtOAc/hexanes. The yield for the reaction was 9.1 mg **2.21** (0.029 mmol, 6% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H), 7.25-7.20 (m, 1H), 6.97 (s, 1H), 6.15-6.13 (m, 1H), 4.19 (br s, 1H, methine based on HSQC

correlation), 3.73 (dd, *J* = 16.2, 1.9 Hz, 1H), 3.60 (dd, *J* = 16.3, 3.8 Hz, 1H), 3.22 (dd, *J* = 14.1, 1.1 Hz, 1H), 2.66 (dd, *J* = 14.1, 5.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 145.0, 142.3, 129.1, 129.1, 128.7, 127.5, 127.4, 126.3, 71.3, 60.3, 45.7, 36.6. **IR** (thin film): cm^{-1} 3560 (m), 3453 (br), 3055 (w), 2925 (w), 1692 (w), 1595 (m), 1489 (m), 1446 (m), 1391 (w), 1322 (w), 1223 (w), 1168 (w), 1117 (w), 1059 (s), 1026 (s), 973 (s), 942 (w), 903 (w), 883 (w), 848 (w), 795 (w), 754 (s), 734 (w), 696 (s), 670 (w), 645 (m), 609 (w), 521 (w), 413 (w). **HRMS** (ESI+): calculated for $C_{14}H_{13}BrNaOS^+$ $[M+Na]^+$ 330.9763, found: 330.9761. **TLC**: R_f = 0.27 (10% EtOAc/hexanes; stains dark blue in Vanillin). **Physical Appearance**: orange oil.

2.5 References and Notes

[1] Zou, Y.; Wang, X.; Sims, J.; Wang, B.; Pandey, P.; Welsh, C. L.; Stone, R. P.; Avery, M. A.; Doerksen, R. J.; Ferreira, D.; Anklin, C.; Valeriote, F. A.; Kelly M.; Hamann M. T. *J. Am. Chem. Soc.* **2019**, *141*, 4338-4344.

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[3] Gatti, M.; Drinkel, E.; Wu, L.; Pusterla, I.; Gaggia, F.; Dorta, R. *J. Am. Chem. Soc.* **2010**, *132*, 15179-15181.

[4] a) Lin, Y. A.; Chalker, J. M.; Floyd N.; Bernardes, G. J. L.; Davis B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642-9643. b) Chalker, J. M. *Aust. J. Chem.* **2015**, *68*, 1801-1809.

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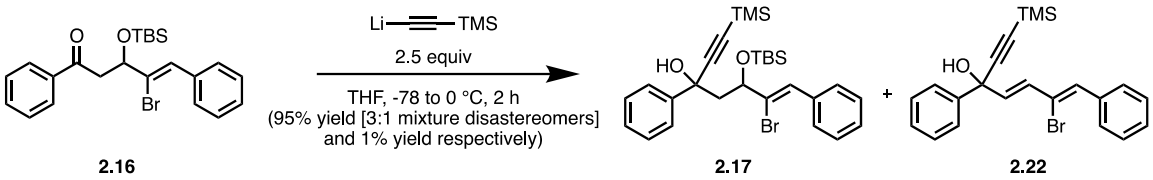
[7] It is edifying to analyze further an intermediate isolated during the acetylide addition reaction, namely tertiary alcohol **2.22**. Because **2.22** was so minor (1% isolated yield!), it went unnoticed during the testing of this model system. Indeed, it was not until many of these tiresome elimination products had been observed on related substrates that we thought to see if such a reaction were taking place in the model system. As will be shown in upcoming chapters, this competitive E1cB elimination was much more pronounced on substrates where the aryl ring was more electron-rich or substituted at the *ortho* positions. Avoiding this undesired reactivity is very

challenging and has led to countless revisions of our synthetic approach to **2.01**. It is remarkable that such a troublesome reaction is so muted on a simple substrate.



2.16 **2.17** **2.22**

[8] Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357-1359.

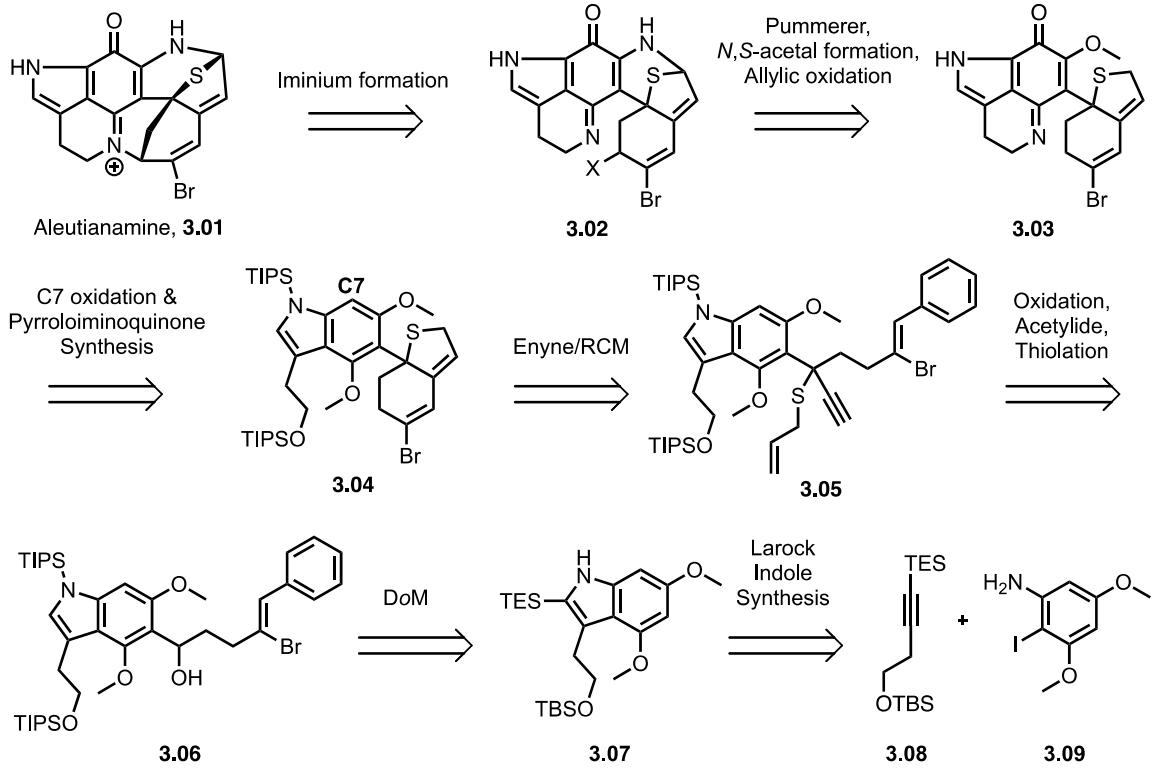
CHAPTER THREE

Aleutianamine: First Directed *Ortho* Metalation Approach with an Indole

3.1 Retrosynthetic Analysis of Aleutianamine

Based on the success of our model study, a more thorough retrosynthetic analysis of aleutianamine (**3.01**) was undertaken. To this end we envisioned the enyne/RCM chemistry as setting the stage for an end-game entailing the formation of two final carbon-nitrogen bonds, with iminium ion generation of **3.01** seen as the final event. This maneuver was inspired by Heathcock's synthetic efforts towards discorhabdin D wherein a similar transformation was employed to assemble the iminium of dethiadiscorhabdin D.[1] The exact nature of the leaving group could not be fully anticipated and is depicted below as 'X' (Heathcock used Br). Breaking the carbon-nitrogen bond of the *N*,*S*-acetal was the next disconnection. Notably, this disconnection to **3.03** illustrates the late-stage exchange of a methoxy group for a nitrogen. This functional group change was based on previous synthetic efforts towards iminoquinones which noted difficulty furnishing the cyclic imine on vinylogous amide substrates but straightforward condensation with the corresponding vinylogous ester.[1, 2] Moreover, the methoxy groups in derived vinylogous imidates of pyrroloiminoquinones such as **3.03** are readily substituted with amines to form vinylogous amidines.[3] A Pummerer-type rearrangement was anticipated as giving rise to the requisite oxidation level at the allylic methylene adjacent to sulfur. It was hypothesized that a vinylogous amidine nitrogen may be capable of collapsing onto the thionium ion generated *in situ* during the Pummerer reaction, thus forming the *N*,*S*-acetal. The synthesis of **3.03**

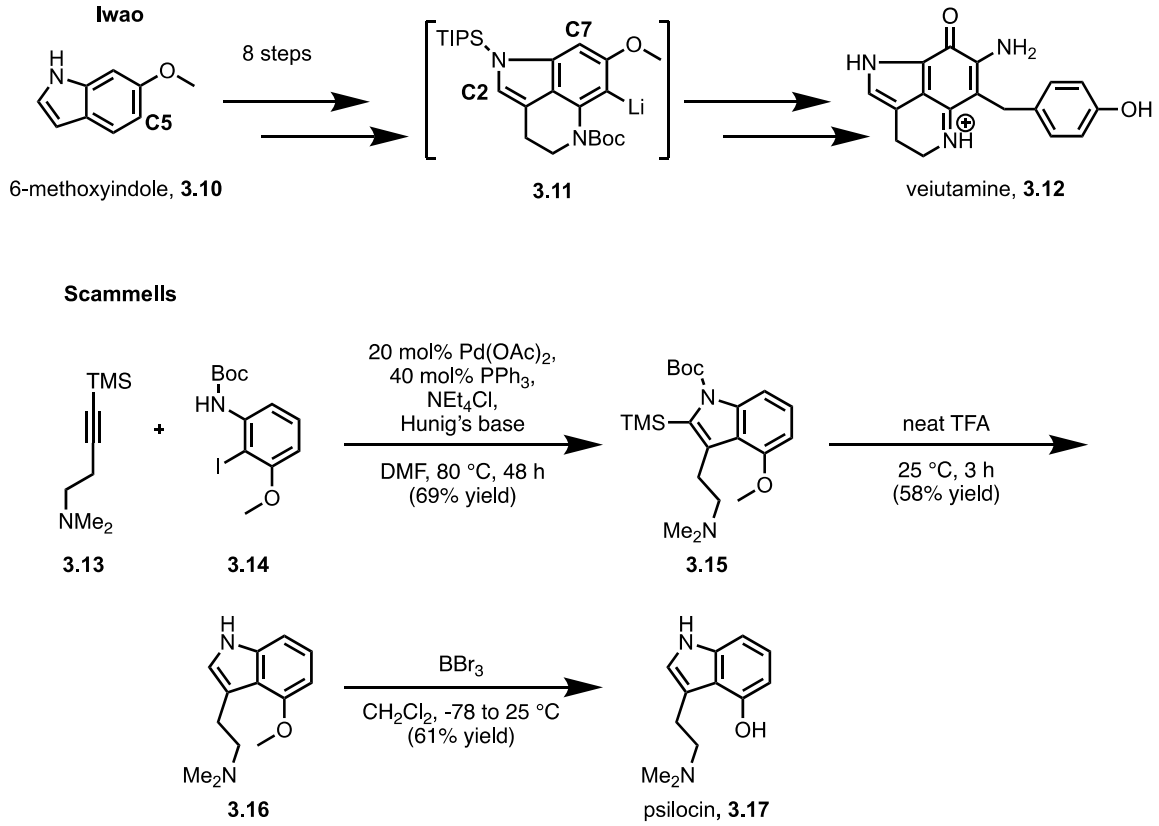
would follow from aryl oxidation of indole **3.04** and conversion of the TIPS ether into a primary amine through deprotection, activation of the alcohol as its corresponding tosylate, displacement of the tosylate with azide, and, lastly, Staudinger reduction to reveal a primary amine which would spontaneously condense onto the quinone carbonyl. Success in the aryl oxidation of **3.04** would require prior oxidation at C7 which may be affected by indole nitrogen deprotection and diboronation/oxidation conditions developed by Movassaghi and applied recently by Burns.[4]



Scheme 3.1. Retrosynthetic Analysis of Aleutianamine

Continuing with the retrosynthetic analysis from pyrroloiminoquinone **3.04** (*vide supra*), the bridged heterocyclic dihydrothiophene would arise through the key enyne/RCM, the development of which was described in Chapter Two. Metathesis precursor **3.05** would likely arise from benzylic alcohol **3.06** through oxidation, acetylide

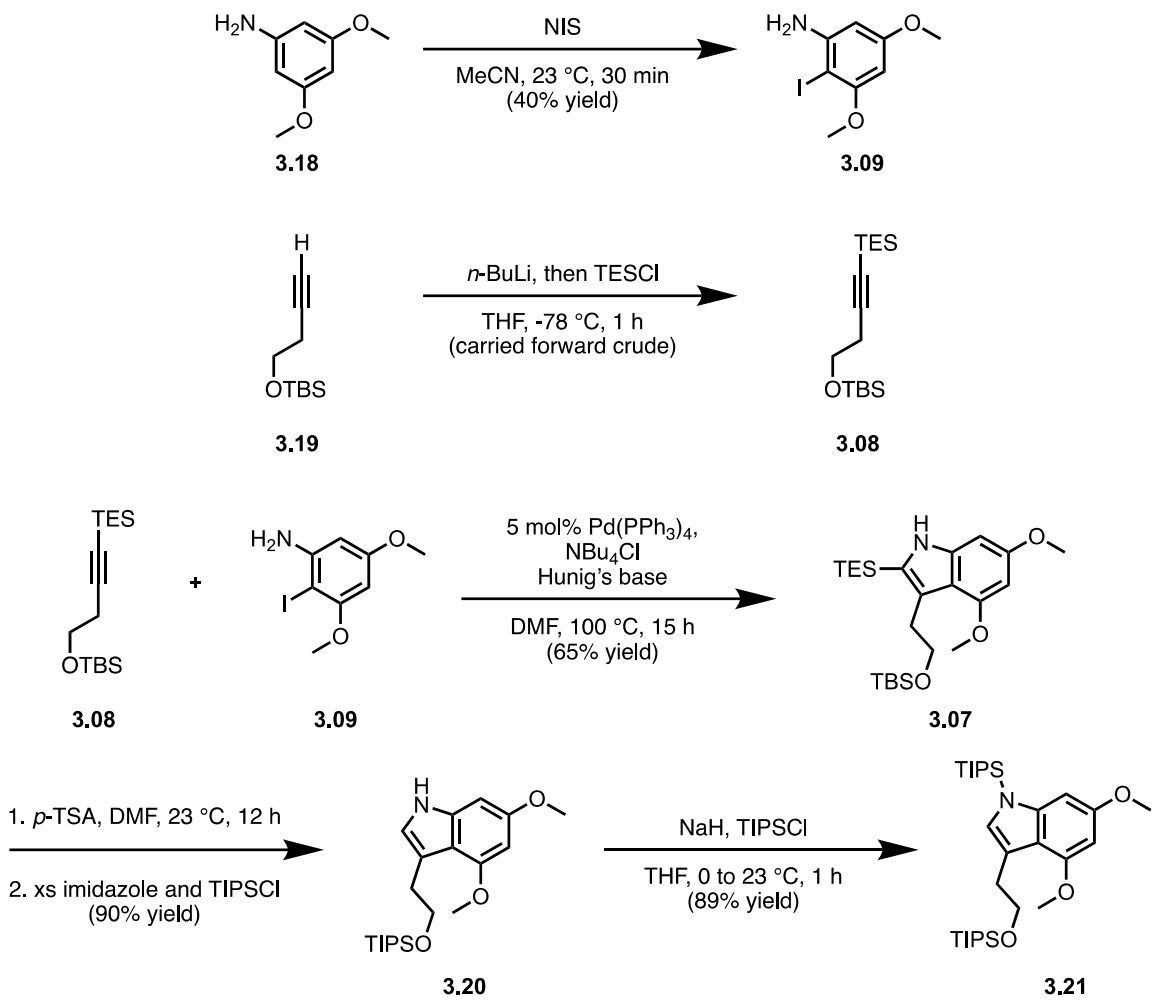
addition and S_N1-type sulfide synthesis. To gain a more convergent approach to the desired substrate, we believed a Directed ortho-Metalation (D*o*M) strategy would allow for the synthesis of **3.06** from indole **3.07** and an appropriately substituted aldehyde. Rapid access to the desired indole would be gained through a Larock indole synthesis on readily accessible substrates such as alkyne **3.08** and aniline **3.09**. Intriguingly, prior to these investigations, a Larock indole synthesis had not been employed in efforts toward pyrroloiminoquinone natural products, a remarkable fact given the expediency and versatility of the approach.[5]



Scheme 3.2. Key Precedent for D*o*M Strategy and Inspiration for Transition-metal Mediated Indole Synthesis.

It is worth discussing the precedents which motivated and inspired our indole synthesis and anionic disconnection strategy. Summarized in Scheme 3.2 (top), Iwao's total synthesis of veiutamine, a pyrroloiminoquinone alkaloid, featured an impressive display of D*o*M and aryne chemistry building to intermediate **3.11**, which elegantly allowed for substitution at the C5 position of the indole ring.[7] The steric bulk imparted by the TIPS protecting group on **3.11** shields the C2 and C7 positions from lithiation whereas the methoxy and BOC groups direct lithiation to C5. Access to **3.11**, however required 8 steps from commercially available 6-methoxyindole, **3.10**, thus despite this compelling precedent there appeared to be room for improvement.

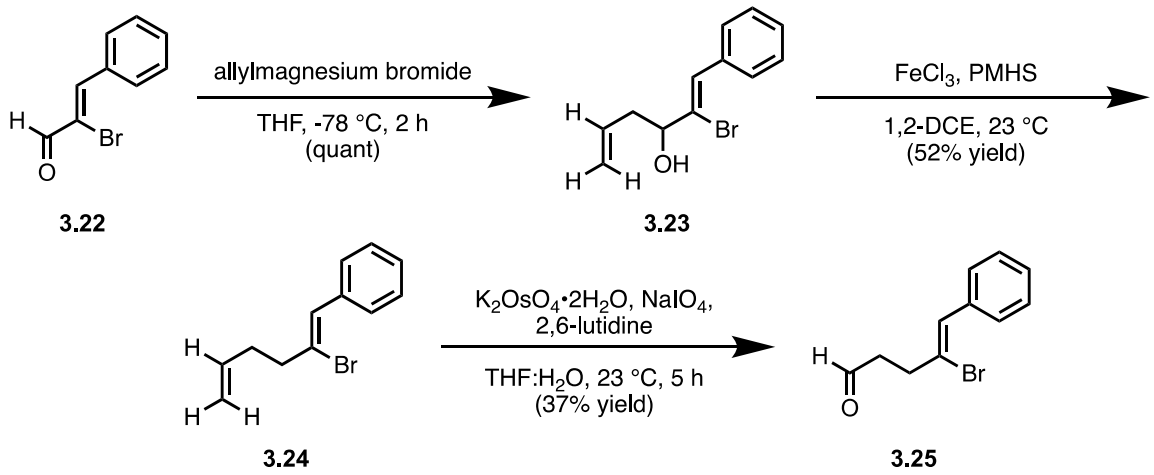
In order to efficiently prepare an indole which might be readily substituted at the C5 position, we drew inspiration from Scammells and Gathergood's total synthesis of indole alkaloid Psilocin.[7] Also shown in Scheme 3.2 (bottom), the authors were able to establish a 3-step synthesis of the indole alkaloid natural product **3.17** by starting from alkyne **3.13** and BOC-protected aniline **3.14**. It was pleasing to see precedent for Larock indole syntheses with electron-rich anilines, and we wondered if, under similar reaction conditions, indole **3.07** could be likewise accessed from aniline **3.09** and alkyne **3.08**. Upon removal of the TES group from **3.07** and protection of the indole nitrogen with TIPS (drawing again on Iwao's precedent) we anticipated lithiation would be blocked at the C2 and C7 position and exclusive lithiation would be observed at C5. As demonstrated by Scammells, the Larock indole synthesis would allow for early introduction of what would become the cyclic imine nitrogen through use of a properly substituted alkyne. We opted however to leave the nitrogen out perceiving its presence would complicate the D*o*M and subsequent steps.



Scheme 3.3. Larock Indole Synthesis

In a forward sense, the components required for the Larock indole synthesis (**3.09**[8] and **3.08**) were readily prepared as depicted in Scheme 3.3. Known aniline **3.09** was accessed by exposure of commercially available 3,5-dimethoxyaniline **3.18** to NIS in MeCN. Alkyne **3.08** was prepared by deprotonation of known alkyne **3.19**[9] with *n*-BuLi and quenching with TESCl. The derived alkyne and aniline were found to smoothly undergo coupling in yields comparable to Scammells and Gathergood's reported synthesis but with lower catalyst loadings and shorter reaction times, despite the use of a more

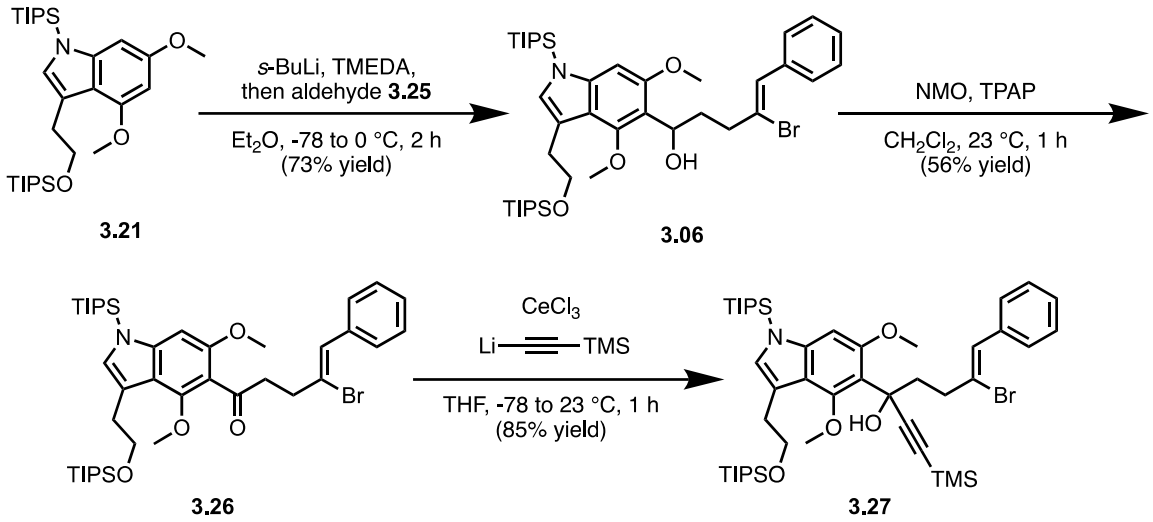
electron-rich aniline which was expected to slow the oxidative addition of palladium. Indole **3.07** was advanced to **3.20** in a one-pot procedure wherein the silyl groups were removed, and the alcohol was re-protected, this time as a TIPS ether. The TES group is important for regioselectivity in the Larock indole synthesis (the bulkier group is typically found adjacent to the resulting indole nitrogen) however, the TES could not be removed without first removing the primary TBS. NOESY correlation between the indole NH and the C2/C7 methines in **3.20** allowed for establishment of regiochemistry. Lastly, with conditions developed by Iwao,[10] the indole nitrogen was protected with NaH and TIPSCl in THF to yield D*o*M precursor **3.21**.



Scheme 3.4. Aldehyde **3.25** Synthesis

As stated in reference 7 at the end of Chapter Two, E1cB elimination of the silyl ether during acetylide addition in the model system (*i.e.* **2.16**→**2.22**) was noted but essentially inconsequential, constituting only a single percent of the resulting product mixture. On more electron-rich substrates, with *ortho* substitution about indole C5, this elimination pathway proved exceedingly problematic during attempts to advance **3.21** to the key enyne/RCM precursor (**3.05**). Numerous substrates were prepared to overcome this

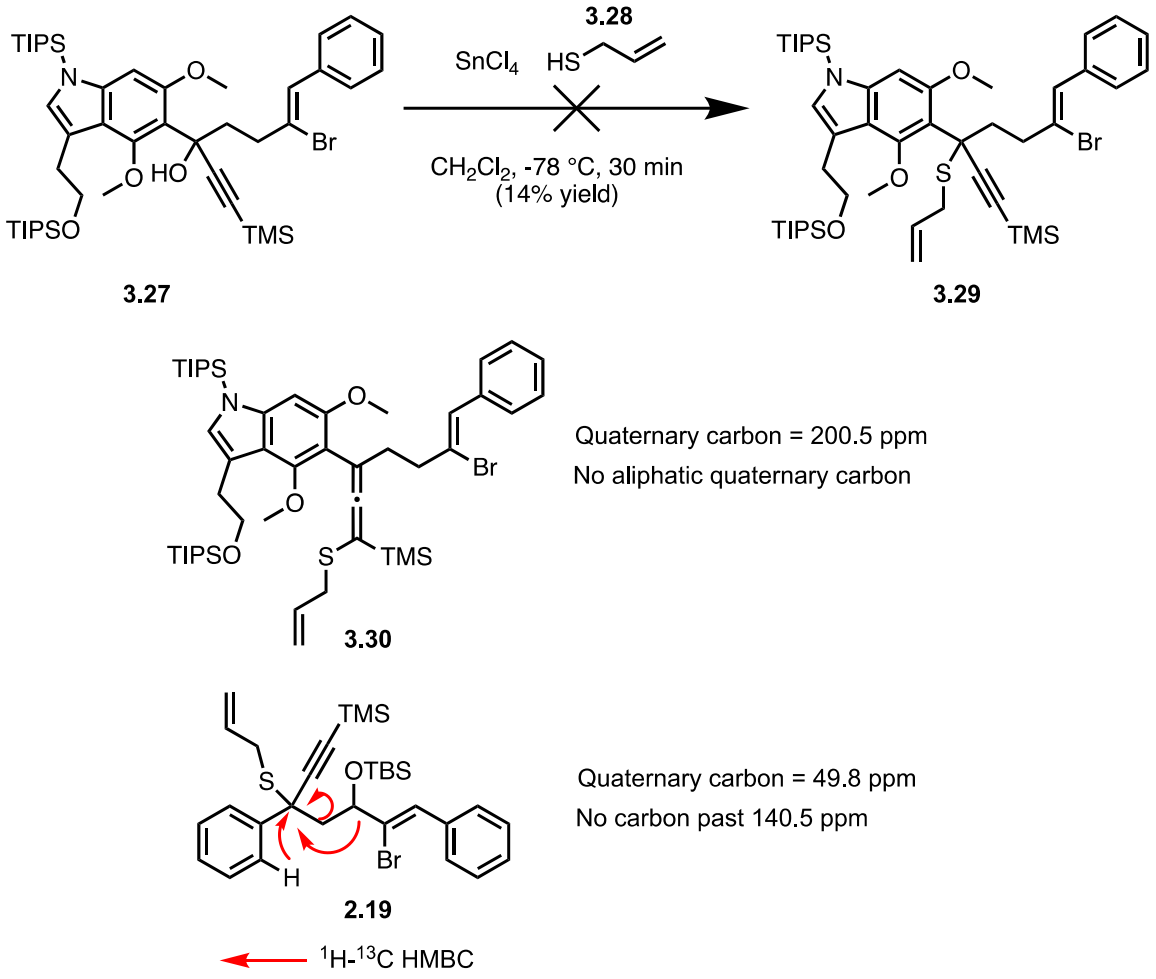
aberrant reactivity to no avail. It was ultimately deemed wise to remove oxidation at the ß-position altogether, which might hopefully allow for expedient testing of the key enyne/RCM chemistry. As shown above in Scheme 3.4, allyl-metal addition to α-bromocinnamaldehyde **3.22**, gave known compound **3.23**.[11] A somewhat capricious deoxygenation followed catalyzed by $FeCl_3$ and an excess of PHMS in 1,2-DCE.[12] The terminal olefin of **3.24** was then converted to aldehyde **3.25** via one-pot dihydroxylation/oxidative cleavage.[13, 14]



Scheme 3.5. Synthesis of Tertiary Alcohol **3.27**

With the modified D*o*M partners in hand, the stage was set for testing this important carbon-carbon bond forming reaction (Scheme 3.5). Deprotonation of **3.21** under conditions similar to those reported by Iwao[6] followed by addition of aldehyde **3.25** allowed for access to the desired benzylic alcohol **3.06**.[15] Oxidation of **3.06** to the corresponding ketone (**3.26**) proceeded smoothly employing Ley's reagent under conditions reported by Boger.[16] Subsequent efforts to affect acetylide addition to **3.26** proved challenging due to the substrate's enolizability. Only after considerable

experimentation was it found that the use of $CeCl_3$ as an additive is required to obtain good yields of the desired adduct. Interestingly, similar conditions wherein the lithium TMS acetylide was added to a solution of **3.26** that had been pre-stirred with $LaCl_3$•2LiCl and THF also failed.[17]

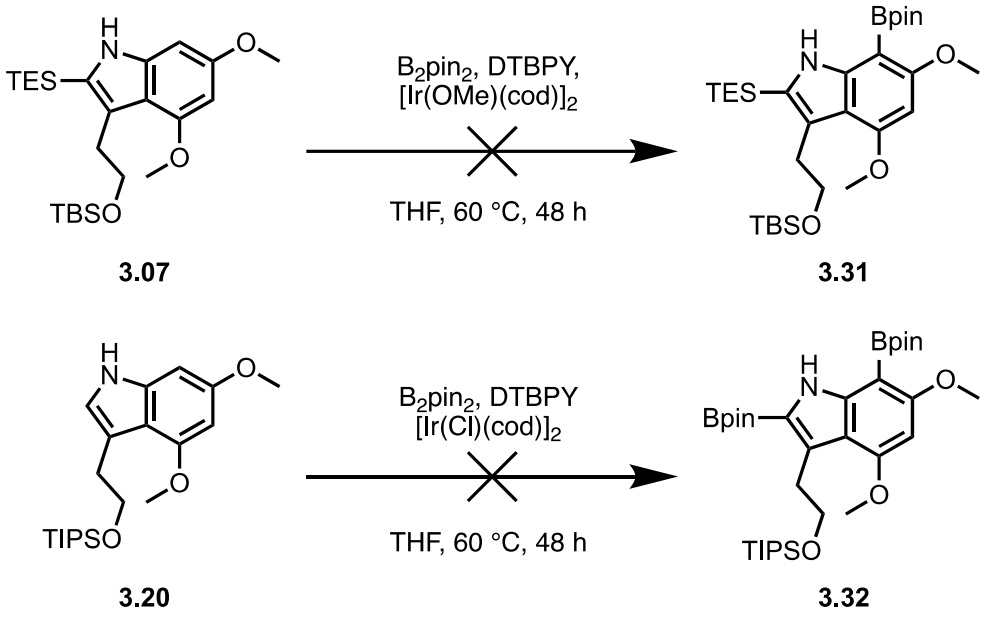


Scheme 3.6. Rationale for Cautious Assertion of Allene Synthesis

With the tertiary alcohol **3.27** in hand, the stage was set for introduction of the allylic sulfide (Scheme 3.6). Based on our model investigation (Chapter Two), these efforts focused on Lewis acid promoted conditions. In contrast to the model system, the aryl ring adjacent to the alcohol in **3.27** is considerably more electron-rich and thus the intermediate

carbocation would be more stabilized. Accordingly, this stabilizing influence was expected to facilitate formation of the reactive intermediate and enable the sulfide incorporation to take place at lower temperatures. In the event, a number of different Lewis acids such as BF_3•OEt_2 and $SnCl_4$ were screened and, ultimately, it was found that the combination of $SnCl_4$ and allyl mercaptan in CH_2Cl_2 at -78 °C were effective at converting the starting material to a new product. Unfortunately, the derived material did not match expectations for the desired sulfide **3.29**. Efforts to determine the outcome of this transformation led only to tentative assignment of structure and are outlined in Scheme 3.6. As illustrated, based on spectral studies, we believe this reaction delivers allene **3.30** rather than the desired allylic thiol **3.29**. This assignment is primarily based on comparison of the $^1H/^{13}C$ NMR data obtained for **3.30** with those of the starting material (**3.27**), and the model system sulfide most analogous to desired **3.29** (*i.e.* **2.19**). The ^1H NMR of **3.30** contained new vinyl peaks suggestive of addition of allyl mercaptan (**3.28**) and was missing a singlet in the location of **3.27**'s alcohol peak (see Appendix C for spectra). Despite enticing comparison with the ^1H NMR of tertiary alcohol **3.27**, the product differed in significant ways from sulfide **2.19**. Unlike **2.19**, which presents only a single aliphatic quaternary carbon resonance at 49.8 ppm (both diastereomers), the product **3.30** *does not* display a corresponding aliphatic quaternary carbon resonance. Curiously, however, **3.30** possesses a quaternary ^{13}C resonance at 200.5 ppm, which is consistent with an allene.[18] In further support of this assignment we note that attempts to remove the TMS group of **3.30** via reactions with K_2CO_3 in methanol and with TBAF/AcOH (a known method for the removal of TMS groups from alkynes) failed to deliver products displaying an alkyne singlet in the ^1H NMR.[19] Indeed, in the case of TBAF/AcOH, the TIPS group of the indole nitrogen was

selectively removed without touching either the TIPS-ether or TMS group. Unfortunately, definitive claims about the structure of **3.30** may not be made at this time because the obtained ^{13}C NMR is missing one aromatic methine from the depicted structure (see Appendix C and *3.3 Experimental*). Although a definitive structural assignment of **3.30** remained elusive, it was clear that the desired product had not formed. At this stage, rather than exploring alternatives for introducing the allylic sulfide, we opted to explore further functionalization of the indole core in hope of preparing an intermediate better suited for advancement to the sulfide.



Scheme 3.7. Attempted Boronation Conditions

As alluded to in the previous section, the difficulties with sulfide introduction led us to turn toward advancing the indole core to the requisite iminoquinone, a transformation that we believed might favorably alter both the steric and electronic environment of the benzylic position targeted for thiolation. Setting the stage for conversion of **3.20** to the corresponding pyrroloiminoquinone would eventually require oxidation at C7, a maneuver

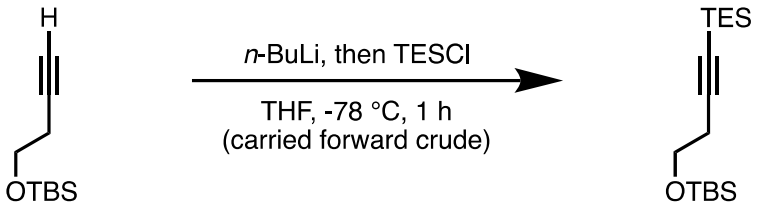
we anticipated as proceeding via an iridium catalyzed approach developed by the Movassaghi group.[4] As illustrated in Scheme 3.7, we tested this chemistry on indoles **3.07** and **3.20**. Much to our chagrin, exposure of either of these compounds to Movassaghi's boronation conditions failed to deliver the desired products (*i.e.* **3.31** and **3.32**).[20] In light of the difficulties associated with installing sulfur (*vide supra*) and inability to extend Movassaghi's boronation chemistry en route to installing the requisite oxidation at the C7 we decided to rethink our retrosynthetic analysis. While having to redesign a retrosynthetic plan is always, at some level, dissatisfying it was particularly so here as we had stopped just short of the key enyne/RCM reaction. Nonetheless, significant progress was gained in the practical realization of our metathesis approach to aleutianamine **3.01**. Additionally, these efforts had clearly highlighted the importance of advancing intermediates carrying the requisite oxidation level at C7. Our efforts to design a substrate amenable to pyrroloiminoquinone synthesis are detailed in Chapter Four.

3.3 Experimental

3.3.1 General

For general experimental information, see 1.2.1.

*Alkyne **3.08***



3.19 **3.08**

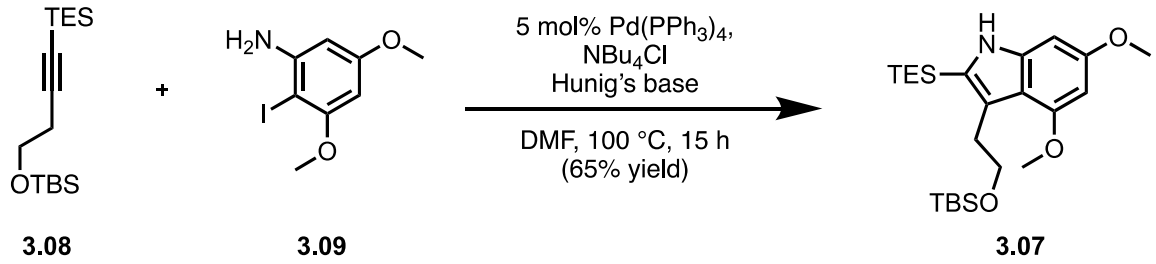
The starting material for this reaction was prepared according to the procedure described by Steven V. Ley *et al* in *Org. Lett.* **2003**, *5*, 1147-1150.

A flame-dried 50 mL round-bottom flask, with stir bar, was charged with **3.19** (489.6 mg, 2.655 mmol, 1.0 equiv). A septum was affixed to the top of the flask. A high vacuum (< 1 Torr) was pulled and then the flask was refilled with N_2; this process was repeated twice. The reaction flask was diluted with THF (13.3 mL, 0.2 M). The solution was then cooled in a dry ice/acetone bath (-78 °C) for approximately 5 min. A 2.5 M solution of *n*-BuLi in hexanes (1.3 mL, 3.25 mmol, 1.2 equiv) was added dropwise. The solution was for 5 min at -78 °C and transferred to an ice/water bath (0 °C). After stirring for 15 min at 0 °C, the solution was cooled again in a -78 °C bath. Thereafter, TESCl (670 μL, 3.992, 1.5 equiv) was added and the reaction was stirred for an additional 15 min. The reaction was then quenched at -78 °C with $NaHCO_3$ (sat.). The aqueous was extracted 3 x EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated

in vacuo to afford 1090.7 mg of a crude **3.08** which was carried forward without further purification.

Analytical purity was not required for the following step and the material was usually carried forward crude. Further purification may be achieved by flash column chromatography, first treating SiO_2 with 4% Et_3N/hexanes, and then eluting with a step-gradient of hexanes to 10% EtOAc/hexanes. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 3.72 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.57 (q, *J* = 7.9 Hz, 9H), 0.07 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 105.4, 82.9, 62.2, 26.0, 24.5, 18.5, 7.6, 4.6, -5.1. **IR** (thin film): cm^{-1} 2954 (m), 2931 (w), 2875 (w), 2176 (w), 1462 (w), 1415 (w), 1382 (w), 1361 (w), 1253 (m), 1106 (s), 1046 (w), 1006 (m), 916 (m), 835 (s), 776 (s), 724 (s), 608 (s). **HRMS** (ESI+): calculated for $C_{16}H_{34}NaOSi_2$ $[M+H]^+$ 321.2040, found: 321.2041. **TLC**: R_f = 0.15 (hexanes; $KMnO_4$). **Physical Appearance**: Clear, colorless oil.

*Larock Indole **3.07***



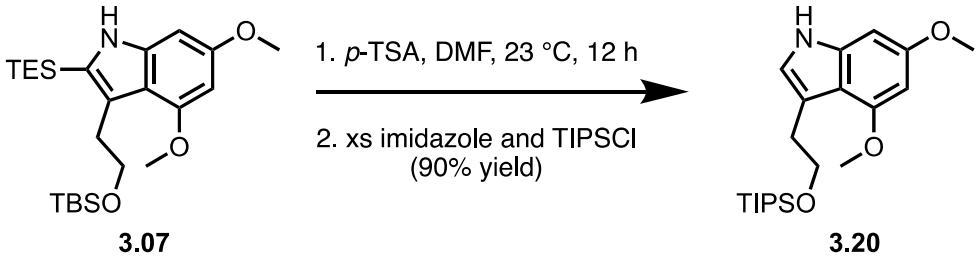
3.08 **3.09** **3.07**

The starting material **3.09** may be prepared according to the procedure described by Laurent Djakovitch *et al* in *Adv. Synth. Catal.* **2009**, *351*, 2055-2062. The same compound may also be prepared by dissolving 3,5-dimethoxyaniline in MeCN (0.2 M), adding 1 equiv NIS at 23 °C and stirring for 30 min.

A flame-dried 100 mL round-bottom flask, with stir bar, was charged with alkyne **3.08** (965.6 mg, 3.234 mmol, 1.2 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled (< 1 Torr) and then the flask was refilled with N_2; this process was repeated twice. Thereafter, **3.09** (747.4 mg, 2.6779 mmol, 1 equiv) was added in a solution of DMF (13 mL, 0.2 M) and the entire solution was sparged with Ar for approximately 5 min. After sparging was complete, Hünig's base (1,370 μL, 8.0337 mmol, 3 equiv), NBu_4Cl (739.4 mg, 2.660 mmol, 1 equiv), and, lastly, $Pd(PPh_3)_4$ (156.4 mg, 0.1353 mmol, 0.05 equiv) were added. The solution was sparged again for approximately 5 min. The solution was then heated to 100 °C and this temperature was maintained for 15 h. The solution was then allowed to cool to 23 °C and filtered through a pad of celite. The filtrate was diluted with NH_4Cl (sat.), and the aqueous was extracted 3 x EtOAc. The combined organic extracts were washed 3 x DI water, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.4 g of a crude product. Further purification was achieved by dry loading the crude onto a flash column and eluting with a step gradient of 0 to 5 to 10% EtOAc/hexanes. The yield for the reaction was 786.8 mg **3.07** (1.749 mmol, 65% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 6.44 (d, *J* = 1.9 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.81-3.79 (m, 2H; some overlap with methoxy singlet), 3.12-3.09 (m, 2H), 1.00 (apparent t, *J* = 8.1 Hz, 9H) 0.93 (s, 9H), 0.91-0.87 (m, 6H), 0.09 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.9, 154.9, 140.4, 128.7, 122.2, 113.9, 91.3, 86.3, 65.9, 55.7, 55.2, 31.8, 26.3, 18.7, 7.6, 4.0, -5.0. **IR** (thin film): cm^{-1} 3402 (w), 2953 (s), 2875 (m), 1621 (m), 1586 (m), 1510 (m), 1464 (m), 1377 (w), 1339 (w), 1315 (w), 1253 (w), 1219 (m), 1201 (m), 1153 (s), 1133 (s), 1087 (s), 1043 (m), 1005 (m), 937 (w), 836 (s), 807 (m), 777 (m), 735 (m), 571 (w). **HRMS** (ESI+): calculated for

$C_{24}H_{43}NNaO_3Si_2^+$ $[M+Na]^+$ 472.2674, found: 472.2674. **TLC**: R_f = 0.19 (10% EtOAc/hexanes). **Physical Appearance**: Yellow amorphous solid.

*Indole **3.20***

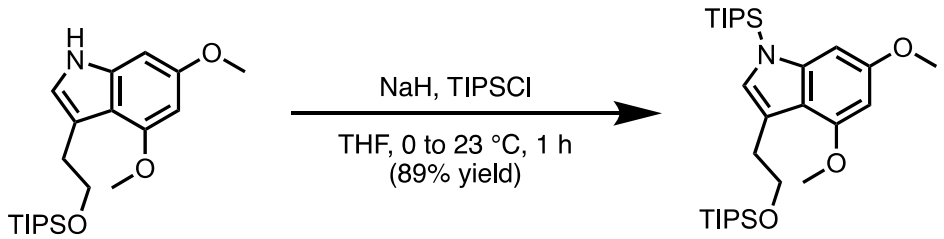


3.07 **3.20**

A flame-dried 50 mL round-bottom flask, with stir bar, was charged with **3.07** (367.5 mg, 0.8170 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled (< 1 Torr) and then the flask was refilled with N_2; this process was repeated twice. Thereafter, **3.07** was dissolved in DMF (1.2 mL, 0.7 M), and *p*-toluenesulfonic acid monohydrate (761.5 mg, 4.003 mmol, 4.9 equiv) was added. The reaction was allowed to stir for 12 h at 23 °C. After the allotted time, imidazole (557.2 mg, 8.184 mmol, 10 equiv) was added and the solution stirred for 15 min at which point TIPSCl (1.3 mL, 6.068 mmol, 7.4 equiv) was added. The reaction was allowed to stir at 23 °C for 10 h and then quenched with NH_4Cl (sat.). The aqueous was extracted 3 x EtOAc, and the combined organic extracts were washed 4 x DI water, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.7 g of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and eluting with a step gradient of 0 to 10 to 20% EtOAc/hexanes. The yield for the reaction was 278.8 mg **3.20** (0.7383 mmol, 90% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 6.80 (d, *J* = 2.0 Hz, 1H),

6.42 (d, *J* = 1.9 Hz, 1H), 6.19 (d, *J* = 1.9 Hz, 1H), 3.93 (apparent t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.11 (apparent t, *J* = 7.7 Hz, 2H), 1.12-1.07 (m, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.5, 155.2, 138.0, 119.8, 113.4, 112.3, 91.5, 86.9, 65.4, 55.7, 55.1, 30.8, 18.2, 12.2. **IR** (thin film): cm^{-1} 3406 (w), 2941 (s), 2864 (w), 1627 (m), 1587 (m), 1552 (w), 1511 (m), 1464 (m), 1377 (w), 1340 (w), 1317 (w), 1251 (w), 1218 (m), 1203 (m), 1153 (s), 1139 (s), 1086 (s), 1044 (m), 1014 (w), 995 (w), 935 (w), 882 (m), 808 (m), 757 (w), 681 (m), 658 (w), 565 (w), 475 (w). **HRMS** (ESI+): calculated for $C_{21}H_{35}NNaO_3Si^+$ $[M+Na]^+$ 400.2278, found: 400.2279. **TLC**: R_f = 0.27 (20% EtOAc/hexanes). **Physical Appearance**: Brown oil.

*Indole **3.21***

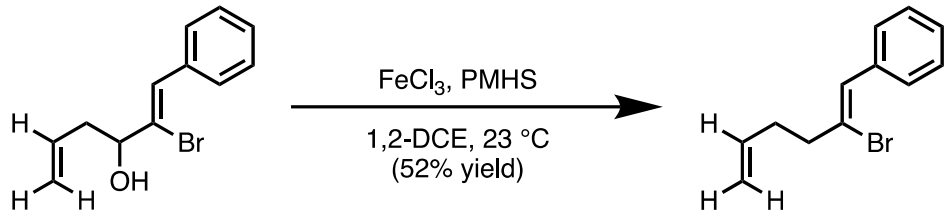


3.20 **3.21**

A flame-dried 50 mL round-bottom flask, with stir bar, was charged with **3.20** (287.5 mg, 0.7614 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled (< 1 Torr) and then the flask was refilled with Ar from a balloon; this process was repeated twice. Thereafter, **3.20** was dissolved in THF (3.8 mL, 0.2 M). The reaction was submerged in an ice/water bath and allowed to cool for approximately 5 min. After the allotted time, NaH (305 mg, 7.625 mmol, 10 equiv) was added and the solution stirred for 30 min at which point TIPSCl (180 μL, 0.8402 mmol, 1.1 equiv) was added.

The reaction was allowed to stir in the ice/water bath for an additional 5 min and then was raised and allowed to attain 23 °C. After stirring for 1 h at 23 °C the reaction was quenched with NH_4Cl (sat.). The aqueous was extracted 3 x Et_2O, and the combined organic extracts were washed 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 667.8 mg of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and flushing with hexanes to remove mineral oil and then eluting with a step gradient of 5 to 10% EtOAc/hexanes. The yield for the reaction was 362.6 mg **3.21** (0.6792 mmol, 89% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 6.22 (d, *J* = 1.8 Hz, 1H), 3.93 (apparent t, *J* = 7.3 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.08 (apparent t, *J* = 7.4 Hz, 2H), 1.64 (sept, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 7.6 Hz, 18H) 1.10-1.05 (m, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.7, 154.7, 143.0, 127.0, 115.6, 115.1, 91.2, 90.8, 65.4, 55.9, 55.1, 31.1, 18.4, 18.2, 13.0, 12.2. **IR** (thin film): cm^{-1} 2943 (m), 2865 (m), 1619 (w), 1587 (w), 1558 (w), 1487 (w), 1464 (w), 1431 (w), 1383 (w), 1253 (w), 1203 (m), 1160 (m), 1126 (s), 1107 (s), 1071 (w), 1051 (w), 1015 (w), 995 (w), 940 (w), 922 (w), 882 (m), 808 (w), 778 (w), 758 (w), 688 (m), 652 (m), 610 (w), 571 (w), 515 (w). **HRMS** (ESI+): calculated for $C_{30}H_{55}NNaO_3Si_2^+$ $[M+Na]^+$ 556.3613, found: 556.3614. **TLC**: R_f = 0.54 (10% EtOAc/hexanes). **Physical Appearance**: Clear, amber oil.

*Terminal Olefin **3.24***

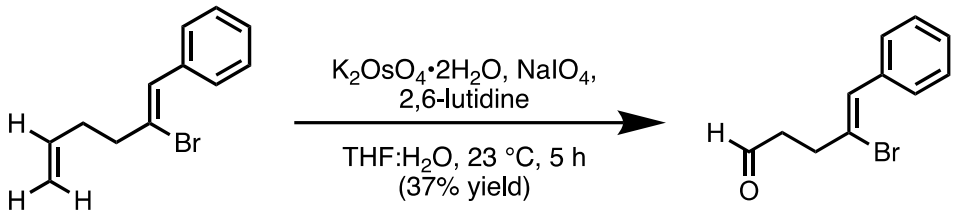


3.23 **3.24**

The starting material (**3.23**) may be prepared according to the procedure described by Jin-Xian Wang *et al* in *Eur. J. Org. Chem.* **2009**, 2983-2986. The same compound (**3.23**) may also be prepared by dissolving α-bromocinnamaldehyde in THF (0.2 M), cooling in an acetone/dry ice bath, and adding 1.5 equiv allylmagnesium bromide; the reaction is typically complete after 1 h.

A flame-dried 50 mL round-bottom flask, with stir bar, was charged with $FeCl_3$ (32.2 mg, 0.1985 mmol, 0.16 equiv), diluted with 1,2-DCE, and stirred for 5 min. Thereafter, PMHS (220 μL, 3.663 mmol, 3 equiv) was added neat and then **3.23** (309.1 mg, 1.221 mmol, 1 equiv) was added as a solution in 1,2-DCE such that the total volume of the flask was 6 mL (0.2 M). After 45 min, the solution was passed through a plug of SiO_2 with EtOAc. The organic solvent was removed *in vacuo* to afford 0.4 g of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and eluting with hexanes. The yield for the reaction was 150.9 mg **3.24** (0.6364 mmol, 52% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.57-7.53 (m, 2H), 7.38-7.27 (m, 3H), 6.76 (s, 1H), 5.91-5.78 (m, 1H), 5.15-5.08 (m, 1H), 5.06-5.02 (m, 1H), 2.73-2.68 (m, 2H), 2.47-2.39 (m, 2H).

*Aldehyde **3.25***

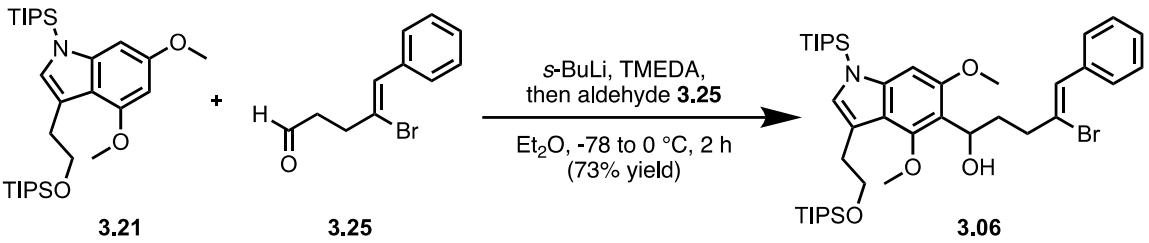


3.24 **3.25**

A 50 mL round-bottom flask, with stir bar and open to air, was charged with **3.24** (117.3 mg, 0.4947 mmol, 1 equiv). The starting material (**3.24**) was diluted with THF (2.5 mL). Thereafter, $NaIO_4$ (424.1 mg, 1.983 mmol, 4 equiv) was added followed by 2,6-lutidine (150 μL, 1.294 mmol, 2.6 equiv) and finally, $K_2OsO_4•2H_2O$ (7.1 mg, 0.019 mmol, 0.04 equiv). Lastly the solution was diluted with DI H_2O (2.5 mL for a final concentration of 0.1 M). A septum was affixed to the top of the flask and the solution was placed under N_2. The reaction was allowed to stir at 23 °C for 5 h and then was quenched with $Na_2S_2O_3$ (sat.). The solution was allowed to stir at 23 °C for 1 h and then the aqueous was extracted 3 x Et_2O. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 175 mg of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and eluting with a step gradient of 0 to 10% EtOAc/hexanes. The yield for the reaction was 43.6 mg **3.25** (0.1824 mmol, 37% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 9.86 (t, *J* = 1.1 Hz, 1H), 7.56-7.54 (m, 2H), 7.37-7.33 (m, 2H), 7.30-7.28 (m, 1H), 6.84 (s, 1H), 2.97-2.95 (m, 2H), 2.86-2.84 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 200.6, 135.7, 129.0, 129.0, 128.2, 128.0, 125.2, 42.8, 35.9. **IR** (thin film): cm^{-1} 2826 (w), 2725 (w), 1720 (s), 1492 (w), 1446 (w), 1387 (w), 1356 (w), 1275 (w), 1087 (w), 919 (w), 854 (w), 750 (s), 693 (s), 553 (w), 524 (w). **HRMS** (ESI+): calculated

for $C_{11}H_{11}BrNaO_2^+$ $[M+Na]^+$ 260.9885, found: 260.9886. Presumably because the sample was dissolved in methanol, the resulting hemiacetal was observed with stronger signal (calculated for $C_{12}H_{15}BrNaO_2^+$ $[M+Na]^+$ 293.0148, found: 293.0147). **TLC**: R_f = 0.29 (10% EtOAc/hexanes). **Physical Appearance**: Orange/brown oil.

*Benzylic Alcohol **3.06***

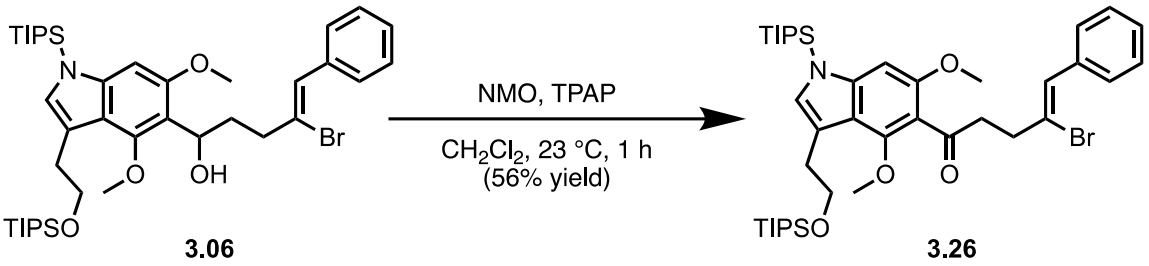


3.21 **3.25** **3.06**

Prior to running the reaction, both **3.21** and **3.25** were azeotropically dried from benzene 3 x by rotary evaporation and then held under a high vacuum (< 1 Torr) for approximately 20 min in flasks which had been flame-dried under the same high vacuum with stir bars. After the allotted time both **3.21** and **3.25** were placed under N_2. Indole **3.21** (169.4 mg, 0.3173 mmol, 1 equiv) was diluted with Et_2O (1 mL, 0.3 M) and then TMEDA (70 μL, 0.47 mmol, 1.5 equiv) was added. The resulting solution was cooled in a dry ice/acetone bath for approximately 5 min. A 1.4 M solution of *s*-BuLi in cyclohexane (340 μL, 0.4759 mmol, 1.5 equiv) was added dropwise. After 20 min in the dry ice/acetone bath, the solution was transferred to an ice/water bath. After 30 min the solution was raised out of the ice/water bath and stirred at 23 °C. After 30 min the solution was cooled again in a dry ice/acetone bath. After cooling for 15 min, **3.25** (102.4 mg, 0.4283 mmol, 1.3 equiv) was added dropwise in Et_2O (0.2 mL, 2.1 M) followed by 2 x 0.8 mL Et_2O washes. After 30 min stirring in the dry ice/acetone bath, the solution was transferred to an ice/water bath. After 1 h and 20 min, the solution was raised out of the ice/water bath and allowed to attain

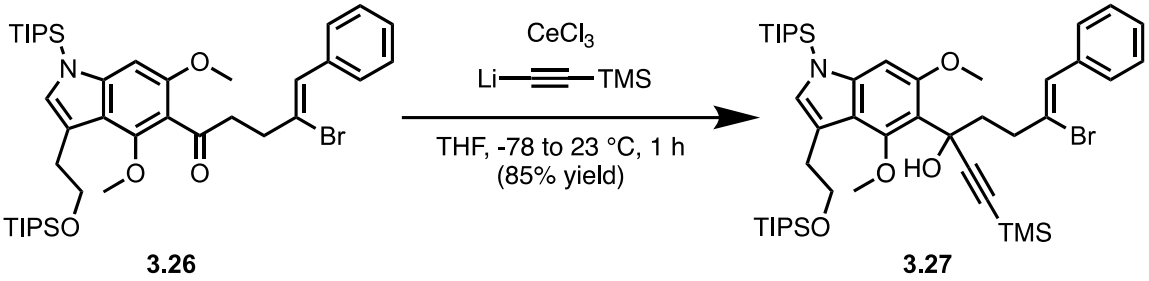
23 °C. the reaction was quenched with NH_4Cl (sat.). The aqueous was extracted 3 x EtOAc, and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 249.3 mg of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and with a step gradient of 0 to 5 to 10 to 20% EtOAc/hexanes. The yield for the reaction was 178.1 mg **3.06** (0.2303 mmol, 73% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27-7.24 (m, 1H; overlaps with $CHCl_3$ peak), 6.95 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 5.19-5.14 (m, 1H), 4.02-3.92 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.10-3.00 (m, 2H), 2.93-2.88 (m, 1H), 2.77-2.71 (m, 1H), 2.41-2.33 (m, 1H), 2.21-2.14 (m, 1H), 1.63 (sept, *J* = 7.6, 3H), 1.15 (d, *J* = 7.6 Hz, 18H), 1.10-1.01 (m, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 154.5, 151.2, 142.4, 136.5, 129.0, 128.2, 128.1, 128.0, 127.7, 127.5, 118.6, 117.0, 114.7, 93.9, 67.9, 64.6, 63.6, 55.8, 40.7, 37.1, 30.5, 18.4, 18.2, 18.2, 13.0, 12.2. **IR** (thin film): cm^{-1} 2943 (m), 2865 (m), 1615 (w), 1551 (w), 1464 (w), 1250 (w), 1207 (w), 1169 (w), 1100 (s), 1016 (w), 920 (w), 883 (w), 748 (w), 691 (w), 653 (w), 517 (w). **HRMS** (ESI+): calculated for $C_{41}H_{66}BrNNaO_4Si_2^+$ $[M+Na]^+$ 794.3606, found: 794.3602. **TLC**: R_f = 0.21 (10% EtOAc/hexanes). **Physical Appearance**: Pale amber oil.

*Ketone **3.26***



A flame-dried 5 mL round-bottom flask, with stir bar, was charged with **3.06** (17 mg, 0.022 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled (< 1 Torr) and then the flask was refilled with N_2; this process was repeated twice. Thereafter, **3.06** was dissolved in CH_2Cl_2. Thereafter, NMO (6.0 mg, 0.051 mmol, 2.3 equiv) was added and a spatula tip of TPAP. The reaction was stirred at 23 °C for 2 h and was then passed through a plug of SiO_2 with EtOAc. The organic was then concentrated *in vacuo* to afford 9.6 mg of 3.27 which required no further purification. The yield for the reaction was 9.6 mg **3.26** (0.012 mmol, 56% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.28-7.24 (m, 1H; overlaps with $CHCl_3$ peak), 6.97 (s, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 3.98 (t, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.26-3.23 (m, 2H), 3.08-3.02 (m, 4H), 1.63 (sept, *J* = 7.5 Hz, 3H), 1.15 (d, *J* = 7.5 Hz, 18H), 1.09-1.01 (m, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 204.3, 152.8, 151.4, 150.0, 143.9, 136.3, 129.0, 128.6, 128.3, 128.2, 127.7, 126.6, 118.4, 115.2, 93.4, 64.5, 64.4, 56.2, 44.1, 37.9, 30.4, 18.3, 18.2, 13.0, 12.2. **IR** (thin film): cm^{-1} 2924 (s), 2866 (s), 1700 (m), 1611 (m), 1549 (w), 1466 (m), 1347 (w), 1260 (w), 1207 (w), 1173 (w), 1107 (s), 1017 (w), 922 (w), 883 (m), 749 (w), 691 (m), 656 (w), 516 (w). **HRMS** (ESI+): calculated for $C_{41}H_{64}BrNNaO_4Si_2^+$ $[M+Na]^+$ 792.3449, found: 792.3447. **TLC**: R_f = 0.26 (10% EtOAc/hexanes). **Physical Appearance**: Brown/orange oil.

*Tertiary Alcohol **3.27***



3.26 **3.27**

The starting material for this reaction was a mixture of ketone **3.26** and tertiary alcohol **3.27** from a preceding reaction which had not gone to completion. The yield was calculated based upon the theoretical yield from the first reaction.

Prior to running the reaction, the starting material (**3.26**:**3.27** [2.9:1]) was azeotropically dried from benzene 3 x by rotary evaporation and then held under a high vacuum (< 1 Torr) for approximately 4.5 h in flasks which had been flame-dried under the same high vacuum with stir bars. After the allotted time the starting material was placed under N_2.

A flame-dried 100 mL round-bottom flask, with stir bar, was charged with $CeCl_3$ (428.3 mg, 1.738 mmol, 22 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled and the solid was heated to 140 °C. The 140 °C temperature was maintained for 2 hours. After the allotted time, the flask was raised and allowed to cool to 23 °C over a 20 min period. Thereafter, THF (4 mL, 0.4M) was added and the solution was stirred for 2 h.

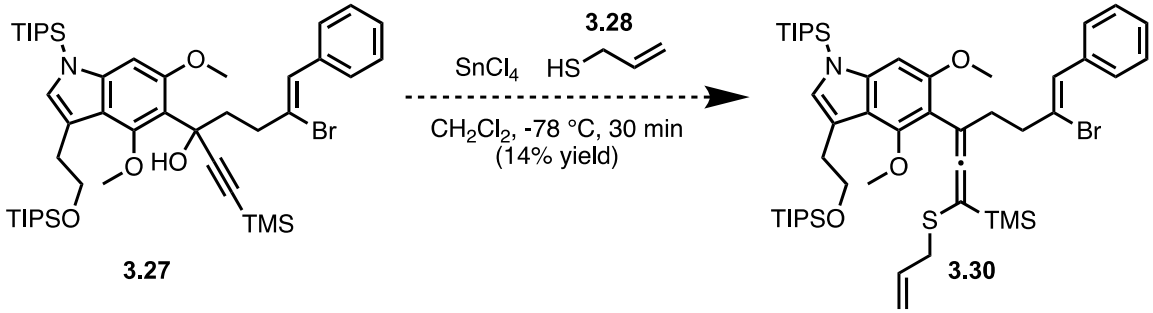
In a separate flame-dried 10 mL roundbottom flask, with stir bar, THF was added followed by TMS acetylene (400 μL, 2.89 mmol, 37 equiv). The flask containing TMS

acetylene and THF was cooled in a dry ice/acetone bath for approximately 5 min and the a 2.5 M solution of *n*-BuLi in hexanes (610 μL, 1.525 mmol, 20 equiv) was added dropwise. The solution was allowed to stir for 30 min in the dry ice/acetone bath and was then transferred to an ice/water bath. After stirring for 25 min on the ice/water bath, the solution was cooled again in a dry ice/acetone bath.

After the $CeCl_3$ and THF had stirred for 2 h at 23 °C, the flask was cooled in a dry ice/acetone bath. The solution of lithium TMS acetylide, also cooled in a dry ice/acetone bath, was transferred via cannula onto the $CeCl_3$ and THF. The resulting solution was stirred in a dry ice/acetone bath for 30 min. After the allotted time, the starting material (0.07782 mmol, 1 equiv) was added as a solution in THF (1 mL, 0.08M) followed by 2 x 1 mL THF washes. After 10 min, the solution was raised out of the dry ice/acetone bath and allowed to attain 23 °C. After 40 min at 23 °C, the reaction was quenched with NH_4Cl (sat.). The aqueous was extracted 3 x Et_2O. The combined organic extracts were washed 1 x DI H_2O, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 68.6 mg of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and with a step gradient of 0 to 5% EtOAc/hexanes. The yield for the reaction was 57.3 mg **3.27** (0.0659 mmol, 85% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.23 (m, 1H; overlaps with $CHCl_3$ peak), 6.97 (s, 1H), 6.85 (s, 1H), 6.78 (s, 1H), 6.68 (s, 1H; alcohol peak as determined by addition of D_2O to NMR tube), 4.02-3.90 (m, 2H; overlaps with methoxy peak), 3.94 (s, 3H), 3.87 (s, 3H), 3.07-2.94 (m, 3H), 2.89-2.81 (m, 1H), 2.71-2.57 (m, 2H), 1.63 (sept, J = 7.5 Hz, 3H), 1.15 (dd, J = 7.5, 2.0 Hz, 18H), 1.10-0.99 (m, 21H), 0.17 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): Unambiguous assignment could not be made of all the carbons in this sample. A

spectrum is attached in Appendix C is meant to make clear the disappearance of the ketone carbon at 204.3 ppm from the starting material (**3.26**). **HRMS** (ESI+): calculated for $C_{46}H_{74}BrNNaO_4Si_3^+$ $[M+Na]^+$ 890.4001, found: 890.4002. **TLC**: R_f = 0.07 (5% EtOAc/hexanes; regardless of the low R_f by TLC, the desired product elutes rapidly in 5% EtOAc/hexanes solvent system).

*Suspected Allene **3.30***



Allene formation is the suspected product of this reaction. The ^{1}H NMR is consistent with the addition of an allyl sulfide. The ^{13}C NMR contains a quaternary carbon at 200.5 ppm which is indicative of the central carbon of an allene. Importantly, the ^{13}C *does not* contain a quaternary carbon in the aliphatic region (in the model system, sulfide **2.19** [the most analogous substrate] bears a quaternary carbon resonance at 49.8 ppm (position of allyl sulfide). Compound **3.30** proved to be unstable even when stored in a -20 °C fridge over several months and so no IR or HRMS was taken of pure **3.30**. An HRMS was taken of a mixture of **3.30** and other unidentified compounds and the desired mass was in fact observed. Unfortunately, one of the expected methine carbons is not present in the aryl region of the ^{13}C. Taken altogether, incontrovertible characterization of **3.30** has not been obtained but a likely structure is cautiously posited above.

Prior to running the reaction, **3.27** (35.2 mg, 0.0405 mmol, 1 equiv) was azeotropically dried from benzene 1 x by rotary evaporation and then held under a high vacuum (< 1 Torr) for approximately 30 min in a 5 mL round bottom flask which had been flame-dried under high vacuum with a stir bar. After the allotted time, the flask was back-filled with N_2. Thereafter, **3.27** was dissolved in CH_2Cl_2 and allyl mercaptan (**3.28**, 40 μL, 0.49 mmol, 12 equiv) was added. The resulting solution was cooled in a dry ice/acetone bath (-78 °C) for ~ 5 min. A 1 M solution of $SnCl_4$ in CH_2Cl_2 was added dropwise (40 μL, 0.040 mmol, 1.0 equiv). The reaction was stirred at the same temperature for 30 min. $NaHCO_3$ (sat.) was added at -78 °C and the solution was allowed to warm to room temperature (rt, 23 °C). The aqueous was extracted 3 x Et_2O, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 41.5 mg of a crude product which could be further purified by flash column chromatography. A pipet column was first run with a step-gradient of 0 to 10 to 20% CH_2Cl_2 followed by 5 to 10% EtOAc/hexanes. Further purification was achieved by repeated developments (3-4) on a preparative TLC plate with a solvent system of 20% CH_2Cl_2/hexanes. The yield for the reaction was 5.4 mg **3.30** (0.0058 mmol, 14% yield based on the mass of the depicted allene). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 1H; overlaps with $CHCl_3$ peak), 6.91 (s, 1H), 6.75 (s, 1H), 6.72 (s, 1H), 5.90-5.84 (m, 1H), 5.17-5.13 (m, 1H), 5.02-5.00 (m, 1H), 4.02-3.98 (m, 1H), 3.95-3.91 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.52-3.43 (m, 2H), 3.10-3.01 (m, 2H), 2.85-2.77 (m, 3H), 2.70-2.65 (m, 1H), 1.63 (sept, *J* = 7.5 Hz, 3H), 1.15 (d, *J* = 7.5 Hz, 18H), 1.05-1.03 (m, 21H), 0.24 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 200.5, 154.0, 151.7, 142.5, 136.4, 134.5, 129.1, 128.1, 127.8, 127.8, 127.6, 118.6, 116.9, 114.7, 113.5, 100.1, 95.4, 92.9, 64.9, 62.6, 55.7, 42.3, 35.3, 33.4, 30.8,

18.4, 18.2, 13.0, 12.2, -1.0. The carbon spectrum is missing one methine carbon in the aryl region. **HRMS** (ESI+): The HRMS was not taken until the ^{1}H NMR showed some decomposition. However the anticipated masses (+H and +Na with the isotopes of Br) were observed. calculated for $C_{49}H_{79}BrNO_3SSi_3^+$ $[M+H]^+$ 924.4266, found: 924.4266. Also observed the mass +Na: calculated for $C_{49}H_{78}BrNNaO_3SSi_3^+$ $[M+Na]^+$ 946.4086, found: 946.4082.

3.4 References and Notes

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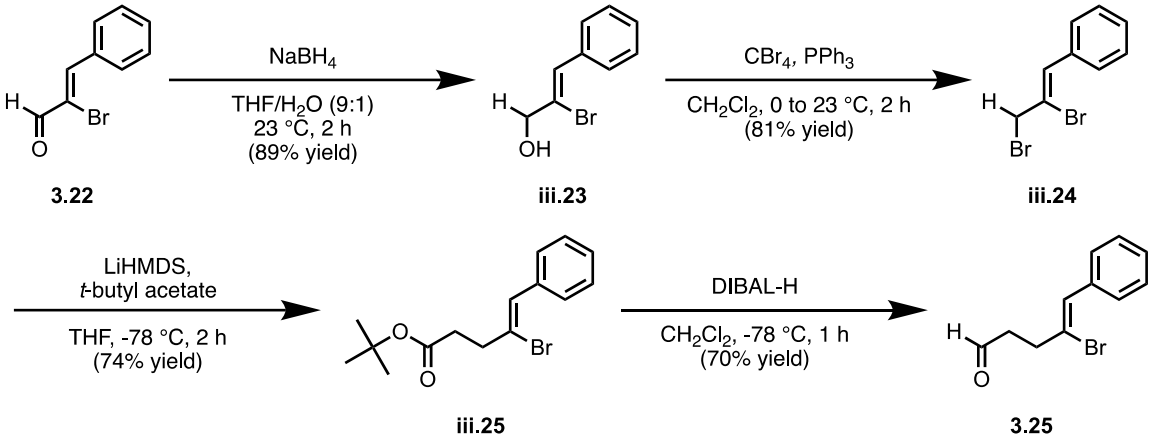
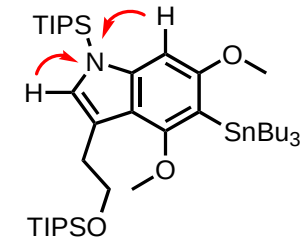
[14] A longer but more scalable/robust route to **3.25** is shown here (Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442-444.):



3.22 **iii.23** **iii.24** **iii.25** **3.25**

[15] The regiochemistry of the lithiation was confirmed by ^{1}H-^{15}N HMBC of stannane **iii.22** which was prepared as part of a parallel study (see Appendix C for spectrum).



iii.22

^{1}H-^{15}N HMBC

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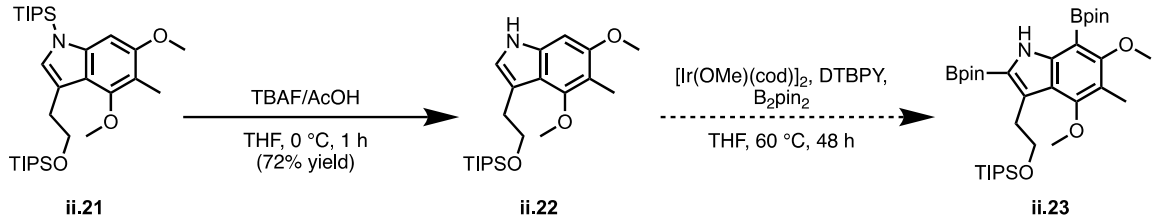
[20] Though the structures of these compounds were not fully delineated, the TBAF/AcOH conditions were applied to a related series of indoles, shown below, in which the TIPS group from the indole nitrogen was selectively removed without touching the TIPS ether (**ii.21**→**ii.22**). Unfortunately, exposure of indole **iii.22** to the Movassaghi's boronation conditions failed to deliver the desired product **iii.23**:



ii.21 **ii.22** **ii.23**

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CHAPTER FOUR

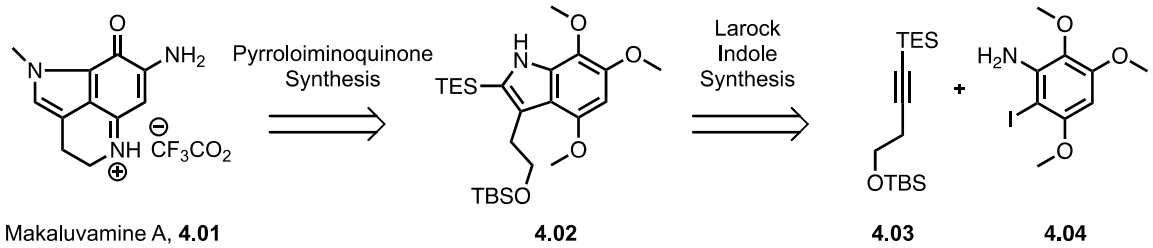
Aleutianamine: Pyrroloiminoquinone Synthesis and Total Synthesis of Makaluvamine A

4.1 The Total Synthesis of Makaluvamine A

As detailed in Chapter Three, our efforts to advance a dimethoxy indole series en route to aleutianamine ended just short of the key enyne/RCM reaction. Nevertheless, these efforts served to highlight the importance of developing a route wherein oxidation at the C7 position is established early. With the synthesis of a more heavily oxidized indole core, we recognized the possibility of advancing intermediates not only to aleutianamine, but also to simplified pyrroloiminoquinone-containing natural products like makaluvamine A (**4.01**, Scheme 4.1). Such a move would not only validate our approach to the pyrroloiminoquinone core, but also furnish additional total syntheses.

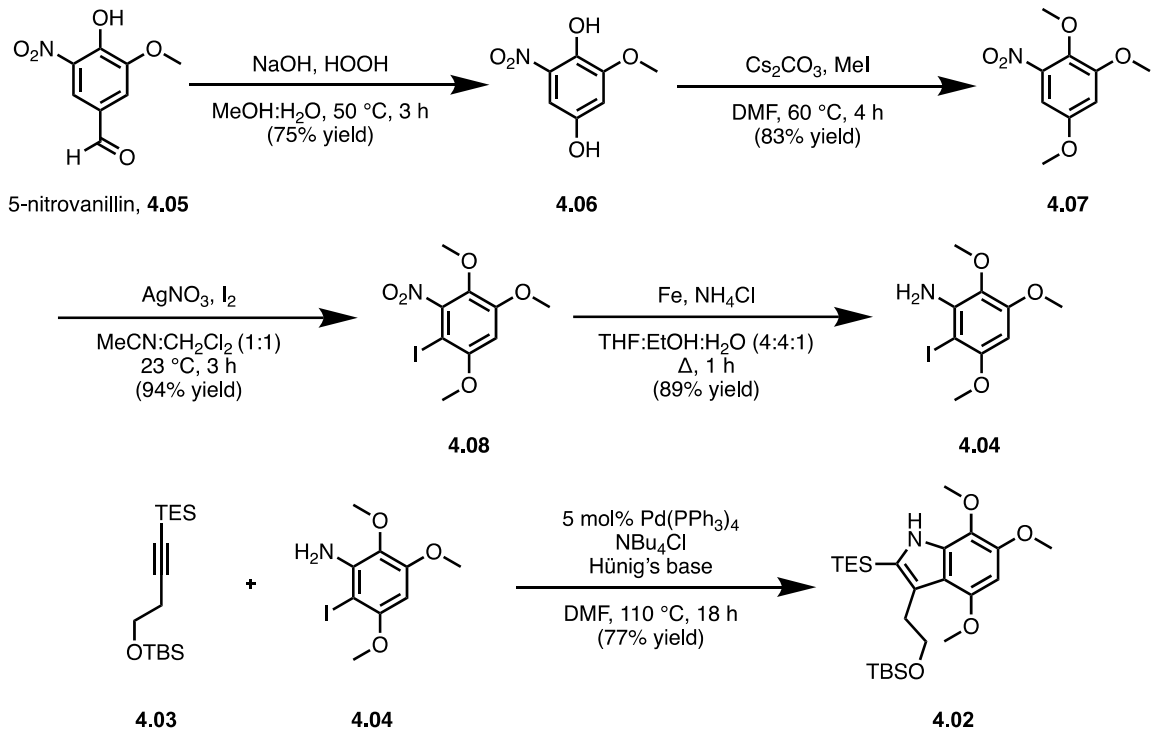
As illustrated retrosynthetically in Scheme 4.1, makaluvamine A (**4.01**) was envisioned as arising from indole **4.02** through an aryl oxidation and a subsequent series of functional group interconversions. Based on our previous experience, we were again drawn to the Larock indole synthesis. The alkyne **4.03** would remain the same but a new aniline (**4.04**) would serve as the coupling partner. As noted previously (Chapter Three), the convergency of this approach could assuredly be improved by employing an alkyne wherein the silyl ether is replaced with a protected amine. However, we again forewent such an approach perceiving that the nitrogen would unnecessarily complicate the planned D*o*M chemistry as well as subsequent steps leading to aleutianamine. Although D*o*M

chemistry would not factor into a synthesis of **4.01**, we wished only to test chemistry which might actually be applied to a total synthesis of aleutianamine.



Scheme 4.1. Retrosynthetic Analysis of Makaluvamine A

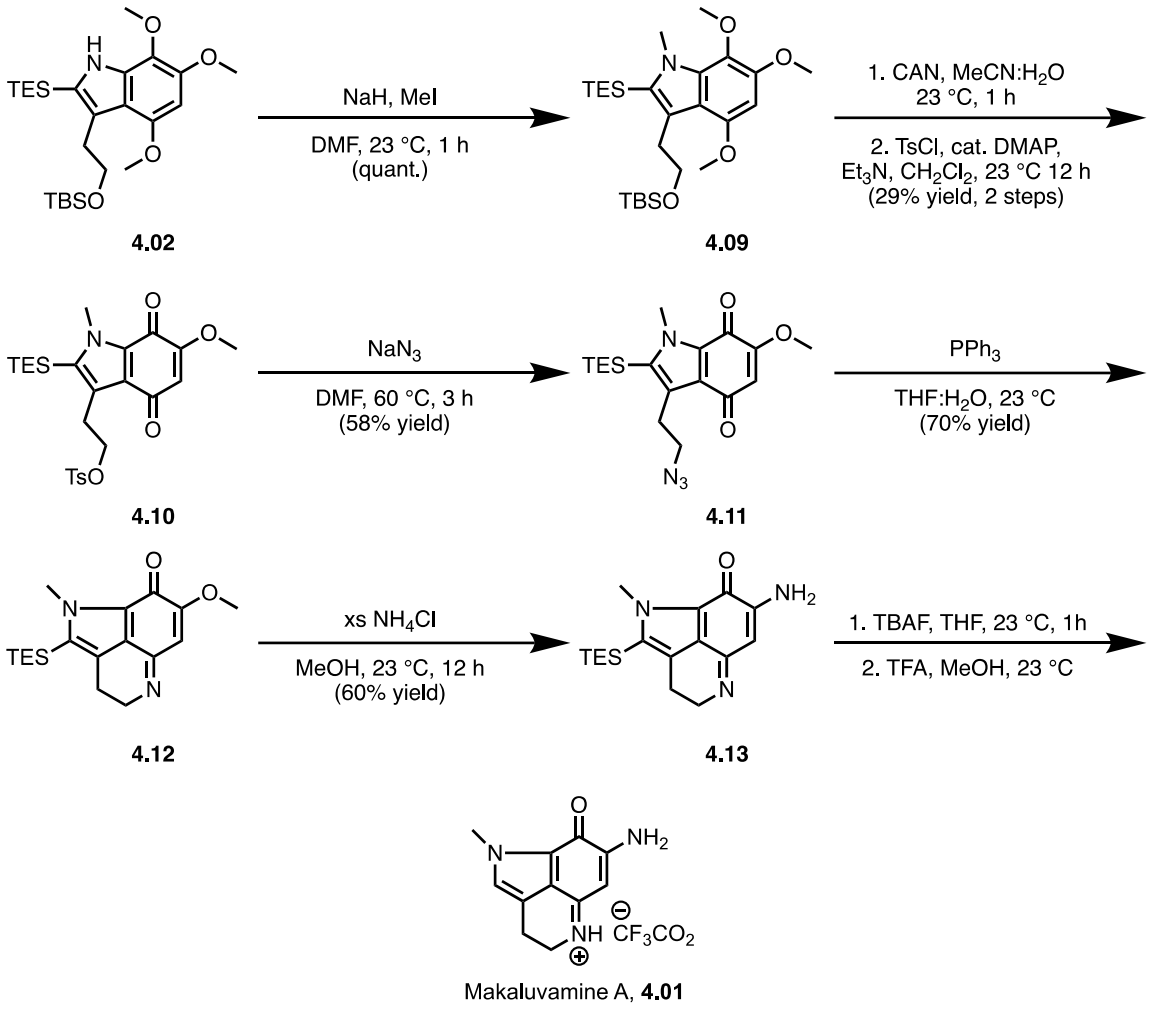
In the forward sense, (Scheme 4.2) we began with commercially available 5-nitrovanillin (**4.05**)[1] which was submitted to Dakin oxidation conditions to bring about bis-phenol **4.06**.[2] The two phenols were protected as their corresponding methyl ethers (**4.07**) by exposure of **4.06** to MeI and Cs_2CO_3 in DMF with heating to 60 °C. Setting the stage for the Larock indole synthesis required selective iodination of **4.07** *ortho* to the nitro group. In exploring this transformation we were pleased to find that simply exposing **4.07** to $AgNO_3$ and I_2 results in selective conversion to iodide **4.08** in excellent yield.[3] The nitro group of **4.08** was reduced with iron powder to yield the requisite aniline **4.04**.[3] With **4.04** in hand, the Larock indole synthesis of was employed to forge the desired compound **4.02**. Again, the catalyst load and reaction times are both lower than precedent would suggest for related indole syntheses.[4]



Scheme 4.2. New Larock Indole Synthesis

Importantly, success in accessing indole **4.02** had addressed the question of C7 oxidation and rapidly positioned us to begin exploring methods for introducing the pyrroloiminoquinone. We undertook the latter task by first methylating the indole nitrogen under standard conditions.[5] Although with the simple methyl electrophile this step was straightforward, the presence of the TES and methoxy groups flanking the indole nitrogen at C2 and C7, respectively, made the installation of other protecting groups (TBS, BOC, Ts) on related compounds *very* challenging. The subsequent aryl oxidation with CAN in wet acetonitrile not only gave access to the indoloquinone, but also deprotected the TBS ether.[6] Treatment of the resulting crude alcohol with tosyl chloride prior to chromatographic purification gave tosylate **4.10**. Exposure of the purified tosylate to sodium azide provided **4.11** which, upon treatment with PPh_3 in wet THF, underwent Staudinger reduction and condensation to yield pyrroloiminoquinone **4.12**.[7] The final

sequence of events was found empirically to proceed best as follows: the vinylogous imidate of **4.12** was converted to vinylogous amidine **4.13** by stirring in methanol with an excess of NH_4Cl.[8] Deprotection of the TES group was accomplished with TBAF. Lastly, since the natural product was isolated and characterized as its TFA salt, we stirred the resulting product in methanol and added a few drops of TFA. After removal of the solvent *in vacuo*, we were able to obtain spectral data matching makaluvamine A **4.01** (see Tables 4.1 and 4.2 in the experimental section of this chapter).[9]



Scheme 4.3 Total Synthesis of Makaluvamine A **4.01**

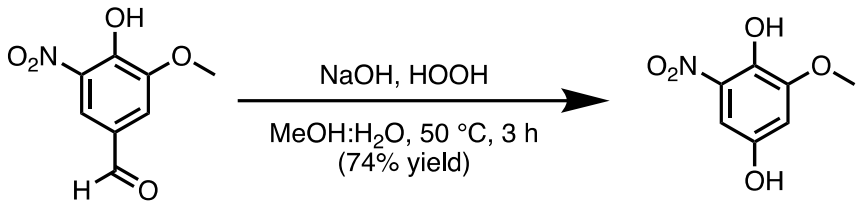
The synthesis of makaluvamine A answered a number of important questions about our approach. Previously, it was not clear if the Larock indole synthesis could be successfully applied to prepare the pyrroloiminoquinone moiety. The efficient synthesis of aniline **4.04** allowed for the correct oxidation to be present at C7 thereby allowing for the necessary aryl oxidation of **4.09**. Thus having addressed the late-stage concerns regarding pyrroloiminoquinone synthesis we returned, as outlined in Chapter Five, to the very thorny questions regarding our metathesis approach to aleutianamine.

4.2 Experimental

4.2.1 General

For general experimental information, see 1.2.1.

*Bis Phenol **4.06***

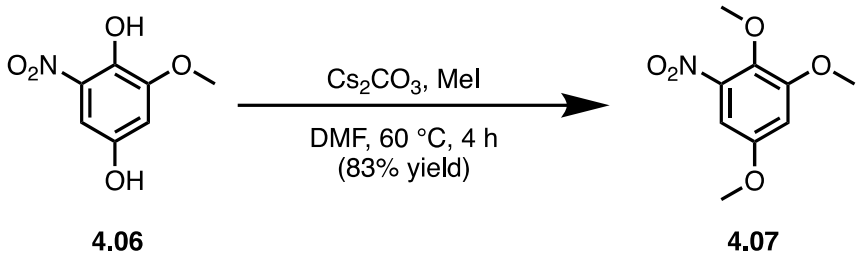


5-nitrovanillin, **4.05** **4.06**

To a solution of **4.05** (5.0 g, 25.4 mmol, 1.0 equiv) in H_2O/MeOH (1:1 mixture, 100 mL, 0.25 M) was added aqueous 1M NaOH (28 mL, 28 mmol, 1.1 equiv) and aqueous H_2O_2 (30%, d = ~ 1 g/mL, 16 mL, 141 mmol, 5.6 equiv). The solution was stirred for 3 h at 50 °C. The mixture was concentrated and the precipitate that formed was filtered and washed with water (5 x 100 mL), to give 3.50 g **4.06** (18.9 mmol, 74% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 7.10 (d, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 2.8

Hz, 1H), 5.00 (apparent s, 1H; exact chemical shift of this phenolic proton varied with concentration between 5.00-4.75), 3.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.0, 147.8, 141.6, 133.3, 108.3, 99.8, 56.9. **IR** (thin film): cm^{-1} 3445 (br), 1542 (s), 1450 (w), 1397 (w), 1341 (w), 1277 (m), 1225 (m), 1199 (m), 1169 (w), 1134 (w), 1059 (w), 989 (w), 923 (w), 812 (w), 774 (w), 762 (w), 608 (w). **HRMS** (ESI-): calculated for $C_7H_6NO_5^-$ $[M-H]^-$ 184.0251, found: 184.0243. **TLC**: R_f = 0.13 (30% EtOAc/hexanes). **Physical Appearance**: Orange solid. **Melting Point**: 139-141 °C.

*Trimethoxy Nitro **4.07***

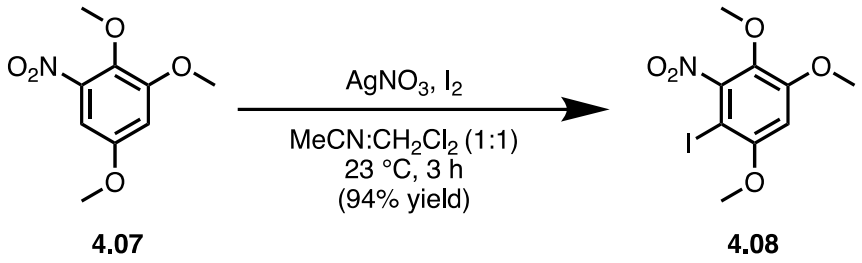


4.06 **4.07**

A flame-dried 300 mL flask, with stir bar, was charged with **4.06** (5.0 g, 27.0 mmol, 1.0 equiv), Cs_2CO_3 (26.4 g, 81.0 mmol, 3 equiv), and DMF (54 mL, 0.5 M). A septum was affixed and the flask was placed under an Ar atmosphere. Thereafter, MeI (5.04 mL, 81.0 mmol, 3 equiv) was added in one portion and the solution was stirred for 2 h at 60 °C. The solution was then allowed to cool to 23 °C and the reaction was quenched with DI water (100 mL). The solution was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with DI water (5 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography on silica gel (30% EtOAc/hexanes). The yield for the reaction was 4.8 g **4.07** (22.5 mmol, 83% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 6.81 (d, *J* = 2.9 Hz, 1H), 6.67 (d, *J* = 2.9 Hz, 1H),

3.91 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.6, 155.0, 144.9, 137.5, 104.8, 98.9, 62.2, 56.5, 56.1. **HRMS** (ESI+): calculated for $C_9H_{11}NNaO_5^+$ $[M+Na]^+$ 236.0529, found: 236.0529. **IR** (thin film): cm^{-1} 2944 (w), 1620 (w), 1584 (w), 1531 (s), 1499 (m), 1456 (m), 1430 (m), 1360 (m), 1282 (m), 1240 (m), 1218 (m), 1196 (m), 1152 (m), 1062 (m), 1048 (m), 996 (m), 946 (w), 921 (w), 841 (w), 786 (w), 769 (w), 623 (w). **TLC**: R_f = 0.21 (20% EtOAc/hexanes). **Physical Appearance**: yellow crystals. **Melting Point**: 79-81 °C.

*Aryl Iodide **4.08***

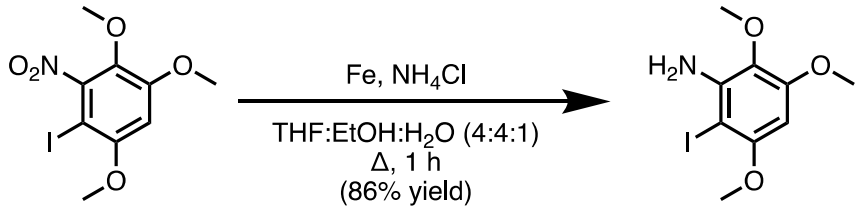


4.07 **4.08**

A flame-dried 1 L flask, with stir bar, was charged with **4.07** (5.0 g, 23.5 mmol, 1 equiv) and $MeCN:CH_2Cl_2$ (1:1 mixture, 240 mL, 0.1 M). Thereafter, $AgNO_3$ (4.4 g, 25.9 mmol, 1.1 equiv) and I_2 (6.6 g, 26.0 mmol, 1.1 equiv) were added, and the mixture was stirred in the dark for 3 h (Note: The reaction should be halted immediately after the disappearance of **4.07** [observed by TLC]. Unidentified byproducts were observed when the reaction was allowed to stir for a longer period of time). The mixture was filtered through a pad of celite and washed with CH_2Cl_2 until the filtrate was colorless. Saturated aqueous $Na_2S_2O_3$ (100 mL) was added to the filtrate, and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The precipitate that

formed was filtered and washed with hexane/Et_2O (80:20, 3 x 20 mL) to give 7.5 g **4.08** as a yellow solid (22.1 mmol, 94% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.55 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.7, 154.5, 151.5, 135.6, 98.0, 65.7, 62.6, 57.4, 56.7. **IR** (thin film): cm^{-1} 2977 (w), 2945 (w), 2847 (w), 1596, (w), 1567 (w), 1533 (s), 1490 (s), 1464 (m), 1435 (m), 1369 (s), 1328 (m), 1279 (w), 1241 (m), 1208 (s), 1092 (m), 1052 (s), 999 (m) 919 (m), 836 (w), 819 (w), 763 (w), 745 (w), 745 (w), 584 (w). **HRMS** (ESI+): calculated for $C_9H_{10}INNaO_5^+$ $[M+Na]^+$ 361.9496, found: 361.9496. **TLC**: R_f = 0.34 (20% EtOAc/hexanes). **Physical Appearance**: Yellow crystals. **Melting Point**: 166-172°C.

*Trimethoxy Iodoaniline **4.04***

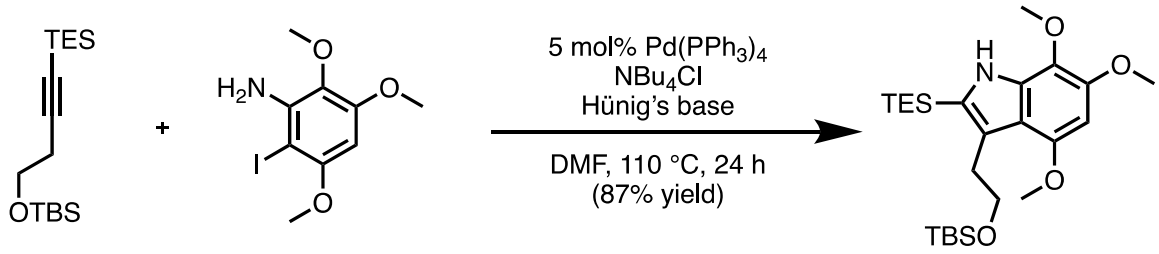


4.08 **4.04**

The starting material (**4.08**, 7.0 g, 20.6 mmol, 1.0 equiv), Fe powder (11.5 g, 206 mmol, 10 equiv), and NH_4Cl (5.7 g, 107 mmol, 5.2 equiv) were added to a round bottom flask. A solution of THF/EtOH/H_2O (4:4:1, 140 mL, 0.15 M) was added and the mixture was heated to reflux and maintained at that same temperature for 1 h. The mixture was allowed to cool to rt and filtered through a pad of celite. The filtrate was washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a crude product which was further purified by flash column chromatography on silica gel (30% EtOAc/hexanes). The yield for the reaction was 5.5 g **4.04** (17.8 mmol, 86% yield). Due to the instability of this

product, it was either used immediately or stored in the freezer under Ar (should be used within a week). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.00 (s, 1H), 4.39 (brs, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 153.2, 142.3, 129.9, 87.1 (the lone methine as observed from DEPT90 and DEPT135), 65.7, 60.3, 56.7, 56.2. **IR** (thin film): cm^{-1} 3468 (w), 3365 (w), 2934 (w), 2839 (w), 1600 (s), 1576 (m), 1485 (s), 1460 (m), 1425 (s), 1342 (s), 1228 (s), 1203 (m), 1176 (w), 1115 (s), 1056 (w), 1000 (s), 975 (m), 952 (w), 773 (m), 577 (w), 416 (w). **HRMS** (ESI+): calculated for $C_9H_{13}INO_3^+$ $[M+H]^+$ 309.9935, found: 309.9932. **TLC**: R_f = 0.24 (20% EtOAc/hexanes; stains yellow with Vanillin). **Physical Appearance**: White amorphous solid.

Indole **4.02**

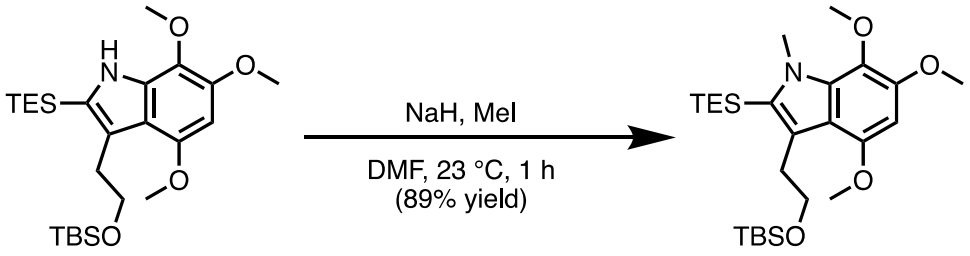


4.03 **4.04** **4.02**

A flame-dried 100 mL round-bottom flask, with stir bar, was charged with **4.03** (947.3 mg, 3.172 mmol, 1.2 equiv) followed by **4.04** (794.2 mg, 2.569 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum (< 1 Torr) was pulled and then the flask was refilled with N_2; this process was repeated twice. The reaction flask was diluted with DMF (9 mL, 0.3 M) and the entire solution was sparged with Ar for approximately 5 min. After sparging was complete, Hünig's base (1,400 μL, 8.200 mmol, 3.2 equiv), NBu_4Cl (742.1 mg, 2.670 mmol, 1 equiv), and, lastly, $Pd(PPh_3)_4$ (157.9 mg,

0.1366 mmol, 0.05 equiv) were added. The solution was sparged again for approximately 5 min. The solution was then heated and the temperature was maintained between 90 and 110 °C and this temperature was maintained for 24 h. The solution was then allowed to cool to 23 °C and diluted with $NaHCO_3$ (sat.). The aqueous was extracted 4 x Et_2O. The combined organic extracts were washed 4 x DI water, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.7 g of a crude product. Further purification was achieved by flash column chromatography eluting with a step gradient of 0 to 5 to 10% EtOAc/hexanes. The yield for the reaction was 1070.7 mg **4.02** (2.232 mmol, 87% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 6.20 (s, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 3.82-3.77 (m, 2H), 3.10-3.06 (m, 2H), 1.02-0.97 (m, 9H), 0.92 (s, 9H), 0.92-0.85 (m, 6H), 0.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 150.0, 147.1, 134.3, 130.2, 128.9, 122.6, 115.5, 90.2, 65.8, 61.1, 58.2, 55.5, 31.7, 26.3, 18.7, 7.6, 4.0, -5.0. **IR** (thin film): cm^{-1} 3485 (w), 3357 (w), 2953 (m), 2933 (m), 2875 (w), 1626 (w), 1594 (w), 1525 (m), 1464 (w), 1417 (w), 1338 (m), 1233 (w), 1204 (w), 1135 (s), 1089 (s), 1041 (w), 1002 (w), 977 (w), 902 (w), 836 (m), 777 (w), 734 (m). **HRMS** (ESI+): calculated for $C_{25}H_{45}NNaO_4Si_2^+$ $[M+Na]^+$ 502.2779, found: 502.2778. **TLC**: R_f = 0.19 (10% EtOAc/hexanes). **Physical Appearance**: Yellow, waxy solid.

*Methyl Indole **4.09***

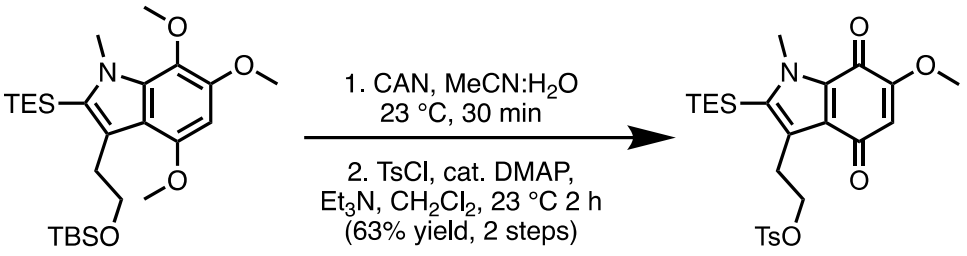


4.02 **4.09**

A flame-dried 100 mL round-bottom flask, with stir bar, was charged with **4.02** (1.780 g, 3.71 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum was pulled (< 1 Torr) and then the flask was refilled with Ar from a balloon; this process was repeated twice. Thereafter, **4.02** was dissolved in DMF (18.6 mL, 0.2 M). The reaction was submerged in an ice/water bath and allowed to cool for approximately 5 min. After the allotted time, NaH (562 mg, 14.05 mmol, 3.8 equiv) was added and the solution stirred for 30 min at which point MeI (1 mL, 14.84 mmol, 4.3 equiv) was added. The reaction was immediately raised out of the ice/water bath and allowed to attain 23 °C. After stirring for 1 h at 23 °C the reaction was submerged in an ice/water bath and quenched with NH_4Cl (sat.). The aqueous was extracted 3 x Et_2O and 3 x EtOAc. The combined organic extracts were washed 5 x DI H_2O, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 2.1 g of a crude product. Further purification was achieved by flash column chromatography. The column was first flushed with hexanes to remove mineral oil and then eluting with a step gradient of 5 to 10% EtOAc/hexanes. The yield for the reaction was 1.627 g **4.02** (3.295 mmol, 89% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.20 (s, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77-3.73 (m, 2H), 3.17-3.13 (m, 2H), 1.03-0.95 (m, 15H), 0.93 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): 150.1, 148.6, 134.4, 133.8, 130.4, 123.6, 115.9, 89.9, 66.4, 61.9, 58.2, 55.4, 35.3, 30.7, 26.2, 18.6, 7.8,

5.1, -0.5. **IR** (thin film): cm^{-1} 2953 (s), 2931 (m), 2875 (w), 1610 (w), 1516 (m), 1463 (m), 1341 (w), 1287 (w), 1255 (m), 1215 (m), 1154 (w), 1117 (w), 1085 (s), 1020 (w), 1003 (w), 982 (w), 930 (w), 865 (w), 836 (m), 776 (w), 733 (m), 418 (w). **HRMS** (ESI+): calculated for $C_{26}H_{47}NNaO_4Si_2^+$ $[M+Na]^+$ 516.2936, found: 516.2936. **TLC**: R_f = 0.33 (10% EtOAc/hexanes; stains purple in Vanillin). **Physical Appearance**: White waxy solid.

*Tosylated Indoloquinone **4.10***

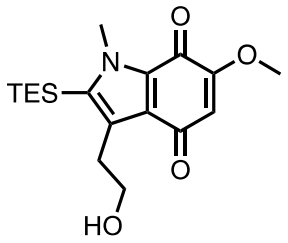


4.09 **4.10**

A 50 mL round-bottom flask, with stir bar, was charged with Methyl Indole **4.09** (0.53 g, 1.07 mmol, 1.0 equiv) and MeCN/H_2O (14 mL, 9:1 mixture, 0.08 M). CAN (1.48 g, 2.70 mmol, 2.5 equiv) was added in one portion and the mixture stirred for 30 min. The contents of the flask were transferred to a separatory funnel with deionized water (100 mL). The solution was extracted with DCM (5 x 50 mL) and the combined organic extracts were washed with deionized water (100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give 0.47 g of a crude product (**SI-4.10**), which was carried forward without further purification.

A flame-dried 10 mL round-bottom flask, with stir bar, was charged with crude **SI-4.10** (471 mg, from previous reaction), DMAP (0.033 g, 0.27 mmol, 0.25 equiv), TsCl (0.51 g, 2.68 mmol, 2.5 equiv), and CH_2Cl_2 (4.5 mL, 0.2 M). Et_3N (0.38 mL, 2.7 mmol,

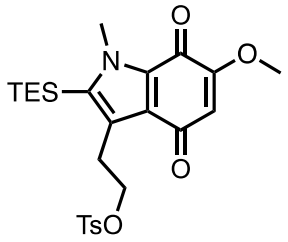
2.5 equiv) was added dropwise and the solution stirred for 2 h. The contents of the flask were transferred to a separatory funnel with deionized water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with deionized water (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (50% EtOAc/hexanes). The yield for the reaction was 0.34 g **4.10** (0.68 mmol, 63% yield, two steps).



SI-4.10

The following is a tabulation of crude Indoloquinone **SI-4.10**. This compound was carried forward without chromatographic purification into the tosylation step:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 4.05 (s, 3H), 3.81 (s, 3H), 3.78 (t, *J* = 6.3 Hz, 2H; overlaps with s at 3.81 ppm), 3.11 (t, *J* = 6.4 Hz, 2H), 1.00-0.93 (m, 15).

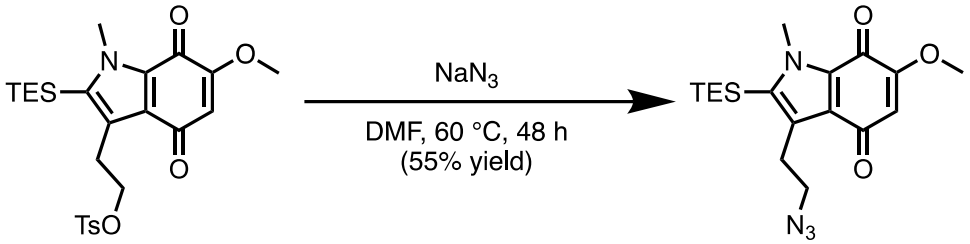


4.10

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65-7.63 (m, 2H), 7.24-7.21 (m, 2H), 5.57 (s, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 4.02 (s, 3H), 3.80 (s, 3H), 3.13 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 3H), 1.00-0.89 (m, 15H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 183.9, 171.9, 159.9, 144.5, 141.2, 133.0, 131.6, 130.4, 129.6, 128.0, 124.0, 107.3, 69.9, 56.7, 36.7, 25.7, 21.6, 7.6, 4.6. **IR** (thin

film): cm^{-1} 2956 (w), 2876 (w), 1663 (m), 1638 (s), 1601 (s), 1519 (m), 1455 (m), 1413 (w), 1357 (m), 1336 (m), 1243 (w), 1210 (s), 1187 (m), 1173 (s), 1109 (m), 1068 (w), 1036 (m), 1000 (w), 959 (m), 901 (s), 843 (m), 814 (m), 782 (m), 728 (s), 662 (s), 569 (w), 553 (s), 522 (w), 494 (w), 452 (w). **HRMS** (ESI+): calculated for $C_{25}H_{33}NNaO_6SSi^+$ $[M+Na]^+$ 526.1690, found: 526.1693. **TLC**: R_f = 0.27 (30% EtOAc/hexanes; developed twice). **Physical Appearance**: Orange foam.

*Azide **4.11***

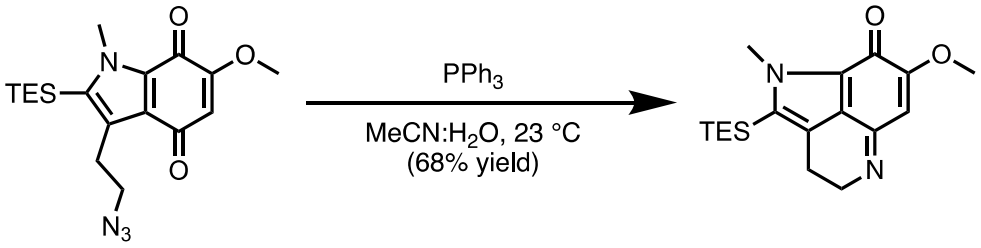


4.10 **4.11**

A flame-dried 6-dram vial, with stir bar, was charged with **4.10** (0.34 g, 0.68 mmol, 1.0 equiv), NaN_3 (0.22 g, 3.38 mmol, 5.0 equiv), and DMF (4 mL, 0.2 M). The solution was stirred at 60 ºC for 48 h. The mixture was allowed to cool to room temperature and DI water (5 mL) was added. The contents of the vial were transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with DI water (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a crude product. Further purification was achieved by flash column chromatography on silica gel (30% EtOAc/hexanes). The yield for the reaction was 0.14 g **4.11** (0.37 mmol, 55% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.67 (s, 1H), 4.05 (s, 3H), 3.80 (s, 3H), 3.45-3.42 (m, 2H), 3.10-3.06 (m, 2H), 1.01-0.90 (m, 15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 184.2,

172.1, 160.1, 140.6, 132.4, 131.8, 124.3, 107.5, 56.7, 51.8, 36.7, 26.0, 7.6, 4.6. **IR** (thin film): cm^{-1} 2955 (w), 2876 (w), 2094 (s), 1665 (s), 1641 (s), 1603 (s), 1519 (w), 1456 (m), 1413 (w), 1337 (w), 1242 (w), 1211 (s), 1110 (w), 1054 (w), 1034 (w), 1002 (w), 925 (w), 892 (w), 844 (w), 794 (w), 735 (m), 486 (w), 456 (w), 426 (w). **HRMS** (ESI+): calculated for $C_{18}H_{26}N_4NaO_3Si^+$ $[M+Na]^+$ 397.1666, found: 397.1671. **TLC**: R_f = 0.22 (20% EtOAc/hexanes). **Physical Appearance**: Orange oil that solidifies in the freezer (~ -20 °C).

*Pyrroloiminoquinone **4.12***

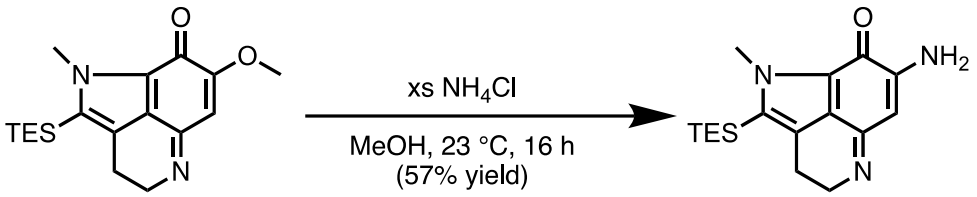


4.11 **4.12**

A 6-dram vial, with a stir bar, was charged with **4.11** (0.14 g, 0.37 mmol, 1.0 equiv), PPh_3 (0.20 g, 0.76 mmol, 2.1 equiv), and THF/H_2O (2.2 mL, 9:1 mixture, 0.2 M). The mixture stirred for 16 h, at which point, complete consumption of starting material was observed by TLC. The contents of the vial were transferred to a flask (rinsing the sides of the vial with CH_2Cl_2) and Na_2SO_4 was added. The mixture was filtered and concentrated *in vacuo* to afford a crude product which was further purified by flash column chromatography on silica gel (2% MeOH/CH_2Cl_2). The yield for the reaction was 82 mg **4.12** (0.25 mmol, 68% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 4.10 (t, *J* = 7.8 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 3H), 2.79 (t, *J* = 7.8 Hz, 2H), 0.99-0.95 (m, 9H), 0.90-0.86 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.6, 158.7, 156.8, 137.8, 127.2, 127.2, 121.1,

105.9, 56.6, 50.9, 35.9, 20.8, 7.5, 4.0. **IR** (thin film): cm^{-1} 2953 (m), 2875 (m), 1654 (s), 1614 (m), 1571 (s), 1452 (m), 1320 (w), 1282 (m), 1218 (s), 1179 (w), 1129 (w), 1044 (s), 1007 (m), 921 (w), 837 (w), 792 (w), 734 (m), 698 (w), 585 (w), 421 (w). **HRMS** (ESI+): calculated for $C_{18}H_{27}N_2O_2Si^+$ $[M+H]^+$ 331.1836, found: 331.1834. **TLC**: R_f = 0.33 (5% MeOH/CH_2Cl_2). **Physical Appearance**: Dark purple oil.

*TES-Makaluvamine A **4.13***

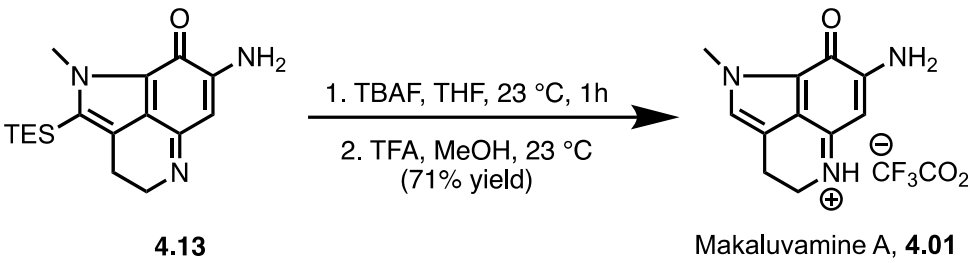


4.12 **4.13**

A 2-dram vial, with stir bar, was charged with **4.12** (71 mg, 0.21 mmol, 1.0 equiv), NH_4Cl (0.11 g, 2.1 mmol, 10 equiv) and MeOH (1 mL, 0.2 M). After observing full consumption of starting material by TLC (16 h), the reaction was concentrated *in vacuo* to afford a crude product. Further purification was achieved by flash column chromatography on silica gel (10% MeOH/CH_2Cl_2). The yield for the reaction was 38 mg **4.13** (0.12 mmol, 57% yield). **^{1}H-NMR** (600 MHz, Methanol-*d4*): δ 5.65 (s, 1H), 4.07 (s, 3H), 3.82 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.04-0.95 (m, 15H). **^{13}C NMR** (151 MHz, Methanol-*d4*): δ 169.8, 160.0, 157.8, 142.5, 129.9, 128.8, 123.3, 87.9, 43.9, 37.1, 21.8, 7.6, 4.5. **IR** (thin film): cm^{-1} 2955 (m), 2875 (m), 1676 (w), 1607 (s), 1530 (m), 1455 (w), 1392 (w), 1343 (w), 1295 (w), 1253 (w), 1223 (w), 1139 (w), 1004 (w), 967 (w) 846 (w), 726 (m).

HRMS (ESI+): calculated for $C_{17}H_{26}N_3OSi^+$ $[M+H]^+$ 316.1840, found: 316.1841. **TLC**: R_f = 0.18 (4% MeOH/CH_2Cl_2). **Physical Appearance**: Dark green solid.

*Makaluvamine A **4.01***



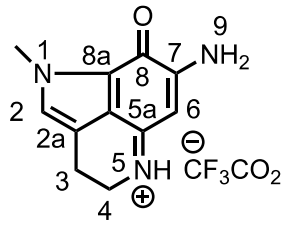
4.13 Makaluvamine A, **4.01**

A flame-dried 2-dram vial, with stir bar, was charged with **4.13** (13 mg, 0.041 mmol, 1.0 equiv) and THF (0.2 mL, 0.2 M). The solution was cooled to 0 ºC (ice bath) and TBAF, as a 1 M solution in THF, (0.08 mL, 0.08 mmol, 2.0 equiv) was added dropwise. The reaction warmed to room temperature (by removing ice/water bath) and reaction progress monitored by TLC. Upon observing full consumption of SM by TLC (~1 h), the contents of the vial were concentrated *in vacuo* to afford a crude product. Further purification was achieved by flash column chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 89:10:1) and the fractions were concentrated *in vacuo* to give makaluvamine A (**4.01**), which was treated with TFA (5 drops) in MeOH (5 mL) to give the corresponding TFA salt. The yield for this reaction was 9 mg makaluvamine A (**4.01**, 0.029 mmol, 71%). *Cf.* Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638. **^{1}H-NMR** (600 MHz, DMSO-*d6*): δ 10.40, (s, 1H), 9.09 (s, 1H), 8.40 (s, 1H), 7.31 (s, 1H), 5.60 (s, 1H), 3.89 (s, 3H), 3.76 (td, = 7.6, 2.7 Hz, 2H), 2.84 (t, = 7.6 Hz, 2H). **^{13}C NMR** (151 MHz,

DMSO-*d6*): δ 168.3, 156.8, 156.1, 131.1, 123.1, 122.4, 117.9, 86.5, 42.1, 35.9, 18.1. **IR** (thin film): cm^{-1} 3470 (br), 2953 (s), 2930 (s), 2856 (m), 1759 (s), 1644 (w), 1542 (w), 1462 (w), 1440 (w), 1376 (m), 1319 (w), 1254 (s), 1204 (m), 1143 (m), 1110 (s), 1007 (s), 894 (m), 836 (s), 808 (w), 776 (s), 698 (w), 650 (w), 588 (w), 544 (w), 491 (w), 435 (w), 424 (w). **HRMS** (ESI+): calculated for $C_{11}H_{12}N_3O^+$ $[M+H]^+$ 202.0975, found: 202.0975. **TLC**: R_f = 0.15 (10% MeOH/CH_2Cl_2). **Physical Appearance**: Dark purple solid.

Table 4.1. Collation of **^{1}H NMR** (600 MHz, DMSO-*d6*) data for Natural and Synthetic Makaluvamine A (**4.01**). (*Cf.* Ireland *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638).

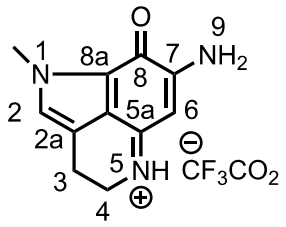
Assignment	^{1}H Natural (ppm)	^{1}H Synthetic (ppm)	Delta (ppm)
N-Me	3.88	3.89	0.01
1	-	-	-
2	7.30	7.31	0.01
2a	-	-	-
3	2.83	2.84	0.01
4	3.75	3.76	0.01
5	10.44	10.40	-0.04
5a	-	-	-
6	5.61	5.60	-0.01
7	-	-	-
8	-	-	-
8a	-	-	-
8b	-	-	-
9	8.37	8.40	0.03
	9.09	9.09	-



Makaluvamine A, **4.01**

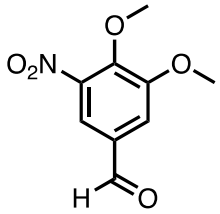
Table 4.2. Collation of **^{13}C NMR** (600 MHz, DMSO-*d6*) data for Natural and Synthetic Makaluvamine A (**4.01**). (*Cf.* Ireland *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638.).

Assignment	^{13}C Natural (ppm)	^{13}C Synthetic (ppm)	Delta (ppm)
N-Me	35.8	35.9	0.1
1	-	-	-
2	131.0	131.1	0.1
2a	117.8	117.9	0.1
3	18.0	18.1	0.1
4	42.0	42.1	0.1
5	-	-	-
5a	156.0	156.1	0.1
6	86.4	86.5	0.1
7	156.7	156.8	0.1
8	168.2	168.3	0.1
8a	123.0	123.1	0.1
8b	122.3	122.4	0.1
9	-	-	-



Makaluvamine A, **4.01**

[1] It should be noted that Yamamura and co-workers start their total syntheses of Discorhabdin C, Batzelline C and Isobatzelline C (*Tetrahedron*, **1994**, *50*, 2017-2028) begin from the very similar 3,4-dimethoxy-5-nitrobenzaldehyde (**iv.05**) but follow a different route to pyrroloiminoquinone natural products through early nitrogen installation at the position of the benzaldehyde through a Curtius rearrangement approach.



iv.05

[2] Wissner, A.; Floyd, M. B.; Johnson, B. D.; Fraser, H.; Ingalls, C.; Nittoli, T.; Dushin, R. G.; Discafani, C.; Nilakantan, R.; Marini, J.; Ravi, M.; Cheung, K.; Tan, X.; Musto, S.; Annable, T.; Siegel, M. M.; Loganzo, F. *J. Med. Chem.* **2005**, *48*, 7560-7581.

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[4] Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921-923.

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[6] Jackson, Y. A.; Billimoria, A. D.; Sadanandan, E. V.; Cava, M. P. *J. Org. Chem.*, **1995**, *60*, 3543-3545.

[7] Hess, W.; Burton, J. W. *Chem. Eur. J.* **2010**, *16*, 12303-12306. Contains a procedure for both tosylate displacement with azide and Staudinger reduction.

[8] Izawa, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron* **1994**, *50*, 13593-13600.

[9] Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638.

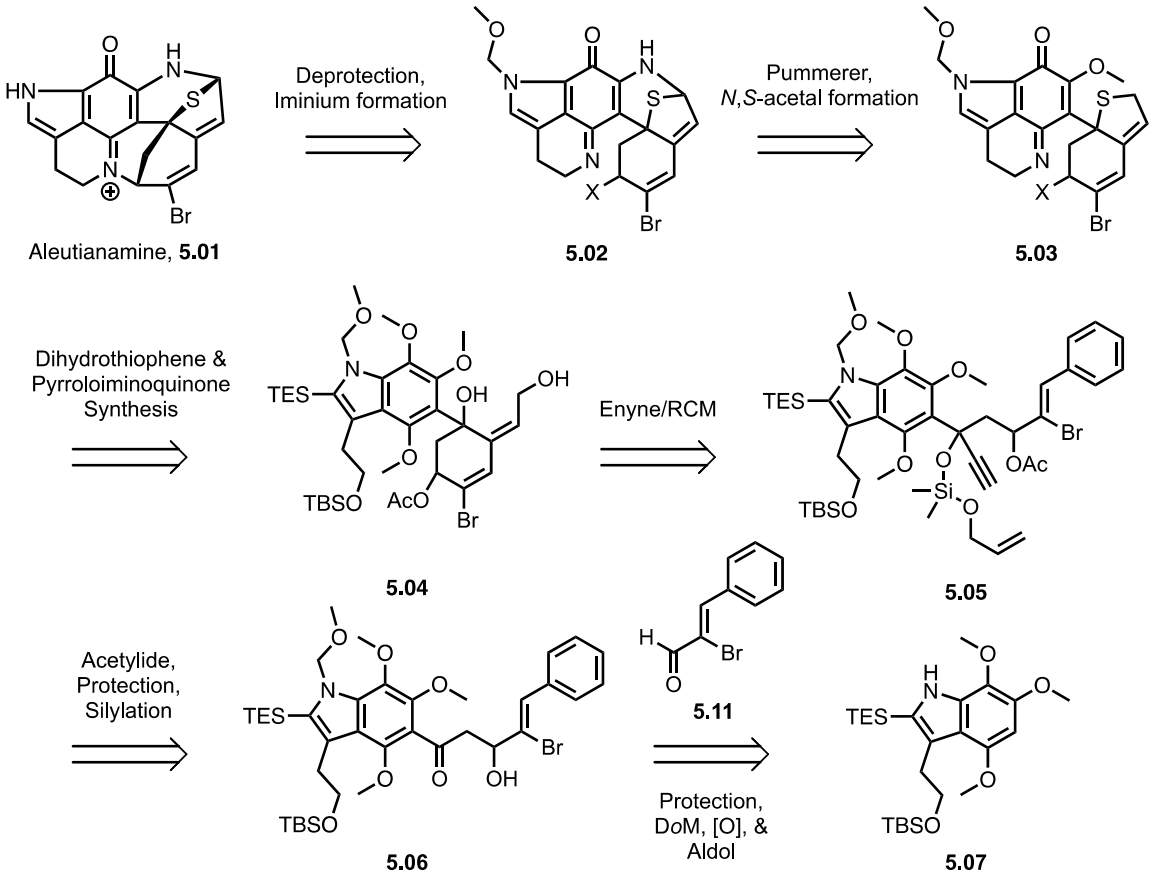
CHAPTER FIVE

Aleutianamine: Current Synthetic Approach, Outlook and Summary

5.1 Development of a Metathesis Approach to Aleutianamine

Encouraged by the success of our total synthesis of makaluvamine A (see Chapter Four), we turned attention back to aleutianamine (**5.01**, Scheme 5.1). The lessons learned and highlighted in Chapters Three and Four led us to revisit our retrosynthetic analysis. As illustrated in Scheme 5.1, the endgame strategy would remain largely unchanged, however a new indole nitrogen protecting group (*i.e.* MOM) was anticipated on this new series of compounds. Aleutianamine (**5.01**) would be accessed from **5.02** by a late-state deprotection and iminium formation, and the *N*,*S*-acetal would be installed via Pummerer rearrangement from an intermediate such as **5.03**. The first major difference in our revised approach centers on the dihydrothiophene wherein late stage thiolation and ring closure is envisioned instead of direct formation of the bicycle via tandem metathesis. This change was prompted by difficulties encountered during efforts to install sulfur at the benzylic position of indole **3.27** via Lewis acid promoted additions of allyl mercaptan to the benzylic/propargylic alcohol (see Chapter Three). Confidence was high regarding metatheses in the presence of methoxymethyl (MOM)-protected indoles[1] and eventual deprotection of the MOM was also precedented.[2] Pyrroloiminoquinone synthesis, through the aryl oxidation strategy developed in Chapter Four, would follow installation of the dihydrothiophene and an enyne/RCM reaction remains the key step. However, instead of employing an allylic sulfide, we imagined this latter reaction as beginning from acyclic silylene **5.05** and

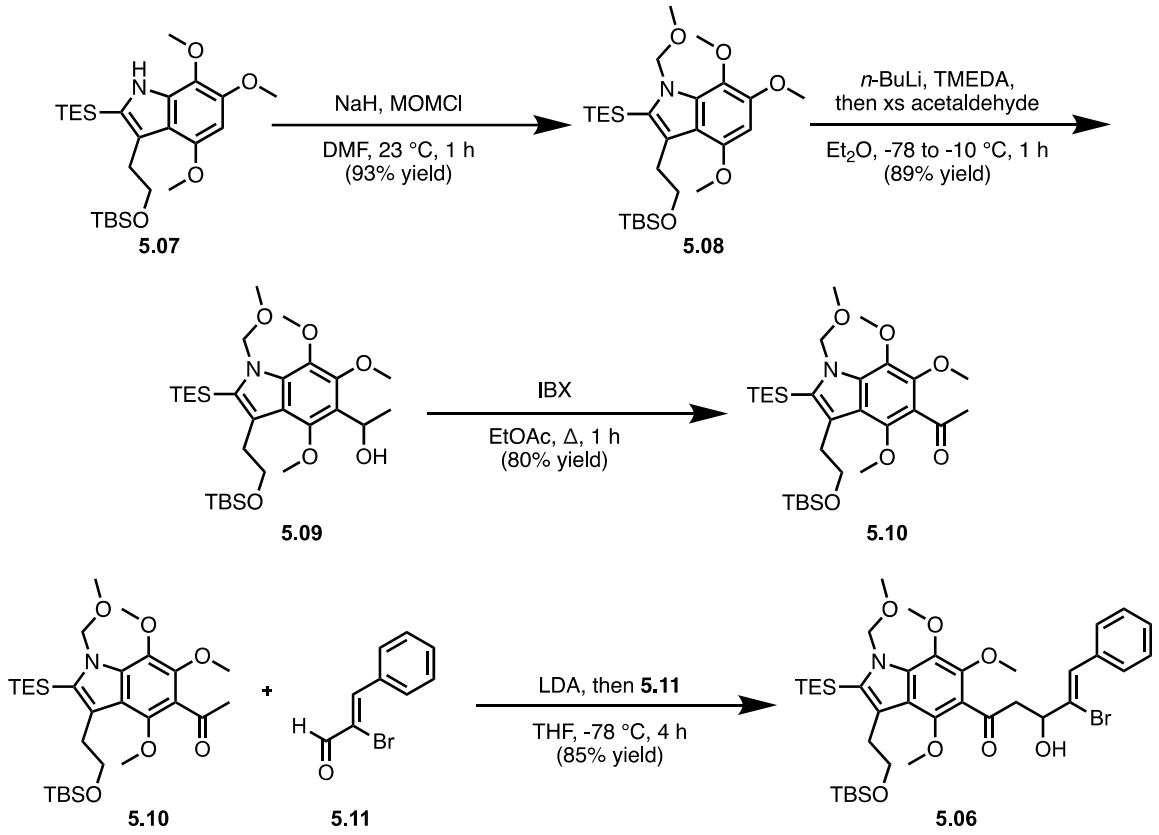
delivering a readily deprotected precursor to diol **5.04**.[3] Silylene **5.05** was seen as arising from aldol product **5.06** through acetylide addition, acetate protection, and silylation. The aldol product **5.06** would arise from indole **5.07** through indole nitrogen protection, D*o*M with acetaldehyde quench, oxidation to the methyl ketone, and an aldol reaction with α-bromocinnamaldehyde (**5.11**).



Scheme 5.1. Retrosynthetic Analysis of Aleutianamine **5.01**

In the forward sense, our current approach begins from **5.07**, the synthesis of which was described was described in Chapter Four. In the event, **5.07** was advanced via MOM protection of the indole by exposure to NaH and treatment with MOM-Cl under standard conditions. As can be seen, the latter protection event produced an intermediate (**5.08**)

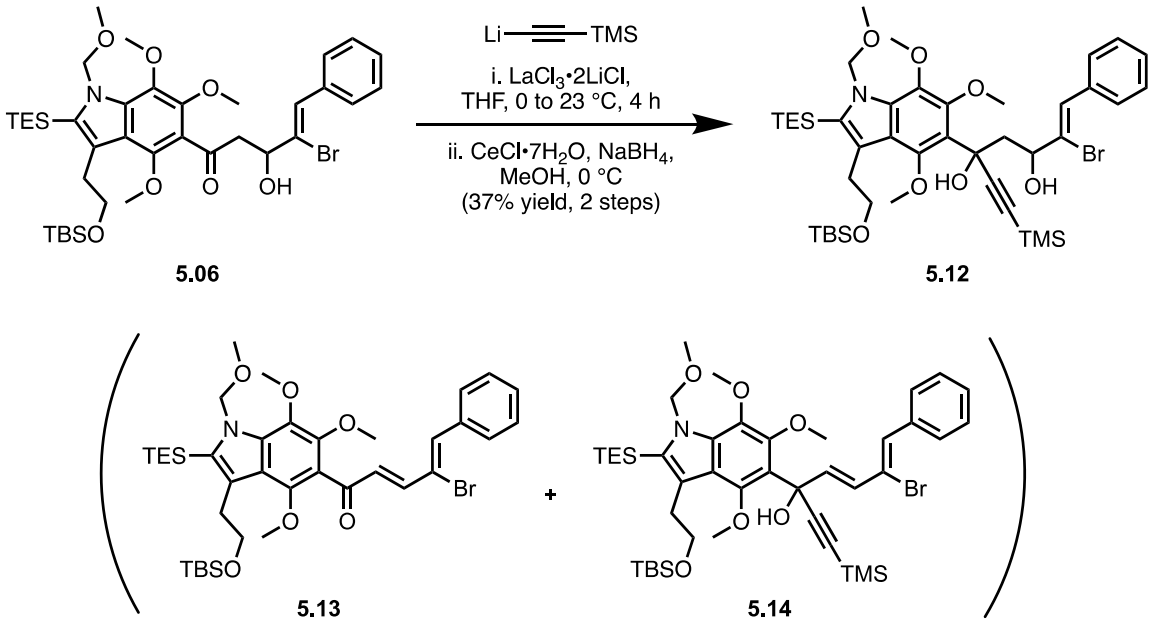
wherein lithiation could only take place at the desired C5 position. Thus, treatment of **5.08** with *n*-BuLi in the presence of TMEDA followed by addition of excess acetaldehyde was found to deliver benzylic alcohol **5.09** in excellent yield. Oxidation of **5.09** to ketone **5.10** (jocularly referred to as "Super Acetophenone") proceeded in good yield and set the stage for a simple aldol reaction with α-bromocinnamaldehyde (**5.11**) to deliver β-hydroxy ketone **5.06**.[4]



Scheme 5.2. Synthesis of Aldol Product **5.06**

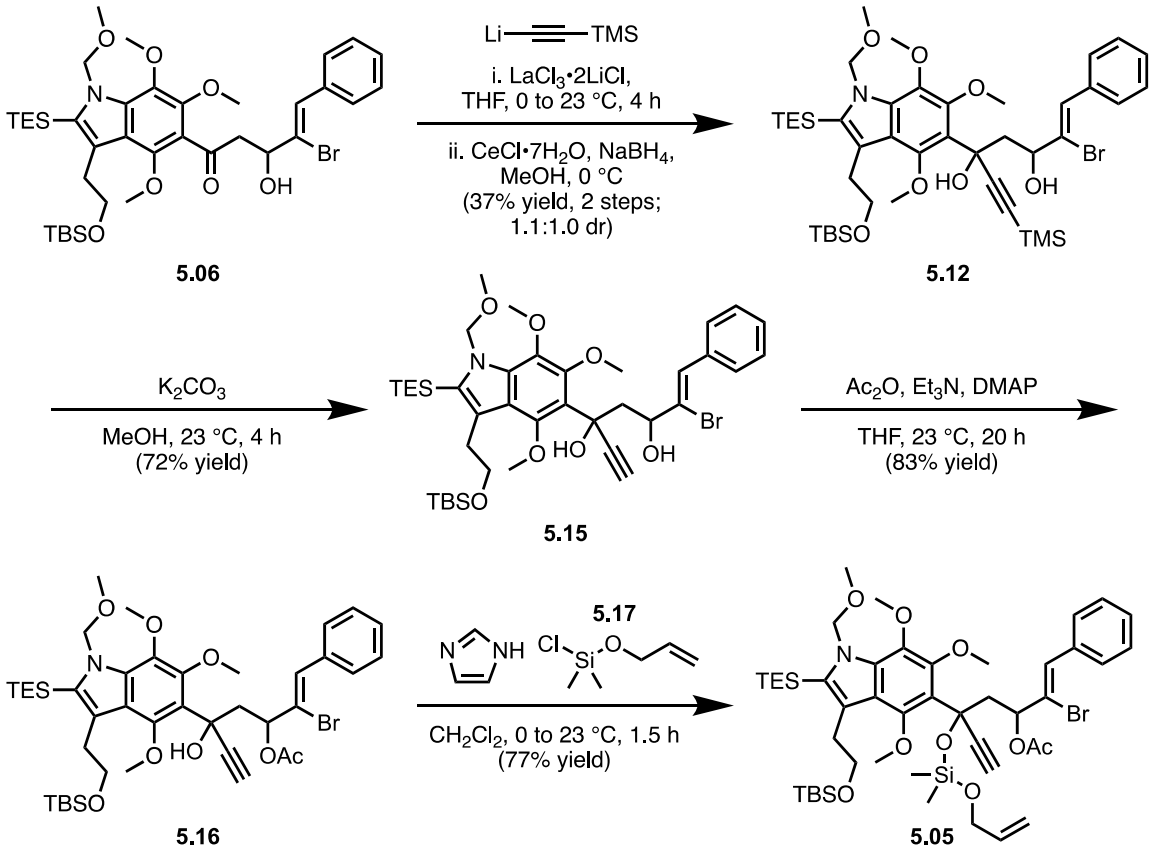
Given that in previous studies (Chapter Three) silyl protected variants of the derived secondary alcohol had demonstrated a propensity toward elimination, we opted to leave the alcohol unprotected in hopes of suppressing this deleterious event.[5] Indeed, exposure of **5.06** to lithium TMS acetylide with additives such as $LaCl_3$•2LiCl and $CeCl_3$,

yielded the desired 1,3-diol **5.12**, however this reaction was also accompanied by elimination products **5.13** and **5.14** whose relative proportions varied depending on equivalents of nucleophile added (see Scheme 5.3). Tremendous synthetic effort was applied to resolving this aberrant reactivity through alteration of the alkynyl nucleophile, additive, and solvent concentration, but overturning the E1cB elimination could not be avoided. Nonetheless, acceptable yields of **5.12** could be obtained by pre-stirring the starting material in $LaCl_3$•2LiCl and diluting with THF (0.1M), maintaining the equivalents of lithium TMS acetylide at 2 (to avoid formation of **5.14**), and treating the crude product directly with $NaBH_4$, $CeCl_3$•$7H_2O$ in MeOH at 0 °C to remove **5.13**.[6]



Scheme 5.3. Synthesis of 1,3-Diol **5.12** and accompanying Elimination Products **5.13** and **5.14**

With access to the requisite 1,3-diol **5.12** gained, we continued with the silylene synthesis (Scheme 5.4 *vide infra*). The diastereomeric ratio (dr) of the acetylide addition reaction was difficult to judge as the peaks of the resulting products overlapped. The mixture was therefore, carried forward crude into the methanolysis step at which point the acetylene singlets of **5.15** were readily apparent in the ^{1}H NMR and integration revealed a very modest 1.1:1.0 dr. The secondary alcohol was protected as an acetate in the presence of a free tertiary alcohol to give **5.16**.[7] Protection of the heavily congested tertiary alcohol proved non-trivial and considerable optimization was required before it was found that pre-stirring imidazole and **5.17** neat, venting the gas which formed, dissolving the resulting product in CH_2Cl_2, and then adding **5.16** as a solution in CH_2Cl_2 provided good access to the desired silylene **5.05** as a mixture of diastereomers.[8]



Scheme 5.4. Synthesis of Silylene **5.05**

The diastereomers of silylene **5.05** were readily separable and the major silylene diastereomer was found to be crystalline.[9] A preliminary structure, shown in Figure 5.1 (*vide infra*), has been obtained through single crystal X-Ray Diffraction (XRD) analysis. The relative stereochemistry about the two alcohols of major diastereomer (**5.05a**) was found to be syn.[10] As detailed below in Scheme 5.5, the value of knowing the relative stereochemistry of **5.05a** and **5.05b** derives from the remarkable fact that one diastereomer reacts in the tandem metathesis to deliver **5.04a**, along with **5.18**, (after selective desilyation with TBAF:AcOH), while the other diastereomer (**5.05b**) halts after the initial enyne metathesis to give compound **5.19**. The origin of this divergent reactivity is unclear since analysis of simple molecular models indicates that both diastereomers have

sufficiently free rotation to adopt conformations necessary for ring-closing metathesis, however, one diastereomer seems more prone to this desired reactivity than the other. As mentioned in Chapter Two, divergent reactivity of the sulfide disastereomers **2.20** was strongly suggested by the fact that *only one diastereomer* of **2.21** was observed and, furthermore, that diastereomer of **2.21** could only be isolated from starting material which predominantly contained one particular diastereomer (the relative stereochemistry of which was never fully delineated). It would seem that our suspicions of divergent diastereomer reactivity hinted at in the model system are confirmed in this current approach.

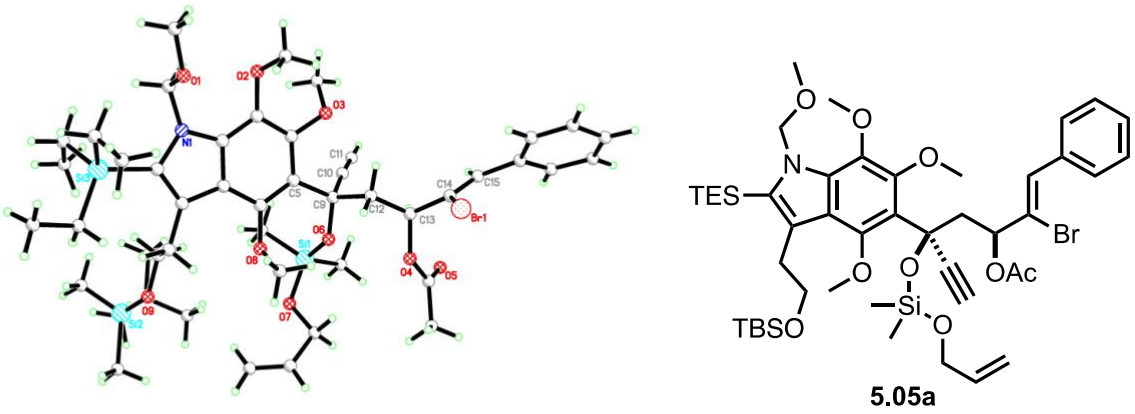
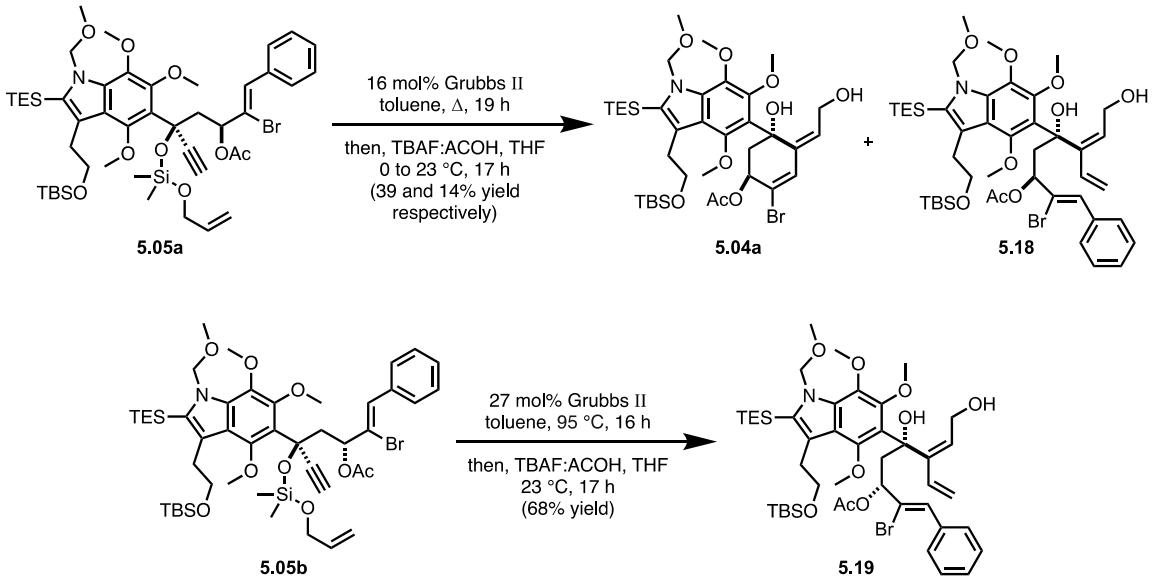


Figure 5.1. Single Crystal XRD Analysis of **5.05a** allows for Assignment of Relative Stereochemistry

The structure of desired compound **5.04a** was confirmed by 1 and 2D NMR analyses and are summarized below in Figure 5.2. Most revealing among these analyses was the NOESY correlation between the newly formed vinyl methines, which aids in confirmation that the double bond geometry is consistent with that found in the natural product. Also noteworthy are the HMBC correlations between the protons of the methylene at C-4, and the two vinyl protons to the aliphatic quaternary carbon of C-5 (aleutianamine

numbering). Not shown in Figure 5.2 for simplicity, the vinyl methine of C-1 has an HMBC correlation to the methine at C-3 and the C-3 methine sees the C-4 methylene through COSY (see Appendix E for spectra).



Scheme 5.5. Synthesis of Desired Diol **5.04a** and Divergent Reactivity of the Diastereomers **5.05a** and **5.05b**.

Also detailed in Figure 5.2, are HMBC data for **5.18** and **5.19** which proved critical in identifying all of the ^{13}C resonances for these compounds as the normal 1D spectrum appears to be one carbon short. In both compounds, the geminal protons of the terminal olefin have an HMBC correlation to the respective missing carbons. In **5.18**, the correlation to the missing carbon appears at 147.6 ppm and in **5.19** the correlation is to a carbon at 145.8 ppm. The missing carbons are thus assigned as the C-6 carbon. Interestingly, this carbon in the natural product (**5.01**) shows a resonance at 141.5 ppm in Methanol-*d4* and 141.2 in DMSO-*d6*. Furthermore, in the ^{13}C NMR of compound **5.04a**, which contains all of the anticipated carbon signals, there is a low-intensity quaternary carbon at 143.4 ppm.

Other spectral data (^{1}H NMR, HRMS, etc.) are consistent with the proposed assignments for **5.18** and **5.19**.

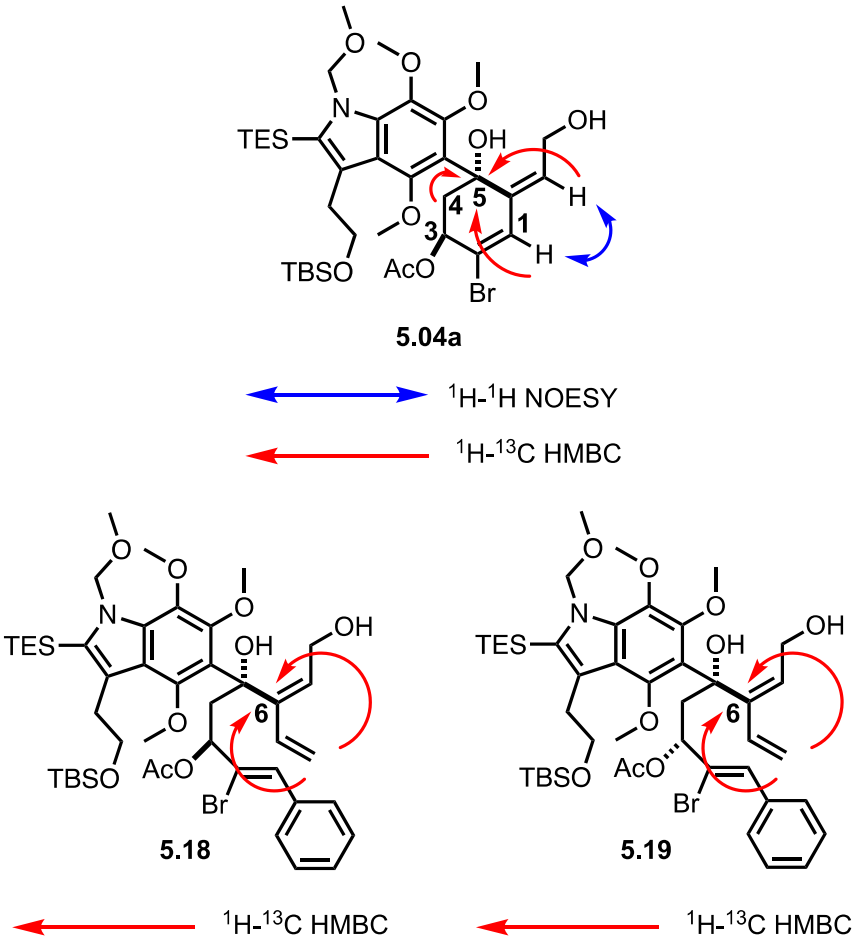


Figure 5.2 Key 2D NMR Analyses of **5.04a**, **5.18**, and **5.19**

The current synthetic approach has delivered diol **5.04a**, which contains all of the carbons found in aleutianamine (**5.01**) and, importantly, in positions poised for synthesis completion. The vinyl bromide-containing 1,3-diene has been assembled through the development of a key tandem metathesis reaction. With the geometry of the double bond fixed in space, should a sulfur be installed at the primary allylic alcohol, and a carbocation formed at the tertiary alcohol, it is hoped that the desired dihydrothiophene would form.

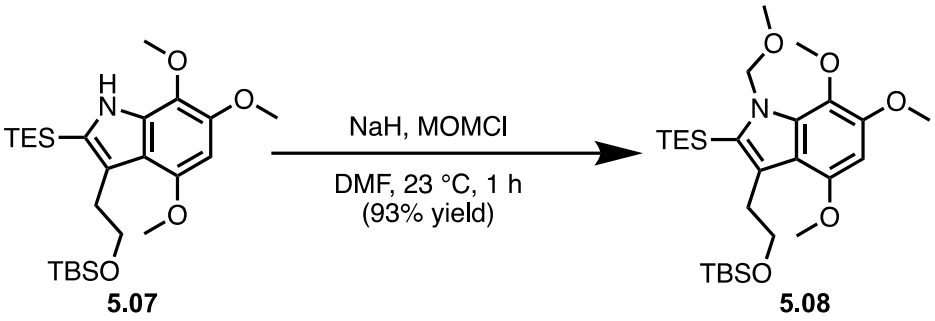
The C-3 carbon, bearing an allylic acetate, is in the desired oxidation state and the stereochemistry may be readily inverted to give that necessary for the natural product. As tested in Chapter Four, the indole is suited for oxidation and then converion to the pyrroloiminoquinone. Exploring the feasibility of *N*,*S*-acetal formation via Pummerer rearrangement on a derived dihydrothiophene-containing vinylogous amidine remains a significant future challenge. With these important synthetic lessons learned, it is hoped that a total synthesis of aleutianamine **5.01** may be completed.

5.2 Experimental

5.2.1 General

For general experimental information, see 1.2.1.

*MOM-Indole **5.08***

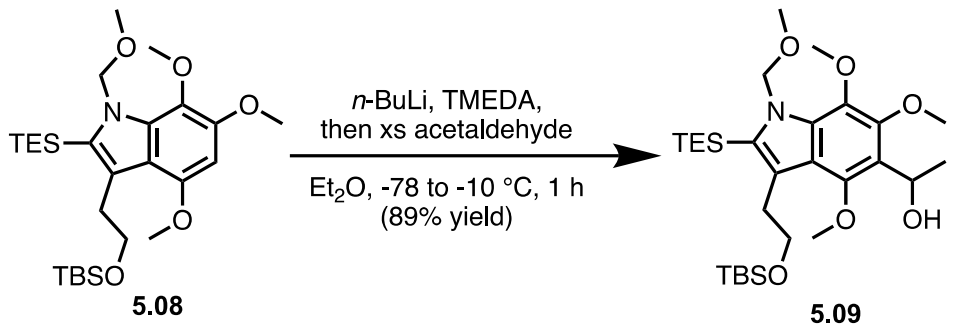


5.07 **5.08**

A flame-dried 100 mL round-bottom flask, with stir bar, was charged with **5.07** (2137. mg, 4.4539 mmol, 1 equiv). A septum was affixed to the top of the flask. A high vacuum (< 1 Torr) was pulled and then the flask was refilled with N_2; this process was repeated twice. Thereafter, **5.07** was dissolved in DMF (22 mL, 0.2 M). The reaction was submerged in an ice/water bath and allowed to cool for approximately 5 min. After the

allotted time, NaH (712.6 mg, 17.82 mmol, 4 equiv) was added and the solution stirred for 1h at which point MOMCl (1 mL, 13.17 mmol, 3 equiv) was added. The reaction was allowed to stir in the ice/water bath for an additional 10 min and then was raised and allowed to attain 23 °C. After stirring for 40 min at 23 °C the solution was submerged again in an ice/water bath the reaction was quenched with NH_4Cl (sat.). The aqueous was extracted 3 x Et_2O, and the combined organic extracts were washed 3 x DI water, 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 2.5 g of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and flushing with hexanes to remove mineral oil and then eluting with a step gradient of 5 to 10% EtOAc/hexanes. The yield for the reaction was 2179. mg **5.08** (4.159 mmol, 93% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 5.66 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.79-3.75 (m, 2H), 3.19 (s, 3H), 3.18-3.13 (m, 2H), 1.02-0.95 (m, 15H), 0.93 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 149.9, 149.1, 134.4, 133.7, 130.3, 125.6, 116.1, 90.3, 77.2 (MOM methylene overlaps with $CDCl_3$ central peak as determined by DEPT 135 analysis), 65.9, 60.7, 57.8, 55.4, 54.7, 31.2, 26.2, 18.6, 7.8, 4.9, -5.0. **IR** (thin film): cm^{-1} 2952 (m), 1609 (w), 1515 (m), 1462 (m), 1395 (w), 1343 (w), 1317 (w), 1251 (m), 1213 (m), 1147 (m), 1116 (m), 1077 (s), 1017 (m), 1002 (m), 979 (m), 959 (m), 934 (m), 909 (m), 834 (s), 774 (m), 730 (s), 603 (w). **HRMS** (ESI+): calculated for $C_{27}H_{49}NNaO_5Si_2^+$ $[M+Na]^+$ 546.3041, found: 546.3039. **TLC**: R_f = 0.28 (10% EtOAc/hexanes). **Physical Appearance**: Yellow oil.

*Benzylic Alcohol **5.09***

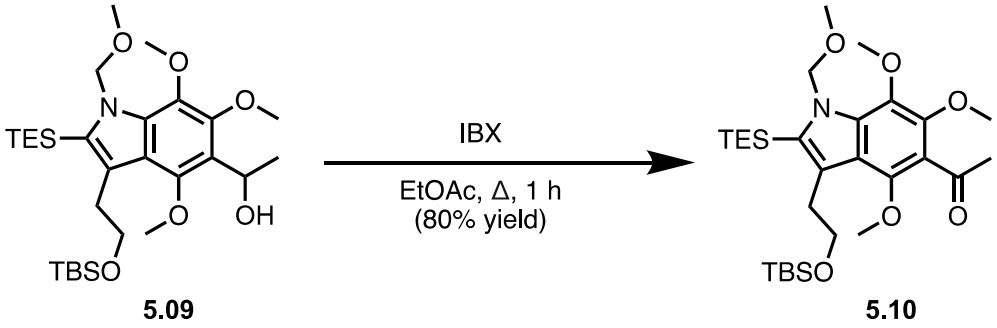


Prior to running the reaction, **5.08** was azeotropically dried from benzene 3 x by rotary evaporation and then held under a high vacuum (< 1 Torr) for 1 h in a 100 mL roundbottom flask, with stir bar, which had been flame-dried under the same high vacuum. After the allotted time **5.08** was placed under N_2.

Indole **5.08** (583.8 mg, 1.114 mmol, 1 equiv) was diluted in Et_2O (5 mL. 0.2 M) and TMEDA (180 μL, 1.20 mmol, 1.1 equiv). The solution was then cooled for approximately 10 min on a dry ice/acetone bath. A 2.5 M solution of *n*-BuLi in hexanes (490 μL, 1.23 mmol, 1.1 equiv) was added dropwise. The solution was stirred at the same temperature for 10 min and then transferred to an ice/water bath (0 °C). After stirring for 1 h at 0 °C the solution was cooled again to -78 °C. An excess of acetaldehyde (~ 1 mL) was added dropwise and the solution was allowed to stir at the same temperature for 45 min. The reaction was quenched with $NaHCO_3$ (sat.), and the aqueous was extracted 3 x Et_2O. The combined organic extracts were washed 1 x brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 651.2 mg of a crude product. Further purification was achieved by liquid loading the crude onto a flash column and eluting with a step gradient of 0 to 5 to 10 to 20 to 25% EtOAc/hexanes. The yield for the reaction was 563.2 mg **5.09**

(0.992 mmol, 89% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.66 (d, *J* = 9.6 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 5.28 (dq, *J* = 10.8, 6.7 Hz, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.81-3.65 (m, 3 H, overlapping alcohol and methylene signals; assessed by addition of D_2O to NMR sample), 3.24 (s, 3H), 3.09-3.05 (m, 2H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.02-0.95 (m, 15H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.1, 145.9, 136.6, 135.9, 133.4, 124.5, 123.4, 120.7, 77.4, 65.7, 65.1, 63.8, 61.2, 60.2, 54.8, 30.7, 26.2, 25.8, 18.5, 7.8, 5.0, -5.1, -5.1. **IR** (thin film): cm^{-1} 2952 (w), 1600 (w), 1473 (w), 1396 (w), 1362 (w), 1307 (w), 1254 (m), 1195 (w), 1166 (w), 1084 (s), 1009 (m), 973 (w), 912 (w), 836 (m), 776 (m), 732 (m). **HRMS** (ESI+): calculated for $C_{29}H_{53}NNaO_6Si_2^+$ $[M+Na]^+$ 590.3304, found: 590.3305. **TLC**: R_f = 0.3 (20% EtOAc/hexanes; stains purple/brown in Vanillin). **Physical Appearance**: Yellow oil.

*Ketone **5.10***

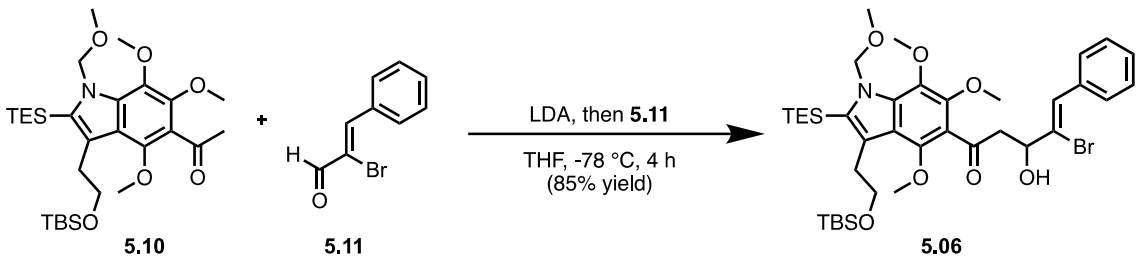


5.09 **5.10**

A flame-dried 50 mL round-bottom flask, with stir bar, was charged with **5.09** (563.2 mg, 3.172 mmol, 1 equiv) and was further diluted with EtOAc (10 mL, 01 M). IBX (contains >30% stabilizer, 1588.3 mg, 3.970 mmol, 4 equiv) was added to the reaction flask and a reflux condenser was affixed. The entire apparatus was placed under N_2 and the

solution was heated to reflux and maintained at this temperature 1 h. The solution was then allowed to cool to 23 °C and was filtered through a pad of packed Celite with EtOAc. The organic was washed with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1) and resulting aqueous layer was extracted 2x EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude product. Further purification was achieved by flash column chromatography eluting with a step gradient of 0 to 5 to 10% EtOAc/hexanes. The yield for the reaction was 446.9 mg **5.10** (0.7897 mmol, 80% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.63 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78-3.73 (m, 2H), 3.24 (s, 3H), 3.09-3.05 (m, 2H), 2.58 (s, 3H), 1.02-0.95 (m, 15H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 202.8, 146.3, 145.8, 136.7, 136.2, 134.5, 125.2, 123.3, 120.9, 77.4, 65.6, 64.2, 62.1, 60.7, 54.9, 33.0, 30.7, 26.2, 18.6, 7.8, 4.9, -5.1. **IR** (thin film): cm^{-1} 2953 (m), 2876 (m), 1703 (m), 1594 (w), 1473 (m), 1409 (w), 1372 (w), 1336 (w), 1308 (w), 1257 (m), 1198 (m), 1139 (w), 1087 (s), 1065 (m), 1012 (m), 967 (w), 837 (m), 776 (m), 733 (m). **HRMS** (ESI+): calculated for $C_{29}H_{51}NNaO_6Si_2^+$ $[M+Na]^+$ 588.3147, found: 588.3145. **TLC**: R_f = 0.26 (10% EtOAc/hexanes; stains purple in Vanillin). **Physical Appearance**: Yellow oil.

*Aldol Product **5.06***

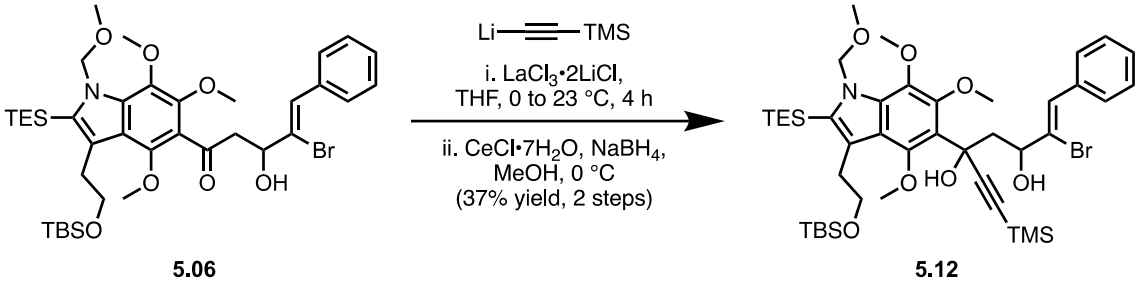


Prior to running the reaction, both **5.10** and α-bromocinnamaldehyde were azeotropically dried from benzene 3 x by rotary evaporation and then held under a high vacuum (< 1 Torr) for approximately 30 min in flasks which had been flame-dried under the same high vacuum with stir bars. After the allotted time the starting material was placed under N_2.

A 100 mL round-bottom flask, with stir bar, was flame-dried under a high vacuum (< 1 Torr) and then the flask was refilled with N_2 upon returning to room temperature (23 °C). Thereafter, THF (5 mL) was added, followed by diisopropylamine (0.872 mL, 6.18 mmol, 2 equiv). The solution was cooled for approximately 10 min on a dry ice/acetone bath. A 2.5 M solution of *n*-BuLi in hexanes (1.85 mL, 4.63 mmol, 1.5 equiv) was added dropwise. The solution was stirred at the same temperature for 1 h and 30 min at which point **5.10** (1.75 g, 3.09 mmol, 1 equiv), dissolved in 10 mL THF, was added dropwise followed by 2 x 3 mL THF washes. After stirring for 1 h and 30 min, α-bromocinnamaldehyde (783 mg, 3.71 mmol, 1.2 equiv) was added dropwise in mL THF followed by 2 x 1 mL THF washes. After stirring for 30 min, still in the dry ice/acetone bath, the reaction was quenched with $NaHCO_3$ (sat.). The aqueous was extracted 3 x Et_2O, and the combined organic extracts were washed 1 x brine, dried with $MgSO_4$, filtered and

concentrated *in vacuo* to afford a crude product. Further purification was achieved by liquid loading the crude onto a flash column and flushing with hexanes to remove mineral oil and then eluting with a step gradient of 0 to 5 to 10 to 20% EtOAc/hexanes. The yield for the reaction was 2.05 g **5.06** (2.64 mmol, 85% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.61 (apparent d, *J* = 7.3 Hz, 2H), 7.38-7.28 (m, 3H), 7.26 (s, 1H; overlaps with chloroform peak), 5.64 (apparent s, 2H), 4.98-4.94 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.78-3.74 (m, 2H), 3.68 (d, *J* = 4.2 Hz, 1H), 3.52 (dd, *J* = 17.5, 3.1 Hz, 1H), 3.30 (dd, *J* = 17.5, 8.8 Hz, 1H), 3.25 (s, 3H), 3.10-3.06 (m, 2H), 1.03-0.96 (m, 15H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.3, 146.5, 145.8, 137.1, 136.4, 135.4, 134.9, 129.3, 128.2, 128.2, 128.2, 127.5, 125.2, 122.3, 121.0, 77.4 (overlaps with $CDCl_3$), 73.8, 65.6, 64.7, 62.2, 60.7, 54.9, 51.0, 30.6, 26.2, 18.6, 7.8, 4.9, -5.1. **IR** (thin film): cm^{-1} 3454 (br), 2953 (m), 1696 (m), 1592 (m), 1472 (m), 1376 (m), 1336 (m), 1309 (m), 1256 (m), 1196 (m), 1169 (m), 1085 (s), 1005 (m), 967 (w), 836 (m), 777 (m), 735 (m), 695 (m), 599 (w). **HRMS** (ESI+): calculated for $C_{38}H_{58}BrNNaO_7Si_2^+$ $[M+Na]^+$ 798.2827, found: 798.2823. **TLC**: R_f = 0.27 (20% EtOAc/hexanes). **Physical Appearance**: Yellow oil.

*Tertiary Alcohol **5.12***



5.06 **5.12**

To a flame-dried 50 mL roundbottom flask, with stir bar, was added **5.06** (522.6 mg, 0.6726 mmol, 1 equiv) was dissolved in a 0.6 M solution of LaCl3•2LiCl in THF (2 mL, 1.2 mmol, 1.8 equiv) and was further diluted with THF (5 mL, total concentration 0.1M). The resulting solution was stirred for 1 hour at room temperature and then cooled in an ice/water bath.

In a separate flame-dried flask, with stir bar, lithium TMS acetylide was generated. THF (2.7 mL, 0.5 M) and TMS acetylene (240 μL, 1.686 mmol, 2.5 equiv) were added. The solution was submerged in a dry ice/acetone bath (-78 °C) and allowed to cool for 5 min. A 2.5 M solution of *n*-BuLi in hexanes (540 μL, 1.35 mmol, 2 equiv) was added dropwise and the solution was allowed to stir for 15 min. Thereafter the solution was transferred to an ice/water bath (0 °C) and allowed to stir for 30 min. The original solution containing **5.06** was also cooled to 0 °C. The solution of lithium TMS acetylide was transferred via cannula onto 5.06 and the solution was stirred at 0 °C for 15 min. The solution was then raised out of the cooling bath and stirred at 23 °C for 40.

Upon complete consumption of starting material, as judged by TLC analysis, the reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 3 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$,

filtered and concentrated *in vacuo* to afford 0.2 g of a crude product. The crude was used directly in the next reaction to remove **5.13** which had formed as a chromatographically inseparable byproduct.

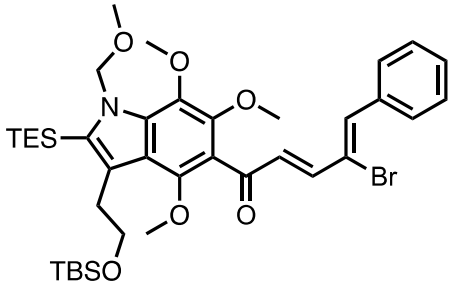
Assuming a theoretical yield in the first reaction, the crude was dilute with MeOH (1.3 mL, 0.5 M). $CeCl_3 \bullet 7H_2O$ (376.4 mg, 1.010 mmol, 1.5 equiv) was then added and the resulting solution was cooled in an ice/water bath (0 °C). $NaBH_4$ (40.5 mg, 1.071 mmol, 1.6 equiv) was added as a single portion and the solution was stirred for approximately 30 min. While still in the ice/water bath, the reaction was quenched with NH_4Cl (sat.). The aqueous was extracted 2 x Et_2O and 1 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford 0.3 g of a crude product which could be further purified by flash column chromatography. The column was first saturated with 2% Et_3N/hexanes and then the crude product was liquid loaded. The desired compound eluted with a step gradient of 0 to 5 to 10 to 15% EtOAc/hexanes. The yield for the reaction was 215.1 mg **5.12** (0.2458 mmol, 37% yield).

Characterized as a mixture of diastereomers:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.61-7.59 (m, 1.2H), 7.38-7.27 (m, 6H), 7.19 (brs, 0.6H), 5.62 (s, 3H), 5.14 (d, *J* = 9.2 Hz, 1H), 4.93 (apparent s, 4.93H), 4.54 (brm, 0.7H), 4.03 (s, 3H), 3.98 (s, 3H), 3.93 (s, 4H), 3.89 (s, 3H), 3.86-3.60 (m, 3.47H), 3.31 (s, 2.5H), 3.27 (s, 3H), 3.12-3.01 (m, 3H), 2.53 (dd, *J* = 14.4, 9.9 Hz, 0.69H), 2.31 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.02-0.99 (m, 20H), 0.87 (s, 9H), 0.87 (s, 4H), 0.19, (s, 9H), 0.13 (s, 4H), 0.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ A ^{13}C showing all of the carbons for both diastereomers was not obtained. The obtained data is listed here. 147.4, 146.1, 137.6, 137.3, 137.0, 136.8, 136.0, 136.0, 133.6, 130.1, 129.7, 129.6, 129.4, 129.3, 129.3,

128.4, 128.2, 128.1, 128.1, 127.8, 127.7, 127.3, 127.0, 124.5, 121.7, 120.9, 120.7, 120.0, 110.4, 109.1, 89.1, 88.4, 77.5, 77.4, 76.2, 75.6, 73.4, 72.4, 65.7, 65.6, 64.1, 63.8, 61.3, 60.5, 60.3, 54.9, 54.9, 47.9, 47.3, 30.8, 26.2, 26.1, 18.5, 18.5, 7.8, 7.8, 5.1, 5.0, 0.0, -0.1, -5.0, -5.1, -5.1, -5.1. **IR** (thin film): cm^{-1} 3422 (br), 2954 (s), 1596 (w), 1471 (m), 1447 (m), 1412 (m), 1329 (w), 1296 (w), 1251 (s), 1196 (w), 1162 (w), 1085 (s), 1007 (m), 963 (w), 916 (w), 842 (s), 777 (m), 757 (m), 735 (m), 695 (m), 599 (w), 541 (w), 424 (w). **HRMS** (ESI+): calculated for $C_{43}H_{68}BrNNaO_7Si_3^+$ $[M+Na]^+$ 896.3379, found: 896.3378. **TLC**: R_f = 0.44 (20% EtOAc/hexanes; stains purple in Vanillin). **Physical Appearance**: pale yellow foam.

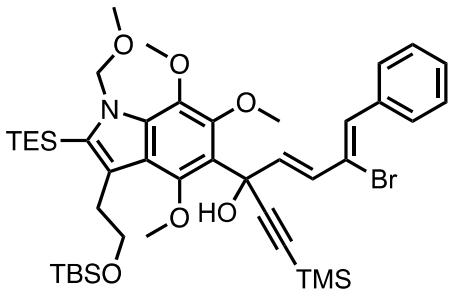
The following two compounds were identified by-products from a number of different reactions. As such, yields were not taken but the identity of these compounds were ascertained through complete characterization.



5.13

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.42-7.36 (m, 3H), 7.28 (apparent d, *J* = 14.6 Hz, 1H; overlaps with $CHCl_3$ peak), 7.25 (s, 1H), 7.04 (apparent d, *J* = 14.6 Hz, 1H), 5.66 (s, 2H), 3.98 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.80-3.76 (m, 2H), 3.29 (s, 3H), 3.12-3.08 (m, 2H), 1.04-0.97 (m, 15H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.8, 147.3, 146.7, 144.7, 139.6, 136.6, 136.2, 135.0, 134.7, 133.4, 130.2, 129.6, 128.5, 125.4, 121.2, 121.0, 120.9, 77.5 (overlaps with $CDCl_3$ peak; see DEPT 135

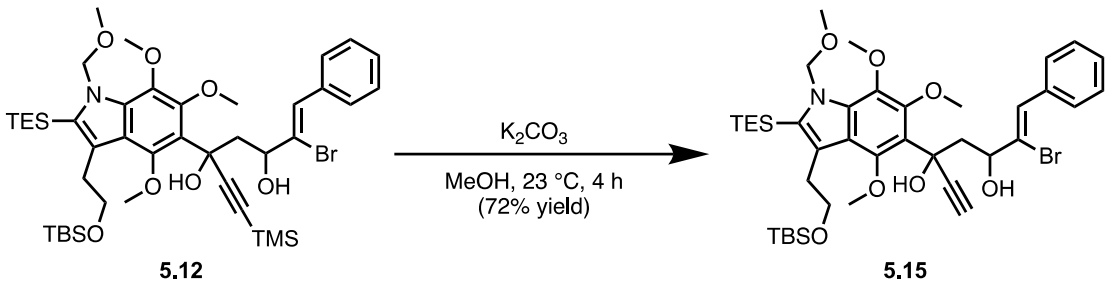
spectrum), 65.7, 63.9, 62.1, 60.7, 54.9, 30.7, 26.2, 18.6, 7.8, 4.9, -5.1. **IR** (thin film): cm^{-1} 2931 (m), 2875 (m), 2855 (m), 1650 (m), 1587 (s), 1471 (s), 1447 (m), 1409 (w), 1371 (m), 1334 (w), 1308 (m), 1256 (s), 1195 (m), 1144 (m), 1081 (s), 1007 (s), 960 (s), 908 (m), 835 (s), 775 (s), 755 (m), 731 (s), 691 (s), 593 (w), 515 (w). **HRMS** (ESI+): calculated for $C_{38}H_{56}BrNNaO_6Si_2^+$ $[M+Na]^+$ 780.2722, found: 780.2719. **TLC**: R_f = 0.19 (20% EtOAc/hexanes; visibly yellow on TLC plate). **Physical Appearance**: yellow/orange oil.



5.14

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.40-7.36 (m, 3H), 7.33-7.28 (m, 1H), 7.04 (s, 1H), 6.92 (d, *J* = 14.6 Hz, 1H), 6.87 (d, *J* = 14.5 Hz, 1H), 6.47 (s, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 5.59 (d, *J* = 9.6 Hz, 1H), 4.06 (s, 3H), 3.95 (s, 3H), 3.87-3.79 (m, 1H), 3.73 (s, 3H), 3.64-3.52 (m, 1H), 3.28 (s, 3H), 3.06 (t, *J* = 8.0 Hz, 2H) 1.03-0.97 (m, 15H), 0.89 (s, 9H), 0.20 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.8, 146.2, 138.1, 137.1, 136.5, 136.2, 133.6, 131.4, 129.7, 128.2, 128.1, 127.8, 124.9, 123.4, 122.7, 121.0, 108.7, 89.8, 77.4 (partial overlap with $CDCl_3$ peak), 70.4, 65.7, 63.6, 61.3, 60.3, 54.9, 30.8, 26.2, 18.6, 7.8, 5.0, 0.1, -5.0, -5.0. **IR** (thin film): cm^{-1} 2953 (m), 1596 (w), 1471 (m), 1330, (w), 1291 (w), 1250 (s), 1195 (w), 1163 (w), 1083 (s), 1004 (s), 957 (w), 911 (w), 838 (s), 776 (m), 733 (s), 694 (m). **HRMS** (ESI+): calculated for $C_{43}H_{66}BrNNaO_6Si_3^+$ $[M+Na]^+$ 878.3274, found: 878.3271. **TLC**: R_f = 0.53 (20% EtOAc/hexanes). **Physical Appearance**: Pale yellow foam.

*Tertiary Alcohol **5.15***



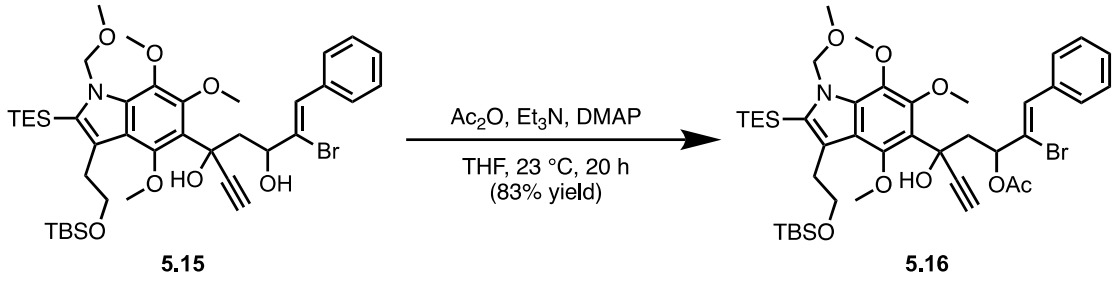
5.12 **5.15**

The diol (**5.12**, 670 mg, 0.766 mmol, 1 equiv) was dissolved in MeOH (7mL, 0.1 M). Thereafter, K_2CO_3 (0.32 g, 2.32 mmol, 3.0 equiv) was added and the solution was stirred until complete consumption of **5.12** was observed by TLC (the length of the reaction varied tremendously with concentration of **5.12** in MeOH; shorter reaction times were observed with greater concentration). Thereafter, the solution was quenched with DI waster and the aqueous was extracted 3 x EtOAc; occasionally solid NaCl was added to break up emulsions that formed. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. The crude was further purified by flash column chromatography eluting over a step gradient of 0 to 5 to 10 to 20% EtOAc/hexanes. The yield for this reaction was 440 mg **5.15** (0.548 mmol, 72% yield). Characterized as a mixture of diastereomers:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.61-7.58 (m, 2.7H), 7.38-7.27 (m, 6.3H), 7.20 (br s, 0.7H), 5.69-5.60 (m, 3.5H), 5.15 (apparent d, *J* = 9.4 Hz, 1H), 4.99 (s, 1H), 4.82 (s, 0.7H), 4.54 (br m, 0.8H), 4.03 (s, 3H), 4.01 (s, 2H), 3.97 (s, 3H), 3.95 (s, 2H), 3.93 (s, 3H), 3.91 (s, 2H), 3.85-3.61 (br m, 3.9H), 3.37-3.33 (br m, 0.9H), 3.29 (s, 2H), 3.26 (s, 3H), 3.24-3.02 (m, 4.9H), 2.78 (s, 1H), 2.71 (s, 0.8H), 2.57 (dd, *J* = 14.6, 9.8 Hz, 0.8H), 2.31 (dd, *J* = 14.4, 9.7 Hz, 1H), 1.05-0.97 (m, 27.8H), 0.90-0.88 (m, 16.2H), 0.04

(s, 6H), 0.02 (s, 2H), 0.01 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ A ^{13}C showing all of the carbons for both diastereomers was not obtained. The obtained data is listed here. 147.2, 146.4, 146.0, 137.6, 137.3, 137.0, 136.9, 135.9, 135.8, 133.8, 129.5, 129.3, 129.3, 129.2, 128.1, 128.1, 127.9, 127.8, 127.4, 127.3, 124.3, 121.0, 120.8, 120.5, 119.3, 88.9, 87.3, 77.4, 77.3, 76.1, 75.5, 73.4, 73.0, 72.3, 65.7, 65.6, 64.5, 64.0, 61.2, 61.0, 60.4, 60.2, 54.9, 54.9, 47.9, 47.2, 30.8, 29.8, 26.1, 26.1, 18.5, 18.5, 7.8, 7.8, 5.0, 5.0, -5.0, -5.1, -5.1. **IR** (thin film): cm^{-1} 3305 (w), 2952 (m), 1596 (w), 1470 (m), 1411 (m), 1329 (w), 1297 (w), 1254 (m), 1196 (w), 1162 (w), 1083 (s), 1005 (m), 962 (w), 916 (w), 836 (m), 777 (w), 734 (m), 695 (m), 600 (w). **HRMS** (ESI+): calculated for $C_{40}H_{60}BrNNaO_7Si_2^+$ $[M+Na]^+$ 824.2984, found: 824.2980. **TLC**: R_f = 0.11 (5, then 10% EtOAc/hexanes). **Physical Appearance**: White foam.

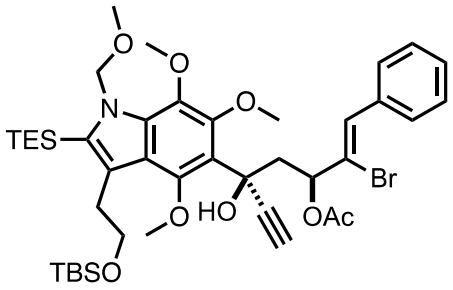
Diastereomers of Acetate **5.16** (**Major Diastereomer 5.16a & SI-5.16-Minor**)



5.15 **5.16**

The starting material (**5.15**, 158.1 mg, 0.1969 mmol, 1 equiv) and DMAP (3.4 mg, 0.028 mmol, 0.1 equiv) were placed under an inert atmosphere through a backfilling process. The mixture was dissolved in CH_2Cl_2 (3 mL, 0.07 M) and cooled in an ice/water bath. Thereafter, Et_3N (40 μL, 0.28 mmol, 1.5 equiv) and acetic anhydride (20 μL, 0.21 mmol, 1.1 equiv) were added sequentially. After addition of the acetic anhydride, the

solution was warmed to room temperature (23 °C) by raising out of the cooling bath. Upon complete consumption of starting material, as judged by TLC analysis, the reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 3 x Et_2O. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. The crude was further purified by flash column chromatography eluting over a gradient of hexanes to 10% to 20% EtOAc/hexanes. The yield for this reaction was 138.5 mg **5.16** (0.1639 mmol, 83% yield).

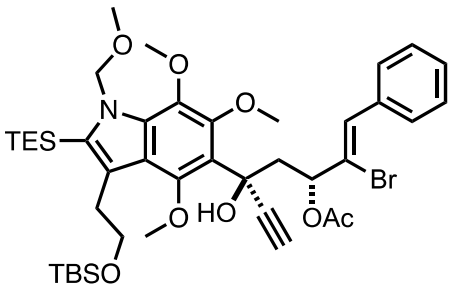


5.16a

5.16a major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63-7.60 (m, 2H), 7.36-7.28 (m, 3H), 7.13 (apparent s, 2H), 6.01 (dd, *J* = 7.6, 3.9 Hz, 2H), 5.66 (d, *J* = 9.6 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.83-3.57 (br m, 2H), 3.23 (s, 3H), 3.08-3.01 (m, 3H), 2.89 (dd, *J* = 14.5, 3.8 Hz, 1H), 2.61 (s, 1H), 1.66 (s, 3H), 1.00-0.97 (m, 15H), 0.90 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 147.5, 146.4, 137.2, 136.6, 135.3, 133.7, 130.7, 129.4, 128.2, 128.2, 125.8, 124.3, 120.5, 120.4, 88.8, 77.4, 75.4, 71.5, 70.7, 65.6, 64.7, 61.2, 60.2, 54.9, 46.0, 30.9, 26.2, 20.9, 18.5, 7.8, 5.0, -5.0. **IR** (thin film): cm^{-1} 3403 (br), 3307 (w), 2952 (w), 2876 (w), 1741 (s), 1596 (w), 1470 (m), 1447 (m), 1393 (m), 1328 (m), 1290 (m), 1228 (s), 1196 (m), 1162 (m), 1080 (s), 1045 (s), 1003 (s), 958 (m), 910 (m), 835 (s), 776 (m), 753 (m), 730 (s), 694 (s), 648 (m), 601 (w), 564 (w), 520

(w). **HRMS** (ESI+): calculated for $C_{42}H_{62}BrNNaO_8Si_2^+$ $[M+Na]^+$ 866.3090, found: 866.3084. **TLC**: R_f = 0.39 (20% EtOAc/hexanes). **Physical Appearance**: Pale yellow oil.

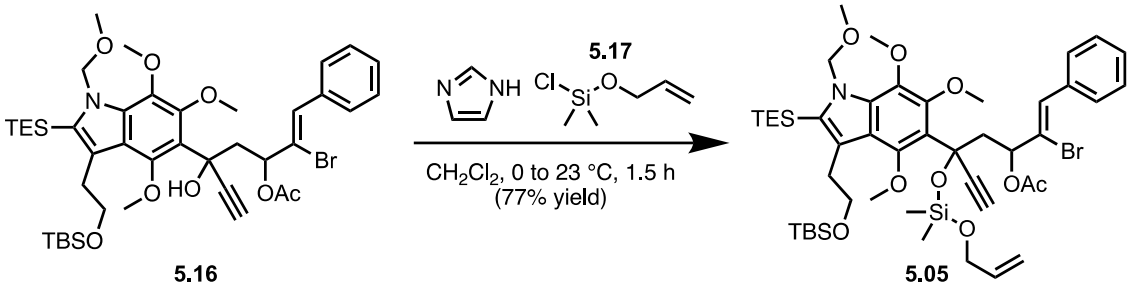


5.16b

5.15b minor diastereomer:

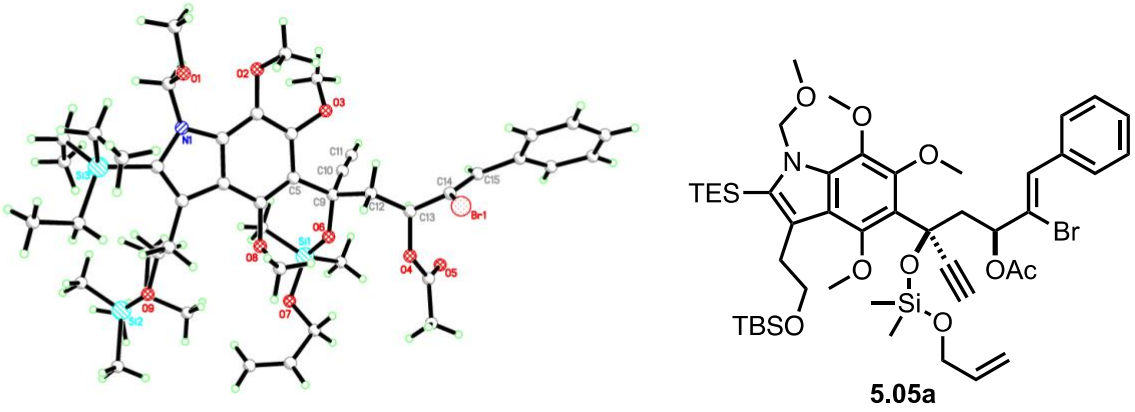
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 6.9 Hz, 2H), 7.32-7.28 (m, 3H), 7.06, (s, 1H), 6.93 (br s, 1H), 6.01 (br m, 1H), 5.64 (d, *J* = 9.7 Hz, 1H), 5.59 (d, *J* = 9.7 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.73-3.62 (br m, 2H), 3.23 (s, 3H), 3.13-3.03 (m, 3H) 2.75 (apparent d, *J* = 14.2 Hz, 1H), 2.61(s, 1H), 2.11 (s, 3H), 1.01-0.97 (m, 15H), 0.88 (s, 9H), 0.03 (6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.9 147.4, 146.3, 137.3, 136.7, 135.2, 133.8, 130.3, 129.3, 128.2, 128.1, 126.0, 124.3, 121.1, 120.5, 88.8, 77.3 (overlaps with $CDCl_3$), 75.3, 71.1, 70.2, 65.6, 64.6, 61.0, 60.1, 54.9, 46.7, 30.9, 26.2, 21.5, 18.5, 7.8, 5.0, -5.1. **IR** (thin film): cm^{-1} 3406 (br), 3306 (w), 2952 (w), 1742 (s), 1596 (w), 1470 (m), 1447 (w), 1371 (m), 1328 (m), 1291 (w), 1230 (s), 1196 (m), 1162 (m), 1081 (s), 1045 (s), 1004 (s), 960 (m), 909 (m), 834 (s), 776 (s), 729 (s), 694 (s), 647 (m), 594 (w), 564 (w), 519 (w). **HRMS** (ESI+): calculated for $C_{42}H_{62}BrNNaO_8Si_2^+$ $[M+Na]^+$ 866.3090, found: 866.3083. **TLC**: R_f = 0.35 (20% EtOAc/hexanes). **Physical Appearance**: Pale yellow oil.

Diastereomers of Silyl Tether ***5.05 (Major Diastereomer 5.05a & Minor Diastereomer 5.05b)***



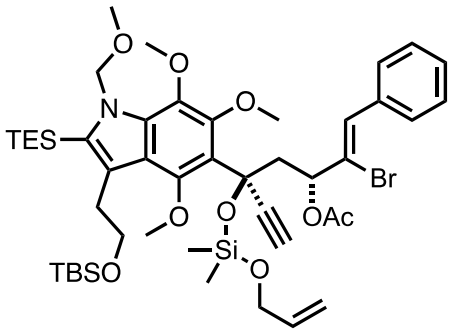
A flame-dried 10 mL flask, with stir bar, was charged with imidazole (129 mg, 1.89 mmol, 4.0 equiv). A high vacuum (< 1 Torr) was pulled and then the flask was refilled with N_2; this process was repeated twice. Thereafter, **5.17** (151μL, d = 0.953 g/mL, 0.956 mmol, 2.0 equiv) was added neat and the mixture was stirred for 30 min. During the neat mixing of imidazole and **5.17**, a gas was formed which was vented by puncturing the septum with a needle and affixing an Ar balloon for positive pressure. After the venting was complete (~5 min) the flask was again placed under N_2. After the allotted time the neat mixture was diluted with 0.5 mL CH_2Cl_2 and was allowed to stir for a further 5 min. The starting tertiary alcohol (**5.16**, 405 mg, 0.479 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1 mL, 0.3 M) and added to the solution of imidazole and **5.17**. Upon complete consumption of starting material, as judged by TLC analysis, the reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 3 x CH_2Cl_2. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. The crude was further purified by flash column chromatography eluting over an isocratic solvent system of (hexanes/EtOAc/Et3N 90:6:4) to 10% to 20% EtOAc/hexanes. The yield for this reaction was 355 mg **5.05** (0.370 mmol, 77% yield). When rendering the

two diastereomers with relative stereochemistry, the major diastereomer was called **5.05a** and the minor diastereomer is called **5.05b**.



5.05a major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.61-7.59 (m, 2H), 7.36-7.28 (m, 3H), 7.13 (s, 1H), 5.98-5.88 (m, 2H; overlapping aliphatic and vinyl methines), 5.69 (d, *J* = 9.6 Hz, 1H), 5.53 (d, *J* = 9.5 Hz, 1H), 5.29-5.23 (m, 1H), 5.07-5.03 (m, 1H), 4.38-4.27 (m, 2H), 3.93 (s, 1H), 3.91-3.89 (m, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.59-3.47 (brm, 1H), 3.25 (s, 3H), 3.16-2.98 (m, 2H), 2.92 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.82-2.77 (m, 1H), 2.70 (s, 1H), 1.93 (s, 3H), 1.03-0.96 (m, 15H), 0.90 (s, 9H), 0.28 (s, 3H), 0.25 (s, 3H) 0.05 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.7, 147.7, 147.1, 137.6, 136.7, 135.5, 135.2, 133.6, 130.4, 129.4, 128.3, 128.2, 125.8, 125.2, 121.3, 121.1, 114.1, 88.0, 77.4, 76.2, 73.0, 72.1, 65.9, 63.8, 63.7, 60.7, 59.7, 54.8, 48.1, 30.9, 26.2, 21.2, 18.5, 7.8, 5.0, -0.8, -0.8, -5.0, -5.1. **IR** (thin film): cm^{-1} 2953 (m), 1743 (s), 1593 (w), 1468 (s), 1405 (w), 1370 (w), 1329 (w), 1289 (w), 1252 (s), 1229 (s), 1164 (w), 1080 (s), 939 (w), 914 (w), 892 (w), 835 (s), 797 (s), 776 (s), 731 (s), 694 (s), 603 (w), 519 (w). **HRMS** (ESI+): calculated for $C_{47}H_{72}BrNNaO_9Si_3^+$ $[M+Na]^+$ 980.3590, found: 980.3586. **TLC**: R_f = 0.53 (20% EtOAc/hexanes). **Physical Appearance**: White Solid. **Melting Point**: 119-120 °C.

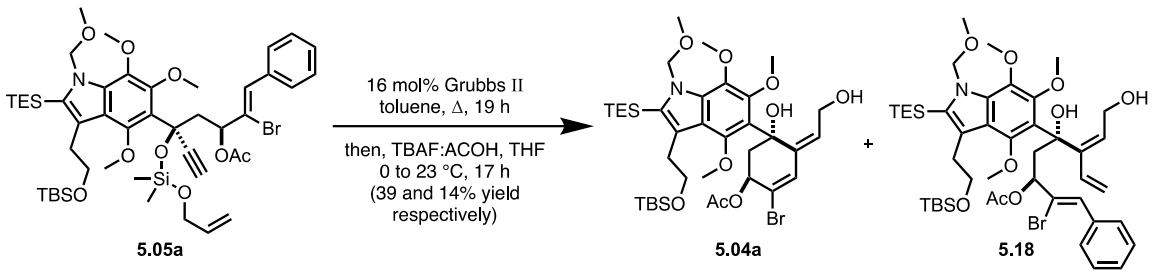


5.05b

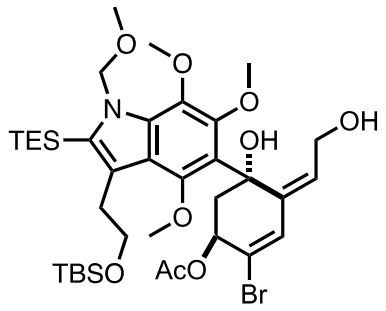
5.05b minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 2H), 7.35-7.27 (m, 3H), 7.09 (s, 1H), 6.01 (dd, *J* = 7.0, 3.0 Hz, 1H), 5.98-5.89 (m, 1H; overlaps with aliphatic methine), 5.68 (d, *J* = 9.5 Hz, 1H), 5.55 (d, *J* = 9.5 Hz, 1H), 5.28-5.23 (m, 1H), 5.07-5.03 (m, 1H), 4.34-4.32 (m, 2H), 3.94 (s, 3H), 3.91-3.88 (br m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.62-3.51 (br m, 1H), 3.25 (s, 3H), 3.15-2.98 (m, 3H), 2.69 (s, 1H), 2.69-2.61 (br m, 1H; overlaps with acetylene proton), 1.97 (s, 3H), 1.03-0.95 (m, 15H), 0.90 (s, 9H), 0.24 (s, 6H), 0.05 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.8, 147.7, 147.3, 137.6, 136.6, 135.5, 135.2, 135.2, 133.7, 129.9, 129.4, 128.3, 128.2, 125.9, 125.2, 121.3, 121.2, 114.1, 87.9, 77.4 (MOM methylene overlaps with $CDCl_3$), 75.7, 72.6, 71.8, 65.9, 63.9, 63.8, 60.7, 59.7, 54.8, 48.4, 30.9, 26.2, 21.3, 18.5, 7.8, 5.0, -0.8, -0.8, -5.0, -5.1. **IR** (thin film): cm^{-1} 2953 (m), 1744 (s), 1593 (w), 1468 (s), 1405 (w), 1370 (w), 1329 (w), 1288 (w), 1253 (s), 1228 (s), 1165 (m), 1081 (s), 974 (m), 914 (m), 893 (m), 835 (s), 798 (s), 776 (s), 731 (s), 694 (s), 603 (w), 521 (w). **HRMS** (ESI+): calculated for $C_{47}H_{72}BrNNaO_9Si_3^+$ $[M+Na]^+$ 980.3590, found: 980.3593. **TLC**: R_f = 0.43 (20% EtOAc/hexanes). **Physical Appearance**: Amorphous white solid.

*Tandem Metathesis Product **5.19** and Enyne Metathesis Product **5.20***

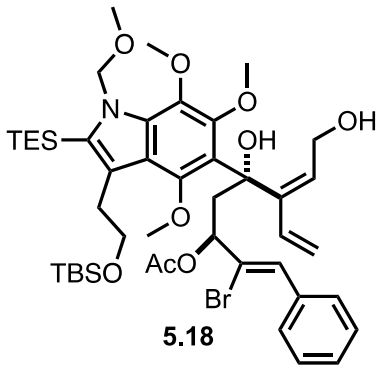


A flame-dried 10 mL roundbottom flask, with stir bar, was charged with silylene **5.05a** (96.4 mg, 0.100 mmol, 1 equiv) and toluene. The resulting solution was sparged for 15 min with Ar. The septum was removed and Grubbs II catalyst (13.8 mg, 0.0163 mmol, 0.16 equiv) was added. The solution was again sparged for 15 min with Ar and then heated to reflux in an aluminum block. The reflux was maintained for 19 h. After the allotted time, the solution was allowed to cool to room temperature (rt, 23 °C) and then cooled in an ice/water bath. A buffered solution of TBAF:AcOH (1:1, 0.4M in THF, 380 μL, 0.151 mmol, 1.5 equiv) was added dropwise. After stirring for 30 min in the ice/water bath, the solution was allowed to warm to rt and stirred for 17 h. The reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 3 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product (124.0 mg). The crude was further purified by flash column chromatography eluting over a step-gradient of hexanes to 10% to 20% EtOAc/hexanes. The yield for this reaction was 31.6 mg **5.04a** (0.395 mmol, 39% yield). Another identified product of the reaction is **5.18** (12.9 mg, 0.0143 mmol, 14% yield).



5.04a

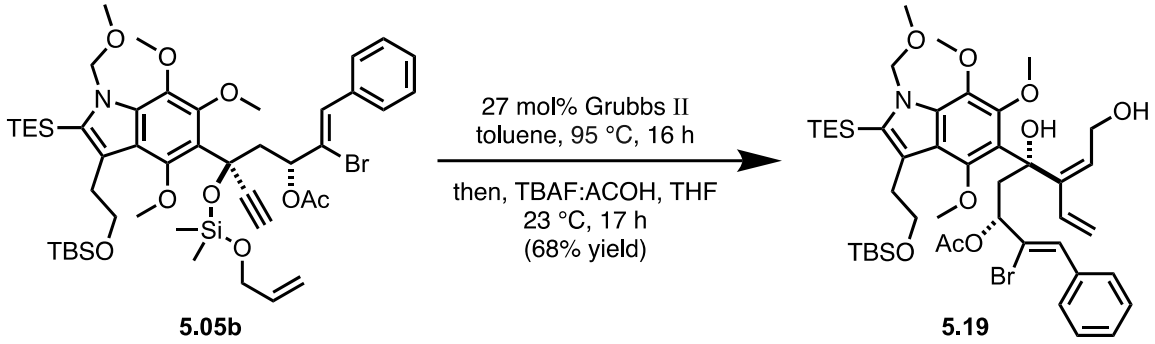
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.64 (apparent s, 1H), 5.90-5.86 (m, 1H), 5.66 (d, *J* = 9.6 Hz, 1H), 5.59-5.56 (m, 1H), 5.52 (d, *J* = 9.6 Hz, 1H), 3.92 (apparent s, 4H; overlapping with diastereotopic methylene proton), 3.81 (s, 3H), 3.78 (br m, 1H; one of the protons of diasterotopic methylene; determined by HSQC with methylene carbon [as determined by DEPT 135]), 3.74 (s, 3H), 3.57 (br m, 2H; 2 overlapping methylene protons from different carbons [HSQC]), 3.23 (s, 3H), 3.10-3.02 (br m, 2H), 2.57-2.51 (br m, 1H), 2.40 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.11 (s, 3H), 1.01-0.99 (m, 15H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.1, 146.4, 145.9, 143.2, 137.1, 136.9, 134.7, 133.9, 129.8, 123.8, 122.9, 122.5, 120.1, 77.5 (overlaps with $CDCl_3$; see DEPT 90 and DEPT 135), 74.9, 68.5, 65.7, 65.1, 60.2, 59.7, 58.7, 54.9, 45.7, 30.8, 26.2, 21.2, 18.6, 7.8, 5.0, -5.1, -5.1. **IR** (thin film): cm^{-1} 3433 (br), 2953 (s), 2935 (s), 2876 (m), 2856 (m), 1742 (s), 1596 (w), 1471 (m), 1397 (m), 1370 (m), 1328 (w), 1293 (w), 1233 (s), 1197 (w), 1164 (w), 1083 (s), 1050 (s), 1004 (s), 960 (m), 936 (w), 910 (w), 837 (s), 777 (m), 732 (s), 704 (w), 604 (w), 452 (w). **HRMS** (ESI+): calculated for $C_{37}H_{60}BrNNaO_9Si_2^+$ $[M+Na]^+$ 820.2882, found: 820.2876. **TLC**: R_f = 0.13 (20% EtOAc/hexanes). **Physical Appearance**: Orange oil.



5.18

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.62-7.60 (m, 2H), 7.36-7.32 (m, 2H), 7.30-7.27 (m, 1H), 7.08 (s, 1H), 6.49-6.43 (m, 1H), 5.98 (t, *J* = 6.9 Hz, 1H), 5.77-5.75 (m, 1H), 5.61 (s, 2H), 5.45 (d, *J* = 17 Hz, 1H), 5.00 (d, *J* = 10.7 Hz, 1H), 4.49 (dd, *J* = 13.3, 7.1 Hz, 1H), 4.08 (dd, *J* = 13.9, 6.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.74-3.68 (br m, 2H), 3.25 (s, 3H), 3.08 (d, *J* = 8.2 Hz, 2H) 2.84 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.76 (br m, 1H), 1.75 (s, 3H), 1.02-0.99 (m, 15H), 0.90 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 170.1, 147.6 (assigned by HMBC correlation with terminal olefinic doublets), 147.4, 146.4, 138.6, 136.8, 136.8, 135.1, 133.8, 130.4, 129.4, 128.3, 128.2, 127.9, 126.1, 123.9, 123.6, 120.5, 115.4, 79.8, 77.4, 75.7, 65.8, 64.0, 60.8, 59.9, 59.2, 54.9, 45.0, 30.9, 26.2, 21.0, 18.6, 7.8, 5.0, -5.1. **IR** (thin film): cm^{-1} 3433 (br), 2953 (m), 1742 (m), 1596 (w), 1467 (m), 1371 (w), 1327 (w), 1289 (w), 1232 (s), 1162 (w), 1083 (s), 1004 (m), 969 (w), 913 (w), 836 (m), 777 (m), 733 (m), 696 (m). **HRMS** (ESI+): calculated for $C_{45}H_{68}BrNNaO_9Si_2^+$ $[M+Na]^+$ 924.3508, found: 924.3506. **TLC**: R_f = 0.31 (40% EtOAc/hexanes). **Physical Appearance**: brown oil.

*Enyne Metathesis Product **5.19***



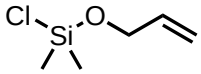
A flame-dried 100 mL roundbottom flask, with stir bar, was charged with silylene **5.05b** (50. mg, 0.052 mmol, 1 equiv) and toluene (11.4 mL, 0.005 M). The resulting solution was sparged for 15 min with Ar. The septum was removed and Grubbs II catalyst (12 mg, 0.014 mmol, 0.27 equiv) was added. The solution was again sparged for 15 min with Ar and then heated to reflux in an aluminum block. The reaction was heated to 95 °C and maintained at that temperature for 16 h. After the allotted time, the solution was allowed to cool to room temperature (rt, 23 °C). A buffered solution of TBAF:AcOH (1:1, 1 M in THF, 50 μL, 0.052 mmol, 1.0 equiv) was added dropwise. After stirring for 2 h the reaction was then quenched by the addition of $NaHCO_3$ (sat.) and the aqueous layer was extracted 2 x EtOAc. The combined organic was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude product. The crude was further purified by flash column chromatography eluting at 40% EtOAc/hexanes. The yield for this reaction was 32 mg **5.19** (0.035 mmol, 68% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.34-7.27 (m, 3H), 7.04 (s, 1H), 6.36 (dd, *J* = 17.0, 10.8 Hz, 1H), 5.98 (br s, 1H), 5.90-5.84 (m, 2H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.35 (dd, *J* = 17.0, 1.4 Hz, 1H) 4.91 (dd, *J* = 10.8, 1.3 Hz, 1H), 4.90 (br m, 1; overlaps with one of the terminal

olefin protons), 4.18 (dd, *J* = 14.3, 5.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.78-3.69 (br m, 1H), 3.51 (br m, 1H), 3.28 (br m, 1H), 3.23 (s, 3H), 3.07 (t, *J* = 8.2 Hz, 2H), 2.63 (apparent d, *J* = 14.6 Hz, 1H), 2.05 (s, 3H), 1.03-0.96 (m, 15H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.9, 147.5, 146.6, 145.8 (assigned by HMBC correlation with both geminal ^{1}H signals of the terminal olefin), 138.1, 137.1, 136.8, 135.0, 133.9, 130.4, 129.4, 128.3, 128.2, 127.1, 126.2, 124.1, 123.9, 120.6, 114.5, 80.3, 77.4, 75.7, 65.8, 64.0, 60.7, 60.0, 59.9, 54.9, 45.0, 31.0, 26.2, 21.5, 18.6, 7.9, 5.1, -5.1, -5.1. **IR** (thin film): cm^{-1} 3453 (br), 2930 (m), 1740 (m), 1594 (w), 1465 (m), 1373 (m), 1327 (w), 1288 (w), 1234 (s), 1160 (w), 1083 (s), 1046 (s), 1004 (m), 968 (m), 911 (m), 836 (m), 777 (m), 732 (s), 695 (m). **HRMS** (ESI+): calculated for $C_{45}H_{68}BrNNaO_9Si_2^+$ $[M+Na]^+$ 924.3508, found: 924.3510. **TLC**: R_f = 0.12 (20% EtOAc/hexanes). **Physical Appearance**: Pale brown foam.

[1] Nishiyama, T.; Choshi, T.; Kitano, K.; Hibino, S. *Tetrahedron Lett.* **2011**, *52*, 3876-3878.

[2] a) Fujioka, H.; Kubo, O.; Senami, K.; Minamitsuji, Y.; Maegawa, T. *Chem. Commun.*, **2009**, 4429-4431. b) Application to indoles: Goto, T.; Natori, Y.; Takeda, K.; Nambu, H.; Hashimoto, S. *Tetrahedron: Asymmetry* **2011**, *22*, 907-915.

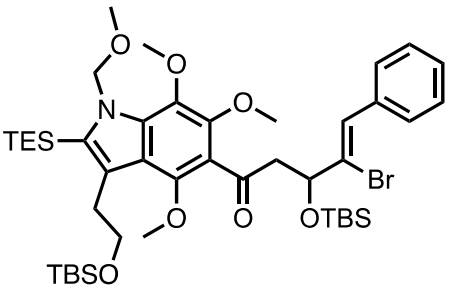
[3] Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. *Angew. Chem. Int. Ed.* **2006**, *45*, 5859-5863. We used the dimethylalkoxychlorosilane (**5.17**) as opposed to the diethyl variant employed by Movassaghi. Alkoxysilane **5.17** was first reported by Krolevets, A. A. (*Zhurnal Obschchei Khimii*, **1988**, *58*, 2274-2281) and may be prepared through the same procedure described by Movassaghi (who also references Krolevets).



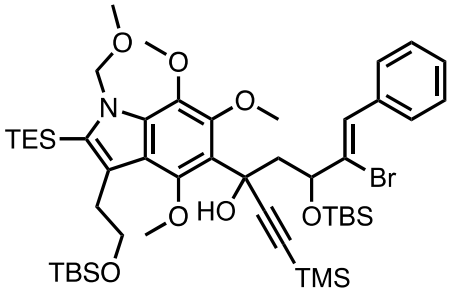
5.17

[4] More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001-3003.

[5] Though not fully delineated, we were able to advance TBS-protected secondary alcohol to the acetylide addition step (**v.06**). Capricious reactivity was observed when this transformation was performed with additives such as $CeCl_3$ and $LaCl_3$•2LiCl. In the absence of additives, conversion to the desired tertiary alcohol (**v.12**) proved to be untenable with this substrate.



v.06



v.12

[6] Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497-500.

[7] Vila-Gisbert, S.; Urbano, A.; Carmen Carreño, M. *Chem. Commun.*, **2013**, *49*, 3561-3563.

[8] Many different bases and electrophiles were tested prior to discovering useful alkoxy chlorosilanes such as **5.17**. Weak bases such as K_2CO_3 or NaOH were inadequate to deliver the allyl-protected tertiary alcohol. Furthermore, attempted deprotonation of the alcohol with NaH had the unhappy effect of delivering a bis-alkyne via loss of the vinyl bromide! The bis-alkyne was never fully elucidated,

however the sensitivity of vinyl bromides to basic conditions is well documented (Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675-2678).

[9] Proof of which diastereomer was major and minor was determined by treating one of the silylene diastereomers with K_2CO_3 and MeOH and comparing the crude ^1H NMR spectrum obtained with that of the crude mixture of diols **5.15**. The diastereomers of the acetate **5.16** were also separable and major and minor was assigned in the same fashion as the silylene.

[10] Disorder about the silyl protecting groups prevented the collection of publishable data for this crystal structure. Fortunately, however, the relative stereochemistry about the alcohols may be confirmed from the obtained preliminary structure.

APPENDICES

APPENDIX A

Spectra Relevant to Chapter One

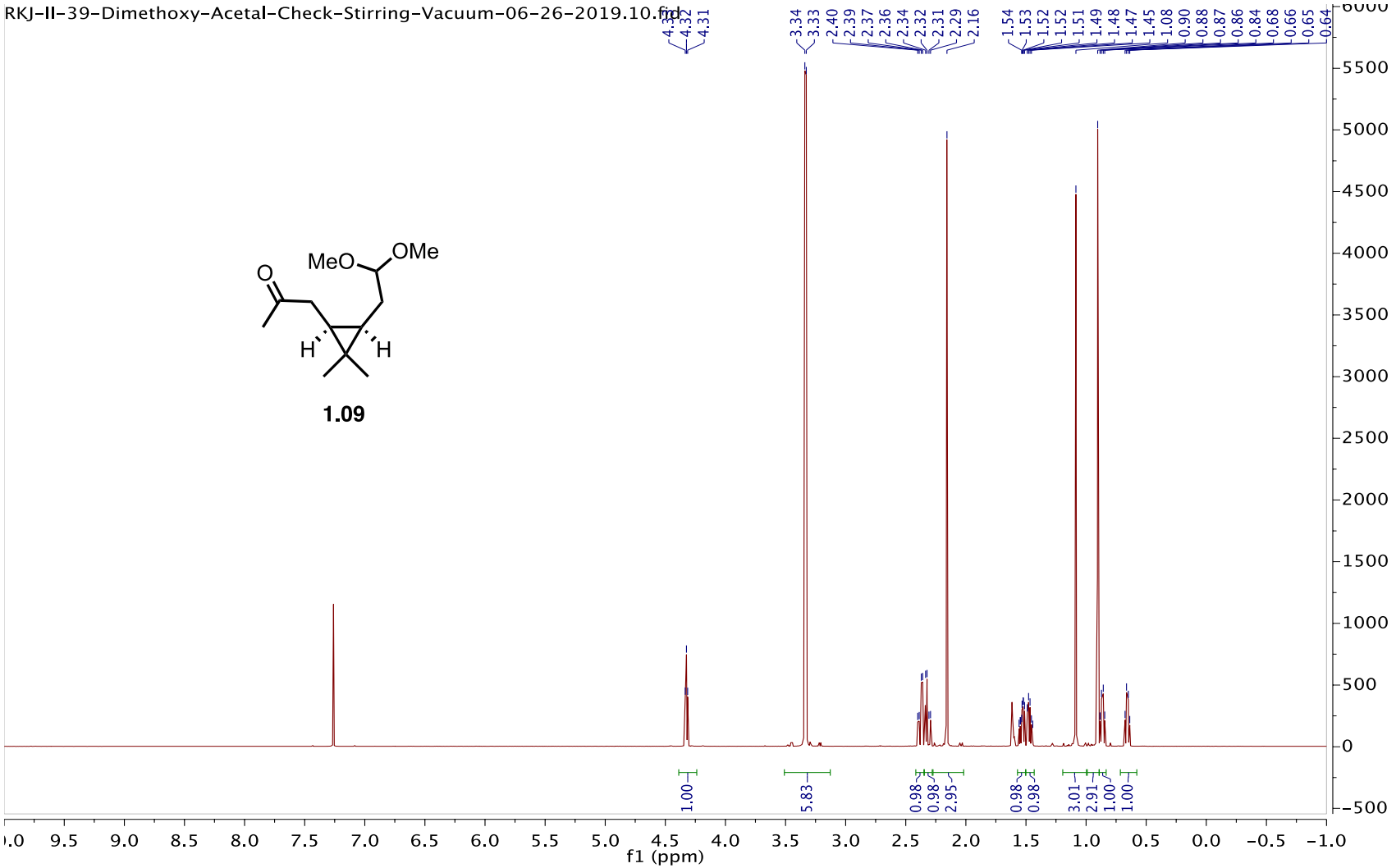


Figure A.01. **^{1}H NMR** (600 MHz, $CDCl_3$) of Acetal **1.09**

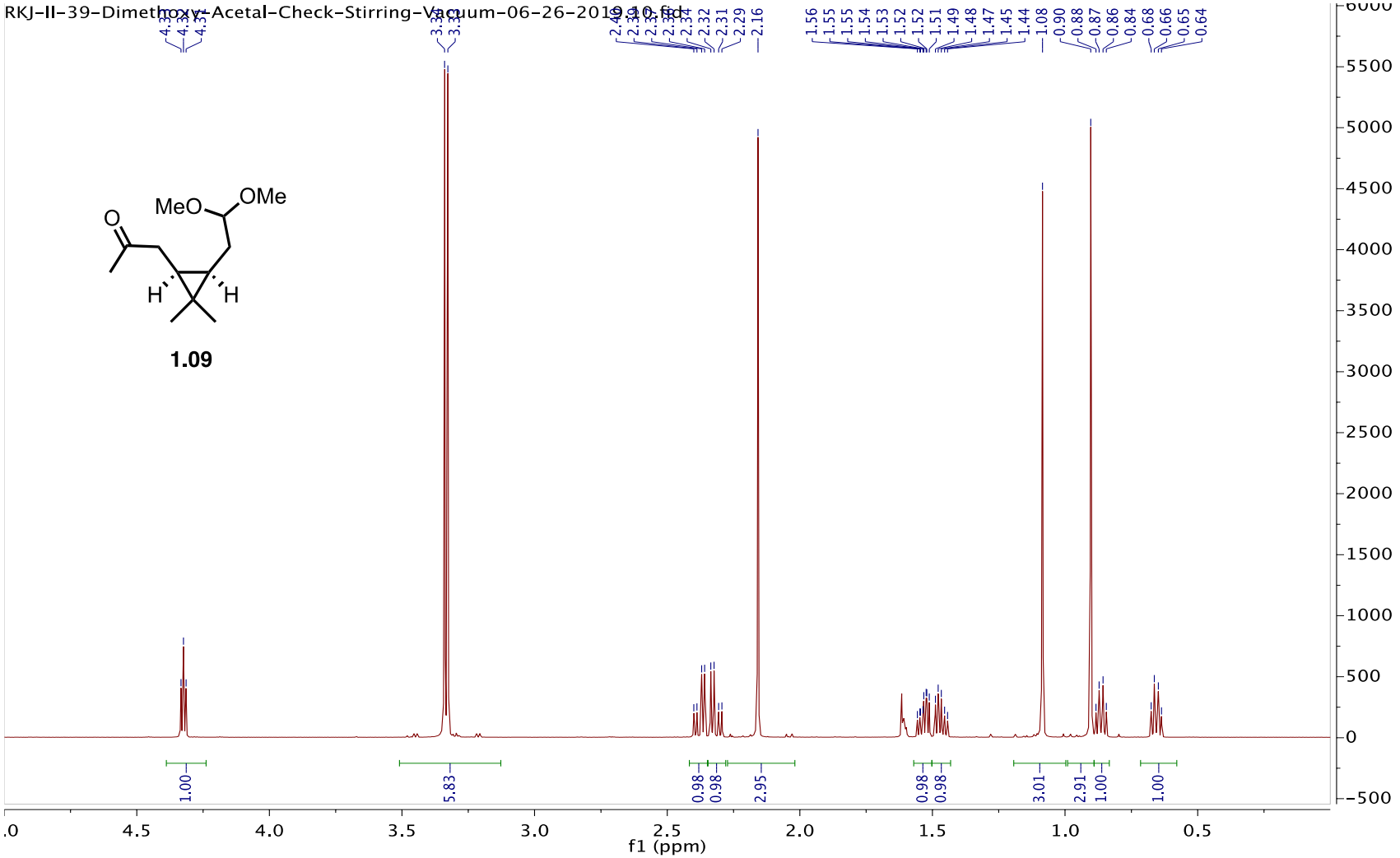


Figure A.02. **^{1}H NMR** (600 MHz, $CDCl_3$) of Acetal **1.09** (5.0 – 0.0 ppm inset)

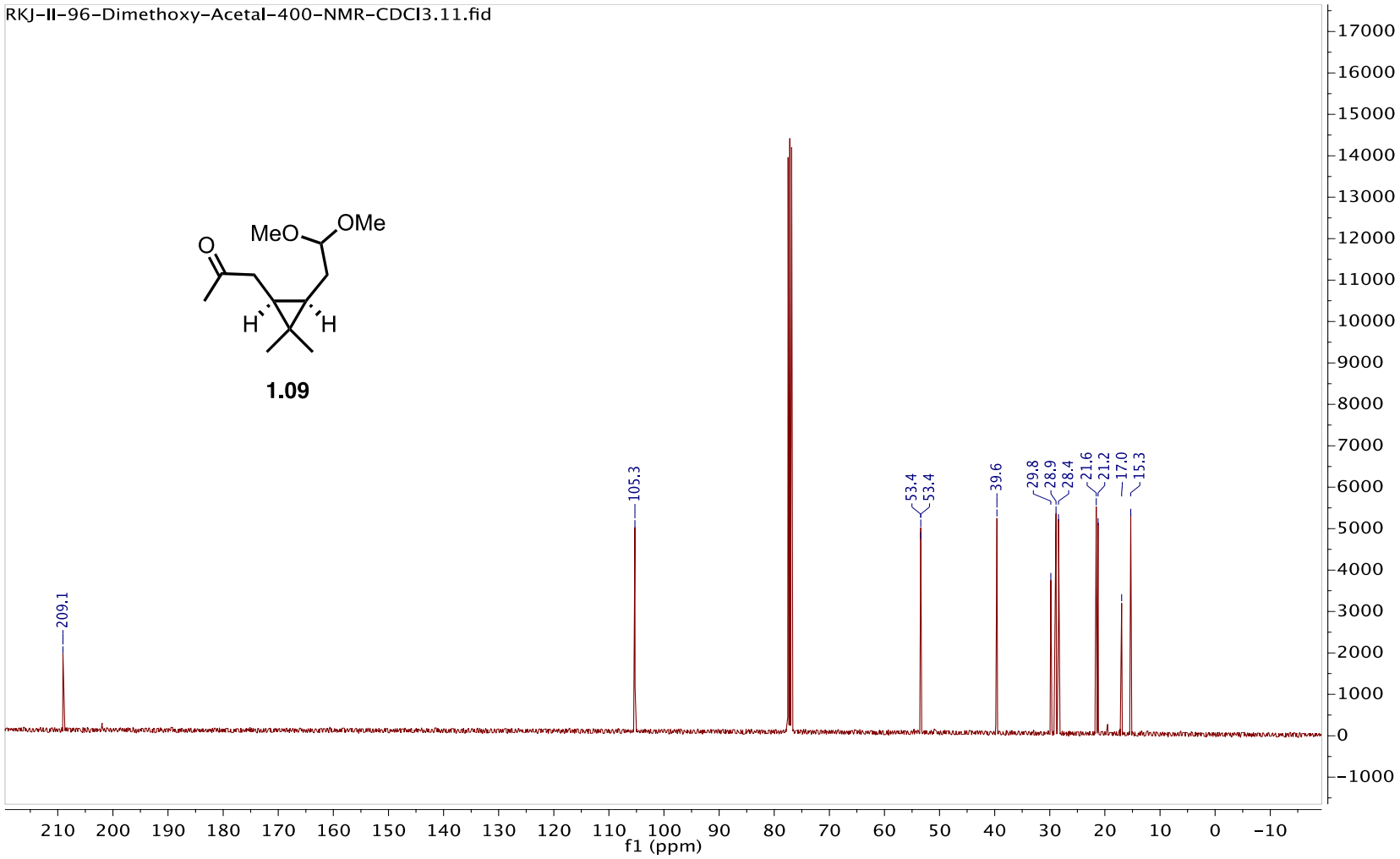


Figure A.03. **^{13}C NMR** (101 MHz, $CDCl_3$) of Acetal **1.09**

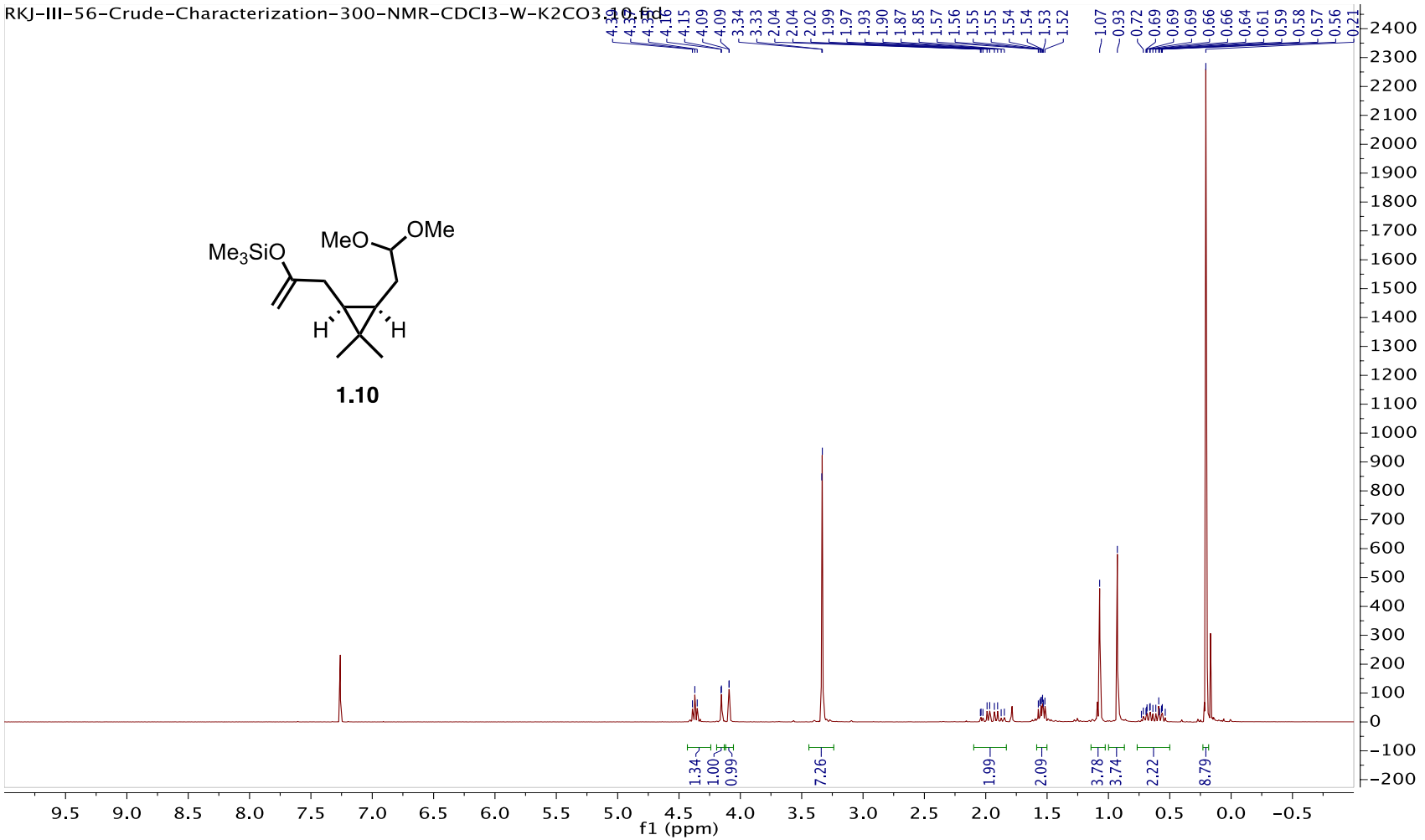


Figure A.04. **^{1}H NMR** (300 MHz, $CDCl_3$) of Crude TMS Silyl Enol Ether **1.10**

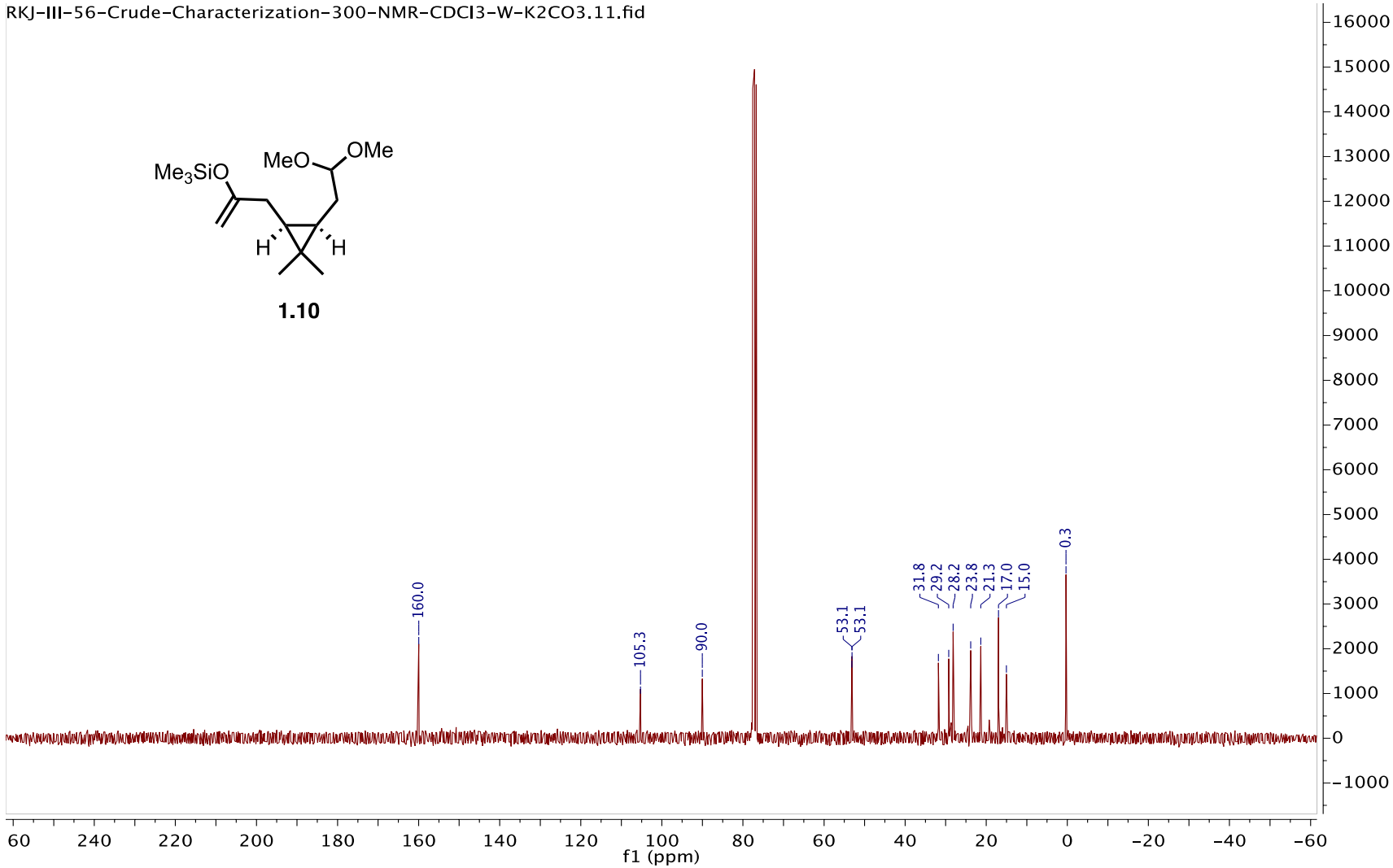


Figure A.05. **^{13}C NMR** (75 MHz, $CDCl_3$) of Crude TMS Silyl Enol Ether **1.10**

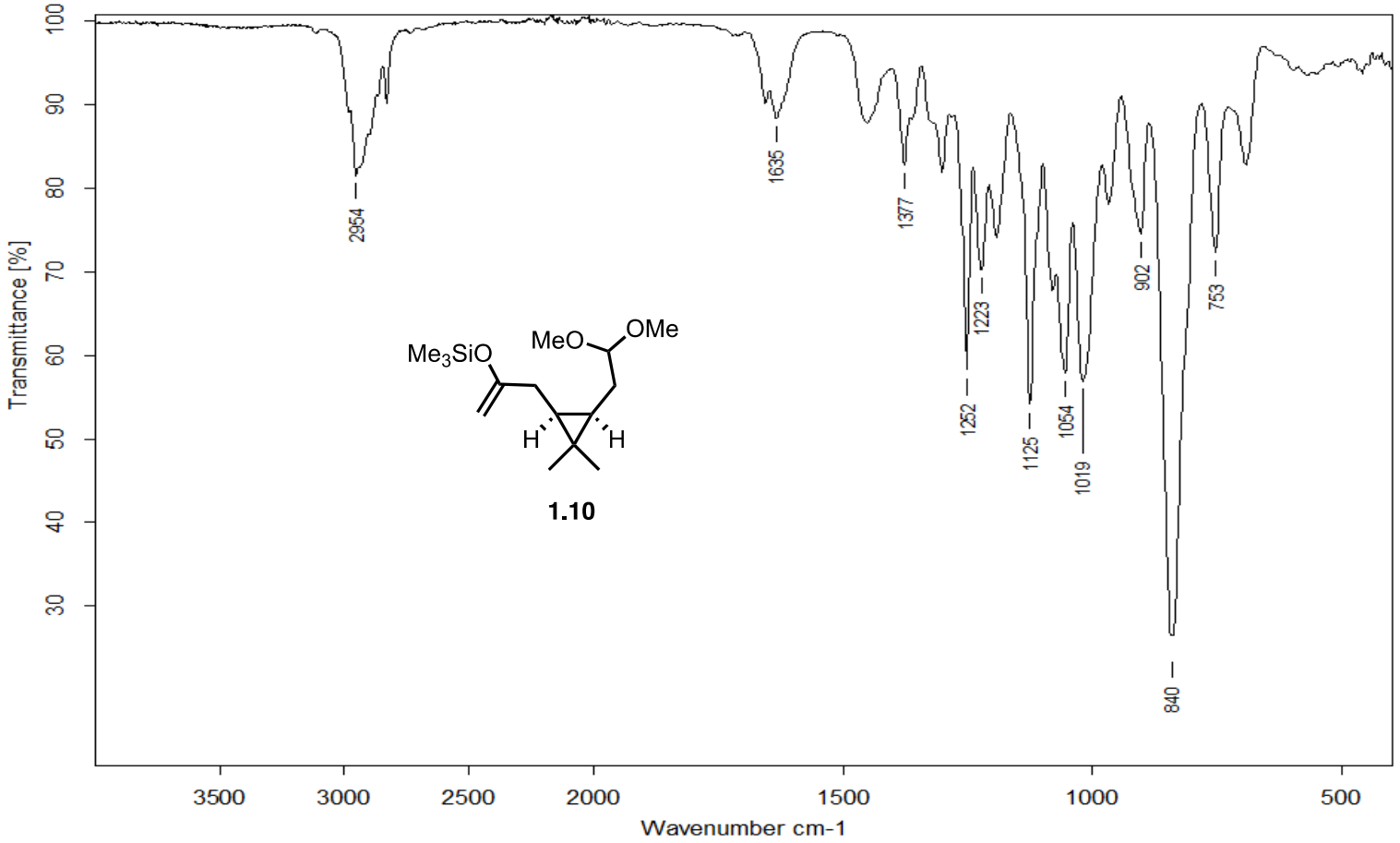


Figure A.06. **FTIR** (thin film) Crude TMS Silyl Enol Ether **1.10**

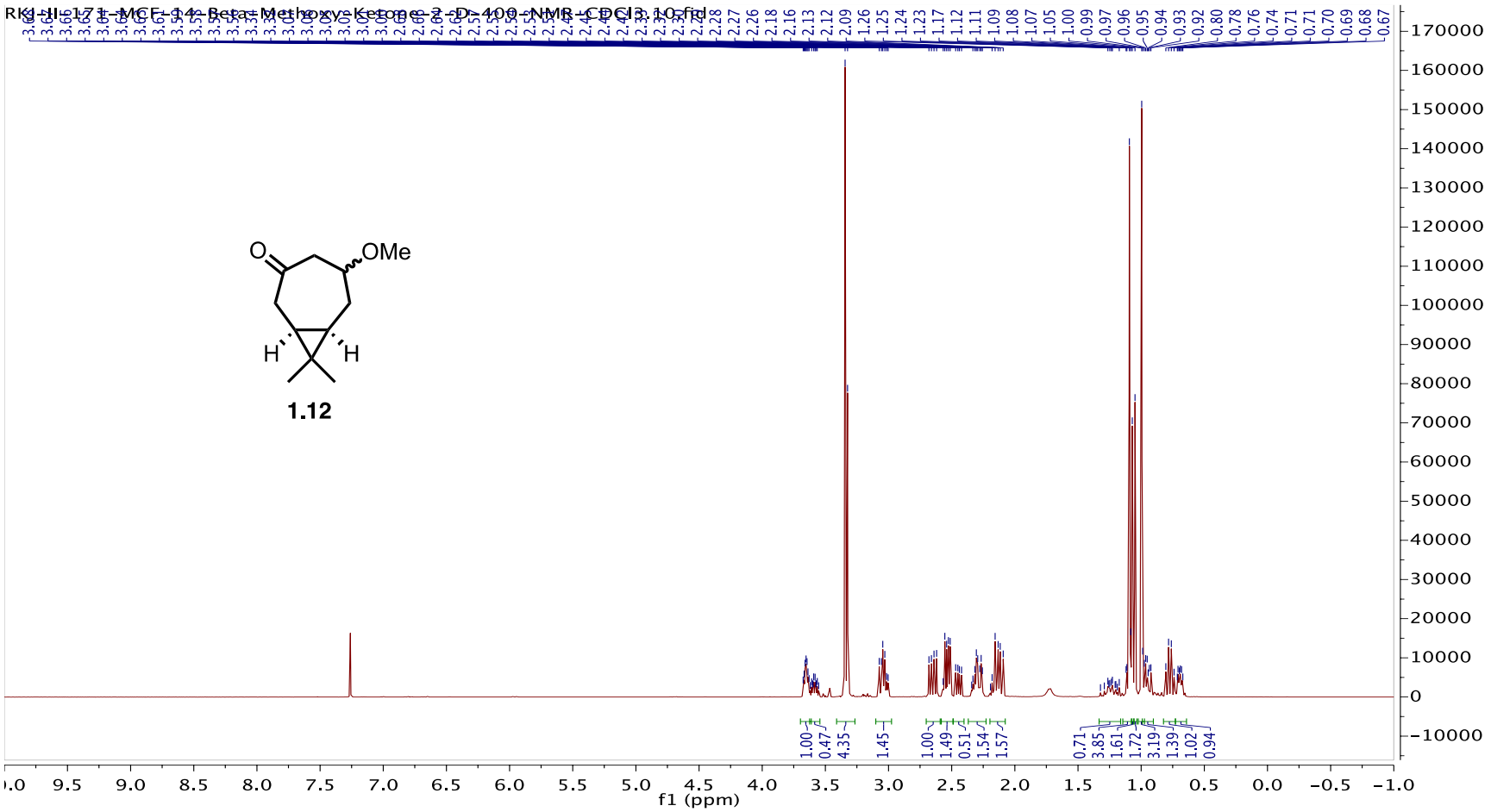


Figure A.07. **^{1}H NMR** (400 MHz, $CDCl_3$) of Ketone **1.12**

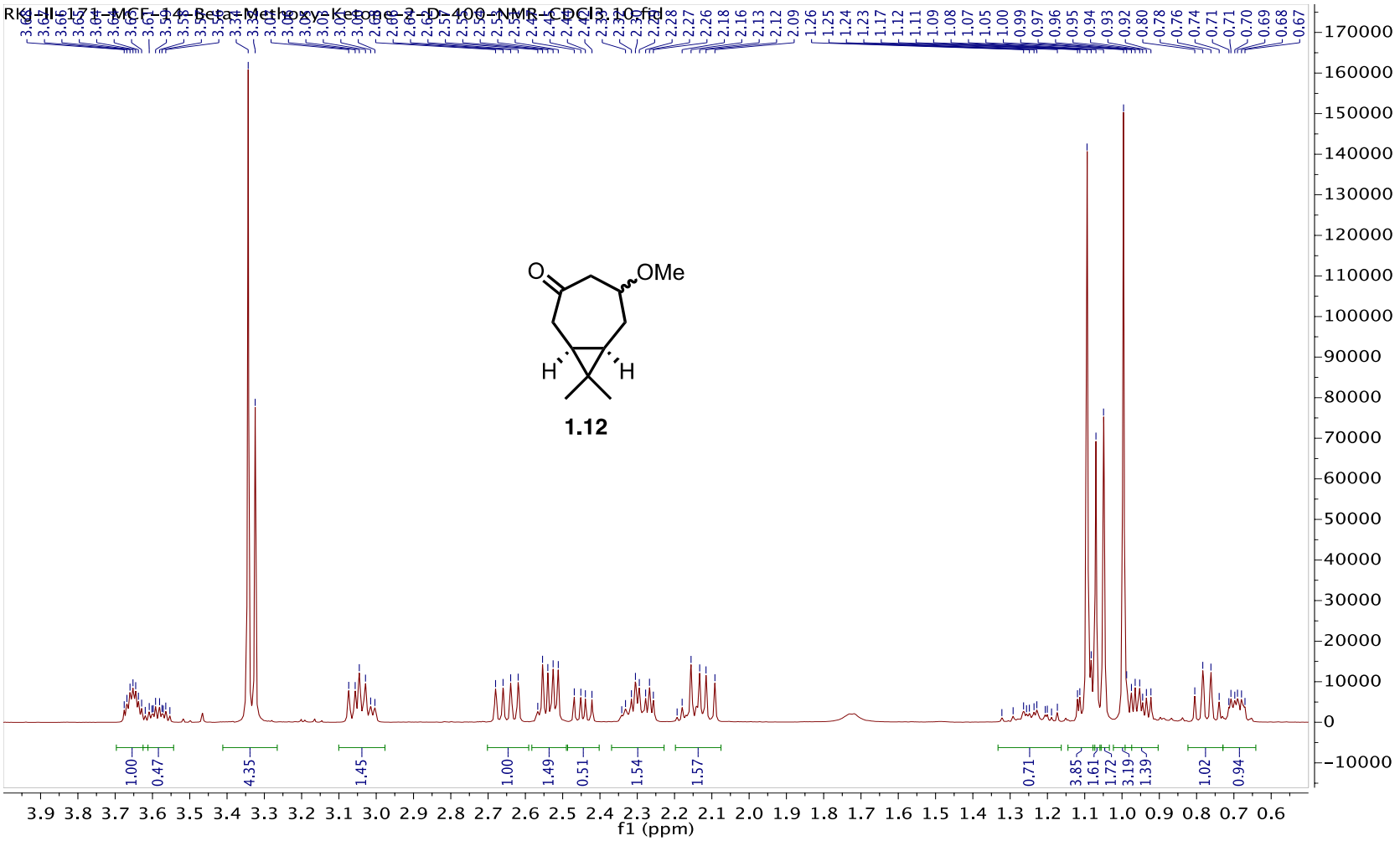


Figure A.08. **^{1}H NMR** (400 MHz, $CDCl_3$) of Ketone **1.12** (4.0 – 0.5 ppm inset)

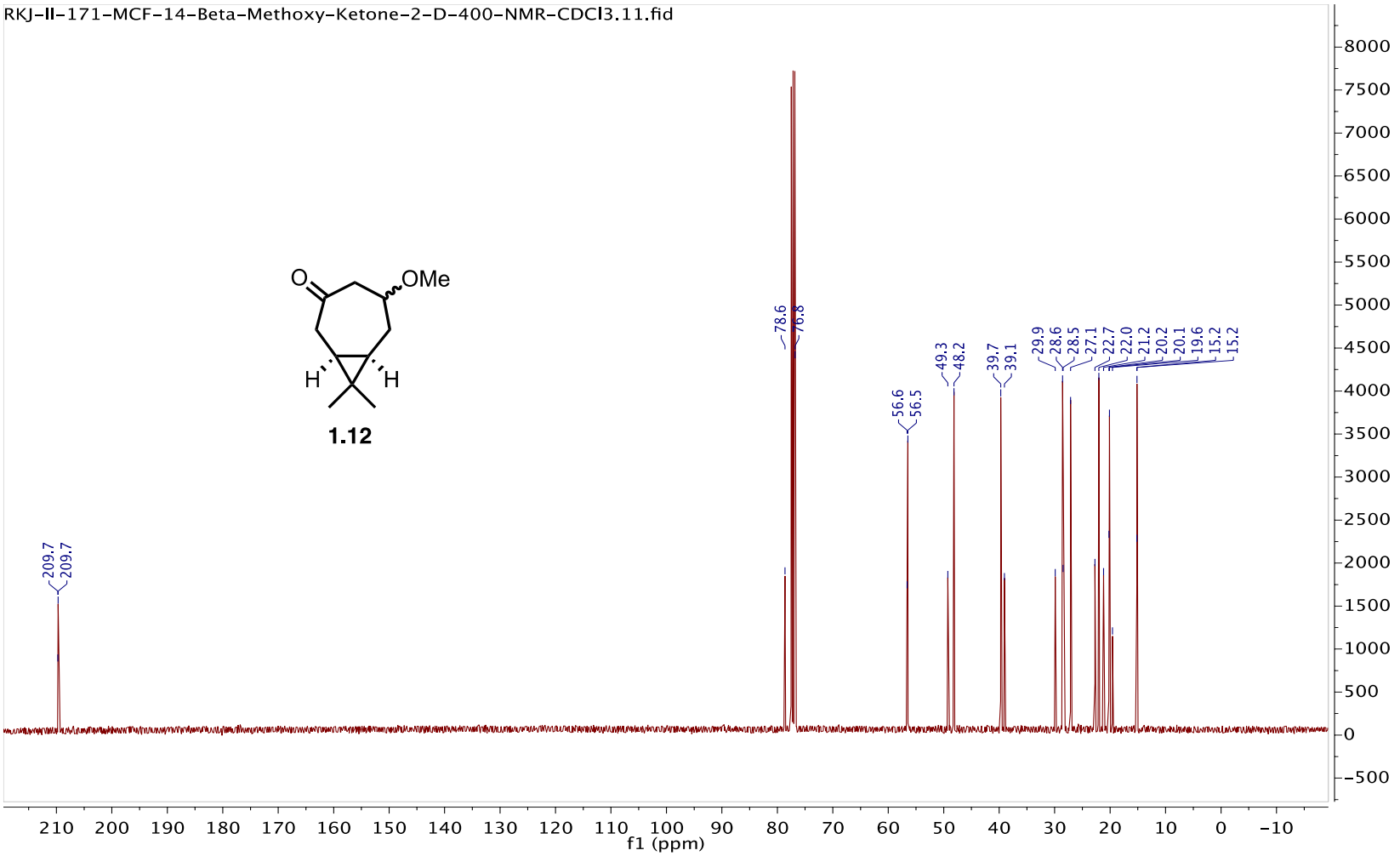


Figure A.09. **^{13}C NMR** (101 MHz, $CDCl_3$) of Ketone **1.12**

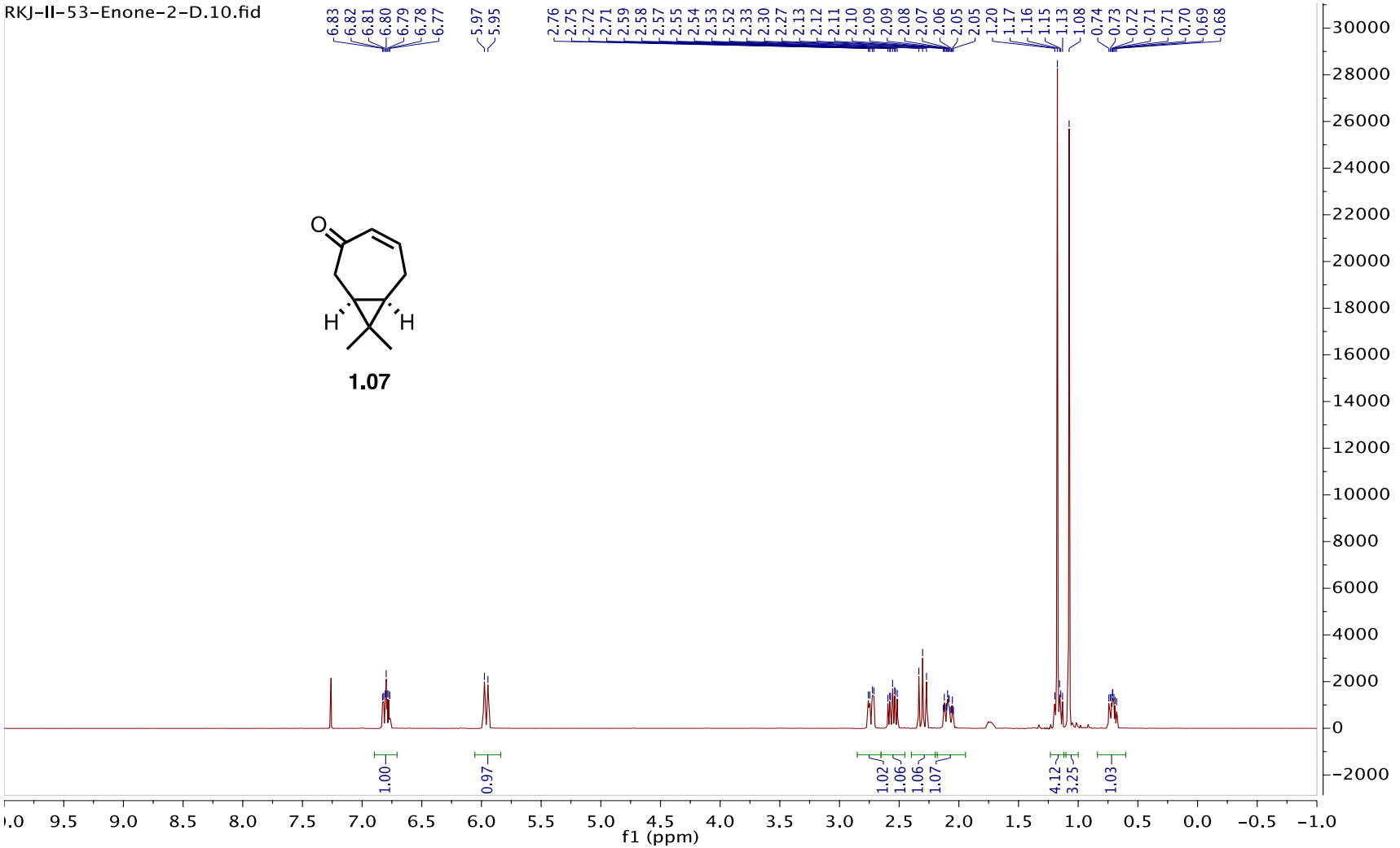


Figure A.10. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07**

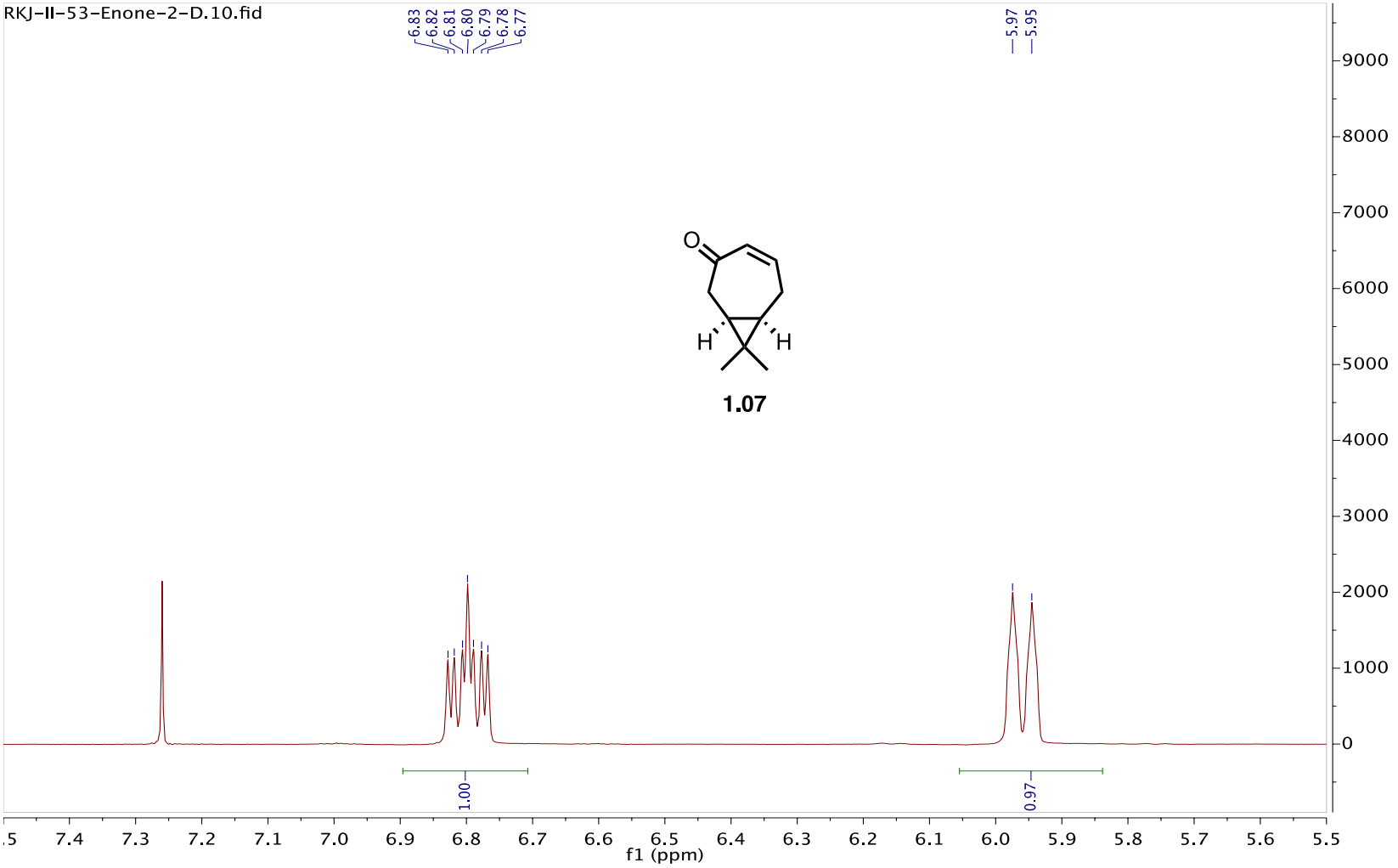


Figure A.11. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** (7.5 – 5.5 ppm inset)

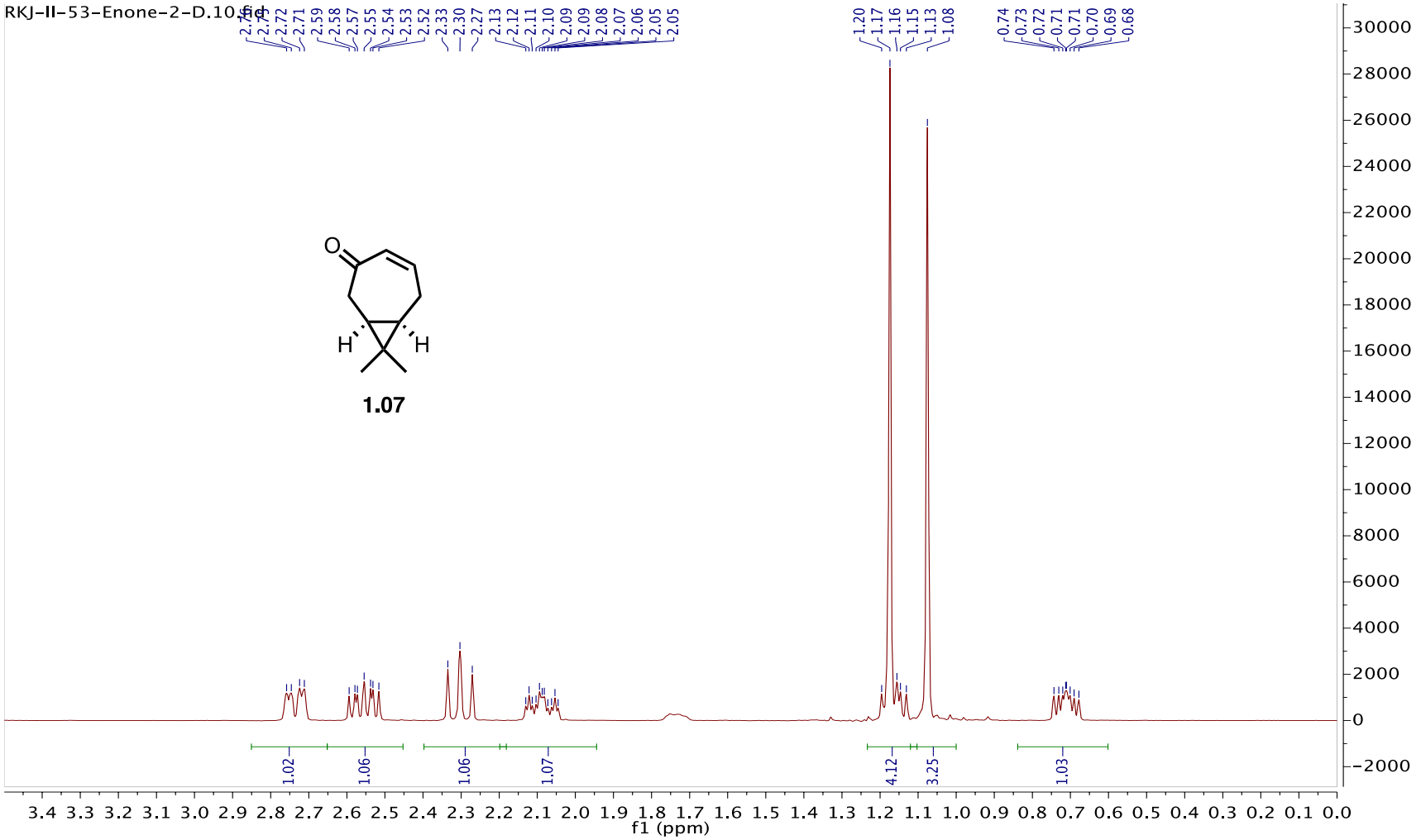


Figure A.12. **^{1}H NMR** (400 MHz, $CDCl_3$) of Yamakawa's Enone **1.07** (3.0 – 0.0 ppm inset)

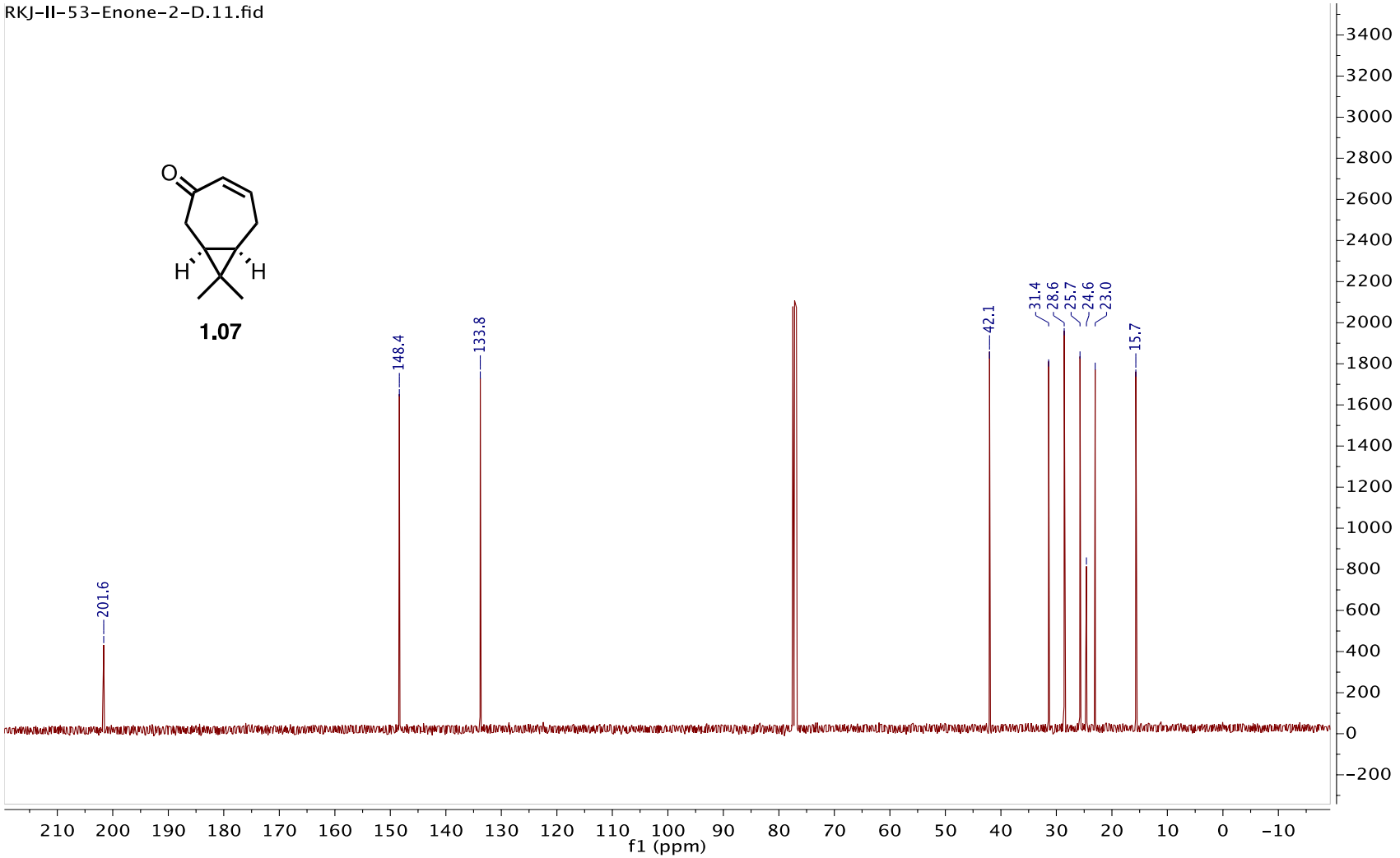


Figure A.13. **^{13}C NMR** (101 MHz, $CDCl_3$) of Yamakawa's Enone **1.07**

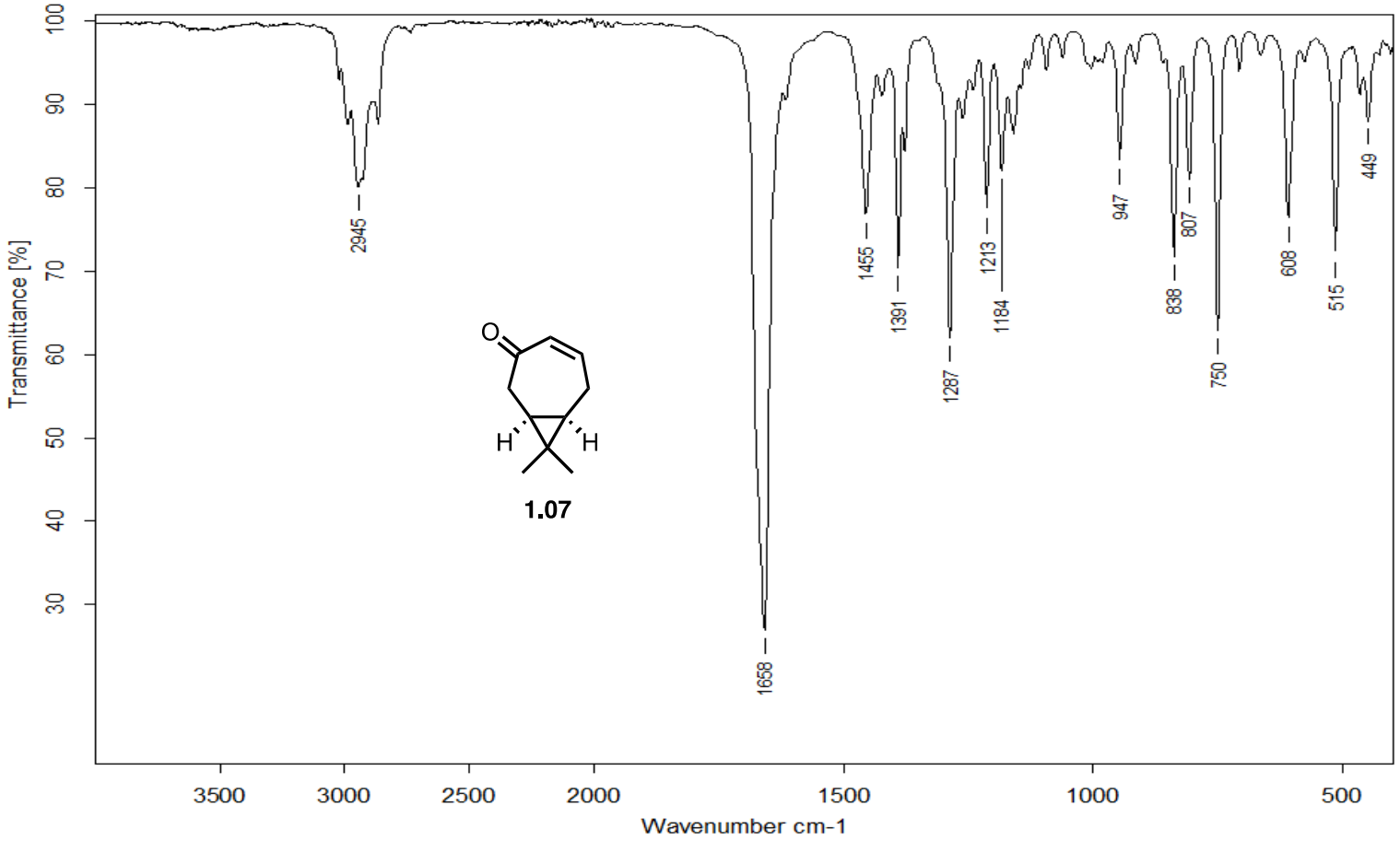


Figure A.14. **FTIR** (thin film) of Yamakawa's Enone **1.07**

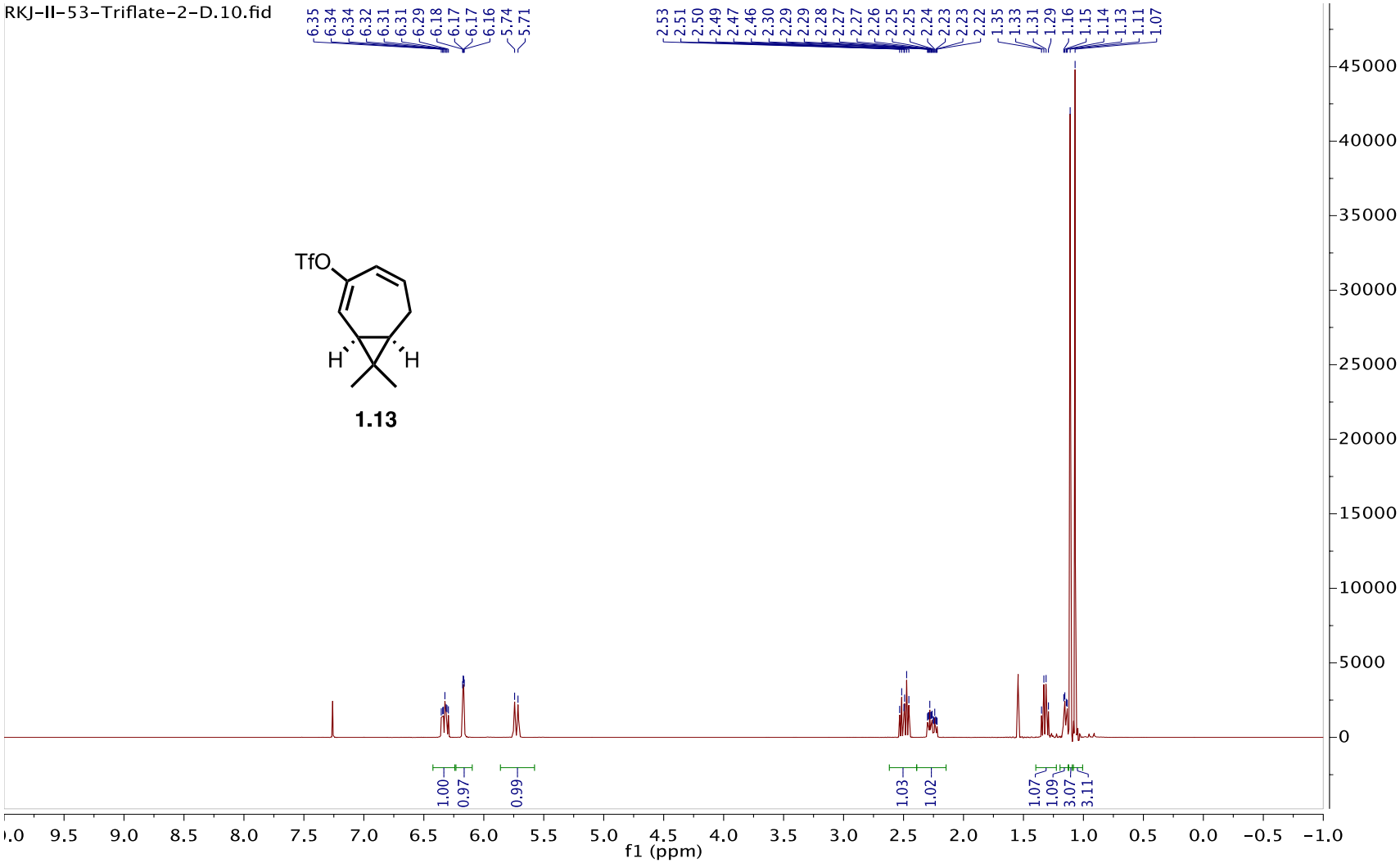


Figure A.15. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13**

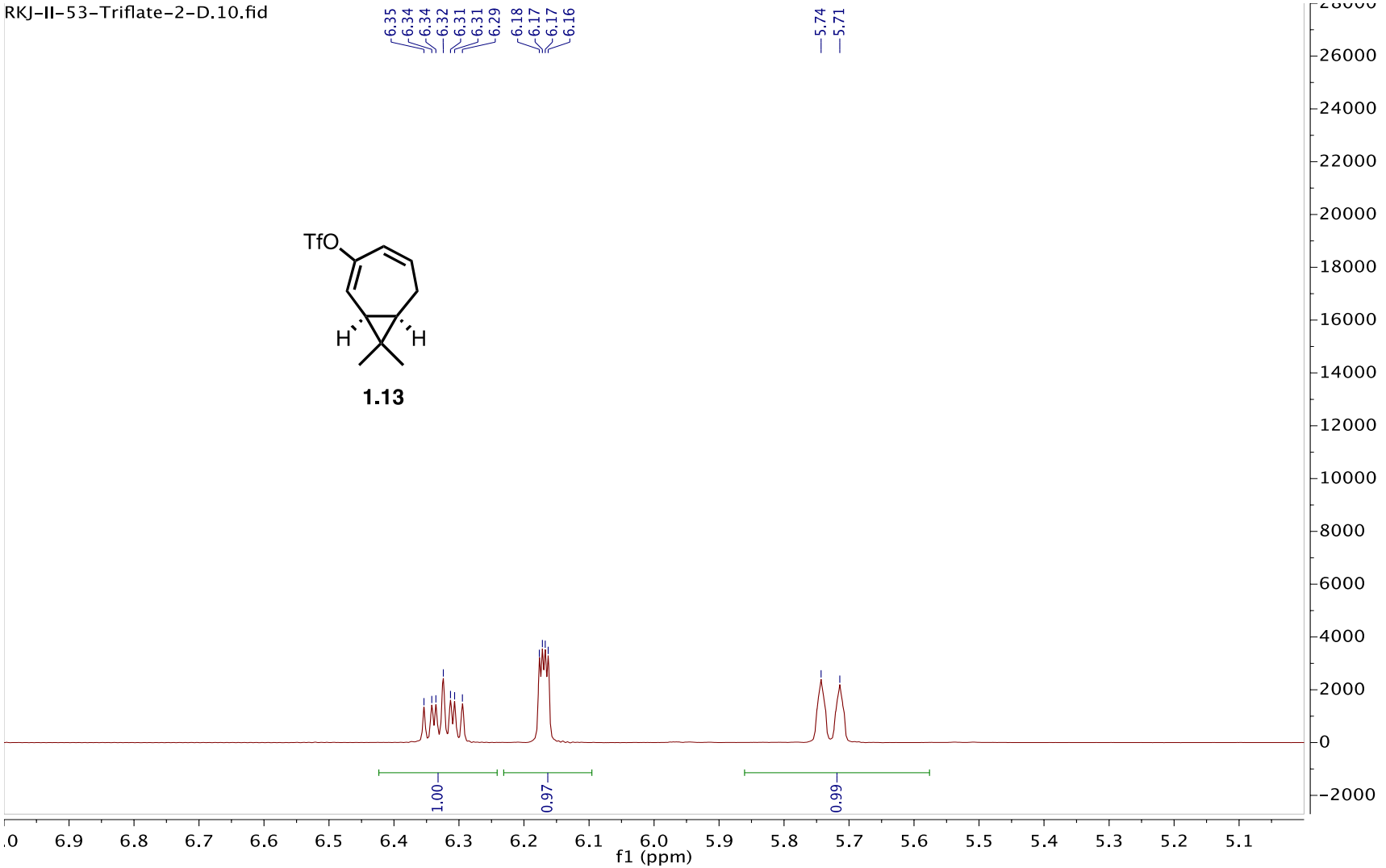


Figure A.16. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13** (7.0 – 5.0 ppm inset)

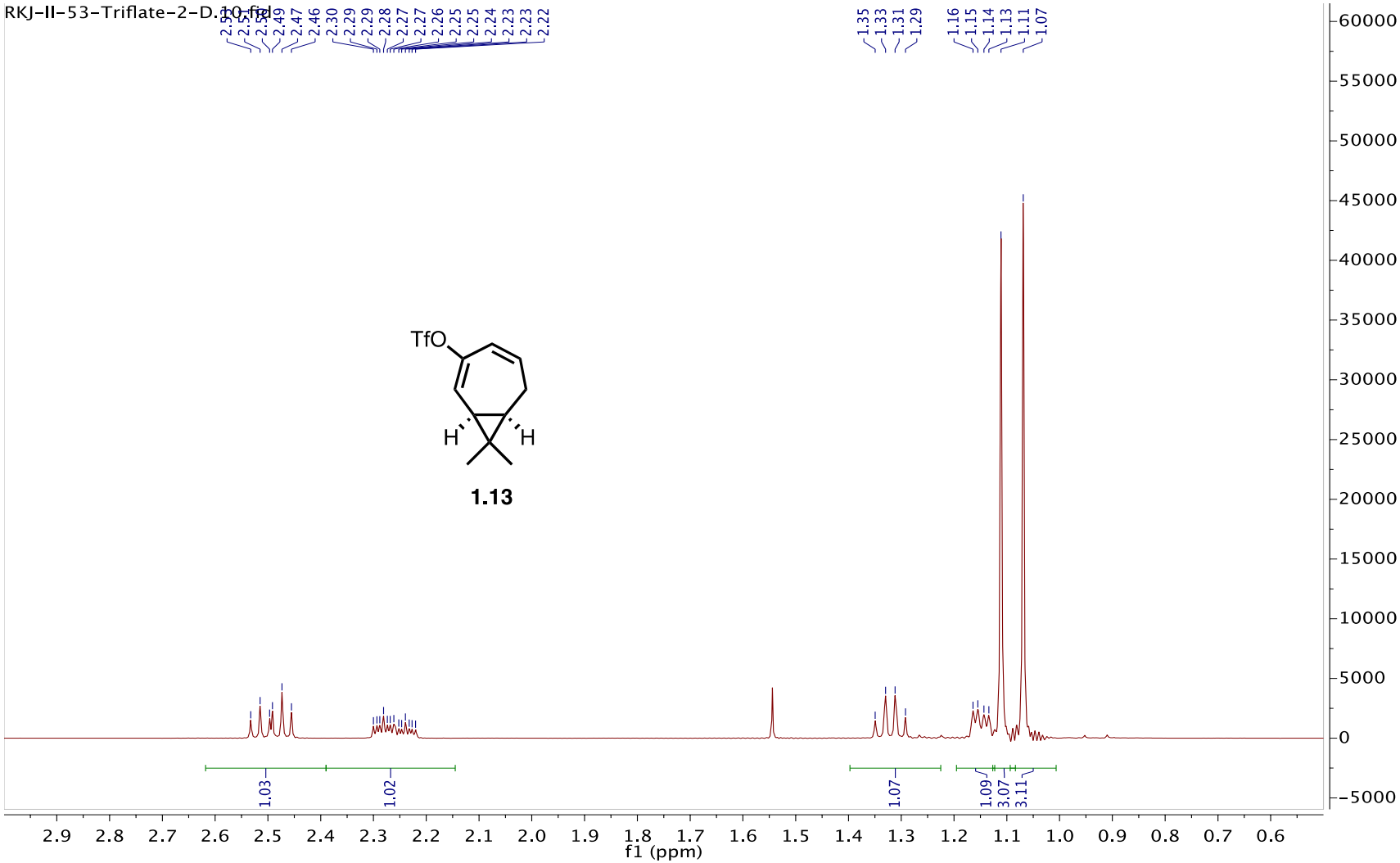


Figure A.17. **^{1}H NMR** (400 MHz, $CDCl_3$) of Triflate **1.13** (3.0 – 0.5 ppm inset)

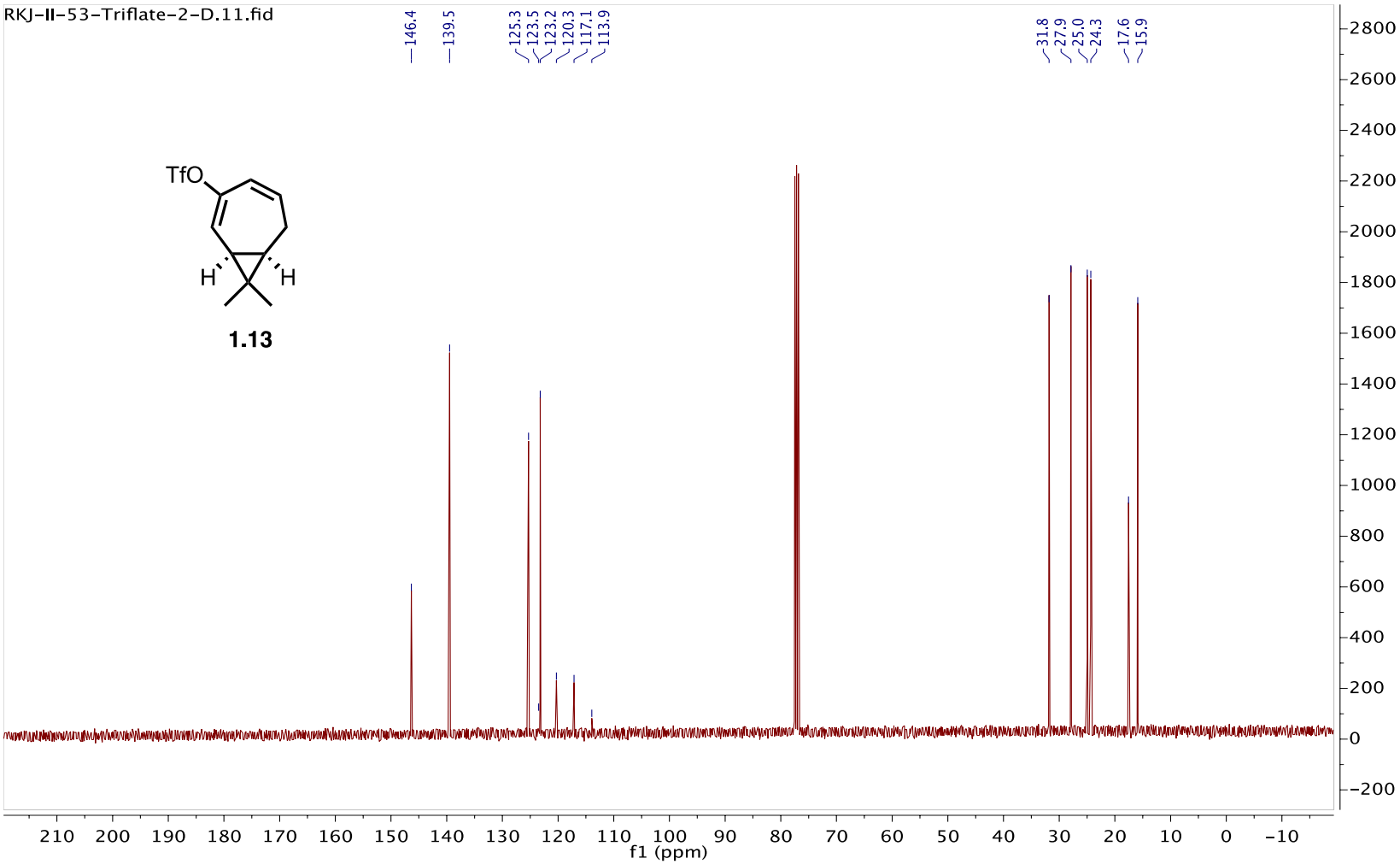


Figure A.18. **^{13}C NMR** (101 MHz, $CDCl_3$) of Triflate **1.13**

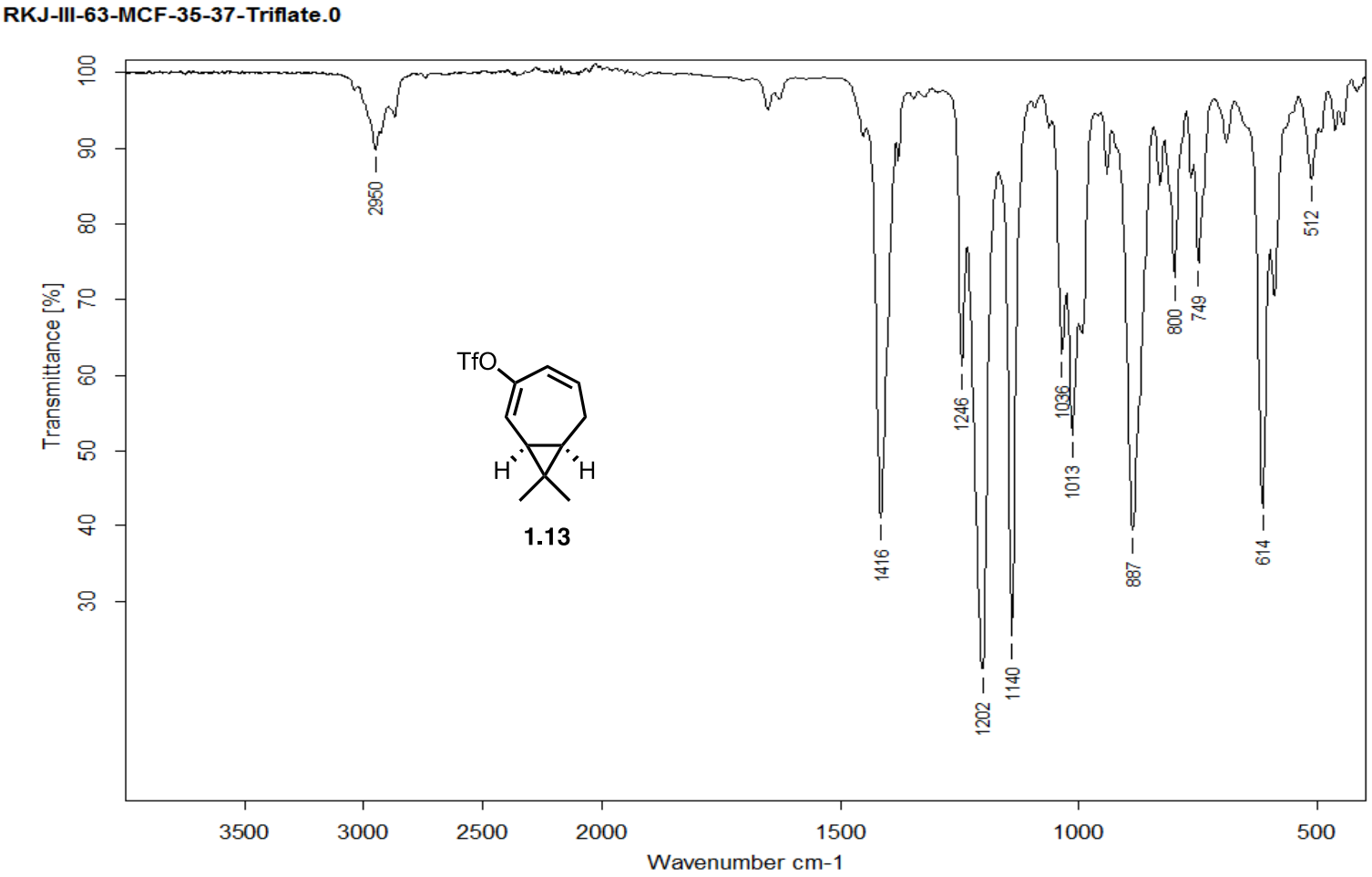


Figure A.19. **FTIR** (thin film) of Triflate **1.13**

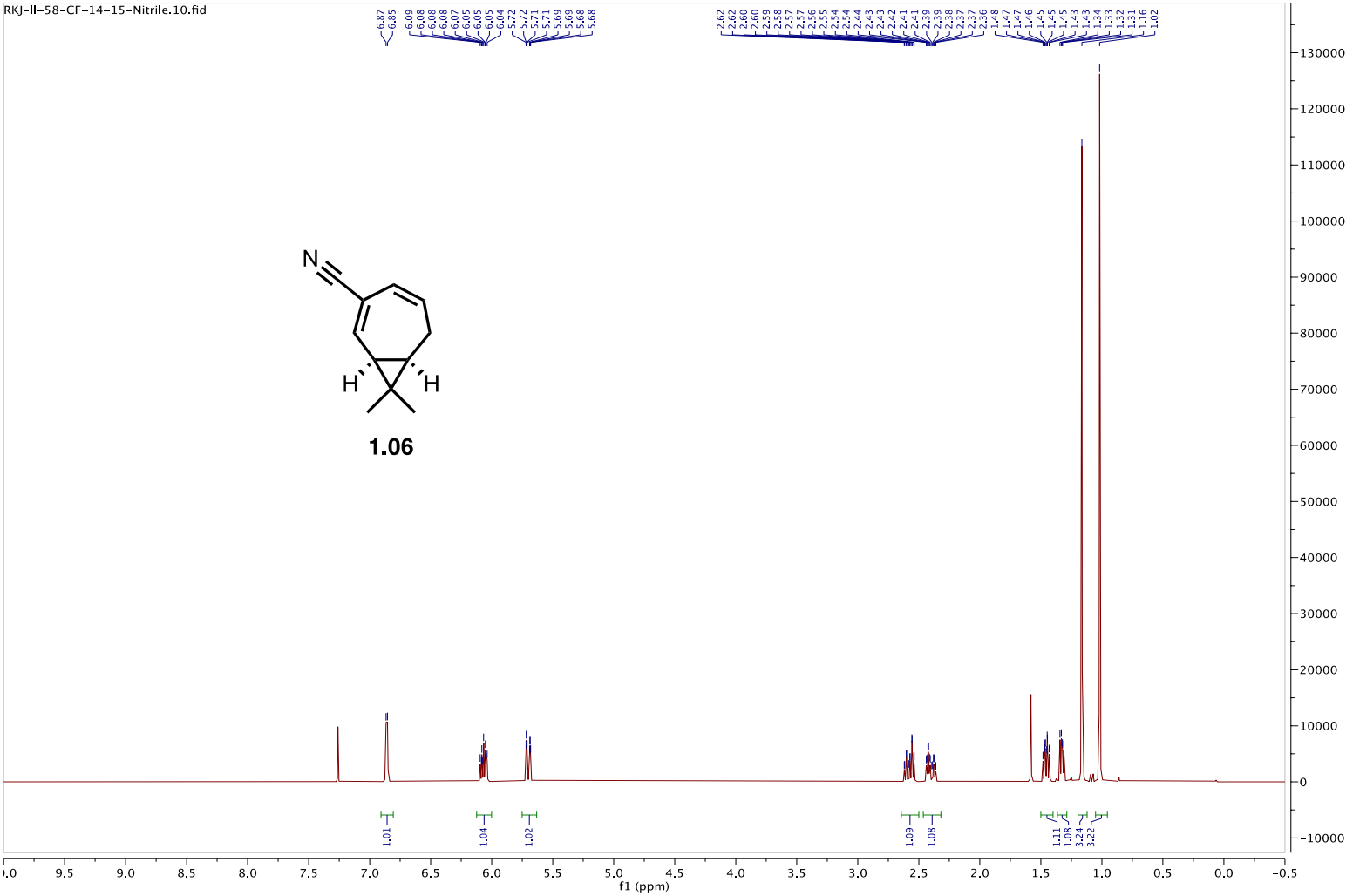


Figure A.20. **^{1}H NMR** (400 MHz, $CDCl_3$) of Vinyl Nitrile **1.06**

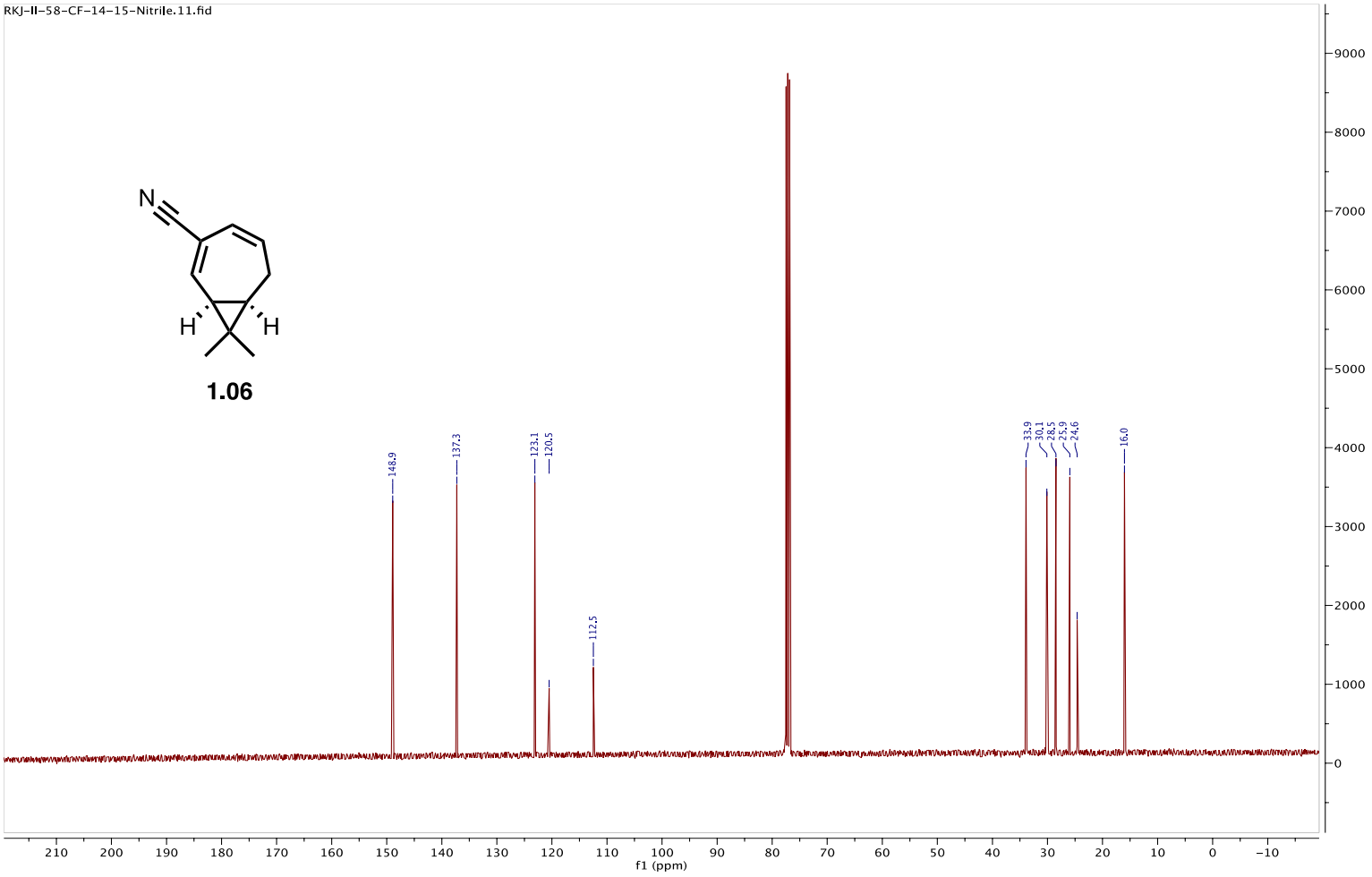


Figure A.21. **^{13}C NMR** (101 MHz, $CDCl_3$) of Vinyl Nitrile **1.06**

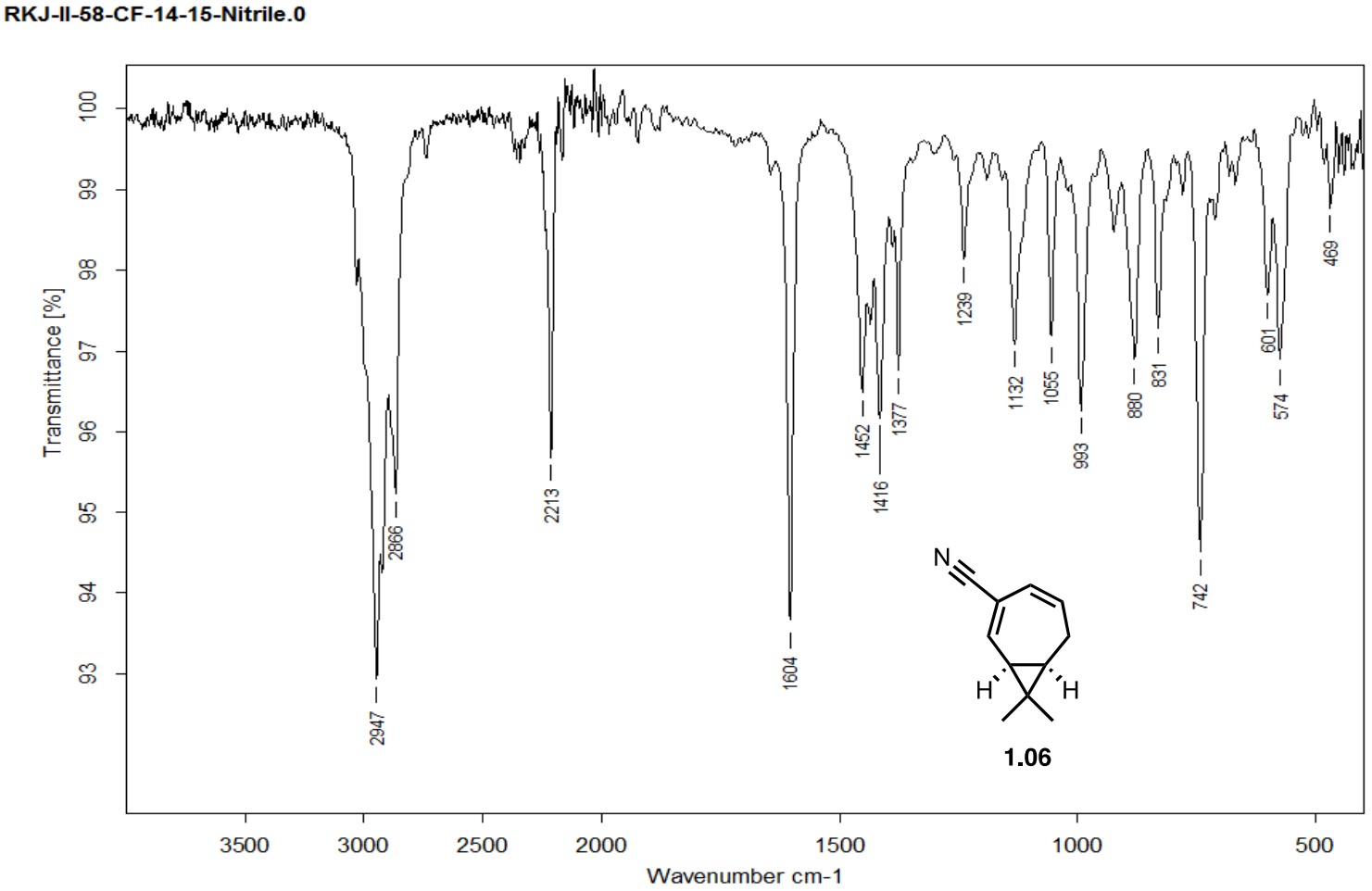


Figure A.22. **FTIR** (thin film) of Vinyl Nitrile **1.06**

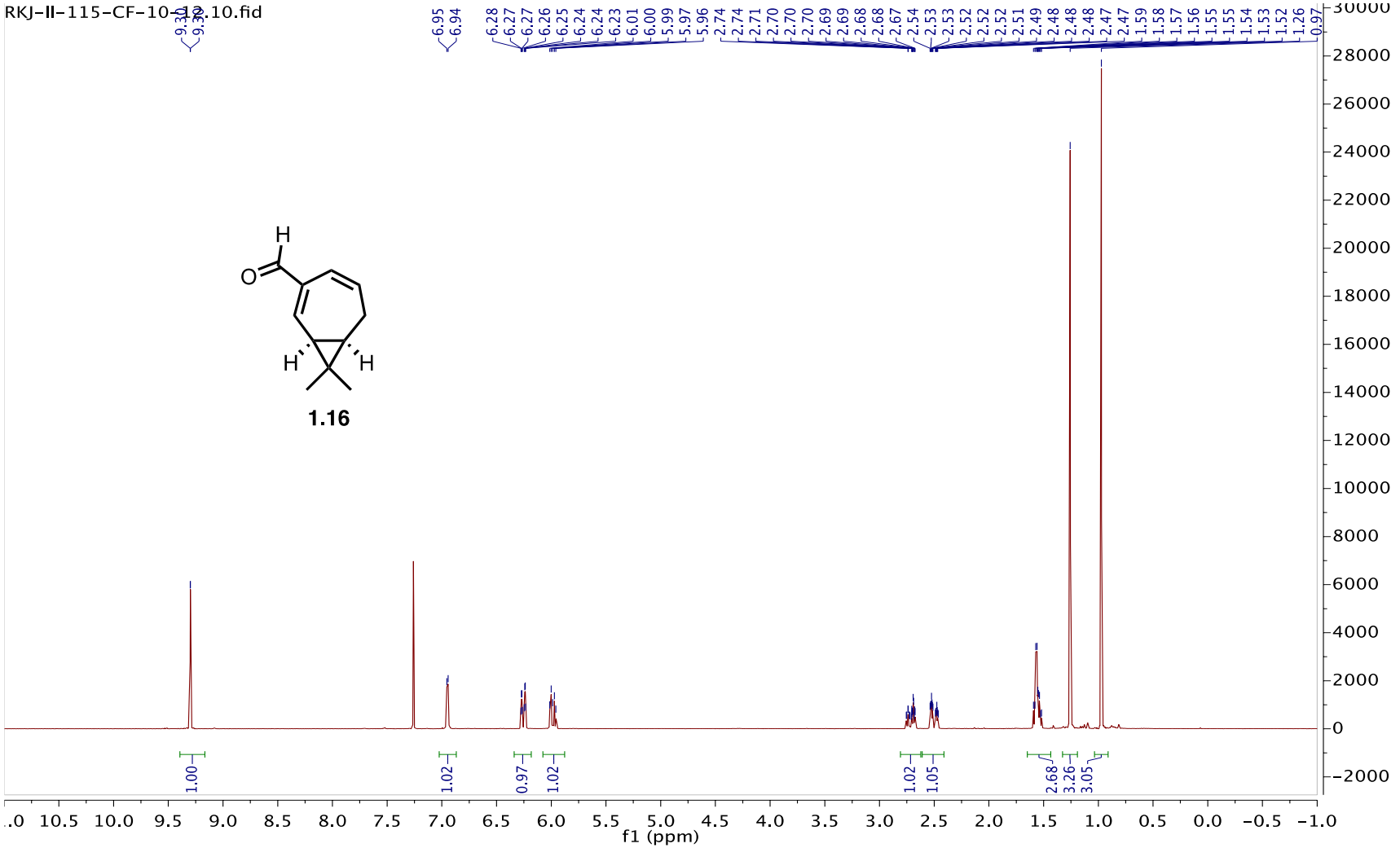


Figure A.23. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16**

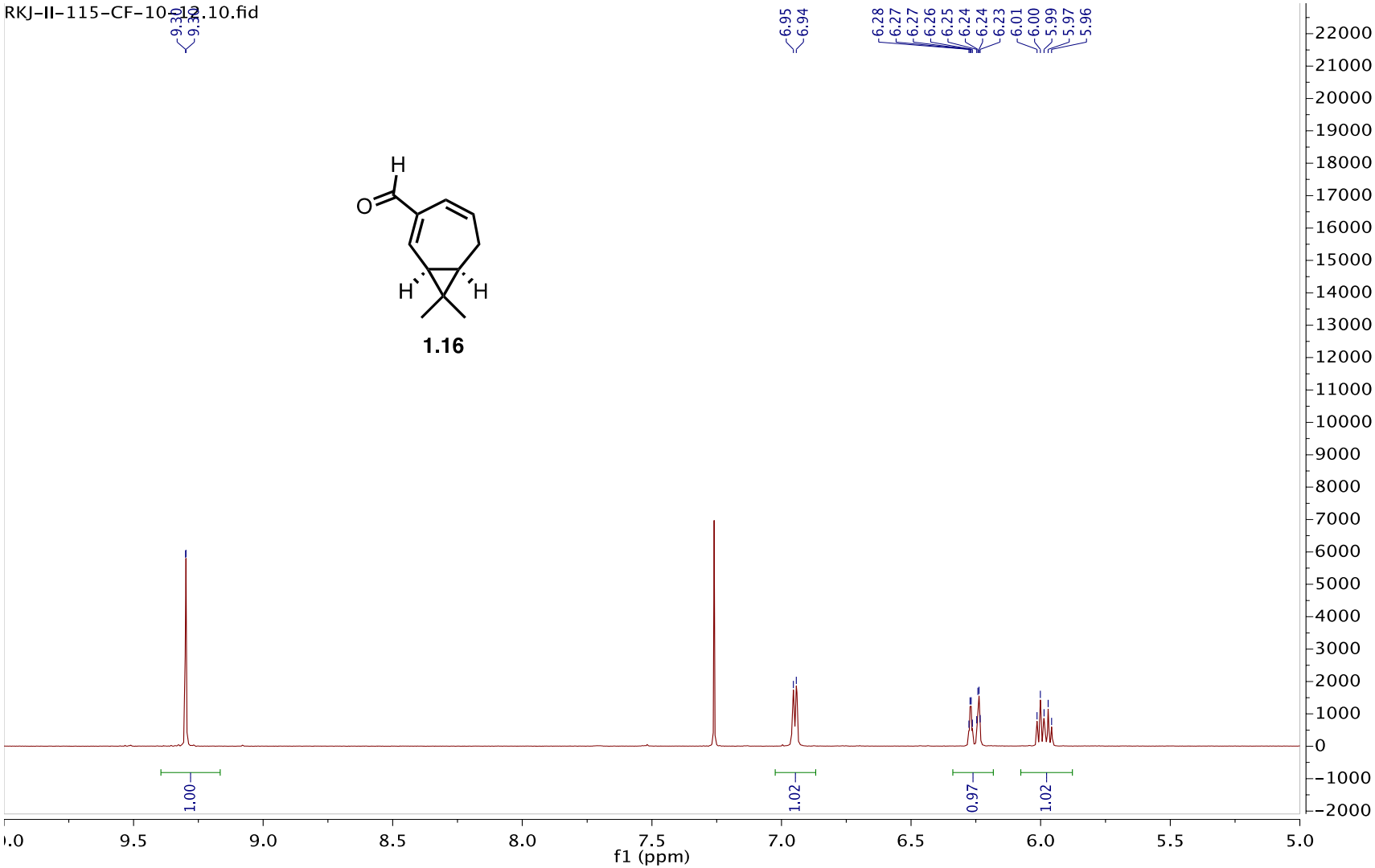


Figure A.24. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16** (10.0 – 5.0 ppm inset)

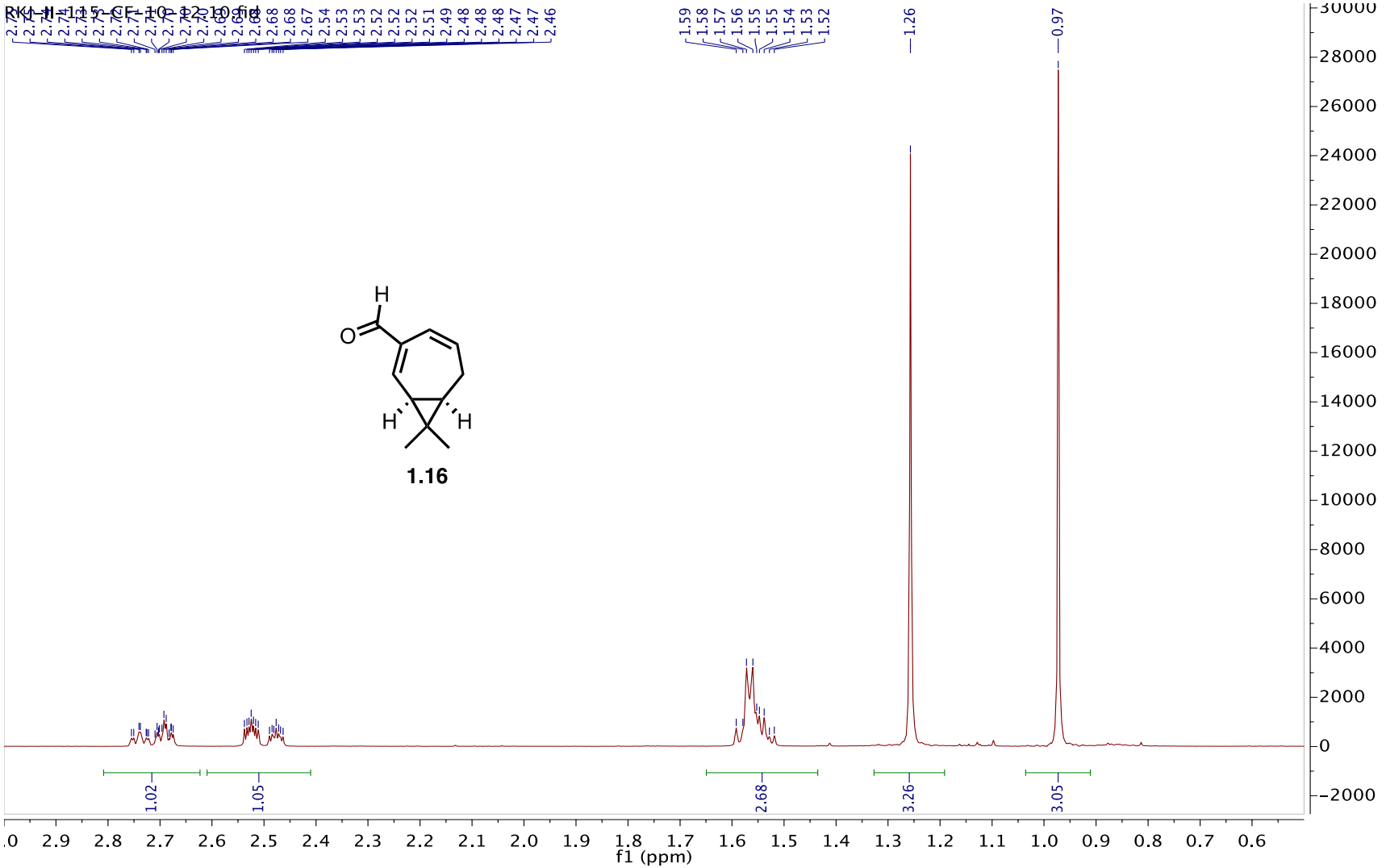


Figure A.25. **^{1}H NMR** (400 MHz, $CDCl_3$) of Aldehyde **1.16** (3.0 – 0.5 ppm inset)

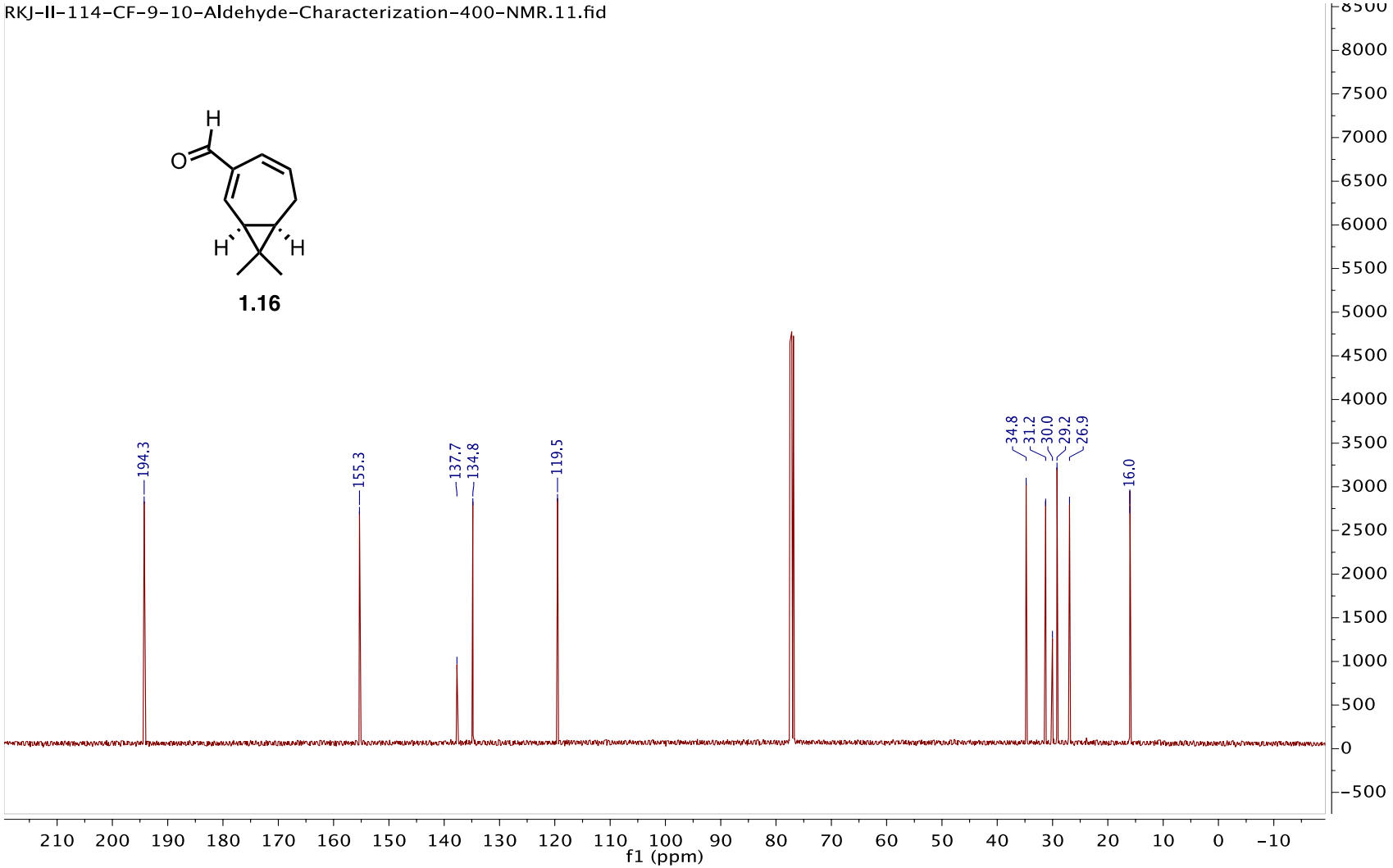


Figure A.26. **^{13}C NMR** (101 MHz, $CDCl_3$) of Aldehyde **1.16**

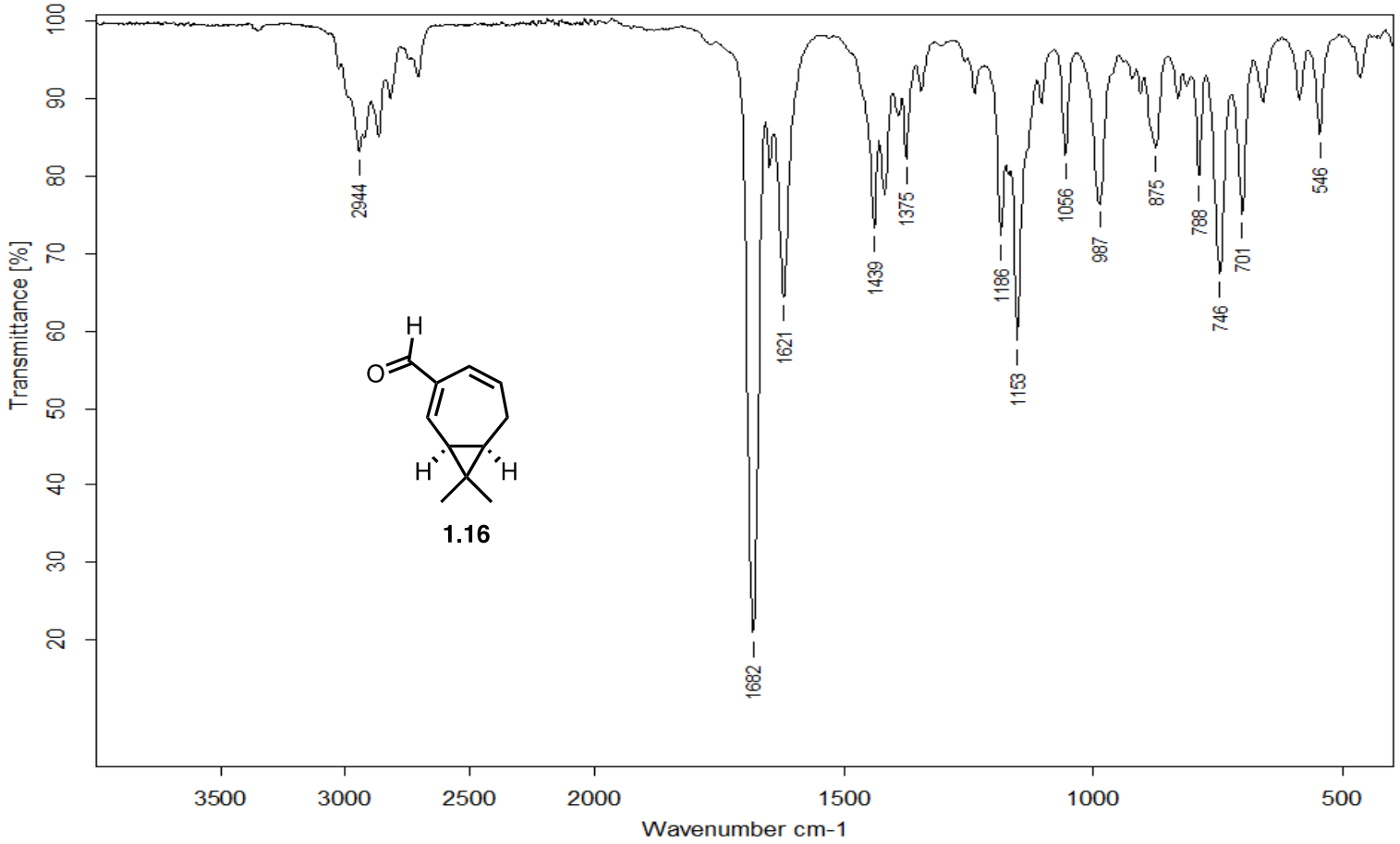


Figure A.27. **FTIR** (thin film) of Aldehyde **1.16**

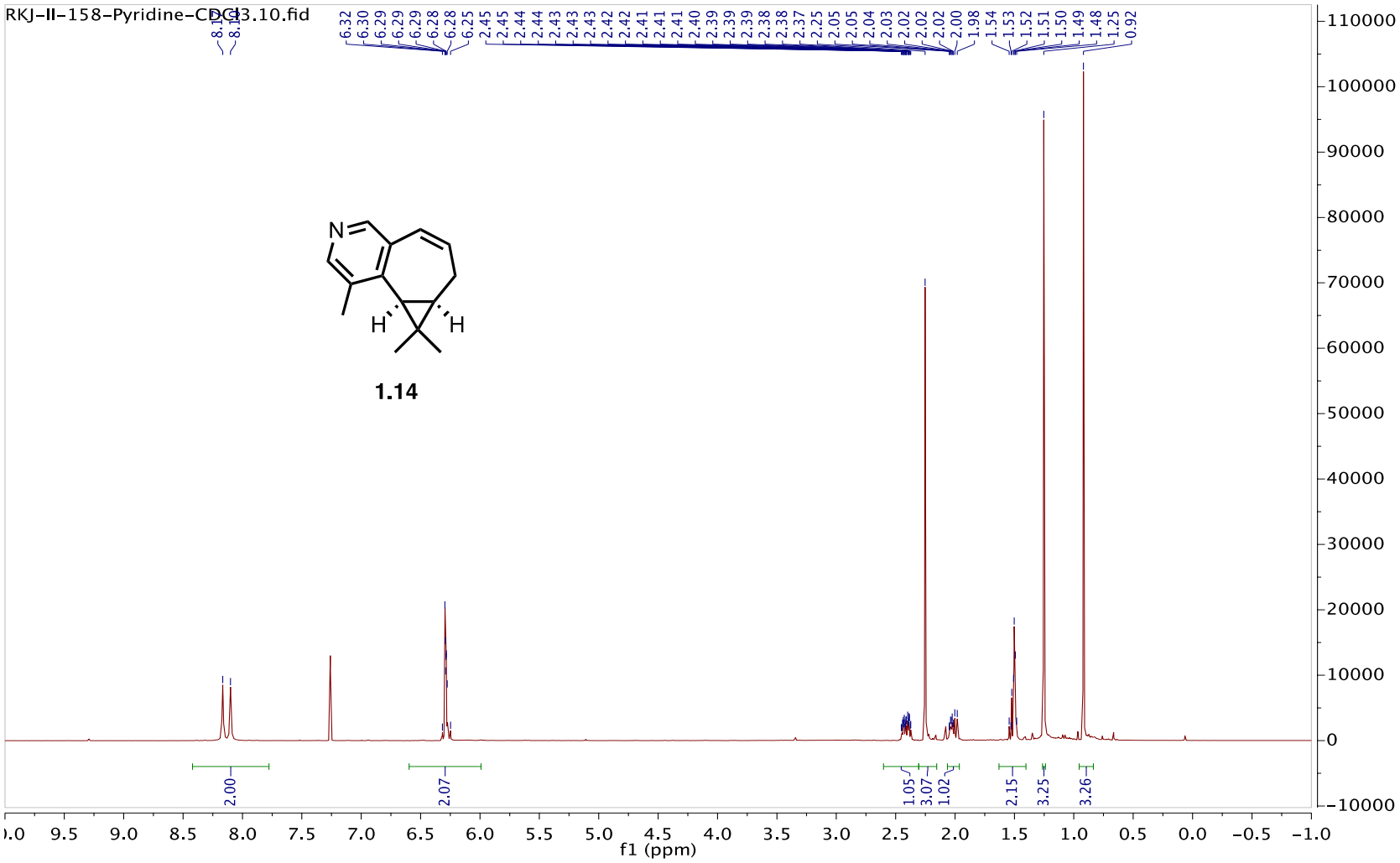


Figure A.28. **^{1}H NMR** (400 MHz, $CDCl_3$) of Pyridine **1.14**

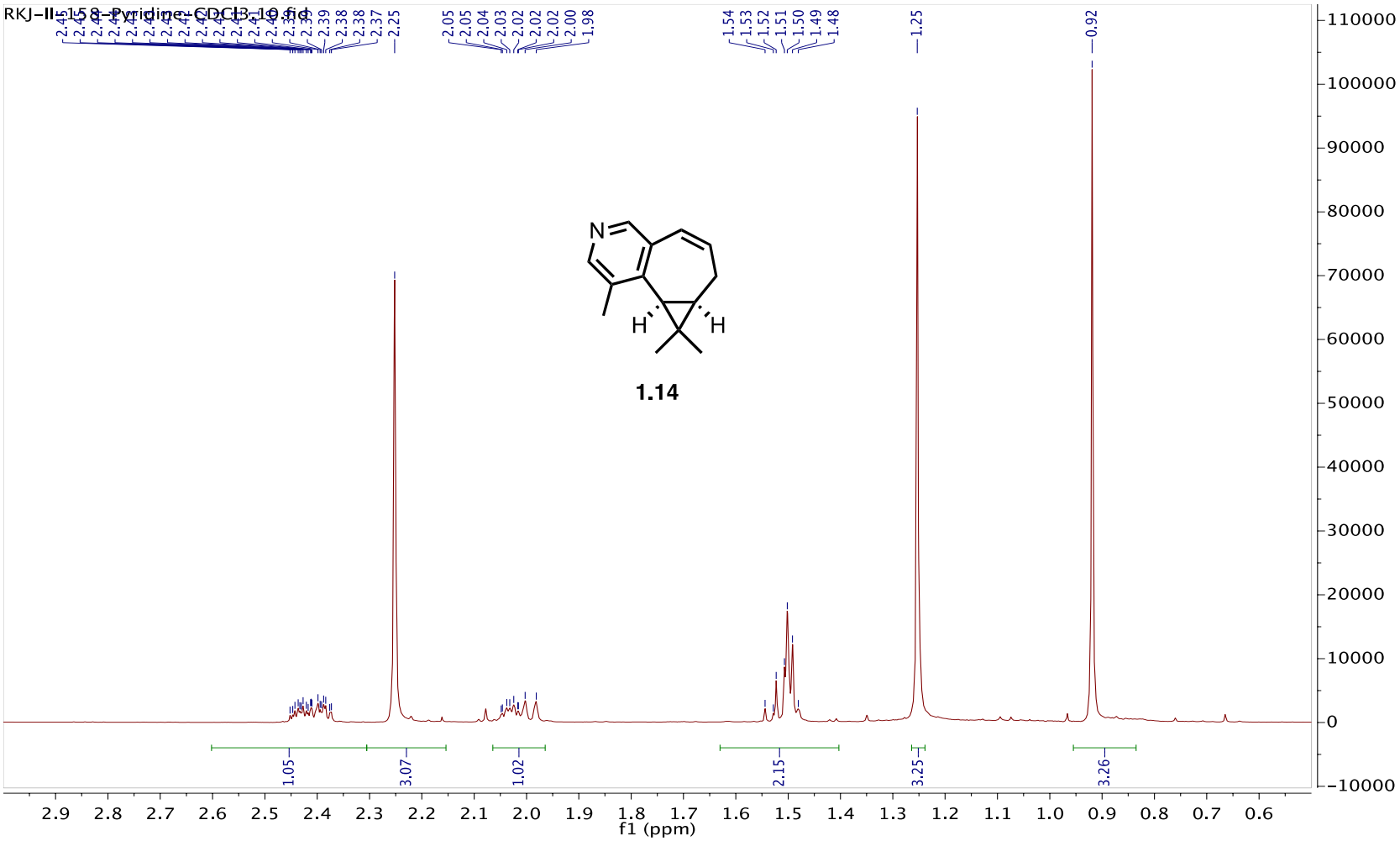


Figure A.29. **^{1}H NMR** (400 MHz, $CDCl_3$) of Pyridine **1.14** (3.0 – 0.5 ppm inset)

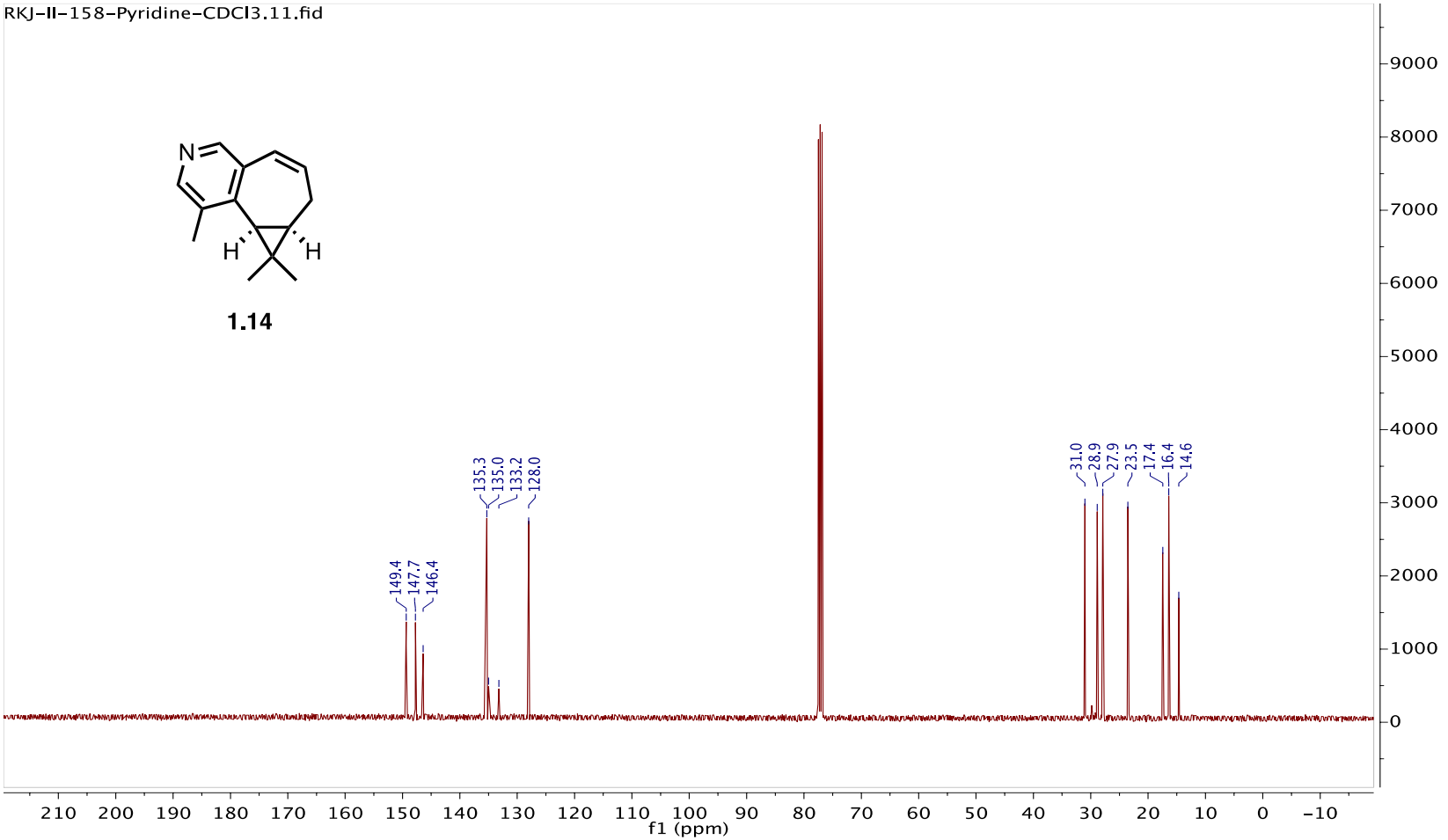


Figure A.30. **^{13}C NMR** (101 MHz, $CDCl_3$) of Pyridine **1.14**

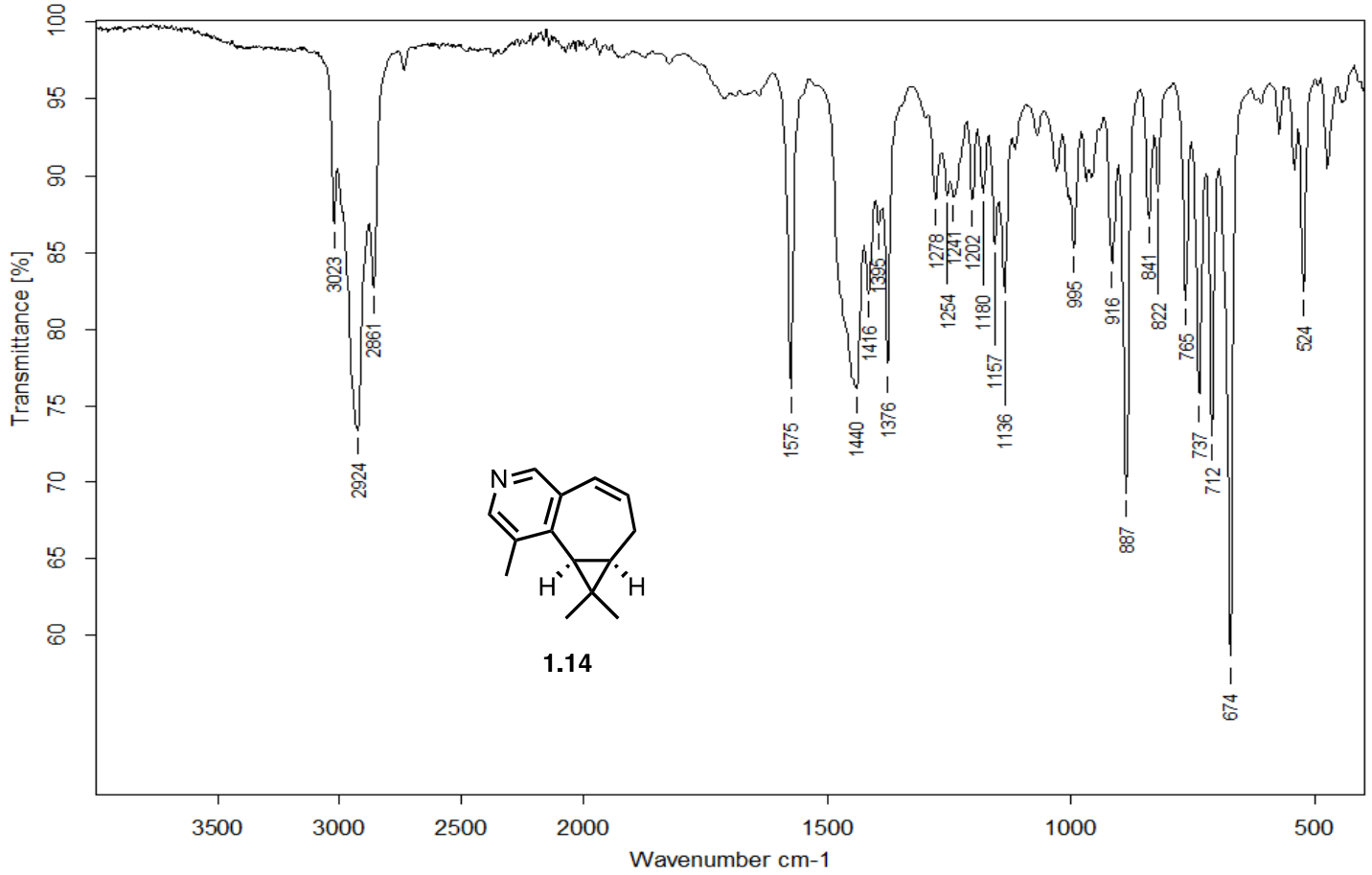


Figure A.31. **FTIR** (thin film) of Pyridine **1.14**

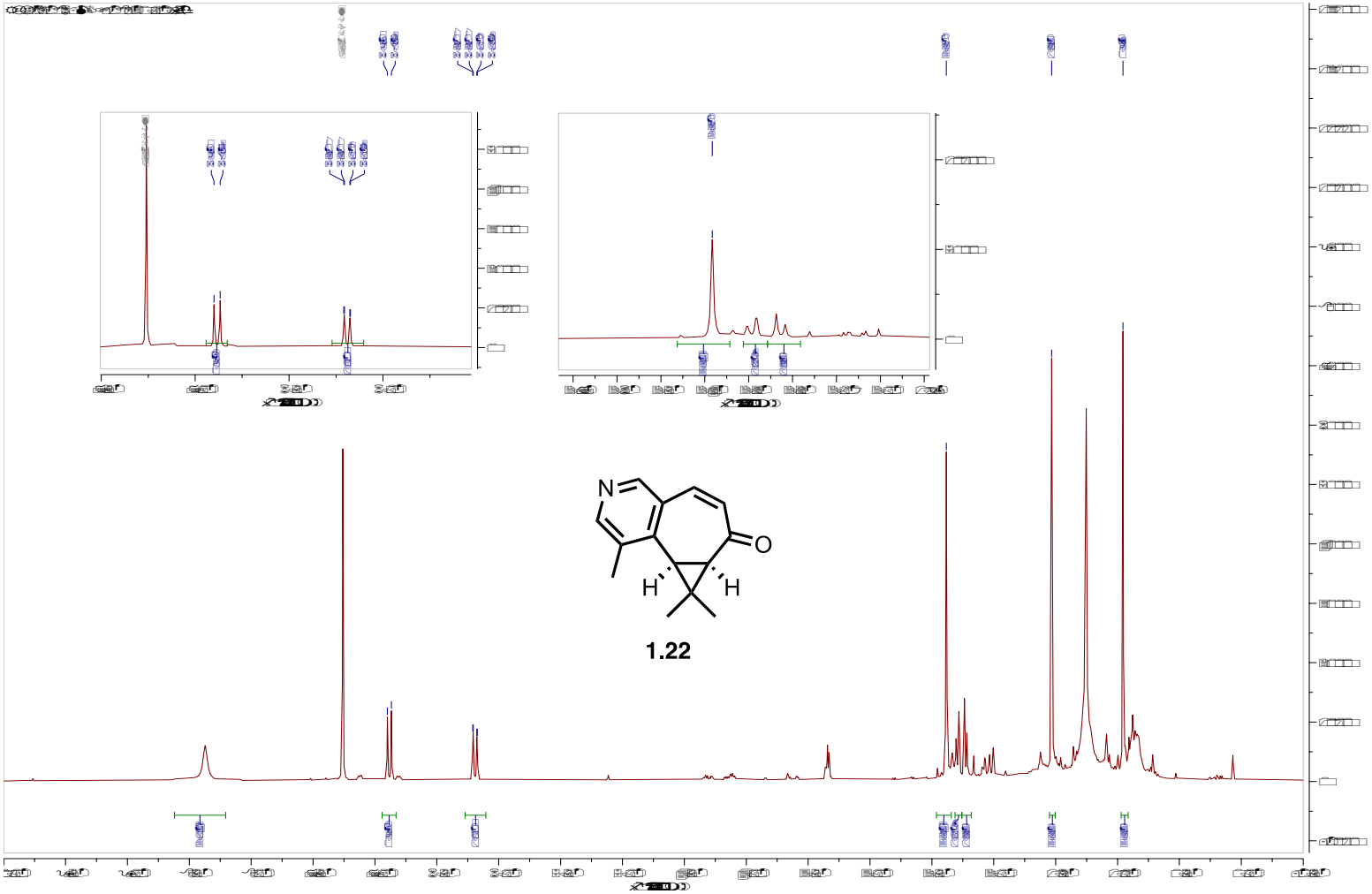


Figure A.32. **^{1}H NMR** (400 MHz, $CDCl_3$) of Enone **1.22**

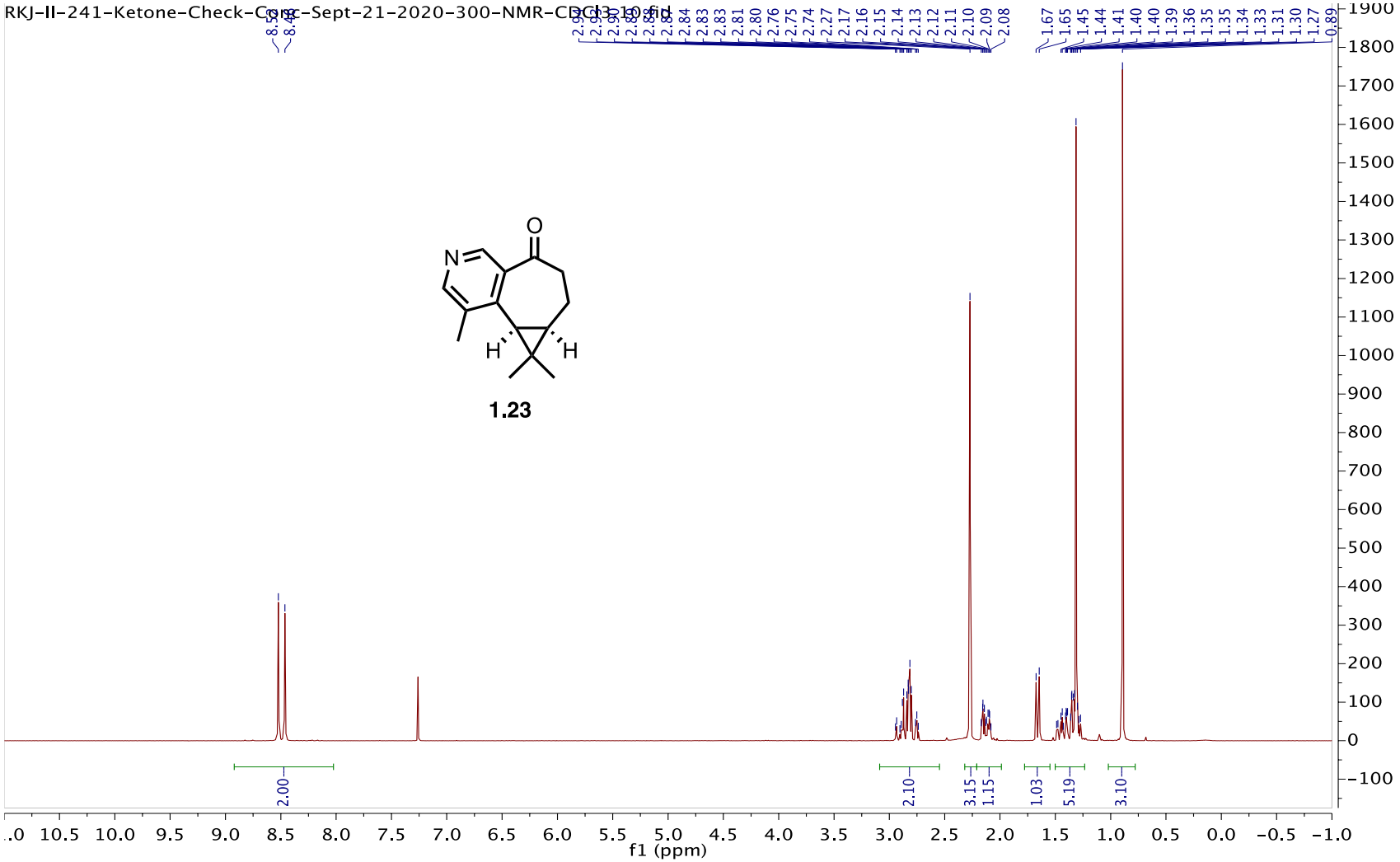


Figure A.33. **^{1}H NMR** (300 MHz, $CDCl_3$) of Ketone **1.23**

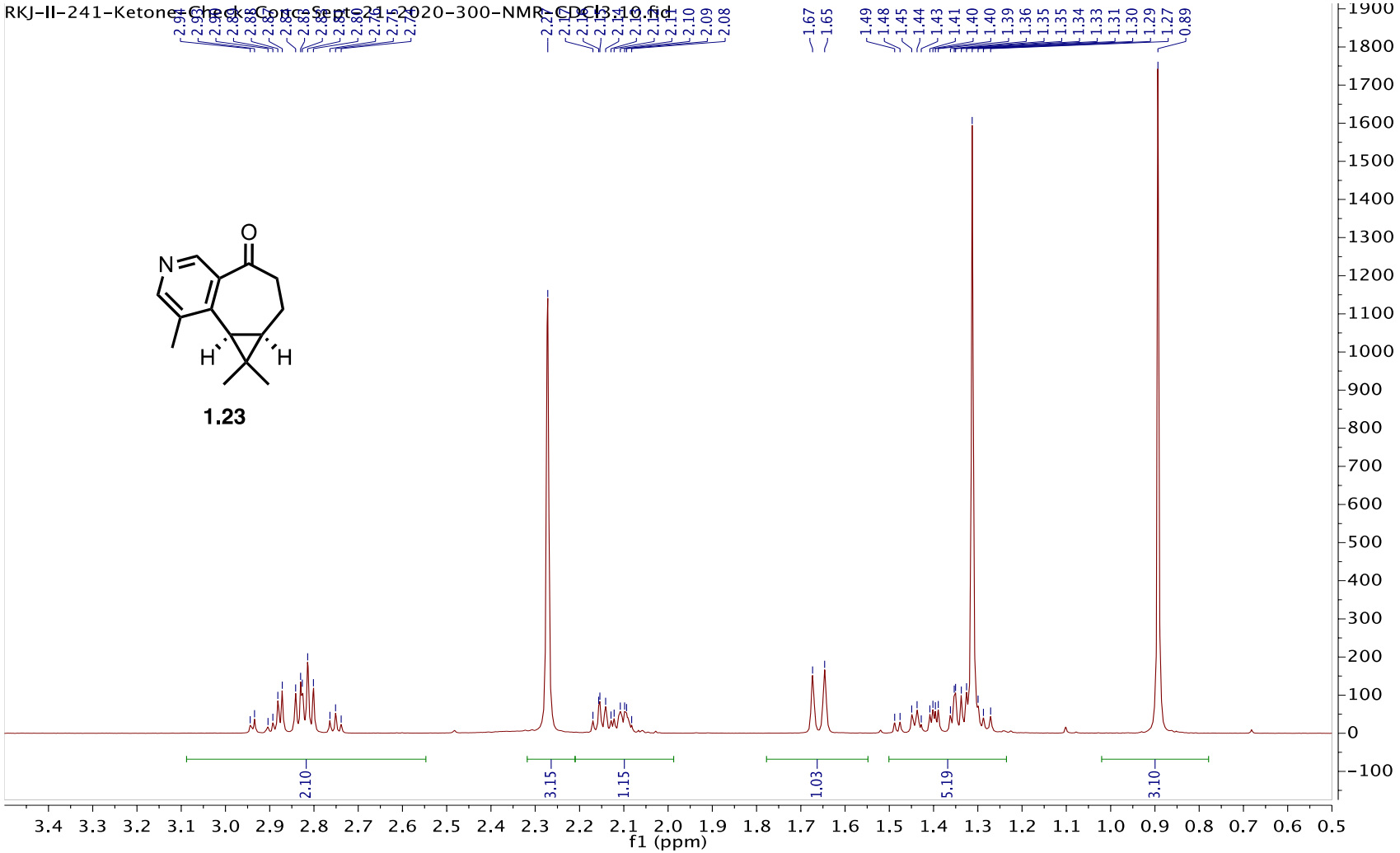


Figure A.34. **^{1}H NMR** (300 MHz, $CDCl_3$) of Ketone **1.23** (3.5 – 0.5 ppm inset)

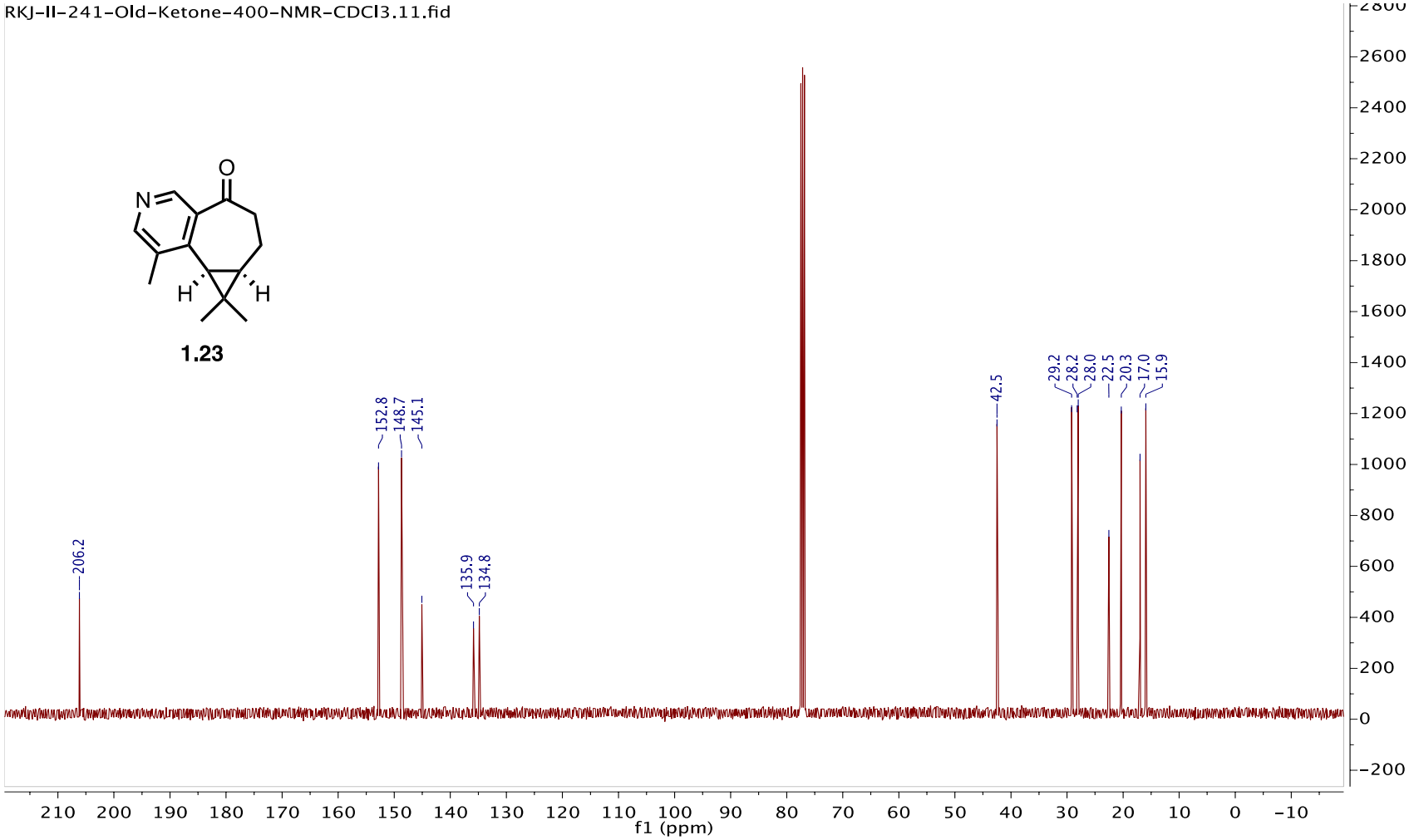


Figure A.35. **^{13}C NMR** (101 MHz, $CDCl_3$) of Ketone **1.23**

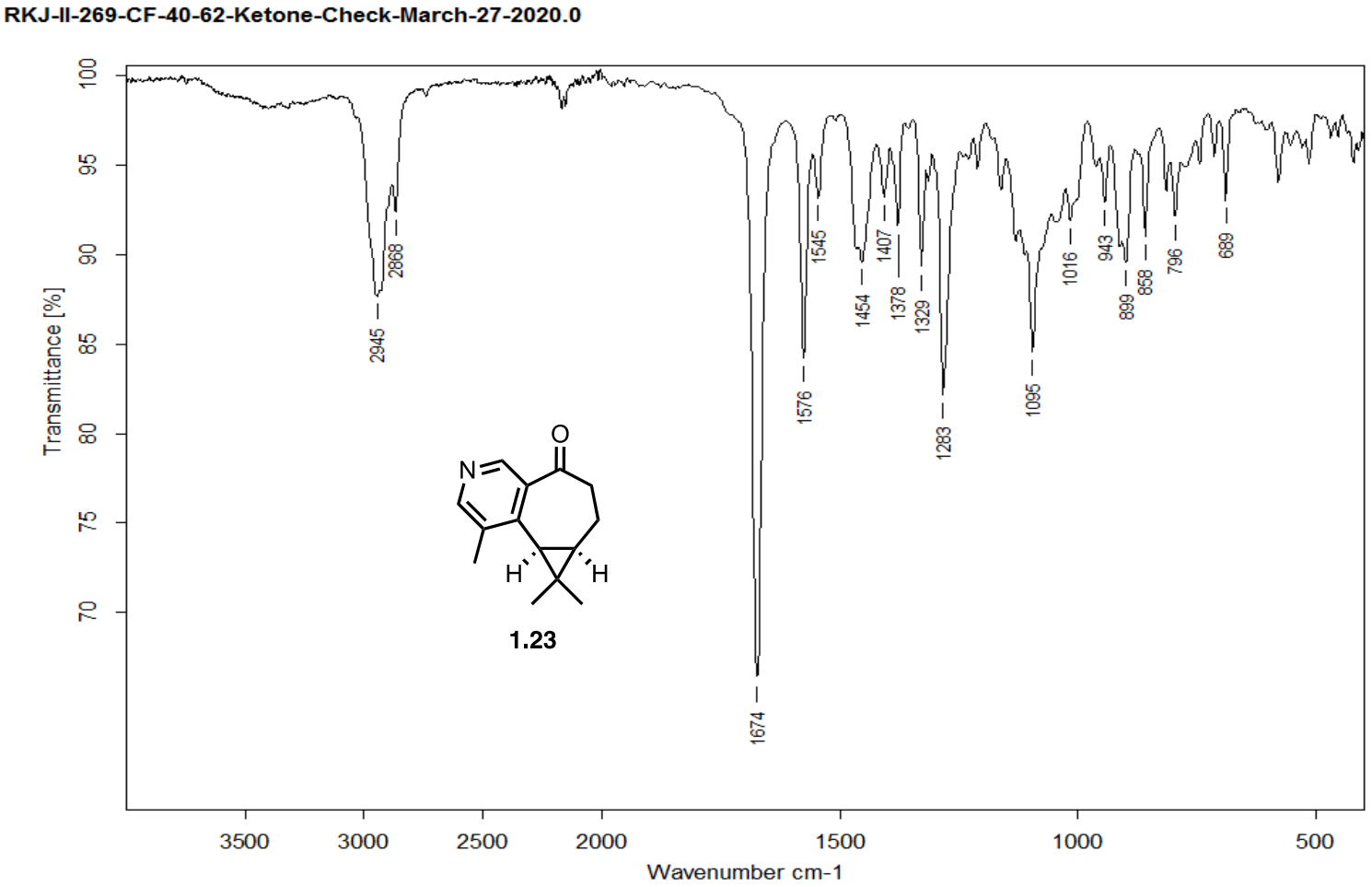


Figure A.36. **FTIR** (thin film) of Ketone **1.23**

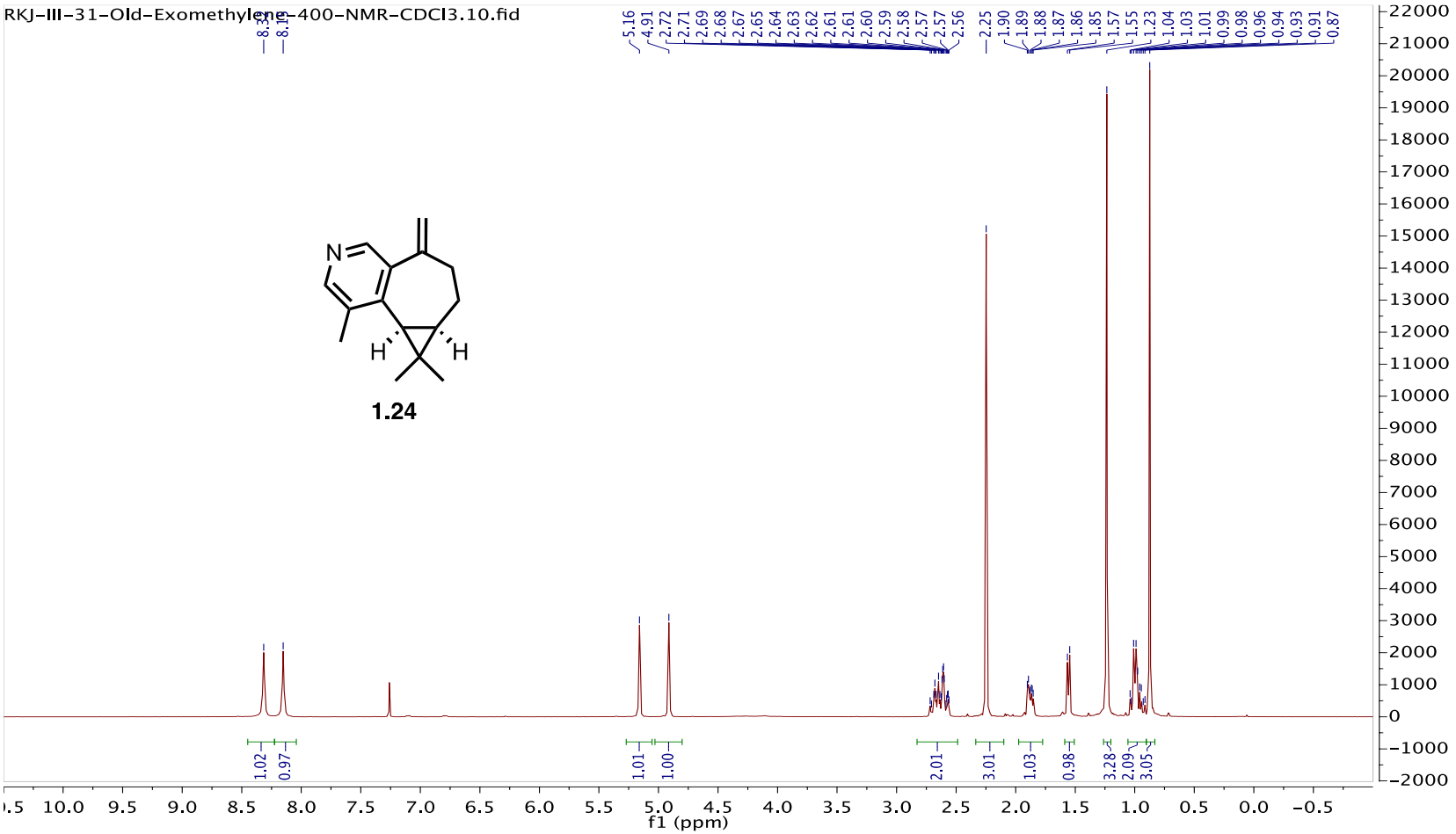


Figure A.37. **^{1}H NMR** (400 MHz, $CDCl_3$) of Olefin **1.24**

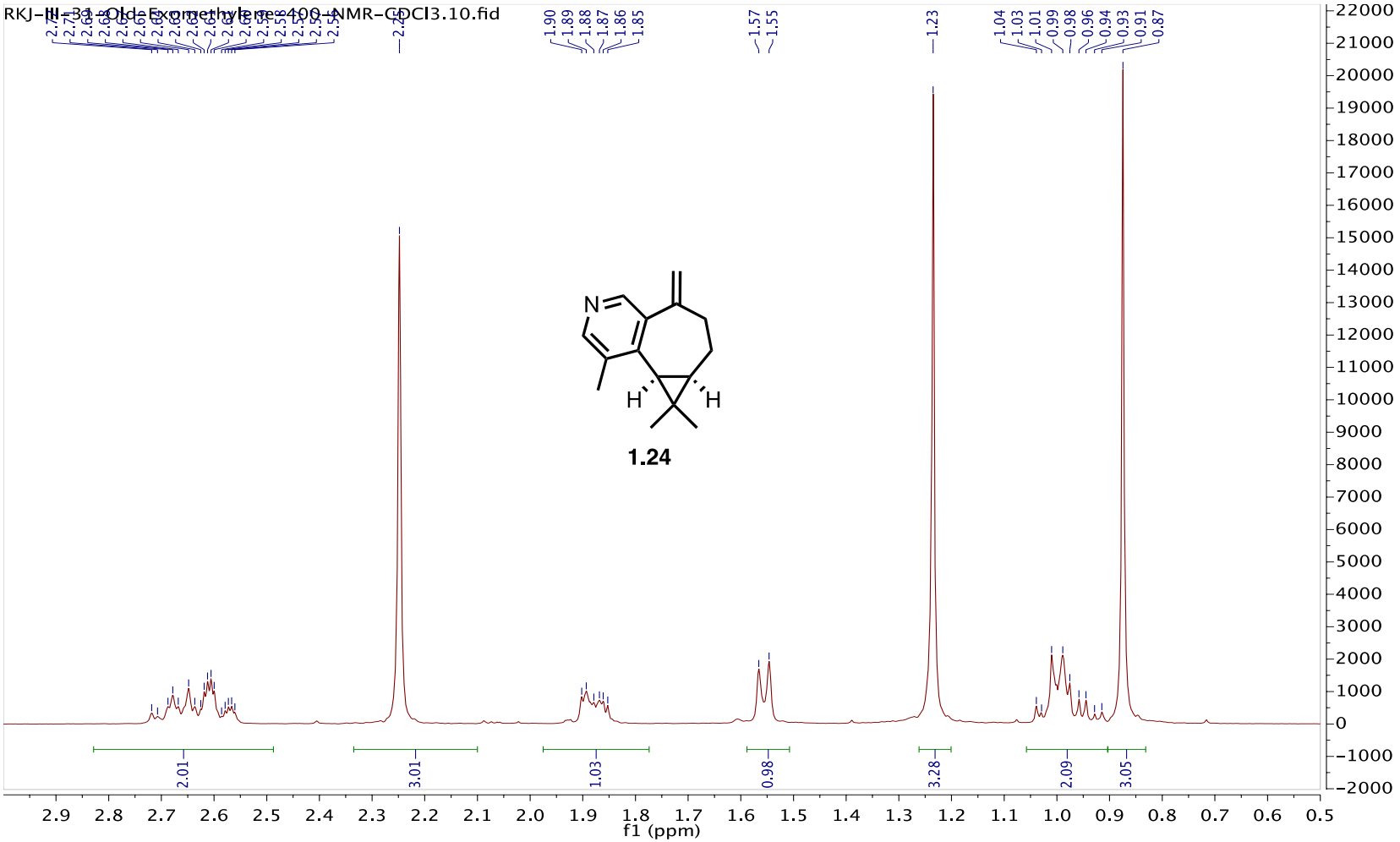


Figure A.38. **^{1}H NMR** (400 MHz, $CDCl_3$) of Olefin **1.24** (3.0 – 0.5 ppm inset)

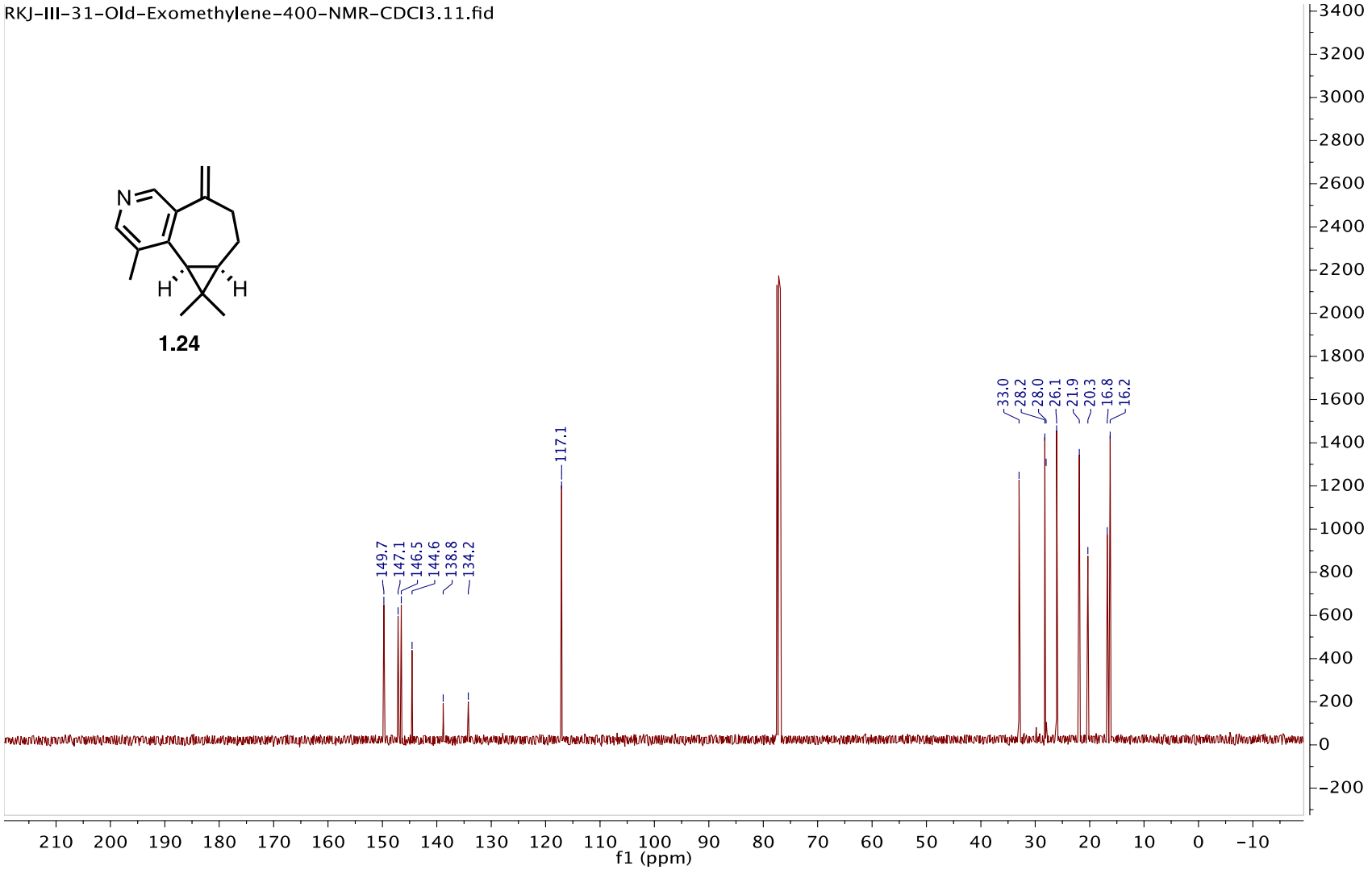


Figure A.39. **^{13}C NMR** (101 MHz, $CDCl_3$) of Olefin **1.24**

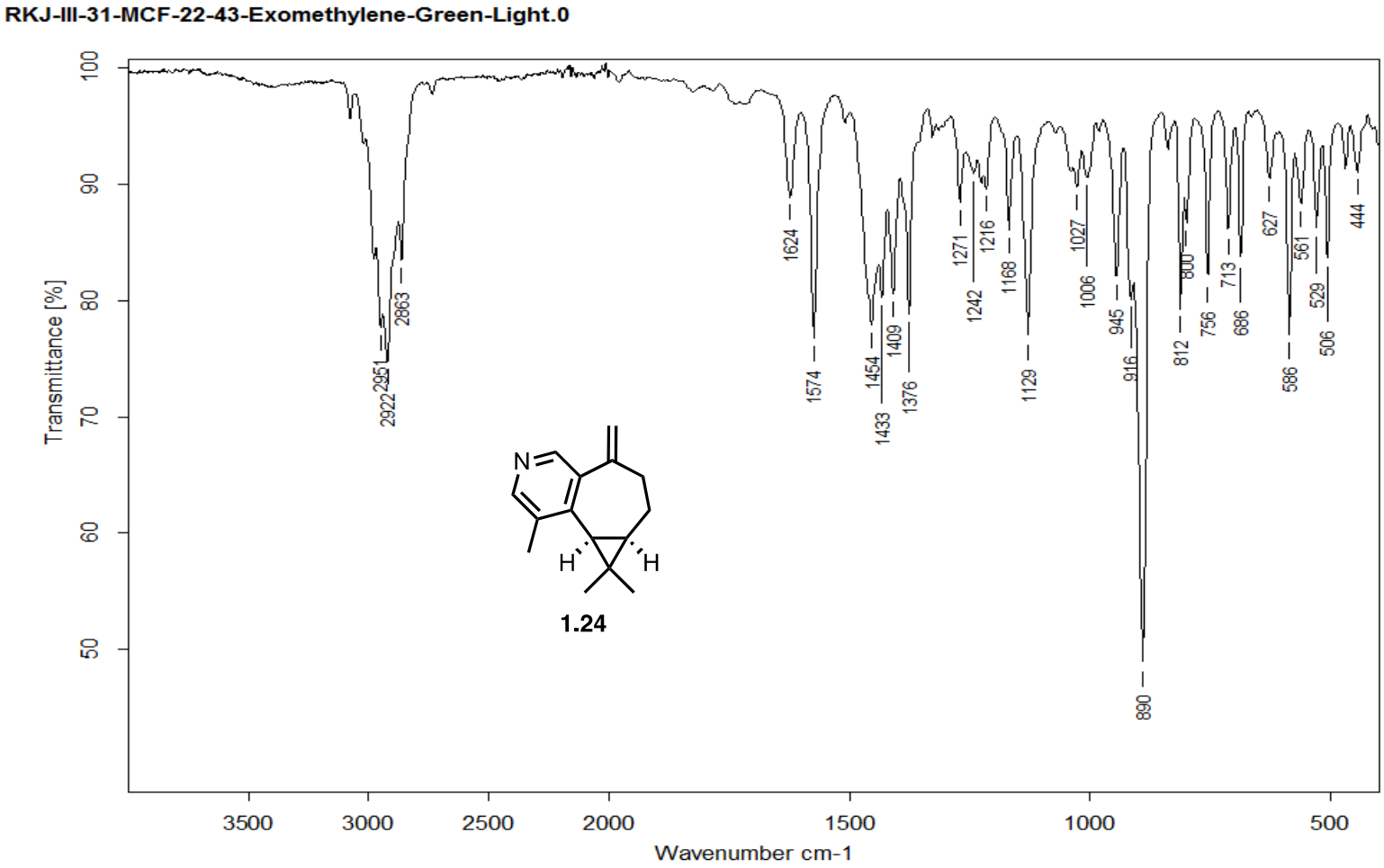


Figure A.40. **FTIR** (thin film) Olefin **1.24**

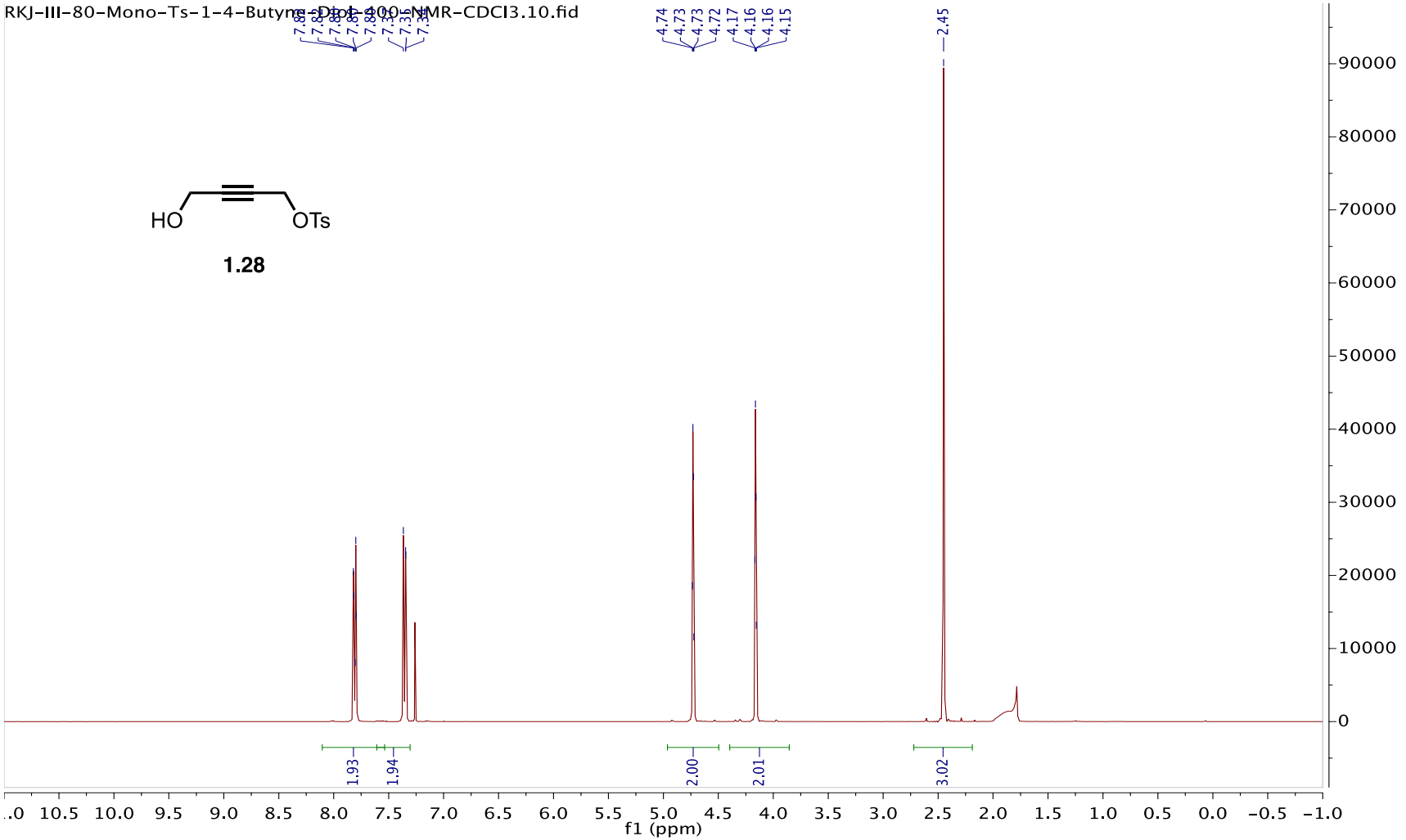


Figure A.41. **^{1}H NMR** (400 MHz, $CDCl_3$) of Tosylate **1.28**

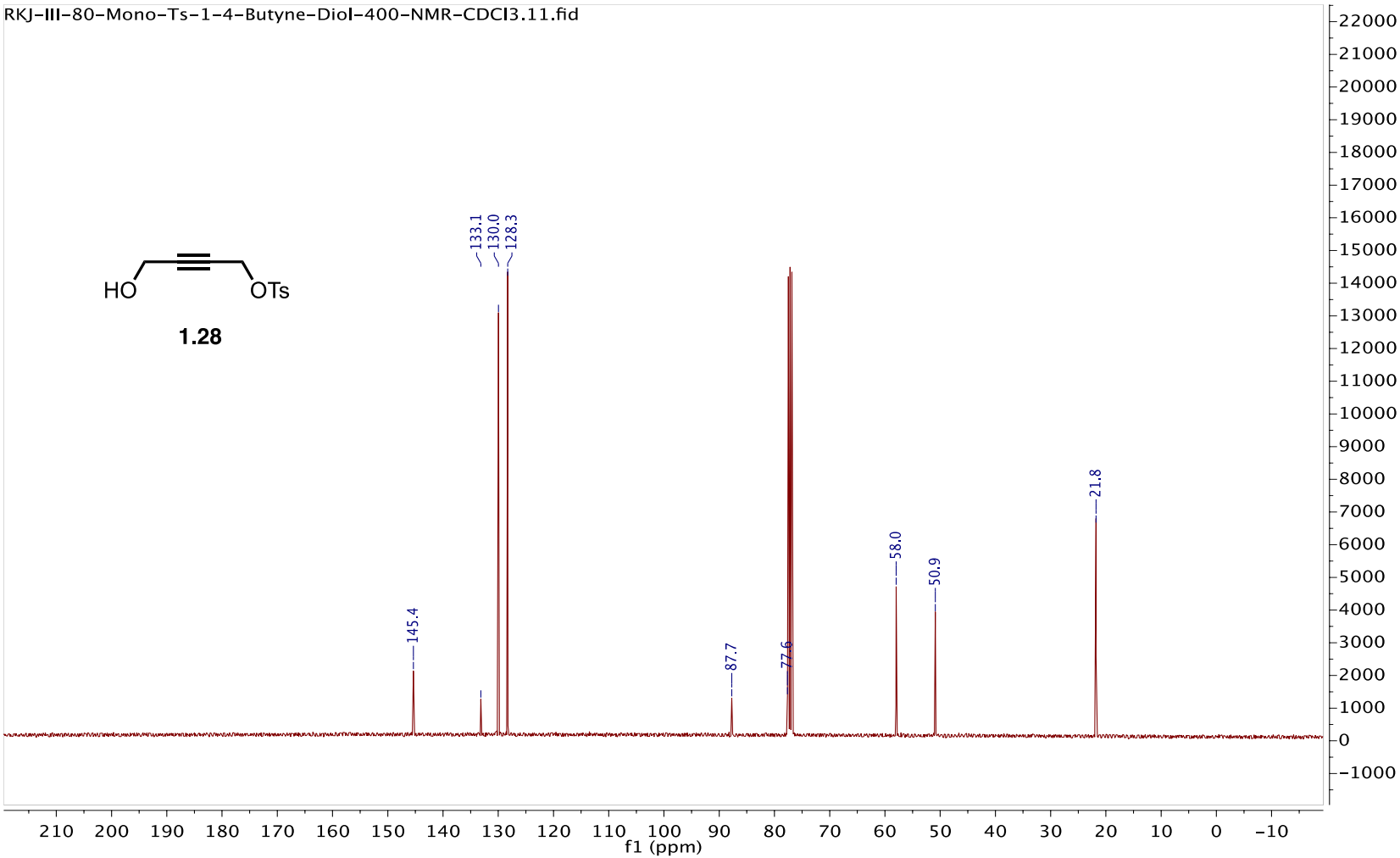


Figure A.42. **^{13}C NMR** (101 MHz, $CDCl_3$) of Tosylate **1.28**

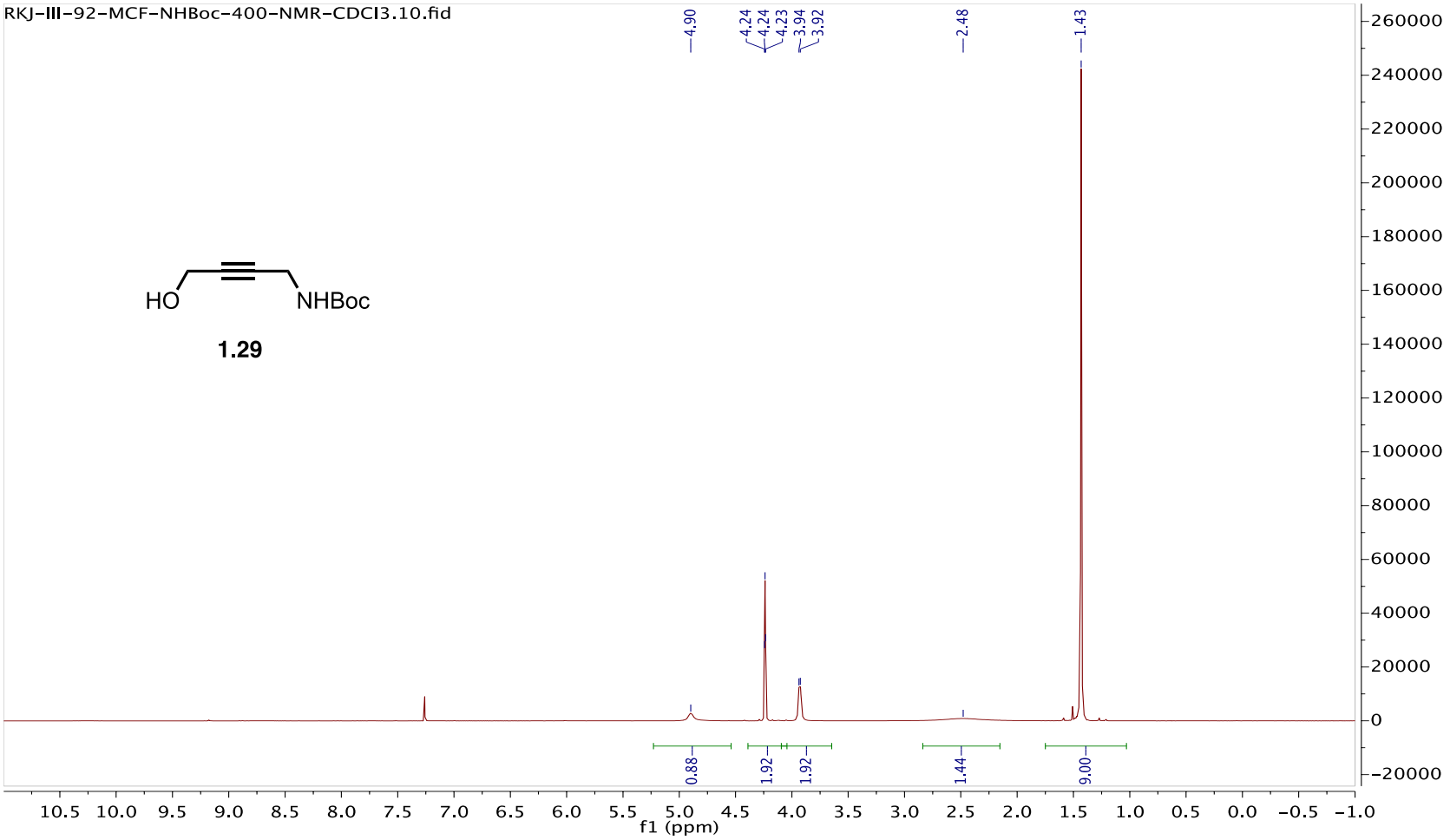


Figure A.43. **^{1}H NMR** (400 MHz, $CDCl_3$) of Propargyl Alcohol **1.29**

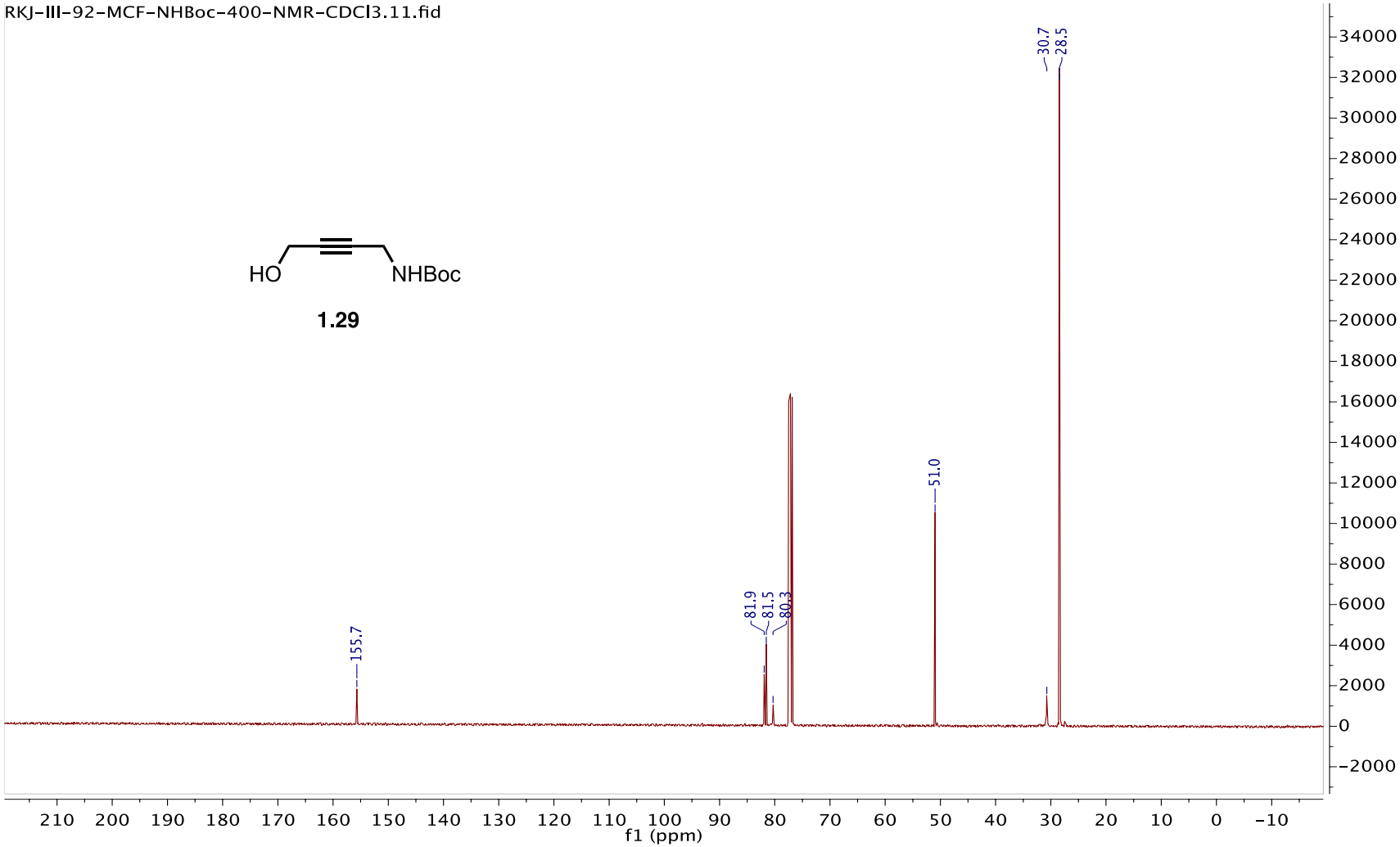


Figure A.44. **^{13}C NMR** (101 MHz, $CDCl_3$) of Propargyl Alcohol **1.29**

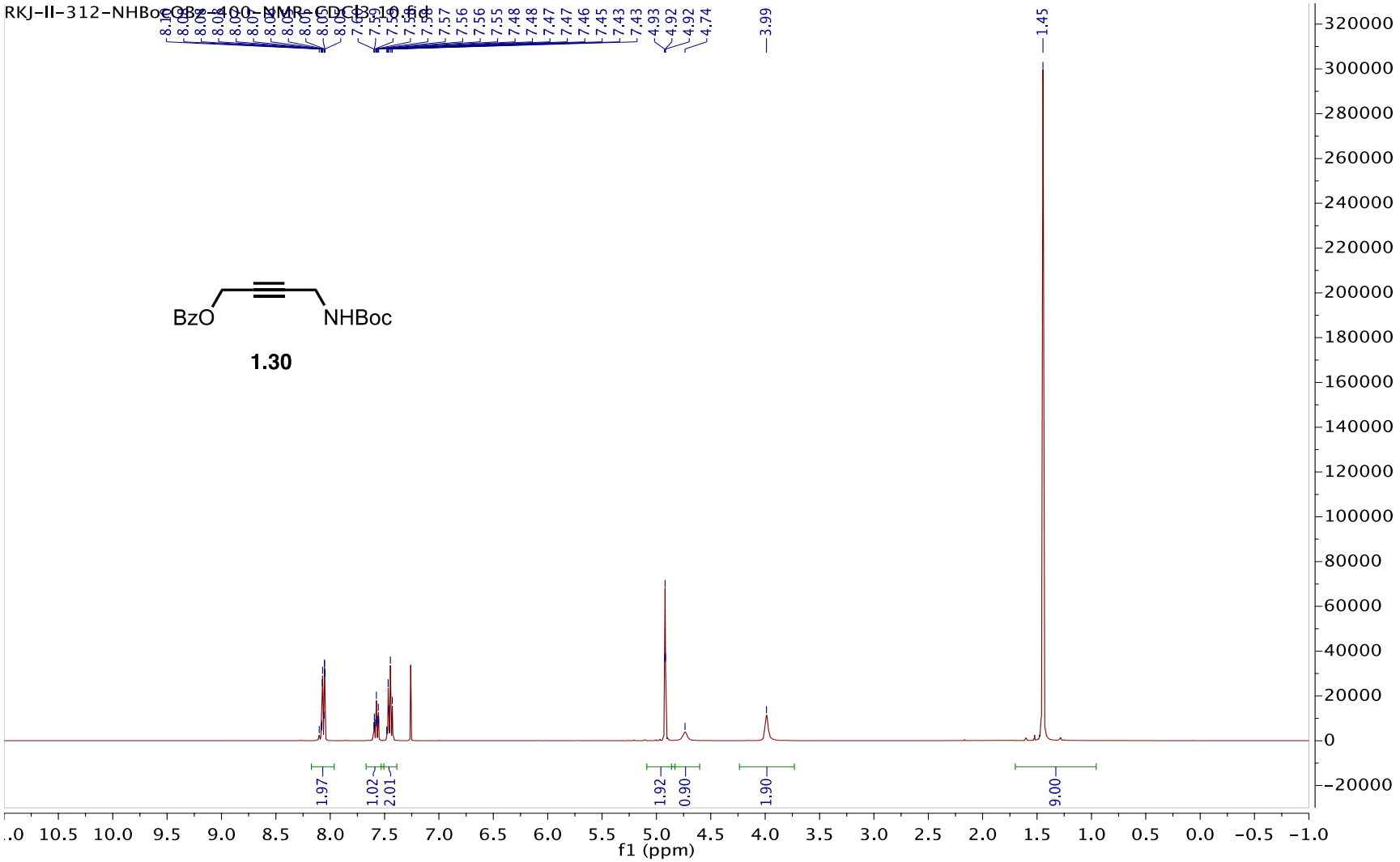


Figure A.45. **^{1}H NMR** (400 MHz, $CDCl_3$) of Benzoate **1.30**

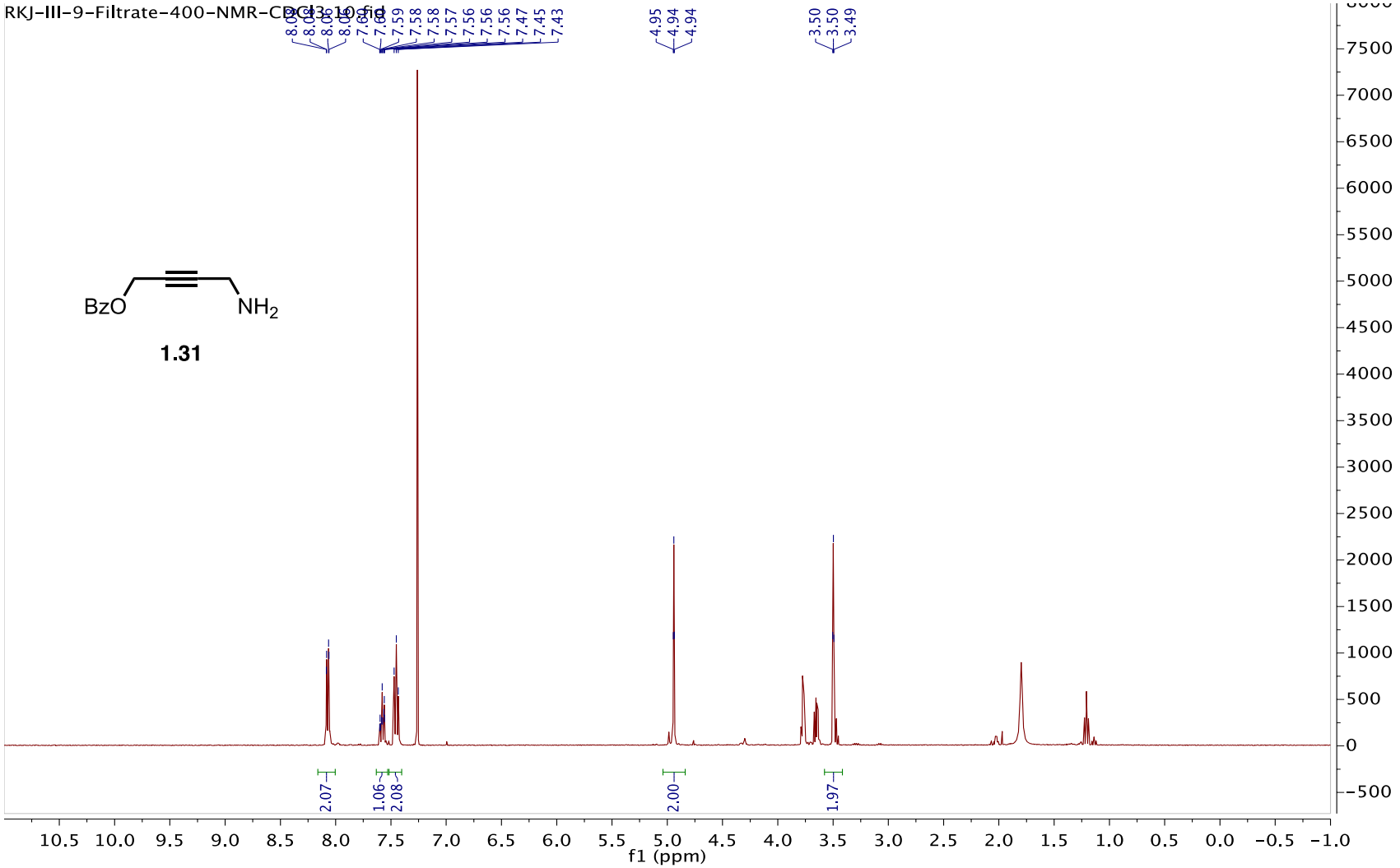


Figure A.46. **^{1}H NMR** (400 MHz, $CDCl_3$) of Crude **1.31**

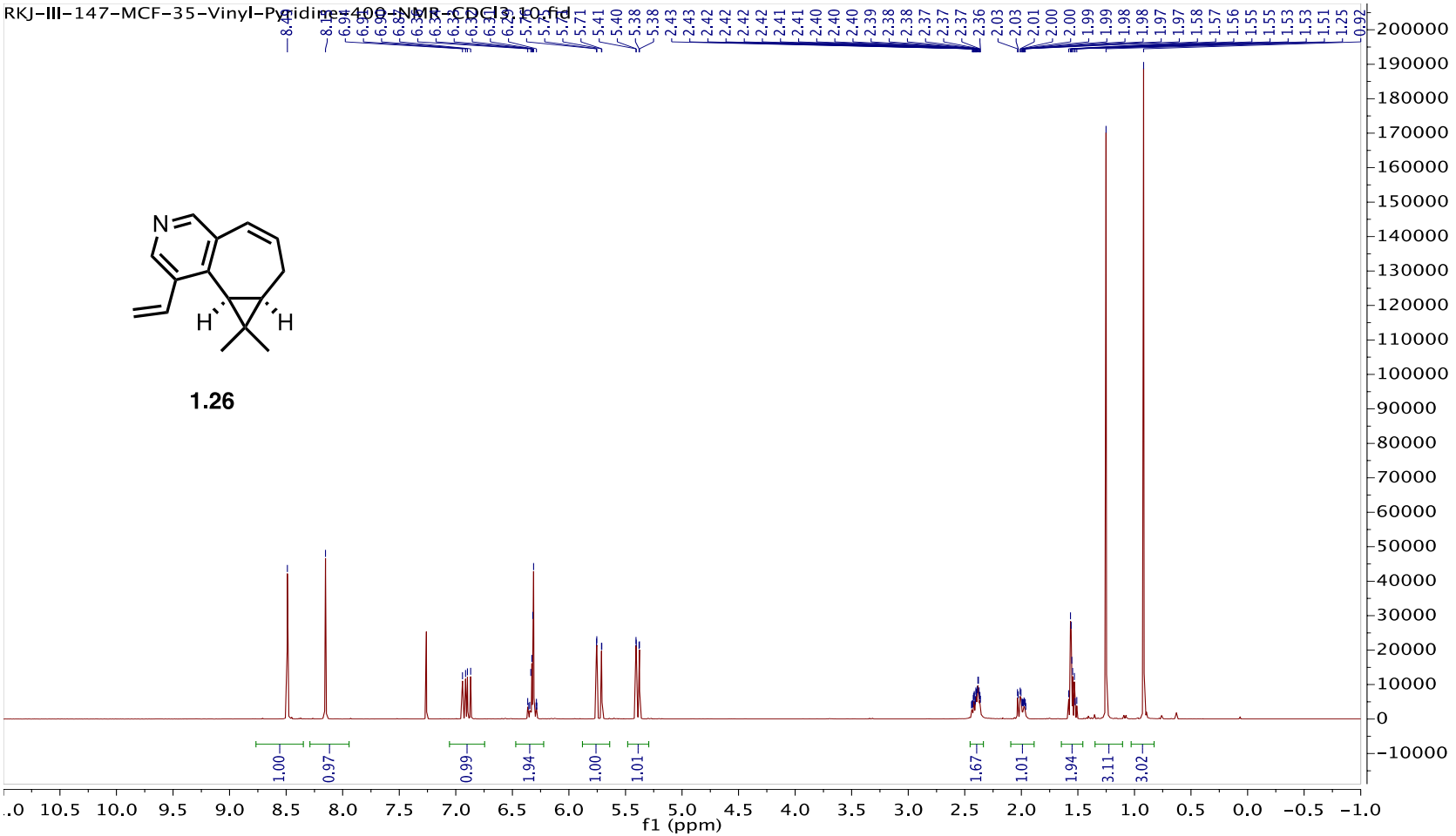


Figure A.47. **^{1}H NMR** (400 MHz, $CDCl_3$) of Terminal Olefin **1.26**

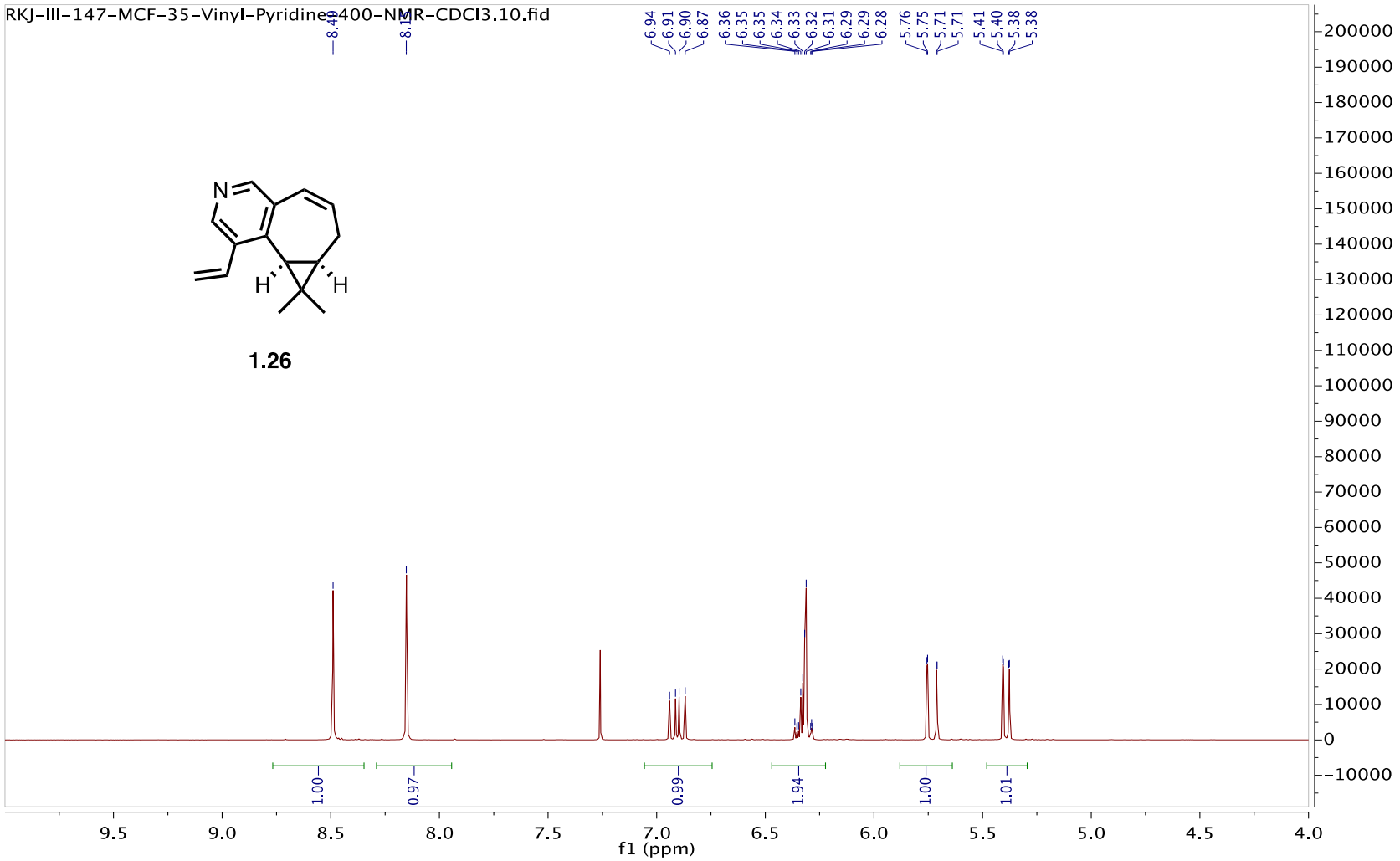


Figure A.48. **^{1}H NMR** (400 MHz, $CDCl_3$) of Terminal Olefin **1.26** (10.0 – 4.0 ppm inset)

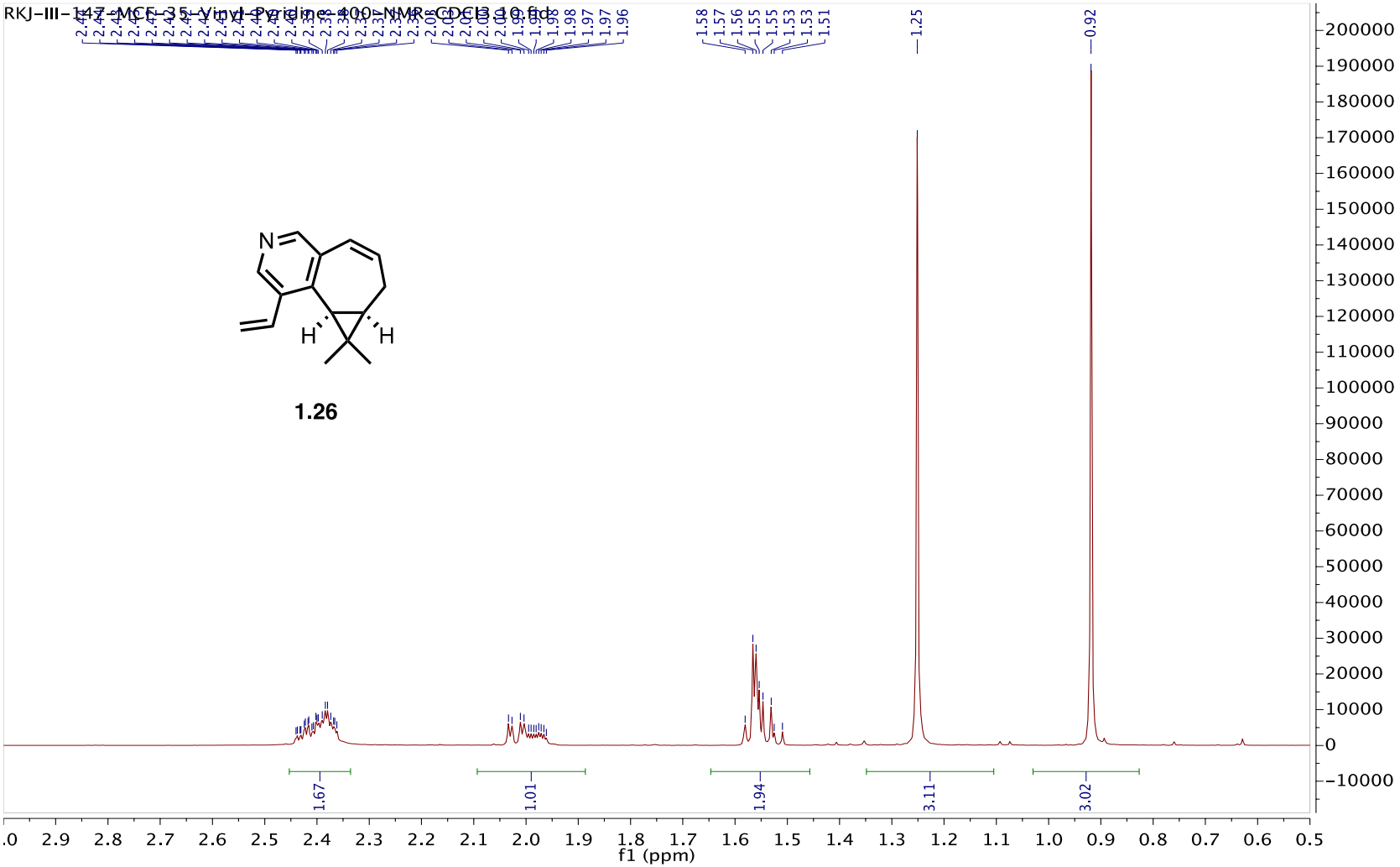


Figure A.49. **^{1}H NMR** (400 MHz, $CDCl_3$) of Terminal Olefin **1.27** (3.0 – 0.5 ppm inset)

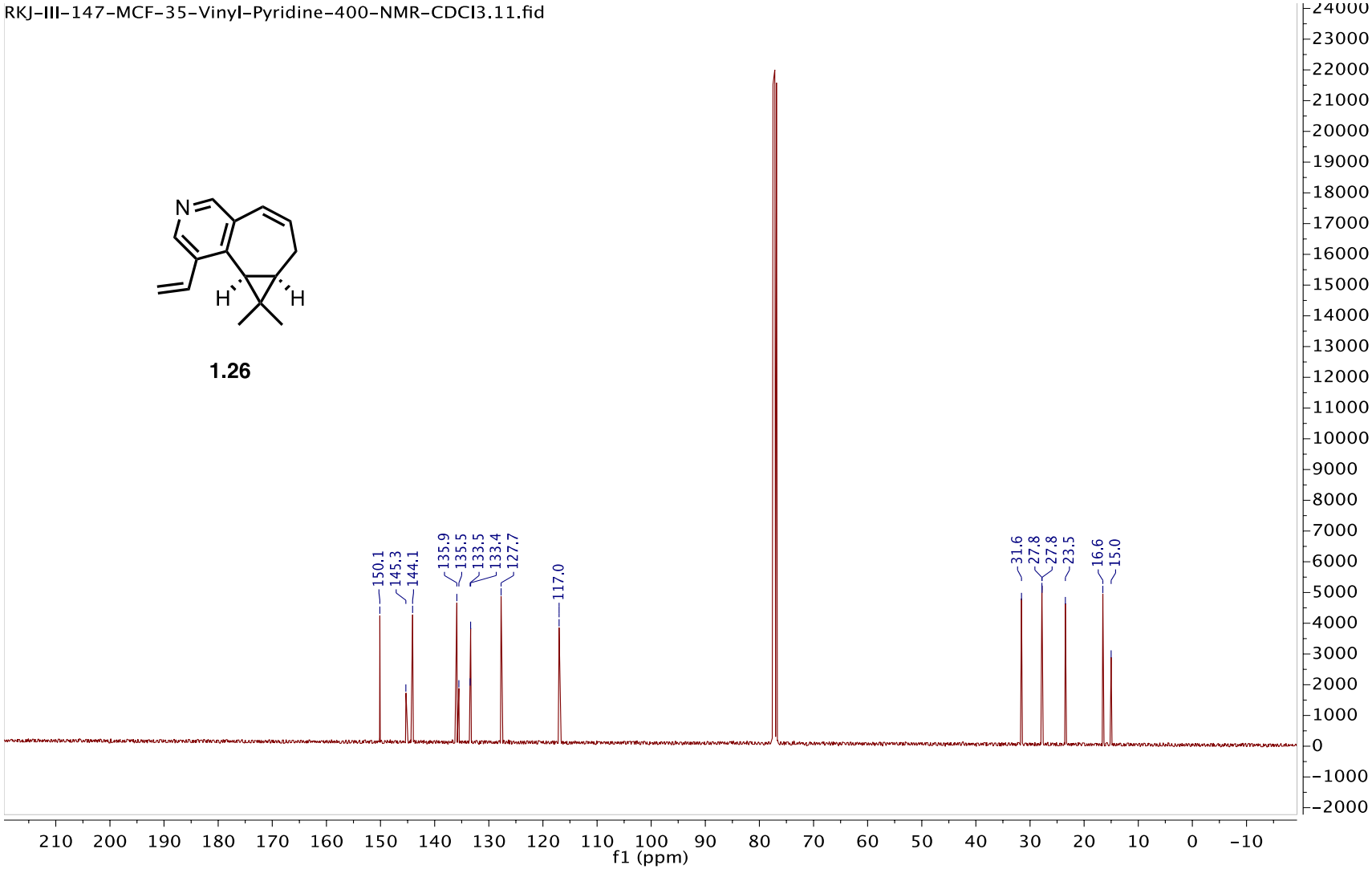


Figure A.50. **^{13}C NMR** (101 MHz, $CDCl_3$) of Terminal Olefin **1.26**

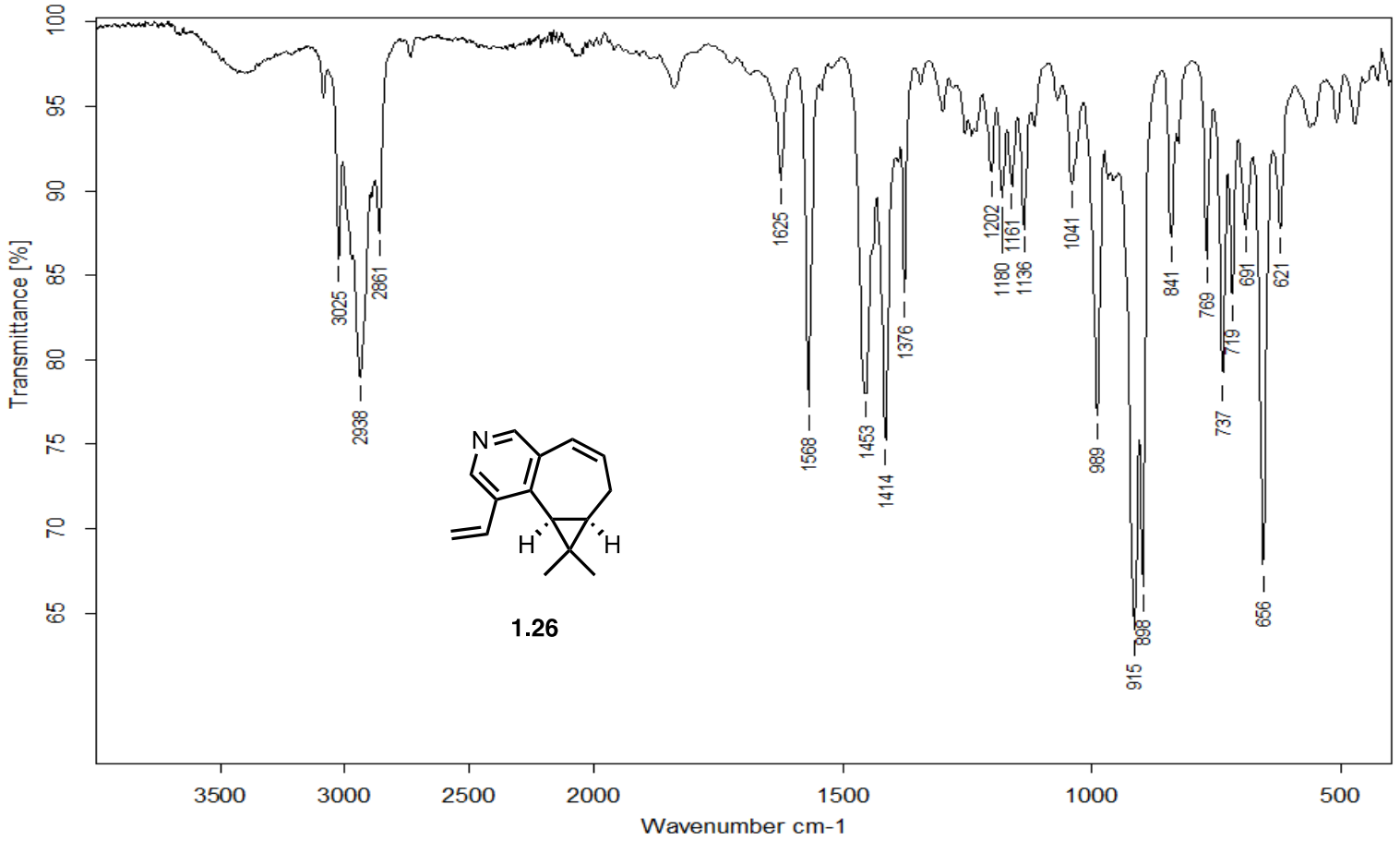


Figure A.51. **FTIR** (thin film) of Terminal Olefin **1.26**

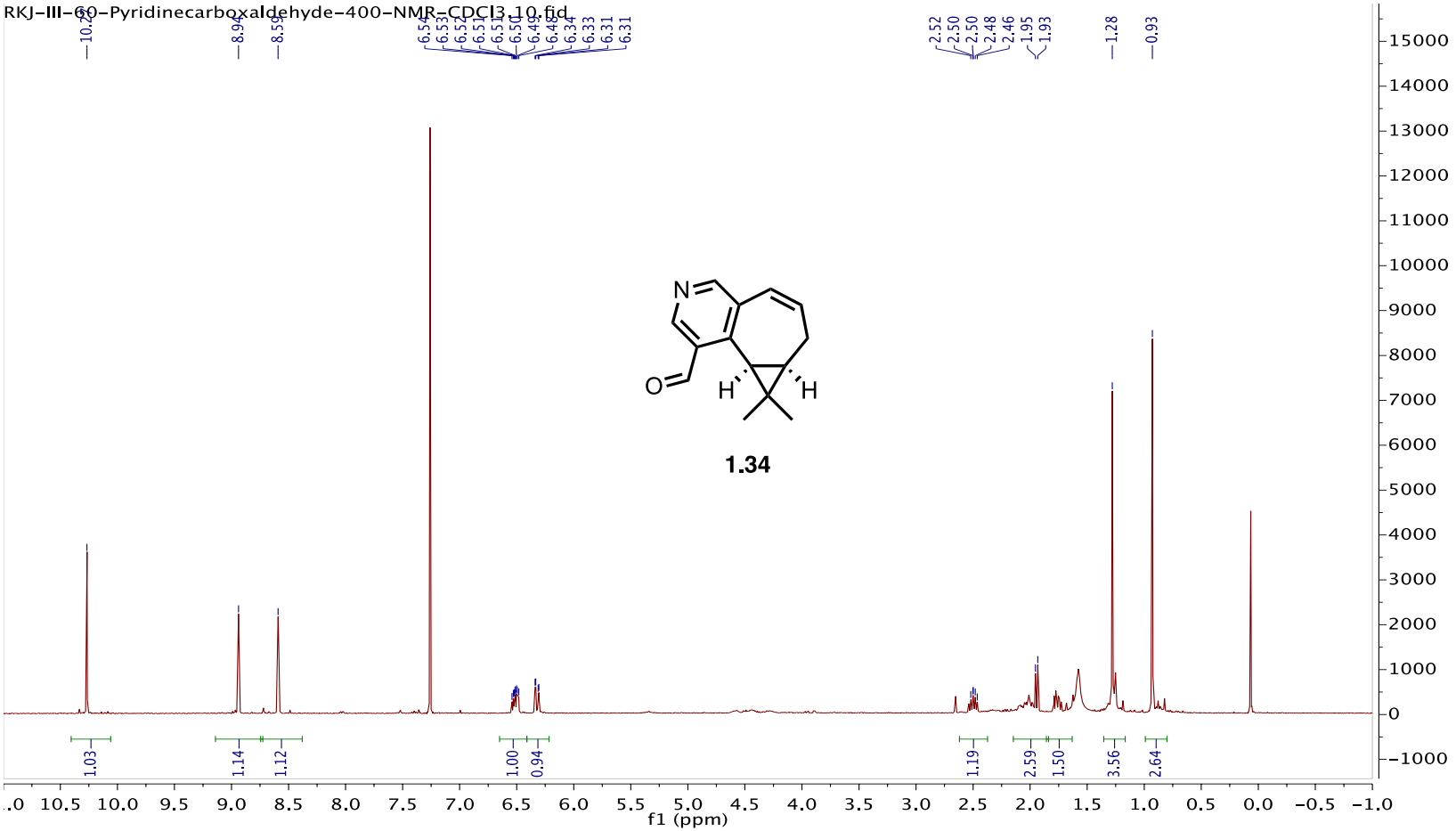


Figure A.52. **^{1}H NMR** (400 MHz, $CDCl_3$) of aldehyde **1.34**

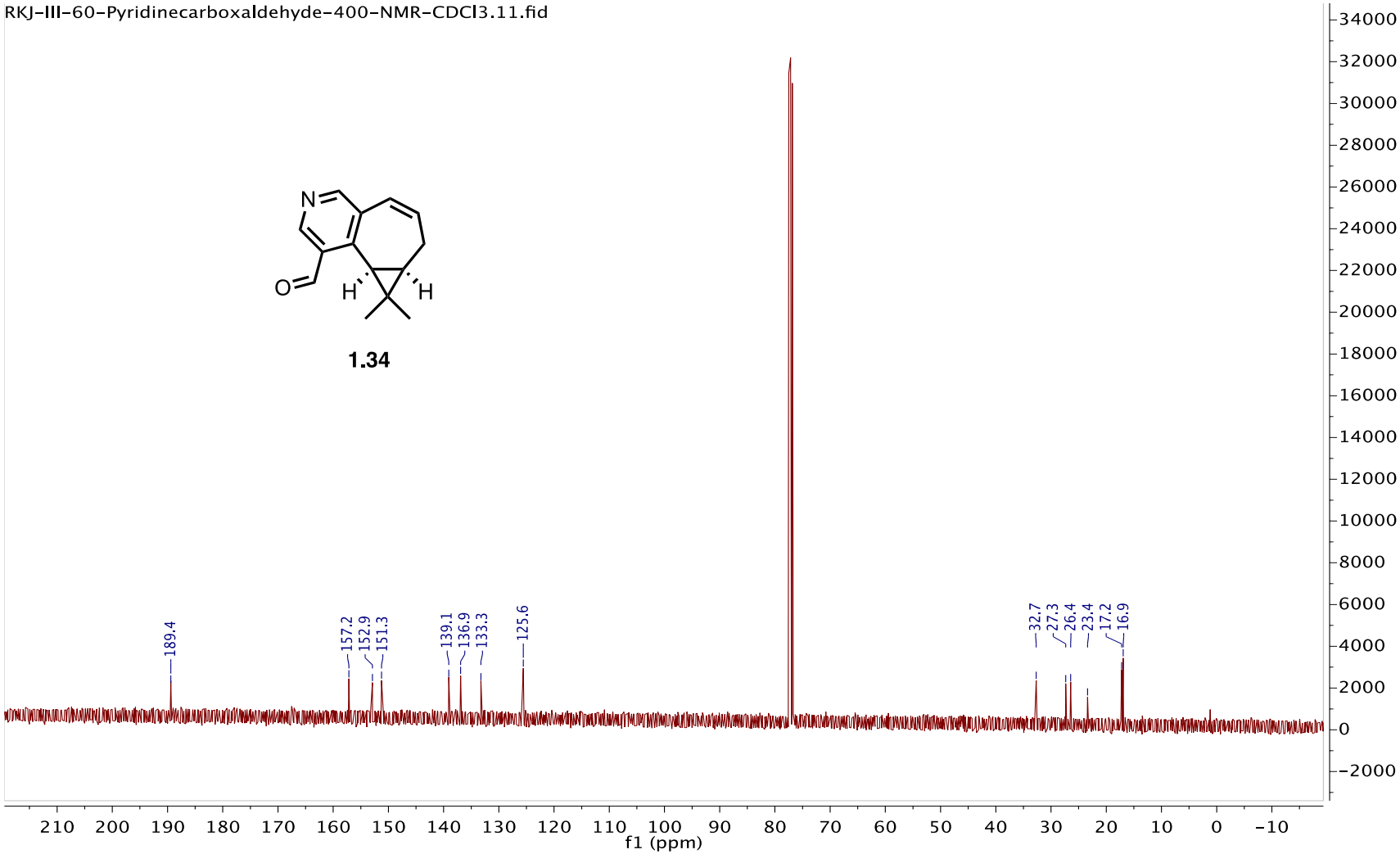


Figure A.53. **^{13}C NMR** (101 MHz, $CDCl_3$) of aldehyde **1.34**

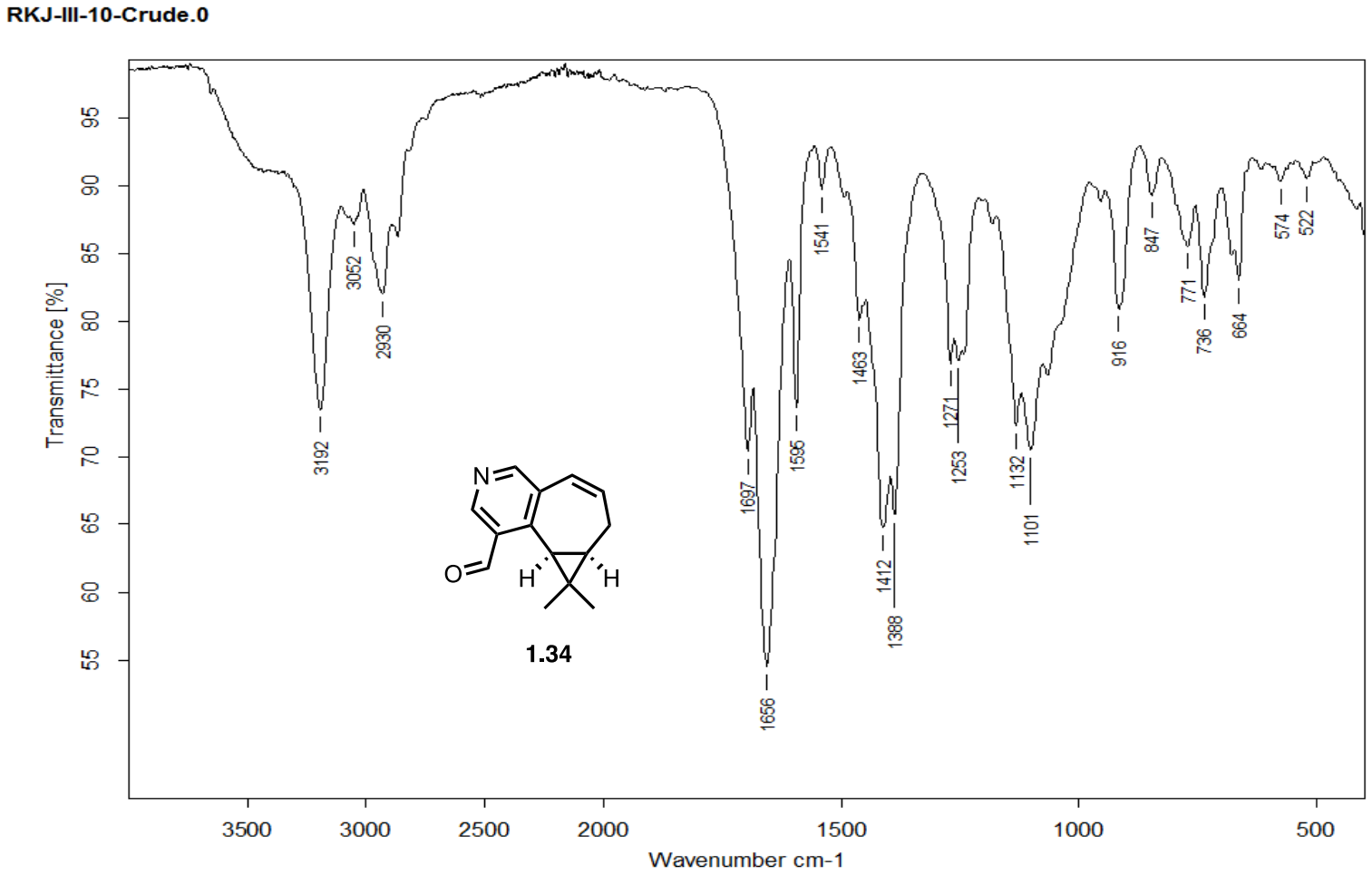


Figure A.54. **FTIR** (thin film) of aldehyde **1.34**

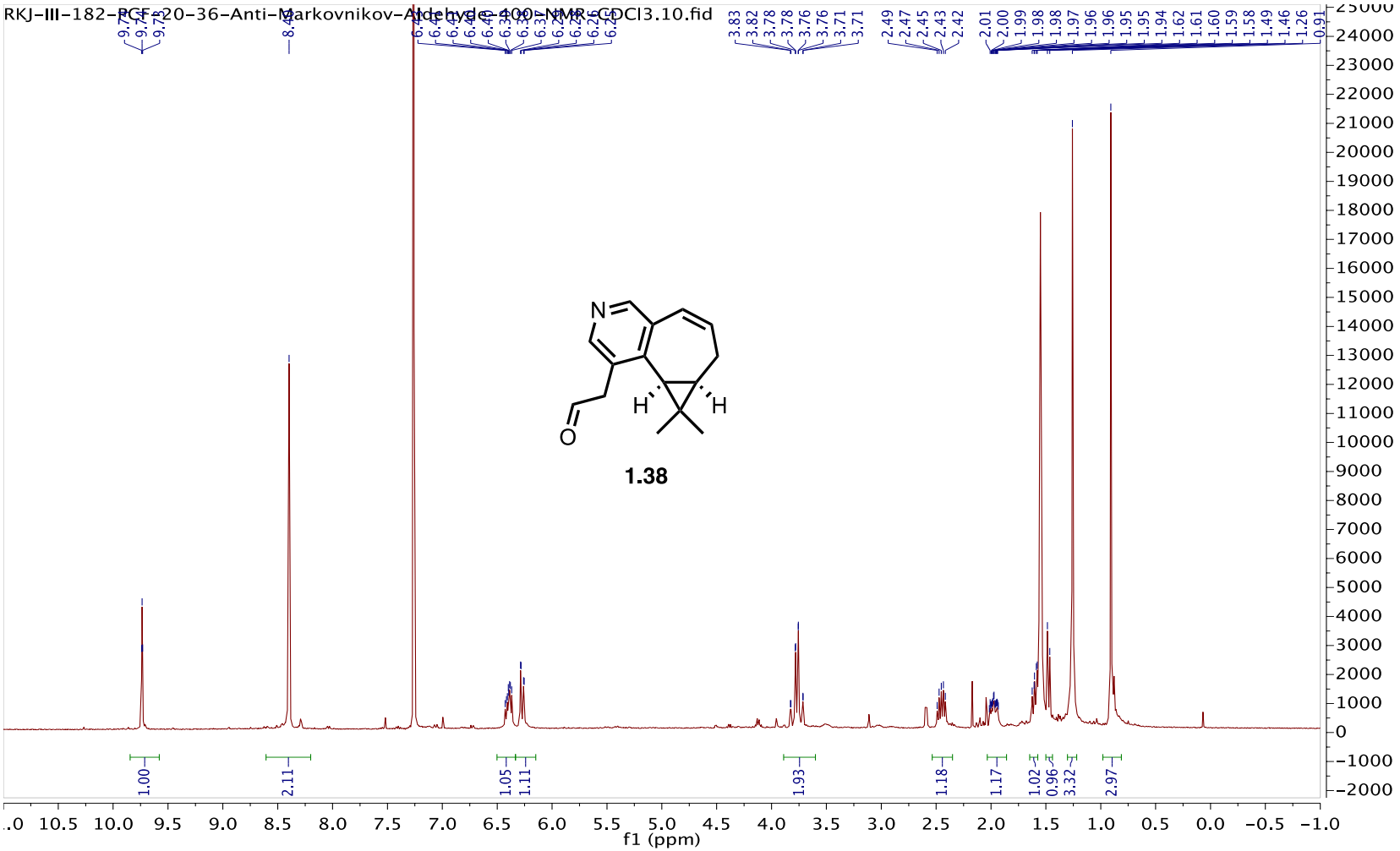


Figure A.55. **^{1}H NMR** (400 MHz, $CDCl_3$) of aldehyde **1.38**

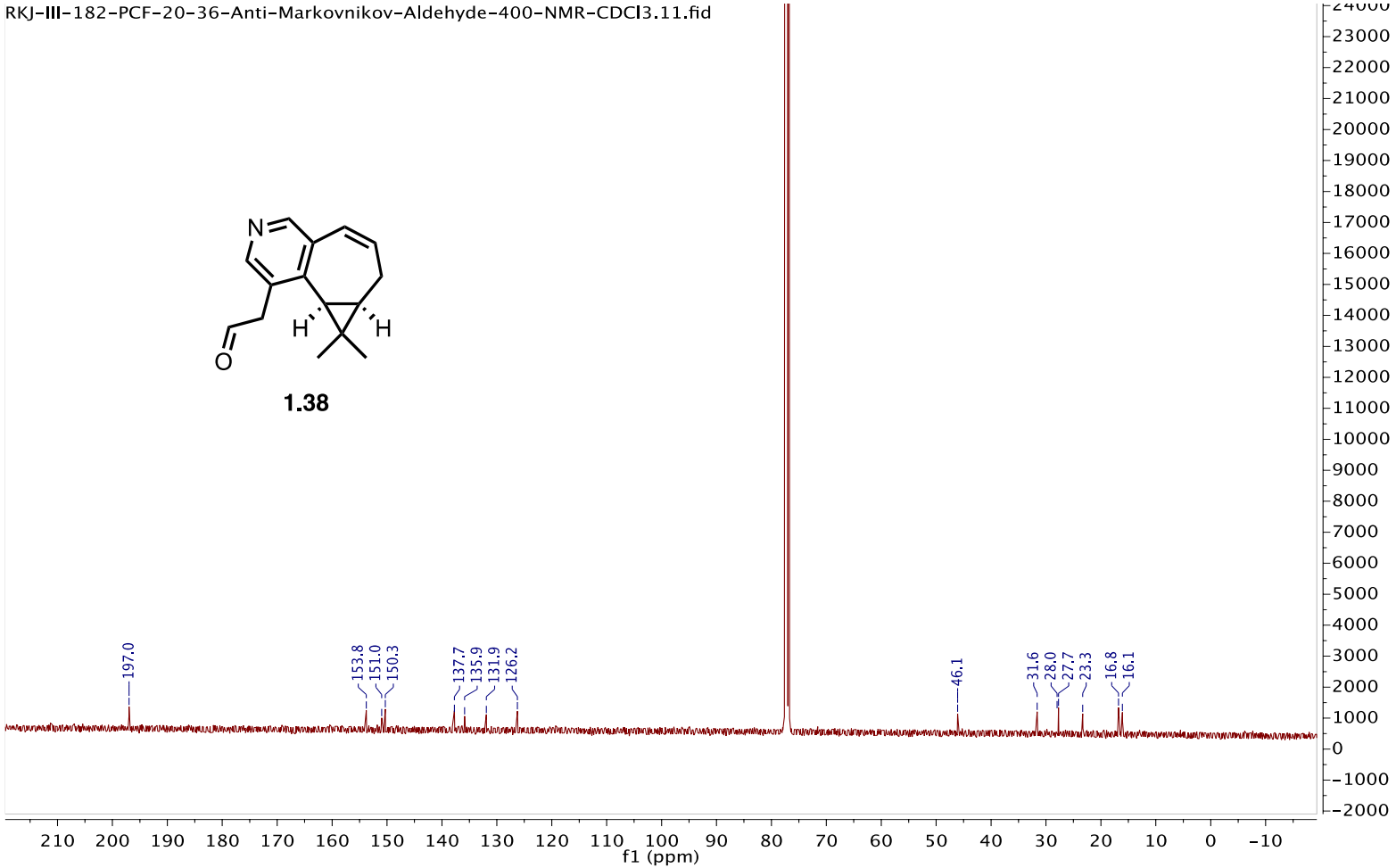


Figure A.56. **^{13}C NMR** (101 MHz, $CDCl_3$) of aldehyde **1.38**

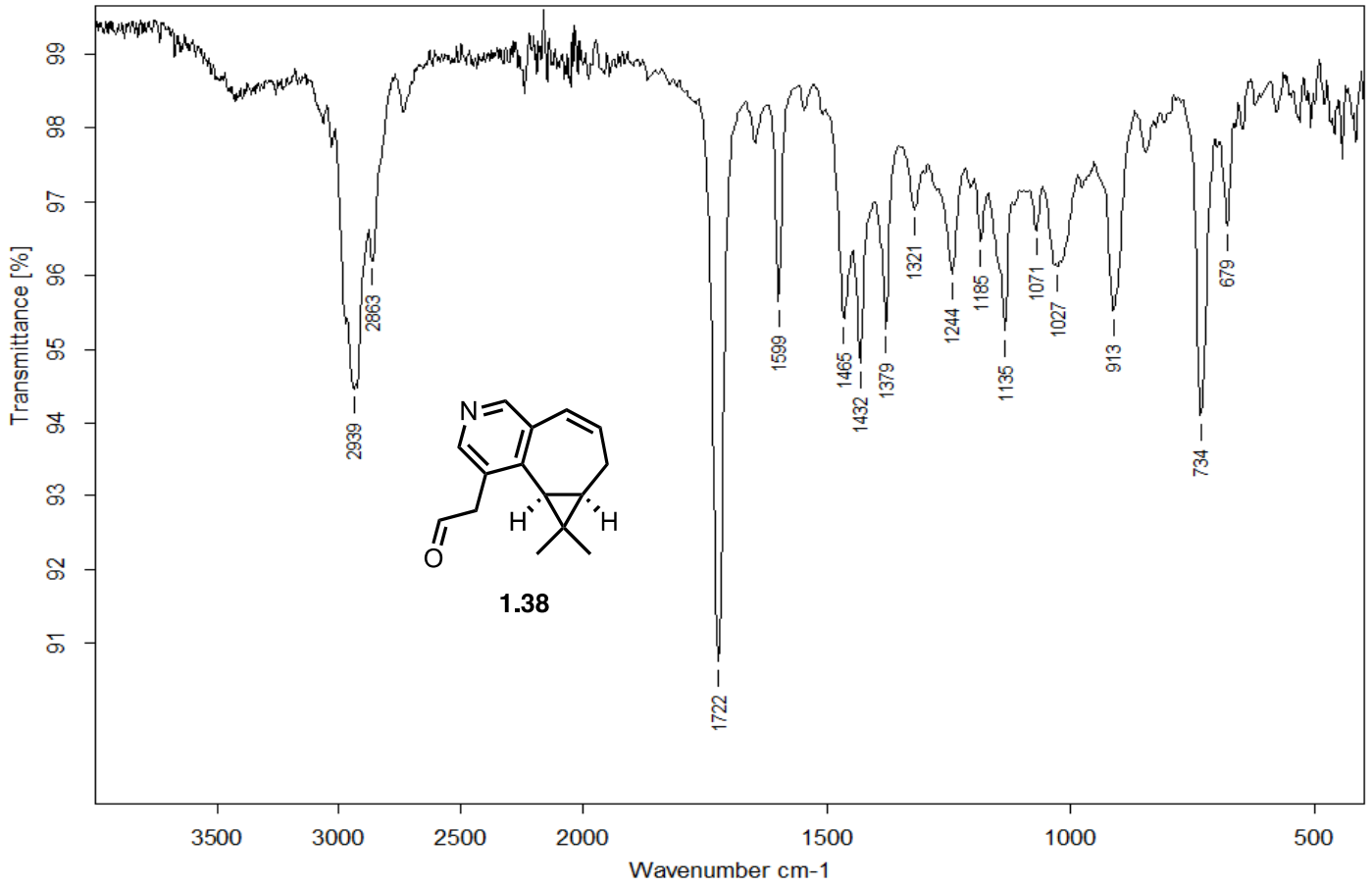


Figure A.57. **FTIR** (thin film) of aldehyde **1.38**

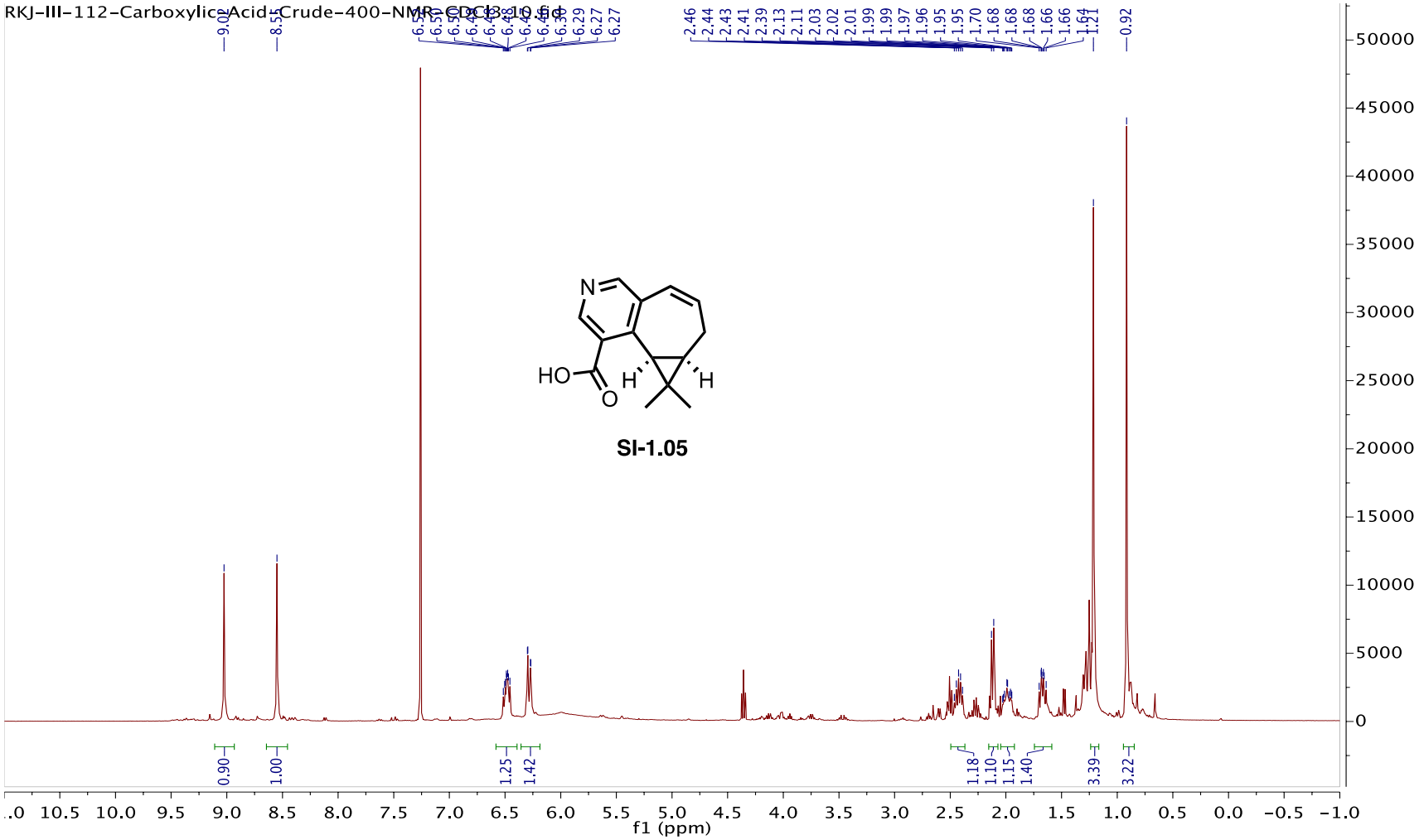


Figure A.58. **^{1}H NMR** (400 MHz, $CDCl_3$) Crude Acid **SI-1.05**

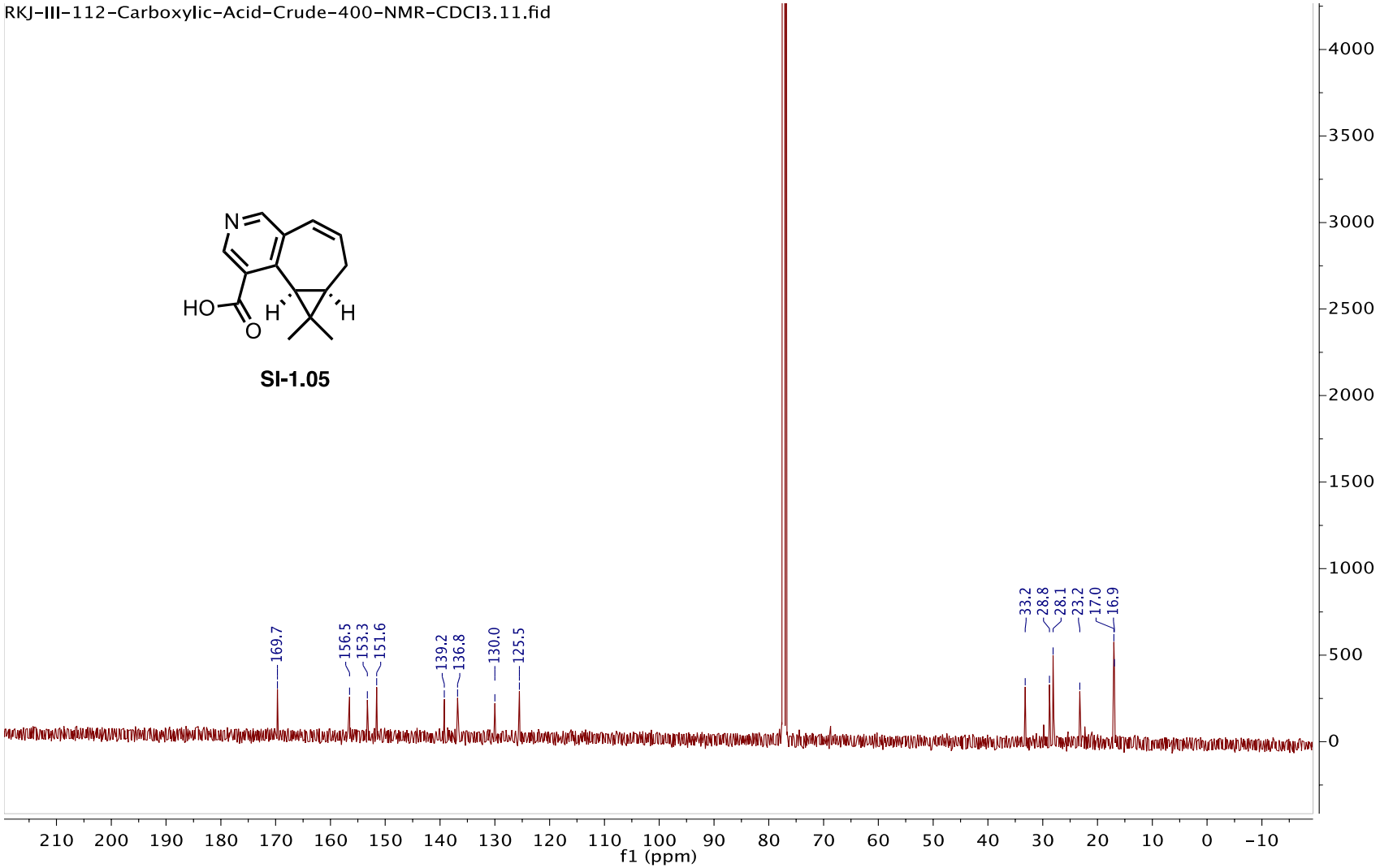


Figure A.59. **^{13}C NMR** (101 MHz, $CDCl_3$) Crude Acid **SI-1.05**

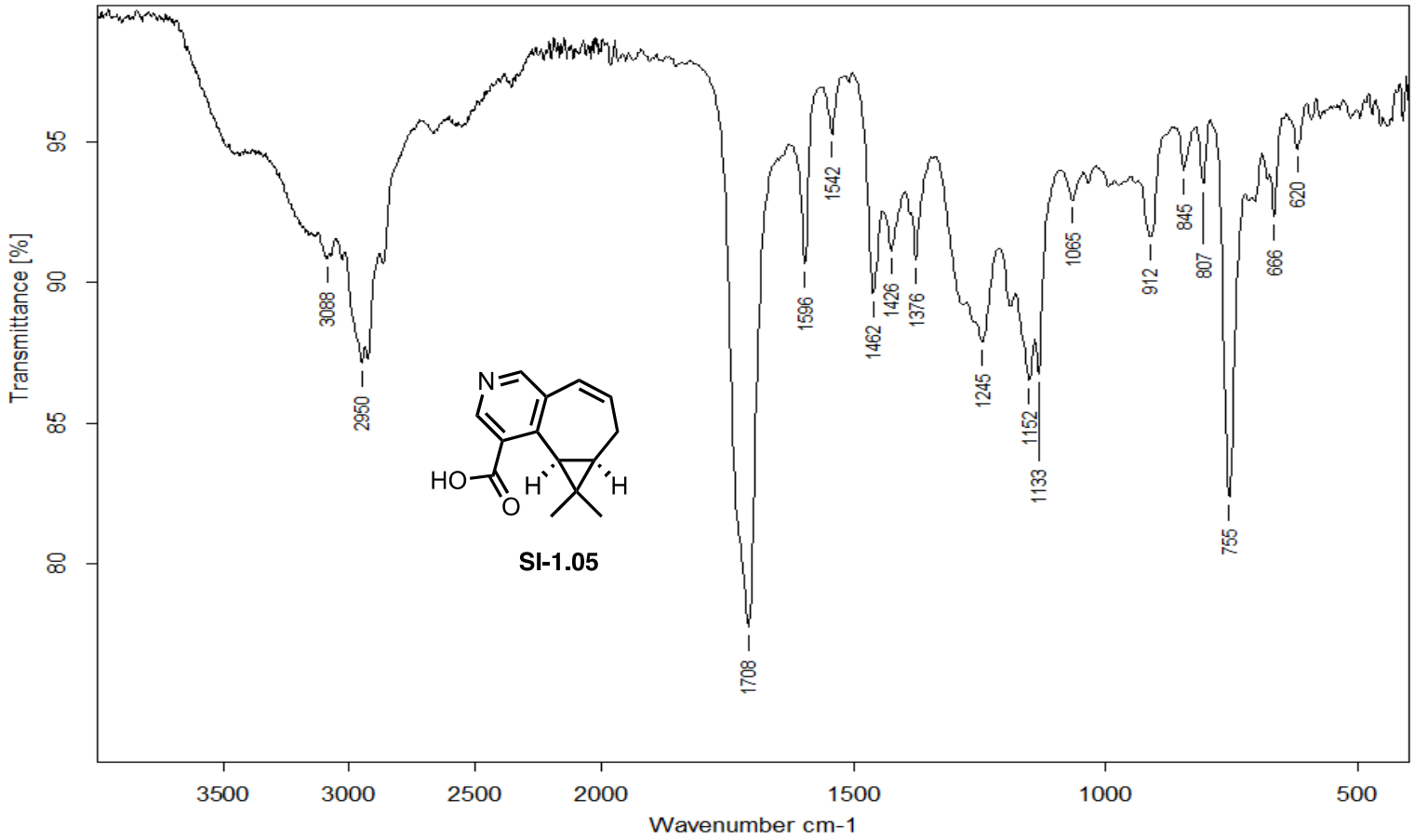


Figure A.60. **FTIR** (thin film) Crude Acid **SI-1.05**

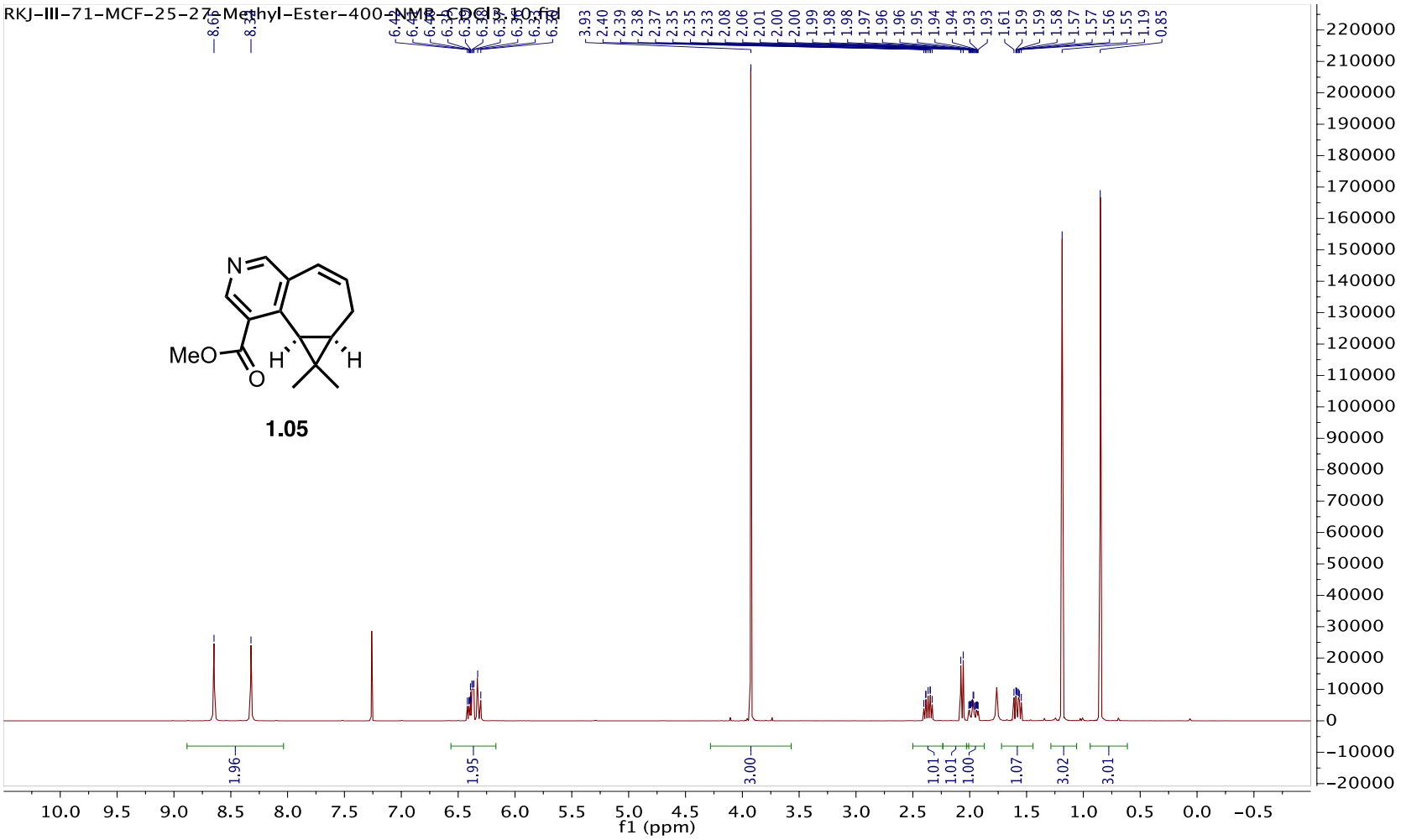


Figure A.61. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05**

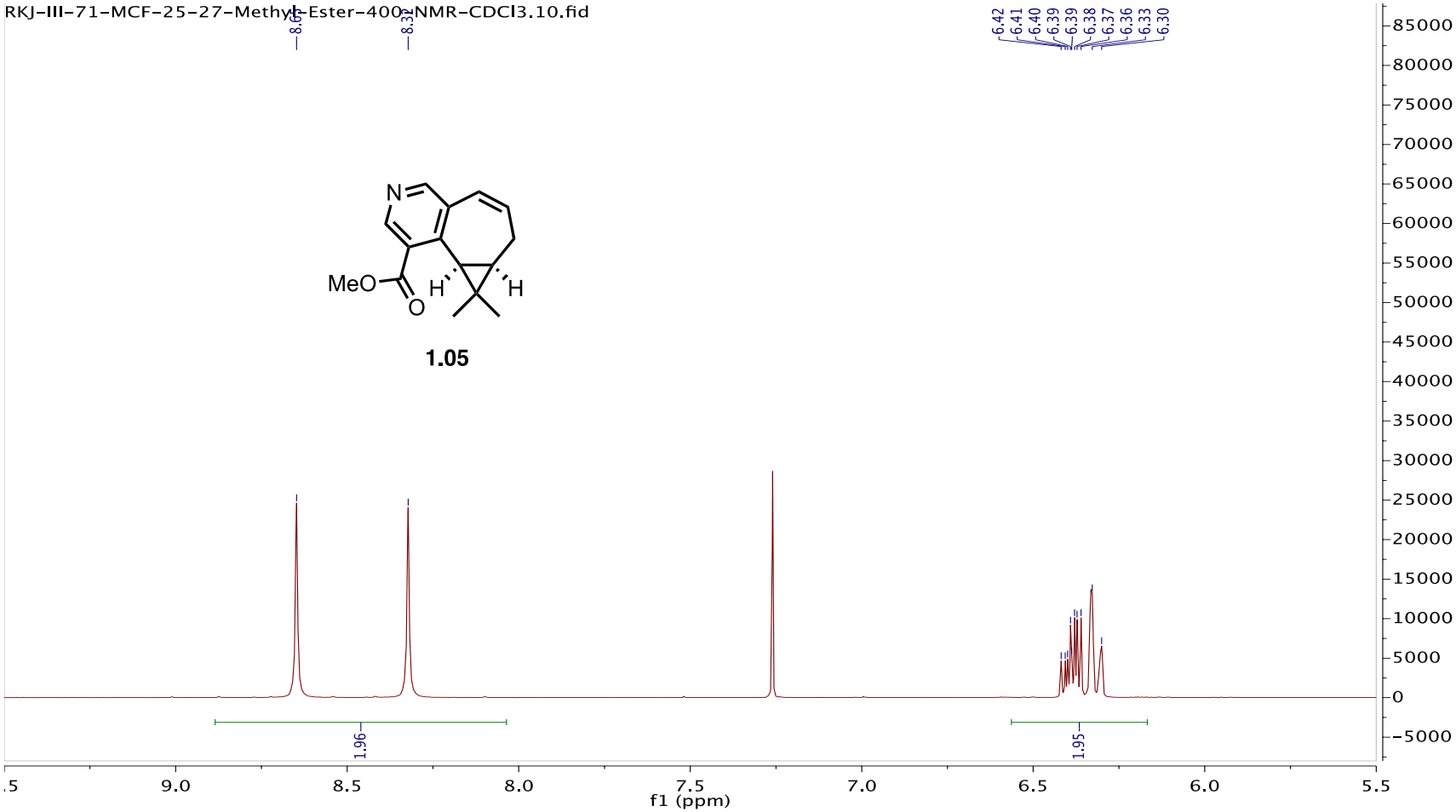


Figure A.62. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05** (9.5 – 5.5 ppm inset)

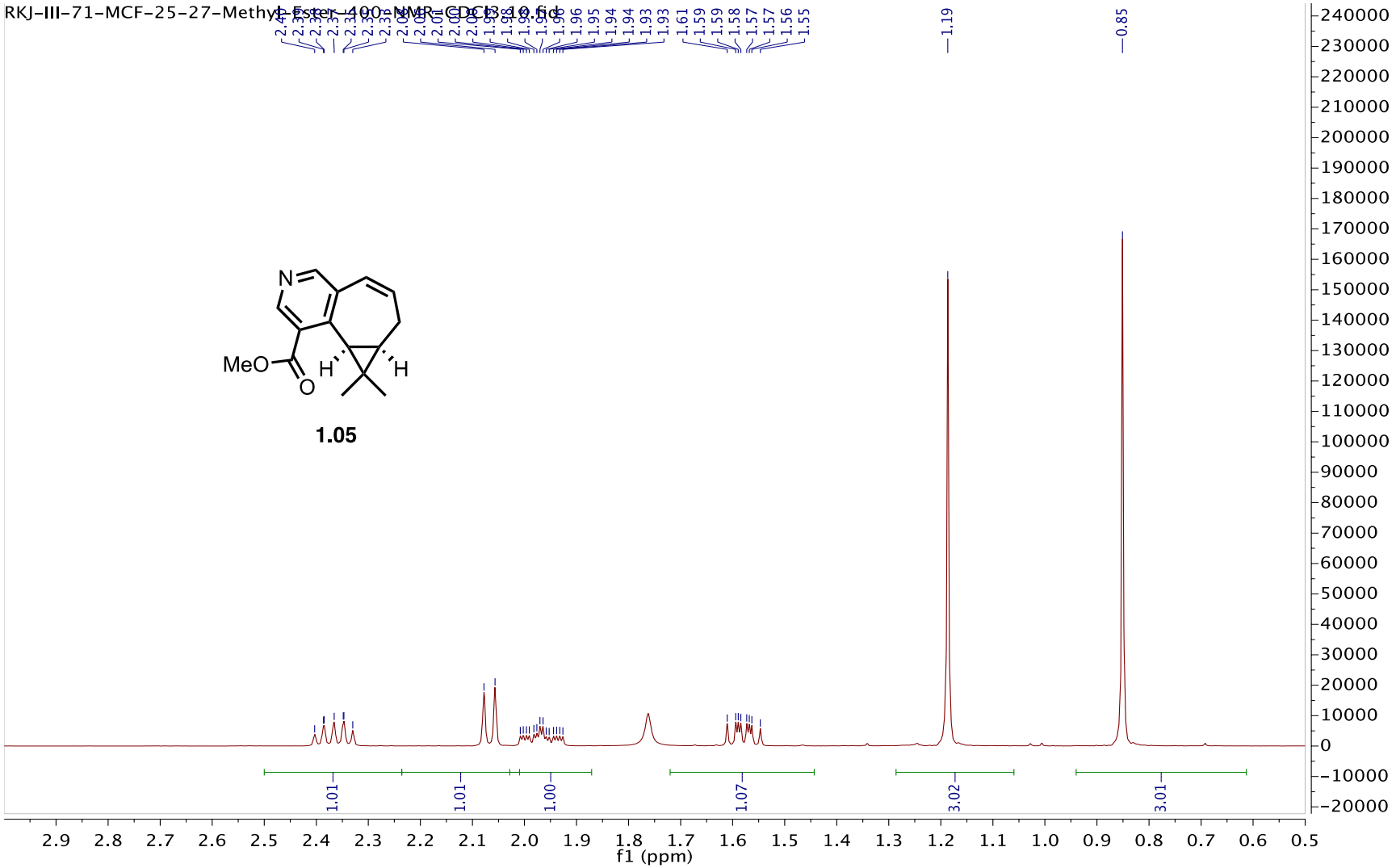


Figure A.63. **^{1}H NMR** (400 MHz, $CDCl_3$) Ester **1.05** (3.0 – 0.5 ppm inset)

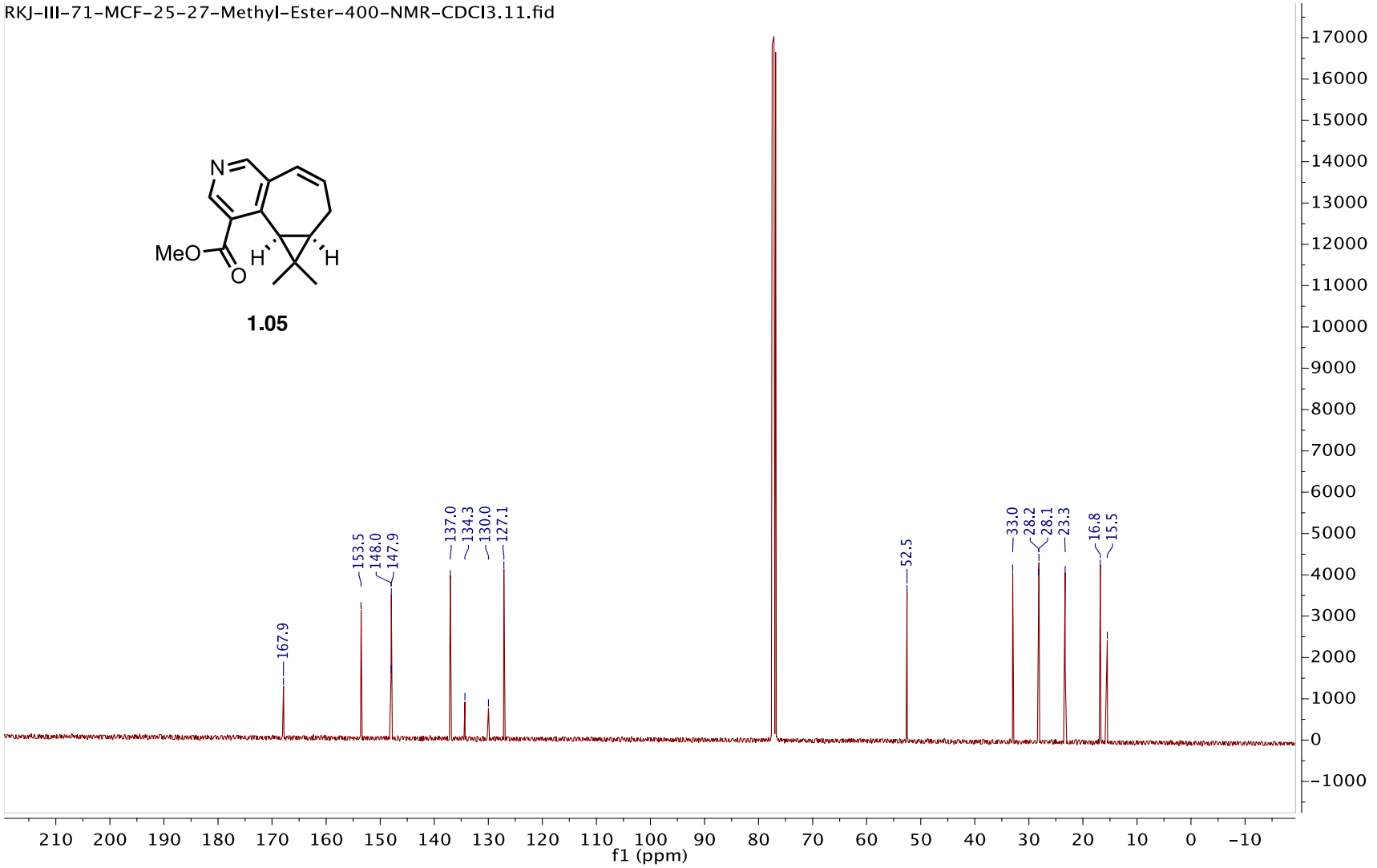


Figure A.64. **^{13}C NMR** (101 MHz, $CDCl_3$) Ester **1.05**

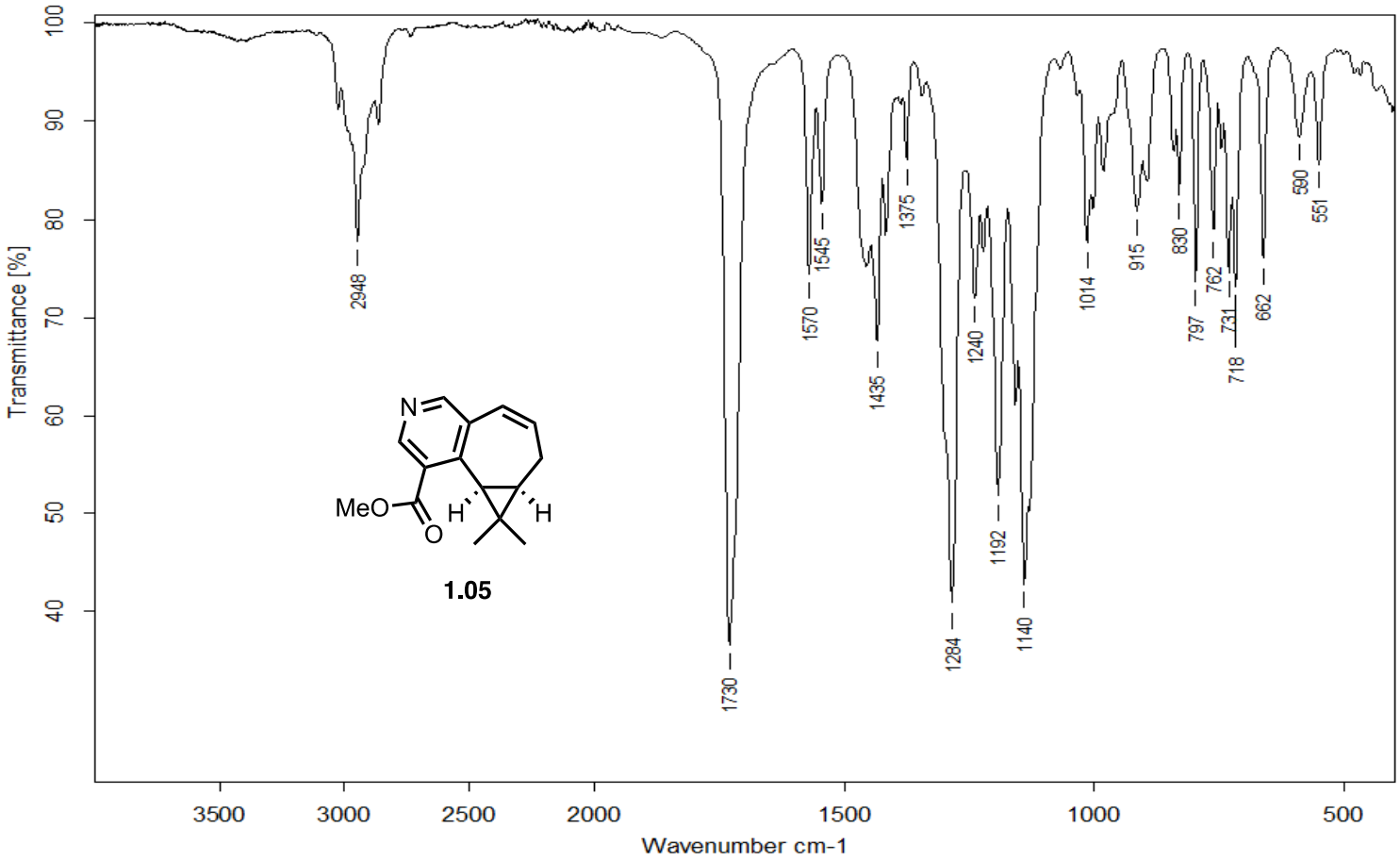


Figure A.65. **FTIR** (thin film) Ester **1.05**

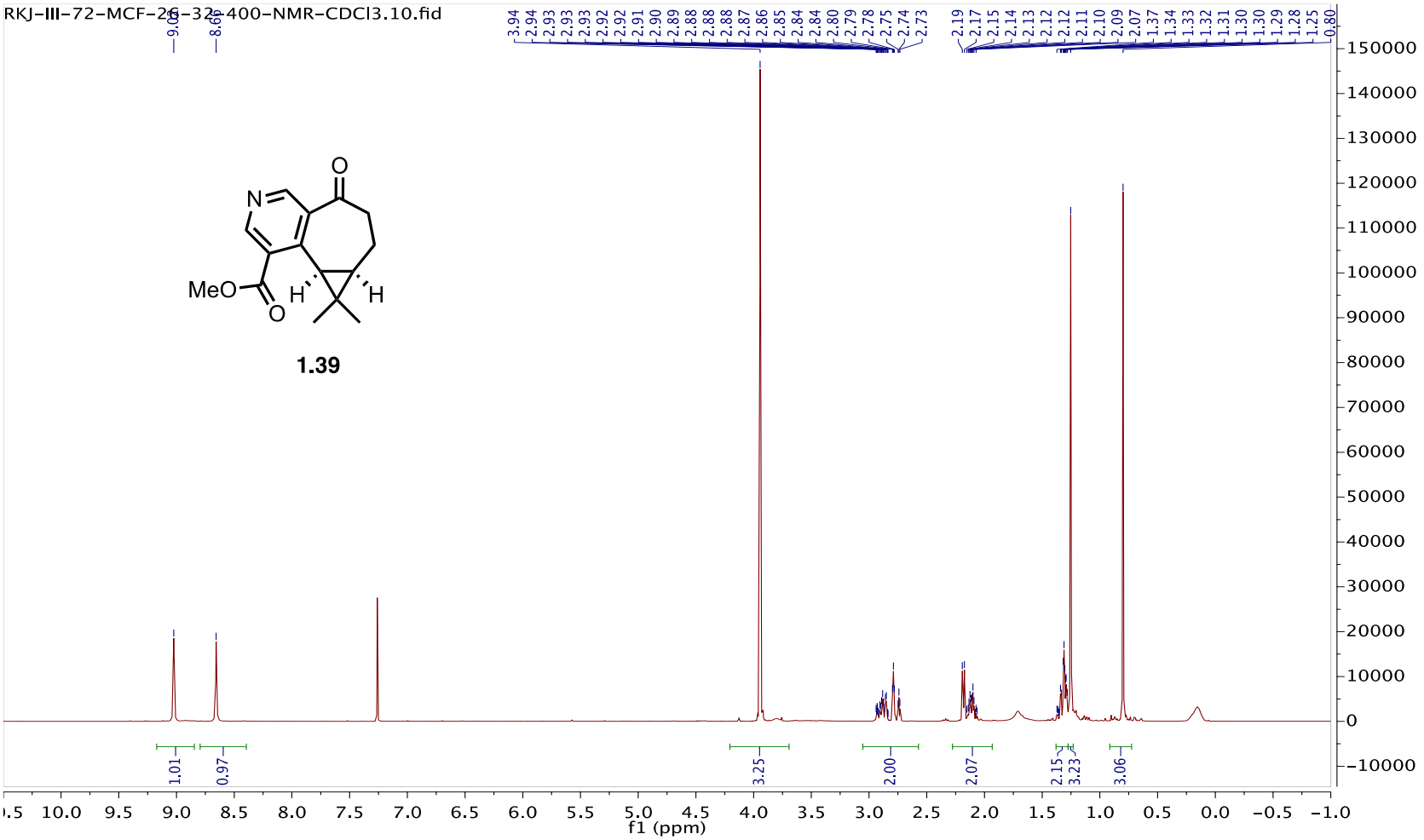


Figure A.66. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **1.39**

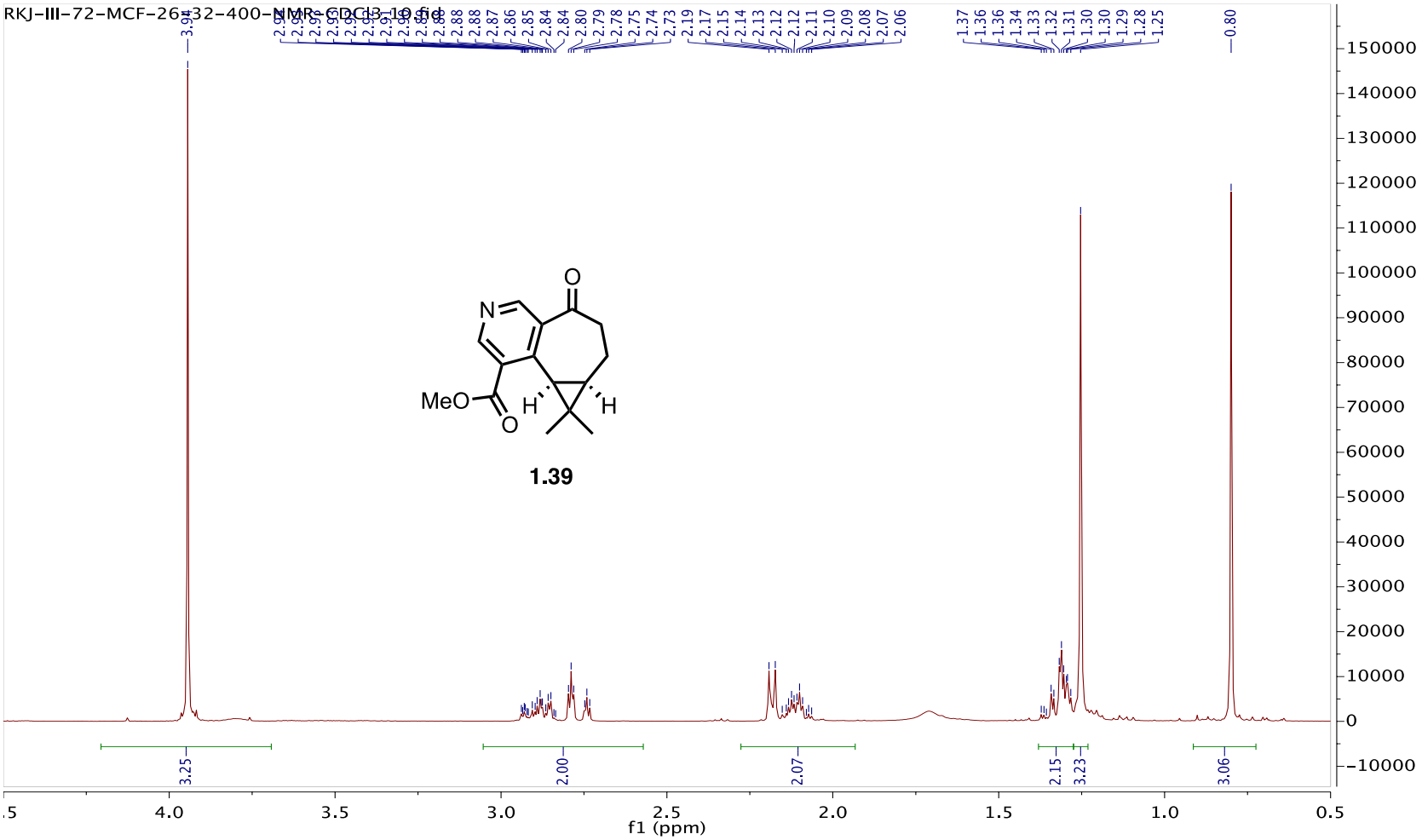


Figure A.67. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **1.39** (4.5 – 0.5 inset)

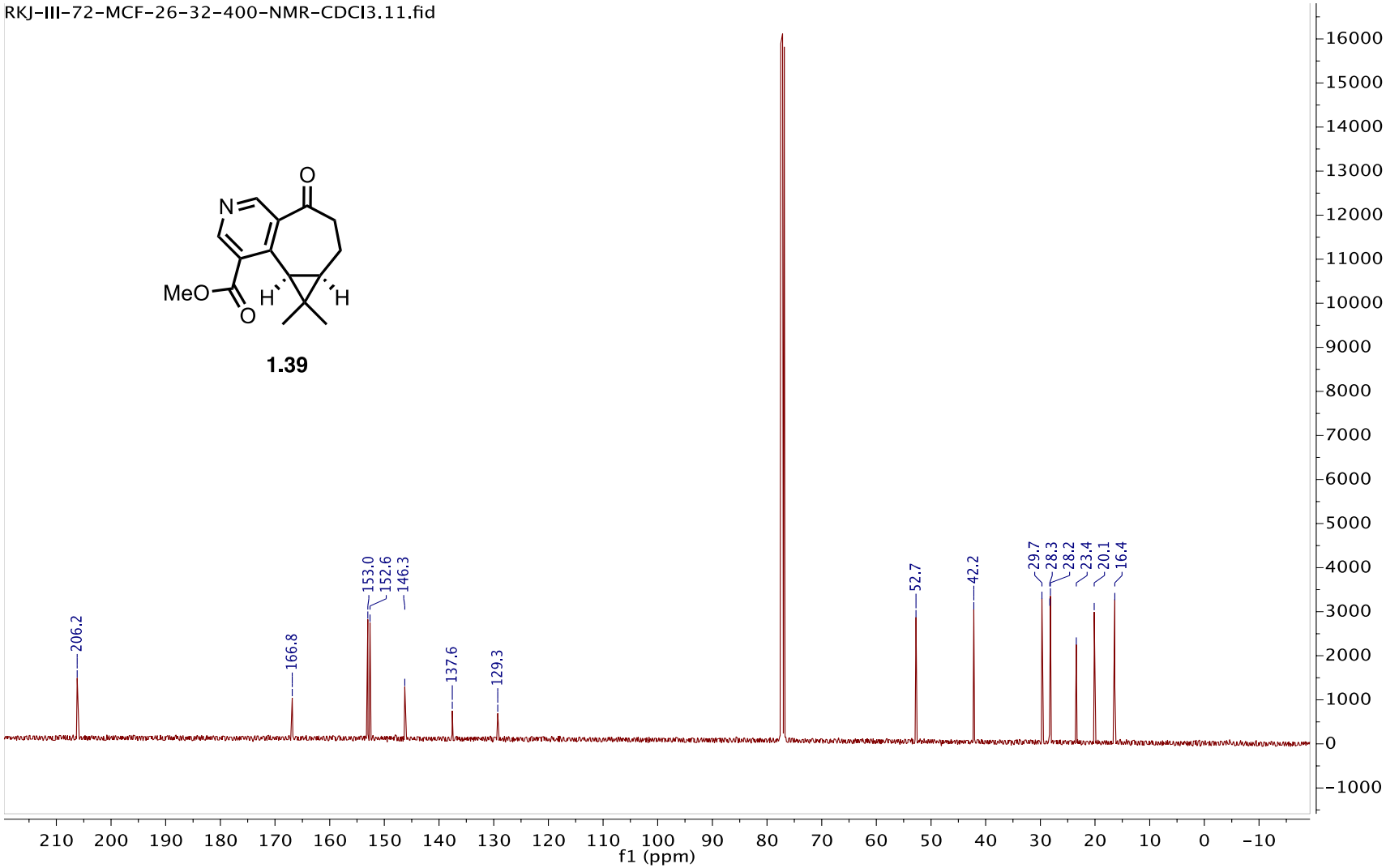


Figure A.68. **^{13}C NMR** ($CDCl_3$) Ketone **1.39**

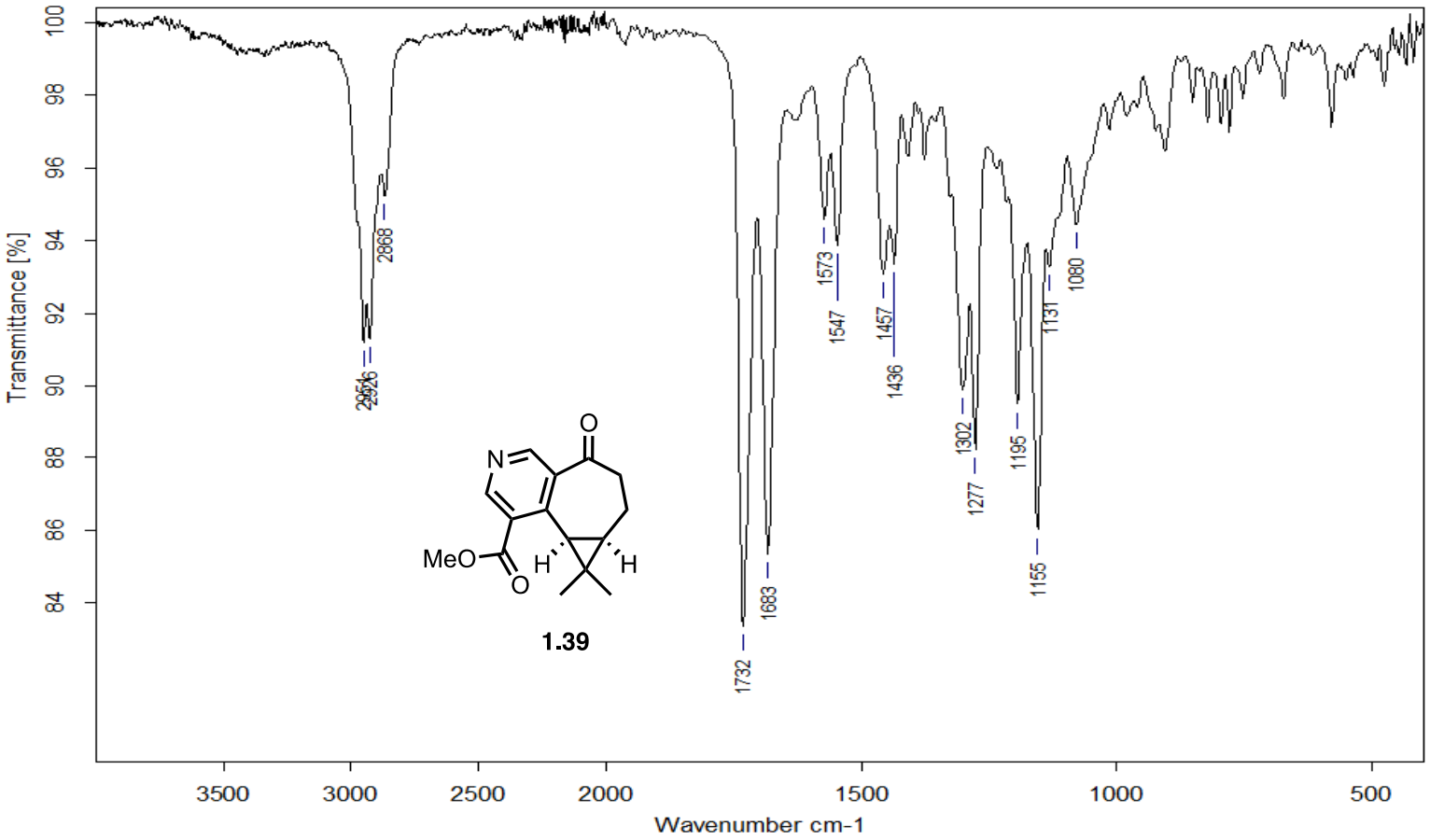


Figure A.69. **FTIR** (thin film) Ketone **1.39**

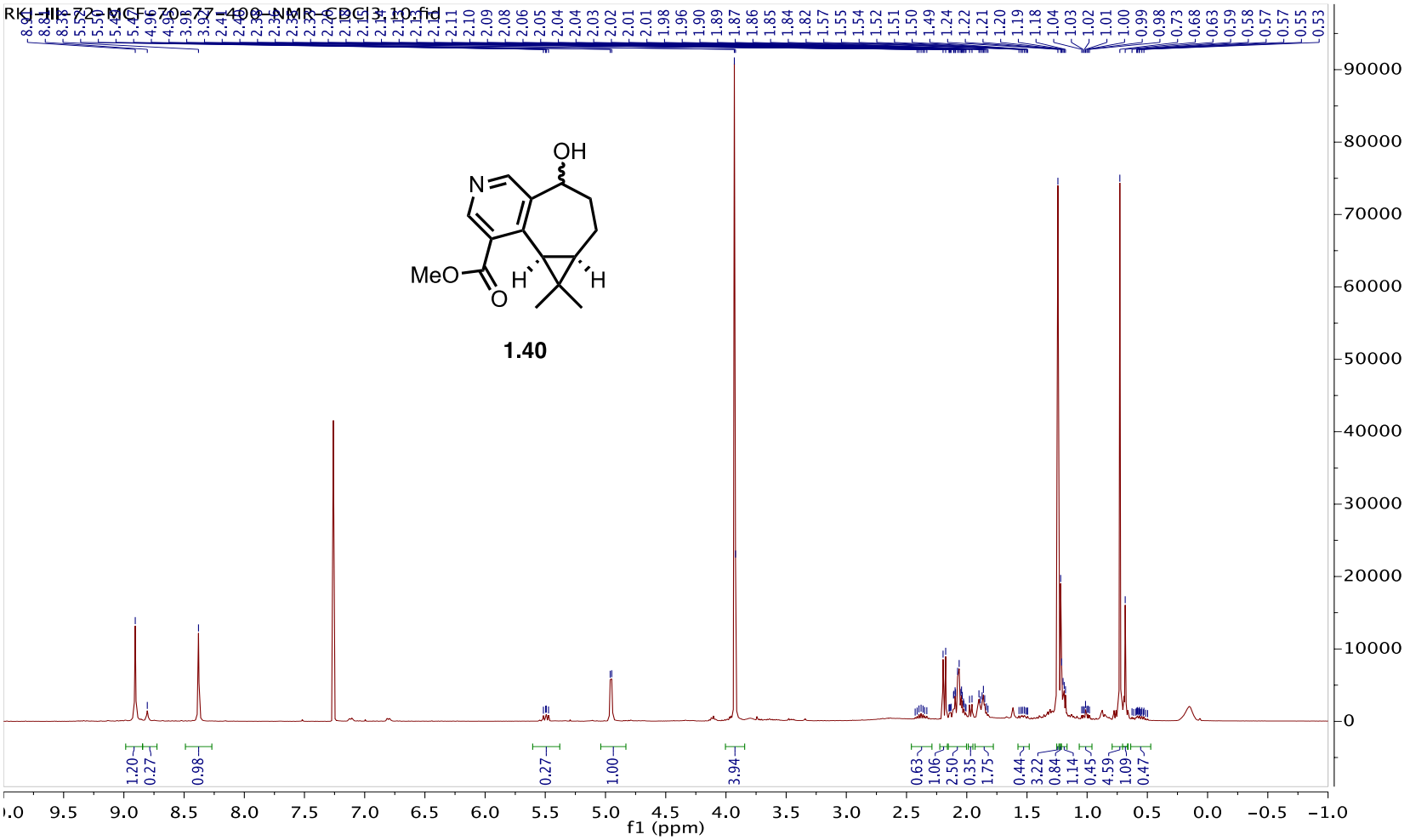


Figure A.70. **^{1}H NMR** (400 MHz, $CDCl_3$) Benzylic Alcohols **1.40**

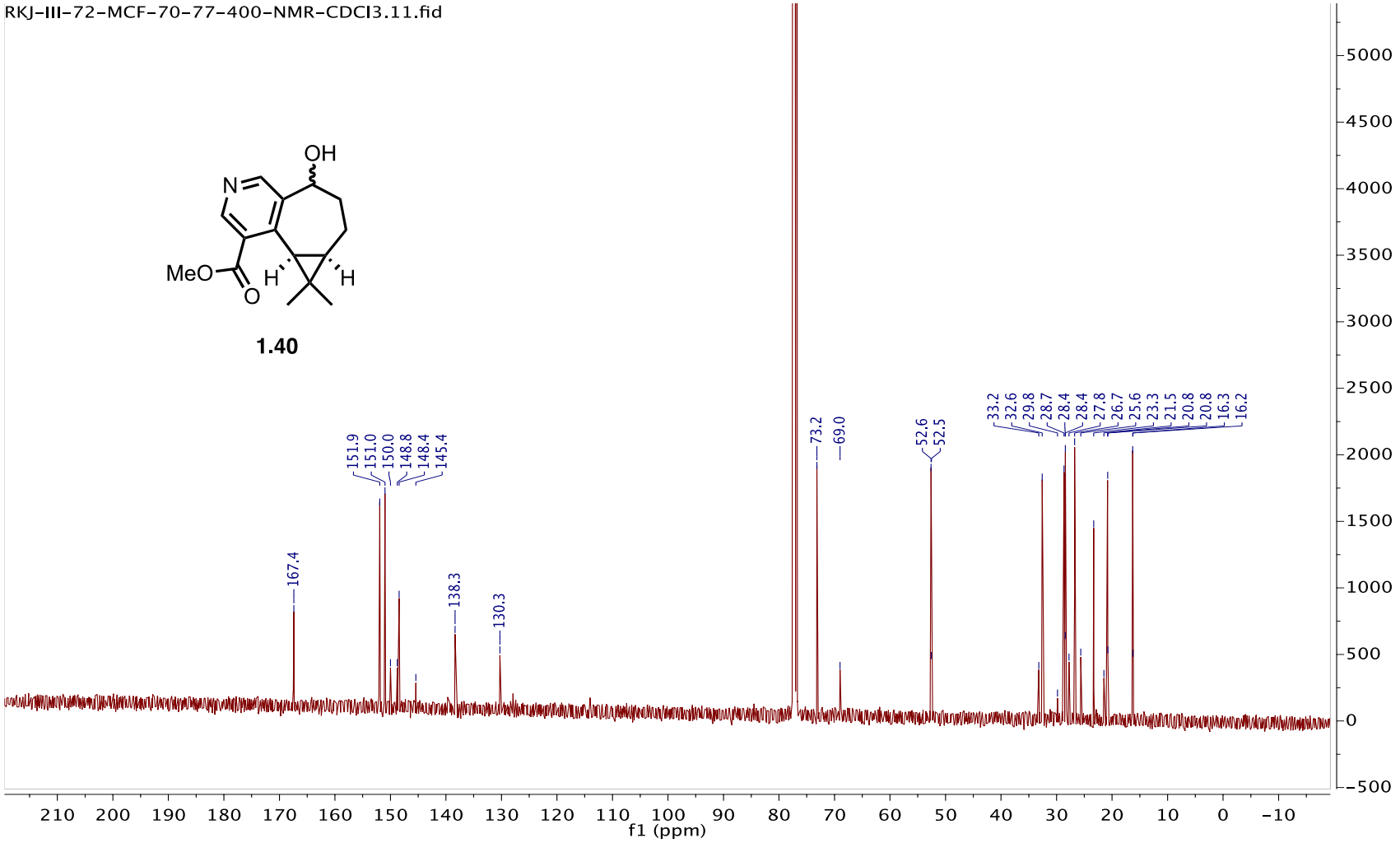


Figure A.71. **^{13}C NMR** (101 MHz, $CDCl_3$) Benzylic Alcohols **1.40**

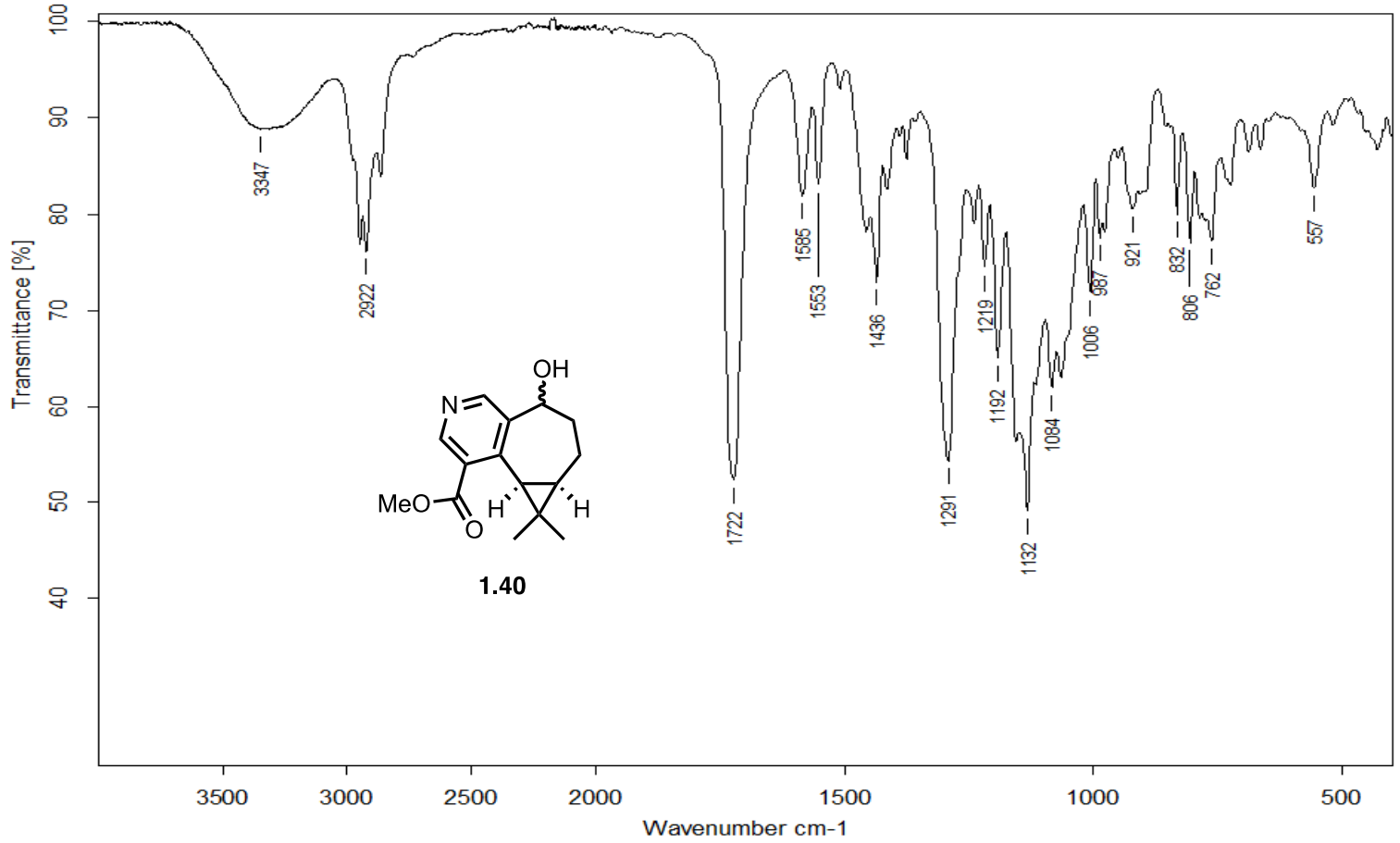


Figure A.72. **FTIR** (thin film) Benzylic Alcohols **1.40**

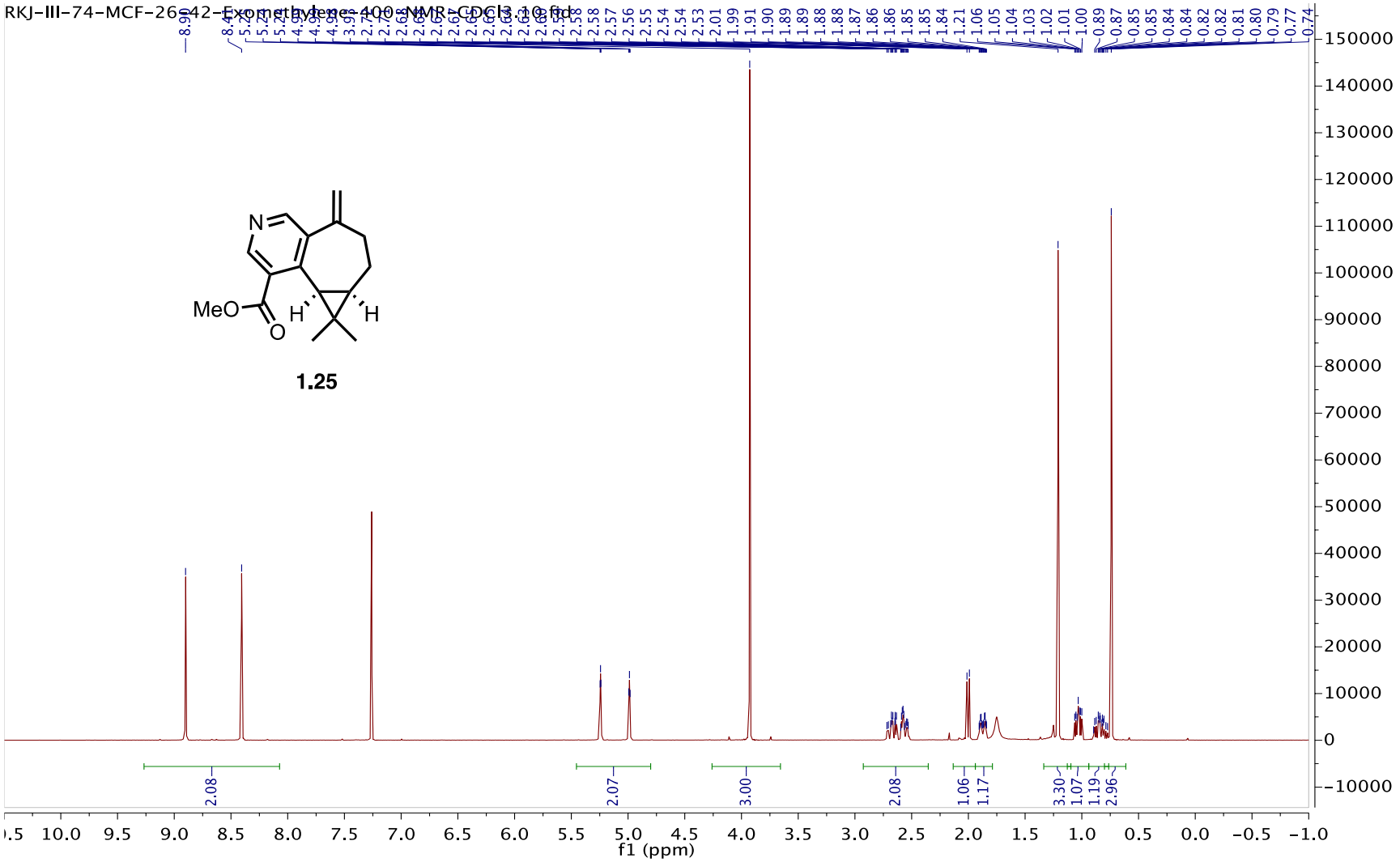


Figure A.73. **^{1}H NMR** (400 MHz, $CDCl_3$) Olefin **1.25**

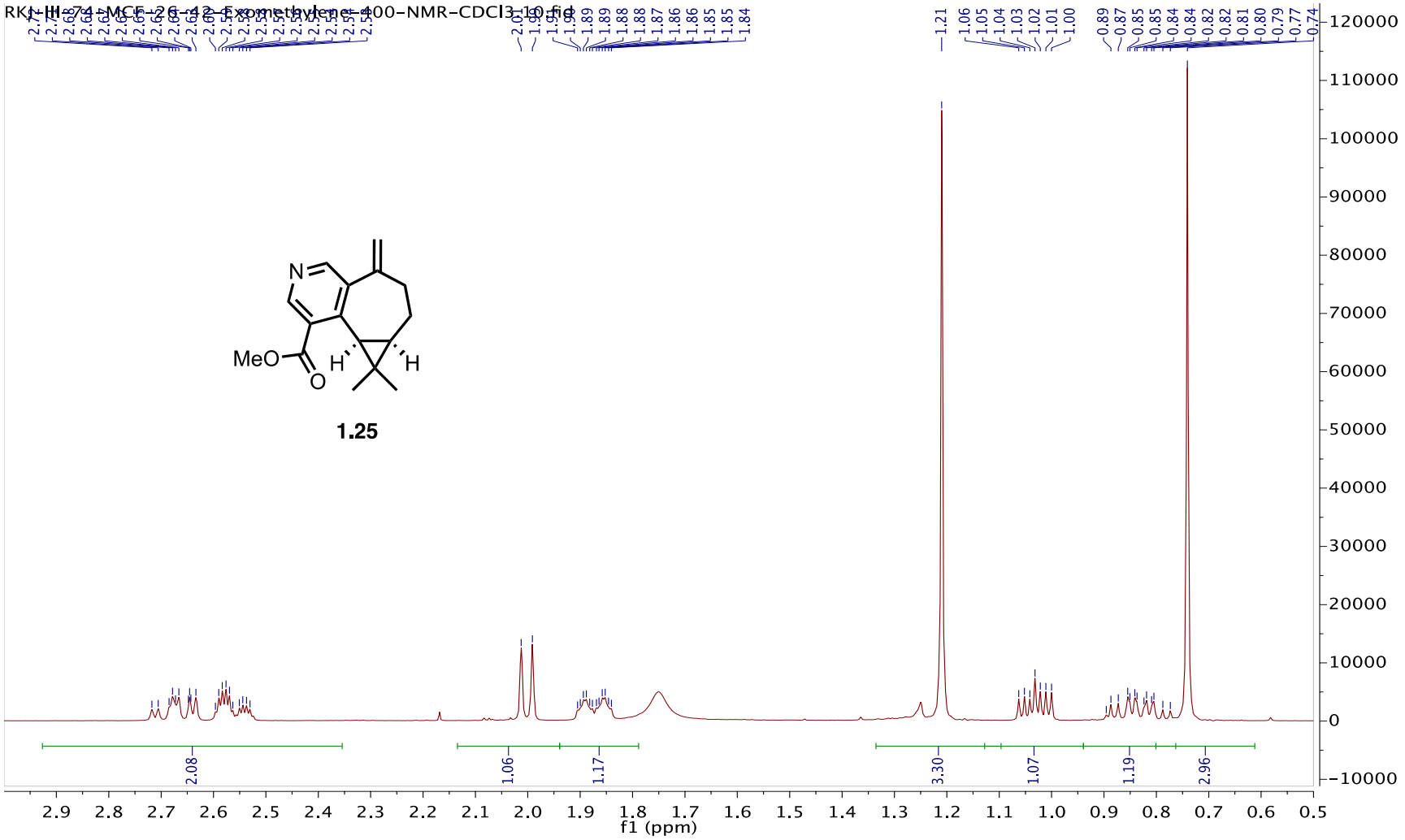


Figure A.74. **^{1}H NMR** (400 MHz, $CDCl_3$) Olefin **1.25** (3.0 – 0.5 ppm inset)

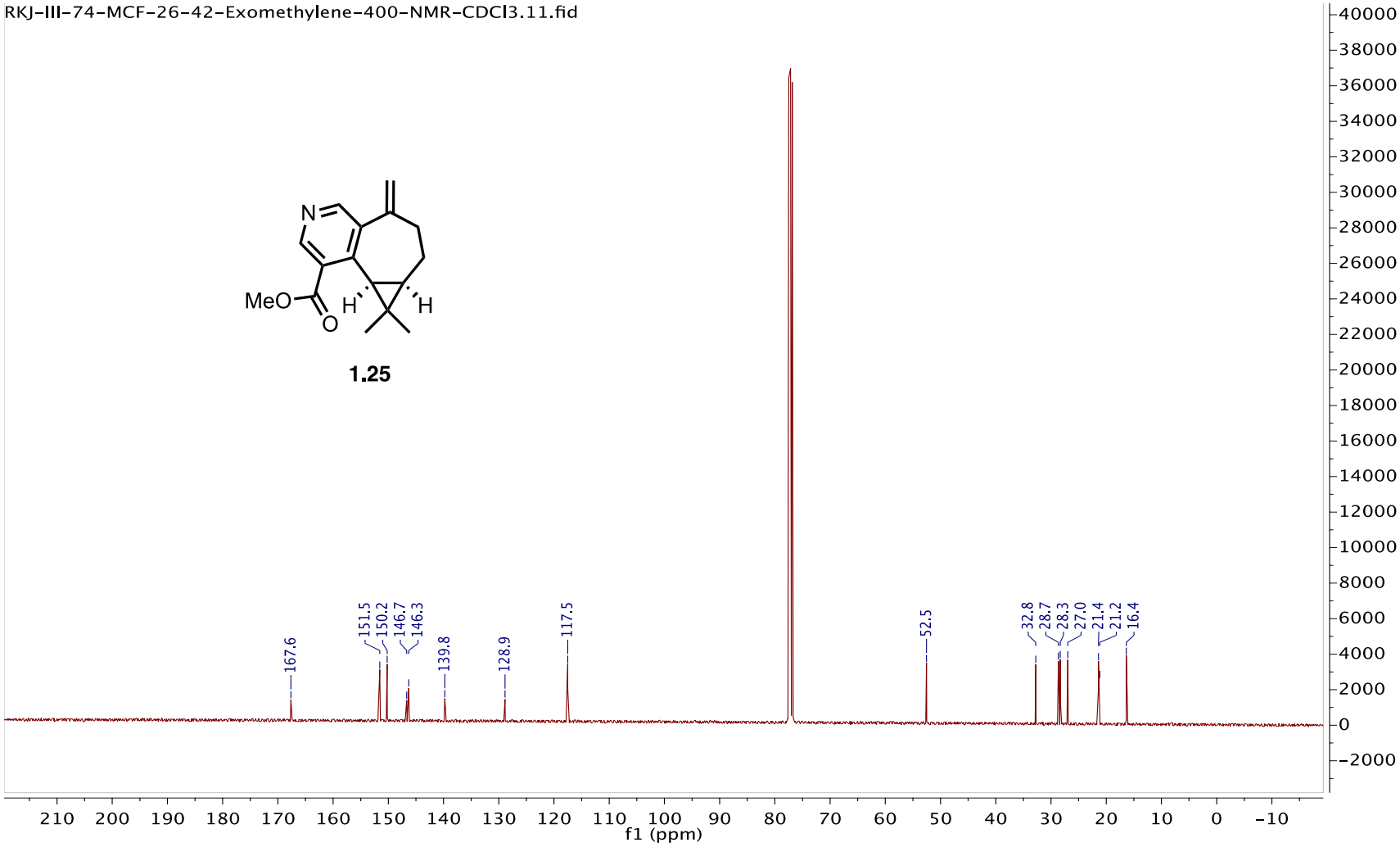


Figure A.75. **^{13}C NMR** (101 MHz, $CDCl_3$) Olefin **1.25**

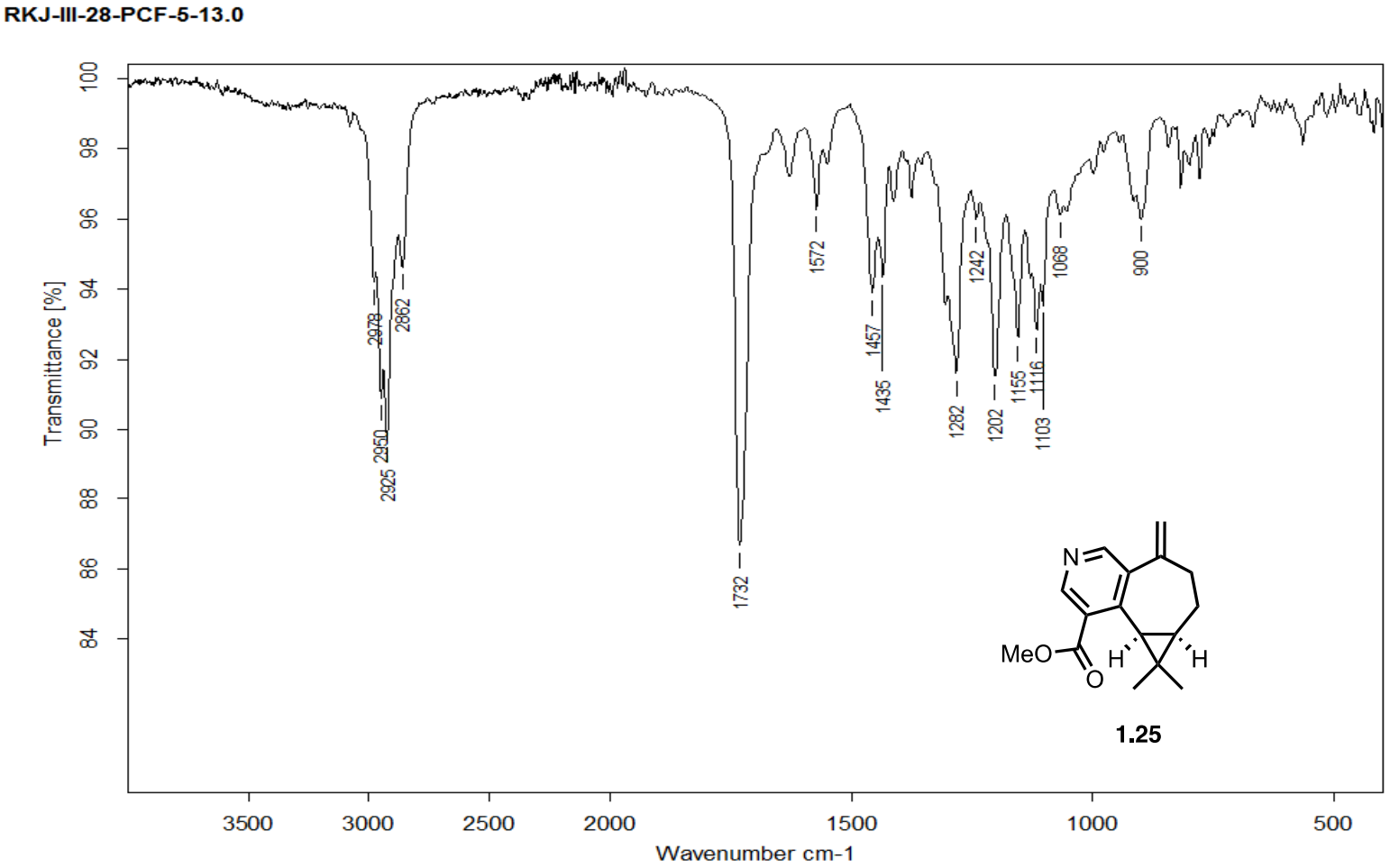


Figure A.76. **FTIR** (thin film) Olefin **1.25**

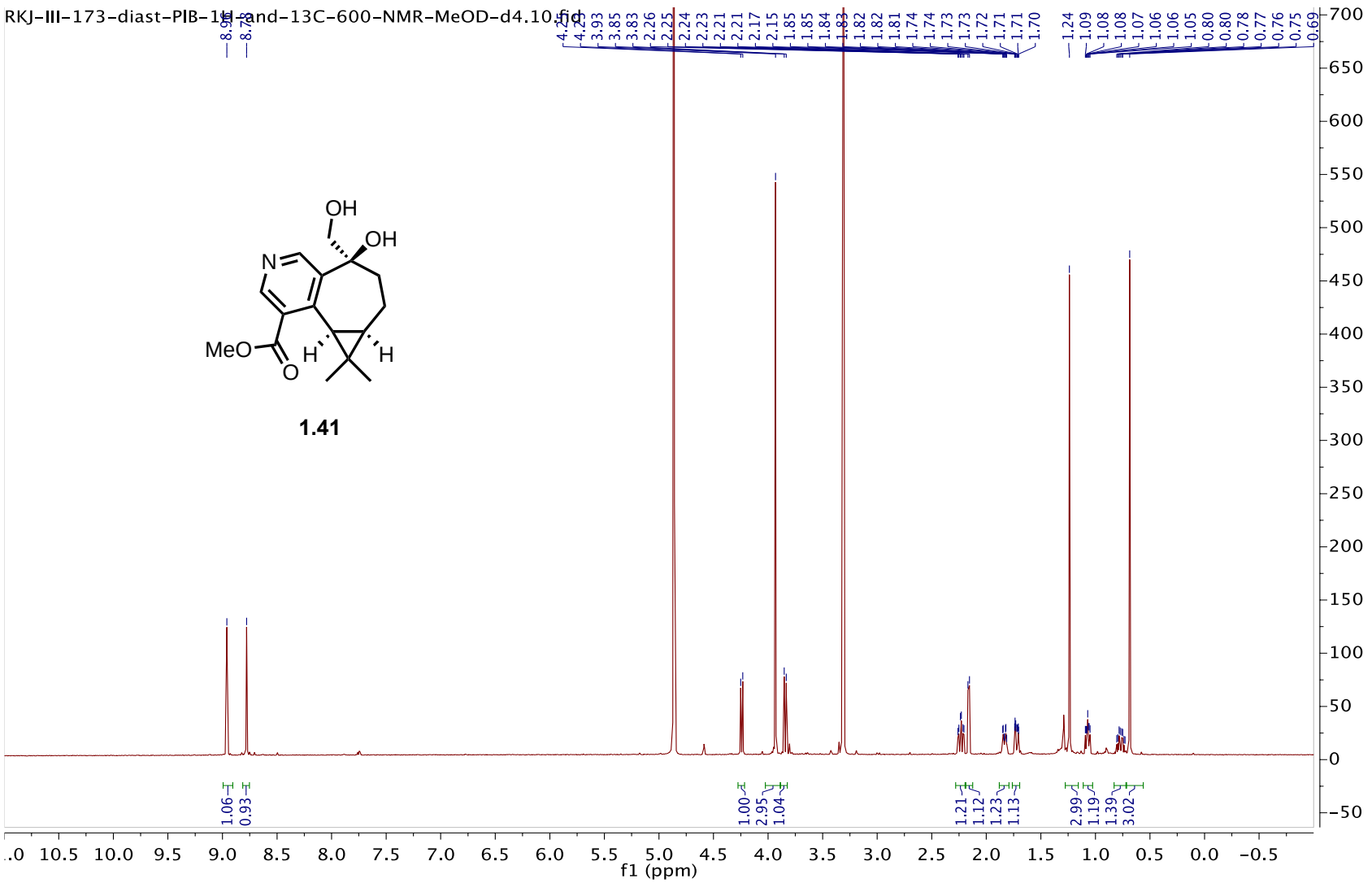


Figure A.77. **^{1}H NMR** (600 MHz, Methanol-*d4*) Diastereomer of *ent*-Plagiochianin B **1.41**

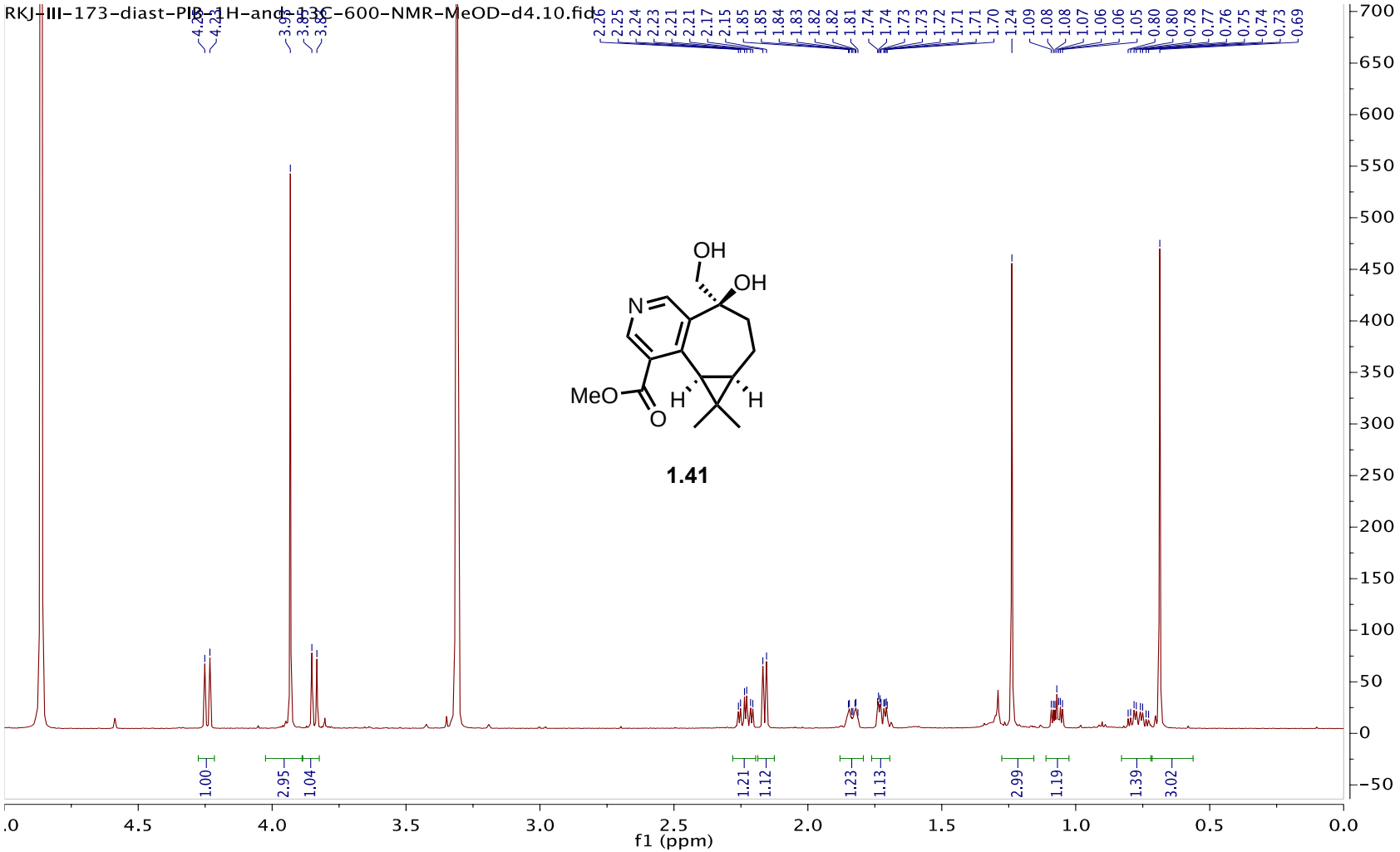


Figure A.78. **^{1}H NMR** (600 MHz, Methanol-*d4*) Diastereomer of *ent*-Plagiochianin B **1.41** (5.0 – 0.0 ppm inset)

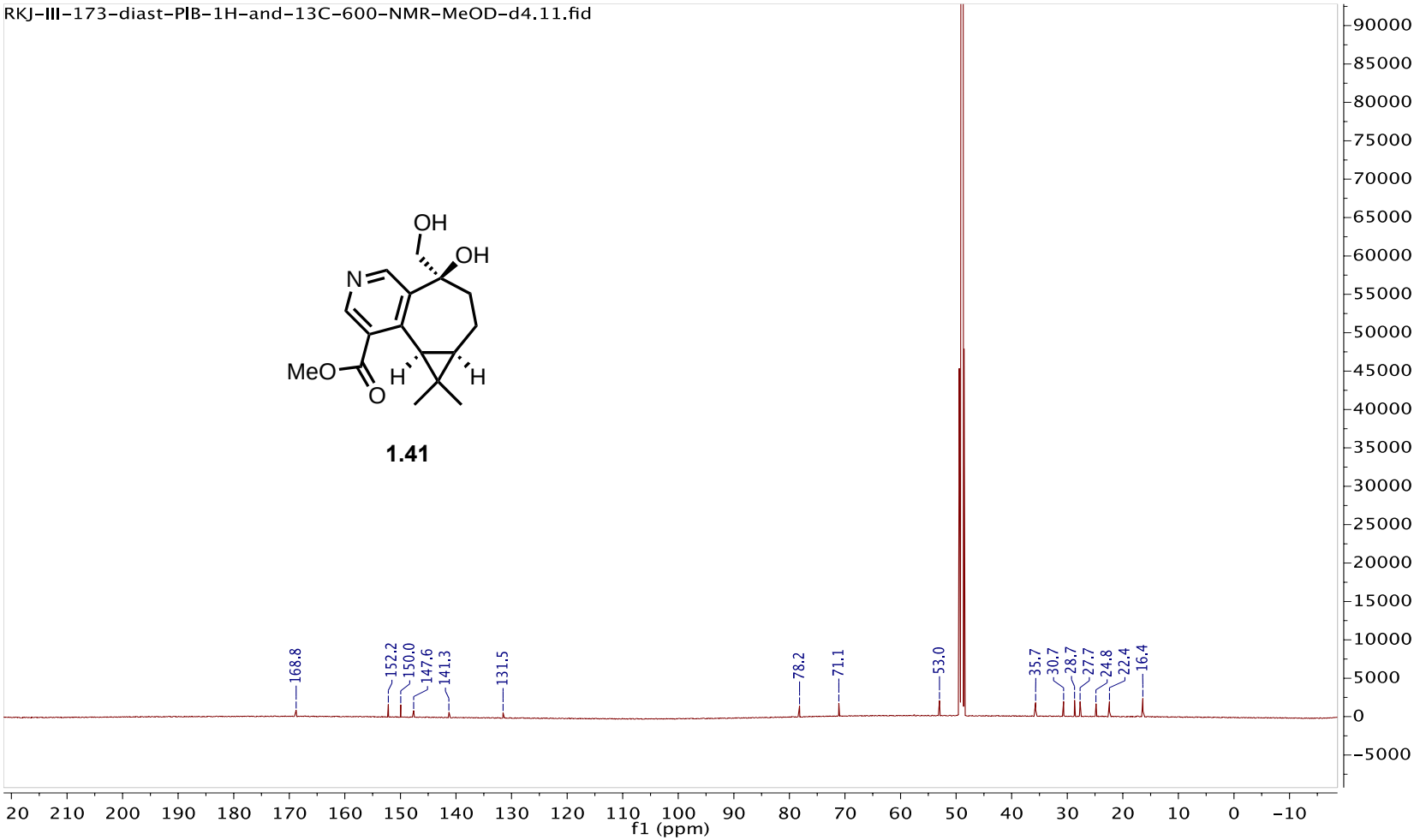


Figure A.79. **^{13}C NMR** (151 MHz, Methanol-*d4*) Diastereomer of *ent*-Plagiochianin B **1.41**

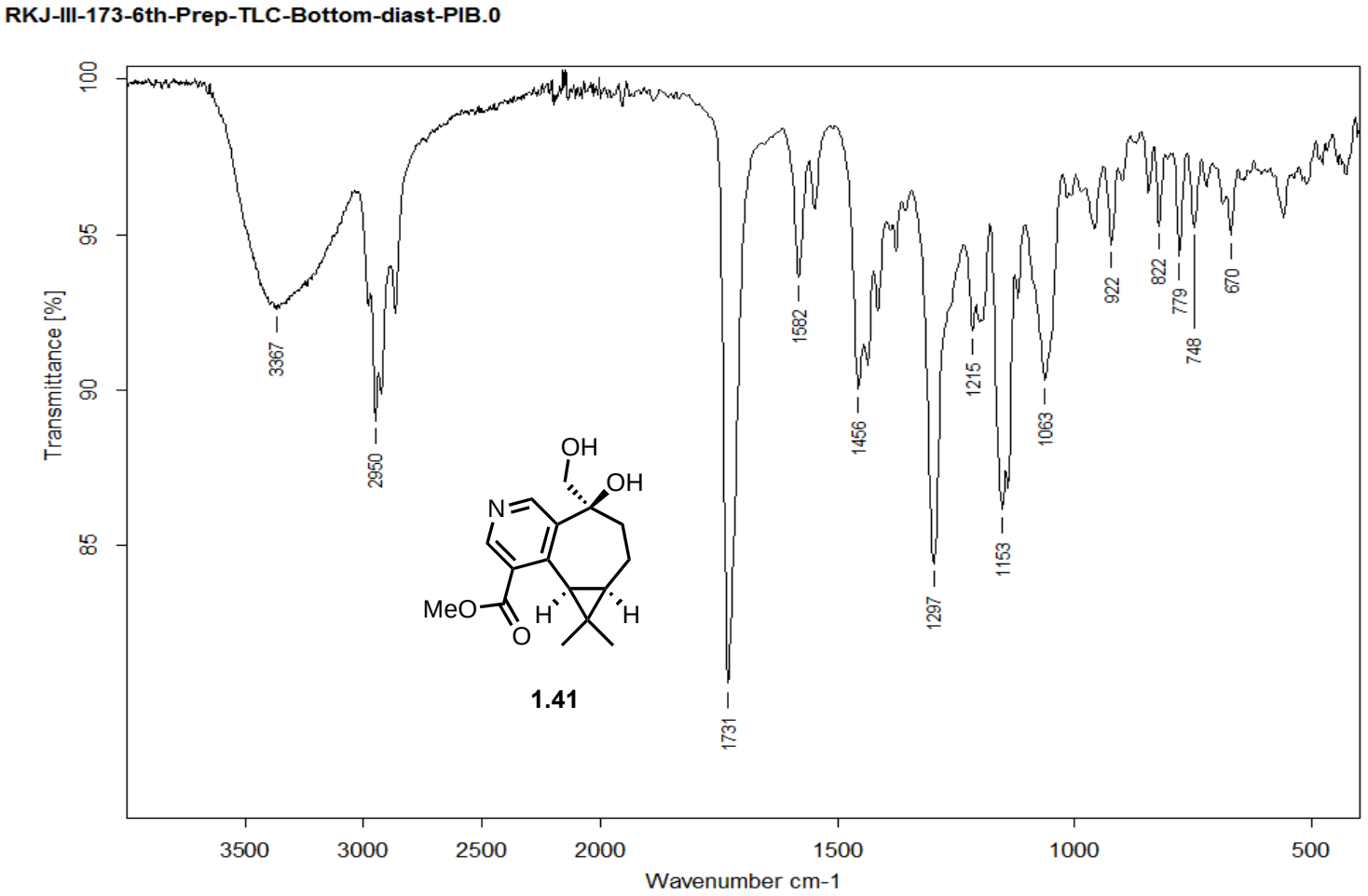


Figure A.80. **FTIR** (thin film) Diastereomer of *ent*-Plagiochianin B **1.41**

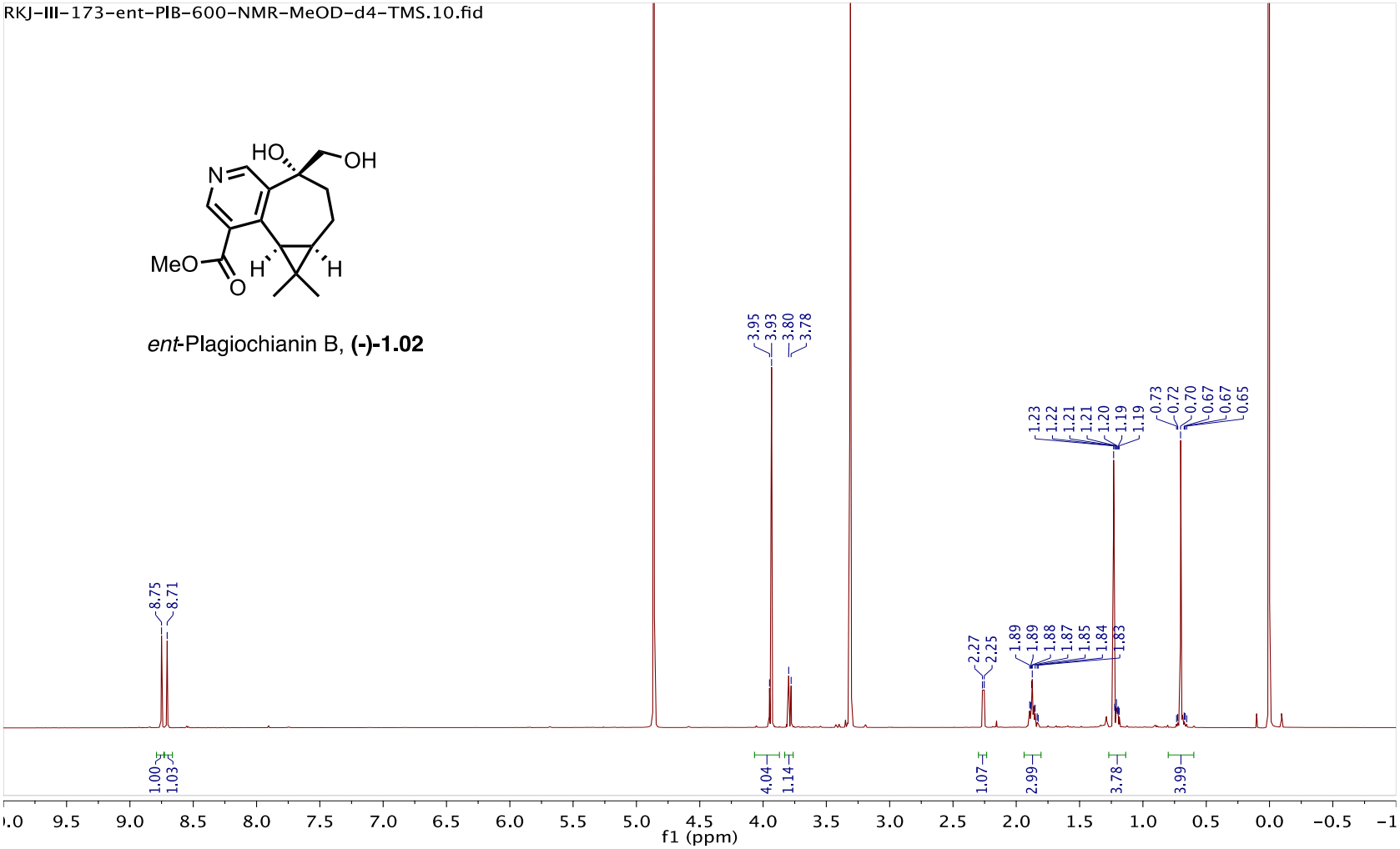
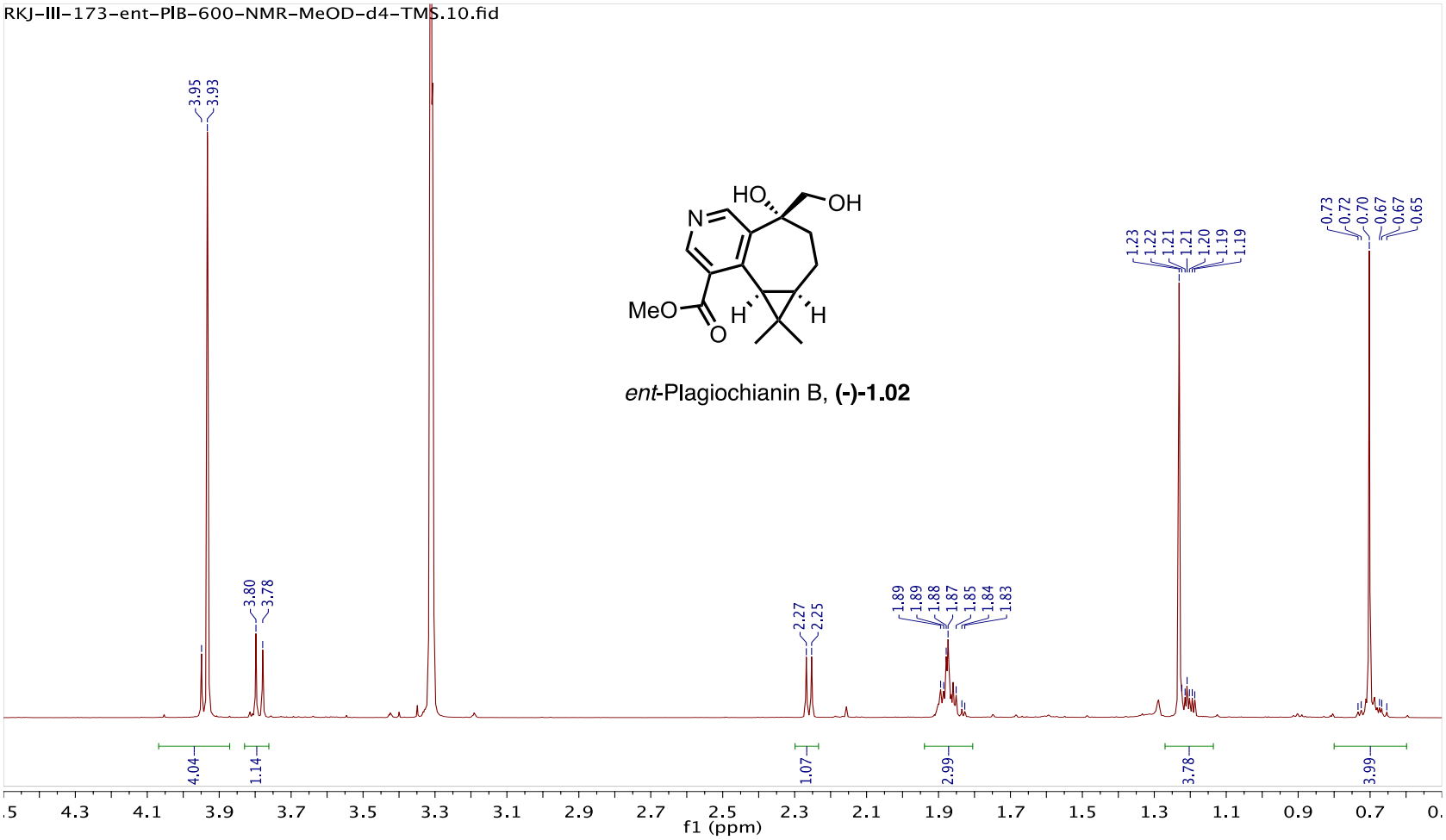


Figure A.81. **^{1}H NMR** (600 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02**



ent-Plagiochianin B, **(-)-1.02**

Figure A.82. **^{1}H NMR** (600 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02** (4.5 – 0.5 ppm inset)

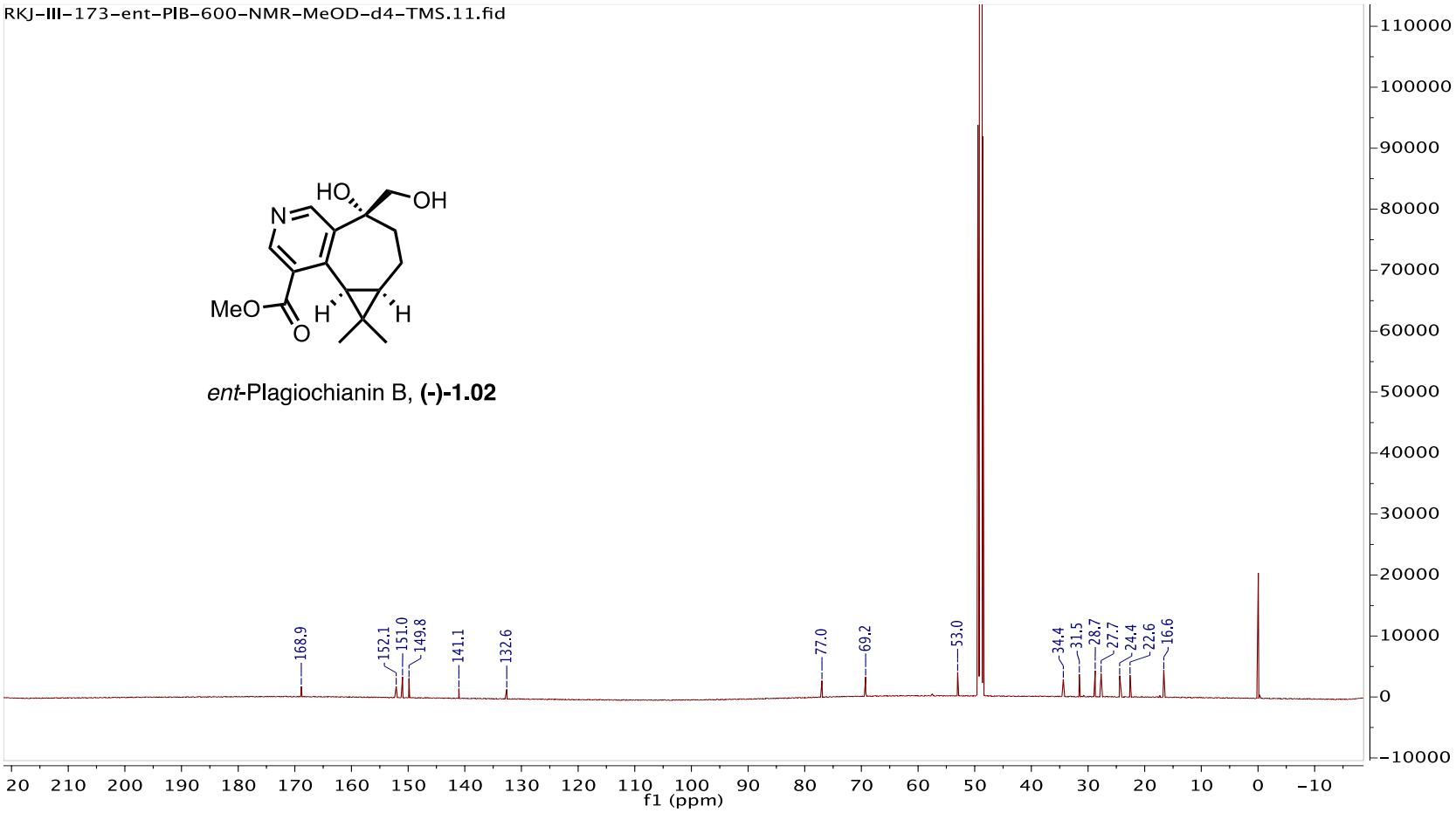


Figure A.83. **^{13}CNMR** (151 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02**

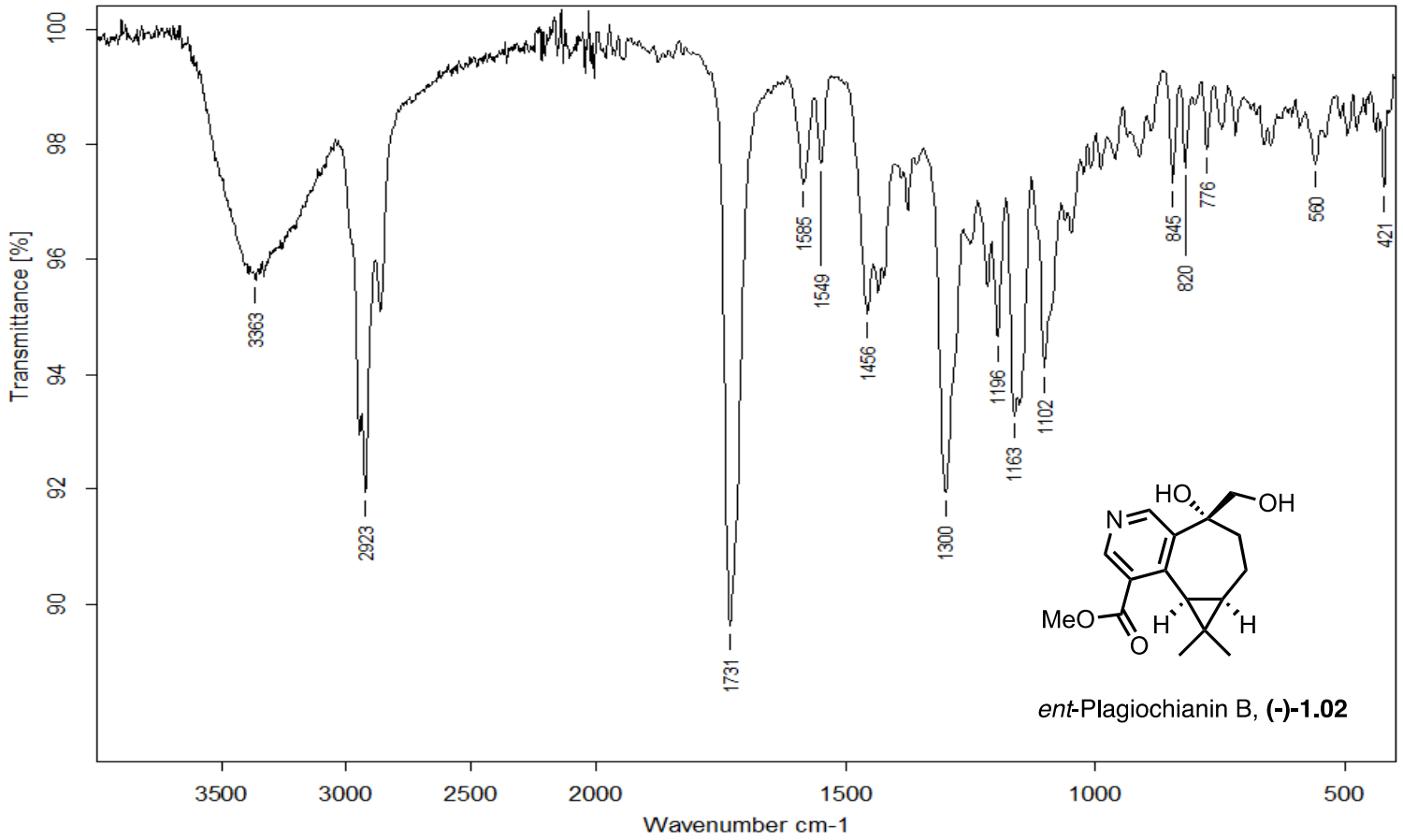


Figure A.84. **FTIR** (Thin film) *ent*-Plagiochianin B **(-)-1.02**

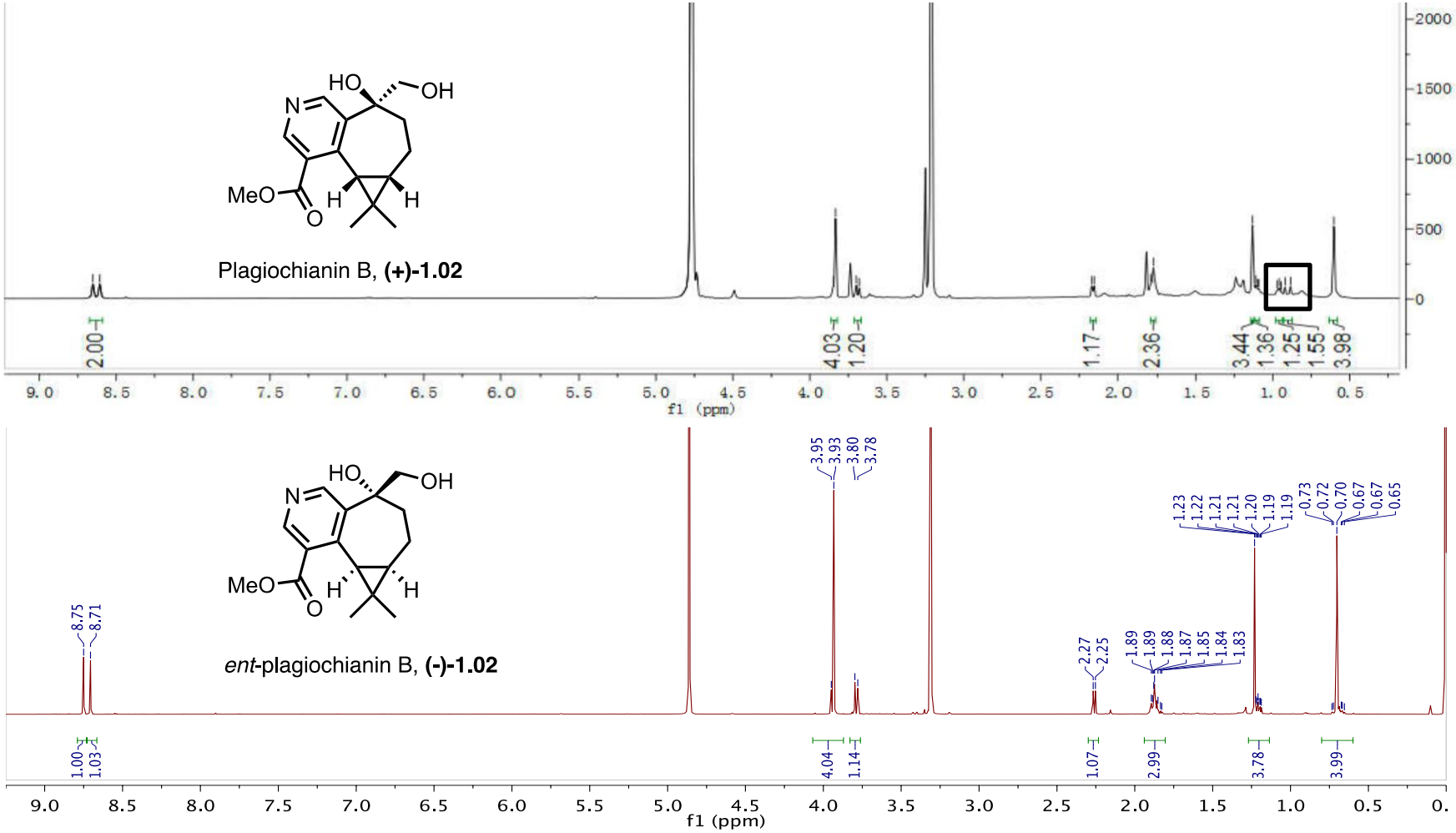


Figure A.85. **^{1}H NMR** (600 MHz, Methanol-*d4*) Overlay of Natural Plagiochianin B **(+)-1.02** & Synthetic *ent*-Plagiochianin B **(-)-1.02**

The peaks boxed in black were not tabulated in the published the isolation paper (Lou *Org. Lett.* **2018**, *20*, 6550-6553).

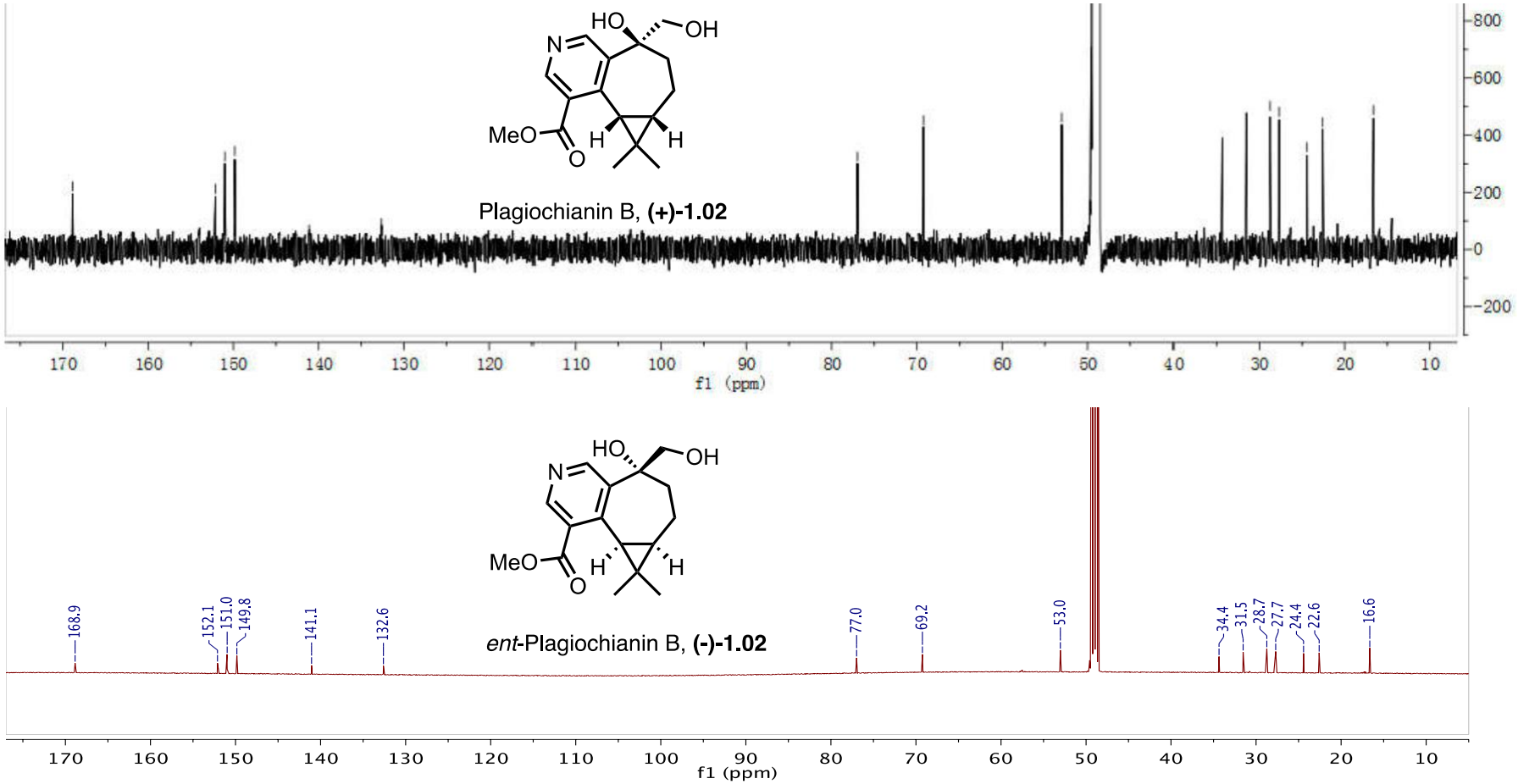


Figure A.86. **^{13}C NMR** (151 MHz, Methanol-*d4*) Overlay of Natural Plagiochianin B **(+)-1.02** & Synthetic *ent*-Plagiochianin B **(-)-1.02**
Compare to: Lou *Org. Lett.* **2018**, *20*, 6550-6553.

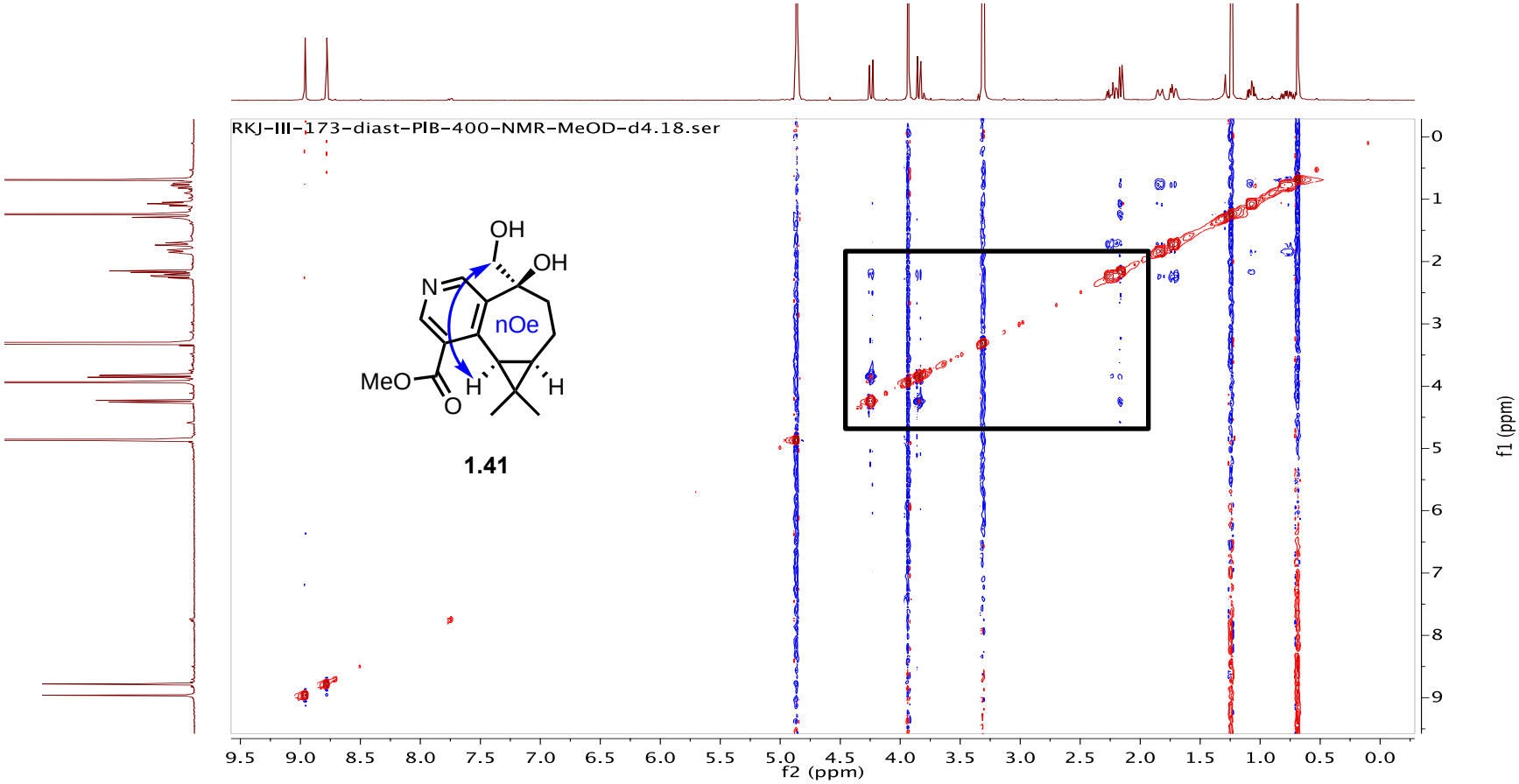


Figure A.87. **NOESY** (400 MHz, Methanol-*d4*) Diastereomer of *ent*-Plagiochianin B **1.41**
Key correlations between the methylene protons (3.85 and 4.25 ppm) of the diol and methine doublet (2.16 ppm).

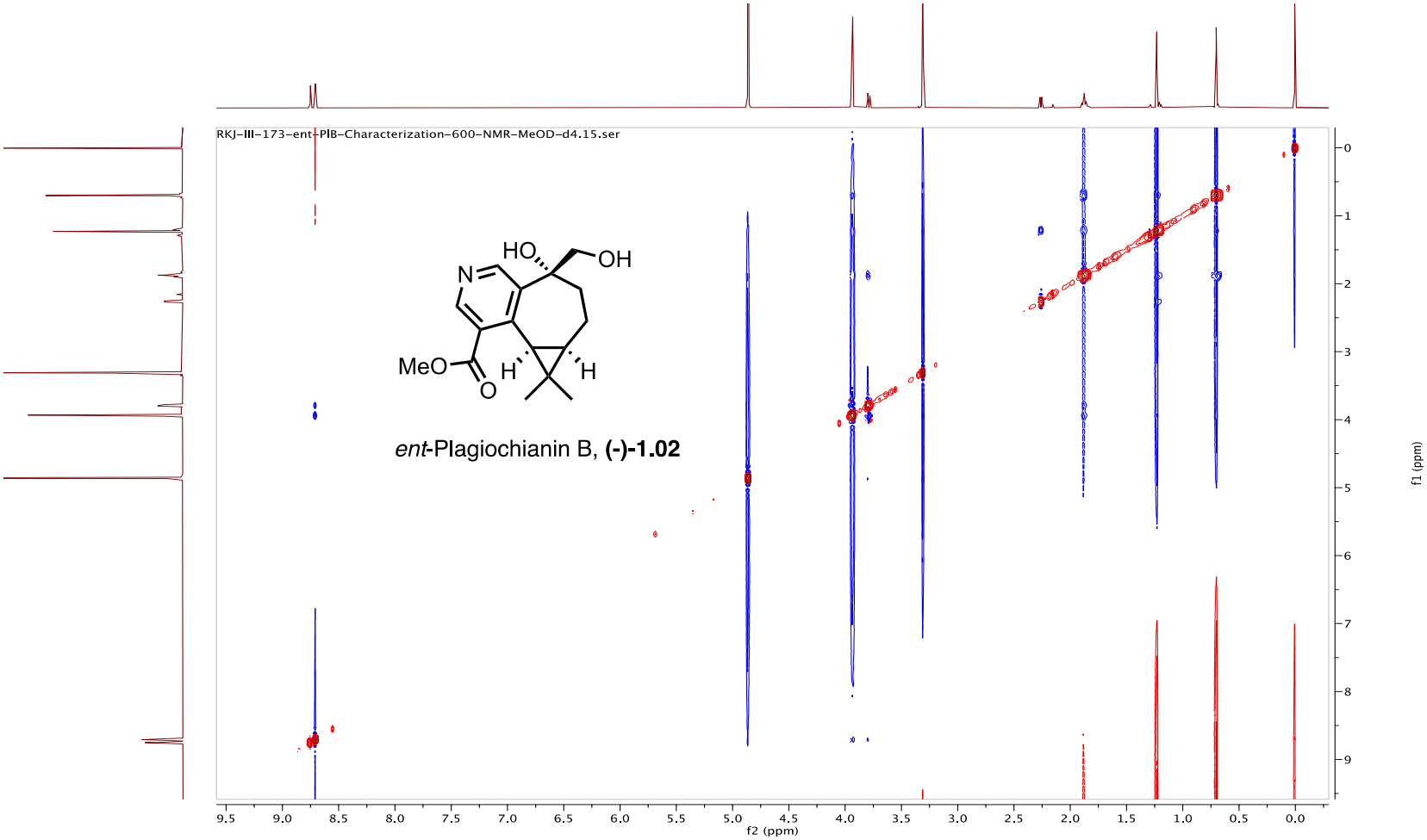


Figure A.88. **NOESY** (600 MHz, Methanol-*d4*) *ent*-Plagiochianin B **(-)-1.02**

Unlike the diastereomer, **1.41**, *ent*-Plagiochianin B **(-)-1.02** does *not* show correlations between methine doublet (2.26) and methylene of the diol (3.79 and 3.94).

APPENDIX B

Spectra Relevant to Chapter Two

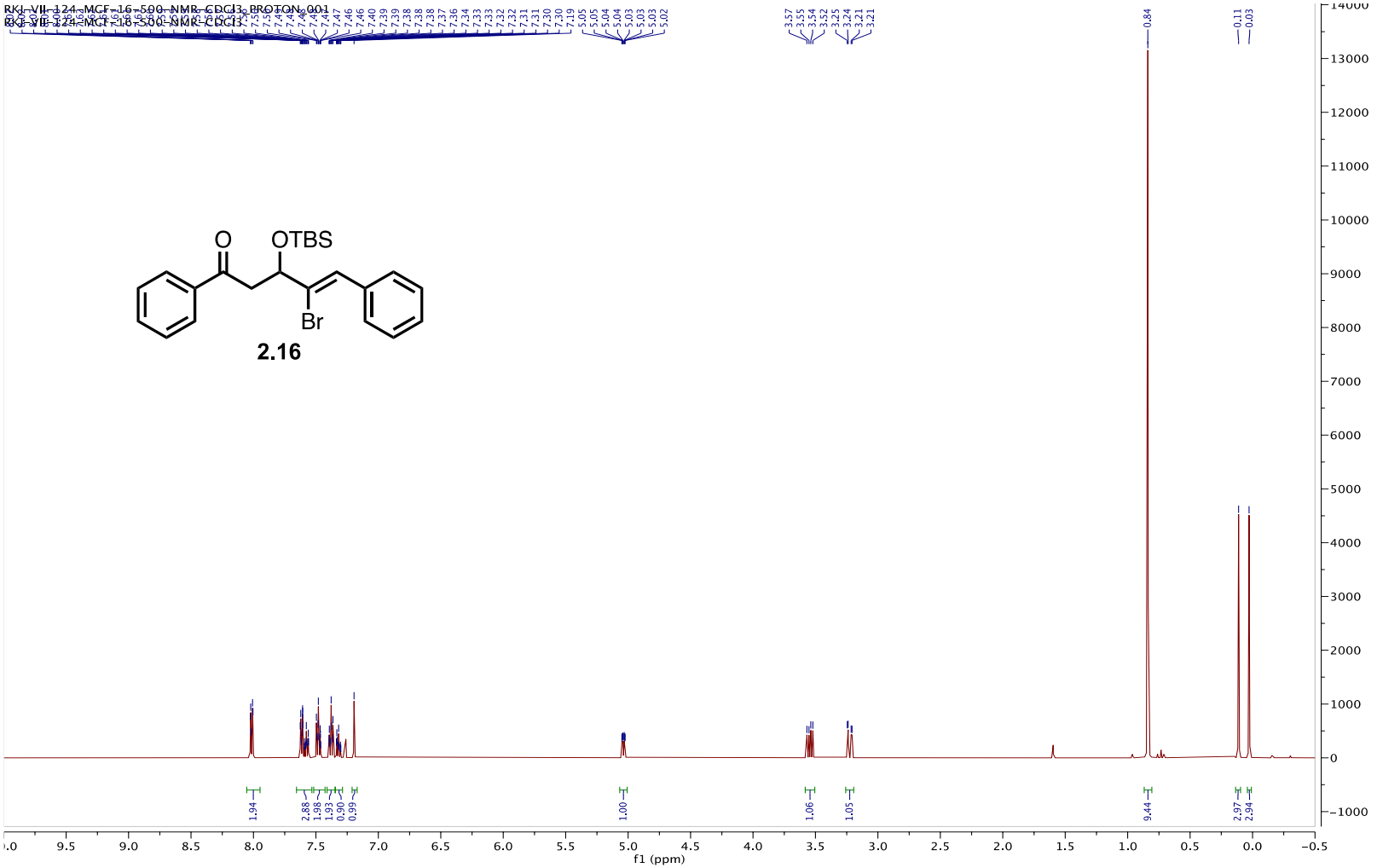


Figure B.01. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **2.16**

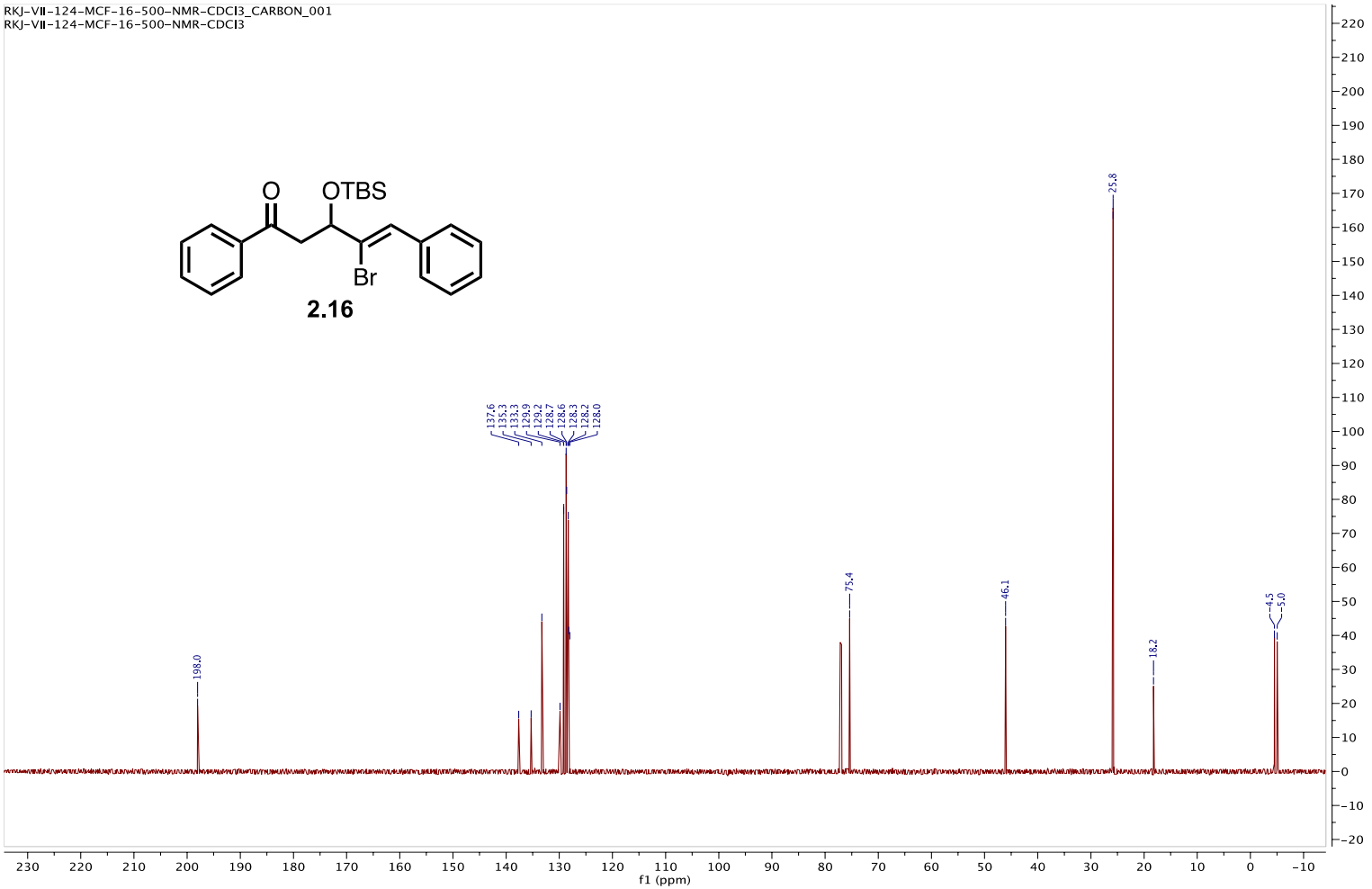


Figure B.02. **^{13}C NMR** (126 MHz, $CDCl_3$) Ketone **2.16**

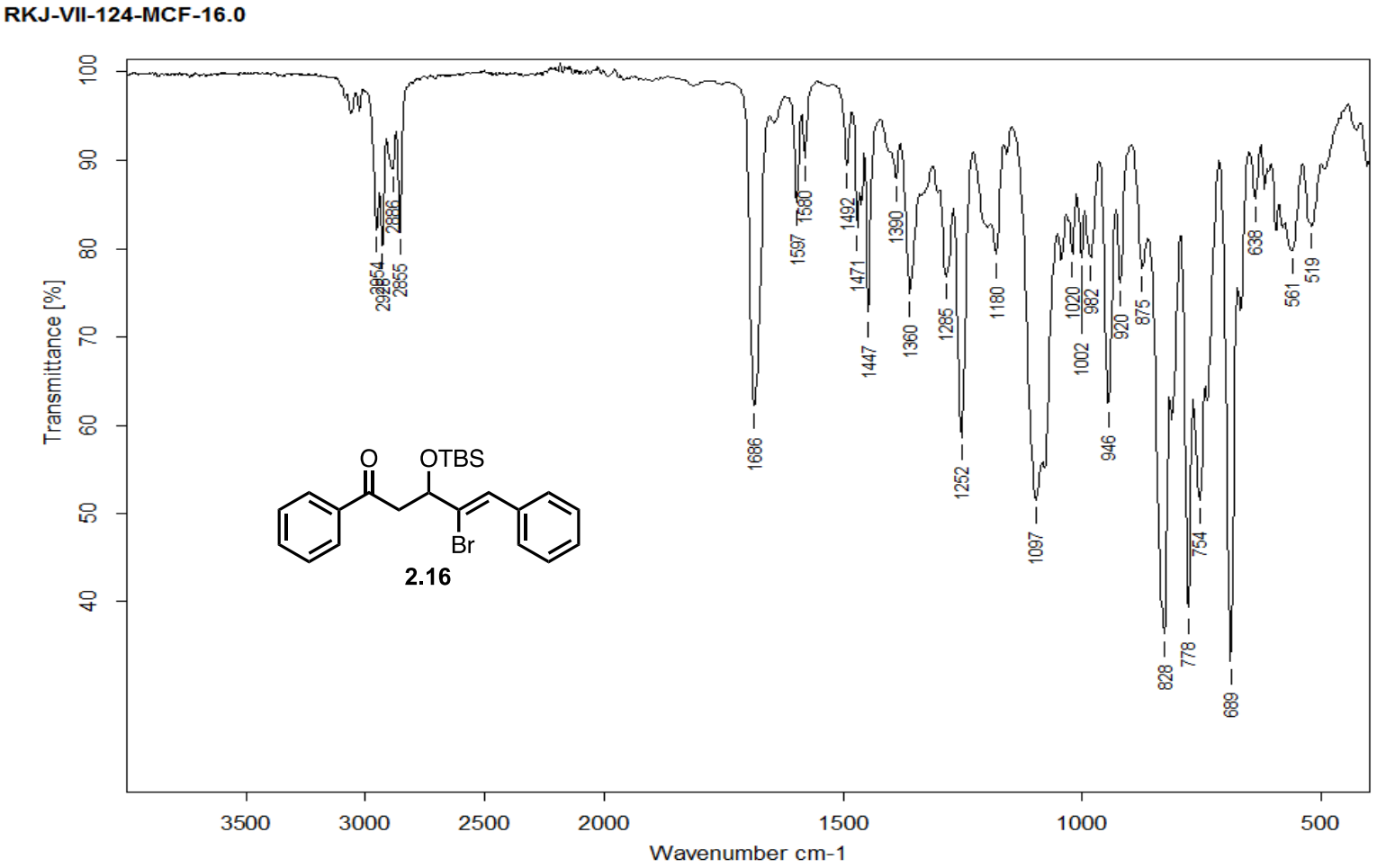


Figure B.03. **FTIR** (thin film) Ketone **2.16**

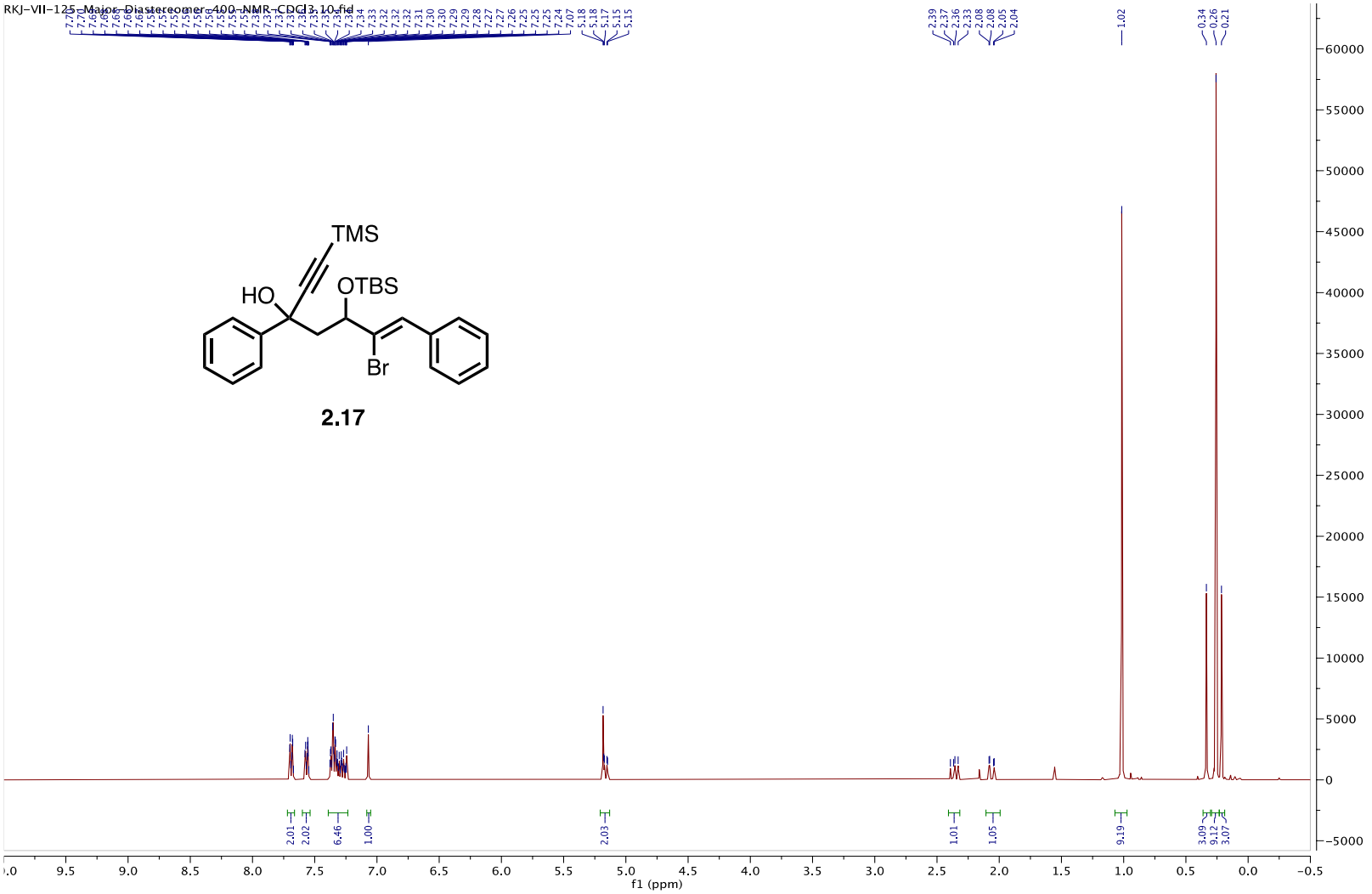


Figure B.04. **^{1}H NMR** (400 MHz, $CDCl_3$) Major Diastereomer Tertiary Alcohol **2.17**

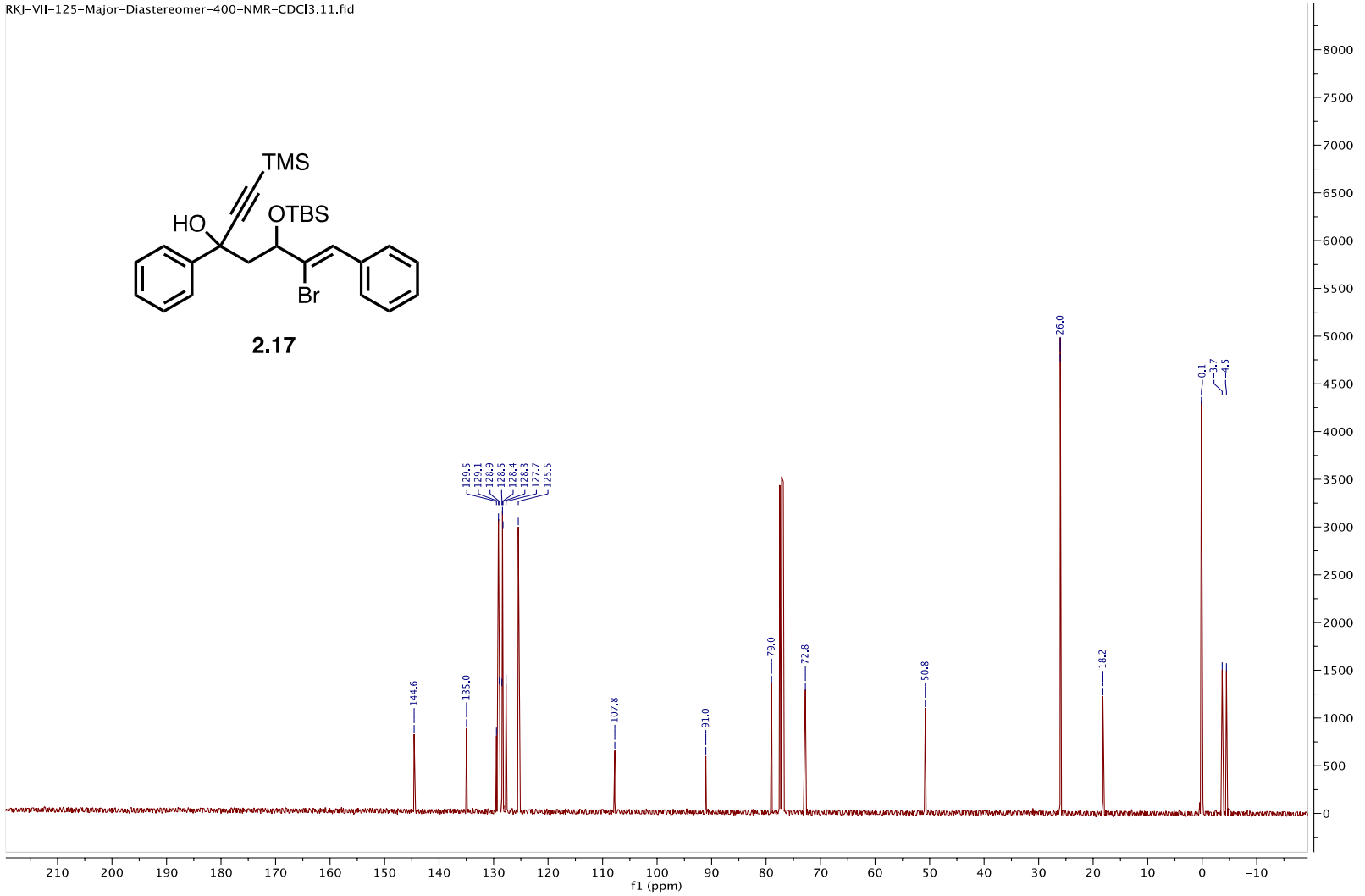


Figure B.05. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Tertiary Alcohol **2.17**

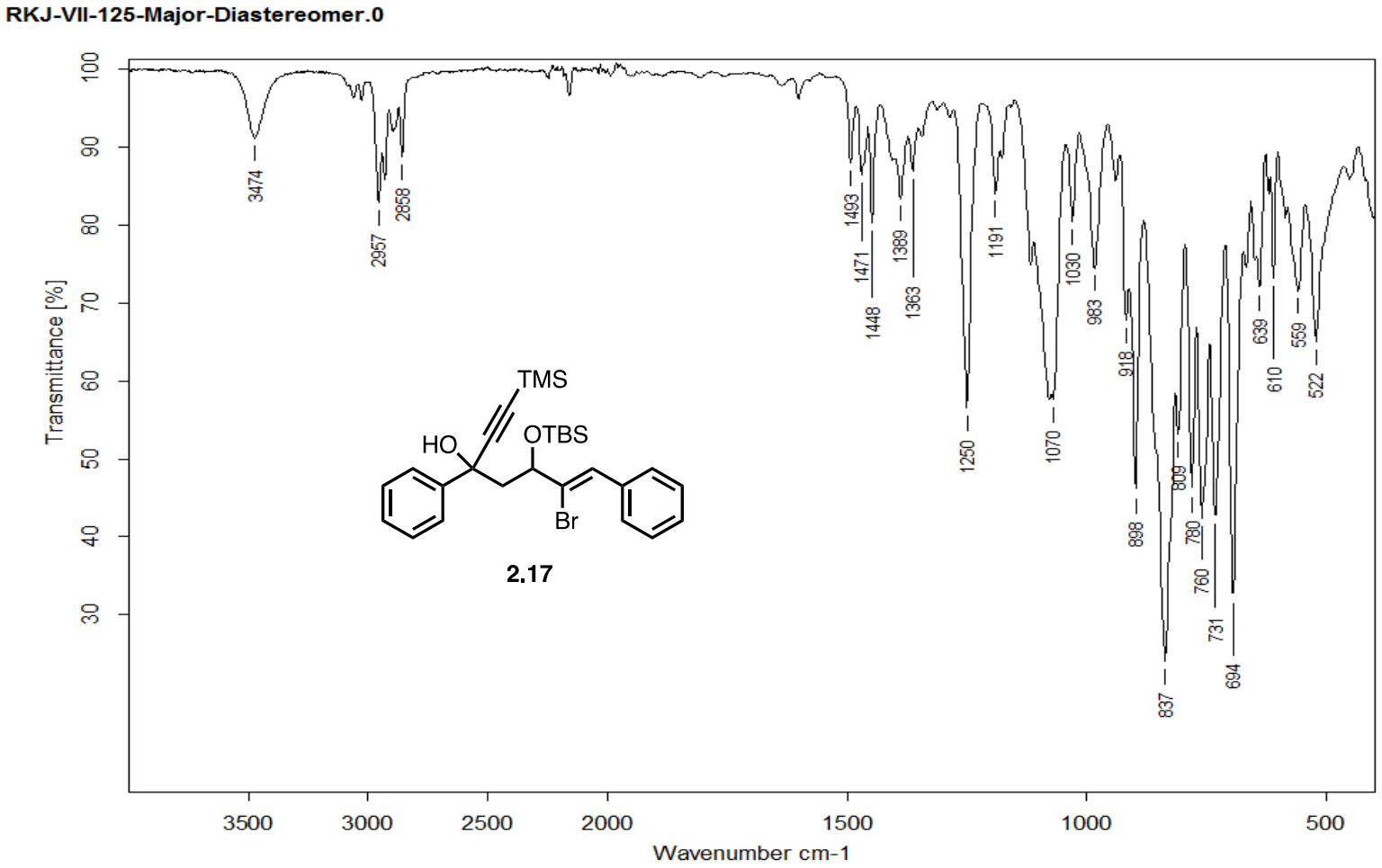


Figure B.06. **FTIR** (thin film) Major Diastereomer Tertiary Alcohol **2.17**

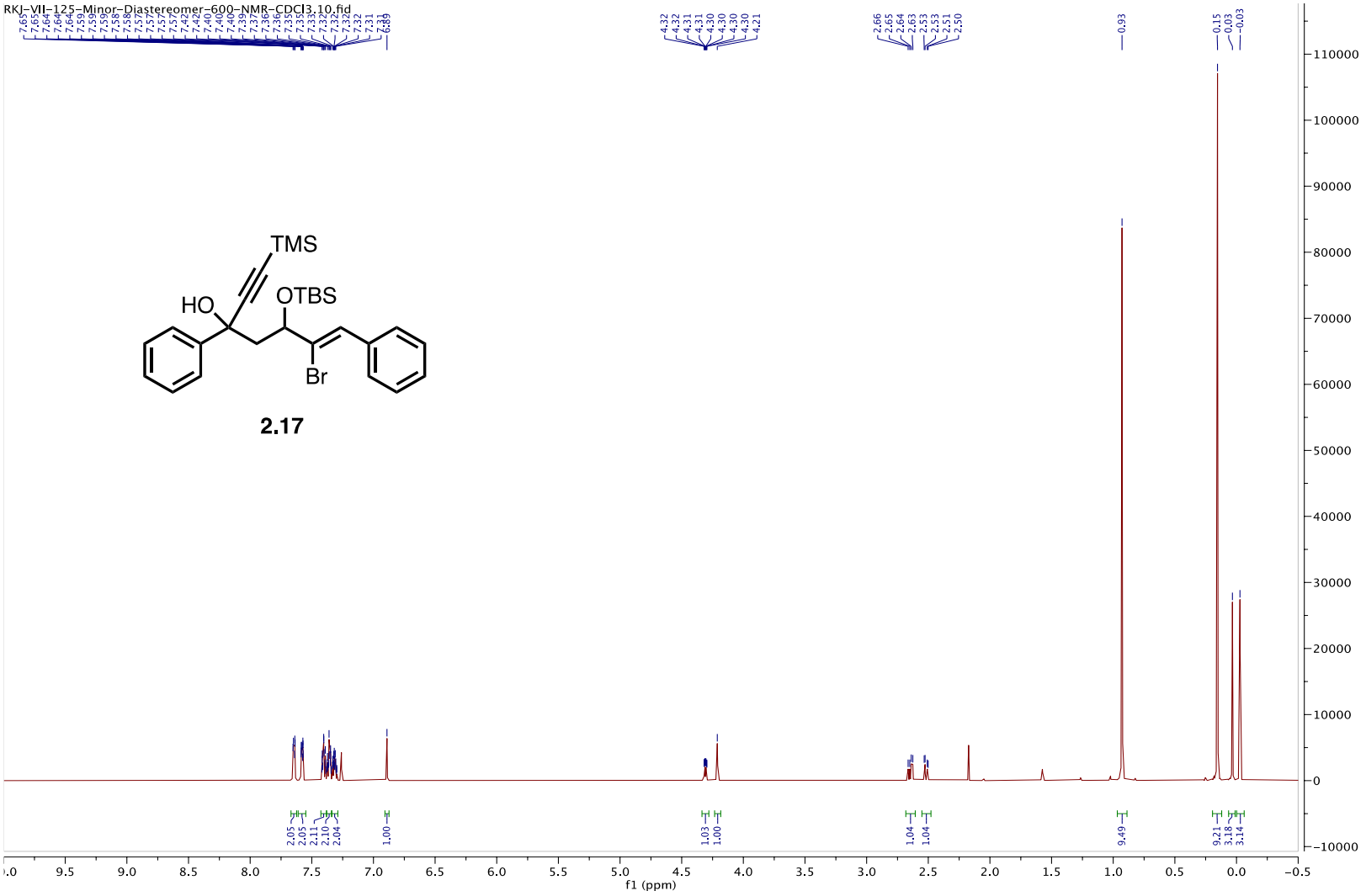


Figure B.07. **^{1}H NMR** (600 MHz, $CDCl_3$) Minor Diastereomer Tertiary Alcohol **2.17**

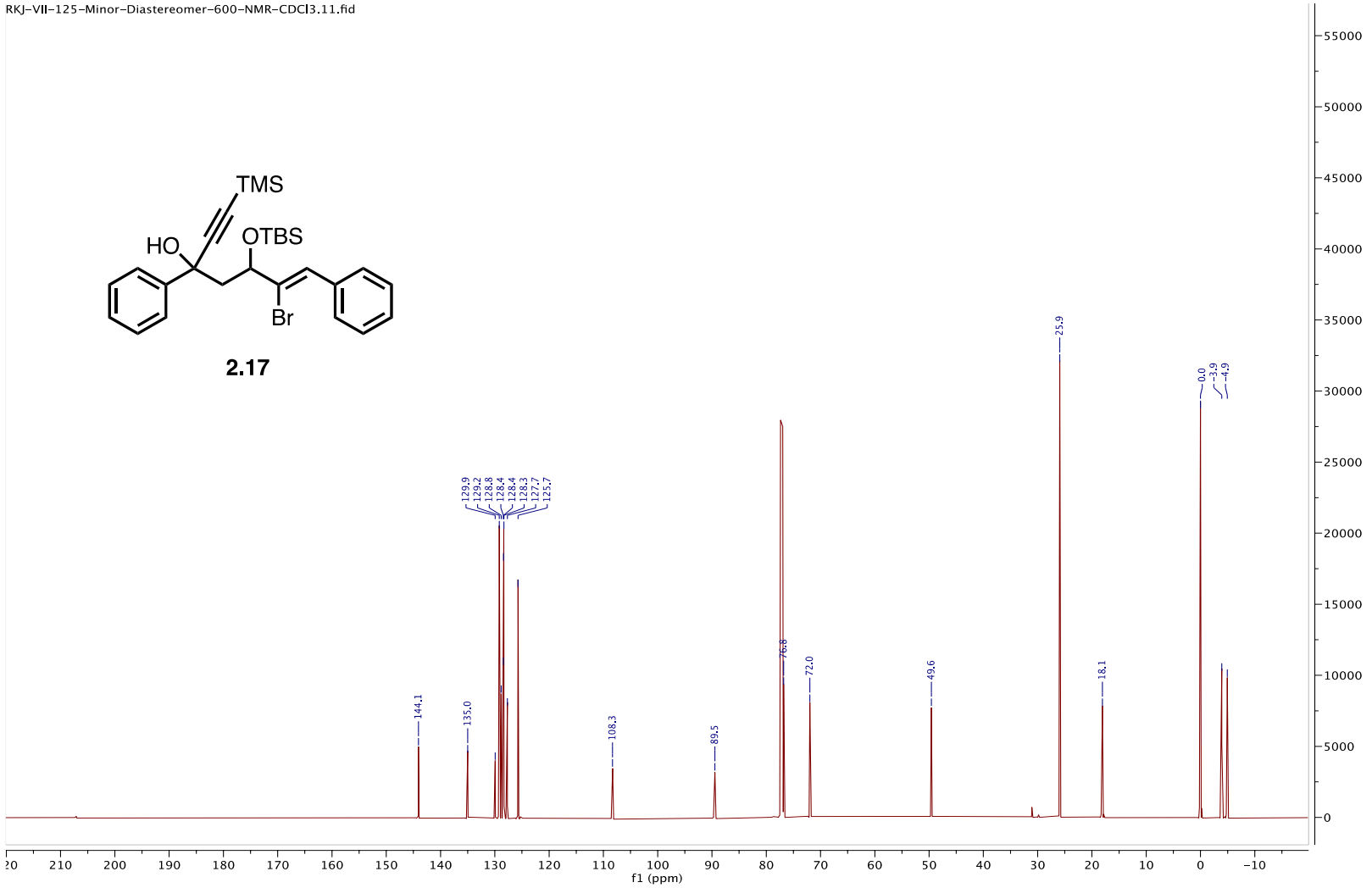


Figure B.08. **^{13}C NMR** (151 MHz, $CDCl_3$) Minor Diastereomer Tertiary Alcohol **2.17**

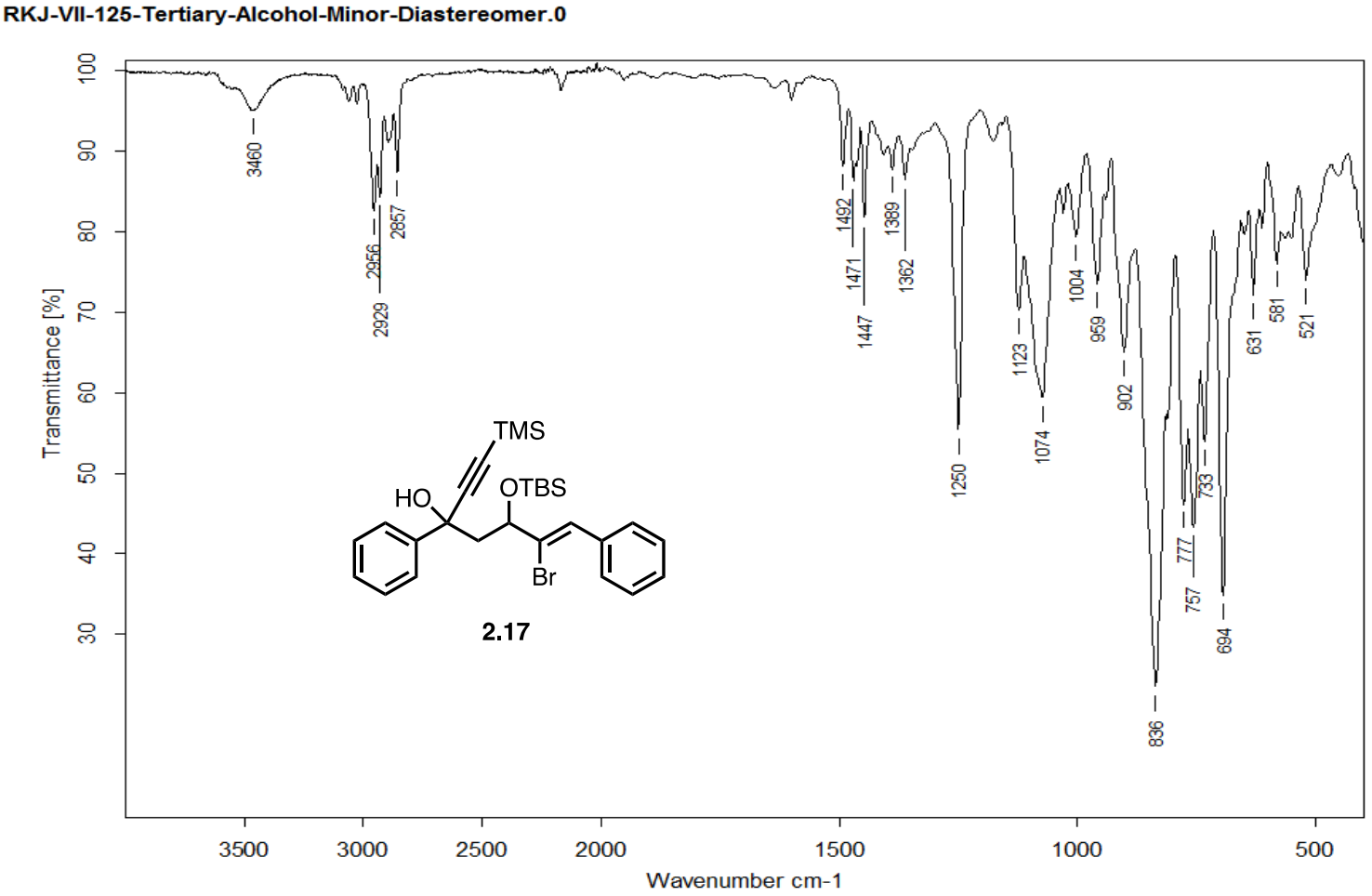


Figure B.09. **FTIR** (thin film) Minor Diastereomer Tertiary Alcohol **2.17**

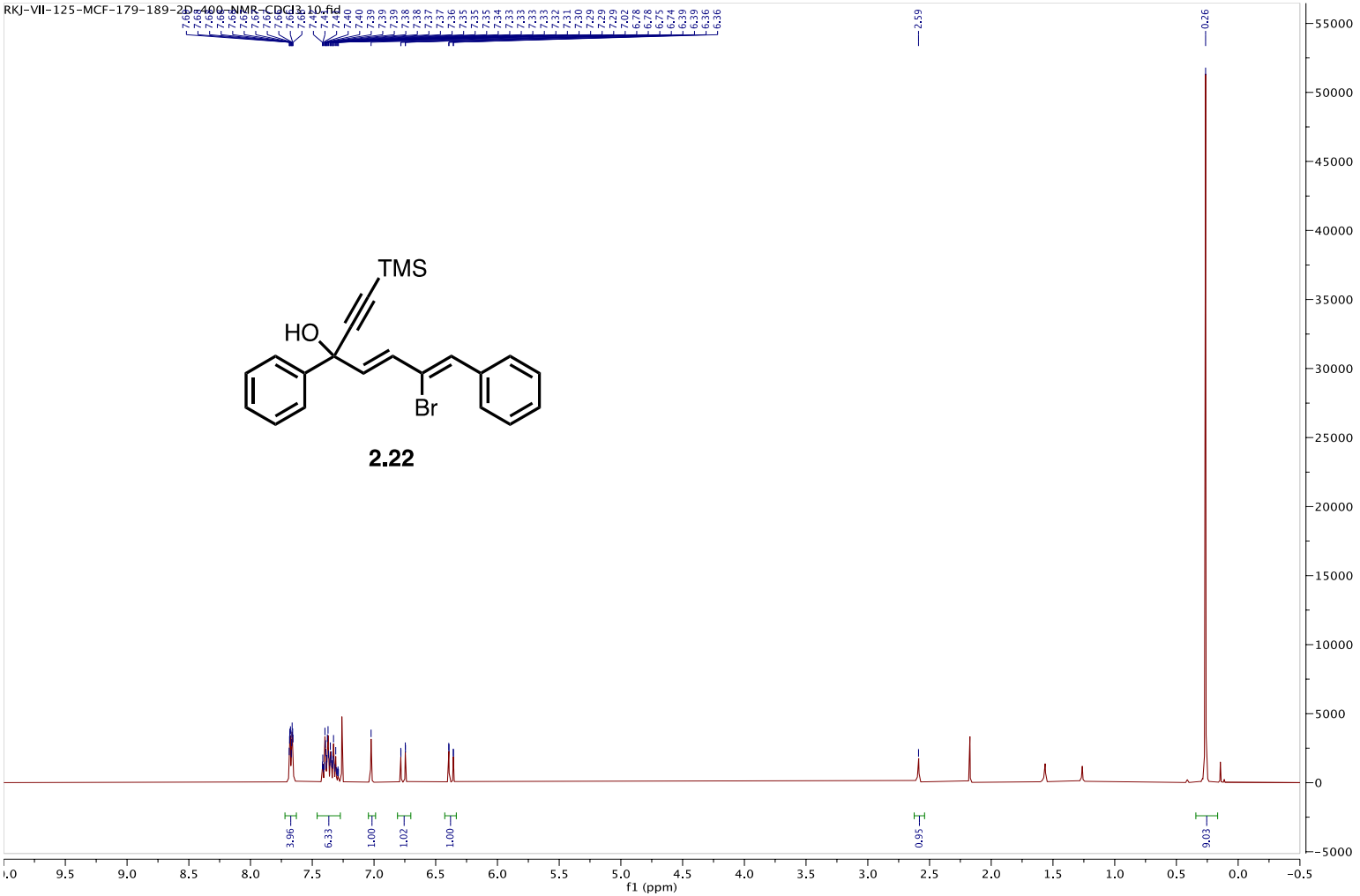


Figure B.10. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **2.22**

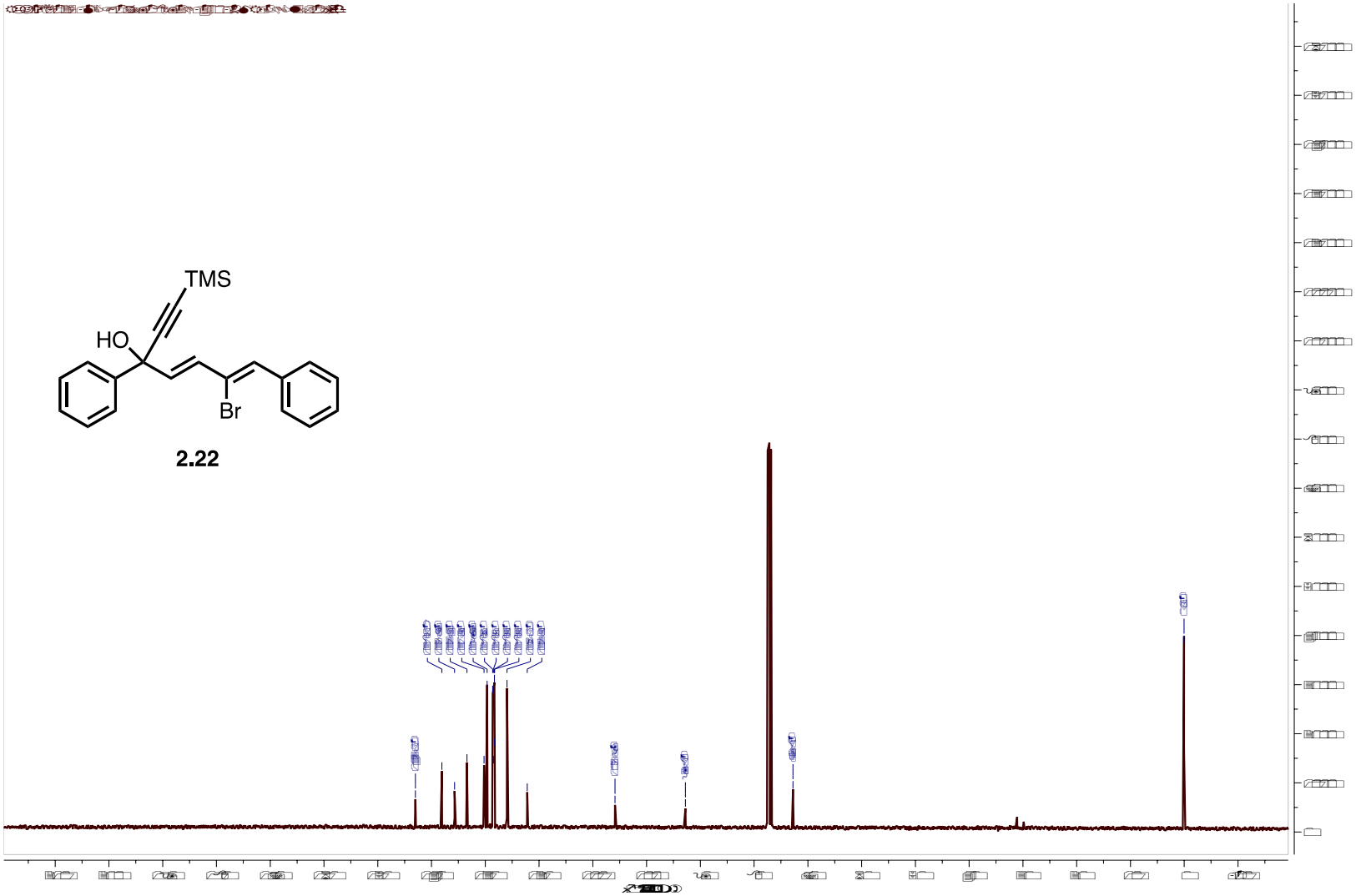


Figure B.11. **^{13}C NMR** (101 MHz, $CDCl_3$) Tertiary Alcohol **2.22** with DEPT 90 (middle) and DEPT 135 (top) overlayed

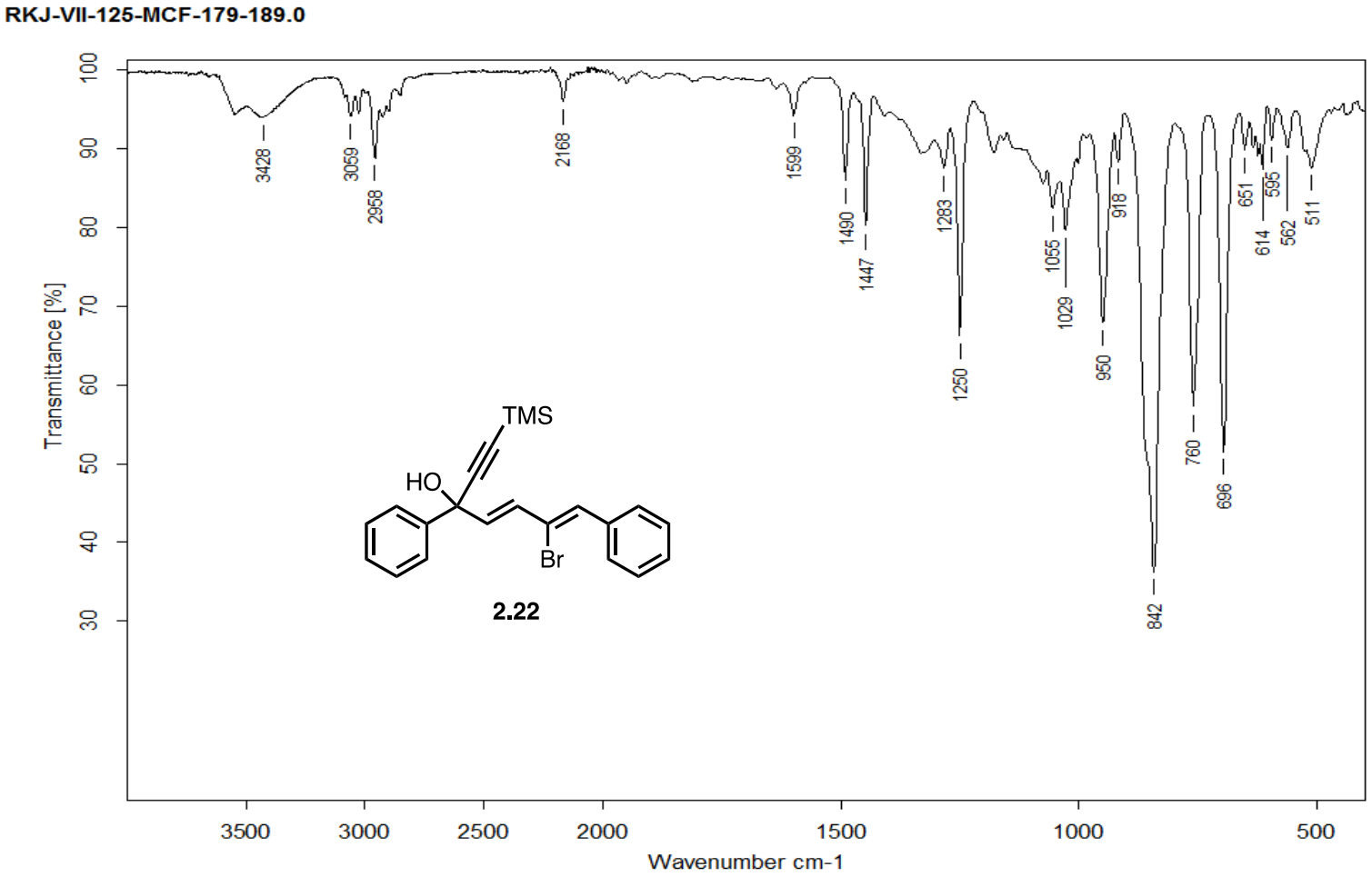


Figure B.12. **FTIR** (thin film) Tertiary Alcohol **2.22**

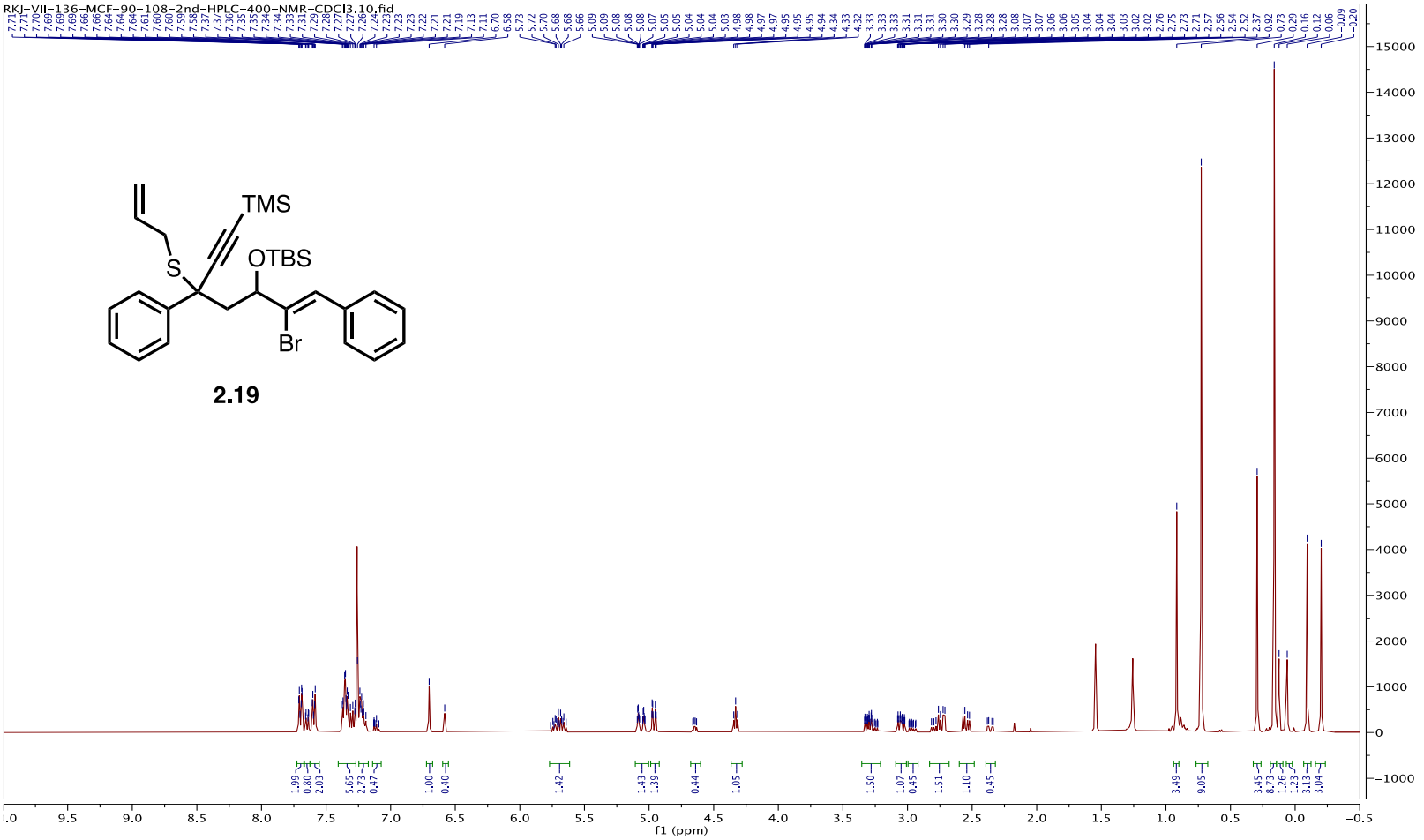


Figure B.13. **^{1}H NMR** (400 MHz, $CDCl_3$) Sulfide **2.19**

The above spectral data do not contain the reported 1.5:1 ratio of diastereomers because repeated chromatographic purifications were necessary to obtain spectral data of analytical purity.

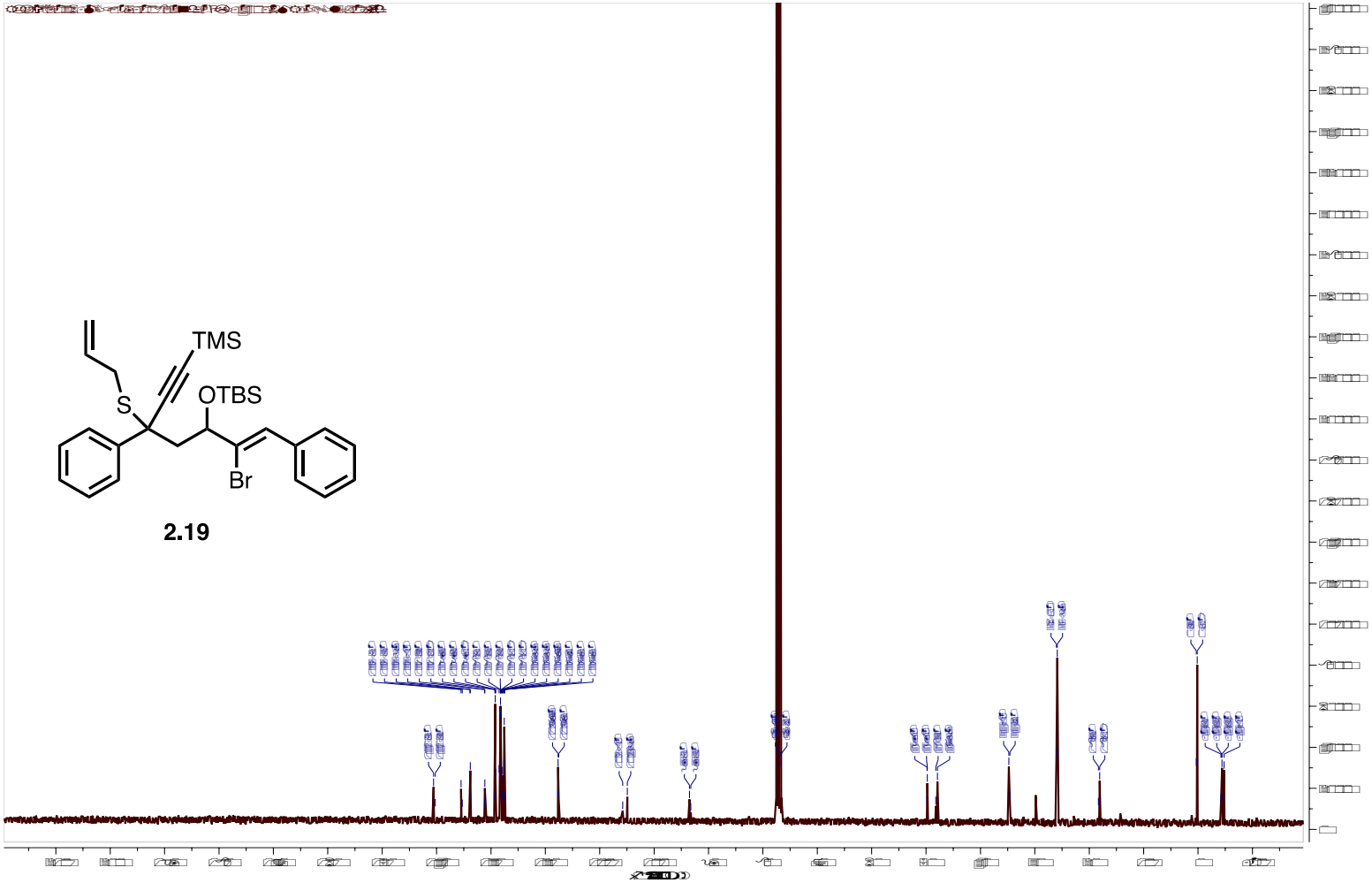


Figure B.14. **^{13}C NMR** (101 MHz, $CDCl_3$) Sulfide **2.19** with DEPT 90 (middle) and DEPT 135 (top) overlayed

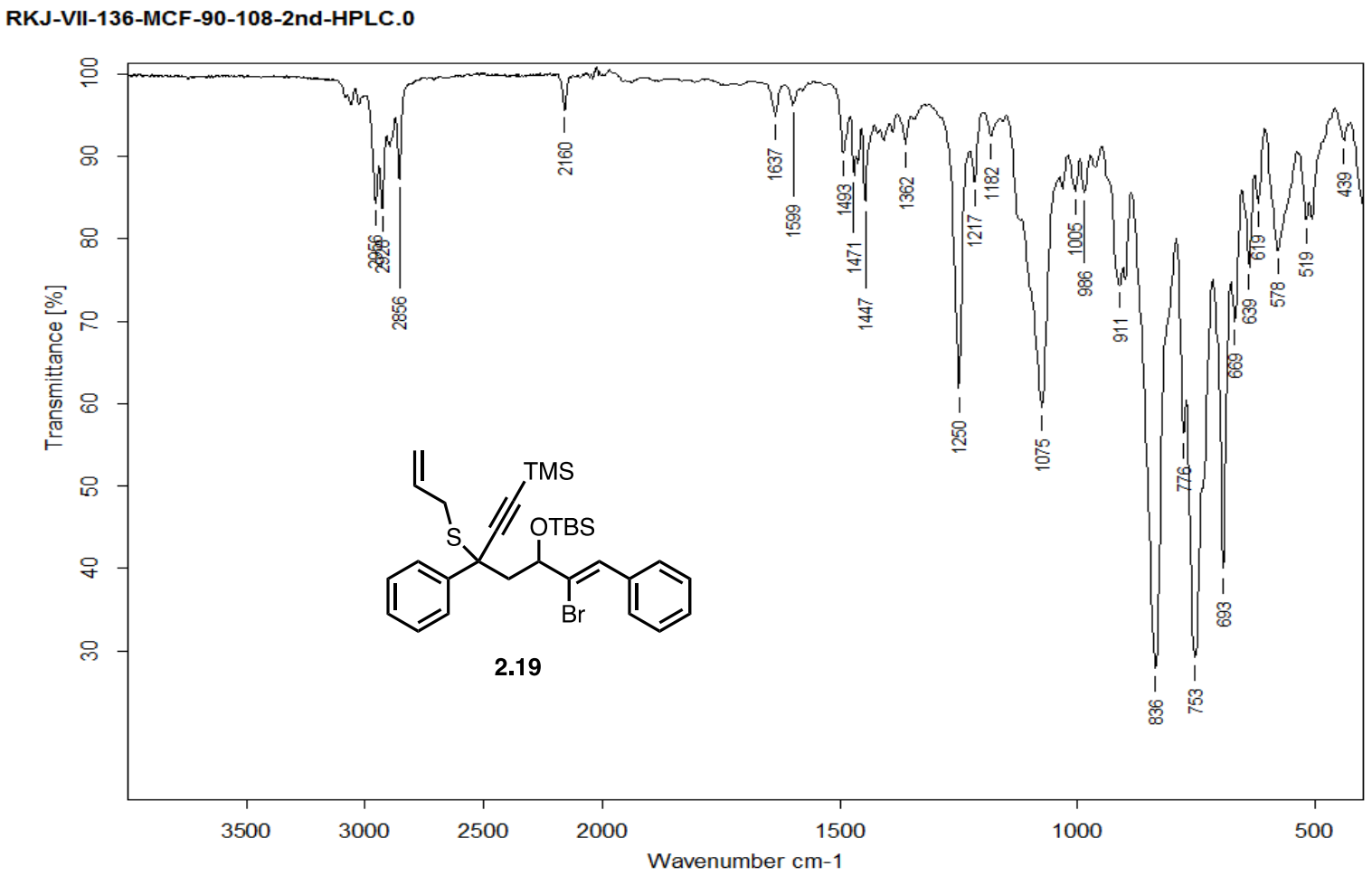


Figure B.15. **FTIR** (thin film) Sulfide **2.19**

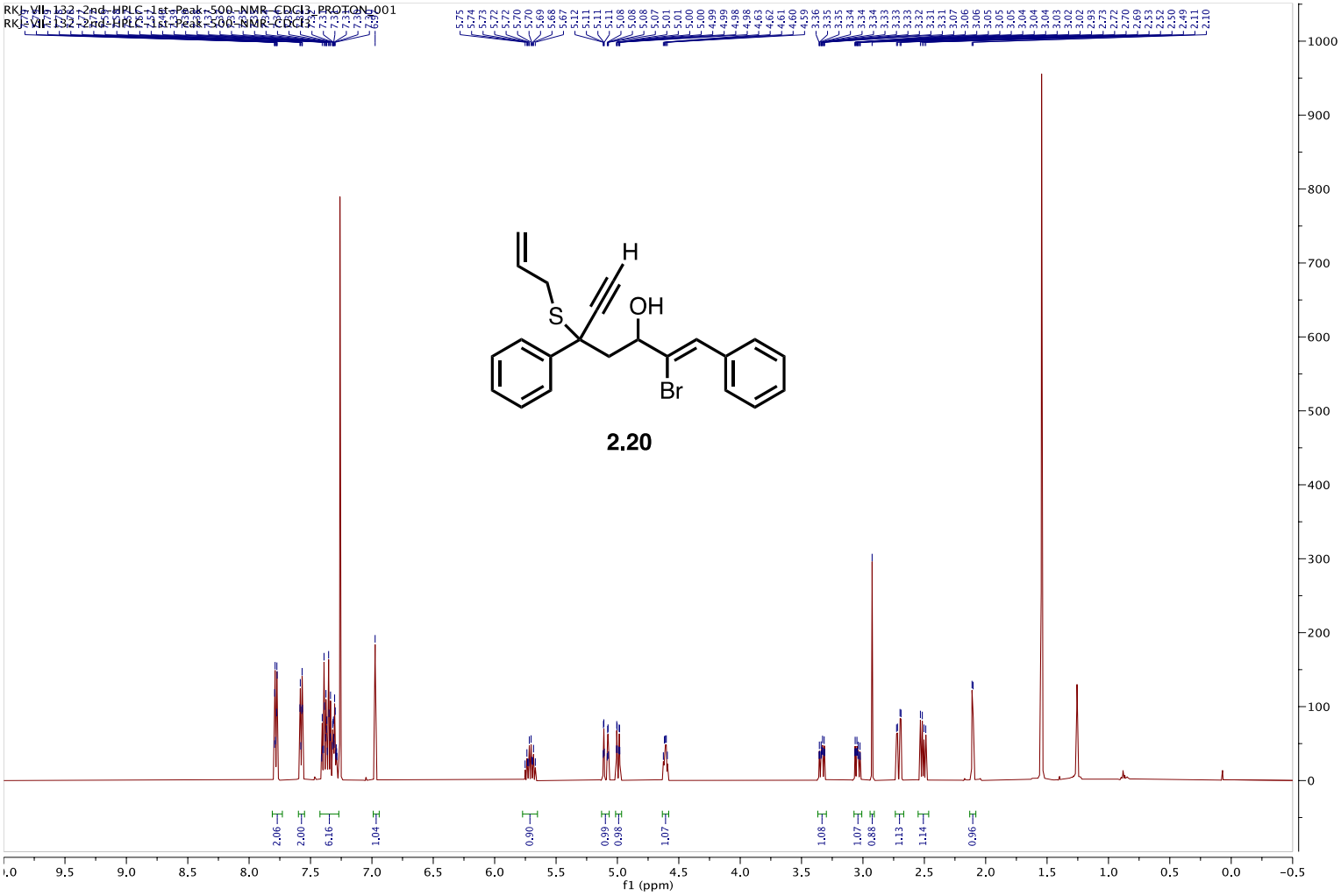


Figure B.16. **^{1}H NMR** (500 MHz, $CDCl_3$) Major Diastereomer of Sulfide **2.20**

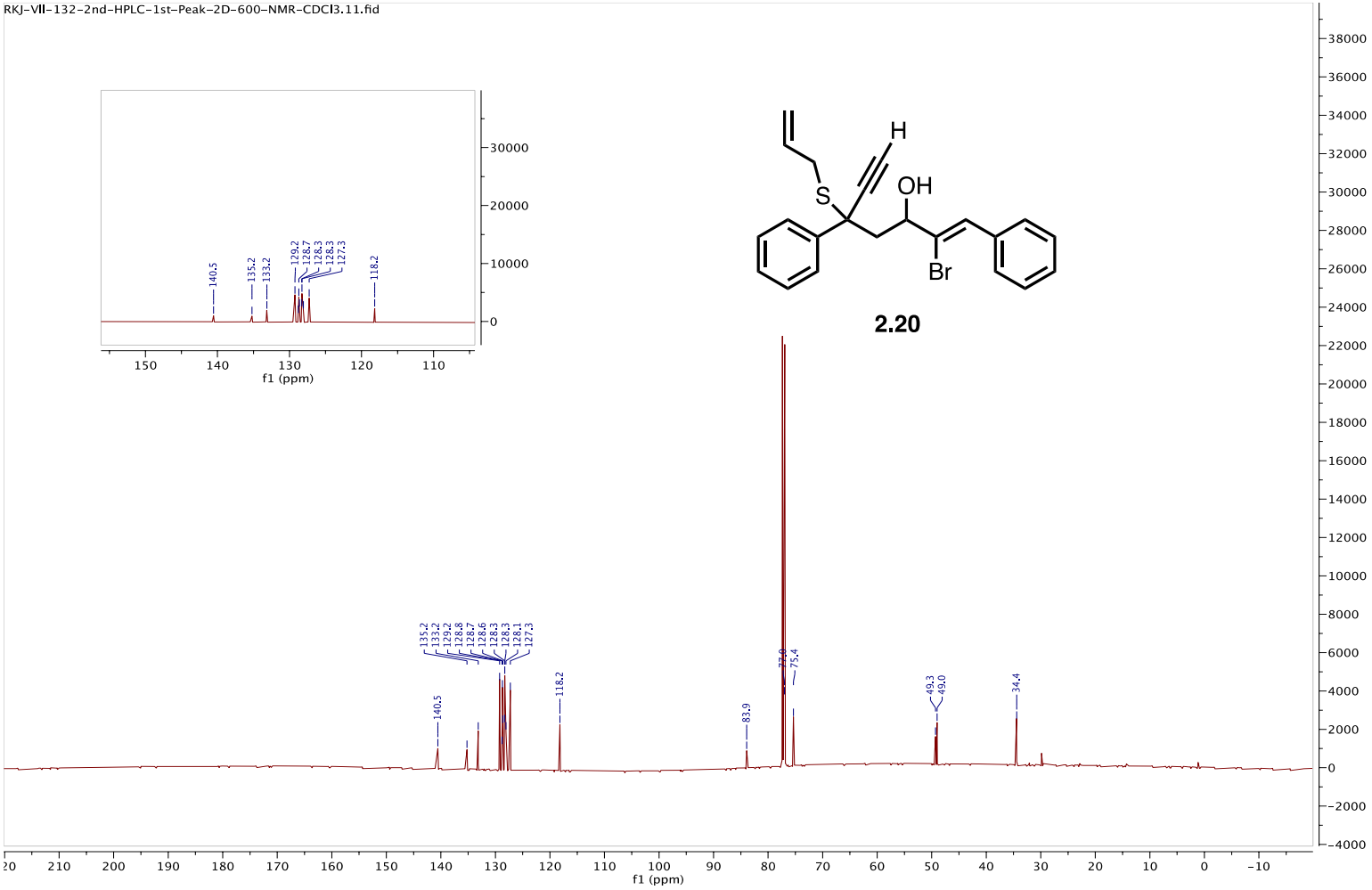


Figure B.17. **^{13}C NMR** (151 MHz, $CDCl_3$) Major Diastereomer of Sulfide **2.20**

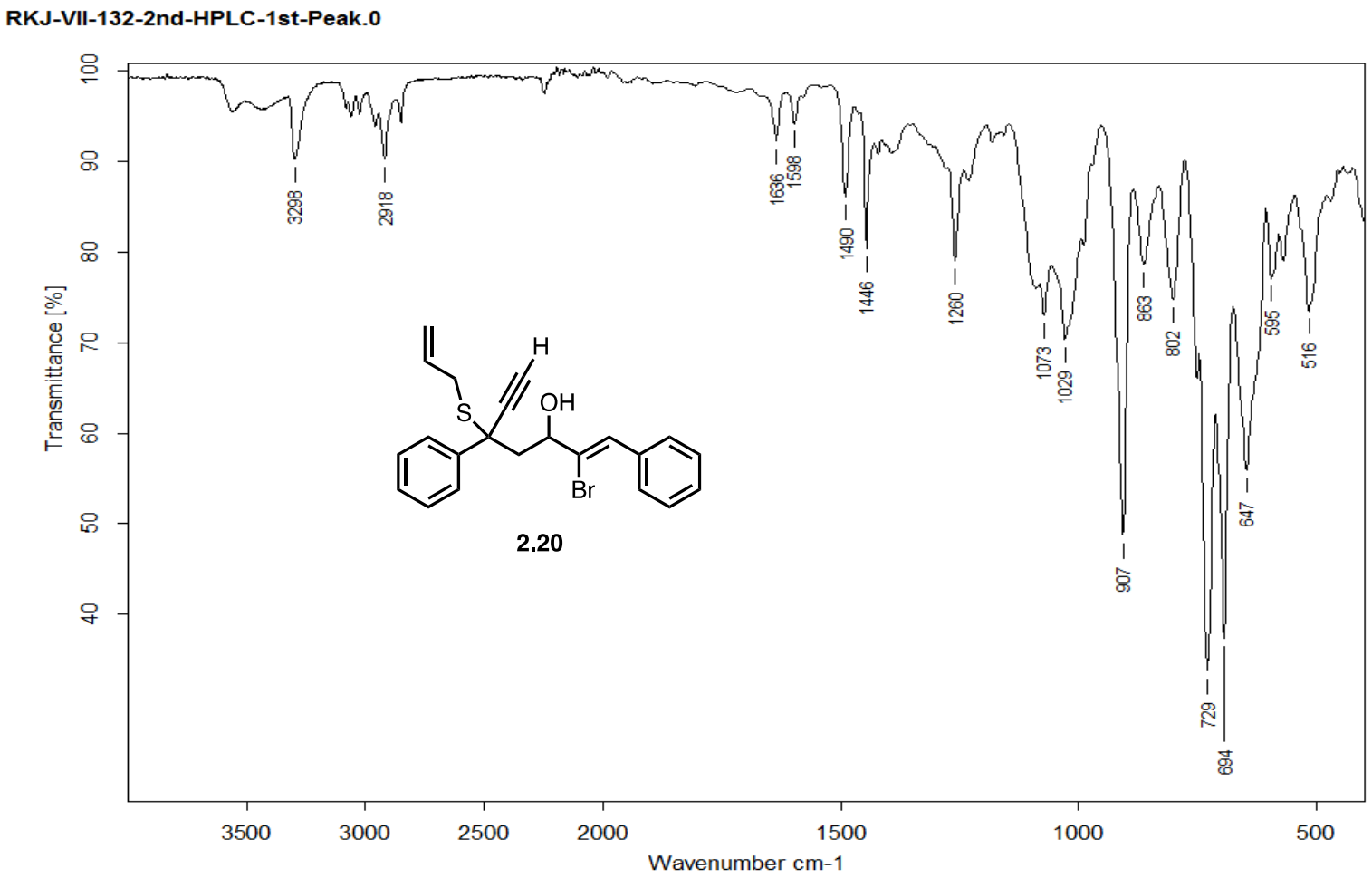


Figure B.18. **FTIR** (thin film) Major Diastereomer of Sulfide **2.20**

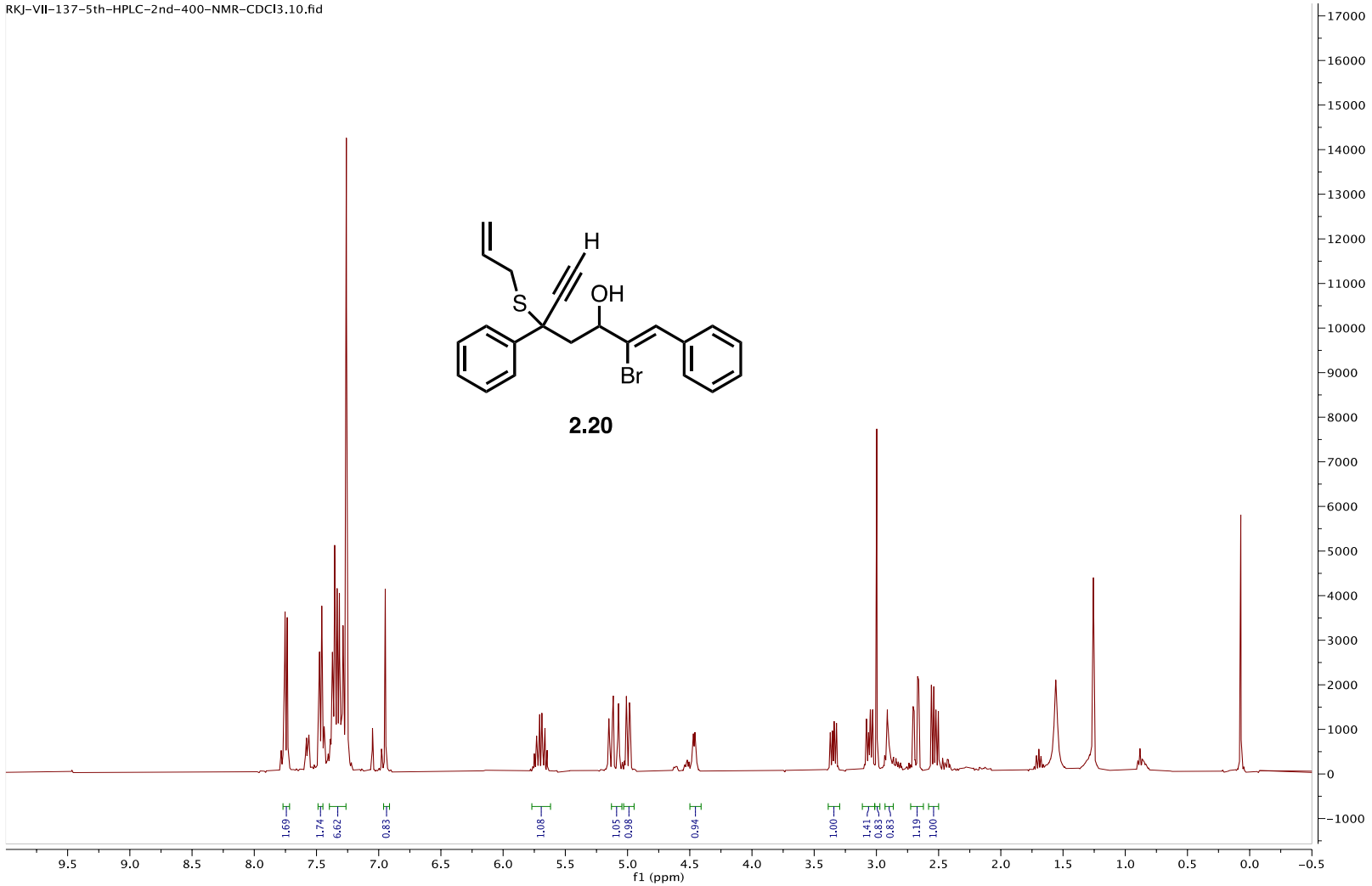


Figure B.19. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer of Sulfide **2.20**

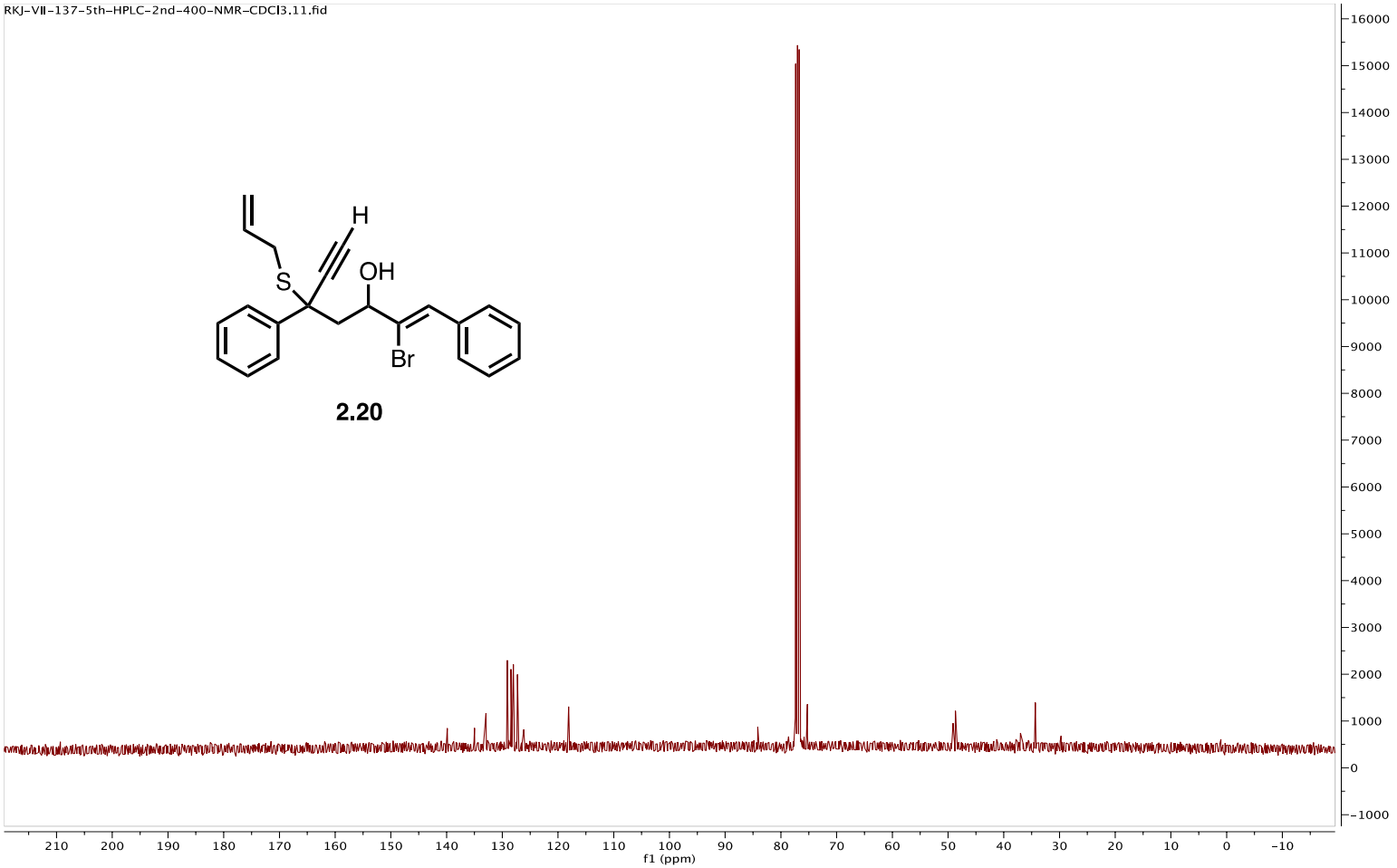


Figure B.20. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Sulfide **2.20**

Unambiguous assignment could not be made of all the carbons in this sample. An unmarked spectrum is attached to aid in comparison should this compound be made again.

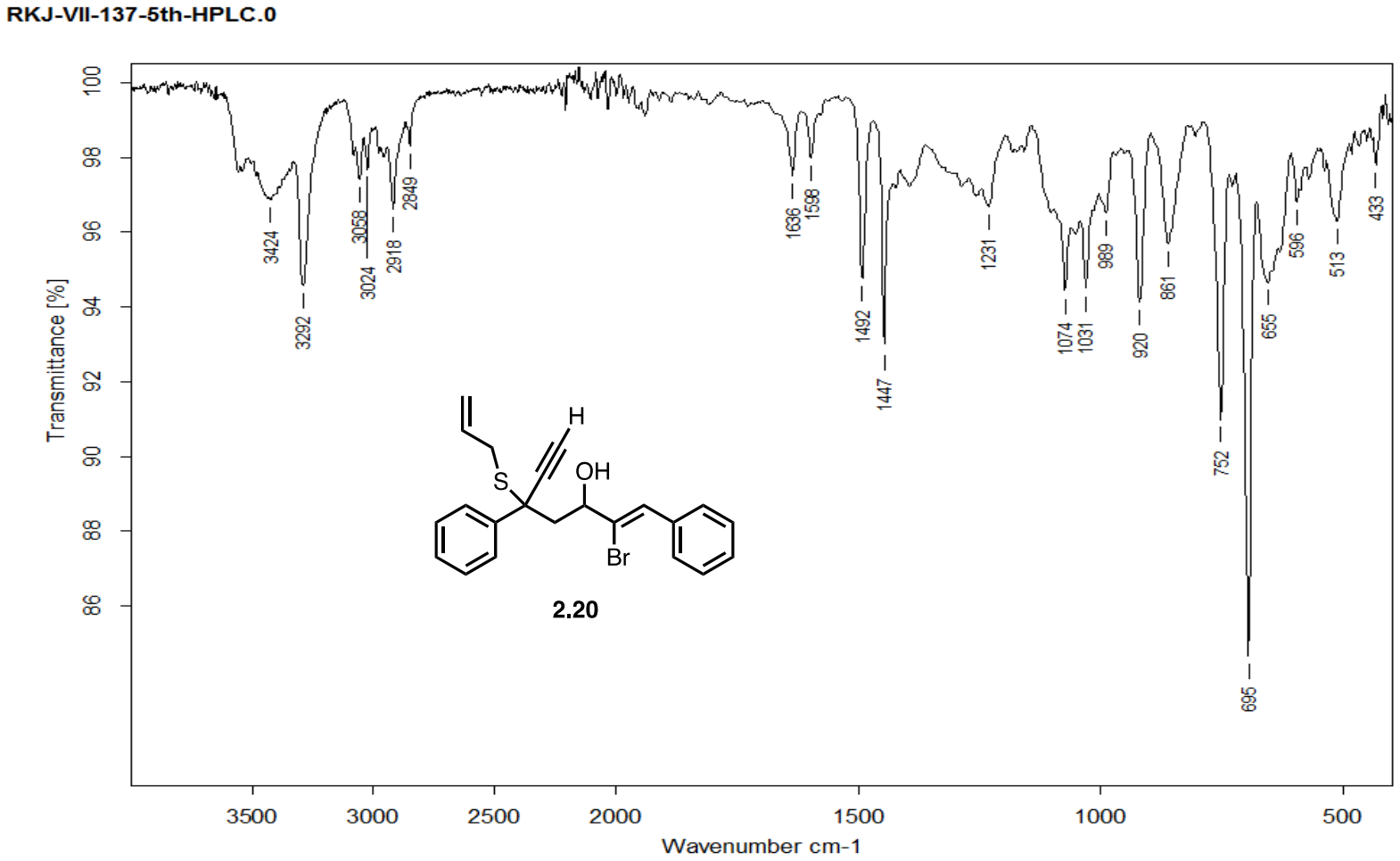


Figure B.21. **FTIR** (thin film) Minor Diastereomer Sulfide **2.20**

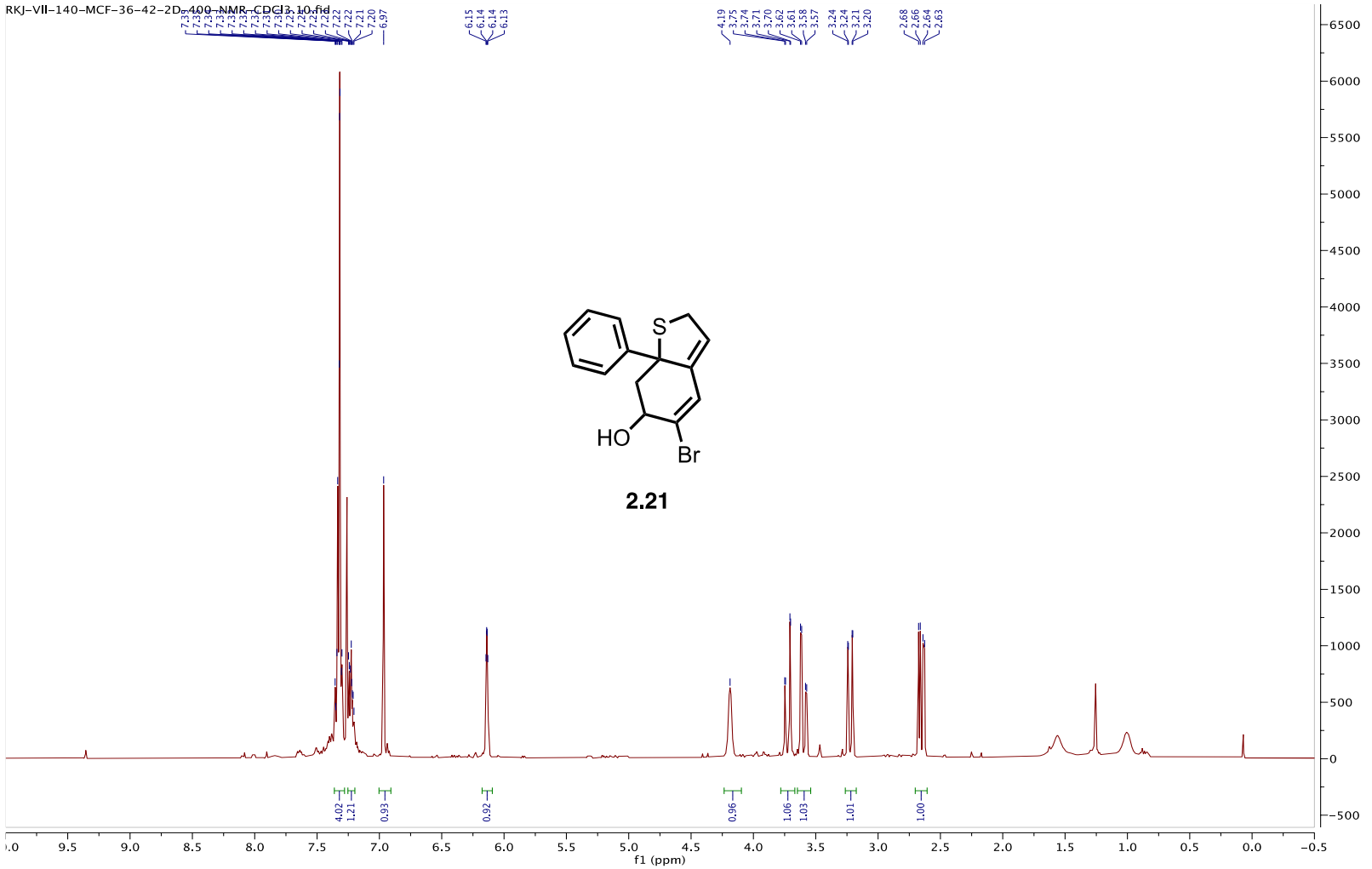


Figure B.22. **^{1}H NMR** (400 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21**

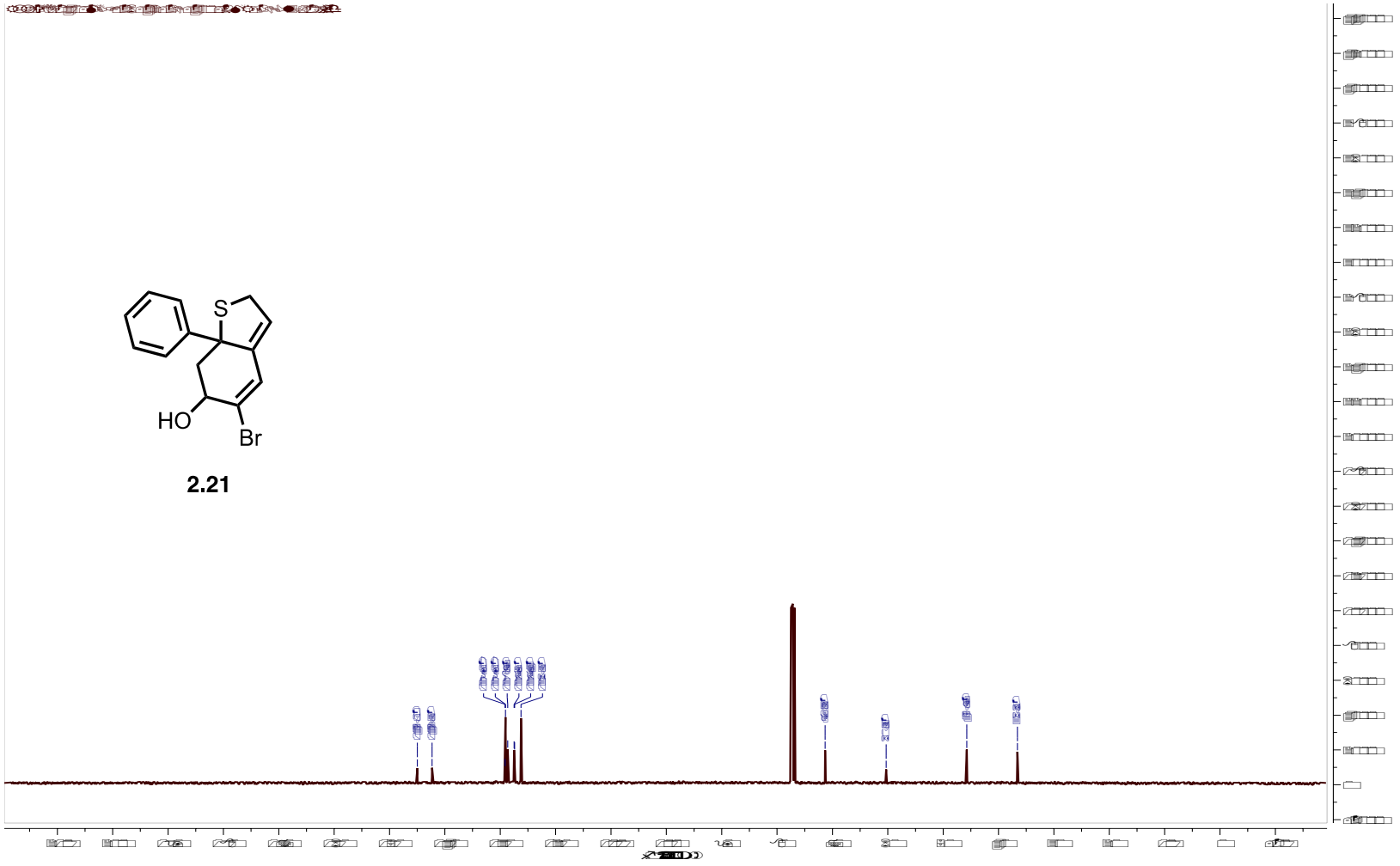


Figure B.23. **^{13}C NMR** (101 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21** with DEPT 90 (middle) and DEPT 135 (top) overlayed

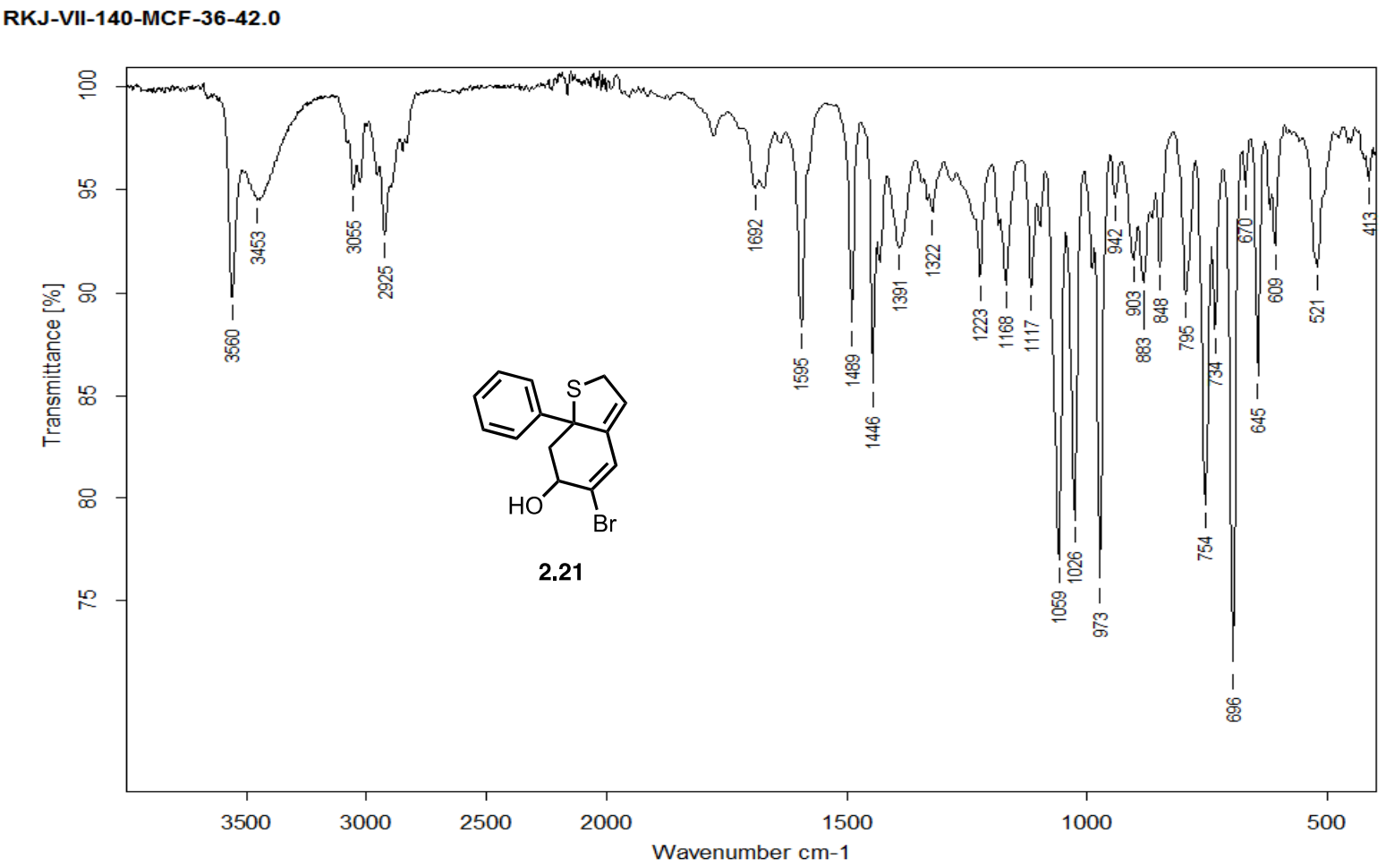


Figure B.24. **FTIR** (thin film) Tetrahydrobenzo[*b*] thiophene **2.21**

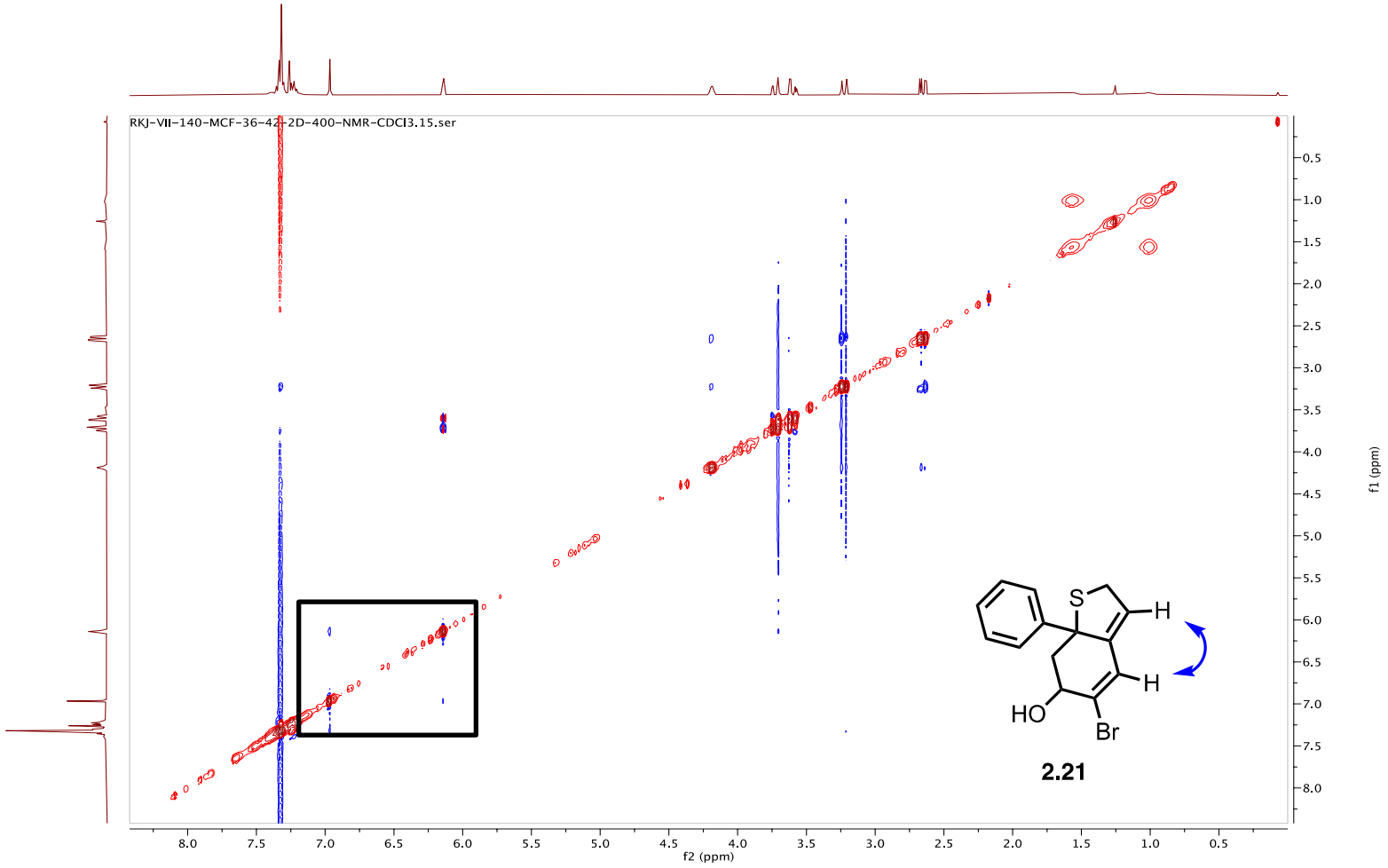


Figure B.25. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21**
Key correlation between vinyl methines (6.97 & 6.15-6.13) boxed in black.

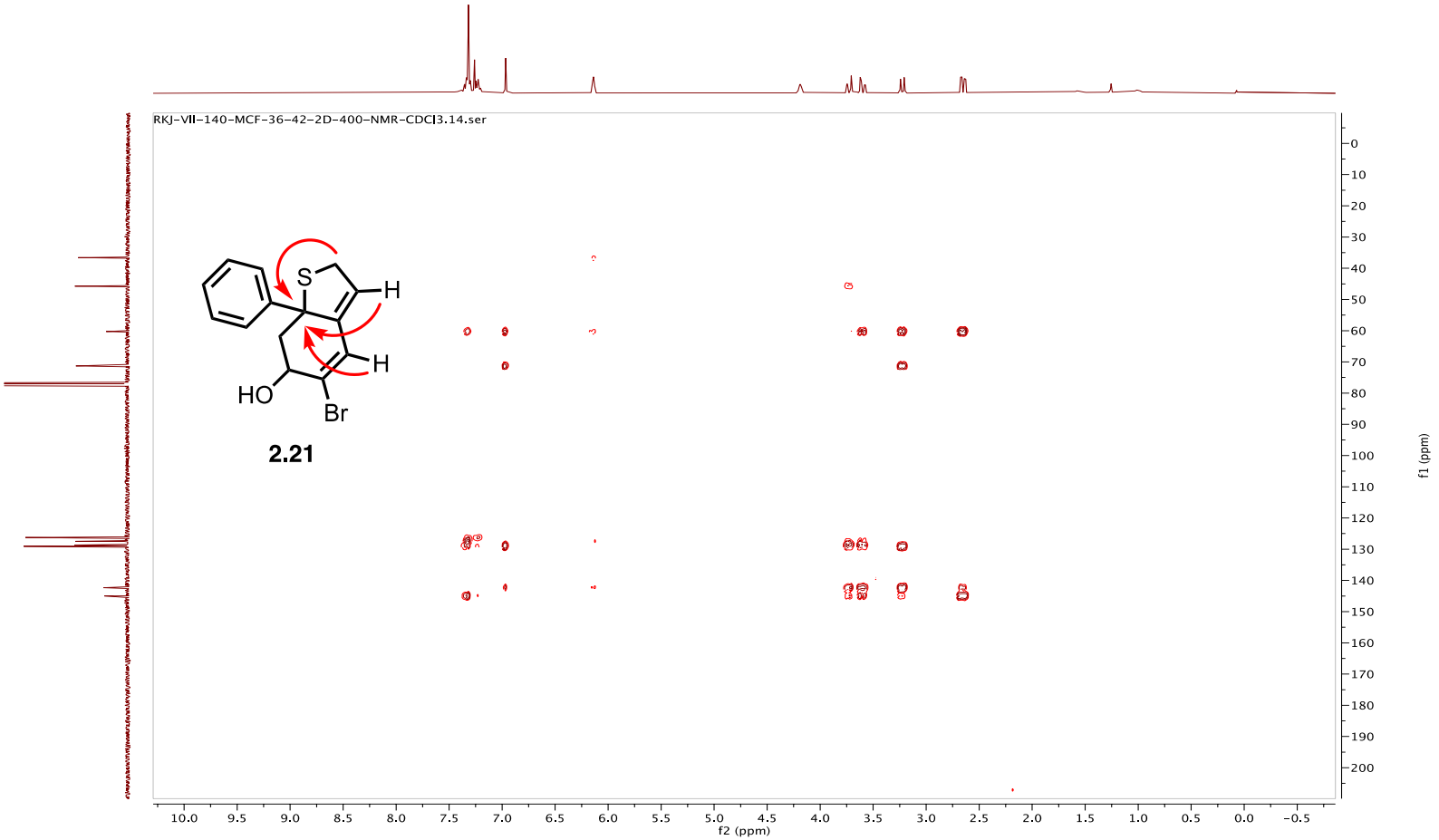


Figure B.26. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) Tetrahydrobenzo[*b*] thiophene **2.21**
Key correlations between vinyl methines (6.97 & 6.14 ppm) and allylic methylene (3.59 ppm) to quaternary carbon (60.3 ppm).

APPENDIX C

Spectra Relevant to Chapter Three

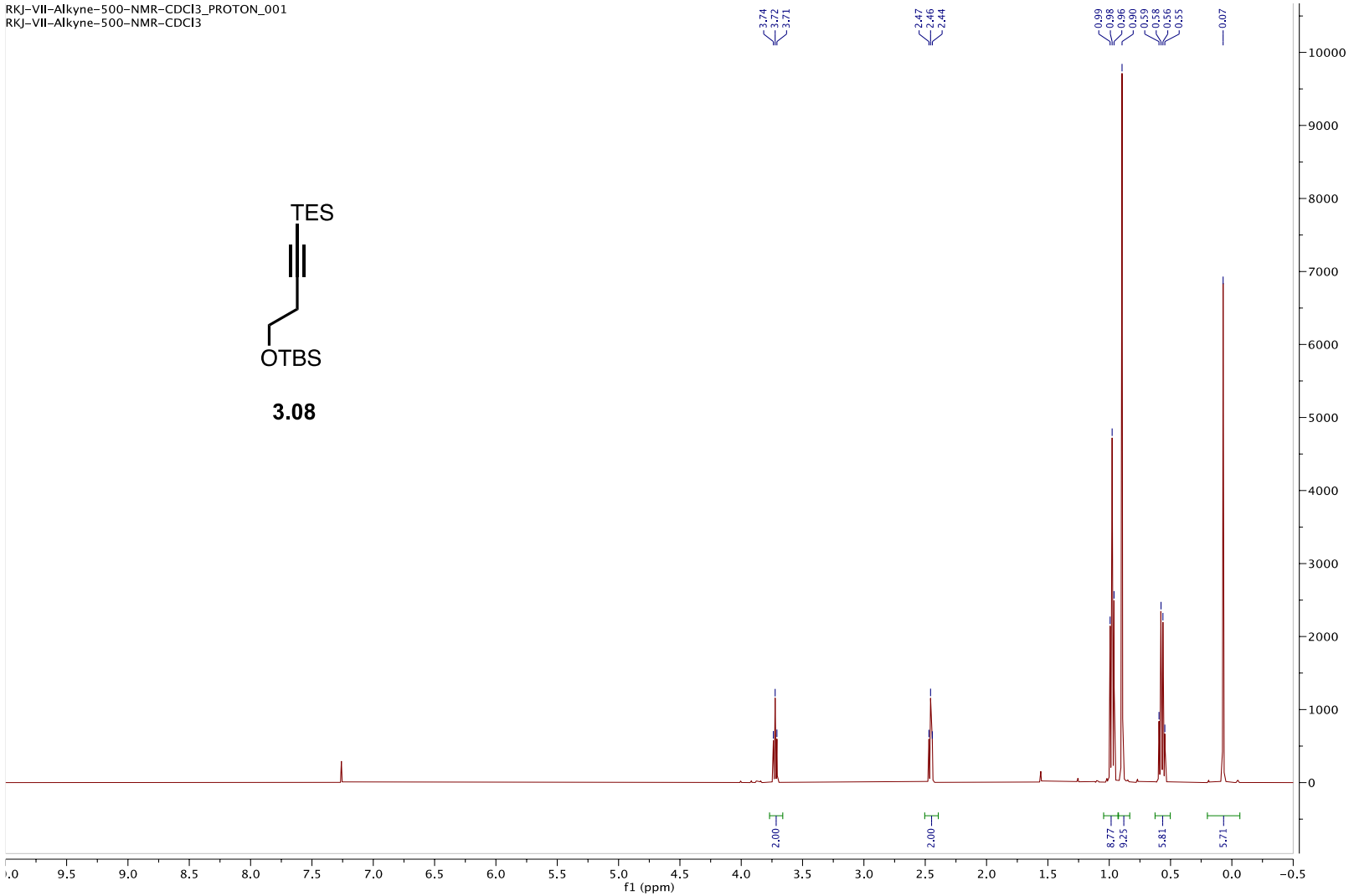


Figure C.01. **^{1}H NMR** (500 MHz, $CDCl_3$) Alkyne **3.08**

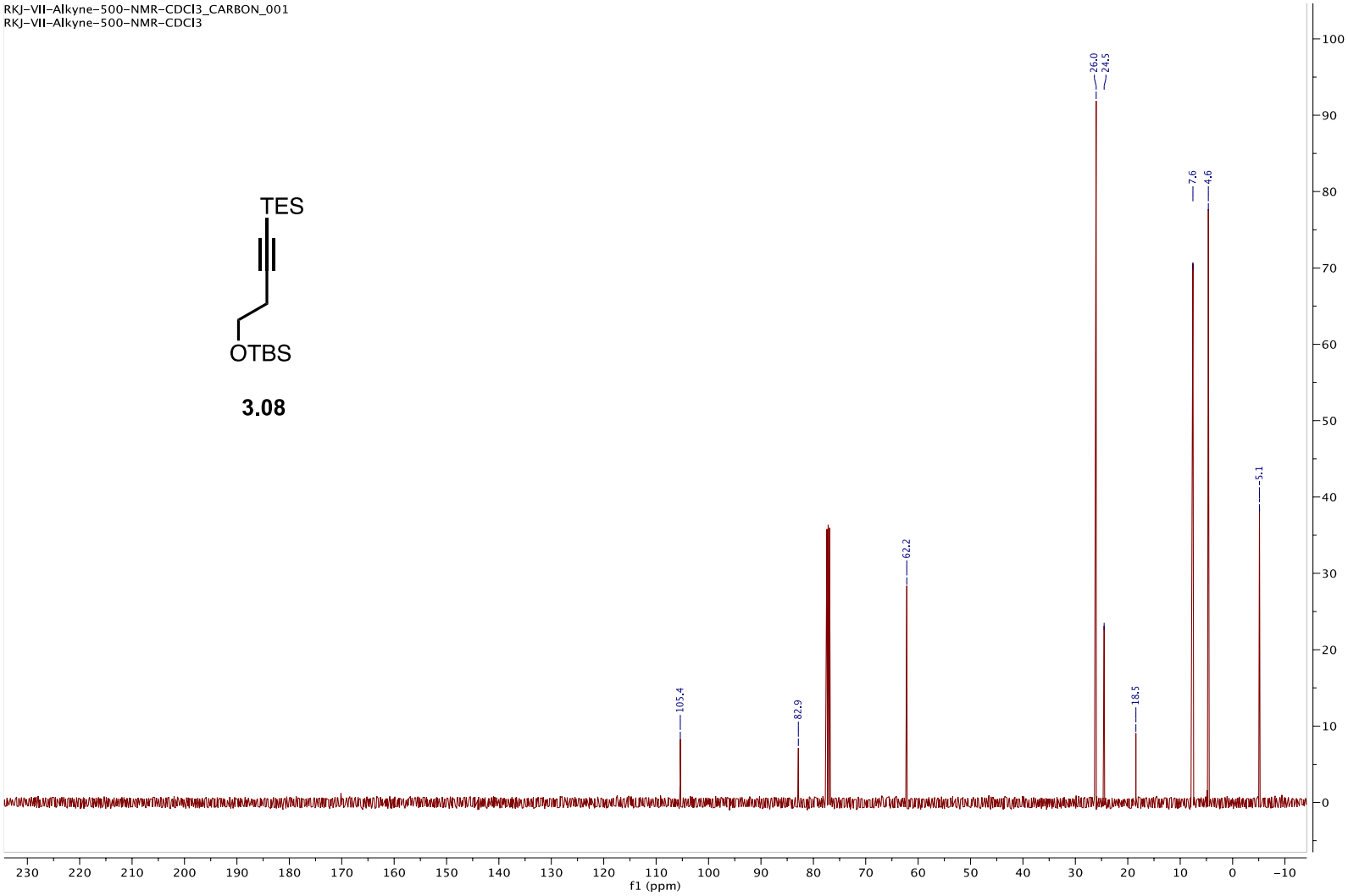


Figure C.02. **^{13}C NMR** (126 MHz, $CDCl_3$) Alkyne **3.08**

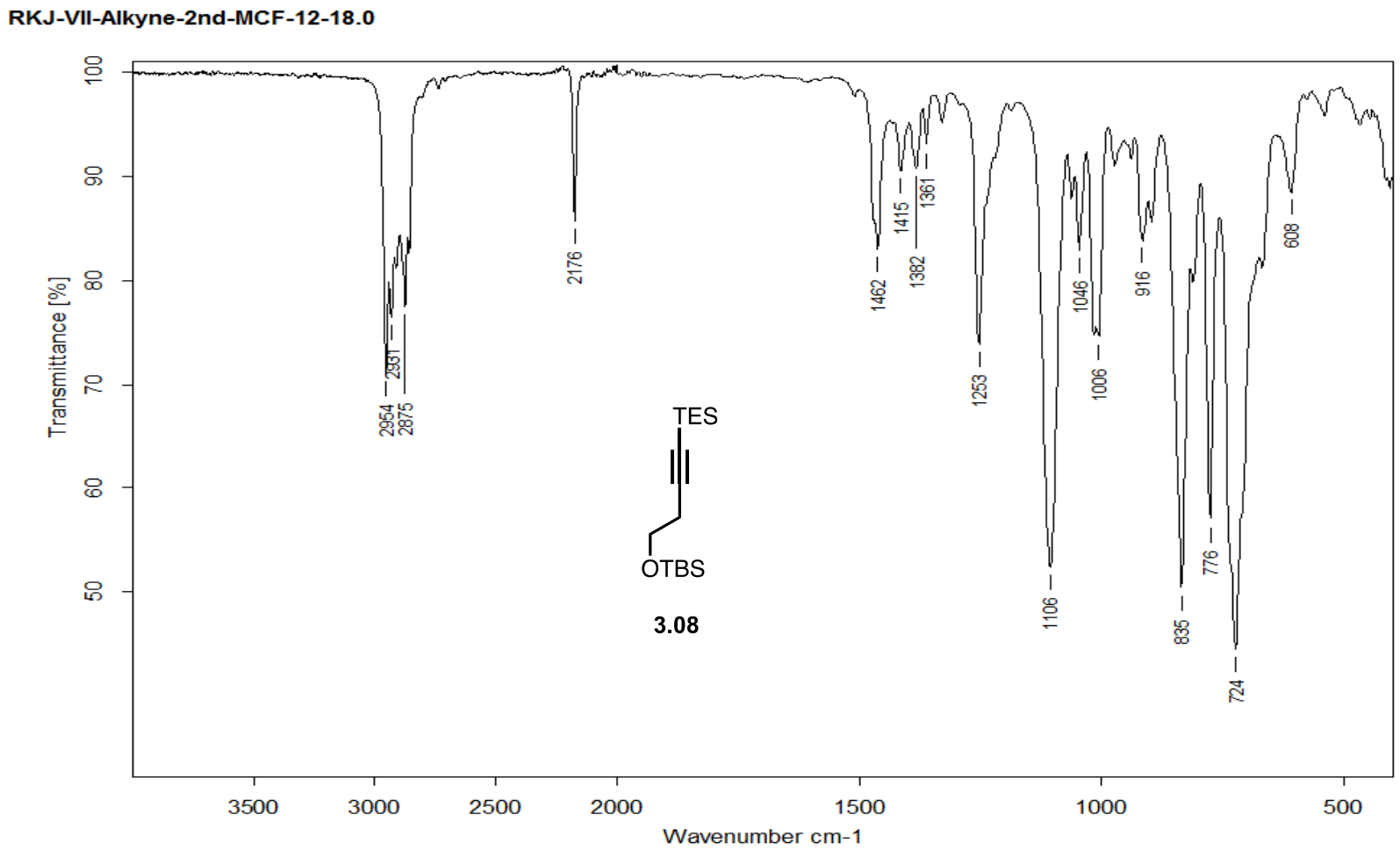


Figure C.03. **FTIR** (thin film) Alkyne **3.08**

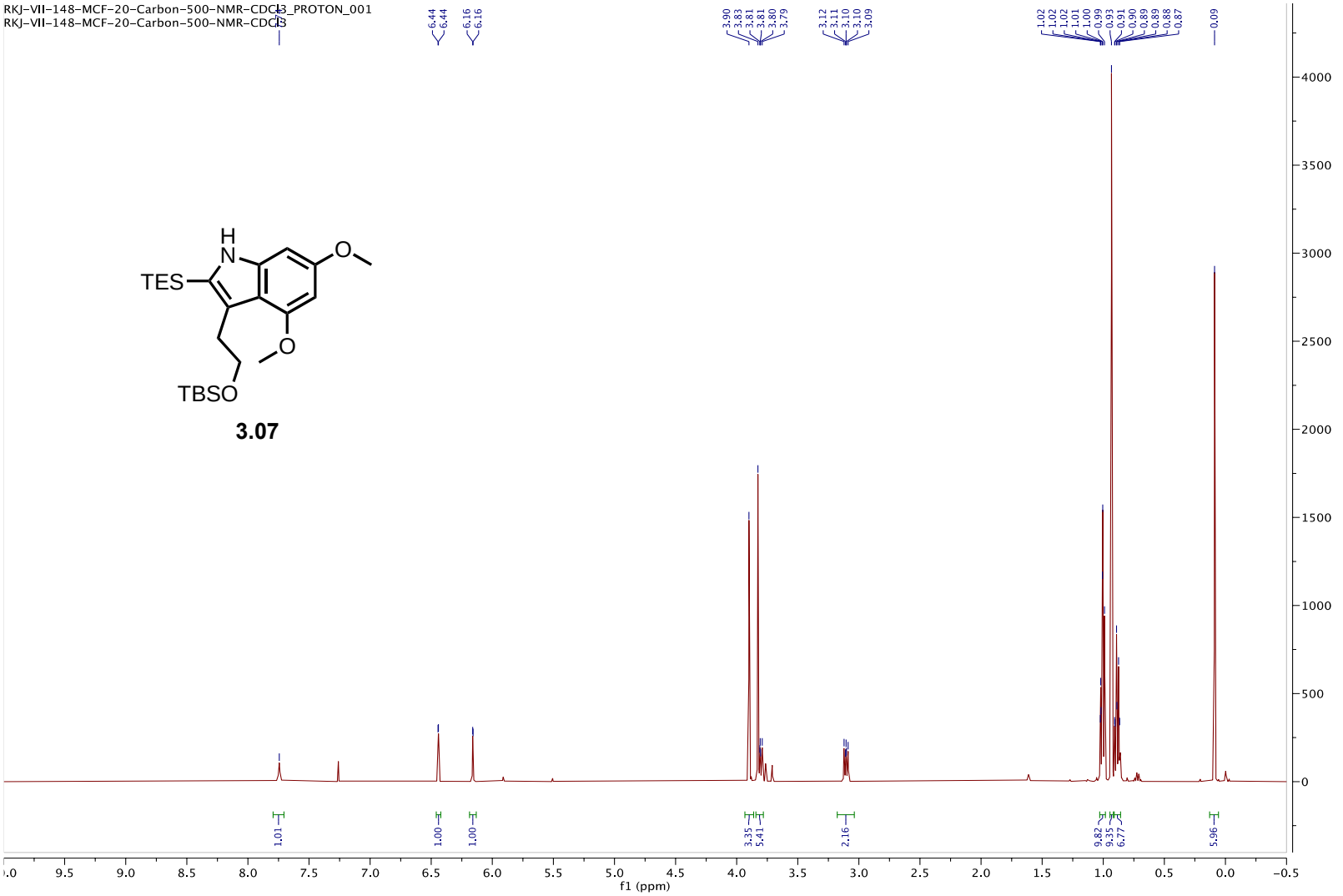


Figure C.04. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.07**

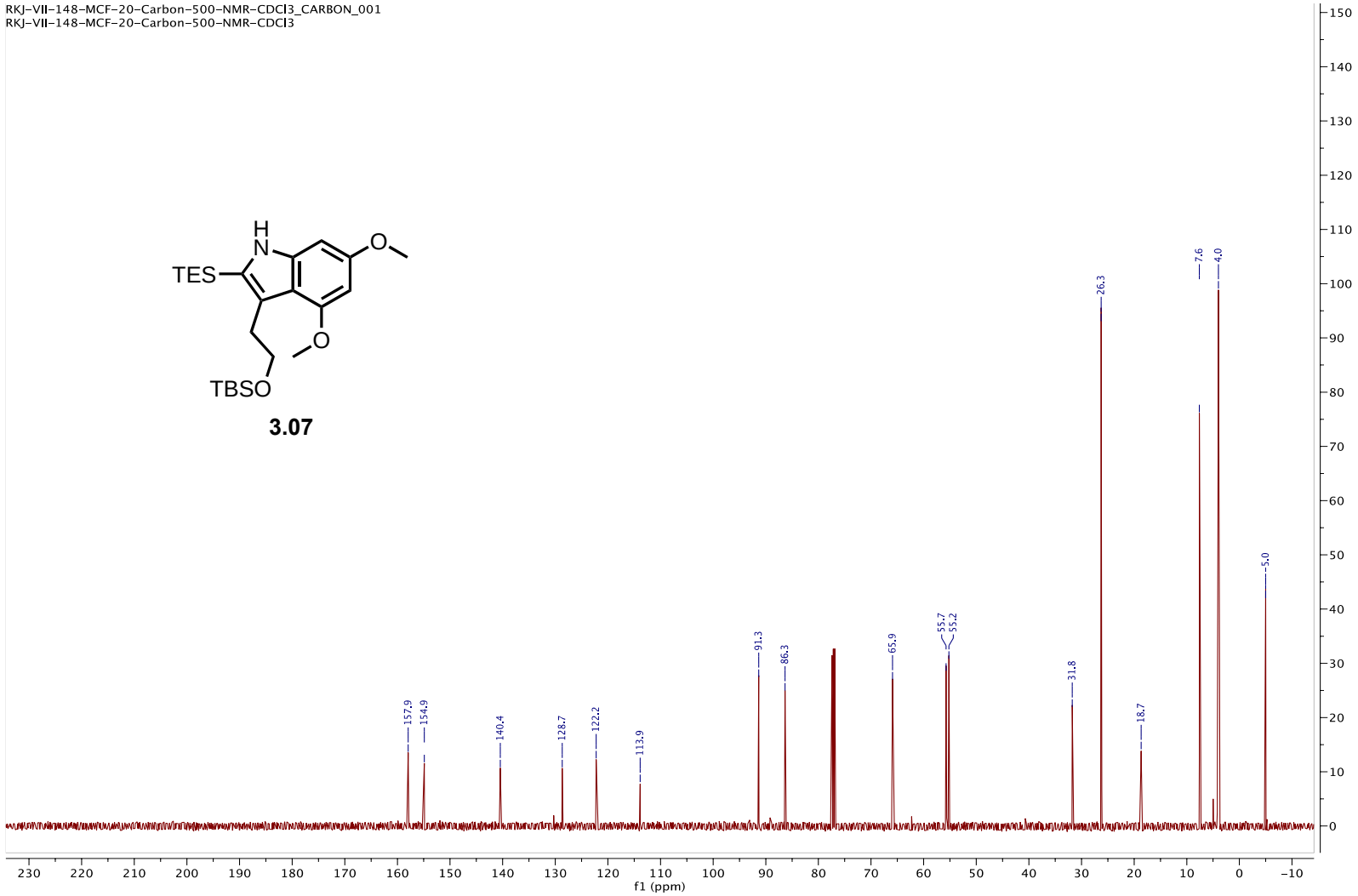


Figure C.05. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.07**

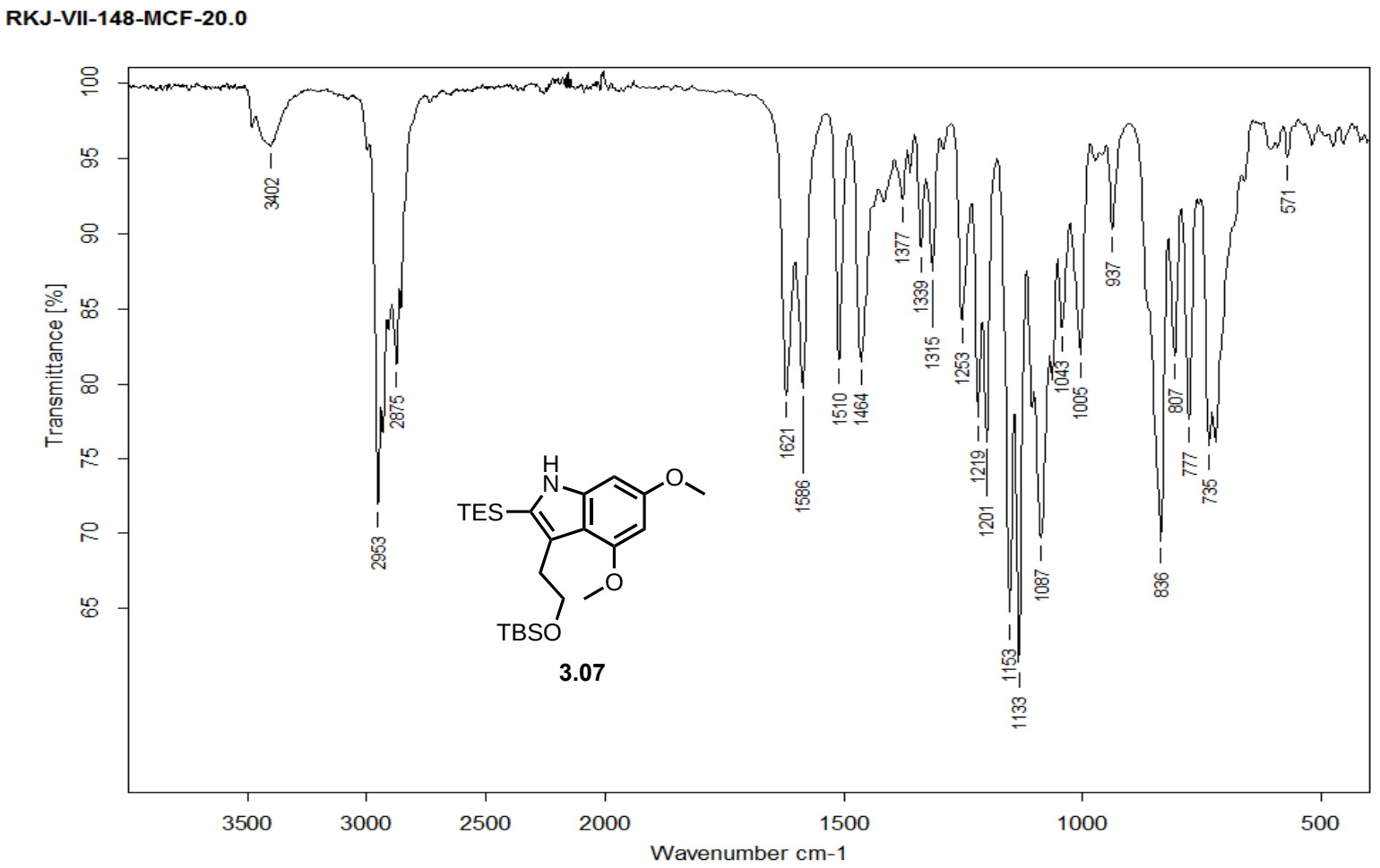


Figure C.06. **FTIR** (thin film) Indole **3.07**

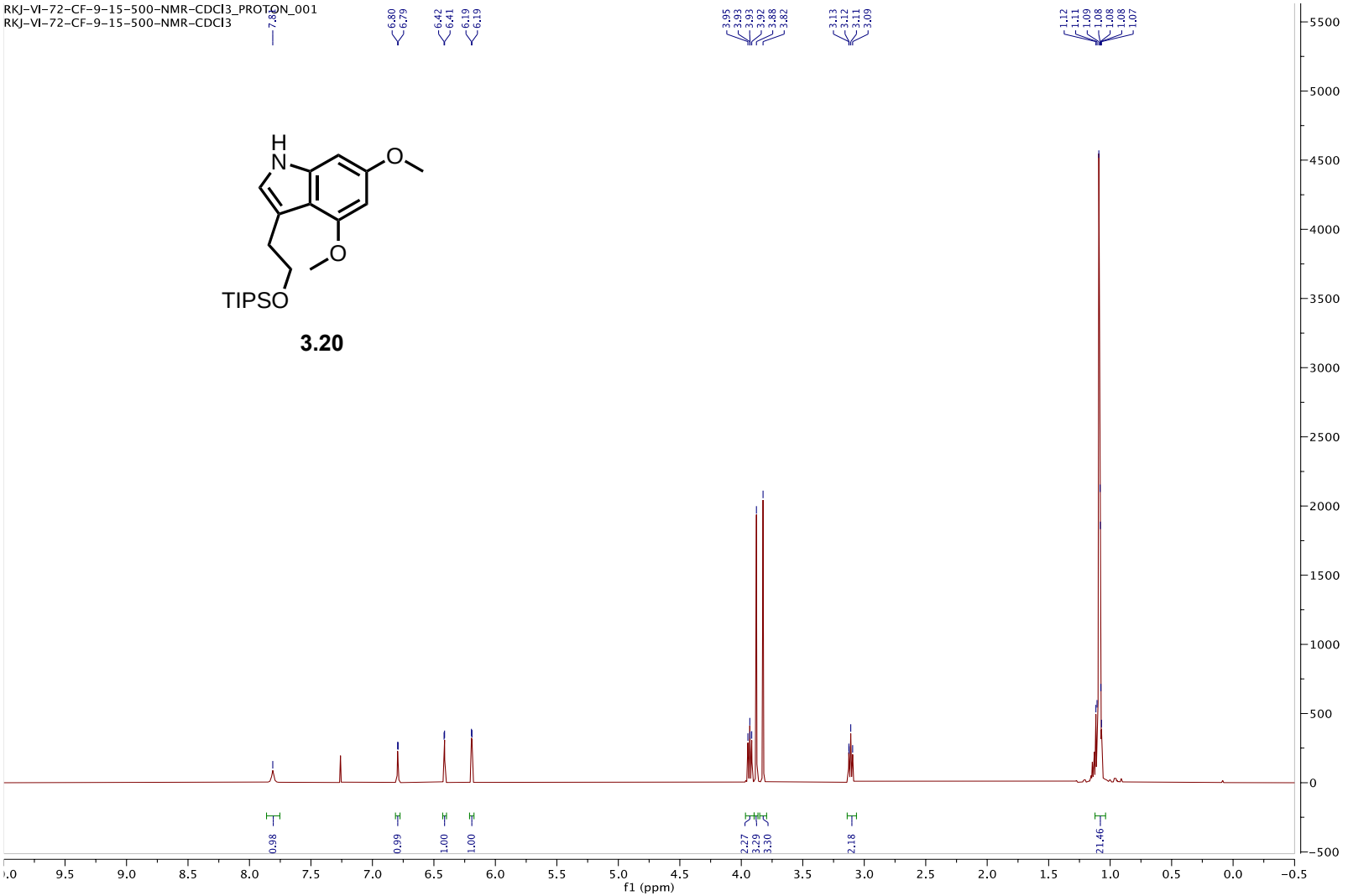


Figure C.07. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.20**

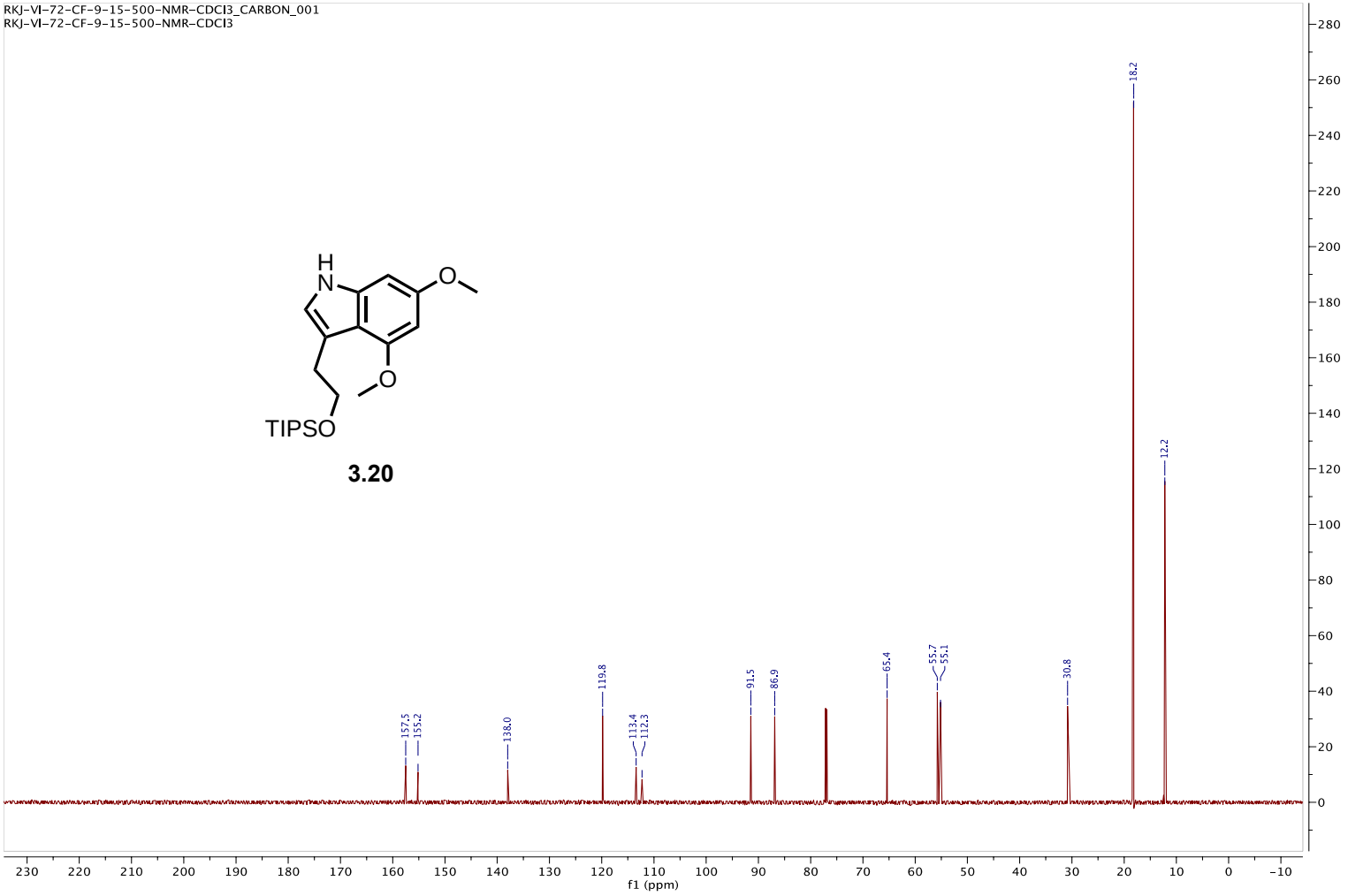


Figure C.08. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.20**

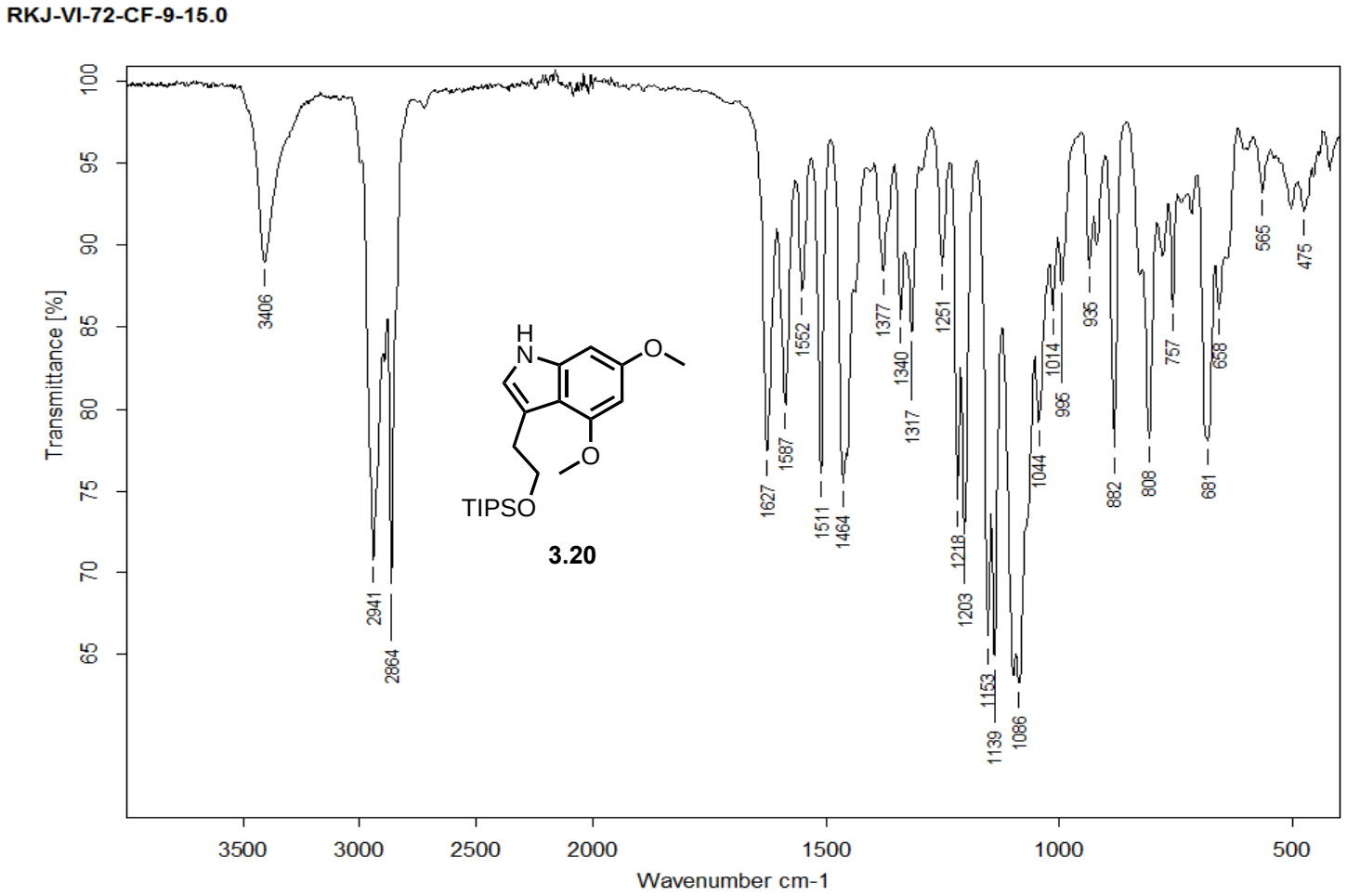


Figure C.09. **FTIR** (thin film) Indole **3.20**

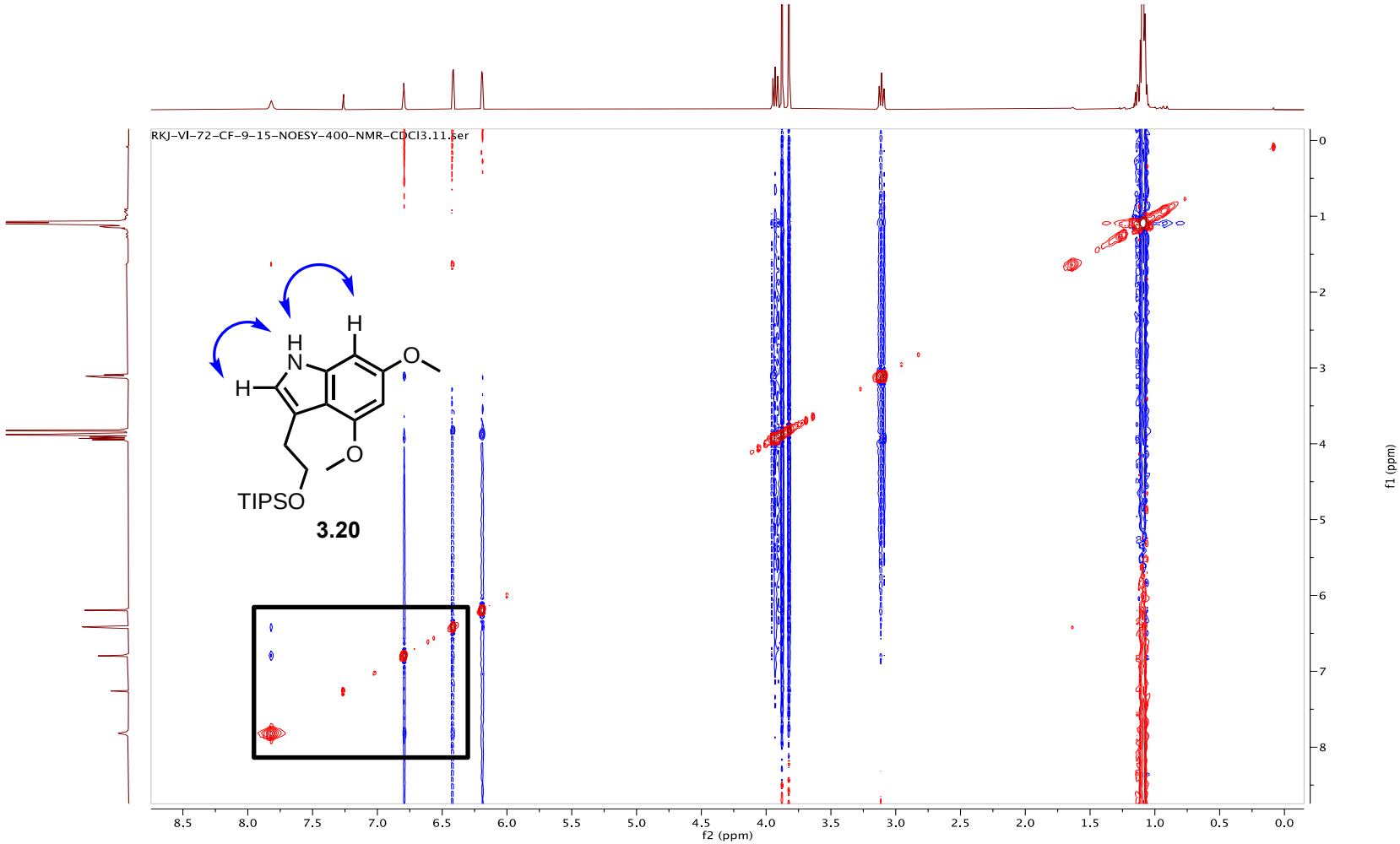


Figure C.10. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Indole **3.20**

Regiochemistry of Larock indole synthesis was established by NOESY correlations between the indole NH (7.81 ppm) and the adjacent aryl methines from the indole (6.80 and 6.42 ppm).

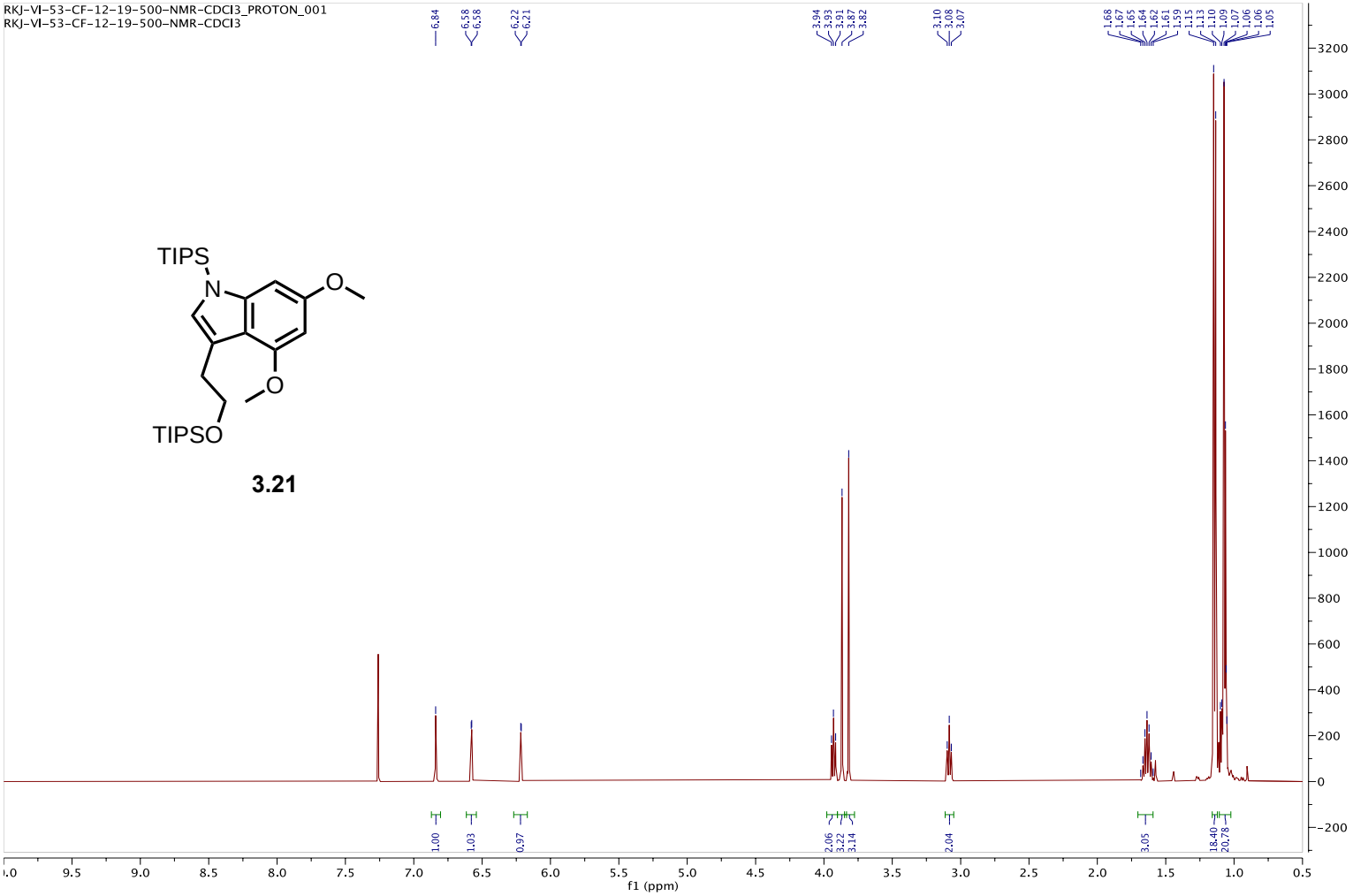


Figure C.11. **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **3.21**

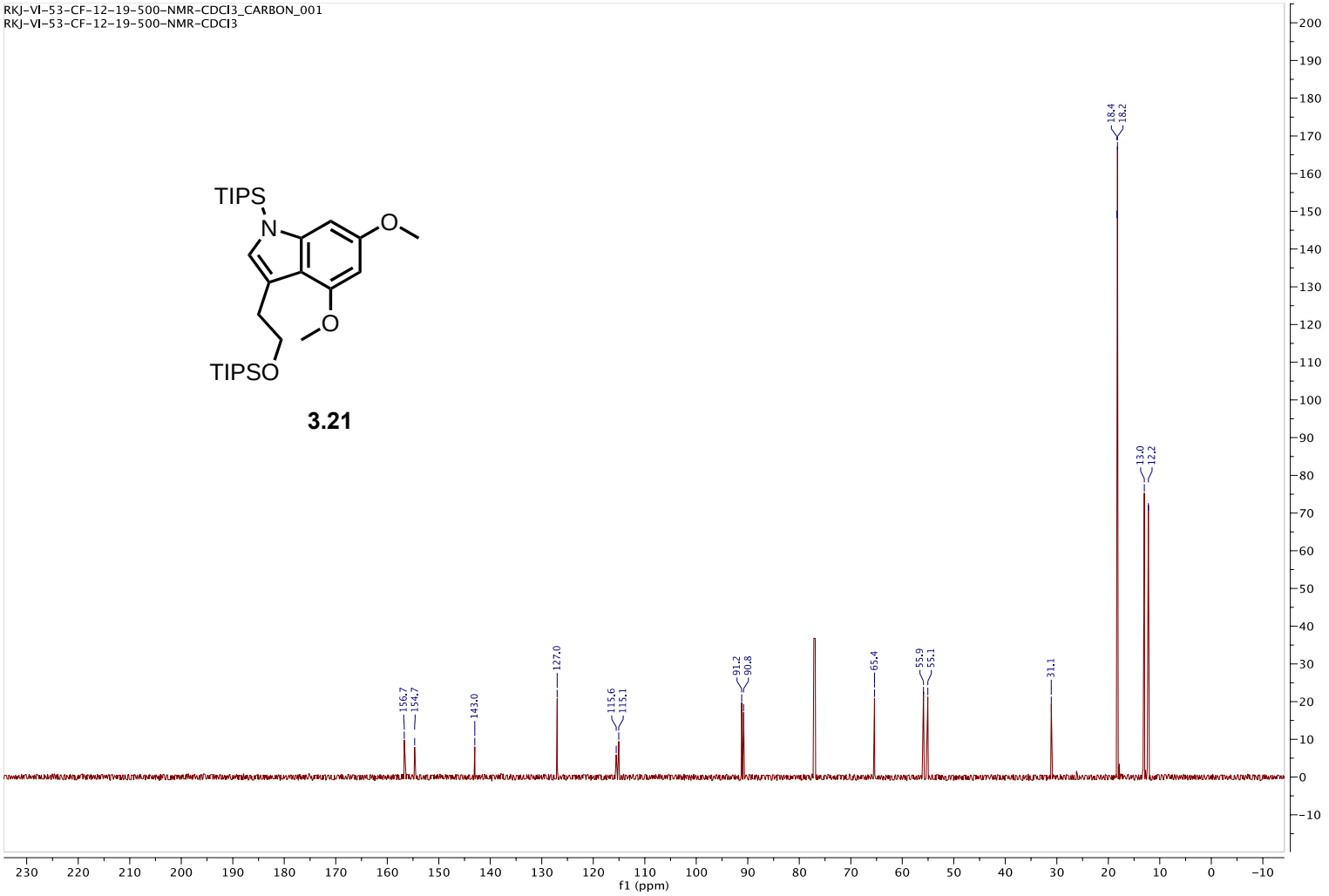


Figure C.12. **^{13}C NMR** (126 MHz, $CDCl_3$) Indole **3.21**

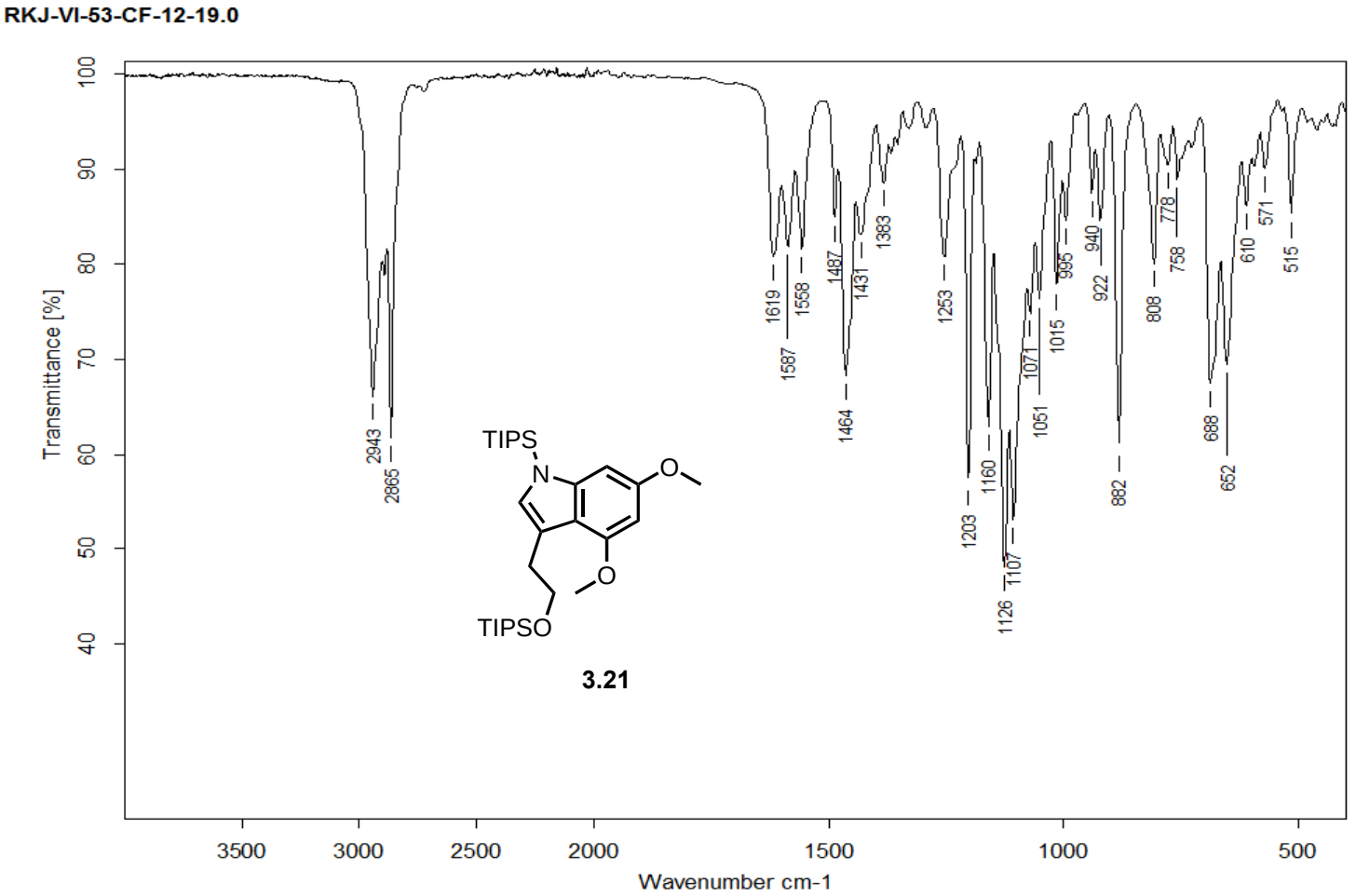


Figure C.13. **FTIR** (thin film) Indole **3.21**

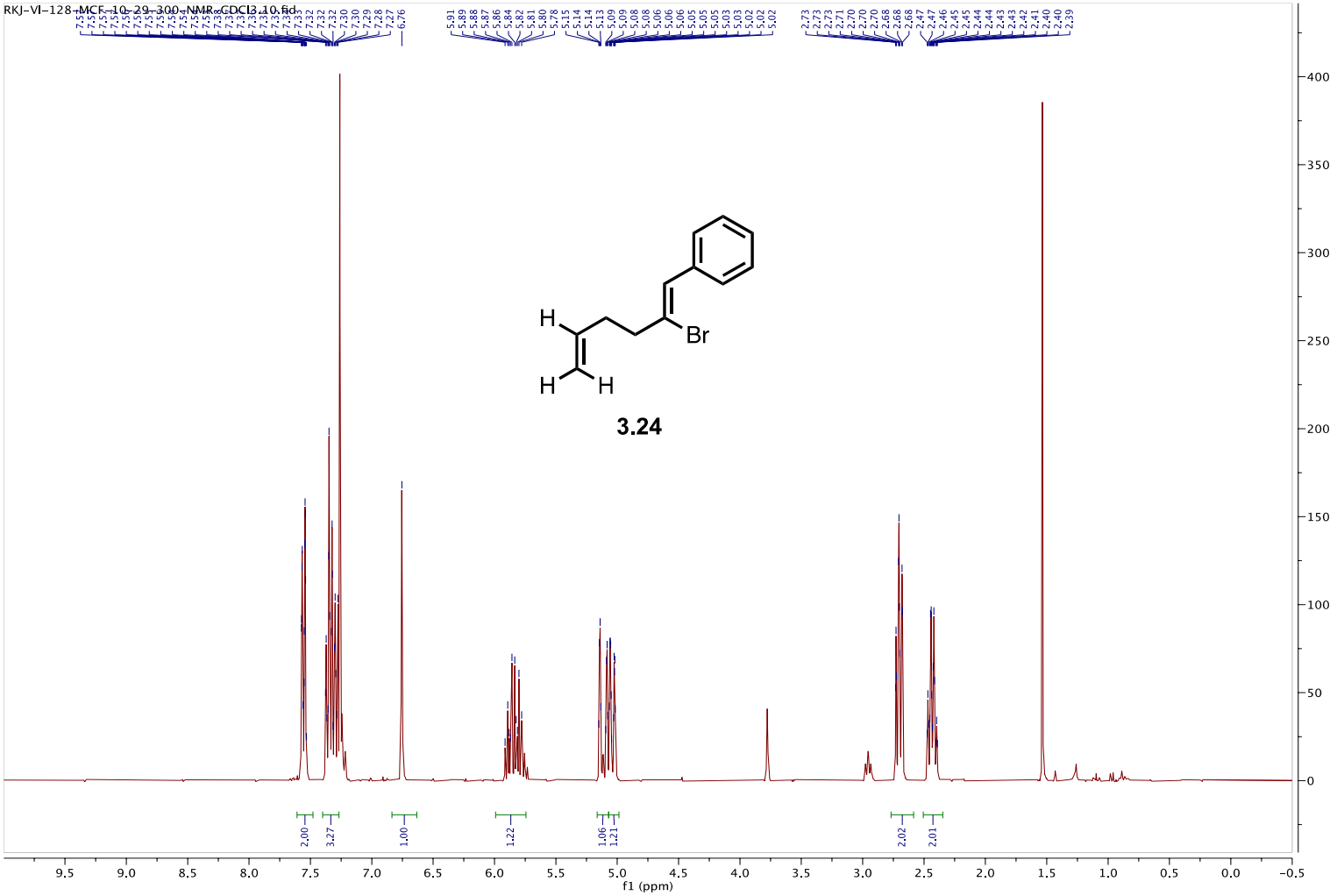


Figure C.14. **^{1}H NMR** (300 MHz, $CDCl_3$) Terminal Olefin **3.24**

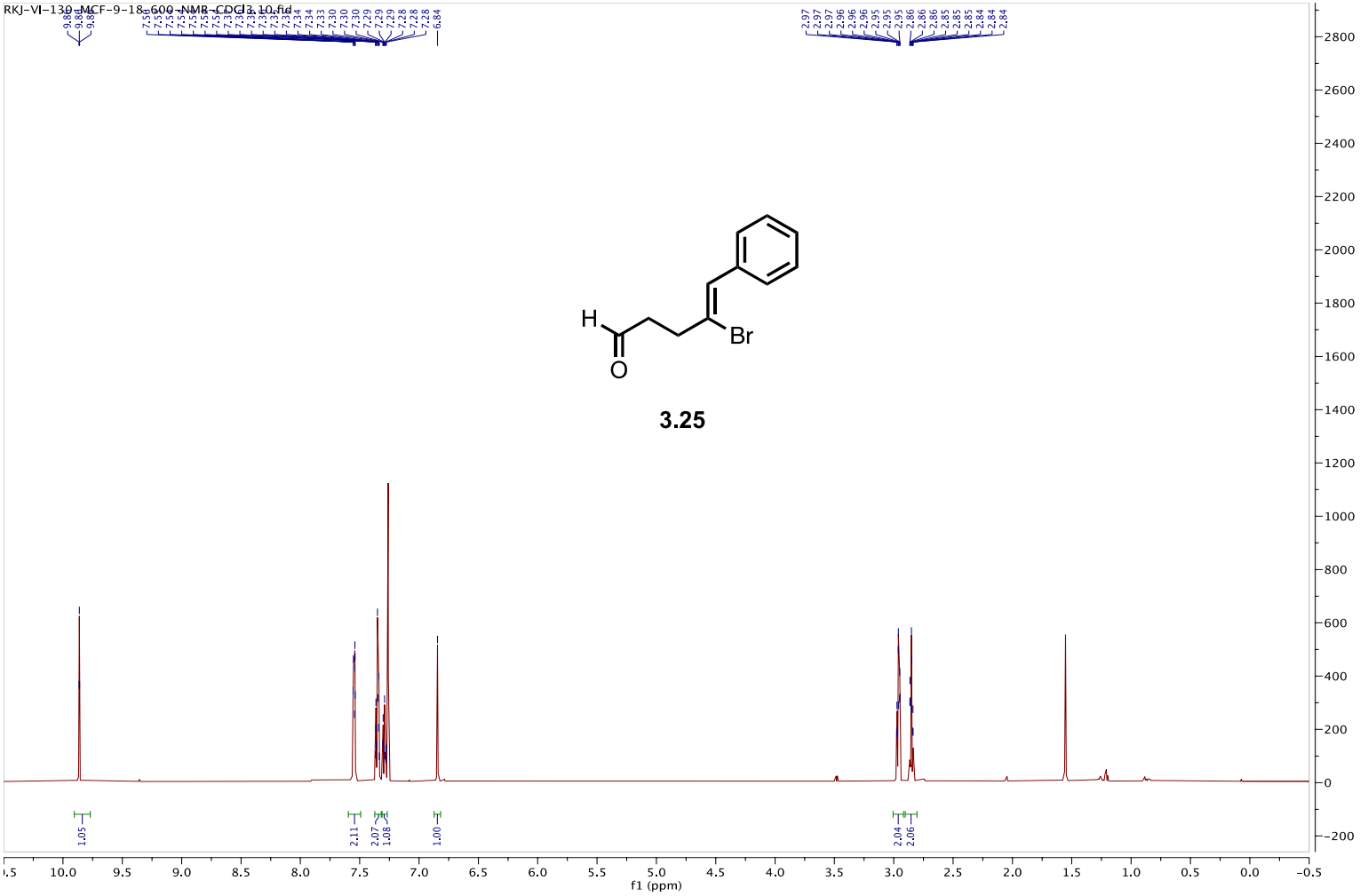


Figure C.15. **^{1}H NMR** (600 MHz, $CDCl_3$) Aldehyde **3.25**

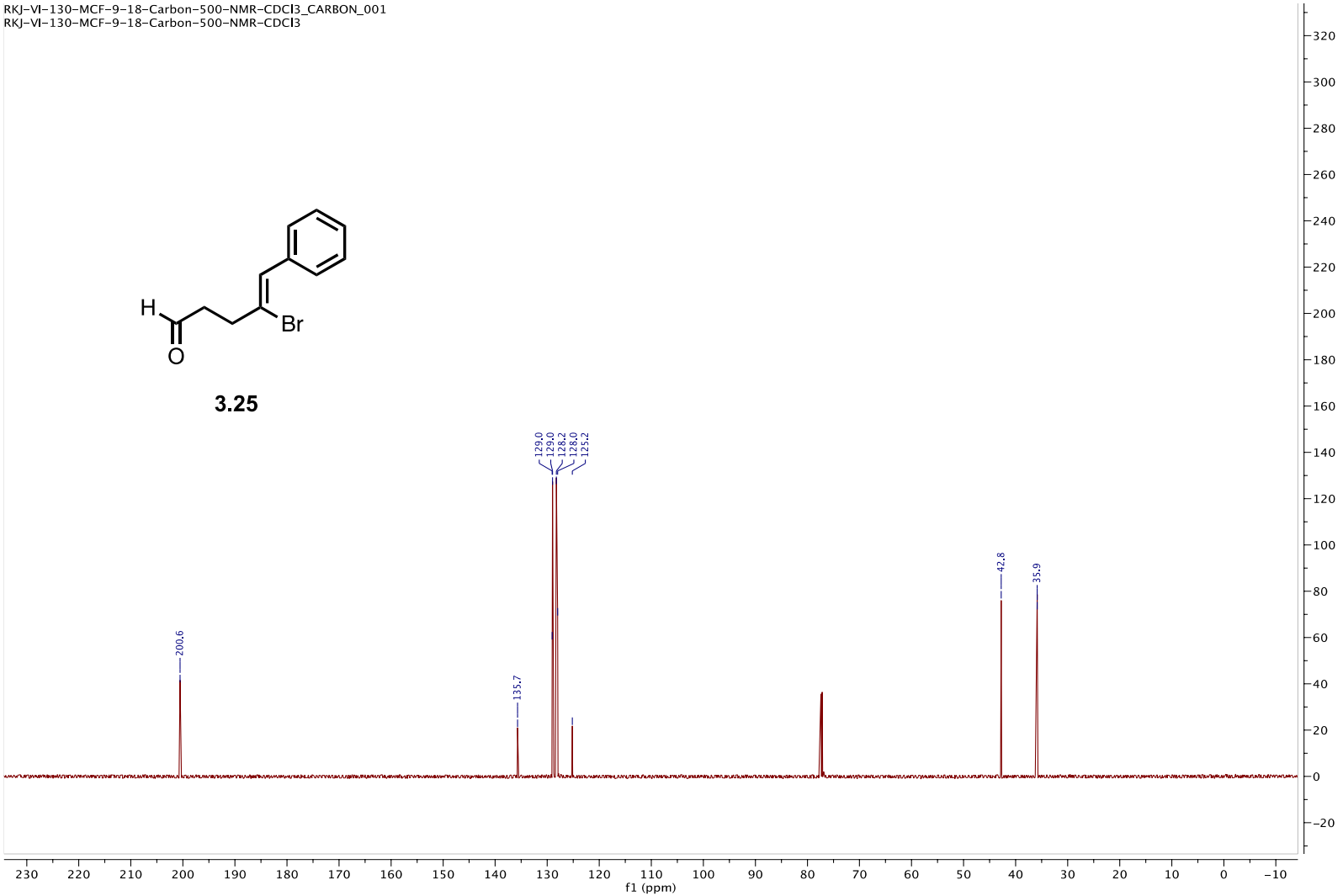


Figure C.16. **^{13}C NMR** (126 MHz, $CDCl_3$) Aldehyde **3.25**

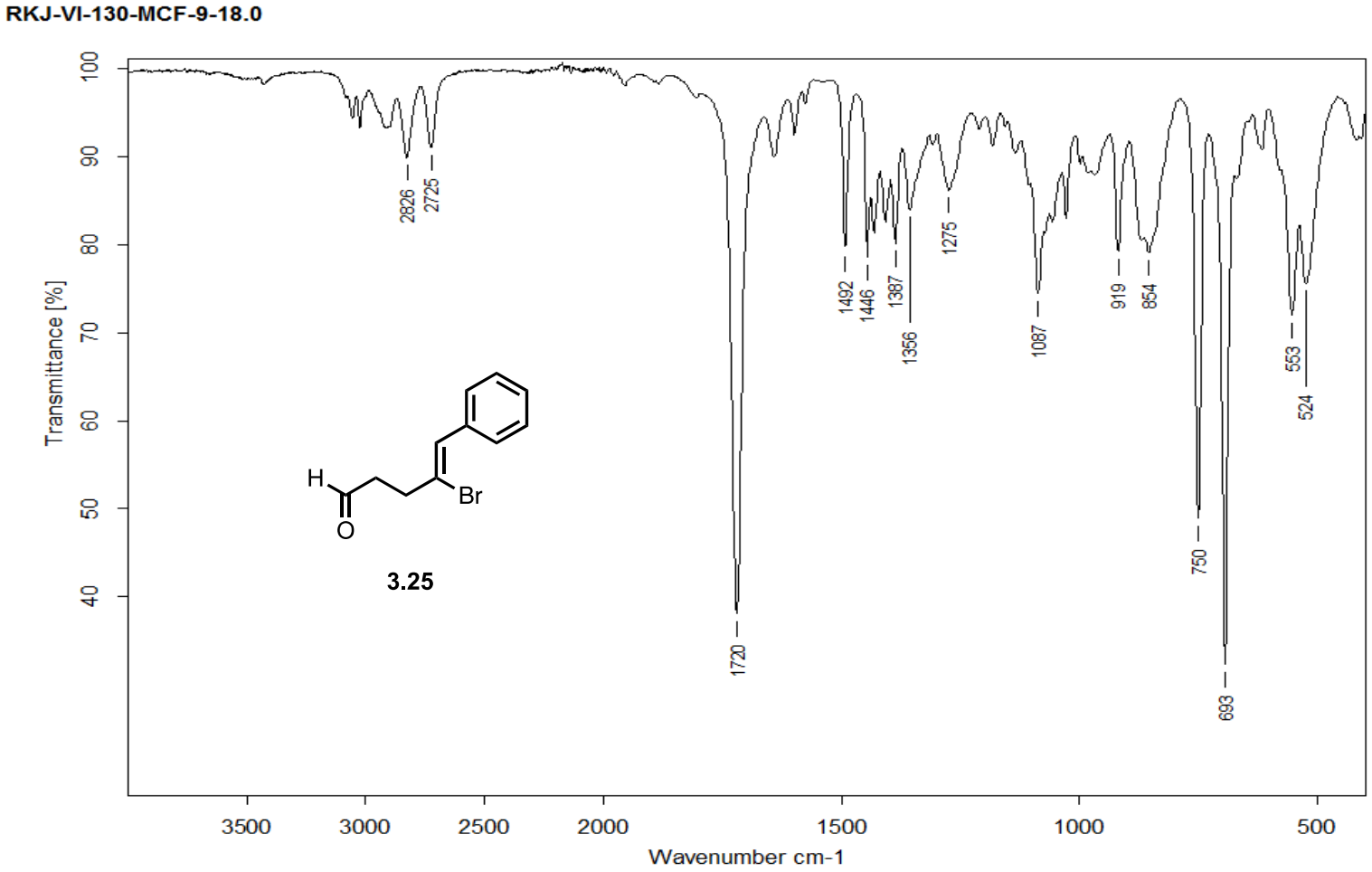


Figure C.17. **FTIR** (thin film) Aldehyde **3.25**

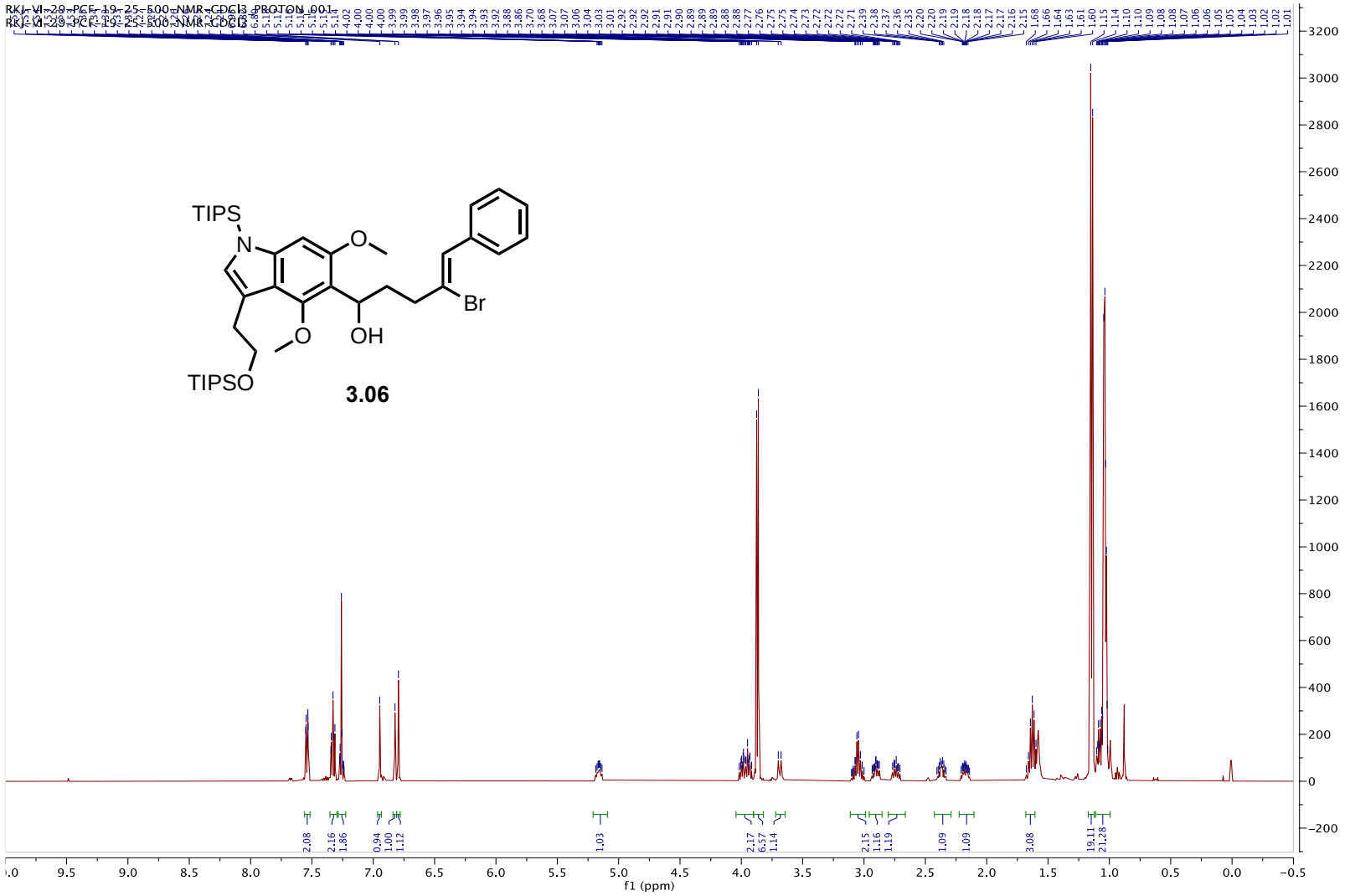


Figure C.18. **^{1}H NMR** (500 MHz, $CDCl_3$) Benzylic Alcohol **3.06**

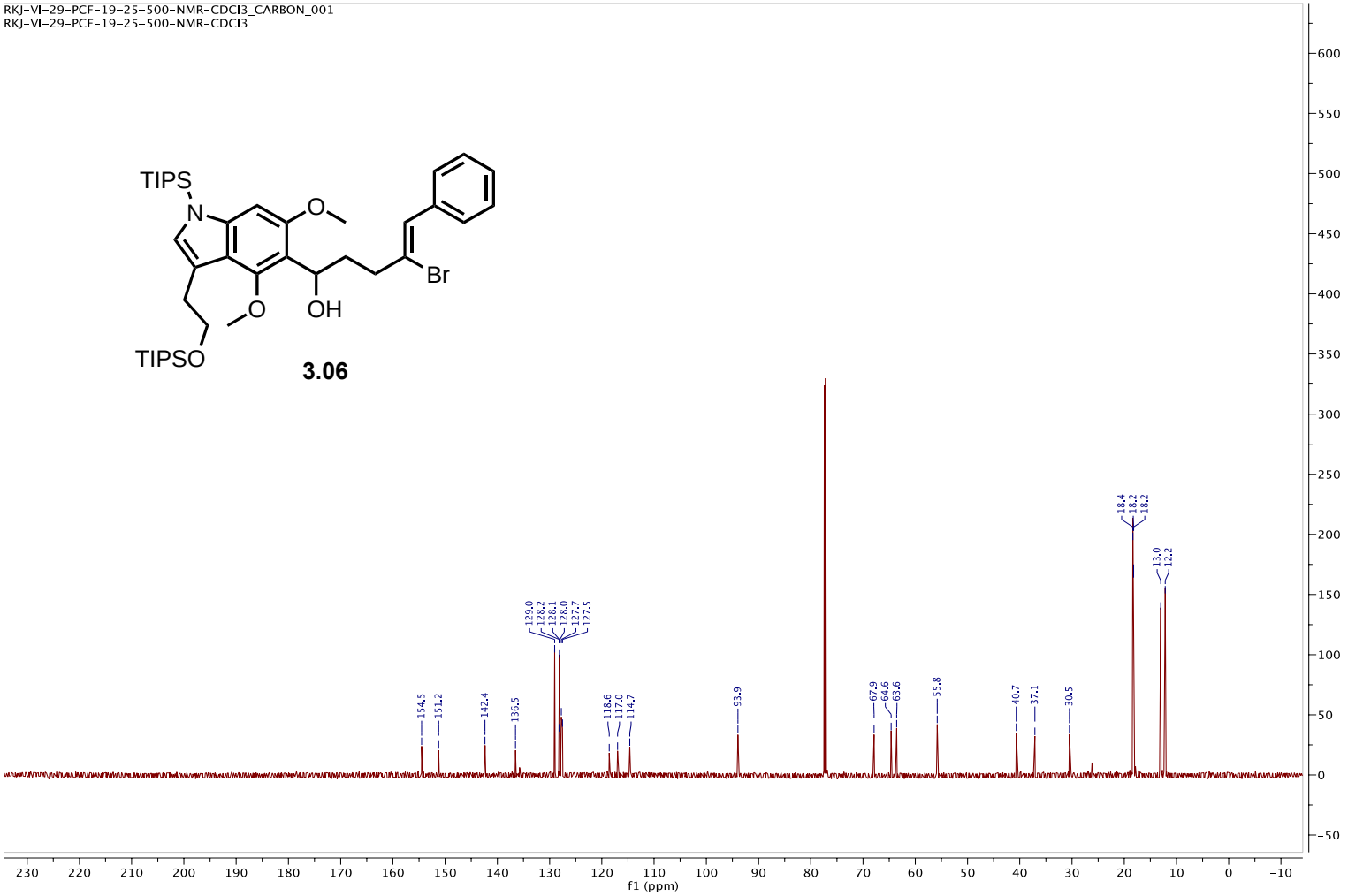


Figure C.19. **^{13}C NMR** (126 MHz, $CDCl_3$) Benzylic Alcohol **3.06**

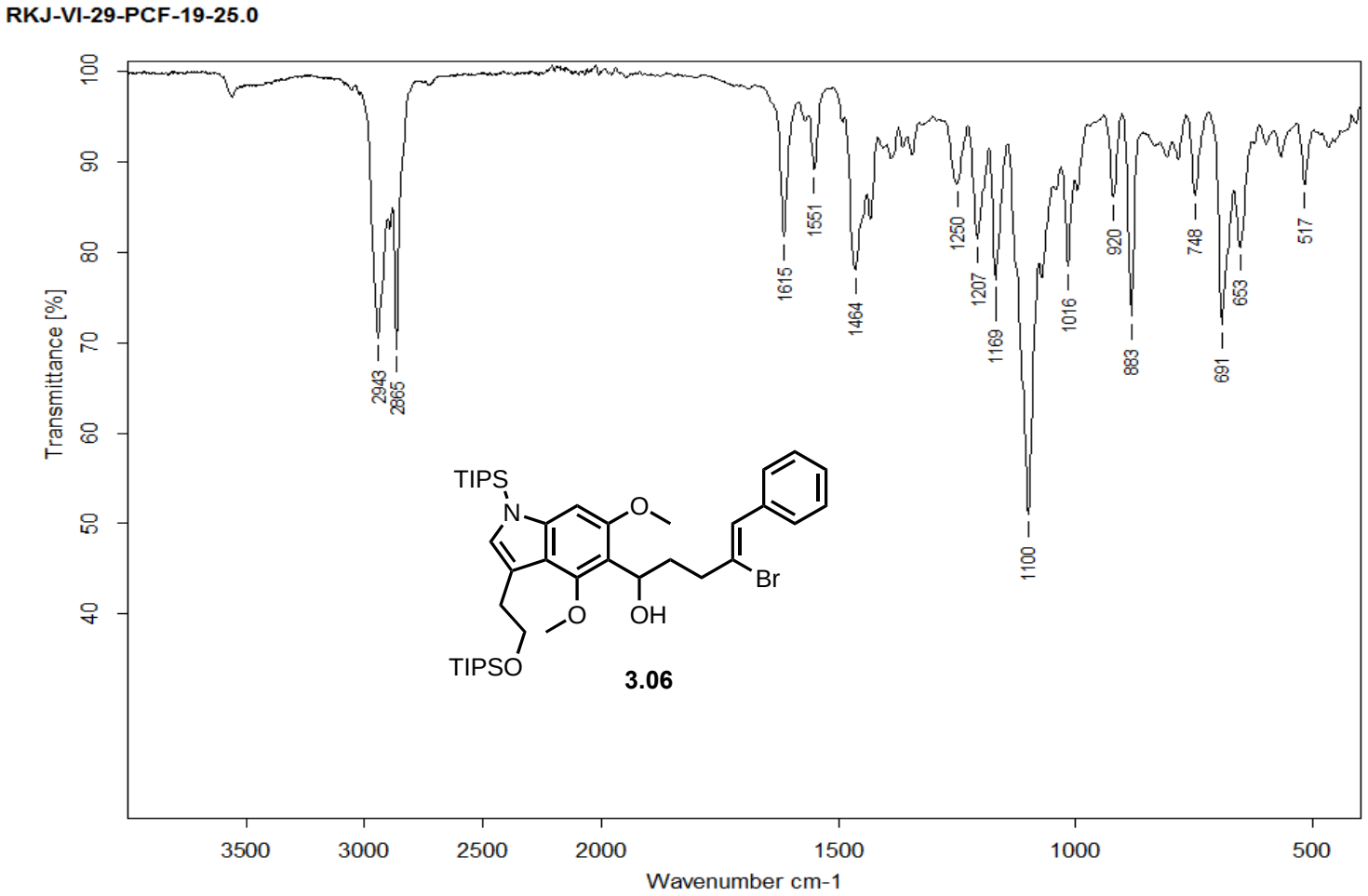


Figure C.20. **FTIR** (thin film) Benzylic Alcohol **3.06**

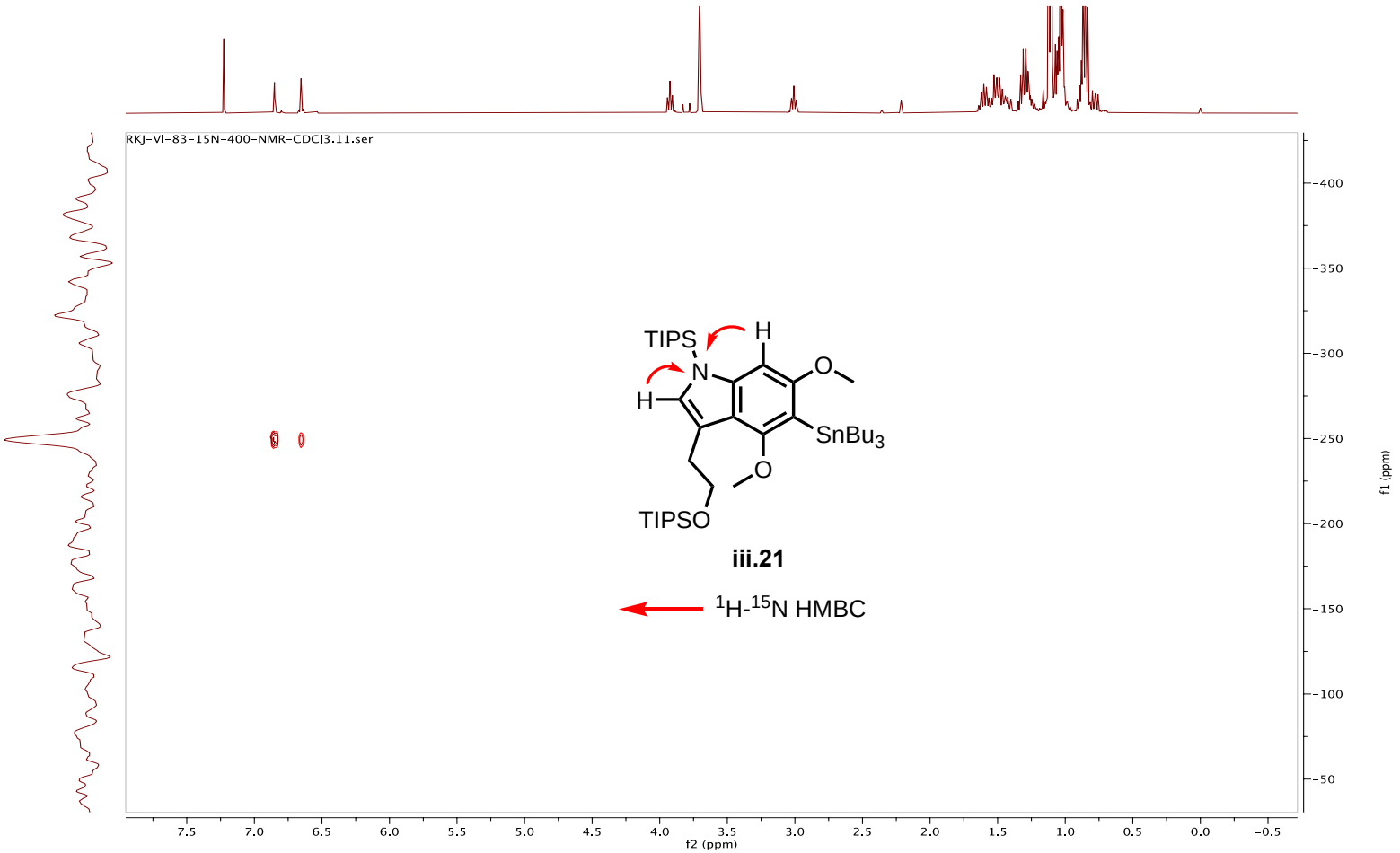


Figure C.21. **^{1}H-^{15}N HMBC** (400, 41 MHz, $CDCl_3$) Stannane **iii.21**

The site of the lithiation was confirmed by ^{1}H-^{15}N HMBC of stannane **iii.21** which was prepared as part of a parallel study but never fully delineated. There are only two aryl methines both of which have a correlation to the same nitrogen.

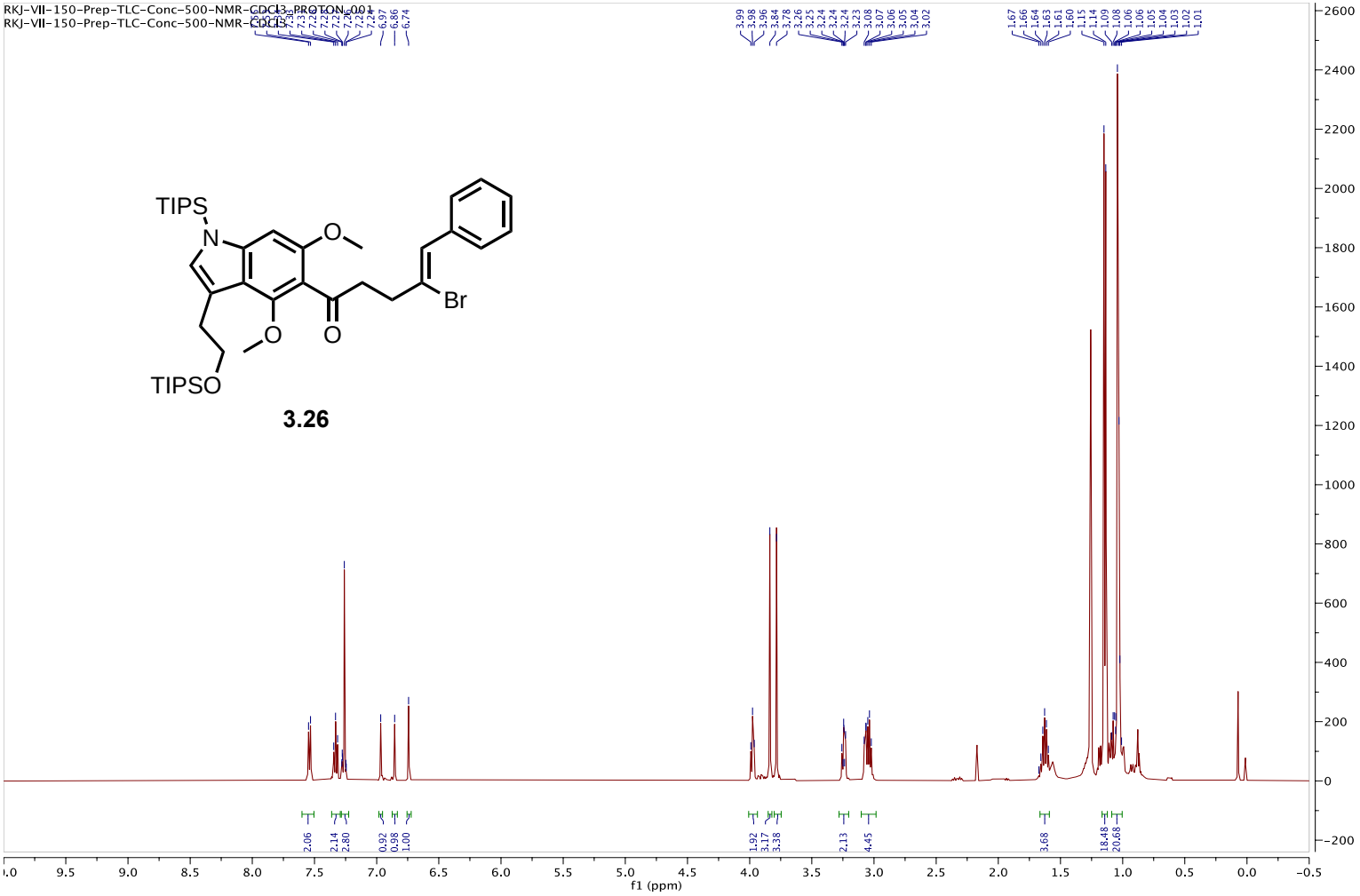


Figure C.22. **^{1}H NMR** (500 MHz, $CDCl_3$) Ketone **3.26**

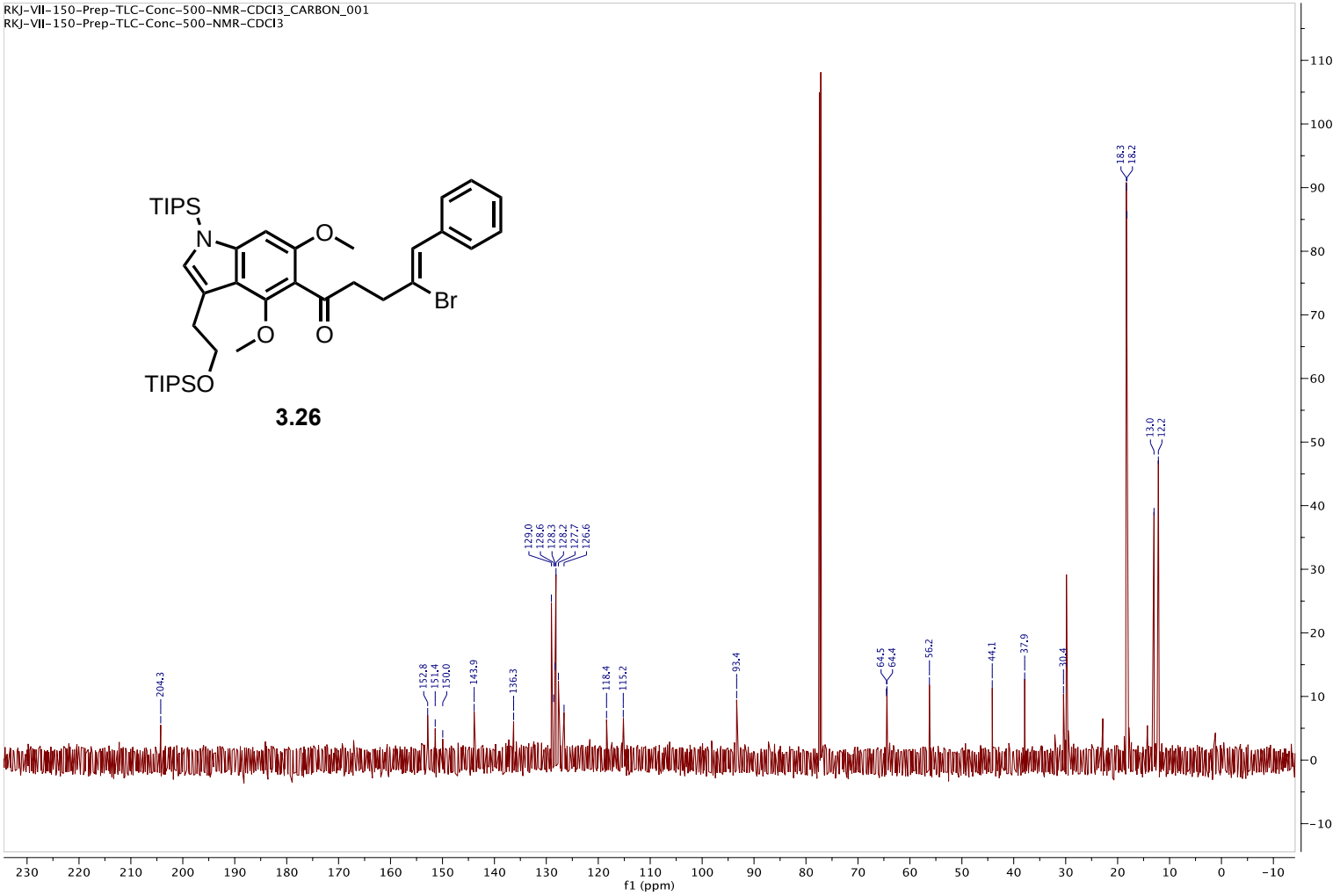


Figure C.23. **^{13}C NMR** (126 MHz, $CDCl_3$) Ketone **3.26**

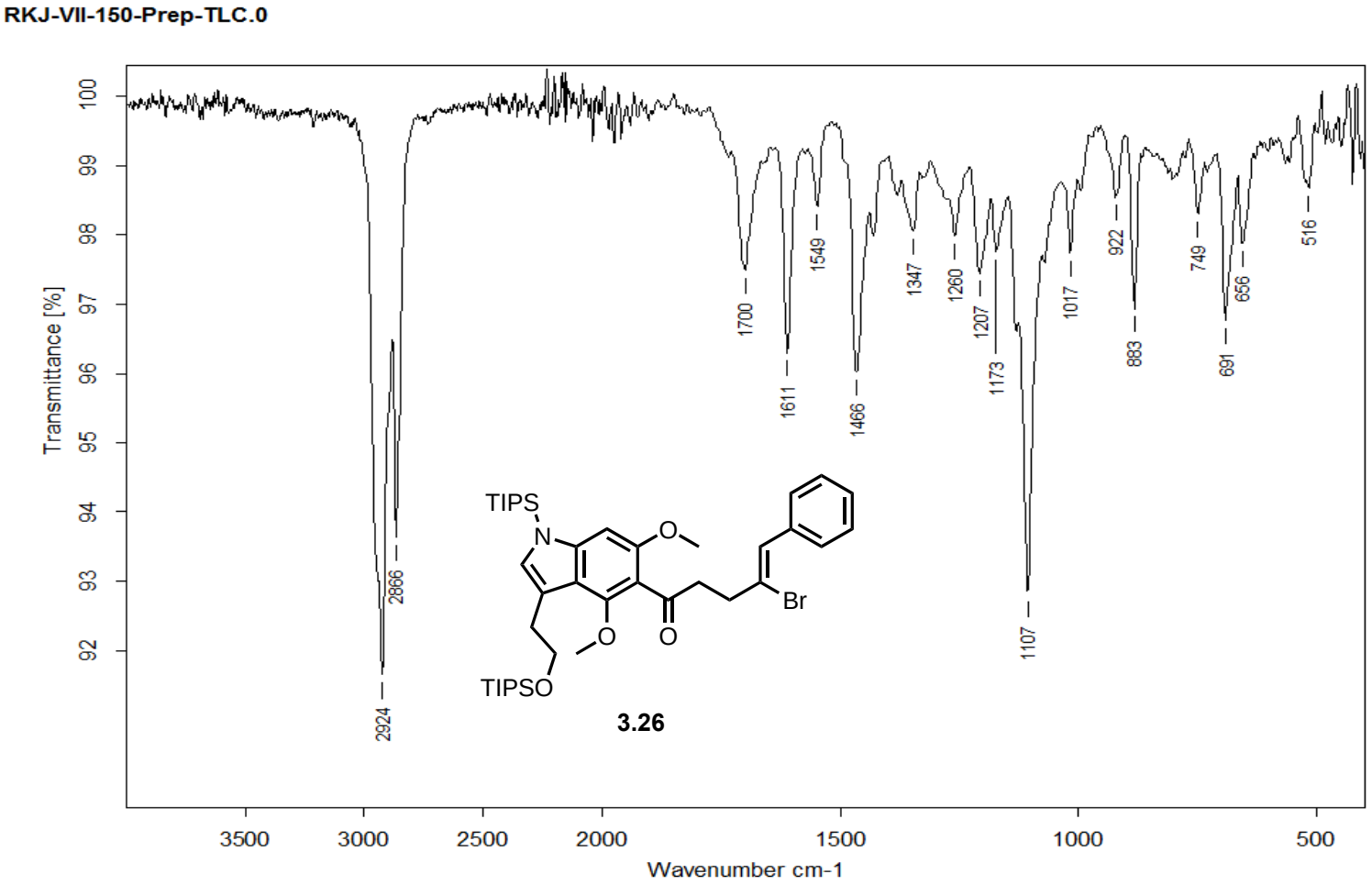


Figure C.24. **FTIR** (thin film) Ketone **3.26**

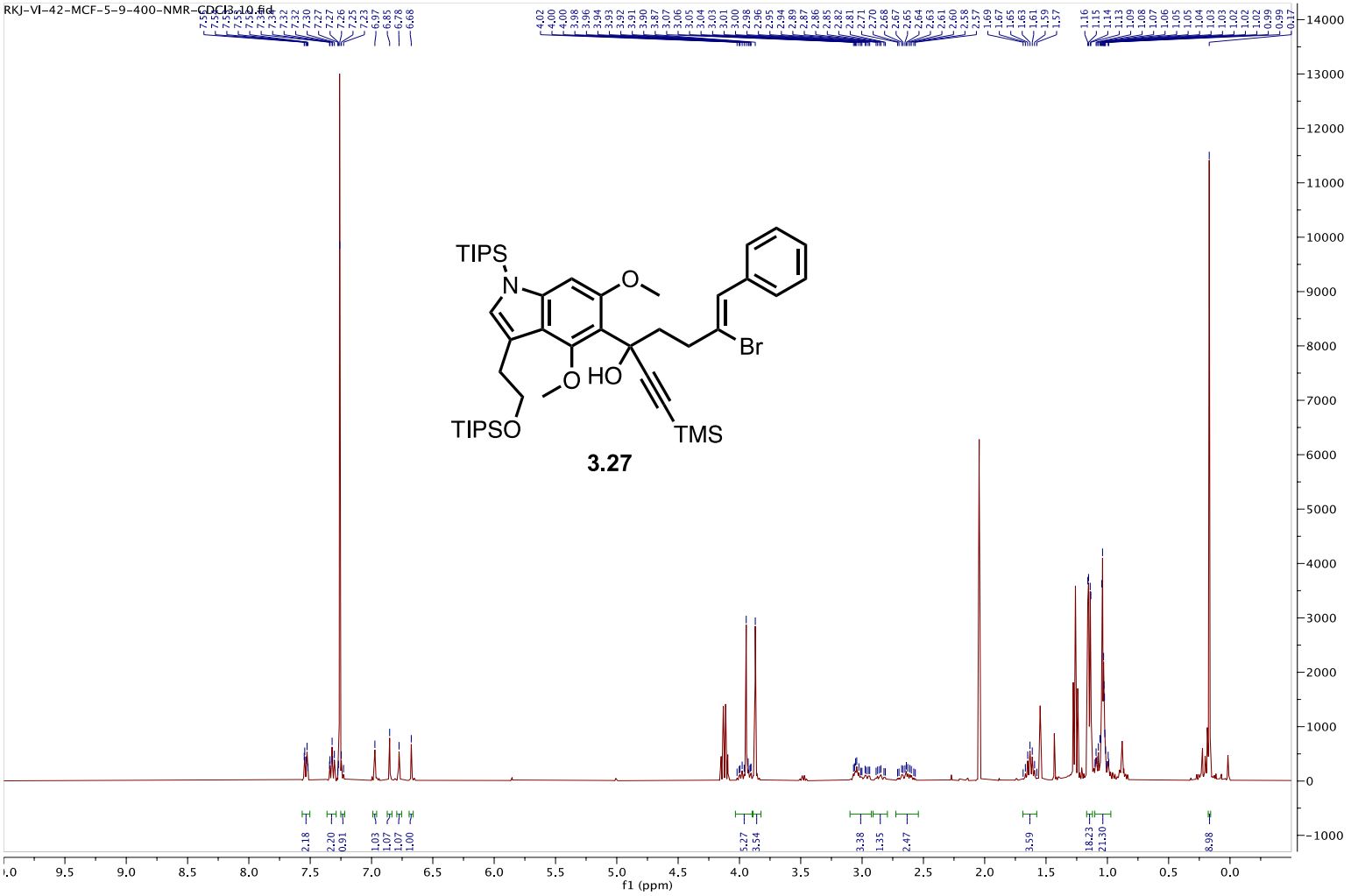


Figure C.25. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **3.26**

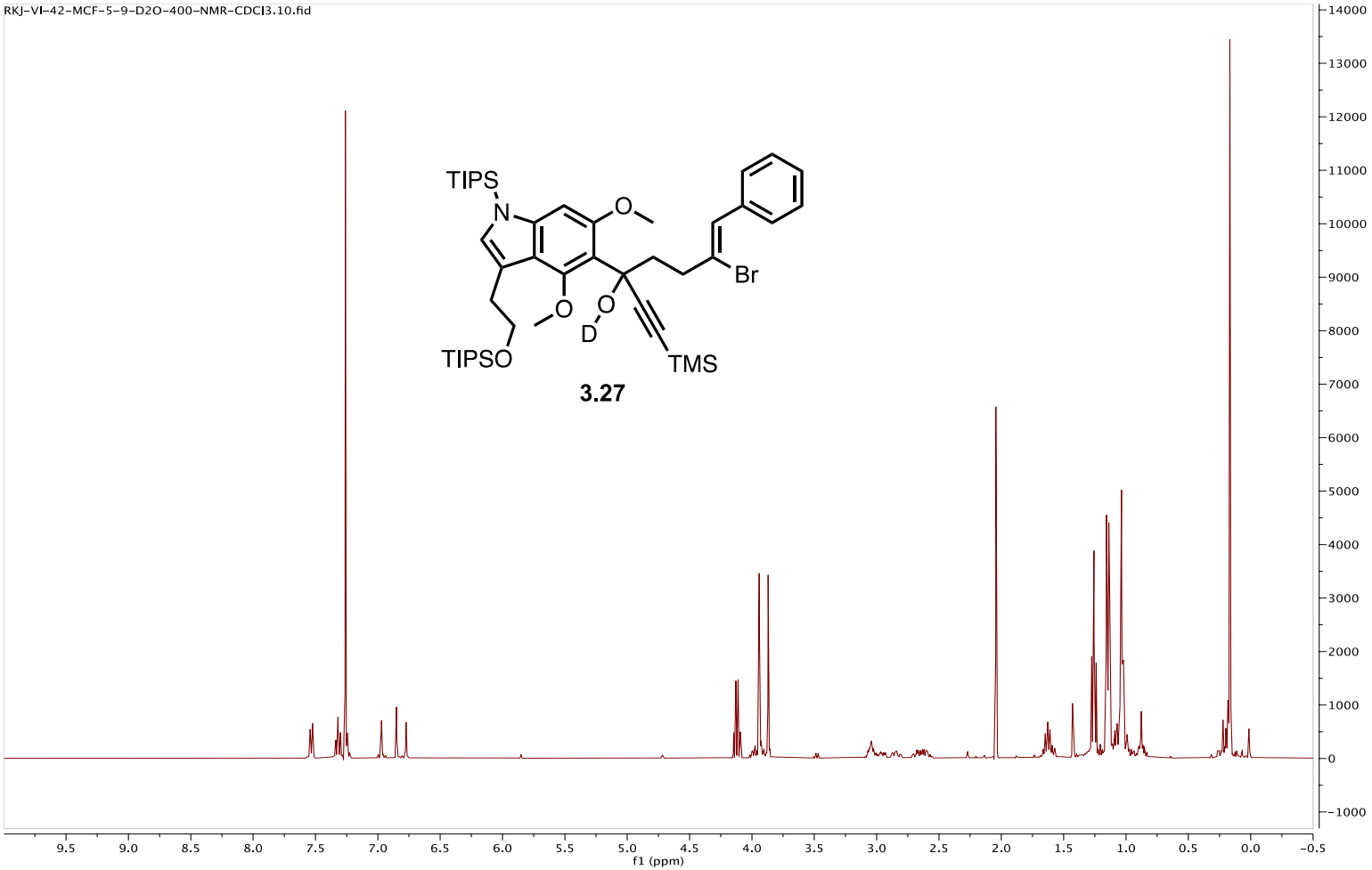


Figure C.26. **^{1}H NMR** (400 MHz, $CDCl_3$) Deuterium Incorporation Experiment with Tertiary Alcohol **3.26**
Disappearance of singlet at 6.68 ppm (*Cf.* previous page) illustrates which singlet between 6.5 and 7.0 ppm corresponds to 3° alcohol.

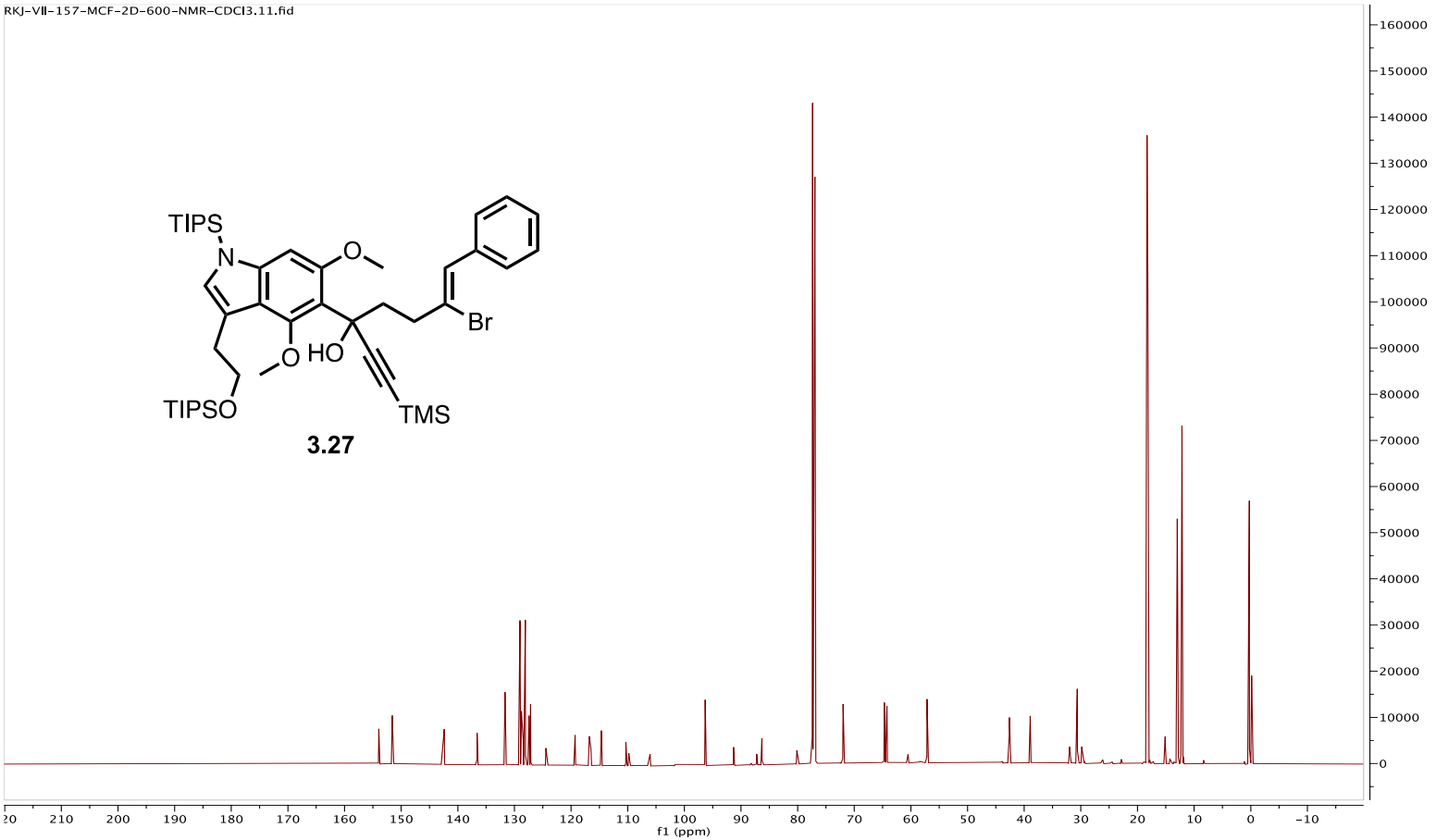


Figure C.27. **^{13}C NMR** (151 MHz, $CDCl_3$) Tertiary Alcohol **3.27**

Unambiguous assignment could not be made of all the carbons in this sample. An unmarked spectrum is attached to aid in comparison should this compound be made again. Furthermore, no ketone quaternary carbon is present which is significant for the next reaction.

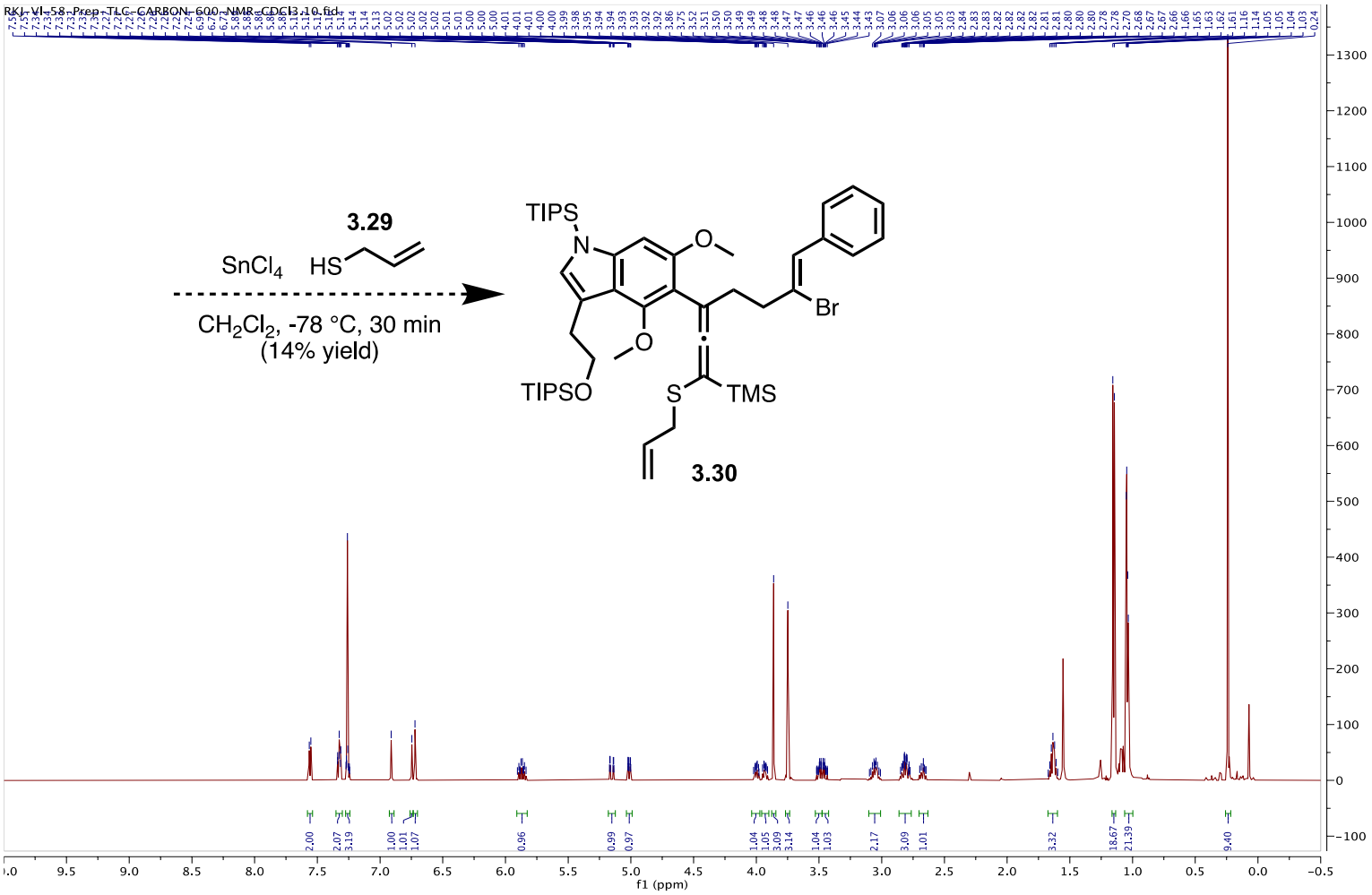


Figure C.28. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30**

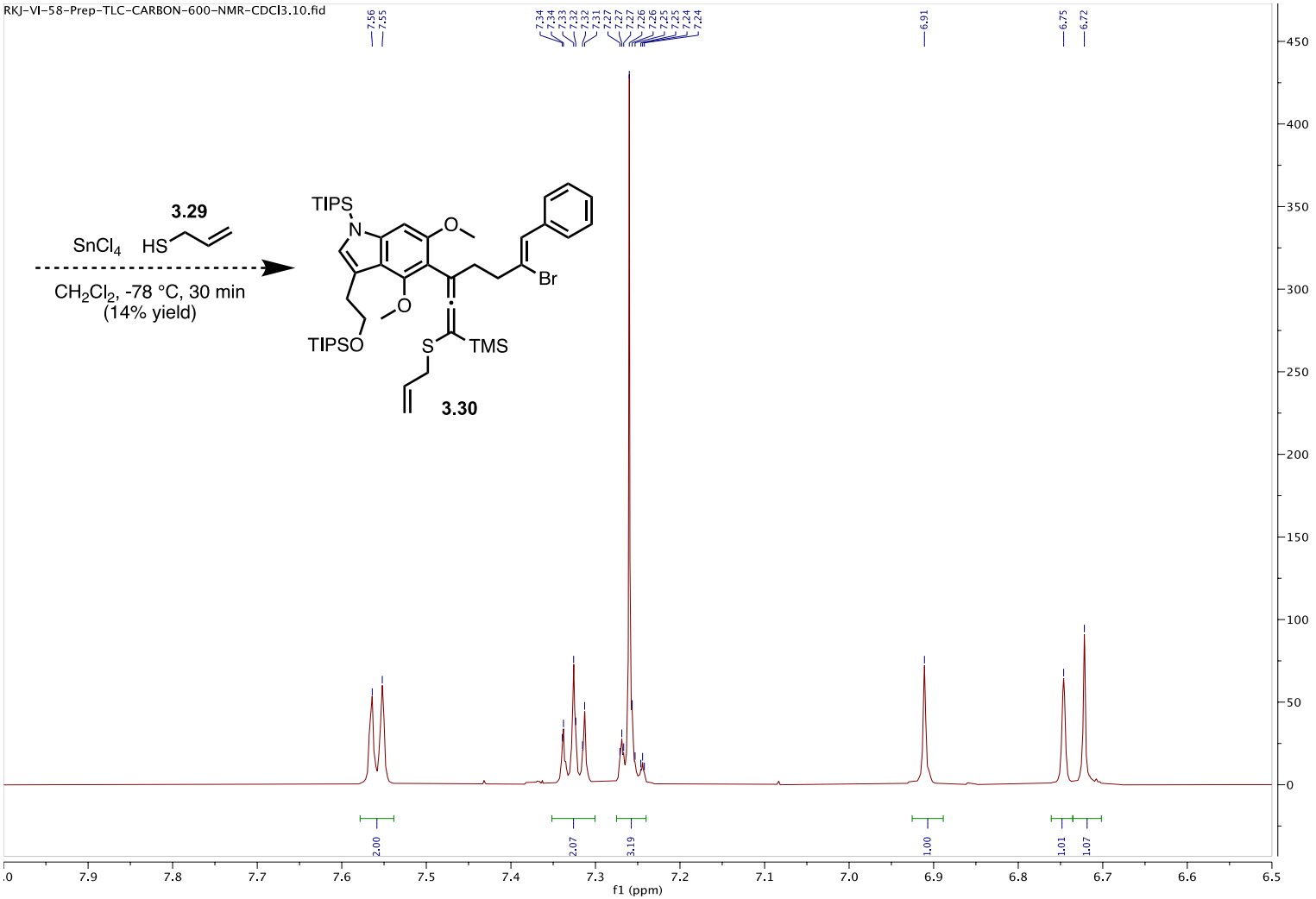


Figure C.29. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30** (8.0 – 6.5 ppm inset)

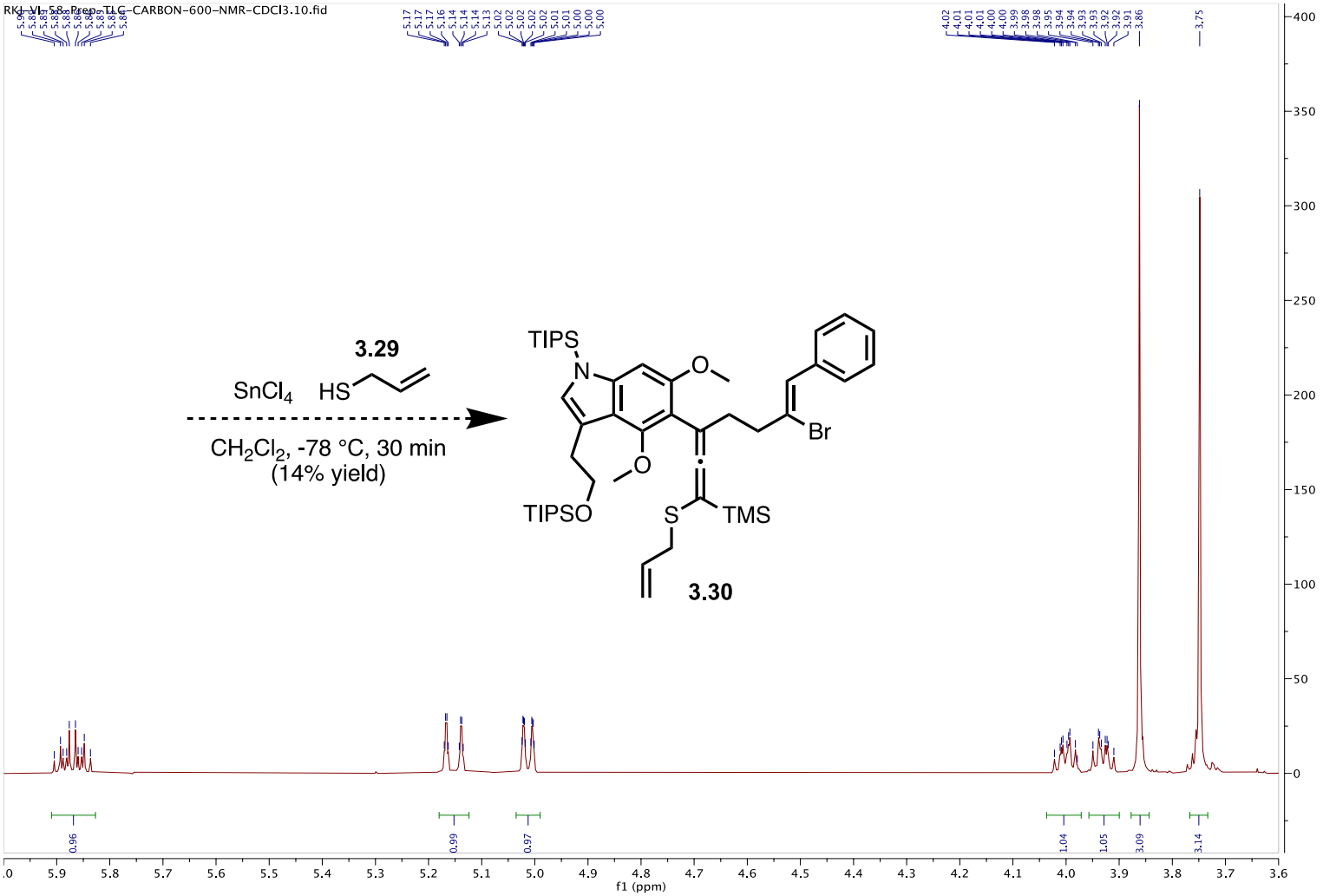


Figure C.30. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30** (6.0 – 3.6 ppm inset)

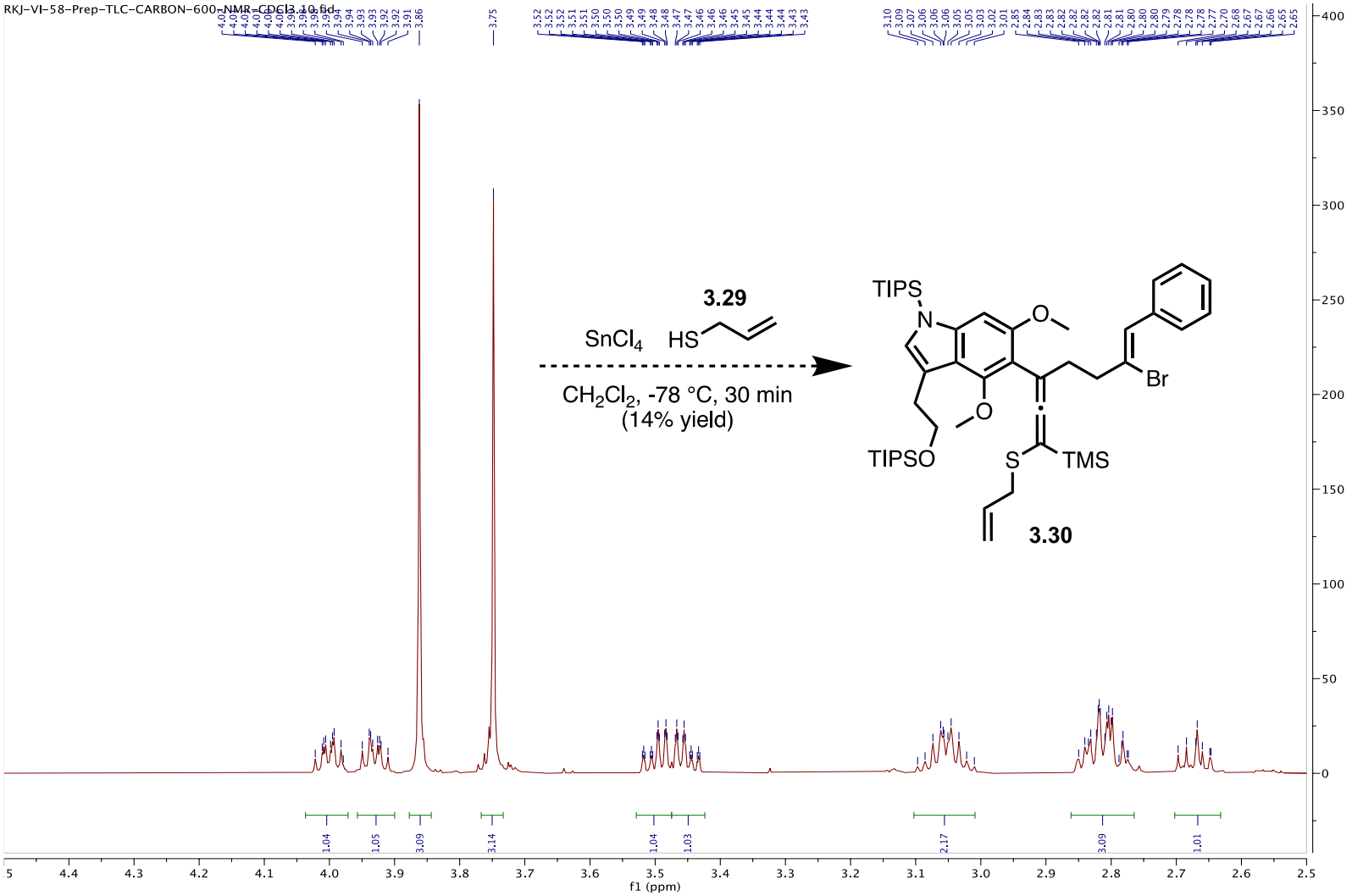


Figure C.31. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30** (4.5 – 2.5 ppm inset)

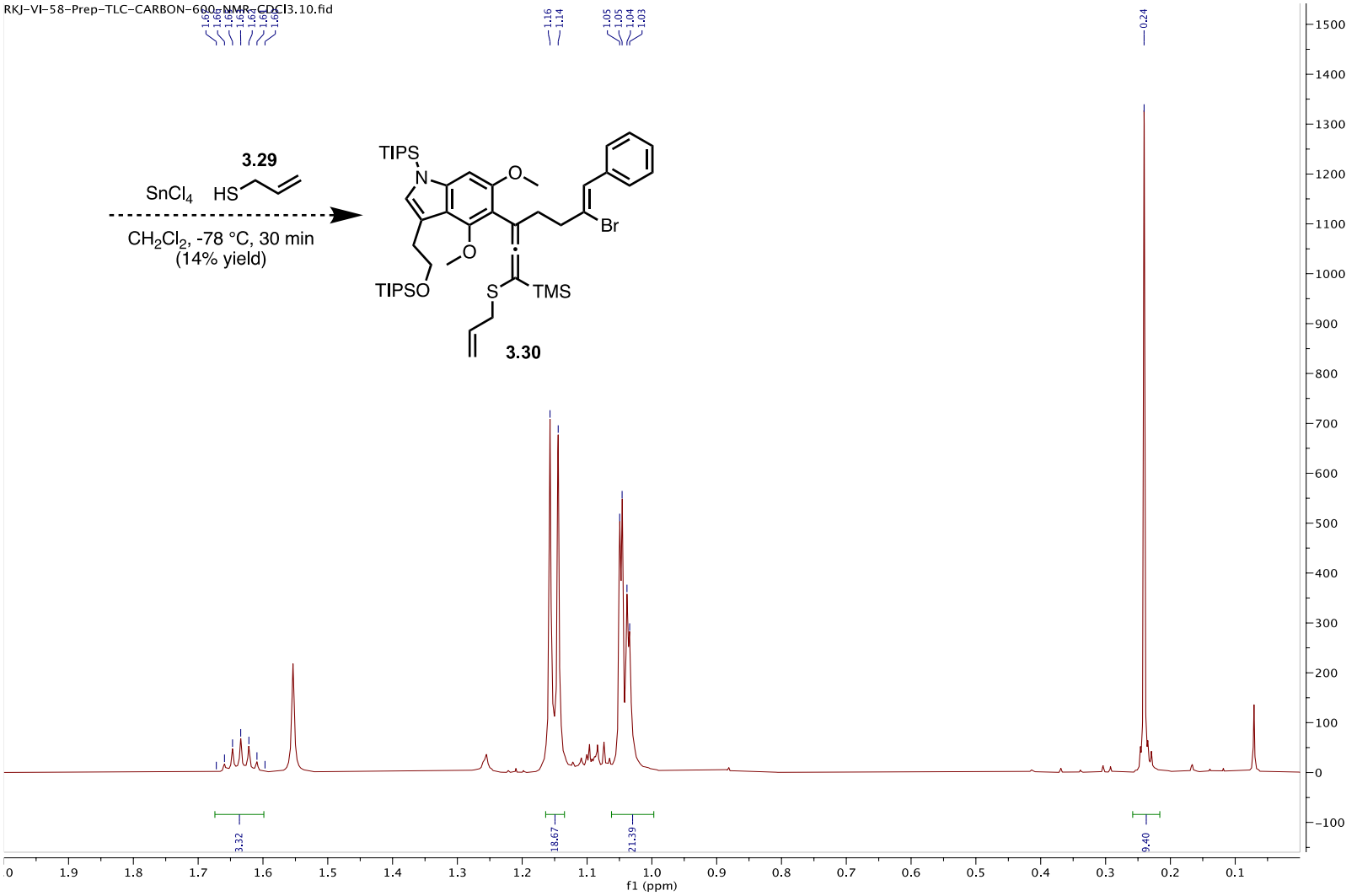


Figure C.32. **^{1}H NMR** (600 MHz, $CDCl_3$) Suspected Allene **3.30** (2.0 – 0.0 ppm inset)

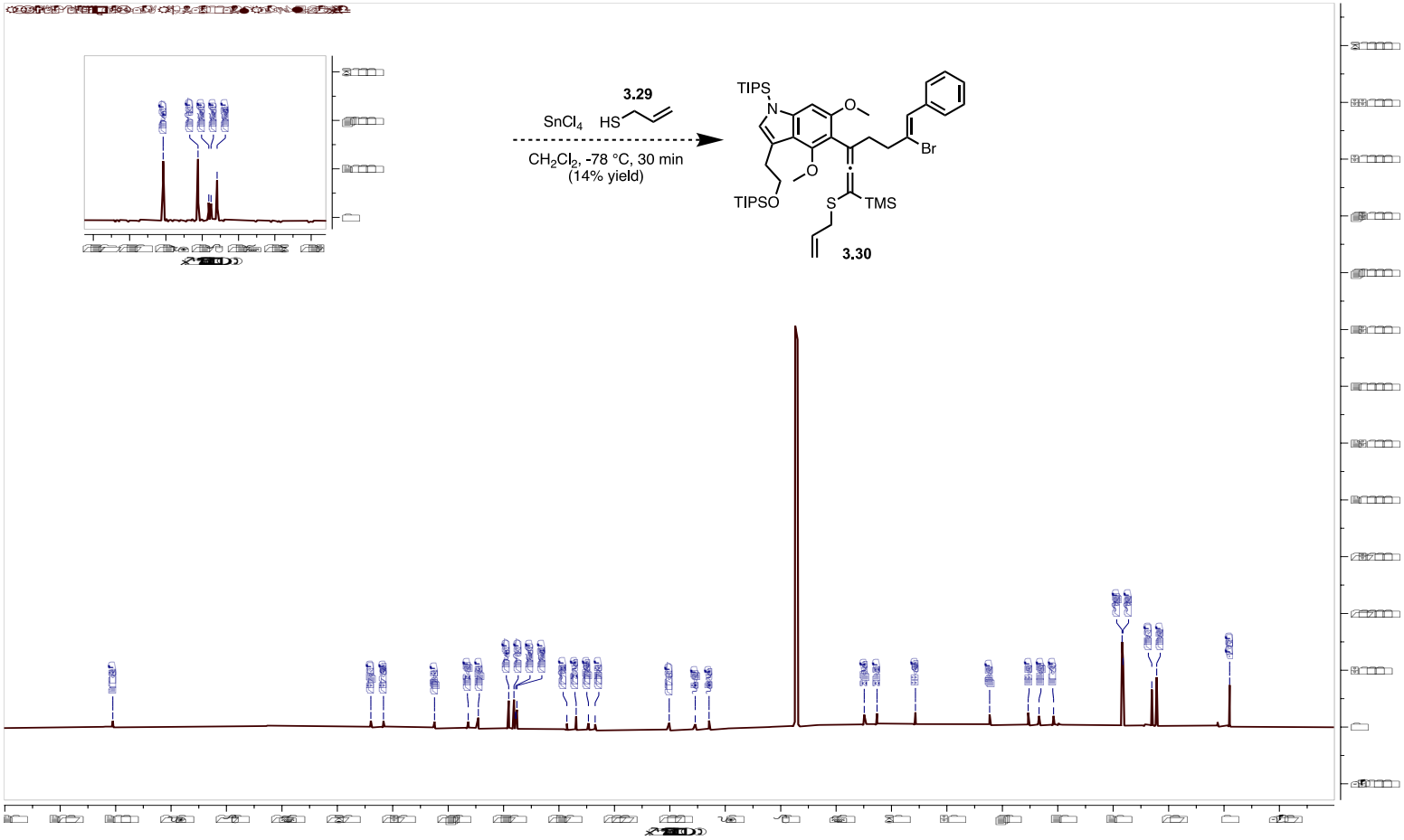


Figure C.33. **^{13}C NMR** (151 MHz, $CDCl_3$) Suspected Allene **3.30** with DEPT 90 (middle) and DEPT 135 (top) overlayed (window at top left to shows an additional peak; nonetheless, 1 aromatic methine is missing in this ^{13}C NMR from the depicted structure of **3.30**)

APPENDIX D

Spectra Relevant to Chapter Four

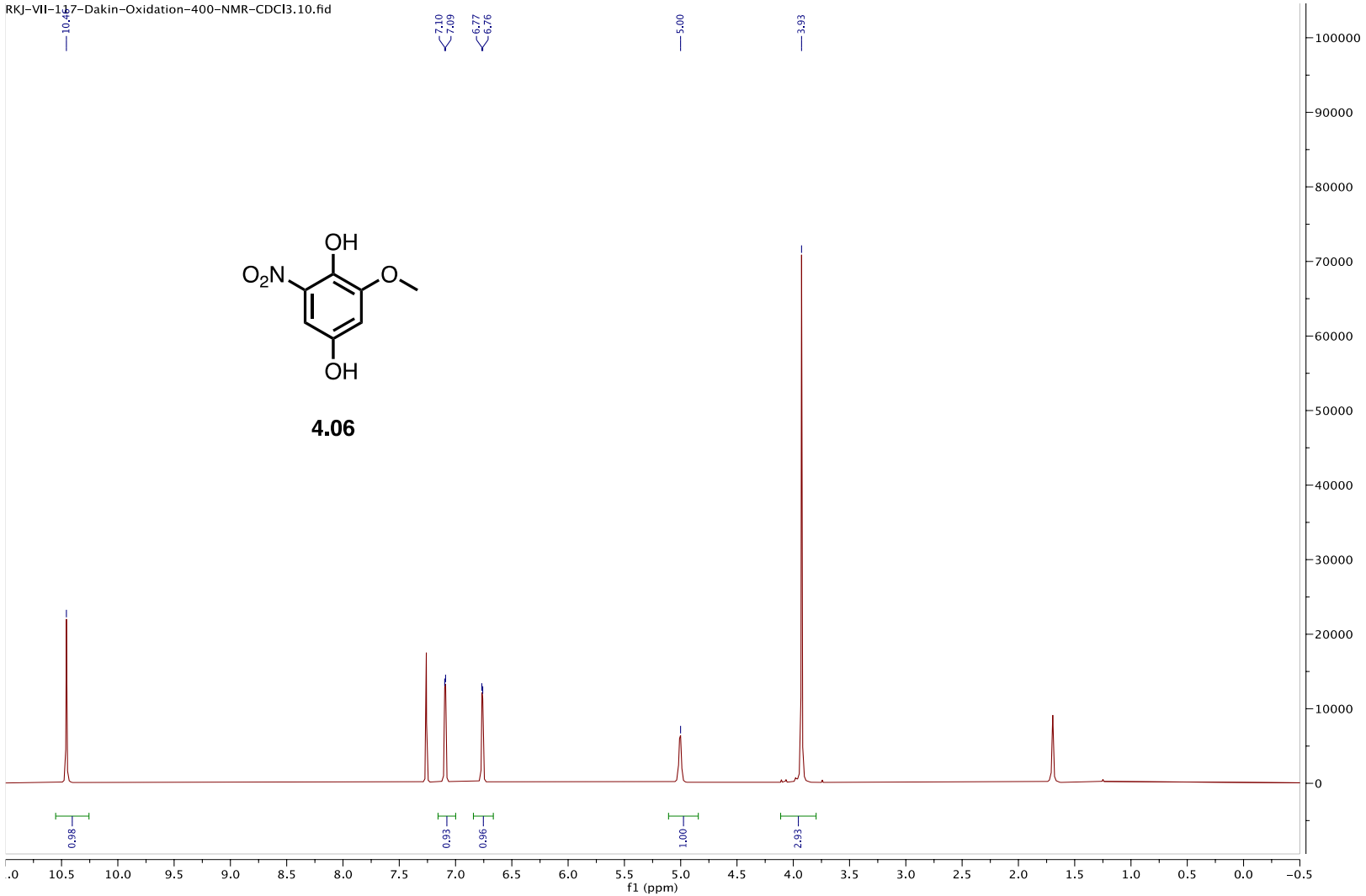


Figure D.01 **^{1}H NMR** (400 MHz, $CDCl_3$) Bis Phenol **4.06**

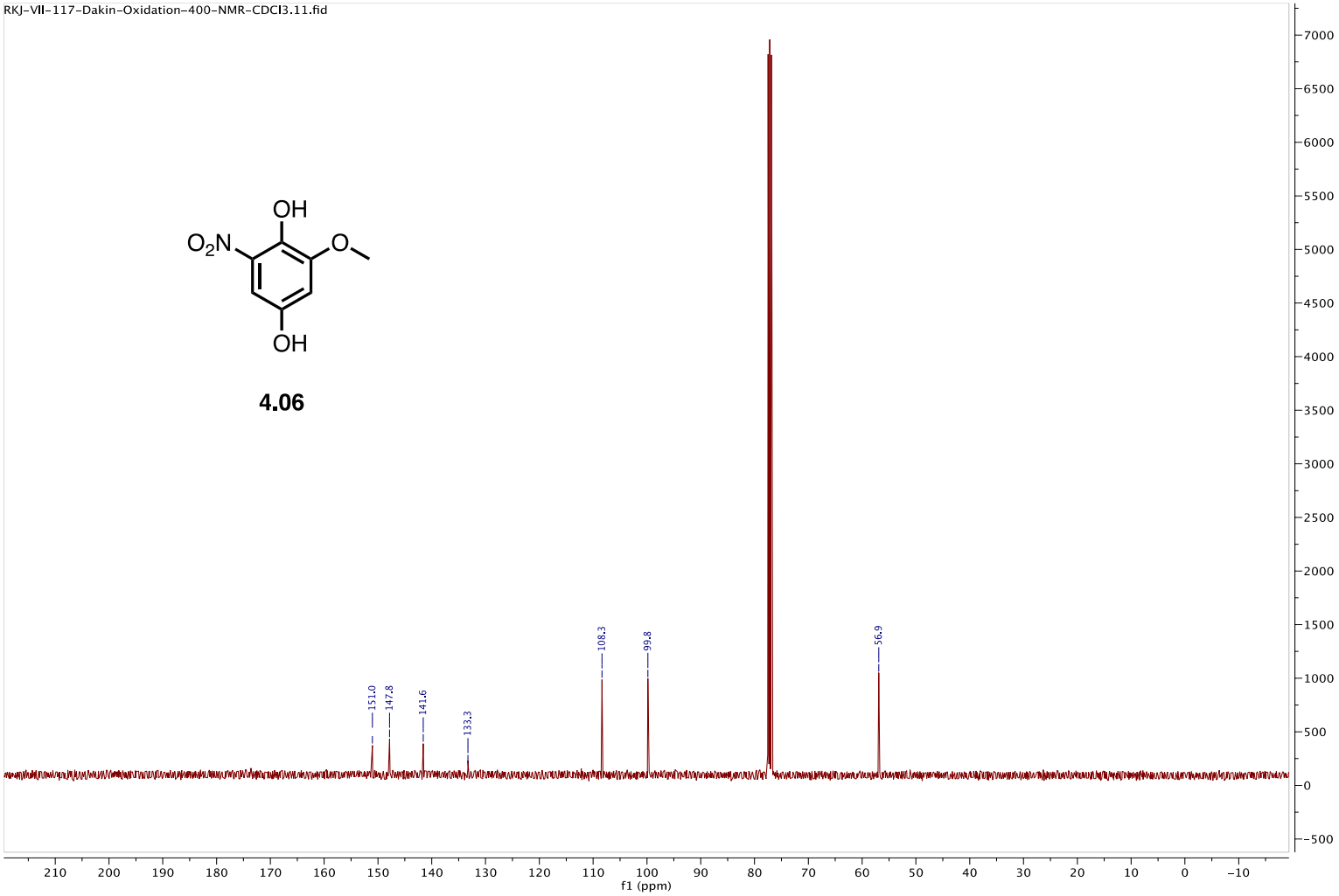


Figure D.02 **^{13}C NMR** ($CDCl_3$) Bis Phenol **4.06**

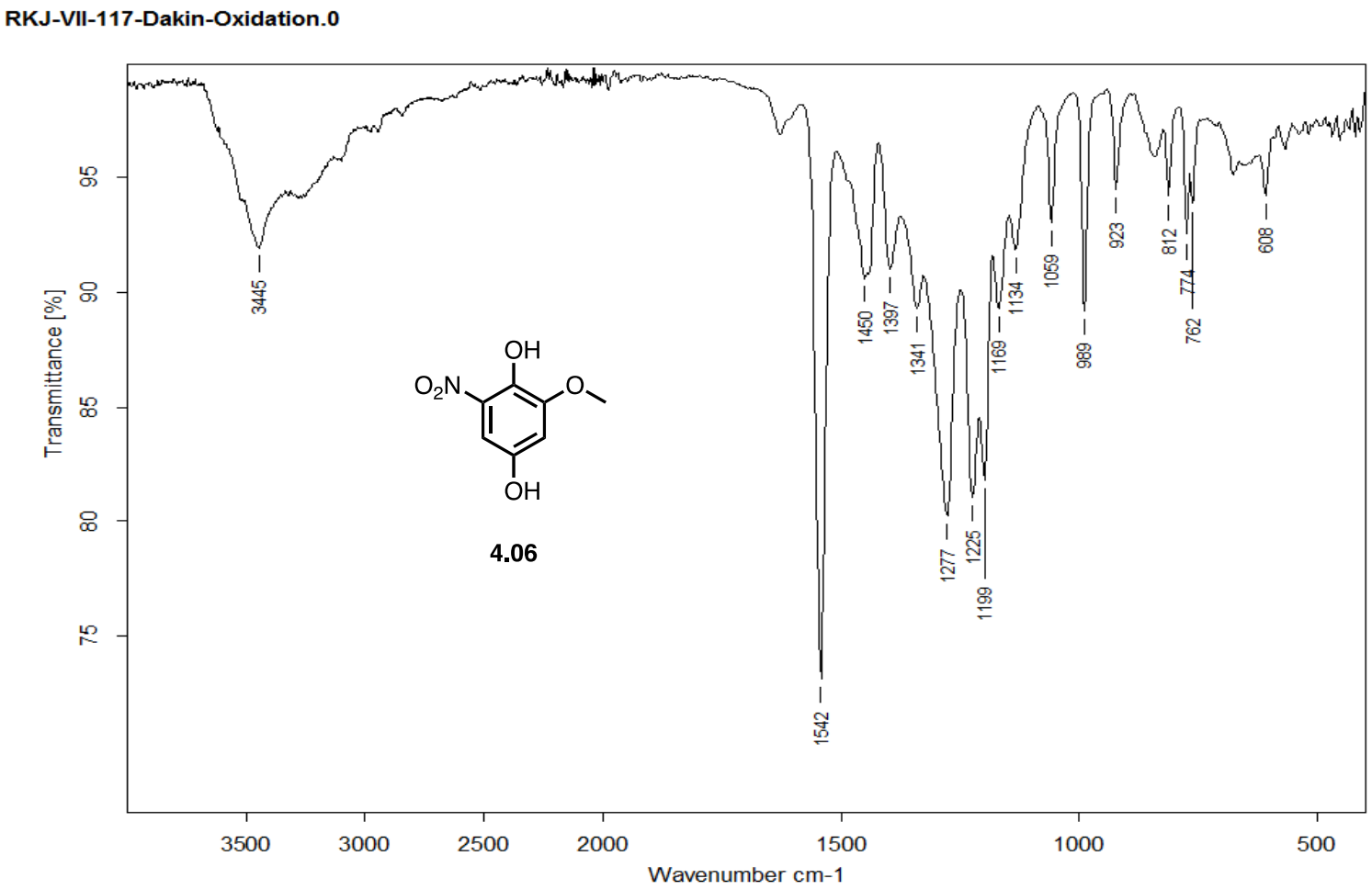


Figure D.03 **^{13}C NMR** (101 MHz, $CDCl_3$) Bis Phenol **4.06**

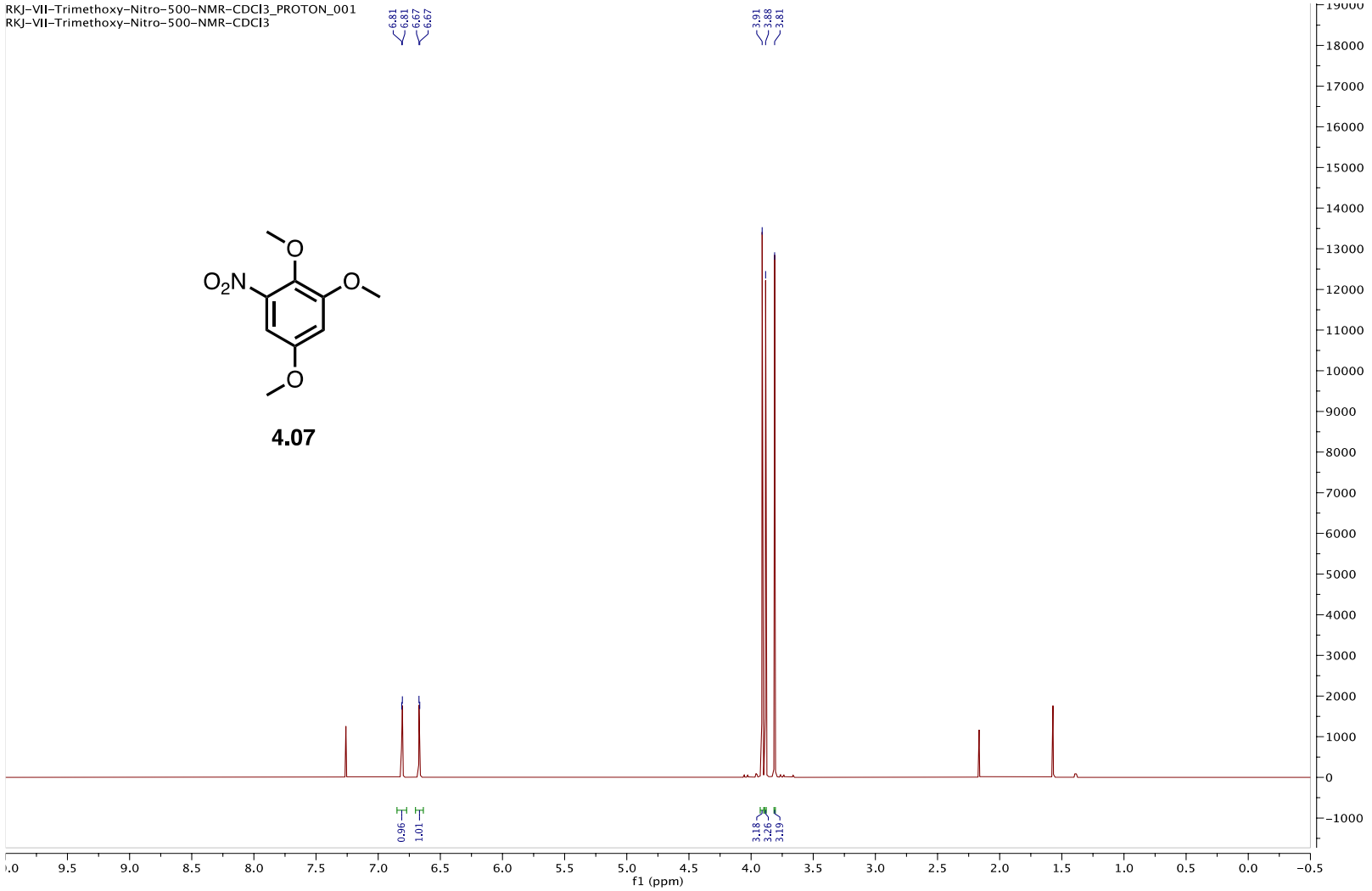


Figure D.04 **^{1}H NMR** (500 MHz, $CDCl_3$) Trimethoxy Nitro **4.07**

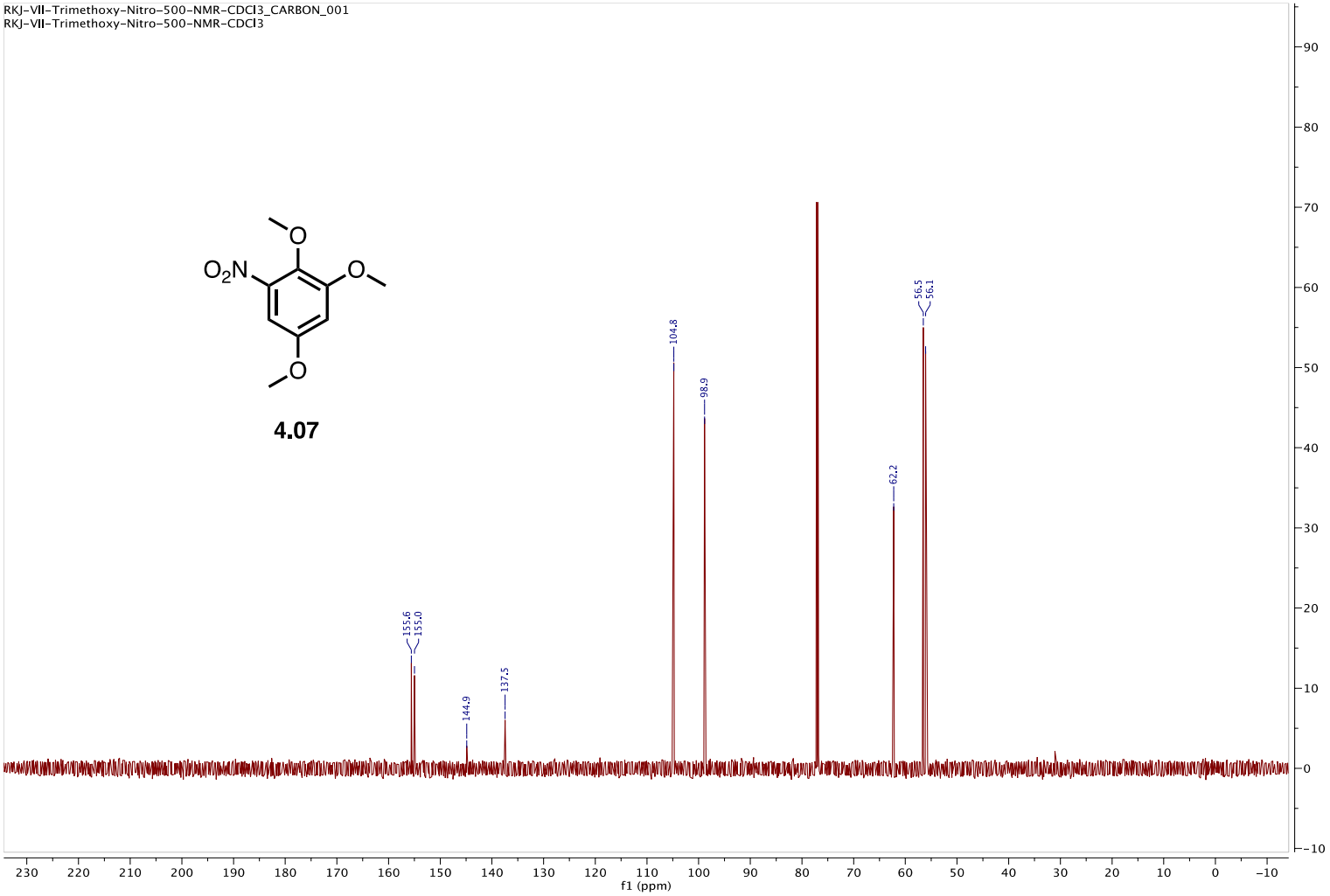


Figure D.05 **^{13}C NMR** (126 MHz, $CDCl_3$) Trimethoxy Nitro **4.07**

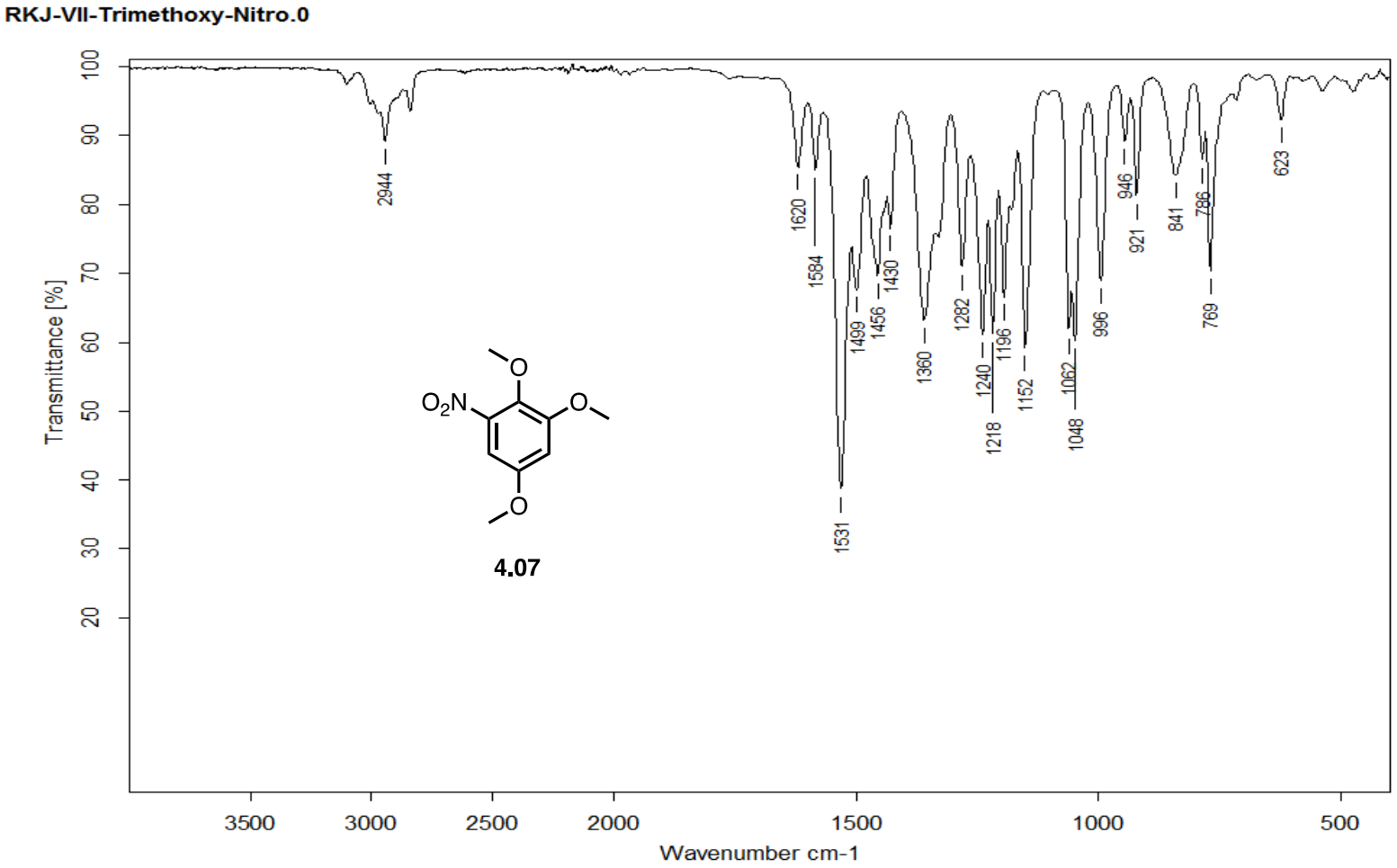


Figure D.06 **FTIR** (thin film) Trimethoxy Nitro **4.07**

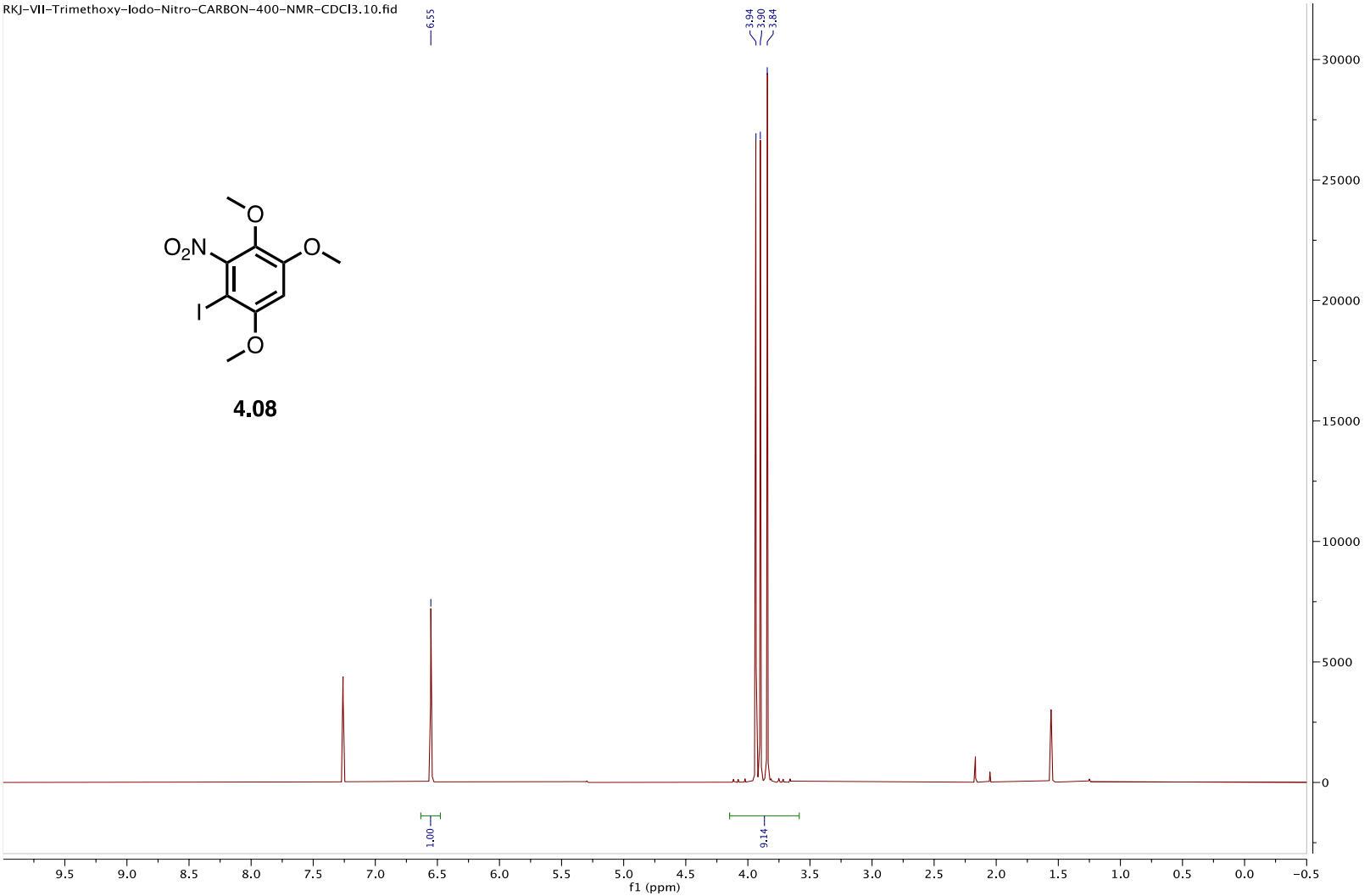


Figure D.07 **^{1}H NMR** (400 MHz, $CDCl_3$) Iodine **4.08**

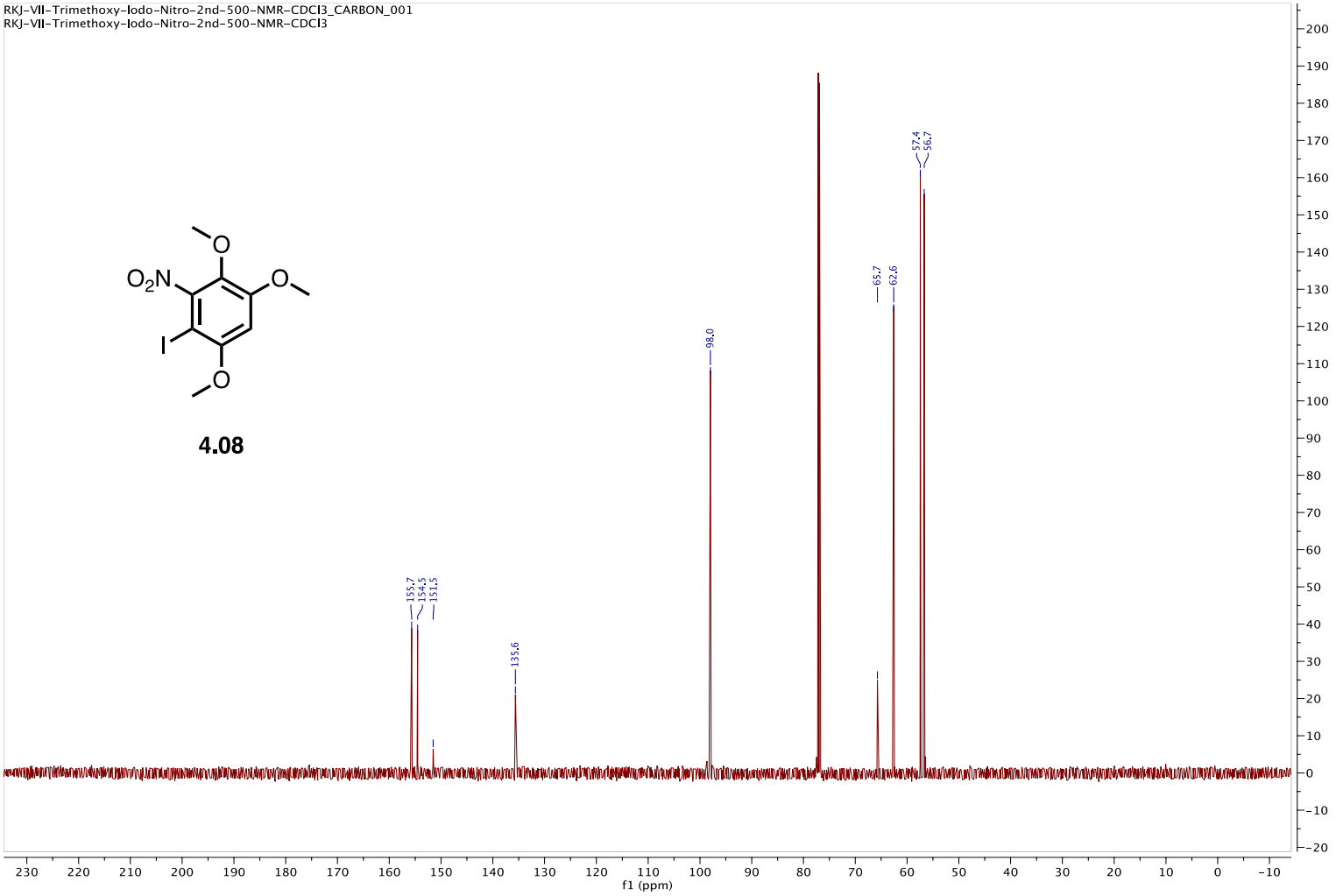


Figure D.08 **^{13}C NMR** (126 MHz, $CDCl_3$) Iodine **4.08**

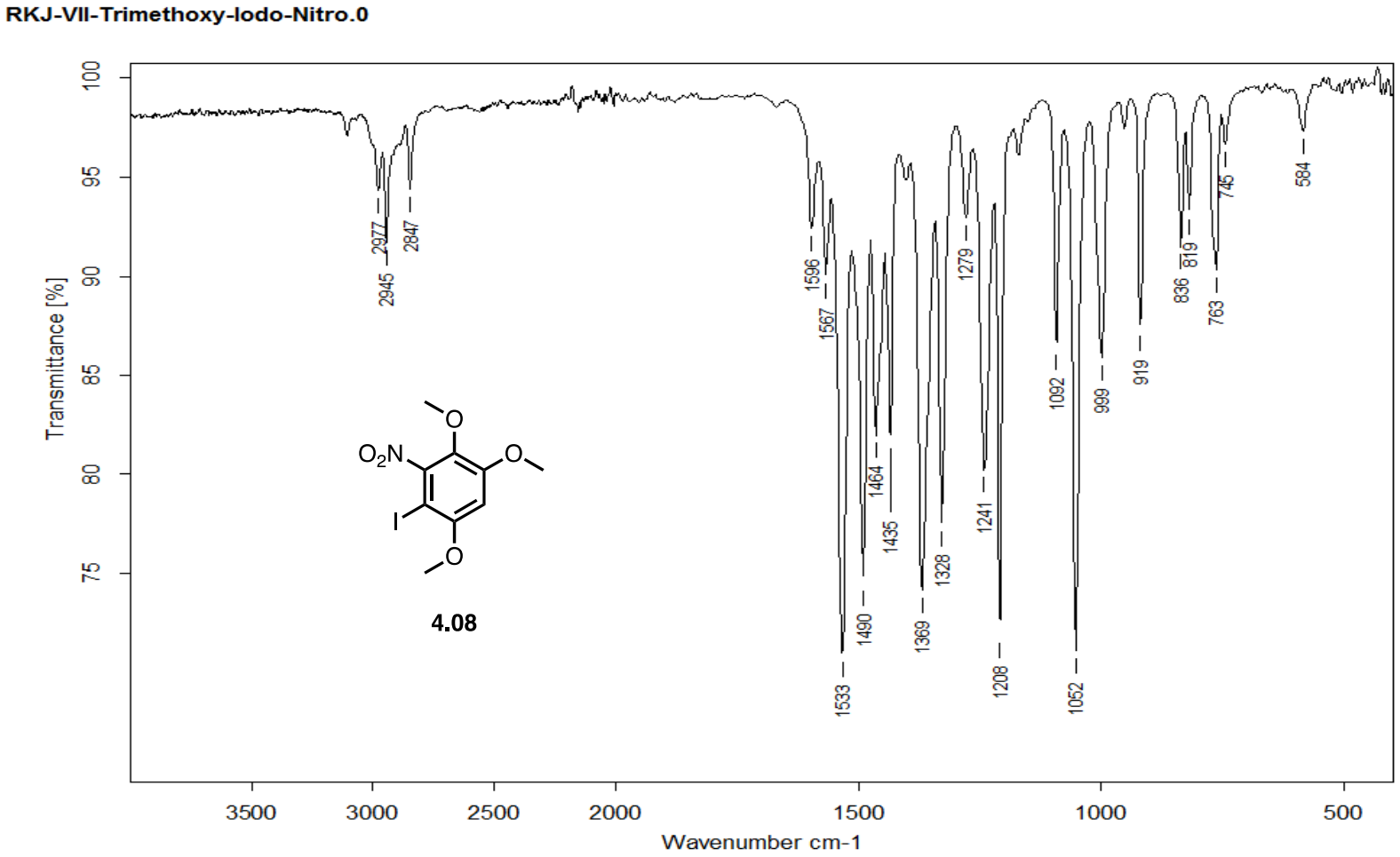


Figure D.09 **FTIR** (thin film) Iodine **4.08**

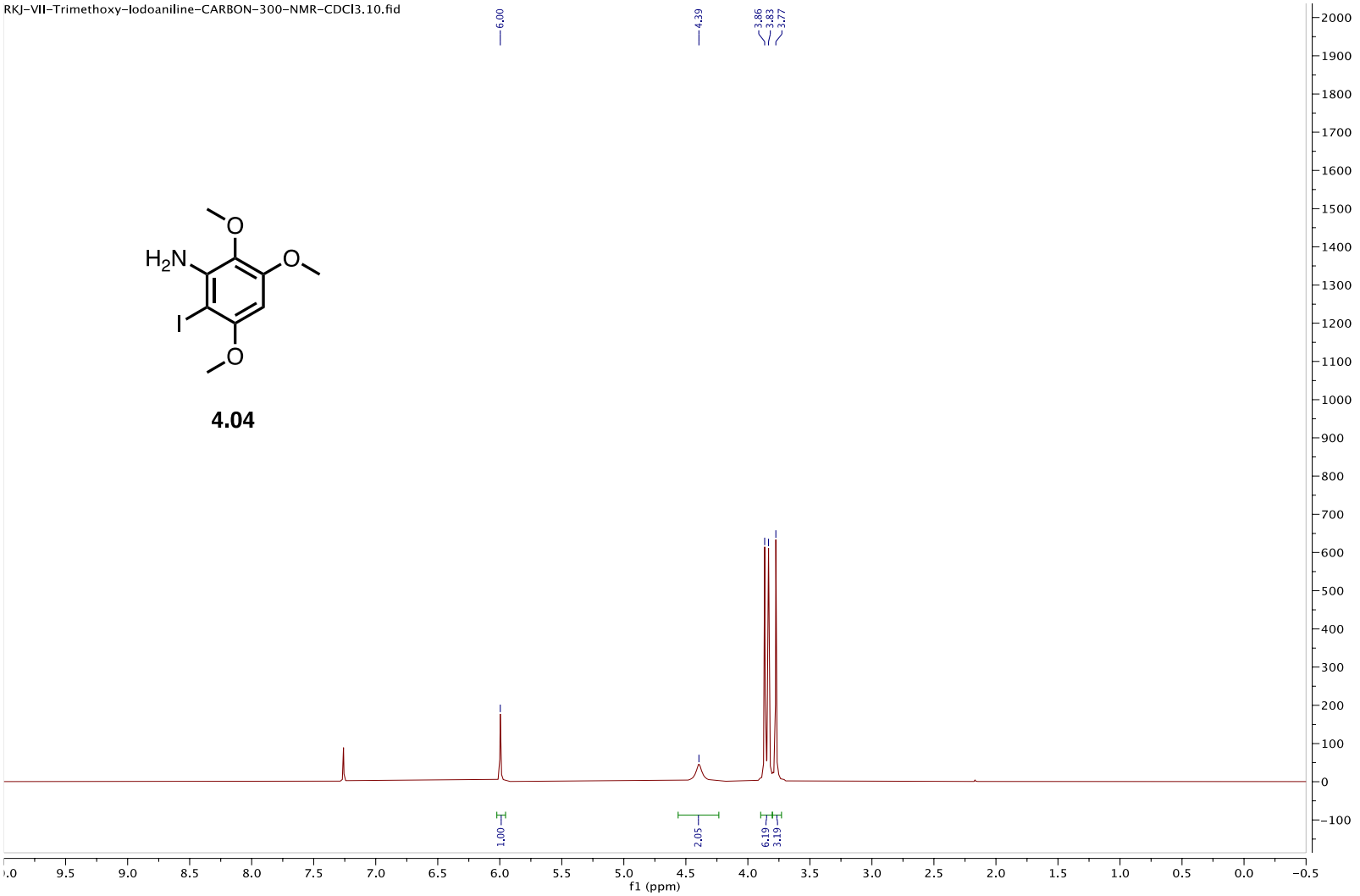


Figure D.10 **^{1}H NMR** (300 MHz, $CDCl_3$) Aniline **4.04**

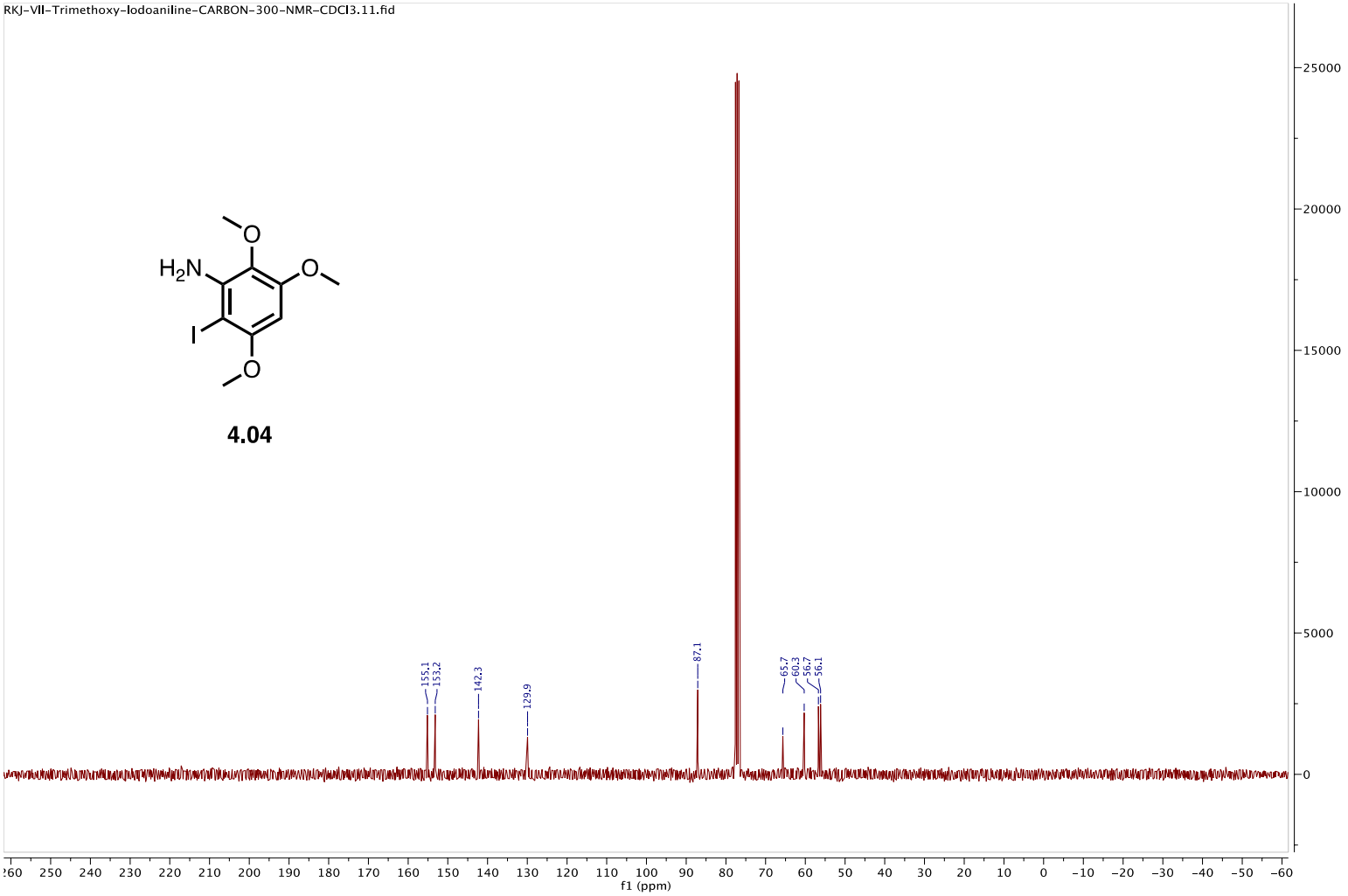


Figure D.11 **^{13}C NMR** (75 MHz, $CDCl_3$) Aniline **4.04**

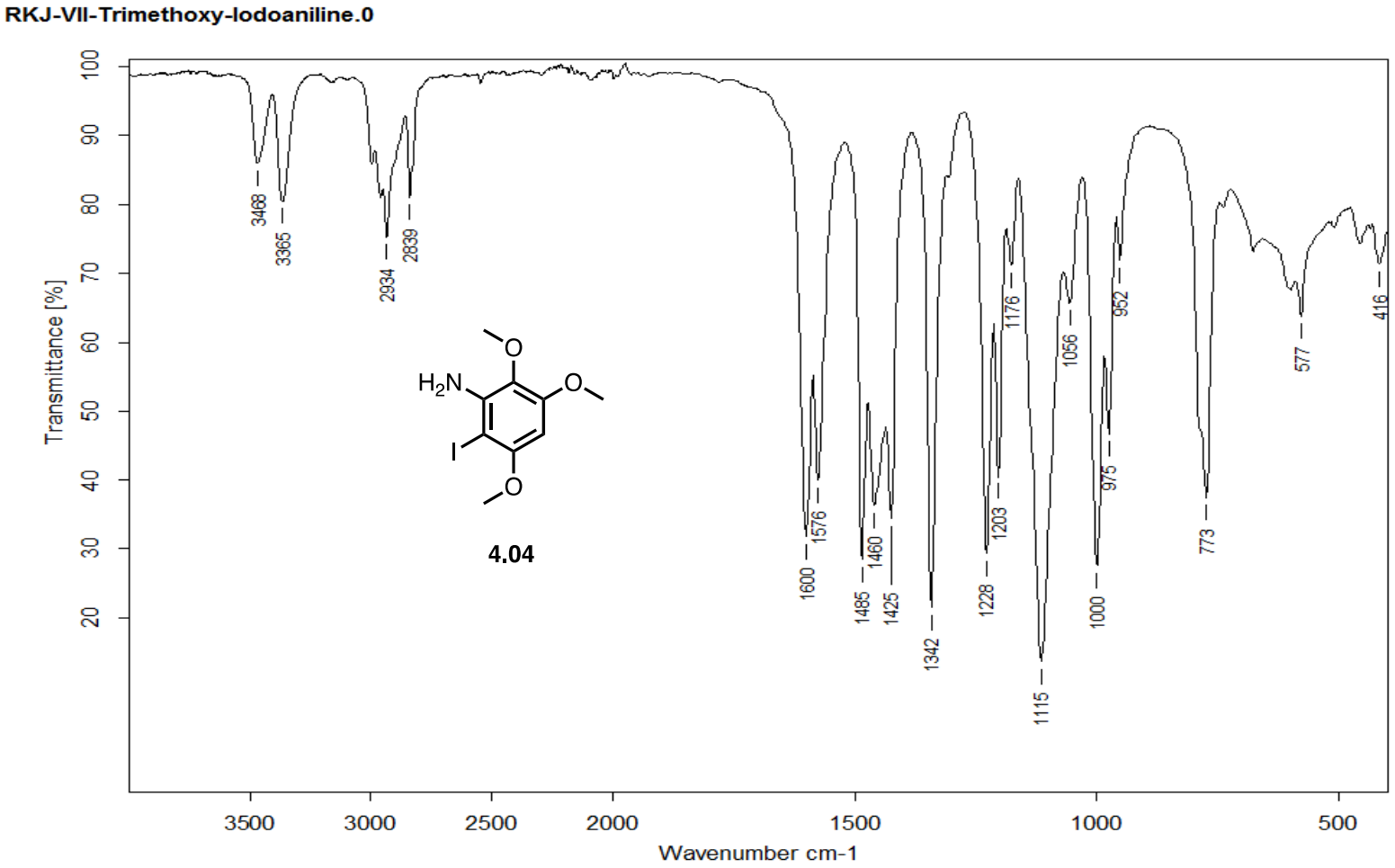


Figure D.12 **FTIR** (thin film) Aniline **4.04**

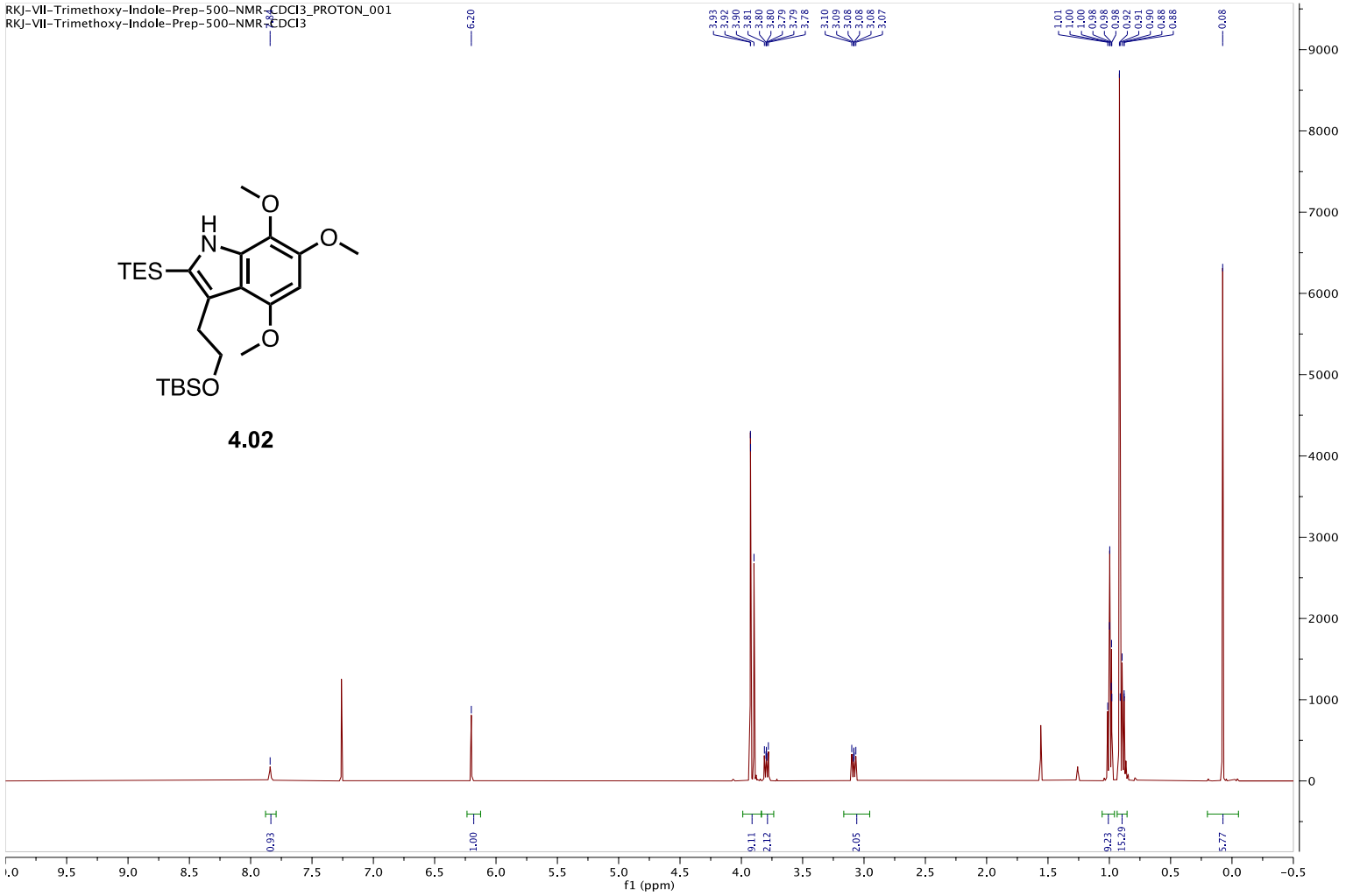


Figure D.13 **^{1}H NMR** (500 MHz, $CDCl_3$) Indole **4.02**

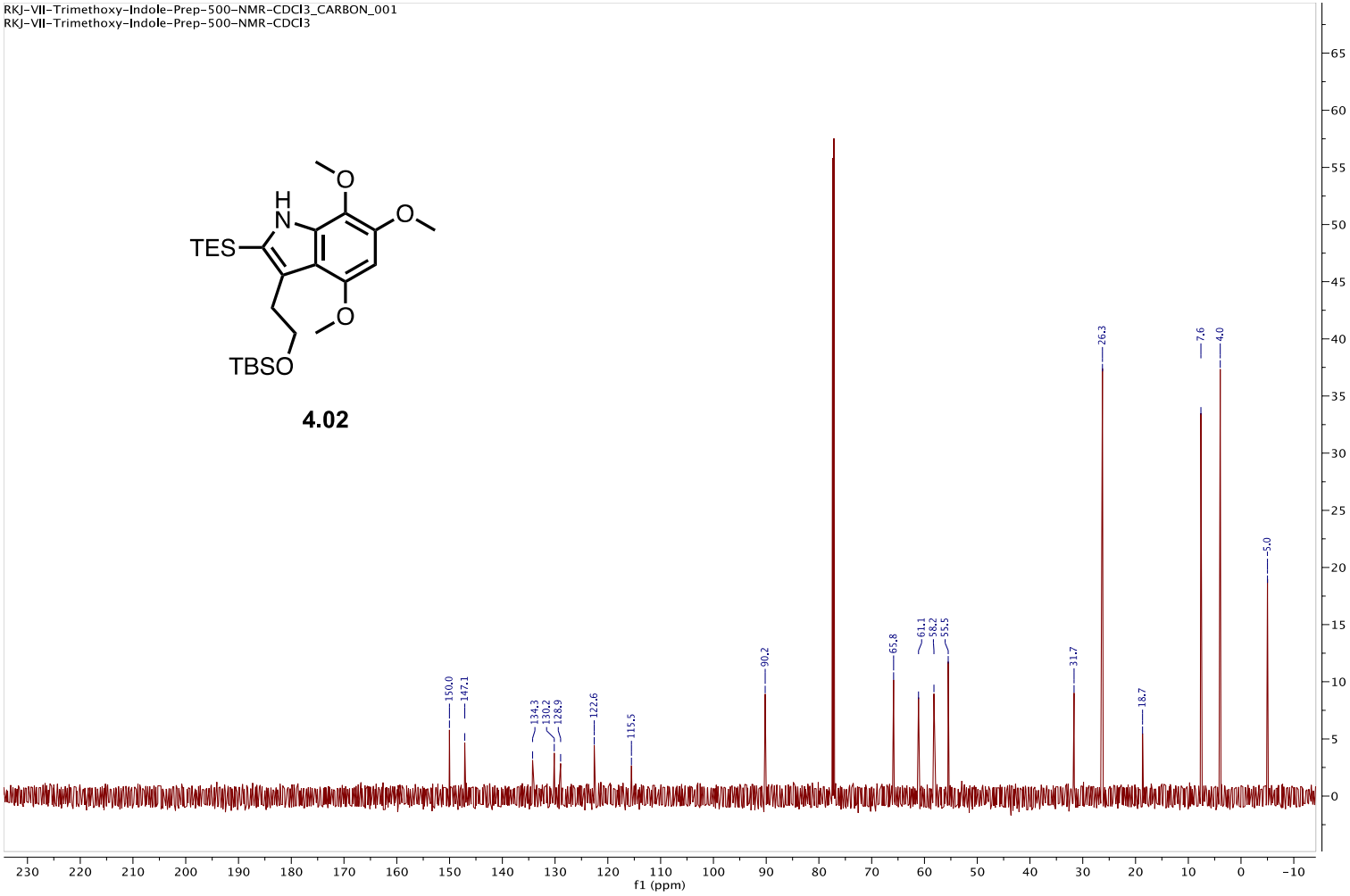


Figure D.14 ^{13}**C NMR** (126 MHz, $CDCl_3$) Indole **4.02**

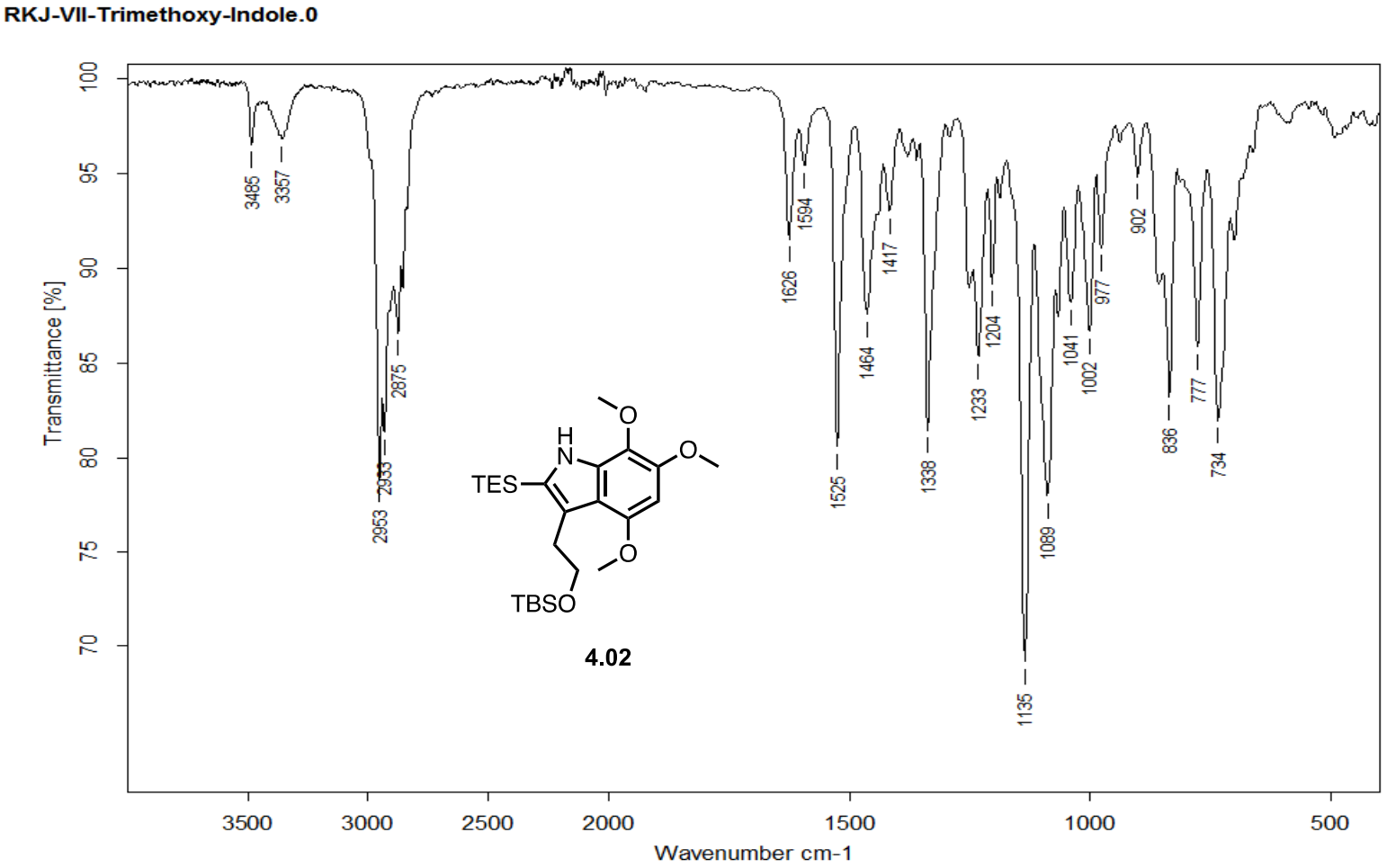


Figure D.15 **FTIR** (thin film) Indole **4.02**

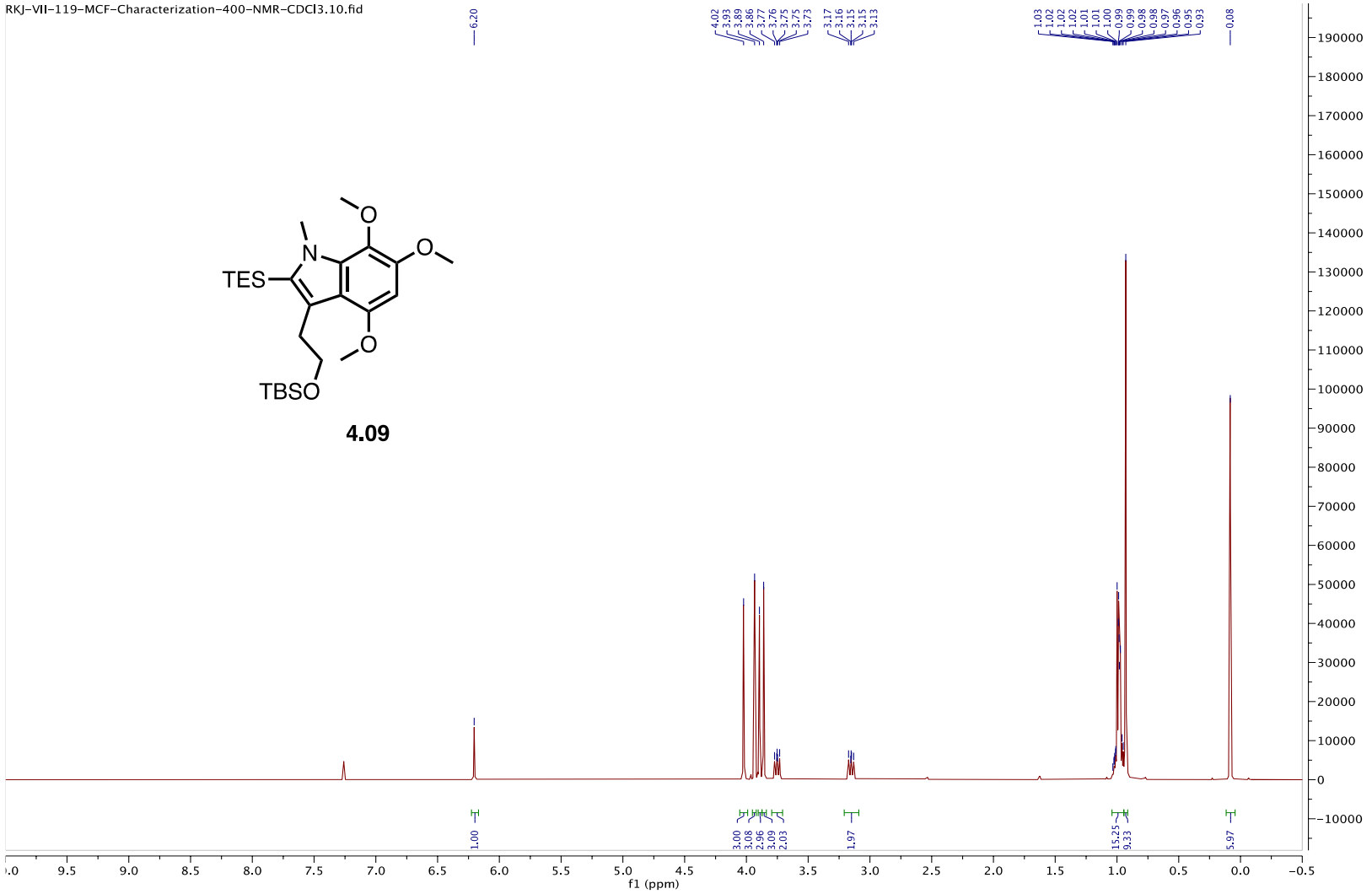


Figure D.16 **^{1}H NMR** (400 MHz, $CDCl_3$) Methyl Indole **4.09**

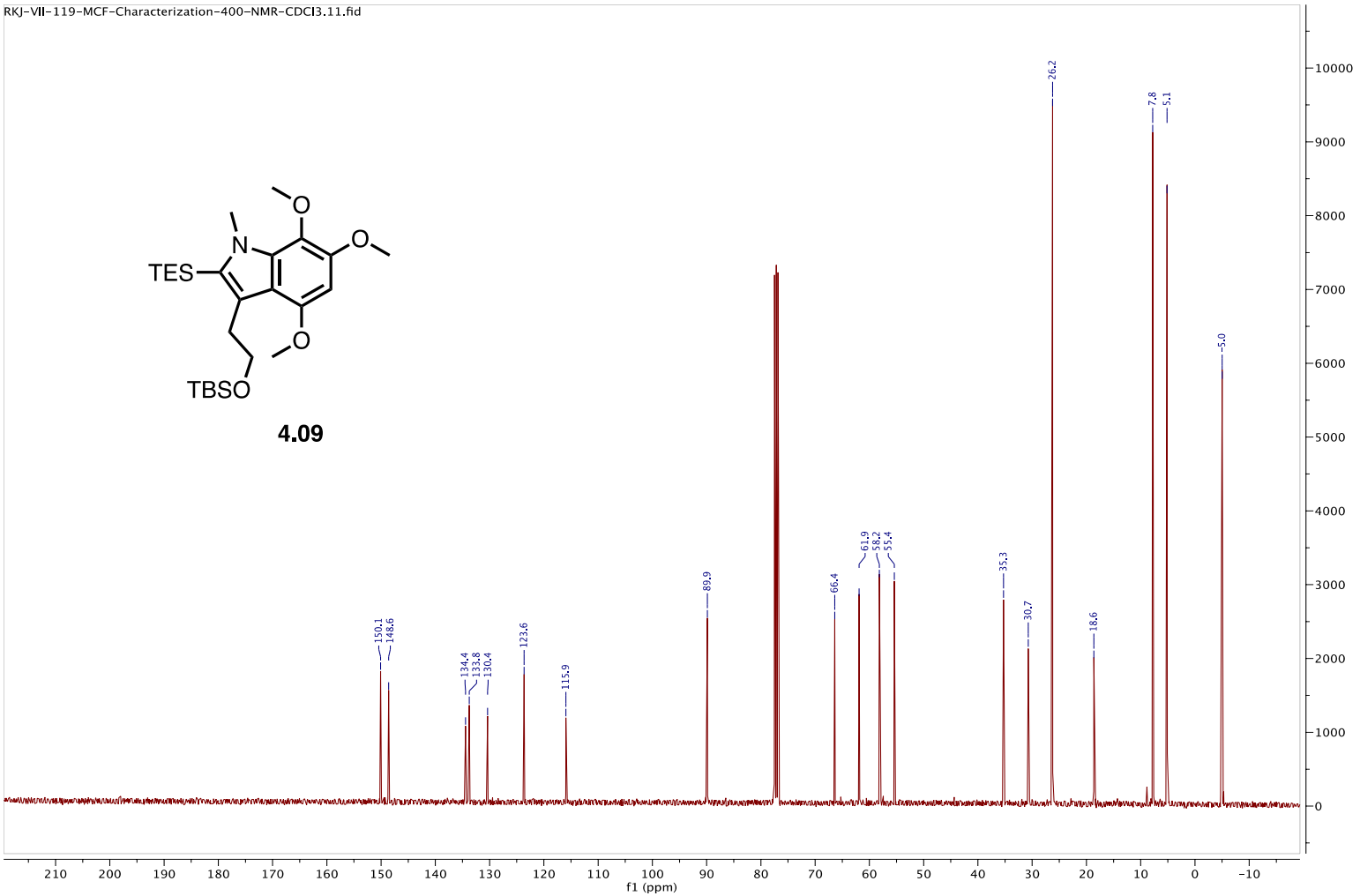


Figure D.17 **^{13}C NMR** (101 MHz, $CDCl_3$) Methyl Indole **4.09**

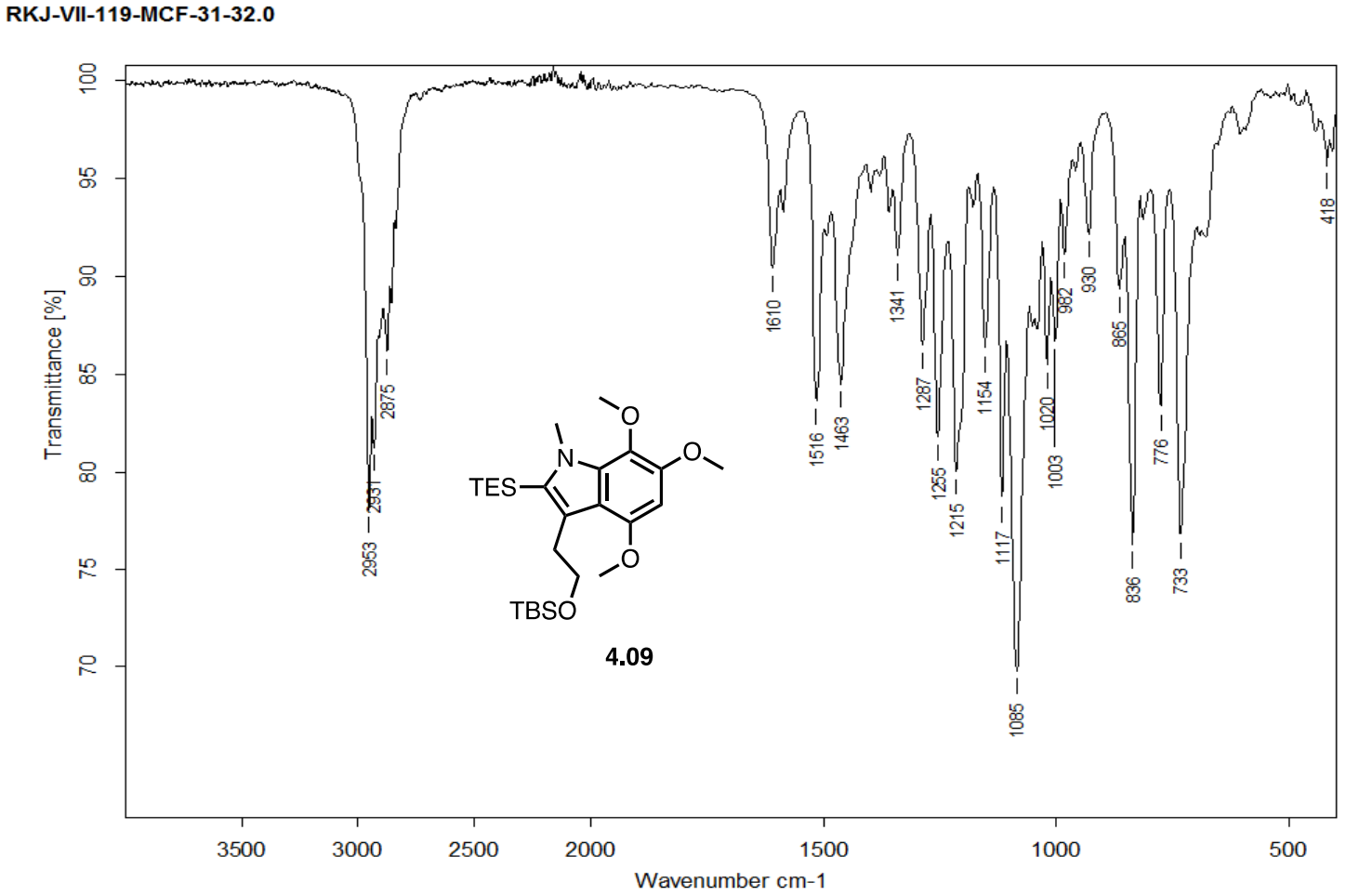


Figure D.18 **FTIR** (thin film) Methyl Indole **4.09**

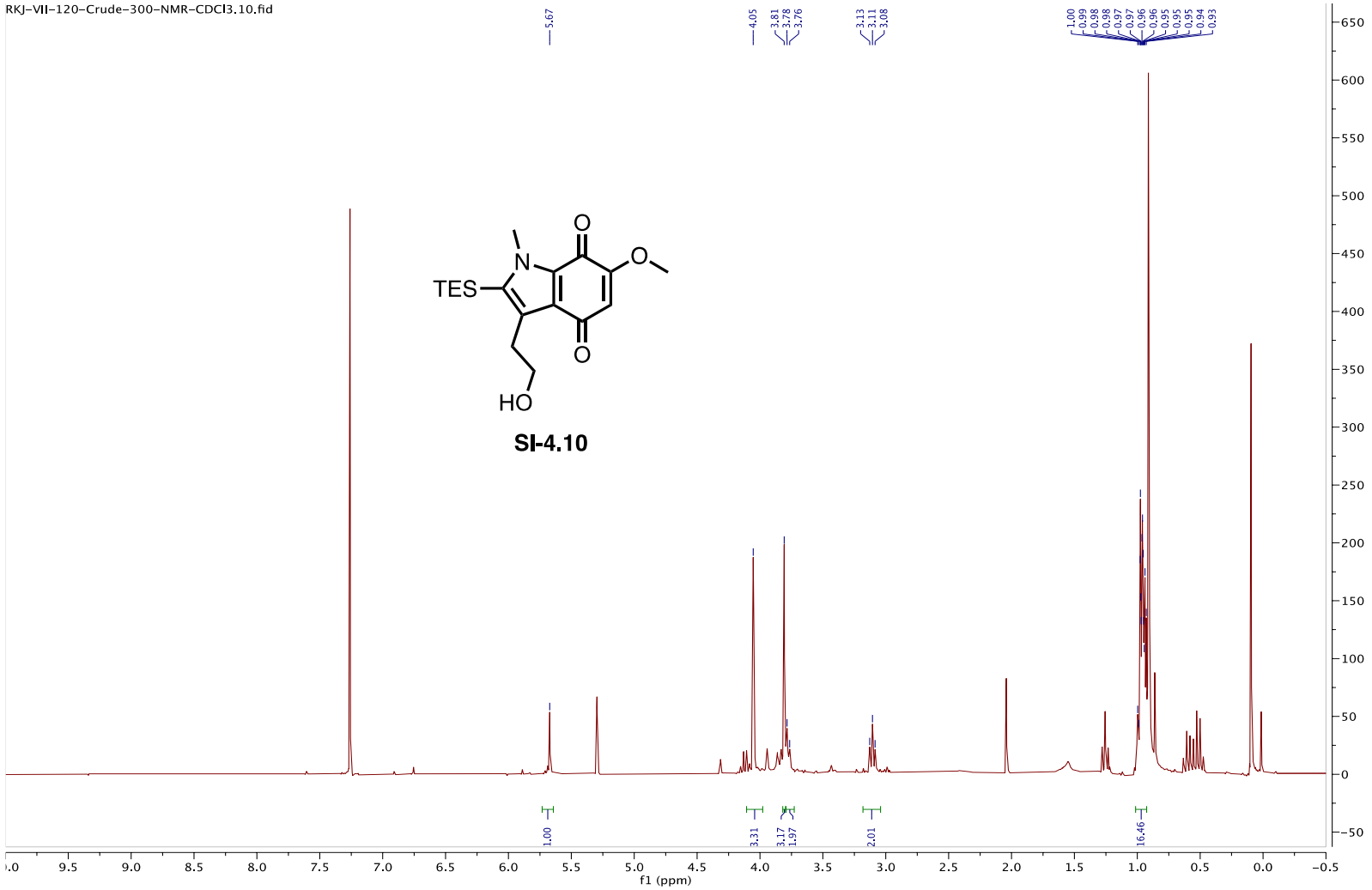


Figure D.19 **^{1}H NMR** (300 MHz, $CDCl_3$) Crude Indoloquinone **SI-4.10**

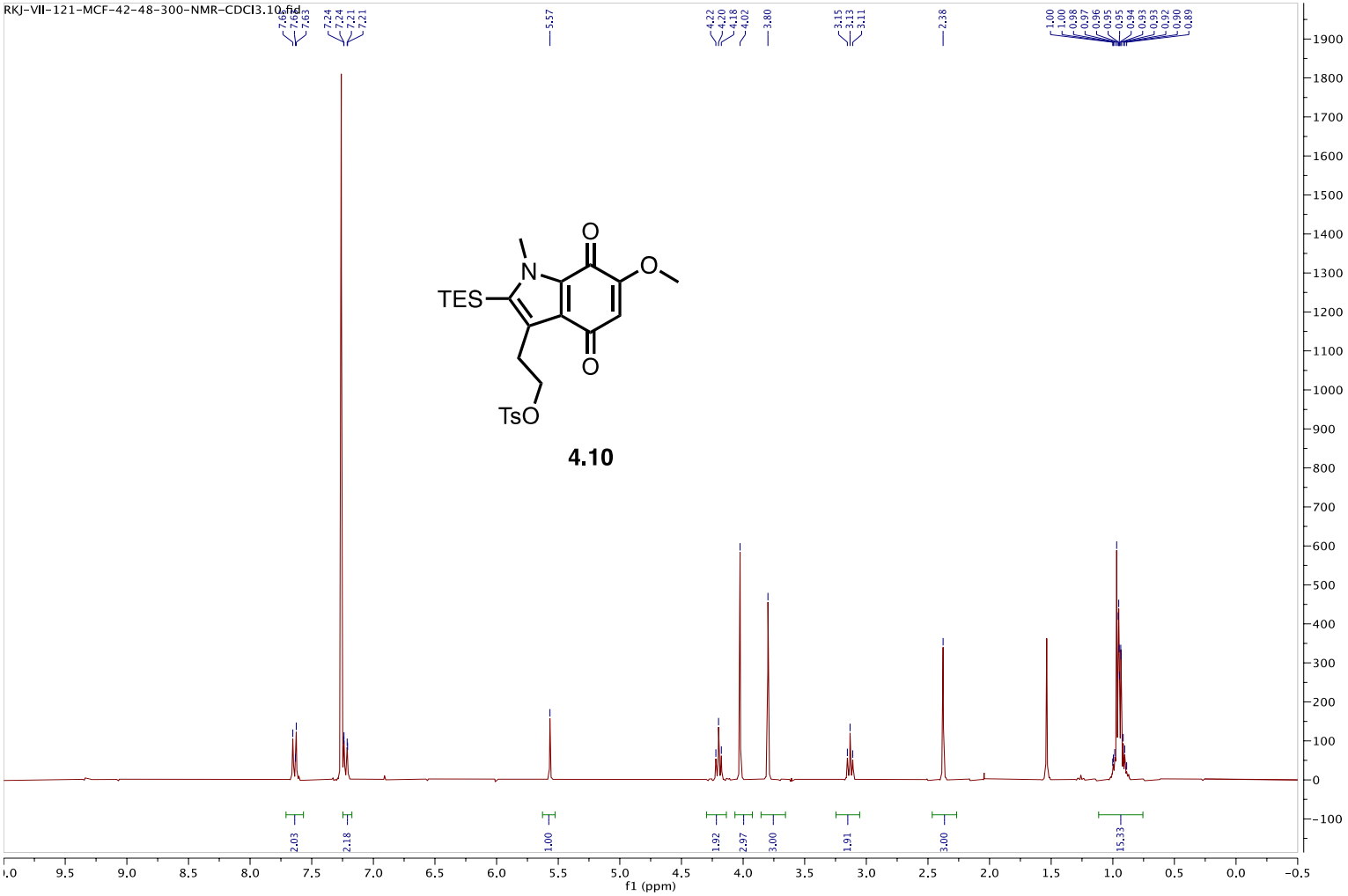


Figure D.20 **^{1}H NMR** (300 MHz, $CDCl_3$) Tosylate **4.10**

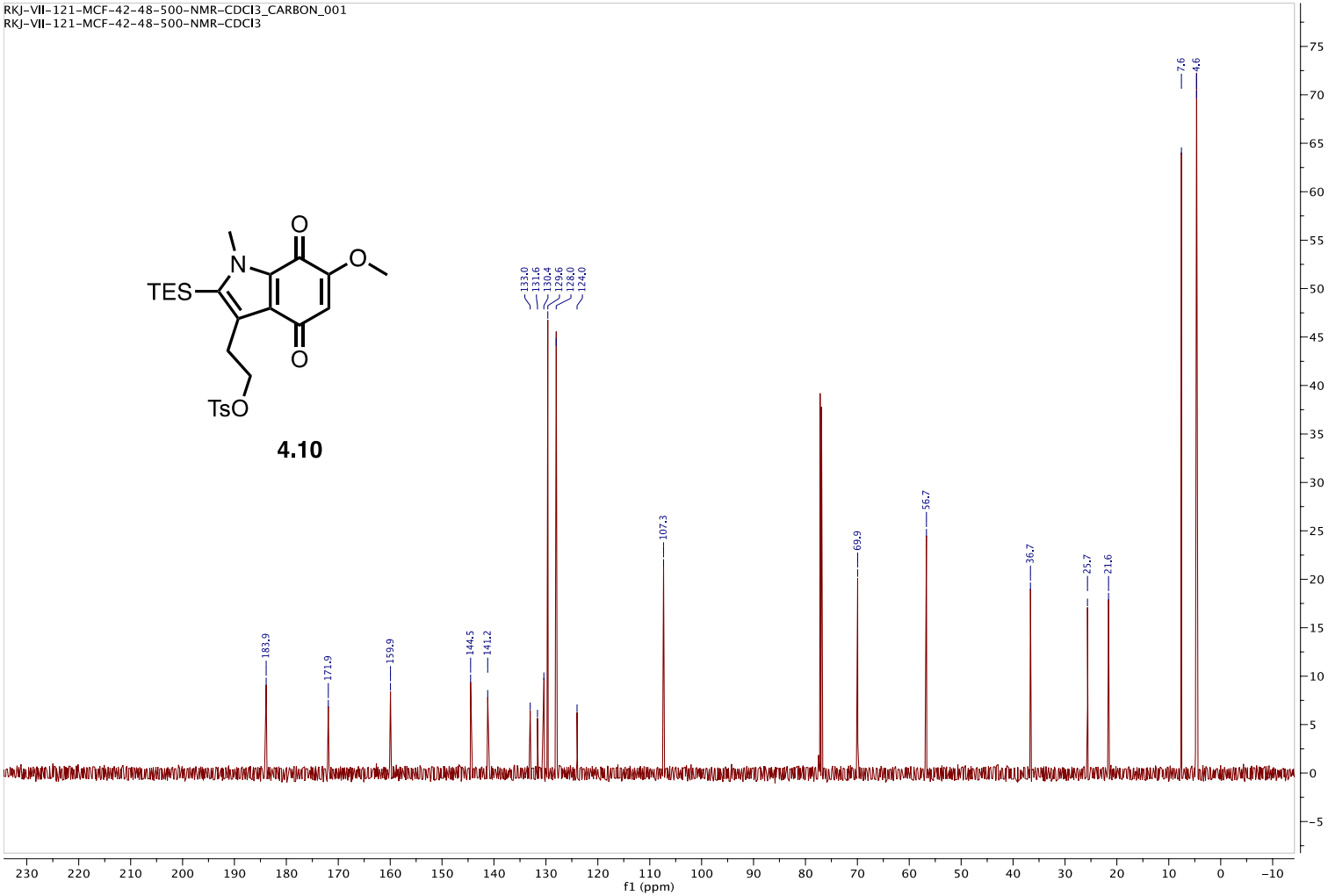


Figure D.21 **^{13}C NMR** (126 MHz, $CDCl_3$) Tosylate **4.10**

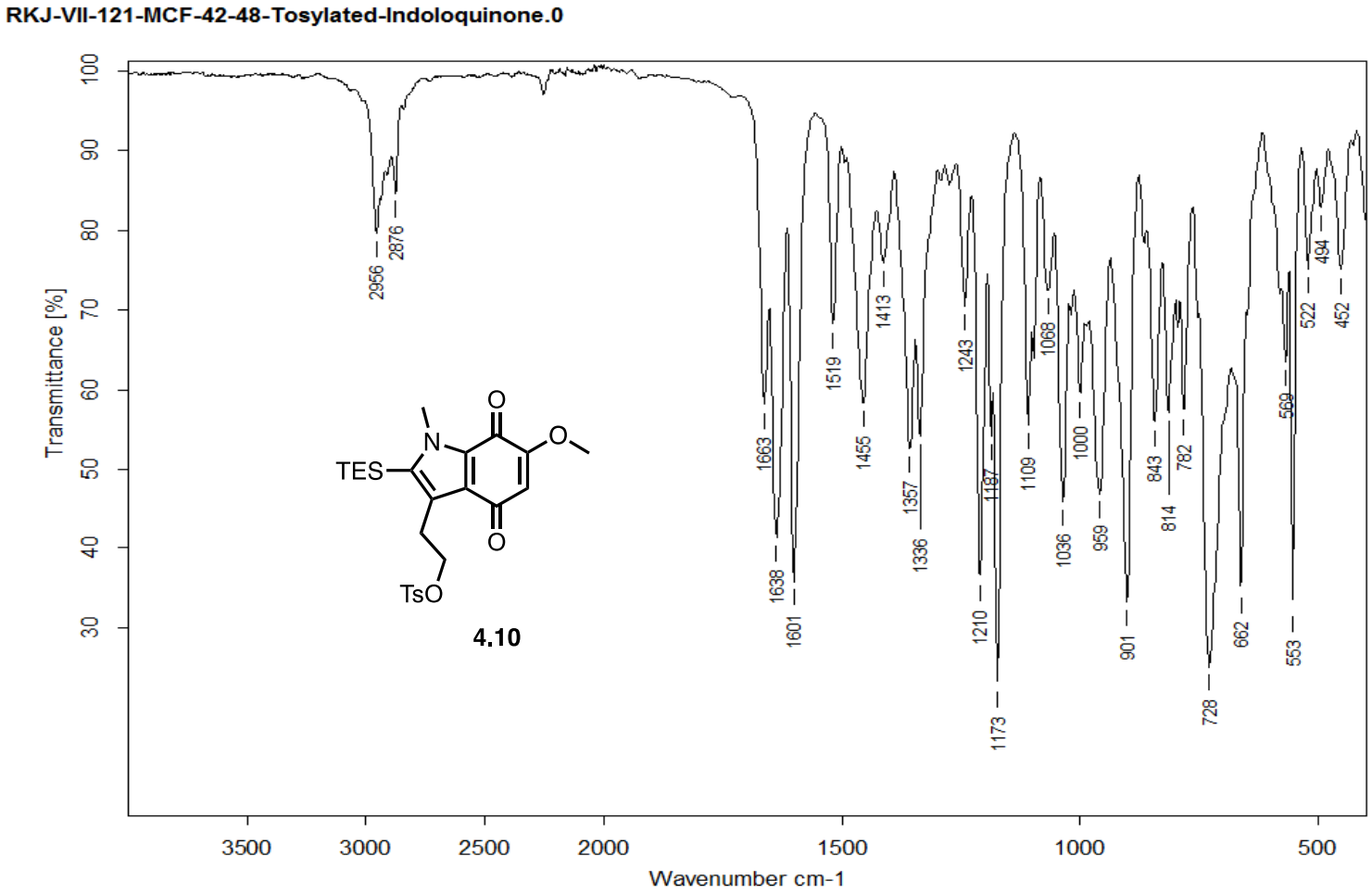


Figure D.22 **FTIR** (thin film) Tosylate **4.10**

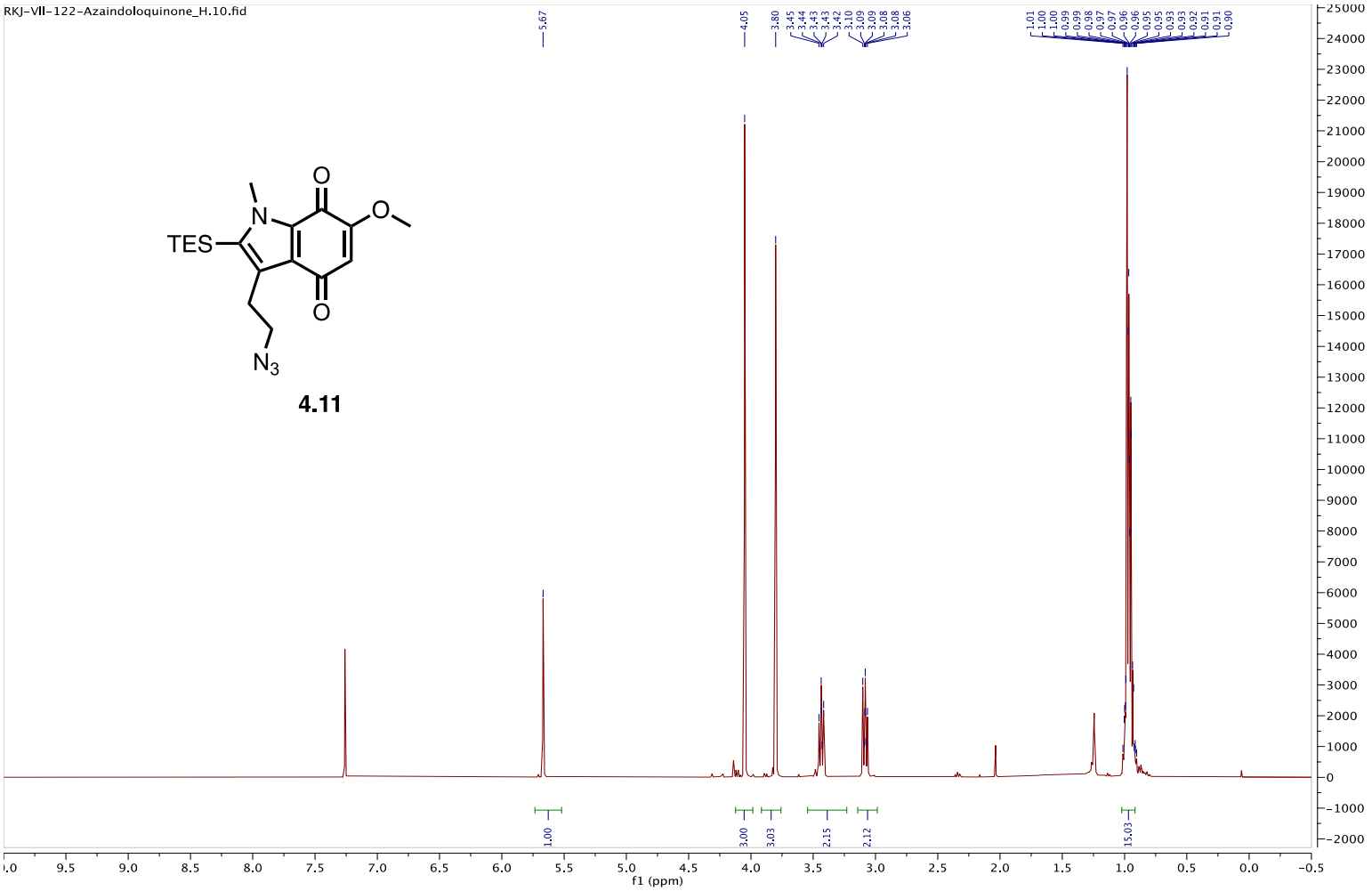


Figure D.23 **^{1}H NMR** (400 MHz, $CDCl_3$) Azide **4.11**

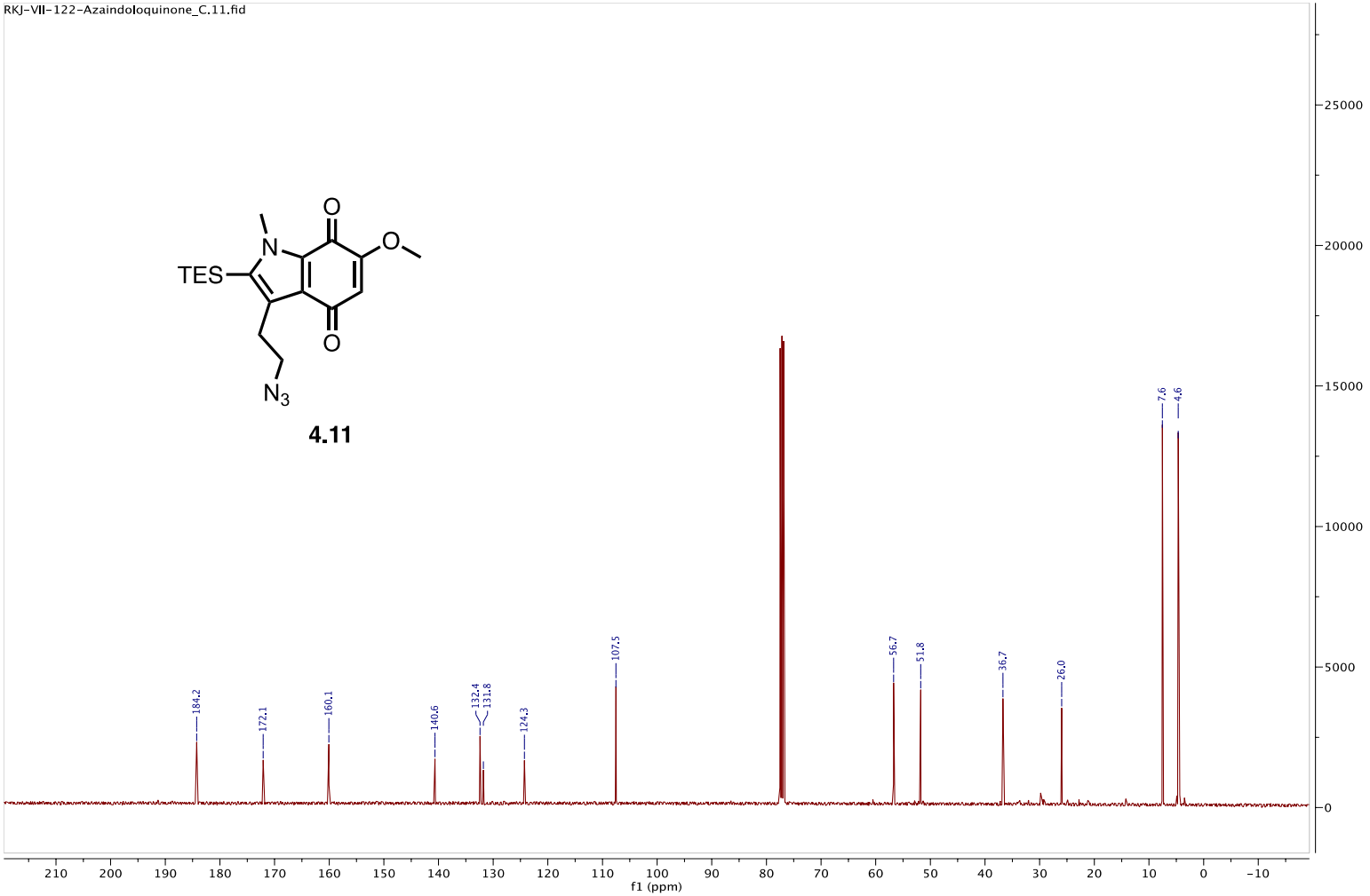


Figure D.24 **^{13}C NMR** ($CDCl_3$) Azide **4.11**

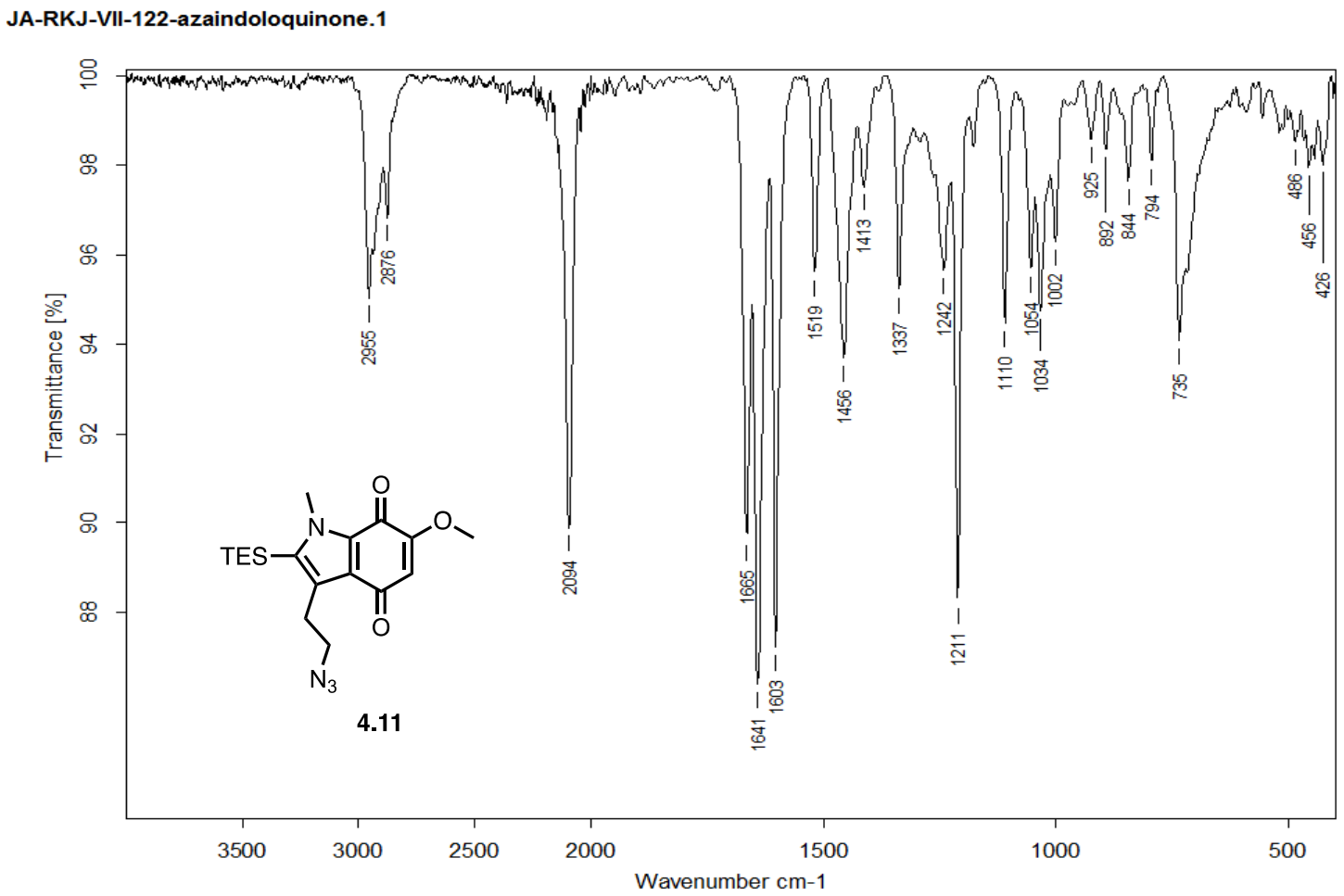


Figure D.25 **FTIR** (thin film) Azide **4.11**

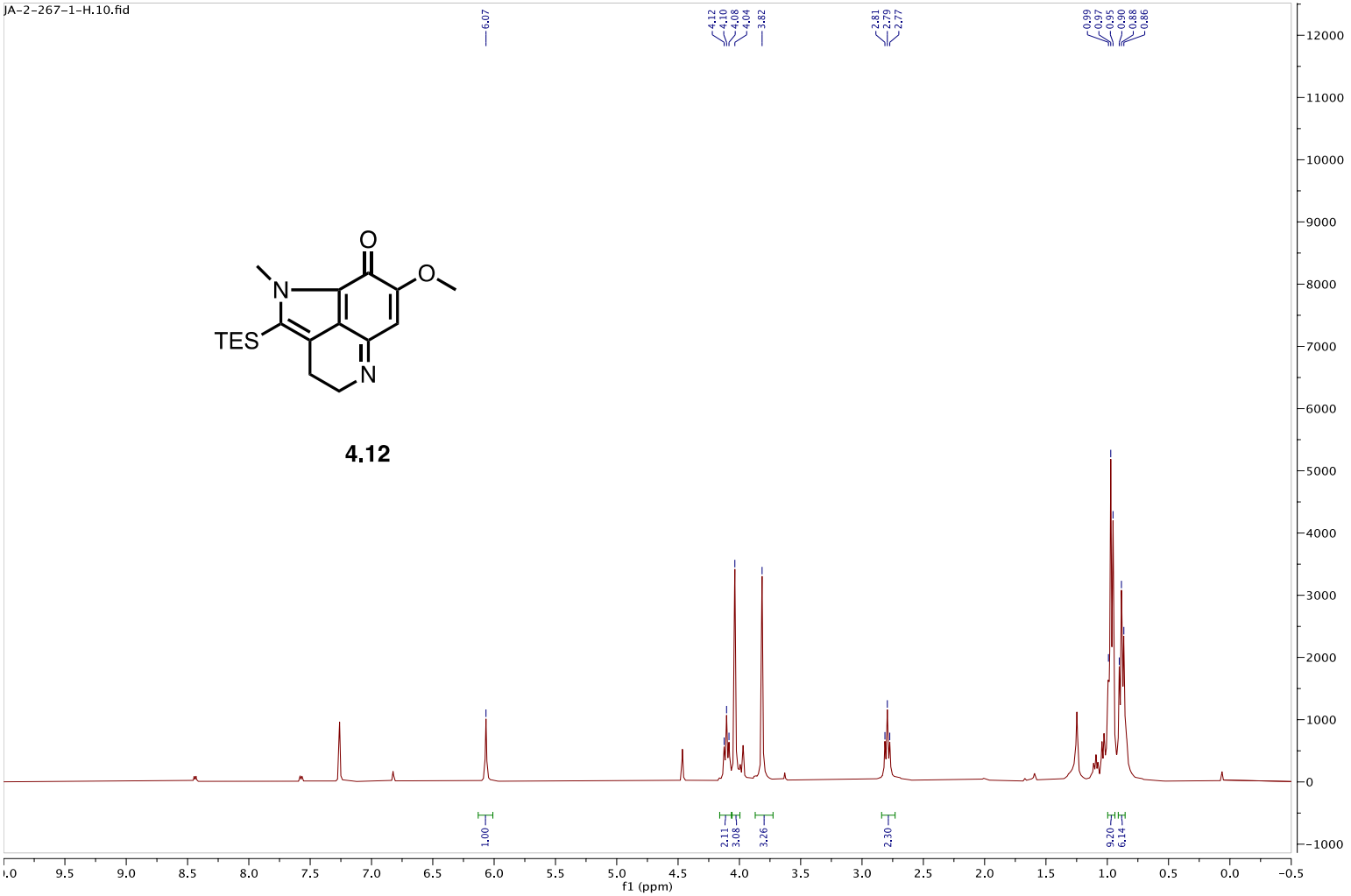


Figure D.26 **^{1}H NMR** (400 MHz, $CDCl_3$) Pyrroloiminoquinone **4.12**

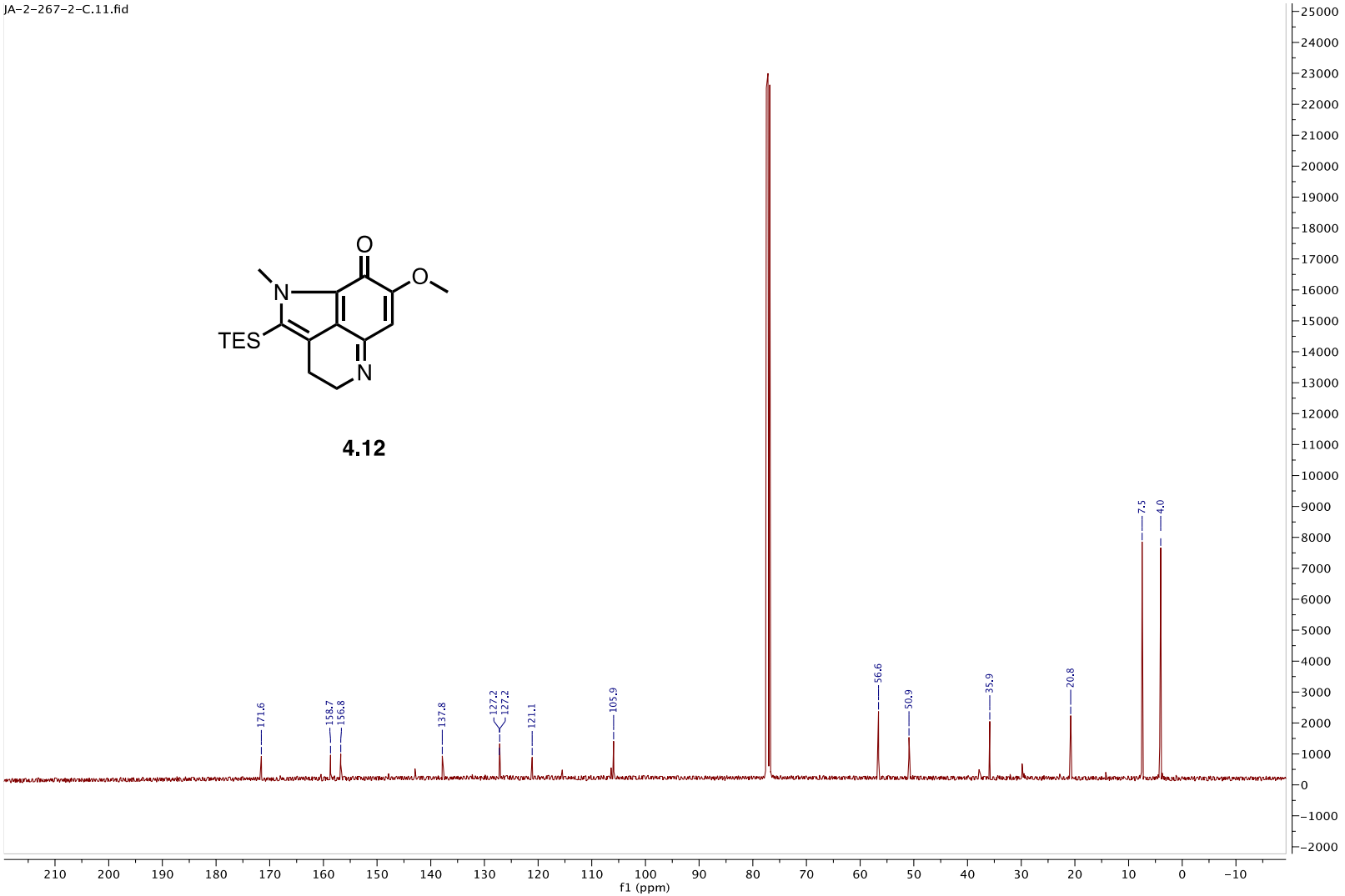


Figure D.27 **^{13}C NMR** (101 MHz, $CDCl_3$) Pyrroloiminoquinone **4.12**

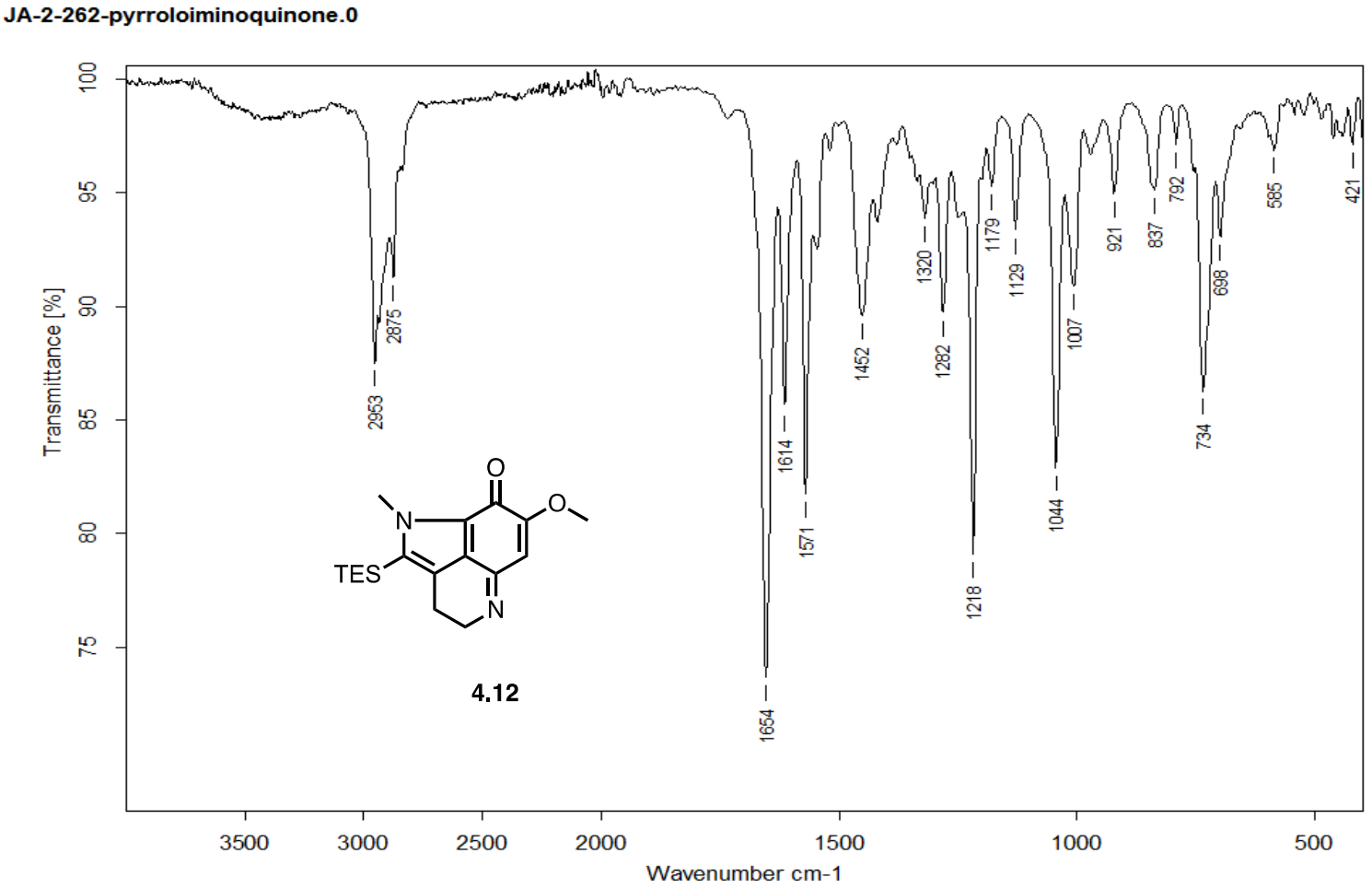


Figure D.28 **FTIR** (thin film) Pyrroloiminoquinone **4.12**

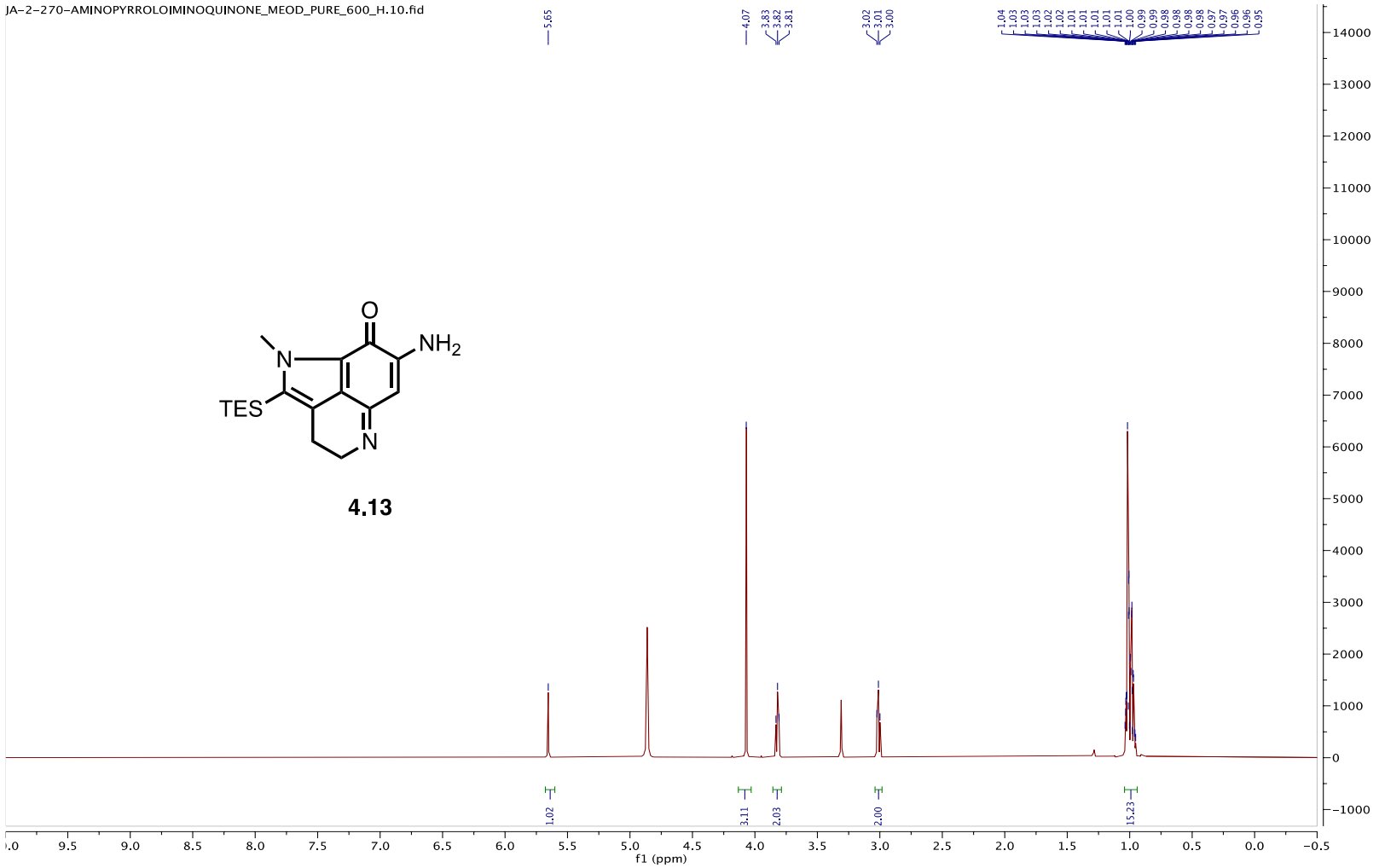


Figure D.29 **^{1}H NMR** (600 MHz, Methanol-*d4*) Vinylogous Amidine **4.13**

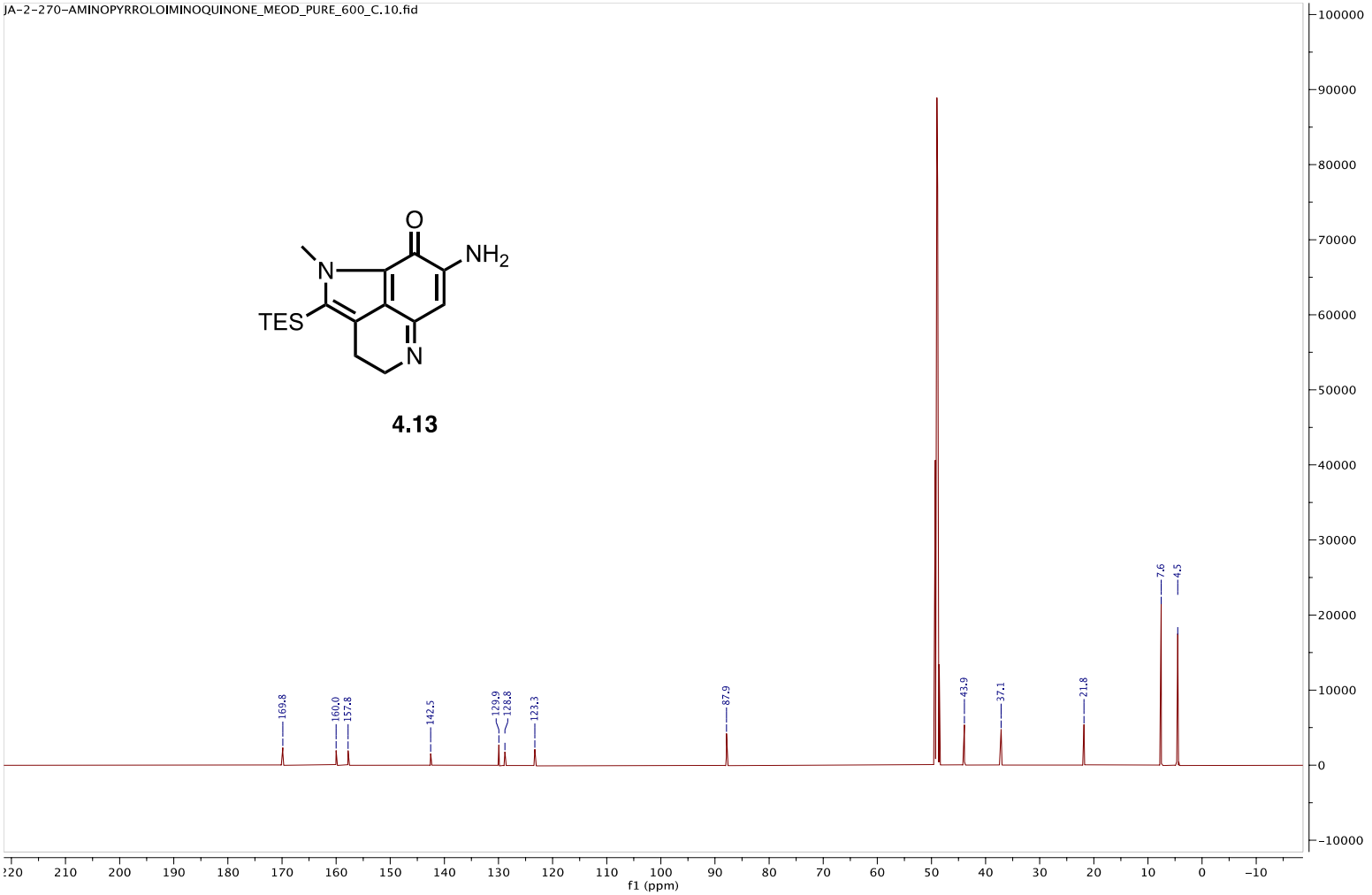


Figure D.30 **^{13}C NMR** (151MHz, Methanol-*d4*) Vinylogous Amidine **4.13**

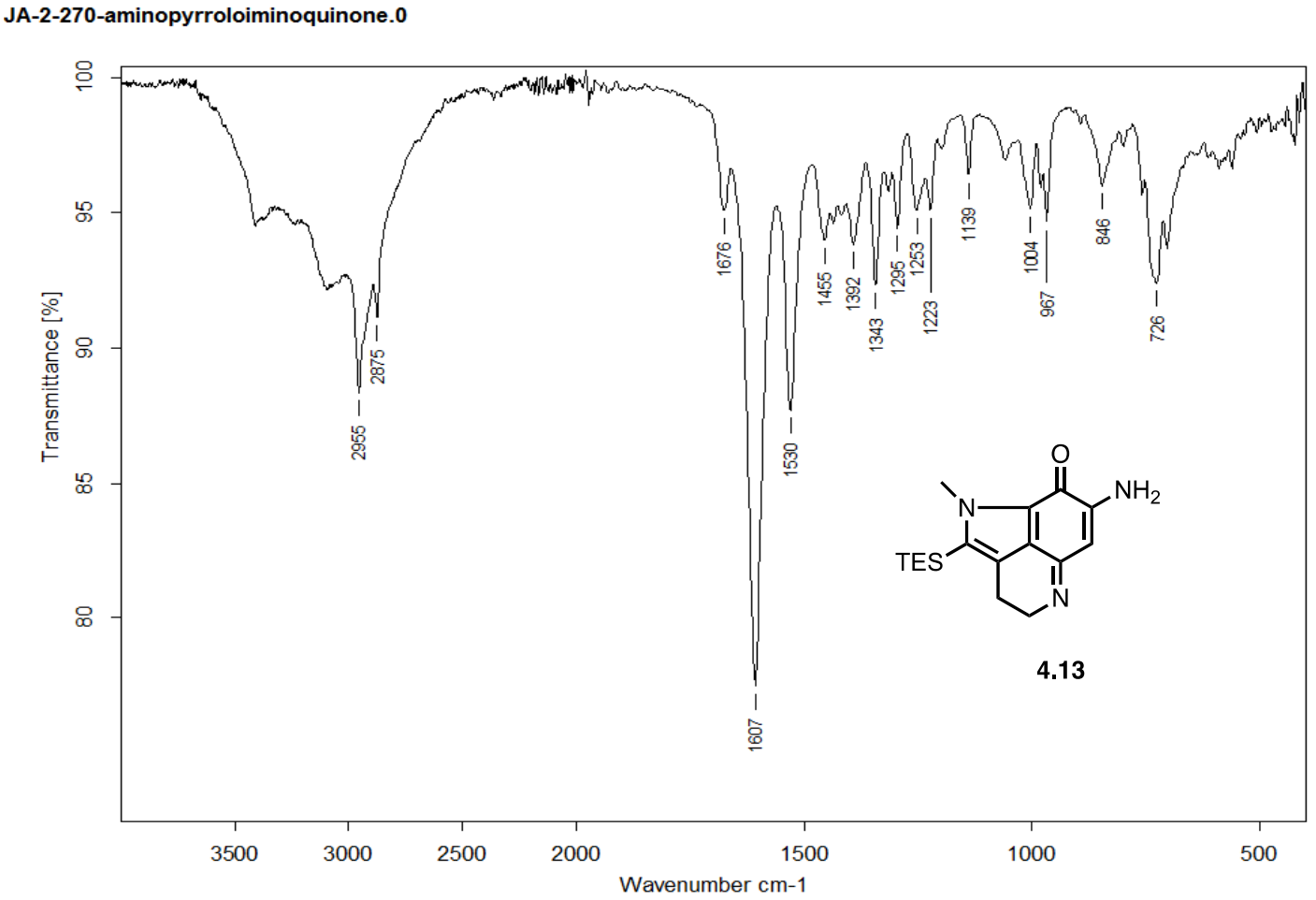


Figure D.31 **FTIR** (thin film) Vinylogous Amidine **4.13**

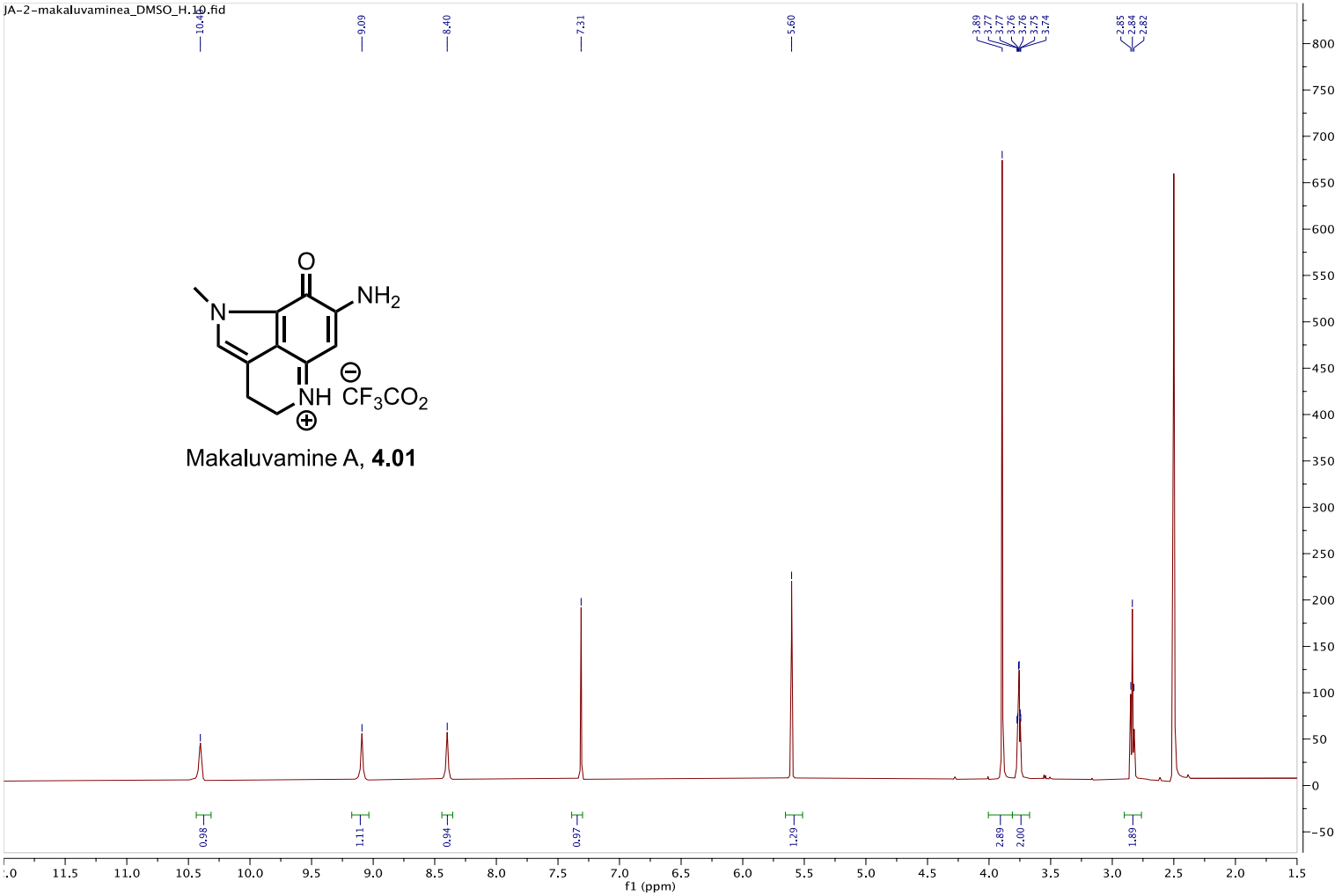


Figure D.32 **^{1}H NMR** (600 MHz, DMSO-*d6*) Makaluvamine A **4.01**

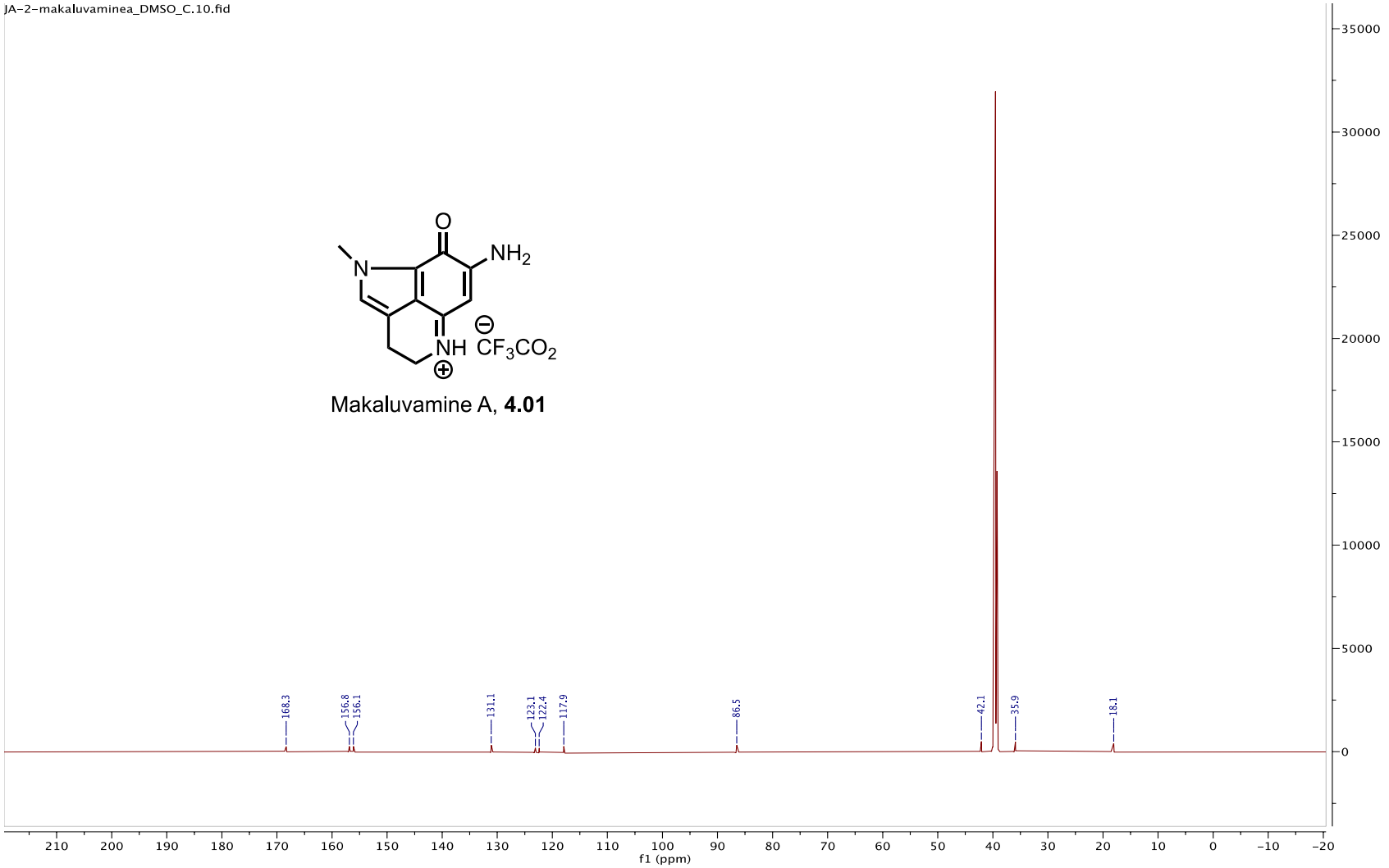


Figure D.33 **^{13}C NMR** (151 MHz, DMSO-*d6*) Makaluvamine A **4.01**

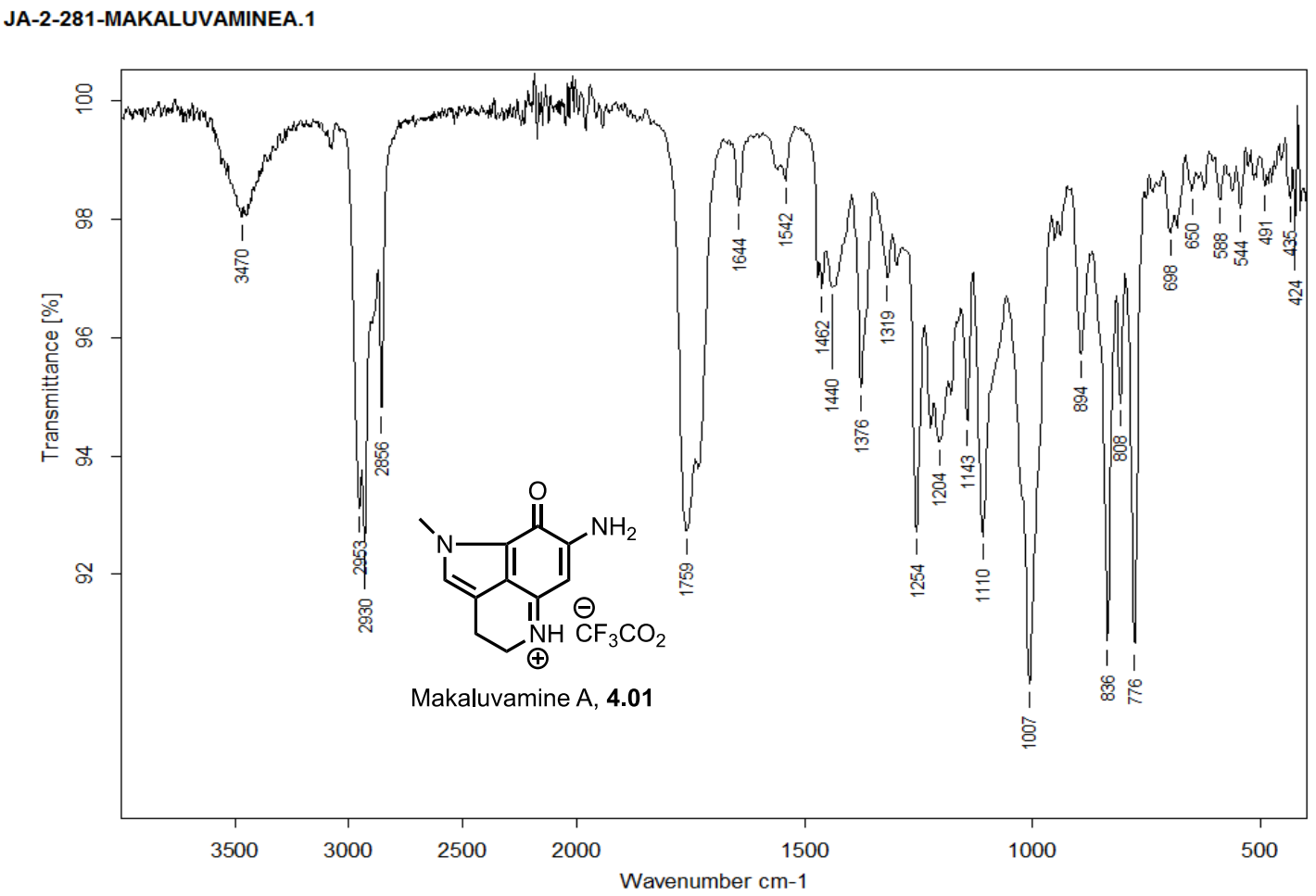


Figure D.34 **FTIR** (thin film) Makaluvamine A **4.01**

APPENDIX E

Spectra Relevant to Chapter Five

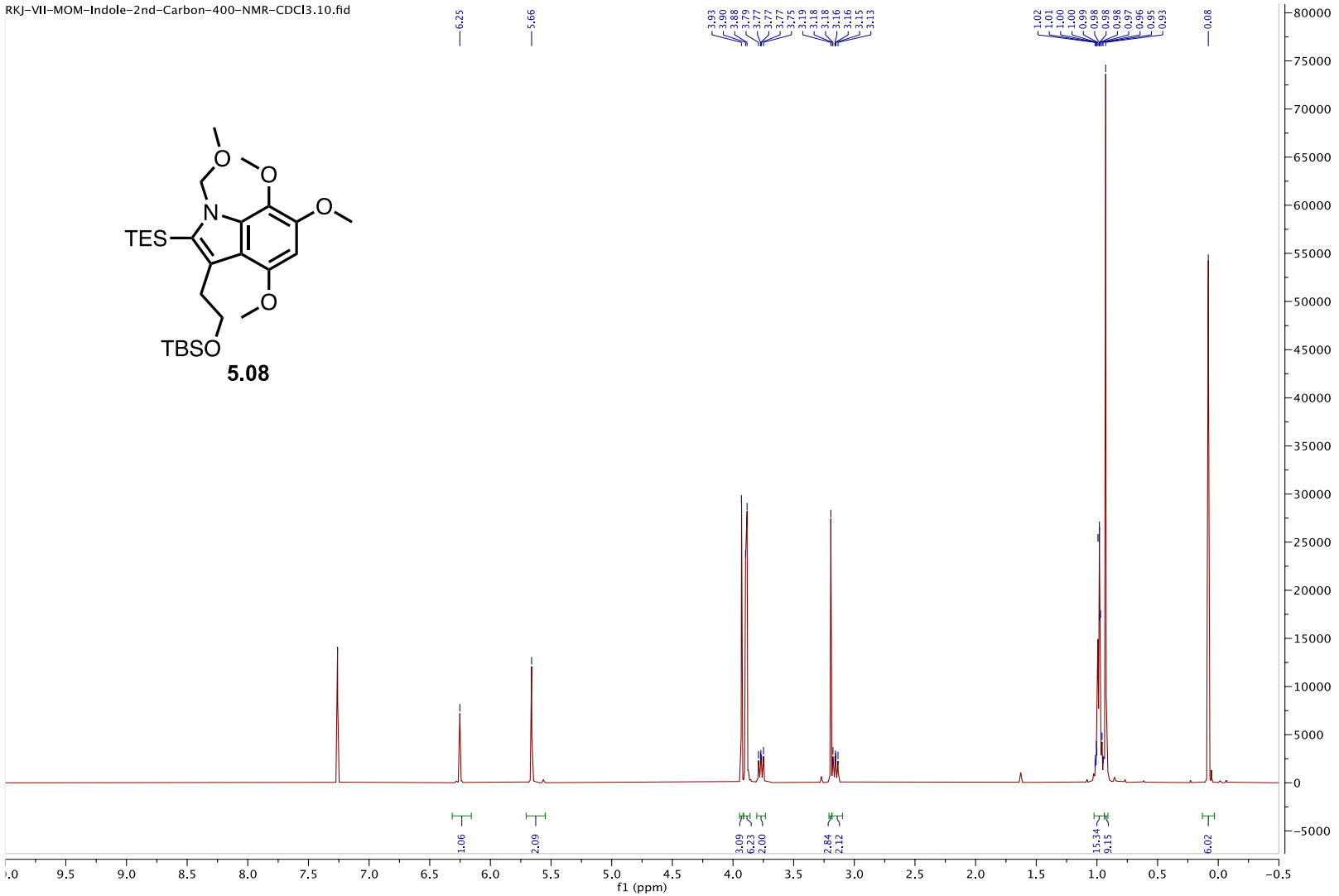


Figure E.01. **^{1}H NMR** (400 MHz, $CDCl_3$) MOM-Indole **5.08**

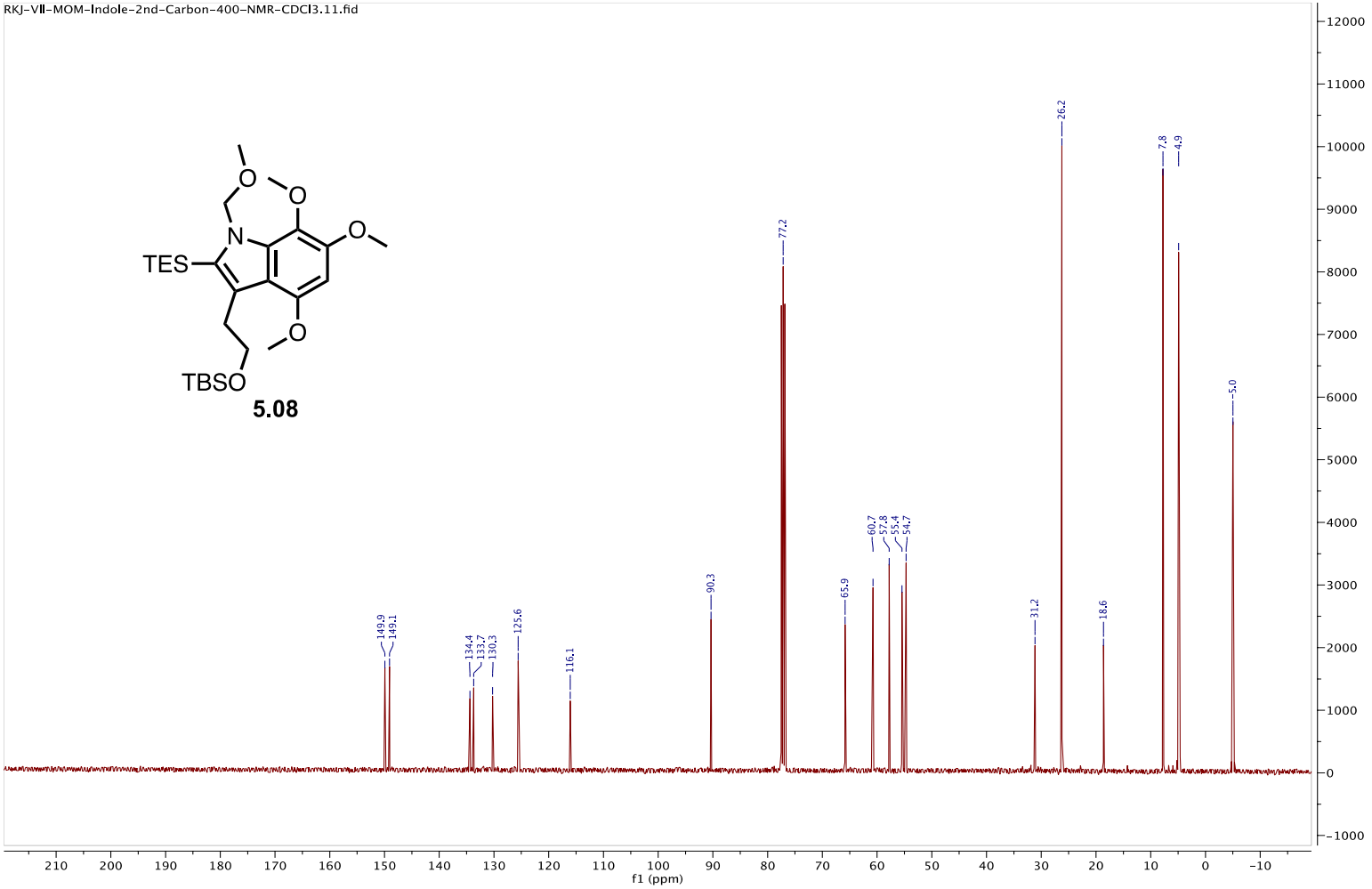


Figure E.02. **^{13}C NMR** (101 MHz, $CDCl_3$) MOM-Indole **5.08**

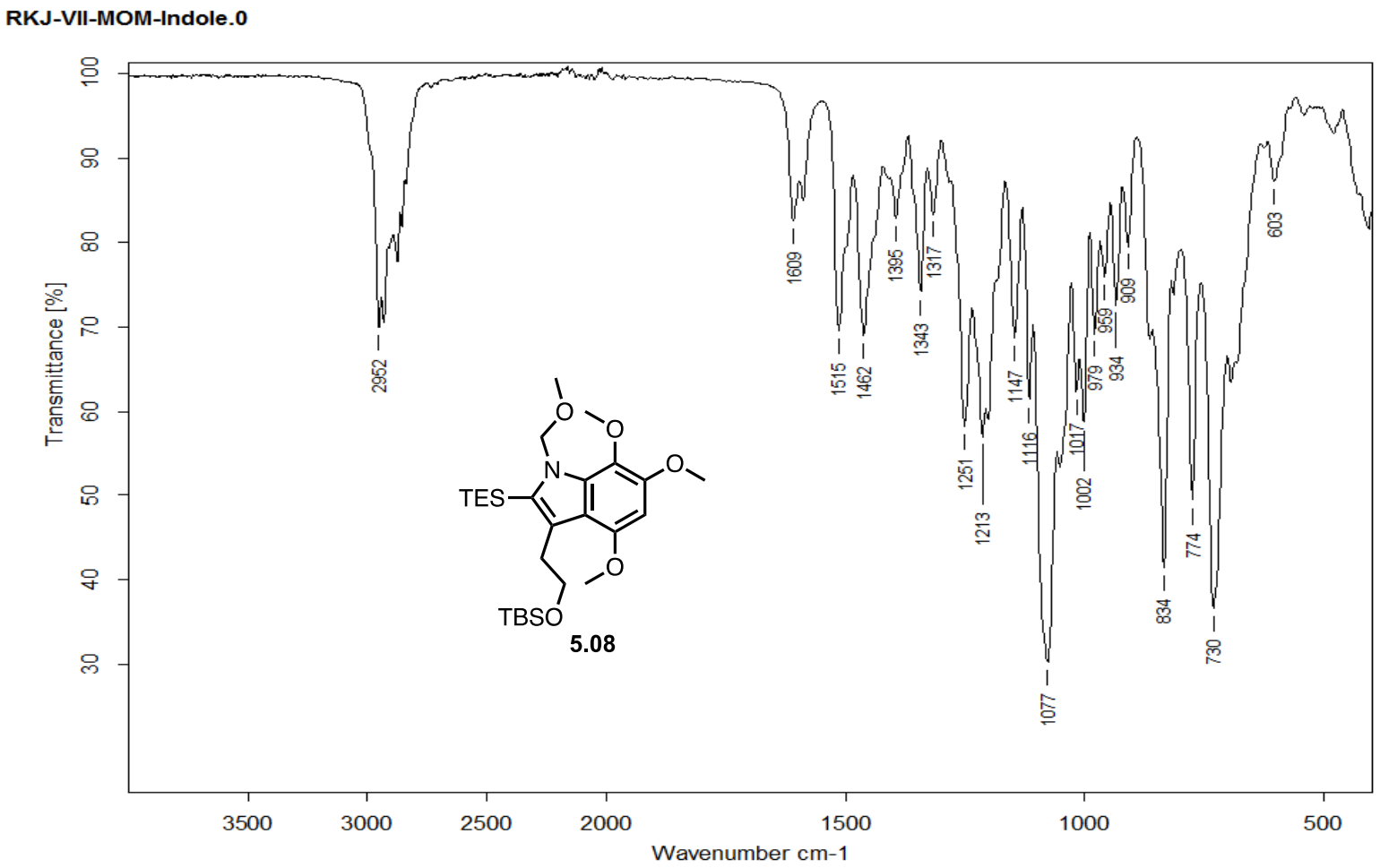


Figure E.03. **FTIR** (thin film) MOM-Indole **5.08**

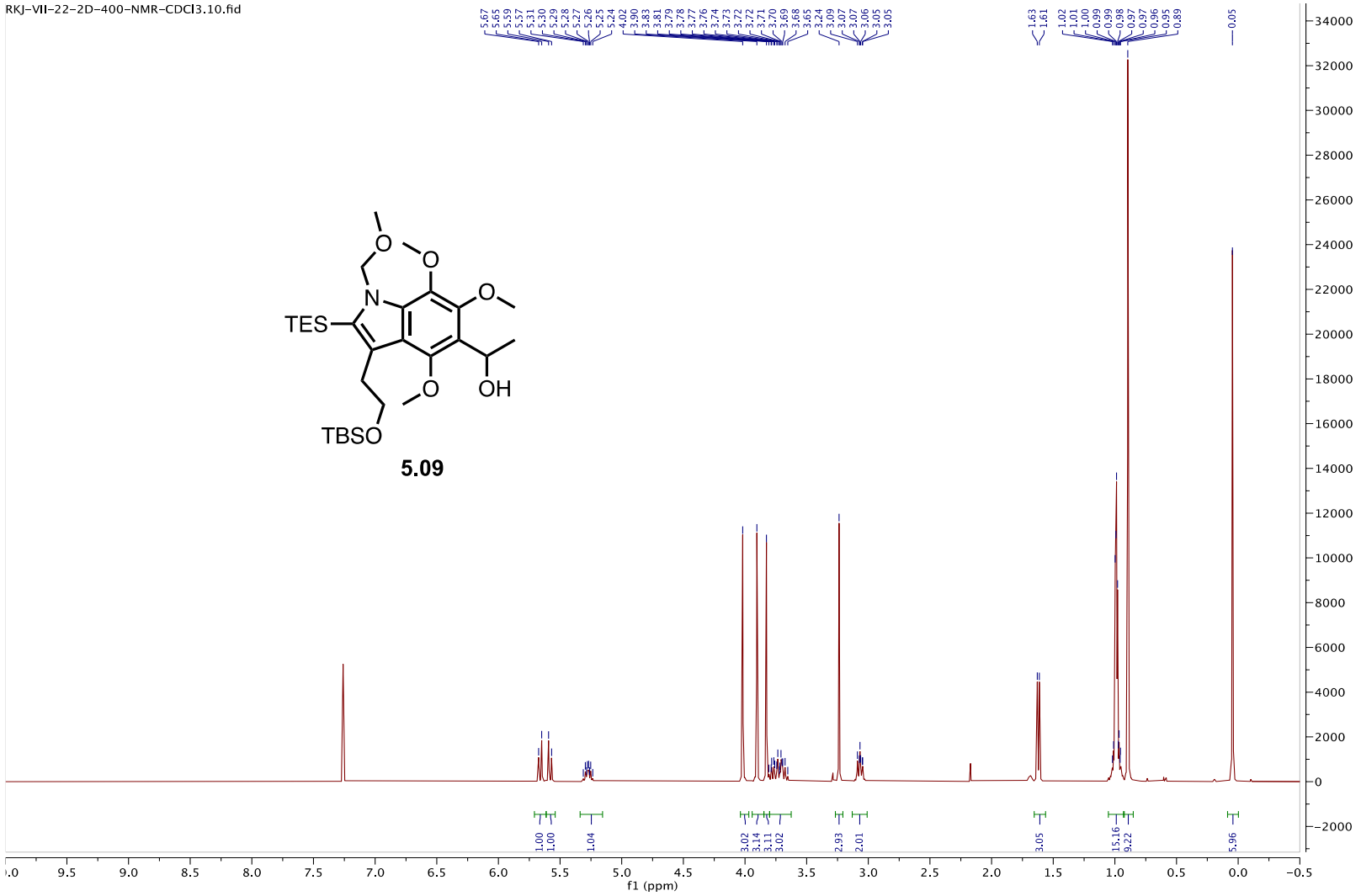


Figure E.04. **^{1}H NMR** (400 MHz, $CDCl_3$) Benzylic Alcohol **5.09**

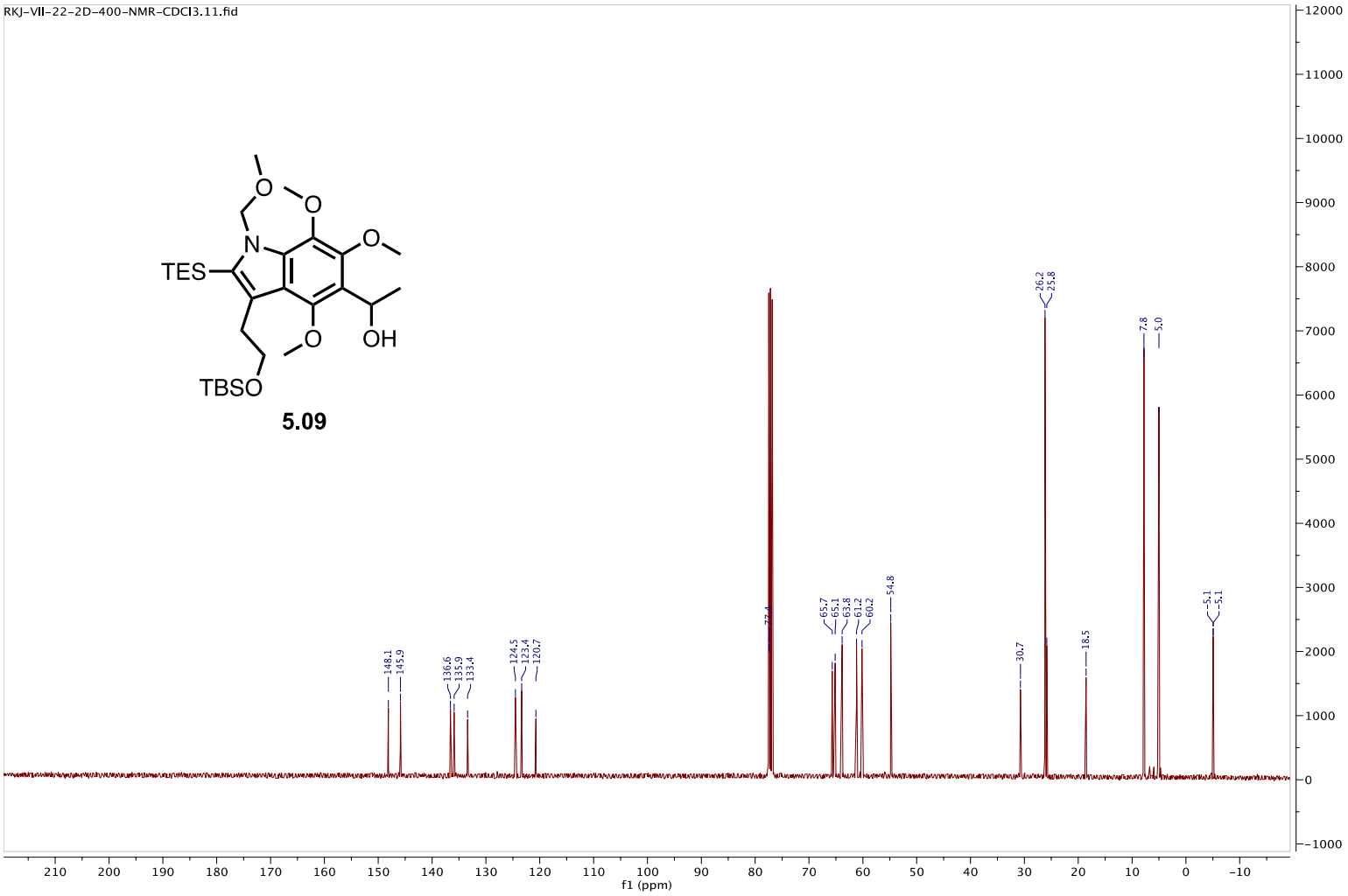


Figure E.05. **^{13}C NMR** (101 MHz, $CDCl_3$) Benzylic Alcohol **5.09**

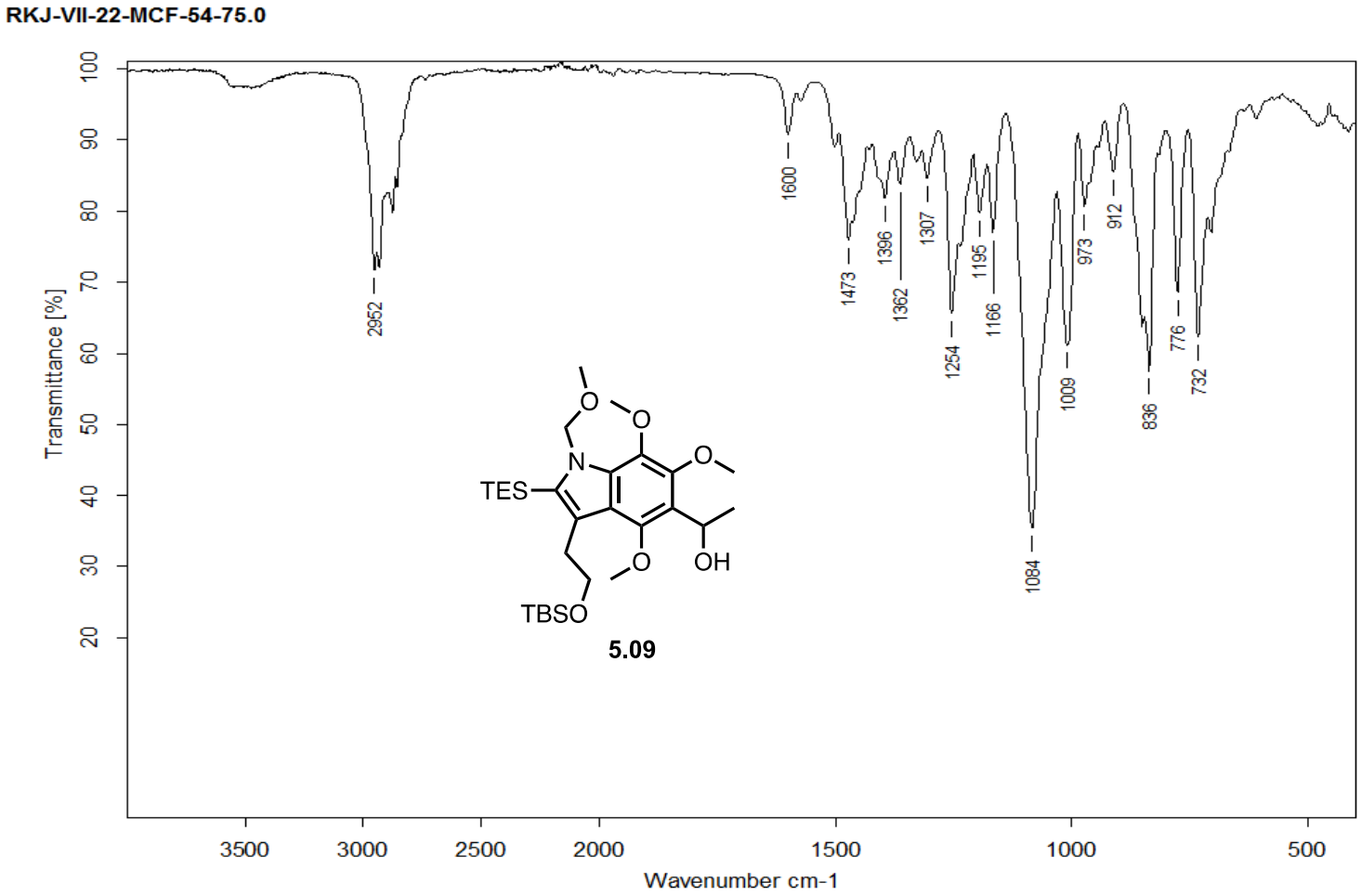


Figure E.06. **FTIR** (thin film) Benzylic Alcohol **5.09**

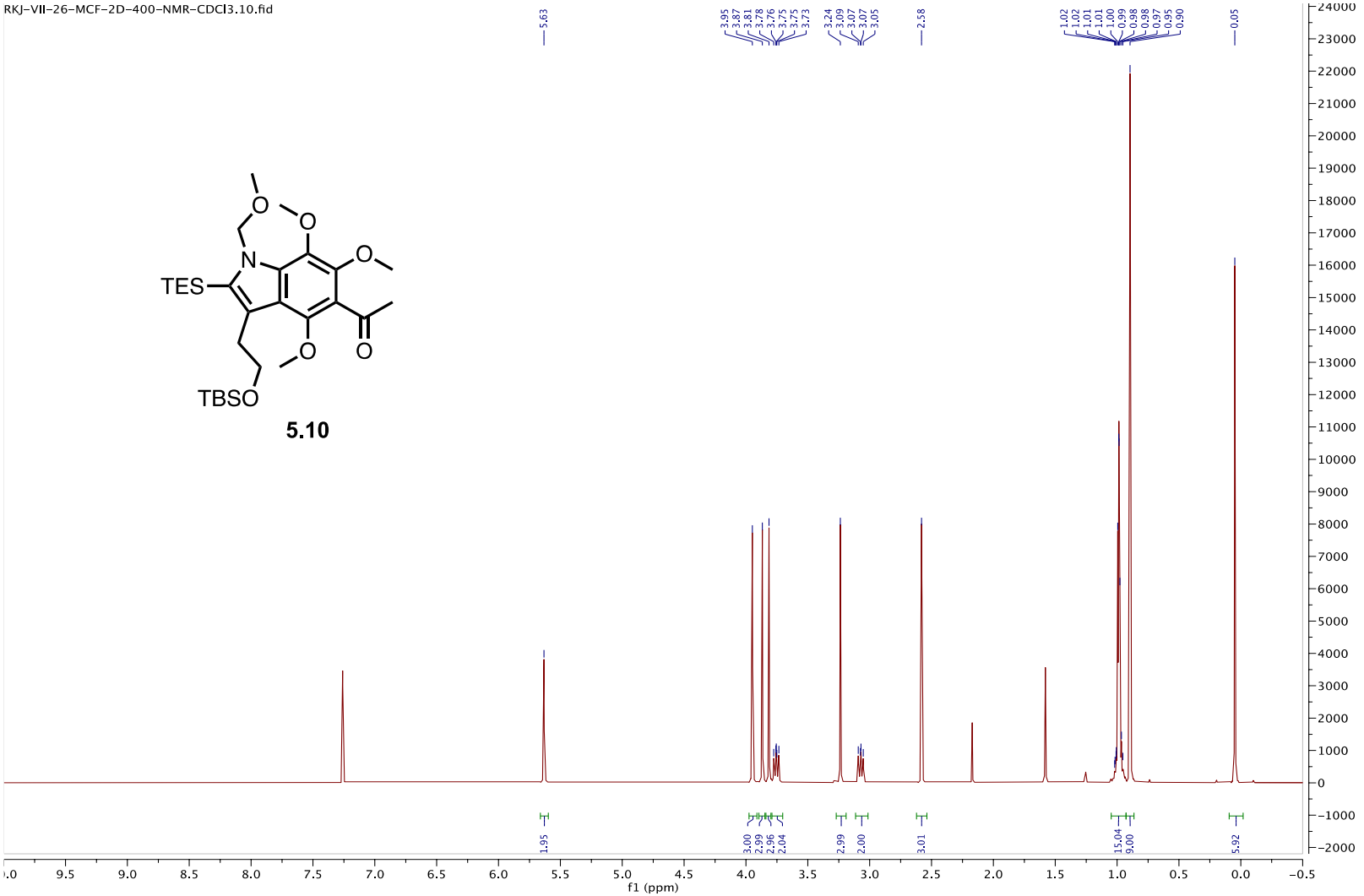


Figure E.07. **^{1}H NMR** (400 MHz, $CDCl_3$) Ketone **5.10**

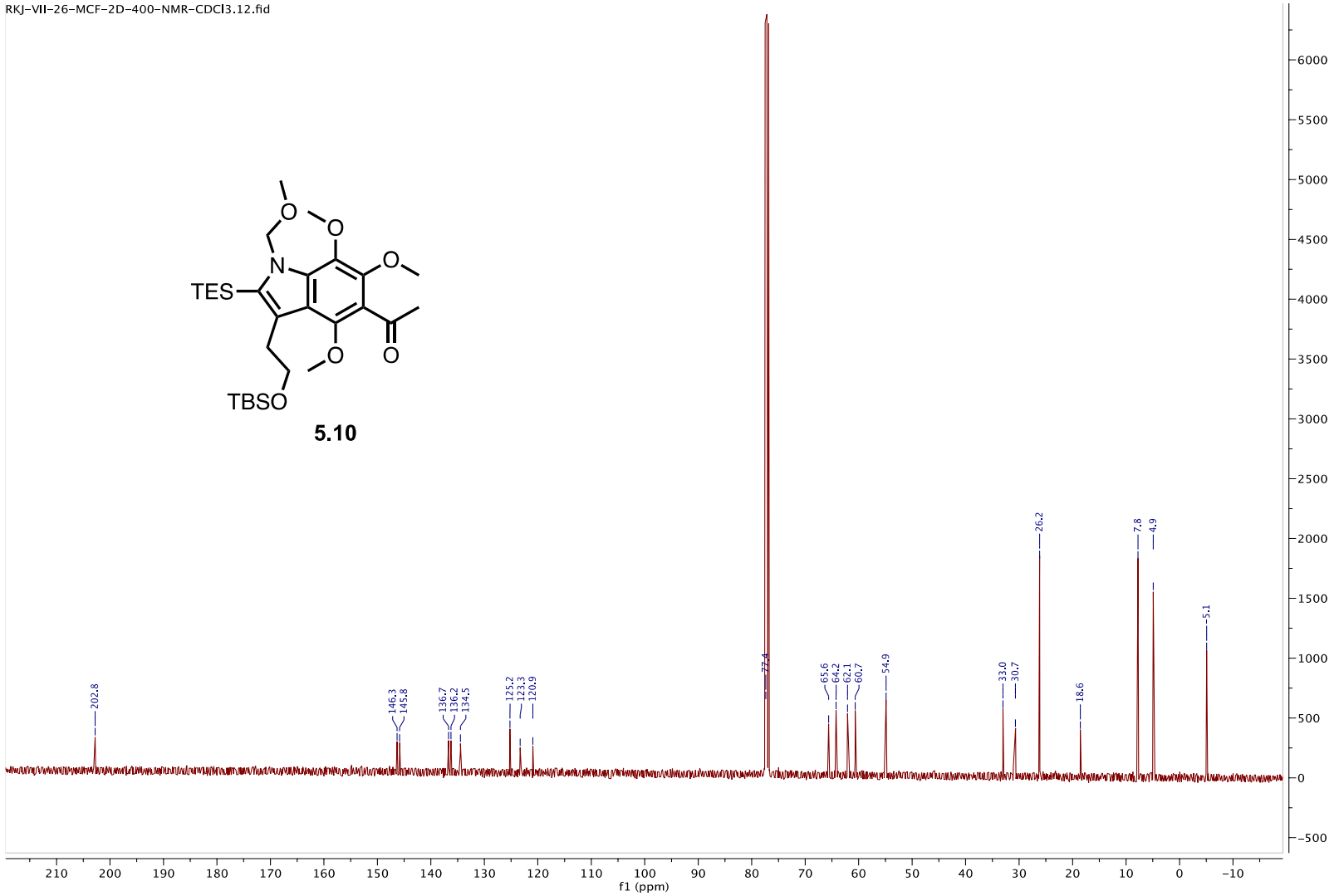


Figure E.08. **^{13}C NMR** (101 MHz, $CDCl_3$) Ketone **5.10**

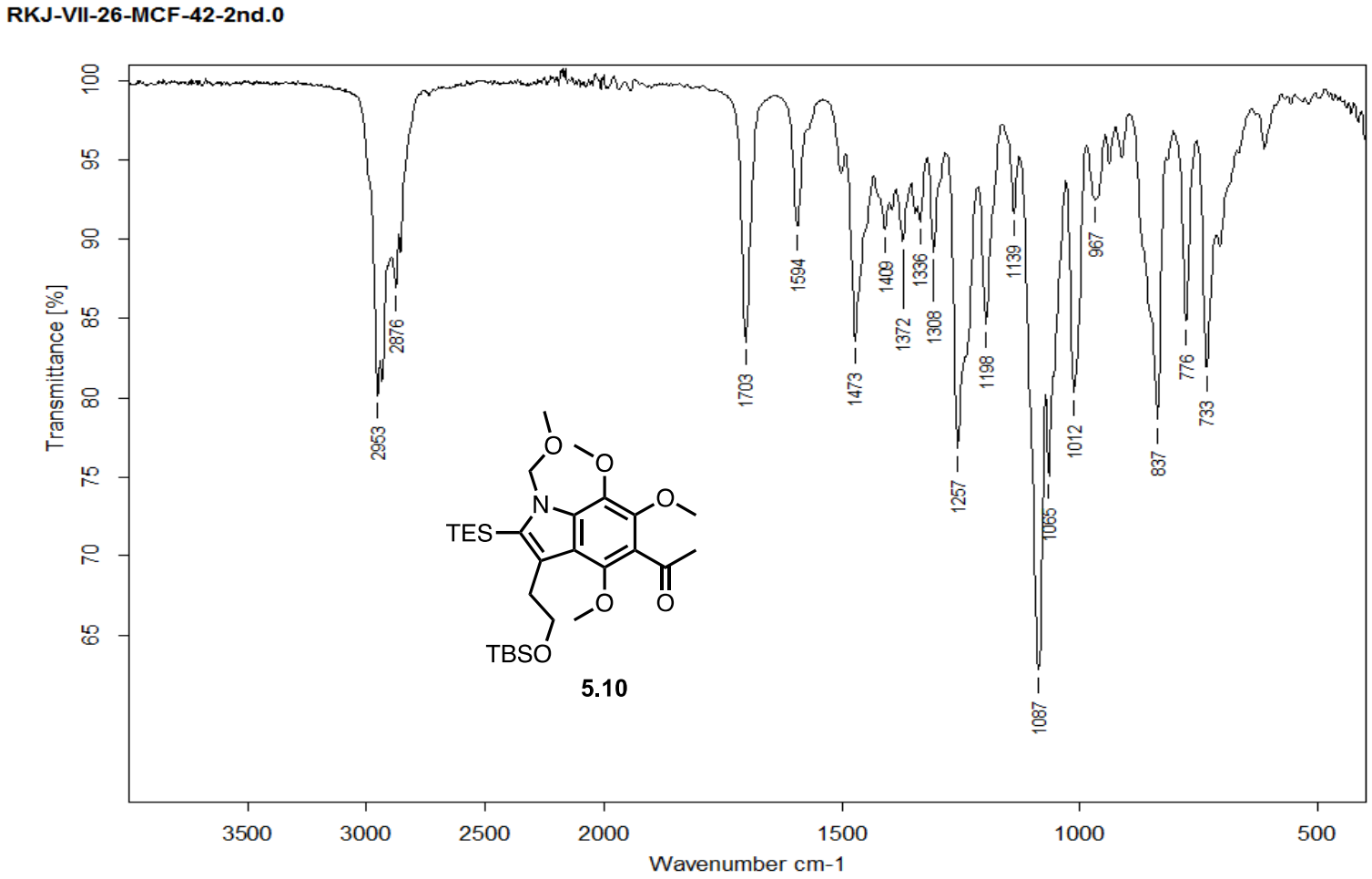


Figure E.09. **FTIR** (thin film) Ketone **5.10**

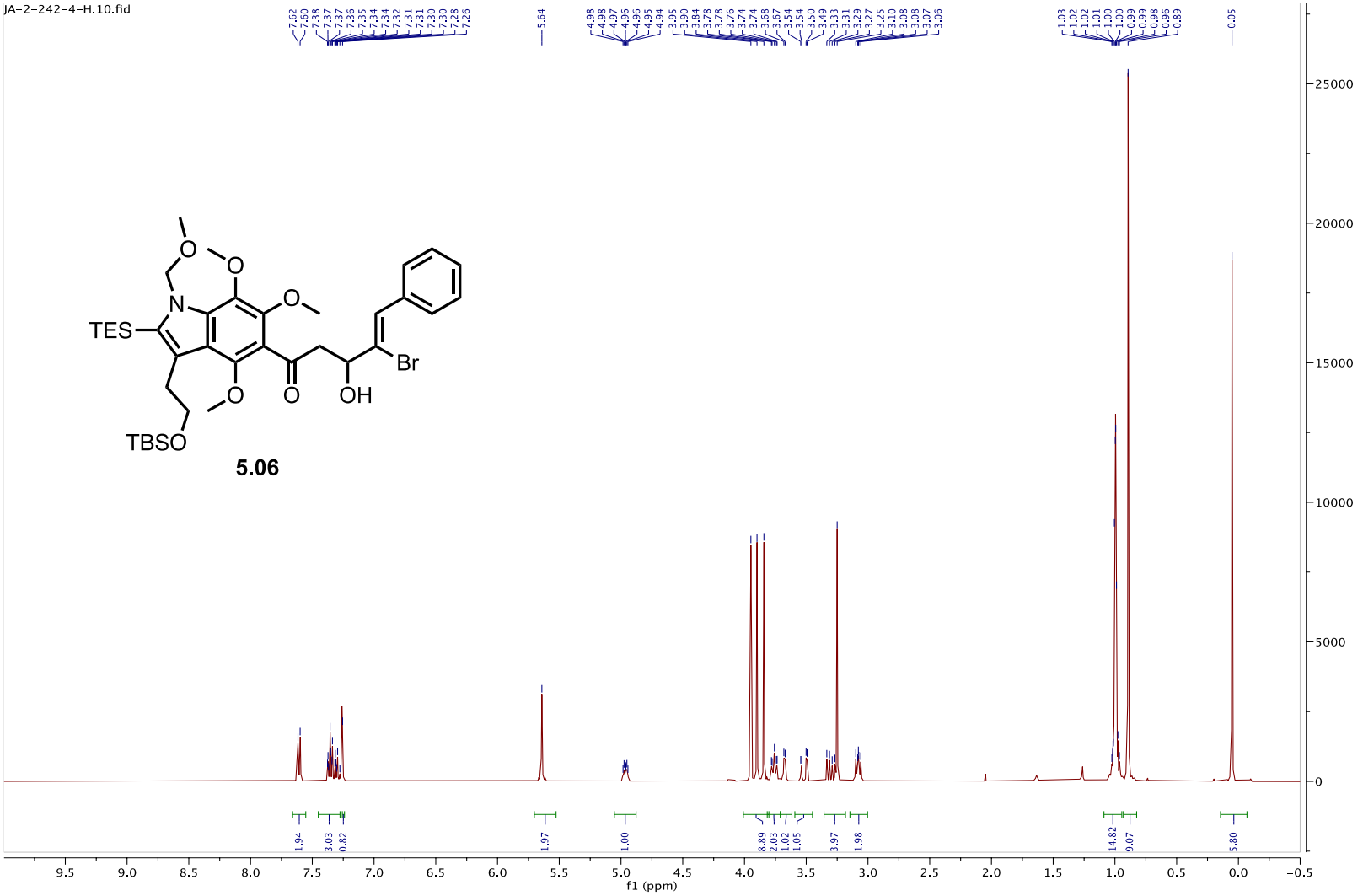


Figure E.10. **^{1}H NMR** (400 MHz, $CDCl_3$) β-Hydroxy Ketone **5.06**

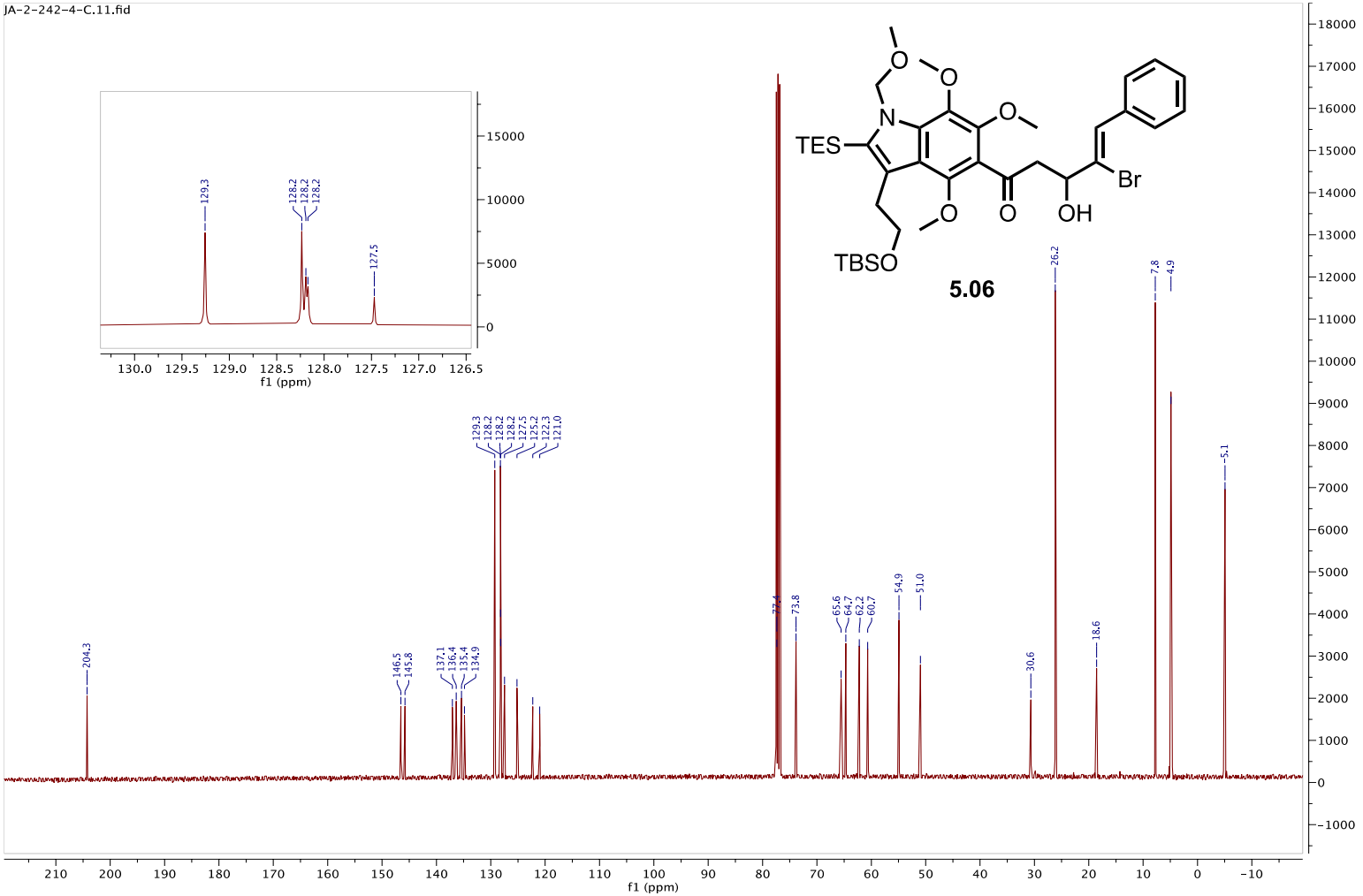


Figure E.11. **^{13}C NMR** ($CDCl_3$) β-Hydroxy Ketone **5.06**

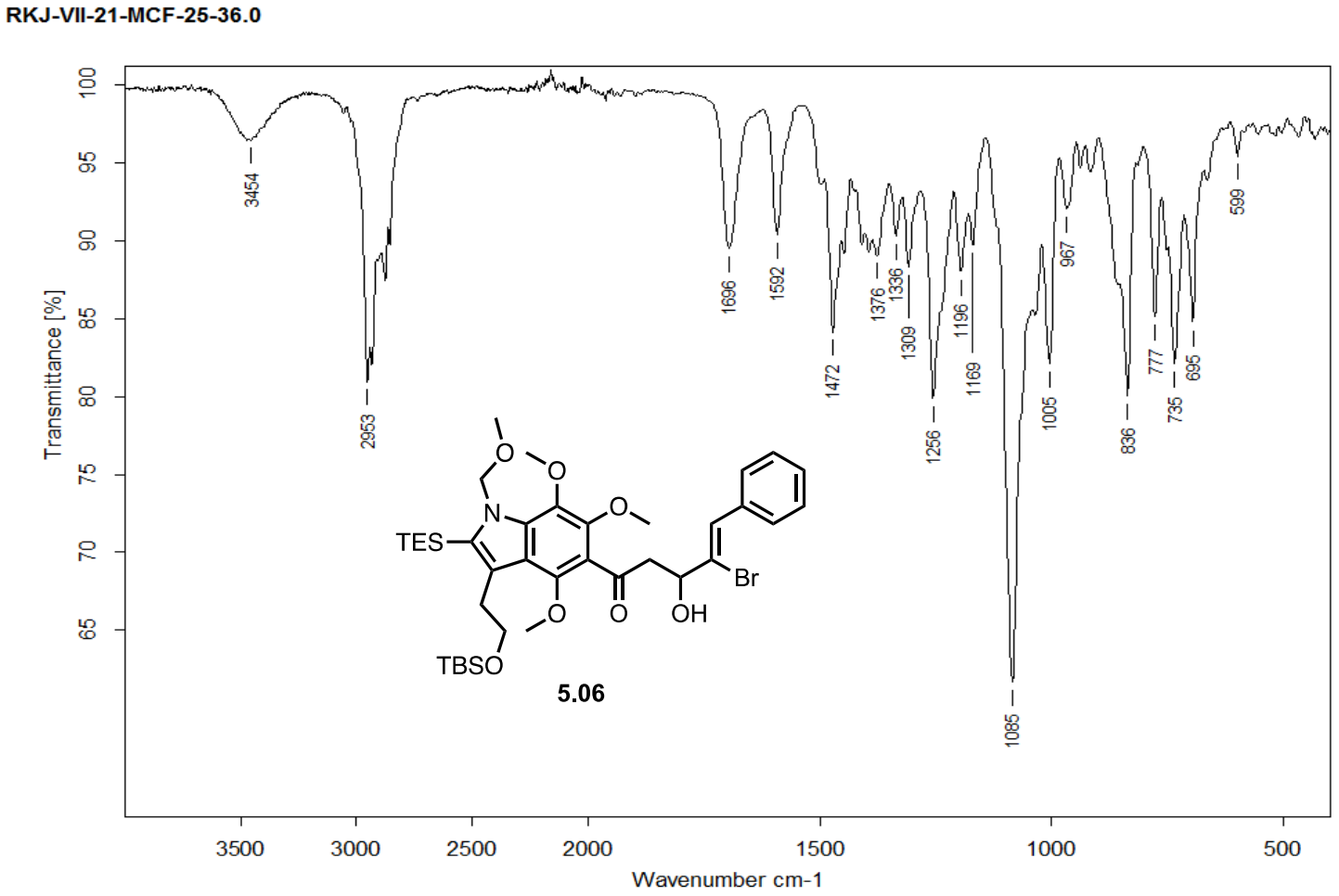


Figure E.12. **FTIR** (thin film) β-Hydroxy Ketone **5.06**

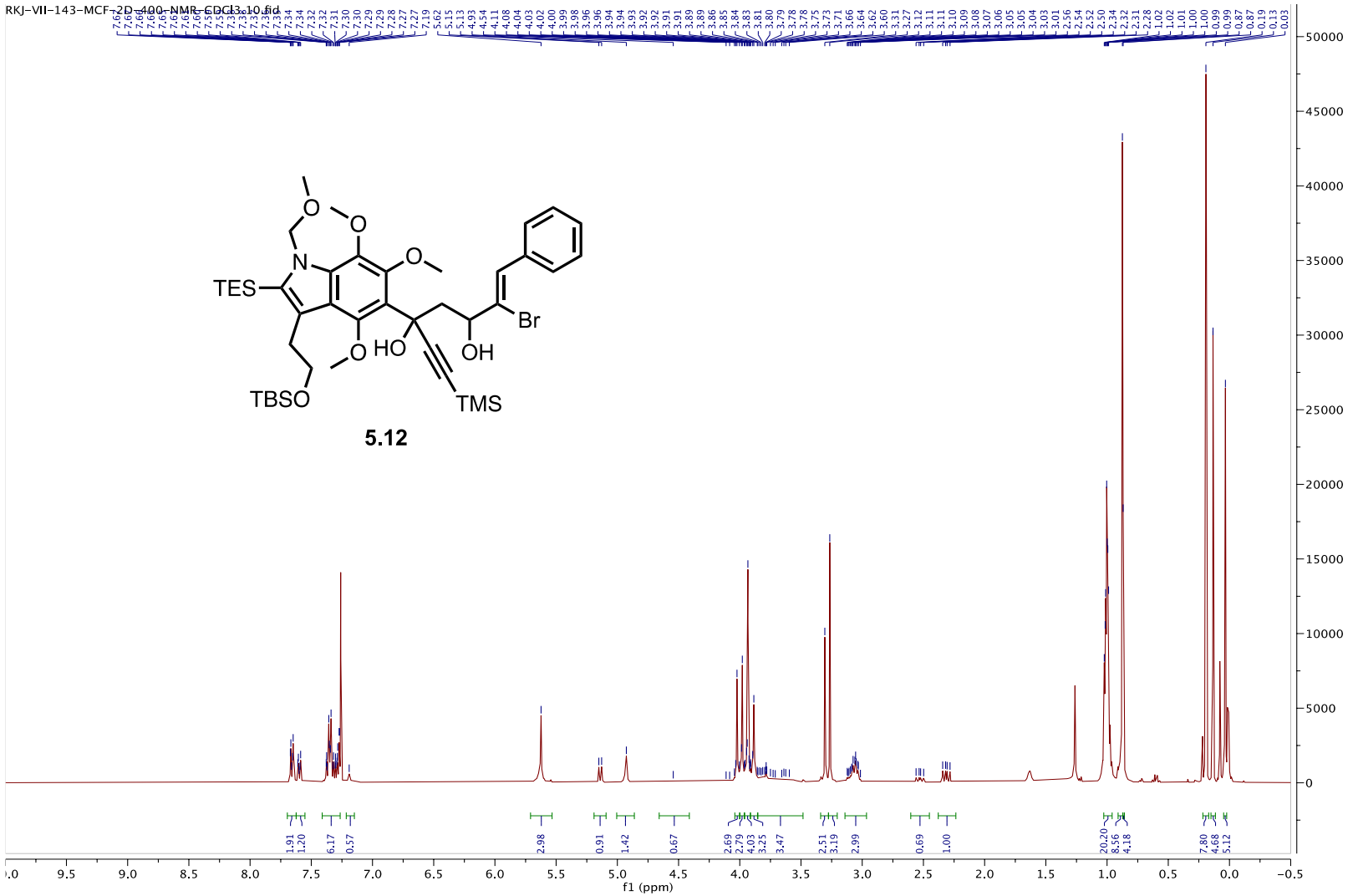


Figure E.13. **^{1}H NMR** (400 MHz, $CDCl_3$) 1,3-Diol **5.12**

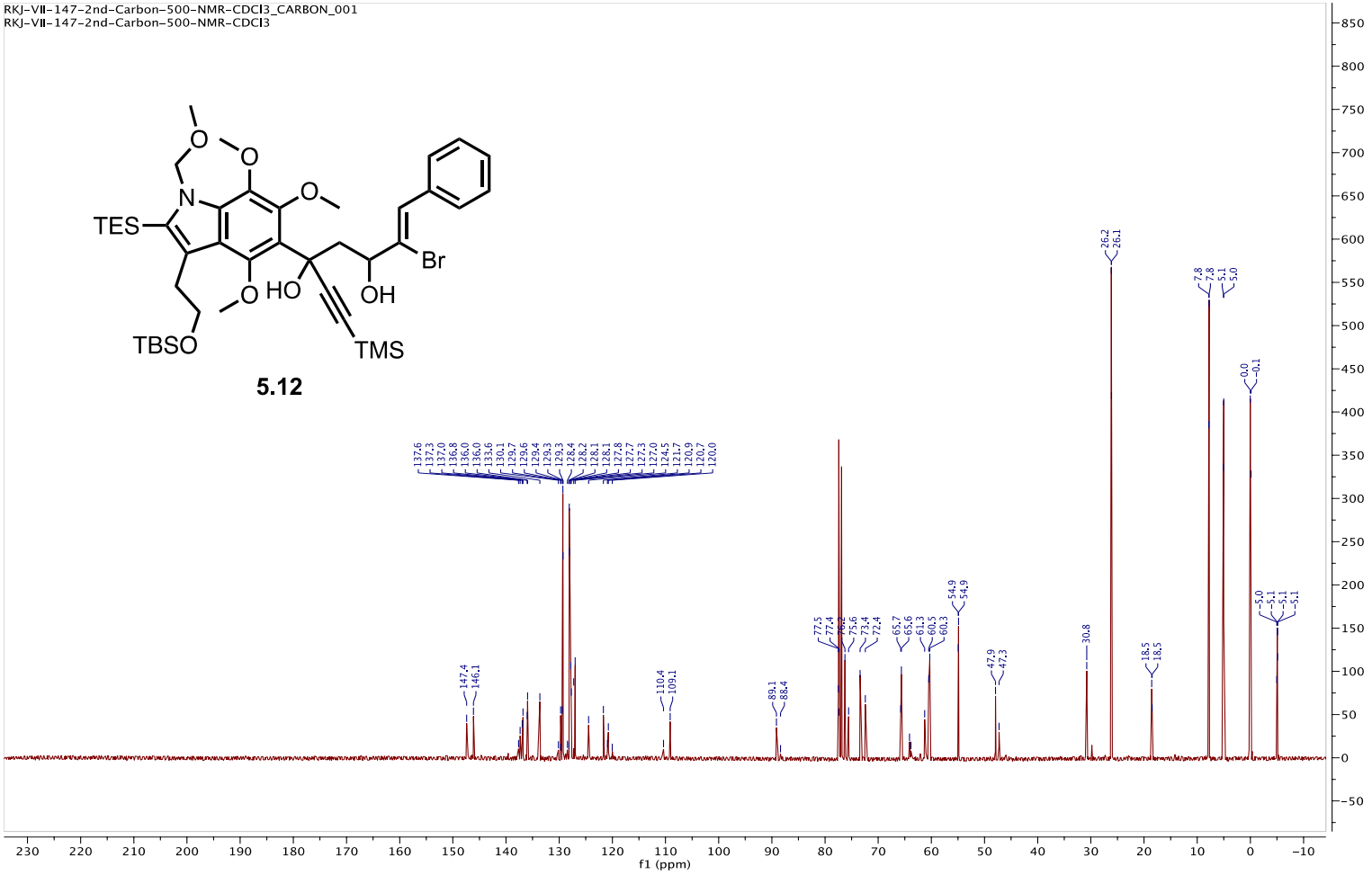


Figure E.14. **^{13}C NMR** (101 MHz, $CDCl_3$) 1,3-Diol **5.12**

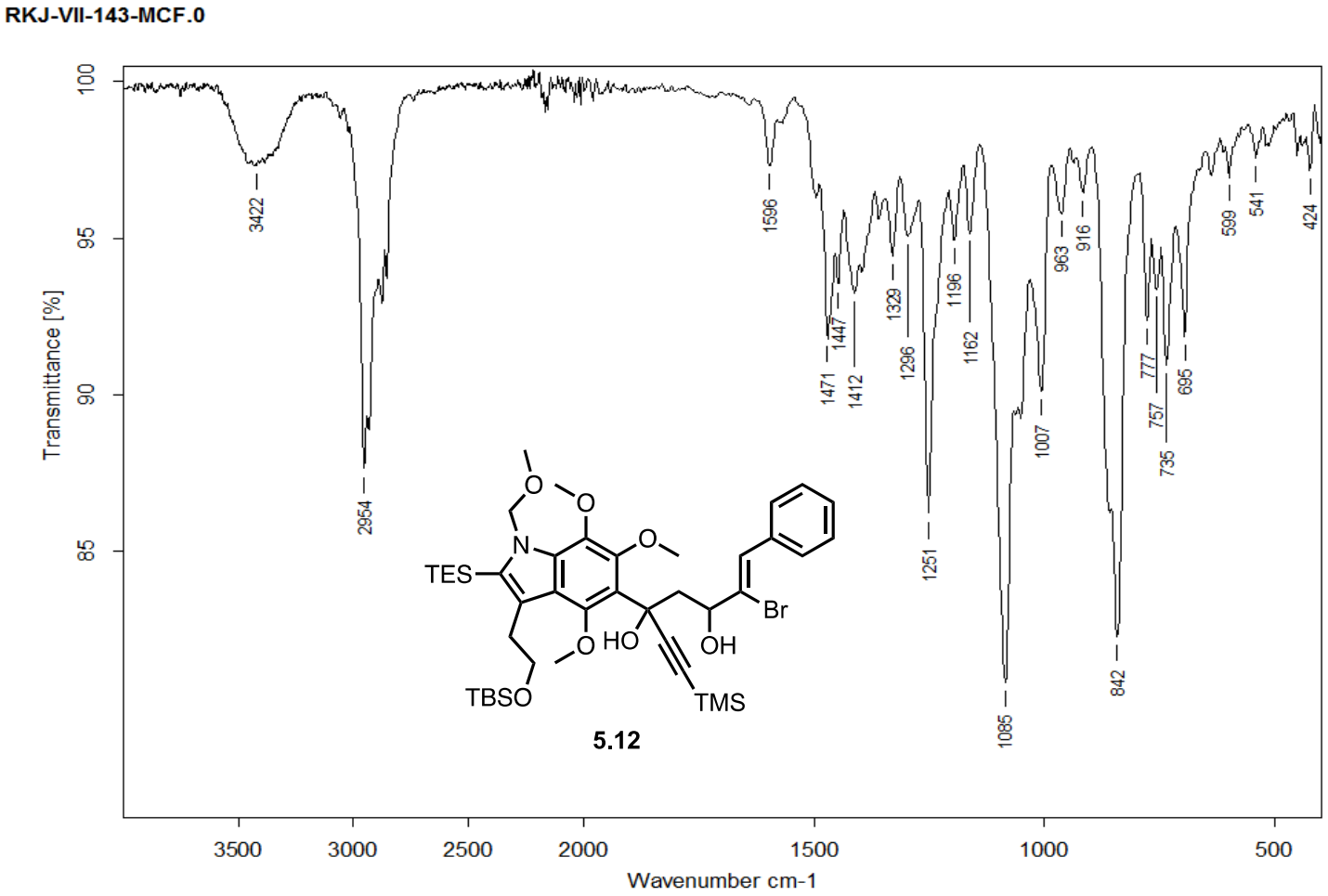


Figure E.15. **FTIR** (thin film) 1,3-Diol **5.12**

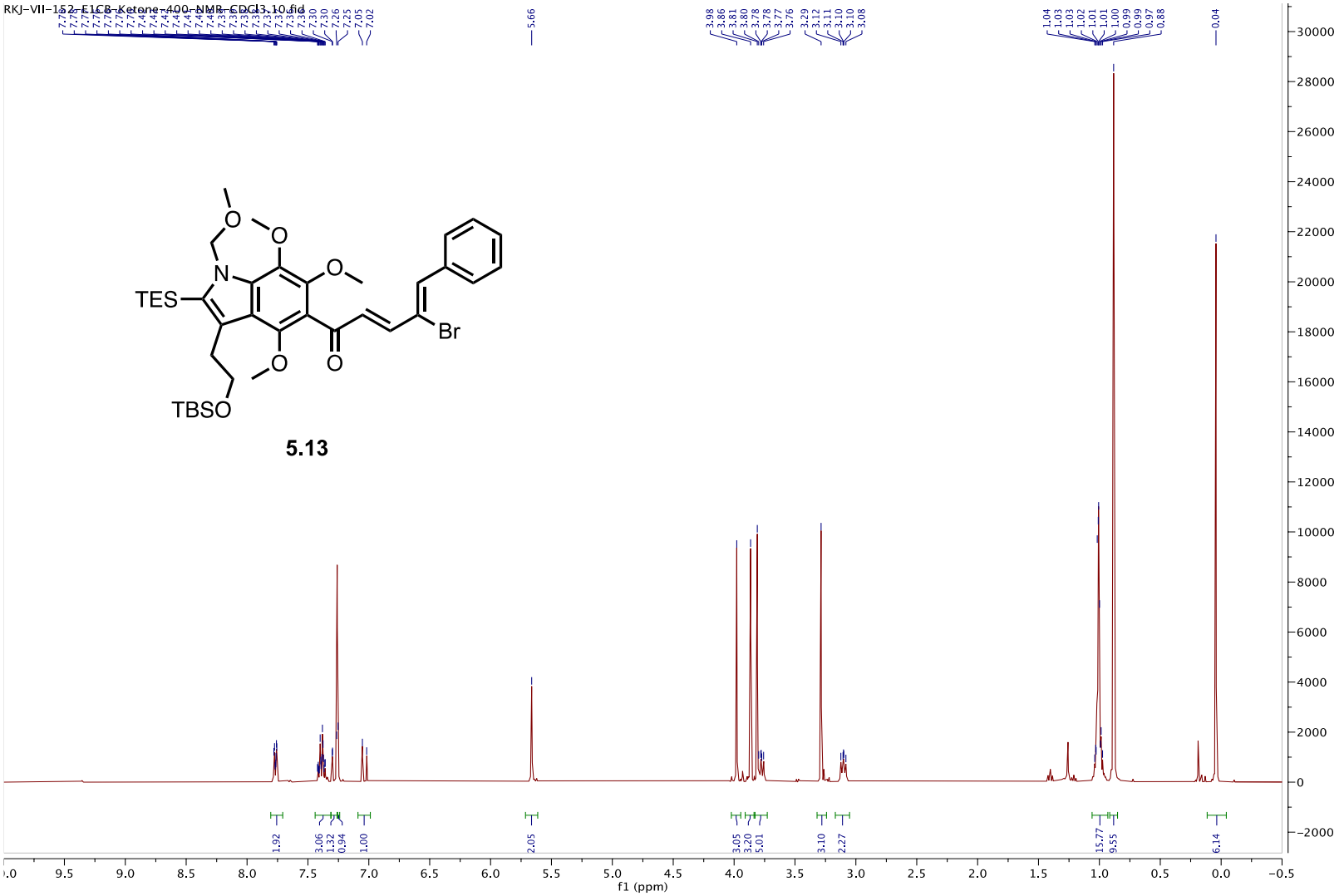


Figure E.16. **^{1}H NMR** (400 MHz, $CDCl_3$) E1$_C$B Ketone **5.13**

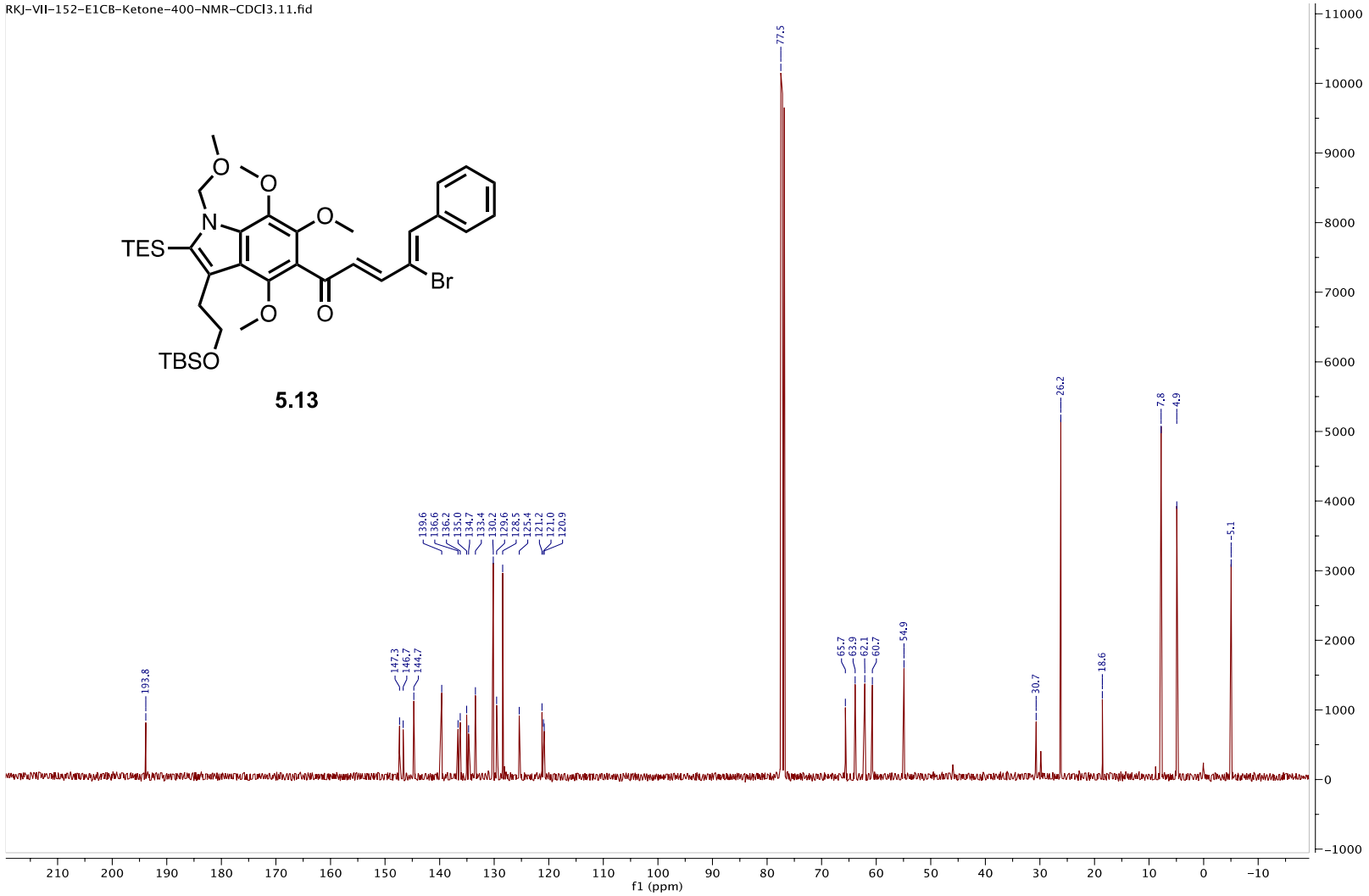


Figure E.17. **^{13}C NMR** (101 MHz, $CDCl_3$) E1cB Ketone **5.13**

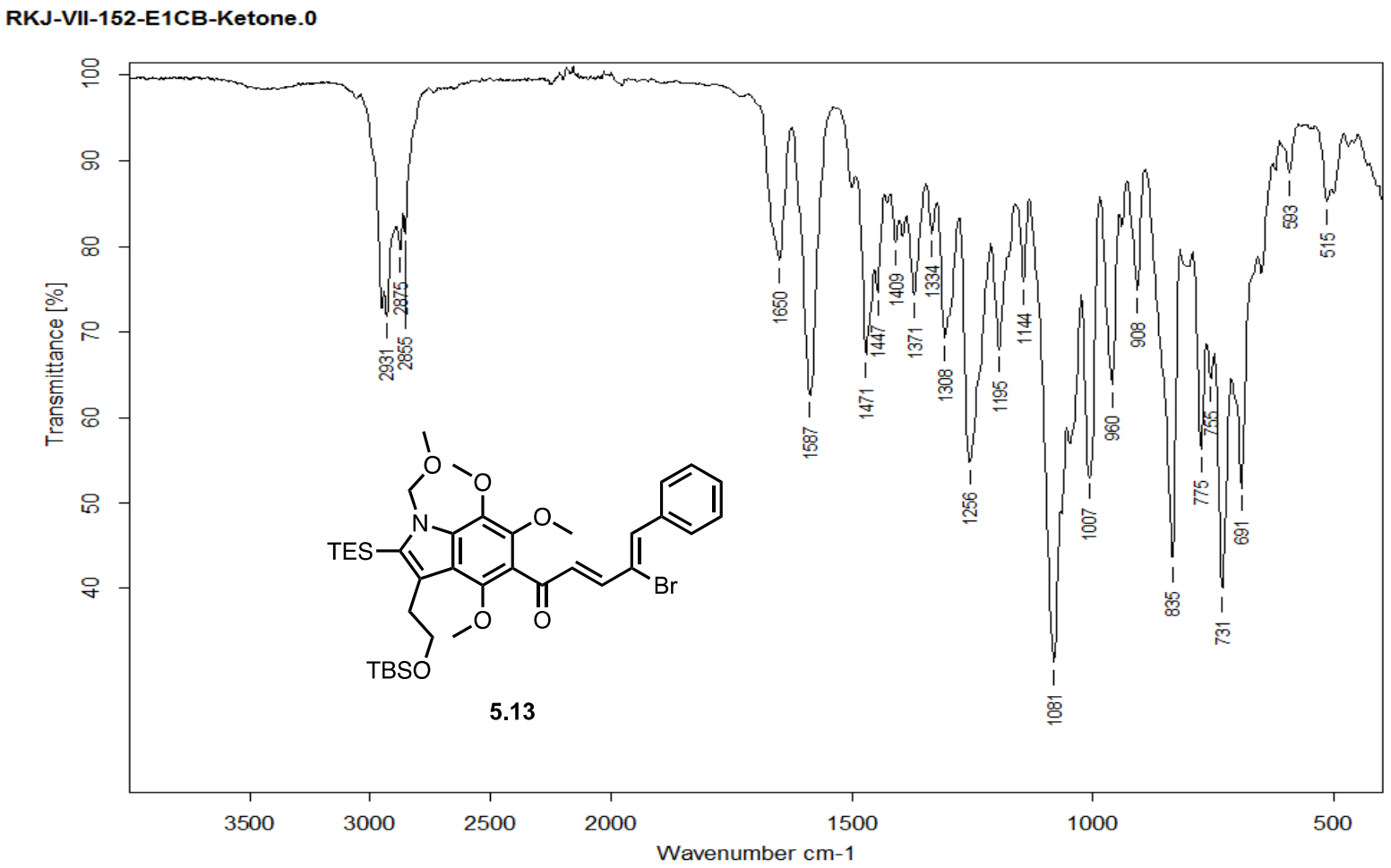


Figure E.18. **^{13}C NMR** (101 MHz, $CDCl_3$) E1cB Ketone **5.13**

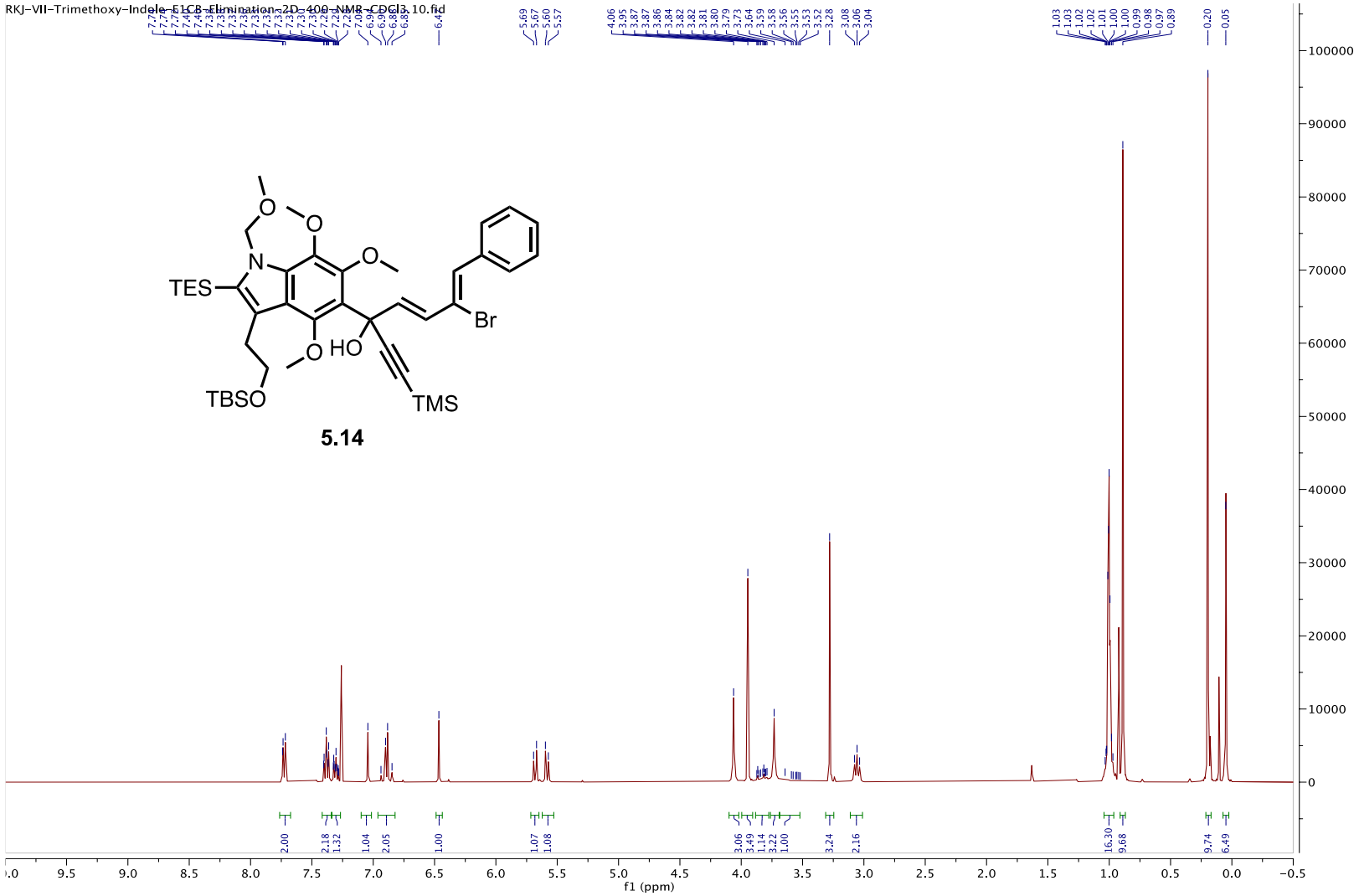


Figure E.19. **^{1}H NMR** (400 MHz, $CDCl_3$) Tertiary Alcohol **5.14**

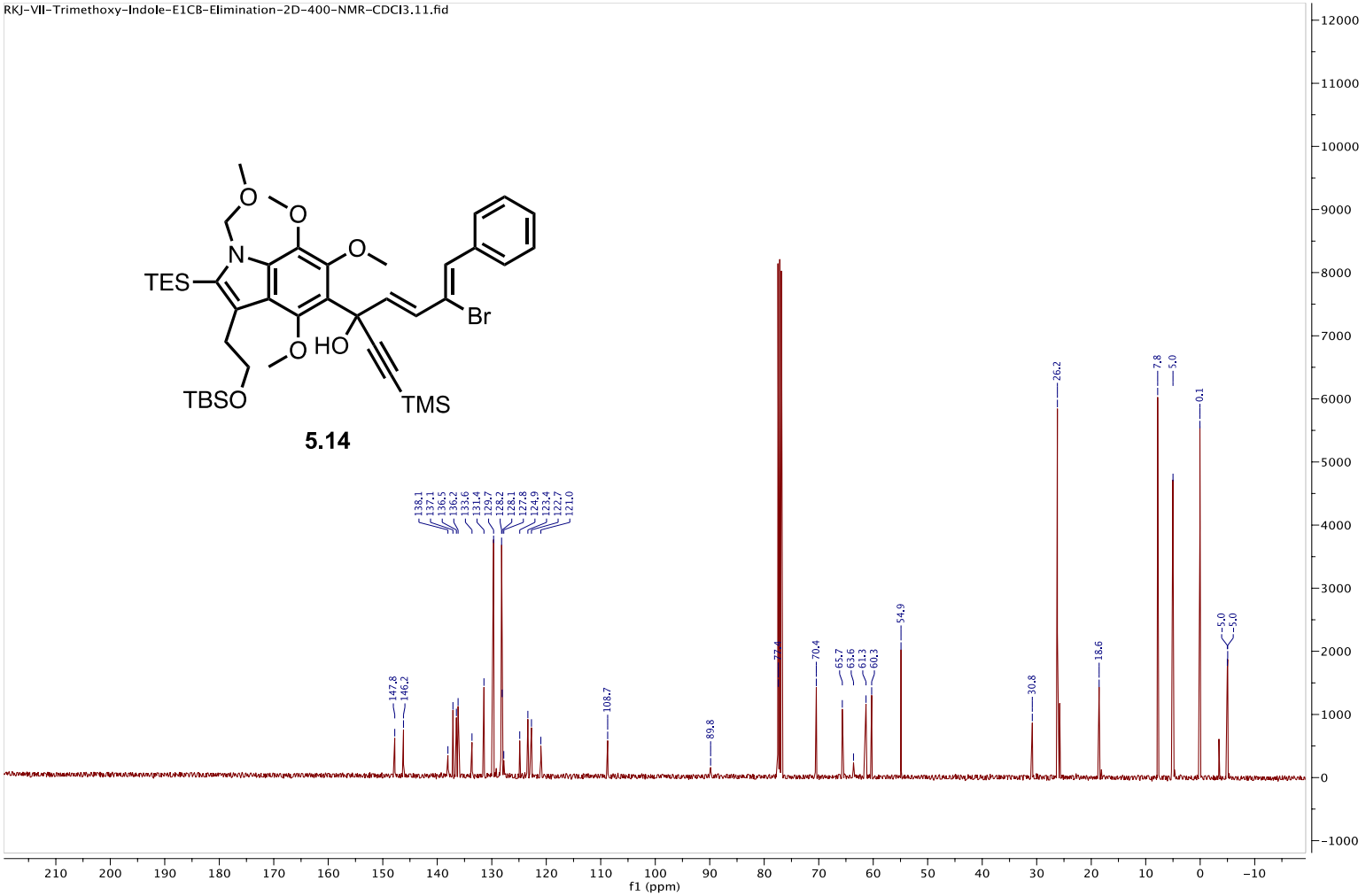


Figure E.20. **^{13}C NMR** (101 MHz, $CDCl_3$) Tertiary Alcohol **5.14**

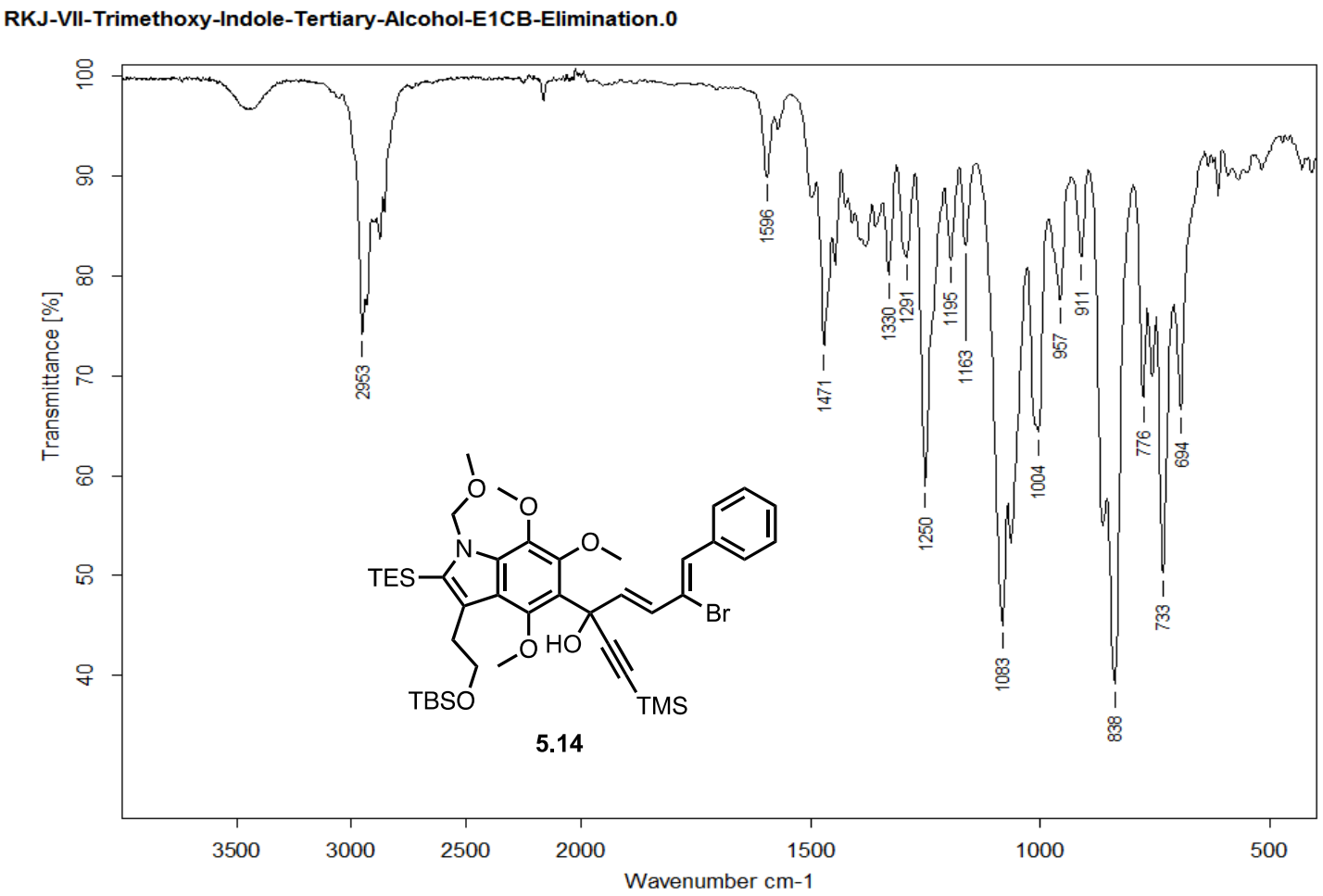


Figure E.21. **FTIR** (thin film) Tertiary Alcohol **5.14**

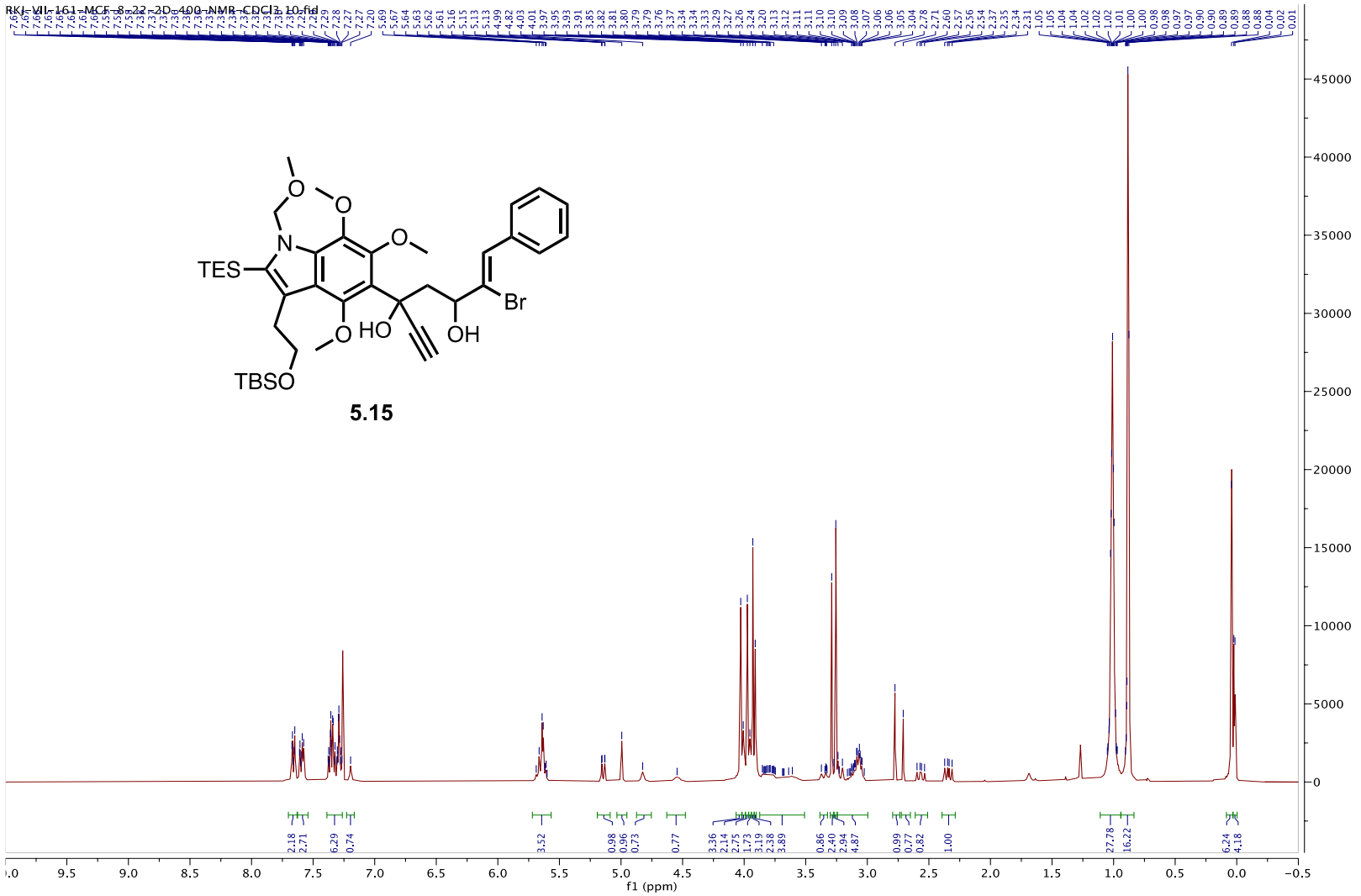


Figure E.22. **^{1}H NMR** (400 MHz, $CDCl_3$) 1,3-Diol **5.15**

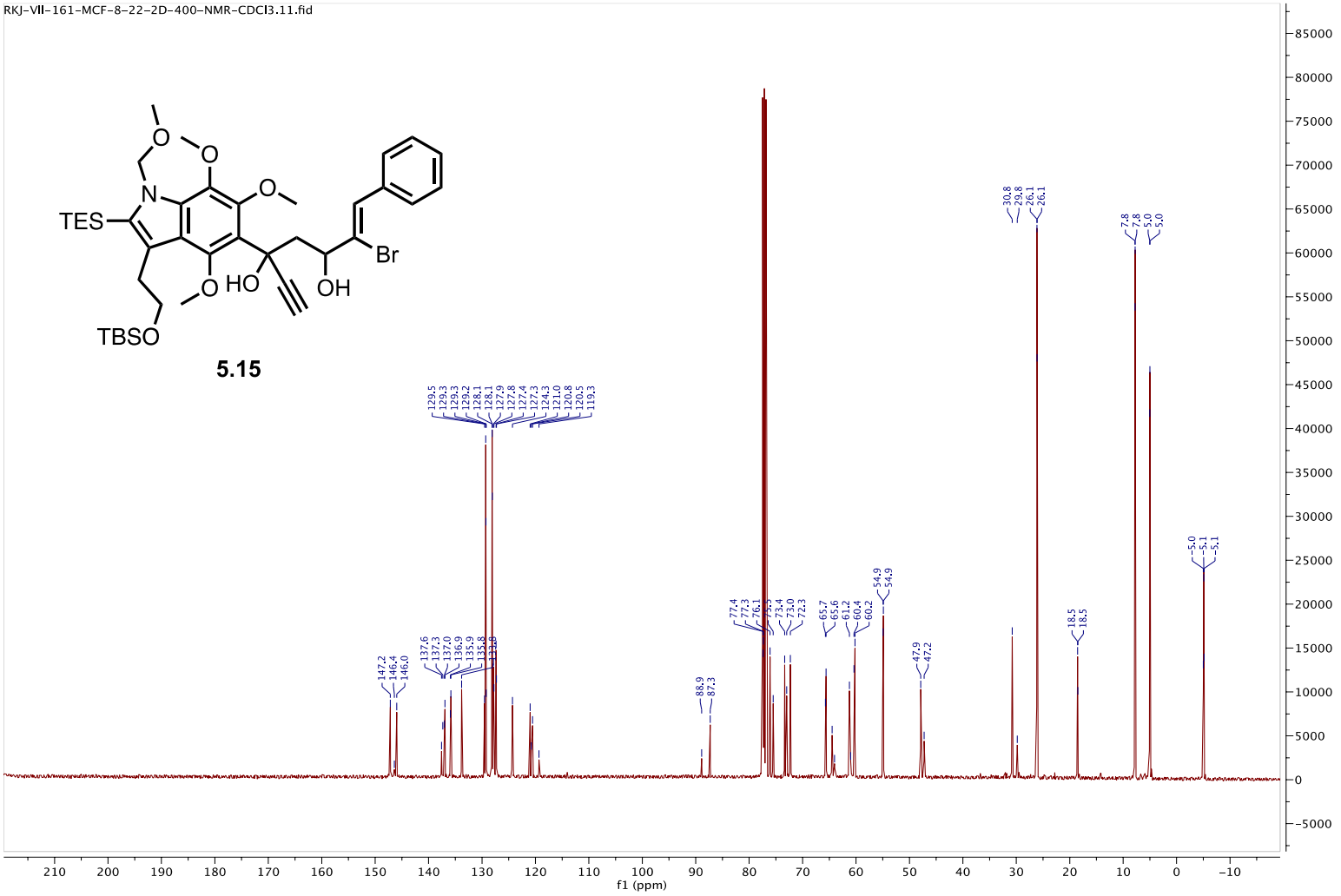


Figure E.23. **^{13}C NMR** ($CDCl_3$) 1,3-Diol **5.15**

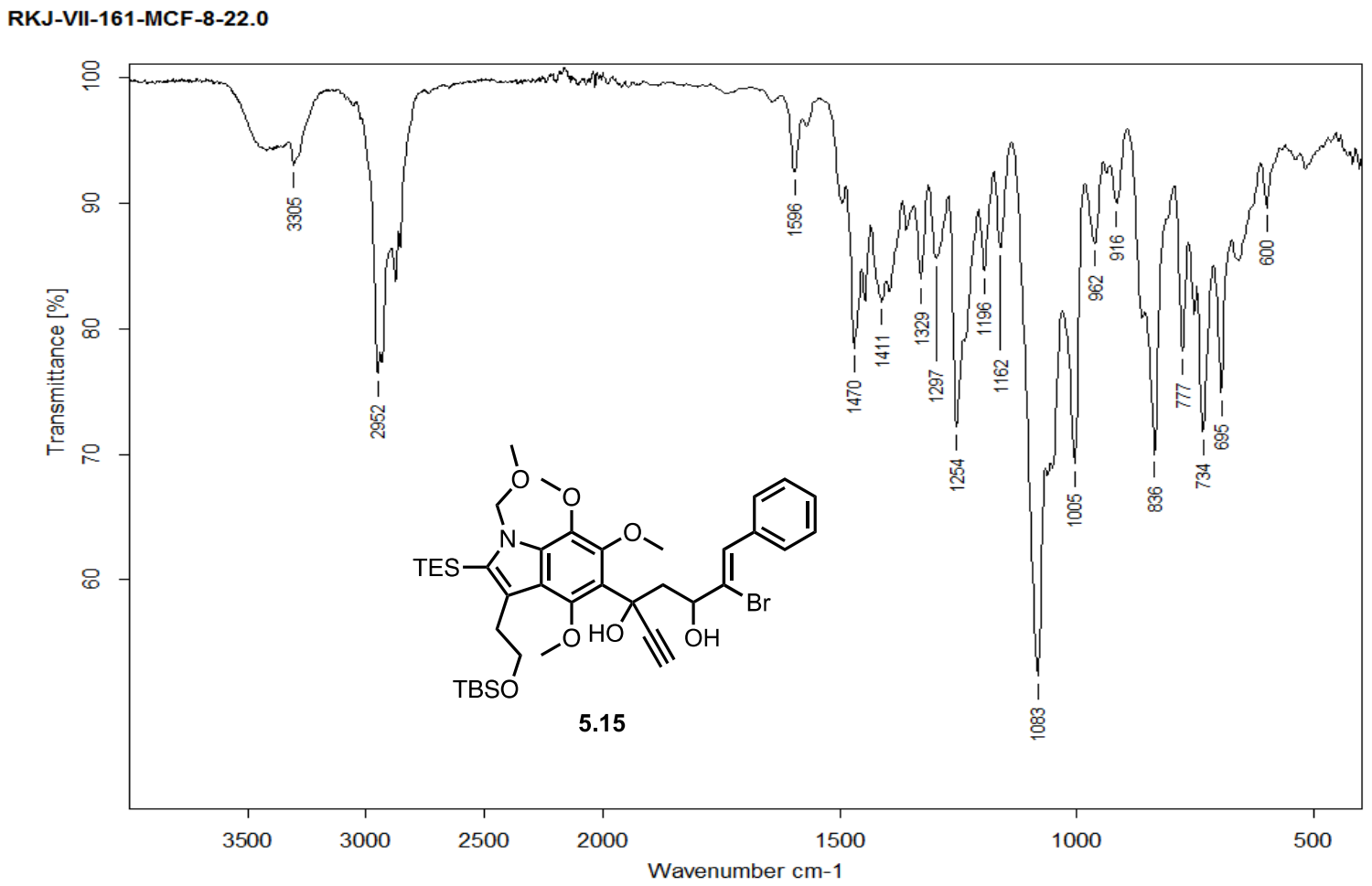


Figure E.24. **FTIR** (thin film) 1,3-Diol **5.15**

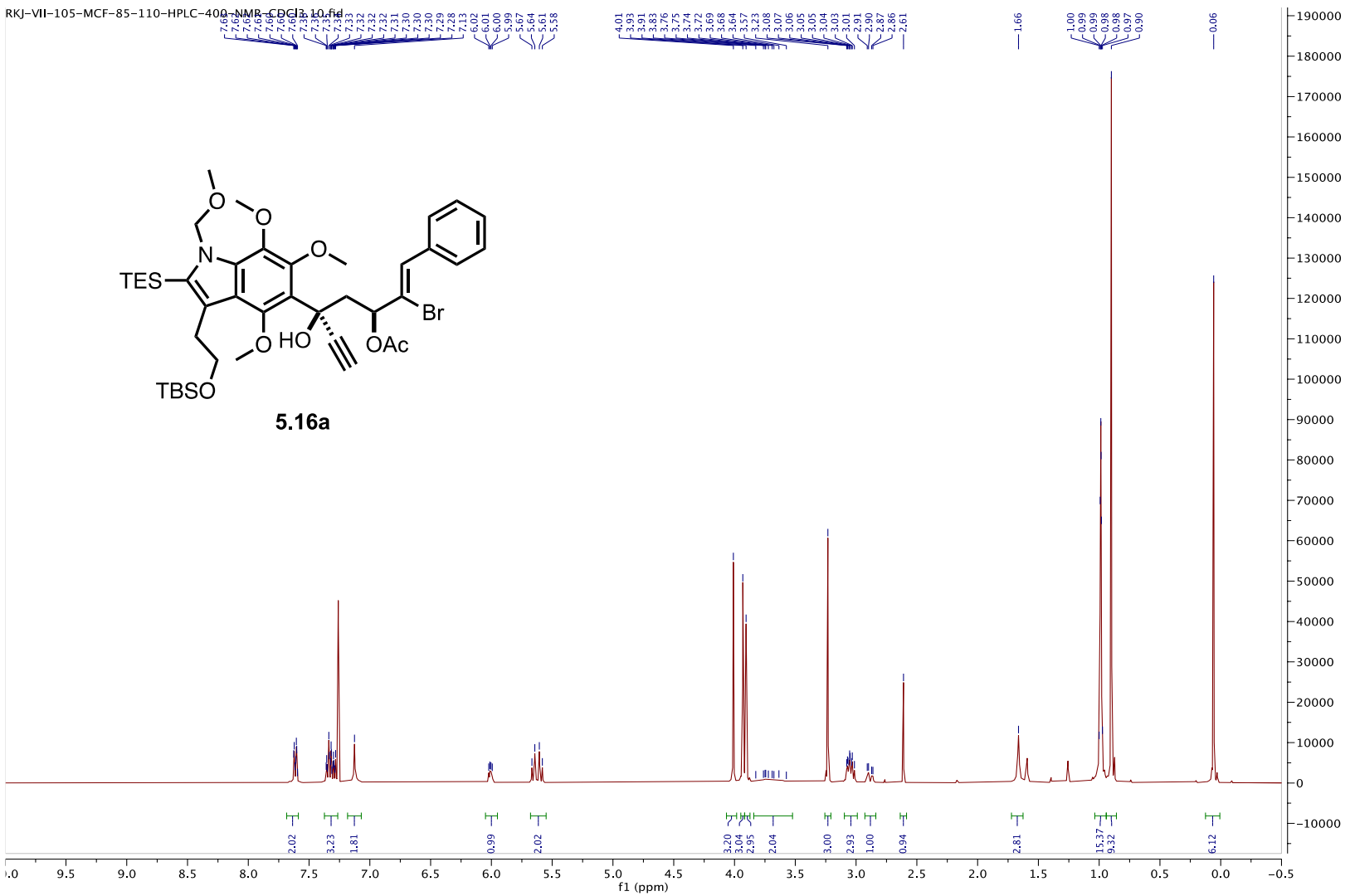


Figure E.25. **^{1}H NMR** (400 MHz, $CDCl_3$) Major Diastereomer Acetate **5.16a**

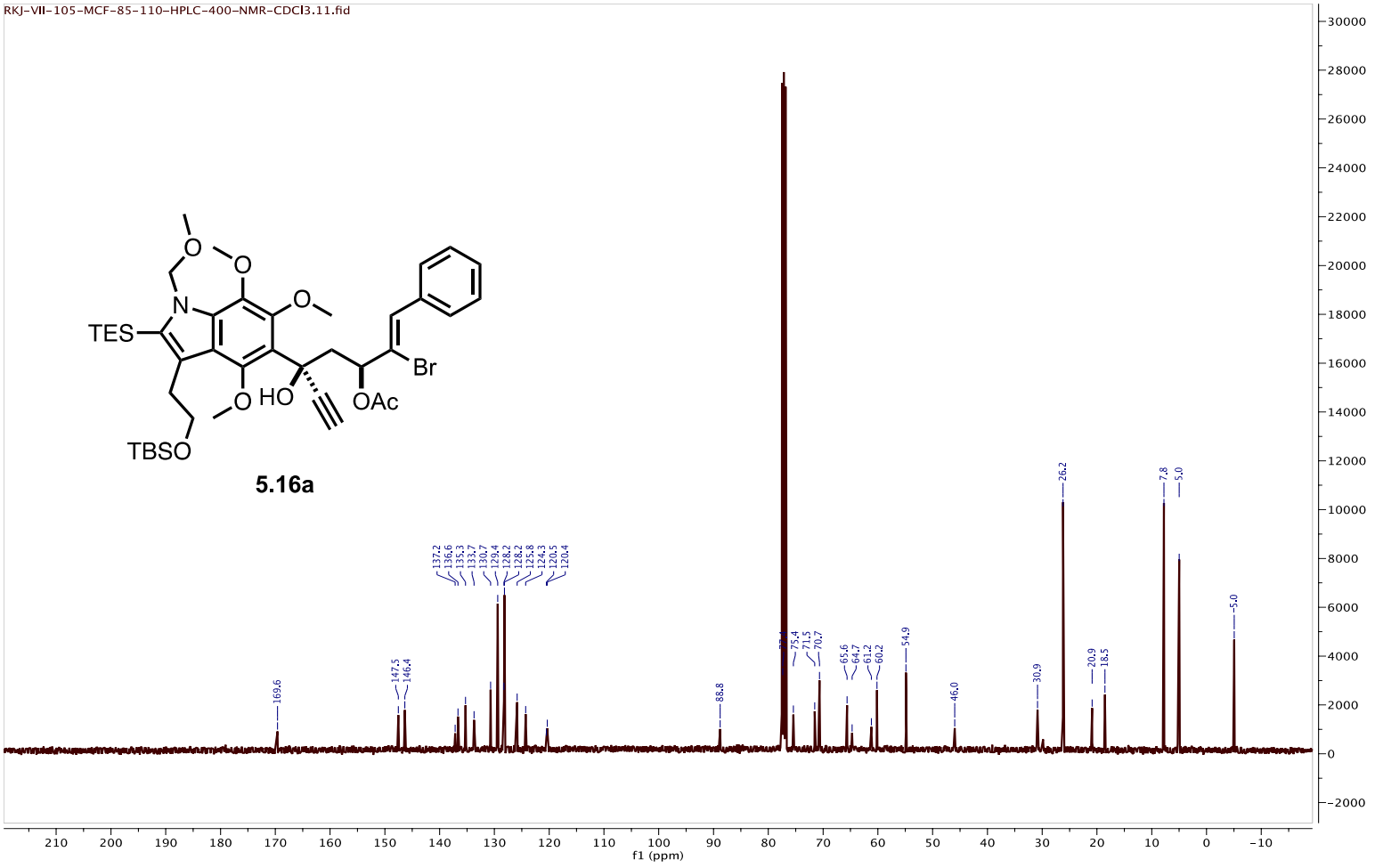


Figure E.26. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Acetate **5.16a**

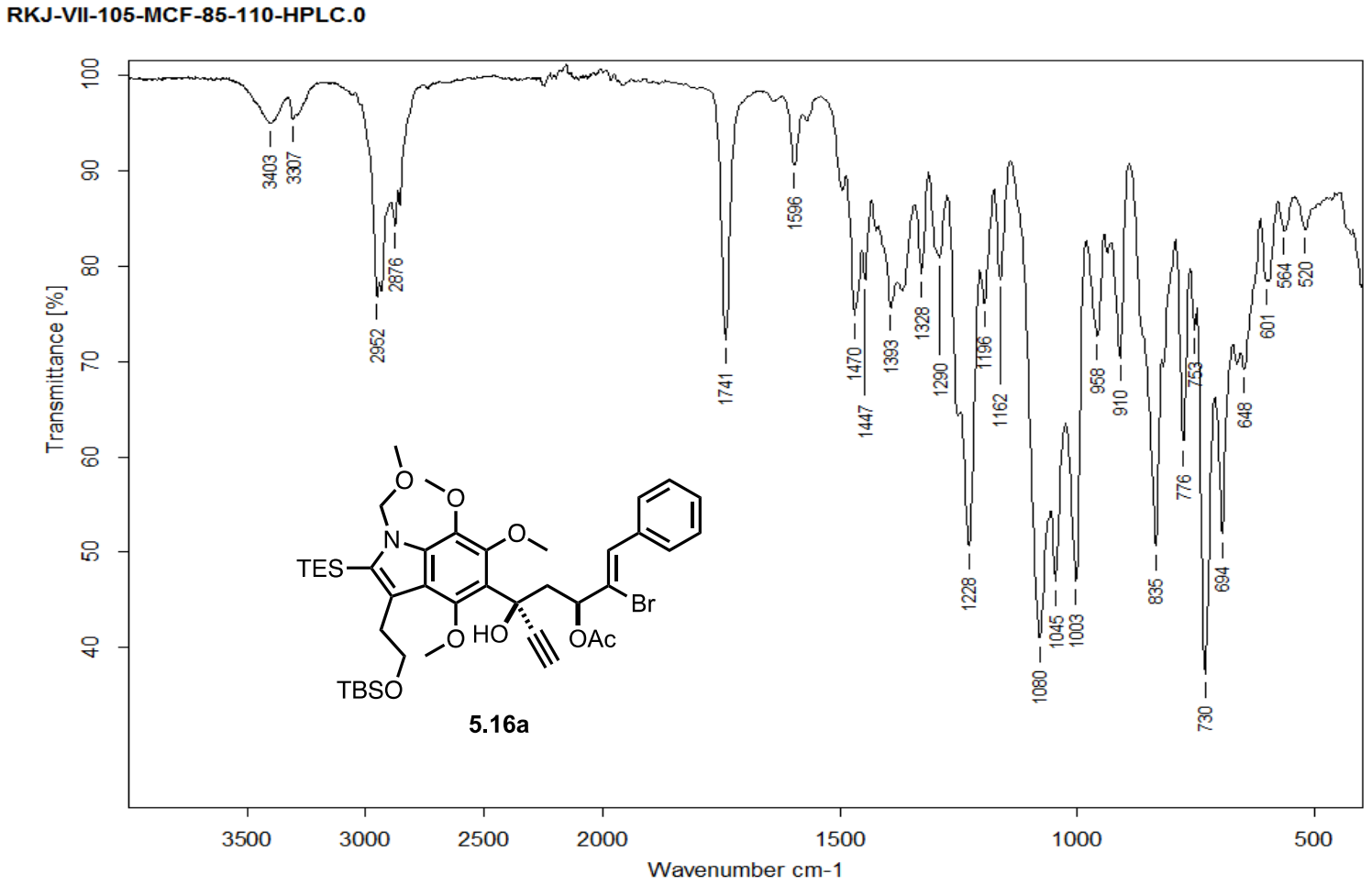


Figure E.27. **^{13}C NMR** ($CDCl_3$) Major Diastereomer Acetate **5.16a**

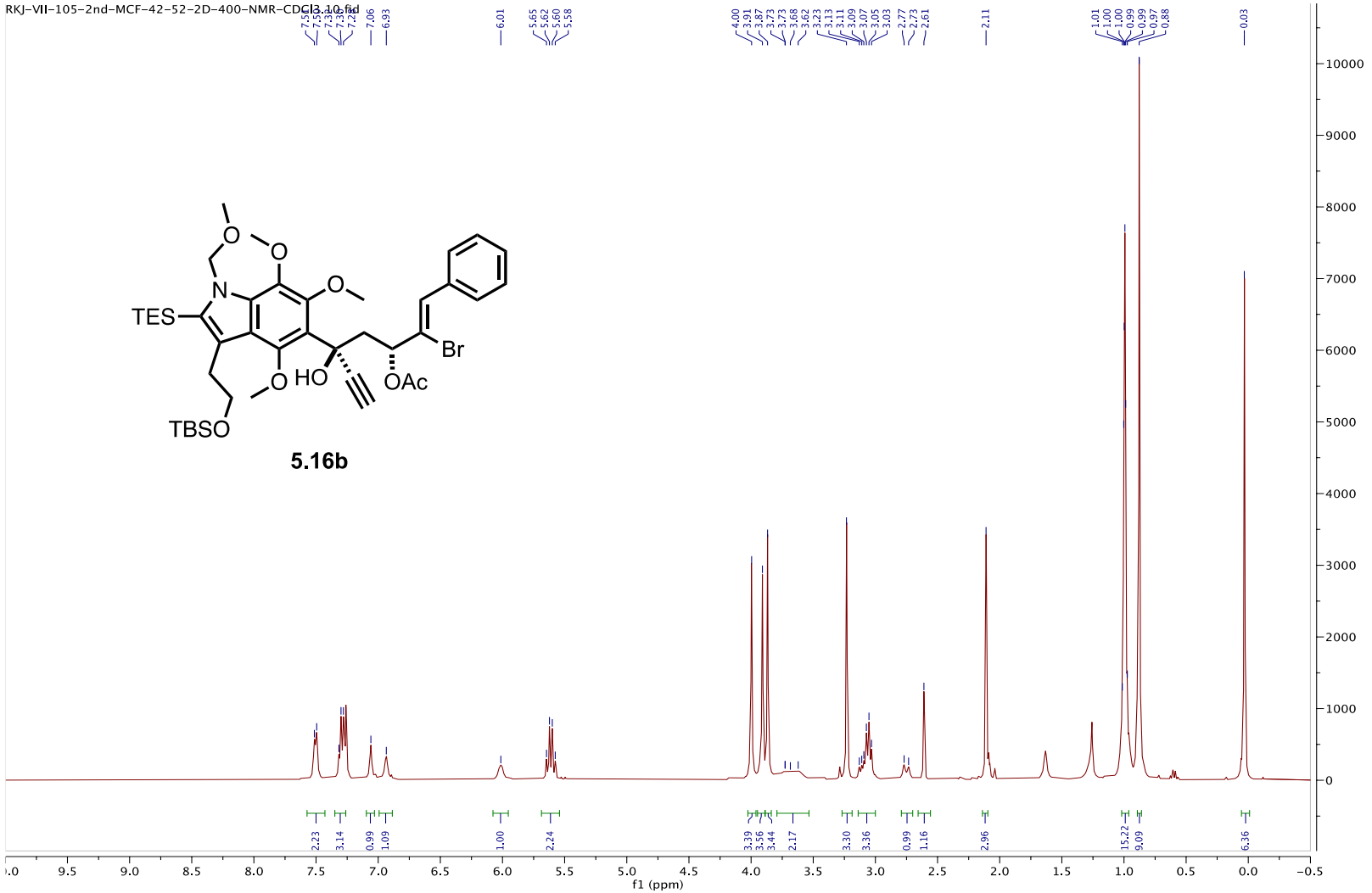


Figure E.28. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer Acetate **5.16b**

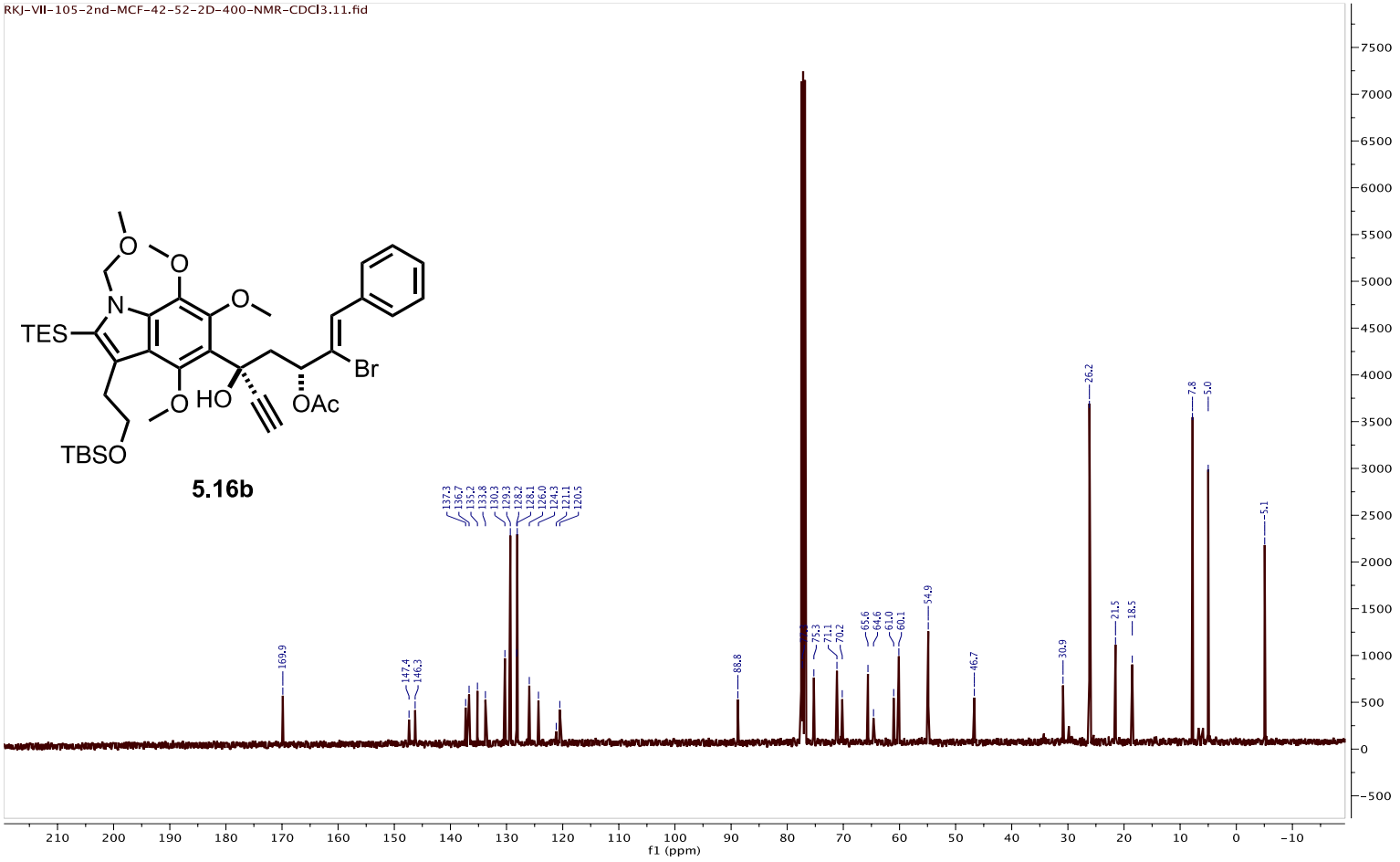


Figure E.29. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Acetate **5.16b**

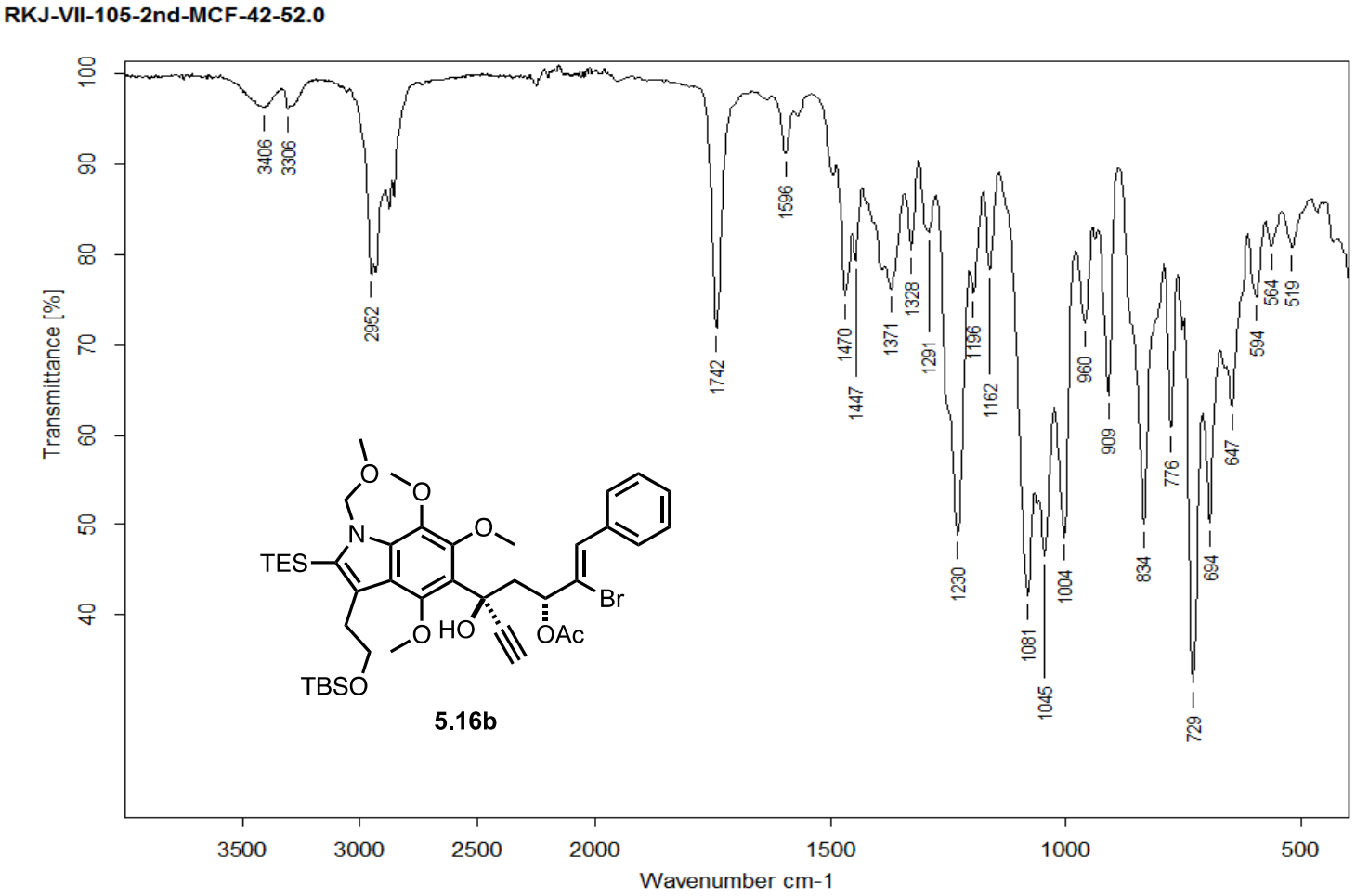


Figure E.30. **FTIR** (thin film) Minor Diastereomer Acetate **5.16b**

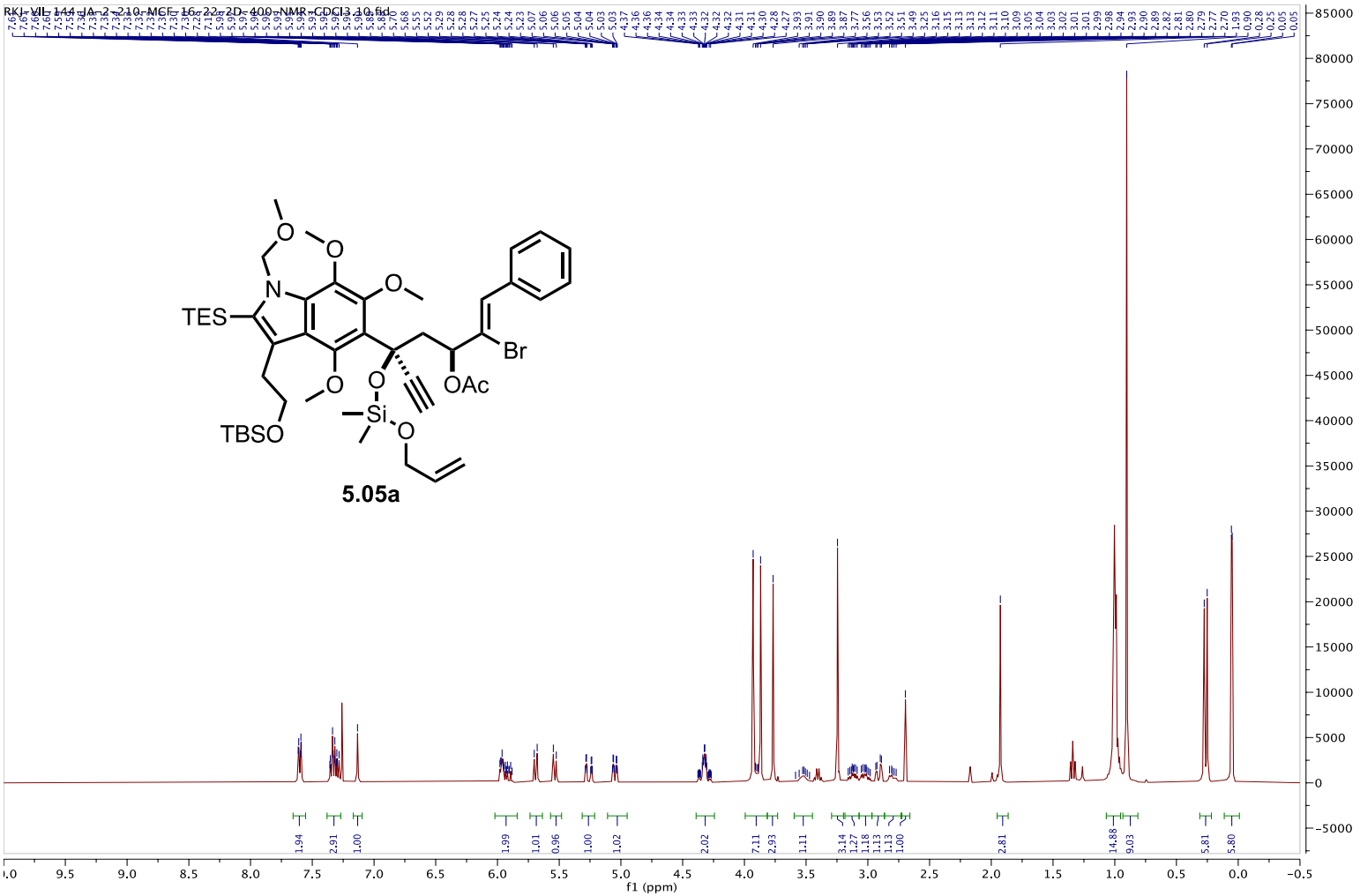


Figure E.31. **^{1}H NMR** (400 MHz, $CDCl_3$) Major Diastereomer Silylene **5.05a**

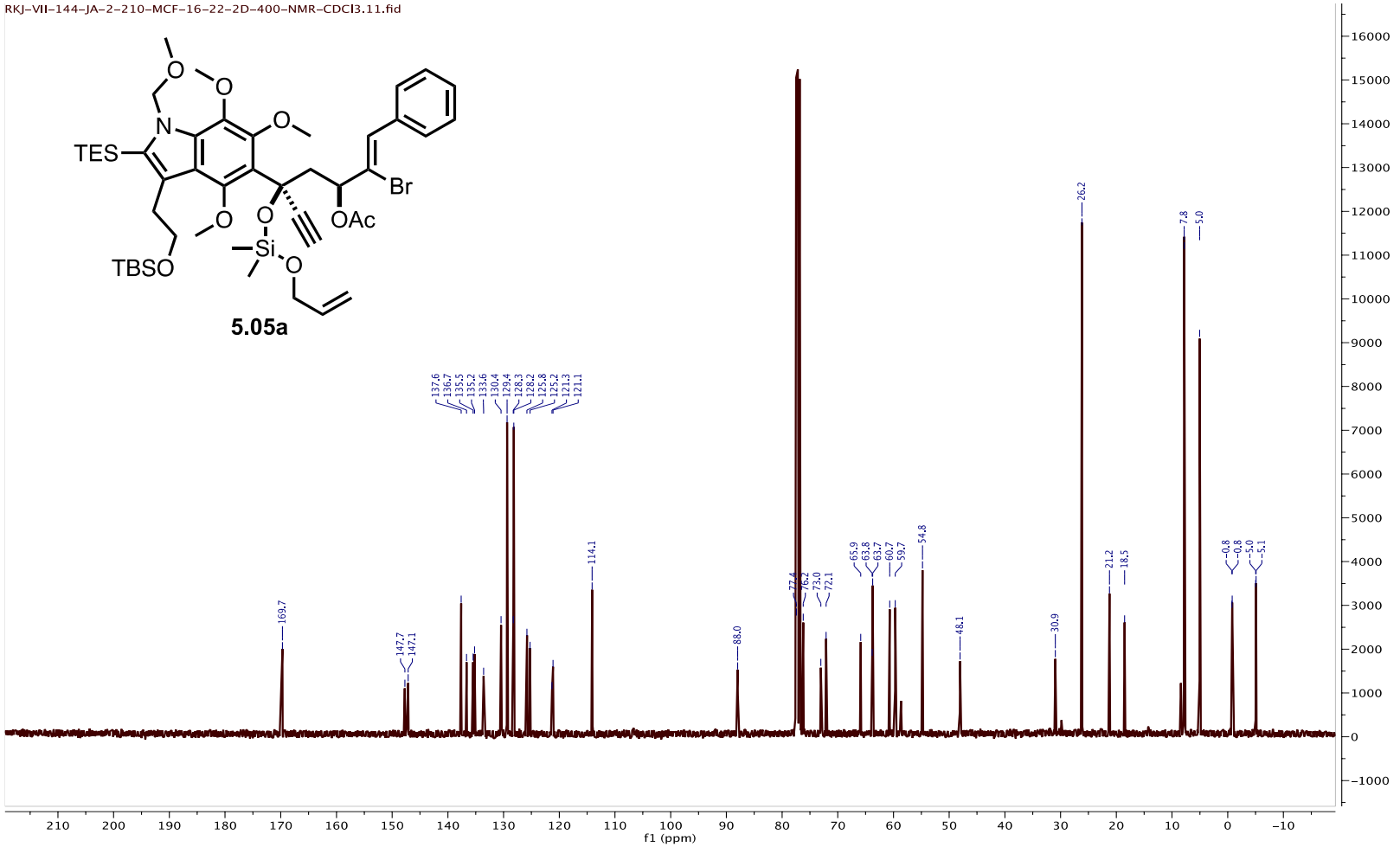


Figure E.32. **^{13}C NMR** (101 MHz, $CDCl_3$) Major Diastereomer Silylene **5.05a**

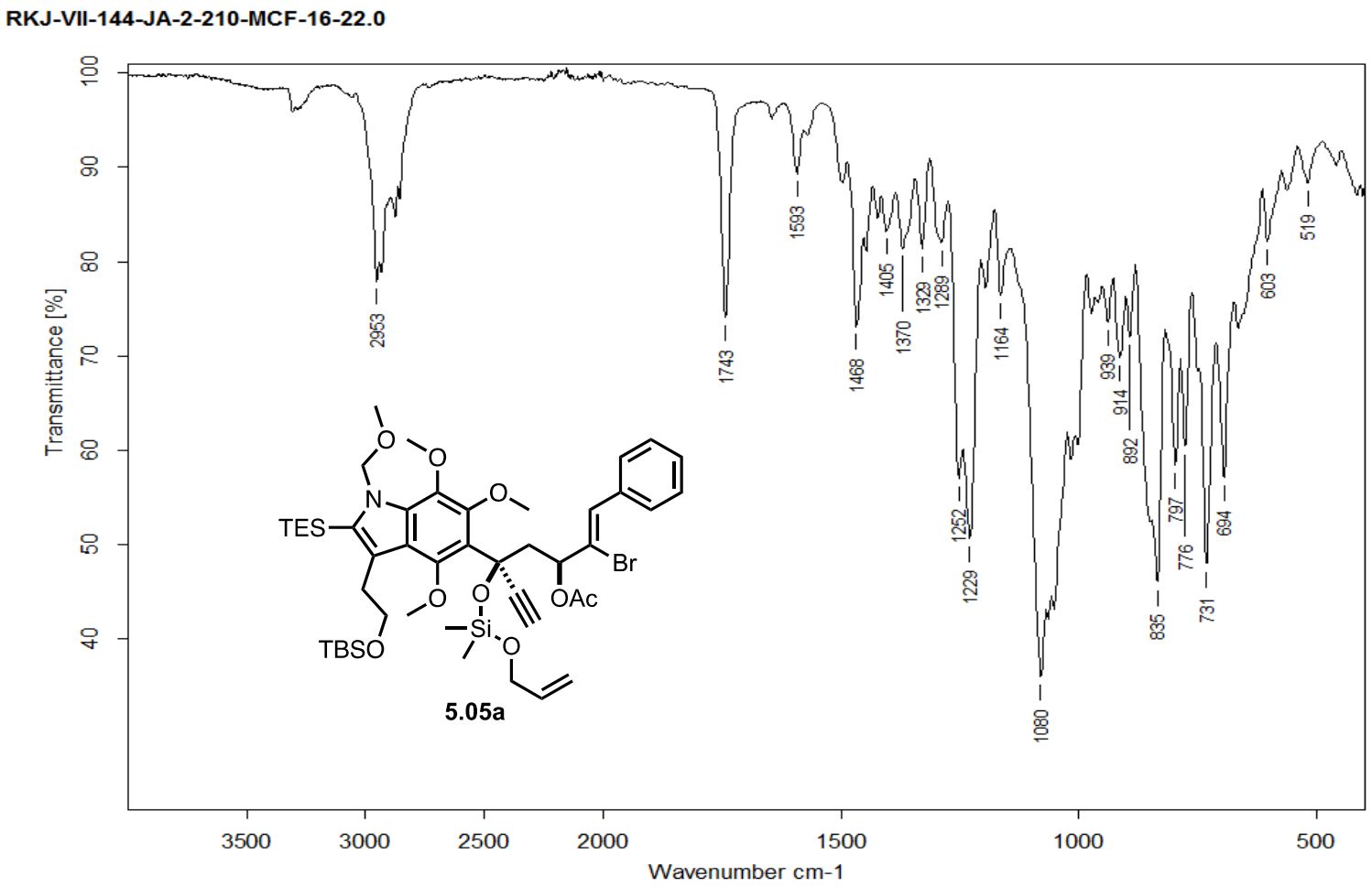


Figure E.33. **FTIR** (thin film) Major Diastereomer Silylene **5.05a**

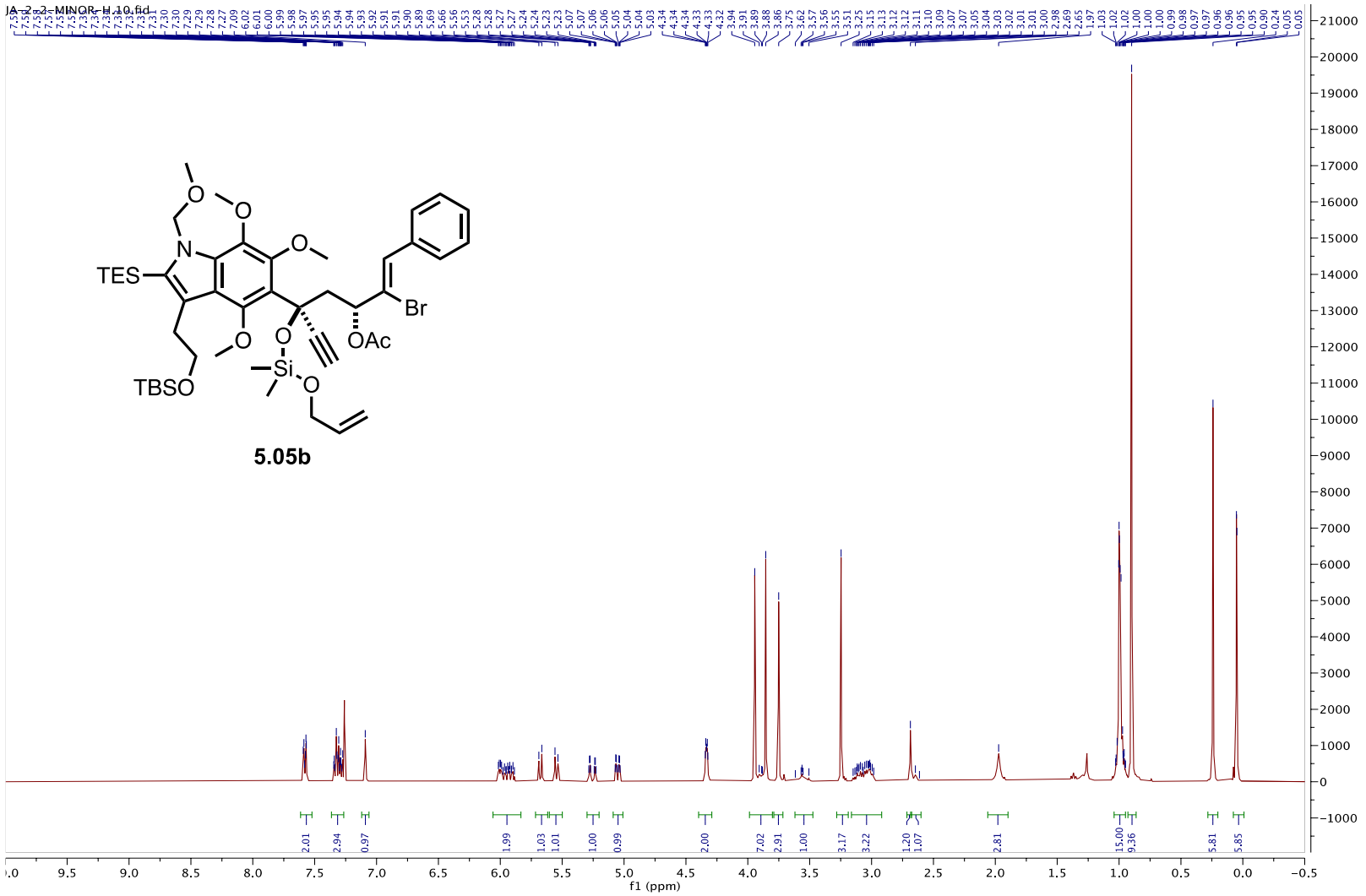


Figure E.34. **^{1}H NMR** (400 MHz, $CDCl_3$) Minor Diastereomer Silylene **5.05b**

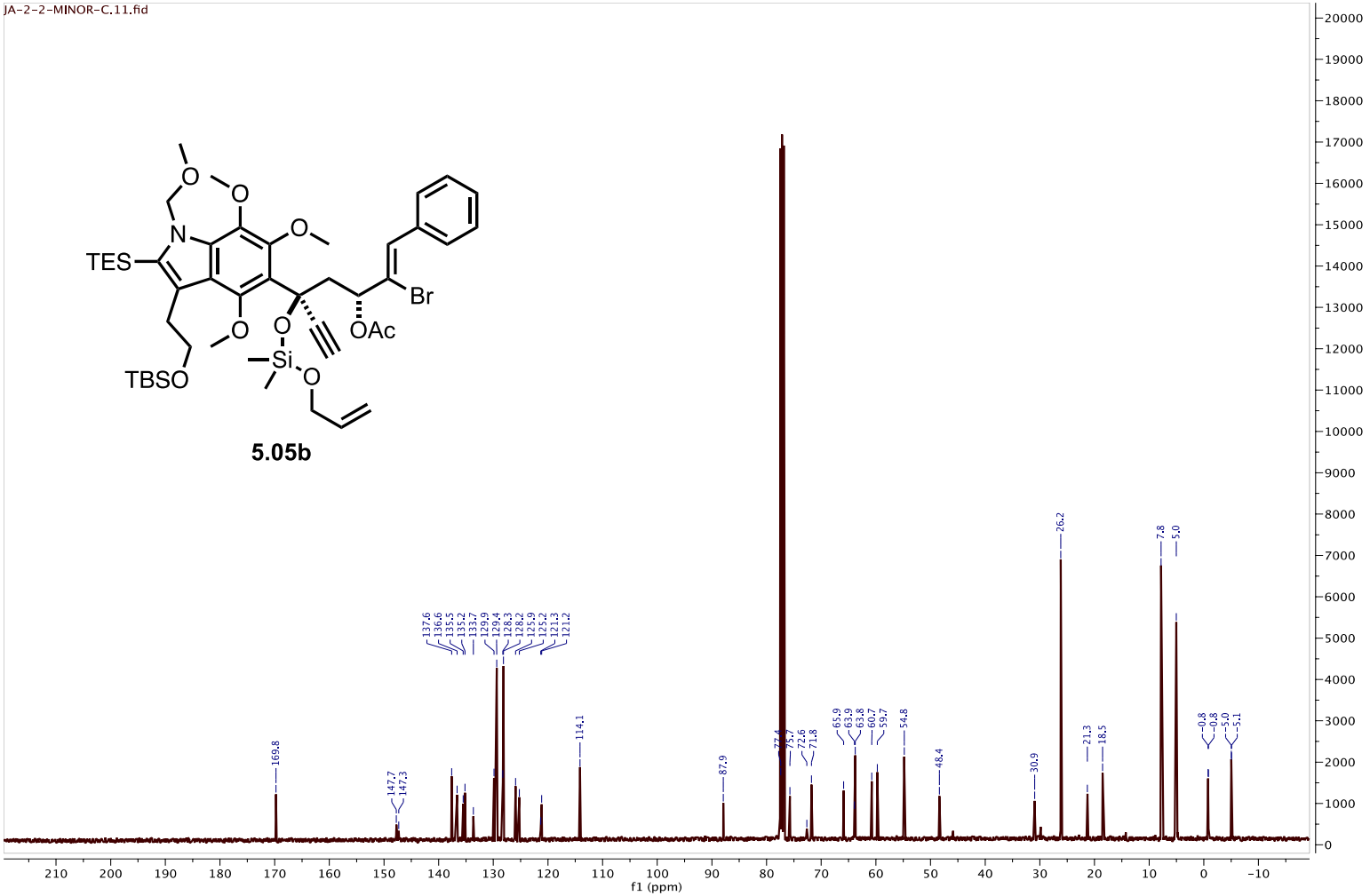


Figure E.35. **^{13}C NMR** (101 MHz, $CDCl_3$) Minor Diastereomer Silylene **5.05b**

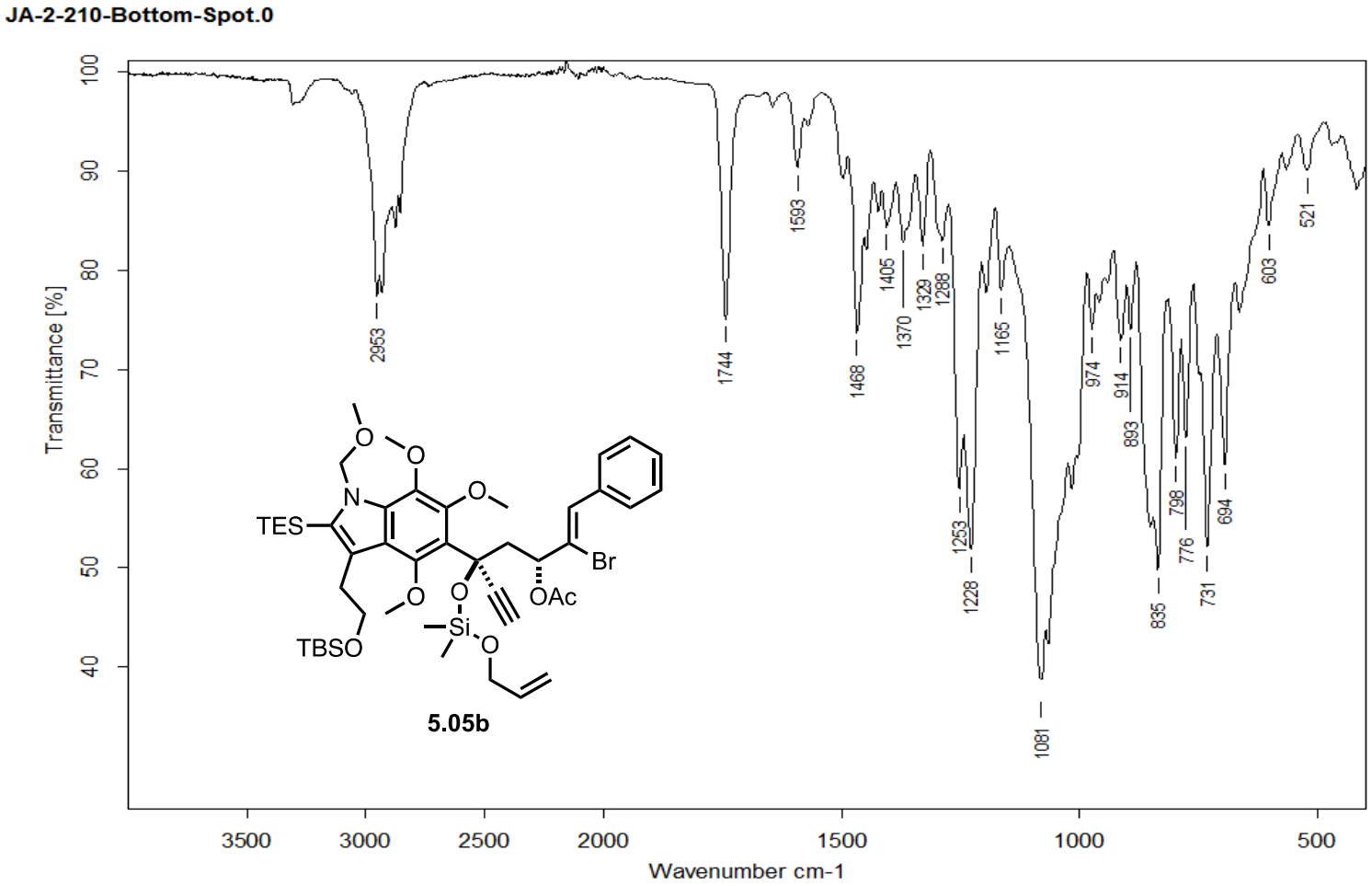


Figure E.36. **FTIR** (thin film) Minor Diastereomer Silylene **5.05b**

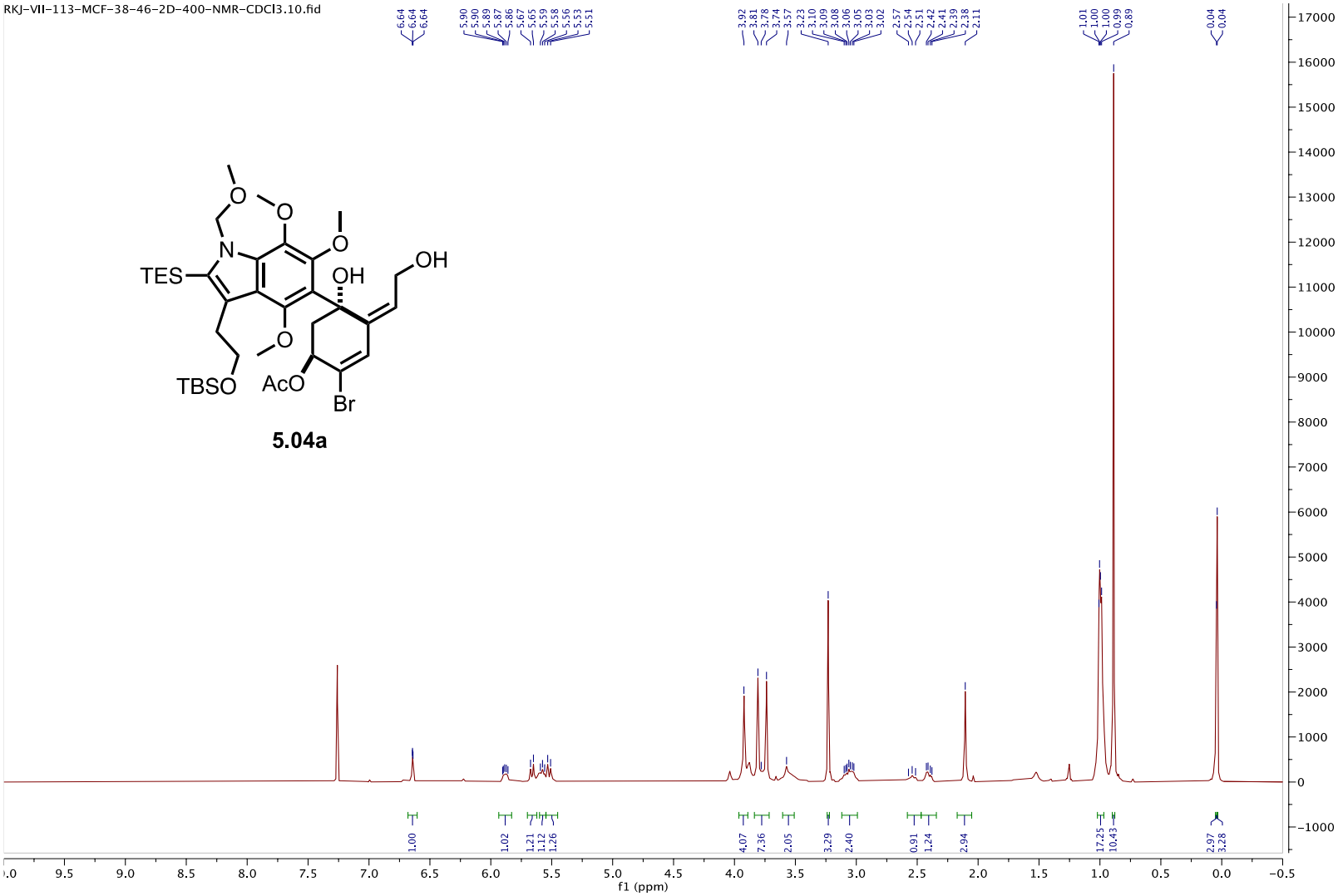


Figure E.37. **^{1}H NMR** (400 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**

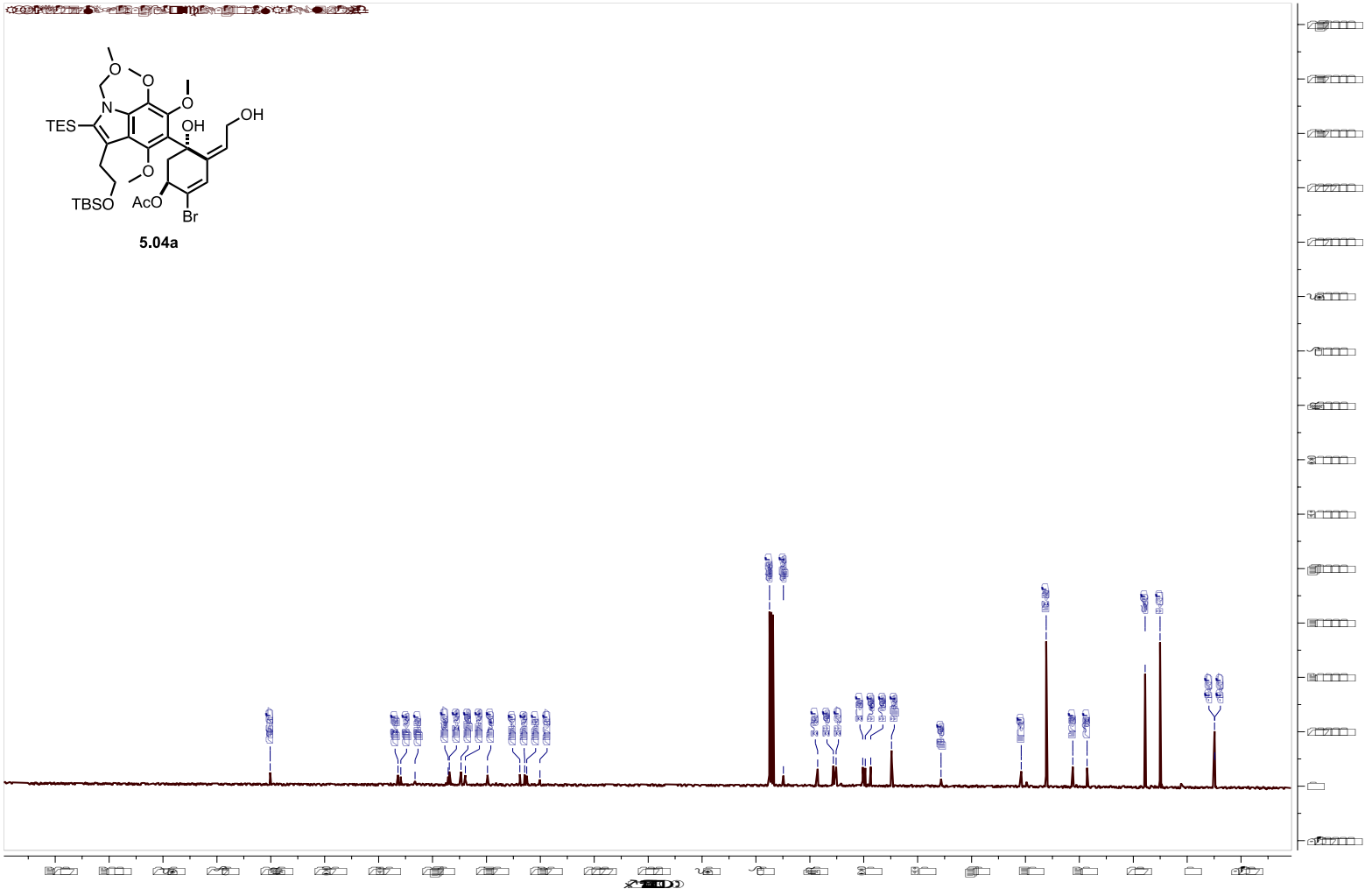


Figure E.38. **^{13}C NMR** (101 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a** with DEPT 90 (middle) and DEPT 135 (top) overlayed

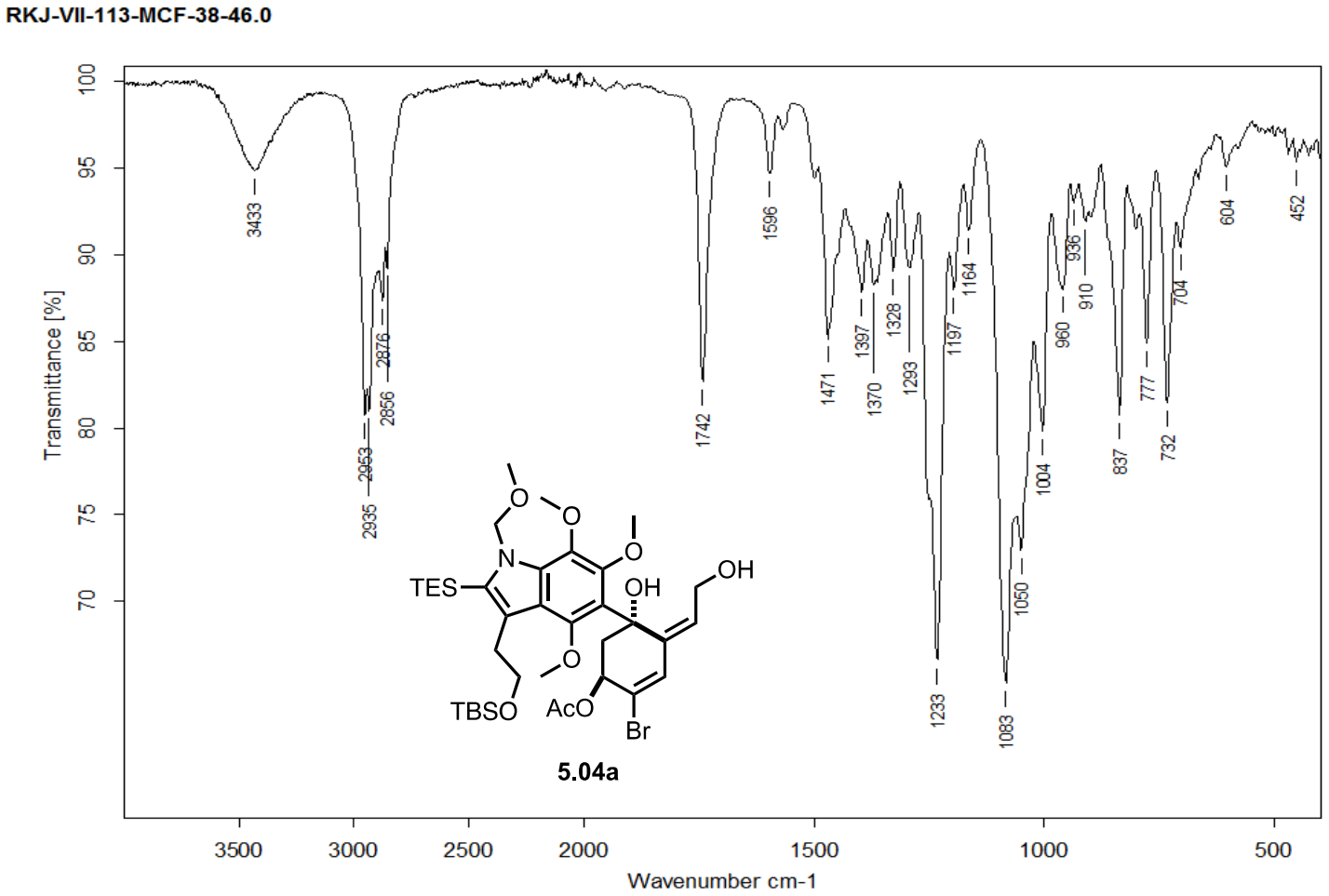


Figure E.39. **FTIR** (thin film) Tandem Metathesis Diol **5.04a**

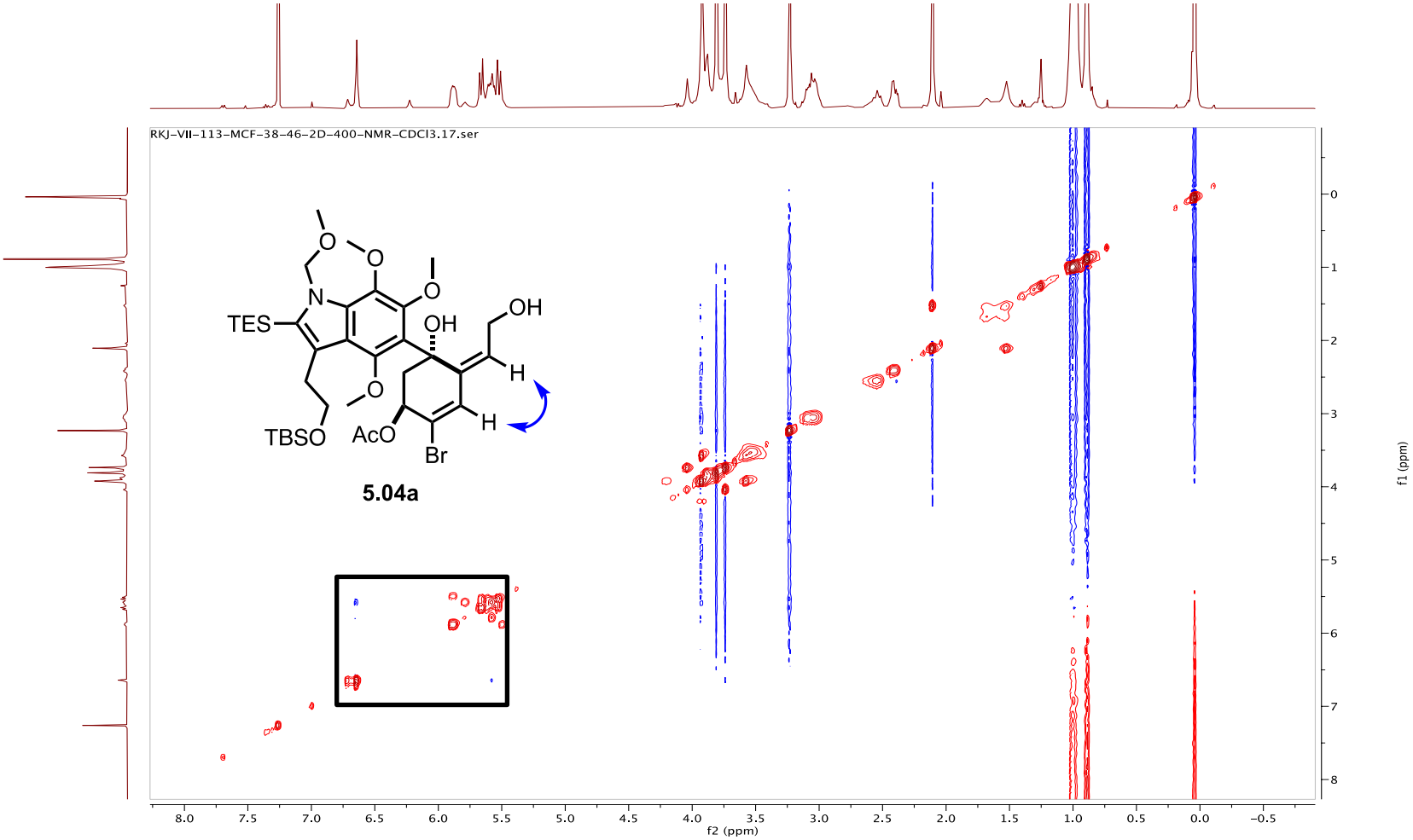


Figure E.40. **^{1}H-^{1}H NOESY** (400 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**
Double bond geometry established by NOESY correlations between the vinyl methines at 6.64 and 5.59-5.56 ppm.

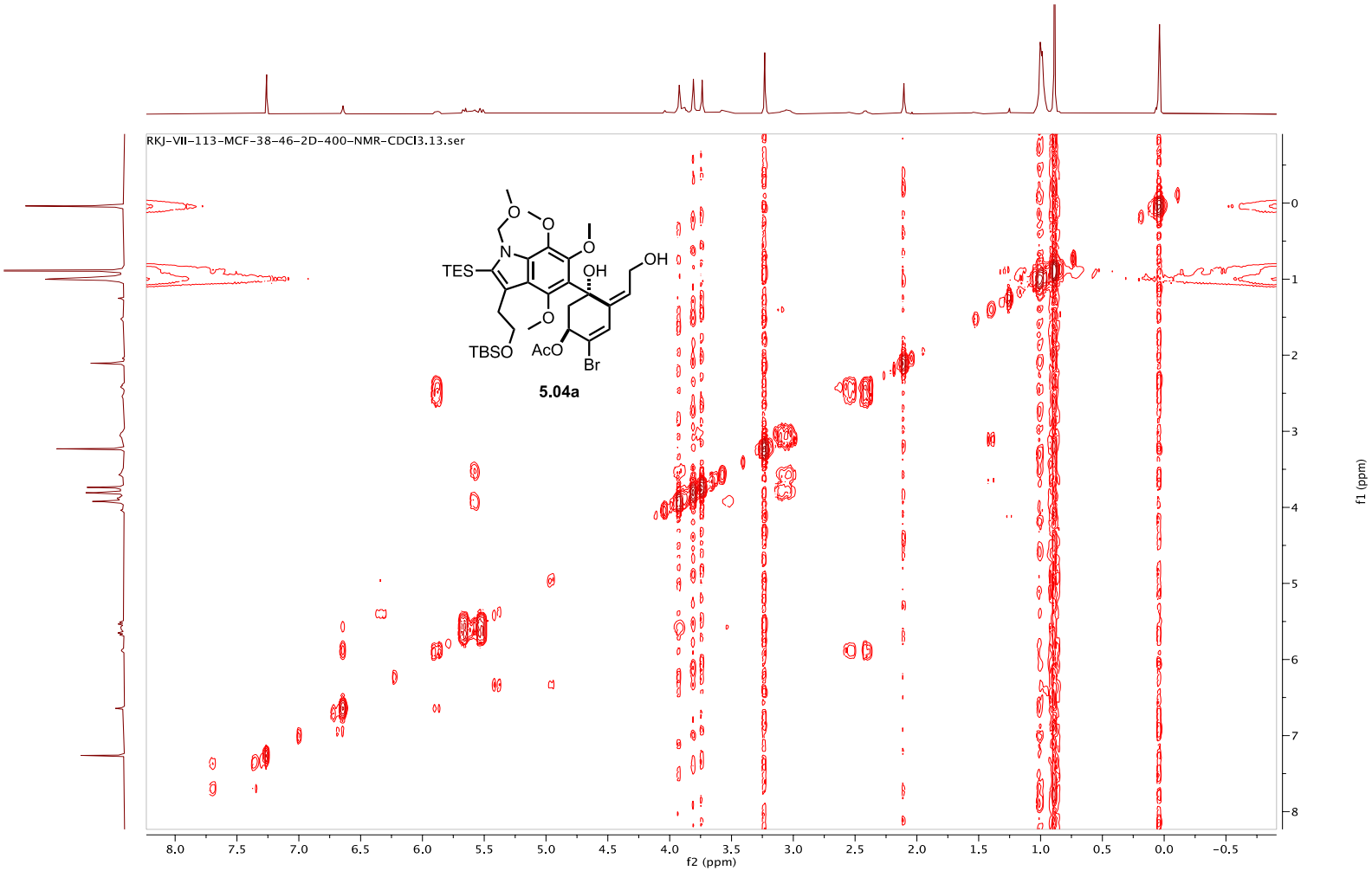


Figure E.41. **^{1}H-^{1}H COSY** (400 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**

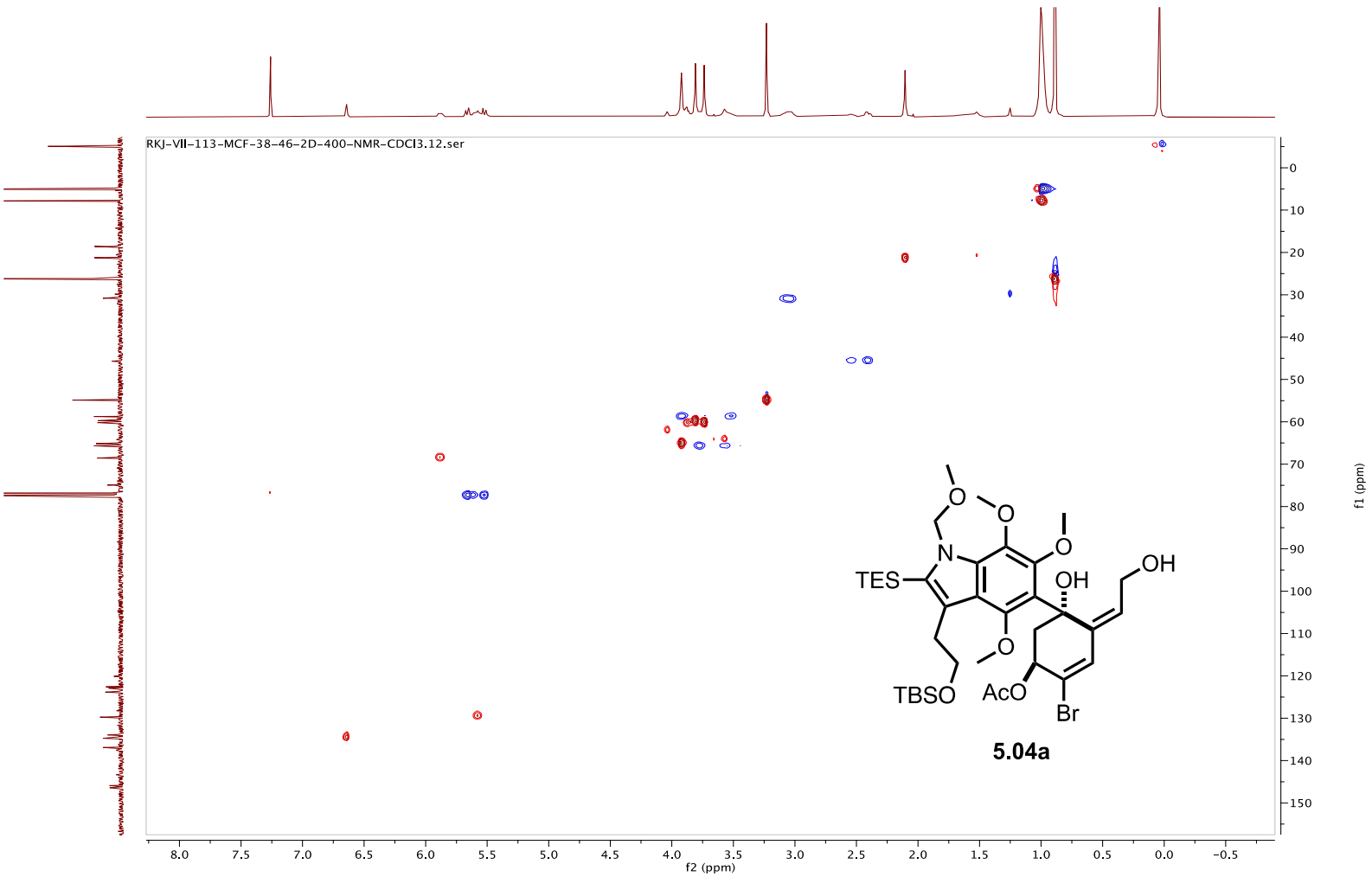


Figure E.42. **^{1}H-^{13}C HSQC** (400, 101 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**

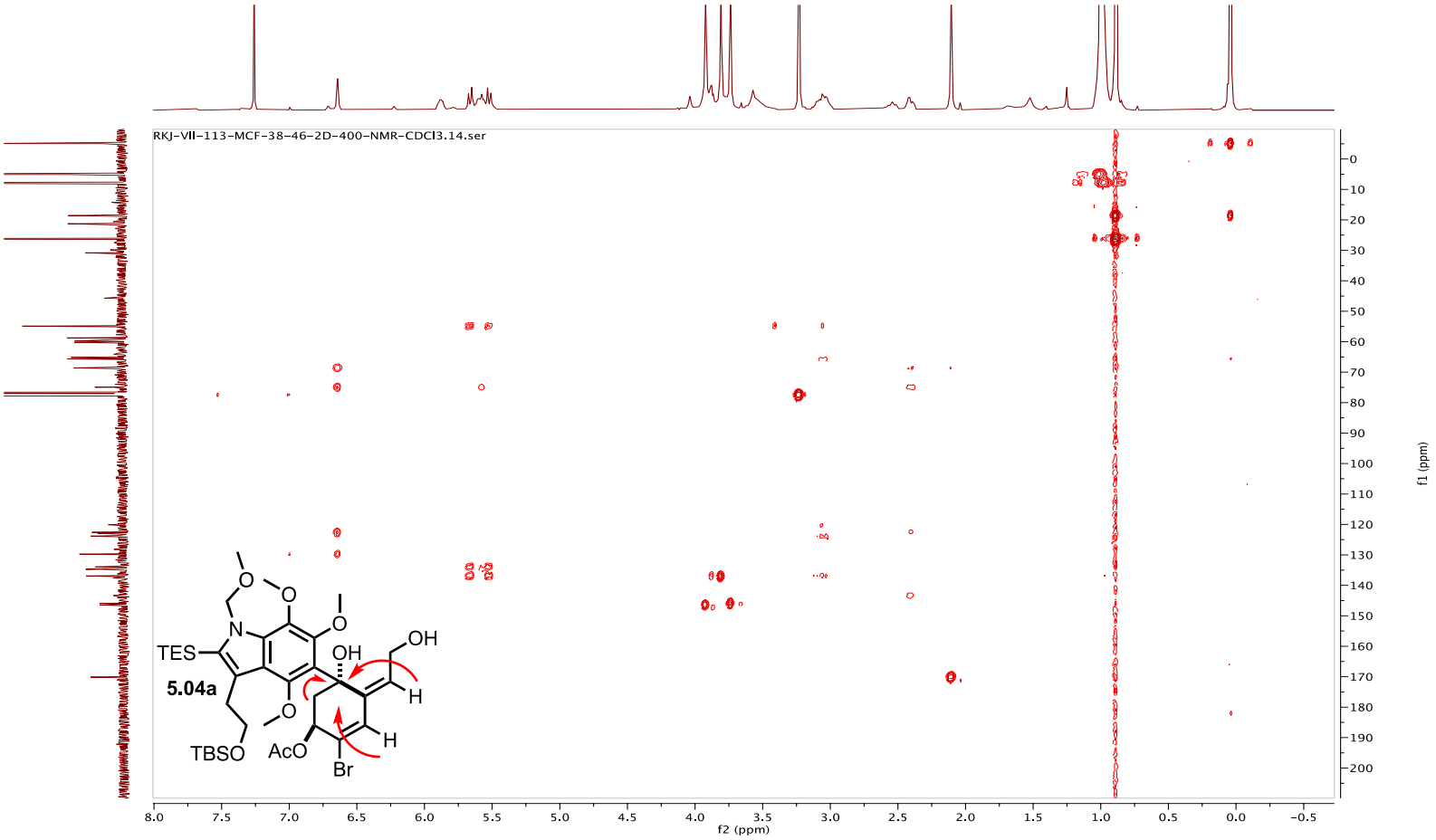


Figure E.43. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) Tandem Metathesis Diol **5.04a**
Key HMBC correlations between vinyl methines at 6.64 and 5.59-5.56 ppm and aliphatic methylene at 2.40 ppm to aliphatic quaternary carbon at 74.9 ppm.

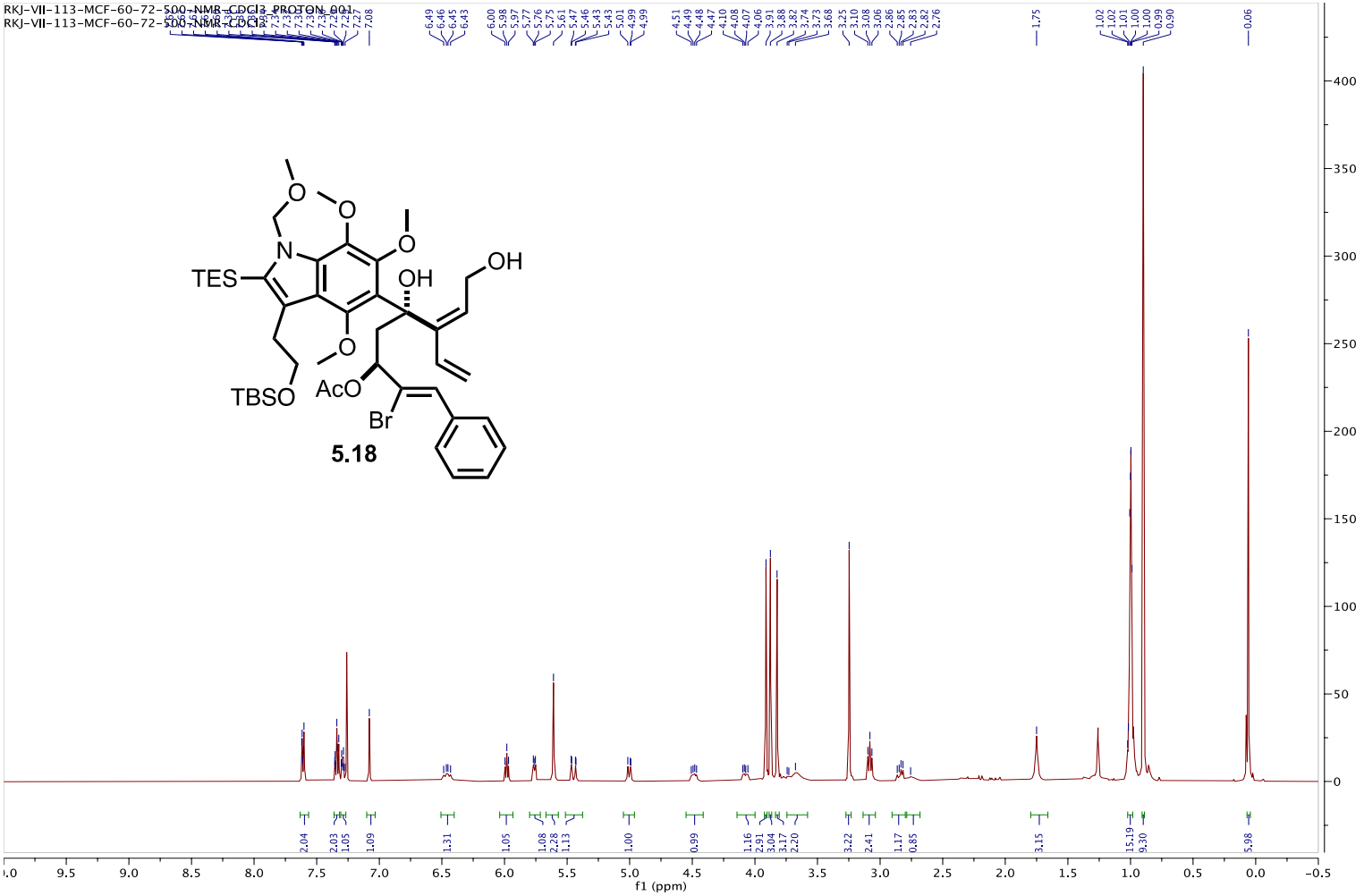


Figure E.44. **^{1}H NMR** (500 MHz, $CDCl_3$) Enyne Metathesis Product **5.18**

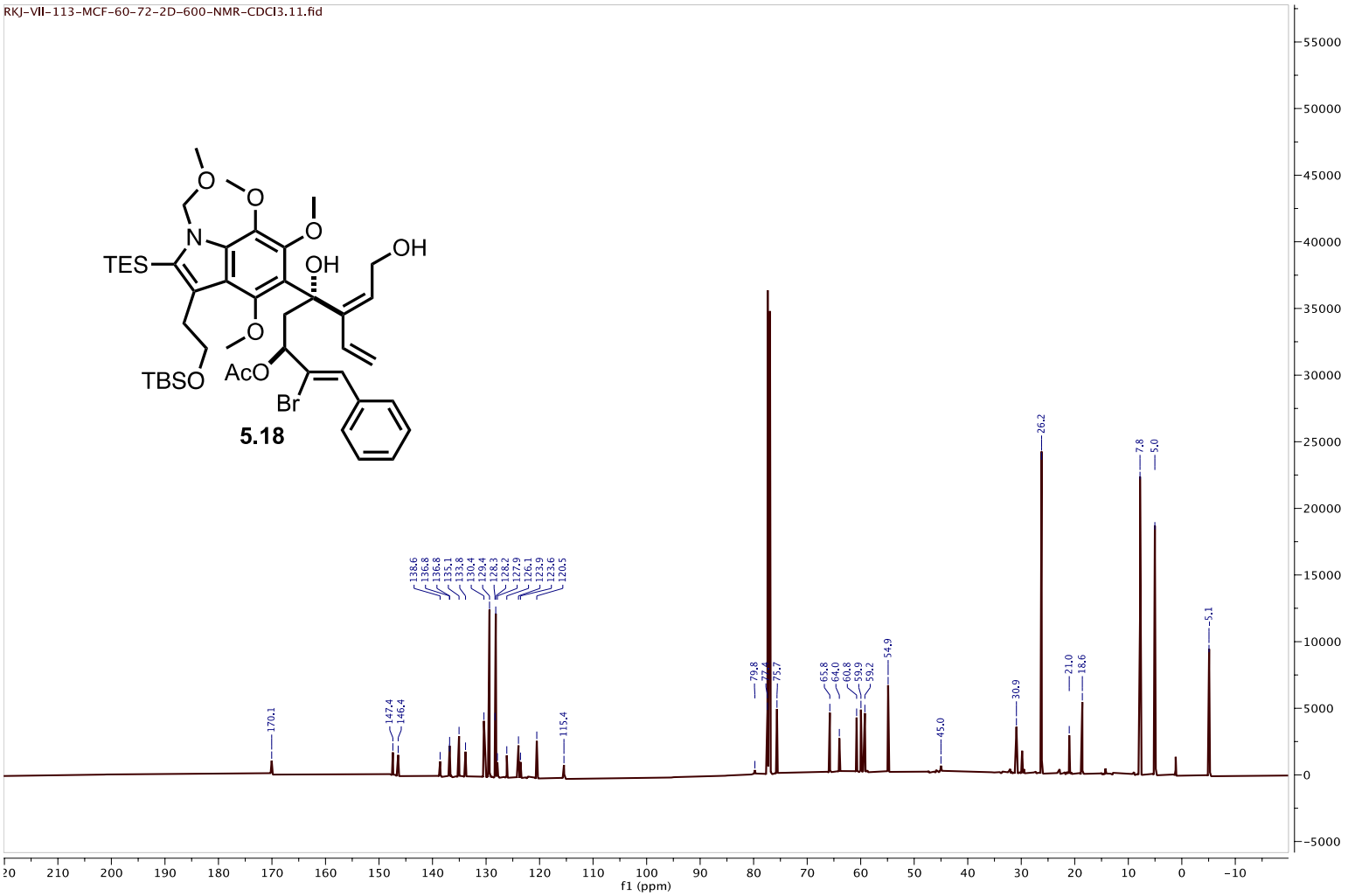


Figure E.45. **^{13}C NMR** (151 MHz, $CDCl_3$) Enyne Metathesis Product **5.18**

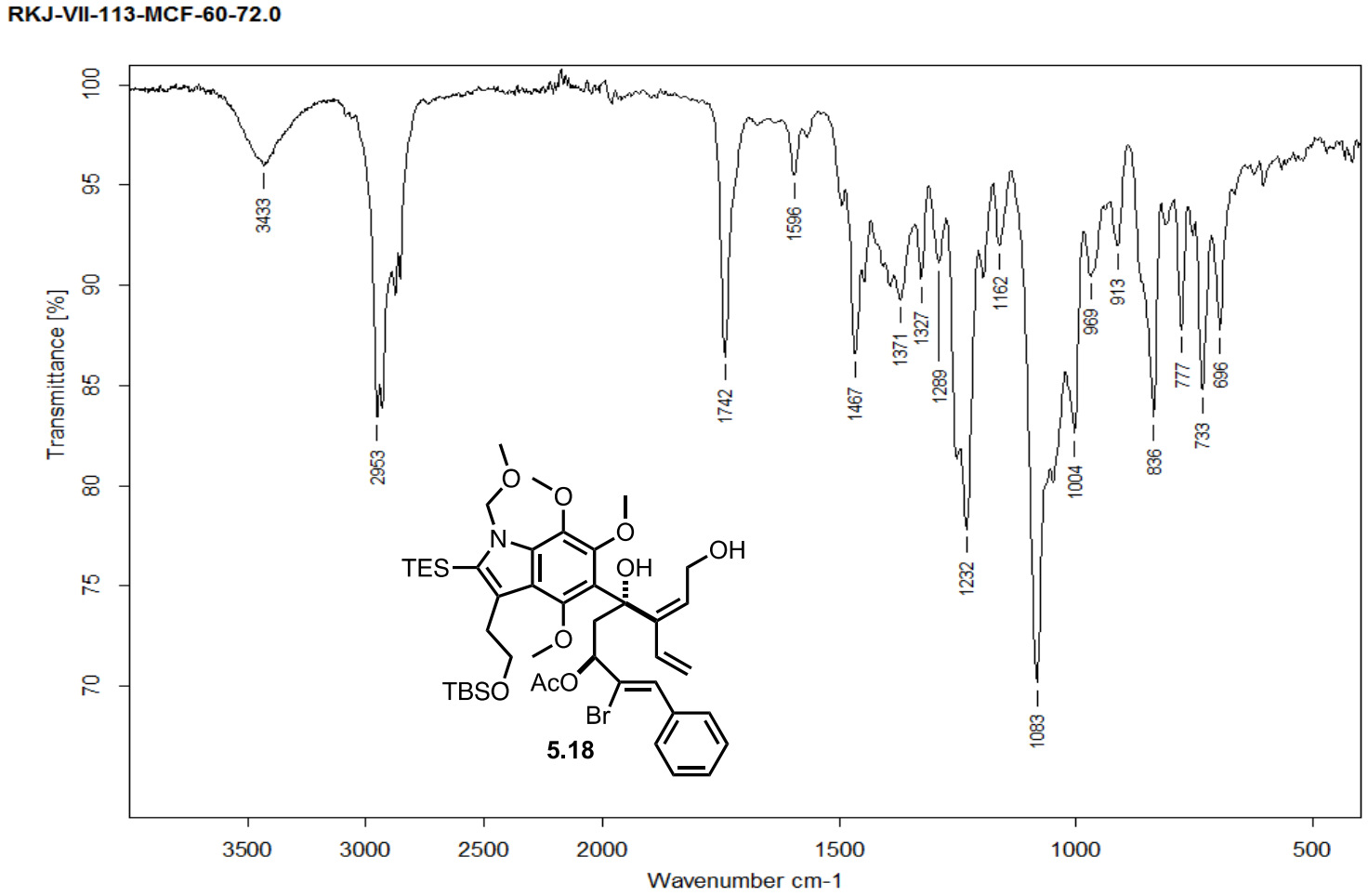


Figure E.46. **FTIR** (thin film) Enyne Metathesis Product **5.18**

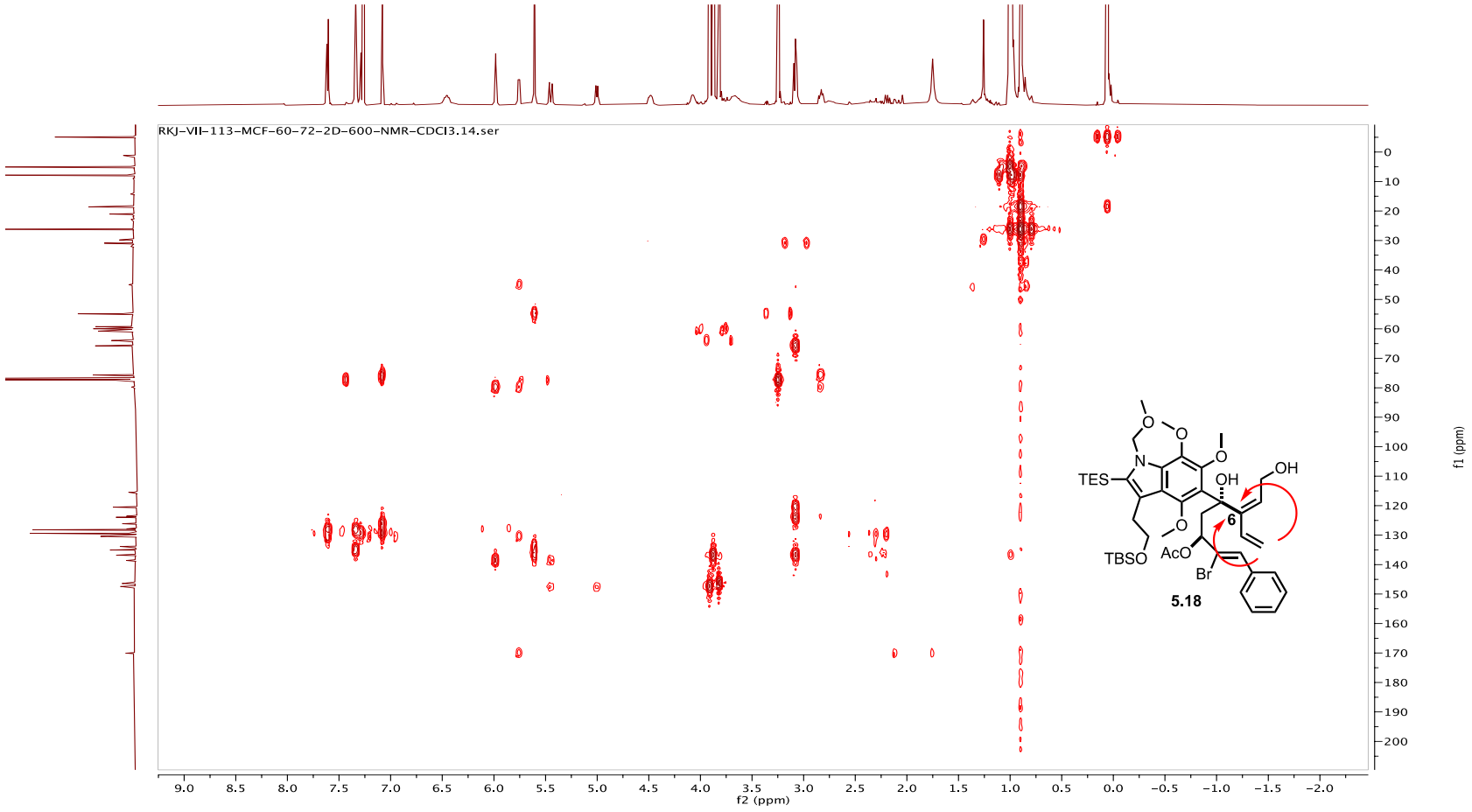


Figure E.47. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.18**
(For further detail, see inset on the next page.)

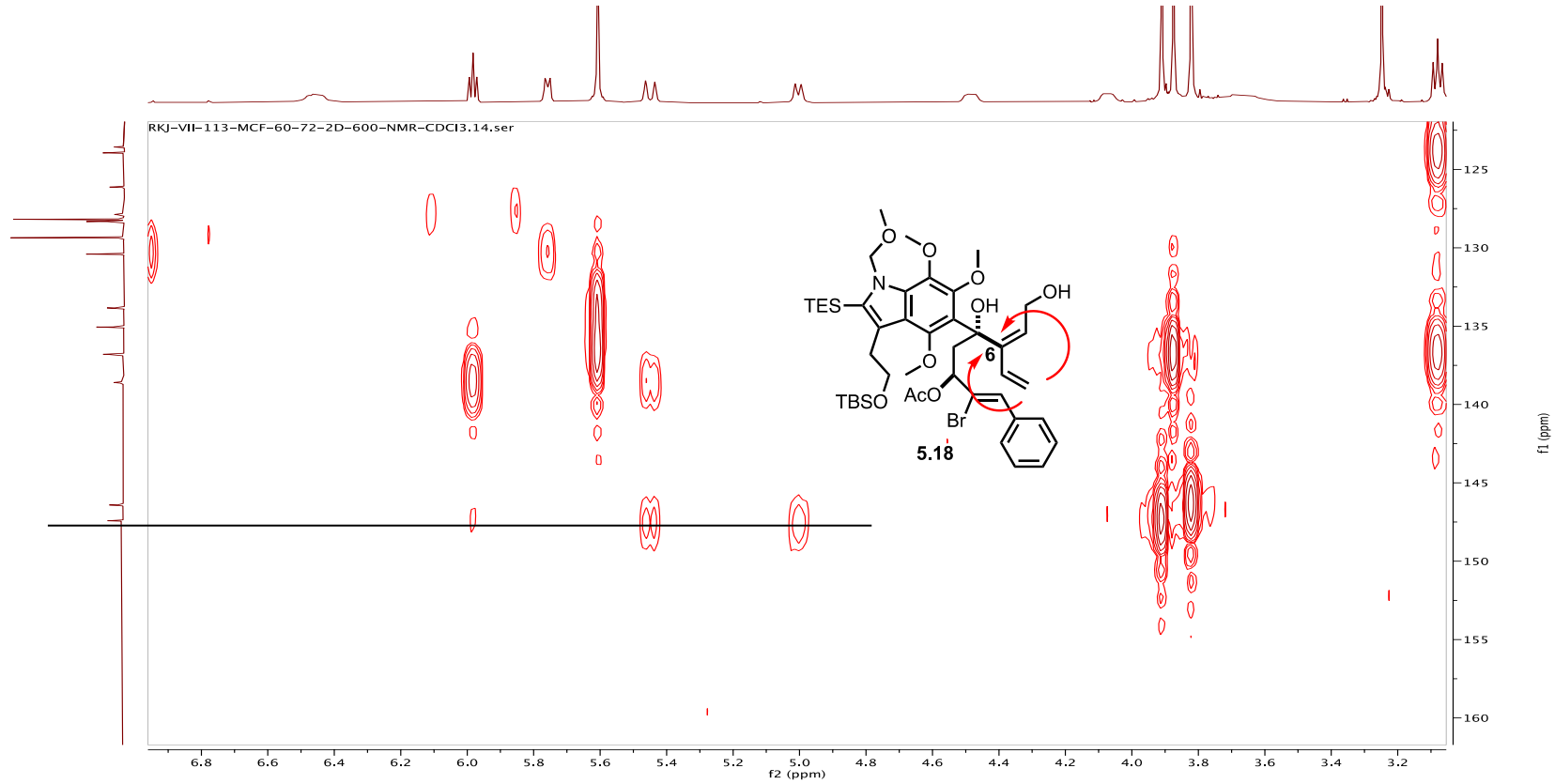


Figure E.48. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.18** Inset

Inset to show correlation between geminal olefin protons at 5.45 and 5.00 ppm to missing carbon at 147.6 ppm. The black line was placed to make the correlation more clear. The carbons located at 147.4 and 146.4 ppm have correlations with methoxy peaks at 3.91 and 3.82 ppm respectively and are resident in the indole's benzene ring.

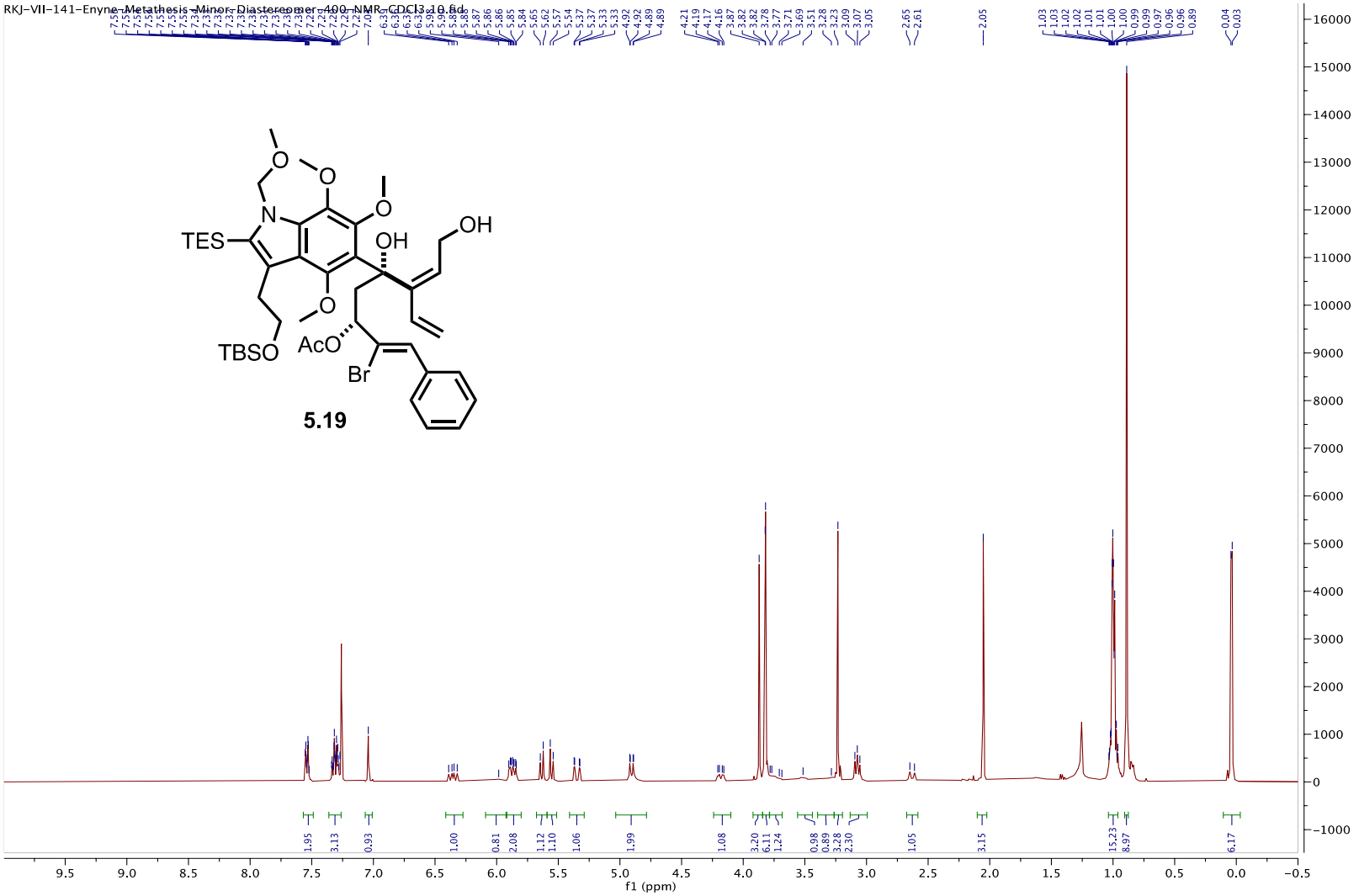


Figure E.49. **^{1}H NMR** (400 MHz, $CDCl_3$) Enyne Metathesis Product **5.19**

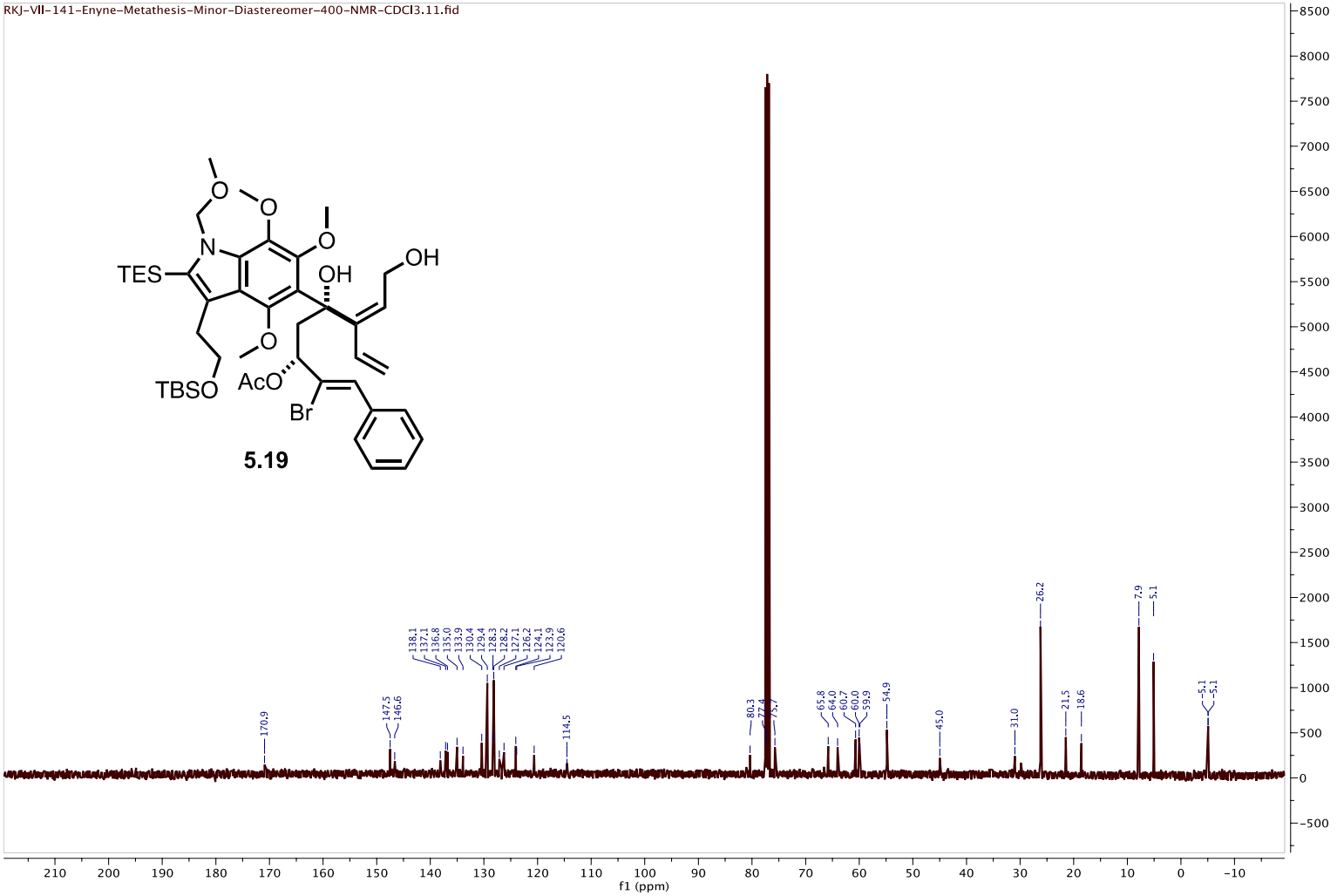


Figure E.50. **^{13}C NMR** (101 MHz, $CDCl_3$) Enyne Metathesis Product **5.19**

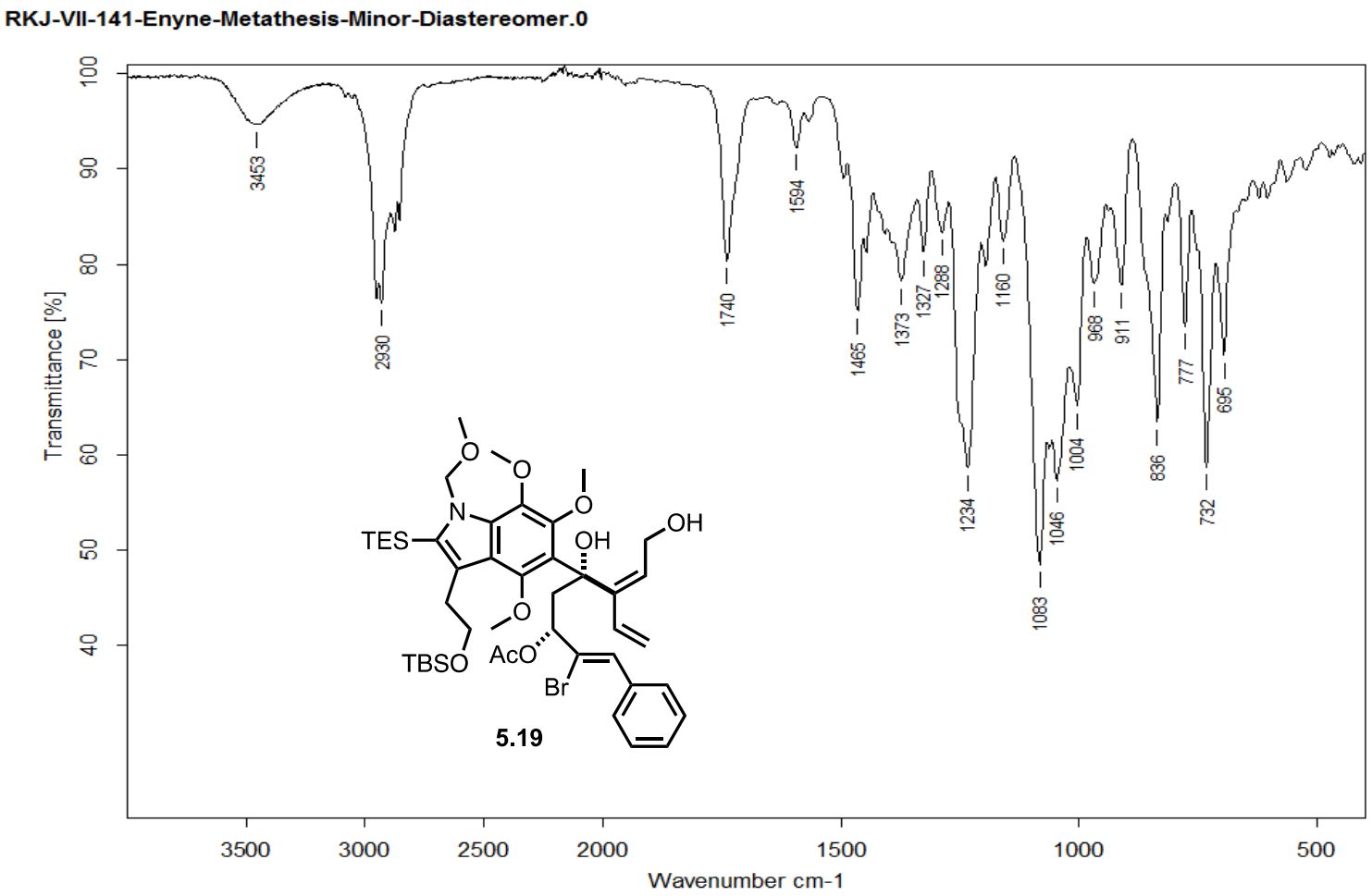


Figure E.51. **FTIR** (thin film) Enyne Metathesis Product **5.19**

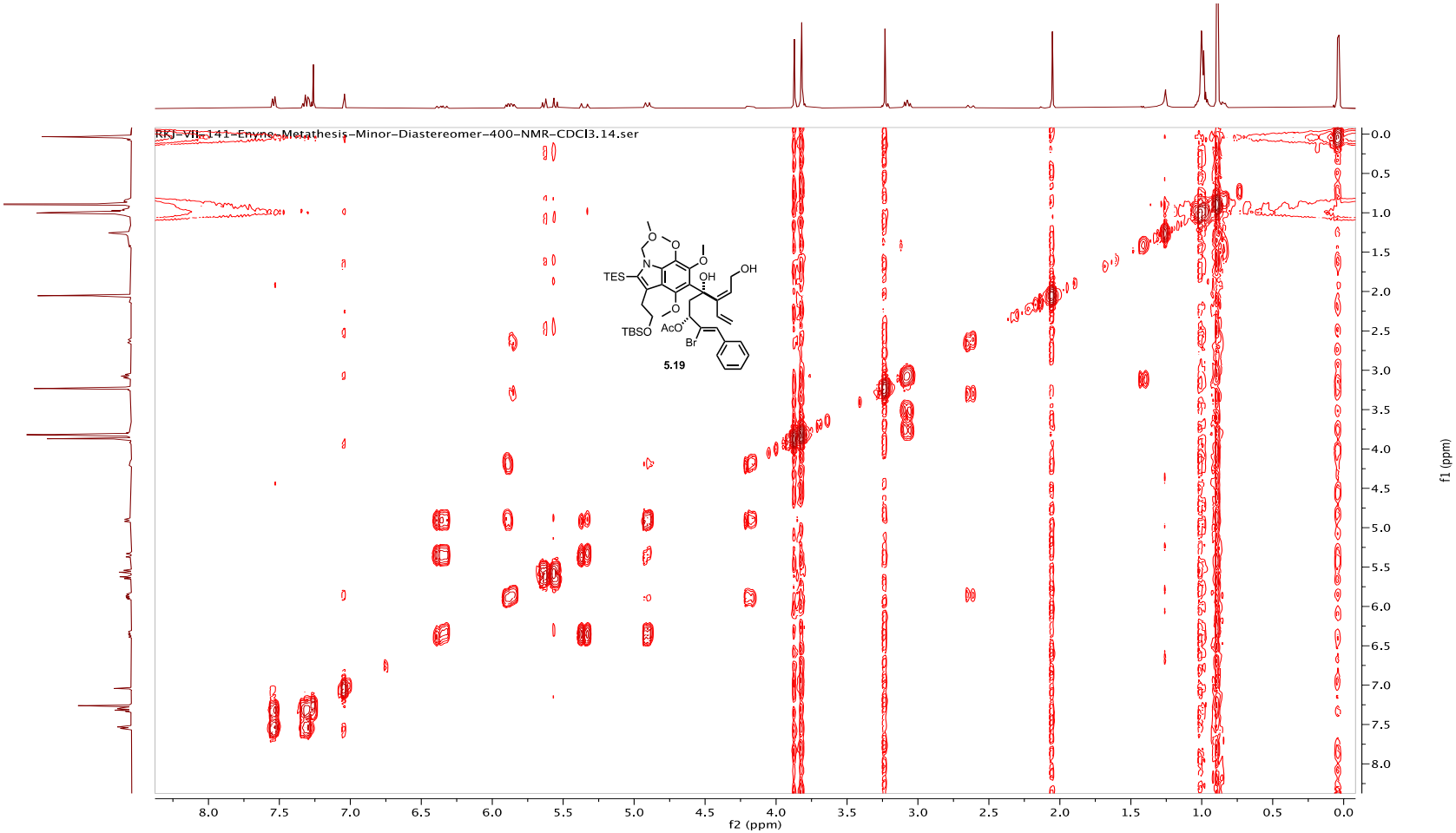


Figure E.52. **^{1}H-^{1}H COSY** (400 MHz, $CDCl_3$) **5.19**

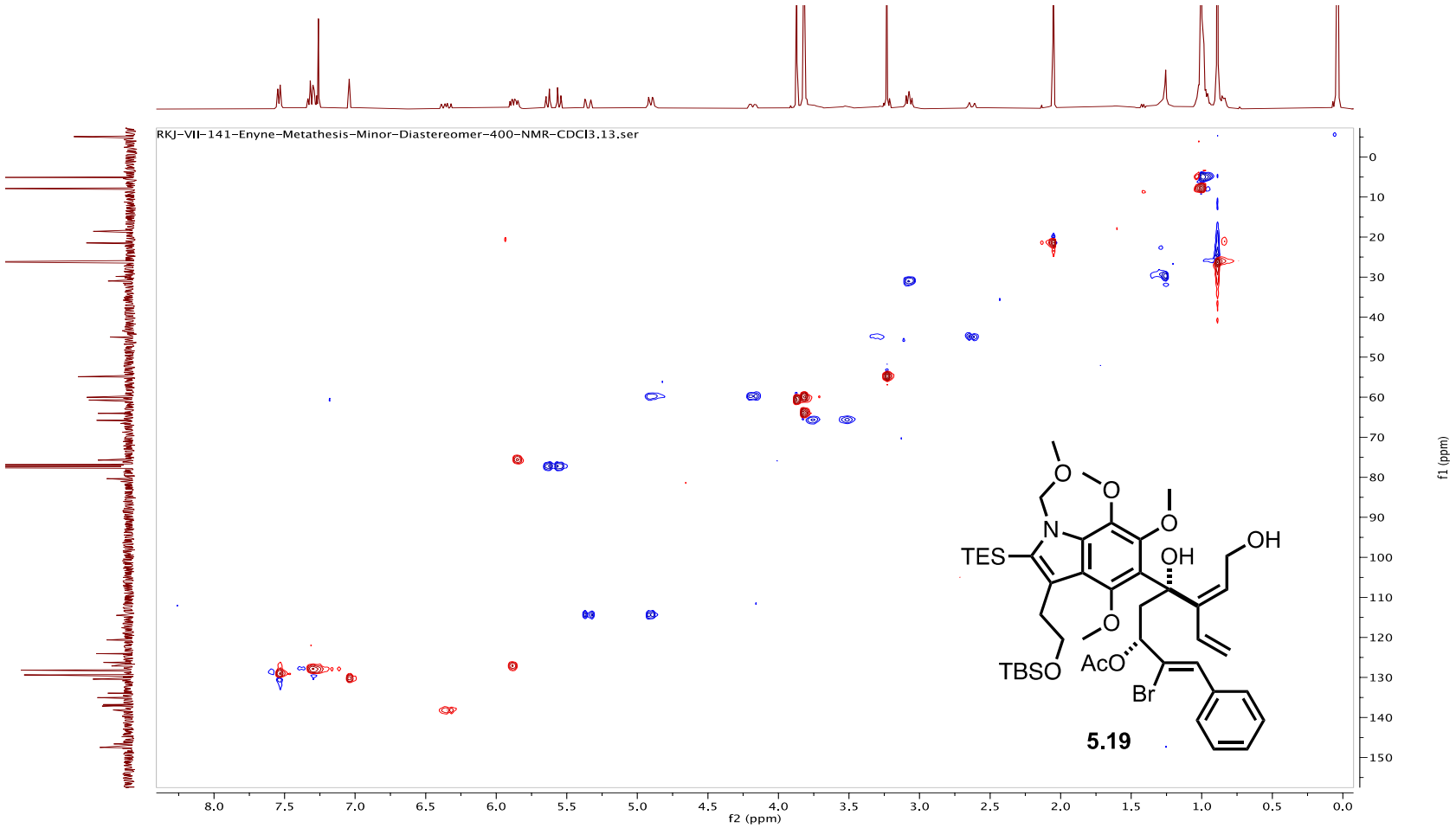


Figure E.53. **^{1}H-^{13}C HSQC** (400, 101 MHz, $CDCl_3$) **5.19**

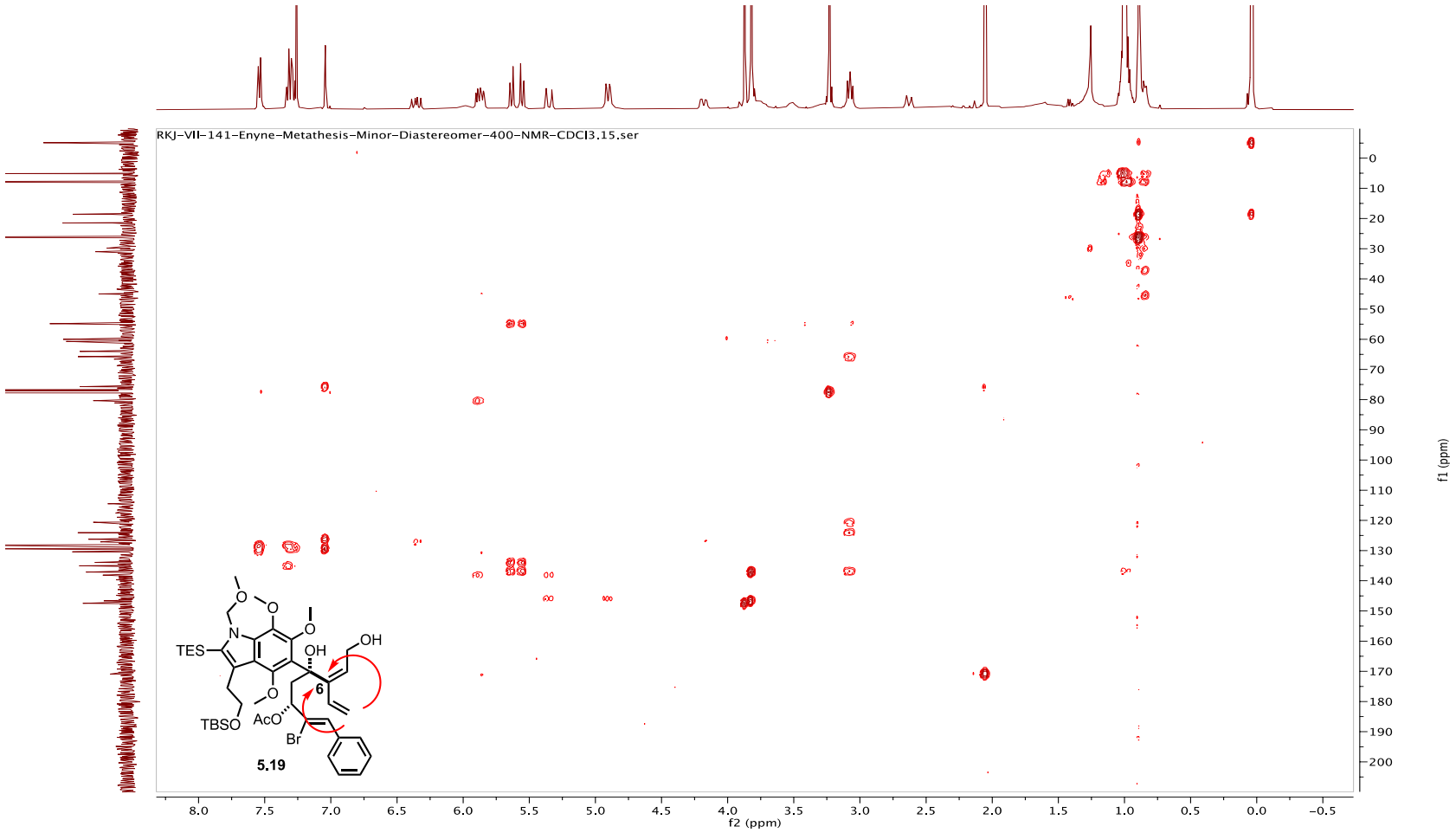


Figure E.54. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.19**
(For further detail regard correlation to missing C-6, see inset on the next page.)

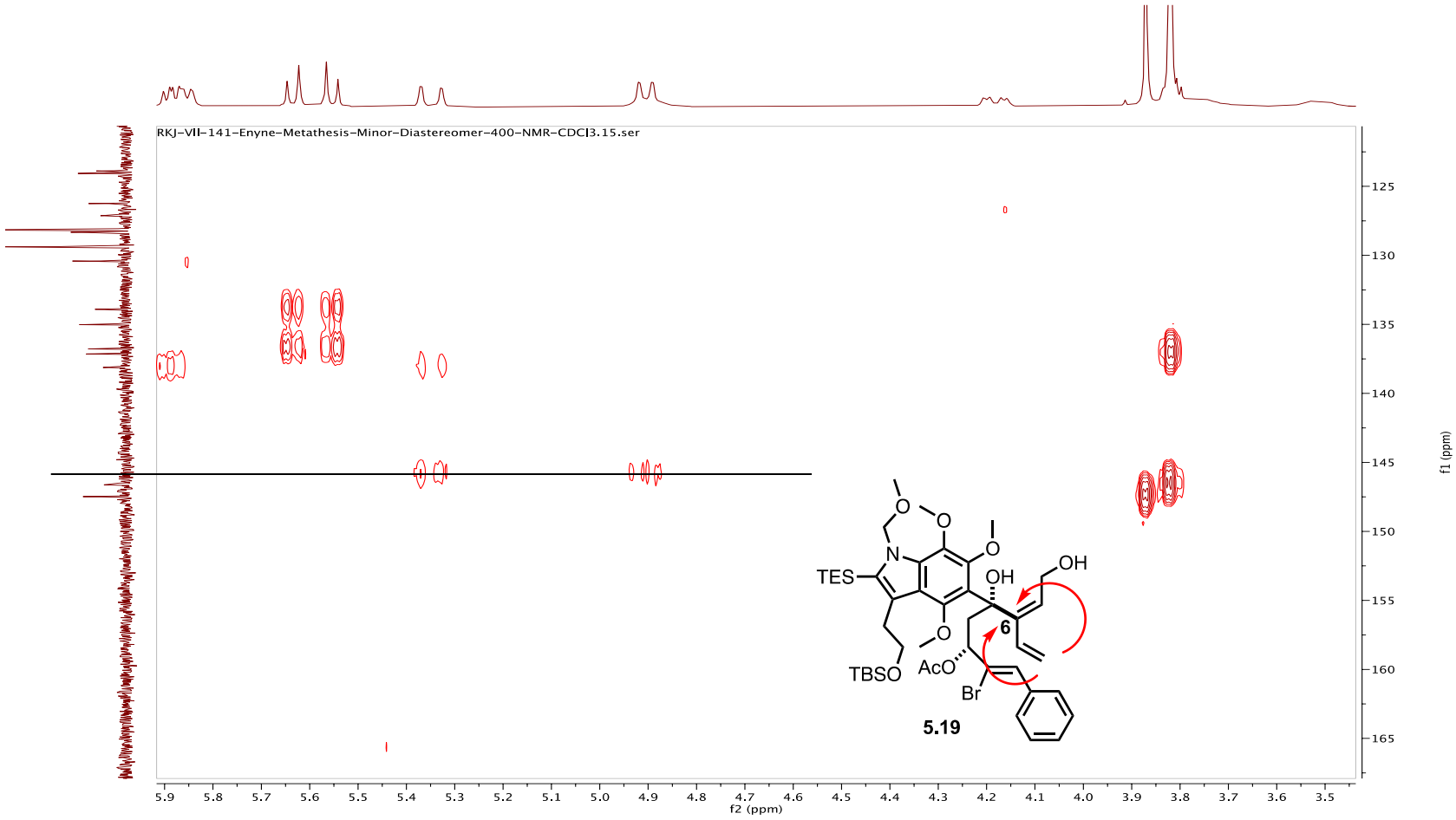


Figure E.55. **^{1}H-^{13}C HMBC** (400, 101 MHz, $CDCl_3$) **5.19** Inset

Inset to show correlation between geminal olefin protons at 5.35 and 4.91 ppm to missing carbon at 145.8 ppm. The black line was placed to make the correlation more clear.

COMPOUND NOTEBOOK CROSS REFERENCE

CHAPTER ONE

1.09.....RKJ-II-39
1.10.....RKJ-III-56
1.12.....RKJ-II-171
1.07.....RKJ-II-53
1.13.....RKJ-II-53
1.16.....RKJ-II-115
1.14.....RKJ-II-158
1.22.....RKJ-II-186
1.23.....RKJ-II-241
1.24.....RKJ-III-31
1.28.....RKJ-III-80
1.29.....RKJ-III-92
1.30.....RKJ-II-312
1.31.....RKJ-III-9
1.26.....RKJ-III-147
1.34.....RKJ-III-60
1.38.....RKJ-III-182
SI-1.05.....RKJ-III-112
1.05.....RKJ-III-71
1.39.....RKJ-III-72
1.40.....RKJ-III-72
1.25.....RKJ-III-74
1.41.....RKJ-III-173
(-)-1.02 .....RKJ-III-173

CHAPTER TWO

2.16.....RKJ-VII-124
2.17.....RKJ-VII-125
2.22.....RKJ-VII-125
2.19.....RKJ-VII-136-137
2.20 Major Diastereomer RKJ-VII-132
2.20 Minor Diastereomer.....RKJ-VII-137
2.21.....RKJ-VII-140

CHAPTER THREE

3.08.....RKJ-V-25
3.07.....RKJ-VII-148
3.20.....RKJ-VI-19
3.21.....RKJ-VI-36

3.24.....RKJ-V-295
3.25.....RKJ-VI-130
3.06.....RKJ-VI-25
3.26.....RKJ-VI-35
3.27.....RKJ-VI-42
3.30.....RKJ-VI-58

CHAPTER FOUR

4.06.....RKJ-VII-117
4.07.....JA-1-258
4.08.....JA-1-252
4.04.....JA-1-256
4.02.....RKJ-VI-136
4.09.....RKJ-VII-119
4.10.....JA-2-262; RKJ-VII-120-121
4.11.....JA-2-264; RKJ-VII-122
4.12.....JA-2-40; JA-2-267
4.13.....JA-2-40; JA-2-270
4.01.....JA-2-281

CHAPTER FIVE

5.08.....RKJ-VI-185
5.09.....RKJ-VII-22
5.10.....RKJ-VII-26
5.06.....RKJ-VI-21
5.12.....RKJ-VII-146-147
5.13.....RKJ-VII-152
5.15.....JA-2-207; RKJ-VII-161
5.16a and 5.16b.....RKJ-VII-105
5.05a and 5.05b.....JA-2-210
5.04a.....RKJ-VII-113
5.18.....RKJ-VII-113
5.19.....JA-2-220 and JA-2-222; RKJ-VII-141-Enyne

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ABOUT THE AUTHOR

Richard K. Jackson, III was born in Austin, TX on December 13, 1991 to Amy and Richard Jackson. His name derives from his early resemblance to his paternal grandfather, also Richard, as well as the abbreviation of his ponderous, fanciful, and kingly name to 'Ricky,' a persistent and apt nickname. Ricky was the only child of Richard and Amy and, as such, was spoiled beyond measure with soda, video games, and essentially no chores for much of his childhood. Indeed, to this day Ricky often jokes about his never having cleaned a bathroom (not entirely true, but gets across his almost total lack of childhood responsibility). Despite nearly complete indulgence, Ricky developed a love for education and diligently labored at schoolwork being particularly fond of History. Indeed, in 2010, when Ricky embarked on a college career at the University of Dallas (humorously located in Irving, TX) he declared History to be his major and continued along that path until his junior year of college. After serious contemplation, Ricky decided he did not want to be a lawyer or a teacher/professor of History (the two career frontrunners), and instead, switched his major to Chemistry being drawn to the discipline by great instruction and the beauty of the science. Upon graduation from UD, Ricky began work testing natural gas samples in the tiny town of Venus, TX (southern suburb in DFW area). Such an occupation gave Ricky the necessary resources to buy a wedding ring and propose to his college sweetheart, Claire Alexis. The wedding bells tolled in July of 2015, and after the couple's honeymoon in New Mexico, Ricky and Claire settled in San Antonio, TX. Ricky found work in blood bank handling

blood platelets which had been gathered through apheresis. After a few years without distinct career trajectory, Ricky, encouraged by his father-in-law, applied to Baylor University in the Department of Chemistry and Biochemistry. Having no meaningful lab experience, and nothing other than a B.S. to recommend himself, Ricky somehow landed in the legendary group of John L. Wood, performing total syntheses of complex natural products. Forged in the testing fires of the Wood Group, in Yu-Wen Huang's tough-love teaching, and in John L. Wood's demand for excellence in everything, Ricky was transformed from 2018-2022 into a chemist capable of tackling total syntheses, testing wild hypotheses, and, at long last, earning an occupation that could support a family. Now nearly 31, Ricky is about to pack up his bags and head out east to start a position as Global R&D Scientist with FMC and start life afresh. The journey has been long and circuitous, but Ricky could not be happier with his decision to attend Baylor University and earn his Ph.D. in Chemistry.