UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Chemistry and Biology of Zoanthamine Alkaloids and *Illicium* Sesquiterpenes

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2012

The dissertation of Lynnie L. Trzoss is approved,
and is acceptable in quality and form
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Chair

University of California, San Diego

2012

DEDICATION

To my daughter and my husband; thank you for the unconditional love and support.

EPIGRAPH

When you feel like giving up, remember why you held on so long in the first place.

TABLE OF CONTENTS

Signature Page ……...… iii

Dedication ……...……...… iv

Epigraph ……..... v

Table of Contents ……..… vi

List of Abbreviations …… xi

List of Figures ……... xiv

List of Schemes ……. xv

List of Tables …… xviii

List of Spectras ……... xix

Acknowledgements ……... xxv

Vita …… xxvi

Abstract of the dissertation ……...… xxviii

Chapter 1 The biology and chemistry of the zoanthamine alkaloids …… 1

1.1 Introduction to the zoanthamine alkaloids …….. 1

1.1.1 Isolation and structural characterization ……... 3

1.1.2 Proposed biosynthesis of zoanthamines …… 6

1.1.3 Reactivity of norzoanthamine ……... 7

1.2 Biological activities of zoanthamines ……. 8

1.2.1 Antiosteoporotic activity ……... 8

1.2.2 Other biological activities ……. 10

1.3 Reported synthetic studies …….. 11

1.3.1 Miyashita's total synthesis of norzoanthamine ……. 11

1.3.2 Kobayashi's total synthesis of norzoanthamine …… 14

1.3.3 Tanner's approach to the ABC ring system of norzoanthamine…….. 16

1.3.4 Uemura's biomimetic approach to the ABC ring system of norzoanthamine …… 17

1.3.5 William's approaches to the AB and EFG ring systems of norzoanthamine ……. 18

1.3.6 Yang's approach to the ABC ring system of norzoanthamine ……. 19

1.3.7 Hirama's strategy for the zoanthenol ABC ring system……. 20

1.3.8 Stoltz's approach to the ABC ring system of zoanthenol ……. 22

1.3.9 Miyashita's total synthesis of zoanthenol ……. 23

1.4 Early efforts towards the synthesis of zoanthamines …… 24

1.4.1 An annulation approach to the ABC ring system of norzoanthamine ……. 24

1.4.2 A biomimetic approach to the ABC ring system of zoanthenol 27

1.5 Concluding remarks …….. 29

1.6 References ……. 29

Chapter 2 Enantioselective synthesis of the ABC ring system of norzoanthamine ……. 35

2.1 Retrosynthetic analysis ……...…… 35

2.2 Synthesis of the BC ring system ……. 36

2.3 Stereoselective synthesis of the ABC ring system …….. 37

2.4 Installation of C9 quaternary carbon ……... 38

2.5 Concluding remarks …… 40

2.6 References ……... 41

2.7 Experimental techniques and characterization data …… 42

Chapter 3 The chemistry and biology of *Illicium* sesquiterpenes ……. 104

3.1 Introduction to the *Illicium* sesquiterpenes ……. 104

3.1.1 Isolation and structural characterization ……... 105

3.1.1.1 *Seco*-prezizaane-type ……. 106

3.1.1.1.1 Anisatin-subtype ……. 106

3.1.1.1.2 Pseudoanisatin-subtype ……... 108

3.1.1.1.3 Minwanensin-subtype ……. 108

3.1.1.1.4 Majucin-subtype …….. 109

3.1.1.1.5 Pseudomajucin-subtype …….. 111

3.1.1.1.6 Cycloparvifloralone-subtype ……... 111

3.1.1.1 *Allo*-cedrane-type …….. 112

3.1.1.2 Anislactone-type ……... 113

3.1.2 Proposed biosynthetic pathway ……. 114

3.2 Biological activities of the *Illicium* sesquiterpenes ……. 115

3.2.1 Neurotoxic activity …… 115

3.2.2 Neurotrophic activity …… 116

3.3 Reported synthetic studies …….. 118

3.3.1 Total synthesis of (±)-8-deoxyanistatin ……. 118

3.3.2 Total syntheses of (–)-Anisatin and (–)-neoanisatin …. 120

3.3.3 Formal synthesis of (±)-8-deoxyanistatin ……. 121

3.3.4 Synthetic studies towards (±)-jiadifenin ……... 122

3.3.4.1 Danishefsky's total synthesis of jiadifenin …... 123

3.3.4.2 Synthesis of the ABC ring system by Fukuyama …….. 124

3.3.5 Total synthesis of (+)-1S-minwanenone ……... 125

3.3.6 Total synthesis of (±)-11-*O*-debenzoyltashironin ……. 126

3.3.7 Total syntheses of merrilactone A …… 128

3.3.7.1 Danishefsky's synthesis …… 128

3.3.7.2 Inoue's synthesis ……... 130

3.3.7.3 Mehta's synthesis …….. 133

3.3.7.4 Frontier's synthesis ……... 133

3.3.7.5 Greaney's synthesis ……... 134

3.4 Concluding remarks …… 135

3.5 References ……... 136

Chapter 4 Total syntheses of (–)-jiadifenolide, (–)-jiadifenin and related compounds and their biological studies ……... 142

4.1 Retrosynthetic analysis ……... 142

4.2 Total synthesis of (–)-jiadifenolide ……. 144

4.2.1 Synthesis of the ABC ring system …… 144

4.2.2 Synthesis of E ring …… 145

4.2.3 Completion of (–)-jiadifenolide …… 147

4.3 Total synthesis of (–)-jiadifenin …… 149

4.3.1 Synthesis of the carbon framework ……... 149

4.3.2 Completion of (–)-jiadifenin ……. 151

4.4 Preparation of analogues ……... 152

4.5 Biological evaluations ……... 156

4.6 Concluding remarks …….. 159

4.7 References ……. 161

4.8 Experimental techniques and characterization data …….. 164

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
t-Bu	*tert*-butyl
Bn	benzyl
°C	degrees Celsius
calcd	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CD_3OD	deuterated methanol
CH_3OH	methanol
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
h	hours

HCl	hydrogen chloride
hν	irradiation with light
HMPA	hexamethylphosphoramide
KHMDS	potassium bis(trimethylsilyl)amide
HRMS	high-resolution mass spectrometry
IBX	*o*-iodoxybenzoic acid
IC_{50}	mean inhibitory concentration
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	m-chloroperoxybenzoic acid
Me	methyl
MeI	methyl iodide
MeOH	methanol
MOM	methoxymethyl
MHz	megahertz
mL	milliliter
RT	room temperature
μL	microliter
μmole	micromole
mmol	millimole
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
NOE	nuclear overhause effect
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)

Ph	phenyl
PMB	*p*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
R_f	retention factor
SAR	structure – activity relationship
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl

LIST OF FIGURES

Figure 1.1.1 Selected zoanthids species …… 1

Figure 1.1.2 Selected natural products isolated from zoanthids ……... 2

Figure 1.1.1.1 Zoanthamines isolated by Rao and Faulkner ……. 3

Figure 1.1.1.2 Zoanthamines isolated by Uemura and Clardy …….. 4

Figure 1.1.1.3 Zoanthamines isolated by Norte and Fattorusso …… 6

Figure 1.2.1 IC_{50} values for IL-6 cell growth inhibition by Uemura and Hirama……... 9

Figure 1.3.1 Retrosynthetic analysis of norzoanthamine by Miyashita …… 12

Figure 3.1.1 *Illicium jiadifengpi* and Chinese star anise ……... 104

Figure 3.1.2 Representative natural products isolated from *Illicium* species ... 105

Figure 3.1.1.1.1 Anisatin-subtype sesquiterpenes ……..… 106

Figure 3.1.1.1.2 Pseudoanisatin-subtype sesquiterpenes …….. 107

Figure 3.1.1.1.3 Minwanensin-subtype sesquiterpenes …… 109

Figure 3.1.1.1.4 Majucin-subtype sesquiterpenes ……. 110

Figure 3.1.1.1.5 Pseudomajucin-subtype sesquiterpenes …….. 111

Figure 3.1.1.1.6 Cycloparvifloralone-subtype sesquiterpenes …….. 112

Figure 3.1.1.2 *Allo*-cedrane-type sesquiterpenes …….. 113

Figure 3.1.1.3 Anislactone-type sesquiterpenes …… 114

Figure 3.2.1 Lethality (LD_{50}) induced by representative *Illicium* Sesquiterpenes …….. 116

Figure 3.2.2 Neurotrophic Illicium sesquiterpenes ……... 117

Figure 4.5 Neurite outgrowths relative to DMSO + NGF control …… 157

LIST OF FIGURES

Scheme 1.1.1.1 Application of Mosher's method to determine the absolute configuration of norzoanthamine by Uemura ……. 5

Scheme 1.1.2 Proposed biosynthesis of norzoanthamine by Uemura …….. 6

Scheme 1.1.3 Equilibrium between lactone and enamine forms of norzoanthamine…….. 8

Scheme 1.3.1.1 Synthesis of the ABC ring system by the Miyashita group … 12

Scheme 1.3.1.2 Completion of norzoanthamine by the Miyashita group ……. 13

Scheme 1.3.2.1 Bisaminal formation strategy developed by the Kobayashi group……..... 14

Scheme 1.3.2.2 Retrosynthetic analysis of norzoanthamine by the Kobayashi group ……... 14

Scheme 1.3.2.3 Kobayashi's synthesis of ABC ring system …… 15

Scheme 1.3.2.4 Completion of norzoanthamine by the Kobayashi group …… 16

Scheme 1.3.3 Diels-Alder cyclization approach by the Tanner group ……. 17

Scheme 1.3.4 Biomimetic approach by Uemura ……... 18

Scheme 1.3.5.1 William's Diels-Alder approach to the AB rings of norzoanthamine …….. 18

Scheme 1.3.5.2 William's approach to a modeled EFG rings of Norzoanthamine ……. 19

Scheme 1.3.6 Yang's approach to the ABC ring system of norzoanthamine ... 20

Scheme 1.3.7 Hirama's Heck strategy for the synthesis of ABC rings of zoanthenol …….. 21

Scheme 1.3.8.1 Retrosynthetic analysis of zoanthenol by the Stoltz group….. 22

Scheme 1.3.8.2 Stoltz's synthesis of the ABC ring system of zoanthenol 23

Scheme 1.3.9 Total synthesis of zoanthenol by the Miyashita group ……... 24

Scheme 1.4.1.1 Retrosynthetic analysis of norzoanthamine via the annulation strategy …… 25

Scheme 1.4.1.2 Synthesis of the ABC ring system of norzoanthamine …… 26

Scheme 1.4.1.3 Installation of the C9 quaternary stereocenter ……. 26

Scheme 1.4.2.1 Proposed biogenetic pathway for zoanthamines ……. 27

Scheme 1.4.2.2 IMDA of 2-amido and 2-oxo-dienes for the formation of C-ring in zoanthenol model system ……... 28

Scheme 2.1 Revised retrosynthetic analysis of norzoanthamine …….. 35

Scheme 2.2 Enantioselective synthesis of BC ring system ……... 36

Scheme 2.3 Stereoselective synthesis of ABC ring system …….. 38

Scheme 2.4.1 Attempt to the installation of C9 quaternary carbon center …... 39

Scheme 2.4.2 Installation of the C9 quaternary carbon center ……. 40

Scheme 2.5 Proposed synthesis of norzoanthamine…….. 41

Scheme 3.1.2 Proposed biosynthetic pathway of *Illicium* sesquiterpenes …… 115

Scheme 3.3.1 Total synthesis of (±)-8-deoxyanisatin by the Kende group ….. 119

Scheme 3.3.2.1 Total synthesis of (–)-anisatin by the Yamada group …….. 120

Scheme 3.3.2.2 Total synthesis of (–)-neoanisatin the Yamada group ……. 121

Scheme 3.3.3 Formal synthesis of (±)-8-deoxyanistatin by the Loh group ….. 122

Scheme 3.3.4.1 Total synthesis of (±)-jiadifenin by the Danishefsky group … 123

Scheme 3.3.4.2 Synthesis of the ABC ring system by the Fukuyama group … 125

Scheme 3.3.5 Total synthesis of (+)-1*S*-minwanenone by the Mehta group … 126

Scheme 3.3.7.1.1 Total synthesis of (±)-merrilactone A by the Danishefsky group …… 129

Scheme 3.3.7.1.2 Enantioselective synthesis of merrilactone A by Danishefsky's group …… 130

Scheme 3.3.7.2.1 Racemic synthesis of merrilactone A by the Inoue group … 130

Scheme 3.3.7.2.2 Enantioselective synthesis of merrilactone A via a chiral base ……... 131

Scheme 3.3.7.2.3 Enantioselective synthesis of merrilactone A by the Inoue group …… 132

Scheme 3.3.7.3 Total synthesis of (±)-merrilactone A by the Mehta group …. 133

Scheme 3.3.7.4 Total synthesis of (±)-merrilactone A by the Frontier group .. 134

Scheme 3.3.7.5 Formal synthesis of (±)-merrilactone A by the Greaney group …… 135

Scheme 4.1 Retrosynthetic analysis of (–)-jiadifenin and (–)-jiadifenolide …. 143

Scheme 4.2.1 Synthesis of ABC ring system of (–)-jiadifenolide …… 145

Scheme 4.2.2 Synthesis of E ring via a cascade translactonization reaction … 146

Scheme 4.2.3 Completion of (–)-jiadifenolide …….. 148

Scheme 4.3.1 Synthesis of carbon framework of jiadifenin ……. 149

Scheme 4.3.2 Completion of (–)-jiadifenin …….. 151

Scheme 4.4.1 Attempts toward the synthesis of pharmacophore **195** ……... 152

Scheme 4.4.2 Revised synthesis of pharmacophore **195** …….. 154

Scheme 4.4.3 Synthesis of analogues ……... 155

LIST OF TABLES

Table 4.5 SAR profile table of jiadifenolide analogues …… 159

Table 4.7.1 1H and 13C NMR data comparison of synthetic 3 with natural (–)-jiadifenolide …… 181

Table 4.7.2 1H NMR data comparison of the synthetic 2 with natural (–)-jiadifenin and synthetic (±)-jiadifenin ……. 189

Table 4.7.3 13C NMR data comparison of the synthetic 2 with natural (–)-jiadifenin and synthetic (±)-jiadifenin ……... 190

Table 4.7.4 Neurite outgrowths of tested compounds after 72 h incubation … 209

Table 4.7.5 Crystal data and structure refinement for **182** …… 211

Table 4.7.6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å2x 10^3) for **182** ……... 213

Table 4.7.7 Bond lengths [Å] and angles [°] for **182** …… 214

Table 4.7.8 Anisotropic displacement parameters (Å^{2}x 10^3) for **182** …….. 216

Table 4.7.9 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å2x 10^3) for **182** …… 217

Table 4.7.10 Crystal data and structure refinement for **198** …….. 218

Table 4.7.11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å2x 10^3) for **198** …… 220

Table 4.7.12 Bond lengths [Å] and angles [°] for **198** …….. 222

Table 4.7.13 Anisotropic displacement parameters (Å^{2}x 10^3) for **198** …… 228

Table 4.7.14 Hydrogen coordinates (x 10^4) and isotropic displacement parameter (Å2x 10^3) for **198** ……... 230

LIST OF SPECTRAS

Spectrum 2.1 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **128** …….. 64

Spectrum 2.2 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **128** ……. 65

Spectrum 2.3 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **126** …….. 66

Spectrum 2.4 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **126** ……. 67

Spectrum 2.5 ^{1}H NMR ($CDCl_3$, 400 MHz) of C13 alcohol …….. 68

Spectrum 2.6 ^{13}C NMR ($CDCl_3$, 100 MHz) of C13 alochol ……. 69

Spectrum 2.7 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **129** …….. 70

Spectrum 2.8 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **129** ……. 71

Spectrum 2.9 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **130** …….. 72

Spectrum 2.10 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **130** ……... 73

Spectrum 2.11 ^{1}H NMR ($CDCl_3$, 400 MHz) of C9 alochol …….. 74

Spectrum 2.12 ^{13}C NMR ($CDCl_3$, 100 MHz) of C9 alcohol ……. 75

Spectrum 2.13 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **131** …… 76

Spectrum 2.14 ^{13}C NMR ($CDCl_3$ 100 MHz) of compound **131** ……... 77

Spectrum 2.15 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **132** …… 78

Spectrum 2.16 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **132** ……... 79

Spectrum 2.17 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **133** …… 80

Spectrum 2.18 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **133** ……... 81

Spectrum 2.19 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **134** …… 82

Spectrum 2.20 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **134** ……... 83

Spectrum 2.21 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **135** 84

Spectrum 2.22 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **135** ……... 85

Spectrum 2.23 ^{1}H NMR ($CDCl_3$, 400 MHz) of di-TIPS ether …….. 86

Spectrum 2.24 ^{13}C NMR ($CDCl_3$, 100 MHz) of di-TIPS ether ……. 87

Spectrum 2.25 ^{1}H NMR ($CDCl_3$, 400 MHz) of C15 alcohol …… 88

Spectrum 2.26 ^{13}C NMR ($CDCl_3$, 100 MHz) of C15 alcohol ……... 89

Spectrum 2.27 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **136** …… 90

Spectrum 2.28 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **136** ……... 91

Spectrum 2.29 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **141** …… 92

Spectrum 2.30 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **141** ……... 93

Spectrum 2.31 ^{1}HNMR ($CDCl_3$, 400 MHz) of C9-C10 olefin …….. 94

Spectrum 2.32 ^{13}C NMR ($CDCl_3$, 100 MHz) of C9-C10 olefin …… 95

Spectrum 2.33 ^{1}HNMR ($CDCl_3$, 400 MHz) of compound **142** ……. 96

Spectrum 2.34 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **142** ……... 97

Spectrum 2.35 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **143** …… 98

Spectrum 2.36 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **143** ……... 99

Spectrum 2.37 ^{1}H NMR ($CDCl_3$, 400 MHz) of methyl enone ether ……. 100

Spectrum 2.38 ^{13}C NMR ($CDCl_3$, 100 MHz) methyl enone ether …… 101

Spectrum 2.39 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **124** …… 102

Spectrum 2.40 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **124** ……... 103

Spectrum 4.1 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **171** ……. 232

Spectrum 4.2 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **171** …… 233

Spectrum 4.3 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **176** ……. 234

Spectrum 4.4 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **176** …… 235

Spectrum 4.5 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **178** ……. 236

Spectrum 4.6 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **178** …… 237

Spectrum 4.7 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **179** ……. 238

Spectrum 4.8 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **179** …… 239

Spectrum 4.9 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **170** ……. 240

Spectrum 4.10 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **170** …….. 241

Spectrum 4.11 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **180** ……... 242

Spectrum 4.12 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **180** …….. 243

Spectrum 4.13 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **181** ……... 244

Spectrum 4.14 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **181** …….. 245

Spectrum 4.15 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **181** …….. 246

Spectrum 4.16 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **182** ……... 247

Spectrum 4.17 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **182** …….. 248

Spectrum 4.18 ^{1}H NMR (CD_3OD, 500 MHz) of compound **169** ……. 249

Spectrum 4.19 ^{13}C NMR (CD_3OD, 125 MHz) of compound **169** …… 250

Spectrum 4.20 ^{1}H NMR (CD_3OD, 500 MHz) of compound **167** ……. 251

Spectrum 4.21 ^{13}C NMR (CD_3OD, 125 MHz) of compound **167** …… 252

Spectrum 4.22 ^{13}C NMR (CD_3OD, 125 MHz) of compound **167** …… 253

Spectrum 4.23 ^{1}H NMR (CD_3OD, 500 MHz) of compound **184** ……. 254

Spectrum 4.24 ^{13}C NMR (CD_3OD, 125 MHz) of compound **184** …… 255

Spectrum 4.25 ^{13}C NMR (CD_3OD, 125 MHz) of compound **184** …… 256

Spectrum 4.26 ^{1}H NMR (CD_3OD, 500 MHz) of compound **185** ……. 257

Spectrum 4.27 ^{13}C NMR (CD_3OD, 125 MHz) of compound **185** …… 258

Spectrum 4.28 ^{13}C NMR (CD_3OD, 125 MHz) of compound **185** …… 259

Spectrum 4.29 ^{1}H NMR (CD_3OD, 500 MHz) of compound **(-)-3** …… 260

Spectrum 4.30 ^{1}H NMR (CD_3OD, 500 MHz) of compound **(-)-3** …… 261

Spectrum 4.31 ^{13}C NMR (CD_3OD, 125 MHz) of compound **(-)-3** ……... 262

Spectrum 4.32 ^{13}C NMR (CD_3OD, 125 MHz) of compound **(-)-3** ……... 263

Spectrum 4.33 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **188** ……... 264

Spectrum 4.34 ^{13}H NMR ($CDCl_3$, 125 MHz) of compound **188** …….. 265

Spectrum 4.35 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **188** …….. 266

Spectrum 4.36 ^{1}H NMR (CD_3OD, 500 MHz) of compound **189** ……. 267

Spectrum 4.37 ^{13}C NMR (CD_3OD, 125 MHz) of compound **189** 268

Spectrum 4.38 ^{1}H NMR (CD_3OD, 500 MHz) of compound **190** ……. 269

Spectrum 4.39 ^{13}C NMR (CD_3OD, 125 MHz) of compound **190** …… 270

Spectrum 4.40 ^{13}C NMR (CD_3OD, 125 MHz) of compound **190** …… 271

Spectrum 4.41 ^{1}H NMR (CD_3OD, 500 MHz) of compound **191** ……. 272

Spectrum 4.42 ^{13}C NMR (CD_3OD, 125 MHz) of compound **191** …… 273

Spectrum 4.43 ^{13}C NMR (CD_3OD, 125 MHz) of compound **191** …… 274

Spectrum 4.44 ^{1}H NMR (CD_3OD, 500 MHz) of compound **192** ……. 275

Spectrum 4.45 ^{13}C NMR (CD_3OD, 125 MHz) of compound **192** …… 276

Spectrum 4.46 ^{13}C NMR (CD_3OD, 125 MHz) of compound **192** …… 277

Spectrum 4.47 ^{1}H NMR (C_5H_5N, 500 MHz) of compound **(-)-2** ……. 278

Spectrum 4.48 ^{13}C NMR (C_5H_5N, 125 MHz) of compound **(-)-2** …… 279

Spectrum 4.49 ^{1}H NMR (CD_3OD, 400 MHz) of compound **193** 280

Spectrum 4.50 ^{1}H NMR (CD_3OD, 500 MHz) of vinyl triflate ……. 281

Spectrum 4.50 ^{1}H NMR (CD_3OD, 500 MHz) of compound **194** ……. 282

Spectrum 4.52 ^{13}C NMR (CD_3OD, 125 MHz) of compound **194** …… 283

Spectrum 4.53 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **196** ……... 284

Spectrum 4.54 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **196** …….. 285

Spectrum 4.55 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **197** ……... 286

Spectrum 4.56 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **197** …….. 287

Spectrum 4.57 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **198** ……... 288

Spectrum 4.58 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **198** …….. 289

Spectrum 4.59 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **199** ……... 290

Spectrum 4.60 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **199** …….. 291

Spectrum 4.61 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **200** 292

Spectrum 4.62 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **200** …….. 293

Spectrum 4.63 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **201** ……... 294

Spectrum 4.64 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **201** …….. 295

Spectrum 4.65 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **201** …….. 296

Spectrum 4.66 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **202** ……... 297

Spectrum 4.67 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **202** …….. 298

Spectrum 4.68 ^{1}H NMR (CD_3OD, 500 MHz) of compound **195** ……. 299

Spectrum 4.69 ^{13}C NMR (CD_3OD, 125 MHz) of compound **195** …… 300

Spectrum 4.70 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **203** ……... 301

Spectrum 4.71 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **203** …….. 302

Spectrum 4.72 ^{1}H NMR (CD_3OD, 500 MHz) of compound **204** ……. 303

Spectrum 4.73 ^{13}C NMR (CD_3OD, 125 MHz) of compound **204** …… 304

Spectrum 4.74 ^{1}H NMR (CD_3OD, 500 MHz) of compound **205** ……. 305

Spectrum 4.75 ^{13}C NMR (CD_3OD, 125 MHz) of compound **205** …… 306

Spectrum 4.76 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **206** ……... 307

Spectrum 4.77 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **206** …….. 308

Spectrum 4.78 ^{1}H NMR (CD_3OD, 500 MHz) of compound **207** ……. 309

Spectrum 4.79 ^{13}C NMR (CD_3OD, 125 MHz) of compound **207** …… 310

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My husband and my daughter deserve the deepest gratitude. Thank you for your unconditional love and support. Without them, this journal could not complete.

Chapter 2, in full, is a reprint of the material as it appears in Enantioselective synthesis of ABC ring motif of norzoanthamine based on asymmetric Robinson annulation reactions in Organic Letter 2011. Nguyen, Thong X.; Dakanali, Marianna;

Trzoss, Lynnie L., 2011. The dissertation author was the primary investigator and author of this paper.

Chapter 4, in part, is reprint of the material as it appears in Enantioselective synthes of (-)-jiadifenin, a potent neurotrophic modulator in Organic Letter, 2011. Trzoss, Lynnie L.; Xu, Jing; Lacoske, Michelle H.; Mobley, William C., 2011. The dissertation author was the primary investigator and author of this paper.

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PUBLICATIONS

1. L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley and E. A. Theodorakis; *Enantioselective synthesis of (-)-jiadifenin, a potent neurotrophic modulator*. *Org. Lett.* **2011**, *13*, 4554-4557.

2. D. Fischer, T. X. Nguyen, L. Trzoss, M. Dakanali and E. A. Theodorakis; *Intramolecular cyclization strategies towards the synthesis of Zoanthamine alkaloids*. *Tetrahedron Lett.* **2011**, *38*, 4920-4923.

3. J. Xu, L. Trzoss, W. K. Chang and E. A. Theodorakis; *Enantioselective total synthesis of (-)-jiadifenolide*. *Angew. Chem. Int. Ed.* **2011**, *50*, 3672-3676.

4. T. X. Nguyen, M. Dakanali, L. Trzoss and E. A. Theodorakis; *Enantioselective synthesis of the ABC ring motif of norzoanthamine based on asymmetric Robinson annulation reactions*. *Org. Lett.* **2011**, *13*, 3308-3311.

ABSTRACT OF THE DISSERTATION

The Chemistry and Biology of Zoanthamine Alkaloids and *Illicium* Sesquiterpenes

by

Lynnie L. Trzoss

Doctor of Philosophy in Chemistry

University of California, San Diego, 2012

Professor Emmanuel A. Theodorakis, Chair

Natural products, or secondary metabolites, have proven significant to the existence of life. They have been used for countless reasons throughout history, including nonessential purposes such as dyes for textiles and paints. Less trivial uses, such as those related to health better demonstrate the importance of natural products. Toxic natural products had been used to bolster hunting efficiency and insect pheromones. Therapeutic natural products have long been used as dietary supplements and medicines. The ubiquitous nature of natural products and their

derivatives in current medicinal validates continued investigations in all areas of natural product research.

Our laboratory has a longstanding tradition in the synthesis and evaluation of biologically interesting natural products. We have viewed natural product synthesis as a tool to expand our understanding of organic chemistry. Of particular are natural products with novel architectures. The synthetic study of these natural products often inspires creativity to solve complicated synthetic challenges, and leads to the development of new methodologies. Novel structural characteristics and attractive bioactivities of two natural product families, zoanthamine alkaloids and *Illicium* sesquiterpenes, caught our interest for the stated reasons.

Research herein describes work directed towards synthesis of the ABC ring system of norzoanthamine, total syntheses of *Illicium* sesquiterpenes jiadifenolide and jiadifenin. Chapters 1 and 2 narrate the background and research related to the norzoanthamine ABC ring motif. Chapters 3 and 4 report the total syntheses of jiadifenolide and jiadifenin, and their biological studies related to their neurotrophic activity.

Chapter 1 The biology and chemistry of the zoanthamine alkaloids

1.1 Introduction to the zoanthamines

The zoanthamine alkaloids constitute a class of marine natural products that have been isolated from colonial zoanthids of the genus *Zoanthus sp*.[1-4] Species of this order are coral-like polyps existing as colonial mats or solitary animals widely dispersed throughout the temperate and tropical littoral regions of the Indian, Pacific and Atlantic Oceans. The typical polyp has a cylindrical body column, topped by a smooth, flat oval disk that is edged by short tentacles. When disturbed, the polys can eject jets of water loaded with toxins. The zoanthids from which zoanthamines were isolated, for example, cause a victim's eyes tear followed by prolonged redness and pain upon contact. It is not clear whether the zoanthids actually produce the toxins. It has been postulated that many or some of the secondary metabolites isolated from zoanthids are actually produced by symbiotic dinoflagellates.[5]

Figure 1.1.1 Selected zoanthids species.

The known secondary metabolites isolated from zoanthids are mainly alkaloids, which are grouped into two classes: the alkaloids of the zoanthoxanthin class,[3,6] known as natural fluorescent pigments; and the alkaloids of the zoanthamine

class that have a complex carbon skeleton. Many natural products with diverse archetypes have also been isolated from species in the order zoantharia (Figure 1.1.2).

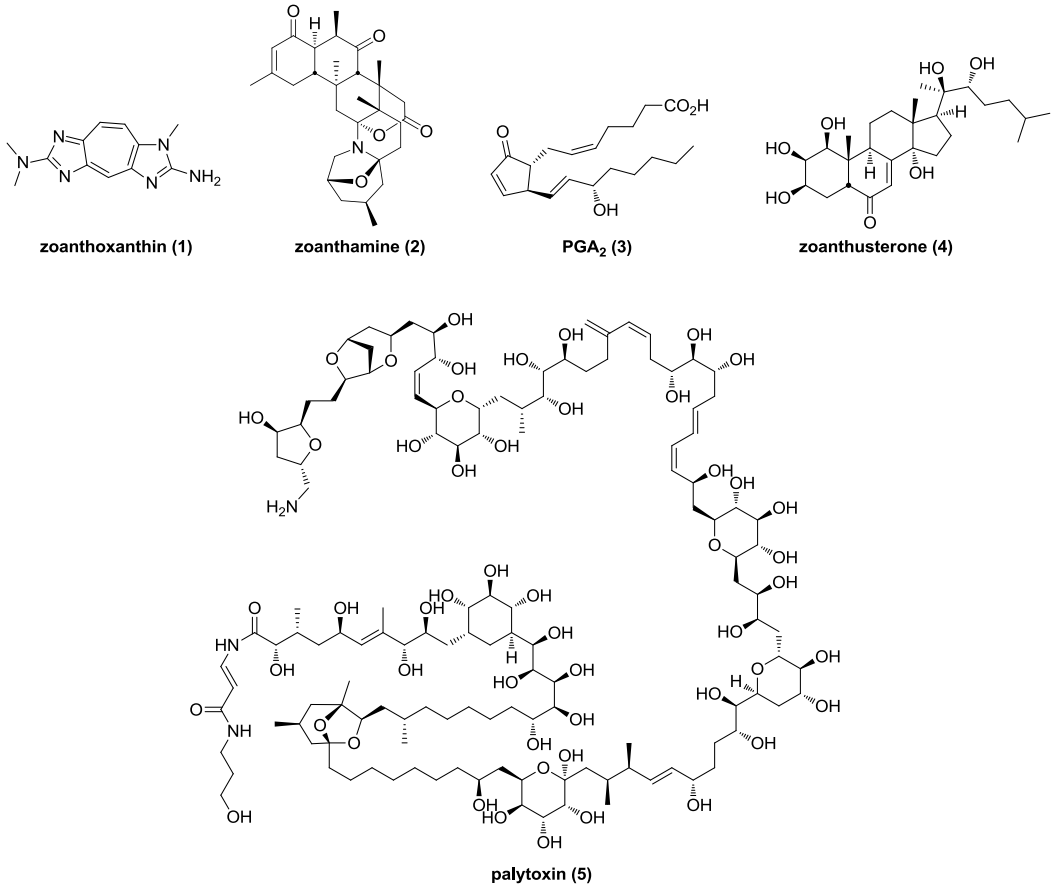


Figure 1.1.2 Selected natural products isolated from zoanthids.

Palytoxin (**5**), perhaps the best-known marine natural product isolated from these marine organisms, is the most toxic substance known apart from polypeptide and protein toxins. It was isolated from *palythoa* species with a lethal dose (LD_{50}) in mice of 0.15 μg kg^{-1} by intravenous injection.[7-9] Unlike the potent toxins batrachotoxin,[10] saxitoxin,[11] and tetrodotoxin[12] that have molecular weights of 500 or less, palytoxin has an estimated molecular weight of 3300 and contains no repetitive amino acid or

sugar units. Prostaglandin PGA_2 (**3**), isolated from the Okinawan zoanthid, *Palythoa kochii*, is a microtubule-stabilizing agent similar to paclitaxel.[13] Zoanthusterone (**4**) is an ecdysteroid isolated from *Zoanthus sp*.[14,15]

1.1.1 Isolation and structural characterization

In 1984, Rao, Faulkner and co-workers reported the isolation of zoanthamine (**2**) from unidentified colonial zoanthids off the Visakhapatnam coast of India. The structure and relative stereochemistry of this previously unknown alkaloid was determined by single-crystal X-ray diffraction studies.[5] Two additional alkaloids, zoanthenamine (**6**) and zoanthenamide (**7**), were also isolated in the initial isolation effort. They were reported later in 1985.[16] In 1989, Rao and co-workers reported the

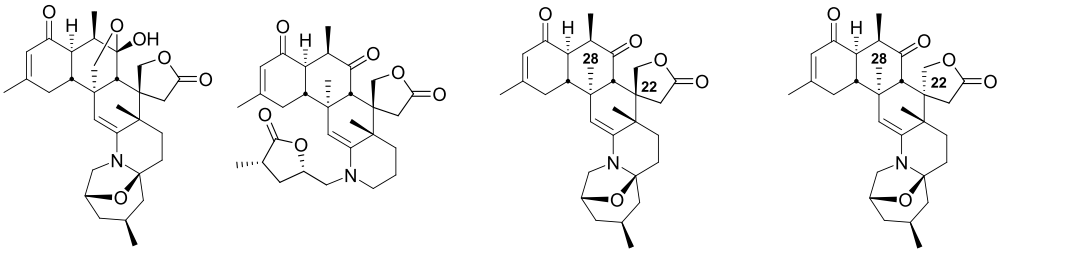


Figure 1.1.1.1 Zoanthamines isolated by Rao and Faulkner.

isolation of two other alkaloids from the Bay of Bengal, namely, 28-deoxyzoanthenamine (**8**) and 22-*epi*-28-deoxyzoanthenamine (**9**). Each of these alkaloids contains the spirocyclic butyrolactone connected at C22, however the stereochemistry of the core point of attachment has been transposed in 22-*epi*-28-deoxyzoanthenamine.[17]

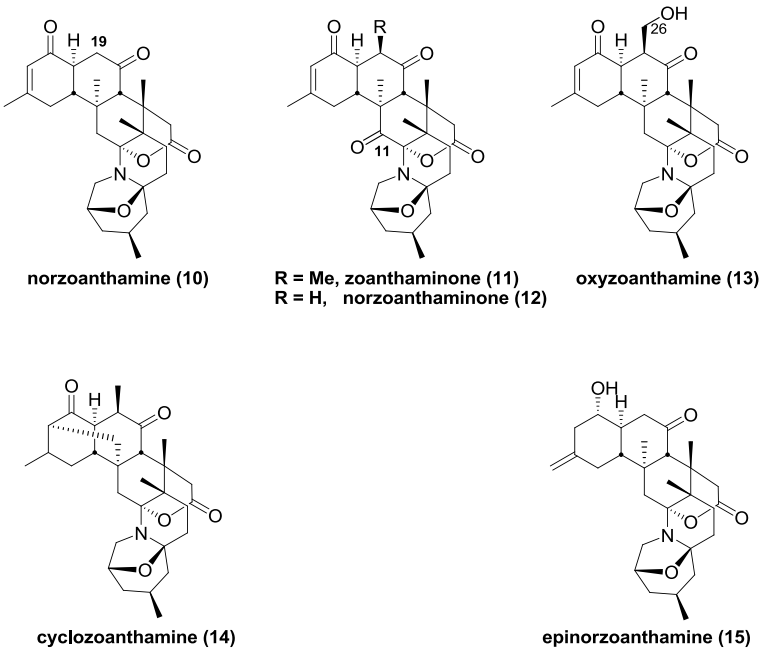
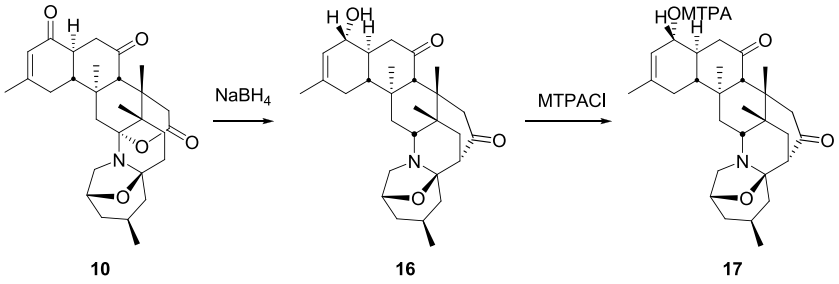


Figure 1.1.1.2 Zoanthamines isolated by Uemura and Clardy.

Continued reports of new zoanthamine natural products have added new members into this family over years. In 1989, Clardy and co-workers reported the isolation of zoanthaminone (**11**) found in the Arabian Sea. The structure, determined by X-Ray analysis, bears strong resemblances to zoanthamine, differing only in the oxidation state at C11.[18] In 1995, norzoanthamine (**10**), along with four other zoanthamine natural products was isolated from the Amami Islands of Japan by Uemura.[19] The relative stereochemistry of norzoanthamine was confirmed by X-ray analysis. The five new isolates display several structural variations. Norzoanthamine (**10**) differs from zoanthamine (**2**) only in the lack of C19 methyl substitution. Norzoanthaminone (**12**) also differs from zoanthaminone (**11**) at the C19 position, while oxyzoanthamine (**13**) is unique due to its C26 oxidation. Cyclozoanthamine (**14**) and epinorzoanthamine (**15**) contain modifications of the A-ring.

The absolute stereochemistry of norzoanthamine (**10**) was later determined through an extensive NMR analysis of MTPA ester **17**, shown in Scheme 1.1.1.1.[20] Due to the similarity in their ABC ring core structure, the entire family of zoanthamine alkaloids has been presumed to have the same absolute stereochemistry.



Scheme 1.1.1.1 Application of Mosher's method to determine the absolute configuration of norzoanthamine by Uemura.

In 1996, Norte and co-workers isolated a number of zoanthamine alkaloids **18** – **23** (Figure 1.1.1.3). Their structures and relative configurations were determined by comparison with NMR data of known zoanthamine alkaloids, extensive HMBC and ROESY correlation experiments were performed.[21,22] In 2008, the newest member of the zoanthamine family, lobozoanthamine (**24**), was isolated from *Lobophytum sp.*, a non-zoanthid genus. The structure was assigned by extensive NOE experiments and its absolute configuration was determined through NMR analysis of MTPA ester.[23]

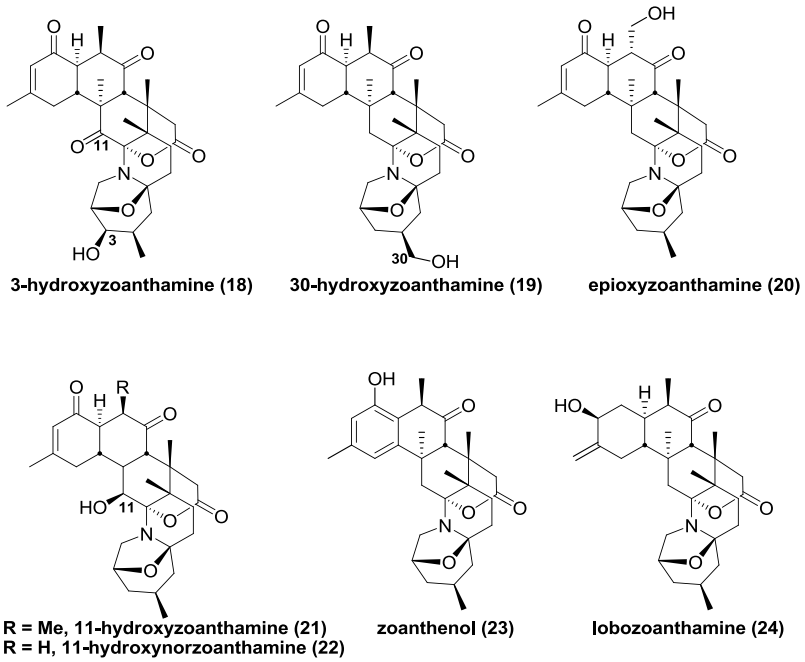
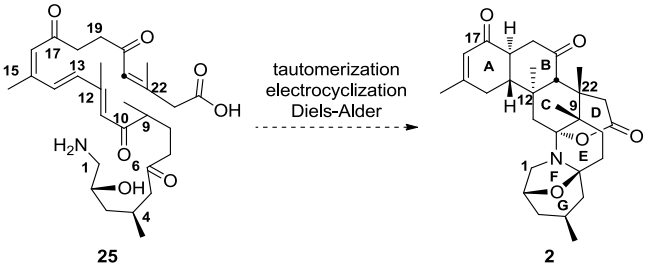


Figure 1.1.1.3 Zoanthamines isolated by Norte and Fattorusso.

1.1.2 Proposed biosynthesis of zoanthamines

To this day, the biosynthesis of zoanthamine natural products is unclear. Faulkner *et al.* suggested a triterpene origin base on the 30 carbons composition for the zoanthamine skeleton.[5] However, it is not possible to explain their biogenesis



Scheme 1.1.2 Proposed biosynthesis of norzoanthamine by Uemura.

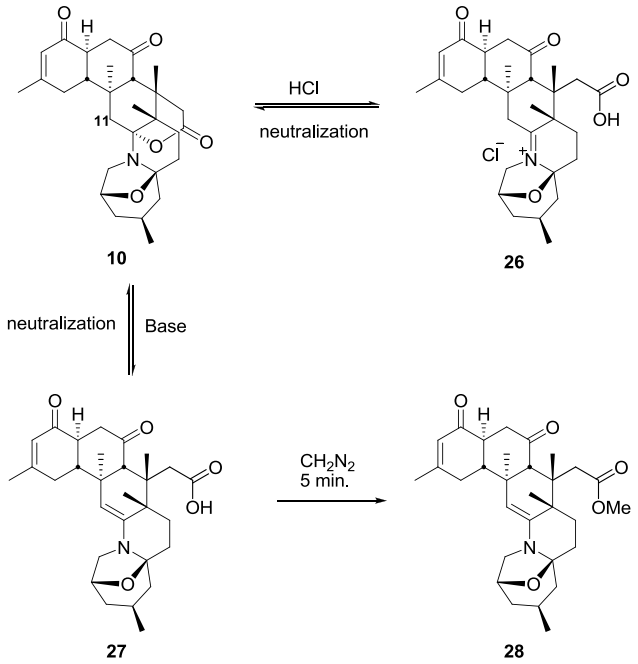
using the general head-to-tail rule. Uemura and co-workers proposed that zoanthamines were produced via a sophisticated polyketide biosynthesis pathway, which was later detailed by Stoltz.[20,24-26] As shown in Scheme 1.1.2, the acyclic polyketide **25** could undergo a series of conjugate additions and electrocyclizations to provide zoanthamine alkaloids. (Throughout the thesis, the carbon numbering and ring naming will refer to that of zoanthamine (**2**) shown in Scheme 1.1.2.)

Nakamura *et al.* have suggested that the zoanthids may play only a small role in the biosynthesis or zoanthamines, such as adjusting the oxidation state of the completed skeleton.[27] Other factors, such as marine environment, different zoanthid hosts and different species of algae are involved in the product of variations in the zoanthamine alkaloid structures.[28] To the best of our knowledge, there is only one published study towards the biogenesis of zoanthamine.[3] However, the results were inconclusive, thus leaving the question of zoanthamine biogenesis unanswered.

1.1.3 Reactivity of norzoanthamine

Upon its isolation, norzoanthamine (**10**) became the subject of study to establish its mechanism of action for various biological activities. When treated with acid, norzoanthamine forms iminium salt **26** and reforms upon neutralization. Under basic conditions, elimination at C11 occurs to form enamine **27**, which also reacts back to norozoanthamine upon neutralization.[25,26] The equilibrium between norzoanthamine (**10)** and enamine **27** was demonstrated by converting norzoanthamine to methyl ester **28** within minutes when treated with diazomethane.

This equilibrium between lactone and enamine/iminium forms in aqueous media at physiologically relevant pHs may help to understand the bioactivities of the zoanthamine alkaloids.[22]



Scheme 1.1.3 Equilibrium between lactone and enamine forms of norzoanthamine.

1.2 Biological activities of zoanthamines

1.2.1 Antiosteoporotic activity

In addition to their impressive chemical architecture, zoanthamines also display an attractive spectrum of biological activities. Perhaps the best-studied and most noticeable biological activity of the zoanthamines is the antiosteoporotic effect of norzoanthamine.[29] Osteoporosis is a condition of decreased bone mineral density resulted when osteoclasts reabsorb bone tissue at rates faster than it is regenerated.[30]

This leads to fragile bones that are at an increased risk for fractures. Normal bone marrow has small holes whereas a bone with osteoporosis will have much larger holes.

Norzoanthamine and its hydrochloride salt have been shown to prevent osteoporosis *in vivo* in ovariectomized mice at concentration of 13 μg/mL and 4.6 μg/mL, respectively.[1] It has been proposed that norzoanthamine acts as both bone growth stimulator and bone resorption suppressor. Its mode of action was thought to involve the inhibition of Interlukin-6 (IL-6).[27] IL-6 is known to stimulate osteoclast

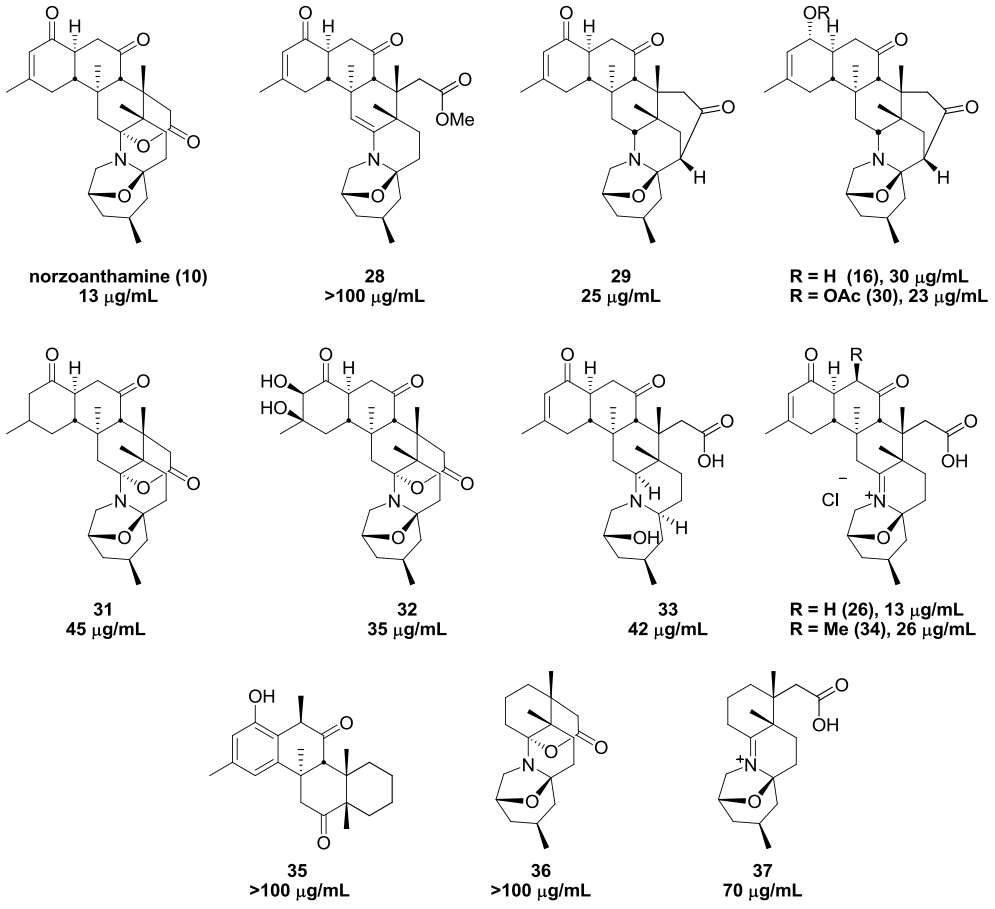


Figure 1.2.1 IC_{50} values for IL-6 cell growth inhibition by Uemura and Hirama.

formation. The ability of norzoanthamine to suppress IL-6 secretion has led the general believe of its therapeutic potential in the treatment of osteoporosis.

The need to find non-estrogen osteoporosis therapies has promoted the Uemura group to synthesize a number of zoanthamine analogues to study the structure-activity relationship (SAR).[25,26] It was found that all the analogues were less active in comparison to norzoanthamine.[1] The removal of olefinic double bond in the A-ring and disruption of the hemiaminal functionality caused losses in activity. In addition, Hirama and co-workers reported a SAR study to determine the functionality needed to its bioactivity, from which two trends were concluded: 1) the hydrochloride salt is typically more active, 2) the A- & D-rings are likely important in the design of a pharmacophore.[31]

1.2.2 Other biological activities

In addition to the antiosteoporotic property, the zoanthamines have demonstrated a numerous other interesting biological activities.[24] For instance, zoanthamine (**2**), zoanthenamine (**6**) and zoanthenamide (**7**) were found to inhibit ear inflammation induced by myristate acetate (PMA) in mice.[5,16] Norzoanthamine (**10**), oxyzoanthamine (**13**), cyclozoanthamine (**14**) and epinorzoanthamine (**15**) displayed significant cytotoxicity against P388 murine leukemia cells with IC_{50} values ranging from 1 to 24 μg/mL.[19] 11-Hydroxyzoanthamine (**21**), zoanthenol (**23**), oxyzoanthamine (**13**) and zoanthaminone (**11**) have all been shown to effect human platelet aggregation.[32] Platelet aggregation has been implicated in thrombosis related

ailments ranging from atherosclerosis to strokes and heart attacks resulting from arterial thrombosis. Zoanthenol (**23**) and 11-hydroxyzoanthamine (**21**) inhibit platelet aggregation, whereas, oxyzoanthamine (**13**) and zoanthaminone (**11**) cause irreversible platelet aggregation. This finding demonstrates the strong effect of subtle structural changes on the biological acitivites.[33]

1.3 Reported synthetic studies

The combination of challenging structures and potent bioactivities of zoanthamines has promoted the design of various synthetic approaches by several groups. These efforts led to two total syntheses of norzoanthamine by Miyashita and Kobayashi groups.[34-38] More recently, Miyashita and co-workers reported the total synthesis of zoanthenol via oxidation of norzoanthamine hydrochloride.[39] The major synthetic challenges posed by this family of natural products are: 1) the stereochemically dense C-ring that contains three adjacent quaternary carbons at C9, C12 and C22 positions; 2) the *trans-anti-trans* fused ABC ring system; 3) two aminoacetal structures of the heterocyclic DEFG ring system. Many groups have focused their efforts on the synthesis of the carbocyclic ABC ring system, whereas others have focused on the heterocyclic DEFG ring system.

1.3.1 Miyashita's total synthesis of norzoanthamine

Ten years after the isolation of norzoanthamine (**10**), Miyashita and co-workers reported its first total synthesis.[34] The retrosynthetic analysis of norzoanthamine is illustrated in Figure 1.3.1. The synthesis featured an intramolecular Diels-Alder

reaction for the formation of the ABC ring system.[40] This impressive 41-step synthesis completed the first enantioselective total synthesis of norzoanthamine with an overall yield of 3.5%.

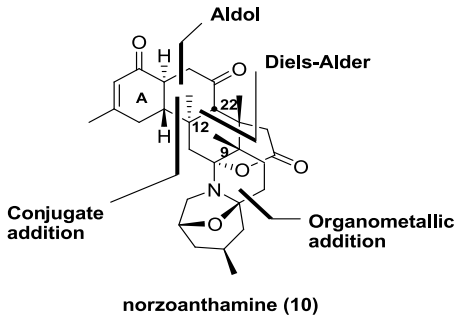
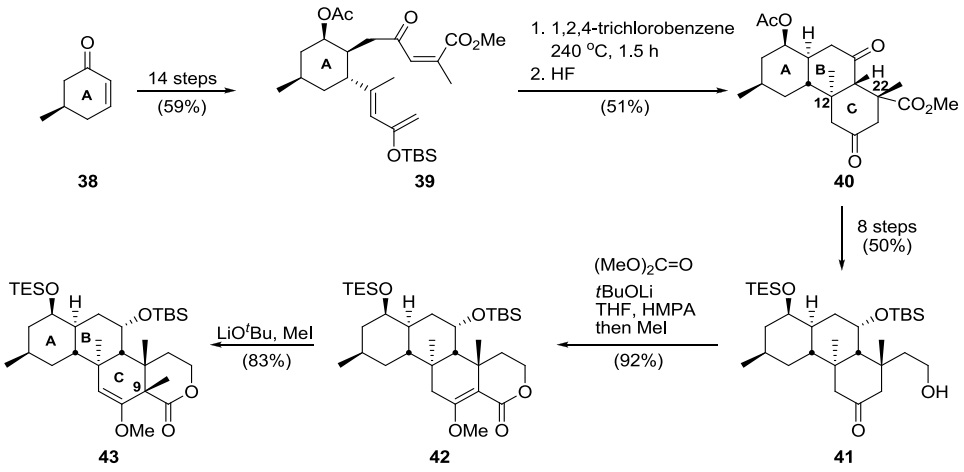


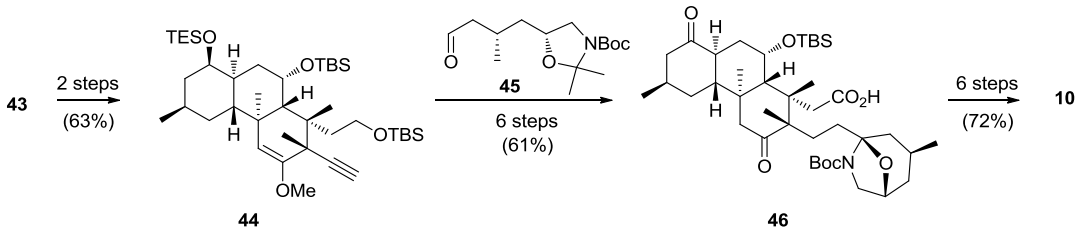
Figure 1.3.1 Retrosynthetic analysis of norzoanthamine by the Miyashita group.

In the forward direction (Scheme 1.3.1.1), the synthesis of norzoanthamine departed from the decoration of the enantiomeric pure enone **38** via conjugated addition and aldol condensation to form triene **39**. Triene **39** then underwent a



Scheme 1.3.1.1 Synthesis of the ABC ring system by the Miyashita group.

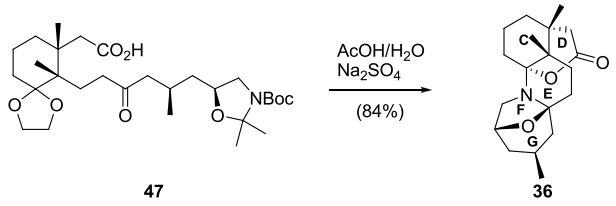
stereoselective intramolecular Diels-Alder (IMDA) reaction to construct the *trans-anti-trans* ABC ring system (ketone **40**). Ketone **40** contains two quaternary carbon centers at C12 and C22 positions with the correct absolute configuration of norzoanthamine. A couple of functional group manipulations led to the formation of *keto*-alcohol **41**, which was poised for the formation of C9 quaternary carbon. To that end, acylation of ketone **41** with dimethyl carbonate in the presence of lithium tert-butoxide followed by quenching with iodomethane provided lactone **42**. Upon treatment with lithium *tert*-butoxide and iodomethane in DMPU, lactone **42** underwent C-alkylation to give rise to the C9-quaternized lactone **43**. Impressively, the difficult C9 quaternary center was installed diastereoselectively. In two steps, the "southern" fragment **44** of norzoanthamine was synthesized and coupled to the aldehyde **45** ("northern" fragment). Northern fragment **45** was synthesized from (R)-citroneral. In 6 steps, carboxylic acid **46** was prepared, which underwent the final bis-aminoacetalization to complete the total synthesis of norzoanthamine.



Scheme 1.3.1.2 Completion of norzoanthamine by the Miyashita group.

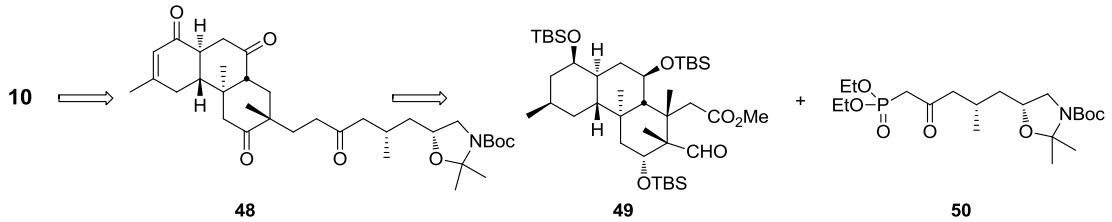
1.3.2 Kobayashi's total synthesis of norzoanthamine

In 2009, Kobayashi and co-workers accomplished the second total synthesis of norzoanthamine.[37,38] Their synthetic strategy was built based on an excellent methodology they have developed for the bisaminal formation to construct the heterocyclic CDEFG ring system, as illustrated in Scheme 1.3.2.1.[41-43]



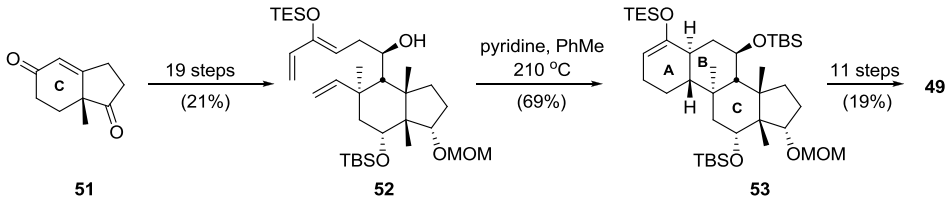
Scheme 1.3.2.1 Bisaminal formation strategy developed by the Kobayashi group.

Based on this efficient bisaminal formation strategy, Kobayashi and co-workers proposed intermediate **48** as the cyclization precursor to the synthesis of norzoanthamine (Scheme 1.3.2.2). Intermediate **48**, in turn, was to be derived from compound **49** by the means of Horner-Emmons reaction with nitrogen-containing *keto*-phosphate **50**. Aldehyde **49** represents the fully functionalized ABC ring system that contains C9, C12 and C22 quaternary carbons.



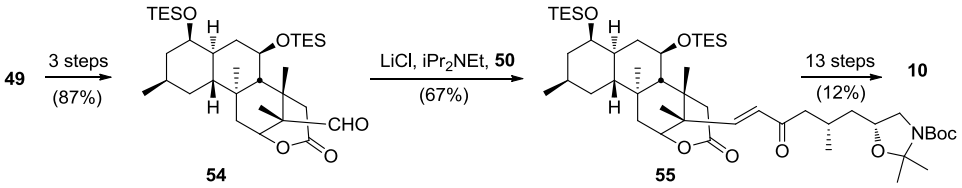
Scheme 1.3.2.2 Retrosynthetic analysis of norzoanthamine by the Kobayashi group.

Similar to Miyashita's approach, Kobayashi's synthesis of the ABC ring system also featured a stereoselective IMDA reaction. Starting from the enantiomeric enriched Hajos-Perrish ketone **51**,[44,45] triene **52** was prepared after several functional group manipulations. Triene **52** then underwent IMDA under thermo-conditions to provide the tetracyclic motif **53** in its desired configurations. After 11 steps of functional group transformations, aldehyde **49** was prepared. It was then treated by *keto*-phosphonate **50** hoping the formation of adduct **48** to exploit the bisaminal formation developed by the group. However, all attempts failed to deliver adduct **48**.



Scheme 1.3.2.3 Kobayashi's synthesis of the ABC ring system.

Instead, lactone **54** was prepared in 3 additional steps from aldehyde **49**, which was then treated with *keto*-phosphonate **50** under modified Horner-Emmons conditions to afford adduct **55**. Lactone **55** contains the complete carbon skeleton of norzoanthamine. The final bisaminal framework was then formed under similar conditions used by the Miyashita group. In 47 steps, norzoanthamine was prepared in an enantioselective manner with an overall yield of 0.3%.



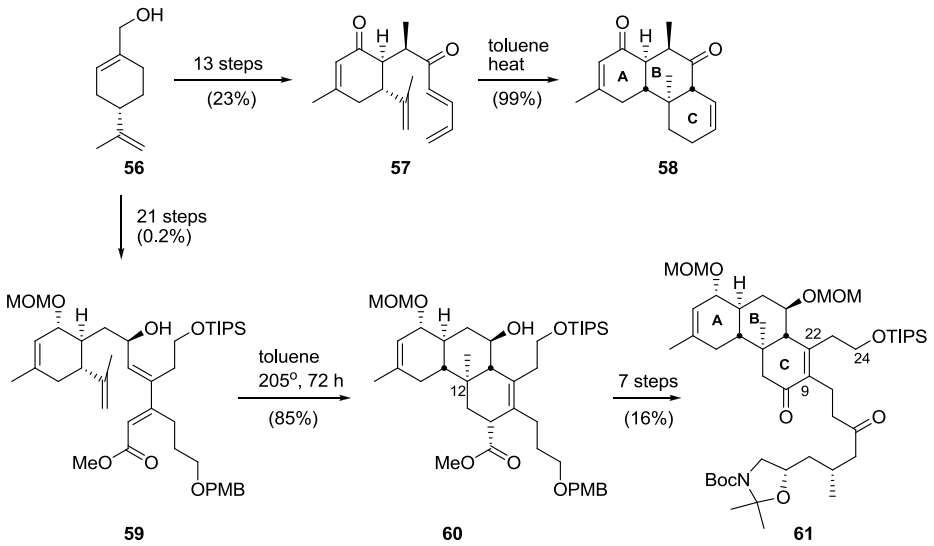
Scheme 1.3.2.4 Completion of norzoanthamine by the Kobayashi group.

1.3.3 Tanner's approach to the zoanthamine ABC ring system

Tanner and co-workers carried out various studies to assemble the ABC ring system of zoanthamine.[46-52] They also used an IMDA approach and began their synthesis with perillyl alcohol **56**, both enantiomers of which are available. They predicted that the configuration of the remaining stereocenters would be set by diastereoselective transformations. Their initial study was set on a model system of ABC ring system of zoanthamine. In 13 steps, the Diels-Alder precursor **57** was prepared, which upon heating in toluene provided tricyclic motif **58** quantitatively. Encouraged by the success of this Diels-Alder cycloaddition, the Tanner group synthesized the more functionalized ABC ring system **60**. Several functional group manipulations and coupling to the "northern" fragment afforded advanced intermediate **61**.

Tanner's Diels-Alder strategy nicely establishes the C12 quaternary center, leaving the difficult vicinal C9 and C22 quaternary centers at a late stage in the synthesis. They proposed to install the quaternary centers via Michael addition and alkylation, respectively. Once the quaternary centers are installed, only oxidation at

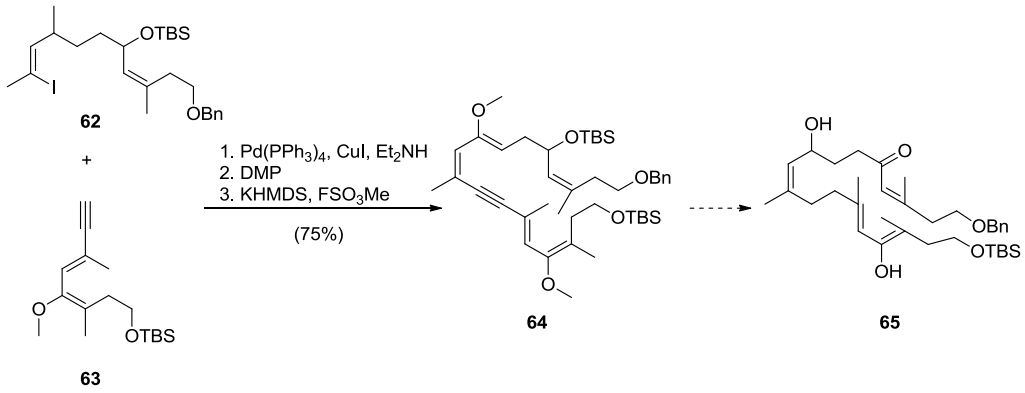
C24 and formation of DEFG rings remain to complete the total synthesis of norzoanthamine.



Scheme 1.3.3 Diels-Alder cyclization approach by the Tanner group.

1.3.4 Uemura's biomimetic approach to the norzoanthamine ABC ring system

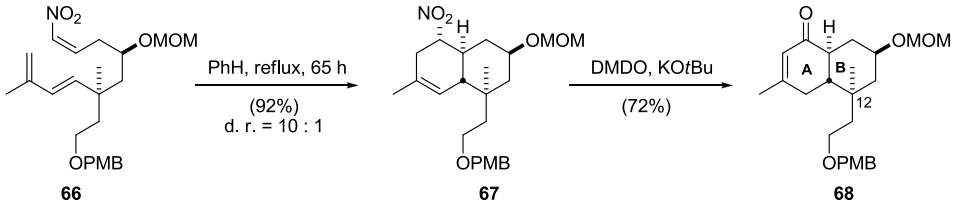
Uemura's approach to norzoanthamine was based on their biosynthetic hypothesis.[53] Uemura proposed that the zoanthamines arise from a linear polyketide skeleton, such as compound **65**. Such polyene would undergo a number of pericyclic reactions to afford norzoanthamine (See biosynthesis of zoanthamines in section 1.1.2). To exam this hypothesis, linear polyene **64** was synthesized featuring a Sonagashira coupling between vinyl iodide **62** and alkyn **63**. To date, no report has been emerged on the synthesis of compound **65** or attempts of its cyclization.



Scheme 1.3.4 Biomimetic approach by the Uemura group.

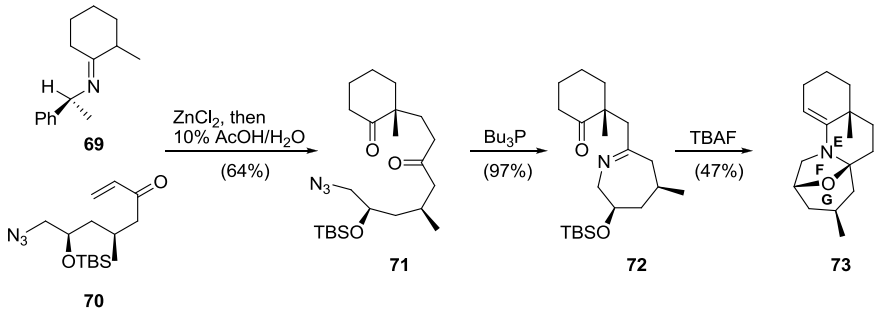
1.3.5 William's approaches to the AB and EFG ring systems of norzoanthamine

William and co-workers have reported the synthesis of AB ring system via an intramolecular Diels-Alder cyclization reaction.[54-56] In details, nitroalkene **66** underwent IMDA in refluxing benzene to afford decalin **67** in good yield and 10:1 d.r. Enone **68** was then synthesized via Nef reaction that transformed the *nitro* group to the desired ketone, along with the migration of the olefinic double bond. Compound **68** contains the fully functionalized A-ring with the correct ring junction, and C12 stereocenter of the zoanthamines.



Scheme 1.3.5.1 William's Diels-Alder approach to the AB ring system.

In addition, Williams and Cortez reported an interesting and efficient strategy to attach the EFG fragment to the C-ring. This strategy established the C9 quaternary center stereospecifically.[57] Michael addition of chiral imine **69** to enone **70** provided diketone **71** with excellent diastereoselectivity (22:1). A Staudinger reduction of **71** provided imine **72**, which underwent hemiaminal formation followed by condensation to give rise to the modeled EFG ring system **73**.



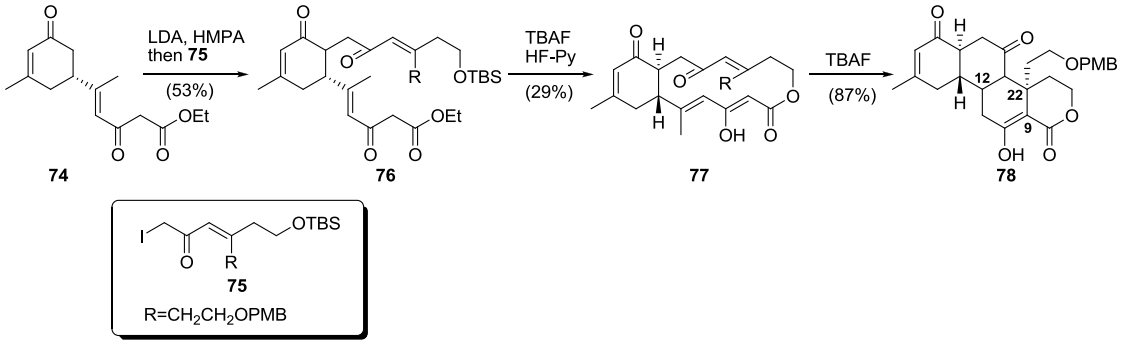
Scheme 1.3.5.2 William's approach to a modeled EFG ring system.

1.3.6 Yang's approach to the ABC ring system of norzoanthamine

Recently, Yang and co-workers reported their synthetic efforts to the carbocyclic motif of norzoanthamine.[58] The key reaction to their strategy was a transannular Michael reaction cascade of macrolactone **77** (Scheme 1.3.6). In the forward direction, coupling between enone **74** and iodoketone **75** led to the formation of compound **76**. Macrocyclization of **76** via acylketene formation gave rise to macrolactone **77**. Treatment of **77** with TBAF at low temperature (-78 to -4 ^{o}C) yielded the formation of carbocyclic motif **78** of norzoanthamine as a single diastereomer. In 12 steps (the longest linear chain), the densely functionalized

carbocyclic core of norzoanthamine was prepared. It contains five consecutive stereocenters including two quaternary carbons.

Yang's transannulation strategy successfully installs the C12 quaternary center, the difficult C9 center is left as an unanswered question. The C22 quaternary center also needs to revisit. Once the two quaternary centers are completed, only the formation of DEFG rings remains to complete the total synthesis of norzoanthamine.

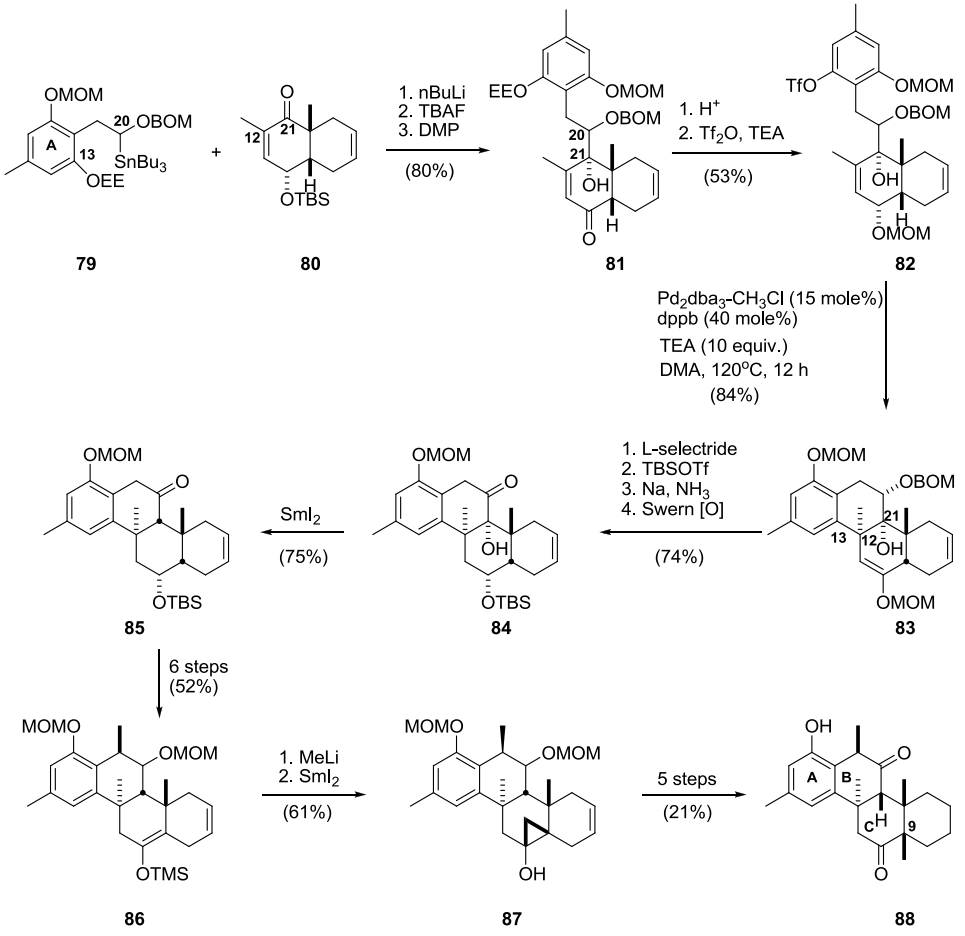


Scheme 1.3.6 Yang's approach to the ABC ring system of norzoanthamine.

1.3.7 Hirama's strategy for the zoanthenol ABC ring system

Hirama and co-workers proposed a unique strategy specifically designed for the synthesis of the ABC ring system of zoanthenol.[59,60] The aromatic A-ring that is exclusive to zoanthenol allows the use of Heck reaction as the key transformation to close the B-ring via the formation of C12-C13 bond (Scheme 1.3.7). In details, transmetalation of stannane **79** and addition to enone **80** produced enone **81**. Aryl triflate **82**, prepared from enone **81**, underwent the key intramolecular Heck reaction to provide the ABC ring system of zoanthenol containing C12 and C22 quaternary

carbon centers. The reduction at C21 tertiary alcohol was then achieved after several functional group manipulations to afford ketone **85**.

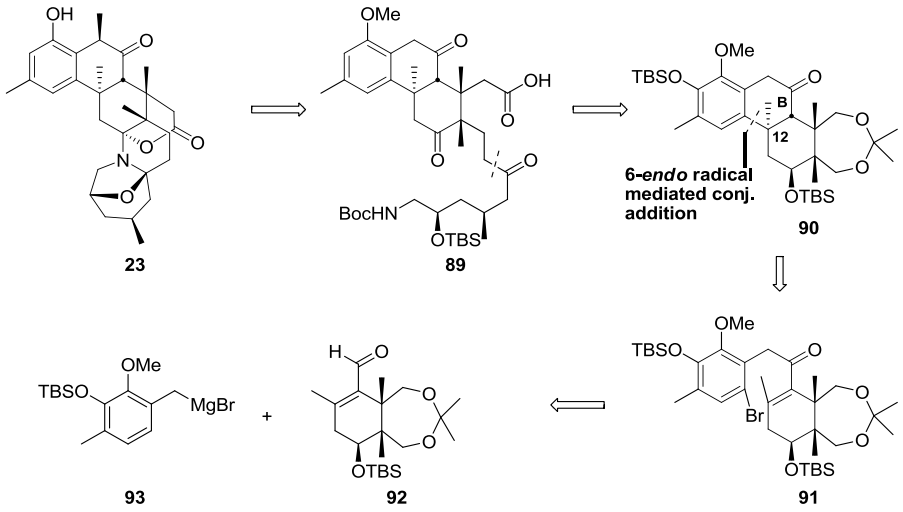


Scheme 1.3.7 Hirama's Heck strategy for the synthesis of ABC ring of zoanthenol.

The greatest challenge remained in Hirama's synthesis is to establish the C9 quaternary center.[61-63] To this end, methylation was achieved by a samarium (II) iodide promoted cyclopropanation followed by an acid-mediated ring opening. This methylation sequence afforded the methylated ketone **88** and its C9 epimer with a favorable 3:1 ratio.

1.3.8 Stoltz's approach to the ABC ring system of zoanthenol

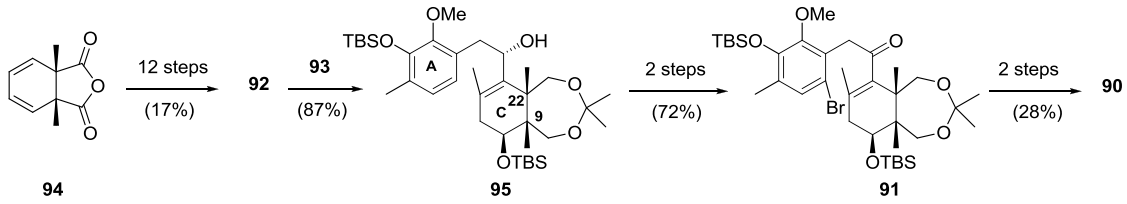
Stoltz and co-workers recently proposed a unique strategy for the synthesis of the ABC ring system of zoanthenol, represented by ketone **90**.[24,64-67] As illustrated in the retrosynthetic analysis in Scheme 1.3.8.1, the key reaction of their strategy involves an intramolecular 6-*endo* radical-mediated conjugate addition of **91** that closes the B-ring in a stereoselective manner, containing C12 quaternary stereocenter.



Scheme 1.3.8.1 Retrosynthetic analysis of zoanthenol by the Stoltz group.

In the forward direction, the C-ring fragment **92** was synthesized first from an enantioselective desymmetrization of anhydride **94**. This transformation simultaneously established the absolute stereochemistry of the two vicinal quaternary carbon centers at C9 and C22. Coupling between the A- and C-rings was accomplished by treatment of enal **92** with benzylic Grignard **93** to afford compound **95**. Oxidation and bromination of **95** led to the formation of aryl bromide **91**. The

ABC ring system of zoanthenol was then prepared after the key 6-*endo* radical-mediated addition. This impressive 17-step synthesis produced an ABC ring system containing all three quaternary centers and necessary functionalities to complete the synthesis of zoanthenol.

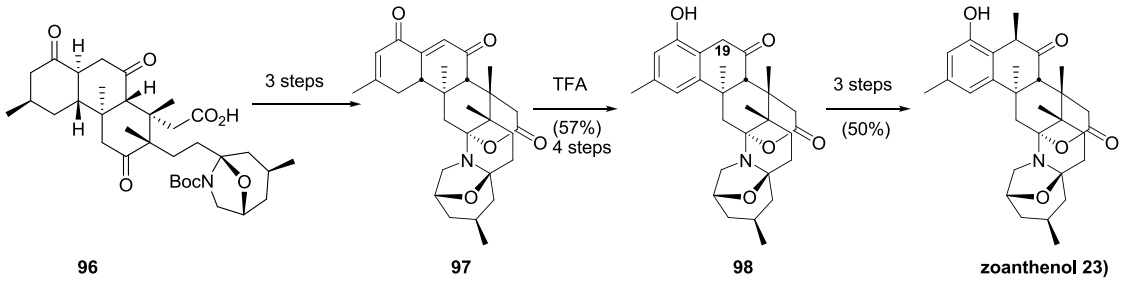


Scheme 1.3.8.2 Stoltz's synthesis of the ABC ring system of zoanthenol.

1.3.9 Miyashita's synthesis of zoanthenol

In 2009, Miyashita and co-workers reported the first total synthesis of zoanthenol.[39] Their key step involved a TFA-promoted isoaromatization to install the aromatic A-ring. Departed from carboxylic acid **96**, an intermediate found in the total synthesis of norzoanthamine, dienone **97** was prepared in three steps. Under acidic conditions, the isoaromatization afforded ketone **98**. At this point, only the methylation at C19 position was required to complete the synthesis zoanthenol, which was achieved in three steps.

Alternatively, Miyashita and co-workers reported that dienone **97** can also be prepared from the commercial available norzoanthamine hydrochloride. This established an efficient access to zoanthenol and opened up a completely new chemical path to the aromatic members of zoanthamine alkaloids.



Scheme 1.3.9 Total synthesis of zoanthenol by the Miyashita group.

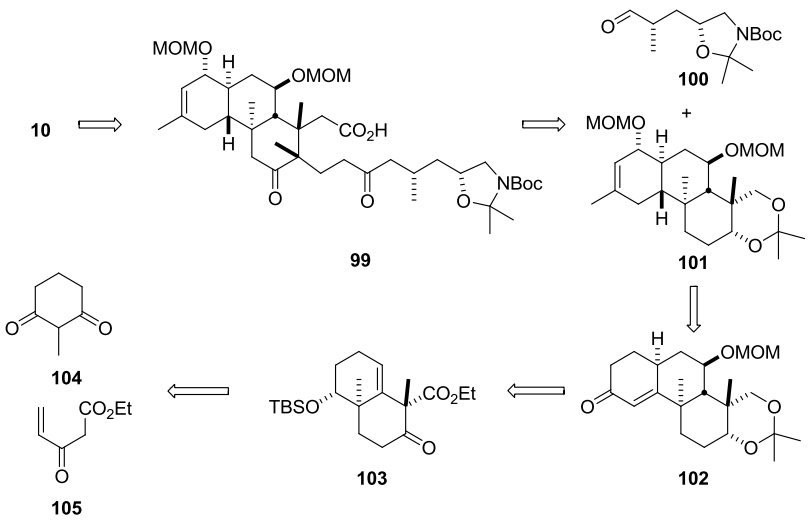
1.4 Early efforts towards the synthesis of zoanthamines

For the past decade, our research group was dedicated to develop an efficient and enantioselective synthetic strategy towards zoanthamine alkaloids. Our initial efforts focused on the synthesis of the tricyclic ABC ring system of norzoanthamine. To this end, we developed a unique annulation strategy that allows us to access the tricyclic system stereoselectively.[68,69] Inspired by the proposed biosynthesis of zoanthamines, we also explored the intramolecular cyclization strategies towards the synthesis of zoanthenol.[70]

1.4.1 Annulation approach to the ABC ring system of norzoanthamine

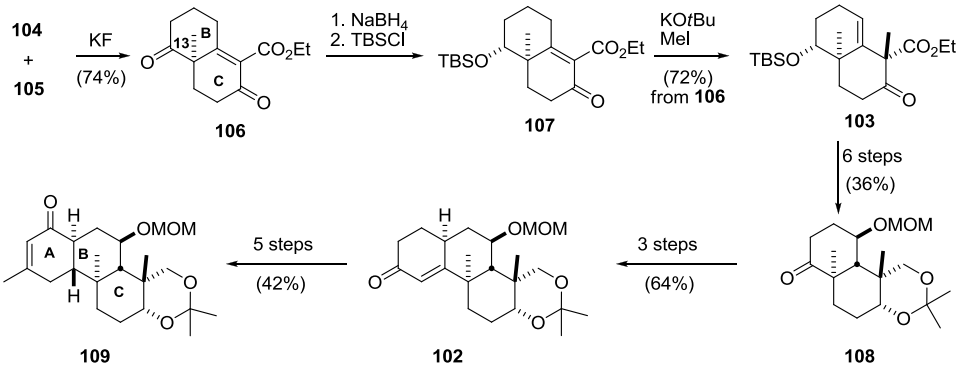
Early studies in our lab focused on the development of a linear approach that prepares the ABC ring system and the DEFG heterocyclic system spontaneously. This strategy is outlined in Scheme 1.4.1.1. We envisioned that norzoanthamine **(10**) can arise from the acid catalyzed cyclization of carboxylic acid **99**. Further disconnections led to aldehyde **100**, precursor to the DEFG ring system; and compound **101** that

represents the ABC ring system. Our initial synthetic efforts were focused on the stereoselective synthesis of compound **101**.[68,69]



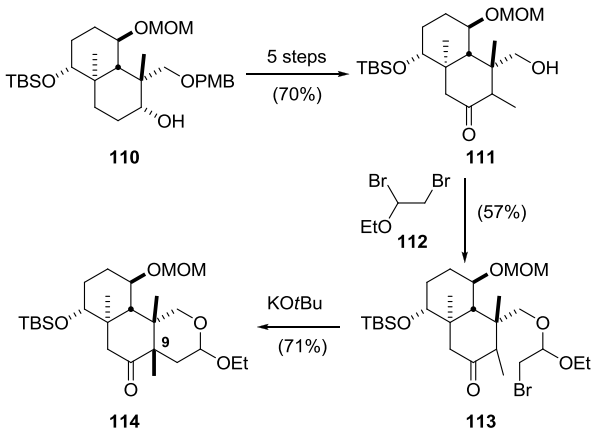
Scheme 1.4.1.1 Retrosynthetic analysis of norzoanthamine via the annulation strategy.

The synthesis began with condensation of *meso*-diketone **104** and ketoester **105** in the presence of potassium fluoride to afford enone **106**. The C13 carbonyl was reduced regio- and stereoselectively, and the resulting alcohol was protected as silyl ether **107**. Treatment of **107** with potassium *tert*-butoxide produced the extended enolate that upon reaction with methyl iodide produced quaternized ketoester **103** with complete diastereomeric control. Several functional group manipulations led to the formation of acetonide **108**. A stepwise Robinson annulation gave rise to enone **102**, which was then transposed to enone **109** that contains all the functionalities and stereochemical features of the AB rings.



Scheme 1.4.1.2 Synthesis of the ABC ring system of norzoanthamine

To this point, we had a feasible approach to the ABC ring system of norzoanthamine. While, the greatest challenge remained was the establishment of the difficult C9 quaternary carbon center. To this end, we explored an intramolecular alkylation strategy as illustrated in Scheme 1.4.1.3. Departed from alcohol **110**, *keto*-



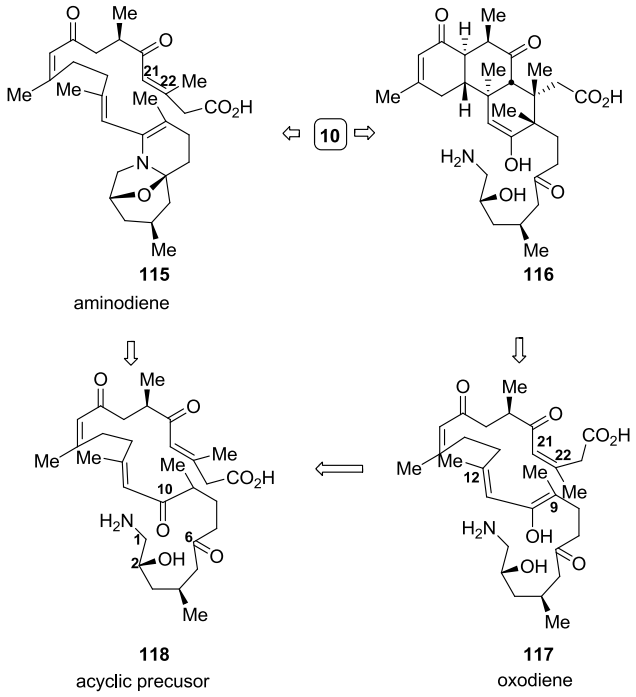
Scheme 1.4.1.3 Installation of the C9 quaternary stereocenter.

alcohol **111** was prepared in 5 steps. Alkylation of **111** with 1,2-dibromo-1-ethoxyethane (**112**) produced the corresponding α-bromo acetal **113** in 57% yield.

Acetal **113** underwent cyclization with complete selectivity for the desired C9 epimer upon exposure to basic conditions to afford ketone **114**.

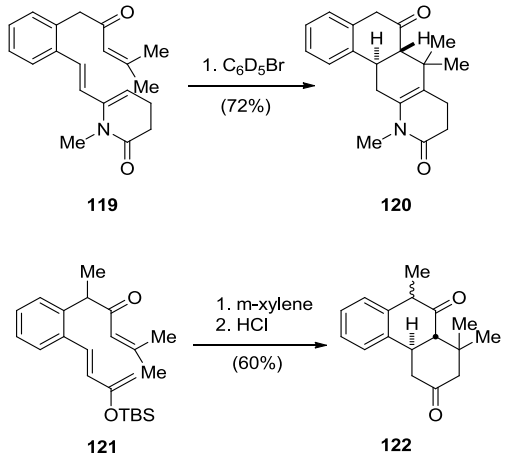
1.4.2 Biomimetic approach to the ABC ring system of zoanthenol

To establish a more convergent and efficient synthesis, we devised a risky but potentially rewarding approach to the zoanthamine alkaloids.[70] The second generation strategy was inspired by the proposed biosynthesis of zoanthamines, in which an acyclic polyketide precursor **118** could undergo a polycyclization cascade to form norzoanthamine (Scheme 1.4.2.1).[20,25]



Scheme 1.4.2.1 Proposed biogenetic pathway for zoanthamines.

Although there were no details provided for such a proposal, one could envision two cyclization scenarios. In the first case, condensation of the 1,2-aminoalcohol at the C6 and C10 carbonyl group of **118** could form a 2-aminodiene intermediate **115**, which upon cyclization with the pendant C21-C22 dienophile would produce the C-ring of norzoanthamine. Alternatively, a C9-C12 oxodiene could undergo cyclization with the C21-C22 dienophile to form the C ring (**117** → **116**) and ultimately norzoanthamine. With these considerations, we explored the intramolecular Diels-Alder reaction of 2-amino- and 2-oxo-dienes for the formation of C-ring in zoanthenol model systems.



119 **120** **121** **122**

Scheme 1.4.2.2 IMDA of 2-amido and 2-oxo-dienes for the formation of C-ring.

We have found that an amide-stabilized 2-aminodiene can efficiently react with a dienophile, in an *exo*-selective IMDA reaction, to produce model system **120**, representing the ABCE ring scaffold of zoanthenol. The reactivity of 2-amido-1,3-diene **119** parallels that of the 2-oxo-diene **121**. In turn, this provides support for the

use of stabilized 2-aminodienes in cycloaddition reactions for the synthesis of zoanthamines.

1.5 Concluding remarks

The zoanthamine alkaloids constitute a distinctive family of marine metabolites. These natural products are characterized by a densely functionalized and stereochemically rich framework. Their biosynthesis is believed to involve a polyketide pathway, but the details are not known to this day. A wide spectrum of interesting biological activities have been observed for this family, such as antiosteoporotic, antibiotic, anti-inflammatory and cytotoxic activities. The combination of such challenging molecular architecture and potent biological profiles has generated a significant body of research, including our laboratory. Any successful synthesis requires expertise in both carbocyclic and heterocyclic chemistry. Yet, with many questions remain unanswered, interest in the zoanthamines is expected to increase in the foreseeable future.

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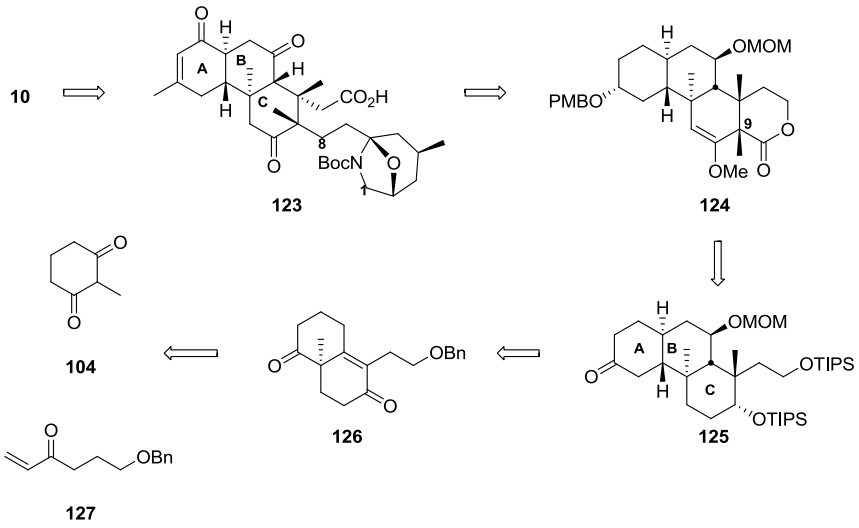
Chapter 2 Enantioselective synthesis of the ABC ring system of norzoanthamine

In continuation to our synthetic studies towards the zoanthamine alkaloids, we developed an extended and improved approach to the ABC ring system based on the first generation annulation strategy. This new strategy allowed us to access an advanced ABC ring motif in an enantioselective manner.[1]

2.1 Retrosynthetic analysis

Inspection of the polycyclic norzoanthamine framework suggests that the ABC ring system is of special challenge due to the AB *trans* decalin system and the stereochemically rich C-ring. In fact, both Miyashita and Kobayashi have shown that the synthesis of norzoanthamine could be achieved from condensation of compound **123** in which a partially folded C1-C8 side chain has been attached to a fully

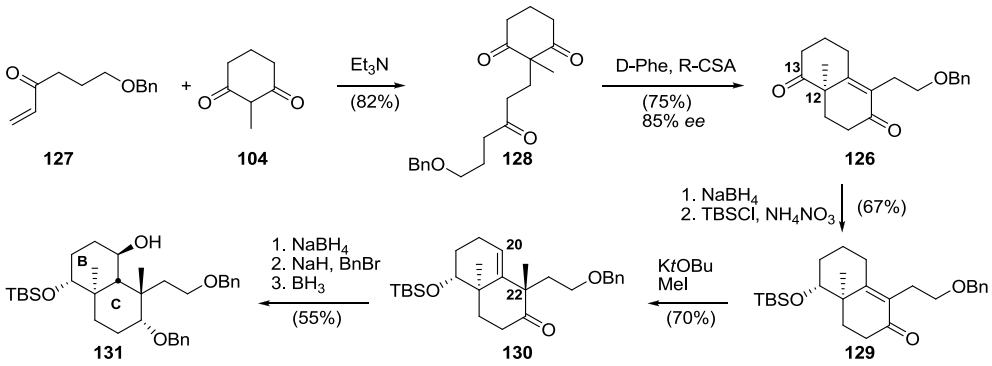


Scheme 2.1 Revised retrosynthetic analysis of norzoanthamine.

functionalized ABC ring motif.[2-4] With this in mind, our retrosynthetic analysis began by unraveling the heterocyclic DEFG rings of norzoanthamine, revealing the tetracyclic structure **124**. Lactone **124** could derive from **125** after functionalization of the periphery of the C-ring and stereocontrolled installation of the C9 methyl group. Construction of the carbon backbone of **125** could be accomplished by two Robinson annulation reactions to install both A- and C-rings. Along these lines, condensation between **104** and **127** would produce bicyclic motif **126**.[5]

2.2 Synthesis of BC ring system

In the forward direction, the synthesis of BC ring began with a Michael addition of 2-methyl-1,3-cyclohexadione (**104)** to enone **127**. The latter was synthesized from butane-1,4-diol according to a reported protocol.[6] Treatment of the Michael adduct **128** with D-Phe and R-CSA in DMF[7,8] gave the annulated product **126**, containing the C12 quaternary center, in 75% yield. The enantioselectivity was determined by the chiral



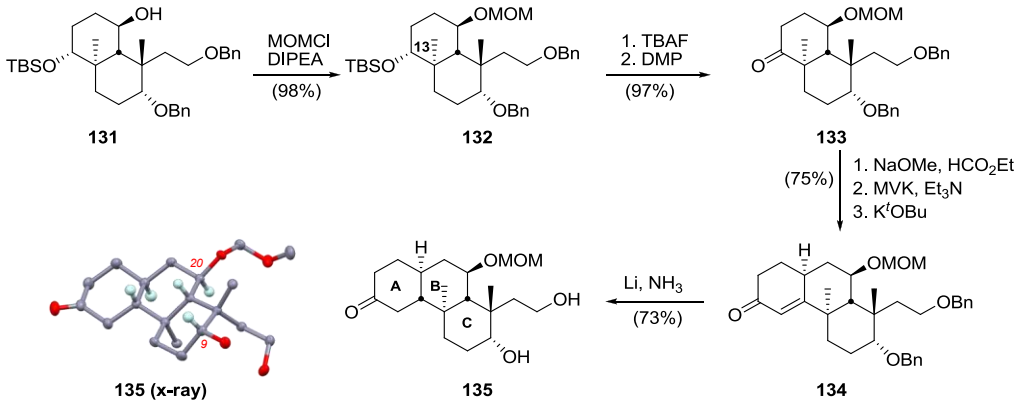
Scheme 2.2 Enantioselective synthesis of the BC ring system.

shift agent $Eu(hfc)_3$.[9-11] The C13 carbonyl group of **126** was then selectively reduced and the resulting alcohol was protected as TBS silyl ether to afford enone **129**. The second quaternary center at C22 was then installed. Methylation of **129** with *t*BuOK and MeI produced **130** as a single stereoisomer. Reduction of ketone **130** led to the formation of the secondary alcohol as a single diastereomer, which was protected as benzyl ether. Stereoselective hydroboration of the C20-C21 alkene, occurred at 0 ^{o}C over 72 hours afforded alcohol **131**.

2.3 Stereoselective synthesis of the ABC ring system

With the fully functionalized BC ring system in hand, we shifted our attention to the stereoselective construction of the *trans-anti-trans* fused ABC ring system of norzoanthamine. To this end, alcohol **131** was protected as the corresponding MOM ether in 98% yield. The C13 silyl ether of **132** was then deprotected using TBAF under microwave radiation at 130 ^{o}C for one hour. It is worth noting that conventional heating in THF under reflux conditions gave only 50% conversion after 5 days. The resulting C13 alcohol was then oxidized using Dess-Martin periodinane (DMP) to provide ketone **133** in 97% yield over two steps. Our initial attempts to react ketone **133** with MVK using a strong base led to a complex mixture of products. To circumvent this problem, we converted **133** to a β-keto aldehyde, which underwent smooth Michael addition with MVK and triethylamine.[12] The Robinson cyclization proceeded cleanly with *t*BuOK to provide the tricyclic motif **134** in 75% yield over three steps. The final ABC ring motif was synthesized after stereo- and regioselective reduction of **134** using lithium-ammonia conditions. Under these reductive

conditions, both benzyl ethers were cleaved, producing diol **135**. The chemical structure and absolute configuration of compound **135** were unambiguously confirmed via a single crystal X-ray analysis.[14]

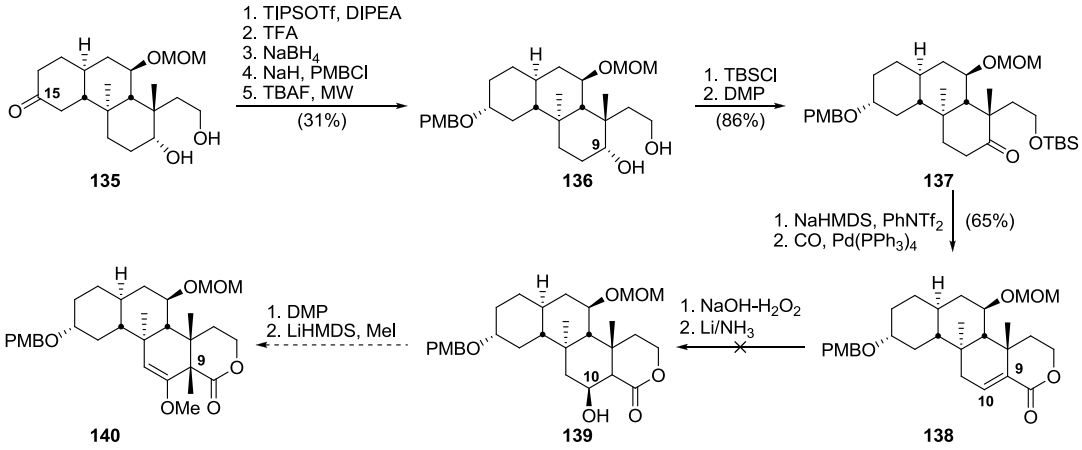


Scheme 2.3 Stereoselective synthesis of the ABC ring system.

2.4 Installation of the C9 quaternary carbon

The next task was to complete the functionalization of the C-ring including the installation of the difficult quaternary center at C9 position. To this end, diol **135** was converted to compound **136** in five steps: (1) exhaustive silylation of both ketone and diol functionalities of **135**; (2) selective deprotection of the silyl enol ether using TFA; (3) the C15 ketone was then reduced stereoselectively at -78 ^{o}C;[13] and (4) the resulting alcohol was protected as *p*-methoxybenzyl (PMB) ether; (5) the two silyl ether groups were then removed to provide diol **136**. Selective monoprotection of the primary alcohol followed by DMP oxidation of the C9 secondary alcohol afforded ketone **137** in excellent yield. Ketone **137** was then converted to the corresponding vinyl triflate that underwent Pd(0)-catalyzed carbomethoxylation. Under such conditions,

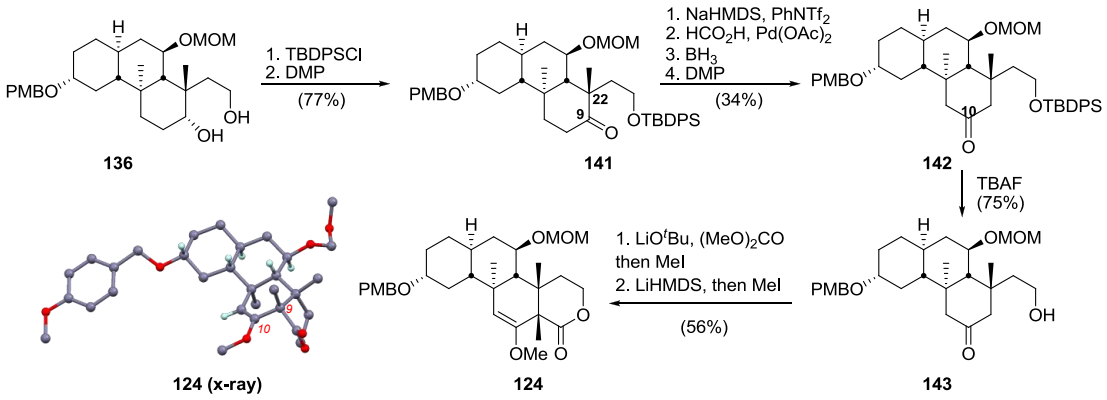
desilylation led to the formation of primary alcohol followed by *in situ* lactonization to form lactone **138**. With lactone **138** in hand, our next task was to oxidize the C10 position. Along these lines, lactone **138** was treated with $NaOH/H_2O_2$ to produce the epoxide across the C9-C10 double bond. We projected that lithium-ammonia reduction should led us to the formation of β-hydroxylactone **139**. However, under all reaction conditions explored, only decomposition of the starting material was observed.



Scheme 2.4.1 Attempt to the installation of C9 quaternary carbon center.

Inspired by Miyashita's synthesis, we next attempted to "switch" the C9 ketone to C10 position.[34] This switch was accomplished via a sequence of four steps from ketone **141**, which include (1) triflation of the C9 ketone; (2) reduction of the resulting vinyl triflate with Pd(II) acetate and formic acid to give C9-C10 alkene; (3) hydration of the C9-C10 alkene; (4) oxidation of the resulting alcohol to ketone **142**. We anticipated that, by virtue of steric hindrance at C22 quaternary carbon center would lead to a regioselective hydroboration reaction in favor of the desired product

with hydroxylation at C10. Indeed, this hydroxylation produced, after further oxidation, a 2:1 mixture of C10 ketone **142** and C9 ketone (34% and 17% yield, respectively). The undesired C9 ketone can be recycled to yield the desired product **142**. Desilylation of ketone **142** afforded primary alcohol **143**. Treatment of **143** with base in dimethyl carbonate, followed by iodomethane led to the formation of methyl enol ether, which upon alkylation with LiHMDS and iodomethane, afforded the desired lactone **124**. The absolute configuration of lactone **124** was confirmed by single crystal X-ray analysis.[14]

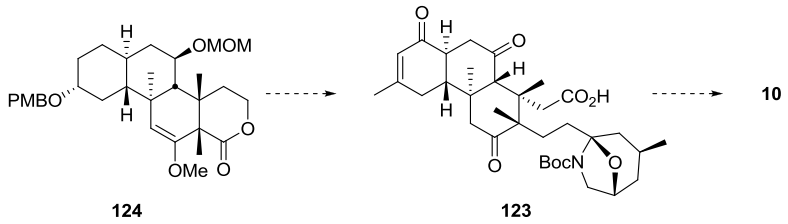


Scheme 2.4.2 Installation of C9 quaternary carbon center.

2.5 Concluding remarks

In conclusion, an enantioselective synthesis to the fully functionalized ABC ring motif of norzoanthamine was accomplished. Key to this strategy is a double Robinson annulation reaction that installs the C- and A-rings. The initial Robinson annulation that installs the C-ring proceeds with excellent enantioselectivity, setting the desired stereochemistry at the C12 quaternary center. The second Robinson

annulation that appends the A-ring in a stereoselective manner, constructing the AB *trans* decalin system. A sequence of stereoselective transformations are then developed to install the remaining stereocenters. Lactone **124** could serve as an attachment point for the remaining side chain of norzoanthamine, as shown in Scheme 2.5 below.



Scheme 2.5 Proposed synthesis of norzoanthamine.

Chapter 2, in full, is a reprint of the material as it appears in Enantioselective synthesis of ABC ring motif of norzoanthamine based on asymmetric Robinson annulation reactions in Organic Letter 2011. Nguyen, Thong X.; Dakanali, Marianna; Trzoss, Lynnie L., 2011. The dissertation author was the primary investigator and author of this paper.

2.6 References

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(14) CCDC-820554 (**135**) and CCDC-820555 (**124**) contain the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

2.7 Experimental techniques and characterization data

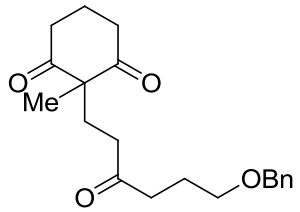
Geneal techniques

All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless

steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2) and benzene (PhH) were purified by passage through a bed of activated alumina. N,N-diisopropylethylamine (DIPEA) and triethylamine (TEA) were distilled from calcium hydride prior to use. Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or p-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectras were recorded on Varian Mercury 400 instrument and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet, dt = doublet of triplet. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]T\lambda$ (*c*: g/100mL, solvent). High resolution mass spectra (HRMS) were recorded on a

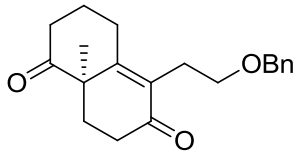
VG 7070HS or on a VG ZAB-ZSE mass spectrometers. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Experimental procedure



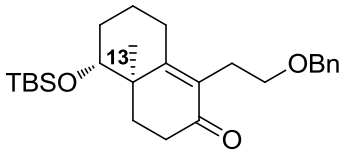
128

Triketone 128: To a solution of 2-methylcyclohexane-1,3-dione **104** (21.8 g, 173 mmol) in ethyl acetate (500 mL) was added Et_3N (31.3 mL, 224 mmol) followed by enone **127** (37 g, 181 mmol) at 25 ^oC. The reaction was then warmed up to 70 ^oC and stirred at that temperature overnight. After evaporation of EtOAc under reduced pressure, the residue was purified by flash chromatography (silica, 30:70 ethyl acetate in hexanes) to give corresponding triketone **128** (47.0 g, 142 mmol, 82%) as yellow oil. R_f (50% EtOAc in hexanes) = 0.25; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.21 (5H, m), 4.56 (2H, s), 3.45 (2H, t, J = 6.07 Hz), 2.77-2.52 (4H, m), 2.47 (2H, t, 7.19 Hz), 2.31(2H, t, 7.19 Hz), 2.11-1.76 (6H, m), 1.23 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$): δ 210.2, 209.6, 138.5, 128.5, 127.8, 73.0, 69.5, 64.6, 39.7, 37.9, 37.6, 30.0, 24.0, 19.7, 17.8; HRMS calcd. for $C_{20}H_{26}O_4Na$ (M+ Na^+) 353.1723, found 353.1724.



126

Enone 126 : To a solution triketone **128** (47.0 g, 142 mmol) in dry DMF (800 mL) was added D-Phe (23.5 g, 142 mmol, 1.0 equiv) followed by R-CSA (16.5 g, 71.1 mmol, 0.5 equiv) at 25 ^{o}C. The reaction was stirred at that temperature for 30 days before quenched with water (500 mL) and extracted with ether (3 x 500 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 20% EtOAc in hexanes) to give enone **126** (33.5 g, 107 mmol, 75%, 85% *ee*) as yellow oil. R_f (50% EtOAc in hexanes) = 0.30; $[\alpha]_D^{23}$ = - 83.8° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.24 (5H, m), 4.45 (2H, s), 3.49-3.37 (2H, m), 2.99 (1H, td, *J* = 15.1, 4.3 Hz), 2.74-2.59 (3H, m), 2.51-2.36 (4H, m), 2.15-2.00 (3H, m), 1.68-1.60 (1H, m), 1.41 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 211.9, 197.2, 160.7, 138.3, 131.7, 128.2, 127.4, 127.4, 72.7, 69.1, 51.0, 37.1, 33.4, 29.4, 27.1, 26.2, 23.4, 21.9; HRMS calcd. for $C_{20}H_{24}O_3Na$ ($M+Na^+$) 335.1618, found 335.1621.



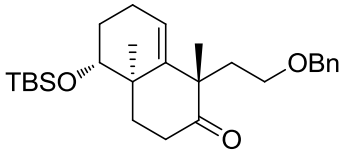
129

Silyl Ether 129 : To a stirred solution of enone **126** (33.5 g, 107 mmol) in dry EtOH (300 mL) at -78 ^{o}C was added $NaBH_4$ (1.02 g, 26.8 mmol, 0.25 equiv)

portionwise. The reaction was stirred at that temperature for 1 h and was quenched with glacial acetic acid (5 mL). After evaporation of EtOH under reduced pressure, the residue was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 40% EtOAc in hexanes) to give the corresponding C13 alcohol (23.6 g, 75.0 mmol, 70%) as yellow oil. $[a]_D^{23}$ = -87.6° (*c* 4.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 4.47 (2H, s), 3.43-3.33 (3H, m), 2.74 (1H, m), 2.67 (2H, m), 2.44-2.40 (2H, m), 2.17-2.61 (2H, m), 1.90-1.77 (3H, m), 1.72-1.57 (2H, m), 1.34-1.21 (1H, m), 1.18 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 198.4, 163.0, 138.5, 131.0, 128.3, 127.5, 127.4, 78.3, 72.7, 69.4, 42.0, 33.5, 33.5, 30.0, 27.2, 26.1, 23.1, 15.8; HRMS calcd. for $C_{20}H_{26}O_3Na$ ($M+Na^+$) 337.1774, found 337.1775.

A solution of the alcohol obtained as described above (23.6 g, 75.0 mmol) in dry DMF (150 mL) was treated with ammonium nitrate (18.1 g 225 mmol, 3.0 equiv) and TBSCl (22.6 g, 150 mmol, 2.0 equiv) at 0 °C. The mixture was warmed to 25 °C and stirred overnight, and then quenched with saturated NH_4Cl solution (60 mL). The reaction mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 5% EtOAc in hexanes) to give silyl ether **129** (30.5 g, 71.0 mmol, 95%) as yellow oil. R_f (5% EtOAc in hexanes) = 0.20; $[\alpha]_D^{23}$ = - 64.8° (*c* 4.0, CHCl3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.24 (5H, m), 4.48 (2H, s), 3.43-3.32 (3H, m), 2.73-2.65 (3H, m), 2.41-2.37 (2H, m), 2.09-2.00 (2H, m), 1.83-1.80 (1H, m), 1.71-1.63 (3H, m), 1.28-1.20 (1H, m), 1.14

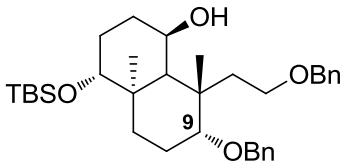
(3H, s), 0.89 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 198.7, 163.6, 138.6, 130.7, 128.2, 127.5, 127.4, 78.9, 72.7, 69.4, 42.6, 33.9, 33.7, 30.4, 27.2, 26.1, 25.8, 22.9, 18.0, 16.1, -3.9, -4.9; HRMS calcd. for $C_{26}H_{40}O_3Si$ (M^+) 428.2741, found 428.2746.



130

Ketone 130 : To a solution enone **129** (3.0 g, 7.0 mmol) in dry benzene (25 mL) was added potassium *tert*-butoxide (785 mg, 7.0 mmol, 1.0 equiv) at 25 ^{o}C. The reaction was then warmed up to 60 ^{o}C for 30 min and allowed to cool to 25 ^{o}C. MeI (1.3 mL, 21.0 mmol, 3.0 equiv) was then added and the reaction was stirred for 15 min before it was quenched with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 20% EtOAc in hexanes) to give ketone **130** (2.20 g, 4.9 mmol, 70%) as yellow oil. R_f (5% EtOAc in hexanes) = 0.22; $[\alpha]_D^{23}$ = -5.5° (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ: 7.34-7.24 (5H, m), 5.50 (1H, t, *J* = 3.6 Hz), 4.47 (1H, d, *J* = 11.7 Hz), 4.40 (1H, d, *J* = 11.7 Hz), 3.48 (1H, dd, *J* = 11.3, 4.5 Hz), 3.43-3.37 (1H, m), 3.31-3.25 (1H, m), 2.50-2.45 (2H, m), 2.41-2.34 (1H, m), 2.17-2.13 (2H, m), 2.08-2.02 (1H, m), 1.82-1.75 (1H, m), 1.72-1.59 (3H, m), 1.23 (3H, s), 0.90 (9H, s), 0.86 (3H, s), 0.07 (3H, s), 0.05 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 214.3, 145.2, 138.6, 128.2, 127.5, 127.3, 120.8, 76.6, 72.7, 67.2, 51.1, 39.3,

38.1, 33.9, 31.4, 29.5, 26.5, 25.8, 24.6, 18.0, 17.7, -3.9, -4.9; HRMS calcd. for $C_{27}H_{42}O_3SiNa$ ($M+Na^+$) 465.2795, found 465.2798.



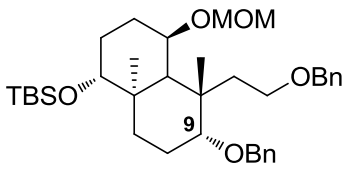
131

Alcohol 131 : To a solution of ketone **130** (26.0 g, 58.7 mmol) in MeOH (300 mL), $NaBH_4$ (2.2 g, 56.7 mmol, 1.0 equiv) was added at 0 ^oC. The reaction was stirred at that temperature for 30 min before quenched with saturated NH_4Cl solution (200 mL). MeOH was then removed under reduced pressure. The reaction mixture was then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 30% EtOAc in hexanes) to give C9 alcohol (24.1 g, 54.0 mmol, 92%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.40 (1H, t, *J* = 3.7 Hz), 4.49 (2H s), 3.50-3.38 (2H, m), 3.32 (1H, dd, *J* = 11.9, 3.7 Hz), 3.20-3.14 (1H, m), 2.39 (1H, m), 2.13-1.96 (3H, m), 1.89-1.50 (6H, m), 1.18 (3H, s), 1.10-1.02 (1H, m), 1.07 (3H, s), 0.89 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 145.9, 138.2, 128.4, 127.7, 127.6, 121.5, 78.7, 78.3, 73.0, 67.7, 44.1, 39.4, 36.1, 33.4, 27.0, 26.6, 25.9, 25.0, 23.6, 19.3, 18.0, -4.0, -4.8; HRMS calcd. for $C_{27}H_{44}O_3SiNa$ ($M+Na^+$) 467.2952, found 467.2954.

To a solution of alcohol obtained as decribed above (24.1 g, 54.0 mmol) in DMF (200 mL), NaH (5.2 g, 135 mmol, 60% w/w, 2.5 equiv) was added at 25 ^oC. The reaction was then heated at 60 ^oC for 30 minutes. Upon cooling to 25 ^oC, benzyl

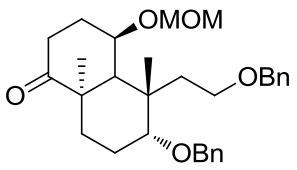
chloride (15.7 mL, 135 mmol, 2.5 equiv) was added dropwise, followed by NaI (200 mg, catalyst). The reaction was stirred overnight at 25 ^{o}C and quenched with saturated NH_4Cl (200 mL). The reaction mixture was then extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as yellow oil. To the crude benzyl ether (4.8 g, 9.0 mmol) in THF (20 mL), BH_3•THF (27.0 mL, 27.0 mmol, 1M in THF, 3.0 equiv) was added at 0 ^{o}C. The reaction was then left at that temperature for 3 days. Upon completion, a solution of pre-mixed 3N NaOH-30% w/w H_2O_2 (20 mL, 1:1) was added dropwise at 0 ^{o}C. The mixture was allowed to warm to 25 ^{o}C slowly and stirred at the same temperature for 5 h. Saturated NH_4Cl solution (50 mL) was then added and extracted with ethyl acetate (3 x 50 mL). The reaction was repeated 5 additional times in 4.81 g batches. The combined organic extracts were washed with brine and dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 20% EtOAc in hexanes) to give alcohol **131** (15.7 g, 32.4 mmol, 60% over 2 steps) as white oil. R_f (20% EtOAc in hexanes) = 0.25; $[\alpha]_D^{23}$ = - 30.3° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ: 7.43-7.29 (10H, m), 4.72 (1H, d, *J* = 11.7 Hz), 4.60 (1H, m), 4.53 (2H, m), 4.42 (1H, d, *J* = 11.7 Hz), 4.02 (1H, dt, *J* = 10.3, 3.7 Hz), 3.76 (1H, m), 3.66 (2H, m), 3.14 (1H, dd, *J* = 10.5, 5.1 Hz), 2.91 (1H, dd, *J* = 11.7, 3.7 Hz), 2.04-1.84 (4H, m), 1.65-1.49 (3H, m), 1.45 (3H, s), 1.24 (2H, t, *J* = 8Hz), 1.01 (1H, m), 0.97 (3H, s), 0.94 (9H, s), 0.08 (6H, br. s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 139.2, 137.7, 128.3, 128.1, 127.9, 127.6, 127.6, 127.0, 88.2, 79.9, 73.0, 71.3, 68.5, 58.3, 40.6, 40.4, 36.5, 34.2, 29.8, 29.3, 26.5,

25.8, 22.0, 17.9, 13.4, -4.1, -4.9; HRMS calcd. For $C_{34}H_{52}O_4SiNa$ ($M+Na^+$) 575.3527, found 575.351



132

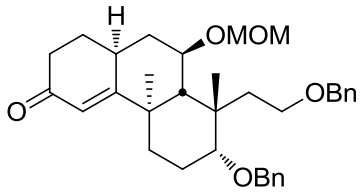
MOM Ether 132 : To a solution alcohol **131** (15.0 g, 27.1 mmol) in dry DCM (100 mL) was added DIPEA (33.2 mL, 190 mmol, 7.0 equiv) followed by MOMCl (10.3 mL,136 mmol, 5.0 equiv) and stirred for 15 h. The reaction was then diluted with water (300 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 10% EtOAc in hexanes) to give MOM ether **132** (15.9 g, 26.6 mmol, 98%) as yellow oil. R_f (10% EtOAc in hexanes) = 0.30; $[a]_D^{23}$ = - 23.3° (*c* 3.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.24 (10H, m), 4.65 (3H, m), 4.48 (1H, d, *J* = 12.0 Hz), 4.40 (1H, d, *J* = 12.0 Hz), 4.34 (1H, d, *J* = 11.7 Hz), 3.91-3.85 (1H, m), 3.79 (1H, dt, *J* = 4.2, 10.7 Hz), 3.53-3.47 (1H, m), 3.34 (3H, s), 3.07 (1H, dd, *J* = 4.8, 10.7 Hz), 2.87 (1H, dd, *J* = 3.5, 11.7 Hz), 2.16-2.05 (2H, m), 1.86-1.82 (2H, m), 1.73-1.45 (5H, m), 1.37-1.30 (1H, m), 1.27 (3H, s), 1.09 (1H, m), 0.92 (3H, s), 0.86 (9H, s), 0.01 (6H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 139.3, 138.9, 128.2, 128.1, 127.6, 127.2, 127.1, 127.0, 96.2, 88.6, 80.0, 76.5, 72.8, 71.7, 69.4, 57.7, 55.9, 41.0, 40.8, 36.9, 32.0, 31.0, 29.5, 26.3, 25.8, 21.9,18.0, 14.0, -4.0, -4.8; HRMS calcd. for $C_{36}H_{56}O_5SiNa$ ($M+Na^+$) 619.3789, found 619.3783.



133

Ketone 133 : To a solution **132** (15.9 g, 26.6 mmol) in THF (20 mL), TBAF (80 mL, 80 mmol, 1M in THF, 3.0 equiv) was added and heated to 130 ^{o}C using microwave irradiation for 60 min. The reaction was diluted with water (300 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure to provide the crude alcohol. The crude product was diluted with DCM (200 mL) and cooled to 0 ^{o}C whereupon DMP (34.5 g, 80.0 mmol, 3.0 equiv) was added and stirred for 2 h. Saturated sodium thiosulfate solution (200 mL) was added and stirred for 1 h. The mixture was diluted with saturated sodium bicarbonate solution (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 10% EtOAc in hexanes) to give ketone **133** (12.3 g, 25.7 mmol, 97% over 2 steps) as yellow oil. R_f (20% EtOAc in hexanes) = 0.2; $[a]_D^{23}$ = -36.2° (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.26 (10H, m), 4.69 (2H, s), 4.64 (1H, d, *J* = 11.7 Hz), 4.49 (1H, d, *J* = 11.7 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.36 (1H, d, *J* = 11.7 Hz), 4.15-4.11 (1H, m), 3.89-3.83 (1H, m), 3.57-3.51 (1H, m), 3.37 (3H, s), 2.90 (1H, dd, *J* = 3.9, 11.5 Hz), 2.50-2.42 (2H, m), 2.28-2.20 (1H, m), 2.14-2.08 (1H, m), 1.99-1.92 (2H, m), 1.80-1.72 (3H, m), 1.48-1.41 (2H, m), 1.19 (3H, s), 1.18 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 214.9,139.0, 138.7, 129.5, 128.3, 128.2,

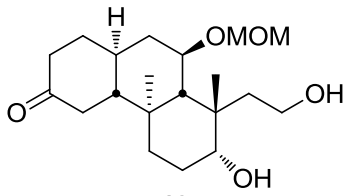
127.7, 127.5, 127.3, 96.4, 87.3, 75.1, 73.1, 71.7, 69.1, 56.1, 55.5, 46.8, 42.3, 33.7, 32.5, 31.9, 28.4, 24.4, 21.8, 20.8; HRMS calcd. for $C_{30}H_{40}O_5Na$ ($M+Na^+$) 503.2773, found 503.2776.



134

Cyclohexenone 134 : To a solution ketone **133** (10.0 g, 20.8 mmol) in ethyl formate (200 mL) at 0 ^oC, NaH (1.7 g, 41.6 mmol, 60% w/w, 2.0 equiv) was added followed by MeOH (0.84 mL, 20.8 mmol, 1.0 equiv). The reaction was stirred for 30 min at 25 ^oC and then it was quenched with saturated NH_4Cl solution (200 mL). The reaction mixture was then extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude formylated product. The crude product was dissolved in DCM (200 mL) and then TEA (11.6 mL, 83.0 mmol, 4.0 equiv) was added followed by methyl vinyl ketone (5.2 mL, 62.4 mmol, 3.0 equiv) and the mixture was stirred for 4 h at 25 ^oC. The reaction mixture was concentrated under reduced pressure to provide the crude triketone. The crude triketone was dissolved in *tert*-butanol (100 mL). Potassium *tert*-butoxide (31.2 mL, 31.2 mmol, 1M in *tert*-butanol, 1.5 equiv) was added and stirred for 30 min at 25 ^oC. The reaction mixture was quenched with saturated NH_4Cl solution (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash

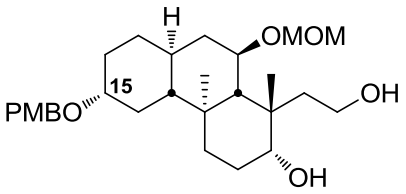
chromatography (silica, 10% EtOAc in hexanes) to give cyclohexenone **134** (8.3 g, 15.6 mmol, 75% over 3 steps) as yellow oil. R_f (30% EtOAc in hexanes) = 0.21; $[\alpha]_D^{23}$ = - 29.7° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.27 (10H, m), 5.83 (1H, s), 4.70 (2H, s), 4.66 (1H, d, *J* = 11.7 Hz), 4.48 (1H, d, *J* = 11.9 Hz), 4.41 (1H, d, *J* = 11.9 Hz), 4.37 (1H, d, *J* = 11.7 Hz), 4.10-4.04 (1H, m), 3.91-3.85 (1H, m), 3.54-3.49 (1H, m), 3.37 (3H, s), 2.89 (1H, dd, *J* = 4.0, 11.6 Hz), 2.71-2.63 (1H, m), 2.46-2.37 (2H, m), 2.30-2.20 (1H, m), 2.15-2.06 (2H, m), 2.01-1.97 (1H, m), 1.80-1.70 (3H, m), 1.67-1.61 (2H, m), 1.54-1.50 (1H, m), 1.35-1.33 (1H, m), 1.28 (3H, s), 1.17 (3H, s); ^{13}C NMR (100MHz, CDCl3) δ: 200.8, 173.3, 139.0, 138.7, 128.2, 128.1, 127.7, 127.3, 127.2, 120.3, 96.4, 87.6, 75.6, 72.9, 71.8, 69.2, 57.8, 56.0, 41.7, 41.5, 41.2, 36.2, 35.2, 33.1, 31.1, 29.6, 26.2, 22.9, 21.9, 14.1; HRMS calcd. for $C_{33}H_{45}O_5$ ($M+H^+$) 533.3262, found 533.3260.



135

Diol 135 : Liquid ammonia (150 mL) was collected in a round bottom flask mounted with a cold finger at -78 °C. Cyclohexenone **134** (5.0 g, 9.4 mmol) in THF (20 mL) and ethanol (1.1 mL, 18.8 mmol, 2.0 equiv) was added to the ammonia. Lithium wire was slowly added until a dark blue reaction mixture persisted. The reaction was stirred at reduced temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) whereupon the dark blue color faded and warmed to

RT over the course of 1 h to allow for the evaporation of liquid ammonia. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (5 x 150 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, concentrated under reduced and purified by flash chromatography (silica, EtOAc) to give diol **135** (2.4 g, 6.9 mmol, 73%) as yellow oil. R_f (EtOAc) = 0.15; $[\alpha]_D^{23}$ = - 20.7° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.71 (1H, d, *J* = 6.9 Hz), 4.59 (1H, d, *J* = 6.9 Hz), 3.84 (1H, dt, *J* = 4.2, 10.7 Hz), 3.74-3.60 (4H, m), 3.35 (3H, s), 3.17 (1H, dd, *J* = 4.0, 11.7 Hz), 2.34-2.27 (3H, m), 2.03-1.92 (3H, m), 1.72-1.54 (6H, m), 1.37 (3H, s), 1.25-1.04 (5H, m), 0.93 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 212.6, 95.8, 78.2, 75.9, 62.4, 59.9, 58.8, 56.1, 54.8, 42.3, 41.1, 40.8, 38.9, 37.4, 34.5, 33.3, 32.6, 26.5, 25.9, 15.5; HRM calcd. for $C_{20}H_{34}O_5Na$ ($M+Na^+$) 377.2298, found 377.2296.



136

Diol 136: To a solution of diol **135** (3.3 g, 9.4 mmol) in DCM (50 mL) at 0 °C, DIPEA (8.2 mL, 46.9 mmol, 5.0 equiv.) and TIPSOTf (10.2 mL, 37.5 mmol, 4.0 equiv) were added and stirred for 2 h at RT. The reaction mixture was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, concentrated under reduced pressure to provide the crude silyl ether. The crude

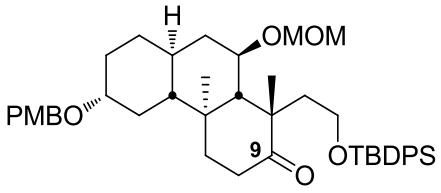
product was dissolved in DCM (100 mL) and cooled to 0 ^{o}C whereupon TFA (1.1 mL, 14.1 mmol, 1.5 equiv) was slowly added and stirred at that temperature for 30 min. The reaction mixture was cautiously quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 5% EtOAc in hexanes) to give di-TIPS ether (3.6 g, 5.4 mmol, 80% over 2 steps) as yellow oil. R_f (20% EtOAc in hexanes) = 0.3; $[\alpha]_D^{23}$ = - 10.8° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.73 (s, 2H), 4.07-4.00 (1H, m), 3.92-3.86 (1H, m), 3.71-3.65 (1H, m), 3.40 (3H, s), 3.29 (1H, dd, *J* = 3.8, 11.7 Hz), 2.36-2.27 (3H, m), 2.10-1.96 (3H, m), 1.76-1.69 (2H, m), 1.63-1.51 (6H, m), 1.32 (3H, s), 1.14-1.11 (3H, m), 1.07-1.04 (43H, m), 0.97 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 212.5, 96.6, 81.6, 76.8, 62.1, 60.4, 55.1, 42.4, 41.7, 41.0, 40.9, 38.5, 37.6, 35.0, 34.6, 33.5, 27.0, 26.8, 18.4, 18.3, 18.1,15.9, 13.0, 12.1; HRMS calcd. for $C_{38}H_{74}O_5Si_2Na$ ($M+Na^+$) 689.4967, found 689.4966.

To a solution di-TIPS ether obtained as described above (2.0 g, 3.0 mmol) in dry THF (10 mL) and EtOH (10 mL) at -78 ^{o}C, sodium borohydride (227 mg, 6.0 mmol, 2.0 equiv) was added and stirred for 3 hours at that temperature. Saturated NH_4Cl solution (100 mL) was cautiously added to the mixture and it was allowed to warm to RT and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 10% EtOAc in hexanes) to give C15 alcohol (1.4 g, 2.1 mmol, 70%) as yellow oil. R_f (20% EtOAc in hexanes) = 0.15; $[\alpha]_D^{23}$ = - 9.81° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.71 (1H, d, *J* = 6.8 Hz), 4.68 (1H, d, *J* = 6.8

Hz), 4.06-3.99 (1H, m), 3.81 (1H, dt, *J* = 4.1, 10.6 Hz), 3.69-3.63 (1H, m), 3.54-3.49 (1H, m), 3.38 (3H, s), 3.28 (1H, dd, *J* = 3.5, 11.7 Hz), 2.23-2.18 (1H, m), 2.09-2.01 (1H, m), 1.91-1.89 (2H, m), 1.80-1.53 (7H, m), 1.30 (3H, s), 1.00-1.09 (48H, m), 0.90 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 96.4, 81.8, 77.0, 71.4, 62.1, 60.8, 55.9, 53.0, 42.4, 42.3, 38.2, 37.9, 35.3, 34.9, 34.8, 34.6, 32.2, 27.2, 26.8, 18.4, 18.3, 18.1, 18.1, 16.3, 13.0, 12.0; HRMS calcd. for $C_{38}H_{76}O_5Si_2Na$ ($M+Na^+$) 691.5123, found 691.5125.

To the alcohol obtained as described above (2.0 g, 3.0 mmol) in DMF (15 mL), sodium hydride (364 mg, 9.1mmol, 3.0 equiv) was added and the reaction was heated to 60 ^oC for 30 min. The mixture was cooled to RT and 4-methoxybenzyl (PMB) chloride (2.1 mL, 15.2 mmol, 5.0 equiv) was added and it was stirred for 15 h. The reaction was quenched slowly with saturated NH_4Cl solution (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude PMB ether. The crude product was dissolved in THF (3 mL), TBAF (9.1 mL, 9.1 mmol, 1M in THF, 3.0 equiv) and the reaction was heated to 130 ^oC using microwave irradiation for 60 min. The mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, EtOAc) to give diol **136** (868 mg, 1.82 mmol, 60% over 2 steps) as yellow oil. R_f (EtOAc) = 0.51; $[\alpha]_D^{23}$ = - 15.9° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.56 (1H, d, *J* = 6.9 Hz), 4.49 (1H, d, *J* = 11.4 Hz), 4.44

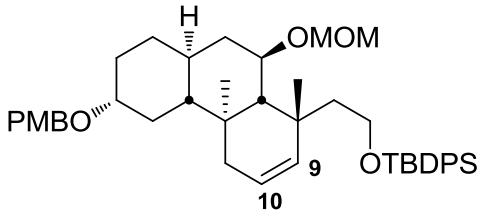
(1H, d, *J* = 11.4 Hz), 3.79 (3H, s), 3.78-3.61 (5H, m), 3.34 (3H, s), 3.29-3.22 (1H, m), 3.17 (1H, dd, *J* = 4.0, 11.8 Hz), 2.16 (1H, dt, *J* = 4.0, 12.4 Hz), 2.07-1.92 (3H, m), 1.75-1.57 (5H, m), 1.37 (3H, s), 1.27-0.91 (7H, m), 0.87 (3H, s), 0.73-0.67 (1H, m); ^{13}C NMR (100MHz, $CDCl_3$) δ: 159.0, 130.9, 129.1, 113.7, 95.7, 78.6, 77.9, 76.2, 69.5, 60.5, 59.1, 56.1, 55.2, 53.0, 42.4, 41.8, 38.6, 37.9, 35.1, 32.6, 32.1, 31.8, 31.5, 26.9, 26.0, 16.0; HRMS calcd. for $C_{28}H_{44}O_6Na$ ($M+Na^+$) 499.3036, found 499.3038.



141

Ketone 141: To diol **136** (1.0 g, 2.1 mmol) in DCM (20 mL), DIPEA (1.5 mL, 8.4 mmol, 4.0 equiv) and TBDPSCl (1.1 mL, 4.2 mmol, 2.0 equiv) were added at 0 ^{o}C. After 2 h, the reaction was diluted with water (100mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude silylated product. The crude product was dissolved in DCM (20 mL) and cooled to 0 ^{o}C whereupon DMP (2.7 g, 6.3 mmol, 3.0 equiv) was added. After 2 h, saturated sodium thiosulfate solution (100 mL) was added and stirred for 1 hour at RT. The reaction was diluted with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 10% EtOAc in hexanes) to give ketone **141** (1.35 g, 1.89

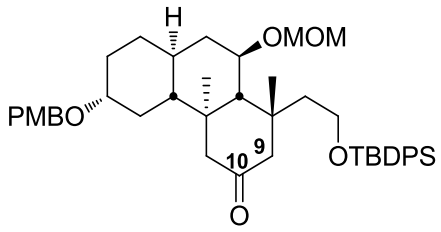
mmol, 86% over 2 steps) as yellow oil. R_f (20% EtOAc in hexanes) = 0.23; $[\alpha]_D^{23}$ = -4.1° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.64 (4H, m), 7.42-7.36 (6H, m), 7.26 (2H, m), 6.87 (2H, d, *J* = 7.6 Hz), 4.68 (1H, d, *J* = 6.6 Hz), 4.59 (1H, d, *J* = 6.6 Hz), 4.51 (1H, d, *J* = 11.2 Hz), 4.45 (1H, d, *J* = 11.2 Hz), 3.85-3.75 (1H, m), 3.79 (3H, s), 3.71-3.66 (1H, m), 3.62-3.58 (1H, m), 3.36 (3H, s), 3.31-3.26 (1H, m), 2.51 (1H, dt, *J* = 5.6, 13.8 Hz), 2.27-2.23 (2H, m), 2.18-1.84 (6H, m), 1.77-1.73 (1H, m), 1.48-1.46 (1H, m), 1.39-1.19 (7H, m), 1.04 (9H, s), 1.00 (3H, s), 1.00-0.93 (1H, m), 0.78-0.72 (1H, m); ^{13}C NMR (100MHz, $CDCl_3$) δ: 159.0, 135.5, 135.5, 133.7, 130.9, 129.5, 129.1, 127.5, 113.7, 95.9, 77.6, 77.2, 75.6, 69.6, 61.2, 60.7, 56.1, 55.2, 52.2, 50.1, 41.6, 38.2, 38.1, 36.4, 34.9, 32.0, 31.8, 31.6, 26.8, 24.7, 19.0, 15.7; HRMS calcd. for $C_{44}H_{61}O_6Si$ ($M+H^+$) 713.4232, found 713.4228.



C9-C10 olefin

C9-C10 olefin : To ketone **141** (3.5 g, 4.9 mmol) in dry THF (25 mL) at -78 ^oC, NaHMDS (24.5 mL, 24.5 mmol, 1M in THF, 5.0 equiv) was added. After 1 h, $PhNTf_2$ (3.5 g, 9.82mmol, 2.0 equiv) was added and stirred for 1 h at that temperature. The reaction was warmed to RT, quenched with saturated NH_4Cl solution (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude vinyl triflate. The crude product was dissolved in DMF (10 mL),

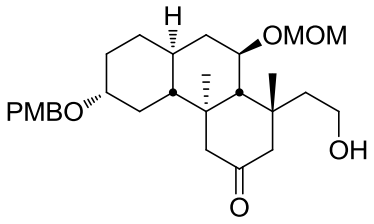
$Pd(OAc)_2$ (110 mg, 0.491 mmol, 0.1 equiv) was added, followed by Ph_3P (258 mg, 0.982 mmol, 0.20 equiv), DIPEA (3.4 mL, 19.6 mmol, 4.0 equiv) and formic acid (0.9 mL, 19.6 mmol, 4.0 equiv). The mixture was heated to 75 ^oC for 60 min. The black mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 5% EtOAc in hexanes) to give C9-C10 olfein (3.08 g, 4.42 mmol, 90% over 2 steps) as yellow oil. R_f (10% EtOAc in hexanes) = 0.52; $[\alpha]_D^{23}$ = - 16.7° (*c* 4.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.67 (4H, m), 7.42-7.36 (6H, m), 7.27 (2H, d, *J* = 8.2 Hz), 6.88 (2H, d, *J* = 8.2 Hz), 5.41-5.39 (2H, m), 4.72 (1H, d, *J* = 6.8 Hz), 4.66 (1H, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 11.3 Hz), 4.47 (1H, d, *J* = 11.3 Hz), 3.86-3.82 (2H, m), 3.80 (3H, s), 3.71-3.64 (1H, m), 3.40 (3H, s), 3.30 (1H, m), 2.26-2.23 (1H, m), 2.09-1.91 (4H, m), 1.79-1.72 (2H, m), 1.65-1.61 (1H, m), 1.40-1.30 (6H, m), 1.18 (3H, s), 1.08-1.02 (1H, m), 1.05 (9H, s), 0.79 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 159.0, 136.6, 135.5, 134.0, 131.0, 129.5, 129.1, 129.1, 127.5, 125.3, 124.3, 120.6, 113.7, 96.2, 78.0, 76.9, 69.5, 61.2, 56.9, 56.1, 55.2, 51.7, 41.4, 39.2, 37.4, 36.9, 36.7, 34.2, 32.3, 31.7, 31.7, 31.6, 26.8, 19.1, 18.1, 14.9; HRMS calcd. for $C_{44}H_{60}O_5SiNa$ ($M+Na^+$) 719.4102, found 719.4107.



142

Ketone 142 : To C9-C10 olefin (3.4 g, 4.9 mmol) in dry THF (25 mL), BH3•THF (10.0 mL, 10.0 mmol, 2.0 equiv) was added and heated to reflux. After 15 h, a solution of pre-mixed 3N NaOH-30% w/w H_2O_2 (20 mL, 1:1) was added at 0 ^oC and the reaction was warmed up to RT. After 60 min, the mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude alcohol. The crude product was disolved in DCM (20 mL), DMP (4.2 g, 9.8 mmol, 3.0 equiv) was added at 0 ^oC and stirred for 2 h at RT. Saturated sodium thiosulfate solution (100 mL) was added and stirred for an additional 60 min. The mixture was diluted with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 10% EtOAc in hexanes) to give ketone **142** (1.19 g, 1.67 mmol, 34% over 2 steps) as a yellow oil and its isomeric C9 ketone (595 mg, 0.835 mmol, 17% over 2 steps) as yellow oil. R_f (20% EtOAc in hexanes) = 0.18; $[\alpha]_D^{23}$ = - 21.0° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.65 (4H, m), 7.43-7.37 (6H, m), 7.25 (2H, d, *J* = 9.2 Hz), 6.87 (2H, d, *J* = 9.2 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 4.60 (1H, d, *J* = 6.8 Hz), 4.48 (1H, d, *J* = 11.2 Hz), 4.45 (1H, d, *J* =11.2 Hz), 3.80 (3H, s), 3.77-3.69 (3H, m), 3.36 (3H, s), 3.31-3.22 (1H, m), 2.58 (1H, d, *J* = 13.6

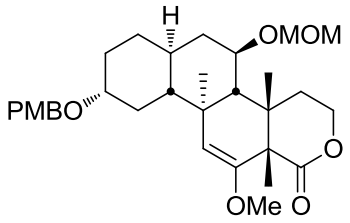
Hz), 2.33 (1H, d, *J* = 15.6 Hz), 2.28-2.24 (1H, m), 2.08-1.97 (3H, m), 1.93-1.84 (3H, m), 1.78-1.74 (1H, m), 1.36 (1H, d, *J* = 10.4 Hz), 1.29-1.21 (3H, m), 1.16 (3H, s), 1.04 (9H, s), 1.09-0.98 (3H, m), 0.95 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 212.0, 159.0, 135.5, 133.7, 130.8, 129.6, 129.1, 127.6, 127.6, 113.8, 96.1, 77.4, 76.2, 69.6, 60.7, 58.7, 56.1, 55.3, 53.9, 53.1, 52.5, 42.2, 41.3, 40.1, 38.0, 34.0, 32.0, 31.7, 31.5, 26.8, 19.0, 16.9; HRMS calcd. for $C_{44}H_{61}O_6Si$ ($M+H^+$) 713.4232, found 713.4231.



143

Alcohol 143 : To ketone **142** (300 mg, 0.4 mmol) in THF (5.0 mL), TBAF (1.3 mL, 1.3 mmol, 1M in THF, 3.0 equiv) was added. After 4 h, the reaction was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, EtOAc) to give alcohol **143** (150 mg, 0.32 mmol, 75%) as yellow oil. R_f (EtOAc) = 0.40; $[\alpha]_D^{23}$ = - 31.2° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (2H, d, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 4.74 (1H, d, *J* = 6.4 Hz), 4.66 (1H, d, *J* = 6.4 Hz), 4.48 (1H, d, *J* = 11.4 Hz), 4.44 (1H, d, *J* = 11.4 Hz), 3.85-3.77 (1H, m), 3.79 (3H, s), 3.75-3.70 (2H, m), 3.38 (3H, s), 3.29-3.24 (1H, m), 2.59 (1H, d, *J* = 13.6 Hz), 2.36-2.25 (2H, m), 2.17-2.14 (1H, m), 1.93-1.74 (5H, m), 1.48 (1H, d, *J* = 10.4 Hz), 1.31-1.17 (2H, m), 1.25 (3H, s), 1.06-0.90 (3H, m)0.99 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 212.1, 159.0, 130.8,

129.1, 113.8, 95.9, 77.4, 76.0, 69.6, 59.4, 59.1, 56.2, 55.2, 53.8, 53.1, 53.0, 43.0, 41.3, 41.1, 37.8, 34.2, 32.1, 31.9, 31.7, 31.5, 16.8; HRMS calcd. for $C_{28}H_{43}O_6$ ($M+H^+$) 475.3024, found 475.3052.

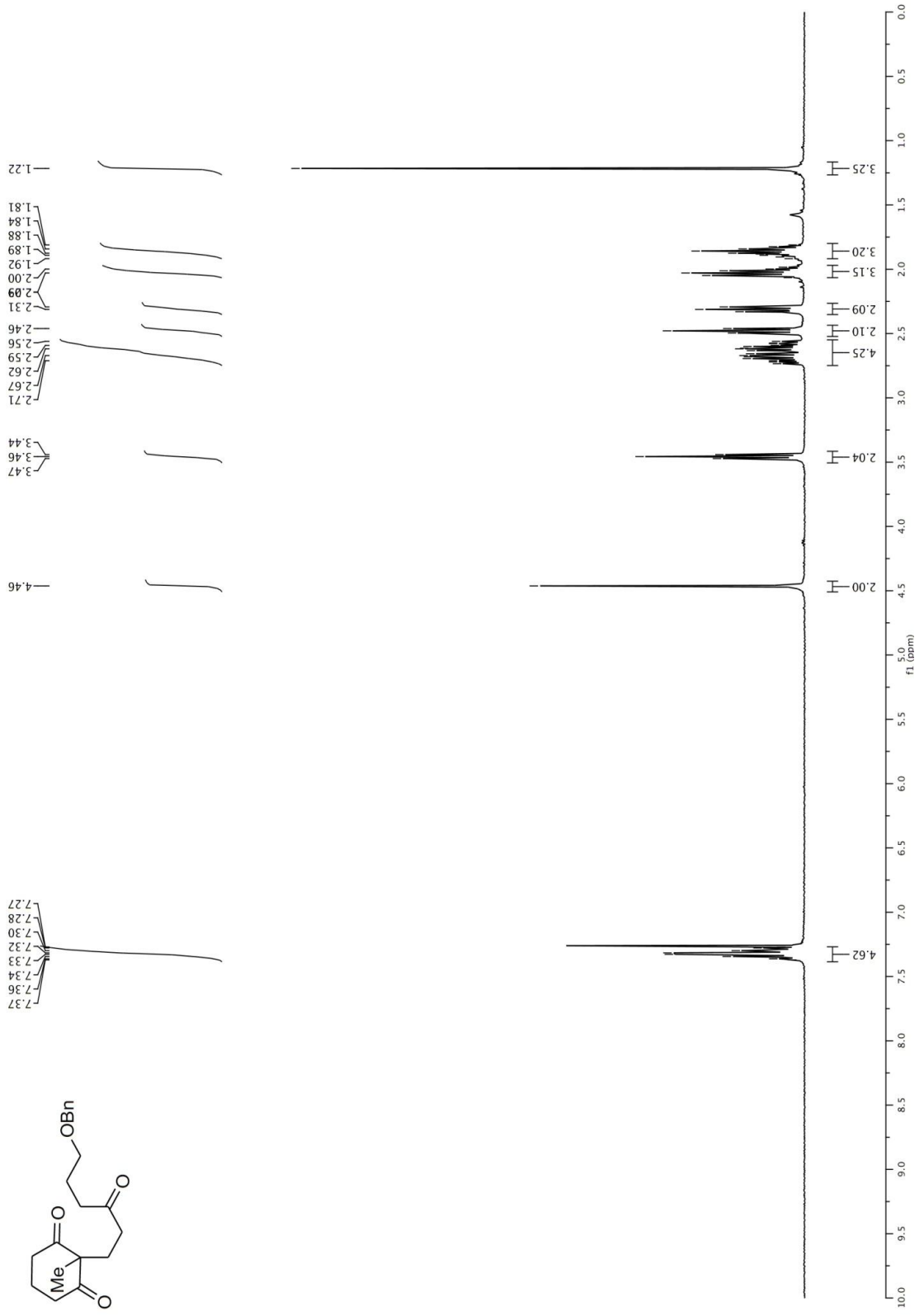


124

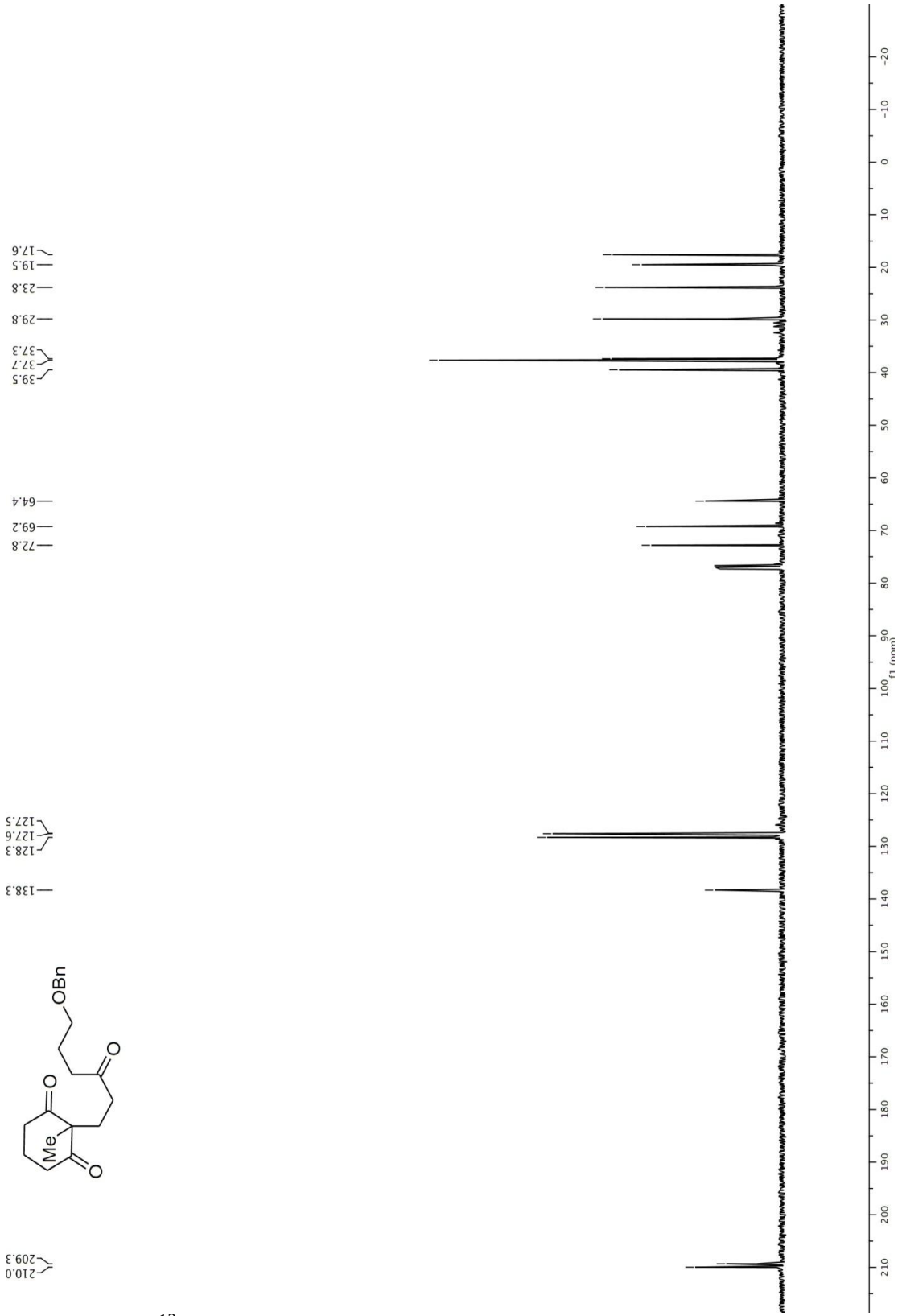
Lactone 124 : To alcohol **143** (78 mg, 0.16 mmol) in THF (2.0 mL) and DMPU (2.0 mL), ^{t}BuOLi (0.82 mL, 0.82 mmol, 5.0 equiv) and dimethyl carbonate (0.14 mL, 1.6 mmol, 10.0 equiv) were added and heated to 70 ^{o}C for 60 min. The reaction was cooled to RT whereupon iodomethane (0.2 mL, 3.3 mmol, 20.0 equiv) was added. After 4 h, the reaction was diluted with water (50 mL) extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 30% EtOAc in hexanes) to give methyl enone ether (66 mg, 0.13 mmol, 78%) as yellow oil. R_f (50% EtOAc in hexanes) = 0.25; $[\alpha]_D^{23}$ = - 11.9° (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (2H, d, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 4.73 (1H, d, *J* = 6.8 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.55 (1H, d, *J* = 11.2 Hz), 4.43 (1H, d, *J* = 11.2 Hz), 4.29-4.24 (1H, m), 4.13-4.06 (1H, m), 3.79 (3H, s), 3.72-3.66 (1H, m), 3.68 (3H, s), 3.37 (3H, s), 3.37-3.20 (1H, m), 2.64 (1H, d, *J* = 9.2 Hz), 2.37 (1H, d, *J* = 16.4 Hz), 2.28-2.25 (1H, m), 2.15-2.11 (1H, m), 2.08-2.03 (1H, m), 1.98-1.92 (1H, m), 1.88 (1H, d, *J* = 16.4 Hz), 1.79-1.75 (1H, m), 1.43-1.40 (1H, m), 1.37 (3H, s), 1.30-1.18 (3H, m), 1.12-0.97 (3H, m), 0.85 (3H, s); ^{13}C NMR

(100MHz, $CDCl_3$) δ: 167.9, 159.1, 157.8, 130.8, 129.2, 113.8, 111.9, 96.0, 77.7, 76.7, 69.9, 64.8, 56.1, 56.0, 55.2, 51.2, 40.8, 39.2, 38.4, 36.9, 34.9, 34.6, 32.1, 31.9, 31.5, 30.7, 14.4; HRMS calcd. for $C_{30}H_{43}O_7$ ($M+H^+$) 515.3009, found 515.3007.

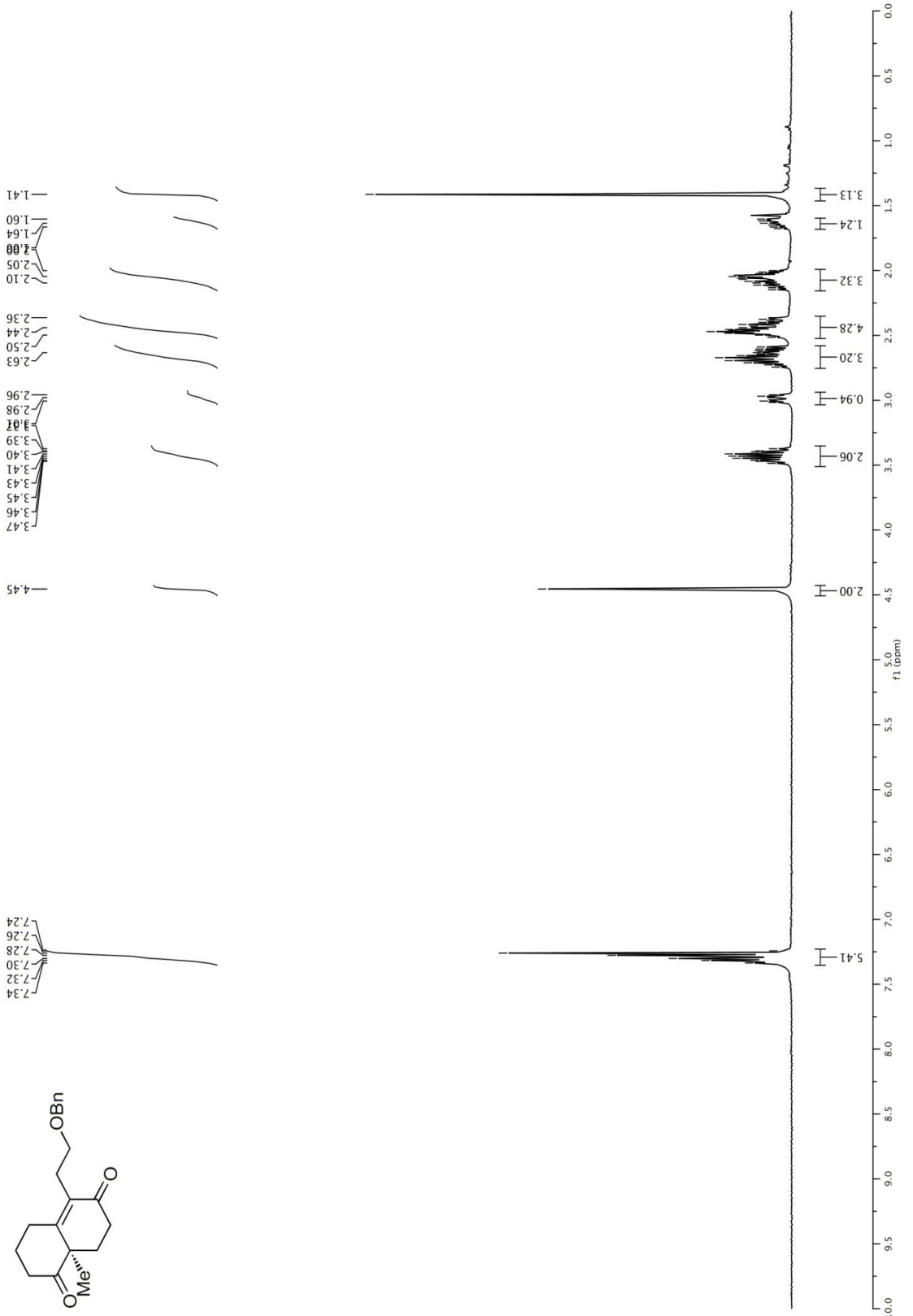
To enone ether obtained as described above (58 mg, 0.11 mmol) in THF (2.0 mL) was added DMPU (2.0 mL), LiHMDS (0.45 mL, 0.45 mmol, 4.0 equiv) at -10 ^oC. After 60 min, iodomethane (0.44 mL, 7.1 mmol, 15.0 equiv) was added and the reaction was allowed to stir at that temperature for an additional 30 min and then it was warmed to RT. After 4 h, the reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (silica, 30% EtOAc in hexanes) to give lactone **124** (45 mg, 0.09 mmol, 80%) as white solid. R_f (50% EtOAc in hexanes) = 0.30; $[\alpha]_D^{23}$ = - 16.3° (*c* 4.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 4.67 (1H, s), 4.60 (1H, d, *J* = 6.8 Hz), 4.55 (1H, d, *J* = 11.2 Hz), 4.43 (1H, d, *J* = 11.2 Hz), 4.13 (1H, ddd, *J* = 2.4, 5.5, 11.3 Hz), 3.97 (1H, dt, *J* = 4.4, 11.3 Hz), 3.79 (3H, s), 3.52 (3H, s), 3.38 (3H, s), 3.38-3.30 (2H, m), 2.40-2.36 (1H, m), 2.28-2.24 (1H, m), 2.16-2.09 (2H, m), 1.79-1.75 (1H, m), 1.71-1.65 (2H, m), 1.42-1.35 (1H, m), 1.38 (3H, s), 1.27-1.21 (1H, m), 1.21 (3H, s), 1.15-1.06 (2H, m), 1.00-0.89 (2H, m), 0.95 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ: 174.3, 159.1, 153.1, 130.9, 129.2, 113.8, 101.1, 95.7, 77.8, 75.0, 69.9, 65.4, 56.1, 55.2, 54.9, 53.2, 52.5, 51.6, 42.1, 39.7, 39.2, 35.9, 33.1, 32.5, 32.0, 31.8, 31.6, 20.9, 17.8; HRMS calcd. for $C_{31}H_{45}O_7$ ($M+H^+$) 529.3160, found 529.3163.



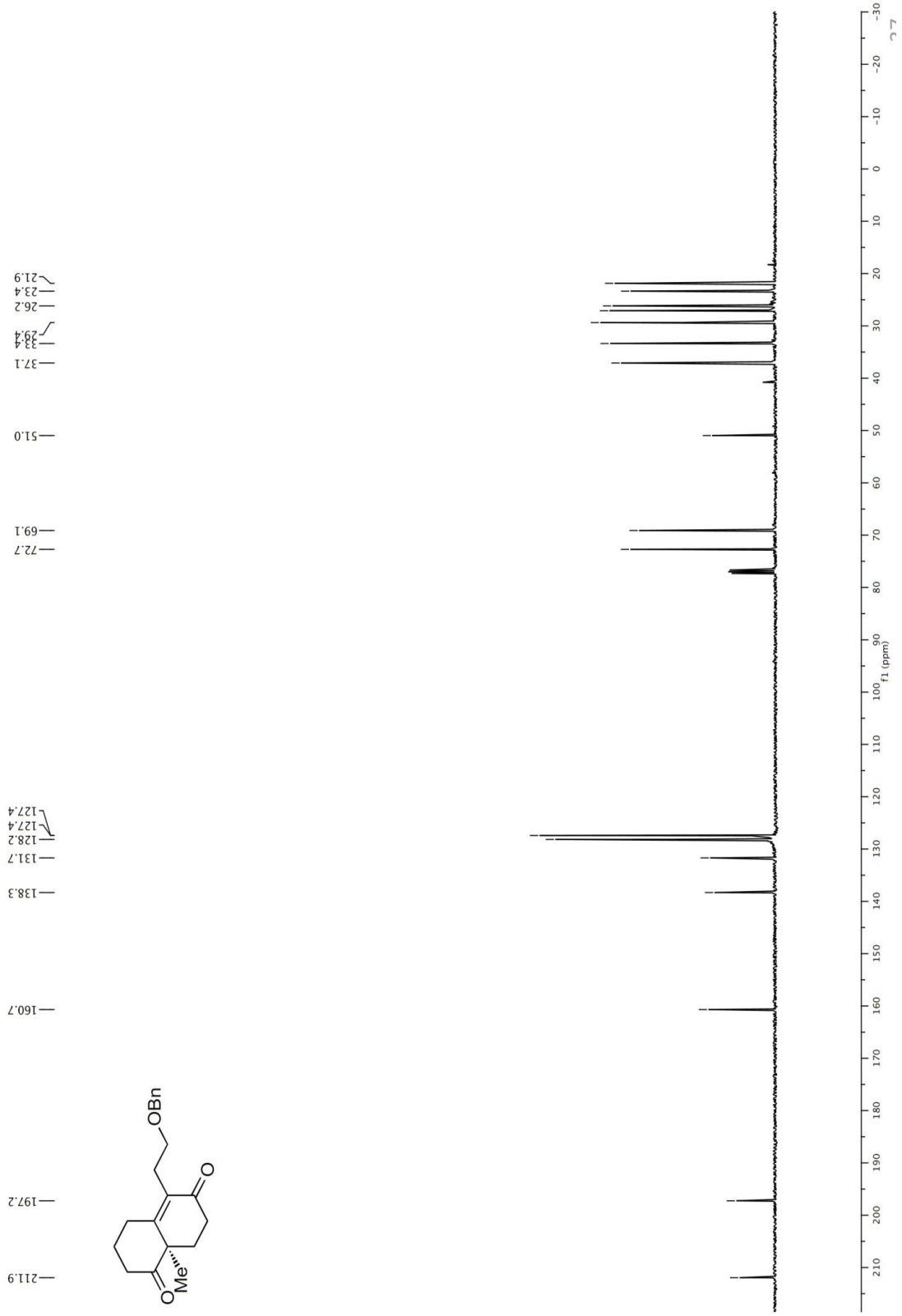
Spectrum 2.1 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **128**.



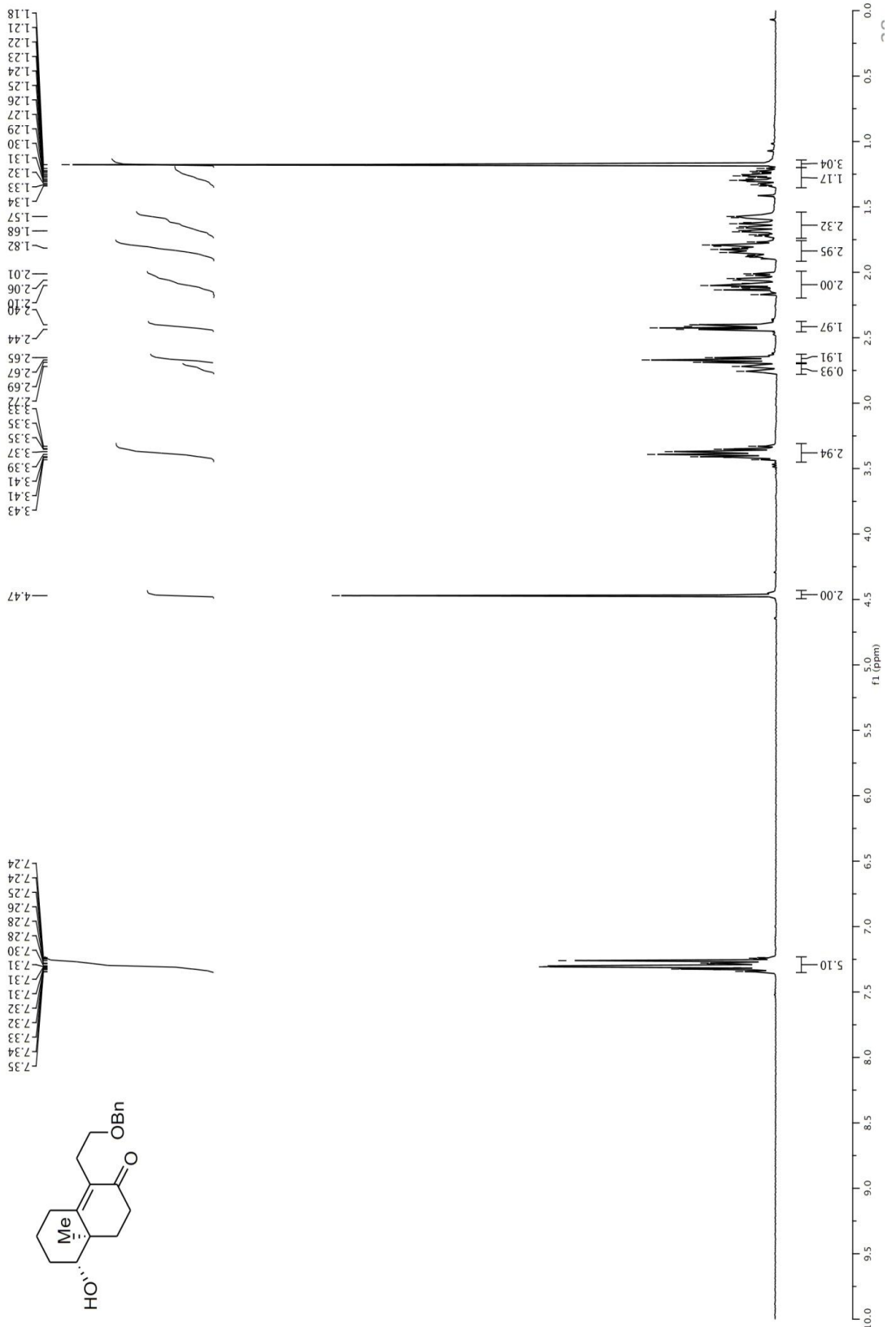
Spectrum 2.2 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **128**.



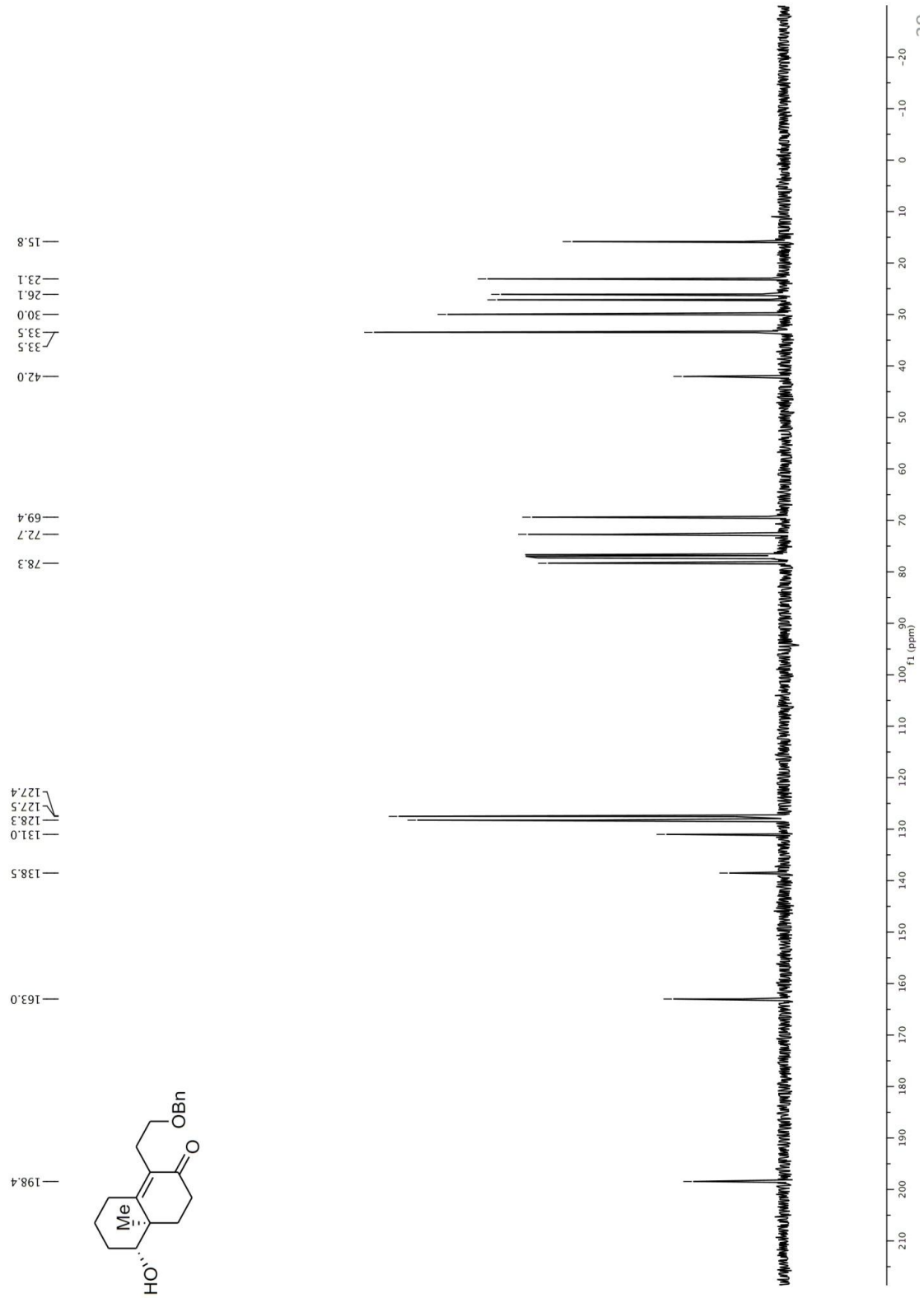
Spectrum 2.3 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **126**.



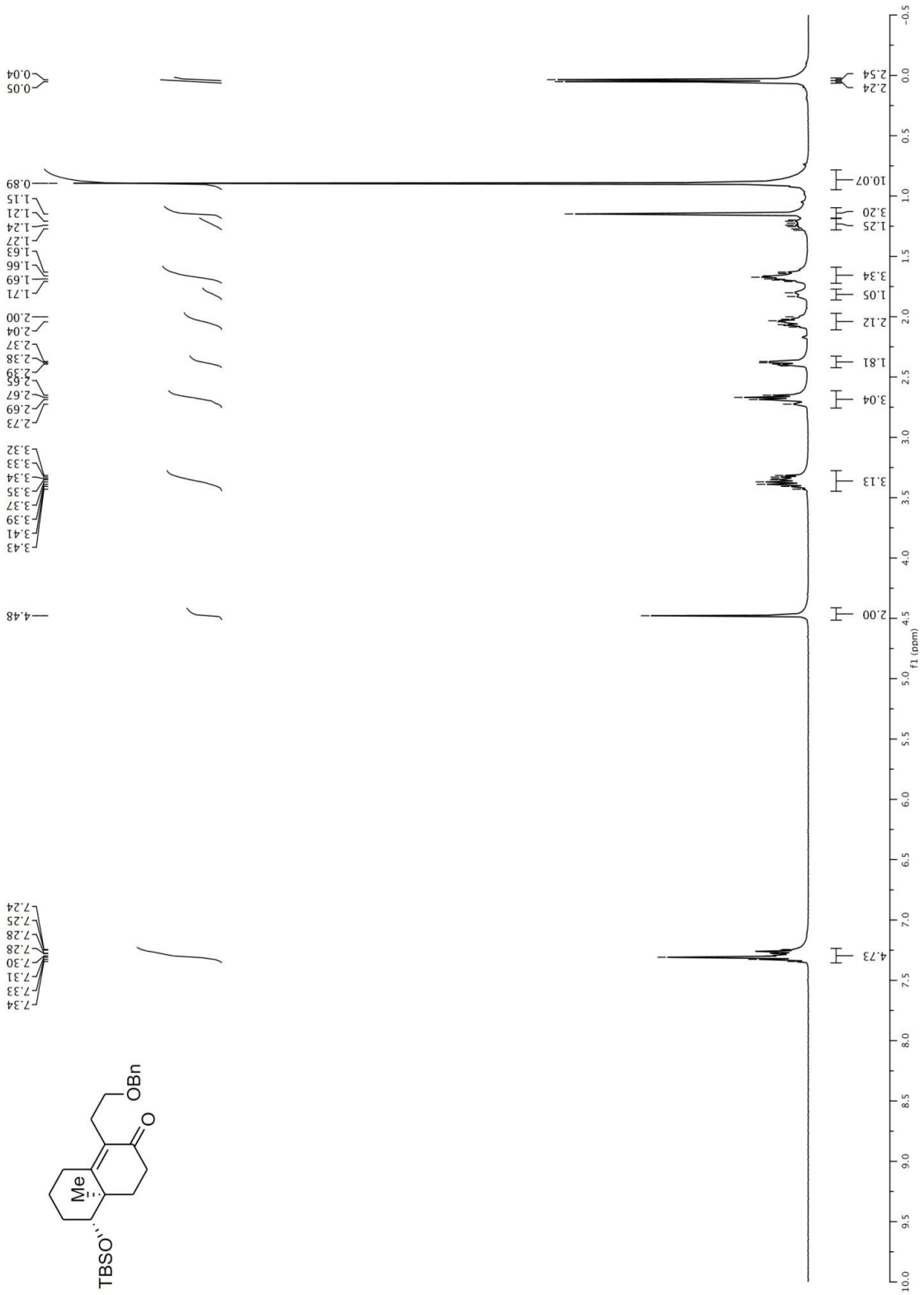
Spectrum 2.4 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **126**.



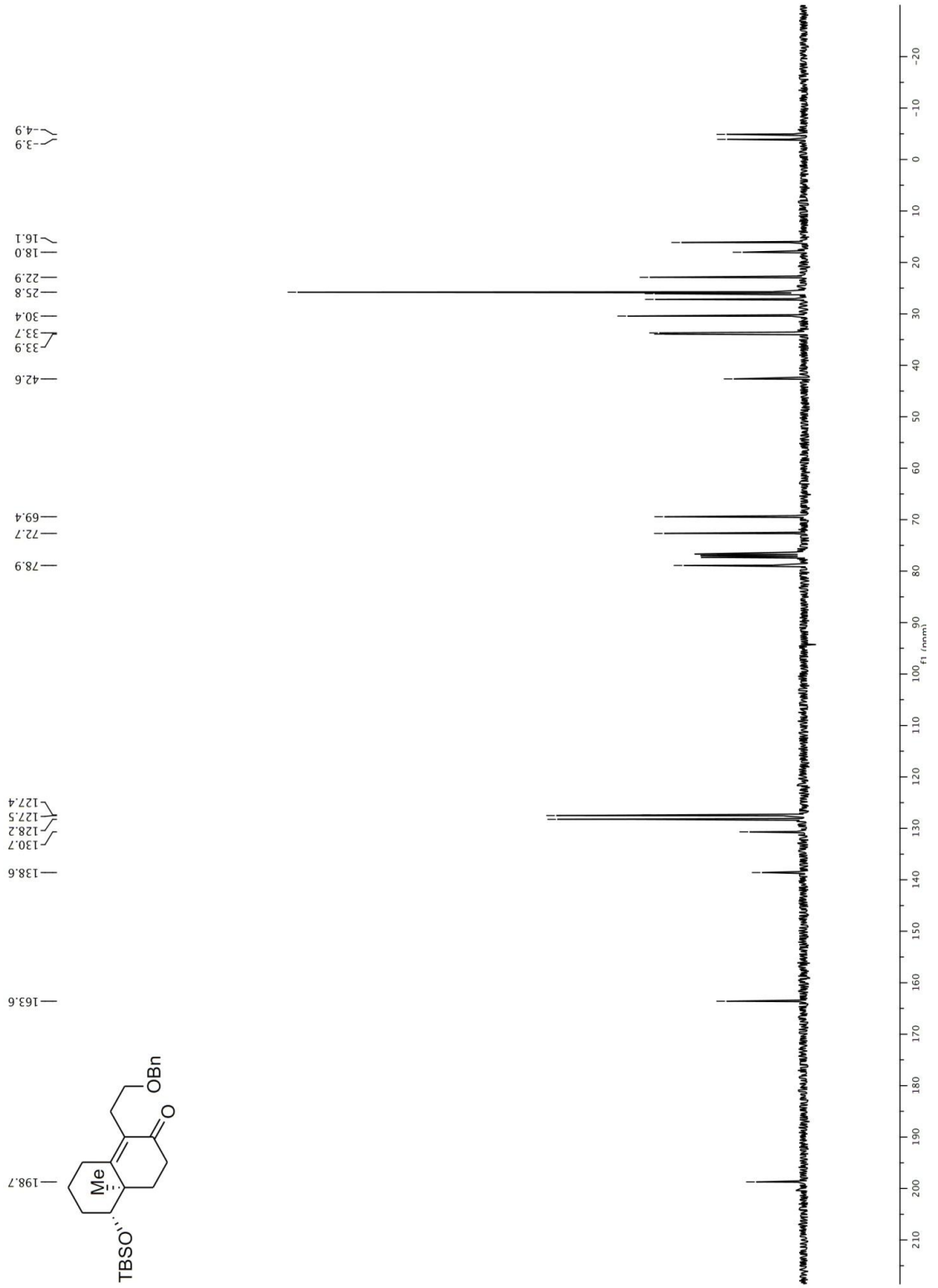
Spectrum 2.5 ^{1}H NMR ($CDCl_3$, 400 MHz) of C13 alcohol.



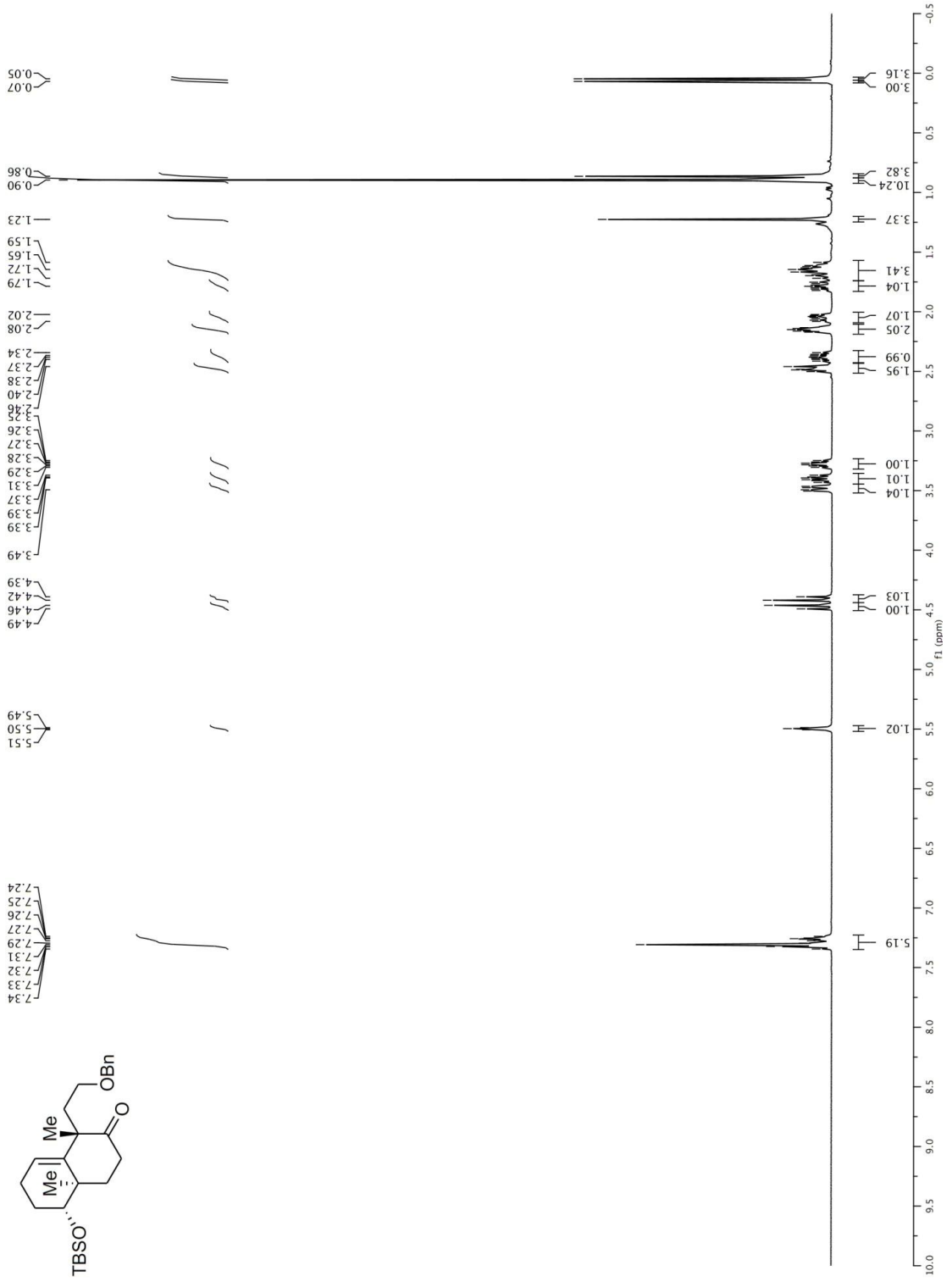
Spectrum 2.6 ^{13}C NMR ($CDCl_3$, 100 MHz) of C13 alochol.



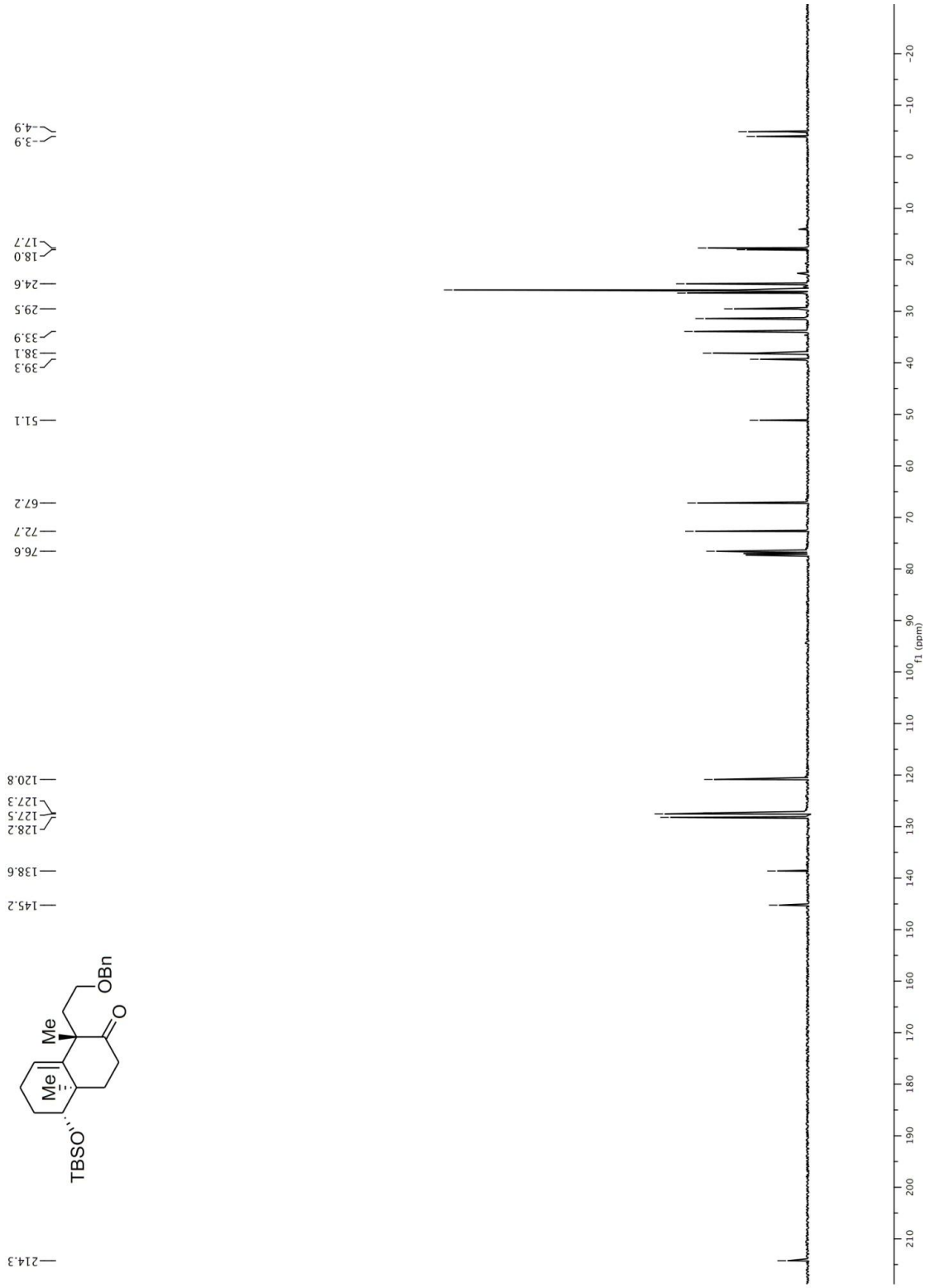
Spectrum 2.7 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **129**.



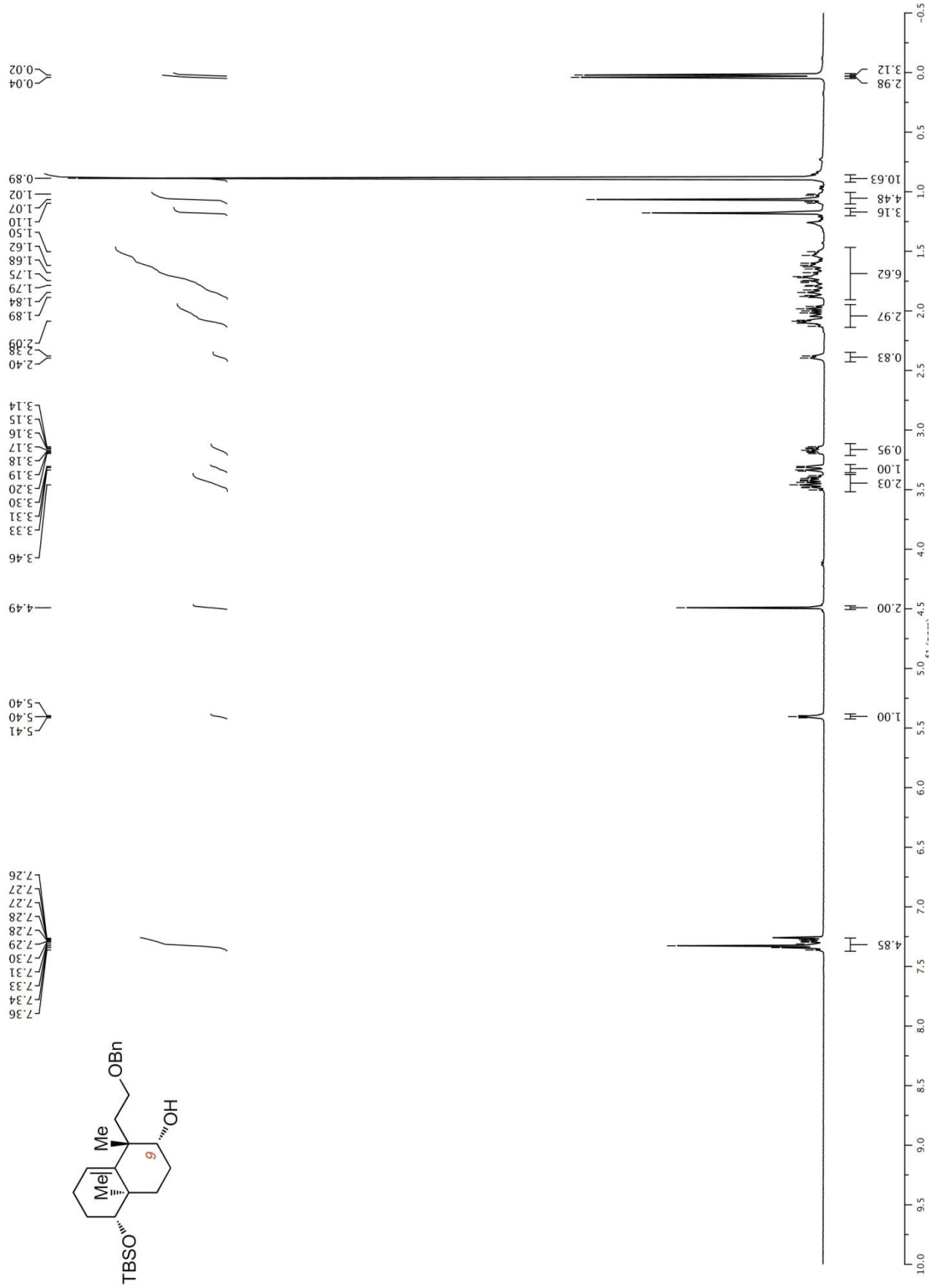
Spectrum 2.8 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **129**.



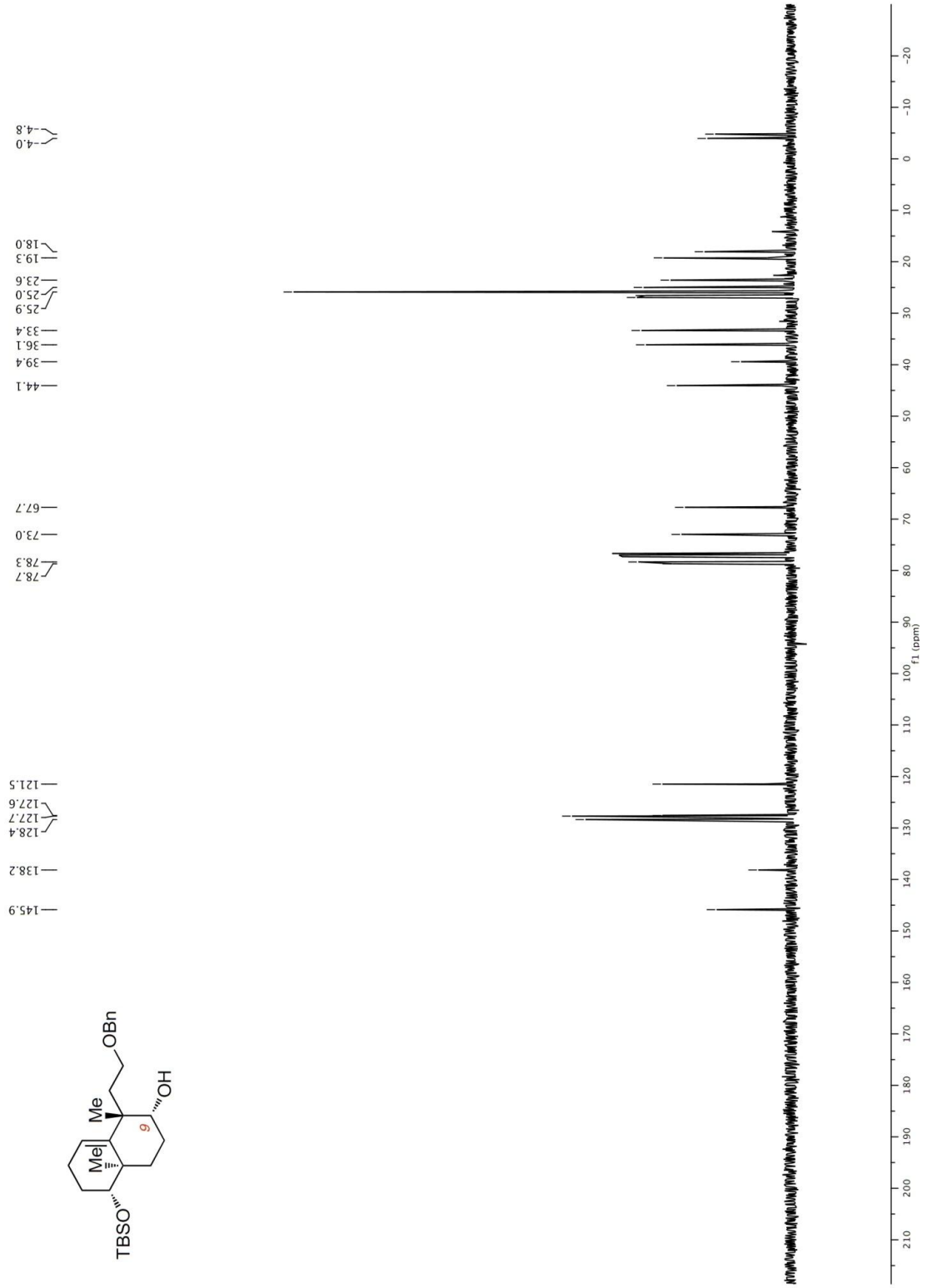
Spectrum 2.9 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **130**.



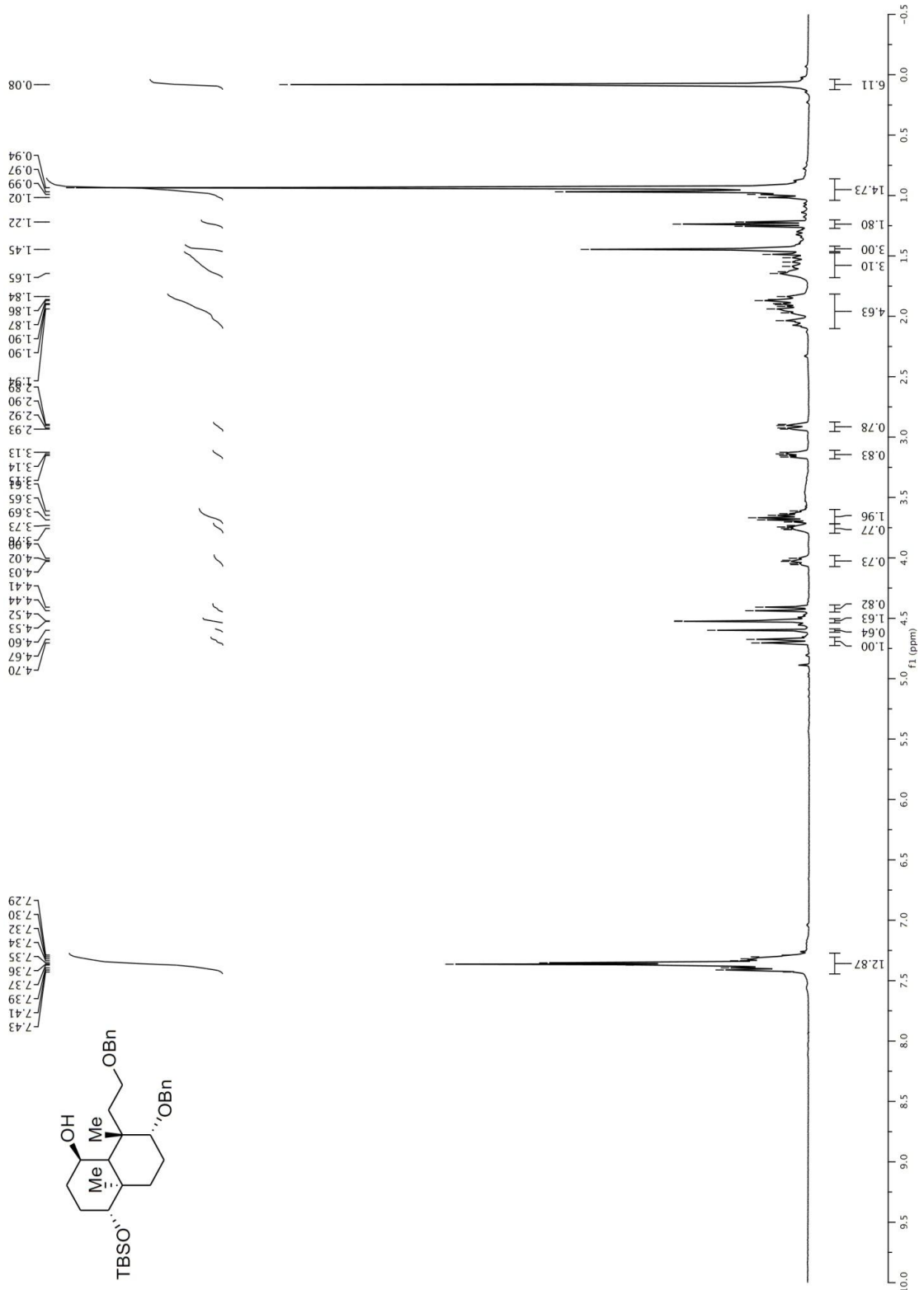
Spectrum 2.10 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **130**.



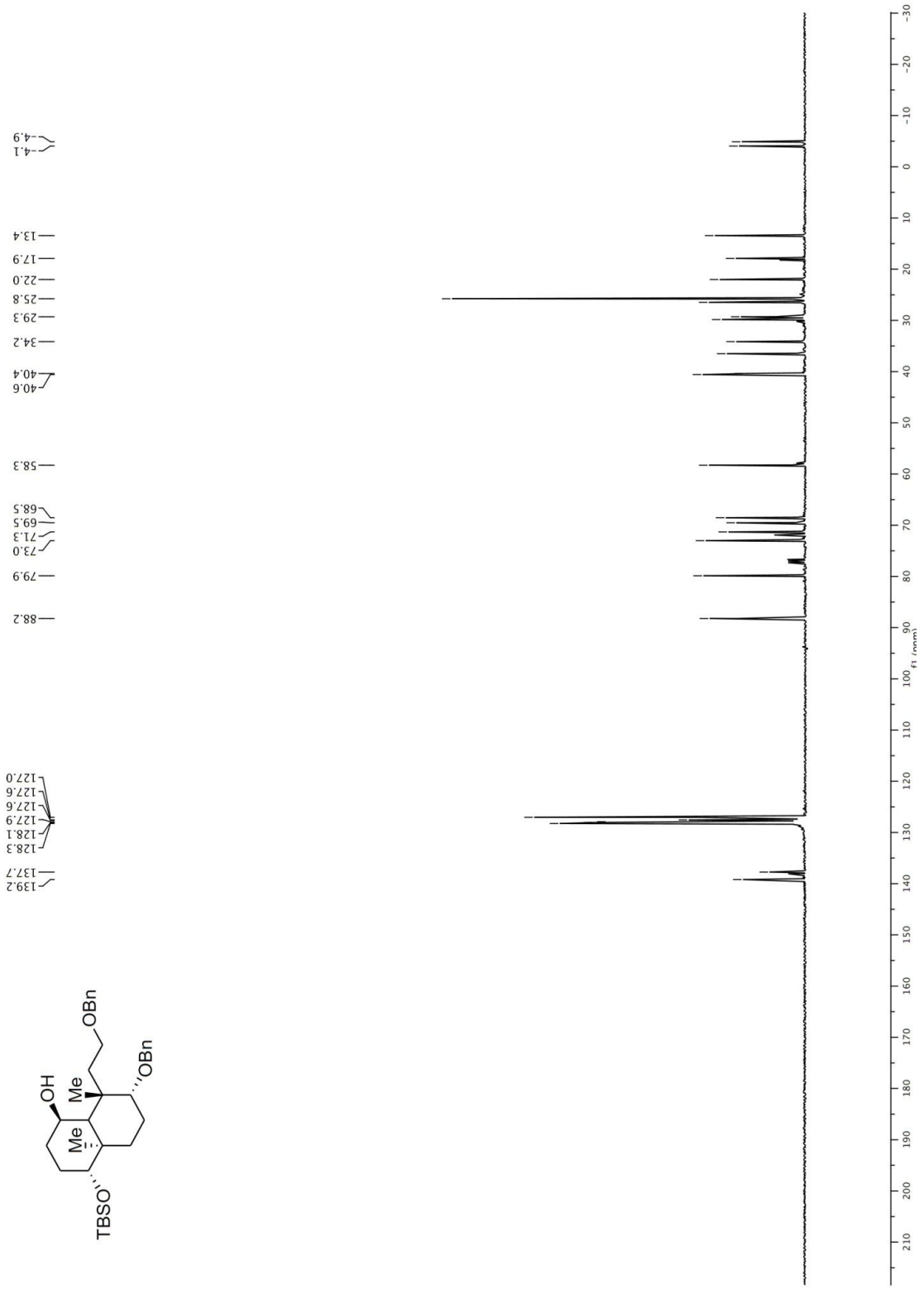
Spectrum 2.11 ^{1}H NMR ($CDCl_3$, 400 MHz) of C9 alochol.



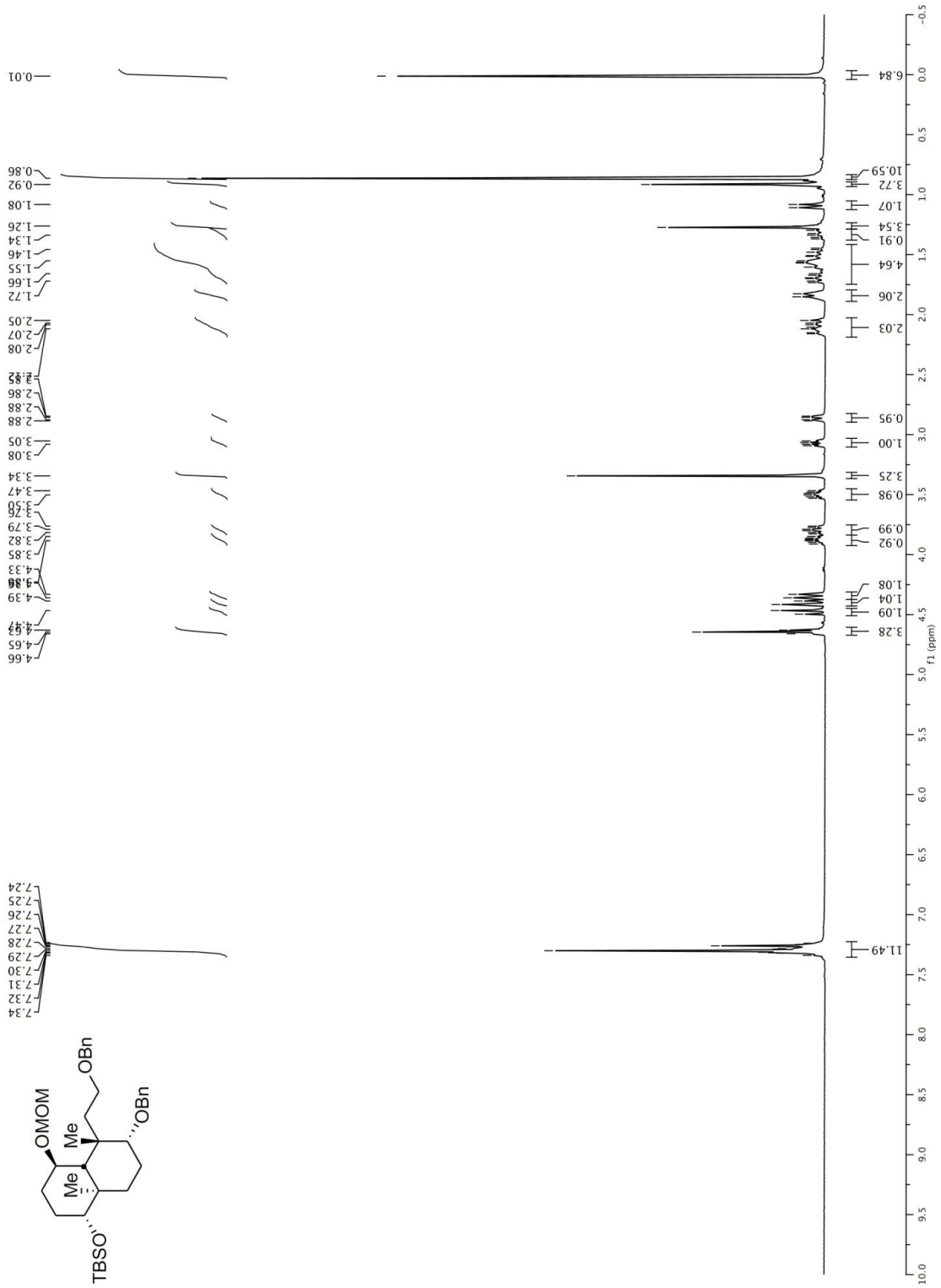
Spectrum 2.12 ^{13}C NMR ($CDCl_3$, 100 MHz) of C9 alcohol.



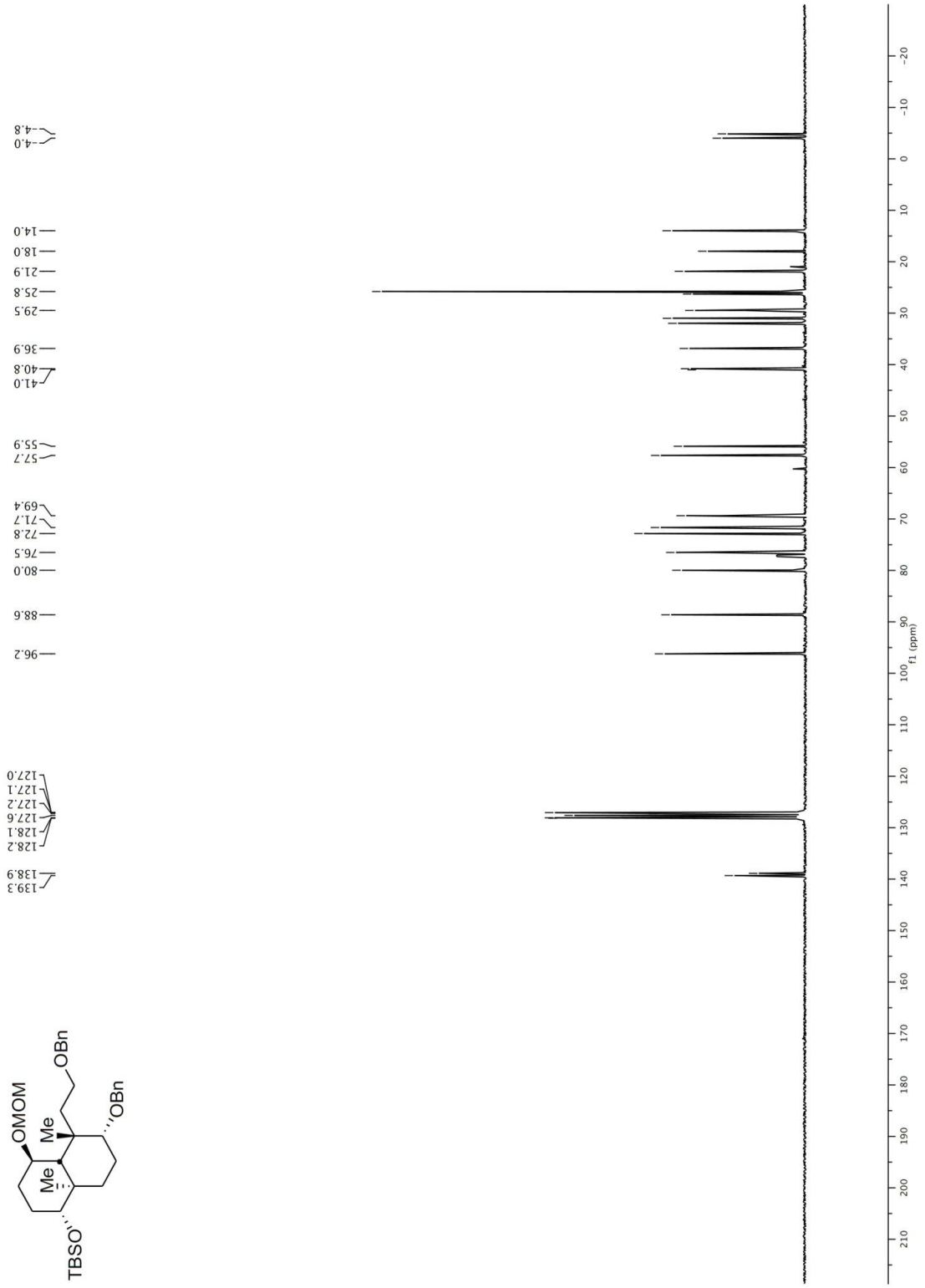
Spectrum 2.13 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **131**.



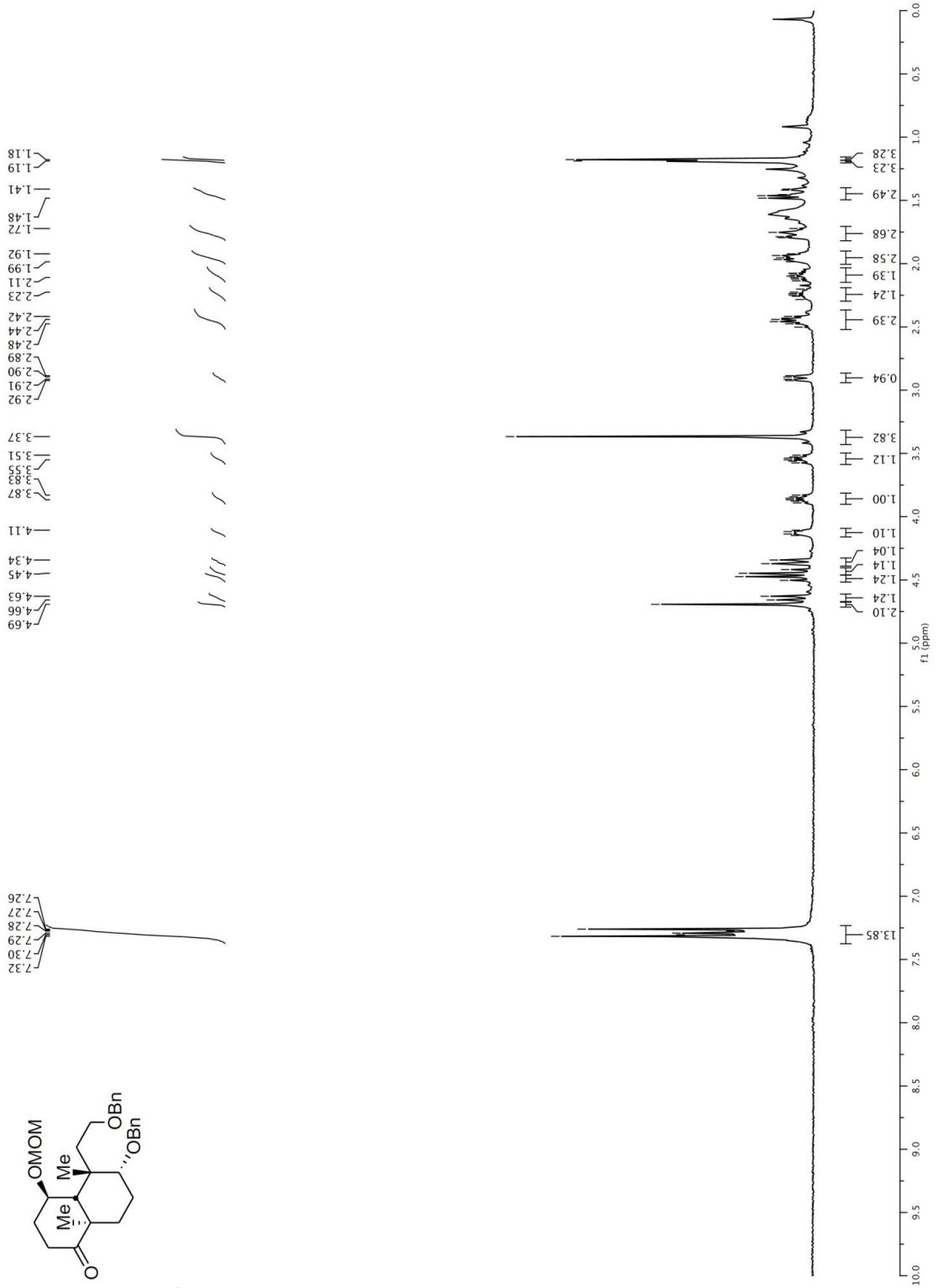
Spectrum 2.14 ^{13}C NMR ($CDCl_3$ 100 MHz) of compound **131**.



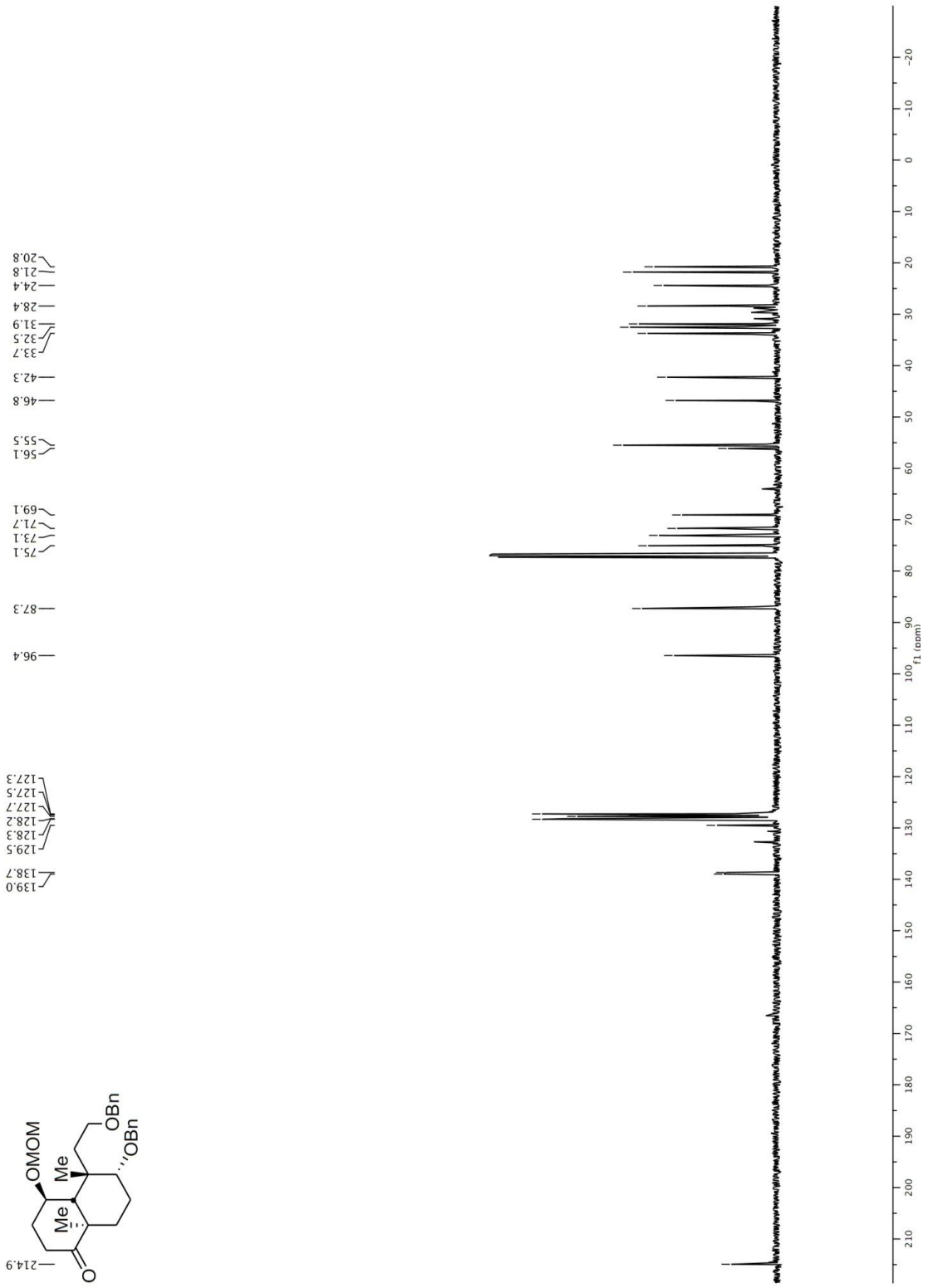
Spectrum 2.15 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **132**.



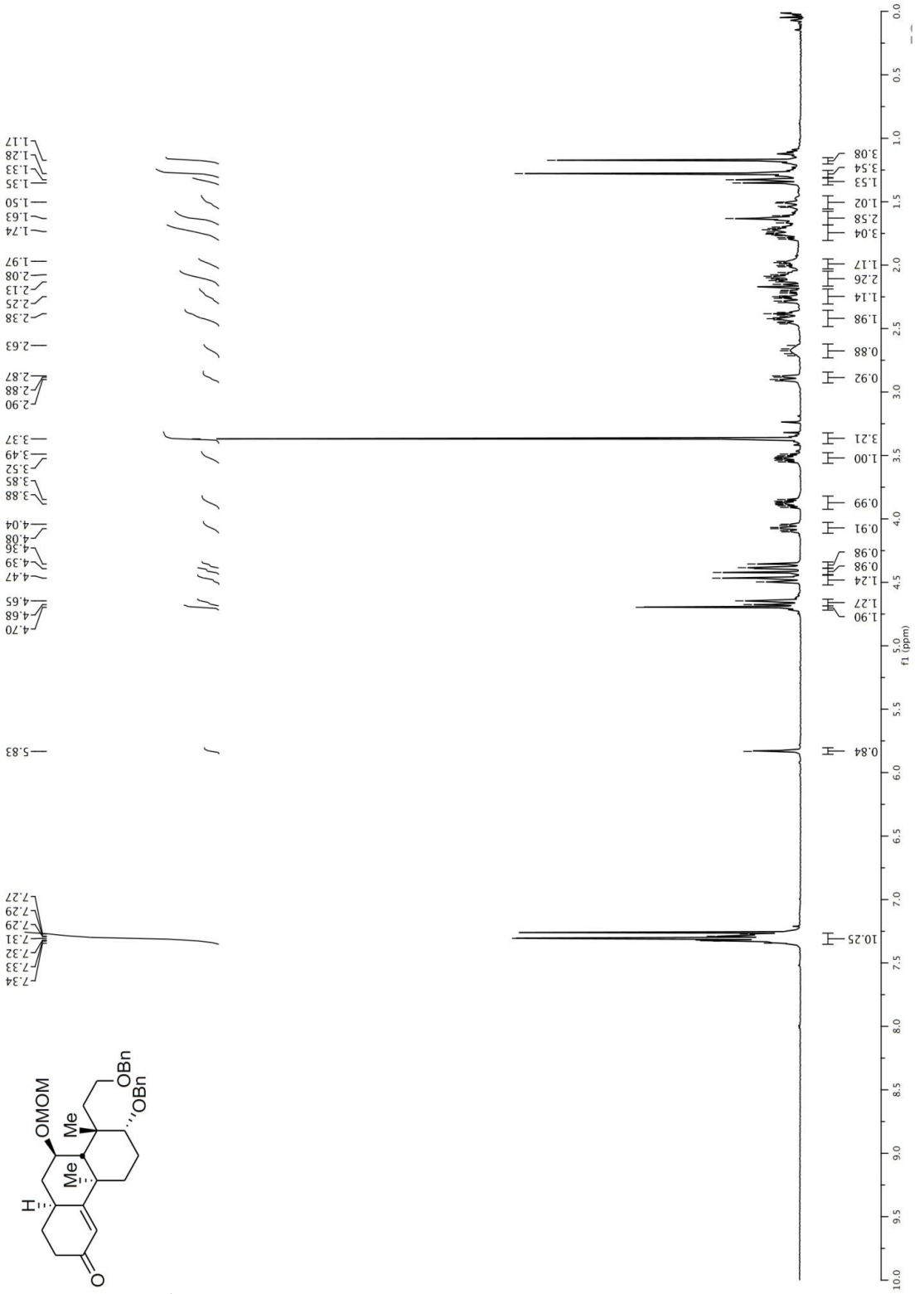
Spectrum 2.16 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **132**.



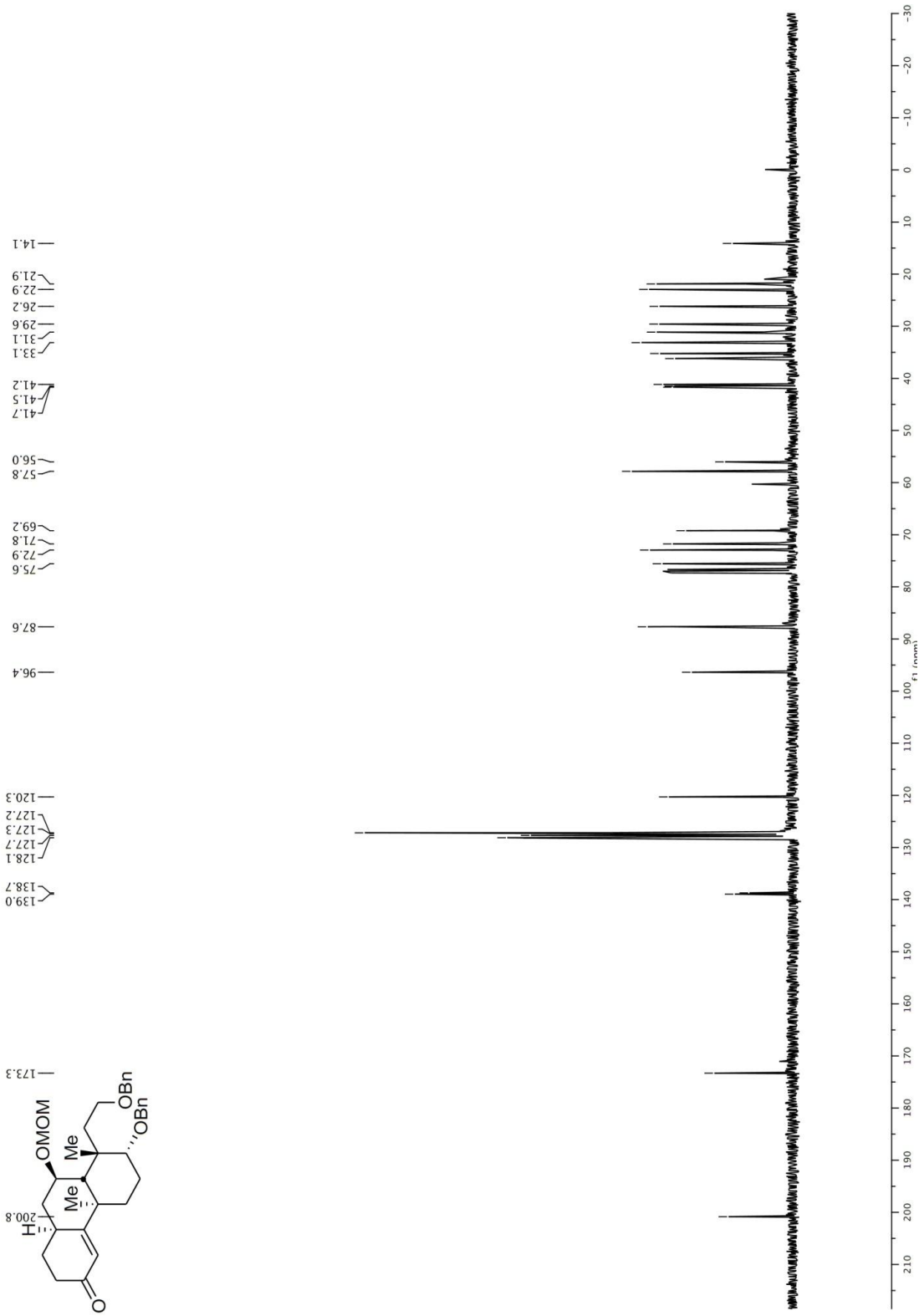
Spectrum 2.17 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **133**.



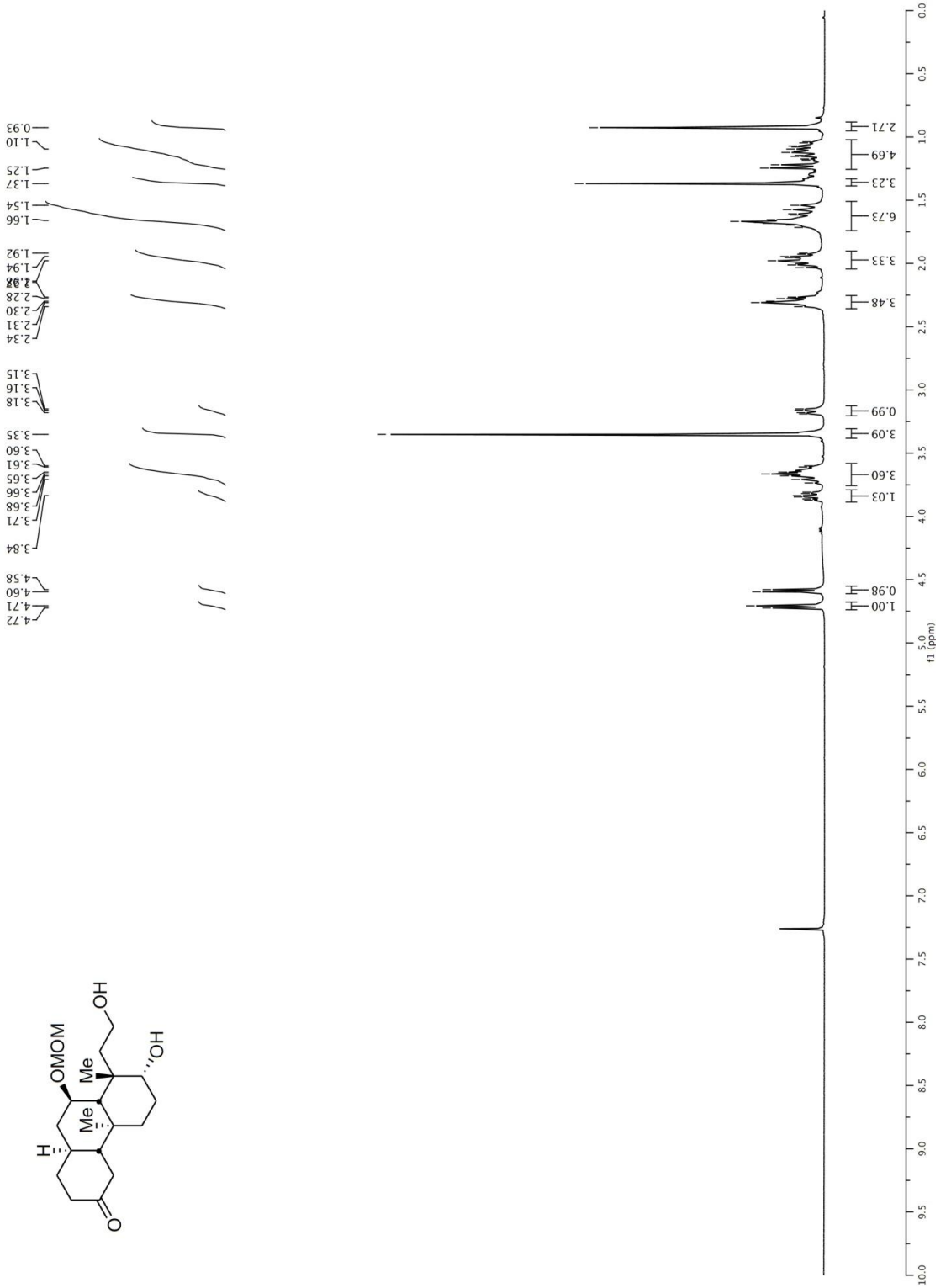
Spectrum 2.18 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **133**.



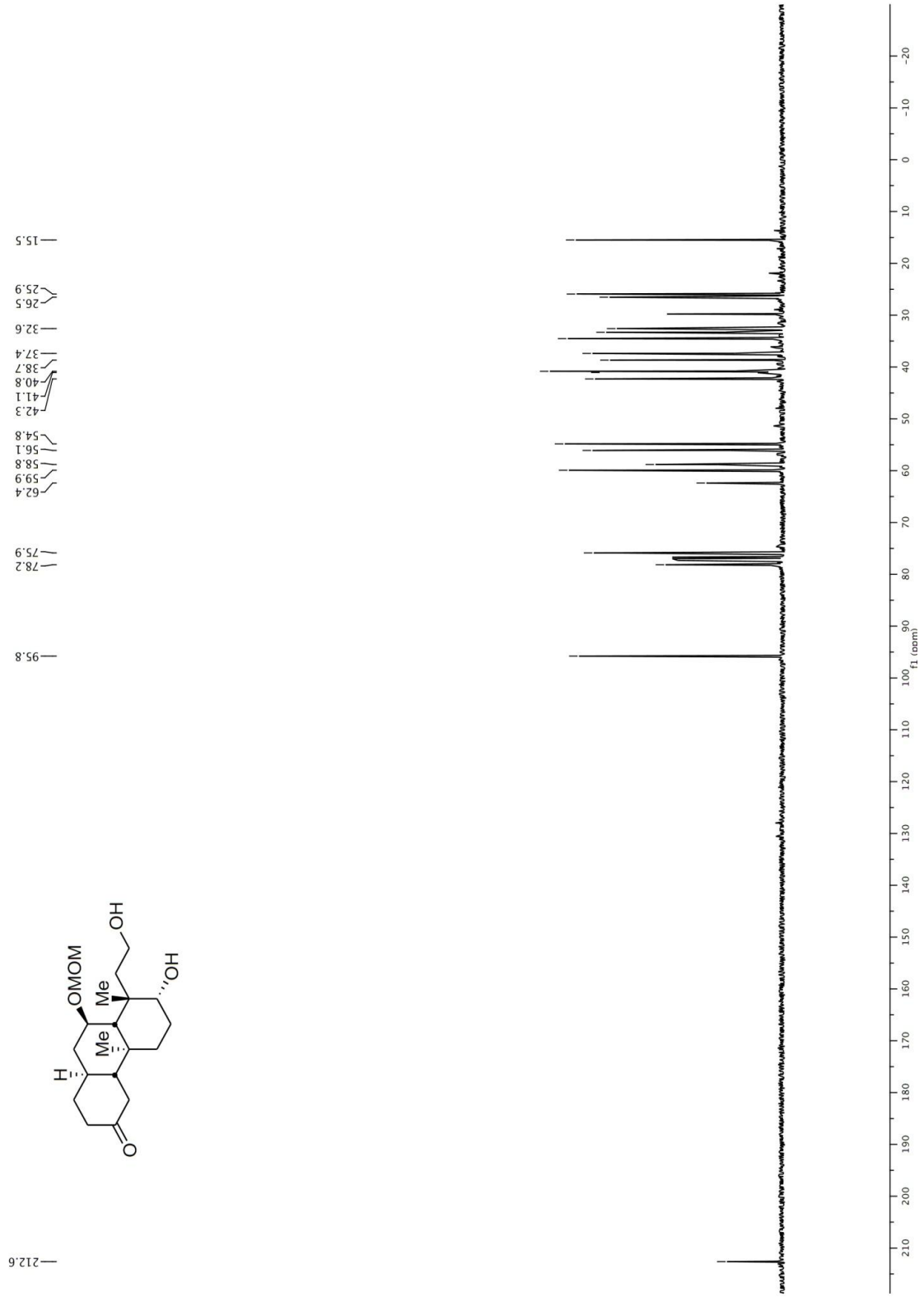
Spectrum 2.19 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **134**.



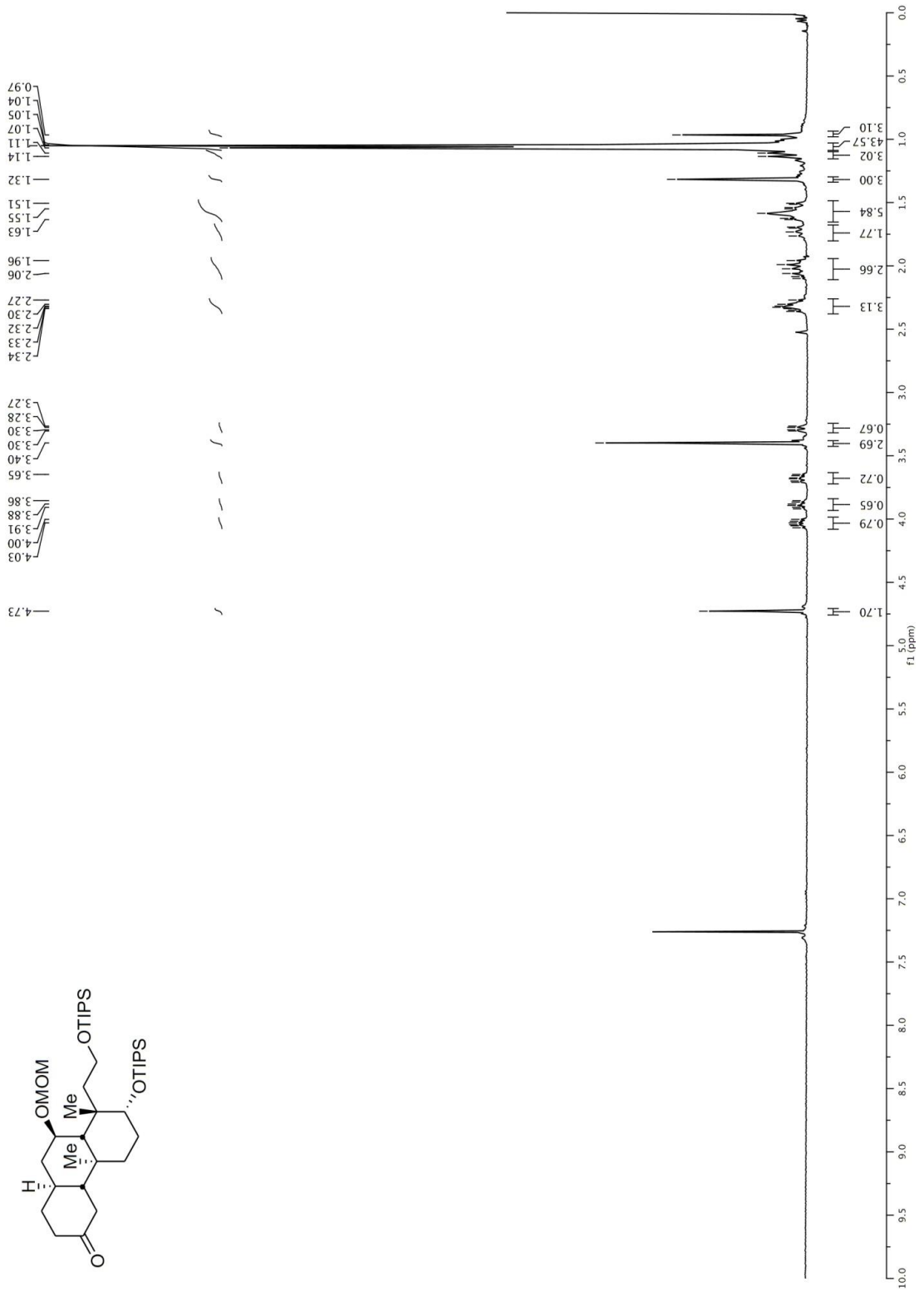
Spectrum 2.20 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **134**.



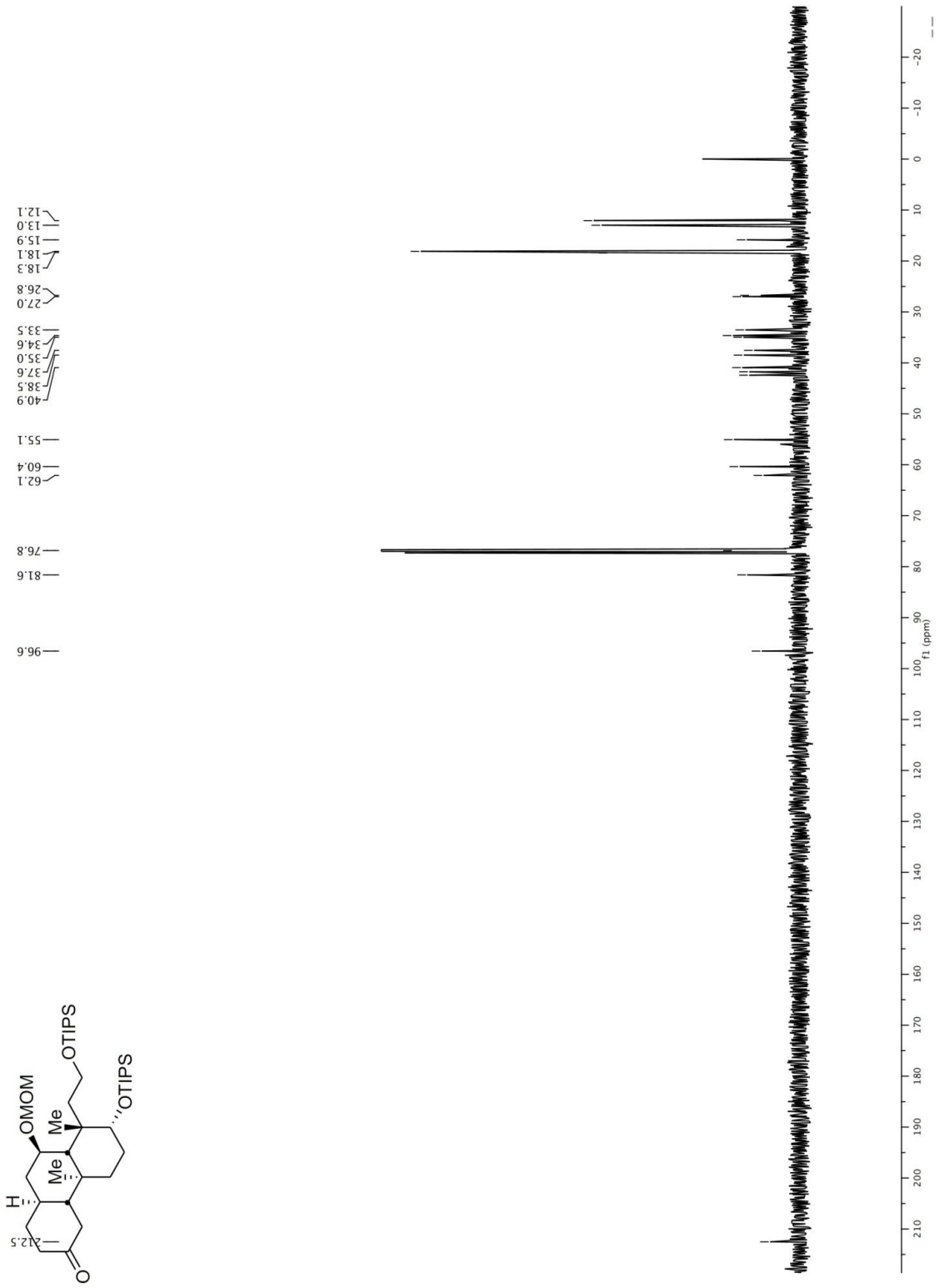
Spectrum 2.21 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **135**.



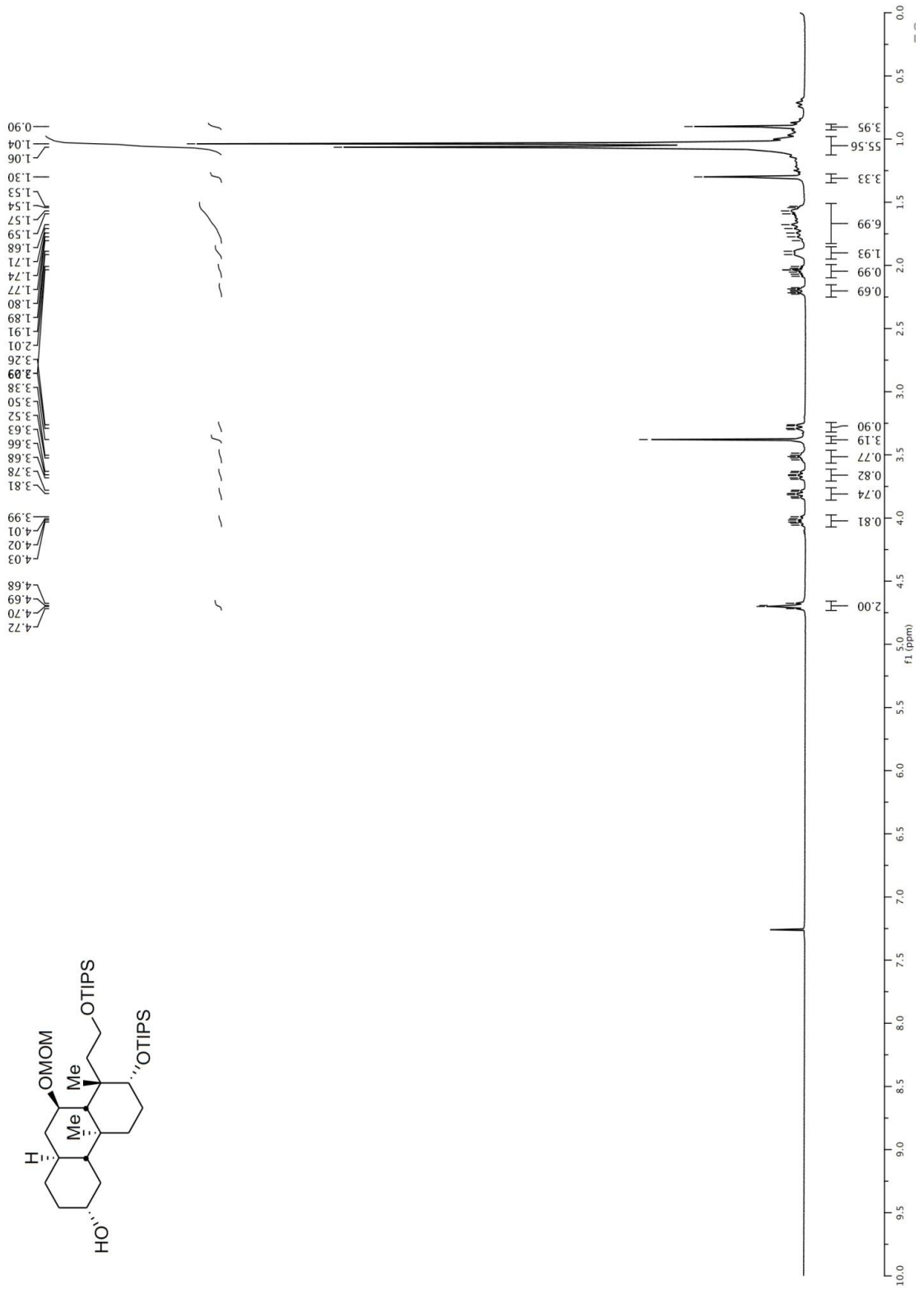
Spectrum 2.22 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **135**.



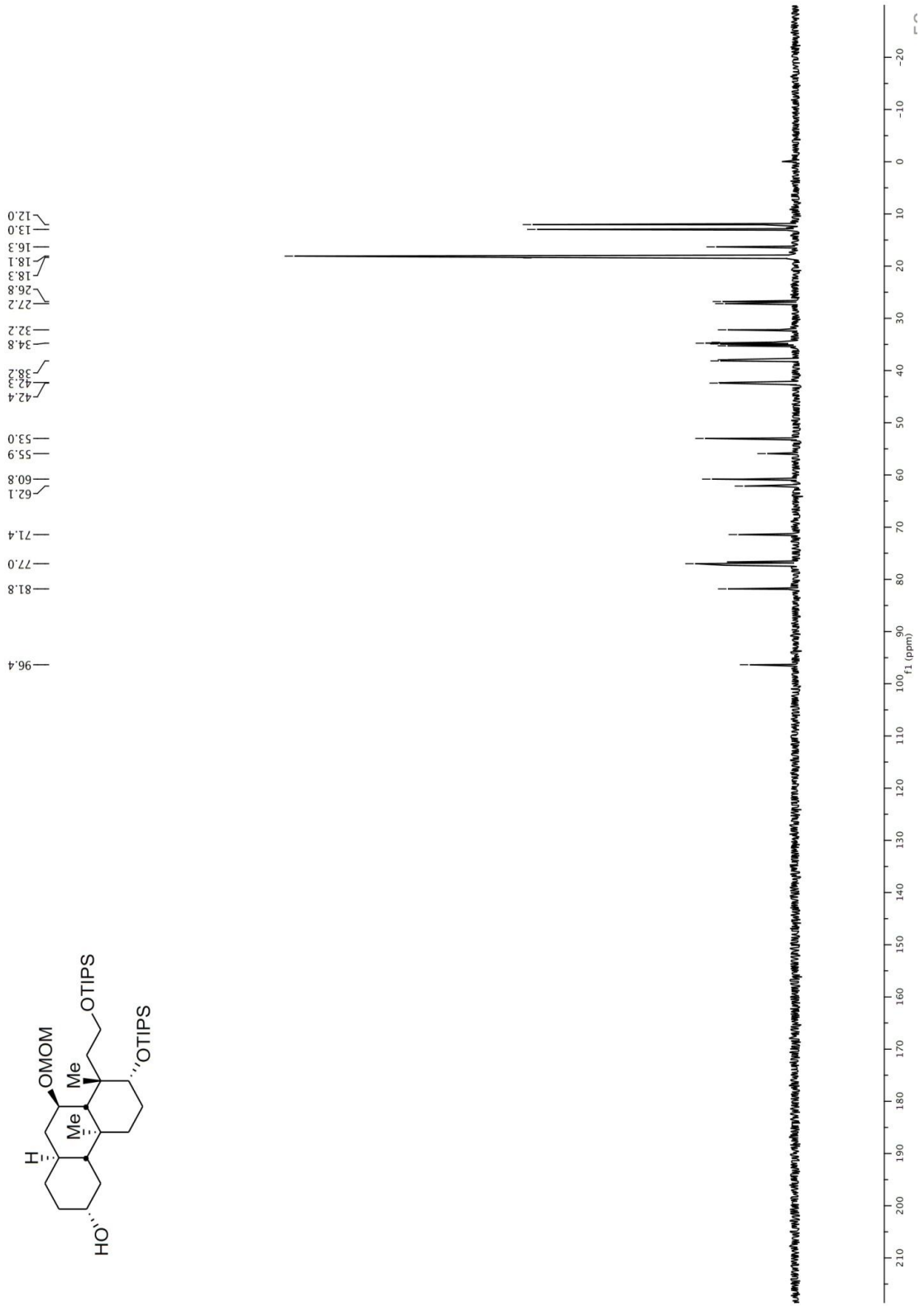
Spectrum 2.23 ^{1}H NMR ($CDCl_3$, 400 MHz) of di-TIPS ether.



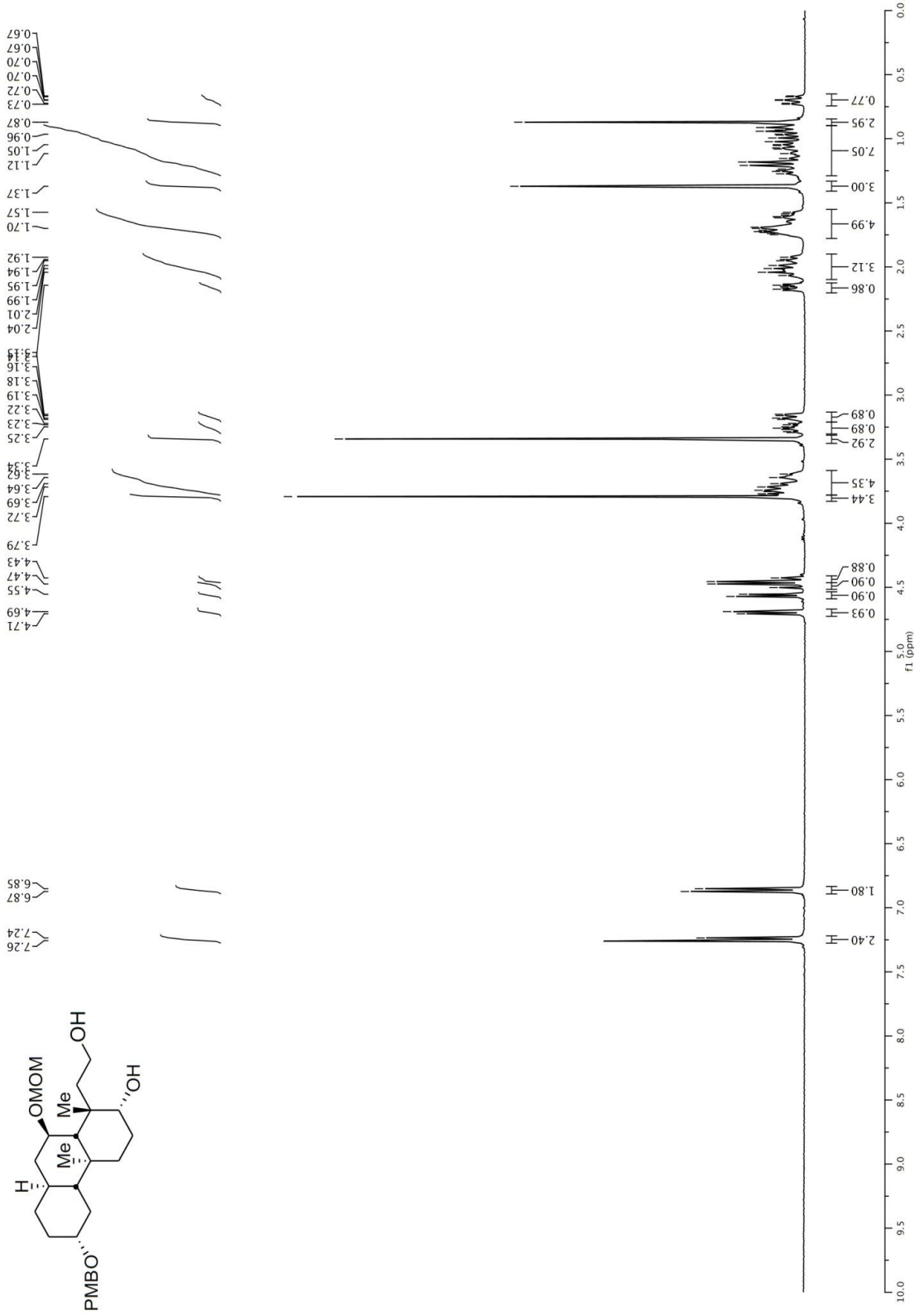
Spectrum 2.24 ^{13}C NMR ($CDCl_3$, 100 MHz) of di-TIPS ether.



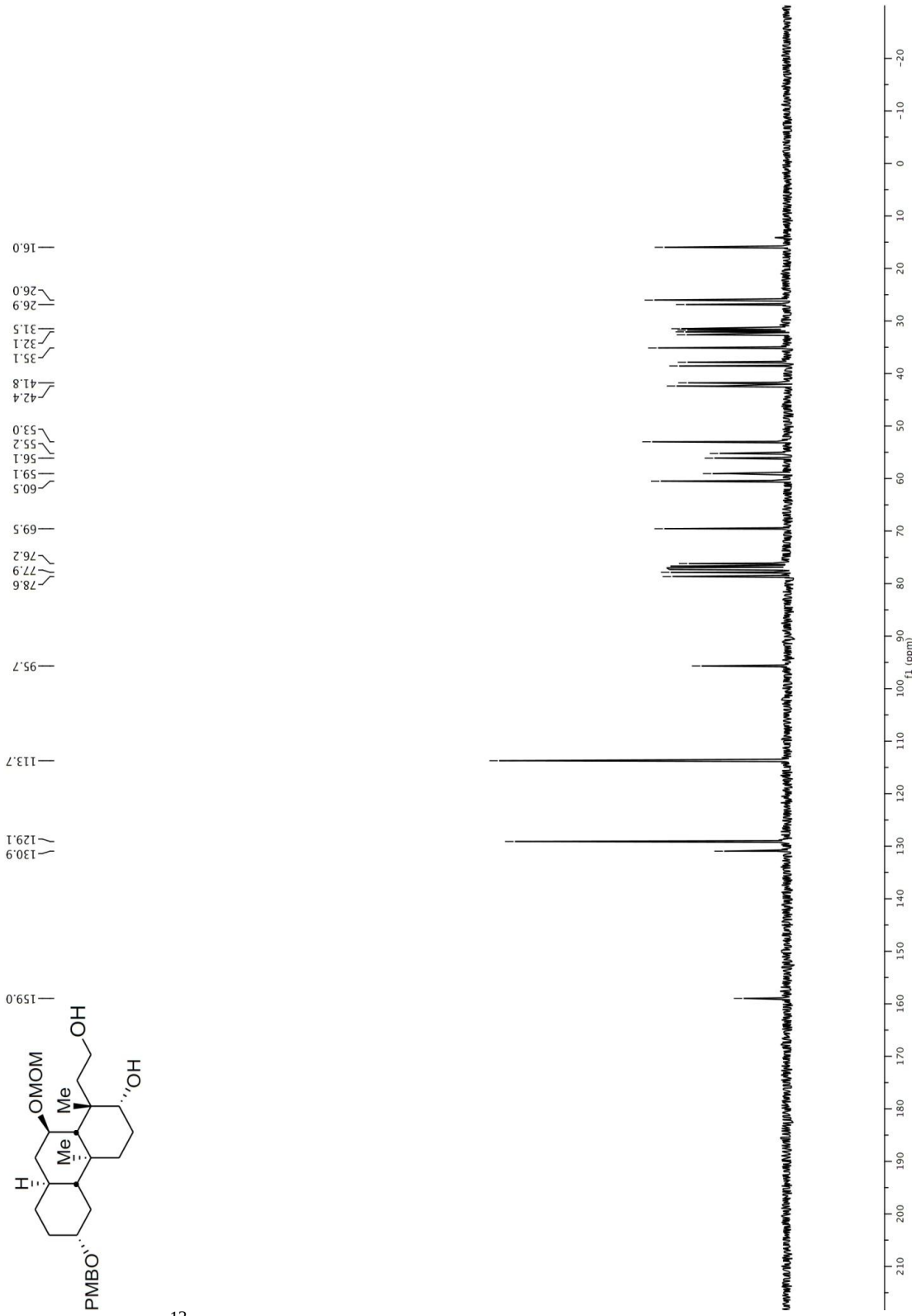
Spectrum 2.25 ^{1}H NMR ($CDCl_3$, 400 MHz) of C15 alcohol.



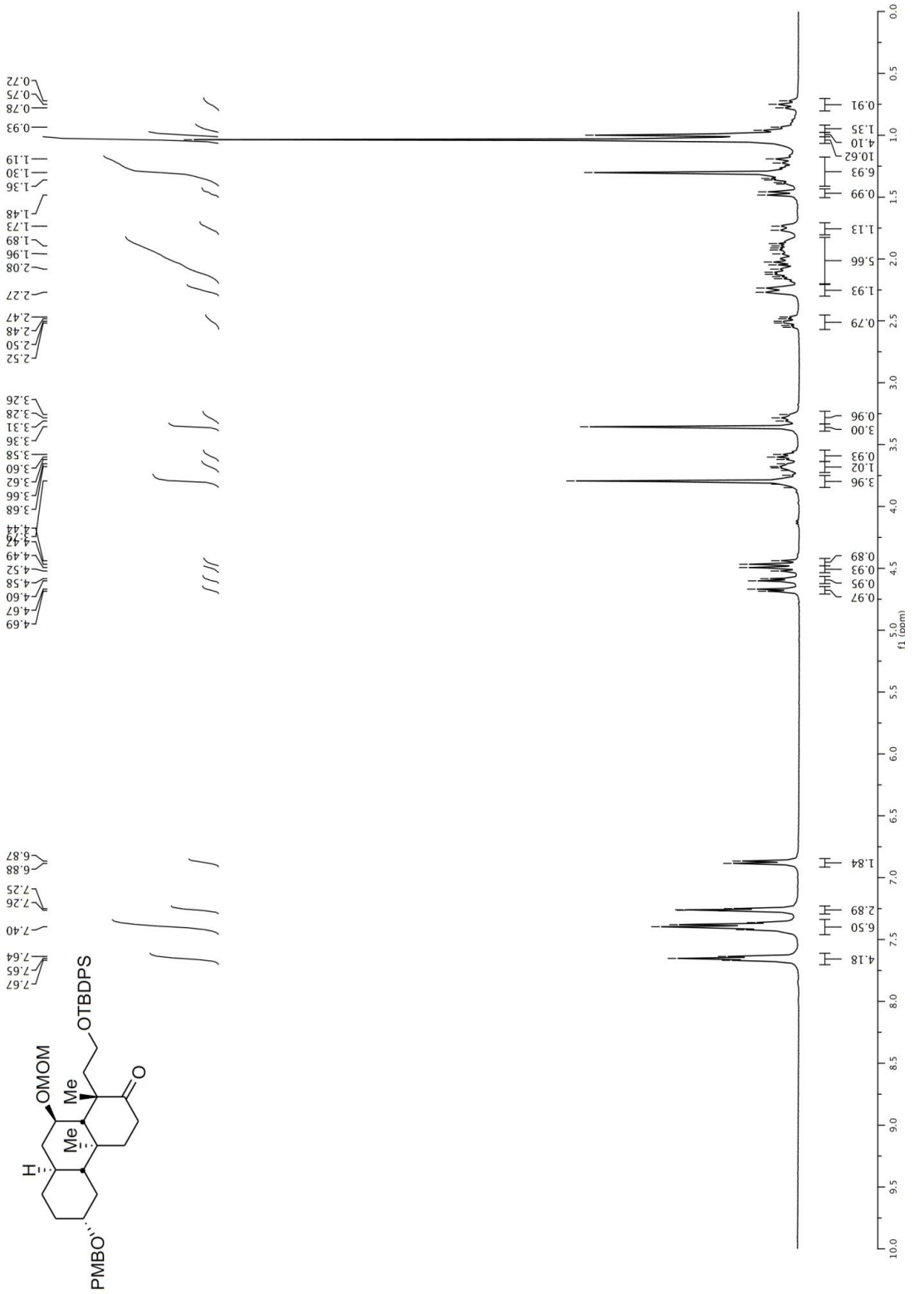
Spectrum 2.26 ^{13}C NMR ($CDCl_3$, 100 MHz) of C15 alcohol.



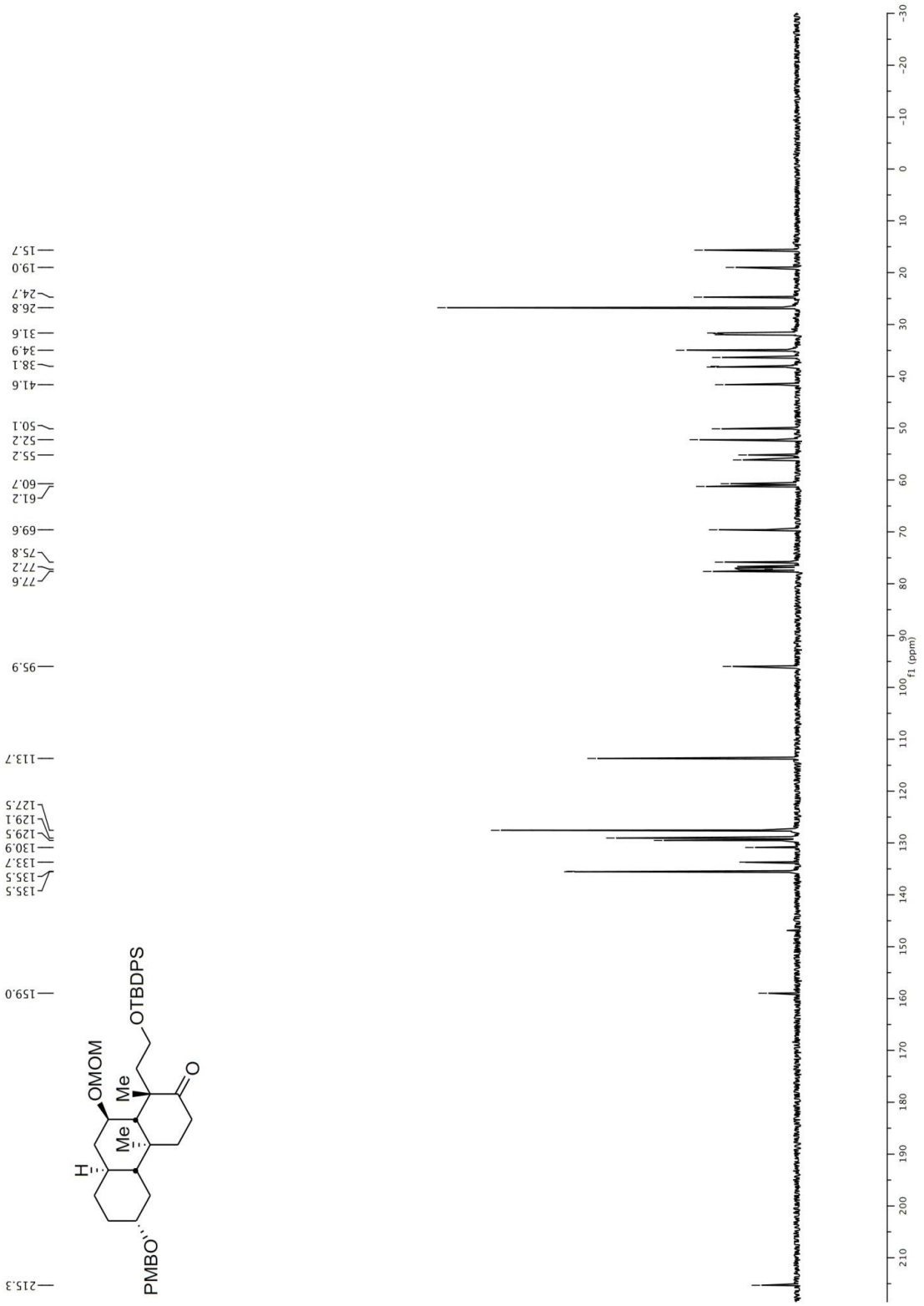
Spectrum 2.27 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **136**.



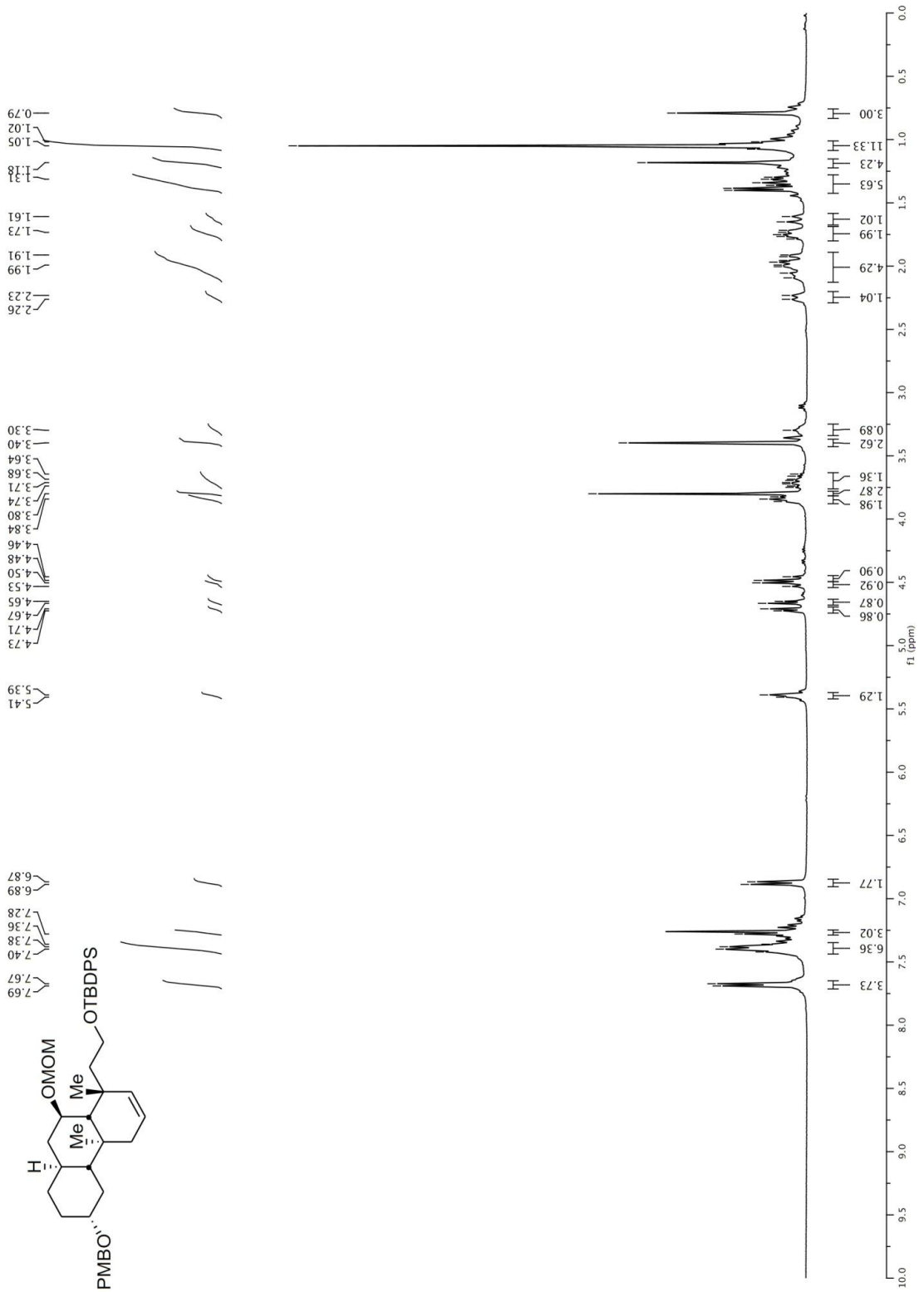
Spectrum 2.28 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **136**.



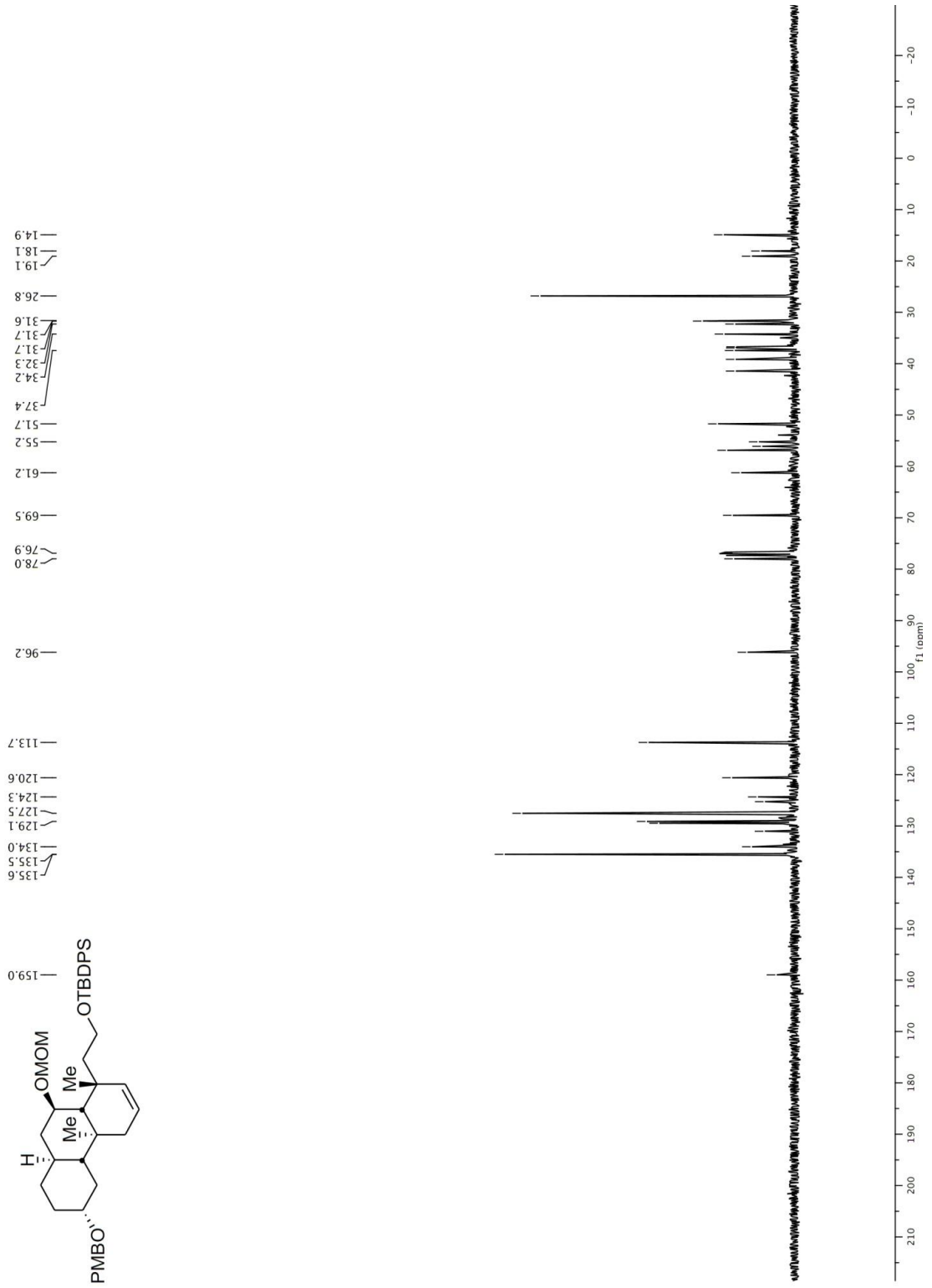
Spectrum 2.29 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **141**.



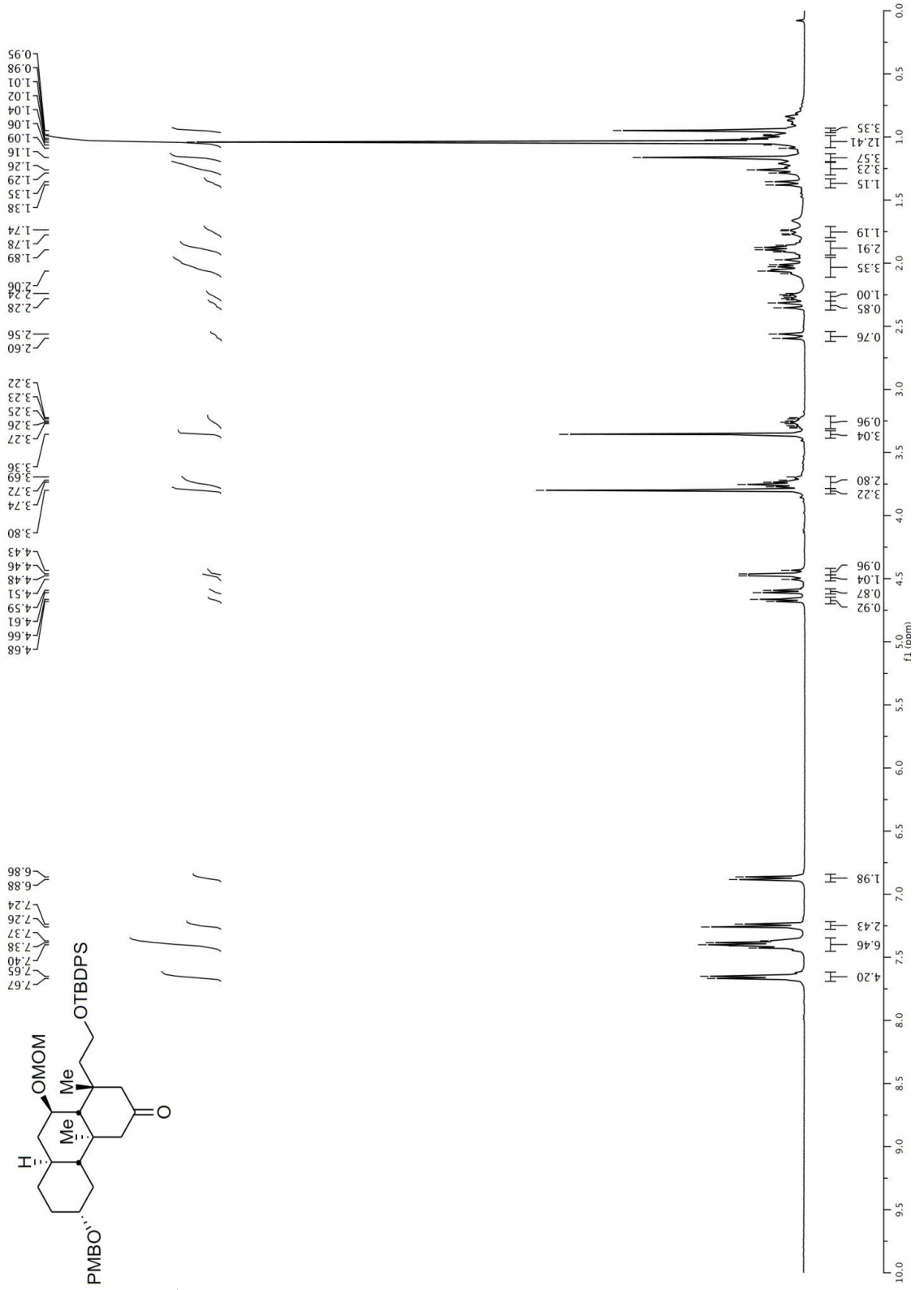
Spectrum 2.30 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **141**.



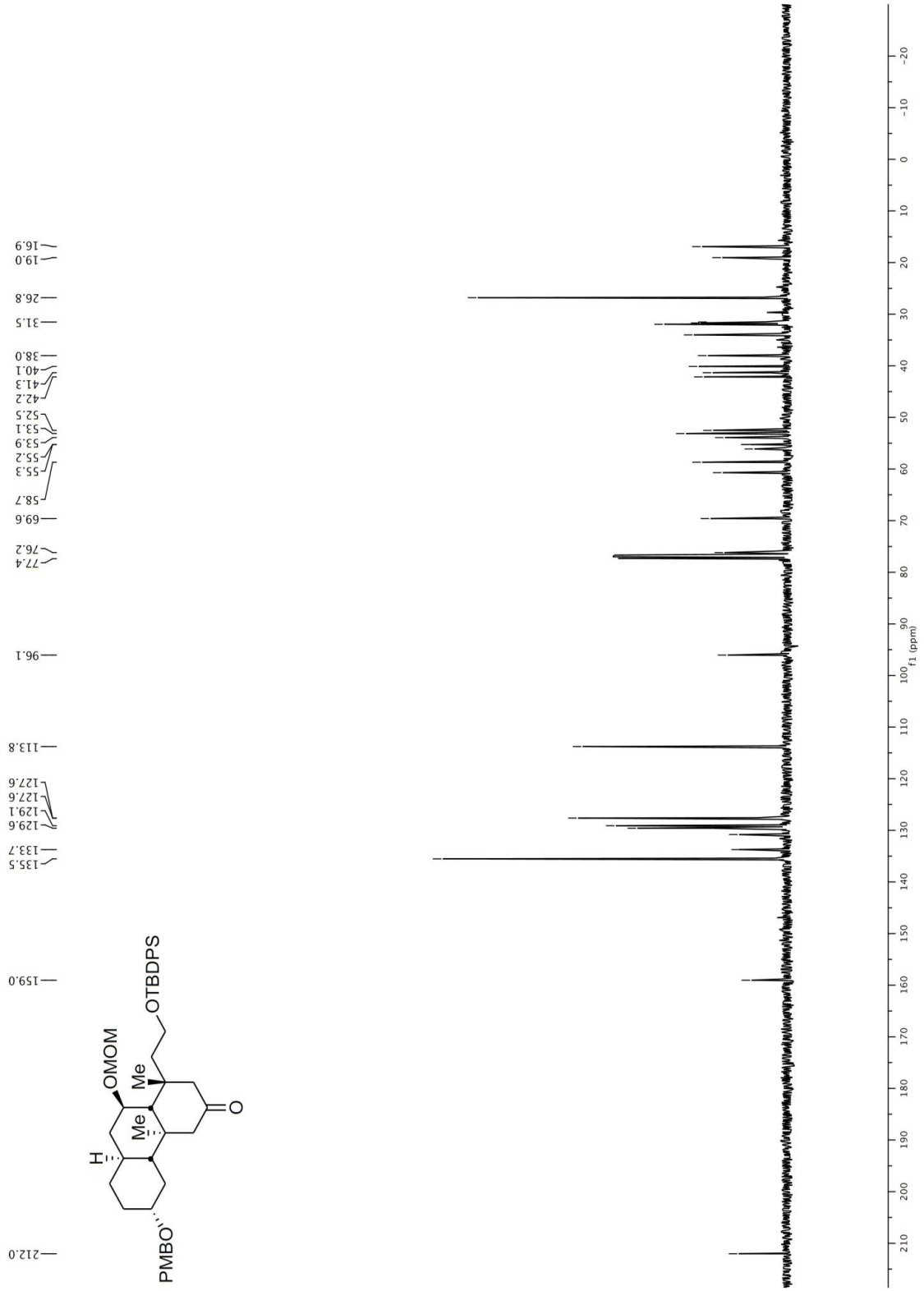
Spectrum 2.31 ^{1}HNMR ($CDCl_3$, 400 MHz) of C9-C10 olefin.



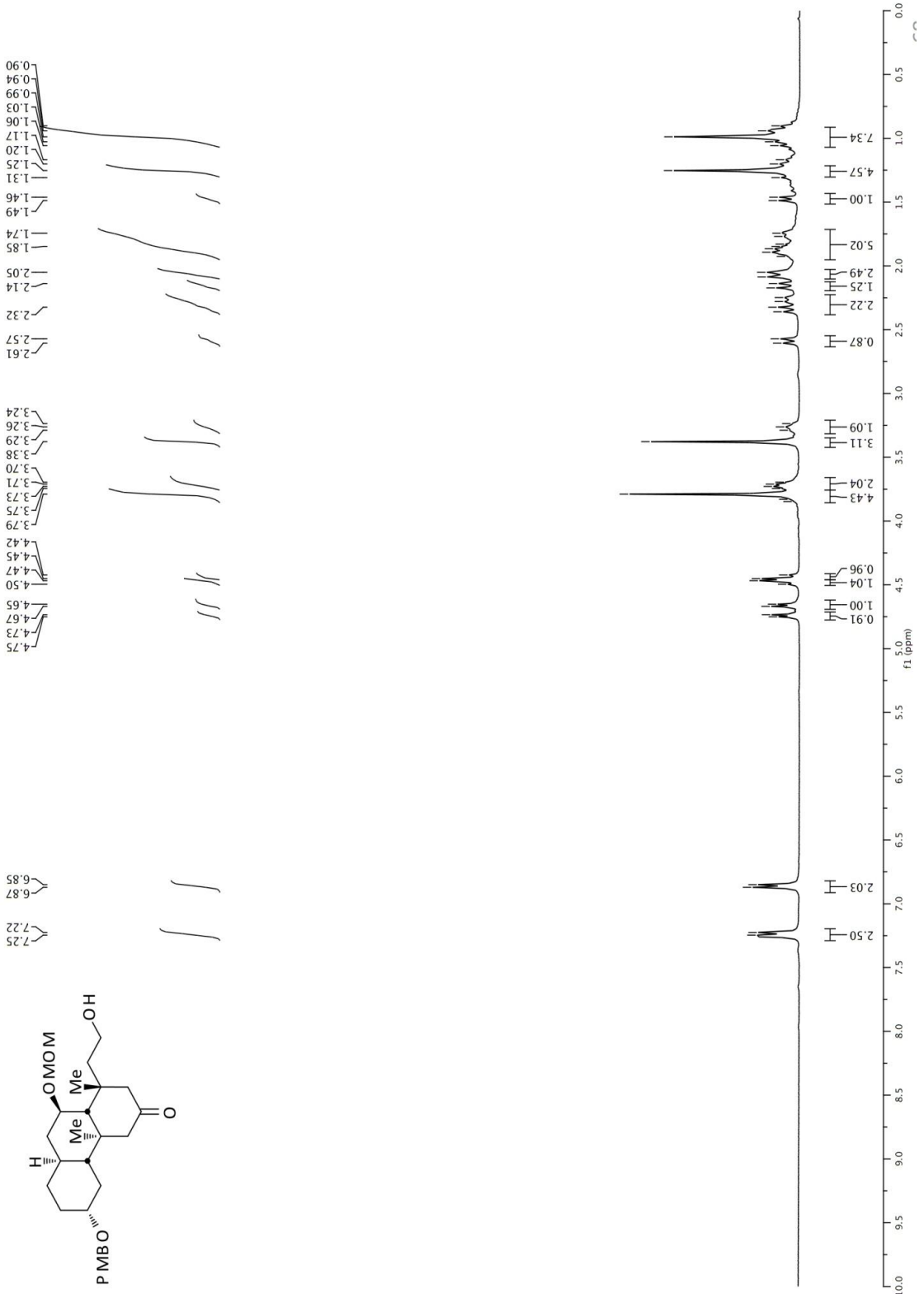
Spectrum 2.32 ^{13}C NMR ($CDCl_3$, 100 MHz) of C9-C10 olefin.



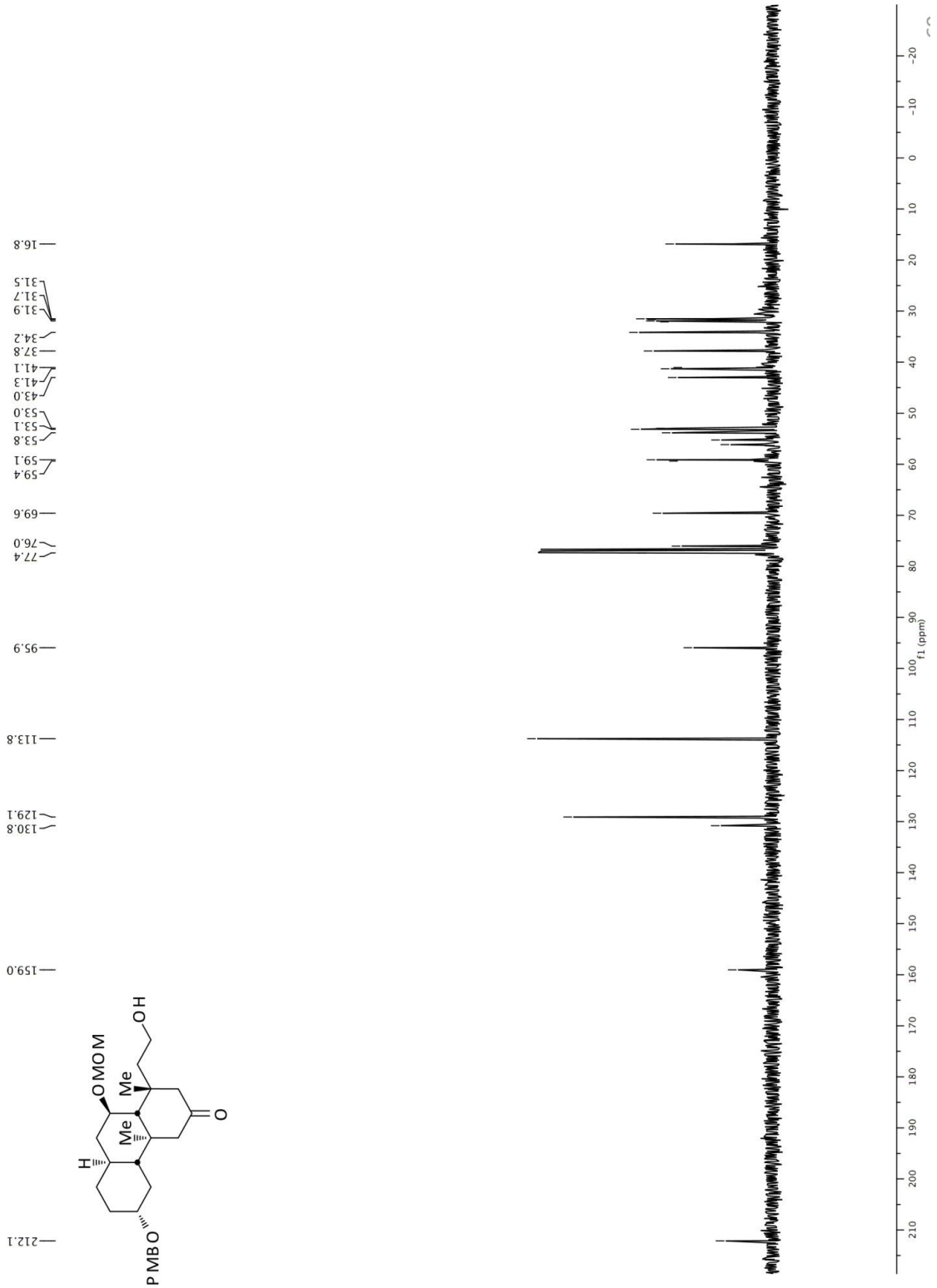
Spectrum 2.33 ^{1}HNMR ($CDCl_3$, 400 MHz) of compound **142**.



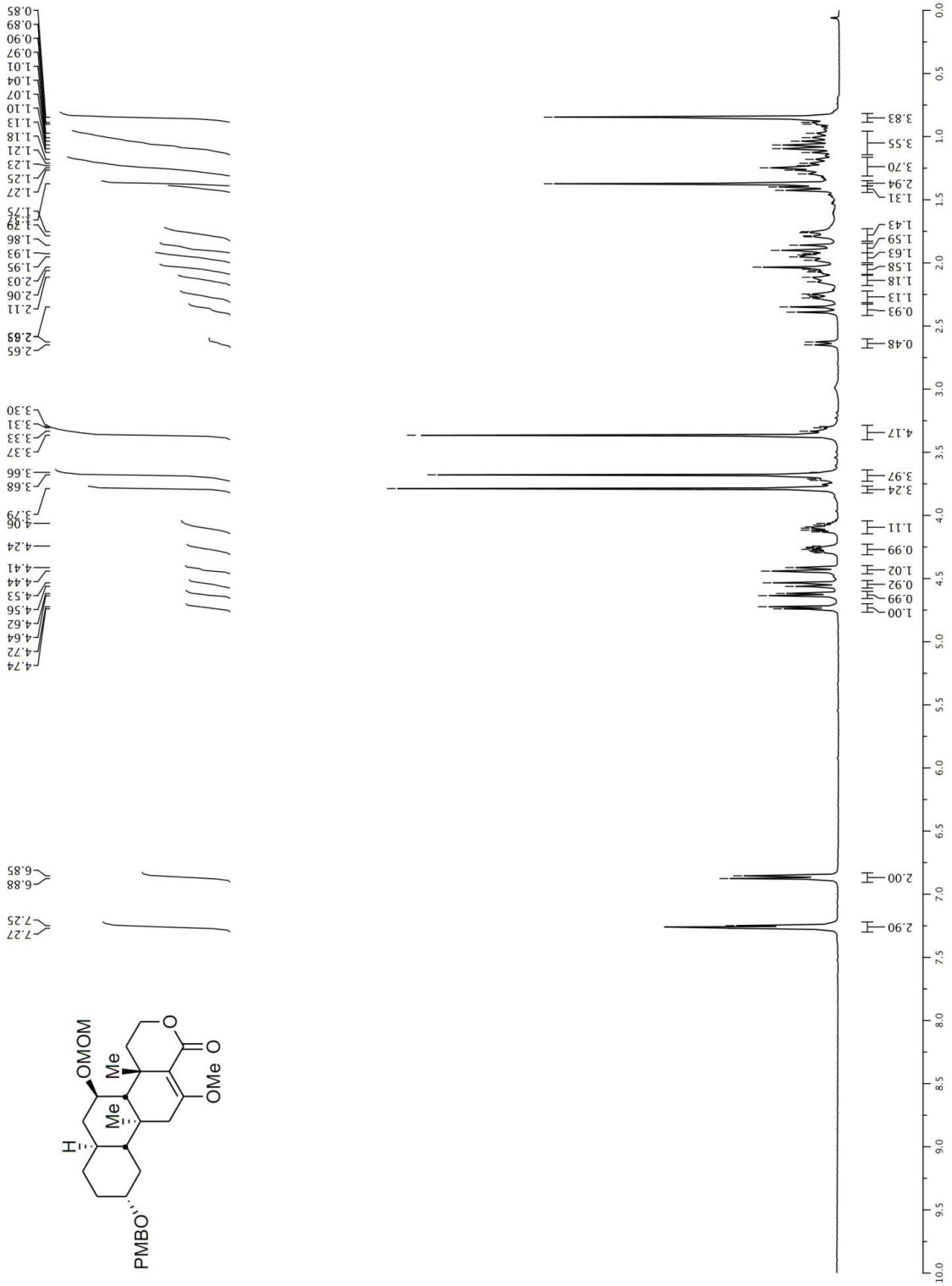
Spectrum 2.34 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **142**.



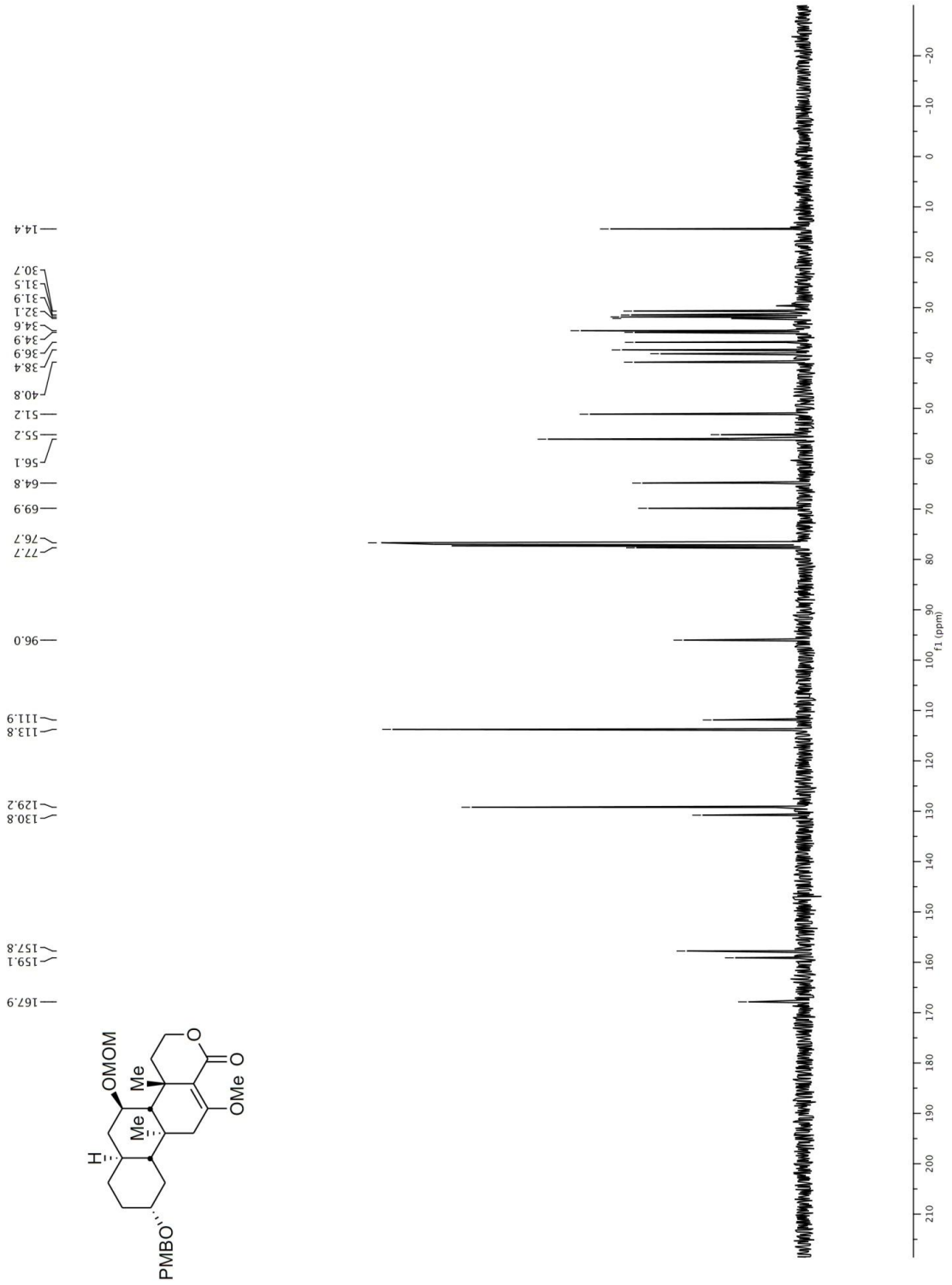
Spectrum 2.35 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **143**.



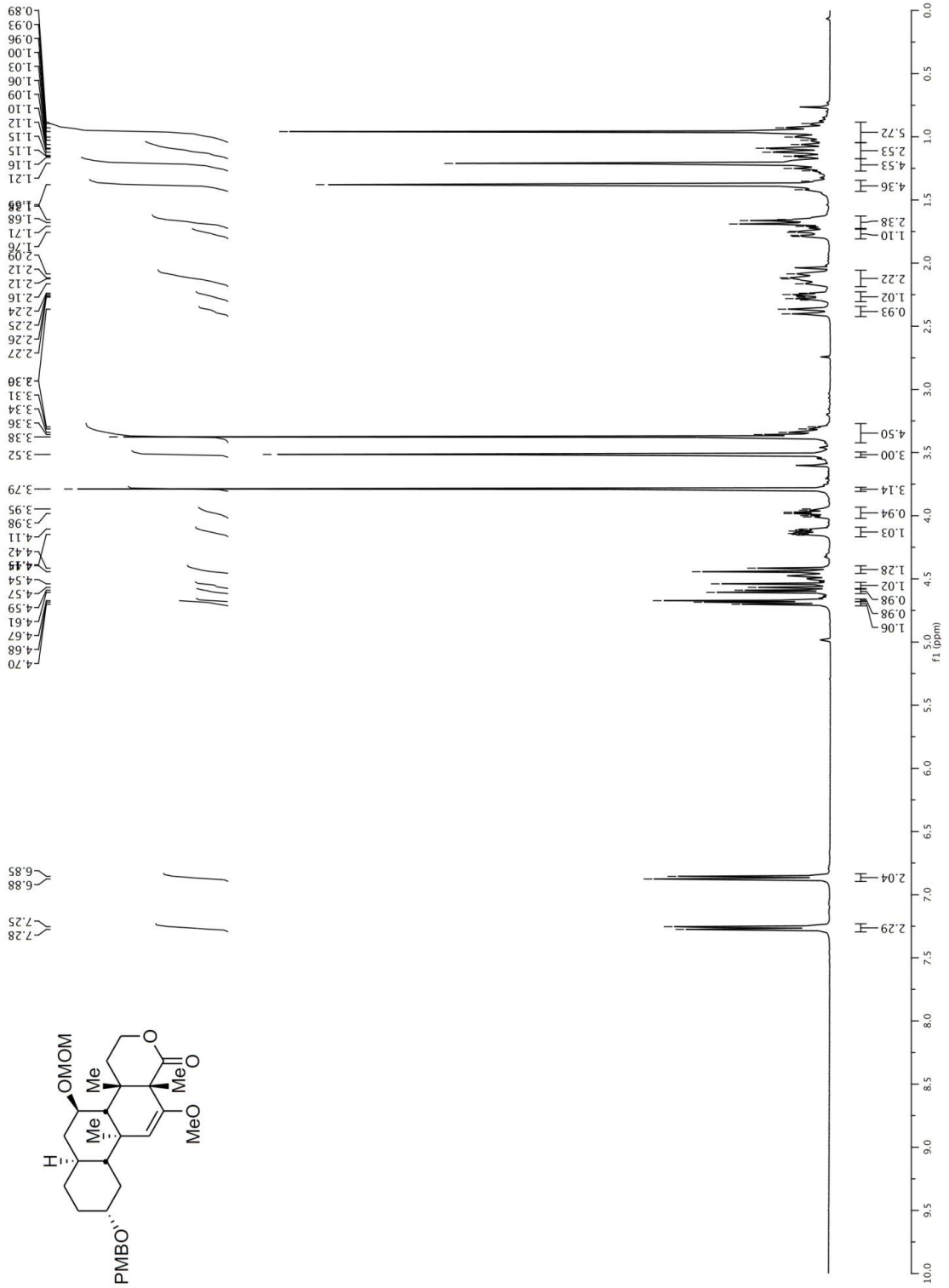
Spectrum 2.36 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **143**.



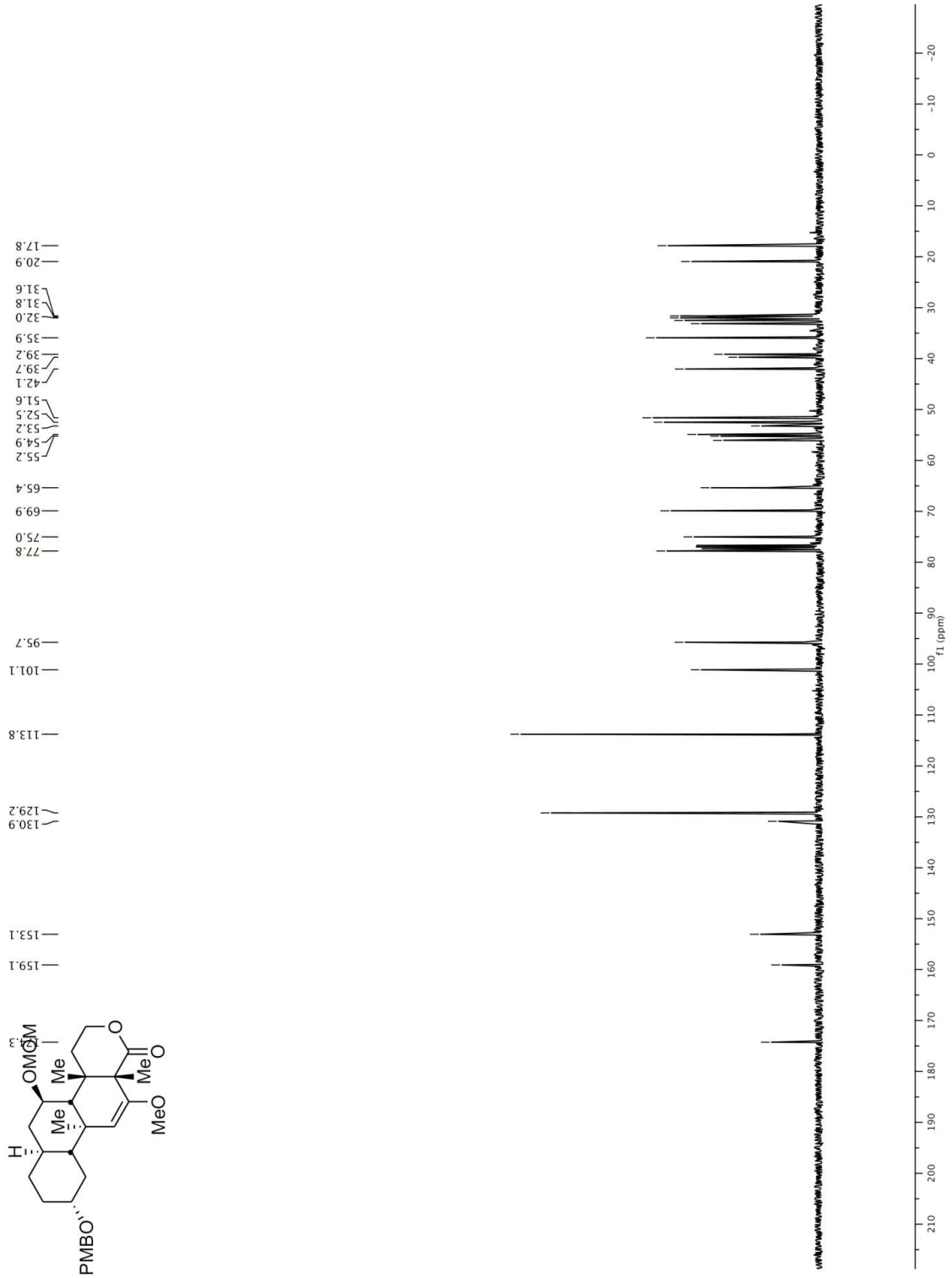
Spectrum 2.37 ^{1}H NMR ($CDCl_3$, 400 MHz) of methyl enone ether.



Spectrum 2.38 ^{13}C NMR ($CDCl_3$, 100 MHz) methyl enone ether.



Spectrum 2.39 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **124**.



Spectrum 2.40 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **124**.

Chapter 3 The chemistry and biology of *Illicium* sesquiterpenes

3.1 Introduction to the *Illicium* sesquiterpenes

Illicium is a genus of flowering plant containing 42 species of everygreen shrubs and small trees. They are native to the tropical and subtropical regions of eastern North America, Mexico, the West India and eastern Asia. The highest concentration of *Illicium* species is found in the southern China where nearly 35 species have been described. The fruits of the *Illicium* species are disintice star-shaped follicles with characterist refreshing flavor. The dry fruits of *Illicium verum* Hook, Chinese star anise in particular, have been used as a spice for cooking for centuries. On the other hand, the furits of *Illicium anisatum*, Janpenses star anise, have been known to contain toxic compounds.

Figure 3.1.1 *Illicium jiadifengpi* (left) and Chinese star anise (right).

Initial chemical research efforts towards *Illicium* plants were directed to the extraction of the essential oils and isolation of the toxic substances. This early research has led to structural determinations of a number of biologically active

compounds. Anisatin (**1**), a *seco*-prezizaane sesquiterpene isolated from *I. anisatum*,[1-3] is regarded as the most potent neurotoxin of plant origin with a LD_{50} of 1 mg/kg in mice.[4] Compounds **2**, **3**, **5** and **7** have shown potent neurite outgrowth activity in primary cultured rat cortical neurons at 0.1 μM, 10 nM, 0.1-10 μM and 0.1 μM, respectively.[5-8] These sesqiterpenes have attracted much attention due to their therapeutic potential in the treatment of neurodegenerative disorders such as Alzheimer's and Pakinson's diseases.[9,10]

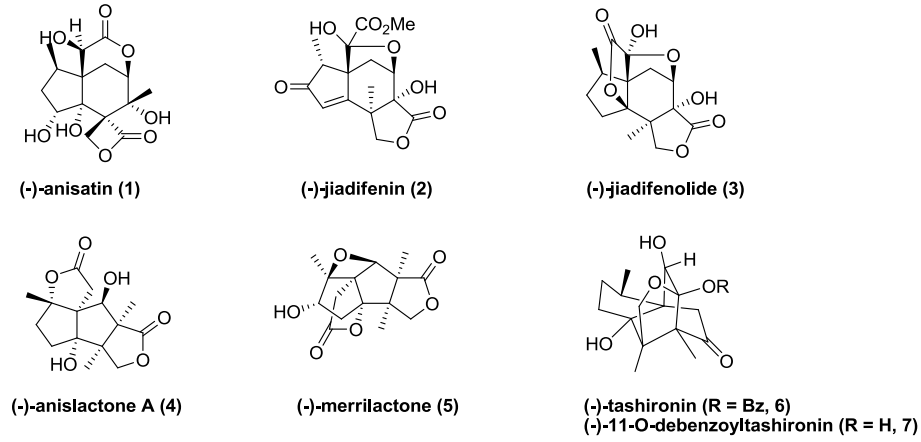


Figure 3.1.2 Representative natural products isolated from *Illicium* species.

3.1.1 Isolation and structural characterization

The chemical investigations of *Illicium* have developed rapidly over the last 20 years. A number of unusual sesquiterpenes were isolated from members of *Illicium* species Theseisolates were grouped into three classes: *seco*-prezizaane-, anislactone- and *allo*-cedrane-type sesquiterpenes. The *seco*-prezizaane-type sesquiterpenes are further categorized into six subgroups according to their carbon skeletons: anisatin-,

pseudoanisatin-, majucin-, minwanensin-, pseudomajucin- and cycloparvifloralone-subtypes.

3.1.1.1 *seco*-prezizaane-type sesquiterpenes

3.1.1.1.1 Anisatin-subtypes

Anisatin-subtype sesquiterpenes are characterized by having a bicyclo[4.3.0]nonane carboskeleton with a 13,14-β-lactone and a 11,7-β-lactone. Anisatin (**1**) was the first natural product isolated from *Illicium* species in 1952 by

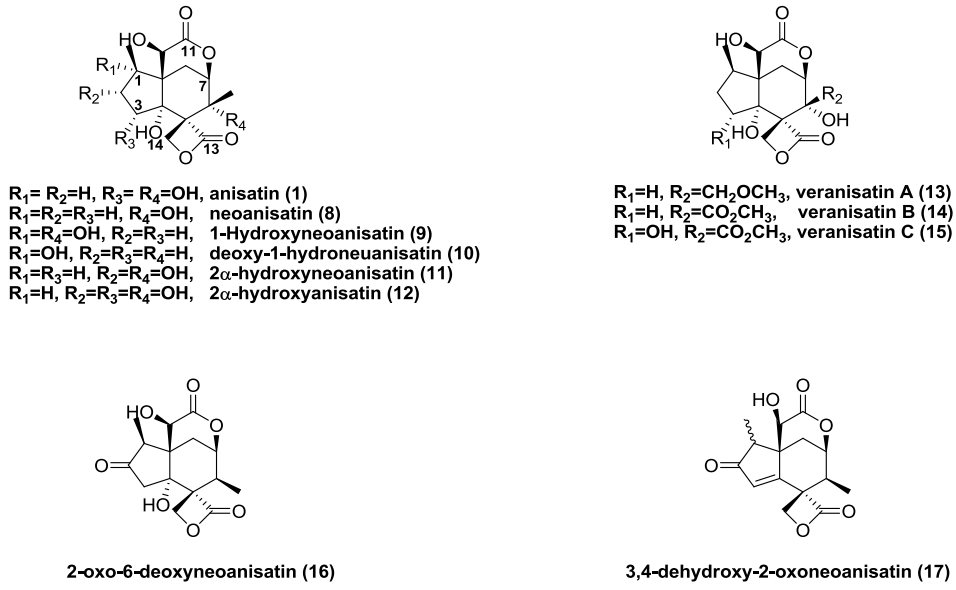


Figure 3.1.1.1.1 Anisatin-subtype sesquiterpenes

Lane and co-workers.[1] Its complete structure was later established by Yamada and Hirata.[2,3] There were 10 anisatin-subtype sesquiterpenes isolated during the late 90s, as shown in Figure 3.1.1.1.1. All of them expect compounds **8** - **11** belong to

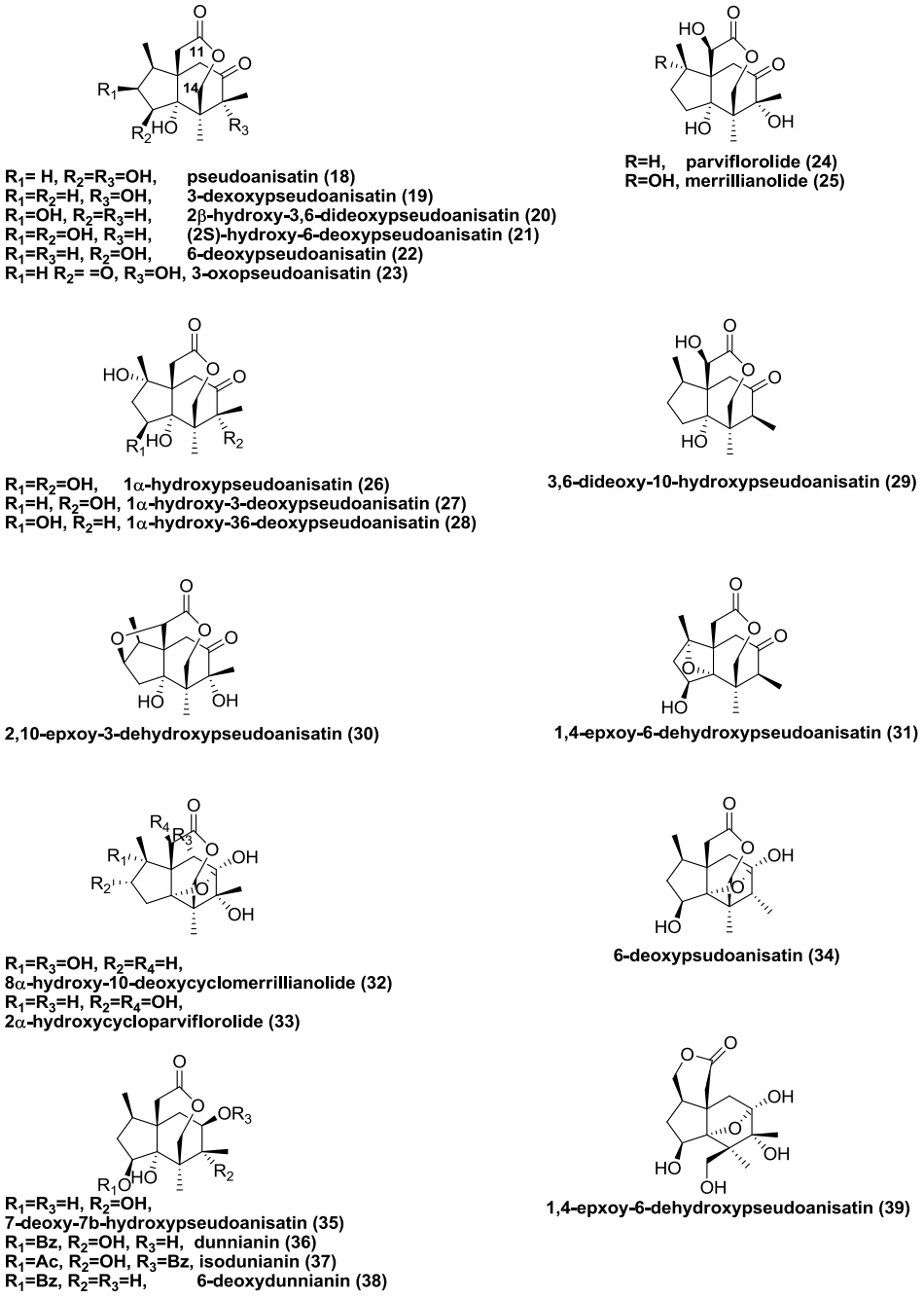


Figure 3.1.1.1.2 Pseudoanisatin-subtype sesquiterpenes.

neoanisatin derivatives lacking the hydroxyl group at the C3 position. Veranisatins A (**13**), B (**14**) and C (**15**), isolated from non-toxic Chinese star anise (*I. verum* Hook),

were found to cause severe convulsions and death at 3 mg/kg in mice.[11] 2-Oxo-6-deoxyneoanisatin (**16**) also exhibits picrotoxin-like convulsion and its LD_{50} is 1.46 mg/kg in mice.[12]

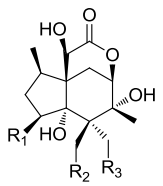
3.1.1.1.2 Pseudoanisatin-subtype

Pseudoanisatin (**18**) was first isolated as a nontoxic compound from *I. anisatum* by Lane and co-workers.[1] Natural products of this subtype are characterized by the same bicyclo[4.3.0]octane skeleton and a 7-membered 11,14-lactone. The incorrect structure of pseudoanisatin (**18**) was first propsoed based on the NMR spectral data.[13] which was later revised via X-ray crystal structure determination.[14] To date, 22 psudoanisatin-subtype sesquiterpenes have been isolated. Among them, pseudoanisatin (**18**), parviflorolide (**24**) and merrillianolide (**25**) were found to coexist in ketone and acetal equibilibrium.[15] Unlike anisatin (**1**), all derivatives tested so far are non-toxic substances. Isodunianin (**37**) was found to not only promotes neurite outgrowth at 10 μM concentration in primary cultured rat cortical neurons, but also increases choline acetyltransferase activity.[16]

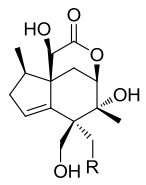
3.1.1.1.3 Minwanensin-subtype

The structure of minwanensin-subtype is considered to be similar to that of anisatin-subtype but with an opened spiro β-lactone. Minwanensin (**45**) was first isolated from *I. minwanense* in 1994.[17] The structure was revised after X-ray cystallographic analysis of its *p*-bromobenzoyl derivative.[18] Nine minwanensin-subtype sesquiterpenes have been isolated, none had shown neurotoxicity or any

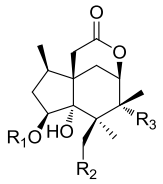
neurotrophic effect. This observation suggests that the presence of a β-lactone may contribute to the biological activities of this family.



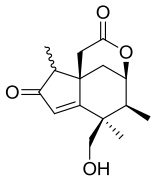
R_1= =O, R_2=OAc. R_3=H, 14-acetoxy-3-oxofloridanolide (40)
R_1=H, R_2=OCO*n*Pr, R_3=OAc,
13-acetoxy-14-(*n*-butyryloxy)floridanolide (41)
R_1=H, R_2=OCO*n*Pr, R_3=H, 14-*O*-*n*-butyrylfloridanolide (42)



R=OH,
3,4-dehydro-13,14-dihydroxyfloridanolide (43)
R=H, 3,4-dehydrofloridanolide (44)



R_1=H, R_2=OH, R_3=H, minwanensin (45)
R_1=Ac. R_2=OCO*n*Pr, R_3=OH,
3-acetoxy-14-*n*-butyryloxy-10-deoxyfloridanolide (46)



minwanenone (47)

Figure 3.1.1.1.3 Minwanensin-subtype sesquiterpenes.

3.1.1.1.4 Majucin-subtype

The structure of majucin-subtype is closely related to that of anisatin-subtype. They are characterized by the same bicyclo[4.3.0]octane skeleton and a γ-lactone. Majucin (**55**), together with neomajucin (**56**) and 2,3-dehydroneomajucin (**50**), was isolated from the pericarps of toxic Chinese *I. majus* in 1988.[19] The structure of neomajucin (**56**) was determined by X-ray crystallogrophic analysis.[20] Structures of other members were assigned by extensive spectroscopic analysis and comparison to the data of neomajucin (**56**).[12] Among the fifteen majucin-subtype sesquiterpenes isolated, only neomajucin (**56**) exhibits anisatin-like toxicity.[19] Whereas, (2R)-hydroxy-3,4-dehydroneomajucin (**48**) was neurotrophic acitive at concentration of 10

μM.[12] Perhaps, the most-studied and best-known compound of this family is jiadifenin (**2**),[5] a unique sesquiterpene with a oxo-functionality at the C10 position. It exhibits neurotropic activity at concentration as low as 1 μM. Majucin-subtype sesquiterpenes with similar bioactivity were also reported recently. Jiadifenolide (**3**), jiadifenoxolane A (**51**) and B (**52**) were isolated by Fukuyama and co-workers in 2009. Compounds **3** and **51** exhibit potent neurotrophic activity at concentrations of 10 nM and 1 μM, respectively.[6]

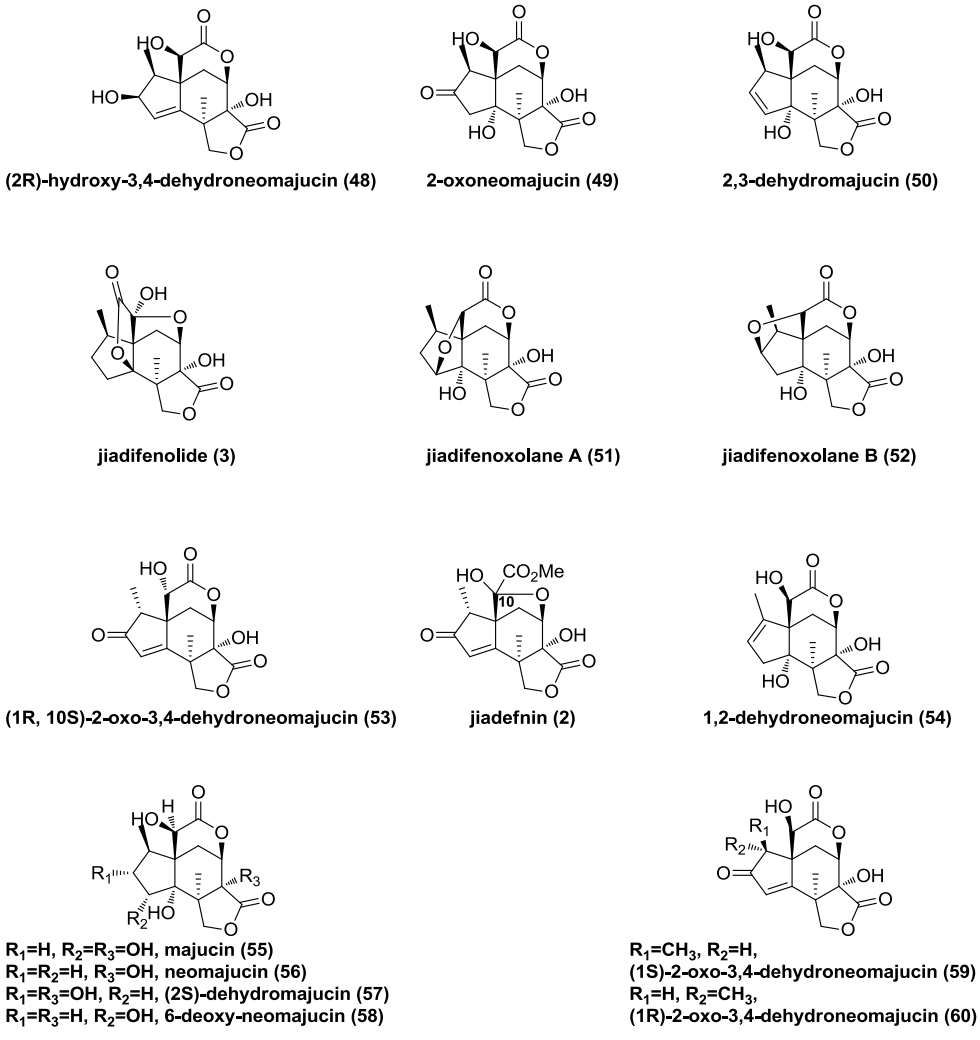
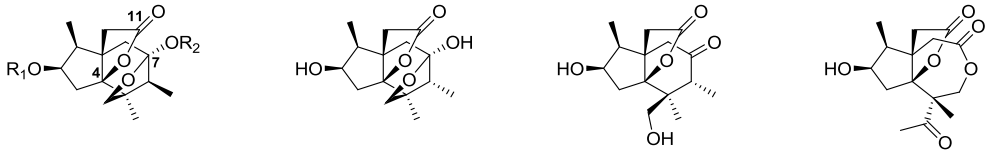


Figure 3.1.1.1.4 Majucin-subtype sesquiterpenes.

3.1.1.1.5 Pseudomajucin-subtype

Pseudomajucin-subtype features a γ-lactone ring closed in a 11,4-manner. Pseudomajucin (**61**) and its 7-*O*-β-D-glucoside derivative (**62**) were isolated from *I. majus* in 1991 by Kouno and co-workers.[21] The structure of **61** was established by X-ray crystallographic analysis. Three additional members of this family were later reported and their structures were elucidated on the basis of the spectral data of pseudomajucin (**61**).[22] To date, no bioactivity has been observed for this subtype. It is worth to mention that some pseudomajucin sesquiterpenes coexist in an acetal/keto equibibrium, such as (6R)-pseudomajucin (**63**) and (6R)-pseudomajucinone (**64**).[12,15]



R_1=R_2=H, pseudomajucin (61)
R_1=H, R_2= glucose, (62)

(6R)-pseudomajucin (63)

(6R)-pseudomajucinone (64)

merrillianin (65)

Figure 3.1.1.1.5 Pseudomajucin-subtype sesquiterpenes.

3.1.1.1.6 Cycloparvifloralone-subtype

The cycloparvifloralone-subtype sesquiterpenes consist of a unique acetal hemiacetal and/or ortholactone structures. Due to these functionalities, it was anticipated that they are in equbilibrium between an acetal/hemiacetal and a ketone/aldehyde, or between an orthoester and a lactone. However, neither the ketone/aldehyde or lactone was detected by NMR spectra when methanol-d_4 was used as solvent.[23] This suggests that these compounds are favored in their acetal/hemiacetal

and orthoester forms in solution, despite the general believe of that they should coexist with each corresponding aldehyde ketone or lactone form. To date, no bioacitivty has been identified.

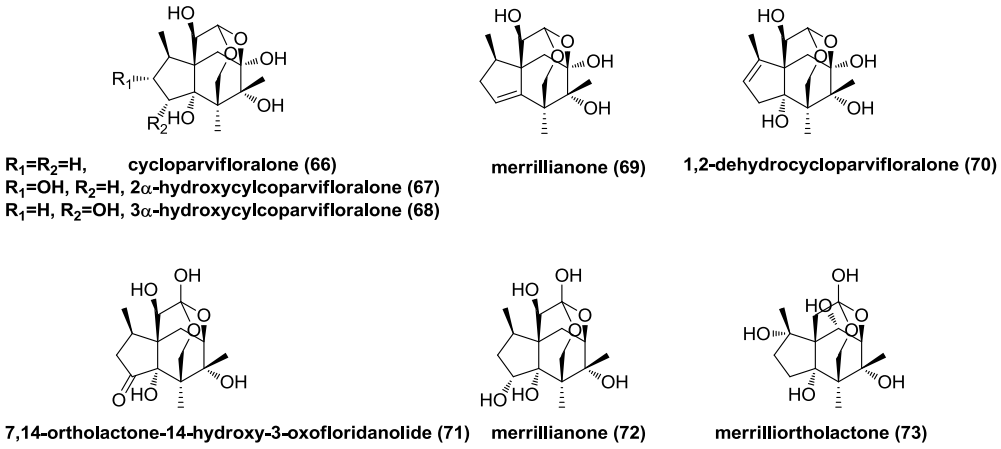


Figure 3.1.1.1.6 Cycloparvifloralone-subtype sesquiterpenes.

3.1.1.2 *Allo*-cedrane-type sesquiterpenes

Sesquiterpenes with novel carbon skeleton, which are not able to make their place in any of the known subtypes of *seco*-prezizaane type sesquiterpenes, are catalogized as the *allo*-cedrane-type. Such sesquiterpenes are shown in Figure 3.1.1.2. Tashironin (**6**) was isolated first from *I. tashiroi* in 1995 by Fukuyama and co-workers.[8] Soon after, other tashironin congeners were reported.[24] Tashironin family consists of a 2-oxatricyclo[4.3.1.0]heptane skeleton, which is regarded as a biogenetic key all *Illicium* sesquiterpenes. The isolation of tashironin is considered as significant in the study of biogenesis of *Illicium* sesquiterpenes.[25]

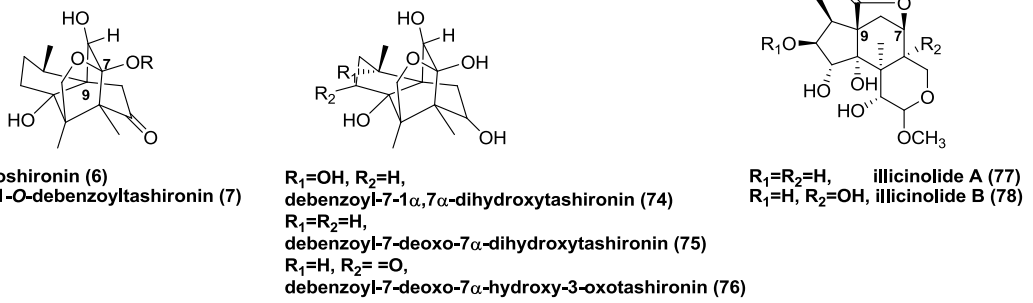


Figure 3.1.1.2 *Allo*-cedrane-type sesquiterpenes.

Other noval sesquiterpenes of this type named illicinolide A (**77**) and B (**78**), were isolated from *I. tashiroi* in early 1990s by Fukuyama and co-workers.[26,27] Their structures are closely related to the previously reported anisatin (**1**) and majucin (**55**), featuring a γ-lactone ring closed between C7 and C9. No compound from this family had either neurotrophic or neurotoxic effects in cultured neurons except 11-debenzoyltashironin (**7**). It was found that **7** promotes neurite outgrowth at a range of concentrations from 0.1 μM to 10 μM.[8]

3.1.1.3 Anislactone-type sesquiterpenes

Anislactones A (**4**) and B (**79**) were isolated in 1989 from the fruits of *I. anisatum*.[28] The structure of anislactone A (**4**) was determined by X-ray crystallographic analysis.[29] The unique carbon skeleton of anislactones differentiates them from previously known *Illicium* sesquiterpenes. Following their isolation, four new sesquiterpenes were discovered from the fruits of *I. merrillianum* in 2000, namely merrilactone A (**5**), B (**80**), C (**81**) and D (**82**).[7] The structure of merrilactone A (**5**) was established by extensive spectroscopic analysis and then confirmed by X-ray

crystallographic analysis. Its absolute configuration was determined by applying the modified Mosher's method.[30] Merrilactone A (**5**) possesses an oxetane ring and a bis-γ-lactones. It has shown to promote neurite outgrowth in primary cultured rat cortical neurons. Accordingly, it has been regarded as a promising lead compound for the development of small molecules as neurotrophic substances.[28]

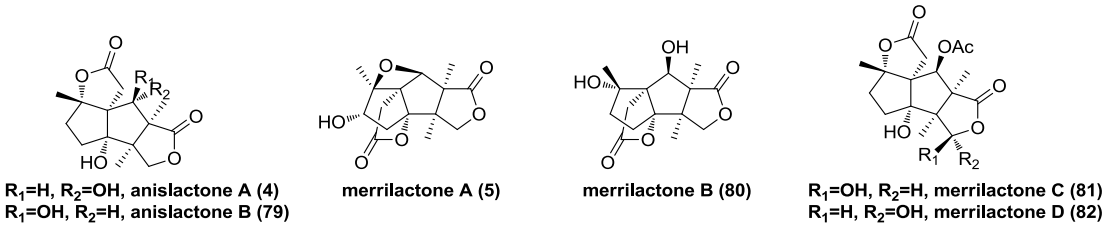
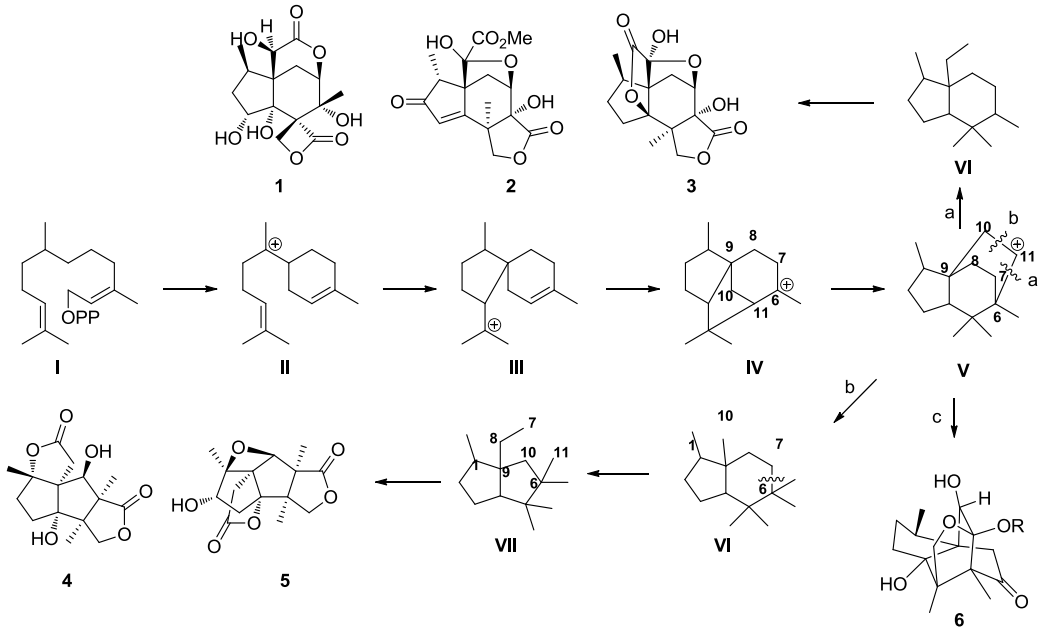


Figure 3.1.1.3 Anislactone-type sesquiterpenes.

3.1.2 Proposed biosynthetic pathway

Despite their structural diversity, all *Illicium* sesquiterpenes are considered to be biosynethcially related.[25,31] The biosynthesis of these sesquiterpenes was proposed to be via the mevalonic acid pathway. Originated from farnesyl diphosphate (FPP), enzyme-catalyzed cyclization leads to the formation of *allo*-cedrane **V**, a common intermediate to all types of sesquiterpenes found in the *Illicium* species. When *allo*-cedrane **V** undergoes cleavage at bond *a*, providing *seco*-prezizaane type sesquiterpenes, such as compounds **1**, **2** and **3**. On the other hand, cleavage of bond *b* leads to the formation of anislactone-type sesquiterpenes, such as compounds **4** and **5**.



Scheme 3.1.2 Proposed biosynthetic pathway of *Illicium* sesquiterpenes.

3.2 Biological activities of *Illicium* sesquiterpenes

In addition to their highly oxygenated caged structure, *Illicium* sesquiterpenes exhibit interesting biological activities.[25] Many members from this family were identified as neurotoxins whereas others as neurotrophic modulators. This finding demonstrates the strong effect of subtle structural changes on biological activities.

3.2.1. Neurotoxic acitivity

The convulsive effect of the Japanese star anise has been known for centuries. The active neurotoxin anisatin (**1**) was isolated in 1952.[1] Ever since, several other potent neurotoxic compounds were isolated from *Illicium* species. The toxicity of representative compounds to mice was examined as outlined in Figure 3.2.1. The

neuropharmacological study suggested anisatin as a potent non-competitive GABA antagonist.[4,32] The GABA receptors are a class of receptors that respond to the neurotransmitter γ-aminobutyric acid. They are the inhibitory neurotransmitter in the vertebrate central nervous system. To date, no systematic study of structure and toxicity-relationship has been carried out due to the insufficient amount of materials isolated from natural sources. Therefore, the question of which structural part of anisatin is to cause convulsive activity remained unanswered.

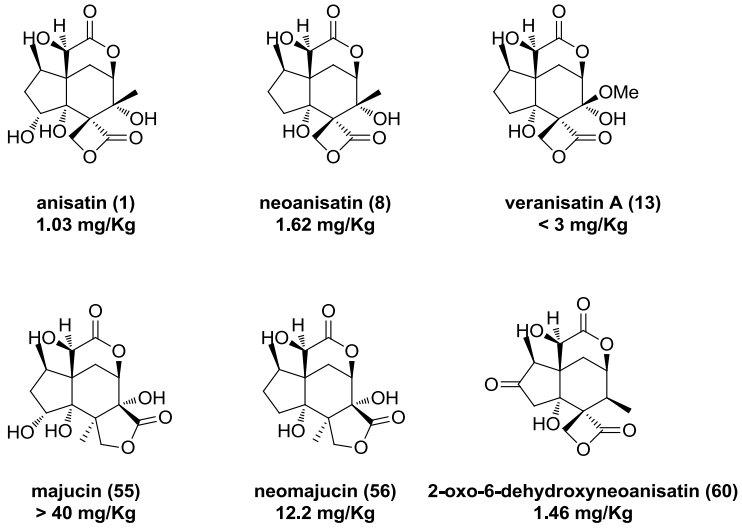


Figure 3.2.1 Lethality (LD_{50}) induced by representative *Illicium* sesquiterpenes.

3.2.2. Neurotrophic activity

Several *Illicium* sesquiterpenes have shown to enhance neurite outgrowth and increase choline acetyltranferase (ChAT) activity in primary cultured rat cortical neurons. Choline acetyltransferase is an enzyme that is synthesized by neurons and then transferred to the nerve terminal. Cholinergic system is implicated in many

neurologic functions. Alterations in any cholinergic neurons may account for the disturbances of Alzheimer disease.[9,25]

Neurotrophic *Illicium* sesquiterpenes are shown in Figure 3.2.2.[6,25] Isodunnianin (**36**) was found to enhance neurite outgrowth in primary cultured neurons at concentration of 10 μM, as well as increasing choline acetyltransferase activity 10 days after seeding. (2S)-hydroxy-3,4-dehydroneomajucin (**48**) and jiadifenin (**2**) show potent neurotrophic activity in primary cultured rat cortical neurons at concentrations ranging from 1 nM to 10 μM. Jiadifenolide (**3**) and jiadifenoxolane A (**51**) exhibit potent activity at concentrations as low as 10 nM and 1 μM, respectively. Tashironin (**6**) didn't show any neurotrophic activity, however, its debenzoylated derivative **7** was found to promote neurite outgrowth with best results at a range of concentrations from 0.1 μM to 10 μM. Merrilactone A (**5**) exhibits potent neurotrophic activity at 10 nM concentration.

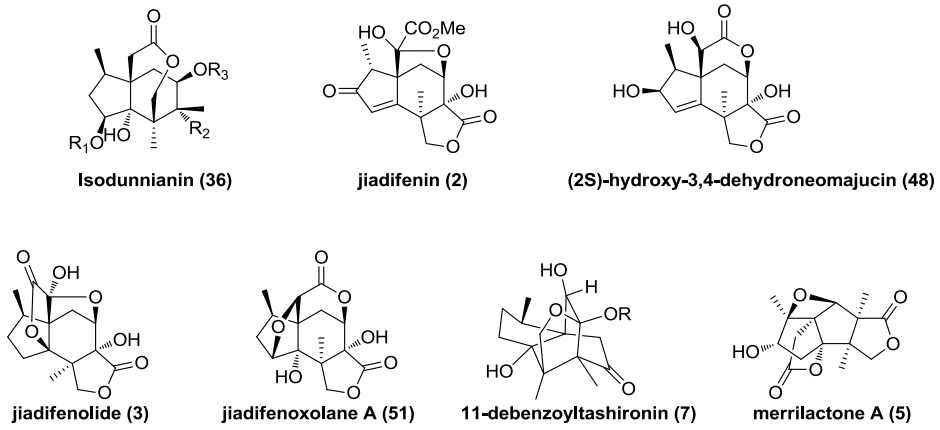


Figure 3.2.2 Neurotrophic *Illicium* sesquiterpenes.

From these data, jiadifenolide (**3**) and merrilactone A (**5**) are regarded as the most potent neurotrophic substances isolated from this family. Thus they are considered as potential nonpeptide neurotrophic agents for the treatment of neurodegenerative disorders.

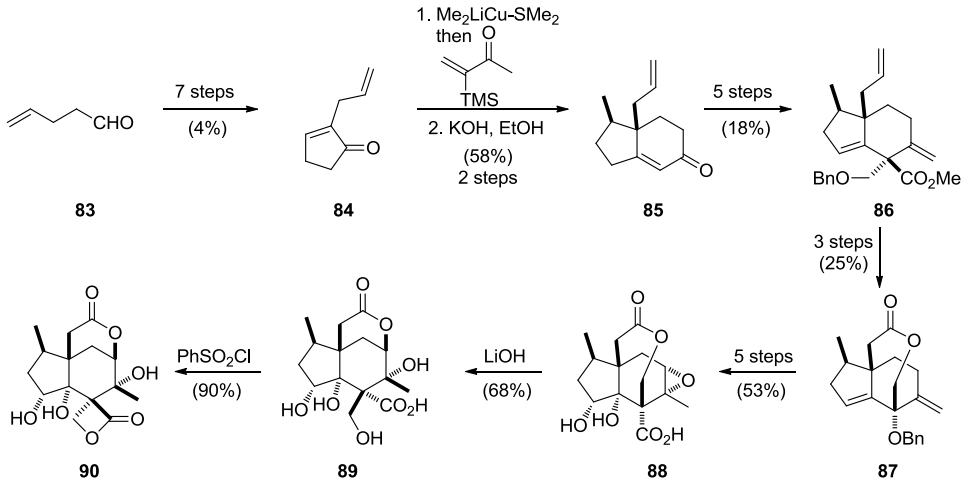
3.3 Reported synthetic studies

In addition to their intriguing biological properties, the highly oxygenated cage architecture of *Illicium* sesquiterpenes invited the development of efficient strategies towards their chemical syntheses. Over the past 20 years, synthetic efforts from many research groups culminated 13 total syntheses of several natural products from this family, including 2 of our own group.[35-37]

3.3.1 Total synthesis of (±)-8-deoxyanisatin

In 1985, the Kende group reported the synthesis of (±)-8-deoxyanisatin **(90)**, an analogue of anisatin (**1**).[38] As outlined in Scheme 3.3.1, their synthesis was divided into two stages - assembly of the carbon core structure (**83** → **86**) and subsequent adjustments of oxidation states and functional groups (**86** → **90**). The difficult spiro β-lactone (**88** → **89**) and the γ-lactone lactone (**89** → **90**) were constructed at the final stages of the synthesis. In the forward direction, 2-allyl-2-cyclopentanone (**84**) was prepared from aldehyde **83** in 7 known steps.[39] A regio- and stereoselective alkylation and subsequent intramolecular aldol condensation[40] under basic condition generated enone **85**. Several functional group transformations led to the formation of carbon core structure **86**. LAH reduction of the methyl ester of **86**, oxidative cleavage[41] of the

terminal alkene and subsequent intramolecular lactonization produced lactone **87** in 25% yield. In 5 additional steps, epoxide **88** was synthesized, with all the oxidation states adjusted. At this point, only the constructions of β- and γ-lactones remained. The preparation of β-lactone was accomplished by the intramolecular translactonization via epoxide opening reaction, whereas the γ-lactone was formed through the intramolecular lactonization in the presence of $PhSO_2Cl$.

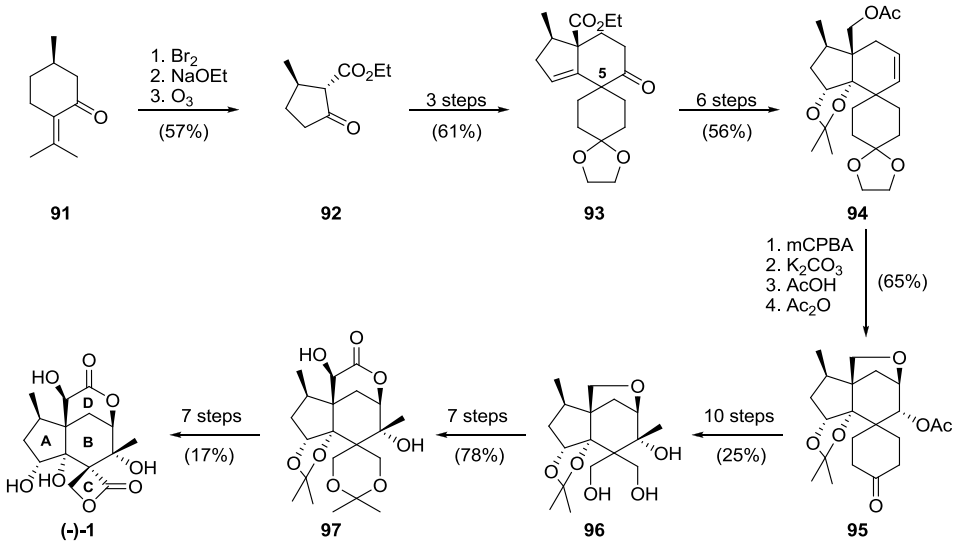


Scheme 3.3.1 Total synthesis of (±)-8-deoxyanisatin by the Kende group.

The synthesis of (±)-8-deoxyanisatin, the first of this family, was completed in 22 steps after nearly 40 years of the isolation of anisatin. The overall yield was 0.025%. This synthesis demonstrated the challenging caged structure and need of efficient synthetic approaches.

3.3.2 Total syntheses of (–)-anisatin and (–)-neoanisatin

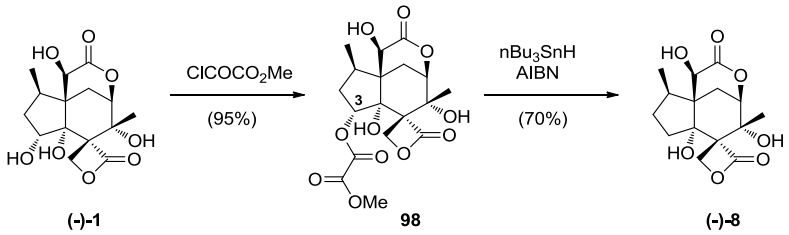
Five years after Kende's synthesis of (±)-8-deoxyanisatin, the Yamada group reported the first enantioselective syntheses of (–)-anistatin (**1**)[42] and (–)-neoanistatin (**8**)[43] from (+)-pulegone (**91**). Similar to Kende's approach, the demanding spiro β- and γ-lactones were constructed at the final stages of the synthesis. The carbon framework was prepared via a Robinson annulation reaction.[44]



Scheme 3.3.2.1 Total synthesis of (–)-anisatin by the Yamada group.

In details, bromination of (+)-pulegone (**91**) followed by Favorskii rearrangement[45] and subsequent ozonolysis to afford ketone **92**. Robinson annulation of ketone **92** with MVK, followed by attaching the spiral cyclohexane moiety established the carbon core structure **93**, containing the C5 quaternary center. Several functional group transformations led to the formation of olefin **94**. Stereoselective epoxidation followed by base induced epoxide opening afforded compound **95**. Triol

96 was then formed via a double oxidative cleavage of cyclohexane moiety. The total synthesis was then completed through the constructions of β- and γ-lactones. The α-hydroxy-γ-lactone (D ring) was constructed via a sequence of oxidations, carbon chain extension and lactonization. The spiro β-lactone (C ring) was then prepared via similar route reported by the Kende group in the synthesis of (±)-8-deoxyanisatin. In a total of 40 steps, the Yamada group accomplished the first enantioselective total synthesis of (−)-anisatin in 0.4% total yield.



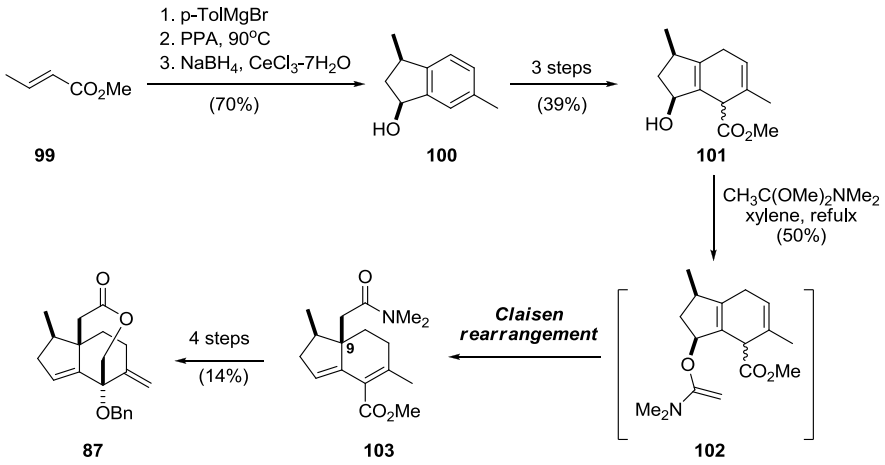
Scheme 3.3.2.2 Total synthesis of (−)-neoanisatin the Yamada group.

(−)-Neoanisatin (**8**) was then synthesized from (−)-anisatin (Scheme 3.3.2.2) by removing the C3 hydroxy group in two steps: a) formation of methyl oxalate b) reduction of the resulting oxalate in the presence of nBu$_3$SnH and AIBN.

3.3.3 Formal synthesis of (±)-8-deoxyanistatin

In 2001, Loh's group reported a formal synthesis of (±)-8-deoxyanistatin.[46] The key step to their synthesis was the [3,3]-Claisen rearrangement to establish the C9 quaternary carbon center (Scheme 3.3.3). The formal synthesis was proven to be less lengthy and higher yielding. Departed from methyl crotonate (**99**), Michael addition

of *p*-TolMgBr in the presence of CuI, followed by intramolecular Friedel-Crafts acylation[47] and Luche reduction[48] led to the formation of alcohol **100**. The Eschenmoser-Claisen rearrangement[49] precursor **101** was then prepared in 3 steps, namely, hydroxy-directed carboxylic acid formation, Birch reduction[50] and methylation. The formation of Kende's intermediate **87** was then accomplished after the key Claisen rearrangment[51] followed by several functional group transformations. In 11 steps and an overall yield of 2%, intermediate **87** was prepared in comparison to 15 steps and 0.5% yield in Kende's synthesis.



Scheme 3.3.3 Formal synthesis of (±)-8-deoxyanistatin by the Loh group.

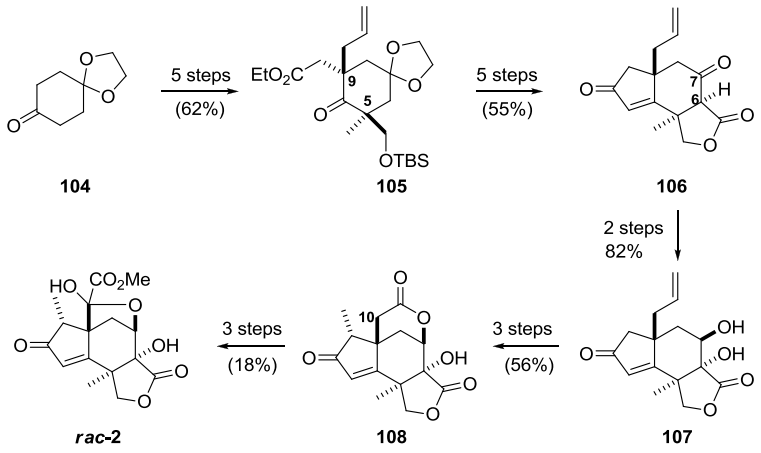
3.3.4 Synthetic studies towards (±)-jiadifenin

In 2002, Fukuyama reported the isolation and structure determination of jiadifenin (**2**) from *Illicium jiadifengpi*.[5] It consists of a highly oxygenated, cage-like tetracycle with a cyclic hemiacetal and a γ-lactone. It was found that jiadifenin significantly promotes neurite outgrowth in primary cultures of fetal rat cortical

neurons at concentrations of 0.1 μM to 10 μM. The attractive biological activity and challenging structure have accumulated one total synthesis by the Danishefsky group and a synthetic study by the Fukuyama group.[52,56]

3.3.4.1 Danishefsky's total synthesis of (±)- jiadifenin

In 2004, the Danishefsky group reported the first total synthesis of (±)-jiadifenin.[52] Their synthesis featured an intramolecular aldol condensation and an intramolecular Claisen condensation to deliver the tricyclic carbon core. The synthesis began with the introduction of C5 and C9 quaternary carbons to ketone **104** by stepwise stereoselective alkylations. Intramolecular aldol and Claisen



Scheme 3.3.4.1 Total synthesis of (±)-jiadifenin by the Danishefsky group.

condensations of **105** led to the formation of tricycle motif **106**. Treatment of **106** with mCPBA introduced the C6 hydroxyl group as a single isomer. Regio- and stereoselective reduction of the C7 ketone delivered *trans* diol **107**. Ozonolysis of the terminal alkene of **107** followed by Jones oxidation and methylation led to the

formation of lactone **108**. The introduction of the C10-hydroxyl group was accomplished by treating with Davis oxaziridine.[54,55] Jones oxidation finally completed the synthesis of (±)-jiadifenin. This impressive 18-step synthesis not only delivered the first total synthesis of jiadifenin, but also provided several synthetic analogues to establish an initial SAR profile of this family. Several non-natural products, compounds **53** and **109** for example, were found to exhibit strong neurotrophic activity. Synthetic jiadifenin displayed a 162% neurite outgrowth activity compared to the control; whereas outgrowths of 184% and 181% were found for compounds **53** and **109**, respectively.[53]

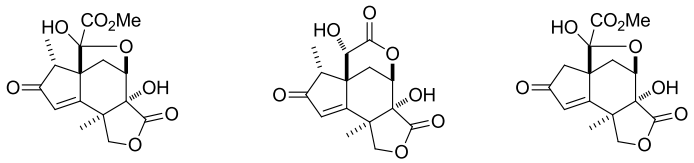


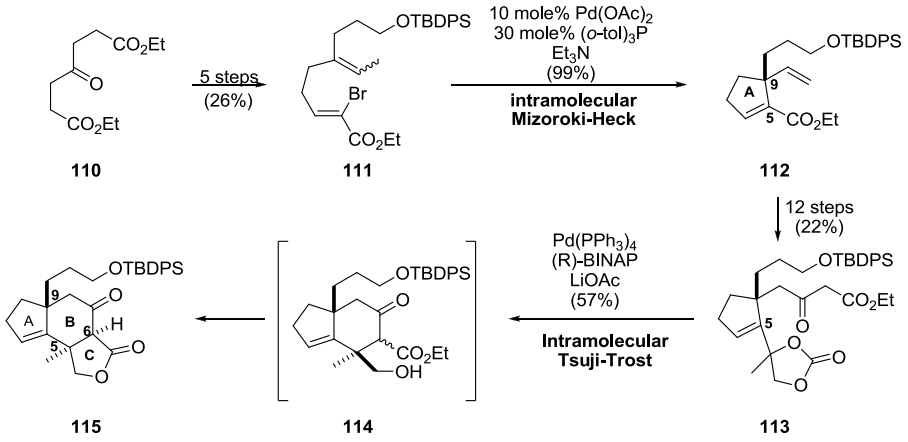
Figure 3.3.4.1 Neurotrophic compounds related to jiadifenin.

Overall, Danishefsky's group completed the first total synthesis of (±)-jiadifenin in 18 steps and 3% yield. The synthesis is short and efficient. It allows access to other synthetic derivatives to establish a preliminary SAR profile to study the neurotrophic activity of compounds from this family.

3.3.4.2 Synthesis of the ABC ring system by Fukuyama

Recently, Fukuyama reported an alternative route towards the central ABC ring system of jiadifenin.[56] The synthesis featured two key Pd-catalyzed cyclizations.

The Mizoroki-Heck reaction[57] constructed the A-ring, containing the C9 quaternary carbon; and a cascade Tsuji-Trost cyclization[58]-lactonization sequence to establish the BC ring system with C5 and C6 stereochemistry.



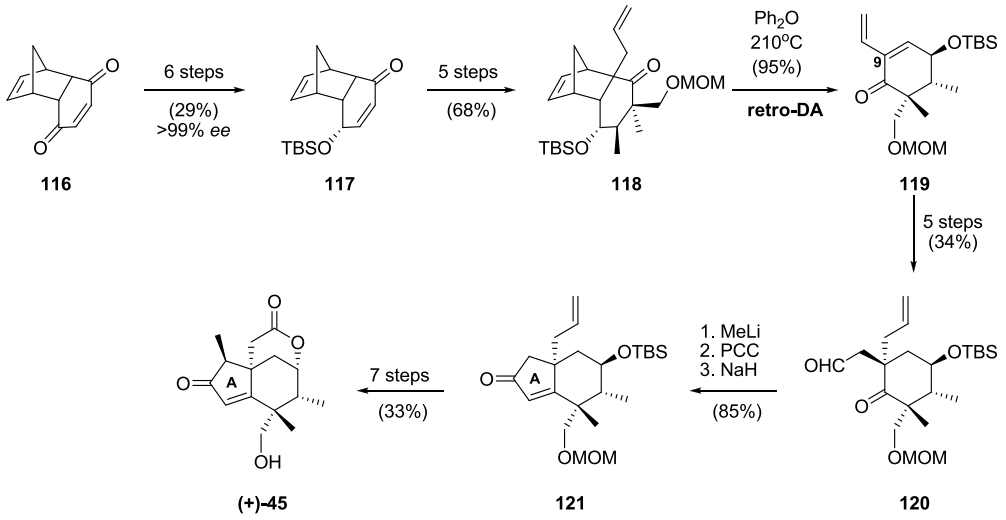
Scheme 3.3.4.2 Synthesis of the ABC ring system by the Fukuyama group.

Departed from commercially available diethyl 4-oxopimelate (**110**), vinyl bromide **111** was prepared in 5 steps. The intramolecular Heck reaction delivered the cyclopentene **112** as a single isomer, containing the A-ring and C9 quaternary carbon. After several functional group manipulations, the Tsuji-Trost reaction precursor **113** was isolated as C5 diastereomers. The 5*R* isomer underwent Tsuji-Trost cyclization followed by *in-situ* lactonization to deliver lactone **115**, which represents the ABC ring core structure of jiadifenin.

3.3.5 Total synthesis of (+)-1*S*-minwanenone

In 2007, Metha's group reported the total synthesis of (+)-1*S*-minwanenone, enantiomer of the natural product.[59] As shown in Scheme 3.3.5, Ogasawara's chiral

synthon[60-64] **117** was prepared from **116** following reported procedure. The intrinsic three-dimensional structure of **117** directed the transformations to ketone **118** stereoselectively. Retro-Diels-Alder reaction followed by alkylation at C9 carbon center led to the formation of ketone **119**. The total synthesis was then completed after the intramolecular aldol condensation to form the A-ring (**120** → **121**) and γ-lactonization (**121** → **45**). Overall, the enantioselective synthesis of (+)-1*S*-minwanenone was accomplished in 27 steps and 2% overall yield.

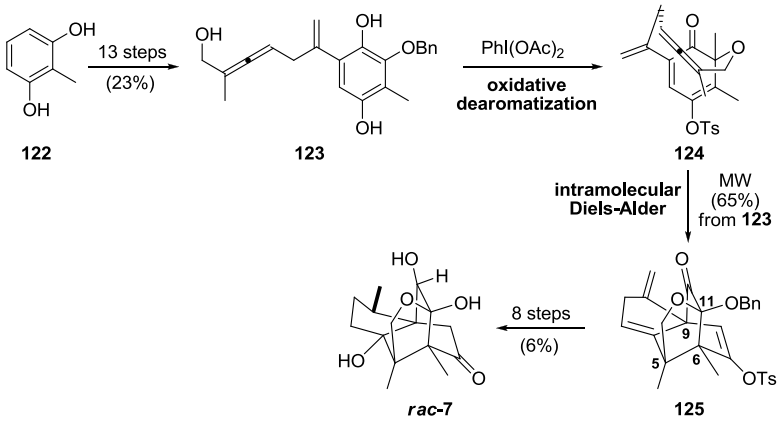


Scheme 3.3.5 Total synthesis of (+)-1*S*-minwanenone by the Mehta group.

3.3.6. Total synthesis of (±)-11-*O*-debenzoyltashironin

11-*O*-debenzoyltashironin (**7**) was isolated along with tashironin (**6**) by the Fukuyama group in 2001.[8] The debenzoylated natural product **7** was found to induce neurite outgrowth in fetal rat cortical neurons at low concentration of 0.1 μM, whereas tashironin (**6**) showed no neurotrophic activity. In 2006, the Danishefsky group

reported the first total synthesis of this highly structural challenging molecule.[65,66] The synthesis employed a biomimetic cascade strategy to establish the tricyclic carbon skeleton containing four tetrasubstituted carbons at C5, C6, C9 and C11 positions. This key transformation was accomplished in only two steps, namely, oxidative dearomatization followed by a transannular Diels-Alder reaction (Scheme 3.3.6).



Scheme 3.3.6 Total synthesis of (±)-11-*O*-debenzoyltashironin by the Danishefsky group.

In the forward direction, the biomimetic cascade reaction precursor **123** was prepared in 13 steps from 2-methylresorcinol (**122**). Exposure of **123** to oxidative dearomatization conditions generated substrate **124**. The latter underwent IMDA reaction under microwave irradiation to deliver adduct **125** as the only isolated compound. In these two steps, three fused rings and four tetrasubstituted carbons were established. The total synthesis of (±)-11-*O*-debenzoyltashironin was then accomplished after 8 steps of functional group manipulations. This impressive 23-step synthesis delivered the first total synthesis of (±)-**7** in 0.9% overall yield.

3.3.7 Total synthesis of merrilactone A

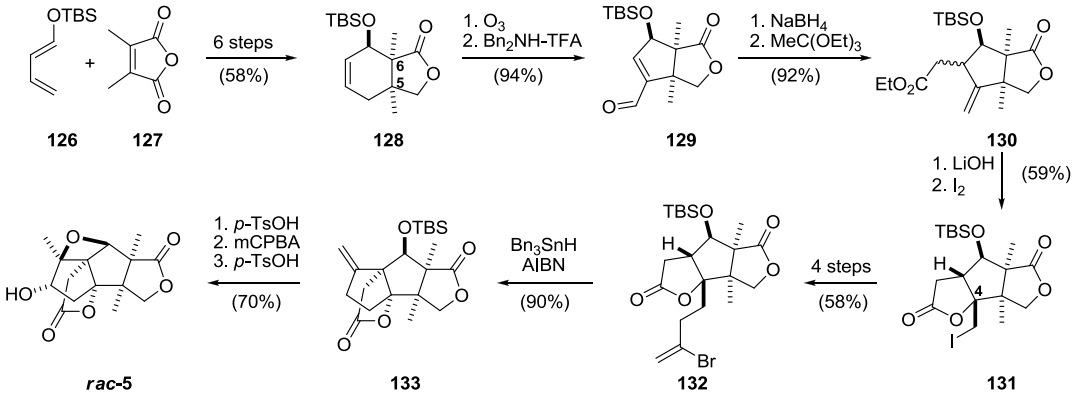
Merrilactone A (**5**) was isolated from *I. merrillianum* by Fukuyama in 2001.[7,30] Preliminary studies have shown that **5** strongly promotes neurite outgrowth in fetal rat cortical neurons at concentrations of 0.1 μM to 10 μM. It is one of the most potent neurotrophic small molecules. Therefore, merrilactone A has been considered as a potential candidate for the treatment of neurodegenerative disorders such as Alzheimer's disease. In addition to its promising biological activity, the compact architecture of merrilactone A has attracted attention from the synthetic community. To date, there have been five total synthesis reported by the Danishefsky,[67,68] Inoue,[69-72] Mehta,[73] Frontier[74] and Greaney[75] groups.

3.3.7.1 Danishefsky's synthesis

In 2002, Danishefsky reported the first racemic synthesis of merrilactone A (Scheme 3.3.7.1.1).[67] The synthesis began with a Diels-Alder reaction between diene **126** and 2,3-dimethylmaleic anhydride (**127**). Over several steps, lactone **128** was prepared. Compound **128** contains the quaternary stereocenters at C5 and C6 positions.

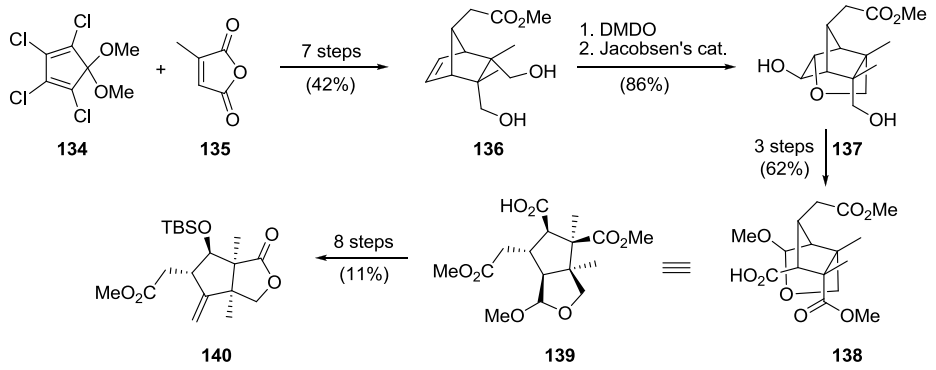
Ring opening via ozonolysis followed by ring reclosing led to enone **129** under Corey's conditions.[76] Reduction followed by Johnson-Claisen rearrangement[77,78] of the resulting allylic alcohol produced lactone **130**, as a diastereomixure. The γ-lactone **131** was then formed in the presence of iodine, which installed the desired C4 tetrasubstituted stereocenter. Carbon chain extension and vinyl bromide formation

were accomplished in 4 steps, yielding compound **132** for the key radical cyclization reaction. The radical cyclization delivered the desired bis-lactone **133**. The completion of merrilactone A was achieved after isomerization of the double bond, epoxidation and acid-induced epoxide opening. In 18 steps and 11% overall yield, Danishefsky's group reported the first racemic synthesis of merrilactone A in a year after its isolation. The key reactions to this approach are the Diels-Alder reaction to install the C5 and C6 quaternary carbons, the iodolactonization that installs the C4 tetrasubstituted carbon and the radical cyclization to form the final five-membered ring.



Scheme 3.3.7.1.1 Total synthesis of (±)-merrilactone A by the Danishefsky group.

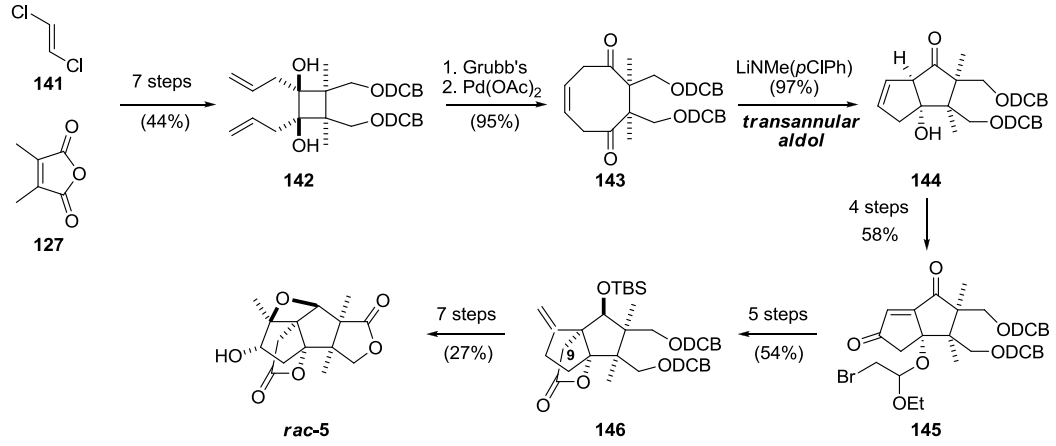
Three years after their first reported synthesis, Danishefsky's group published their second approach (Scheme 3.3.7.1.2).[68] It was designed to synthesize their advanced intermediate **140** in an enantioselective manner. The enantioselectivity was accomplished via the asymmetric epoxidation of meso-diol **136** employing Jacobsen's catalyst.[79] In 19 steps, the advanced intermediate **140** was prepared in 2% yield from diene **134**.



Scheme 3.3.7.1.2 Enantioselective synthesis of merrilactone A by Danishefsky's group.

3.3.7.2 Inoue's synthesis

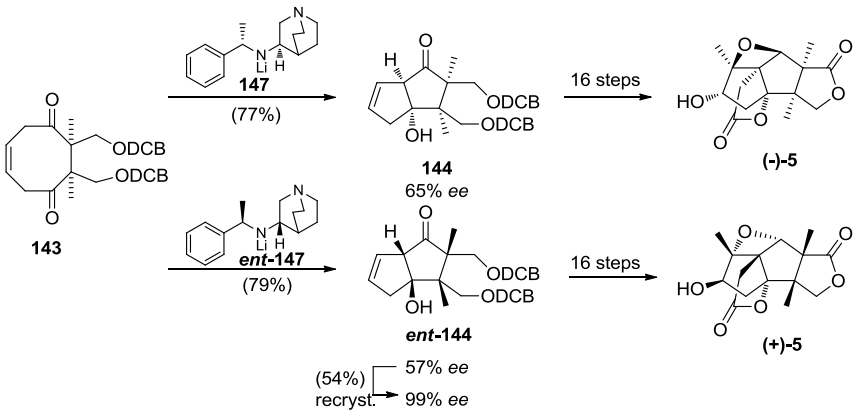
In 2003, Inoue and co-workers reported a racemic synthesis of merrilactone A (Scheme 3.3.7.2.1).[69] The key reaction to their synthesis was the transannular aldol reaction of the eight-membered ring diketone **143** to tricyclic motif **144**. Diketone **143** was introduced using a [2+2] cycloaddition[80,81] followed by ring closing metathesis.[82]



Scheme 3.3.7.2.1 Racemic synthesis of merrilactone A by the Inoue group.

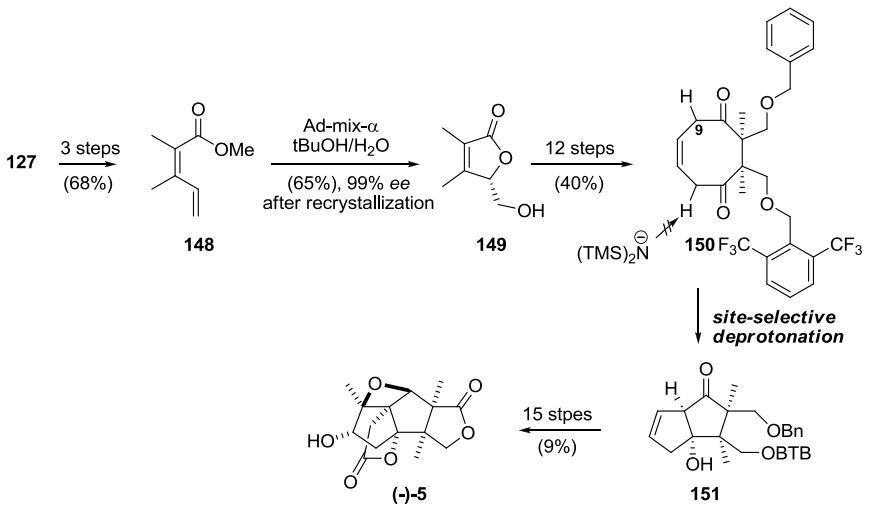
Lactone **146** was formed via radical cyclization of bromo acetal **145** that establish the stereochemistry of C9 quaternary carbon center. From lactone **146**, merrilactone A was synthesized through several functional group manipulations. In 26 steps, Inoue's group completed the racemic synthesis of merrilactone A in 3.5% overall yield.

Next, the Inoue group explored the enantioselective synthesis of merrilactone A (Scheme 3.3.7.2.2).[70] Towards that end, many chiral bases were screened to achieve enantioselective deprotonation of *meso*-diketone **143**, so that the key transannular aldol reaction would proceed in an enantioselective manner. Ultimately, chiral lithium base **147** was found to yield the best enantioselectivity to afford the desired enantiomer **144** in 65% *ee*. On the other hand, *ent*-**147** enabled the formation of *ent*-**144** in 57% *ee*, which led to isolation of enantiomerically pure **144** and *ent*-**144** after crystallization. With both enantiomers in hand, the total synthesis of both enantiomers of merrilactone A were achieved through the same route described for the racemic compound.



Scheme 3.3.7.2.2 Enantioselective synthesis of merrilactone A via a chiral base.

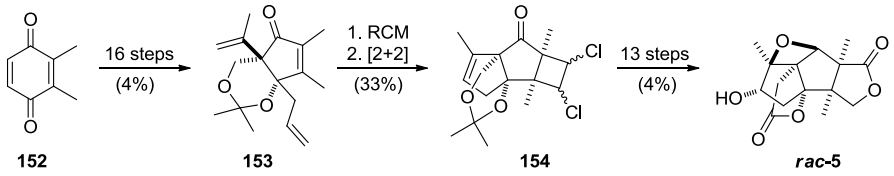
An alternative route[71] followed by the Inoue group to access the enantiomerically pure merrilactone A was to utilize the long-range steric effect of the bulky BTB protective group. The steric hinderance of BTB group promotes the site-selective deprotonation of chiral pseudo-meso diketone **150**. The later was synthesized as shown in Scheme 3.3.7.2.3. Lactone **149** was prepared by enantioselective dihydroxylation using AD-mix-α,[83,84] followed by *in situ* lactonization. In 12 steps, diketone **150** was synthesized, which underwent the desired transannulation aldol reaction. In this reaction, the base selectively deprotonated the hydrogen at C9 due to the steric hinderance of BTB ether protective group, giving ketone **151** as the single product isolated. In a total of 32 steps, (–)-merrilactone A was prepared in 1.6% total yield.



Scheme 3.3.7.2.3 Enantioselective synthesis of merrilactone A by the Inoue group.

3.3.7.3 Mehta's synthesis

In 2006, Mehta and co-workers reported the total synthesis of (±)-merrilactone (Scheme 3.3.7.3).[70] Their synthesis featured a ring closing metathesis (RCM) and a [2+2] cycloaddition. Departed from 2,3-dimethyl-1,4-benzoquinone (**152**), diene **153** was prepared after 16 steps. RCM of diene **153** constructed the cyclopentene moiety. [2+2] cycloaddition of the resulting ketone with dichloroethylene led to the formation of ketone **154** as diastereomixture, from which the desired isomer was isolated as the major product. The total synthesis of **5** was then accomplished in 13 steps. Overall, the Mehta group completed the racemic synthesis of merrilactone A in 31 steps and 0.05% yield.

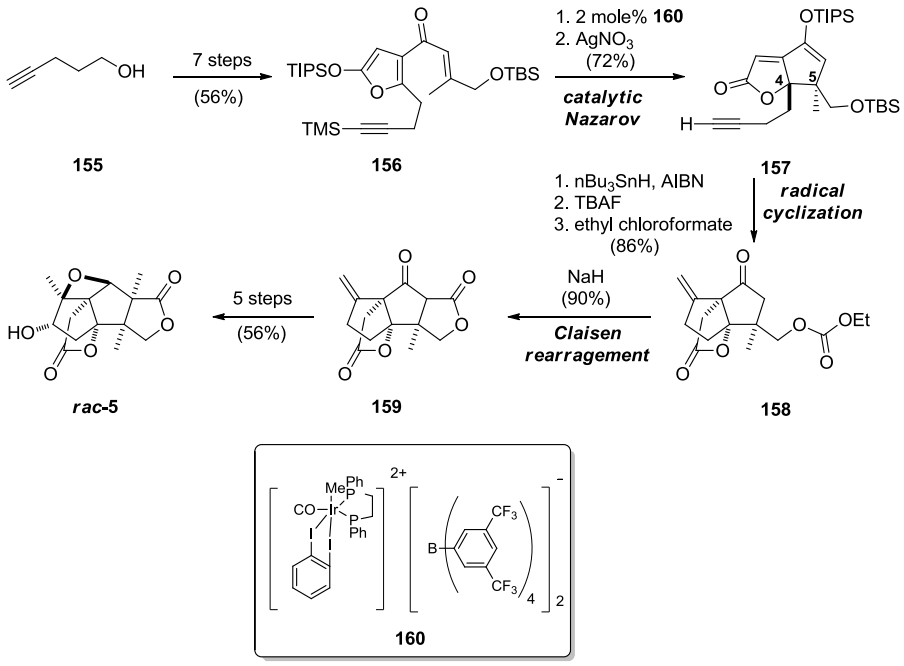


Scheme 3.3.7.3 Total synthesis of (±)-merrilactone A by the Mehta group.

3.3.7.4 Frontier's synthesis

The Frontier group developed a unique approach employing an Ir-catalyzed Nazarov cyclization reaction[74] towards the synthesis of merrilactone A. Starting from alcohol **155**, enone **156** was prepared in 7 steps. The Ir-catalyzed Nazarov cyclization[85,86] constructed compound **157** and simultaneously installed the quaternary carbon centers at C4 and C5 positions. Radical cyclization[87] of **157** generated the

lactone motif **158**. Treatment of **158** with NaH led to the formation of substrate **159** through a cascade of Claisen rearrangement followed by lactonization. Finally, lactone **159** was converted to merrilactone A after several functional group transformations. In summary, Frontier and co-workers accomplished the racemic synthesis of merrilactone A in 18 steps and 17% overall yield.

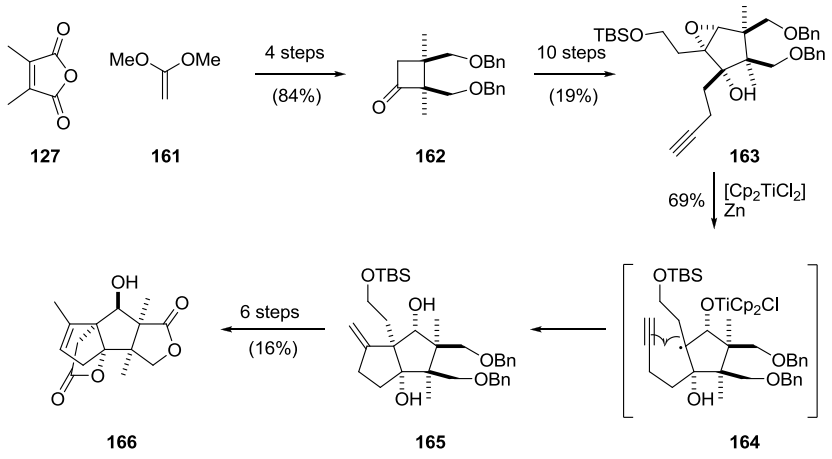


Scheme 3.3.7.4 Total synthesis of (±)-merrilactone A by the Frontier group.

3.3.7.5 Greaney's synthesis

Recently, Greaney and co-workers published a formal synthesis of merrilactone A (Scheme 3.3.7.5).[75] Their synthesis featured a [2+2] photocycloaddition (**161** → **162**), a regioselective Tiffeneau-Demjanov ring expansion[168] (**162** → **163**) and a radical cyclization reaction (**164** → **165**).[89] In the

forward direction, ketone **162** was prepared in 4 steps via [2+2] cyclization between 4,5-dimethylmaleic anhydride (**127**) and dimethylketene acetal (**161**). The Tiffeneau-Demjanov ring expansion followed by Tsuji-Trost decarboxylation-dehydrogenation sequence led to the formation of epoxide **163.** Epoxide **163** then underwent reductive epoxide cleavage followed by radical cyclization to afford *exo*-cyclic olefin **165**. Finally, γ-lactone **166**, prepared in 3 steps from olefin **165**, completed a formal synthesis of merrilactone A. In an overall of 2.4% yield, known intermediate **166** was prepared in 22 steps.



Scheme 3.3.7.5 Formal synthesis of (±)-merrilactone A by the Greaney group.

3.4 Concluding Remarks

Illicium sesquiterpenes occur exclusively in plants of the *Illicium* genus and possess various complex, highly oxygenated fused-ring structures. What is more interesting of these sesquiterpenes is that a number of them have high affinity for receptors associated with neuronal functions. This feature may cause either

neurotoxicity or neurotrophic activity, presumably related to their structure types. Accordingly, these sesquiterpenes have attracted much attention from the synthetic community aiming the development of efficient synthesis that allows readily accessibility to the natural products and their analogues. Over the last 10 years, a great deal of research has been accomplished and several biologically active natural products have been synthesized. However, to date, only limited SAR profile has been charted and many questions still remain unanswered. Thus, the development of even more general strategies is necessary for systematic SAR studies and to identify the unknown biological targets of the neurotrophic sesquiterpenes. The interest in *Illicium* sesquiterpenes is expected to increase in the foreseeable future.

3.4 References

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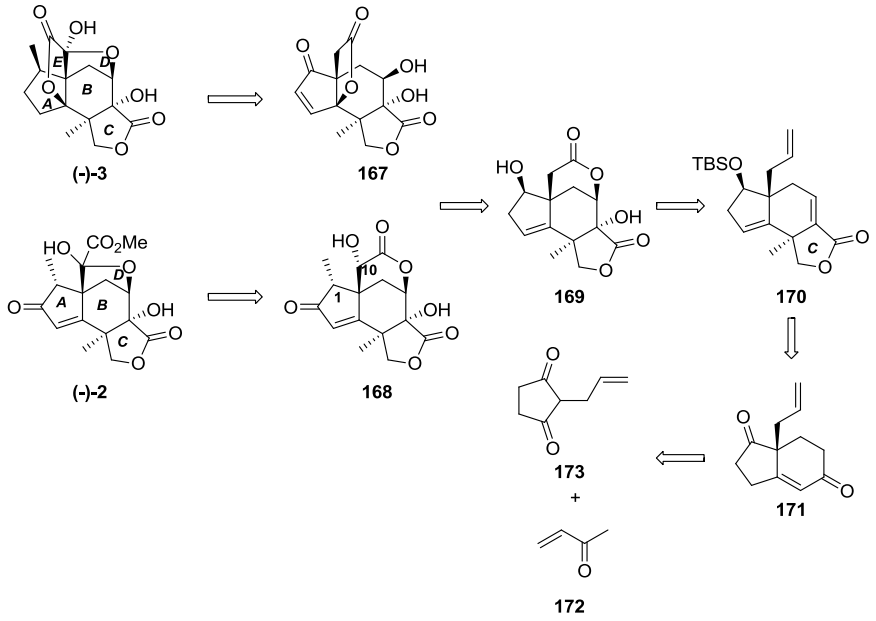
Chapter 4 Total syntheses of (–)-jiadifenolide and (–)-jiadifenin and their biological studies

In the search of new small molecules with neurotrophic modulatory properties, Fukuyama and co-workers isolated three novel pentacyclic sesquiterpenoids from the pericarps of *Illicium jiadifengpi*, same species from which jiadifenin was isolated. The three sesquiterpenoids are jiadifenolide (**3**) and jiadifenoxolanes A (**51**) and B (**52**).[1] All three natural products exhibit the caged seco-prezizaane type structure and can be future categorized to the majucin subtype. Among them, compounds **3** and **51** have shown potent activities in promoting neurite outgrowth in primary cultured cortical neurons at concentrations as low as 10 nM and 1 μM, respectively. The combination of the challenging caged-like motif and intriguing biological properties have invited the development of efficient strategies toward their chemical syntheses. Our goal was to develop an efficient synthetic route that provides readily access to the natural products and analogues of this family in an enantioselective manner; hence, to explore and enhance the biological and pharmacological activities of this family.

4.1 Retrosynthetic analysis

Scheme 4.1 highlights the overall retrosynthetic strategies towards (–)-jiadifenin (**3**)[2] and (–)-jiadifenolide (**2**).[3] Jiadifenolide (**3**) was envisioned to arise from enone **167** through functionalization on the A ring. Enone **167** was to be constructed via translactonization of lactone **169**. The carbon framework of lactone **169** can be traced to the tricyclic motif **170**. Further disconnection across the C ring of

170 suggest the Hajos-Parrish-like[4] diketone **171** as an appropriate synthetic precursor that is available in high enantiomeric purity.[4-9]



Scheme 4.1 Retrosynthetic analysis of (–)-jiadifenin (**2**) and (–)-jiadifenolide (**3**).

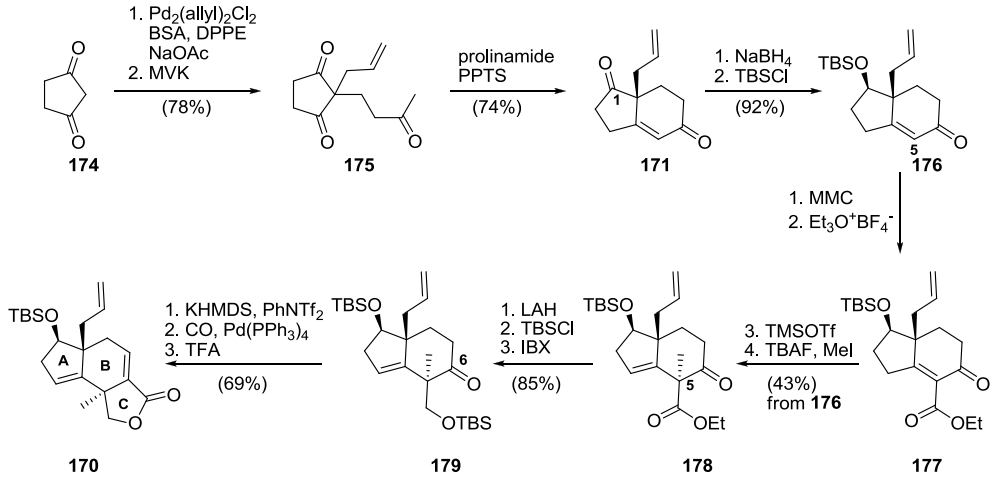
Jiadifenin (**2**), on the other hand, could rise from tetracyclic intermediate **168** via oxidation and hemiacetalization. A sequential diastereoselective C10 hydroxylation and C1 methylation could be used to install the desired functional groups on the jiadifenin framework. Moreover, the A-ring of **168** was projected to arise from selective manipulation at the C1 and C2 centers of motif **169**, a common intermediate found in the jiadifenolide synthesis.

4.2 Total synthesis of (–)-jiadifenolide

4.2.1 Synthesis of the ABC ring system

As depicted in Scheme 4.2.1, our synthetic approach began with the commercially available diketone **174** that was converted into triketone **175** in two steps and 78% yield following reported protocol.[10-12] When triketone **175** was treated with D-prolinamide in the presence of catalytical PPTS,[12] the Hajos-Parrish diketone **171** was generated via an optimized asymmetric aldol condensation. Diketone **171** was produced in a highly enantioselective manner in 74% yield. Regio- and stereoselective reduction of the more electrophilic C1 carbonyl group of **171** and subsequent selective silylation of the resulting alcohol under literature reported procedure[13,14] produced compound **176** in 2 steps and 92% yield. The conversion from **176** to **178** was then accomplished through a sequence of reactions: (1) carboxylation of the C5 enolate with magnesium methyl carbonate[15,16] and (2) subsequent trapping of the resulting carboxylic acid with Meerwein's salt;[17-19] (3) formation of the extended TMS-enolate[20] and (4) subsequent methylation under TBAF/MeI conditions. This sequence of reactions delivered β-*keto* ester **178** as a single isomer containing the C5 quaternary stereocenter in 43% overall yield. Global reduction of **178** followed by selective silylation of the primary alcohol and oxidation at C6 position to afford **179** in 85% yield over three steps. The ketone at C6 position of **179** was then converted to the corresponding vinyl triflate that underwent Pd-catalyzed carbomethoxylation[21,22] to install the necessary carbonyl group for the formation of γ-lactone. Indeed, under acid treatment, desilylation followed by *in situ*

lactonization led to the formation of lactone **170**, which represents the carbon skeleton for the ABC ring system of jiadifenolide.

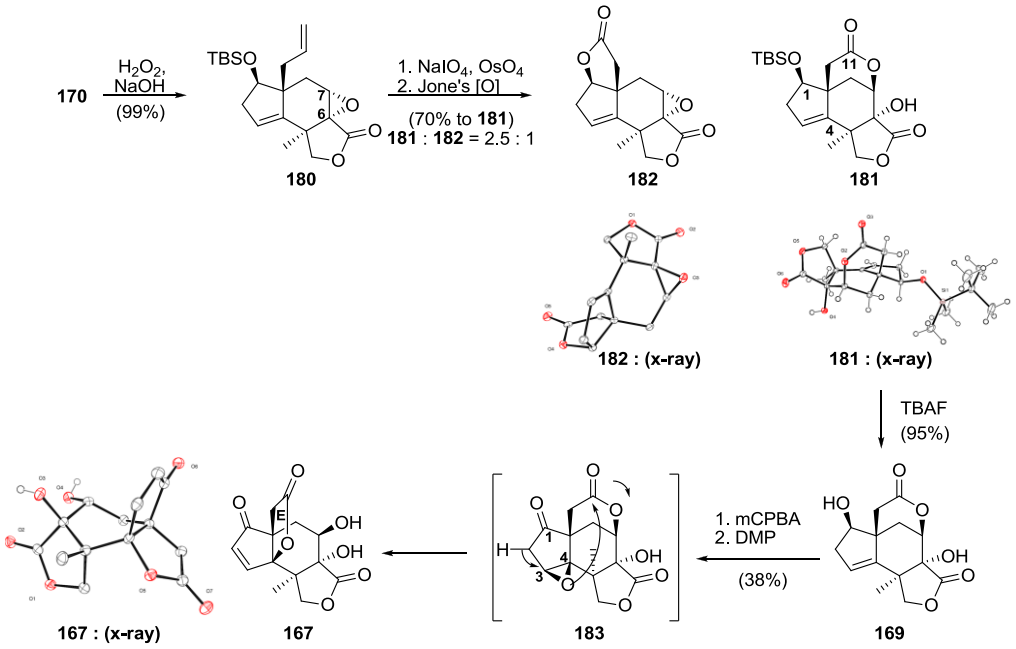


Scheme 4.2.1 Synthesis of ABC ring system of (–)-jiadifenolide.

4.2.2 Synthesis of E ring

The next task was to install the desired C6-C7 *trans*-diol functionality on the tricyclic motif **167** (Scheme 4.2.2). Along these lines, lactone **170** was treated with $NaOH/H_2O_2$ to selectively and quantitatively produce epoxide **180**. We projected that Ru(III)-based[25] direct oxidative cleavage of the terminal alkene into the corresponding carboxylic acid that would trigger a "6-*exo*-tet" epoxide opening[26,27] to furnish the desired lactone **181** in one pot. However, under all reaction conditions explored, this reaction led to only the decomposition of starting material. Instead, we were pleased to find out that the stepwise sequence can achieve the desired conversion. The optimized approach involves (1) oxidative cleavage of the terminal alkene to form the corresponding aldehyde under catalytical OsO_4 in the presence of $NaIO_4$, and (2)

subsequent Jones oxidation to produce the C11 carboxylic acid. Gratifyingly, these conditions triggered the desired "6-*exo*-tet" epoxide opening to produce lactone **181** in 70% overall yield, along with the desilylated by-product **182**. The structure of lactones **181** and **182** were unambiguously confirmed by single-crystal X-ray analysis. Notably, compound **181** represents the core structure of several natural products of *Illicium* species and can be readily produced in multigram scale.



Scheme 4.2.2 Synthesis of E ring via a cascade translactonization reaction.

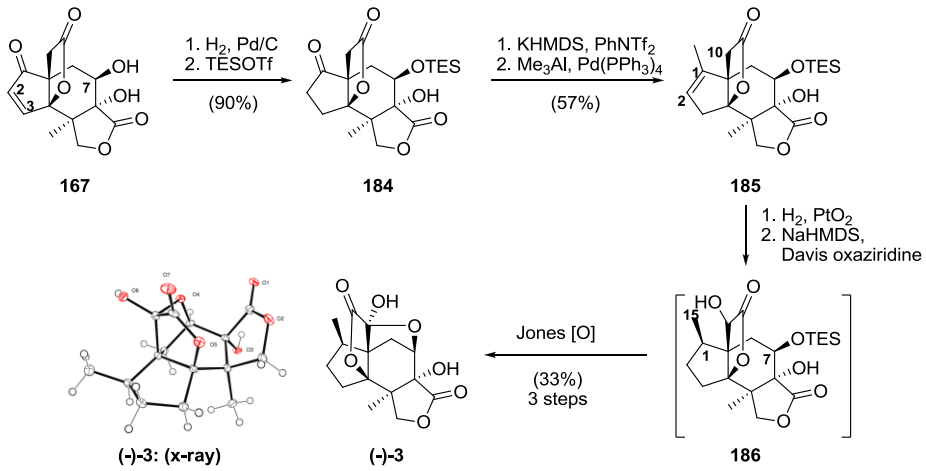
With compound **181** in hand, we sought to introduce a hydroxyl group at C4. To this end, removal of the C1 silyl ether produced alcohol **169**. Epoxidation of the C3-C4 olefin, and subsequent treatment of the resulting epoxide with Dess-Marin periodinane (DMP) gave rise to lactone **167** that contains the desired E ring. The structure of **167** was also confirmed by single crystal X-ray analysis. A reasonable

scenario for the conversion of **169** into **167** can be postulate that the epoxidation was directed by the C1 homoallylic alcohol and occurred from the β face of the A-ring of **169**. Treatment with DMP induced the oxidation at the C1 position to yield the corresponding ketone **183** and generated acid *in situ*. The latter could further induce the formation of C2-C3 enone with concomitant generation of C4 tertiary alcohol, which is in the axial orientation and in close proximity to the C11 carbonyl group, thus triggering the desired translactonization. The driving force to this rearrangement may be due to the formation of a thermodynamically more favored five-membered lactone.

4.2.3. Completion of (-)-jiadifenolide

With enone **167** in hand, we then focused on the final modifications of the A-ring (Scheme 4.2.3). The C2-C3 double bond of **167** was reduced under standard hydrogenation condition. The C7 secondary alcohol was silylated using TESOTf to afford **184**. To install the methyl group at C1 position, various approaches were attempted. All these efforts, Wittig reaction, Tebb's reagent [28,29] or Nysted[30,31] reagent, were unsuccessful, presumably due to the steric hindrance of C1 carbonyl group. Gratifyingly, an alternative strategy based on Pd(0)-mediated cross-coupling was employed. To this end, selective conversion of ketone at C1 position to the corresponding vinyl triflate and subsequent treatment with excess $AlMe_3$ under palladium catalysis[32-34] furnished compound **185** in 57% yield. Eventually, the C1-C2 double bond of **185** was selectively reduced form the α face under high pressure hydrogenation conditions with catalytical PtO_2 to form the corresponding C1-C15 equatorial methyl group. The remaining functionalization at C10 was performed using

conditions employed by the Danishefsky group toward the synthesis of jiadifenin.[23,24] An α-hydroxylation with NaHMDS and Davis oxaziridine,[35,36] producing the α-hydroxy lactone **186** as a single isomer. Without extensive purification, compound **186** was oxidized under Jones conditions that concomitant the desilylation at C7 to produce (–)-jiadifenolide. The synthetic material, thus obtained, possessed identical spectroscopic and analytical properties to those reported for the natural product. The absolute stereochemistry of **3** was confirmed by copper-radiation X-ray analysis, which was in agreement with the original assignment.[1]



Scheme 4.2.3 Completion of (–)-jiadifenolide.

In conclusion, we have accomplished the first enantioselective total synthesis of jiadifenolide in 25 steps and 1.5% overall yield. Key to the strategy is an acid-induced cascade translactonization reaction to form the E ring. The C- and A-rings were produced through Pd(0)-catalyzed carbomethoxylation and Pd(0)-mediated methylation, respectively. The overall approach is enantioselective, efficient and suitable for scale-up. Importantly, the advanced intermediate **169** is readily accessible

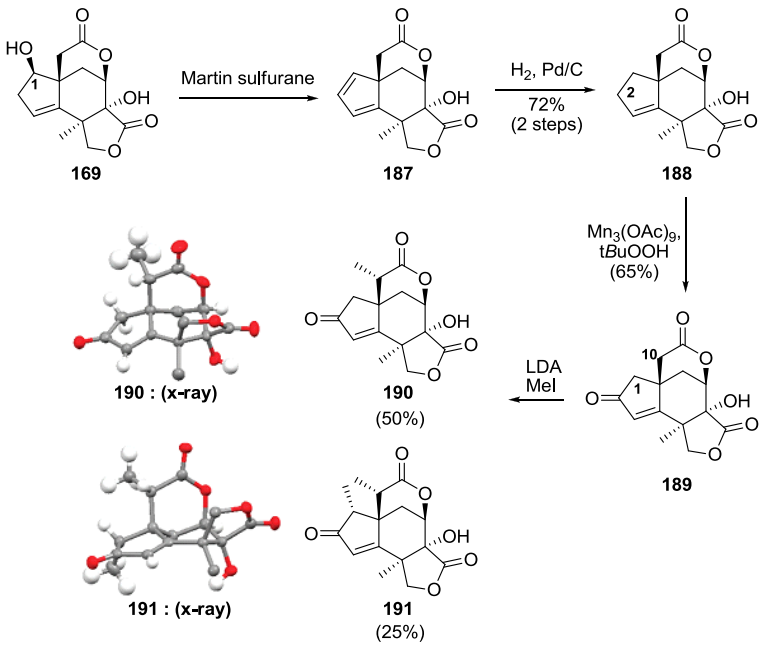
and it represents a significant scaffold for the synthesis of related natural products and analogues.

4.3 Total synthesis of (–)-jiadifenin

The synthetic approach we had followed offered the opportunity to diversify our chemistry towards other members of this family. From the common intermediate **169**, we also completed the first enantioselective total synthesis of jiadifenin.[2]

4.3.1 Synthesis of the carbon framework of jiadifenin

As outlined in Scheme 4.3.1, the elimination of C1 hydroxy moiety of **169** was the first challenge. Various attempts of the C1 deoxygenation under standard or



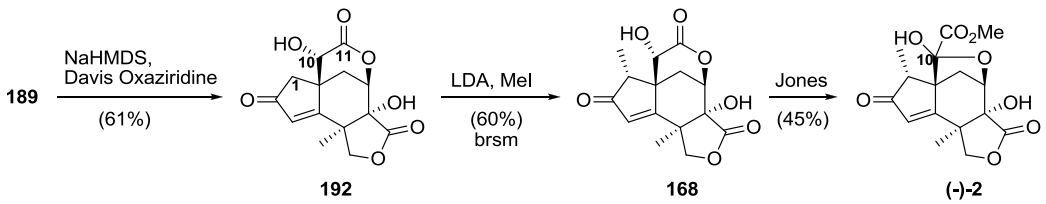
Scheme 4.3.1 Synthesis of carbon framework of jiadifenin.

modified Barton-McCombie conditions[37] proved unsuccessful. Moreover, mesylation of **169** followed by treatment with a variety of bases failed to produce the corresponding alkene **187**. The dehydration finally proceeded smoothly using Martin sulfurane,[38-40] and the derived crude diene **187** was reduced selectively under standard hydrogenation conditions to produce compound **188** in 72% yield over 2 steps.

The ensuing allylic oxidation at the C2 position of **188** proved to be difficult, presumably due to the sensitive six-membered lactone moiety. Several standard or modified conditions were evaluated, including SeO_2,[41] CrO_3/TBHP,[42,43] PDC/TBHP,[44] $PdI(OAc)_2$/TBHP,[45] $Pd(OCOCF_3)_2$/BQ[46] and $Rh_2(cap)_4$/TBHP,[47] but none of them could yield a satisfactory result. Gratifyingly, Mn(III) acetate/TBHP[48] produced trances of **189** after 72 h at ambient temperature. To avoid side reactions and accelerate the desired transformation, the reaction temperature was then raised to 40^{o}C, which significantly improved the yield to 65% and shortened the reaction time to 16 hours. With **189** in hand, we attempted to methylate at the C1 position. We hypothesized that this reaction would install the methyl group α to the enone in a chemoselective fashion. To our surprise, deprotonation followed by treatment of 1.2 equiv. of MeI afforded the C10 methylation adduct. The C1 position could be methylated upon excess amount of MeI, producing the dimethylated product **191**, along with compound **190**. The structures of **190** and **191** were unambiguously confirmed via single crystal X-ray analysis.

4.3.2 Completion of (–)-jiadifenin

On the basis of the observation from the methylation reaction, it became obvious that the C10 center is more sterically accessible than the C1 position. Thus, an alternative sequence for the A-ring functionalization was developed (Scheme 4.3.2). Treatment of **189** with NaHMDS and quenching of the C11 enolate with Davis oxaziridine[35,36] produced α-hydroxylated lactone **192** as a single diastereomer in 61% yield. Alkylation of **192** under LDA/MeI/HMPA conditions furnished the desired C1 methylated product **168** with the desired stereochemistry. Without extensive purification, alcohol **168** was oxidized with Jones reagent,[23,24] which promoted the rearrangement to afford (–)-jiadifenin upon methanolic workup. Jiadifenin was isolated in 45% yield as C10 anomeric mixtures with 2.5:1 ratio. Synthetic jiadifenin was found to have identical spectroscopic and analytical properties and similar optical rotation values as previously reported.



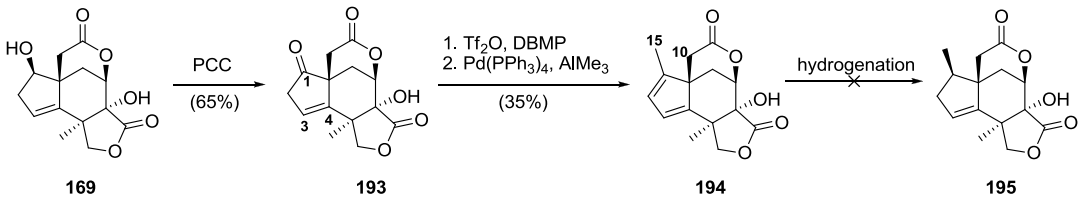
Scheme 4.3.2 Completion of (–)-jiadifenin.

In summary, we accomplished an efficient and enantioselective approach to (–)-jiadifenin. This approach departs from readily available diketone **174** and proceeds in 19 steps and 1% overall yield. The synthesis of jiadifenin has indeed proved the diversity of our synthetic strategy, which paves the way for the synthesis of several

natural products of this family and designed analogues thereof that could shine into the unexplored biological mode of action of these compounds.

4.4 Preparation of analogues

Our laboratory has a longstanding tradition in the synthesis and evaluation of biologically interesting natural products. Upon the complete syntheses of jiadifenin (**2**) and jiadifenolide (**3**), we launched a synthesis-based initiative directed toward the development of lead compounds with potential neurotrophic activity. Along these lines, we aimed to derivatize the synthetic natural product to build a SAR profile through the preparation and evaluation of the structurally modified analogues. To do so, our primary aim was to identify the pharmacophore for this family of natural products. Previous studies from Danishefsky's group demonstrated the superior activity of the pre-arrangement precursor to jiadifenin in neurotrophic acitivity.[23,24] Therefore, we proposed lactone **195** (Scheme 4.4.1) as the pharmacophore.



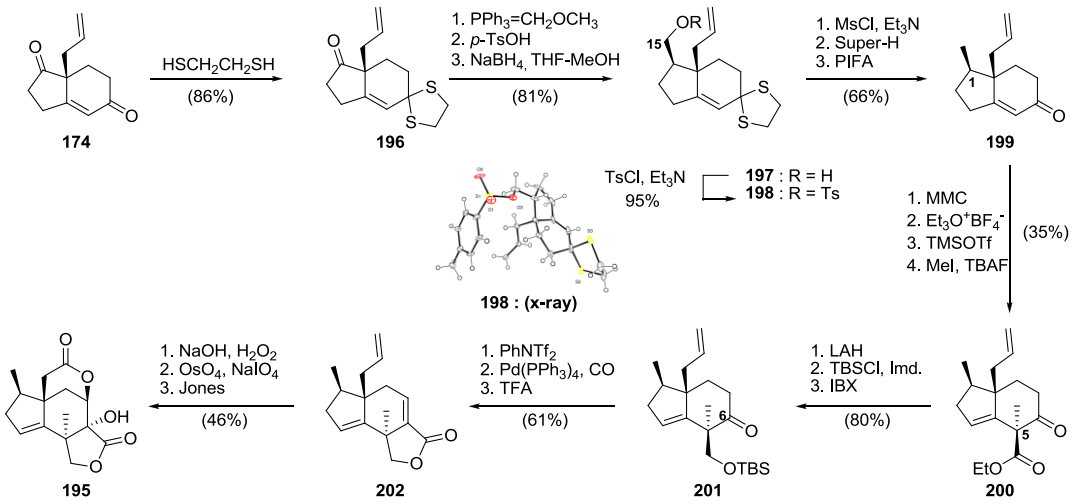
Scheme 4.4.1 Attempts toward the synthesis of pharmacophore **195**.

With advance intermediate **169** in hand, we attempted the synthesis of lactone **195** as illustrated in Scheme 4.4.1. First, the oxidation of C1 hydroxy group was proven to be difficult. To avoid the migration of C3-C4 double bond, various mild

oxidants were explored, from which only a mixture of products were obtained. To our surprise, treatment of **169** with PCC provided the desired ketone in 65% yield. Our next task was to install the C15 methyl group following previously developed protocol, namely, triflation of the C1-ketone followed by Pd(0)-mediated coupling with Me_3Al. However, the triflation reaction was proved to be difficult. Under standard conditions, the triflate was found to form at the C10 position. Only when ketone **193** was treated with 2,6-di-*tert*-butyl-4-methylpyridine in the presence of triflate anhydride,[49] the desired triflate was isolated after 16 hours. Pd(0)-mediated coupling installed the C15 methyl group smoothly. With diene **194** in hand, we attempted the regio- and stereoselective hydrogenation across C1-C2 double bond. To this end, various hydrogenation conditions led to the formation of mixture of mono- and di-reduced products along with their stereoisomers.

The attempt to prepare pharmacophore **195** from lactone **169** was proven to be a fruitless. Therefore, we revised our synthetic strategy to install the C15 methyl group at an early stage of the synthesis. Along this line, diketone **174** was converted to enone **199** using the protocol mortified from previously reported procedure (Scheme 4.4.2).[50] In details, selective protection of enone moiety of diketone **174** produced ketone **196.** Wittig reaction and hydrolysis of the resulting methyl enol ether furnished the formation of the C15-aldehyde**.** The C15-aldehyde was then reduced by $NaBH_4$ in THF-MeOH at -78 ^oC to yield the desired kinetic product **197**. Mesylation, super hydride reduction of resulting mesylate and removal of thioketal led to the formation of enone **199** with desired C15 methyl group. The absolute

stereochemistry at C1 was confirmed via single crystal X-ray analysis of the tosylate derivative **198**.

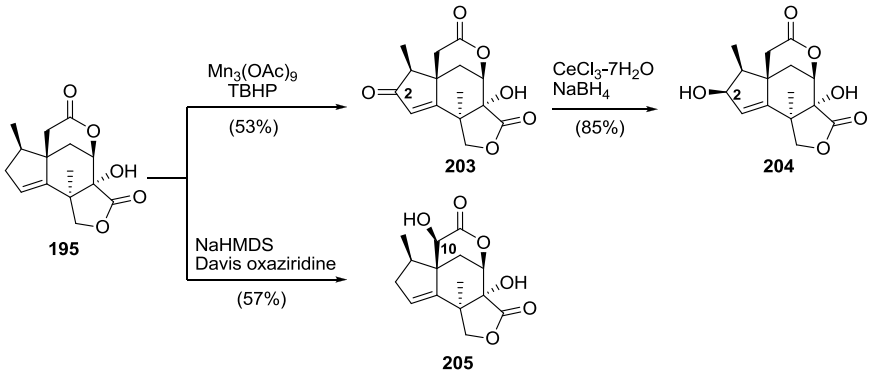


Scheme 4.4.2 Revised synthesis of pharmacophore **195**.

With enone **199** in hand, we followed the synthetic route developed for jiadifenolide to generate the desired pharmacophore smoothly.[3] In details (Scheme 4.4.2), enone **199** was first treated with MMC to provide the C5 carboxylic acid, which was subsequent trapped with Meerwein's salt. Formation of the extended enolate and methylation under mild TBAF condition led to the formation of ester **200** as a single isomer, containing C5 quaternary center. Global reduction of **200** with subsequent selective silylation of the primary alcohol and oxidation of the C6 secondary alcohol produced **201** in 80% yield. The C6 ketone of **201** was converted to the corresponding vinyl triflate under standard conditions. The latter underwent Pd(0)-catalyzed carbomethoxylation, TFA-mediated desilylation-lactonization to produce lactone **202** in 61% yield over three steps. The formation of the γ-lactone

moiety was achieved in three additional steps, (1) selective epoxidation of the enone, (2) selective oxidative cleavage of the terminal olefin and (3) lactone formation under Jones oxidation conditions. Overall, we achieved the synthesis of our target molecule **195** in 18 steps and 5.9% yield from **174**. The synthetic approach is enantioselective, efficient and suitable for scale-up.

To explore the biological profile of this class of compounds, we designed and synthesized several analogues from lactone **195**, as shown in Scheme 4.4.3. Treatment of **195** with Mn(III) acetate/TBHP produced enone **203** after 16 h at ambient temperature.[2] The conversion to **204** was accomplished via Luche reduction in 85% yield from **203**.[23,24] Compounds **203** and **204** were designed to highlight the



Scheme 4.4.3 Synthesis of analogues.

effect of different substituent/oxidation state at C2 position. On the other hand, lactone **195** was treated with NaHMDS and Davis oxaziridine[2,3] to produce α-hydroxylated lactone **205** as single diastereomer isolated in 57% yield. We were

hoping that compound **205** would provide evidence on the effect of hydroxyl group at C10 position.

4.5 Biological evaluations

At this point, we had completed the synthesis of two natural products and several analogues, while a number of advance intermediates had been collected throughout the syntheses. We were at a position to corroborate the claimed neurotrophic activity of the natural products and to begin to map a preliminary SAR profile.

Neurotrophic factors (neurotrophins) are a family of proteins that regulate nervous system development and maintain mature nervous system plasticity and structural integrity.[51,52] Their ability to exhibit neuroprotective properties explains the interest they have received in the context of acute nervous system injury and for the treatment of chronic neurodegenerative diseases. Unfortunately, as a result of their chemical structure, these proteins cannot persist in the body for an extended period and also cannot cross the blood-brain barrier. In contrast, small molecules that are able to mimic neurotrophic factors, or to induce neurotrophic factor biosynthesis, possess a distinct pharmacological advantage and provide an attractive starting point for the development of medicines against various neurodegenerative disorders, including Alzheimer's and Parkinson's disease.[51,53] Both jiadifenin (**2**) and jiadifenolide (**3**) have shown potent activities in promoting neurite outgrowth in primary cultured rat cortical neurons at concentration as low as 0.1 μM and 10 nM,

respectively.[1,54] Although, the use of small molecules with neuronal enhancing characteristics is still in its infancy, it is not inconceivable that, they could be used to medical advantages.

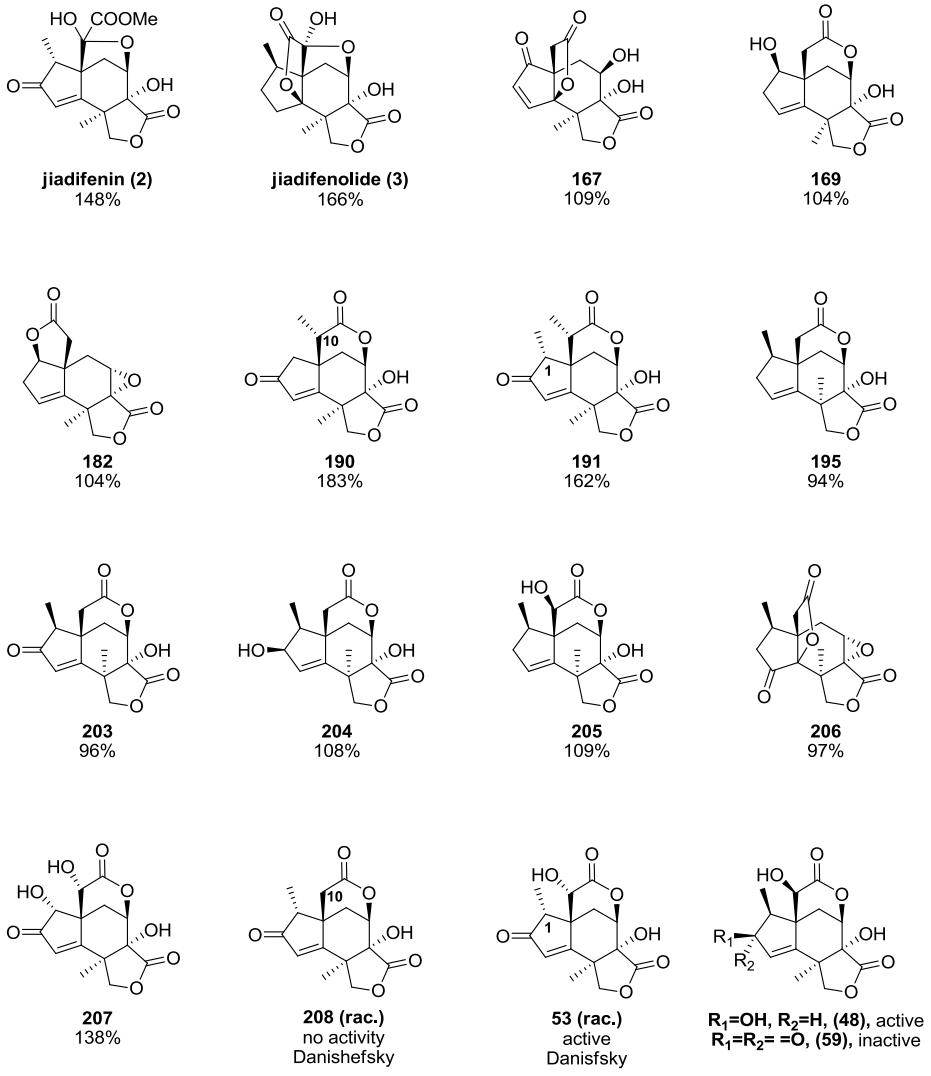


Figure 4.5 Neurite outgrowths relative to DMSO + NGF control.

With the synthetic natural products in hand, our first task was to validate the biological profile of synthetic jiadifenin and jiadifenolide with regard to the

stimulation of NGF-mediated neurite outgrowth using PC12 cellular assay.[23,55] It is well known that the PC12 cell line, derived from rat pheochromocytoma cells, undergoes biochemical and morphological neuronal differentiation into neuron-like cells with elongated outgrowth in response to NGF. This cell line has provided a useful model to study NGF's actions.

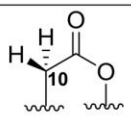
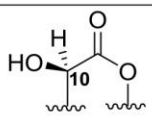
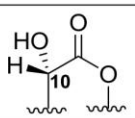
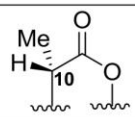
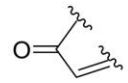
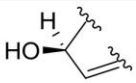
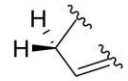
The ability of jiadifenin (**2**) and jiadifenolide (**3**) to promote neurite outgrowth was measured in both the presence and absence of NGF. In the presence of NGF (50 ng/mL), significant increases of neuronal differentiation could be observed upon 72 hour of incubation. The neurite length enhanced by **2** and **3**, at 0.3 μM, were 148% and 166%, respectively, compare to the DMSO + NGF control (Figure 4.5). No neurite outgrowth was observed in the absence of NGF, in agreement with previous findings.[24] This indicates that both jiadifenin and jiadifenolide operate by up-regulating the action of NGF rather than functioning independently.

Our next task was to evaluate the *in vitro* neurotrophic activity of the synthetic analogues to establish a SAR profile. As shown in Figure 4.5, the most active analogue was found to be compound **190**, which enhances neurite outgrowth by 183%. It has a methyl group at C10 position and carbonyl at C2 carbon, and shows superior activity in comparison to the natural products. The C1-methylated analogue **191** also exhibits good activity, promoting neurite outgrowth by 162%.

The preliminary SAR is charted in Table 4.5. Compounds with the absence of a C10 substituent, such as **195, 203**, **204** and **208**, showed no neurotrophic activity.[24]

This observation suggests that a substituent at C10 is essential to the biological activity of these compounds. An oxygen-substituted at C2 carbon was also found to be important for the neurotrophic acitivity. Compound **205**, which is substituted at C10 but lacks oxygenation at C2 carbon, showed no activity. The C1 and C5 bis-hydroxylated analogue **207** was found to be less active than the bis-methylated compound **191**. Interestingly, compound **53** exhibits potent activity while its diastereomer **59** is inactive. This suggests that a complex SAR profile for this family of molecules. Clearly, additional entries will be necessary to chart a systematic SAR profile.

Table 4.5 SAR profile table of jiadifenolide analogues.

				
	**203** Inactive	**59** Inactive	**207/53** Active	**190** Active
	**204** Inactive	**48** Active	None	None
	**195** Inactive	**205** Inactive	None	None

4.6 Concluding Remarks

In summary, at the chemical level, the enantioselective total syntheses of jiadifenin and jiadifenolide have been accomplished. Important chemical transformations are the formation of AB ring system via an asymmetric Robinson annulation reaction; the formation of C-ring through a Pd(0)-catalyzed

carbomethoxylation followed by acid-induced lactonization; and 6-*exo*-tet epoxide opening to form the D-ring lactone; finally, the cascade translactonization to form the E-ring in the synthesis of jiadifenolide. The overall approach is enantioselective, efficient and suitable for scale-up.

At the biological level, we validated the claimed neurotrophic activities of both natural products. A very preliminary SAR has been established but future studies are definite necessary. Already it has been found that C10 must appear substituted and C2 must be in its oxidized forms. It seems that synthetic analogues could exceed the natural products in their neurite outgrowth activity. However, large questions still remain to be answered: what is the mechanism or action of this class of compounds? Future studies designed to address these questions are currently among the mission of our laboratory.

Chapter 4, in part, is reprint of the material as it appears in Enantioselective synthes of (-)-jiadifenin, a potent neurotrophic modulator in Organic Letter, 2011. Trzoss, Lynnie L.; Xu, Jing; Lacoske, Michelle H.; Mobley, William C., 2011. The dissertation author was the primary investigator and author of this paper.

Chapter 4, in part, is reprint of the material as appears in Enantioselective total synthesis of (-)-jiadifenolide in Angewandte Chemie International Edition, 2011. Xu, Jing; Trzoss, Lynnie L.; Chang, Weng K., 2011. The dissertation author was the primary investigator and author of this paper.

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(56) CCDC-807620 (**181**), 8073241 (**167**), 807950 (**3**), 831791 (**190**) and 831792 (**191**) contain the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

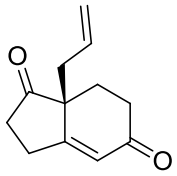
4.8 Experimental techniques and characterization data

General Procedures

Unless indicated, all commercial available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2) and dimethylformamide (DMF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using hexane-EtOAc or CH_2Cl_2-MeOH mixtures of increasing polarity. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F_{254} to a thickness of 0.5 mm (Merck). ^{13}C NMR and ^{1}H NMR spectra were recorded on either 400 MHz/500 MHz Varian instrument or a 500 MHz JEOL instrument. $CDCl_3$

was treated with flame dried K_2CO_3, chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak ($CHCl_3$ or CD_3OD), with the abbreviations s, br s, d, t, q, and m denoting singlet, broad singlet, doublet, triplet, quartet and multiplet respectively. *J* = coupling constants given in Hertz (Hz). High resolution Mass spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade $CHCl_3$ (dried over molecular sieves) or anhydrous MeOH.

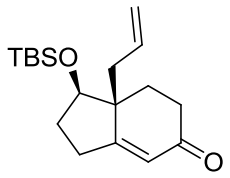
Experimental procedures



171

171: To a solution of **175** (36.0 g, 0.17 mol) in dry MeCN (600 mL) was added D-prolinamide (5.92 g, 52.0 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (13.0 g, 52.0 mmol). This solution was warmed up to 40 ºC for 14 days before it was cooled to RT and quenched with water (300 mL). The mixture was extracted with EtOAc (3 x 500 mL), dried over Na_2SO_4, concentrated and loaded on a short silica pad and washed thoroughly with EtOAc and concentrated under reduced pressure to afford **171** as a yellow oil (22.0 g, 74%) in good purity and was used to next step directly. A pure sample of **171** was purified via silica flash column chromatography (hexanes:EtOAc = 20:1 to 1.5:1) to afford a colorless oil. (*ee* > 90%); R_f = 0.38 (silica gel, hexanes:EtOAc = 2:1); $[\alpha]_D^{23}$ – 288.2 (*c* 1.0, $CHCl_3$);

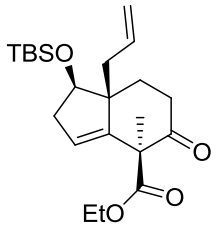
All the spectroscopic data are in the agreement with the reported data. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (br s, 1H), 5.72 (m, 1H), 5.14 (m, 2H), 2.93 (m, 1H), 2.79 (m, 1H), 2.66 (m, 1H), 2.55-2.36 (m, 5H), 2.23 (m, 1H), 1.76 (m, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 215.8, 198.2, 169.1, 131.8, 124.7, 119.8, 52.7, 39.0, 36.2, 32.6, 27.3, 27.3; HRMS (ESI) m/e 191.1067 [$M+H^+$] calcd for $C_{12}H_{15}O_2^+$: 191.1068.



176

176: The enone **171** (21.0 g, 0.11 mol) was dissolved in absolute ethanol (220 mL), $NaBH_4$ (1.05 g, 27.6 mmol) was added portionwise at 0 ºC and the reaction was stirred for 30 min. Then this reaction was carefully quenched with saturated NH_4Cl solution (100 mL) and the solvent was removed under reduced pressure. The mixture was extracted with EtOAc (3 x 200 mL), dried over Na_2SO_4 and concentrated. The crude alcohol was then dissolved in dry DMF (220 mL) and was cooled to 0 ºC. To this solution NH_4NO_3 (26.4 g, 0.33 mol) was added followed by TBSCl (33.2 g, 0.22 mol). The reaction was then warmed up to RT for 12 h before it was quenched with saturated NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (3 x 200 mL), dried over Na_2SO_4 and concentrated. The crude product was then purified by silica flash column chromatography (hexanes:EtOAc = 100:1 to 10:1) to afford the product **176** as light yellow solid (31.1 g, 92% over 2 steps). R_f = 0.67 (silica gel, hexanes:EtOAc = 4:1); $[\alpha]_D^{24}$ – 72.0 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (m, 1H),

5.82 (br s, 1H), 5.06 (d, *J* = 14.7 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 3.81 (t, *J* = 7.8 Hz, 1H), 2.64 (m, 1H), 2.58-2.45 (m, 2H), 2.37 (m, 1H), 2.30-2.21 (m, 3H), 2.00 (m, 1H), 1.84 (m, 1H), 1.69 (m, 1H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 173.6, 136.2, 124.2, 117.0, 82.3, 48.8, 36.4, 33.5, 33.4, 30.0, 27.3, 26.0, 18.1, -4.5, -4.8; HRMS (ESI) m/e 307.2089 [M+H$^+$] calcd for $C_{18}H_{31}O_2Si^+$: 307.2088.

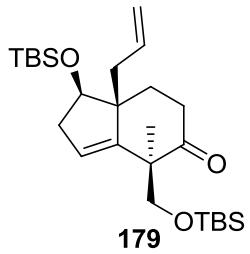


178

178: To a solution of **176** (17.0 g, 55.5 mmol) in anhydrous DMF (110 mL) was added magnesium methyl carbonate (111 mL, 0.22 mol, 2.0 M in DMF). This solution was degassed for 5 min under argon, then immersed in an oil bath which was pre-heated to 130 ºC and stirred for 3 h. The reaction was cooled to 0 ºC and poured in to a mixture of ice/2N HCl (300 mL). Then this mixture was acidified to pH = 2~3 with 2N HCl. Ether (500 mL) was added to form a two-phase clear solution. The aqueous phase was separated and it was re-extracted with ether (2 x 500 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure at 30 ºC. The residue was dried on high-vacuum pump for 1 h to remove the trace of DMF to afford a yellow solid. This solid was dissolved in dry CH_2Cl_2 (100 mL), triethyloxonium tetrafluoroborate (50.0 mL, 50.0 mmol, 1 M in CH_2Cl_2) was added at 0 ºC, then DIPEA (13.1 mL, 75.0 mmol) was added

dropwise. After 1 minute, TLC showed that the completion of this reaction. Then this reaction was quenched with saturated NH4Cl solution (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The unstable crude product was passed through a short silica pad (hexanes:EtOAc = 6:1, 2000 mL), concentrated and dried on high-vacuum pump and was used to next step directly. To a solution of this crude ester **177** (20.0 g, ~ 55.5 mmol) in dry CH_2Cl_2 (200 mL) was added 2,6-lutidine (13.1 mL, 111 mmol) at 0 ºC, followed by addition of TMSOTf (13.0 mL, 72.0 mmol) dropwise. After 30 min, the reaction was diluted with hexanes (500 mL), quenched with 5% $NaHCO_3$ solution (200 mL), extracted with hexanes (3 x 300 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further dried on high-vacuum pump for 10 min. The unstable crude TMS-enol ether was dissolved in dry THF (200 mL), cooled to -78 ºC, methyl iodide (17.0 mL, 0.27 mol) was added in, followed by addition of TBAF solution dropwise (55.5 mL , 55.5 mmol, 1M in THF). This reaction was then allowed to warm to RT slowly over 30 min, and stirred at RT for extra 2 h before it was quenched with saturated NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (3 x 200 mL), the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 10:1) to afford **178** as a yellow oil (9.33 g, 43% over 2 steps). R_f = 0.70 (silica gel, hexanes:EtOAc = 6:1); $[\alpha]_D^{23}$ – 91.3 (*c* 1.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (m, 1H), 5.72 (t, *J* = 2.3 Hz, 1H), 5.02 (d, *J* = 16.6 Hz, 1H), 4.96 (d, *J* = 10.3 Hz, 1H), 4.19 (m,

1H), 4.10 (m, 1H), 4.03 (t, *J* = 8.7 Hz, 1H), 2.81 (m, 1H), 2.44-2.30 (m, 5H), 2.07 (m, 1H), 1.53 (m, 1H), 1.47 (s, 3H), 1.25 (t, *J* = 12.5 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 172.0, 145.4, 136.4, 125.9, 116.5, 82.9, 61.9, 58.9, 50.8, 39.8, 36.5, 36.2, 34.4, 26.0, 19.8, 18.2, 14.0, -4.4, -4.8; HRMS (ESI) m/e 393.2458 [M+H$^+$] calcd for $C_{22}H_{37}O_4Si^+$: 393.2456.



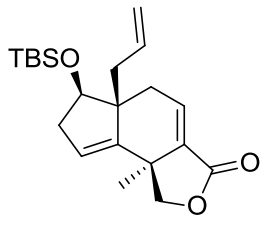
179

179: To a solution of **178** (17 g, 43 mmol) in dry THF (200 mL) was added $LiAlH_4$ solution (165 mL, 0.32 mol, 2M in THF) at 0 ºC. This reaction was stirred for 30 min before it was carefully quenched with 2N NaOH solution (200 mL). The mixture was taken with EtOAc (200 mL) and filtrated through Celite® and washed thoroughly with EtOAc (1000 mL). The organic phase was separated and the aqueous phase was re-extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude diol was used to next step directly.

The crude diol was dissolved in CH_2Cl_2 (200 mL) and was cooled to 0 ºC. Imidazole (5.37 g, 80.0 mmol) was added in followed by the adding of TBS-Cl solution (6.78 g, 45.0 mmol) in CH_2Cl_2 (20 mL) slowly. After 30 min, this reaction was quenched with saturated NH_4Cl solution (200 mL), extracted with CH_2Cl_2 (3 x 200 mL), washed with brine and dried over Na_2SO_4, then concentrated under reduced

pressure. The crude mono-TBS- ether was used to next step directly.

The crude mono-TBS-ether was dissolved in dry DMSO (200 mL), IBX (33.6 g, 0.12 mol) was added in and this reaction was heated to 80 ºC for 1 h. Upon completion, the reaction was cooled to RT and water (200 mL) was added in and the reaction was filtered through Celite®, the filtrates were extracted with EtOAc (3 x 200 mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 20:1) to afford **179** as a white solid (17.4 g, 85% over 3 steps). R_f = 0.32 (silica gel, hexanes:EtOAc = 20:1); $[\alpha]_D^{23}$ -22.1 (*c* 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.51 (br s, 1H), 5.04 (d, *J* = 18.4 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.01 (t, *J* = 8.6 Hz, 1H), 3.73 (d, *J* = 9.7 Hz, 1H), 3.65 (d, *J* = 9.7 Hz, 1H), 2.58-2.45 (m, 3H), 2.32 (m, 3H), 2.00 (m, 1H), 1.17 (s, 3H), 1.16 (m, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.05 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 149.0, 136.9, 123.7, 116.3, 83.3, 69.6, 55.1, 50.4, 39.7, 36.4, 35.8, 34.0, 26.0, 25.9, 20.7, 18.5, 18.2, -4.5, -4.7, -5.4, -5.4; HRMS (ESI) m/e 465.3219 [$M+H^+$] calcd for $C_{26}H_{49}O_3Si_2^+$: 465.321.



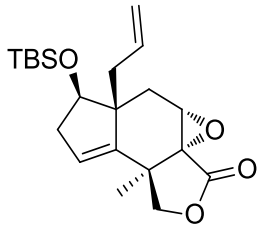
170

170: To a solution of ketone **179** (10.5 g, 22.6 mmol) in dry THF (200 mL)

was added in KHMDS (226 mL, 113 mmol, 0.5 M in Toluene) dropwise at – 78 ºC and stirred for 30 min. A solution of $PhNTf_2$ (24.2 g, 67.8 mmol) in THF (50 mL) was added in and the reaction was stirred for 30 min at the same temperature before it was warmed up to RT over 30 min. The reaction was quenched by solution with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phase was washed with brine and dried over Na_2SO_4, concentrated under reduced pressure and purified via silica flash column chromatography (hexanes:EtOAc = 100:1) to afford the vinyl triflate as a white solid (11.5 g, 86%).

The vinyl triflate obtained above (11.5 g, 19.4 mmol) was dissolved in DMF/MeOH (150 mL/50 mL, 3:1), $Pd(PPh_3)_4$ (224 mg, 0.19 mmol) and triethylamine (8.10 mL, 58.1 mmol) was added. This orange solution was degassed under argon atmosphere for 5 min, followed by bubbling in carbon monoxide for 5 min. This solution was then heated to 50 ºC for 2 h under carbon monoxide atmosphere before it was concentrated under reduced pressure. The residue was passed through a short silica pad (hexanes:EtOAc = 50:1, 2000 mL), concentrated and re-dissolved in dry CH_2Cl_2 (200 mL), TFA (2.94 mL, 38.4 mmol) was added in and this reaction was stirred at RT for 5 h before it was quenched with saturated $NaHCO_3$ solution (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic phase was washed with brine and dried over Na_2SO_4, concentrated under reduced pressure and purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 10:1) to afford the lactone **170** as a white solid (5.62 g, 80%; 69% over two steps). R_f = 0.20 (silica gel,

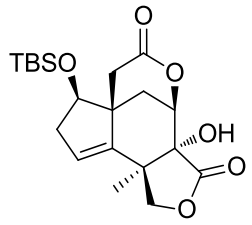
hexanes:EtOAc = 20:1); $[\alpha]_D^{23}$ – 1.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 7.9 Hz, 3.0 Hz, 1H), 5.86 (m, 1H), 5.64 (br s, 1H), 4.90 (d, *J* = 13.2 Hz, 1H), 4.87 (d, *J* = 19.1 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 4.10 (t, *J* = 9.8 Hz, 1H), 3.99 (d, *J* = 8.3 Hz, 1H), 2.56 (dd, *J* = 15.6 Hz, 7.8 Hz, 1H), 2.47 (m, 1H), 2.36 (m, 1H), 2.19 (m, 2H), 1.95 (dd, *J* = 16.1 Hz, 3.0 Hz, 1H), 1.32 (s, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 147.8, 136.6, 135.0, 134.7, 124.3, 116.6, 82.5, 76.3, 54.8, 41.7, 40.1, 37.0, 35.8, 27.5, 25.9, 18.2, -4.4, -4.7; HRMS (ESI) m/e 361.2196 [M+H$^+$] calcd for $C_{21}H_{33}O_3Si^+$: 361.2193.



180

180: To a solution of **170** (4.70 g, 13.0 mmol) in MeOH (100 mL) was added a pre-mixed solution of 3N NaOH (13 mL) and 30% H_2O_2 (13 mL) dropwise at 0 ºC. This reaction was warmed up to RT and vigorous stirred for 5 h. The mixture was then diluted with water, acidified with 2N HCl to pH = 1, separated with EtOAc/brine (200mL/200mL) and the aqueous phase was extracted with EtOAc (2 x 200 mL). The organic phase was combined, dried over Na_2SO_4 and concentrate under reduced pressure to afford **180** (4.86 g, 99%) as a white solid. The obtained epoxide **180** was pure enough to use without further purification. R_f = 0.18 (silica hexanes:EtOAc = 20:1); $[\alpha]_D^{22}$ + 9.0 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.70 (m, 1H), 5.03 (m, 2H), 4.34 (d, *J* = 8.8 Hz, 1H), 4.17 (d, *J* = 9.3

Hz, 1H), 3.94 (t, *J* = 9.8 Hz, 1H), 3.61 (dd, *J* = 6.3 Hz, 2.4 Hz, 1H), 2.52-2.40 (m, 3H), 2.28-2.20 (m, 2H), 1.39 (m, 1H), 1.38 (s, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 143.3, 135.8, 126.3, 117.7, 82.1, 75.6, 61.4, 58.5, 52.5, 40.6, 39.0, 38.2 40.6, 39.0, 38.2, 37.5, 26.0, 21.8, 18.2, -4.3, -4.7; HRMS (ESI) m/e 399.1960 [M+Na^+] calcd for $C_{21}H_{32}O_4SiNa^+$: 399.1962.

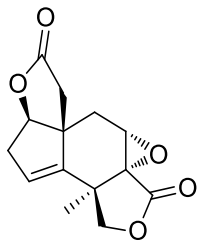


181

181: Epoxide **180** (6.25 g, 16.6 mmol) was dissolved in 1,4-dioxane (180 mL) and water (60 mL). To this solution 2,6-lutidine (3.84 mL, 33.2 mmol), OsO_4 (1.05 mL, 4% solution in H_2O, 0.166 mmol) was added, then $NaIO_4$ (14.4 g, 66.4 mmol) was added portionwise at 0 ºC. This reaction was then warmed up to RT and stirred for 12 h. The reaction was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the aldehyde as a white solid, which was clean enough to be used for next reaction.

To a solution of the aldehyde obtained above (~ 6.2 g, 16.4 mmol) in acetone (400 mL) was added Jones reagent (37.0 mL, 98.4 mmol, 2.67 M) dropwise at 0 ºC, and this reaction was stirred at 0 ºC for 30 min. Ethanol (50 mL) was carefully dropped in to quench this reaction, followed by dropping the saturated $NaHCO_3$ solution (50 mL). The mixture was stirred for 5 min before it

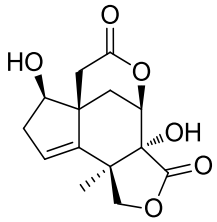
was filtrated through Celite®, and the filter cake was then washed thoroughly with EtOAc (1000 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified via column chromatography (hexanes:CH_2Cl_2 = 1:1 to 1:3 to 100% CH_2Cl_2, then CH_2Cl_2:MeOH =200:1 to 50:1) afford the product **181** as a white solid (4.58 g, 70% over 2 steps), and side product **182** (1.64 g, 25% over 2 steps) as a white solid. For product **181**, R_f = 0.48 (silica gel, hexanes:EtOAc = 2:1); $[\alpha]_D^{22}$ – 2.6 (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.65 (dd, *J* = 4.4 Hz, 1.5 Hz, 1H), 4.06 (t, *J* = 7.8 Hz, 1H), 3.97 (d, *J* = 9.8 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.02 (d, *J* = 19.1 Hz, 1H), 2.51- 2.43 (m, 2H), 2.20 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.32 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 170.2, 144.1, 126.5, 79.3, 79.3, 76.8, 76.3, 45.4, 42.5, 37.6, 36.7, 29.6, 25.9, 21.6, 18.1, -4.3, -4.7; HRMS (ESI) m/e 395.1886 [M+H$^+$] calcd for $C_{20}H_{31}O_6Si^+$: 395.1884.



182

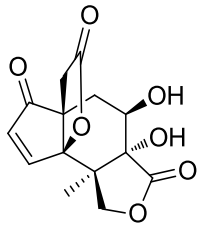
182: $[\alpha]_D^{22}$ – 41.8 (*c* 0.5, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (m, 1H), 4.76 (dd, *J* = 6.0 Hz, 2.4 Hz, 1H), 4.27 (d, *J* = 3.6 Hz, 2H), 3.73 (dd, *J* = 4.8 Hz, 2.0 Hz, 1H), 2.92 (m, 1H), 2.78 (d, *J* = 14.4 Hz, 1H), 2.69- 2.62 (m, 2H), 2.49 (dd, *J* = 11.6 Hz, 1.2 Hz, 1H), 1.73 (dd, *J* = 11.6 Hz, 2.0 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 171.5, 141.1, 128.6, 86.8, 74.5, 62.1, 57.4, 53.8,

39.0, 38.8, 38.2, 36.5, 21.3; HRMS (ESI) m/e 263.0873 [M+H$^+$] calcd for $C_{14}H_{16}O_5^+$: 263.0841.



169

169: To a solution of **181** (3.95 g, 10.0 mmol) in THF (100 mL) was added TBAF solution (20.0 mL, 20.0 mmol, 1 M in THF) dropwise at RT, then this reaction was stirred at RT for 30 min. pH = 7 buffer solution (20 mL) was added to quench this reaction, and the mixture was diluted with EtOAc (1000 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 100:1 to 20:1) afford the product **169** as a white foam (2.66 g, 95%). R_f = 0.70 (silica gel, CH_2Cl_2:MeOH = 5:1); $[\alpha]_D^{23}$ – 38.1 (*c* 0.67, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.85 (m, 1H), 4.70 (dd, *J* = 4.6 Hz, 1.7 Hz, 1H), 4.02 (t, *J*= 7.9 Hz, 1H), 3.99 (d, *J* = 10.3 Hz, 1H), 3.72 (d, *J* = 9.7 Hz, 1H), 2.95 (d, *J* = 18.9 Hz, 1H), 2.52-2.41 (m, 2H), 2.24-2.14 (m, 2H), 1.91 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.4, 171.4, 144.6, 126.1, 79.7, 78.3, 76.6, 75.3, 44.8, 42.2, 36.1, 36.0, 29.0, 20.5; HRMS (ESI) m/e 281.1021 [M+H$^+$] calcd for $C_{14}H_{17}O_6^+$: 281.1020.

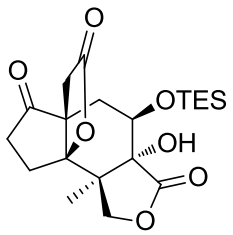


167

167: To a solution of **169** (870 mg, 3.10 mmol) in THF (30 mL) was added *m*CPBA (3.20 g, 13 mmol, ~ 70%) portionwise and warmed up to 50 ºC for 3 h. This mixture was then cooled to RT and quenched with saturated $NaHCO_3$ solution/saturated $Na_2S_2O_3$ solution (10mL/10mL). Then the mixture was diluted with EtOAc (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The afforded crude epoxide was used to next step directly.

This crude epoxide (~ 3 mmol) was diluted with acetone (30 mL), sonicated for 10 min, and the Dess-Martin-Periodinane (2.54 g, 6 mmol) was added. This reaction was stirred vigorously (sonication was applied in larger scale) at RT for 2 h and quenched with saturated $NaHCO_3$ solution/saturated $Na_2S_2O_3$ solution (10mL/10mL). Then the mixture was diluted with EtOAc (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 100:1 to 20:1) afford the product **167** as a white solid (346 mg, 38%). R_f = 0.50 (silica gel, CH_2Cl_2:MeOH = 20:1 x 2 times); $[\alpha]_D^{23}$ – 13.1 (*c* 0.40, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, *J* = 5.9 Hz, 1H), 6.52 (d, *J* = 5.9 Hz, 1H), 4.49 (d, *J* = 9.8 Hz, 1H), 4.02 (d, *J* = 9.8 Hz, 1H), 3.69 (dd, *J* = 9.8 Hz, 3.9 Hz, 1H), 3.21 (d, *J* = 19.0 Hz, 1H), 2.86 (d, *J* = 19.1 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.41

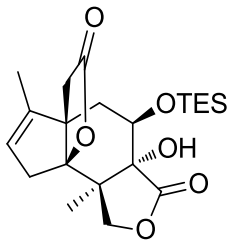
(s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 209.1, 177.5, 174.8, 160.5, 136.2, 93.3, 80.1, 74.9, 72.9, 52.1, 49.5, 39.8, 34.1, 19.4; HRMS (ESI) m/e 317.0634 [M+Na^+] calcd for $C_{14}H_{14}O_7Na^+$: 317.0633.



184

184: A pressure glass reactor was filled with **167** (294 mg, 1.00 mmol), MeOH (5 mL) and palladium (53.0 mg, 5 mol%, 10% on charcoal), then this reactor was loaded on a shaking-hydrogenator and was shaken under hydrogen atmosphere (6 bar) at RT for 24 h. The pressure was released slowly and the mixture was filtered through a short silica pad. The filter pad was washed with MeOH (5 x 20 mL), and the combined filtrates were concentrated to afford the corresponding reduced ketone, then it was dissolved in THF (5 mL), 2,6-lutidine (463 µL, 4.00 mmol) was added followed by TESOTf (452 µL, 2.00 mmol) at 0 ºC. This reaction was then allowed to warm up to RT and stirred for 30 min before it was quenched with saturated $NaHCO_3$ solution (5 mL). This mixture was diluted with EtOAc (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 200:1 to 50:1) afford the product **184** as a colorless oil (369 mg, 90%). R_f = 0.85 (silica gel, CH_2Cl_2:MeOH = 20:1); $[\alpha]_D^{23}$ – 8.5 (*c* 1.32, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.36 (d, *J* = 9.8 Hz, 1H), 4.10 (m, 1H), 3.90 (d, *J* = 8.6 Hz, 1H), 3.51 (d, *J* = 18.9 Hz,

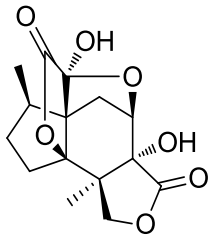
1H), 2.75 (d, *J* = 18.9 Hz, 1H), 2.56-2.35 (m, 3H), 2.25 (m, 1H), 1.95 (dd, *J* = 15.5 Hz, 3.5 Hz, 1H), 1.81 (dd, *J* = 14.9 Hz, 2.9 Hz, 1H), 1.33 (s, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.65 (q, *J* = 8.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 217.9, 177.6, 174.2, 93.1, 79.3, 72.8, 72.2, 53.6, 47.4, 37.4, 32.8, 28.2, 27.3, 17.2, 5.8, 4.1; HRMS (ESI) m/e 433.1655 [M+Na^+] calcd for $C_{20}H_{30}O_7SiNa^+$: 433.1653.



185

185: To a solution of **184** (41.0 mg, 0.10 mmol) in dry THF (600 µL) was added KHMDS (150 µL, 0.15 mmol, 1 M in THF) at –78 ºC and stirred for 30 min, then a solution of Comins reagent (*N*-(5-chloro-2-pyridyl)triflimide, 34.2 mg, 0.11 mmol) in THF (200 µL) was added in dropwise and stirred for another 30 min at –78 ºC before it was warmed up to RT and stirred for another 30 min. This reaction was then quenched with saturated NH_4Cl solution (500 µL), diluted with EtOAc (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (hexanes:EtOAc = 50:1 to 4:1) to afford the corresponding vinyl triflate as light colorless oil (34.7 mg, 64%). This vinyl triflate (34.7 mg, 0.064 mmol) was then dissolved in dry THF (300 µL), $Pd(PPh_3)_4$ (37.0 mg, 0.032 mmol) was added in, followed by a solution of $AlMe_3$ (640 µL, 1.28 mmol, 2M in hexanes). This reaction was stirred at RT for 2 h before it was carefully quenched with saturated $NaHCO_3$ solution (500 µL). This

mixture was diluted with EtOAc (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (hexanes:EtOAc = 50:1 to 4:1) to afford the **185** as light colorless oil (23.3 mg, 89%; 57% over 2 steps). R_f = 0.37 (silica gel, hexanes:EtOAc= 3:1); $[\alpha]_D^{23}$ + 9.6 (*c* 1.40, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.37 (br s, 1H), 4.38 (d, *J* = 8.6 Hz, 1H), 3.94 (dd, *J* = 6.9 Hz, 3.5 Hz, 1H), 3.88 (d, *J* = 9.2 Hz, 1H), 3.23 (d, *J* = 18.9 Hz, 1H), 2.74 (m, 1H), 2.70 (d, *J* = 18.9 Hz, 1H), 2.55 (d, *J* = 17.8 Hz, 1H), 2.07(dd, *J* = 14.9 Hz, 6.9 Hz, 1H), 1.78 (dd, *J* = 14.9 Hz, 3.4 Hz, 1H), 1.69 (br s, 3H), 1.28 (s, 3H), 0.97 (t, *J* = 8.1 Hz, 9H), 0.64 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.0, 175.8, 142.6, 121.1, 96.0, 79.6, 73.3, 72.8, 54.3, 47.8, 40.8, 37.4, 32.9, 18.1, 10.7, 5.8, 4.2; HRMS (ESI) m/e 431.1864 [M+Na^+] calcd for $C_{21}H_{32}O_6SiNa^+$: 431.1860.



(-)-3

(–)-3 : A high pressure steel autoclave equipped with magnetic stir bar was filled with olefin **185** (20.0 mg, 0.049 mmol), platinum dioxide (2.2 mg, 9.8 μmol) and MeOH (2.0 mL). The autoclave was pressurized to 90 atm with H_2 and the suspension was vigorously stirred at RT for 24 h. The pressure was released slowly and the mixture was filtered through a short silica pad. The filter pad was washed with MeOH (5 x 10 mL), and the combined filtrates were concentrated to

afford the crude reduced product with some inseparable impurities. This crude mixture (~ 20 mg, ~ 0.049 mmol) was then dissolved in dry THF (300 µL) and cooled to – 78 ºC, to this solution was added NaHMDS (196 µL, 0.196 mmol) dropwise and stirred for 15 min, then a solution of (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (64.0 mg, 0.245 mmol) in THF (100 µLl) was added in dropwise and stirred for 30 min before it was warmed up slowly to RT. Then this reaction was quenched with saturated NH_4Cl solution (1 mL) and diluted with EtOAc (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification via silica flash column chromatography (hexanes:EtOAc = 40:1 to 5:1) afforded the α-hydroxyl lactone (~ 10 mg) with trace of inseparable impurities. This α-hydroxyl lactone (~ 10 mg, ~ 0.024 mmol) was dissolved in acetone (1 mL) then was added Jones reagent (44 µL, 0.120 mmol, 2.67 M) at 0 ºC, stirred for 15 min and carefully quenched with MeOH (100 µL) followed by saturated $NaHCO_3$ solution (100 µL). This mixture was diluted with EtOAc (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 200:1 to 20:1) to afford (–)-jiadifenolide (**3**) as small white crystals (5.10 mg, 33% over 3 steps). R_f = 0.23 (silica gel, CH_2Cl_2:MeOH = 20:1); $[\alpha]_D^{23}$ – 73.7 (*c* 0.38, MeOH), Reported value for natural **3**: $[\alpha]_D^{23}$ – 56.8 (*c* 1.14, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 4.61 (d, *J* = 9.2 Hz, 1H), 4.42 (d, *J* = 6.3 Hz, 1H), 3.80 (d, *J* = 9.8 Hz, 1H), 2.47 (dd, *J* = 13.2 Hz, 5.8 Hz, 1H), 2.22 (m, 1H), 2.09 (d, *J* = 13.2 Hz, 1H), 2.08 (m, 1H), 2.01 (m, 1H), 1.89(m, 1H), 1.29 (m, 1H), 1.23 (s, 3H), 1.21 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (125

MHz, CD_3OD) δ 178.3, 173.6, 101.9, 97.4, 79.1, 77.6, 74.6, 58.8, 48.1, 41.6, 35.2, 33.0, 32.1, 19.9, 14.7; HRMS (ESI) m/e 333.0942 [M+Na^+] calcd for $C_{15}H_{18}O_7Na^+$: 333.0945.

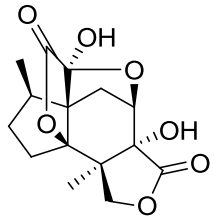
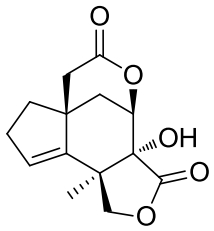


Table 4.7.1 ^{1}H NMR and ^{13}C NMR data comparison of synthetic 3 with natural (–)-jiadifenolide

Position	δ **^{1}H (natural) (CD_3OD, 600MHz)**	δ **^{1}H (synthetic) (CD_3OD, 500MHz)**	Δ	δ **^{13}C (natural)**	δ **^{13}C (synthetic)**	Δ
1	2.21 (qdd, 12.3, 12.3, 7.1)	2.22 (m)	0.01	41.62	41.63	0.01
2α	1.27 (dddd, 12.3, 12.3, 12.3, 6.0)	1.29 (m)	0.02	33.03	33.03	0.00
2β	1.88 (brdddd, 12.3, 12.3, 12.3, 4.1)	1.89 (m)	0.01			
3α	2.08 (ddd, 12.9, 12.3, 6.0)	2.08 (m)	0.00	35.17	35.16	-0.01
3β	2.00 (brdd, 12.9, 4.1)	2.01 (m)	0.01			
4				97.45	97.44	-0.01
5				48.06	48.06	0.00
6				77.62	77.62	0.00
7	4.41 (d, 5.8)	4.42 (d, 6.3)	0.01	79.13	79.12	-0.01
8α	2.09 (d, 12.9)	2.09 (d, 13.2)	0.00	32.06	32.06	0.00
8β	2.46 (dd, 12.9, 5.8)	2.47 (dd, 13.2, 5.8)	0.01			
9				58.81	58.82	0.01
10				101.92	101.92	0.00
11				173.64	173.63	-0.01
12				178.25	178.24	-0.01

Table 4.7.1 (cont.) ^{1}H NMR and ^{13}C NMR data comparison of synthetic 3 with natural (–)-jiadifenolide

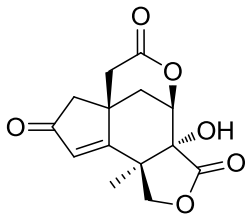
13	1.22 (s, 3H)	1.23 (s, 3H)	0.01	19.89	19.91	0.02
14α	3.79 (d, 9.3)	3.80 (d, 9.8)	0.01	74.57	74.58	0.01
14β	4.60 (d, 9.3)	4.61 (d, 9.2)	0.01			
15	1.20 (d, 7.1, 3H)	1.21 (d, 7.6, 3H)	0.01	14.66	14.65	-0.01



188

188: To a solution of alcohol **169** (420 mg, 1.5 mmol) in anhydrous THF (20 mL) was added Martin sulfurane (4.0 g, 9.0 mmol) in one portion at RT. This dark brown solution was allowed to stir at the same temperature for 2 hrs before rotavaped to dryness. The residue was re-dissolved in MeOH (20 mL), Pd/C (10%, 530 mg, 0.5 mmol) was then loaded under argon atmosphere. This crude diene was then selectively hydrogenated using a double-layer H_2-balloon for 30 min. The mixture was passed through a short silica pad and thoroughly rinsed (CH_2Cl_2:MeOH, 20:1) and the filtrate was concentrated under reduced pressure. The residue was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 200:1 to 100:1) to afford compound **188** as white foams (284 mg, 72% over 2 steps). R_f = 0.65 (silica gel, EtOAc:Hexanes = 2:1); $[\alpha]_D^{23}$ – 44.6 (*c* 1.21, CH_2Cl_2); ^{1}H NMR (500 MHz, CDCl3) δ 5.88, (br s, 1H), 4.69 (dd, *J* = 2.7 Hz, 2.7 Hz, 1H), 3.98 (d, *J* = 9.8 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.08 (br s, 1H), 2.77 (d, *J* = 18.9 Hz, 1H), 2.62 (d, *J* = 18.9 Hz, 1H), 2.45-2.33 (m, 2H), 1.94 (m, 1H), 1.84 (m, 1H),

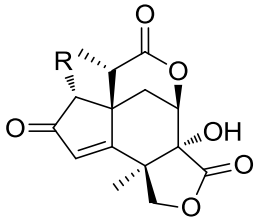
1.71-1.60 (m, 2H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 169.1, 144.4, 130.5, 79.9, 77.0, 75.9, 43.9, 43.4, 42.4, 40.0, 31.9, 29.1, 22.3; HRMS (ESI): m/e 265.1072 $[M+H]^+$ calcd for $C_{14}H_{17}O_5^+$: 265.1071.



189

189: To a solution of compound **188** (140 mg, 0.53 mmol) in anhydrous EtOAc (4 mL) was added *tert*-butyl hydroperoxide (960 µL, ~ 10 eq., 5~6 M in decane) and 3Å molecular sieves (200 mg). The mixture was stirred for 30 min at RT. Manganese(III) acetate dehydrate (71.0 mg, 0.27 mmol) was added to this mixture in one portion, and this reaction was heated at 40 °C for 16 hrs. The solution was cooled down, silica gel (2 g) was added in and rotavaped to dryness. The silica-absorbed crude product was then purified via silica flash column chromatography (CH_2Cl_2:MeOH = 100:1 to 20:1) to afford enone **189** as white solid (96 mg, 65%). R_f = 0.25 (silica gel, CH_2Cl_2:MeOH = 20:1); $[\alpha]_D^{24}$ – 82.3 (*c* 1.42, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.29, (s, 1H), 4.78 (dd, *J* = 4.6 Hz, 1.7 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 4.03 (d, *J* = 10.9 Hz, 1H), 3.11 (d, *J* = 18.9 Hz, 1H), 2.87 (dd, *J* = 19.5 Hz, 2.7 Hz, 1H), 2.64 (d, *J* = 18.9 Hz, 1H), 2.43 (dd, *J* = 14.3Hz, 4.0 Hz, 1H), 2.40 (d, *J* = 18.9 Hz, 1H), 2.32 (dt, 14.3 Hz, 2.3 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 206.8, 181.1, 177.3, 170.4, 133.9, 80.2, 80.0, 74.4, 51.3, 45.5, 43.2, 42.4, 32.1, 22.4; HRMS (ESI): m/e 277.0719 [M–

H]$^-$ calcd for $C_{14}H_{13}O_6^-$: 277.0718.

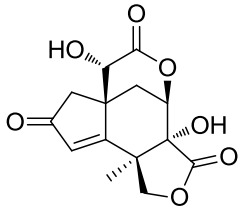


R = H, **190**
R = Me, **191**

190 and 191: To a solution of enone **189** (20 mg, 71.9 μmol) in THF (800 μL) was added freshly prepared LDA solution (360 μL, 1M in THF) at –78 °C, this solution was slowly warmed up to –15 °C over 1 h and stirred at –15 °C for 30 min. This solution was cooled to –40 °C, MeI (14 μL, 216 μmol) was dropped in slowly. This reaction was slowly warmed up to –10 °C over 1 h and stirred at –10 °C for 30 min before quenched with saturated NH_4Cl solution (1 mL). This mixture was diluted with EtOAc (200 mL) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified via preparative TLC (CH_2Cl_2:MeOH:THF = 80:1:1 x 8 times) to afford compounds **190** and **191** as small white crystals.

190: 11 mg, 50%; R_f = 0.38 (silica gel, CH_2Cl_2:MeOH:THF = 60:1:1 x 2 times); $[\alpha]_D^{22}$ – 286.4 (*c* 0.16, THF); ^{1}H NMR (500 MHz, CD_3OD) δ 6.32 (s, 1H), 4.74 (dd, *J* = 4.6 Hz, 1.2 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 4.09 (d, *J* = 10.9 Hz, 1H), 2.83 (qd, *J* = 7.5 Hz, 1.7 Hz, 1H), 2.76 (d, *J* = 18.4 Hz, 1H), 2.63 (dd, *J* = 14.9 Hz, 4.6 Hz, 1H), 2.42 (d, *J* = 18.4 Hz, 1H), 2.16 (dt, 14.9 Hz, 1.8 Hz, 1H), 1.49 (d, *J* = 7.4 Hz, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 206.8, 182.0, 177.4, 174.9, 134.3, 79.9, 79.6, 74.5, 47.8, 46.5, 45.8, 45.3, 27.7, 23.2, 18.6; HRMS (ESI): m/e 293.1023 [M+H$^+$] calcd for $C_{15}H_{17}O_6^+$: 293.1020.

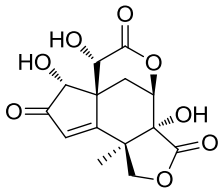
191: 6 mg, 25%; R_f = 0.4 (silica gel, CH_2Cl_2:MeOH:THF = 60:1:1 x 2 times); $[\alpha]_D^{23}$ – 276.6 (*c* 0.30, THF); ^{1}H NMR (500 MHz, CD_3OD) δ 6.32 (s, 1H), 4.77 (dd, *J* = 4.6 Hz, 1.2 Hz, 1H), 4.15 (d, *J* = 10.3 Hz, 1H), 4.11 (d, *J* = 10.9 Hz, 1H), 2.77 (qd, *J* = 7.5 Hz, 1.8 Hz, 1H), 2.58 (q, *J* = 7.6 Hz, 1H), 2.51 (dd, *J* = 14.9 Hz, 4.3 Hz, 1H), 2.07 (dt, *J* = 14.3, 1.8 Hz, 1H), 1.51 (d, *J* = 7.5 Hz, 3H), 1.45 (s, 3H), 1.14 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 210.2, 181.3, 177.4, 175.0, 133.0, 80.1, 79.8, 74.5, 50.0, 49.4, 46.8, 45.5, 23.7, 23.3, 18.2, 12.7; HRMS (ESI): m/e 307.1177 $[M+H]^+$ calcd for $C_{16}H_{19}O_6^+$: 307.1176.



192

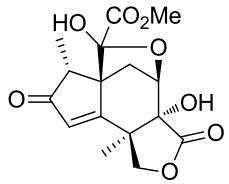
192: To a solution of enone **189** (20 mg, 71.9 μmol) in THF (500 μL) was added NaHMDS (216 μL, 216 μmol, 1M in THF) dropwise at –78 °C, this solution was stirred for 20 min. Then the Davis oxaziridine (18.8 mg, 71.9 μmol) in THF (200 μL) was added in dropwise. This solution was stirred at the same temperature for 30 min before quenched with saturated NH_4Cl solution (1 mL). This mixture was diluted with EtOAc (200 mL) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified via silica flash column chromatography (CH_2Cl_2:MeOH = 100:1 to 20:1) to afford compound **192** as small white crystals (13 mg, 61%) and compound **207** as white crystals (2 mg, 10%). For compound **192**: R_f = 0.4 (silica gel, CH_2Cl_2:MeOH = 20:1 x 2 times); $[\alpha]_D^{25}$ – 136.4 (*c* 0.83, THF); ^{1}H

NMR (500 MHz, CD_3OD) δ 6.38 (s, 1H), 4.75 (dd, *J* = 4.6 Hz, 1.2 Hz, 1H), 4.12 (d, *J* = 10.9 Hz, 1H), 3.94 (d, *J* = 10.9 Hz, 1H), 4.09 (d, *J* = 1.2 Hz, 1H), 3.90 (d, *J* = 10.3 Hz, 1H), 3.00 (d, *J* = 18.9 Hz, 1H), 2.70 (dd, *J* = 14.4 Hz, 4.6 Hz, 1H), 2.38 (d, *J* = 18.9 Hz, 1H), 2.17(dt, *J* = 14.3, 1.8 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 207.4, 178.8, 177.4, 171.2, 135.6, 80.2, 79.4, 74.5, 73.2, 49.5, 47.1, 45.3, 26.8, 22.9; HRMS (ESI): m/e 293.0668 $[M–H]^-$ calcd for $C_{14}H_{13}O_7^-$: 293.0667.



207

207: $[\alpha]_D^{22}$ – 38.8 (*c* 0.4, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 6.35 (s, 1H), 4.78 (dd, *J* = 4.6 Hz, 1.2 Hz, 1H), 4.25 (s, 1H), 4.11 (d, *J* = 10.9 Hz, 1H), 3.96 (d, *J* = 1.7 Hz, 1H), 3.87 (d, *J* = 10.9 Hz, 1H), 2.53 (dd, *J* = 18.9 Hz, 4.0 Hz, 1H), 2.17(m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 205.7, 176.6, 176.0, 169.7, 131.6, 79.1, 78.5, 74.3, 73.7, 71.3, 51.3, 44.3, 29.4, 21.1; HRMS (ESI): m/e 309.0667 $[M–H]^-$ calcd for $C_{14}H_{13}O_8^-$: 309.0689.



(-)-2

(–)-Jiadifenin (2): To freshly prepared LDA solution (476 µL, 1M in THF) was added a solution of **192** (28 mg, 95.2 µmol) in THF (1 mL) at –78 °C, this solution was slowly warmed up to –20 °C over 1 h and stirred at –20 °C for 30

min. This solution was cooled to –40 °C, HMPA (19.9 µL, 114 µmol) and MeI (7.1 µL, 114 µmol) was dropped in slowly. This reaction was slowly warmed up to –10 °C over 1 h and stirred at –10 °C for 4 h before quenched with saturated NH_4Cl solution (1 mL). This mixture was diluted with EtOAc (200 mL) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified via preparative TLC (CH_2Cl_2:MeOH = 20:1 x 5 times) to afford methylated enone **168** (~ 11 mg, 60% brsm, contaminated with trace of **192**) and recovered compound **192** (10 mg). Without intensive purification of **168**, to a solution of this methylated enone **168** (11.0 mg, 35.7 µmol) in acetone (3 mL) was added Jones reagent (2.6 M, 200 µL, 2.67 M) at RT and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with MeOH at RT (1 mL) and stirred for 15 min. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ (1 mL), diluted with EtOAc (100 mL) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified via preparative TLC (CH_2Cl_2:MeOH = 50:1 x 3 times, then CH_2Cl_2:MeOH = 35:1 x 3 times) to afford **(–)-Jiadifenin** (**2**) as white foams (5.4 mg, 45%). R_f = 0.3 (silica gel, CH_2Cl_2:MeOH = 20:1 x 2 times); $[\alpha]_D^{24}$ – 123.8 (*c* 0.17, EtOH); ^{1}H NMR (500 MHz, pyridine-d_5-TMS) δ 10.94 (major C-10 anomer, br s, 1H), 10.64* (minor C-10 anomer, br s, 1H), 9.14* (br s, 1H), 9.08 (br s, 1H), 6.59 (s, 1H), 6.52* (s, 1H), 5.89 (d, *J* = 8.6 Hz, 1H), 5.14* (d, *J* = 6.3 Hz, 1H), 5.07 (d, *J* = 6.3 Hz, 1H), 4.44* (d, *J* = 9.2 Hz, 1H), 4.22 (d, *J* = 8.6 Hz, 1H), 4.18* (d, *J* = 9.2 Hz, 1H), 3.69 (s, 3H), 3.57* (s, 3H), 3.53* (q, *J* = 7.5 Hz, 1H), 3.19* (dd, *J* = 12.0, 6.3 Hz, 1 H), 3.04 (dd, *J* = 12.6, 6.3 Hz, 1 H), 2.97 (q, *J* = 7.6 Hz, 1 H), 2.64* (d, *J* =

12.1 Hz, 1 H), 2.54 (d, *J* = 12.6 Hz, 1 H), 1.70 (s, 3 H), 1.65* (s, 3 H), 1.39* (d, *J* = 7.4 Hz, 3 H), 1.25 (d, *J* = 8.0 Hz, 3 H); ^{13}C NMR (200 MHz, pyridine-d_5-TMS) δ 209.7* (minor C-10 anomer), 208.9 (major C-10 anomer), 180.2, 179.0, 178.7*, 177.4*, 171.6169.2*, 131.3*, 130.7, 106.0, 104.1*, 81.0, 80.6, 80.4*, 79.5*, 76.1, 75.4*, 61.5*, 60.3, 52.7, 52.0*, 45.2, 44.9*, 44.8*, 43.0, 31.6*, 31.4, 23.3, 23.2*, 14.5*, 13.1; HRMS (ESI): m/e 339.1072 $[M+H]^+$ calcd for $C_{16}H_{19}O_8^+$: 339.1074.

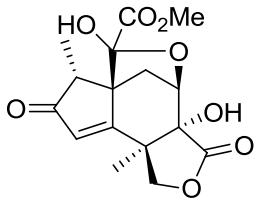


Table 4.7.2 ^{1}H NMR data comparison of the synthetic 2 with natural (–)-jiadifenin and synthetic (±)-jiadifenin

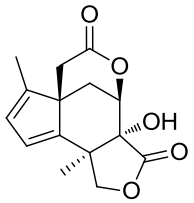
Position	δ (natural) (C_5D_5N, 600MHz)[2]	δ (synthetic 2, ±) (C_5D_5N, 500MHz)[3]	δ (synthetic 2, –) (C_5D_5N, 500MHz)	Δ 1	Δ 2
1	2.93, q, 7.7 Hz	2.95, q, 7.6 Hz	2.97, q, 7.6 Hz	+ 0.04	+ 0.02
1*	3.49, q, 7.7 Hz	3.51, q, 7.7 Hz	3.52, q, 7.5 Hz	+ 0.03	+ 0.01
3		6.57, s	6.59,	+ 0.03	+0.02
3*	6.48, s	6.50, s	6.52,	+ 0.04	+0.02
7	5.03, d, 6.3 Hz	5.05, d, 6.2 Hz	5.07, d, 6.3 Hz	+ 0.04	+ 0.02
7*	5.11, d, 6.3 Hz	5.12, d, 6.2 Hz	5.14, d, 6.3 Hz	+ 0.03	+ 0.02
8	2.55, d, 12.3 Hz	2.53, d, 12.4 Hz	2.54, d, 12.6 Hz	– 0.01	+ 0.01
	3.00, dd, 12.3 Hz, 6.3 Hz	3.03, dd, 12.4 Hz, 6.2 Hz	3.04, dd, 12.6 Hz,	+ 0.04	+ 0.01
8*	2.60, d, 11.8 Hz	2.62, d, 11.8 Hz	2.64, d, 12.1 Hz	+ 0.04	+ 0.02
	3.15, dd, 11.8 Hz, 6.3 Hz	3.17, dd, 11.8 Hz, 6.3 Hz	3.19, dd, 12.0 Hz,	+ 0.04	+ 0.02
13	1.67, s	1.69, s	1.70,	+ 0.03	+ 0.01
13*	1.62, s	1.64, s	1.65,	+ 0.03	+ 0.01
14	4.19, d, 8.5 Hz	4.20, d, 8.4 Hz	4.22, d, 8.6 Hz	+ 0.03	+ 0.02
	5.85, d, 8.5 Hz	5.87, d, 8.5 Hz	5.89, d, 8.6 Hz	+ 0.04	+ 0.02
14*	4.15, d, 9.1 Hz	4.16, d, 9.0 Hz	4.18, d, 9.2 Hz	+ 0.03	+ 0.02
	4.41, d, 9.1 Hz	4.43, d, 9.0 Hz	4.44, d, 9.2 Hz	+ 0.03	+ 0.01
15	1.22, d, 7.7 Hz	1.24, d, 7.7 Hz	1.25, d, 8.0 Hz	+ 0.03	+ 0.01
15*	1.32, d, 7.7 Hz	1.38, d, 7.7 Hz	1.39, d, 7.4 Hz	+ 0.07	+ 0.01
OCH_3	3.66, s	3.68, s	3.69,	+ 0.03	+ 0.02
OCH_3*	3.54, s	3.56, s	3.57,	+ 0.03	+ 0.01

Table 4.7.3 ^{13}C NMR data comparison of the synthetic 2 with natural (–)-jiadifenin and synthetic (±)-jiadifenin

Position	δ **(natural)** **(C_5D_5N, 150MHz)[2]**	δ **(synthetic 2, ±)** **(C_5D_5N, 125MHz)[3]**	δ **(synthetic 2, –)** **(C_5D_5N, 200MHz)**	Δ 1	Δ 2
1	42.9	42.8	43.0	+ 0.1	+ 0.2
1*	44.8	44.7	44.9	+ 0.1	+ 0.2
2	208.9	208.7	208.9	+ 0.0	+ 0.2
2*	209.8	209.6	209.7	– 0.1	+ 0.1
3	130.6	130.5	130.7	+ 0.1	+ 0.2
3*	131.2	131.1	131.3	+ 0.1	+ 0.2
4	180.2	180.0	180.2	+ 0.0	+ 0.2
4*	177.4	177.2	177.4	+ 0.0	+ 0.2
5	45.2	45.1	45.2	+ 0.0	+ 0.1
5*	44.8	44.6	44.8	+ 0.0	+ 0.2
6	80.5	80.4	80.6	+ 0.1	+ 0.2
6*	79.4	79.3	79.5	+ 0.1	+ 0.2
7	80.9	80.8	81.0	+ 0.1	+ 0.2
7*	80.3	80.2	80.4	+ 0.1	+ 0.2
8	31.4	31.3	31.4	+ 0.0	+ 0.1
8*	31.6	31.5	31.6	+ 0.0	+ 0.1
9	60.2	60.1	60.3	+ 0.1	+ 0.2
9*	60.2	61.3	61.5	+ 1.3	+ 0.2
10	105.9	105.8	106.0	+ 0.1	+ 0.2
10*	104.1	103.9	104.1	+ 0.0	+ 0.2
11	171.5	171.4	171.6	+ 0.1	+ 0.2
11*	169.2	169.0	169.2	+ 0.0	+ 0.2
12	178.9	178.8	179.0	+ 0.1	+ 0.2
12*	178.9	178.6	178.7	– 0.2	+ 0.1
13	23.2	23.1	23.3	+ 0.1	+ 0.2
13*	23.1	23.0	23.2	+ 0.1	+ 0.2
14	76.0	75.9	76.1	+ 0.1	+ 0.2
14*	75.3	75.2	75.4	+ 0.1	+ 0.2
15	13.6	12.9	13.1	– 0.5	+ 0.2

Table 4.7.3 (cont.) ^{13}C NMR data comparison of the synthetic 2 with natural (–)-jiadifenin and synthetic (±)-jiadifenin

15*	14.5	14.4	14.5	+ 0.0	+ 0.1
OCH_3	52.7	52.6	52.7	+ 0.0	+ 0.1
OCH_3*	52.0	51.9	52.0	+ 0.0	+ 0.1



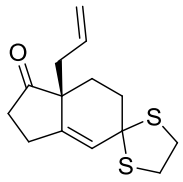
194

194: To a solution of alcohol **169** (100 mg, 0.357 mmol) in DCM (7.2 mL) was added Celite® (0.22 g) followed by PCC (0.154 g, 0.714 mmol). The reaction was allowed to stir at RT for 30 minutes. The reaction mixture was filtered through Celite®, washed thoroughly with EtOAc (200 mL). The filtrate was dried over Na_2SO_4 and the solvent was removed. The crude product was purified via flash column chromatography (silica, Hexane:EtOAc = 50:1 to 4:1) to afford unstable ketone **193** as white solid (65.5 mg, 65%). ^1H NMR (500 MHz, CD_3OD) δ 6.27 (bs, 1H), 4.75 (d, *J* = 2.9 Hz, 1H), 4.05 (d, *J* = 10.3 Hz, 1H), 3.90 (d, *J* = 10.3 Hz, 1H), 3.11 (d, *J* = 23.5 Hz, 1H), 3.01 (d, *J* = 23.5 Hz**,** 1H), 2.82 (d, *J* = 7.4 Hz, 1H), 2.70 (d, *J* = 7.4 Hz, 1H), 2.23 (dd, 13.8 Hz, 3.5 Hz, 1H), 1.96 (d, *J* = 14.3 Hz, 1H), 1.39 (s, 3H).

To a solution of the unstable ketone **193** (20.0 mg, 72 μmol) in anhydrous THF (450 μL) was added 1,5-di-tert-butyl-3-methylpyridine (45.0 mg, 216 mol) followed by triflate anhydride (25.0 μL, 144 μmol) at 0 ^oC. Upon complete addition, the

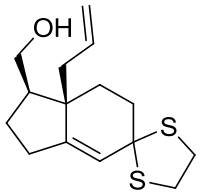
reaction was warmed up to RT and left overnight. The solvent was removed and the crude product was purified by flash column chromatography (silica, Hexane:EtOAc = 50:1 to 6:1) to afford triflate as white solid (18.0 mg, 61%). ^{1}H NMR (500 MHz, CD_3OD) δ 6.46 (d, *J* = 2.9 Hz, 1H), 6.41 (d, *J* = 2.9 Hz, 1H), 4.80 (dd, *J* = 2.9 Hz, 1.7 Hz, 1H), 4.08 (d, *J* = 10.3 Hz, 1H), 3.94 (d, *J* = 10.3 Hz, 1H), 3.08 (d, *J* = 18.9 Hz, 1H), 2.59 (dd, *J* = 13.8 Hz, 4.6 Hz, 1H), 2.46 (dd, *J* = 16.1 Hz, 2.3 Hz, 1H), 1.87 (td, *J* = 15.4 Hz, 2.5 Hz, 1H), 1.40 (s, 3H).

This vinyl triflate (18.0 mg, 44 μmol) was then dissolved in dry THF (300 μL), $Pd(PPh_3)_4$ (15.0 mg, 13 μmol) was added in, followed by a solution of $AlMe_3$ (210 μL, 440 μmol, 2M in hexanes). This reaction was stirred at RT for 1 h before it was carefully quenched with saturated $NaHCO_3$ solution (200 μL). This mixture was diluted with EtOAc (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (hexanes:EtOAc = 50:1 to 3:1) to afford the **194** as white solid (6.8 mg, 57%). $[\alpha]_D^{23}$ – 38.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 6.37 (d, *J* = 2.3 Hz, 1H), 6.12 (m, 1H), 4.76 (dd, *J* = 4.0 Hz, 2.9 Hz, 1H), 4.02 (d, *J* = 10.3 Hz, 1H), 3.93 (d, *J* = 10.3 Hz, 1H), 2.99 (d, *J* = 19.5 Hz, 1H), 2.42 (dd, *J* = 13.8 Hz, 4.0 Hz, 1H), 2.14 (dd, *J* = 18.9 Hz, 7.1 Hz, 1H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.60 (td, *J* = 13.8 Hz, 2.3 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.9, 169.9, 150.3, 148.8, 129.5, 126.1, 80.4, 79.7, 74.5, 50.2, 43.8, 35.8, 28.8, 20.5, 10.8; HRMS (ESI) m/e 277.1069 [$M+H^+$] calcd for $C_{15}H_{17}O_5^+$: 277.1071.



196

196: To a vigorous stirred solution of **174** (10.0 g, 52.6 mmol) in glacial AcOH (20 mL), was added at room temperature a solution of ethane-1,2-dithiol (5.45 g, 57.8 mmol) and *p*-TsOH (1.71 g, 15.8 mmol) in glacial AcOH (40 mL). The mixture was stirred for 2 h and was quenched by water (100 mL). The solid was separated by filtration and washed with water (50 mL), with 10% aqueous solution of $NaHCO_3$ solution (50 mL), and with water (50 mL), and dried under reduced pressure. The crude product was then dissolved in EtOAc, rotavaped on silica and purified by a plug of silica (hexane:EtOAc = 100:5) to afford **196** as white crystals. (12 g, 86%); $[\alpha]_D^{25}$ – 373.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 5.71 (m, 1H), 5.11 (m, 2H), 3.42 (m, 3H), 3.23 (m, 1H), 2.69 (m, 1H), 2.52 (m, 2H), 2.24 (m, 5H), 1.96 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 142.3, 132.8, 126.4, 118.7, 64.9, 51.0, 40.8, 39.9, 38.4, 37.8, 36.5, 26.6, 26.6; HRMS (ESI): m/e 267.0871 $[M+H]^+$ calcd for $C_{14}H_{18}OS_2^+$: 267.0872.



197

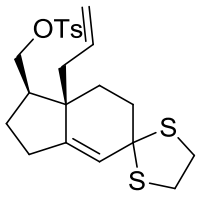
197: To a suspension of $Ph_3P^+CH_2OCH_3Cl^-$ (27.8 g, 81 mmol) in anhydrous THF (400 mL) at 0 ^oC, was added a solution of KHMDS (90

mL, 90 mmol, 1 M in THF). The resulting red solution was stirred at the same temperature for 30 minutes and was added a solution of ketone **196** (12.0 g, 45 mmol) in THF (100 mL) slowly. The mixture was then warmed up to RT and left for overnight. Upon completion, the reaction was quenched by saturated NH_4Cl solution (200 mL) and brine (200 mL). The residue was extracted with EtOAc (3 x 200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified through a plug of silica (Hexane:EtOAc = 10:1 as elute) to afford enol ether as a yellow oil.

The methyl enol ether obtained above (~ 13.5 g, 45 mmol) was dissolved in acetone (1.5 L). To this solution was added PPTS (25.6 g, 134 mmol) at 0 ^oC. The reaction was then warmed up to RT and allowed to stir for 2 h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ solution (30 mL) and the solvent was removed by rotavap (water bath temperature below 30 ^oC). The residue was diluted with water (400 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was then removed and the crude aldehyde was isolated as 9:1 mixture of diastereomers at C1, which was used without further purification.

Aldehyde obtained as described above (~ 12.5 g, 45 mmol) was dissolved in MeOH (300 mL) and in THF (300 mL) at -78 ^oC, was added $NaBH_4$ in small portions. The resulting suspension was stirred at the same temperature for 30 minutes before quenched with saturated NH_4Cl solution (100 mL). The solvent was removed by rotavap (water bath temperature below 30 ^oC). The residue was diluted with water

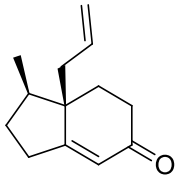
(300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed brine (100 mL) and dried over Na_2SO_4. The solvent was removed and the crude alcohol was purified by flash column chromatography (silica, Hexane:EtOAc = 4:1) to afford **197** as a yellow oil (10.2 g, 81% over 3 steps); $[\alpha]_D^{25}$ – 60.7 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.52 (s, 1H), 5.08 (d, *J* = 18.9 Hz, 1H), 5.00 (d, *J* = 5.9 Hz, 1H), 3.76 (dd, *J* = 10.4 Hz, 7.5 Hz, 1H), 3.69 (dd, *J* = 10.9 Hz, 7.5 Hz, 1H), 3.38 (m, 3H), 3.22 (m, 1H), 2.43–2.28 (m, 2H), 2.26 (m, 1H), 2.15–2.11 (m, 4H), 1.79 (m, 1H), 1.72 (m, 1H), 1.53 (m, 1H), 1.43 (m,1H), 1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 136.5, 123.3, 116.9, 65.9, 63.9, 54.2, 44.9, 40.5, 39.8, 38.9, 37.0, 34.8, 28.2, 24.7; HRMS (ESI): m/e 283.1186 $[M+H]^+$ calcd for $C_{15}H_{23}OS_2^+$: 283.1185.



198

198: To a solution of alcohol **197** (20 mg, 71 µmol) in anhydrous DCM (350 µL) was added Et_3N (20 µL, 142 µmole) and TsCl (25 µg, 135 µmol) at 0 ^oC. The reaction was then warmed up to RT and left overnight. Upon completion, brine (3 mL) and pH 7 buffer solution (3 mL) was added and the residue was extracted with DCM (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was then purified by

flash column chromatography (silica, Hexane:EtOAc = 10:1) to afford tosylate **198** as white crystal. (30 mg, 95%); $[\alpha]_D^{25}$ – 68.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.64 (m, 1H), 5.52 (s, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 4.93 (bs, 1H), 4.11 (dd, *J* = 9.7 Hz, 6.0 Hz, 1H), 4.09 (dd, *J* = 9.2 Hz, 6.9 Hz, 1H), 3.39 (m, 3H), 3.21 (m, 1H), 2.45 (s, 3H), 2.38–2.13 (m, 3H), 2.10 (m, 1H), 2.02 (m, 3H), 1.85 (m, 2H), 1.50 (dt, *J* = 13.8 Hz, 2.9 Hz, 1H), 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 144.9, 135.7, 133.0, 129.9, 128.0, 124.2, 117.0, 70.8, 65.4, 50.2, 44.8, 40.4, 39.7, 38.6, 36.8, 34.6, 27.9, 24.3, 21.7; HRMS (ESI): m/e 437.1275 $[M+H]^+$ calcd for $C_{22}H_{29}O_3S_3^+$: 437.1273.



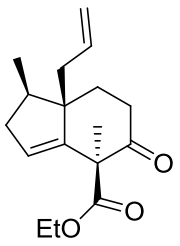
199

199: To a solution of alcohol **198** (10.2 g, 36.1 mmol) in anhydrous DCM (180 mL) was added Et_3N (10.2 mL, 72.2 mmol) and MsCl (5.35 mL, 68.6 mmol) at 0 ^oC. The reaction was then warmed up to RT and stirred for additional of 30 minutes. Upon completion, brine (80 mL) and pH 7 buffer solution (80 mL) was added and the residue was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was used for the next step without future purification.

Mesylate obtained above (~ 13 g, 36.1 mmol) was dissolved anhydrous THF (150 mL). Super-Hydride® (181 mL, 1M in THF, 181 mmol) was added slowly at 0

^{o}C via cannula. The reaction was then warmed up to RT and left to stir for 24 h before quenched by saturated NH_4Cl solution (50 mL) and diluted by brine (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated.

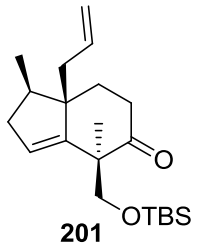
The crude product obtained as described above (~ 10 g, 36.1 mmol) was dissolved in MeOH (150 mL) and DCM (150 mL) and water (0.75 mL). PIFA (23.2 g, 54.0 mmol) was then added in small portions. Upon complete addition, the reaction was allowed to stir at RT for an additional 15 minutes before Na_2SO_3 (4.5 g, 36 mmol) was added. The reaction was stirred for 15 minutes and quenched by water (100 mL) and the excess solvent was removed under reduced pressure. The residue was extracted with DCM (3 x 100 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography (silica, Hexane:EtOAc = 10:1) to afford enone **199** as 15:1 diastereomeric mixture of C15 methyl group (4.5 g, 66% 3 steps). $[\alpha]_D^{25}$ – 174.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.82 (m, 1H), 5.07 (d, *J* = 18.4 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 2.63 (m, 2H), 2.32 (m, 1H), 2.29 (m, 2H), 2.18 (m, 2H), 1.90 (m, 1H), 1.72 (m, 2H), 1.59 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.84* (d, *J* = 7.5 Hz, 0.2H, diastereomer at C15); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 179.8, 135.4, 122.4, 117.6, 47.6, 46.7, 36.4, 33.7, 33.5, 29.9, 29.2, 13.5; HRMS (ESI): m/e 191.1432 $[M+H]^+$ calcd for $C_{13}H_{19}O^+$: 191.1430.



200

200: To a solution of **199** (3.0 g, 15.8 mmol) in anhydrous DMF (35 mL) was added magnesium methyl carbonate (27.6 mL, 55.2 mmol, 2.0 M in DMF). This solution was degassed for 5 min under argon, then immersed in an oil bath which was pre-heated to 130 ºC and stirred for 3 h. The reaction was cooled to 0 ºC and poured in to a mixture of ice/2N HCl (50 mL). Then this mixture was acidified to pH = 2~3 with 2N HCl. Ether (200 mL) was added to form a two-phase clear solution. The aqueous phase was separated and it was re-extracted with ether (2 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure at 30 ºC. The residue was dried on high-vacuum pump for 1 h to remove the trace of DMF to afford yellow oil. The crude product was dissolved in dry CH_2Cl_2 (35 mL), triethyloxonium tetrafluoroborate (23.6 mL, 23.6 mmol, 1M in CH_2Cl_2) was added at 0 ºC, then DIPEA (5.5 mL, 31.5 mmol) was added dropwise. After 1 minute, TLC showed that the completion of this reaction. Then this reaction was quenched with saturated NH_4Cl solution (30 mL), extracted with CH_2Cl_2 (3 x 30 mL), washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The unstable crude product was used to next step directly. To a solution of this crude ester (4.2 g, ~ 15.8 mmol) in dry CH_2Cl_2 (60 mL) was added 2,6-lutidine (5.5 mL, 41.3 mmol) at 0 ºC, followed by

addition of TMSOTf (5.7 mL, 13.6 mmol) dropwise. After 30 min, the reaction was diluted with hexanes (100 mL), quenched with 5% (not saturated!) $NaHCO_3$ solution (50 mL), extracted with hexanes (3 x 80 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further dried on high-vacuum pump for 10 min (not longer!). The unstable crude TMS-enol ether was dissolved in dry THF (60 mL), cooled to -78 ºC, methyl iodide (9.8 mL, 0.16 mol) was added in, followed by addition of TBAF solution dropwise (15.8 mL , 15.8 mmol, 1 M in THF). This reaction was then allowed to warm to RT slowly over 30 min, and stirred at RT for extra 2 h before it was quenched with saturated NH_4Cl solution (50 mL). The mixture was extracted with EtOAc (3 x 80 mL), the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 10:1) to afford **200** as a yellow oil (1.5 g, 35% over 2 steps). $[\alpha]_D^{23}$ – 257.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dd, *J* = 3.5 Hz, 1.7 Hz, 1H), 5.78 (m, 1H), 5.08 (d, *J* = 2.3 Hz, 1H), 5.00 (td, *J* = 9.7 Hz, 2.3 Hz, 1H), 4.15 (m, 1H), 4.08 (m, 1H), 2.80 (m, 1H), 2.40 – 2.36 (m, 2H), 2.28 (m, 1H), 2.17 – 2.02 (m, 2H), 1.98 (m, 2H), 1.51 (m, 1H), 1.48 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.08 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 172.3, 147.2, 136.4, 129.2, 116.5, 61.7, 58.8, 49.8, 47.6, 39.4, 36.8, 36.5, 35.7, 13.1, 13.0; HRMS (ESI) m/e 299.1617 [M+Na^+] calcd for $C_{17}H_{24}O_3Na^+$: 299.1618.



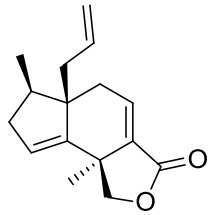
201

201: To a solution of **200** (1.5 g, 5.4 mmol) in dry THF (30 mL) was added $LiAlH_4$ solution (21.7 mL, 43.4 mmol, 2M in THF) at 0 ºC. This reaction was stirred for 30 min before it was carefully quenched with water (1.5 mL) followed by 15% NaOH solution (1.5 mL) and water (4.5 mL). The reaction mixture was allowed warm up to room temperature and stirred for an additional 15 minutes before adding anhydrous $MgSO_4$ and dilute with ether (30 mL). The mixture was allowed to stir for 15 minutes before was filtrated through Celite® and washed thoroughly with ether (200 mL). The solvent was then removed under reduce pressure and the crude diol was used to next step directly.

The crude diol was dissolved in CH_2Cl_2 (30 mL) and was cooled to 0 ºC. Imidazole (0.74 g, 10.8 mmol) was added in followed by the adding of TBSCl (0.90 g, 6.0 mmol). After 30 min, this reaction was quenched with saturated NH_4Cl solution (200 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine and dried over Na_2SO_4, then concentrated under reduced pressure. The crude mono-TBS- ether was used to next step directly.

The crude mono-TBS-ether was dissolved in dry DMSO (30 mL), IBX (4.6 g, 16.3 mmol) was added in and this reaction was heated to 80 ºC for 1 h. Upon completion, the reaction was cooled to RT and water (50 mL) was added in and the reaction was filtered through Celite®, the filtrates were extracted with EtOAc (3 x 50

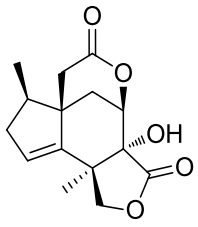
mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 20:1) to afford **201** as a yellow oil (1.52 g, 80% over 3 steps). $[\alpha]_D^{23}$ – 29.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.66 (m, 1H), 5.07 (d, *J* = 16.6 Hz, 1H), 4.96 (d, *J* = 10.3 Hz, 1H), 3.68 (d, *J* = 4.0 Hz, 2H), 2.49 (m, 2H), 2.32 (m, 2H), 2.23 (m, 2H), 2.04 (m, 2H), 1.92 (m, 1H), 1.58 m, 1H), 1.19 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.007 (s, 3H), -0.0045 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 214.0, 150.9, 136.9, 127.1, 116.2, 69.3, 54.9, 49.4, 48.0, 39.3, 37.1, 36.1, 34.4, 26.1, 21.1, 21.5, 13.3, -5.5; HRMS (ESI) m/e 349.2556 [M+H$^+$] calcd for $C_{21}H_{37}O_2Si^+$: 349.2557



202

202: To a solution of ketone **201** (1.52 g, 4.36 mmol) in dry THF (40 mL) was added $PhNTf_2$ (4.67 g, 13.1 mmol) at room temperature. KHMDS (21.8 mL, 21.8 mmol, 1 M in THF) dropwise at – 78 ºC and stirred for 30 min before was warmed up to RT over 30 min. The reaction was quenched by solution with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine and dried over Na_2SO_4, concentrated under reduced pressure and purified via silica flash column chromatography (hexanes:EtOAc = 100:1) to afford the vinyl triflate as a white solid. (1.7 g, 81%)

The vinyl triflate obtained above (1.7 g, 3.54 mmol) was dissolved in DMF/MeOH (27mL/9 mL, 3:1), $Pd(PPh_3)_4$ (41 mg, 35 μmol) and triethylamine (1.5 mL, 10.6 mmol) was added. This orange solution was degassed under argon atmosphere for 5 min, followed by bubbling in carbon monoxide for 5 min. This solution was then heated to 70ºC for 1 h under carbon monoxide atmosphere before it was concentrated under reduced pressure. The residue was passed through a short silica pad (hexanes:EtOAc = 50:1, 1000 mL), concentrated and re-dissolved in dry CH_2Cl_2 (35 mL), TFA (0.83 mL, 10.8 mmol) was added in and this reaction was stirred at RT for 5 h before it was quenched with saturated $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic phase was washed with brine and dried over Na_2SO_4, concentrated under reduced pressure and purified via silica flash column chromatography (hexanes:EtOAc = 100:1 to 10:1) to afford the lactone **202** as a white solid (0.65 g, 61% from **201**). $[\alpha]_D^{23}$ – 28.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 3.1 Hz, 2.9 Hz, 1H), 5.77 (m, 1H), 5.66 (m, 1H), 4.96 (m, 2H), 4.14 (d, *J* = 8.0 Hz, 1H), 3.94 (d, *J* = 8.6 Hz, 1H), 2.52 (dd, *J* = 16.1 Hz, 7.5 Hz, 1H), 2.49 (m, 1H), 2.10 (m, 4H), 2.05 (dd, *J* = 16.0 Hz, 2.9 Hz, 1H), 1.33 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 149.5, 135.9, 135.1, 134.8, 127.3, 117.0, 76.3, 53.9, 46.9, 41.7, 39.8, 37.0, 36.5, 27.7, 13.7; HRMS (ESI) m/e 267. 1358 [M+Na^+] calcd for $C_{16}H_{20}O_2Na^+$: 267.1356.



195

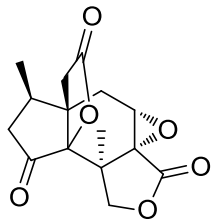
195 : To a solution of enone **202** (0.65 g, 2.66 mmol) in MeOH (20 mL) was added a pre-mixed solution of 3N NaOH (2.5 mL) and 30% H_2O_2 (2.5 mL) dropwise at 0 ºC. This reaction was warmed up to RT and vigorous stirred for 5 h. The mixture was then diluted with water, acidified with 2N HCl to pH = 1, separated with EtOAc/brine (20mL/20mL) and the aqueous phase was extracted with EtOAc (2 x 20 mL). The organic phase was combined, dried over Na_2SO_4 and concentrate under reduced pressure to afford epoxide as a white solid. The product was used without future purification.

Epoxide obtained above (~ 0.7 g, 2.66 mmol) was dissolved in 1,4-dioxane (30 mL) and water (10 mL). To this solution 2,6-lutidine (0.63 mL, 5.4 mmol), OsO_4 (0.17 mL, 4% solution in H_2O, 27 µmol) was added, then $NaIO_4$ (2.3 g, 10.8 mmol) was added portionwise at 0 ºC. This reaction was then warmed up to RT and stirred for overnight. The reaction was diluted with water (60 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the aldehyde as a white solid, which was clean enough to be used for next reaction.

To a solution of the aldehyde obtained above (~ 0.7 g, 2.66 mmol) in acetone (20 mL) was added Jones reagent (2.3 mL, 6.2 mmol, 2.67 M) dropwise

at 0 ºC, and this reaction was stirred at 0 ºC for 30 min. Ethanol (10 mL) was carefully dropped in to quench this reaction, followed by dropping the saturated $NaHCO_3$ solution (10 mL). The mixture was stirred for 5 min before it was filtrated through Celite®, and the filter cake was then washed thoroughly with EtOAc (100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified via column chromatography (hexanes:CH_2Cl_2 = 1:1 to 1:3 to 100% CH_2Cl_2, then CH_2Cl_2:MeOH =200:1 to 50:1) afford the product **195** as a white form (340 mg, 46% over 3 steps) and side product **206** (17 mg, 2%) as white solid.

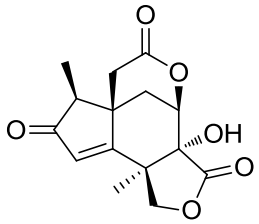
195 : $[\alpha]_D^{22}$ – 20.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 5.95 (appeared as t, *J* = 5.6 Hz, 1H), 4.71 (dd, *J* = 2.9 Hz, 1.7 Hz, 1H), 3.99 (d, *J* = 9.8 Hz, 1H), 3.73 (d, *J* = 10.3 Hz, 1H), 2.69 (d, *J* = 18.3 Hz, 1H), 2.40 (m, 2H), 2.16 (dd, *J* = 13.8 Hz, 4.6 Hz, 1H), 2.06 (m, 2H), 1.85 (m, 1H), 1.30 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 171.3, 146.5, 129.3, 129.1, 79.9, 76.7, 75.3, 44.9, 44.6, 42.0, 37.1, 29.5, 21.2, 12.4; HRMS (ESI) m/e 301.1048 [M+Na^+] calcd for $C_{15}H_{18}O_5Na^+$: 301.1046.



206

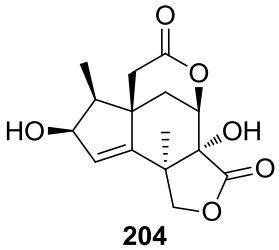
206: $[\alpha]_D^{22}$ – 56.1 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 9.7 Hz, 1H), 4.18 (d, *J* = 9.8 Hz, 1H), 3.81 (t, *J* = 4.0 Hz, 1H), 2.80 (d, *J* = 18.3 Hz,

1H), 2.60 (dd, *J* = 17.8 Hz, 6.3 Hz, 1H), 2.48 (dd, *J* = 16.1 Hz, 5.8 Hz, 1H), 2.39 (d, *J* = 18.9 Hz, 1H), 2.22 (m, 2H), 1.90 (dd, *J* = 16.1 Hz, 3.5 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 171.5, 171.3, 87.4, 74.3, 74.3, 59.1, 55.9, 55.8, 50.4, 39.1, 36.9, 34.0, 18.0, 13.3; HRMS (ESI) m/e 315.0840 [M+Na^+] calcd for $C_{15}H_{16}O_6Na^+$: 315.0539.



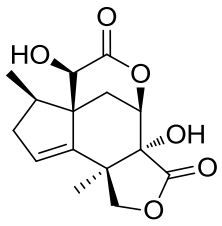
203

203: To a solution of compound **195** (20 mg, 72 μmol) in anhydrous EtOAc (720 μL) was added *tert*-butyl hydroperoxide (145 μL, ~ 10 eq., 5~6 M in decane) and 3Å molecular sieves. The mixture was stirred for 30 min at RT. Manganese(III) acetate dehydrate (3.5 mg, 14 μmol) was added to this mixture in one portion, and this reaction was left stirred overnight. Upon, silica gel (500 mg) was added in and rotavaped to dryness. The silica-absorbed crude product was then purified via silica flash column chromatography (CH_2Cl_2:MeOH = 100:1 to 20:1) to afford enone **203** as white solid (9.6 mg, 53%). $[\alpha]_D^{24}$ – 111.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H), 4.75 (t, *J* = 2.9 Hz, 1H), 4.12 (d, *J* = 10.3 Hz, 1H), 4.05 (d, *J* = 10.3 Hz, 1H), 2.92 (m, 2H), 2.48 (q, *J* = 7.5 Hz, 1H), 2.29 (m, 2H), 1.48 (s, 3H), 1.15 (d, d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 205.3, 176.2, 175.6, 167.3, 132.2, 78.0, 74.3, 53.3, 44.0, 43.6, 39.9, 30.1, 29.7, 22.4, 9.1; HRMS (ESI): m/e 291.9877 [M-H]$^-$ calcd for $C_{15}H_{15}O_6^-$: 291.0874.



204

204: To a solution of enone **203** (7 mg, 24 μmol) and $CeCl_3$-$7H_2O$ (27 mg, 72 μmol) in THF (1.3 mL)-MeOH (0.4 mL) was cooled to -78 ^oC and treated with a solution of $NaBH_4$ (144 μL, 72 μmol) in 2-methoxyethyl ether (0.5 M). The resulting mixture was stirred at -55~50 ^oC for 35 minutes. The reaction mixture was quenched with 1N HCl (60 μL), diluted with brine (10 mL) and extracted with EtOAc (5 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via pre-plate (elute DCM:MeOH = 30:1 4x) to afford allylic alcohol **204** as white slid (6.0 mg, 85%). $[\alpha]_D^{24}$ + 10.4 (*c* 0.3, EtOH); ^1H NMR (500 MHz, CD_3OD) δ 5.90 (s, 1H), 4.69 (dd, *J* = 4.6 Hz, 1.2 Hz, 1H), 4.38 (d, *J* = 8.6 Hz, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 3.74 (d, *J* = 9.7 Hz, 1H), 2.86 (d, *J* = 18.9 Hz, 1H), 2.37 (dd, *J* = 18.4 Hz, 2.9 Hz, 1H), 2.15 (dd, *J* = 14.3 Hz, 4.6 Hz, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.33 (s, 3H), 1.09 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.2, 170.7, 147.1, 133.9, 80.0, 79.4, 76.8, 74.8, 53.9, 44.7, 41.7, 38.1, 29.5, 21.1, 10.0; HRMS (ESI): m/e 295.1178 $[M+H]^+$ calcd for $C_{15}H_{19}O_6^+$: 295.1176.



205

205: To a solution of lactone **195** (10 mg, 71.9 μmol) in THF (350 μL) was added NaHMDS (180 μL, 180 μmol, 1M in THF) dropwise at -78 °C, this solution was stirred for 20 min. Then the Davis oxaziridine (14 mg, 54.0 μmol) in THF (100 μL) was added in dropwise. This solution was stirred at the same temperature for 30 min before quenched with saturated NH_4Cl solution (1 mL). This mixture was diluted with EtOAc (200 mL) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified by pre-plate (elute, DCM:MeOH = 50:1, 8 x) afford compound **205** as white foam (6mg, 57%). $[\alpha]_D^{25}$ – 9.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 6.09 (d, *J* = 3.8 Hz, 1H), 4.70 (d, *J* = 4.6 Hz, 1H), 4.15 (s, 1H), 3.97 (d, *J* = 9.8 Hz, 1H), 3.78 (d, *J* = 9.8 Hz, 1H), 2.80 (dd, *J* = 13.7 Hz, 4.6 Hz, 1H), 2.39 (m, 1H), 2.17 (m, 2H), 1.82 (d, *J* = 13.8 Hz, 1H), 1.32 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.7, 170.5, 143.6, 133.9, 79.9, 76.8, 75.6, 70.3, 49.2, 47.9, 41.9, 37.3, 29.5, 23.4, 16.1; HRMS (ESI): m/e 293.1034 $[M-H]^-$ calcd for $C_{15}H_{17}O_6^-$: 293.1031.

Biological Assay Protocols: Rat PC-12M pheochromocytoma cells (obtained from the laboratories of Drs. Paul C. Sternweis, Elliott M. Ross and Joseph Goldstein; University of Texas Southwestern Medical Center) were cultured at a density of 2 x 10^4 cells/well in a 24-well plate in growth medium containing

DMEM (Cellgro), 10% normal horse serum (Hyclone), 5% fetal calf serum (Gibco), 100 U/mL penicillin G, 100 µg/mL streptomycin sulfate (Cellgro) and incubated at 37ºC, 5% CO_2. Four hours after plating, growth medium was replaced with differentiation medium (DMEM; 1% normal horse serum, 0.5% fetal calf serum) containing nerve growth factor (NGF, 50 ng/mL). After 24 hours of incubation, fresh differentiation medium was added containing NGF (50 ng/mL) with and without jiadifenin (0.3 or 0.5 µM, 1% DMSO) and allowed to incubate an additional 48 hours. Triplicate wells were used for controls and experimental agents.

Live cell images were obtained using a Leica EL6000 microscope (20X). Five regions with similar cell density from each well were selected for imaging. Cells from each well were photographed and analyzed, and from the data of the triplicate wells, the mean values were obtained. Total neurite outgrowth length was measured by randomly selecting 15 neurons from the images of each treatment. The ratio was calculated by comparing the average neurite length found in the treatment to the NGF with 1% DMSO control. Student T test was performed.

Table 4.7.4 Neurite outgrowth of tested compounds after 72 h incubation

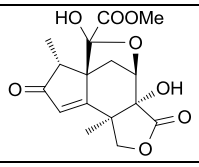
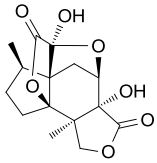
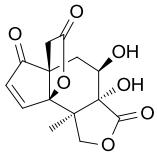
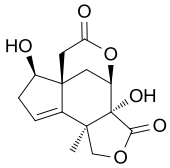
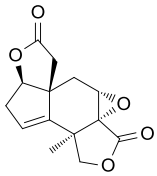
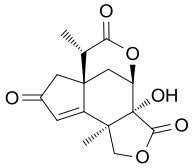
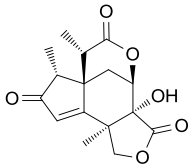
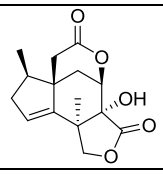
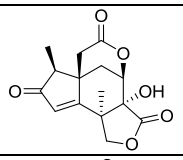
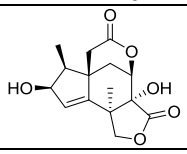
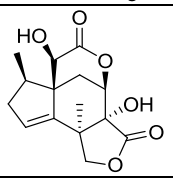
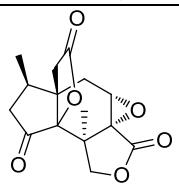
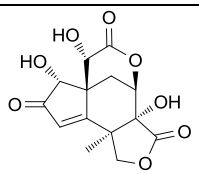
Treatment	Structure	Average neurite length (mean ± SE, arbitrary unit)	Outgrowth	*P*-value
Control DMSO+NGF	--	12.6 ± 1.1	100%	--
Jiadifenin (2)		18.7 ± 2.2	148%	<0.0001
Jiadifenolide (3)		20.9 ± 2.3	166%	<0.0001
167		13.7 ± 1.1	109%	<0.001
169		13.1 ± 1.5	104%	0.17
182		13.0 ± 1.0	104%	0.15
190		23.1 ± 1.5	183%	<0.0001
191		20.4 ± 0.9	162%	<0.0001
195		11.8 ± 0.7	94%	0.02

Table 4.7.4 (cont.) Neurite outgrowth of tested compounds after 72 h incubation

203		12.1 ± 1.1	96%	0.02
204		13.6 ± 0.9	108%	0.9
205		13.7 ± 1.9	109%	0.9
206		12.2 ± 1.1	97%	0.3
207		17.4 ± 1.4	138%	<0.0001

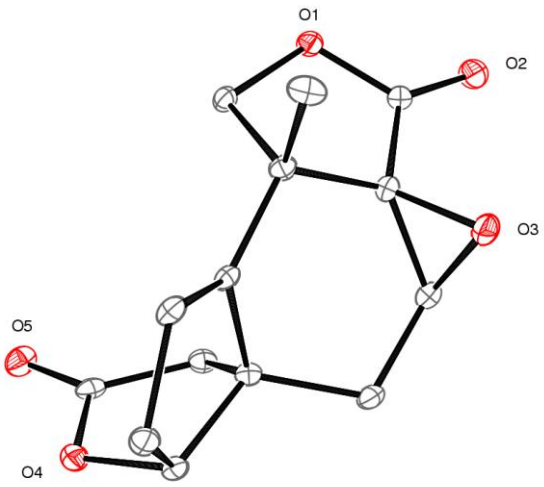


Table 4.7.5 Crystal data and structure refinement for **182**

Identification code	XJ-J33	
Empirical formula	C14 H14 O5	
Formula weight	262.25	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.5324(4) Å	α= 90°.
	b = 8.2386(5) Å	β= 90°.
	c = 21.8222(15) Å	γ = 90°.
Volume	1174.42(13) $Å^3$	
Z	4	
Density (calculated)	1.483 Mg/m^3	
Absorption coefficient	0.949 mm^{-1}	
F(000)	552	
Crystal size	0.20 x 0.08 x 0.05 mm^3	
Crystal size	Colorless Needle	
Theta range for data collection	4.05 to 66.08°.	
Index ranges	-7<=h<=7, -6<=k<=9, -23<=l<=25	
Reflections collected	6072	
Independent reflections	1954 [R(int) = 0.0325]	
Completeness to theta = 66.08°	96.1 %	

Table 4.7.5 (cont.) Crystal data and structure refinement for **182**

Absorption correction	Multi-scan
Max. and min. transmission	0.9541 and 0.8328
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1954 / 0 / 173
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0308, wR2 = 0.0707
R indices (all data)	R1 = 0.0351, wR2 = 0.0737
Absolute structure parameter	0.0(2)
Largest diff. peak and hole	0.150 and -0.176 e.$Å^{-3}$

Table 4.7.6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **182**

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9546(2)	5313(2)	8583(1)	19(1)
O(2)	12971(2)	5389(2)	8600(1)	28(1)
O(3)	12500(2)	8791(2)	8170(1)	25(1)
O(4)	5837(2)	11541(2)	9568(1)	20(1)
O(5)	4947(2)	9416(2)	10141(1)	26(1)
C(1)	11361(3)	6089(2)	8564(1)	18(1)
C(2)	10967(3)	7863(2)	8477(1)	18(1)
C(3)	8739(3)	8032(2)	8291(1)	16(1)
C(4)	7876(3)	6498(2)	8603(1)	17(1)
C(5)	8535(3)	7815(2)	7598(1)	23(1)
C(6)	12123(3)	9117(2)	8814(1)	20(1)
C(7)	11101(3)	10708(2)	8979(1)	18(1)
C(8)	8806(3)	10433(2)	9087(1)	16(1)
C(9)	7902(3)	9626(2)	8516(1)	15(1)
C(10)	6679(3)	10631(2)	8214(1)	17(1)
C(11)	6487(3)	12262(2)	8518(1)	19(1)
C(12)	7481(3)	11984(2)	9142(1)	17(1)
C(13)	8379(3)	9582(2)	9697(1)	18(1)
C(14)	6237(3)	10094(2)	9840(1)	18(1)

Table 4.7.7 Bond lengths [Å] and angles [°] for **182**

O(1)-C(1)	1.347(2)	C(12)-H(12)	1.0000
O(1)-C(4)	1.465(2)	C(13)-C(14)	1.495(3)
O(2)-C(1)	1.202(2)	C(13)-H(13A)	0.9900
O(3)-C(2)	1.427(2)	C(13)-H(13B)	0.9900
O(3)-C(6)	1.452(2)		
O(4)-C(14)	1.357(2)	C(1)-O(1)-C(4)	109.88(14)
O(4)-C(12)	1.468(2)	C(2)-O(3)-C(6)	61.69(13)
O(5)-C(14)	1.205(2)	C(14)-O(4)-C(12)	110.82(15)
C(1)-C(2)	1.496(3)	O(2)-C(1)-O(1)	122.70(17)
C(2)-C(6)	1.477(3)	O(2)-C(1)-C(2)	128.86(18)
C(2)-C(3)	1.517(3)	O(1)-C(1)-C(2)	108.41(16)
C(3)-C(9)	1.505(3)	O(3)-C(2)-C(6)	59.98(12)
C(3)-C(5)	1.529(3)	O(3)-C(2)-C(1)	117.58(16)
C(3)-C(4)	1.542(3)	C(6)-C(2)-C(1)	122.11(18)
C(4)-H(4A)	0.9900	O(3)-C(2)-C(3)	119.90(16)
C(4)-H(4B)	0.9900	C(6)-C(2)-C(3)	124.02(18)
C(5)-H(5A)	0.9800	C(1)-C(2)-C(3)	106.81(16)
C(5)-H(5B)	0.9800	C(9)-C(3)-C(2)	110.02(16)
C(5)-H(5C)	0.9800	C(9)-C(3)-C(5)	113.10(15)
C(6)-C(7)	1.515(3)	C(2)-C(3)-C(5)	109.70(16)
C(6)-H(6)	1.0000	C(9)-C(3)-C(4)	116.01(15)
C(7)-C(8)	1.534(3)	C(2)-C(3)-C(4)	99.06(14)
C(7)-H(7A)	0.9900	C(5)-C(3)-C(4)	107.99(16)
C(7)-H(7B)	0.9900	O(1)-C(4)-C(3)	105.11(14)
C(8)-C(13)	1.530(3)	O(1)-C(4)-H(4A)	110.7
C(8)-C(9)	1.531(3)	C(3)-C(4)-H(4A)	110.7
C(8)-C(12)	1.548(3)	O(1)-C(4)-H(4B)	110.7
C(9)-C(10)	1.325(3)	C(3)-C(4)-H(4B)	110.7
C(10)-C(11)	1.504(3)	H(4A)-C(4)-H(4B)	108.8
C(10)-H(10)	0.9500	C(3)-C(5)-H(5A)	109.5
C(11)-C(12)	1.525(3)	C(3)-C(5)-H(5B)	109.5
C(11)-H(11A)	0.9900	H(5A)-C(5)-H(5B)	109.5
C(11)-H(11B)	0.9900	C(3)-C(5)-H(5C)	109.5

Table 4.7.7 (cont.) Bond lengths [Å] and angles [°] for **182**

H(5A)-C(5)-H(5C)	109.5	O(4)-C(12)-C(11)	106.93(16)
H(5B)-C(5)-H(5C)	109.5	O(4)-C(12)-C(8)	104.63(14)
O(3)-C(6)-C(2)	58.33(12)	C(11)-C(12)-C(8)	107.07(15)
O(3)-C(6)-C(7)	117.69(17)	O(4)-C(12)-H(12)	112.6
C(2)-C(6)-C(7)	119.90(17)	C(11)-C(12)-H(12)	112.6
O(3)-C(6)-H(6)	116.2	C(8)-C(12)-H(12)	112.6
C(2)-C(6)-H(6)	116.2	C(14)-C(13)-C(8)	102.92(15)
C(7)-C(6)-H(6)	116.2	C(14)-C(13)-H(13A)	111.2
C(6)-C(7)-C(8)	109.85(15)	C(8)-C(13)-H(13A)	111.2
C(6)-C(7)-H(7A)	109.7	C(14)-C(13)-H(13B)	111.2
C(8)-C(7)-H(7A)	109.7	C(8)-C(13)-H(13B)	111.2
C(6)-C(7)-H(7B)	109.7	H(13A)-C(13)-H(13B)	109.1
C(8)-C(7)-H(7B)	109.7	O(5)-C(14)-O(4)	120.74(19)
H(7A)-C(7)-H(7B)	108.2	O(5)-C(14)-C(13)	129.61(18)
C(13)-C(8)-C(9)	116.03(16)	O(4)-C(14)-C(13)	109.65(16)
C(13)-C(8)-C(7)	112.27(15)		
C(9)-C(8)-C(7)	108.41(15)		
C(13)-C(8)-C(12)	102.11(14)		
C(9)-C(8)-C(12)	101.86(15)		
C(7)-C(8)-C(12)	115.86(15)		
C(10)-C(9)-C(3)	127.08(17)		
C(10)-C(9)-C(8)	111.43(17)		
C(3)-C(9)-C(8)	120.25(16)		
C(9)-C(10)-C(11)	112.92(17)		
C(9)-C(10)-H(10)	123.5		
C(11)-C(10)-H(10)	123.5		
C(10)-C(11)-C(12)	102.93(15)		
C(10)-C(11)-H(11A)	111.2		
C(12)-C(11)-H(11A)	111.2		
C(10)-C(11)-H(11B)	111.2		
C(12)-C(11)-H(11B)	111.2		
H(11A)-C(11)-H(11B)	109.1		

Table 4.7.8 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **182**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	18(1)	14(1)	24(1)	0(1)	-1(1)	1(1)
O(2)	20(1)	22(1)	42(1)	-5(1)	-2(1)	5(1)
O(3)	23(1)	26(1)	26(1)	-4(1)	7(1)	-9(1)
O(4)	20(1)	18(1)	22(1)	-2(1)	4(1)	0(1)
O(5)	29(1)	29(1)	19(1)	0(1)	4(1)	-8(1)
C(1)	17(1)	18(1)	20(1)	-4(1)	1(1)	-1(1)
C(2)	16(1)	18(1)	20(1)	-1(1)	3(1)	-3(1)
C(3)	17(1)	13(1)	16(1)	1(1)	-1(1)	-1(1)
C(4)	14(1)	14(1)	22(1)	1(1)	0(1)	-1(1)
C(5)	32(1)	19(1)	19(1)	-2(1)	0(1)	1(1)
C(6)	16(1)	20(1)	24(1)	-2(1)	-1(1)	-4(1)
C(7)	18(1)	16(1)	20(1)	-2(1)	-2(1)	-5(1)
C(8)	18(1)	13(1)	15(1)	0(1)	-1(1)	-1(1)
C(9)	14(1)	14(1)	16(1)	2(1)	1(1)	-5(1)
C(10)	16(1)	16(1)	19(1)	2(1)	-3(1)	-5(1)
C(11)	18(1)	12(1)	26(1)	4(1)	-2(1)	1(1)
C(12)	17(1)	13(1)	20(1)	-1(1)	2(1)	-3(1)
C(13)	23(1)	17(1)	15(1)	-1(1)	-1(1)	-1(1)
C(14)	26(1)	16(1)	14(1)	-3(1)	-1(1)	-5(1)

Table 4.7.9 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **182**

	x	y	z	U(eq)
H(4A)	7477	6732	9032	20
H(4B)	6664	6089	8379	20
H(5A)	9308	8669	7388	35
H(5B)	7088	7886	7482	35
H(5C)	9076	6751	7480	35
H(6)	13184	8713	9107	24
H(7A)	11296	11500	8643	21
H(7B)	11734	11159	9354	21
H(10)	5995	10350	7845	20
H(11A)	5033	12582	8563	22
H(11B)	7221	13109	8283	22
H(12)	8286	12945	9285	20
H(13A)	8478	8388	9654	22
H(13B)	9344	9946	10018	22

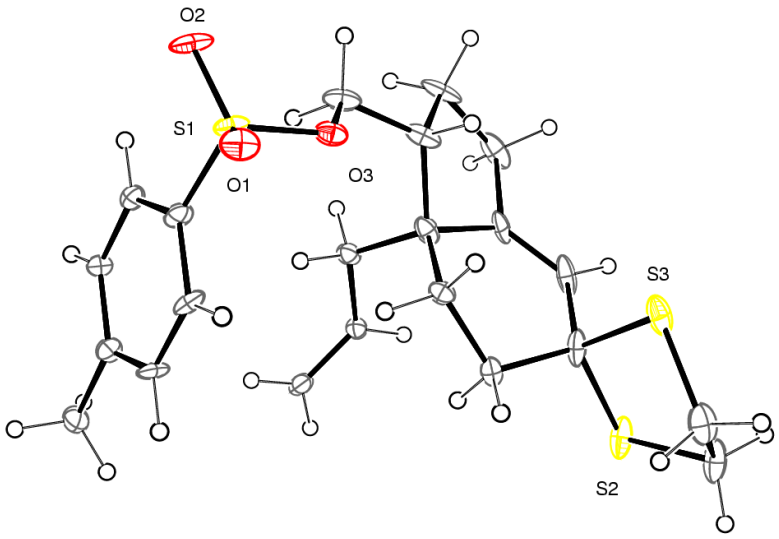


Table 4.7.10 Crystal data and structure refinement for **192**

Identification code	LT-330	
Empirical formula	C22 H28 O3 S3	
Formula weight	436.62	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.2187(12) Å	α= 90°.
	b = 22.080(4) Å	β= 94.960(3)°.
	c = 15.747(3) Å	γ = 90°.
Volume	2154.2(7) $Å^3$	
Z	4	
Density (calculated)	1.346 Mg/m^3	
Absorption coefficient	0.365 mm^{-1}	
F(000)	928	
Crystal size	0.25 x 0.23 x 0.11 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.30 to 28.12°.	
Index ranges	-8<=h<=2, -27<=k<=27, -18<=l<=20	
Reflections collected	9502	
Independent reflections	7176 [R(int) = 0.0284]	

Table 4.7.10 (cont.) Crystal data and structure refinement for **192**

Completeness to theta = 25.00°	97.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9610 and 0.9144
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7176 / 1 / 507
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0677, wR2 = 0.1481
R indices (all data)	R1 = 0.0823, wR2 = 0.1583
Absolute structure parameter	0.06(10)
Largest diff. peak and hole	0.526 and -1.111 e.$Å^{-3}$

Table 4.7.11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **192**

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4088(2)	5937(1)	923(1)	26(1)
S(2)	1674(2)	3285(1)	4702(1)	38(1)
S(3)	4443(2)	3145(1)	3292(1)	36(1)
O(1)	6387(7)	5967(2)	1040(3)	33(1)
O(2)	2997(7)	6110(3)	119(3)	37(1)
O(3)	3543(6)	5256(2)	1127(3)	26(1)
C(1)	2945(9)	6336(3)	1733(4)	25(1)
C(2)	4065(10)	6361(3)	2535(4)	26(1)
C(3)	3093(10)	6644(3)	3197(4)	27(2)
C(4)	1031(10)	6898(3)	3054(4)	26(1)
C(5)	-33(9)	6874(3)	2245(4)	22(1)
C(6)	915(9)	6596(3)	1573(4)	22(1)
C(7)	-31(12)	7188(3)	3781(4)	33(2)
C(8)	1286(10)	5059(4)	871(4)	32(2)
C(9)	863(10)	4487(3)	1346(4)	32(2)
C(10)	-1302(11)	4202(4)	972(4)	41(2)
C(11)	-2064(10)	3791(3)	1690(5)	41(2)
C(12)	-380(9)	3903(3)	2437(5)	29(2)
C(13)	644(9)	4516(3)	2315(4)	26(1)
C(14)	2815(9)	4568(3)	2855(4)	23(1)
C(15)	2763(10)	4266(3)	3724(4)	25(1)
C(16)	2206(9)	3596(3)	3649(5)	30(2)
C(17)	313(10)	3495(3)	3005(5)	37(2)
C(18)	-933(9)	5038(3)	2523(4)	24(1)
C(19)	-1813(9)	5003(3)	3370(4)	22(1)
C(20)	-1904(10)	5467(3)	3893(4)	28(2)
C(21)	3977(10)	2787(3)	4888(6)	42(2)
C(22)	5739(10)	3007(3)	4335(5)	38(2)
S(1')	4197(2)	6113(1)	5986(1)	22(1)

Table 4.7.11 (cont.) Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **192**

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

S(2')	1683(2)	3240(1)	9421(1)	24(1)
S(3')	4499(2)	3170(1)	8016(1)	22(1)
O(1')	6499(6)	6131(2)	6117(3)	27(1)
O(2')	3141(7)	6337(2)	5197(3)	31(1)
O(3')	3595(6)	5427(2)	6104(2)	20(1)
C(1')	3090(9)	6467(3)	6851(4)	24(1)
C(2')	4192(10)	6458(3)	7642(4)	23(1)
C(3')	3234(10)	6702(3)	8340(4)	29(2)
C(4')	1155(11)	6944(3)	8225(5)	32(2)
C(5')	64(10)	6956(3)	7421(4)	28(2)
C(6')	1016(9)	6716(3)	6713(4)	24(1)
C(7')	80(14)	7194(4)	8981(5)	46(2)
C(8')	1321(9)	5261(3)	5841(4)	22(1)
C(9')	872(9)	4651(3)	6212(3)	18(1)
C(10')	-1317(9)	4400(3)	5822(4)	20(1)
C(11')	-1973(9)	3910(3)	6457(4)	20(1)
C(12')	-301(8)	3980(3)	7216(3)	16(1)
C(13')	710(9)	4605(3)	7185(4)	17(1)
C(14')	2909(9)	4622(3)	7720(4)	19(1)
C(15')	2829(9)	4268(3)	8551(3)	18(1)
C(16')	2281(9)	3605(3)	8409(4)	19(1)
C(17')	382(8)	3532(3)	7736(3)	17(1)
C(18')	-841(9)	5108(3)	7482(3)	19(1)
C(19')	-1727(9)	5001(3)	8323(4)	23(1)
C(20')	-1772(11)	5418(3)	8934(4)	32(2)
C(21')	4037(10)	2754(3)	9572(5)	35(2)
C(22')	5776(10)	2995(3)	9052(4)	33(2)

Table 4.7.12 Bond lengths [Å] and angles [°] for **192**

S(1)-O(1)	1.427(4)	C(11)-C(12)	1.525(9)
S(1)-O(2)	1.435(4)	C(11)-H(11B)	0.9900
S(1)-O(3)	1.579(5)	C(11)-H(11A)	0.9900
S(1)-C(1)	1.751(7)	C(12)-C(17)	1.316(10)
S(2)-C(21)	1.809(7)	C(12)-C(13)	1.515(9)
S(2)-C(16)	1.851(7)	C(13)-C(14)	1.536(8)
S(3)-C(22)	1.792(8)	C(13)-C(18)	1.565(8)
S(3)-C(16)	1.838(6)	C(14)-C(15)	1.525(9)
O(3)-C(8)	1.491(7)	C(14)-H(14A)	0.9900
C(1)-C(6)	1.389(8)	C(14)-H(14B)	0.9900
C(1)-C(2)	1.389(8)	C(15)-C(16)	1.523(9)
C(2)-C(3)	1.397(9)	C(15)-H(15A)	0.9900
C(2)-H(2)	0.9500	C(15)-H(15B)	0.9900
C(3)-C(4)	1.400(9)	C(16)-C(17)	1.502(10)
C(3)-H(3)	0.9500	C(17)-H(17)	0.9500
C(4)-C(5)	1.385(8)	C(18)-C(19)	1.487(8)
C(4)-C(7)	1.513(9)	C(18)-H(18B)	0.9900
C(5)-C(6)	1.398(8)	C(18)-H(18A)	0.9900
C(5)-H(5)	0.9500	C(19)-C(20)	1.318(9)
C(6)-H(6)	0.9500	C(19)-H(19)	0.9500
C(7)-H(7C)	0.9800	C(20)-H(20B)	0.9500
C(7)-H(7B)	0.9800	C(20)-H(20A)	0.9500
C(7)-H(7A)	0.9800	C(21)-C(22)	1.536(9)
C(8)-C(9)	1.503(10)	C(21)-H(21B)	0.9900
C(8)-H(8A)	0.9900	C(21)-H(21A)	0.9900
C(8)-H(8B)	0.9900	C(22)-H(22A)	0.9900
C(9)-C(13)	1.545(9)	C(22)-H(22B)	0.9900
C(9)-C(10)	1.556(8)	S(1')-O(1')	1.429(4)
C(9)-H(9)	1.0000	S(1')-O(2')	1.442(4)
C(10)-C(11)	1.555(11)	S(1')-O(3')	1.574(4)
C(10)-H(10B)	0.9900	S(1')-C(1')	1.761(6)
C(10)-H(10A)	0.9900	S(2')-C(21')	1.814(7)

Table 4.7.12 (cont.) Bond lengths [Å] and angles [°] for **192**

S(2')-C(16')	1.852(6)	S(3')-C(22')	1.793(7)
S(3')-C(16')	1.832(6)	C(13')-C(14')	1.544(7)
O(3')-C(8')	1.485(6)	C(13')-C(18')	1.570(8)
C(1')-C(2')	1.370(8)	C(14')-C(15')	1.528(8)
C(1')-C(6')	1.401(8)	C(14')-H(14C)	0.9900
C(2')-C(3')	1.401(9)	C(14')-H(14D)	0.9900
C(2')-H(2')	0.9500	C(15')-C(16')	1.516(8)
C(3')-C(4')	1.396(9)	C(15')-H(15C)	0.9900
C(3')-H(3')	0.9500	C(15')-H(15D)	0.9900
C(4')-C(5')	1.385(10)	C(16')-C(17')	1.525(8)
C(4')-C(7')	1.519(9)	C(17')-H(17A)	0.9500
C(5')-C(6')	1.409(9)	C(18')-C(19')	1.496(8)
C(5')-H(5')	0.9500	C(18')-H(18D)	0.9900
C(6')-H(6')	0.9500	C(18')-H(18C)	0.9900
C(7')-H(7'B)	0.9800	C(19')-C(20')	1.334(9)
C(7')-H(7'C)	0.9800	C(19')-H(19A)	0.9500
C(7')-H(7'A)	0.9800	C(20')-H(20C)	0.9500
C(8')-C(9')	1.504(8)	C(20')-H(20D)	0.9500
C(8')-H(8'A)	0.9900	C(21')-C(22')	1.509(9)
C(8')-H(8'B)	0.9900	C(21')-H(21D)	0.9900
C(9')-C(13')	1.547(8)	C(21')-H(21C)	0.9900
C(9')-C(10')	1.547(7)	C(22')-H(22C)	0.9900
C(9')-H(9')	1.0000	C(22')-H(22D)	0.9900
C(10')-C(11')	1.552(8)	O(1)-S(1)-O(2)	119.5(3)
C(10')-H(10C)	0.9900	O(1)-S(1)-O(3)	104.4(3)
C(10')-H(10D)	0.9900	O(2)-S(1)-O(3)	109.8(3)
C(11')-C(12')	1.523(7)	O(1)-S(1)-C(1)	110.4(3)
C(11')-H(11D)	0.9900	O(2)-S(1)-C(1)	108.5(3)
C(11')-H(11C)	0.9900	O(3)-S(1)-C(1)	102.9(3)
C(12')-C(17')	1.330(8)	C(21)-S(2)-C(16)	99.8(3)
C(12')-C(13')	1.518(8)	C(22)-S(3)-C(16)	95.9(3)

Table 4.7.12 (cont.) Bond lengths [Å] and angles [°] for **192**

C(8)-O(3)-S(1)	115.9(4)	C(8)-C(9)-C(13)	119.4(6)
C(6)-C(1)-C(2)	121.7(6)	C(8)-C(9)-C(10)	109.5(6)
C(6)-C(1)-S(1)	119.7(5)	C(13)-C(9)-C(10)	104.1(5)
C(2)-C(1)-S(1)	118.6(5)	C(8)-C(9)-H(9)	107.8
C(1)-C(2)-C(3)	118.7(6)	C(13)-C(9)-H(9)	107.8
C(1)-C(2)-H(2)	120.6	C(10)-C(9)-H(9)	107.8
C(3)-C(2)-H(2)	120.6	C(11)-C(10)-C(9)	105.6(6)
C(2)-C(3)-C(4)	120.6(5)	C(11)-C(10)-H(10B)	110.6
C(2)-C(3)-H(3)	119.7	C(9)-C(10)-H(10B)	110.6
C(4)-C(3)-H(3)	119.7	C(11)-C(10)-H(10A)	110.6
C(5)-C(4)-C(3)	119.4(6)	C(9)-C(10)-H(10A)	110.6
C(5)-C(4)-C(7)	120.5(6)	H(10B)-C(10)-H(10A)	108.8
C(3)-C(4)-C(7)	120.1(6)	C(12)-C(11)-C(10)	103.5(5)
C(4)-C(5)-C(6)	121.0(6)	C(12)-C(11)-H(11B)	111.1
C(4)-C(5)-H(5)	119.5	C(10)-C(11)-H(11B)	111.1
C(6)-C(5)-H(5)	119.5	C(12)-C(11)-H(11A)	111.1
C(1)-C(6)-C(5)	118.7(6)	C(10)-C(11)-H(11A)	111.1
C(1)-C(6)-H(6)	120.7	H(11B)-C(11)-H(11A)	109.0
C(5)-C(6)-H(6)	120.7	C(17)-C(12)-C(13)	125.5(6)
C(4)-C(7)-H(7C)	109.5	C(17)-C(12)-C(11)	125.2(6)
C(4)-C(7)-H(7B)	109.5	C(13)-C(12)-C(11)	108.4(6)
H(7C)-C(7)-H(7B)	109.5	C(12)-C(13)-C(14)	110.8(5)
C(4)-C(7)-H(7A)	109.5	C(12)-C(13)-C(9)	99.3(5)
H(7C)-C(7)-H(7A)	109.5	C(14)-C(13)-C(9)	113.6(5)
H(7B)-C(7)-H(7A)	109.5	C(12)-C(13)-C(18)	110.7(5)
O(3)-C(8)-C(9)	108.2(5)	C(14)-C(13)-C(18)	111.5(5)
O(3)-C(8)-H(8A)	110.1	C(9)-C(13)-C(18)	110.3(5)
C(9)-C(8)-H(8A)	110.1	C(15)-C(14)-C(13)	112.2(5)
O(3)-C(8)-H(8B)	110.1	C(15)-C(14)-H(14A)	109.2
C(9)-C(8)-H(8B)	110.1	C(13)-C(14)-H(14A)	109.2
H(8A)-C(8)-H(8B)	108.4	C(15)-C(14)-H(14B)	109.2

Table 4.7.12 (cont.) Bond lengths [Å] and angles [°] for **192**

C(13)-C(14)-H(14B)	109.2	S(2)-C(21)-H(21B)	110.1
H(14A)-C(14)-H(14B)	107.9	C(22)-C(21)-H(21A)	110.1
C(16)-C(15)-C(14)	112.2(6)	S(2)-C(21)-H(21A)	110.1
C(16)-C(15)-H(15A)	109.2	H(21B)-C(21)-H(21A)	108.4
C(14)-C(15)-H(15A)	109.2	C(21)-C(22)-S(3)	106.7(5)
C(16)-C(15)-H(15B)	109.2	C(21)-C(22)-H(22A)	110.4
C(14)-C(15)-H(15B)	109.2	S(3)-C(22)-H(22A)	110.4
H(15A)-C(15)-H(15B)	107.9	C(21)-C(22)-H(22B)	110.4
C(17)-C(16)-C(15)	110.8(5)	S(3)-C(22)-H(22B)	110.4
C(17)-C(16)-S(3)	106.5(5)	H(22A)-C(22)-H(22B)	108.6
C(15)-C(16)-S(3)	112.2(4)	O(1')-S(1')-O(2')	119.4(3)
C(17)-C(16)-S(2)	111.1(5)	O(1')-S(1')-O(3')	104.8(2)
C(15)-C(16)-S(2)	110.4(5)	O(2')-S(1')-O(3')	109.6(3)
S(3)-C(16)-S(2)	105.8(3)	O(1')-S(1')-C(1')	109.3(3)
C(12)-C(17)-C(16)	123.3(6)	O(2')-S(1')-C(1')	109.5(3)
C(12)-C(17)-H(17)	118.3	O(3')-S(1')-C(1')	102.9(3)
C(16)-C(17)-H(17)	118.3	C(21')-S(2')-C(16')	98.7(3)
C(19)-C(18)-C(13)	115.8(5)	C(22')-S(3')-C(16')	95.3(3)
C(19)-C(18)-H(18B)	108.3	C(8')-O(3')-S(1')	115.8(4)
C(13)-C(18)-H(18B)	108.3	C(2')-C(1')-C(6')	121.9(6)
C(19)-C(18)-H(18A)	108.3	C(2')-C(1')-S(1')	119.9(5)
C(13)-C(18)-H(18A)	108.3	C(6')-C(1')-S(1')	118.1(5)
H(18B)-C(18)-H(18A)	107.4	C(1')-C(2')-C(3')	119.6(6)
C(20)-C(19)-C(18)	124.1(6)	C(1')-C(2')-H(2')	120.2
C(20)-C(19)-H(19)	118.0	C(3')-C(2')-H(2')	120.2
C(18)-C(19)-H(19)	118.0	C(4')-C(3')-C(2')	119.8(6)
C(19)-C(20)-H(20B)	120.0	C(4')-C(3')-H(3')	120.1
C(19)-C(20)-H(20A)	120.0	C(2')-C(3')-H(3')	120.1
H(20B)-C(20)-H(20A)	120.0	C(5')-C(4')-C(3')	120.0(6)
C(22)-C(21)-S(2)	108.0(5)	C(5')-C(4')-C(7')	119.8(7)
C(22)-C(21)-H(21B)	110.1	C(3')-C(4')-C(7')	120.2(7)

Table 4.7.12 (cont.) Bond lengths [Å] and angles [°] for **192**

C(4')-C(5')-C(6')	120.7(6)		
C(4')-C(5')-H(5')	119.7	C(12')-C(11')-H(11D)	111.0
C(6')-C(5')-H(5')	119.7	C(10')-C(11')-H(11D)	111.0
C(1')-C(6')-C(5')	117.9(6)	C(12')-C(11')-H(11C)	111.0
C(1')-C(6')-H(6')	121.0	C(10')-C(11')-H(11C)	111.0
C(5')-C(6')-H(6')	121.0	H(11D)-C(11')-H(11C)	109.0
C(4')-C(7')-H(7'B)	109.5	C(17')-C(12')-C(13')	125.8(5)
C(4')-C(7')-H(7'C)	109.5	C(17')-C(12')-C(11')	124.6(5)
H(7'B)-C(7')-H(7'C)	109.5	C(13')-C(12')-C(11')	108.8(5)
C(4')-C(7')-H(7'A)	109.5	C(12')-C(13')-C(14')	110.7(5)
H(7'B)-C(7')-H(7'A)	109.5	C(12')-C(13')-C(9')	98.9(4)
H(7'C)-C(7')-H(7'A)	109.5	C(14')-C(13')-C(9')	114.1(5)
O(3')-C(8')-C(9')	108.5(4)	C(12')-C(13')-C(18')	111.5(4)
O(3')-C(8')-H(8'A)	110.0	C(14')-C(13')-C(18')	111.0(5)
C(9')-C(8')-H(8'A)	110.0	C(9')-C(13')-C(18')	110.1(4)
O(3')-C(8')-H(8'B)	110.0	C(15')-C(14')-C(13')	111.3(5)
C(9')-C(8')-H(8'B)	110.0	C(15')-C(14')-H(14C)	109.4
H(8'A)-C(8')-H(8'B)	108.4	C(13')-C(14')-H(14C)	109.4
C(8')-C(9')-C(13')	118.3(5)	C(15')-C(14')-H(14D)	109.4
C(8')-C(9')-C(10')	110.6(5)	C(13')-C(14')-H(14D)	109.4
C(13')-C(9')-C(10')	103.8(4)	H(14C)-C(14')-H(14D)	108.0
C(8')-C(9')-H(9')	107.9	C(16')-C(15')-C(14')	113.0(5)
C(13')-C(9')-H(9')	107.9	C(16')-C(15')-H(15C)	109.0
C(10')-C(9')-H(9')	107.9	C(14')-C(15')-H(15C)	109.0
C(9')-C(10')-C(11')	105.3(4)	C(16')-C(15')-H(15D)	109.0
C(9')-C(10')-H(10C)	110.7	C(14')-C(15')-H(15D)	109.0
C(11')-C(10')-H(10C)	110.7	H(15C)-C(15')-H(15D)	107.8
C(9')-C(10')-H(10D)	110.7	C(15')-C(16')-C(17')	110.9(5)
C(11')-C(10')-H(10D)	110.7	C(15')-C(16')-S(3')	113.0(4)
H(10C)-C(10')-H(10D)	108.8	C(17')-C(16')-S(3')	105.7(4)
C(12')-C(11')-C(10')	103.6(4)	C(15')-C(16')-S(2')	110.6(4)

Table 4.7.12 (cont.) Bond lengths [Å] and angles [°] for **192**

S(3')-C(16')-S(2')	106.0(3)
C(12')-C(17')-C(16')	122.4(5)
C(12')-C(17')-H(17A)	118.8
C(16')-C(17')-H(17A)	118.8
C(19')-C(18')-C(13')	115.7(5)
C(19')-C(18')-H(18D)	108.3
C(13')-C(18')-H(18D)	108.3
C(19')-C(18')-H(18C)	108.3
C(13')-C(18')-H(18C)	108.3
H(18D)-C(18')-H(18C)	107.4
C(20')-C(19')-C(18')	124.2(6)
C(20')-C(19')-H(19A)	117.9
C(18')-C(19')-H(19A)	117.9
C(19')-C(20')-H(20C)	120.0
C(19')-C(20')-H(20D)	120.0
H(20C)-C(20')-H(20D)	120.0
C(22')-C(21')-S(2')	109.2(5)
C(22')-C(21')-H(21D)	109.8
S(2')-C(21')-H(21D)	109.8
C(22')-C(21')-H(21C)	109.8
S(2')-C(21')-H(21C)	109.8
H(21D)-C(21')-H(21C)	108.3
C(21')-C(22')-S(3')	106.7(4)
C(21')-C(22')-H(22C)	110.4
S(3')-C(22')-H(22C)	110.4
C(21')-C(22')-H(22D)	110.4
S(3')-C(22')-H(22D)	110.4
H(22C)-C(22')-H(22D)	108.6

Table 4.7.13 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **198**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	22(1)	44(1)	14(1)	1(1)	3(1)	3(1)
S(2)	24(1)	24(1)	69(1)	16(1)	16(1)	6(1)
S(3)	20(1)	25(1)	63(1)	-10(1)	3(1)	4(1)
O(1)	20(2)	48(3)	31(2)	-3(2)	4(2)	2(2)
O(2)	31(2)	68(4)	11(2)	3(2)	-1(2)	7(2)
O(3)	20(2)	36(3)	21(2)	-6(2)	0(2)	0(2)
C(1)	21(3)	31(4)	21(3)	3(3)	-8(2)	1(3)
C(2)	26(3)	35(4)	18(3)	12(3)	-2(2)	0(3)
C(3)	32(3)	38(4)	10(3)	1(3)	-6(2)	1(3)
C(4)	31(3)	26(4)	22(3)	3(3)	5(3)	-2(3)
C(5)	22(3)	26(4)	17(3)	0(3)	1(2)	0(3)
C(6)	21(3)	23(4)	23(3)	4(3)	-1(2)	0(2)
C(7)	46(4)	26(4)	27(4)	-3(3)	10(3)	2(3)
C(8)	22(3)	54(5)	20(3)	-10(3)	0(2)	-7(3)
C(9)	26(3)	44(5)	27(4)	-18(3)	5(3)	-7(3)
C(10)	26(3)	63(6)	33(4)	-35(4)	1(3)	-5(3)
C(11)	20(3)	36(5)	67(5)	-26(4)	3(3)	-3(3)
C(12)	18(3)	16(3)	53(4)	-11(3)	-2(3)	6(3)
C(13)	20(3)	24(4)	34(4)	-8(3)	0(3)	-1(3)
C(14)	22(3)	24(4)	24(3)	-5(3)	0(2)	-4(2)
C(15)	24(3)	18(3)	33(4)	-1(3)	3(3)	1(3)
C(16)	18(3)	16(3)	57(5)	5(3)	4(3)	3(2)
C(17)	19(3)	15(4)	78(6)	-6(4)	10(3)	-3(3)
C(18)	24(3)	25(4)	23(3)	-4(3)	-2(2)	0(3)
C(19)	23(3)	20(3)	22(3)	-1(3)	0(2)	2(3)
C(20)	35(4)	30(4)	19(3)	6(3)	1(3)	8(3)
C(21)	25(3)	25(4)	76(6)	10(4)	7(3)	6(3)
C(22)	21(3)	31(4)	65(5)	-2(4)	9(3)	3(3)
S(1')	20(1)	27(1)	20(1)	11(1)	4(1)	2(1)
S(2')	21(1)	29(1)	22(1)	10(1)	1(1)	4(1)

Table 4.7.13 (cont.) Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **198**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

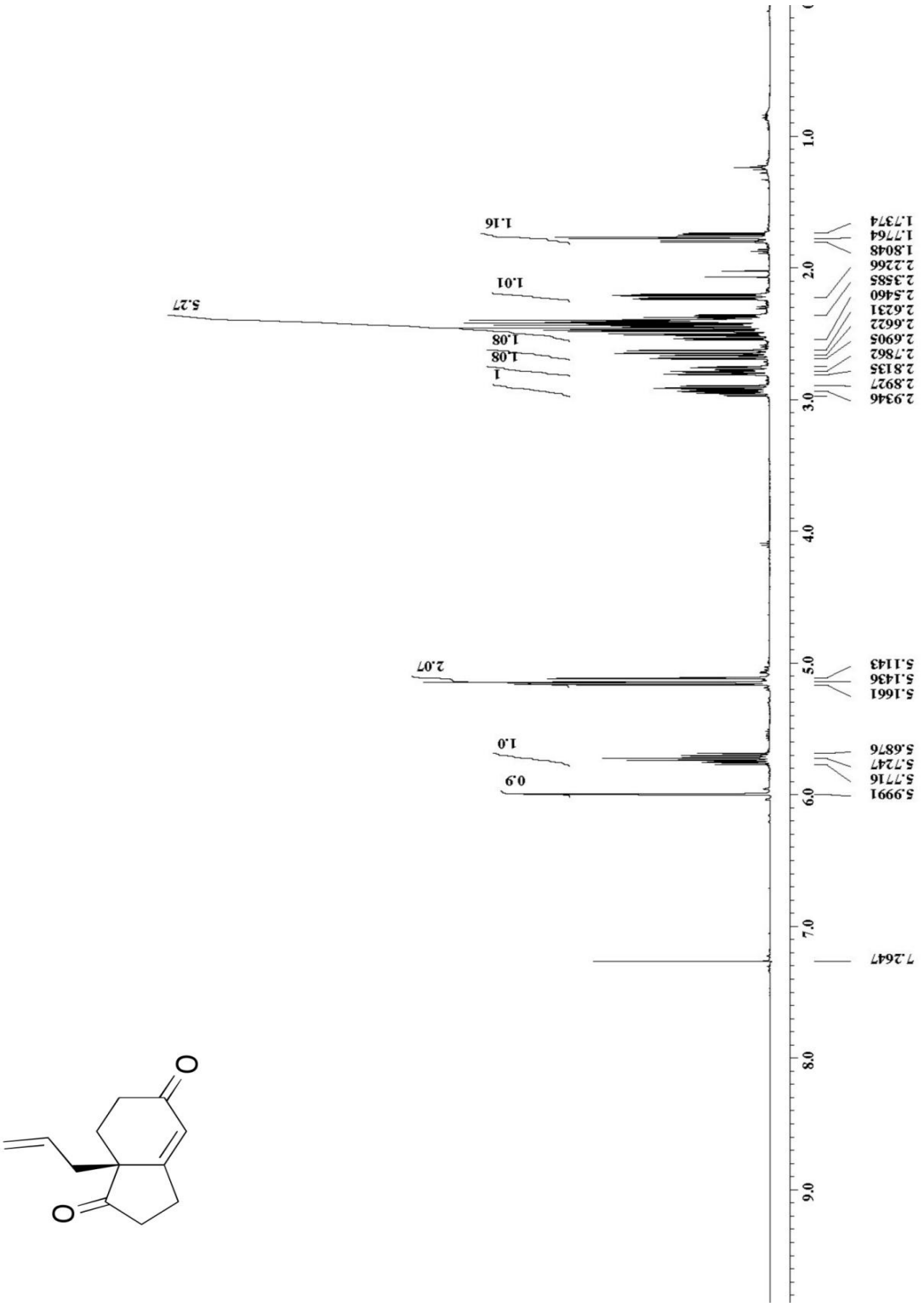
S(3')	20(1)	21(1)	25(1)	6(1)	6(1)	3(1)
O(1')	21(2)	26(2)	36(2)	7(2)	7(2)	-1(2)
O(2')	31(2)	40(3)	21(2)	18(2)	-1(2)	2(2)
O(3')	22(2)	19(2)	20(2)	8(2)	4(2)	-3(2)
C(1')	22(3)	17(3)	32(4)	6(3)	4(2)	-1(2)
C(2')	29(3)	20(3)	19(3)	8(3)	5(2)	2(3)
C(3')	39(4)	25(4)	24(3)	2(3)	4(3)	-2(3)
C(4')	39(4)	18(4)	40(4)	0(3)	13(3)	-4(3)
C(5')	27(3)	13(3)	45(4)	8(3)	8(3)	4(3)
C(6')	25(3)	14(3)	34(4)	7(3)	6(3)	4(2)
C(7')	63(5)	25(4)	53(5)	-15(4)	26(4)	-4(4)
C(8')	18(3)	27(4)	19(3)	5(3)	-3(2)	2(2)
C(9')	22(3)	19(3)	12(3)	4(2)	0(2)	-4(2)
C(10')	17(3)	28(4)	16(3)	-3(3)	1(2)	-5(2)
C(11')	21(3)	20(3)	19(3)	3(3)	-2(2)	-5(2)
C(12')	15(2)	18(3)	15(3)	-4(2)	0(2)	-1(2)
C(13')	23(3)	15(3)	12(3)	4(2)	0(2)	2(2)
C(14')	21(3)	20(3)	14(3)	5(2)	-4(2)	-2(2)
C(15')	26(3)	19(3)	10(3)	4(2)	-2(2)	2(2)
C(16')	19(3)	20(3)	17(3)	0(2)	1(2)	2(2)
C(17')	16(3)	14(3)	20(3)	5(2)	2(2)	0(2)
C(18')	23(3)	20(3)	12(3)	3(2)	0(2)	-1(2)
C(19')	25(3)	21(3)	24(3)	0(3)	-5(2)	7(3)
C(20')	41(4)	38(4)	18(3)	0(3)	4(3)	11(3)
C(21')	31(3)	31(4)	41(4)	15(3)	-3(3)	6(3)
C(22')	24(3)	35(4)	40(4)	12(3)	-4(3)	6(3)

Table 4.7.14 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **198**

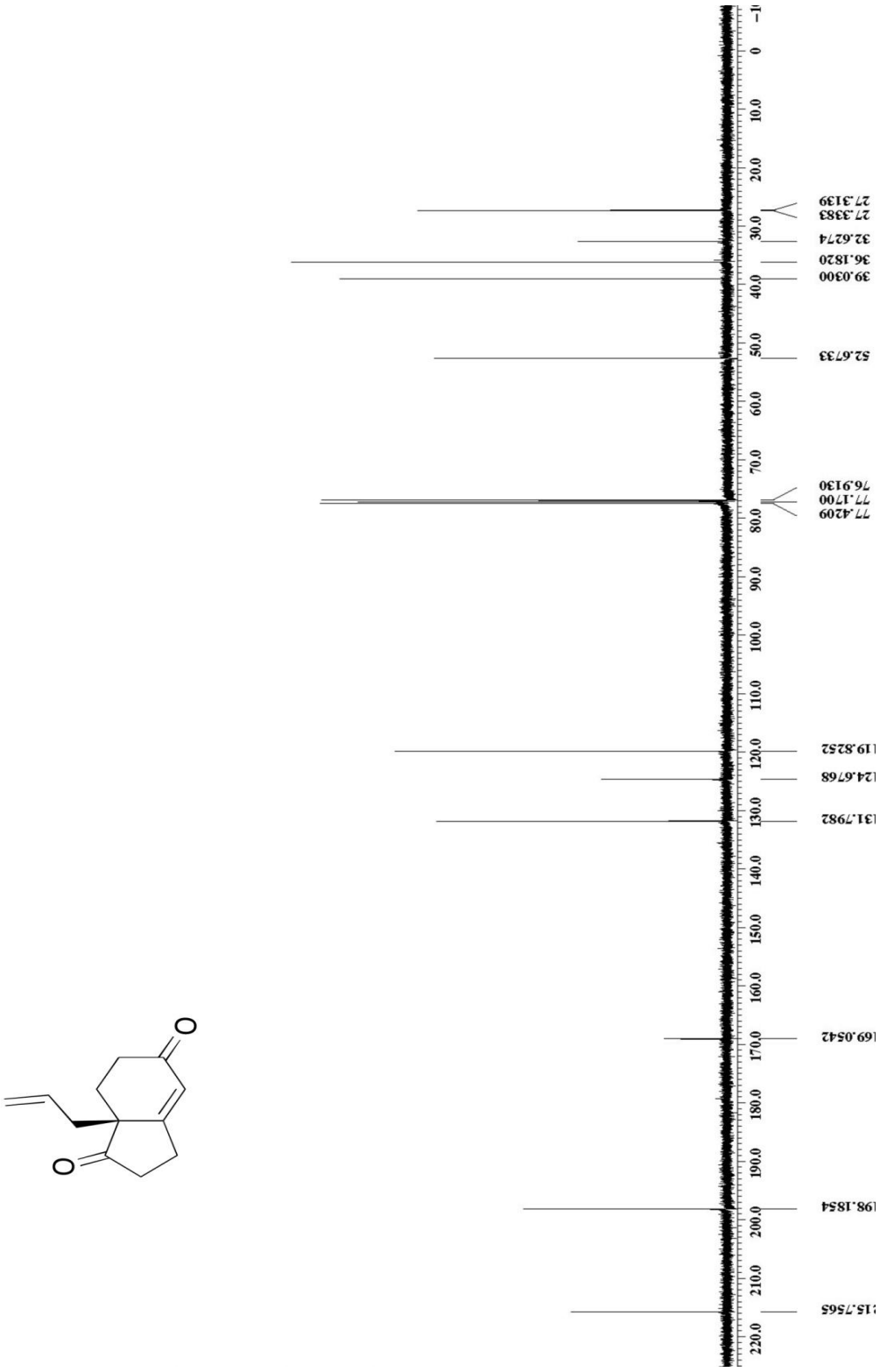
	x	y	z	U(eq)
H(2)	5466	6189	2631	32
H(3)	3838	6664	3749	33
H(5)	-1427	7049	2146	26
H(6)	186	6584	1017	27
H(7C)	190	7627	3769	49
H(7B)	610	7025	4324	49
H(7A)	-1581	7100	3721	49
H(8A)	1098	4985	249	39
H(8B)	258	5379	1012	39
H(9)	2046	4195	1250	38
H(10B)	-2383	4521	816	49
H(10A)	-1081	3960	458	49
H(11B)	-3522	3909	1837	49
H(11A)	-2086	3360	1518	49
H(14A)	3956	4377	2545	28
H(14B)	3187	5002	2937	28
H(15A)	4192	4313	4047	30
H(15B)	1682	4473	4048	30
H(17)	-422	3118	3009	44
H(18B)	-165	5428	2486	29
H(18A)	-2159	5040	2078	29
H(19)	-2342	4624	3545	26
H(20B)	-1388	5852	3737	34
H(20A)	-2486	5415	4427	34
H(21B)	4520	2796	5498	50
H(21A)	3559	2366	4734	50
H(22A)	6876	2696	4311	46
H(22B)	6411	3384	4575	46
H(2')	5597	6287	7718	27

Table 4.7.14 (cont.) Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **198**.

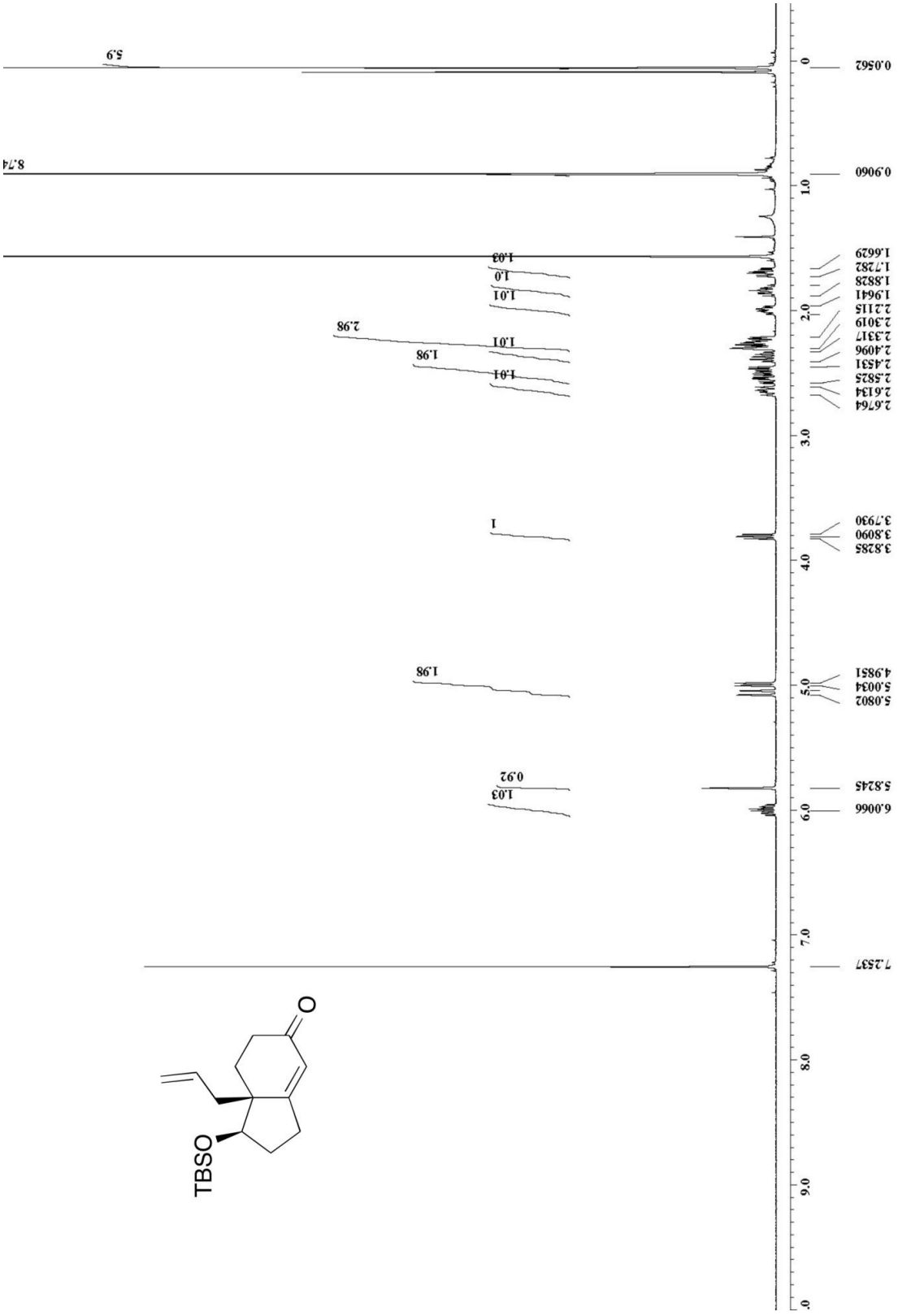
H(3')	3998	6703	8889	35
H(5')	-1340	7127	7345	34
H(6')	274	6723	6160	29
H(7'B)	-675	7571	8816	68
H(7'C)	1179	7275	9452	68
H(7'A)	-958	6897	9164	68
H(8'A)	1086	5246	5212	26
H(8'B)	332	5568	6051	26
H(9')	2030	4367	6059	21
H(10C)	-1166	4221	5254	25
H(10D)	-2412	4727	5761	25
H(11D)	-3448	3984	6626	25
H(11C)	-1913	3500	6206	25
H(14C)	4032	4445	7386	22
H(14D)	3308	5047	7852	22
H(15C)	4249	4300	8885	22
H(15D)	1737	4455	8891	22
H(17A)	-337	3152	7686	20
H(18D)	-50	5498	7512	22
H(18C)	-2067	5151	7042	22
H(19A)	-2293	4611	8428	28
H(20C)	-1219	5812	8849	39
H(20D)	-2358	5321	9455	39
H(21D)	4569	2743	10182	42
H(21C)	3648	2336	9388	42
H(22C)	6919	2688	9008	40
H(22D)	6437	3363	9322	40



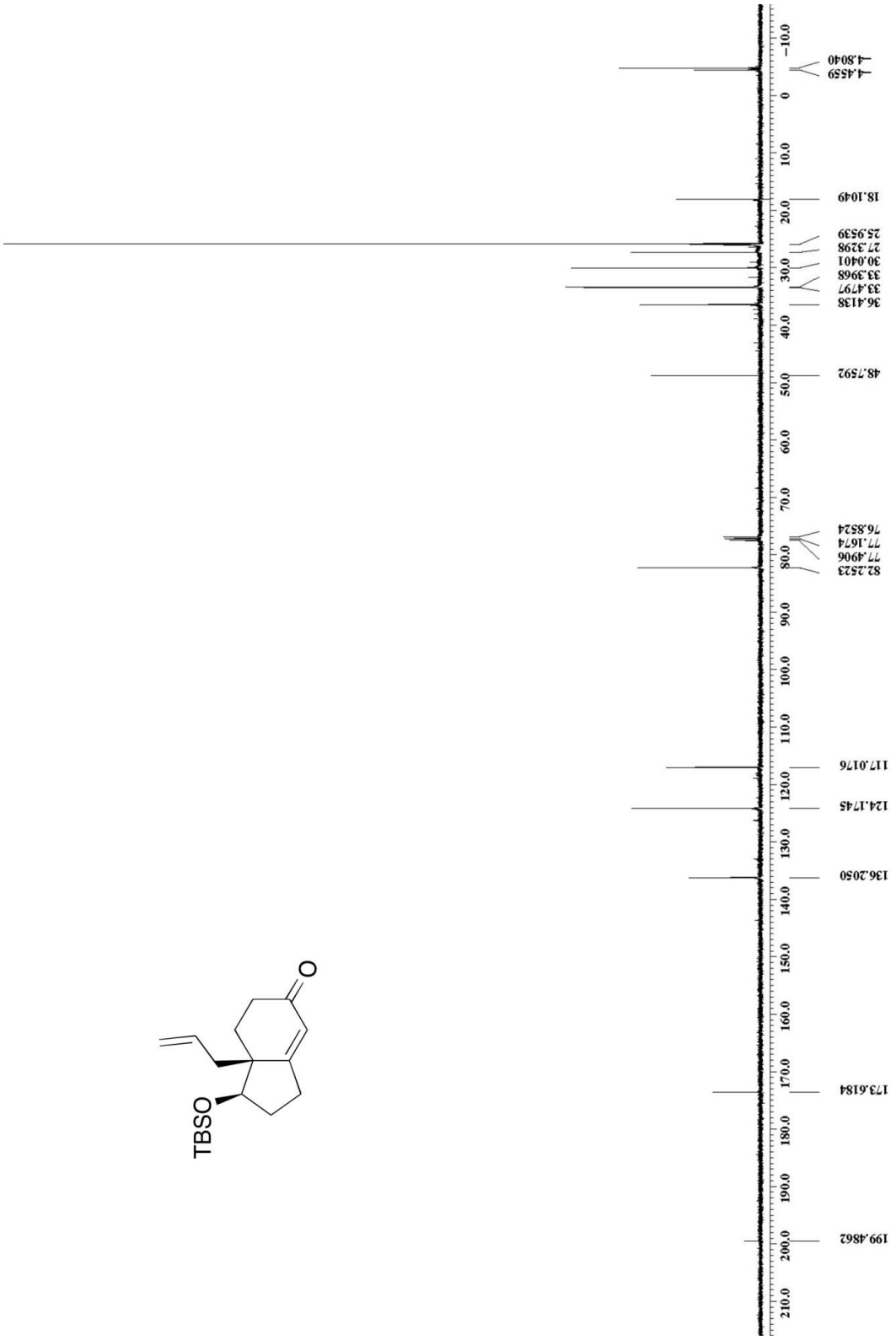
Spectrum 4.1 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **171**.



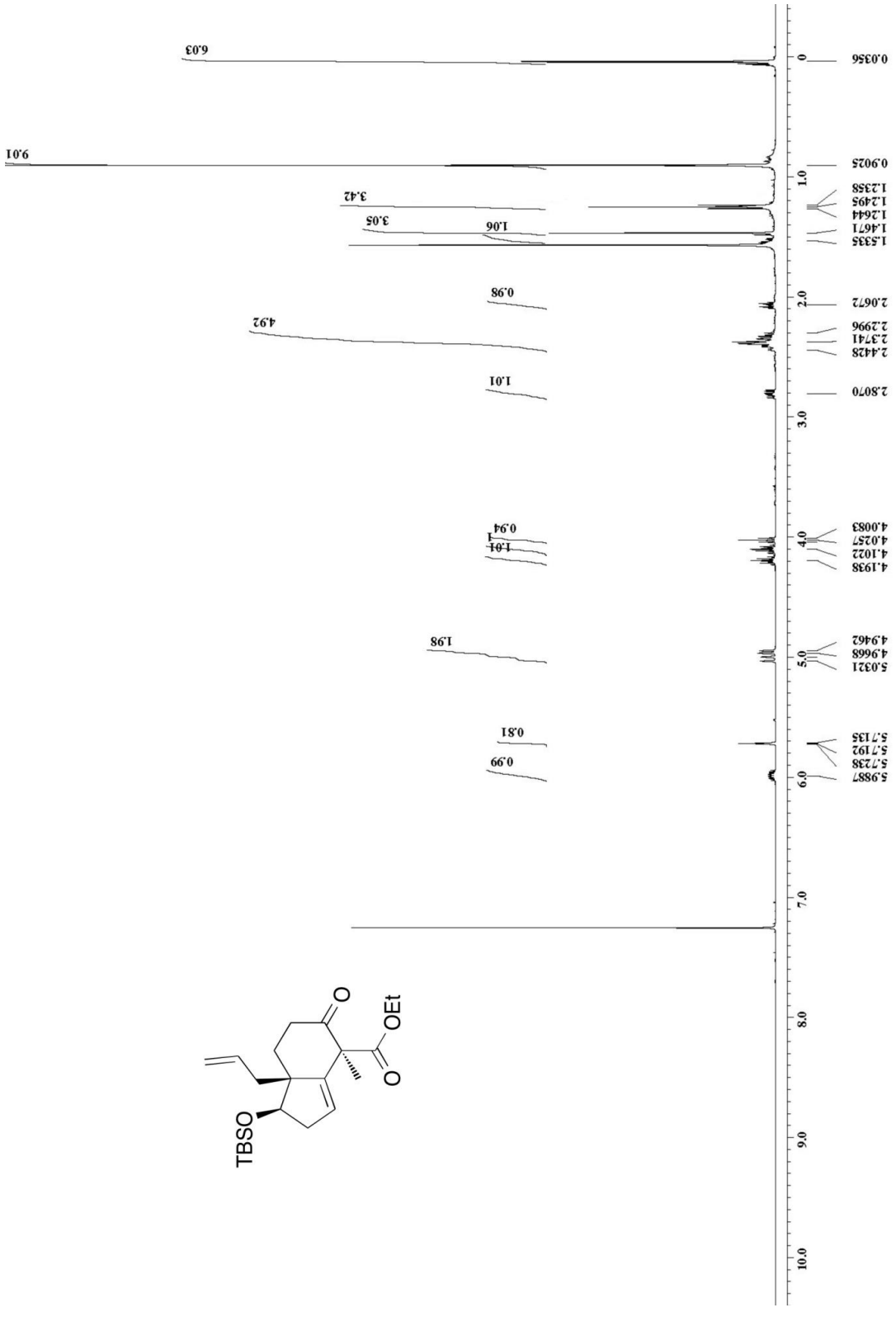
Spectrum 4.2 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **171**.



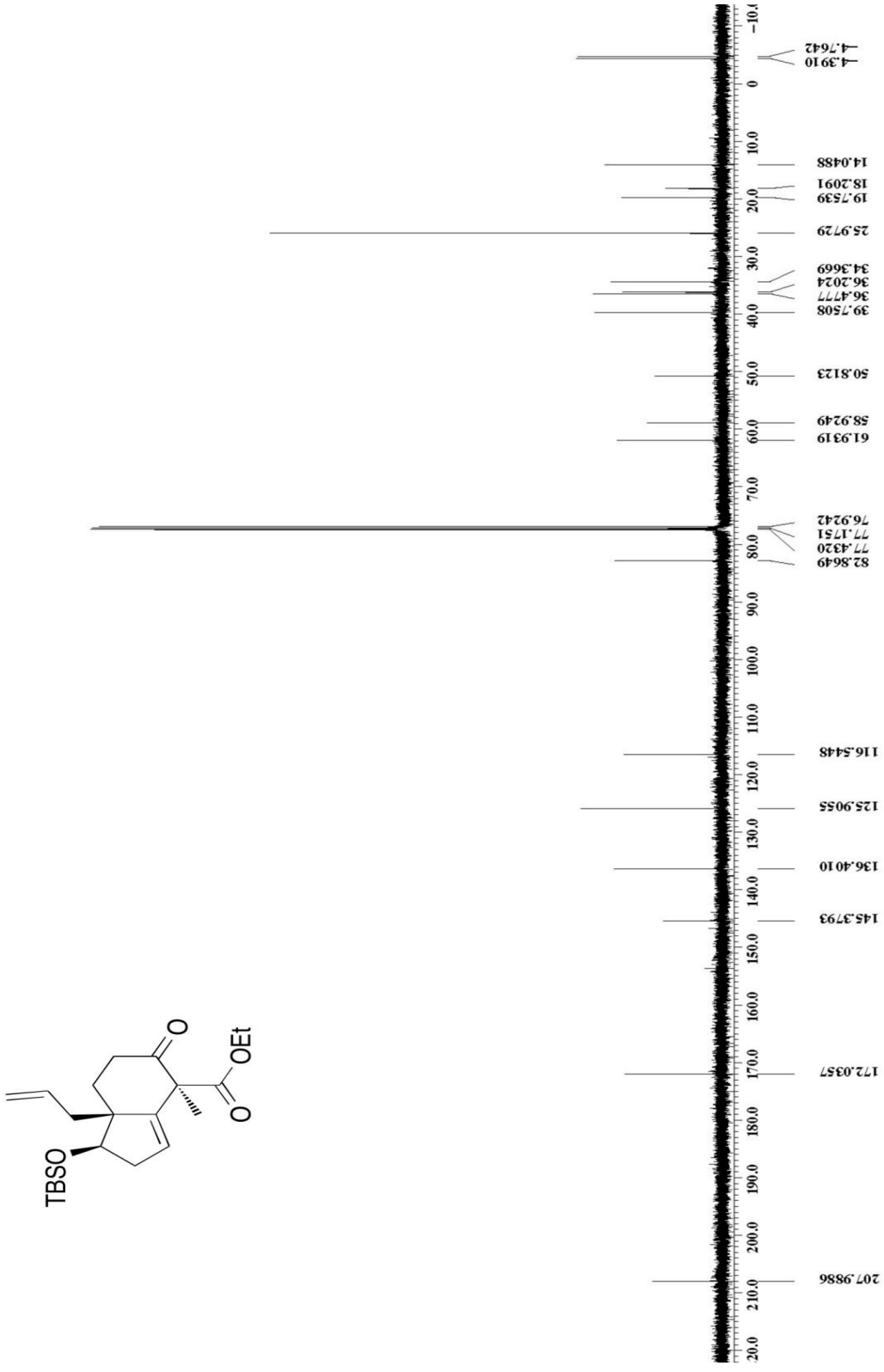
Spectrum 4.3 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **176**.



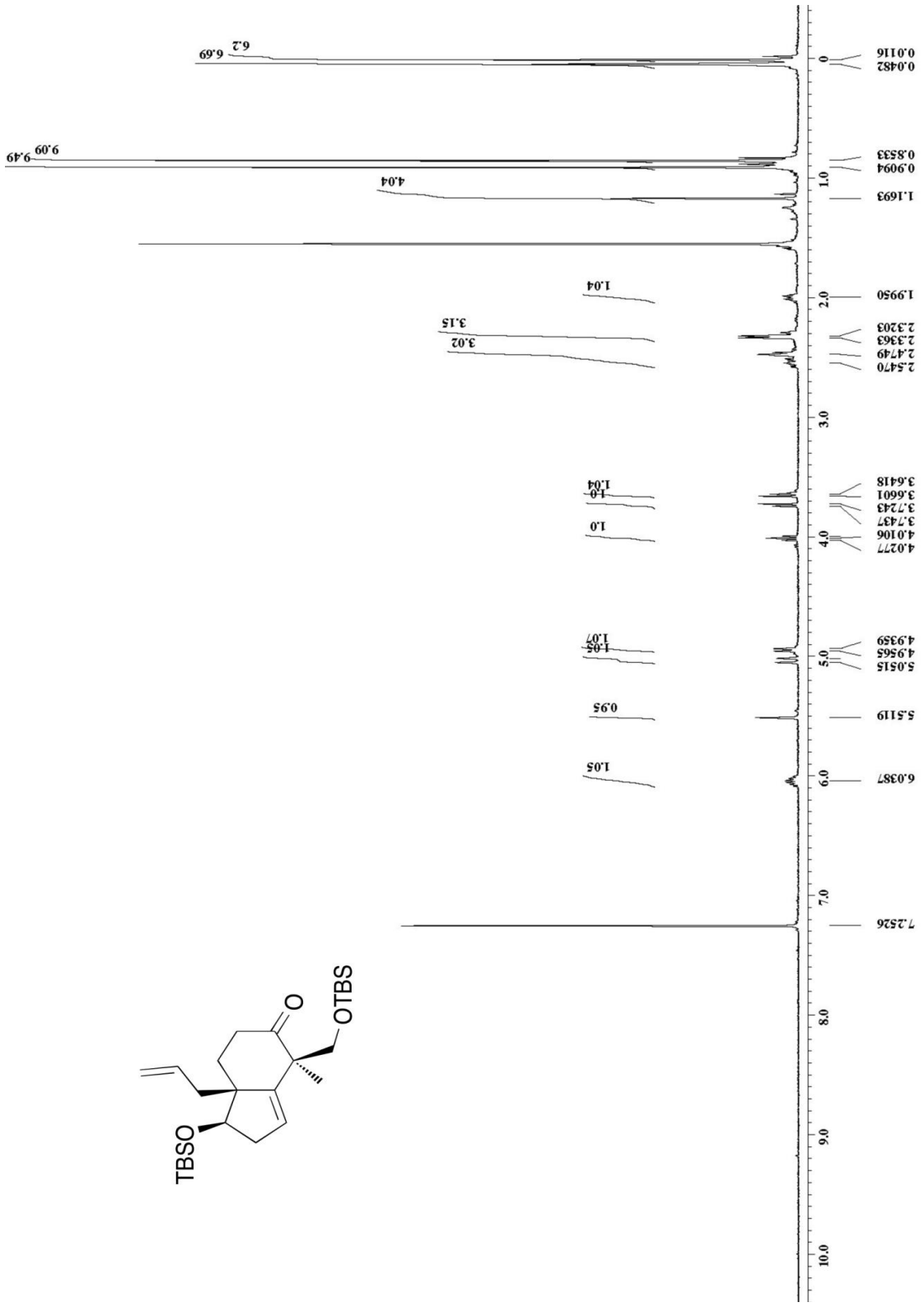
Spectrum 4.4 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **176**.



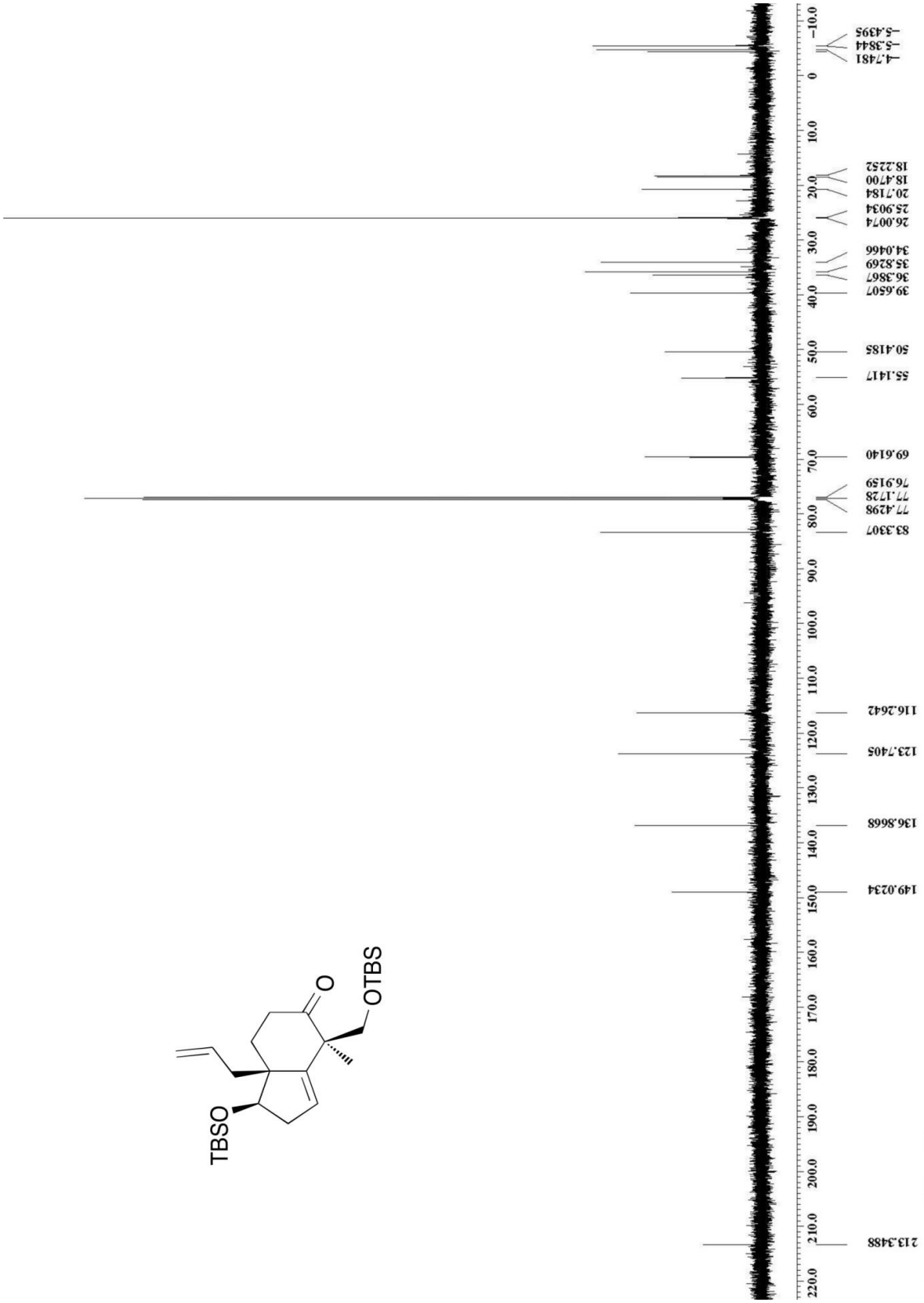
Spectrum 4.5 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **178**.



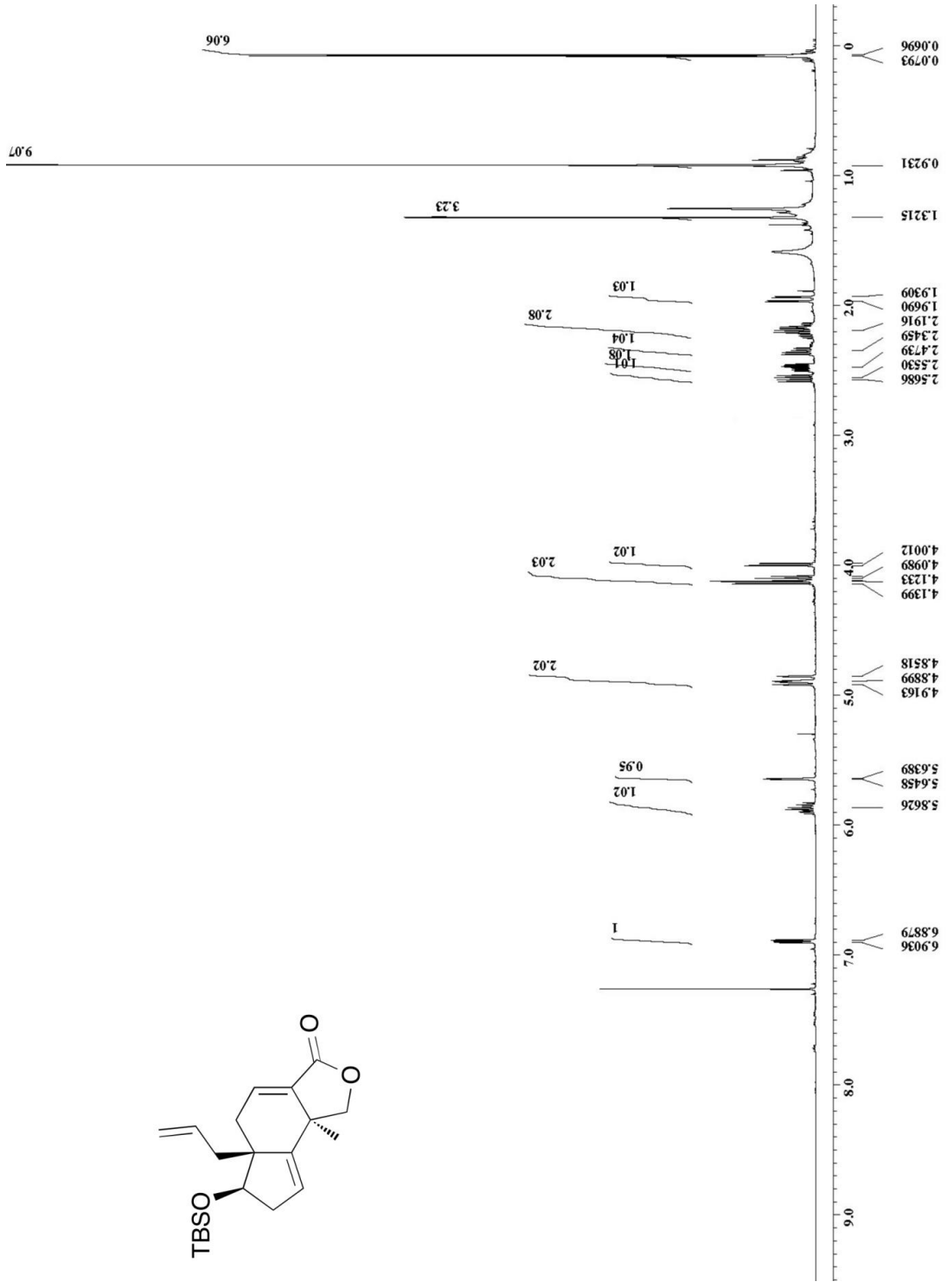
Spectrum 4.6 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **178**.



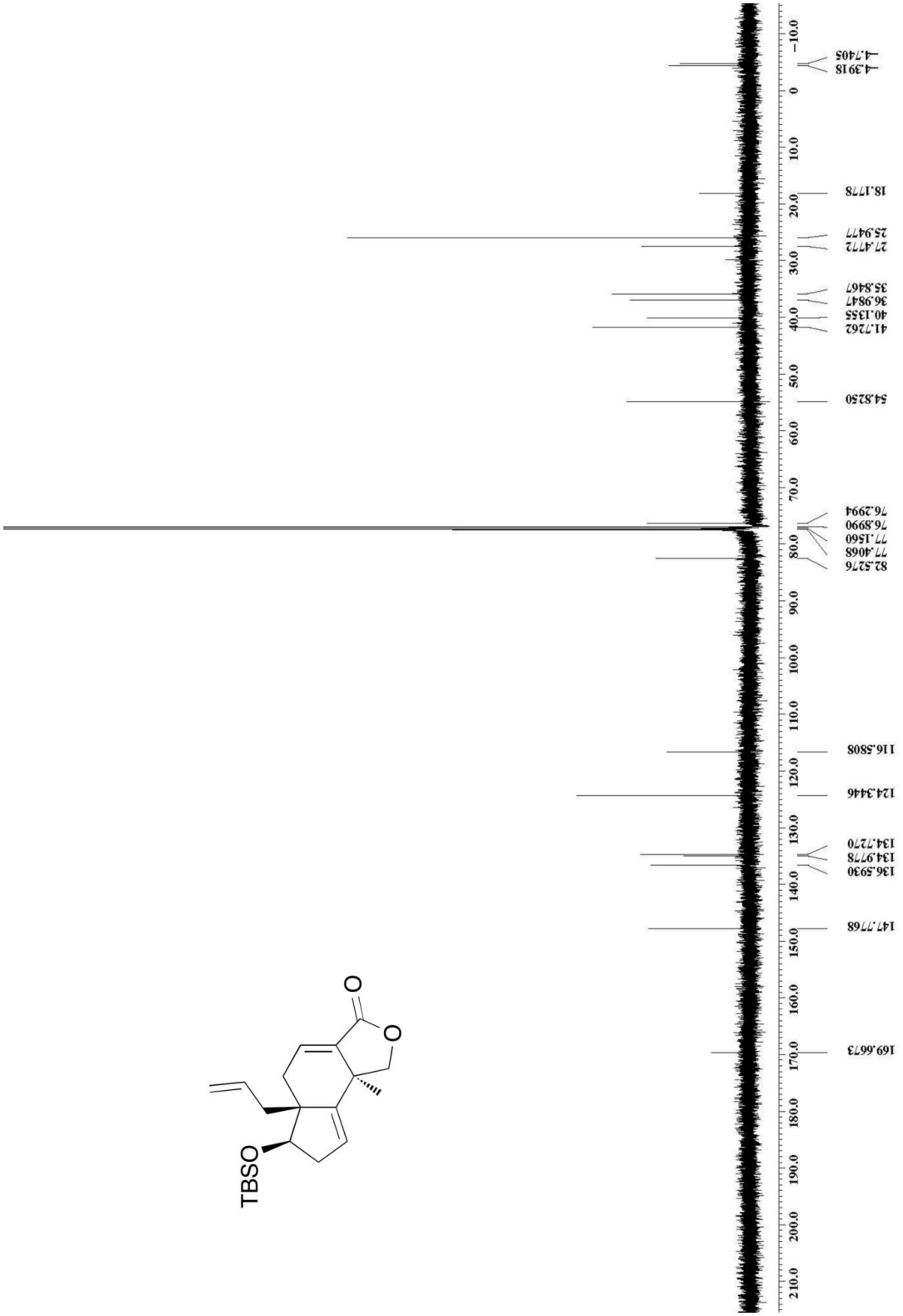
Spectrum 4.7 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **179**.



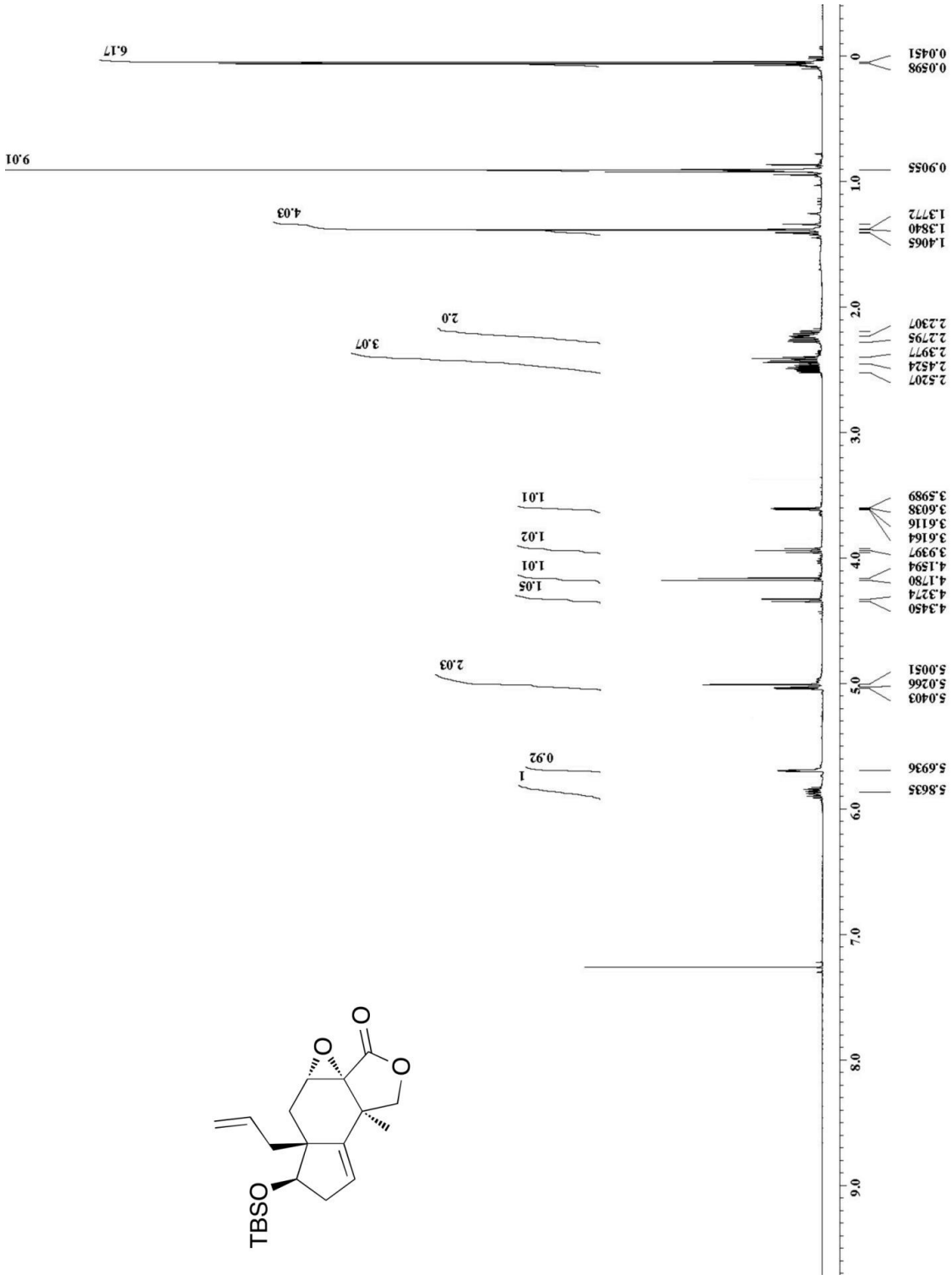
Spectrum 4.8 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **179**.



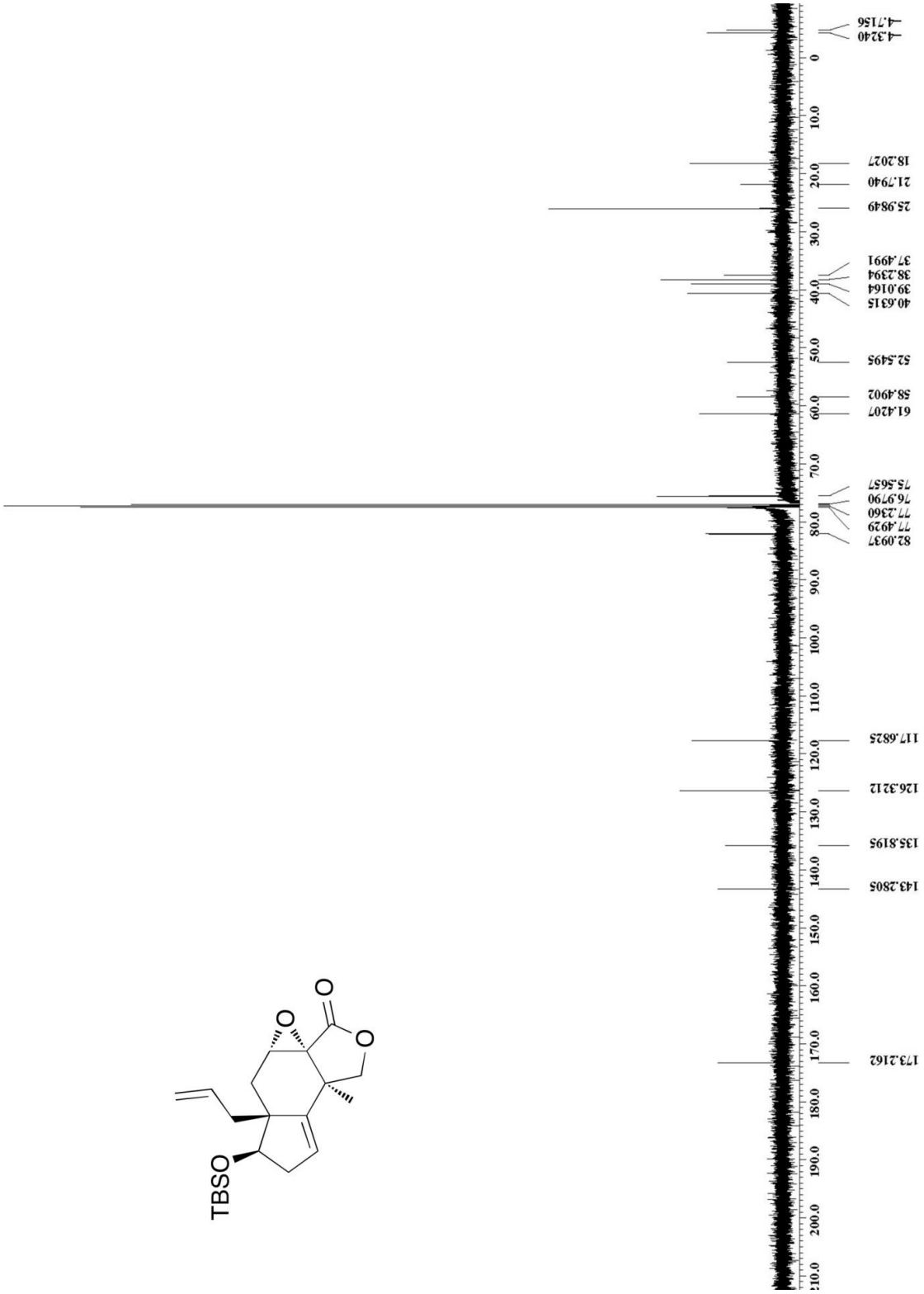
Spectrum 4.9 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **170**.



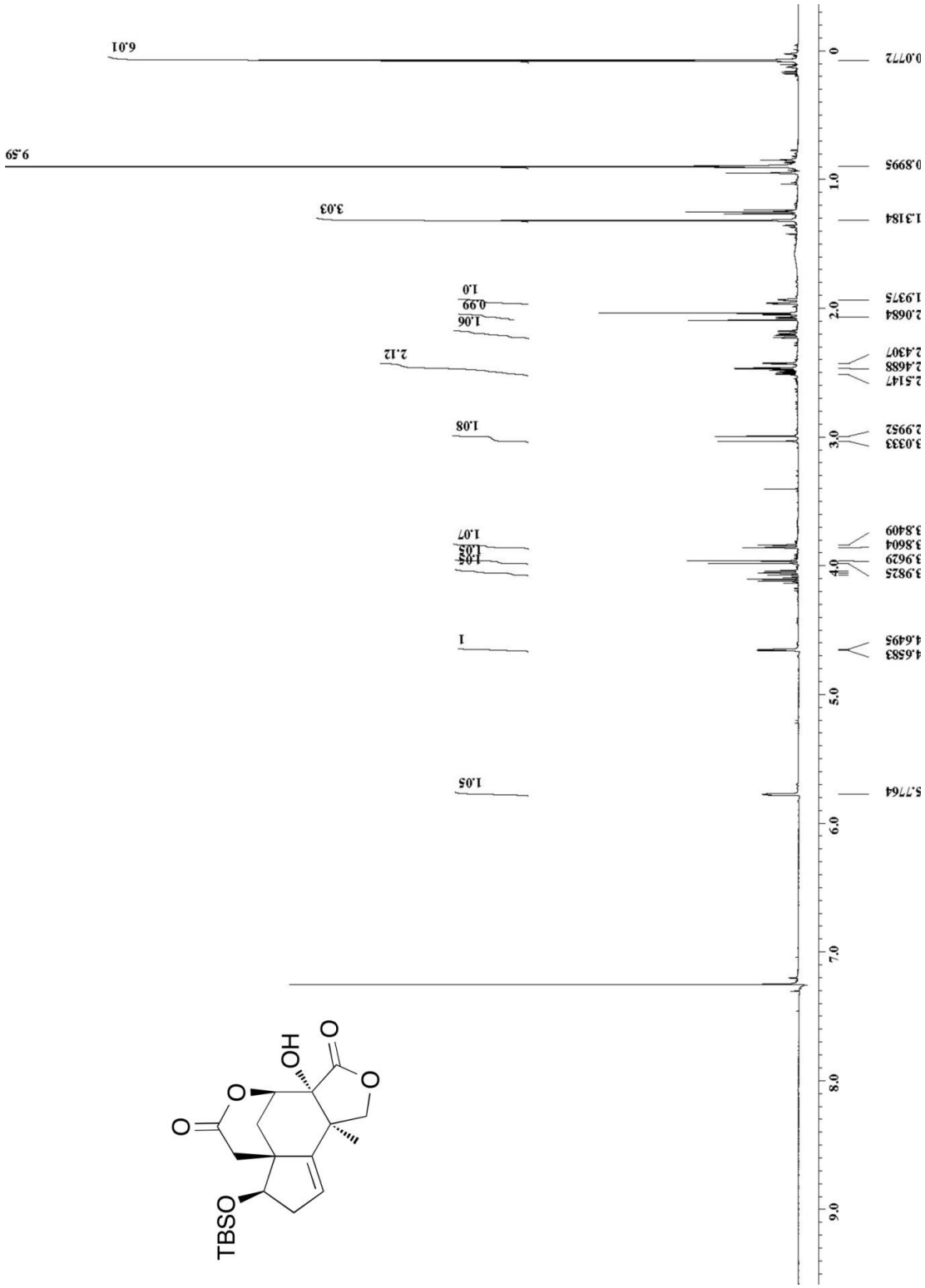
Spectrum 4.10 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **170**.



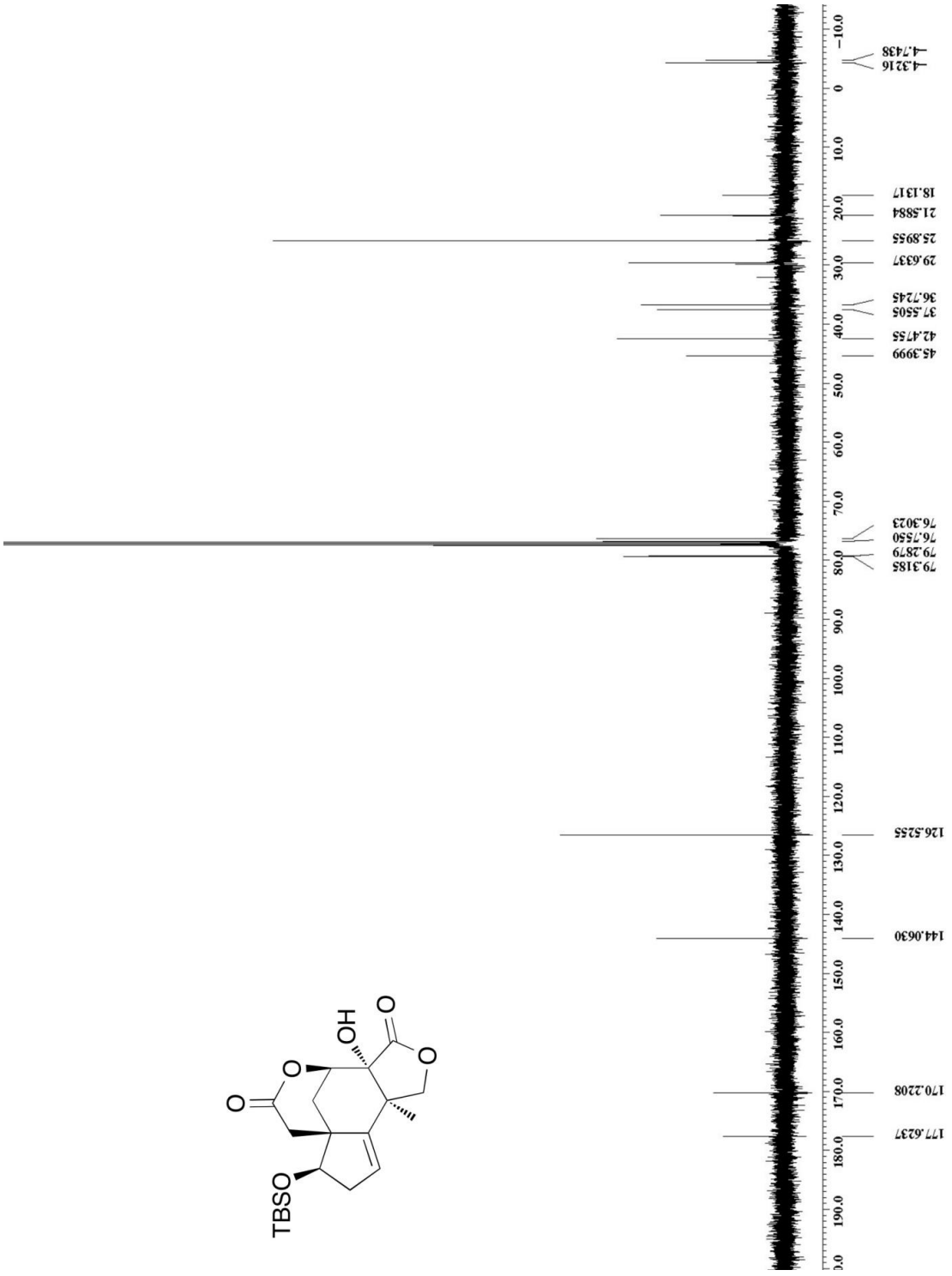
Spectrum 4.11 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **180**.



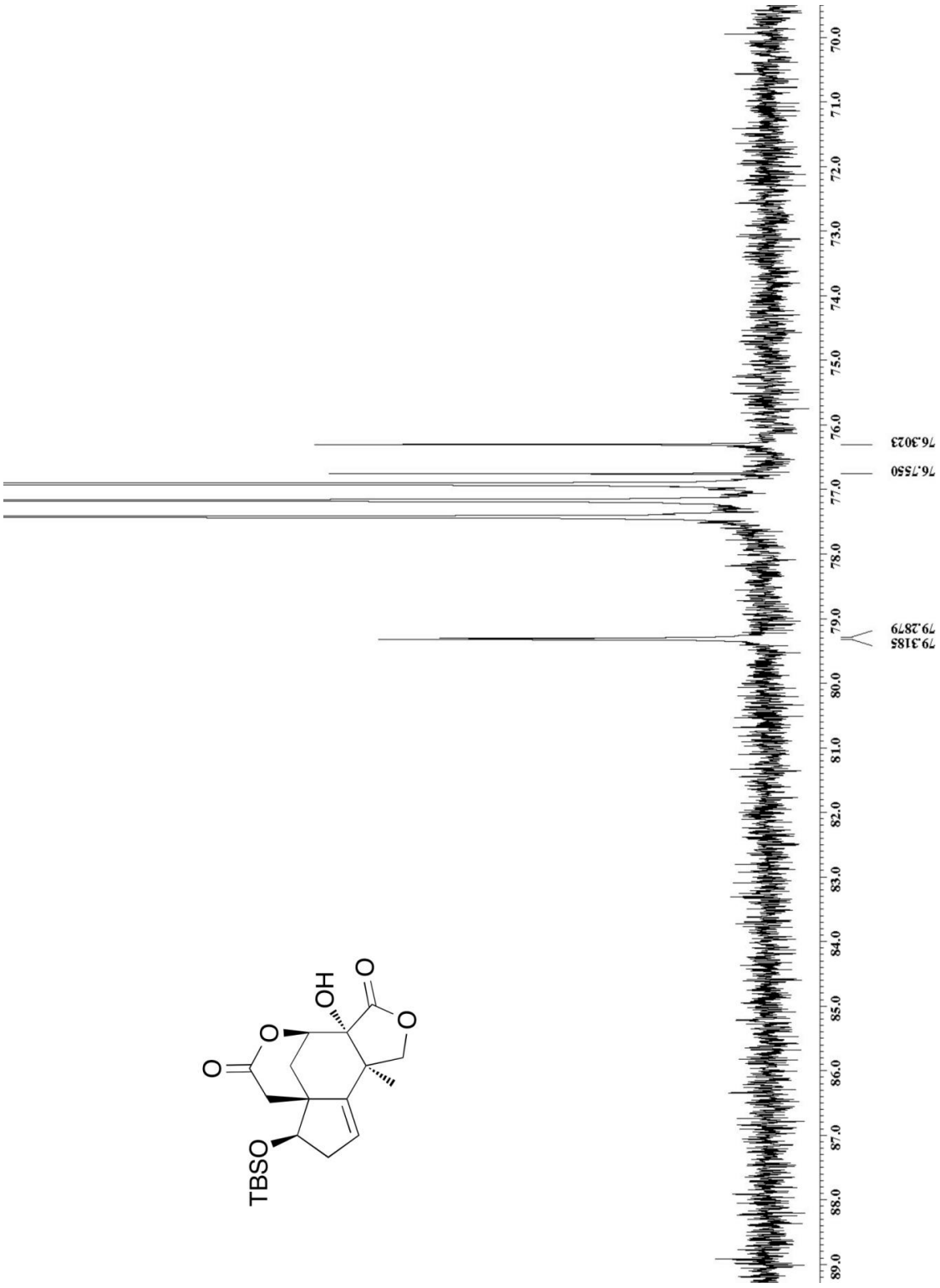
Spectrum 4.12 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **180**.



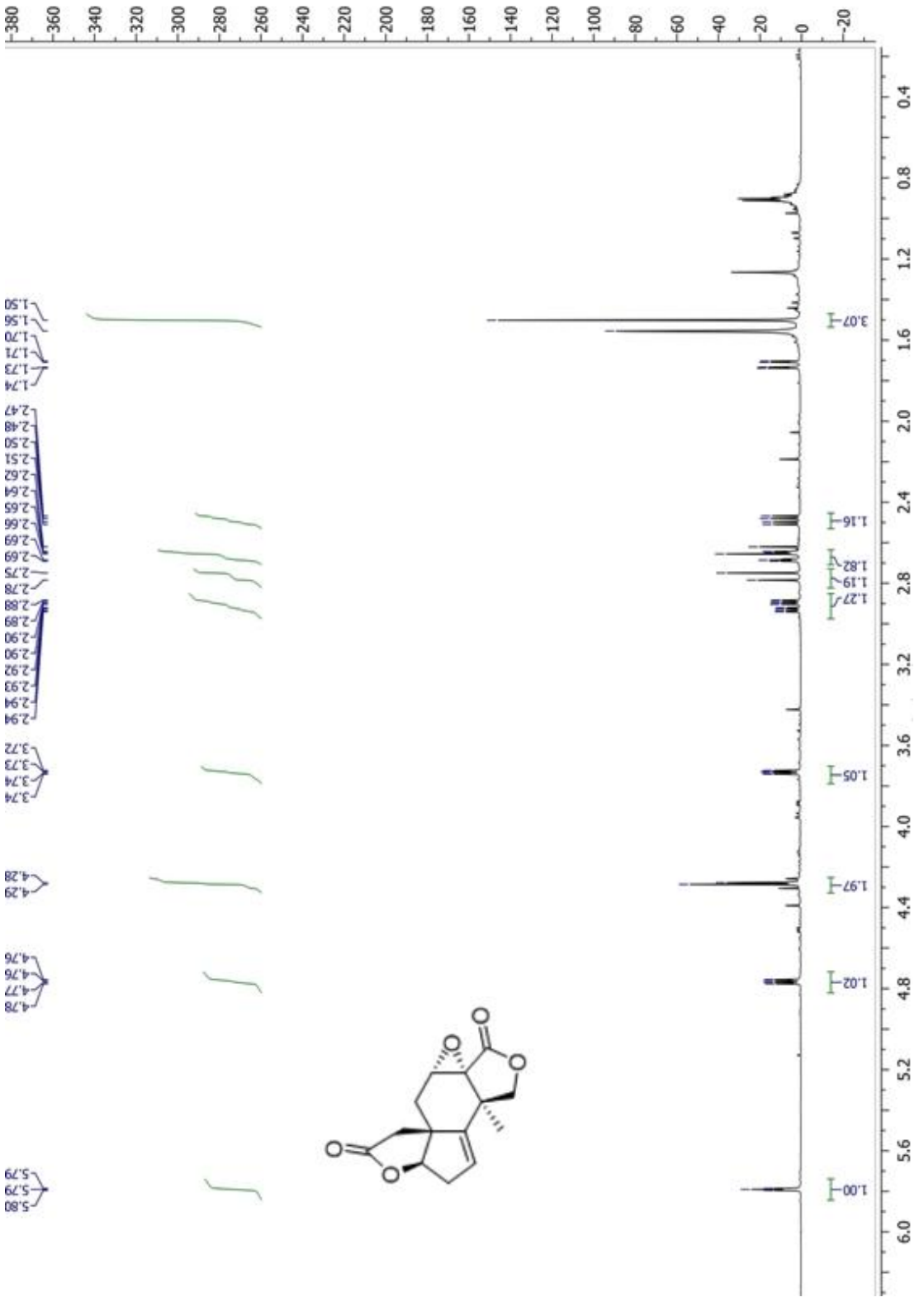
Spectrum 4.13 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **181**.



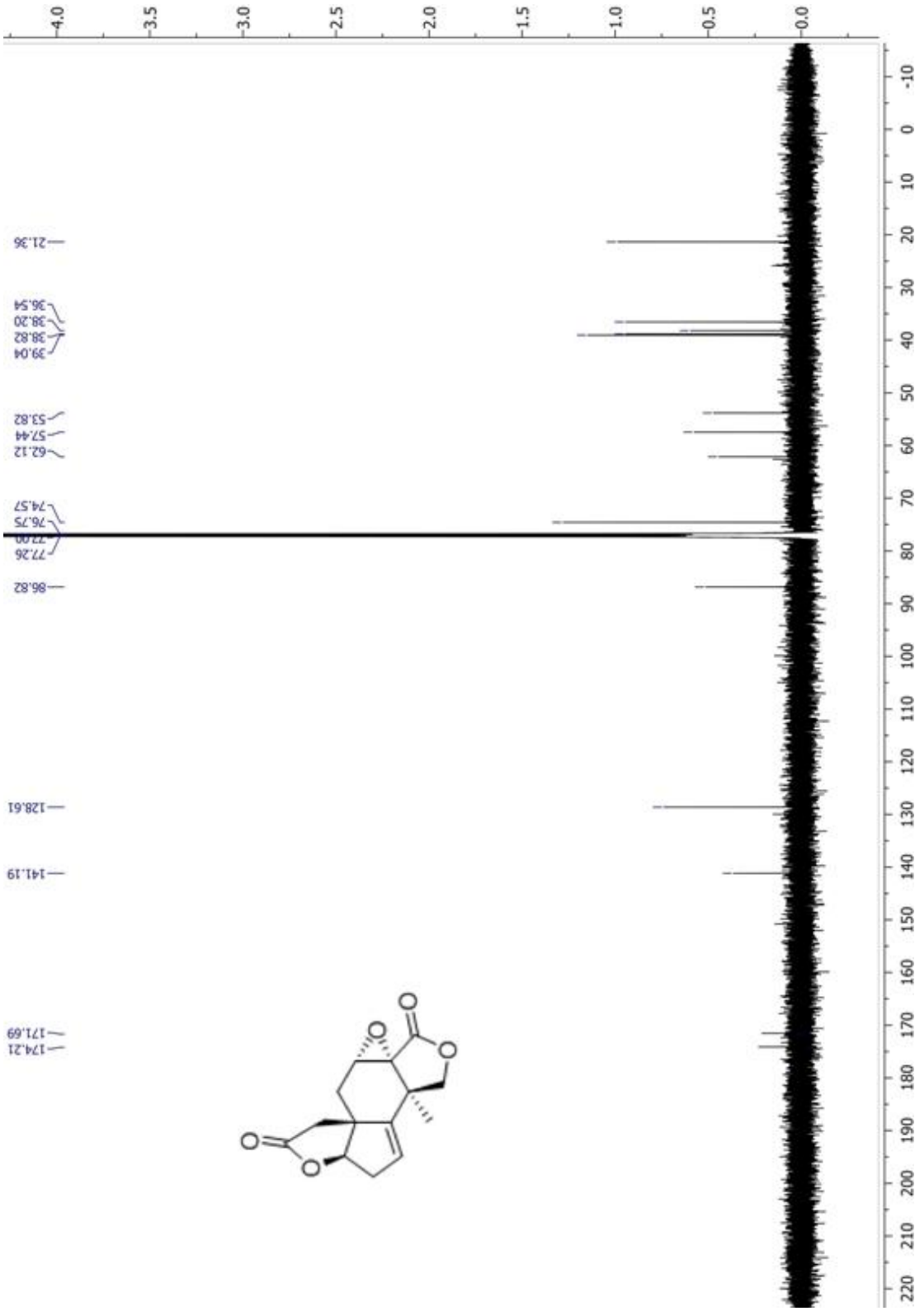
Spectrum 4.14 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **181**.



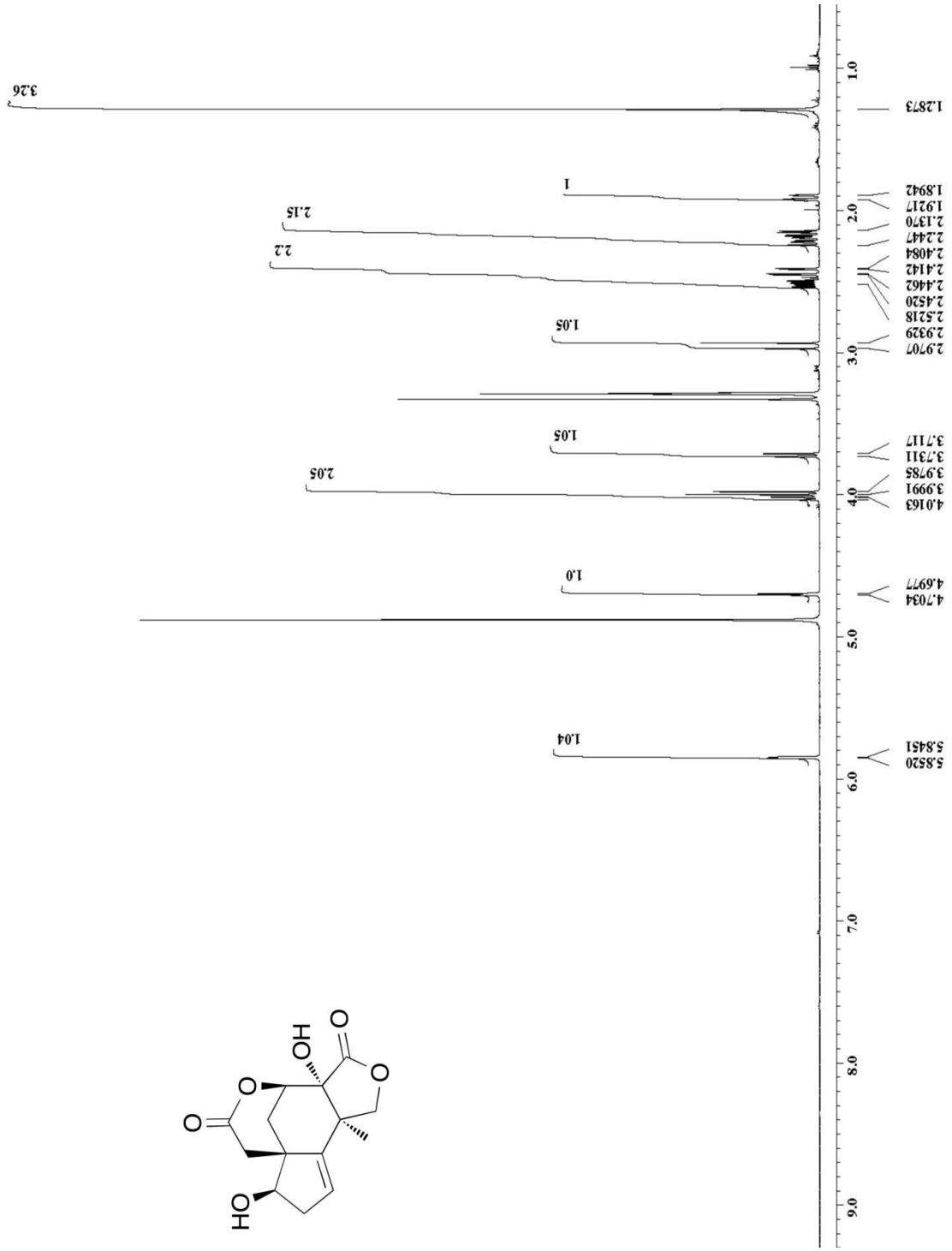
Spectrum 4.15 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **181.**



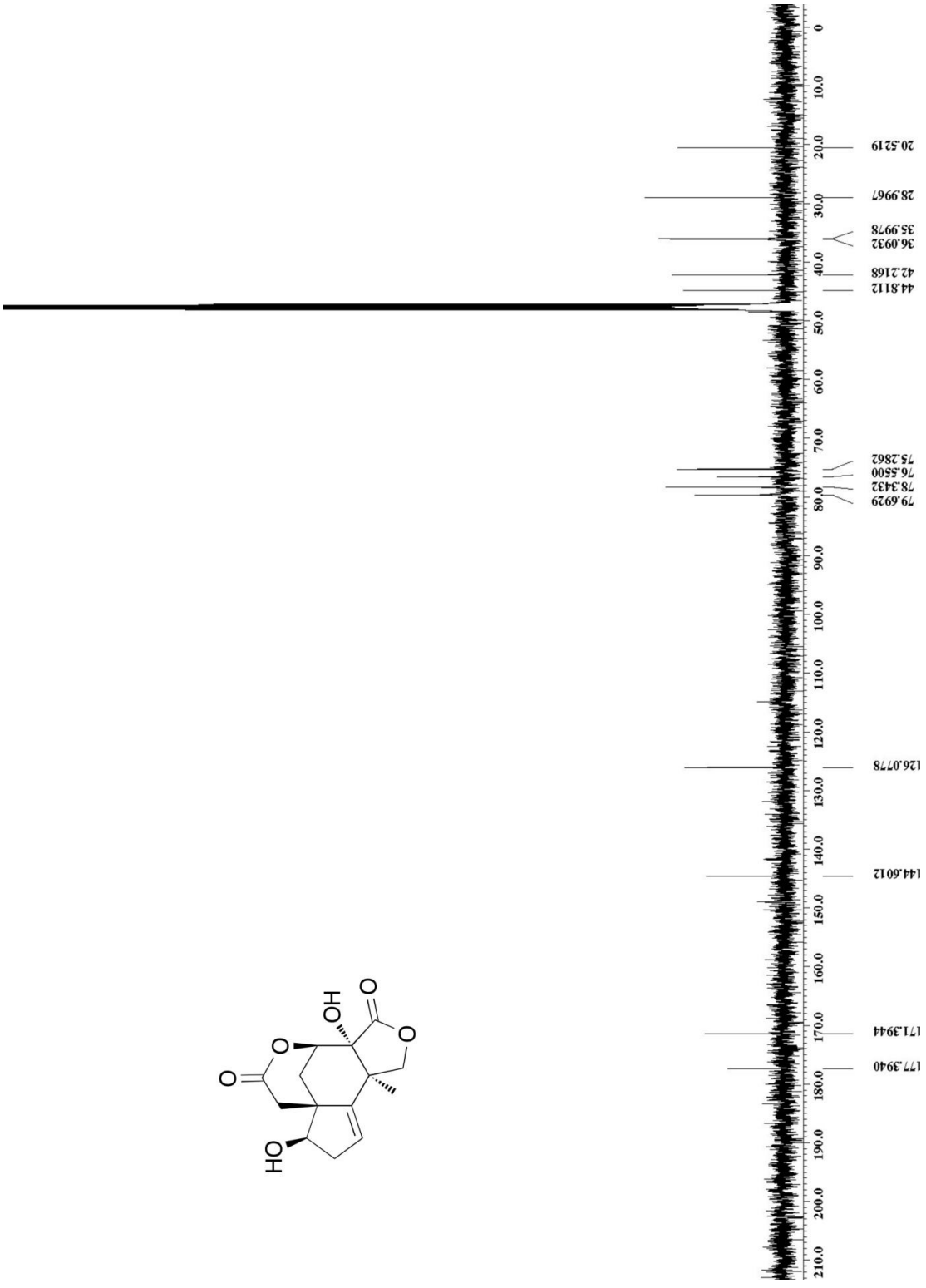
Spectrum 4.16 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **182**.



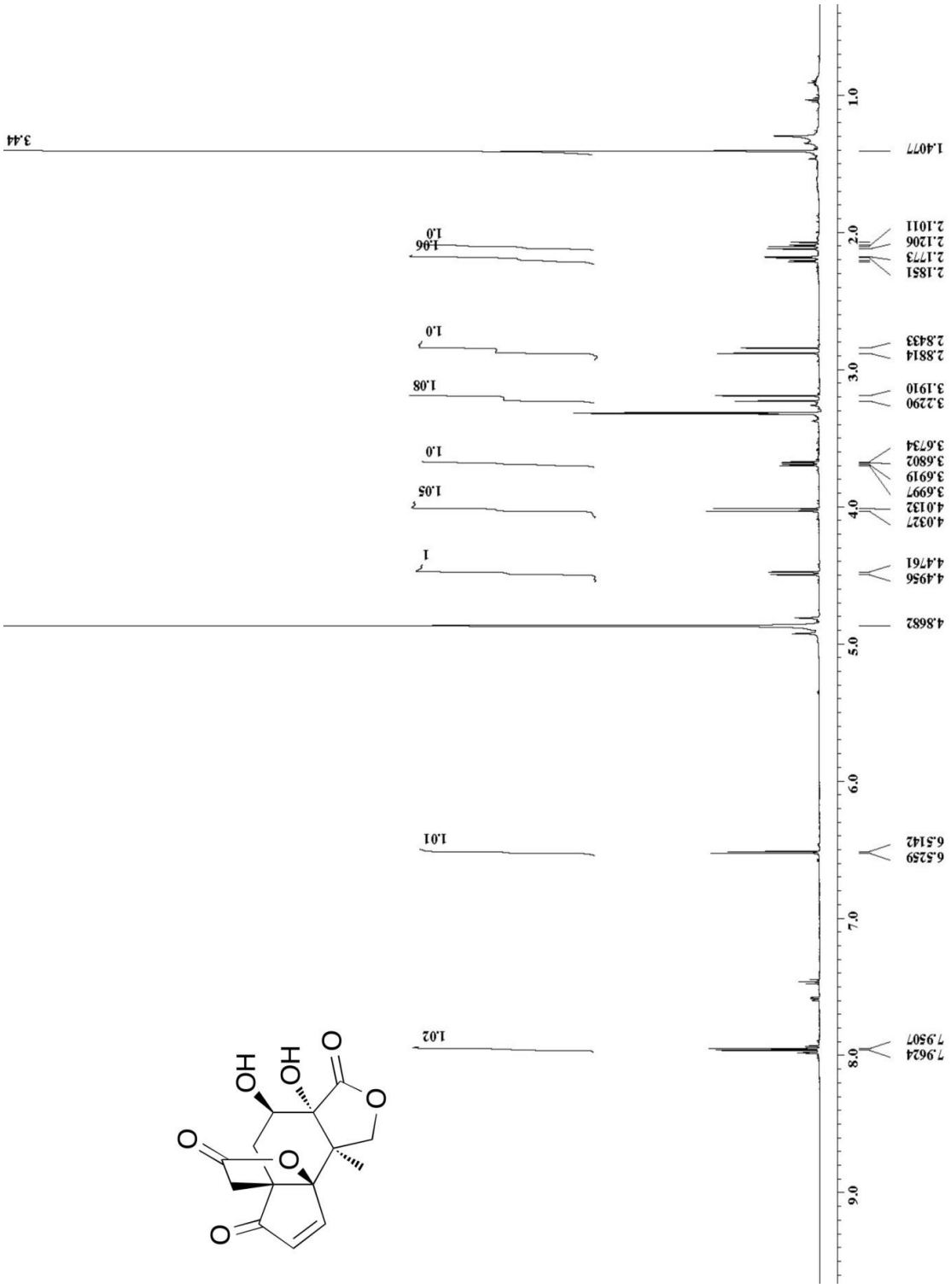
Spectrum 4.17 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **182**.



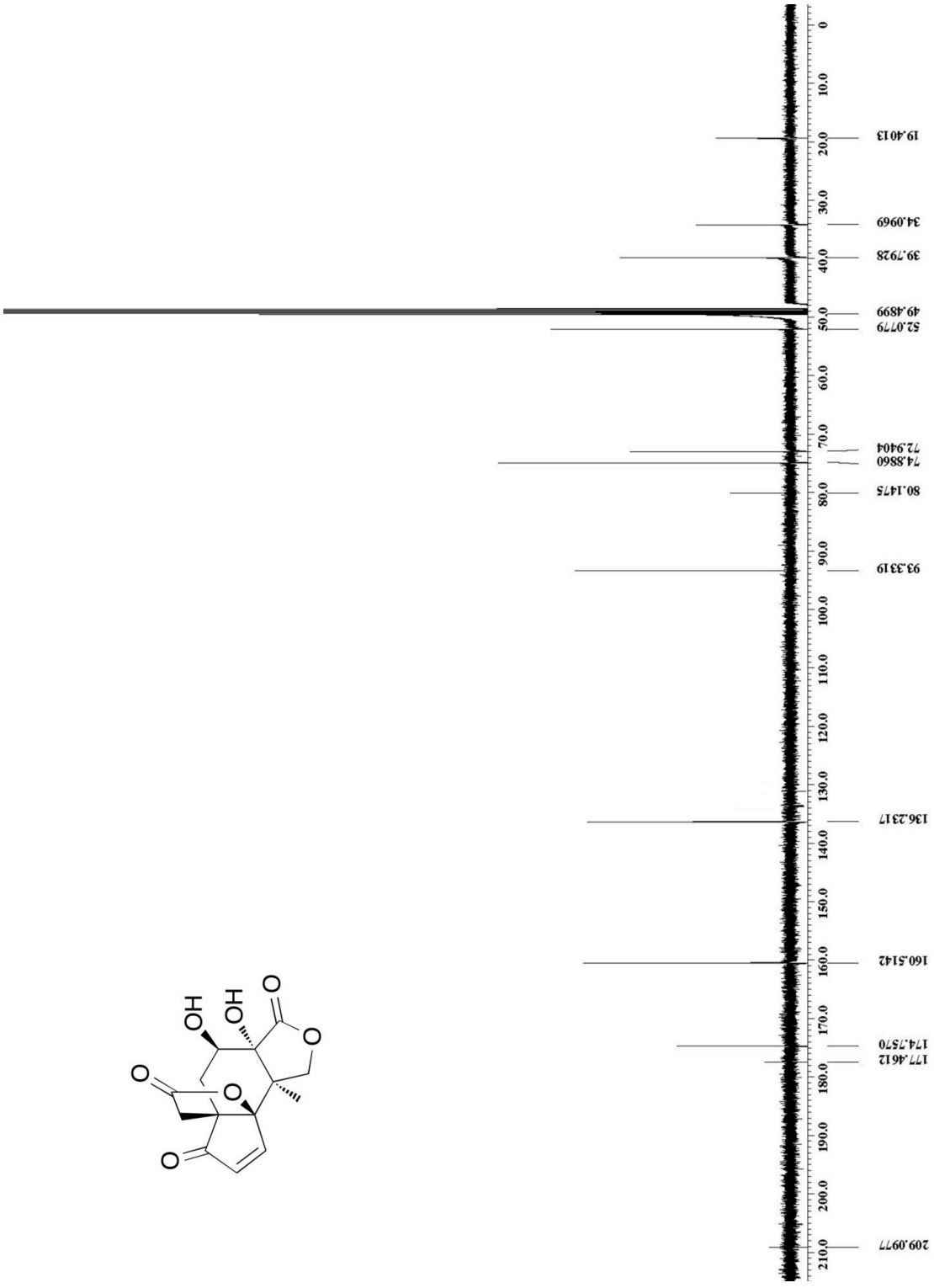
Spectrum 4.18 ^{1}H NMR (CD_3OD, 500 MHz) of compound **169**.



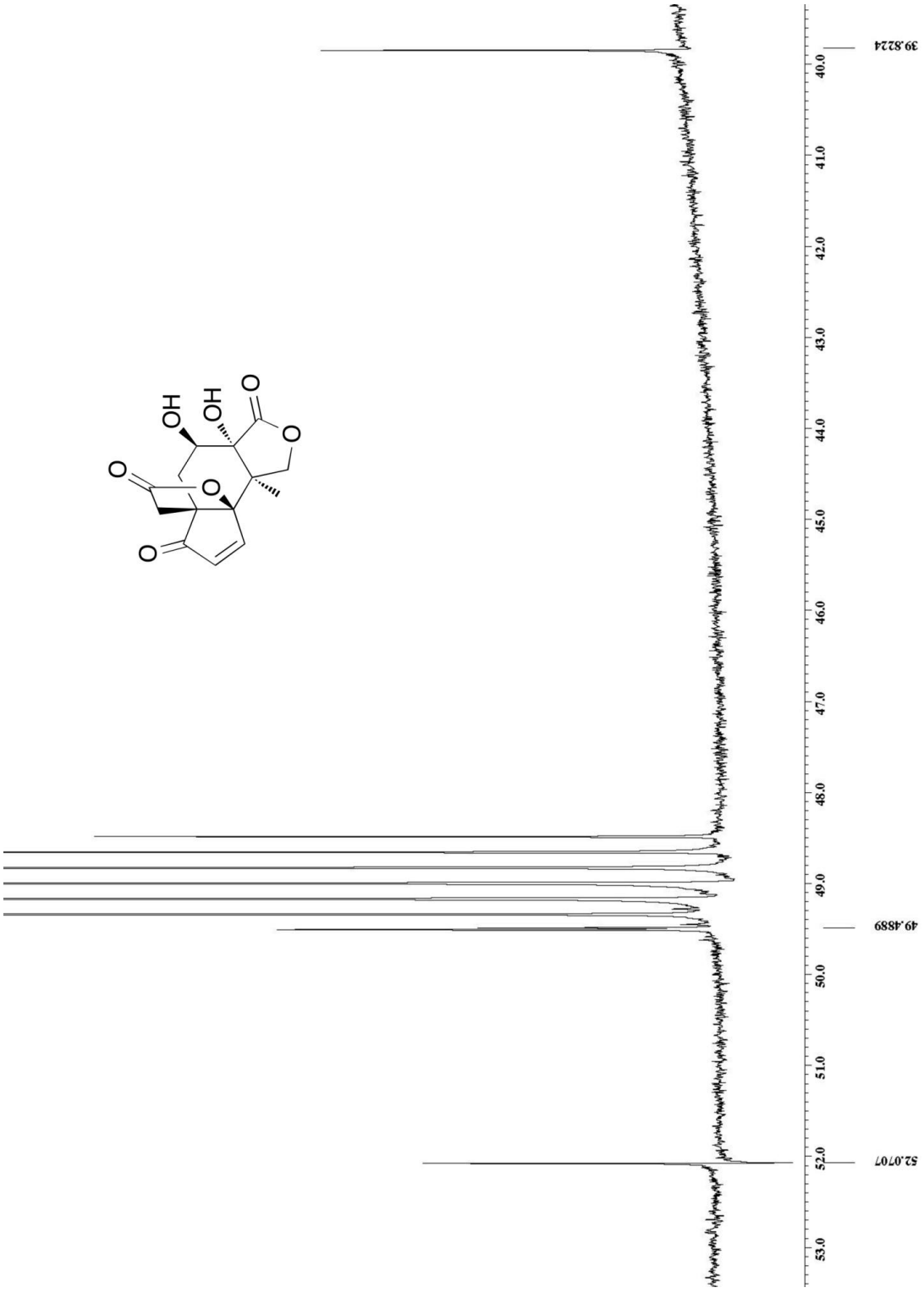
Spectrum 4.19 ^{13}C NMR (CD_3OD, 125 MHz) of compound **167**.



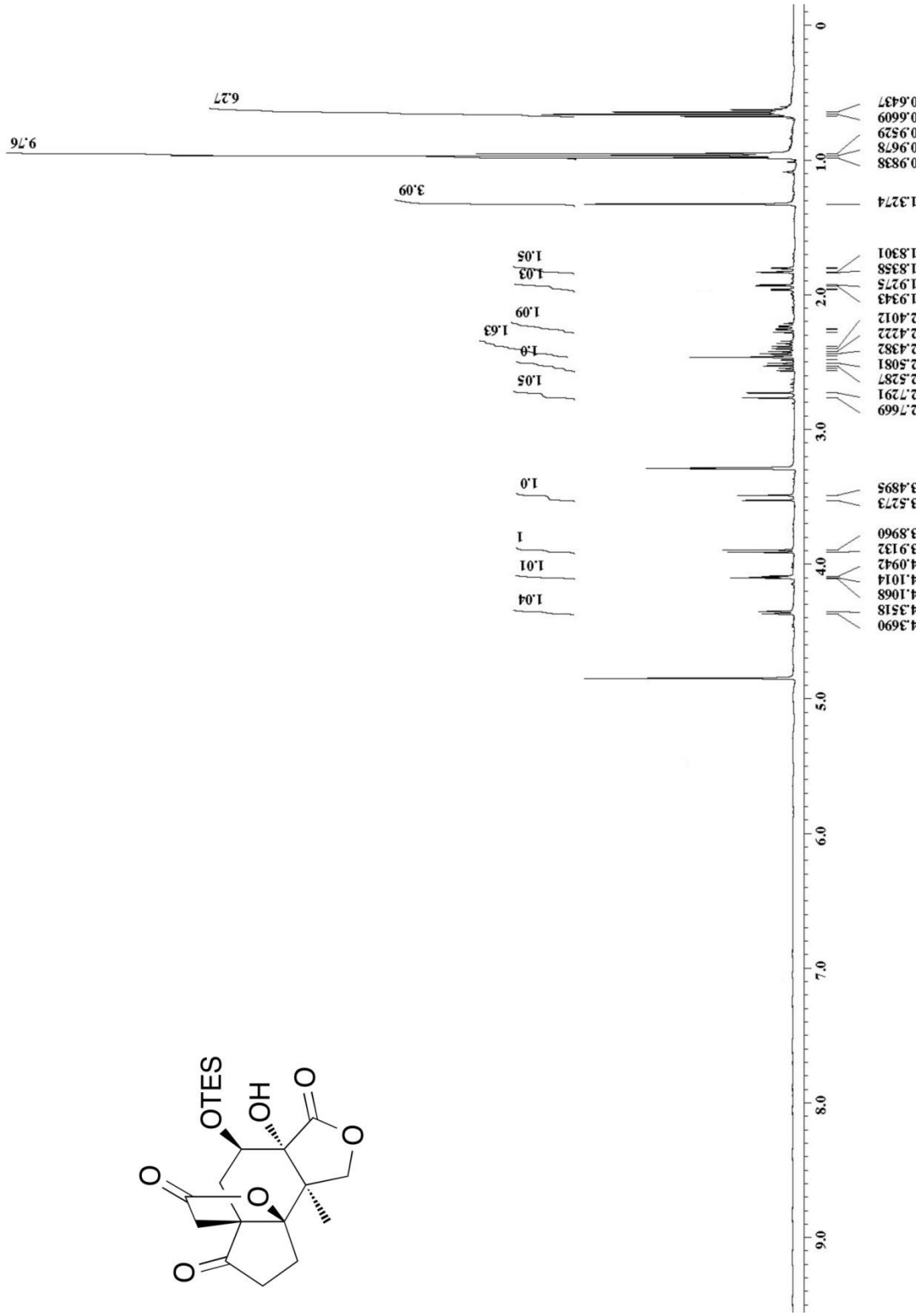
Spectrum 4.20 ^{1}H NMR (CD_3OD, 500 MHz) of compound **167**.



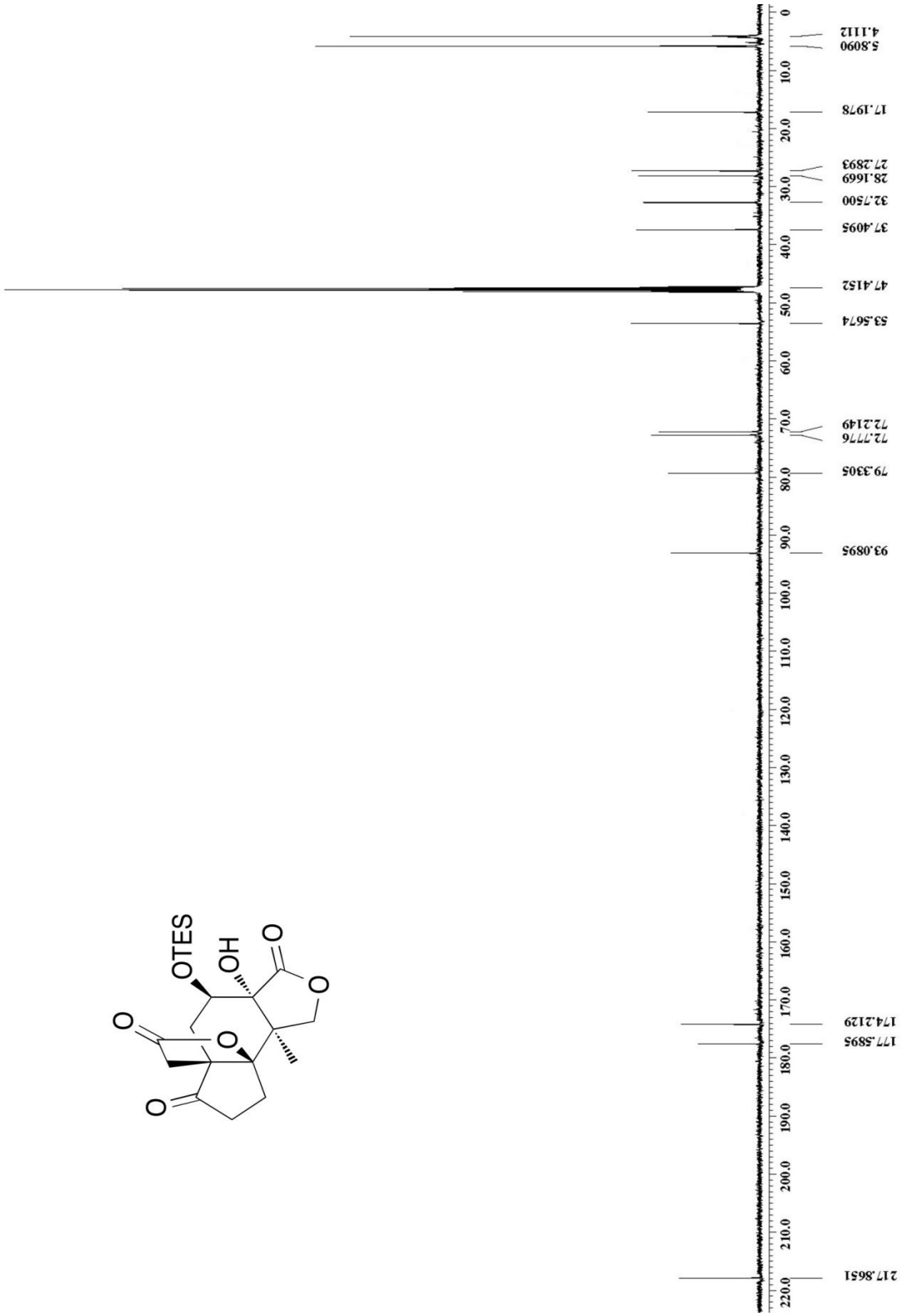
Spectrum 4.21 ^{13}C NMR (CD_3OD, 125 MHz) of compound **167**.



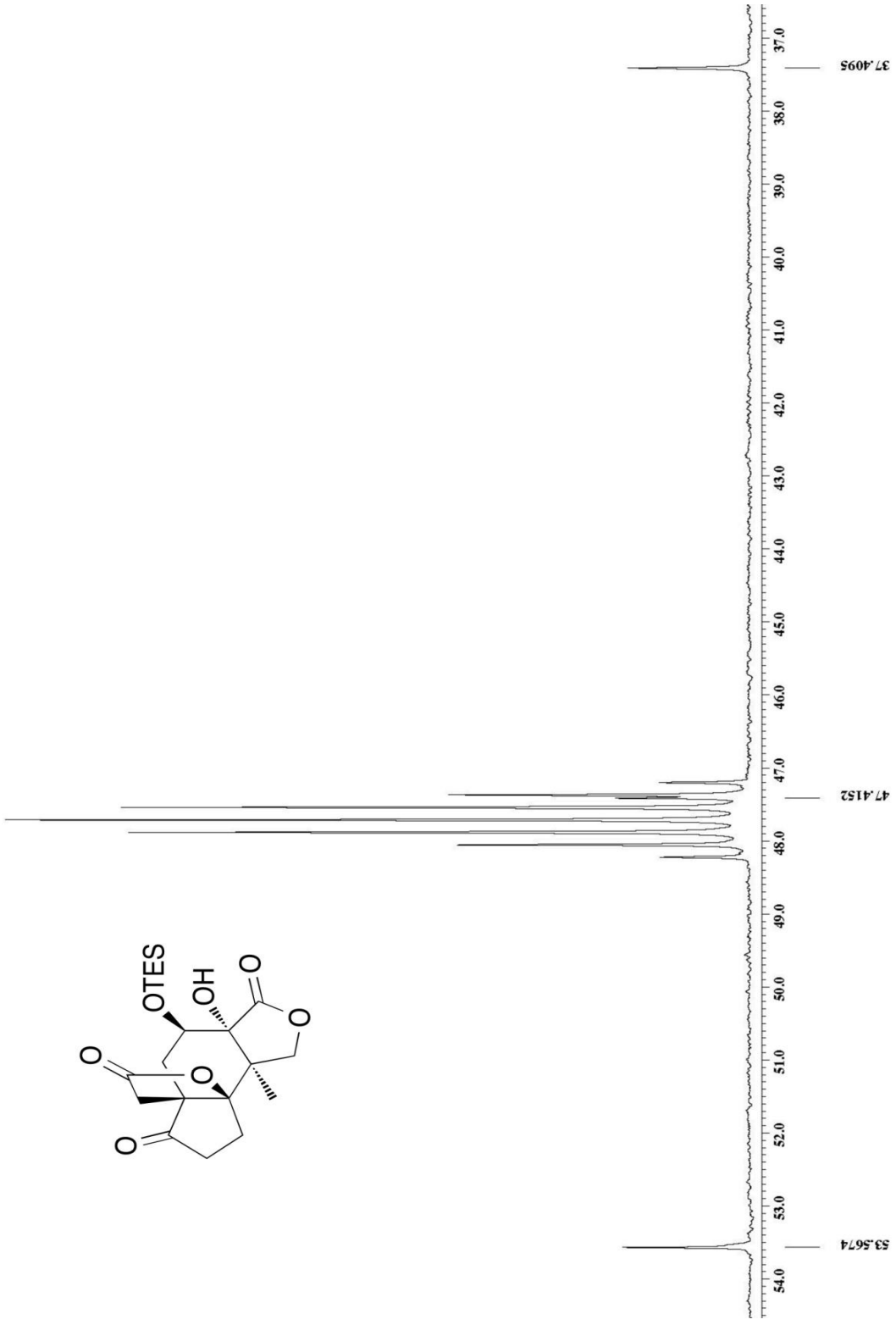
Spectrum 4.22 ^{13}C NMR (CD_3OD, 125 MHz) of compound **167**.



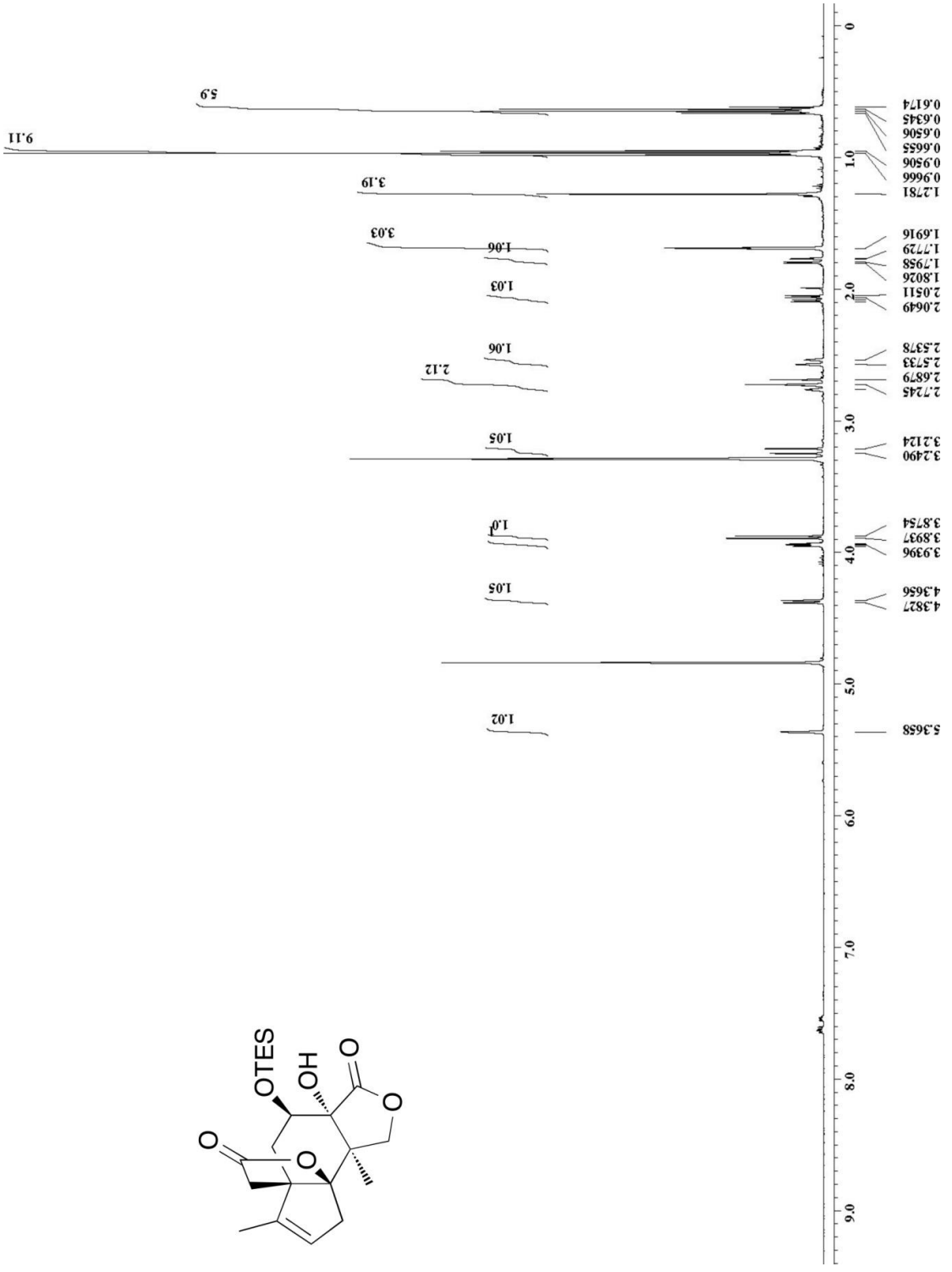
Spectrum 4.23 ^{1}H NMR (CD_3OD, 500 MHz) of compound **184**.



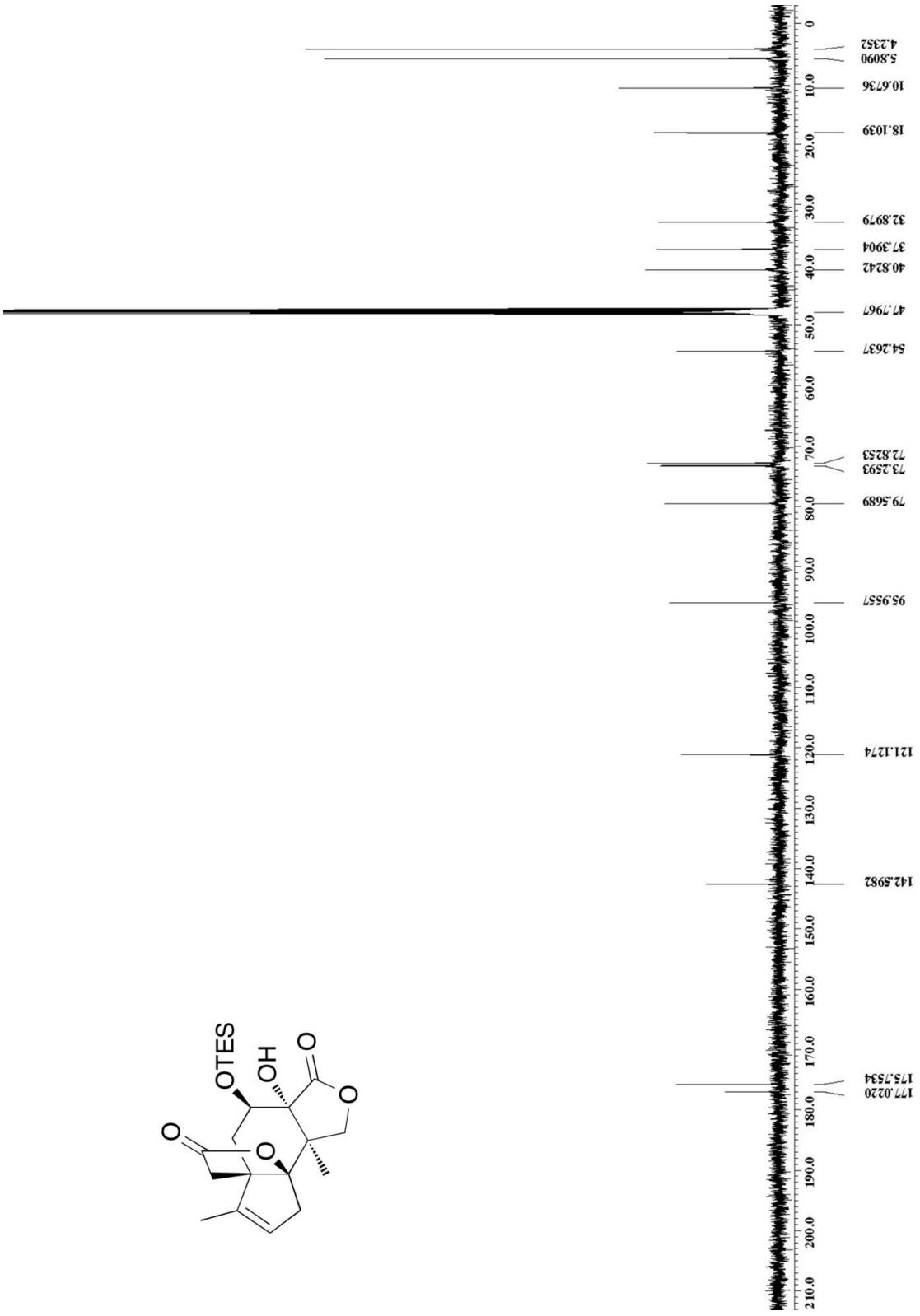
Spectrum 4.24 ^{13}C NMR (CD_3OD, 125 MHz) of compound **184**.



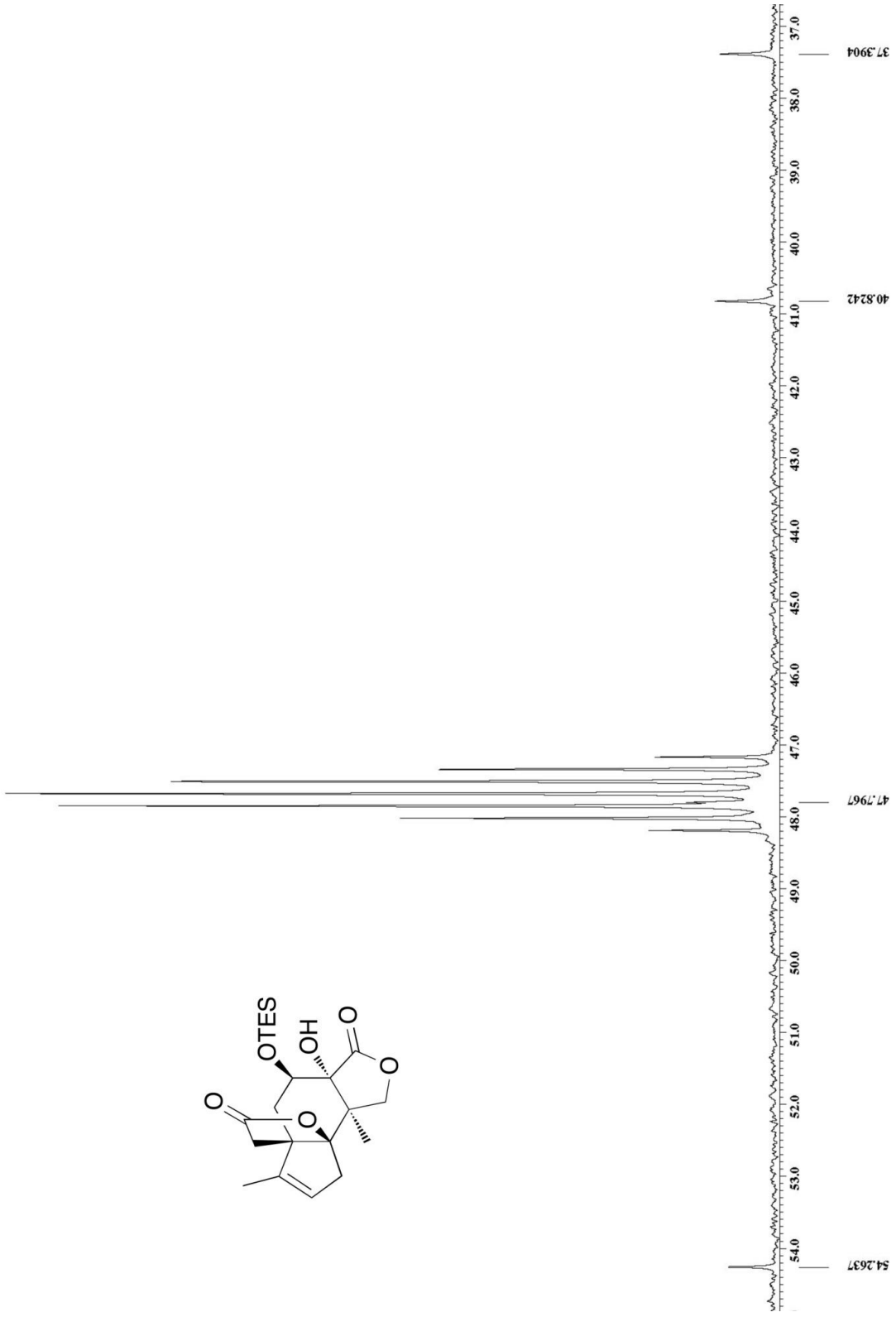
Spectrum 4.25 ^{13}C NMR (CD_3OD, 125 MHz) of compound **184**.



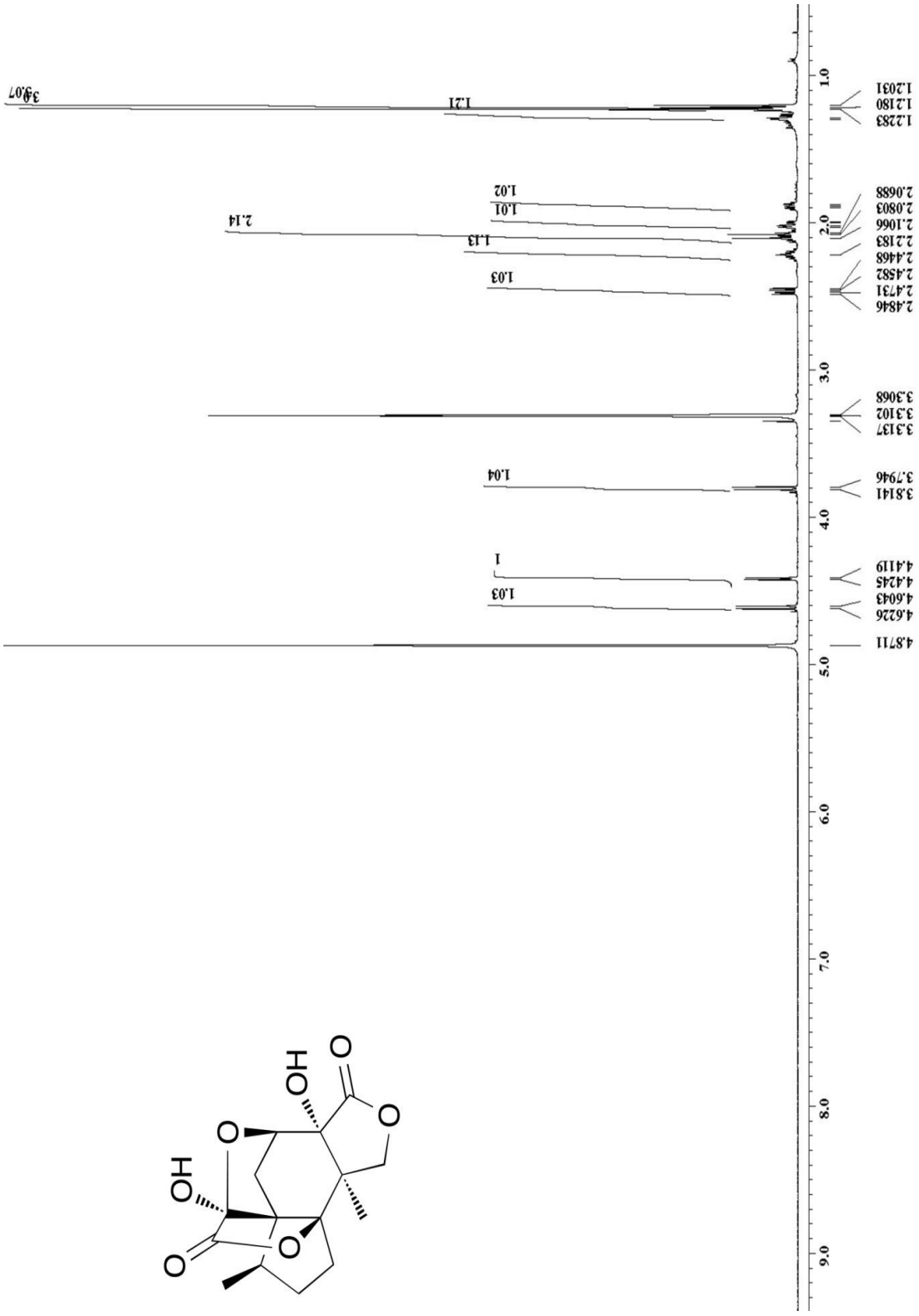
Spectrum 4.26 ^{1}H NMR (CD_3OD, 500 MHz) of compound **185**.



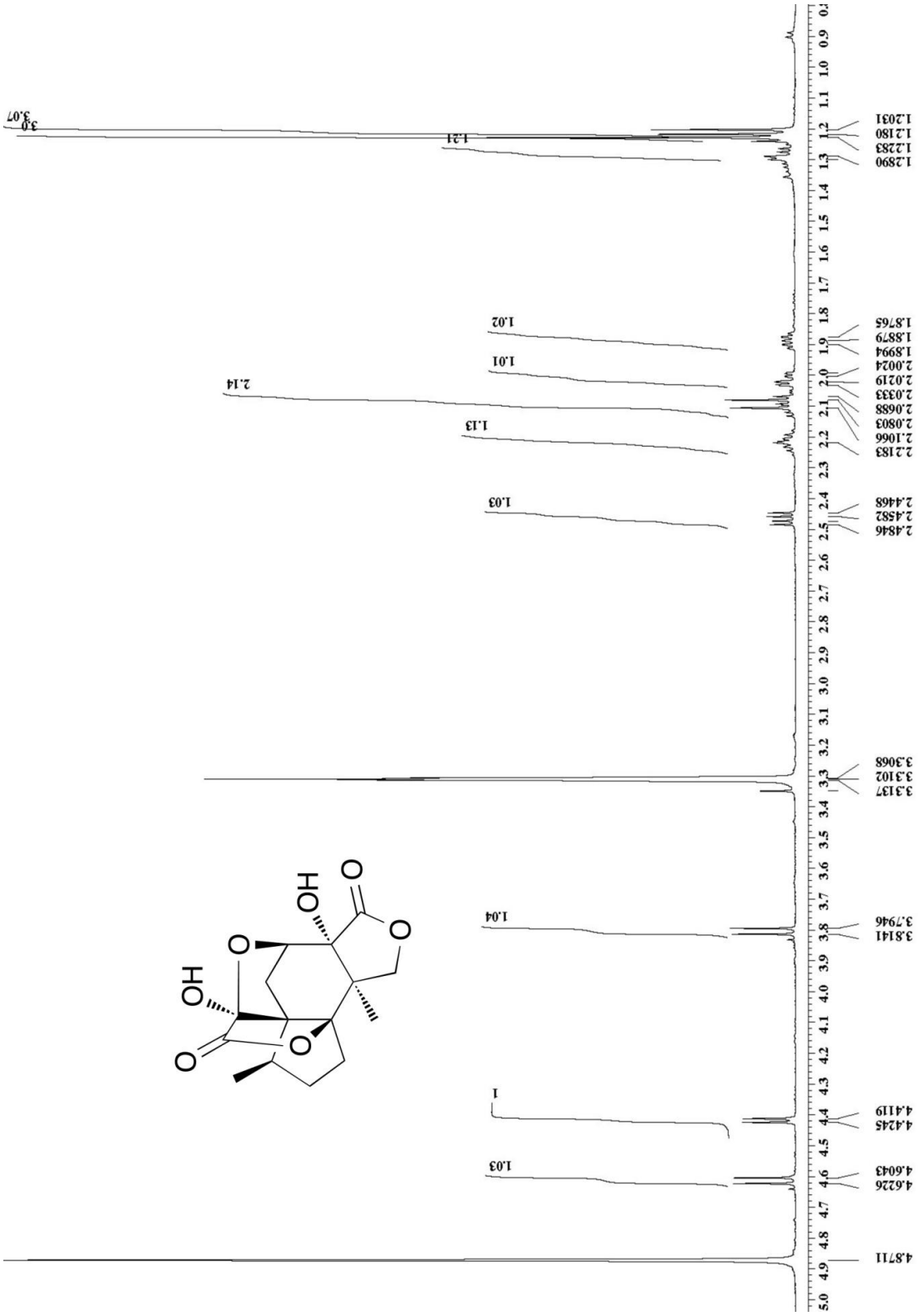
Spectrum 4.27 ^{13}C NMR (CD_3OD, 125 MHz) of compound **185**.



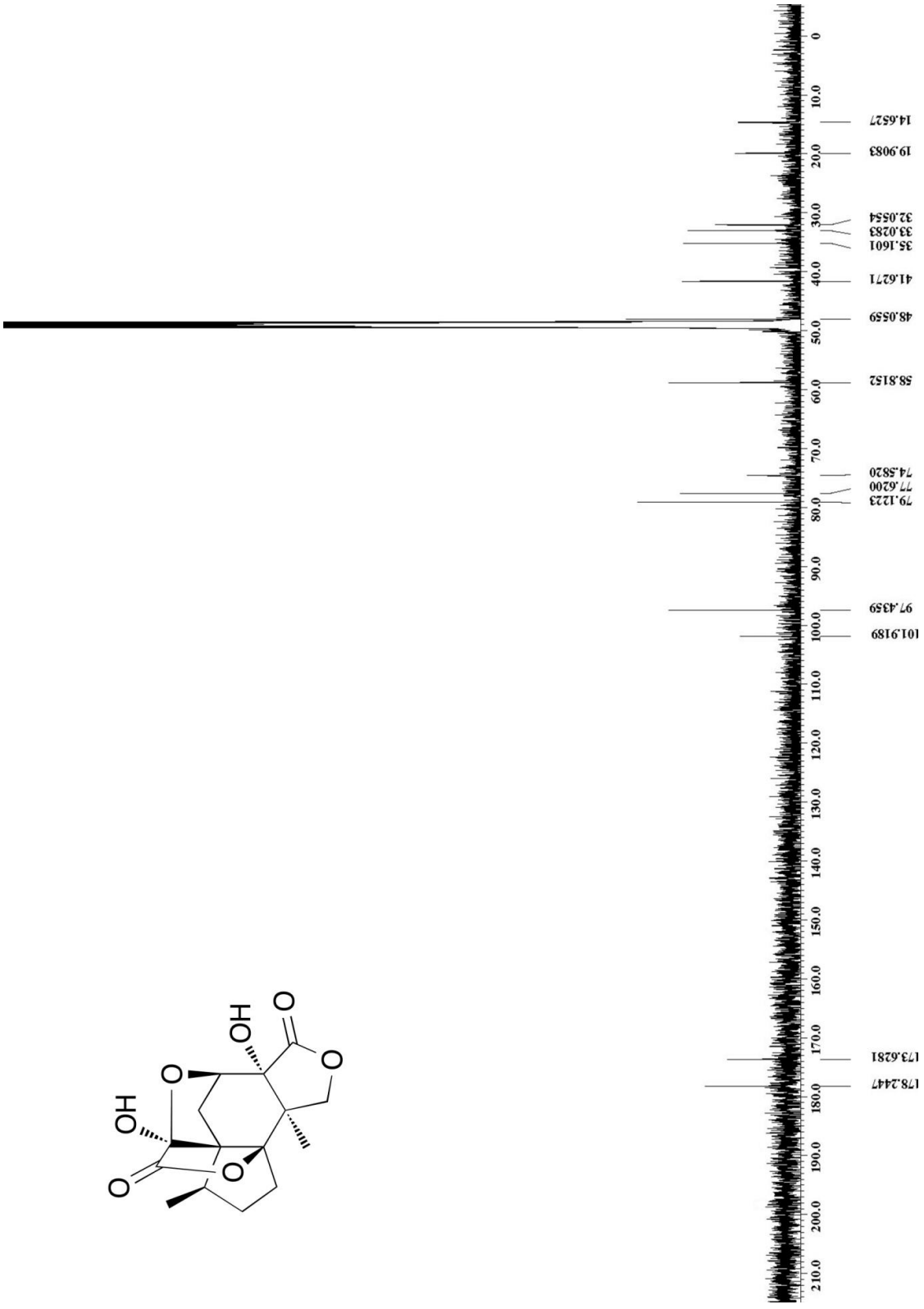
Spectrum 4.28 ^{13}C NMR (CD_3OD, 125 MHz) of compound **185**.



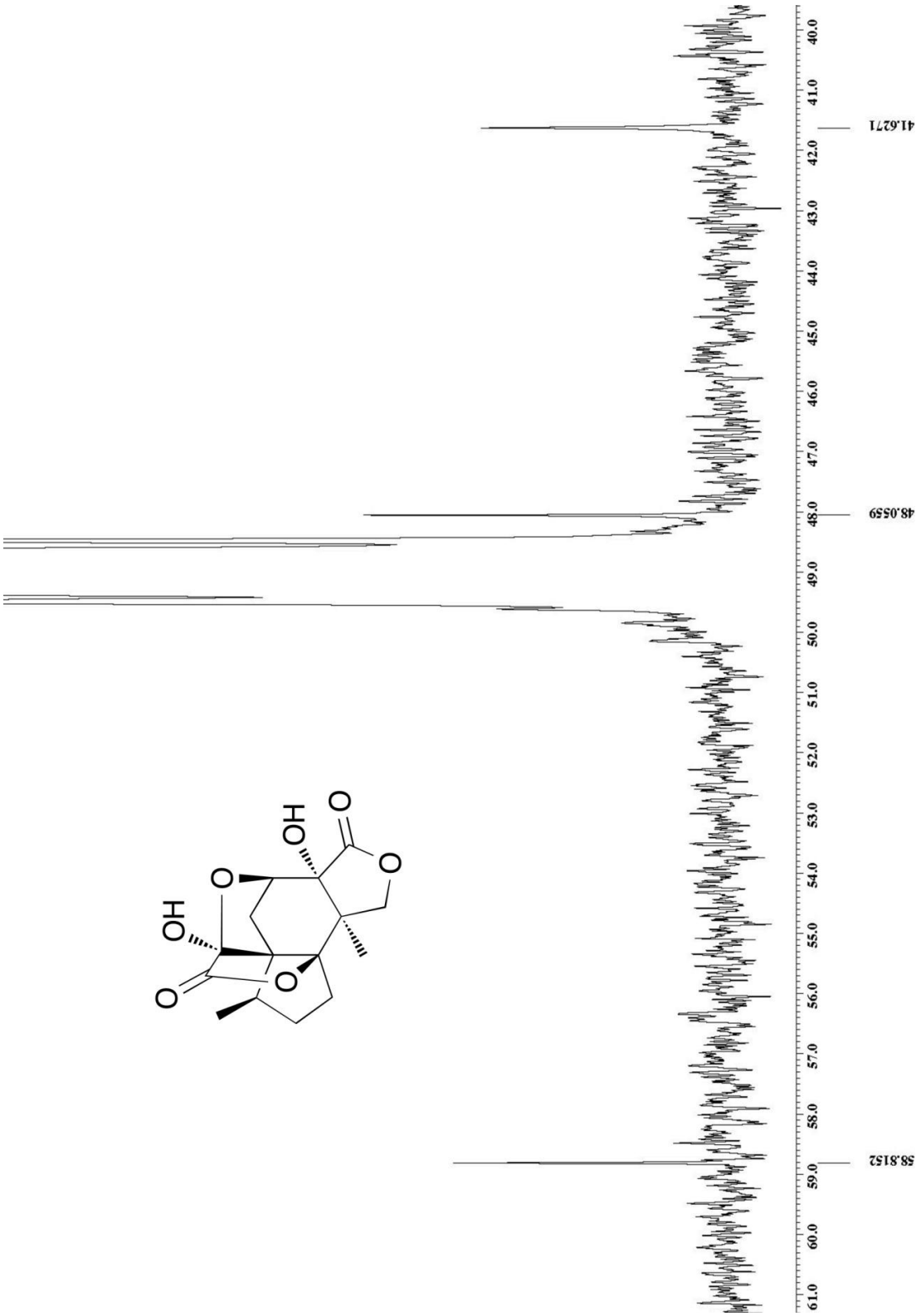
Spectrum 4.29 ^{1}H NMR (CD_3OD, 500 MHz) of compound **(-)-3**.



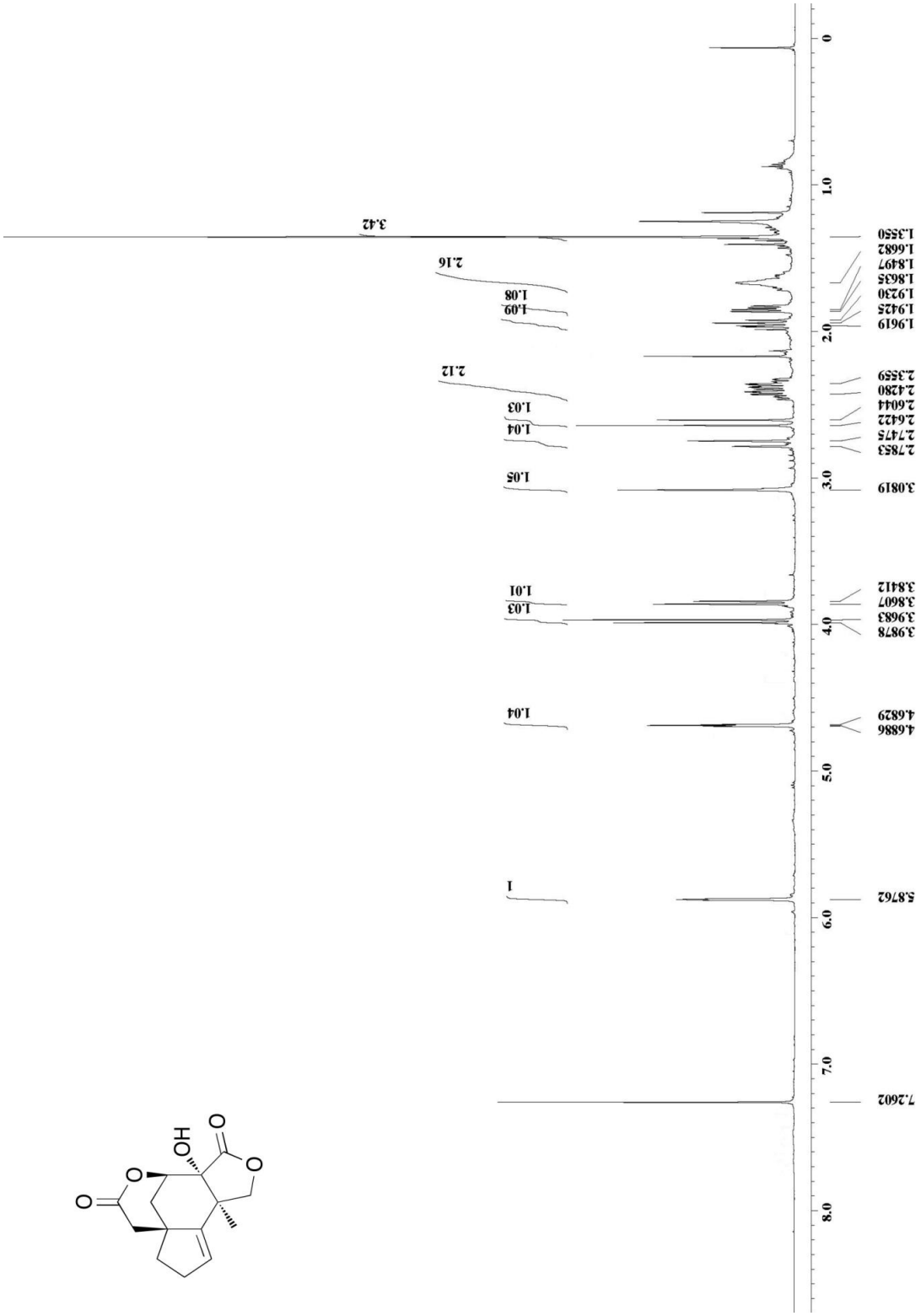
Spectrum 4.30 ^{1}H NMR (CD_3OD, 500 MHz) of compound **(-)-3**.



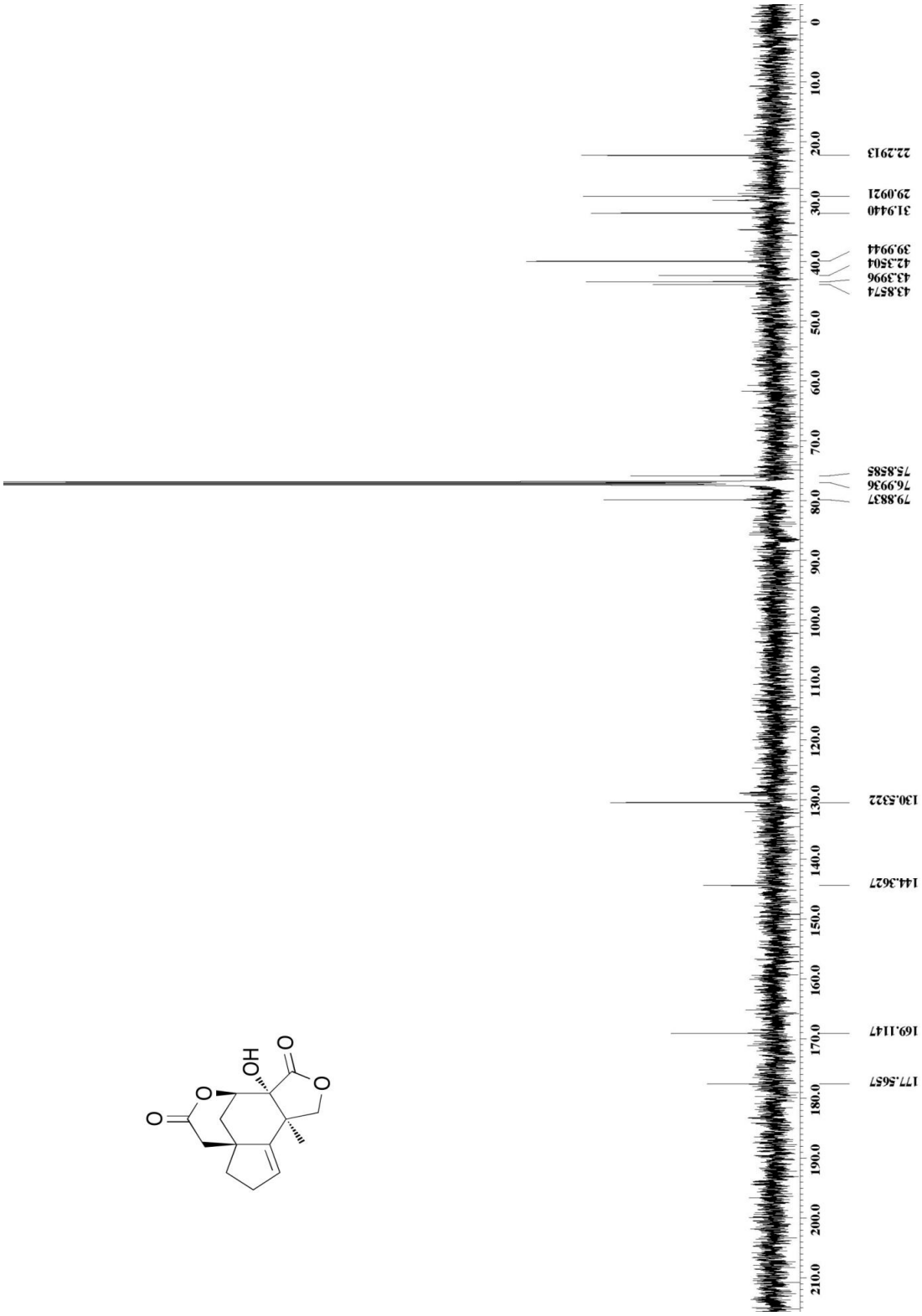
Spectrum 4.31 ^{13}C NMR (CD_3OD, 125 MHz) of compound **(-)-3**.



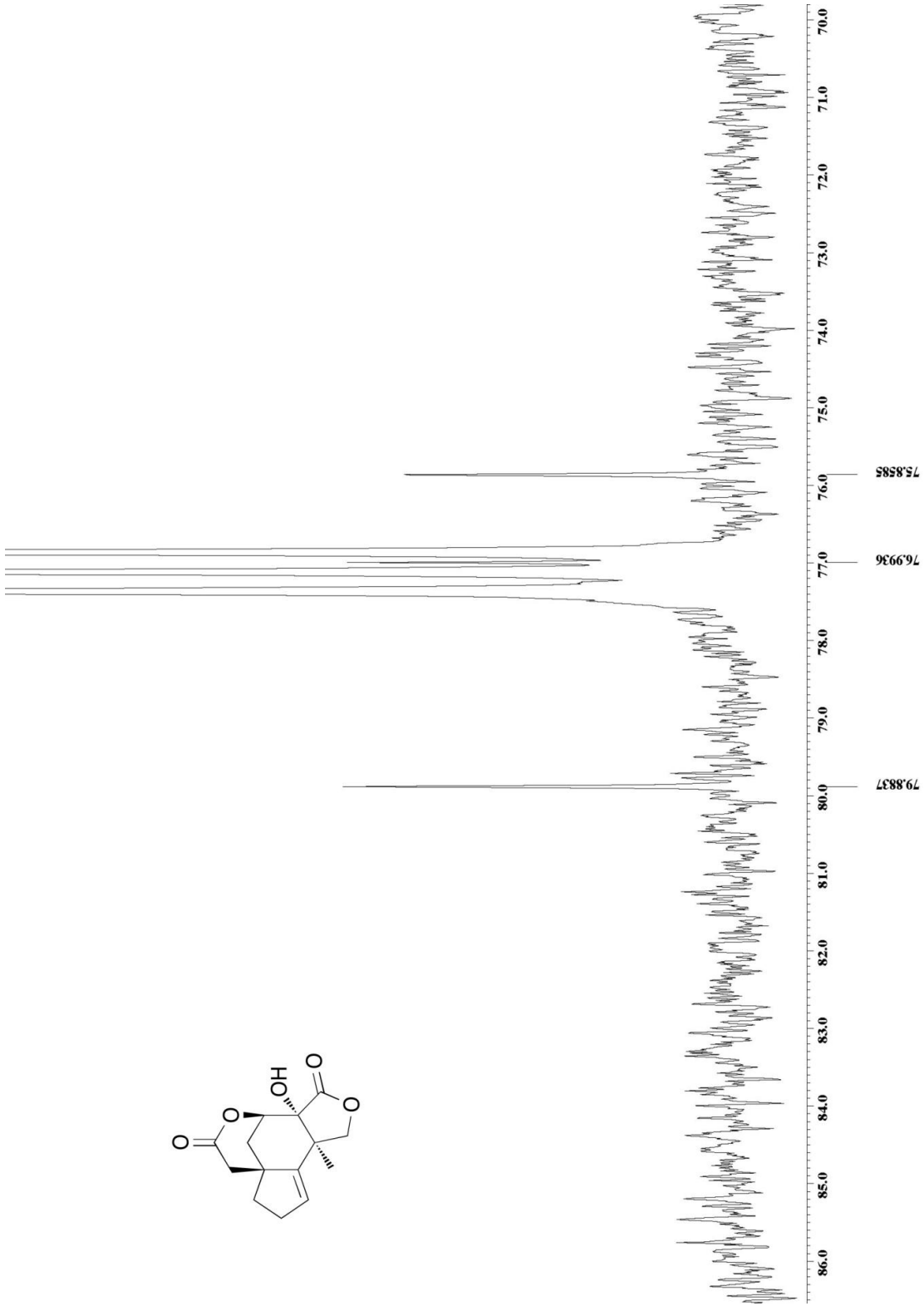
Spectrum 4.32 ^{13}C NMR (CD_3OD, 125 MHz) of compound **(-)-3**.



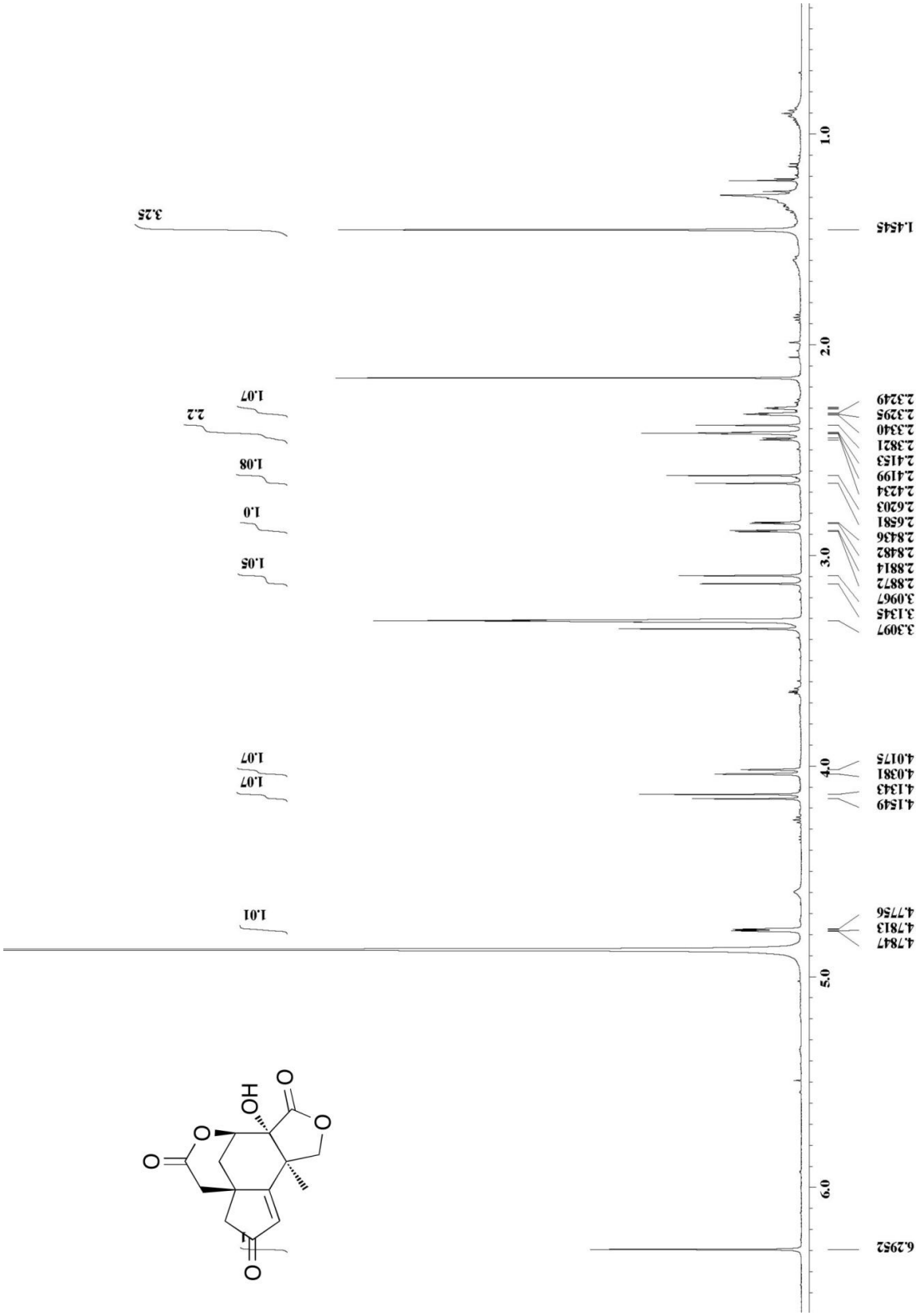
Spectrum 4.33 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **188**.



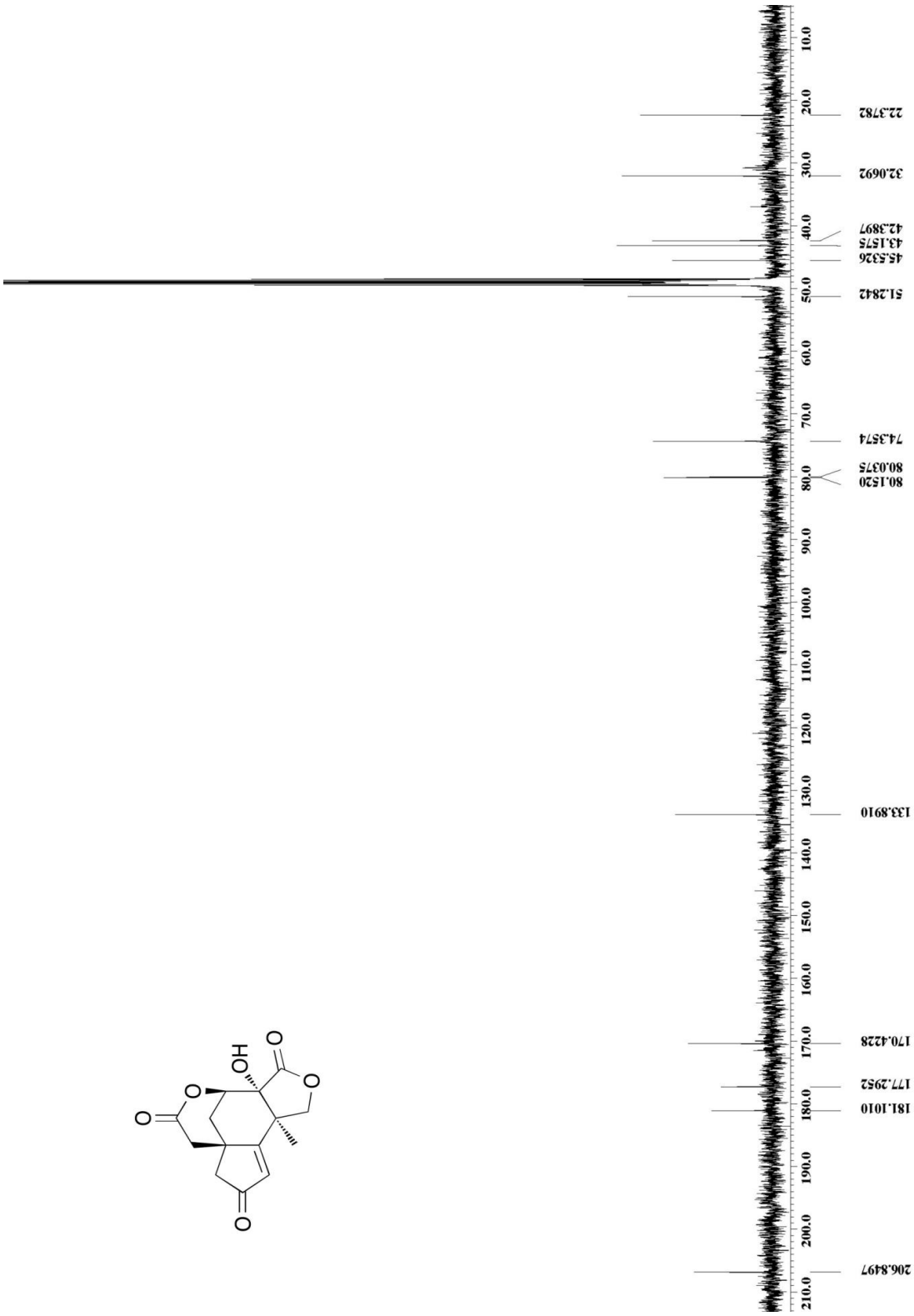
Spectrum 4.34 ^{13}H NMR ($CDCl_3$, 125 MHz) of compound **188**.



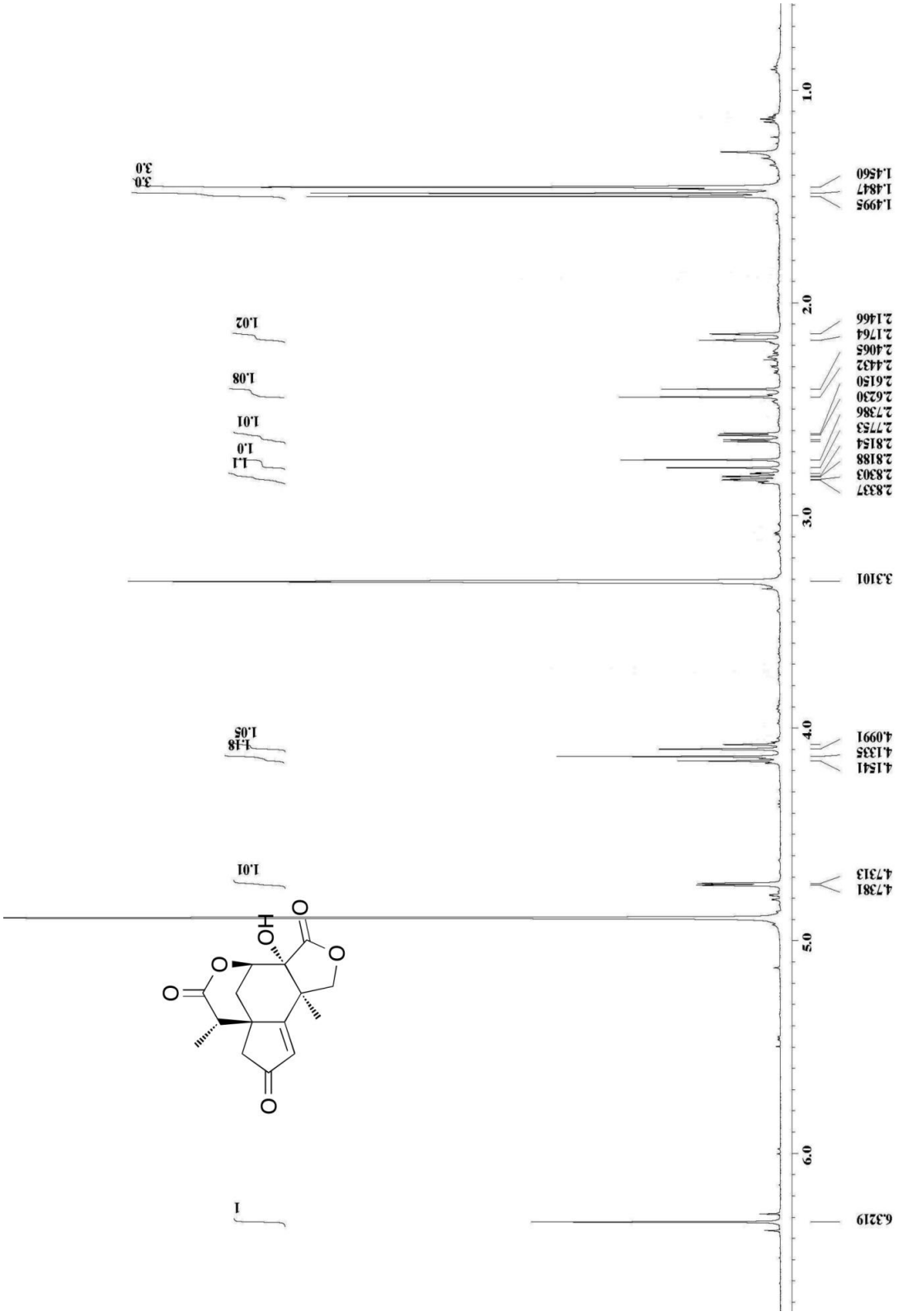
Spectrum 4.35 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **188**.



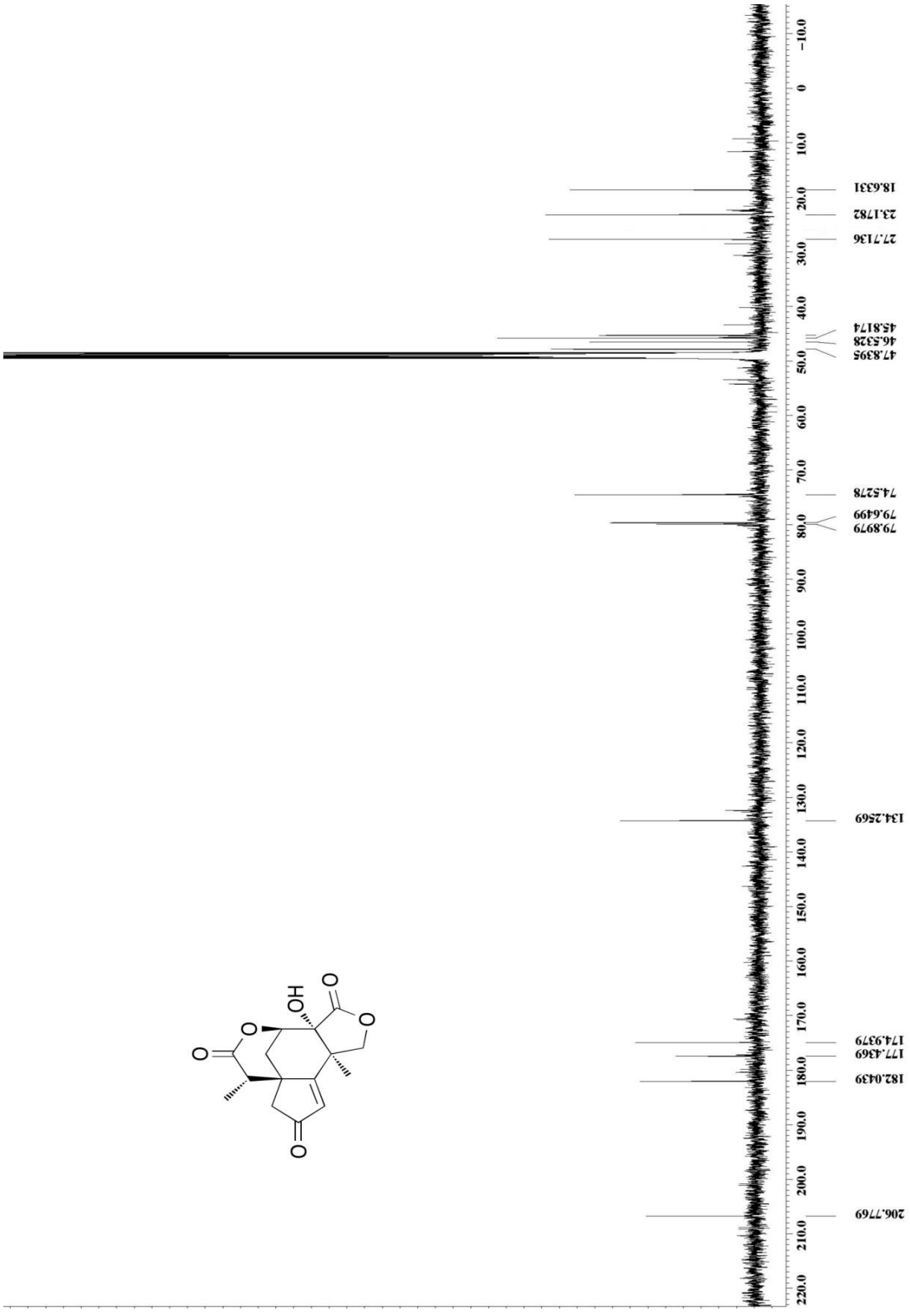
Spectrum 4.36 ^{1}H NMR (CD_3OD, 500 MHz) of compound **189**.



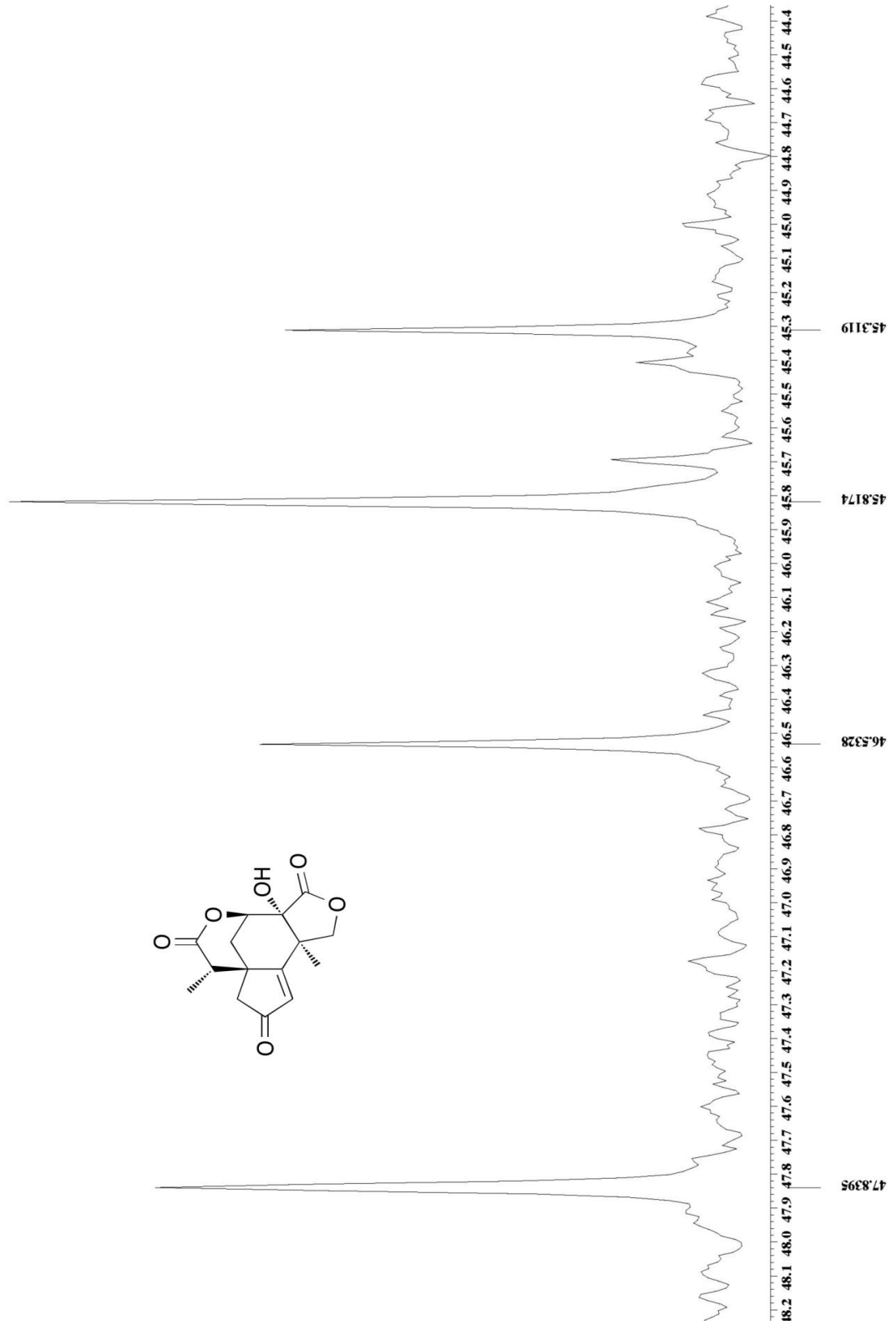
Spectrum 4.37 ^{13}C NMR (CD_3OD, 125 MHz) of compound **189**.



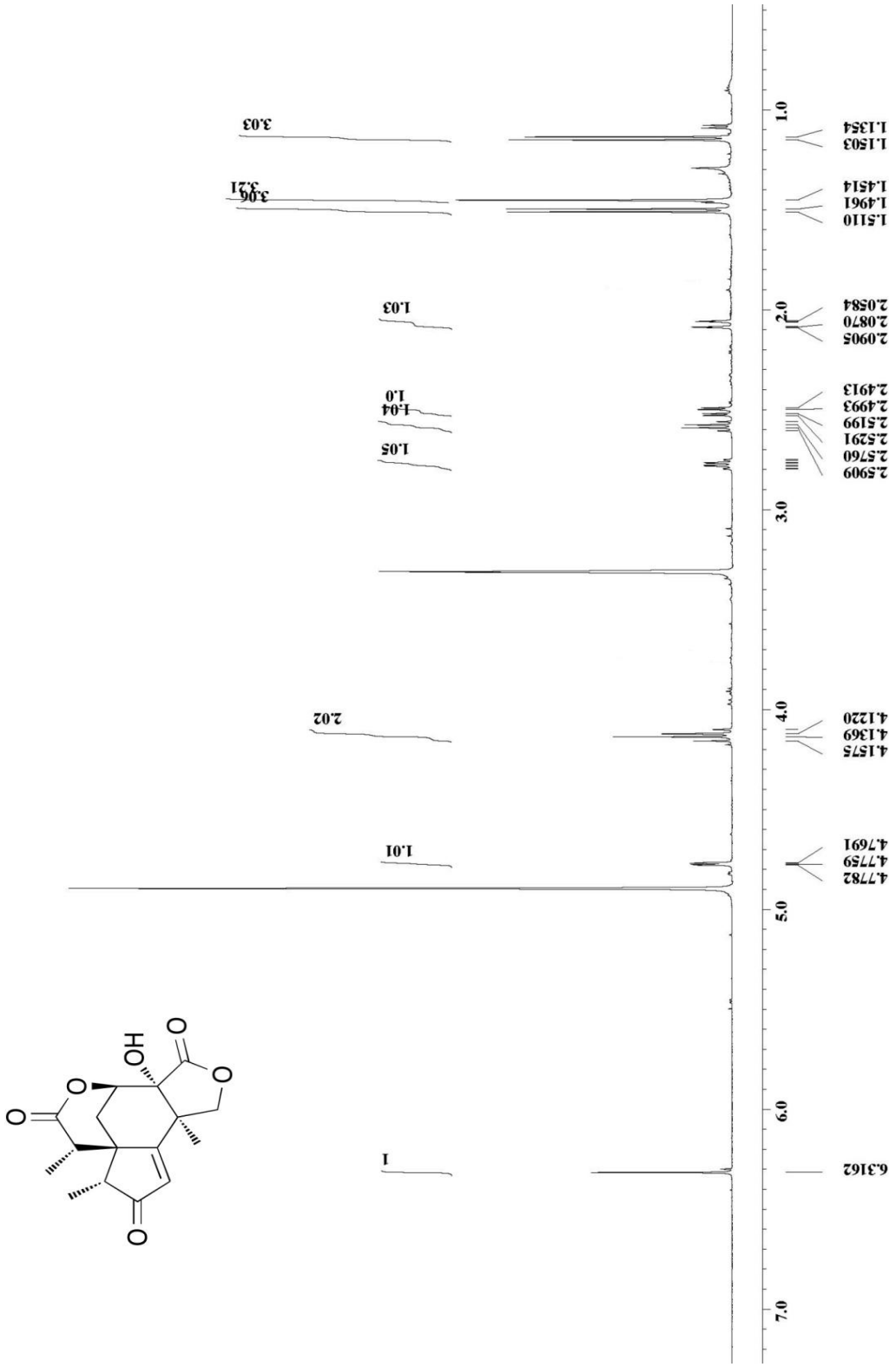
Spectrum 4.38 ^{1}H NMR (CD_3OD, 500 MHz) of compound **190**.



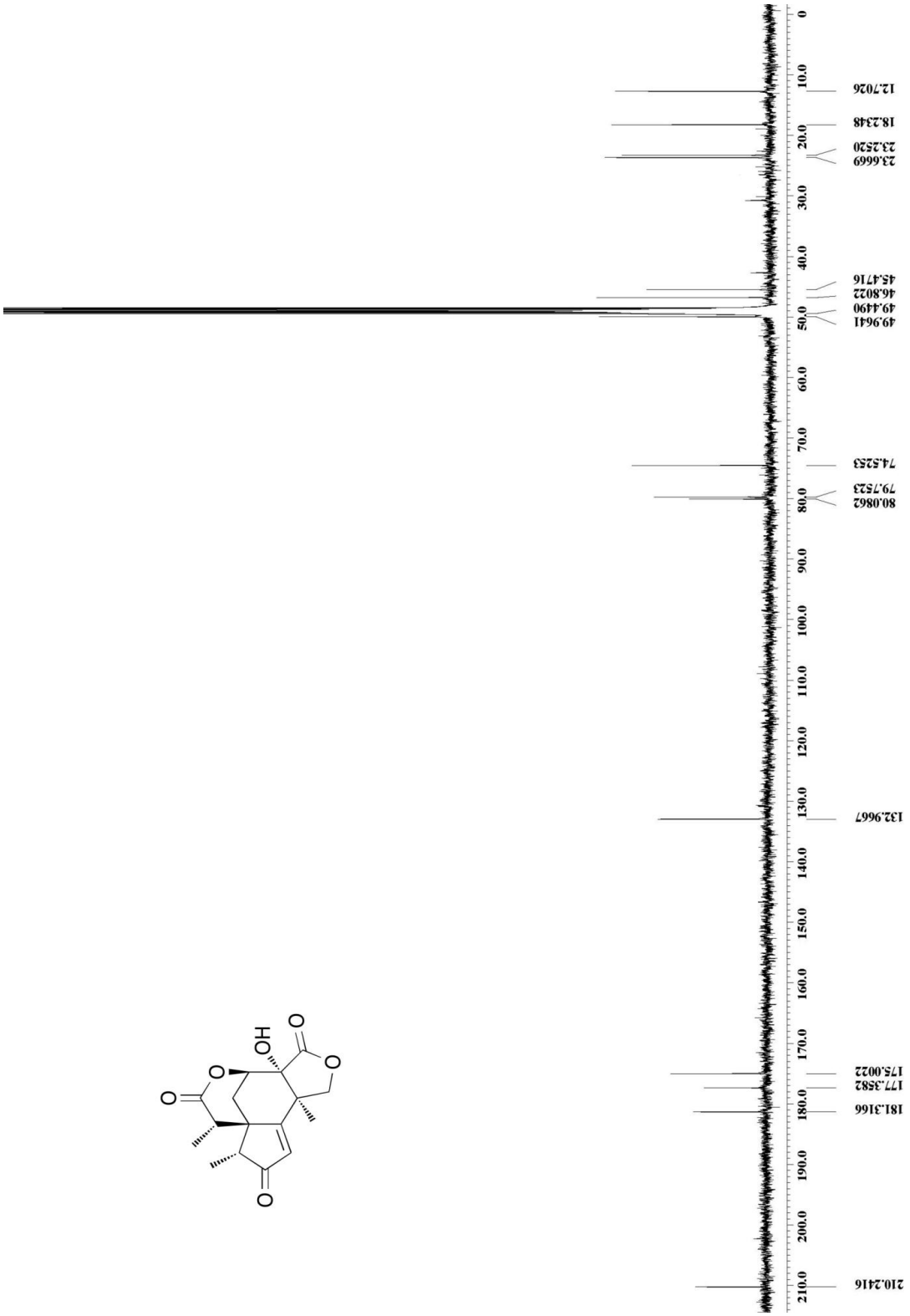
Spectrum 4.39 ^{13}C NMR (CD_3OD, 125 MHz) of compound **190**.



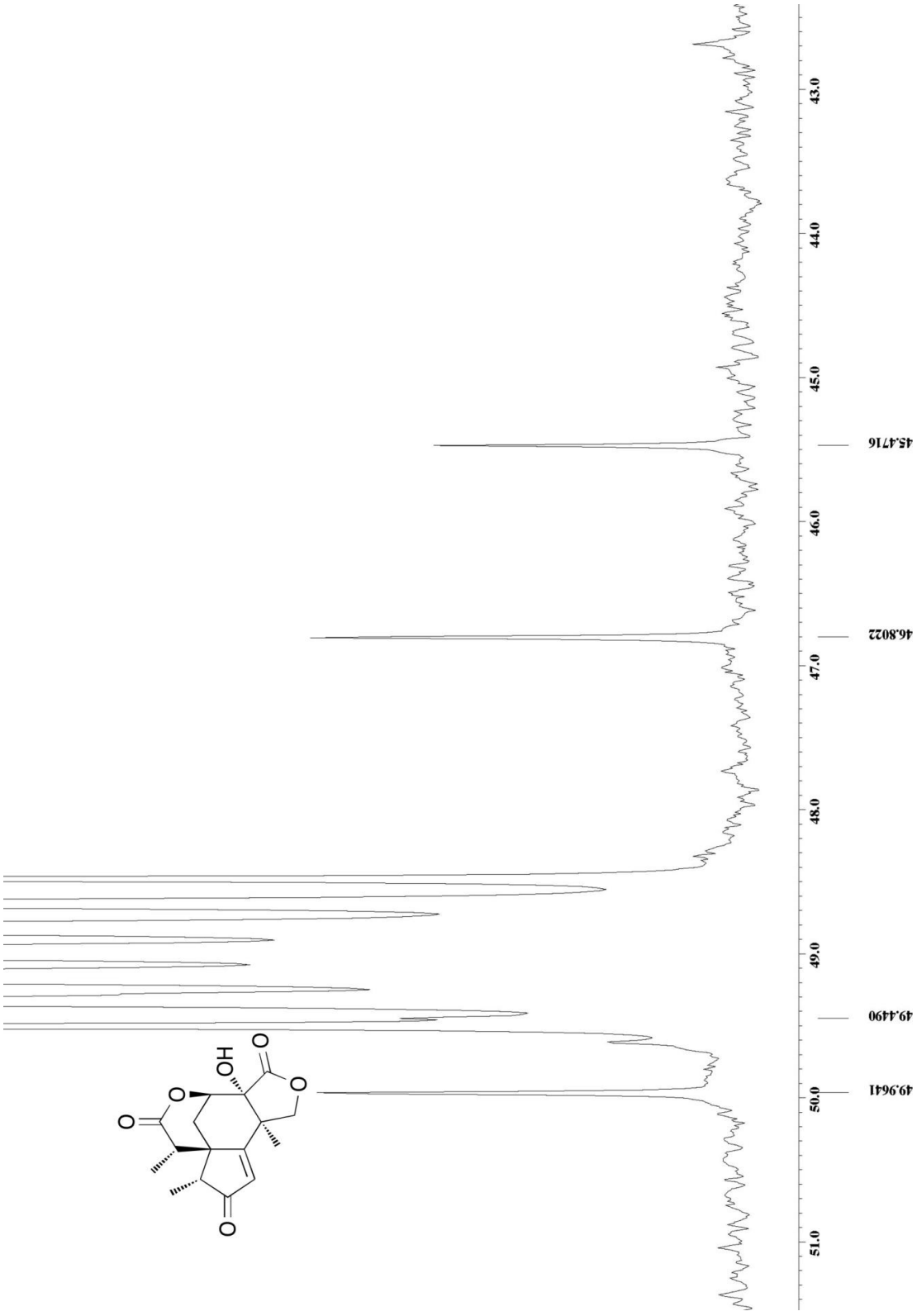
Spectrum 4.40 ^{13}C NMR (CD_3OD, 125 MHz) of compound **190**.



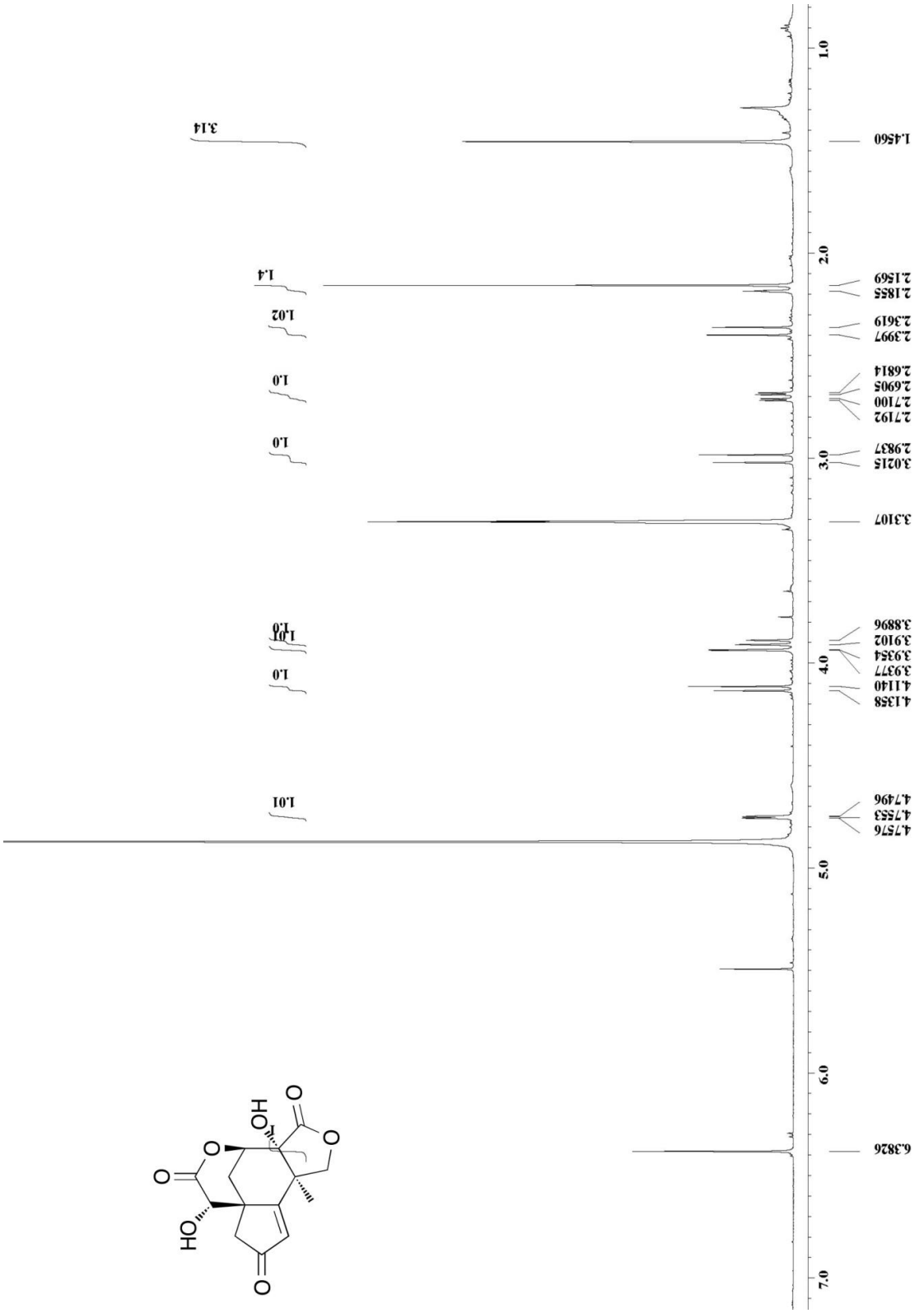
Spectrum 4.41 ^{1}H NMR (CD_3OD, 500 MHz) of compound **191**.



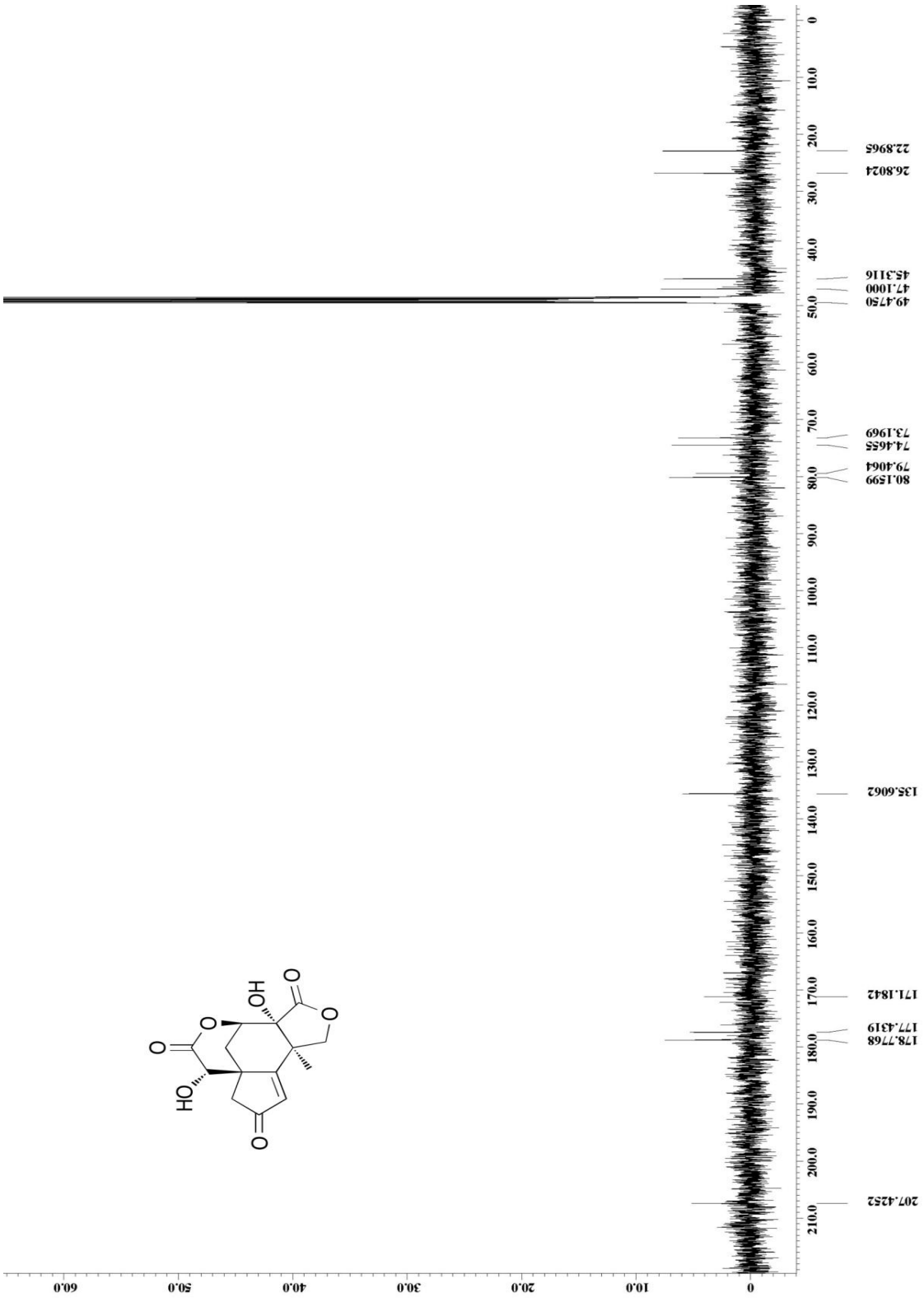
Spectrum 4.42 ^{13}C NMR (CD_3OD, 125 MHz) of compound **191**.



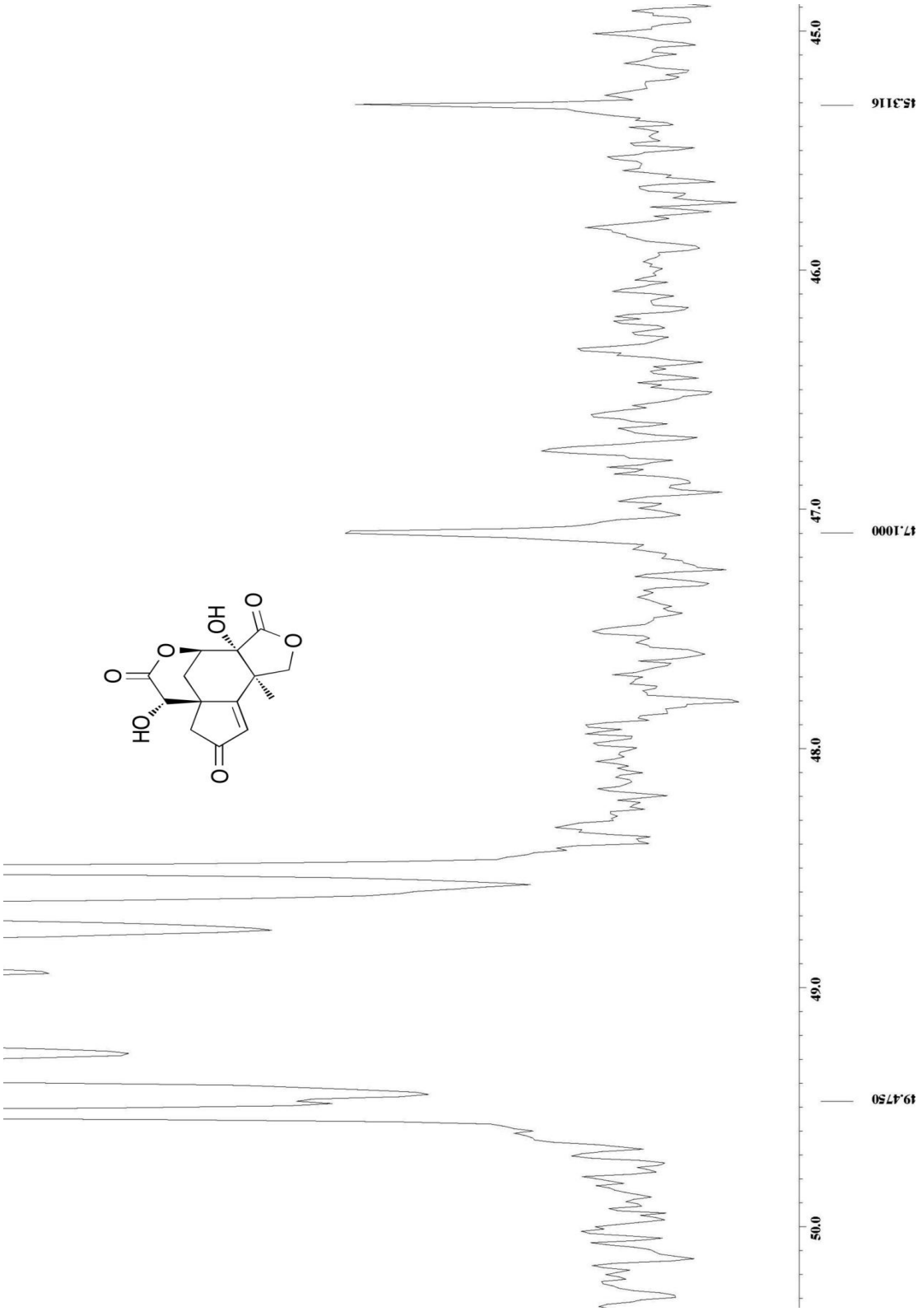
Spectrum 4.43 ^{13}C NMR (CD_3OD, 125 MHz) of compound **191**.



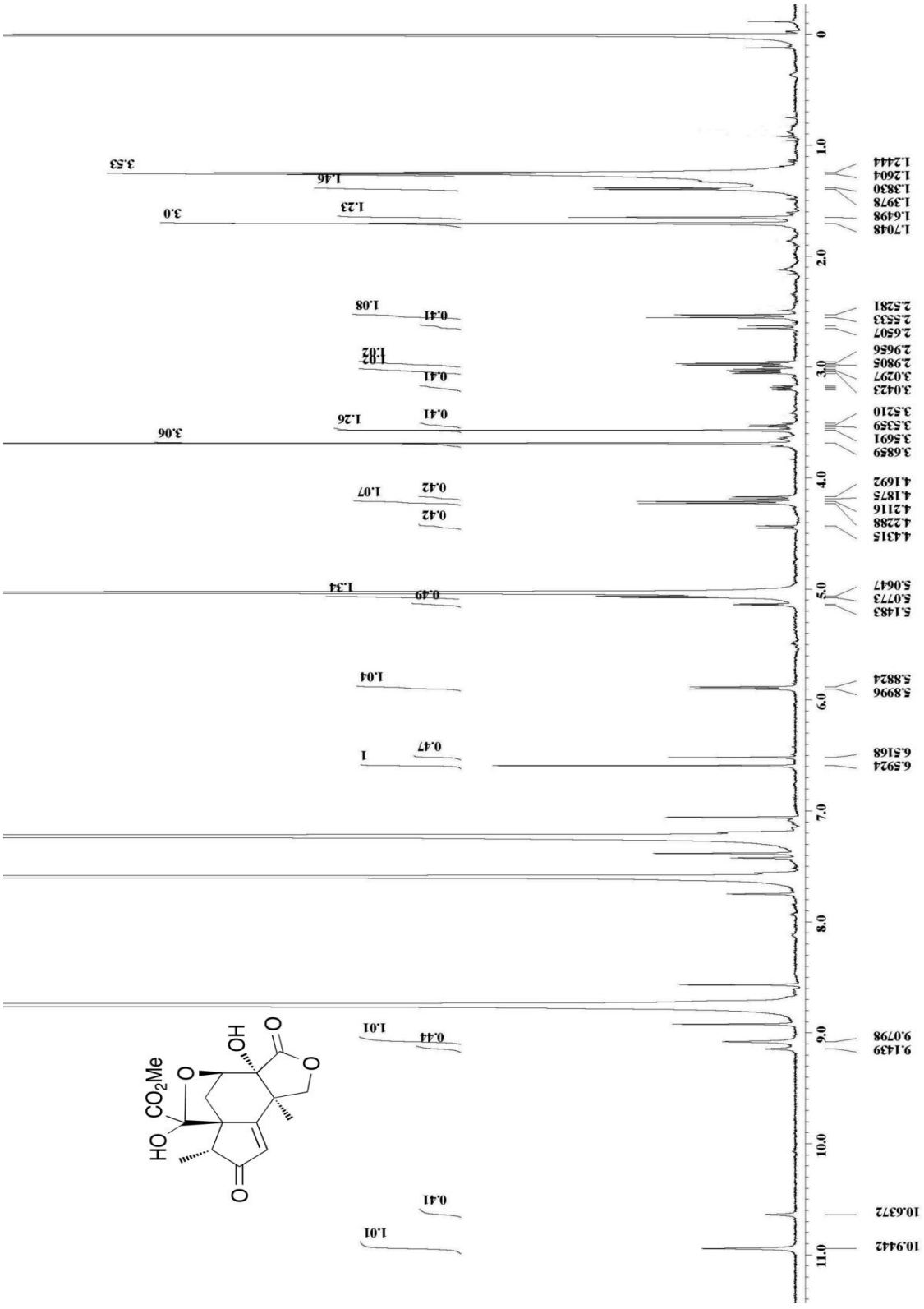
Spectrum 4.44 ^{1}H NMR (CD_3OD, 500 MHz) of compound **192**.



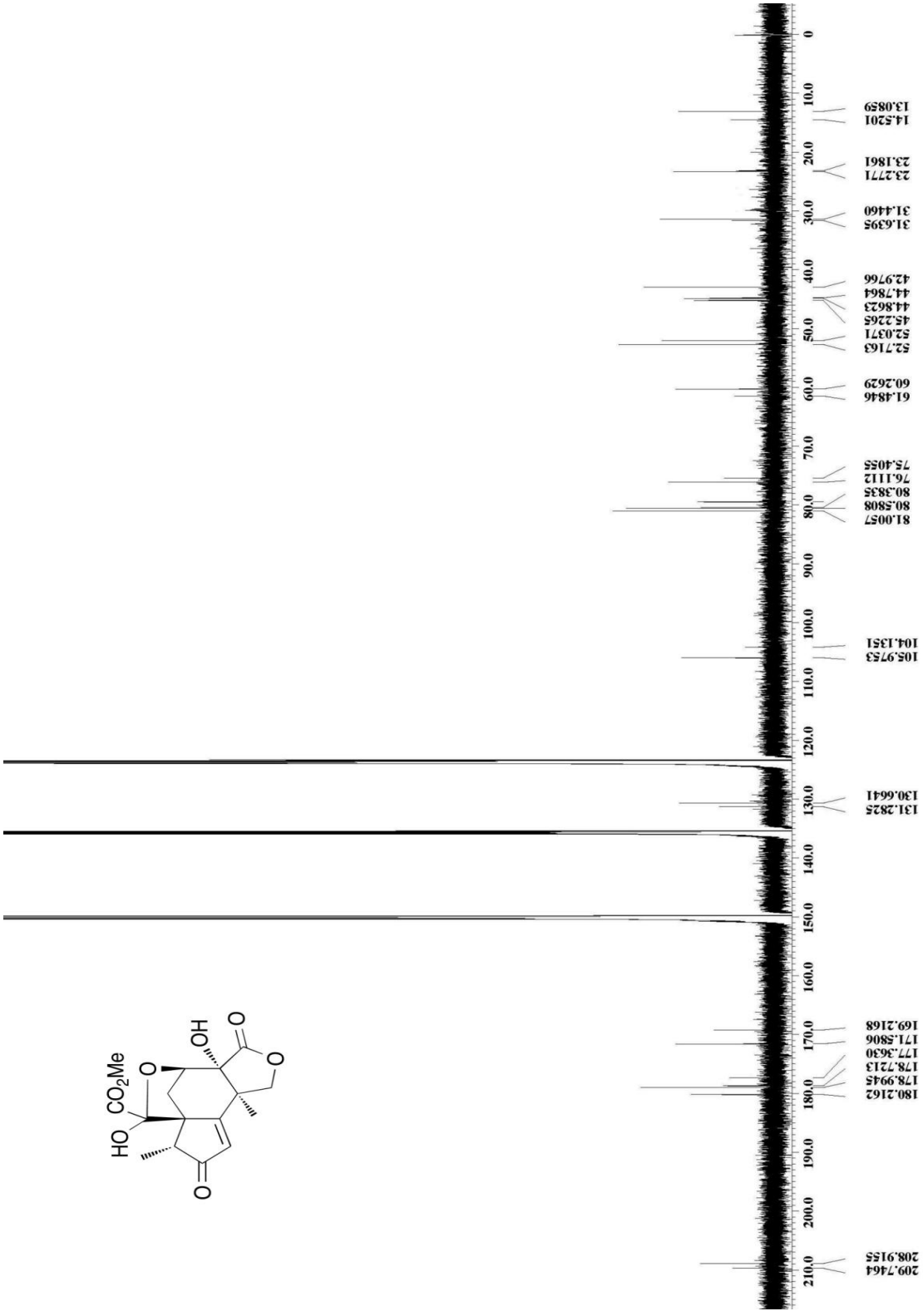
Spectrum 4.45 ^{13}C NMR (CD_3OD, 125 MHz) of compound **192**.



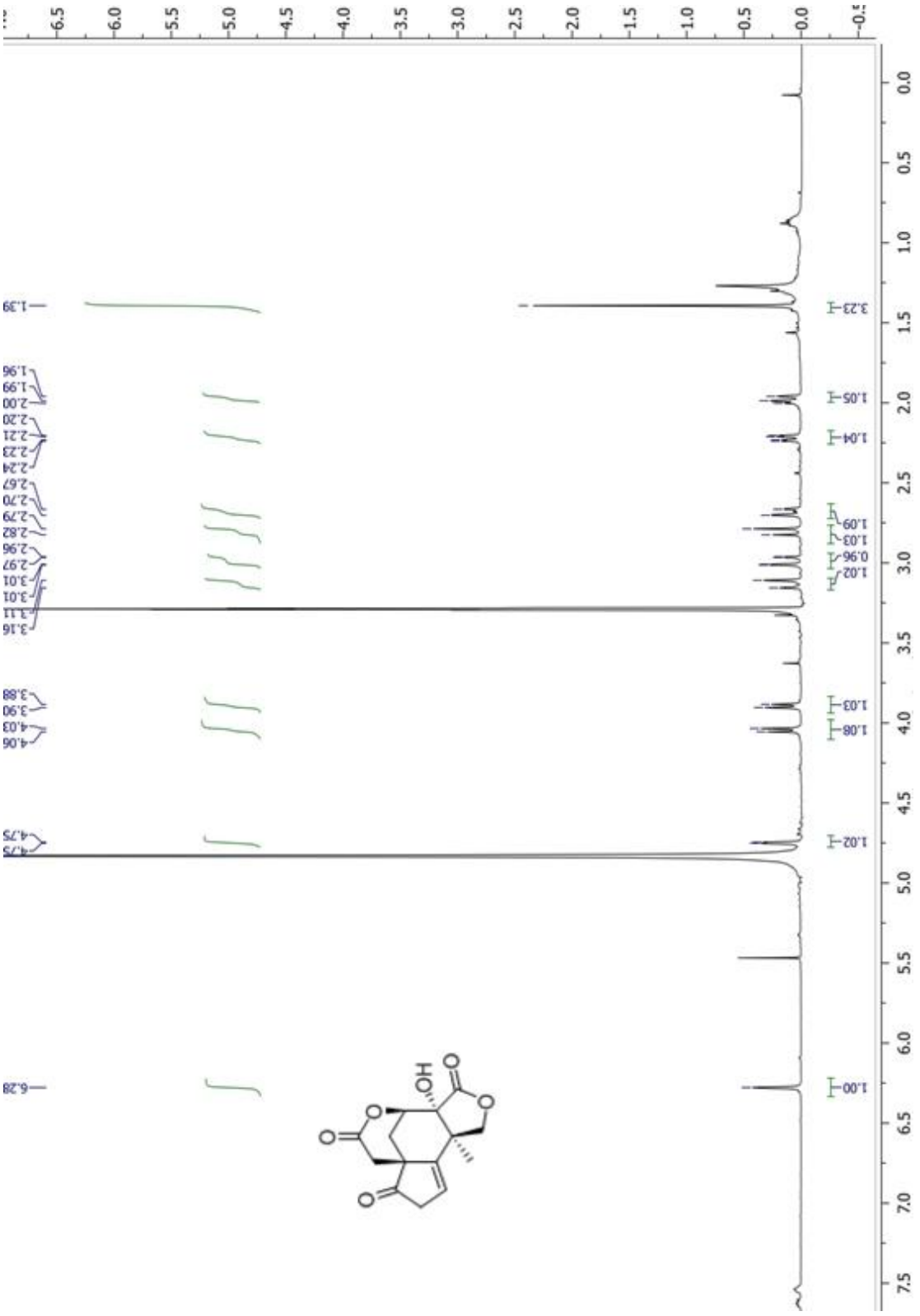
Spectrum 4.46 ^{13}C NMR (CD_3OD, 125 MHz) of compound **192**.



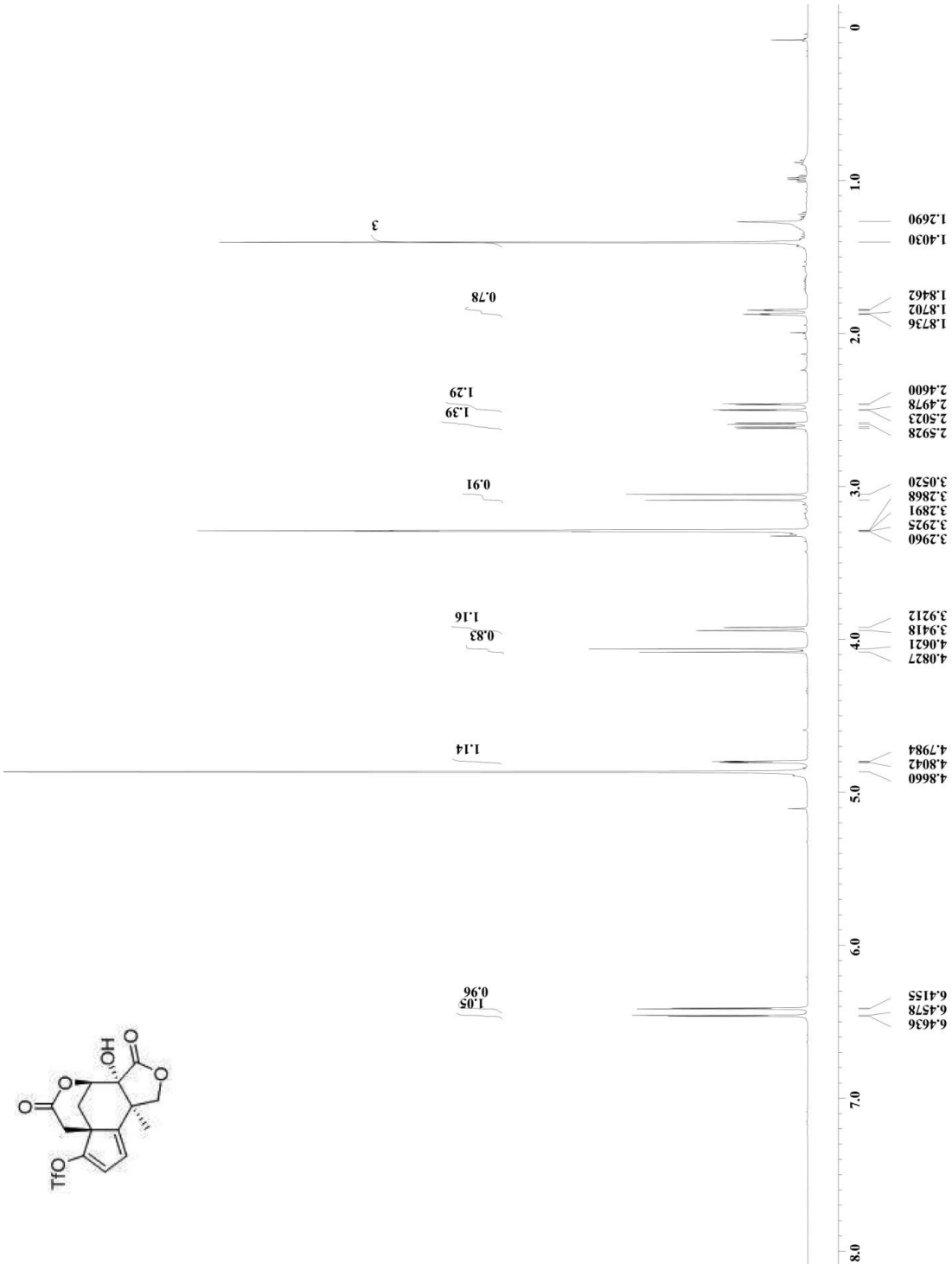
Spectrum 4.47 ^{1}H NMR (C_5H_5N, 500 MHz) of compound **(-)-2**.



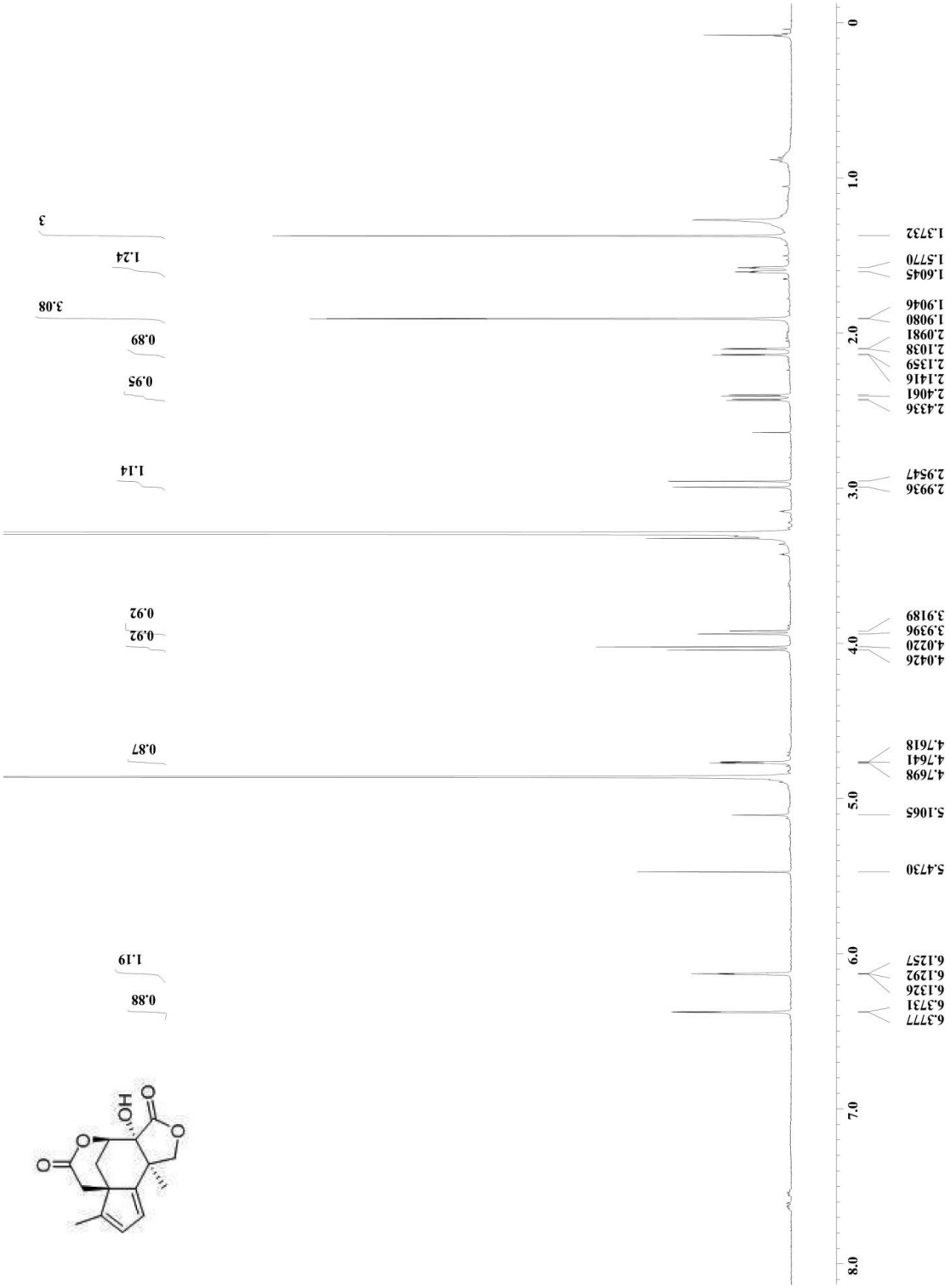
Spectrum 4.48 ^{13}C NMR (C_5H_5N, 125 MHz) of compound **(-)-2**.



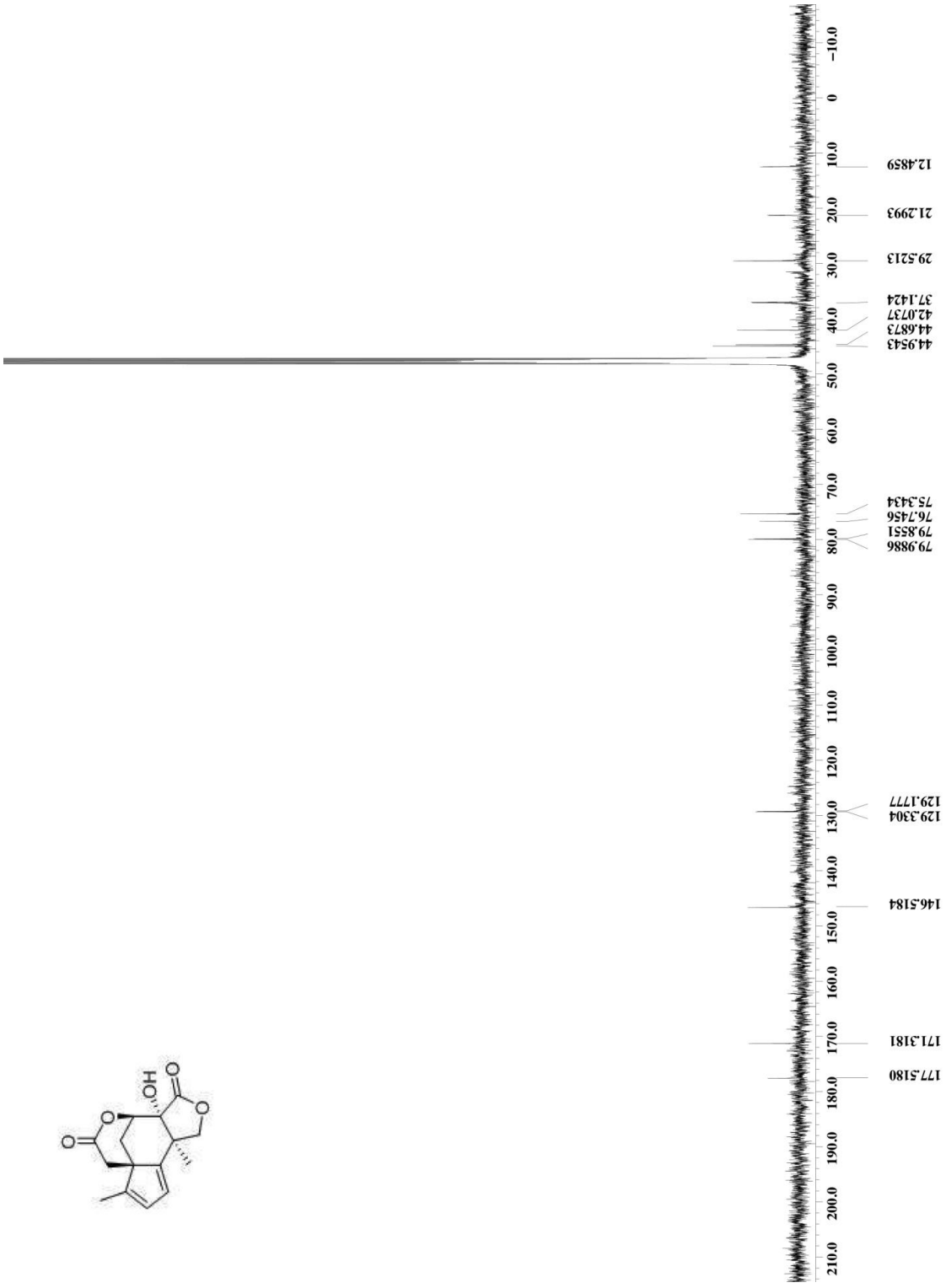
Spectrum 4.49 ^{1}H NMR (CD_3OD, 400 MHz) of compound **193**.



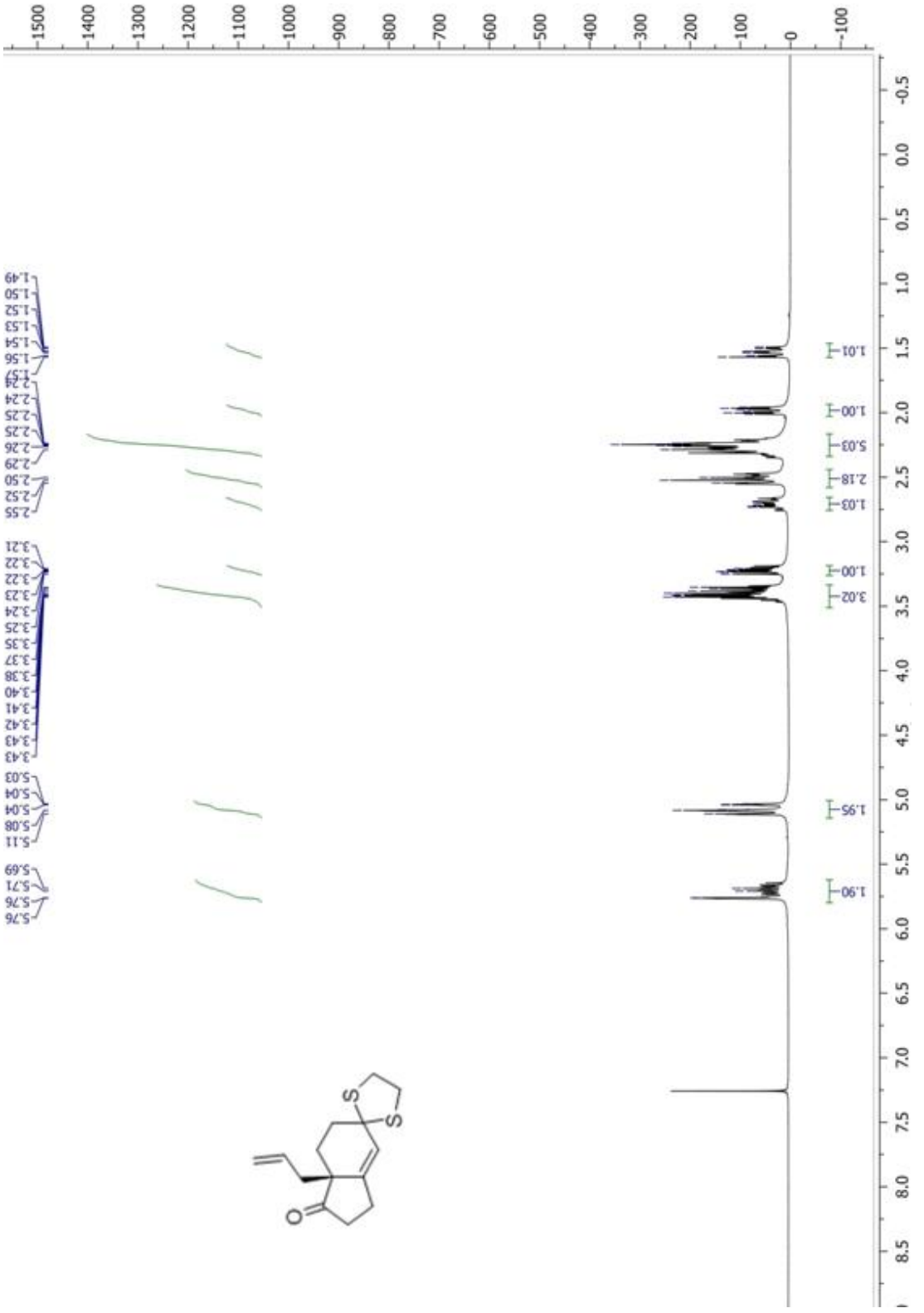
Spectrum 4.50 ^{1}H NMR (CD_3OD, 500 MHz) of vinyl trflate.



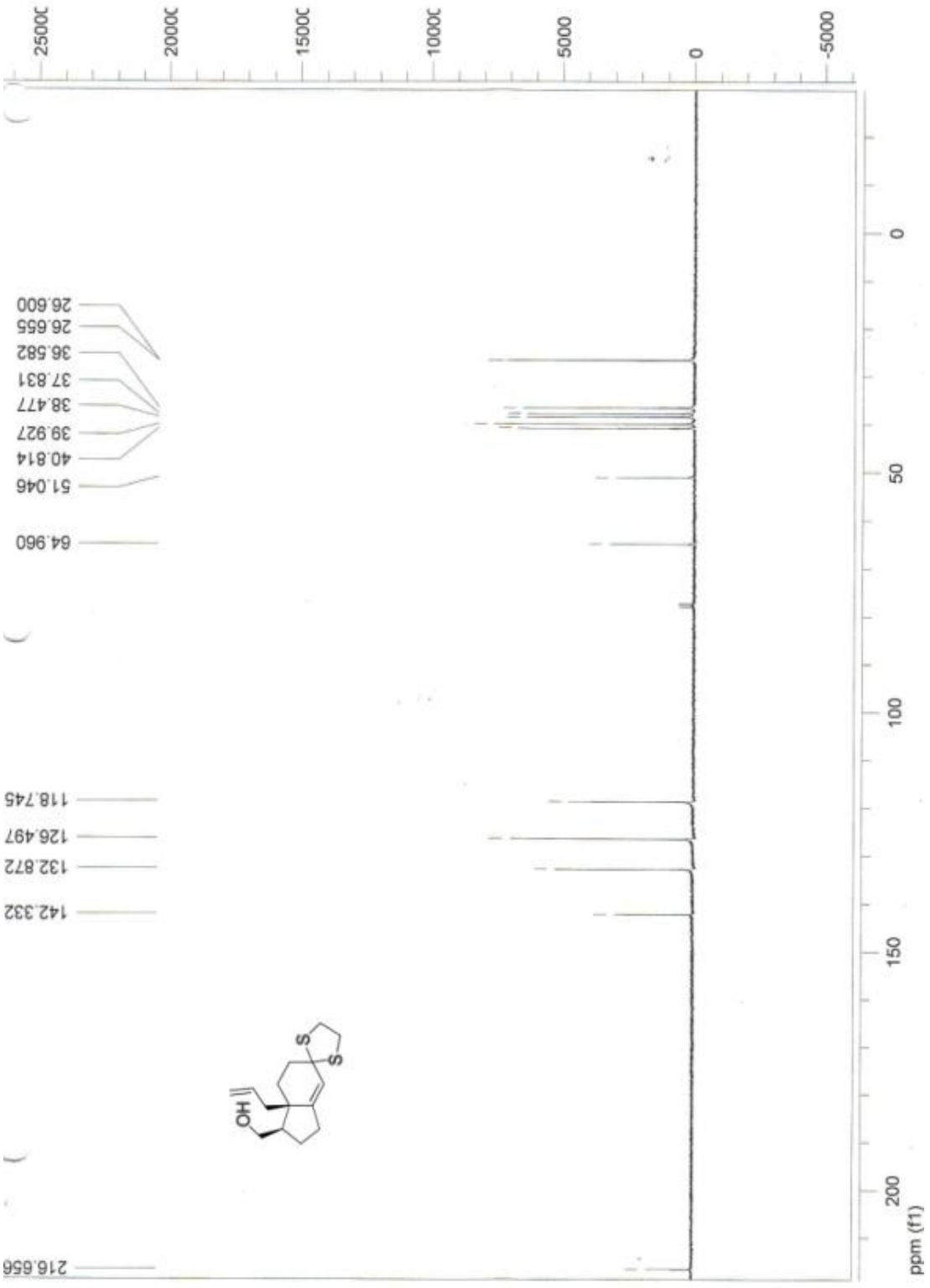
Spectrum 4.51 ^{1}H NMR (CD_3OD, 500 MHz) of compound **194**.



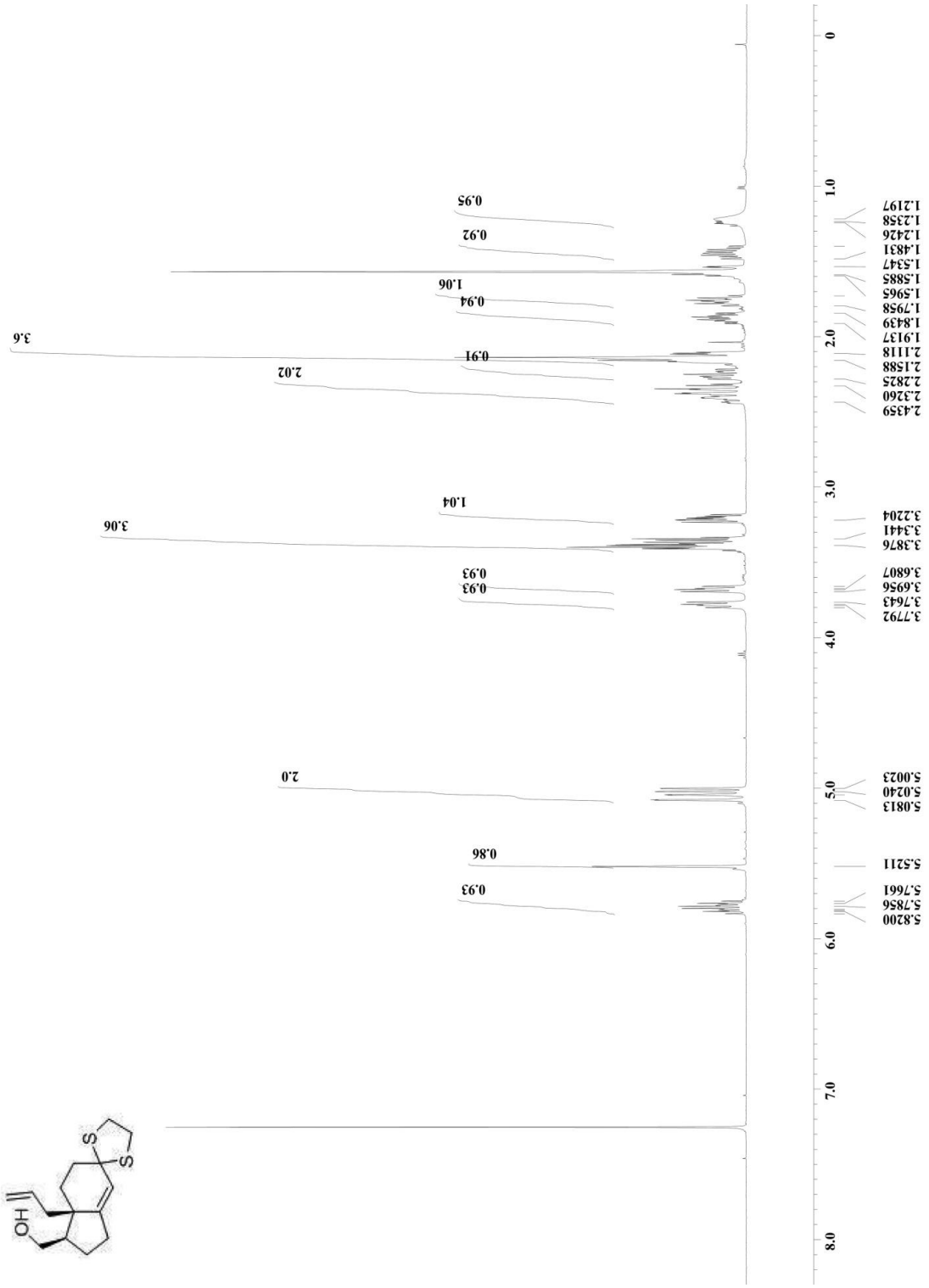
Spectrum 4.52 ^{13}C NMR (CD_3OD, 125 MHz) of compound **194**.



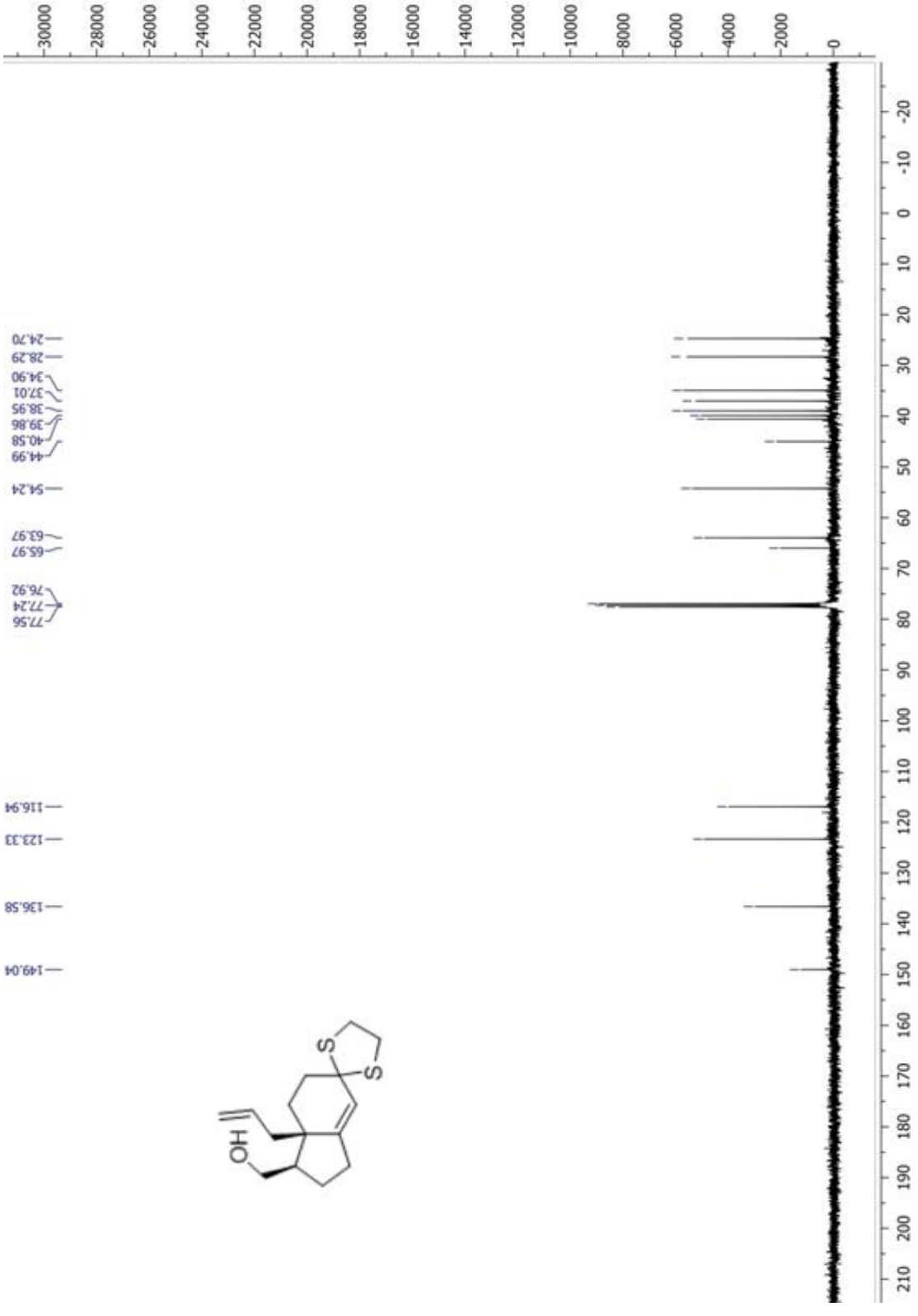
Spectrum 4.53 ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **196**.



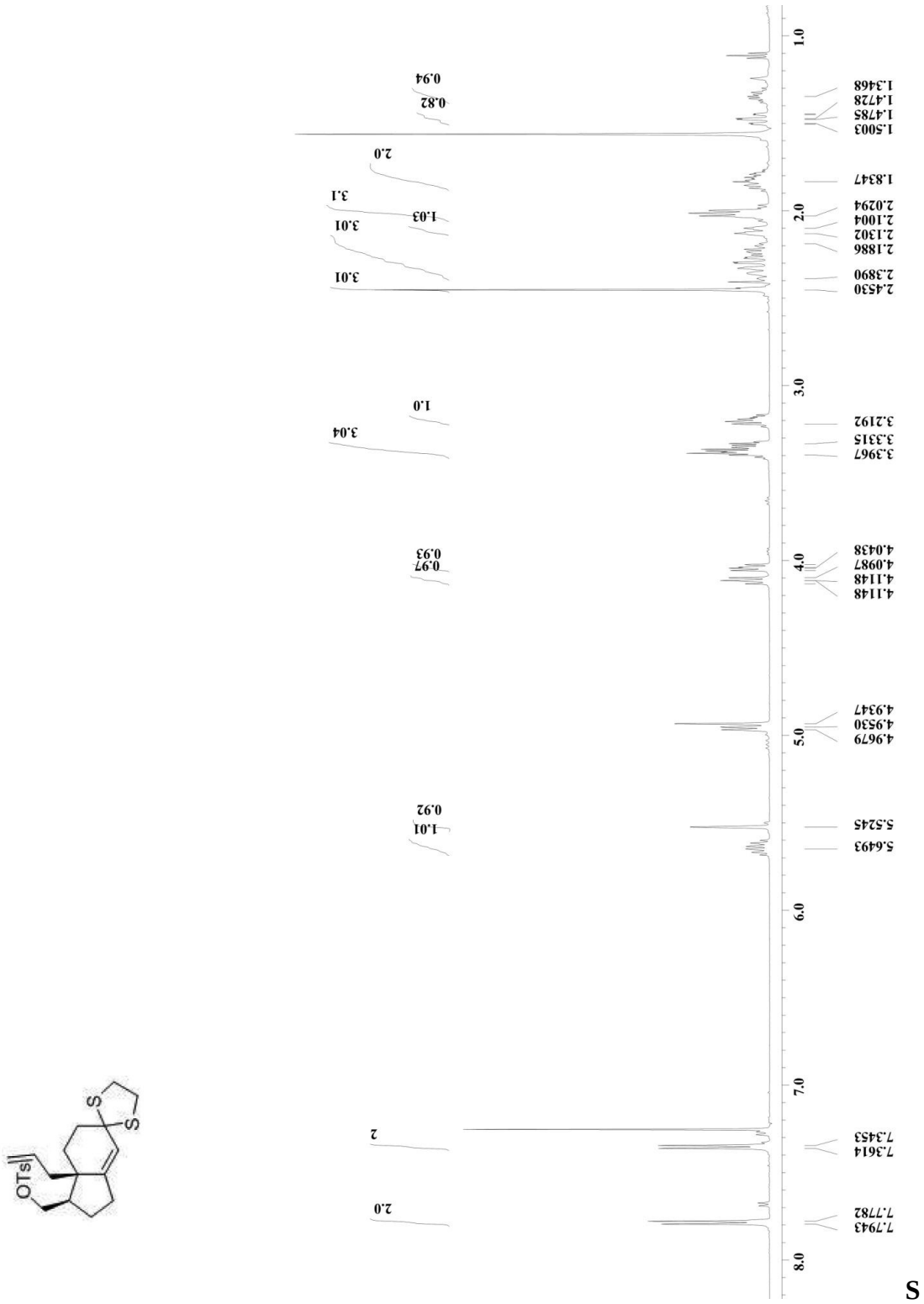
Spectrum 4.54 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **196**.



Spectrum 4.55 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **197**.



Spectrum 4.56 ^{13}C NMR ($CDCl_3$, 100 MHz) of compound **197**.



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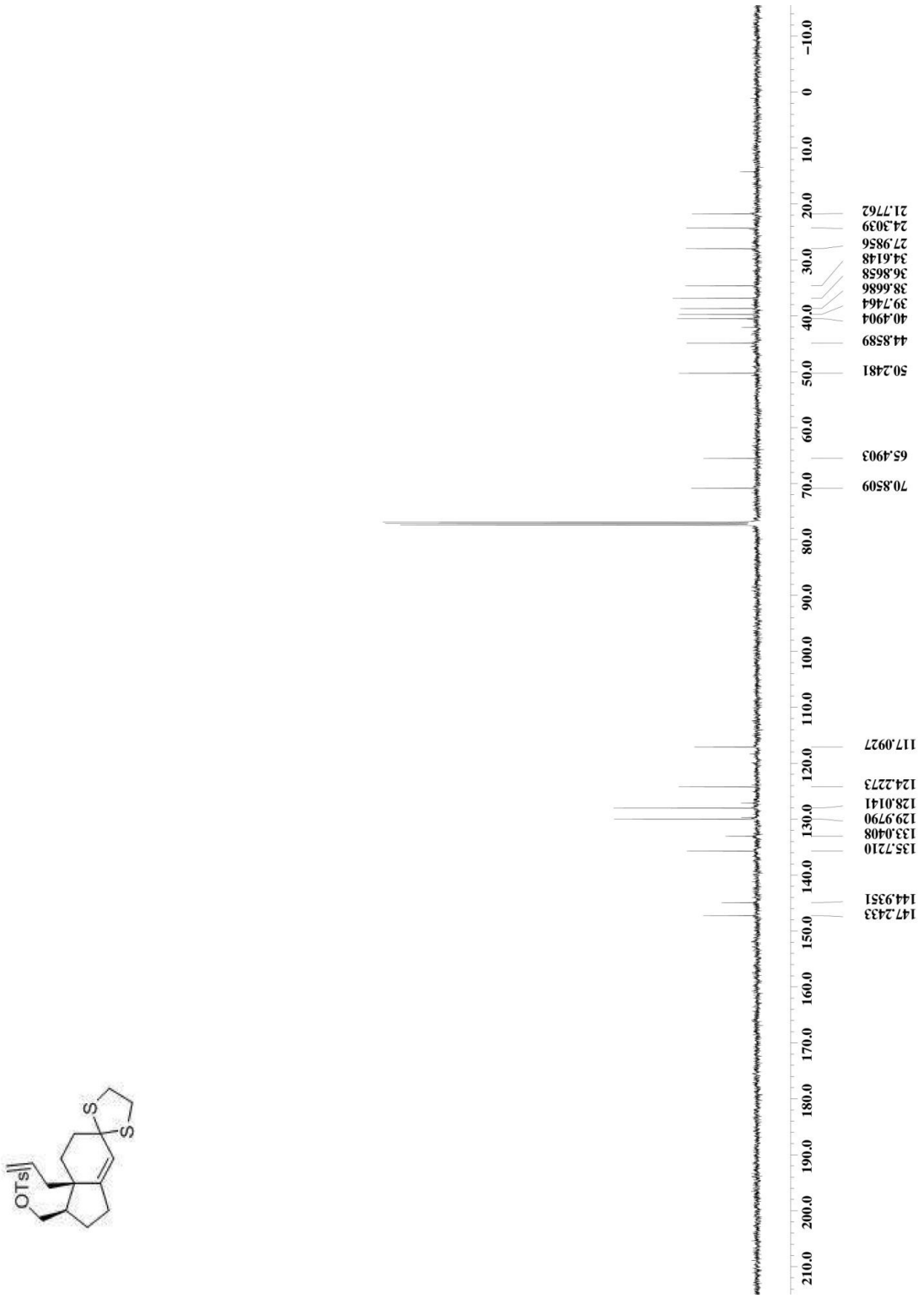
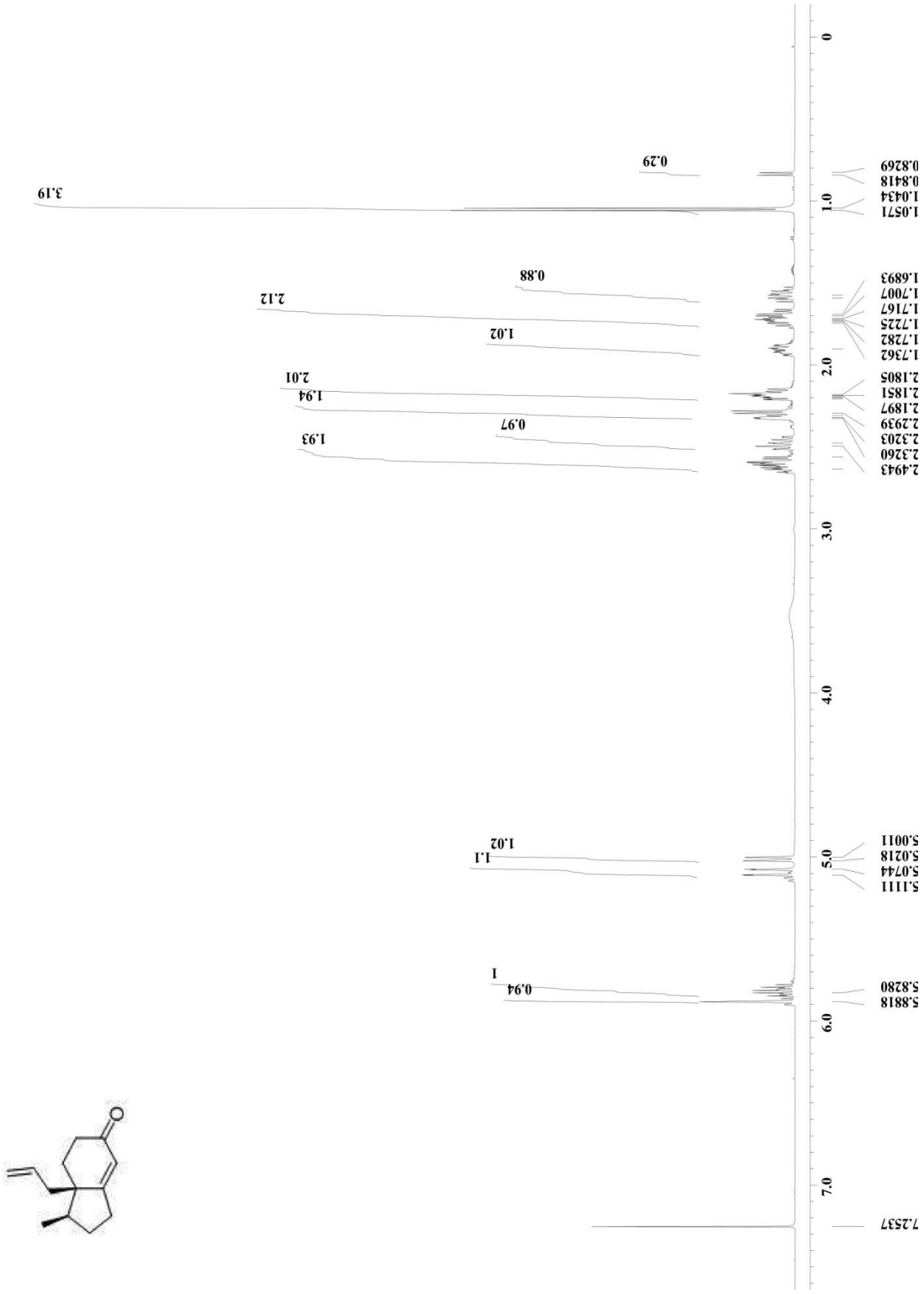
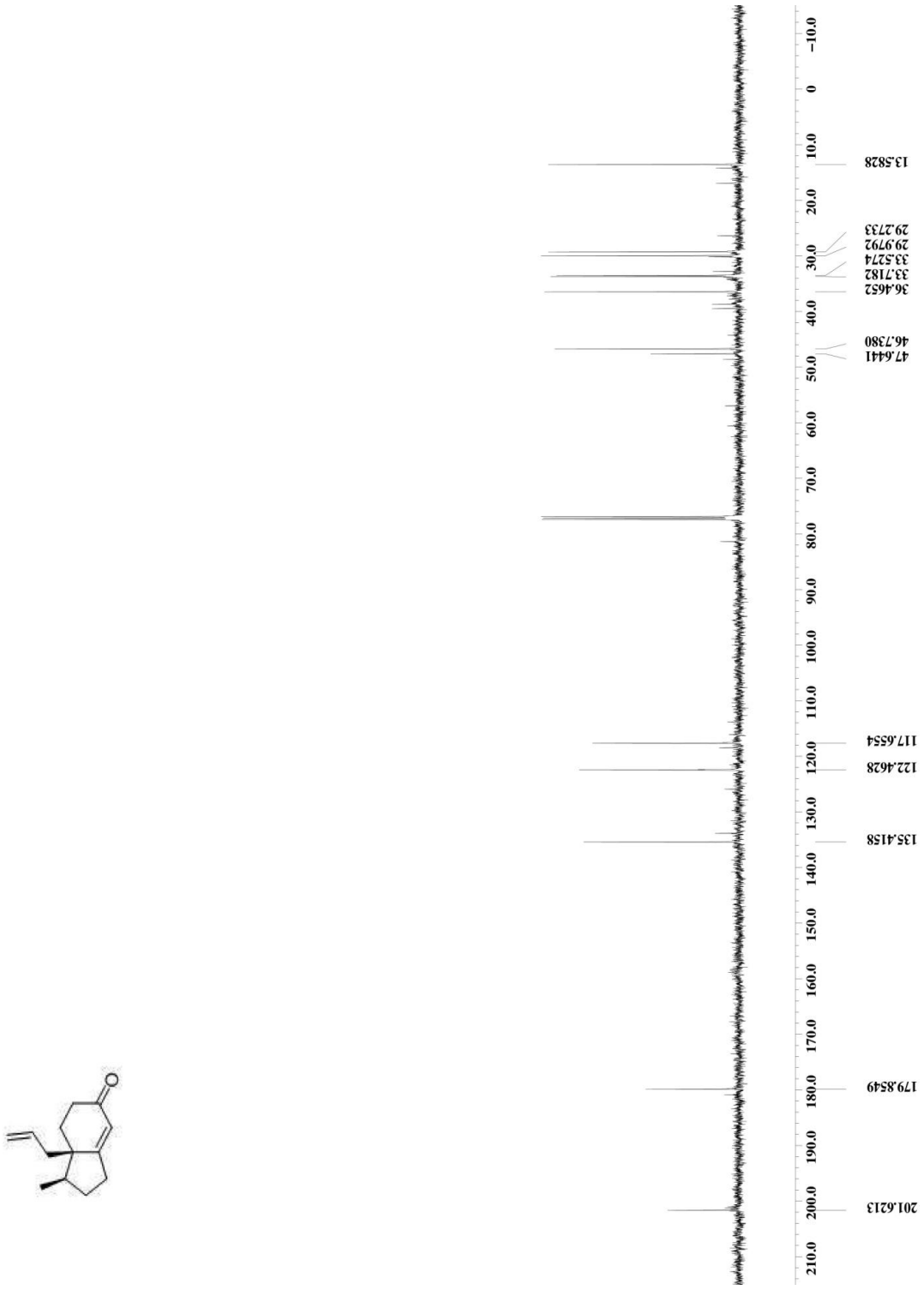
pectrum 4.57 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **198**.



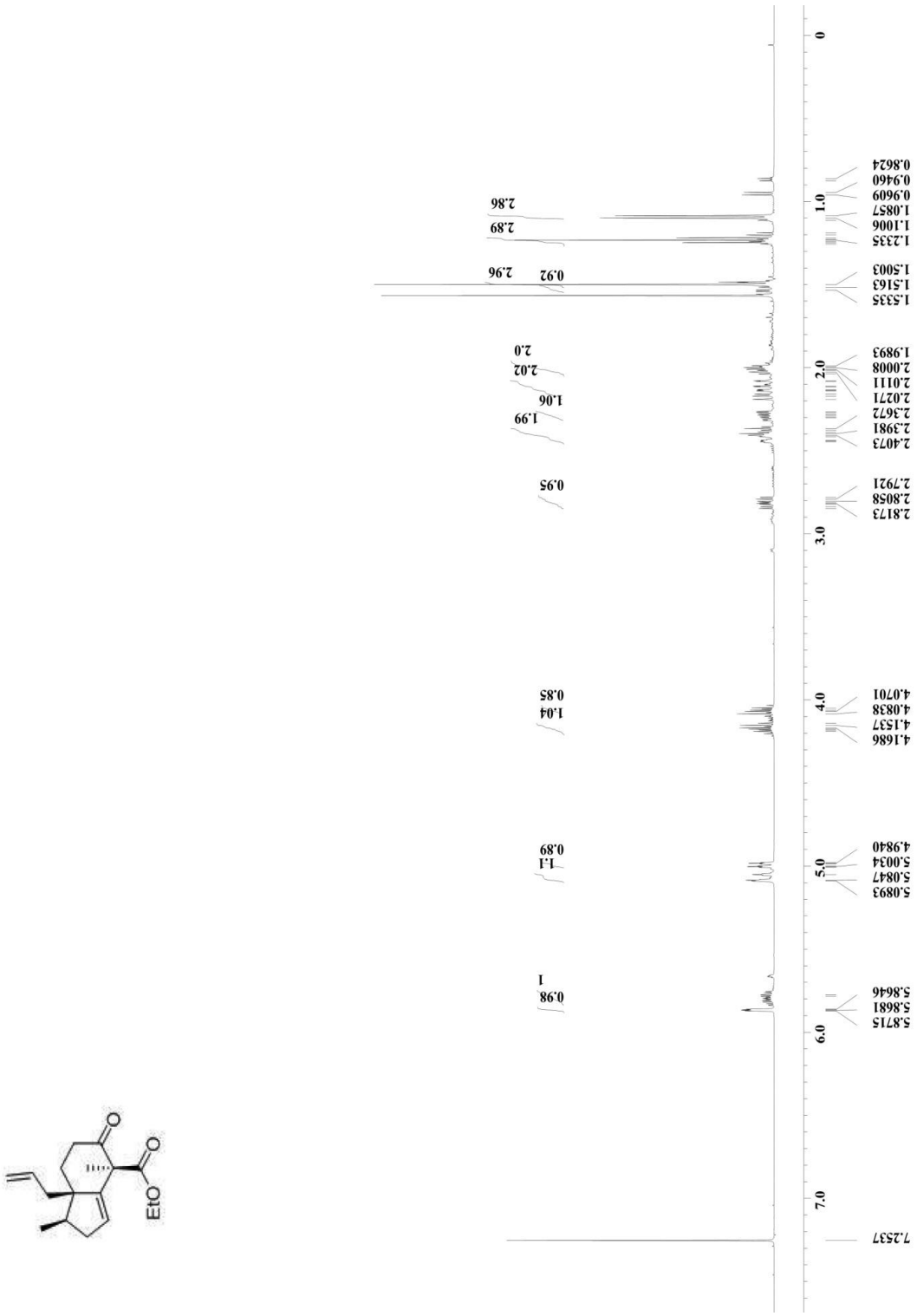
Spectrum 4.58 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **198**.



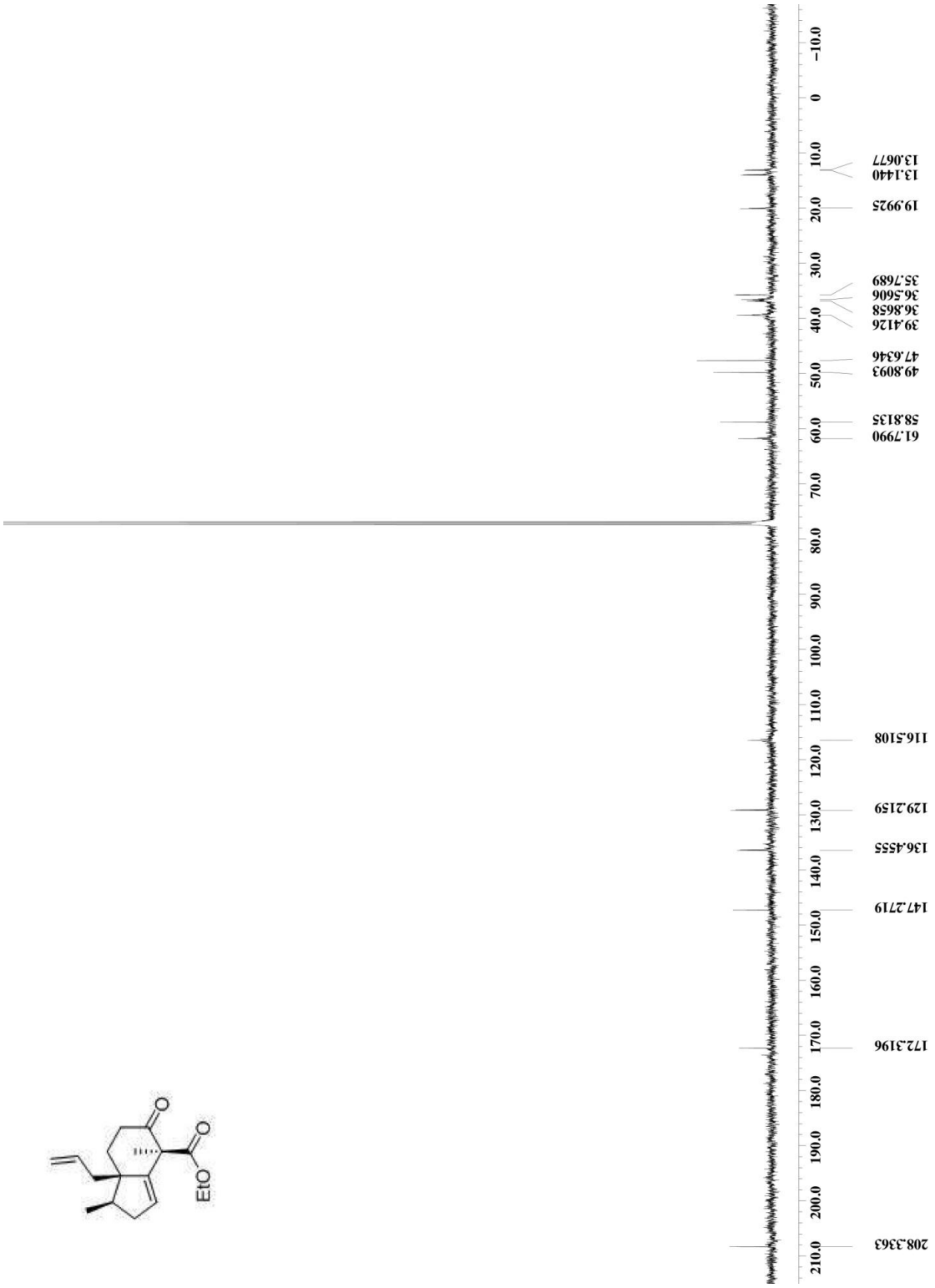
Spectrum 4.59 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **199**. .



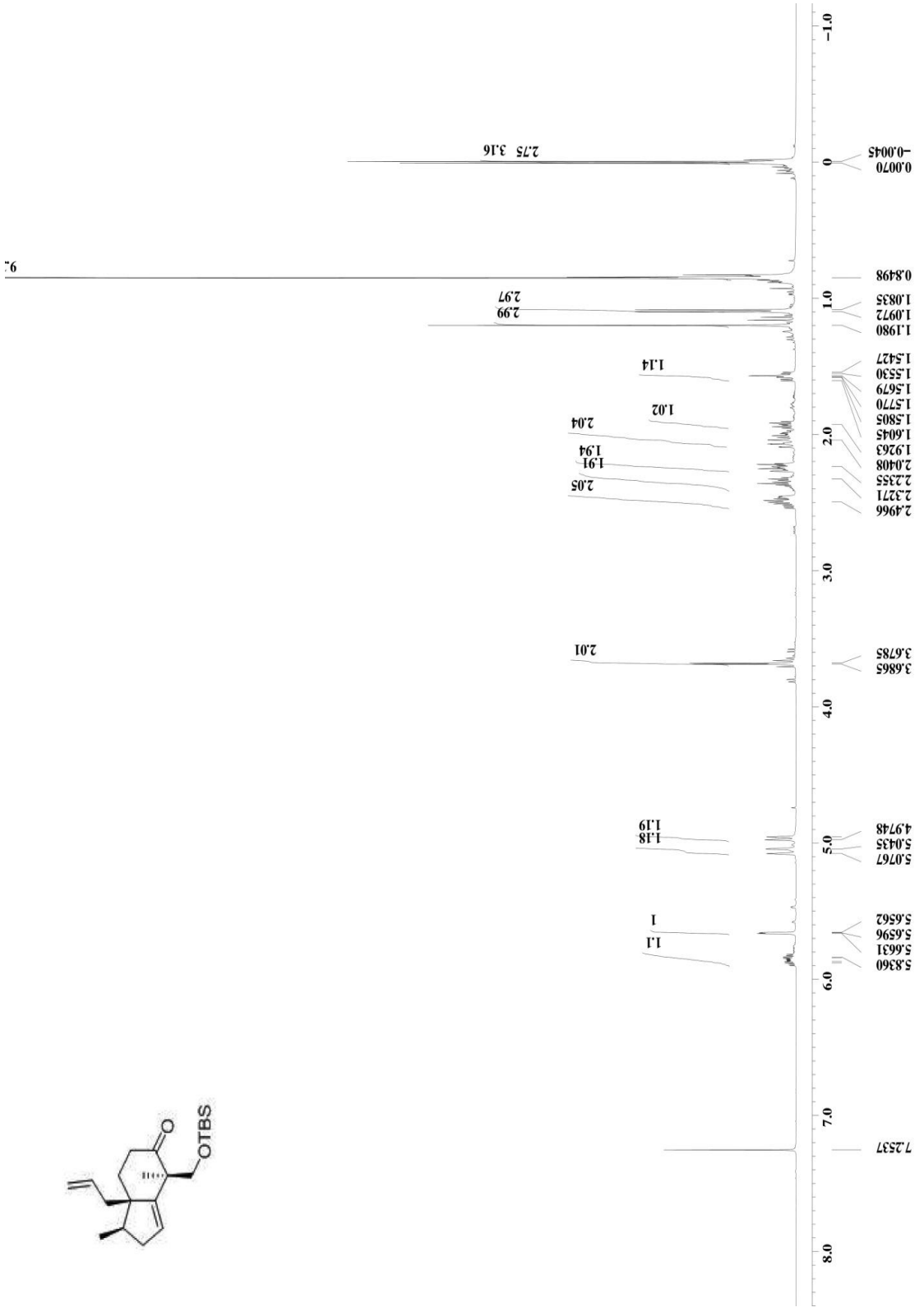
Spectrum 4.60 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **199**.



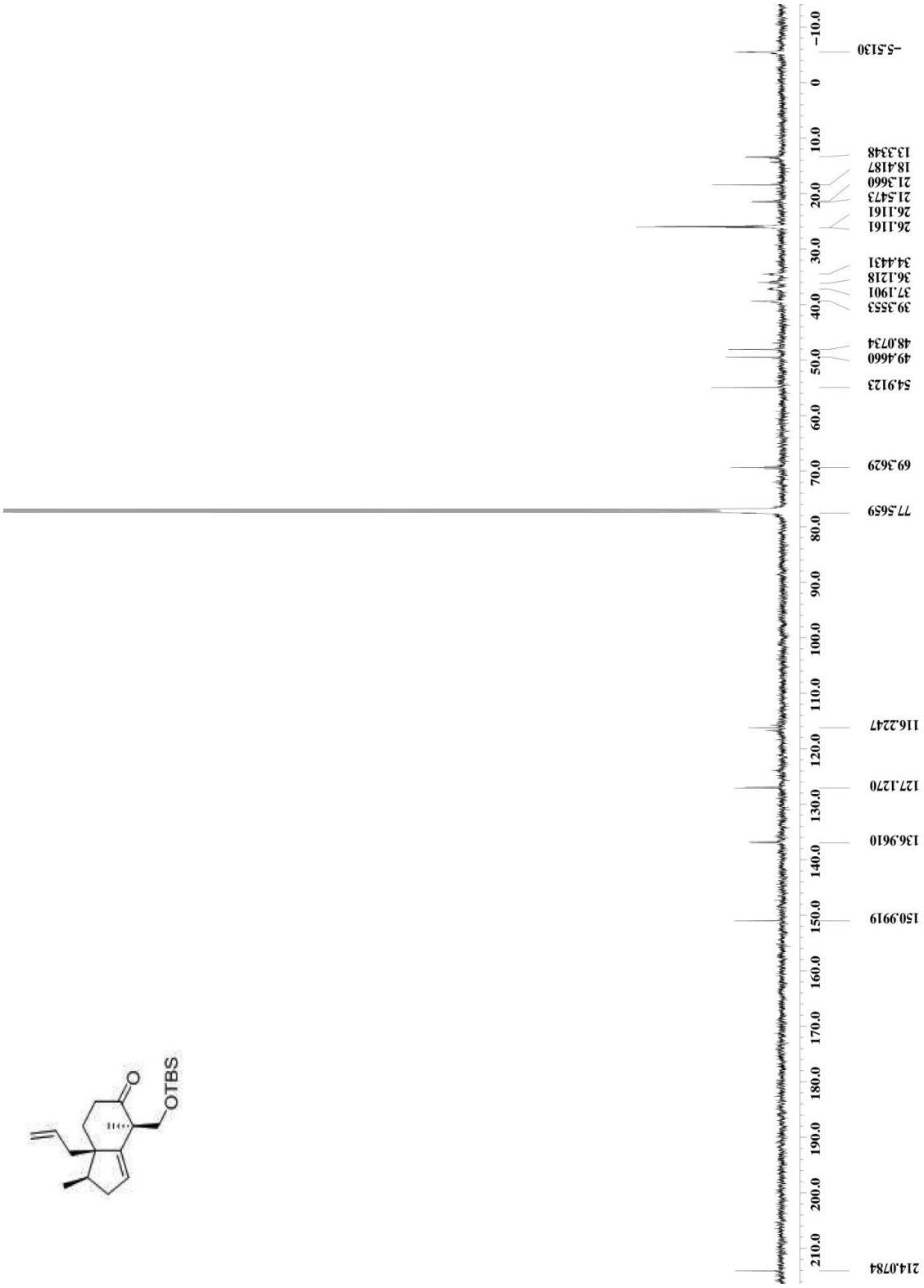
Spectrum 4.61 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **200**.



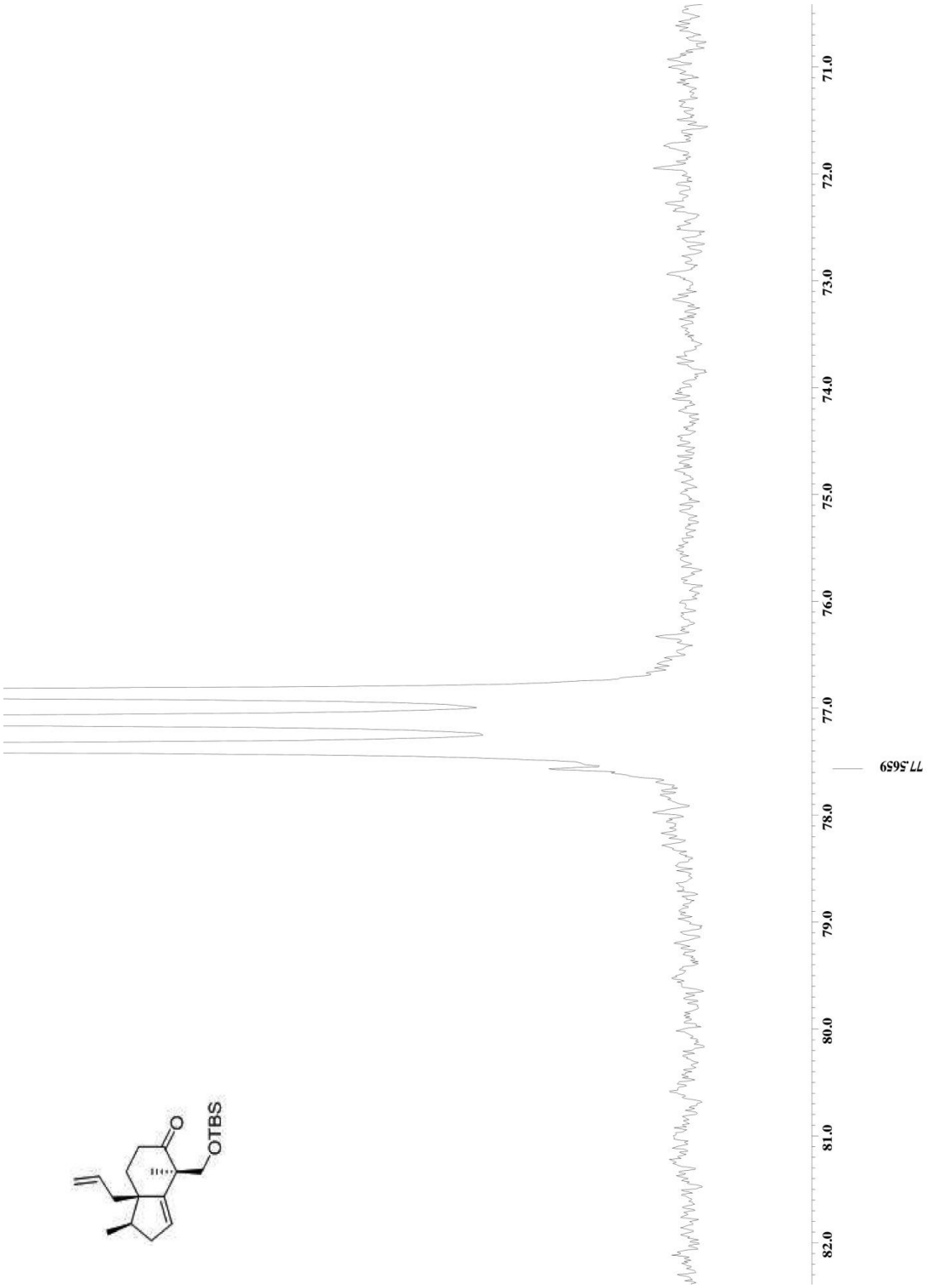
Spectrum 4.62 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **200**.



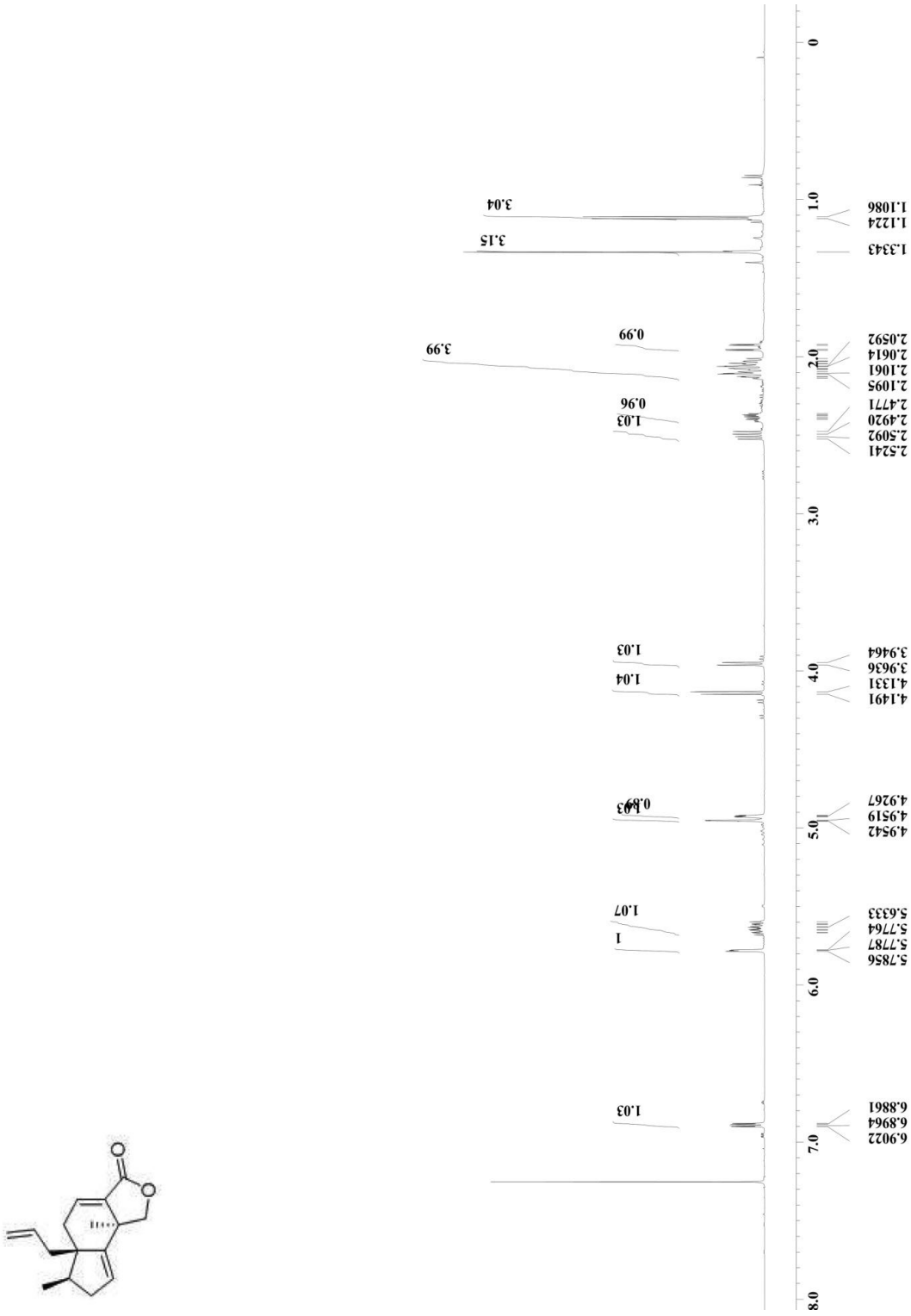
Spectrum 4.63 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **201**.



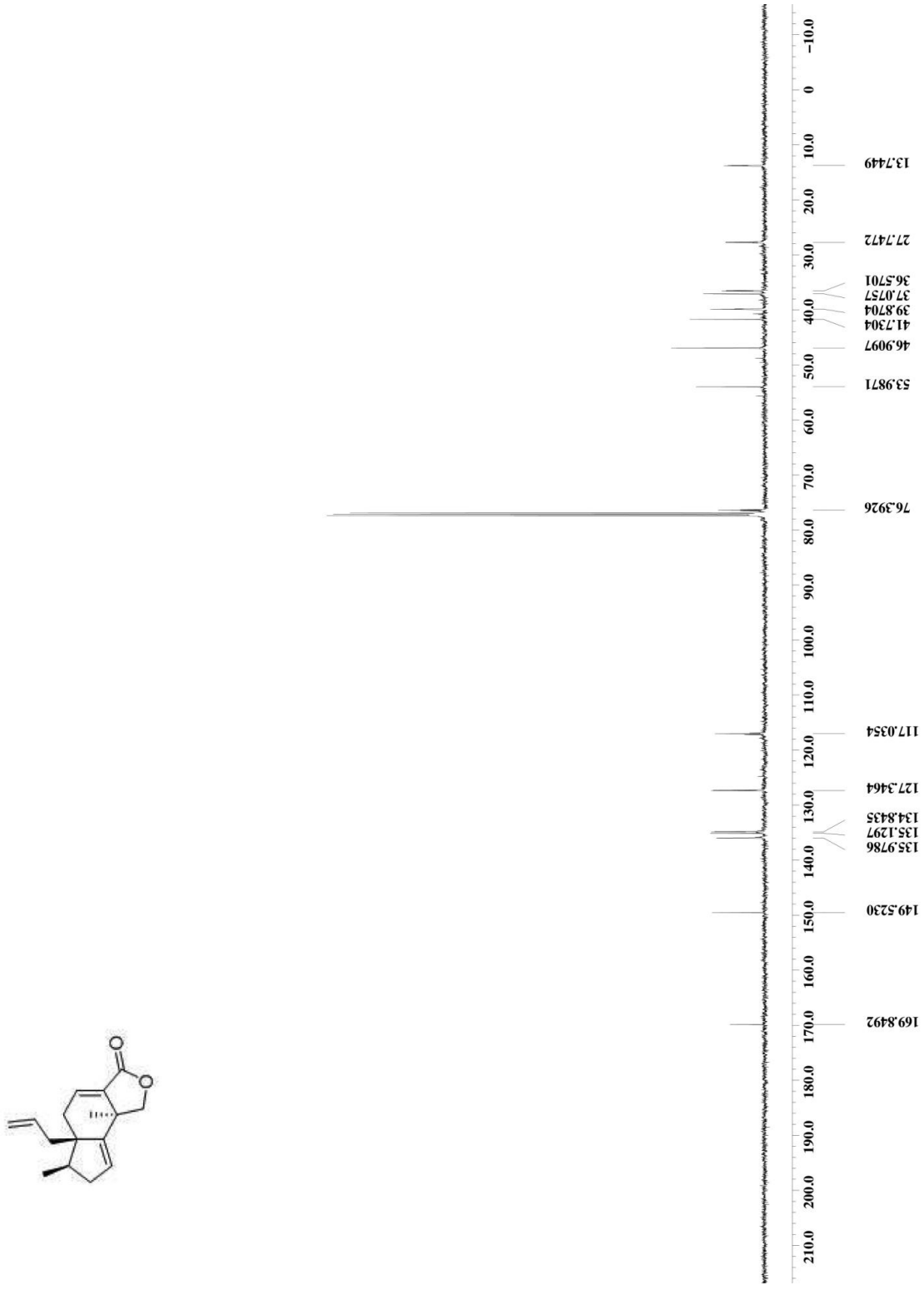
Spectrum 4.64 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **201**.



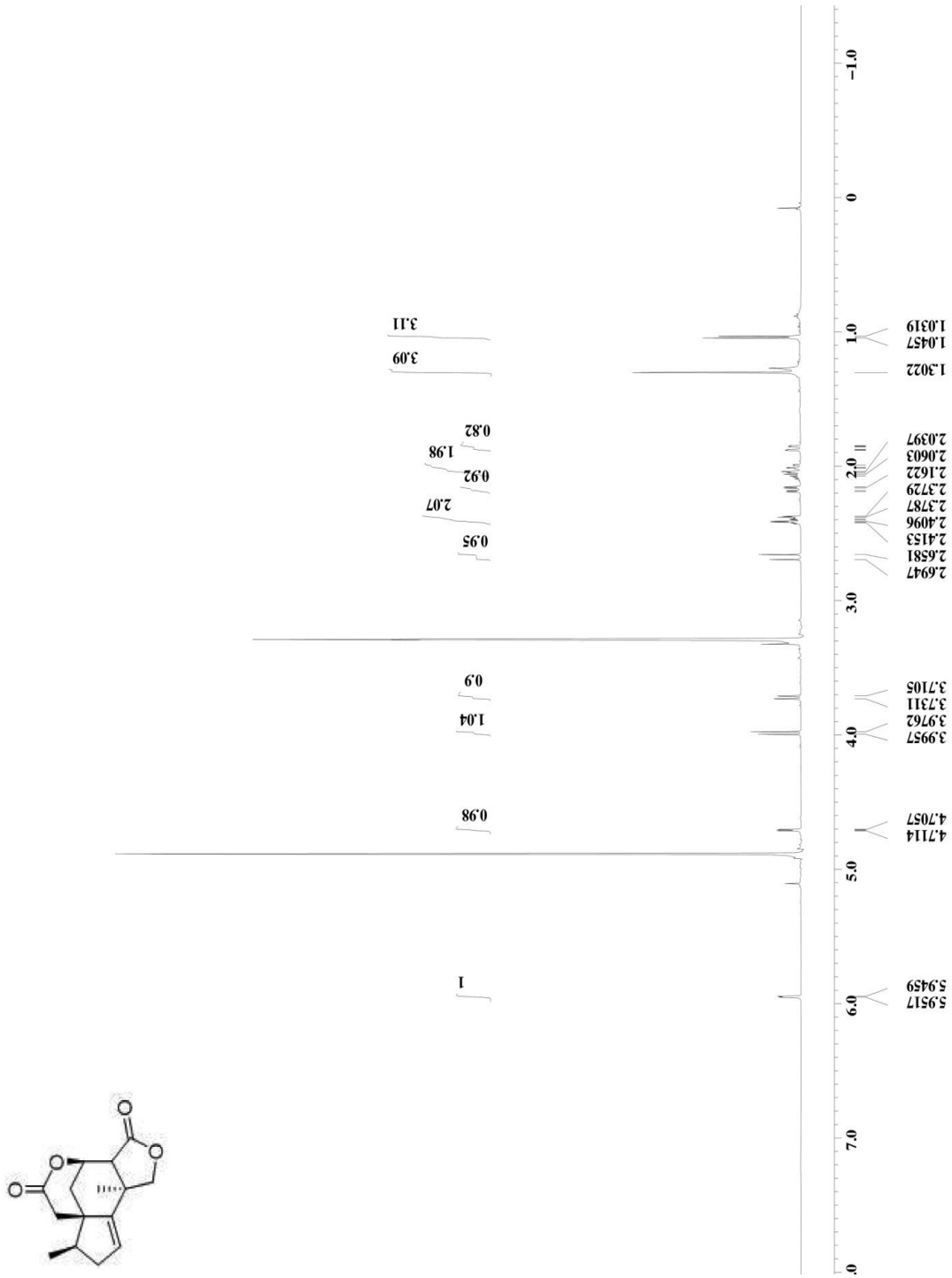
Spectrum 4.65 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **201**.



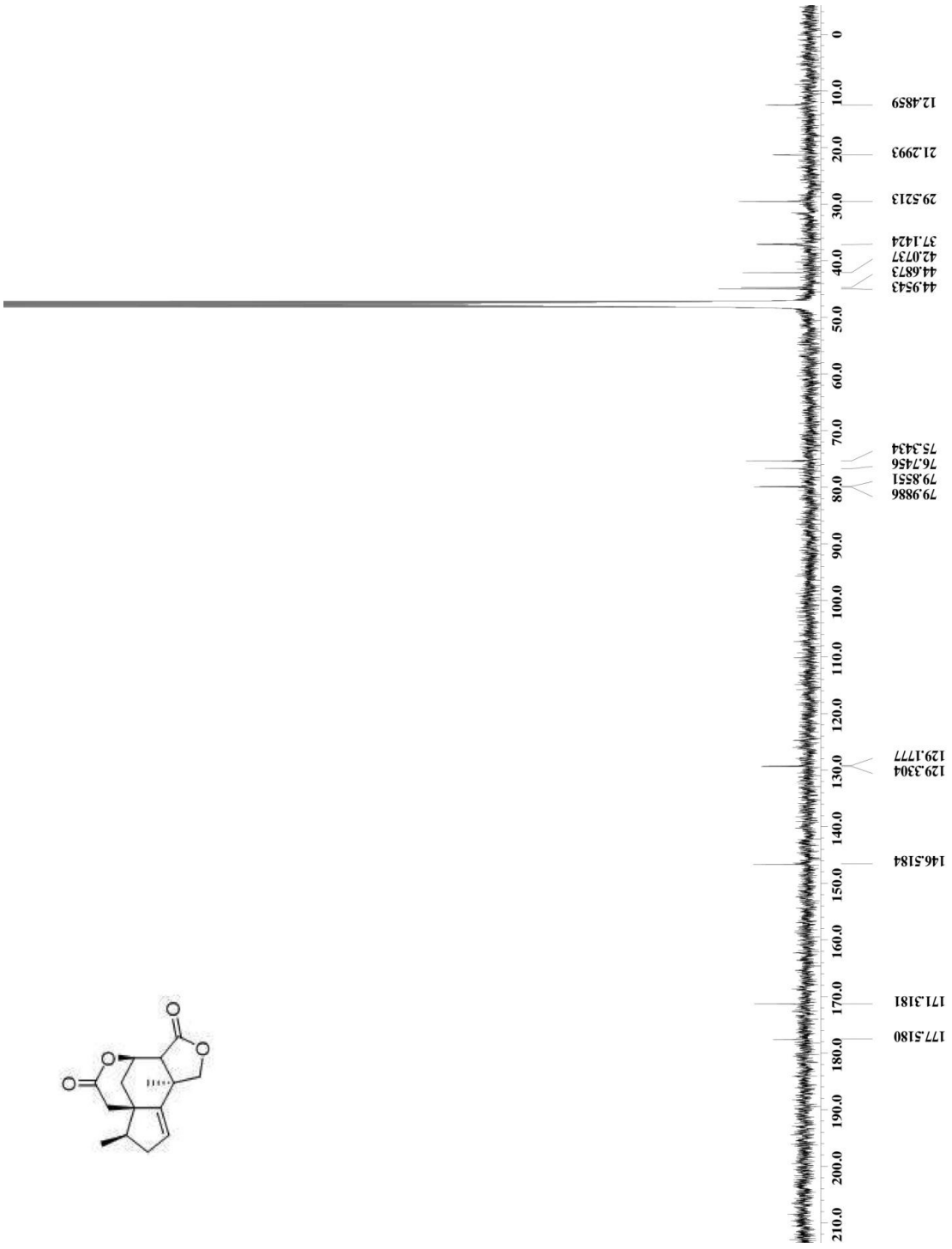
Spectrum 4.66 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **202**.



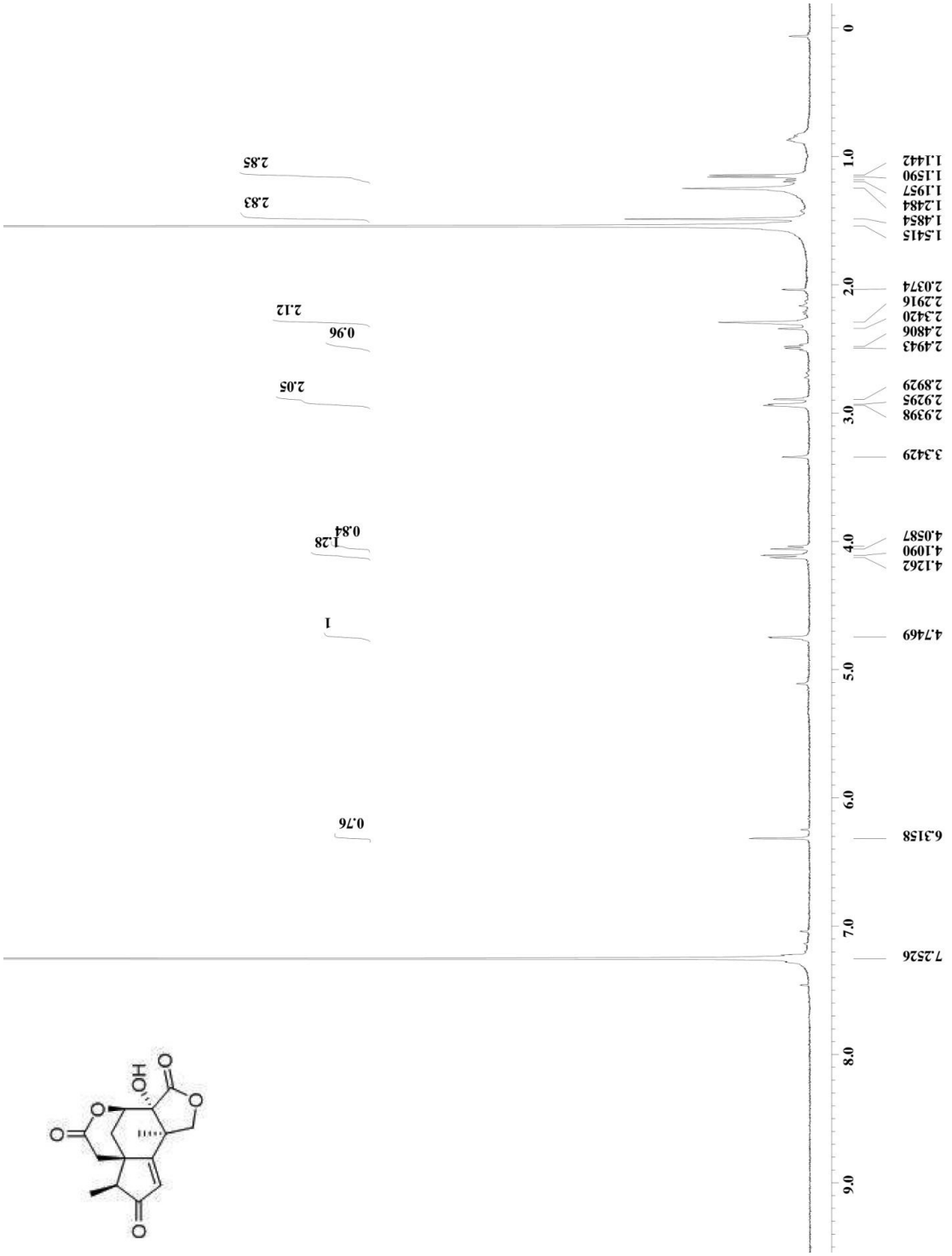
Spectrum 4.67 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **202**.



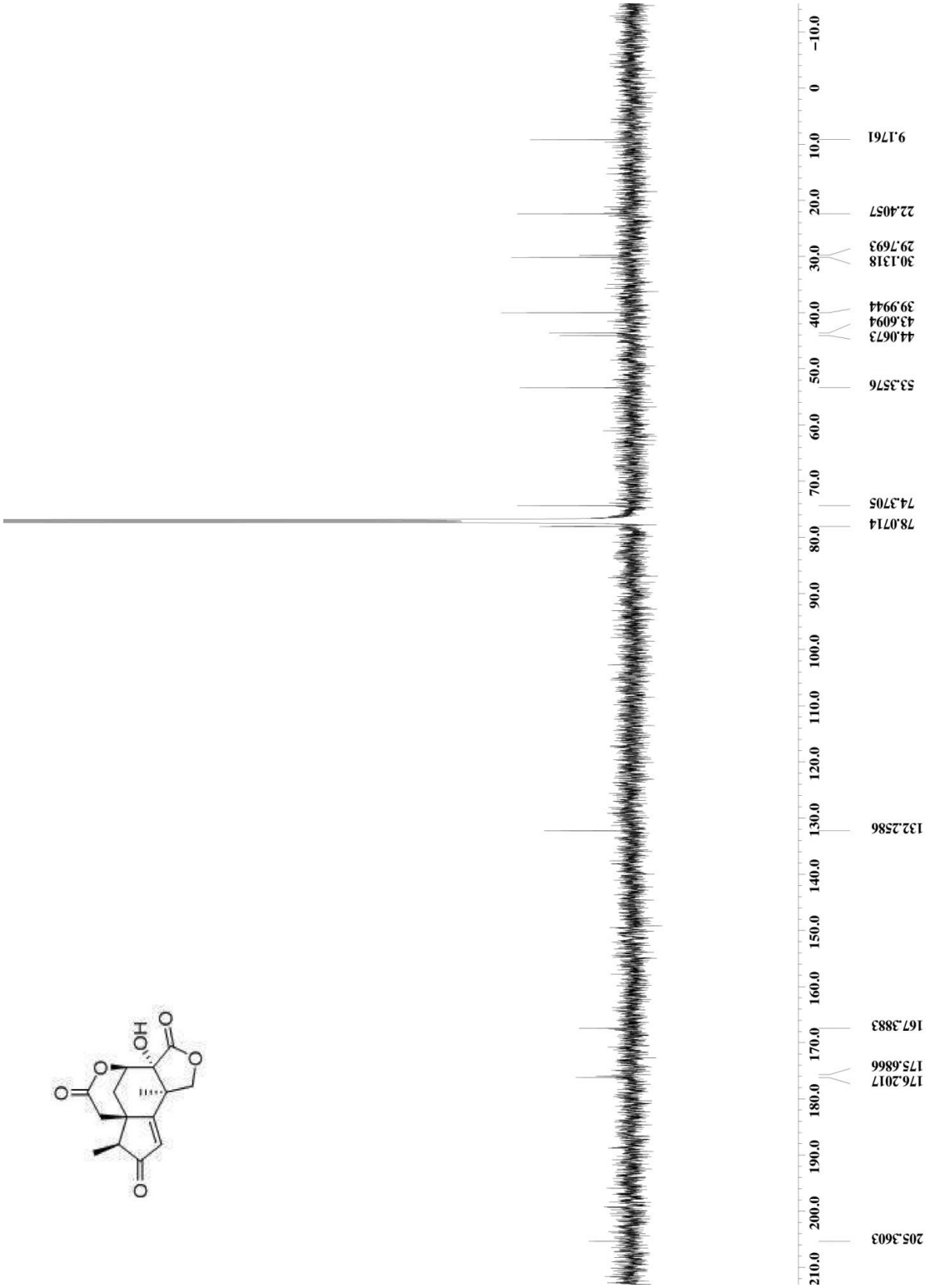
Spectrum 4.68 ^{1}H NMR (CD_3OD, 500 MHz) of compound **195**.



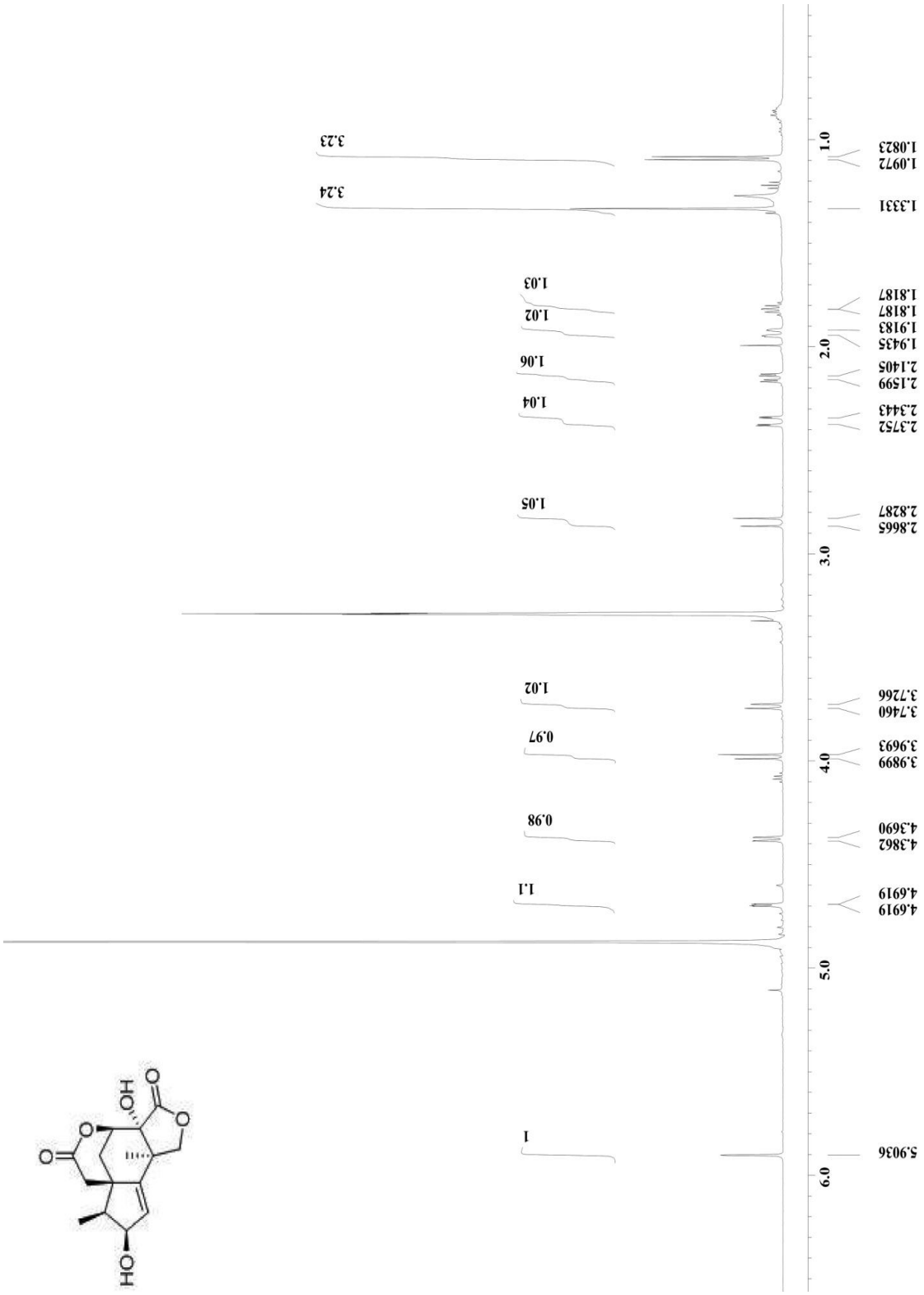
Spectrum 4.69 ^{13}C NMR (CD_3OD, 125 MHz) of compound **195**.



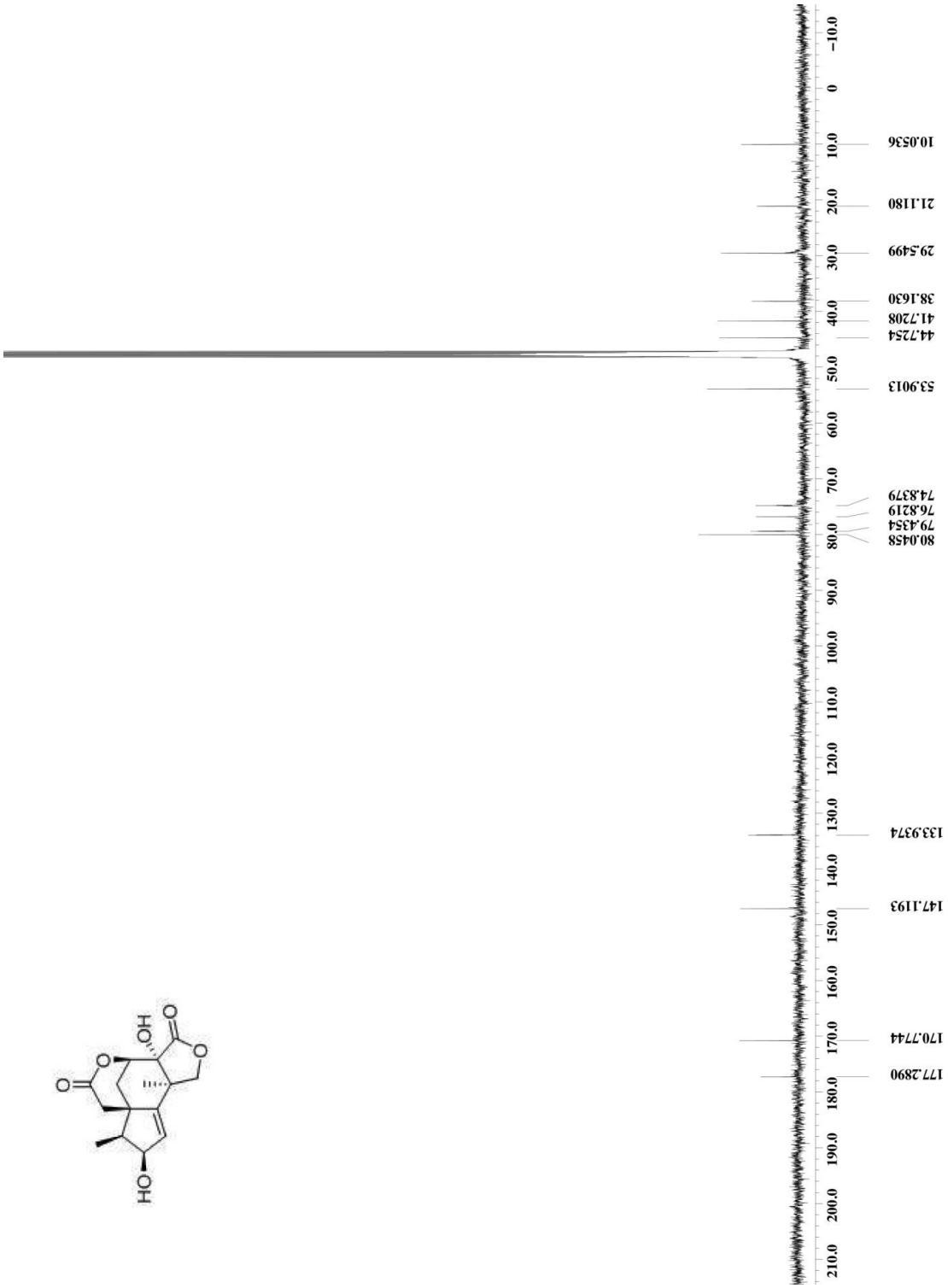
Spectrum 4.70 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **203**.



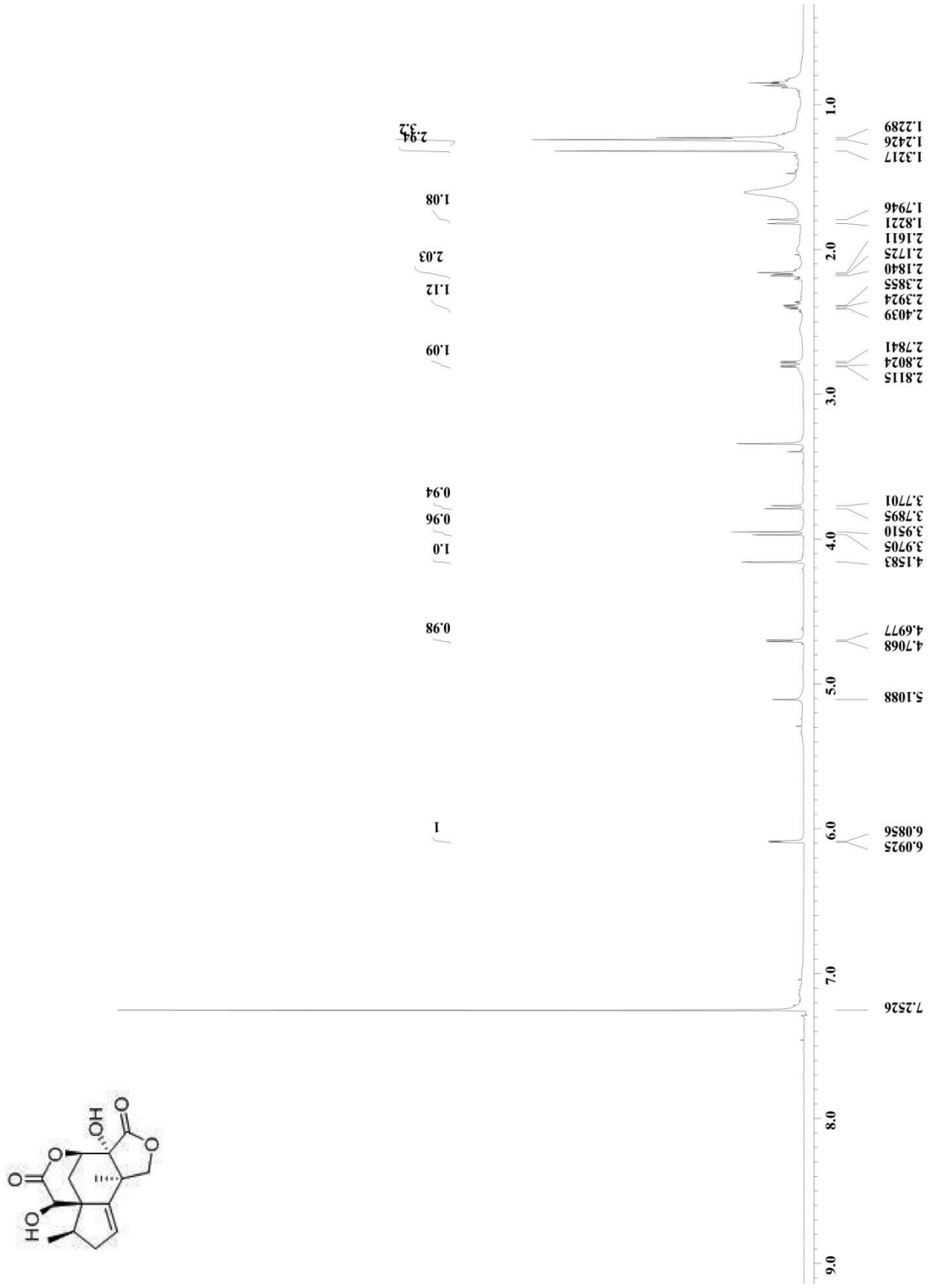
Spectrum 4.71 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **203**.



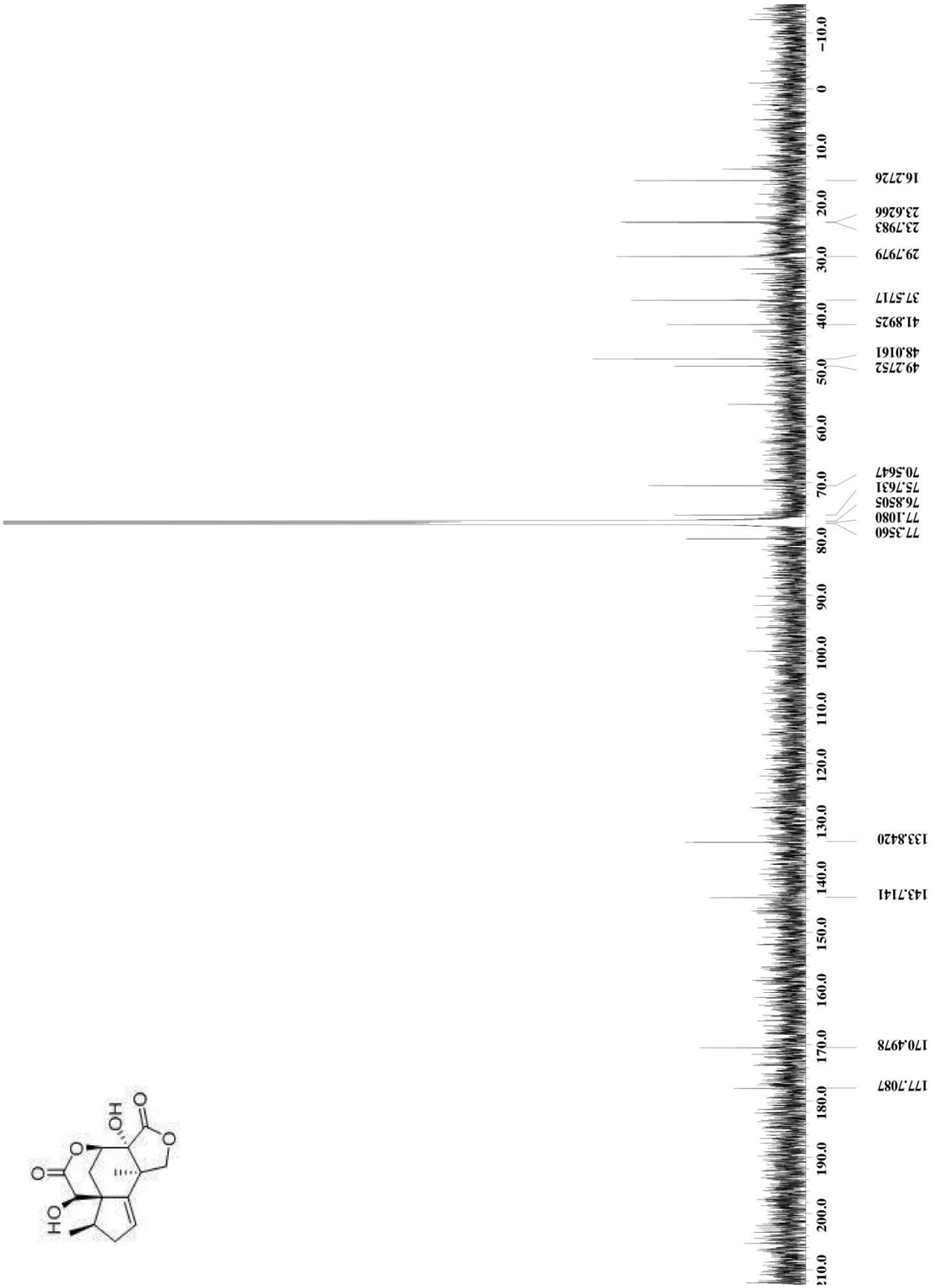
Spectrum 4.72 ^{1}H NMR (CD_3OD, 500 MHz) of compound **204**.



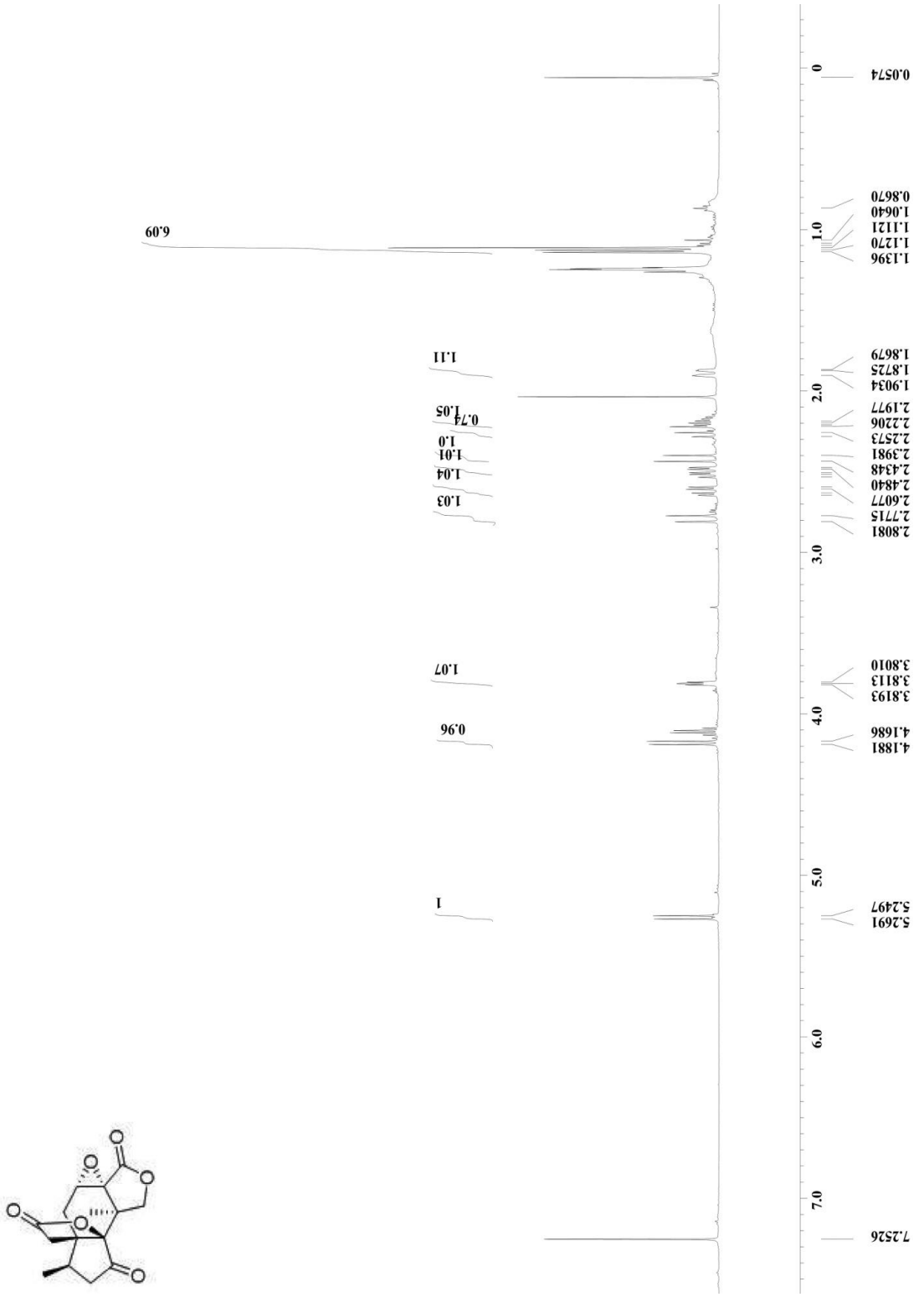
Spectrum 4.73 ^{13}C NMR (CD_3OD, 125 MHz) of compound **204**.



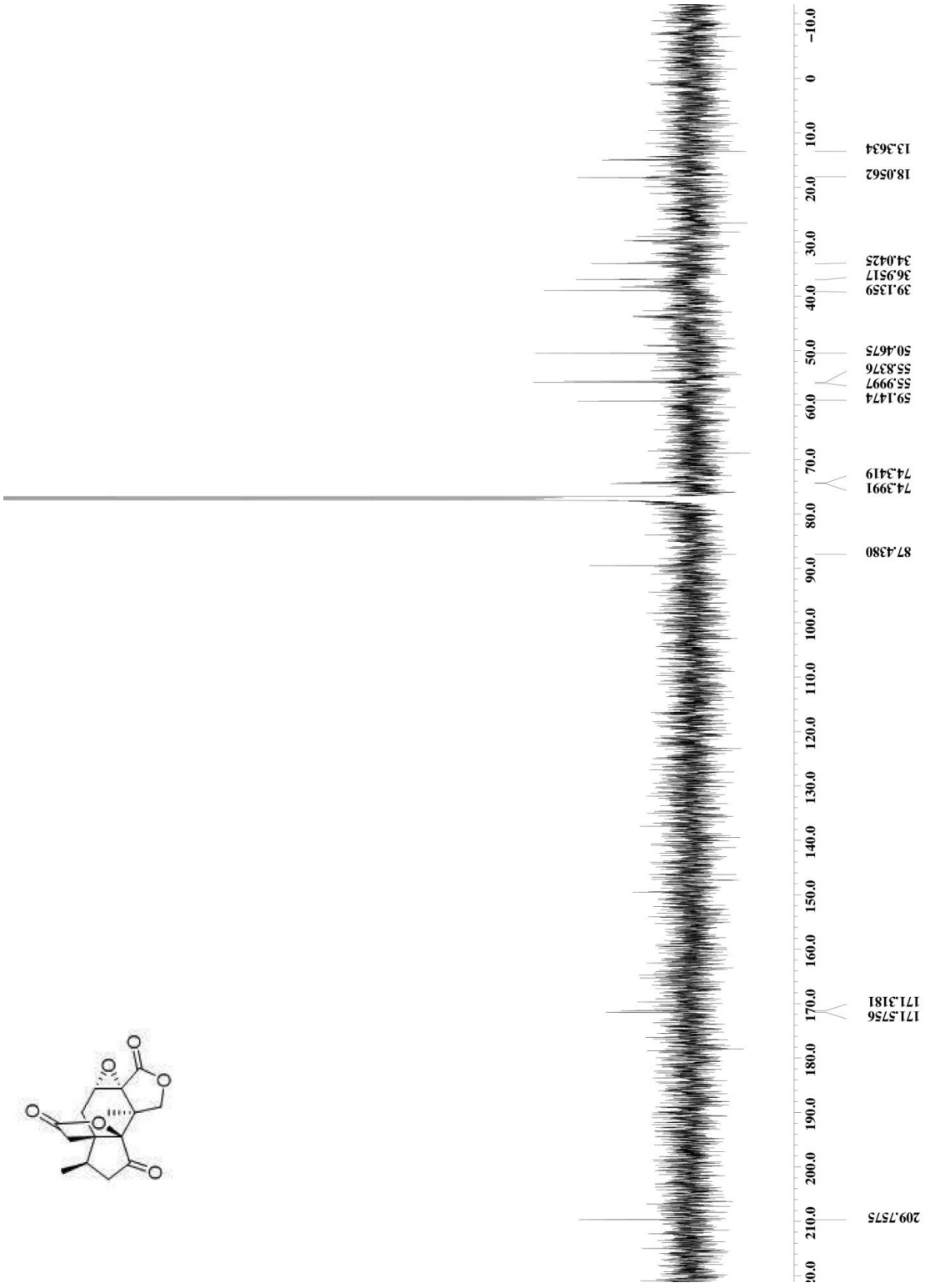
Spectrum 4.74 ^{1}H NMR (CD_3OD, 500 MHz) of compound **205**.



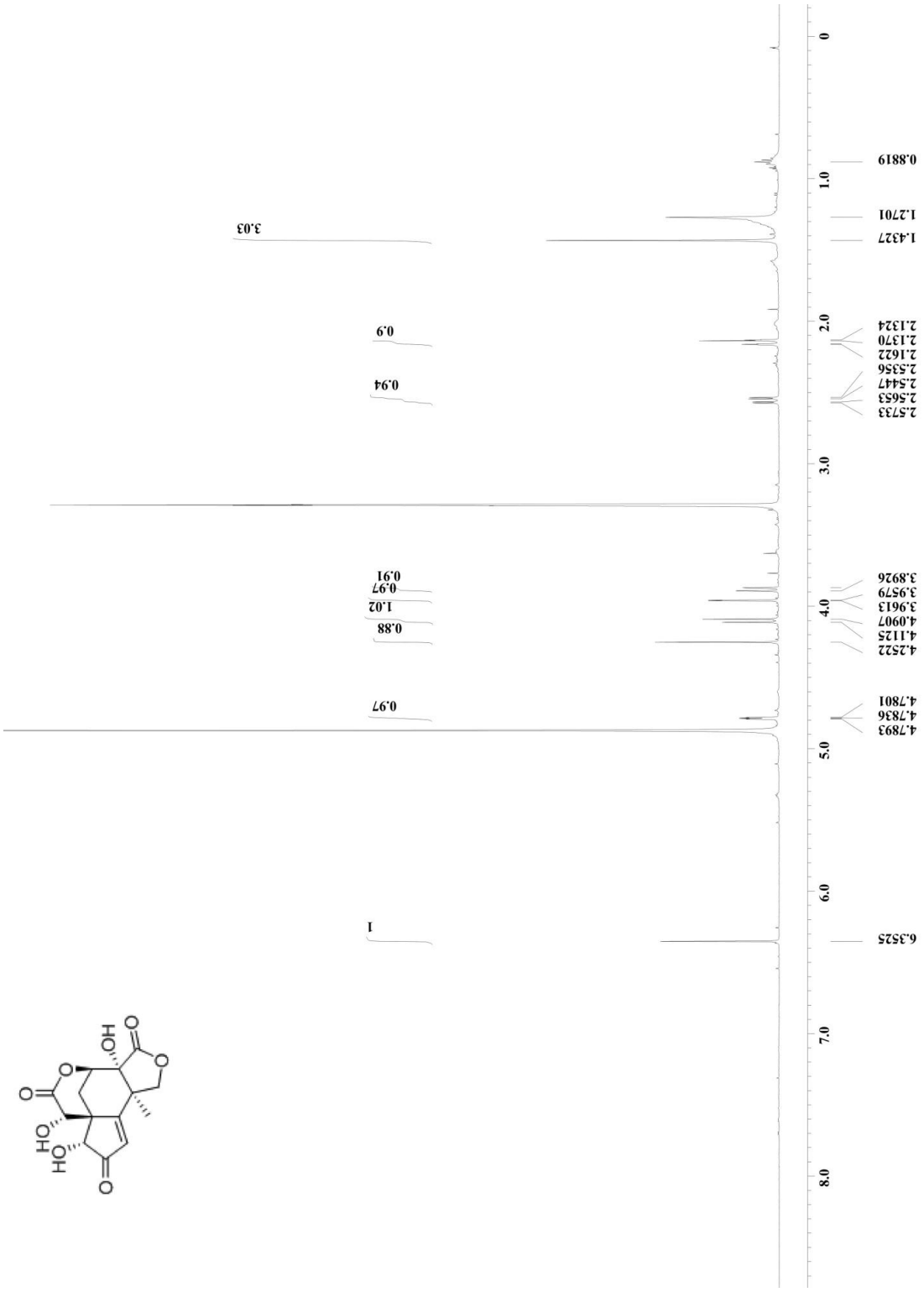
Spectrum 4.75 ^{13}C NMR (CD_3OD, 125 MHz) of compound **205**.



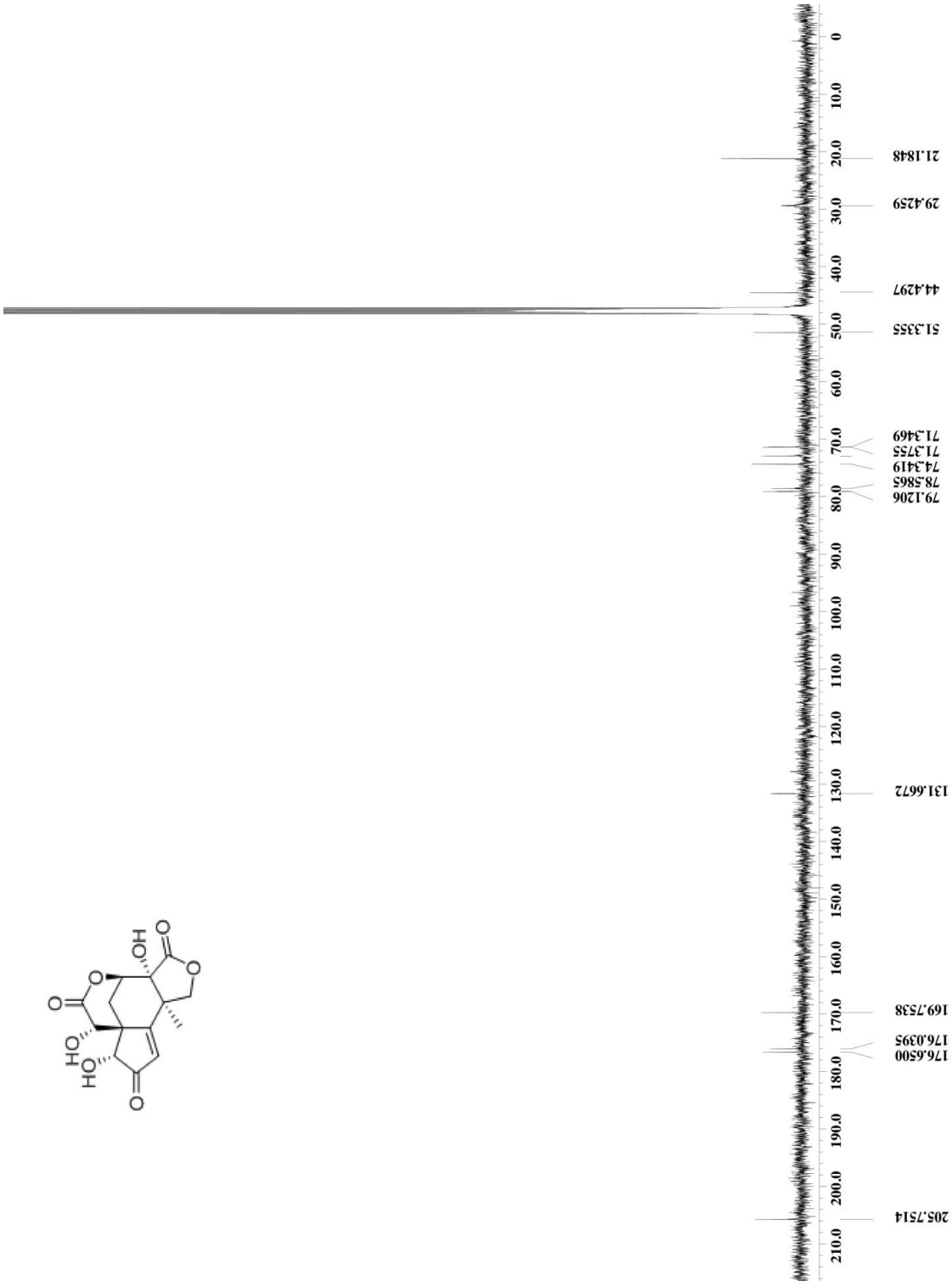
Spectrum 4.76 ^{1}H NMR ($CDCl_3$, 500 MHz) of compound **206**.



Spectrum 4.77 ^{13}C NMR ($CDCl_3$, 125 MHz) of compound **206**.



Spectrum 4.78 ^{1}H NMR (CD_3OD, 500 MHz) of compound **207**.



Spectrum 4.79 ^{13}C NMR (CD_3OD, 125 MHz) of compound **207**.