β-HETERO VINYLZINC REAGENTS: VERSATILE PRECURSORS FOR A BROAD SPECTRUM OF HIGH IMPACT CHEMICALS.

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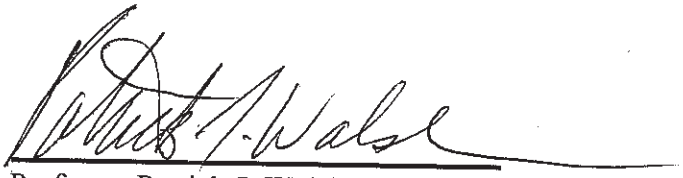

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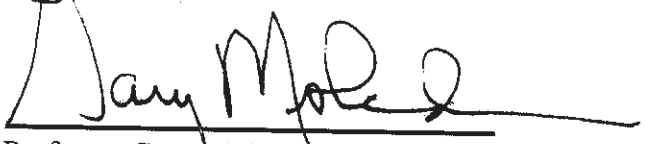

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ABSTRACT

β-HETERO VINYLZINC REAGENTS: VERSATILE PRECURSORS FOR A BROAD SPECTRUM OF HIGH IMPACT CHEMICALS.

Petr Valenta

Patrick J. Walsh

Tandem methods for the catalytic asymmetric preparation of enantioenriched *β*-hydroxy (*E*)-enamines and cyclopropylamines are presented. The diastereoselective hydrogenation of enantioenriched (*E*)-trisubstituted hydroxy enamines to generate 1,2-disubstituted 1,3-amino alcohols is also outlined. These methods are initiated by highly regioselective hydroboration of *N*-tosyl substituted ynamides with diethylborane to generate *β*-amino alkenyl boranes. In situ boron to zinc transmetalation generates *β*-amino alkenyl zinc reagents. These functionalized vinylzinc intermediates were subsequently added to aldehydes in the presence of catalyst derived from an enantioenriched amino alcohol (morpholino isoborneol, MIB). The catalyst promotes highly enantioselective C–C bond-formation to provide *β*-hydroxy enamines in good isolated yields (68–86%) with 54–98% enantioselectivity. The intermediate zinc *β*-

alkoxy enamines can be subjected to a tandem cyclopropanation to afford amino cyclopropyl carbinols with three continuous stereocenters in a one-pot procedure with good yields (72–82%), enantioselectivities of 76–94% and diastereomeric ratios >20:1. Diastereoselective hydrogenation of isolated enantioenriched *β*-hydroxy enamines over Pd/C furnished *syn*-1,2-disubstituted-1,3-amino alcohols with high yields (82–90%) and moderate to excellent diastereoselectivities. These methods were used in an efficient preparation of the enantioenriched precursor to PRC200-SS derivatives, which are potent serotonin-norepinephrine-dopamine reuptake inhibitors.

A simple and efficient method to convert aldehydes into *α*,*β*-unsaturated aldehydes with a two-carbon homologation is presented. Hydroboration of ethoxy acetylene with BH_3•SMe_2 generates tris(ethoxyvinyl) borane. Transmetallation with diethylzinc, addition to aldehydes or ketones, and acidic workup affords enals. When the addition is quenched with anilinium hydrochloride, 1,2-dithioglycol, or acetic anhydride the unsaturated imine, dithiolane, or 1,1-diacetate is isolated in high yield. These transformations can be carried out in a one-pot procedure.

Table of Contents

Abstract ii

Table of Contents iv

List of Figures ix

List of Schemes xii

List of Tables xiii

Chapter 1. Catalytic Asymmetric Synthesis of *β*-Hydroxy Enamines 1

1.1. Introduction 2

1.1.1. *β*-Hydroxy enamines in nature and organic synthesis 2

1.1.2. Methods to synthesize *β*-hydroxy enamines 4

1.1.3. Hydroboration of ynamides 6

1.2. Results and Discussion 7

1.2.1. Optimization of electron withdrawing groups on nitrogen 8

1.2.2. Optimization of hydroboration and transmetalation steps 10

1.2.3. Substrate scope of synthesis of *β*-hydroxy enamines 11

1.3. Conclusions 15

1.4. Experimental Section 16

1.5. References 35

Chapter 2. One-Pot Catalytic Asymmetric Synthesis of Amino Cyclopropyl Carbinols 39

2.1. Introduction 40

2.1.1. Amino cyclopropanes and their biological activities 41

2.1.2. Amino cyclopropyl carbinols in nature 42

2.1.3. Methods to synthesize amino cyclopropyl carbinols 44

2.2. Results and Discussion 46

2.2.1. Synthesis of amino cyclopropyl carbinols with 3-contiguous stereocenters 46

2.3. Conclusions 50

2.4. Experimental Section 50

2.5. References 56

Chapter 3. Diastereoselective Synthesis of 1,3-Aminoalcohols via Catalytic Hydrogenation of *β*-Hydroxy Enamines 61

3.1. Introduction 62

3.1.1. 1,3-Aminoalcohols in asymmetric catalysis 62

3.1.2. Methods to synthesize 1,3-aminoalcohols 65

3.1.3. Substrate directed catalytic hydrogenation 67

3.2. Results and Discussion 69

3.2.1. Optimization of hydrogenation conditions 69

3.2.2. Substrate scope of hydrogenation of β-hydroxy enamines 71

3.2.3. Conformational analysis of β-hydroxy enamines in catalytic hydrogenation 73

3.3. Conclusions 74

3.4. Experimental Section 75

3.5. References 84

Chapter 4. Enantio- and Diastereoselective Synthesis of PRC200-SS and derivatives 86

4.1. Introduction 87

4.1.1. 1,3-Aminoalcohols as a common structural motif in SNRI's 87

4.1.2. PRC200-SS and derivatives, potent triple reuptake inhibitors 88

4.1.3. Original synthesis of PRC200-SS and derivatives 89

4.2. Results and Discussion 91

4.2.1. Enantio- and diastereoselective synthesis of derivatives of PRC200-SS 91

4.3. Conclusions 94

4.4. Experimental Section 94

4.5. References 101

Chapter 5. A Simple One-Pot Synthesis of Enals and Derivatives 102

5.1. Introduction 103

5.1.1. Enals in organic syntheses 103

5.1.2. Current syntheses of enals with their pros and cons 103

5.2. Results and Discussion 105

5.2.1. A one-pot synthesis of enals from aldehydes 105

5.2.2. Substrate scope of synthesis of enals 106

5.2.3. One-pot syntheses of derivatives of enals 109

5.3. Conclusions 110

5.4. Experimental Section 111

5.5. References 125

Appendix A. ^{1}H NMR and ^{13}C{^{1}H} NMR Spectra 128

A-1. Chapter 1 Spectra 129

A-2. Chapter 2 Spectra 148

A-3. Chapter 3 Spectra 155

A-4. Chapter 4 Spectra 166

A-5. Chapter 5 Spectra 173

Appendix B. Single Crystal X-Ray Diffraction Data 195

B-1. Chapter 1 Compound 1b 196

B-2. Chapter 2 Compound 2f 213

B-1. Chapter 3 Compound 3a 221

B-1. Chapter 4 Compound 1b 230

List of Figures

Figure 1-1. Representative Natural Products Containing β-Hydroxy Enamines 2

Figure 2-1. Penciclovir and Amino Cyclopropyl Carbinol Derivative 42

Figure 2-2. Guanine Derived Amino Cyclopropyl Carbinols Showing Anti-Herpes Simplex Acivity 43

Figure 2-3. Biologically Active Amino Cyclopropyl Carbinol Nucleosides 43

Figure 2-4. Proposed transition state for diastereoselective cyclopropanation of β-alkoxy enamines 49

Figure 3-1. Proposed Conformation of Hydroxy Enamines on the Surface of Catalyst 74

Figure 4-1. 1,3-Aminoalcohols in Commercial Medications 87

Figure 4-2. 1,2-Disubstituted-1,3-aminoalcohols in Commercial Medications and Drug-Candidates 88

Figure 5-1. Internal Hemiacetal Formed During Homologation of *o*-Phthalaldehyde 108

Figure A-1. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1a** in $CDCl_3$ 130

Figure A-2. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1b** in $CDCl_3$ 131

Figure A-3. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1c** in $CDCl_3$ 132

Figure A-4. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1d** in $CDCl_3$ 133

Figure A-5. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1e** in $CDCl_3$ 134

Figure A-6. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1f** in $CDCl_3$ 135

Figure A-7. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1g** in $CDCl_3$ 136

Figure A-8. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1h** in $CDCl_3$ 137

Figure A-9. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1i** in $CDCl_3$ 138

Figure A-10. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1j** in $CDCl_3$ 139

Figure A-11. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1k** in $CDCl_3$ 140

Figure A-12. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1l** in $CDCl_3$ 141

Figure A-13. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1m** in $CDCl_3$ 142

Figure A-14. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1n** in $CDCl_3$ 143

Figure A-15. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1o** in $CDCl_3$ 144

Figure A-16. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1p** in $CDCl_3$ 145

Figure A-17. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1q** in $CDCl_3$ 146

Figure A-18. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1r** in $CDCl_3$ 147

Figure A-19. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2a** in $CDCl_3$ 149

Figure A-20. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2b** in $CDCl_3$ 150

Figure A-21. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2c** in $CDCl_3$ 151

Figure A-22. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2d** in $CDCl_3$ 152

Figure A-23. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2e** in $CDCl_3$ 153

Figure A-24. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2f** in $CDCl_3$ 154

Figure A-25. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3a** in $CDCl_3$ 156

Figure A-26. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3b** in $CDCl_3$ 157

Figure A-27. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3c** in $CDCl_3$ 158

Figure A-28. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3d** in $CDCl_3$ 159

Figure A-29. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3e** in $CDCl_3$ 160

Figure A-30. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3f** in $CDCl_3$ 161

Figure A-31. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3g** in $CDCl_3$ 162

Figure A-32. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3h** in $CDCl_3$ 163

Figure A-33. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3i** in $CDCl_3$ 164

Figure A-34. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3j** in $CDCl_3$ 165

Figure A-35. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5-5** in $CDCl_3$ 167

Figure A-36. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5-6** in $CDCl_3$ 168

Figure A-37. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5-7** in $CDCl_3$ 169

Figure A-38. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5-4** in $CDCl_3$ 170

Figure A-39. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5-8** in $CDCl_3$ 171

Figure A-40. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **PRC200** in $CDCl_3$ 172

Figure A-41. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5a** in $CDCl_3$ 174

Figure A-42. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5b** in $CDCl_3$ 175

Figure A-43. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5c** in $CDCl_3$ 176

Figure A-44. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5d** in $CDCl_3$ 177

Figure A-45. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5e** in $CDCl_3$ 178

Figure A-46. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5f** in $CDCl_3$ 179

Figure A-47. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5g** in $CDCl_3$ 180

Figure A-47. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5h** in $CDCl_3$ 181

Figure A-49. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5i** in $CDCl_3$ 182

Figure A-50. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5j** in $CDCl_3$ 183

Figure A-51. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5k** in $CDCl_3$ 184

Figure A-52. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5l** in $CDCl_3$ 185

Figure A-53. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5m** in $CDCl_3$ 186

Figure A-54. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5n** in $CDCl_3$ 187

Figure A-55. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5o** in $CDCl_3$ 188

Figure A-56. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5p** in $CDCl_3$ 189

Figure A-57. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5q** in $CDCl_3$ 190

Figure A-58. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5r** in $CDCl_3$ 191

Figure A-59. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **5s** in $CDCl_3$ 192

Figure A-59. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-*N*-((2*E*,4*E*)-5-phenylpenta-2,4-dienylidene)aniline **5-2** in $CDCl_3$ 193

Figure A-60. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 2-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)-1,3-dithiolane **5-3** in $CDCl_3$. 194

Figure A-61. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (2*E*,4*E*)-5-phenylpenta-2,4-diene-1,1-diyl diacetate **5-4** in $CDCl_3$ 195

List of Schemes

Scheme 1-1. *β*-Hydroxy Enamine as an Adducts of MX with 2'-Deoxyadenosine 3

Scheme 1-2. *β*-Hydroxy Enamine in the Synthesis of 1,2-Amino Alcohols 4

Scheme 1-3. Meyer's Multi-Step Synthesis of *β*-Hydroxy Enamines 5

Scheme 1-4. Urabe's Addition of Ynamide-Titanium Complexes to Aldehydes to form *β*-Hydroxy Enamines 5

Scheme 1-5. Hydroboration of Terminal Ynamide with Catecholborane 6

Scheme 1-6. Zirconocene-Catalyzed Hydroboration of Terminal Ynamide 6

Scheme 1-7. Oppolzer's Alkenylation of Aldehydes 7

Scheme 1-8. Stahl's Oxidative Coupling of Alkynes with Amides 8

Scheme 1-9. Synthesis of **1a** on 3.5 mmol scale 15

Scheme 2-1. Utilization of *β*-Hydroxy Enamines in Substrate-Directed Reactions 40

Scheme 2-2. Barret's, de Meijere's and Reiser's Syntheses of Amino Cyclopropyl Carbinols 45

Scheme 2-3. Asymmetric and Diastereoselective One-Pot Generation of Amino Cyclopropyl Carbinols 46

Scheme 3-1. Utilization of *β*-Hydroxy Enamines in Substrate-Directed Hydrogenation 62

Scheme 3-2. 1,2-Substituted-1,3-aminoalcohols in Asymmetric Catalysis of Carbonyl Additions 63

Scheme 3-3. 1,2-Substituted-1,3-aminoalcohols in Asymmetric Catalysis of Allylation and Hydrogenation 64

Scheme 3-4. Available Methods to Synthesize 1,2-Disubstituted -1,3-aminoalcohols 65

Scheme 3-5. Lithium Ephedrinate Mediated Aldol Reaction of Arylacetonitriles 66

Scheme 3-6. Representative Examples of Hetero-Atom Directed Heterogeneous Hydrogenations 67

Scheme 3-7. Partial Hydrogenolysis of Benzyl Group **3b** at High Pressure and Catalyst 73

Scheme 4-1. Carlier's synthesis of PRC200-SS and Derivatives 90

Scheme 4-2. Lithium Ephedrinate Mediated Aldol Reaction of Arylacetonitriles 91

Scheme 4-3. Our Synthesis of PRC200-SS and Derivatives 92

Scheme 5-1. Existing Syntheses of Enals 104

Scheme 5-2. Our One-Pot Synthesis of Enals 106

Scheme 5-3. One-Pot Synthesis of Derivatized Enals 109

List of Tables

Table 1-1. Examination of Various Electron Withdrawing Groups on the Ynamide 9

Table 1-2. Optimization of Yield and Enantioselectivity in the Synthesis of β-Hydroxy Enamines 10

Table 1-3. Substrate Scope of the Asymmetric One-Pot Generation of β-Hydroxy Enamines 13

Table 2-1. Enantio- and Diastereoselective One-Pot Generation of Amino Cyclopropyl Carbinols 48

Table 3-1. Optimization of Diastereoselective Hydrogenation of *β*-Hydroxy Enamines 70

Table 3-2. Diastereoselective Hydrogenation of *β*-Hydroxy Enamines 72

Table 4-1. Optimization of Diastereoselective Hydrogenation of *β*-Hydroxy Enamine **4-6** 93

Table 5-1. Substrate Scope of Two-carbon Homologation of Aldehydes and Ketones 107

Chapter 1. Catalytic Asymmetric Synthesis of β-Hydroxy Enamines

1.1. Introduction

1.1.1. *β*-Hydroxy enamines in nature and organic synthesis

β-Hydroxy enamines are present in several natural and unnatural products[1–5] and are valuable synthetic intermediates.[6–8] For example the *β*-hydroxy-enamino amino acid Pinnatanine is very common (Figure 1-1). It was originally isolated from the fresh bulbs of *Hemerocallis longituba*, a perennial plant native to Japan, China and Taiwan. Pinnatanine is responsible for antifebrile and diuretic effects, which were used in folk medicine for more than thousand years. More recently lipid peroxidation inhibitory properties of Pinnatanine, related with cardiovascular diseases, cancer and aging related disorders were found.[2] Oxidative stress refers to the undue oxidation of biomolecules leading to cellular damage. Very recently Pinnatanine derived glycoside Kwansonine B (Figure 1-1) was isolated. It is probably responsible for sedative activity of *Hemerocallis fulva* var. *sempervirens* and is taken as an aid to sleeping in Okinawa, Japan.[1]

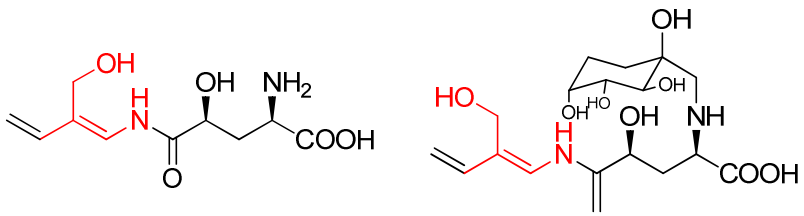
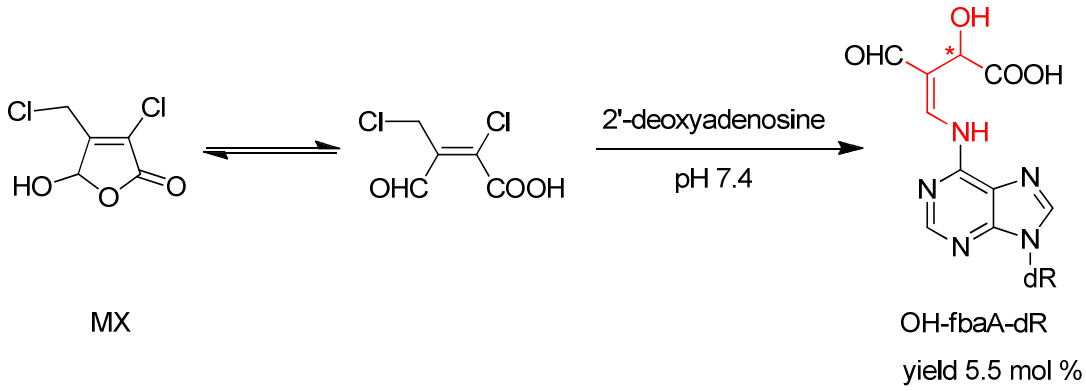


Figure 1-1. Representative Natural Products Containing *β*-Hydroxy Enamines

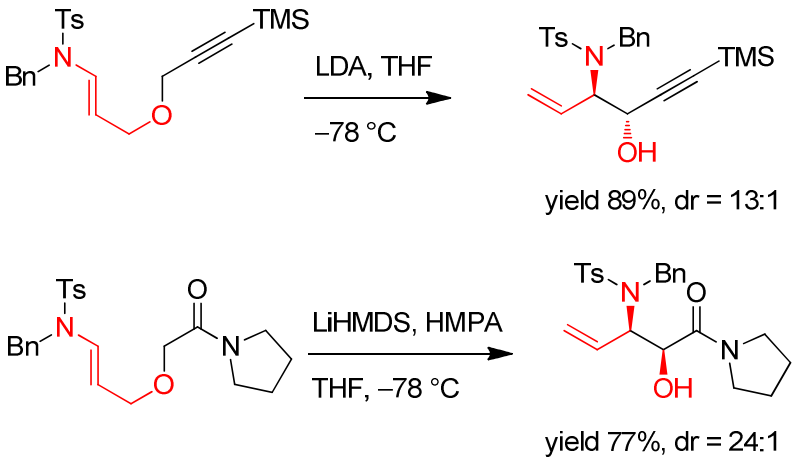
Some β-hydroxy enamines that are harmful to our health can be found in human bodies. Chlorohydroxyfuranones (CHFs) are formed during chlorine disinfection of drinking water as a result of the reaction of chlorine with naturally occurring humic substances.[3] One of these compounds, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) (Scheme 1-1), is a very potent bacterial mutagen and accounts for about one-third of the mutagenicity of chlorinated drinking water. Recently, MX was demonstrated to be a multisite carcinogen in rats. A possible mechanism involves the formation of adducts of MX with nucleobases such as 2'-deoxyadenosine. A β-hydroxy enamine adduct is formed as a single diastereomer, but the absolute configuration of secondary alcohol was not determined.



Scheme 1-1. β-Hydroxy Enamine Formed in Reaction of MX with 2'-Deoxyadenosine

β-Hydroxy enamines were recently used as starting materials in diastereoselective synthesis of 1,2-aminoalcohols via [2,3]-Wittig rearrangement (Scheme 1-2).[7,8]

Depending on the anionic stabilizing group (amide or alkyne), high *syn* or *anti* diastereoselectivity was achieved.

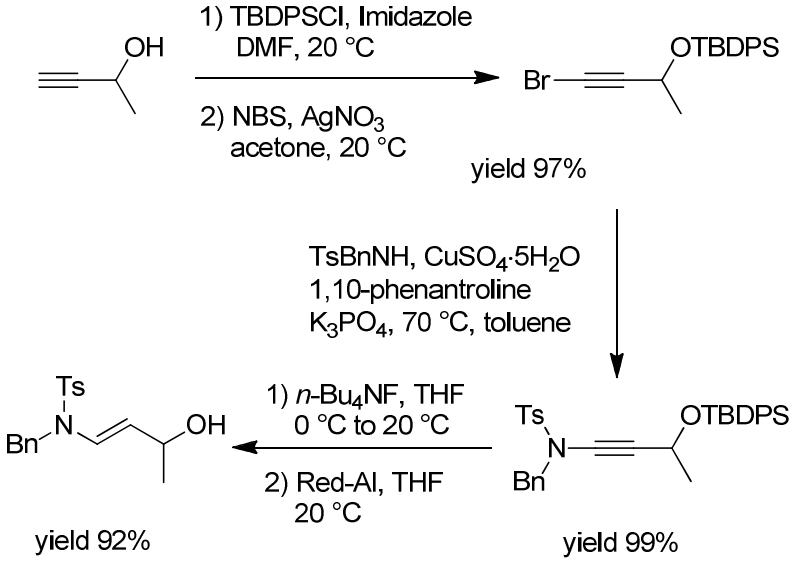


Scheme 1-2. *β*-Hydroxy Enamines in the Synthesis of 1,2-Aminoalcohols

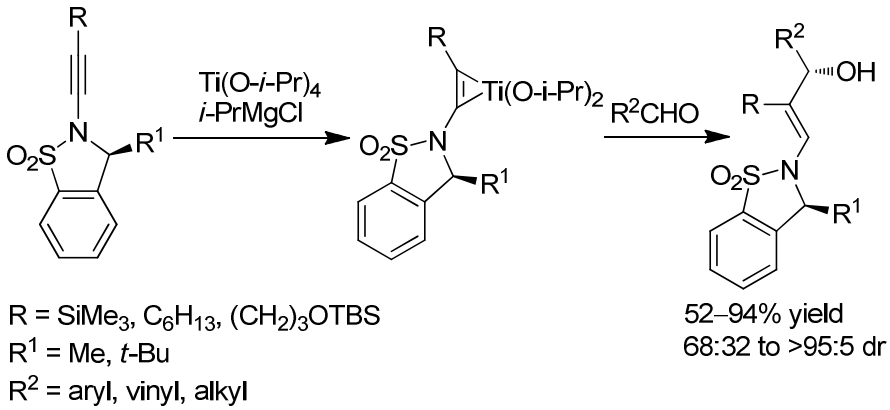
1.1.2. Methods to synthesize *β*-hydroxy enamines

The absence of efficient catalytic enantioselective methods for preparation of *β*-hydroxy enamines impedes their wider utilization in synthesis and drug discovery. Several methods for the synthesis of racemic *β*-hydroxy enamines have been introduced. Meyer has recently developed a five step synthesis of *β*-hydroxy enamines from propargyl alcohols (Scheme 1-3).[7,8] Derivatization followed by Wittig rearrangement gave aminoalcohols, highlighting the utility of *β*-hydroxy enamines. The only one-step method for the synthesis of *β*-hydroxy enamines is Urabe's reaction of ynamide-titanium complexes with aldehydes (Scheme 1-4).[6, 9, 10] Yields as high as 94% were achieved

with moderate to excellent diastereoselectivities (2:1 to <20:1) and good substrate scope. The method, however, requires the use of enantioenriched sulfonamide-based auxiliaries that were synthesized in four steps, one of which employed another chiral auxiliary.[11]



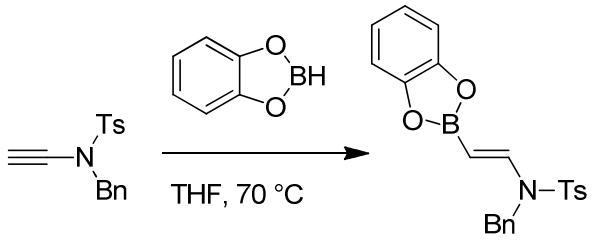
Scheme 1-3. Meyer's Multi-Step Synthesis of *β*-Hydroxy Enamines



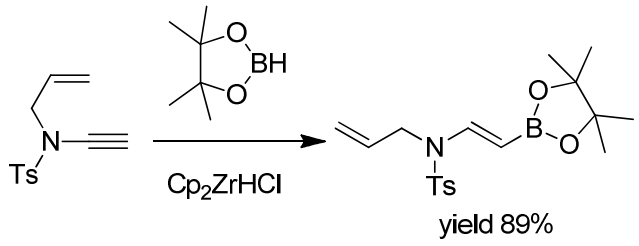
Scheme 1-4. Urabe's Addition of Ynamide-Titanium Complexes to Aldehydes to form *β*-Hydroxy Enamines

1.1.3. Hydroboration of ynamides

It was not clear at the outset of our work whether the uncatalyzed hydroboration of internal ynamides would proceed with high regioselectivity. Only hydroboration of terminal ynamides was previously reported with good regioselectivity.[11, 12] Reaction with catecholborane gives the unstable monohydroboration product (Scheme 1-5).[11] In situ cross-coupling with aryl halides then gave protected styryl amides. Unfortunately, only terminal ynamide was used and the reactivity of other classes of ynamides, including nonterminal ones, remained to be evaluated. An additional example of metal-catalyzed hydroboration with pinacolborane was reported a year later (Scheme 1-6).[12]



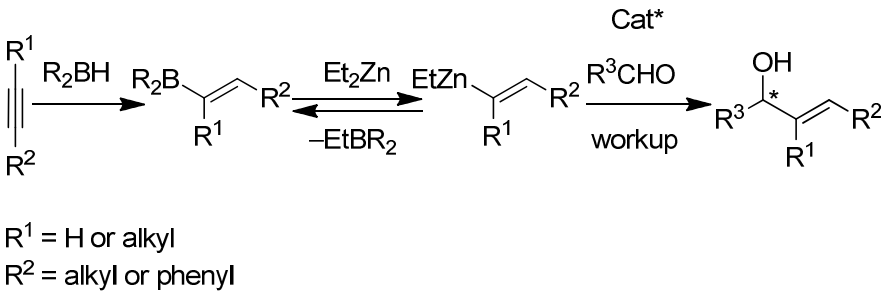
Scheme 1-5. Hydroboration of Terminal Ynamide with Catecholborane



Scheme 1-6. Zirconocene-Catalyzed Hydroboration of Terminal Ynamide

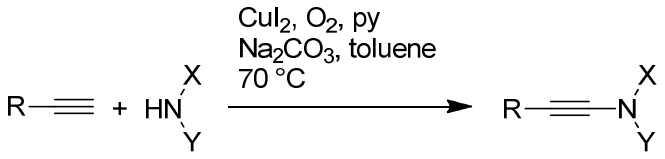
1.2. Results and Discussion

Our interest in enantiomerically enriched *β*-hydroxy enamines with stereodefined double bonds stems from their potential utility in medicinal chemistry and as synthetic intermediates. We therefore setout to develop a highly enantioselective, practical and efficient one-pot method for their generation. For the synthesis of enantioenriched *β*-hydroxy enamines, we envisaged use of Oppolzer's method[13] for the key C–C bond-forming step. Based on Srebnik's observation[14] that alkenyl boranes undergo reversible transmetalation with dialkylzinc reagents to generate vinylzinc intermediates, Oppolzer[13] developed a catalytic asymmetric synthesis of allylic alcohols involving hydroboration of alkynes, transmetalation of the vinyl group to zinc, and enantioselective addition to aldehydes to afford enantioenriched allylic alcohols (Scheme 1-7). We, [15–19] and others, [13, 20–28] have used this method to make allylic alcohols, and we have applied it to the synthesis of *α*-and *β*-amino acid derivatives,[29, 30] epoxy alcohols,[16, 17, 31] and cyclopropyl and vinyl cyclopropyl alcohols.[19, 32, 33] This method works well with terminal and internal alkynes and we have shown that ethoxy ethynyl ether can also be employed.[18, 34]



Scheme 1-7. Oppolzer's Alkenylation of Aldehydes

Our synthesis of β-hydroxy enamines involves application of Oppolzer's procedure to ynamides, which are readily available using Stahl's copper catalyzed oxidative coupling of alkynes with amines (Scheme 1-8).[35]



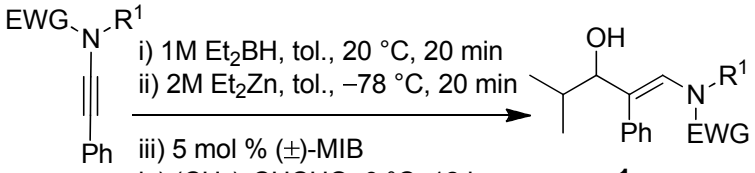
Scheme 1-8. Stahl's Oxidative Coupling of Alkynes with Amides

1.2.1. Optimization of electron withdrawing groups on nitrogen

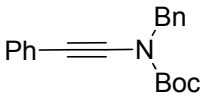
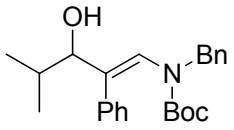
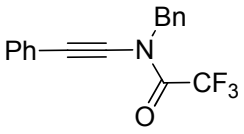
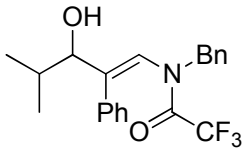
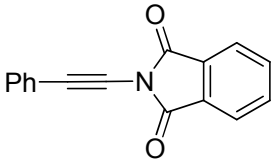
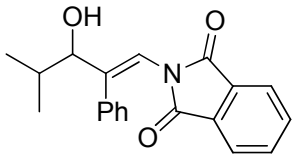
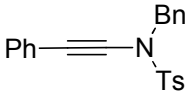
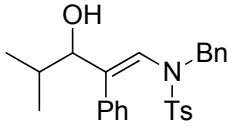
As outlined in Table 1-1, several phenyl-substituted ynamides were synthesized using amines with electron withdrawing groups (EWG) on the nitrogen. The presence of the EWG is important for the synthesis and stabilization of ynamides and the resulting β-hydroxy enamines.

The synthesis of β-hydroxy enamines begins with hydroboration of ynamides with diethyborane and transmetalation of vinylborane with Et_2Zn to generate the β-amino vinyl zinc intermediates. The aldehyde alkenylation was performed in the presence of catalyst derived from Nugent's racemic isoborneol-based amino alcohol ligand (±)-MIB.[36] As illustrated in Table 1-1, yields of the addition product are strongly dependent on a nature of the EWG. Although the Boc group resulted in formation of the desired

Table 1-1. Examination of Various Electron Withdrawing Groups on the Ynamide



1a

entry	ynamide	(*E*)-trisubstituted hydroxy enamide	isolated yield (%)
1			25
2			0
3			0
4			**82**

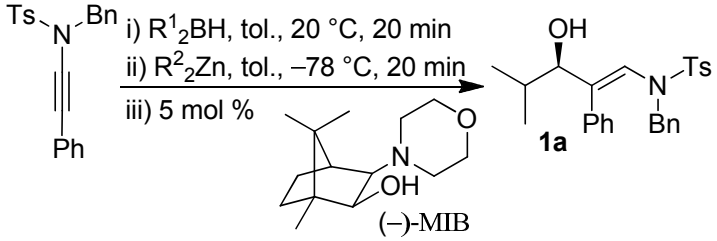
addition product, the isolated yield did not exceed 25% (entry 1). More electron withdrawing carbonyl groups on the nitrogen such as trifluoro acetyl or imide did not result in formation of the *β*-hydroxy enamine product (entries 2–3), perhaps because the borohydride added to the carbonyl group. In contrast, the more robust tosyl group led to formation of the β-hydroxy enamine in 82% yield (entry 4). The tosyl group serves a

dual role in the chemistry, both enabling the generation of the product in good yield and preventing the elimination of *β*-hydroxy enamine. Decomposition via elimination eventually affords *α,β*-unsaturated aldehydes after reaction with water.

1.2.2. Optimization of hydroboration and transmetalation steps

To perform the analogous asymmetric addition, we used catalyst derived from enantiomerically pure (–)-MIB (Table 2), which is readily prepared in three steps or can be purchased.[37] Following the general procedure in Table 1-1, entry 4, several hydroborating agents were examined (Table 1-2).

Table 1-2. Optimization of Yield and Enantioselectivity in the Synthesis of *β*-Hydroxy Enamines



entry	R^1_2BH	R^2_2Zn	isolated yield (%)	*ee* (%)
1	BH_3•SMe_2	Et_2Zn	trace	–
2	9-BBN	Et_2Zn	44	82
3	Cy_2BH	Et_2Zn	78	92
4	Et_2BH	Et_2Zn	**82**	**92**
5	Et_2BH	Me_2Zn	80	91

After the hydroboration and addition of the dialkylzinc reagent, (–)-MIB (5 mol %) and isobutyraldehyde were added. When BH_3•SMe_2 was used in the hydroboration, only trace addition product was observed (entry 1). This may have been due to inhibition of the MIB-based Lewis catalyst by the liberated SMe_2. Use of 9-BBN resulted in formation of the β-hydroxy enamine in 44% yield with 82% ee (entry 2). Screening combinations of diethyl- and dicyclohexyl borane with diethyl- and dimethylzinc (entries 3–5) led to identification of diethylborane and diethylzinc as the optimal combination, with formation of the *β*-hydroxy enamine in 82% yield and 92% ee. It is noteworthy that under the reaction conditions the addition of Et_2Zn to the aldehyde is very slow compared to the reaction of the vinyl zinc species and less then 5% of ethyl addition product was observed. The optimized conditions in Table 1-2 were then used to determine the substrate scope, as outlined in the following section.

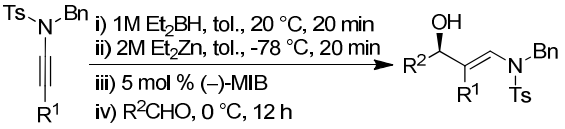
1.2.3. Substrate scope of synthesis of *β*-hydroxy enamines

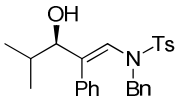
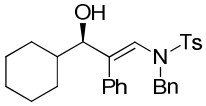
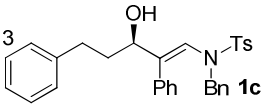
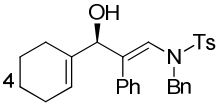
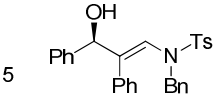
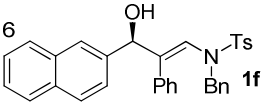
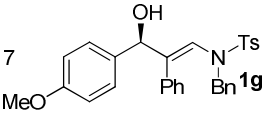
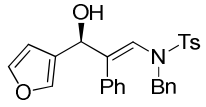
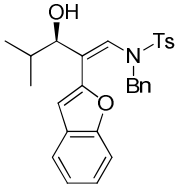
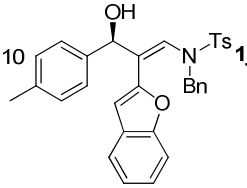
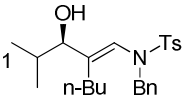
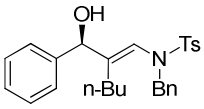
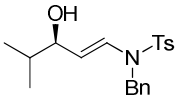
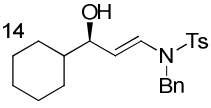
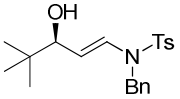
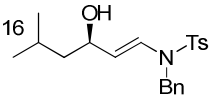
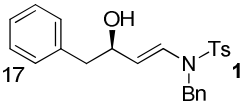
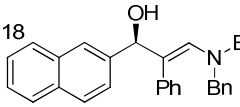
To determine the scope and limitations of our one-pot synthesis of enantioenriched β-hydroxy enamines, a series of aldehydes and ynamides were tested using the conditions in Table 1-2 (entry 4). As shown in Table 1-3, the asymmetric vinylation reaction is compatible with a range of ynamides and aldehydes. Initially, ynamides derived from phenyl acetylene were employed (entries 1–8). With this coupling partner, aliphatic aldehydes with *α*-branching underwent additions with enantioselectivities >90% and yields of 73–82% (entries 1 and 2). With

dihydrocinnamaldehyde, which lacks α-branching, a significant drop in enantioselectivity to 54% was observed (entry 3). The α,β-unsaturated aldehyde cyclohexenecarboxaldehyde afforded β-hydroxy enamine in 92% enantioselectivity with 70% yield (entry 4). This product also contains an allylic alcohol, which is a useful functional group for further elaboration.[38] Aromatic aldehydes proved to be excellent substrates undergoing the reaction with enantioselectivities ranging from 91–98% and yields >80% (entries 5–7). The heteroaromatic 3-furan carboxaldehyde resulted in formation of the product with 89% enantioselectivity in 68% yield (entry 8). Ynamides with a 2-benzofuranyl substituent also exhibited excellent enantioselectivities when used in the asymmetric addition to isobutyraldehyde (91% ee, entry 9) and 4-methylbenzaldehyde (98% ee, entry 10). Yields >80% were achieved in both cases. Comparison of the enantioselectivities with phenyl- (entries 1–8) and 2-benzofuranyl-substituted ynamides (entries 9 and 10) suggests that the addition is not strongly dependent on the nature of the aryl group and may be compatible with other aryl and heteroaryl substituents.

The *n*-Bu-substituted ynamide underwent addition with representative aliphatic and aromatic aldehydes with high levels of enantioselectivity. Thus, with isobutyraldehyde and benzaldehyde, the addition products were obtained with 93% and 96% enantioselectivity, respectively (entries 11–12). The yields were >80% in both cases. The parent ynamide (R=H) was also a useful coupling partner as shown in entries 13–17. With aliphatic aldehydes isobutyraldehyde and cyclohexanecarboxaldehyde,

Table 1-3. Substrate Scope of the Asymmetric One-Pot Generation of β-Hydroxy Enamines



entry	β-hydroxy enamide	isolated yield (%)	ee (%)[a]
1		**1a** 82	92
2		**1b** 73	91
3		**1c** 78	54
4		**1d** 70	92
5		**1e** 85	91
6		**1f** 81	98
7		**1g** 86	96
8		**1h** 68	89
9		**1i** 82	91
10		**1j** 85	98
11		**1k** 81	93
12		**1l** 85	96
13		**1m** 80	93
14		**1n** 77	94
15		**1o** 67	93
16		**1p** 81	76
17		**1q** 79	83
18		**1r** 25	97

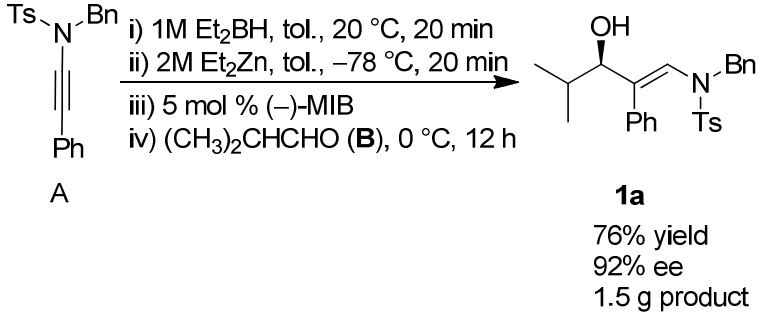
[a] Enantioselectivities were determined by HPLC

yields were 80% and 77%, respectively, and enantioselectivities were ≥93% (entries 13–14). Bulky pivaldehyde reacted with high enantioselectivity (93%), albeit decreased yield (67%, entry 15). Not surprisingly, aliphatic aldehydes lacking α-branching were difficult substrates with (–)-MIB (entries 16–17), as with most amino alcohol catalysts.[39-50] Isovaleraldehyde and phenyl acetaldehyde gave 76% and 83% enantioselectivities, respectively. Presumably the advent of more enantioselective catalysts will enable additions to these challenging substrates to occur with higher stereoselectivities.

As indicated in Table 1-1, entry 1, the Boc protected ynamide gave low yield. Nonetheless, the product was formed with 97% enantioselectivity in the presence of (–)-MIB (Table 1-3, entry 18).

The absolute stereochemistry was determined for a derivative of **1b** by single crystal X-ray diffraction (see the Appendix B). Accordingly, the (–)-MIB-based catalyst promoted the formation of (*R*)-hydroxy enamines, consistent with transition state proposed by Noyori[51, 52] for the asymmetric alkylation of aldehydes with dialkyl zinc reagents and the aminoalcohol-based catalyst derived from DAIB. The stereochemistry of the remaining entries in Table 1-3 was assigned by analogy. It is noteworthy that coordination of the heteroatoms, such as the nitrogens present in the ynamides and oxygens of the sulfonamides and benzofuryl groups (entries 9 and 10) to zinc was not problematic in the enantioselective vinyl addition step. Finally, only (*E*)-isomers of the β-hydroxy enamines were observed in all cases by ^{1}H NMR spectroscopy, indicating that isomerization of the double bond does not occur during the transmetalation, addition,

work-up or purification steps. As will be seen in subsequent sections, the conservation of the double bond geometry of the enamine is essential for diastereoselective elaboration of these products.



Scheme 1-9. Synthesis of **1a** on 3.5 mmol scale

In order for a method to be useful, scalability must be demonstrated. As shown in Scheme 1-9, the phenyl substituted ynamide and isobutyraldehyde were used in the catalytic asymmetric β-amimo vinylation to afford 1.5 g of *β*-hydroxy enamine **1a** (92% ee).

1.3. Conclusions

We have developed the first catalytic asymmetric synthesis of *β*-hydroxy enamines. The synthesis is an experimentally simple one-pot process that affords *β*-hydroxy enamines in high yields, excellent enantioselectivities and very general substrate scope. While optimizing reaction condition, we found that hydroboration of internal

ynamides proceeds with high regioselectivity, directing the boron to the position further from the nitrogen. We believe that our method will open the door to the further utilization of highly enantioenriched *β*-hydroxy enamines in organic syntheses and drug discovery.

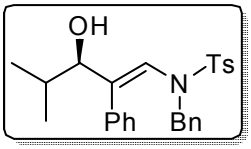
1.4. Experimental Section

General Methods. All reactions were performed under a nitrogen atmosphere with oven dried glassware using standard Schlenk or vacuum line techniques. The progress of reactions was monitored by thin-layer chromatography performed on Whatman precoated silica gel 60 Å K6F plates and visualized by ultra-violet light or by staining with ceric ammonium molybdate. THF was distilled from Na/benzophenone and toluene was dried through an alumina column. The optical rotations were recorded using a JASCO DIP-370. Melting points were determined using automatic melting-point meter Buchi Melting Point B-545, with temperature gradient 1 °C/min. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained on a Brüker Fourier transform NMR spectrometer at either 360 and 90.6 MHz, respectively. ^{1}H NMR spectra were referenced to tetramethylsilane in $CDCl_3$ or residual protonated solvent; $^{13}C\{1H\}$ NMR spectra were referenced to residual solvent. Analysis of enantiomeric excess was performed using a Hewlett-Packard 1100 Series HPLC and a chiral column. Infrared spectra were obtained using a Perkin-Elmer Spectrum 100 Series spectrometer. All reagents were purchased from Aldrich or Acros. All solvents were purchased from Fischer Scientific. All the commercially available liquid aldehyde substrates were distilled prior to use. Silica gel (Silicaflash P60 40–63

μm, Silicycle) and basic alumina (Fisher, 60–325 mesh) were used for air-flashed chromatography. Ynamides were prepared by method of Stahl.[35] *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide was synthesized by method of Bruckner.[53]

Caution. Diethylzinc is pyrophoric. Care must be used when handling this reagent.

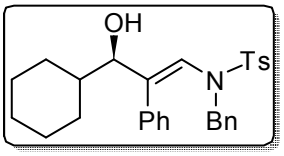
General Procedure A. Asymmetric Amino Vinylation of Aldehydes with *β*-Amino Vinyl Zinc Reagents:



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1a).

A 10 mL Schlenk flask was charged with a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol) and a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 20 min. The reaction flask was then cooled to –78 °C and Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol) was added and the reaction mixture was stirred for 20 min. (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) was added followed by dropwise addition of isobutyraldehyde (24 μL, 0.3 mmol) at –78 °C. The reaction flask was placed in a –30 °C cold bath and allowed to warm to 0 °C over several hours. The solution was stirred at 0 °C until vinyl addition was complete by TLC (typically 12 h). The reaction was then quenched by addition of brine (2 mL). The organic and aqueous layers were separated, and the

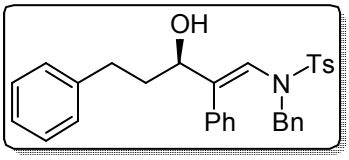
aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were then washed with 50 mL of water and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 107 mg (82% yield) of **1a** as an amorphous solid. $[\alpha]_D^{20}$: –19.5 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ 0.82 (d, 3H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 7.0 Hz), 1.57 (sept., 1H, *J* = 7.0 Hz), 2.07 (s, 3H), 3.84 (d, 1H, *J* = 6.4 Hz), 4.27 (dd, 2H, *J* = 21.3 Hz, 15.0 Hz), 6.54 (s, 1H), 6.94–7.02 (m, 4H), 7.09–7.19 (m, 7H), 7.29 (s, 1H), 7.84–7.90 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 27.65, 28.66, 35.45, 44.95, 77.47, 127.52, 127.66, 127.89, 128.81, 129.09, 129.62, 129.91, 134.50, 136.20, 136.32, 156.2; IR (neat): 3537 (OH), 2961, 2870, 1723, 1643, 1598, 1494, 1455, 1343, 1162, 1092, 1026, 814 cm^{-1}; HRMS-CI: *m*/*z* 458.1766 $[(M + Na)^+$; calculated for $C_{26}H_{29}NO_3SNa$: 458.1766].



(*R*, *E*)-*N*-Benzyl-*N*-(3-cyclohexyl-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1b).

Title compound **1b** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and cyclohexane carboxaldehyde (36 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 104 mg (73% yield) of **1b** as a white

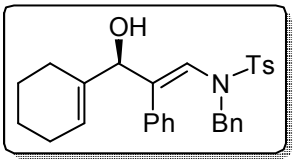
solid (mp = 137.3–142.0 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 15.0 min, t_r (2) = 18.7 min, $[\alpha]_D^{20}$: –30.0 (c = 0.04, $CHCl_3$, 91% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.49–0.61 (m, 1H), 0.61–0.81 (m, 1H), 0.86–1.20 (m, 3H), 1.20–1.38 (m, 2H), 1.50–1.75 (m, 4H), 2.45 (s, 3H), 3.75–3.85 (m, 1H), 4.21 (iso(AB)quadruplet, J_{AB} = 15.2 Hz, Δ = 120.0 Hz, 2H), 6.62 (s, 1H), 7.02–7.10 (m, 4H), 7.18–7.24 (m, 7H), 7.35–7.39 (m, 1H), 7.92–7.98 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.6, 26.1, 26.6, 28.2, 28.9, 44.3, 51.8, 76.3, 124.0, 127.6, 127.7, 128.1, 128.3, 128.6, 129.0, 129.9, 135.9, 136.1, 136.3, 140.9, 143.9. IR (neat): 3543 (OH), 3061, 2921, 2852, 1951, 1643, 1598, 1495, 1452, 1338, 1155, 1091, 1026, 936, 811 cm^{-1}; HRMS-CI: m/z 498.2059 [(M + Na)$^+$; calculated for $C_{29}H_{33}NO_3SNa$: 498.2079].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-2,5-diphenylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1c).

Title compound **1c** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and hydrocinnamaldehyde (40 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 116 mg (78% yield) of **1c** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column

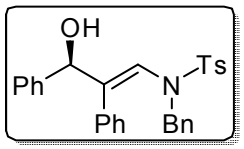
(hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 19.2 min, t_r (2) = 29.1 min, $[\alpha]_D^{20}$: –5.11 (c = 0.09, $CHCl_3$, 54% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.60–1.68 (m, 2H), 2.45 (s, 3H), 2.47–2.60 (m, 2H), 4.09 (s, 2H), 4.20–4.27 (m, 1H), 6.32 (s, 1H), 6.68–6.71 (m, 1H), 6.71–6.73 (m, 1H), 6.92–6.96 (m, 2H), 7.02–7. 07 (m, 2H), 7.13–7.15 (m, 1H), 7.15–7.17 (m, 2H), 7.17–7.19 (m, 2H), 7.19–7.21 (m, 2H), 7.21–7.23 (m, 2H), 7.30–7.35 (m, 2H), 7.67–7.72 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 31.6, 36.9, 52.2, 74.9, 123.8, 125.9, 127.5, 127.9, 128.2, 128.3, 128.4, 128.46, 128.51, 129.0, 129.9, 135.4, 136.1, 136.2, 140.3, 141.8, 143.9. IR (neat): 3449 (OH), 3028, 2927, 2862, 1951, 1648, 1599, 1495, 1454, 1344, 1163, 1090, 1029, 939, 814 cm^{-1}; HRMS-CI: m/z 520.1922 [(M – Na)+; calculated for $C_{31}H_{31}NO_3SNa$: 520.1922] and 398.2103 [$(M + H)^+$; calculated for $C_{31}H_{32}NO_3S$: 498.2103].



(*R*,*E*)-*N*-Benzyl-*N*-(3-(cyclohex-1-en-1-yl)-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1d).

Title compound **1d** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and 1-cyclohexene-1-carboxaldehyde (34 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 99 mg (70% yield) of **1d** as an yellow oil. The enantiomeric excess was determined by HPLC

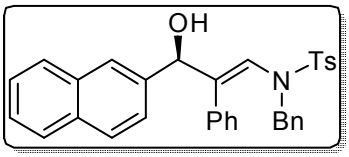
with a Chiralcel OD-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 29.8 min, t_r (2) = 38.4 min, $[\alpha]_D^{20}$: –29.6 (c = 0.05, $CHCl_3$, 93% ee). ^{1}H NMR (C_6D_6, 360 MHz): δ 1.52–1.66 (m, 4H), 1.88–2.04 (m, 4H), 2.17 (s, 3H), 4.42 (iso(AB)quadruplet, J_{AB} = 15.2 Hz, Δ = 43.2 Hz, 2H), 4.66 (s, 1H), 5.58 (s, 1H), 6.92 (s, 1H), 7.02–7.08 (m, 3H), 7.08–7.11 (m, 1H), 7.19–7.26 (m, 7H), 7.38–7.42 (m, 1H), 7.98–8.03 (m, 2H); ^{13}C{1H} NMR (C_6D_6, 90 MHz): δ 21.5, 23.2, 23.3, 24.6, 25.6, 52.7, 79.5, 124.4, 124.8, 127.9, 128.0, 128.2, 128.3, 128.7, 129.0, 129.7, 130.1, 137.2, 137.7, 137.8, 138.6, 143.6. IR (neat): 3490 (OH), 2925, 1598, 1494, 1455, 1344, 1162, 1091, 1029, 941, 813 cm^{-1}; HRMS-CI: m/z 496.1936 [$(M + Na)^+$; calculated for $C_{29}H_{31}NO_3SNa$: 496.1922].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-2,3-diphenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1e).

Title compound **1e** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and benzaldehyde (30 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 119 mg (85% yield) of **1e** as a white solid (mp = 99.8–103.2 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 47.9 min, t_r

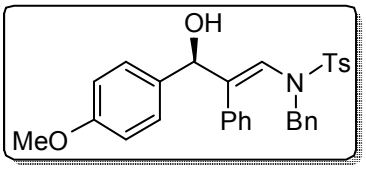
(2) = 65.6 min, $[\alpha]_D^{20}$: –108.0 (c = 0.1, $CHCl_3$, 91% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 2.43 (s, 3H), 4.11 (d, *J* = 5.8 Hz, 2H), 4.90–4.99 (m, 1H), 7.16–7.23 (m, 7H), 7.23–7.41 (m, 7H), 7.42–7.58 (m, 3H), 7.58–7.66 (m, 1H), 7.73–7.82 (m, 2H), 8.08–8.18 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.7, 52.0, 77.1, 123.9, 126.7, 127.5, 127.6, 127.8, 127.9, 128.28, 128.34, 129.1, 129.9, 135.3, 136.1, 136.3, 139.1, 141.4, 143.8. IR (neat): 3504 (OH), 3031, 2957, 2837, 1893, 1609, 1511, 1495, 1456, 1344, 1249, 1162, 1091, 1034, 943, 815 cm^{-1}; HRMS-CI: m/z 452.1684 [$(M - OH)^+$; calculated for $C_{29}H_{26}NO_2S$: 452.1679].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-3-(naphthalen-2-yl)-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1f).

Title compound **1f** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and 2-naphtaldehyde (47 mg dissolved in 0.5 mL of dry toluene, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 126 mg (81% yield) of **1f** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 34.7 min, t_r (2) = 44.1 min, $[\alpha]_D^{20}$: –270.1 (c = 0.03, $CHCl_3$, 98% ee). ^1H NMR ($CDCl_3$,

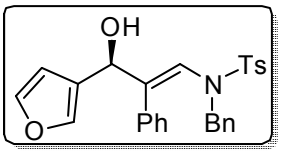
360 MHz): δ 2.43 (s, 3H), 4.09 (iso(AB)quadruplet, J_{AB} = 15.3 Hz, Δ = 88.2 Hz, 2H), 5.44 (s, 1H), 6.39–6.44 (m, 2H), 6.58–6.61 (m, 1H), 6.88–6.94 (m, 2H), 6.95–7.02 (m, 2H), 7.03–7.09 (m, 2H), 7.10–7.14 (m, 1H), 7.17–7.19 (m, 1H), 7.19–7.21 (m, 1H), 7.21–7.25 (m, 2H), 7.25–7.27 (m, 1H), 7.27–7.30 (m, 1H), 7.41–7.46 (m, 2H), 7.55–7.59 (m, 1H), 7.61–7.65 (m, 1H), 7.67–7.71 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.7, 51.9, 77.3, 124.4, 125.6, 127.5, 127.6, 127.8, 128.0, 128.08, 128.13, 128.3, 129.2, 129.9, 133.0, 135.3, 136.2, 138.6, 139.0, 143.9. IR (neat): 3503 (OH), 3057, 2927, 2867, 1952, 1682, 1598, 1495, 1455, 1344, 1163, 1090, 1041, 942, 815 cm^{-1}; HRMS-CI: m/z 542.1743 [$(M + Na)^+$; calculated for $C_{33}H_{29}NO_3SNa$: 542.1766].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-3-(4-methoxyphenyl)-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1g).

Title compound **1g** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and *p*-anisaldehyde (37 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 129 mg (86% yield) of **1g** as a white solid (mp = 172.0–174.2 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 53.3 min, t_r

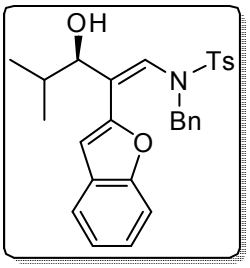
(2) = 86.4 min, $[\alpha]_D^{20}$: –69.5 (c = 0.05, $CHCl_3$, 96% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.44 (s, 3H), 3.74 (s, 3H), 4.06 (iso(AB)quadruplet, J_{AB} = 15.0 Hz, Δ = 44.2 Hz, 2H), 5.20 (s, 1H), 6.39 (s, 1H), 6.40–6.42 (m, 1H), 6.48–6.52 (m, 1H), 6.65–6.70 (m, 2H), 6.86–6.92 (m, 4H), 6.97–7.04 (m, 2H), 7.09–7.22 (m, 4H), 7.28–7.35 (m, 2H), 7.66–7.72 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 52.1, 55.4, 76.7, 113.7, 123.5, 127.6, 127.8, 128.0, 128.1, 128.4, 129.1, 129.7, 129.9, 133.7, 135.6, 135.6, 136.2, 136.4, 139.4, 143.8. IR (neat): 3504 (OH), 3032, 2956, 2837, 1891, 1610, 1511, 1495, 1456, 1344, 1249, 1162, 1090, 1034, 943, 814 cm^{-1}; HRMS-CI: m/z 500.1912 [$(M + H)^+$; calculated for $C_{30}H_{30}NO_4S$: 500.1896].



(*S*,*E*)-*N*-Benzyl-*N*-(3-(furan-3-yl)-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1h).

Title compound **1h** was prepared by General Procedure A using a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and 3-furalaldehyde (26 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 94 mg (68% yield) of **1h** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 17.7 min, t_r (2) = 24.1 min, $[\alpha]_D^{20}$: –29.8 (c = 0.04, $CHCl_3$, 89% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.46 (s, 3H),

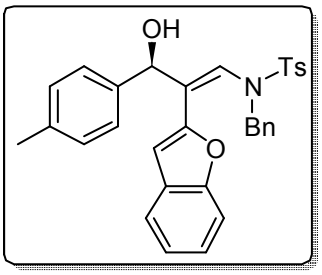
4.08 (iso(AB)quadruplet, J_{AB} = 15.2 Hz, Δ = 116.3 Hz, 2H), 5.22 (d, J = 5.2 Hz, 1H), 6.40–6.45 (m, 1H), 6.49–6.52 (m, 1H), 6.54–6.59 (m, 2H), 6.85–6.87 (m, 1H), 6.87–6.90 (m, 1H), 6.93–6.95 (m, 1H), 7.04–7.10 (m, 2H), 7.16–7.21 (m, 4H), 7.22–7.23 (m, 1H), 7.30–7.36 (m, 2H), 7.66–7.72 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.8, 51.9, 70.8, 109.2, 123.8, 123.9, 127.5, 127.7, 128.1, 128.3, 128.4, 129.1, 130.0, 135.2, 136.1, 138.2, 140.0, 144.0. IR (neat): 3515 (OH), 3062, 2925, 2877, 1953, 1644, 1598, 1496, 1456, 1345, 1267, 1159, 1089, 1024, 940, 874, 813 cm^{-1}; HRMS-CI: m/z 460.1583 [$(M + H)^+$; calculated for $C_{30}H_{30}NO_3S$: 460.1583].



(*R*,*Z*)-*N*-(2-(Benzofuran-2-yl)-3-hydroxy-4-methylpent-1-en-1-yl)-*N*-benzyl-4-methylbenzenesulfonamide (1i).

Title compound **1i** was prepared by General Procedure A using *N*-(benzofuran-2-ylethynyl)-*N*-benzyl-4-methylbenzenesulfonamide (161 mg dissolved in 1 mL dry toluene, 0.40 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and isobutyraldehyde (24 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 117 mg (82% yield) of **1i** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 25.0 min, t_r (2) = 30.7 min, $[\alpha]_D^{20}$: –88.1 (c = 0.07, $CHCl_3$, 91% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.69 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7

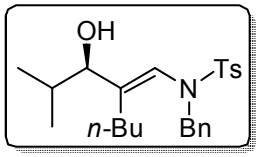
Hz, 3H), 1.71 (sept., J = 6.7 Hz, 1H), 2.45 (s, 3H), 4.01 (m, 1H), 4.32 (iso(AB)quadruplet, J_{AB} = 14.6 Hz, Δ = 39.5 Hz, 2H), 6.21 (s, 1H), 6.73 (s, 1H), 6.96–7.05 (m, 2H), 7.08–7.16 (m, 3H), 7.16–7.24 (m, 2H), 7.25–7.28 (m, 1H), 7.30–7.37 (m, 2H), 7.48–7.54 (m, 1H), 7.73–7.80 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 18.1, 19.5, 21.8, 32.9, 53.0, 79.6, 108.3, 111.2, 121.4, 123.1, 124.8, 126.9, 127.7, 127.8, 128.3, 128.7, 129.9, 130.9, 135.6, 135.9, 144.1, 150.8, 154.3. IR (neat): 3432 (OH), 2959, 1638, 1453, 1349, 1163, 1092, 1019, 930, 815 cm^{-1}; HRMS-CI: m/z 498.1694 $[(M + Na)^+$; calculated for $C_{28}H_{29}NO_3SNa$: 498.1715] and 476.1896 $[(M + H)^+$; calculated for $C_{28}H_{30}NO_3S$: 476.1896].



(*R*,*Z*)-*N*-(2-(Benzofuran-2-yl)-3-hydroxy-3-(p-tolyl)prop-1-en-1-yl)-*N*-benzyl-4-methylbenzenesulfonamide (1j).

Title compound **1j** was prepared by General Procedure A using *N*-(benzofuran-2-ylethynyl)-*N*-benzyl-4-methylbenzenesulfonamide (161 mg dissolved in 1 mL dry toluene, 0.40 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and *p*-tolualdehyde (35 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 133 mg (85% yield) of **1j** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 49.8 min, t_r (2) = 56.2 min,

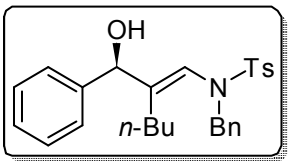
$[\alpha]_D^{20}$: –90.7 (c = 1.0, $CHCl_3$, 98% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 2.29 (s, 3H), 2.44 (s, 3H), 4.37 (iso(AB)quadruplet, J_{AB} = 14.7 Hz, Δ = 22.1 Hz, 2H), 5.48 (s, 1H), 6.44 (s, 1H), 6.50 (s, 1H), 6.93–7.02 (m, 4H), 7.02–7.07 (m, 2H), 7.10–7.15 (m, 2H), 7.15–7.22 (m, 4H), 7.30–7.34 (m, 2H), 7.39–7.44 (m, 1H), 7.76–7.84 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.3, 21.8, 52.8, 74.8, 108.1, 111.1, 121.5, 123.0, 124.8, 126.6, 127.1, 127.8, 127.9, 128.3, 128.5, 128.7, 129.3, 129.4, 129.9, 135.9, 136.1, 137.6, 138.5, 144.0, 150.6, 154.2. IR (neat): 3431 (OH), 2958, 1638, 1452, 1346, 1162, 1092, 1019, 930, 814 cm^{-1}; HRMS-CI: m/z 546.1698 [$(M + Na)^+$; calculated for $C_{28}H_{29}NO_3SNa$: 546.1715].



(*R*,*E*)-*N*-Benzyl-*N*-(2-(1-hydroxy-2-methylpropyl)hex-1-en-1-yl)-4-methylbenzenesulfonamide (1k).

Title compound **1k** was prepared by General Procedure A using *N*-benzyl-*N*-(hex-1-yn-1-yl)-4-methylbenzenesulfonamide (137 mg dissolved in 1 mL dry toluene, 0.4 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and isobutyraldehyde (24 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 101 mg (81% yield) of **1k** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 48.3 min, t_r (2) = 54.1 min, $[\alpha]_D^{20}$: –11.6 (c = 0.10, $CHCl_3$, 93% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.76 (t, J = 7.2

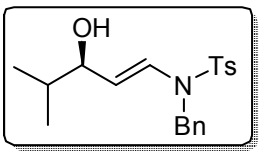
Hz, 3H), 0.81 (t, J = 7.1 Hz, 6H), 0.87–1.03 (m, 2H), 1.08 (sept., J = 7.2 Hz, 2H), 1.75 (sept., J = 7.1 Hz, 1H), 1.69–1.92 (m, 1H), 2.20–2.32 (m, 1H), 2.43 (s, 3H), 3.74 (d, J = 5.3 Hz, 1H), 4.14 (iso(AB)quadruplet, J_{AB} = 13.3 Hz, Δ = 33.7 Hz, 2H), 5.29 (s, 1H), 7.20–7.29 (m, 5H), 7.29–7.36 (m, 2H), 7.66–7.72 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 14.0, 16.9, 19.7, 21.7, 23.4, 28.4, 30.2, 31.8, 55.2, 78.1, 122.2, 127.8, 127.9, 128.5, 129.5, 129.8, 135.0, 135.9, 143.7, 150.9. IR (neat): 3369 (OH), 2959, 1598, 1455, 1344, 1261, 1163, 1091, 1028, 801 cm^{-1}; HRMS-CI: m/z 438.2082 [$(M + Na)^+$; calculated for $C_{26}H_{29}NO_3SNa$: 438.2079].



(*R*,*E*)-*N*-Benzyl-*N*-(2-(hydroxy(phenyl)methyl)hex-1-en-1-yl)-4-methylbenzenesulfonamide (1l).

Title compound **1l** was prepared by General Procedure A using *N*-benzyl-*N*-(hex-1-yn-1-yl)-4-methylbenzenesulfonamide (137 mg dissolved in 1 mL dry toluene, 0.4 mmol), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and benzaldehyde (30 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 114 mg (85% yield) of **1l** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 51.6 min, t_r (2) = 58.9 min, $[\alpha]_D^{20}$: –28.5 (c = 0.08, $CHCl_3$, 96% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.68 (t, J = 7.2 Hz, 3H), 0.76–0.91 (m, 2H), 0.93–1.10 (m, 2H), 1.53–1.65 (m, 1H), 2.14–2.26 (m, 1H),

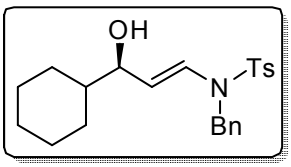
2.42 (s, 3H), 4.06–4.09 (m, 1H), 4.16 (iso(AB)quadruplet, J_{AB} = 13.4 Hz, Δ = 30.0 Hz, 2H), 5.08 (s, 1H), 5.50 (s, 1H), 7.07–7.13 (m, 2H), 7.13–7.21 (m, 2H), 7.25–7.41 (m, 6H), 7.65–7.76 (m, 3H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 13.9, 21.7, 23.3, 28.4, 29.8, 55.2, 75.0, 122.5, 127.1, 127.4, 127.9, 128.1, 128.5, 128.6, 129.6, 129.9, 135.0, 135.9, 142.0, 143.8, 150.0. IR (neat): 3496 (OH), 2957, 1953, 1598, 1455, 1338, 1162, 1092, 1028, 814 cm^{-1}; HRMS-CI: m/z 472.1904 [$(M + Na)^+$; calculated for $C_{27}H_{31}NO_3SNa$: 472.1922] and 450.2095 [$(M + H)^+$; calculated for $C_{27}H_{32}NO_3S$: 450.2103].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-methylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1m).

Title compound **1m** was prepared by General Procedure A using *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (114 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and isobutyraldehyde (24 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 86 mg (80% yield) of **1m** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 54.4 min, t_r (2) = 60.1 min, $[\alpha]_D^{20}$: –5.6 (c = 0.06, $CHCl_3$, 93% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.55 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H), 1.50 (sext., *J* = 6.6 Hz, 1H), 2.40 (s, 3H), 3.67–3.74 (m, 1H), 4.49 (iso(AB)quadruplet, J_{AB} = 15.9 Hz, Δ = 73.8 Hz, 2H), 4.63 (dd, J_1 = 14.3

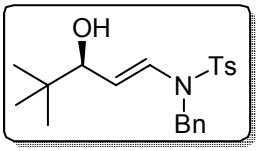
Hz, J_2 = 7.9 Hz, 1H), 6.83 (d, J = 14.3 Hz, 1H), 7.18–7.34 (m, 7H), 7.64–7.71 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 17.7, 18.3, 21.7, 34.4, 49.7, 77.0, 113.4, 127.13, 127.15, 127.6, 128.0, 128.7, 130.1, 135.4, 136.2, 144.1. IR (neat): 3285 (OH), 2961, 2080, 1600, 1455, 1330, 1160, 1093, 1062, 815 cm^{-1}; HRMS-CI: m/z 382.1451 [$(M + Na)^+$; calculated for $C_{20}H_{25}NO_3SNa$: 382.1453].



(*R*,*E*)-*N*-Benzyl-*N*-(3-cyclohexyl-3-hydroxyprop-1-en-1-yl)-4-methylbenzenesulfonamide (1n).

Title compound **1n** was prepared by General Procedure A using *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (114 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and cyclohexane carboxaldehyde (36 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 92 mg (77% yield) of **1n** as a white solid (mp = 123.0–125.2 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 18.9 min, t_r (2) = 22.9 min, $[\alpha]_D^{20}$: –10.3 (c = 0.09, $CHCl_3$, 94% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.48–0.63 (m, 1H), 0.63–0.79 (m, 1H), 0.95–1.09 (m, 2H), 1.12–1.23 (m, 1H), 1.24–1.31 (m, 1H), 1.32–1.42 (m, 1H), 1.52–1.71 (m, 4H), 2.43 (s, 3H), 3.67–3.80 (m, 1H), 4.52 (iso(AB)quadruplet, J_{AB} = 15.7 Hz, Δ = 201.4 Hz, 2H), 4.59–4.69 (dd, overlapped with AB-quadruplet, 1H), 6.80 (d, J = 14.2 Hz, 1H), 7.19–7.44 (m, 7H),

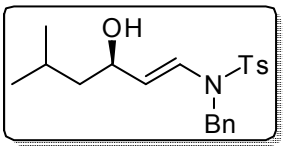
7.66–7.80 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.7, 26.1, 26.6, 28.2, 28.9, 44.3, 49.7, 76.3, 114.2, 127.2, 127.3, 127.6, 127.7, 128.7, 130.1, 135.5, 136.2, 144.1. IR (neat): 3284 (OH), 2960, 2082, 1599, 1455, 1332, 1160, 1094, 1062, 814 cm^{-1}; HRMS-CI: m/z 422.1775 [$(M + Na)^+$; calculated for $C_{23}H_{29}NO_3SNa$: 422.1766].



(*S*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4,4-dimethylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1o).

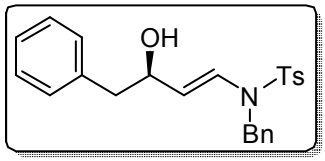
Title compound **1o** was prepared by General Procedure A using *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (114 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and pivalaldehyde (36 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 90 mg (80% yield) of **1o** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 24.0 min, t_r (2) = 29.0 min, $[\alpha]_D^{20}$: –8.1 (c = 0.1, $CHCl_3$, 93% ee). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.71 (s, 9H), 1.99 (s, 3H), 3.47 (d, J = 7.7 Hz, 1H) 4.41 (iso(AB)quadruplet, J_{AB} = 15.6 Hz, Δ = 102.7 Hz, 2H), 4.74 (dd, J_1 = 14.5 Hz, J_2 = 7.7 Hz, 1H), 6.87 (d, J = 14.5 Hz, 1H), 7.00–7.07 (m, 7H), 7.74–7.78 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.4, 26.0, 47.7, 50.1, 79.6, 113.6, 127.7, 127.8, 127.9, 128.5, 129.0, 130.1, 135.4, 136.6, 144.0. IR (neat): 3285 (OH), 2961, 2082, 1599, 1456, 1330, 1160, 1090, 1062, 815 cm^{-1}; HRMS-CI: m/z

396.1621 [(M – Na)+; calculated for $C_{21}H_{27}NO_3SNa$: 396.1609] and 374.1801 [$(M + H)^+$; calculated for $C_{21}H_{28}NO_3S$: 374.1790].



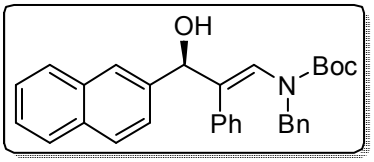
(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-5-methylhex-1-en-1-yl)-4-methylbenzenesulfonamide (1p).

Title compound **1p** was prepared by General Procedure A using *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (114 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and isovaleraldehyde (32 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 91 mg (81% yield) of **1p** as a white solid (mp = 112.0–114.3 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 24.7 min, t_r (2) = 29.4 min, $[\alpha]_D^{20}$: –4.8 (c = 0.7, $CHCl_3$, 76% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.78 (t, J = 6.9 Hz, 6H), 1.32–1.41 (m, 3H), 2.43 (s, 3H), 4.06 (pent., J = 7.1 Hz, 1H), 4.51 (iso(AB)quadruplet, J_{AB} = 15.9 Hz, Δ = 32.3 Hz, 2H), 4.66 (dd, J_1 = 14.0 Hz, J_2 = 7.8 Hz, 1H), 6.89 (d, J = 14.0 Hz, 1H), 7.20–7.38 (m, 7H), 7.66–7.77 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 22.7, 22.8, 24.6, 46.9, 49.7, 77.2, 115.6, 127.1, 127.6, 127.7, 128.7, 130.1, 135.5, 136.2, 144.1. IR (neat): 3284 (OH), 2960, 2082, 1599, 1455, 1330, 1160, 1093, 1062, 814 cm^{-1}; HRMS-CI: m/z 396.1610 $[(M + Na)^+$; calculated for $C_{21}H_{27}NO_3SNa$: 396.1609].



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-phenylbut-1-en-1-yl)-4-methylbenzenesulfonamide (1q).

Title compound **1q** was prepared by General Procedure A using *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (114 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and phenylacetaldehyde (35 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 96 mg (79% yield) of **1q** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 32.1 min, t_r (2) = 38.9 min, $[\alpha]_D^{20}$: –21.5 (c = 0.1, $CHCl_3$, 83% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.59–2.74 (m, 2H), 4.20–4.28 (m, 1H), 4.47 (iso(AB)quadruplet, J_{AB} = 16.0 Hz, Δ = 48.7 Hz, 2H), 4.71 (dd, J_1 = 14.1 Hz, J_2 = 7.4 Hz, 1H), 6.87 (d, J = 14.1 Hz, 1H), 6.89–6.97 (m, 2H), 7.16–7.39 (m, 10H), 7.58–7.68 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 44.6, 49.7, 72.6, 113.4, 126.6, 127.1, 127.7, 128.2, 128.6, 128.8, 129.7, 130.1, 135.4, 136.2, 144.1. IR (neat): 3289 (OH), 2964, 2080, 1601, 1455, 1330, 1160, 1093, 1062, 815 cm^{-1}; HRMS-CI: m/z 408.1623 $[(M + Na)^+$; calculated for $C_{24}H_{25}NO_3SH$: 408.1633] and 390.1509 $[(M – OH)^+$; calculated for $C_{24}H_{24}NO_2S$: 390.1522].



(*R*,*E*)-Tert-butyl benzyl(3-hydroxy-3-(naphthalen-2-yl)-2-phenylprop-1-en-1-yl)carbamate (1r).

Title compound **1r** was prepared by General Procedure A using *tert*-butyl benzyl(phenylethynyl)carbamate (123 mg dissolved in 1 mL dry toluene), a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol), a solution of Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol), (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) and 2-naphtaldehyde (47 mg dissolved in 0.5 mL of dry toluene, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 34 mg (25% yield) of **1r** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 19:1, flow rate = 0.5 mL/min), t_r (1) = 15.0 min, t_r (2) = 19.5 min, $[\alpha]_D^{20}$: +56.5 (c = 0.1, $CHCl_3$, 97% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.42 (s, 9H), 4.59 (s, 2H), 5.33 (s, 1H), 6.70–6.76 (m, 2H), 6.84–6.90 (m, 3H), 6.91–7.03 (m, 3H), 7.03–7.11 (m, 2H), 7.14–7.19 (m, 2H), 7.19–7.38 (m, 6H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 28.5, 55.5, 65.2, 81.3, 113.7, 127.1, 127.67, 127.8, 128.0, 128.4, 128.8, 129.1, 129.2, 129.3, 131.3, 133.4, 134.3, 136.5, 139.3, 159.1. IR (neat): 3553 (OH), 3057, 2927, 2867, 1952, 1682, 1598, 1495, 1455, 1344, 1163, 1090, 1041, 942, 815 cm^{-1}; HRMS-CI: m/z 466.2391 $[(M + H)^+$; calculated for $C_{31}H_{32}NO_3S$: 466.2382].

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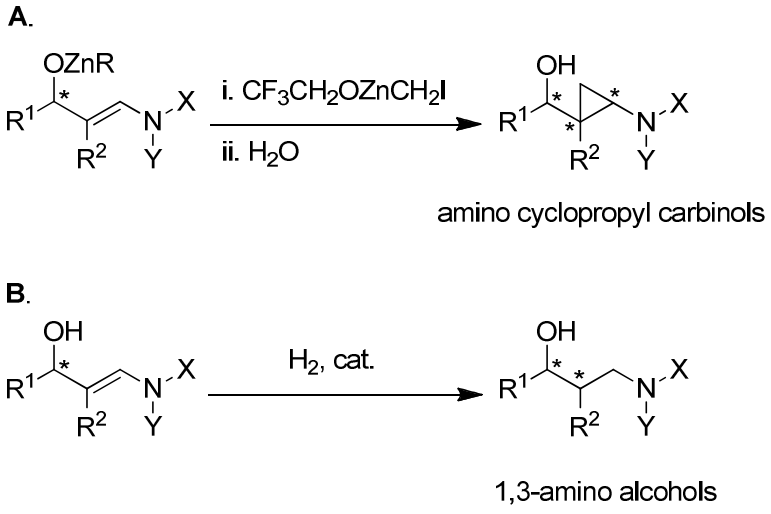
Chapter 2. One-Pot Catalytic Asymmetric Synthesis of Amino Cyclopropyl Carbinols

2.1. Introduction

In addition to their intrinsic value, *β*-hydroxy enamines are also potentially important synthetic intermediates for further elaboration via alkoxide and hydroxyl directed diastereoselective reactions.[1] Alkoxide directed cyclopropanation of *β*-alkoxide enamines could provide access to amino cyclopropyl alcohols (Scheme 2-1, A). The intermediate *β*-alkoxide enamine can be subjected to a tandem diastereoselective cyclopropanation to afford amino cyclopropyl carbinols with high enantio- and diastereoselectivity. We have also developed an efficient diastereoselective hydrogenation of *β*-hydroxy enamines leading to 1,2-disubstituted 1,3-amino alcohols with high enantio- and diastereoselectivities (Scheme 2-1, B).



Scheme 2-1. Utilization of *β*-Hydroxy Enamines in Substrate-Directed Reactions

2.1.1. Amino cyclopropanes and their biological activities

The cyclopropane ring, due to its unusual bonding and inherent ring strain is unique among carbocycles in both its properties and reactions.[2] Thus, cyclopropane derivatives provide building blocks of unprecedented synthetic potential. Moreover natural and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to antibiotic, antiviral, antitumor and neurochemical properties.[3] Present in animals, plants and microorganisms, or generated transiently in primary and secondary metabolisms, amino cyclopropanes provide convenient biological probes for mechanistic studies and allow the design of new drugs.[4, 5] Cyclopropyl moieties can induce deactivation of specific target enzymes and are commonly utilized in medicinal chemistry.[6] The deactivation is not only related to the inherent chemical reactivity of the three-membered ring, resulting from its intrinsic ring strain (enzymatic cleavage, oxidation, etc.), but also from heteroatomic (nitrogen and oxygen) or electron-rich substituents (carbinols or hydroxymethyl). Through the formation of cyclopropyloxy radical, cyclopropylamine radical cation, cyclopyliminium cation, or cyclopropylcarbinyl radical or cation they can provide suicide substrates for specific enzymes.[7-9] Enantioenriched amino cyclopropanes are pharmacophores that are present in numerous natural products, synthetic materials[10–12] and several commercial medications.[13–21] As a result, their synthesis has attracted significant attention.[22–42] Direct methods to effectively synthesize functionalized enantio- and diastereoenriched cyclopropyl amines remain challenging, however.

2.1.2. Amino cyclopropyl carbinols nature

More than 60% of all diseases in Europe, North America and Japan are caused by the action of viruses, amongst them bronchitis, hepatitis, influenza, infections by several strains of herpes as well as by human immunodeficiency viruses (HIV).[43] Modified nucleosides that inhibit replication of viruses have been used in the chemotherapy of these infections.[44] These analogues, which act through similar mechanisms, can be divided into three categories: 1) phosphate modified, 2) base modified, and 3) sugar modified. Most of the known active compounds belong to the two latter groups.[45] Of main interest are compounds in which the ribose unit has been subject to major changes, either by replacement by a cyclopentane, cyclopentene (carbasugars), oxetane or cyclobutane ring, or by an acyclic chain. Penciclovir emerged as a potent and selective anti herpes-virus agent, particularly active against herpes simplex types 1 and 2 (HSV-1 and HSV-2) and varicella zoster virus (VZV).[46, 47] Derivatives of Penciclovir, amino cyclopropyl carbinols containing guanine, purine and pyrimidine nucleosides, such as **2-1** (Figure 2-1) for instance, have been synthesized in order to test their potential anti-

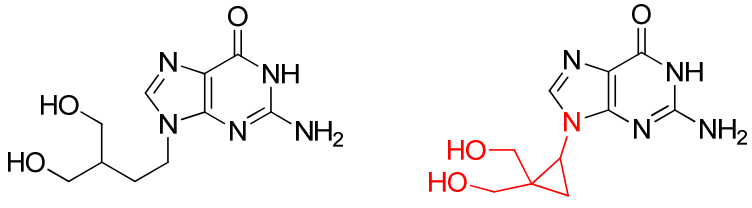


Figure 2-1. Penciclovir and Amino Cyclopropyl Carbinol Derivative

retroviral activity.[48] Activity against HSV-1, HSV-2, VZV and the cytomegalovirus (CMV) in human fibroblast (MRC-5) cells were tested.[48]

Guanine derivative **2-2** (Figure 2-2) showed activity against herpes simplex HSV-1 strain

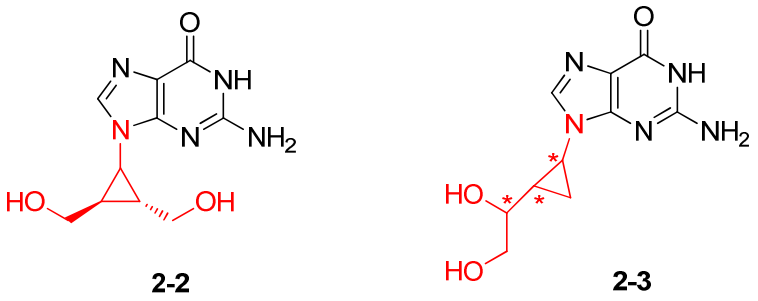


Figure 2-2. Guanine Derived Amino Cyclopropyl Carbinols Showing Anti-Herpes Simplex Acivity

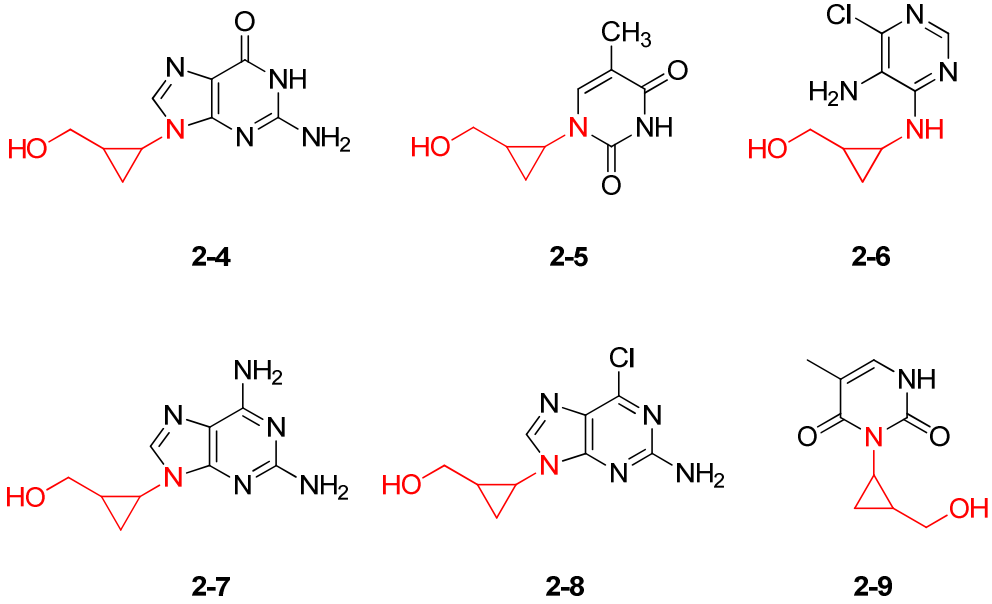


Figure 2-3. Biologically Active Amino Cyclopropyl Carbinol Nucleosides

KOS in cell cultures (ID_{50} of 0.023–120 mg/mL).[49] In vitro, **2-3** (Figure 2-2) produced an inhibition of virus-induced cytopathogenic effects in E-377 cells challenged with herpes simplex virus (virus rating of 1.8 at 101 mg/mL).

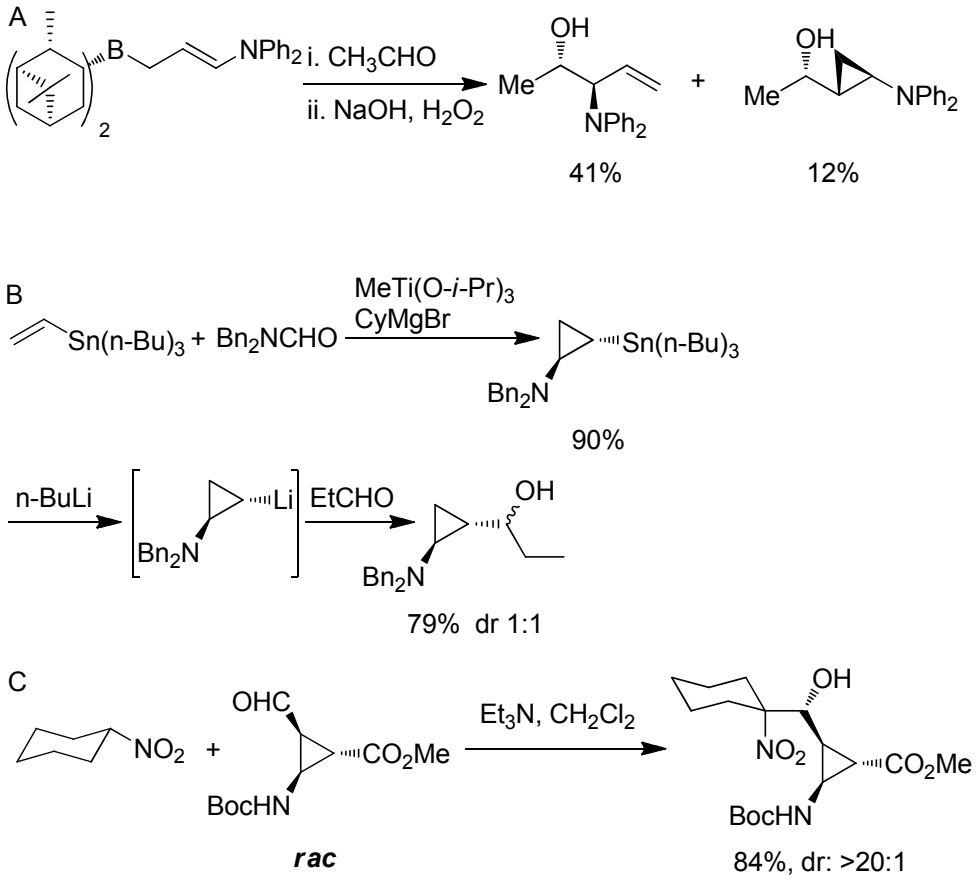
The amino cyclopropyl carbinol nucleosides **2-4** to **2-9** (Figure 2-3) have also been prepared and tested as antiviral, antitumoral, antibacterial agents and neoplasm inhibitors.[51-53]

Because amino cyclopropyl carbinols are compounds of biological relevance,[40,54–56] their direct, enantio- and diastereoselective synthesis is highly desirable.

2.1.3. Methods to synthesize amino cyclopropyl carbinols

Existing routes to prepare amino cyclopropyl carbinols suffer from either low yields[57], low diastereoselectivities[58, 59] or are not enantioselective (Scheme 2-2).[60–62] Barret observed a formation amino cyclopropyl carbinols as unwanted side-products during diastereoselective amino-propargylation of aldehydes (Scheme 2-2, A).[57] Isolated yields did not exceed 15%. A targeted approach was introduced by de Meijere utilizing the addition of trialkyl tin titanocylpropane to formamides. Next transmetalation of isolated amino cyclopropyl tin to lithium and subsequent addition to aldehydes gave amino cyclopropyl alcohols (Scheme 2-2, B).[58] Although the reaction afforded high isolated yields, it showed virtually no diastereoselectivity. Reiser introduced Felkin-Anh controlled addition of nucleophiles to β-amino cyclopropyl carbaldehydes, affording high

isolated yields and excellent diastereoselectivity (Scheme 2-2, C).[60] Unfortunately the starting β-amino cyclopropyl carbaldehydes were available only as racemates.

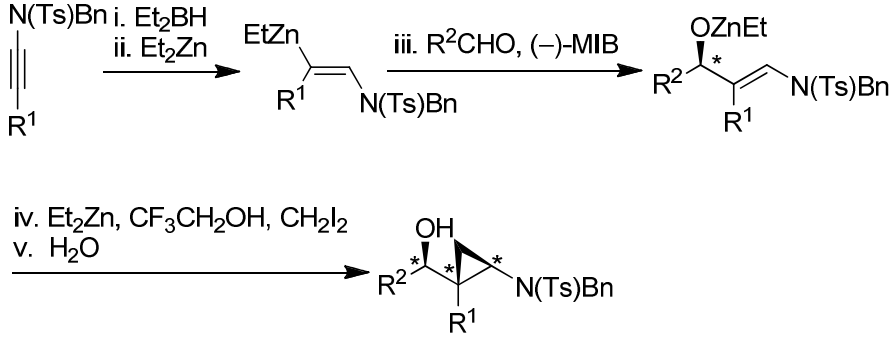


Scheme 2-2. Barret's (**A**), de Meijere's (**B**) and Reiser's (**C**) Syntheses of Amino Cyclopropyl Carbinols

2.2. Results and Discussion

2.2.1. Synthesis of amino cyclopropyl carbinols with 3-contiguous stereocenters

Our approach to the catalytic enantio- and diastereoselective synthesis of amino cyclopropyl carbinols is based on our prior efforts involving the diastereoselective directed cyclopropanation of allylic alcohols.[63–65] At the outset of this study, however, it was not clear how the nitrogen of the enamine would impact the reactivity of the double bond toward cyclopropanation or if it would affect the diastereoselectivity. A search of the literature revealed very few examples of Simmons-Smith cyclopropanations of enamines.[66,67] Nonetheless, we attempted the tandem asymmetric amino vinylation/diastereoselective cyclopropanation. Following our synthesis of β-hydroxy enamines, hydroboration of ynamides, transmetalation, and asymmetric addition to aldehydes generated zinc β-alkoxy enamine intermediates (Scheme 2-3). The alkoxide

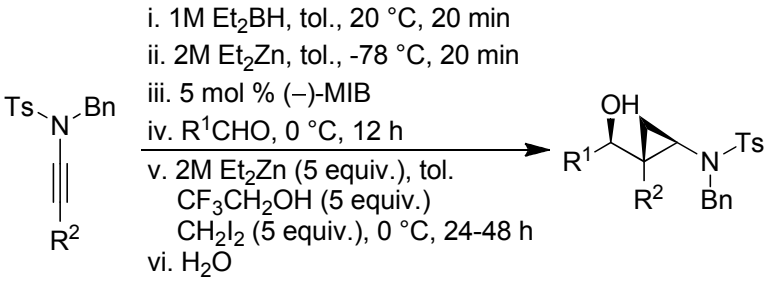


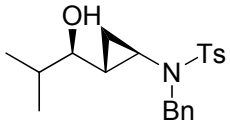
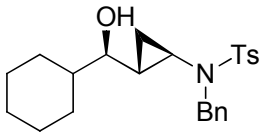
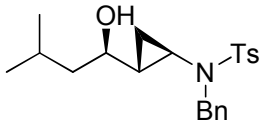
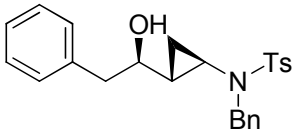
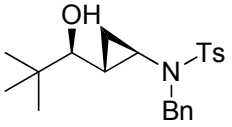
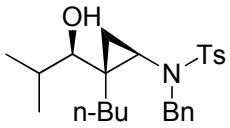
Scheme 2-3. Asymmetric and Diastereoselective One-Pot Generation of Amino Cyclopropyl Carbinols

complex was then subjected to a directed Simmons–Smith cyclopropanation using a carbenoid introduced by Shi.[68, 69]

The generation of the Shi modified carbenoid involves reaction of CF_3CH_2OH with diethylzinc to form the monoalkoxide complex, CF_3CH_2OZnEt. Reaction of this intermediate with diiodomethane resulted in formation of the Shi carbenoid, $CF_3CH_2OZnCH_2I$. Upon combining $CF_3CH_2OZnCH_2I$ with zinc β-alkoxy enamine intermediates, we were pleased to see formation of the desired cyclopropyl amines as a single diastereomer, although the yields were moderate. As we have observed with other systems,[63–65] the cyclopropanation proceeds in low to moderate yield in the presence of the triethylborane, a byproduct formed in the transmetalation of the *β*-amino vinyl group from boron to zinc (Scheme 2-3). To achieve high yields the triethyborane was removed from the reaction mixture before the cyclopropanation step. Removal of the volatile triethylborane can be accomplished by subjecting the reaction mixture to reduced pressure. The best results were obtained when hexane was added to the residue and the volatile materials were removed under reduced pressure. This procedure was repeated two more times. Under these conditions, aliphatic aldehydes (entries 1–5, Table 4) underwent the addition/cyclopropanation with terminal ynamides in 72–82% isolated yields, 76–94% enantioselectivities and excellent diastereoselectivities (>20:1 in all cases). Under our current conditions, the tandem reaction is capricious when the sequence is initiated with substituted ynamides. Although we were able to generate a tri-substituted amino cyclopropyl carbinol (entry 6), the isolated yield was low (28%) and

Table 2-1. Enantio- and Diastereoselective One-Pot Generation of Amino Cyclopropyl Carbinols



entry	aminocyclopropylalcohol		isolated yield (%)	ee (%)[a]	dr[b]
1		**2a**	80	93	>20:1
2		**2b**	76	94	>20:1
3		**2c**	78	76	>20:1
4		**2d**	78	83	>20:1
5		**2e**	72	93	>20:1
6		**2f**	28[c]	93	>20:1

[a] Ee determined by HPLC of the intermediate enamines.
[b] Diastereoselectivity determined by ^{1}H NMR analysis of crude reaction mixture. [c] Reaction time 60 h.

reaction time long (60 h). Cyclopropanation of *β*-alkoxy enamines generated from aromatic aldehydes or aryl-substituted ynamides did not proceed, resulting in isolation of *β*-hydroxy enamines.

The diastereomeric ratios in Table 2-1 were determined by ^{1}H NMR of crude reaction products. The absolute and relative configuration of **2f** was determined by X-ray diffraction (see Appendix B). The structure revealed that cyclopropanation occurred *syn* to the carbinol, as observed in the cyclopropanation of allylic alcohols via the Simmons–Smith cyclopropanation. [63–65, 70, 71] A possible transition state for the directed cyclopropanation is illustrated in Figure 2-4. [70, 71]

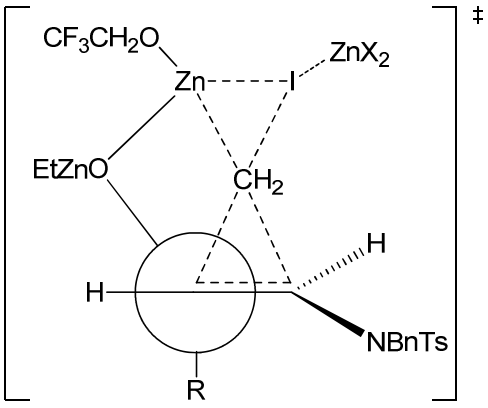


Figure 2-4. Proposed transition state for diastereoselective cyclopropanation of β-alkoxy enamines

The amino vinylation/cyclopropanation method introduced above affords amino cyclopropyl carbinols containing *trans*-disubstituted cyclopropane motifs. The products are formed with good to excellent enantioselectivities, very high diastereoselectivities,

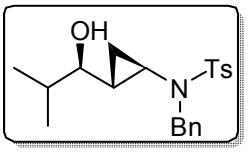
and good yields. This one-pot procedure results in generation of three C–C bonds and three continuous stereocenters and is conducted without isolation of any intermediates.

2.3. Conclusions

We have developed the first enantio- and diastereoselective synthesis of amino cyclopropyl carbinols. Tandem of hydroboration of ynamides, transmetalation from boron to zinc, enantioselective addition of beta-amino vinyl zinc intermediates to aldehydes followed by diastereoselective Simmons-Smith cyclopropanation affords amino cyclopropyl carbinols with high yields, good to excellent enantioselectivities, excellent diastereoselectivities in one-pot fashion.

2.4. Experimental Section

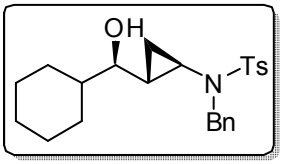
General Procedure B. Asymmetric Amino Vinylation of Aldehydes/Diastereoselective Cyclopropanation:



***N*-Benzyl-*N*-((1*R*,2*R*)-2-((*R*)-1-hydroxy-2-methylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2a).** A 10 mL Schlenk flask was charged with a solution of *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (1.0 mL, 0.25 M in toluene, 0.25 mmol) and a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol) was added dropwise at

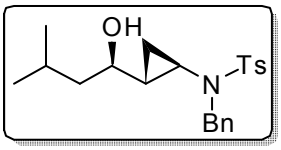
room temperature. The resulting solution was stirred at room temperature for 20 min. The reaction flask was then cooled to –78 °C, Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol) was added, and the reaction mixture was stirred for 20 min. (–)-MIB (3.0 mg, 0.012 mmol, 5 mol %) was added followed by dropwise addition of isobutyraldehyde (24 μL, 0.3 mmol) at –78 °C. The reaction flask was placed in a –30 °C IPA/dry ice cold bath and allowed to warm to 0 °C over 12 h. The solution was stirred at 0 °C until vinyl addition was complete by TLC (typically 12 h). The volatile materials, including Et_3B byproduct, were removed in vacuo at 0 °C. Hexanes (2 mL) was added, and the volatile materials were again removed under reduced pressure. This step was repeated two more times to ensure the complete removal of Et_3B. A solution of Et_2Zn (0.63 mL, 2.0 M in toluene, 1.25 mmol) and neat CF_3CH_2OH (91 μL, 1.25 mmol) were added slowly at 0 °C and the Schlenk flask was wrapped in aluminum foil to exclude light. The resulting mixture was stirred at 0 °C for 5 min and diiodomethane (101 μL, 1.25 mmol) was added. The stirring was continued at 0 °C for 40 h, after which the reaction mixture was quenched with brine (2 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were then washed with 50 mL of water and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 59 mg (80% yield) of **2a** as an yellow oil. $[\alpha]_D^{20}$: –28.1 (*c* = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ 0.68 (dd, 1H, *J* = 14.32 Hz, 6.95 Hz), 0.74 (d, 3H, *J* = 6.7 Hz), 0.77 (d, 3H, *J* = 6.7 Hz), 1.00 (d, 1H, *J* = 5.2 Hz), 1.09 (m, 1H), 1.52 (m, 1H), 2.00 (m, 1H), 2.42 (s, 3H), 3.16 (q, 1H, *J* =

4.6 Hz), 4.18 (d, 1H, *J* = 14.6 Hz), 4.38 (d, 1H, *J* = 14.6 Hz), 7.20–7.38 (m, 7H), 7.67–7.76 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 9.90, 17.22, 18.94, 21.77, 23.69, 34.11, 34.44, 54.96, 74.52, 127.78, 127.86, 128.61, 128.65, 129.84, 135.68, 137.40, 143.67; IR (neat): 3538 (OH), 2960, 2873, 1598, 1495, 1455, 1341, 1163, 1093, 927, 815 cm^{-1}; HRMS-CI: *m*/*z* 396.1604 [(M + Na)+; calculated for $C_{21}H_{27}NO_3SNa$: 396.1609].



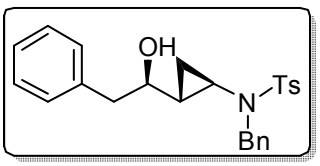
_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-cyclohexyl(hydroxy)methyl)cyclopropyl)-4-methylbenzenesulfonamide (2b).

Title compound **2b** was prepared by General Procedure B using cyclohexane carboxaldehyde (36 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 94 mg (76% yield) of **2b** as an yellow oil. $[\alpha]_D^{20}$: –5.0 (c = 0.07, $CHCl_3$). ^{1}H NMR (C_6D_6, 360 MHz): δ 0.68–0.76 (m, 1H), 0.80–0.87 (m, 1H), 1.09–1.19 (m, 4H), 1.19–1.27 (m, 2H), 1.48 (d, *J* = 12.8 Hz, 1H), 1.54–1.63 (m, 2H), 1.63–1.77 (m, 3H), 2.01 (s, 3H), 2.17–1.22 (m, 1H), 3.21 (t, *J* = 4.1 Hz, 1H), 4.62 (iso(AB)quadruplet, J_{AB} = 14.7 Hz, Δ = 53.3 Hz, 2H), 6.91–6.98 (m, 2H), 7.08–7.20 (m, 3H), 7.35–7.42 (m, 2H), 7.83–7.89 (m, 2H); $^{13}C\{1H\}$ NMR (C_6D_6, 90 MHz): δ 10.0, 21.5, 24.0, 26.9, 27.0, 27.2, 28.2, 29.7, 34.9, 44.7, 55.3, 73.7, 128.0, 128.5, 129.0, 130.0, 137.1, 138.5, 143.4. IR (neat): 3543 (OH), 3031, 2925, 2852, 1600, 1495, 1451, 1341, 1163, 1094, 815 cm^{-1}; HRMS-CI: m/z 436.1927 [$(M + Na)^+$; calculated for $C_{24}H_{31}NO_3SNa$: 436.1922].



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-1-hydroxy-3-methylbutyl)cyclopropyl)-4-methylbenzenesulfonamide (2c).

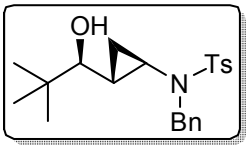
Title compound **2c** was prepared by General Procedure B using isovaleraldehyde (32 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 90 mg (78% yield) of **2c** as an yellow oil. $[\alpha]_D^{20}$: –5.4 (c = 0.08, $CHCl_3$). ^{1}H NMR (C_6D_6, 360 MHz): δ 0.44–0.52 (m, 1H), 0.72–0.76 (m, 1H), 0.77 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 0.97 (dd, J_1 = 8.7 Hz, J_2 = 4.2 Hz, 1H), 1.06 (dd, J_1 = 8.6 Hz, J_2 = 5.2 Hz, 1H), 1.10–1.20 (m, 1H), 1.55–1.70 (m, 1H), 1.92 (s, 3H), 2.08 (pent., J = 3.4 Hz, 1H), 3.26–3.36 (m, 1H), 4.19 (iso(AB)quadruplet, J_{AB} = 14.6 Hz, Δ = 17.7 Hz, 2H), 6.80–6.87 (m, 2H), 7.04–7.14 (m, 3H), 7.28–7.36 (m, 2H), 7.77–7.86 (m, 2H); ^{13}C{1H} NMR (C_6D_6, 90 MHz): δ 9.5, 20.8, 21.7, 23.2, 24.2, 26.5, 34.3, 45.6, 54.5, 67.7, 128.3, 128.5, 129.3, 136.4, 137.6, 142.7. IR (neat): 3545 (OH), 3031, 2925, 2852, 1599, 1495, 1450, 1341, 1163, 1094, 814 cm^{-1}; HRMS-CI: m/z 410.1765 [$(M + Na)^+$; calculated for $C_{22}H_{29}NO_3SNa$: 410.1766].



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-1-hydroxy-2-phenylethyl)cyclopropyl)-4-methylbenzenesulfonamide (2d).

Title compound **2d** was prepared by General Procedure B using phenylacetaldehyde (35 μL, 0.3 mmol). The product was purified by column chromatography on deactivated

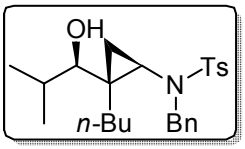
silica gel (10% ethyl acetate in hexanes) to afford 98 mg (78% yield) of **1q** as an yellow oil. $[\alpha]_D^{20}$: –6.2 (c = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.68–0.75 (m, 1H), 0.78–0.85 (m, 1H), 1.31 (d, J = 3.9 Hz, 1H), 2.10–2.16 (m, 1H), 2.44 (s, 3H), 2.50 (dd, J_1 = 12.5 Hz, J_2 = 8.9 Hz, 1H), 2.75 (dd, J_1 = 13.8 Hz, J_2 = 3.8 Hz, 1H), 3.53–3.61 (m, 1H), 4.31 (iso(AB)quadruplet, J_{AB} = 14.6 Hz, Δ = 40.0 Hz, 2H), 7.08–7.14 (m, 2H), 7.18–7.24 (m, 2H), 7.25–7.29 (m, 2H), 7.29–7.35 (m, 6H), 7.70–7.75 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 10.1, 21.8, 26.2, 34.6, 43.6, 54.8, 71.3, 126.8, 127.9, 128.6, 128.7, 128.8, 129.5, 129.9, 135.8, 137.2, 138.1, 143.7. IR (neat): 3543 (OH), 3031, 2925, 2852, 1599, 1495, 1451, 1341, 1163, 1094, 814 cm^{-1}; HRMS-CI: m/z 422.1779 $[(M + H)^+$; calculated for $C_{25}H_{28}NO_3S$: 422.1790] and 444.1609 $[(M + Na)^+$; calculated for $C_{25}H_{27}NO_3SNa$: 444.1612].



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_S_)-1-hydroxy-2,2-dimethylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2e).

Title compound **2e** was prepared by General Procedure B using pivalaldehyde (36 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 84 mg (72% yield) of **2e** as an yellow oil. $[\alpha]_D^{20}$: –6.3 (c = 0.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.73 (s, 9H), 0.75–0.77 (m, 1H), 1.14 (d, J = 5.9 Hz, 1H), 1.98–2.04 (m, 1H), 2.43 (s, 3H), 3.18–3.22 (m, 1H), 4.27 (iso(AB)quadruplet, J_{AB} = 14.4 Hz, Δ = 62.3 Hz, 2H), 4.89–4.91 (m, 1H), 7.15–7.22 (m, 1H), 7.22–7.28 (m, 4H), 7.70–7.80 (m, 4H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 9.6,

21.2, 21.7, 25.7, 33.5, 35.8, 54.8, 75.8, 127.3, 127.9, 128.0, 128.8, 129.8, 135.5, 136.5, 137.4. IR (neat): 3545 (OH), 3030, 2925, 2852, 1603, 1495, 1450, 1341, 1163, 1094, 815 cm^{-1}; HRMS-CI: m/z 388.1961 [$(M + H)^+$; calculated for $C_{22}H_{30}NO_3S$: 388.1946].



_N_-Benzyl-_N_-((1_R_,2_R_)-2-butyl-2-((_R_)-1-hydroxy-2-methylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2f).

Title compound **2f** was prepared by General Procedure B using *N*-benzyl-*N*-(hex-1-yn-1-yl)-4-methylbenzenesulfonamide (137 mg dissolved in 1 mL dry toluene, 0.4 mmol) and isobutyraldehyde (24 μL, 0.3 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 36 mg (28% yield) of **2f** as an yellow oil. $[\alpha]_D^{20}$: –8.7 (c = 0.06, $CHCl_3$). ^1H NMR (C_6D_6, 360 MHz): δ 0.44–0.48 (m, 1H), 0.62 (d, *J* = 6.8 Hz, 1H), 0.69 (d, *J* = 6.6 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.14–1.28 (m, 3H), 1.29–1.36 (m, 1H), 1.40–1.49 (m, 1H), 1.77–1.88 (m, 1H), 1.90 (s, 3H), 2.54 (t, *J* = 6.8 Hz, 1H), 3.28–3.33 (m, 1H), 3.41 (iso(AB)quadruplet, J_{AB} = 15.4 Hz, Δ = 276.0 Hz, 2H), 6.78–6.86 (m, 2H), 7.01–7.07 (m, 1H), 7.08–7.14 (m, 2H), 7.32–7.40 (m, 2H), 7.81–7.88 (m, 2H); $^{13}C\{1H\}$ NMR (C_6D_6, 90 MHz): δ 14.6, 17.1, 18.7, 20.7, 21.4, 23.4, 23.8, 30.3, 30.8, 32.0, 32.3, 42.1, 55.6, 77.7, 128.3, 129.0, 129.2, 130.1, 136.5, 138.5, 143.6. IR (neat): 3516 (OH), 2956, 1603, 1456, 1160, 1093, 1042, 815 cm^{-1}; HRMS-CI: m/z 430.2420 [$(M + H)^+$; calculated for $C_{25}H_{36}NO_3S$: 430.2416].

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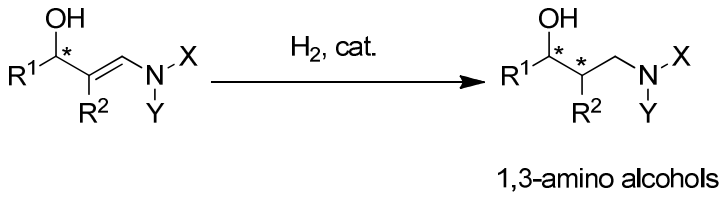
Chapter 3. Diastereoselective Synthesis of 1,3-Aminoalcohols via Catalytic Hydrogenation of β-Hydroxy Enamines

3.1. Introduction

Enantioenriched β-hydroxy enamines are anticipated to be useful precursors in the synthesis of 1,2-disubstituted 1,3-aminoalcohols (Scheme 3-1), a class of compounds that has garnered much interest for their biological activity.[1–4] 1,3-Aminoalcohols are common structural motifs in many biologically active compounds and are extensively used in asymmetric synthesis both as chiral ligands and auxiliaries.[5]



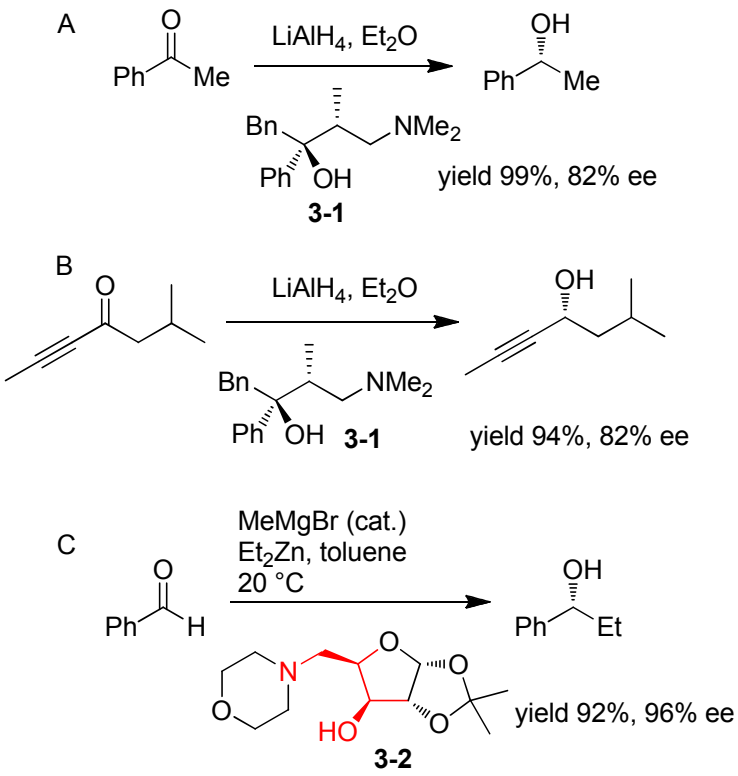
Scheme 3-1. Substrate-Directed Hydrogenation of β-Hydroxy Enamines

3.1.1. 1,3-Aminoalcohols in asymmetric catalysis

Aminoalcohols have been used extensively in asymmetric synthesis, both as chiral ligands and auxiliaries. The two heteroatoms allow great flexibility, as one or both can be bound to a Lewis acid, transition metal, or starting material. While less abundant than the 1,2-aminoalcohols, 1,3-aminoalcohols have also contributed significantly to the advancement of asymmetric synthesis. Many have found use as chiral ligands or auxiliaries, and there have also been applications as a resolving agent and as a phase transfer catalyst. One of the classical examples of use of 1,2-substituted-1,3-aminoalcohols in enantioselective synthesis is "Darvon" alcohol **3-1** (Scheme 3-2, A).[6]

Compound **3-1** was reacted with $LiAlH_4$ to generate active reducing agent. The first to perform this reaction was Yamaguchi, who used **3-1** to reduce acetophenone in 1972.[6, 7] Reaction with fresh reagent in Et_2O at –65 °C gave secondary alcohol (82% ee) quantitatively after 3 minutes. Five years later, Brinkmeyer used this method in the asymmetric reduction of acetylenic ketones to propargylic alcohols (Scheme 3-2, B).[8] This chemistry was applied to the asymmetric synthesis of 11α-hydroxyprogesterone, a key intermediate in commercial production of hydrocortisone acetate.

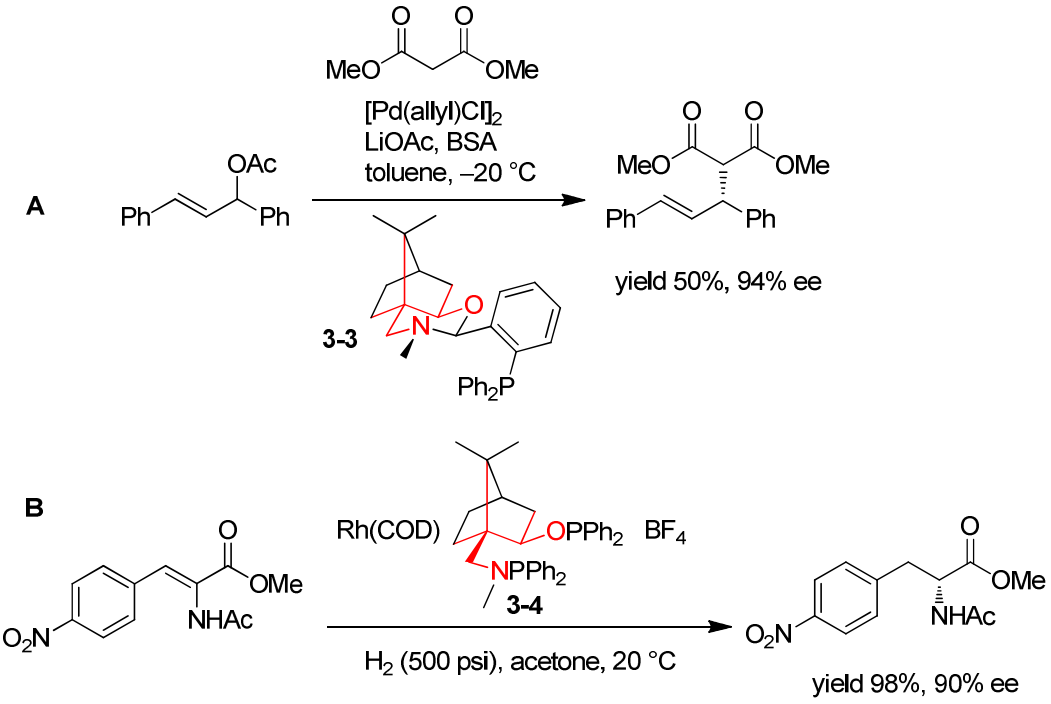
In 1994, Cho and Kim prepared amino alcohol **3-2** from D-xylose and used it as ligand for asymmetric Et_2Zn addition reactions (Scheme 3-2, C).[9, 10]



Scheme 3-2. 1,2-Substituted-1,3-aminoalcohols in Asymmetric Addition to Carbonyl

For addition to benzaldehyde **3-2** offered excellent chiral induction, giving 1-phenyl-1-propanol with 96% ee (Scheme 3-2, C).

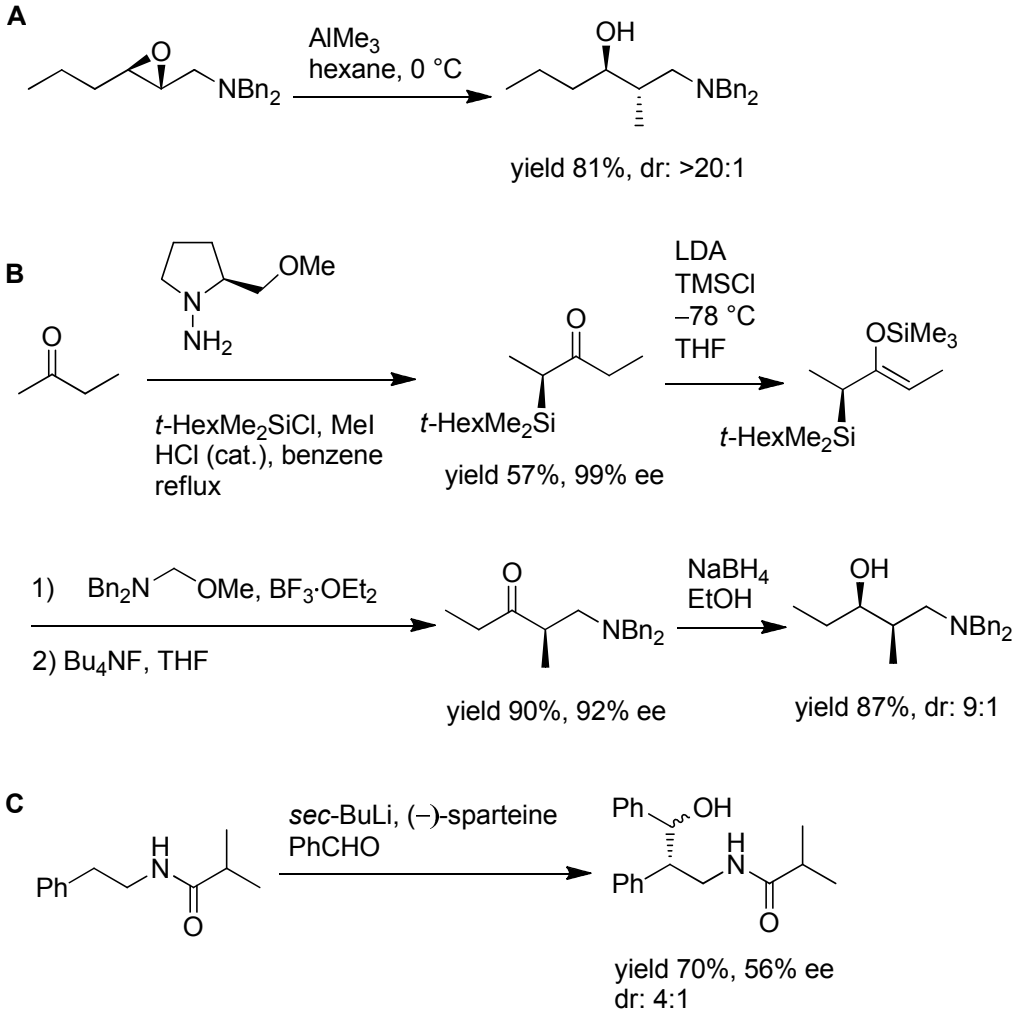
Mino reported a synthesis of phosphinooxazinane **3-3** (Scheme 3-3, A) by condensation of camphor-derived 1,2-substituted-1,3-aminoalcohol with 2-diphenylphosphinobenzaldehyde.[11] This ligand was then applied to asymmetric Pd-catalyzed allylic alkylation. Camphor-based aminoalcohols have also been used as skeletons for phosphine ligands. Yeung made *exo* aminophosphine phosphinite **3-4**



Scheme 3-3. 1,2-Substituted-1,3-aminoalcohols as Ligand Backbones in Asymmetric Allylic Substitution and Asymmetric Hydrogenation

(Scheme 3-3, B).[13] This ligand was used in the Rh-catalyzed hydrogenation of enamines, giving chiral amidoesters with 95-100% conversion and moderate to good enantioselectivity.

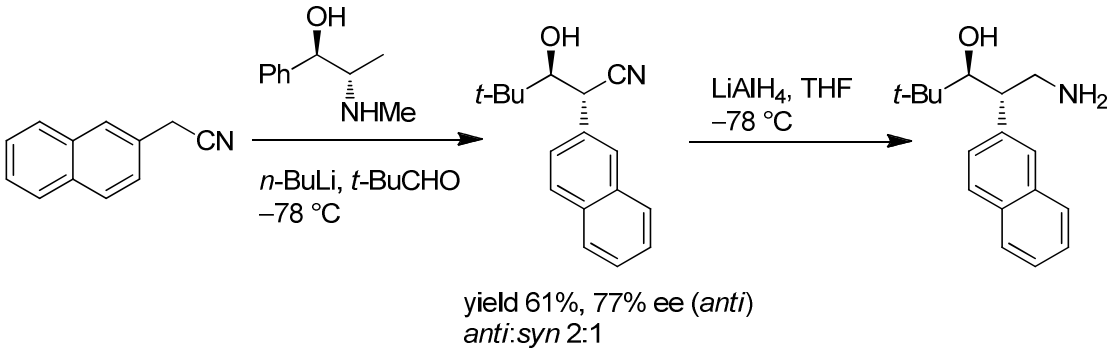
3.1.2. Methods to synthesize 1,3-aminoalcohols



Scheme 3-4. Available Methods to Synthesize 1,2-Disubstituted-1,3-aminoalcohols

There are many methods available for the synthesis of enantio- and diastereoselectively 1,3-disubstituted-1,3-amino alcohols.[18–24] In contrast, the stereoselective synthesis 1,2-disubstituted-1,3-amino alcohols remains a significant challenge.[25–33]

Opening of amino-epoxides with organoaluminum reagents requires elaborate multi-step synthesis of starting materials (Scheme 3-4, A).[27] Furthermore, the limited availability of commercial organoaluminum reagents narrows the scope of the reaction. Hydrolysis of oxazines requires harsh acidic conditions incompatible with many of functional groups.[28, 29] Reduction of *β*-keto-amines requires inefficient multi-step synthesis of *β*-keto-amines (Scheme 3-4, B).[32] Beak's asymmetric *β*-lithiation and subsequent addition to aldehydes provides poor enantio- and diastereoselectivities (Scheme 3-4, C).[34] The best approach to enantioenriched 1,2-disubstituted-1,3-amino alcohols is an addition of lithium arylacetonitriles to aldehydes,[35] leading to *β*-hydroxy

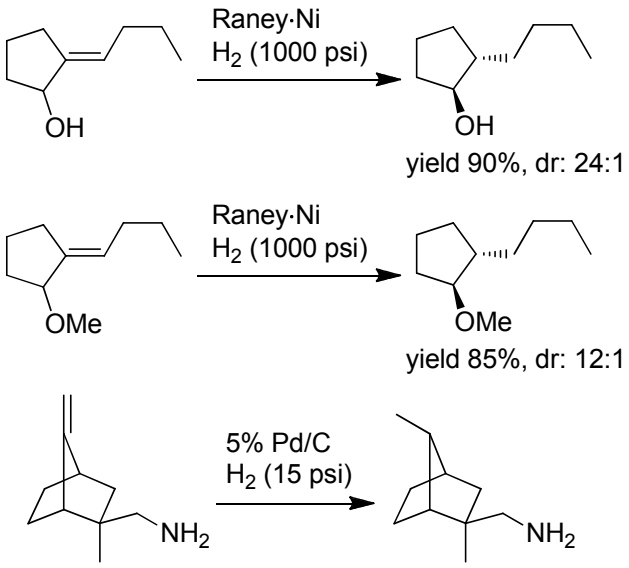


Scheme 3-5. Lithium Ephedrinate Mediated Aldol Reaction of Arylacetonitriles

nitriles with moderate enantio- and diastereoselectivities (Scheme 3-5). This method employs superstoichiometric amount of chiral ligand.

Efficient methods for the synthesis of enantio- and diastereoenriched 1,2-disubstituted-1,3-amino alcohols would facilitate their use in medicinal chemistry and asymmetric catalysis. We envisioned a catalytic diastereoselective hydrogenation of enantio-enriched *β*-hydroxy enamines as a straightforward route to 1,2-disubstituted-1,3-amino alcohols.

3.1.3. Substrate directed catalytic hydrogenations



Scheme 3-6. Representative Examples of Hetero-Atom Directed Heterogeneous Hydrogenations

The stereochemical course of heterogeneous hydrogenation of carbon-carbon double bond may be influenced by a neighboring heteroatom.[36] Association of an internal polar group with the metal surface can lead to the delivery of hydrogen to the unsaturation site in a *syn* fashion. This catalyst-substrate interaction may be largely preempted or facilitated, depending on the nature of the metal, the support, or the solvent employed. For example, catalytic hydrogenation of allylic alcohols affords the *syn* isomer as the major product.[37]

Polarity of solvent does not have predictable influence on the course of heterogeneous reductions. Highly polar solvents such as DMF, which compete for metal binding sites afford the *anti* adduct preferentially, whereas non-polar media (hexane) enforce heteroatom-catalyst association and thereby favor formation of the *syn* isomer. On the other hand hydrogenations in alcohol solvents often lead *syn* products, which suggest that simple conclusions can not be made.[38] Hydrogenation of the cyclopentylidene allylic methyl ether indicates that, although less effectively than parent alcohols, alkyl ethers can also direct the addition reaction (Scheme 3-6).[37] Although heteroatom functional groups can influence the stereochemical course of heterogeneous reductions, number of variables, such as the nature of the directing group, solvent, catalyst, support, and hydrogen pressure are important and often must be optimized to achieve useful levels of selectivity. These changes in reaction conditions cannot be effected predictably. Furthermore, poisoning is often a problem and different catalyst batches seldom show identical reactivity or selectivity. For these reasons, heterogeneous

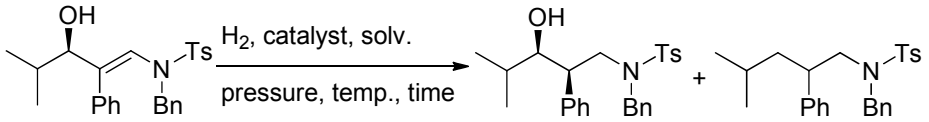
catalysis often does not offer a general and reliable solution to the notion of heteroatom-directed hydrogenation reactions.

3.2. Results and Discussion

3.2.1. Optimization of hydrogenation conditions

Our initial efforts to reduce *β*-hydroxy enamines focused on homogenous hydrogenation catalysts and variation of the solvent, hydrogen pressure, and reaction time (Table 3-1). Both Crabtree's[39] and Wilkinson's[40] catalysts resulted in loss of the hydroxy group, probably by elimination to form an *α*,*β*-unsaturated iminium intermediate. This intermediate could then undergo subsequent hydrogenation resulting in formation of the observed alkyl sulfonamide **3a'** (entries 1–6). These examples illustrate the sensitivity of *β*-hydroxy enamines to elimination even under very mild conditions. Next we turned to common heterogeneous catalysts. PtO_2 did not catalyze the hydrogenation at room temperature, but caused decomposition of the hydroxy enamine at elevated temperature or pressure (entries 7–9). On the other hand, rhodium on alumina (5 mol %) was completely inactive (entry 10). Palladium on carbon (10 mol %) was the most promising catalyst, providing the desired 1,3-amino alcohol as the major product. Atmospheric pressure at room temperature (entry 11) or above (entry 12) was not sufficient for full conversion, so higher pressure was used (entries 13 and 14). With 10 mol % of Pd/C catalyst in methanol at 8 MPa of hydrogen the reaction provided 90% isolated yield with

Table 3-1. Optimization of Diastereoselective Hydrogenation of *β*-Hydroxy Enamines



3a **3a'**

entry	catalyst (mol %)/solvent	pressure (MPa)	temp. (°C)	time (h)	product[a]	isolated yield (%)	dr[b]
1	Crabtree's cat. (10)/CH_2Cl_2	0.1	20	12	**3a'**	40	-
2	Crabtree's cat. (10)/MeOH:CH_2Cl_2, 1:1	0.1	20	12	**3a'**	50	-
3	Crabtree's cat. (10)/MeOH:CH_2Cl_2, 1:1	1.0	20	5	**3a'**	50	-
4	Crabtree's cat. (10)/MeOH:CH_2Cl_2, 1:1	8.0	20	12	**3a'**	60	-
5	Wilkinson's cat. (1.0)/benzene	0.1	20	12	NR	0	-
6	Wilkinson's cat. (10)/benzene	1.0	20	12	**3a'**	60	-
7	PtO_2 (10)/MeOH	0.1	20	12	NR	0	-
8	PtO_2 (10)/MeOH	0.1	50	12	dec.	0	-
9	PtO_2 (10)/MeOH	8.0	20	12	dec.	0	-
10	5% Rh/Al_2O_3 (10)/AcOEt	1.0	20	12	NR	0	-
11	10% Pd/C (10)/MeOH	0.1	20	12	**3a**	10	>20:1
12	10% Pd/C (10)/MeOH	0.1	50	5	**3a**	14	>20:1
13	10% Pd/C (10)/MeOH	1.0	20	12	**3a**	55	>20:1
14	**10% Pd/C (10)/MeOH**	**8.0**	**20**	**12**	**3a**	**90**	**>20:1**

[a] NR: only starting material recovered, dec: starting material decomposed to an inseparable mixture.
[b] Diastereoselectivity determined by ^{1}H NMR analysis of crude reaction mixture.

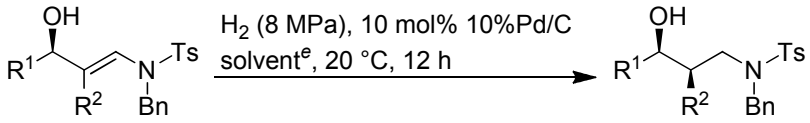
excellent diastereoselectivity (>20:1, entry 14). Unlike the *β*-hydroxy enamines with aliphatic carbinols, which undergo highly diastereoselective reductions in methanol, we found that the enamine hydrogenation of substrates with benzylic hydroxyl groups led to elimination/reduction in methanol to give **3a'**. Therefore the choice of the solvent was

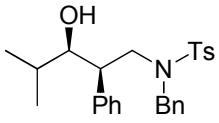
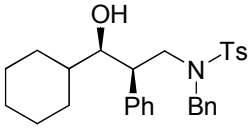
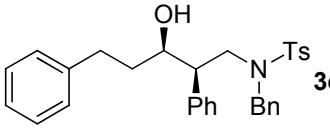
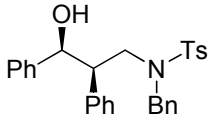
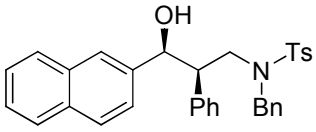
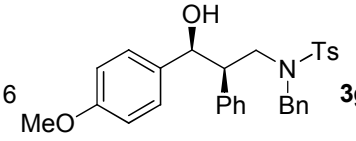
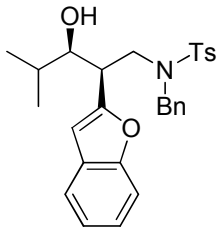
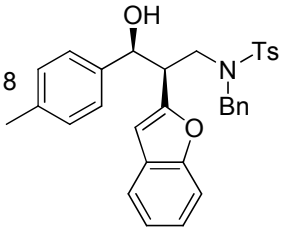
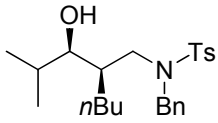
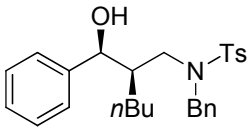
crucial and dependent on the substituent attached to the carbinol. We reasoned that protic solvents would hydrogen bond to the hydroxyl of the *β*-hydroxy enamine and facilitate the elimination pathway. To reduce elimination, *β*-hydroxy enamines with aromatic carbinols were hydrogenated in aprotic solvents. After screening several solvents, ethyl acetate was determined to be the most effective. Interestingly, hydrogenation of *β*-hydroxy enamines with aliphatic carbinols in ethyl acetate resulted in lower conversions (entry 15) than in methanol.

3.2.2. Substrate scope of hydrogenation of *β*-hydroxy enamines

The results of the diastereoselective hydrogenation of *β*-hydroxy enamines are shown in Table 3-2. Catalytic hydrogenation of *β*-hydroxy enamines with aliphatic (entries 1, 2, 3, 7 and 9) or aromatic (entries 4, 5, 6, 8 and 10) carbinol substituents and aromatic (entries 1–6) or heteroaromatic (entries 7 and 8) substituents in the 2-position led to 1,2-disubstituted-1,3-aminoalcohols with good isolated yields (80–92%) and excellent diastereoselectivities (>20:1). When an alkyl group was in the 2-position of the *β*-hydroxy enamine, however, the diastereoselectivity was only moderate (entries 9 and 10). The diastereomeric ratios in Table 3-2 were determined by ^{1}H NMR of the crude reaction products. The ee of the *β*-hydroxy enamines **1a**, **1e** and **1j** were determined before the hydrogenation to be 92, 91 and 98%. Their hydrogenation products **3a**, **3e** and **3j** were found to have ee's of 91, 90 and 95%, respectively. These results indicate a slight drop in ee during the hydrogenation. The absolute and relative stereochemistries in

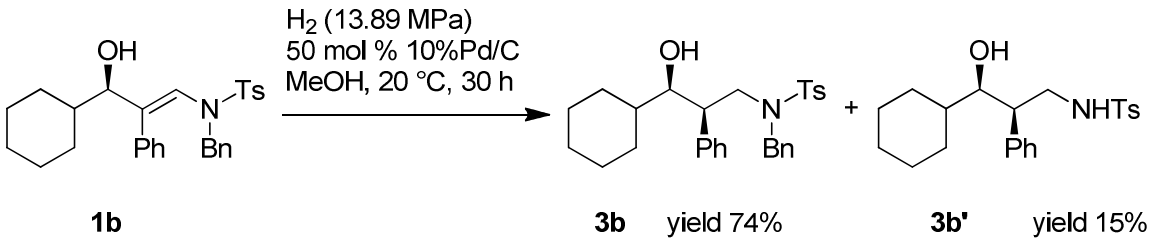
Table 3-2. Diastereoselective Hydrogenation of β-Hydroxy Enamines



entry	aminoalcohol		isolated yield (%)	dr[a]
1		**3a**	90	>20:1[b]
2		**3b**	80	>20:1
3		**3c**	80	>20:1
4		**3e**	92	>20:1[c]
5		**3f**	86	>20:1
6		**3g**	90	>20:1
7		**3i**	88	>20:1
8		**3j**	82	>20:1[d]
9		**3k**	85	3:1
10		**3l**	90	4:1

[a] Diastereoselectivity determined by ^{1}H NMR analysis of crude reaction mixture. [b] 91% *ee* (HPLC). [c] 90% *ee* (HPLC). [d] 95% *ee*. [e] For aliphatic R^1: MeOH; for aromatic R^1: EtOAc.

Table 6 were based on the X-ray structural determination of **3a**, which revealed that the hydrogenation is *syn*-selective (see the Appendix B). It is noteworthy that under the optimized hydrogenation conditions, no debenzylation was observed. At high pressures as high as 2000 psi, catalyst loading 50 mol % and extended reaction time 30 h, 15% of the debenzylated **3b'** was isolated (Scheme 3-7).



Scheme 3-7. Partial Hydrogenolysis of Benzyl Group at High Pressure and Catalyst Loading and Extended Reaction Time

3.2.3. Conformational analysis of *β*-hydroxy enamines in catalytic hydrogenation

The diastereoselective outcome of the hydrogenation can be rationalized by a conformational analysis of the *β*-hydroxy enamine when associated with the surface of the palladium catalyst (Figure 3-1, A). The *β*-hydroxy enamine binds to the surface of the catalyst through coordination of the hydroxy group. The substrate then adopts a conformation that minimizes unfavorable interaction between R^1 and the hydroxyl. The dihydrogen is then delivered to give the *syn*-product. It is possible to disfavor the association of the hydroxyl group with the metal catalyst by introduction of bulky protecting group. In this case, the two conformers differ in steric interactions between *i*Pr–Ph and OTBS-Ph (Figure 3-1, B). The difference in energy between the conformers is not sufficient for good diastereoselection, resulting in 0.7:1 *syn*:*anti* mixture of diastereomers in case of TBS and 1:1 mixture in case of TIPS.

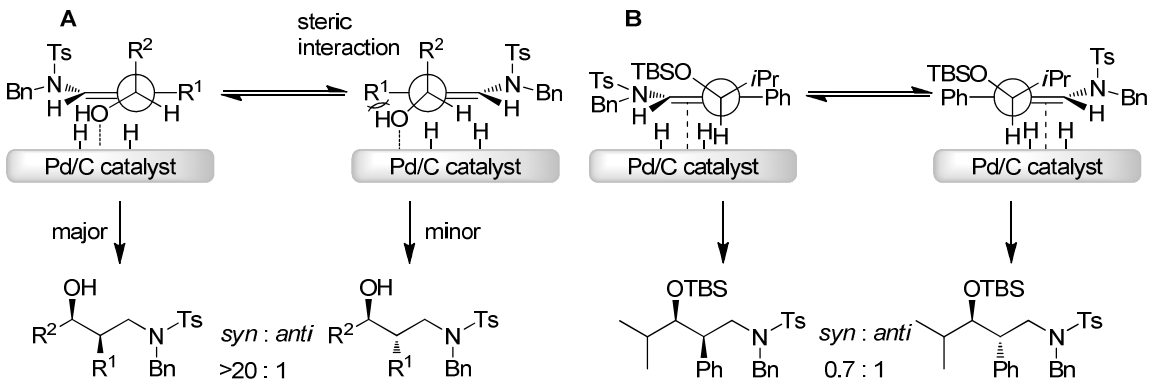


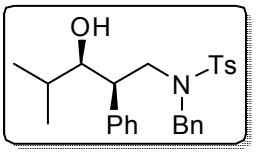
Figure 3-1. **A**: proposed conformation of hydroxy enamines on the surface of catalyst to rationalize the *syn* selective hydrogenation. **B**: conformation of TBS protected *β*-hydroxy enamine slightly favors *anti* diastereomer.

3.3. Conclusions

We have developed highly enantio- and diastereoselective two-step synthesis 1,2-disubstituted-1,3-aminoalcohols. Utilizing the fact that *β*-hydroxy enamines are excellent substrate for substrate-directed reactions, the heterogeneous catalyzed hydrogenation affords *syn* 1,2-disubstituted-1,3-aminoalcohols with high yields and moderate to excellent diastereoselectivities.

3.4. Experimental Section

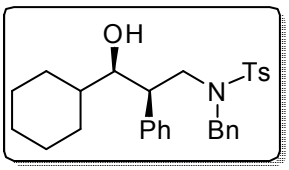
General Procedure C. Diastereoselective Hydrogenation of *β*-Hydroxy Enamines with Aliphatic Substituents in 3-Position:



***N*-Benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpentyl)-4-methylbenzenesulfonamide (3a).**

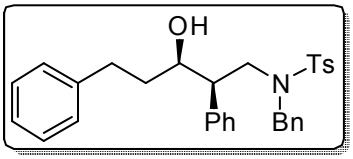
In a 10 × 75 mm glass test tube was dissolved (*E*)-*N*-benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpent-1-enyl)-4-methylbenzenesulfonamide (44 mg, 0.1 mmol) in methanol (4 mL) at room temperature. The space above solution was purged with nitrogen to remove most of the air. 10% Palladium on carbon (8 mg, 7 mol %) was added and the test tube was placed in a Parr hydrogenator. Good stirring was confirmed before closing apparatus. After flushing three times with hydrogen, the system was pressured with 9.65 MPa (1400 psi) of hydrogen and the reaction was stirred for 12 h at room temperature. After opening the apparatus, the palladium catalyst was removed *via* filtration through a plug of Celite. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (10% ethyl acetate in hexanes) to afford 39 mg (90% yield) of **3a** as an amorphous solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.30 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 1.05-1.15 (m, 1H), 2.35 (s, 3H), 2.67 (dd, J_1 = 14.7 Hz, J_2 = 4.5 Hz, 1H), 3.01 (d, J = 5.4 Hz, 1H), 3.35-3.46 (m, 1H), 3.90 (dd, J_1 = 14.1 Hz, J_2 = 11.4 Hz, 1H), 4.18 (iso(AB)quadruplet, J_{AB} = 14.1 Hz, Δ = 352.0 Hz, 2H), 7.00-7.19 (m, 5H), 7.19-7.32 (m, 7H), 7.60-7.67 (m, 2H); ^{13}C{1H} NMR

($CDCl_3$, 90 MHz): δ 18.8, 20.2, 21.8, 31.1, 46.7, 53.5, 55.2, 75.2, 127.0, 127.4, 128.4, 128.5, 129.0, 129.2, 129.6, 130.1, 136.8, 139.6, 143.9. IR (neat): 3532 (OH), 2924, 1599, 1494, 1330, 1156, 1094, 925, 814 cm^{-1}; HRMS-CI: *m/z* 438.2103 [$(M + H)^+$; calculated for $C_{26}H_{32}NO_3S$: 438.2103].



_N_-Benzyl-_N_-((2_R_,3_R_)-3-cyclohexyl-3-hydroxy-2-phenylpropyl)-4-methylbenzenesulfonamide (3b).

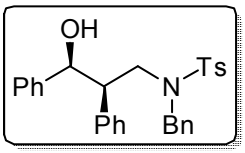
Title compound **3b** was prepared by General Procedure C using **1b** (48 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 38 mg (80% yield) of **3b** as an yellow oil. $[\alpha]_D^{20}$: –39.9 (c = 0.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.36–0.51 (m, 1H), 0.77–0.86 (m, 1H), 0.86–0.95 (m, 2H), 1.10–1.19 (m, 2H), 1.20–1.35 (m, 1H), 1.44–1.56 (m, 2H), 1.58–1.67 (m, 1H), 1.92–2.02 (m, 1H), 2.42 (s, 3H), 2.77 (dd, J_1 = 14.3 Hz, J_2 = 4.6 Hz, 1H), 2.88–2.94 (m, 1H), 3.54–3.62 (m, 1H), 3.96 (dd, J_1 = 13.4 Hz, J_2 = 11.4 Hz, 1H), 4.25 (iso(AB)quadruplet, J_{AB} = 14.2 Hz, Δ = 320.0 Hz, 2H), 7.08–7.15 (m, 2H), 7.15–7.23 (m, 3H), 7.30–7.40 (m, 7H), 7.68–7.75 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.7, 25.9, 26.0, 26.7, 28.9, 30.1, 40.3, 46.1, 53.1, 55.0, 74.0, 126.9, 127.4, 128.4, 129.0, 129.2, 129.6, 130.1, 136.1, 136.7, 139.6, 143.9. Dr > 20:1 from ^1H NMR of crude reaction mixture. IR (neat): 3532 (OH), 2925, 2870, 1600, 1495, 1454, 1330, 1157, 1096, 925, 900, 814 cm^{-1}; HRMS-CI: m/z 500.2237 [$(M + Na)^+$; calculated for $C_{29}H_{35}NO_3SNa$: 500. 2352].



_N_-Benzyl-_N_-((2_R_,3_R_)-3-hydroxy-2,5-diphenylpentyl)-4-methylbenzenesulfonamide (3c).

Title compound **3c** was prepared by General Procedure C using **1c** (48 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 40 mg (80% yield) of **3c** as an yellow oil. $[\alpha]_D^{20}$: –9.1 (c = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 1.05–1.16 (m, 1H), 1.27–1.40 (m, 1H), 2.09–2.17 (m, 1H), 2.42 (s, 3H), 2.51–2.62 (m, 1H), 2.78 (dd, J_1 = 14.3 Hz, J_2 = 4.7 Hz, 1H), 3.04 (d, J = 5.0 Hz, 1H), 3.97 (dd, J_1 = 14.2 Hz, J_2 = 11.5 Hz, 1H), 4.00–4.06 (m, 1H), 4.23 (iso(AB)quadruplet, J_{AB} = 14.1 Hz, Δ = 317.8 Hz, 2H), 7.00–7.08 (m, 4H), 7.11–7.19 (m, 4H), 7.19–7.25 (m, 4H), 7.25–7.33 (m, 5H), 7.33–7.54 (m, 5H), 7.68–7.73 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.8, 32.8, 36.7, 49.4, 52.6, 54.9, 68.8, 125.9, 127.2, 127.4, 128.4, 128.5, 128.7, 129.0, 129.1, 129.5, 130.1, 136.1, 136.7, 138.9, 142.6, 144.0. Dr > 20:1 from ^1H NMR of crude reaction mixture. IR (neat): 3533 (OH), 2924, 2871, 1599, 1497, 1454, 1330, 1154, 1095, 924, 900, 814 cm^{-1}; HRMS-CI: m/z 522.2128 $[(M + Na)^+$; calculated for $C_{31}H_{33}NO_3SNa$: 522. 2079] and 500.2252 $[(M + H)^+$; calculated for $C_{31}H_{34}NO_3S$: 500. 2259].

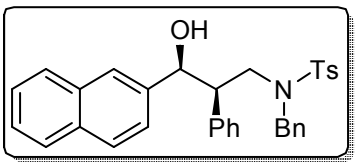
General Procedure D. Diastereoselective Hydrogenation of *β*-Hydroxy Enamines with Aromatic Substituents in 3-Position:



_N_-Benzyl-_N_-((2_R_,3_S_)-3-hydroxy-2,3-diphenylpropyl)-4-methylbenzenesulfonamide (3e).

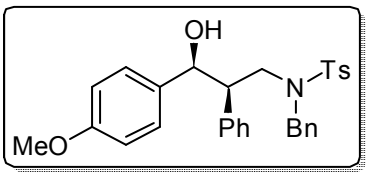
In a 10 × 75 mm glass test tube was dissolved (*E*)-*N*-benzyl-*N*-(3-hydroxy-2,3-diphenylprop-1-enyl)-4-methylbenzenesulfonamide (47 mg, 0.1 mmol) in ethyl acetate (3 mL) at room temperature. 10% Palladium on carbon (8 mg, 7 mol %) was added and the test tube was placed in a Parr hydrogenator. Good stirring was confirmed before closing the apparatus. After flushing three times with hydrogen, the system was pressured with 9.65 MPa (1400 psi) of hydrogen and the reaction was stirred for 12 h at room temperature. After opening the apparatus, the palladium catalyst was removed *via* filtration through a plug of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (10% ethyl acetate in hexanes) to afford 43 mg (92% yield) of **3d** as an amorphous solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.65 (m, 1H), 2.79 (d, 1H, *J* = 4.3 Hz), 2.99 (dd, 1H, *J* = 14.3 Hz, 6.1 Hz), 3.88 (d, 1H, *J* = 14.5 Hz), 4.55 (d, 1H, *J* = 14.5 Hz), 4.96 (t, 1H, *J* = 4.3 Hz), 6.59–6.70 (m, 4H), 6.82–6.89 (m, 2H), 7.04–7.13 (m, 3H), 7.25–7.36 (m, 8H), 7.61–7.66 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 21.78, 52.15, 54.66, 55.36, 72.28, 127.09, 127.32, 127.53, 128.16, 128.33, 129.03, 129.10, 129.62, 130.05, 134.51, 136.12, 136.79, 138.21, 143.83, 158.61. IR (neat): 3519 (OH), 2919, 1611, 1513, 1454, 1331, 1246, 1156, 1103,

1034, 928 cm^{-1}. HRMS-CI: *m*/*z* 494.1760 [(M + Na)$^+$; calcd for $C_{29}H_{29}NO_3SNa$: 494.1766].



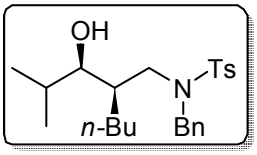
_N_-Benzyl-_N_-((2_R_,3_S_)-3-hydroxy-3-(naphthalen-2-yl)-2-phenylpropyl)-4-methylbenzenesulfonamide (3f).

Title compound **3f** was prepared by General Procedure D using **1f** (52 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 45 mg (86% yield) of **3f** as an yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (1) = 28.8 min, t_r (2) = 31.5 min, $[\alpha]_D^{20}$: –79.2 (c = 0.1, $CHCl_3$, 91% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.70–2.76 (m, 1H), 3.03 (dd, J_1 = 14.6 Hz, J_2 = 6.7 Hz, 1H), 3.76 (dd, J_1 = 14.3 Hz, J_2 = 9.2 Hz, 1H), 4.19 (iso(AB)quadruplet, J_{AB} = 14.4 Hz, Δ = 214.5 Hz, 2H), 4.88 (t, J = 4.3 Hz, 1H), 6.43–6.48 (m, 1H), 6.48–6.58 (m, 1H), 6.75–6.82 (m, 1H), 6.86–6.94 (m, 2H), 7.07–7.20 (m, 4H), 7.23–7.45 (m, 5H), 7.58–7.67 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 23.5, 29.3, 51.9, 54.4, 73.0, 123.5, 127.0, 127.1, 127.5, 128.2, 128.3, 128.7, 129.0, 129.1, 129.6, 130.0, 131.3, 132.7, 136.2, 136.3, 136.8, 143.7. Dr > 20:1 from ^{1}H NMR of crude reaction mixture. IR (neat): 3555 (OH), 2922, 2870, 1602, 1499, 1449, 1330, 1154, 1095, 922, 900, 814 cm^{-1}; HRMS-CI: m/z 544.1925 [(M + Na)$^+$; calculated for $C_{33}H_{31}NO_3SNa$: 544.1922].



***N*-Benzyl-*N*-((2*R*,3*S*)-3-hydroxy-3-(4-methoxyphenyl)-2-phenylpropyl)-4-methylbenzenesulfonamide (3g).**

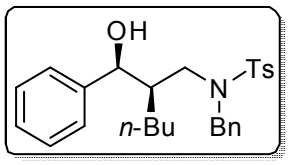
Title compound **3g** was prepared by General Procedure D using **1g** (50 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 45 mg (90% yield) of **3f** as an yellow oil. $[\alpha]_D^{20}$: –45.8 (c = 0.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.62–2.69 (m, 1H), 2.80 (d, J = 4.4 Hz, 1H), 2.99 (dd, J_1 = 14.5 Hz, J_2 = 6.2 Hz, 1H), 3.70 (s, 3H), 3.82 (dd, J_1 = 13.7 Hz, J_2 = 9.5 Hz, 1H), 4.21 (iso(AB)quadruplet, J_{AB} = 14.4 Hz, Δ = 240.0 Hz, 2H), 6.59–6.70 (m, 4H), 6.82–6.90 (m, 2H), 7.04–7.13 (m, 3H), 7.25–7.38 (m, 7H), 7.60–7.67 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.8, 52.0, 52.1, 54.6, 55.4, 72.3, 113.3, 127.1, 127.3, 127.5, 128.2, 128.3, 129.1, 129.6, 130.1, 134.5, 136.1, 136.8, 138.2, 143.8, 158.6. Dr > 20:1 from ^{1}H NMR of crude reaction mixture. IR (neat): 3535 (OH), 2925, 2870, 1599, 1497, 1452, 1330, 1154, 1095, 924, 900, 814 cm^{-1}; HRMS-CI: m/z 524.1871 [$(M + Na)^+$; calculated for $C_{30}H_{31}NO_3SNa$: 524. 1871].



***N*-Benzyl-*N*-((*R*)-2-((*R*)-1-hydroxy-2-methylpropyl)hexyl)-4-methylbenzenesulfonamide (3k).**

Title compound **3k** was prepared by General Procedure C using **1k** (42 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl

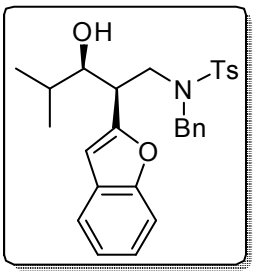
acetate in hexanes) to afford 35 mg (85% yield) of **3k** as an yellow oil. $[\alpha]_D^{20}$: –8.7 (c = 0.07, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.35 (d, J = 6.7 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H), 0.84–0.92 (m, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.04–1.17 (m, 4H), 1.20–1.23 (m, 1H), 2.46 (s, 3H), 2.62–2.67 (m, 1H), 3.25 (dd, J_1 = 9.9 Hz, J_2 = 5.4 Hz, 1H), 3.46 (dd, J_1 = 14.9 Hz, J_2 = 12.1 Hz, 1H), 4.25 (iso(AB)quadruplet, J_{AB} = 14.3 Hz, Δ = 327.0 Hz, 2H), 7.27–7.31 (m, 5H), 7.33–7.37 (m, 2H), 7.71–7.77 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 15.1, 18.8, 20.2, 21.8, 23.2, 24.4, 29.2, 31.1, 36.0, 46.6, 53.5, 76.6, 127.0, 128.4, 128.5, 129.0, 129.6, 136.8, 139.6, 143.9. Dr = 3.2:1 from ^1H NMR of crude reaction mixture. IR (neat): 3530 (OH), 2925, 2870, 1599, 1494, 1453, 1330, 1156, 1094, 925, 900, 814 cm^{-1}; HRMS-CI: m/z 440.2240 $[(M + Na)^+$; calculated for $C_{26}H_{31}NO_3SNa$: 440.2235].



_N_-Benzyl-_N_-((_R_)-2-((_S_)-hydroxy(phenyl)methyl)hexyl)-4-methylbenzenesulfonamide (3l).

Title compound **3l** was prepared by General Procedure D using **1l** (45 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 41 mg (90% yield) of **3l** as an yellow oil. $[\alpha]_D^{20}$: –12.6 (c = 0.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.81 (t, J = 7.2 Hz, 3H), 0.85–0.95 (m, 2H), 1.06–1.20 (m, 4H), 1.23–1.26 (m, 1H), 2.43 (s, 3H), 2.72–2.77 (m, 1H), 3.31 (dd, J_1 = 9.7 Hz, J_2 = 5.2 Hz, 1H), 3.62 (dd, J_1 = 13.8 Hz, J_2 = 11.1 Hz, 1H), 4.36 (iso(AB)quadruplet, J_{AB} = 14.2 Hz, Δ = 195.6 Hz, 2H), 7.22–7.32 (m, 6H), 7.33–7.45 (m,

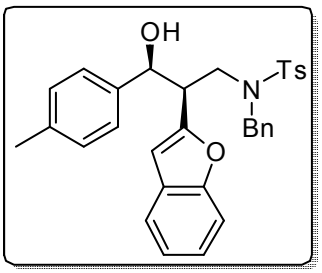
4H), 7.54–7.60 (m, 2H), 7.70–7.75 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 15.2, 21.8, 23.2, 25.0, 29.8, 39.2, 46.3, 53.7, 77.9, 127.0, 127.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.6, 134.5, 136.8, 139.6, 143.9. Dr = 4.1:1 from ^1H NMR of crude reaction mixture. IR (neat): 3542 (OH), 2925, 2870, 1599, 1492, 1453, 1330, 1156, 1094, 925, 900, 815 cm^{-1}; HRMS-CI: m/z 452.2238 [$(M + H)^+$; calculated for $C_{27}H_{34}NO_3S$: 452.2259].



***N*-((2*R*,3*R*)-2-(Benzofuran-2-yl)-3-hydroxy-4-methylpentyl)-*N*-benzyl-4-methylbenzenesulfonamide (3i).**

Title compound **3i** was prepared by General Procedure C using **1i** (48 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 42 mg (88% yield) of **3i** as an yellow oil. $[\alpha]_D^{20}$: –39.0 (c = 0.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 0.50 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 1.29-1.37 (m, 1H), 2.43 (s, 3H), 2.70 (d, J = 7.1 Hz, 1H), 2.95-3.01 (m, 1H), 3.15 (dd, J_1 = 14.3 Hz, J_2 = 5.8 Hz, 1H), 3.38–3.46 (m, 1H), 3.87 (dd, J_1 = 14.0 Hz, J_2 = 9.6 Hz, 1H), 4.27 (iso(AB)quadruplet, J_{AB} = 14.4 Hz, Δ = 222.0 Hz, 2H), 6.43 (s, 1H), 7.13–7.23 (m, 2H), 7.28–7.32 (m, 6H), 7.33–7.47 (m, 1H), 7.41–7.48 (m, 1H), 7.69–7.75 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 19.0, 19.9, 21.8, 30.6, 41.7, 51.2, 54.7, 75.3, 105.4, 111.2, 120.8, 122.8, 123.7, 125.7, 127.4, 128.4, 128.6, 129.0, 130.1, 136.2, 136.5, 143.9, 154.5, 156.2. Dr > 20:1 from ^1H NMR of crude reaction mixture. IR (neat): 3448 (OH), 2925,

2107, 1648, 1495, 1455, 1332, 1254, 1159, 1093, 928, 901, 814 cm^{-1}; HRMS–CI: m/z 500.1848 $[(M + Na)^+$; calculated for $C_{28}H_{31}NO_3SNa$: 500.1871] and 478.2038 $[(M + H)^+$; calculated for $C_{28}H_{32}NO_3S$: 478.2052].



***N*-((2*R*,3*S*)-2-(Benzofuran-2-yl)-3-hydroxy-3-(*p*-tolyl)propyl)-*N*-benzyl-4-methylbenzenesulfonamide (3j).**

Title compound **3j** was prepared by General Procedure D using **1j** (52 mg, 0.1 mmol). The product was purified by column chromatography on deactivated silica gel (10% ethyl acetate in hexanes) to afford 43 mg (82% yield) of **3j** as a white solid (mp = 78.6–83.0 °C). $[\alpha]_D^{20}$: –65.5 (c = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.44 (s, 3H), 2.95–3.02 (m, 1H), 3.19 (dd, J_1 = 13.5 Hz, J_2 = 9.3 Hz, 1H), 4.09 (iso(AB)quadruplet, J_{AB} = 14.7 Hz, Δ = 44.3 Hz, 2H), 4.14 (m, overlapped with AB-quadruplet, 1H), 4.56–4.54 (m, 1H), 4.65–4.72 (m, 1H), 7.15–7.21 (m, 5H), 7.23–7.25 (m, 3H), 7.27–7.34 (m, 6H), 7.54–7.59 (m, 2H), 7.74–7.78 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.7, 23.0, 35.4, 44.1, 54.2, 74.1, 104.8, 111.8, 126.1, 127.3, 127.4, 127.6, 127.9, 128.1, 128.2, 128.4, 128.6, 128.88, 128.93, 129.8, 130.0, 136.1, 136.9, 137.0, 139.6, 143.3, 156.4, 156.6. Dr > 20:1 from ^1H NMR of crude reaction mixture. IR (neat): 3450 (OH), 2924, 2105, 1645, 1495, 1456, 1330, 1254, 1159, 1093, 928, 900, 815 cm^{-1}; HRMS–CI: m/z 548.1877 $[(M + Na)^+$; calculated for $C_{32}H_{31}NO_3SNa$: 548.1871].

3.5. References

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Chapter 4. Enantio- and Diastereoselective Synthesis of PRC200-SS and derivatives

4.1. Introduction

To demonstrate synthetic power of our method to synthesize 1,2-disubstituted-1,3-aminoalcohols via *β*-hydroxy enamines, we decided to apply our new method to synthesis of PRC200-SS and derivatives, which are potent serotonin-norepinephrine-dopamine triple reuptake inhibitors.

4.1.1. 1,3-Aminoalcohols as a common structural motif in SNRI's

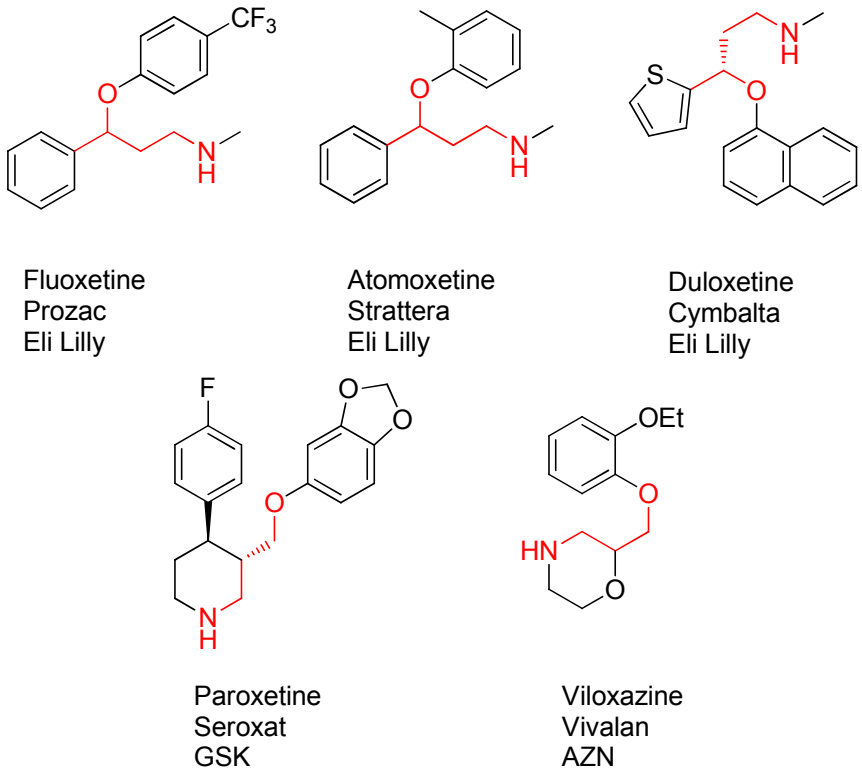
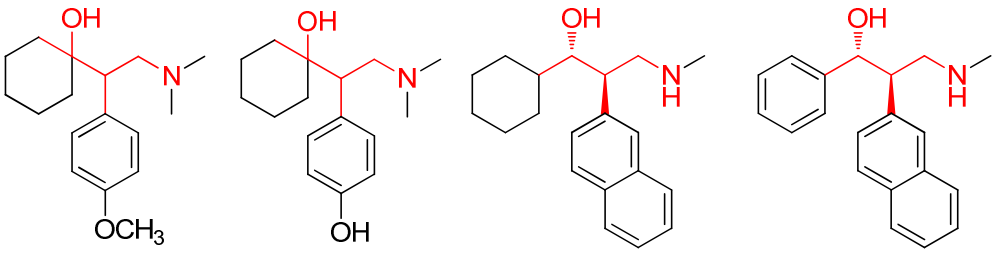


Figure 4-1. 1,3-Aminoalcohols in Commercial Medications

The 1,3-amino alcohol moiety is present in hundreds known biologically active compounds. Several of them are active ingredients of the best-selling commercial medications (Figures 4-1 and 4-2). Most are antidepressants acting as serotonin-norepinephrine reuptake inhibitors (SNRIs).



Venlafaxine	Desvenlafaxine	PRC025	PRC200-SS
Effexor	Pristiq	terminated	pre-clinical trials
Wyeth	Wyeth	Mayo Clinic	Mayo Clinic

Figure 4-2. 1,2-Disubstituted-1,3-aminoalcohols in Commercial Medications and Drug-Candidates

4.1.2. PRC200-SS and derivatives, potent triple reuptake inhibitors

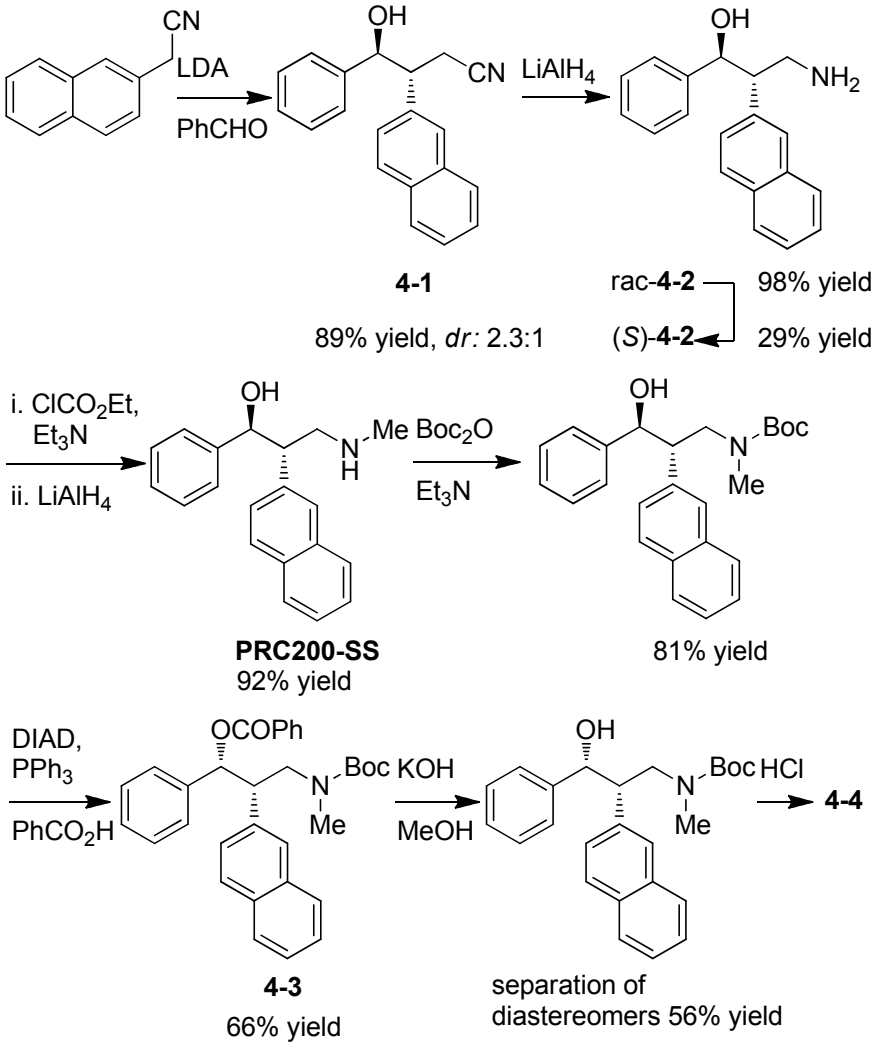
Most antidepressants prescribed at this time target serotonergic and noradrenergic neurotransmission, resulting in enhanced dopamine neurotransmission. Influencing the combination of serotonergic, noradrenergic and dopaminergic neurotransmission (SNDRIs) can result in significant improvement of depressive symptoms. Due to the putative involvement of dopaminergic circuits in depression, triple reuptake inhibitors are

being developed as a new class of antidepressant, which is hypothesized to produce a more rapid onset and better efficacy than current antidepressants selective for serotonin or norepinephrine neurotransmission. There are no approved SNDRIs on the market yet, but several are in development. One family of SNDRIs includes PRC200-SS[1–4] and its derivatives (Figure 4-2).[5]

4.1.3. Original synthesis of PRC200-SS and derivatives

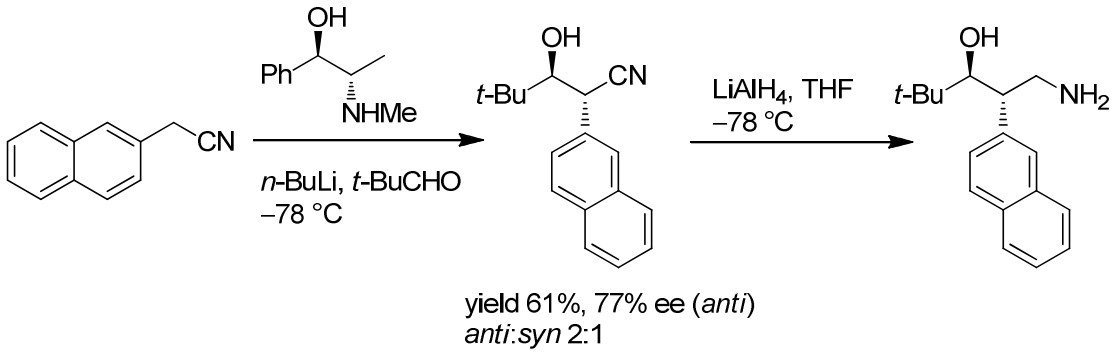
The original synthesis of PRC200-SS and its derivatives was developed and patented Paul R. Carlier (Virginia Tech). It utilizes *anti*-selective aldol reaction of benzylic nitriles with aldehydes (Scheme 4-1).[6,7] First 2-naphtylacetonitrile was deprotonated with LDA and added to benzaldehyde to form *anti*-*β*-hydroxy nitrile **4-1** with low diastereoselectivity (2.3:1). Reduction of the nitrile the afforded the racemic 1,3-aminoalcohol **4-2**. The aminoalcohol was resolved by crystallization with L-tartaric acid. Unfortunately more that 70% of material was lost in this resolution. A two-step monomethylation of the primary amine lead to **PRC200-SS**.[5] To make derivatives of the same configuration the secondary amine was protected and Mitsunobu inversion performed to convert the *R* secondary alcohol configuration to *S*. Due to low diastereoselectivity of the initial aldol reaction, the product contained at least 30% of the undesired diastereomer, diminishing efficiency of all the previous steps (additional amounts of reagents were used for the reactions of the undesired diastereomer). It was not possible to separate the undesired diastereomer in the form of the benzoate **4-3** from

Mitsunobu reaction by column chromatography. The separation was accomplished in the late stage of the synthesis, before the final deprotection of the amine **4-4**.[6] The overall yield of the synthesis was 2.1%.



Scheme 4-1. Carlier's synthesis of PRC200-SS and Derivatives

An asymmetric version of the initial aldol reaction has been developed, utilizing lithium ephedrinate mediated aldol reaction of arylacetonitriles (Scheme 4-2).[8] This method was not applied in the synthesis of PRC200 and derivatives due to poor diastereoselectivity, moderate enantioselectivity and mediocre isolated yield.



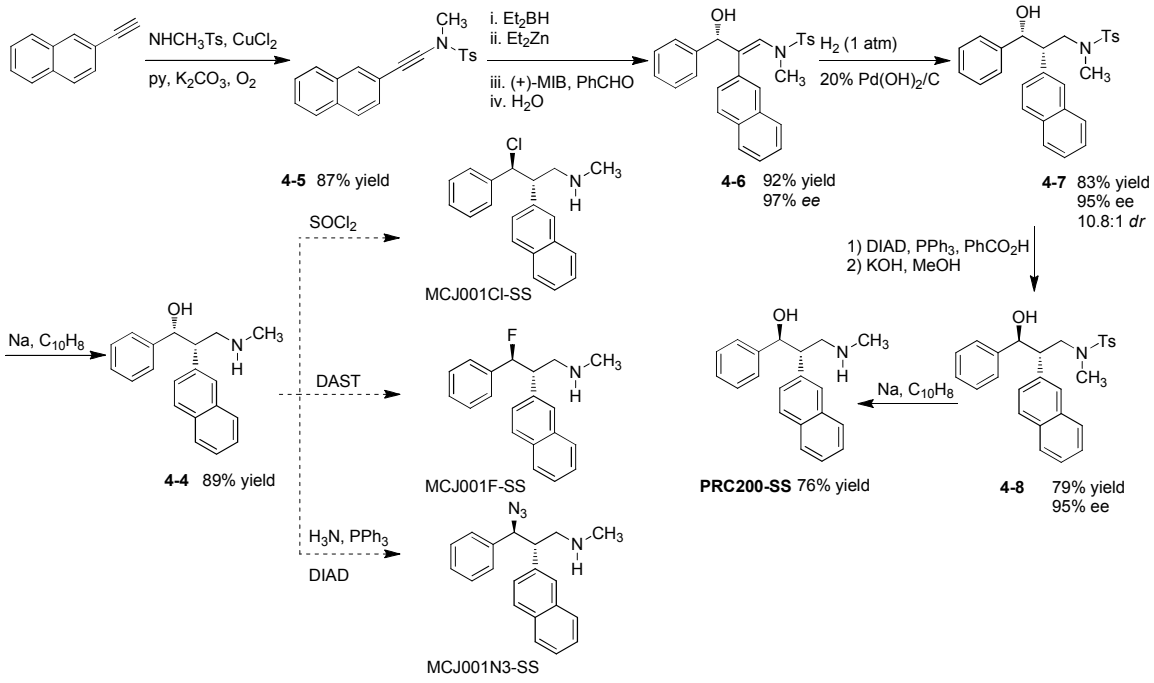
Scheme 4-2. Lithium Ephedrinate Mediated Aldol Reaction of Arylacetonitriles

4.2. Results and Discussion

4.2.1. Enantio- and diastereoselective synthesis of derivatives of PRC200-SS

To demonstrate the utility of our methods, we performed a short formal enantio- and diastereoselective synthesis of derivatives of PRC200-SS.[6] Our synthesis (Scheme 4-3) starts with the copper catalyzed oxidative coupling of commercially available 2-naphtyl acetylene with *N*-methyl toluene sulfonamide, which proceeded in 87% yield. Hydroboration of the resulting 2-naphtyl ynamide **4-5** with diethylborane followed by transmetalation to zinc and (+)-MIB catalyzed enantioselective addition to benzaldehyde

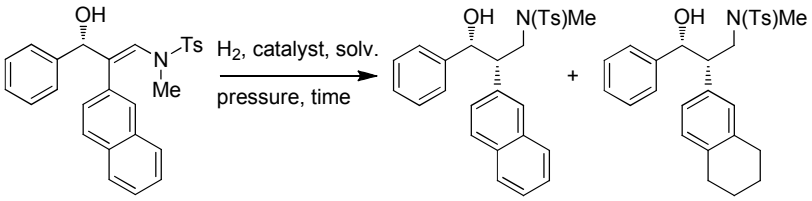
provided *β*-hydroxy enamine **4-6** in high yield (92%) and excellent enantioselectivity (97%). Due to the presence of the *N*-methyl in place the of *N*-benzyl in the examples in Tables 3–1 and 3-2, the hydrogenation of *β*-hydroxy enamine **4-6** under the original conditions (Table 4-1, entry 1) or related conditions (Table 4-1, entries 2 and 3) provided only mediocre diastereoselectivity of **4-7** (2:1). Upon screening additional heterogeneous catalysts, however, it was found that 6 mol % of 20% $Pd(OH)_2/C$ in methanol under 1 atm of hydrogen provided the *syn*-product **4-7** of high diastereoselectivity (dr=10.8:1, ^1H NMR) in 65% yield and with 95% ee (entry 4). When higher hydrogen pressure (entry 5) or higher catalyst loading (entry 6) was applied, partial hydrogenation of 2-naphtyl group



Scheme 4-3. Our Synthesis of PRC200-SS and Derivatives

was observed and **4-7'** was the major product. Structure of **4-7**' was confirmed by X-ray diffraction (see Appendix B). The diastereomers formed in entry 4 were easily separable by column chromatography, allowing isolation of the pure *syn* isomer. Detosylation with sodium naphthalenide afforded **4-4** in 89% yield. Biologically active

Table 4-1. Optimization of Diastereoselective Hydrogenation of *β*-Hydroxy Enamine **6**



4-6 **4-7** **4-7'**

entry	catalyst (mol %)/solvent	pressure (MPa)	time (h)	major product	isolated yield (%)	dr[a]
1	10% Pd/C (10)/AcOEt	8.0	5	**4-7**	48	2:1
2	10% Pd/C (10)/MeOH	0.1	48	**4-7**	64	4:1
3	10% Pd/C (10)/MeOH	8.0	5	**4-7**	83	2:1
4	10% $Pd(OH)_2$/C (10)/MeOH	8.0	8	**4-7'**	78	2:1
5	**10% $Pd(OH)_2$/C (6)/MeOH**	**0.1**	48	**4-7**	**65**	**10.8:1**
6	10% $Pd(OH)_2$/C (20)/MeOH	0.1	48	**4-7'**	68	3:1

[a] Diastereoselectivity determined by ^{1}H NMR analysis of crude reaction mixture.

chloride, fluoride and azide derivatives can be obtained from the common intermediate **4-4**, as shown in Scheme 4-3.[5] Mitsunobu reaction of **4-7** and subsequent hydrolysis afforded **4-8** in 79% yield with 95% ee. After the detosylation **PRC200-SS** was isolated in 76% yield.

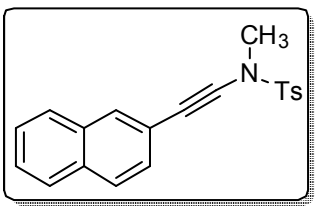
In contrast to the original 9-step synthesis of **4-4** (Scheme 4-1), which involved resolution of racemic intermediate **4-2** and late-stage separation of diastereomers

(Scheme 4-1, step 8), our procedure is highly efficient and both enantio- and diastereoselective, affording **4-4** in four steps from commercially available materials in 46% overall yield. Although the original *anti*-selective nitrile aldol method allows synthesis of PRC200-SS, the absolute configuration of carbinol must be inverted to prepare the bioactive chloride, fluoride and azide derivatives. Our *syn*-selective method opens the door to direct synthesis of PRC200-SS derivatives without the need for a Mitsunobu reaction.

4.3. Conclusions

We have developed the first highly enantio- and diastereoselective synthesis of potent SNDR inhibitors PRC200-SS and derivatives. The overall yield of our synthesis is 46% of common intermediate **4-4**. In contrast, the original synthesis is not enantioselective and gives intermediates of low diastereoselectivity. Furthermore, yield of the Carliers synthesis is only 2.1%.

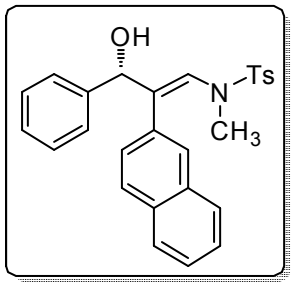
4.4. Experimental Section



_N_,4-Dimethyl-_N_-(naphthalen-2-ylethynyl)benzenesulfonamide (4-5).

Title compound **4-5** was prepared by the method of Stahl and

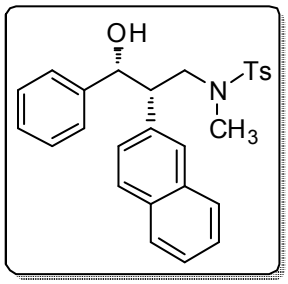
co-workers.[1] In a 500 ml Schlenk flask equipped with a stir-bar, $CuCl_2$ (1.4 mmol, 191 mg), *N*,4-dimethylbenzenesulfonamide (35.5 mmol, 6.58 g) and Na_2CO_3 (14.2 mmol, 1.51 g) were combined. The reaction flask was purged with oxygen gas for 10 minutes. A solution of pyridine (14.2 mmol, 1150 μL) in 36 ml dry toluene was added to the reaction flask via a syringe. A balloon filled with oxygen gas was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated to 70 °C. A solution of 2-naphtylacetylene (7.1 mmol, 1.08 g) in 36.0 ml dry toluene was added to the flask over 5 h by using a syringe pump. After the addition of 2-naphtylacetylene/toluene solution, the reaction mixture was allowed to stir at 70 ºC for another 16 h and then cooled to room temperature. After the crude mixture was concentrated under vacuum, the reaction mixture was purified by column chromatography on silica gel with 5% ethyl acetate in hexanes to yield the ynamide **4-5** (2.07 g, 87% yield) as a a white solid (mp = 117.7–119.3 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H), 2.07 (s, 3H), 7.21–7.30 (m, 2H), 7.30–7.43 (m, 3H), 7.59–7.73 (m, 3H), 7.73–7.84 (m, 3H); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz): δ 21.8, 39.5, 69.7, 84.5, 120.2, 126.6, 126.7, 127.7, 127.9, 128.0, 128.1, 128.4, 130.0, 131.0, 132.7, 133.1, 133.4, 145.0. IR (neat): 2234, 1922, 1625, 1597, 1451, 1365, 1240, 1166, 1090, 982, 939, 861, 816 cm^{-1}; HRMS-CI: m/z 358.0888 [$(M + Na)^+$; calculated for $C_{20}H_{17}NO_2SNa$: 358.0878].



(*S*,*E*)-*N*-(3-Hydroxy-2-(naphthalen-2-yl)-3-phenylprop-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide (4-6).

In a flame dried 25 mL Schlenk flask **4-6** (1.49 mmol, 500 mg) was dissolved in 2 mL dry toluene. Solution of diethylborane (1.45 mL, 1.0 M in toluene, 1.45 mmol) was added dropwise. The resulting solution was stirred at room temperature for 30 min. The reaction flask was then cooled to –78 °C and Et_2Zn (1.49 mL, 2.0 M in toluene, 2.98 mmol) was added and the reaction mixture was stirred for 20 min. (+)-MIB (14.3 mg, 0.06 mmol, 5 mol %) was added followed by dropwise addition of (121 μL, 1.19 mmol) at this temperature. The reaction flask was placed in a –30 °C IPA/dry ice cold bath and allowed to warm to 0 °C over several hours. The solution was stirred at 0 °C until vinyl addition was complete by TLC (typically 12 h). The reaction was then quenched by addition of brine (10 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 50 mL of diethyl ether. The combined organic layers were then washed with 50 mL of water and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 486 mg (92% yield) of **4-6** as a white solid (mp = 129.8–131.2 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 56.2 min, t_r (2) = 71.3 min, $[\alpha]_D^{20}$: +80.2 (c = 0. 3, $CHCl_3$, 97% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.39 (s, 3H), 2.46 (s, 3H), 5.49 (s, 1H), 6.83 (dd, J_1 = 8.5 Hz, J_2 = 1.4 Hz, 1H), 6.91 (s, 1H), 7.02 (s, 1H), 7.21–7.29 (m, 3H), 7.29–7.35

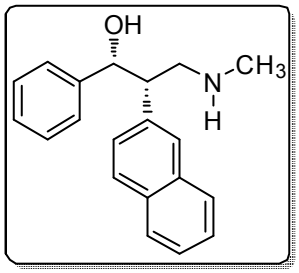
(m, 3H), 7.36–7.41 (m, 2H), 7.51–7.56 (m, 1H), 7.56–7.63 (m, 1H), 7.63–7.67 (m, 2H), 7.67–7.74 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 21.8, 36.6, 77.8, 126.3, 126.7, 127.2, 127.5, 127.56, 127.59, 127.7, 127.8, 128.0, 128.4, 128.7, 130.0, 132.3, 132.7, 132.8, 133.4, 138.9, 141.9, 144.0. IR (neat): 3501 (OH), 3057, 1649, 1597, 1492, 1450, 1347, 1166, 1088, 971, 941, 867, 814 cm^{-1}; HRMS-CI: m/z 466.1452 $[(M + Na)^+$; calculated for $C_{27}H_{25}NO_3SNa$: 466.1453] and 426.1525 $[(M - OH)^+$; calculated for $C_{27}H_{24}NO_2S$: 426.1522].



_N_-((2_S_,3_R_)-3-Hydroxy-2-(naphthalen-2-yl)-3-phenylpropyl)-_N_,4-dimethylbenzenesulfonamide (4-7).

In a 100 mL Schlenk tube was dissolved **4-6** (500 mg, 1.13 mmol) in methanol (10 mL). The space above solution was purged with nitrogen to remove most of the air. 20 wt. % palladium hydroxide on carbon (50 mg, 6 mol %) was added and a balloon with hydrogen was plugged through the rubber septa. Reaction mixture was vigorously stirred until the hydrogenation was complete by TLC (30 h). The palladium catalyst was removed *via* filtration through a plug of Celite. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (10% ethyl acetate in hexanes) to afford 326 mg (65% yield) of **4-7** as a white solid. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 32.7 min, t_r (2) = 44.1 min, $[\alpha]_D^{20}$: +39.6 (c = 0.08, $CHCl_3$, 95% ee). ^1H NMR ($CDCl_3$, 360

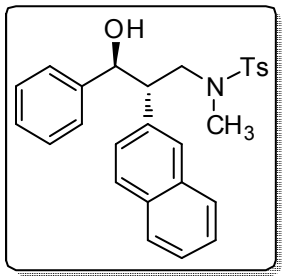
MHz): δ 2.42 (s, 3H), 2.72 (s, 3H), 3.09 (q, J = 6.9 Hz, 1H), 3.32–3.42 (m, 1H), 3.74 (dd, J_1 = 13.4 Hz, J_2 = 8.8 Hz, 1H), 4.29–4.42 (m, 1H), 5.23–5.33 (m, 1H), 7.13–7.27 (m, 6H), 7.30–7.35 (m, 2H), 7.42–7.48 (m, 2H), 7.55–7.62 (m, 2H), 7.71–7.79 (m, 4H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 36.1, 52.3, 52.8, 73.8, 125.9, 126.1, 126.5, 127.5, 127.6, 127.8, 127.9, 128.0, 128.3, 128.7, 129.89, 129.93, 132.8, 133.5, 134.6, 135.5, 142.3, 143.7. Dr = 10.8:1 from ^{1}H NMR of crude reaction mixture. IR (neat): 3523 (OH), 2927, 1598, 1494, 1338, 1160, 1089, 931, 815 cm^{-1}; HRMS-CI: m/z 468.1627 [(M + Na)$^+$; calculated for $C_{27}H_{27}NO_3SNa$: 468.1609].



(1*R*,2*S*)-3-(Methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (4-4).

In a flame dried two-neck round bottom flask was mixed 75 mg of sodium metal, 525 mg of naphthalene and 2.5 mL of dry glyme and let stirred for 2 h. In a flame dried 10 mL Schlenk flask was dissolved **7** (50 mg, 0.11 mmol) in dry glyme (1.0 mL). The solution of sodium naphtalenide was added dropwise until the dark-green color persisted. The reaction was quenched with couple drops of water and concentrated in vacuo. The residue was chromatographed on silica gel with 1 to 5% methanol in dichloromethane to afford 28 mg (89% yield) of **4-4** as a white solid (mp = 180.4–184.2 °C). $[\alpha]_D^{20}$: –66.9 (c = 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.53 (s, 3H), 3.16 (dd, J_1 = 12.1 Hz, J_2 = 3.0 Hz, 1H), 3.37 (td, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 1H), 3.49–3.55 (m, 1H), 5.14 (d, J = 8.6 Hz, 1H), 7.06–7.09 (m, 1H), 7.09–

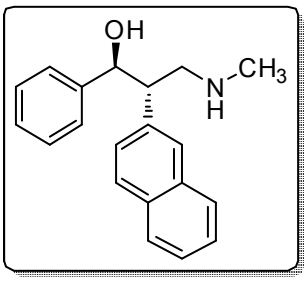
7.13 (m, 2H), 7.14–7.17 (m, 2H), 7.17–7.21 (m, 1H), 7.29–7.36 (m, 2H), 7.61–7.66 (m, 1H), 7.67–7.70 (m, 1H), 7.71–7.76 (m, 2H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 35.6, 47.1, 51.1, 80.5, 125.9, 126.2, 126.3, 126.6, 127.0, 127.2, 127.5, 127.8, 127.9, 128.2, 128.3, 129.2, 132.6, 133.6, 137.3, 143.3. IR (neat): 3354 (OH), 2925, 2774, 1585, 1450, 1388, 1348, 1093, 1060, 913, 813 cm^{-1}; HRMS-CI: m/z 292.1798 $[(M + H)^+$; calculated for $C_{20}H_{22}NO$: 292.1701].



_N_-((2S,3S)-3-Hydroxy-2-(naphthalen-2-yl)-3-phenylpropyl)-N,4-dimethylbenzenesulfonamide (4-8).

In a dry 10 mL Schlenk flask **4-7** (0.14 mmol, 50 mg), triphenyl phosphine (0.16 mmol, 42 mg) and benzoic acid (0.16 mmol, 20 mg) were dissolved in 1 mL dry THF. DIAD (0.16 mmol, 30 μL) was added dropwise. The resulting solution was stirred at room temperature for 48 h. The reaction was quenched with 5 mL aqueous $NaHCO_3$. The organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were then washed with 20 mL of water and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 67 mg (88% yield) of benzoate. 67 mg of benzoate and 150 mg of KOH were dissolved in 1 mL methanol and the reaction mixture was stirred for 15 h. The organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were

then washed with 20 mL of water and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 67 mg (88% yield) of benzoate. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r (1) = 48.9 min, t_r (2) = 56.3 min, $[\alpha]_D^{20}$: –1.8 (c = 0. 53, $CHCl_3$, 95% ee). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.39 (s, 3H), 2.44 (s, 3H), 3.43–3.51 (m, 1H), 3.53–3.69 (m, 2H), 5.09 (dd, J_1 = 7.1 Hz, J_2 = 3.9 Hz, 1H), 7.14–7.25 (m, 5H), 7.27–7.36 (m, 3H), 7.39–7.49 (m, 2H), 7.50–7.60 (m, 3H), 7.68–7.80 (m, 3H); ^{13}C{1H} NMR ($CDCl_3$, 90 MHz): δ 21.7, 36.4, 52.1, 52.5, 76.7, 125.9, 126.2, 126.7, 127.0, 127.5, 127.7, 128.1, 128.2, 128.4, 129.8, 130.0, 132.7, 133.5, 134.3, 137.1, 142.3, 143.6. IR (neat): 3501 (OH), 3057, 1649, 1597, 1492, 1450, 1347, 1166, 1088, 971, 941, 867, 814 cm^{-1}; HRMS-CI: m/z 468.1619 [$(M + Na)^+$; calculated for $C_{27}H_{27}NO_3SNa$: 468.1609].



(1S,2S)-3-(Methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS).

In a flame dried two-neck round bottom flask was mixed 75 mg of sodium metal, 525 mg of naphthalene and 2.5 mL of dry glyme and let stirred for 2 h. In a flame dried 10 mL Schlenk flask was dissolved **4-8** (50 mg, 0.11 mmol) in dry glyme (1.0 mL). The solution of sodium naphtalenide was added dropwise until the dark-green color persisted. The reaction was quenched with couple drops of water and concentrated in vacuo. The residue was chromatographed on silica gel

with 1 to 5% methanol in dichloromethane to afford 24 mg (76% yield) of **PRC200-SS** as a white solid. $[\alpha]_D^{20}$: –4.28 (c = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 360 MHz): δ 2.64 (s, 3H), 3.08–3.14 (m, 1H), 3.23–3.28 (m, 1H), 3.56–3.61 (m, 1H), 5.16 (d, J = 5.8 Hz, 1H), 7.08–7.16 (m, 5H), 7.22–7.25 (m, 2H), 7.43–7.48 (m, 2H), 7.71–7.76 (m, 3H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 90 MHz): δ 36.1, 51.5, 53.2, 80.2, 126.0, 126.2, 126.5, 127.0, 127.5, 127.8, 128.1, 128.3, 128.5, 129.2, 129.9, 132.8, 133.4, 134.2, 141.8. IR (neat): 3354 (OH), 2925, 2774, 1585, 1450, 1388, 1348, 1093, 1060, 913, 813 cm^{-1}; HRMS-CI: m/z 292.1764 [$(M + H)^+$; calculated for $C_{20}H_{22}NO$: 292.1701].

4.5. References

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Chapter 5. A Simple One-Pot Synthesis of Enals and Derivatives

5.1. Introduction

5.1.1. Enals in organic syntheses

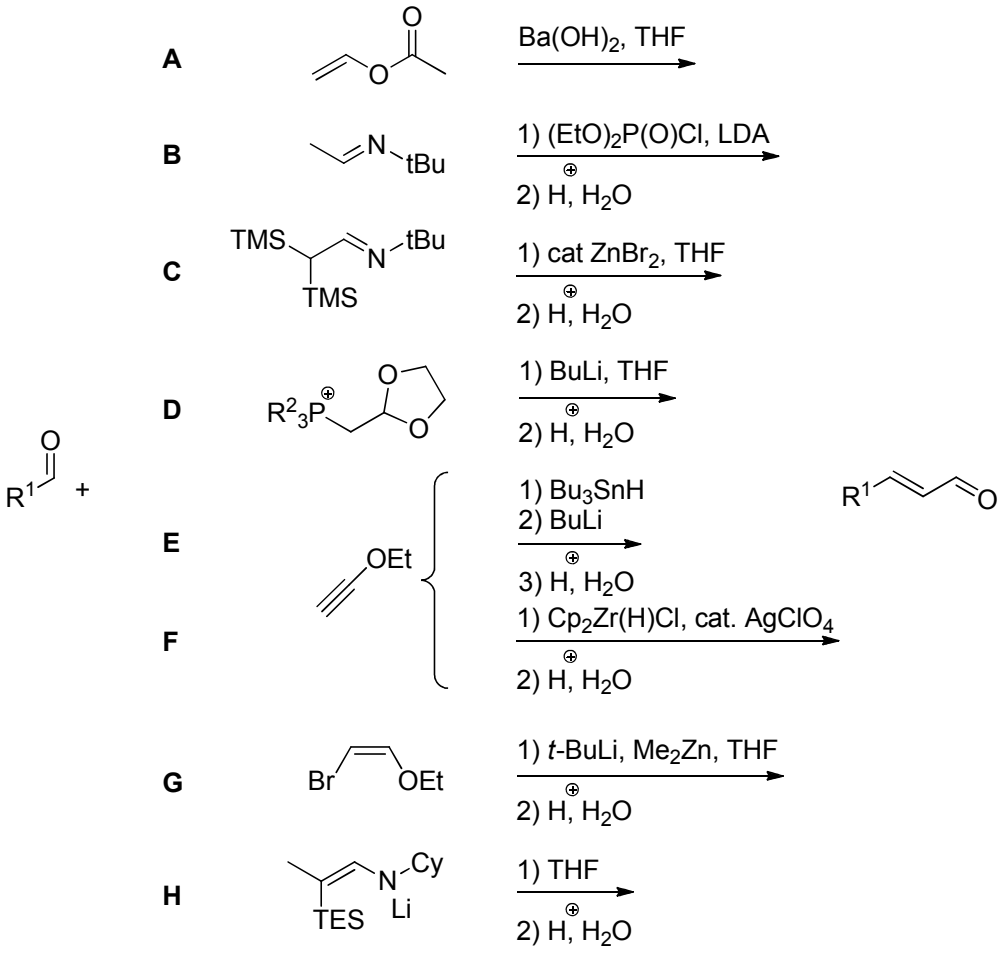
The field of organocatalysis has witnessed explosive growth in the last decade and will continue to be a dynamic area of chemical research.[1–5] A wide variety of organocatalysts and reaction classes have been recently advanced, and many of these are based on α,β-unsaturated aldehydes as substrates. As a result, enals have arguably become the single most important class of substrates for development and applications of organocatalytic transformations[6–13] while remaining a mainstay of metal-based catalytic asymmetric processes.

5.1.2. Current syntheses of enals with their pros and cons

A practical synthesis of enals would meet the following criteria: it must be general, employ commercially available and inexpensive reagents, use common laboratory techniques, be functional group compatible, and be tolerant of α-stereogenic centers in enantioenriched aldehyde and ketone substrates. Furthermore, the transformation should be amenable to a one-pot procedure to enable rapid generation of an array of enals.

Existing methods for conversion of aldehydes and ketones to enals do not satisfythese criteria (Scheme 5-1). For example, cross aldol reactions with acetaldehyde

enolates are not general, yielding self-condensation products with aliphatic aldehyde partners (Scheme 5-1, **A**).[14] This difficulty can be circumvented with *C*-silated imines (**B** and **C**),[15, 16] but these imines must be prepared, silylated, and distilled, adding additional steps.Wittig,[17–23] Horner-Emmons,[24–26] and Peterson-type reagents[27,28] are generally not



Scheme 5-1. Existing Syntheses of Enals

compatible with base-sensitive functional groups and/or can require additional synthetic steps to generate enals (**D**). Methods employing commercially available ethoxy acetylene are most attractive (Scheme 1, **E** and **F**). Hydrostannylation of ethoxy acetylene provides

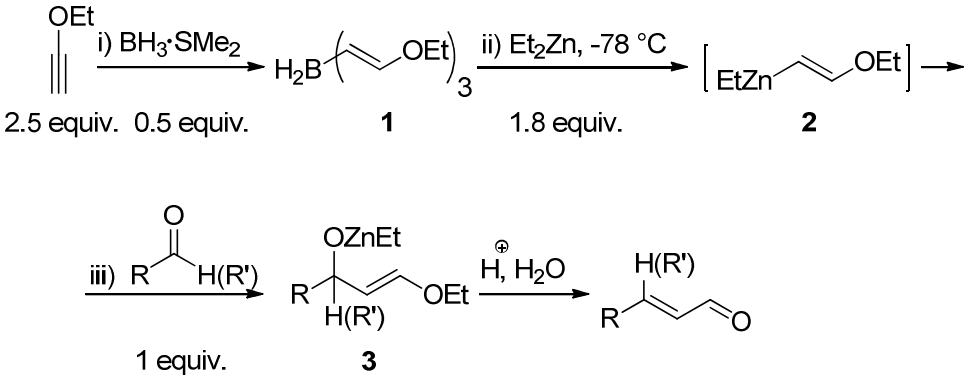
a vinylstannane. Transmetallation with *n*-BuLi leads to a highly reactive vinyllithium that readily adds to aldehydes and ketones to afford enals on acidic workup.[29] The drawback of such methods is the incompatibility of the vinyllithium with most functional groups. Suzuki introduced a method that combines the two-steps above into one and circumvents the highly reactive vinyllithium intermediate in **E**.[30, 31] Thus, hydrozirconation of ethoxy acetylene, in situ transmetallation of the vinylzirconocene intermediate with catalytic $AgClO_4$, addition to aldehydes and elimination provides enals (**F**). Although this method has advantages over those outlined above, it is not economically viable because Schwartz's reagent is prohibitively expensive (>$2,000/mol from Aldrich). *Z*-Ethoxyvinyl bromide is not commercially available and the excess *t*-BuLi is not compatible with base-sensitive functional groups (**G**). The Peterson olefination with lithium amide (**H**) similarly uses harsh reagents.

5.2. Results and Discussion

5.2.1. A one-pot synthesis of enals from aldehydes

Our approach to *α,β*-unsaturated aldehydes involves hydroboration of ethoxy acetylene with BH_3•SMe_2 to generate the tris(vinyl) borane **1** (Scheme 5-2). This intermediate can be prepared on scale and stored for months under a nitrogen atmosphere or used directly in situ. Transmetallation from boron to zinc at –78 °C and addition to

aldehydes or ketones affords zinc alkoxy enol ethers,12 which readily undergo elimination on workup with 2M HCl.

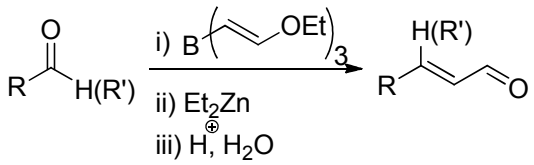


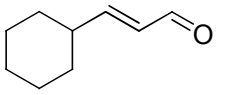
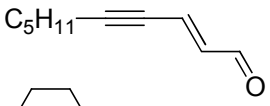
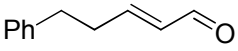
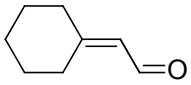
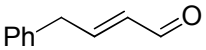
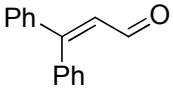
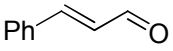
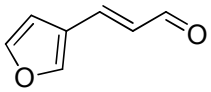
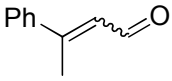
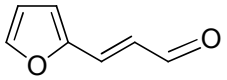
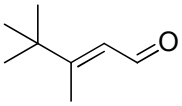
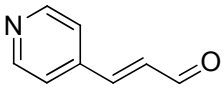
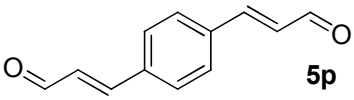
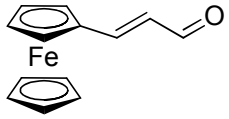
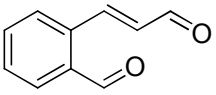
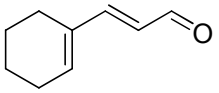
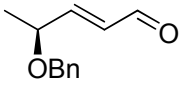
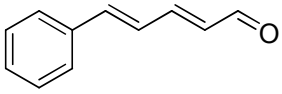
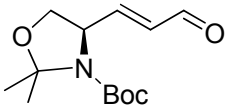
Scheme 5-2. Our One-Pot Synthesis of Enals

5.2.2. Substrate scope of synthesis of enals

The broad substrate scope of this tandem reaction is illustrated in Table 5-1. Aliphatic (entries 1–3), aromatic (entries 4 and 8), and heteroaromatic aldehydes (entries 5–7) and conjugated enals (entries 9 and 10) and ynals (entry 11) undergo homologation to afford enals with 72–96% yield. Particularly noteworthy is the successful conversion of phenyl acetaldehyde to the expected enal in 89% yield, despite the acidic nature of its α-hydrogens (entry 3). Ketone substrates were more challenging and exhibited variable results. Cyclohexanone (entry 12) was an excellent substrate and furnished the enal in 86% yield. Given the low reactivity of benzophenone and the mild nature of organozinc reagents,[32] we were surprised to isolate 54% yield of the enal (entry 13). Unsymmetrical

Table 5-1. Substrate Scope of Two-carbon Homologation of Aldehydes and Ketones



Entry	Product		Yield (%)[a]	Entry	Product		Yield (%)[a]
1		**5a**	94	11		**5k**	87
2		**5b**	94	12		**5l**	86
3		**5c**	89	13		**5m**	54
4		**5d**	96				
5		**5e**	92	14		**5n**	83[b]
6		**5f**	91	15		**5o**	53[c]
7		**5g**	72	16		**5p**	70
8		**5h**	93	17		**5q**	54[e]
9		**5i**	95	18		**5r**	88 (98%$_{ee}$)[d]
10		**5j**	95	19		**5s**	94 (98%$_{ee}$)[d]

[a] Isolated yield. [b] *E*/*Z* ratio 3:1 (^{1}H NMR). [c] *E*/*Z* ratio >15:1 (^{1}H NMR).
[d] *ee* determined by HPLC.

ketones, such as acetophenone (entry 14), gave little *E*:*Z* selectivity (3:1) unless the two groups flanking the carbonyl were significantly different in size, such as *tert*-butyl vs. methyl (*E*:*Z*=15:1, 53% yield, entry 15). To examine the selectivity of the vinylzinc intermediate toward aldehydes vs. ketones, a 1:1 mixture of cyclohexane carboxaldehyde and cyclohexanone were subjected to one equivalent ethoxy vinylzinc reagent. The more reactive aldehyde was converted to the enal product and the ketone was left untouched.

In the case of *p*-phthalaldehyde the di(enal) was isolated in 70% yield (entry 16). The *o*-derivative (entry 17), however, furnished the monoenal in 54% yield, most likely because the second aldehyde forms an internal hemiacetal derivative after the first addition, preventing further reaction (Figure 5-1).

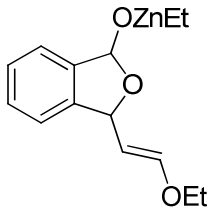


Figure 5-1. Internal Hemiacetal Formed During Homologation of *o*-Phthalaldehyde

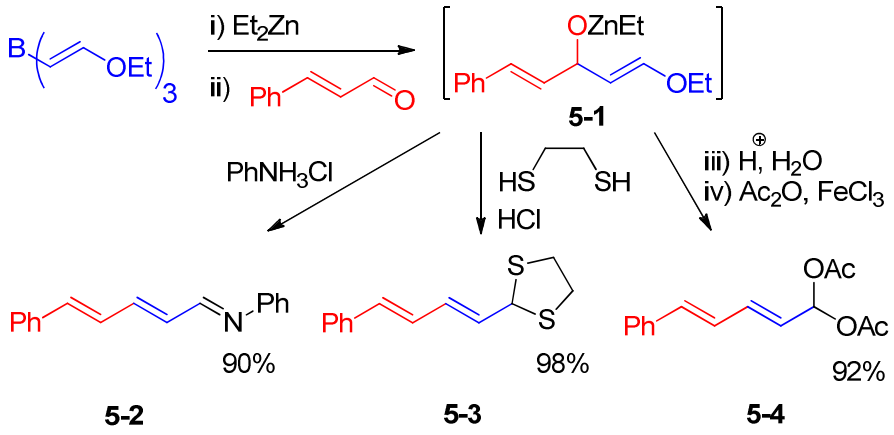
Enantioenriched aldehydes are important starting materials and intermediates in synthesis. We therefore examined two optically active aldehyde substrates each with a stereocenter flanking the carbonyl. Benzyl protected 2-hydroxy propanal and Garner's aldehyde were converted to enals in 88 and 94% yield, respectively (entries 18 and 19).

Both enals had >98% *ee* after isolation and purification, indicating the organozinc intermediate in this process is indeed mild.

In the development of practical and useful methods, scalability must be demonstrated. The homologation of cyclohexenecarboxaldehyde was therefore performed on a 10 mmol scale, affording the dienal in 95% yield (entry 9).

5.2.3. One-pot syntheses of derivatives of enals

Although enals are very important synthetic intermediates, derivatized enals are often desired. Under the assumption that the mechanism of conversion of hydroxy enol ethers to enals proceeds via oxocarbenium ions, we rationalized that these intermediates could be trapped by other nucleophiles.



Scheme 5-3. One-Pot Synthesis of Derivatized Enals

Thus, after addition of cinnamaldehyde to the vinylzinc reagent to generate the alkoxide **5-1**, 3 equivalents of anilinium hydrochloride were added leading to the imine **5-2** in 90% isolated yield (Scheme 5-3).. Likewise, trapping **5-1** with 2 equivalents 1,2-dithioglycol afforded the unsaturated 1,3-dithiolane **5-3** in 98% yield. Unsaturated 1,1-diacetates are useful intermediated in palladium allylation chemistry.[33] The diacetate **5-4** was isolated in 92% yield after treatment of the alkoxide intermediate with aqueous HCl, removal of the volatile materials under reduced pressure and addition of 7 equivalents acetic anhydride and catalytic $FeCl_3$ (5 mol %).

5.3. Conclusions

In summary, we have developed a simple and efficient one-pot procedure that enables rapid access to α,β-unsaturated aldehydes from aldehydes and ketones. The advantages of this method include its extensive substrate scope, functional group compatibility, tolerance of stereocenters alpha to carbonyl groups, and low cost. The method can also be employed in the one-pot synthesis of synthetically valuable unsaturated aldimines, dithiolanes, and 1,1-diacetates. We anticipate this method will facilitate advances in organocatalysis with enal substrates.

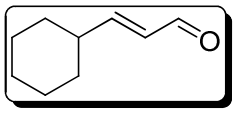
5.4. Experimental Section

General Procedure A. An oven-dried 25 mL Schlenk flask that had been thoroughly purged with N_2 was charged with an ethoxy acetylene solution (2.5 equiv., 1.7 mL 40% wt in hexanes, 7.1 mmol) and 1 mL THF and was cooled to 0 °C. Borane dimethylsulfide (0.5 equiv., 140 μL, 1.42 mmol) was dissolved in 1 mL of THF under nitrogen and the resulting solution was added over 30 min with the aid of a syringe pump to the stirred solution of ethoxy acetylene at 0 °C. The reaction mixture was warmed to 20 °C, stirred for 12 h and heated to 60 °C for 1 h. After cooling the reaction mixture to 20 °C, the volatile materials were removed under reduced pressure. The Schlenk flask was put under a nitrogen atmosphere and the brown residue was dissolved in 4.8 mL toluene. The resulting 0.28 molar solution can be stored in a refrigerator and used as a stock solution of tris(ethoxyvinyl)borane for General Procedure B. In General Procedure A the stirred solution was cooled to –78 °C in a dry ice/acetone bath and diethylzinc (1.8 equiv., 2.5 mL of a 2 M solution in toluene, 5 mmol) was added. After 20 min of stirring at –78 °C, cyclohexanecarboxaldehyde (1 equiv., 319 μL, 2.84 mmol) was added. The mixture was allowed to warm to 20 °C over 2 h and stirred for an additional 12 h. After the aldehyde had been consumed (by TLC analysis), the reaction mixture was cooled to 0 °C, diluted with 5 mL of diethyl ether and carefully quenched with 5 mL of brine. The zinc salts precipitated out of the solution over 5 min as a white solid. After 5 min of vigorous stirring, 2 M aqueous HCl was added dropwise until all solids dissolved and the pH of the aqueous phase was lower than 4. The reaction mixture was stirred for another 10 min,

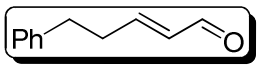
until the elimination reaction was complete (by TLC analysis). The layers were separated and the aqueous layer was extracted 3 × 20 mL of diethyl ether. The combined organic layer was washed with saturated sodium bicarbonate, dried over $MgSO_4$, filtered and the volatile materials were removed under reduced pressure. For acid sensitive aldehydes (**5s**), the aqueous layer was neutralized with saturated sodium bicarbonate before extraction.

General Procedure B. A stirred solution of tris(ethoxyvinyl)borane (0.5 equiv., 5 mL of a 0.28 M solution in toluene, 1.42 mmol) prepared with General Procedure A was cooled to –78 °C in a dry ice/acetone bath and diethylzinc (1.8 equiv., 2.5 mL of a 2 M solution in toluene, 5 mmol) was added. After 20 min of stirring at –78 °C, cyclohexanecarboxaldehyde (1 equiv., 319 μL, 2.84 mmol) was added. The mixture was allowed to warm to 20 °C over 2 h and stirred for an additional 12 h. After the aldehyde had been consumed (by TLC analysis), the reaction mixture was cooled to 0 °C, diluted with 5 mL of diethyl ether and carefully quenched with 5 mL of brine. The zinc salts precipitated out of the solution over 5 min as a white solid. After 5 min of vigorous stirring, 2 M aqueous HCl was added dropwise until all solids dissolved and the pH of aqueous phase was lower than 4. The reaction mixture was stirred for another 10 min, until the elimination reaction was complete (by TLC analysis). The layers were separated and the aqueous layer was extracted 3 × 20 mL of diethyl ether. The combined organic layer was washed with saturated sodium bicarbonate, dried over $MgSO_4$, filtered and the volatile materials were removed under reduced pressure. For acid sensitive aldehydes

(**5e**, **5f** and **5s**), the aqueous layer was neutralized with saturated sodium bicarbonate before extraction. For aldehyde **5g**, the aqueous layer was neutralized with aqueous 4 M NaOH. The crude products were purified by column chromatography on silica gel.

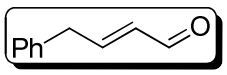


(*E*)-3-Cyclohexylacrylaldehyde (5a). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and cyclohexanecarboxaldehyde (69 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and cyclohexanecarboxaldehyde (69 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5a** (71 mg, 92% yield for General Procedure A and 73 mg, 94% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[34]

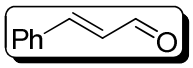


(*E*)-5-Phenylpent-2-enal (5b). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and dihydrocinnamaldehyde (75 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and dihydrocinnamaldehyde

(75 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5b** (84 mg, 93% yield for General Procedure A and 85 mg, 94% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[35]

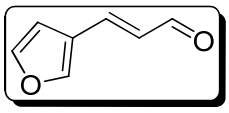


(*E*)-4-Phenylbut-2-enal (5c). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and phenylacetaldehyde (66 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and phenylacetaldehyde (66 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5c** (76 mg, 91% yield for General Procedure A and 74 mg, 89% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[36]

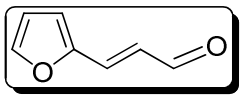


Cinnamaldehyde (5d). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and benzaldehyde (58 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc

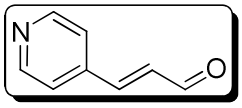
(0.5 mL, 2 M in toluene, 1 mmol) and benzaldehyde (58 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 97/3) to give **5d** (72 mg, 96% yield for General Procedure A and 72 mg, 96% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[37]



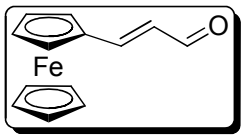
(*E*)-3-(Furan-3-yl)acrylaldehyde (5e). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and 3-furancarboxaldehyde (49 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5e** (64 mg, 92% yield) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[38]



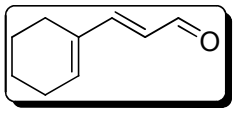
(*E*)-3-(Furan-2-yl)acrylaldehyde (5f). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and 2-furancarboxaldehyde (49 μL, 0.57 mmol) were. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5f** (63 mg, 91% yield) as an yellow solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[39]



(E)-3-(Pyridin-4-yl)acrylaldehyde (5g). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and 4-pyridincarboxaldehyde (54 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/IPA : 80/20) to give **5g** (47 mg, 72% yield) as a yellow solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[40]

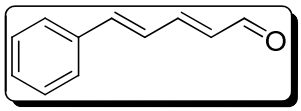


3-Ferrocenylacrolein (5h). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and ferrocenecarboxaldehyde (122 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5h** (127 mg, 93% yield) as a red solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[41]

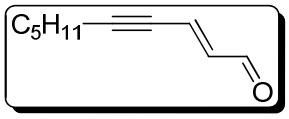


(*E*)-3-Cyclohexenylacrylaldehyde (5i). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and cyclohexenecarboxaldehyde (65 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and cyclohexenecarboxaldehyde (65 μL, 0.57 mmol) were used. The crude product was

purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5i** (73 mg, 95% yield for General Procedure A and 72 mg, 94% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[42]

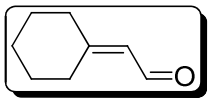


(2*E*,4*E*)-5-Phenylpenta-2,4-dienal (5j). Both General Procedure A and B were applied. In General Procedure A borane dimethylsulfide (28 μL, 0.28 mmol), ethoxy acetylene (340 μL, 40% wt solution in hexanes, 1.42 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and cinnamaldehyde (72 μL, 0.57 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and cinnamaldehyde (72 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5j** (85 mg, 95% yield for General Procedure A and 85 mg, 95% yield for General Procedure B) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[43]

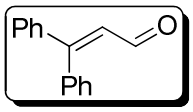


(*E*)-Dec-2-en-4-ynal (5k). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and 2-octynal (81 μL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel

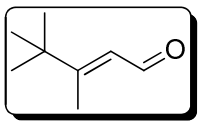
(hexanes/EtOAc : 95/5) to give **5k** (74 mg, 87% yield) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[44]



2-Cyclohexylideneacetaldehyde (5l). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and cyclohexanone (59 µL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5l** (60 mg, 86% yield) as an oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[45]

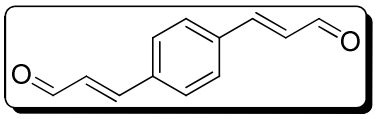


3,3-Diphenylacrylaldehyde (5m). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and benzophenone (106 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5m** (64 mg, 54% yield) as a white solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[46]

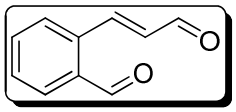


(*E*)-3,4,4-Trimethylpent-2-enal (5o). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and 3,3-dimethyl-2-butanone (71 µL, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5o** (38 mg, 53% yield) as an

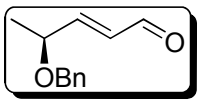
oil. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[47]



l,4-Benzenedipropenal (5p). General Procedure B was applied. Tris(ethoxyvinyl)borane (2 mL, 0.28 M solution in toluene, 0.56 mmol), diethylzinc (1.0 mL, 2 M in toluene, 2 mmol) and terephthaldialdehyde (76 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5p** (74 mg, 70% yield) as a white solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[48]

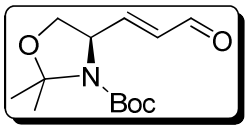


(*E*)-2-(3-Oxoprop-1-enyl)benzaldehyde (5q). General Procedure B was applied. Tris(ethoxyvinyl)borane (2 mL, 0.28 M solution in toluene, 0.56 mmol), diethylzinc (1.0 mL, 2 M in toluene, 2 mmol) and phthaldialdehyde (76 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5q** (49 mg, 54% yield) as a white solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra are identical to those previously reported in the literature.[20]



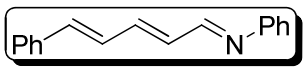
(*S*,*E*)-4-(Benzyloxy)pent-2-enal (5r). General Procedure B was applied. Tris(ethoxyvinyl)borane (1 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M in toluene, 1 mmol) and (*S*)-2-(benzyloxy)propanal

(93 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5r** (136 mg, 94% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes : 2-propanol = 95 : 5, flow rate = 0.5 mL/min), t_r (1) = 20.6 min, t_r (2) = 24.2 min. The ^{1}H and ^{13}C{^{1}H} NMR spectra are identical to those previously reported in the literature.[49]



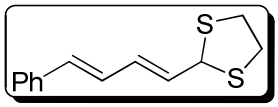
(*R*,*E*)-*tert*-Butyl 2,2-dimethyl-4-(3-oxoprop-1-enyl)oxazolidine-3-carboxylate (5s). Both General Procedure A and B were applied. In General Procedure A ethoxy acetylene (170 µL 40% wt solution in hexanes, 0.71 mmol), borane dimethylsulfide (14 µL, 0.142 mmol), diethylzinc (0.25 mL, 2 M solution in toluene, 0.5 mmol) and (*S*)-*tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (60 mg, 0.26 mmol) were used. In General Procedure B tris(ethoxyvinyl)borane (1.0 mL, 0.28 M solution in toluene, 0.28 mmol), diethylzinc (0.5 mL, 2 M solution in toluene, 1 mmol) and (*S*)-*tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (131 mg, 0.57 mmol) were used. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **5s** (131 mg, 90% yield for General Procedure A and 137 mg, 94% yield for General Procedure B) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes : 2-propanol = 95 : 5, flow rate = 0.5 mL/min), t_r (1) = 16.8 min, t_r (2) = 19.7 min. The ^{1}H and ^{13}C{^{1}H} NMR spectra are identical to those previously reported in the literature.[50]

Synthesis of Enal Derivatives



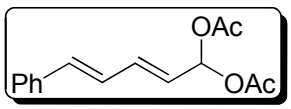
(*E*)-*N*-((2*E*,4*E*)-5-Phenylpenta-2,4-dienylidene)aniline (5-2). An oven dried 25 mL Schlenk flask that had been thoroughly purged with N_2 was charged with an ethoxy acetylene solution (2.5 equiv., 340 μL, 40% wt solution in hexanes, 1.42 mmol) and 1 mL THF and was cooled to 0 °C. Borane dimethylsulfide (0.5 equiv., 28 μL, 0.28 mmol) was dissolved in 1 mL of THF under nitrogen and the resulting solution was added over 30 min with the aid of a syringe pump to the stirred solution of ethoxy acetylene at 0 °C. The reaction mixture was warmed to 20 °C for 12 h and heated to 60 °C for 1 h. After cooling the reaction mixture to 20 °C, the volatile materials were removed under reduced pressure. The Schlenk flask was put under a nitrogen atmosphere again and the brown residue was dissolved in 2 mL toluene. The stirred solution was cooled to –78 °C in a dry ice/acetone bath and diethylzinc (1.8 equiv., 0.5 mL, 2 M solution in toluene, 1 mmol) was added. After 20 min stirring at –78 °C, cinnamaldehyde (1 equiv., 72 μL, 0.57 mmol) was added. The mixture was allowed to warm to 20 °C over 2 h and stirred for an additional 12 h. After the aldehyde had been consumed (by TLC analysis), the solution was cooled to 0 °C and anhydrous solid aniline hydrochloride (3 equiv., 500 mg, 1.71 mmol) and 2 mL of toluene were added. The red suspension was stirred for 20 min at 0 °C. After the reaction was complete (by TLC analysis), it was diluted with 5 mL of diethyl ether, filtered and solid materials were washed with 10 mL of hexanes. The filtrate was washed with 20 mL of saturated aqueous sodium bicarbonate and the aqueous phase was washed with 20 mL

of diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on basic alumina (hexanes/EtOAc : 95/5) to give **5-2** (119 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 6.60-6.70 (m, 1H), 6.77-6.87 (m, 1H), 6.92-7.02 (m, 2H), 7.10-7.18 (m, 2H), 7.18-7.22 (m, 1H), 7.26-7.30 (m, 1H), 7.31-7.40 (m, 4H), 7.43-7.50 (m, 2H), 8.17 (d, 9.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 90.6 MHz): δ 126.27, 126.30, 127.26, 127.90, 128.94, 129.02, 129.37, 132.47, 135.26, 136.64, 138.14, 144.18, 161.60 ppm; IR (neat): 3026, 1677, 1611, 1597, 1577, 1494, 1447, 994, 693, 763, 748 cm^{-1}; HRMS calcd for $C_{17}H_{15}N$ $(M+H)^+$: 234.1279, found 234.1259.



2-((1*E*,3*E*)-4-Phenylbuta-1,3-dienyl)-1,3-dithiolane (5-3). An oven dried 25 mL Schlenk flask that had been thoroughly purged with N_2 was charged with an ethoxy acetylene solution (2.5 equiv., 340 μL, 40% wt solution in hexanes, 1.42 mmol) and 1 mL THF was and cooled to 0 °C. Borane dimethylsulfide (0.5 equiv., 28 μL, 0.28 mmol) was dissolved in 1 mL of THF under nitrogen and the resulting solution was added over 30 min with the aid of a syringe pump to the stirred solution of ethoxy acetylene at 0 °C. The reaction was warmed to 20 °C, stirred for an additional 12 h and heated to 60 °C for 1 h. After cooling the reaction mixture to 20 °C, the volatile materials were removed under reduced pressure. The Schlenk flask was put under a nitrogen atmosphere and the brown residue was dissolved in 2 mL toluene. The stirred solution was cooled to –78 °C in a dry ice/acetone bath and diethylzinc (1.8 equiv., 0.5 mL, 2 M solution in toluene, 1 mmol) was added. After 20

min of stirring at –78 °C, cinnamaldehyde (1 equiv., 72 μL, 0.57 mmol) was added. The mixture was allowed to warm to 20 °C over 2 h and stirred for an additional 12 h. After the aldehyde had been consumed (by TLC analysis), the solution was cooled to 0 °C. Under nitrogen a solution of 1,2-ethanedithiol (2.0 equiv., 100 μL, 1.14 mmol) dissolved in 1M HCl in diethyl ether (3 equiv., 1.7 mL, 1.7 mmol) was added to the reaction mixture over 30 min with the aid of a syringe pump. The reaction mixture was stirred for 5 min. After the vinyl ether had been consumed (by TLC analysis) the reaction mixture was diluted with 20 mL of diethyl ether and washed with 20 mL of saturated aqueous sodium bicarbonate. The aqueous phase was then washed with 20 mL of diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 98/2) to give **5-3** (131 mg, 98% yield) as an oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.23-3.41 (m, 4H), 5.15 (d, J = 8.8 Hz, 1H), 5.82 (dd, J = 15.0, 9.1 Hz, 1H), 6.31 (dd, J = 14.8, 10.5 Hz, 1H), 6.48-6.62 (m, 1H), 6.71 (dd, J = 15.0, 10.5 Hz, 1H), 7.17-7.43 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 90.6 MHz): δ 39.54, 54.19, 126.39, 126.59, 127.48, 127.65, 128.57, 130.69, 132.88, 133.20 ppm; IR (neat): 3023, 2923, 1673, 1618, 1595, 1070, 1028, 987, 750, 697 cm^{-1}; HRMS calcd for $C_{13}H_{14}S_2$ $(M+Na)^+$: 257.3705, found 257.3711.



(2*E*,4*E*)-5-Phenylpenta-2,4-diene-1,1-diyl diacetate (5-4). An oven dried 25 mL Schlenk flask that had been thoroughly purged with N_2 was charged with ethoxy acetylene (2.5 equiv., 340 μL, 40% wt solution

in hexanes, 1.42 mmol) and 1 mL THF and was cooled to 0 °C. Borane dimethylsulfide (0.5 equiv., 28 μL, 0.28 mmol) was dissolved in 1 mL of THF under nitrogen and the resulting solution was added over 30 min with the aid of a syringe pump to the stirred solution of ethoxy acetylene at 0 °C. The reaction mixture was warmed to 20 °C, stirred for an additional 12 h and heated to 60 °C for 1 h. After cooling the reaction mixture to 20 °C, the volatile materials were removed under reduced pressure. The Schlenk flask was put under a nitrogen atmosphere again and the brown residue was dissolved in 2 mL toluene. The stirred solution was cooled to –78 °C in a dry ice/acetone bath and diethylzinc (1.8 equiv., 0.5 mL, 2 M solution in toluene, 1 mmol) was added. After 20 min of stirring at –78 °C, cinnamaldehyde (1 equiv., 72 μL, 0.57 mmol) was added. The mixture was allowed to warm to 20 °C over 2 h and stirred for an additional 12 h. After the aldehyde had been consumed (by TLC analysis), the solution was cooled to 0 °C and aqueous HCl (500 μL of 2 M solution, 1 mmol) was added. The suspension was stirred for 20 min at 20 °C and then volatile materials were removed under reduced pressure. Toluene (1 mL) was added, stirred for 5 min and the volatile materials were removed under reduced pressure. The addition of toluene and subsequent evaporation was repeated two more times. Freshly distilled acetic anhydride (22 equiv., 1.2 mL, 12.7 mmol) was then added at 20 °C. After 20 min of stirring, anhydrous iron(III) chloride (10% mol, 10 mg, 0.06 mmol) was added. The reaction was stirred for an additional 24 h and then was diluted with 20 mL of diethyl ether and washed with 2 × 20 mL of water. Organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc :

95/5) to give **5-4** (136 mg, 92% yield) as an oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 5.78 (dd, *J* = 15.4, 6.4 Hz, 1H), 6.57-6.79 (m, 3H), 7.19-7.27 (m, 2H), 7.27-7.34 (m, 2H), 7.36-7.41 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 90.6 MHz): δ 21.07, 89.70, 125.21, 126.91, 128.45, 128.60, 128.90, 135.87, 136.42, 136.75, 168.86 ppm; IR (neat): 3027, 1760, 1649, 1240, 1203, 1129, 1007, 990, 956, 749, 692 cm^{-1}; HRMS calcd for $C_{15}H_{16}O_4$ $(M+Na)^{+}$: 283.0930, found 283.0932.

5.5. References

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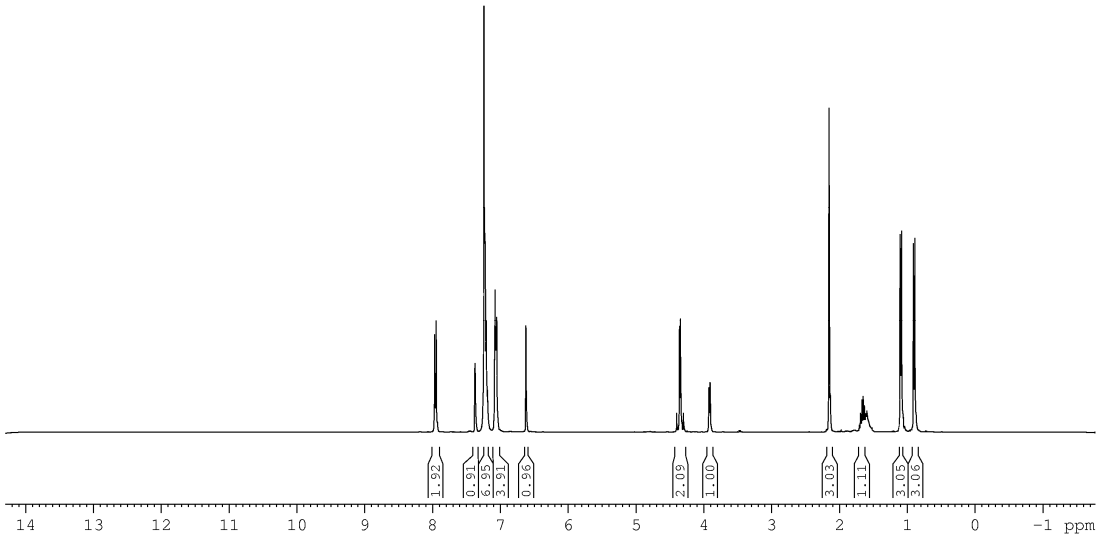
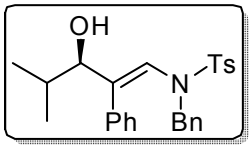
Appendix A. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR Spectra

A-1. Chapter 1 Spectra





(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1a)

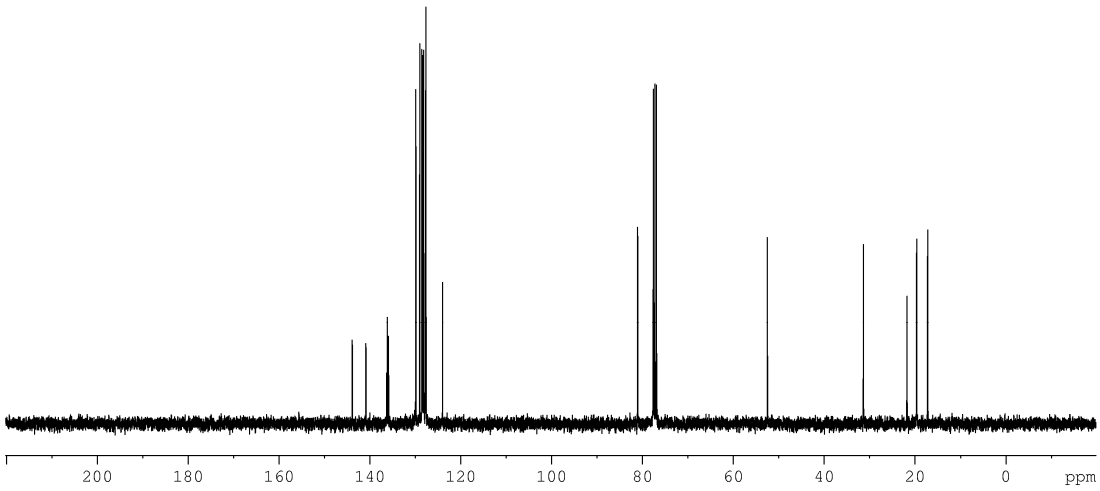
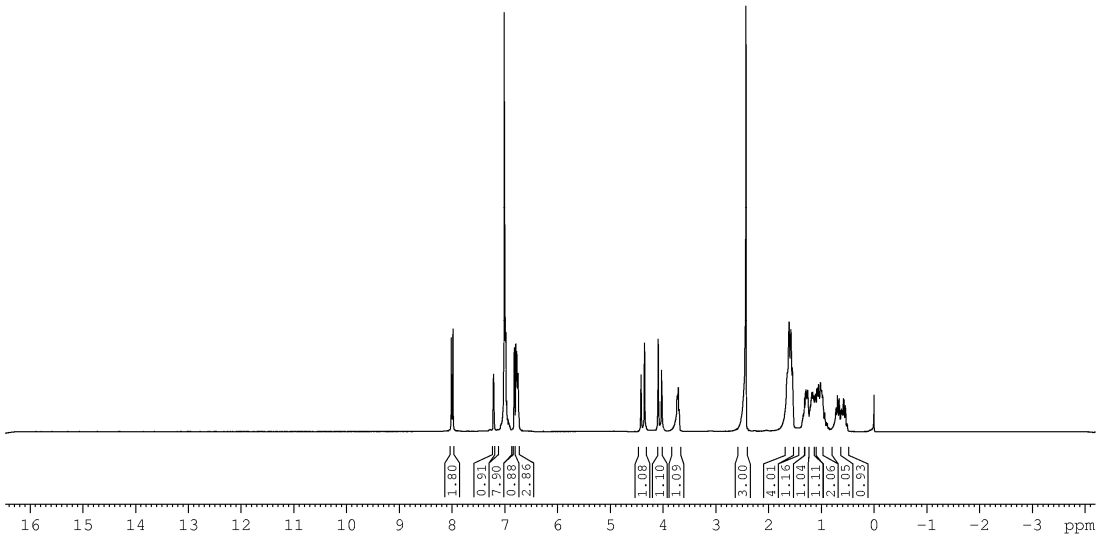
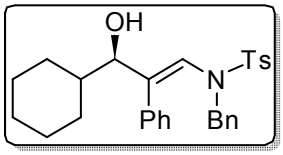


Figure A-1. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1a** in $CDCl_3$





(*R*, *E*)-*N*-Benzyl-*N*-(3-cyclohexyl-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1b)

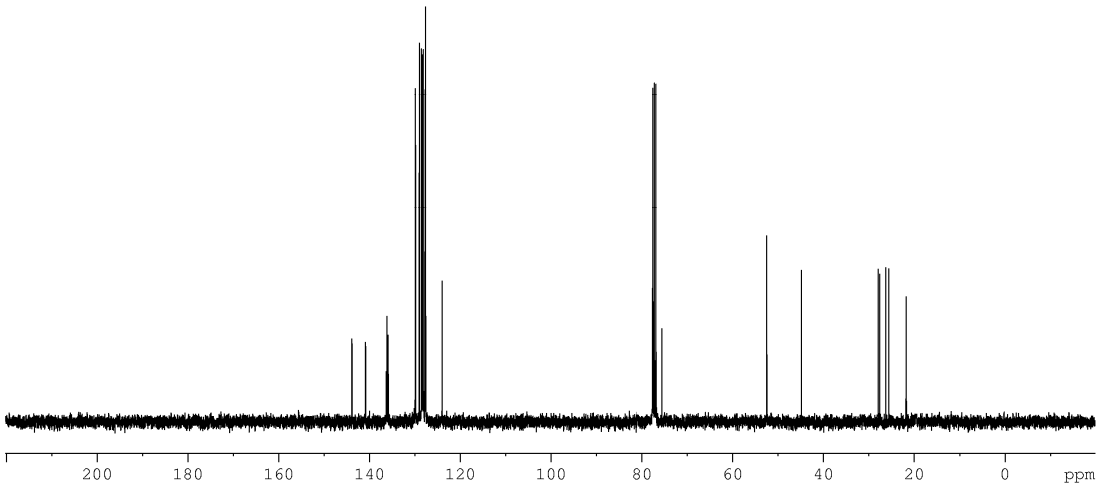
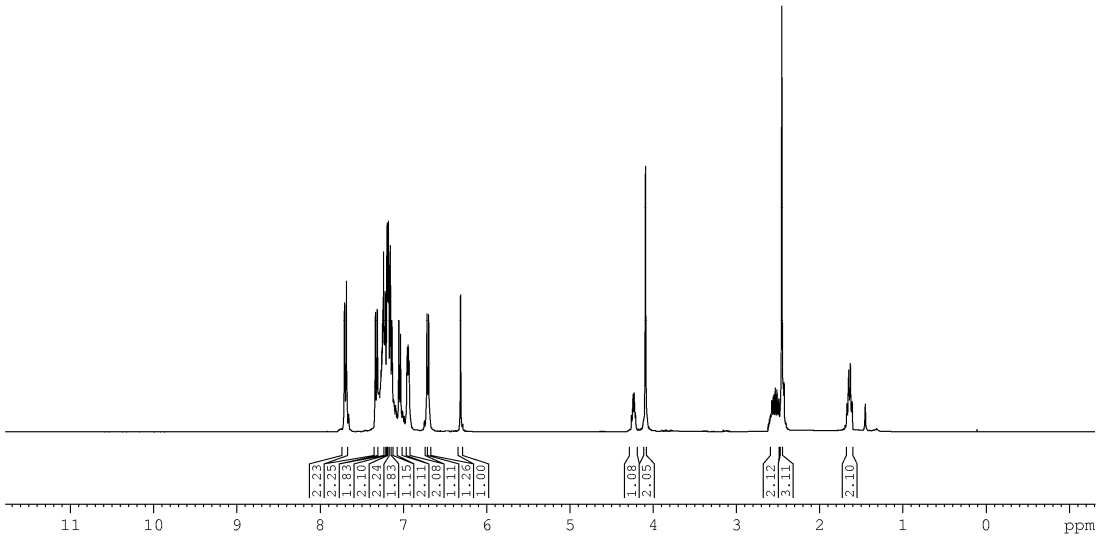
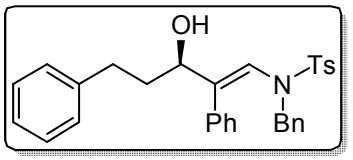


Figure A-2. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1b** in $CDCl_3$





(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-2,5-diphenylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1c)

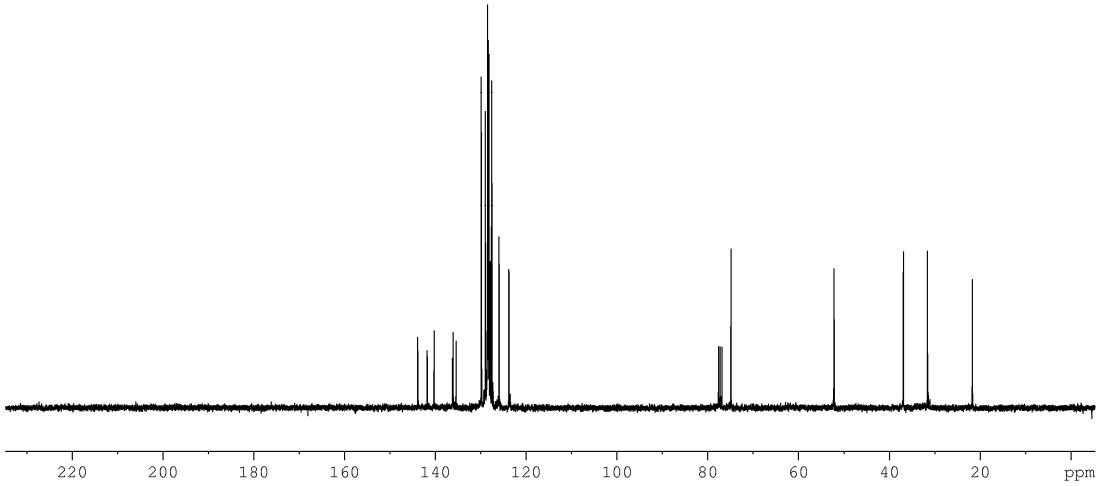
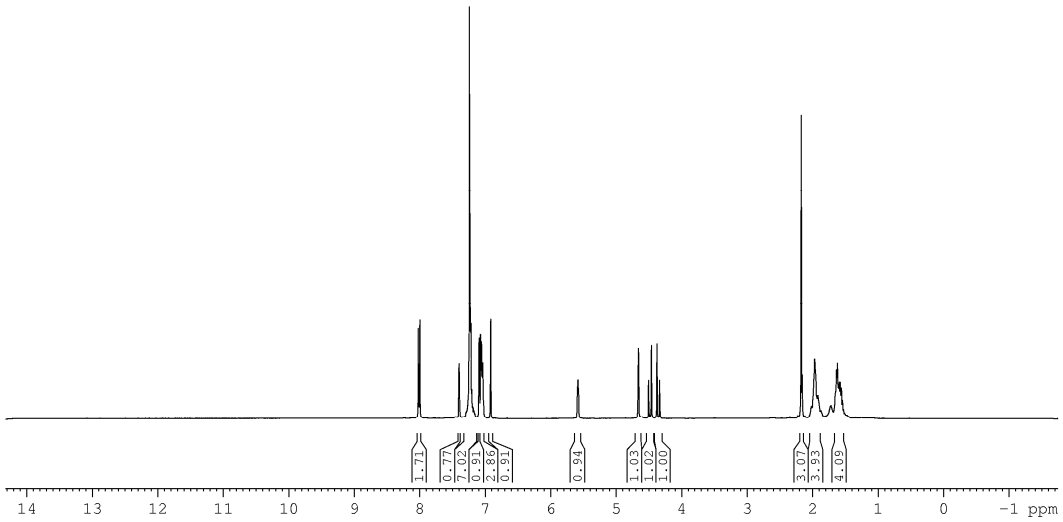
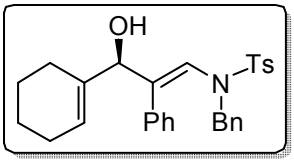


Figure A-3. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1c** in $CDCl_3$.





(*R*,*E*)-*N*-Benzyl-*N*-(3-(cyclohex-1-en-1-yl)-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1d)

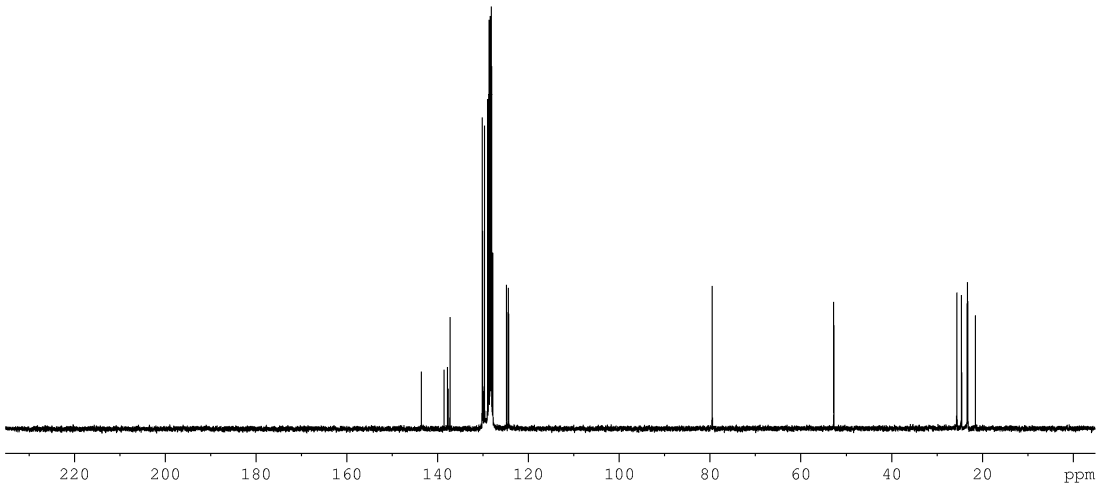
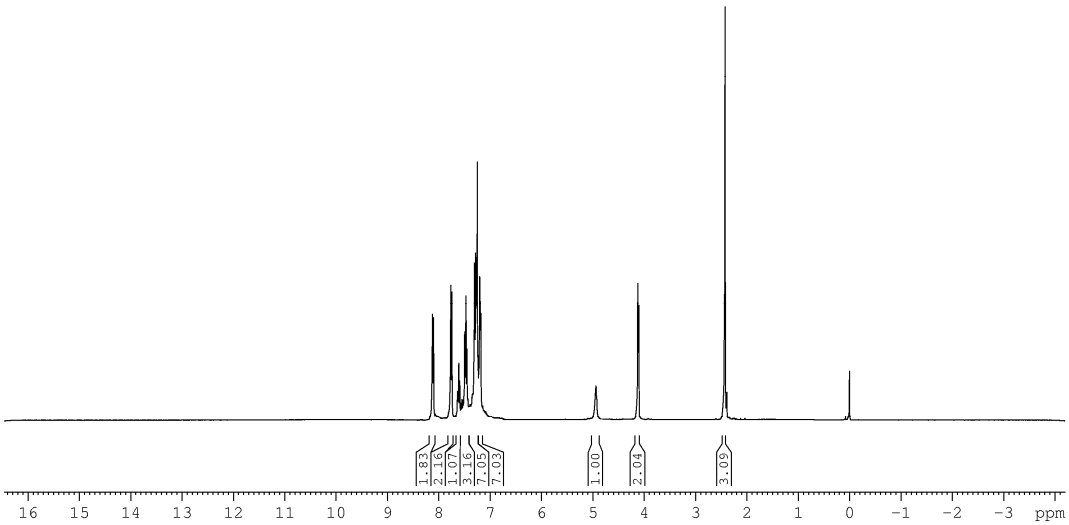
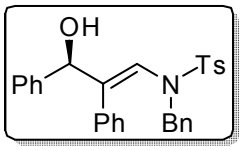


Figure A-4. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1d** in $CDCl_3$.





(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-2,3-diphenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1e)

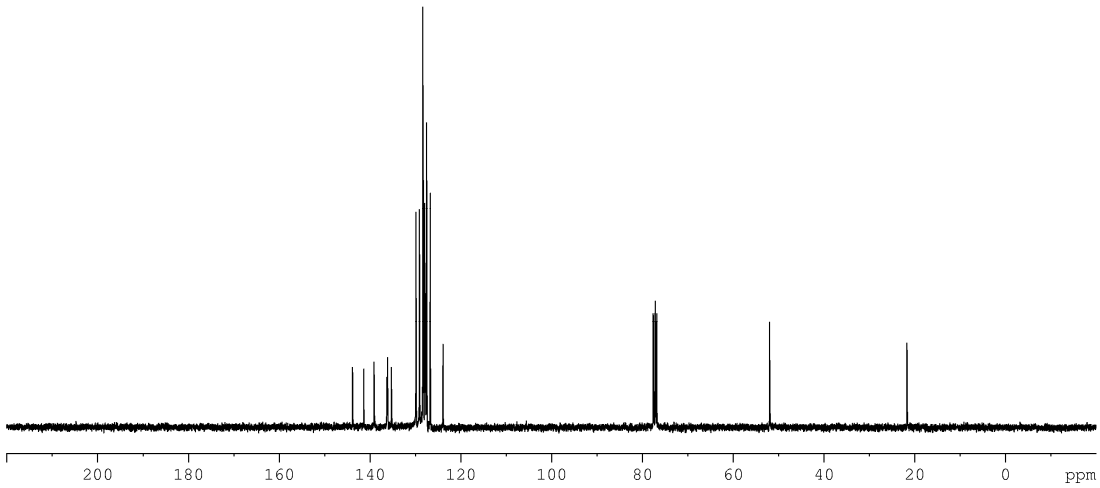
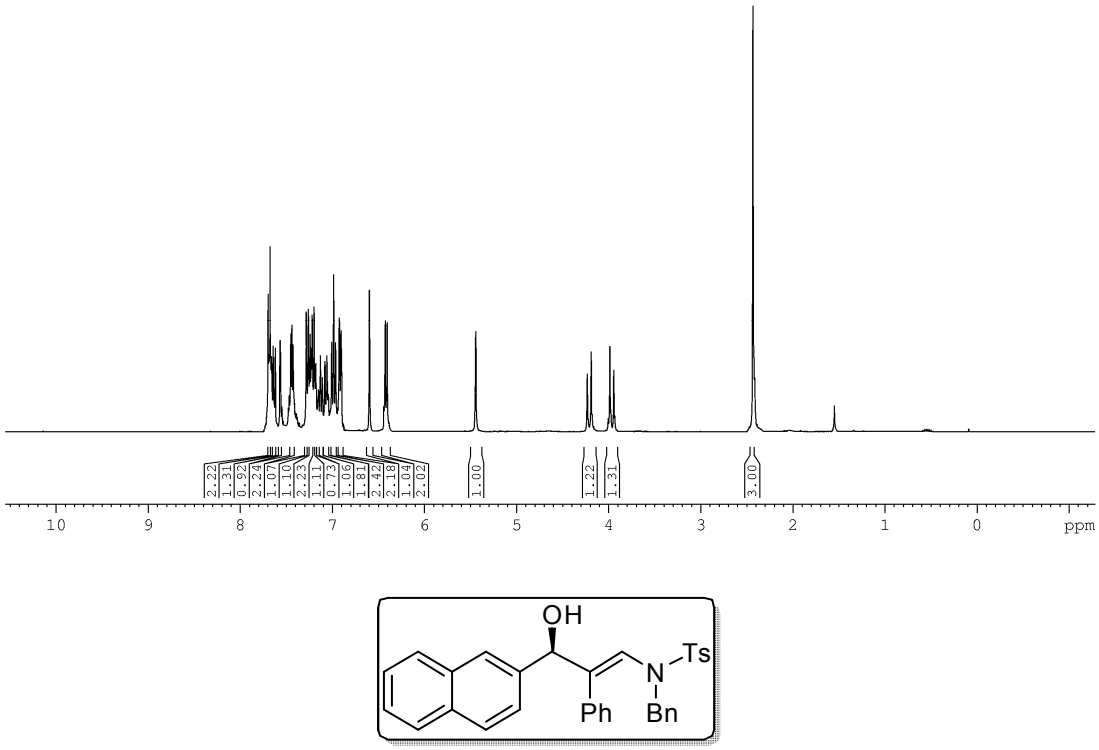


Figure A-5. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1e** in $CDCl_3$.



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-3-(naphthalen-2-yl)-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1f)

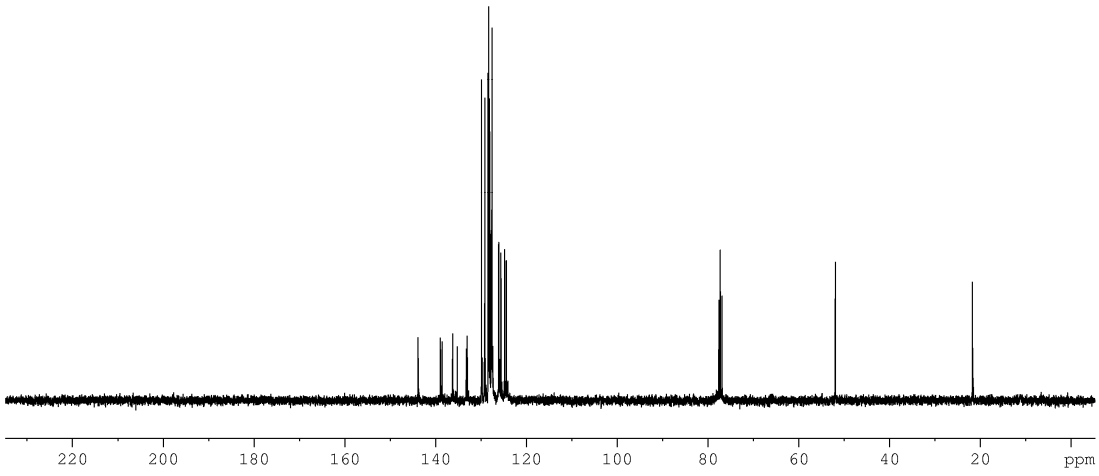
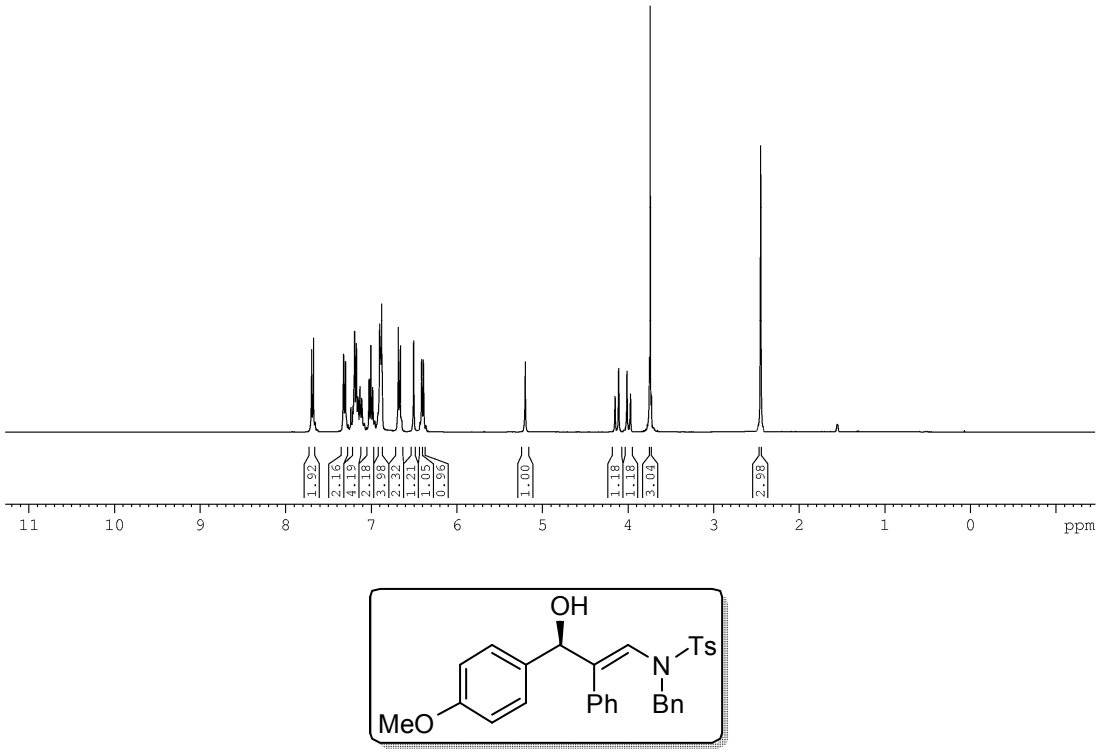


Figure A-6. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1f** in $CDCl_3$.



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-3-(4-methoxyphenyl)-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1g)

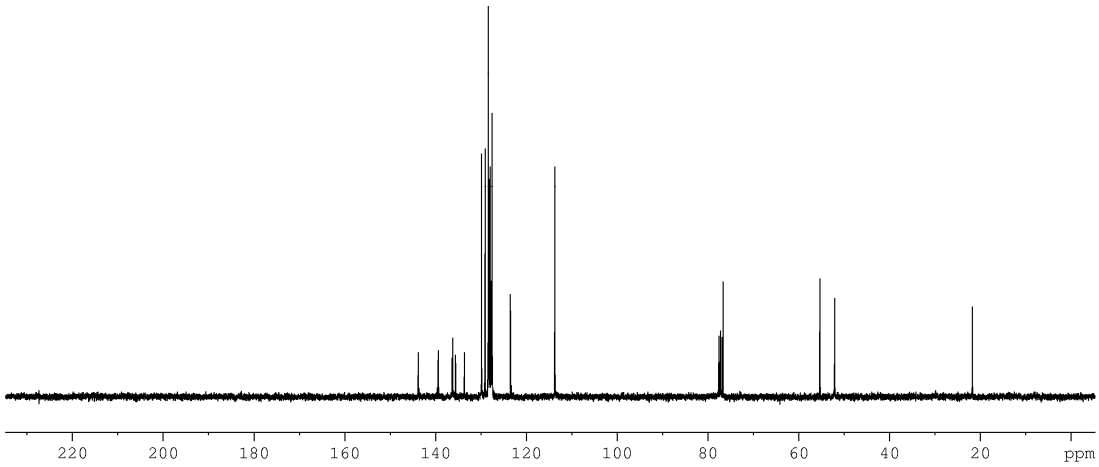
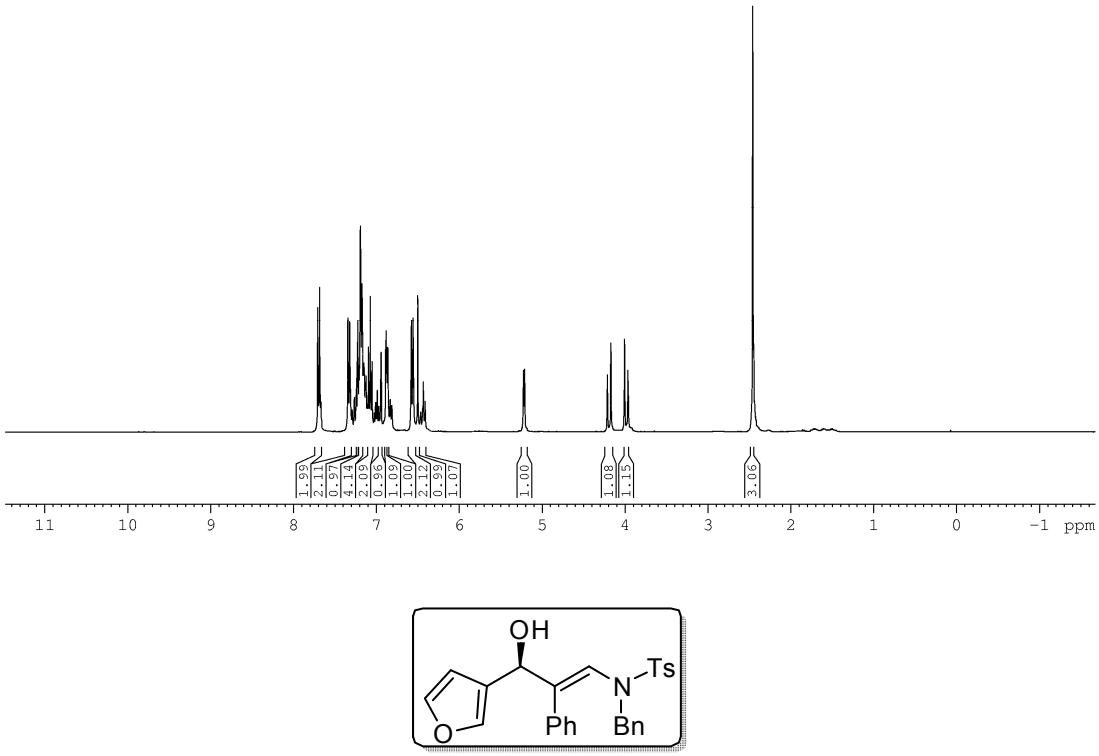


Figure A-7. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1g** in $CDCl_3$.



(*S*,*E*)-*N*-Benzyl-*N*-(3-(furan-3-yl)-3-hydroxy-2-phenylprop-1-en-1-yl)-4-methylbenzenesulfonamide (1h)

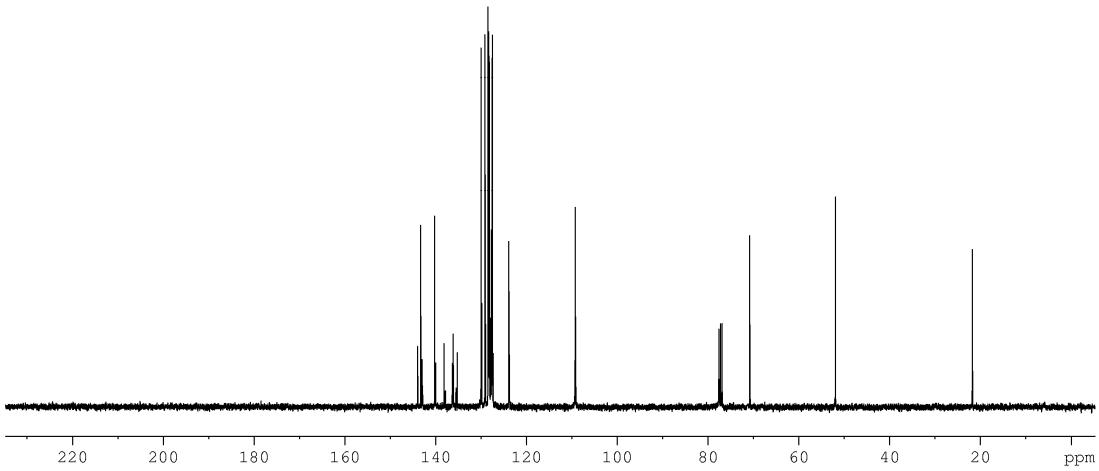
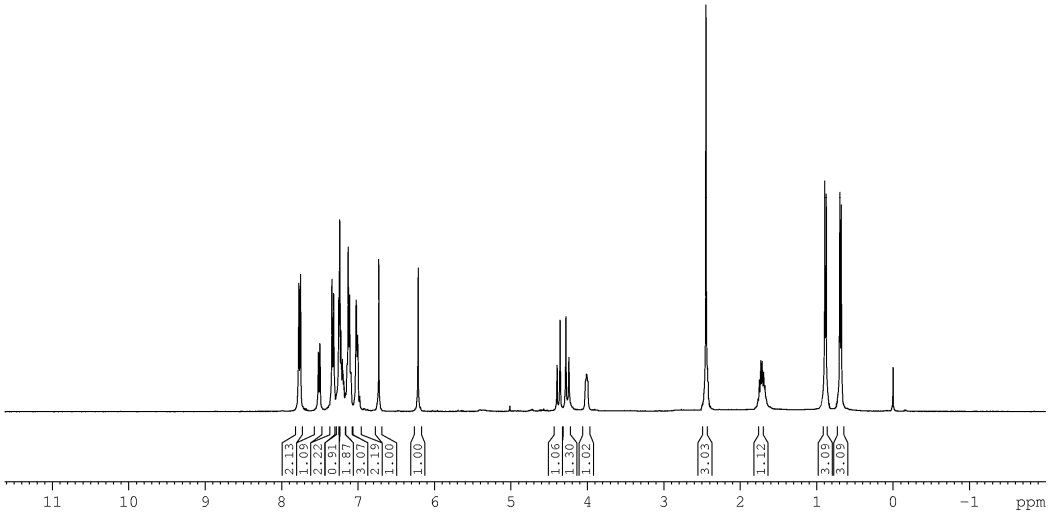
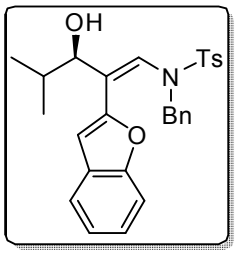


Figure A-8. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1h** in $CDCl_3$.





(*R*,*Z*)-*N*-(2-(Benzofuran-2-yl)-3-hydroxy-4-methylpent-1-en-1-yl)-*N*-benzyl-4-methylbenzenesulfonamide (1i)

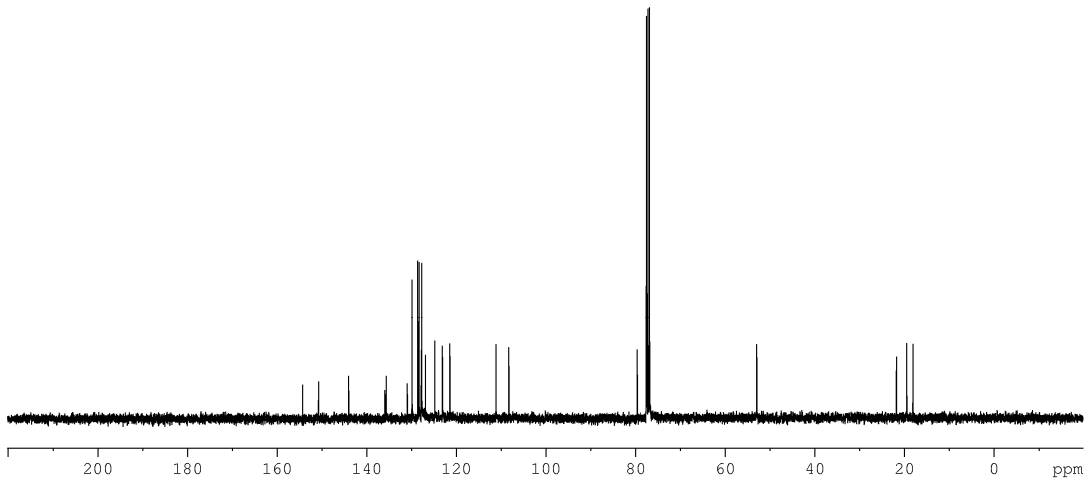
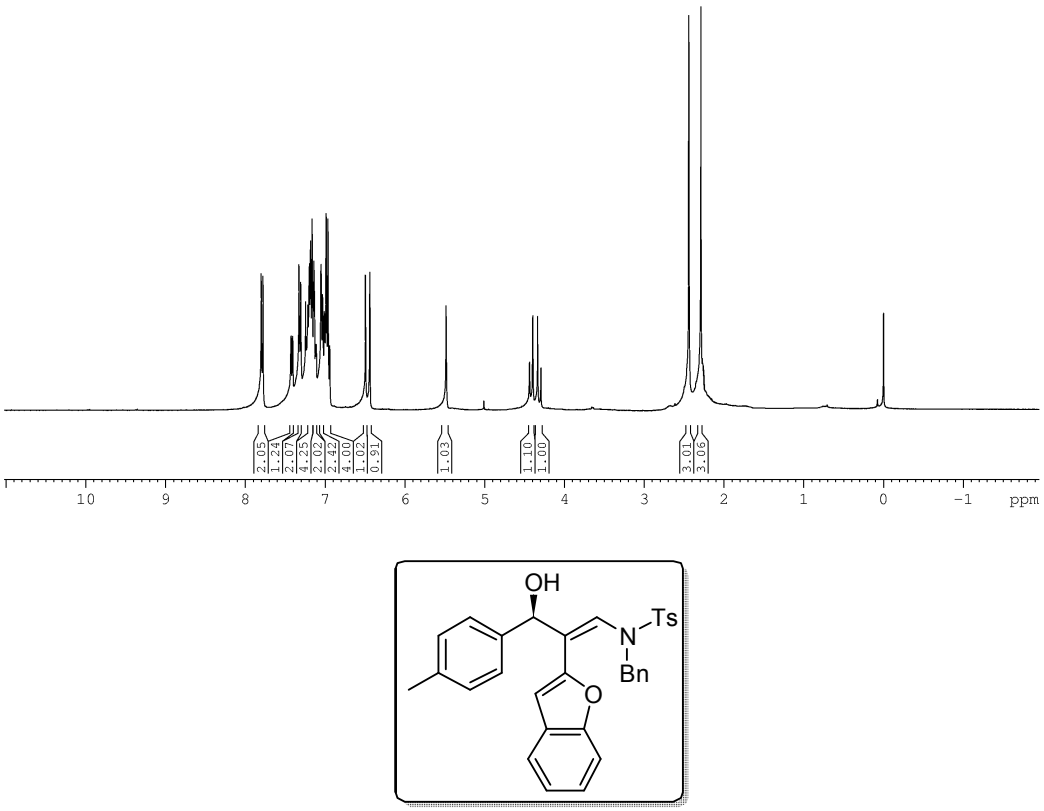


Figure A-9. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1i** in $CDCl_3$.



(*R*,*Z*)-*N*-(2-(Benzofuran-2-yl)-3-hydroxy-3-(p-tolyl)prop-1-en-1-yl)-*N*-benzyl-4-methylbenzenesulfonamide (1j)

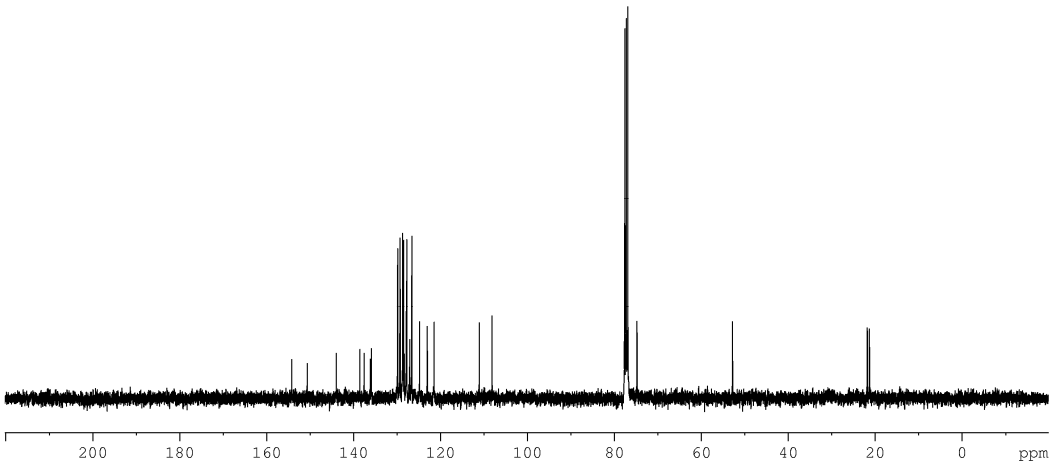
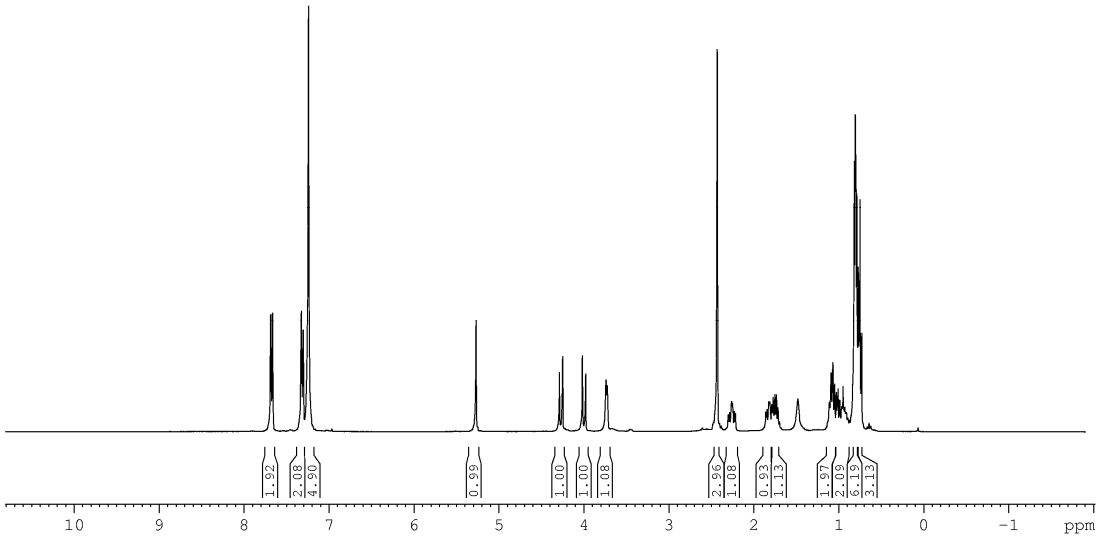
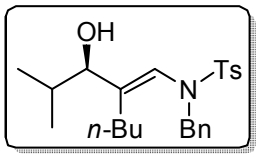


Figure A-10. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1j** in $CDCl_3$.





(*R*,*E*)-*N*-Benzyl-*N*-(2-(1-hydroxy-2-methylpropyl)hex-1-en-1-yl)-4-methylbenzenesulfonamide (1k)

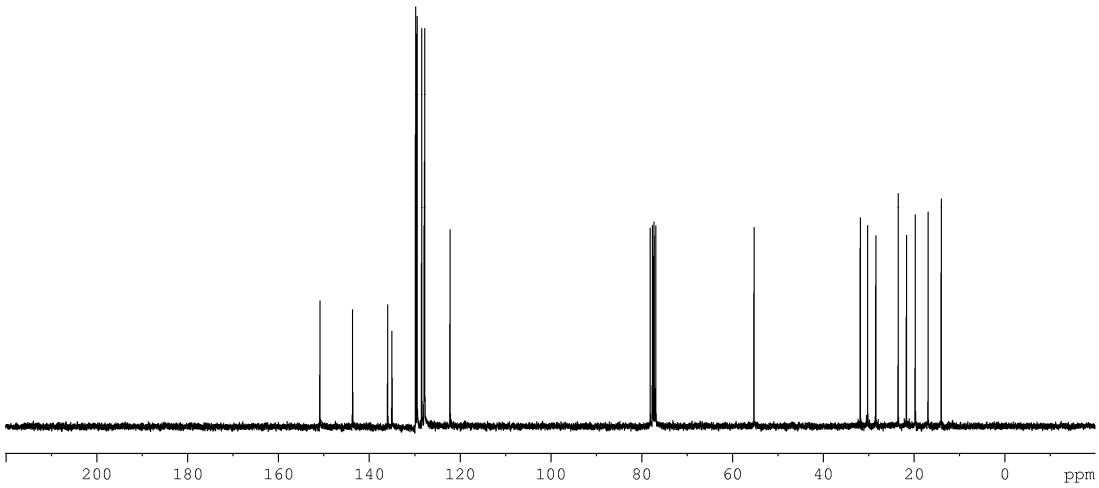
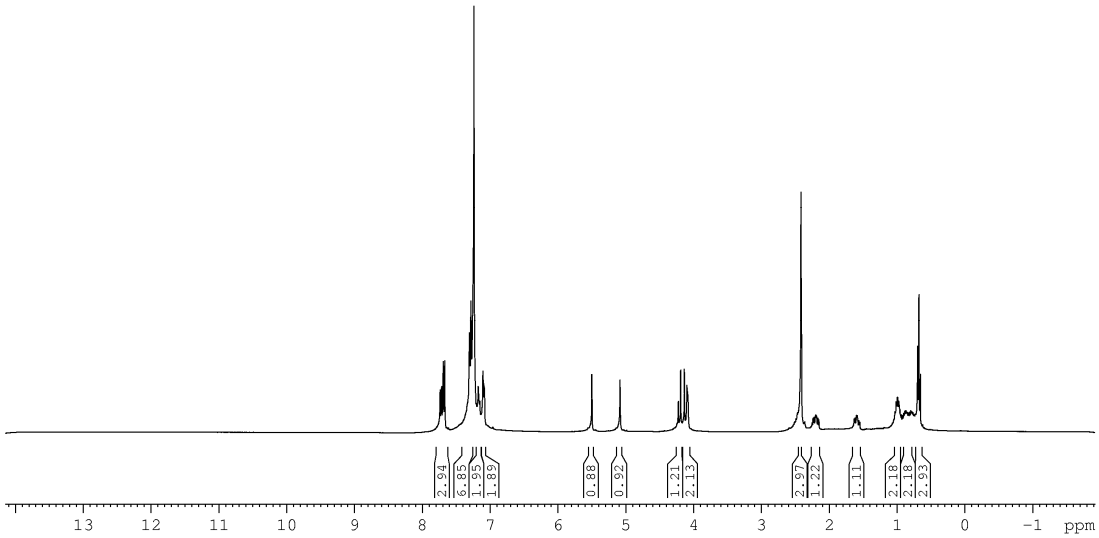
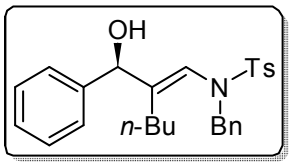


Figure A-11. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1k** in $CDCl_3$.





(*R*,*E*)-*N*-Benzyl-*N*-(2-(hydroxy(phenyl)methyl)hex-1-en-1-yl)-4-methylbenzenesulfonamide (1l)

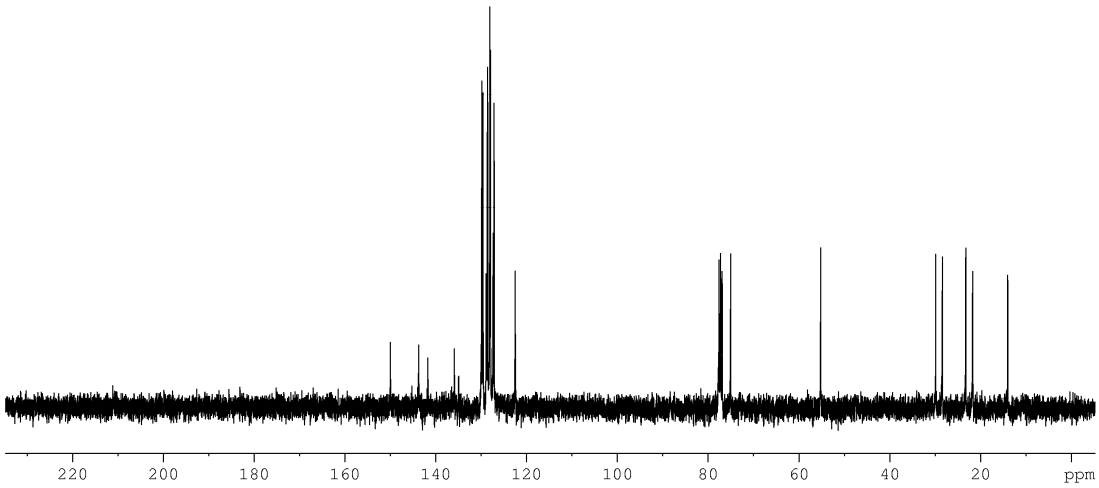
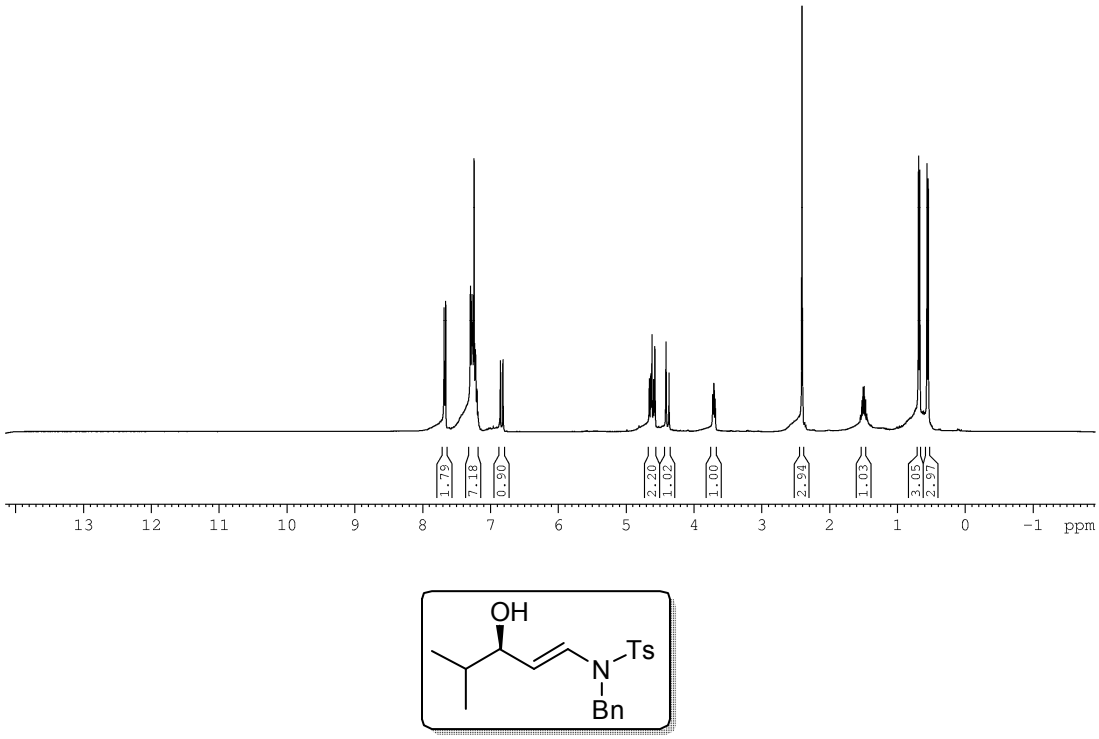


Figure A-12. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1l** in $CDCl_3$.



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-methylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1m)

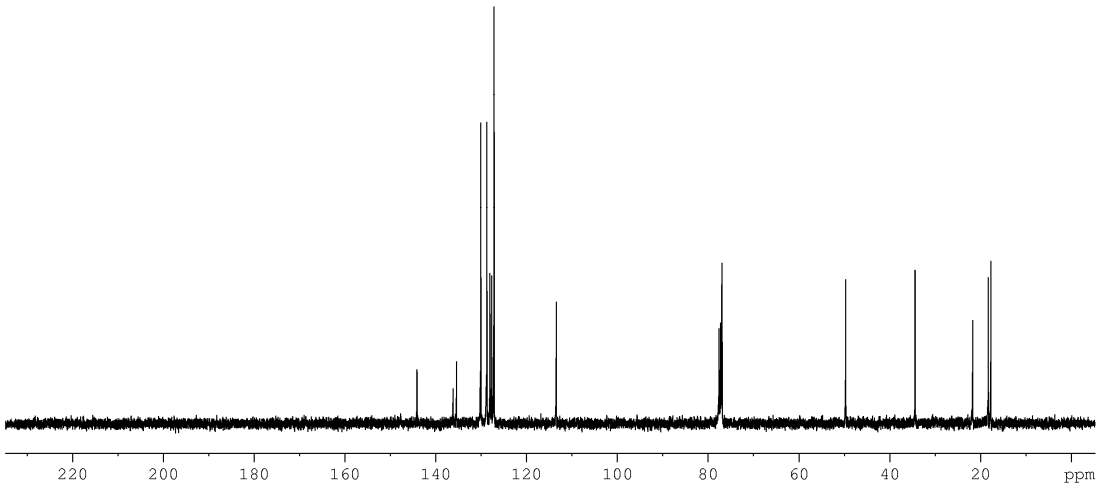
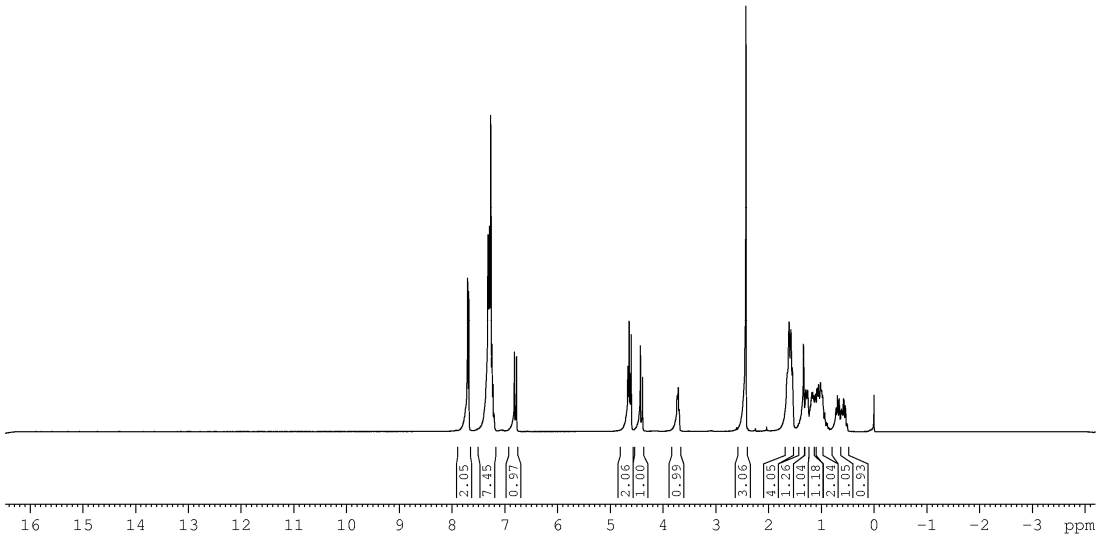


Figure A-13. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1m** in $CDCl_3$.



(*R*,*E*)-*N*-Benzyl-*N*-(3-cyclohexyl-3-hydroxyprop-1-en-1-yl)-4-methylbenzenesulfonamide (1n)

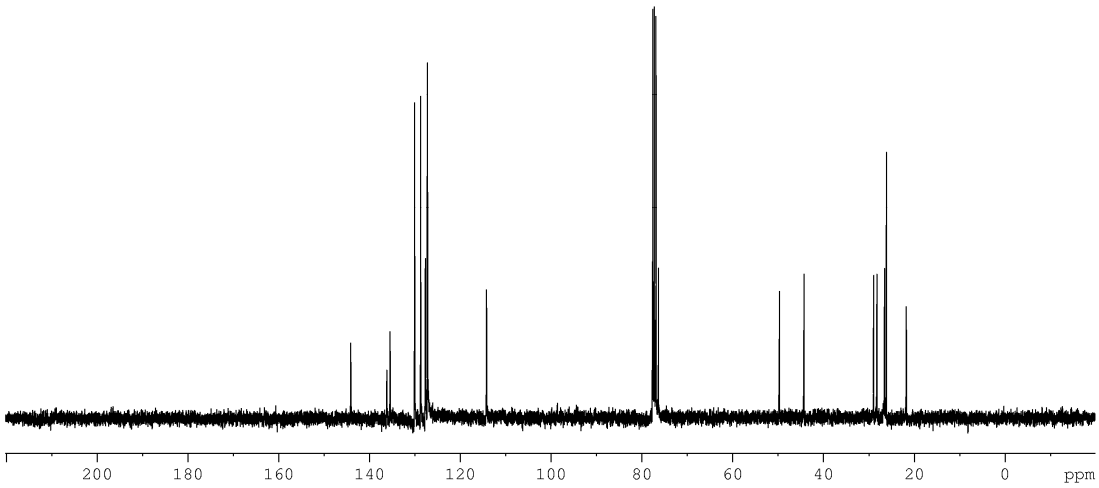
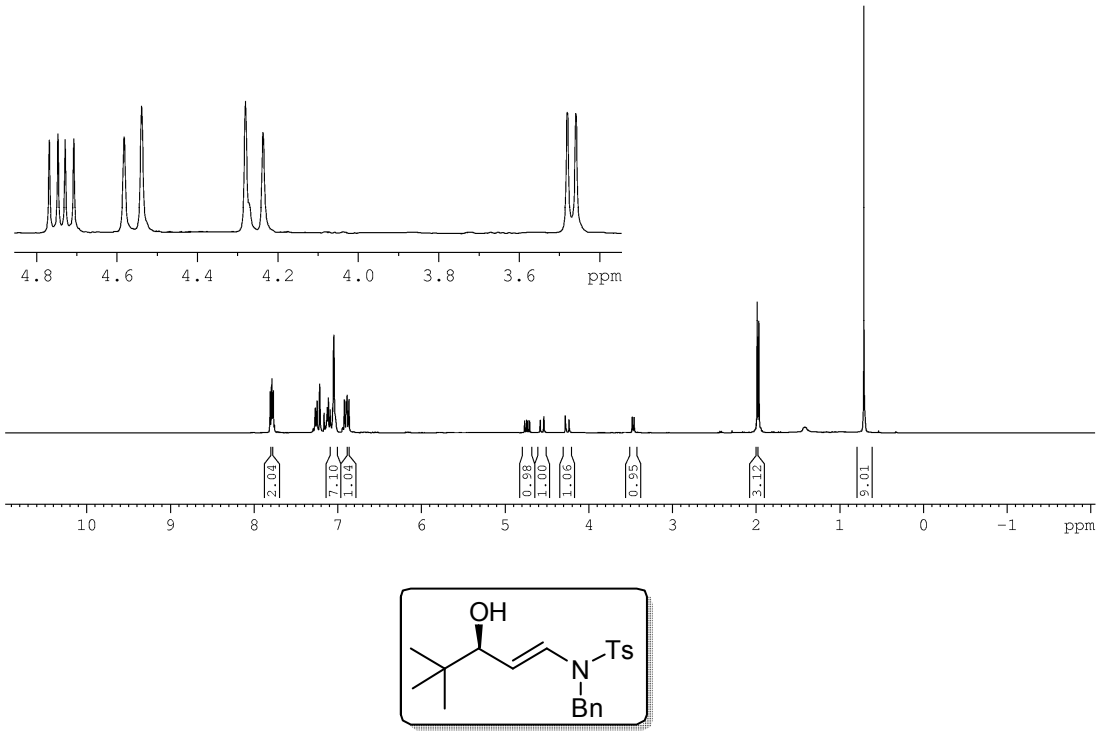


Figure A-14. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1n** in $CDCl_3$.



(*S*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4,4-dimethylpent-1-en-1-yl)-4-methylbenzenesulfonamide (1o)

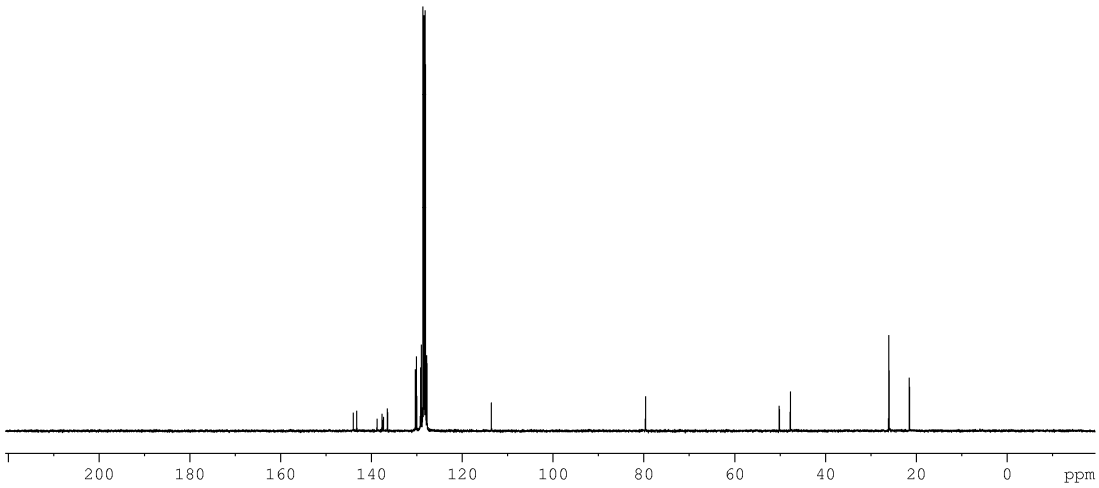
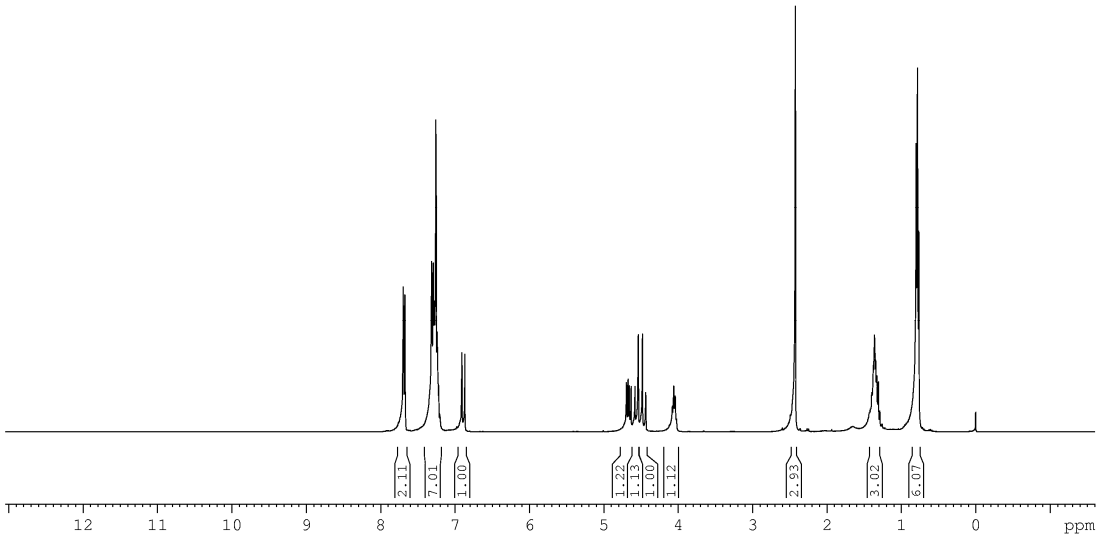


Figure A-15. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1o** in C_6D_6.



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-5-methylhex-1-en-1-yl)-4-methylbenzenesulfonamide (1p)

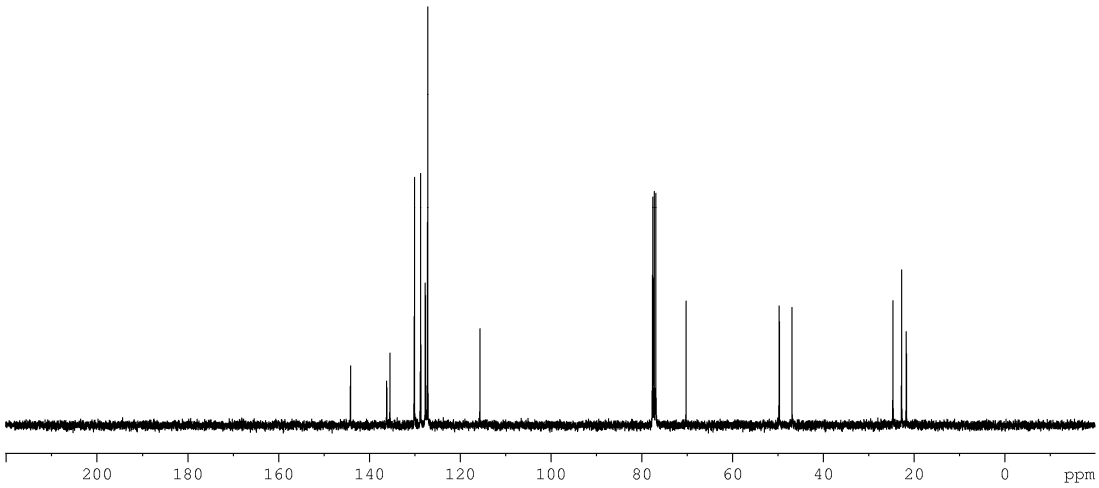
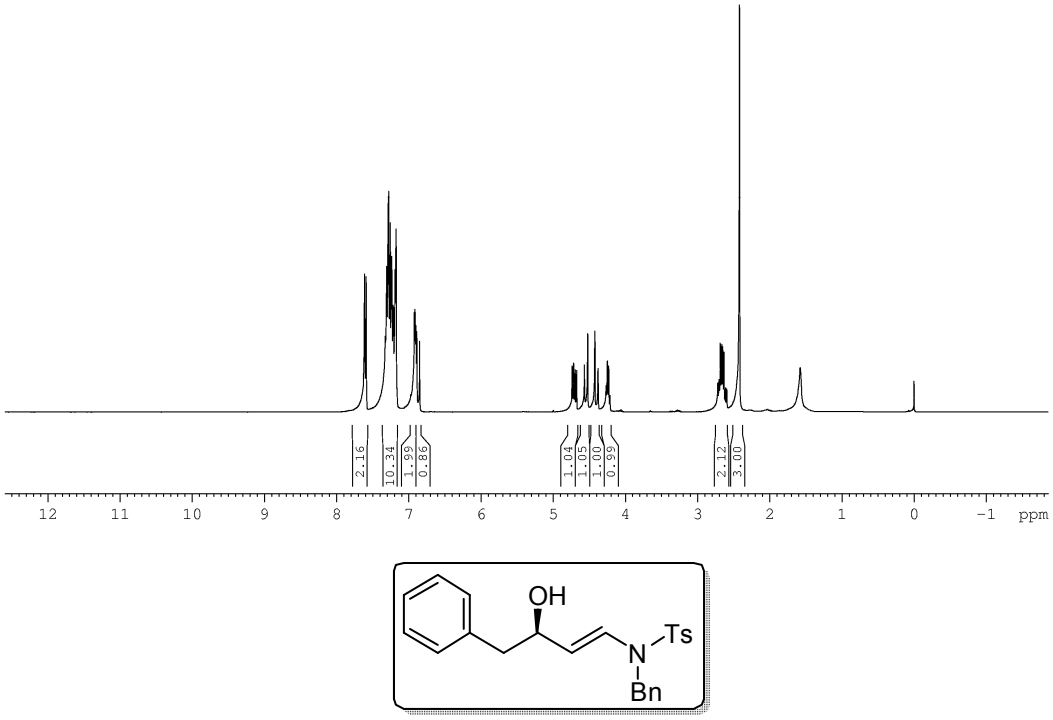


Figure A-16. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1p** in $CDCl_3$.



(*R*,*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-phenylbut-1-en-1-yl)-4-methylbenzenesulfonamide (1q)

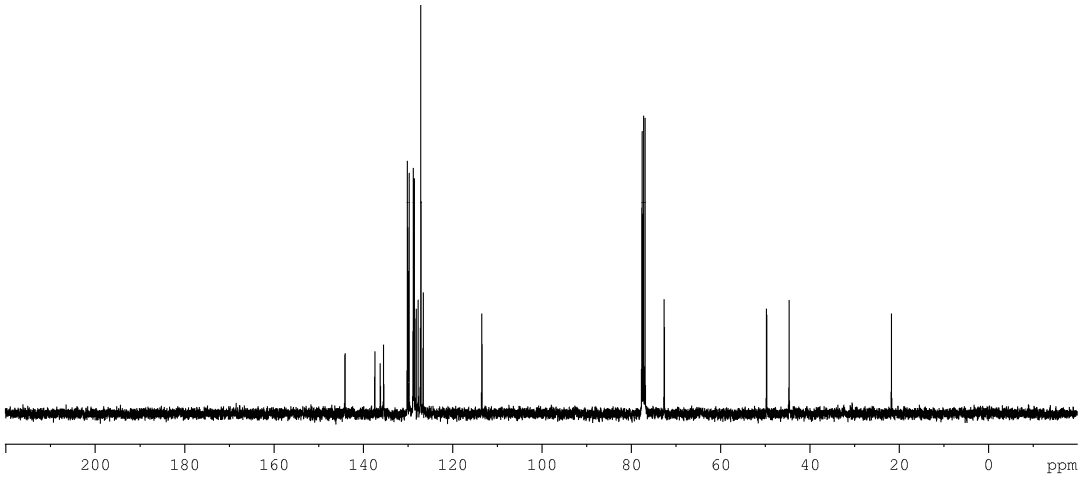
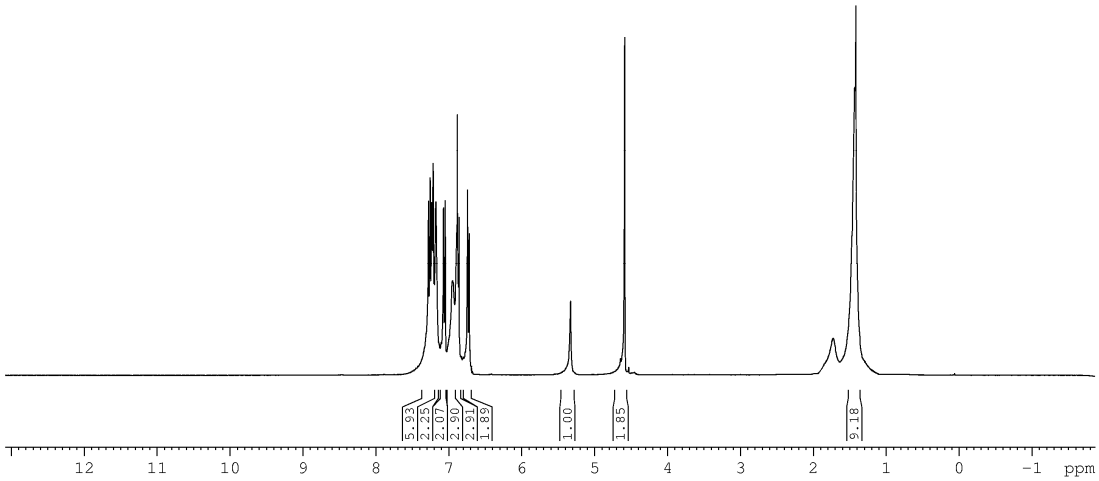
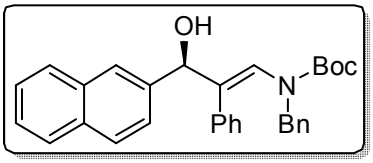


Figure A-17. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1q** in $CDCl_3$.





(*R*,*E*)-Tert-butyl benzyl(3-hydroxy-3-(naphthalen-2-yl)-2-phenylprop-1-en-1-yl)carbamate

(1r)

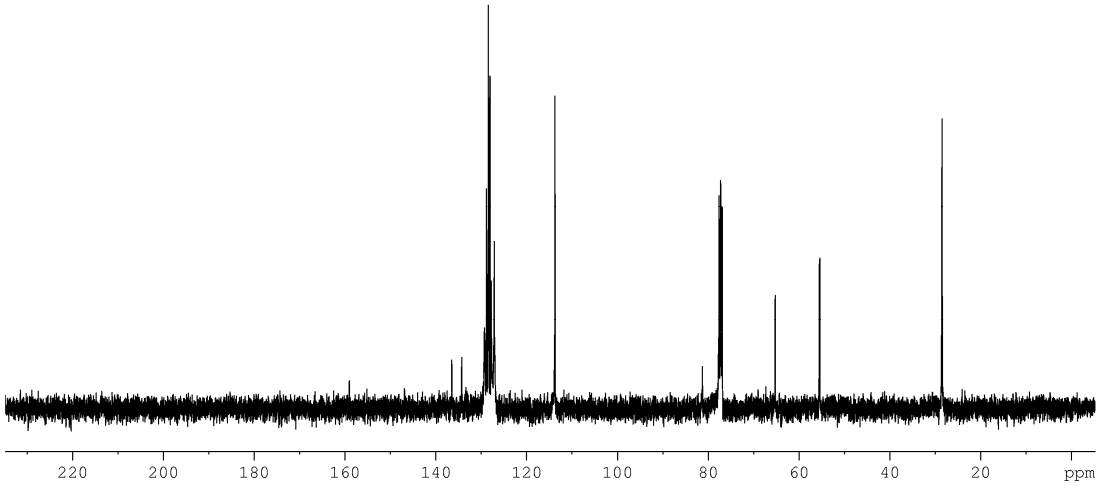
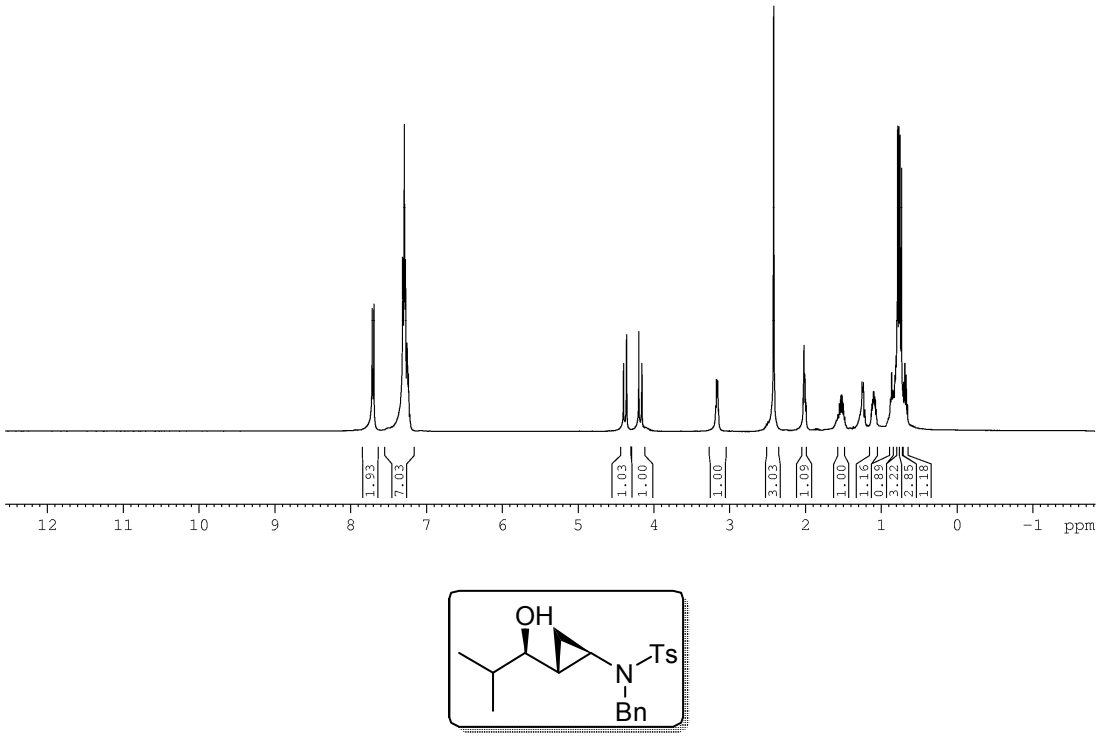


Figure A-18. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **1r** in $CDCl_3$.

A-2. Chapter 2 Spectra



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-1-hydroxy-2-methylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2a)

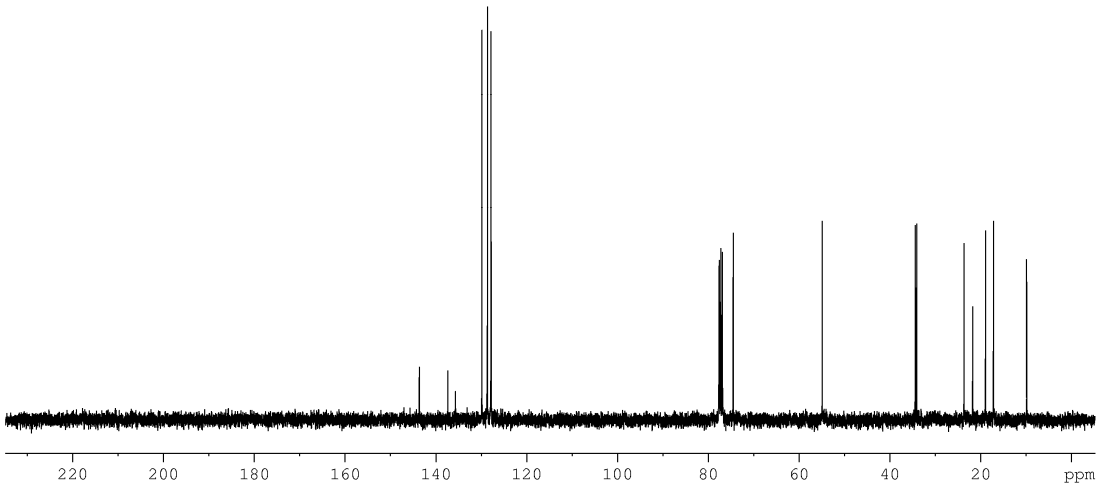
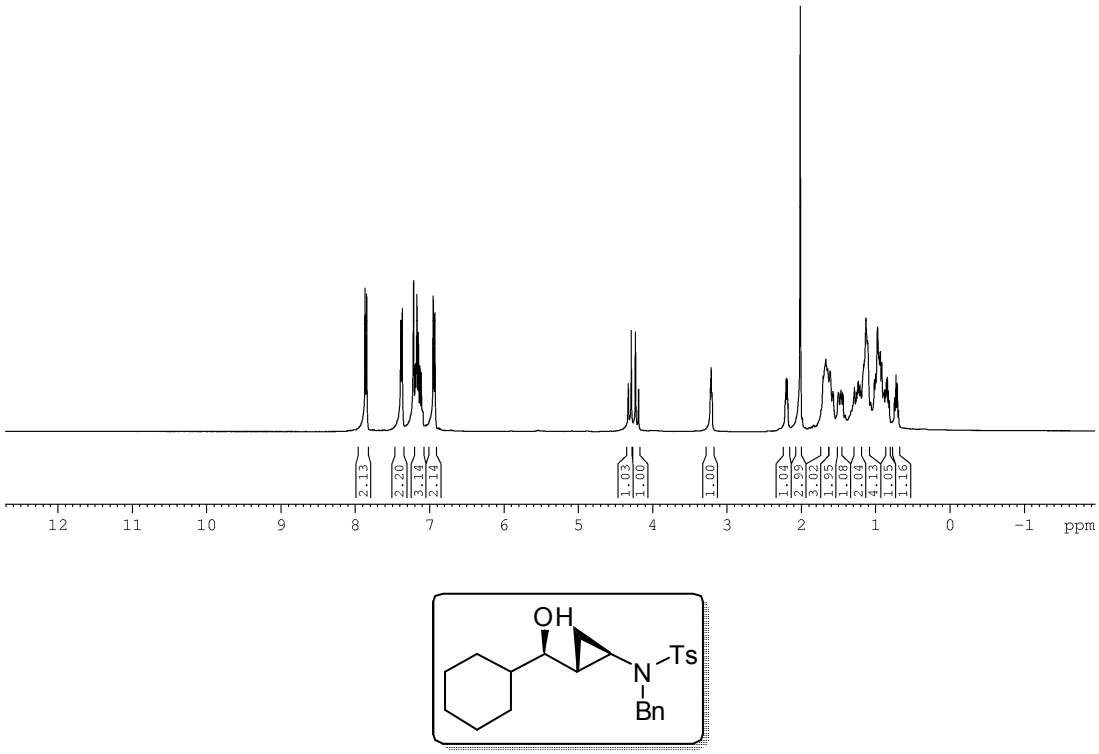


Figure A-19. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2a** in $CDCl_3$.



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-cyclohexyl(hydroxy)methyl)cyclopropyl)-4-methylbenzenesulfonamide (2b)

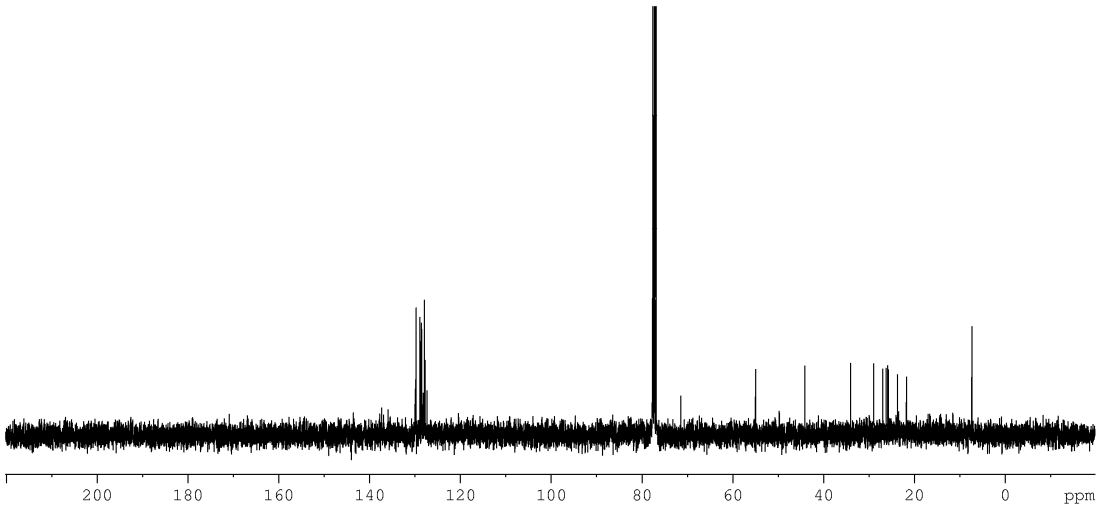
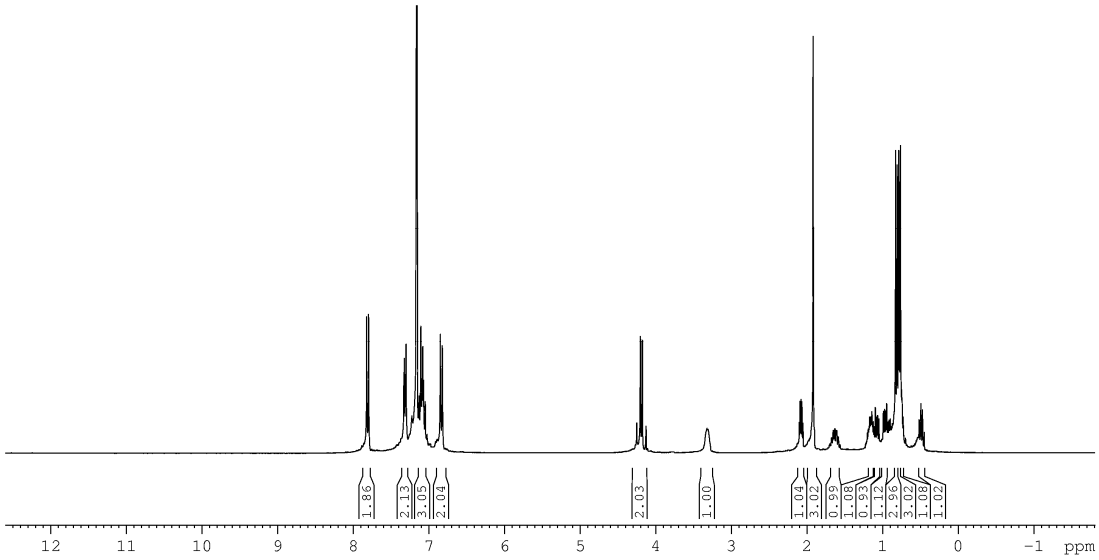


Figure A-20. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2b** in $CDCl_3$.



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-1-hydroxy-3-methylbutyl)cyclopropyl)-4-methylbenzenesulfonamide (2c)

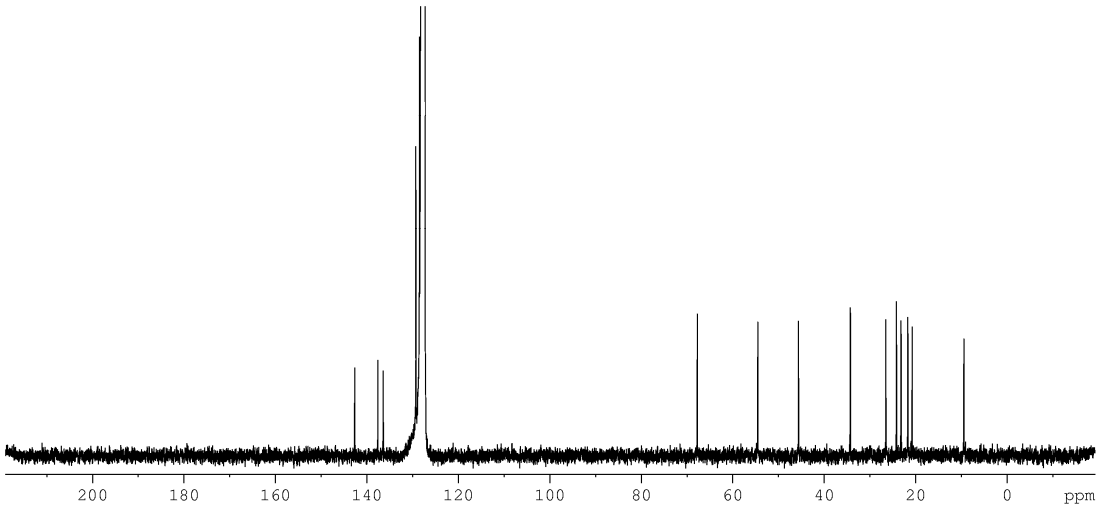
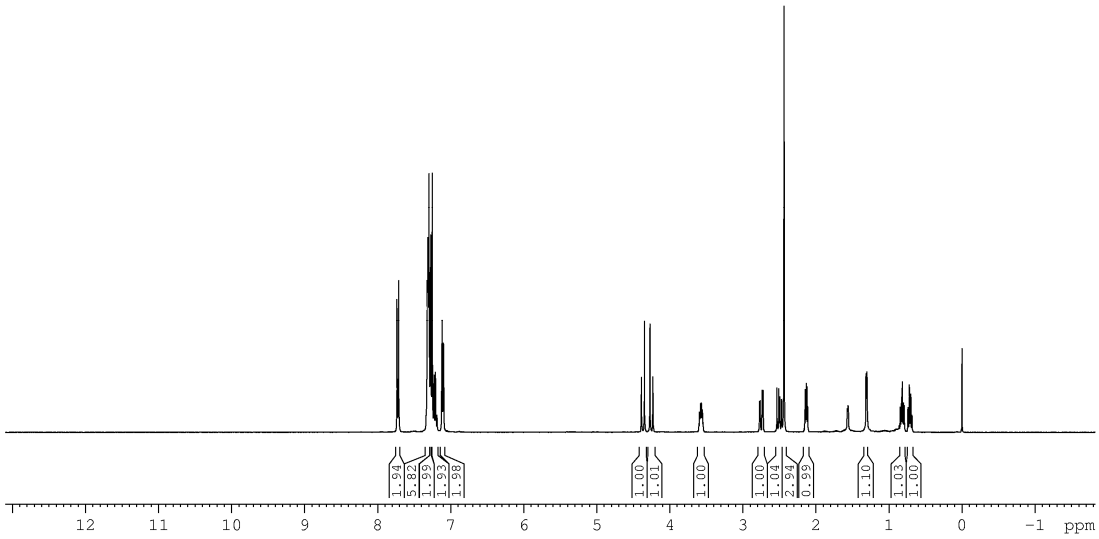


Figure A-21. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2c** in C_6D_6.



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_R_)-1-hydroxy-2-phenylethyl)cyclopropyl)-4-methylbenzenesulfonamide (2d)

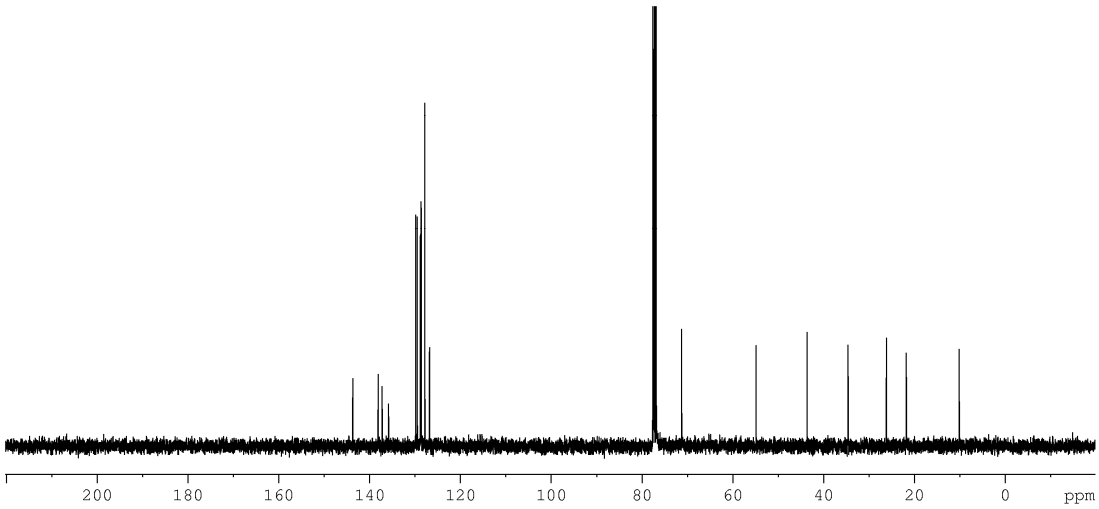
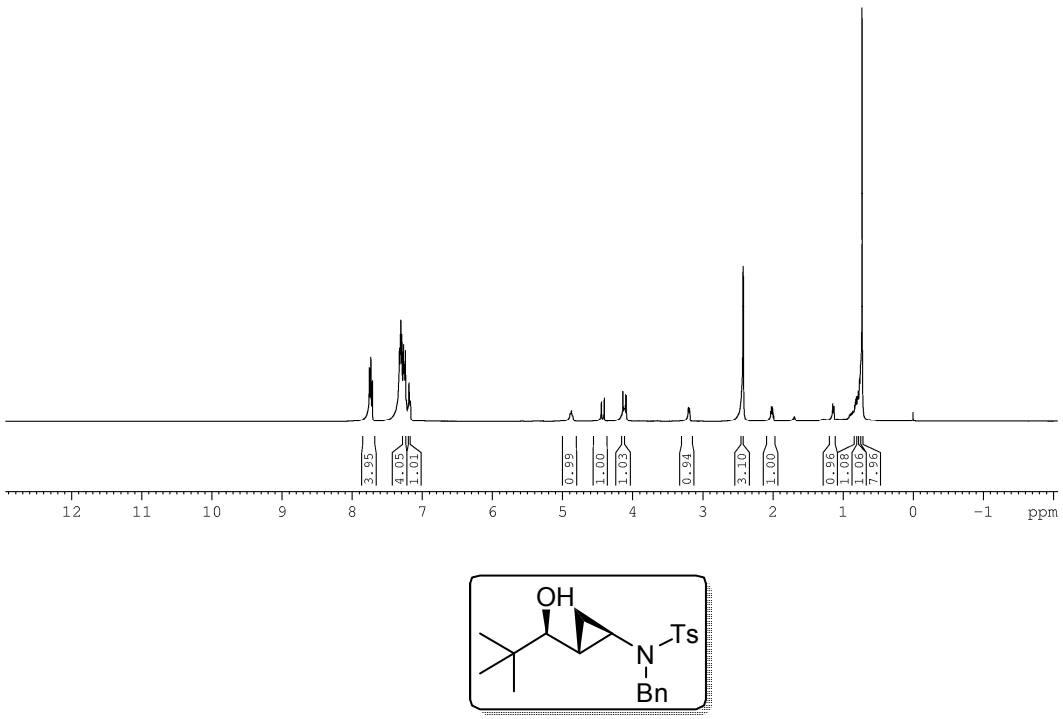


Figure A-22. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2d** in $CDCl_3$.



_N_-Benzyl-_N_-((1_R_,2_R_)-2-((_S_)-1-hydroxy-2,2-dimethylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2e)

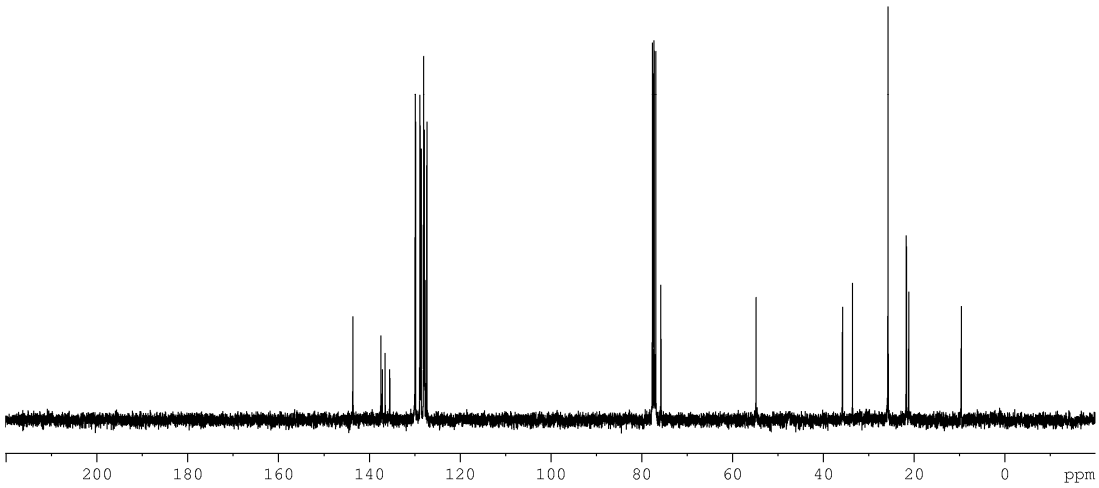
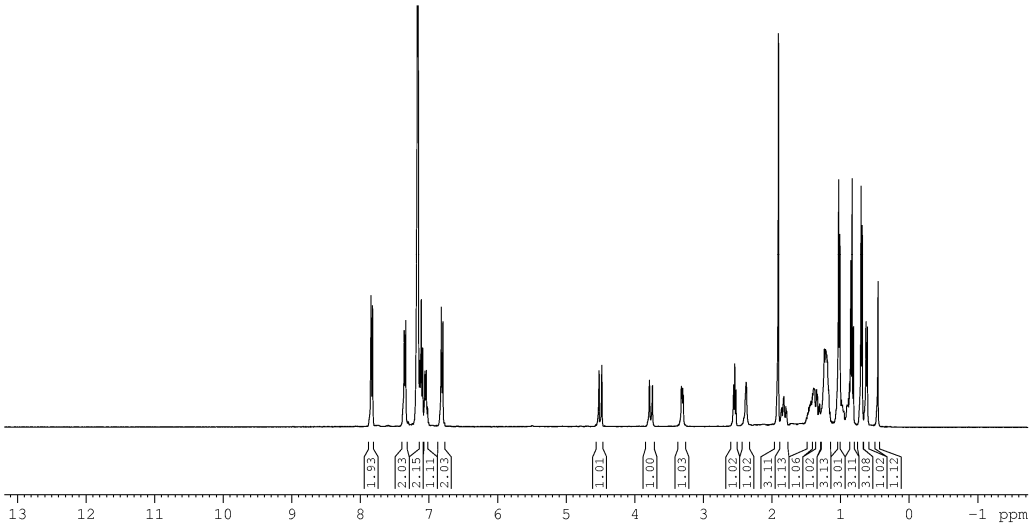
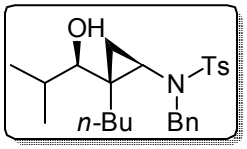


Figure A-23. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2e** in $CDCl_3$.





_N_-Benzyl-_N_-((1_R_,2_R_)-2-butyl-2-((_R_)-1-hydroxy-2-methylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2f)

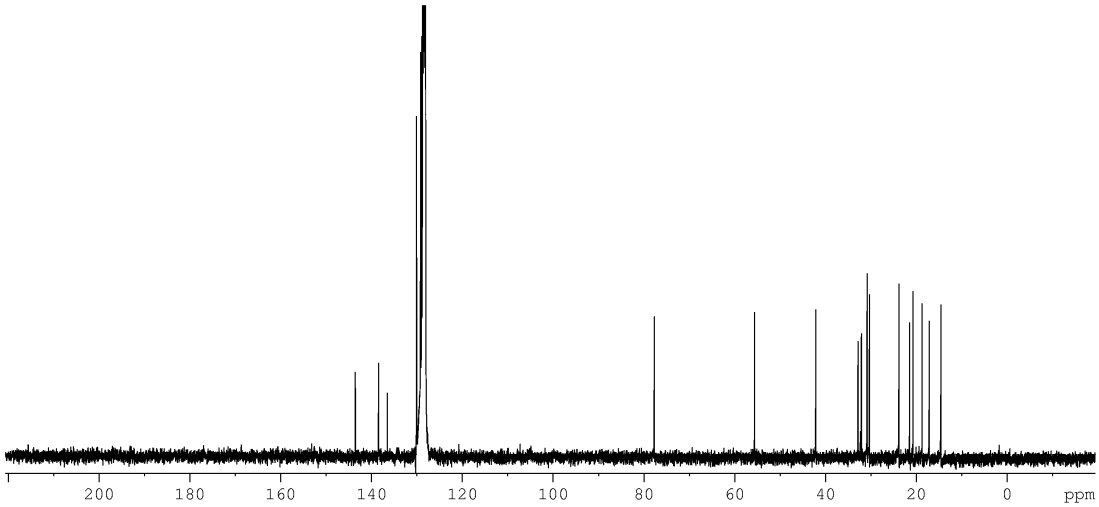
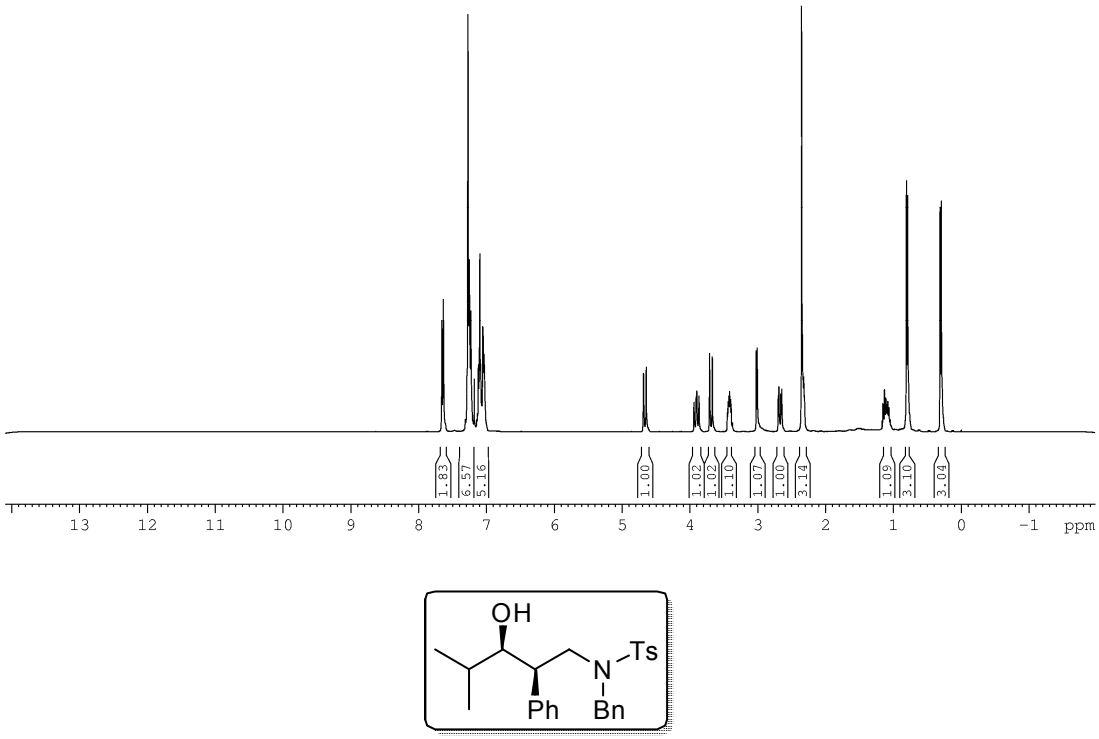


Figure A-24. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **2f** in C_6D_6.

A-3. Chapter 3 Spectra



_N_-Benzyl-_N_-(3-hydroxy-4-methyl-2-phenylpentyl)-4-methylbenzenesulfonamide (3a)

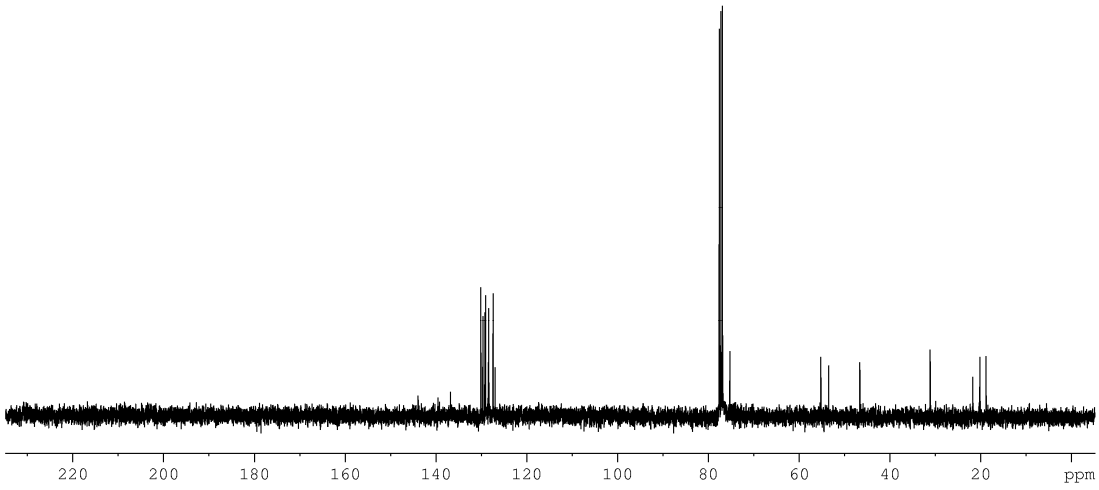
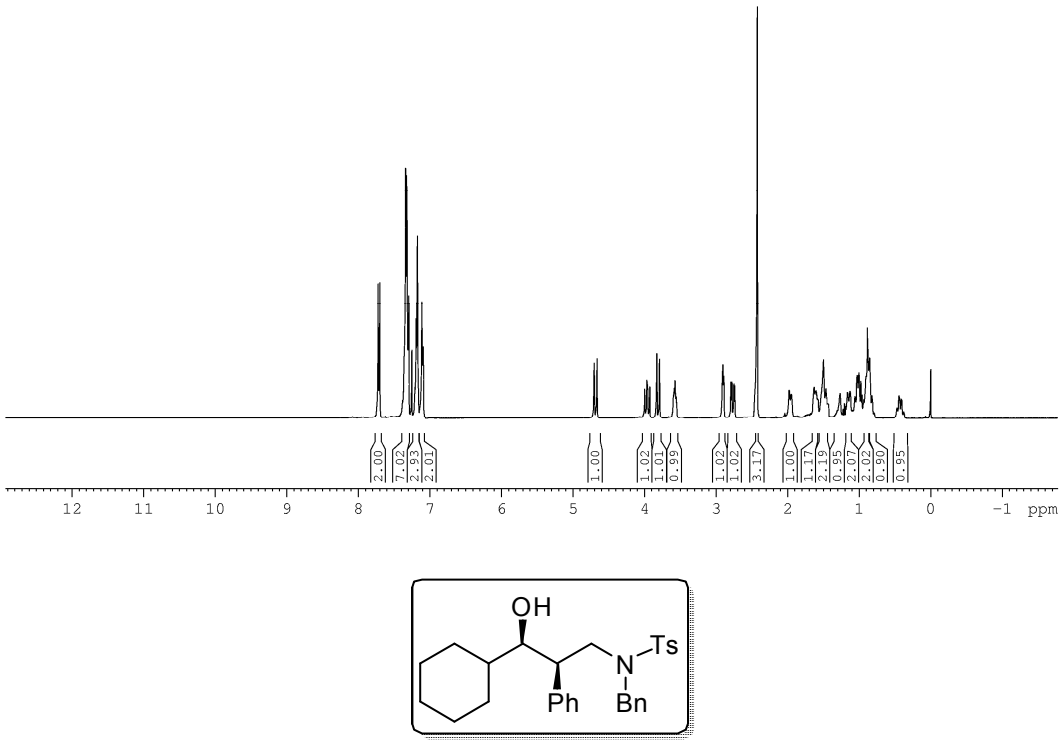


Figure A-25. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3a** in $CDCl_3$.



_N_-Benzyl-_N_-((2_R_,3_R_)-3-cyclohexyl-3-hydroxy-2-phenylpropyl)-4-methylbenzenesulfonamide (3b)

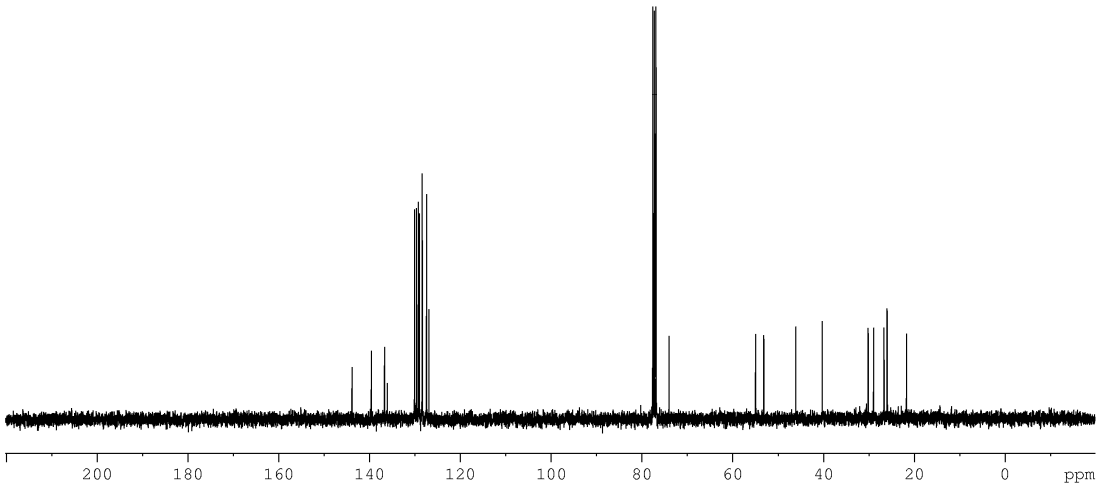
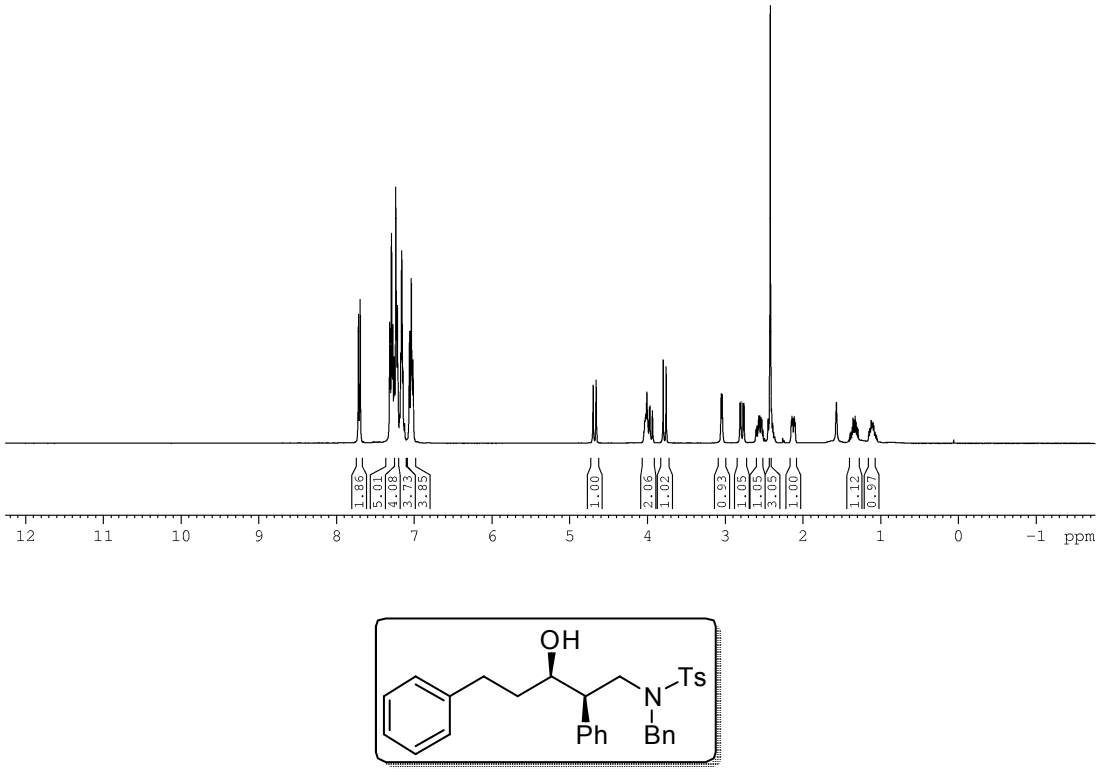


Figure A-26. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3b** in $CDCl_3$.



_N_-Benzyl-_N_-((2_R_,3_R_)-3-hydroxy-2,5-diphenylpentyl)-4-methylbenzenesulfonamide (3c)

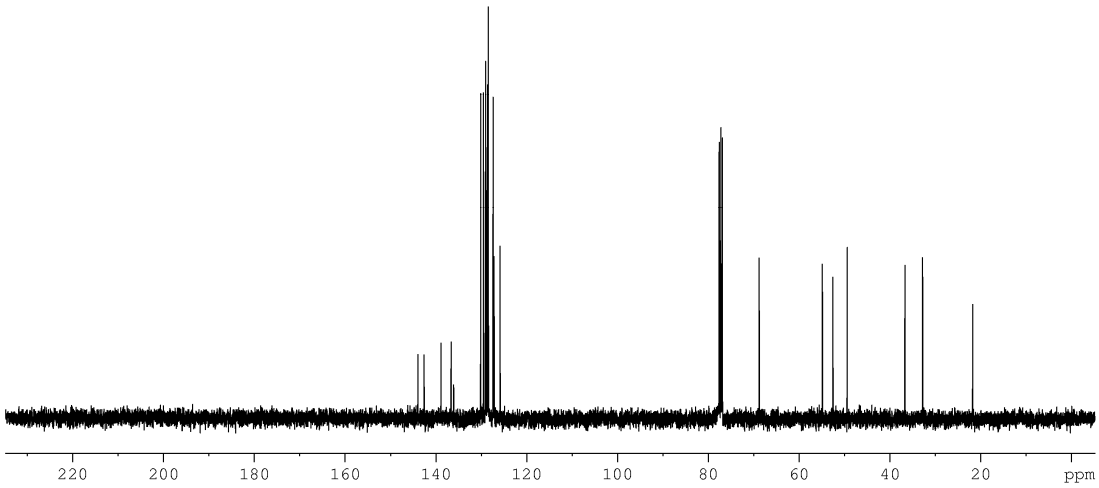
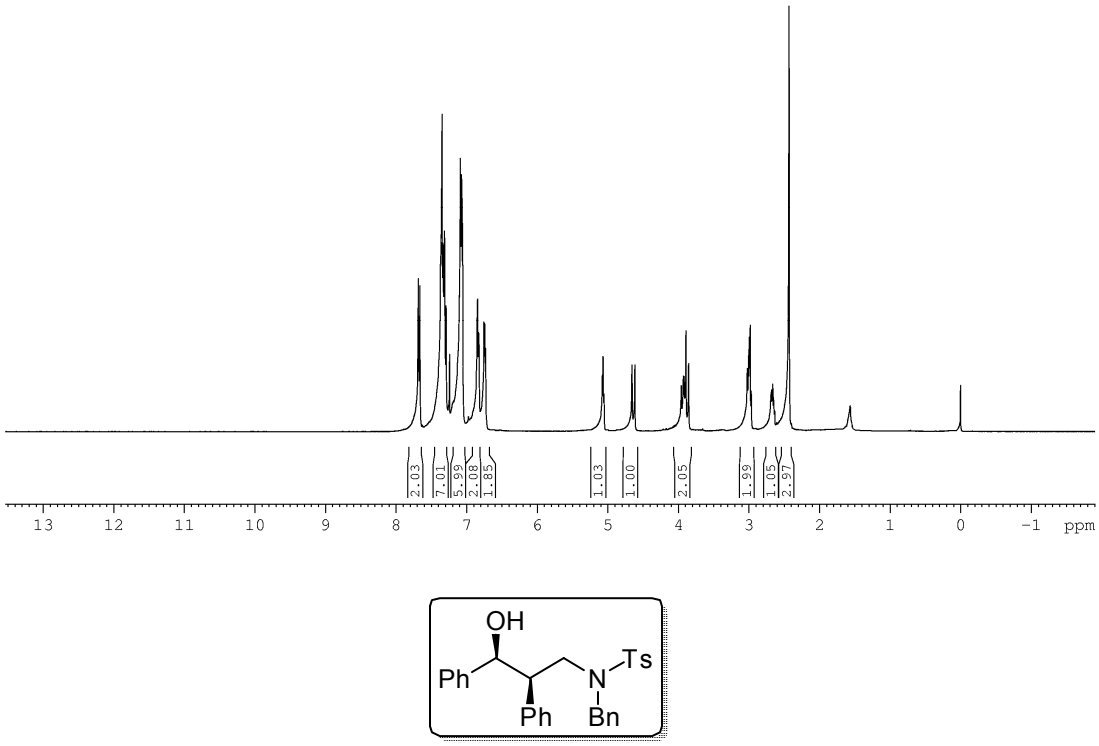


Figure A-27. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3c** in $CDCl_3$.



_N_-Benzyl-_N_-((2_R_,3_S_)-3-hydroxy-2,3-diphenylpropyl)-4-methylbenzenesulfonamide (3d)

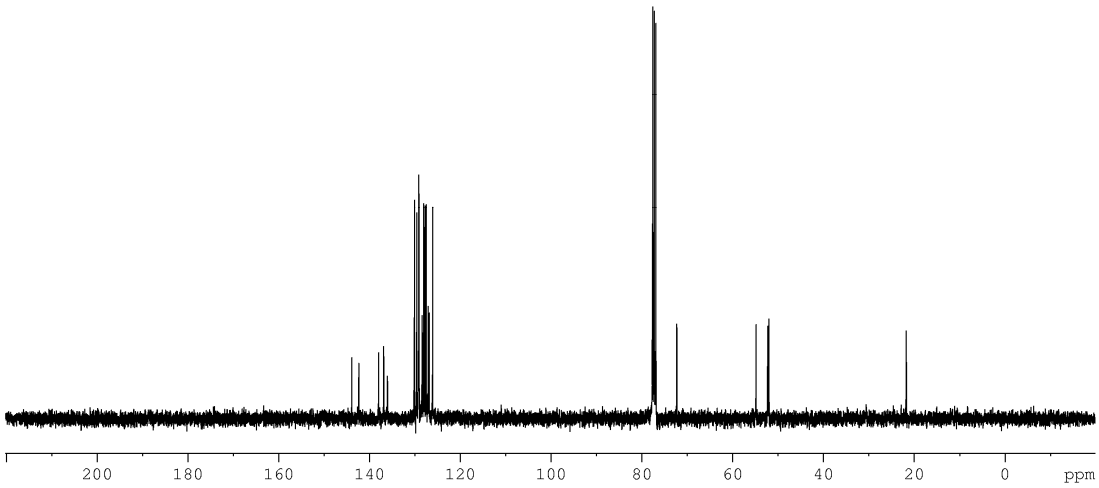
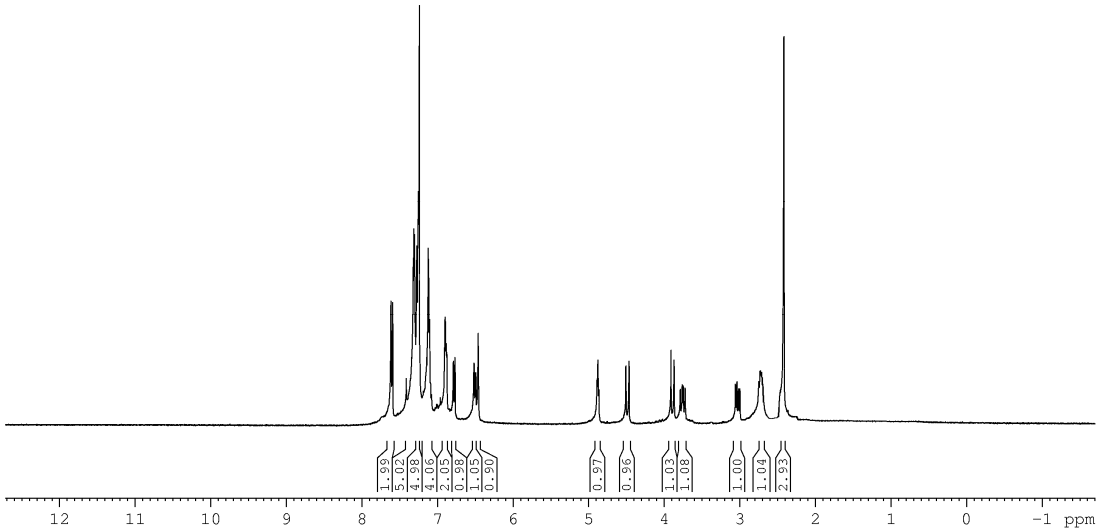
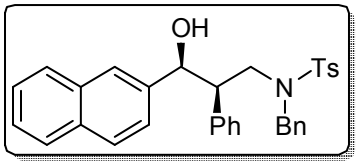


Figure A-28. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3d** in $CDCl_3$.





_N_-Benzyl-_N_-((2_R_,3_S_)-3-hydroxy-3-(naphthalen-2-yl)-2-phenylpropyl)-4-methylbenzenesulfonamide (3e)

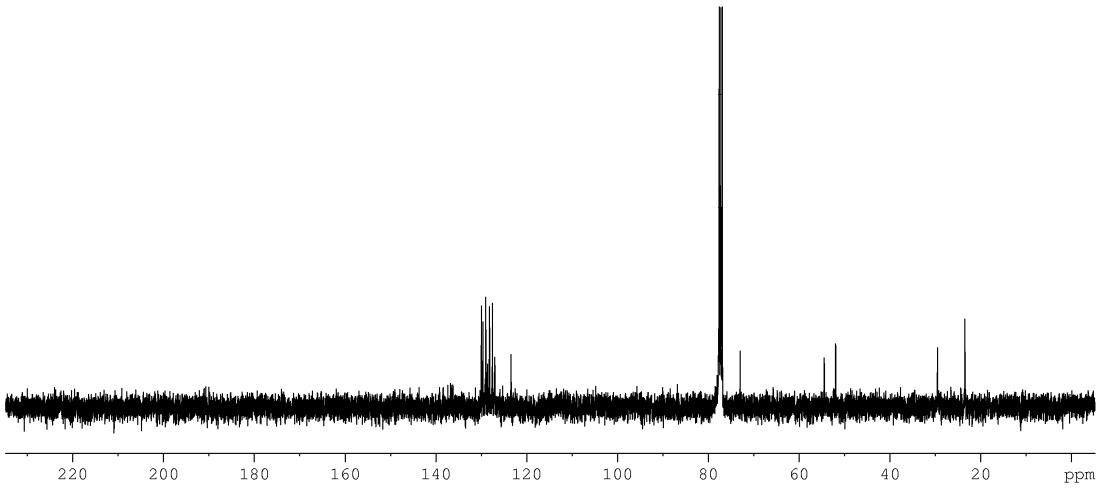
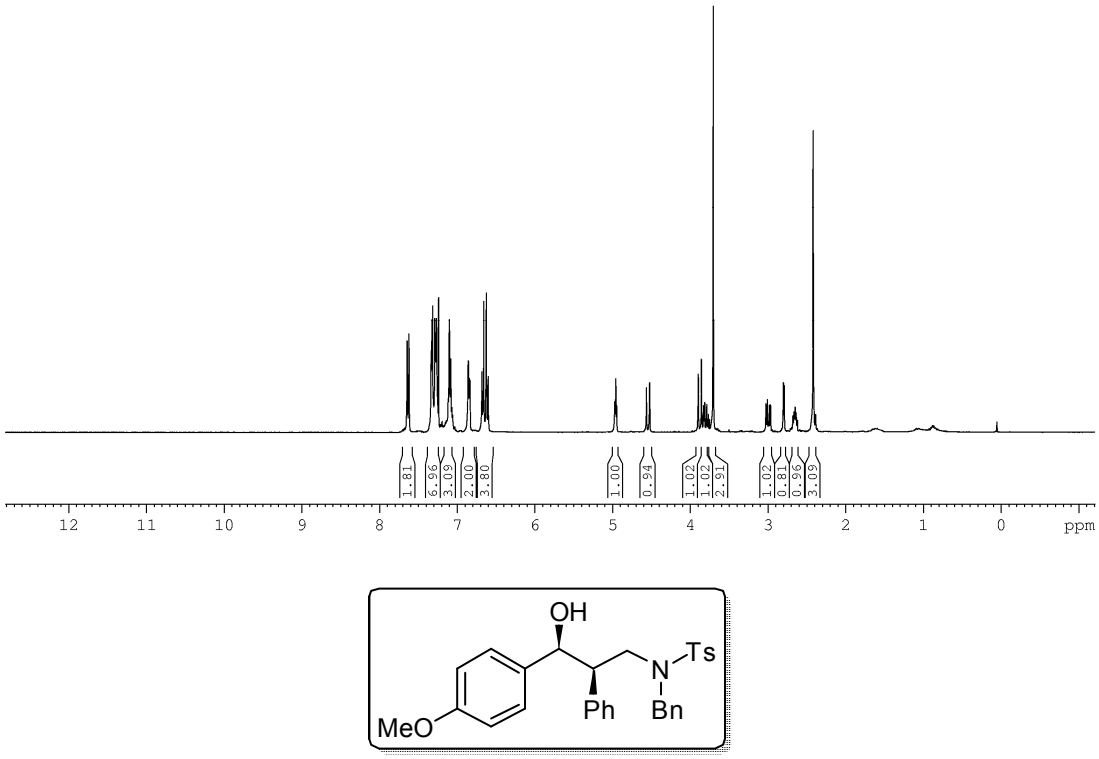


Figure A-29. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3e** in $CDCl_3$.



_N_-Benzyl-_N_-((2_R_,3_S_)-3-hydroxy-3-(4-methoxyphenyl)-2-phenylpropyl)-4-methylbenzenesulfonamide (3f)

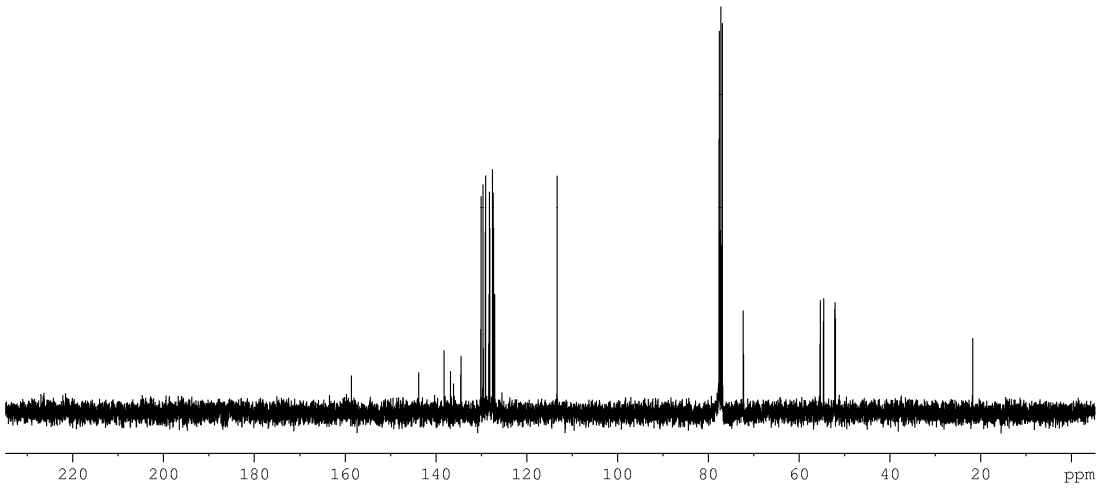
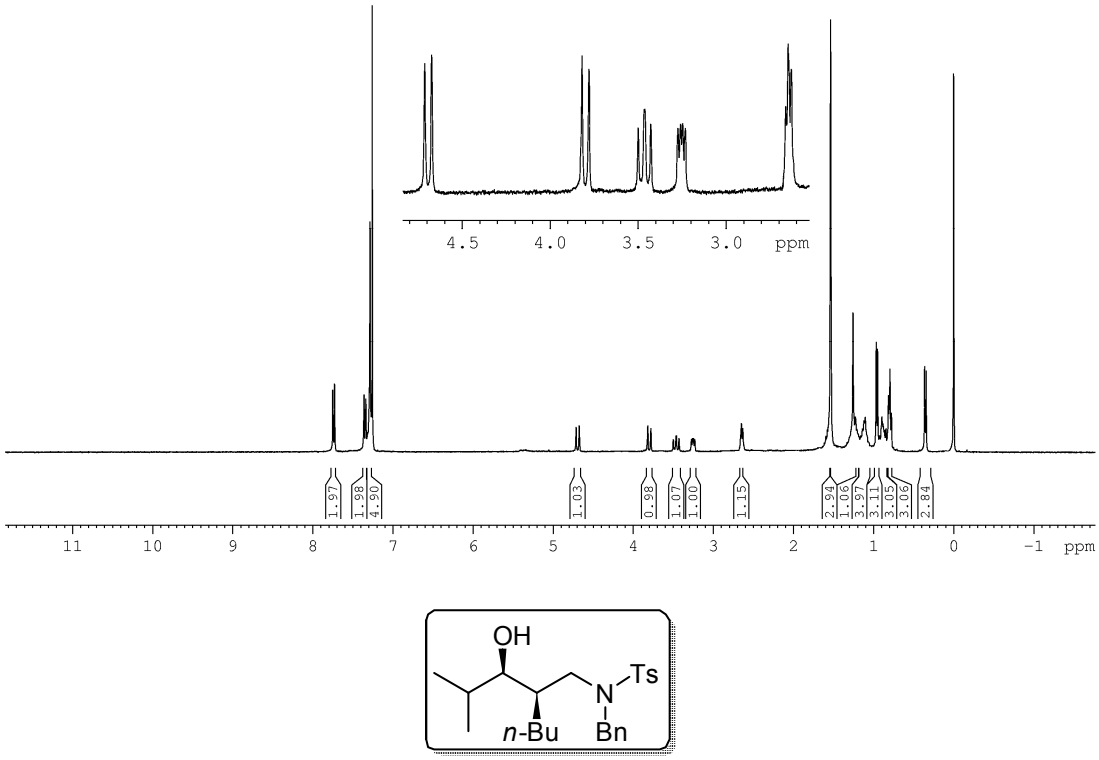


Figure A-30. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3f** in $CDCl_3$.



_N_-Benzyl-_N_-((_R_)-2-((_R_)-1-hydroxy-2-methylpropyl)hexyl)-4-methylbenzenesulfonamide (3g)

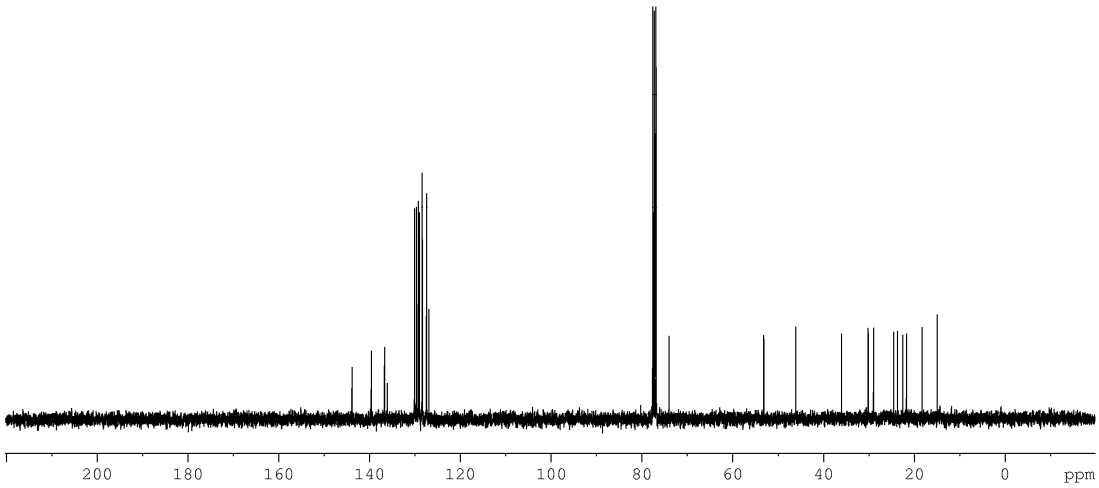
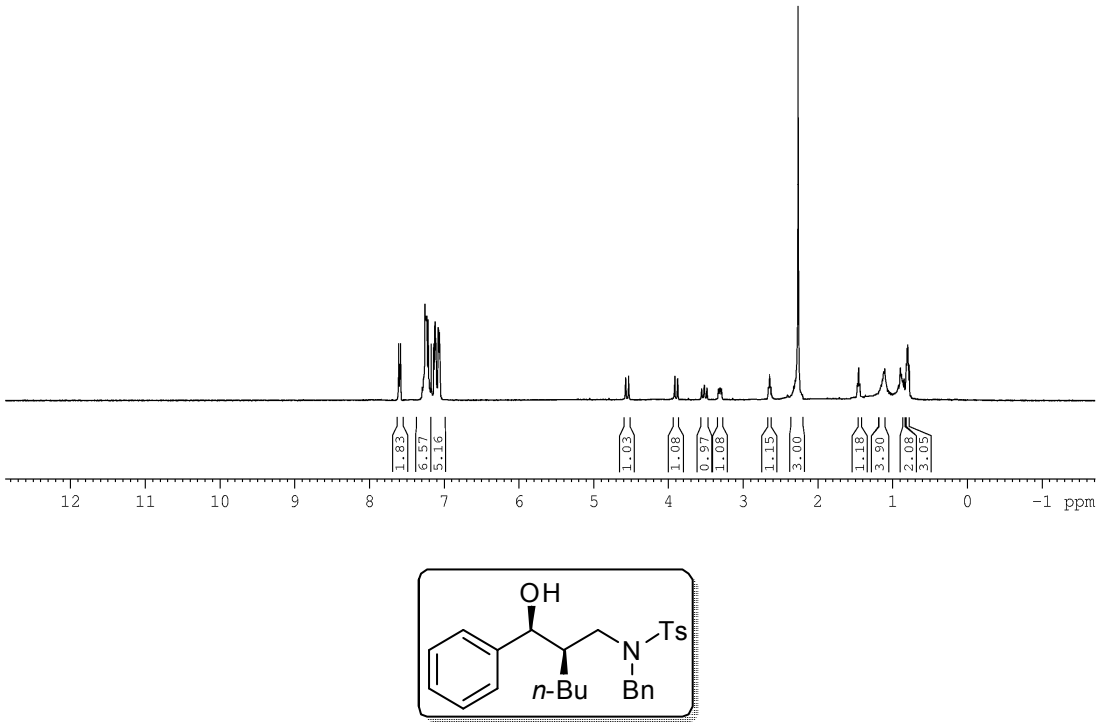


Figure A-31. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3g** in $CDCl_3$.



_N_-Benzyl-_N_-((_R_)-2-((_S_)-hydroxy(phenyl)methyl)hexyl)-4-methylbenzenesulfonamide (3h)

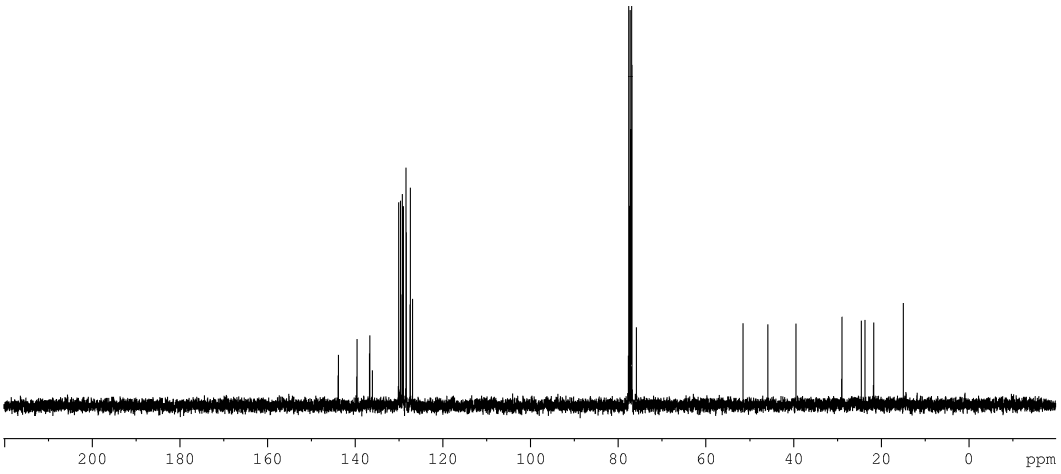
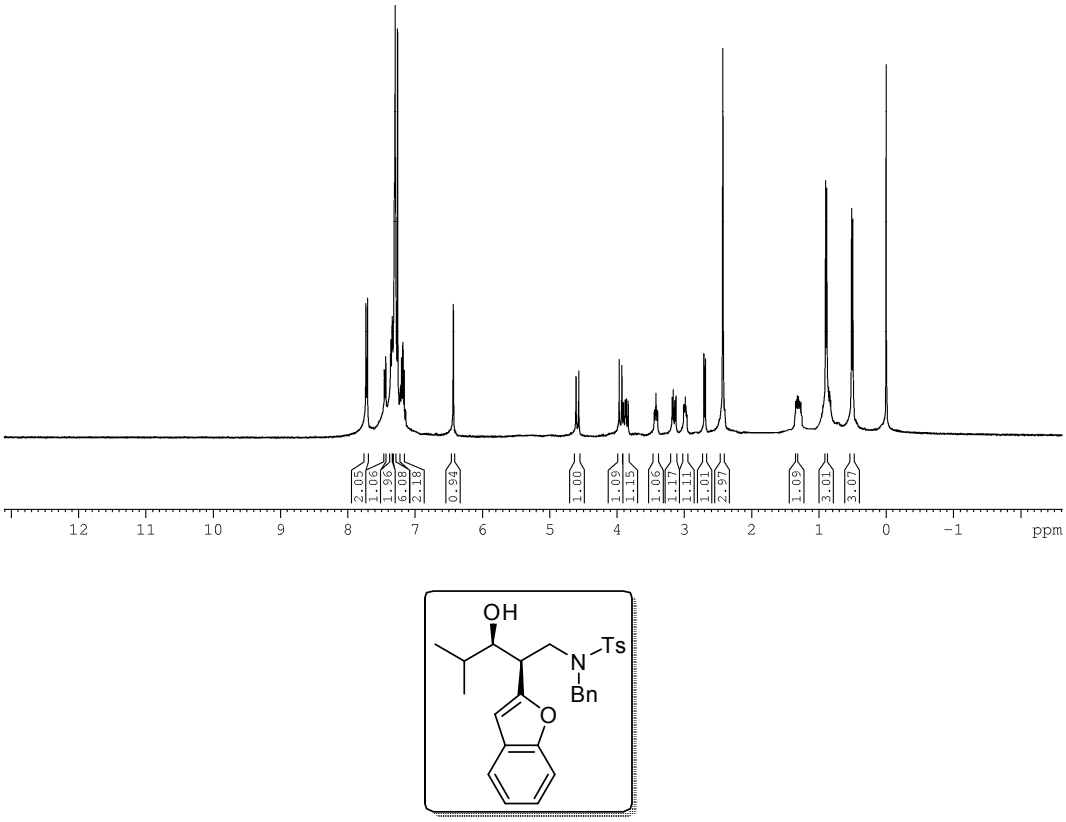


Figure A-32. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3h** in $CDCl_3$.



_N_-((2_R_,3_R_)-2-(Benzofuran-2-yl)-3-hydroxy-4-methylpentyl)-_N_-benzyl-4-methylbenzenesulfonamide (3i)

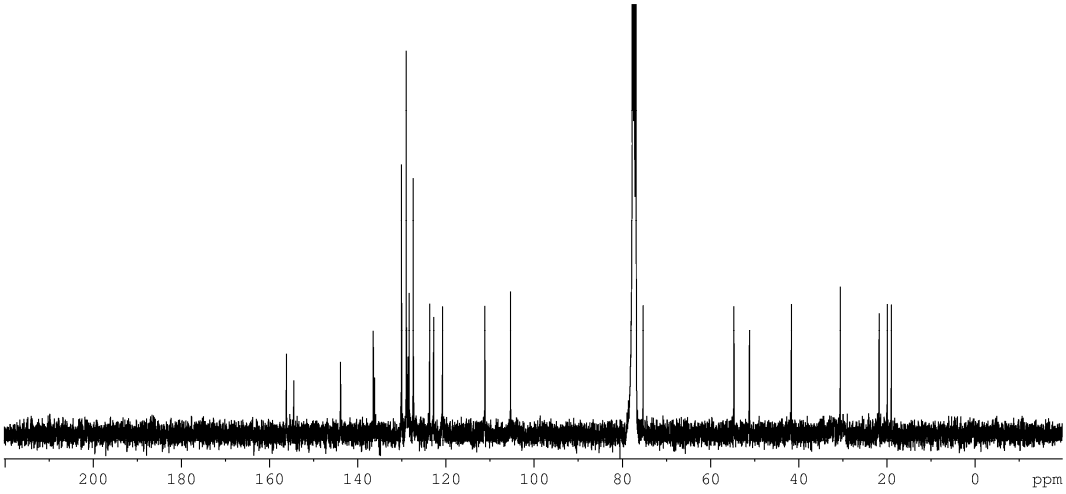
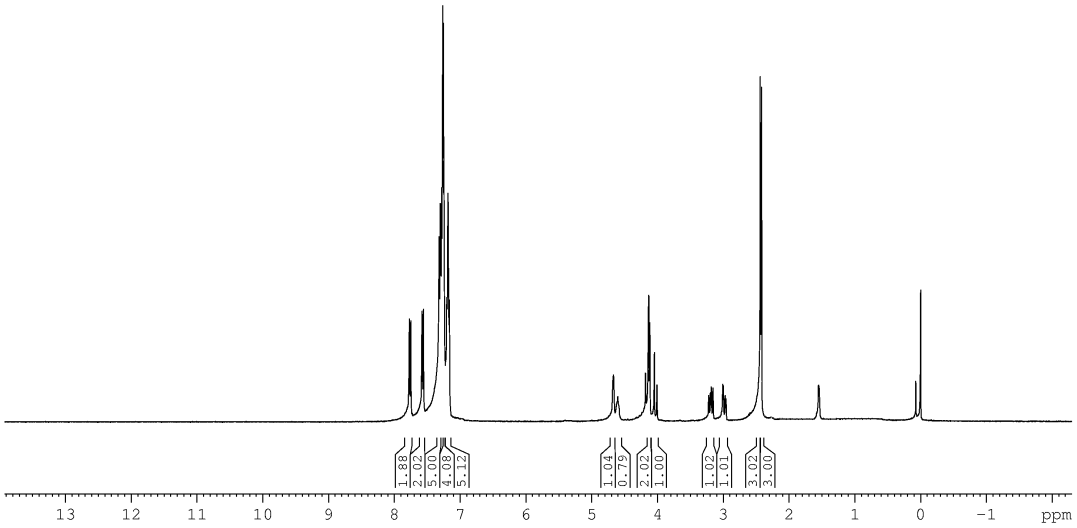
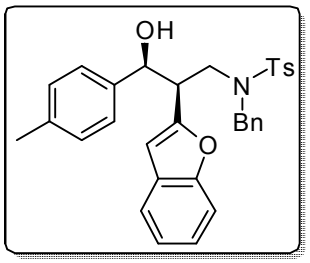


Figure A-33. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3i** in $CDCl_3$.





***N*-((2*R*,3*S*)-2-(Benzofuran-2-yl)-3-hydroxy-3-(*p*-tolyl)propyl)-*N*-benzyl-4-methylbenzenesulfonamide (3j)**

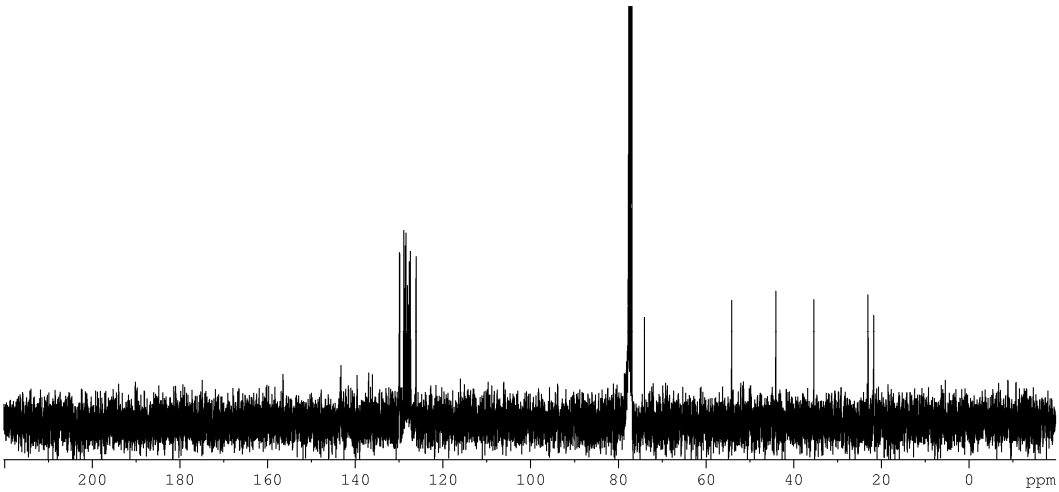
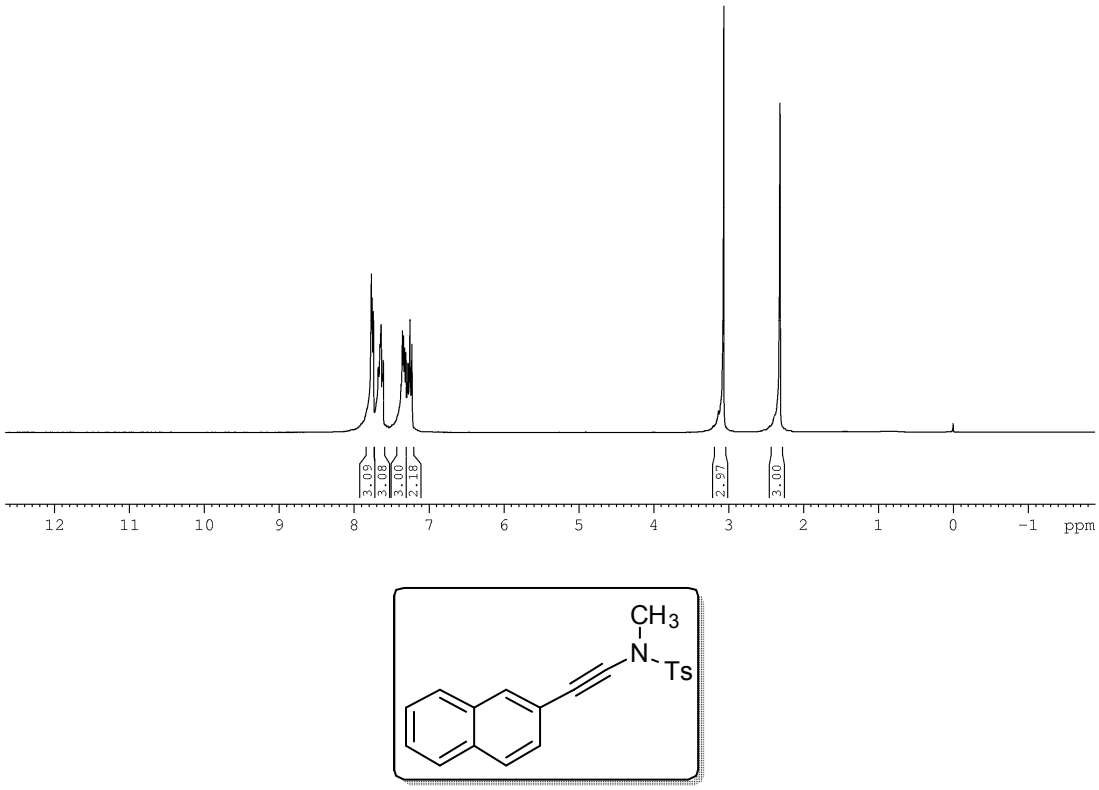


Figure A-34. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **3j** in $CDCl_3$.

A-4. Chapter 4 Spectra



_N_,4-Dimethyl-_N_-(naphthalen-2-ylethynyl)benzenesulfonamide (4-5)

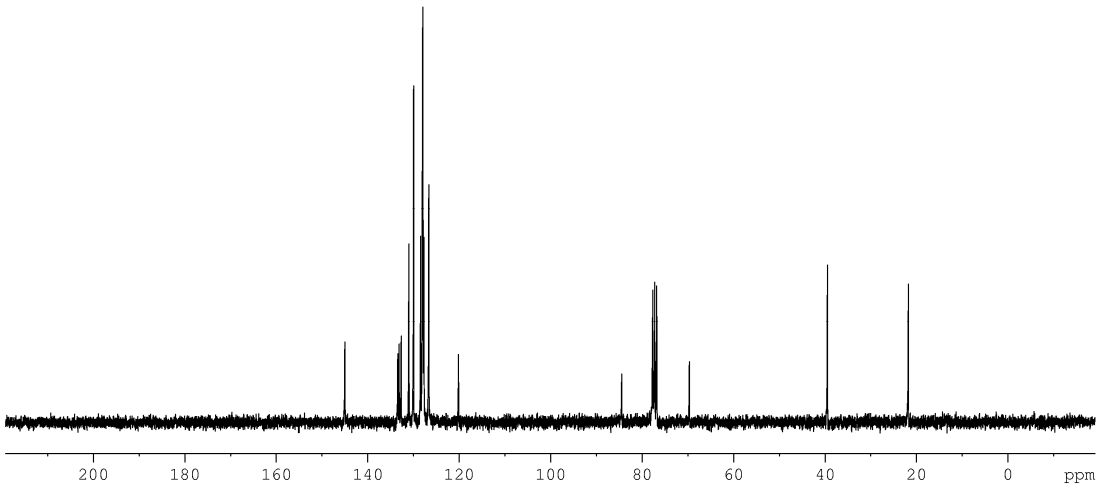
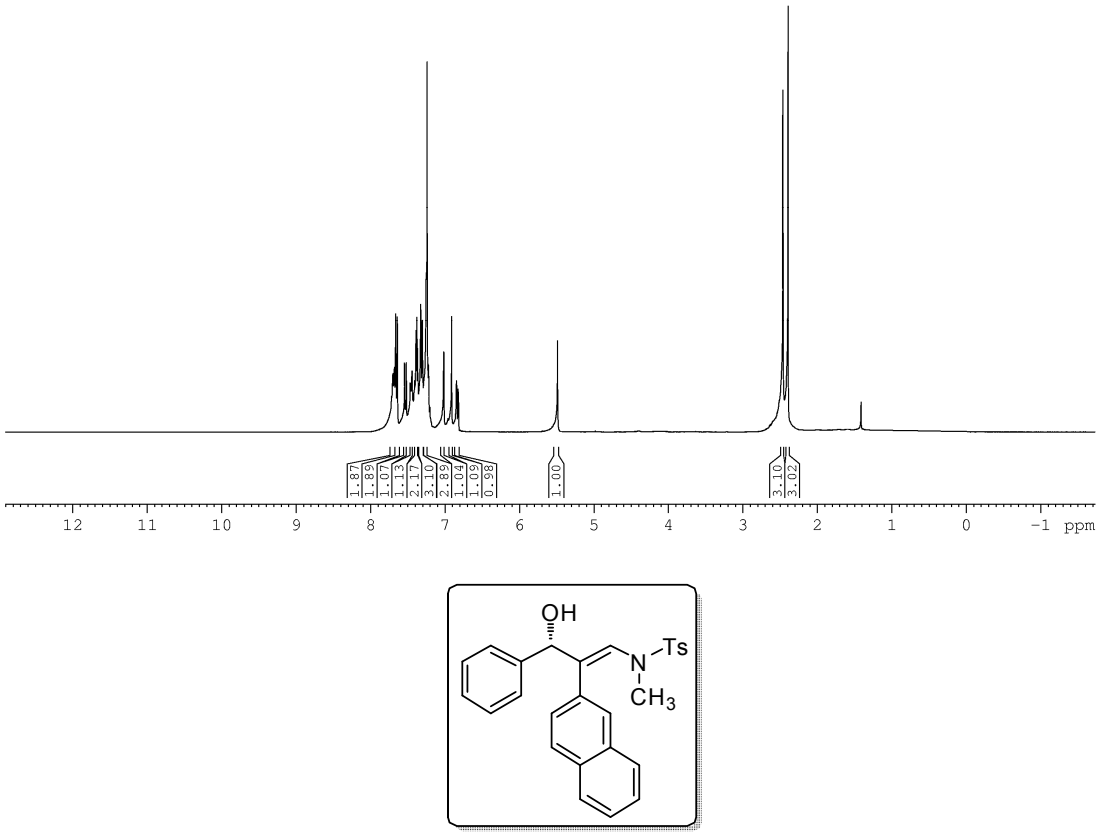


Figure A-35. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **4-5** in $CDCl_3$.



(*S*,*E*)-*N*-(3-Hydroxy-2-(naphthalen-2-yl)-3-phenylprop-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide (4-6)

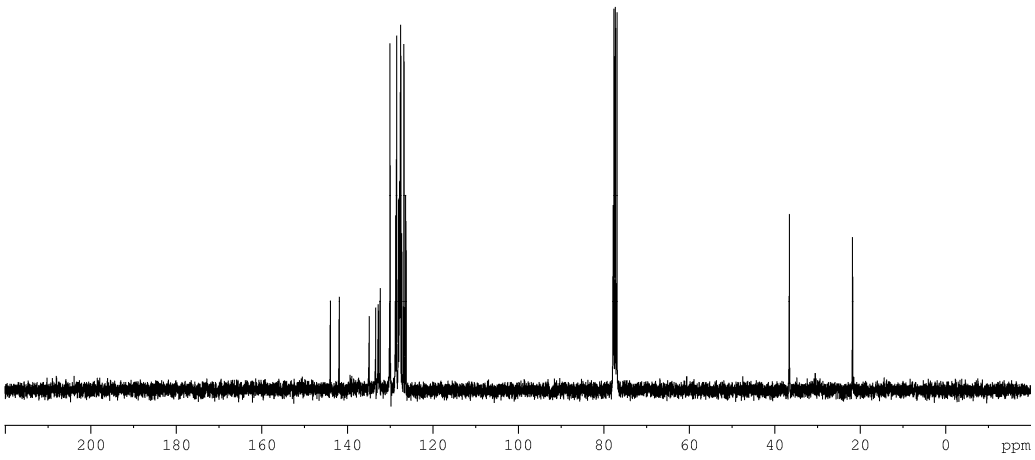
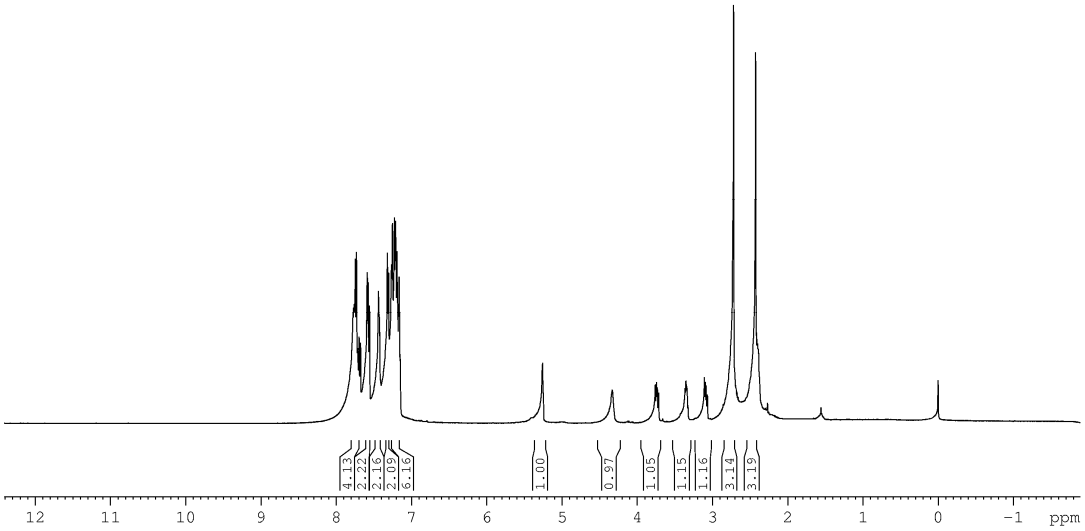
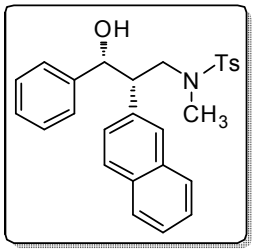


Figure A-36. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **4-6** in $CDCl_3$.





_N_-((2_S_,3_R_)-3-Hydroxy-2-(naphthalen-2-yl)-3-phenylpropyl)-_N_,4-dimethylbenzenesulfonamide (4-7)

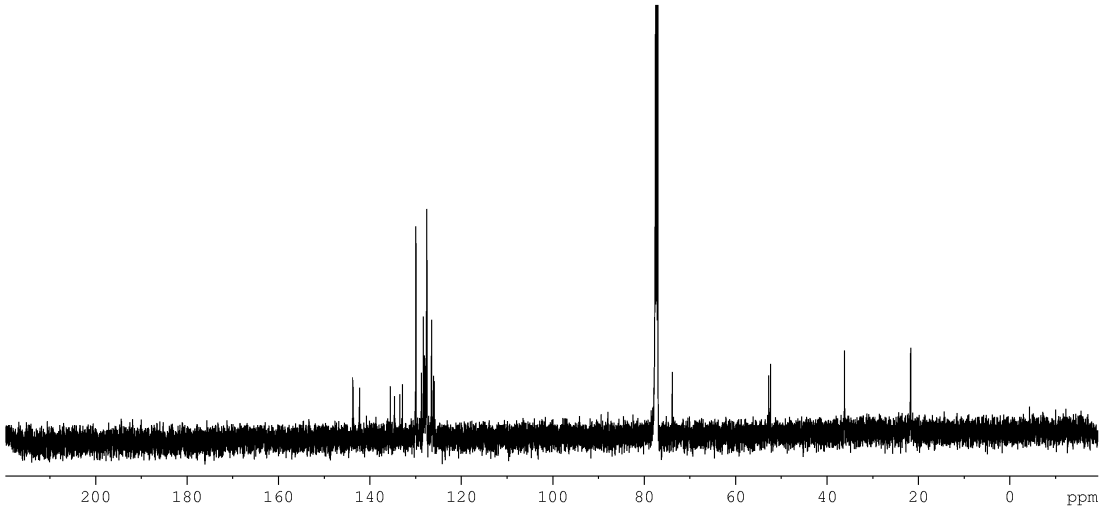
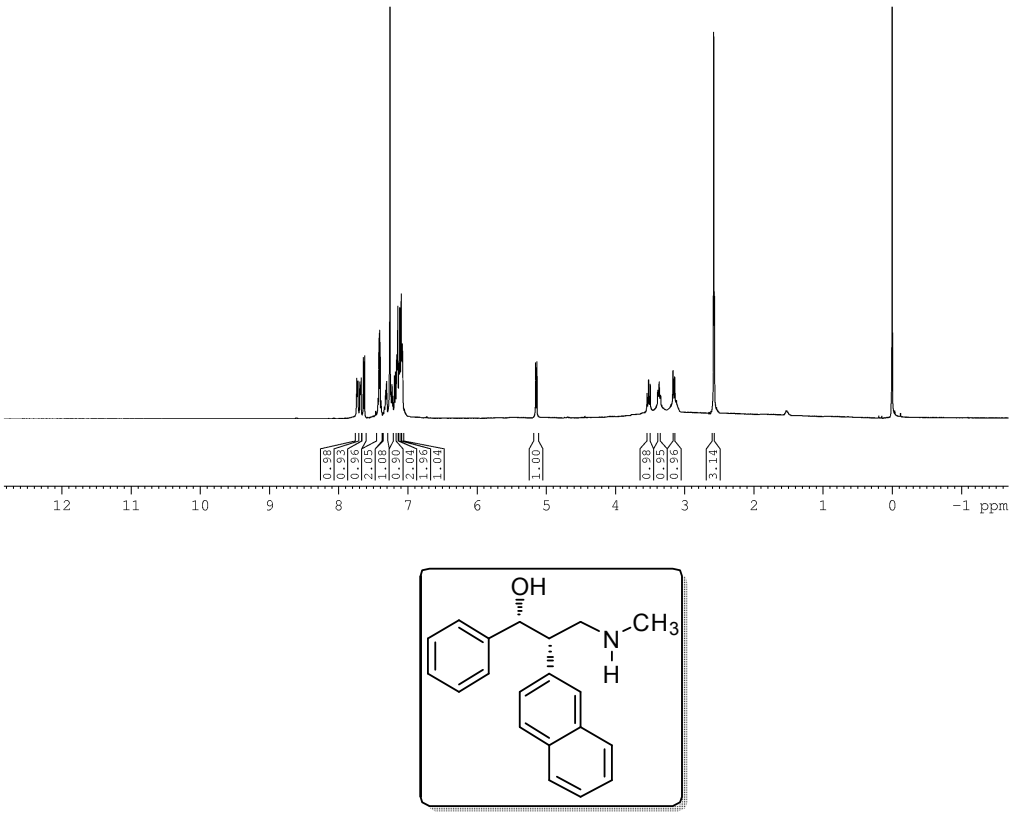


Figure A-37. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **4-7** in $CDCl_3$.



(1*R*,2*S*)-3-(Methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (4-4)

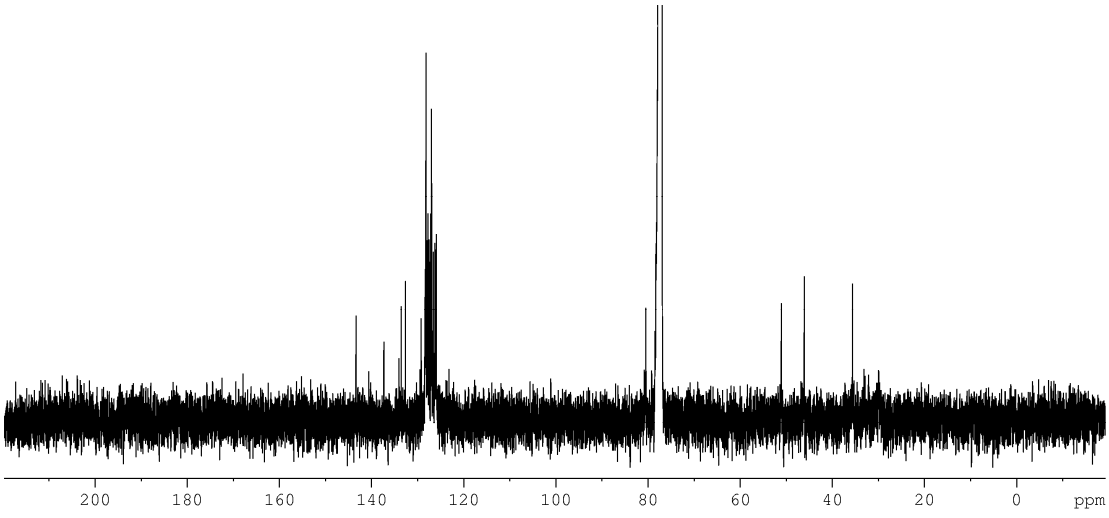
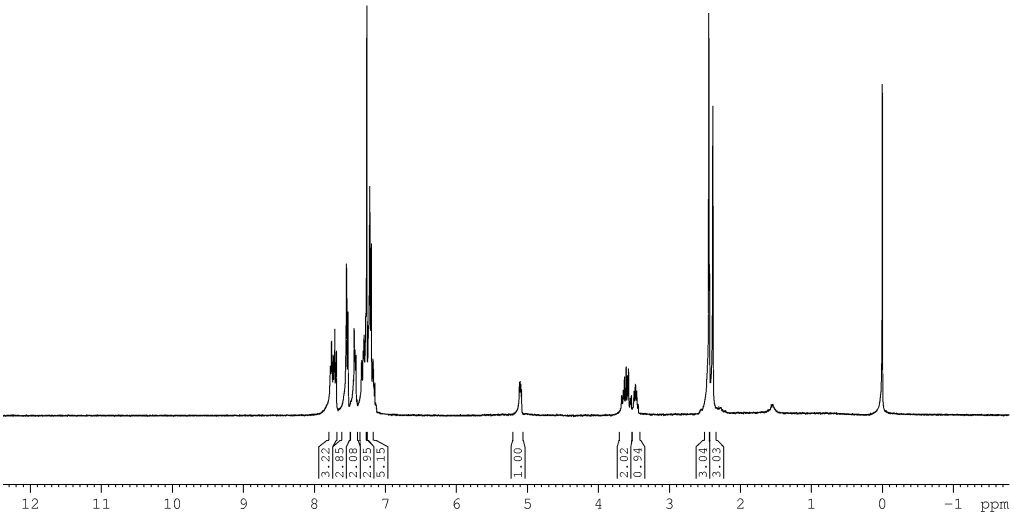
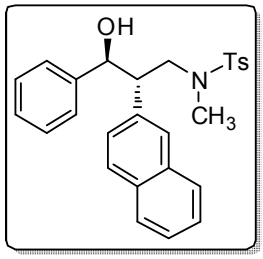


Figure A-38. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **4-4** in $CDCl_3$.





_N_-((2S,3S)-3-Hydroxy-2-(naphthalen-2-yl)-3-phenylpropyl)-N,4-dimethylbenzenesulfonamide (4-8)

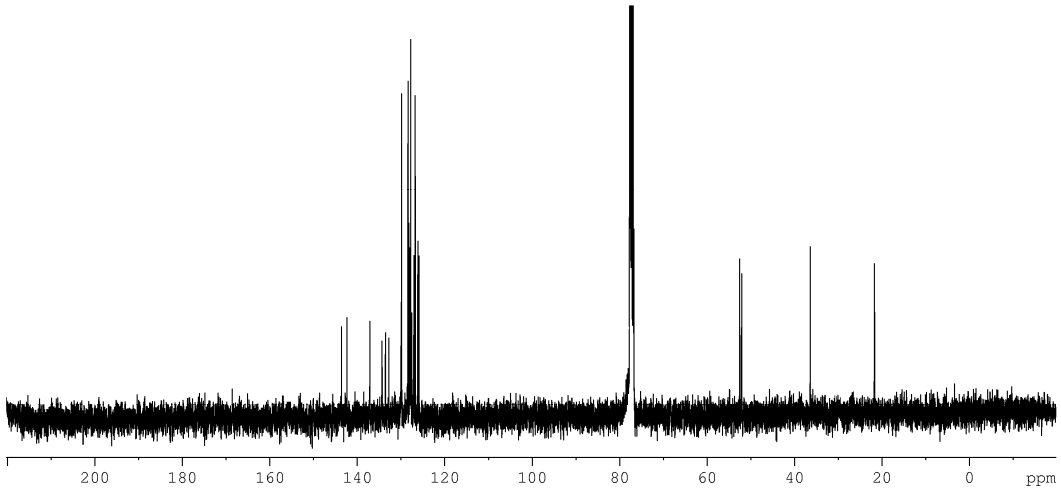
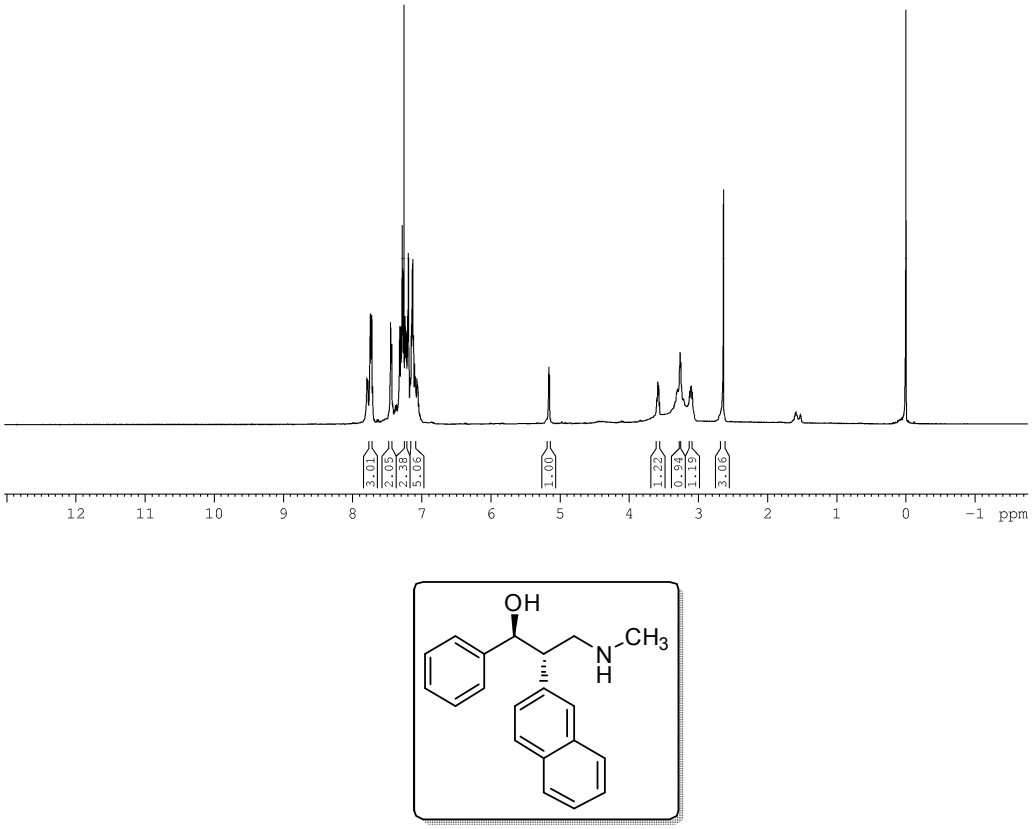


Figure A-39. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **4-8** in $CDCl_3$.



(1S,2S)-3-(Methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS)

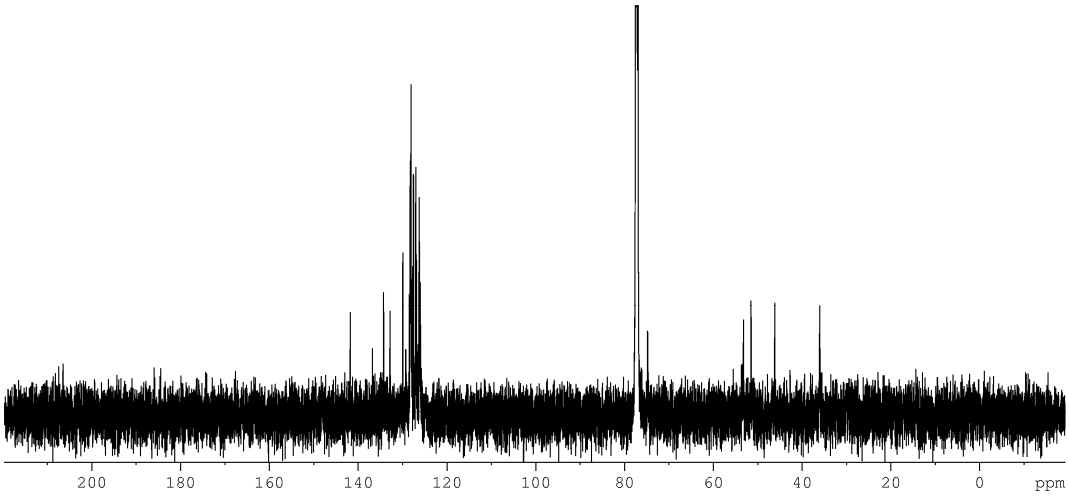


Figure A-40. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of compound **PRC200-SS** in $CDCl_3$.

A-5. Chapter 5 Spectra

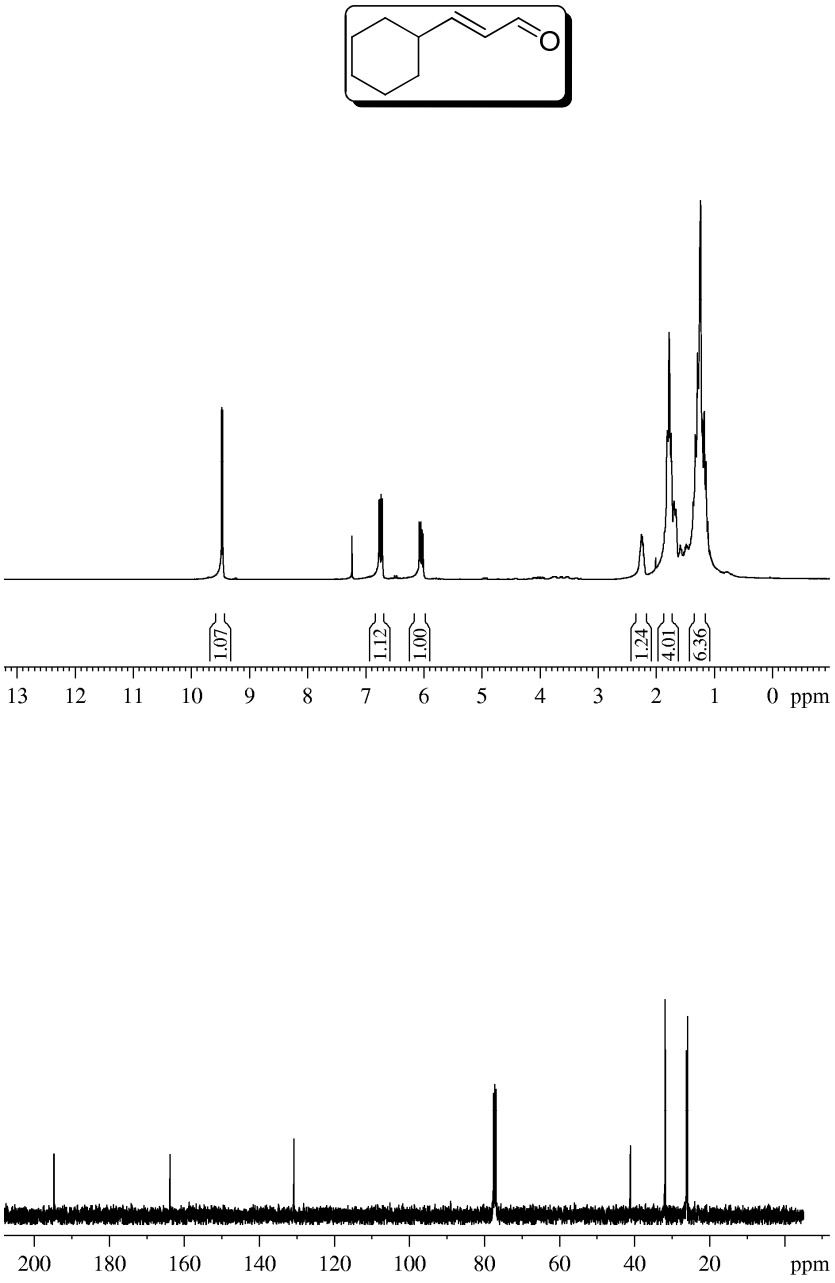


Figure A-41. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3-cyclohexylacrylaldehyde **5a** in $CDCl_3$.

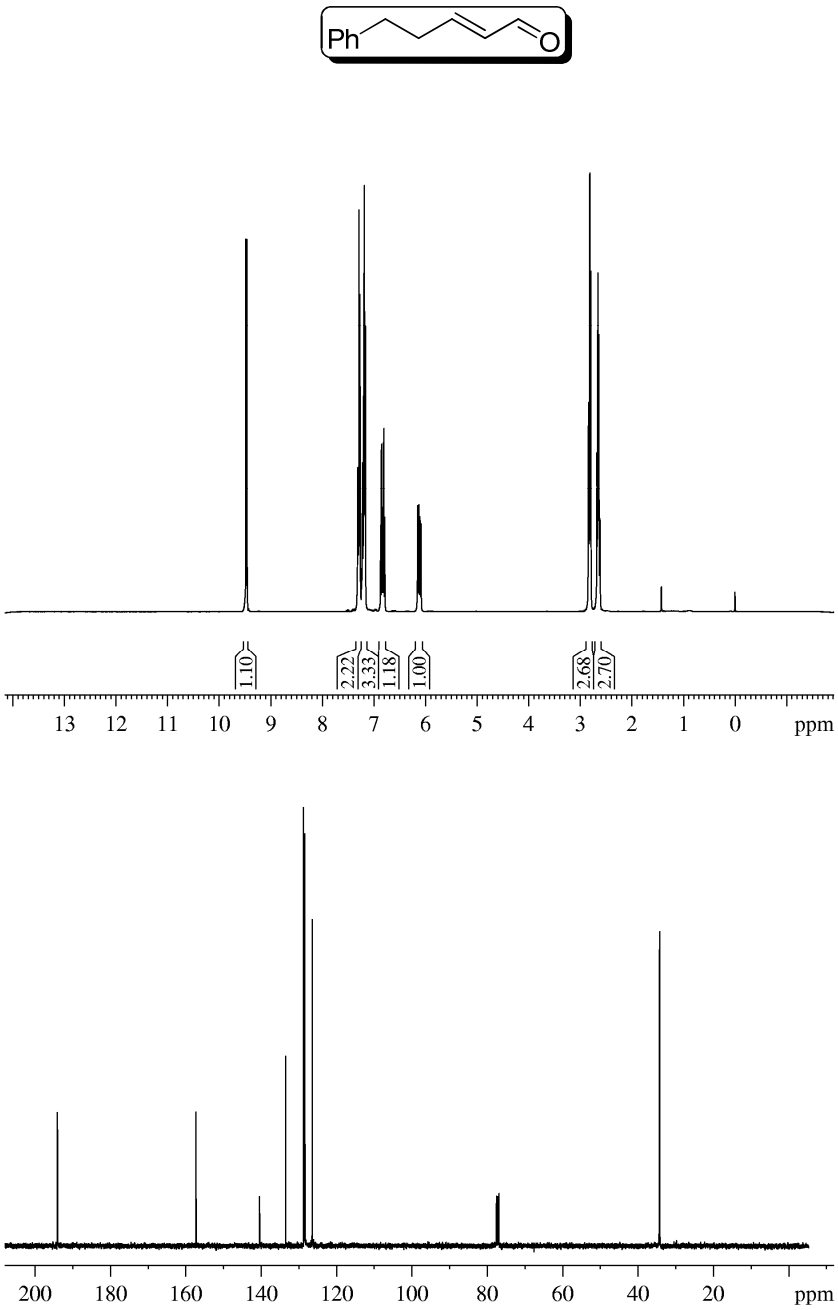


Figure A-42. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-5-phenylpent-2-enal **5b** in $CDCl_3$.

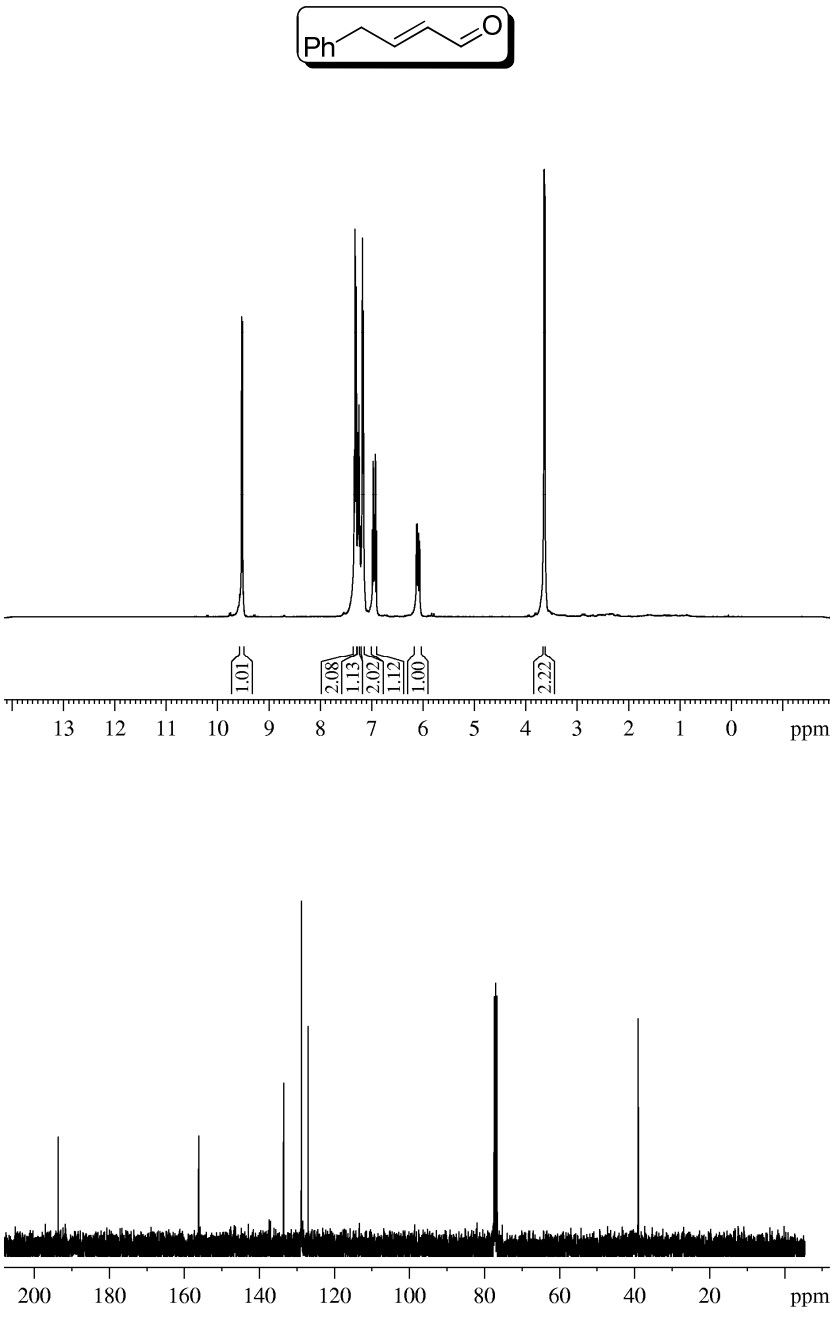


Figure A-43. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-4-phenylbut-2-enal **5c** in $CDCl_3$.

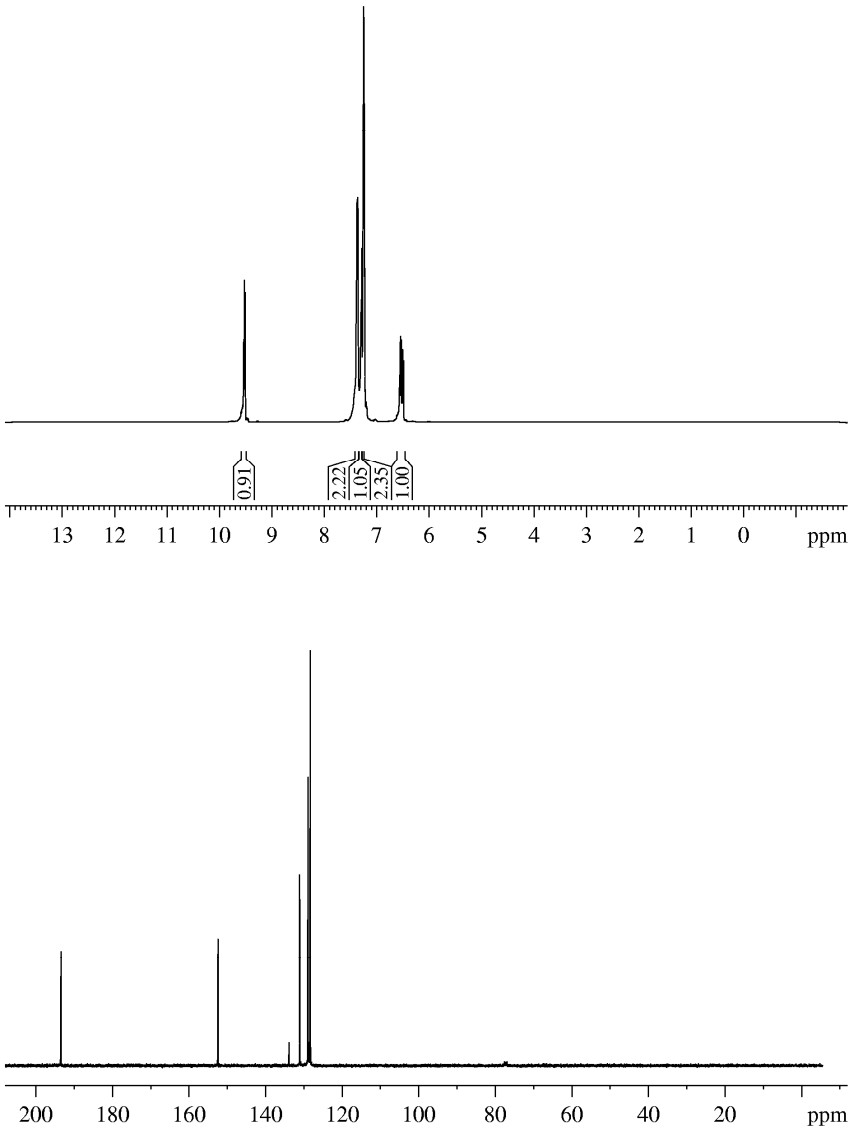


Figure A-44. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of cinnamaldehyde **5d** in $CDCl_3$.

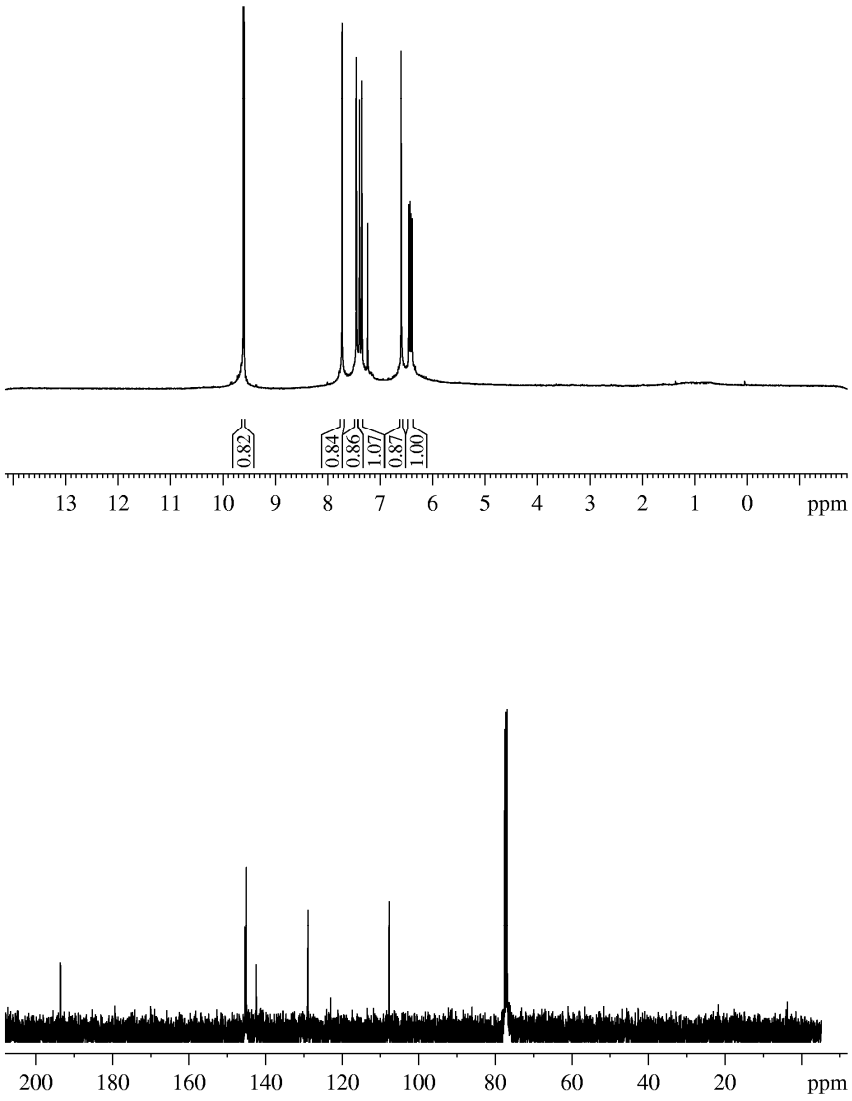


Figure A-45. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3-(furan-3-yl)acrylaldehyde **5e** in $CDCl_3$.

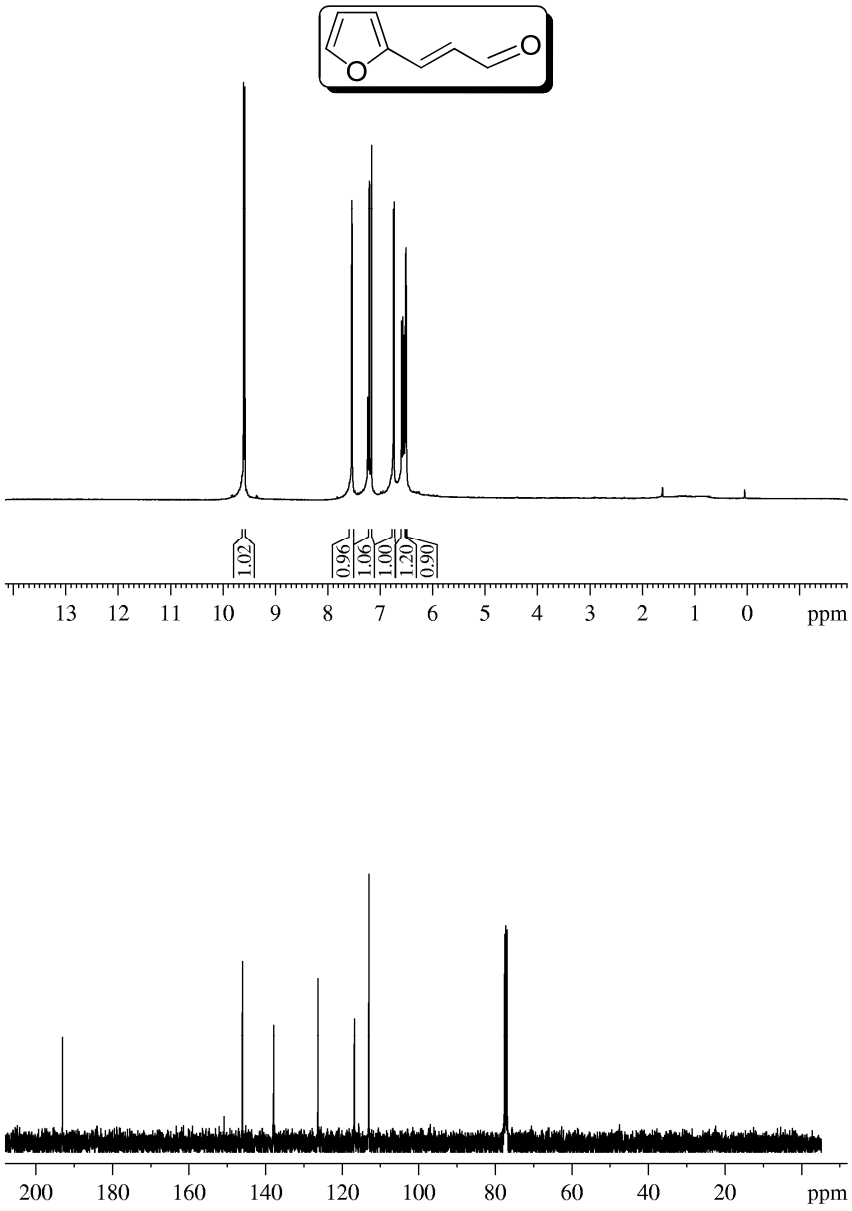


Figure A-46. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3-(furan-2-yl)acrylaldehyde **5f** in $CDCl_3$.

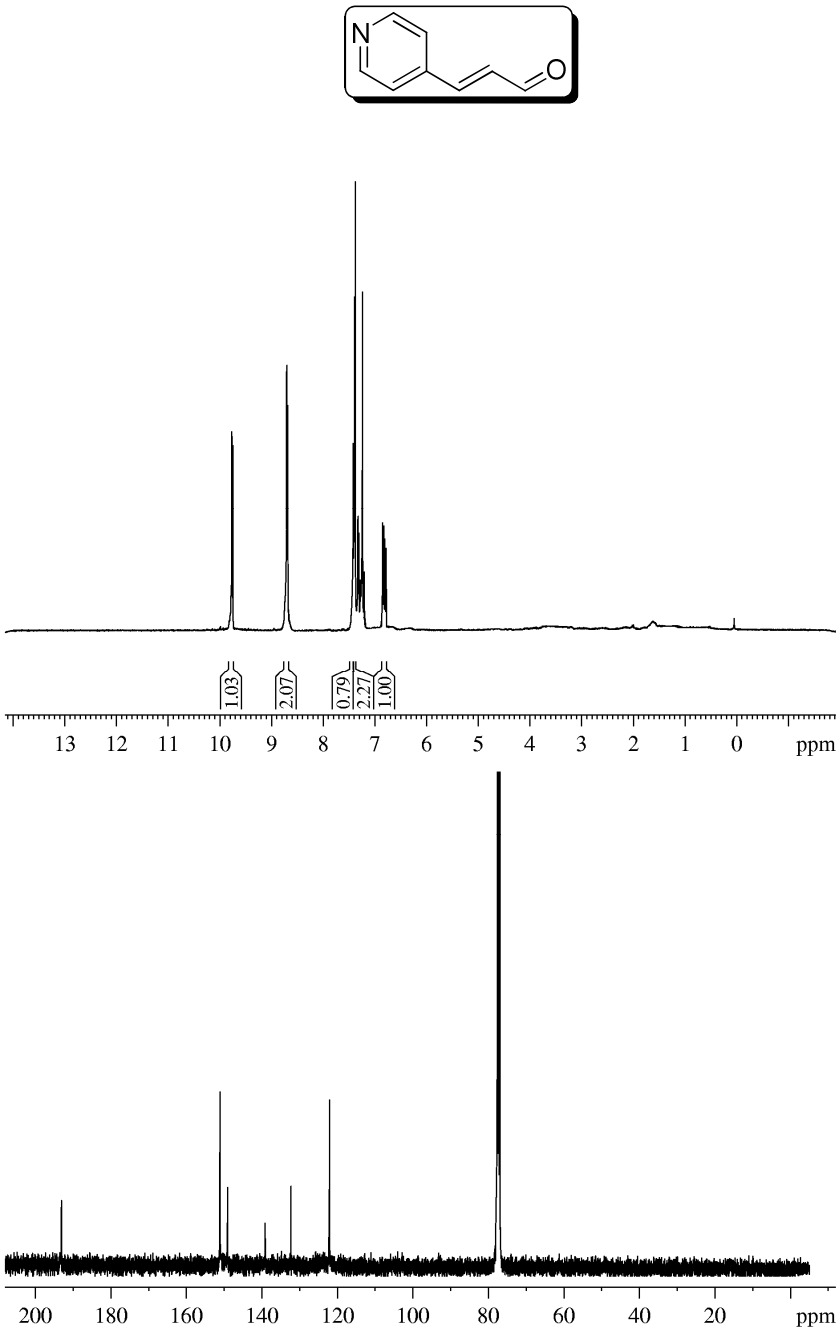


Figure A-47. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3-(furan-2-yl)acrylaldehyde **5g** in $CDCl_3$.

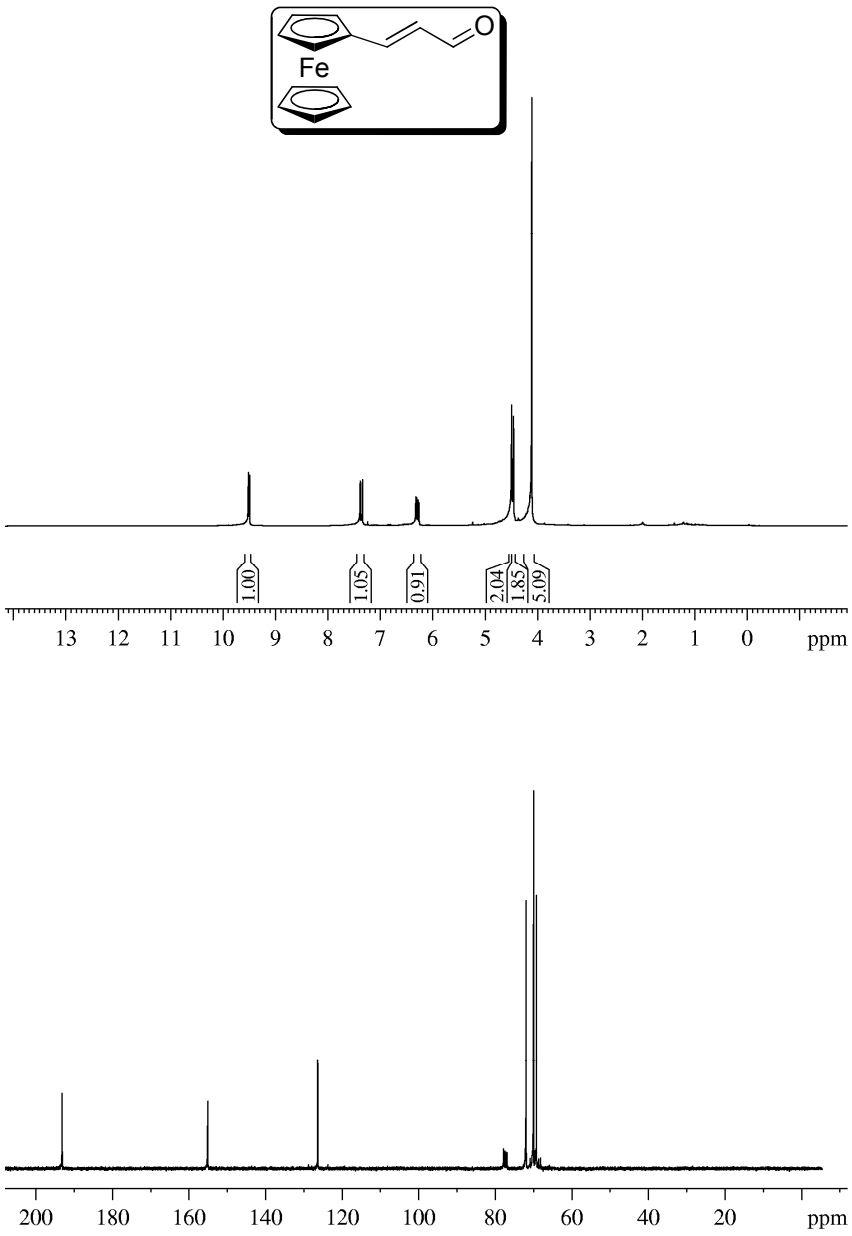


Figure A-48. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 3-ferrocenylacrolein **5h** in $CDCl_3$.

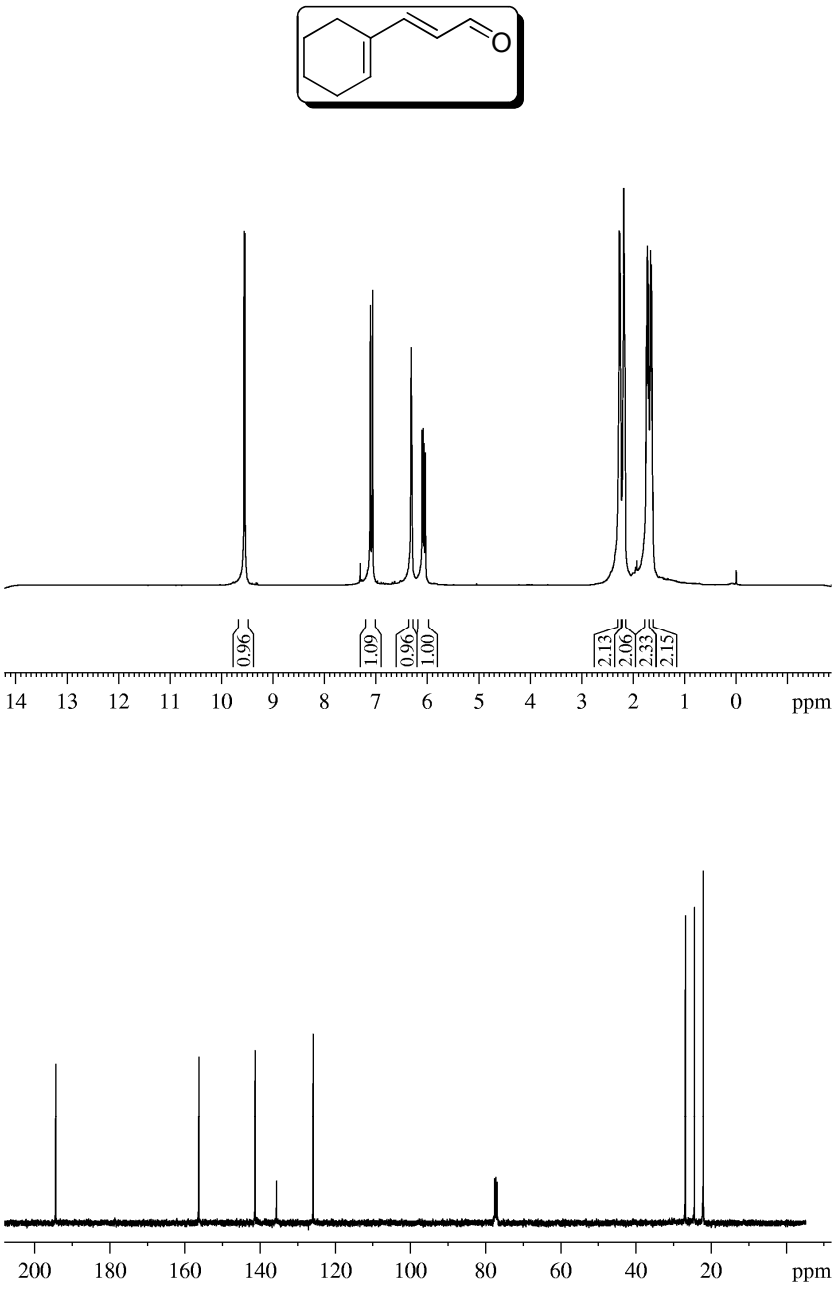


Figure A-49. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3-cyclohexenylacrylaldehyde **5i** in $CDCl_3$.

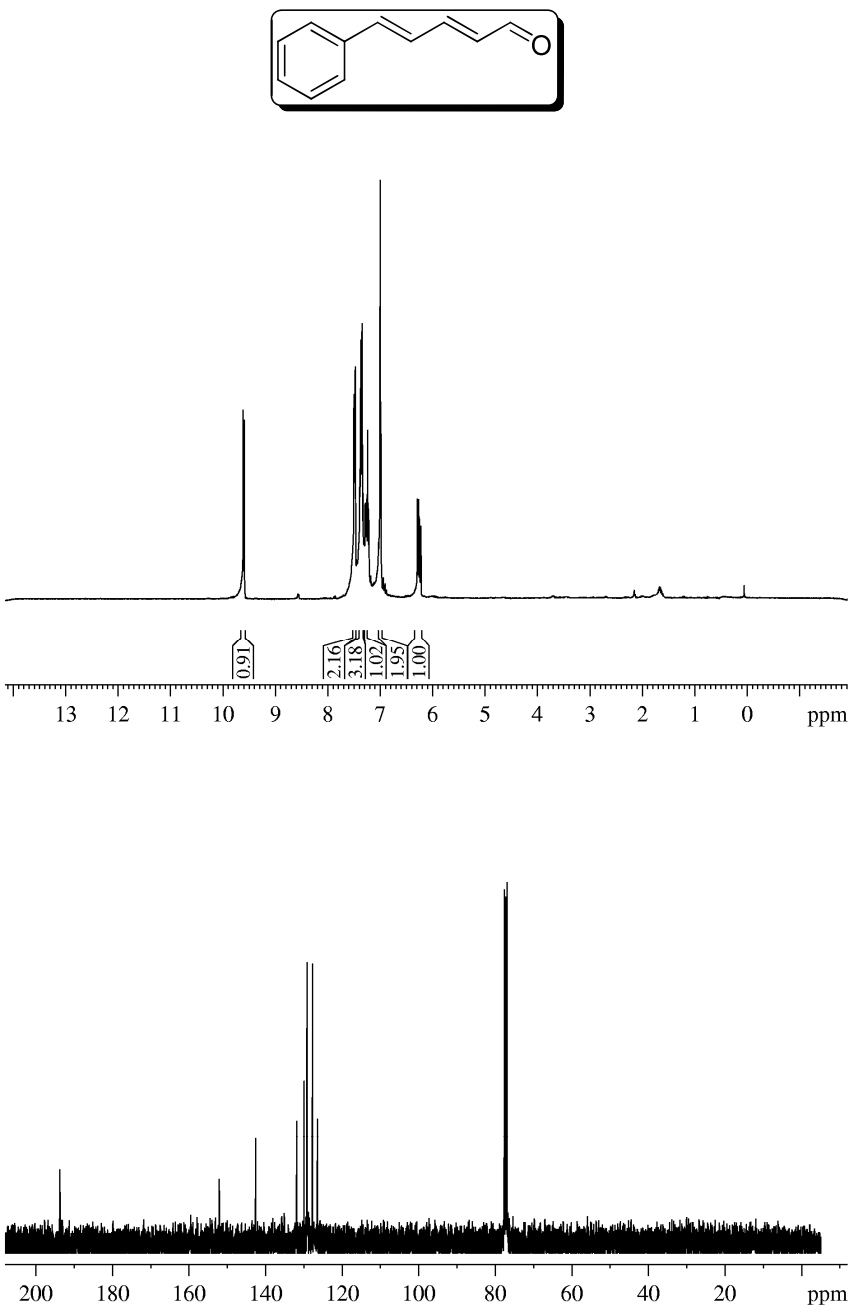


Figure A-50. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (2*E*,4*E*)-5-phenylpenta-2,4-dienal **5j** in $CDCl_3$.

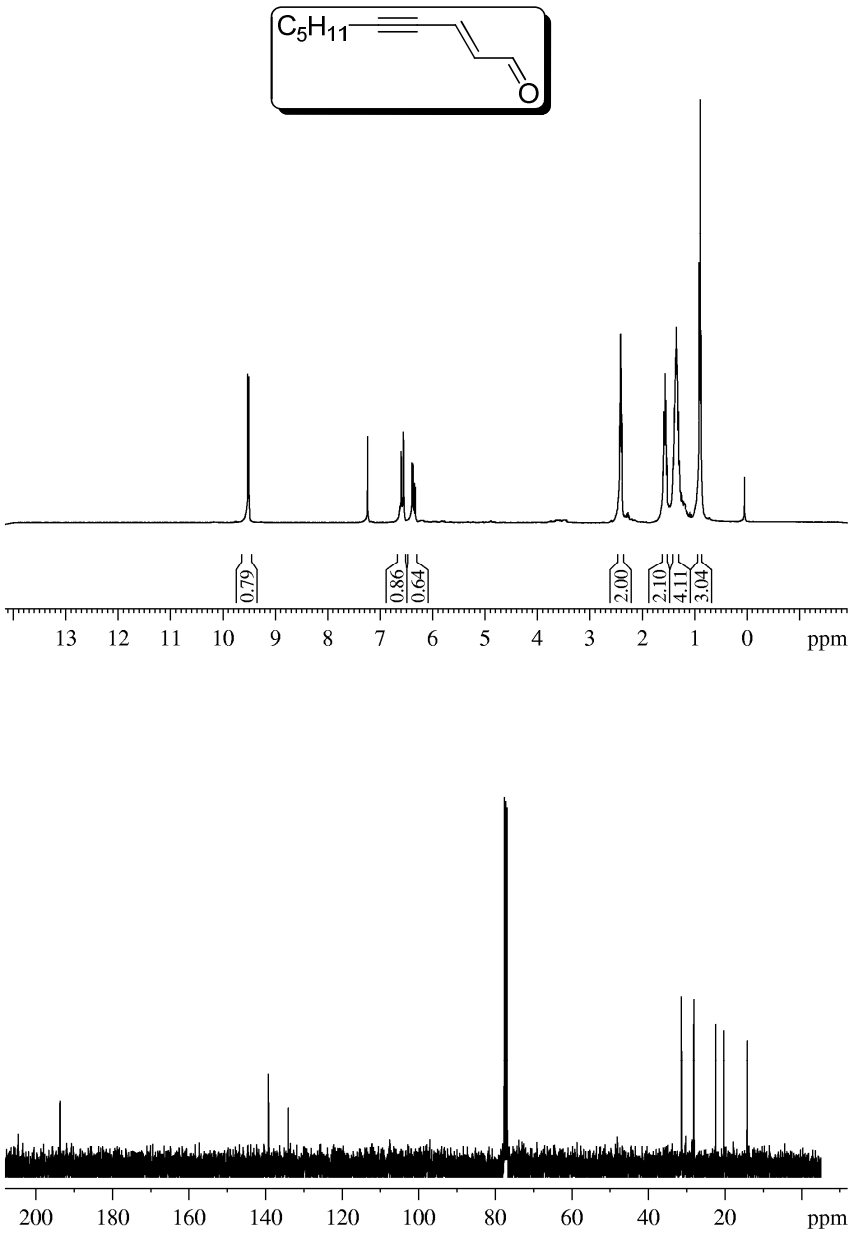


Figure A-51. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-dec-2-en-4-ynal **5k** in $CDCl_3$.

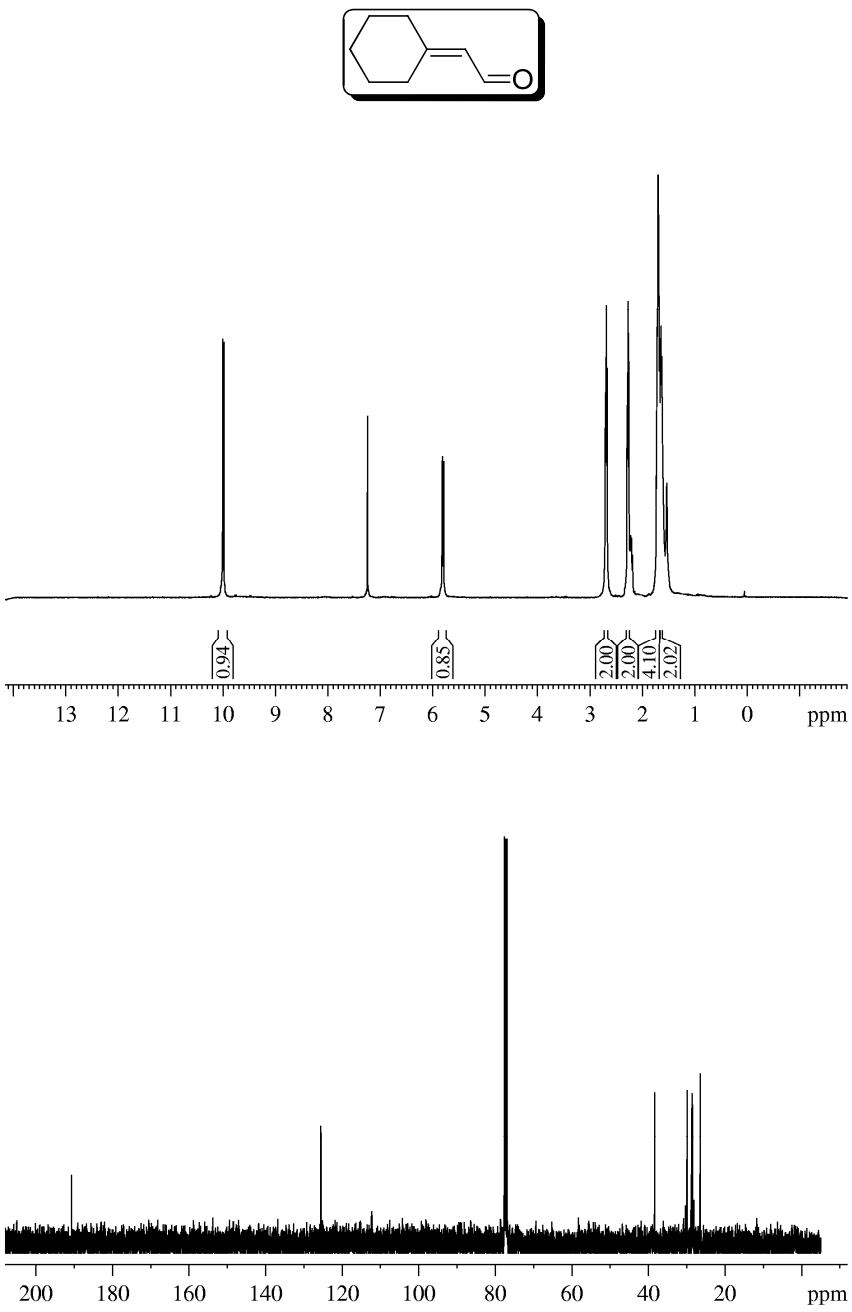


Figure A-52. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 2-cyclohexylideneacetaldehyde **5l** in $CDCl_3$.

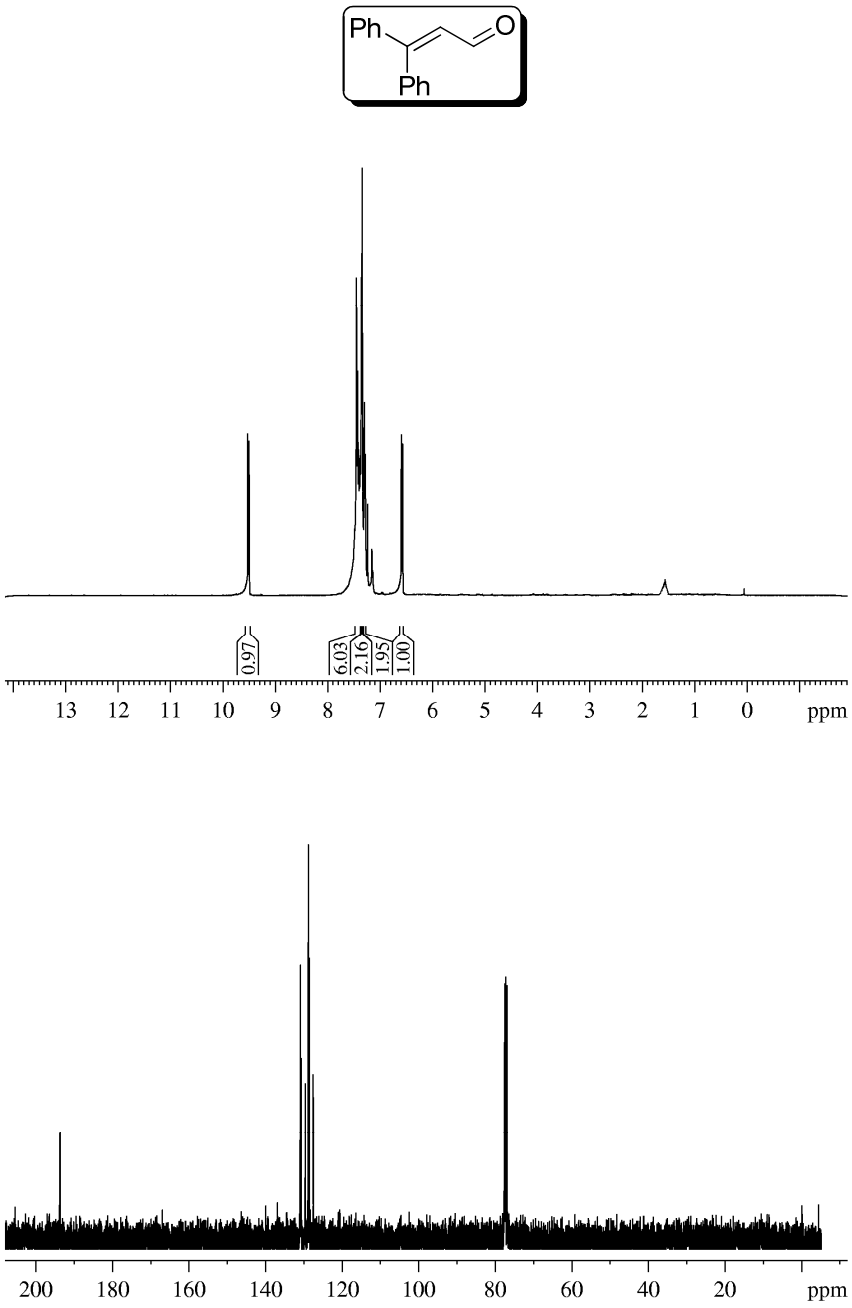


Figure A-53. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 3,3-diphenylacrylaldehyde **5m** in $CDCl_3$.

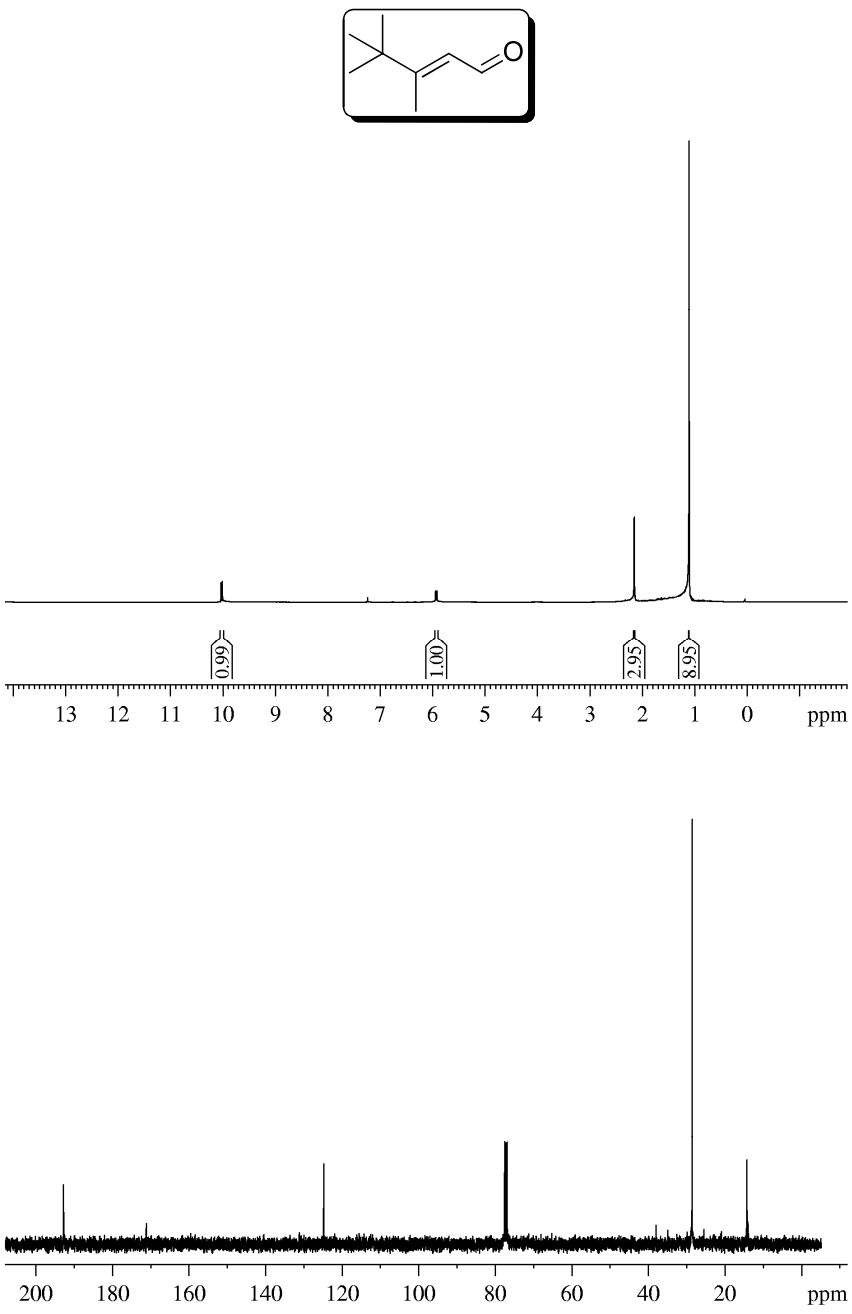


Figure A-54. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-3,4,4-trimethylpent-2-enal **5o** in $CDCl_3$.

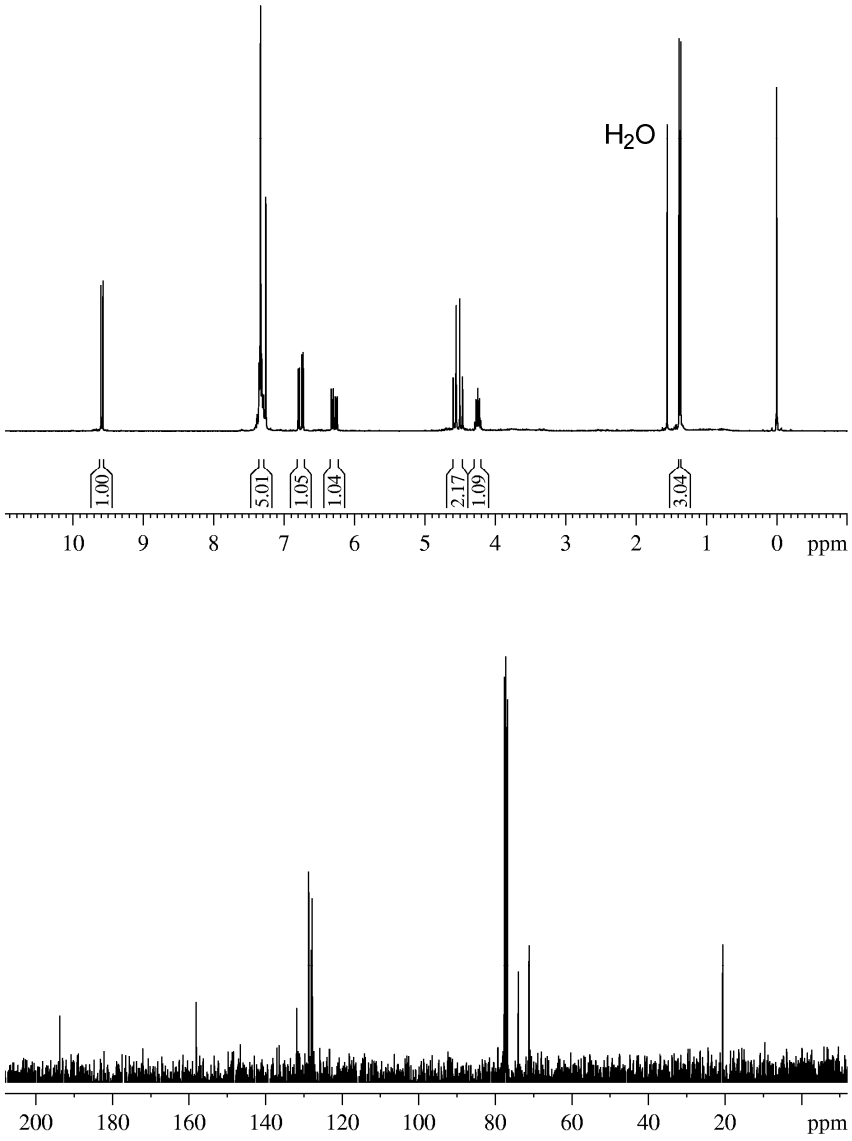


Figure A-55. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*S*,*E*)-4-(benzyloxy)pent-2-enal **5p** in $CDCl_3$.

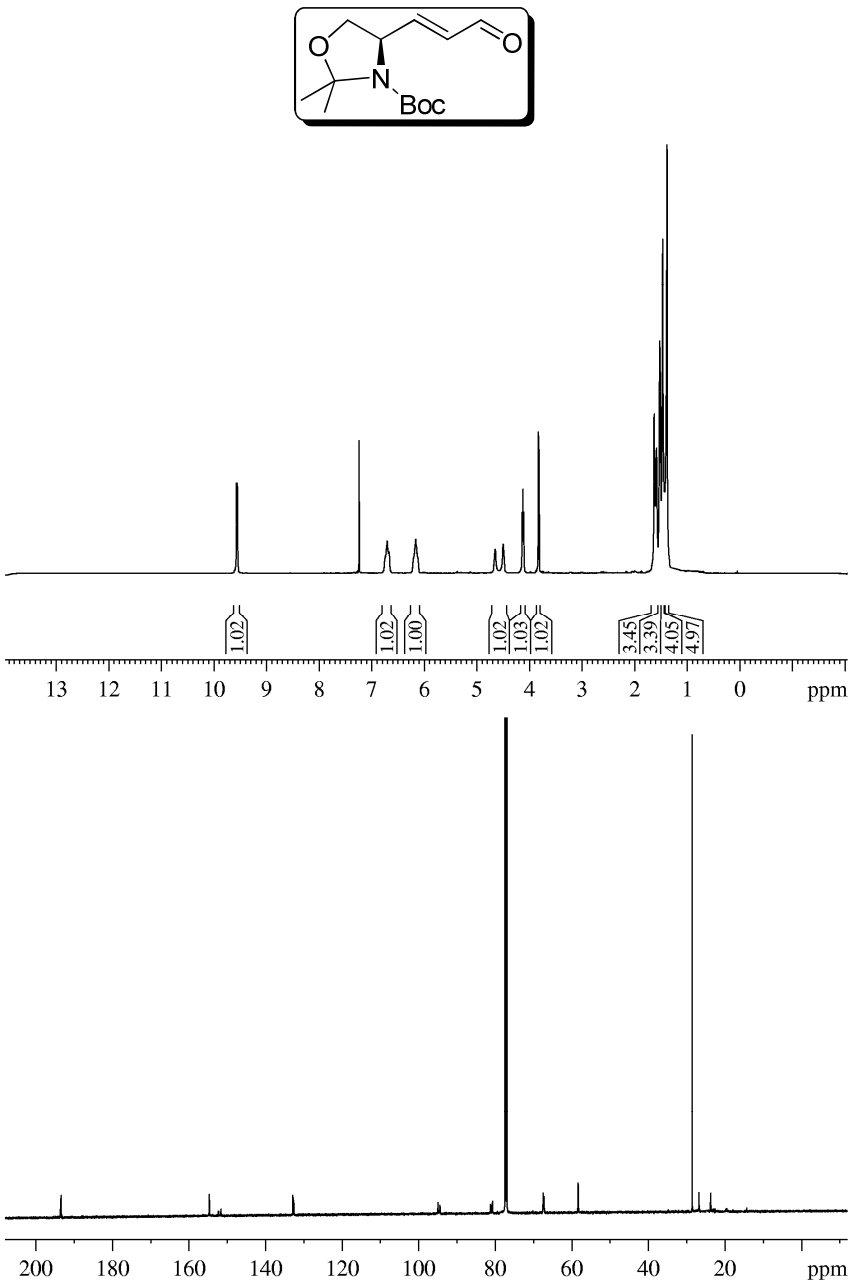


Figure A-56. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*R*,*E*)-tert-butyl 2,2-dimethyl-4-(3-oxoprop-1-enyl)oxazolidine-3-carboxylate **5s** in $CDCl_3$.

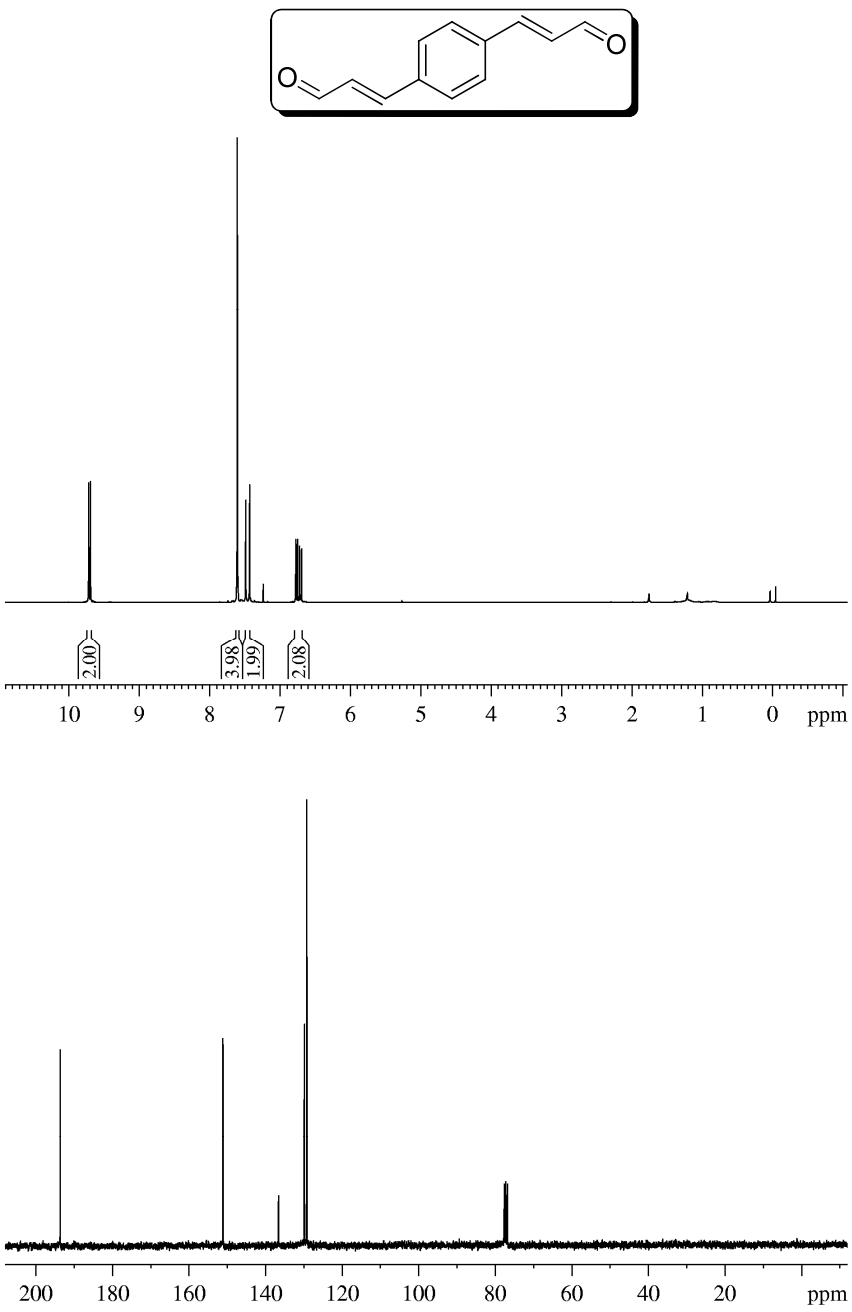


Figure A-57. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 1,4-Benzenedipropenal **5p** in $CDCl_3$.

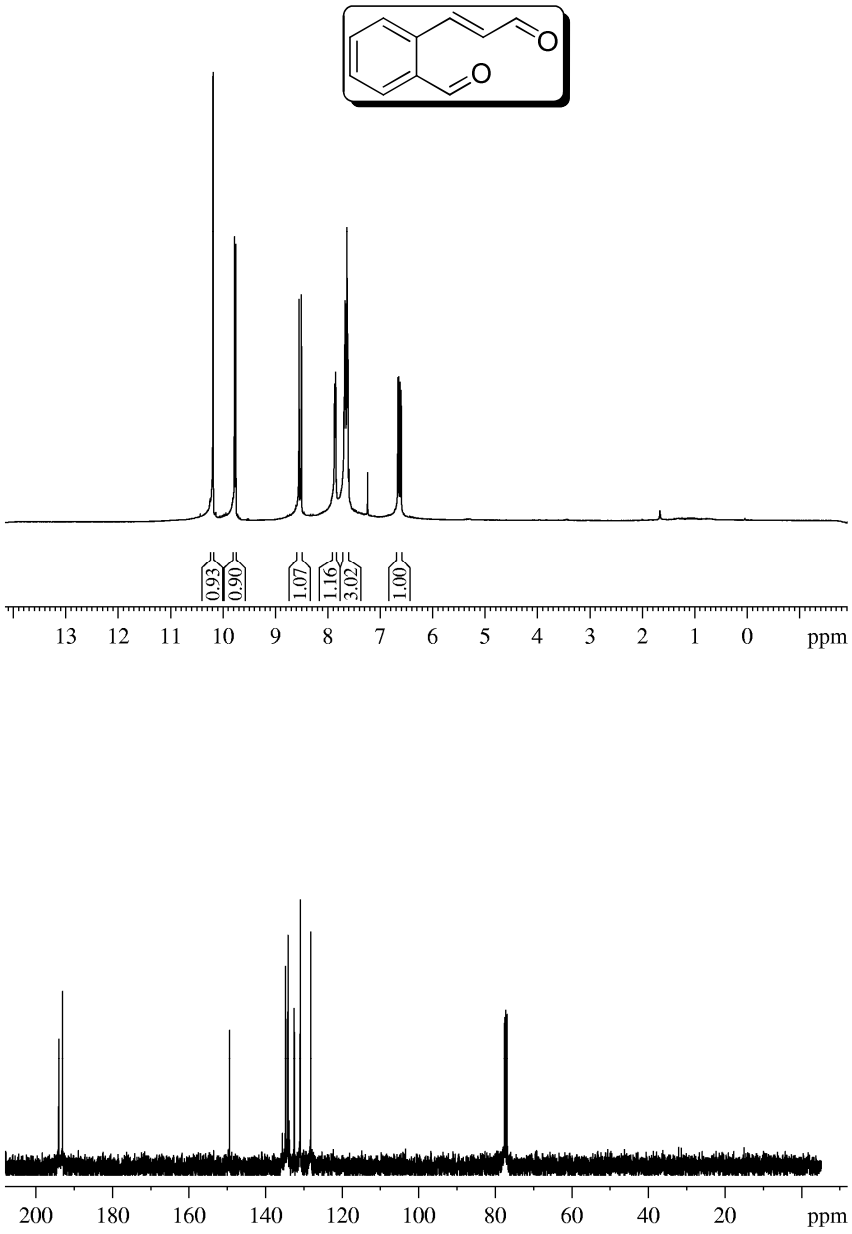


Figure A-58. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-2-(3-oxoprop-1-enyl)benzaldehyde **5q** in $CDCl_3$.

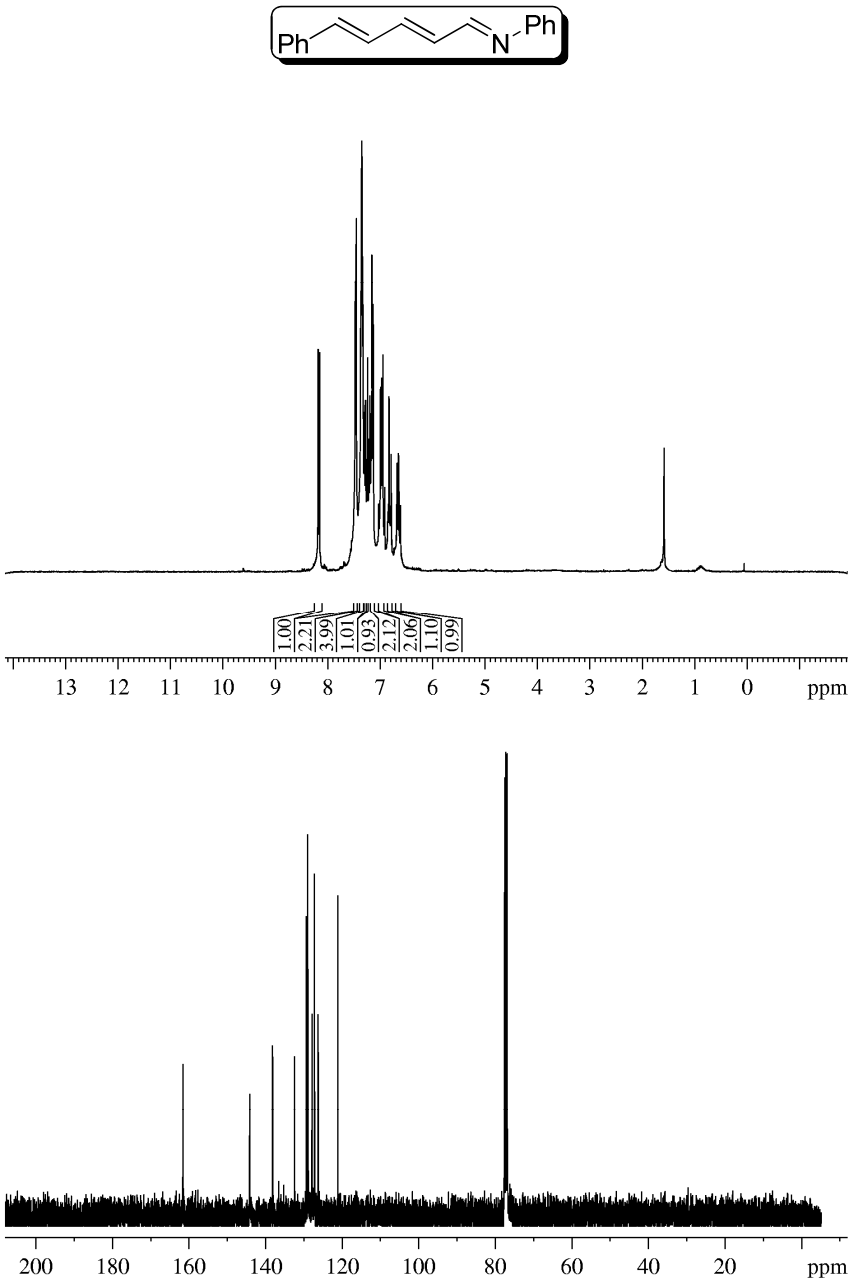


Figure A-59. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-*N*-((2*E*,4*E*)-5-phenylpenta-2,4-dienylidene)aniline **5-2** in $CDCl_3$.

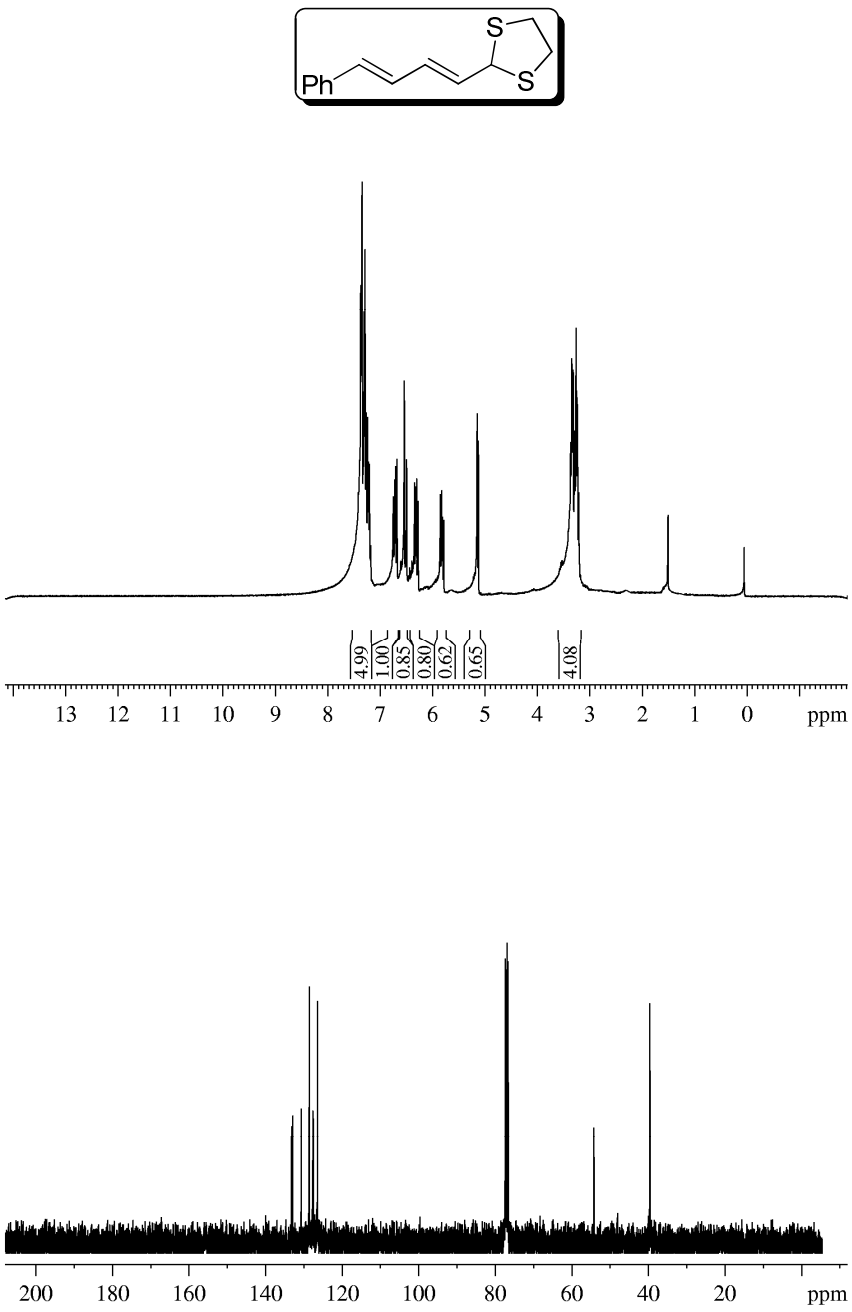


Figure A-60. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of 2-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)-1,3-dithiolane **5-3** in $CDCl_3$.

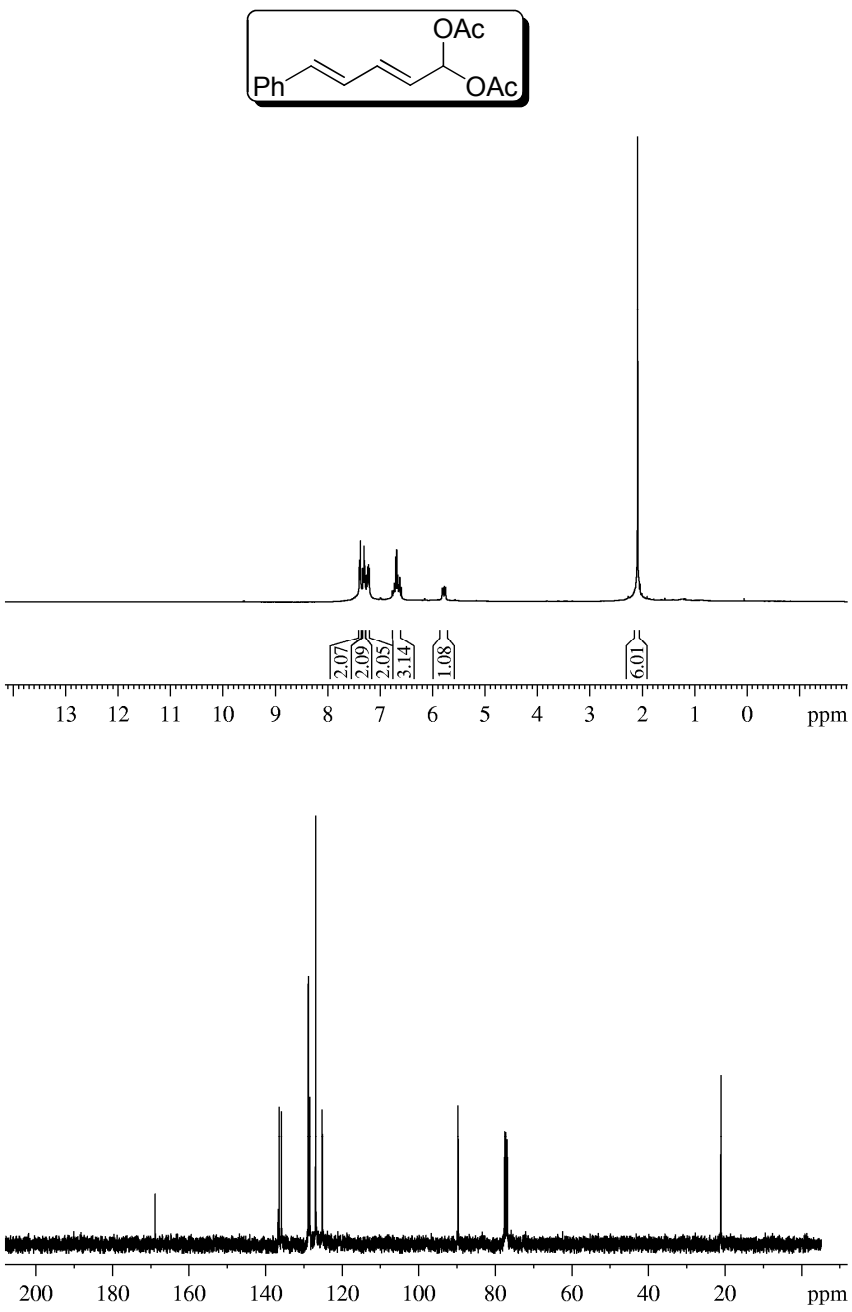
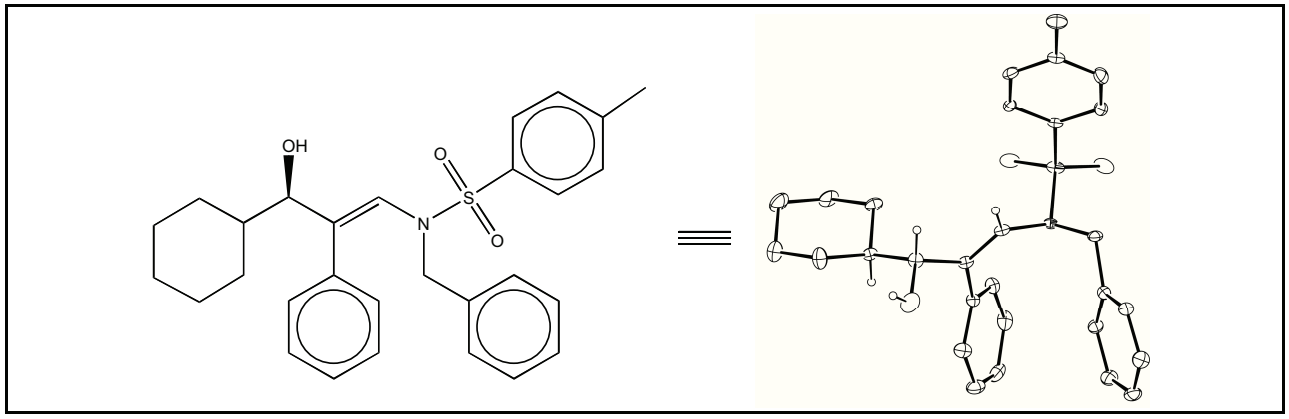


Figure A-61. 360 MHz ^{1}H and 90.6 MHz $^{13}C\{^{1}H\}$ NMR of (2*E*,4*E*)-5-phenylpenta-2,4-diene-1,1-diyl diacetate **5-4** in $CDCl_3$.

Appendix B. Single Crystal X-Ray Diffraction Data

X-ray Structure Determination of Compound 1a



Compound 1a, $C_{29}H_{33}NSO_3$, crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k=odd) with a=17.8473(19)Å, b=11.6887(13)Å, c=24.162(3)Å, β=90.760(6)°, V=5040.0(10)Å^3, Z=8, and d_{calc}=1.254 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 30 seconds. A total of 1978 frames were collected with a crystal to detector distance of 37.542 mm, rotation widths of 0.5° and exposures of 30 seconds:

scan type	2θ	ω	ϕ	χ	frames
ϕ	19.50	59.55	-10.72	-26.26	721
ω	-20.50	-25.48	-25.48	-181.36	197
ω	17.00	-34.35	-41.64	83.36	85
ω	17.00	-29.33	-175.56	82.07	97
ϕ	-15.50	-10.67	143.15	-77.44	134
ω	-18.00	-112.94	-49.03	36.30	140
ω	-15.50	-98.55	18.69	41.79	174
ω	14.50	-67.39	54.11	21.36	173
ϕ	-20.50	-17.45	-3.92	-73.06	257

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution on a Dell Pentium 4 computer. A total of 85324 reflections were measured over the ranges 1.69 $\leq \theta \leq$ 25.18°, -21 $\leq$ h $\leq$ 21, -13 $\leq$ k $\leq$ 13, -28 $\leq$ l $\leq$ 28 yielding 17838 unique reflections (Rint = 0.0531).

The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6038, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). The asymmetric unit consists of four crystallographically independent molecules. Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0628P)^2 + 3.1236P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0550 and wR2=0.1304 for 13640 observed reflections for which $F > 4\sigma(F)$ and R1=0.0786 and wR2=0.1426 and GOF =1.099 for all 17838 unique, non-zero reflections and 1234 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.020 and the two most prominent peaks in the final difference Fourier were +0.826 and -0.326 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

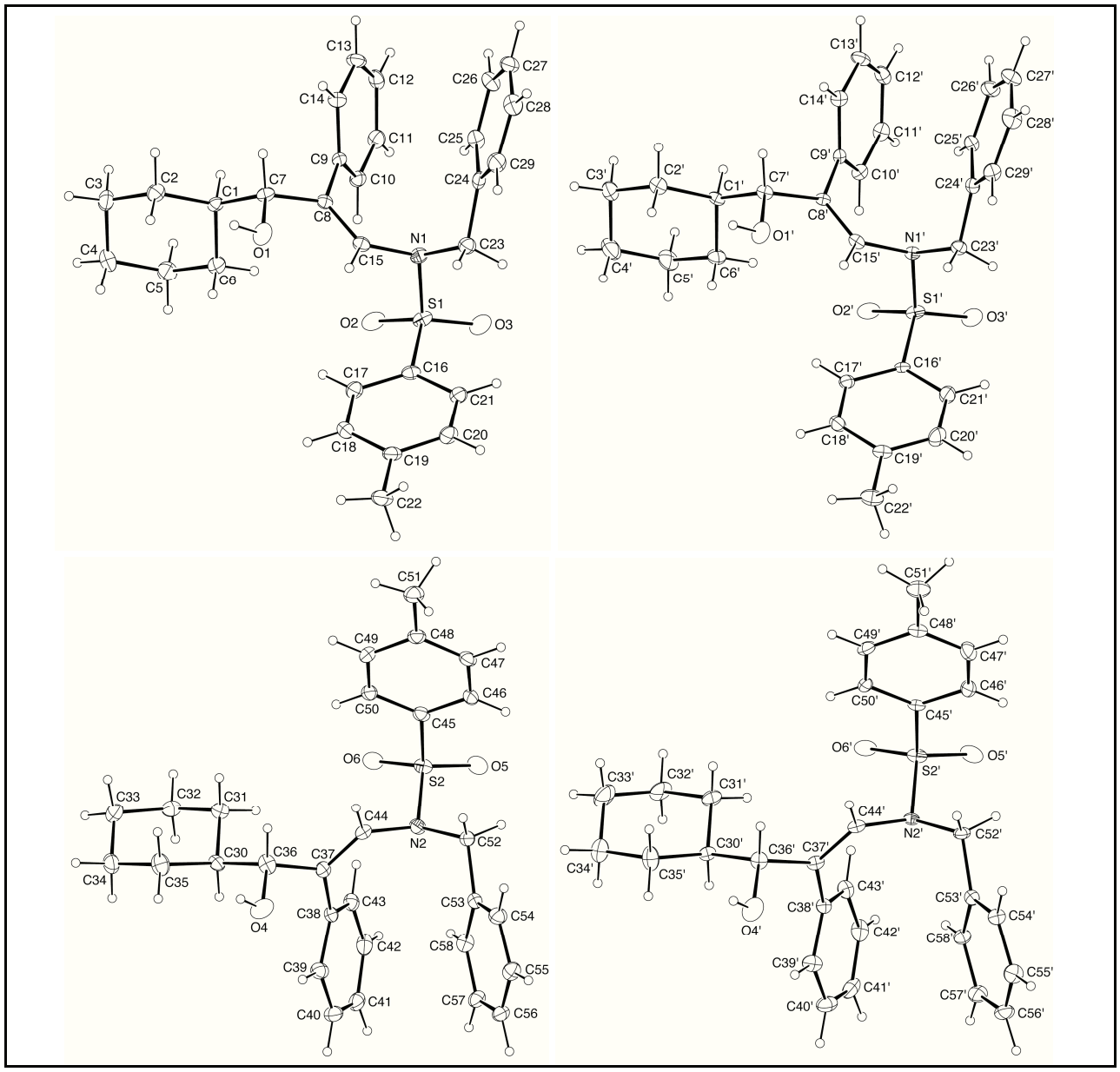


Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 1a

Empirical formula	$C_{29}H_{33}NSO_3$
Formula weight	475.62
Temperature	143(1) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Cell constants:	
a	17.8473(19) Å
b	11.6887(13) Å
c	24.162(3) Å
β	90.760(6)°
Volume	5040.0(10) $Å^3$
Z	8
Density (calculated)	1.254 Mg/m^3
Absorption coefficient	0.159 mm^{-1}
F(000)	2032
Crystal size	0.46 x 0.12 x 0.03 mm^3
Theta range for data collection	1.69 to 25.18°
Index ranges	$-21 \leq h \leq 21$, $-13 \leq k \leq 13$, $-28 \leq l \leq 28$
Reflections collected	85324
Independent reflections	17838 [R(int) = 0.0531]
Completeness to theta = 25.18°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6038
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	17838 / 1 / 1234
Goodness-of-fit on F^2	1.099
Final R indices [I>2sigma(I)]	R1 = 0.0550, wR2 = 0.1304
R indices (all data)	R1 = 0.0786, wR2 = 0.1426
Absolute structure parameter	0.06(5)
Largest diff. peak and hole	0.826 and -0.326 $e.Å^{-3}$

Table 2. Refined Positional Parameters for Compound 1a

Atom	x	y	z	U_{eq}, Å^2
C1	0.0778(2)	0.8859(3)	1.06919(14)	0.0210(8)
C2	0.0850(2)	0.8236(4)	1.12442(16)	0.0307(9)
C3	0.0645(2)	0.9001(4)	1.17312(16)	0.0367(10)
C4	-0.0123(3)	0.9520(4)	1.16566(16)	0.0434(11)
C5	-0.0191(2)	1.0160(4)	1.11090(16)	0.0379(10)
C6	-0.0003(2)	0.9372(4)	1.06237(15)	0.0322(9)
C7	0.1009(2)	0.8095(3)	1.02060(15)	0.0224(8)
C8	0.09903(19)	0.8741(3)	0.96654(14)	0.0191(7)
C9	0.15065(19)	0.9736(3)	0.96173(13)	0.0200(7)
C10	0.1253(2)	1.0818(3)	0.94587(14)	0.0248(8)
C11	0.1757(2)	1.1691(3)	0.93646(15)	0.0282(9)
C12	0.2520(2)	1.1504(4)	0.94337(15)	0.0300(9)
C13	0.2765(2)	1.0455(4)	0.96086(16)	0.0313(9)
C14	0.2271(2)	0.9581(3)	0.97072(15)	0.0256(8)
C15	0.05300(19)	0.8402(3)	0.92553(14)	0.0218(8)
C16	-0.1030(2)	0.8456(3)	0.86270(15)	0.0234(8)
C17	-0.1328(2)	0.8080(4)	0.91237(15)	0.0292(9)
C18	-0.1825(2)	0.7166(4)	0.91229(15)	0.0319(9)
C19	-0.2027(2)	0.6607(3)	0.86345(16)	0.0276(9)
C20	-0.1714(2)	0.6979(3)	0.81422(15)	0.0291(9)
C21	-0.1220(2)	0.7896(3)	0.81334(15)	0.0271(9)
C22	-0.2565(2)	0.5632(4)	0.86385(17)	0.0353(10)
C23	0.0686(2)	0.8232(4)	0.82554(15)	0.0283(9)
C24	0.1530(2)	0.8094(3)	0.82201(14)	0.0241(8)
C25	0.2010(2)	0.9005(3)	0.83320(15)	0.0273(9)
C26	0.2774(2)	0.8866(4)	0.82612(16)	0.0328(10)
C27	0.3056(2)	0.7835(4)	0.80698(16)	0.0350(10)
C28	0.2585(2)	0.6951(4)	0.79531(16)	0.0344(10)
C29	0.1817(2)	0.7069(4)	0.80388(15)	0.0340(9)
N1	0.04570(17)	0.8964(3)	0.87220(12)	0.0236(7)
O1	0.05451(16)	0.7109(2)	1.01508(10)	0.0337(6)
O2	-0.05085(15)	1.0247(2)	0.91104(11)	0.0340(7)
O3	-0.03761(16)	1.0106(2)	0.80956(12)	0.0373(7)
S1	-0.03773(5)	0.95662(8)	0.86275(4)	0.0263(2)
C1'	0.91881(19)	0.6331(3)	0.42825(14)	0.0184(7)
C2'	0.9077(2)	0.5710(3)	0.37262(15)	0.0254(8)
C3'	0.9290(2)	0.6446(4)	0.32371(16)	0.0328(9)
C4'	1.0079(3)	0.6920(5)	0.33024(18)	0.0450(12)
C5'	1.0173(2)	0.7566(4)	0.38451(17)	0.0424(11)
C6'	0.9982(2)	0.6799(4)	0.43404(16)	0.0297(9)
C7'	0.89600(19)	0.5566(3)	0.47743(14)	0.0181(7)
C8'	0.89987(18)	0.6216(3)	0.53184(13)	0.0143(7)
C9'	0.84873(18)	0.7213(3)	0.53829(13)	0.0163(7)
C10'	0.8738(2)	0.8275(3)	0.55558(14)	0.0207(8)
C11'	0.8232(2)	0.9142(3)	0.56734(15)	0.0238(8)
C12'	0.7476(2)	0.8965(3)	0.56185(15)	0.0293(9)
C13'	0.7218(2)	0.7916(3)	0.54253(16)	0.0276(9)
C14'	0.7710(2)	0.7056(3)	0.53057(14)	0.0230(8)
C15'	0.94565(19)	0.5845(3)	0.57190(14)	0.0172(7)

C16'	1.10428(18)	0.5887(3)	0.63280(14)	0.0164(7)
C17'	1.12969(19)	0.5458(3)	0.58290(15)	0.0226(8)
C18'	1.1802(2)	0.4550(3)	0.58338(15)	0.0266(8)
C19'	1.2050(2)	0.4060(3)	0.63265(16)	0.0242(8)
C20'	1.1788(2)	0.4493(4)	0.68184(16)	0.0352(10)
C21'	1.1281(2)	0.5404(3)	0.68239(16)	0.0302(9)
C22'	1.2590(2)	0.3079(3)	0.63271(18)	0.0343(10)
C23'	0.93381(19)	0.5664(3)	0.67242(14)	0.0206(8)
C24'	0.8500(2)	0.5547(3)	0.67812(14)	0.0204(8)
C25'	0.8019(2)	0.6457(3)	0.66766(14)	0.0224(8)
C26'	0.7257(2)	0.6344(3)	0.67907(16)	0.0311(9)
C27'	0.6990(2)	0.5356(4)	0.70177(17)	0.0345(10)
C28'	0.7457(2)	0.4443(4)	0.71161(16)	0.0333(10)
C29'	0.8212(2)	0.4547(3)	0.69946(15)	0.0281(8)
N1'	0.95521(15)	0.6401(2)	0.62514(11)	0.0166(6)
O1'	0.94140(16)	0.4583(2)	0.48288(11)	0.0332(6)
O2'	1.05065(14)	0.7685(2)	0.58527(11)	0.0283(6)
O3'	1.03946(15)	0.7529(2)	0.68707(11)	0.0320(6)
S1'	1.03857(5)	0.70031(7)	0.63359(4)	0.0216(2)
C30	0.4322(2)	0.3935(3)	1.07528(15)	0.0249(8)
C31	0.5036(2)	0.4647(4)	1.06905(16)	0.0321(9)
C32	0.5145(2)	0.5473(4)	1.11723(17)	0.0374(10)
C33	0.5133(2)	0.4869(5)	1.17266(17)	0.0439(12)
C34	0.4441(3)	0.4131(4)	1.17874(16)	0.0393(11)
C35	0.4346(3)	0.3294(4)	1.12999(16)	0.0376(10)
C36	0.4223(2)	0.3135(3)	1.02556(16)	0.0304(9)
C37	0.4112(2)	0.3798(3)	0.97170(14)	0.0221(8)
C38	0.3542(2)	0.4730(3)	0.96786(14)	0.0232(8)
C39	0.2799(2)	0.4490(4)	0.98300(15)	0.0300(9)
C40	0.2246(2)	0.5289(4)	0.97298(17)	0.0388(11)
C41	0.2413(2)	0.6350(4)	0.95019(16)	0.0370(11)
C42	0.3159(2)	0.6611(4)	0.93899(15)	0.0348(10)
C43	0.3713(2)	0.5806(3)	0.94817(14)	0.0266(8)
C44	0.4549(2)	0.3510(3)	0.92953(14)	0.0224(8)
C45	0.6054(2)	0.3592(3)	0.86462(15)	0.0256(8)
C46	0.6206(2)	0.3044(3)	0.81476(15)	0.0270(9)
C47	0.6692(2)	0.2121(4)	0.81420(15)	0.0289(9)
C48	0.7029(2)	0.1705(3)	0.86218(16)	0.0281(9)
C49	0.6864(2)	0.2260(4)	0.91190(15)	0.0298(9)
C50	0.6383(2)	0.3186(4)	0.91364(15)	0.0289(9)
C51	0.7551(2)	0.0717(4)	0.86113(17)	0.0356(10)
C52	0.4340(2)	0.3375(3)	0.82841(15)	0.0270(9)
C53	0.3505(2)	0.3171(3)	0.82510(14)	0.0260(8)
C54	0.3250(2)	0.2152(4)	0.80296(15)	0.0310(9)
C55	0.2496(2)	0.1973(4)	0.79316(16)	0.0314(9)
C56	0.1981(2)	0.2791(4)	0.80735(16)	0.0329(10)
C57	0.2229(2)	0.3821(3)	0.83064(15)	0.0282(9)
C58	0.2984(2)	0.4010(3)	0.83828(15)	0.0270(9)
N2	0.45774(17)	0.4088(3)	0.87676(12)	0.0252(7)
O4	0.36209(16)	0.2376(3)	1.03306(13)	0.0449(8)
O5	0.53728(16)	0.5280(2)	0.81481(11)	0.0350(7)
O6	0.55529(15)	0.5365(2)	0.91667(11)	0.0327(7)
S2	0.54037(5)	0.47112(8)	0.86748(4)	0.0274(2)

C30'	0.57398(19)	0.1355(3)	0.42117(14)	0.0193(7)
C31'	0.5011(2)	0.2030(4)	0.42688(16)	0.0293(9)
C32'	0.4894(2)	0.2815(4)	0.37737(17)	0.0372(10)
C33'	0.4912(3)	0.2197(4)	0.32346(18)	0.0479(12)
C34'	0.5632(3)	0.1496(4)	0.31750(17)	0.0401(11)
C35'	0.5760(3)	0.0723(4)	0.36670(15)	0.0361(10)
C36'	0.5856(2)	0.0569(3)	0.47129(14)	0.0233(8)
C37'	0.59292(19)	0.1230(3)	0.52524(14)	0.0184(7)
C38'	0.64979(19)	0.2174(3)	0.53107(13)	0.0193(7)
C39'	0.7242(2)	0.1944(3)	0.51801(16)	0.0284(9)
C40'	0.7784(2)	0.2754(4)	0.53019(17)	0.0343(10)
C41'	0.7603(2)	0.3781(4)	0.55359(16)	0.0374(11)
C42'	0.6856(2)	0.4049(3)	0.56387(15)	0.0314(9)
C43'	0.6308(2)	0.3239(3)	0.55207(14)	0.0252(8)
C44'	0.54807(19)	0.0918(3)	0.56622(14)	0.0183(7)
C45'	0.39348(19)	0.1014(3)	0.62829(14)	0.0185(7)
C46'	0.3749(2)	0.0544(3)	0.67906(15)	0.0282(9)
C47'	0.3251(2)	-0.0372(4)	0.68099(15)	0.0320(9)
C48'	0.2947(2)	-0.0835(3)	0.63319(16)	0.0251(8)
C49'	0.31455(19)	-0.0358(3)	0.58285(15)	0.0268(8)
C50'	0.36354(19)	0.0559(3)	0.57987(14)	0.0244(8)
C51'	0.2410(2)	-0.1835(4)	0.63591(19)	0.0376(10)
C52'	0.56362(19)	0.0788(3)	0.66757(15)	0.0226(8)
C53'	0.6474(2)	0.0624(3)	0.67513(14)	0.0203(8)
C54'	0.6731(2)	-0.0374(3)	0.69898(14)	0.0227(8)
C55'	0.7486(2)	-0.0513(4)	0.71327(16)	0.0318(9)
C56'	0.7984(2)	0.0352(4)	0.70262(16)	0.0326(10)
C57'	0.7738(2)	0.1337(3)	0.67698(16)	0.0311(9)
C58'	0.6987(2)	0.1494(3)	0.66397(14)	0.0241(8)
N2'	0.54244(15)	0.1491(2)	0.61913(11)	0.0175(6)
O4'	0.64789(18)	-0.0159(3)	0.46393(13)	0.0459(8)
O5'	0.46149(15)	0.2696(2)	0.67870(11)	0.0323(7)
O6'	0.44681(14)	0.2773(2)	0.57642(11)	0.0279(6)
S2'	0.45957(5)	0.21273(7)	0.62630(4)	0.0230(2)

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 1a

Atom	x	y	z	U_{iso}, Å^2
H1	0.1132	0.9500	1.0705	0.028
H2a	0.1361	0.7969	1.1293	0.041
H2b	0.0524	0.7571	1.1239	0.041
H3a	0.0658	0.8555	1.2069	0.049
H3b	0.1013	0.9608	1.1768	0.049
H4a	-0.0218	1.0044	1.1959	0.058
H4b	-0.0498	0.8920	1.1667	0.058
H5a	0.0148	1.0809	1.1113	0.050
H5b	-0.0697	1.0448	1.1063	0.050
H6a	-0.0369	0.8761	1.0601	0.043
H6b	-0.0029	0.9804	1.0281	0.043
H7	0.1525	0.7838	1.0275	0.030
H10	0.0742	1.0952	0.9416	0.033
H11	0.1584	1.2407	0.9255	0.037
H12	0.2862	1.2085	0.9362	0.040
H13	0.3275	1.0330	0.9662	0.042
H14	0.2449	0.8880	0.9835	0.034
H15	0.0235	0.7760	0.9317	0.029
H17	-0.1196	0.8439	0.9454	0.039
H18	-0.2027	0.6922	0.9455	0.042
H20	-0.1838	0.6607	0.7813	0.039
H21	-0.1017	0.8138	0.7801	0.036
H22a	-0.2645	0.5392	0.9013	0.053
H22b	-0.2363	0.5006	0.8431	0.053
H22c	-0.3032	0.5868	0.8474	0.053
H23a	0.0498	0.8563	0.7912	0.038
H23b	0.0458	0.7484	0.8296	0.038
H25	0.1820	0.9700	0.8453	0.036
H26	0.3099	0.9467	0.8342	0.044
H27	0.3568	0.7749	0.8021	0.047
H28	0.2774	0.6268	0.7816	0.046
H29	0.1498	0.6453	0.7973	0.045
H1a	0.0627	0.6673	1.0411	0.051
H1'	0.8849	0.6990	0.4279	0.024
H2a'	0.9380	0.5020	0.3726	0.034
H2b'	0.8556	0.5484	0.3686	0.034
H3a'	0.8938	0.7075	0.3202	0.044
H3b'	0.9258	0.5994	0.2901	0.044
H4a'	1.0183	0.7430	0.2996	0.060
H4b'	1.0436	0.6295	0.3292	0.060
H5a'	0.9847	0.8231	0.3843	0.056
H5b'	1.0686	0.7832	0.3883	0.056
H6a'	1.0335	0.6168	0.4361	0.039
H6b'	1.0027	0.7236	0.4680	0.039
H7'	0.8441	0.5317	0.4712	0.024
H10'	0.9250	0.8411	0.5594	0.028
H11'	0.8408	0.9851	0.5791	0.032
H12'	0.7140	0.9541	0.5710	0.039
H13'	0.6706	0.7797	0.5377	0.037

H14'	0.7530	0.6361	0.5172	0.031
H15'	0.9733	0.5185	0.5653	0.023
H17'	1.1132	0.5773	0.5496	0.030
H18'	1.1978	0.4266	0.5500	0.035
H20'	1.1952	0.4175	0.7151	0.047
H21'	1.1104	0.5683	0.7158	0.040
H22a'	1.3059	0.3321	0.6487	0.051
H22b'	1.2667	0.2828	0.5954	0.051
H22c'	1.2390	0.2460	0.6541	0.051
H23a'	0.9546	0.5985	0.7063	0.027
H23b'	0.9555	0.4911	0.6675	0.027
H25'	0.8202	0.7137	0.6532	0.030
H26'	0.6930	0.6944	0.6712	0.041
H27'	0.6486	0.5301	0.7106	0.046
H28'	0.7271	0.3766	0.7262	0.044
H29'	0.8530	0.3929	0.7058	0.037
H1a'	0.9333	0.4152	0.4567	0.050
H30	0.3894	0.4460	1.0758	0.033
H31a	0.5465	0.4139	1.0671	0.043
H31b	0.5007	0.5076	1.0347	0.043
H32a	0.5621	0.5864	1.1134	0.050
H32b	0.4751	0.6044	1.1160	0.050
H33a	0.5146	0.5434	1.2020	0.058
H33b	0.5576	0.4394	1.1765	0.058
H34a	0.4002	0.4618	1.1807	0.052
H34b	0.4478	0.3702	1.2130	0.052
H35a	0.4761	0.2757	1.1301	0.050
H35b	0.3886	0.2863	1.1342	0.050
H36	0.4681	0.2680	1.0223	0.040
H39	0.2682	0.3796	0.9997	0.040
H40	0.1752	0.5116	0.9816	0.052
H41	0.2035	0.6876	0.9426	0.049
H42	0.3284	0.7329	0.9253	0.046
H43	0.4209	0.5992	0.9410	0.035
H44	0.4863	0.2882	0.9346	0.030
H46	0.5982	0.3298	0.7820	0.036
H47	0.6796	0.1770	0.7806	0.038
H49	0.7084	0.1998	0.9446	0.040
H50	0.6278	0.3537	0.9472	0.038
H51a	0.7292	0.0053	0.8474	0.053
H51b	0.7737	0.0568	0.8979	0.053
H51c	0.7964	0.0889	0.8374	0.053
H52a	0.4593	0.2642	0.8306	0.036
H52b	0.4497	0.3749	0.7947	0.036
H54	0.3591	0.1579	0.7945	0.041
H55	0.2335	0.1294	0.7768	0.042
H56	0.1471	0.2661	0.8015	0.044
H57	0.1885	0.4376	0.8409	0.038
H58	0.3149	0.4707	0.8524	0.036
H4	0.3757	0.1843	1.0529	0.067
H30'	0.6152	0.1908	0.4213	0.026
H31a'	0.4593	0.1503	0.4294	0.039
H31b'	0.5031	0.2481	0.4606	0.039

H32a'	0.4414	0.3198	0.3807	0.049
H32b'	0.5281	0.3397	0.3778	0.049
H33X	0.4876	0.2747	0.2935	0.064
H33Y	0.4482	0.1691	0.3207	0.064
H34a'	0.5598	0.1038	0.2841	0.053
H34b'	0.6055	0.2011	0.3139	0.053
H35a'	0.6243	0.0351	0.3632	0.048
H35b'	0.5378	0.0132	0.3666	0.048
H36'	0.5411	0.0082	0.4740	0.031
H39'	0.7372	0.1256	0.5013	0.038
H40'	0.8282	0.2598	0.5223	0.046
H41'	0.7979	0.4302	0.5627	0.050
H42'	0.6728	0.4758	0.5784	0.042
H43'	0.5807	0.3413	0.5583	0.034
H44'	0.5179	0.0279	0.5604	0.024
H46'	0.3955	0.0840	0.7116	0.038
H47'	0.3121	-0.0678	0.7151	0.043
H49'	0.2945	-0.0661	0.5503	0.036
H50'	0.3762	0.0865	0.5457	0.032
H51a'	0.2126	-0.1881	0.6020	0.056
H51b'	0.2075	-0.1729	0.6663	0.056
H51c'	0.2688	-0.2531	0.6412	0.056
H52a'	0.5402	0.0042	0.6639	0.030
H52b'	0.5440	0.1145	0.7006	0.030
H54'	0.6395	-0.0965	0.7057	0.030
H55'	0.7650	-0.1187	0.7299	0.042
H56'	0.8486	0.0273	0.7127	0.043
H57'	0.8081	0.1905	0.6683	0.041
H58'	0.6825	0.2175	0.6479	0.032
H4'	0.6350	-0.0720	0.4458	0.069

Table 4. Refined Thermal Parameters (U's) for Compound 1a

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0196(19)	0.0205(19)	0.0228(19)	-0.0018(15)	-0.0036(14)	-0.0051(15)
C2	0.030(2)	0.032(2)	0.030(2)	0.0045(18)	-0.0030(16)	0.0034(18)
C3	0.039(3)	0.048(3)	0.023(2)	0.0056(19)	-0.0015(17)	-0.010(2)
C4	0.042(3)	0.060(3)	0.028(2)	-0.001(2)	0.0118(18)	-0.001(2)
C5	0.033(2)	0.045(3)	0.035(2)	-0.005(2)	0.0033(18)	0.012(2)
C6	0.028(2)	0.041(3)	0.028(2)	0.0011(19)	-0.0016(16)	0.0049(19)
C7	0.0196(19)	0.0189(19)	0.029(2)	0.0008(16)	-0.0047(14)	0.0005(15)
C8	0.0171(18)	0.0167(18)	0.0235(18)	-0.0026(15)	0.0020(14)	0.0015(14)
C9	0.0186(19)	0.0229(19)	0.0186(17)	-0.0007(15)	-0.0011(13)	-0.0031(15)
C10	0.023(2)	0.027(2)	0.0240(19)	0.0014(16)	-0.0025(14)	-0.0037(16)
C11	0.032(2)	0.025(2)	0.027(2)	0.0027(16)	-0.0009(16)	-0.0035(17)
C12	0.034(2)	0.032(2)	0.024(2)	-0.0039(17)	0.0064(16)	-0.0180(19)
C13	0.017(2)	0.042(3)	0.035(2)	-0.0067(19)	0.0009(16)	-0.0071(18)
C14	0.021(2)	0.025(2)	0.031(2)	-0.0008(17)	-0.0009(15)	-0.0013(16)
C15	0.0195(19)	0.0181(19)	0.028(2)	-0.0003(15)	0.0022(14)	-0.0020(15)
C16	0.0174(19)	0.021(2)	0.032(2)	-0.0026(16)	-0.0030(15)	0.0049(15)
C17	0.027(2)	0.036(2)	0.025(2)	-0.0114(18)	-0.0020(15)	-0.0045(18)
C18	0.025(2)	0.044(3)	0.027(2)	-0.003(2)	0.0044(15)	-0.0039(19)
C19	0.017(2)	0.033(2)	0.033(2)	-0.0066(18)	-0.0014(15)	0.0011(16)
C20	0.030(2)	0.028(2)	0.029(2)	-0.0102(18)	-0.0043(15)	-0.0058(18)
C21	0.024(2)	0.031(2)	0.026(2)	-0.0028(17)	-0.0023(15)	-0.0005(17)
C22	0.021(2)	0.042(3)	0.043(2)	-0.009(2)	0.0018(17)	-0.0031(19)
C23	0.025(2)	0.033(2)	0.027(2)	-0.0071(17)	0.0000(15)	-0.0028(17)
C24	0.028(2)	0.029(2)	0.0154(18)	0.0011(16)	-0.0008(14)	0.0008(17)
C25	0.034(2)	0.022(2)	0.026(2)	-0.0022(16)	0.0045(16)	-0.0046(17)
C26	0.031(2)	0.035(2)	0.033(2)	0.0036(19)	0.0089(17)	-0.0037(19)
C27	0.022(2)	0.049(3)	0.034(2)	0.011(2)	0.0028(16)	0.0026(19)
C28	0.040(3)	0.028(2)	0.035(2)	0.0037(19)	0.0040(17)	0.006(2)
C29	0.036(2)	0.036(2)	0.030(2)	-0.0063(19)	0.0000(16)	-0.006(2)
N1	0.0227(17)	0.0222(17)	0.0260(16)	-0.0020(13)	-0.0032(12)	-0.0015(13)
O1	0.0482(17)	0.0208(14)	0.0319(15)	0.0045(12)	-0.0067(12)	-0.0125(13)
O2	0.0329(16)	0.0244(15)	0.0445(17)	-0.0119(13)	-0.0103(12)	0.0059(12)
O3	0.0400(17)	0.0315(16)	0.0400(16)	0.0076(13)	-0.0123(13)	-0.0049(13)
S1	0.0242(5)	0.0225(6)	0.0319(5)	-0.0015(4)	-0.0081(4)	0.0004(4)
C1'	0.0165(18)	0.0109(17)	0.0279(19)	-0.0018(15)	0.0049(14)	0.0031(13)
C2'	0.029(2)	0.0155(19)	0.032(2)	-0.0029(16)	0.0021(16)	0.0002(16)
C3'	0.033(2)	0.037(2)	0.028(2)	0.0007(19)	0.0066(16)	-0.0001(19)
C4'	0.039(3)	0.055(3)	0.041(2)	0.003(2)	0.0158(19)	-0.001(2)
C5'	0.032(2)	0.054(3)	0.042(3)	0.002(2)	0.0121(18)	-0.020(2)
C6'	0.020(2)	0.036(2)	0.034(2)	-0.0021(18)	0.0017(15)	-0.0081(17)
C7'	0.0210(19)	0.0062(16)	0.0272(19)	-0.0011(14)	0.0012(14)	0.0009(14)
C8'	0.0125(17)	0.0074(15)	0.0231(18)	0.0017(13)	0.0014(13)	-0.0042(13)
C9'	0.0207(19)	0.0125(17)	0.0157(16)	0.0015(14)	0.0009(13)	0.0017(14)
C10'	0.024(2)	0.0141(18)	0.0237(19)	0.0032(15)	-0.0021(14)	0.0012(15)
C11'	0.035(2)	0.0103(17)	0.0263(19)	-0.0014(15)	-0.0009(15)	0.0038(15)
C12'	0.034(2)	0.027(2)	0.027(2)	0.0072(17)	0.0086(16)	0.0134(18)
C13'	0.018(2)	0.029(2)	0.036(2)	0.0092(18)	0.0062(15)	0.0072(16)
C14'	0.025(2)	0.0171(19)	0.0273(19)	0.0048(16)	-0.0006(15)	0.0005(16)
C15'	0.0183(18)	0.0065(16)	0.0270(19)	-0.0023(14)	0.0050(14)	-0.0013(14)

C16'	0.0106(17)	0.0132(18)	0.0254(19)	-0.0025(14)	-0.0034(13)	0.0015(13)
C17'	0.0171(19)	0.029(2)	0.0221(18)	0.0084(16)	0.0004(14)	-0.0015(16)
C18'	0.023(2)	0.030(2)	0.0269(19)	0.0003(17)	0.0052(15)	0.0036(17)
C19'	0.0165(19)	0.0195(19)	0.037(2)	0.0047(16)	0.0001(15)	0.0000(15)
C20'	0.041(2)	0.037(2)	0.028(2)	0.0067(19)	-0.0060(17)	0.014(2)
C21'	0.032(2)	0.033(2)	0.025(2)	-0.0048(17)	-0.0023(16)	0.0110(18)
C22'	0.027(2)	0.024(2)	0.053(3)	0.0026(19)	0.0007(18)	0.0069(18)
C23'	0.0201(19)	0.0173(18)	0.0245(19)	0.0033(15)	0.0008(14)	0.0041(15)
C24'	0.024(2)	0.0169(18)	0.0206(18)	-0.0024(15)	0.0015(14)	0.0020(15)
C25'	0.025(2)	0.0207(19)	0.0218(18)	0.0009(15)	0.0044(14)	0.0019(16)
C26'	0.026(2)	0.031(2)	0.036(2)	0.0058(18)	0.0023(16)	0.0121(18)
C27'	0.024(2)	0.037(2)	0.042(2)	0.003(2)	0.0102(17)	-0.0025(19)
C28'	0.038(2)	0.025(2)	0.037(2)	0.0139(19)	0.0074(18)	-0.0083(19)
C29'	0.031(2)	0.024(2)	0.029(2)	0.0032(17)	0.0003(16)	0.0024(18)
N1'	0.0159(15)	0.0096(14)	0.0243(15)	-0.0018(12)	-0.0004(11)	-0.0022(12)
O1'	0.0505(18)	0.0169(14)	0.0320(15)	-0.0061(12)	-0.0072(12)	0.0116(13)
O2'	0.0258(15)	0.0115(13)	0.0473(17)	0.0109(12)	-0.0055(11)	-0.0013(11)
O3'	0.0337(16)	0.0188(14)	0.0434(16)	-0.0161(12)	-0.0100(12)	0.0022(12)
S1'	0.0199(5)	0.0100(5)	0.0346(5)	-0.0023(4)	-0.0058(4)	-0.0005(4)
C30	0.026(2)	0.024(2)	0.025(2)	0.0060(16)	0.0058(15)	0.0085(16)
C31	0.029(2)	0.037(2)	0.030(2)	0.0002(19)	0.0016(16)	0.0024(19)
C32	0.027(2)	0.046(3)	0.038(2)	0.002(2)	-0.0020(17)	-0.004(2)
C33	0.036(3)	0.065(3)	0.031(2)	-0.001(2)	-0.0082(18)	0.011(2)
C34	0.041(3)	0.052(3)	0.025(2)	0.007(2)	0.0034(17)	0.012(2)
C35	0.050(3)	0.030(2)	0.032(2)	0.0068(19)	0.0044(19)	-0.001(2)
C36	0.040(2)	0.021(2)	0.030(2)	0.0017(17)	0.0048(17)	0.0024(18)
C37	0.024(2)	0.0190(19)	0.0226(19)	-0.0036(15)	-0.0005(15)	-0.0019(15)
C38	0.023(2)	0.028(2)	0.0185(17)	-0.0047(16)	0.0019(14)	0.0013(16)
C39	0.027(2)	0.032(2)	0.031(2)	-0.0069(18)	0.0021(16)	0.0005(18)
C40	0.023(2)	0.057(3)	0.035(2)	-0.012(2)	-0.0021(17)	0.007(2)
C41	0.034(2)	0.051(3)	0.026(2)	-0.013(2)	-0.0060(17)	0.016(2)
C42	0.047(3)	0.033(2)	0.025(2)	-0.0016(18)	-0.0027(17)	0.012(2)
C43	0.030(2)	0.027(2)	0.0227(19)	-0.0036(16)	0.0011(15)	0.0017(17)
C44	0.0204(19)	0.0199(19)	0.027(2)	-0.0011(16)	-0.0042(14)	0.0010(15)
C45	0.020(2)	0.028(2)	0.028(2)	-0.0027(17)	0.0042(15)	-0.0048(16)
C46	0.023(2)	0.036(2)	0.0223(19)	0.0016(17)	0.0037(14)	-0.0062(17)
C47	0.022(2)	0.037(2)	0.0286(19)	-0.0099(19)	0.0060(14)	-0.0002(18)
C48	0.019(2)	0.032(2)	0.033(2)	-0.0013(17)	0.0010(15)	-0.0043(16)
C49	0.022(2)	0.040(3)	0.0267(19)	0.0016(18)	-0.0051(14)	-0.0006(18)
C50	0.023(2)	0.039(2)	0.025(2)	-0.0104(18)	0.0009(15)	0.0002(18)
C51	0.027(2)	0.039(3)	0.041(2)	-0.007(2)	0.0001(17)	0.0051(19)
C52	0.022(2)	0.036(2)	0.0227(19)	-0.0057(17)	0.0002(15)	0.0001(17)
C53	0.024(2)	0.034(2)	0.0204(19)	-0.0009(17)	0.0017(14)	-0.0029(17)
C54	0.028(2)	0.033(2)	0.032(2)	-0.0054(19)	0.0011(15)	0.0027(18)
C55	0.032(2)	0.029(2)	0.033(2)	0.0033(19)	-0.0035(16)	-0.0050(19)
C56	0.022(2)	0.047(3)	0.030(2)	0.0097(19)	-0.0027(16)	-0.0018(19)
C57	0.026(2)	0.029(2)	0.029(2)	0.0007(17)	-0.0047(16)	0.0045(17)
C58	0.034(2)	0.017(2)	0.029(2)	-0.0018(16)	-0.0023(16)	0.0034(17)
N2	0.0234(17)	0.0271(18)	0.0252(16)	-0.0023(14)	0.0036(13)	-0.0013(14)
O4	0.0356(17)	0.0434(19)	0.055(2)	0.0116(16)	-0.0109(13)	-0.0133(14)
O5	0.0339(17)	0.0318(17)	0.0395(16)	0.0089(13)	0.0078(12)	0.0007(13)
O6	0.0290(16)	0.0290(16)	0.0403(16)	-0.0060(13)	0.0039(12)	-0.0069(12)
S2	0.0220(5)	0.0276(6)	0.0328(5)	-0.0002(4)	0.0040(4)	-0.0008(4)

C30'	0.0184(19)	0.0120(17)	0.0275(19)	0.0017(15)	-0.0023(14)	0.0029(14)
C31'	0.023(2)	0.027(2)	0.038(2)	0.0039(18)	-0.0053(15)	0.0086(17)
C32'	0.031(2)	0.033(2)	0.047(3)	0.015(2)	-0.0104(18)	0.0154(19)
C33'	0.044(3)	0.055(3)	0.045(3)	0.014(2)	-0.016(2)	0.010(2)
C34'	0.052(3)	0.039(3)	0.030(2)	0.002(2)	-0.0044(19)	0.002(2)
C35'	0.057(3)	0.024(2)	0.027(2)	-0.0020(18)	0.0018(19)	0.005(2)
C36'	0.029(2)	0.0129(18)	0.028(2)	-0.0010(15)	0.0004(15)	0.0066(15)
C37'	0.0181(18)	0.0075(16)	0.0294(19)	0.0046(14)	-0.0027(14)	0.0037(13)
C38'	0.0216(19)	0.0145(18)	0.0217(17)	0.0037(15)	0.0010(13)	-0.0015(15)
C39'	0.026(2)	0.021(2)	0.038(2)	0.0113(17)	0.0025(16)	0.0029(17)
C40'	0.023(2)	0.037(3)	0.043(2)	0.014(2)	-0.0032(17)	-0.0052(18)
C41'	0.036(3)	0.044(3)	0.032(2)	0.020(2)	-0.0140(18)	-0.022(2)
C42'	0.047(3)	0.020(2)	0.028(2)	0.0042(16)	-0.0001(17)	-0.0144(18)
C43'	0.031(2)	0.0198(19)	0.025(2)	0.0026(16)	0.0029(15)	-0.0025(16)
C44'	0.0151(18)	0.0098(17)	0.030(2)	0.0000(15)	-0.0031(14)	0.0003(14)
C45'	0.0111(17)	0.0146(18)	0.0299(19)	-0.0028(15)	0.0034(14)	-0.0003(14)
C46'	0.026(2)	0.036(2)	0.0226(19)	-0.0081(17)	0.0003(15)	-0.0049(18)
C47'	0.033(2)	0.038(2)	0.025(2)	0.0043(18)	0.0057(16)	-0.0069(19)
C48'	0.0161(19)	0.023(2)	0.037(2)	0.0011(17)	0.0034(15)	0.0006(15)
C49'	0.0168(19)	0.032(2)	0.032(2)	-0.0030(18)	-0.0064(14)	-0.0030(17)
C50'	0.0182(19)	0.034(2)	0.0205(18)	0.0072(17)	-0.0027(14)	0.0019(17)
C51'	0.026(2)	0.033(2)	0.055(3)	0.001(2)	0.0031(19)	-0.0119(19)
C52'	0.0133(18)	0.027(2)	0.028(2)	0.0028(16)	-0.0002(14)	-0.0031(15)
C53'	0.0218(19)	0.0175(18)	0.0215(18)	-0.0029(15)	0.0018(14)	-0.0041(15)
C54'	0.023(2)	0.0159(18)	0.0290(19)	0.0031(16)	-0.0002(14)	-0.0021(16)
C55'	0.034(2)	0.026(2)	0.036(2)	0.0136(19)	0.0006(17)	0.0061(19)
C56'	0.021(2)	0.039(2)	0.038(2)	0.0039(19)	-0.0026(16)	0.0066(18)
C57'	0.027(2)	0.031(2)	0.036(2)	0.0047(18)	-0.0006(16)	-0.0113(18)
C58'	0.022(2)	0.022(2)	0.028(2)	0.0001(16)	-0.0017(15)	-0.0026(16)
N2'	0.0134(15)	0.0143(15)	0.0250(15)	-0.0010(12)	0.0020(11)	0.0030(12)
O4'	0.053(2)	0.0388(19)	0.0452(18)	-0.0115(15)	-0.0120(14)	0.0245(16)
O5'	0.0291(15)	0.0197(14)	0.0482(17)	-0.0173(13)	0.0113(12)	-0.0032(12)
O6'	0.0227(14)	0.0128(13)	0.0484(17)	0.0067(12)	0.0028(11)	0.0020(11)
S2'	0.0185(5)	0.0117(5)	0.0391(5)	-0.0039(4)	0.0043(4)	0.0005(4)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 1a, Å

C1-C6	1.524(5)	C1-C2	1.524(5)	C1-C7	1.535(5)
C2-C3	1.527(6)	C3-C4	1.507(6)	C4-C5	1.523(6)
C5-C6	1.532(5)	C7-O1	1.425(4)	C7-C8	1.508(5)
C8-C15	1.338(5)	C8-C9	1.489(5)	C9-C14	1.390(5)
C9-C10	1.395(5)	C10-C11	1.382(5)	C11-C12	1.387(6)
C12-C13	1.367(6)	C13-C14	1.371(5)	C15-N1	1.451(5)
C16-C17	1.390(5)	C16-C21	1.398(5)	C16-S1	1.744(4)
C17-C18	1.389(6)	C18-C19	1.392(5)	C19-C20	1.390(5)
C19-C22	1.490(6)	C20-C21	1.389(5)	C23-N1	1.477(5)
C23-C24	1.519(5)	C24-C29	1.377(6)	C24-C25	1.391(5)
C25-C26	1.386(6)	C26-C27	1.387(6)	C27-C28	1.359(6)
C28-C29	1.395(6)	N1-S1	1.660(3)	O2-S1	1.434(3)
O3-S1	1.432(3)	C1'-C6'	1.524(5)	C1'-C2'	1.538(5)
C1'-C7'	1.546(5)	C2'-C3'	1.514(5)	C3'-C4'	1.519(6)
C4'-C5'	1.521(6)	C5'-C6'	1.538(5)	C7'-O1'	1.411(4)
C7'-C8'	1.520(5)	C8'-C15'	1.331(5)	C8'-C9'	1.489(4)
C9'-C10'	1.383(5)	C9'-C14'	1.409(5)	C10'-C11'	1.389(5)
C11'-C12'	1.370(6)	C12'-C13'	1.388(6)	C13'-C14'	1.369(5)
C15'-N1'	1.450(4)	C16'-C21'	1.387(5)	C16'-C17'	1.387(5)
C16'-S1'	1.754(3)	C17'-C18'	1.393(5)	C18'-C19'	1.388(5)
C19'-C20'	1.379(5)	C19'-C22'	1.497(5)	C20'-C21'	1.397(5)
C23'-N1'	1.485(4)	C23'-C24'	1.511(5)	C24'-C29'	1.380(5)
C24'-C25'	1.388(5)	C25'-C26'	1.397(5)	C26'-C27'	1.367(6)
C27'-C28'	1.373(6)	C28'-C29'	1.388(5)	N1'-S1'	1.656(3)
O2'-S1'	1.432(3)	O3'-S1'	1.431(3)	C30-C35	1.520(5)
C30-C31	1.530(6)	C30-C36	1.531(5)	C31-C32	1.523(6)
C32-C33	1.514(6)	C33-C34	1.515(6)	C34-C35	1.539(6)
C36-O4	1.408(5)	C36-C37	1.525(5)	C37-C44	1.335(5)
C37-C38	1.492(5)	C38-C43	1.381(5)	C38-C39	1.408(5)
C39-C40	1.378(6)	C40-C41	1.391(6)	C41-C42	1.396(6)
C42-C43	1.380(6)	C44-N2	1.444(5)	C45-C46	1.394(5)
C45-C50	1.397(5)	C45-S2	1.751(4)	C46-C47	1.384(5)
C47-C48	1.387(5)	C48-C49	1.400(5)	C48-C51	1.486(6)
C49-C50	1.383(6)	C52-N2	1.492(5)	C52-C53	1.509(5)
C53-C54	1.381(6)	C53-C58	1.391(5)	C54-C55	1.379(5)
C55-C56	1.373(6)	C56-C57	1.398(6)	C57-C58	1.377(5)
N2-S2	1.663(3)	O5-S2	1.436(3)	O6-S2	1.435(3)
C30'-C35'	1.510(5)	C30'-C31'	1.529(5)	C30'-C36'	1.532(5)
C31'-C32'	1.521(5)	C32'-C33'	1.490(6)	C33'-C34'	1.533(6)
C34'-C35'	1.508(5)	C36'-O4'	1.413(4)	C36'-C37'	1.520(5)
C37'-C44'	1.333(5)	C37'-C38'	1.505(5)	C38'-C43'	1.388(5)
C38'-C39'	1.395(5)	C39'-C40'	1.382(6)	C40'-C41'	1.367(6)
C41'-C42'	1.395(6)	C42'-C43'	1.388(5)	C44'-N2'	1.448(4)
C45'-C50'	1.386(5)	C45'-C46'	1.388(5)	C45'-S2'	1.758(3)
C46'-C47'	1.393(6)	C47'-C48'	1.380(5)	C48'-C49'	1.388(5)
C48'-C51'	1.514(5)	C49'-C50'	1.385(5)	C52'-N2'	1.475(4)
C52'-C53'	1.517(5)	C53'-C54'	1.377(5)	C53'-C58'	1.396(5)
C54'-C55'	1.397(5)	C55'-C56'	1.373(6)	C56'-C57'	1.376(5)
C57'-C58'	1.385(5)	N2'-S2'	1.667(3)	O5'-S2'	1.430(3)
O6'-S2'	1.438(3)				

Table 6. Bond Angles in Compound 1a, °

C6-C1-C2	110.4(3)	C6-C1-C7	113.6(3)	C2-C1-C7	111.8(3)
C1-C2-C3	112.1(3)	C4-C3-C2	111.8(3)	C3-C4-C5	111.3(3)
C4-C5-C6	110.7(4)	C1-C6-C5	111.3(3)	O1-C7-C8	108.5(3)
O1-C7-C1	112.3(3)	C8-C7-C1	111.6(3)	C15-C8-C9	123.2(3)
C15-C8-C7	120.0(3)	C9-C8-C7	116.8(3)	C14-C9-C10	118.3(3)
C14-C9-C8	119.5(3)	C10-C9-C8	122.1(3)	C11-C10-C9	120.4(3)
C10-C11-C12	120.3(4)	C13-C12-C11	119.1(4)	C12-C13-C14	121.3(4)
C13-C14-C9	120.5(4)	C8-C15-N1	124.8(3)	C17-C16-C21	119.8(4)
C17-C16-S1	119.9(3)	C21-C16-S1	120.2(3)	C18-C17-C16	119.6(3)
C17-C18-C19	121.4(4)	C20-C19-C18	118.4(4)	C20-C19-C22	120.7(3)
C18-C19-C22	120.9(4)	C21-C20-C19	121.1(3)	C20-C21-C16	119.7(4)
N1-C23-C24	112.9(3)	C29-C24-C25	119.8(4)	C29-C24-C23	119.0(3)
C25-C24-C23	121.1(4)	C26-C25-C24	119.4(4)	C25-C26-C27	120.2(4)
C28-C27-C26	120.3(4)	C27-C28-C29	120.0(4)	C24-C29-C28	120.3(4)
C15-N1-C23	113.2(3)	C15-N1-S1	112.6(2)	C23-N1-S1	113.4(2)
O3-S1-O2	119.20(17)	O3-S1-N1	107.36(17)	O2-S1-N1	106.20(15)
O3-S1-C16	109.66(17)	O2-S1-C16	107.29(18)	N1-S1-C16	106.42(17)
C6'-C1'-C2'	111.0(3)	C6'-C1'-C7'	113.0(3)	C2'-C1'-C7'	111.5(3)
C3'-C2'-C1'	112.5(3)	C2'-C3'-C4'	111.6(3)	C3'-C4'-C5'	111.3(3)
C4'-C5'-C6'	111.0(4)	C1'-C6'-C5'	110.7(3)	O1'-C7'-C8'	107.9(3)
O1'-C7'-C1'	112.7(3)	C8'-C7'-C1'	111.5(3)	C15'-C8'-C9'	123.4(3)
C15'-C8'-C7'	119.1(3)	C9'-C8'-C7'	117.5(3)	C10'-C9'-C14'	118.1(3)
C10'-C9'-C8'	122.5(3)	C14'-C9'-C8'	119.2(3)	C9'-C10'-C11'	120.5(3)
C12'-C11'-C10'	120.9(3)	C11'-C12'-C13'	119.2(3)	C14'-C13'-C12'	120.5(4)
C13'-C14'-C9'	120.7(4)	C8'-C15'-N1'	124.3(3)	C21'-C16'-C17'	120.2(3)
C21'-C16'-S1'	119.4(3)	C17'-C16'-S1'	120.3(3)	C16'-C17'-C18'	119.2(3)
C19'-C18'-C17'	121.4(3)	C20'-C19'-C18'	118.7(3)	C20'-C19'-C22'	120.4(3)
C18'-C19'-C22'	120.9(3)	C19'-C20'-C21'	121.0(4)	C16'-C21'-C20'	119.6(3)
N1'-C23'-C24'	112.8(3)	C29'-C24'-C25'	119.0(3)	C29'-C24'-C23'	119.0(3)
C25'-C24'-C23'	121.7(3)	C24'-C25'-C26'	119.5(4)	C27'-C26'-C25'	120.3(4)
C26'-C27'-C28'	120.8(4)	C27'-C28'-C29'	119.0(4)	C24'-C29'-C28'	121.3(4)
C15'-N1'-C23'	113.2(3)	C15'-N1'-S1'	113.3(2)	C23'-N1'-S1'	113.1(2)
O3'-S1'-O2'	119.79(16)	O3'-S1'-N1'	107.05(15)	O2'-S1'-N1'	106.30(15)
O3'-S1'-C16'	109.26(16)	O2'-S1'-C16'	107.27(16)	N1'-S1'-C16'	106.42(15)
C35-C30-C31	109.9(3)	C35-C30-C36	112.5(3)	C31-C30-C36	110.0(3)
C32-C31-C30	111.6(3)	C33-C32-C31	112.2(4)	C32-C33-C34	111.9(3)
C33-C34-C35	111.7(4)	C30-C35-C34	110.7(3)	O4-C36-C37	109.8(3)
O4-C36-C30	111.4(3)	C37-C36-C30	111.8(3)	C44-C37-C38	122.8(3)
C44-C37-C36	116.9(3)	C38-C37-C36	120.3(3)	C43-C38-C39	119.0(4)
C43-C38-C37	122.2(3)	C39-C38-C37	118.8(3)	C40-C39-C38	119.6(4)
C39-C40-C41	121.1(4)	C40-C41-C42	118.8(4)	C43-C42-C41	120.2(4)
C42-C43-C38	121.0(4)	C37-C44-N2	125.7(3)	C46-C45-C50	119.5(4)
C46-C45-S2	120.9(3)	C50-C45-S2	119.4(3)	C47-C46-C45	119.7(4)
C46-C47-C48	122.0(3)	C47-C48-C49	117.5(4)	C47-C48-C51	121.6(4)
C49-C48-C51	120.9(3)	C50-C49-C48	121.7(3)	C49-C50-C45	119.6(3)
N2-C52-C53	113.6(3)	C54-C53-C58	118.6(4)	C54-C53-C52	118.5(3)
C58-C53-C52	122.6(4)	C55-C54-C53	121.0(4)	C56-C55-C54	120.4(4)
C55-C56-C57	119.4(4)	C58-C57-C56	119.8(4)	C57-C58-C53	120.8(4)
C44-N2-C52	114.6(3)	C44-N2-S2	111.4(2)	C52-N2-S2	112.5(2)

O6-S2-O5	119.48(18)	O6-S2-N2	106.07(16)	O5-S2-N2	107.37(16)
O6-S2-C45	108.33(17)	O5-S2-C45	109.17(17)	N2-S2-C45	105.53(17)
C35'-C30'-C31'	111.2(3)	C35'-C30'-C36'	113.0(3)	C31'-C30'-C36'	110.1(3)
C32'-C31'-C30'	110.4(3)	C33'-C32'-C31'	113.0(4)	C32'-C33'-C34'	111.7(3)
C35'-C34'-C33'	111.4(4)	C34'-C35'-C30'	112.9(3)	O4'-C36'-C37'	110.8(3)
O4'-C36'-C30'	111.1(3)	C37'-C36'-C30'	112.5(3)	C44'-C37'-C38'	122.9(3)
C44'-C37'-C36'	116.9(3)	C38'-C37'-C36'	120.3(3)	C43'-C38'-C39'	119.6(3)
C43'-C38'-C37'	121.6(3)	C39'-C38'-C37'	118.7(3)	C40'-C39'-C38'	119.0(4)
C41'-C40'-C39'	121.5(4)	C40'-C41'-C42'	120.1(4)	C43'-C42'-C41'	118.9(4)
C42'-C43'-C38'	120.7(4)	C37'-C44'-N2'	125.4(3)	C50'-C45'-C46'	120.0(3)
C50'-C45'-S2'	120.8(3)	C46'-C45'-S2'	119.0(3)	C45'-C46'-C47'	119.6(3)
C48'-C47'-C46'	121.1(3)	C47'-C48'-C49'	118.3(4)	C47'-C48'-C51'	120.5(4)
C49'-C48'-C51'	121.2(3)	C50'-C49'-C48'	121.7(3)	C49'-C50'-C45'	119.3(3)
N2'-C52'-C53'	114.1(3)	C54'-C53'-C58'	118.9(3)	C54'-C53'-C52'	118.6(3)
C58'-C53'-C52'	122.2(3)	C53'-C54'-C55'	121.1(3)	C56'-C55'-C54'	119.5(4)
C55'-C56'-C57'	119.8(4)	C56'-C57'-C58'	121.0(4)	C57'-C58'-C53'	119.6(4)
C44'-N2'-C52'	115.0(3)	C44'-N2'-S2'	111.7(2)	C52'-N2'-S2'	112.6(2)
O5'-S2'-O6'	119.99(16)	O5'-S2'-N2'	106.79(15)	O6'-S2'-N2'	106.14(15)
O5'-S2'-C45'	109.17(16)	O6'-S2'-C45'	108.22(16)	N2'-S2'-C45'	105.60(15)

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

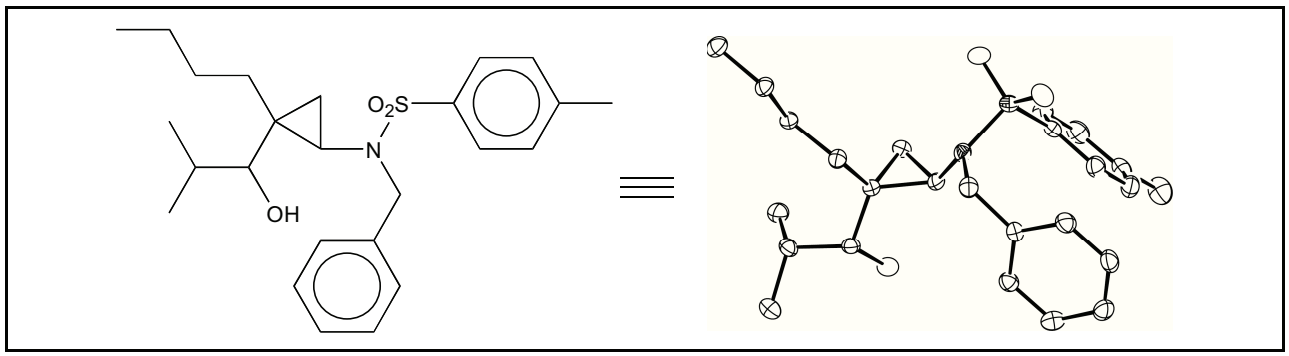
[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi]$R1 = \Sigma||F_o| - |F_c|| / \Sigma |F_o|$
$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{½}$
where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

X-ray Structure Determination of Compound 2f



Compound 2f, $C_{25}H_{35}NSO_3$, crystallizes in the orthorhombic space group Pbcn (systematic absences hk0: h+k=odd, 0kl: k=odd, and h0l: l=odd) with a=24.2849(11)Å, b=8.0847(4)Å, c=24.1022(11)Å, V=4732.1(4)Å^3, Z=8, and d_{calc}=1.206 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 163(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 30 seconds. A total of 1774 frames were collected with a crystal to detector distance of 49.939 mm, rotation widths of 0.5° and exposures of 30 seconds:

scan type	2θ	ω	ϕ	χ	frames
ω	19.50	-62.65	-21.72	19.46	240
ω	27.00	-12.04	59.97	48.96	108
ω	27.00	-46.67	-10.06	23.24	64
ϕ	24.50	68.74	-322.48	-42.87	623
ϕ	19.50	275.98	-337.53	48.96	739

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution on a Dell Pentium 4 computer. A total of 45382 reflections were measured over the ranges $1.68 \leq \theta \leq 25.05°$, $-25 \leq h \leq 28$, $-9 \leq k \leq 9$, $-28 \leq l \leq 28$ yielding 4195 unique reflections (Rint = 0.0761). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6661, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). Refinement was by full-matrix least

squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0615P)^2 + 4.1741P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0529 and wR2=0.1263 for 2957 observed reflections for which $F > 4\sigma(F)$ and R1=0.0848 and wR2=0.1428 and GOF =1.032 for all 4195 unique, non-zero reflections and 277 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.007 and the two most prominent peaks in the final difference Fourier were +0.473 and -0.329 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

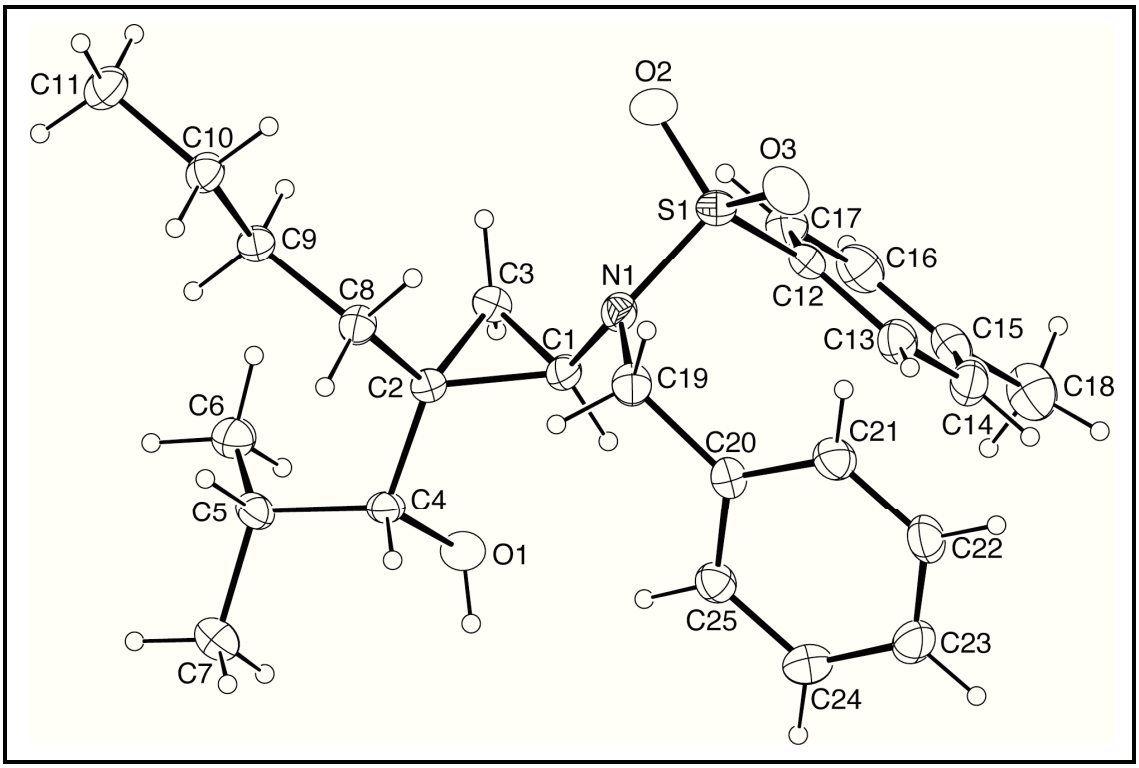


Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 2f

Empirical formula	$C_{25}H_{35}NSO_3$
Formula weight	429.60
Temperature	163(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	Pbcn
Cell constants:	
a	24.2849(11) Å
b	8.0847(4) Å
c	24.1022(11) Å
Volume	4732.1(4) $Å^3$
Z	8
Density (calculated)	1.206 Mg/m^3
Absorption coefficient	0.162 mm^{-1}
F(000)	1856
Crystal size	0.45 x 0.12 x 0.08 mm^3
Theta range for data collection	1.68 to 25.05°
Index ranges	$-25 \leq h \leq 28$, $-9 \leq k \leq 9$, $-28 \leq l \leq 28$
Reflections collected	45382
Independent reflections	4195 [R(int) = 0.0761]
Completeness to theta = 25.05°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6661
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4195 / 0 / 277
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0529, wR2 = 0.1263
R indices (all data)	R1 = 0.0848, wR2 = 0.1428
Largest diff. peak and hole	0.473 and -0.329 $e.Å^{-3}$

Table 2. Refined Positional Parameters for Compound 2f

Atom	x	y	z	U_{eq}, Å^2
C1	0.13431(11)	0.2089(3)	0.48151(11)	0.0307(6)
C2	0.13094(10)	0.1439(3)	0.42226(10)	0.0280(6)
C3	0.17783(11)	0.2571(3)	0.43997(11)	0.0336(7)
C4	0.14044(11)	-0.0407(3)	0.41715(11)	0.0308(6)
C5	0.15616(12)	-0.0987(3)	0.35832(12)	0.0352(7)
C6	0.21034(12)	-0.0288(4)	0.33845(13)	0.0435(7)
C7	0.15719(14)	-0.2870(4)	0.35633(13)	0.0472(8)
C8	0.08768(11)	0.2173(3)	0.38448(11)	0.0317(6)
C9	0.10691(11)	0.2829(3)	0.32852(11)	0.0324(6)
C10	0.06254(11)	0.3783(4)	0.29848(11)	0.0354(7)
C11	0.08064(13)	0.4488(4)	0.24336(12)	0.0428(7)
C12	0.16867(12)	0.4324(3)	0.57697(11)	0.0344(7)
C13	0.15497(12)	0.3622(4)	0.62752(12)	0.0398(7)
C14	0.19634(12)	0.3156(4)	0.66339(12)	0.0425(7)
C15	0.25140(13)	0.3367(4)	0.64974(12)	0.0413(7)
C16	0.26388(13)	0.4033(4)	0.59905(13)	0.0477(8)
C17	0.22381(13)	0.4513(4)	0.56211(13)	0.0442(8)
C18	0.29582(13)	0.2859(5)	0.68995(15)	0.0588(10)
C19	0.03924(11)	0.2555(4)	0.51613(12)	0.0358(7)
C20	0.03748(11)	0.1656(3)	0.57084(11)	0.0320(6)
C21	0.01335(12)	0.2392(4)	0.61693(12)	0.0428(7)
C22	0.01343(14)	0.1618(4)	0.66786(13)	0.0488(8)
C23	0.03809(13)	0.0088(4)	0.67359(13)	0.0490(8)
C24	0.06052(13)	-0.0688(4)	0.62789(13)	0.0449(8)
C25	0.05991(11)	0.0083(4)	0.57693(12)	0.0362(7)
N1	0.09332(9)	0.3266(3)	0.50045(9)	0.0331(5)
O1	0.18195(9)	-0.0896(2)	0.45594(9)	0.0447(5)
O2	0.14159(10)	0.5963(3)	0.49039(9)	0.0566(6)
O3	0.07080(9)	0.5604(3)	0.56177(9)	0.0514(6)
S1	0.11601(3)	0.49339(9)	0.53117(3)	0.0397(2)

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 2f

Atom	x	y	z	U_{iso}, Å^2
H1	0.1460	0.1275	0.5093	0.041
H3a	0.2141	0.2086	0.4441	0.045
H3b	0.1776	0.3700	0.4263	0.045
H4	0.1062	-0.0966	0.4275	0.041
H5	0.1274	-0.0608	0.3328	0.047
H6a	0.2083	0.0898	0.3380	0.065
H6b	0.2179	-0.0685	0.3017	0.065
H6c	0.2393	-0.0631	0.3630	0.065
H7a	0.1653	-0.3227	0.3192	0.071
H7b	0.1219	-0.3294	0.3674	0.071
H7c	0.1850	-0.3276	0.3811	0.071
H8a	0.0699	0.3072	0.4042	0.042
H8b	0.0599	0.1333	0.3778	0.042
H9a	0.1385	0.3544	0.3341	0.043
H9b	0.1186	0.1908	0.3056	0.043
H10a	0.0503	0.4683	0.3220	0.047
H10b	0.0313	0.3057	0.2923	0.047
H11a	0.1121	0.5189	0.2488	0.064
H11b	0.0511	0.5120	0.2275	0.064
H11c	0.0902	0.3601	0.2187	0.064
H13	0.1182	0.3467	0.6372	0.053
H14	0.1872	0.2690	0.6974	0.057
H16	0.3007	0.4164	0.5893	0.063
H17	0.2333	0.4957	0.5278	0.059
H18a	0.3137	0.1878	0.6766	0.088
H18b	0.2797	0.2643	0.7256	0.088
H18c	0.3223	0.3734	0.6933	0.088
H19a	0.0279	0.1794	0.4872	0.048
H19b	0.0124	0.3444	0.5172	0.048
H21	-0.0031	0.3425	0.6133	0.057
H22	-0.0030	0.2125	0.6983	0.065
H23	0.0396	-0.0419	0.7082	0.065
H24	0.0761	-0.1733	0.6315	0.060
H25	0.0747	-0.0454	0.5462	0.048
H1a	0.1745	-0.1812	0.4684	0.067

Table 4. Refined Thermal Parameters (U's) for Compound 2f

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0384(15)	0.0275(14)	0.0263(14)	0.0021(11)	0.0000(12)	0.0051(12)
C2	0.0306(14)	0.0256(13)	0.0278(13)	0.0020(12)	-0.0009(11)	0.0008(11)
C3	0.0379(16)	0.0276(14)	0.0352(15)	-0.0009(13)	-0.0010(13)	-0.0019(12)
C4	0.0346(15)	0.0248(14)	0.0330(14)	0.0031(12)	-0.0049(12)	-0.0009(11)
C5	0.0408(16)	0.0281(15)	0.0368(15)	-0.0048(13)	-0.0073(13)	0.0053(13)
C6	0.0521(18)	0.0359(16)	0.0424(17)	0.0017(14)	0.0039(15)	0.0043(14)
C7	0.058(2)	0.0351(17)	0.0490(19)	-0.0080(15)	0.0012(16)	0.0002(15)
C8	0.0315(14)	0.0334(15)	0.0302(14)	0.0004(12)	-0.0004(12)	0.0058(12)
C9	0.0382(15)	0.0280(14)	0.0308(14)	0.0015(12)	-0.0028(12)	0.0052(13)
C10	0.0395(16)	0.0359(15)	0.0309(15)	0.0032(13)	-0.0036(13)	0.0058(13)
C11	0.0449(18)	0.0459(18)	0.0376(16)	0.0095(14)	-0.0057(14)	-0.0002(15)
C12	0.0470(17)	0.0235(13)	0.0326(15)	-0.0054(12)	0.0002(13)	0.0022(13)
C13	0.0414(17)	0.0419(17)	0.0360(16)	-0.0041(14)	0.0033(14)	0.0005(14)
C14	0.0511(19)	0.0452(18)	0.0313(15)	-0.0007(14)	-0.0029(14)	0.0045(15)
C15	0.0441(17)	0.0356(16)	0.0443(17)	-0.0121(15)	-0.0040(15)	0.0042(14)
C16	0.0385(17)	0.0487(19)	0.056(2)	-0.0108(17)	0.0027(15)	-0.0062(15)
C17	0.054(2)	0.0385(17)	0.0400(17)	-0.0011(14)	0.0056(15)	-0.0075(15)
C18	0.050(2)	0.064(2)	0.062(2)	-0.010(2)	-0.0123(17)	0.0095(18)
C19	0.0353(15)	0.0371(15)	0.0350(15)	-0.0017(13)	-0.0027(12)	0.0095(13)
C20	0.0306(14)	0.0354(15)	0.0301(14)	-0.0044(13)	-0.0001(12)	-0.0008(12)
C21	0.0489(18)	0.0367(16)	0.0429(18)	-0.0044(14)	0.0096(15)	0.0010(14)
C22	0.061(2)	0.0501(19)	0.0352(17)	-0.0116(16)	0.0121(15)	-0.0156(17)
C23	0.059(2)	0.0501(19)	0.0379(17)	0.0067(16)	-0.0014(15)	-0.0219(18)
C24	0.0435(18)	0.0392(17)	0.052(2)	0.0083(16)	0.0035(15)	-0.0027(14)
C25	0.0355(15)	0.0349(15)	0.0384(16)	-0.0029(14)	0.0033(13)	-0.0023(13)
N1	0.0401(13)	0.0316(12)	0.0276(12)	-0.0003(10)	0.0011(10)	0.0074(10)
O1	0.0572(13)	0.0320(11)	0.0451(12)	0.0046(10)	-0.0141(11)	0.0065(10)
O2	0.0904(18)	0.0316(11)	0.0479(13)	0.0079(10)	-0.0042(12)	-0.0045(12)
O3	0.0633(14)	0.0379(11)	0.0530(13)	-0.0103(11)	-0.0057(11)	0.0238(11)
S1	0.0580(5)	0.0251(3)	0.0359(4)	0.0022(3)	-0.0034(4)	0.0065(4)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 2f, Å

C1-N1	1.451(3)	C1-C3	1.507(4)	C1-C2	1.524(4)
C2-C8	1.512(4)	C2-C4	1.515(4)	C2-C3	1.522(4)
C4-O1	1.431(3)	C4-C5	1.542(4)	C5-C6	1.510(4)
C5-C7	1.523(4)	C8-C9	1.523(4)	C9-C10	1.510(4)
C10-C11	1.510(4)	C12-C13	1.385(4)	C12-C17	1.395(4)
C12-S1	1.760(3)	C13-C14	1.378(4)	C14-C15	1.387(4)
C15-C16	1.369(4)	C15-C18	1.507(4)	C16-C17	1.375(4)
C19-N1	1.483(4)	C19-C20	1.506(4)	C20-C21	1.390(4)
C20-C25	1.391(4)	C21-C22	1.378(4)	C22-C23	1.382(5)
C23-C24	1.380(4)	C24-C25	1.378(4)	N1-S1	1.634(2)
O2-S1	1.430(2)	O3-S1	1.429(2)		

Table 6. Bond Angles in Compound 2f, °

N1-C1-C3	121.3(2)	N1-C1-C2	118.9(2)	C3-C1-C2	60.29(17)
C8-C2-C4	116.3(2)	C8-C2-C3	116.9(2)	C4-C2-C3	120.1(2)
C8-C2-C1	117.8(2)	C4-C2-C1	114.0(2)	C3-C2-C1	59.32(17)
C1-C3-C2	60.39(17)	O1-C4-C2	109.1(2)	O1-C4-C5	110.0(2)
C2-C4-C5	114.4(2)	C6-C5-C7	110.5(2)	C6-C5-C4	113.2(2)
C7-C5-C4	109.7(2)	C2-C8-C9	117.2(2)	C10-C9-C8	112.6(2)
C9-C10-C11	114.0(2)	C13-C12-C17	120.1(3)	C13-C12-S1	119.5(2)
C17-C12-S1	120.4(2)	C14-C13-C12	119.3(3)	C13-C14-C15	121.3(3)
C16-C15-C14	118.3(3)	C16-C15-C18	121.5(3)	C14-C15-C18	120.2(3)
C15-C16-C17	122.1(3)	C16-C17-C12	118.8(3)	N1-C19-C20	115.8(2)
C21-C20-C25	118.2(3)	C21-C20-C19	120.3(3)	C25-C20-C19	121.5(2)
C22-C21-C20	121.2(3)	C21-C22-C23	119.8(3)	C24-C23-C22	119.9(3)
C25-C24-C23	120.1(3)	C24-C25-C20	120.8(3)	C1-N1-C19	115.7(2)
C1-N1-S1	116.91(18)	C19-N1-S1	120.19(18)	O3-S1-O2	117.92(14)
O3-S1-N1	106.70(13)	O2-S1-N1	108.36(12)	O3-S1-C12	109.92(13)
O2-S1-C12	106.17(14)	N1-S1-C12	107.33(12)		

[i] Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii] Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii] Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv] Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

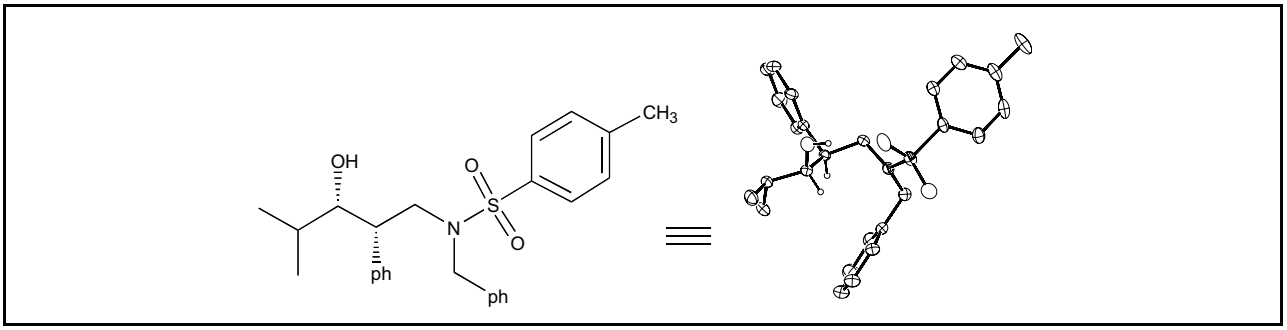
[v] Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi] $R1 = \Sigma||F_o| - |F_c|| / \Sigma |F_o|$

$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{½}$
where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

X-ray Structure Determination of Compound 3a



Compound 3a, $C_{26}H_{31}NSO_3$, crystallizes in the monoclinic space group C2/c (systematic absences hkl: h+k=odd and h0l: l=odd) with a=37.270(3)Å, b=7.0743(6)Å, c=18.198(2)Å, β=93.537(2)°, V=4789.0(7)Å^3, Z=8 and d_{calc}=1.214 g/cm^3. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-K_α radiation (λ=0.71073 Å) at a temperature of 143K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 642 rotation images were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -12°, rotation widths of 0.5° and exposures of 45 seconds: scan no. 1 was a ϕ-scan from 210° to 420° at ω = 10° and χ = °; scan no. 2 was an ω-scan from -20° to 5° at χ = -90° and ϕ = 135°; scan no. 3 was an ω-scan from -20° to 4° at χ = -90° and ϕ = 315°; scan no. 4 was an ω-scan from -20° to 2° at χ = -90° and ϕ = 45°; scan no. 5 was an ω-scan from -20° to 20° at χ = -90° and ϕ = 225°. Rotation images were processed using CrystalClear[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure[ii] program package for further processing and structure solution on a Dell Pentium III computer. A total of 18771 reflections were measured over the ranges 5.12 $\leq 2\theta \leq$ 50.04 °, -37 $\leq$ h $\leq$ 44, -8 $\leq$ k $\leq$ 8, -21 $\leq$ l $\leq$ 20 yielding 4232 unique reflections (R_{int} = 0.0297). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB[iii] (minimum and maximum transmission 0.816, 1.000).

The structure was solved by direct methods (SIR97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97[v]. All reflections were used during refinement (F^2's that were experimentally negative were replaced by F^2 = 0). The weighting scheme used was $w=1/[\sigma^2(F_o^2)+$

$0.0548P^2 + 3.7369P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a "riding" model. Refinement converged to R_1=0.0455 and wR_2=0.1111 for 3417 reflections for which $F > 4\sigma(F)$ and R_1=0.0578, wR_2=0.1210 and GOF = 1.078 for all 4232 unique, non-zero reflections and 285 variables[vi]. The maximum Δ/σ in the final cycle of least squares was 0.060 and the two most prominent peaks in the final difference Fourier were +0.229 and -0.320 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 2. Anisotropic thermal parameters are in Table 3. Tables 4. and 5. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

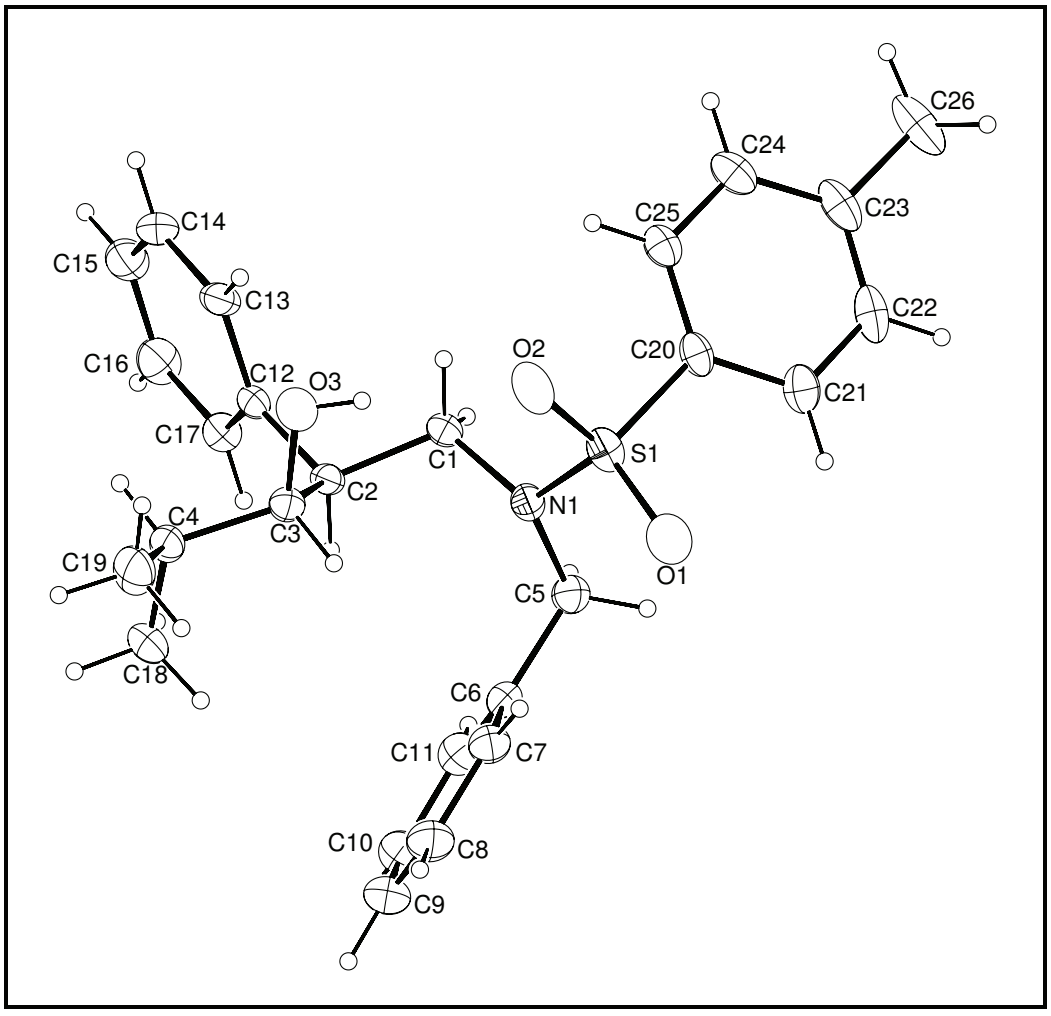


Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 3a

Formula:	$C_{26}H_{31}NSO_3$
Formula weight:	437.58
Crystal class:	monoclinic
Space group:	C2/c (#15)
Z	8
Cell constants:	
a	37.270(3)Å
b	7.0743(6)Å
c	18.198(2)Å
β	93.537(2)°
V	4789.0(7)Å^3
μ	1.62 cm^{-1}
crystal size, mm	0.38 x 0.27 x 0.04
D_{calc}	1.214 g/cm^3
F(000)	1872
Radiation:	Mo-K_α (λ=0.71073Å)
2θ range	5.12 – 50.04 °
hkl collected:	-37≤ h ≤44; -8≤ k ≤8; -21≤ l ≤20
No. reflections measured:	18771
No. unique reflections:	4232 (R_{int}=0.0297)
No. observed reflections	3417 (F>4σ)
No. reflections used in refinement	4232
No. parameters	285
R indices (F>4σ)	R_1=0.0455
	wR_2=0.1111
R indices (all data)	R_1=0.0578
	wR_2=0.1210
GOF:	1.078
Final Difference Peaks, e/Å^3	+0.229, -0.320

Table 2. Refined Positional Parameters for Compound 3a

Atom	x	y	z	U_{eq}, Å^2
C1	0.86259(5)	0.6109(3)	0.66686(10)	0.0310(4)
H1a	0.8563	0.7269	0.6407	0.041
H1b	0.8620	0.5090	0.6311	0.041
C2	0.90097(4)	0.6288(3)	0.70220(9)	0.0289(4)
H2	0.9009	0.7337	0.7374	0.038
C3	0.91279(5)	0.4506(3)	0.74581(10)	0.0335(4)
H3	0.8976	0.4390	0.7877	0.045
C4	0.95190(5)	0.4569(3)	0.77587(10)	0.0380(5)
H4	0.9672	0.4604	0.7339	0.051
C5	0.82290(5)	0.7388(3)	0.76169(11)	0.0398(5)
H5a	0.7979	0.7199	0.7722	0.053
H5b	0.8242	0.8506	0.7311	0.053
C6	0.84500(5)	0.7707(3)	0.83332(10)	0.0373(5)
C7	0.84886(6)	0.6273(3)	0.88507(11)	0.0464(5)
H7	0.8381	0.5106	0.8753	0.062
C8	0.86852(6)	0.6555(4)	0.95099(12)	0.0599(6)
H8	0.8712	0.5575	0.9849	0.080
C9	0.88403(7)	0.8270(5)	0.96654(13)	0.0650(7)
H9	0.8969	0.8463	1.0113	0.086
C10	0.88052(6)	0.9715(4)	0.91580(14)	0.0625(7)
H10	0.8912	1.0881	0.9263	0.083
C11	0.86105(6)	0.9433(3)	0.84873(12)	0.0500(5)
H11	0.8589	1.0408	0.8144	0.067
C12	0.92524(4)	0.6864(3)	0.64175(9)	0.0303(4)
C13	0.93496(5)	0.5607(3)	0.58761(10)	0.0386(5)
H13	0.9275	0.4354	0.5892	0.051
C14	0.95564(6)	0.6211(4)	0.53128(11)	0.0487(6)
H14	0.9618	0.5359	0.4953	0.065
C15	0.96703(6)	0.8052(4)	0.52820(12)	0.0520(6)
H15	0.9809	0.8446	0.4902	0.069
C16	0.95793(6)	0.9310(3)	0.58142(12)	0.0503(6)
H16	0.9658	1.0557	0.5797	0.067
C17	0.93702(5)	0.8724(3)	0.63791(11)	0.0387(5)
H17	0.9308	0.9588	0.6735	0.051
C18	0.95976(6)	0.6332(4)	0.82218(12)	0.0510(6)
H18a	0.9578	0.7431	0.7912	0.076
H18b	0.9837	0.6257	0.8448	0.076
H18c	0.9428	0.6420	0.8597	0.076
C19	0.96128(6)	0.2792(4)	0.82033(13)	0.0555(6)
H19a	0.9859	0.2851	0.8388	0.083
H19b	0.9578	0.1700	0.7894	0.083
H19c	0.9460	0.2705	0.8608	0.083
C20	0.77912(5)	0.4430(3)	0.63021(11)	0.0356(4)
C21	0.74569(5)	0.5221(3)	0.64080(13)	0.0458(5)
H21	0.7386	0.5449	0.6881	0.061
C22	0.72316(5)	0.5665(3)	0.57997(14)	0.0519(6)
H22	0.7008	0.6200	0.5870	0.069
C23	0.73293(6)	0.5333(3)	0.50886(13)	0.0473(6)
C24	0.76676(6)	0.4569(3)	0.49949(12)	0.0433(5)
H24	0.7740	0.4369	0.4522	0.058
C25	0.78972(5)	0.4104(3)	0.55930(11)	0.0372(5)

H25	0.8121	0.3576	0.5522	0.049
C26	0.70749(7)	0.5789(3)	0.4437(2)	0.0674(8)
H26a	0.6847	0.5195	0.4498	0.101
H26b	0.7173	0.5328	0.3995	0.101
H26c	0.7043	0.7133	0.4402	0.101
N1	0.83545(4)	0.5736(2)	0.72079(8)	0.0340(4)
O1	0.78799(4)	0.3775(2)	0.77027(9)	0.0580(4)
O2	0.83087(4)	0.2379(2)	0.68684(9)	0.0486(4)
O3	0.90807(4)	0.2837(2)	0.70179(8)	0.0430(4)
H3a	0.8867	0.2558	0.6978	0.064
S1	0.808660(13)	0.39353(7)	0.70673(3)	0.0398(2)

$U_{eq}=1/3[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*cos\gamma+2U_{13}aa^*cc^*cos\beta+2U_{23}bb^*cc^*cos\alpha]$

Table 3. Refined Thermal Parameters (U's) for Compound 3a

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0337(9)	0.0317(10)	0.0270(10)	0.0018(8)	-0.0022(7)	0.0002(7)
C2	0.0306(9)	0.0299(10)	0.0257(9)	-0.0028(7)	-0.0017(7)	0.0008(7)
C3	0.0336(10)	0.0376(11)	0.0292(10)	0.0015(8)	0.0018(7)	0.0014(8)
C4	0.0322(9)	0.0529(12)	0.0287(10)	0.0072(9)	-0.0006(7)	0.0058(9)
C5	0.0382(10)	0.0441(12)	0.0371(11)	-0.0003(9)	0.0017(8)	0.0050(9)
C6	0.0331(9)	0.0462(12)	0.0331(11)	-0.0020(9)	0.0058(8)	0.0031(8)
C7	0.0451(12)	0.062(2)	0.0327(11)	0.0028(10)	0.0059(9)	0.0003(10)
C8	0.0591(14)	0.086(2)	0.0342(13)	0.0052(12)	0.0046(10)	0.0048(14)
C9	0.0566(14)	0.101(2)	0.0369(13)	-0.0126(14)	-0.0012(10)	0.0016(14)
C10	0.0516(13)	0.076(2)	0.060(2)	-0.0210(14)	0.0038(11)	-0.0099(12)
C11	0.0479(12)	0.0544(14)	0.0482(13)	-0.0037(11)	0.0063(10)	-0.0020(10)
C12	0.0282(9)	0.0356(10)	0.0265(9)	0.0011(8)	-0.0038(7)	0.0009(7)
C13	0.0428(11)	0.0440(12)	0.0284(10)	-0.0046(9)	-0.0028(8)	-0.0043(9)
C14	0.0463(12)	0.073(2)	0.0270(11)	-0.0083(10)	0.0030(9)	-0.0005(11)
C15	0.0477(12)	0.073(2)	0.0351(12)	0.0088(11)	0.0034(9)	-0.0151(11)
C16	0.0499(12)	0.0521(14)	0.0486(13)	0.0105(11)	0.0010(10)	-0.0122(10)
C17	0.0390(10)	0.0384(11)	0.0385(11)	0.0007(9)	0.0006(8)	-0.0013(8)
C18	0.0419(11)	0.071(2)	0.0382(12)	-0.0027(11)	-0.0099(9)	-0.0006(10)
C19	0.0461(12)	0.070(2)	0.0491(14)	0.0167(12)	-0.0050(10)	0.0111(11)
C20	0.0296(9)	0.0290(10)	0.0470(12)	0.0070(9)	-0.0061(8)	-0.0052(8)
C21	0.0343(10)	0.0451(13)	0.0578(14)	0.0064(10)	0.0001(9)	-0.0052(9)
C22	0.0297(10)	0.0416(12)	0.083(2)	0.0103(12)	-0.0105(11)	0.0001(9)
C23	0.0471(12)	0.0249(11)	0.066(2)	0.0084(10)	-0.0245(10)	-0.0091(9)
C24	0.0539(12)	0.0271(10)	0.0469(12)	0.0018(9)	-0.0134(9)	-0.0094(9)
C25	0.0372(10)	0.0256(10)	0.0476(12)	-0.0008(8)	-0.0065(9)	-0.0034(8)
C26	0.070(2)	0.0374(13)	0.088(2)	0.0091(12)	-0.0471(14)	-0.0092(11)
N1	0.0299(8)	0.0378(9)	0.0339(9)	0.0022(7)	-0.0004(6)	-0.0015(6)
O1	0.0518(9)	0.0742(12)	0.0482(9)	0.0214(8)	0.0038(7)	-0.0170(8)
O2	0.0461(8)	0.0299(8)	0.0673(10)	0.0083(7)	-0.0160(7)	0.0003(6)
O3	0.0449(8)	0.0326(8)	0.0507(9)	-0.0005(6)	-0.0031(7)	0.0048(6)
S1	0.0365(3)	0.0388(3)	0.0433(3)	0.0112(2)	-0.0049(2)	-0.0065(2)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+ 2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$.

Table 4. Bond Distances in Compound 3a, Å

C1-N1	1.476(2)	C1-C2	1.537(2)	C2-C12	1.522(2)
C2-C3	1.540(3)	C3-O3	1.432(2)	C3-C4	1.526(3)
C4-C19	1.524(3)	C4-C18	1.524(3)	C5-N1	1.477(2)
C5-C6	1.515(3)	C6-C11	1.381(3)	C6-C7	1.386(3)
C7-C8	1.381(3)	C8-C9	1.366(4)	C9-C10	1.378(4)
C10-C11	1.395(3)	C12-C17	1.390(3)	C12-C13	1.391(3)
C13-C14	1.387(3)	C14-C15	1.372(3)	C15-C16	1.373(3)
C16-C17	1.391(3)	C20-C21	1.390(3)	C20-C25	1.392(3)
C20-S1	1.756(2)	C21-C22	1.384(3)	C22-C23	1.386(3)
C23-C24	1.392(3)	C23-C26	1.507(3)	C24-C25	1.382(3)
N1-S1	1.629(2)	O1-S1	1.433(2)	O2-S1	1.437(2)

Table 5. Bond Angles in Compound 3a, °

N1-C1-C2	113.25(14)	C12-C2-C1	107.39(14)	C12-C2-C3	115.32(14)
C1-C2-C3	112.18(14)	O3-C3-C4	107.8(2)	O3-C3-C2	111.44(14)
C4-C3-C2	113.4(2)	C19-C4-C18	110.6(2)	C19-C4-C3	110.4(2)
C18-C4-C3	111.7(2)	N1-C5-C6	112.3(2)	C11-C6-C7	118.9(2)
C11-C6-C5	120.8(2)	C7-C6-C5	120.2(2)	C8-C7-C6	120.8(2)
C9-C8-C7	120.2(2)	C8-C9-C10	119.9(2)	C9-C10-C11	120.2(3)
C6-C11-C10	120.0(2)	C17-C12-C13	118.2(2)	C17-C12-C2	119.6(2)
C13-C12-C2	122.2(2)	C14-C13-C12	120.5(2)	C15-C14-C13	120.7(2)
C14-C15-C16	119.7(2)	C15-C16-C17	120.1(2)	C16-C17-C12	120.8(2)
C21-C20-C25	120.2(2)	C21-C20-S1	119.6(2)	C25-C20-S1	120.13(14)
C22-C21-C20	119.0(2)	C21-C22-C23	121.8(2)	C22-C23-C24	118.2(2)
C22-C23-C26	120.7(2)	C24-C23-C26	121.1(2)	C25-C24-C23	121.2(2)
C24-C25-C20	119.5(2)	C1-N1-C5	116.4(2)	C1-N1-S1	118.29(12)
C5-N1-S1	119.18(12)	O1-S1-O2	119.29(10)	O1-S1-N1	106.86(9)
O2-S1-N1	106.36(8)	O1-S1-C20	108.28(9)	O2-S1-C20	107.20(9)
N1-S1-C20	108.47(8)				

References

i. CrystalClear: Rigaku Corporation, 1999.

ii. CrystalStructure: Crystal Structure Analysis Package, Rigaku Corp. Rigaku/MSC (2002).

iii. REQAB4: R.A. Jacobsen, (1994). Private Communication.

iv. SIR97: Altomare, A., M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. Moliterni, G. Polidori & R. Spagna (1999). *J. Appl. Cryst.*, **32**, 115-119.

v. SHELXL-97: Program for the Refinement of Crystal Structures, Sheldrick, G.M. (1997), University of Göttingen, Germany.

vi. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$

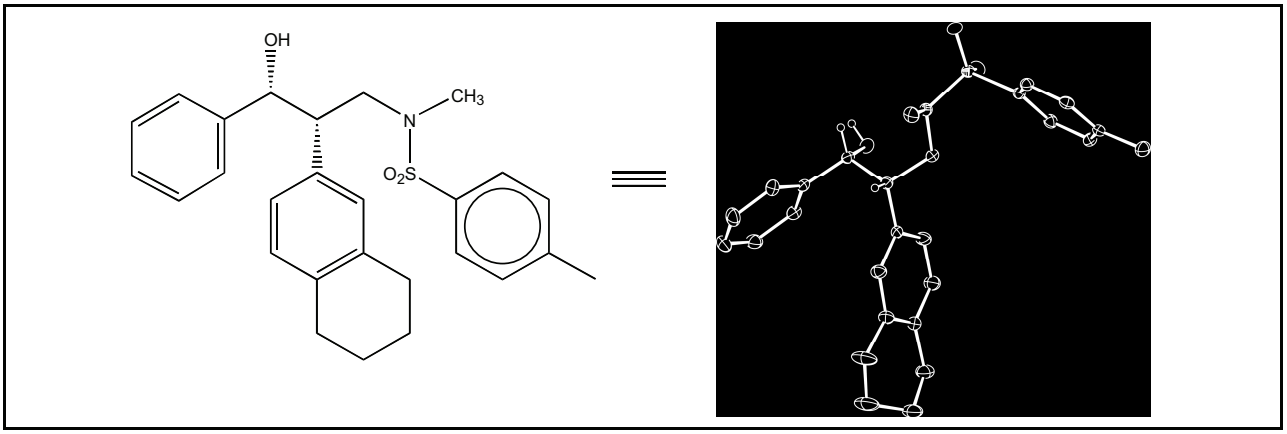
$wR_2 = \{ \sum w (F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \}^{1/2}$

$GOF = \{ \sum w (F_o^2 - F_c^2)^2 / (n - p) \}^{1/2}$

where n = the number of reflections and p = the number of parameters refined.

vii. “ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations”. C.K. Johnson (1976) ORNL-5138.

X-ray Structure Determination of Compound 4-7'



Compound 5-7', $C_{27}H_{31}NSO_3$, crystallizes in the monoclinic space group $P2_1/n$ (systematic absences 0k0: k=odd and h0l: h+l=odd) with a=16.7153(15)Å, b=6.1216(7)Å, c=23.543(2)Å, β=101.350(6)°, V=2361.9(4)Å^3, Z=4, and d_{calc}=1.264 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 30 seconds. A total of 1541 frames were collected with a crystal to detector distance of 49.936 mm, rotation widths of 0.5° and exposures of 30 seconds:

scan type	2θ	ω	ϕ	χ	frames
ϕ	-23.00	-13.80	-345.79	32.61	739
ω	29.50	-39.88	-176.20	85.83	149
ω	-23.00	-120.89	-174.06	50.72	205
ω	27.00	-51.59	-36.78	99.23	174
ω	27.00	-78.78	-10.06	23.24	274

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution on a Dell Pentium 4 computer. A total of 23965 reflections were measured over the ranges $1.66 \leq \theta \leq 25.17°$, $-19 \leq h \leq 20$, $-7 \leq k \leq 7$, $-28 \leq l \leq 27$ yielding 4238 unique reflections (Rint = 0.0579). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii]

(minimum and maximum transmission 0.6502, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0472P)^2 + 1.0015P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0420 and wR2=0.0944 for 3092 observed reflections for which $F > 4\sigma(F)$ and R1=0.0693 and wR2=0.1055 and GOF =1.022 for all 4238 unique, non-zero reflections and 293 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.417 and -0.353 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

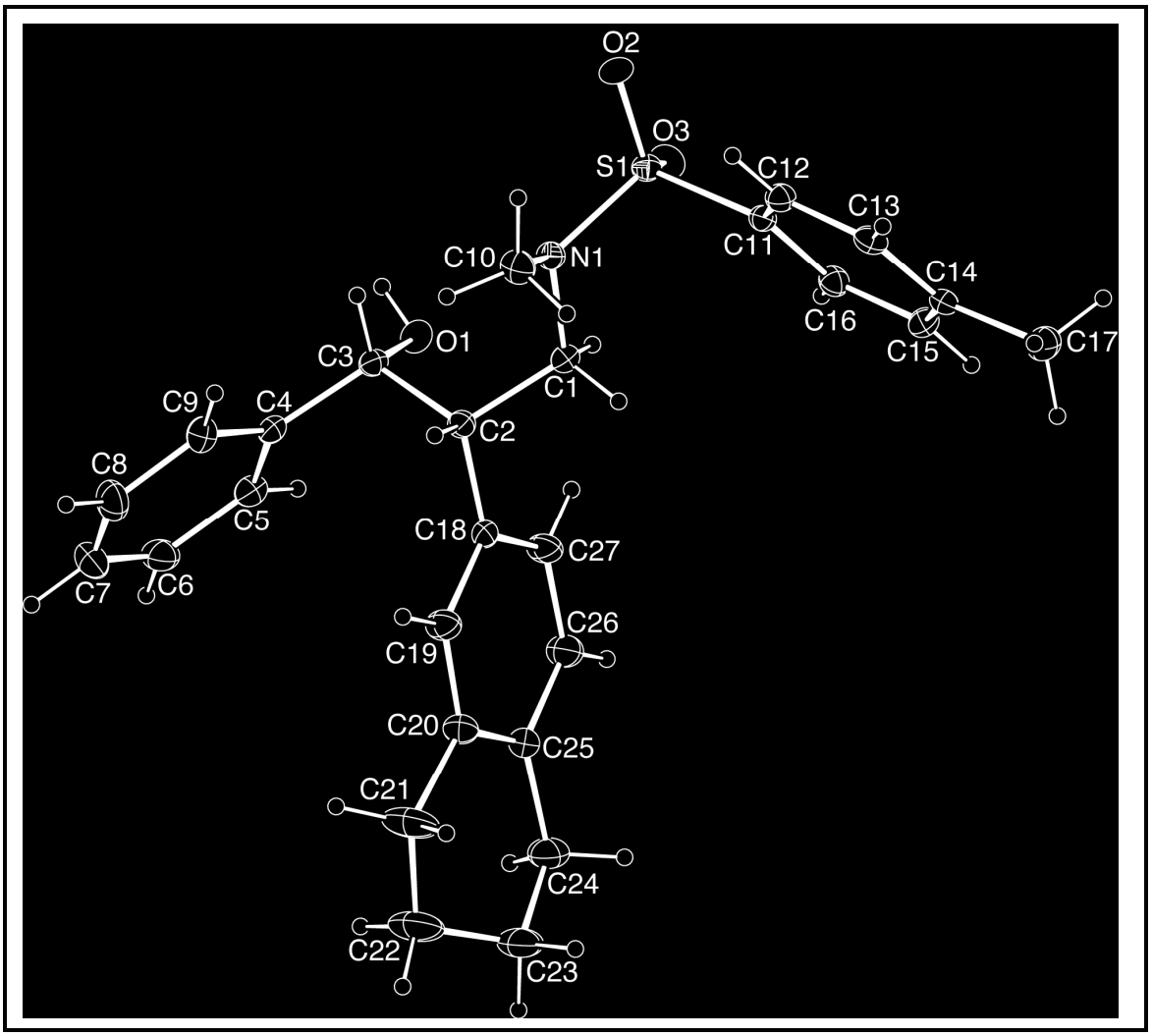


Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 5-7'

Empirical formula	$C_{27}H_{31}NSO_3$
Formula weight	449.59
Temperature	143(1) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1/n$
Cell constants:	
a	16.7153(15) Å
b	6.1216(7) Å
c	23.543(2) Å
β	101.350(6)°
Volume	2361.9(4) $Å^3$
Z	4
Density (calculated)	1.264 Mg/m^3
Absorption coefficient	0.166 mm^{-1}
F(000)	960
Crystal size	0.55 x 0.03 x 0.02 mm^3
Theta range for data collection	1.66 to 25.17°
Index ranges	$-19 \leq h \leq 20$, $-7 \leq k \leq 7$, $-28 \leq l \leq 27$
Reflections collected	23965
Independent reflections	4238 [R(int) = 0.0579]
Completeness to theta = 25.17°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6502
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4238 / 0 / 293
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.0944
R indices (all data)	R1 = 0.0693, wR2 = 0.1055
Largest diff. peak and hole	0.417 and -0.353 $e.Å^{-3}$

Table 2. Refined Positional Parameters for Compound 5-7'

Atom	x	y	z	U_{eq}, Å^2
C1	0.42261(12)	0.2130(4)	0.61421(8)	0.0244(5)
C2	0.33408(12)	0.2416(4)	0.58223(8)	0.0223(5)
C3	0.31811(12)	0.1297(4)	0.52221(9)	0.0239(5)
C4	0.23006(13)	0.1594(4)	0.49189(8)	0.0246(5)
C5	0.17263(13)	-0.0015(4)	0.49423(9)	0.0307(5)
C6	0.09128(14)	0.0314(4)	0.46863(10)	0.0377(6)
C7	0.06675(15)	0.2254(5)	0.44125(10)	0.0423(7)
C8	0.12339(14)	0.3868(5)	0.43886(10)	0.0399(6)
C9	0.20498(14)	0.3539(4)	0.46372(9)	0.0308(5)
C10	0.47500(14)	0.5462(4)	0.57475(10)	0.0307(5)
C11	0.61188(11)	0.3235(3)	0.67400(8)	0.0200(5)
C12	0.64690(12)	0.5294(4)	0.68148(9)	0.0245(5)
C13	0.67304(12)	0.6102(4)	0.73706(9)	0.0254(5)
C14	0.66507(12)	0.4888(4)	0.78551(9)	0.0244(5)
C15	0.62891(13)	0.2836(4)	0.77693(9)	0.0285(5)
C16	0.60220(12)	0.1999(4)	0.72182(9)	0.0254(5)
C17	0.69662(14)	0.5731(5)	0.84552(9)	0.0378(6)
C18	0.27603(12)	0.1642(4)	0.62037(8)	0.0237(5)
C19	0.21086(13)	0.2954(4)	0.62686(9)	0.0309(5)
C20	0.15458(13)	0.2330(4)	0.66057(9)	0.0307(5)
C21	0.08414(17)	0.3809(5)	0.66426(14)	0.0580(8)
C22	0.01943(18)	0.2771(5)	0.69150(14)	0.0615(9)
C23	0.05323(16)	0.1447(5)	0.74238(12)	0.0511(8)
C24	0.10783(15)	-0.0330(5)	0.72909(11)	0.0452(7)
C25	0.16505(13)	0.0362(4)	0.69017(9)	0.0299(5)
C26	0.23018(14)	-0.0973(4)	0.68318(10)	0.0368(6)
C27	0.28401(14)	-0.0358(4)	0.64840(10)	0.0338(6)
O1	0.33974(9)	-0.0929(3)	0.53121(6)	0.0316(4)
O2	0.62400(8)	0.3203(3)	0.56620(6)	0.0278(4)
O3	0.57380(9)	-0.0121(2)	0.60699(6)	0.0293(4)
N1	0.48216(10)	0.3080(3)	0.58250(7)	0.0222(4)
S1	0.57600(3)	0.22084(9)	0.60360(2)	0.02209(15)

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 5-7'

Atom	x	y	z	U_{iso}, Å^2
H1a	0.4292	0.2817	0.6520	0.032
H1b	0.4340	0.0584	0.6202	0.032
H2	0.3248	0.3984	0.5757	0.030
H3	0.3535	0.1964	0.4985	0.032
H5	0.1886	-0.1325	0.5131	0.041
H6	0.0532	-0.0783	0.4700	0.050
H7	0.0122	0.2476	0.4244	0.056
H8	0.1069	0.5184	0.4205	0.053
H9	0.2430	0.4629	0.4615	0.041
H10a	0.4242	0.5804	0.5494	0.046
H10b	0.5193	0.5989	0.5581	0.046
H10c	0.4768	0.6147	0.6117	0.046
H12	0.6528	0.6127	0.6495	0.033
H13	0.6964	0.7485	0.7420	0.034
H15	0.6225	0.2010	0.8089	0.038
H16	0.5781	0.0626	0.7168	0.034
H17a	0.6588	0.5369	0.8699	0.057
H17b	0.7027	0.7289	0.8443	0.057
H17c	0.7486	0.5076	0.8608	0.057
H19	0.2043	0.4299	0.6081	0.041
H21a	0.0595	0.4289	0.6255	0.077
H21b	0.1047	0.5094	0.6865	0.077
H22a	-0.0147	0.3907	0.7028	0.082
H22b	-0.0148	0.1854	0.6630	0.082
H23a	0.0088	0.0804	0.7576	0.068
H23b	0.0838	0.2385	0.7721	0.068
H24a	0.0744	-0.1527	0.7108	0.060
H24b	0.1399	-0.0872	0.7652	0.060
H26	0.2375	-0.2307	0.7024	0.049
H27	0.3260	-0.1297	0.6438	0.045
H1	0.3480	-0.1460	0.5009	0.049

Table 4. Refined Thermal Parameters (U's) for Compound 5-7'

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0245(11)	0.0285(13)	0.0208(10)	0.0021(9)	0.0064(8)	0.0008(9)
C2	0.0234(11)	0.0226(12)	0.0213(10)	0.0019(9)	0.0057(8)	0.0056(9)
C3	0.0249(11)	0.0271(12)	0.0208(10)	0.0004(9)	0.0073(8)	0.0036(9)
C4	0.0268(11)	0.0304(14)	0.0171(10)	-0.0012(9)	0.0060(9)	0.0030(10)
C5	0.0326(12)	0.0351(14)	0.0258(11)	0.0012(10)	0.0092(9)	0.0010(11)
C6	0.0288(12)	0.0486(17)	0.0376(14)	-0.0046(12)	0.0114(11)	-0.0053(12)
C7	0.0269(12)	0.0579(19)	0.0398(14)	-0.0027(14)	0.0013(11)	0.0089(13)
C8	0.0386(14)	0.0400(16)	0.0376(13)	0.0058(12)	-0.0010(11)	0.0109(12)
C9	0.0340(13)	0.0308(14)	0.0264(12)	0.0029(10)	0.0029(10)	0.0012(10)
C10	0.0328(12)	0.0225(13)	0.0369(13)	0.0052(10)	0.0072(10)	0.0050(10)
C11	0.0188(10)	0.0209(12)	0.0209(10)	0.0013(9)	0.0051(8)	0.0013(8)
C12	0.0228(11)	0.0262(13)	0.0254(11)	0.0027(10)	0.0072(9)	0.0000(9)
C13	0.0206(10)	0.0236(12)	0.0330(12)	-0.0029(10)	0.0077(9)	-0.0023(9)
C14	0.0161(10)	0.0331(13)	0.0244(11)	-0.0011(10)	0.0050(8)	0.0012(9)
C15	0.0274(11)	0.0360(14)	0.0234(11)	0.0068(10)	0.0080(9)	-0.0020(10)
C16	0.0220(11)	0.0258(13)	0.0281(11)	0.0028(10)	0.0045(9)	-0.0025(9)
C17	0.0321(13)	0.0527(18)	0.0286(12)	-0.0071(12)	0.0061(10)	-0.0087(12)
C18	0.0220(11)	0.0305(13)	0.0183(10)	-0.0024(9)	0.0031(8)	0.0046(9)
C19	0.0325(12)	0.0291(13)	0.0334(12)	0.0036(11)	0.0123(10)	0.0072(10)
C20	0.0282(12)	0.0329(14)	0.0327(12)	-0.0028(11)	0.0102(10)	0.0053(10)
C21	0.0468(16)	0.0490(18)	0.090(2)	0.0088(17)	0.0423(16)	0.0164(14)
C22	0.0500(17)	0.064(2)	0.082(2)	0.0119(18)	0.0420(16)	0.0224(16)
C23	0.0342(14)	0.074(2)	0.0512(16)	-0.0066(16)	0.0231(12)	-0.0033(14)
C24	0.0365(14)	0.060(2)	0.0446(15)	0.0125(14)	0.0203(12)	0.0056(13)
C25	0.0245(11)	0.0391(15)	0.0265(11)	0.0014(11)	0.0064(9)	0.0021(10)
C26	0.0354(13)	0.0395(15)	0.0387(13)	0.0162(12)	0.0148(11)	0.0109(11)
C27	0.0310(12)	0.0365(15)	0.0369(13)	0.0107(11)	0.0144(10)	0.0148(11)
O1	0.0384(9)	0.0327(10)	0.0242(8)	-0.0025(7)	0.0071(7)	0.0149(8)
O2	0.0290(8)	0.0331(10)	0.0244(8)	-0.0032(7)	0.0125(6)	-0.0016(7)
O3	0.0302(8)	0.0197(8)	0.0378(9)	-0.0041(7)	0.0060(7)	0.0029(7)
N1	0.0225(9)	0.0219(10)	0.0225(9)	0.0012(8)	0.0052(7)	0.0009(7)
S1	0.0226(3)	0.0219(3)	0.0226(3)	-0.0018(2)	0.0065(2)	0.0013(2)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 5-7', Å

C1-N1	1.476(3)	C1-C2	1.533(3)	C2-C18	1.522(3)
C2-C3	1.546(3)	C3-O1	1.415(3)	C3-C4	1.515(3)
C4-C5	1.384(3)	C4-C9	1.387(3)	C5-C6	1.389(3)
C6-C7	1.375(4)	C7-C8	1.377(4)	C8-C9	1.389(3)
C10-N1	1.472(3)	C11-C12	1.387(3)	C11-C16	1.392(3)
C11-S1	1.764(2)	C12-C13	1.386(3)	C13-C14	1.389(3)
C14-C15	1.391(3)	C14-C17	1.499(3)	C15-C16	1.385(3)
C18-C27	1.385(3)	C18-C19	1.386(3)	C19-C20	1.398(3)
C20-C25	1.386(3)	C20-C21	1.501(3)	C21-C22	1.503(4)
C22-C23	1.464(4)	C23-C24	1.492(4)	C24-C25	1.510(3)
C25-C26	1.396(3)	C26-C27	1.383(3)	O2-S1	1.4380(15)
O3-S1	1.4288(16)	N1-S1	1.6386(17)		

Table 6. Bond Angles in Compound 5-7', °

N1-C1-C2	112.87(16)	C18-C2-C1	109.92(16)	C18-C2-C3	112.72(17)
C1-C2-C3	112.01(16)	O1-C3-C4	112.47(18)	O1-C3-C2	107.27(16)
C4-C3-C2	110.76(16)	C5-C4-C9	118.9(2)	C5-C4-C3	120.8(2)
C9-C4-C3	120.2(2)	C4-C5-C6	120.5(2)	C7-C6-C5	120.3(2)
C6-C7-C8	119.7(2)	C7-C8-C9	120.3(2)	C4-C9-C8	120.3(2)
C12-C11-C16	120.32(19)	C12-C11-S1	120.02(16)	C16-C11-S1	119.63(16)
C13-C12-C11	119.4(2)	C12-C13-C14	121.4(2)	C13-C14-C15	118.20(19)
C13-C14-C17	121.1(2)	C15-C14-C17	120.7(2)	C16-C15-C14	121.4(2)
C15-C16-C11	119.3(2)	C27-C18-C19	117.7(2)	C27-C18-C2	122.92(19)
C19-C18-C2	119.4(2)	C18-C19-C20	122.4(2)	C25-C20-C19	119.4(2)
C25-C20-C21	121.2(2)	C19-C20-C21	119.4(2)	C20-C21-C22	114.1(2)
C23-C22-C21	112.9(2)	C22-C23-C24	112.7(2)	C23-C24-C25	114.2(2)
C20-C25-C26	118.3(2)	C20-C25-C24	121.1(2)	C26-C25-C24	120.6(2)
C27-C26-C25	121.6(2)	C26-C27-C18	120.7(2)	C10-N1-C1	114.00(18)
C10-N1-S1	114.19(14)	C1-N1-S1	114.78(14)	O3-S1-O2	118.70(9)
O3-S1-N1	107.95(9)	O2-S1-N1	107.03(9)	O3-S1-C11	108.10(10)
O2-S1-C11	107.28(9)	N1-S1-C11	107.28(9)		

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi] $R1 = \Sigma||F_o| - |F_c|| / \Sigma |F_o|$
$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{½}$
where n = the number of reflections and p = the number of parameters refined.

[vii] "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.