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UNIVERSITY OF CALIFORNIA, SAN DIEGO

Zwittermicin A: Determination of its Complete Configuration and Total Synthesis of its
Enantiomer

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor
of Philosophy
in
Chemistry
by
Evan W. Rogers

Committee in charge:

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2008

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Chair

University of California, San Diego

2008

TABLE OF CONTENTS

| | |
|--|------|
| Signature Page..... | iii |
| Table of Contents..... | iv |
| List of Symbols and Abbreviations..... | vii |
| List of Figures..... | x |
| List of Schemes..... | xi |
| List of Tables..... | xiii |
| List of Spectra..... | xiv |
| Acknowledgements | xx |
| Vita | xxii |
| Abstract of the Dissertation | xxiv |
| Chapter 1 Zwittermicin A Background and Review of Aminoalcohol Syntheses | 1 |
| 1.1. Introduction | 1 |
| 1.1.1. Background on (+)-Zwittermicin A | 3 |
| 1.2. Open-Chain Aminopolyol Synthesis | 6 |
| 1.2.1. Synthesis of 2-amino-1,3-diols: Key Strategies in Sphingolipid Synthesis | 7 |
| 1.2.1.1. Carbohydrate Approach..... | 9 |
| 1.2.1.2. Chiral Catalysts and Asymmetric Induction..... | 9 |
| 1.2.1.3. Chirality Through use of Serine..... | 11 |
| 1.2.2. Synthesis of 2-amino-1,3-diols: Non-Sphingolipid Synthesis..... | 12 |
| 1.2.2.1. Chirality Through use of Amino Acid Chiral Pool..... | 12 |
| 1.2.2.2. Chirality Through Asymmetric Catalyst | 25 |
| 1.2.3. Other Open-Chain Aminopolyols | 38 |
| 1.3. References | 41 |
| Chapter 2 Determination of Absolute Configuration at C4 and Relative Configuration for C8-C14 in (+)-Zwittermicin A: Proposed Configuration of (+)-Zwittermicin A..... | 47 |
| 2.1. Introduction | 47 |
| 2.1.1. Marfey's Analysis..... | 48 |
| 2.1.2. Pair-wise ¹³ C NMR Chemical Shift Difference Analysis | 49 |
| 2.2. Determination of C4 Configuration in (+)-Zwittermicin A by Marfey's Analysis..... | 49 |
| 2.3. Determination of C10-C14 Relative Configuration in (+)-Zwittermicin A..... | 51 |
| 2.3.1. Retrosynthesis..... | 52 |

| | |
|--|-----|
| 2.3.2. Synthesis of Model Compounds | 54 |
| 2.3.3. Pair-wise ¹³ C NMR Chemical Shift Difference Analysis | 70 |
| 2.4. Configuration of (+)-Zwittermicin A | 72 |
| 2.5. Acknowledgments | 72 |
| 2.6. References | 73 |
| Chapter 3 Synthesis of (-)-Zwittermicin A | 75 |
| 3.1. Retrosynthesis | 75 |
| 3.2. Evaluation of Strategy Using Model Compound | 76 |
| 3.2.1. Synthesis of Aldehyde 303 | 80 |
| 3.3. Evaluation of Final Synthetic Steps Using Model Compound | 81 |
| 3.4. Synthesis of Proposed (+)-Zwittermicin A Structure | 87 |
| 3.5. Synthesis of (+)- 319 | 91 |
| 3.6. Synthesis of (-)-Zwittermicin A | 91 |
| 3.7. Configuration of (+)-Zwittermicin A | 93 |
| 3.8. Conclusion | 94 |
| 3.9. Acknowledgements | 94 |
| 3.10. References | 95 |
| Chapter 4 Improved Synthesis of the C9-C15 Portion of (+)-Zwittermicin A | 98 |
| 4.1. Retrosynthesis | 98 |
| 4.2. Synthesis of Known Compounds | 99 |
| 4.3. Epoxide Synthesis, Azide Opening and Desymmetrization | 100 |
| 4.3.1. Interception of Previous Synthetic Route | 103 |
| 4.4. Conclusion | 105 |
| 4.5. References | 105 |
| Chapter 5 Synthesis of (+)-Zwittermicin A Diastereomers and Analogs: Structure-Activity Relationships | 108 |
| 5.1. Introduction | 108 |
| 5.2. Synthesis of Aminopolyol 350 | 110 |
| 5.3. Synthesis of Analogs Representing C1-C11 of (+)-Zwittermicin A | 110 |
| 5.4. Synthesis of Two (+)-Zwittermicin A Diastereomers | 111 |
| 5.5. Determination of % Enantiomeric Excess for Synthetic (-)-Zwittermicin A and Diastereomers | 114 |
| 5.6. Biological Testing | 115 |
| 5.7. Conclusion | 117 |
| 5.8. Acknowledgements | 118 |
| 5.9. References: | 118 |
| Chapter 6 Synthesis of Sulfone Aminopolyols | 119 |
| 6.1. Introduction and Retrosynthesis | 119 |
| 6.2. Route A, Synthesis of Diene 363 | 121 |
| 6.3. Route B, Sulfone Anion Addition | 122 |
| 6.3.1. Preliminary Investigation of Sulfone Removal | 126 |
| 6.3.2. Initial Attempts at Dianion Addition | 127 |
| 6.3.3. New Sulfone Addition Products | 129 |
| 6.3.4. Sulfone Dianion Additions | 132 |
| 6.3.4.1. Bioassay | 134 |

| | |
|---|------------|
| 6.3.5. Investigation of Sulfone Removal..... | 134 |
| 6.3.6. Protection of Free Hydroxyls and Attempted Sulfone Removal..... | 136 |
| 6.4. Synthesis of Model Sulfone..... | 137 |
| 6.4.1. Attempts to Remove Sulfone from 403 | 138 |
| 6.5. Other Sulfur Based Dianion Additions..... | 139 |
| 6.6. Use of Sulfone Chemistry for Synthesis of LC/MS Standards..... | 142 |
| 6.6.1. Synthesis of Internal Standard..... | 142 |
| 6.6.2. Synthesis of Surrogate Standard..... | 143 |
| 6.7. Conclusion..... | 144 |
| 6.8. Acknowledgements..... | 145 |
| 6.9. References..... | 145 |
| Chapter 7 Experimental..... | 149 |
| 7.1. Materials and Methods..... | 149 |
| 7.1.1. General Procedures..... | 149 |
| 7.1.2. Determination of configuration of C4 in Zwittermicin [(+)- 1]..... | 150 |
| 7.1.3. Chapter 2 Methods..... | 151 |
| 7.1.4. Chapter 3 Methods..... | 184 |
| 7.1.5. Chapter 4 Methods..... | 220 |
| 7.1.6. Chapter 5 Methods..... | 227 |
| 7.1.7. Chapter 6 Methods..... | 239 |
| 7.2. X-ray CIF Data..... | 259 |
| 7.3. Spectra..... | 299 |
| 7.3.1. Chapter 2 Spectra..... | 299 |
| 7.3.2. Chapter 3 Spectra..... | 372 |
| 7.3.3. Chapter 4 Spectra..... | 448 |
| 7.3.4. Chapter 5 Spectra..... | 462 |
| 7.3.5. Chapter 6 Spectra..... | 486 |

LIST OF SYMBOLS AND ABBREVIATIONS

| | |
|--------|---|
| Ac | acetyl |
| Aq | aqueous |
| ACN | acetonitrile |
| Bn | benzyl |
| Boc | <i>t</i> -butoxycarbonyl |
| Bu | butyl |
| CAN | ceric ammonium nitrate |
| CSA | camphorsulfonic acid |
| DCC | <i>N,N</i> -dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| D-FDAA | 5-fluoro-2,4-dinitrophenyl-D-alaninamide |
| DIBAL | diisobutylaluminum hydride |
| DMAP | <i>N,N</i> -dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | <i>N,N</i> -dimethylformamide |
| DMP | Dess-Martin periodane |
| DMSO | dimethylsulfoxide |
| EDCI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| Et | ethyl |
| Fmoc | 9-fluorenylmethyl carbonoyl |
| FT-IR | Fourier transform-infrared |

| | |
|----------------|--|
| HMPA | hexamethylphosphoramide |
| HOBt | <i>N</i> -hydroxybenzotriazole |
| HPLC | high performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| HWE | Horner-Wadworth-Emmons reaction |
| IR | infrared |
| LC | liquid chromatography |
| L-FDAA | 5-fluoro-2,4-dinitrophenyl-L-alaninamide |
| LAH | lithium aluminumhydride |
| <i>m</i> -CPBA | <i>m</i> -chloroperoxybenzoic acid |
| MIC | minimum inhibitory concentration |
| Me | methyl |
| MHz | megahertz |
| MPM | <i>p</i> -methoxybenzyl |
| MOM | methoxymethyl |
| MS | mass spectrometry |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NBS | <i>N</i> -bromosuccinimide |
| NMM | <i>N</i> -methylmorpholine |
| NMO | 4-methylmorpholine <i>N</i> -oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| <i>i</i> Pr | isopropyl |

| | |
|-------------------|---------------------------------------|
| PG | protecting group |
| Piv | pivaloyl |
| Ph | phenyl |
| PMB | <i>p</i> -methoxybenzyl |
| PPTS | pyridinium <i>p</i> -toluenesulfonate |
| Pyr | pyridine |
| SAE | Sharpless asymmetric epoxidation |
| Ser | serine |
| S _N Ar | nucleophilic aromatic substitution |
| TBAF | tetrabutylammonium fluoride |
| TBDPSCI | <i>t</i> -butyldiphenylsilyl chloride |
| TBSCl | <i>t</i> -butyldimethylsilyl chloride |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPSCI | triisopropylsilyl chloride |
| TLC | thin-layer chromatography |
| TMSCl | trimethylsilyl chloride |
| TrCl | trityl chloride |
| Ts | <i>p</i> -toluenesulfonyl |
| UV | ultraviolet |

LIST OF FIGURES

| | |
|---|-----|
| Figure 1.1: Natural Zwittermicin A..... | 1 |
| Figure 1.2: Examples of fungicides..... | 2 |
| Figure 1.3: Proposed biosynthetic pathway..... | 5 |
| Figure 1.4: Degradation of zwittermicin A..... | 6 |
| Figure 1.5: Examples of sphingolipids and sphingosine..... | 8 |
| Figure 1.6: Structure of galantin I, galantinamic acid and galantinic acid..... | 13 |
| Figure 2.1: Model Compounds for NMR Comparisons..... | 52 |
| Figure 2.2: ^1H NMR (500 MHz, D_2O) of compounds 220 and 221 | 61 |
| Figure 2.3: X-ray crystal structure of compound 271 | 67 |
| Figure 2.4: ^{13}C chemical shift dependence on concentration..... | 70 |
| Figure 2.5: Pairwise ^{13}C NMR NMR chemical shifts of models 220-225 with 1 | 71 |
| Figure 2.6: Tentatively proposed configuration of zwittermicin A (279)..... | 72 |
| Figure 3.1: X-ray crystal structure of acid 312 | 83 |
| Figure 3.2: ^1H NMR spectra (400 MHz, D_2O) of (a) natural (+)- 1 , (b) 1:3 mole ratio of synthetic (-)- 279 and natural (+)- 1 , and (c) (-)- 279 . Concentrations ~10 mM, no solvent suppression..... | 90 |
| Figure 3.3: ^1H NMR spectra (400 MHz, D_2O) of (a) natural (+)- 1 , (b) 1:2 mole ratio of synthetic (-)- 1 and natural (+)- 1 , and (c) (-)- 1 . Concentrations ~10 mM, no solvent suppression..... | 93 |
| Figure 3.4: Revised configuration of natural zwittermicin A..... | 94 |
| Figure 5.1: Compounds for biological testing..... | 109 |
| Figure 6.1: X-ray crystal structure of sulfone 378 | 126 |
| Figure 6.2: Side product 382 | 128 |
| Figure 6.3: X-ray crystal structure of acetate 389 | 132 |

LIST OF SCHEMES

| | |
|---|----|
| Scheme 1.1: Zimmermann's D-sphingosine synthesis from D-galactose..... | 9 |
| Scheme 1.2: Julina's sphingosine synthesis using SAE for stereocontrol..... | 10 |
| Scheme 1.3: Nicolaou's sphingosine synthesis using asymmetric induction for stereocontrol..... | 11 |
| Scheme 1.4: Herold's synthesis starting from serine..... | 12 |
| Scheme 1.5: Ohfuné's first synthesis of galantinic acid core structure..... | 14 |
| Scheme 1.6: Ohfuné's second synthesis of galantinic acid core structure..... | 16 |
| Scheme 1.7: Koskinen's investigation of diastereoselective enone reduction..... | 17 |
| Scheme 1.8: Somfai's investigation of diastereoselective allyl ketone reduction..... | 18 |
| Scheme 1.9: Somfai's investigation of aldol additions to aldehyde 66a-d | 19 |
| Scheme 1.10: Somfai's investigation of aldol additions to aldehyde 70a-d | 20 |
| Scheme 1.11: Reyes's investigation of aldol additions to aldehyde Garner's aldehyde..... | 21 |
| Scheme 1.12: Hulme's acetate aldol addition to serine-derived aldehyde 81 | 22 |
| Scheme 1.13: Hulme's aldol addition to serine-derived aldehyde 85 | 23 |
| Scheme 1.14: Hulme's attempted diastereoselective dihydroxylation..... | 24 |
| Scheme 1.15: Kim's dihydroxylations of 98a and 98b | 25 |
| Scheme 1.16: Lin's synthesis of penaresidin A..... | 26 |
| Scheme 1.17: Miyashita's boron-mediated azide opening of simple epoxides..... | 27 |
| Scheme 1.18: Miyashita's boron mediated azide opening of epoxides 112 and 115 | 28 |
| Scheme 1.19: Jung's use of epoxides for synthesis of β -hydroxy- α -amino acids..... | 29 |
| Scheme 1.20: Righi's isoxazole method for synthesis of aminopolyols..... | 30 |
| Scheme 1.21: Somfai's use of vinylaziridine for synthesis of aminopolyols..... | 31 |
| Scheme 1.22: Kumar's 2004 synthesis of galantinic acid (35)..... | 33 |
| Scheme 1.23: Keenan's 2004 work on tethered aminohydroxylation..... | 35 |
| Scheme 1.24: Reddy's synthesis of galantinic acid..... | 37 |
| Scheme 1.25: Concellón's synthesis of aminoepoxides..... | 39 |
| Scheme 1.26: Takabe's synthesis of penaresidin B..... | 40 |
| Scheme 2.1: Degradation of Zwittermicin A..... | 47 |
| Scheme 2.2: Marfey's analysis standards..... | 50 |
| Scheme 2.3: Hydrolysis and derivatization of Zwittermicin A..... | 51 |
| Scheme 2.4: Retrosynthetic analysis of model compounds..... | 54 |
| Scheme 2.5: Synthesis of aldehyde 226 and ester 227 | 55 |
| Scheme 2.6: Synthesis of epoxide 228 and carbon chain extension..... | 56 |
| Scheme 2.7: Synthesis of alkene 249 | 58 |
| Scheme 2.8: Synthesis of separable epoxides 252 and 253 | 59 |
| Scheme 2.9: Synthesis of model 220 | 60 |
| Scheme 2.10: Synthesis of model 221 | 61 |
| Scheme 2.11: Synthesis of internal acetonide 258 | 62 |
| Scheme 2.12: Synthesis of epoxide 229 | 63 |
| Scheme 2.13: Synthesis of allylic alcohols 235 and 236 | 64 |
| Scheme 2.14: Synthesis of azides 269 through 272 | 66 |
| Scheme 2.15: Synthesis of models 222 and 223 | 67 |
| Scheme 2.16: Synthesis of azides 275 through 278 | 69 |

| | |
|---|-----|
| Scheme 2.17: Synthesis of models 224 and 225 | 69 |
| Scheme 3.1: Retrosynthetic analysis of 279 | 76 |
| Scheme 3.2: Synthesis of alcohol 287 | 77 |
| Scheme 3.3: Synthesis of alcohol 290 | 78 |
| Scheme 3.4: Synthesis of alcohol 294 | 79 |
| Scheme 3.5: Synthesis of aldehyde 297 | 80 |
| Scheme 3.6: Synthesis of alcohol 300 | 80 |
| Scheme 3.7: Synthesis of aldehyde 303 | 81 |
| Scheme 3.8: Synthesis of model aldehyde 307 | 82 |
| Scheme 3.9: Synthesis of acid 312 | 82 |
| Scheme 3.10: Synthesis of acid 314 | 85 |
| Scheme 3.11: Synthesis of lactam 316 | 85 |
| Scheme 3.12: Synthesis of α -aminoamide (-)- 319 | 86 |
| Scheme 3.13: Synthesis of amide 320 | 86 |
| Scheme 3.14: Synthesis of acid 323 | 88 |
| Scheme 3.15: Synthesis of proposed zwittermicin A structure (-)- 279 | 89 |
| Scheme 3.16: Synthesis of α -aminoamide (+)- 319 | 91 |
| Scheme 3.17: Synthesis of (-)-zwittermicin A [(-)- 1]..... | 92 |
| Scheme 4.1: Retrosynthetic analysis of (+)-zwittermicin A..... | 98 |
| Scheme 4.2: Synthesis of diol 338 | 100 |
| Scheme 4.3: Synthesis of diazide 334 | 101 |
| Scheme 4.4: Synthesis of diazide 341 | 102 |
| Scheme 4.5: Synthesis of diazide 344 | 103 |
| Scheme 4.6: Synthesis of alcohol (-)- 302 | 105 |
| Scheme 5.1: Synthesis of aminopolyol 350 | 110 |
| Scheme 5.2: Synthesis of analog 351 | 110 |
| Scheme 5.3: Synthesis of analog 352 | 111 |
| Scheme 5.4: Synthesis of acid 357 | 112 |
| Scheme 5.5: Synthesis of zwittermicin A diastereomers 353 and 354 | 113 |
| Scheme 5.6: Mosher's derivatization of 296 | 115 |
| Scheme 6.1: Retrosynthetic analysis of zwittermicin A..... | 120 |
| Scheme 6.2: Synthesis of diene 364 | 122 |
| Scheme 6.3: Synthesis of starting materials 368 and 369 | 122 |
| Scheme 6.4: More sulfone dianion additions..... | 129 |
| Scheme 6.5: Deprotection of sulfone anion addition products..... | 131 |
| Scheme 6.6: Deprotection of sulfone diaddition products..... | 133 |
| Scheme 6.7: Protection of sulfone 390 | 136 |
| Scheme 6.8: Synthesis of protected sulfone 403 | 138 |
| Scheme 6.9: Dianion addition reactions with dithianes..... | 141 |
| Scheme 6.10: Dianion addition using thioanisole..... | 142 |
| Scheme 6.11: Synthesis of internal standard 416 | 143 |
| Scheme 6.12: Synthesis of surrogate standard 421 | 144 |

LIST OF TABLES

| | |
|---|-----|
| Table 1.1: Somfai's investigation of aldol additions to aldehyde 66a-d | 19 |
| Table 1.2: Somfai's investigation of aldol additions to aldehyde 70a-d | 20 |
| Table 1.3: Kim's dihydroxylations of 98a and 98b | 25 |
| Table 1.4: Miyashita's boron-mediated azide opening of simple epoxides..... | 27 |
| Table 2.1: Removal of PMB protecting group..... | 57 |
| Table 2.2: Epoxidation of 249 | 59 |
| Table 2.3: Epoxidation of 235 | 65 |
| Table 2.4: Epoxidation of 236 | 68 |
| Table 3.1: Attempted oxidation of alcohol 287 | 77 |
| Table 3.2: Attempted protection of alcohol 285 | 78 |
| Table 3.3: Dihydroxylation of alkene 308 | 84 |
| Table 4.1: Reduction of di-acetylene 338 | 100 |
| Table 4.2: Desymmetrization of 334 using TrCl..... | 103 |
| Table 4.3: Synthesis of acetonide 346 | 104 |
| Table 5.1: Biological testing of zwittermicin A and synthetic compounds..... | 116 |
| Table 6.1: Sulfone anion addition to aldehyde 369 | 123 |
| Table 6.2: Sulfone anion addition to Garner's aldehyde 54 | 124 |
| Table 6.3: Sulfone removal from compound 378 | 127 |
| Table 6.4: Sulfone dianion synthesis of 381 | 128 |
| Table 6.5: Sulfone anion addition to aldehyde 193 | 130 |
| Table 6.6: Sulfone dianion addition to aldehyde 54 | 133 |
| Table 6.7: Biological testing of zwittermicin A and synthetic sulfones..... | 134 |
| Table 6.8: Sulfone removal from compound 390 | 135 |
| Table 6.9: Sulfone removal from compound 396 | 137 |
| Table 6.10: Sulfone removal from compound 403 | 139 |
| Table 6.11: Dithiane addition to aldehyde 193 | 140 |
| Table 7.1: ¹³ C NMR data for 220-225 and Zwittermicin A [(+)- 1]..... | 183 |

LIST OF SPECTRA

| | | |
|----------------|---|-----|
| Spectrum 7.1: | ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound 220 | 300 |
| Spectrum 7.2: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 220 | 301 |
| Spectrum 7.3: | ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound 221 | 302 |
| Spectrum 7.4: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 221 | 303 |
| Spectrum 7.5: | ^1H NMR (D_2O , 400 MHz) of compound 222 | 304 |
| Spectrum 7.6: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 222 | 305 |
| Spectrum 7.7: | ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound 223 | 306 |
| Spectrum 7.8: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 223 | 307 |
| Spectrum 7.9: | ^1H NMR (D_2O , 400 MHz) of compound 224 | 308 |
| Spectrum 7.10: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 224 | 309 |
| Spectrum 7.11: | ^1H NMR (D_2O , 400 MHz) of compound 225 | 310 |
| Spectrum 7.12: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 225 | 311 |
| Spectrum 7.13: | ^1H NMR (CDCl_3 , 400 MHz) of compound 228 | 312 |
| Spectrum 7.14: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 228 | 313 |
| Spectrum 7.15: | ^1H NMR (CDCl_3 , 400 MHz) of compound 229 | 314 |
| Spectrum 7.16: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 229 | 315 |
| Spectrum 7.17: | ^1H NMR (CDCl_3 , 400 MHz) of compound 230 | 316 |
| Spectrum 7.18: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 230 | 317 |
| Spectrum 7.19: | ^1H NMR (CDCl_3 , 400 MHz) of compound 231 | 318 |
| Spectrum 7.20: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 231 | 319 |
| Spectrum 7.21: | ^1H NMR (CDCl_3 , 400 MHz) of compound 233 | 320 |
| Spectrum 7.22: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 233 | 321 |
| Spectrum 7.23: | ^1H NMR (CDCl_3 , 400 MHz) of compound 234 | 322 |
| Spectrum 7.24: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 234 | 323 |
| Spectrum 7.25: | ^1H NMR (CDCl_3 , 400 MHz) of compound 235 | 324 |
| Spectrum 7.26: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 235 | 325 |
| Spectrum 7.27: | ^1H NMR (CDCl_3 , 400 MHz) of compound 236 | 326 |
| Spectrum 7.28: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 236 | 327 |
| Spectrum 7.29: | ^1H NMR (CDCl_3 , 400 MHz) of compound 243 | 328 |
| Spectrum 7.30: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 243 | 329 |
| Spectrum 7.31: | ^1H NMR (CDCl_3 , 400 MHz) of compound 244 | 330 |
| Spectrum 7.32: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 244 | 331 |
| Spectrum 7.33: | ^1H NMR (CDCl_3 , 400 MHz) of compound 245 | 332 |
| Spectrum 7.34: | ^{13}C dept NMR (CDCl_3 , 100 MHz) of compound 245 | 333 |
| Spectrum 7.35: | ^1H NMR (CDCl_3 , 400 MHz) of compound 246 | 334 |
| Spectrum 7.36: | ^{13}C dept NMR (CDCl_3 , 75 MHz) of compound 246 | 335 |
| Spectrum 7.37: | ^1H NMR (CDCl_3 , 500 MHz) of compound 247 | 336 |
| Spectrum 7.38: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 247 | 337 |
| Spectrum 7.39: | ^1H NMR (CDCl_3 , 400 MHz) of compound 249 | 338 |
| Spectrum 7.40: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 249 | 339 |
| Spectrum 7.41: | ^1H NMR (CDCl_3 , 400 MHz) of compound 250 | 340 |
| Spectrum 7.42: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 250 | 341 |
| Spectrum 7.43: | ^1H NMR (CDCl_3 , 400 MHz) of compound 251 | 342 |

| | | |
|----------------|---|-----|
| Spectrum 7.44: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 251 | 343 |
| Spectrum 7.45: | ^1H NMR (CDCl_3 , 400 MHz) of compound 252 | 344 |
| Spectrum 7.46: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 252 | 345 |
| Spectrum 7.47: | ^1H NMR (CDCl_3 , 400 MHz) of compound 253 | 346 |
| Spectrum 7.48: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 253 | 347 |
| Spectrum 7.49: | ^1H NMR (CDCl_3 , 500 MHz) of compound 256 | 348 |
| Spectrum 7.50: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 256 | 349 |
| Spectrum 7.51: | ^1H NMR (CDCl_3 , 400 MHz) of compound 257 | 350 |
| Spectrum 7.52: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 257 | 351 |
| Spectrum 7.53: | ^1H NMR (CDCl_3 , 400 MHz) of compound 258 | 352 |
| Spectrum 7.54: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 258 | 353 |
| Spectrum 7.55: | ^1H NMR (CDCl_3 , 400 MHz) of compound 260 | 354 |
| Spectrum 7.56: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 260 | 355 |
| Spectrum 7.57: | ^1H NMR (CDCl_3 , 400 MHz) of compound 261 | 356 |
| Spectrum 7.58: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 261 | 357 |
| Spectrum 7.59: | ^1H NMR (CDCl_3 , 400 MHz) of compound 262 | 358 |
| Spectrum 7.60: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 262 | 359 |
| Spectrum 7.61: | ^1H NMR (CDCl_3 , 400 MHz) of compound 269 | 360 |
| Spectrum 7.62: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 269 | 361 |
| Spectrum 7.63: | ^1H NMR (CDCl_3 , 400 MHz) of compound 271 | 362 |
| Spectrum 7.64: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 271 | 363 |
| Spectrum 7.65: | ^1H NMR (CDCl_3 , 400 MHz) of compound 273 | 364 |
| Spectrum 7.66: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 273 | 365 |
| Spectrum 7.67: | ^1H NMR (CDCl_3 , 400 MHz) of compound 274 | 366 |
| Spectrum 7.68: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 274 | 367 |
| Spectrum 7.69: | ^1H NMR (CDCl_3 , 400 MHz) of compound 275 | 368 |
| Spectrum 7.70: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 275 | 369 |
| Spectrum 7.71: | ^1H NMR (CDCl_3 , 400 MHz) of compound 277 | 370 |
| Spectrum 7.72: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 277 | 371 |
| Spectrum 7.73: | ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound (-)-1 | 372 |
| Spectrum 7.74: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound (-)-1 | 373 |
| Spectrum 7.75: | ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound (-)-279 | 374 |
| Spectrum 7.76: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound (-)-279 | 375 |
| Spectrum 7.77: | ^1H NMR (CDCl_3 , 400 MHz) of compound 285 | 376 |
| Spectrum 7.78: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 285 | 377 |
| Spectrum 7.79: | ^1H NMR (CDCl_3 , 400 MHz) of compound 286 | 378 |
| Spectrum 7.80: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 286 | 379 |
| Spectrum 7.81: | ^1H NMR (CDCl_3 , 400 MHz) of compound 287 | 380 |
| Spectrum 7.82: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 287 | 381 |
| Spectrum 7.83: | ^1H NMR (CDCl_3 , 400 MHz) of compound 290 | 382 |
| Spectrum 7.84: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 290 | 383 |
| Spectrum 7.85: | ^1H NMR (CDCl_3 , 400 MHz) of compound 291 | 384 |
| Spectrum 7.86: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 291 | 385 |
| Spectrum 7.87: | ^1H NMR (CDCl_3 , 400 MHz) of compound 292 | 386 |
| Spectrum 7.88: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 292 | 387 |

| | | |
|-----------------|---|-----|
| Spectrum 7.89: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 293 | 388 |
| Spectrum 7.90: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 293 | 389 |
| Spectrum 7.91: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 294 | 390 |
| Spectrum 7.92: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 294 | 391 |
| Spectrum 7.93: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 295 | 392 |
| Spectrum 7.94: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 295 | 393 |
| Spectrum 7.95: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 296 | 394 |
| Spectrum 7.96: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 296 | 395 |
| Spectrum 7.97: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 297 | 396 |
| Spectrum 7.98: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 297 | 397 |
| Spectrum 7.99: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 298 | 398 |
| Spectrum 7.100: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 298 | 399 |
| Spectrum 7.101: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 299 | 400 |
| Spectrum 7.102: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 299 | 401 |
| Spectrum 7.103: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 300 | 402 |
| Spectrum 7.104: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 300 | 403 |
| Spectrum 7.105: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound (+)- 301 | 404 |
| Spectrum 7.106: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound (+)- 301 | 405 |
| Spectrum 7.107: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound (+)- 302 | 406 |
| Spectrum 7.108: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound (+)- 302 | 407 |
| Spectrum 7.109: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 303 | 408 |
| Spectrum 7.110: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 303 | 409 |
| Spectrum 7.111: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 305 | 410 |
| Spectrum 7.112: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 305 | 411 |
| Spectrum 7.113: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 306 | 412 |
| Spectrum 7.114: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 306 | 413 |
| Spectrum 7.115: | ¹ H NMR (CDCl ₃ , 500 MHz) of compound 307 | 414 |
| Spectrum 7.116: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 307 | 415 |
| Spectrum 7.117: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 308 | 416 |
| Spectrum 7.118: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 308 | 417 |
| Spectrum 7.119: | ¹ H NMR (CDCl ₃ , 500 MHz) of compound 309 | 418 |
| Spectrum 7.120: | ¹³ C NMR (CDCl ₃ , 75 MHz) of compound 309 | 419 |
| Spectrum 7.121: | ¹ H NMR (CDCl ₃ , 500 MHz) of compound 310 | 420 |
| Spectrum 7.122: | ¹³ C NMR (CDCl ₃ , 75 MHz) of compound 310 | 421 |
| Spectrum 7.123: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 311 | 422 |
| Spectrum 7.124: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 311 | 423 |
| Spectrum 7.125: | ¹ H NMR (CDCl ₃ , 500 MHz) of compound 312 | 424 |
| Spectrum 7.126: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 312 | 425 |
| Spectrum 7.127: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 313 | 426 |
| Spectrum 7.128: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 313 | 427 |
| Spectrum 7.129: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 314 | 428 |
| Spectrum 7.130: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 314 | 429 |
| Spectrum 7.131: | ¹ H NMR (CDCl ₃ , 400 MHz) of compound 315 | 430 |
| Spectrum 7.132: | ¹³ C NMR (CDCl ₃ , 100 MHz) of compound 315 | 431 |
| Spectrum 7.133: | ¹ H NMR (CD ₃ OD, 400 MHz) of compound (–)- 319 | 432 |

| | | |
|-----------------|---|-----|
| Spectrum 7.134: | ^{13}C NMR (CD_3OD , 100 MHz) of compound (–)- 319 | 433 |
| Spectrum 7.135: | ^1H NMR (CD_3OD , 400 MHz) of compound (+)- 319 | 434 |
| Spectrum 7.136: | ^{13}C NMR (CD_3OD , 100 MHz) of compound (+)- 319 | 435 |
| Spectrum 7.137: | ^1H NMR (CD_3OD , 400 MHz) of compound 320 | 436 |
| Spectrum 7.138: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 320 | 437 |
| Spectrum 7.139: | ^1H NMR (CDCl_3 , 400 MHz) of compound 321 | 438 |
| Spectrum 7.140: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 321 | 439 |
| Spectrum 7.141: | ^1H NMR (CDCl_3 , 400 MHz) of compound 322 | 440 |
| Spectrum 7.142: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 322 | 441 |
| Spectrum 7.143: | ^1H NMR (CDCl_3 , 400 MHz) of compound 323 | 442 |
| Spectrum 7.144: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 323 | 443 |
| Spectrum 7.145: | ^1H NMR (CD_3OD , 400 MHz) of compound 324 | 444 |
| Spectrum 7.146: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 324 | 445 |
| Spectrum 7.147: | ^1H NMR (CD_3OD , 500 MHz) of compound 329 | 446 |
| Spectrum 7.148: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 329 | 447 |
| Spectrum 7.149: | ^1H NMR (CD_3OD , 500 MHz) of compound 334 | 448 |
| Spectrum 7.150: | ^{13}C NMR (CD_3OD , 125 MHz) of compound 334 | 449 |
| Spectrum 7.151: | ^1H NMR (CDCl_3 , 500 MHz) of compound 339 | 450 |
| Spectrum 7.152: | ^{13}C NMR (CDCl_3 , 125 MHz) of compound 339 | 451 |
| Spectrum 7.153: | ^1H NMR (CDCl_3 , 400 MHz) of compound 342 | 452 |
| Spectrum 7.154: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 342 | 453 |
| Spectrum 7.155: | ^1H NMR (CDCl_3 , 500 MHz) of compound 344 | 454 |
| Spectrum 7.156: | ^{13}C NMR (CDCl_3 , 125 MHz) of compound 344 | 455 |
| Spectrum 7.157: | ^1H NMR (CDCl_3 , 500 MHz) of compound 346 | 456 |
| Spectrum 7.158: | ^{13}C NMR (CDCl_3 , 125 MHz) of compound 346 | 457 |
| Spectrum 7.159: | ^1H NMR (CDCl_3 , 500 MHz) of compound 349 | 458 |
| Spectrum 7.160: | ^{13}C NMR (CDCl_3 , 125 MHz) of compound 349 | 459 |
| Spectrum 7.161: | ^1H NMR (CDCl_3 , 500 MHz) of compound (–)- 302 | 460 |
| Spectrum 7.162: | ^{13}C NMR (CDCl_3 , 125 MHz) of compound (–)- 302 | 461 |
| Spectrum 7.163: | ^1H NMR (D_2O , 400 MHz) of compound 350 | 462 |
| Spectrum 7.164: | ^{13}C NMR (D_2O , 100 MHz) of compound 350 | 463 |
| Spectrum 7.165: | ^1H NMR (D_2O , 500 MHz) of compound 351 | 464 |
| Spectrum 7.166: | ^{13}C NMR (D_2O , 125 MHz) of compound 351 | 465 |
| Spectrum 7.167: | ^1H NMR (D_2O , 400 MHz) of compound 352 | 466 |
| Spectrum 7.168: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 125 MHz) of compound 352 | 467 |
| Spectrum 7.169: | ^1H NMR (D_2O , 400 MHz) of compound 353 | 468 |
| Spectrum 7.170: | ^{13}C NMR (D_2O , 100 MHz) of compound 353 | 469 |
| Spectrum 7.171: | ^1H NMR (D_2O , 400 MHz) of compound 354 | 470 |
| Spectrum 7.172: | ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 354 | 471 |
| Spectrum 7.173: | ^1H NMR (CD_3OD , 400 MHz) of compound 355 | 472 |
| Spectrum 7.174: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 355 | 473 |
| Spectrum 7.175: | ^1H NMR (CDCl_3 , 400 MHz) of compound 356 | 474 |
| Spectrum 7.176: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 356 | 475 |
| Spectrum 7.177: | ^1H NMR (CDCl_3 , 400 MHz) of compound 357 | 476 |
| Spectrum 7.178: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 357 | 477 |

| | | |
|-----------------|--|-----|
| Spectrum 7.179: | ^1H NMR (CD_3OD , 400 MHz) of compound 358 | 478 |
| Spectrum 7.180: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 358 | 479 |
| Spectrum 7.181: | ^1H NMR (CD_3OD , 400 MHz) of compound 359 | 480 |
| Spectrum 7.182: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 359 | 481 |
| Spectrum 7.183: | ^1H NMR (CDCl_3 , 500 MHz) of compound 361 | 482 |
| Spectrum 7.184: | ^{19}F NMR (CDCl_3 , 376 MHz) of compound 361 | 483 |
| Spectrum 7.185: | ^1H NMR (CDCl_3 , 500 MHz) of compound 362 | 484 |
| Spectrum 7.186: | ^{19}F NMR (CDCl_3 , 376 MHz) of compound 362 | 485 |
| Spectrum 7.187: | ^1H NMR (CDCl_3 , 400 MHz) of compound 363 | 486 |
| Spectrum 7.188: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 363 | 487 |
| Spectrum 7.189: | ^1H NMR (CDCl_3 , 400 MHz) of compound 364 | 488 |
| Spectrum 7.190: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 364 | 489 |
| Spectrum 7.191: | ^1H NMR (CDCl_3 , 400 MHz) of compound 370a | 490 |
| Spectrum 7.192: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 370a | 491 |
| Spectrum 7.193: | ^1H NMR (CDCl_3 , 400 MHz) of compound 370b | 492 |
| Spectrum 7.194: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 370b | 493 |
| Spectrum 7.195: | ^1H NMR (CDCl_3 , 400 MHz) of compound 378 | 494 |
| Spectrum 7.196: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 378 | 495 |
| Spectrum 7.197: | ^1H NMR (CDCl_3 , 400 MHz) of compound 379 | 496 |
| Spectrum 7.198: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 379 | 497 |
| Spectrum 7.199: | ^1H NMR (CDCl_3 , 400 MHz) of compound 385 | 498 |
| Spectrum 7.200: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 385 | 499 |
| Spectrum 7.201: | ^1H NMR (CDCl_3 , 400 MHz) of compound 386 | 500 |
| Spectrum 7.202: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 386 | 501 |
| Spectrum 7.203: | ^1H NMR (CD_3OD , 400 MHz) of compound 387 | 502 |
| Spectrum 7.204: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 387 | 503 |
| Spectrum 7.205: | ^1H NMR (CD_3OD , 400 MHz) of compound 388 | 504 |
| Spectrum 7.206: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 388 | 505 |
| Spectrum 7.207: | ^1H NMR (CDCl_3 , 400 MHz) of compound 389 | 506 |
| Spectrum 7.208: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 389 | 507 |
| Spectrum 7.209: | ^1H NMR (CDCl_3 , 400 MHz) of compound 390 | 508 |
| Spectrum 7.210: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 390 | 509 |
| Spectrum 7.211: | ^1H NMR (CDCl_3 , 400 MHz) of compound 391 | 510 |
| Spectrum 7.212: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 391 | 511 |
| Spectrum 7.213: | ^1H NMR (CD_3OD , 400 MHz) of compound 392 | 512 |
| Spectrum 7.214: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 392 | 513 |
| Spectrum 7.215: | ^1H NMR (CD_3OD , 400 MHz) of compound 393 | 514 |
| Spectrum 7.216: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 393 | 515 |
| Spectrum 7.217: | ^1H NMR (CDCl_3 , 400 MHz) of compound 403 | 516 |
| Spectrum 7.218: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 403 | 517 |
| Spectrum 7.219: | ^1H NMR (CDCl_3 , 400 MHz) of compound 407 | 518 |
| Spectrum 7.220: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 407 | 519 |
| Spectrum 7.221: | ^1H NMR (CDCl_3 , 400 MHz) of compound 408 | 520 |
| Spectrum 7.222: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 408 | 521 |
| Spectrum 7.223: | ^1H NMR (CDCl_3 , 400 MHz) of compound 414 | 522 |

| | | |
|-----------------|--|-----|
| Spectrum 7.224: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 414 | 523 |
| Spectrum 7.225: | ^1H NMR (CD_3OD , 400 MHz) of compound 416 | 524 |
| Spectrum 7.226: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 416 | 525 |
| Spectrum 7.227: | ^1H NMR (CDCl_3 , 400 MHz) of compound 418 | 526 |
| Spectrum 7.228: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 418 | 527 |
| Spectrum 7.229: | ^1H NMR (CDCl_3 , 400 MHz) of compound 420 | 528 |
| Spectrum 7.230: | ^{13}C NMR (CDCl_3 , 100 MHz) of compound 420 | 529 |
| Spectrum 7.231: | ^1H NMR (CD_3OD , 400 MHz) of compound 421 | 530 |
| Spectrum 7.232: | ^{13}C NMR (CD_3OD , 100 MHz) of compound 421 | 531 |

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ABSTRACT OF THE DISSERTATION

Zwittermicin A: Determination of its Complete Configuration and Total Synthesis of its
Enantiomer

by

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(+)-Zwittermicin A (**1**) is a water-soluble natural antibiotic isolated from the fermentation of the soil-born bacterium *Bacillus cereus*. This dissertation research describes the elucidation of the configuration of **1** and total synthesis of its enantiomer.

Chapter two describes determination of absolute configuration at C4, relative configuration for C8-C14 in Zwittermicin A and proposes an absolute configuration for **1**. Determination of carbon 4 absolute configuration was accomplished using Marfey's method. Construction of model compounds and evaluated by pair-wise ¹³C NMR chemical

shift difference analysis gave relative configuration for the C10-C14 stereocenters. A configuration for **1** was proposed based on this data in conjunction with previously published biosynthesis data and relative configuration for C8-C10.

Chapter three describes the synthesis of the proposed structure for (+)-**1**, revision of the structure and synthesis of (-)-**1**. The proposed structure for **1** was synthesized and evaluation of this compound with authentic natural (+)-**1** revealed difference that resulted in a revision of the proposed structure of **1**. A 22-step synthesis of (-)-**1** revealed this compound to be identical to (+)-**1** by NMR while having an equal but opposite $[\alpha]_D$ thereby verifying the revised structure.

Chapter four describes a short enantioselective synthesis of the C9-C15 portion of zwittermicin A. Taking advantage of the symmetry in the C9-C15 portion of **1** allowed for rapid synthesis of this portion to give an enantiomer of an advanced intermediate in the synthesis of (-)-**1**.

Chapter five describes the synthesis of analogs and diastereomers of **1** and bioassay of them and previously synthesized compounds. Two diastereomeric analogs representing the C1-C10 portion of **1** were synthesized. In addition two diastereomers of **1** were synthesized. These compounds along with previously synthesized compounds representing C9-C15 in **1** were tested for biological activity.

Chapter six describes work on sulfone chemistry related to synthesis of **1**. Sulfone anion and dianion additions to various aldehydes were evaluated. Techniques for removal of the sulfone moiety from addition products were also investigated. Sulfone chemistry was used to synthesize two standards for use in a HPLC sphingolipid analysis method.

A has the potential to be a more environmentally friendly pesticide with less non-target effects.

Fungicide consumption is 500 million pounds per year comprising at least 150 different compounds with a sales value of \$7.4 billion dollars. Figure 1.2 shows some examples of common fungicides used today. Some of these compounds such as the copper based compounds like Bordeaux mix (2) have been used for hundreds of years.

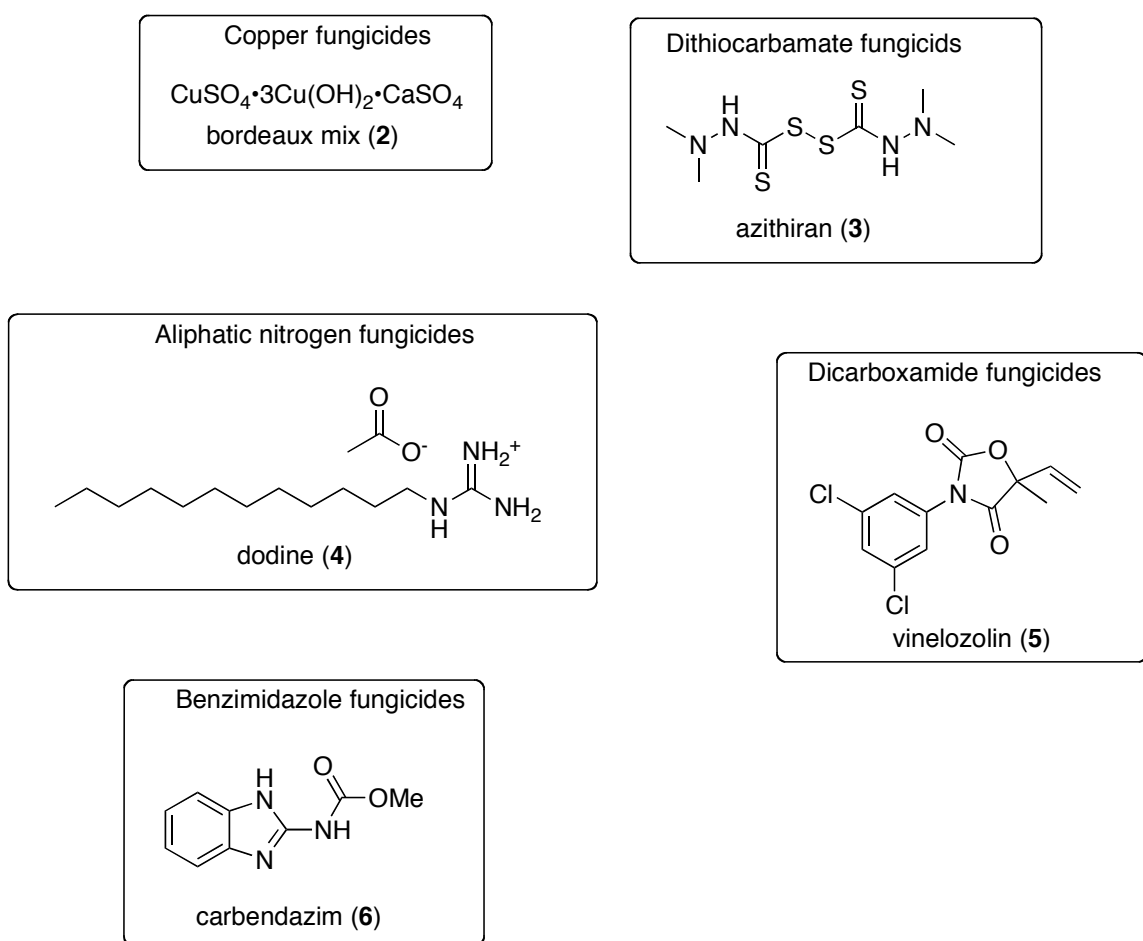


Figure 1.2: Examples of fungicides.

Even various early synthetic compounds such as the dithiocarbamate fungicide azithiran (**3**) have been used for more than forty years. Modern fungicides include compounds such as dodine (**4**), vinelozolin (**5**) and the benzimidazole fungicide carbendazim (**6**). While many of these fungicides have proven effective there are many factors that necessitate the development of new fungicides including resistance and de-registration of more toxic fungicides. Toxic pollution from use of copper based fungicides includes runoff into streams and consequent poisoning of aquatic environments. Questions are being raised about possible human health effects for compounds such as **6**, which is a known endocrine disrupter. The development of resistant organisms is another factor that requires continued development of new fungicides. With some classes of compounds such as the benzimidazoles, fungicide resistance has developed within a few years of introduction.⁷

The need to constantly develop new pesticides in a time when stricter regulations, more concerns about long-term health effects and a public desire for more “naturally produced” products has led to a desire for more natural pesticides. Zwittermicin A holds the promise of possibly being less harmful to the environment and humans. This is partially due to the fact that **1** is produced by the common soil bacterium *Bacillus cereus* and is therefore already ubiquitous to the environment, suggesting to some that it may have less harmful non-target effects than current synthetic fungicides.⁸

1.1.1. Background on (+)-Zwittermicin A

Zwittermicin A was first reported in 1994 by Handelsman and coworkers.⁹ This discovery was the result of studies into the ability of cultures and culture filtrates of *B.*

cereus UW85 to suppress damping-off of alfalfa caused by *Phytophthora medicaginis*. Bioassay guided fractionation of these culture filtrates led to the isolation of two fungistatic antibiotics, zwittermicin A and kanosamine that contributed to suppression of damping-off of alfalfa.¹⁰ Kanosamine is an aminosugar and shows activity that is less potent than zwittermicin A. Further studies into the activity of zwittermicin A showed that it is particularly active against plant pathogenic fungi.¹¹ Zwittermicin A showed some activity against gram-negative bacteria but little activity against gram-positive bacteria. Protists were also sensitive to **1** with some oomycetes having a minimum inhibitory concentration (MIC) of 1 µg/well. More interestingly zwittermicin A showed a synergism when used in conjunction with *Bacillus thuringiensis* against larvae of the gypsy moth *Lymantria dispar*.^{12, 13}

Studies of culture conditions for zwittermicin A production and accumulation revealed that phosphate reduced accumulation of **1** while ferric iron enhanced accumulation.¹⁴ Other micronutrients seemed to have no effect on zwittermicin A production. Investigations into the mechanism that allow zwittermicin A producing strains to be tolerant to its effects (self-resistance) led to the discovery of a resistance gene, *zmaR*.¹⁵ This resistance gene was shown to deactivate **1** by acetylating the amine at C14.¹⁶ *N*-Acetyl zwittermicin A showed no biological activity. It was also found that this resistance gene has unusual abundance in the environment among gram-positive and gram-negative bacteria. In a worldwide study it was found that 25% of *B. cereus* contained the *zmaR* gene. Attempts to elucidate the mechanism of action with zwittermicin A resistant *Escherichia coli* were inclusive and suggested a unique mechanism of antibiosis.¹⁷

The genetics of the biosynthesis of zwittermicin A have also been examined. Handelsman's group published work on the genotypic and phenotypic analysis of zwittermicin A producing strains in 1996.¹⁸ In 1999 the biosynthetic cluster for zwittermicin A production was identified, leading to the genes responsible for zwittermicin A production.¹⁹⁻²⁰ Sequencing analysis showed that **1** is synthesized by a mixed nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) pathway. Figure 1.3 shows the structure of zwittermicin A and the proposed precursors for its biosynthesis. L-Serine was proposed as the starter unit based on sequence similarity to known serine loading domains. In addition, two new type I polyketide synthase extender units were proposed; hydroxylmalonyl-acy carrier protein (ACP) and aminomalonyl-ACP.^{21, 22}

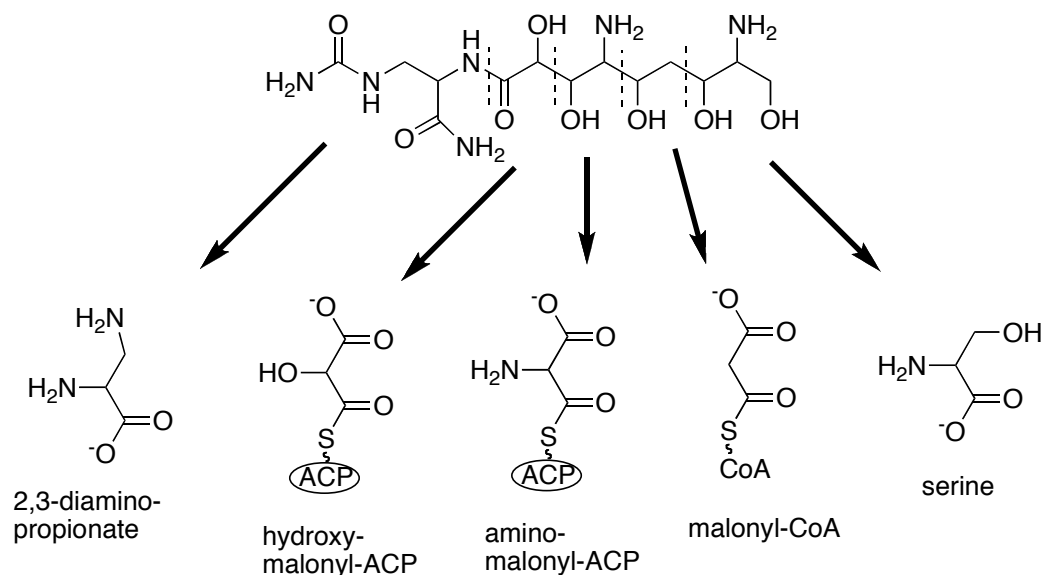


Figure 1.3: Proposed biosynthetic pathway.

Zwittermicin A has a structure that is unique when compared with other fungicides such as those in figure 2. It is a novel, linear aminopolyol having two free

amines, five hydroxyl groups, a urea group and two amides all in a molecule with only 13 carbons making it extremely polar. This high polarity is evident in the original purification procedure that was done using cation-exchange chromatography followed by high-voltage paper electrophoresis.⁹ The difficulty in purification has resulted in continued work on this process.²³ The original report published a planar structure for **1** with relative stereochemistry for the C8-C10 stereocenters derived through degradation of **1** to lactam **7** under basic conditions as shown in Figure 1.4.

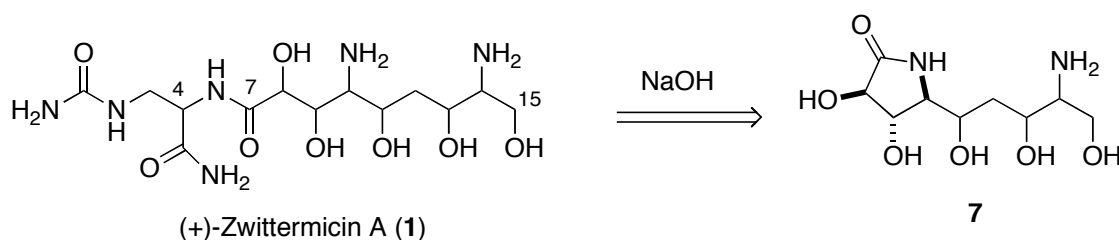


Figure 1.4: Degradation of zwittermicin A.

The unique structure of zwittermicin A may also portend a unique mechanism of action. Elucidating the absolute stereochemistry for **1** could provide valuable insight into the mechanism of action as well as the biosynthesis. Investigating the biological activity of diastereomers and analogs of **1** could also provide valuable insight into the mechanism of action. Synthesis of **1** could potentially be accomplished using techniques developed for the synthesis of other open chain aminopolyols.

1.2. Open-Chain Aminopolyol Synthesis

The C7-C15 backbone of zwittermicin A contains five hydroxyl groups and two amino groups. This segment can be broken down into the symmetrical C9-C15 fragment that contains two 2-amino-1,3-diol units (C9-C11 and C13-C15) separated by a

methylene group (C12) and connected to the hydroxyl methine C8 which in turn is connected to the carbonyl at C7. A search of the literature for syntheses of open-chain amino alcohol compounds provided valuable insight into possible synthetic strategies for synthesis of zwittermicin A.

The most common source of syntheses of 2-amino-1,3-diols pertains to synthesis of sphingolipids and related compounds. Because there are a number of good reviews on sphingolipid synthesis these will not be covered here, however a number of synthesis of 2-amino-1,3-diols in sphingolipid synthesis are of importance to the synthesis of zwittermicin A.^{24-26xs} A brief survey of the key strategies used for sphingolipid synthesis follows.

Synthesis of 2-amino-1,3-diols in compounds other than sphingolipids will also be reviewed here. These include papers directed specifically at the synthesis of this functionality as well as those that contain this motif within their structure. The focus will be on those papers that may provide insight into a possible synthesis of zwittermicin A.

Finally a brief review of some papers directed at other open-chain aminopolyols will be presented with the aim of identifying synthetic techniques that are relevant to the synthesis of zwittermicin A.

1.2.1. Synthesis of 2-amino-1,3-diols: Key Strategies in Sphingolipid Synthesis

Sphingolipids comprise a family of long chain amino bases and their derivatives are important to eukaryotic organisms as well as some viruses and prokaryotes (Figure 1.5).²⁷ They are structurally the most diverse class of membrane lipids with hundreds of different sphingolipids known.²⁸ Sphingolipids contain a long chain (sphingoid) base, the

most common of which is sphingosine (**8**) (D-erythro-1,3-dihydroxy-2-amino-octadec-4-ene). The sphingoid backbone is typically linked to a fatty acid through an amide bond to form a ceramide. In more complexed sphingolipids the terminal hydroxyl is typically modified by glycosylation, phosphorylation or sulfation giving rise to over 300 different sphingoid head-groups.²⁹

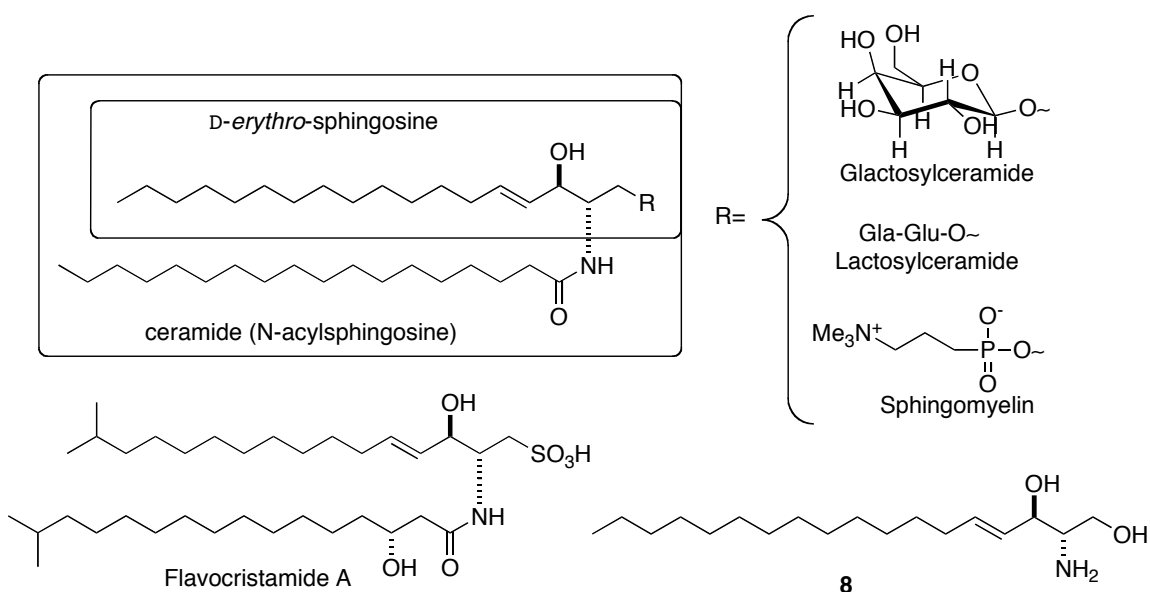
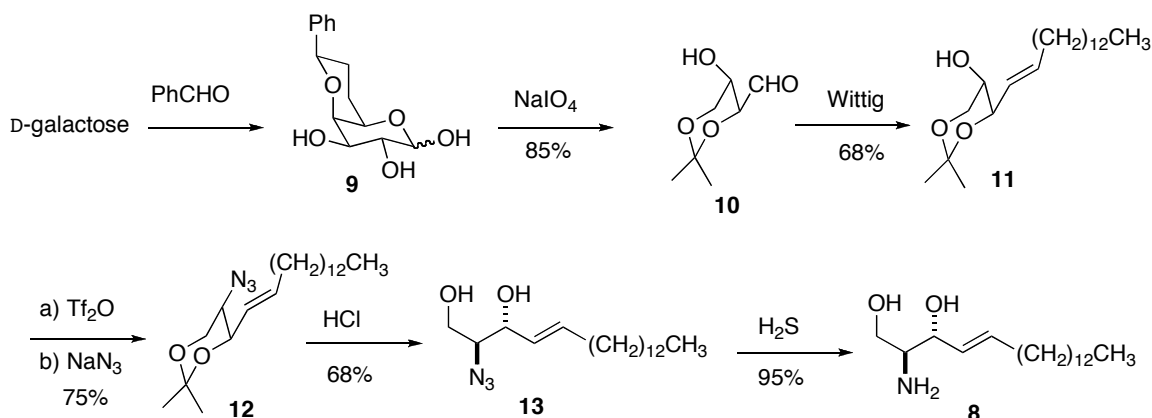


Figure 1.5: Examples of sphingolipids and sphingosine.

Syntheses of sphingolipid compounds tend to fall into three categories based on control of the absolute stereochemistry of the sphingosine base. The three approaches for generating configuration of sphingosines include asymmetric induction and synthesis from serine or carbohydrate chiral pools.

1.2.1.1. Carbohydrate Approach

Exploitation of carbohydrates to for the stereocontrol of sphingosine is one of the more common approaches and have utilized D-galactose, D-xylose, D-arabinose.³⁰⁻³² Most of these strategies utilize azide displacement of an activated secondary hydroxyl group to introduce the nitrogen functionality. An example of this method is the use of D-galactose by Zimmermann (Scheme 1.1).³¹ D-galactose was protected with benzaldehyde in one step to give **9**, which was subjected to sodium periodate cleavage followed by Wittig olefination to give alkene **11**.³³ Conversion of the free hydroxyl to a leaving group with Tf₂O/pyridine and displacement with azide gave **12** in 75% yield. Removal of the acetonide with hydrochloric acid (68%) followed by reduction of the azide with H₂S (95%) gave D-sphingosine (**8**).

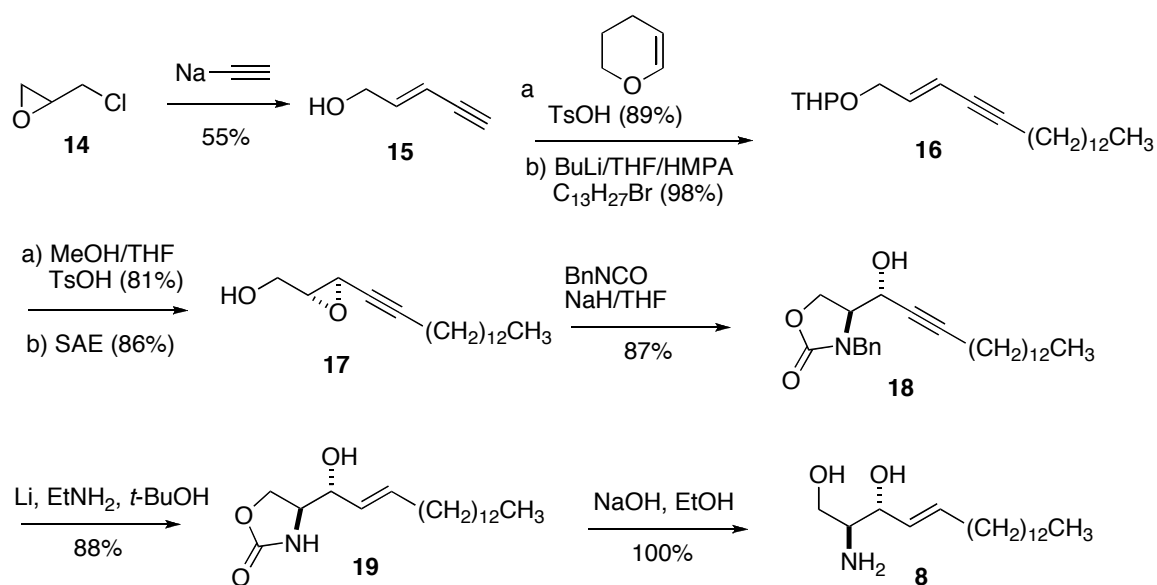


Scheme 1.1: Zimmermann's D-sphingosine synthesis from D-galactose.

1.2.1.2. Chiral Catalysts and Asymmetric Induction

Sphingosine has also been synthesized using the Sharpless asymmetric epoxidation (SAE) to set the configuration.³⁴ The synthesis of sphingosine by Julina is an

example of this (Scheme 1.2).³⁵ Some of the key steps are the sodium acetylide addition to epichlorohydrin to give allylic alcohol **15**, SAE reaction to give chiral epoxide **17**, and the regioselective intramolecular ring opening of epoxide **17** using the Roush³⁶ procedure to give oxazolidinone **18**. Also important to this synthesis was the simultaneous removal of the benzyl group and reduction of the triple bond using Li in ethylamine and *t*-butyl alcohol. Attempts to use Birch conditions for this step with either Li or Na failed to properly reduce the triple bond.

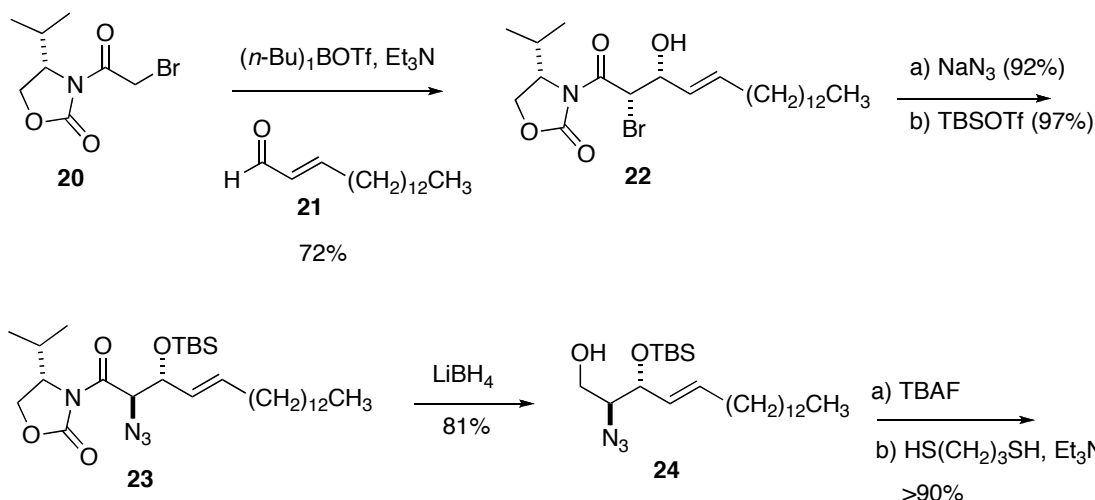


Scheme 1.2: Julina's spingosine synthesis using SAE for stereocontrol.

An approach using aldol chemistry with a chiral boron enolate for asymmetric induction has become more popular in recent years. An example of this method can be seen in Nicolaou's synthesis of globotriaosylceramide (Gb_3).³⁷ In this synthesis chiral

oxazolidinone **20** was used to set the stereochemistry of the sphingosine (Scheme 1.3).

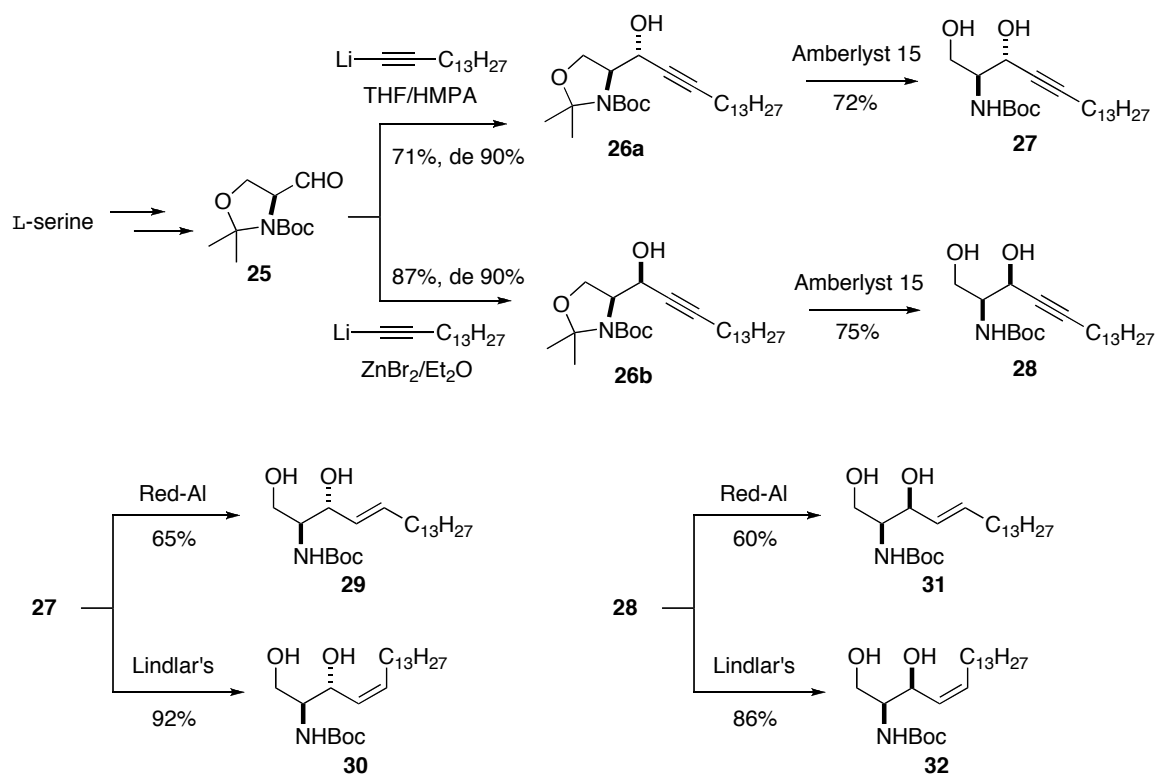
Again azide is used for introduction of the nitrogen functionality.



Scheme 1.3: Nicolaou's sphingosine synthesis using asymmetric induction for stereocontrol.

1.2.1.3. Chirality Through use of Serine

Modern sphingosine synthesis is most often draws from the amino acid chiral pool. More specifically, aldehydes derived from L-serine are used to incorporate the 2-amino-1,3-diol portion of sphingosine. A good example of this is the use of Garner's aldehyde (**25**) by Herold in the synthesis of four sphingosine derivatives (Scheme 1.4).^{38,}
³⁹ Key steps in this synthesis include diastereoselective control of alkyne anion addition through use of solvent and counter ion effects. Addition of the lithiated acetylide to **25** in THF/HMPA gave the anti addition product in 71% yield with 90% de while addition of the Zn salt in ether gave the *syn* product in 87% yield and 90% de. Removal of the acetonide with Amberlyst 15 followed by reduction with either Red-Al or H₂ / Lindlar's catalyst gave the four sphingosine derivatives **29-32** in respectable yields.



Scheme 1.4: Herold's synthesis starting from serine.

1.2.2. Synthesis of 2-amino-1,3-diols: Non-Sphingolipid Synthesis

The importance of 2-amino-1,3-diol syntheses has led to a number of papers that focus strictly on synthesis of this functionality. Vicinal amino alcohol synthesis has been accomplished by using the amino acid chiral pool or by reagent control with asymmetric induction or using chiral catalyst.

1.2.2.1. Chirality Through use of Amino Acid Chiral Pool

The use of the amino acid chiral pool for non-sphingolipid synthesis was again the most commonly used method to set stereochemistry. An example of this can be seen in Ohfuné's total synthesis of galantin I (**33**), a peptide antibiotic isolated from the culture

broth of *Bacillus pulvifaciens* (Figure 1.6).^{40, 41} Galantin I contains the two unique amino acids galantinamic acid (**34**) and galantinic acid (**35**) which are open-chain aminopolyols the latter of which has the 2-amino-1,3-diol motif.

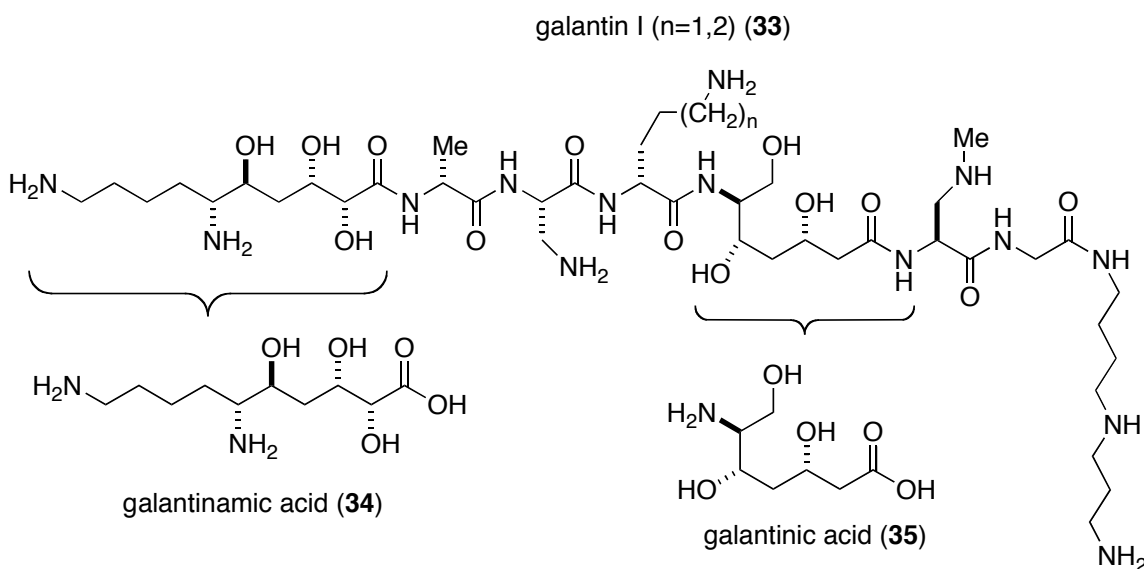
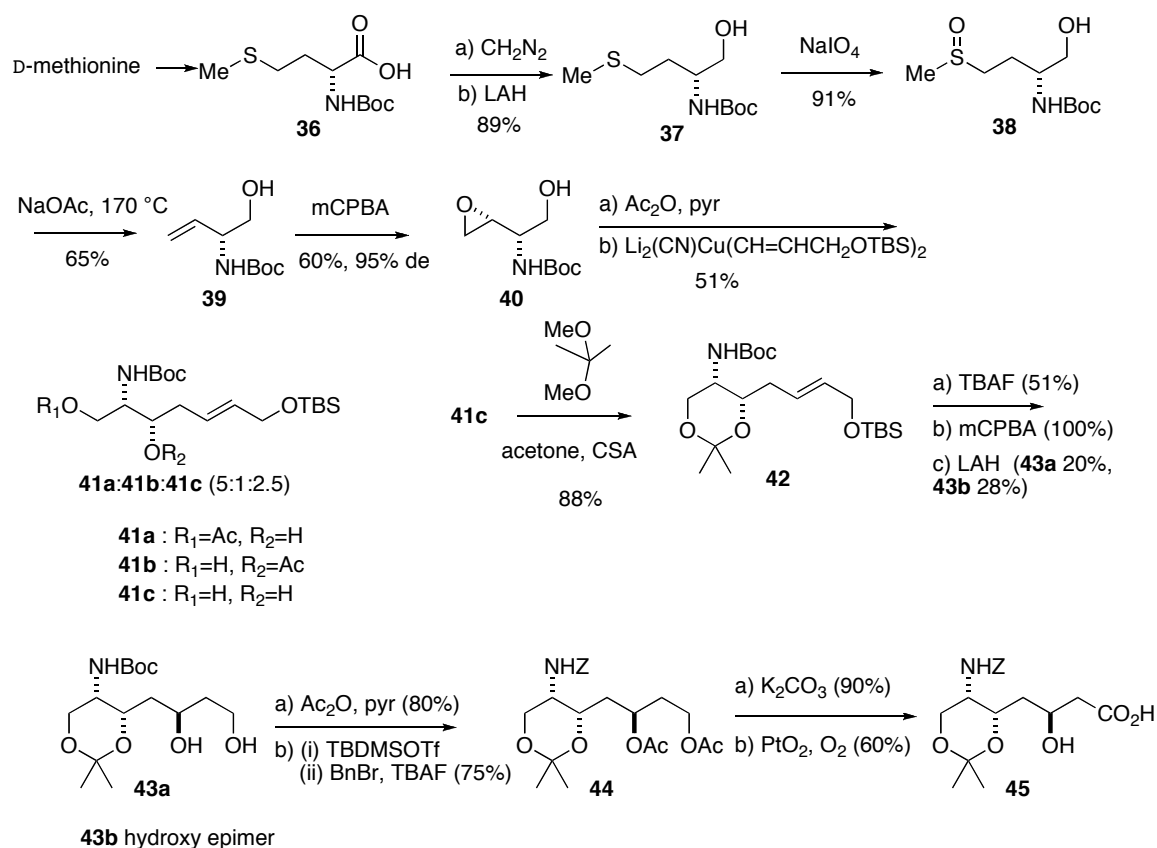


Figure 1.6: Structure of galantin I, galantinamic acid and galantinic acid.

Ohfuné's original synthesis of protected **35** started with methionine and proceeded through the serine equivalent (2*R*)-amino-3-butenol (**39**) (Scheme 1.5).⁴²⁻⁴⁴ The synthesis started from D-methionine which is converted to alcohol **37** by Boc protection of the amino group followed by esterification with diazomethane and reduction to the alcohol with lithium aluminum hydride with overall yield of 89%. Oxidation of the sulfide with NaIO₄ gave sulfoxide **38** (91%) which was then converted to the serine equivalent **39** (60%) by eliminating the sulfone with NaOAc at elevated temperature. Epoxidation of this alkene with *m*-CPBA gave epoxide **40** in moderate yield (60%) but with high diastereoselectivity (95% de). Protection of the terminal alcohol as an acetate ester followed by addition of a higher-order divinylcuprate prepared from TBS

protected propargyl alcohol gave addition products **41a-c** in poor yield, 51%. The selectivity for desired compound **41c** was poor and no mention of conversion of **41a** or **41b** to **41c** was made in the paper covering its synthesis or the following paper covering synthesis of **42** through **45**.⁴³

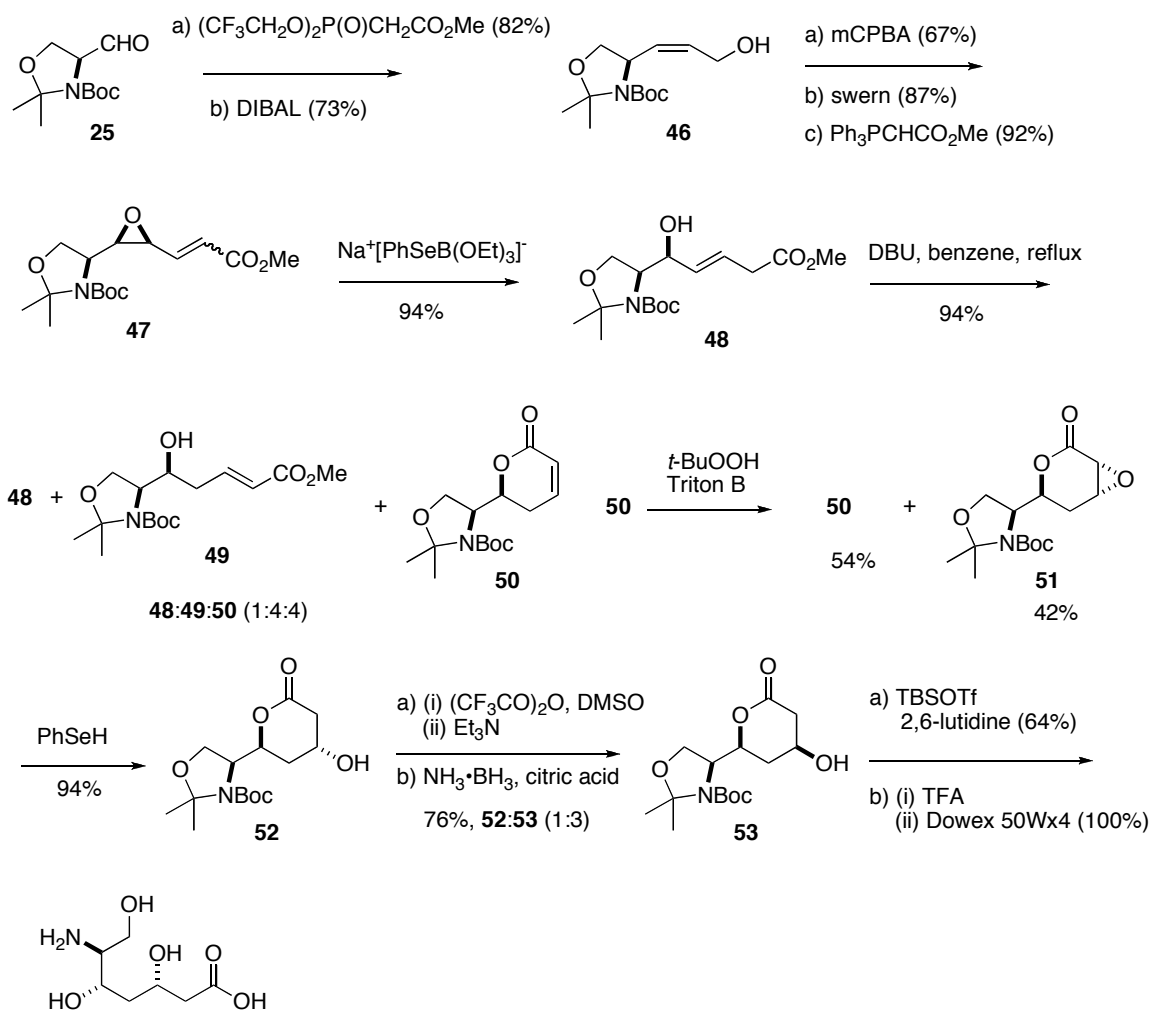


Scheme 1.5: Ohfuné's first synthesis of galantinic acid core structure.

Compound **41c** was converted under standard procedures to acetoneide **42** (88%). Next the TBS group was removed with TBAF (51%), epoxidized with *m*-CPBA (100%) and reduced with LAH to give **43a** and **43b** in 20% and 28% yield respectively. No mention was made of the diastereoselectivity of the epoxidation reaction and the poor yield of the LAH reduction precludes a good estimate of this ratio. The free hydroxyls in

43a were protected as acetate esters (Ac_2O /pyridine, 80%) then the Boc group was converted to a benzyloxycarbonyl group (TBDMSOTf then BnBr/TBAF, 75%) using a procedure developed in Ohfuné's lab.⁴⁵ Finally removal of the acetates (K_2CO_3 , 90%) followed by oxidation of the terminal hydroxyl (PtO_2/O_2 , 60%) gave the protected galantinic acid **45**. While this was the procedure used in the original synthesis, the poor yield and diastereoselectivity of a number of reactions along with the fact that it required 16 steps makes it a poor synthesis for this compound. Perhaps because of this, Ohfuné published a second improved synthesis of galantinic acid (Scheme 1.6), beginning with conversion of Garner's aldehyde (**25**) to the *Z*-allyl alcohol **46** under standard conditions.^{46, 47} Diastereoselective epoxidation using *m*-CPBA (67%) followed by oxidation using Swern conditions (87%) and chain elongation with a stabilized Wittig (92%) gave **47** as a mixture of *E* and *Z* isomers. The epoxide in **47** was cleaved using Miyashita's reagent to give alkene **48** as a single regioisomer in 94% yield.⁴⁸ Double bond migration ester cleavage and lactone formation with DBU gave desired product **50** as well as starting material **48** and conjugated isomer **49** in a ratio of 4:1:4 respectively. Recovered **48** and **49** could be re-treated with DBU and re-equilibrated to give more **50**, thereby improving yield. Compound **50** was epoxidized with basic *t*-BuOOH to give **51** (42%) as a single diastereomer and recovered starting material (54%). Reduction of epoxide **51** using modified Miyashita's reagent gave the undesired isomer **52** in 94% yield requiring inversion to the correct configuration. The authors had some difficulty achieving this and the conditions that were eventually used were oxidation with trifluoroacetic anhydride/DMSO followed by immediate reduction using $\text{NH}_3 \cdot \text{BH}_3$ (76%) to give a mixture of desired alcohol **53** and undesired epimer **52** in a 3:1 ratio

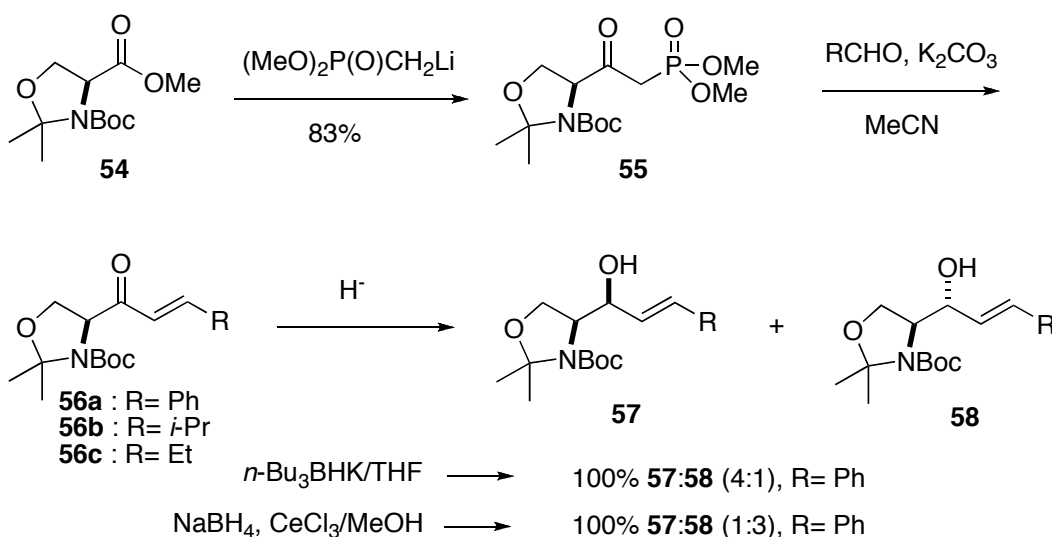
respectively. Protection of the free hydroxyl with TBS (64%) allowed chromatographic separation of the isomers followed by deprotection using TFA then treatment with Dowex 50Wx4 (elution with 1N ammonia) to give (-)-galantinic acid (**35**) in quantitative yield.



Scheme 1.6: Ohfuné's second synthesis of galantinic acid core structure.

One of the earlier papers focusing on diastereoselective synthesis from the chiral pool was by Koskinen who investigated diastereoselective hydride reductions of enones derived from serine ester **54**, which is an intermediate in the synthesis of Garner's

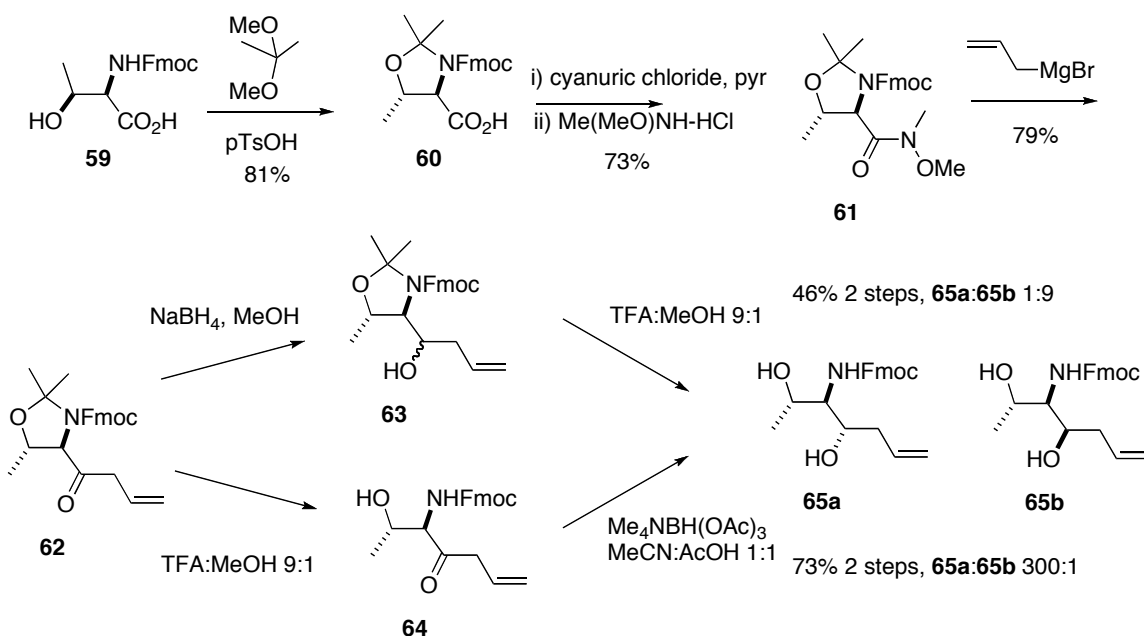
aldehyde (Scheme 1.7).^{49, 38} Chain elongation of **54** to phosphonate **55** (83%) followed by the HWE reaction with various aldehydes gave enones **56a-c**.⁵⁰ Various combinations of reagents and solvents were tried with the optimal conditions shown in Scheme 1.7. Selectivity can be tuned from 4:1 *syn:anti* to 1:3. In addition the R group had a large effect on the selectivity, for example with L-selectride/THF and R being phenyl, ethyl or *i*-propyl the selectivity was 4:1, 2:1 and 3:7 respectively.



Scheme 1.7: Koskinen's investigation of diastereoselective enone reduction.

In 1998, Somfai explored hydride reduction of an allyl ketones to generate a 3-amino-2,4-diols during the synthesis of kadosamine (Scheme 1.8).⁵¹ Allyl ketone **62** was synthesized starting from Fmoc-protected D-threonine as follows: protection of **59** with 2,2-dimethoxypropane (81%), conversion to Weinreb amide **61** (73%) and allylation with allylmagnesium bromide (79%) gave **62**.⁵² Because the stereochemical outcome of nucleophilic additions to α -amino aldehydes was known to be affected by the choice of amine protecting group the authors chose to investigate reduction of both the fully

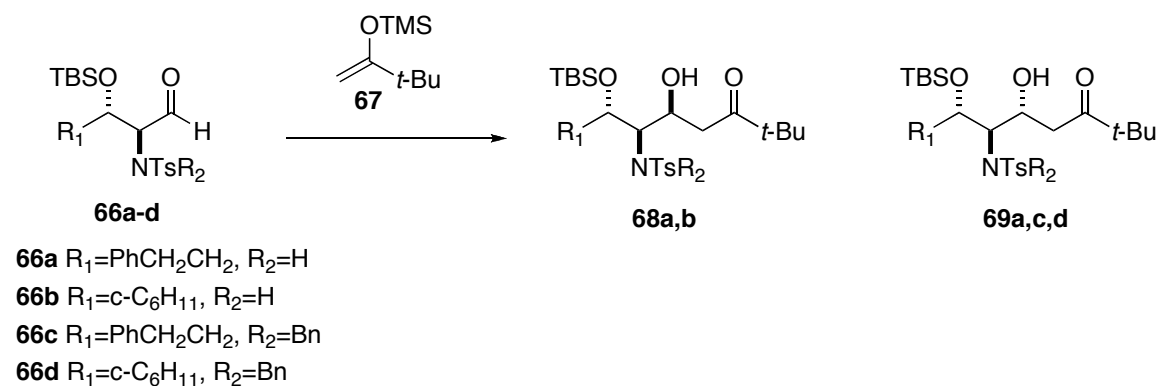
protected ketone **62** and the partially deprotected ketone **64**. Investigation of reducing agents and solvent conditions revealed that *syn* product **65b** was favored when NaBH₄ in methanol was used to reduce the fully protected ketone **62**. Acetonide removal with TFA gave a 1:9 ration of **65a**:**65b** (46% yield). Optimum conditions for reduction of **64** to *anti* product **65a** were NMe₄BH(OAc)₃ in 1:1 CH₃CN : AcOH (73% yield, 300:1 **65a**:**65b**).



Scheme 1.8: Somfai's investigation of diastereoselective allyl ketone reduction.

Nucleophilic additions to amino acid derived aldehydes for preparation of vicinal aminodiols is commonly seen in the literature. Good reviews for these types of reactions are available; consequently only some of the more recent and relevant papers will be discussed here.⁵³⁻⁵⁶ Two of the more noteworthy reviews are Reetz's 1999 review titled 'Synthesis and Diastereoselective Reactions of *N,N*-Dibenzylamino Aldehydes and Related Compounds' and Bols's 2001 review titled 'Garner's Aldehyde'.^{53,54}

Somfai's investigation of Mukaiyama additions to α -amino- β -silyloxy aldehydes published in 2005 found the diastereoselectivity of addition of **67** to aldehydes with *anti* configuration of the amino and silyloxy groups was very dependent on the nitrogen protecting group (Scheme 1.9 and Table 1.1).^{57, 58}



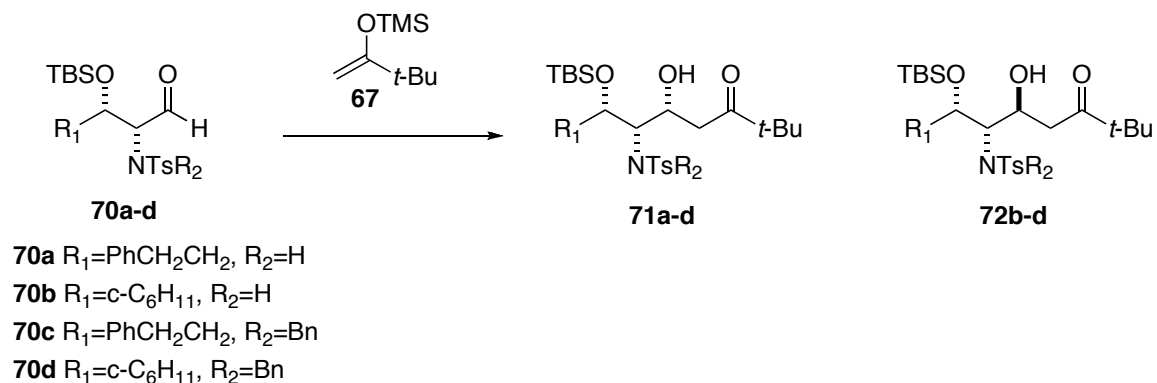
Scheme 1.9: Somfai's investigation of aldol additions to aldehyde **66a-d**.

Table 1.1: Somfai's investigation of aldol additions to aldehyde **66a-d**.

| Entry # | Substrate | Lewis acid | Yield % | dr (68:69) | Products |
|---------|------------|----------------------------------|---------|---------------------|-------------------------|
| 1 | 66a | $\text{BF}_3 \cdot \text{OEt}_2$ | 91 | 92:8 | 68a , 69a |
| 2 | 66a | TiCl_4 | 85 | 90:10 | 68a , 69a |
| 3 | 66b | $\text{BF}_3 \cdot \text{OEt}_2$ | 94 | >98:2 | 68b |
| 4 | 66c | $\text{BF}_3 \cdot \text{OEt}_2$ | 92 | <2:98 | 69c |
| 5 | 66d | $\text{BF}_3 \cdot \text{OEt}_2$ | 81 | <2:98 | 69d |

As expected aldehydes **66a** and **66b** with only partial protection of the amino group showed a strong preference for the *syn* addition products favored in chelation-controlled reactions. Fully protected aldehydes **66c** and **66d** gave predominately the Felkin-Anh *anti* addition products. The use of lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ produced improved yield and selectivity than TiCl_4 . Mukaiyama additions to the *syn* aldehydes **70a-d** gave equivocal results (Scheme 1.10 and Table 1.2). Under conditions of chelation control diastereoselectivities were still high (entry 1 and 2 Table 1.2). However reactions with

the fully protected amino aldehydes **70c** and **70d** were slow and gave no diastereoselectivity. This was attributed to the presence of the polar OTBS group.

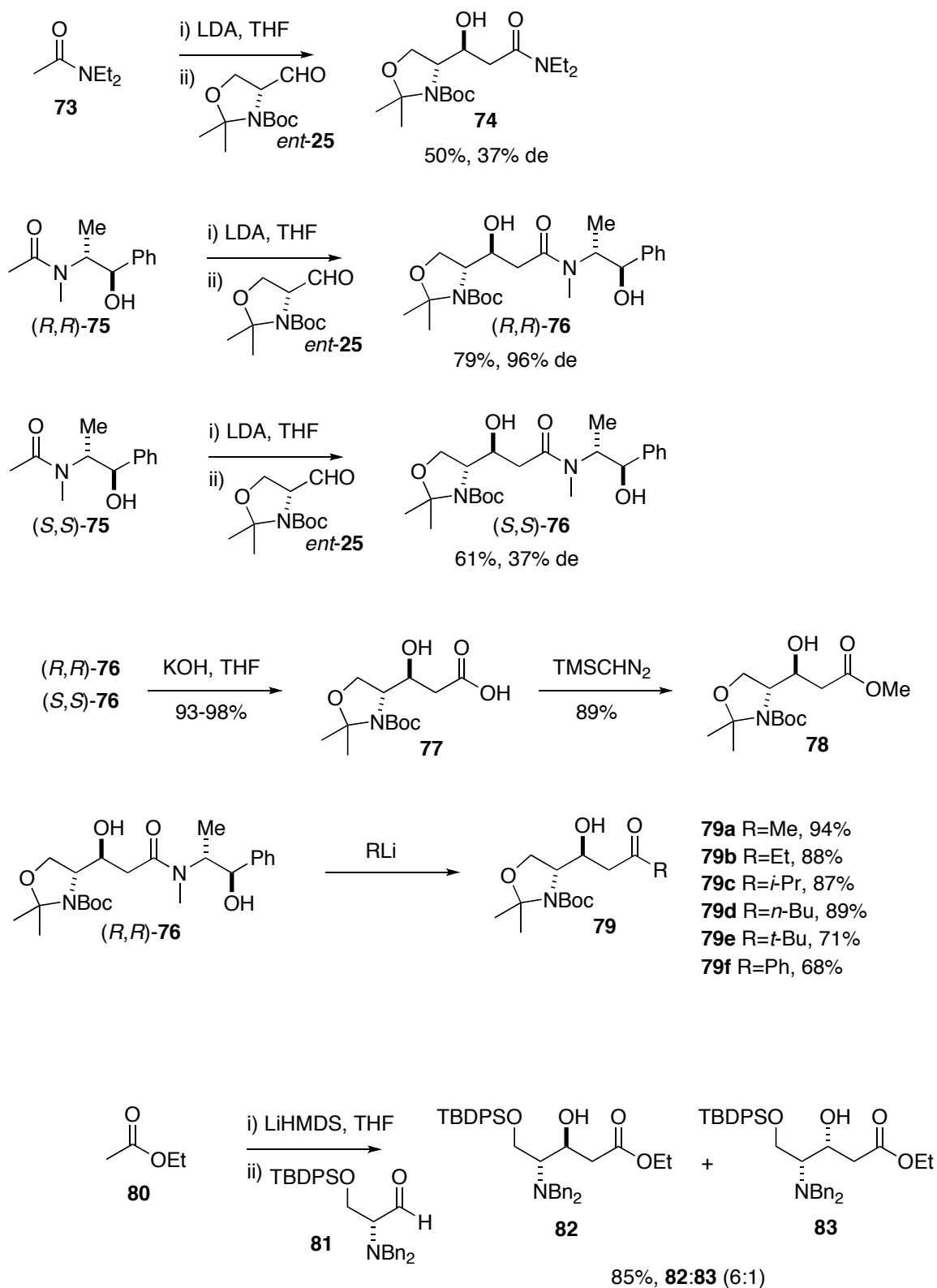


Scheme 1.10: Somfai's investigation of aldol additions to aldehyde **70a-d**.

Table 1.2: Somfai's investigation of aldol additions to aldehyde **70a-d**.

| Entry # | Substrate | Lewis acid | Yield % | dr (71:72) | Products |
|---------|------------|----------------------------------|---------|---------------------|-----------------|
| 1 | 70a | $\text{BF}_3 \cdot \text{OEt}_2$ | 88 | >98:2 | 71a |
| 2 | 70b | $\text{BF}_3 \cdot \text{OEt}_2$ | 89 | 88:12 | 71b, 72b |
| 3 | 70c | $\text{BF}_3 \cdot \text{OEt}_2$ | 91 | 47:53 | 71c, 72c |
| 4 | 70d | $\text{BF}_3 \cdot \text{OEt}_2$ | 49 | 44:56 | 71d, 72d |

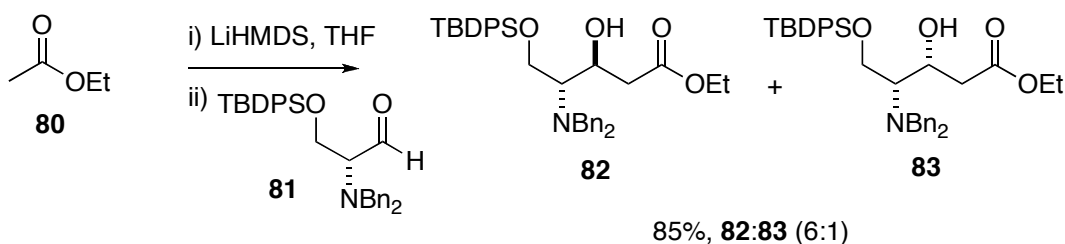
A 2004 paper by Reyes looked at acetate equivalent aldol reactions with Garner's aldehyde for preparation of polyhydroxylated γ -amino carbonyl compounds.⁵⁹ The enolate of achiral diethylacetamide **73** added to *ent*-**25** to give **74** in both low yield (50%) and low selectivity (37% de) (Scheme 1.11).



Scheme 1.11: Reyes's investigation of aldol additions to aldehyde Garner's aldehyde.

Double asymmetric induction conditions for the aldol reaction gave a large variation in diastereoselectivity. Aldol additions of pseudoephedrine-derived acetamides (*R,R*)-**75** and (*S,S*)-**75** to Garner's aldehyde gave addition products (*R,R*)-**76** and (*S,S*)-**75**, respectively. Use of (*R,R*)-**75** represents the matched case giving 79% yield and 96% de while the mismatched (*S,S*)-**75** gave lower yield and de (61% yield, 12% de). The addition products were carried forward to ester **78** and ketones **79a-f** in high yield.

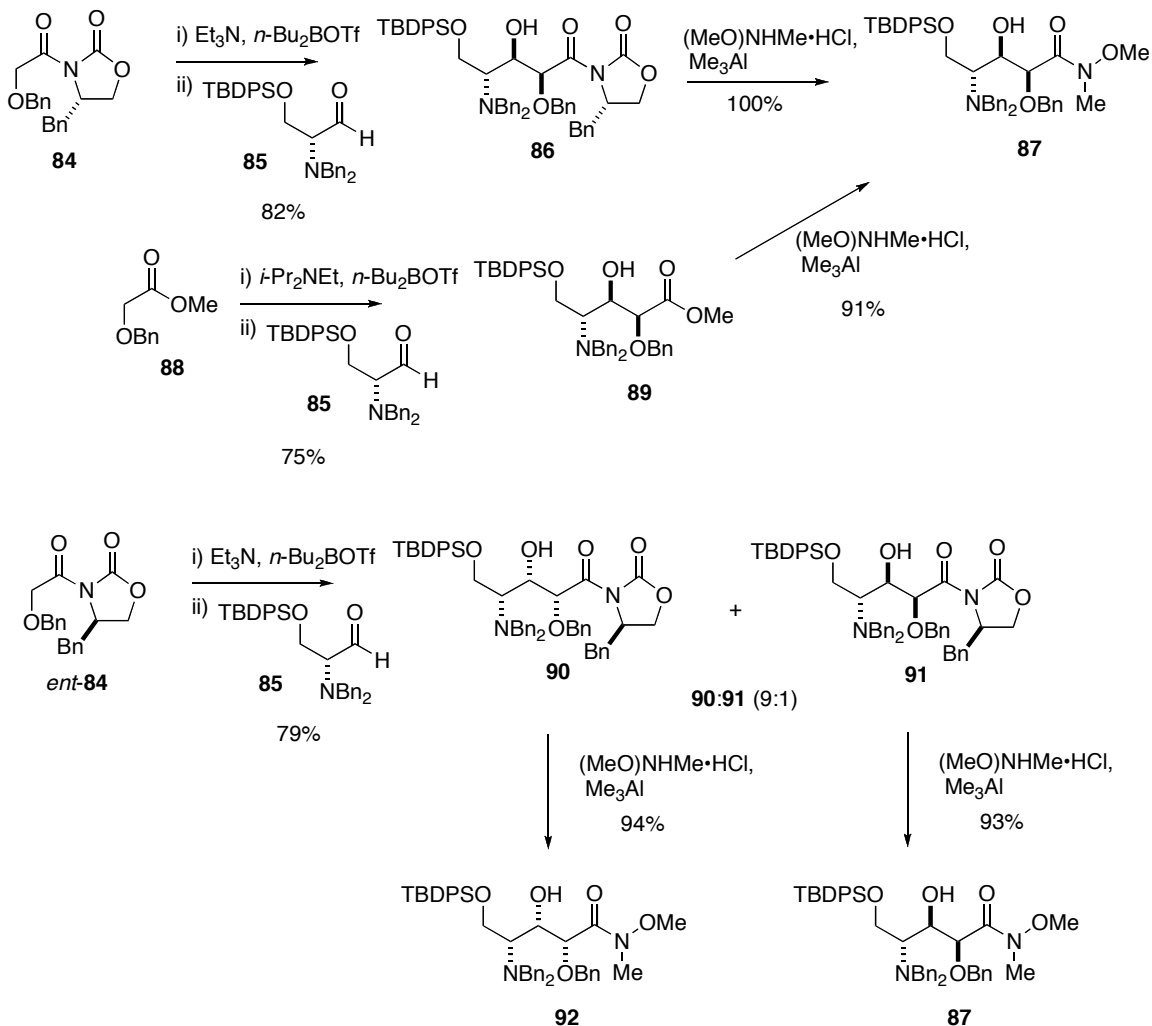
Acetate equivalents aldol additions were also used in earlier work by Hume.⁶⁰ The enolate of ethyl acetate was reacted with serine-derived aldehyde **81** to give addition products **82** and **83** (Scheme 1.12). Yield for this reaction was good at 85% and again the diastereoselectivity favored the *anti* addition product with dr 6:1 in favor of **82**.



Scheme 1.12: Hulme's acetate aldol addition to serine-derived aldehyde **81**.

Hulme's also exploited aldol additions of a glycolate equivalent to a serine-derived aldehyde for the synthesis of glucosidase inhibitors.^{61, 62} The significant relevance of this work is the aldol products which represent a motif also seen in the C7-C11 portion of zwittermicin A (Scheme 1.13). Addition of the acetylated Evan's auxiliary **84** and *ent*-**84** to serine-derived aldehyde **85**.⁶³ The matched case gave **86** in 82%. This represents an improved yield when compared with addition using the glycolate equivalent

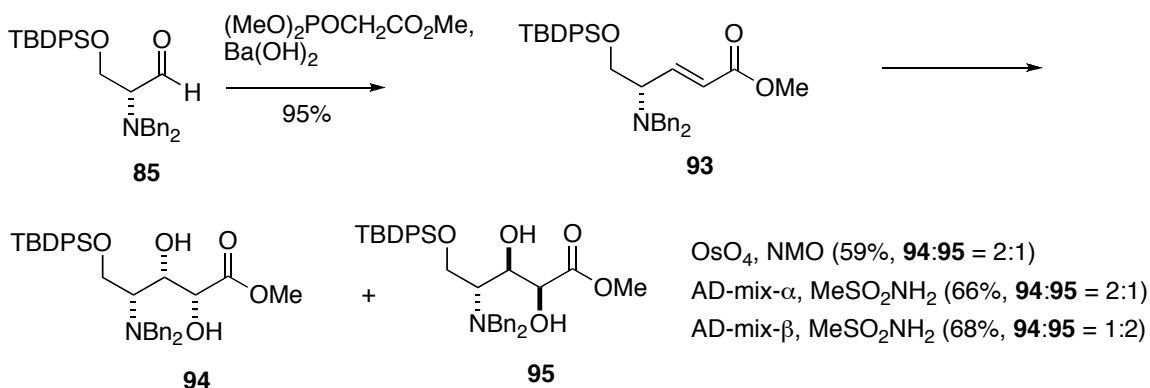
88 (75% yield). Conversion of these products to the Weinreb amide **87** proceeded smoothly in 100% and 91% yield, respectively.



Scheme 1.13: Hulme's aldol addition to serine-derived aldehyde **85**.

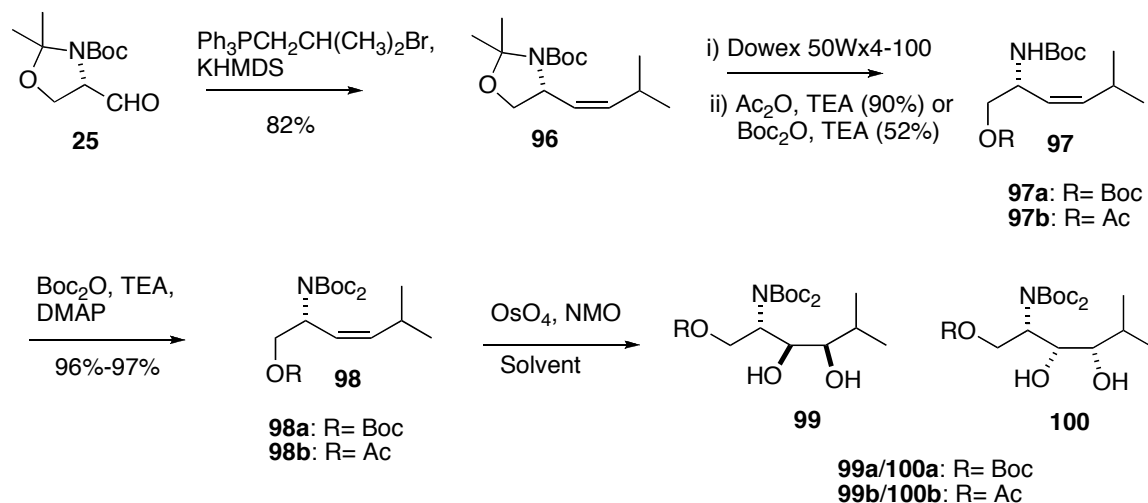
Addition of the mismatched glycolate equivalent *ent*-**84** to **85** gave **90** and **91** in 79% yield but lower diastereoselectivity (9:1). The latter two products were also converted to the Weinreb amides **92** and **87** in high yields.

Hulme also looked at using diastereoselective dihydroxylation for the synthesis of the aminopolyol (Scheme 1.14), unfortunately ratios of only 2:1 to 1:2 could be achieved.⁶⁴



Scheme 1.14: Hulme's attempted diastereoselective dihydroxylation.

This difficulty in tuning selectivity for dihydroxylation reactions when there is nitrogen functionality near the double bond is well described in the literature.⁶⁵⁻⁶⁷ An example of this can be seen in Kim's development of conditions for *anti*-selective dihydroxylation of *Z*-allylic amines (Scheme 1.15 and Table 1.3).⁶⁸ Starting alkene **98** was prepared from Garner's aldehyde by Wittig olefination giving **97** (82%), removal of acetonide with Dowex 50Wx4-100 and reprotection with a combination of Boc and acetate protecting groups.⁶⁹ It should be noted that the use of *N,N*-di-Boc protecting group was employed by Sharpless for improving the selectivity in asymmetric dihydroxylation reactions on allylic and homoallylic amines.⁷⁰ It can be seen that the dihydroxylation of **98** shows a strong solvent effect (entries 1-4, Table 1.3) as well as an effect due to the protecting group on the terminal hydroxyl (entry 5).



Scheme 1.15: Kim's dihydroxylations of **98a** and **98b**.

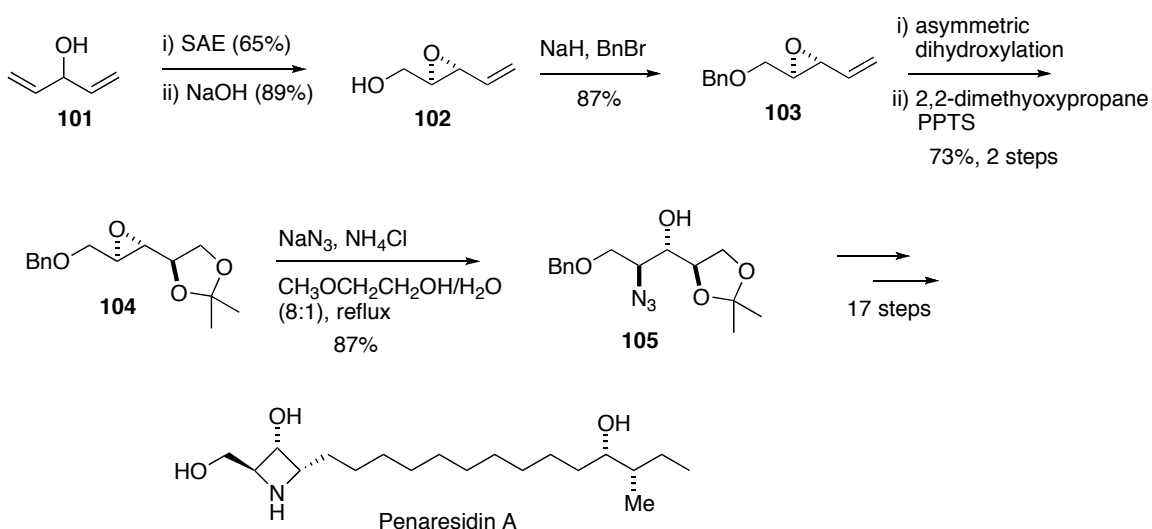
Table 1.3: Kim's dihydroxylations of **98a** and **98b**.

| Entry # | Substrate | Solvent | Yield % | dr (99:100) | Products |
|---------|------------|----------------------------|---------|----------------------|--------------------------|
| 1 | 98a | THF-H ₂ O (2:1) | 52 | 3.3:1 | 99a , 100a |
| 2 | 98a | <i>i</i> -PrOH | 82 | 4.0:1 | 99a , 100a |
| 3 | 98a | Toluene | 84 | 6.3:1 | 99a , 100a |
| 4 | 98a | DCM | 83 | 10:1 | 99a , 100a |
| 5 | 98b | DCM | 78 | 20:1 | 99b , 100b |

1.2.2.2. Chirality Through Asymmetric Catalyst

The use of SAE^{71, 72} for synthesis of aminodiols is common but requires displacement of a C-O bond by nitrogen after the generation of the epoxide; for example opening of the epoxide ring with an amine equivalent. The regioselectivity of nucleophilic ring opening of 2,3-epoxy alcohols is mainly at the 3 position.⁷³ Synthesis of 2-amino-1,3-diols requires nucleophilic attack at the 2 position of the epoxide with an amine equivalent such as azide. Azide opening of epoxides in the presence of ammonium chloride only slightly favors C2 selectivity if the substrate is hindered at C3. One example of the successful use of this technique was in Lin's synthesis of penaresidin A (Scheme 1.16).⁷⁴ The synthesis starts with SAE reaction on substrate **101** followed by a

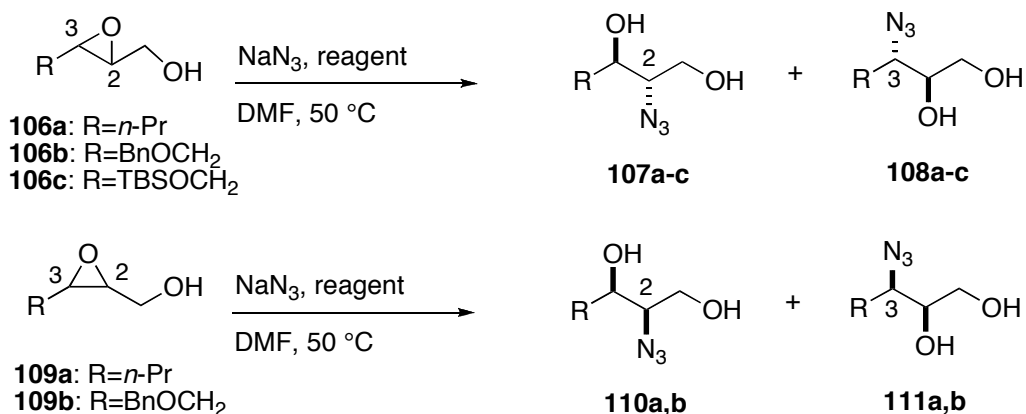
Payne rearrangement to give epoxide **102** in good yield.⁷⁵ Benzyl protection of the terminal alcohol gave **103** in 87% yield. Asymmetric dihydroxylation of **103** followed by protection of the diol as an acetonide gave epoxide **104** in 73% yield.⁷⁶ The key nitrogen insertion was then accomplished using sodium azide and ammonium chloride in refluxing ethyleneglycol mono-methyl ether /water (8:1) to give azide **105** in 87% yield. This compound was then taken forward in 17 steps to synthesize penaresidin A.



Scheme 1.16: Lin's synthesis of penaresidin A.

The poor C2 regioselectivity for azide openings of 2,3-epoxy alcohols led Miyashita to develop an improved technique involving the use of phenylboronic acid to direct attack at C2.⁷⁷ An improved technique with $(\text{MeO})_3\text{B}$ or $(\text{EtO})_3\text{B}$ gave azido alcohols in good diastereoselectivity (Scheme 1.17 and Table 1.4).⁷⁸ The reaction works best for *trans* epoxides with C2:C3 ratios of 82:18 to 92:8. Use of ammonium chloride as an activating reagent only gave a C2:C3 ratio of 15:85. The selectivity was poorer with

cis epoxides (e.g. **109a**, 1:2 ratio of C2:C3). Greater steric hindrance at the C3 position of **109b** improves the to 73:27 (entry 6).



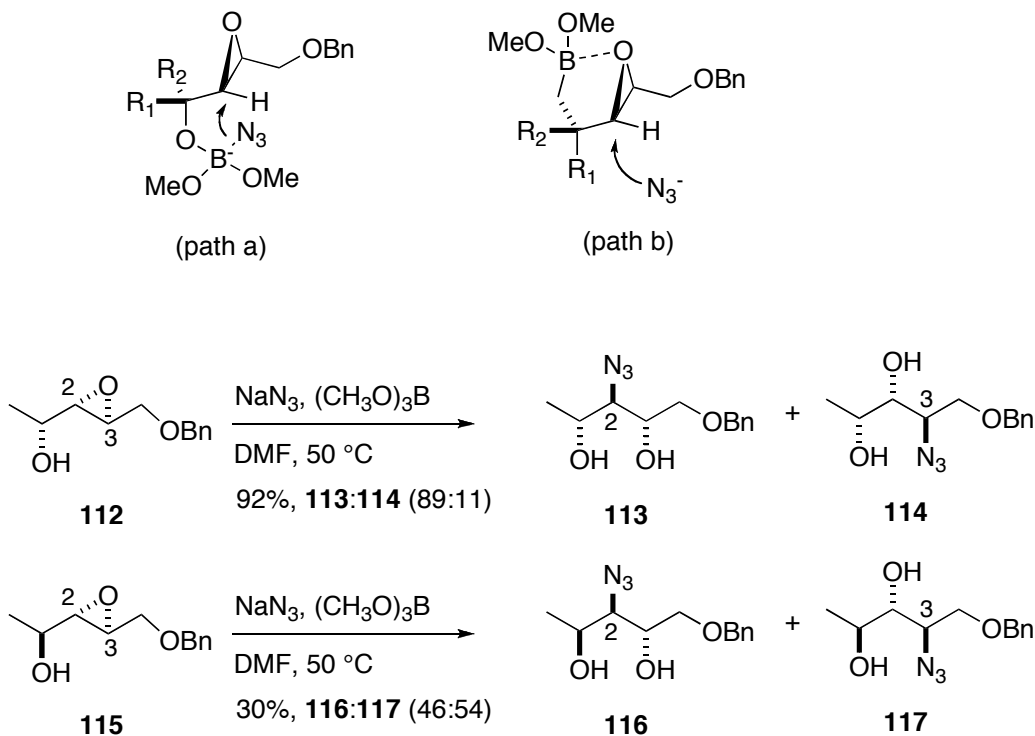
Scheme 1.17: Miyashita's boron-mediated azide opening of simple epoxides.

Table 1.4: Miyashita's boron-mediated azide opening of simple epoxides.

| Entry # | Substrate | Reagent | Yield % | dr (C2:C3) | Products |
|---------|-------------|------------------------------------|---------|------------|-------------------|
| 1 | 106a | (CH ₃ O) ₃ B | 97 | 82:18 | 107a, 108a |
| 2 | 106a | NH ₄ Cl | 95 | 15:85 | 107a, 108a |
| 3 | 106b | (CH ₃ O) ₃ B | 96 | 92:8 | 107b, 108b |
| 4 | 106c | (CH ₃ O) ₃ B | 99 | 92:8 | 107c, 108c |
| 5 | 109a | (CH ₃ O) ₃ B | 89 | 31:69 | 110a, 111a |
| 6 | 109b | (CH ₃ O) ₃ B | 96 | 73:27 | 110b, 111b |

Miyashita postulated that the transition state for this reaction involved an intramolecular chelate of a transesterified borate or boronate ester to the epoxide. Support for the chelation theory was seen in the azide opening of epoxides **112** and **115** (Scheme 1.18). If (path a) is correct then **112** should react slower and have less selectivity than **115** due to steric interference of the methyl group and epoxide ring. If on the other hand (path b) is correct then **115** should react slower and have less selectivity than **112** due to steric interaction between the methyl group and a nucleophile. Epoxide **115** (30% yield, dr

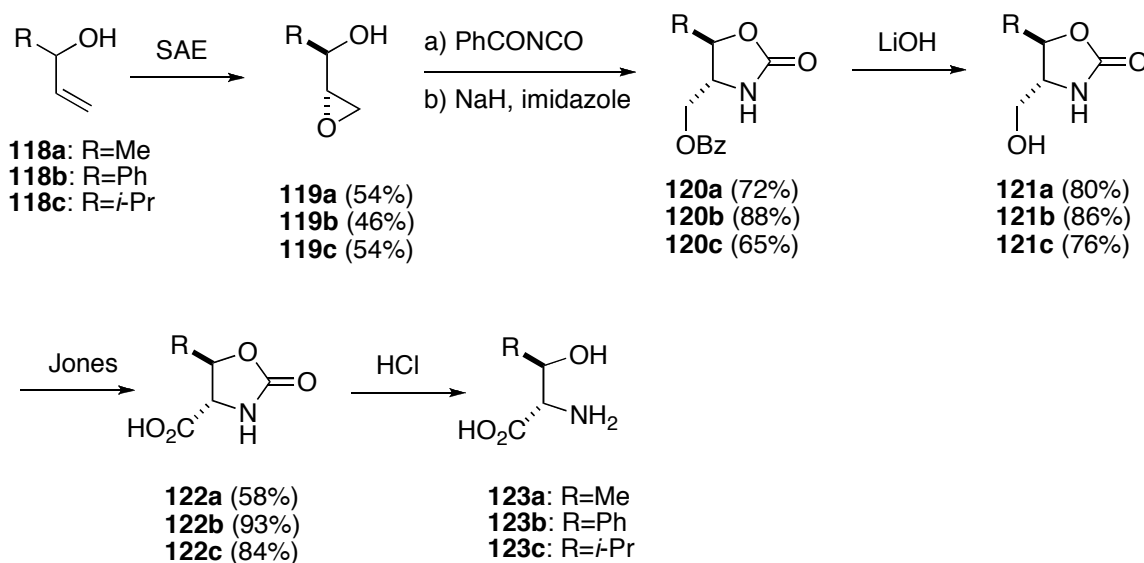
46:54) is less reactive than **112** (92% yield, dr 89:11) supporting (path b) as the correct pathway.



Scheme 1.18: Miyashita's boron mediated azide opening of epoxides **112** and **115**.

Direct opening of a 2,3-epoxyalcohol by reaction with isocyanate followed by intra-molecular displacement by the nitrogen has been used by investigators for synthesis of amino alcohols.⁷⁹⁻⁸⁰ The original method, developed by Roush, involves converting the terminal alcohol into a carbamate followed by treatment with base to facilitate intramolecular attack at the proximal C2 carbon to give an oxazolidinone.³⁶ The reactions are typically done in one pot without isolation of the intermediate carbamate as illustrated by Jung's synthesis of β -hydroxy- α -amino acids (Scheme 1.19).⁸¹ SAE resolution of alcohols **118a-c** followed by treatment of the epoxy alcohols with benzoyl isocyanate and

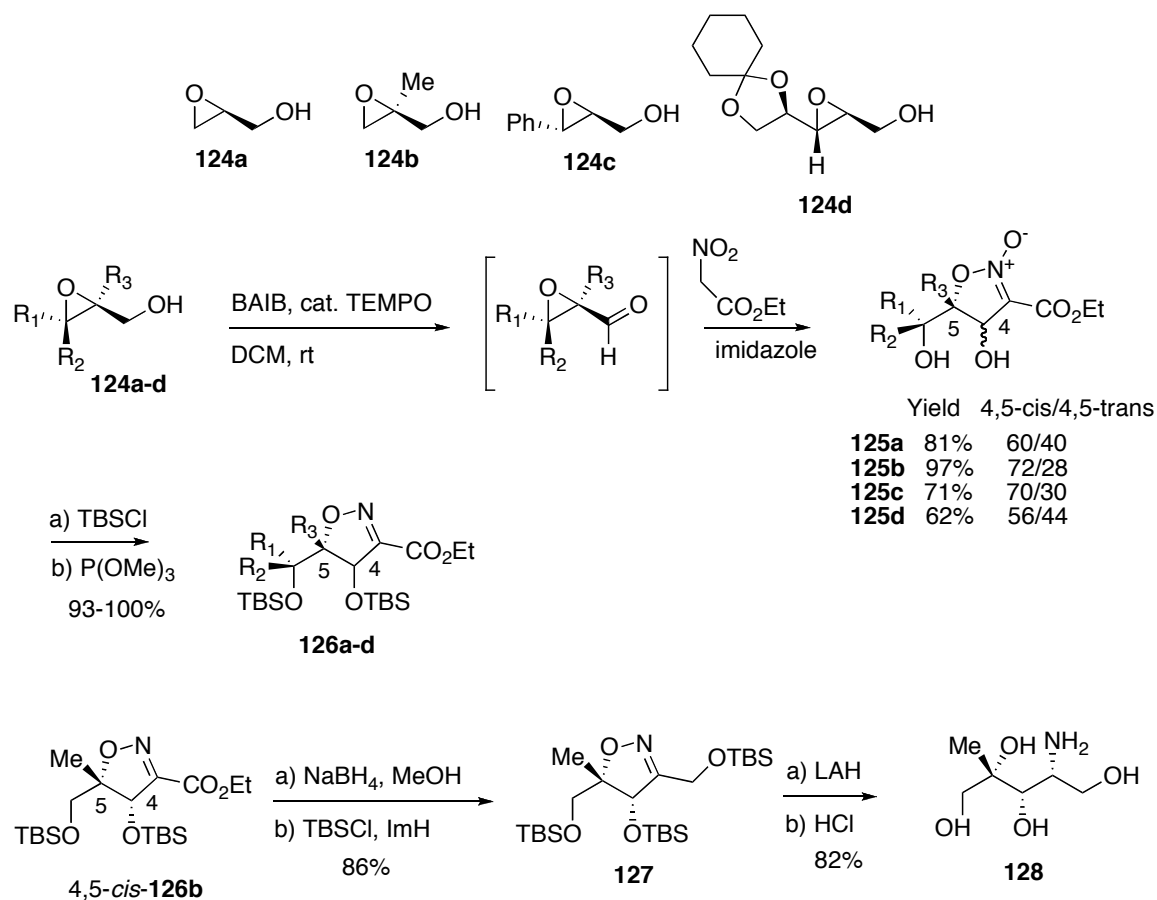
sodium hydride gave oxazolidinones **120a-c** in good yields (65%-85%). Removal of the benzoyl group (LiOH), Jones oxidation and finally acid hydrolysis with aqueous HCl completes the synthesis of the β -hydroxy- α -amino acids **123a-c**.



Scheme 1.19: Jung's use of epoxides for synthesis of β -hydroxy- α -amino acids.

One of the more interesting means of epoxide displacement by amine equivalents to a chiral epoxide was developed by Righi.⁸² In this procedure 2,3-epoxy alcohols are converted into 4-hydroxy-4,5-dihydroisoxazole 2-oxides in a one-pot reaction. These isoxazoles can then be easily transformed into aminopolyols (Scheme 1.20). Epoxides **124a-c** were converted into isoxazole-N-oxides **125a-c** by oxidation to give to an aldehyde followed by tandem nitroaldol-intramolecular cyclization. The use of Piancatelli oxidation which is compatible with the rest of the one-pot reaction is a key component of this successful transformation.^{83,84} The epoxide opening is stereospecific and yields for the reaction are respectable (62-97%), but suffer from low diastereoselectivity with the 4,5-*cis* to 4,5-*trans* ratios between 56:44 and 72:28. The diastereomeric compounds were

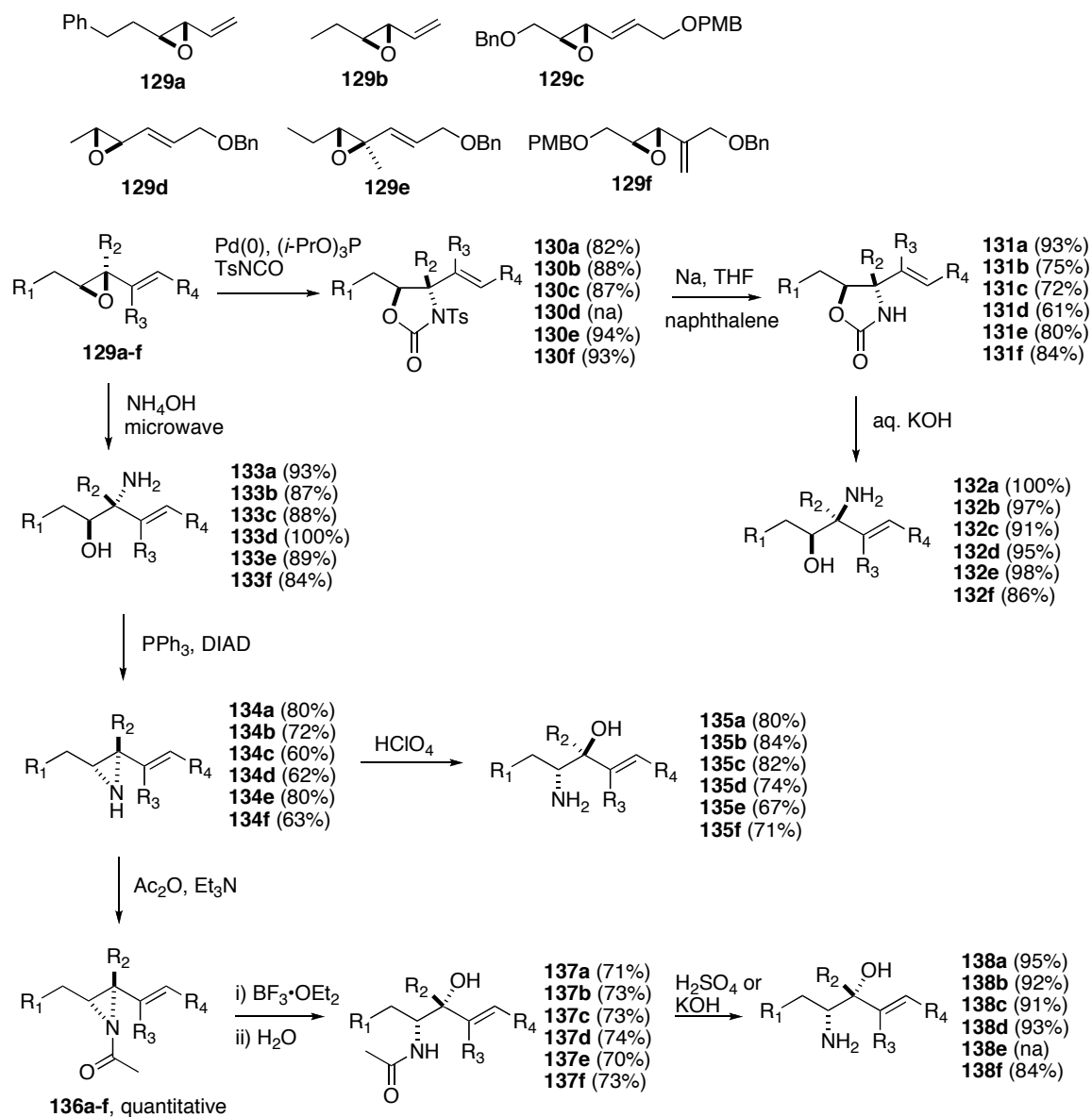
separable by chromatography as the free diol or after conversion to the bis-TBS protected compounds. Conversion to isoxazoles **126a-c** in 93-100% yield was achieved by protection with TBSCl and deoxygenation with P(OMe)₃. For example, 4,5-*cis*-**126b** was converted to isoxazole **127** (86% yield) by reduction of the ester (NaBH₄) and protection of the alcohol (TBSCl) and the resultant isoxazole reduced with LAH to give aminopolyol **128** (82% yield, dr > 9:1) after acidic work up.



Scheme 1.20: Righi's isoxazole method for synthesis of aminopolyols.

Somfai's stereospecific vinyloxy opening with ammonium hydroxide delivers a nitrogen at the C3 position, which is transformed to a vinylaziridine.^{85, 86} Subsequent

opening of this ring leaves the NH₂ group at C2. Together with Trost's Pd(0)-catalyzed ring opening of vinyloxydes, this method was used to generate all isomers for *vic*-amino alcohols (Scheme 1.21).⁸⁷



Scheme 1.21: Somfai's use of vinylaziridine for synthesis of aminopolyols.

Epoxides **129a-f** were converted to oxazolidinones **130a-f** using Pd(0) in the presence of tosyl isocyanate in good yields (82-94%) and diastereoselectivity of greater

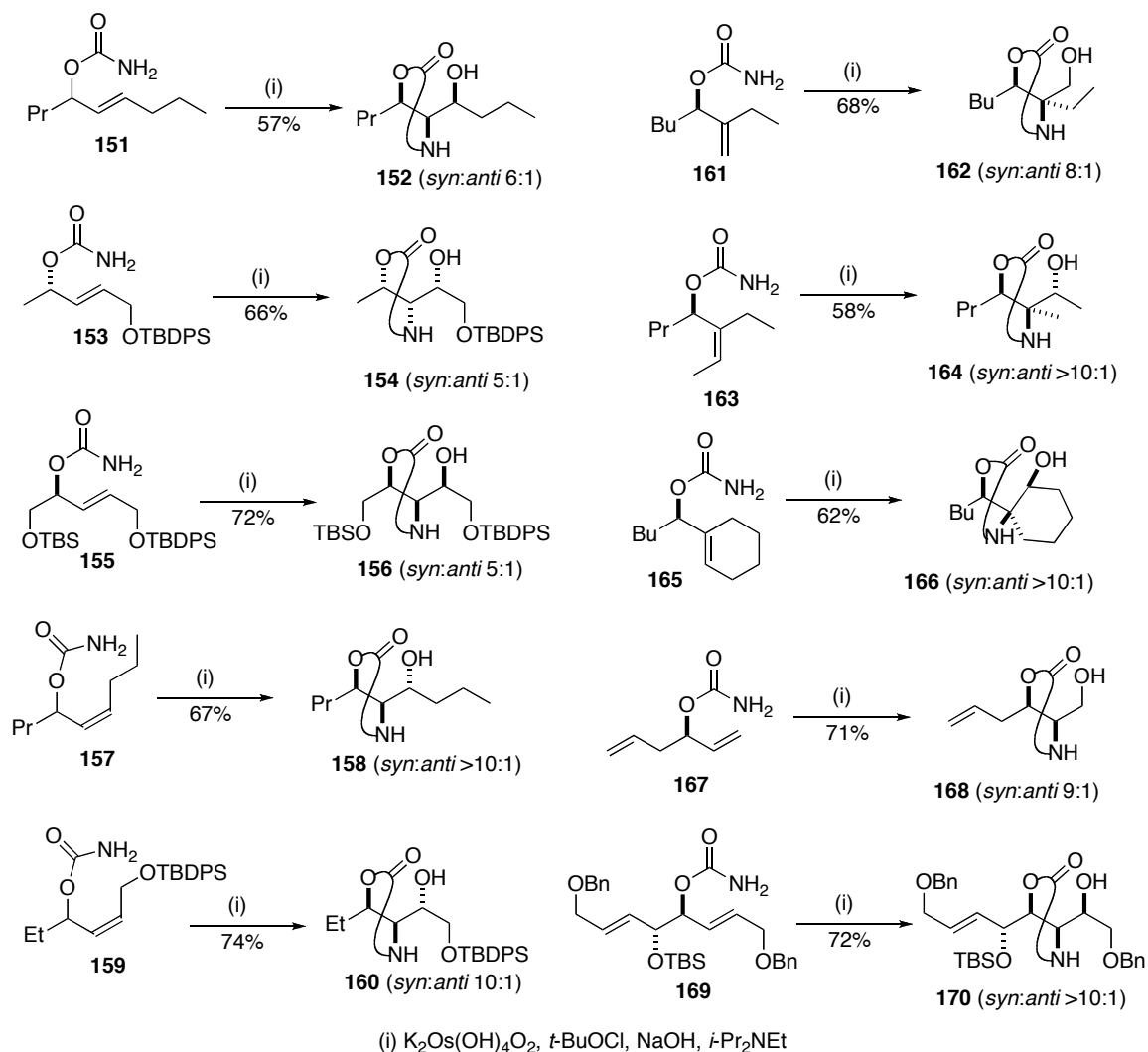
than 20:1 for all compounds except **130a** (6:1) and **130b** (14:1). Removal of the tosyl group gave oxazolidinones **131a-f** in good yields (72-93%, **131d** 61% for 2 steps). Diastereomers could be separated at this stage by silica chromatography. Hydrolysis of the oxazolidinones gave aminoalcohols **132a-f** in very good yields (86-100%). Alternatively, epoxides **129a-f** could be opened with NH_4OH under microwave irradiation to give aminoalcohols **133a-f**. These aminoalcohols could be converted into aziridines **134a-f** in moderate yields (60-80%). Followed by **134** ring opening under acidic conditions (HClO_4) to give aminoalcohols **135a-f** in reasonable yields (67-84%). Again diastereoselectivity was greater than 20:1 except for **135d** (10:1) and **135e** (2.5:1). Alternatively, aziridines **134a-f** could be acylated with acetic anhydride to give acetamides **136a-f** in quantitative yield then converted into allylic alcohols **137a-f** by treatment with boron trifluoride diethyl etherate and then water. Yields were moderate (70-74%) but diastereoselectivity was greater than 20:1 except for **137d** which was 10:1. Hydrolysis of the amide gave amino alcohols **138a-f** in good yields (84-95%) except for **138e**, which had to be made using a different route (not shown). Together the series of compounds comprising **132**, **133**, **135**, and **138** represent all of the possible diastereomeric 2,3-substituted amino alcohols.

In 2004 Kumar published a synthesis of galantinic acid that utilized both SAE and asymmetric dihydroxylation to set the absolute stereochemistry (Scheme 1.22).⁸⁸ Desymmetrization of diol **139** with PMBCl (86%) followed by oxidation with PCC, olefination using HWE (81%) and reduction with DIBAL (92%) gave allylic alcohol **142**.

followed by acid hydrolysis using sulfuric acid gave acid **150** with complete selectivity for attack at the α carbon. Azide **150** was then reduced under standard conditions to give galantinic acid (**35**) in 88% yield. With the exception to the selective reduction of the sulfite most of the steps in this synthesis were very standard reactions.

Asymmetric dihydroxylation of allylic alcohols, amines and their derivatives is another means of setting absolute stereochemistry and was partially covered in a previous section and in Kim's review titled 'Synthetic Applications of Stereoselective Dihydroxylation in Natural Products Synthesis', in addition to several other reviews.⁸⁹⁻⁹²

Asymmetric aminohydroxylation of olefins inserts both oxygen and nitrogen simultaneously.⁹³⁻⁹⁵ Most aminohydroxylation reagents tend to place the nitrogen at the C3 position when the substrate is an allylic alcohol or any other alkene containing a α heteroatom. Attempts to circumvent this problem using an intramolecular tethered aminohydroxylation reaction resulted in complete loss of asymmetric induction.⁹⁶ Nevertheless, for regioselective construction of vicinal amino alcohols the use of tethered aminohydroxylation can be a valuable tool when the absolute stereochemistry can be set by some other means. Scheme 1.23 shows examples of tethered aminohydroxylations by Keenan.⁹⁷

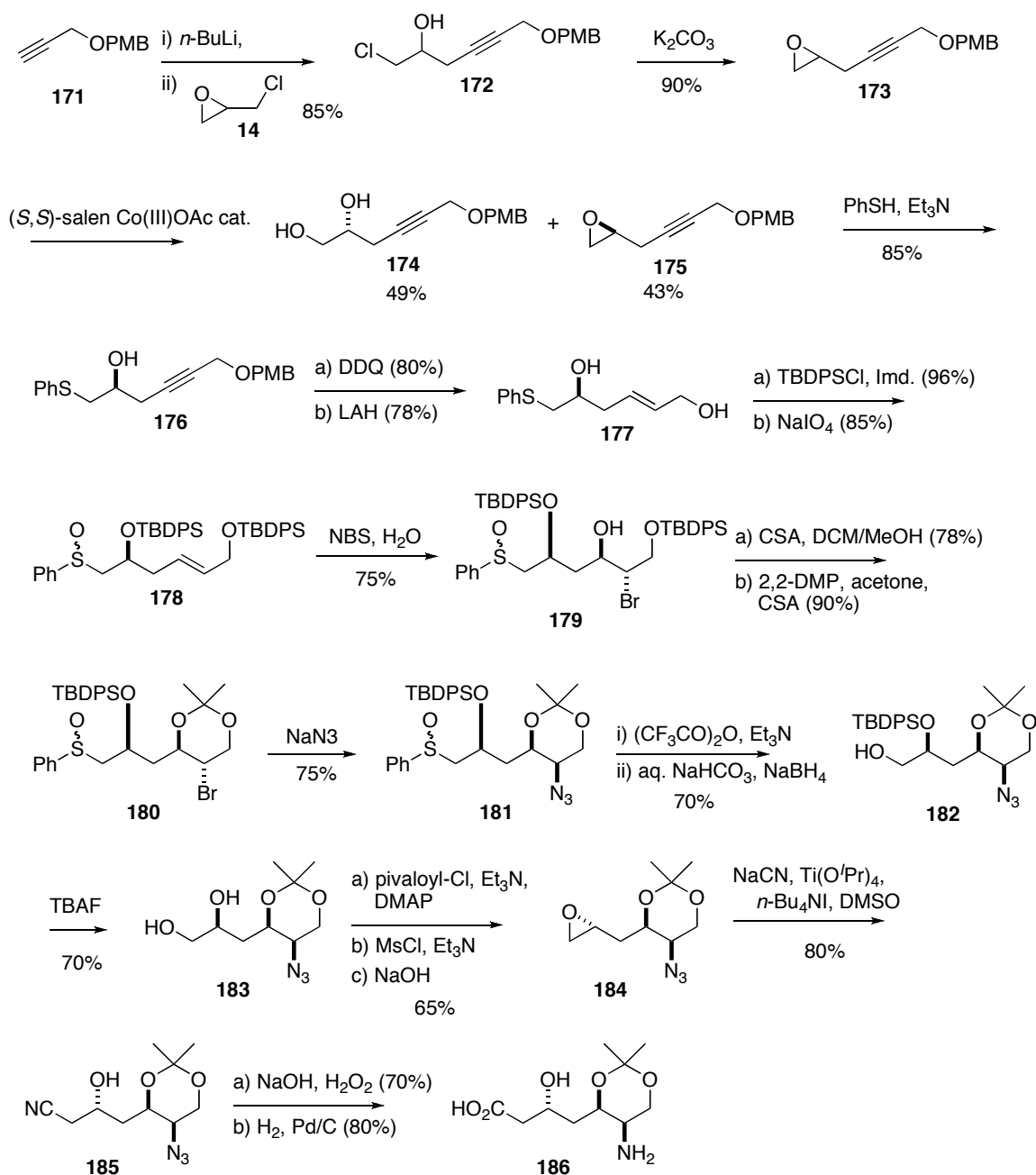


Scheme 1.23: Keenan's 2004 work on tethered aminohydroxylation.

Yields for these reactions were modest (~60-75%) with diastereoselectivity ranging from 5:1 to >10:1 (*syn:anti*). The authors rationalize the high selectivity for *syn* addition as due to transition state that minimizes $A^{[1,3]}$ strain between the R group *cis* to the allylic constituent in the inside position.

Finally, another synthesis of galantinic acid will serve to demonstrate the use of kinetic resolution of epoxides derived from halohydrins followed by azide displacement

to introduce the nitrogen functionality. The synthesis of galantinic acid by Reddy (Scheme 1.24) starts by addition of protected propargyl alcohol **171** to epichlorohydrin to give **172** (85%) followed by base promoted cyclization to give epoxide **173** (90%).⁹⁸ Hydrolytic kinetic resolution of this epoxide with Jacobsen's salen(Co) catalyst gave a mixture of diol **174** (49%) and optically pure epoxide **175** (43%).⁹⁹ Epoxide opening of **175** with thiophenoxide gave thioether **176** in 85% yield. Removal of the PMB group (DDQ, 80%) and reduction of the triple bond (LAH, 78%) gave *E*-alkene **177**. Protection of hydroxyls (TBDPSCI, 96%) and oxidation (NaIO₄, 85%) gave **178** as a mixture of epimeric sulfoxides. Treatment of alkene **178** with NBS gave bromohydrin **179** (75%) in a regio and stereospecific manner. Deprotection of the primary alcohol (CSA, 78%) followed by protection of the subsequently formed diol as an acetonide (90%) provided compound **180**. Nitrogen insertion was accomplished by azide displacement of bromide using NaN₃ to give **181** in 75% yield. The sulfoxide was removed by a one-pot Pummerer rearrangement¹⁰⁰ ((CF₃CO)₂O, Et₃N) and reduction of the resulting aldehyde (NaBH₄) to yield **182** (70%). Removal of the TBDPS group (TBAF, 70%) provided diol **183**. This diol was converted into epoxide **184** (65% overall yield) in three steps; selective protection of the primary alcohol as pivalate ester, mesylation of secondary alcohol and hydrolysis of the pivalate ester with concomitant displacement of the mesyl group.

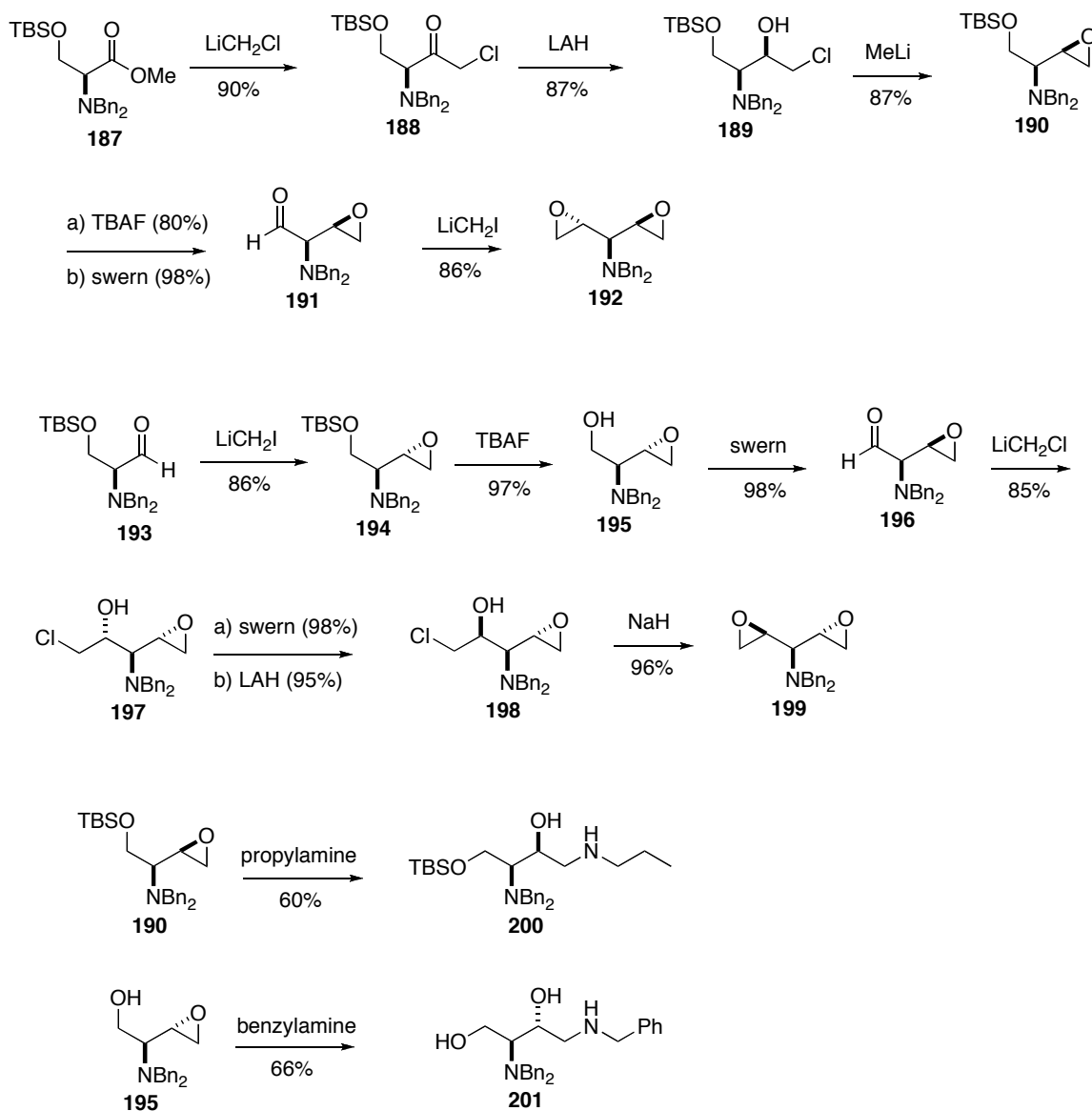


Scheme 1.24: Reddy's synthesis of galantinic acid.

Opening of the epoxide with sodium azide using Sharpless protocol¹⁰¹ gave alcohol **185** (80%). Hydrolysis of the cyano group (NaOH, H₂O₂, 70%) followed by reduction of the azide (H₂, Pd/C, 80%) yielded protected galantinic acid **186**.

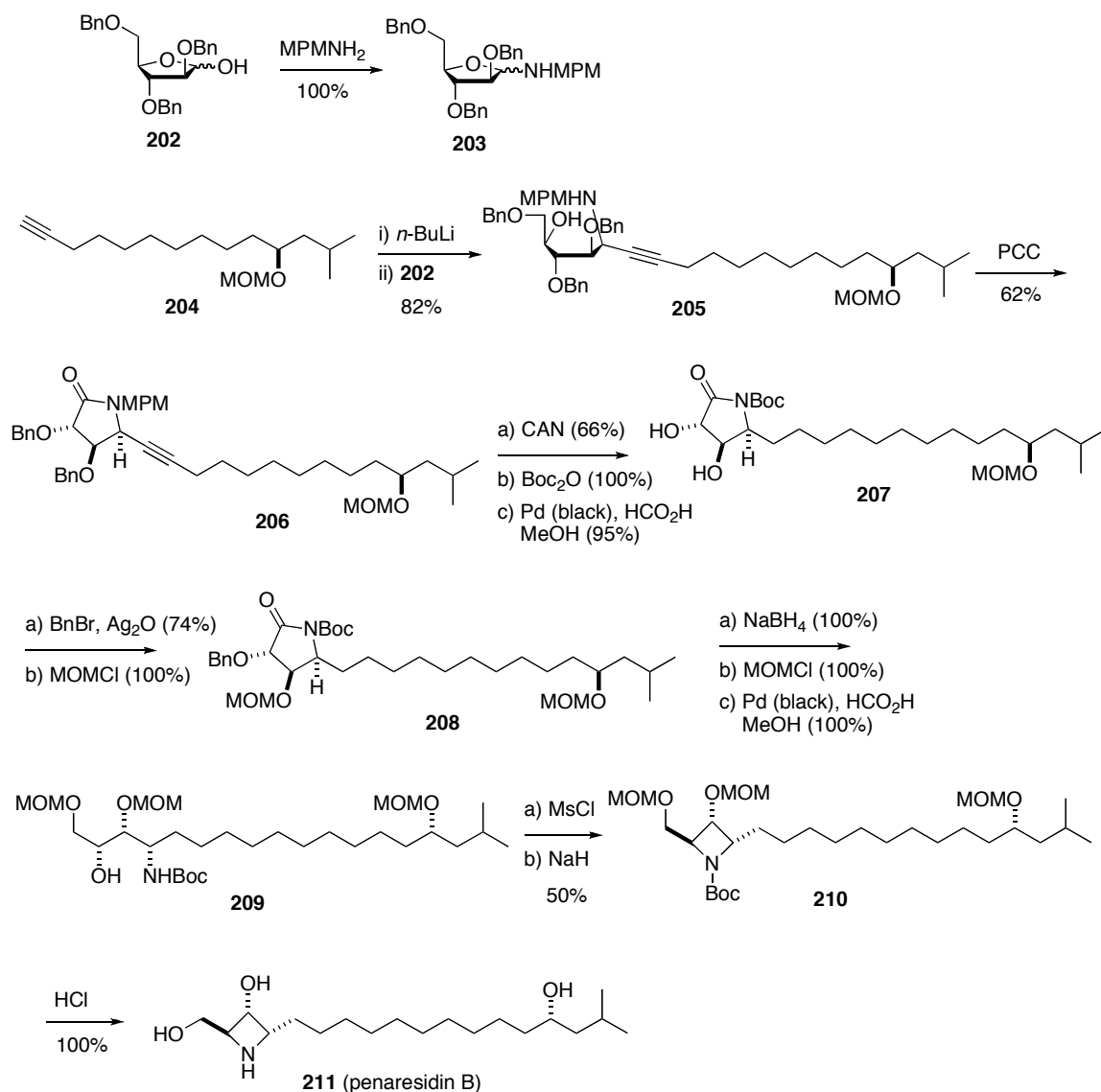
1.2.3. Other Open-Chain Aminopolyols

Concellón developed complimentary methods for diastereoselective synthesis of aminoalkyl epoxides from amino acids which can serve as chiral building block for more complex aminopolyol compounds (Scheme 1.25).¹⁰²⁻¹⁰⁴ Addition of chloromethyl lithium to serine-derived ester **187** afforded ketone **188** (90%). Stereospecific reduction with LAH at low temperature (−100 °C) gave chlorohydrin **189** (87%) which, upon treatment with methyl lithium, provided epoxide **190** in 87% yield. Removal of the TBS group (TBAF, 80%) and oxidation (Swern, 98%) gave aldehyde **191**. Addition of iodomethyl lithium resulted in addition and subsequent ring closing to give diepoxide **192** in 86% yield. In a complementary manner, serine-derived aldehyde **193** could be converted to epoxide **194** (86%) by treatment with iodomethyl lithium. This epoxide could be further elaborated to diepoxide **199** in six high yielding steps as shown. Chloro compounds **188**, **197**, **198**, epoxides **190**, **194**, and diepoxides **192**, and **199** represent compounds that are useful in the synthesis of amino alcohols. For example treatment of **190** with propylamine and compound **195x** with benzylamine generated **200** (60%) and **201** (66%), respectively.



Scheme 1.25: Concellón's synthesis of aminoepoxides.

The final aminoalcohol synthesis to be presented is that of Takabe's penaresidin B synthesis.¹⁰⁵ Absolute configuration is set through use of sugar synthons following previously reported procedures.^{106, 107} Protected aldose **202** was treated with MPMNH₂ to give **203** quantitatively (Scheme 1.26). Addition of the anion of **204** gave **205** (82%). PCC oxidation of this compound provided lactam **206** in 62% yield.



Scheme 1.26: Takabe's synthesis of penaresidin B.

Functional and protecting group manipulation provided lactam **208** in good yield. Reduction of the lactam with sodium borohydride followed by protecting group Mesylation of the hydroxyl group (MsCl) followed by treatment with sodium hydride gave azetidene **210** in 50% yield. Deprotection of **210** with HCl provided penaresidin B (**211**) in quantitative yield.

1.3. References

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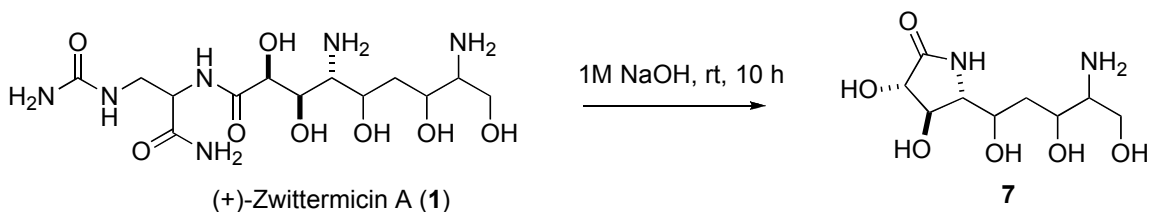
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Chapter 2 Determination of Absolute Configuration at C4 and Relative Configuration for C8-C14 in (+)-Zwittermicin A: Proposed Configuration of (+)-Zwittermicin A

2.1. Introduction

Zwittermicin A (**1**) is an asymmetric molecule with 7 stereocenters and therefore has 128 possible stereoisomers. This meant that initial work be directed toward determining the absolute configuration of **1** or at least reducing the number of possible isomers that would need to be synthesized. Clardy and coworkers had determined the relative stereochemistry for the C8-C10 portion of **1A** by means of degradation in 1 N sodium hydroxide solution to the cyclic lactam **7** and subsequent analysis of nOe analysis (Scheme 2.1).¹ This reduced the number of possible isomers to 32.



Scheme 2.1: Degradation of Zwittermicin A.

With the C1-C5 portion of **1** having structural similarity to the known compound (–)-albizziin,² it was likely that the configuration of the C4 stereocenter in **1** could be determined using Marfey's^{3,4} analysis. Symmetry within the C9-C15 portion of **1** led to the possibility of using pair-wise ¹³C NMR chemical shift difference analysis⁵⁻⁸ of model

compounds with the natural product as a means for determining the relative stereochemistry within this portion of the molecule.

A tentative configuration of **1** would arise from the above analysis. Verification of the configuration of **1** would be obtained by a completion of the total synthesis of the natural product and comparison with an authentic sample (provided as a courtesy, by D. Manker).

2.1.1. Marfey's Analysis

Marfey's analysis is a technique developed for determination of absolute configurations of α -amino acids.³ In practice the technique utilizes an S_NAr coupling of an amino acid with a known chiral auxiliary, e.g. 5-fluoro-2,4-dinitrophenyl-L-alaninamide (L-FDAA) to form a single diastereomer which is then analyzed by HPLC analysis on a C_{18} column. Comparison of the retention times of the diastereomers with standards prepared from both the D- and L-amino acids gives the configuration of the amino acid. If only one enantiomeric form of the amino acid is available, then diastereomers can be generated by derivatization with both L- and D-FDAA. This works because enantiomeric pairs of diastereomers behave identically on HPLC and therefore a L-FDAA derivative of a D-amino acid has the same retention time as a D-FDAA derivative of a L-amino acid. This method is sensitive and works for both primary and secondary amines.

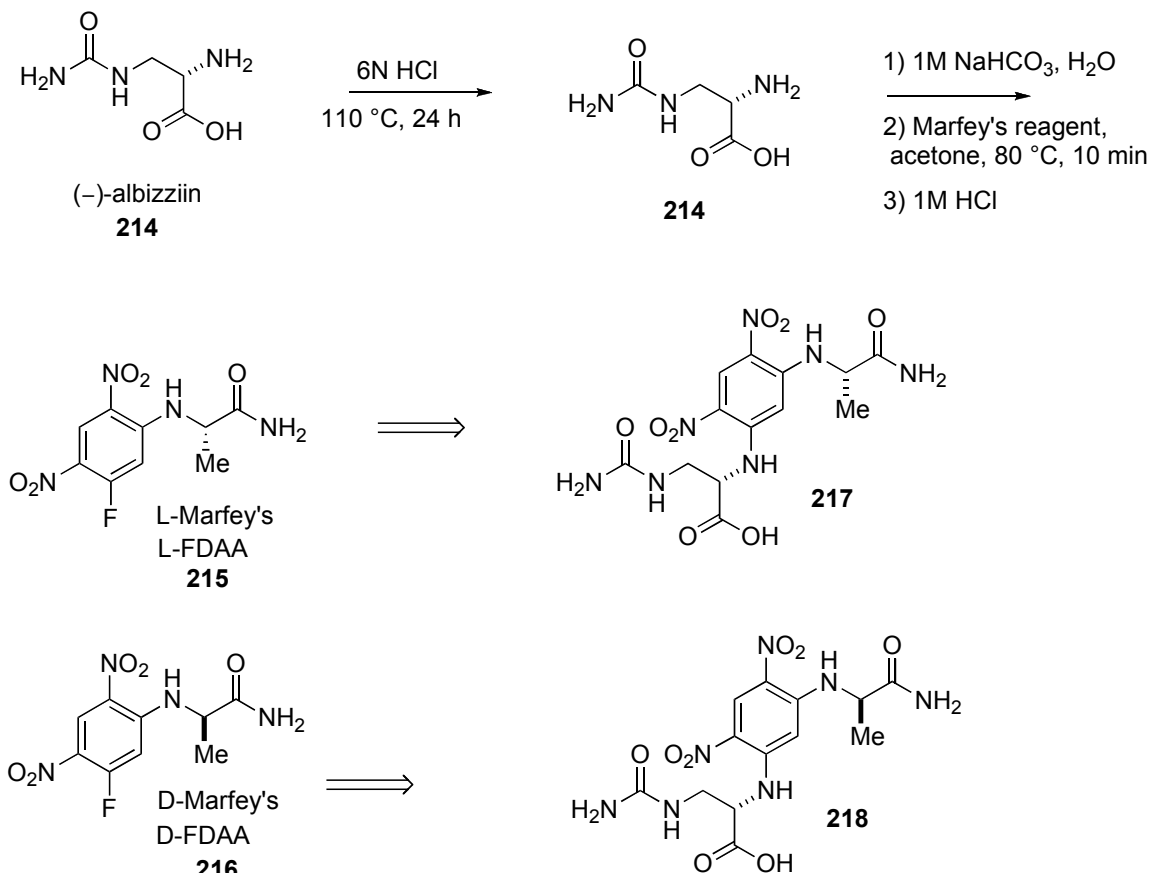
2.1.2. Pair-wise ^{13}C NMR Chemical Shift Difference Analysis

Pair-wise ^{13}C NMR chemical shift difference analysis involves comparing the ^{13}C chemical shifts of a known compound with those of model compounds representing all the possible relative configurations of the unknown compound.⁵ The correct relative configuration is that which matches most closely however, the reliability is somewhat dependent upon the similarity of constitution of the models with the unknown. This technique has been useful when other methods such as chemical degradation, nOe assignment⁹⁻¹⁰ or *J*-based analysis¹⁰⁻¹² are inappropriate. Compounds having more than three or four stereocenters require preparation of a substantial number of models. Additionally, if the compound is complex, the synthesis of these models is not trivial. For these reasons it is desirable to reduce the number or complexity of models needed for analysis by one or more of the above mentioned methods such as *J*-based analysis. In the case of zwittermicin A, Clardy and coworkers had already determined the relative configuration of the C8-C10 portion of **1** leaving only configurational assignment of the remaining relative stereochemistry for the C10-C14 portion and the amino acid.¹ The inherent symmetry in the C9-C15 portion of **1** further reduces complexity and pair-wise comparison of this portion of the molecule would only require with only six models. In addition, the synthetic route to these six models might also be adaptable to the total synthesis of zwittermicin A.

2.2. Determination of C4 Configuration in (+)-Zwittermicin A by Marfey's Analysis

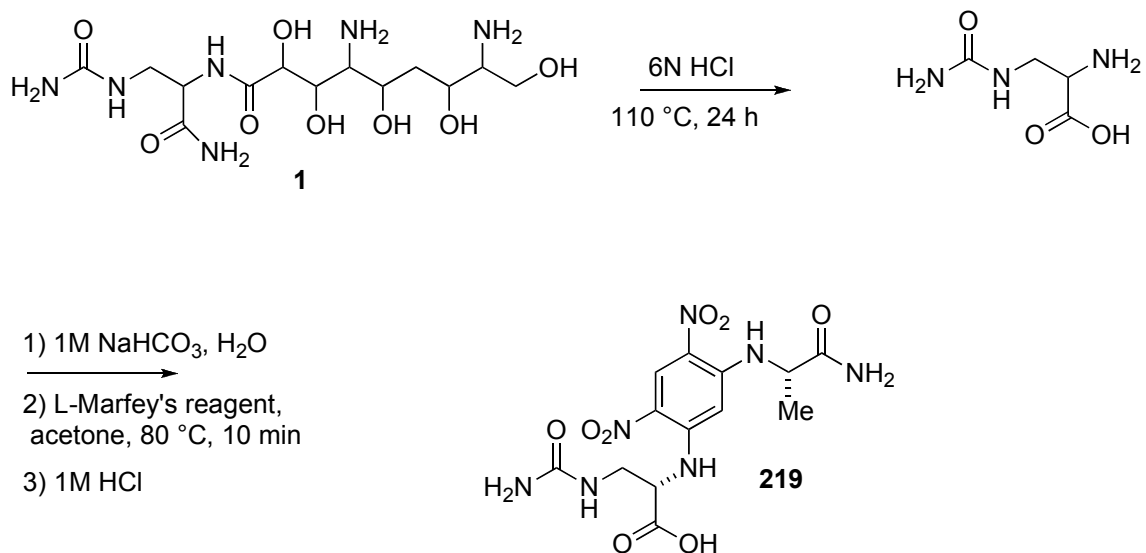
(-)-Albizziin (**214**) was subjected to hydrolysis conditions (6 N HCl, 110 °C, 24 h) (Scheme 2.2). The reaction mixture was concentrated to dryness then resuspended in a

small amount of water, split into two portions and derivatized separately with L-FDAA (**215**) and D-FDAA (**216**) in the presence of Na_2CO_3 to give the two derivatives **217** and **218** respectively (Scheme 2.2).



Scheme 2.2: Marfey's analysis standards.

Authentic zwittermicin A was hydrolyzed (6M HCl, 110 °C) and treated in a similar manner with L-FDAA to give compound **219** (Scheme 2.3).



Scheme 2.3: Hydrolysis and derivatization of Zwittermicin A.

Analysis of the derivatization products by C₁₈ HPLC-MS (0.40 mL/min; 1:9 CH₃CN:H₂O w/ 0.1% formic acid to 7:1 CH₃CN:H₂O w/ 0.1% formic acid; 30 min) showed two peaks with UV absorption at 340 nm and a mass corresponding to the **217** and **218**. The peaks corresponding to **217** and **218** eluted at 14.15 and 14.75 minutes respectively. Analysis of **219** using the same conditions gave a retention time and mass corresponding to that of **217** with a co-injection of **217** and **219** showing a single peak. Therefore, the configuration **219** and C4 in **1** are *S*.

2.3. Determination of C10-C14 Relative Configuration in (+)-Zwittermicin A

The *pseudo*-symmetry in the C9-C15 portion of **1** meant that only six models, **220-225**, would be necessary to represent all the possible diastereomers (Figure 2.1). Models **220** and **224** are *meso* while models **221** and **225** are C₂ symmetric. Models **222** and **223** are C₁ diastereomers and therefore each can represent two possible zwittermicin

A diastereomers for pair-wise analysis. Models **222b** and **223b** are identical to **222** and **223** but flipped end-for-end in order to compare with **1**. All of the models have been numbered according to the numbering scheme of **1**. Synthesis of these models allowed comparison with **1** and determination of the relative stereochemistry of the C10-C14 portion of **1**.

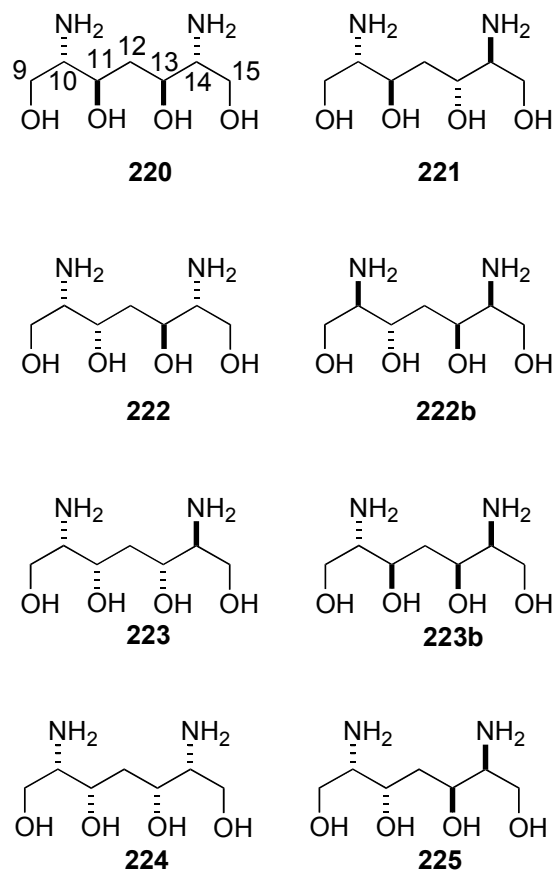
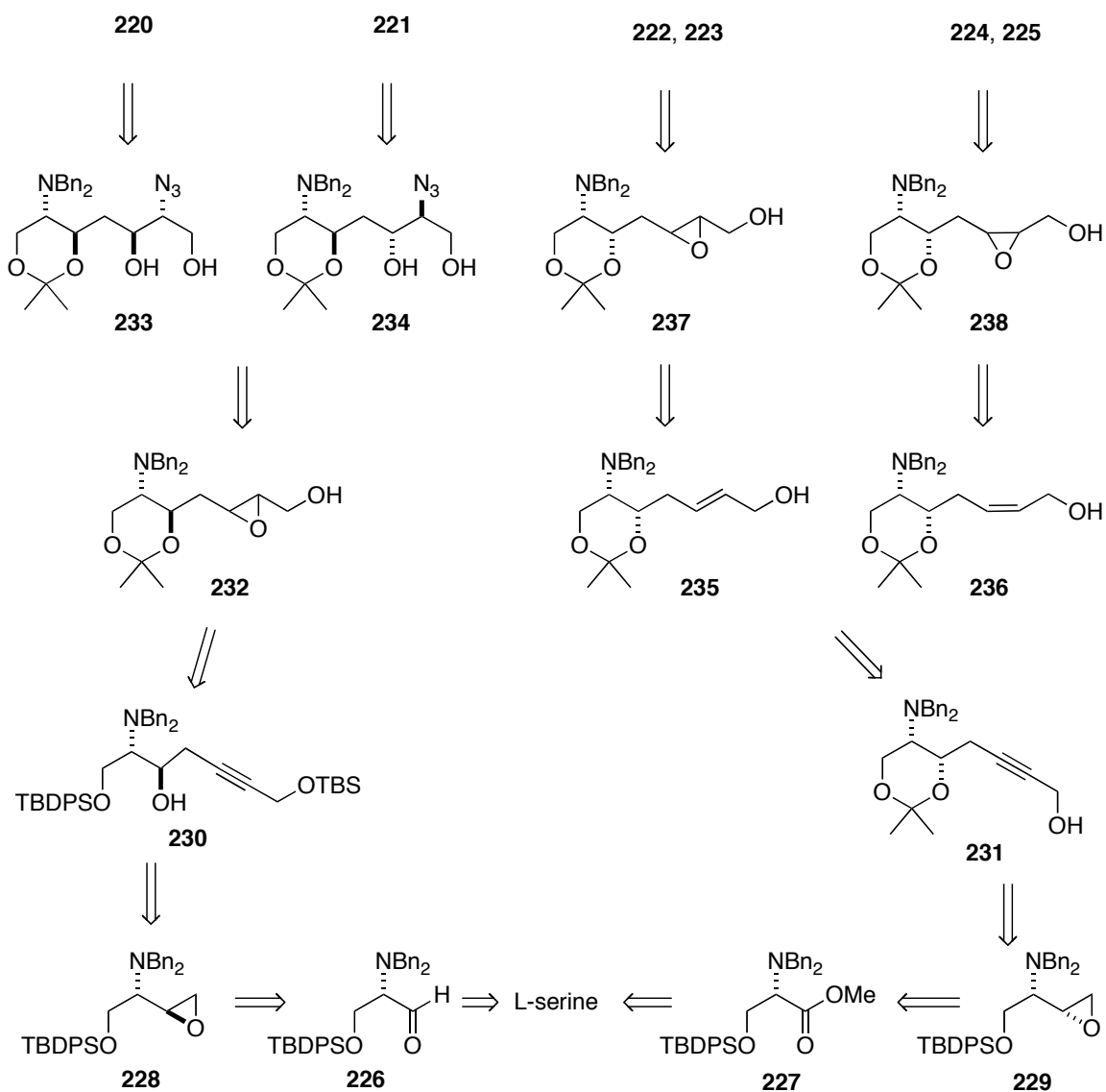


Figure 2.1: Model Compounds for NMR Comparisons.

2.3.1. Retrosynthesis

The retrosynthetic analysis for the model compounds **220-225** (Scheme 2.4) reveal key considerations including an ability to generate all possible configurations as well as the ability to adapt the synthesis to a total synthesis of **1**. The synthesis of the

models was envisioned starting from L-serine. Protected L-serine¹³ derived compounds **226** and **227** would be elaborated to epoxides **228** and **229** respectively using the method of Concellón.^{14,15} While L-serine set the absolute configuration at C10 epoxides **228** and **229** made available both configurations at C11. Chain extension of epoxides **228** and **229** using an anion derived from a protected propargyl alcohol¹⁶ would give alkynes **230** and **231** respectively. Control of the configuration at C13 and C14 would now be determined by *E* versus *Z* selectivity of alkyne reduction and subsequent epoxidation of the resultant alkenes. Alkyne **230** would be reduced to the *E* alkene and epoxidized to give a mixture of epoxides **232**. These epoxides would be separated and subjected to nitrogen insertion using Miyashita's boron-directed azide opening of epoxy alcohols to give compounds **233** and **234**.^{17,18} Deprotection of **233** and **234** would provide models **220** and **221** conversely. Alkyne **231** would be selectively reduced to either alkene **235** or **236**. Epoxidation of alkenes **235** and **236** would give two mixtures of epoxides **237** and **238**. Separation of these mixtures of epoxides, nitrogen insertion as before and deprotection would provide models **222** through **225**.

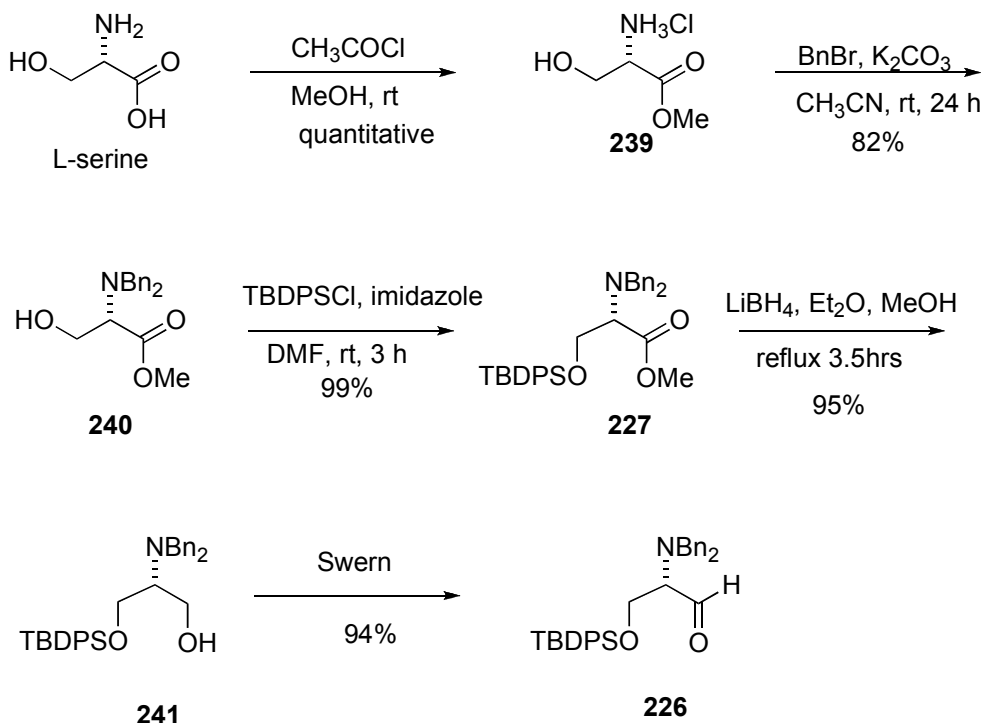


Scheme 2.4: Retrosynthetic analysis of model compounds.

2.3.2. Synthesis of Model Compounds

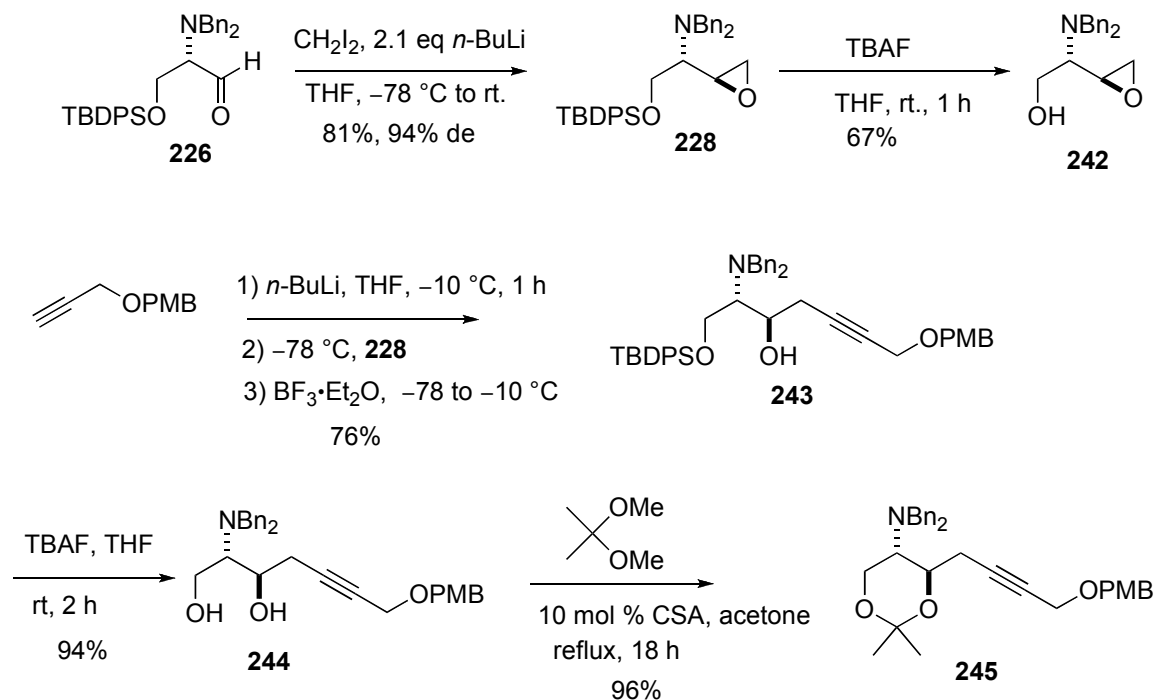
Synthesis of known compounds **226** and **227** began with L-serine and used a combination of methods from Dondoni,¹³ Hulme,¹⁹ and Laieb²⁰ (Scheme 2.5). Aldehyde **226** was elaborated to compound **228** using the method of Concellón (Scheme 2.6).¹⁴ Iodomethyl lithium addition to the aldehyde followed by in situ intra-molecular

displacement of iodide gave epoxide **228**. Initial anion addition followed Felkin-Anh transition state²¹ giving *anti* addition epoxide **228** (94% de by NMR). Treatment of epoxide **228** with TBAF gave known alcohol **242**,¹⁴ thereby verifying the relative stereochemistry for **228**.



Scheme 2.5: Synthesis of aldehyde **226** and ester **227**.

Carbon chain extension was initially accomplished by addition of lithiated PMB protected propargyl alcohol²² to epoxide **228** to give alkyne **243** (Scheme 2.6). Removal of the TBDPS group (TBAF, THF, rt) gave diol **244**, which was protected as the acetonide (dimethoxypropane, acetone, CSA, reflux).



Scheme 2.6: Synthesis of epoxide **228** and carbon chain extension.

Removal of the PMB protecting group from alkyne **245** proved to be more difficult than expected. Most standard removal techniques²³ resulted in removal of the benzyls from the nitrogen (Table 2.1). Although some reactions gave respectable yields, the procedures looked irreproducible. Because of these difficulties the use of PMB as a protecting group for the propargyl alcohol was abandoned. Use of a TBS protected propargyl alcohol proved to be more effective.²⁴ Scheme 2.7 shows the revised carbon chain extension sequence. The propargyl anion addition formed **230** with 71% yield. Removal of the silyl protecting groups (TBAF, THF, $-20\text{ }^\circ\text{C}$) gave triol **247** in 97% yield. Reprotection gave propargyl alcohol **246**. The configuration at stereocenters C13 and C14 would now be determined by stereoselectivity of the alkyne reduction and subsequent epoxidation. Reduction of this alkyne (Red-Al, Et_2O)²⁵ gave alkene **249** in 78% yield.

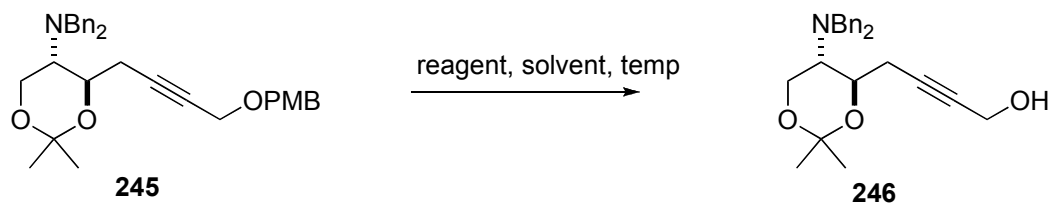


Table 2.1: Removal of PMB protecting group

| Entry # | Solvent | Reagents | Rxn. Temp (°C) | Time (min) | Notes | Yield % |
|---------|---|---|----------------|------------|---------|---------|
| 1 | CH ₂ Cl ₂ /H ₂ O | 5 eq DDQ | 24 | 300 | -NBn | 0 |
| 2 | CH ₂ Cl ₂ /H ₂ O | 1.0 eq DDQ | 24 | 40 | | 7 |
| 3 | CH ₂ Cl ₂ | 1) 2.5 eq TMSOTf; 2) Et ₃ N; 3) TBAF | 24 | 90 | | trace |
| 4 | CH ₂ Cl ₂ | 1) BSTFA; 2) Et ₃ N; 3) TBAF | 24 | 120 | no rxn. | 0 |
| 5 | CH ₂ Cl ₂ | 1) 2.5 eq TMSOTf; 2) Et ₃ N; 3) TBAF | 24 | 45 | | 60 |
| 6 | CH ₂ Cl ₂ | 1) 2.2 eq TMSOTf; 2) Et ₃ N; 3) TBAF | 0 to 24 | 45 | | 50 |
| 7 | CH ₂ Cl ₂ | 3 eq MgBr ₂ •Et ₂ O | 24 | 180 | no rxn. | 0 |
| 8 | DMF | 3 eq MgBr ₂ •Et ₂ O | 24 | 180 | no rxn. | 0 |
| 9 | CH ₂ Cl ₂ | 1) 2.3 eq TMSOTf; 2) Et ₃ N; 3) HF/pyr | 24 | 60 | | 42 |
| 10 | CH ₂ Cl ₂ | 1) 2.2 eq TMSOTf; 2) NaOH | 24 | 60 | dec | 0 |
| 11 | CH ₂ Cl ₂ | 1) 1.2 eq TMSOTf; 2) Et ₃ N; 3) HF/pyr | 24 | 60 | | 70 |
| 12 | ACN/H ₂ O | 3 eq CAN | 0 | 60 | -NBn | 0 |
| 13 | CH ₂ Cl ₂ | 1) 1.1 eq TMSOTf; 2) Et ₃ N; 3) HF/pyr | 24 | 60 | dec | 0 |

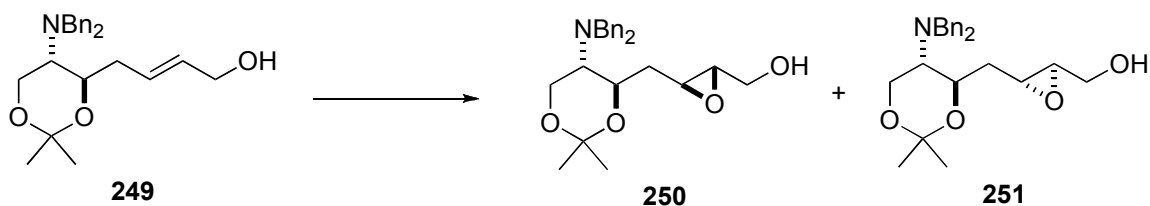
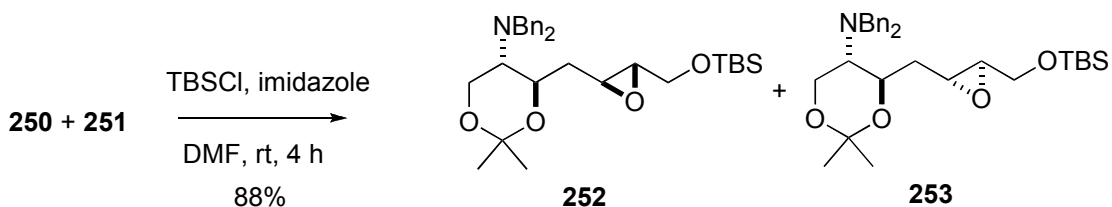


Table 2.2: Epoxidation of **249**.

| Entry # | Reagent | Temp (°C) | Time (h) | Ratio (250:251) | Recovered Starting Material (%) | Yield (%) |
|---------|----------------|------------|----------|--------------------------|---------------------------------|-----------|
| 1 | SAE (+DET) | -20 | 16 | 1.0 : 5.9 | 36 | 44 |
| 2 | SAE (-DET) | -20 | 16 | na | >90 | no rxn |
| 3 | <i>m</i> -CPBA | -20 | 1.25 | 1.7 : 1.0 | 0 | 80 |
| 4 | SAE(+DET) | -20 to -10 | 63 | 1.0 : 5.0 | 38 | 29 |
| 5 | SAE (-DET) | -20 to -10 | 63 | 1.0 : 3.0 | 38 | 14 |
| 6 | <i>m</i> -CPBA | 0 | 1 | 1.0 : 1.0 | 0 | 59 |
| 7 | <i>m</i> -CPBA | rt | 4 min | 1.8 : 1.0 | 0 | 69 |

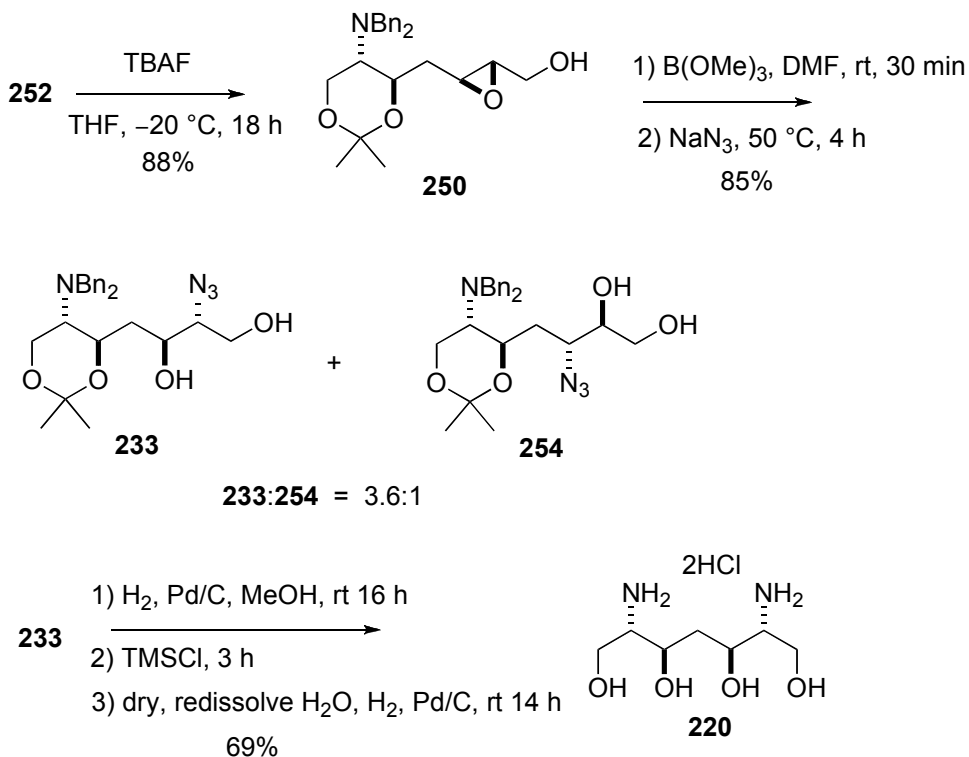
Separation of the diastereomers was achieved after protection (TBSCl, imidazole, DMF) to give **252** and **253** (Scheme 2.8).



Scheme 2.8: Synthesis of separable epoxides **252** and **253**.

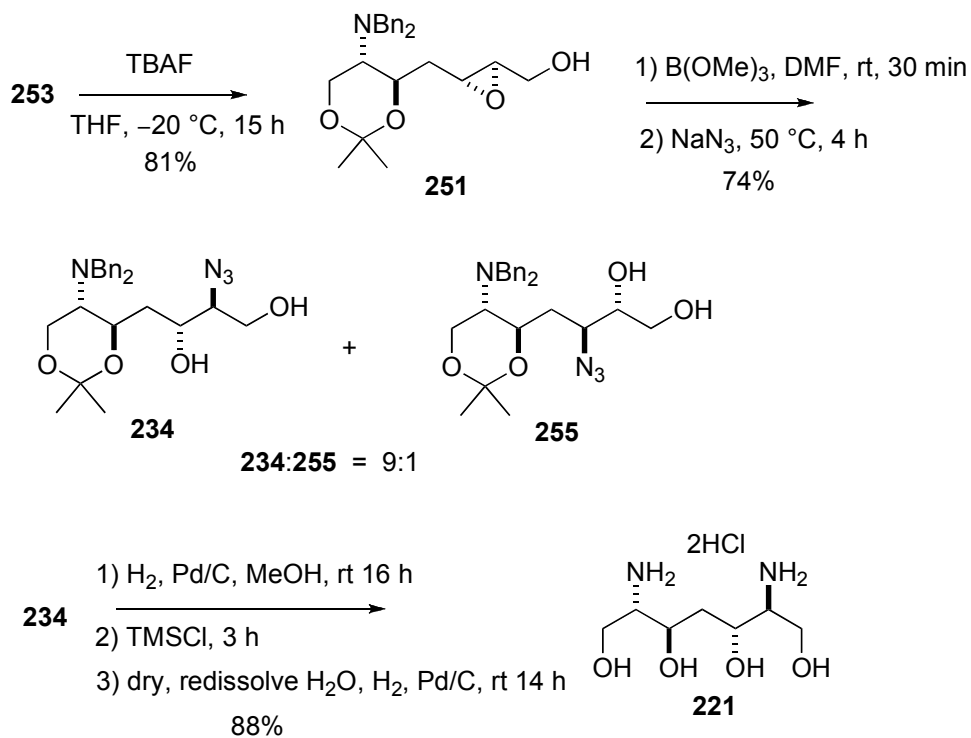
Compound **252** was deprotected (TBAF, THF) to give alcohol **250** (Scheme 2.9), which was subjected to Miyashita's boron-directed azide opening of this epoxide (B(OMe)_3 , NaN_3 , DMF) to give compounds **233** and **254** in 85% yield. The ratio of the desired azide **233** to undesired **254** was 3.6 to 1 respectively, which was comparable to

the ratios seen by Miyashita.¹⁷ Global deprotection of **233** gave model **220** as the hydrochloride salt in 69% yield.



Scheme 2.9: Synthesis of model **220**.

Model **221** was synthesized in a similar manner starting with deprotection of azide **253** (TBAF, THF) (Scheme 2.10). Azide opening provided desired azide **234** and unwanted azide **255** in 9:1 ratio, respectively, with an overall yield of 74%. Global deprotection of **234** gave model **221** in 88% yield. Assignment of the relative stereochemistry across the CH₂ group in the case of **220** and **221**, and thereby correlation of the intermediates back to the respective epoxides, was made based on NMR analysis. ¹H NMR chemical shifts of the internal CH₂ protons in *meso* **220** showed diastereotopicity and magnetic inequivalence while the C₂ symmetric **221** showed



Scheme 2.10: Synthesis of model **221**.

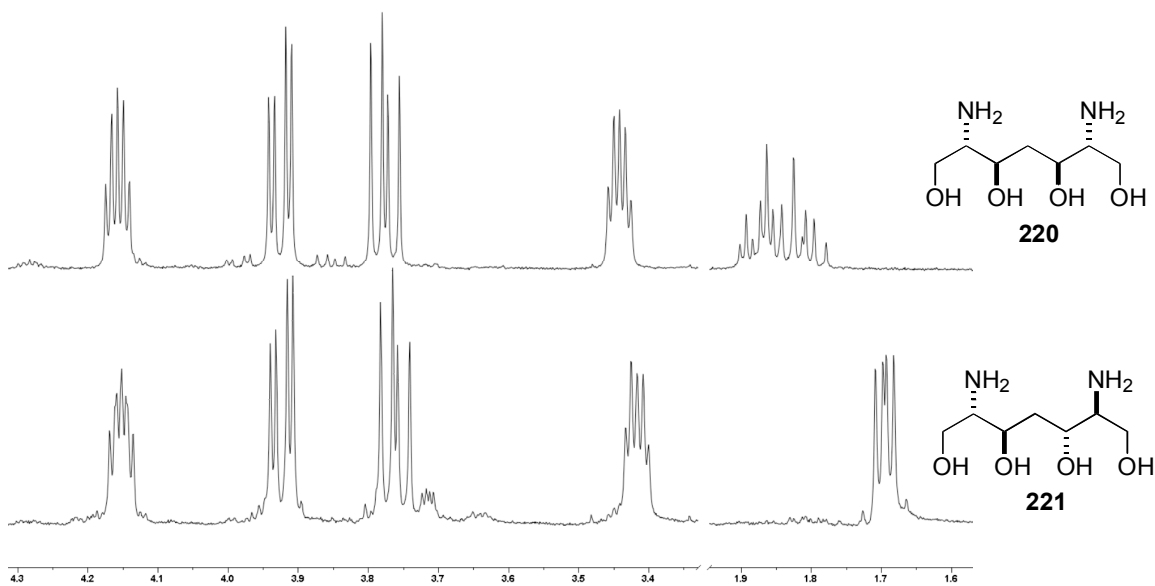
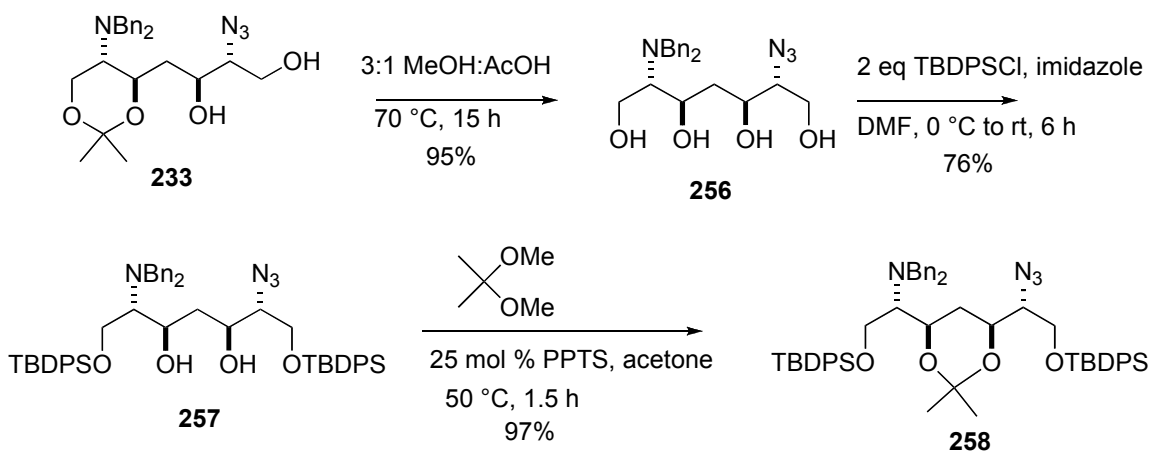


Figure 2.2: ^1H NMR (500 MHz, D_2O) of compounds **220** and **221**.

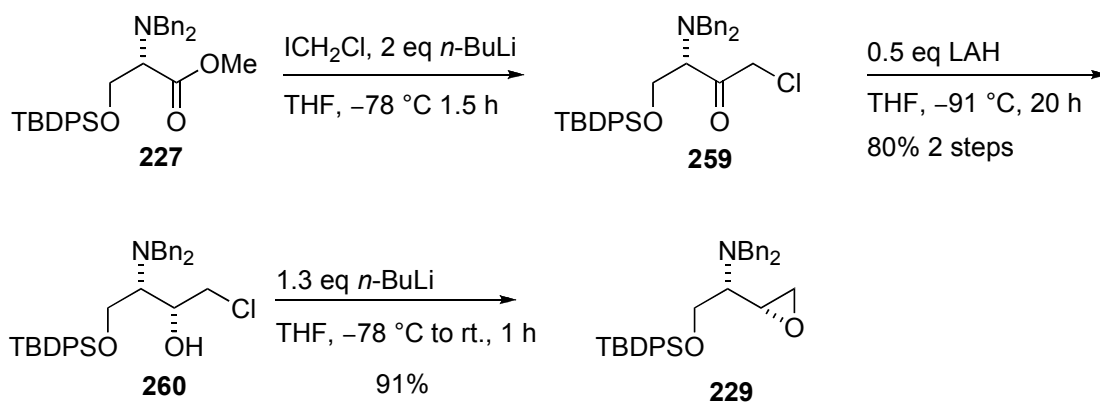
enantiotopicity and magnetic inequivalence (protons furthest up field in Figure 2.2).

Further verification of stereochemical assignments of **220** and **221** were made as shown in Scheme 2.11. Azide **233** was treated with acetic acid methanol to give tetraol **257** (95% yield), selectively protected with TBDPSCI (76% yield) and an internal acetonide installed (97% yield) to give **258**. The ^1H NMR spectrum of **258** showed the expected large diaxial vicinal couplings (δ 4.14, ddd, J 10.4, 8.0, 2.4 Hz; δ 3.83, ddd, J = 11.6, 6.4, 2.4 Hz) for a *syn*-4,6-disubstituted 1,3-dioxane and large ^{13}C chemical shift differences for the *gem* CH_3 signals of the isopropylidene group (δ 29.9, q; 19.7, q).²⁸



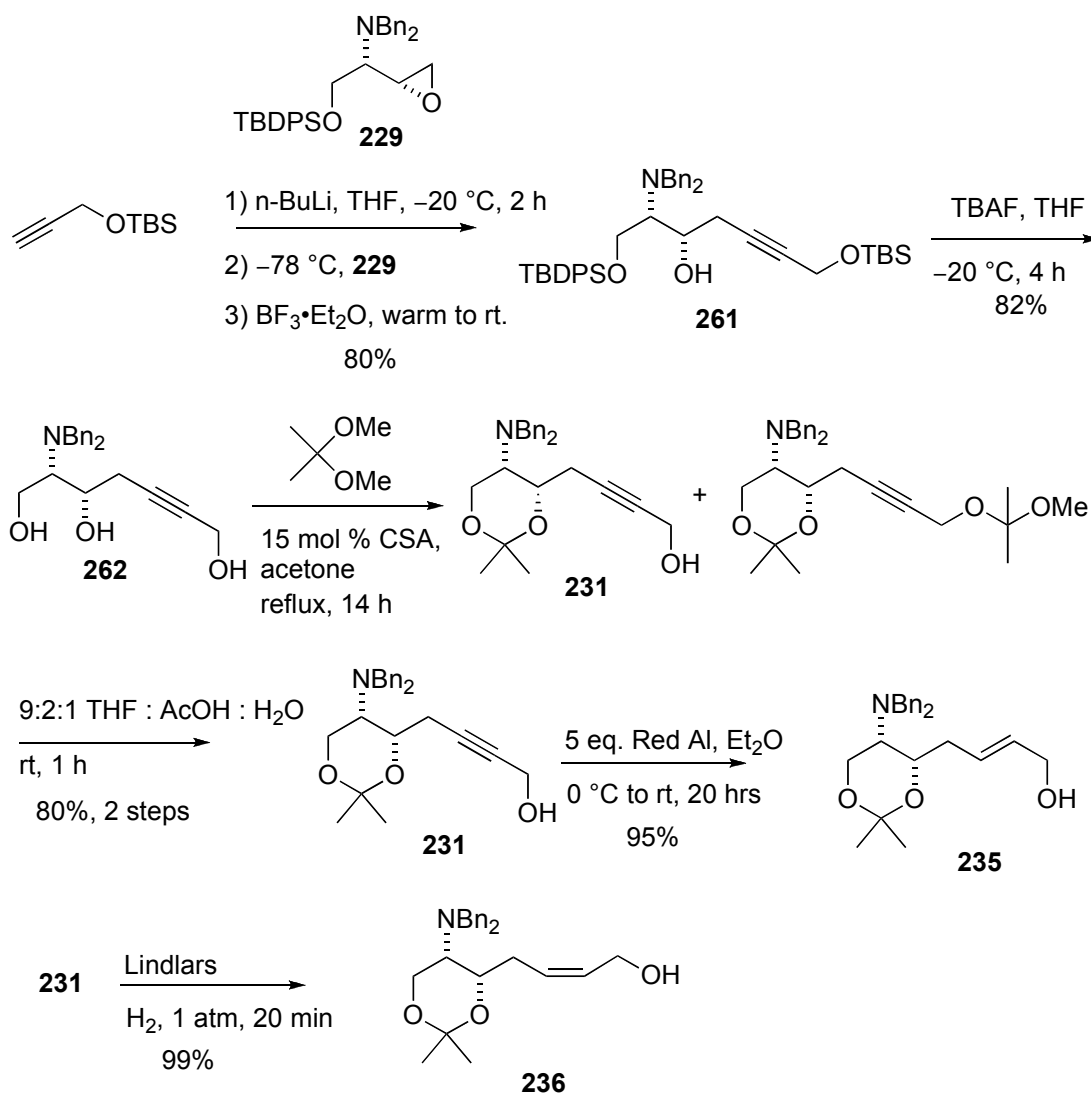
Scheme 2.11: Synthesis of internal acetonide **258**.

The remaining four models were synthesized from serine-derived ester **227** starting with the synthesis of epoxide **229** using the method of Concellón¹⁴ as shown in Scheme 2.12. Addition of chloromethyl lithium to **227** at -78°C gave ketone **259** which was reduced at -91°C with LAH to give crystalline alcohol **260** in 80% yield over two steps. Epoxide formation (*n*-BuLi, THF, -78°C to rt) gave **229** in 91% yield.



Scheme 2.12: Synthesis of epoxide **229**.

Epoxide **229** was treated with O-TBS-protected propargyl lithium to form **261** with 80% yield (Scheme 2.13). Removal of the silyl protecting groups (TBAF, THF, $-20\text{ }^\circ\text{C}$) gave triol **262** (82% yield) and reprotection gave propargyl alcohol **231**. Reduction of alcohol **231** using Red-Al gave the *E*-alkene **235** in 95% yield while reduction using Lindlar's catalyst²⁹ gave *Z*-alkene **236** in 99% yield.



Scheme 2.13: Synthesis of allylic alcohols **235** and **236**.

Epoxidation of allylic alcohol **235** was investigated under various conditions (Table 2.3).³⁰⁻³² None of the reagents gave good yields. This was most likely due to instability of the formed epoxides. The epoxides formed were also inseparable requiring that they be carried forward as mixture (Scheme 2.14).

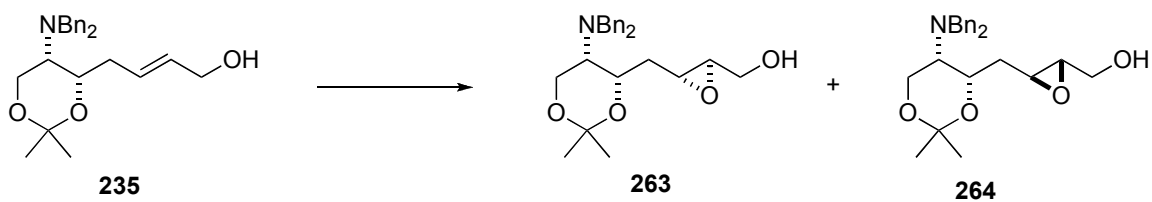
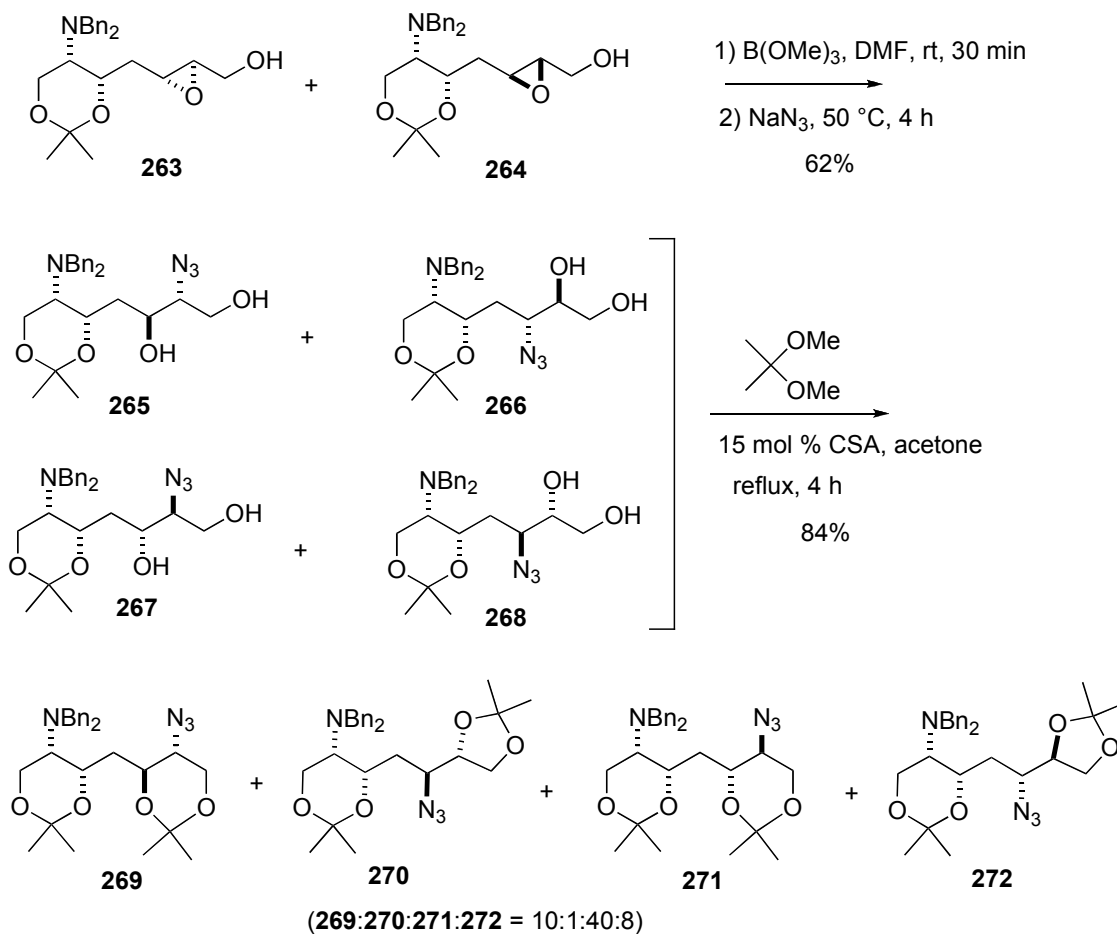


Table 2.3: Epoxidation of **235**.

| Entry # | Reagent | Temp (°C) | Time (h) | Ratio (263:264) | Recovered Starting Material (%) | Yield (%) |
|---------|--|-----------|----------|-----------------|---------------------------------|-----------|
| 1 | <i>m</i> -CPBA | 0 | 1 | 7:1 | 0 | 35 |
| 2 | <i>m</i> -CPBA w/NaHCO ₃ | 0 | 1 | 7:1 | 0 | 34 |
| 3 | <i>m</i> -CPBA | 40 | 5 min | 2:1 | 37 | 31 |
| 4 | MTO | rt | 1 | 1:1 | 24 | 14 |
| 5 | VOacac | 0 | 1 | 1:1 | 10 | 11 |
| 6 | dimethyldioxirane | 0 | 1 | na | 0 | dec. |

Azide opening of the epoxide mixture was performed as before giving an inseparable mixture of compounds **265** through **268**. Conversion to acetonides gave separable compounds **269**, **270**, **271**, and **272** in a ratio of 10:1:40:8, respectively.



Scheme 2.14: Synthesis of azides **269** through **272**.

Fortuitously compound **271** was crystalline and an X-ray of this compound assigned the relative stereochemistry (Figure 2.3).

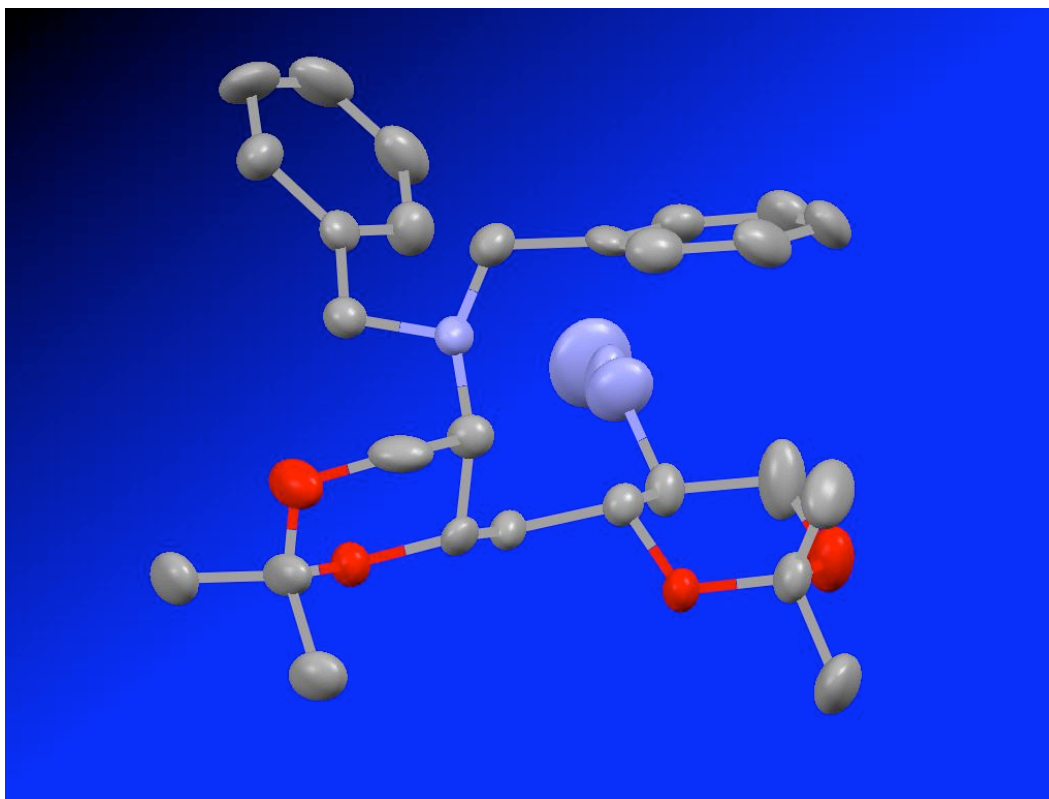
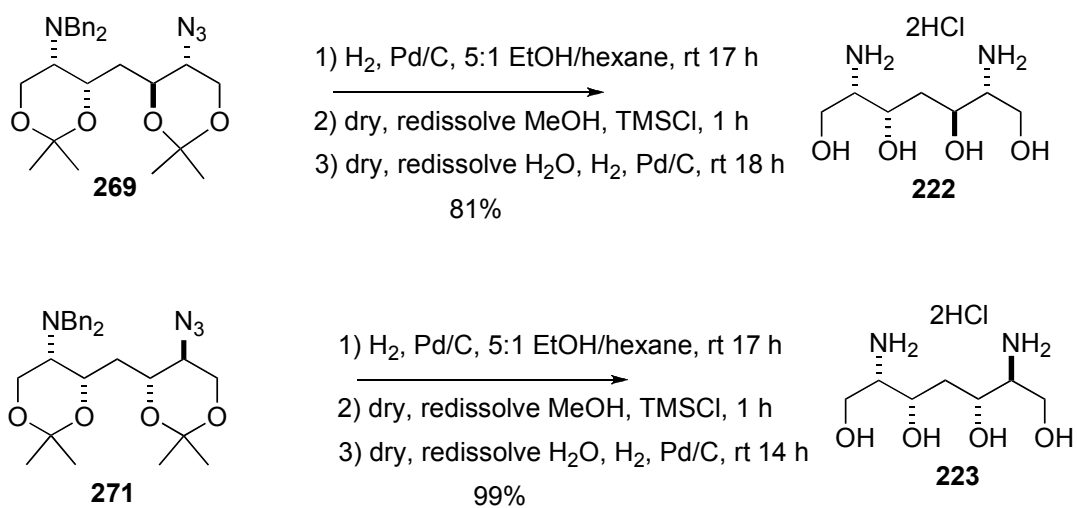


Figure 2.3: X-ray crystal structure of compound **271**.

Deprotection of compounds **269** and **271** provided models **222** and **223** respectively (Scheme 2.15).



Scheme 2.15: Synthesis of models **222** and **223**.

Epoxidation of alcohol **236** was evaluated with two different epoxidation reagents with both showing diastereoselectivity favoring **273** with a *syn* relationship across the CH₂ group (Table 2.4).

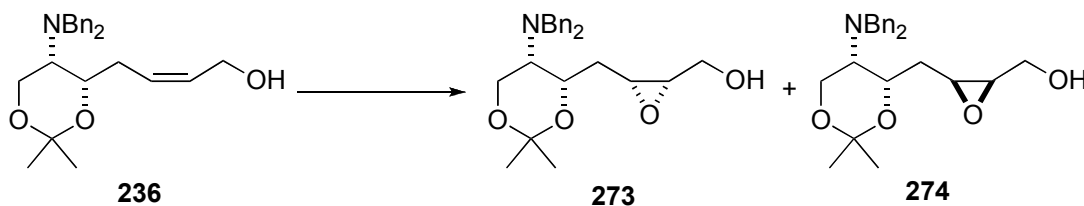
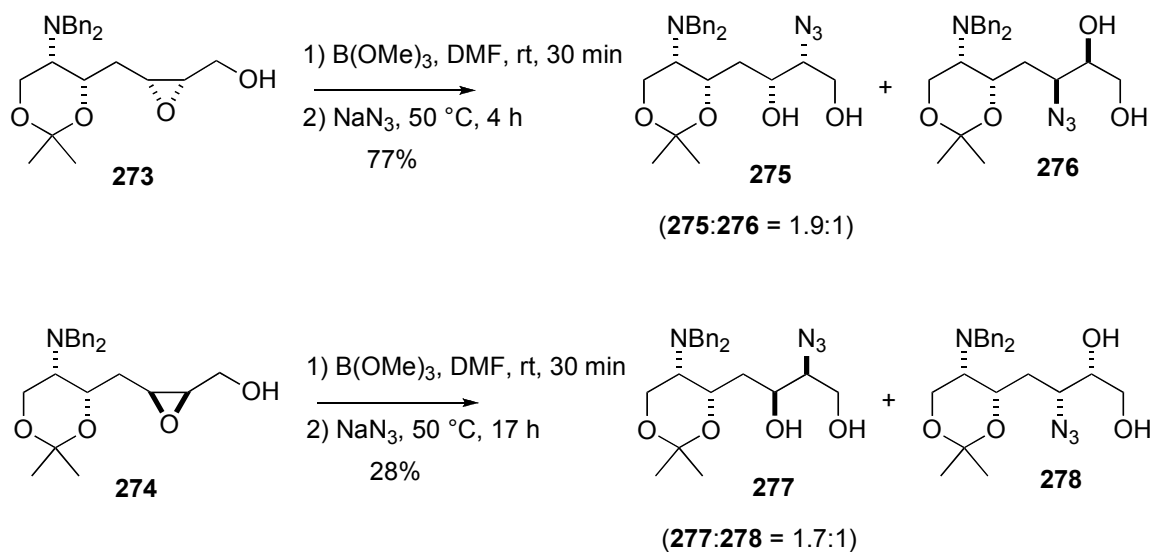


Table 2.4: Epoxidation of **236**.

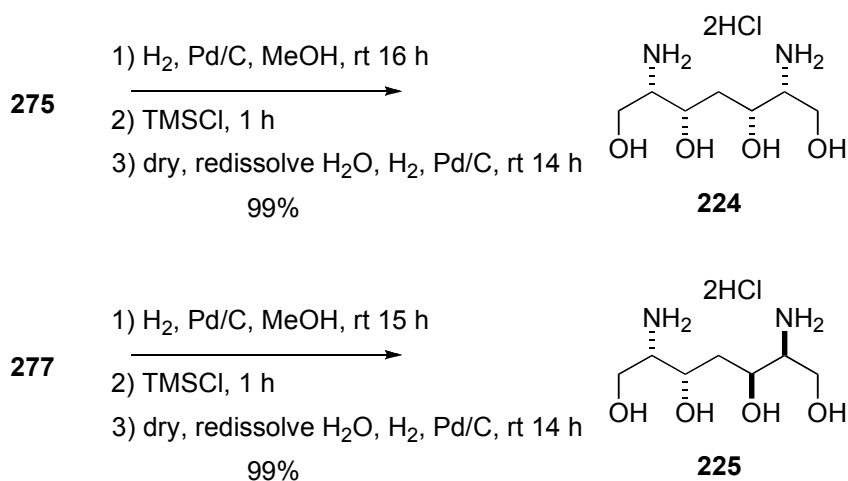
| Entry # | Reagent | Temp (°C) | Time (h) | Ratio (273:274) | Recovered Starting Material (%) | Yield (%) |
|---------|----------------|-----------|----------|-----------------|---------------------------------|-----------|
| 1 | <i>m</i> -CPBA | 0 | 0.66 | 25:1 | 0 | 48 |
| 2 | MTO | 25 | 4 | 1.8:1 | 22 | 24 |

In the case of *m*-CPBA there was almost no *anti* compound formed and yields were low as was seen previously. In order to obtain compound **274**, MTO was required for epoxidation. Nitrogen insertion was again accomplished using Miyashita's method (Scheme 2.16). Miyashita found the regioselectivity for this reaction to be poor when using *cis* epoxides and this was the case for both epoxides **273** and **274** as was the case where desired products **275** and **277** showed diastereomeric ratios of 2:1.¹⁷



Scheme 2.16: Synthesis of azides **275** through **278**.

Deprotection of compounds **275** and **277** provided models **224** and **225** respectively (Scheme 2.17).



Scheme 2.17: Synthesis of models **224** and **225**.

Assignment of relative configuration for models **224** and **225** was again accomplished using analysis of the ^1H NMR. Compound **225** showed no anisotropy for

the enantiotopic CH₂ protons while the corresponding ¹H NMR signals in **224** showed different chemical shifts.

2.3.3. Pair-wise ¹³C NMR Chemical Shift Difference Analysis

Pair-wise ¹³C NMR chemical shift comparisons of the model compounds with authentic Zwittermicin A were made at 50-100 mM concentrations in D₂O with 0.5% acetonitrile.³³ An evaluation of the concentration dependence on ¹³C NMR chemical shifts with model **224** showed little change from 50-250 mM (Figure 2.4).

$\Delta\delta$ (δ_c NMR at 53 mM - δ_c NMR at x mM)

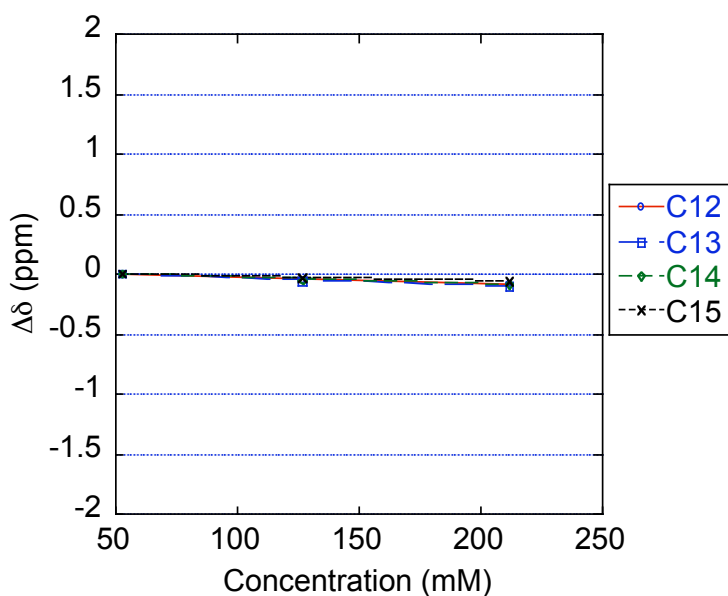


Figure 2.4: ¹³C chemical shift dependence on concentration.

Pairwise comparisons of ¹³C NMR chemical shifts of zwittermicin A with the model compounds are shown in Figure 2.5. Model **211** is the only compound with a close match to **1** for every carbon except C9, which is the point of difference between the model and **1**.

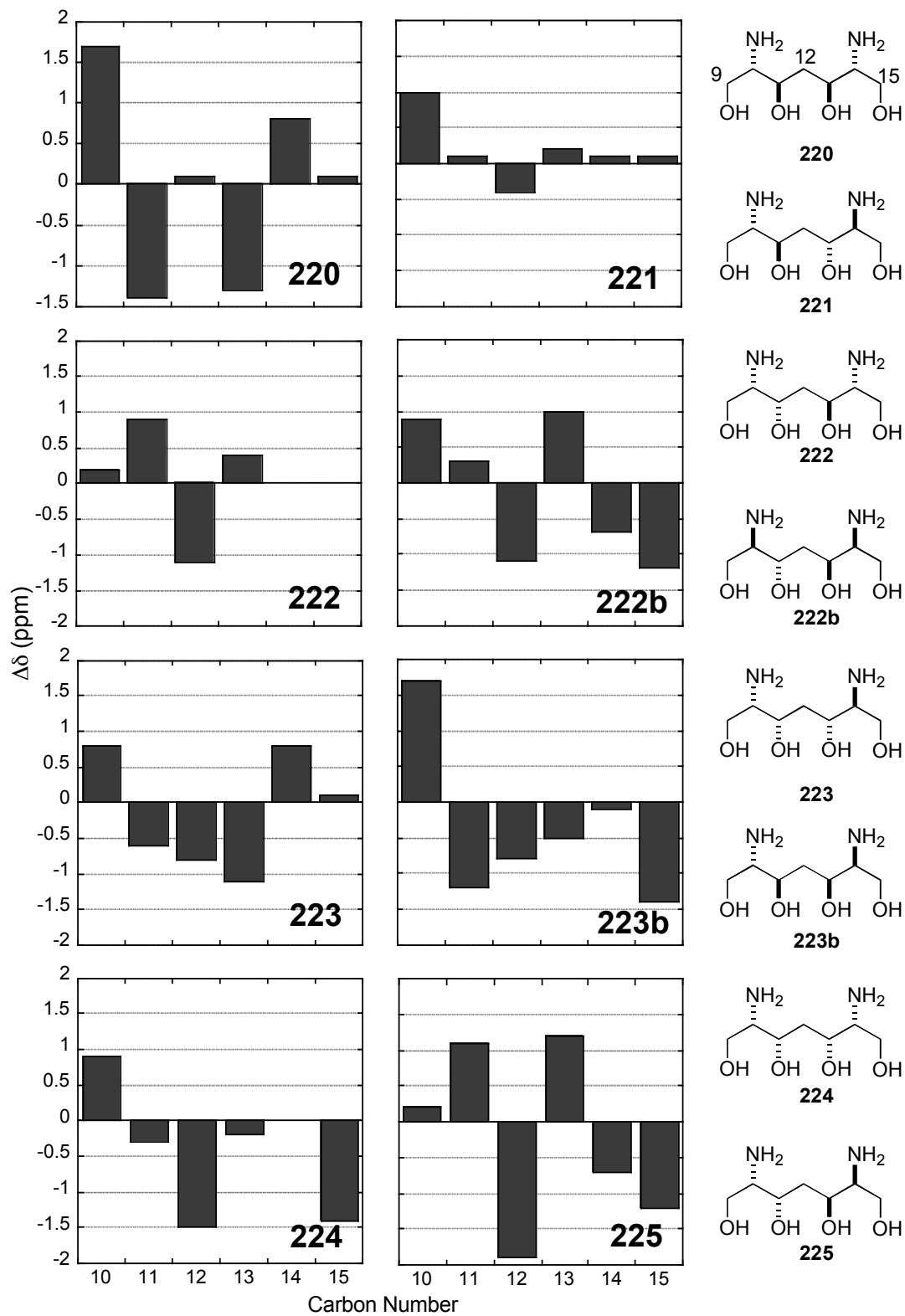


Figure 2.5: Pairwise ^{13}C NMR NMR chemical shifts of models 220-225 with 1.

2.4. Configuration of (+)-Zwittermicin A

It has been assumed that the biosynthesis of **1** starts with L-serine with the assumption that the C14 configuration is also L. There was some concern as to the possibility of epimerization at the C8 position due to the strongly basic conditions under which the degradation had been conducted.¹ However, spontaneous conversion of **1** under neutral condition in D₂O (4 °C, 30 days) to **7** that showed no deuterium exchange at H8. Since epimerization at C8 would require enolization and reprotonation, we may safely assume that **7** retains the C8 configuration assigned to **1** by Clardy.¹

In conclusion the configuration of zwittermicin A is (4*S*,8*S*,9*R*,10*R*,11*R*,13*R*,14*S*) based on the integrated approach using synthesis and pairwise comparisons with model compounds, Marfey's analysis, and published data. Figure 2.6 shows the tentatively proposed structure of zwittermicin A (**279**).

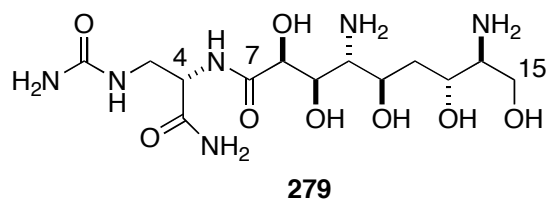


Figure 2.6: Tentatively proposed configuration of zwittermicin A (**279**).

2.5. Acknowledgments

This work is in part a reprint of published results: Rogers, E. W.; Molinski, T. F. Asymmetric Synthesis of Diastereomeric Diaminoheptanetetraols. A Proposal for the Configuration of (+)-Zwittermicin A. *Org. Lett.* **2007**, *9*, 437.

2.6. References

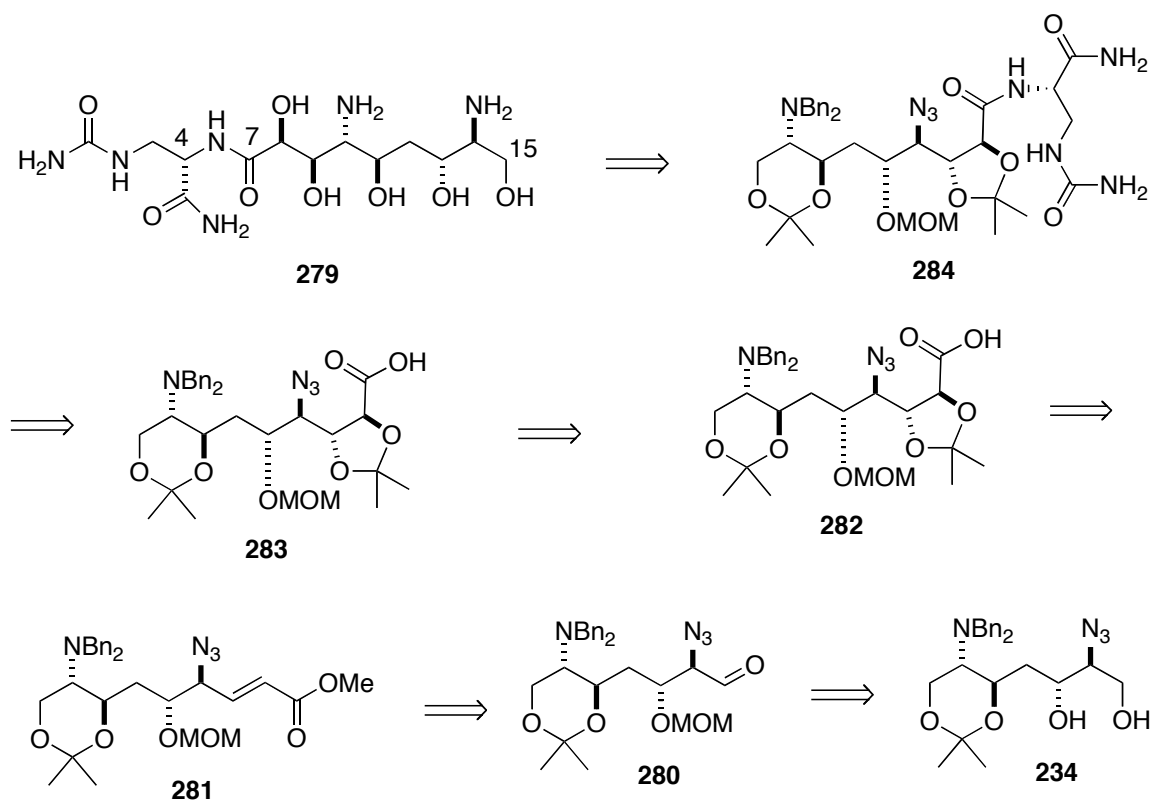
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Chapter 3 Synthesis of (-)-Zwittermicin A

3.1. Retrosynthesis

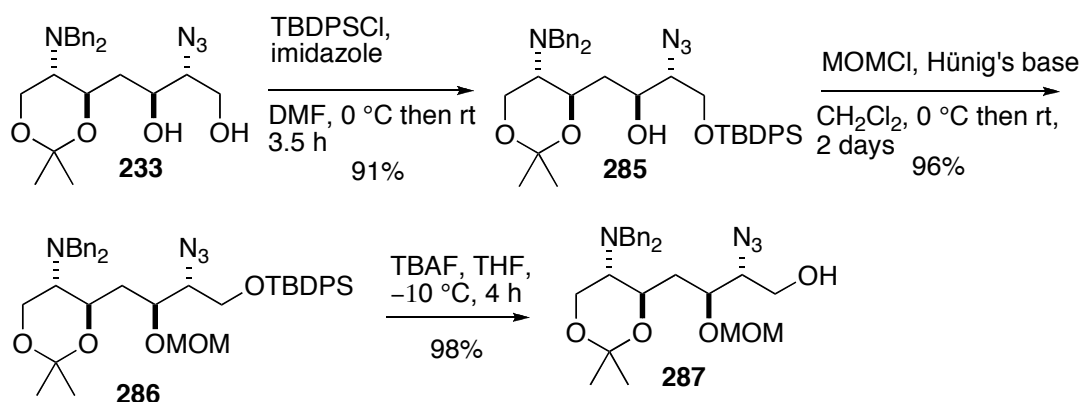
Synthesis of the proposed structure for proposed zwittermicin A (**279**) was envisioned as starting with **234**, previously made for model synthesis (Scheme 3.1). Key considerations for this synthesis included the carbon-carbon bond forming step and control of stereochemistry as well as appropriate protecting groups that could be readily removed in the final deprotection. MOM protection^{1,2} for the secondary alcohol prior to carbon-carbon bond forming was envisioned as being suitable for the final global deprotection. Chain elongation was to be accomplished by HWE^{3,4} with dihydroxylation⁵ providing the *cis*-diol. Protection of the *cis*-diol as an acetal⁶ would set the stage for eventual amide bond formation. Finally global deprotection using hydrogenation under acidic conditions would provide **279**. Use of acidic conditions for the deprotection would serve the twofold purpose of removing acid labile protecting groups as well as preventing decomposition of zwittermicin A known to occur under basic conditions.



Scheme 3.1: Retrosynthetic analysis of **279**.

3.2. Evaluation of Strategy Using Model Compound

The protecting group strategy for synthesis of **279** was evaluated on compound **233** in order to “scout” the synthetic route that would be used on **234** (Scheme 3.2). The primary hydroxyl in **233** was protected with a TBDPS⁷ followed by MOM^{1,8} protection of the secondary hydroxyl and removal of the TBDPS group⁹ to give **287** in 86% overall yield.



Scheme 3.2: Synthesis of alcohol **287**.

Attempts to oxidize alcohol **287** to aldehyde **289** were unsuccessful and significant byproducts from *beta*-elimination were observed (Table 3.1).¹⁰ In the case of the Swern oxidation reaction there was *beta*-elimination as one side product. Dess-Martin oxidation¹¹⁻¹³ gave a mixture of aldehydes and attempts to purify this mixture by chromatography resulted in decomposition.

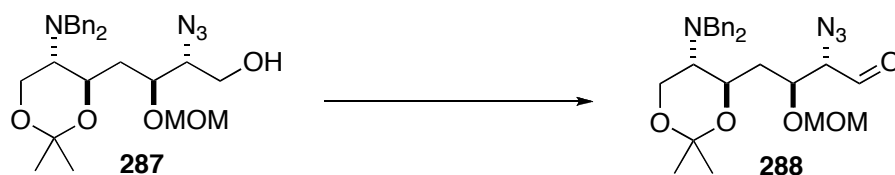


Table 3.1: Attempted oxidation of alcohol **287**.

| Entry # | Reagent | Temp (°C) | Time (min) | Recovered 287 (%) | Yield (%) |
|---------|-----------------------------|-----------|------------|--------------------------|-----------|
| 1 | Swern oxidation | -78 | 90 | 0 | dec. |
| 2 | DMP ^a w/pyridine | rt | 90 | 0 | dec. |
| 3 | DMP ^a w/pyridine | rt | 30 | 0 | dec. |

^a Dess-Martin periodane oxidation

It was suspected that the MOM group was a factor in the decomposition of **288**. Consequently attempts were made to protect the secondary hydroxyl of **285** as a benzyl ether (Table 3.2).¹⁴⁻¹⁷

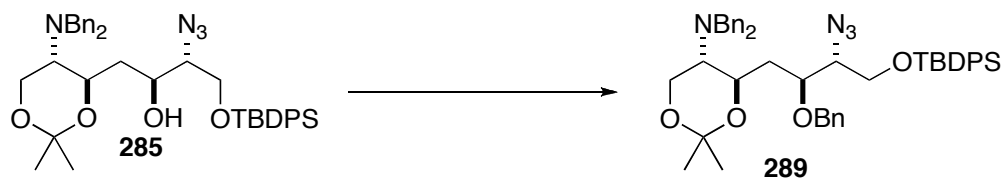
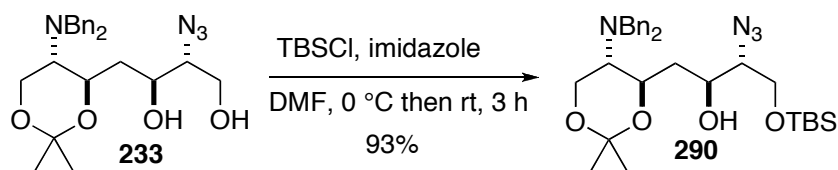


Table 3.2: Attempted protection of alcohol **285**.

| Entry # | Reagent | Solvent | Temp (°C) | Time (h) | Recovered 285 (%) | Yield (%) |
|---------|--|-----------------|-----------|----------|--------------------------|-----------|
| 1 | BnO(CO)Cl, TMSOTf | DCM | 0 to rt | 24 | 0 | dec. |
| 2 | BnO(CO)Cl, TFMSA | DCM | 0 to rt | 20 | >90 | 0 |
| 3 | BnO(CO)Cl, BF ₃ •Et ₂ O | toluene | 0 to rt | 24 | >95 | 0 |
| 4 | BnO(CO)Cl, TfOH | toluene | -30 to 50 | 24 | 0 | dec |
| 5 | BnO(CO)Cl, TfOH | cyclohexane/DCM | 0 to rt | 24 | >90 | 0 |
| 6 | NaH, BnBr, | DMF | 0 to rt | 72 | >80 | 0 |
| 7 | NaH, BnBr, <i>n</i> -Bu ₄ NI | DMF | 0 to 50 | 72 | ~30 | dec |
| 8 | <i>n</i> -BuLi, BnBr, <i>n</i> -Bu ₄ NI | THF | -20 to 50 | 24 | >90 | 0 |
| 9 | Ag ₂ O, BnBr | toluene | rt to 50 | 72 | >80 | 0 |

Despite numerous attempts, benzylation of alcohol **285** gave no discrete product.

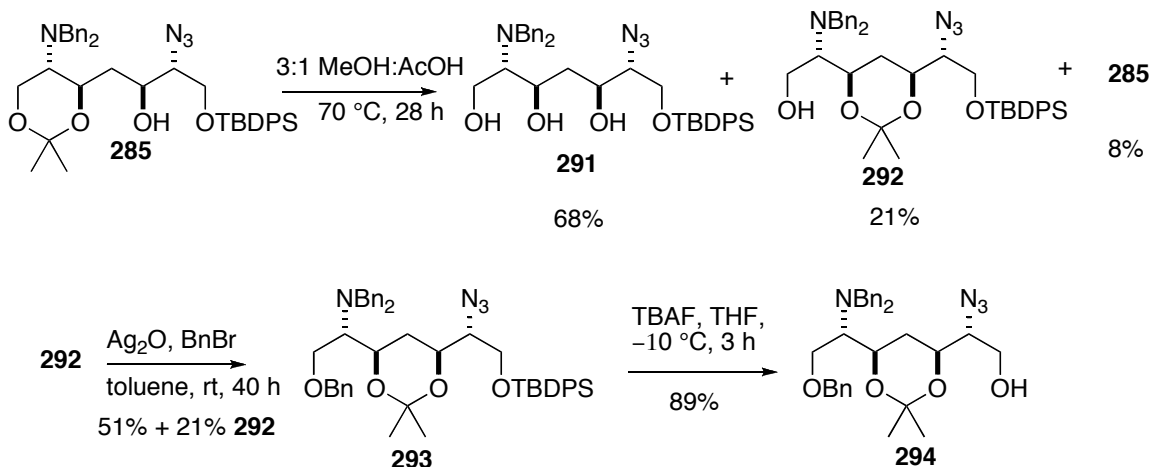
Interchange of the TBDPS group in **285** with the smaller TBS group (Scheme 3.3) did not change the outcome of benzylation attempts (data not shown).



Scheme 3.3: Synthesis of alcohol **290**.

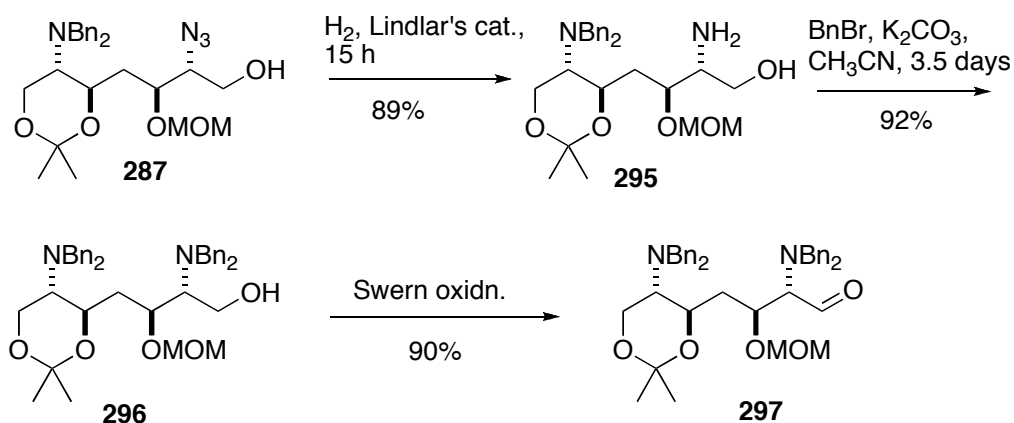
To circumvent the problem of benzyl protection of the secondary hydroxyl the acetonide of **285** was removed with the intention of placing the benzyl on the primary hydroxyl and relocating the acetonide on the internal secondary hydroxyls. Fortunately, when removal of the acetonide was stopped before completion, a mixture of acetonides

was obtained that included the internal acetonide **292** (Scheme 3.4). Benzylation of **292** then proceeded smoothly and removal of the TBDPS group gave alcohol **294**.



Scheme 3.4: Synthesis of alcohol **294**.

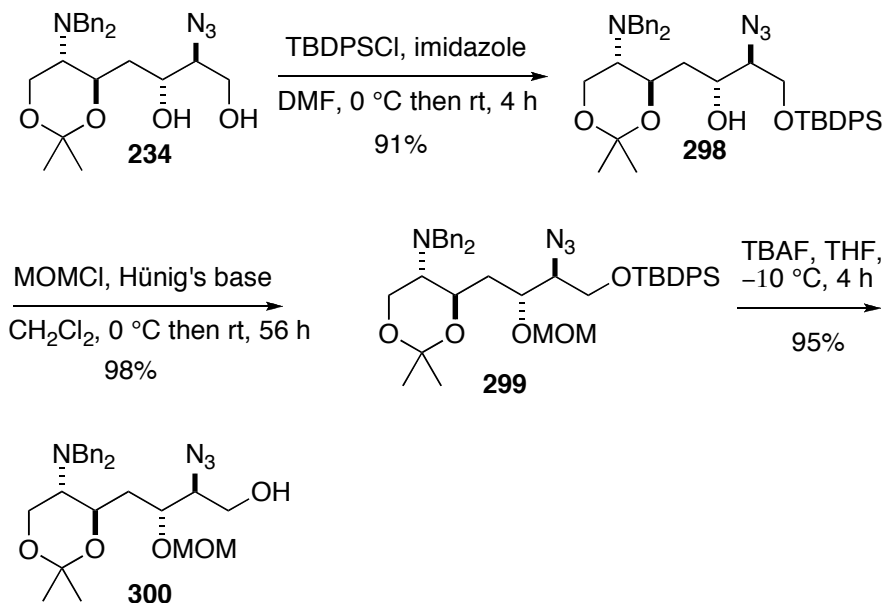
Unfortunately attempted oxidation of alcohol **294** under Swern conditions gave only decomposition products. This result indicated that the problems with oxidation probably resided with the presence of the azido group. There are few examples of *alpha*-azido aldehydes in the literature and therefore little guidance on compatibility with Swern conditions.¹⁹⁻²² Consequently it was necessary to convert the azido group to a more stable amine equivalent. Compound **287** was converted to the corresponding primary amine²³ which was protected as an *N,N*-dibenzylamino group.²⁴ Subsequent oxidation under Swern conditions smoothly gave aldehyde **297** in good yield (Scheme 3.5).



Scheme 3.5: Synthesis of aldehyde **297**.

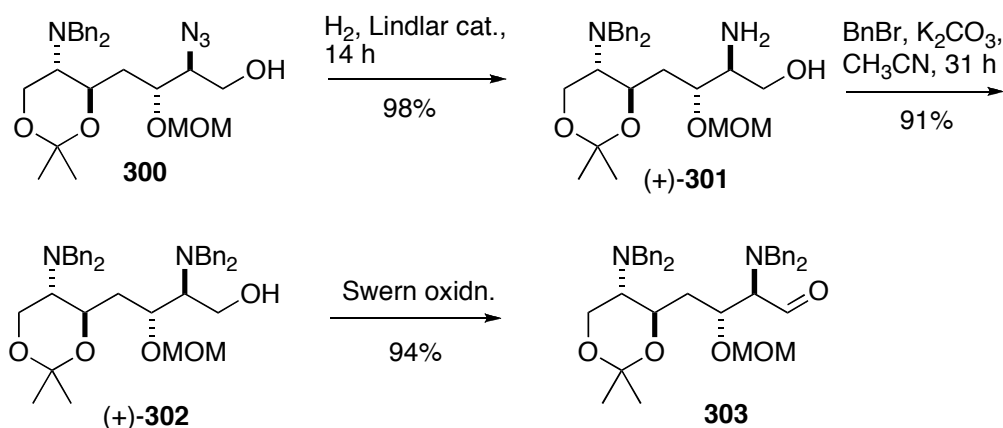
3.2.1. Synthesis of Aldehyde 303

Having a viable route to a stable aldehyde for carbon-carbon bond forming, work commenced on diol **234** having correct configuration for synthesis of **297**. Conversion to primary alcohol **300** proceeded in excellent yield (Scheme 3.6).



Scheme 3.6: Synthesis of alcohol **300**.

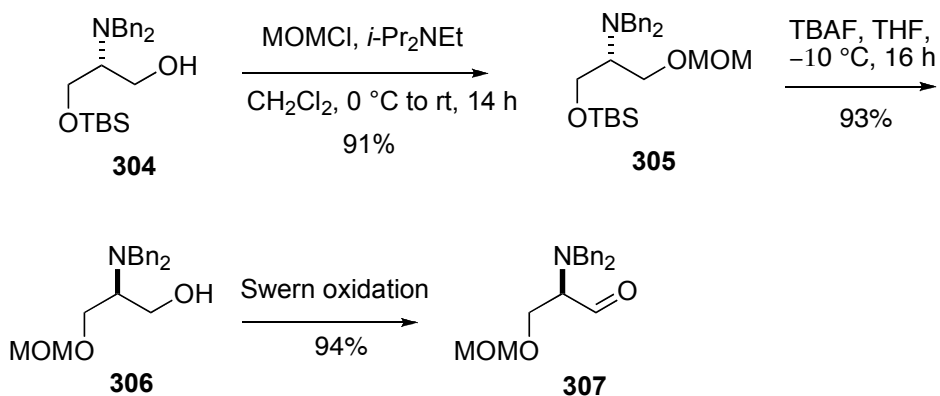
Synthesis of aldehyde **303** followed the same procedures as that used for synthesis of **297** (Scheme 3.7). Higher yields for the steps leading to aldehyde **303** were obtained which was attributed to optimization of conditions.



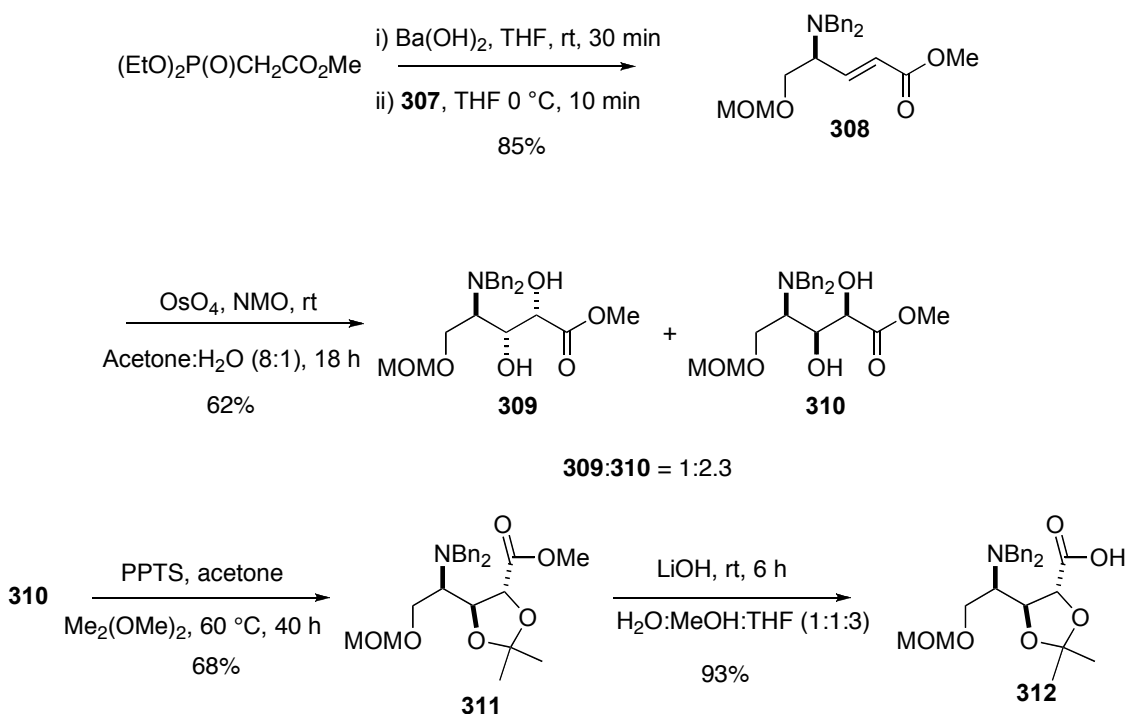
Scheme 3.7: Synthesis of aldehyde **303**.

3.3. Evaluation of Final Synthetic Steps Using Model Compound

To evaluate the carbon-carbon bond forming and subsequent steps without committing valuable synthetic intermediates, it was decided to synthesize a representative model of aldehyde **303**. Preparation of the model started with MOM protection of known alcohol **304**²⁵ followed by removal of the TBS group and Swern oxidation to give aldehyde **307** in 80% overall yield (Scheme 3.8). Both aldehydes **303** and **307** share similar features including MOM and *N,N*-dibenzyl protecting groups and are of the same absolute configuration.



Scheme 3.8: Synthesis of model aldehyde **307**.



Scheme 3.9: Synthesis of acid **312**.

Carbon-carbon bond forming using HWE with barium hydroxide²⁶ as a mild base provided alkene **308** in 85% yield (Scheme 3.9). Dihydroxylation²⁷ provided diols **309** and **310** in 62% yield. The ratio of the diols was 1:2.3. Literature precedent would imply that the undesired all *syn* configuration would be the major compound.²⁸ In order to

verify this, the major compound was taken forward with the intention to eventually form a cyclic six-membered lactone. Installation of an acetonide gave ester **311** (68% yield) followed by conversion to acid **312** (98% yield). Fortunately acid **312** proved to be crystalline and an X-ray structure verified the relative configuration of this compound (Figure 3.1).

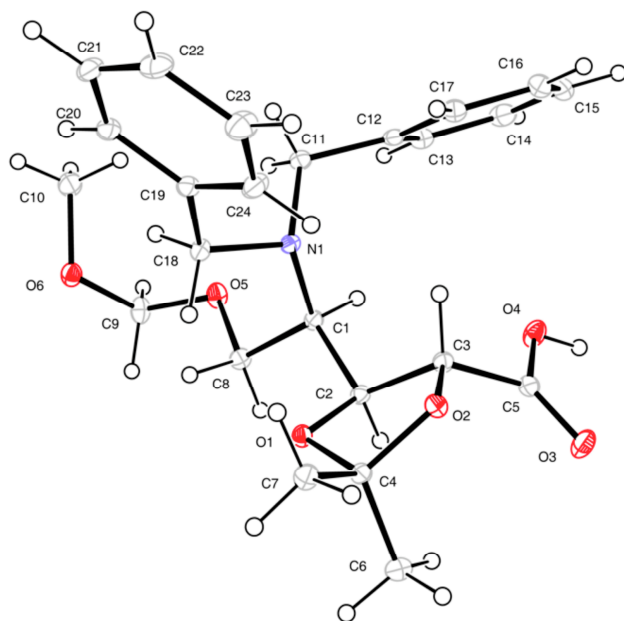


Figure 3.1: X-ray crystal structure of acid **312**.

In attempts to reverse the diastereoselectivity of the dihydroxylation reaction, variation of conditions were explored however no improvement was seen without significant reduction of yield (Table 3.3).²⁹⁻³¹

Failure of OsO₄ mediated dihydroxylation undermined chain extension by HWE reaction. Addition of an enolate equivalent to aldehyde **307** seemed the next best step. Serine-derived aldehyde **307** was converted to methyl ester **313** and used to evaluate aldol addition with methyl benzyloxyacetate (**88**) (Scheme 3.10).³²

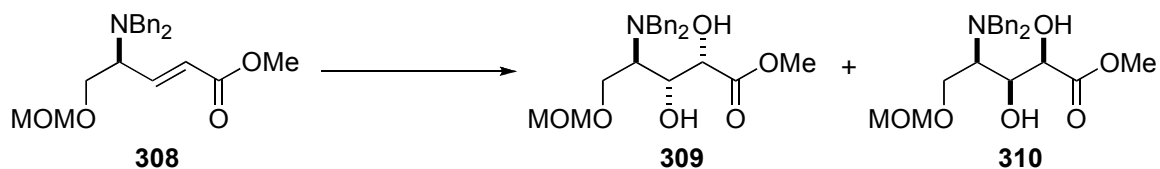
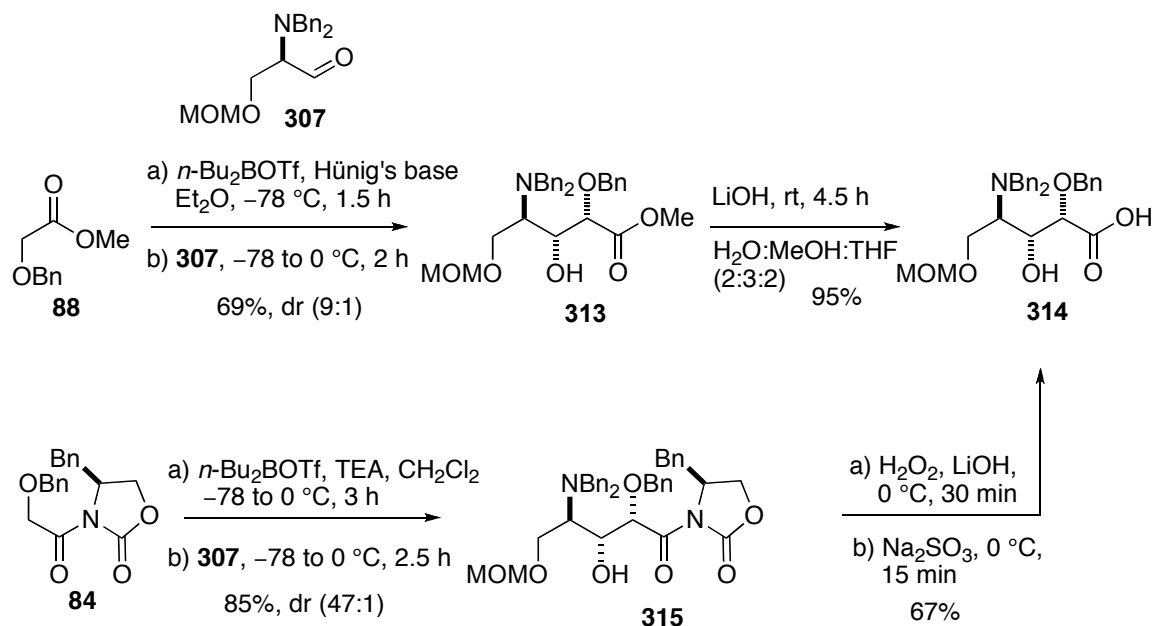


Table 3.3: Dihydroxylation of alkene **308**.

| Entry # | OsO ₄ equiv. | NMO equiv. | Conc. (M) | Solvent | Temp (°C) | Time (h) | Ratio 309:310 | Yield (%) | Recovered 308 (%) |
|----------------|-------------------------|------------|-----------|------------------------------|-----------|----------|----------------------|-----------|--------------------------|
| 1 | 0.15 | 2.3 | 0.2 | 8:1 acetone:H ₂ O | rt | 18 | 1.0:2.3 | 62 | 0 |
| 2 | 0.15 | 2.3 | 0.17 | 2:1 DCM: <i>t</i> -butanol | rt | 168 | 1.0:1.6 | 40 | 0 |
| 3 | 2.1 | 0 | 0.04 | <i>t</i> -butanol | rt | 240 | 1.7:1.0 | 6 | 10 |
| 4 | 0.25 | 2.3 | 0.2 | DCM | rt | 24 | 1.0:1.5 | 38 | 0 |
| 5 ^a | 1.2 | 0 | 0.18 | 8:1 acetone:H ₂ O | rt | 48 | 4.6:1.0 | 3 | 16 |
| 6 ^a | 1.2 | 0 | 0.18 | DCM | rt | 48 | 1.0:2.1 | 19 | 69 |
| 7 | 1.2 | 0 | 0.18 | pyridine | rt | 2.5 | 1.7:1.0 | 2 | 0 |

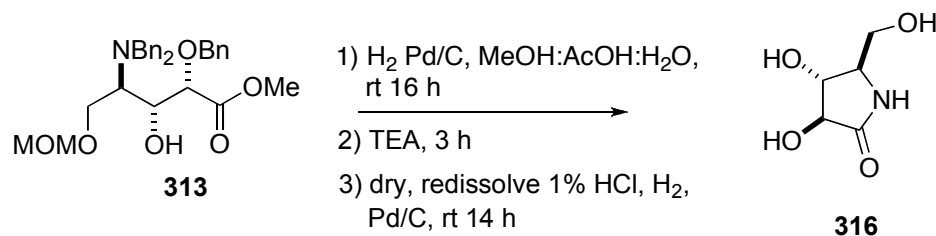
^a Ratio based on NMR.

Diastereoselectivity was high (9:1) but overall yield was only 69%. Conversion to the acid **314** was straightforward with a yield of 95%.³³ Use of Evan's chiral glycolate equivalent³⁴ (**84**) gave a better yield (85%) and diastereoselectivity (47:1). Conversion of **315** to the acid was poor yielding (67%) but has not been optimized.³⁵



Scheme 3.10: Synthesis of acid **314**.

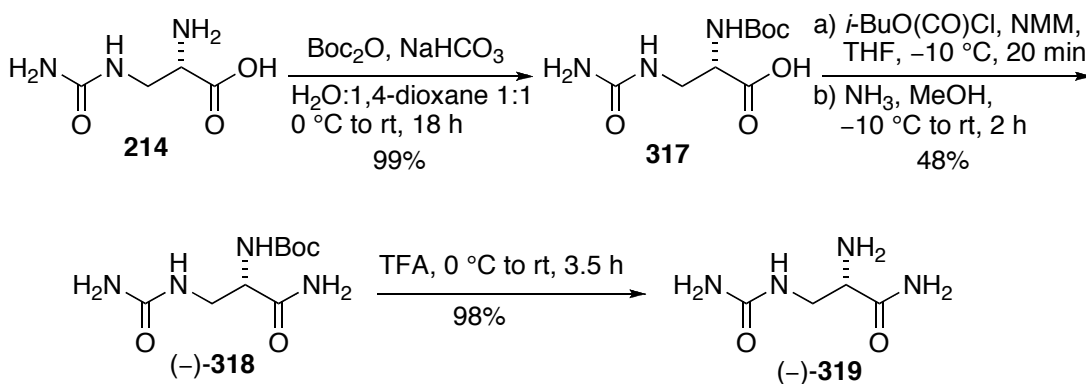
To verify the configuration of the glycolate addition product, compound **313** was converted into the cyclic lactam **316** (Scheme 3.11). However the reaction was difficult, not optimized and no yield was calculated. The ^1H NMR chemical shifts and coupling constants of known **316** matched literature values³⁶ exactly. This verified the configuration of **313**, **314** and **315**.



Scheme 3.11: Synthesis of lactam **316**.

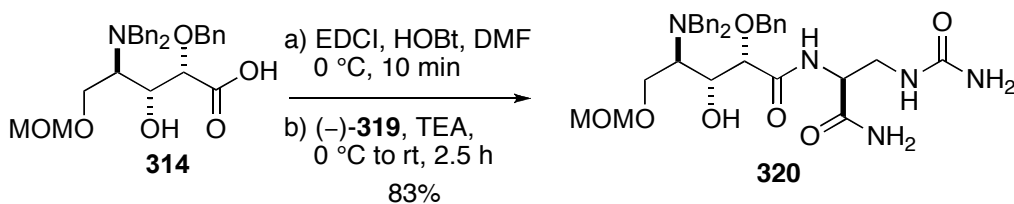
The C1-C5 portion of **279** was synthesized from the naturally occurring amino acid (–)-albizziin (**214**) to give α -aminoamide (–)-**319** (Scheme 3.12). Although both

compounds **317** and (–)-**318** are known compounds, the synthesis of these proved to be difficult. Literature procedure for synthesis of (–)-**318** called for use of ethyl chloroformate and triethylamine followed by treatment with concentrated ammonium hydroxide.³⁷ This procedure gave poor yield that did not improve with minor modifications. Therefore the procedure was modified by substitution of isobutyl chloroformate and *N*-methylmorpholine (NMM) followed by treatment with 2M ammonia in methanol which gave an acceptable yield of 48%.³⁸ The Boc group was removed using TFA to give (–)-**319** in 93% yield (94% ee by Marfey's analysis).³⁹



Scheme 3.12: Synthesis of α -aminoamide (–)-**319**.

Acid **314** was coupled to amine (–)-**319** using standard procedures⁴⁰ to provide **320** in 83% yield (Scheme 3.13).

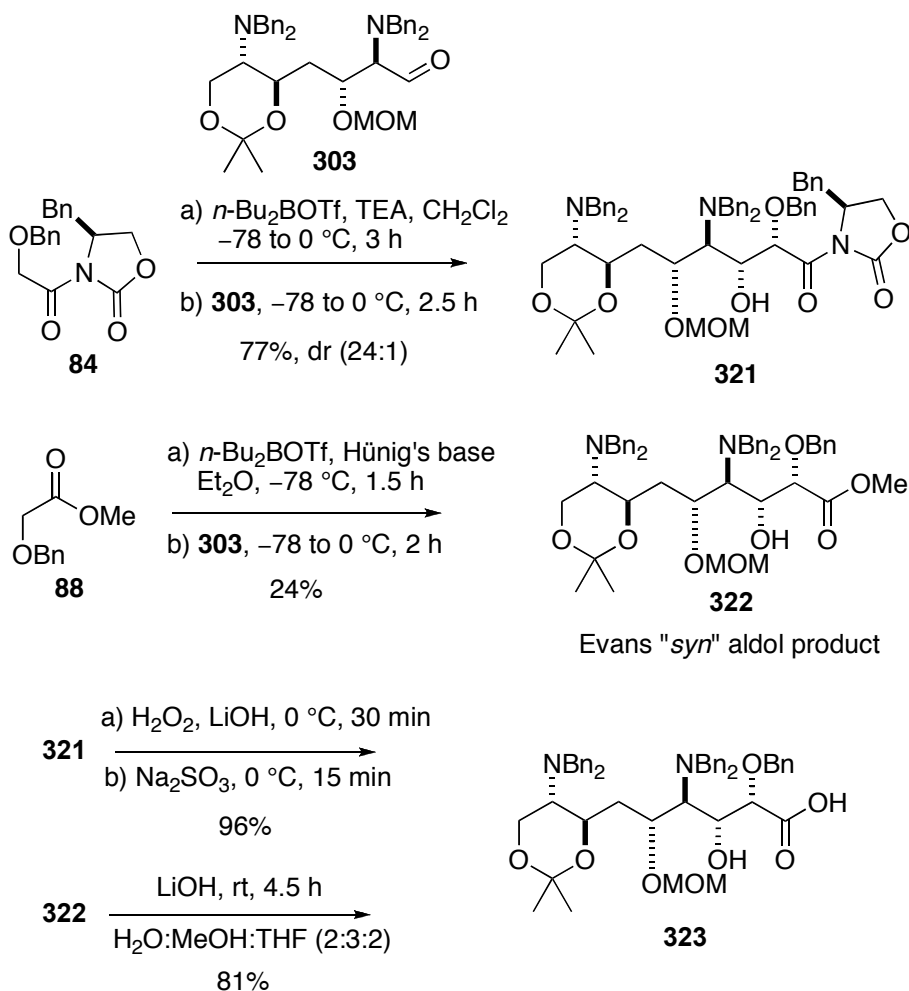


Scheme 3.13: Synthesis of amide **320**.

Successful synthesis of **320** validated the sequence for satisfactory completion of **279**.

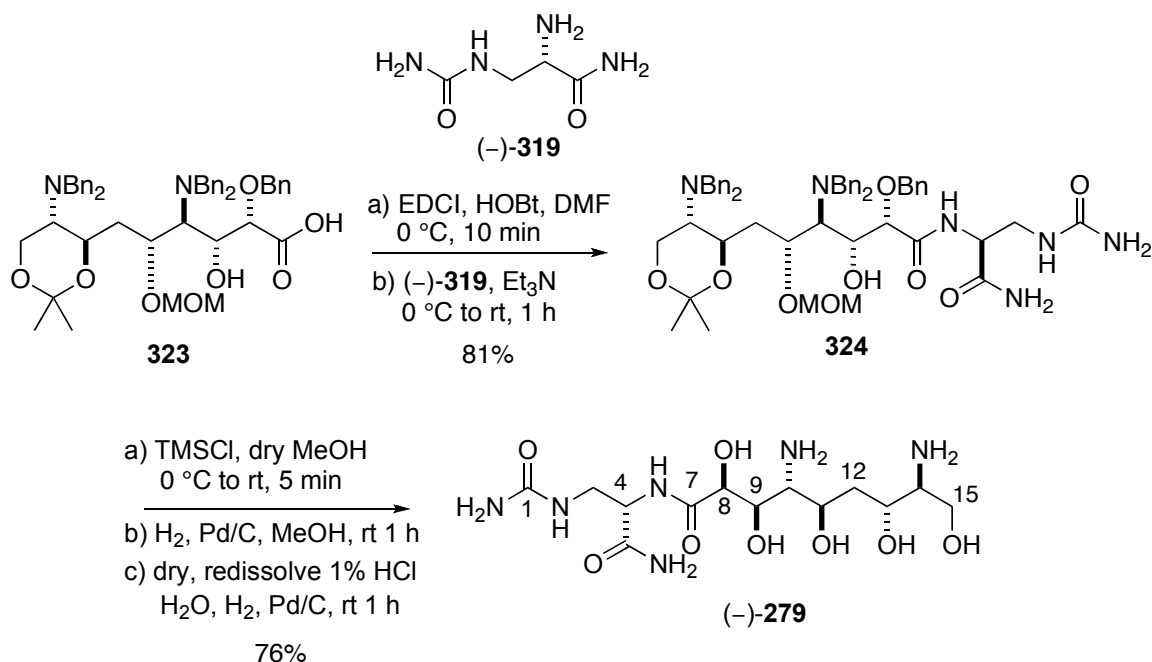
3.4. Synthesis of Proposed (+)-Zwittermicin A Structure

Carbon chain extension of **303** followed the same procedure used for the model compound to give **321** in an acceptable yield of 77% (Scheme 3.14) and excellent diastereoselectivity (24:1). Verification of correct configuration in **321** was obtained by repeating the aldol addition with methyl benzyloxyacetate to give **322** with the expected “Evans-*syn*” configuration. Yield for this reaction was very low (24%), possibly a consequence of the use of aged boron triflate (~2 weeks), the maximum recommended time for usefulness of this reagent.⁴¹ Conversion of **321** and **322** to acid **323** proceeded smoothly in 96% and 81% yields respectively.



Scheme 3.14: Synthesis of acid **323**.

Coupling of **323** to (–)-**319** gave amide **324** in 81% yield, which was globally deprotected to give the proposed zwittermicin A structure (–)-**279** (Scheme 3.15). Purification of highly polar (–)-**279** was not trivial. After development of HPLC conditions, (–)-**279** was finally separated on a Synergi Hydro-RP column using very high aqueous mobile phase (1.3% MeOH and 0.1% TFA in water).



Scheme 3.15: Synthesis of proposed zwittermicin A structure **(-)-279**.

The ^1H NMR spectrum of **(-)-279** closely resembled that of natural **(+)-zwittermicin A**, however minor differences were obvious, especially corresponding to H8 and H3. When the ^1H NMR spectrum of a 1:3 mixture of **(-)-279** and **(+)-1** was measured, two sets of spin systems were observed (Figure 3.2). In addition the ^{13}C NMR spectrum of **(-)-279** also showed slight differences. Finally, the specific rotation of **(-)-279** ($[\alpha]_{\text{D}} -23.0^\circ$, H_2O) was opposite in sign and of larger magnitude than values measured for natural **(+)-1** ($[\alpha]_{\text{D}} = +8.1^\circ$, H_2O ; lit.⁴² $+8.9^\circ$) under the same conditions.

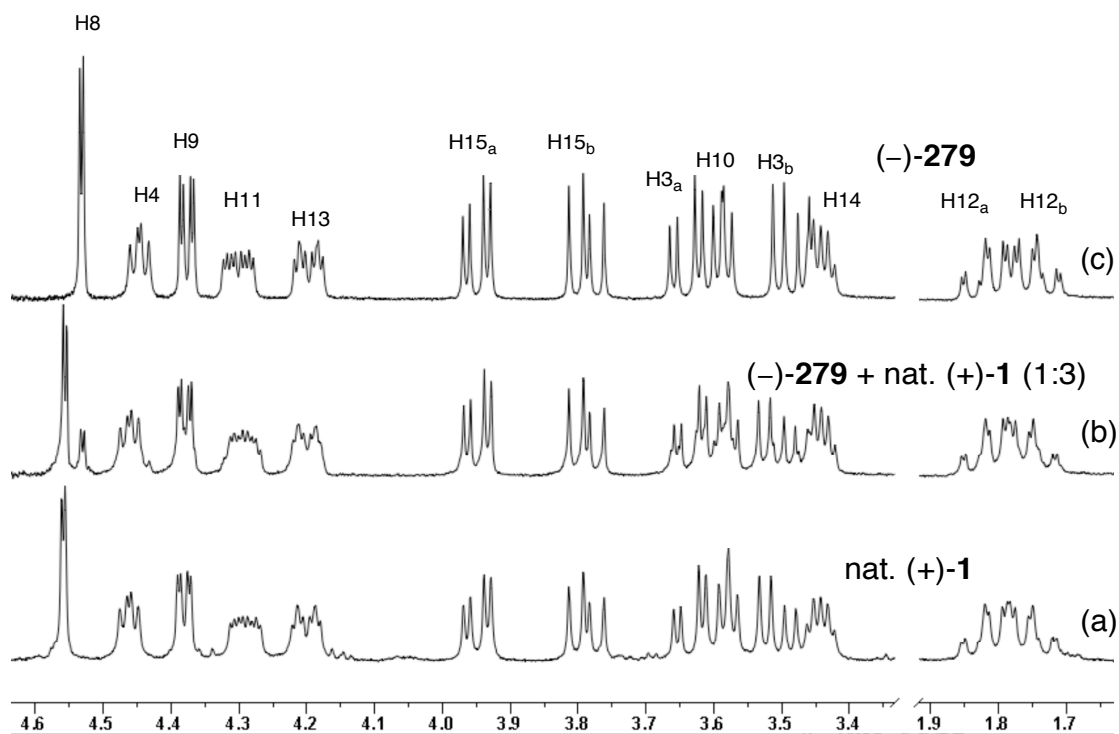


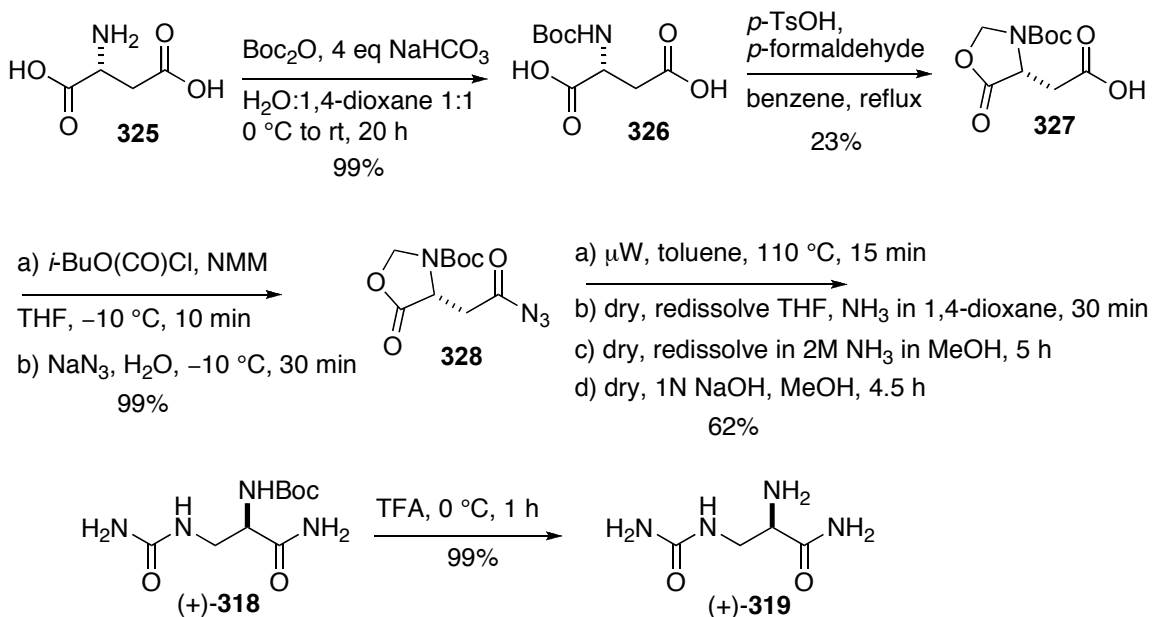
Figure 3.2: ¹H NMR spectra (400 MHz, D₂O) of (a) natural (+)-**1**, (b) 1:3 mole ratio of synthetic (–)-**279** and natural (+)-**1**, and (c) (–)-**279**. Concentrations ~10 mM, no solvent suppression.

The primary difference in the ¹H spectrum occurs at H8, the proton α to the carbonyl linking the C7-C15 portion to the albizziin-derived portion of (–)-**279**. Since the relative configuration of (+)-**1** at C8-C11, C13 and C14 were assigned unambiguously from pairwise ¹³C NMR comparisons (see Chapter 2), it was speculated that perhaps the absolute configuration of the C7-C15 unit was incorrect. If so, the biosynthetic assumption that C14 retains the configuration of L-serine in (+)-**1** must also be in error.⁴³ Due to the significant amount of work required to synthesize the C7-C15 portion of (+)-**1**, it was decided to prepare a zwittermicin A isomer by inverting only the configuration of the α-aminoamide at C5. If the hypothesis was correct this should lead to a synthesis of

(-)-**1** with identical ^1H and ^{13}C NMR properties to (+)-**1** but equal magnitude and opposite sign of the specific rotation $[\alpha]_{\text{D}}$.

3.5. Synthesis of (+)-**319**

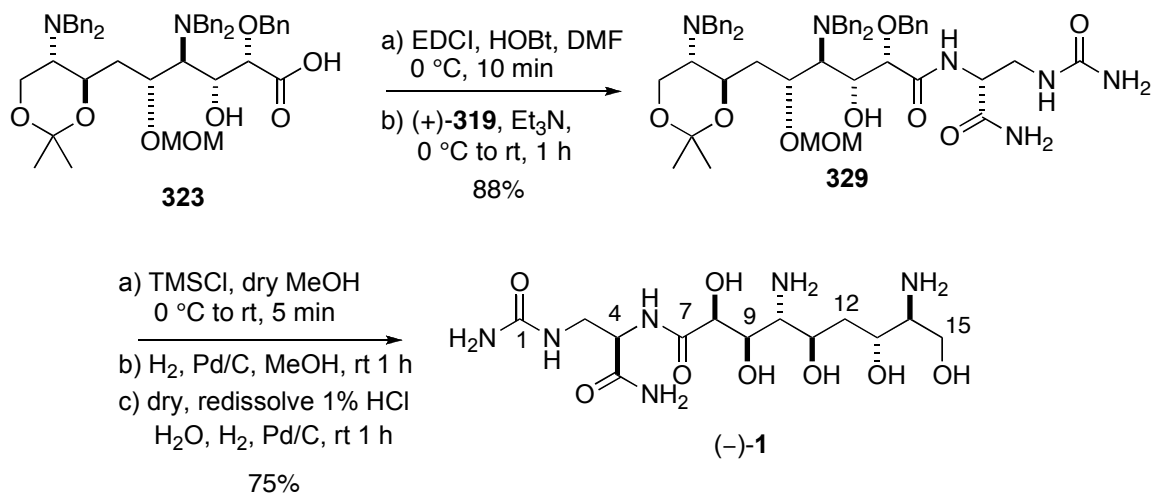
The synthesis of (+)-**319** began with preparation of **328** by literature methods (Scheme 3.16).^{44,45} Known compound **328** was converted to the amide (+)-**318** in 62% yield and the Boc group removed to give (+)-**319** in 99% yield.



Scheme 3.16: Synthesis of α -aminoamide (+)-**319**.

3.6. Synthesis of (-)-Zwittermicin A

Synthesis of (-)-**1** began with coupling of **323** and (+)-**319** to give **329** in 88% yield (Scheme 3.17). Deprotection of **329** under conditions identical to those described in Scheme 3.15 gave (-)-**1** in 75% yield.



Scheme 3.17: Synthesis of (-)-zwittermicin A [(-)-**1**].

The ¹H NMR of synthetic (-)-**1** matched natural (+)-**1** exactly (Figure 3.3) and gave only one set of ¹H and ¹³C NMR when admixed with (+)-**1**. Finally, the specific rotation of synthetic (-)-**1** ($[\alpha]_D -7.9^\circ$, H₂O) was opposite in sign and equal in magnitude to natural (+)-zwittermicin A ($[\alpha]_D = +8.1^\circ$, H₂O; lit. +8.9°).

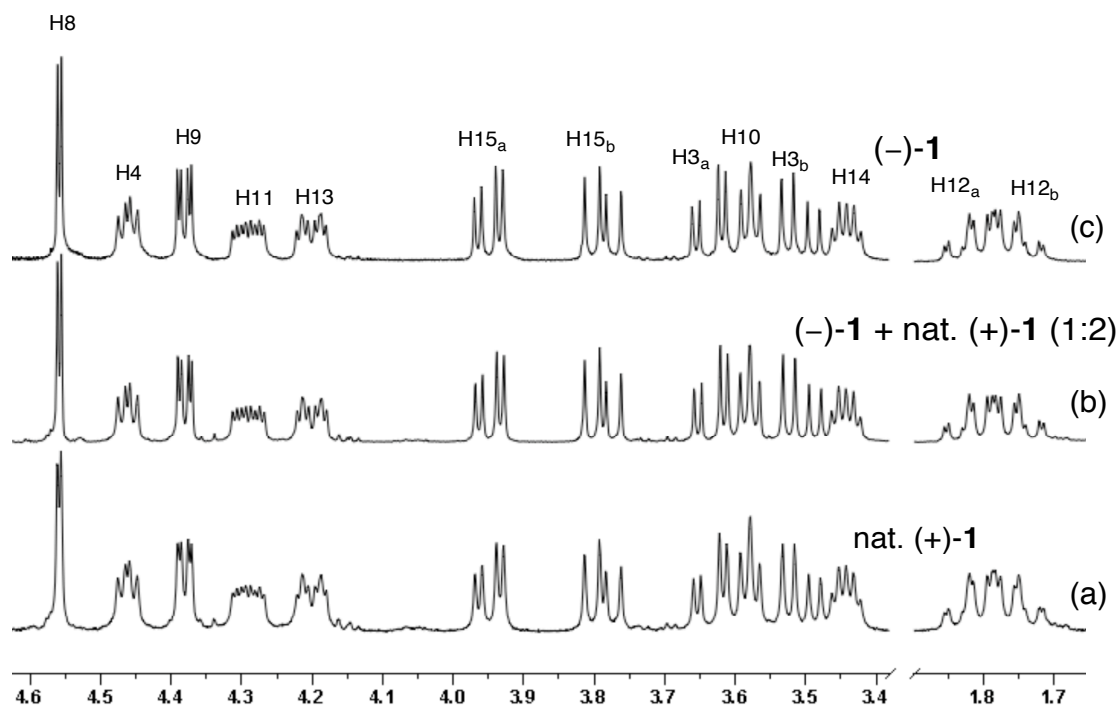


Figure 3.3: ^1H NMR spectra (400 MHz, D_2O) of (a) natural (+)-**1**, (b) 1:2 mole ratio of synthetic (–)-**1** and natural (+)-**1**, and (c) (–)-**1**. Concentrations ~ 10 mM, no solvent suppression.

3.7. Configuration of (+)-Zwittermicin A

The correct configuration for natural (+)-zwittermicin A is (4*S*,8*R*,9*S*,10*S*,11*S*,13*S*,14*R*) as depicted in Figure 3.4. The original proposed 14*S* configuration was based on a biosynthetic assumption, although details of gene sequences or adenylation domains for the serine (Ser) loading have yet to appear. The 14*R* configuration leads to a prediction with respect to loading of the Ser starter unit. One possibility is that D-serine is used as the starter unit. Precedence for unnatural D-amino acids as starter units is seen in the D-Ala residue of cyclosporin.⁴⁶

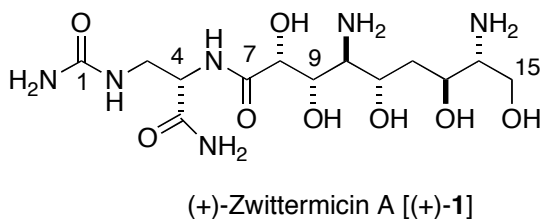


Figure 3.4: Revised configuration of natural zwittermicin A.

The other possibilities are that L-Ser is loaded and subjected to α -epimerization of the carrier protein-bound L-Ser, or the presence of a dual function condensation and epimerization domain. The latter two mechanisms have been observed in the biosynthesis of arthrofactin and enduracidin.^{47,48}

3.8. Conclusion

The tentative structure of zwittermicin A [(–)-279] was found to not match the natural product (+)-1. Zwittermicin A [(+)-1] was assigned completely by analysis of ¹H and ¹³C NMR, stereotopicity,⁴⁹ and total synthesis of its enantiomer (–)-1.⁵⁰ The synthesis entailed 22 steps from L-serine with an overall yield of 1.8%. The correct structure for (+)-zwittermicin A implies a ‘D-serine’ motif in the biosynthesis of the C13-C15 unit of (+)-1.

3.9. Acknowledgements

I thank Dr. Doralyn S. Dalisay for bioassay of the natural and synthetic compounds. This work is in part a reprint of published results: Rogers, E. W.; Dalisay, D. S.; Molinski, T. F. (+)-Zwittermicin A: Assignment of its Complete Configuration by

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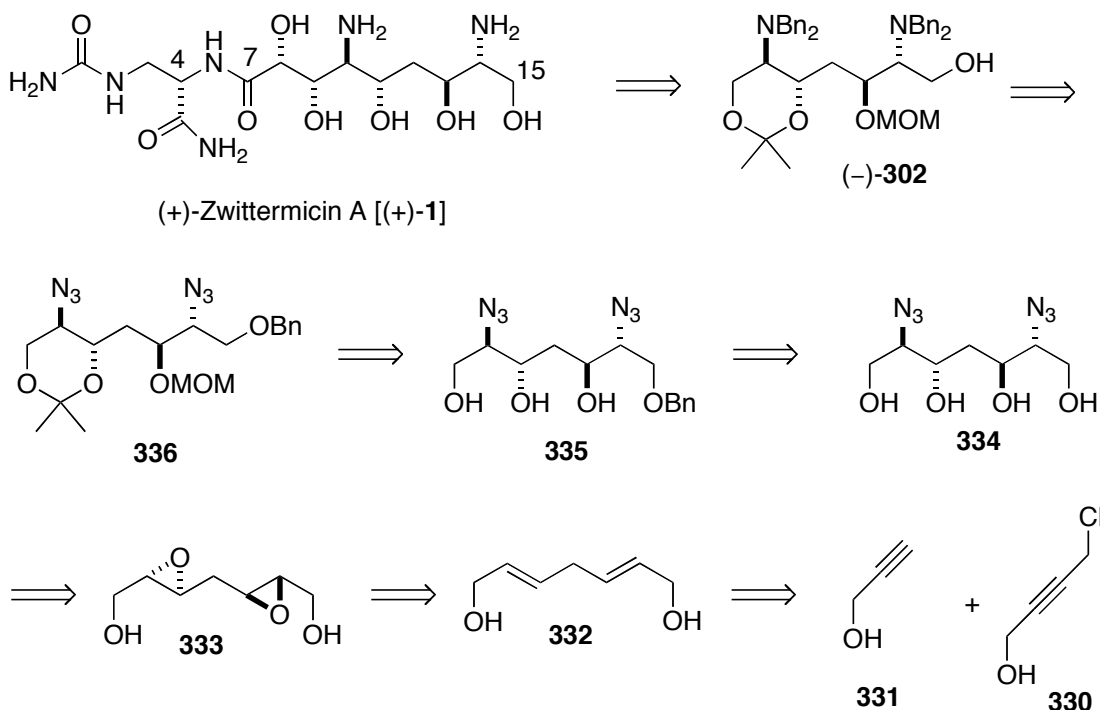
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Chapter 4 Improved Synthesis of the C9-C15 Portion of (+)-Zwittermicin A

4.1. Retrosynthesis

Synthesis of (-)-zwittermicin A required 22 steps with an overall yield of 1.8%.

The majority of the poor-yielding steps occurred in the early part of the scheme while the last 10 steps had an overall yield of 31%.



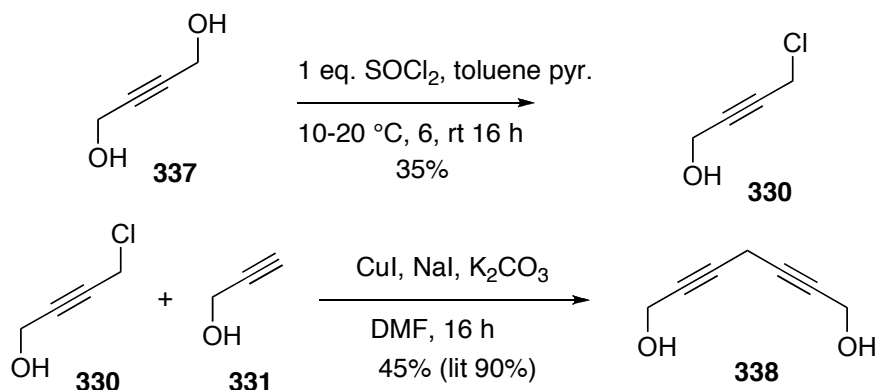
Scheme 4.1: Retrosynthetic analysis of (+)-zwittermicin A.

In order to improve the early sequence and prepare a common intermediate, but of the correct configuration for (+)-1, a new route to an advanced intermediate was desired that might lead to a more efficient synthesis of natural (+)-zwittermicin A (Scheme 4.1).

This new route again takes advantage of the symmetry in the C9-C15 portion of (+)-**1** and intercepts the previous route at compound (-)-**302**, but utilizes asymmetric reagent control of all four stereocenters rather than D-Ser from the chiral pool. Key steps in this synthesis are de-symmetrization of C₂ symmetric **334** to give compound **335**. Diazide **334** is obtained by Miyashita's boron-mediated azide addition to **333**.¹ Epoxide **333** is a known compound generated by Sharpless asymmetric epoxidation (SAE) of diene **332**.² Compound **332** could be prepared by a literature procedure in two steps from propargylic alcohols **330** and **331**.^{2,3} The overall number of synthetic steps was expected to diminish from 22 in the first generation synthesis to 16. Counting from the known compound **333**, this second generation synthesis would give (-)-**302** in only 11 steps. The major improvement in this route is the reduction in protecting group manipulation steps from 10 to five.

4.2. Synthesis of Known Compounds

The literature procedures of Hoffmann and Bailey were followed for the synthesis of compound **338** (Scheme 4.2).^{2,3} The initial step had low yield (35%) relative to that reported in the literature (69%), and is made difficult by the fact that it is a desymmetrization reaction. The low yield observed for the second reaction was probably due to an exotherm experienced with the much larger scale used (25 g versus literature 7 g). Nevertheless, these lower yields are acceptable at the earliest phase of the synthesis.



Scheme 4.2: Synthesis of diol **338**.

Attempts to follow various literature procedures for reduction of di-acetylene **338** to diene **332** gave very poor yields (Table 4.1).⁴⁻⁹ It should be noted that literature yield for this reaction is only 38%.²

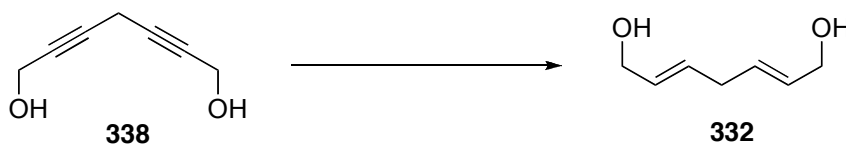


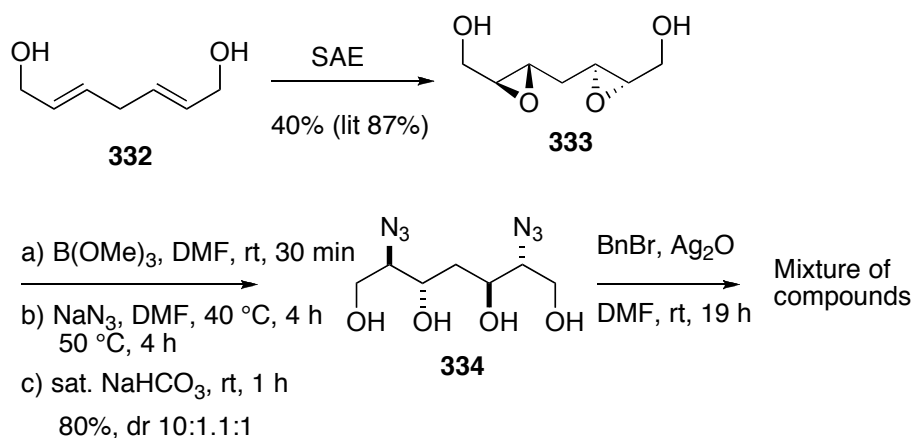
Table 4.1: Reduction of di-acetylene **338**.

| Entry # | Reagents | Temp (°C) | Time (h) | Yield (%) | Comments |
|---------|--|-----------|----------|-----------|-----------------|
| 1 | Red-Al, THF | -20 to rt | 14 | dec. | decomposition |
| 2 | LAH, THF | -50 to rt | 16 | 0 | decomposition |
| 3 | Li, NH ₃ (l) | -78 | 2 | na | mix of isomers |
| 4 | Li, NH ₃ (l), THF | -78 | 2.5 | ~15 | mix of isomers |
| 5 | Na, NH ₃ (l), THF | -78 | 1 | ~10 | mix of isomers |
| 6 | Na, NH ₃ (l), THF, <i>t</i> -BuOH | -78 | 0.5 | 11 | ~85% one isomer |

4.3. Epoxide Synthesis, Azide Opening and Desymmetrization

Epoxidation of diene **332** gave symmetrical crystalline diepoxide **333** in 40% yield (Scheme 4.3). Boron mediated azide opening of **333** gave diazide **334** in a

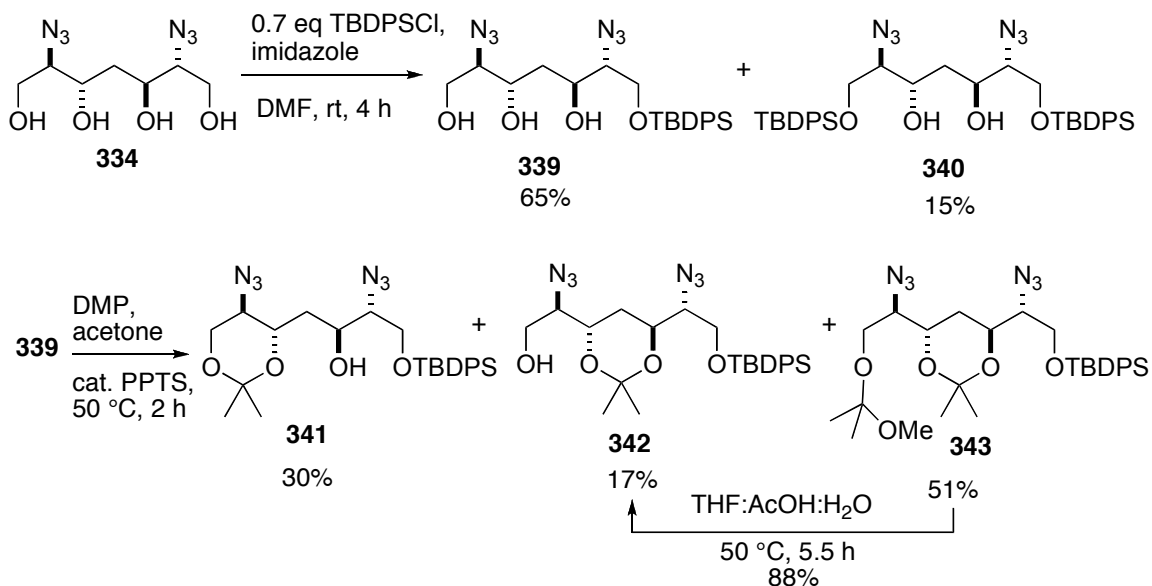
respectable yield of 80%.^{10,11} Workup and purification of both the epoxide and the diazide were made difficult due to the fact that both compounds were water-soluble. In the case of the diazide **334**, purification required both normal phase and reverse phase flash chromatography to obtain a mixture of diastereomers that was pure enough to be recrystallized. Recrystallization gave pure **334** but resulted in recovery of only 87% of the diazide. Initial desymmetrization of **334** was attempted using BnBr and Ag₂O with the hope that a monoprotected benzyl alcohol would be formed; however, this reaction gave a mixture of compounds that proved to be inseparable.¹²



Scheme 4.3: Synthesis of diazide **334**.

With the failure of this reaction, another attempt at mono-protection/desymmetrization was made using TBDPSCl and imidazole;¹³⁻¹⁴ the yield of the desired monoprotected diazide **339** (65%) was acceptable (Scheme 4.4). The doubly protected C₂ symmetrical **340** was formed in 15% yield and essentially all of the unreacted starting material was also recovered. An acetonide protecting group was installed in **339** using dimethoxypropane and acetone with catalytic PPTS to give **341** in

30% yield.¹⁵ The low yield of the desired product **341** was not encouraging for this route. In addition, the TBDPS protecting group would require an additional deprotection step for the overall synthesis. It was therefore decided to try a desymmetrization that would provide a terminal protecting group that could be removed simultaneously with reduction of the azido groups.



Scheme 4.4: Synthesis of diazide **341**.

Table 4.2 lists the results for various desymmetrization reactions by tritylation (TrCl).¹⁶ The optimum yield of **344** was with 0.8 equivalents of TrCl at 60 °C (69% yield). Symmetrical azide **345** could be converted to **344** by hydrolysis of one trityl group as shown in Scheme 4.5.^{17,18} Completely deprotected **334** was also recovered from the reaction but could not be purified sufficiently to provide an accurate yield.

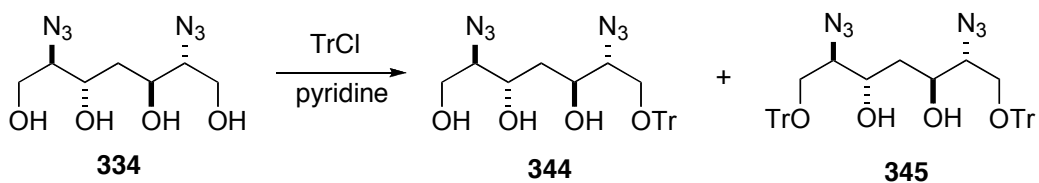
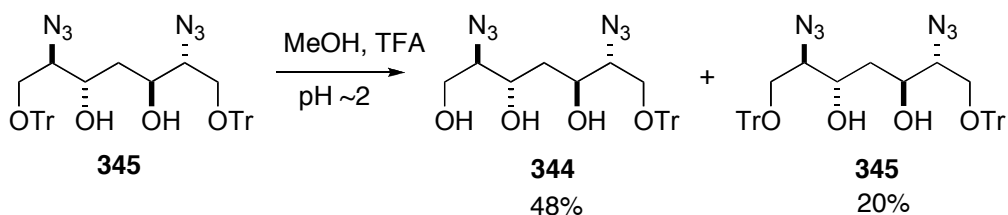


Table 4.2: Desymmetrization of **334** using TrCl .

| Entry # | equivalents TrCl | Temp ($^{\circ}\text{C}$) | Time (h) | Yield 344 (%) | Yield ^a 345 (%) |
|---------|---------------------------|-----------------------------|----------|----------------------|-----------------------------------|
| 1 | 1.0 | 50 | 4 | 54 | 19 |
| 2 | 0.8 | rt | 17 | 54 | 17 |
| 3 | 0.8 | 60 | 5 | 69 | 14 |

^a Also recovered remaining unreacted **334**.



Scheme 4.5: Synthesis of diazide **344**.

4.3.1. Interception of Previous Synthetic Route

Attempts were next made to achieve selective 1,3-diol protection with an acetonide group (Table 4.3). Optimum yield for synthesis of acetonide **346** was Entry 6 using 2.5 equivalents of 2-methoxypropene and catalyst PPTS (73% yield).¹⁹⁻²² The secondary hydroxyl in acetonide **346** was protected with a MOM group to give **349** in 90% yield (Scheme 4.6).^{23,24} Conversion of **349** to amine (–)-**301** was effected with Pd/C and H_2 in trifluoroethanol followed by addition of TFA and further hydrogenation.²⁵

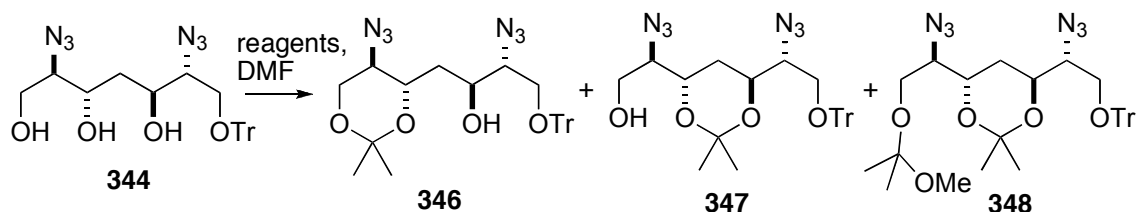


Table 4.3: Synthesis of acetonide **346**.

| Entry # | Reagent | equiv. reagent | Catalyst | Temp (°C) | Time (h) | Yields | |
|----------------|---------------------------------|----------------|----------|-----------|----------|------------------------|--------------------------|
| | | | | | | 346/347/348 (%) | Recovered 344 (%) |
| 1 ^a | 1:1 dimethoxy propane : acetone | excess | PPTS | 50 | 4 | 24 | 0 |
| 2 | 2-methoxypropene | 2.5 | PPTS | 0 to rt | 36 | 0 | 100 |
| 3 ^b | 2-methoxypropene | 2.5 | TsOH | 0 to rt | 28 | 0 | 100 |
| 4 | 2-methoxypropene | 2.0 | TsOH | 0 to rt | 2 | 0 | na |
| 5 ^c | 2-methoxypropene | 2.0 | CSA | 0 to rt | 20 | 47/18/0 | na |
| 6 ^d | 2-methoxypropene | 2.5 | PPTS | 50 | 4 | 73/17/0 | na |
| 7 | 2-methoxypropene | 2.0 | PPTS | 50 | 4 | 64/8/14 | na |

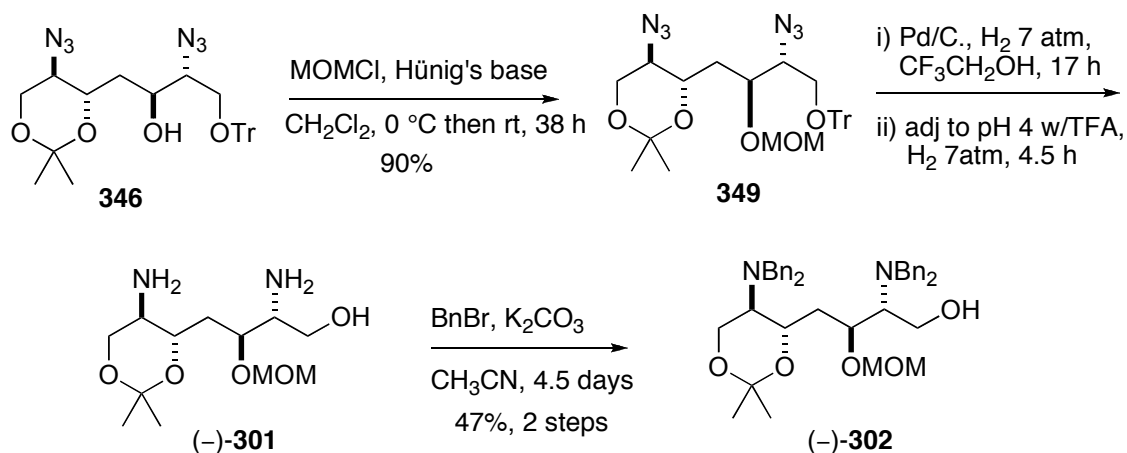
^a No DMF solvent.

^b Reaction mixture had molecular sieves present.

^c Trityl group partially removed.

^d Some starting material still remaining.

The crude reaction mixture was concentrated and *N*-benzylated to yield the desired alcohol (–)-**302** (47% over two steps).²⁶ Compound (–)-**302** intercepted the previous total synthesis of *ent*-zwittermicin A [(–)-**1**] and provided a key intermediate of correct configuration to complete a total synthesis of natural zwittermicin A [(+)-**1**].



Scheme 4.6: Synthesis of alcohol (-)-**302**.

4.4. Conclusion

Synthesis of (-)-**302** was completed in six steps from known compound **333** with an overall yield of 14%. This compound intercepted a previous synthesis and is therefore a formal total synthesis of (+)-zwittermicin A [(+)-**1**]. Although this route seems feasible for the synthesis of (+)-**1** from the known compound **333**, the overall yield from purchased material was only 0.1% over 10 steps due mostly to the poor yields of the literature steps. Some of the difficulties involved in this synthesis are the result of having two desymmetrization steps as well as three double functional group manipulations on C₂ symmetric intermediates that are also highly water-soluble.

4.5. References

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Chapter 5 Synthesis of (+)-Zwittermicin A Diastereomers and Analogs: Structure-Activity Relationships

5.1. Introduction

The synthesis of the model compounds and *ent*-(-)-zwittermicin A provided a number of compounds that could be made into zwittermicin A diastereomers or analogs.¹ Biological testing of these diastereomers (Figure 5.1) and analogs could provide insight into the structural activity of zwittermicin A.² Compounds **350** through **354** would be available by conversion of previously prepared intermediates.

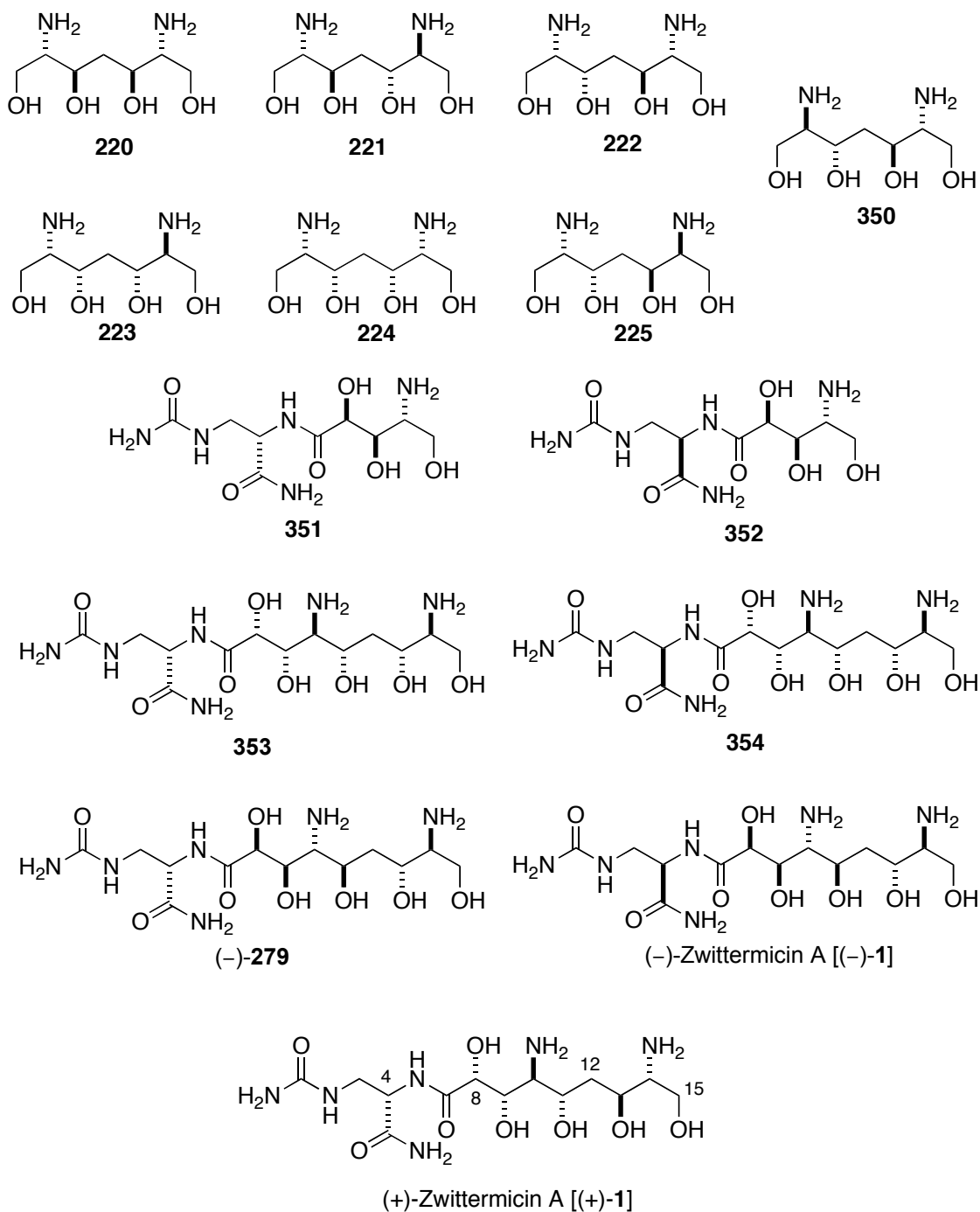
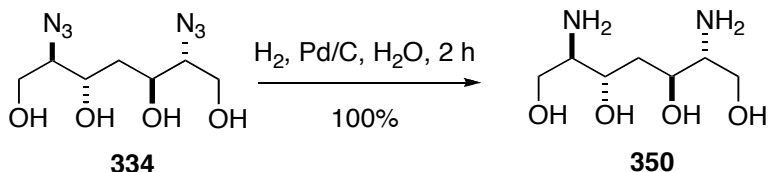


Figure 5.1: Compounds for biological testing.

5.2. Synthesis of Aminopolyol 350

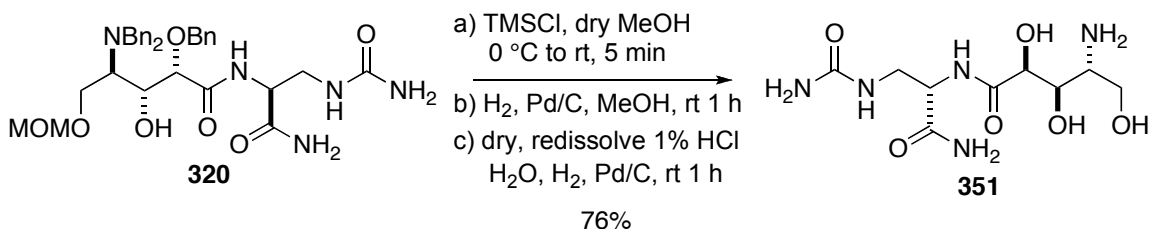
Compound **350** is the enantiomer of **221** and represents the C9-C15 portion of (+)-zwittermicin A with the same absolute stereochemistry. This aminopolyol was synthesized in quantitative yield by hydrogenolysis of **334** with Pd/C (Scheme 5.1).³



Scheme 5.1: Synthesis of aminopolyol **350**.

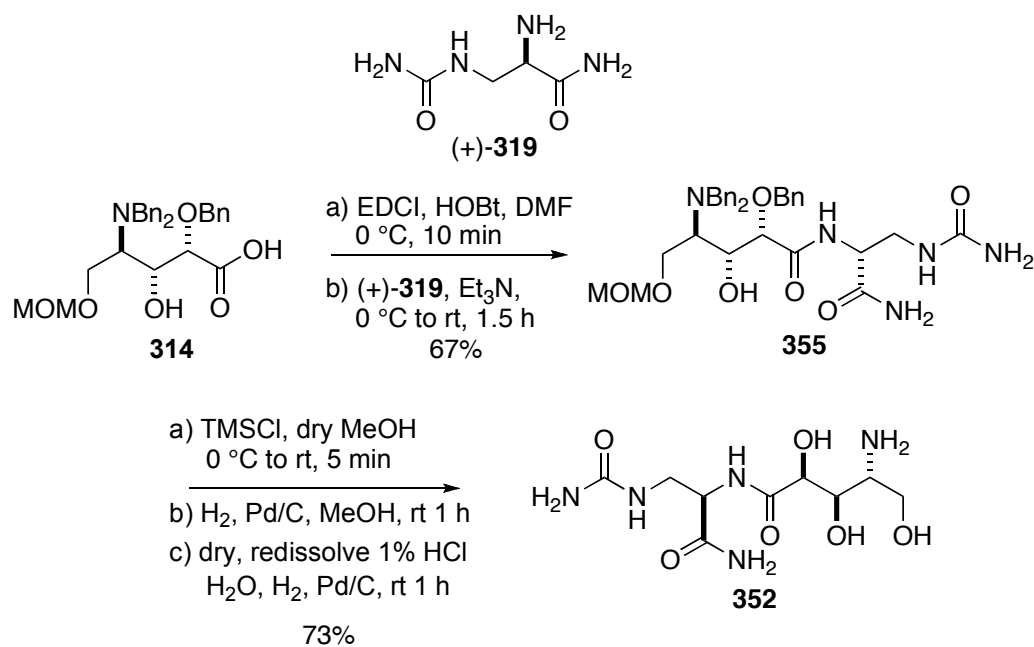
5.3. Synthesis of Analogs Representing C1-C11 of (+)-Zwittermicin A

The truncated analog **351** of zwittermicin A was synthesized from **320** (76% , Scheme 5.2).



Scheme 5.2: Synthesis of analog **351**.

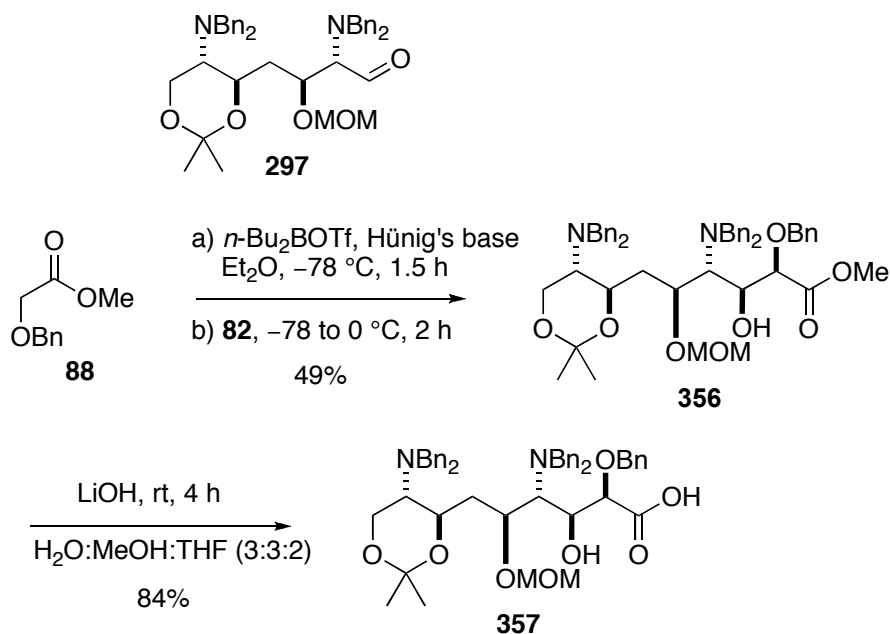
Analog **352** was synthesized in two steps by coupling of **314** and (+)-**319** (67% yield) followed by deprotection to give **352** (73% yield, Scheme 5.3).^{4,5} In both analogs, the stereocenters representing C8-C10 in zwittermicin A are of opposite configuration to those in the natural product. For **351**, the C4 configuration is the same as that in the natural product.



Scheme 5.3: Synthesis of analog **352**.

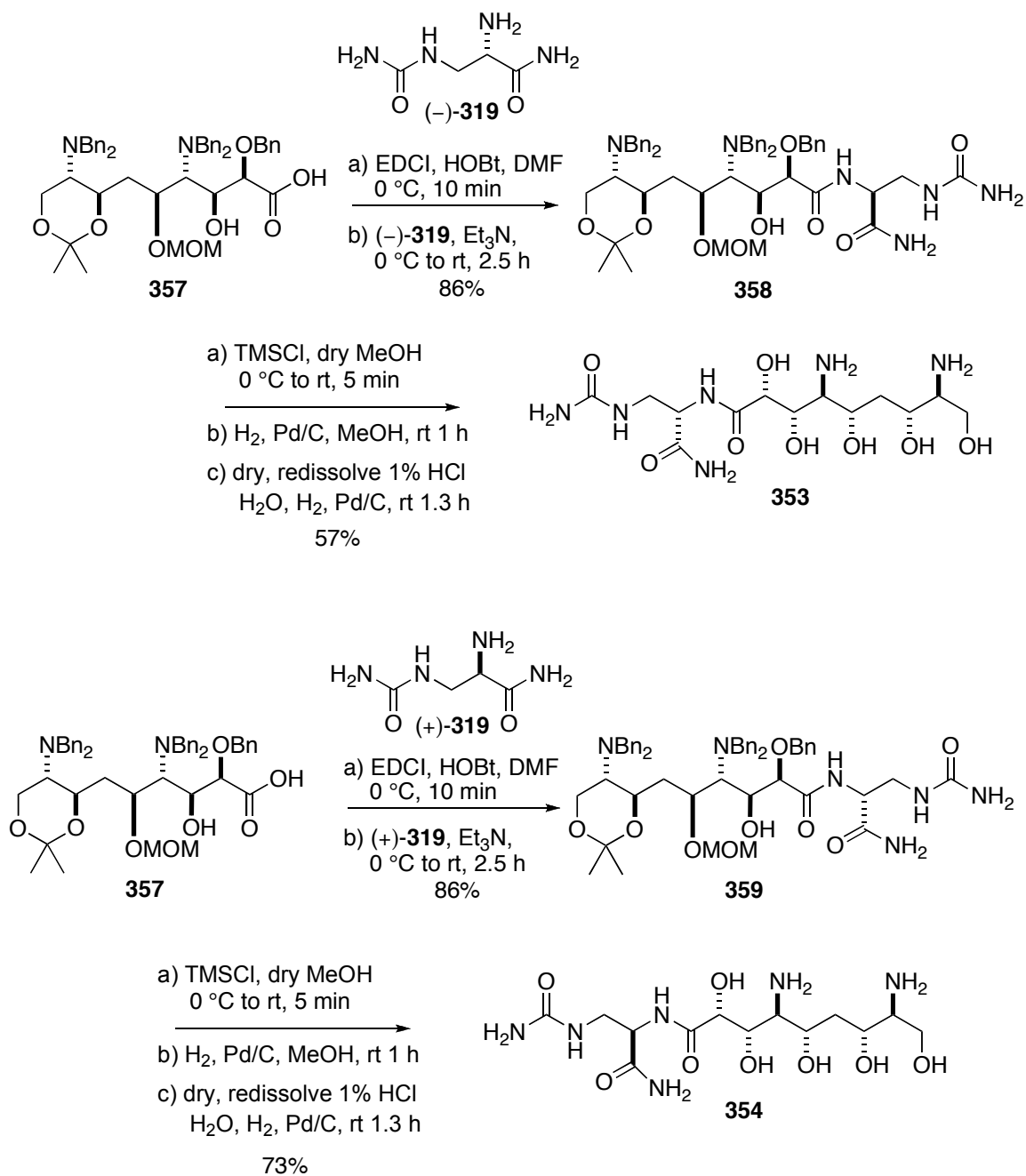
5.4. Synthesis of Two (+)-Zwittermicin A Diastereomers

Preparation of two more zwittermicin A diastereomers began with aldehyde **297** (Scheme 5.4). Boron-mediated aldol addition of methyl benzyloxyacetate **88** to aldehyde **297** gave ester **356** in 49% yield, with a relative stereochemistry the same as (+)-zwittermicin A at the stereocenters representing C8-C11.^{6,7} Conversion of the ester to the free acid **357** was achieved using lithium hydroxide followed by acidic workup (84% yield).⁸



Scheme 5.4: Synthesis of acid **357**.

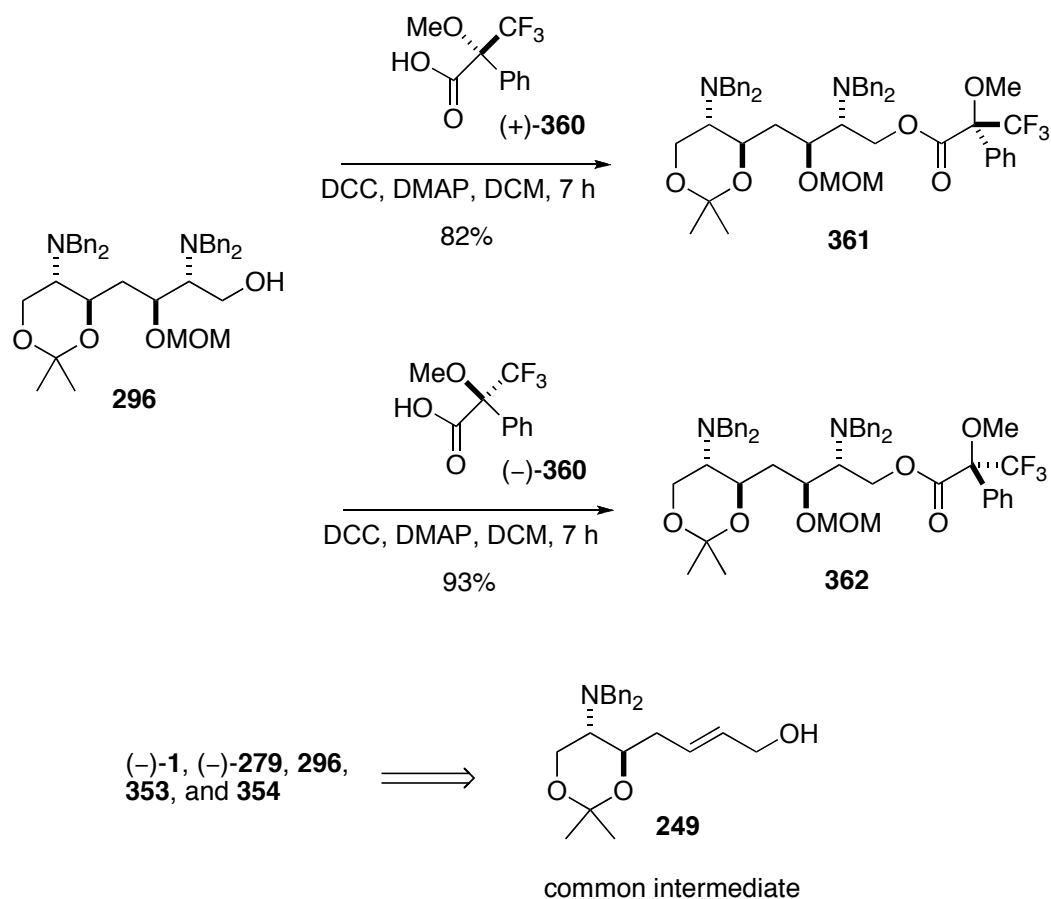
Separately amide couplings of acid **357** to the amines (–)-**319** and (+)-**319** using EDCI gave **358** and **359** (86% yield for each, Scheme 5.5).^{9,10} Deprotection of each of these amides gave the two new zwittermicin A diastereomers **353** and **354** in 57% and 73% yield, respectively. Compound **353** represents a diastereomer with C13 and C14 configuration opposite to that of natural (+)-**1**, while **354** has different configurations at C4, C13 and C14.



Scheme 5.5: Synthesis of zwittermicin A diastereomers **353** and **354**.

5.5. Determination of % Enantiomeric Excess for Synthetic (-)-Zwittermicin A and Diastereomers

To verify the enantiometric excess of the synthetic (-)-**1**, (-)-**279**, **353**, and **354**, intermediate **296** was derivatized with both *R* and *S* Mosher's acid and analyzed by NMR (Scheme 5.6).^{11,12} Determination of the % ee for **296** will give a lower ee limit on all the compounds listed because they come from common intermediate **249**. The Mosher's derivatives **361** and **362** are diastereomers representing the two possible compounds that would be generated from the derivatization reaction. Any enantiomer of **296** in the reaction with (+)-**360** would generate the enantiomer of **362** and therefore have identical ¹H NMR to **362**.



Scheme 5.6: Mosher's derivatization of **296**.

Signals representing **362** present in the ¹H NMR of **361** would represent the amount of original enantiomer in **296** and could be integrated and compared to the amount of **361** for ee determination. Attempted analysis by ¹H NMR failed due to overlap of signals, however use of ¹⁹F NMR did allow for separation of signals and determination of ee. The % ee of **296** was found to be in excess of 94%.

5.6. Biological Testing

Biological testing of natural (+)-**1** and the 13 synthetic compounds was conducted against the fungal strains *Candida albicans* 96-489, *C. glabrata*, *C. albicans* UCDFR1, *C. albicans* ATCC 144503, and *C. krusei*, the bacterial strains *Erwinia carotovora*, and

E. amylovora and oomycete *Phytophthora infestans* (Table 5.1). During the course of the biological testing it was found that the hydrochloride salt of (+)-**1** was not biologically active and previous studies have shown a pH dependence on zwittermicin A activity with higher pH showing increased activity.^{13, 14} This meant that the compounds had to be converted to the free amine by titration with sodium hydroxide. This procedure was also performed on natural (+)-**1** that was in the hydrochloride form to ensure uniformity and reproducibility.

Table 5.1: Biological testing of zwittermicin A and synthetic compounds.

| Biological Strains ^c | MIC ^{a,b} (µg/mL) | | | | | | | | | | | | | |
|---|----------------------------|---------------|-----------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | (+)- 1 | (-)- 1 | (-)- 279 | 353 | 354 | 351 | 352 | 350 | 220 | 221 | 222 | 223 | 224 | 225 |
| <i>Candida albicans</i> 96-489 ^c | 55.7 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 |
| <i>C. glabrata</i> ^c | 59.5 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 |
| <i>C. albicans</i> UCDFR1 ^c | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 |
| <i>C. albicans</i> ATCC 144503 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 |
| <i>C. krusei</i> | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 |
| <i>Erwinia carotovora</i> | 22.2 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | na | na | na | na | na | na |
| <i>E. amylovora</i> | 18.8 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | na | na | na | na | na | na |
| <i>Phytophthora infestans</i> ^d | >32 | >32 | >32 | >32 | >32 | >32 | >32 | >32 | na | na | na | na | na | na |

^aThe MIC endpoint is defined as the lowest concentration (µg/mL) with 90% growth inhibition.

^bCompounds (+)-**1**, (-)-**1**, (-)-**279**, and **350-354** were converted to the free amine before testing while compounds **220-225** were tested in the hydrochloride salt form.

^cFluconazole-resistant strains.

^d*Phytophthora infestans* was tested using a range where (+)-**1** had shown activity against *Phytophthora medicaginis* M2913 and was limited to a maximum concentration of 32 due to being a nutrient agar well diffusion assay.

Results of susceptibility assays against a panel of fungi (*Candida albicans* 96-489, *C. glabrata*, *C. albicans* UCDFR1, *C. albicans* ATCC 144503, and *C. krusei*), bacteria (*Erwinia carotovora* and *E. amylovora*) and oomycete (*Phytophthora infestans*)

are shown in Table 5.1. *C. albicans* 96-489, *C. glabrata*, *C. albicans* UCDFR1, *C. albicans* ATCC 144503, and *C. krusei* are all human pathogenic fungi most often affecting those with compromised immune systems such as AIDS patients. *E. carotovora* and *E. amylovora* are plant pathogens affecting potato, tomato, carrot and other vegetables causing cell death through plant cell wall destruction. *P. infestans* is a plant pathogen that caused late-blight in potato, tomato and eggplant. The synthetic *ent*-zwittermicin A [($-$)-**1**], ($-$)-**279**, **220-225** and **350-354** showed no activity against all of the pathogens. The biological data indicates that the mechanism of actions is highly stereospecific and requires the complete zwittermicin A structure of natural configuration to be effective.

5.7. Conclusion

One new aminopolyol representing the C9-C15 portion of (+)-**1** and two analogs representing the C1-C11 portion were synthesized. Two additional zwittermicin A diastereomers (**353** and **354**) were also synthesized. All of these compounds as well as natural (+)-**1** and the previously synthesized compounds ($-$)-**1**, ($-$)-**279**, and the six model compounds **220-225** were tested for biological activity. It was found that the salt form of zwittermicin A was important for biological activity with the free amine showing activity while the hydrochloride salt was found to be inactive. None of the synthetic compounds showed activity against a panel of pathogenic fungi and bacteria indicating that the activity of zwittermicin A is stereospecific.

5.8. Acknowledgements

Dr. Doralyn S. Dalisay performed the bioassay of synthetic and natural compounds.

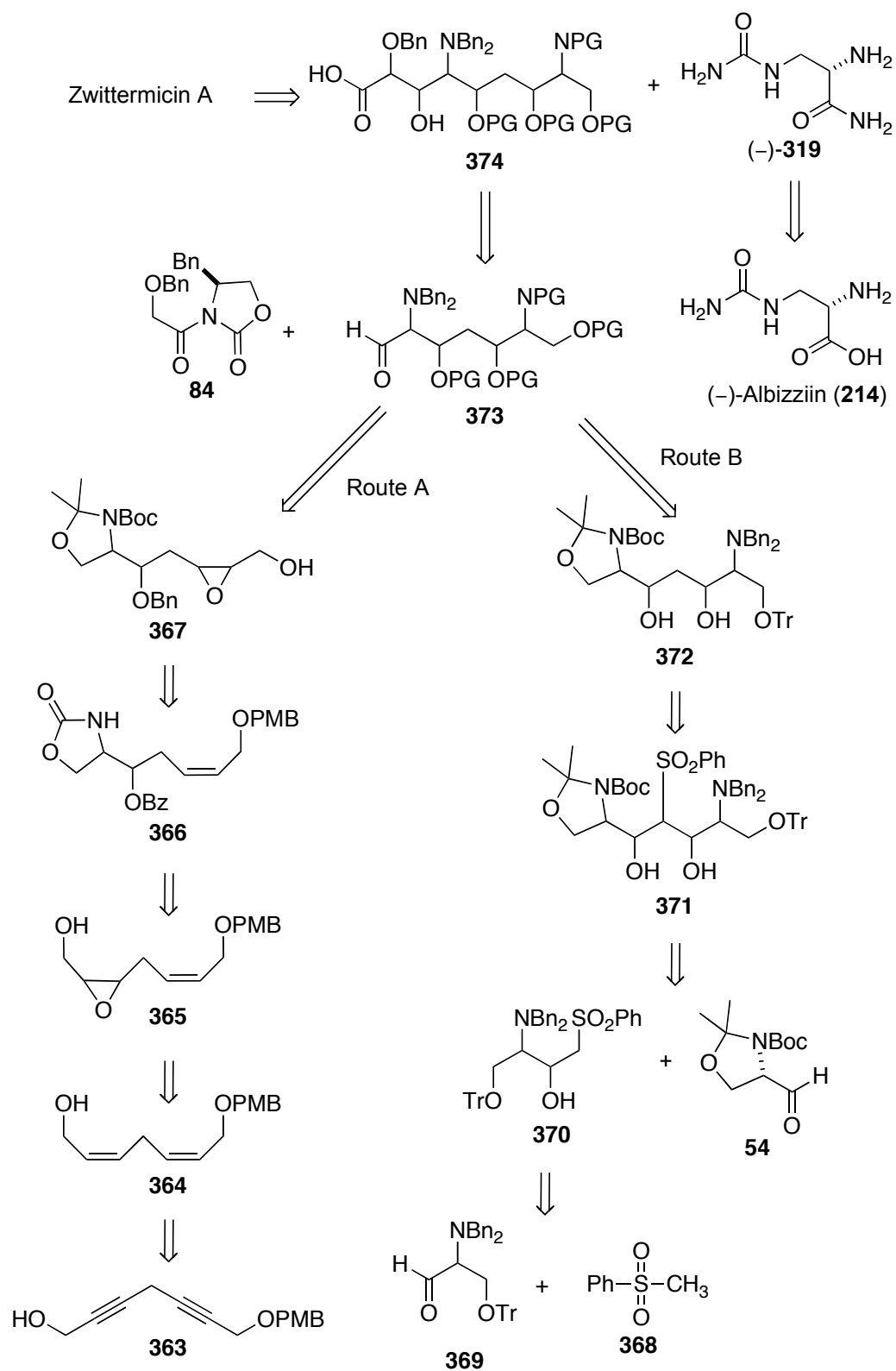
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Chapter 6 Synthesis of Sulfone Aminopolyols

6.1. Introduction and Retrosynthesis

Initial work toward the synthesis of zwittermicin A [(+)-**1**] focused on two routes with most of the work carried out on substituted sulfones. The retrosynthesis for these two routes is shown in Scheme 6.1. Because this work was developed before the configuration on zwittermicin A was known, it was necessary that each route provide stereo control at all stereocenters in the C7-C15 portion of (+)-**1**. Both routes would use Evan's aldol addition reactions to set the C8 and C9 stereocenters starting with **373**.¹ At this point, the retrosynthesis diverges with route A leading back to diyne **363**. The configuration of the double bond (*E* or *Z*) in combination with appropriate SAE catalyst allows for independent control of two vicinal amino- and hydroxy- constituent stereocenters formed and generation of maximum diversity.² Regiochemical control over which double bond is epoxidized is obtained through selectively protected diol **365** thus allowing full regio and asymmetric control over the four stereocenters created from the diene. Epoxide opening and regioselective N-C bond formation would be achieved through the Roush method; addition of benzoyl isocyanate to the primary alcohol followed by intramolecular displacement of the epoxide to form a cyclic carbamate and transfer of the benzoyl group to the newly formed alcohol.³⁻⁴ This route follows well established chemistry for assembly of the C9-C15 portion of zwittermicin A.

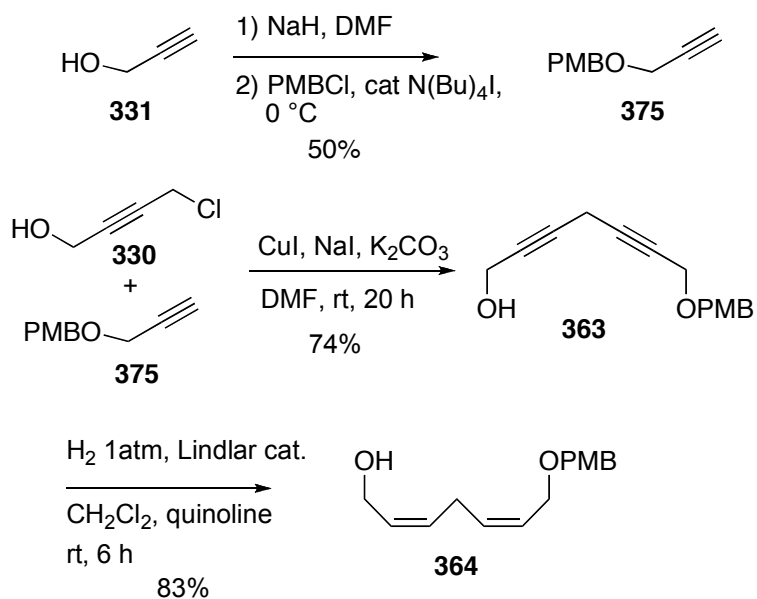


Scheme 6.1: Retrosynthetic analysis of zwittermicin A.

In route B key steps are the addition of a sulfone anion to a serine-derived aldehyde, sulfone dianion addition to a second serine-derived aldehyde and finally desulfonization. Control over the diastereoselectivity of sulfone anion additions would be required for both C-C bond-forming reactions. Sulfone dianion additions to aldehydes are known but have not been used often.^{5,6} The final hurdle in this route is the removal of the sulfone in the presence of two beta-leaving groups. While this route has more risks in terms of chemistry, it also is highly convergent with a rapid assembly of the C9-C15 portion of zwittermicin A. Neither of these routes worked for the synthesis of zwittermicin A, but the substantial amount of development of the sulfone route allowed for other applications, including preparation of two aminopolyols for use as internal and surrogate standards in LC/MS analysis of sphingolipids.

6.2.Route A, Synthesis of Diene 363

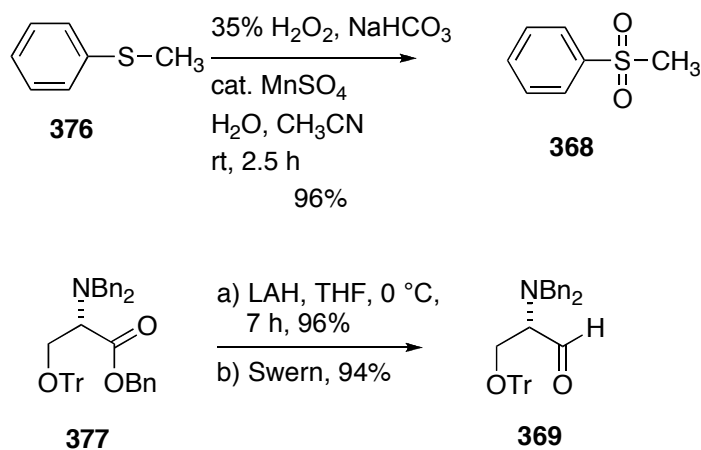
The known PMB protected propargyl alcohol **375** was prepared in reasonable yield followed by Cu-mediated coupling with chloroalkyne **330** (74% yield) and Lindlar's reduction to give diene **363** in 83% yield (Scheme 6.2).⁷ This was followed by copper mediated coupling to.⁸⁻¹⁰



Scheme 6.2: Synthesis of diene **364**.

6.3. Route B, Sulfone Anion Addition

Known phenylmethylsulfone **368**¹¹ was synthesized (Scheme 6.3) from thioanisole in 96% yield while known aldehyde **369**¹² was synthesized in two steps from material previously made in our lab.



Scheme 6.3: Synthesis of starting materials **368** and **369**.

Optimization of sulfone anion addition of **368** to **369** (Table 6.1) was carried out under various conditions.^{13,14}

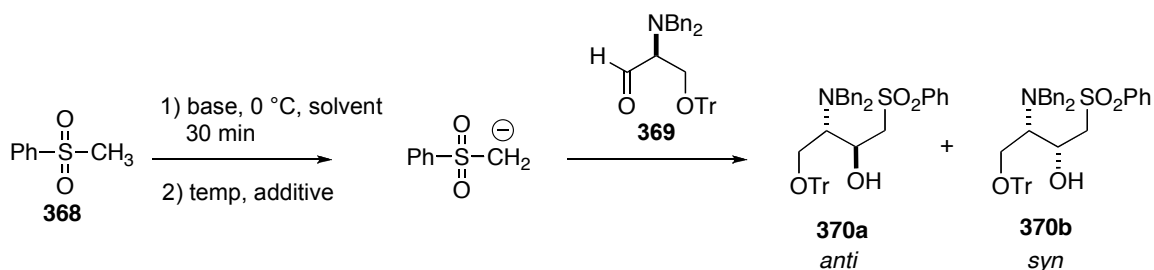


Table 6.1: Sulfone anion addition to aldehyde **369**.

| Entry # | Solvent | Base | Additive | Time (min) | Temp (°C) | Ratio <i>anti</i> : <i>syn</i> | Yield % |
|---------|-------------------|------------------|--------------------------------|------------|-----------|--------------------------------|---------|
| 1 | THF | <i>n</i> -BuLi | | 75 | -78 | 2.0 : 1 | 35 |
| 2 | THF | <i>n</i> -BuLi | | 60 | -78 | 2.5 : 1 | 52 |
| 3 | THF | <i>n</i> -BuLi | ZnCl ₂ | 60 | -78 | - | 0 |
| 4 | THF | <i>n</i> -BuLi | MgBr ₂ | 60 | -78 | 2.0 : 1 | 47 |
| 5 | THF | <i>n</i> -BuLi | CuBr ₂ ^a | 60 | -78 | 2.0 : 1 | 46 |
| 6 | THF | <i>n</i> -BuLi | YbTf ₃ | 1140 | -78 to rt | - | 0 |
| 7 | THF | <i>i</i> -PrMgCl | | 90 | -78 | 3.0 : 1 | 50 |
| 8 | DME | <i>n</i> -BuLi | | 90 | -40 | 2.9 : 1 | 54 |
| 9 | DME | <i>i</i> -PrMgCl | | 90 | -40 | 2.2 : 1 | 79 |
| 10 | Et ₂ O | <i>n</i> -BuLi | | 90 | -78 | 2.9 : 1 | 66 |
| 11 | Et ₂ O | <i>i</i> -PrMgCl | | 90 | -78 | 2.4 : 1 | 13 |

^aCuBr₂ did not fully dissolve in the solvent and exact percent was below 1 equivalent.

The initial reaction showed poor yield and low diastereoselectivity, (reaction 1 and 2). Four different additives were tried in an attempt to improve both yield and diastereoselectivity without any success (entries 3 through 6). Base and solvent were varied with some improvement in yield and diastereoselectivity, and the highest yield was obtained using *i*-PrMgCl as the base and 1,2-dimethoxyethane as the solvent (entry 9, 79%). Diastereoselectivity was poor (3 : 1, *anti* : *syn*) and the products, although not

separable by flash chromatography, were obtained pure by HPLC. The poor outcomes for the synthesis of **370** necessitated a different aldehyde for the sulfone anion addition

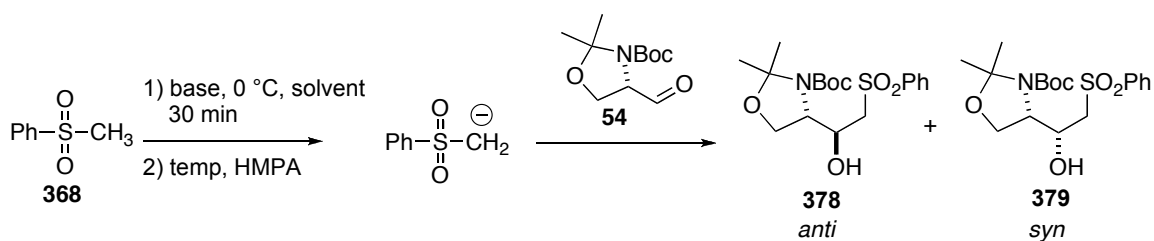


Table 6.2: Sulfone anion addition to Garner's aldehyde **54**.

| Entry # | Solvent | Base | HMPA Equiv. to Anion | Temp (°C) | Rxn Conc (M) ^c | Anion Equiv. | Time (min) | Ratio 378 : 379 | Yield % |
|-----------------|-------------------|------------------|----------------------|-----------|---------------------------|--------------|------------|-------------------------------|---------|
| 1 | THF | <i>n</i> -BuLi | 0 | -78 | 0.20 | 1 | 60 | 1 : 1 | 53 |
| 2 | THF | <i>n</i> -BuLi | 0 | -78 | 0.20 | 1 | 45 | 2 : 1 | 54 |
| 3 ^a | THF | <i>n</i> -BuLi | 0 | -78 | 0.20 | 1 | 1200 | - | 0 |
| 3 | THF | <i>i</i> -PrMgCl | 0 | -78 | 0.20 | 1 | 45 | 1.6 : 1 | 49 |
| 4 | DME | <i>n</i> -BuLi | 0 | -40 | 0.20 | 1 | 60 | 1.7 : 1 | 15 |
| 5 | DME | <i>i</i> -PrMgCl | 0 | -40 | 0.20 | 1 | 90 | 1.2 : 1 | 53 |
| 6 | Et ₂ O | <i>n</i> -BuLi | 0 | -78 | 0.20 | 1 | 90 | 1.4 : 1 | 42 |
| 7 | Et ₂ O | <i>i</i> -PrMgCl | 0 | -78 | 0.20 | 1 | 90 | 1 : 1 | 19 |
| 8 | THF | <i>t</i> -BuLi | 2 | -78 | 0.16 | 1.2 | 90 | 3 : 1 | 27 |
| 9 ^b | THF | <i>t</i> -BuLi | 0 | -78 | 0.17 | 1.2 | 90 | 2 : 1 | 24 |
| 10 | THF | <i>t</i> -BuLi | 0 | 0 | 0.13 | 1 | 90 | 1 : 2 | 52 |
| 11 ^b | THF | <i>t</i> -BuLi | 10 | -78 | 0.14 | 1 | 240 | 12 : 1 | 16 |
| 12 | THF | <i>t</i> -BuLi | 13 | -78 | 0.11 | 0.6 | 90 | 14 : 1 | 46 |
| 13 | THF | <i>t</i> -BuLi | 18 | -78 | 0.10 | 1 | 90 | 9 : 1 | 53 |
| 14 | THF | <i>t</i> -BuLi | 11 ^d | -78 | 0.08 | 1.8 | 120 | 22 : 1 | 50 |
| 15 | THF | <i>t</i> -BuLi | 13 | -78 | 0.08 | 4.9 | 120 | 23 : 1 | 57 |
| 16 | THF | <i>t</i> -BuLi | 15 | -40 | 0.06 | 1.4 | 2880 | 23 : 1 | 47 |
| 17 | THF | <i>t</i> -BuLi | 12 | -78 | 0.05 | 0.4 | 120 | 7 : 1 | 50 |
| 18 | THF | <i>t</i> -BuLi | 15 | -78 | 0.09 | 1 | 180 | 1 : 1 | 1 |

^aYb(OTf)₃ added to a solution of aldehyde, cooled to -78 °C then a solution of anion added.

^bReaction quenched with TMSCl.

^cReaction concentration based on anion.

^dHMPA was precipitated out of solution at -78 °C and was redissolved by addition of THF. Most likely entries 4-6 also resulted in HMPA precipitation.

reaction. Garner's aldehyde (**54**) synthesized from serine in five high yielding steps, following a literature procedure and used in sulfone addition reactions summarized in Table 6.2.¹⁵

Low yields were obtained uniformly regardless of variation of base, solvent, equivalencies, or additives. The highest yields obtained were in the mid 50% range. While solvent and base showed little effect on the diastereometric ratio, addition of HMPA greatly improved diastereoselectivity of **378** to **379** (23 : 1, entries 14-16).¹⁶ No further improvement to the ratio could be obtained by higher amounts of HMPA. The products were inseparable by flash chromatography and were purified by HPLC for characterization. However, compounds **378** and **379** were crystalline and product **378** could be separated by recrystallization alone when the diastereoselectivity was high. With the exception of entry 10, (Table 6.2) the favored *anti* product **378** was consistent with Felkin-Ann addition.¹⁷

The configuration of **378** was determined by X-ray crystallography, and by deduction **379** was revealed (Figure 6.1). The X-ray structure of **378** shows an *anti* periplanar relationship for the nitrogen and the hydroxyl.

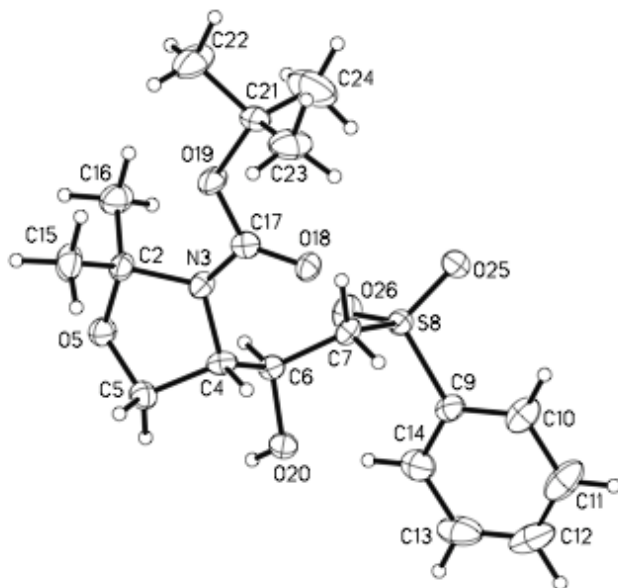
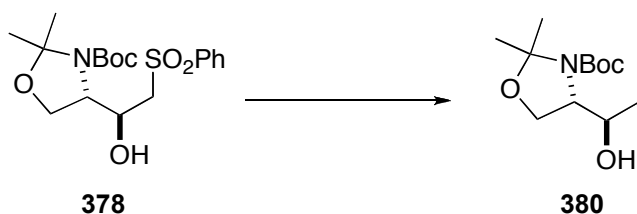


Figure 6.1: X-ray crystal structure of sulfone **378**.

6.3.1. Preliminary Investigation of Sulfone Removal

A preliminary investigation on the removal of the sulfone from **378** was performed using a number of literature and modified literature procedures (Table 6.3).¹⁸⁻
²⁵ Many of these reactions showed no reaction or decomposition of the starting material. However the use of nickel aluminum hydride (“Ni-Al-H”) showed promise with 73% yield (entry 5). The only other reaction that showed any product was the NaHg reduction in DMF/MeOH using a buffer (37%, entry 9). Spectroscopic data for known compound **380** matched literature values.²⁶

**Table 6.3:** Sulfone removal from compound **378**.

| Entry # | Solvent | Reagents (Equiv) | Rxn. Temp (°C) | Time (h) | Obs. | Yield % |
|----------------|----------------------|--|----------------|----------|---------|---------|
| 1 | EtOH | Raney Ni | 80 | 20 | no rxn. | 0 |
| 2 | MeOH/THF | NiCl ₂ (4), NaBH ₄ (32) | 24 | 4 | no rxn. | 0 |
| 3 | THF | NiCl ₂ (7), LAH (87) | 24 | 4 | dec. | trace |
| 4 | THF | NiCl ₂ (10), LAH (105), PPh ₃ (20) | 24 | 24 | dec. | 0 |
| 5 | THF | NiBr ₂ (15), LAH (180), PPh ₃ (30) | 24 | 42 | | 73 |
| 6 ^a | DCM/buffer | NaHg (excess) | 24 | 1.25 | no rxn. | 0 |
| 7 | DMF/H ₂ O | Na ₂ S ₂ O ₄ (7), NaHCO ₃ (10) | 110 | 120 | no rxn. | 0 |
| 8 | THF | NiAc ₂ (0.4), i-PrMgCl (3), | 24 | 3 | no rxn. | 0 |
| 9 | DMF/MeOH | NaHg (49), Na ₂ HPO ₄ (23) | -20 | 1 | | 37 |
| 10 | MeOH | NaHg (31), Na ₂ HPO ₄ (11) | -20 | 1 | no rxn. | 0 |
| 11 | DMF/MeOH | NaHg (70), NiCl ₂ (37) | 24 | 1 | dec. | 0 |

^a buffer was pH 7 sodium phosphate buffer. The reaction showed a trace of elimination product after 5 min.

6.3.2. Initial Attempts at Dianion Addition

Successful removal of the sulfone from **378** suggested that this functionality might be removed in the presence of a β -hydroxyl leaving group. Unfortunately, sulfone **378** proved to be unsuitable for dianion addition reactions (Table 6.4). The maximum yield observed for **381** was only 7% when **378** was used as the starting material and no product was observed with **368** (entry 4 and 5).

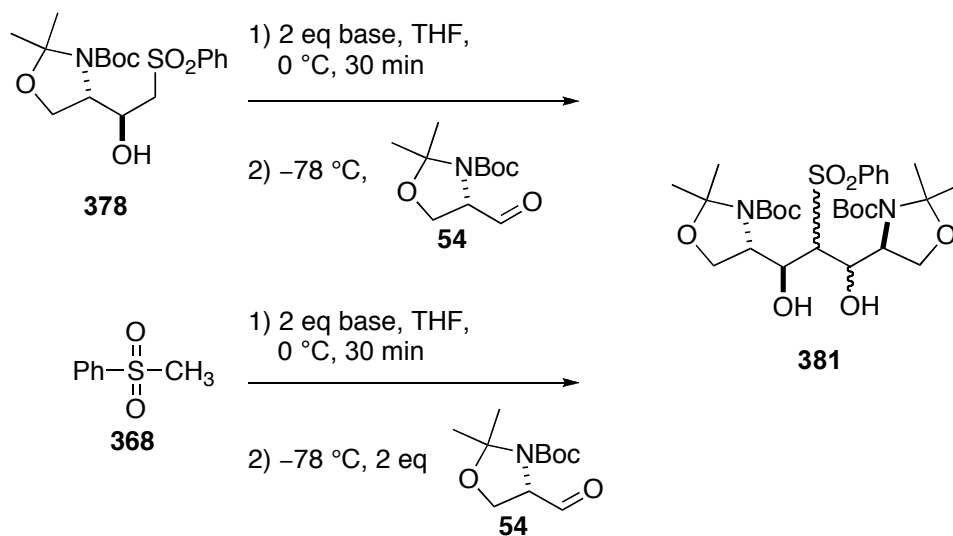


Table 6.4: Sulfone dianion synthesis of **381**.

| Entry # | Starting Material | Base | Additive (equiv.) | Time (h) | Yield % |
|---------|-------------------|------------------|-------------------|----------|---------|
| 1 | 378 | <i>n</i> -BuLi | | 1 | 0 |
| 2 | 378 | NaHMDS | | 2 | 0 |
| 3 | 378 | <i>n</i> -BuLi | | 1.75 | 7 |
| 4 | 368 | <i>n</i> -BuLi | | 1 | 0 |
| 5 | 368 | <i>i</i> -PrMgCl | HMPA (10) | 4 | 0 |

It appeared that during generation of the dianion most of the starting material **378** was channeled to intramolecular cyclization product **382** (Figure 6.2). A small amount of this side product was also seen upon additions to **54** using **368**.

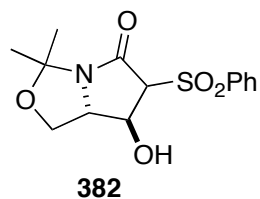
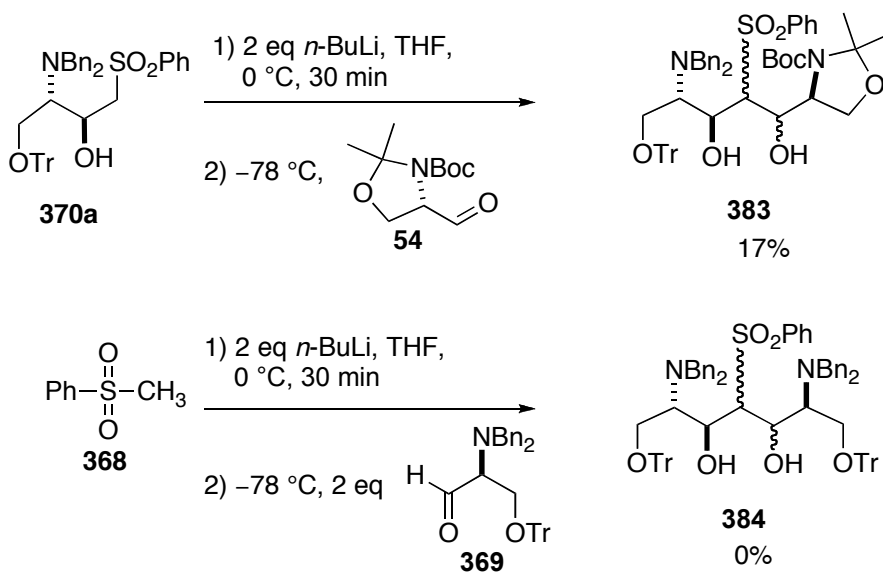


Figure 6.2: Side product **382**.

A few other attempts were made to perform dianion addition reactions; the only successful reaction was the addition of **370a** to **54** as shown in Scheme 6.4. Compound

370a showed promise in the dianion addition reaction but due to the difficulty in purifying starting material **370a** this work was suspended.



Scheme 6.4: More sulfone dianion additions.

6.3.3. New Sulfone Addition Products

The inability to generate a stable dianion from **378** and the difficulty in obtaining **370a** required a diversion in tactics. Table 6.5 shows the results for the sulfone anion addition to the serine-derived aldehyde **193**.²⁷ Aldehyde **193** could be made from serine in five high yielding steps according to literature procedures,^{15,28,29} and the addition reaction proved to be high yielding but diastereoselectivity remained low (~2 : 1). Fortunately, compounds **385** and **386** were separable by flash chromatography alleviating one of the difficulties of the previous sulfone addition reactions.

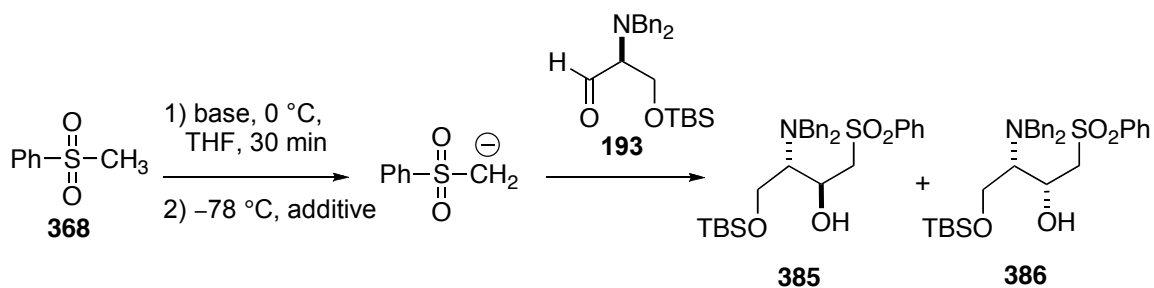
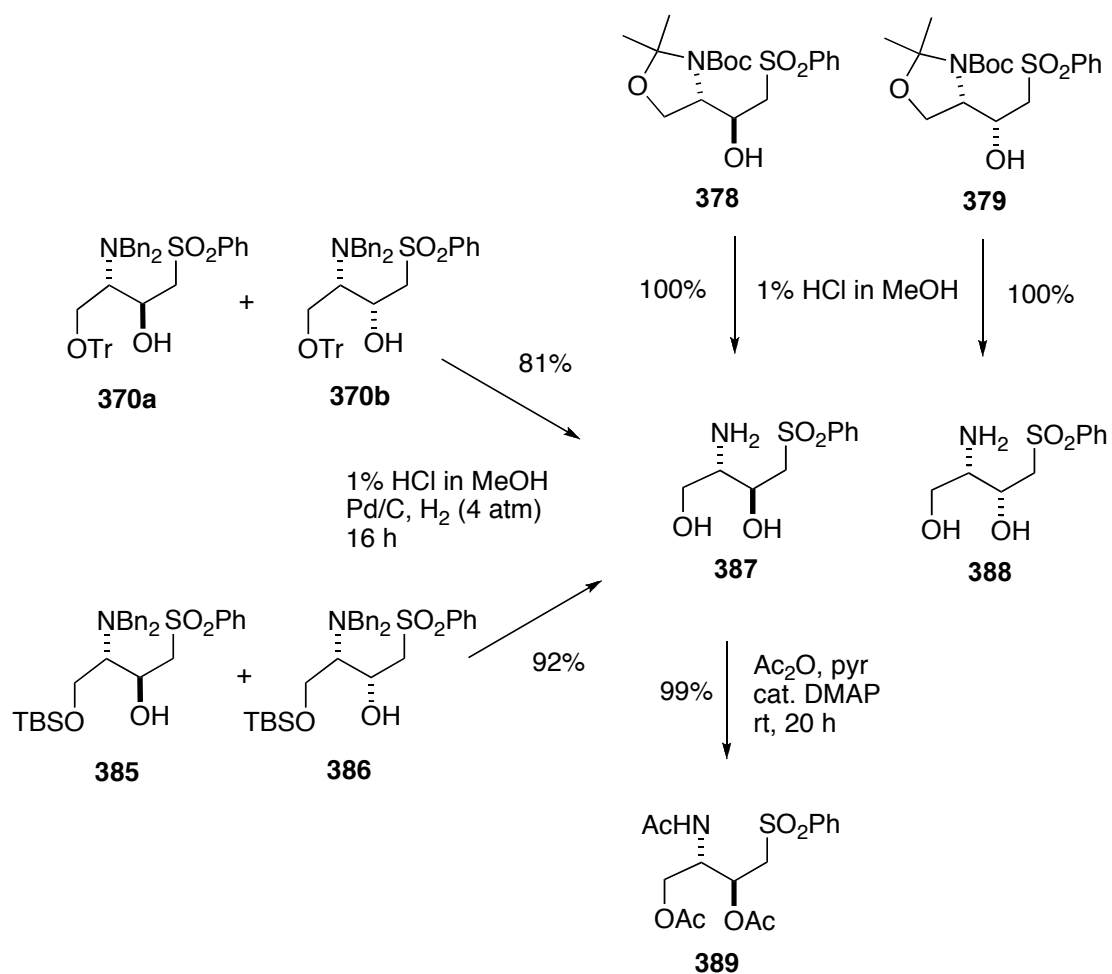


Table 6.5: Sulfone anion addition to aldehyde **193**.

| Entry # | Base | Additive (equiv) | Anion (equiv) | Time (h) | Ratio 385 : 386 | Yield % |
|---------|---------------------------------|---------------------------------------|---------------|----------|-------------------------------|---------|
| 1 | <i>i</i> -PrMgCl | HMPA (9) | 2.1 | 1.5 | 2.1 : 1 | 59 |
| 2 | <i>t</i> -BuLi | HMPA (13) | 2.3 | 3 | 2.3 : 1 | 55 |
| 3 | <i>t</i> -BuLi/CuI ^a | Et ₂ O•BF ₃ (3) | 1.5 | 3 | 1.8 : 1 | 50 |
| 4 | <i>i</i> -PrMgCl | | 2.0 | 1.5 | 2.0 : 1 | 99 |
| 5 | <i>t</i> -BuLi | | 1.3 | 3 | 2.8 : 1 | 83 |
| 6 | <i>t</i> -BuLi | | 1.4 | 0.3 | 2.5 : 1 | 94 |

^a CuI (1eq) added to anion at -78 °C then aldehyde added with Et₂O•BF₃.

The relative configurations for the products **385** and **386** as well as the previously synthesized OTr protected versions was secured by deprotecting sulfones **378** and **379** of known configuration, and comparing the ¹H NMR with that of those deprotected **370a/370b** and **385/386** (Scheme 6.5). Deprotection was quantitative for preparation of **387** and **388** from **378** and **379**, respectively. For comparison, mixtures of **370a/370b** and **385/386** were deprotected in dry HCl in methanol under hydrogenation conditions to give a mixture of products in 81% and 92% yields respectively.³⁰



Scheme 6.5: Deprotection of sulfone anion addition products.

Compound **387** was converted into the peracetate using standard conditions to give the crystalline product **389** in 99% yield.³¹ An X-ray structure verified the relative configuration of this compound (Figure 6.3).

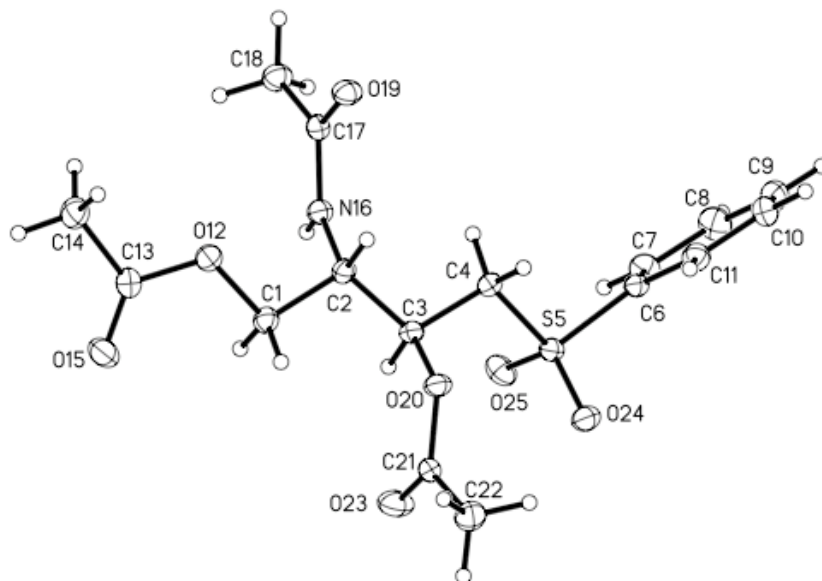


Figure 6.3: X-ray crystal structure of acetate **389**.

6.3.4. Sulfone Dianion Additions.

The new sulfone **385** was now available in sufficient quantity for evaluation of sulfone dianion addition reactions. This new sulfone proved to be stable to the conditions for dianion generation (Table 6.6).^{32,33} The highest yield was 52% when three equivalents of *t*-BuLi were used for deprotonation (entry 4). The low yields were consistent with those observed with previous additions to aldehyde **54**. Compounds **390** and **391** were separated by silica chromatography as a mixture of epimers at the carbon adjacent to S.

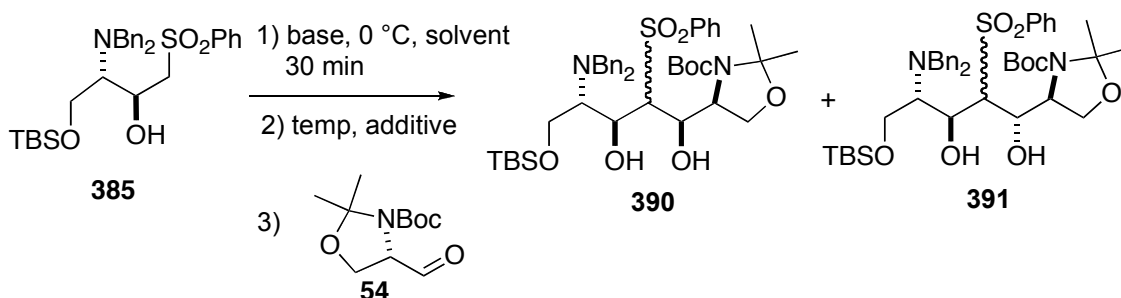
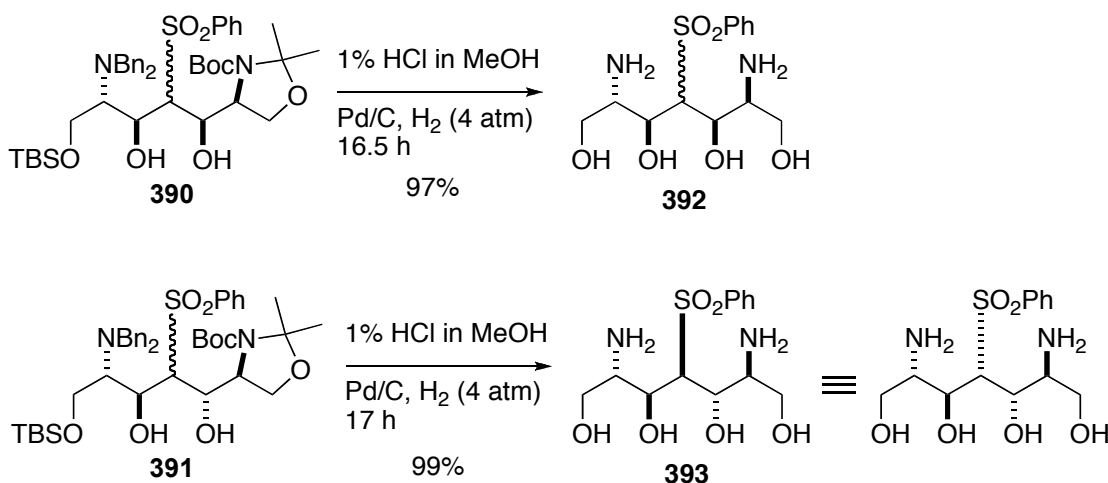


Table 6.6: Sulfone dianion addition to aldehyde **54**.

| Entry # | Base (Equiv.) | Additive (Equiv. to Anion) | Temp (°C) | Aldehyde Equiv. | Time (h) | Ratio 390 : 391 | Yield % |
|----------------|----------------------|----------------------------|-----------|-----------------|----------|-------------------------------|---------|
| 1 ^a | <i>t</i> -BuLi (2.6) | na | -20 | 1.9 | 23 | na | 49 |
| 2 | <i>t</i> -BuLi (2.0) | HMPA (12) | -20 | 1.2 | 16 | na | 0 |
| 3 | <i>t</i> -BuLi (2.0) | na | -20 | 1.2 | 16 | na | 0 |
| 4 | <i>t</i> -BuLi (3.0) | na | -20 | 1.4 | 23 | 1 : 1 | 52 |
| 5 | <i>t</i> -BuLi (3.0) | HMPA (14) | -20 | 1.4 | 23 | 1 : 1 | 43 |
| 6 | <i>t</i> -BuLi (2.0) | HMPA (15) | 0 | 1.2 | 4 | na | 0 |
| 7 | <i>t</i> -BuLi (3.0) | HMPA (15) | -40 | 1.2 | 17 | 1 : 1 | 35 |
| 8 | <i>t</i> -BuLi (3.0) | na | -40 | 1.5 | 3 | 1 : 1 | 37 |

Assignment of the new hydroxyl center in compounds **390** and **391** was made by fully deprotecting the compounds and evaluating their ¹H NMR spectra (Scheme 6.6).



Scheme 6.6: Deprotection of sulfone diaddition products.

Due to symmetry **393** gave a single set of ^1H NMR signals and was a single compound, however **392** was observed as a mixture of epimers.

6.3.4.1. Bioassay

Compounds **387**, **388**, **392**, and **393** was assayed for biological activity against the fungal strains *Candida albicans* 96-489, *C. krusei*, *C. glabrata*, *C. albicans* ATCC 14503 (Table 6.7).

Table 6.7: Biological testing of zwittermicin A and synthetic sulfones.

| Biological Strains | MIC ^{a,b} ($\mu\text{g}/\text{mL}$) | | | | |
|---|--|------------|------------|------------|------------|
| | (+)- 1 | 387 | 388 | 392 | 393 |
| <i>Candida albicans</i> 96-489 ^d | 55.7 | >100 | >100 | >100 | >100 |
| <i>C. glabrata</i> ^d | 59.5 | >100 | >100 | >100 | >100 |
| <i>C. albicans</i> ATCC 144503 | >100 | >100 | >100 | >100 | >100 |
| <i>C. krusei</i> | >100 | >100 | >100 | >100 | >100 |

^aThe MIC endpoint is defined as the lowest concentration ($\mu\text{g}/\text{mL}$) with 90% growth inhibition.

^bCompounds (+)-**1** was tested as a free amine before testing while the remaining compounds were tested as hydrochloride salts.

^dFluconazole-resistant strains.

Results indicated there was no activity except for natural zwittermicin A. This is consistent with the results of chapter 5 where only (+)-**1** showed biological activity.

6.3.5. Investigation of Sulfone Removal

Removal of the sulfone moieties in **390** and **391** would give compounds representing the C9-C15 portion of zwittermicin A. Table 6.8 shows the results of a number of attempts to remove the sulfone from **390**, but it can clearly be seen that no practical method was found.³⁴⁻⁴⁴ The difficulty lies primarily in the presence of two beta-

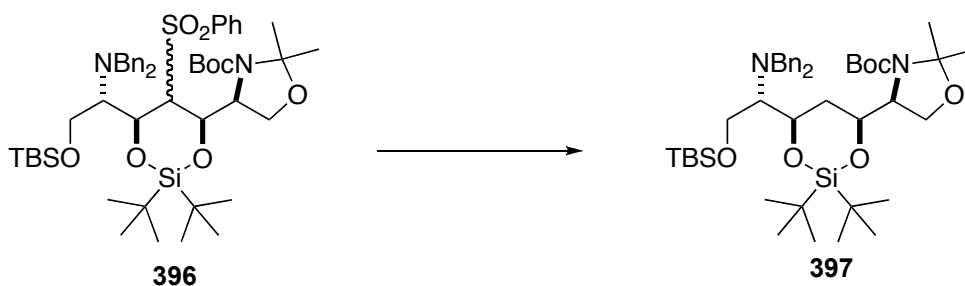
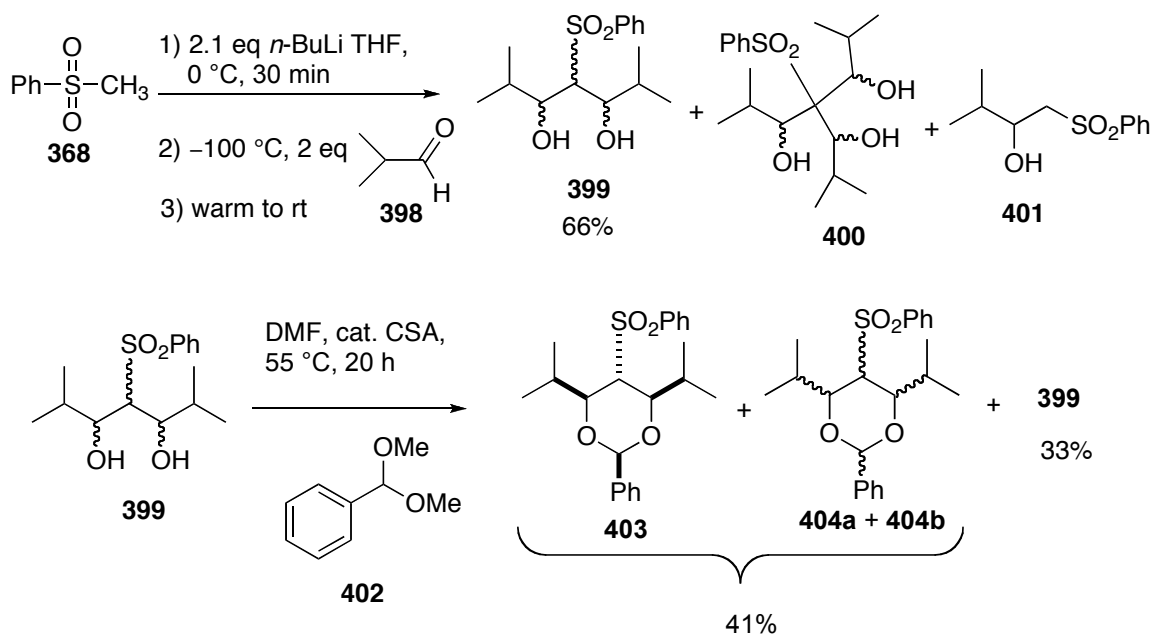


Table 6.9: Sulfone removal from compound **396**.

| Entry # | Solvent | Reagents (Equiv) | Rxn. Temp (°C) | Time (min) | Notes | Yield % |
|---------|----------|---|----------------|------------|-------|---------|
| 1 | MeOH | NaHg (30), Na ₂ HPO ₄ (10) | 24 | 90 | elim | 0 |
| 2 | THF/MeOH | NaHg (200), Na ₂ HPO ₄ (100), 1,4-cyclohexadiene (20) | 24 | 45 | elim | 0 |
| 3 | EtOH | Mg (100), Na ₂ HPO ₄ (10), 1,4-cyclohexadiene (20) | 24 | 60 | elim | 0 |
| 4 | THF | Na (50), naphthalene (excess), 1,4-cyclohexadiene (20) | 24 | 20 | dec | 0 |

6.4. Synthesis of Model Sulfone

Quantities of sulfone **390** were now scarce and therefore an alternate compound for sulfone removal reactions was prepared (Scheme 6.8). Diaddition product **399** was formed in 66% yield with the remaining material being either monoaddition product or triaddition product. Similar mixtures have been reported in the literature with sulfone anion reactions.⁴⁷ Diaddition product **399** was then protected as the benzylidene acetal in 41% yield (33% recovered starting material).⁴⁸



Scheme 6.8: Synthesis of protected sulfone **403**.

The isomer **403** was separable by flash chromatography (silica) and the configuration of this compound was evident from the large vicinal coupling ($J = 9.0$ Hz) of the protons in the dioxane ring as well as an observed nOe between the ring acetal proton at δ 5.37 ppm and the CH-O signals at δ 4.04 ppm.

6.4.1. Attempts to Remove Sulfone from **403**

Attempts to remove the sulfone from **403** were uniformly unsuccessful, giving mostly partial decomposition or no reaction (Table 6.10).

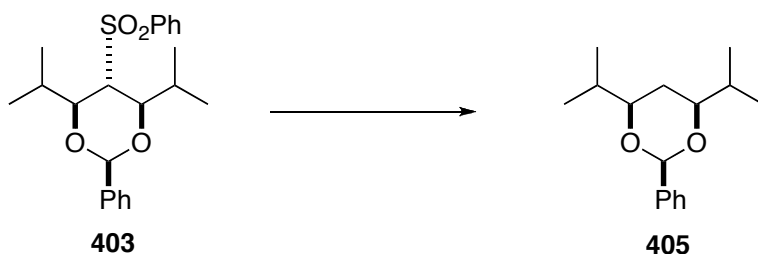


Table 6.10: Sulfone removal from compound **403**.

| Entry # | Solvent | Reagents | Rxn. Temp (°C) | Time (min) | Notes | Yield % |
|---------|---------|---|----------------|------------|-------------|---------|
| 1 | THF | Na, naphthalene | -80 | 20 | no rxn | 0 |
| 2 | THF | Na, naphthalene | -80 | 90 | partial dec | 0 |
| 3 | THF | Li, naphthalene | -80 | 20 | partial dec | 0 |
| 4 | THF | SmI | -80 | 720 | no rxn | 0 |
| 5 | THF | Na, naphthalene | -78 | 20 | | 0 |
| 6 | THF | Li, naphthalene, 1,4-cyclohexadiene | -20 | 20 | | 0 |
| 7 | THF | SmI, HMPA | -80 | 20 | | 0 |
| 8 | THF | NiBr ₂ , LAH, PPh ₃ | -80 | 960 | | 0 |

6.5. Other Sulfur Based Dianion Additions

Failure of the sulfone methodology required an alternate strategy for the synthesis of the C9-C15 portion of zwittermicin A. The sulfone in **390** was resistant to reductive cleavage by Raney nickel however it is known that this reagent will also remove dithianes, which like sulfones, function as “umpulong” equivalents.⁴⁹ Consequently, a short investigation was made of dithiane addition to aldehyde **193** (Table 6.11).⁵⁰ Diastereoselectivity for the anion addition could be partially reversed by addition of HMPA to the reaction mixture however this also resulted in a decreased yield.

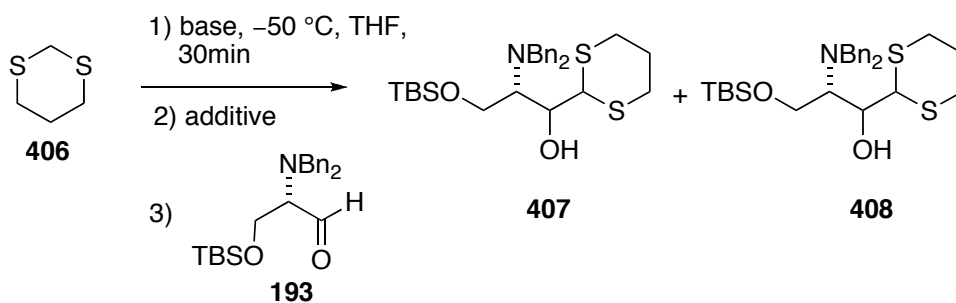


Table 6.11: Dithiane addition to aldehyde **193**.

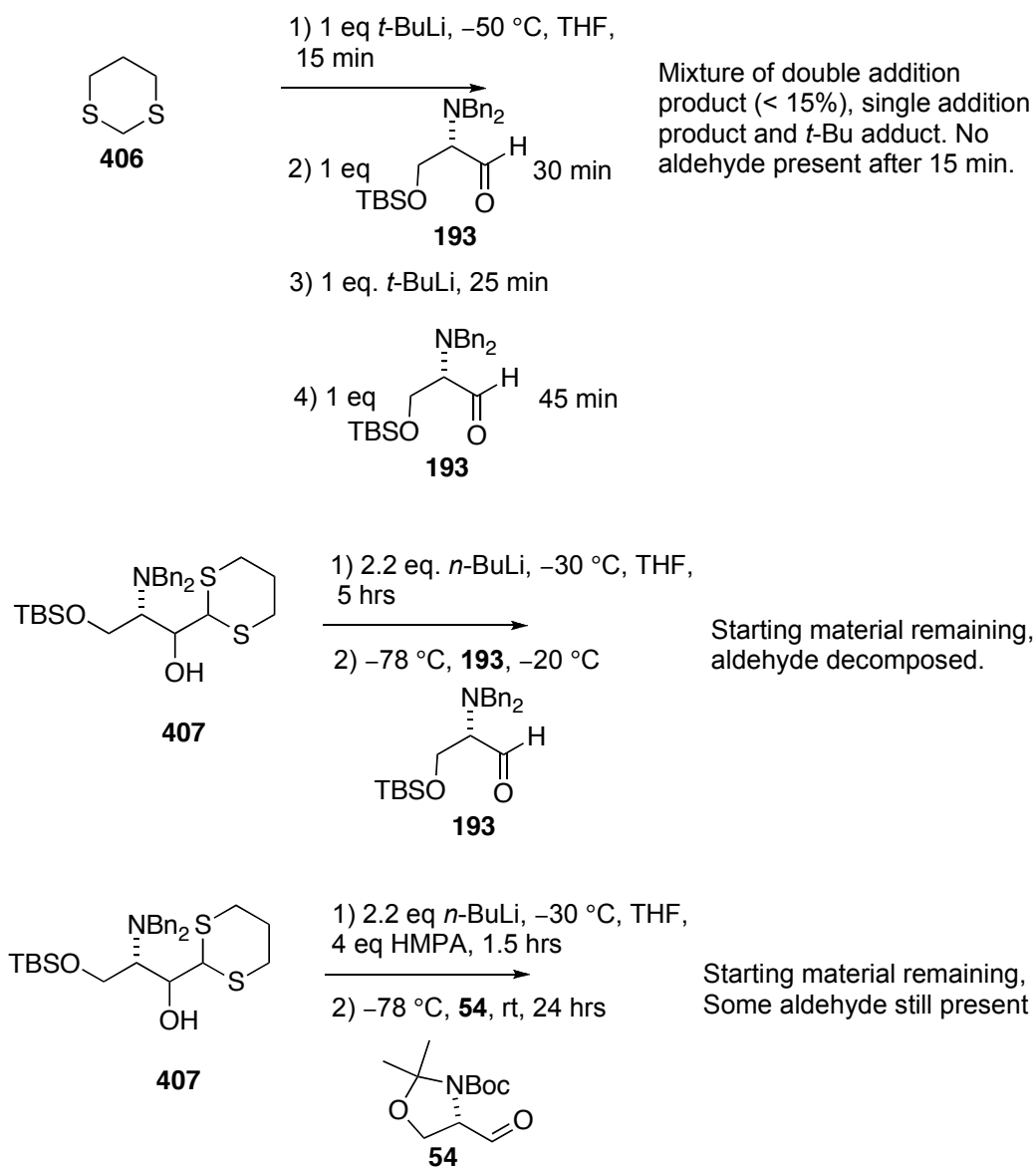
| Entry # | Base (Equiv.) | Additive (Equiv) | Rxn. Temp ($^{\circ}\text{C}$) | Anion Equiv | Time (min) | Ratio 407 : 408 | Yield % |
|----------------|----------------------|------------------|----------------------------------|-------------|------------|-------------------------------|---------|
| 1 ^a | <i>t</i> -BuLi (0.8) | HMPA (29) | -78 | 2 | 150 | na ^b | 17 |
| 2 | <i>t</i> -BuLi (1.1) | na | -20^{c} | 1 | 75 | 1 : 10 | 79 |
| 3 | <i>t</i> -BuLi (1.1) | HMPA (15) | -20^{c} | 1 | 75 | 1.3 : 1 | 30 |

^aAnion generated at $0\text{ }^{\circ}\text{C}$ for 30 min, HMPA added and solution stirred a further 30 min.

^bMaterial lost on alumina column.

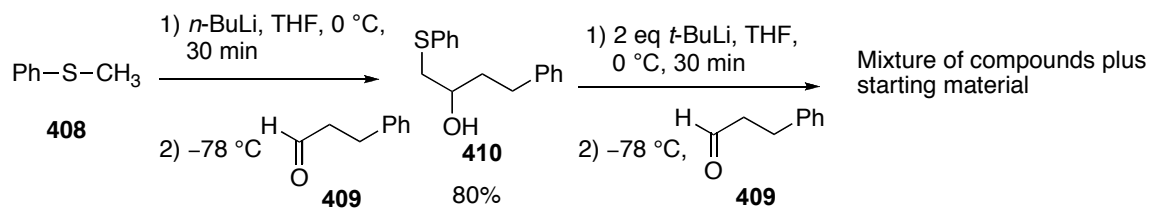
^cReaction started at $-50\text{ }^{\circ}\text{C}$ for 45 min then warmed to $-20\text{ }^{\circ}\text{C}$ for 30 min.

A survey of dianion addition reactions with 1,3-dithiane were carried out (Scheme 6.9).⁵¹ Only one reaction showed some diaddition products in very low yield. These diaddition products were inseparable mixtures and unsuitable for synthesis of zwittermicin A.



Scheme 6.9: Dianion addition reactions with dithianes.

One final attempt was made to use thioanisole for a diaddition reaction to hydrocinnamaldehyde (Scheme 6.10).⁵² The first addition went well with 80% yield giving the known monoaddition product **410**. However the dianion addition reaction gave a mixture of products and left over starting material. With this final failure the use of sulfur chemistry for the synthesis of zwittermicin A was abandoned.



Scheme 6.10: Dianion addition using thioanisole.

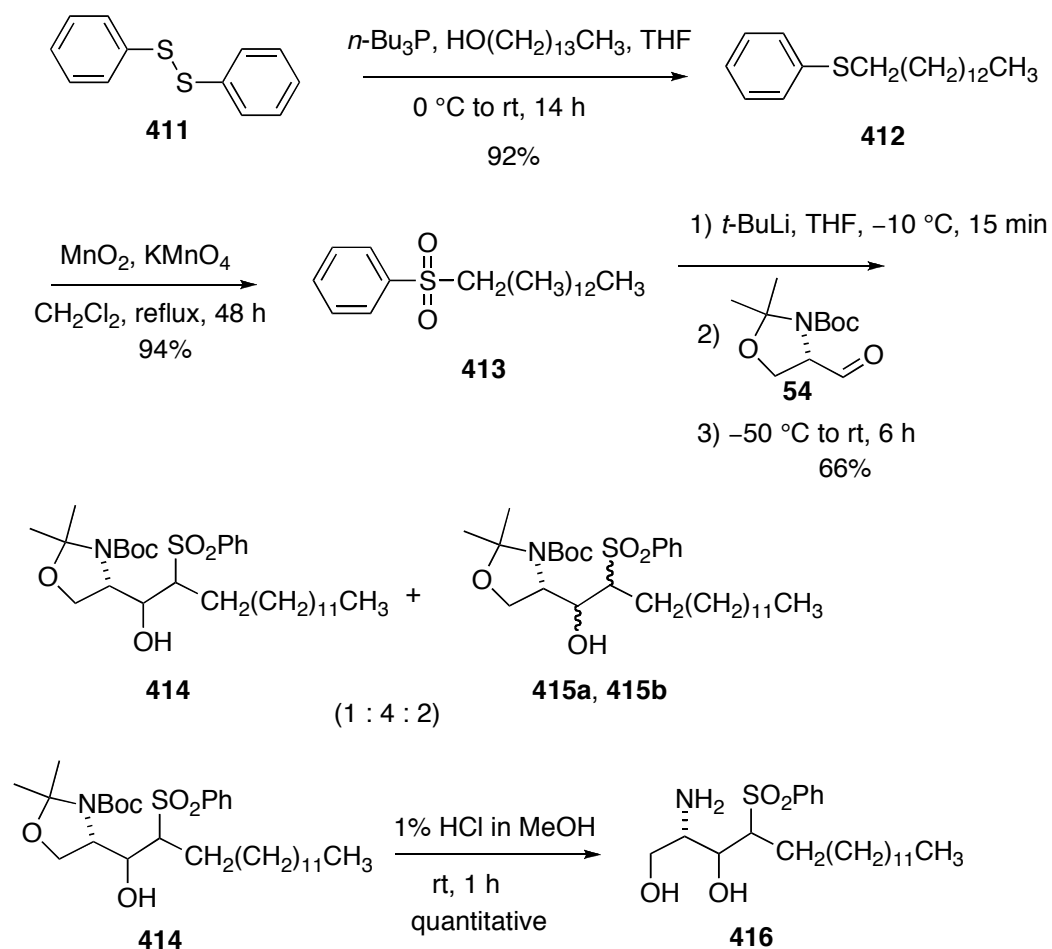
6.6. Use of Sulfone Chemistry for Synthesis of LC/MS Standards

While working on developing a method for analysis of sphingolipids there arose a need for suitable surrogate and internal standards for LC/MS analysis. The desire was to have a surrogate standard with similar properties to those of the sphingolipids to be analyzed. For the internal standard the requirement was a standard that had some of the ionization characteristics of the compounds to be analyzed. The synthesis should provide compounds with a chain length that could not be generated biologically and therefore would not be present in a biological matrix.

6.6.1. Synthesis of Internal Standard

The internal standard was synthesized as shown in Scheme 6.11. The first step proceeded smoothly using phenyldisulfide to convert tetradecanol to known thioether **412** (92% yield).^{53,54} After a number of attempts to oxidize sulfide **412** using reagents including basic NaOCl and hydrogen peroxide it was found that the best yield was obtained with MnO₂ and KMnO₄ which gave **413** in 94% yield.⁵⁵⁻⁵⁷ NMR data for the known compound **413** matched literature values.⁵⁸ The anion derived from sulfone **413** was added to Garner's aldehyde, giving diastereomers **414**, **415a**, and **415b** in 66% yield and a ratio of 1 : 4 : 2 respectively. This yield is consistent with the previously observed modest yields of sulfone additions to this aldehyde. Compound **414** was separable by

flash chromatography and therefore was taken forward and deprotected to give the internal standard **416** in quantitative yield. This compound proved to be effective as an internal standard for the sphingosine LC/MS method.

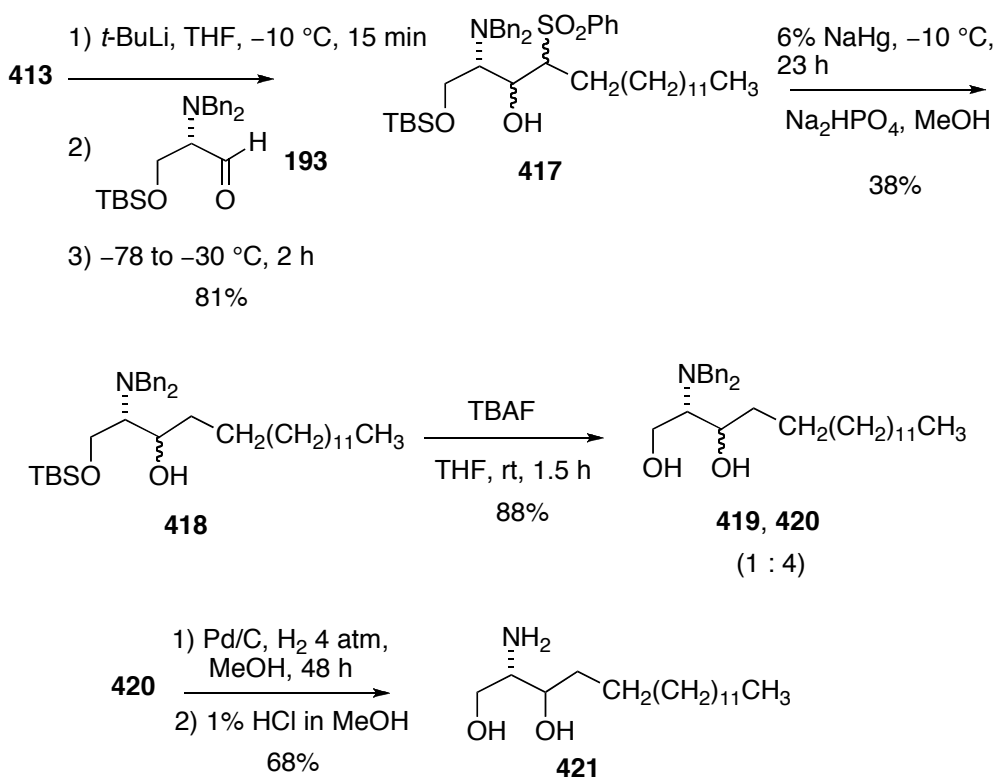


Scheme 6.11: Synthesis of internal standard **416**.

6.6.2. Synthesis of Surrogate Standard

The synthesis of a C₁₇ sphingosine surrogate standard began with addition of the anion of **413** to aldehyde **193** to give **417** in 81% yield and, following removal of the sulfone with NaHg, gave **418** in 38% yield (Scheme 6.12). Both **417** and **418** were mixtures of diastereomers which were not separable by flash chromatography (silica).

The low yield for the sulfone removal is most likely due to the β -elimination side products. The TBS protecting group in **418** was removed to give **419** and **420** in a 1 : 4 ratio and 88% yield. These two compounds were separable by flash chromatography (silica).



Scheme 6.12: Synthesis of surrogate standard **421**.

Compound **420** was taken forward and fully deprotected to give surrogate C₁₇ standard **421** in 68% yield.

6.7. Conclusion

Initial attempts at synthesis of zwittermicin A focused on two primary routes for the synthesis of the C₉-C₁₅ portion of the molecule. The first diyne route was discontinued after only a few steps. The second route that was pursued most extensively

involved sulfone anion and dianion additions to serine-derived aldehydes. While some control over yield or diastereoselectivity for the first anion addition could be achieved, the second dianion addition showed little selectivity and mediocre yields. Even worse was the fact that the sulfone could not be removed from the diaddition product without extensive decomposition. A short investigation of model compounds revealed that competing beta-elimination in reductive removal of the sulfone from the diaddition product could not be surmounted and this route was abandoned in the synthesis of zwittermicin A. A brief investigation of dithiane and thioanisole revealed other difficulties with these substrates as possible precursors for the C9-C15 unit of zwittermicin A.

Although sulfone chemistry did not work for the synthesis of zwittermicin A, it was satisfactory for synthesis of two compounds that were used as standards in LC/MS analysis of sphingolipids. The first was a sulfonyl sphingosine derivative synthesized in two steps from a serine-derived aldehyde while the second was a surrogate C₁₇ sphingosine standard synthesized in four steps from a similar aldehyde.

6.8. Acknowledgements

Dr. Doralyn S. Dalisay performed the bioassay of synthetic and natural compounds.

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Chapter 7 Experimental

7.1. Materials and Methods

7.1.1. General Procedures

All non-aqueous reactions were carried out in oven-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. Solvents for dry reactions (DCM, DMF, THF, toluene, acetonitrile, Et₂O) were passed through twin alumina columns (J. C. Myer, Glass Contour). DMSO was distilled from calcium hydride under reduced pressure and stored over 4 Å molecular sieves. Dry MeOH was prepared and stored over 4 Å molecular sieves. Triethylamine, pyridine and Hünig's base were distilled from calcium hydride. All other commercially available reagents were used as received. Reactions were monitored by thin layer chromatography (TLC) using 0.25-mm E. Merck per-coated silica gel plates.

NMR spectra were recorded on a Varian Mercury-400 (400 MHz), a Varian Unity-500 (500 MHz) or a Varian Inova-400 (400 MHz) spectrometer. NMR solvents were obtained from Cambridge Isotope Laboratories. Chemical shifts are reported in parts per million (ppm) and referenced to residual solvent signal as the internal standard relative [CHCl₃ (δ 7.26) or CD₂HOD (δ 3.31) for ¹H, or CDCl₃ (δ 77.16) or CD₃OD (δ 49.0) for ¹³C] unless otherwise stated. HRMS were run by either University of California, Riverside mass spectrometry facility, University of California, San Diego mass spectrometry facility or the Scripps Research Institute's Center for Mass Spectrometry. Optical rotations were obtained using a Jasco DIP-370 digital polarimeter, a Jasco P-1010

or a Jasco P-2000 polarimeters in cells of 10 mm, 50 mm or 100 mm pathlength (concentrations, c , expressed in g/100 mL). Optical rotations for certain compounds were not reported due to being too small for accurate measurements. IR spectra were obtained on a Mattson Galaxy Series FTIR 3000 or a Nicolet Magna IR 550 spectrometer as thin films (deposited on KBr plates) or on a Jasco 4100 FTIR using ATR (ZnSe plate). The ee analysis for diaminopropionamides (-)-**319** and (+)-**319** were conducted using Marfey's method by derivatization with 2,4-dinitrophenyl-5-fluoro-L-leucinamide under standard conditions followed by analysis (C_{18} HPLC-MS). Normal-phase HPLC was carried out on a Rainin Rabbit HP systems using a 100 Å SiO_2 10 x 250 mm Microsorb column with a UV detector.

7.1.2. Determination of configuration of C4 in Zwittermicin [(+)-**1**]

A solution of **1** (148 µg) in 50 µL water and 6 N HCl (1 mL) was heated in a sealed tube at 110 °C for 24 hours. The solution was concentrated to dryness under a N_2 stream to and the hydrolysate redissolved in 1.0 mL of H_2O .

Marfey's Method. The above hydrolysate solution (100 µL) was treated with a solution of 2,4-dinitrophenyl-5-fluoro-L-alaninamide (100µL, 1% w/v in acetone), or its enantiomer 2,4-dinitrophenyl-5-fluoro-D-alaninamide, followed by 1.0 M $NaHCO_3$ (20 µL), then heated in a sealed tube at 80 °C for 10 min. The mixture was cooled and quenched with 1.0 M HCl (20 µL). The preceding paired derivatization procedure was applied to authentic (2*S*)-(-)-albizziin (Sigma-Aldrich).

LC Analysis. The solutions from Marfey's method were analyzed by LC-MS using an Agilent series 1100 HPLC with a Phenomenex Luna C-18 column (100 mm x

2.00 mm, 3 μ m) connected to a Thermo Finnigan MSQ. LC parameters were as follows; Flow rate 0.40 mL/min, initial 90% solvent A (H₂O + 0.1% formic acid) 10% solvent B (acetonitrile), @ 15 min 70% A, @ 20 min 100% B hold for 5 min, @ 28 min 90% A hold for 2 min. Injection volume was 6 μ L. MSQ parameters were as follows; ESI-MS, selected ion monitoring at m/z 400 [M+H]⁺, span 2.0 amu, dwell 1.00 sec, cone 90 V, probe temperature 350 °C. Retention times for the two peaks were t_R =14.15 min and t_R =14.75 min for the “L-Marfey’s(-)-albizziin” (**217**) and “D-Marfey’s(-)-albizziin” (**218**) products, respectively.

The L-Marfey’s derivative of the hydrolysate from **1** had a retention time of t_R =14.13 min. Coinjection of this sample with **217** showed a single peak with retention time of 14.15 min indicating an *S* configuration for the *N*³-ureido-2,3-diaminopropionic acid residue in **1**.

7.1.3. Chapter 2 Methods

Compounds **226**, **227**, and **239** through **241** were synthesized according to literature procedure and matched literature values.

(S)-N,N-dibenzyl-2-(tert-butyl-diphenylsilyloxy)-1-((S)-oxiran-2-yl)ethanamine (228).

Under an atmosphere of nitrogen, *n*-BuLi (3.76 mL, 9.41 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (*S*)-aldehyde **226** (1.60 g, 3.15 mmol) and CH₂I₂ (0.76 mL, 9.41 mmol) in anhydrous THF at -78 °C. The mixture was stirred for 30 min then warmed to room temperature. The solution was stirred at room temperature for 1 hour then quenched with 10 mL saturated aqueous NH₄Cl. The mixture was extracted

with ethyl ether (4 x 15 mL) and combined extracts washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography on triethylamine-saturated silica (1% triethylamine in 1:19 EtOAc:hexane) provided **228** (1.34 g, 81%, de = 94%) as a light yellow viscous oil: IR (neat) ν 3069, 3026, 2998, 2956, 2888, 2857, 2803, 1602, 1589, 1493, 1471, 1453, 1428, 1390, 1362, 1253, 1112, 1027, 866, 823, 740, 699, 612 cm⁻¹; [α]_D²³ +5.6 (*c* 5.64, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 1.11 (s, 9H), 2.60 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.73-2.79 (m, 2H), 3.19 (m, 1H), 3.83-3.98 (m, 6H), 7.20-7.50 (m, 16H), 7.71 (d, *J* = 8.0 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 19.3 (C), 27.0 (CH₃), 46.1 (CH₂), 51.3 (CH), 55.3 (CH₂), 60.5 (CH), 61.7 (CH₂), 127.0 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 129.8 (CH), 129.9 (CH), 133.2 (C), 133.4 (C), 135.7 (CH), 135.8 (CH), 140.3 (C); HRMS *m/z* 522.2813 [M+H]⁺, calcd. for C₃₄H₄₀N₁O₂Si₁ 522.2828.

(S)-2-(dibenzylamino)-2-((S)-oxiran-2-yl)ethanol (242). Under an atmosphere of nitrogen TBAF (100 μ g, 100 μ mol, 1 M in THF) was added to a stirred solution of epoxide **228** (7.2 mg, 14 μ mol) in THF (50 μ L) at room temperature. The mixture was stirred for 1 hour then quenched by addition of saturated aqueous NH₄Cl (5 mL). The mixture was extracted with ethyl ether (3 x 3 mL) and combined extracts washed with brine (3 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 1:3 ethyl acetate : hexane) provided the **242** (2.7 mg, 67%) as a viscous oil. Compound **242** matched literature values and was used to verify the configuration of **228** as well as determine de by NMR.

(2*S*,3*R*)-1-(*tert*-butyldiphenylsilyloxy)-2-(dibenzylamino)-7-(4-methoxybenzyloxy)hept-5-yn-3-ol (243). Under an atmosphere of nitrogen, n-BuLi (255 μ L, 633 μ mol, 2.5 M in hexane) was added dropwise to a stirred solution of PMB protected propargyl alcohol (121 mg, 690 μ mol) in anhydrous THF at -10 $^{\circ}$ C. The mixture was stirred for 1 hour then cooled to -78 $^{\circ}$ C and epoxide **228** (300 mg, 575 μ mol in THF) was added dropwise followed by slow addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (24.3 μ L, 575 μ mol in THF). The mixture was stirred for 1 hour then slowly warmed to -10 $^{\circ}$ C. The solution was quenched with 10 mL saturated aqueous NH_4Cl , extracted with CH_2Cl_2 (3 x 20 mL) and combined extracts washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 10% ethyl acetate in hexane, 15 mL/min flow rate) provided **243** (307 mg, 76%) as a viscous oil: IR (neat) ν 3463, 3068, 3027, 2931, 2856, 2804, 1612, 1587, 1513, 1493, 1471, 1453, 1428, 1389, 1360, 1302, 1249, 1173, 1112, 1072, 1037, 939, 823, 743, 700, 614 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +6.2$ (*c* 6.14, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 1.09 (s, 9H), 2.35 (ddt, $J = 16.8, 8.0, 2.0$ Hz, 1H), 2.76-2.89 (m, 3H), 3.55 (d, $J = 14.0$ Hz, 2H), 3.80 (s, 3H), 3.85 (d, $J = 14.0$ Hz, 2H), 4.04-4.14 (m, 5H), 4.47 (s, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.18-7.31 (m, 12H), 7.39-7.51 (m, 6H), 7.70-7.76 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2 (C), 25.9 (CH_2), 27.0 (CH_3), 55.37 (CH_2), 55.39 (CH_3), 57.5 (CH_2), 61.4 (CH), 61.5 (CH_2), 70.3 (CH), 71.2 (CH_2), 78.3 (C), 84.1 (C), 113.9 (CH), 127.99 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.8 (C), 129.9 (CH), 130.1 (CH), 132.8 (C), 133.0 (C), 135.81 (CH), 135.84 (CH), 139.8 (C), 159.0 (C); HRFABMS m/z 698.3658 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{45}\text{H}_{52}\text{N}_1\text{O}_4\text{Si}_1$ 698.3666.

(2*S*,3*R*)-2-(dibenzylamino)-7-(4-methoxybenzyloxy)hept-5-yne-1,3-diol (244). Under an atmosphere of nitrogen, TBAF (500 μ L, 500 μ mol, 1.0 M in THF) was added dropwise to a stirred solution of alkyne **243** (292 mg, 418 μ mol) in anhydrous THF at -20 $^{\circ}$ C. The mixture was stirred for 1.5 hours then quenched with 5 mL saturated aqueous NH_4Cl , extracted with ethyl ether (5 x 5 mL) and combined extracts washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica plug, 1:3 ethyl acetate : hexane, then 1:1 ethyl acetate : hexane) provided **244** (181 mg, 94%) as a viscous oil: IR (neat) ν 3422, 2061, 3027, 2935, 2836, 2806, 2283, 2233, 1950, 1884, 1811, 1612, 1585, 1513, 1494, 1454, 1421, 1356, 1302, 1249, 1174, 1132, 1069, 1033, 914, 849, 821, 749, 700 cm^{-1} ; $[\alpha]_{\text{D}}^{23} -2.6$ (c 16.0, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 2.30 (ddt, $J = 16.8, 8.0, 2.0$ Hz, 1H), 2.42 (d, $J = 4.4$ Hz, 1H), 2.65-2.74 (m, 2H), 2.77 (ddt, $J = 16.8, 4.0, 2.0$ Hz, 1H), 3.67 (d, $J = 14.0$ Hz, 2H), 3.75 (d, $J = 14.0$ Hz, 2H), 3.80 (s, 3H), 3.89 (p, $J = 5.4$ Hz, 1H), 3.98 (p, $J = 5.4$ Hz, 1H), 4.02-4.10 (m, 3H), 4.48 (s, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 7.20-7.34 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.4 (CH_2), 54.7 (CH_2), 55.3 (CH_3), 57.4 (CH_2), 59.2 (CH_2), 61.7 (CH), 70.1 (CH), 71.5 (CH_2), 79.0 (C), 83.3 (C), 127.2 (CH), 128.4 (CH), 129.0 (CH), 129.5 (C), 129.8 (CH), 128.9 (CH), 139.4 (C), 159.4 (C); HRMS m/z 460.2481 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{29}\text{H}_{34}\text{N}_1\text{O}_4$ 460.2488.

(4*R*,5*S*)-*N,N*-dibenzyl-4-(4-(4-methoxybenzyloxy)but-2-ynyl)-2,2-dimethyl-1,3-dioxan-5-amine (245). Alkyne **244** (150 mg, 326 μ mol) and camphorsulfonic acid (3.8 mg, 0.016 μ mol) in dimethoxypropane (3 mL) and acetone (3 mL) was refluxed for 18 hours under an atmosphere of nitrogen. The mixture was quenched with 8 mL saturated

aqueous NaHCO₃, extracted with ethyl ether (4 x 5 mL) and combined extracts washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 15% ethyl acetate in hexane) provided **245** (157 mg, 96%) as a viscous oil: IR (neat) ν 3084, 3061, 3028, 2991, 2937, 2835, 2806, 1949, 1880, 1812, 1612, 1586, 1513, 1493, 1454, 1378, 1302, 1249, 1225, 1173, 1142, 1073, 1035, 976, 894, 822, 748, 700 cm⁻¹; [α]_D²³ +7.6 (*c* 9.20, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.38 (s, 3H), 1.45 (s, 3H), 2.37 (ddt, *J* = 16.8, 7.2, 2.0 Hz, 1H), 2.80-2.92 (m, 2H), 3.57 (d, *J* = 13.6 Hz, 2H), 3.82 (s, 3H), 3.88-4.04 (m, 5H), 4.08-4.12 (m, 2H), 4.53 (s, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.24-7.38 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 21.5 (CH₃), 23.5 (CH₂), 26.9 (CH₃), 54.8 (CH₂), 55.3 (CH₃), 57.31 (CH₂), 57.34 (CH), 58.0 (CH₂), 69.1 (CH), 70.7 (CH₂), 77.2 (C), 84.1 (C), 99.4 (C), 113.8 (CH), 127.2 (CH), 128.4 (CH), 128.8 (CH), 129.8 (C), 129.9 (CH), 139.3 (C), 159.3 (C); HRMS *m/z* 500.2801 [M+H]⁺, calcd. for C₃₂H₃₈N₁O₄ 500.2801.

(6*S*,7*R*)-6-(dibenzylamino)-2,2,13,13,14,14-hexamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-9-yn-7-ol (230). Under an atmosphere of nitrogen, *n*-BuLi (253 μ L, 632 μ mol, 2.5 M in hexane) was added dropwise to a stirred solution of *O*-*t*-butyldimethylsilyl propargyl ether (118 mg, 690 μ mol) in anhydrous THF (1.5 mL) at -20 °C. The mixture was stirred for 1 hour then cooled to -78 °C and epoxide **228** (300 mg, 575 μ mol in THF (1.2 mL)) was added dropwise followed by slow addition of BF₃·Et₂O (73 μ L, 575 μ mol). The mixture was stirred for 1 hour then warmed to room temperature overnight. The solution was quenched with 10 mL saturated aqueous NH₄Cl, extracted with ethyl ether (3 x 20 mL) and combined extracts washed with brine (20 mL), dried over Na₂SO₄

and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica cartridge, 1:19 EtOAc:hexane, 13 mL/min flow rate) provided **230** (283 mg, 71%) as a viscous oil: IR (neat) ν 3472, 3059, 3018, 2960, 2927, 2853, 1475, 1433, 1359, 1252, 1112, 1079, 831, 691 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +24.5$ (c 18.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.72-7.76 (m, 4H), 7.40-7.49 (m, 6H), 7.20-7.30 (m, 10H), 4.23 (s, 2H), 4.11 (dd, $J = 11.0, 5.0$ Hz, 1H), 4.06 (m, 2H), 3.87 (d, $J = 13.5$ Hz, 2H), 3.58 (d, $J = 13.5$ Hz, 2H), 2.79-2.84 (m, 1H), 2.78 (dt, $J = 8.0, 5.0$ Hz, 1H), 2.74 (d, $J = 5.0$ Hz, 1H), 2.29 (ddt, $J = 17.0, 8.0, 2.5$ Hz, 1H), 1.10 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.9 (C), 135.9 (CH), 135.8 (CH), 133.1 (C), 132.9 (C), 130.0 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.1 (CH), 82.4 (C), 81.0 (C), 70.1 (CH), 61.5 (CH), 61.4 (CH_2), 55.4 (CH_2), 52.1 (CH_2), 27.1 (CH_3), 26.0 (CH_3), 25.9 (CH_2), 19.2 (C), 18.5 (C), -5.0 (CH_3); HREIMS m/z 691.3871 $[\text{M}]^+$, calcd. for $\text{C}_{43}\text{H}_{57}\text{N}_1\text{O}_3\text{Si}_2$ 691.3871.

(2*S*,3*R*)-2-(dibenzylamino)hept-5-yne-1,3,7-triol (247). Under an atmosphere of nitrogen TBAF (296 mg, 938 μmol) was added to a stirred solution of alkyne **230** (270 mg, 390 μmol) in THF (3 mL) at -20 $^\circ\text{C}$. The mixture was stirred for 2 hours then quenched by addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with ethyl acetate (4×3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica cartridge, 1:19 MeOH: CH_2Cl_2 , 12 mL/min flow rate) provided the **247** (129 mg, 97%) as a viscous oil: IR (neat) ν 3355, 2920, 2843, 1499, 1452, 1367, 1134, 1072, 1033 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +1.3$ (c 0.7, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.20-7.35 (m,

10H), 4.11 (s, 3H), 4.00 (dd, $J = 11.8, 5.2$ Hz, 1H), 3.93 (dd, $J = 11.8, 6.4$ Hz, 1H), 3.80 (d, $J = 12.4$ Hz, 2H), 3.67 (d, $J = 12.4$ Hz, 2H), 2.62-2.80 (m, 2H), 2.36 (dd, $J = 17.2, 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 129.0 (CH), 128.3 (CH), 127.1 (CH), 82.8 (C), 81.0 (C), 69.9 (CH), 61.5 (CH), 59.0 (CH_2), 54.7 (CH_2), 50.7 (CH_2), 25.9 (CH_2); HREIMS m/z 339.1824 $[\text{M}]^+$, calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_1\text{O}_3$ 339.1829.

4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-yn-1-ol (246). A sealed vial containing **247** (44.3 mg, 130 μmol , in 1:1 2,2-dimethoxypropane /acetone (2 mL)) and CSA (4.5 mg, 20 μmol) was heated at 50 °C with stirring for 2 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO_3 (5 mL). The mixture was extracted with ethyl ether (3 \times 5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was redissolved in 1.5 mL of 4:2:1 THF/acetic acid/water and stirred for 1 hour at room temperature. The stirred mixture was quenched with saturated aqueous NaHCO_3 (10 mL) extracted with ethyl ether (3 \times 5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica cartridge, 20% ethyl acetate in hexane, 12 mL/min flow rate) provided **246** (399 mg, 79%) as a viscous oil: IR (neat) ν 3445, 3085, 3060, 3027, 2991, 2935, 2834, 2806, 1949, 1871, 1816, 1602, 1585, 1494, 1453, 1378, 1245, 1224, 1198, 1161, 1142, 1106, 1057, 1027, 974, 894, 822, 748, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ 8.1 (c 0.75, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 1.34 (s, 3H), 1.41 (s, 3H), 2.38 (ddt, $J = 17.0, 6.6, 2.1$ Hz, 1H), 2.71 (dq, $J = 17.0, 2.1$ Hz, 1H), 2.86 (dt, $J = 9.9, 5.7$ Hz, 1H), 3.52 (d, $J = 13.5$ Hz, 2H), 3.86-4.02 (m, 5H), 4.12 (m, 2H), 7.22-7.36

(m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.7 (CH_3), 23.3 (CH_2), 26.8 (CH_3), 51.5 (CH_2), 54.9 (CH_2), 57.0 (CH), 57.9 (CH_2), 68.9 (CH), 79.8 (C), 83.1 (C), 99.6 (C), 127.3 (CH), 128.5 (CH), 128.9 (CH), 139.5 (C); HRMS m/z 380.2212 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_1\text{O}_3$ 380.2226.

(E)-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-en-1-ol (249).

Under an atmosphere of nitrogen, Red-Al 65 wt% in toluene (87.4 μL , 291 μmol) was added dropwise to a stirred solution of **246** (22 mg, 58.2 μmol) in anhydrous ethyl ether (600 μL) at $-10\text{ }^\circ\text{C}$. The mixture was allowed to warm to room temperature and stirred overnight. After 20 hours the reaction was cooled to $-10\text{ }^\circ\text{C}$ and quenched by dropwise addition of a 1:3 $\text{H}_2\text{O}:\text{THF}$ (300 μL), warmed to room temperature and added to saturated aqueous NH_4Cl (5 mL). The mixture was extracted with ethyl ether (4 x 3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 30% ethyl acetate in hexane) provided **249** (17.2 mg, 78%) as a viscous oil: IR (neat) ν 3432, 3060, 3026, 2990, 2938, 2835, 2807, 1494, 1453, 1378, 1224, 1201, 1105, 973, 745, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ 11.5 (c 1.78, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.36 (bm, 10H), 5.61(dt, J = 15.2, 6.4 Hz, 1H), 5.53 (dt, J = 15.2, 5.2 Hz, 1H), 4.00-4.10 (bm, 2H), 3.80-4.00 (m, 6H), 3.50 (d, J = 13.6 Hz, 2H), 2.75 (dt, J = 9.6, 6.0 Hz, 1H), 2.59 (m, 1H), 2.08 (p, J = 7.6 Hz, 1H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.7 (C), 131.1 (CH), 129.3 (CH), 129.0 (CH), 128.4 (CH), 127.2 (CH), 99.3 (C), 69.7 (CH), 63.9 (CH_2), 57.9 (CH_2), 57.5 (CH), 54.9 (CH_2), 35.2 (CH_2), 26.7 (CH_3), 21.8 (CH_3); HRMS m/z 382.2386 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_1\text{O}_3$ 382.2382.

(3-(((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (250 + 251). To a solution of **249** (4.57 g, 12.0 mmol) in dichloromethane (66 mL) at room temperature was added *m*-chloroperoxybenzoic acid (1.97 g, 11.4 mmol). The solution was stirred for 4 minutes and then quenched with saturated aqueous NaHCO₃ (200 mL). The aqueous layer was extracted with hexane (4 × 100 mL) and the combined extracts washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography on triethylamine saturated silica (25%, 30% then 50% ethyl acetate in hexane) provided an inseparable mixture of **250** and **251** (3.12 g, 69%, 1.8:1 of **250:251** by NMR analysis) as a viscous oil.

Synthesis of protected epoxides 252 and 253. To a solution of a 1:1 mixture of **250** and **251** (69 mg, 173 μmol) in DMF (1.0 mL) at 0 °C under nitrogen was added imidazole (25 mg, 347 μmol) and *tert*-butylchlorodimethylsilane (34 mg, 226 μmol). The mixture was warmed to room temperature and stirred for 4 hours. The reaction was quenched with 7 mL water, extracted with ethyl ether (3 × 3 mL) and the combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 3% ethyl acetate in hexane) provided **252** and **253** (41.2 mg and 37.0 mg respectively, 88%) as viscous oils:

(4*R*,5*S*)-*N,N*-dibenzyl-4-(((2*S*,3*S*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-5-amine (252). IR (neat) ν 3026, 2952, 2926, 2853, 1442, 1376, 1252, 1227, 1103, 831, 773, 749, 699 cm⁻¹; $[\alpha]_D^{24}$ +6.2 (*c* 2.24, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.34 (m, 8H), 7.20-7.27 (m, 2H), 3.84-3.96 (m, 5H),

3.75 (dd, $J = 12.0, 3.2$ Hz, 1H), 3.57 (dd, $J = 12.0, 5.0$ Hz, 1H), 3.51 (d, $J = 14.0$ Hz, 2H), 2.83-2.88 (m, 2H), 2.76 (dt, $J = 9.6, 6.0$ Hz, 1H), 1.95 (ddd, $J = 14.4, 6.0, 2.4$ Hz, 1H), 1.79 (ddd, $J = 14.4, 8.8, 4.4$ Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 128.9 (CH), 128.5 (CH), 127.3 (CH), 99.2 (C), 67.8 (CH), 63.9 (CH_2), 58.3 (CH), 58.1 (CH_2), 58.0 (CH), 54.8 (CH_2), 53.8 (CH), 34.6 (CH_2), 26.9 (CH_3), 26.0 (CH_3), 21.6 (CH_3), 18.5 (C), -5.1 (CH_3), -5.2 (CH_3); HREIMS m/z 511.3107 $[\text{M}]^+$, calcd. for $\text{C}_{30}\text{H}_{45}\text{N}_1\text{O}_4\text{Si}_1$ 511.3112.

((4*R*,5*S*)-*N,N*-dibenzyl-4-(((2*R*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-5-amine (253). IR (neat) ν 3018, 2919, 2853, 1450, 1376, 1252, 1112, 839, 782, 740 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +10.5$ (c 1.82, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.32 (m, 8H), 7.20-7.27 (m, 2H), 4.04 (td, $J = 9.6, 2.0$ Hz, 1H), 3.96 (dd, $J = 12.0, 6.4$ Hz, 1H), 3.90 (d, $J = 13.6$ Hz, 2H), 3.88 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.79 (dd, $J = 12.0, 3.0$ Hz, 1H), 3.57 (dd, $J = 12.0, 4.8$ Hz, 1H), 3.50 (d, $J = 13.6$ Hz, 2H), 2.92 (m, 1H), 2.81 (m, 1H), 2.69 (dt, $J = 10.0, 5.4$ Hz, 1H), 2.06 (ddd, $J = 14.4, 6.8, 2.0$ Hz, 1H), 1.48 (ddd, $J = 14.4, 9.6, 4.4$ Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 129.0 (CH), 128.5 (CH), 127.2 (CH), 99.3 (C), 67.7 (CH), 63.7 (CH_2), 59.4 (CH), 58.1 (CH_2), 57.9 (CH), 54.8 (CH_2), 53.3 (CH), 35.6 (CH_2), 27.0 (CH_3), 26.0 (CH_3), 21.6 (CH_3), 18.5 (C), -5.1 (CH_3), -5.2 (CH_3); HREIMS m/z 511.3116 $[\text{M}]^+$, calcd. for $\text{C}_{30}\text{H}_{45}\text{N}_1\text{O}_4\text{Si}_1$ 511.3112.

((2*S*,3*S*)-3-(((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (250). Under an atmosphere of nitrogen, TBAF (20 mg, 63 μmol) was added to a stirred solution of epoxide **252** (22 mg, 43 μmol) in THF (400 μL) at -20 $^\circ\text{C}$.

The mixture was stirred for 18 hours then quenched by addition of water (2 mL). The mixture was extracted with ethyl acetate (4 × 3 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica saturated with Et₃N, 1:3 EtOAc:hexane) provided **250** (15 mg, 88%) as a viscous oil: IR (neat) ν 3439, 2989, 2930, 1494, 1460, 1222, 1103, 746, 695 cm⁻¹; [α]_D²³ +8.1 (*c* 1.48, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.34 (m, 8H), 7.22-7.28 (m, 2H), 3.80-4.00 (m, 6H), 3.46-3.56 (m, 3H), 2.87-2.94 (m, 2H) 2.77 (dt, *J* = 10.0, 6.0 Hz, 1H), 1.98 (ddd, *J* = 14.4, 6.0, 2.8 Hz, 1H), 1.79 (ddd, *J* = 14.4, 8.0, 4.4 Hz, 1H), 1.70 (t, *J* = 6.0 Hz, 1H), 1.39 (s, 3H), 1.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 139.5 (C), 128.9 (CH), 128.5 (CH), 127.3 (CH), 99.3 (C), 67.6 (CH), 62.0 (CH₂), 58.0 (CH₂), 57.9 (CH), 57.8 (CH), 54.9 (CH₂), 53.4 (CH), 34.3 (CH₂), 26.9 (CH₃), 21.6 (CH₃); HREIMS *m/z* 397.2251 [M]⁺, calcd. for C₂₄H₃₁N₁O₄ 397.2248.

((2*R*,3*R*)-3-(((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (251). Under an atmosphere of nitrogen, TBAF (13 mg, 41 μ mol) was added to a stirred solution of epoxide **253** (18 mg, 35 μ mol) in THF (400 μ L) at -20 °C. The mixture was stirred for 15 hours then quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 × 5 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica saturated with Et₃N, 1:3 EtOAc:hexane) provided **251** (11.3 mg, 81%) as a viscous oil: IR (neat) ν 3448, 2981, 2921, 1494, 1451, 1375, 1222, 1112, 746, 695 cm⁻¹; [α]_D²³ +15.3 (*c* 1.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.33 (m, 8H), 7.22-7.27 (m, 2H), 4.04 (td, *J* = 9.4, 2.5 Hz, 1H), 3.97 (dd, *J* = 12.0, 6.4 Hz, 1H),

3.91 (d, $J = 13.6$ Hz, 2H), 3.89 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.84 (ddd, $J = 12.4, 5.4, 3.0$ Hz, 1H), 3.56 (m, 1H), 3.50 (d, $J = 13.6$ Hz, 2H), 3.00 (ddd, $J = 6.8, 4.8, 2.0$ Hz, 1H), 2.84 (dt, $J = 4.4, 2.4$ Hz, 1H), 2.71 (dt, $J = 9.6, 6.2$ Hz, 1H), 2.08 (ddd, $J = 14.4, 7.2, 2.2$ Hz, 1H), 1.65 (t, $J = 6.0$ Hz, 1H), 1.49 (ddd, $J = 14.4, 9.6, 5.0$ Hz, 1H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 129.0 (CH), 128.5 (CH), 127.3 (CH), 99.3 (C), 67.6 (CH), 61.9 (CH_2), 59.0 (CH), 58.0 (CH_2), 57.8 (CH), 54.8 (CH_2), 53.2 (CH), 35.3 (CH_2), 26.9 (CH_3), 21.6 (CH_3); HREIMS m/z 397.2250 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_1\text{O}_4$ 397.2248.

(2R,3S)-2-azido-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butane-1,3-diol (233). Under an atmosphere of nitrogen, $(\text{MeO})_3\text{B}$ (8.0 μL , 7.3 mg, 70 μmol) was added to a solution of **250** (14 mg, 35 μmol) in anhydrous DMF (180 μL). The solution was stirred for 30 min at room temperature then NaN_3 (4.6 mg, 70 μmol) was added and the reaction was heated to 50 $^\circ\text{C}$ and stirred for 4 hours. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO_3 (3.0 mL) and the solution stirred a further 30 minutes. The mixture was extracted with ethyl ether (4 \times 3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 2:3 EtOAc:hexane) provided **233** and **254** (10.2 mg and 2.8 mg respectively, 85%) as viscous oils. Characterization for **233**: IR (neat) ν 3456, 2989, 2938, 2879, 2089, 1494, 1451, 1383, 1265, 1222, 1069, 967, 891, 823, 738 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +8.0$ (c 1.12, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.24-7.37 (m, 10H), 3.96-4.06 (m, 3H), 3.88-3.94 (m, 3H), 3.74-3.86 (m, 2H), 3.67 (t, $J = 7.6$ Hz, 1H), 3.53 (d, $J = 13.6$ Hz, 2H), 3.27 (dt, $J = 6.8, 5.2$

Hz, 1H), 2.78 (dt, $J = 9.6, 6.0$ Hz, 1H), 2.42 (t, $J = 6.0$ Hz, 1H), 2.32 (dt, $J = 14.8, 2.4$ Hz, 1H), 1.43 (s, 3H), 1.37 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.1 (C), 129.0 (CH), 128.6 (CH), 127.6 (CH), 99.5 (C), 73.3 (CH), 71.5 (CH), 66.8 (CH), 63.2 (CH₂), 58.4 (CH), 57.8 (CH₂), 55.2 (CH₂), 36.7 (CH₂), 26.9 (CH₃), 21.8 (CH₃); HREIMS m/z 440.2429 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4$ 440.2418.

(2R,3S,5R,6S)-2,6-diaminoheptane-1,3,5,7-tetraol (220). A mixture of Pd/C (1.5 mg, 1.3 μmol , 10 mol % Pd) and azide **233** (6.0 mg, 13.6 μmol) in methanol (0.5 mL) was placed under H_2 (1 atm) and stirred at room temperature. After 16 hours TMSCl (10.0 μL , 8.5 mg, 80 μmol) was added and the mixture stirred a further 3 hours. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (1.5 mg, 1.3 μmol , 10 mol % Pd) added. The mixture was placed under H_2 (1 atm) and stirred at room temperature for 14 hours. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure provided the hydrochloride salt of **220** (2.5 mg, 69%) as a white solid: ^1H NMR (400 MHz, D_2O , ref CH_3CN) δ 4.16 (apparent p, $J = 4.4$ Hz, 2H), 3.93 (dd, $J = 12.0, 4.4$ Hz, 2H), 3.78 (dd, $J = 12.0, 8.2$ Hz, 2H), 3.45 (apparent p, $J = 4.0$ Hz, 2H), 1.88 (dt, $J = 10.3, 4.4$ Hz, 1H), 1.82 (dt, $J = 10.3, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O , ref CH_3CN) δ 67.4 (CH), 58.0 (CH₂), 56.6 (CH), 35.3 (CH₂); HRESIMS m/z 195.1333 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_7\text{H}_{19}\text{N}_2\text{O}_4$ 195.1339.

(2S,3R)-2-azido-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butane-1,3-diol (234). Under an atmosphere of nitrogen, $(\text{MeO})_3\text{B}$ (6.3 μL , 5.8 mg, 55 μmol)

was added to a solution of **251** (11 mg, 28 μmol) in anhydrous DMF (140 μL). The solution was stirred for 30 min at room temperature then NaN_3 (3.6 mg, 55 μmol) was added and the reaction was heated to 50 $^\circ\text{C}$ and stirred for 4 hours. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO_3 (3.0 mL) and the solution stirred a further 30 minutes. The mixture was extracted with ethyl ether (4×3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:3 to 2:3 EtOAc: hexane) provided **234** and **255** (8.2 mg and 0.8 mg respectively, 74%) as a viscous oil. Characterization of **234**: IR (neat) ν 3439, 3032, 2989, 2921, 2887, 2802, 2097, 1494, 1451, 1375, 1265, 1103, 1018, 967, 823, 755, 695 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +10.0$ (c 0.99, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.35 (m, 10H), 3.96-4.06 (m, 3H), 4.12-4.20 (m, 2H), 3.98 (dd, $J = 12.0, 6.4$ Hz, 1H), 3.88-3.98 (m, 3H), 3.80 (m, 2H), 3.68 (m, 1H), 3.52 (d, $J = 14.0$ Hz, 2H), 2.28 (q, $J = 5.4$ Hz, 1H), 2.89 (dt, $J = 9.6, 6.2$ Hz, 1H), 2.50 (t, $J = 5.6$ Hz, 1H), 1.94 (ddd, $J = 14.6, 8.8, 4.4$ Hz, 1H), 1.81 (ddd, $J = 14.6, 6.0, 2.4$ Hz, 1H), 1.41 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.8 (C), 129.2 (CH), 128.6 (CH), 127.6 (CH), 99.7 (C), 70.2 (CH), 68.7 (CH), 66.3 (CH), 63.2 (CH_2), 57.8 (CH_2), 57.5 (CH), 54.9 (CH_2), 36.0 (CH_2), 26.8 (CH_3), 21.6 (CH_3); HREIMS m/z 440.2417 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4$ 440.2418.

(2S,3R,5R,6S)-2,6-diaminoheptane-1,3,5,7-tetraol (221). A mixture of Pd/C (1.5 mg, 1.3 μmol , 10 mol % Pd) and azide **234** (6.0 mg, 13.6 μmol) in methanol (0.5 mL) was placed under H_2 (1 atm) and stirred at room temperature. After 16 hours TMSCl (10.0 μL , 8.5 mg, 80 μmol) was added and the mixture stirred a further 3 hours. The mixture

was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (1.5 mg, 1.3 μmol , 10 mol % Pd) added. The mixture was placed under H_2 (1 atm) and stirred at room temperature for 14 hours. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure provided the hydrochloride salt of **221** (3.2 mg, 88%) as a white solid: ^1H NMR (400 MHz, D_2O , ref CH_3CN) δ 4.16 (m, 2H), 3.93 (dd, $J = 12.0, 4.2$ Hz, 2H), 3.77 (dd, $J = 12.0, 8.8$ Hz, 2H), 3.42 (apparent dt, $J = 8.4, 4.0$ Hz, 2H), 1.70 (dd, $J = 8.0, 5.2$ Hz, 2H); ^{13}C NMR (100 MHz, D_2O , ref CH_3CN) δ 65.9 (CH), 58.0 (CH_2), 57.3 (CH), 35.8 (CH_2); HREIMS m/z 194.1260 $[\text{M}]^+$, calcd. for $\text{C}_7\text{H}_{18}\text{N}_2\text{O}_4$ 194.1267.

(2R,3S,5R,6S)-2-azido-6-(dibenzylamino)heptane-1,3,5,7-tetraol (256). Compound **233** (13.0 mg, 29.5 μmol) in methanol:acetic acid 3:1 (900 μL) was heated to 70 $^\circ\text{C}$. The mixture was stirred for 23 hours then concentrated under reduced pressure. Flash chromatography (silica, 1:1 ethyl acetate:hexane then 10% methanol in chloroform) provided **256** (11.2 mg, 95%) as a viscous oil: IR (neat) ν 3371, 3023, 2921, 2794, 2097, 1494, 1451, 1367, 1307, 1265, 1112, 1061, 1018. 848, 746, 704 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +0.6$ (c 2.19, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.24 (m, 10H), 4.15 (ddd, $J = 10.0, 8.5, 1.5$ Hz, 1H), 4.04 (dd, $J = 11.0, 5.0$ Hz, 1H), 3.97 (dd, $J = 11.0, 6.5$ Hz, 1H), 3.91 (ddd, $J = 10.0, 6.0, 1.5$ Hz, 1H), 3.86-3.80 (m, 4H), 3.61 (d, $J = 13.5$ Hz, 2H), 3.33 (q, $J = 5.0$ Hz, 1H), 2.66 (q, $J = 6.0$ Hz, 1H), 2.21 (d, $J = 14.5$ Hz, 1H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 129.1 (CH), 128.6 (CH), 127.4 (CH), 74.0 (CH), 73.5 (CH), 66.8, 62.8 (CH_2), 62.7 (CH), 59.8 (CH_2), 55.1 (CH_2), 37.8 (CH_2); HRFABMS m/z 401.2190 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}_4$ 401.2183.

(6R,7S,9R,10S)-6-azido-10-(dibenzylamino)-2,2,14,14-tetramethyl-3,3,13,13-tetraphenyl-4,12-dioxo-3,13-disilapentadecane-7,9-diol (257). Under an atmosphere of nitrogen *tert*-butyldiphenylchlorosilane (13.5 μ L, 51.9 μ mol) was added to a stirred solution of tetraol **256** (10.4 mg, 26.0 μ mol) and imidazole (4.9 mg, 68 μ mol) in dimethylformamide (130 μ L) at room temperature. The mixture was stirred for 2 hours then quenched by addition of water (5 mL). The mixture was extracted with ethyl ether (4 \times 3 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) provided **257** (17.3 mg, 76%) as a viscous oil: IR (neat) ν 3465, 3066, 3023, 2930, 2853, 2097, 1468, 1434, 1265, 1112, 814, 746, 704, 610 cm⁻¹; [α]_D²⁴ +3.1 (*c* 5.46, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.66 (m, 8H), 7.52-7.36 (m, 12H), 7.28-7.16 (m, 10H), 4.16-4.02 (m, 4H), 3.93 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.88 (d, *J* = 3.6 Hz, 1H), 3.82-3.76 (m, 4H), 3.46-3.38 (m, 3H), 2.74 (q, *J* = 5.6 Hz, 1H), 2.21 (d, *J* = 14.8 Hz, 1H), 1.32-1.20 (m, 1H), 1.09 (s, 9H), 1.06 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.5 (C), 135.8 (CH), 137.7 (CH), 133.3 (C), 133.2 (C), 132.6 (C), 132.5 (C), 130.3 (CH), 130.2 (CH), 130.0 (CH), 128.9 (CH), 128.5 (CH), 128.8 (CH), 127.9 (CH), 127.3 (CH), 74.1 (CH), 72.3 (CH), 68.2 (CH), 64.5 (CH₂), 62.0 (CH), 61.9 (CH₂), 55.4 (CH₂), 37.2 (CH₂), 27.0 (CH₃), 26.9 (CH₃), 19.3 (C), 19.2 (C); HRFABMS *m/z* 877.4553 [M+H]⁺, calcd. for C₅₃H₆₅N₄O₄Si₂ 877.4539.

(S)-1-((4R,6S)-6-((R)-1-azido-2-(*tert*-butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-N,N-dibenzyl-2-(*tert*-butyldiphenylsilyloxy)ethanamine (258). A sealed

vial containing diol **257** (17.0 mg, 19.4 μmol) and PPTS (2.4 mg, 9.7 μmol) in 1:1 2,2-dimethoxypropane:acetone (1 mL) was heated at 50 $^{\circ}\text{C}$ with stirring for 1.5 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO_3 (5 mL). The mixture was extracted with ethyl ether (4×3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:19 EtOAc:hexane) provided **258** (17.2 mg, 97%) as a viscous oil: IR (neat) ν cm^{-1} ; $[\alpha]_{\text{D}}^{25} +6.5$ (c 6.44, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.80 (m, 8H), 7.38-7.48 (m, 12H), 7.36-7.20 (m, 10H), 4.22 (ddd, $J = 11.6, 7.6, 2.4$ Hz, 1H), 4.06-3.92 (m, 5H), 3.81 (d, $J = 4.4$ Hz, 2H), 3.71 (d, $J = 14.0$ Hz, 2H), 2.80 (dt, $J = 7.2, 4.4$ Hz, 1H), 2.65 (m, 1H), 2.01 (dt, $J = 13.2, 2.0$ Hz, 1H), 1.32 (s, 3H), 1.24 (s, 3H), 1.11 (s, 9H), 1.08 (s, 9H); ^1H NMR (400 MHz, 1:1 $\text{CDCl}_3:\text{C}_6\text{D}_6$) δ 7.74-7.64 (m, 8H), 7.32-7.24 (m, 12H), 7.22-7.14 (m, 8H), 7.12-7.06 (m, 2H), 4.14 (ddd, $J = 10.4, 8.0, 2.4$ Hz, 1H), 4.01 (dd, $J = 10.8, 2.4$ Hz, 1H), 3.96-3.90 (m, 3H), 3.83 (ddd, $J = 11.6, 6.4, 2.4$ Hz, 1H), 3.74 (d, $J = 4.4$ Hz, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.17 (dt, $J = 9.6, 5.2$ Hz, 1H), 2.68-2.63 (m, 1H), 1.98 (d, $J = 9.2$ Hz, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 1.08 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.4 (C), 135.9 (CH), 135.8 (CH), 135.74 (CH), 135.71 (CH), 133.6 (C), 133.5 (C), 133.2 (C), 133.1 (C), 129.9 (CH), 129.8 (CH), 129.7 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 98.8 (C), 68.0 (CH), 67.2 (CH), 67.1 (CH), 63.2 (CH_2), 62.9 (CH), 59.2 (CH_2), 55.9 (CH_2), 32.1 (CH_2), 29.9 (CH_3), 27.1 (CH_3), 26.8 (CH_3), 19.7 (CH_3), 19.3 (C), 19.2 (C); HRMS m/z $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{53}\text{H}_{65}\text{N}_4\text{O}_4\text{Si}_2$.

(2*R*,3*S*)-4-(*tert*-butyldiphenylsilyloxy)-1-chloro-3-(dibenzylamino)butan-2-ol (260).

Under an atmosphere of nitrogen, *n*-BuLi (7.50 mL, 1.87 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of ester **227** (5.04 g, 0.94 mmol) and chloriodomethane (1.36 mL, 1.87 mmol) in anhydrous THF at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 90 min then quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with dichloromethane (4x25 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure, providing crude **259** (5.7 g) as a yellow viscous oil. The crude ketone **259** was reduced without further purification. Under an atmosphere of nitrogen, LAH (0.47 mL, 1 M in THF) was added dropwise to a stirred solution of ketone **259** (5.2 g, 0.93 mmol) in anhydrous THF (45 mL) at $-91\text{ }^{\circ}\text{C}$. The mixture was stirred for 20 hours then quenched by addition of dropwise addition of water (5 mL). The solution was stirred at $-91\text{ }^{\circ}\text{C}$ for 1 hour then quenched with 30 mL saturated aqueous NH_4Cl . The mixture was extracted with dichloromethane (3x50 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization from 30:1 hexane : dichloromethane gave pure **260** (3.82 g) as white crystals. The mother liquor was concentrated under reduced pressure and chromatographed on silica (1:19 EtOAc:hexane) providing additional **260** (336 mg) as a mixture with other diastereomers. Combined yield was 80% over two steps, de = 94% based on NMR: IR (neat) ν 3415, 3065, 3030, 2925, 2855, 1955, 1885, 1816, 1588, 1495, 1472, 1452, 1425, 1390, 1359, 1262, 1105, 742, 703, 610, 501 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +41.4$ (*c* 14.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, *J* = 8.0 Hz, 4H), 7.40-7.55 (m, 6H), 7.20-7.38 (m, 10H), 4.31 (s, 1H), 3.96 (d, *J* = 13.2 Hz, 2H), 3.91 (bm, 3H), 3.59 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.54 (d, *J* =

13.2 Hz, 2H), 3.34 (dd, $J = 11.6, 5.6$ Hz, 1H), 2.92 (dt, $J = 8.8, 5.2$ Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.7 (C), 135.7 (CH), 135.6 (CH), 132.7 (C), 132.6 (C), 130.1 (CH), 130.0 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.3 (CH), 68.3 (CH), 61.1 (CH), 60.3 (CH_2), 54.8 (CH_2), 47.8 (CH_2), 27.1 (CH_3), 19.4 (C); HRMS m/z 557.2520 $[\text{M}]^+$, calcd. for $\text{C}_{34}\text{H}_{40}\text{Cl}_1\text{N}_1\text{O}_2\text{Si}_1$ 557.2517.

(S)-N,N-dibenzyl-2-(tert-butyldiphenylsilyloxy)-1-((R)-oxiran-2-yl)ethanamine (229).

Under an atmosphere of nitrogen, *n*-BuLi (197 μL , 492 μmol , 2.5 M in hexane) was added dropwise to a stirred solution of alcohol **260** (211 mg, 379 μmol) in anhydrous THF at -78 °C. The stirred mixture was warmed to room temperature for 45 min then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with dichloromethane (3x15 mL) and combined extracts washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on triethylamine saturated silica (3% ethyl acetate in hexane) provided **229** (181 mg, 91%) as a light yellow viscous oil: IR (neat) ν 3458, 3065, 3030, 2960, 2917, 2855, 1947, 1894, 1816, 1588, 1495, 1472, 1452, 1425, 1359, 1254, 1115, 823, 742, 695, 610 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +21.0$ (c 8.91, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.72 (m, 4H), 7.38-7.52 (m, 10H), 7.30-7.36 (m, 4H), 7.22-7.28 (m, 2H) 3.84-4.00 (m, 6H), 3.26 (ddd, $J = 4.8, 4.4, 2.4$ Hz, 1H), 2.77 (dd, $J = 4.8, 4.4$ Hz, 1H), 2.72 (q, $J = 6.4$ Hz, 1H), 2.60 (dd, $J = 4.8, 2.4$ Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.2 (C), 135.52 (CH), 135.49 (CH), 133.2 (C), 133.1 (C), 129.7 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 126.7 (CH), 63.5 (CH_2), 61.4 (CH), 55.6 (CH_2), 51.8 (CH), 44.9 (CH_2), 27.0 (CH_3), 19.3 (C); HRMS m/z 521.2752 $[\text{M}]^+$, calcd. for $\text{C}_{34}\text{H}_{39}\text{N}_1\text{O}_2\text{Si}_1$ 521.2750.

(6*S*,7*S*)-6-(dibenzylamino)-2,2,13,13,14,14-hexamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-9-yn-7-ol (261). Under an atmosphere of nitrogen, *n*-BuLi (2.1 mL, 5.25 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of *O*-*t*-butyldimethylsilyl propargyl ether (970 mg, 5.73 mmol) in anhydrous THF (16 mL) at –20 °C. The mixture was stirred for 1 hour then cooled to –78 °C and epoxide **229** (2.49 g, 4.77 mmol in THF (8 mL)) was added dropwise followed by slow addition of BF₃·Et₂O (605 μL, 4.77 mmol). The mixture was stirred for 1 hour then warmed to room temperature overnight. The solution was cooled to –78 °C and quenched with 25 mL saturated aqueous NH₄Cl, extracted with dichloromethane (3 × 50 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 7% ethyl acetate in hexane) provided **261** (2.63 g, 80%) as a viscous oil: IR (neat) ν 3439, 3067, 2960, 2919, 2853, 1475, 1425, 1244, 1079, 831, 691 cm⁻¹; $[\alpha]_D^{24}$ +28.1 (*c* 7.54, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.71 (bs, 4H), 7.40-7.52 (m, 6H), 7.20-7.30 (m, 10H), 4.29 (bs, 1H), 4.11 (dt, *J* = 15.6, 2.0 Hz, 1H), 4.06 (dt, *J* = 15.6, 2.0 Hz, 1H), 3.97 (m, 3H), 3.76-3.90 (m, 2H), 3.58 (d, *J* = 13.2 Hz, 2H), 2.88 (bs, 1H), 2.43 (bd, *J* = 17.6 Hz, 1H), 2.17 (bd, *J* = 17.6 Hz, 1H), 1.12 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 138.9 (C), 135.7 (CH), 135.6 (CH), 132.8 (C), 132.7 (C), 130.0 (CH), 129.9 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 81.4 (C), 80.5 (C), 65.9 (CH), 62.4 (CH₂), 60.3 (CH), 54.7 (CH₂), 51.9 (CH₂), 27.2 (CH₃), 26.1 (CH₃), 24.5 (CH₂), 19.4 (C), 18.5 (C), -4.80 (CH₃), -4.84 (CH₃); HREIMS *m/z* 691.3875 [M]⁺, calcd. for C₄₃H₅₇N₁O₃Si₂ 691.3871.

(2*S*,3*S*)-2-(dibenzylamino)hept-5-yne-1,3,7-triol (262). Under an atmosphere of nitrogen TBAF (2.60 g, 8.24 mmol) was added to a stirred solution of alkyne **261** (2.48 g, 3.58 mmol) in THF (20 mL) at $-20\text{ }^{\circ}\text{C}$. The mixture was stirred for 4 hours then quenched by addition of water (75 mL). The mixture was extracted with ethyl acetate (4 \times 50 mL) and combined extracts washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:1 EtOAc:hexane then 6:94 MeOH: CH_2Cl_2) provided **262** (0.99 g, 82%) as a viscous oil: IR (neat) ν 3373, 2927, 1861, 1491, 1458, 1136, 1070, 1013, 763, 695 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +31.5$ (c 9.05, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.35 (m, 10H), 4.09 (b, 2H), 3.98 (d, $J = 13.2$ Hz, 2H), 3.80-3.88 (m, 3H), 3.68 (d, $J = 13.2$ Hz, 2H), 2.88 (dt, $J = 9.2, 6.4$ Hz, 1H), 2.49 (dm, $J = 17.2$ Hz, 1H), 2.37 (dm, $J = 17.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.0 (C), 129.3 (CH), 128.6 (CH), 127.4 (CH), 82.2 (C), 80.8 (C), 67.1 (CH), 62.2 (CH), 58.5 (CH_2), 54.6 (CH_2), 50.8 (CH_2), 24.5 (CH_2); HREIMS m/z 339.1835 $[\text{M}]^+$, calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_1\text{O}_3$ 339.1829.

4-((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-yn-1-ol (231). A sealed vial containing alkyne **262** (842 mg, 2.48 mmol, in 1:1 2,2-dimethoxypropane /acetone (10 mL)) and CSA (120 mg, 520 μmol) was heated at $50\text{ }^{\circ}\text{C}$ with stirring for 14 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO_3 (50 mL). The mixture was extracted with ethyl ether (3 \times 50 mL) and combined extracts washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was redissolved in 4 mL of 4:2:1 THF/acetic acid/water and stirred for 1 hour at room temperature. The stirred mixture was quenched

with saturated aqueous NaHCO₃ (100 mL) extracted with ethyl ether (3 × 50 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 1:3 EtOAc:hexane, 20 mL/min flow rate) provided **231** (755 mg, 80%) as a viscous oil: IR (neat) ν 3439, 3032, 2989, 2930, 2862, 2802, 1604, 1494, 1451, 1383, 1188, 1137, 1103, 1010, 746, 695 cm⁻¹; $[\alpha]_D^{24}$ +97.1 (*c* 6.58, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.43 (bd, *J* = 7.2 Hz, 4H), 7.35 (bt, *J* = 7.2 Hz, 4H), 7.26 (bt, *J* = 7.2 Hz, 2H), 4.43 (d, *J* = 12.8 Hz, 1H), 4.33 (bd, *J* = 14.0 Hz, 2H), 4.17 (m, 1H), 4.11 (bs, 2H), 3.97 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.59 (d, *J* = 14.0 Hz, 2H), 2.90 (ddt, *J* = 18.0, 7.6, 2.0 Hz, 1H), 2.64 (ddt, *J* = 18.0, 6.0, 2.0 Hz, 1H), 2.53 (t, *J* = 3.4 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.2 (C), 128.9 (CH), 128.3 (CH), 126.9 (CH), 99.0 (C), 83.0 (C), 79.7 (C), 72.1 (CH), 58.4 (CH₂), 56.1 (CH₂), 51.2 (CH₂), 50.2 (CH), 29.5 (CH₃), 22.3 (CH₂), 18.7 (CH₃); HREIMS *m/z* 379.2136 [M]⁺, calcd. for C₂₄H₂₉N₁O₃ 379.2142.

(E)-4-((4S,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-en-1-ol (235).

Under an atmosphere of nitrogen, Red-Al 65 wt% in toluene (764 μ L, 2.67 mmol) was added dropwise to a stirred solution of alkyne **231** (191 mg, 535 μ mol) in anhydrous ethyl ether (5.0 mL) at -10 °C. The mixture was allowed to warm to room temperature and stirred overnight. After 20 hours the reaction was cooled to -10 °C and quenched by dropwise addition of a 1:3 H₂O:THF (1.5 mL), warmed to room temperature and added to saturated aqueous NH₄Cl (5 mL). The mixture was extracted with ethyl ether (4x5 mL) and combined extracts washed with water (5 mL), brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica

cartridge, 20% ethyl acetate in hexane, 13 mL/min flow rate) provided **235** (183.1 mg, 95%) as a viscous oil: IR (neat) ν 3406, 3026, 2993, 2935, 2861, 2795, 2366, 2325, 1491, 1458, 1376, 1367, 1260, 1194, 1095, 1004, 963, 740, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +42.8$ (c 8.39, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 7.2$ Hz, 4H), 7.36 (t, $J = 7.2$ Hz, 4H), 7.27 (t, $J = 7.2$ Hz, 2H), 5.72 (dt, $J = 15.2, 6.0$ Hz, 1H), 5.55 (dt, $J = 15.2, 7.2$ Hz, 1H), 4.45 (d, $J = 12.8$ Hz, 1H), 4.37 (bd, $J = 14.0$ Hz, 2H), 4.02-3.97 (m, 3H), 3.95 (dd, $J = 12.8, 3.6$ Hz, 1H), 3.59 (d, $J = 14.0$ Hz, 2H), 2.59 (t, $J = 6.4$ Hz, 2H), 2.37 (t, $J = 3.2$ Hz, 1H), 2.03 (bs, 1H), 1.47 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.3 (C), 131.2 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 126.8 (CH), 98.6 (C), 72.7 (CH), 63.4 (CH₂), 58.1 (CH₂), 56.0 (CH₂), 50.6 (CH), 34.6 (CH₂), 29.6 (CH₃), 18.7 (CH₃); HRMS m/z 381.2302 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_1\text{O}_3$ 381.2298.

(Z)-4-((4S,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-en-1-ol (236).

To a solution of alkyne **231** (25 mg, 66 μmol) in 1:1 ethanol:hexane (5.0 mL) was added quinoline (100 μL of 20 $\mu\text{L}/10$ mL solution in hexane) and Lindlar catalyst (14 mg, 6.6 μmol). The mixture was placed under hydrogen (1 atm) at room temperature and stirred for 20 minutes. The solution was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure to provided **236** (25 mg, 99%) as a viscous oil: IR (neat) ν 3423, 2026, 2992, 2923, 2854, 1493, 1450, 1381, 1260, 1200, 1148, 1070, 1010, 958, 898, 821, 752, 700 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +9.6$ (c 2.44, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, $J = 7.0$ Hz, 4H), 7.33 (t, $J = 7.0$ Hz, 4H), 7.24 (t, $J = 7.0$ Hz, 2H), 5.81 (dt, $J = 10.8, 7.2$ Hz, 1H), 5.58-5.50 (m, 1H), 4.38 (d, $J = 13.2$ Hz, 1H), 4.32 (bd, $J = 14.0$ Hz, 2H), 4.21 (dd, $J = 11.6, 7.6$ Hz, 1H), 4.02-3.90 (m, 3H), 3.56 (d, $J = 14.0$ Hz, 2H), 2.92

(dtd, $J = 14.8, 9.6, 0.8$ Hz, 1H), 2.36 (t, $J = 3.2$ Hz, 1H), 2.24 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.4 (C), 131.0 (CH), 130.1 (CH), 128.8 (CH), 128.4 (CH), 127.0 (CH), 99.1 (C), 72.0 (CH), 58.3 (CH_2), 57.7 (CH_2), 56.1 (CH_2), 51.8 (CH), 30.5 (CH_2), 29.4 (CH_3), 18.9 (CH_3); HRMS m/z 382.2380 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_1\text{O}_3$ 382.2377.

3-(((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (263 + 264). To a solution of alkene **235** (100 mg, 262 μmol) in dichloromethane (0.4 mL) at 0 °C was added pyridine (2.5 μL , 31 μmol), methyltrioxorhenium (3.3 mg, 12 μmol) and hydrogen peroxide (40 μL of 30% solution, 393 μmol). Solution was warmed to room temperature and stirred for 1 hour, then quenched with water (3 mL). The mixture was extracted with ethyl ether (4 \times 3 mL) combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica saturated with triethylamine, 1:3 EtOAc:hexane) provided recovered starting material **235** (24.2 mg, 24%) and an inseparable mixture of **263** and **264** (10.9 mg, 14% adjusted for recovered starting material, dr 1:1 of **263:264** by NMR) as a viscous oil.

2-azido-4-(((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butane-1,3-diol (265-268). Under an atmosphere of nitrogen, $(\text{MeO})_3\text{B}$ (11.3 μL , 10.4 mg, 99.6 μmol) was added to a solution of **263** and **264** (18 mg, 45 μmol) in anhydrous DMF (250 μL). The solution was stirred for 30 min at room temperature then NaN_3 (6.47 mg, 99.6 μmol) was added and the reaction was heated to 50 °C and stirred for 4 hours. The reaction was

cooled to room temperature and quenched by addition of a saturated solution of NaHCO₃ (3.0 mL) and the solution stirred a further 30 minutes. The mixture was extracted with ethyl ether (4 × 3 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 40% ethyl acetate in hexane) provided **265**, **266**, **267** and **268** (12.4 mg, 62%) as an inseparable mixture.

Synthesis of azides 269 and 272. A sealed vial containing a mixture of diols **265-268** (12.0 mg, 27 μmol) and CSA (0.7 mg, 2.7 μmol) in 1:1 2,2-dimethoxypropane:acetone (600 μL) was heated at 50 °C with stirring for 4 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO₃ (3 mL). The mixture was extracted with ethyl ether (4 × 3 mL) and combined extracts washed with brine (3 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) followed by HPLC purification (silica 10 × 250 mm column, 1:19 EtOAc:hexane, 3.5 mL/min) provided pure samples of **269**, **270**, **271** and **272** (10.9 mg, 10:1:40:8 ratio respectively, 84%). Compound **269**, **270**, and **272** were viscous oils while compound **271** was a crystalline solid.

(4*S*,5*S*)-4-(((4*S*,5*R*)-5-azido-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-*N,N*-dibenzyl-2,2-dimethyl-1,3-dioxan-5-amine (269). IR (neat) ν 2993, 2921, 2853, 2802, 2097, 1494, 1451, 1375, 1265, 1197, 1163, 1120, 1069, 1001, 967, 882, 814, 746 cm⁻¹; $[\alpha]_D^{25}$ -21.2 (*c* 0.94, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.5 Hz, 2H), 4.35 (d, *J* = 13.0 Hz, 1H), 4.32 (bs, 2H), 4.22 (dt, *J* = 12.0, 2.0 Hz, 1H), 3.97 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.92 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.86

(td, $J = 11.0, 2.0$ Hz, 1H), 3.65 (dd, $J = 11.5, 10.0$ Hz, 1H), 3.54 (d, $J = 14.0$ Hz, 2H), 3.30 (dt, $J = 9.5, 5.5$ Hz, 1H), 2.66 (ddd, $J = 13.5, 11.0, 2.0$ Hz, 1H), 2.29 (t, $J = 3.5$ Hz, 1H), 1.39 (s, 3H), 1.38 (bs, 6H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.6 (C), 128.8 (CH), 128.5 (CH), 127.0 (CH), 99.1 (C), 98.8 (C), 68.3 (CH), 67.1 (CH), 62.9 (CH₂), 59.9 (CH), 58.6 (CH₂), 56.2 (CH₂), 52.1 (CH), 35.4 (CH₂), 29.7 (CH₃), 28.7 (CH₃), 19.5 (CH₃), 19.0 (CH₃); HRFABMS m/z 481.2816 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{27}\text{H}_{37}\text{N}_4\text{O}_4$ 481.2809.

(4*S*,5*S*)-4-(((4*R*,5*S*)-5-azido-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-*N,N*-dibenzyl-2,2-dimethyl-1,3-dioxan-5-amine (271). IR (neat) ν 2989, 2921, 2853, 2106, 1494, 1451, 1375, 1265, 1205, 1205, 1061, 950, 746, 695 cm^{-1} ; mp 138 °C; $[\alpha]_{\text{D}}^{25} +38.0$ (c 2.47, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 7.2$ Hz, 4H), 7.32 (t, $J = 7.2$ Hz, 4H), 7.23 (t, $J = 7.2$ Hz, 2H), 4.47 (d, $J = 13.2$ Hz, 1H), 4.40-4.26 (m, 3H), 3.98 (dd, $J = 12.8, 3.6$ Hz, 1H), 3.91 (dd, $J = 11.2, 4.4$ Hz, 1H), 3.60-3.46 (m, 3H), 3.37 (m, 2H), 2.43 (ddd, $J = 13.2, 8.4, 1.6$ Hz, 1H), 2.27 (t, $J = 2.8$ Hz, 1H), 1.80 (m, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.26 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.4 (C), 129.3 (CH), 128.4 (CH), 127.1 (CH), 98.8 (C), 98.7 (C), 68.8 (CH), 68.1 (CH), 62.8 (CH₂), 59.4 (CH), 58.2 (CH₂), 56.2 (CH₂), 50.4 (CH), 34.5 (CH₂), 29.7 (CH₃), 28.9 (CH₃), 19.0 (CH₃), 18.9 (CH₃); HRFABMS m/z 481.2806 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{27}\text{H}_{37}\text{N}_4\text{O}_4$ 481.2809.

(2*R*,3*S*,5*S*,6*S*)-2,6-diaminoheptane-1,3,5,7-tetraol (222). A mixture of Pd/C (1.5 mg, 1.3 μmol , 10 mol % Pd) and azide **269** (1.8 mg, 3.7 μmol) in 5:1 ethanol:hexane (0.5 mL) was placed under H_2 (1 atm) and stirred at room temperature. After 17 hours the mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure.

The residue was redissolved in dry methanol and TMSCl (10.0 μ L, 8.5 mg, 80 μ mol) was added and the mixture stirred for 1 hour. The mixture concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (1.5 mg, 1.3 μ mol, 10 mol % Pd) added. The mixture was placed under H₂ (1 atm) and stirred at room temperature for 18 hours. Filtration through a 0.45 μ m syringe filter and concentration under reduced pressure provided the hydrochloride salt of **222** (0.8 mg, 81%) as a white solid: ¹H NMR (400 MHz, D₂O, ref CH₃CN) δ 4.05 (m, 2H), 3.85 (dd, J = 12.4, 4.0 Hz, 2H), 3.73 (dd, J = 12.4, 7.2 Hz, 2H), 3.35 (m, 2H), 1.93 (dt, J = 14.8, 4.0 Hz, 1H), 1.79 (dt, J = 14.8, 8.0 Hz, 1H); ¹³C NMR (100 MHz, D₂O, ref CH₃CN) δ 65.7 (CH), 65.1 (CH), 59.3 (CH₂), 58.1 (CH), 58.1 (CH₂), 57.4 (CH), 36.5 (CH₂); HRESIMS m/z 195.1339 [M+H]⁺, calcd. for C₇H₁₉N₂O₄ 195.1339.

(2R,3R,5S,6S)-2,6-diaminoheptane-1,3,5,7-tetraol (223). A mixture of Pd/C (6.8 mg, 6.4 μ mol, 10 mol % Pd) and azide **271** (14 mg, 31.8 μ mol) in methanol (0.75 mL) was placed under H₂ (1 atm) and stirred at room temperature. After 16 hours TMSCl (10.0 μ L, 8.5 mg, 80 μ mol) was added and the mixture stirred a further 1 hour. The mixture was filtered through a 0.45 μ m syringe filter and concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (6.8 mg, 6.4 μ mol, 10 mol % Pd) added. The mixture was placed under H₂ (1 atm) and stirred at room temperature for 14 hours. Filtration through a 0.45 μ m syringe filter and concentration under reduced pressure provided the hydrochloride salt of **223** (8.4 mg, 99%) as a white solid: ¹H NMR (400 MHz, D₂O, ref ACN) δ 4.19 (p, J = 4.0 Hz, 1H), 3.99 (m, 1H), 3.91 (dd, J = 12.4, 4.4 Hz, 1H), 3.85 (dd, J = 12.4, 4.0 Hz, 1H), 3.80-3.70 (m, 2H), 3.43

(apparent p, $J = 4.0$ Hz, 1H), 3.33 (m, 1H), 1.90 (dt, $J = 14.8, 4.4$ Hz, 1H), 1.80 (dt, $J = 14.8, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O , ref ACN) δ 67.2 (CH), 66.6 (CH), 59.5 (CH₂), 58.0 (CH₂), 57.5 (CH), 56.6 (CH), 36.2 (CH₂); HRESIMS m/z 195.1337 [M+H]⁺, calcd. for C₇H₁₉N₂O₄ 195.1339.

Synthesis of epoxides 273 and 274. To a solution of alkene **236** (250 mg, 655 μmol) in dichloromethane (1 mL) at 0 °C was added pyridine (10 μL , 124 μmol), methyltrioxorhenium (8.2 mg, 33 μmol) and hydrogen peroxide (100 μL of 30% solution, 983 μmol). Solution was warmed to room temperature and stirred for 4 hours, then quenched by addition of a saturated solution of NaHCO₃ (5 mL). The mixture was extracted with ethyl ether (4 \times 3 mL) combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica saturated with triethylamine, step gradient of 15, 20, 25, and 30% ethyl acetate in hexane) provided recovered starting material **236** (54.3 mg, 22%) and **273** and **274** (30.9 mg and 17.2 mg respectively, 24% adjusted for recovered starting material) as a viscous oils.

((2*S*,3*R*)-3-(((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (273): IR (neat) ν 3431, 3026, 2985, 2935, 2869, 2795, 2358, 2333, 1491, 1458, 1384, 1260, 1194, 1070, 947, 740, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +32.0$ (c 5.18, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 7.36 (d, $J = 7.2$ Hz, 4H), 7.31 (t, $J = 7.2$ Hz, 4H), 7.23 (t, $J = 7.2$ Hz, 2H), 4.41 (d, $J = 12.8$ Hz, 1H), 4.30 (bs, 2H), 4.17 (td, $J = 6.8, 4.0$ Hz, 1H), 3.98 (dd, $J = 12.8, 3.6$ Hz, 1H), 3.78 (dd, $J = 12.0, 4.4$ Hz, 1H), 3.65 (dd, $J = 12.0, 6.8$ Hz, 1H), 3.54 (d, $J = 13.6$ Hz, 2H), 3.06 (td, $J = 6.8, 4.4$ Hz, 1H), 2.86 (m, 1H), 2.40 (t, $J = 3.2$ Hz, 1H), 2.08 (dt, $J = 11.2, 5.2$ Hz, 1H), 1.99 (dt, $J = 11.2, 7.2$ Hz, 1H), 1.46 (s, 3H),

1.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.2 (C), 128.9 (CH), 128.4 (CH), 127.1 (CH), 99.8 (C), 70.9 (CH), 60.9 (CH_2), 58.3 (CH_2), 56.4 (CH), 56.1 (CH_2), 54.3 (CH), 50.9 (CH), 30.5 (CH_2), 29.6 (CH_3), 18.8 (CH_3); HREIMS m/z 397.2245 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_1\text{O}_4$ 397.2248.

((2*R*,3*S*)-3-(((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methanol (274): $[\alpha]_{\text{D}}^{25} -1.4$ (c 6.40, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 7.6$ Hz, 4H), 7.31 (t, $J = 7.6$ Hz, 4H), 7.23 (t, $J = 7.6$ Hz, 2H), 4.38 (d, $J = 13.2$ Hz, 1H), 4.28-4.18 (m, 3H), 3.98 (dd, $J = 13.2, 3.6$ Hz, 1H), 3.85 (dd, $J = 12.0, 5.2$ Hz, 1H), 3.52 (d, $J = 14.0$ Hz, 2H), 3.45 (dd, $J = 12.4, 8.4$ Hz, 1H), 3.17 (p, $J = 4.2$ Hz, 1H), 3.00 (dt, $J = 10.0, 4.0$ Hz, 1H), 2.35 (t, $J = 3.4$ Hz, 1H), 2.21 (dt, $J = 14.8, 10.4$ Hz, 1H), 2.04 (ddd, $J = 14.8, 4.0, 2.0$ Hz, 1H), 1.49 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.9 (C), 128.6 (CH), 128.4 (CH), 127.0 (CH), 99.4 (C), 70.7 (CH), 60.1 (CH_2), 58.3 (CH_2), 56.1 (CH_2), 55.6 (CH), 55.1 (CH), 51.9 (CH), 30.7 (CH_2), 29.4 (CH_3), 19.1 (CH_3); HREIMS m/z 398.2323 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_1\text{O}_4$ 398.2326.

(2*R*,3*R*)-2-azido-4-(((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butane-1,3-diol (275). Under an atmosphere of nitrogen, $(\text{MeO})_3\text{B}$ (23.4 μL , 21.4 mg, 206 μmol) was added to a solution of **273** (36.9 mg, 92.8 μmol) in anhydrous DMF (600 μL). The solution was stirred for 20 min at room temperature then NaN_3 (13.4 mg, 206 μmol) was added and the reaction was heated to 50 $^\circ\text{C}$ and stirred for 15 hours. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO_3 (3.0 mL) and the solution stirred a further 60 minutes. The mixture was extracted with ethyl ether (4 \times 3 mL) and combined extracts washed with brine (5 mL), dried over

Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 50% ethyl acetate in hexane) followed by HPLC purification (silica 10 × 250 mm column, 8% isopropanol in hexane, 3.5 mL/min) provided **275** and **276** (20.6 mg and 10.8 mg respectively, 77%) as viscous oils. **275**: IR (neat) ν 3433, 2990, 2928, 2850, 2104, 1499, 1452, 1383, 1266, 1204, 1150, 1072, 971 cm⁻¹; [α]_D²³ +4.5 (*c* 3.48, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 7.6 Hz, 4H), 7.32 (t, *J* = 7.6 Hz, 4H), 7.24 (t, *J* = 7.6 Hz, 2H), 4.38 (d, *J* = 13.2 Hz, 1H), 4.29 (m, 3H), 4.00-3.80 (m, 4H), 3.54 (d, *J* = 13.6 Hz, 2H), 3.79 (dt, *J* = 7.4, 4.4 Hz, 1H), 2.45 (dt, *J* = 14.6, 10.0 Hz, 1H), 3.35 (t, *J* = 3.2 Hz, 1H), 1.68 (dt, *J* = 14.6, 2.4 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.1 (C), 128.9 (CH), 128.5 (CH), 127.2 (CH), 99.1 (C), 73.4 (CH), 72.7 (CH₂), 66.8 (CH), 63.2 (CH₂), 58.3 (CH₂), 56.1 (CH₂), 51.5 (CH), 35.4 (CH₂), 29.6 (CH₃), 19.0 (CH₃); HRESIMS *m/z* 441.2493 [M+H]⁺, calcd. for C₂₄H₃₃N₄O₄ 441.2496.

(2*S*,3*S*)-2-azido-4-((4*S*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butane-1,3-diol (277). Under an atmosphere of nitrogen, (MeO)₃B (9.80 μ L, 8.90 mg, 86 μ mol) was added to a solution of **274** (17.1 mg, 43.0 μ mol) in anhydrous DMF (220 μ L). The solution was stirred for 10 minutes at room temperature then NaN₃ (5.6 mg, 86 μ mol) was added and the reaction was heated to 50 °C and stirred for 17 hours. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO₃ (3.0 mL) and the solution stirred a further 60 minutes. The mixture was extracted with ethyl ether (4 × 3 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 50% ethyl acetate in hexane) followed by HPLC purification (silica 10 × 250 mm

column, 8% isopropanol in hexane, 3.5 mL/min) provided **277** and **278** (3.3 mg and 2.0 mg respectively, 28%) as viscous oils. **277**: IR (neat) ν 3425, 2923, 2851, 2105, 1493, 1452, 1198, 1093, 1069, 1027, 748, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +27.9$ (c 1.48, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38 (d, $J = 7.2$ Hz, 4H), 7.32 (t, $J = 7.6$ Hz, 4H), 7.24 (t, $J = 7.2$ Hz, 2H), 4.38 (d, $J = 12.8$ Hz, 1H), 4.29 (m, 3H), 3.97-3.81 (m, 4H), 3.56 (d, $J = 14.4$ Hz, 2H), 3.40 (m, 1H), 2.37 (t, $J = 2.8$ Hz, 1H), 2.21 (ddd, $J = 14.4, 8.8, 3.2$ Hz, 1H), 1.89 (ddd, $J = 14.4, 9.6, 4.8$ Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.6 (C), 128.8 (CH), 128.5 (CH), 127.1 (CH), 99.9 (C), 69.7 (CH), 69.6 (CH_2), 67.5 (CH), 64.0 (CH_2), 58.2 (CH_2), 56.2 (CH_2), 51.9 (CH), 37.1 (CH_2), 29.7 (CH_3), 19.1 (CH_3); HREIMS m/z 440.2421 $[\text{M}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4$ 440.2418.

(2R,3R,5S,6S)-2,6-diaminoheptane-1,3,5,7-tetraol (224). A mixture of Pd/C (6.8 mg, 6.4 μmol , 10 mol % Pd) and azide **275** (14 mg, 31.8 μmol) in methanol (0.75 mL) was placed under H_2 (1 atm) and stirred at room temperature. After 16 hours TMSCl (10.0 μL , 8.5 mg, 80 μmol) was added and the mixture stirred a further 1 hour. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (6.8 mg, 6.4 μmol , 10 mol % Pd) added. The mixture was placed under H_2 (1 atm) and stirred at room temperature for 14 hours. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure provided the hydrochloride salt of **224** (8.4 mg, 99%) as a white solid: ^1H NMR (400 MHz, D_2O , ref internal CH_3CN) δ 4.05 (m, 2H), 3.85 (dd, $J = 12.4, 4.0$ Hz, 2H), 3.73 (dd, $J = 12.4, 7.2$ Hz, 2H), 3.35 (m, 2H), 1.93 (dt, $J = 14.8, 4.0$ Hz, 1H), 1.79 (dt, $J = 14.8, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O , ref internal CH_3CN) δ

66.3 (CH), 59.5 (CH₂), 57.4 (CH), 36.9 (CH₂); HRESIMS m/z 195.1337 [M+H]⁺, calcd. for C₇H₁₉N₂O₄ 195.1339.

(2S,3S,5S,6S)-2,6-diaminoheptane-1,3,5,7-tetraol (225). A mixture of Pd/C (1.4 mg, 1.4 μmol, 10 mol % Pd) and azide **277** (3.0 mg, 6.8 μmol) in methanol (0.5 mL) was placed under H₂ (1 atm) and stirred at room temperature. After 15 hours TMSCl (10.0 μL, 8.5 mg, 80 μmol) was added and the mixture stirred a further 1 hour. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. The crude material was resuspended in water (0.5 mL) and Pd/C (1.4 mg, 1.4 μmol, 10 mol % Pd) added. The mixture was placed under H₂ (1 atm) and stirred at room temperature for 14 hours. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure provided the hydrochloride salt of **225** (1.8 mg, 99%) as a white solid: ¹H NMR (400 MHz, D₂O, ref CH₃CN) δ 4.05 (m, 2H), 3.88 (dd, $J = 12.4, 3.6$ Hz, 2H), 3.74 (dd, $J = 12.4, 6.8$ Hz, 2H), 3.30 (m, 2H), 1.75 (apparent dd, $J = 7.6, 5.2$ Hz, 2H); ¹³C NMR (100 MHz, D₂O, ref CH₃CN) δ 64.9 (CH), 59.3 (CH₂), 58.1 (CH), 37.3 (CH₂); HRESIMS m/z 195.1330 [M+H]⁺, calcd. for C₇H₁₉N₂O₄ 195.1339.

Table 7.1: ^{13}C NMR data for **220-225** and Zwittermicin A [(+)-**1**].

| C# | $\delta_{\text{C}}^{\text{a}}$ | | | | | | | | |
|----|--------------------------------|------------|------------|-------------|------------|-------------|------------|------------|------------------------------------|
| | 220 | 221 | 222 | 222b | 223 | 223b | 224 | 225 | Zwittermicin A [(+)- 1] |
| 9 | 58.0 | 58.0 | 59.3 | 58.1 | 59.5 | 58.0 | 59.5 | 59.3 | |
| 10 | 56.6 | 57.3 | 58.1 | 57.4 | 57.5 | 56.6 | 57.4 | 58.1 | 58.3 |
| 11 | 67.4 | 65.9 | 65.1 | 65.7 | 66.6 | 67.2 | 66.3 | 64.9 | 66.0 |
| 12 | 35.3 | 35.8 | 36.5 | 36.5 | 36.2 | 36.2 | 36.9 | 37.3 | 35.4 |
| 13 | 67.4 | 65.9 | 65.7 | 65.1 | 67.2 | 66.6 | 66.3 | 64.9 | 66.1 |
| 14 | 56.6 | 57.3 | 57.4 | 58.1 | 56.6 | 57.5 | 57.4 | 58.1 | 57.4 |
| 15 | 58.0 | 58.0 | 58.1 | 59.3 | 58.0 | 59.5 | 59.5 | 59.3 | 58.1 |

a. ^{13}C NMR spectra (100 MHz, D_2O) referenced to internal CH_3CN (δ 1.47 ppm). For ease of comparison, carbons are numbered with respect to zwittermicin A (**1**).

7.1.4. Chapter 3 Methods

(2*S*,3*R*)-3-azido-4-(*tert*-butyldiphenylsilyloxy)-1-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-ol (285). Under an atmosphere of nitrogen *tert*-butyldiphenylchlorosilane (175 μ L, 656 μ mol) was added to a stirred solution of alcohol **233** (275 mg, 624 μ mol) and imidazole (117 mg, 1.62 mmol) in dimethylformamide (3.1 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 3.5 hours then quenched by addition of water (85 mL). The mixture was extracted with ethyl ether (3 \times 25 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 1.5%, 2.5%, 5%, and 7% ethyl acetate in hexane, 24 mL/min flow rate) provided **285** (385 mg, 91%) as a viscous oil: IR (neat) ν 3500, 3070, 2929, 2851, 2101, 1452, 1421, 1382, 1272, 1225, 1116, 827 cm⁻¹; [α]_D²³ +15.5 (*c* 4.96, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.70 (m, 4H), 7.48-7.38 (m, 6H), 7.30-7.20 (m, 10H), 3.99-3.80 (m, 6H), 3.73 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.64 (s, 1H), 3.56-3.49 (m, 3H), 3.42 (ddd, *J* = 10.8, 8.4, 3.6 Hz, 1H), 2.74 (dt, *J* = 9.6, 5.6 Hz, 1H), 2.24 (dt, *J* = 14.4, 2.0 Hz, 1H), 1.39 (s, 3H), 1.30 (m, 1H), 1.28 (s, 3H), 1.11 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.1 (C), 135.8 (CH), 135.7 (CH), 133.3 (C), 133.2 (C), 129.9 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 99.5 (C), 71.3 (CH), 71.2 (CH), 68.0 (CH), 64.6 (CH₂), 58.5 (CH), 57.9 (CH₂), 55.1 (CH₂), 36.2 (CH₂), 26.9 (CH₃), 26.8 (CH₃), 21.8 (CH₃), 19.3 (C); HREIMS *m/z* 678.3588 [M]⁺, calcd. for C₄₀H₅₀N₄O₄Si₁ 678.3596.

(4*R*,5*S*)-4-((2*S*,3*R*)-3-azido-4-(*tert*-butyldiphenylsilyloxy)-2-(methoxymethoxy)butyl)-*N,N*-dibenzyl-2,2-dimethyl-1,3-dioxan-5-amine (286). Under an atmosphere of nitrogen chloromethyl methyl ether (52.0 μ L, 689 μ mol) was added to a stirred solution of alcohol **285** (78.0 mg, 115 μ mol) and Hünig's base (190 μ L, 1.15 mmol) in dichloromethane (575 μ L) at 0 °C. The mixture was warmed to room temperature and stirred for 2 days then quenched by addition of saturated aqueous NH₄Cl (5 mL). The mixture was extracted with ethyl ether (4 \times 3 mL) and combined extracts washed with water (5 mL), brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 5% ethyl acetate in hexane) provided **286** (80.0 mg, 96%) as a viscous oil: IR (neat) ν 3060, 3037, 2936, 2889, 2850, 2105, 1592, 1491, 1476, 1452, 1429, 1383, 1320, 1274, 1219, 1111, 1033, 823 cm⁻¹; [α]_D²³ +17.9 (*c* 11.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.66 (m, 4H), 7.46-7.34 (m, 6H), 7.32-7.20 (m, 10H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.10 (d, *J* = 6.8 Hz, 1H), 3.96-3.82 (m, 6H), 3.77 (ddd, *J* = 9.2, 6.4, 2.4 Hz, 1H), 3.69 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.56 (ddd, *J* = 10.4, 6.8, 4.0 Hz, 1H), 3.47 (d, *J* = 14.4 Hz, 2H), 3.12 (s, 3H), 2.70 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.14 (ddd, *J* = 10.8, 6.0, 2.0 Hz, 1H), 1.54 (ddd, *J* = 14.8, 9.6, 4.0 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.08 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.4 (C), 135.7 (CH), 135.6 (CH), 133.3 (C), 133.2 (C), 129.9 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 99.3 (C), 95.7 (CH₂) 74.0 (CH), 67.1 (CH), 66.6 (CH), 65.3 (CH₂), 58.5 (CH), 57.9 (CH₂), 55.9 (CH₃), 54.7 (CH₂), 34.3 (CH₂), 26.8 (CH₃), 26.7 (CH₃), 21.8 (CH₃), 19.3 (C); HREIMS *m/z* 722.3868 [M]⁺, calcd. for C₄₂H₅₄N₄O₅Si₁ 722.3858.

(2*R*,3*S*)-2-azido-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (287). Under an atmosphere of nitrogen, TBAF 1 M in THF (138 μ L, 138 μ mol) was added to a stirred solution of azide **286** (80.0 mg, 111 μ mol) in THF (750 μ L) at -10 $^{\circ}$ C. The mixture was stirred for 4 hours then quenched by addition of water (5 mL). The mixture was extracted with ethyl ether (3×5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:3 ethyl acetate:hexane) provided **287** (52.6 mg, 98%) as a viscous oil: IR (neat) ν 3453, 2984, 2937, 2101, 1491, 1444, 1374, 1265, 1225, 1100, 1038, 913 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +55.5$ (c 2.17, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.30 (m, 8H), 7.29-7.22 (m, 2H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.52 (d, $J = 6.8$ Hz, 1H), 4.02-3.91 (m, 4H), 3.87 (dd, $J = 12.0, 9.6$ Hz, 1H), 3.82 (m, 2H), 3.75 (ddd, $J = 9.6, 6.0, 3.6$ Hz, 1H), 3.54 (dt, $J = 7.2, 4.0$ Hz, 1H), 3.51 (d, $J = 13.6$ Hz, 2H), 3.37 (s, 3H), 2.73 (dt, $J = 9.6, 6.0$ Hz, 1H), 2.56 (s, 1H), 2.24 (ddd, $J = 15.2, 6.4, 2.0$ Hz, 1H), 1.57 (ddd, $J = 14.8, 9.6, 3.6$ Hz, 1H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 128.8 (CH), 128.5 (CH), 127.3 (CH), 99.4 (C), 96.3 (CH_2) 75.1 (CH), 66.7 (CH), 65.5 (CH), 62.5 (CH_2), 58.6 (CH), 57.8 (CH_2), 56.2 (CH_3), 54.9 (CH_2), 34.4 (CH_2), 26.6 (CH_3), 21.9 (CH_3); HREIMS m/z 484.2671 $[\text{M}]^+$, calcd. for $\text{C}_{26}\text{H}_{36}\text{N}_4\text{O}_5$ 484.2680.

(2*S*,3*R*)-3-azido-4-(*tert*-butyldimethylsilyloxy)-1-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-ol (290). Under an atmosphere of nitrogen *tert*-butyldimethylchlorosilane (19.2 mg, 127 μ mol) was added to a stirred solution of alcohol **233** (53.4 mg, 121 μ mol) and imidazole (22.7 mg, 315 μ mol) in dimethylformamide

(606 μL) at 0 $^{\circ}\text{C}$. The mixture was warmed to room temperature and stirred for 3 hours then quenched by addition of water (10 mL). The mixture was extracted with ethyl ether (4 \times 4 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 15% ethyl acetate in hexane) provided **290** (58.0 mg, 93%) as a viscous oil: IR (neat) ν 3511, 3056, 2986, 2925, 2873, 2095, 1606, 1501, 1449, 1387, 1265, 1248, 1117, 1029, 968, 898, 837, 784, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +26.9$ (c 5.48, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.25 (m, 10H), 4.05-3.86 (m, 6H), 3.75-3.69 (m, 2H), 3.59 (ddd, $J = 9.6, 7.6, 1.6$ Hz, 1H), 3.54 (d, $J = 13.2$ Hz, 2H), 3.29 (td, $J = 7.2, 3.6$ Hz, 1H), 2.77 (dt, $J = 9.6, 5.6$ Hz, 1H), 2.34 (dt, $J = 14.4, 2.0$ Hz, 1H), 1.42 (s, 3H), 1.33 (m, 1H), 1.31 (s, 3H), 0.95 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.2 (C), 129.0 (CH), 128.6 (CH), 127.4 (CH), 99.5 (C), 71.4 (CH), 71.4 (CH), 67.7 (CH), 63.9 (CH_2), 58.4 (CH), 57.9 (CH_2), 55.1 (CH_2), 36.4 (CH_2), 26.8 (CH_3), 26.0 (CH_3), 21.8 (CH_3), 18.4 (C) -5.4 (CH_3), -5.3 (CH_3); HREIMS m/z 554.3276 $[\text{M}]^+$, calcd. for $\text{C}_{30}\text{H}_{46}\text{N}_4\text{O}_4\text{Si}_1$ 554.3283.

Synthesis of alcohols 291 and 292. Compound **285** (332 mg, 489 μmol) in methanol:acetic acid 3:1 (56 mL) was heated to 70 $^{\circ}\text{C}$. The mixture was stirred for 28 hours then concentrated under reduced pressure. Flash chromatography (silica, step gradient of 15, 25, and 50% ethyl acetate in hexane) provided recovered starting material **285** (27.8 mg, 8%), **291** (212 mg, 68%) and **292** (70.7 mg, 21%) as viscous oils.

(2*S*,3*R*,5*S*,6*R*)-6-azido-7-(*tert*-butyldiphenylsilyloxy)-2-(dibenzylamino)heptane-1,3,5-triol (291). IR (neat) ν 3388, 3065, 3030, 2925, 2855, 2095, 1588, 1466, 1422, 1352, 1265, 1117, 1029, 819, 741, 697, 610, 505 cm^{-1} ; $[\alpha]_{\text{D}}^{24} -11.6$ (c 4.79, CHCl_3); ^1H

NMR (400 MHz, CDCl₃) δ 7.74-7.69 (m, 4H), 7.50-7.40 (m, 6H), 7.29-7.19 (m, 10H), 4.09 (td, $J = 8.0, 1.6$ Hz, 1H), 3.99 (dd, $J = 11.2, 4.8$ Hz, 1H), 3.96-3.82 (m, 4H), 3.79 (d, $J = 13.6$ Hz, 2H), 3.63 (d, $J = 13.6$ Hz, 2H), 3.38 (q, $J = 6.0$ Hz, 1H), 2.60 (q, $J = 6.4$ Hz, 1H), 2.07 (d, $J = 12.8$ Hz, 1H), 1.22 (m, 1H), 1.10 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.6 (C), 135.7 (CH), 132.6 (C), 132.5 (C), 130.3 (CH), 130.2 (CH), 129.1 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 73.6 (CH), 73.4 (CH), 66.9 (CH), 64.5 (CH₂), 62.7 (CH), 59.7 (CH₂), 55.0 (CH₂), 37.4 (CH₂), 26.9 (CH₃), 19.2 (C); HREIMS m/z 609.3156 [M-N₂-H]⁺, calcd. for C₃₇H₄₅N₂O₄Si₁ 609.3143.

(S)-2-((4R,6S)-6-((R)-1-azido-2-(tert-butylidiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-(dibenzylamino)ethanol (292). IR (neat) ν 3467, 3065, 3030, 2986, 2925, 2855, 2357, 2095, 1422, 1265, 1204, 1108, 968, 819, 741, 715, 610, 505 cm⁻¹; [α]_D²⁴ -35.8 (c 4.47, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.72-7.68 (m, 4H), 7.48-7.38 (m, 6H), 7.34-7.22 (m, 10H), 4.17 (ddd, $J = 12.0, 6.0, 2.5$ Hz, 1H), 3.99 (ddd, $J = 9.5, 7.0, 2.5$ Hz, 1H), 3.87 (dd, $J = 11.0, 6.0$ Hz, 1H), 3.82-3.74 (m, 5H), 3.66 (d, $J = 13.5$ Hz, 2H), 3.29 (dt, $J = 7.0, 5.0$ Hz, 1H), 2.67 (m, 2H), 1.78 (dt, $J = 13.0, 2.5$ Hz, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 1.17 (m, 1H), 1.08 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.5 (C), 135.7 (CH), 135.6 (CH), 133.1 (C), 133.0 (C), 130.0 (CH), 129.9 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 98.9 (C), 68.4 (CH), 67.8 (CH), 66.7 (CH), 63.0 (CH₂), 62.9 (CH), 59.0 (CH₂), 54.9 (CH₂), 32.1 (CH₂), 29.9 (CH₃), 26.8 (CH₃), 19.6 (CH₃), 19.3 (C); HREIMS m/z 678.3585 [M]⁺, calcd. for C₄₀H₅₀N₄O₄Si₁ 678.3596.

(S)-1-((4R,6S)-6-((R)-1-azido-2-(tert-butylidiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-N,N-dibenzyl-2-(benzyloxy)ethanamine (293). Under an atmosphere of nitrogen, benzylbromide (24.3 μL , 203 μmol) was added dropwise to a stirred solution of alcohol **292** (46.0 mg, 67.8 μmol) and silver oxide (47.1 mg, 203 μmol) in anhydrous toluene (340 μL) at room temperature. The mixture was stirred for 40 hours then filtered through celite. Flash chromatography (silica, step gradient of 2 and 3% ethyl ether in hexane then 15% ethyl acetate in hexane) provided recovered starting material **292** (16.8 mg, 21%), and **293** (26.6 mg, 51%) as a viscous oil: IR (neat) ν 3065, 3030, 2995, 2934, 2855, 2104, 1580, 1492, 1422, 1431, 1379, 1265, 1195, 1117, 1029, 968, 881, 819, 706, 618 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ -5.8 (c 8.14, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.70 (m, 4H), 7.49-7.20 (m, 21H), 4.60 (d, $J = 12.0$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.06 (ddd, $J = 11.6, 7.2, 2.4$ Hz, 1H), 3.95 (ddd, $J = 11.2, 7.2, 2.4$ Hz, 1H), 3.92-3.78 (m, 6H), 3.74 (d, $J = 14.0$ Hz, 2H), 3.29 (dt, $J = 6.8, 4.8$ Hz, 1H), 2.81 (td, $J = 6.8, 3.2$ Hz, 1H), 1.94 (dt, $J = 13.2, 2.4$ Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H), 1.13 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.5 (C), 139.0 (C), 135.7 (CH), 135.7 (CH), 133.2 (C), 133.1 (C), 129.9 (CH), 129.8 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 98.8 (C), 73.4 (CH_2), 68.2 (CH), 68.0 (CH), 67.2 (CH_2), 67.1 (CH), 63.2 (CH_2), 61.4 (CH), 55.8 (CH_2), 32.0 (CH_2), 30.0 (CH_3), 26.8 (CH_3), 19.7 (CH_3), 19.3 (C); HREIMS m/z $[\text{M}]^+$, calcd. for $\text{C}_{47}\text{H}_{56}\text{N}_4\text{O}_4\text{Si}_1$ 768.4071.

(R)-2-azido-2-((4S,6R)-6-((S)-2-(benzyloxy)-1-(dibenzylamino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (294). Under an atmosphere of nitrogen, TBAF 1 M in THF (51.9 μL , 51.9 μmol) was added to a stirred solution of azide **293** (25.1 mg, 32.6 μmol) in

THF (210 μ L) at -10 $^{\circ}$ C. The mixture was stirred for 3 hours then quenched by addition of water (3 mL). The mixture was extracted with ethyl ether (3×3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:3 ethyl acetate:hexane) provided **294** (15.4 mg, 89%) as a viscous oil: IR (neat) ν 3432, 3065, 3030, 2995, 2934, 2855, 2104, 1597, 1492, 1449, 1379, 1265, 1204, 1169, 1108, 1029, 968, 872, 750, 697 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +29.9$ (c 7.16, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.20 (m, 15H), 4.61 (d, $J = 12.2$ Hz, 1H), 4.52 (d, $J = 12.2$ Hz, 1H), 4.07 (ddd, $J = 10.0, 7.2, 2.4$ Hz, 1H), 3.95 (ddd, $J = 12.0, 6.4, 2.4$ Hz, 1H), 3.92-3.86 (m, 3H), 3.82-3.66 (m, 5H), 3.33 (dt, $J = 6.0, 5.6$ Hz, 1H), 2.81 (td, $J = 5.6, 3.2$ Hz, 1H), 2.16 (t, $J = 6.4$ Hz, 1H), 1.94 (dt, $J = 13.2, 2.4$ Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.16 (q, $J = 11.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.4 (C), 139.0 (C), 129.0 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 99.1 (C), 73.4 (CH_2), 70.9 (CH), 68.0 (CH), 67.0 (CH_2), 66.5 (CH), 62.6 (CH_2), 61.3 (CH), 55.8 (CH_2), 32.2 (CH_2), 30.0 (CH_3), 19.7 (CH_3); HREIMS m/z 530.2882 $[\text{M}]^+$, calcd. for $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_4$ 530.2888.

(2R,3S)-2-amino-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (295). To a solution of alcohol **277** (404 mg, 834 μ mol) in ethanol (60 mL) was added Lindlar catalyst (266 mg, 125 μ mol). The mixture was placed under hydrogen (1 atm) at room temperature and stirred for 15 hours. The solution was filtered through a 0.45 μ m syringe filter and concentrated under reduced pressure. Flash chromatography (silica, 10% methanol in dichloromethane) provided **295** (341 mg, 89%) as a viscous oil: IR (neat) ν 3371, 3065, 3030, 2995, 2925, 2882, 2829, 1597, 1501,

1501, 1457, 1379, 1265, 1230, 1151, 1108, 1038, 968, 916, 750, 697, 522 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ +76.4 (*c* 7.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.21 (m, 10H), 4.71 (d, J = 7.0 Hz, 1H), 4.50 (d, J = 7.0 Hz, 1H), 4.02 (t, J = 9.2 Hz, 1H), 3.98-3.90 (m, 3H), 3.86 (dd, J = 12.0, 5.6 Hz, 1H), 3.73 (dd, J = 10.8, 3.2 Hz, 1H), 3.64-3.56 (m, 2H), 3.49 (d, J = 13.6 Hz, 2H), 3.37 (s, 3H), 2.90 (m, 1H), 2.70 (dt, J = 9.2, 6.0 Hz, 1H), 2.55 (bs, 3H), 2.18 (dd, J = 14.4, 4.8 Hz, 1H), 1.52 (ddd, J = 15.2, 9.6, 3.6 Hz, 1H), 1.41 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.4 (C), 128.8 (CH), 128.5 (CH), 127.3 (CH), 99.3 (C), 96.0 (CH_2), 77.8 (CH), 66.5 (CH), 63.5 (CH_2), 58.4 (CH), 57.8 (CH_2), 56.1 (CH_3), 54.7 (CH_2), 54.6 (CH), 33.5 (CH_2), 26.7 (CH_3), 21.8 (CH_3); HREIMS m/z 458.2784 $[\text{M}]^+$, calcd. for $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_5$ 458.2775.

(2*R*,3*S*)-2-(dibenzylamino)-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (296). Under an atmosphere of nitrogen, benzylbromide (284 μL , 2.37 mmol) was added dropwise to a stirred solution of amine **295** (340 mg, 742 μmol) and K_2CO_3 (655 mg, 4.74 mmol) in anhydrous acetonitrile (4.7 mL) at room temperature. The mixture was stirred for 3.5 days then quenched by addition of water (10 mL). The mixture was extracted with ethyl acetate (4×15 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, step gradient of 3% and 10% ethyl ether in hexane then 15% and 25% ethyl acetate in hexane then 20% methanol in dichloromethane) provided **296** (437 mg, 92%) as a viscous oil: IR (neat) ν 3467, 3065, 3030, 2986, 2934, 2882, 2803, 1597, 1501, 1449, 1379, 1265, 1230, 1204, 1151, 1108, 1029, 924, 750, 697, 514 cm^{-1} ; $[\alpha]_{\text{D}}^{24}$ +71.4 (*c* 4.12, CHCl_3); ^1H NMR (400 MHz,

CDCl₃) δ 7.33-7.10 (m, 20H), 4.70 (d, J = 6.4 Hz, 1H), 4.55 (d, J = 6.4 Hz, 1H), 4.04 (p, J = 4.0 Hz, 1H), 3.96 (dd, J = 11.2, 6.8 Hz, 1H), 3.92-3.84 (m, 4H), 3.81-3.67 (m, 6H), 3.45 (d, J = 14.0 Hz, 2H), 3.37 (s, 3H), 3.06 (bs, 1H), 2.90 (dt, J = 6.4, 4.8 Hz, 1H), 2.64 (dt, J = 9.6, 6.4 Hz, 1H), 2.29 (ddd, J = 10.8, 7.6, 2.0 Hz, 1H), 1.49 (ddd, J = 14.0, 9.6, 4.0 Hz, 1H), 1.34 (s, 3H), 1.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 139.9 (C), 139.4 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.2 (CH), 127.1 (CH), 98.9 (C), 96.8 (CH₂), 74.8 (CH), 67.4 (CH), 62.1 (CH), 57.9 (CH₂), 57.8 (CH₂), 56.5 (CH₃), 54.7 (CH₂), 54.6 (CH₂), 36.7 (CH₂), 27.1 (CH₃), 21.6 (CH₃); HREIMS m/z 638.3709 [M]⁺, calcd. for C₄₀H₅₀N₂O₅ 638.3720.

(2*S*,3*S*)-2-(dibenzylamino)-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butanal (297). Under an atmosphere of nitrogen, DMSO (69 μ L, 76 mg, 971 μ mol) in CH₂Cl₂ (69 μ L) was added dropwise to a stirred solution of oxalyl chloride (40 μ L, 60 mg, 470 μ mol) in anhydrous CH₂Cl₂ (400 μ L) at -78 °C. The mixture was stirred for 10 minutes then a solution of alcohol **296** (100 mg, 157 μ mol) in CH₂Cl₂ was added dropwise. The mixture was stirred for 1.5 hours at -78 °C then triethylamine (196 μ L, 143 mg, 1.41 mmol) was added dropwise and the solution was allowed to warm to room temperature. Water (50 mL) was added and the mixture was extracted with ethyl ether (3 \times 50 mL) and combined extracts washed with 1% HCl solution (50 mL), water (2 \times 50 mL), saturated NaHCO₃ solution (50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 25% ethyl acetate in hexane) provided **297** (90 mg, 90%) as a viscous oil: IR (neat) ν 3083, 2995, 2934, 2882, 2820, 2716, 1728, 1606, 1501, 1449, 1379, 1230, 1204,

1151, 1099, 1038, 977, 916, 828, 750, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +72.9$ (c 4.24, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 10.0 (d, $J = 1.6$ Hz, 1H), 7.34-7.14 (m, 20H), 4.65 (d, $J = 6.8$ Hz, 1H), 4.51 (d, $J = 6.8$ Hz, 1H), 4.14 (p, $J = 4.0$ Hz, 1H), 3.94 (d, $J = 14.0$ Hz, 2H), 3.87 (d, $J = 14.0$ Hz, 2H), 3.84 (dd, $J = 12.0, 6.8$ Hz, 1H), 3.77-3.64 (m, 4H), 3.43 (d, $J = 14.0$ Hz, 2H), 3.38 (dd, $J = 4.4, 2.4$ Hz, 1H), 3.27 (s, 3H), 2.63 (dt, $J = 9.2, 6.8$ Hz, 1H), 2.45 (ddd, $J = 14.4, 8.8, 1.2$ Hz, 1H), 1.63 (ddd, $J = 14.0, 10.0, 3.6$ Hz, 1H), 1.25 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.1 (CH), 139.5 (C), 139.4 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 99.0 (C), 96.5 (CH_2), 76.0 (CH), 68.8 (CH), 67.0 (CH), 57.8 (CH_2), 57.7 (CH), 56.3 (CH_3), 55.5 (CH_2), 54.7 (CH_2), 36.4 (CH_2), 27.0 (CH_3), 21.4 (CH_3); HREIMS m/z 636.3559 $[\text{M}]^+$, calcd. for $\text{C}_{40}\text{H}_{48}\text{N}_2\text{O}_5$ 636.3563.

(2*R*,3*S*)-3-azido-4-(*tert*-butyldiphenylsilyloxy)-1-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-ol (298). *tert*-Butyldiphenylchlorosilane (492 μL , 1.90 mmol) was added to a stirred solution of alcohol **234** (760 mg, 1.73 mmol) and imidazole (311 mg, 4.31 mmol) in dimethylformamide (8.6 mL) at 0 $^\circ\text{C}$. The mixture was warmed to room temperature and stirred for 4 hours then quenched by addition of water (175 mL). The mixture was extracted with ethyl ether (3 \times 50 mL) and combined extracts washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 40 g silica cartridge, 1.5%, 2.5% and 5% ethyl acetate in hexane, 34 mL/min flow rate) provided **298** (1.07 g, 91%) as a viscous oil: IR (neat) ν 3500, 3070, 2929, 2859, 2101, 1791, 1460, 1429, 1374, 1265, 1225, 1100, 819 cm^{-1} ; $[\alpha]_{\text{D}}^{23} +42.3$ (c 9.52, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.78-7.71 (m, 4H),

7.50-7.40 (m, 6H), 7.34-7.21 (m, 10H), 4.17 (ddd, $J = 10.0, 7.5, 4.0$ Hz, 1H), 3.98-3.86 (m, 5H), 3.81 (dd, $J = 11.0, 7.5$ Hz, 1H), 3.64 (m, 1H), 3.52 (d, $J = 13.5$ Hz, 2H), 3.43 (ddd, $J = 7.5, 7.5, 3.3$ Hz, 1H), 3.35 (d, $J = 5.0$ Hz, 1H), 2.80 (dt, $J = 9.5, 6.3$ Hz, 1H), 1.99 (ddd, $J = 14.8, 9.0, 3.5$ Hz, 1H), 1.65 (ddd, $J = 14.8, 7.5, 2.0$ Hz, 1H), 1.40 (s, 3H), 1.29 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.1 (C), 135.73 (CH), 135.71 (CH), 133.1 (C), 133.0 (C), 129.9 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 99.4 (C), 68.3 (CH), 68.2 (CH), 67.5 (CH), 64.6 (CH_2), 58.0 (CH_2), 57.3 (CH), 54.8 (CH_2), 35.4 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 21.4 (CH_3), 19.2 (C); HREIMS m/z 678.3586 $[\text{M}]^+$, calcd. for $\text{C}_{40}\text{H}_{50}\text{N}_4\text{O}_4\text{Si}$ 678.3596.

(4*R*,5*S*)-4-((2*R*,3*S*)-3-azido-4-(*tert*-butyldiphenylsilyloxy)-2-(methoxymethoxy)butyl)-*N,N*-dibenzyl-2,2-dimethyl-1,3-dioxan-5-amine (299). Chloromethyl methyl ether (628 μL , 8.27 mmol) was added to a stirred solution of alcohol **298** (936 mg, 1.38 mmol) and Hünig's base (2.30 mL, 13.8 mmol) in dichloromethane (6.9 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 56 hours then quenched by addition of saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ethyl ether (3 \times 50 mL) and combined extracts washed with water (2 \times 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 3-7% ethyl acetate in hexane) provided **299** (977.4 mg, 98%) as a viscous oil: IR (neat) ν 3067, 3034, 3001, 2944, 2894, 2861, 2110, 1508, 1475, 1458, 1433, 1392, 1277, 1235, 1128, 1037, 831, 757, 724 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +30.8$ (c 6.68, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.84-7.75 (m, 4H), 7.54-7.43 (m, 6H), 7.41 (d, $J = 7.2$ Hz, 4H), 7.34 (t, $J = 7.2$ Hz, 4H), 7.27 (t, $J = 7.2$ Hz, 2H), 4.77 (d, $J = 6.6$ Hz, 1H), 4.72 (d, $J = 6.6$ Hz, 1H), 4.13 (t, $J = 9.8$

Hz, 1H), 4.06-3.92 (m, 6H), 3.80-3.64 (m, 2H), 3.59 (d, $J = 13.6$ Hz, 2H), 3.44 (s, 3H), 2.70 (dt, $J = 9.6, 6.8$ Hz, 1H), 3.35 (dd, $J = 14.4, 10.8$ Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.6 (C), 135.7 (CH), 133.1 (C), 133.0 (C), 129.9 (CH), 129.0 (CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 98.9 (C), 97.7 (CH_2) 75.6 (CH), 67.5 (CH), 66.4 (CH), 63.6 (CH_2), 58.3 (CH_2), 57.8 (CH), 55.9 (CH_3), 54.7 (CH_2), 34.2 (CH_2), 27.3 (CH_3), 26.8 (CH_3), 21.2 (CH_3), 19.2 (C); HRESIMS m/z 723.3939 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{42}\text{H}_{55}\text{N}_4\text{O}_5\text{Si}_1$ 723.3942.

(2*S*,3*R*)-2-azido-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (300). Tetrabutylammonium fluoride (TBAF, 1M in THF, 1.69 mL, 1.69 mmol) was added to a stirred solution of azide **299** (977 mg, 1.35 mmol) in THF (5.0 mL) at -10 °C. The mixture was stirred for 4 hours then quenched by addition of water (125 mL). The mixture was extracted with ethyl ether (3×75 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1:3 ethyl acetate:hexane) provided **300** (620 mg, 95%) as a crystalline solid (needles): IR (neat) ν 3458, 2985, 2929, 2812, 2101, 1444, 1374, 1265, 1225, 1140, 1108, 1022, 913 cm^{-1} ; mp 74 °C; $[\alpha]_{\text{D}}^{23} +28.8$ (c 2.01, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.29 (m, 8H), 7.27-7.22 (m, 2H), 4.71 (d, $J = 6.8$ Hz, 1H), 4.69 (d, $J = 6.8$ Hz, 1H), 4.01 (td, $J = 10.0, 1.2$ Hz, 1H), 3.98-3.83 (m, 5H), 3.67 (bs, 3H), 3.52 (d, $J = 13.2$ Hz, 2H), 3.41 (s, 3H), 2.65 (m, 1H), 2.41 (bs, 1H), 2.33 (ddd, $J = 14.8, 9.6, 2.0$ Hz, 1H), 1.39 (s, 3H), 1.29 (s, 1H), 1.21 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.5 (C), 129.0 (CH), 128.5 (CH), 127.3 (CH), 99.1 (C), 97.8 (CH_2) 76.2 (CH), 66.9 (CH), 66.8 (CH), 62.0 (CH_2), 58.2 (CH_2), 57.9 (CH), 56.2 (CH_3),

54.9 (CH₂), 35.2 (CH₂), 27.3 (CH₃), 21.4 (CH₃); HREIMS m/z 484.2682 [M]⁺, calcd. for C₂₆H₃₆N₄O₅ 484.2680.

(2*S*,3*R*)-2-amino-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (301). To a solution of alcohol **300** (600 mg, 1.24 mmol) in ethanol (90 mL) was added Lindlar's catalyst (395 mg, 190 μmol). The mixture was placed under hydrogen (1 atm) at room temperature and stirred for 14 hours. The solution was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. Flash chromatography (silica, 10% MeOH in dichloromethane) provided recovered starting material **301** (558 mg, 98%) as a viscous oil: IR (neat) ν 3467, 3362, 3292, 3030, 2986, 2934, 2882, 2829, 1597, 1492, 1457, 1387, 1230, 1160, 1108, 1038, 977, 916, 758, 706 cm⁻¹; [α]_D²¹ +24.5 (*c* 3.82, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.20 (m, 10H), 4.67 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.02-3.84 (m, 5H), 3.70 (bd, *J* = 9.6 Hz, 1H), 3.57 (m, 1H), 3.50 (d, *J* = 14.0 Hz, 2H), 3.36 (s, 3H), 2.87 (bs, 1H), 2.65 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.28 (bs, 2H), 2.19 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.18 (ddd, *J* = 14.4, 11.6, 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.5 (C), 128.9 (CH), 128.3 (CH), 127.2 (CH), 99.0 (C), 97.9 (CH₂) 79.4 (CH), 66.8 (CH), 63.1 (CH₂), 58.1 (CH₂), 58.0 (CH), 56.0 (CH₂), 55.9 (CH₃), 54.7 (CH), 35.4 (CH₂), 27.1 (CH₃), 21.4 (CH₃); HREIMS m/z 458.2781 [M]⁺, calcd. for C₂₆H₃₈N₂O₅ 458.2775.

(2*S*,3*R*)-2-(dibenzylamino)-4-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (302). Benzylbromide (642 μL, 5.37 mmol) was added dropwise to a stirred solution of amine **301** (547 mg, 1.19 mmol) and K₂CO₃ (2.47

g, 17.9 mmol) in anhydrous acetonitrile (5.96 mL) at room temperature. The mixture was stirred for 31 hours then quenched by addition of water (75 mL). The mixture was extracted with ethyl acetate (3 × 50 mL) and combined extracts washed with brine (75 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, step gradient of 3% and 10% ethyl ether in hexane then 25% ethyl acetate in hexane) provided **302** (690 mg, 91%) as an amorphous solid: IR (neat) ν 3476, 3065, 3030, 2995, 2943, 2882, 2812, 1597, 1492, 1457, 1379, 1265, 1221, 1151, 1108, 1029, 977, 916, 758, 706 cm⁻¹; [α]_D²⁰ +28.8 (*c* 6.48, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.23 (m, 20H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.15 (m, 1H), 4.02 (t, *J* = 9.6 Hz, 1H), 4.00-3.88 (m, 6H), 3.84 (d, *J* = 13.6 Hz, 2H), 3.70 (d, *J* = 13.6 Hz, 2H), 3.59 (d, *J* = 14.0 Hz, 2H), 3.40 (s, 3H), 3.31 (bs, 1H), 2.78-2.70 (m, 2H), 2.14 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.90 (ddd, *J* = 14.8, 10.8, 2.4 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.0 (C), 139.6 (C), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.2 (CH), 127.0 (CH), 98.8 (CH), 98.7 (C), 76.2 (CH), 67.0 (CH), 62.6 (CH), 58.5 (CH₂), 58.0 (CH), 57.9 (CH₂), 56.4 (CH₃), 54.9 (CH₂), 54.8 (CH₂), 38.6 (CH₂), 27.9 (CH₃), 20.9 (CH₃); HRMS *m/z* 639.3973 [M+H]⁺, calcd. for C₄₀H₅₁N₂O₅ 639.3793.

(2R,3R)-2-(dibenzylamino)-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butanal (303). DMSO (138 μ L, 152 mg, 1.94 mmol) in CH₂Cl₂ (138 μ L) was added dropwise to a stirred solution of oxalyl chloride (82.6 μ L, 122 mg, 939 μ mol) in anhydrous CH₂Cl₂ (800 μ L) at -78 °C. The mixture was stirred for 15 minutes then a solution of alcohol **302** (200 mg, 313 μ mol) in CH₂Cl₂ (800 μ L) was

added dropwise. The mixture was stirred for 1.25 hours at $-78\text{ }^{\circ}\text{C}$ then triethylamine (393 μL , 285 mg, 2.82 mmol) was added dropwise and the solution was allowed to warm to room temperature. Water (100 mL) was added and the mixture was extracted with ethyl ether ($3 \times 60\text{ mL}$) and combined extracts washed with 1% HCl solution (100 mL), water ($2 \times 100\text{ mL}$), saturated NaHCO_3 solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% then 25% ethyl acetate in hexane) provided **303** (188 mg, 94%) as a viscous oil: IR (neat) ν 3091, 3065, 3039, 2995, 2934, 2890, 2820, 2782, 1955, 1719, 1606, 1492, 1449, 1379, 1265, 1230, 1204, 1151, 1108, 1029, 977, 924, 819, 750, 706, 514, 461 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +47.6$ (c 10.3, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.97 (d, $J = 3.2\text{ Hz}$, 1H), 7.39-7.26 (m, 20H), 4.68 (d, $J = 6.6\text{ Hz}$, 1H), 4.61 (d, $J = 6.6\text{ Hz}$, 1H), 4.39 (ddd, $J = 9.2, 9.2, 2.0\text{ Hz}$, 1H), 4.15 (t, $J = 9.6\text{ Hz}$, 1H), 4.02-3.93 (m, 4H), 3.92 (d, $J = 13.6\text{ Hz}$, 2H), 3.73 (d, $J = 13.6\text{ Hz}$, 2H), 3.58 (d, $J = 14.0\text{ Hz}$, 2H), 3.26 (s, 3H), 3.20 (dd, $J = 8.4, 3.2\text{ Hz}$, 1H), 2.76 (m, 1H), 2.18 (ddd, $J = 14.8, 9.6, 1.6\text{ Hz}$, 1H), 1.37 (s, 3H), 1.27 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 204.6 (CH), 139.6 (C), 139.1 (C), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 98.8 (C), 98.2 (CH_2), 74.8 (CH), 68.9 (CH), 66.6 (CH), 58.4 (CH_2), 57.9 (CH), 56.1 (CH_3), 55.0 (CH_2), 54.8 (CH_2), 37.5 (CH_2), 27.8 (CH_3), 20.9 (CH_3); HREIMS m/z 636.3562 $[\text{M}]^+$, calcd. for $\text{C}_{40}\text{H}_{48}\text{N}_2\text{O}_5$ 636.3563.

(R)-N,N-dibenzyl-9,9,10,10-tetramethyl-2,4,8-trioxa-9-silaundecan-6-amine (305).

Under an atmosphere of nitrogen chloromethyl methyl ether (3.55 mL, 46.7 mmol) was added to a stirred solution of alcohol **304** (3.00 g, 7.78 mmol) and Hünig's base (12.9 mL, 77.8 mmol) in dichloromethane (24 mL) at $0\text{ }^{\circ}\text{C}$. The mixture was warmed to room

temperature and stirred for 14 hours then quenched by addition of saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ethyl ether (4×50 mL) and combined extracts washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) provided **305** (3.05 g, 91%) as a viscous oil: IR (neat) ν 3083, 3030, 2960, 2925, 2882, 2890, 1606, 1501, 1475, 1457, 1370, 1265, 1213, 1151, 1108, 1047, 959, 924, 776, 741, 697 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +13.7$ (c 1.30, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, $J = 7.2$ Hz, 4H), 7.30 (t, $J = 7.2$ Hz, 4H), 7.21 (t, $J = 7.2$ Hz, 2H), 4.61 (s, 2H), 3.88-3.78 (m, 6H), 3.75 (d, $J = 6.4$ Hz, 2H), 3.37 (s, 3H), 2.99 (p, $J = 5.5$ Hz, 1H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.1 (C), 128.7 (CH), 128.2 (CH), 126.8 (CH), 96.8 (CH_2), 66.5 (CH_2), 62.0 (CH_2), 58.3 (CH), 55.4 (CH_2), 55.4 (CH_3), 26.0 (CH_3), 18.3 (C), -5.3 (CH_3), -5.4 (CH_3); HRESIMS m/z 430.2782 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_1\text{O}_3\text{Si}_1$ 430.2777.

(S)-2-(dibenzylamino)-3-(methoxymethoxy)propan-1-ol (306). Under an atmosphere of nitrogen, TBAF 1 M in THF (8.15 mL, 8.15 mmol) was added to a stirred solution of amine **305** (2.80 g, 6.52 mmol) in THF (32 mL) at -10 °C. The mixture was stirred for 16 hours then quenched by addition of water (100 mL). The mixture was extracted with ethyl ether (3×50 mL) and combined extracts washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 40% ethyl acetate in hexane) provided **306** (1.90 g, 93%) as a viscous oil: IR (neat) ν 3458, 3065, 3056, 2934, 2882, 2820, 1597, 1492, 1449, 1405, 131, 132, 1256, 1213, 1151, 1117, 1029, 950, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{23} -81.3$ (c 8.95, CHCl_3); ^1H NMR (400 MHz,

CDCl₃) δ 7.36-7.23 (m, 10H), 4.64 (s, 2H), 3.92 (d, $J = 13.2$ Hz, 2H), 3.82 (dd, $J = 10.0$, 6.0 Hz, 1H), 3.66-3.56 (m, 5H), 3.41 (s, 3H), 3.12 (m, 1H), 2.93 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.4 (C), 129.0 (CH), 128.5 (CH), 127.3 (CH), 96.7 (CH₂), 65.0 (CH₂), 59.7 (CH₂), 58.2 (CH), 55.5 (CH₃), 54.0 (CH₂); HRESIMS m/z 316.1916 [M+H]⁺, calcd. for C₁₉H₂₆N₁O₃ 316.1913.

(R)-2-(dibenzylamino)-3-(methoxymethoxy)propanal (307). Under an atmosphere of nitrogen, DMSO (698 μ L, 768 mg, 9.83 mmol) in CH₂Cl₂ (698 μ L) was added dropwise to a stirred solution of oxalyl chloride (408 μ L, 604 mg, 4.76 mmol) in anhydrous CH₂Cl₂ (5.0 mL) at -78 °C. The mixture was stirred for 10 minutes then a solution of alcohol **306** (500 mg, 1.59 mmol) in CH₂Cl₂ (3.0 mL) was added dropwise. The mixture was stirred for 25 minutes at -78 °C then triethylamine (1.99 mL, 1.44 g, 14.3 mmol) was added dropwise and the solution was allowed to warm to room temperature. Water (100 mL) was added and the mixture was extracted with ethyl ether (3 \times 75 mL) and combined extracts washed with 1% HCl solution (100 mL), water (2 \times 100 mL), saturated NaHCO₃ solution (50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to provided **307** (465 mg, 94%) as a viscous oil: IR (neat) ν 3084, 3034, 2944, 2894, 2828, 2721, 1945, 1731, 1607, 1508, 1458, 1376, 1260, 1219, 1161, 1112, 1062, 963, 922 765, 699 cm⁻¹; $[\alpha]_D^{24}$ +35.1 (c 10.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.72 (s, 1H), 7.42 (d, $J = 7.5$ Hz, 4H), 7.34 (t, $J = 7.5$ Hz, 4H), 7.27 (t, $J = 7.5$ Hz, 2H), 4.65 (s, 2H), 3.99 (dd, $J = 10.5$, 5.5 Hz, 1H), 3.95 (dd, $J = 10.5$, 5.5 Hz, 1H), 3.90 (d, $J = 13.5$ Hz, 2H), 3.81 (d, $J = 13.5$ Hz, 2H), 3.50 (t, $J = 5.8$ Hz, 1H), 3.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.3 (CH), 139.2 (C), 128.9 (CH), 128.5 (CH), 127.4 (CH), 96.7

(CH₂), 66.3 (CH), 55.7 (CH₂), 55.6 (CH₃); HRESIMS m/z 314.7755 [M+H]⁺, calcd. for C₁₉H₂₄N₁O₃ 314.1756.

(*S,E*)-methyl 4-(dibenzylamino)-5-(methoxymethoxy)pent-2-enoate (308). Under an atmosphere of nitrogen, methyl (diethylphosphono)acetate (260 μ L, 373 mg, 1.78 mmol) was added dropwise to a stirred solution of barium hydroxide (330 mg, 1.93 mmol) in anhydrous THF (3.7 mL) at room temperature. The mixture was stirred for 30 minutes then cooled to 0 °C and a solution of aldehyde **307** (464 mg, 1.48 mmol) in 40:1 THF:H₂O (3.7 mL) was added dropwise. The mixture was stirred for 10 minutes then quenched by addition of saturated NaHCO₃ solution (50 mL). The mixture was extracted with CH₂Cl₂ (3 \times 75 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 15% ethyl acetate in hexane) provided **308** (463 mg, 85%) as a viscous oil: IR (neat) ν 3084, 3026, 2952, 2886, 2828, 1731, 1648, 1491, 1450, 1433, 1367, 1178, 1153, 1103, 1037, 914, 749, 699 cm⁻¹; [α]_D²⁴ +101.9 (*c* 3.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 7.2 Hz, 4H), 7.34 (t, *J* = 7.2 Hz, 4H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.10 (dd, *J* = 16.0, 7.0 Hz, 1H), 6.10 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.61 (s, 2H), 3.90-3.76 (m, 7H), 3.65 (d, *J* = 14.0 Hz, 2H), 3.57 (m, 1H), 3.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7 (C), 146.1 (CH), 139.6 (C), 128.5 (CH), 128.4 (CH), 127.1 (CH), 123.7 (CH), 96.6 (CH₂), 67.6 (CH₂), 58.2 (CH), 55.5 (CH₃), 54.6 (CH₂), 51.7 (CH₃); HRESIMS m/z 370.2023 [M+H]⁺, calcd. for C₂₂H₂₈N₁O₄ 370.2018.

Synthesis of alcohols 309 and 310. Under an atmosphere of nitrogen, 4-methylmorpholine N-oxide (84 mg, 716 μmol) was added to a stirred solution of osmium tetroxide (608 μL of 2.5% solution in *t*-butanol, 11.9 mg, 47 μmol) and **308** (115 mg, 311 μmol) in 8:1 acetone: H_2O (1.56 mL) at room temperature. The mixture was stirred for hours then quenched by addition of saturated NaHSO_3 solution (30 mL). The mixture was extracted with ethyl acetate (3×35 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 50% ethyl acetate in hexane) provided **309** (23.8 mg, 19%) and **310** (54.8 mg, 43%) as viscous oils.

(2*S*,3*R*,4*R*)-methyl 4-(dibenzylamino)-2,3-dihydroxy-5-

(methoxymethoxy)pentanoate (309). ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.24 (m, 10H), 4.70-4.65 (m, 2H), 4.15 (d, $J = 9.5$ Hz, 1H), 3.99 (dd, $J = 10.0, 3.5$ Hz, 1H), 3.93-3.90 (m, 3H), 3.77 (s, 3H), 3.59 (d, $J = 13.5$ Hz, 2H), 3.42 (s, 3H), 3.07 (m, 1H), 2.81 (bm, 1H), 2.75 (bm, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.5 (C), 139.4 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 97.0 (CH_2), 72.0 (CH), 70.6 (CH), 65.2 (CH_2), 57.7 (CH), 55.8 (CH_3), 55.2 (CH_2), 52.7 (CH_3); LRESIMS m/z 404 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_1\text{O}_6$ 404.2070.

(2*R*,3*S*,4*R*)-methyl 4-(dibenzylamino)-2,3-dihydroxy-5-

(methoxymethoxy)pentanoate (310). IR (neat) ν 3450, 3065, 3030, 2951, 2890, 2847, 1746, 1501, 1457, 1405, 1370, 1274, 1213, 1143, 1108, 1029, 916, 740, 697 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ -30.1 (c 5.16, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.29 (m, 4H), 7.27-7.23 (m, 6H), 4.68 (d, $J = 6.5$ Hz, 1H), 4.67 (d, $J = 6.5$ Hz, 1H), 4.13 (s, 1H), 4.02 (dd, $J = 9.0, 1.0$ Hz, 1H), 3.98 (d, $J = 13.0$ Hz, 2H), 3.89 (dd, $J = 10.5, 6.0$ Hz, 1H), 3.84 (dd, $J = 10.5, 4.5$

Hz, 1H), 3.79 (s, 3H), 3.57 (d, $J = 13.0$ Hz, 2H), 3.44 (s, 3H), 3.20 (p, $J = 4.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.5 (C), 138.5 (C), 129.3 (CH), 128.7 (CH), 127.6 (CH), 96.8 (CH_2), 70.8 (CH), 69.1 (CH), 63.6 (CH_2), 57.6 (CH), 55.9 (CH_3), 54.5 (CH_2), 52.6 (CH_3); HRESIMS m/z 404.2070 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_1\text{O}_6$ 404.2070.

(4*R*,5*S*)-methyl 5-((*R*)-1-(dibenzylamino)-2-(methoxymethoxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (311). A sealed vial containing diol **310** (43.0 mg, 107 μmol) and PPTS (2.7 mg, 10.7 μmol) in 1:1 dimethoxypropane:acetone (2 mL) was heated at 60 °C with stirring for 40 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO_3 (20 mL). The mixture was extracted with ethyl ether (3 \times 25 mL) and combined extracts washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 25% ethyl acetate in hexane) provided recovered starting material **310** (11.9 mg, 28%) and **311** (32.3 mg, 68%) as viscous oils: IR (neat) ν 3065, 3030, 2995, 2943, 2882, 2820 1763, 1501, 1457, 1387, 1274, 1213, 1151, 1117, 1055, 924, 872, 819, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ -21.2 (c 4.13, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 7.2$ Hz, 4H), 7.30 (t, $J = 7.2$ Hz, 4H), 7.23 (t, $J = 7.2$ Hz, 2H), 4.78 (d, $J = 7.6$ Hz, 1H), 4.69 (s, 2H), 4.34 (dd, $J = 7.6, 3.2$ Hz, 1H), 4.12 (d, $J = 13.4$ Hz, 2H), 4.08 (dd, $J = 10.0, 6.0$ Hz, 1H), 3.88 (dd, $J = 10.0, 8.0$ Hz, 1H), 3.57 (d, $J = 13.4$ Hz, 2H), 3.44 (s, 3H), 3.42 (s, 3H), 3.06 (ddd, $J = 8.0, 6.0, 3.2$ Hz, 1H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.2 (C), 140.1 (C), 129.4 (CH), 128.3 (CH), 127.0 (CH), 110.8 (C), 96.7 (CH_2), 79.7 (CH), 75.0 (CH), 64.9 (CH_2), 56.0 (CH_2), 55.5 (CH_3), 55.1 (CH), 52.0 (CH_3), 26.5 (CH_3), 24.6 (CH_3); HRESIMS m/z 444.2390 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_1\text{O}_6$ 444.2386.

(4*R*,5*S*)-5-((*R*)-1-(dibenzylamino)-2-(methoxymethoxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (312). A solution of ester **311** (32.0 mg, 72 μ mol) and lithium hydroxide (3.0 mg, 72 μ mol) in 3:1:1 methanol:THF:water (1 mL) was stirred for 4 hours then quenched with saturated aqueous NH_4Cl (5 mL) with the pH adjusted to 4 with HCl. The mixture was extracted with ethyl acetate (3×5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% methanol in dichloromethane) provided **312** (28.9 mg, 93%) as a crystalline solid: IR (neat) ν 3458, 3091, 3065, 2039, 3004, 2951, 2890, 1737, 1606, 1501, 1466, 1387, 1274, 1221, 1151, 1117, 1055, 959, 924, 881, 819, 758, 697 cm^{-1} ; mp 109 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{23}$ -18.0 (c 7.98, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 7.2$ Hz, 4H), 7.30 (t, $J = 7.2$ Hz, 4H), 7.22 (t, $J = 7.2$ Hz, 2H), 4.78 (d, $J = 7.5$ Hz, 1H), 4.67 (s, 2H), 4.40 (dd, $J = 7.5, 3.5$ Hz, 1H), 4.10 (d, $J = 13.2$ Hz, 2H), 4.02 (dd, $J = 9.8, 5.5$ Hz, 1H), 3.87 (dd, $J = 9.8, 7.8$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 2H), 3.40 (s, 3H), 3.11 (ddd, $J = 7.8, 5.5, 3.5$ Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.3 (C), 139.8 (C), 129.3 (CH), 128.4 (CH), 127.2 (CH), 111.1 (C), 96.6 (CH_2), 79.7 (CH), 74.8 (CH), 64.9 (CH_2), 56.0 (CH_2), 55.8 (CH), 55.5 (CH_3), 26.5 (CH_3), 24.6 (CH_3); HRESIMS m/z 430.2235 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_1\text{O}_6$ 430.2230.

(2*S*,3*R*,4*R*)-methyl 2-(benzyloxy)-4-(dibenzylamino)-3-hydroxy-5-(methoxymethoxy)pentanoate (313). Under an atmosphere of nitrogen freshly distilled *n*-BuBOTf (288 μ L, 1.14 mmol) and Hünig's base (227 μ L, 1.30 mmol) was added to a stirred solution of **88** (176 mg, 0.98 mmol) in ethyl ether (1.5 mL) at -78 $^\circ\text{C}$. The mixture

was stirred for 1.5 hours then aldehyde **307** (255 mg, 0.81 mmol) in ethyl ether (0.5 mL) was added dropwise. The mixture was stirred for 15 minutes then warmed to 0 °C and stirred a further 2 hours. The mixture was quenched with addition of pH 7 phosphate buffer (1.06 mL), methanol (3.2 mL) and 2:1 methanol:30% hydrogen peroxide (3.2 mL) at 0 °C. This mixture was stirred at 0 °C for 1 hour then 5% NaHCO₃ solution (100 mL) added and the mixture extracted with ethyl ether (3 × 50 mL) and combined extracts washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 10%, 15%, 20%, and 25% ethyl acetate in hexane, 24 mL/min flow rate) provided **313** (279 mg, 69%, dr 9:1) as a viscous oil: IR (neat) ν 3537, 3065, 3039, 2960, 2890, 2829, 1754, 1501, 1457, 1405, 1361, 1274, 1204, 1143, 1108, 1047, 916, 740, 706 cm⁻¹; [α]_D²⁵ -38.6 (*c* 4.38, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.22 (m, 13H), 7.16 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 2H), 4.67 (m, 2H), 4.43 (d, *J* = 1.6 Hz, 1H), 4.38 (d, *J* = 10.0 Hz, 1H), 4.13 (t, *J* = 8.8 Hz, 1H), 4.03 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.96 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.92 (d, *J* = 13.6 Hz, 2H), 3.77 (s, 3H), 3.64 (d, *J* = 13.6 Hz, 2H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.44 (s, 3H), 3.17 (ddd, *J* = 10.0, 5.5, 5.0 Hz, 1H), 2.63 (d, *J* = 10.0 Hz, OH); ¹³C NMR (100 MHz, CDCl₃) δ 172.5 (C), 139.9 (C), 137.5 (C), 129.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 96.9 (CH₂), 77.2 (CH), 72.6 (CH), 72.4 (CH₂), 65.1 (CH₂), 57.8 (CH), 55.6 (CH₃), 55.0 (CH₂), 52.1 (CH₃); HRMS *m/z* 494.2540 [M+H]⁺, calcd. for C₂₉H₃₆N₁O₆ 494.2543.

(S)-4-benzyl-3-((2S,3R,4R)-2-(benzyloxy)-4-(dibenzylamino)-3-hydroxy-5-(methoxymethoxy)pentanoyl)oxazolidin-2-one (315). Under an atmosphere of nitrogen

freshly distilled *n*-BuBOTf (288 μ L, 1.14 mmol) and triethylamine (182 μ L, 1.30 mmol) was added to a stirred solution of **84** (317 mg, 0.98 mmol) in dichloromethane (1.5 mL) at -78 $^{\circ}$ C. The mixture was warmed to 0 $^{\circ}$ C and stirred for 3 hours then cooled to -78 $^{\circ}$ C and aldehyde **307** (255 mg, 0.81 mmol) in dichloromethane (0.5 mL) was added dropwise. The mixture was stirred for 10 minutes then warmed to 0 $^{\circ}$ C and stirred a further 2.5 hours. The mixture was quenched with addition of pH 7 phosphate buffer (1.06 mL), methanol (3.2 mL) and 2:1 methanol:30% hydrogen peroxide (3.2 mL) at 0 $^{\circ}$ C. This mixture was stirred at 0 $^{\circ}$ C for 1 hour then 5% NaHCO₃ solution (100 mL) added and the mixture extracted with ethyl ether (3 \times 50 mL) and combined extracts washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 10%, 15%, 20%, 25%, and 50% ethyl acetate in hexane, 24 mL/min flow rate) provided **315** (443 mg, 85%, dr 47:1) as a viscous oil: IR (neat) ν 3502, 3065, 3030, 2934, 2890, 1781, 1702, 1501, 1457, 1387, 1291, 1213, 1117, 1047, 924, 828, 758, 697 cm^{-1} ; $[\alpha]_{\text{D}}^{21} +29.6$ (*c* 12.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 8.0 Hz, 4H), 7.38-7.26 (m, 12H), 7.17 (m, 2H), 5.46 (d, *J* = 4.4 Hz, 1H), 4.60 (s, 2H), 4.42-4.20 (m, 4H), 4.05 (d, *J* = 9.2 Hz, 1H), 3.98-3.82 (m, 5H), 3.69 (d, *J* = 14.0 Hz, 2H), 3.37 (s, 3H), 3.13 (m, 2H), 2.53 (dd, *J* = 13.2, 10.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 171.3 (C), 153.0 (C), 140.1 (C), 137.3 (C), 135.4 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.4 (CH), 126.9 (CH), 96.6 (CH₂), 78.4 (CH), 72.9 (CH₂), 72.2 (CH), 66.7 (CH₂), 65.1 (CH₂), 57.9 (CH), 55.9 (CH₂), 55.5 (CH₃), 54.9 (CH₂), 37.6 (CH₂); HREIMS *m/z* 638.2985 [M]⁺, calcd. for C₃₈H₄₂N₂O₇ 638.2987.

(2*S*,3*R*,4*R*)-2-(benzyloxy)-4-(dibenzylamino)-3-hydroxy-5-

(methoxymethoxy)pentanoic acid (314). Method a) Under an atmosphere of nitrogen, lithium hydroxide monohydrate (1.7 mg, 40.5 μmol) was added to a stirred solution of ester **313** (20.0 mg, 40.5 μmol) in 3:2:2 MeOH:H₂O:THF (700 μL) at room temperature. The mixture was stirred for 4.5 hours then diluted with water (2 mL) and the pH adjusted to 2 with 1 N HCl. The mixture was extracted with ethyl acetate (3 \times 5 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 50% then 75% ethyl acetate in hexane then 5% AcOH + 20% MeOH in dichloromethane) provided **314** (18.5 mg, 95%) as a viscous oil.

Method b) Under an atmosphere of nitrogen, 30% hydrogen peroxide (130 μL , 1.28 mmol) and lithium hydroxide monohydrate (17.9 mg, 426 μmol) was added to a stirred solution of **315** (136 mg, 213 μmol) in 1:3 H₂O:THF (4.25 mL) at 0 °C. The mixture was stirred for 30 minutes then quenched by addition of 1.5 N Na₂SO₃ solution (940 μL) and the mixture stirred for 10 minutes at 0 °C then the pH adjusted to 2 with 2 M HCl. The solution was concentrated to remove THF then extracted with ethyl acetate (3 \times 5 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 50% then 75% ethyl acetate in hexane then 5% AcOH + 20% MeOH in dichloromethane) provided **314** (68 mg, 67%) as a viscous oil: IR (neat) ν 3336, 3065, 3030, 2943, 2890, 1737, 1597, 1501, 1457, 1405, 1213, 1108, 1029, 916, 750, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{22}$ -16.4 (*c* 9.38, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.37 (bd, *J* = 7.0 Hz, 4H), 7.32-7.23 (m, 9H), 7.14 (m, 2H), 4.63 (d, *J* = 6.5 Hz,

1H), 4.61 (d, $J = 6.5$ Hz, 1H), 4.51 (d, $J = 10.5$ Hz, 1H), 4.28 (d, $J = 2.5$ Hz, 1H), 4.26 (d, $J = 13.2$ Hz, 2H), 4.12-4.02 (m, 2H), 3.94 (d, $J = 13.2$ Hz, 2H), 3.87 (d, $J = 10.5$ Hz, 1H), 3.51 (m, 1H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2 (C), 137.1 (C), 135.1 (C), 130.2 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 96.9 (CH_2), 78.6 (CH), 72.7 (CH_2), 69.9 (CH), 64.0 (CH_2), 60.7 (CH), 55.8 (CH_3), 55.5 (CH_2); HREIMS m/z 478.2227 $[\text{M}-\text{H}]^-$, calcd. for $\text{C}_{28}\text{H}_{32}\text{N}_1\text{O}_6$ 478.2224.

(3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (316). 10% Pd/C (9.7 mg, 8.7 μmol , 20 mol % Pd) was added to **313** (21.5 mg, 43.6 μmol) in MeOH : AcOH : H_2O (5 : 1 : 1) (1.5 mL). The mixture was placed under H_2 (5 atm) and agitated for 16 hours on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 10% triethylamine in MeOH (1 mL) and stirred then concentration under reduced pressure and dried on a high vac for 4 hours. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (9.7 mg, 8.7 μmol , 20 mol % Pd) added. The mixture was placed under H_2 (5 atm) and agitated for 14 hours on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided **316** (70% purity by NMR). Compound **316** matched literature values.

Known compounds **317** and (-)-**318** were synthesized using standard procedures and matched literature values.

(S)-2-amino-3-ureidopropanamide ((-)-319). CF₃COOH (600 μL) was added dropwise to (-)-**318** (14.5 mg, 58.9 μmol, neat) with stirring at 0 °C. The mixture was stirred 1 hour at 0 °C then warmed to room temperature and stirred for 2.5 hours. The reaction mixture was blown to dryness with a stream of N₂ and then dried under azeotropic distillation with 1:1 MeOH:toluene (2 × 1 mL) to provide (-)-**319** (14.9 mg, 98%, 94% ee by Marfey's analysis¹) as a viscous oil: [α]_D²¹ -15.1 (*c* 6.63, CH₃OH); ¹H NMR (400 MHz, CD₃OD) δ 3.99 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.67 (dd, *J* = 15.0, 3.6 Hz, 1H), 3.48 (dd, *J* = 15.0, 6.4 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 170.4 (C), 162.6 (C), 55.4 (CH), 42.3 (CH₂); HRMS *m/z* 147.0882 [M+H]⁺, calcd. for C₄H₁₁N₄O₂ 147.0877.

(2S,3R,4R)-N-((S)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-3-hydroxy-5-(methoxymethoxy)pentanamide (320). A solution of **314** (20.3 mg, 42.3 μmol) in DMF (60 μL) was cooled to 0 °C under nitrogen and treated with EDCI (10.6 mg, 55.2 μmol) and HOBT (8.0 mg, 59 μmol). After 5 minutes amine (-)-**319** (12.1 mg, 46.6 μmol) in DMF (50 μL) and triethylamine (6.5 μL, 46.6 μmol) was added. The mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 10% isopropyl alcohol in chloroform (30 mL) was added, and the mixture washed with water (5 × 7 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 2.5%, 5%, and 7.5% methanol in dichloromethane) provided **320** (21.2 mg, 83%) as a viscous oil: IR (neat) ν 3362, 3030, 2934, 2882, 1658, 1527, 1449, 1387, 1344, 1151, 1108, 1038, 916, 750, 697 cm⁻¹; [α]_D²¹ -28.9 (*c* 2.35, CH₃OH); ¹H NMR (400 MHz, CD₃OD) δ 7.36 (d, *J* = 7.2 Hz,

4H), 7.30-7.22 (m, 7H), 7.18 (m, 4H), 4.70 (m, 2H), 4.44 (dd, $J = 6.8, 4.4$ Hz, 1H), 4.27 (d, $J = 1.2$ Hz, 1H), 4.12 (d, $J = 10.8$ Hz, 1H), 4.07-4.00 (m, 2H), 3.94 (dd, $J = 10.8, 6.4$ Hz, 1H), 3.89 (d, $J = 13.4$ Hz, 2H), 3.68 (d, $J = 13.4$ Hz, 2H), 3.62 (dd, $J = 14.4, 4.0$ Hz, 1H), 3.56 (d, $J = 10.8$ Hz, 1H), 3.44 (s, 3H), 3.34 (m, 1H), 3.24 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.5 (C), 172.8 (C), 161.1 (C), 140.3 (C), 137.3 (C), 129.6 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.0 (CH), 96.8 (CH_2), 79.9 (CH), 73.3 (CH_2), 71.9 (CH), 65.3 (CH_2), 57.8 (CH), 54.7 (CH_2), 54.6 (CH_3), 53.6 (CH), 41.6 (CH_2); HRMS m/z 630.2912 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{32}\text{H}_{41}\text{N}_5\text{O}_7\text{Na}$ 630.2898.

(*R*)-4-benzyl-3-((2*S*,3*R*,4*S*,5*R*)-2-(benzyloxy)-4-(dibenzylamino)-6-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-

(methoxymethoxy)hexanoyl)oxazolidin-2-one (321). Freshly distilled *n*-BuBOTf (51.9 μL , 206 μmol) and triethylamine (32.7 μL , 235 μmol) was added to a stirred solution of **84** (31.8 mg, 176 μmol) in dichloromethane (250 μL) at -78 $^\circ\text{C}$. The mixture was warmed to 0 $^\circ\text{C}$ and stirred for 3 hours then cooled to -78 $^\circ\text{C}$ and aldehyde **303** (93.0 mg, 147 μmol) in dichloromethane (150 μL) was added dropwise. The mixture was stirred for 10 minutes then warmed to 0 $^\circ\text{C}$ and stirred a further 2.5 hours. The mixture was quenched with addition of pH 7 phosphate buffer (206 μL), MeOH (620 μL) and 2:1 MeOH:30% v/v H_2O_2 (620 μL) at 0 $^\circ\text{C}$. This mixture was stirred at 0 $^\circ\text{C}$ for 1 hour then 5% NaHCO_3 solution (50 mL) added and the mixture extracted with ethyl ether (3×50 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 12 g silica cartridge, 5%, 10%, and 20% ethyl acetate in hexane, 24 mL/min flow rate) provided **321**

(109 mg, 77%, dr 24:1) as a viscous oil: IR (neat) ν 3432, 3065, 3039, 2917, 1798, 1702, 1501, 1457, 1387, 1274, 1204, 1117, 1073, 1038, 924, 872, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ +86.5 (*c* 3.45, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 7.2$ Hz, 2H), 7.40-7.15 (m, 26H), 7.11 (d, $J = 7.2$ Hz, 2H), 5.56 (d, $J = 6.0$ Hz, 1H), 4.64 (s, 2H), 4.62 (m, 2H), 4.55 (m, 1H), 4.27 (m, 1H), 4.02 (m, 2H), 3.93 (dd, $J = 8.5, 1.5$ Hz, 1H), 3.87 (d, $J = 6.8$ Hz, 2H), 3.82 (d, $J = 14.0$ Hz, 4H), 3.77 (t, $J = 8.0$ Hz, 1H), 3.71 (d, $J = 14.0$ Hz, 2H), 3.57-3.50 (m, 3H), 3.27 (s, 3H), 3.19 (dd, $J = 12.0, 2.8$ Hz, 1H), 2.70-2.66 (m, 2H), 2.61 (dd, $J = 13.6, 10.0$ Hz, 1H), 2.12 (m, 2H), 1.24 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8 (C), 153.2 (C), 140.2 (C), 139.6 (C), 137.8 (C), 135.5 (C), 129.6 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.5 (C), 127.2 (C), 126.8 (C), 98.9 (C), 97.9 (CH_2), 80.1 (CH), 74.6 (CH), 73.2 (CH_2), 70.3 (CH), 67.3 (CH), 66.6 (CH_2), 60.9 (CH), 58.5 (CH_2), 58.0 (CH), 56.2 (CH), 56.1 (CH_3), 54.7 (CH_2), 38.3 (CH_2), 37.7 (CH_2), 28.0 (CH_3), 20.5 (CH_3); HRESIMS m/z 962.4959 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{59}\text{H}_{68}\text{N}_3\text{O}_9$ 962.4956.

(2*S*,3*R*,4*S*,5*R*)-methyl-2-(benzyloxy)-4-(dibenzylamino)-6-((4*R*,5*S*)-5-

(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-

(methoxymethoxy)hexanoate (322). Freshly distilled *n*-BuBOTf (51.9 μL , 206 μmol)

and Hünig's base (40.9 μL , 235 μmol) was added to a stirred solution of **88** (31.8 mg,

176 μmol) in ethyl ether (250 μL) at -78 $^\circ\text{C}$. The mixture was stirred for 1.5 hours then

aldehyde **303** (93.0 mg, 147 μmol) in ethyl ether (150 μL) was added dropwise. The

mixture was stirred for 15 minutes then warmed to 0 $^\circ\text{C}$ and stirred a further 2 hours. The

mixture was quenched with addition of pH 7 phosphate buffer (206 μL), MeOH (620 μL)

and 2:1 MeOH:30% v/v H₂O₂ (620 μL) at 0 °C. This mixture was stirred at 0 °C for 1 hour then 5% NaHCO₃ solution (50 mL) added and the mixture extracted with ethyl ether (3 × 50 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica cartridge, 5% ethyl acetate in hexane, 13 mL/min flow rate) provided **322** (52.6 mg, 44%, 37% de by NMR). Further HPLC purification (silica 10 × 250 mm column, 3% IPA in hexane, 4 mL/min) provided pure **322** (28.4 mg, 24%) as a viscous oil: IR (neat) ν 3432, 3065, 3030, 2986, 2934, 2890, 2838, 1754, 1597, 1492, 1449, 1379, 1265, 1213, 1151, 1082, 1029, 916, 819, 758, 706 cm⁻¹; [α]_D²⁴ -31.0 (*c* 4.81, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.18 (m, 23H), 7.06 (m, 2H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 6.4 Hz, 1H), 4.28-4.18 (m, 3H), 4.16-4.05 (m, 2H), 4.00 (d, *J* = 13.4 Hz, 2H), 3.94-3.75 (m, 9H), 3.73 (d, *J* = 13.4 Hz, 2H), 3.49 (d, *J* = 14.0 Hz, 2H), 3.32 (m, 1H), 3.30 (s, 3H), 2.57 (m, 1H), 2.31 (dd, *J* = 13.2, 9.6 Hz, 1H), 1.44 (s, 3H), 1.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.7 (C), 139.6 (C), 139.3 (C), 137.7 (C), 129.3 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 99.0 (C), 97.3 (CH₂), 78.5 (CH), 74.5 (CH), 72.3 (CH₂), 69.9 (CH), 67.6 (CH), 60.9 (CH), 58.3 (CH₂), 58.2 (CH), 56.3 (CH₃), 55.3 (CH₂), 54.7 (CH₂), 52.2 (CH), 39.5 (CH₂), 27.5 (CH₃), 21.5 (CH₃); HRMS *m/z* 817.4438 [M+H]⁺, calcd. for C₅₀H₆₁N₁O₈N₂ 817.4422.

(2*S*,3*R*,4*S*,5*R*)-2-(benzyloxy)-4-(dibenzylamino)-6-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanoic acid (323).

Method a) A mixture of 30% v/v H₂O₂ (12.7 μL, 125 μmol) and lithium hydroxide

monohydrate (1.74 mg, 41.6 μmol) was added to a stirred solution of **321** (21.0 mg, 21.8 μmol) in 1:3 H_2O :THF (430 μL) at 0 $^\circ\text{C}$. The mixture was stirred for 30 minutes then quenched by addition of 1.5 N Na_2SO_3 solution (94 μL) and the mixture stirred for 10 minutes at 0 $^\circ\text{C}$ then warmed to room temperature and stirred a further 5 minutes. The mixture was diluted with ethyl acetate (50 mL) and washed with 1% HCl (20 mL), water (2×15 mL), and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica saturated with AcOH, 1% AcOH + 25% ethyl acetate in hexane) provided **323** (16.8 mg, 96%) as a viscous oil.

Method b) Lithium hydroxide monohydrate (0.33 mg, 7.96 μmol) was added to a stirred solution of ester **322** (6.50 mg, 7.96 μmol) in 3:2:2 MeOH: H_2O :THF (350 μL) at room temperature. The mixture was stirred for 8 hours then diluted with water (2 mL) and the pH adjusted to 2 with 1 N HCl. The mixture was extracted with ethyl acetate (3×5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 25% then 50% ethyl acetate in hexane then 5% AcOH + 20% MeOH in dichloromethane) provided **323** (5.2 mg, 81%) as a viscous oil: IR (neat) ν 3450, 3065, 3021, 2925, 2847, 1728, 1492, 1449, 1379, 1265, 1213, 1108, 1073, 1029, 968, 916, 750, 697 cm^{-1} ; $[\alpha]_{\text{D}}^{21} +7.7$ (c 4.03, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.14 (m, 25H), 4.74 (m, 2H), 4.45-4.30 (m, 4H), 3.98-3.80 (m, 8H), 3.60-3.50 (m, 4H), 3.33 (s, 3H), 3.06 (m, 1H), 2.63-2.54 (m, 2H), 1.57 (m, 1H), 1.20 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2 (C), 139.6 (C), 139.5 (C), 137.1 (C), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.3 (CH), 99.0

(C), 97.6 (CH₂), 78.5 (CH), 75.3 (CH), 72.9 (CH₂), 71.5 (CH), 67.9 (CH), 60.8 (CH), 58.4 (CH₂), 57.9 (CH), 56.5 (CH₃), 55.1 (CH₂), 54.9 (CH₂), 39.6 (CH₂), 27.5 (CH₃), 20.9 (CH₃); HRMS m/z 803.4267 [M+H]⁺, calcd. for C₄₉H₅₉N₂O₈ 803.4271.

(2*S*,3*R*,4*S*,5*R*)-*N*-((*S*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-6-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanamide (324). A solution of **323** (16.5 mg, 20.6 μmol) in DMF (100 μL) was cooled to 0 °C under nitrogen and treated with EDCI (5.12 mg, 26.7 μmol) and HOBt (3.89 mg, 28.8 μmol). After 10 minutes, amine (–)**319** (6.0 mg, 23.1 μmol) in DMF (50 μL) and triethylamine (2.86 μL, 20.6 μmol) was added. The mixture was warmed to room temperature and stirred for 1 hour. A solution of 10% isopropyl alcohol in chloroform (15 mL) was added, and the mixture washed with water (5 × 3 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 2.5-10% MeOH in dichloromethane) provided **324** (15.0 mg, 81%) as a amorphous solid: IR (neat) ν 3450, 3362, 2065, 3030, 2986, 2934, 2838, 2523, 2418, 1658, 1606, 1492, 1449, 1379, 1221, 1151, 1099, 1064, 1029, 916, 750, 697 cm⁻¹; [α]_D²⁰ +4.3 (*c* 5.66, CHCl₃); ¹H NMR (400 MHz, CD₃OD) δ 7.40-7.13 (m, 25H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.49 (dd, *J* = 7.2, 4.4 Hz, 1H), 4.39-4.31 (m, 3H), 4.28 (dd, *J* = 8.0, 2.8 Hz, 1H), 4.22 (t, *J* = 10.0 Hz, 1H), 3.97 (dd, *J* = 12.0, 8.8 Hz, 1H), 3.92-3.80 (m, 6H), 3.69 (d, *J* = 13.2 Hz, 2H), 3.62 (m, 1H), 3.57 (d, *J* = 13.6 Hz, 2H), 3.36 (m, 1H), 3.32 (s, 3H), 3.07 (dd, *J* = 8.4, 3.6 Hz, 1H), 2.61-2.53 (m, 2H), 1.62 (ddd, *J* = 14.0, 11.6, 2.6 Hz, 1H), 1.34 (s, 3H), 1.22 (s, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 174.5 (C), 174.0 (C), 162.2 (C), 141.4 (C), 141.1 (C), 138.6 (C),

130.6 (CH), 130.0 (CH), 129.9 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 100.1 (C), 98.9 (CH₂), 81.9 (CH), 76.9 (CH), 74.3 (CH₂), 72.3 (CH), 69.4 (CH), 62.0 (CH), 59.5 (CH₂), 58.9 (CH), 56.7 (CH₃), 56.1 (CH₂), 55.6 (CH₂), 54.7 (CH), 43.1 (CH₂), 40.1 (CH₂), 28.3 (CH₃), 21.2 (CH₃); HRMS m/z 931.4951 [M+H]⁺, calcd. for C₅₃H₆₇N₆O₉ 931.4970.

(2*S*,3*R*,4*R*,5*R*,7*R*,8*S*)-4,8-diamino-*N*-((*S*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5,7,9-pentahydroxynonanamide ((-)-279**)**. TMSCl (15.0 μL, 12.7 mg, 120 μmol) was added to **324** (11.5 mg, 12.4 μmol) in dry MeOH (1.5 mL) at 0 °C. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (13.1 mg, 12.4 μmol, 100 mol % Pd) was added and the mixture placed under H₂ (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (13.1 mg, 12.4 μmol, 100 mol % Pd) added. The mixture was placed under H₂ (5 atm) and agitated for 1 hour on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided the hydrochloride salt of (-)-**279** (5.9 mg, (76% purity by NMR)). Further HPLC purification (Synergi Hydro-RP 10 × 250 mm column, 1.3 MeOH: 0.1 CF₃COOH: 98.6 H₂O, 3.5 mL/min, (product converted to HCl salt by resuspending in 1% HCl and re-drying)) provided pure (-)-**279** (2.3 mg) as a white solid: $[\alpha]_D^{21}$ -23.0 (*c* 1.49, H₂O); ¹H NMR (400 MHz, 0.2% acetonitrile:D₂O (ref δ 2.06)) δ 4.53 (d, *J* = 2.0 Hz, 1H), 4.45 (dd, *J* = 6.4, 4.4 Hz, 1H), 4.38 (dd, *J* = 6.0, 2.0 Hz, 1H), 4.30 (ddd, *J* = 10.0, 3.6, 2.0 Hz, 1H), 4.20 (ddd, *J* = 10.0, 2.8, 3.2 Hz, 1H), 3.95 (dd,

$J = 12.2, 4.0$ Hz, 1H), 3.79 (dd, $J = 12.2, 8.4$ Hz, 1H), 3.64 (dd, $J = 14.6, 4.4$ Hz, 1H), 3.59 (dd, $J = 5.6, 5.6$ Hz, 1H), 3.48 (dd, $J = 14.6, 2.4$ Hz, 1H), 3.44 (m, 1H), 1.79 (ddd, $J = 14.4, 12.0, 2.0$ Hz, 1H), 1.72 (ddd, $J = 14.4, 12.0, 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, 0.2% acetonitrile:D₂O (ref δ 1.47)) δ 175.1 (C), 174.7 (C), 162.3 (C), 72.7 (CH), 67.6 (CH), 65.8 (CH), 65.5 (CH), 58.4 (CH), 58.1 (CH₂), 57.3 (CH), 55.0 (CH), 41.4 (CH₂), 35.6 (CH₂); HRMS m/z 419.1871 [M+Na]⁺, calcd. for C₁₃H₂₈N₆O₈Na₁ 419.1866.

Compounds **326-328** were synthesized according to literature procedures.

(R)-tert-butyl 1-amino-1-oxo-3-ureidopropan-2-ylcarbamate ((+)-318). Compound **328** (500 mg, 1.85 mmol) in dry toluene (5 mL) was heated to 110 °C in a microwave reactor for 15 minutes. The mixture was cooled to room temperature and NH₃ (11.1 mL, 5.55 mmol, 0.5 M in dioxane) was added. The mixture was stirred for 30 minutes. The reaction dried then dissolved in 2 M NH₃ in MeOH (4.6 mL, 9.25 mM) and stirred for 5 hours. The reaction mixture was dried and redissolved in MeOH (15 mL) and NaOH (0.9 mL of 1 N solution, 0.9 mmol) added. The mixture stirred for 4.5 hours and then diluted with THF (1 L), dried with MgSO₄, filtered and dried. Flash chromatography (silica, 20% MeOH in dichloromethane) provided (+)-**318** (316 mg, 62%) as a crystalline solid (mp 141.5 °C). Compound (+)-**318** matched literature values.

(R)-2-amino-3-ureidopropanamide ((+)-319). CF₃COOH (1.0 mL) was added dropwise to (+)-**318** (24.8 mg, 101 μ mol, neat) with stirring at 0 °C. The mixture was stirred 1 hour at 0 °C. The reaction mixture was blown to dryness with a stream of N₂ at 0 °C and then

dried under azeotropic distillation with 1:1 MeOH:toluene (2 × 1 mL) to provided (+)-**319** (25.8 mg, 99% yield, 87% ee by Marfey's analysis) as a viscous oil: $[\alpha]_D^{20} +15.7$ (*c* 9.91, CH₃OH); ¹H NMR (400 MHz, CD₃OD) δ 3.99 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.67 (dd, *J* = 15.0, 3.6 Hz, 1H), 3.49 (dd, *J* = 15.0, 6.4 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 170.5 (C), 162.7 (C), 55.4 (CH), 42.2 (CH₂); HRMS *m/z* 147.0882 [M+H]⁺, calcd. for C₄H₁₁N₄O₂ 147.0877.

(2*S*,3*R*,4*S*,5*R*)-*N*-((*R*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-6-((4*R*,5*S*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanamide (329). A solution of **323** (21.0 mg, 26.1 μ mol) in DMF (150 μ L) was cooled to 0 °C under nitrogen and treated with EDCI (6.52 mg, 34.0 μ mol) and HOBt (4.95 mg, 36.6 μ mol). After 10 minutes amine (+)-**319** (7.48 mg, 28.8 μ mol) in DMF (50 μ L) and triethylamine (4.0 μ L, 29 μ mol) was added. The mixture was warmed to room temperature and stirred for 20 minutes. A solution of 10% isopropyl alcohol in chloroform (20 mL) was added, and the mixture washed with water (5 × 4 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 2.5%, 5%, and 10% MeOH in dichloromethane) provided **329** (21.5 mg, 88%) as an amorphous solid: IR (neat) ν 3361, 3061, 3026, 2932, 1666, 1602, 1540, 1453, 1377, 1147, 1103, 1070, 1027, 749, 699 cm⁻¹; $[\alpha]_D^{20} +7.0$ (*c* 8.34, CHCl₃); ¹H NMR (500 MHz, CD₃OD) δ 7.40-7.11 (m, 25H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.41 (dd, *J* = 6.0, 3.5 Hz, 1H), 4.33 (d, *J* = 2.5 Hz, 1H), 4.27 (m, 2H), 4.08 (t, *J* = 10.0 Hz, 1H), 4.00-3.94 (m, 2H), 3.90-

3.81 (m, 5H), 3.67 (d, $J = 14.0$ Hz, 2H), 3.56 (m, 1H), 3.55 (d, $J = 14.0$ Hz, 2H), 3.42 (dd, $J = 14.0, 6.5$ Hz, 1H), 3.33 (s, 3H), 3.11 (dd, $J = 8.5, 3.0$ Hz, 1H), 2.61 (dd, $J = 14.8, 8.5$ Hz, 1H), 2.54 (m, 1H), 1.55 (ddd, $J = 14.8, 10.4, 4.0$ Hz, 1H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.0 (C), 174.8 (C), 162.4 (C), 141.3 (C), 141.0 (C), 138.6 (C), 130.5 (CH), 130.1 (CH), 130.0 (CH), 129.4 (CH), 129.3 (CH), 129.3 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 100.2 (C), 98.7 (CH_2), 82.0 (CH), 77.0 (CH), 74.4 (CH_2), 73.1 (CH), 69.2 (CH), 61.8 (CH), 59.2 (CH_2), 58.6 (CH), 56.7 (CH_3), 56.1 (CH_2), 55.7 (CH), 55.6 (CH_2), 42.3 (CH_2), 39.7 (CH_2), 28.4 (CH_3), 21.2 (CH_3); HRMS m/z 931.4949 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{53}\text{H}_{67}\text{N}_6\text{O}_9$ 931.4964.

(2*S*,3*R*,4*R*,5*R*,7*R*,8*S*)-4,8-diamino-*N*-((*R*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5,7,9-pentahydroxynonanamide ((-)-1). TMSCl (15.0 μL , 12.7 mg, 120 μmol) was added to **329** (16.0 mg, 17.2 μmol) in dry MeOH (1.5 mL) at 0 °C. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (18.3 mg, 17.2 μmol , 100 mol % Pd) was added and the mixture placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (18.3 mg, 17.2 μmol , 100 mol % Pd) added. The mixture was placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided the hydrochloride salt of (-)-**1** (7.9 mg, (75% purity by NMR)). Further HPLC purification (Synergi Hydro-RP 10 \times 250 mm column, 1.3 MeOH: 0.1 CF_3COOH : 98.6 H_2O , 3.5 mL/min, (product converted to HCl

salt by resuspending in 1% HCl and re-drying)) provided pure (-)-**1** (4.4 mg) as a white solid: $[\alpha]_D^{21} -7.9$, (c 2.39, H₂O); ¹H NMR (400 MHz, 0.2% acetonitrile:D₂O (ref δ 2.06)) δ 4.56 (d, J = 2.0 Hz, 1H), 4.46 (dd, J = 6.4, 4.0 Hz, 1H), 4.38 (dd, J = 5.8, 2.0 Hz, 1H), 4.29 (ddd, J = 10.0, 4.8, 2.4 Hz, 1H), 4.20 (ddd, J = 10.0, 3.2, 2.8 Hz, 1H), 3.95 (dd, J = 12.2, 4.0 Hz, 1H), 3.79 (dd, J = 12.2, 8.6 Hz, 1H), 3.64 (dd, J = 14.8, 4.4 Hz, 1H), 3.58 (dd, J = 5.4, 5.4 Hz, 1H), 3.51 (dd, J = 14.8, 6.4 Hz, 1H), 3.45 (m, 1H), 1.82 (ddd, J = 14.0, 11.6, 2.0 Hz, 1H), 1.75 (ddd, J = 14.0, 11.6, 2.0 Hz, 1H); ¹³C NMR (100 MHz, 0.2% acetonitrile:D₂O (ref δ 1.47)) δ 175.3 (C7), 174.8 (C5), 162.4 (C1), 72.7 (C8), 67.9 (C9), 65.8 (C13), 65.5 (C11), 58.5 (C10), 58.1 (C15), 57.3 (C14), 55.2 (C4), 41.3 (C3), 35.7 (C12); HRMS m/z [M+H]⁺ 397.2054, calcd. for C₁₃H₂₉N₆O₈ 397.2047.

7.1.5. Chapter 4 Methods

Compounds **330**, **332**, **333**, and **338** matched literature values.

(2R,3S,5S,6R)-2,6-diazoheptane-1,3,5,7-tetraol (334). Under an atmosphere of nitrogen, B(MeO)₃ (1.56 mL, 1.43 g, 13.7 mmol) was added to a solution of **333** (550 mg, 3.43 mmol) in anhydrous DMF (17.2 mL). The solution was stirred for 30 min at room temperature then NaN₃ (893 mg, 13.7 mmol) was added and the reaction was heated to 40 °C and stirred for 4 hours then heated to 50 °C. for a further 4 hours. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO₃ (50 mL) and the solution stirred a further 1 hour. The mixture concentrated to dryness under reduced pressure then 200 mL methanol added and the mixture filtered. The mixture concentrated to dryness under reduced pressure then 200 mL of 6:4 methanol:dichloromethane added and the mixture filtered. The mixture concentrated to dryness under reduced pressure. Flash chromatography (silica, 5% to 60% methanol in dichlormethane) followed by reverse phase chromatography (20g C18, 5% methanol in water) provided **334** (672 mg, 80%, dr 10:1.1:1 by NMR) as white solid. Further recrystallization from methanol gave pure **334** (393 mg): mp 132 °C; IR (neat) ν 3201, 2950, 2919, 2871, 2137, 2097, 1445, 1405, 1320, 1267, 1137, 1078, 1064, 1029, 1006, 910, 862 cm⁻¹; $[\alpha]_D^{21} +5.3$ (*c* 2.13, CH₃OH); ¹H NMR (500 MHz, CD₃OD) δ 3.87 (m, 2H), 3.81 (dd, *J* = 11.6, 3.7 Hz, 2H), 3.60 (dd, *J* = 11.6, 8.1 Hz, 2H), 3.45 (m, 2H), 1.59 (dd, *J* = 7.8, 5.2 Hz, 2H); ¹³C NMR (125 MHz, CD₃OD) δ 70.4 (CH), 68.5 (CH), 63.0 (CH₂), 37.0 (CH₂); HRMS *m/z* 245.1004 [M-H]⁻, calcd. for C₇H₁₃N₆O₄ 245.1004.

(2*R*,3*S*,5*S*,6*R*)-2,6-diazido-7-(*tert*-butyldiphenylsilyloxy)heptane-1,3,5-triol (339).

Under an atmosphere of nitrogen *tert*-butyldiphenylchlorosilane (35 μ L, 134 μ mol) was added to a stirred solution of tetraol **334** (50 mg, 203 μ mol) and imidazole (20.5 mg, 284 μ mol) in dimethylformamide (1.0 mL) at room temperature. The mixture was stirred for 4 hours the mixture was then concentrated under reduced pressure. Flash chromatography (silica, 50 to 100% ethyl acetate in hexane then 20% methanol in dichloromethane) provided **339** (42.2 mg, 65%) and **340** (14.9 mg, 15%) as a viscous oils plus recovered **334**. Characterization for **339**: IR (neat) ν 3338, 3071, 2930, 2857, 2094, 1659, 1589, 1471, 1427, 1390, 1314, 1262, 1188, 1104, 823, 797, 740 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -29.9 (*c* 7.41, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.72-7.66 (m, 4H), 7.48-7.39 (m, 6H), 3.99 (m, 2H), 3.91-3.78 (m, 4H), 3.60-3.50, (m, 4H), 3.39 (m, 1H), 1.66 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.7 (CH), 137.6 (CH), 132.7 (C), 132.6 (C), 130.1 (CH), 128.0 (CH), 68.6 (CH), 68.5 (CH), 67.0 (CH), 66.5 (CH), 64.5 (CH_2), 62.3 (CH_2), 35.5 (CH_2), 26.8 (CH_3), 19.2 (C); HRESIMS m/z 507.2150 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{23}\text{H}_{32}\text{N}_6\text{O}_4\text{Na}_1\text{Si}_1$ 507.2147.

(*R*)-2-azido-2-((4*S*,6*S*)-6-((*R*)-1-azido-2-(*tert*-butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (342). Method 1: Triol **339** (39.5 mg, 81.5 μ mol) and PPTS (4.1 mg, 16 μ mol) in dimethoxypropane (0.5 mL) and acetone (0.5 mL) was heated to 50 $^\circ\text{C}$ and stirred for 2 hours under an atmosphere of nitrogen. The mixture was quenched with 5 mL saturated aqueous NaHCO_3 , extracted with ethyl ether (3 x 3 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated

under reduced pressure. Flash chromatography (silica, 5%, 7.5% and 10% ethyl acetate in hexane) provided **341** (25.9 mg, 53%), **342** (13.5 mg, 31%) and **343** (7.6 mg, 18%) as a viscous oils.

Method 2: Under an atmosphere of nitrogen **343** (25 mg, 42 μmol) in THF:AcOH:H₂O (9:2:1, 1.2 mL) was stirred at 50 °C for 5.5 hours. The mixture was diluted with toluene (10 mL) and concentrated under reduced pressure. Flash chromatography (silica, 20% ethyl acetate in hexane) provided **342** (19.4 mg, 88%) and recovered **343** (1.7 mg, 6.8%) as a viscous oils.

Characterization for **342**: IR (neat) ν 3429, 3386, 3072, 3049, 2987, 2955, 2931, 2889, 2099, 1428, 1380, 1262, 1027, 823, 800, 740, 701 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -20.7 (c 9.64, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.67 (m, 4H), 7.48-7.39 (m, 6H), 4.06 (m, 1H), 3.79-3.74 (m, 3H), 3.68 (dd, $J = 12.0, 1.8$ Hz, 2H), 3.54 (dd, $J = 11.2, 5.6$ Hz, 1H), 3.49 (m, 1H), 1.88-1.73 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 1.08 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 135.8 (CH), 137.7 (CH), 133.0 (C), 132.9 (C), 130.1 (CH), 130.0 (CH), 128.0 (CH), 127.9 (CH), 101.3 (C), 67.5 (CH), 66.3 (CH), 66.1 (CH), 65.9 (CH), 63.3 (CH₂), 62.5 (CH₂), 30.7 (CH₂), 26.9 (CH₃), 24.7 (CH₃), 24.5 (CH₃), 19.3 (C); HRESIMS m/z 547.2447 [M+Na]⁺, calcd. for C₂₆H₃₆N₆O₄Na₁Si₁ 547.2460.

(2R,3S,5S,6R)-2,6-diazido-7-(trityloxy)heptane-1,3,5-triol (344). Method 1: Under an atmosphere of nitrogen triphenylmethyl chloride (104 mg, 374 μmol) was added to a stirred solution of tetraol **334** (115 mg, 467 μmol) in pyridine (2.3 mL) at room temperature. The mixture was heated to 60 °C and stirred for 5 hours. The mixture was then concentrated under reduced pressure. Flash chromatography (silica, 25 to 50% ethyl

acetate in hexane then 20% methanol in dichloromethane) provided **344** (125 mg, 69%) and **345** (39 mg, 14%) as a viscous oils and recovered **334**.

Method 2: Under an atmosphere of nitrogen diol **345** (38 mg, 52 μmol) in methanol adjusted to pH 2 with TFA was stirred at room temperature was stirred for 10 hours. The mixture was quenched with triethylamine (0.5 mL) and concentrated under reduced pressure. Flash chromatography (silica, 50% ethyl acetate in hexane then 20% methanol in dichloromethane) provided **344** (12.2 mg, 48%) and recovered **345** (7.6 mg, 20%) as a viscous oils and some **334**.

Characterization for **344**: IR (neat) ν 3349, 3086, 3058, 3032, 2928, 2883, 2094, 1658, 1595, 1489, 1448, 1317, 1264, 1218, 1072, 1031, 900, 855, 747 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -21.6 (c 6.25, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.47-7.44 (m, 6H), 7.34-7.30 (m, 6H), 7.25 (tt, $J = 7.2, 1.2$ Hz, 3H), 4.00-3.93 (m, 2H), 3.81, (m, 2H), 3.49-3.44 (m, 2H), 3.40-3.35 (m, 2H), 1.59 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.4 (C), 128.7 (CH), 128.2 (CH), 127.5 (CH), 87.8 (C), 69.0 (CH), 68.9 (CH), 66.4 (CH), 65.5 (CH), 63.7 (CH_2), 62.5 (CH_2), 35.4 (CH_2); HRESIMS m/z 511.2067 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_6\text{O}_4\text{Na}_1$ 511.2064.

(2S,3R)-3-azido-1-((4S,5R)-5-azido-2,2-dimethyl-1,3-dioxan-4-yl)-4-(trityloxy)butan-2-ol (346). Under an atmosphere of nitrogen 2-methoxypropene (3.6 μL , 19 μmol) was added to a stirred solution of triol **344** (9.2 mg, 19 μmol) and PPTS (0.4 mg, 2 μmol) in DMF (100 μL) at room temperature. The mixture was heated to 50 $^\circ\text{C}$ and stirred for 4 hours. The stirred mixture was cooled to room temperature and quenched with saturated aqueous NaHCO_3 (3 mL). The mixture was extracted with ethyl acetate (3 \times 4 mL) and

combined extracts washed with brine (3 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) provided **346** (7.3 mg, 73%) and **347** (1.7 mg, 17%) as viscous oils. Characterization for **346**: IR (neat) ν 3465, 3058, 2993, 2923, 2877, 2101, 1596, 1489, 1448, 1380, 1264, 1200, 1159, 1070, 980, 898, 821, 747, 701 cm⁻¹; [α]_D²² -29.0 (*c* 6.56, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.49-7.44 (m, 6H), 7.35-7.30 (m, 6H), 7.26 (tt, *J* = 7.4, 1.2 Hz, 3H), 3.96 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.94-3.84 (m, 2H), 3.69 (dd, *J* = 11.5, 10.0 Hz, 1H), 3.49, (m, 1H), 3.45 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.35 (dd, *J* = 10.0, 6.9 Hz, 1H), 3.24 (ddd, *J* = 10.0, 10.0, 5.8 Hz, 1H), 1.78 (ddd, *J* = 14.3, 9.5, 2.6 Hz, 1H), 1.58 (ddd, *J* = 14.3, 8.6, 2.3 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.6 (C), 128.7 (CH), 128.1 (CH), 127.4 (CH), 99.3 (C), 87.6 (C), 69.7 (CH), 68.0 (CH), 65.9 (CH), 63.6 (CH₂), 62.4 (CH₂), 58.0 (CH), 35.4 (CH₂), 28.8 (CH₃), 19.2 (CH₃); HRESIMS *m/z* 551.2372 [M+Na]⁺, calcd. for C₂₉H₃₂N₆O₄Na₁ 551.2377.

(4*S*,5*R*)-5-azido-4-((2*S*,3*R*)-3-azido-2-(methoxymethoxy)-4-(trityloxy)butyl)-2,2-dimethyl-1,3-dioxane (349). Chloromethyl methyl ether (115 μ L, 1.51 mmol) was added to a stirred solution of alcohol **346** (80.0 mg, 151 μ mol) and Hünig's base (500 μ L, 3.03 mmol) in dichloromethane (200 μ L) at 0 °C. The mixture was warmed to room temperature and stirred for 38 hours then quenched by addition of water (5 mL). The mixture was extracted with ethyl ether (4 \times 5 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) provided **349** (75.2 mg, 90%) as a viscous oil: IR (neat) ν 3058, 2992, 2935, 2886, 2100, 1596, 1490, 1448, 1371, 1264,

1221, 1197, 1154, 1076, 1030, 981, 918, 808, 763, 747, 702 cm^{-1} ; $[\alpha]_{\text{D}}^{21} -33.6$ (c 4.55, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.47-7.44 (m, 6H), 7.34-7.30 (m, 6H), 7.25 (tt, $J = 7.3, 1.2$ Hz, 3H), 4.63 (d, $J = 6.8$ Hz, 1H), 4.56 (d, $J = 6.8$ Hz, 1H), 3.96 (dd, $J = 11.5, 5.4$ Hz, 1H), 3.87 (m, 1H), 3.81 (m, 1H), 3.75-3.65 (m, 2H), 3.36 (s, 3H), 3.26 (dd, $J = 10.0, 7.7$ Hz, 1H), 3.15 (dd, $J = 10.0, 5.2$ Hz, 1H), 3.12 (dd, $J = 9.7, 5.4$ Hz, 1H), 1.92 (ddd, $J = 14.0, 10.0, 2.0$ Hz, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.28 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.7 (C), 128.8 (CH), 128.0 (CH), 127.3 (CH), 99.0 (C), 97.6 (CH_2), 87.4 (C), 75.0 (CH), 68.5 (CH), 65.8 (CH), 63.3 (CH_2), 62.5 (CH_2), 58.8 (CH), 56.1 (CH_3), 34.4 (CH_2), 28.8 (CH_3), 19.3 (CH_3); HRESIMS m/z 595.2629 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_5\text{Na}_1$ 595.2639.

(2*R*,3*S*)-2-amino-4-((4*S*,5*R*)-5-amino-2,2-dimethyl-1,3-dioxan-4-yl)-3-

(methoxymethoxy)butan-1-ol ((-)-301). 10% Pd/C (6.3 mg, 5.9 μmol , 25 mol % Pd) was added to **349** (13.1 mg, 23.5 μmol) in dry trifluoroethanol (1.5 mL) and the mixture placed under H_2 (7 atm) and agitated for 17 hour on a Parr shaker. The mixture was adjusted to pH 4 with TFA placed under H_2 (7 atm) and agitated for 4.5 hour on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure provided crude ((-)-**301** which was used without further purification.

(2*R*,3*S*)-2-(dibenzylamino)-4-((4*S*,5*R*)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol ((-)-302). Benzylbromide (56.3 μL , 471 μmol) was added dropwise to a stirred solution of amine ((-)-**301** (<6.6 mg, 23.5 μmol) and K_2CO_3

(195 mg, 1.41 mmol) in anhydrous acetonitrile (550 μ L) at room temperature. The mixture was stirred for 4.5 days then quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (4 \times 4 mL) and combined extracts washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, step gradient of 10% and 20% and then 25% ethyl acetate in hexane) provided (–)-**302** (7.0 mg, 47%) as an amorphous solid: IR (neat) ν 3476, 3065, 3030, 2995, 2943, 2882, 2812, 1597, 1492, 1457, 1379, 1265, 1221, 1151, 1108, 1029, 977, 916, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -25.2 (c 2.80, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.23 (m, 20H), 4.77 (d, J = 6.4 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 4.15 (m, 1H), 4.02 (t, J = 9.6 Hz, 1H), 4.00-3.88 (m, 6H), 3.84 (d, J = 13.6 Hz, 2H), 3.70 (d, J = 13.6 Hz, 2H), 3.59 (d, J = 14.0 Hz, 2H), 3.40 (s, 3H), 3.31 (bs, 1H), 2.78-2.70 (m, 2H), 2.14 (dd, J = 13.6, 9.6 Hz, 1H), 1.90 (ddd, J = 14.8, 10.8, 2.4 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 140.0 (C), 139.7 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 127.1 (CH), 98.9 (CH), 98.7 (C), 76.2 (CH), 67.0 (CH), 62.6 (CH), 58.5 (CH₂), 58.0 (CH), 57.9 (CH₂), 56.5 (CH₃), 54.9 (CH₂), 54.8 (CH₂), 38.7 (CH₂), 27.9 (CH₃), 20.9 (CH₃); HRMS m/z 639.3971 [M+H]⁺, calcd. for C₄₀H₅₁N₂O₅ 639.3793.

7.1.6. Chapter 5 Methods

(2*R*,3*S*,5*S*,6*R*)-2,6-diaminoheptane-1,3,5,7-tetraol (350). A mixture of 10% Pd/C (13 mg, 12 μ mol, 20 mol % Pd) and azide **334** (15.0 mg, 60.9 μ mol) in water (1.5 mL) was placed under H₂ (1 atm) and stirred at room temperature. After 2 hours the mixture was filtered through a 0.45 μ m syringe filter and concentrated under reduced pressure to provide the **350** (11.8 mg, 100%) as a white solid. **350** was converted to the hydrochloride salt for analysis: ¹H NMR (400 MHz, D₂O, ref CH₃CN) δ 4.16 (m, 2H), 3.93 (dd, J = 12.0, 4.2 Hz, 2H), 3.77 (dd, J = 12.0, 8.8 Hz, 2H), 3.42 (apparent dt, J = 8.4, 4.0 Hz, 2H), 1.70 (dd, J = 8.0, 5.2 Hz, 2H); ¹³C NMR (100 MHz, D₂O, ref CH₃CN) δ 65.8 (CH), 58.0 (CH₂), 57.3 (CH), 35.8 (CH₂); HRMS m/z 195.1341 [M+H]⁺, calcd. for C₇H₁₉N₂O₄ 195.1339.

(2*S*,3*R*,4*R*)-4-amino-*N*-((*S*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5-trihydroxypentanamide (351). TMSCl (15.0 μ L, 12.7 mg, 120 μ mol) was added to **320** (16.4 mg, 27 μ mol) in dry MeOH (1.5 mL) at 0 °C. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (29 mg, 27 μ mol, 100 mol % Pd) was added and the mixture placed under H₂ (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μ m syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (29 mg, 27 μ mol, 100 mol % Pd) added. The mixture was placed under H₂ (5 atm) and agitated for 1 hour on a Parr shaker. Filtration through a 0.45 μ m syringe filter and concentration under reduced pressure at or below

room temperature. HPLC purification (Synergi Hydro-RP 10 × 250 mm column, 3 MeOH: 0.1 CF₃COOH: 96.9 H₂O, 3.5 mL/min, (product converted to HCl salt by resuspending in 1% HCl and re-drying)) provided pure **351** (4.3 mg, 49%) as a white solid: $[\alpha]_D^{22} -21.2$ (*c* 1.13, H₂O); ¹H NMR (500 MHz, 0.2% acetonitrile:D₂O (ref δ 2.06)) δ 4.45 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.37 (d, *J* = 2.3 Hz, 1H), 4.27 (dd, *J* = 5.6, 2.3 Hz, 1H), 4.01 (dd, *J* = 12.3, 4.3 Hz, 1H), 3.85 (dd, *J* = 12.3, 7.8 Hz, 1H), 3.63 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.60 (m, 1H), 3.48 (dd, *J* = 14.6, 6.9 Hz, 1H); ¹³C NMR (125 MHz, 0.2% acetonitrile:D₂O (ref δ 1.47)) δ 174.9 (C), 174.7 (C), 162.2 (C), 72.3 (CH), 68.8 (CH), 58.8 (CH₂), 55.8 (CH), 41.4 (CH₂); HRMS *m/z* 316.1235 [M+Na]⁺, calcd. for C₉H₁₉N₅O₆Na₁ 316.1233.

(2*S*,3*R*,4*R*)-*N*-((*R*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-3-hydroxy-5-(methoxymethoxy)pentanamide (355). A solution of **314** (20.3 mg, 42.3 μ mol) in DMF (60 μ L) was cooled to 0 °C under nitrogen and treated with EDCI (10.6 mg, 55.0 μ mol) in DMF (100 μ L) and HOBt (8.0 mg, 59.3 μ mol) in DMF (40 μ L). After 5 minutes amine (+)-**319** (12.1 mg, 46.6 μ mol) in DMF (50 μ L) and triethylamine (6.5 μ L, 46.6 μ mol) was added. The mixture was warmed to room temperature and stirred for 1.5 hours. A solution of 10% isopropyl alcohol in chloroform (50 mL) was added, and the mixture washed with water (3 × 5 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 5% then 10% methanol in dichloromethane) provided **355** (17.2 mg, 67%) as a

viscous oil: IR (neat) ν 3346, 3063, 3027, 2930, 1655, 1544, 1494, 1453, 1342, 1149, 1106, 1046, 916, 750, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{22}$ -29.7 (c 5.13, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.33 (d, $J = 6.8$ Hz, 4H), 7.30-7.23 (m, 7H), 7.18 (m, 4H), 4.67 (s, 2H), 4.37 (dd, $J = 6.8, 4.0$ Hz, 1H), 4.27 (d, $J = 1.2$ Hz, 1H), 4.22 (d, $J = 10.8$ Hz, 1H), 4.03-3.95 (m, 2H), 3.91 (dd, $J = 10.8, 6.4$ Hz, 1H), 3.86 (d, $J = 13.6$ Hz, 2H), 3.69 (d, $J = 10.4$ Hz, 1H), 3.66 (d, $J = 13.2$ Hz, 2H), 3.55 (dd, $J = 14.0, 3.6$ Hz, 1H), 3.42 (s, 3H), 3.40 (m, 1H), 3.26 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.2 (C), 174.8 (C), 162.4 (C), 141.3 (C), 138.5 (C), 130.6 (CH), 129.8 (CH), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.1 (CH), 97.9 (CH_2), 81.3 (CH), 74.5 (CH_2), 73.9 (CH), 66.3 (CH_2), 59.1 (CH), 55.9 (CH_2), 55.8 (CH_3), 55.7 (CH), 42.3 (CH_2); HRMS m/z 608.3063 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{32}\text{H}_{42}\text{N}_5\text{O}_7$ 608.3079.

(2*S*,3*R*,4*R*)-4-amino-*N*-((*R*)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5-

trihydroxypentanamide (352). TMSCl (15.0 μL , 12.7 mg, 120 μmol) was added to **355** (13.5 mg, 22 μmol) in dry MeOH (1.5 mL) at 0 $^\circ\text{C}$. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (24 mg, 22 μmol , 100 mol % Pd) was added and the mixture placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (24 mg, 22 μmol , 100 mol % Pd) added. The mixture was placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided the hydrochloride salt of **352** (4.9 mg, (73% purity by

NMR)). Further HPLC purification (Synergi Hydro-RP 10 × 250 mm column, 1.3 MeOH: 0.1 CF₃COOH: 98.6 H₂O, 3.5 mL/min, (product converted to HCl salt by resuspending in 1% HCl and re-drying)) provided pure **352** (1.8 mg) as a white solid: $[\alpha]_D^{20} -12.4$ (*c* 1.42, H₂O); ¹H NMR (400 MHz, 0.2% acetonitrile:D₂O (ref δ 2.06)) δ 4.46 (dd, *J* = 6.4, 4.0 Hz, 1H), 4.38 (d, *J* = 2.8 Hz, 1H), 4.27 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.00 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.85 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.66-3.58 (m, 2H), 3.50 (dd, *J* = 14.8, 6.8 Hz, 1H); ¹³C NMR (100 MHz, 0.2% acetonitrile:D₂O (ref δ 1.47)) δ 175.1 (C), 174.8 (C), 162.4 (C), 72.3 (CH), 69.0 (CH), 58.8 (CH₂), 55.9 (CH), 41.3 (CH₂); HRMS *m/z* 294.1411 [M+H]⁺, calcd. for C₉H₂₀N₅O₆ 294.1414.

(2R,3S,4R,5S)-methyl 2-(benzyloxy)-4-(dibenzylamino)-6-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-

(methoxymethoxy)hexanoate (356). Under an atmosphere of nitrogen freshly distilled *n*-BuBOTf (55.5 μ L, 220 μ mol) and Hünig's base (43.8 μ L, 251 μ mol) was added to a stirred solution of **88** (34.0 mg, 188 μ mol) in ethyl ether (250 μ L) at -78 °C. The mixture was stirred for 1.5 hours then aldehyde **297** (90.0 mg, 141 μ mol) in ethyl ether (150 μ L) was added dropwise. The mixture was stirred for 15 minutes then warmed to 0 °C and stirred a further 2 hours. The mixture was quenched with addition of pH 7 phosphate buffer (206 μ L), methanol (620 μ L) and 2:1 methanol:30% hydrogen peroxide (620 μ L) at 0 °C. This mixture was stirred at 0 °C for 1 hour then 5% NaHCO₃ solution (50 mL) added and the mixture extracted with ethyl ether (3 × 50 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (Analogix 4 g silica cartridge, 5% ethyl acetate in hexane, 13

mL/min flow rate) followed by HPLC purification (silica 10 × 250 mm column, 3% IPA in hexane, 4 mL/min) provided **356** (57.2 mg, 49%) as a viscous oil: IR (neat) ν 3476, 3065, 3056, 2986, 2934, 2882, 1754, 1606, 1501, 1457, 1379, 1265, 1204, 1151, 1099, 1038, 916, 819, 750, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +29.2$ (c 10.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.15 (m, 25H), 4.74 (d, $J = 6.4$ Hz, 1H), 4.68 (d, $J = 12.6$ Hz, 1H), 4.57 (d, $J = 6.4$ Hz, 1H), 4.51-4.44 (m, 2H), 4.35 (d, $J = 2.0$ Hz, 1H), 4.18 (m, 1H), 4.10-4.02 (m, 3H), 3.90-3.64 (m, 11H), 3.48 (d, $J = 13.6$ Hz, 2H), 3.38 (s, 3H), 3.31 (m, 1H), 2.71 (dt, $J = 9.2, 7.0$ Hz, 1H), 2.29 (m, 1H), 1.67 (m, 1H), 1.35 (s, 3H), 1.29 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.6 (C), 139.4 (C), 137.8 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 98.9 (C), 96.7 (CH₂), 78.7 (CH), 74.3 (CH), 72.2 (CH₂), 70.0 (CH), 68.0 (CH), 62.1 (CH), 58.6 (CH₂), 58.4 (CH), 56.6 (CH₃), 55.2 (CH₂), 54.7 (CH₂), 52.1 (CH₃), 38.4 (CH₂), 27.0 (CH₃), 21.7 (CH₃); HRMS m/z 817.4437 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{50}\text{H}_{61}\text{N}_1\text{O}_8\text{N}_2$ 817.4422.

(2R,3S,4R,5S)-2-(benzyloxy)-4-(dibenzylamino)-6-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanoic acid (357).

Lithium hydroxide monohydrate (6.5 mg, 64 μmol) was added to a stirred solution of ester **356** (50 mg, 61 μmol) in 3:2:2 MeOH:H₂O:THF (1.40 mL) at room temperature. The mixture was stirred for 4 hours then diluted with ethyl acetate (90 mL). The mixture was washed with 1% HCl solution till neutral then dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica saturated with AcOH, 25% then 50% ethyl acetate with 1% AcOH in hexane) provided **357** (41.3 mg, 84%) as a viscous oil: IR (neat) ν 3338, 3061, 3027, 2935, 2888, 1733, 1601, 1494, 1453, 1378, 1219, 1146,

1101, 1026, 916, 747, 698 cm^{-1} ; $[\alpha]_{\text{D}}^{20} +33.4$ (c 11.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.14 (m, 25H), 4.73 (d, $J = 6.4$ Hz, 1H), 4.67 (d, $J = 11.6$ Hz, 1H), 4.58-4.51 (m, 2H), 4.42-4.37 (m, 2H), 4.34-4.26 (m, 3H), 3.89-3.70 (m, 7H), 3.56 (m, 1H), 3.46 (d, $J = 14.0$ Hz, 2H), 3.35 (s, 3H), 2.69 (m, 1H), 2.27 (m, 1H), 1.65 (ddd, $J = 14.4$, 9.6, 4.4 Hz, 1H), 1.27 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2 (C), 139.3 (C), 137.5 (C), 136.7 (C), 129.6 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 98.9 (C), 96.4 (CH_2), 79.6 (CH), 73.8 (CH), 72.0 (CH_2), 69.4 (CH), 67.5 (CH), 61.9 (CH), 58.3 (CH_2), 57.9 (CH), 56.8 (CH_3), 56.3 (CH_2), 54.7 (CH_2), 37.8 (CH_2), 27.4 (CH_3), 21.4 (CH_3); HRMS m/z 803.4248 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{49}\text{H}_{59}\text{N}_2\text{O}_8$ 803.4266.

(2R,3S,4R,5S)-N-((S)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-6-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanamide (358). A solution of **357** (18.7 mg, 23.3 μmol) in DMF (50 μL) was cooled to 0 $^\circ\text{C}$ under nitrogen and treated with EDCI (5.80 mg, 30.3 μmol) in DMF (75 μL) and HOBt (4.40 mg, 32.6 μmol) in DMF (50 μL). After 5 minutes amine (–)-**319** (6.67 mg, 25.6 μmol) in DMF (50 μL) and triethylamine (3.57 μL , 25.6 μmol) were added. The mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 10% isopropyl alcohol in chloroform (16 mL) was added, and the mixture washed with water (5×3 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 2.5%, 5%, and 10% methanol in dichloromethane) provided **358** (18.7 mg, 86%) as an amorphous solid. Further HPLC purification (silica 10 \times 250 mm column, 17% methanol in

dichloromethane, 3.5 mL/min) provided pure **358** (12.7 mg) as a amorphous solid: IR (neat) ν 3344, 3208, 3061, 3027, 2989, 2931, 1664, 1519, 1494, 1453, 1377, 1342, 1222, 1142, 1105, 1027, 915, 747, 698 cm^{-1} ; $[\alpha]_{\text{D}}^{21} +13.9$ (c 4.85, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 7.32-7.17 (m, 25H), 4.64 (d, $J = 10.8$ Hz, 1H), 4.56-4.46 (m, 3H), 4.39-4.33 (m, 2H), 4.20 (d, $J = 1.2$ Hz, 1H), 4.08-3.95 (m, 4H), 3.92 (dd, $J = 12.0, 7.6$ Hz, 1H), 3.84-3.74 (m, 5H), 3.64 (dd, $J = 14.2, 4.6$ Hz, 1H), 3.50 (d, $J = 13.6$ Hz, 2H), 3.44-3.35 (m, 2H), 3.28 (s, 3H), 2.69 (m, 1H), 2.26 (m, 1H), 1.66 (ddd, $J = 14.4, 8.4, 5.6$ Hz, 1H), 1.37 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.2 (C), 173.6 (C), 162.2 (C), 141.3 (C), 140.9 (C), 138.5 (C), 130.3 (CH), 130.0 (CH), 129.5 (CH), 129.43 (CH), 129.39 (CH), 129.3 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 100.1 (C), 97.4 (CH_2), 82.3 (CH), 76.1 (CH), 74.2 (CH_2), 72.4 (CH), 69.5 (CH), 63.4 (CH), 59.4 (CH_2), 59.3 (CH), 56.9 (CH_3), 56.8 (CH_2), 55.7 (CH_2), 54.8 (CH), 42.8 (CH_2), 38.7 (CH_2), 27.7 (CH_3), 21.8 (CH_3); HRMS m/z 931.4939 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{53}\text{H}_{67}\text{N}_6\text{O}_9$ 931.4964.

(2R,3S,4S,5S,7R,8S)-4,8-diamino-N-((S)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5,7,9-pentahydroxynonanamide (353). TMSCl (15.0 μL , 12.7 mg, 120 μmol) was added to **358** (12.5 mg, 13.4 μmol) in dry MeOH (1.5 mL) at 0 $^\circ\text{C}$. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (14.3 mg, 13.4 μmol , 100 mol % Pd) was added and the mixture placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (14.3 mg, 13.4 μmol , 100 mol % Pd) added. The mixture was placed under H_2 (5 atm) and agitated for 1 hour on a

Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided the hydrochloride salt of **353**. Further HPLC purification (Synergi Hydro-RP 10 \times 250 mm column, 1.3 MeOH: 0.1 CF_3COOH : 98.6 H_2O , 3.5 mL/min, (product converted to HCl salt by resuspending in 1% HCl and re-drying)) provided pure **353** (3.61 mg, 57%) as a white solid: $[\alpha]_{\text{D}}^{22} -25.8$ (c 2.41, H_2O); ^1H NMR (400 MHz, 0.2% acetonitrile: D_2O (ref δ 2.06)) δ 4.44 (dd, $J = 6.4, 4.8$ Hz, 1H), 4.36-4.30 (m, 2H), 4.23 (m, 2H), 3.94 (dd, $J = 12.4, 4.2$ Hz, 1H), 3.80 (dd, $J = 12.0, 8.0$ Hz, 1H), 3.64 (dd, $J = 14.8, 4.4$ Hz, 1H), 3.59 (dd, $J = 4.6, 4.6$ Hz, 1H), 3.52-3.44 (m, 2H), 1.93 (ddd, $J = 14.4, 3.6, 3.6$ Hz, 1H), 1.83 (m, 1H); ^{13}C NMR (100 MHz, 0.2% acetonitrile: D_2O (ref δ 1.47)) δ 174.7 (C), 174.6 (C), 162.3 (C), 74.1 (CH), 67.3 (CH), 67.2 (CH), 58.1 (CH_2), 57.8 (CH), 56.5 (CH), 54.9 (CH), 41.4 (CH_2), 34.1 (CH_2); HRMS m/z 397.2035 $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{29}\text{N}_6\text{O}_8$ 397.2041.

(2R,3S,4R,5S)-N-((R)-1-amino-1-oxo-3-ureidopropan-2-yl)-2-(benzyloxy)-4-(dibenzylamino)-6-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-5-(methoxymethoxy)hexanamide (359). A solution of **357** (19.4 mg, 24.2 μmol) in DMF (50 μL) was cooled to 0 $^\circ\text{C}$ under nitrogen and treated with EDCI (6.02 mg, 31.4 μmol) in DMF (80 μL) and HOBt (4.57 mg, 33.8 μmol) in DMF (50 μL). After 5 minutes amine (+)-**319** (6.91 mg, 26.6 μmol) in DMF (50 μL) and triethylamine (3.70 μL , 26.6 μmol) were added. The mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 10% isopropyl alcohol in chloroform (16 mL) was added, and the mixture washed with water (5 \times 3 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 2.5%, 5%, and 10%

methanol in dichloromethane) provided **359** (19.4 mg, 86%) as an amorphous solid.

Further HPLC purification (silica 10 × 250 mm column, 17% methanol in dichloromethane, 3.5 mL/min) provided pure **359** (14.0 mg) as a amorphous solid: IR (neat) ν 3343, 3220, 3061, 3027, 2989, 2934, 1670, 1603, 1520, 1494, 1454, 1377, 1223, 1144, 1105, 1027, 749, 698 cm^{-1} ; $[\alpha]_{\text{D}}^{21} +23.3$ (c 5.30, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 7.31-7.17 (m, 25H), 4.70 (d, $J = 12.0$ Hz, 1H), 4.56 (d, $J = 6.0$ Hz, 1H), 4.48-4.40 (m, 2H), 4.38 (d, $J = 6.8$ Hz, 1H), 4.25 (d, $J = 9.2$ Hz, 1H), 4.15 (d, $J = 1.2$ Hz, 1H), 4.02-3.88 (m, 5H), 3.82-3.74 (m, 5H), 3.59 (dd, $J = 14.2, 3.8$ Hz, 1H), 3.54-3.47 (m, 3H), 3.38 (dd, $J = 9.4, 4.2$ Hz, 1H), 3.29 (s, 3H), 2.66 (m, 1H), 2.21 (m, 1H), 1.59 (m, 1H), 1.35 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.1 (C), 174.3 (C), 162.4 (C), 141.0 (C), 140.9 (C), 138.5 (C), 130.3 (CH), 130.1 (CH), 129.5 (CH), 129.45 (CH), 129.42 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 100.1 (C), 97.7 (CH_2), 81.9 (CH), 76.1 (CH), 73.9 (CH_2), 72.2 (CH), 69.6 (CH), 63.4 (CH), 59.5 (CH), 59.2 (CH_2), 56.9 (CH_3), 56.5 (CH_2), 55.8 (CH), 55.7 (CH_2), 42.0 (CH_2), 39.1 (CH_2), 27.6 (CH_3), 21.9 (CH_3); HRMS m/z 931.4945 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{53}\text{H}_{67}\text{N}_6\text{O}_9$ 931.4964.

(2R,3S,4S,5S,7R,8S)-4,8-diamino-N-((R)-1-amino-1-oxo-3-ureidopropan-2-yl)-2,3,5,7,9-pentahydroxynonanamide (354). TMSCl (15.0 μL , 12.7 mg, 120 μmol) was added to **359** (13.8 mg, 14.8 μmol) in dry MeOH (1.5 mL) at 0 °C. The mixture was warmed to room temperature over 5 minutes with agitation. 10% Pd/C (15.8 mg, 14.8 μmol , 100 mol % Pd) was added and the mixture placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. The mixture was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure at room temperature or below. The crude material

was resuspended in 1% HCl in water (1.5 mL) and 10% Pd/C (15.8 mg, 14.8 μmol , 100 mol % Pd) added. The mixture was placed under H_2 (5 atm) and agitated for 1 hour on a Parr shaker. Filtration through a 0.45 μm syringe filter and concentration under reduced pressure at or below room temperature provided the hydrochloride salt of **354**. Further HPLC purification (Synergi Hydro-RP 10 \times 250 mm column, 1.3 MeOH: 0.1 CF_3COOH : 98.6 H_2O , 3.5 mL/min, (product converted to HCl salt by resuspending in 1% HCl and re-drying)) provided pure **354** (5.06 mg, 73%) as a white solid: $[\alpha]_{\text{D}}^{22} -7.8$ (c 3.37, H_2O); ^1H NMR (400 MHz, 0.2% acetonitrile: D_2O (ref δ 2.06)) δ 4.47 (dd, $J = 7.0, 4.2$ Hz, 1H), 4.36 (m, 2H), 4.22 (m, 2H), 3.94 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.80 (dd, $J = 12.4, 8.0$ Hz, 1H), 3.63 (dd, $J = 14.8, 4.2$ Hz, 1H), 3.60 (dd, $J = 4.0, 4.0$ Hz, 1H), 3.54-3.43 (m, 2H), 1.93 (ddd, $J = 14.4, 4.0, 4.0$ Hz, 1H), 1.84 (m, 1H); ^{13}C NMR (100 MHz, 0.2% acetonitrile: D_2O (ref δ 1.47)) δ 174.8 (C), 174.7 (C), 162.4 (C), 74.2 (CH), 67.5 (CH), 67.2 (CH), 58.1 (CH_2), 57.7 (CH), 56.5 (CH), 55.1 (CH), 41.3 (CH_2), 34.3 (CH_2); HRMS m/z 397.2033 $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{29}\text{N}_6\text{O}_8$ 397.2041.

(R)-((2R,3S)-2-(dibenzylamino)-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (361). *R*-(+)-MPTA (7.5 mg, 31 μmol), DCC (8.9 mg, 43 μmol) and DMAP (0.8 mg, 6.3 μmol) were added to **296** (10.0 mg, 15.7 μmol) in DCM (100 μL) at room temperature under nitrogen. The mixture was stirred for 7 hours then quenched with water (1 mL) and saturated NaHCO_3 solution (5 mL). The mixture extracted with ethyl ether (3 \times 5 mL) and washed with brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10%

ethyl acetate in hexane) provided **361** (11.0 mg, 82%) as a viscous oil: ^1H NMR (500 MHz, CDCl_3) δ 7.62 (d, $J = 8.0$ Hz, 2H), 7.40 (m, 3H), 7.32-7.22 (m, 10H), 7.18-7.08 (m, 10H), 4.71-4.61 (m, 2H), 4.60 (d, $J = 7.0$ Hz, 1H), 4.52 (d, $J = 7.0$ Hz, 1H), 3.90 (m, 1H), 3.81 (dd, $J = 12.5, 7.0$ Hz, 1H), 3.74 (d, $J = 12.0$ Hz, 2H), 3.72-3.67 (m, 2H), 3.62 (d, $J = 14.0$ Hz, 2H), 3.56-3.50 (m, 5H), 3.43 (d, $J = 14.0$ Hz, 2H), 3.30 (s, 3H), 3.25 (m, 1H), 2.59 (m, 1H), 2.17 (dd, $J = 13.5, 8.5$ Hz, 1H), 1.59 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -71.3 (s, 3F, (minor 0.02)), -71.7 (s, 3F, (major 1.00)).

(S)-((2R,3S)-2-(dibenzylamino)-4-((4R,5S)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (362). *S*-(-)-MPTA (7.5 mg, 31 μmol), DCC (8.9 mg, 43 μmol) and DMAP (0.8 mg, 6.3 μmol) were added to **296** (10.0 mg, 15.7 μmol) in DCM (100 μL) at room temperature under nitrogen. The mixture was stirred for 7 hours then quenched with water (1 mL) and saturated NaHCO_3 solution (5 mL). The mixture extracted with ethyl ether (3 x 5 mL) and washed with brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane) provided **362** (12.5 mg, 93%) as a viscous oil: ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, $J = 7.5$ Hz, 2H), 7.40 (m, 3H), 7.32-7.22 (m, 10H), 7.21-7.10 (m, 10H), 4.67 (d, $J = 5.5$ Hz, 2H), 4.60 (d, $J = 6.5$ Hz, 1H), 4.53 (d, $J = 6.5$ Hz, 1H), 3.90 (m, 1H), 3.82-3.63 (m, 10H), 3.56 (s, 3H), 3.43 (d, $J = 14.0$ Hz, 2H), 3.31 (s, 3H), 3.23 (m, 1H), 2.57 (m, 1H), 2.16 (dd, $J = 13.0, 8.0$ Hz, 1H), 1.59 (m, 1H), 1.12 (s, 3H),

1.08, (s, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -71.3 (s, 3F, (major 1.00)), -71.7 (s, 3F, (minor 0.04)).

7.1.7. Chapter 6 Methods

Compounds **54**, **193**, **368**, **369** and **375** were synthesized according to literature procedure.

7-(4-methoxybenzyloxy)hepta-2,5-diyne-1-ol (363) To a nitrogen filled dry round bottom flask with stirrer was added finely ground and anhydrous NaI (808 mg, 5.39 mmol), CuI (525 mg, 2.76 mmol), and K₂CO₃ (732 mg, 5.30 mmol). Dry DMF (2 mL) was added followed by **375** (500 μ L, 599 mg, 5.72 mmol) and **330** (914 mg, 5.19 mmol) in DMF (3 mL). The mixture was stirred for 20 hours at room temperature quenched with saturated NH₄Cl solution (5 mL). The mixture was extracted with benzene (5 \times 7 mL) and combined extracts washed with water (4 \times 10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in MeOH and conc. NH₄OH (2 mL) added. Mixture was stirred for 30 minutes then water (5 mL) added. MeOH was removed under vacuo. and remaining mixture was extracted with benzene (4 \times 2mL), combined extracts were washed with water till pH 7 and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate : hexane 2 : 3) provided **363** (940 mg, 74%) and a viscous clear oil: IR (neat) ν 3403, 2910, 2281, 2219, 1722, 1612, 1513, 1249, 1174, 1070, 1031 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (m, 2H), 6.88 (m, 2H), 4.51 (s, 2H), 4.24 (t, J=2.4 Hz, 2H), 4.12 (t, J=2.4 Hz, 2H), 3.80 (s, 3H), 3.27 (q, J= 2.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.6 (C), 130.1 (CH), 129.7 (C), 114.1 (CH), 80.5 (C), 79.8 (C), 79.3 (C), 77.1 (C), 71.5 (CH₂), 57.4 (CH₂), 55.6 (CH₃), 51.3 (CH₂), 10.3 (CH₂); HRFAB *m/z* 267.1003 [M+Na]⁺, calcd. for C₁₅H₁₆O₃Na 267.0997.

(2Z,5Z)-7-(4-methoxybenzyloxy)hepta-2,5-dien-1-ol (364) Lindlar's cat. (32.6 mg, 15 μ mol) and quinoline (20 μ L, 21.9 mg, 0.17 mmol) was added to **363** (100 mg, 0.41 mmol) in CH₂Cl₂ (15 mL). The mixture was placed under H₂ (1 atm) and stirred for 6 hours. The mixture was filtered through a Celosite plug, and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate : hexane 2 : 3) provided **364** (84.8 mg, 83%) as a clear viscous oil: IR (neat) ν 3389, 2987, 2924, 2857, 1593, 1491, 1213 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (m, 2H), 6.88 (m, 2H), 5.47-5.67 (m, 4H), 4.45 (s, 2H), 4.17 (d, J=6.4 Hz, 2H), 4.05 (d, J=6.8 Hz, 2H), 3.81 (s, 3H), 2.85 (t, J=7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.6 (C), 131.5 (CH), 130.6 (CH), 129.8 (CH), 129.4 (CH), 127.1 (CH), 114.1 (CH), 72.2 (CH₂), 65.4 (CH₂), 58.7 (CH₂), 55.6 (CH₃), 26.5 (CH₂); HRFAB *m/z* 271.1323 [M+Na]⁺, calcd. for C₁₅H₂₀O₃Na 271.1310.

General procedure for synthesis of 370a and 370b. Under an atmosphere of nitrogen, *n*-BuLi (0.255 mmol, 2.5 M in hexane) was added dropwise to a solution of **368** (40 mg, 0.255 mmol) in THF (1.2 mL) at 0 °C. The mixture was stirred for 30 minutes then cooled to -78 °C and **369** (58.6 mg, 0.114 mmol in THF) was added dropwise over 5 minutes. The solution was stirred for 1 hour then quenched with saturated NH₄Cl solution (15 mL). The mixture was extracted with ethyl ether (5 \times 15 mL) and combined extracts washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate : hexane 1 : 3) provided a mixture of **370a** and **370b** (39.6 mg, 52%, 2 : 1 ratio by NMR). HPLC chromatography (Silica, 1% IPA in hexane) gave **370a** and **370b** viscous clear oils.

(2S,3S)-3-(dibenzylamino)-1-(phenylsulfonyl)-4-(trityloxy)butan-2-ol (370a): IR

(neat) ν 3518, 3085, 3060, 3026, 2938, 2887, 2839, 2806, 1959, 1812, 1596, 1492, 1447, 1305, 1216, 1147, 1082, 1056 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +1.5$ (c 0.45, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J=8.4$ Hz, 2H), 7.62 (t, $J=6.8$ Hz, 1H), 7.20-7.51 (m, 22H), 7.05 (d, $J=6.4$ Hz, 4H), 4.32 (t, $J=10.4$ Hz, 1H), 3.84 (d, $J=14.4$ Hz, 1H), 3.46-3.58 (m, 4H), 3.26 (d, $J=13.6$ Hz, 2H), 2.23 (d, $J=2.4$ Hz, 1H), 2.82 (dd, $J=14.8, 10.4$ Hz, 1H), 2.75 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.6 (C), 139.3 (C), 139.2 (C), 129.3 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 87.6 (C), 65.7 (CH), 60.5 (CH_2), 60.2 (CH), 59.2 (CH_2), 54.9 (CH_2); HRFAB m/z 668.2806 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{43}\text{H}_{42}\text{O}_4\text{N}_1\text{S}_1$ 668.2835.

(2R,3S)-3-(dibenzylamino)-1-(phenylsulfonyl)-4-(trityloxy)butan-2-ol (370b): IR

(neat) ν 3518, 3085, 3060, 3027, 2930, 2880, 2812, 1962, 1815, 1597, 1585, 1493, 1447, 1306, 1218, 1147, 1084 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +16.6$ (c 0.17, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, $J=8.0$ Hz, 2H), 7.62 (t, $J=7.2$ Hz, 1H), 7.49 (t, $J=8.0$ Hz, 3H), 7.20-7.44 (m, 19H), 4.17 (bs, 1H), 7.17 (bs, 4H), 3.99 (bs, 1H), 3.84 (bd, $J=12$ Hz, 2H), 3.51 (m, 1H), 3.2-3.7 (m, 5H), 2.76 (bs, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.6 (C), 140.2 (C), 138.9 (C), 133.6 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 87.9 (C), 65.1 (CH), 61.4 (CH), 61.2 (CH_2), 59.2 (CH_2), 54.7 (CH_2); HRFAB m/z 668.2838 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{43}\text{H}_{42}\text{O}_4\text{N}_1\text{S}_1$ 668.2835.

General procedure for synthesis of 378 and 379. Under an atmosphere of nitrogen, *n*-BuLi (0.160 mmol, 2.5 M in hexane) was added dropwise to a solution of **368** (25 mg, 0.16 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 minutes then cooled

to $-78\text{ }^{\circ}\text{C}$ and **54** (29.3 mg, 0.127 mmol in THF) was added dropwise over 5 minutes. The solution was stirred for 1 hour then quenched with saturated NH_4Cl solution (15 mL). The mixture was extracted with ethyl ether (5×15 mL) and combined extracts washed with brine (20 mL), dried over MgSO_4 and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate : hexane 1 : 3) provided a mixture of **378** and **379** (26.0 mg, 53%, 1 : 1 ratio by HPLC). HPLC chromatography (Silica, 10% IPA in hexane) followed by recrystallization from 5% IPA in hexane gave **378** and **379** as solids.

(S)-tert-butyl 4-((S)-1-hydroxy-2-(phenylsulfonyl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (378) : mp $164\text{-}167\text{ }^{\circ}\text{C}$; IR (neat) ν 3411, 3306, 3063, 3007, 2981, 2933, 2874, 1655, 1478, 1448, 1401, 1367, 1302, 1273, 1243, 1225, 1139, 1106 cm^{-1} ; $[\alpha]_{\text{D}}^{24} -34.8$ (c 0.16, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.93 (td, $J=1.2, 7.6$ Hz, 2H), 7.67 (bs, 1H), 7.59 (bd, $J=7.6$ Hz, 2H), 3.70-4.3 (bm, 4H), 3.20-3.60 (bm, 2H), [1.23, 1.34, 1.45, (broad overlapping singlets, 16H)]; ^{13}C NMR (100 MHz, CDCl_3) δ 154.1 (C), 139.3 (C), 133.8 (CH), 129.3 (CH), 128.0 (CH), 94.3 (C), 81.5 (C), 68.1 (CH), 64.8 (CH_2), 60.9 (CH), 60.0 (CH_2), 28.3 (CH_3), 27.0 (CH_3), 23.9 (CH_3); HRMS m/z 386.1643 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_6\text{N}_1\text{S}_1$ 386.1637.

(S)-tert-butyl 4-((R)-1-hydroxy-2-(phenylsulfonyl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (379) : mp $123\text{-}125\text{ }^{\circ}\text{C}$; IR (neat) ν 3518, 3060, 2999, 2987, 2971, 2925, 2888, 2878, 1681, 1585, 1480, 1469, 1446, 1381, 1369, 1306, 1258, 1239, 1143, 1111, $1085, 1061\text{ cm}^{-1}$; $[\alpha]_{\text{D}}^{24} -61.2$ (c 0.19, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J=7.2$ Hz, 2H), 7.69 (bm, 1H), 7.61 (bm, 2H), 4.42 (bs, 1H), 3.90-4.15 (m, 2.5H), 3.50-3.80 (bm, 0.5H), 3.20-3.40 (bm, 2H), 1.54 (bs, 3H), [1.31, 1.39, 1.42, 1.43, 1.44 (broad overlapping singlets, 16H)]; ^{13}C NMR (100 MHz, CDCl_3) δ 153.4 (C), 152.0 (C), 139.3

(C), 139.0 (C), 134.2 (CH), 133.9 (CH), 133.6 (C), 129.7 (CH), 129.6 (CH), 129.4 (CH), 128.9 (CH), 128.3 (C), 128.0 (CH), 99.4 (C), 94.7 (C), 94.2 (C), 81.2 (C), 80.7 (C), 80.2 (C), 67.4 (C), 66.6 (CH), 65.4 (CH), 64.9 (C), 63.6 (CH₂), 63.1 (CH₂), 60.3 (CH), 59.4 (CH), 59.0 (CH₂), 57.4 (CH₂), 47.1 (C), 31.0 (CH₃), 29.1 (CH₃), 28.4 (CH₃), 28.36 (CH₃), 28.30 (CH₃), 27.1 (CH₃), 26.4 (CH₃), 23.8 (CH₃), 22.1 (CH₃), 18.3 (CH₃); HRMS m/z 386.1645 [M+H]⁺, calcd. for C₁₈H₂₈O₆N₁S₁ 386.1637.

Typical procedure for synthesis of 381. (4S,4'S)-tert-butyl 4,4'-((S)-1,3-dihydroxy-2-(phenylsulfonyl)propane-1,3-diyl)bis(2,2-dimethyloxazolidine-3-carboxylate) (381).

Under an atmosphere of nitrogen, *n*-BuLi (83 μmol, 2.5 M in hexane) was added dropwise to a solution of **378** (16 mg, 41 μmol) in THF (0.2 mL) at 0 °C. The mixture was stirred for 30 minutes then cooled to -78 °C and **54** (12 mg, 52 μmol in THF) was added dropwise over 5 minutes. The solution was stirred for 1.75 hours then quenched with saturated NH₄Cl solution (2 mL). The mixture was extracted with ethyl ether (4 × 5 mL) and combined extracts washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate : hexane 2 : 3) provided **381** (1.9 mg, 7%) as a viscous oil: ¹H NMR (400 MHz, CDCl₃) δ 7.90-8.00 (bm, 2H), 7.40-7.70 (bm, 3H), 3.20-4.60 (bm, 9H), 1.20-1.70 (broad overlapping signals, 30H); LRESIMS m/z 637.4 [M+Na]⁺, calcd. for C₂₉H₄₆N₂O₁₀S₁Na₁ 637.2771.

Typical procedure for synthesis of 383. (S)-tert-butyl 4-((3S,4S)-4-(dibenzylamino)-1,3-dihydroxy-2-(phenylsulfonyl)-5-(trityloxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (383). Under an atmosphere of nitrogen, *n*-BuLi (93 μmol, 1.5 M in

hexane) was added dropwise to a solution of **370a** (29.3 mg, 44 μmol) in THF (0.3 mL) at 0 °C. The mixture was stirred for 30 minutes then cooled to -78 °C and **54** (10 mg, 43 μmol in THF) was added dropwise over 5 minutes. The solution was stirred for 41 hours then quenched with saturated NH_4Cl solution (2 mL). The mixture was extracted with ethyl ether (4×10 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 20% ethyl acetate in hexane) provided **383** (6.7 mg, 17%) as a viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.00 (bm, 20H), 3.80-4.60 (bm, 13H), 1.20-1.70 (bm, 6H); LRESIMS m/z 897.4 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{54}\text{H}_{60}\text{N}_2\text{O}_8\text{S}_1$ 896.4070.

General procedure for synthesis of 385 and 386. Under an atmosphere of nitrogen, *i*-PrMgCl (1.45 mmol, 2.0 M in THF) was added dropwise to a solution of **368** (227 mg, 1.45 mmol) in THF (7 mL) at 0 °C. The mixture was stirred for 30 min then hexamethylphosphoramide (2.5 mL, 14.4 mmol) was added. The solution was cooled to -78 °C and **2** (270 mg, 0.71 mmol in THF) was added dropwise over 5 min. The solution was stirred for 1.5 hours then quenched with saturated NH_4Cl solution (15 mL). The mixture was extracted with ethyl ether (5×15 mL) and combined extracts washed with water (15 mL), brine (20 mL), dried over NaSO_4 and concentrated under reduced pressure. Flash chromatography (silica, 25% ethyl acetate in hexane, followed by second purification on silica, 10% hexane in dichloromethane) provided **385** and **386** (224 mg, 59%, 2:1 ratio) as pale yellow viscous oils.

(2*S*,3*S*)-4-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-1-(phenylsulfonyl)butan-2-ol (385). IR (neat) ν 3527, 3085, 3062, 3026, 2953, 2928, 2856, 1602, 1586, 1494, 1471,

1447, 1388, 1359, 1305, 1252, 1210, 1138, 1090, 1026, 997 cm^{-1} ; $[\alpha]_{\text{D}}^{22} -7.1$ (c 2.51, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 2.60 (ddd, $J = 9.2, 5.2, 3.6$ Hz, 1H), 2.82 (dd, $J = 14.8, 10.0$ Hz, 1H), 3.36 (d, $J = 2.0$ Hz, 1H), 3.51 (d, $J = 13.6$ Hz, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.87 (d, $J = 14.0$ Hz, 1H), 3.91 (dd, $J = 11.2, 5.6$ Hz, 1H), 4.08 (dd, $J = 11.2, 4.0$ Hz, 1H), 4.28 (td, $J = 9.6, 2.0$ Hz, 1H), 7.11 (d, $J = 6.8$ Hz, 4H), 7.12-7.28 (m, 6H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.57 (t, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.6 (CH_3), -5.4 (CH_3), 18.2 (C), 26.0 (CH_3), 55.0 (CH_2), 59.1 (CH_2), 60.5 (CH_2), 60.7 (CH), 65.3 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.3 (CH), 133.8 (CH), 139.2 (C), 139.4 (C); HRFABMS m/z 540.2623 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{30}\text{H}_{42}\text{N}_1\text{O}_4\text{Si}_1\text{S}_1$ 540.26038.

(2*R*,3*S*)-4-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-1-(phenylsulfonyl)butan-2-ol (386). IR (neat) ν 3515, 3085, 3062, 3027, 2954, 2928, 2883, 2856, 2808, 1602, 1586, 1494, 1471, 1447, 1388, 1361, 1306, 1257, 1145, 1087, 1027, 1004, 837, 779, 749, 700, 688 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +8.8$ (c 3.11, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 2.63 (q, $J = 5.2$ Hz, 1H), 3.16 (dd, $J = 14.4, 1.2$ Hz, 1H), 3.27 (dd, $J = 14.8, 8.4$ Hz, 1H), 3.52 (d, $J = 13.6$ Hz, 2H), 3.86 (dd, $J = 10.4, 5.2$ Hz, 1H), 3.93-3.97 (m, 2H), 4.00 (d, $J = 13.2$ Hz, 2H), 4.23 (t, $J = 7.20$ Hz, 1H), 7.22-7.31 (m, 10H), 7.52 (t, $J = 8.0$ Hz, 2H), 7.62 (t, $J = 5.6$ Hz, 1H), 7.84 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.44 (CH_3), -5.40 (CH_3), 18.2 (C), 26.0 (CH_3), 54.9 (CH_2), 59.2 (CH_2), 61.1 (CH_2), 62.4 (CH), 65.1 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 129.2 (CH), 129.3 (CH), 133.6 (CH), 139.2 (C), 140.2 (C); HRFABMS m/z 540.2603 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{30}\text{H}_{42}\text{N}_1\text{O}_4\text{Si}_1\text{S}_1$ 540.26038.

(2*S*,3*S*)-2-amino-4-(phenylsulfonyl)butane-1,3-diol hydrochloride (387). A solution of **378** (11.0 mg, 28 μmol) in MeOH (1 mL) with 1% HCl was stirred for 26 hours at room temperature. The solution was concentrated under reduced pressure to give **387** (8.1 mg, quantitative) as a white solid.: IR (neat) ν 3216, 2931, 1598, 1504, 1448, 1303, 1145, 1083 cm^{-1} ; $[\alpha]_{\text{D}}^{22}$ -6.1 (c 0.52, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 3.40 (m, 1H), 3.48 (dd, $J = 14.0, 8.0$ Hz, 1H), 3.60 (dd, $J = 14.4, 4.4$ Hz, 1H), 3.71 (dd, $J = 11.6, 7.6$ Hz, 1H), 3.85 (dd, $J = 11.6, 4.4$ Hz, 1H), 4.45 (m, 1H), 7.65 (t, $J = 7.6$ Hz, 2H), 7.75 (t, $J = 7.6$ Hz, 1H), 7.98 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 57.5 (CH), 58.5 (CH_2), 59.6 (CH_2), 65.6 (CH), 129.2 (CH), 130.6 (CH), 135.3 (CH), 141.3 (C); HRMS m/z 246.0803 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_1\text{O}_4\text{S}_1$ 246.0800.

(2*S*,3*R*)-2-amino-4-(phenylsulfonyl)butane-1,3-diol hydrochloride (388). A solution of **379** (10.4 mg, 27 μmol) in MeOH (1 mL) with 1% HCl was stirred for 24 hours at room temperature. The solution was concentrated under reduced pressure to give **388** (7.6 mg, quantitative) as a white solid.: IR (neat) ν 3220, 2946, 1596, 1504, 1448, 1301, 1145, 1083 cm^{-1} ; $[\alpha]_{\text{D}}^{22}$ -0.9 (c 0.46, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 3.35 (m, 1H), 3.55 (m, 2H), 3.66 (dd, $J = 11.6, 6.8$ Hz, 1H), 3.75 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.31 (m, 1H), 7.64 (t, $J = 7.2$ Hz, 2H), 7.74 (t, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 57.8 (CH), 60.2 (CH_2), 60.3 (CH_2), 64.5 (CH), 129.2 (CH), 130.5 (CH), 135.2 (CH), 141.5 (C); HRMS m/z 246.0791 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_1\text{O}_4\text{S}_1$ 246.0800.

(2*S*,3*S*)-2-acetamido-4-(phenylsulfonyl)butane-1,3-diy diacetate (389). To a 1:1 solution of acetic anhydride and pyridine (1.5 mL) was added **387** (8.1 mg, 29 μmol) and a catalytic amount of DMAP. The mixture was stirred for 20 hours at room temperature. The solution was concentrated to dryness under reduced pressure. Flash chromatography (silica, methanol : dichloromethane 1 : 9) provided **389** (10.6 mg, 99%) as a white solid. recrystallization from a mixture of hexane and IPA (9 : 1) afforded an analytical sample: mp 142-143 $^{\circ}\text{C}$; IR (neat) ν 3320, 2917, 2850, 1745, 1660, 1373, 1307, 1224, 1147 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +7.2$ (c 0.89, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.84 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 3.44-3.55 (m, 2H), 3.95 (dd, $J=11.6, 3.6$ Hz, 1H), 4.24 (dd, $J=11.6, 4.4$ Hz, 1H), 4.40 (m, 1H), 5.43 (m, 1H), 6.12 (d, $J=9.2$ Hz, 1H), 7.59 (t, $J=7.2$ Hz, 2H), 7.69 (t, $J=8.0$ Hz, 1H), 7.90 (d, $J=6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7 (CH_3), 20.9 (CH_3), 23.5 (CH_3), 50.3 (CH), 57.6 (CH_2), 62.3 (CH_2), 66.8 (CH), 128.2 (CH), 129.6 (CH), 134.2 (CH), 139.4 (C), 169.7 (C), 170.4 (C), 170.9 (C); HRESITOFMS m/z 372.1105 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_1\text{O}_7\text{S}_1$ 372.1117.

General procedure for synthesis of 390 and 391. Under an atmosphere of nitrogen, *t*-BuLi (579 μmol , 1.7 M in pentane) was added dropwise to a solution of **385** (101 mg, 187 μmol) in anhydrous THF at 0 $^{\circ}\text{C}$. The mixture was stirred for 30 minutes, cooled to -78 $^{\circ}\text{C}$ and hexamethylphosphoramide (487 μL , 2.80 mmol) was added. The solution was stirred for a further 15 minutes then **54** (51.3 mg, 224 μmol in THF) was added dropwise over 5 minutes. The solution was stirred for 6 hours then warmed to -40 $^{\circ}\text{C}$ and held for 16 hours. The reaction was quenched with 15 mL saturated aqueous NH_4Cl . The mixture was extracted with ethyl ether (5×15 mL) and combined extracts washed with water (15

mL), brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was resuspended in anhydrous THF (5 mL) and 0.5 mL anhydrous MeOH added. The solution was cooled to 0 °C and NaBH₄ (30 mg, 793 μmol) added. The reaction mixture was warmed to room temperature and stirring continued for 3 hours. The reaction was quenched with 15 mL saturated aqueous NH₄Cl. The mixture was extracted with ethyl ether (5 × 15 mL) and combined extracts washed with, brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 20% ethyl acetate in hexane) provided **390** and **391** (49.7 mg, 35%, 1:1 ratio) as white solids as well as starting material **385** (28.4 mg).

(S)-tert-butyl 4-((1R,3S,4S)-5-(tert-butyldimethylsilyloxy)-4-(dibenzylamino)-1,3-dihydroxy-2-(phenylsulfonyl)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (390).

IR (neat) ν 3478, 3027, 2977, 2954, 2930, 2884, 2857, 1694, 1659, 1462, 1401, 1367, 1299, 1252, 1147, 838, 754, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.09-0.13 (m, 6H), 0.93-0.95 (m, 9H), 1.30-1.55 (bm, 15H), 2.62 (bs, 1H), 2.94-3.07 (m, 1H), 3.46 (d, J = 3.6 Hz, 1H), 3.50-3.65 (bm, 2H), 3.65-3.85 (bm, 1H), 3.85-4.00 (bm, 2H), 4.00-4.20 (bm, 2H), 4.23-4.40 (bm, 1H), 4.40-4.60 (bm, H), 5.26 (bs, 2H), 5.53 (bs, 1H), 7.10-7.35 (bm, 9H), 7.35-7.45 (bm, 2H), 7.50-7.60 (bm, 2H), 7.85-8.05 (bm, 2H); ¹³C NMR (100 MHz, CDCl₃) δ -5.5 (CH₃), -5.4 (CH₃), 18.2 (C), 26.0 (CH₃), 28.3 (CH₃), 28.4 (CH₃), 55.0 (CH₂), 55.1 (CH₂), 59.7 (CH₂), 60.5 (CH₂), 61.0 (CH), 61.3 (CH), 62.0 (CH), 62.2 (CH₂), 62.3 (CH), 64.3 (CH₂), 65.5 (CH), 81.1 (C), 94.5 (C), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.2 (CH), 130.8 (CH), 133.1 (CH), 139.5 (C), 141.9 (C); HRDCMMS m/z 769.3892 [M+H]⁺, calcd. for C₄₁H₆₁N₂O₈S₁Si₁ 769.3918.

(S)-tert-butyl 4-((1S,3S,4S)-5-(tert-butyldimethylsilyloxy)-4-(dibenzylamino)-1,3-dihydroxy-2-(phenylsulfonyl)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (391).

IR (neat) ν 3520, 3019, 2932, 2856, 1690, 1447, 1391, 1366, 1305, 1259, 1215, 1145, 1103, 836, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ -0.05--0.13 (bm, 6H), 0.78-0.95 (bm, 12H), 1.30-1.60 (bm, 12H), 3.00-4.60 (bm, 15H), 7.10-7.50 (bm, 13H), 7.97 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.7 (CH_3), -5.4 (CH_3), 18.0 (C), 25.9 (CH_3), 26.0 (CH_3), 28.5 (CH_3), 28.6 (CH_3), 53.9 (CH_2), 54.8 (CH_2), 55.1 (CH_2), 55.4 (CH_2), 60.1 (CH_2), 60.8 (CH_2), 61.6 (CH), 63.6 (CH_2), 68.4 (CH), 70.1 (CH), 70.8 (CH), 80.6 (C), 93.8 (C), 127.2 (CH), 128.5 (CH), 128.9 (CH), 129.3 (CH), 133.5 (CH), 138.6 (C), 139.5 (C), 140.0 (C), 153.2 (C); HRDCMMS m/z 769.3954 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{41}\text{H}_{61}\text{N}_2\text{O}_8\text{S}_1\text{Si}_1$ 769.3918.

(2S,3R,5S,6S)-2,6-diamino-4-(phenylsulfonyl)heptane-1,3,5,7-tetraol (392). To **390** (9.3 mg, 12.1 μmol) was added 1% HCl in methanol (1.5 mL) and Pd on carbon (26 mg, 24 μmol , 10% Pd on activated carbon). The mixture was placed on a Parr hydrogenator under H_2 (4 atm) and shaken for 16.5 hours. The solution was filtered through a celite plug and concentrated under reduced pressure. The residue was redissolved in 1 : 1 methanol : water and run through a C18 SPE cartridge (1 g) and eluted with 3 mL of 1% HCl in 1 : 1 methanol : water to obtain the hydrochloride salt of **392** (4.6 mg, 97%) as a white solid: IR (neat) ν 3235, 2924, 1989, 1593, 1509, 1303, 1147, 1051, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.38-4.10 (m, 10H), 4.46-4.58 (m, 1H), 4.70-4.80 (m, 1H), 5.75 (d, J = 3.6 Hz, 0.5H), 5.78 (d, J = 3.2 Hz, 0.2H), 7.55-8.10 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 57.2 (CH), 58.2 (CH_2), 58.4 (CH_2), 60.1 (CH_2), 65.5 (CH), 68.3 (CH),

129.8 (C), 130.0 (CH), 130.1 (C), 131.5 (CH), 135.2 (CH), 138.2 (C), 141.6 (C);

HRESITOFMS m/z 335.1264 $[M+H]^+$, calcd. for $C_{13}H_{23}N_2O_6S_1$ 335.1277.

(2*S*,3*S*,5*S*,6*S*)-2,6-diamino-4-(phenylsulfonyl)heptane-1,3,5,7-tetraol (393). To **391**

(9.7 mg, 12.6 μ mol) was added 1% HCl in methanol (1.5 mL) and Pd on carbon (31 mg,

29 μ mol, 10% Pd on activated carbon). The mixture was placed on a Parr hydrogenator

under H_2 (4 atm) and shaken for 17 hours. The solution was filtered through a celite plug

and concentrated under reduced pressure. The residue was redissolved in 1 : 1 methanol :

water and run through a C18 SPE cartridge (1 g) and eluted with 3 mL of 1% HCl in 1 : 1

methanol : water to obtain the hydrochloride salt of **393** (5.14 mg, 99%) as a white solid:

IR (neat) ν 3224, 3045, 2927, 1988, 1597, 1502, 1447, 1292, 1146, 1050 cm^{-1} ; $[\alpha]_D^{22} -$

13.9 (c 0.71, CH_3OH); 1H NMR (400 MHz, $CDCl_3$) δ 3.60-4.00 (m, 5H), 4.14 (t, $J = 2.8$

Hz, 1H), 4.55 (d, $J = 5.6$ Hz, 1H), 4.74 (m, 1H), 5.00 (m, 1H), 7.68 (t, $J = 7.6$ Hz, 2H),

7.78 (t, $J = 7.6$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0

(CH), 56.3 (CH), 59.1 (CH_2), 59.9 (CH_2), 66.3 (CH), 66.5 (CH), 69.4 (CH), 130.0 (CH),

130.6 (CH), 135.6 (CH), 140.0 (C); HRESITOFMS m/z 335.1278 $[M+H]^+$, calcd. for

$C_{13}H_{23}N_2O_6S_1$ 335.1277.

(*S*)-tert-butyl 4-((4*R*,6*S*)-2,2-di-tert-butyl-6-((*S*)-2-(tert-butyldimethylsilyloxy)-1-

(dibenzylamino)ethyl)-5-(phenylsulfonyl)-1,3,2-dioxasilinan-4-yl)-2,2-

dimethyloxazolidine-3-carboxylate (396). Under an atmosphere of nitrogen, **395** (23.6

mg, 26 μ mol) was added to a solution of **390** (20.0 mg, 26 μ mol) and 2,6-lutidine (9.0

mg, 84 μ mol) in anhydrous DCM (100 μ L) at room temperature. The mixture was stirred

for 14 hours then quenched with saturated NH_4Cl solution (2 mL). The mixture was extracted with ethyl ether (3×5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 12% ethyl acetate in hexane) provided **396** (14.9 mg, 63%) as a viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 8.10-7.10 (bm, 25H), 6.50-6.35 (bm, 1H), 4.60-3.50 (bm, 13H), 2.00-0.80 (m, 31H); ESIMS m/z 927.2 $[\text{M}+\text{H}_3\text{O}]^+$, calcd. for $\text{C}_{49}\text{H}_{79}\text{N}_2\text{O}_9\text{S}_1\text{Si}_2$ 927.50.

2,6-dimethyl-4-(phenylsulfonyl)heptane-3,5-diol (399). Under an atmosphere of nitrogen, *n*-BuLi (27 mL, 67.4 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of sulfone **368** (5.01 g, 32.1 mmol) in anhydrous THF at 0 °C. The mixture was stirred for 30 minutes then cooled to -100 °C and isobutyraldehyde (6.41 mgL 70.6 mmol in THF) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 16 hours. The solution was cooled to 0 °C and quenched with 150 mL saturated aqueous NH_4Cl , extracted with ethyl ether (4×50 mL) and combined extracts washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 30% ethyl acetate in hexane) provided **399** (6.40 g, 66%, mixture of diastereomers) as a viscous oil. All silica fractions contained at least 3 compounds and were used without further characterization.

4,6-diisopropyl-2-phenyl-5-(phenylsulfonyl)-1,3-dioxane (403). Sulfone **399** (1.31 g, 4.36 mmol), benzaldehyde dimethoxy acetal (1.45 mL, 10.5 mmol) and camphorsulfonic acid (10.1 mg, 436 μmol) in dimethylformamide (4.5 mL) were heated to 55 °C for 20

hours under an atmosphere of nitrogen. The mixture was quenched by the addition of solid NaHCO_3 , stirred for 30 min, then diluted with water and extracted with 1 : 1 ethyl ether : hexane (3×50 mL). Combined extracts washed with saturated aqueous NaHCO_3 (150 mL), brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 1 : 16 ethyl acetate : hexane) provided **403** and a mixture of **404a** and **404b** (692 mg, 41%, 1 : 1 : 2 respectively by wt. and NMR) as well as 33% recovered **399**. Compound **403** was a solid and the mixture of **404a** and **404b** was a clear viscous oil. Stereochemistry for compound **399** was determined by the large coupling (9.0 Hz) of the protons in the dioxane ring as well as an observed nOe between the ring acetal proton at δ 5.37 ppm and the ring protons at δ 4.04 ppm.

Characterization for **403**: IR (neat) ν 3066, 3033, 2963, 2933, 2874, 1467, 1447, 1402, 133366, 1306, 1214, 1136, 1098, 1083, 1029, 755, 720, 700, 646, 605 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (d, $J = 6.8$ Hz, 6H), 1.02 (d, $J = 6.8$ Hz, 6H), 2.36 (hep.d, $J = 6.8, 2.8$ Hz, 2H), 3.50 (t, $J = 9.0$ Hz, 1H), 4.04 (dd, $J = 9.0, 2.8$ Hz, 2H), 5.37 (s, 1H), 7.32-7.42 (m, 5H), 7.62 (t, $J = 7.6$ Hz, 2H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 15.3 (CH_3), 20.0 (CH_3), 31.0 (CH), 61.1 (CH), 78.4 (CH), 98.7 (CH), 126.0 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 129.5 (CH), 134.2 (CH), 138.5 (C), 139.5 (C); LRMS m/z 411.1 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{22}\text{H}_{28}\text{Na}_1\text{O}_4\text{S}_1$ 411.1606.

General procedure for synthesis of 407 and 408. Under an atmosphere of nitrogen, *t*-BuLi (1.25 mmol, 1.7 M in pentane) was added dropwise to a solution of 1,3-dithiane (155 mg, 1.25 mmol) in anhydrous THF at -50 °C. The mixture was stirred for 30 min

then **193** (468 mg, 1.22 mmol in THF) was added dropwise over 5 min. The solution was stirred for 30 min at $-50\text{ }^{\circ}\text{C}$ then warmed to $-20\text{ }^{\circ}\text{C}$ over 45 min and quenched with 15 mL saturated aqueous NH_4Cl . The mixture was extracted with ethyl ether (5x20 mL) and combined extracts washed with brine (5 mL), dried over NaSO_4 and concentrated under reduced pressure. Flash chromatography (Analogix 40 g silica cartridge, 7% ethyl acetate in hexane) provided **407** and **408** (485 mg, 79%, 1:10 ratio by NMR) as pale yellow viscous oils.

(2S)-3-(tert-butyldimethylsilyloxy)-2-(dibenzylamino)-1-(1,3-dithian-2-yl)propan-1-ol (407). IR (neat) ν 3431, 3085, 3062, 3026, 2952, 2927, 2894, 2855, 1602, 1494, 1470, 1454, 1360, 1253, 1138, 1094, 975, 837, 777, 750, 699 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +2.4$ (c 4.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.95 (s, 9H), 1.85-2.05 (m, 2H), 2.57 (ddd, $J = 13.6, 9.6, 3.2$ Hz, 1H), 2.71 (m, 1H), 2.83 (m, 1H), 2.99 (m, 1H), 3.20 (m, 1H), 3.60 (d, $J = 12.8$ Hz, 2H), 3.88-4.04 (m, 5H), 4.39 (s, 1H), 7.20-7.35 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.49 (CH_3), -5.34 (CH_3), 18.2 (C), 26.0 (CH_3), 26.1 (CH_2), 29.1 (CH_2), 29.9 (CH_2), 49.6 (CH), 54.8 (CH_2), 59.7 (CH), 60.0 (CH_2), 71.7 (CH), 127.3 (CH), 128.6 (CH), 129.3 (CH), 139.1 (C); HRMS m/z 504.2437 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{27}\text{H}_{42}\text{N}_1\text{O}_2\text{Si}_1\text{S}_2$ 504.2426.

(2S)-3-(tert-butyldimethylsilyloxy)-2-(dibenzylamino)-1-(1,3-dithian-2-yl)propan-1-ol (408). IR (neat) ν 3466, 3084, 3061, 3026, 2953, 2928, 2894, 2856, 2710, 1946, 1872, 1806, 1602, 1493, 1471, 1453, 1422, 1360, 1251, 1092, 939, 910, 836, 777, 749, 698 cm^{-1} ; $[\alpha]_{\text{D}}^{22} -2.8$ (c 9.77, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.91 (m, 1H), 2.00 (m, 1H), 2.48 (ddd, $J = 14.0, 10.0, 2.8$ Hz, 1H), 2.72-2.86 (m, 2H), 2.95 (ddd, $J = 13.6, 6.8, 2.8$ Hz, 1H), 3.21 (m, 2H), 3.63 (d, $J = 13.6$ Hz,

2H), 3.87 (d, $J = 13.6$ Hz, 2H), 3.97 (dd, $J = 10.4, 5.2$ Hz, 1H), 4.05 (dd, $J = 10.4, 6.0$ Hz, 1H), 4.15 (dt, $J = 7.6, 4.0$ Hz, 1H), 4.31 (d, $J = 3.6$ Hz, 1H), 7.20-7.26 (m, 2H), 7.27-7.32 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.49 (CH_3), -5.43 (CH_3), 18.2 (C), 25.9 (CH_3), 26.0 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 50.3 (CH), 55.2 (CH_2), 59.1 (CH), 60.9 (CH_2), 75.7 (CH), 127.0 (CH), 128.3 (CH), 129.1 (CH), 140.0 (C); HRMS m/z 504.2437 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{27}\text{H}_{42}\text{N}_1\text{O}_2\text{Si}_1\text{S}_2$ 504.2426.

Phenyl(tetradecyl)sulfane (412). Under an atmosphere of nitrogen, $n\text{-Bu}_3\text{P}$ (7.26 mL, 29.1 mmol) was added dropwise to a solution of diphenyldisulfide (6.36 g, 29.1 mmol) in anhydrous THF at 0 °C. The mixture was stirred for 15 min then tetradecan-1-ol (5.0 g, 23.3 mmol in THF) was added dropwise. The solution was warmed to 24 °C over 24 hrs and quenched with 150 mL water and the mixture was extracted with ethyl ether (5×50 mL) and combined extracts washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 3% ethyl acetate in hexane) provided **412** (6.35 g, 92%) as white solid. Compound **412** matched literature values.

Phenyl(tetradecyl)sulfone (413). Under an atmosphere of nitrogen, finely ground KMnO_4 (2.5 g, 15.8 mmol) and MnO_4 (508 mg, 5.8 mmol) was added to a solution of **412** (1.0 g, 3.26 mmol) in anhydrous dichloromethane. The mixture was refluxed for 2 days then filtered through celite and rotovaped to dryness. Flash chromatography (silica, dichloromethane) provided **413** (1.04 g, 94%) as white solid. Compound **413** matched literature values.

(4S)-tert-butyl 4-(1-hydroxy-2-(phenylsulfonyl)pentadecyl)-2,2-dimethyloxazolidine-3-carboxylate (414). Under an atmosphere of nitrogen, *t*-BuLi (192 μ mol, 1.7 M in pentane) was added dropwise to a solution of **413** (65 mg, 192 μ mol) in anhydrous THF at -10 °C. The mixture was stirred for 15 min then cooled to -50 °C and **54** (43.7 mg, 191 μ mol in THF) was added dropwise over 5 min. The solution was warmed to 24 °C over 6 hrs and quenched with 5 mL saturated aqueous NH_4Cl . The mixture was extracted with ethyl ether (5×5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane then 25% ethyl acetate in hexane) provided **414**, **415a**, and **415b** (71.5 mg, 66%, 1 : 4 : 2 ratio) as pale yellow viscous oils.

Characterization for **414**: IR (neat) ν 3442, 2925, 2854, 1711, 1498, 1447, 1392, 1366, 1301, 1287, 1246, 1167, 1142, 1081, 847, 727, 690 cm^{-1} ; $[\alpha]_{\text{D}}^{22} -4.6$ (*c* 0.88, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ .88 (t, $J = 6.8$ Hz, 3H), 1.10-1.30 (bm, 22H), 1.45-1.60 (bm, 16H), 1.79 (bs, 1H), 3.12 (dt, $J = 10.8, 2.4$ Hz, 1H), 3.98 (bm, 1H), 4.14 (bm, 1H), 4.98 (bm, 1H), 5.11 (bs, 1H), 7.54(t, $J = 7.2$ Hz, 2H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.94 (d, $J = 7.2$ Hz, 2H); selected ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (CH_3), -22.8 (CH_2), 26.4 (CH_2), 28.4 (CH_3), 28.5 (CH_3), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.0 (CH_2), 52.1 (CH), 64.6 (CH_2), 67.5 (CH), 71.0 (CH), 80.1 (C), 99.4 (C), 128.1 (CH), 128.6 (CH), 129.0 (CH), 129.5 (CH), 133.6 (CH), 134.3 (CH), 137.8 (C), 156.0 (C); HRFABMS m/z 568.3662 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{31}\text{H}_{54}\text{N}_1\text{O}_6\text{S}_1$ 568.3672.

(2S)-2-amino-4-(phenylsulfonyl)heptadecane-1,3-diol (416). A solution of **414** (7.0 mg, 12.3 μmol) in MeOH (1 mL) with 1% HCl was stirred for 1 hour at room temperature. The solution was concentrated under reduced pressure to give the hydrochloride salt of **416** (5.7 mg, quantitative) as a white solid.: IR (neat) ν 3216, 2954, 2923, 2853, 1712, 1586, 1493, 1467, 1446, 1299, 1144, 1083, 759, 730, 689, 655 cm^{-1} ; $[\alpha]_{\text{D}}^{22} +0.1$ (c 0.73, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 0.90 (t, $J = 6.8$ Hz, 3H), 1.15-1.35 (bm, 22H), 1.78 (bm, 2H), 3.41 (m, 1H), 3.86 (dd, $J = 12.0, 5.2$ Hz, 1H), 3.91 (dd, $J = 12.0, 4.0$ Hz, 1H), 4.02 (p, $J = 4.0$ Hz, 1H), 4.18 (dd, $J = 8.0, 2.4$ Hz, 1H), 7.63 (t, $J = 7.2$ Hz, 2H), 7.73 (t, $J = 7.2$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4 (CH_3), 23.7 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 30.0 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (CH_2), 30.76 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 56.7 (CH), 60.3 (CH_2), 67.3 (CH), 68.4 (CH), 130.1 (CH), 130.3 (CH), 135.0 (CH), 140.9 (C); HRFABMS m/z 428.2831 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{23}\text{H}_{42}\text{N}_1\text{O}_4\text{S}_1$ 428.2835.

(S)-1-(tert-butyldimethylsilyloxy)-2-(dibenzylamino)-4-(phenylsulfonyl)heptadecan-3-ol (417). Under an atmosphere of nitrogen, *t*-BuLi (2.04 mL, 3.48 mmol, 1.7 M in pentane) was added dropwise to a solution of **413** (1.10 g, 3.25 mmol) in anhydrous THF at -20 $^\circ\text{C}$. The mixture was stirred for 2 hours then cooled to -78 $^\circ\text{C}$ and **193** (1.00 g, 2.60 mmol in THF) was added dropwise over 15 min. The solution was warmed to -30 $^\circ\text{C}$ over 2 hrs and quenched with 50 mL saturated aqueous NH_4Cl . The mixture was extracted with ethyl ether (5×50 mL) and combined extracts washed with brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexane then 25% ethyl acetate in hexane) provided **417** (1.52

g, 81% by NMR, mixture of diastereomers) and starting sulfone **413** as an inseparable viscous oil. Product was not characterized and was used as is.

(S)-1-(tert-butyldimethylsilyloxy)-2-(dibenzylamino)heptadecan-3-ol (418). Under an atmosphere of nitrogen, 6% NaHg (838 mg, 2.1 mmol) was added to a solution of **417** (330 mg, 0.45 mmol) and Na₂HPO₄ (308 mg, 2.16 mmol) in anhydrous MeOH at -20 °C. The mixture was stirred for 23 hours then the reaction was quenched with 25 mL saturated aqueous NH₄Cl. The mixture was extracted with ethyl ether (5 × 10 mL) and combined extracts washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (silica, 20% dichloromethane in hexane) provided **418** (76.6 mg, 38%, mixture of diastereomers 1 : 4.8 by NMR) as a viscous oil.: IR (neat) ν 3476, 3085, 3063, 3027, 2953, 2925, 2854, 2803, 1494, 1462, 1360, 1256, 1073, 836, 776, 746, 698 cm⁻¹; [α]_D²⁴ +0.6 (*c* 4.56, CHCl₃); For major diastereomer ¹H NMR (400 MHz, CDCl₃) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.91 (s, 9H), 1.26 (bm, 25H), 1.67 (m, 1H), 2.66 (q, *J* = 5.2 Hz, 1H), 3.00 (d, *J* = 4.8 Hz, 1H), 3.62 (d, *J* = 13.6 Hz, 2H), 3.83-3.92 (m, 3H), 3.97-4.05 (m, 2H), 7.20-7.35 (m, 10H); ¹³C NMR (100 MHz, CDCl₃) δ -5.48 (CH₃), -5.41 (CH₃), 14.3 (CH₃), 18.2 (C), 22.8 (CH₂), 25.6 (CH₂), 26.0 (CH₃), 29.5 (CH₂), 29.8 (CH₂), 29.9 (CH₂), 32.0 (CH₂), 35.1 (CH₂), 55.4 (CH), 61.3 (CH₂), 61.5 (CH), 72.4 (CH₂), 127.1 (CH), 128.4 (CH), 129.0 (CH), 140.2 (C); HRFABMS *m/z* 582.4735 [M+H]⁺, calcd. for C₃₇H₆₄N₁O₂Si₁ 582.4706.

(S)-2-(dibenzylamino)heptadecane-1,3-diol (420). Under an atmosphere of nitrogen, tetrabutylammonium fluoride (300 μ L, 300 μ mol, 1.0 M in THF) was added to a solution

of **418** (40 mg, 68.7 μmol) in anhydrous THF at room temperature. The mixture was stirred for 30 min then quenched with 20 mL saturated aqueous NH_4Cl . The mixture was extracted with ethyl ether (5×5 mL) and combined extracts washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (12 g Analogix silica column, 20% ethyl acetate in hexane) provided **419** and **420** (1 : 4.5) (28.2 mg, 88%) as viscous oils. Characterization for **420**: IR (neat) ν 3381, 3085, 3062, 3027, 2923, 2853, 2804, 1602, 1494, 1454, 1364, 1250, 1117, 1071, 1027, 747, 698 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ -1.0 (c 3.45, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.28 (bm, 24H), 1.65 (bm, 1H), 1.83 (bs, 1H), 2.69 (q, $J = 5.6$ Hz, 1H), 2.81 (bs, 1H), 3.69 (d, $J = 13.6$ Hz, 1H), 3.75-3.85 (bm, 3H), 3.94 (dd, $J = 11.2, 6.8$ Hz, 1H), 4.01 (bs, 1H), 7.21-7.35 (bm, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (CH_3), 22.8 (CH_2), 25.6 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 35.9 (CH_2), 54.7 (CH_2), 58.9 (CH_2), 62.3 (CH), 71.3 (CH), 127.3 (CH), 128.5 (CH), 129.1 (CH), 139.7 (C); HRFABMS m/z 468.3844 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{31}\text{H}_{50}\text{N}_1\text{O}_2$ 468.3842.

(2S)-2-aminoheptadecane-1,3-diol (421). To **420** (20 mg, 42.8 μmol) in methanol (1.5 mL) was added Pd on carbon (30 mg, 28 μmol , 10% Pd on activated carbon). The mixture was placed on a Parr hydrogenator under 4 atm of H_2 and shaken for 48 hrs. The solution was filtered through a celite plug and concentrated under reduced pressure. The residue was redissolved in 1% HCl in methanol and run through a C18 SPE cartridge (1 g) and eluted with 10 mL of 0.5% HCl in acetonitrile : methanol : water (2 : 1 : 1) to obtain the hydrochloride salt of **421** (9.4 mg, 68%) as a viscous oil.: IR (neat) ν 3331, 2917, 2850, 1596, 1497, 1467, 1159, 1124, 1048, 1018, 721 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ $+3.9$ (c 0.29, CH_3OH);

^1H NMR (400 MHz, CD_3OD) δ 0.90 (t, $J = 7.2$ Hz, 3H), 1.29 (bm, 24H), 1.49 (m, 2H), 3.91 (m, 1H), 3.69 (dd, $J = 11.4, 8.8$ Hz, 1H), 3.77 (m, 1H), 3.83 (dd, $J = 11.4, 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4 (CH_3), 23.7 (CH_2), 27.0 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (CH_2), 30.73 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 58.5 (CH_2), 58.8 (CH), 70.3 (CH); HRFABMS m/z 288.2898 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{17}\text{H}_{38}\text{N}_1\text{O}_2$ 288.2903.

7.2. X-ray CIF Data

Compound 271

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| _diffrn_measurement_method | 'phi and omega scans' |
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Refinement of F^2 against ALL reflections. The weighted R-factor wR and

goodness of fit S are based on F^2 , conventional R-factors R are based

on F, with F set to zero for negative F^2 . The threshold expression of

$F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is

not relevant to the choice of reflections for refinement. R-factors based

on F^2 are statistically about twice as large as those based on F, and R-

factors based on ALL data will be even larger.

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H7B H 0.3486 0.4795 0.9488 0.076 Uiso 1 1 calc R . .
C8 C 0.3805(5) 0.1705(4) 0.5357(2) 0.0509(13) Uani 1 1 d . . .
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H8B H 0.3500 0.1656 0.4865 0.076 Uiso 1 1 calc R . .
H8C H 0.3905 0.1017 0.5556 0.076 Uiso 1 1 calc R . .
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C10 C 0.1568(5) 0.1791(4) 0.5832(3) 0.0493(13) Uani 1 1 d . . .
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H10C H 0.1230 0.1746 0.5347 0.074 Uiso 1 1 calc R . .
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H13A H 0.1807 0.5254 0.8767 0.097 Uiso 1 1 calc R . .
H13B H 0.0706 0.5211 0.9341 0.097 Uiso 1 1 calc R . .
H13C H 0.0457 0.4864 0.8534 0.097 Uiso 1 1 calc R . .
C14 C 0.4997(4) 0.4333(3) 0.6270(2) 0.0330(10) Uani 1 1 d . . .
H14A H 0.4818 0.4524 0.5769 0.040 Uiso 1 1 calc R . .
H14B H 0.5016 0.3577 0.6299 0.040 Uiso 1 1 calc R . .
C15 C 0.6267(4) 0.4755(3) 0.6481(3) 0.0356(11) Uani 1 1 d . . .
C16 C 0.7110(5) 0.5068(4) 0.5966(3) 0.0498(13) Uani 1 1 d . . .
H16A H 0.6868 0.5080 0.5479 0.060 Uiso 1 1 calc R . .
C17 C 0.8330(5) 0.5371(5) 0.6161(4) 0.0688(18) Uani 1 1 d . . .
H17A H 0.8913 0.5556 0.5803 0.083 Uiso 1 1 calc R . .
C18 C 0.8666(5) 0.5396(4) 0.6867(4) 0.0659(18) Uani 1 1 d . . .
H18A H 0.9474 0.5617 0.7000 0.079 Uiso 1 1 calc R . .
C19 C 0.7826(5) 0.5099(4) 0.7384(3) 0.0578(15) Uani 1 1 d . . .
H19A H 0.8058 0.5110 0.7873 0.069 Uiso 1 1 calc R . .
C20 C 0.6635(5) 0.4782(4) 0.7187(3) 0.0480(13) Uani 1 1 d . . .
H20A H 0.6064 0.4580 0.7547 0.058 Uiso 1 1 calc R . .
C21 C 0.3801(4) 0.5824(3) 0.6617(2) 0.0380(11) Uani 1 1 d . . .
H21A H 0.3368 0.5919 0.6155 0.046 Uiso 1 1 calc R . .

H21B H 0.4626 0.6155 0.6577 0.046 Uiso 1 1 calc R . .
C22 C 0.3071(4) 0.6364(3) 0.7187(2) 0.0354(11) Uani 1 1 d . . .
C23 C 0.1892(5) 0.6791(4) 0.7048(3) 0.0452(12) Uani 1 1 d . . .
H23A H 0.1543 0.6711 0.6586 0.054 Uiso 1 1 calc R . .
C24 C 0.1220(5) 0.7325(4) 0.7562(3) 0.0538(14) Uani 1 1 d . . .
H24A H 0.0421 0.7592 0.7454 0.065 Uiso 1 1 calc R . .
C25 C 0.1726(5) 0.7460(4) 0.8230(3) 0.0525(14) Uani 1 1 d . . .
H25A H 0.1287 0.7834 0.8583 0.063 Uiso 1 1 calc R . .
C26 C 0.2891(6) 0.7043(4) 0.8384(3) 0.0555(15) Uani 1 1 d . . .
H26A H 0.3239 0.7132 0.8846 0.067 Uiso 1 1 calc R . .
C27 C 0.3539(5) 0.6505(3) 0.7873(3) 0.0410(12) Uani 1 1 d . . .
H27A H 0.4326 0.6223 0.7991 0.049 Uiso 1 1 calc R . .
N1 N 0.3985(3) 0.4725(3) 0.67354(18) 0.0282(8) Uani 1 1 d . . .
N2 N 0.5232(4) 0.4025(4) 0.8778(2) 0.0629(13) Uani 1 1 d . . .
N3 N 0.6181(4) 0.3738(4) 0.9072(2) 0.0587(12) Uani 1 1 d . . .
N4 N 0.7138(5) 0.3540(6) 0.9307(3) 0.102(2) Uani 1 1 d . . .
O1 O 0.2809(3) 0.3303(2) 0.55148(15) 0.0449(9) Uani 1 1 d . . .
O2 O 0.3413(2) 0.2341(2) 0.65038(14) 0.0295(7) Uani 1 1 d . . .
O3 O 0.1960(3) 0.3252(2) 0.85259(14) 0.0303(7) Uani 1 1 d . . .
O4 O 0.2251(3) 0.3759(3) 0.97094(17) 0.0558(10) Uani 1 1 d . . .

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_atom_site_aniso_U_22

_atom_site_aniso_U_33

_atom_site_aniso_U_23

_atom_site_aniso_U_13

_atom_site_aniso_U_12

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C2 0.030(2) 0.036(2) 0.033(2) 0.002(2) -0.005(2) -0.002(2)
C3 0.019(2) 0.032(2) 0.032(2) 0.0001(18) 0.0067(18) -0.0012(18)
C4 0.030(2) 0.025(2) 0.029(2) 0.0019(17) 0.0073(19) 0.0032(18)
C5 0.026(2) 0.031(2) 0.031(2) 0.0024(18) 0.0013(19) 0.0039(19)
C6 0.035(3) 0.043(3) 0.030(2) -0.003(2) 0.001(2) 0.009(2)
C7 0.048(3) 0.100(5) 0.040(3) -0.015(3) -0.008(3) 0.025(3)
C8 0.065(4) 0.052(3) 0.036(3) -0.014(2) -0.001(3) -0.012(3)
C9 0.053(3) 0.040(3) 0.025(2) -0.002(2) -0.006(2) -0.015(2)
C10 0.051(3) 0.052(3) 0.044(3) -0.001(3) -0.011(3) -0.013(3)
C11 0.053(3) 0.078(4) 0.060(4) -0.011(3) 0.027(3) -0.008(3)
C12 0.034(2) 0.045(3) 0.025(2) -0.001(2) 0.003(2) 0.004(2)
C13 0.064(4) 0.063(4) 0.066(4) 0.012(3) 0.018(3) 0.030(3)
C14 0.035(2) 0.029(2) 0.035(3) -0.0006(19) 0.001(2) -0.001(2)
C15 0.033(2) 0.025(2) 0.049(3) -0.006(2) 0.012(2) 0.004(2)
C16 0.050(3) 0.046(3) 0.054(3) -0.005(2) 0.020(3) -0.008(3)
C17 0.051(3) 0.060(4) 0.096(5) -0.006(4) 0.033(4) -0.028(3)
C18 0.038(3) 0.049(3) 0.111(6) -0.025(4) 0.002(3) -0.012(3)
C19 0.045(3) 0.054(3) 0.074(4) -0.027(3) -0.005(3) -0.001(3)
C20 0.041(3) 0.055(3) 0.048(3) -0.010(3) 0.004(2) -0.003(3)
C21 0.037(3) 0.037(2) 0.039(3) 0.004(2) 0.009(2) -0.002(2)
C22 0.044(3) 0.017(2) 0.045(3) 0.0009(19) 0.006(2) -0.008(2)
C23 0.039(3) 0.038(3) 0.059(3) 0.008(3) -0.004(2) 0.000(2)
C24 0.037(3) 0.034(3) 0.090(4) -0.011(3) 0.005(3) 0.004(2)
C25 0.052(3) 0.041(3) 0.065(4) -0.026(3) 0.011(3) -0.010(3)
C26 0.061(4) 0.053(3) 0.053(3) -0.016(3) -0.004(3) -0.020(3)
C27 0.036(3) 0.036(3) 0.051(3) 0.000(2) 0.002(2) -0.011(2)

N1 0.0283(18) 0.0227(17) 0.0337(19) 0.0009(16) 0.0051(16) 0.0050(16)
N2 0.039(3) 0.089(4) 0.061(3) 0.005(3) -0.015(2) -0.007(3)
N3 0.038(3) 0.094(4) 0.044(2) -0.019(3) 0.003(2) 0.006(3)
N4 0.038(3) 0.151(6) 0.118(5) -0.004(4) -0.021(3) 0.013(4)
O1 0.065(2) 0.0408(19) 0.0287(16) 0.0032(15) -0.0125(16) -0.0049(18)
O2 0.0295(16) 0.0337(16) 0.0254(15) -0.0026(13) -0.0020(13) 0.0011(13)
O3 0.0290(16) 0.0345(15) 0.0274(14) -0.0047(13) 0.0036(13) 0.0000(13)
O4 0.046(2) 0.081(3) 0.0398(19) -0.0129(18) 0.0017(16) 0.000(2)

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All esds (except the esd in the dihedral angle between two l.s. planes)

are estimated using the full covariance matrix. The cell esds are taken

into account individually in the estimation of esds in distances, angles

and torsion angles; correlations between esds in cell parameters are only

used when they are defined by crystal symmetry. An approximate (isotropic)

treatment of cell esds is used for estimating esds involving l.s. planes.

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C1 C2 1.520(6) . ?
C2 N1 1.475(5) . ?
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C3 O2 1.434(5) . ?
C3 C4 1.529(6) . ?
C4 C5 1.488(5) . ?
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C9 C10 1.538(6) . ?
C11 C12 1.500(7) . ?
C12 O3 1.412(5) . ?
C12 O4 1.413(5) . ?
C12 C13 1.491(7) . ?
C14 N1 1.470(5) . ?
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C15 C20 1.368(7) . ?
C15 C16 1.371(6) . ?
C16 C17 1.404(8) . ?
C17 C18 1.359(9) . ?
C18 C19 1.366(8) . ?
C19 C20 1.381(7) . ?

C21 N1 1.452(5) . ?
C21 C22 1.487(6) . ?
C22 C27 1.377(6) . ?
C22 C23 1.396(7) . ?
C23 C24 1.378(7) . ?
C24 C25 1.361(8) . ?
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N2 N3 1.208(6) . ?
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O2 C3 C4 105.2(3) . . ?
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C5 C4 C3 115.5(3) . . ?
O3 C5 C4 108.8(3) . . ?

O3 C5 C6 108.2(3) . . ?
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N2 C6 C5 107.0(4) . . ?
C7 C6 C5 109.5(4) . . ?
O4 C7 C6 113.2(5) . . ?
O1 C9 O2 110.1(3) . . ?
O1 C9 C8 106.7(4) . . ?
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C8 C9 C10 112.7(4) . . ?
O3 C12 O4 109.9(3) . . ?
O3 C12 C13 112.8(4) . . ?
O4 C12 C13 112.1(4) . . ?
O3 C12 C11 106.5(4) . . ?
O4 C12 C11 104.2(4) . . ?
C13 C12 C11 110.9(4) . . ?
N1 C14 C15 112.3(3) . . ?
C20 C15 C16 118.2(5) . . ?
C20 C15 C14 120.9(4) . . ?
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C15 C16 C17 120.6(5) . . ?
C18 C17 C16 119.9(5) . . ?
C17 C18 C19 119.9(5) . . ?
C18 C19 C20 119.9(5) . . ?
C15 C20 C19 121.6(5) . . ?
N1 C21 C22 115.0(4) . . ?

C27 C22 C23 116.3(4) . . ?
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 C23 C22 C21 121.6(4) . . ?
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 C21 N1 C2 112.0(3) . . ?
 C14 N1 C2 115.2(3) . . ?
 N3 N2 C6 117.8(5) . . ?
 N4 N3 N2 172.9(7) . . ?
 C9 O1 C1 115.0(3) . . ?
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Compound 312

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  '-x, y+1/2, -z'

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Refinement of F2 against ALL reflections. The weighted R-factor wR
and
goodness of fit S are based on F2, conventional R-factors R are
based
on F, with F set to zero for negative F2. The threshold expression
of
F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-factors
based
on F2 are statistically about twice as large as those based on F,
and R-
factors based on ALL data will be even larger.

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P=(Fo^2^+2Fc^2^)/3'
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C1 C 0.99896(15) 0.67046(12) 0.95939(13) 0.0151(3) Uani 1 1 d . . .
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C2 C 0.83500(16) 0.65592(12) 0.86358(13) 0.0151(3) Uani 1 1 d . . .
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C4 C 0.67163(16) 0.53002(12) 0.73111(14) 0.0167(3) Uani 1 1 d . . .
C5 C 0.73908(17) 0.78442(12) 0.66311(14) 0.0182(3) Uani 1 1 d . . .
C6 C 0.51727(17) 0.56956(13) 0.73086(15) 0.0232(3) Uani 1 1 d . . .
H6A H 0.4870 0.5297 0.8003 0.035 Uiso 1 1 calc R . .
H6B H 0.4418 0.5583 0.6386 0.035 Uiso 1 1 calc R . .
H6C H 0.5235 0.6462 0.7535 0.035 Uiso 1 1 calc R . .
C7 C 0.67118(16) 0.41333(12) 0.69429(15) 0.0209(3) Uani 1 1 d . . .

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H7A H 0.7750 0.3905 0.7046 0.031 Uiso 1 1 calc R . .
H7B H 0.6055 0.4025 0.5978 0.031 Uiso 1 1 calc R . .
H7C H 0.6327 0.3709 0.7564 0.031 Uiso 1 1 calc R . .
C8 C 1.00938(16) 0.65073(13) 1.11033(14) 0.0179(3) Uani 1 1 d . . .
H8A H 0.9257 0.6884 1.1309 0.021 Uiso 1 1 calc R . .
H8B H 1.0010 0.5731 1.1267 0.021 Uiso 1 1 calc R . .
C9 C 1.19820(19) 0.65187(13) 1.33449(14) 0.0224(3) Uani 1 1 d . . .
H9A H 1.1068 0.6415 1.3621 0.027 Uiso 1 1 calc R . .
H9B H 1.2636 0.7059 1.3977 0.027 Uiso 1 1 calc R . .
C10 C 1.42774(17) 0.56560(15) 1.34013(17) 0.0286(4) Uani 1 1 d . . .
H10A H 1.4195 0.5918 1.2472 0.043 Uiso 1 1 calc R . .
H10B H 1.4794 0.4960 1.3562 0.043 Uiso 1 1 calc R . .
H10C H 1.4863 0.6170 1.4103 0.043 Uiso 1 1 calc R . .
C11 C 1.25082(15) 0.66597(13) 0.93314(14) 0.0189(3) Uani 1 1 d . . .
H11A H 1.3242 0.6159 0.9146 0.023 Uiso 1 1 calc R . .
H11B H 1.2924 0.6875 1.0321 0.023 Uiso 1 1 calc R . .
C12 C 1.23687(16) 0.76419(13) 0.84349(15) 0.0181(3) Uani 1 1 d . . .
C13 C 1.26047(17) 0.86614(14) 0.90164(16) 0.0224(3) Uani 1 1 d . . .
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C14 C 1.25377(18) 0.95670(13) 0.82004(19) 0.0270(3) Uani 1 1 d . . .
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C15 C 1.22151(19) 0.94586(14) 0.67811(18) 0.0292(4) Uani 1 1 d . . .
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C16 C 1.19739(18) 0.84476(15) 0.61886(16) 0.0276(4) Uani 1 1 d . . .
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C18 C 1.13144(16) 0.49915(12) 0.96141(14) 0.0181(3) Uani 1 1 d . . .
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H21 H 1.4459 0.2427 0.8921 0.030 Uiso 1 1 calc R . .
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are estimated using the full covariance matrix. The cell esds are
taken
into account individually in the estimation of esds in distances,
angles
and torsion angles; correlations between esds in cell parameters are
only
used when they are defined by crystal symmetry. An approximate
(isotropic)
treatment of cell esds is used for estimating esds involving l.s.
planes.

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Refinement of F^2^ against ALL reflections. The weighted R-factor wR
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goodness of fit S are based on F^2^, conventional R-factors R are
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on F, with F set to zero for negative F^2^. The threshold expression
of
F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-factors
based
on F^2^ are statistically about twice as large as those based on F,
and R-
factors based on ALL data will be even larger. The H atoms are riding
on their
bonded carbons. The hydroxyl H was located on a difference Fourier map
and
refined with Uiso = 1.2 time the equivalent Uiso of the bonded H and a
distance restraint of 0.84(2)\%A.
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P=(Fo^2^+2Fc^2^)/3'

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O18 O 0.2756(2) 0.2861(2) 0.27145(9) 0.0235(5) Uani 1 1 d . . .
O19 O 0.1653(2) 0.1806(2) 0.35322(10) 0.0301(6) Uani 1 1 d . . .
O20 O 0.6362(2) 0.0449(2) 0.19556(10) 0.0261(5) Uani 1 1 d D . .
H20 H 0.681(3) -0.025(2) 0.2039(16) 0.031 Uiso 1 1 d D . .
O25 O 0.2517(2) 0.0392(2) 0.07655(10) 0.0293(6) Uani 1 1 d . . .
O26 O 0.3991(2) -0.1459(2) 0.12035(10) 0.0315(6) Uani 1 1 d . . .
N3 N 0.3672(3) 0.0978(2) 0.31939(11) 0.0217(6) Uani 1 1 d . . .
C2 C 0.3745(3) -0.0066(3) 0.37162(14) 0.0254(7) Uani 1 1 d . . .
C4 C 0.5000(3) 0.1086(3) 0.28593(13) 0.0220(7) Uani 1 1 d . . .
H4 H 0.5280 0.2066 0.2811 0.026 Uiso 1 1 calc R . .
C5 C 0.5939(3) 0.0353(3) 0.33315(15) 0.0246(8) Uani 1 1 d . . .
H5A H 0.6744 -0.0061 0.3115 0.030 Uiso 1 1 calc R . .
H5B H 0.6270 0.0989 0.3664 0.030 Uiso 1 1 calc R . .
C6 C 0.5007(3) 0.0358(3) 0.22164(13) 0.0223(7) Uani 1 1 d . . .
H6 H 0.4767 -0.0628 0.2281 0.027 Uiso 1 1 calc R . .
C7 C 0.4021(3) 0.0971(3) 0.17423(13) 0.0226(8) Uani 1 1 d . . .
H7A H 0.4361 0.1890 0.1620 0.027 Uiso 1 1 calc R . .
H7B H 0.3110 0.1090 0.1947 0.027 Uiso 1 1 calc R . .
C9 C 0.5131(3) 0.0413(3) 0.04987(14) 0.0252(8) Uani 1 1 d . . .

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C10 C 0.4880(4) 0.1463(4) 0.00702(15) 0.0339(9) Uani 1 1 d . . .
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H11 H 0.5721 0.2535 -0.0664 0.053 Uiso 1 1 calc R . . .
C12 C 0.7111(4) 0.1114(4) -0.03764(18) 0.0472(11) Uani 1 1 d . . .
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C13 C 0.7355(4) 0.0063(5) 0.00457(17) 0.0485(10) Uani 1 1 d . . .
H13 H 0.8208 -0.0417 0.0033 0.058 Uiso 1 1 calc R . . .
C14 C 0.6358(3) -0.0298(4) 0.04911(15) 0.0349(9) Uani 1 1 d . . .
H14 H 0.6521 -0.1021 0.0784 0.042 Uiso 1 1 calc R . . .
C15 C 0.3760(4) 0.0599(4) 0.43716(14) 0.0359(9) Uani 1 1 d . . .
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H15B H 0.3984 -0.0093 0.4692 0.054 Uiso 1 1 calc R . . .
H15C H 0.2849 0.0990 0.4462 0.054 Uiso 1 1 calc R . . .
C16 C 0.2678(4) -0.1172(3) 0.36499(17) 0.0360(9) Uani 1 1 d . . .
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C17 C 0.2684(3) 0.1954(3) 0.31187(15) 0.0227(8) Uani 1 1 d . . .
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C22 C -0.0463(4) 0.2059(4) 0.40388(19) 0.0510(11) Uani 1 1 d . . .
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H23C H 0.0855 0.4328 0.3036 0.066 Uiso 1 1 calc R . . .
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H24B H 0.0181 0.2235 0.2488 0.106 Uiso 1 1 calc R . . .
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C12 0.045(3) 0.061(3) 0.036(2) -0.020(2) 0.017(2) -0.029(2)
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 C21 0.0186(17) 0.033(2) 0.0330(18) 0.0026(17) 0.0015(16) 0.0018(16)
 C22 0.040(2) 0.048(3) 0.066(3) 0.018(2) 0.027(2) 0.018(2)
 C23 0.028(2) 0.035(2) 0.069(3) 0.002(2) 0.011(2) 0.0074(18)
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All esds (except the esd in the dihedral angle between two l.s.
 planes)
 are estimated using the full covariance matrix. The cell esds are
 taken
 into account individually in the estimation of esds in distances,
 angles
 and torsion angles; correlations between esds in cell parameters are
 only
 used when they are defined by crystal symmetry. An approximate
 (isotropic)
 treatment of cell esds is used for estimating esds involving l.s.
 planes.

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H5A C5 H5B 109.1 . . ?
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O18 C17 O19 124.9(3) . . ?
O18 C17 N3 123.1(3) . . ?

O19 C17 N3 112.0(3) . . ?
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Compound 389

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Refinement of F2 against ALL reflections. The weighted R-factor wR
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on F, with F set to zero for negative F2. The threshold expression
of
F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-factors
based
on F2 are statistically about twice as large as those based on F,
and R-

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factors based on ALL data will be even larger.

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;

All esds (except the esd in the dihedral angle between two l.s. planes)

are estimated using the full covariance matrix. The cell esds are taken

into account individually in the estimation of esds in distances, angles

and torsion angles; correlations between esds in cell parameters are only

used when they are defined by crystal symmetry. An approximate (isotropic)

treatment of cell esds is used for estimating esds involving l.s. planes.

;

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C6 S5 C4 105.62(9) . . ?
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C21 O20 C3 117.86(15) . . ?
C17 N16 C2 123.28(15) . . ?
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O12 C1 H1B 110.6 . . ?
C2 C1 H1B 110.6 . . ?
H1A C1 H1B 108.8 . . ?
N16 C2 C1 109.51(16) . . ?
N16 C2 C3 109.50(15) . . ?
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O20 C3 C4 107.35(15) . . ?

O20 C3 C2 107.66(14) . . ?
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C3 C4 S5 110.66(13) . . ?
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C3 C4 H4B 109.5 . . ?
S5 C4 H4B 109.5 . . ?
H4A C4 H4B 108.1 . . ?
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H14A C14 H14C 109.5 . . ?
H14B C14 H14C 109.5 . . ?
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C17 C18 H18B 109.5 . . ?
H18A C18 H18B 109.5 . . ?
C17 C18 H18C 109.5 . . ?
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H18B C18 H18C 109.5 . . ?
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O23 C21 C22 124.74(19) . . ?
O20 C21 C22 110.77(17) . . ?
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C21 C22 H22B 109.5 . . ?
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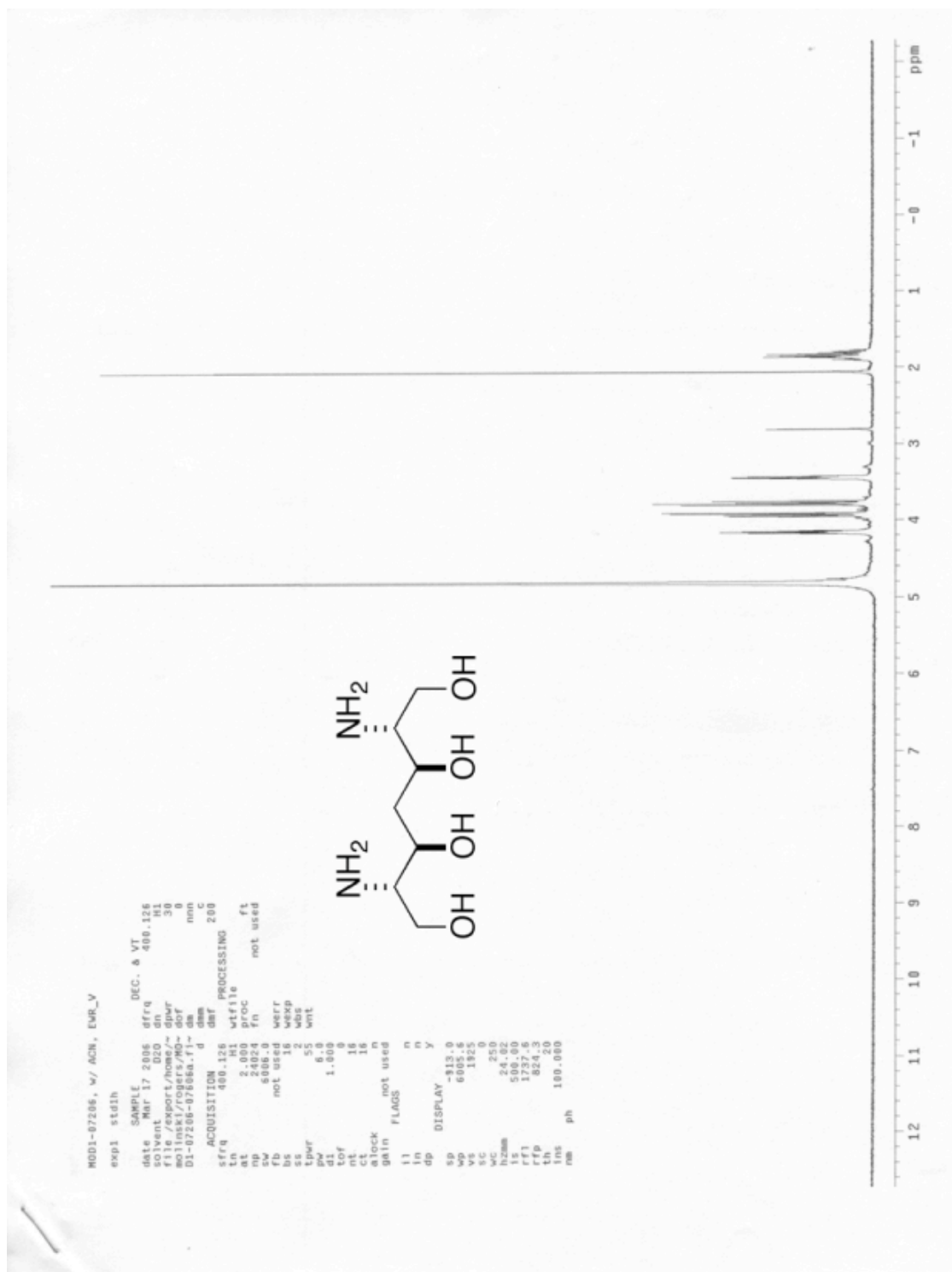
¹H NMR (CDCl₃, 400 MHz) of compound 220
¹³C NMR (CDCl₃, 100 MHz) of compound 220

¹³C NMR (D₂O, 100 MHz) of compound 224
¹H NMR (D₂O, 400 MHz) of compound 224

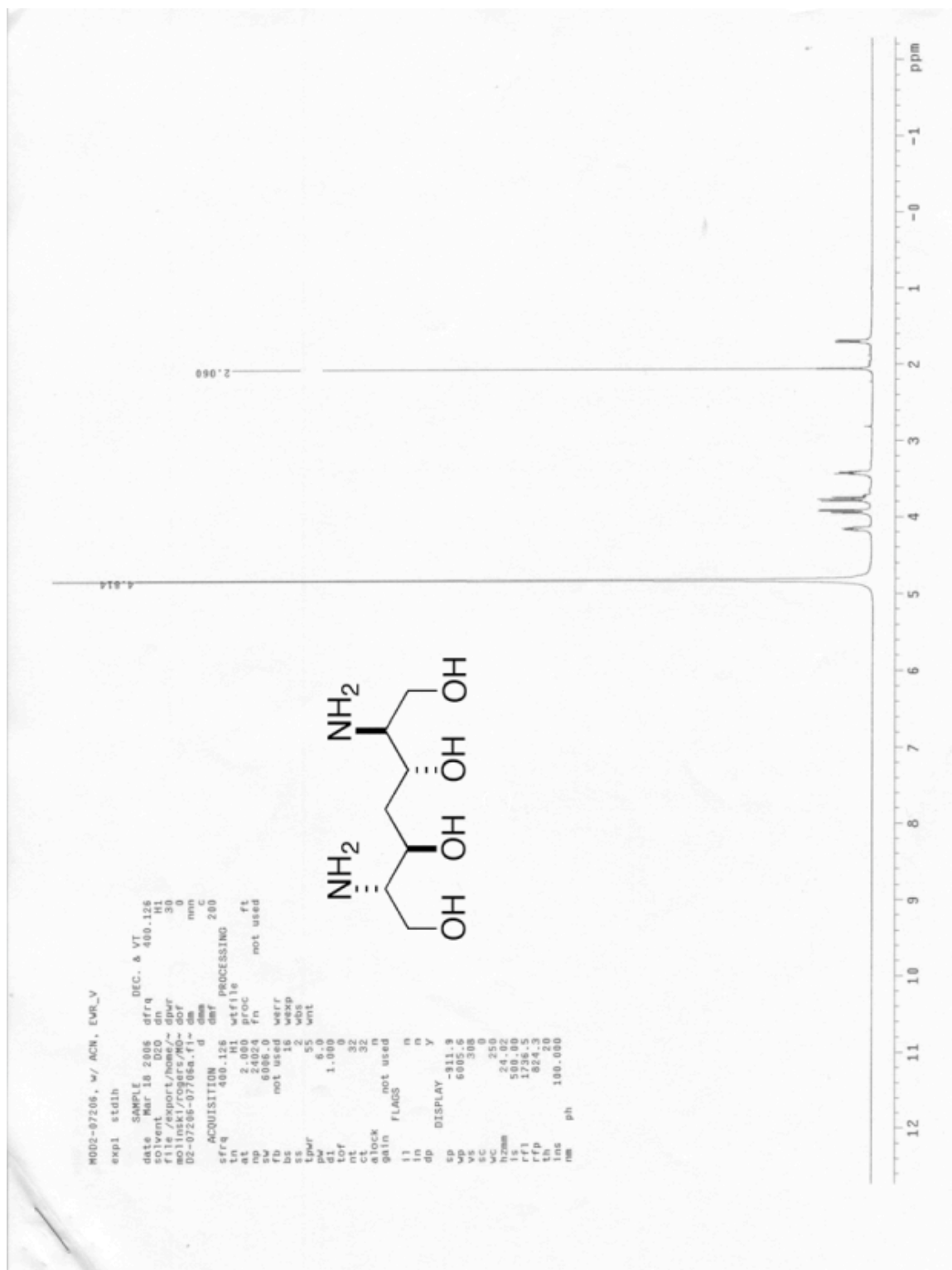
w/ 0.5% CH₃CN

7.3. Spectra

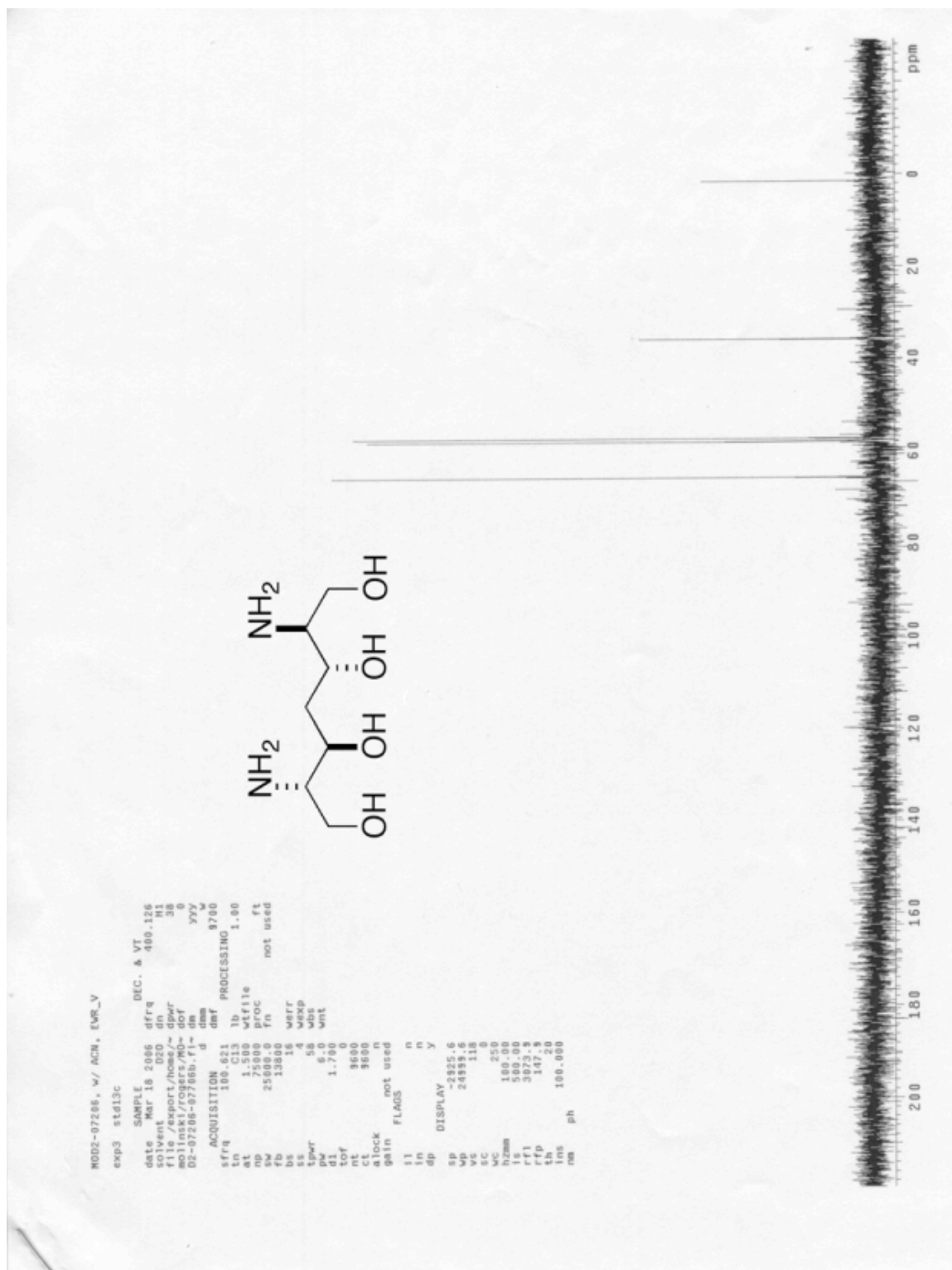
7.3.1. Chapter 2 Spectra



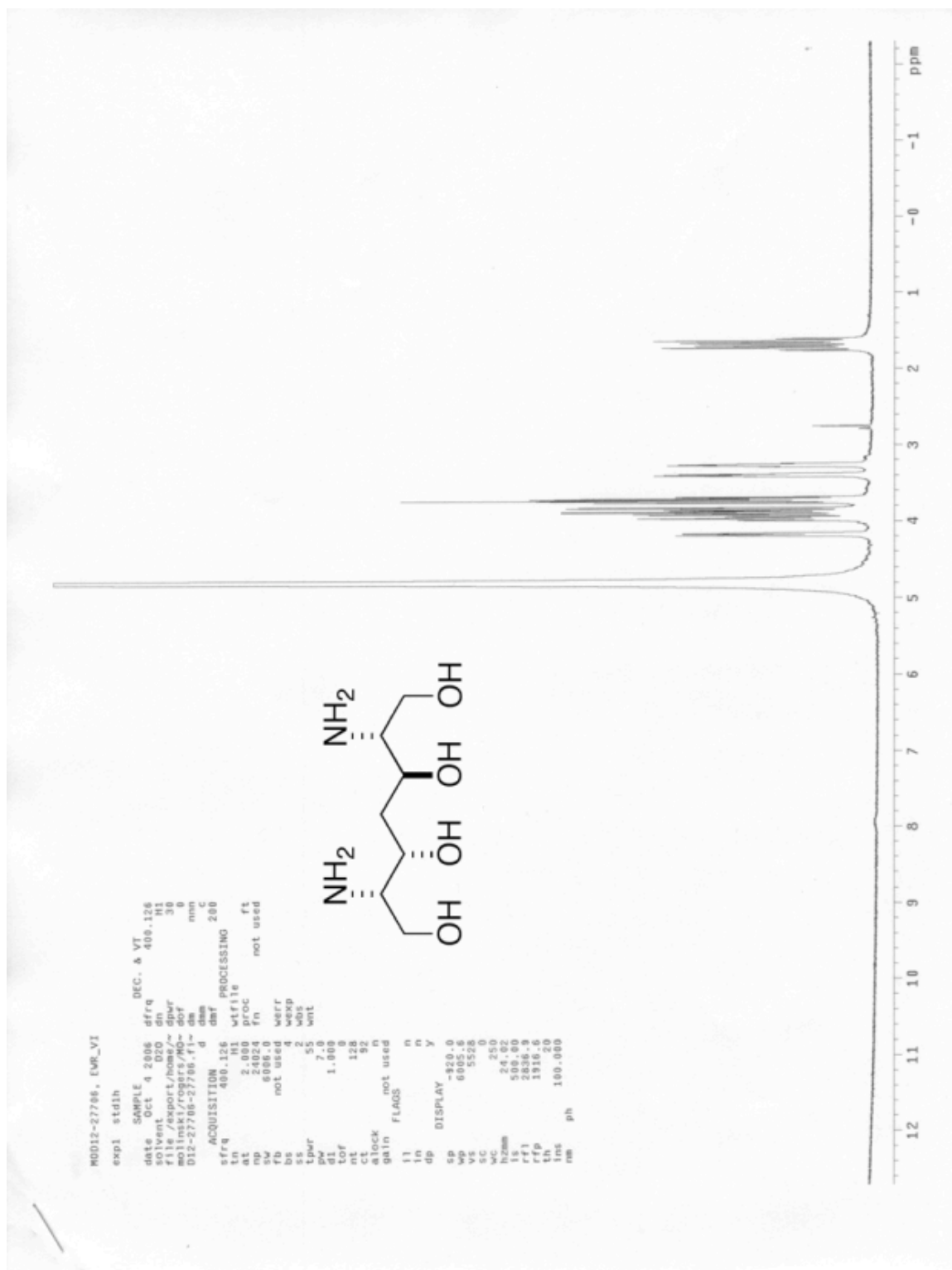
Spectrum 7.1: ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound **220**



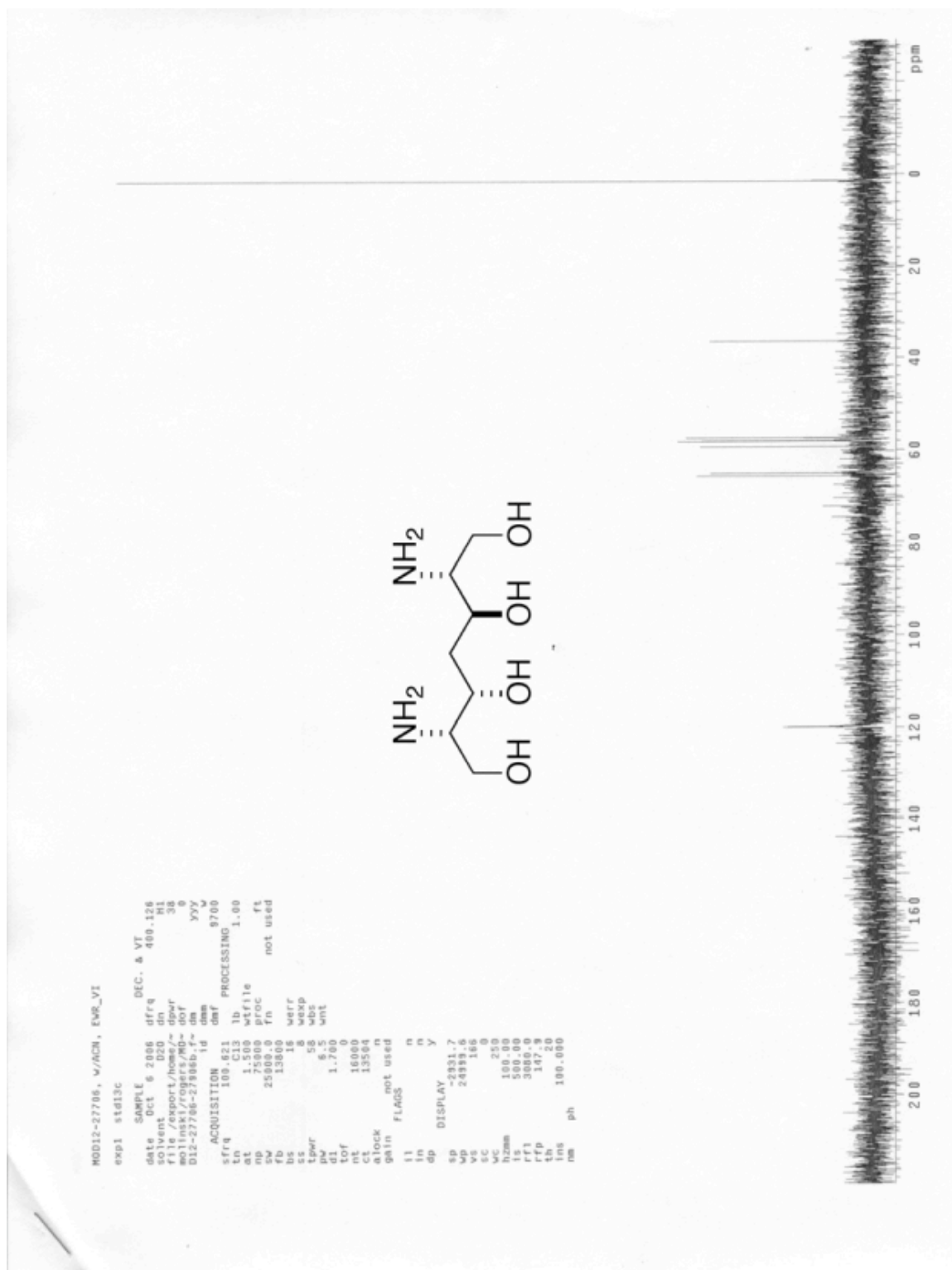
Spectrum 7.3: ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound **221**



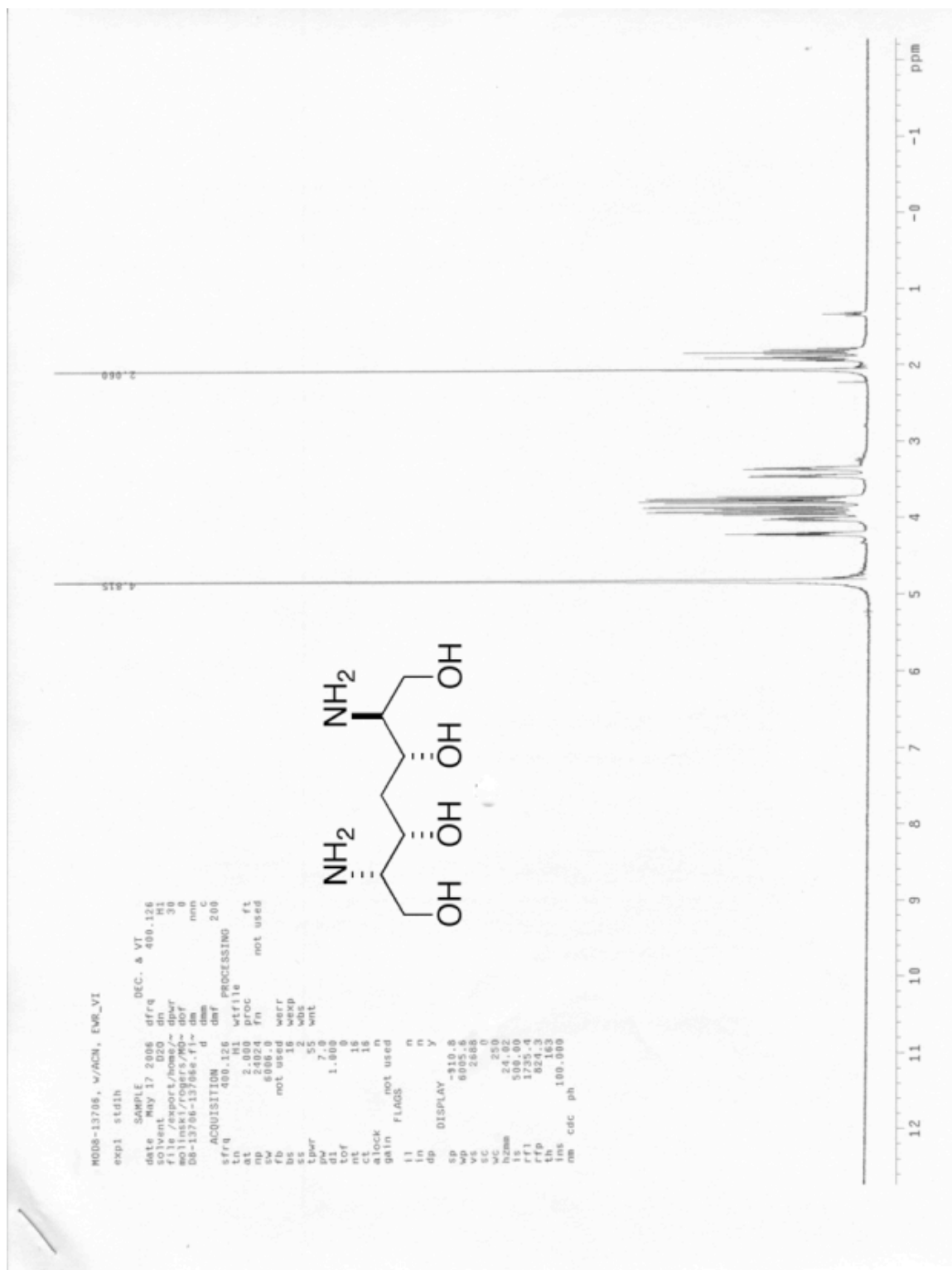
Spectrum 7.4: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 221



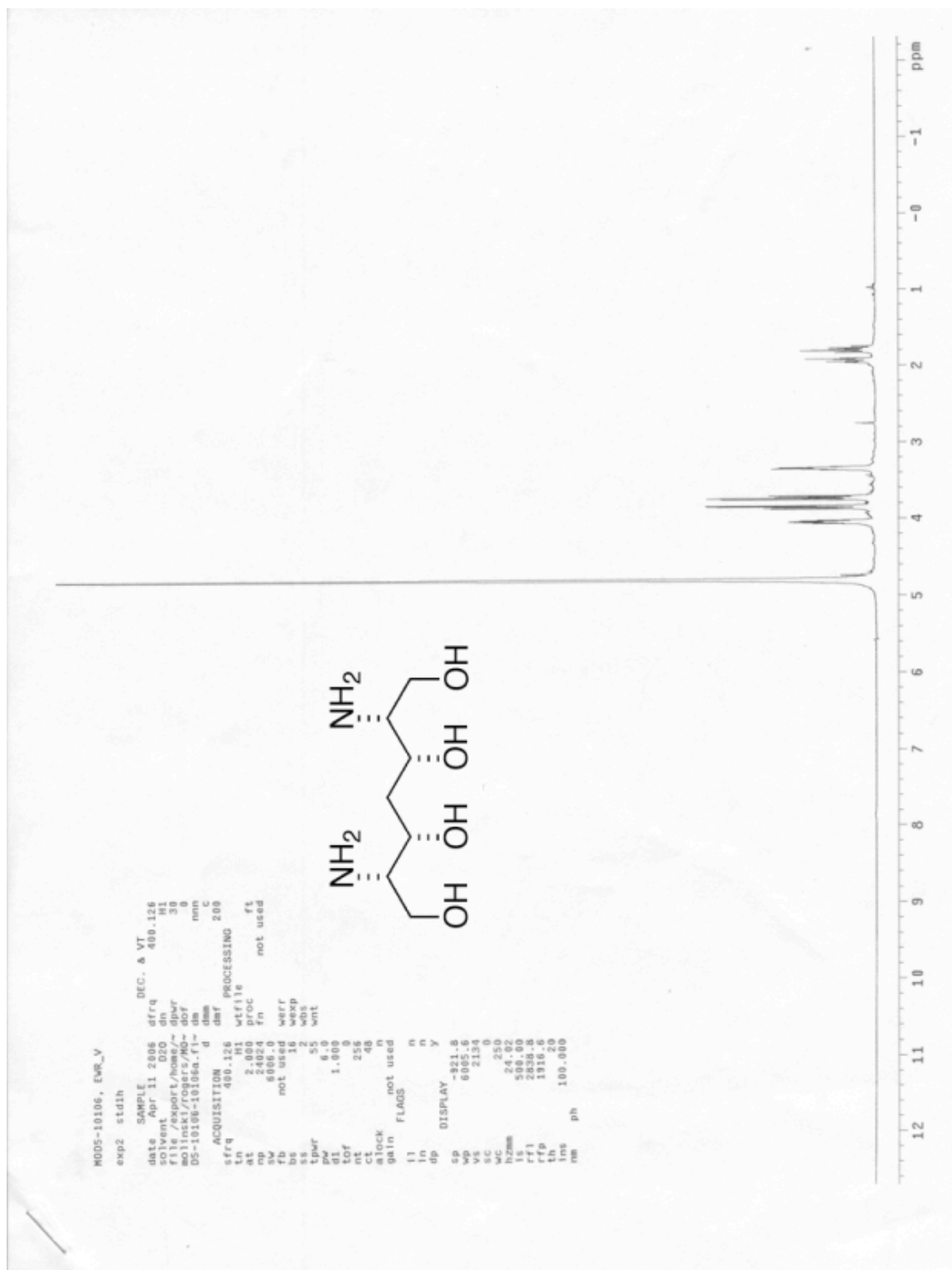
Spectrum 7.5: ^1H NMR (D_2O , 400 MHz) of compound 222



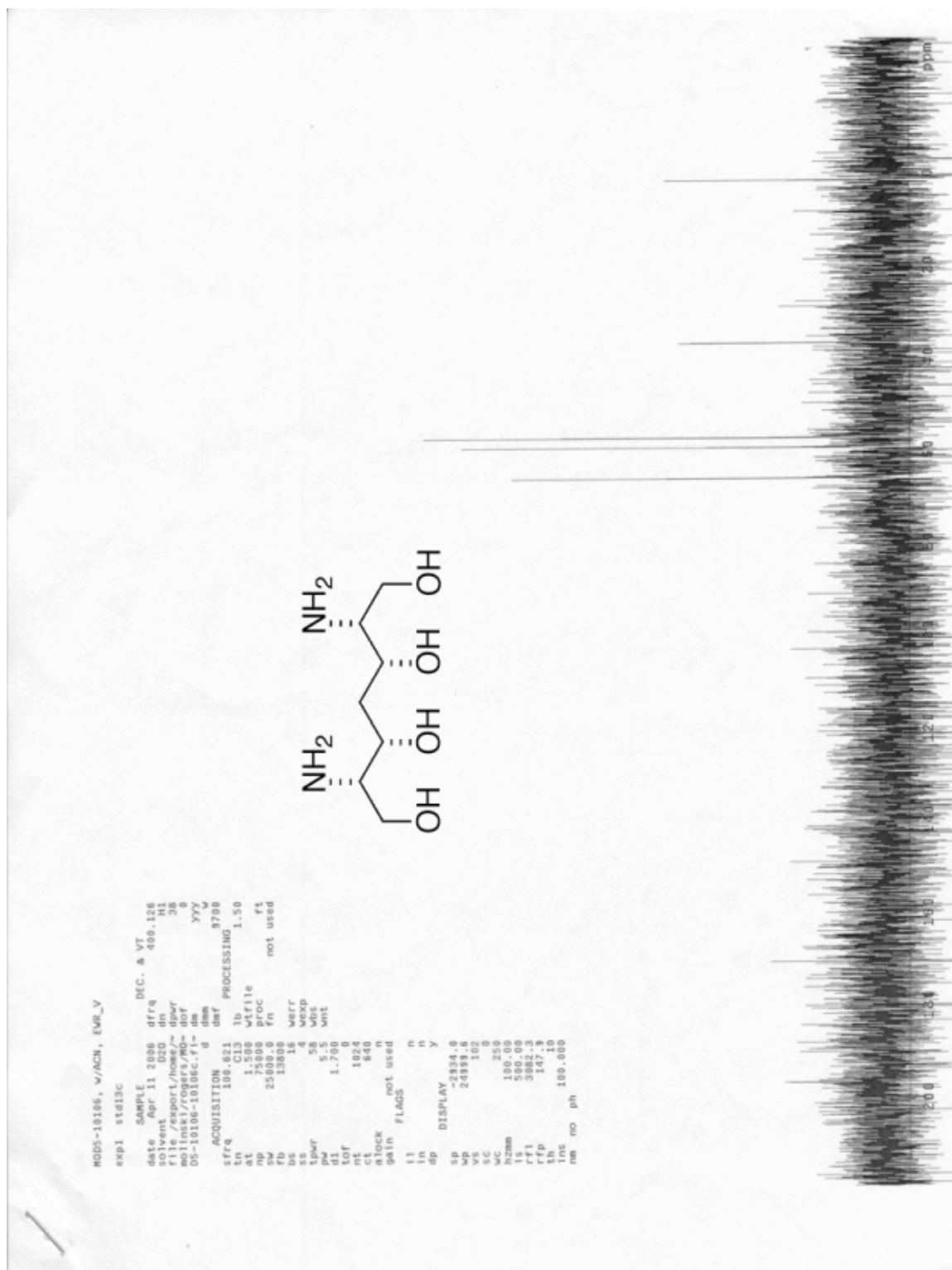
Spectrum 7.6: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound **222**



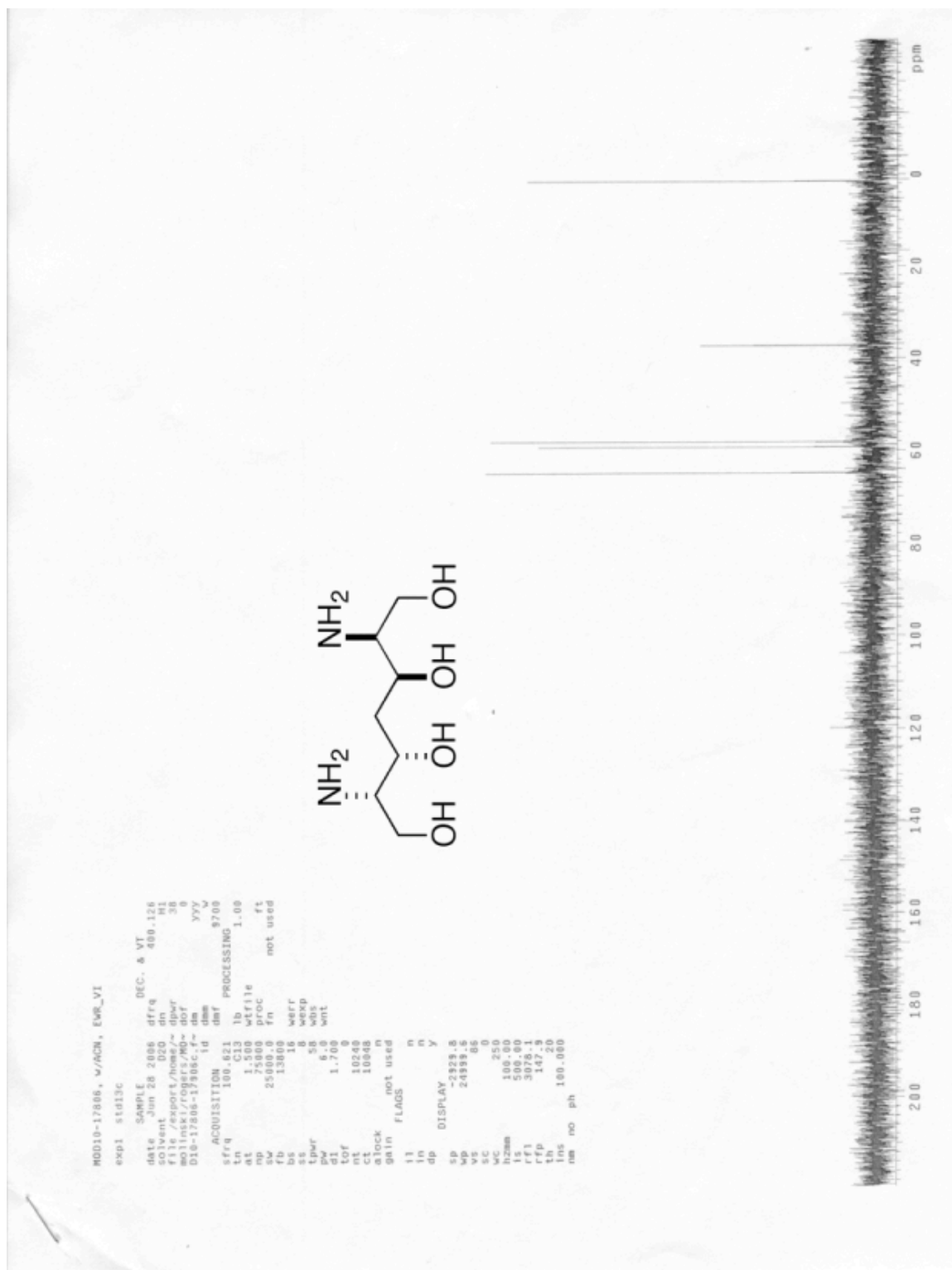
Spectrum 7.7: ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound **223**



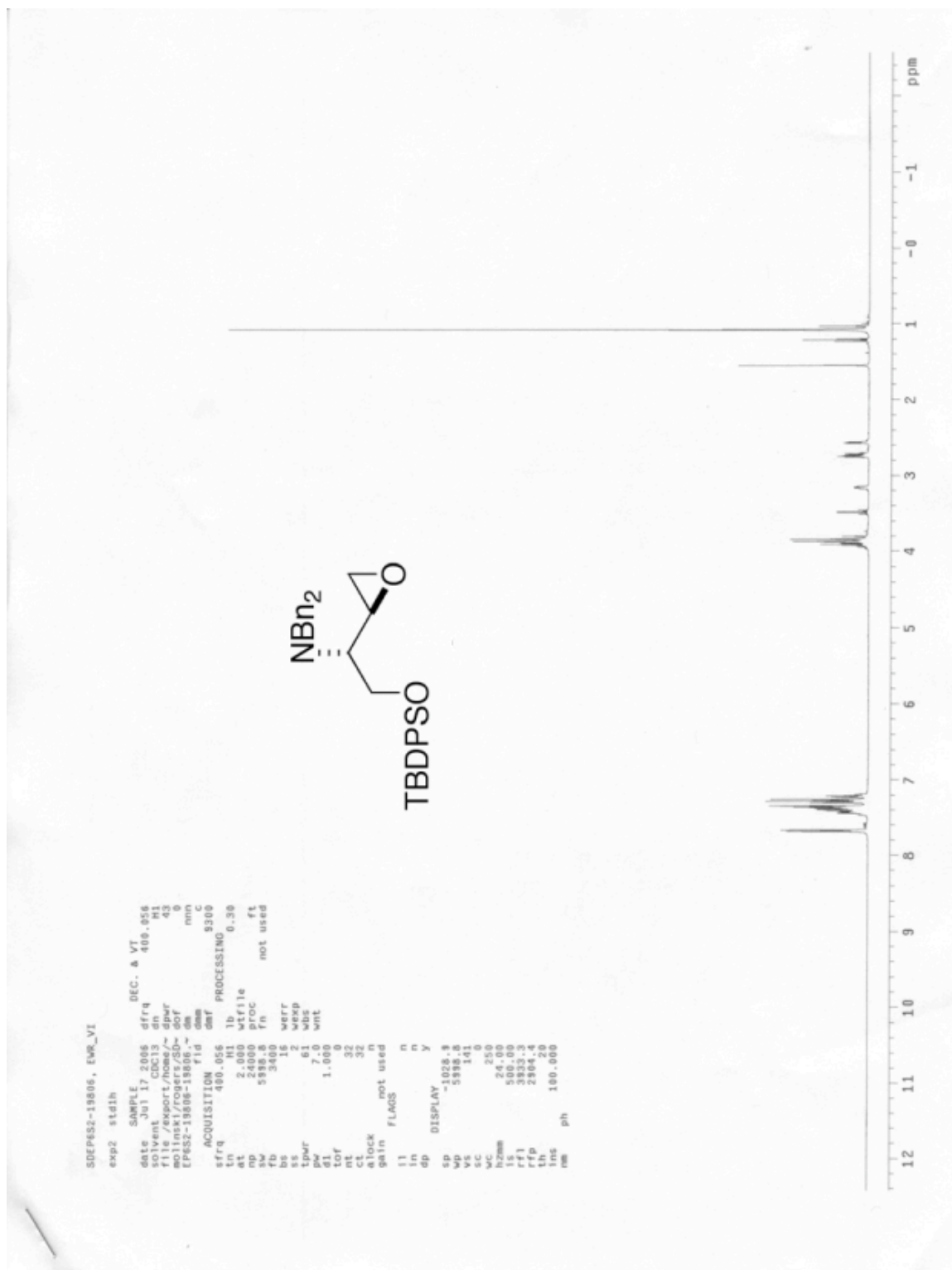
Spectrum 7.9: ^1H NMR (D_2O , 400 MHz) of compound **224**



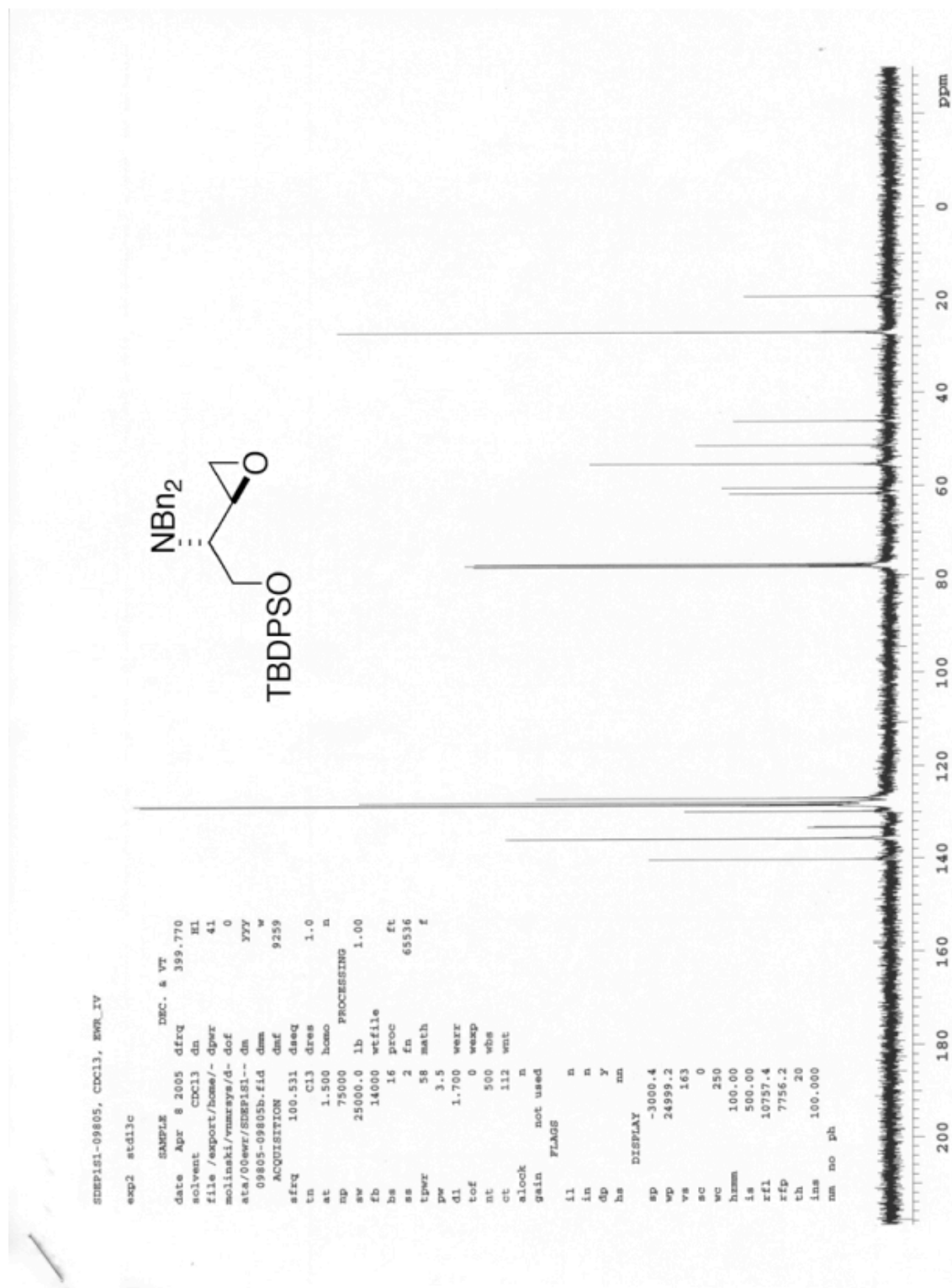
Spectrum 7.10: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound **224**



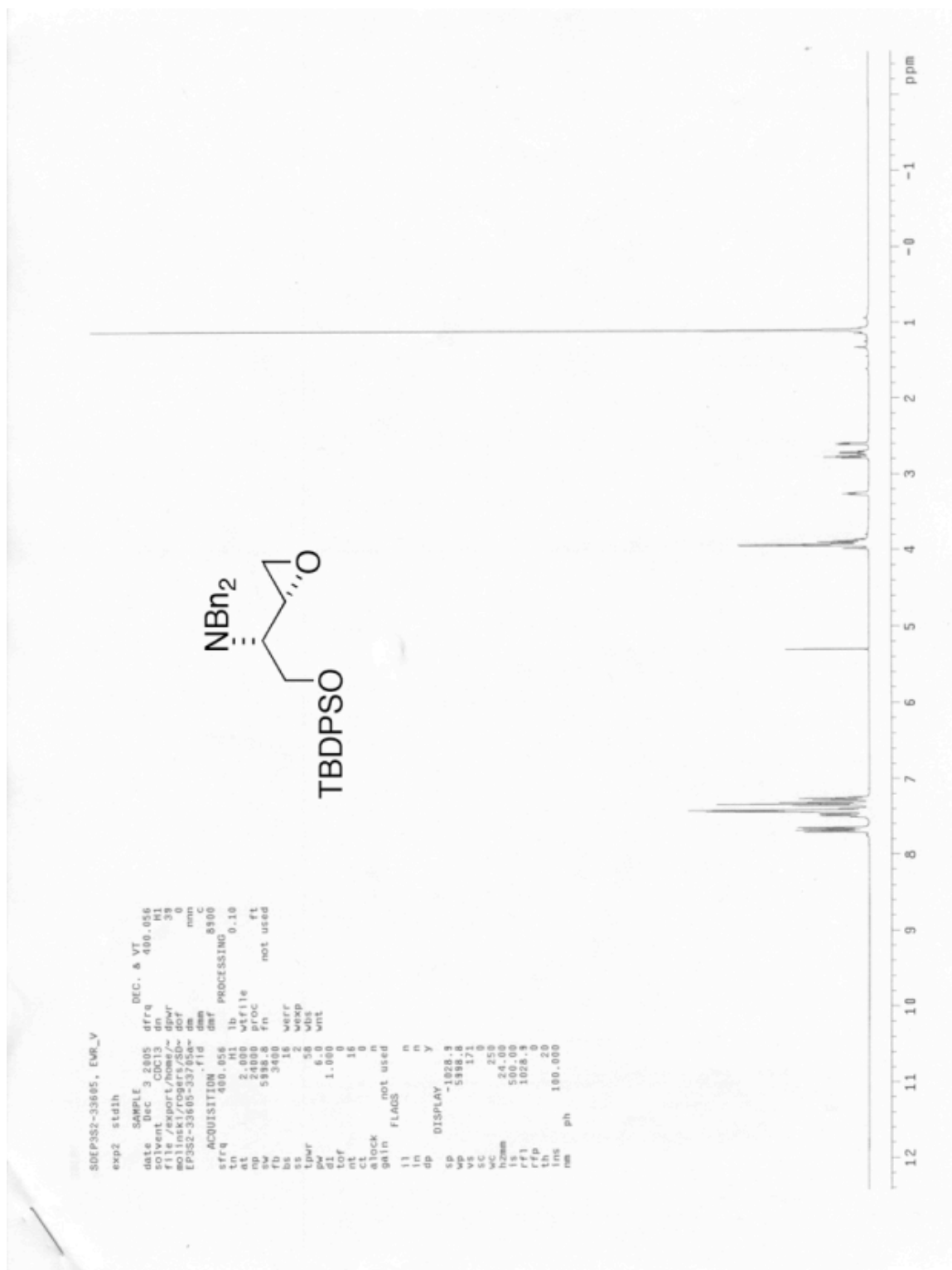
Spectrum 7.12: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound **225**



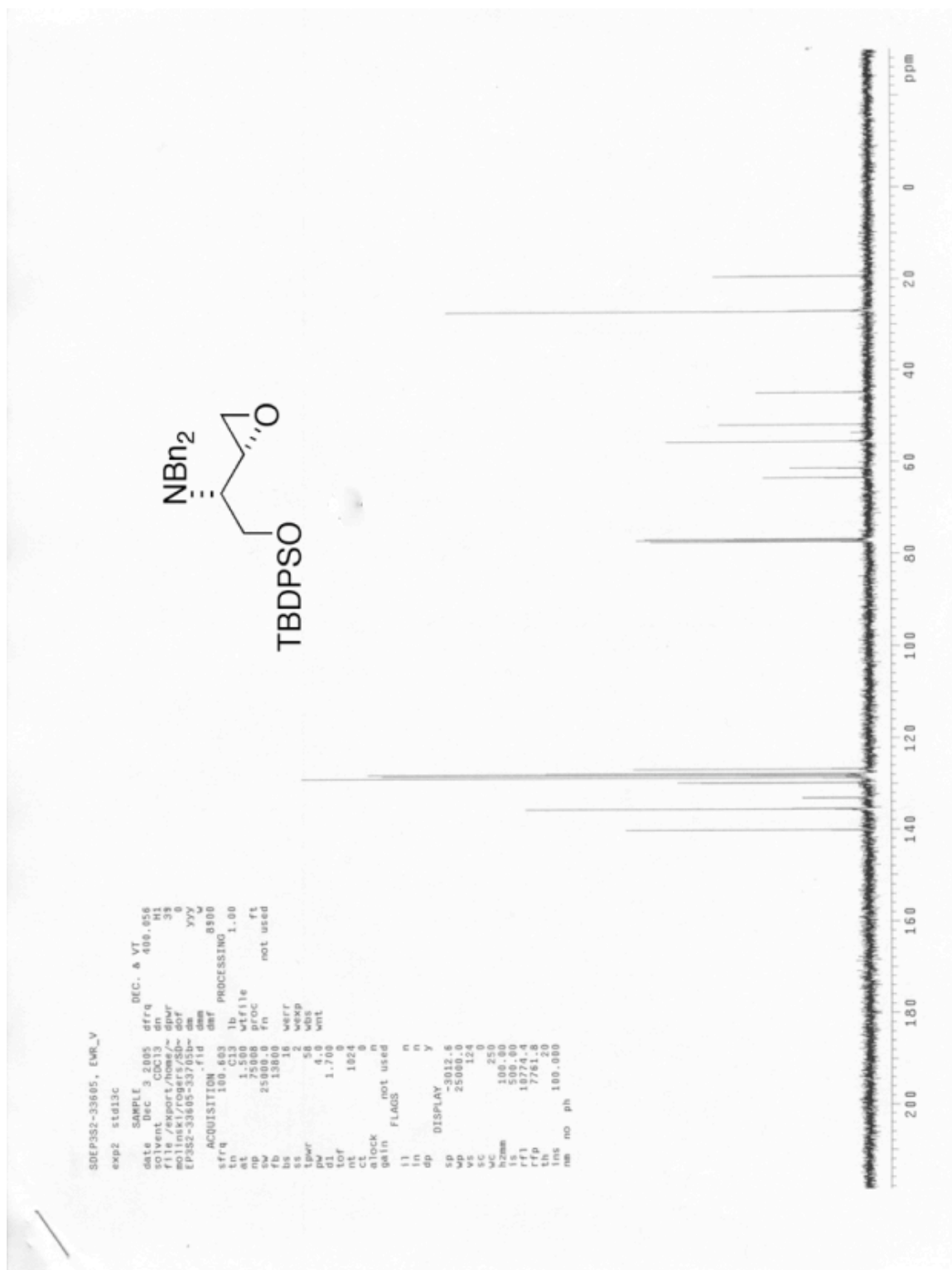
Spectrum 7.13: ^1H NMR (CDCl_3 , 400 MHz) of compound **228**



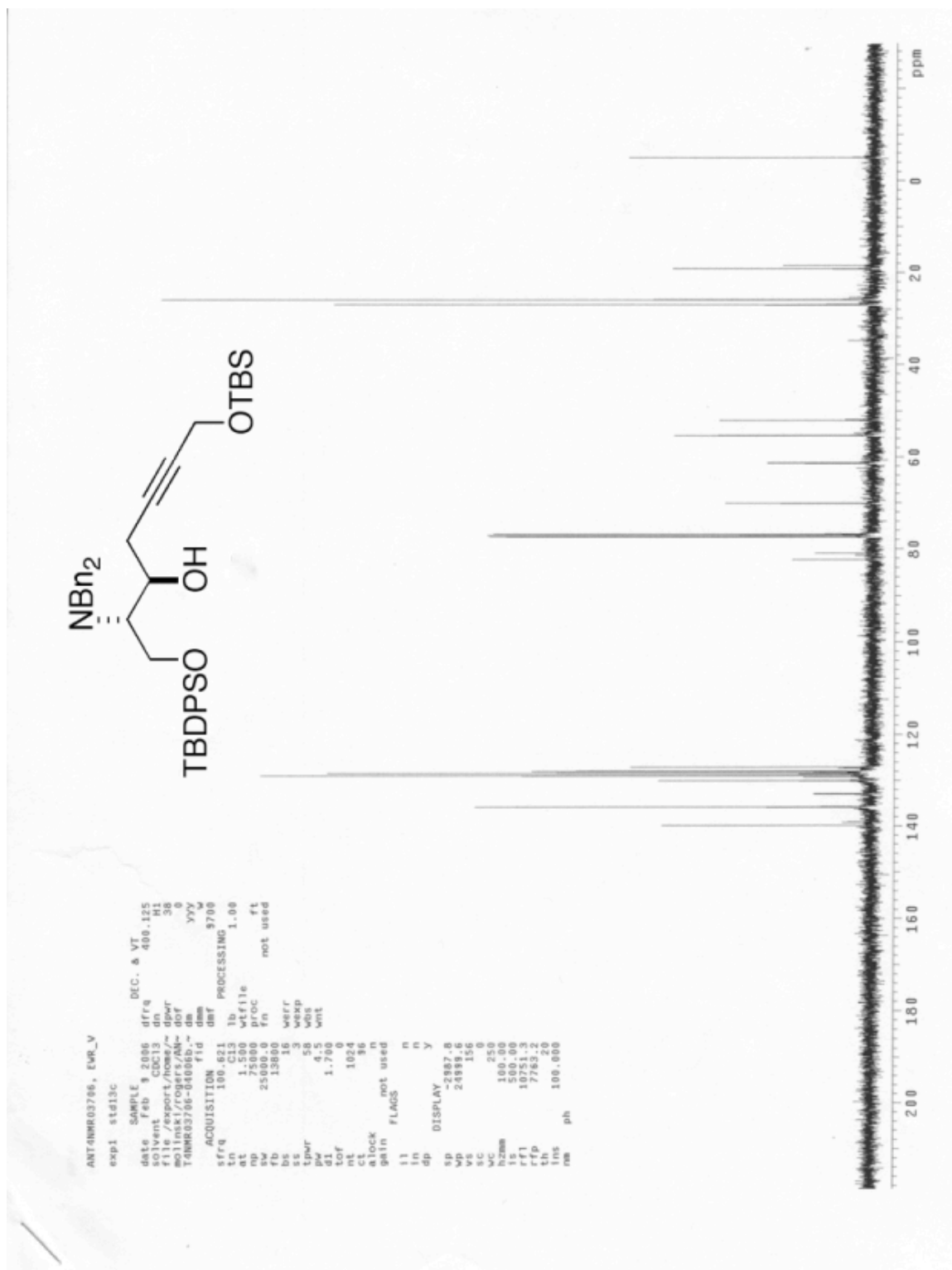
Spectrum 7.14: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 228



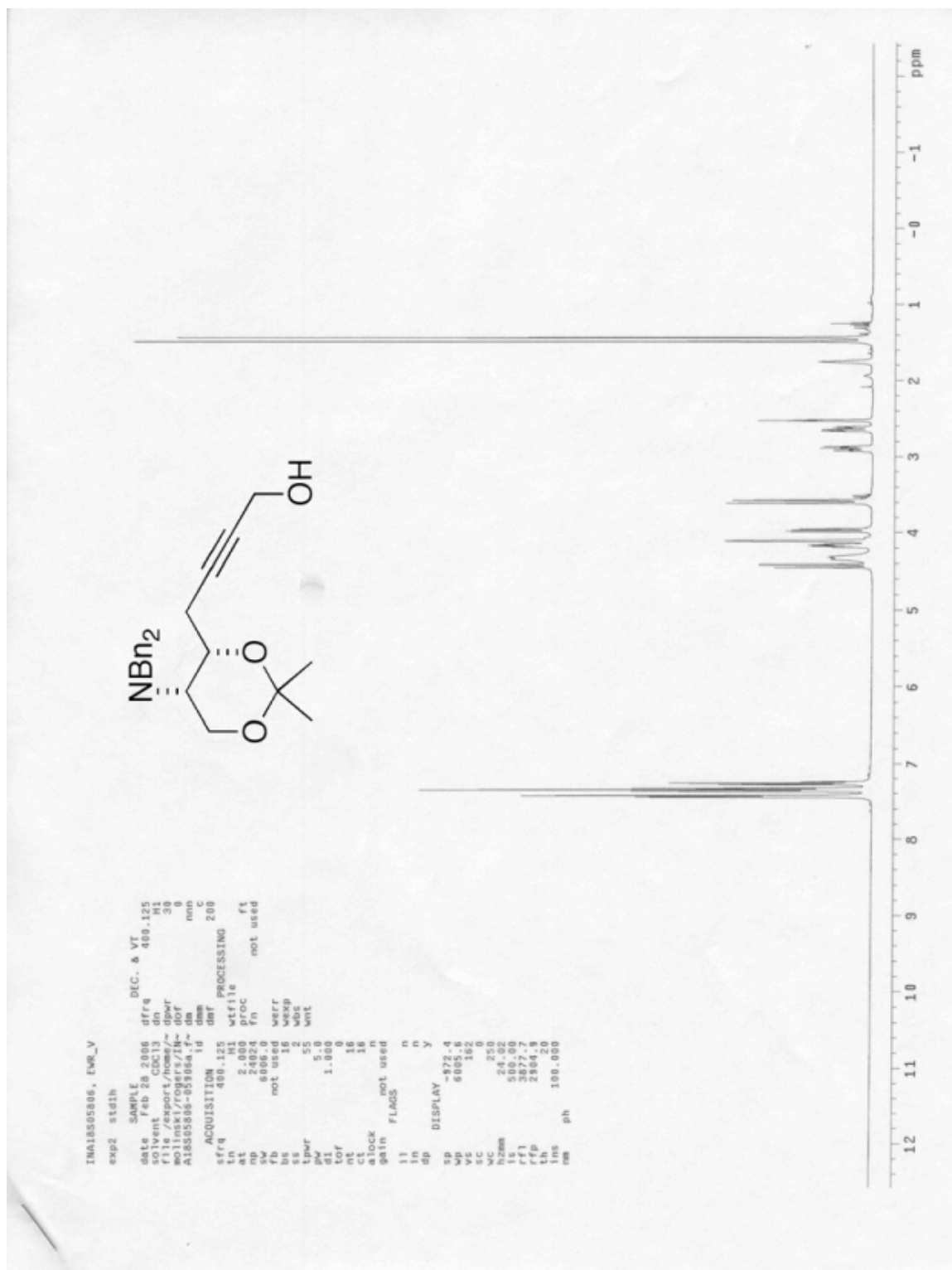
Spectrum 7.15: ^1H NMR (CDCl_3 , 400 MHz) of compound 229



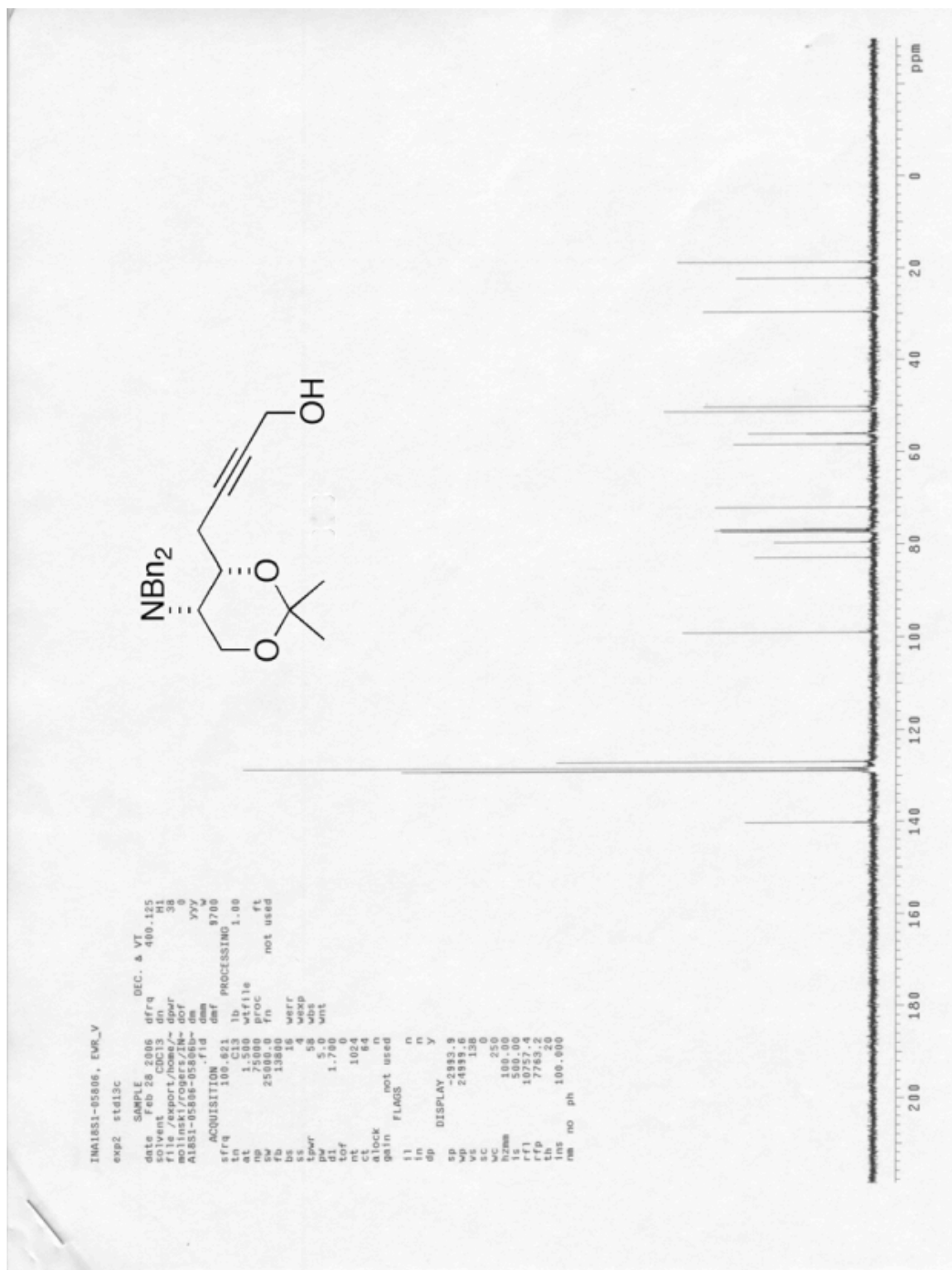
Spectrum 7.16: ^{13}C NMR (CDCl_3 , 100 MHz) of compound **229**



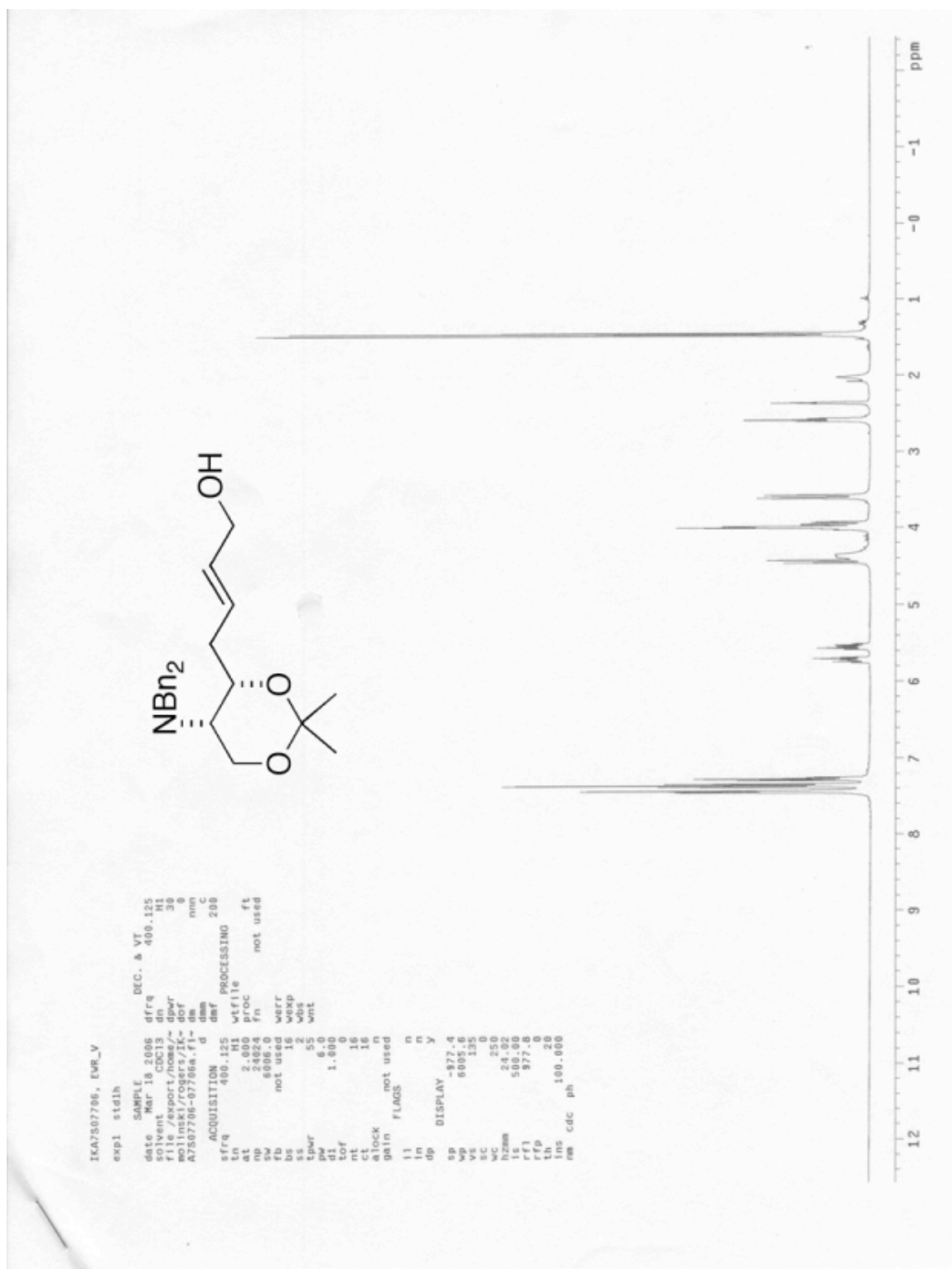
Spectrum 7.18: ¹³C NMR (CDCl₃, 100 MHz) of compound 230



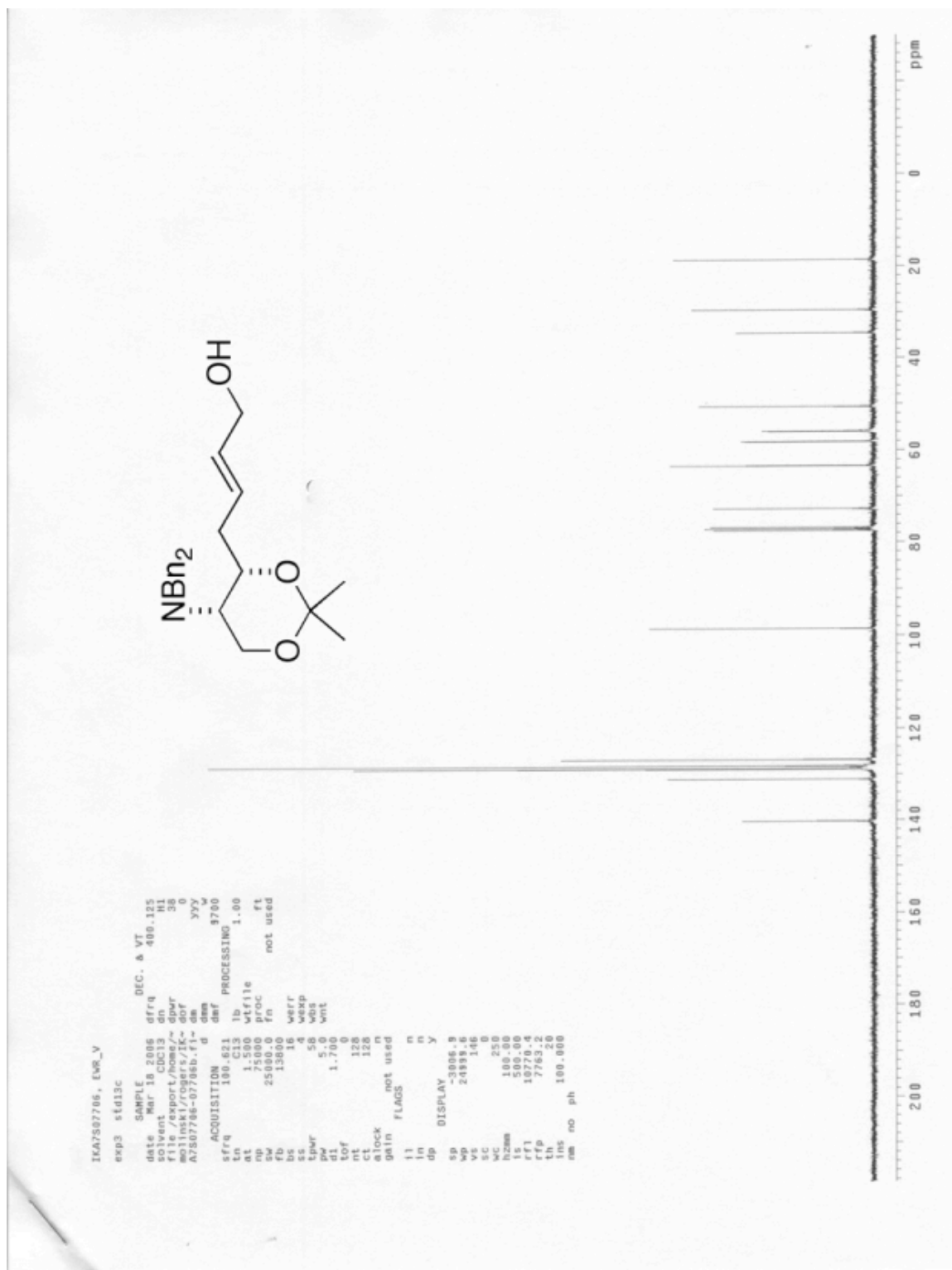
Spectrum 7.19: ^1H NMR (CDCl_3 , 400 MHz) of compound 231

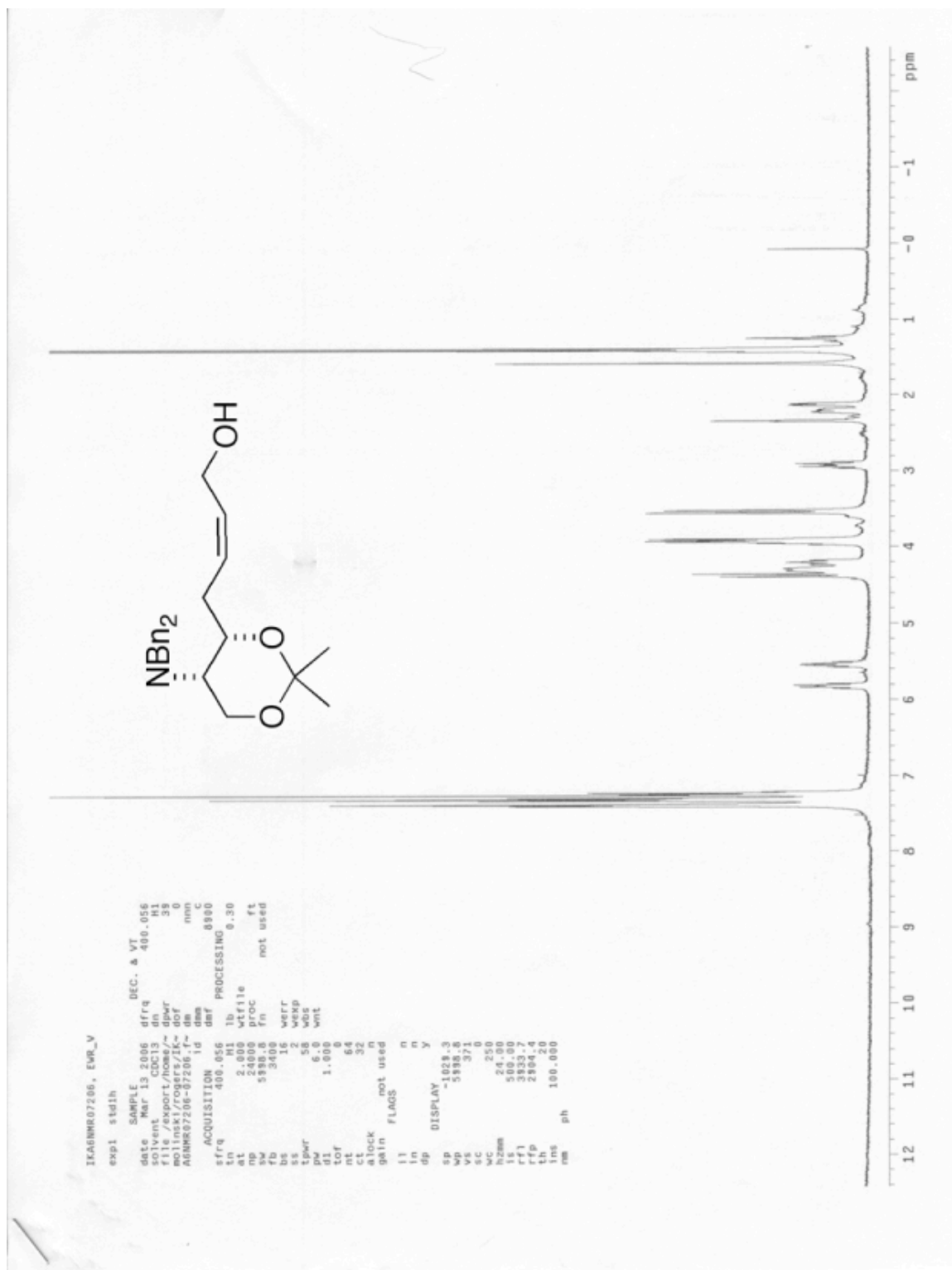


Spectrum 7.20: ^{13}C NMR (CDCl_3 , 100 MHz) of compound **231**

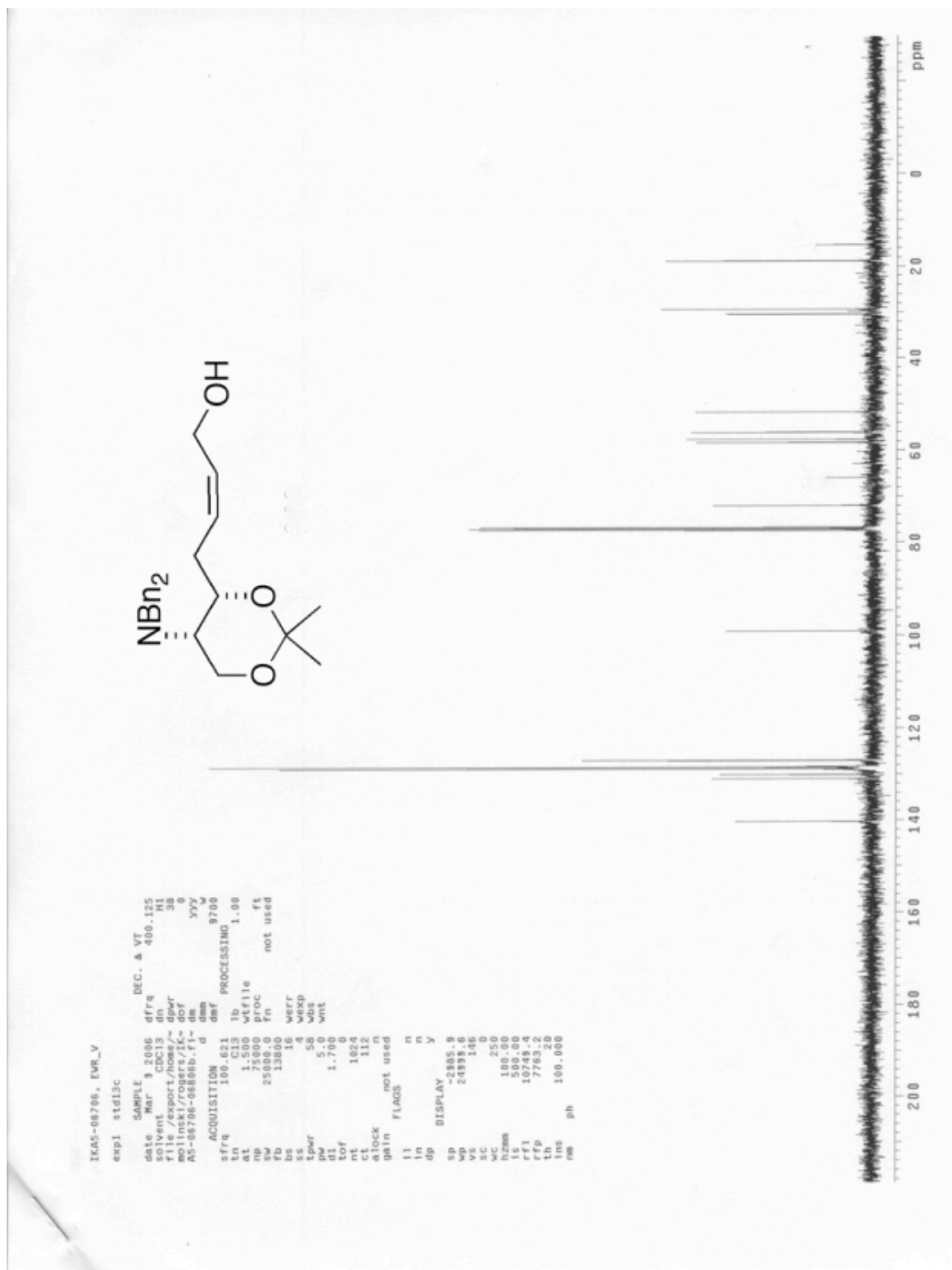


Spectrum 7.25: ^1H NMR (CDCl_3 , 400 MHz) of compound **235**

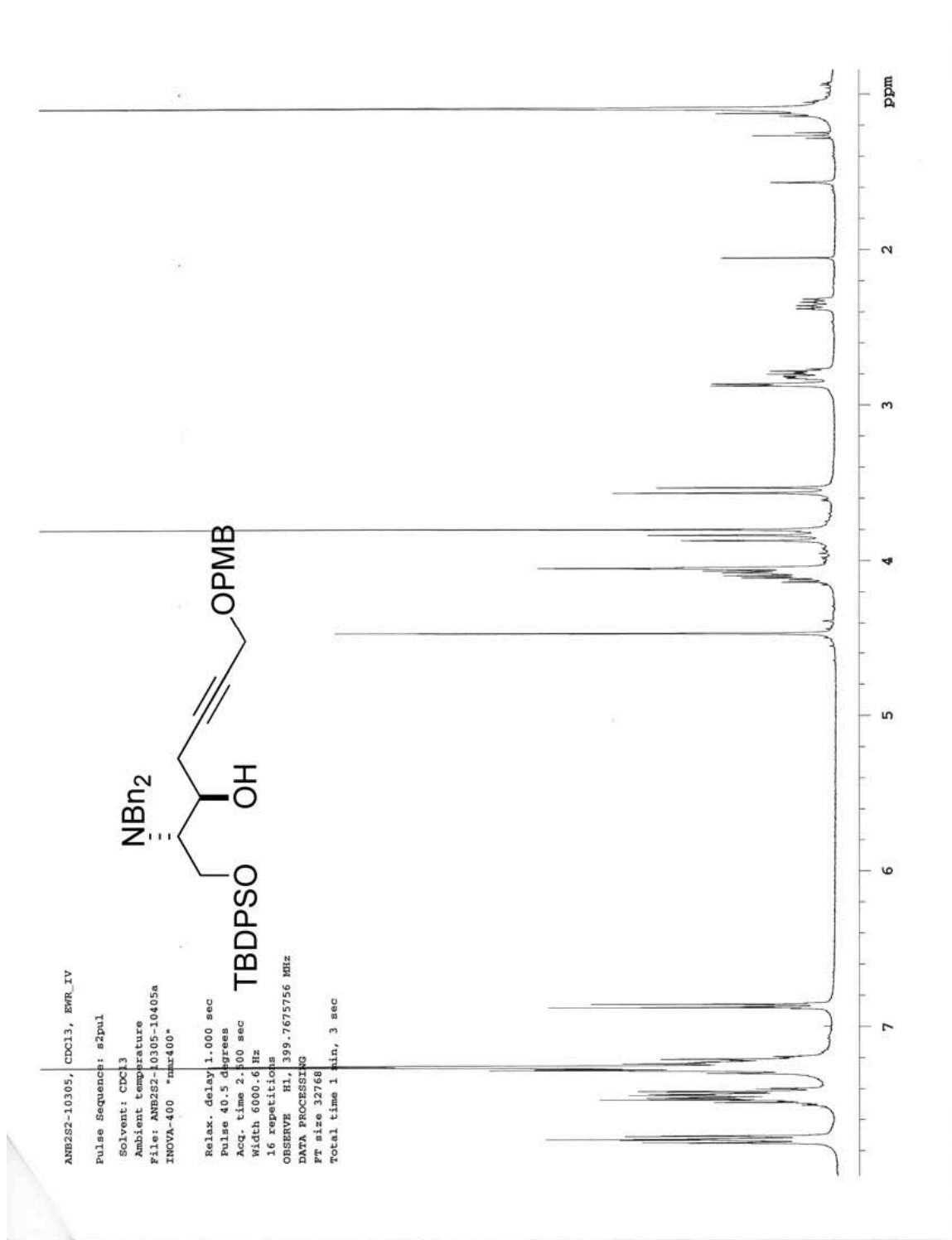




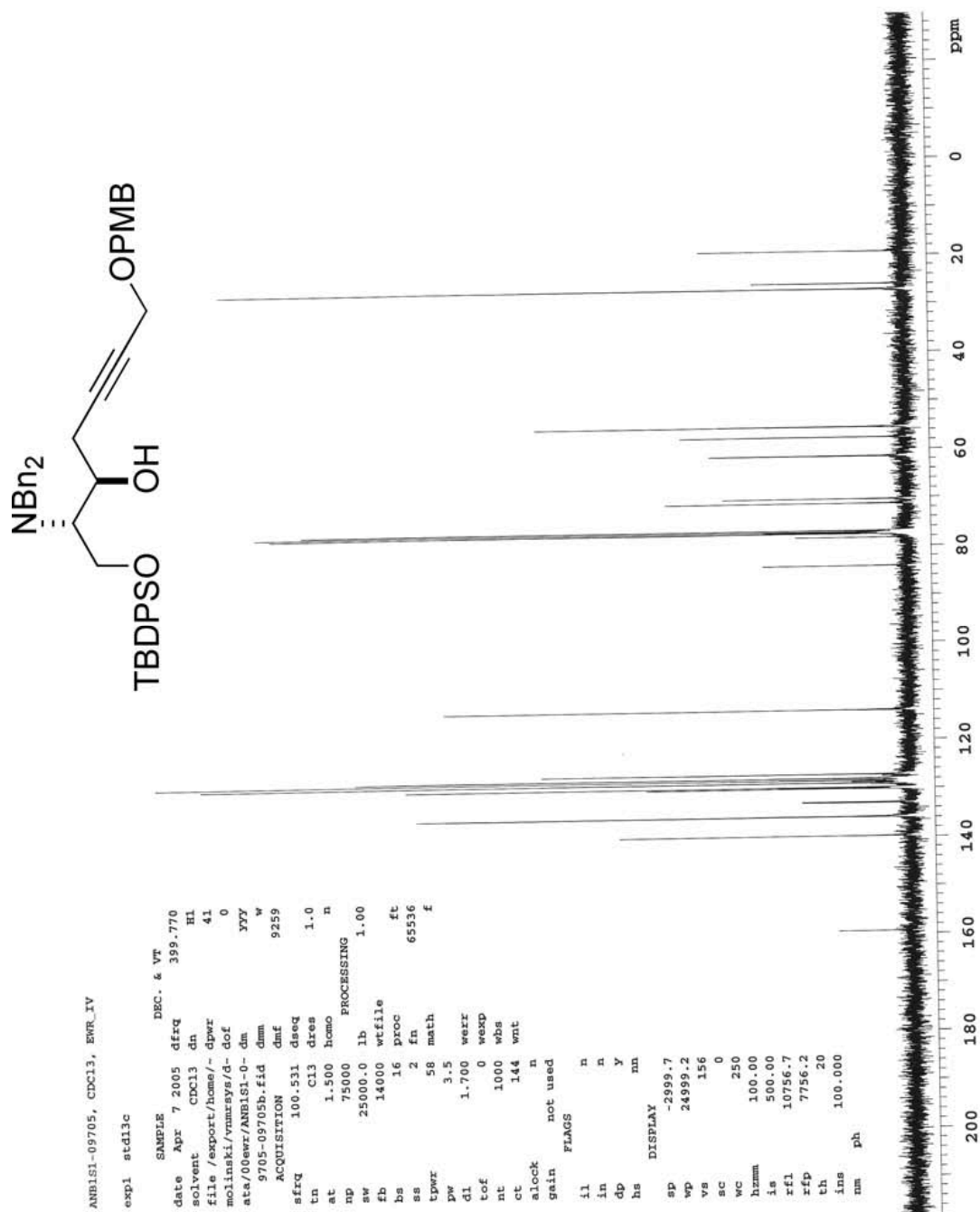
Spectrum 7.27: ^1H NMR (CDCl_3 , 400 MHz) of compound 236



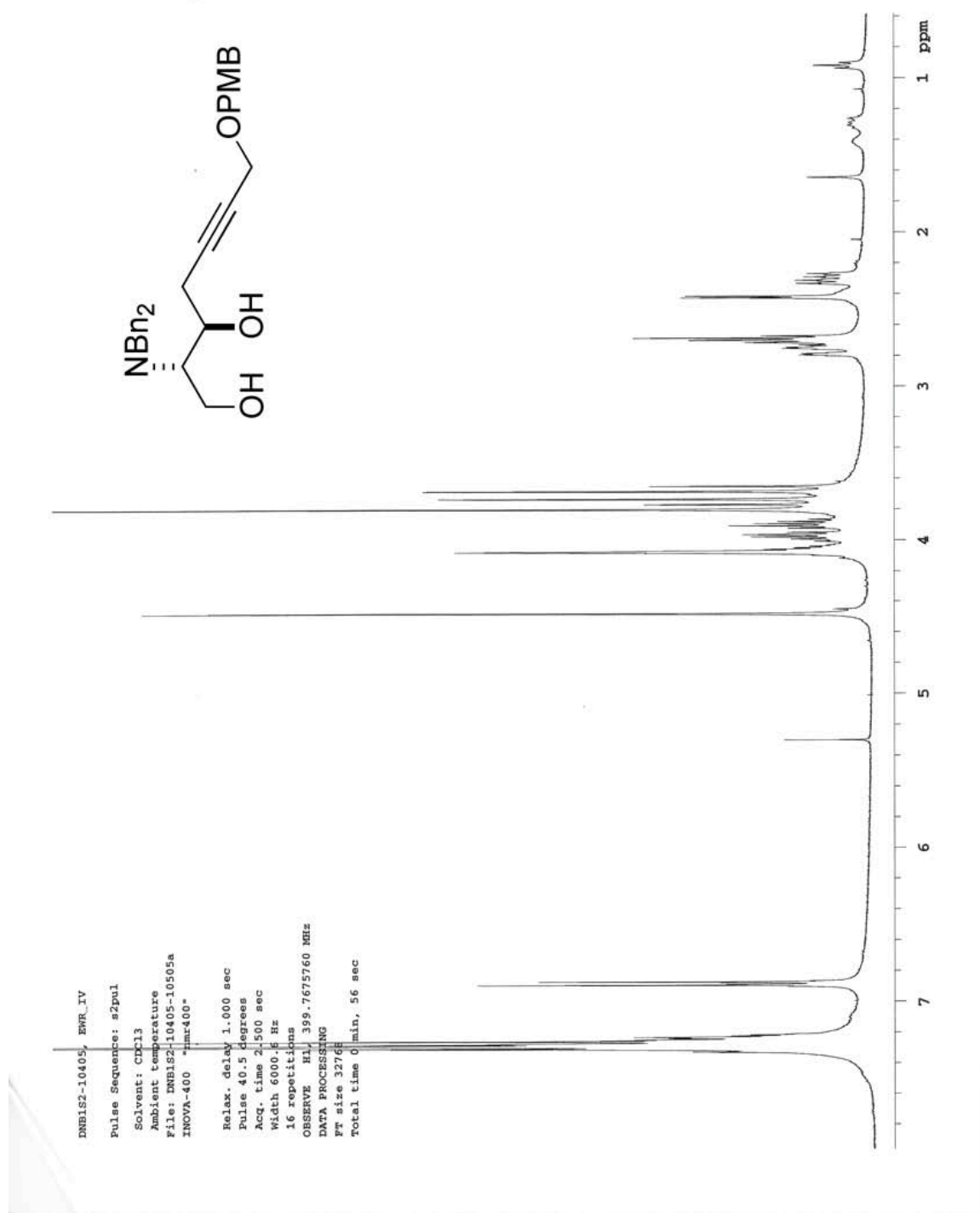
Spectrum 7.28: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 236



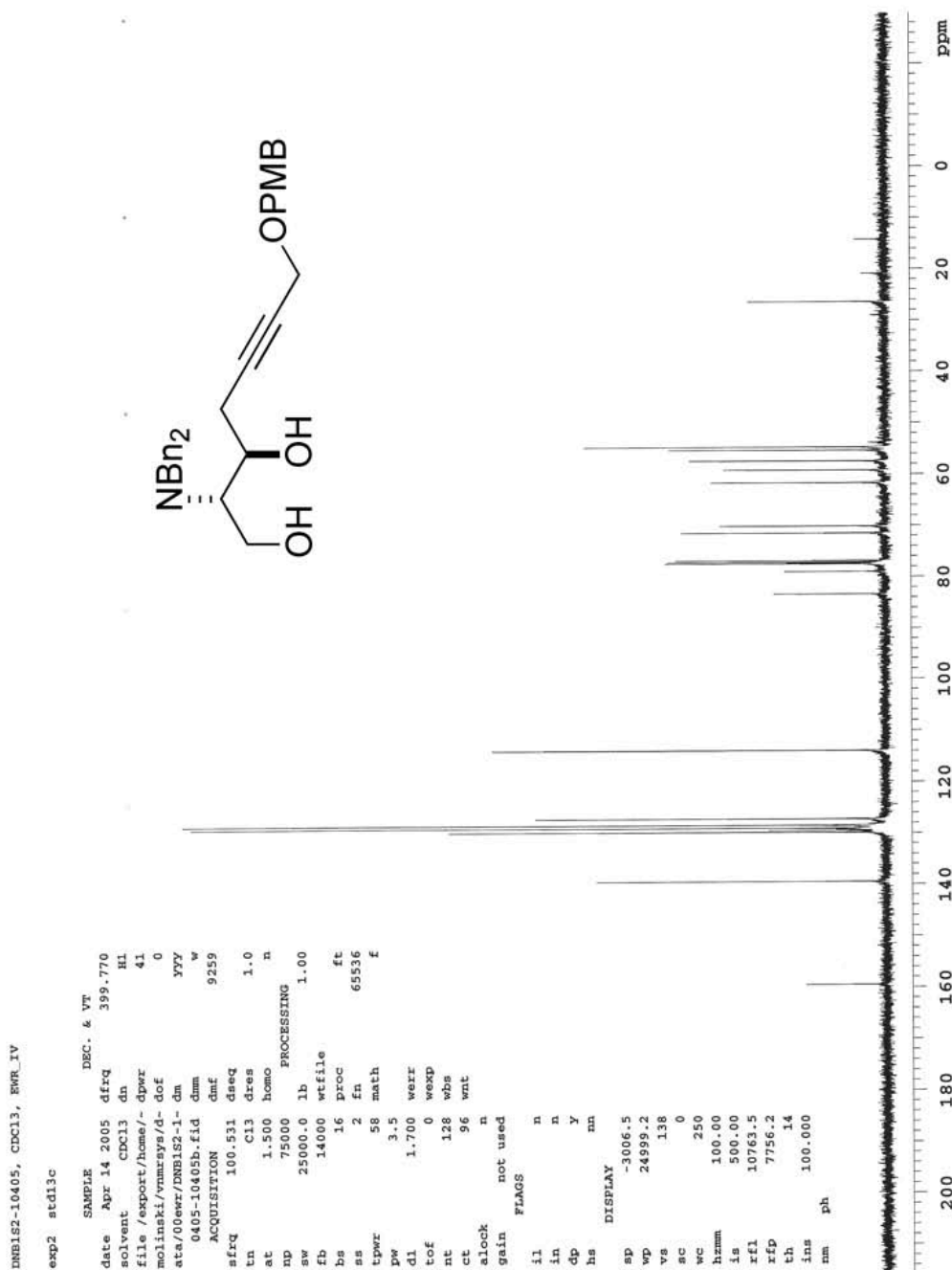
Spectrum 7.29: ¹H NMR (CDCl₃, 400 MHz) of compound 243



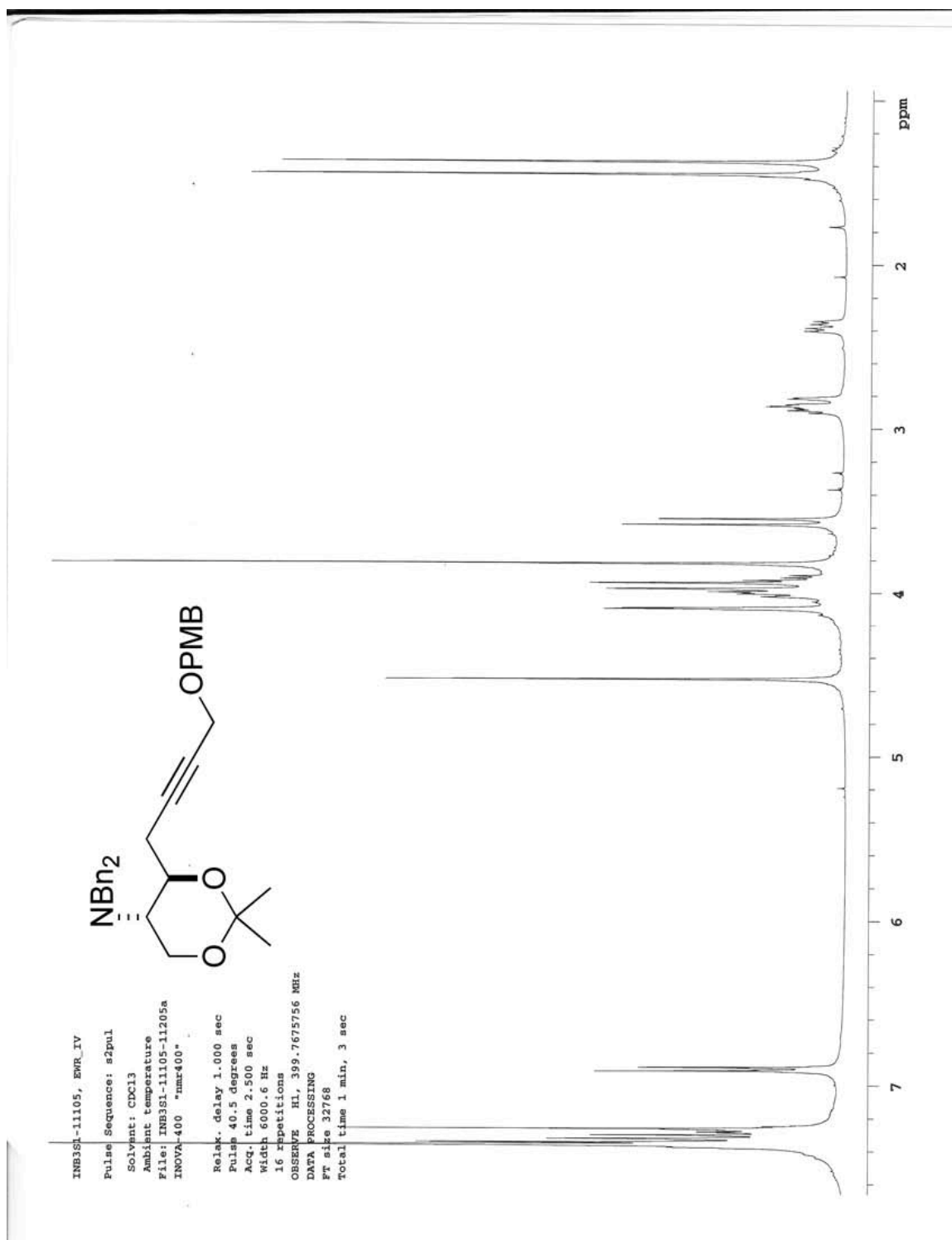
Spectrum 7.30: ¹³C NMR (CDCl₃, 100 MHz) of compound 243



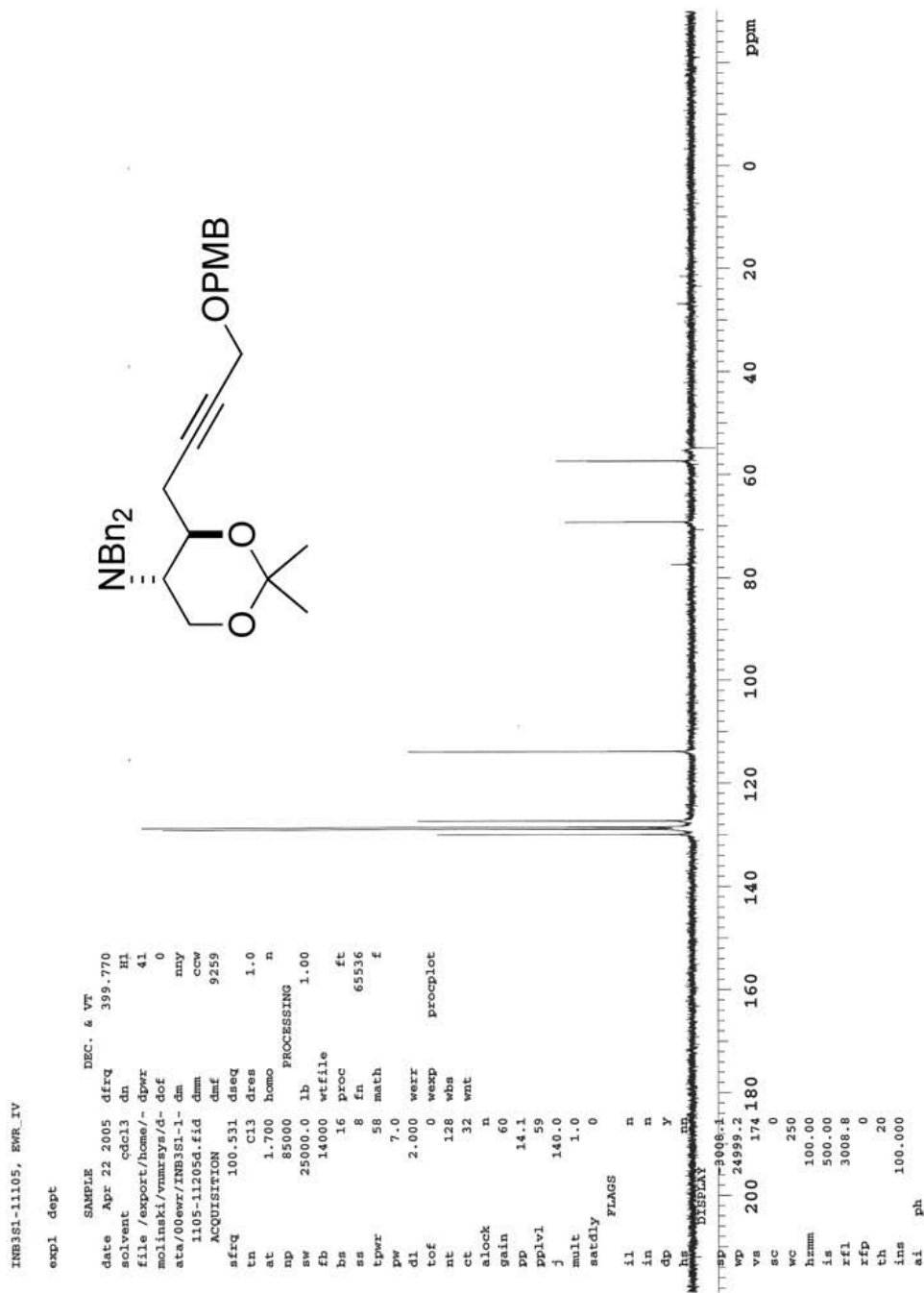
Spectrum 7.31: ^1H NMR (CDCl_3 , 400 MHz) of compound 244



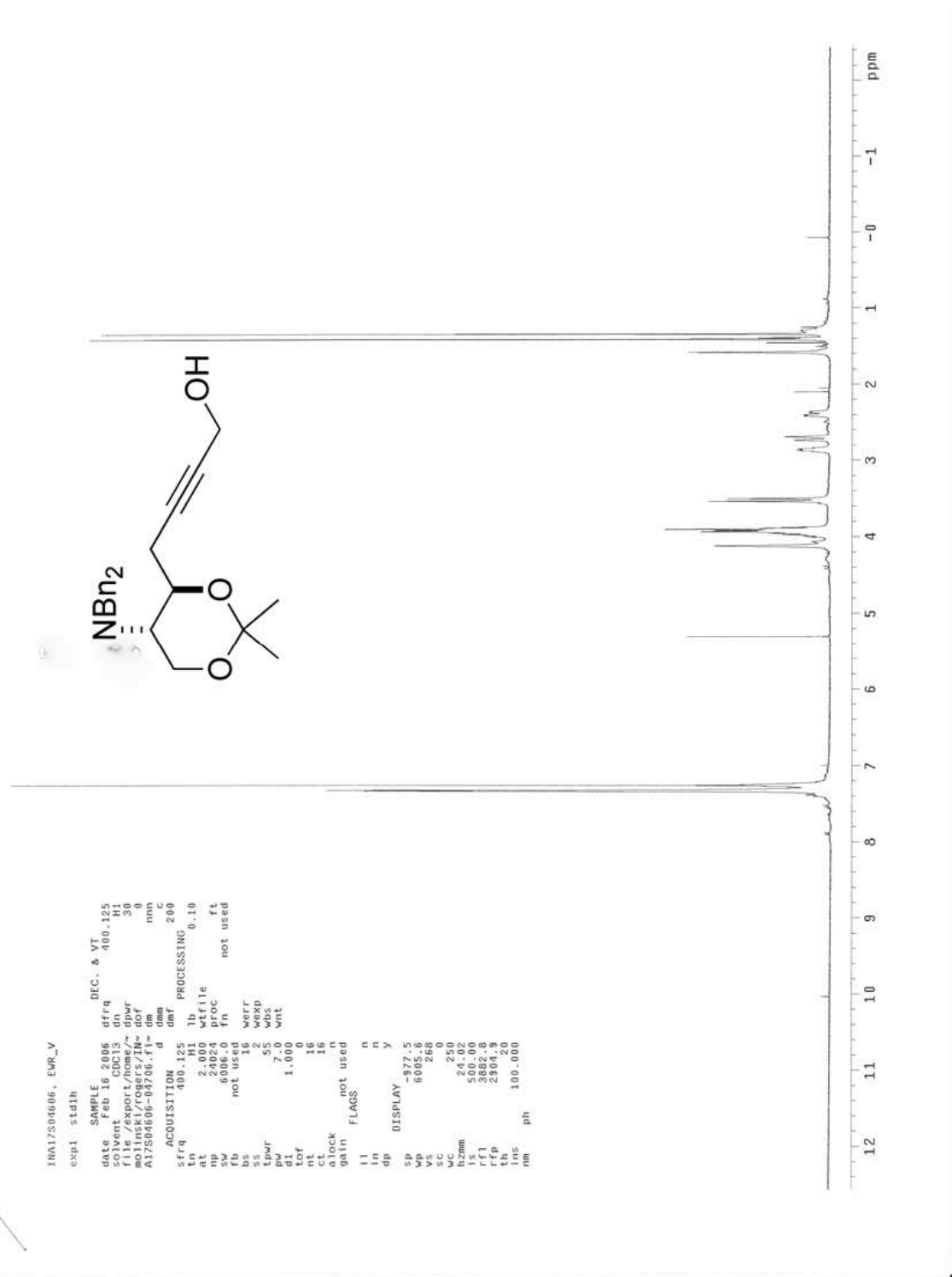
Spectrum 7.32: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 244



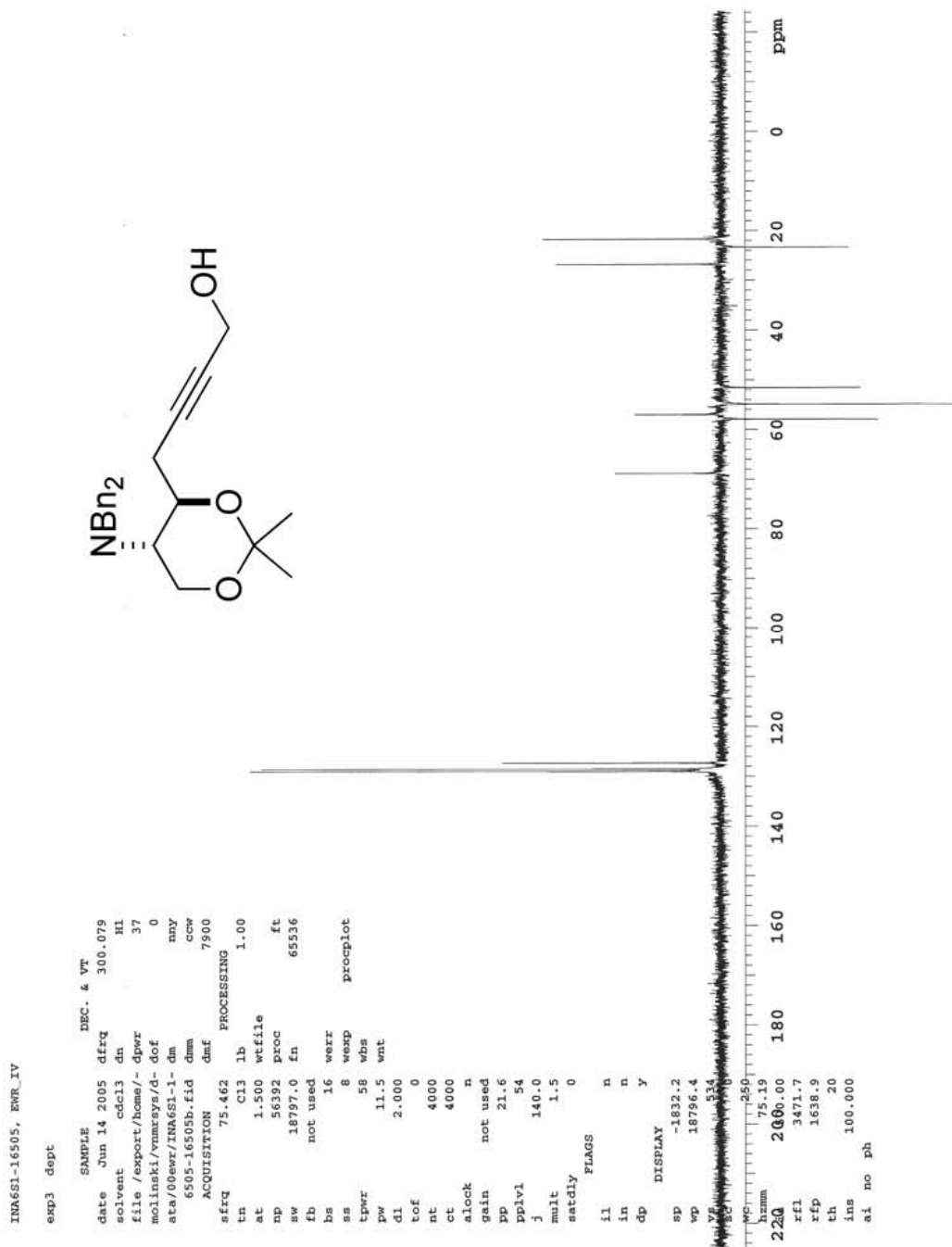
Spectrum 7.33: ^1H NMR (CDCl_3 , 400 MHz) of compound 245



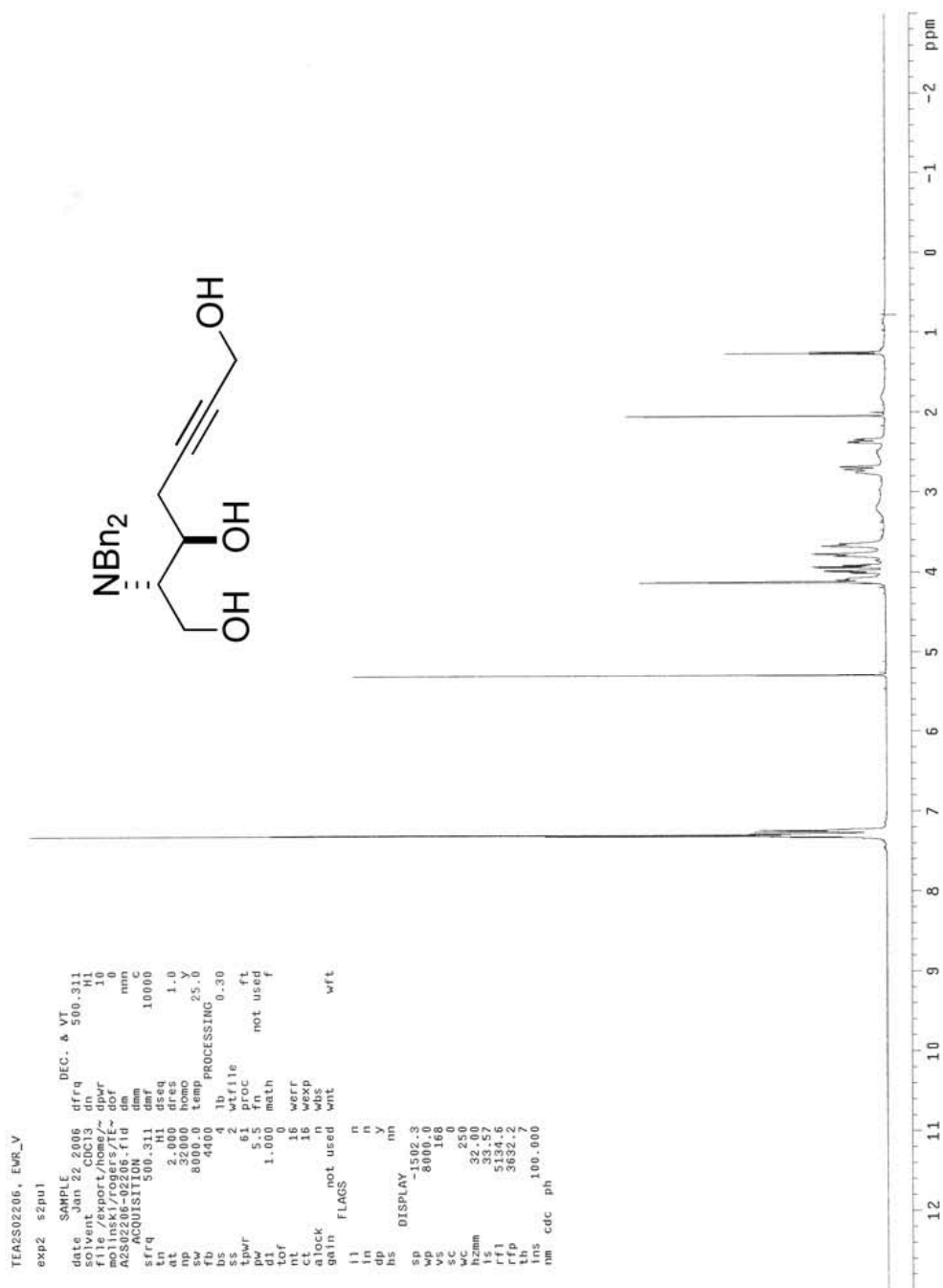
Spectrum 7.34: ^{13}C dept NMR (CDCl_3 , 100 MHz) of compound 245



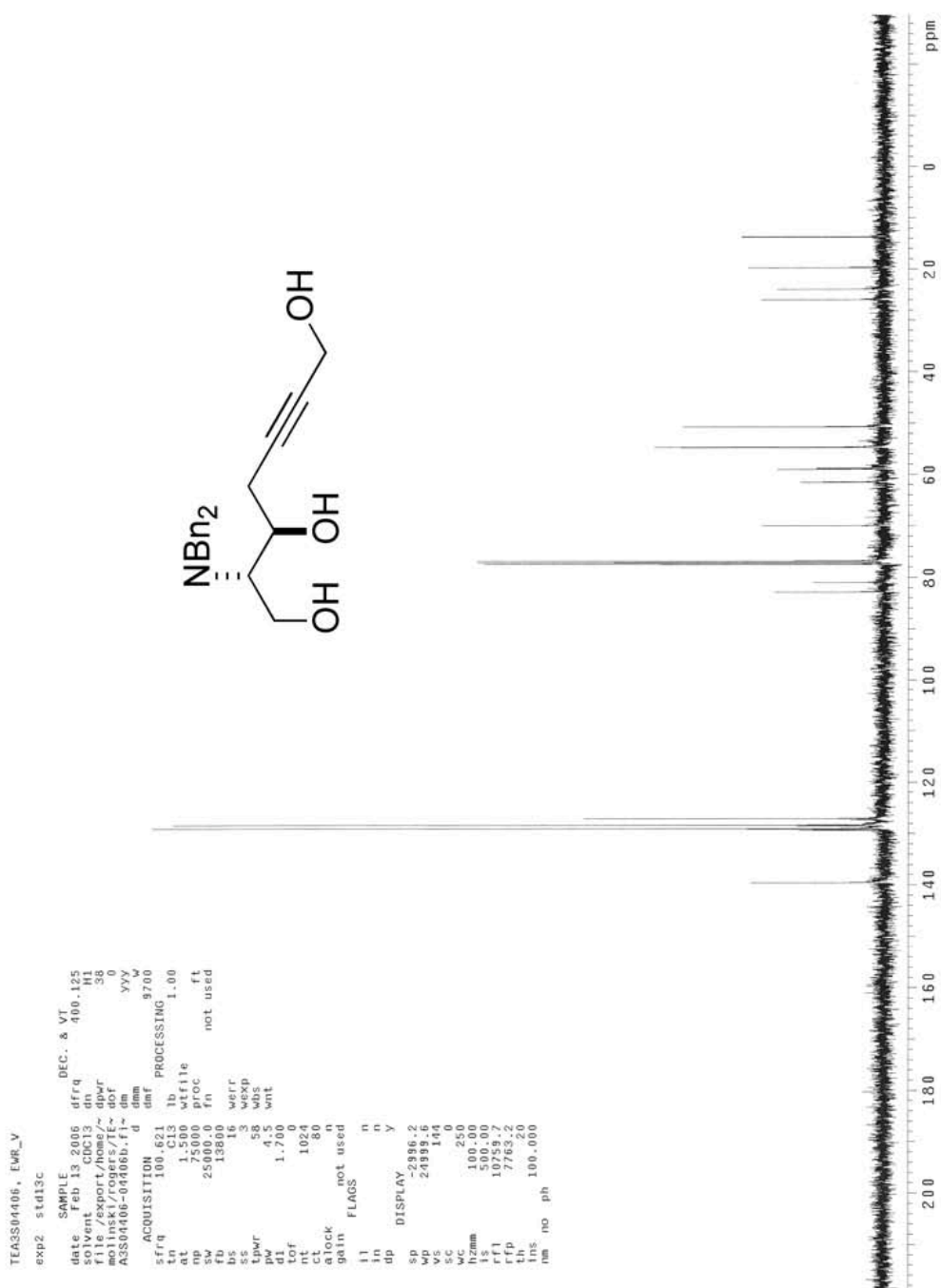
Spectrum 7.35: ¹H NMR (CDCl₃, 400 MHz) of compound 246



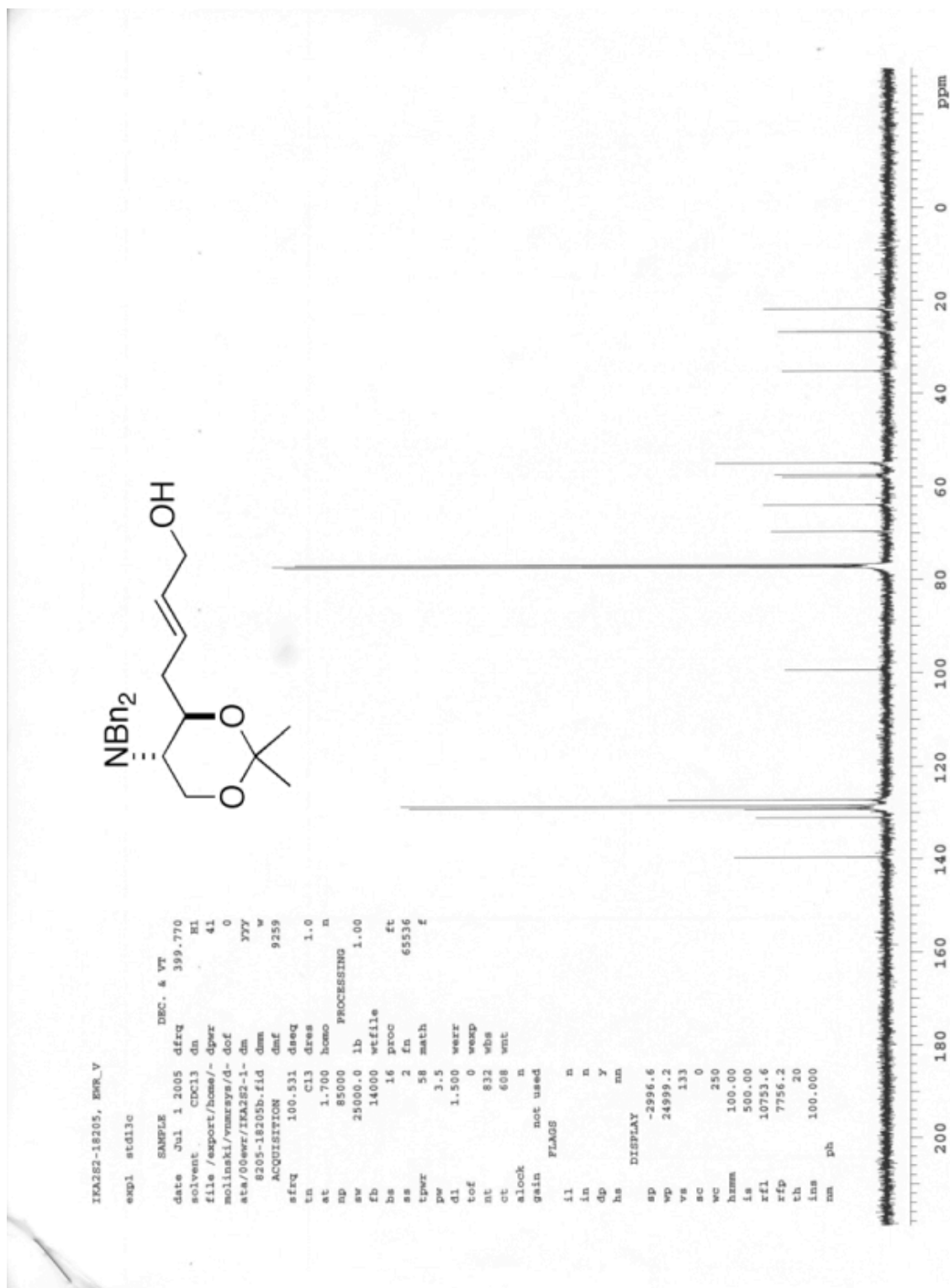
Spectrum 7.36: ^{13}C dept NMR (CDCl_3 , 75 MHz) of compound 246



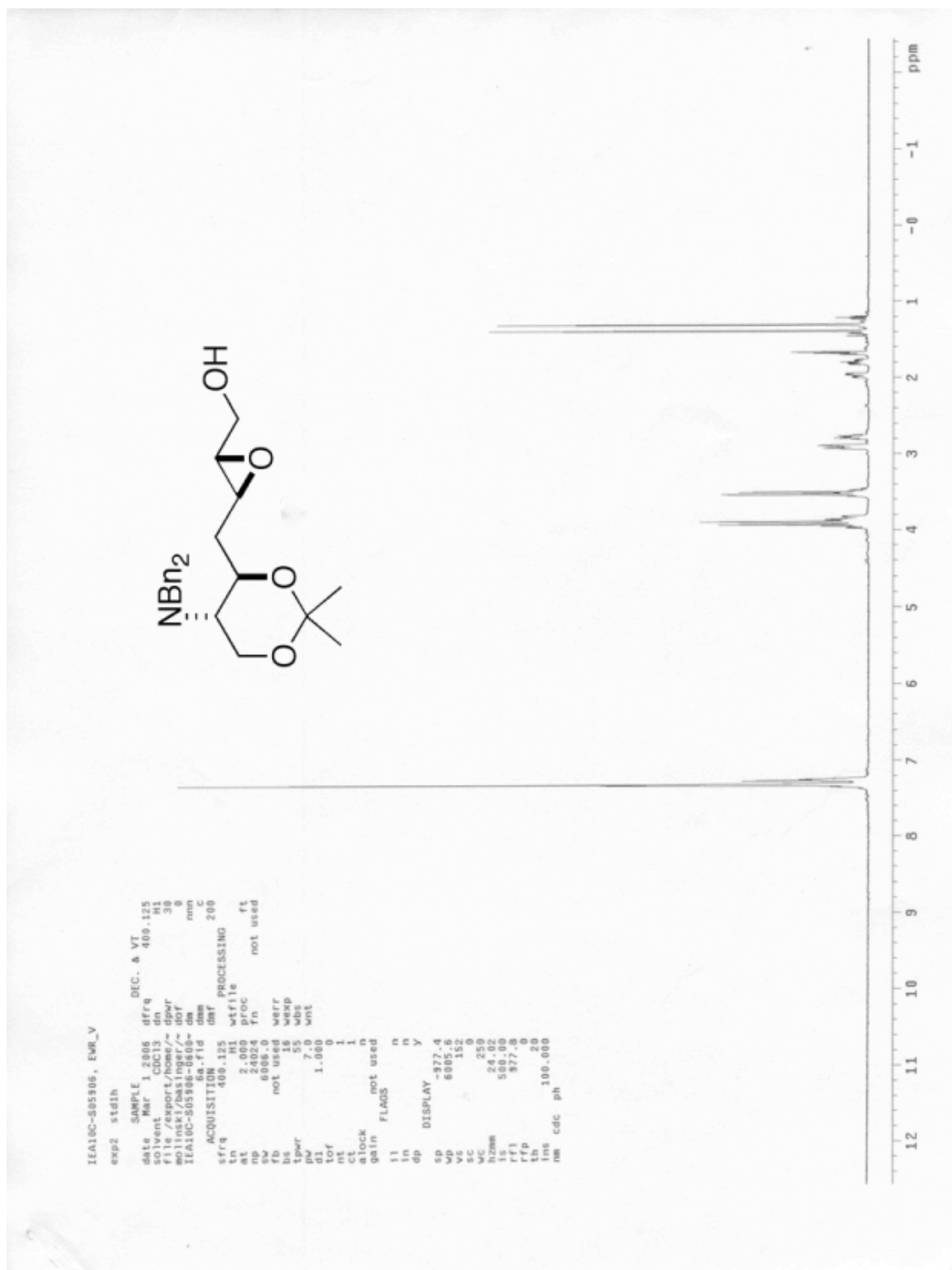
Spectrum 7.37: ^1H NMR (CDCl_3 , 500 MHz) of compound 247



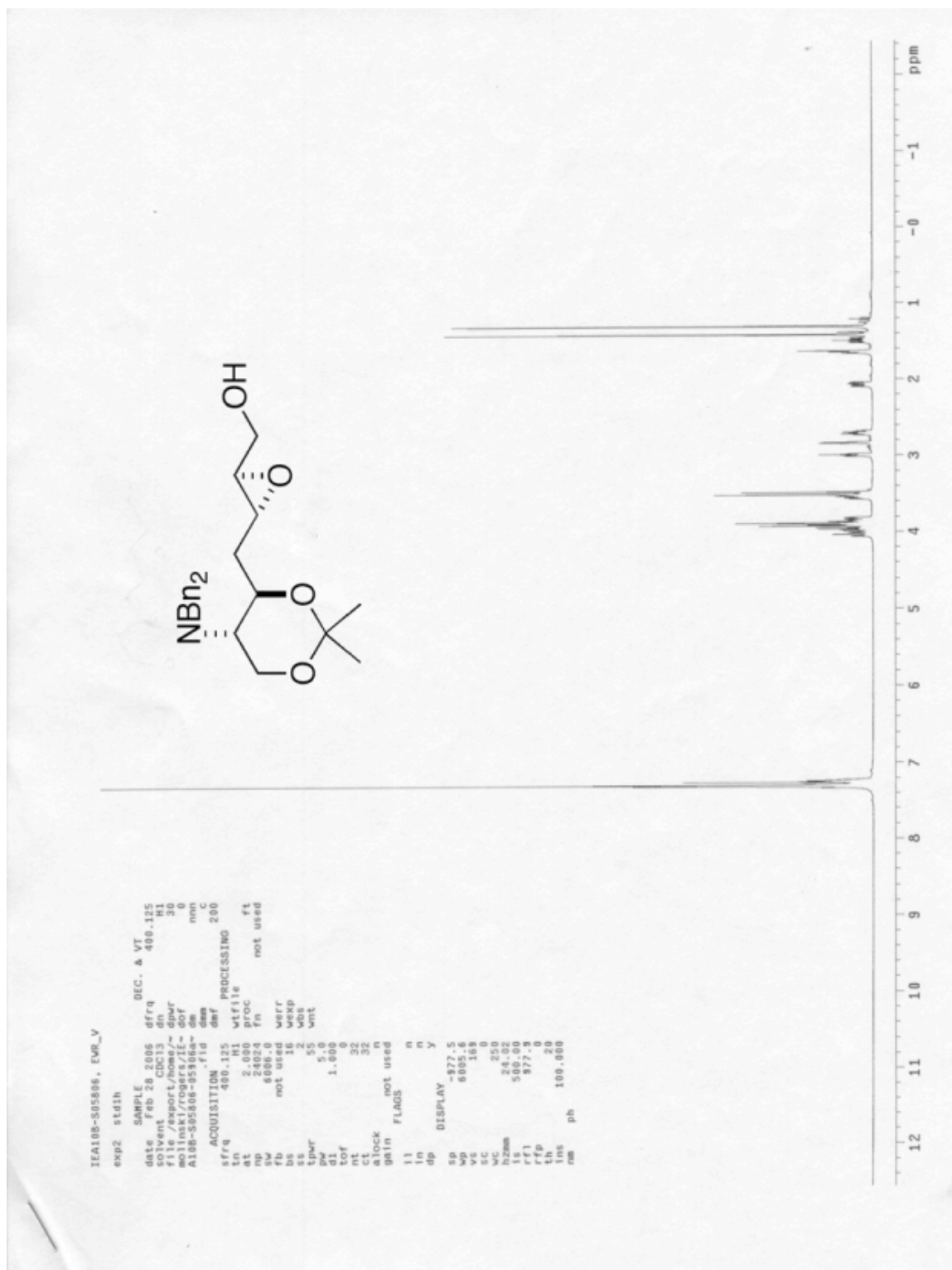
Spectrum 7.38: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 247



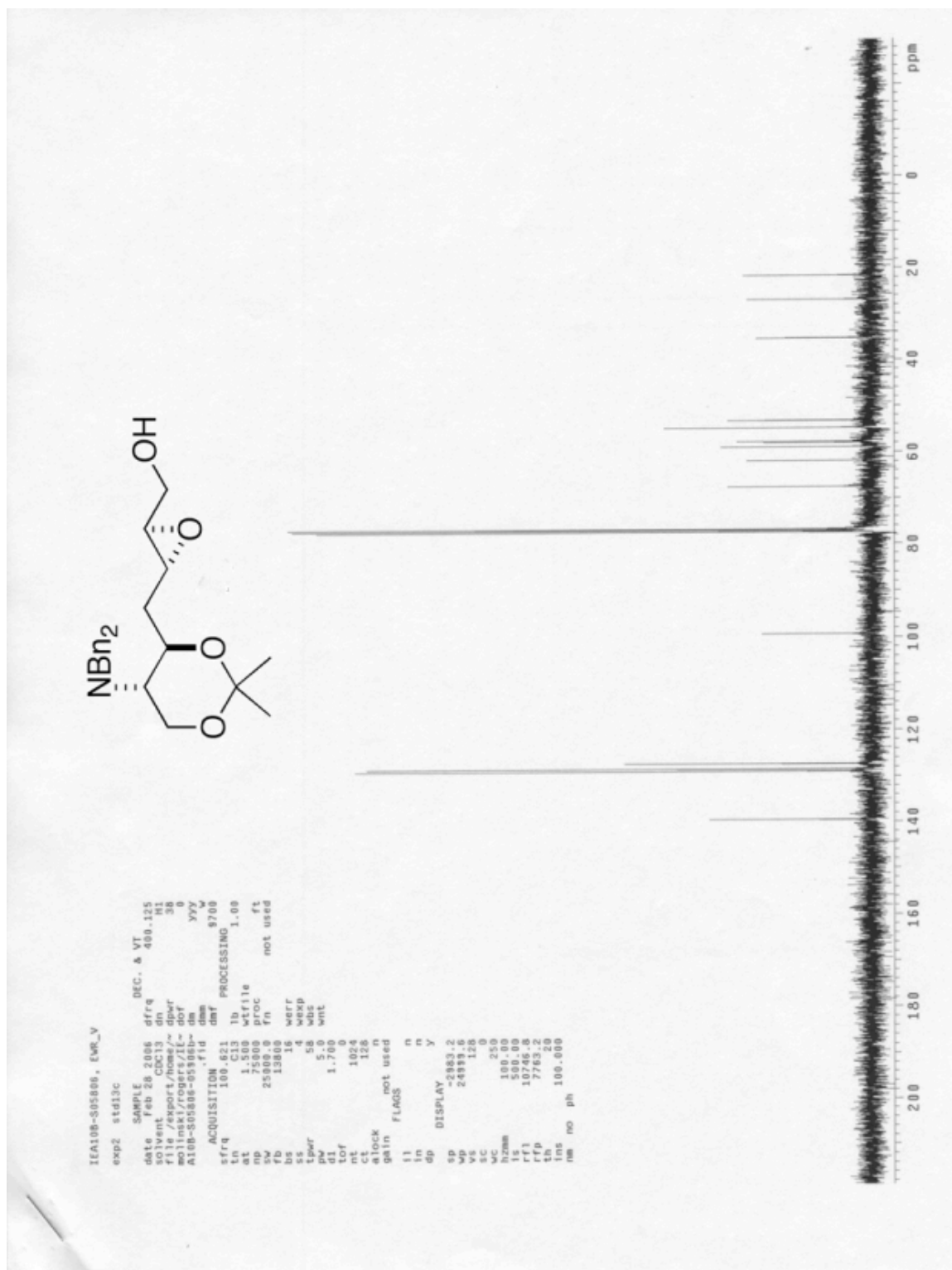
Spectrum 7.40: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 249



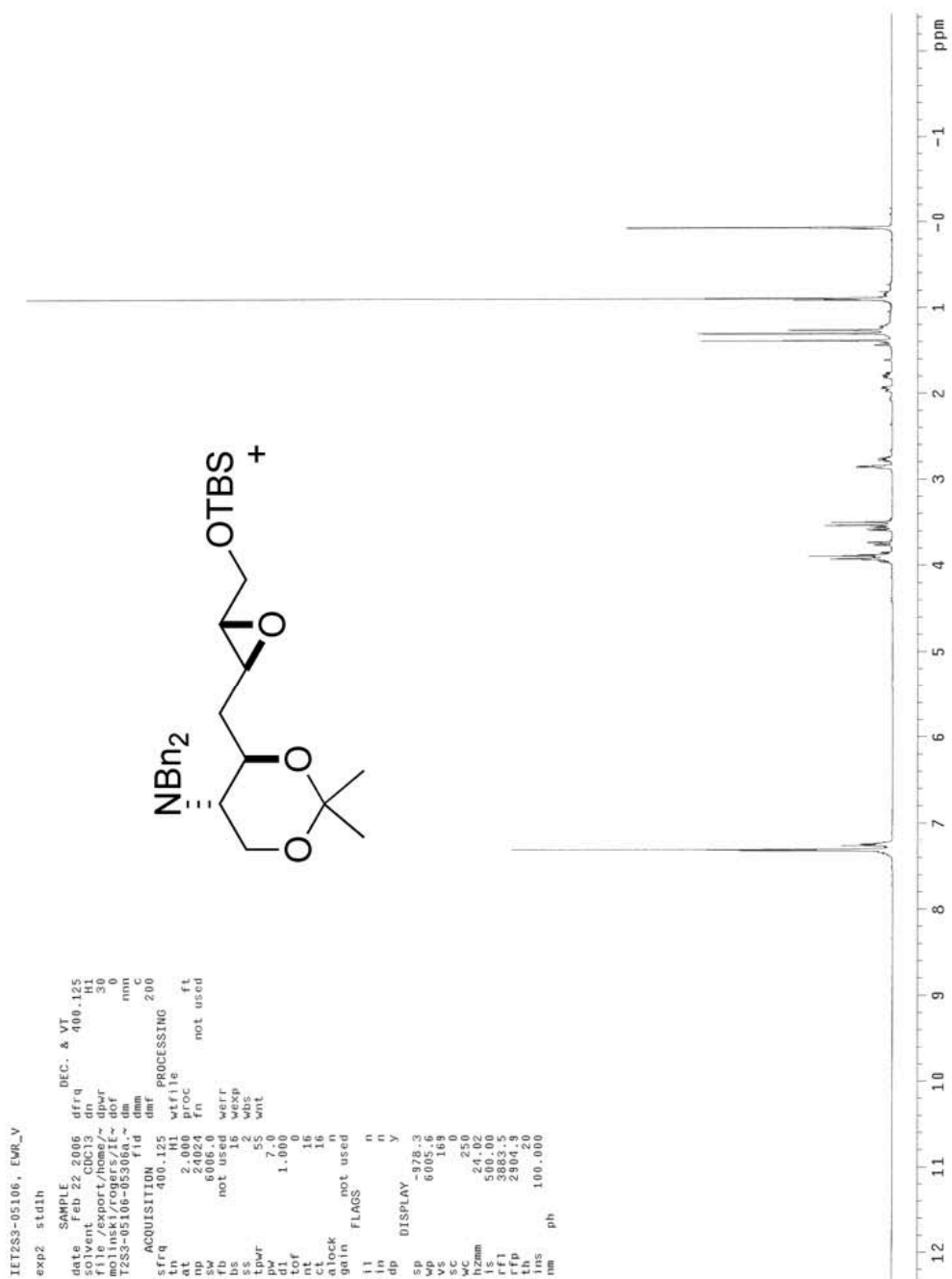
Spectrum 7.41: ^1H NMR (CDCl_3 , 400 MHz) of compound 250



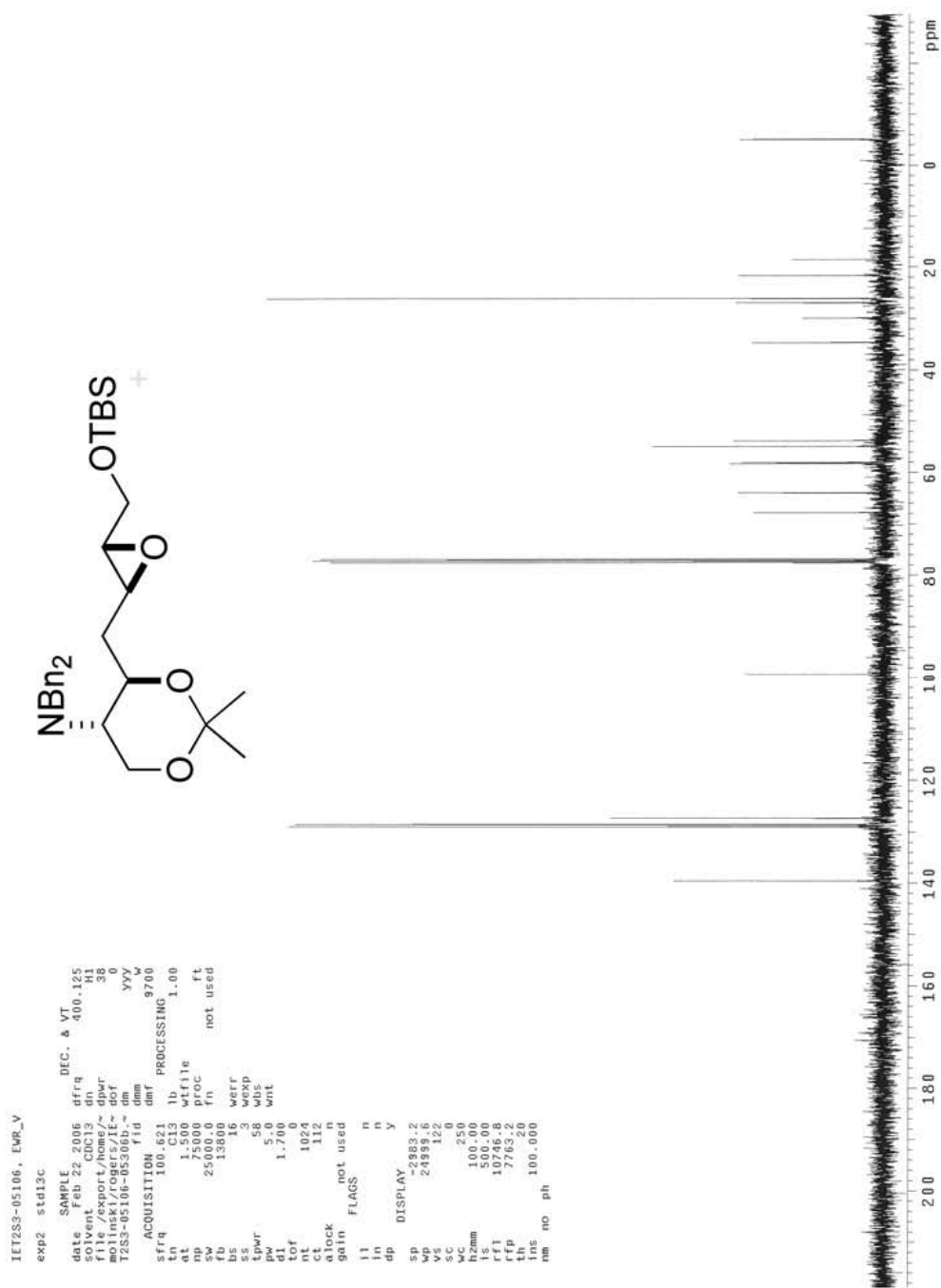
Spectrum 7.43: ¹H NMR (CDCl₃, 400 MHz) of compound 251



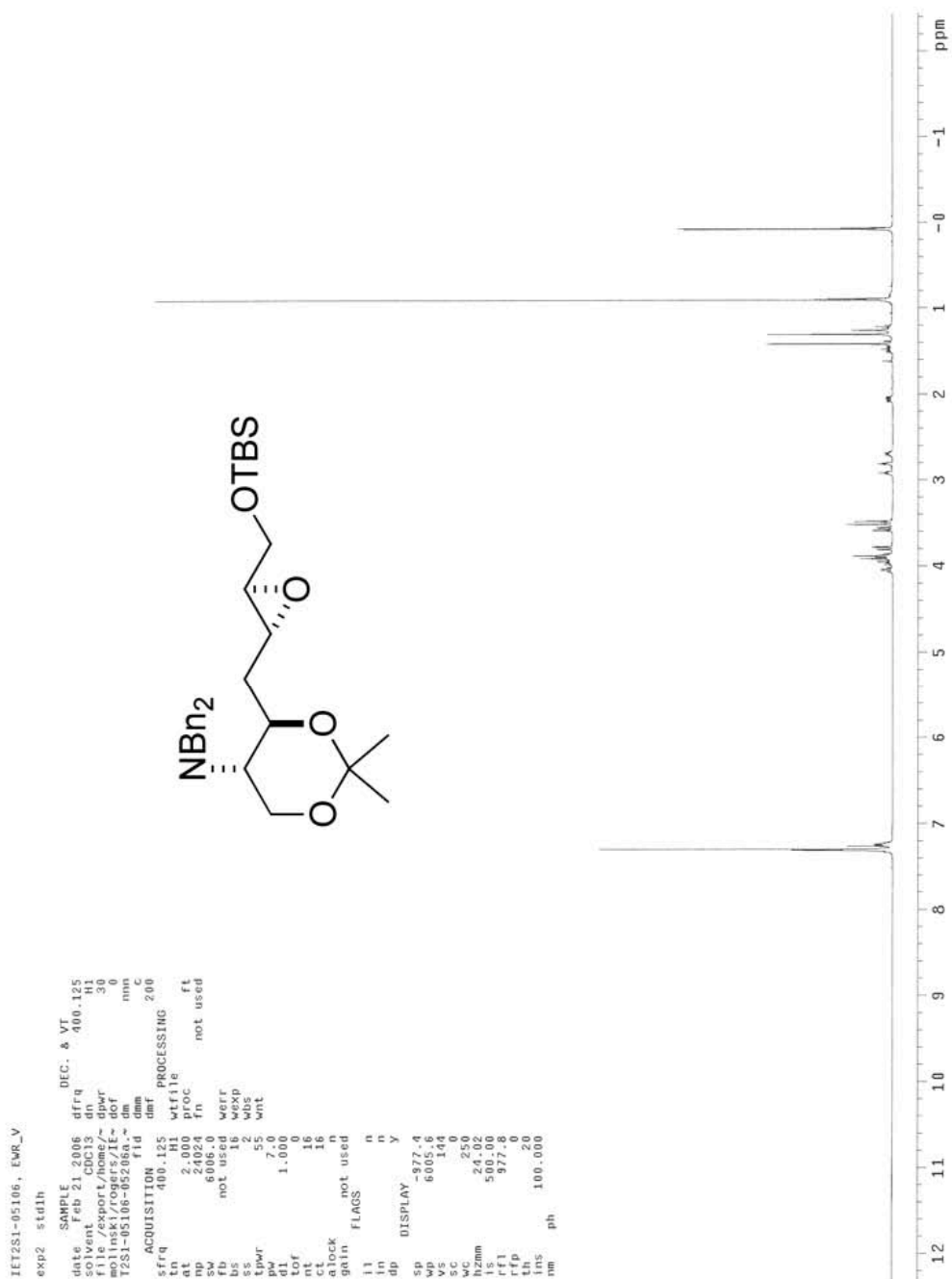
Spectrum 7.44: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 251



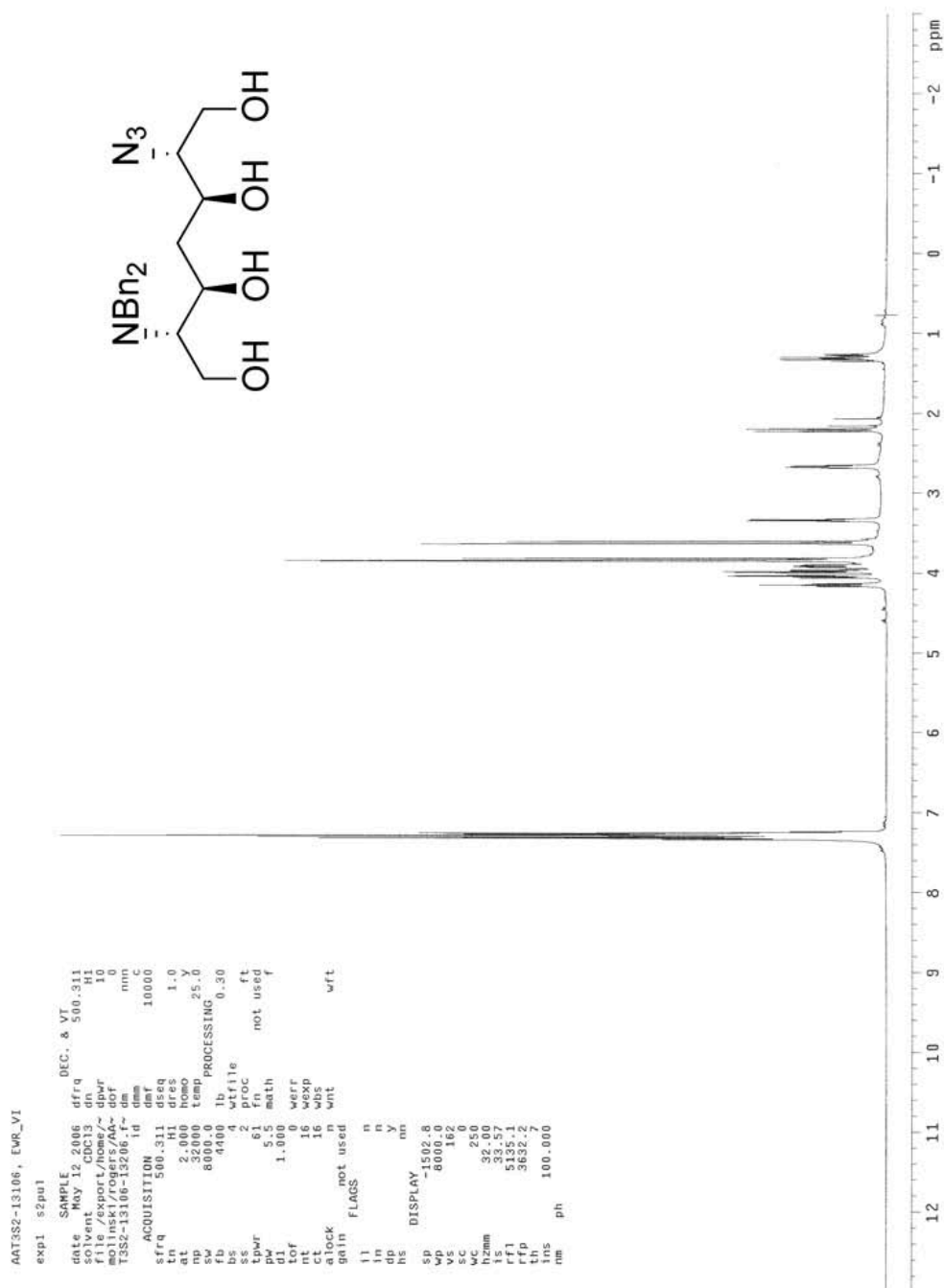
Spectrum 7.45: ^1H NMR (CDCl_3 , 400 MHz) of compound 252



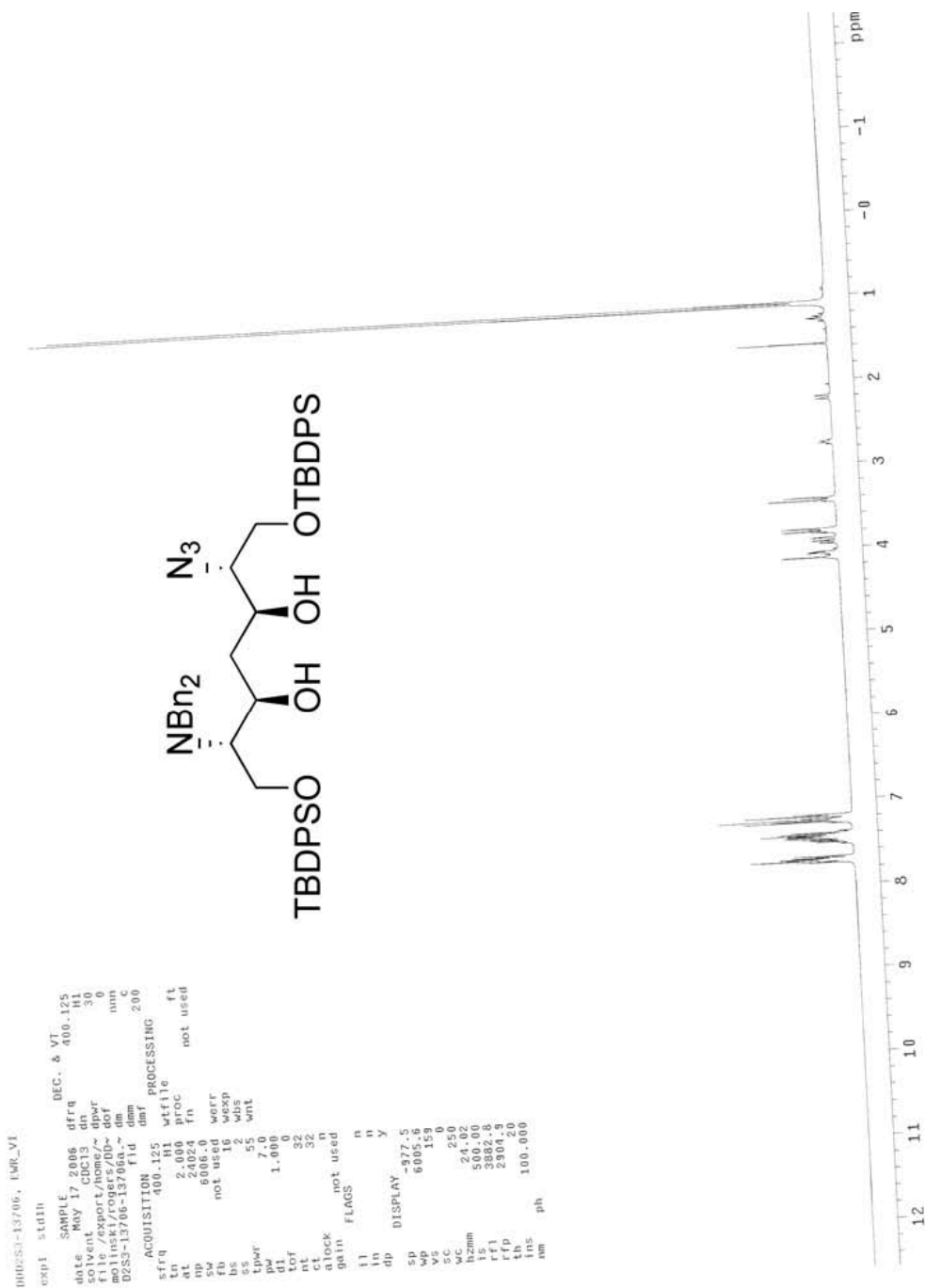
Spectrum 7.46: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 252



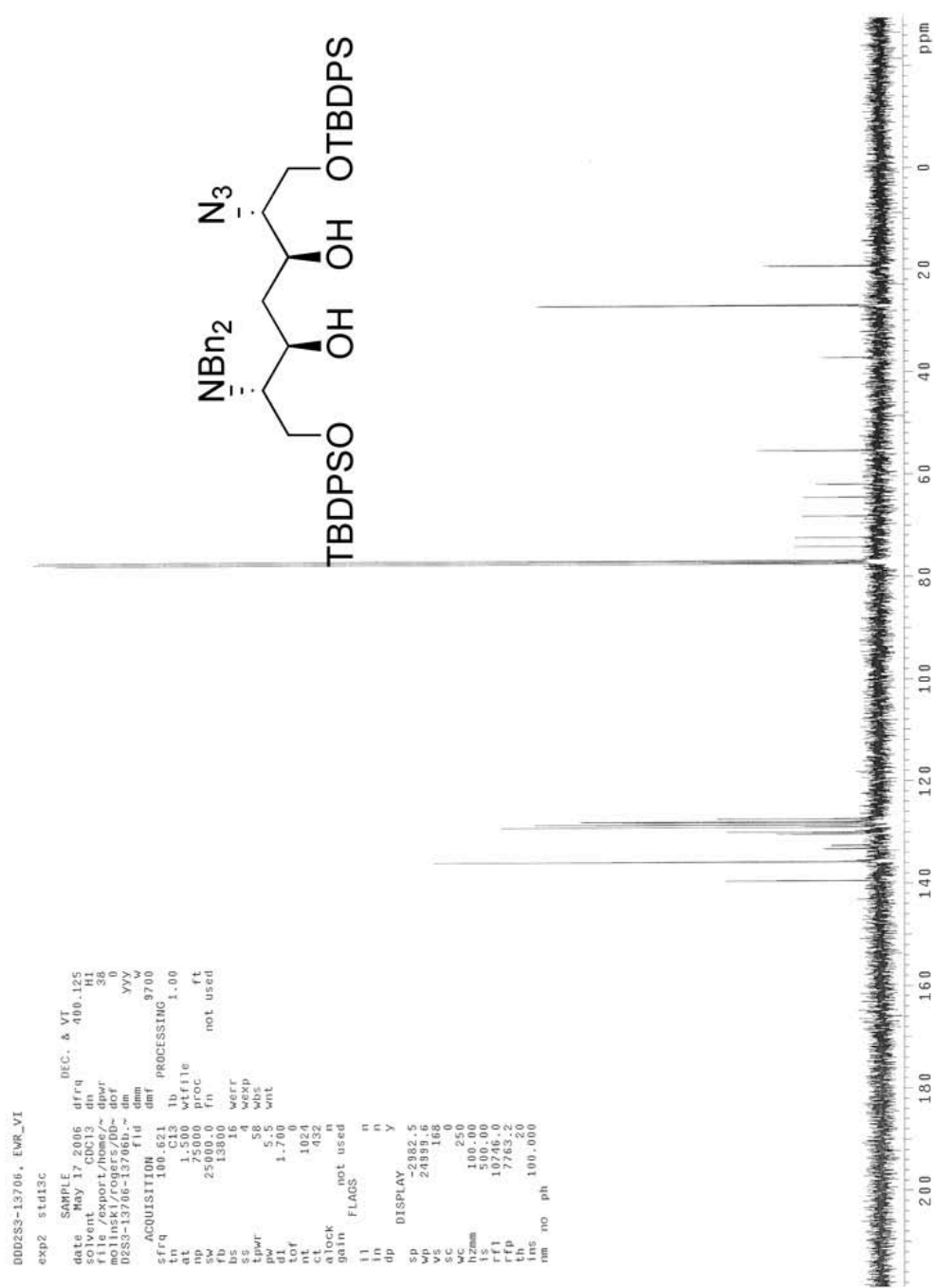
Spectrum 7.47: ^1H NMR (CDCl_3 , 400 MHz) of compound 253



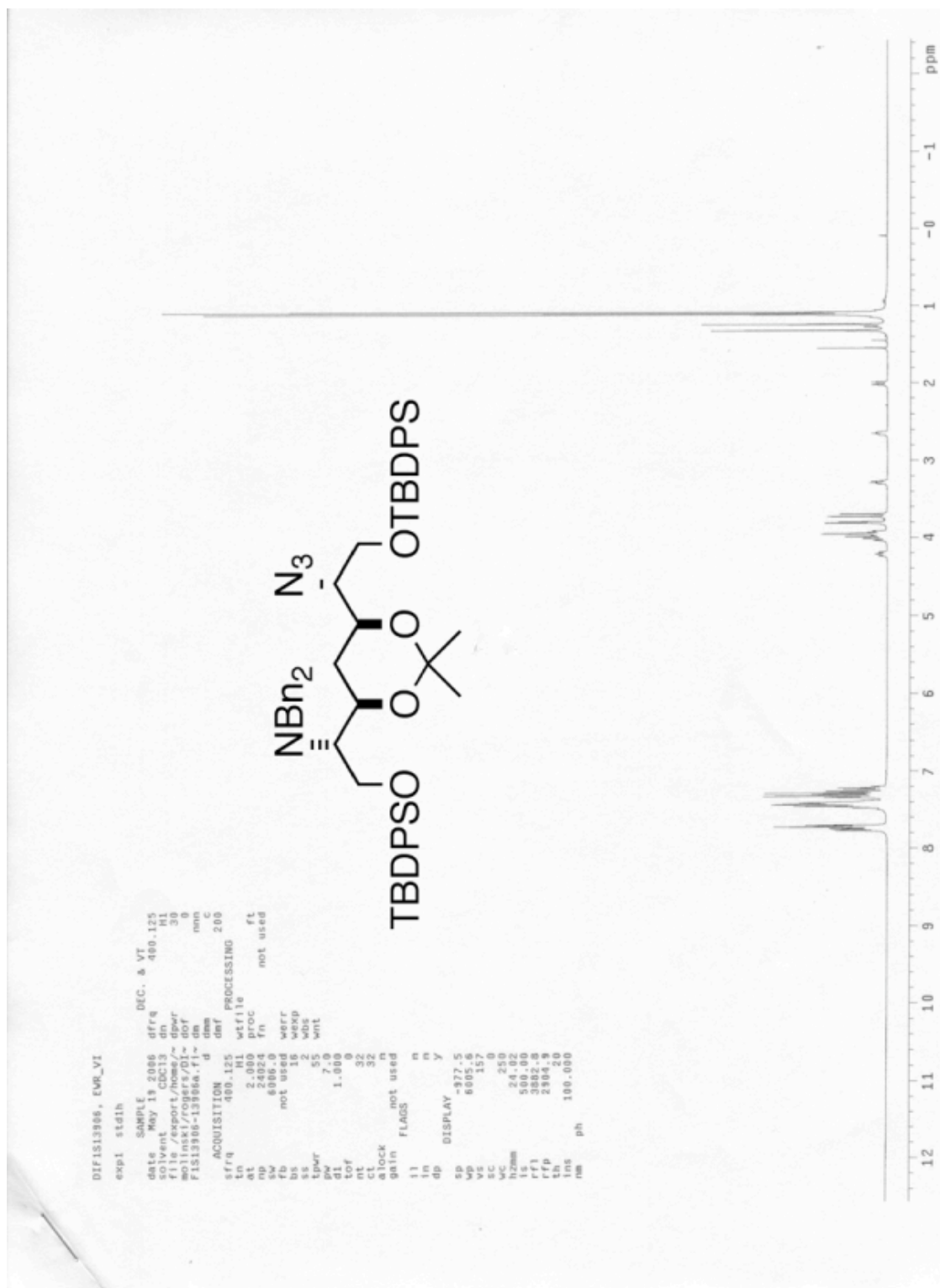
Spectrum 7.49: ^1H NMR (CDCl_3 , 500 MHz) of compound 256



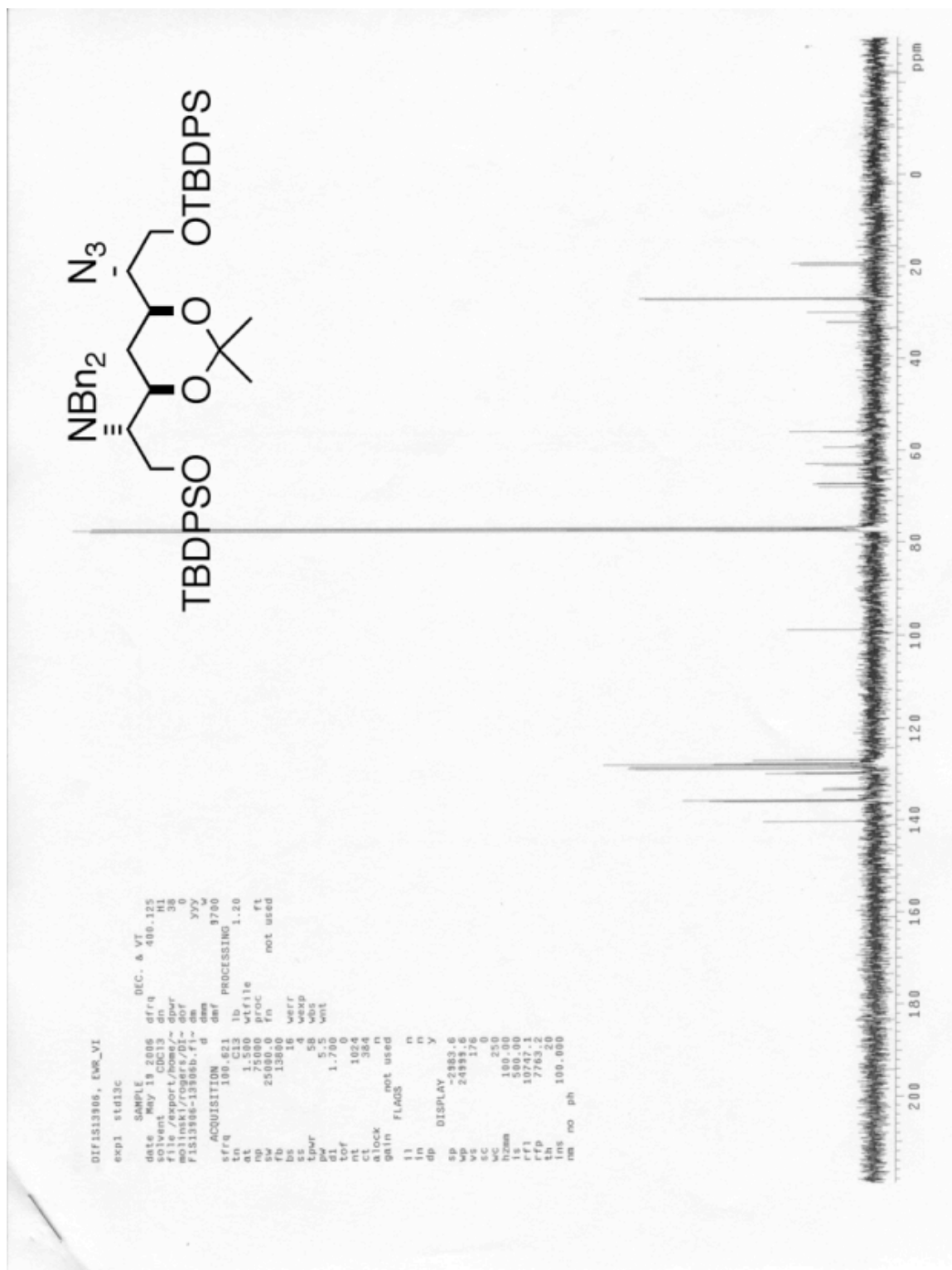
Spectrum 7.51: ^1H NMR (CDCl_3 , 400 MHz) of compound 257



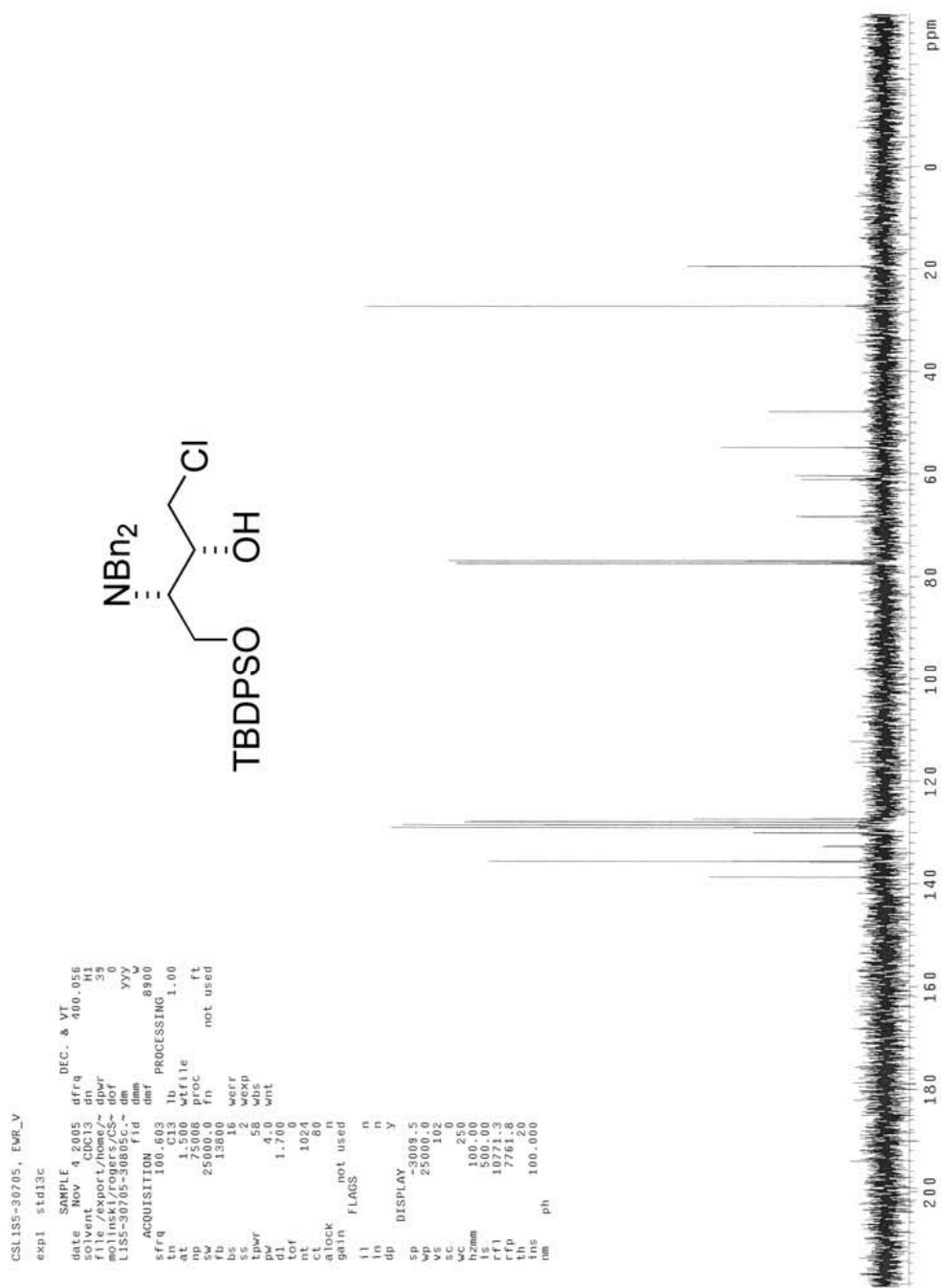
Spectrum 7.52: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 257



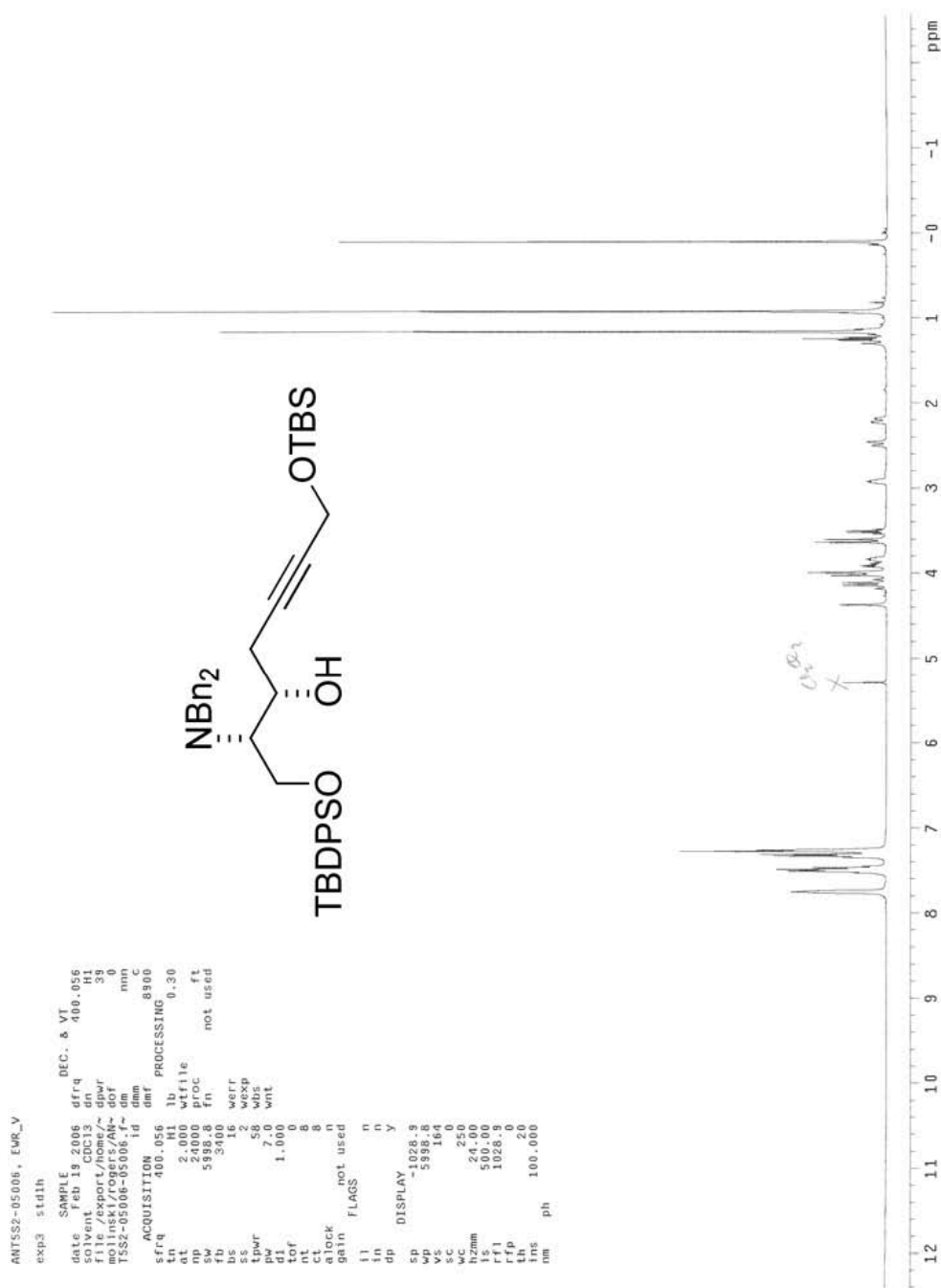
Spectrum 7.53: ^1H NMR (CDCl_3 , 400 MHz) of compound **258**



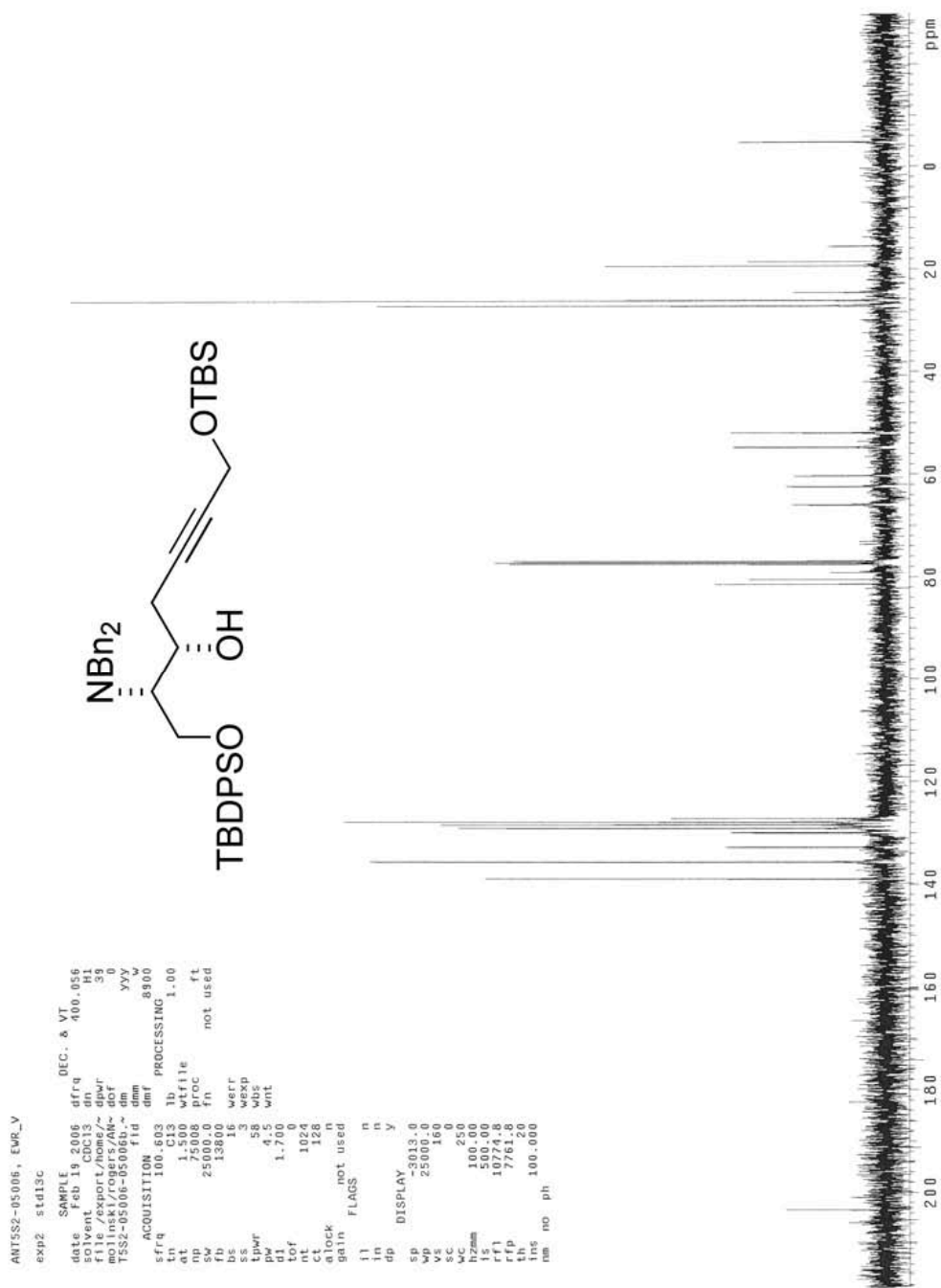
Spectrum 7.54: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 258



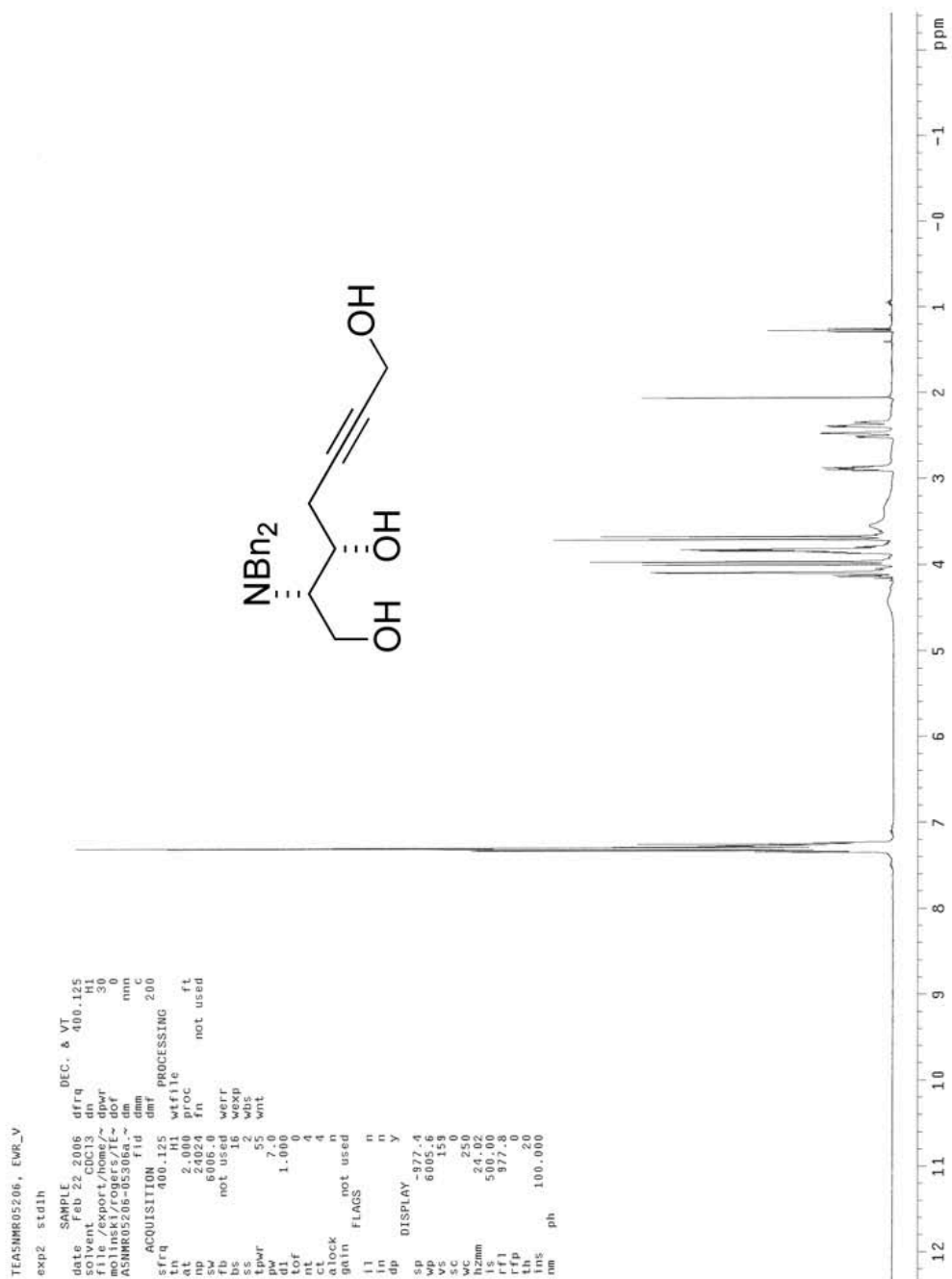
Spectrum 7.56: ¹³C NMR (CDCl₃, 100 MHz) of compound 260



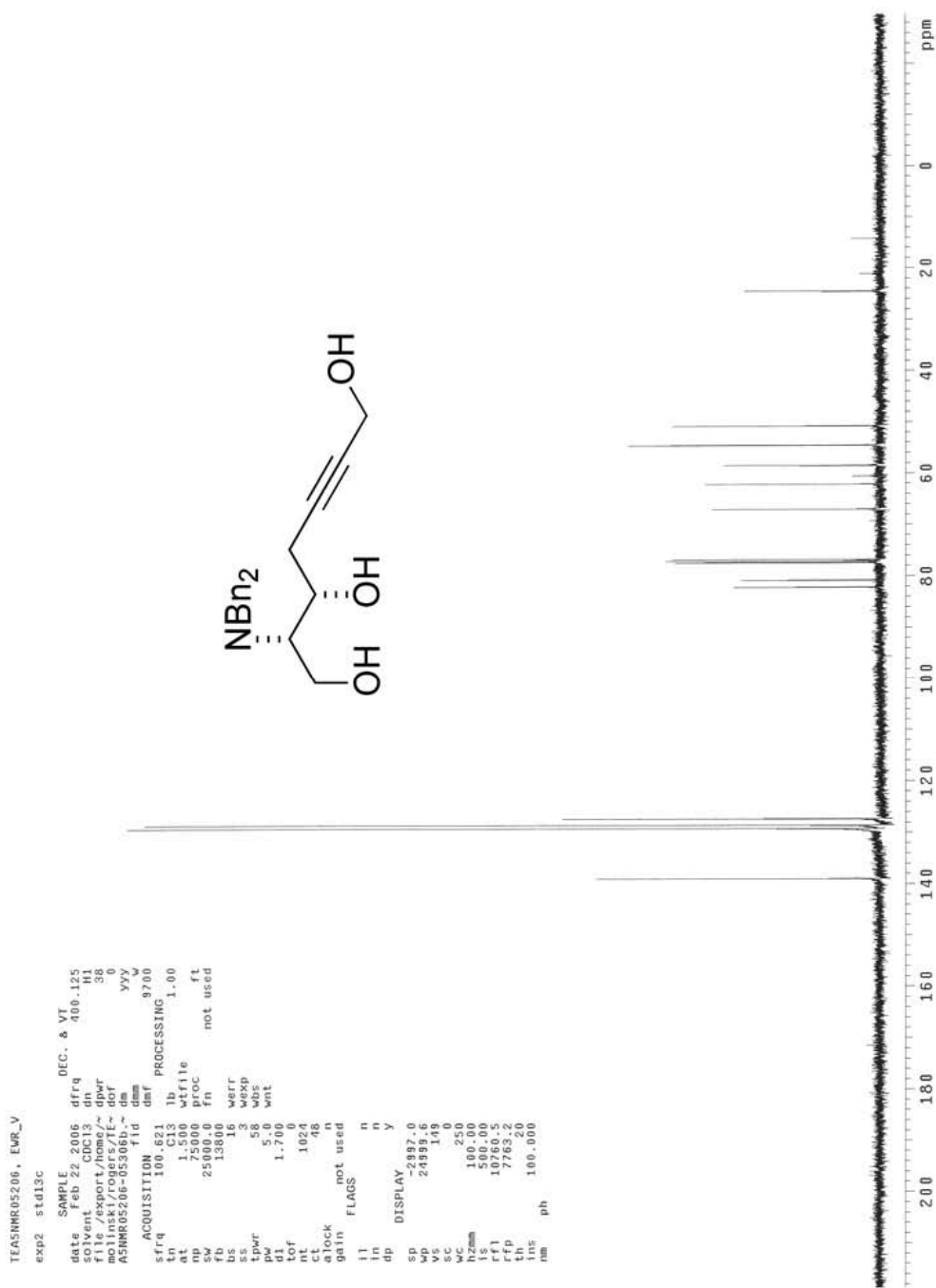
Spectrum 7.57: ¹H NMR (CDCl₃, 400 MHz) of compound 261



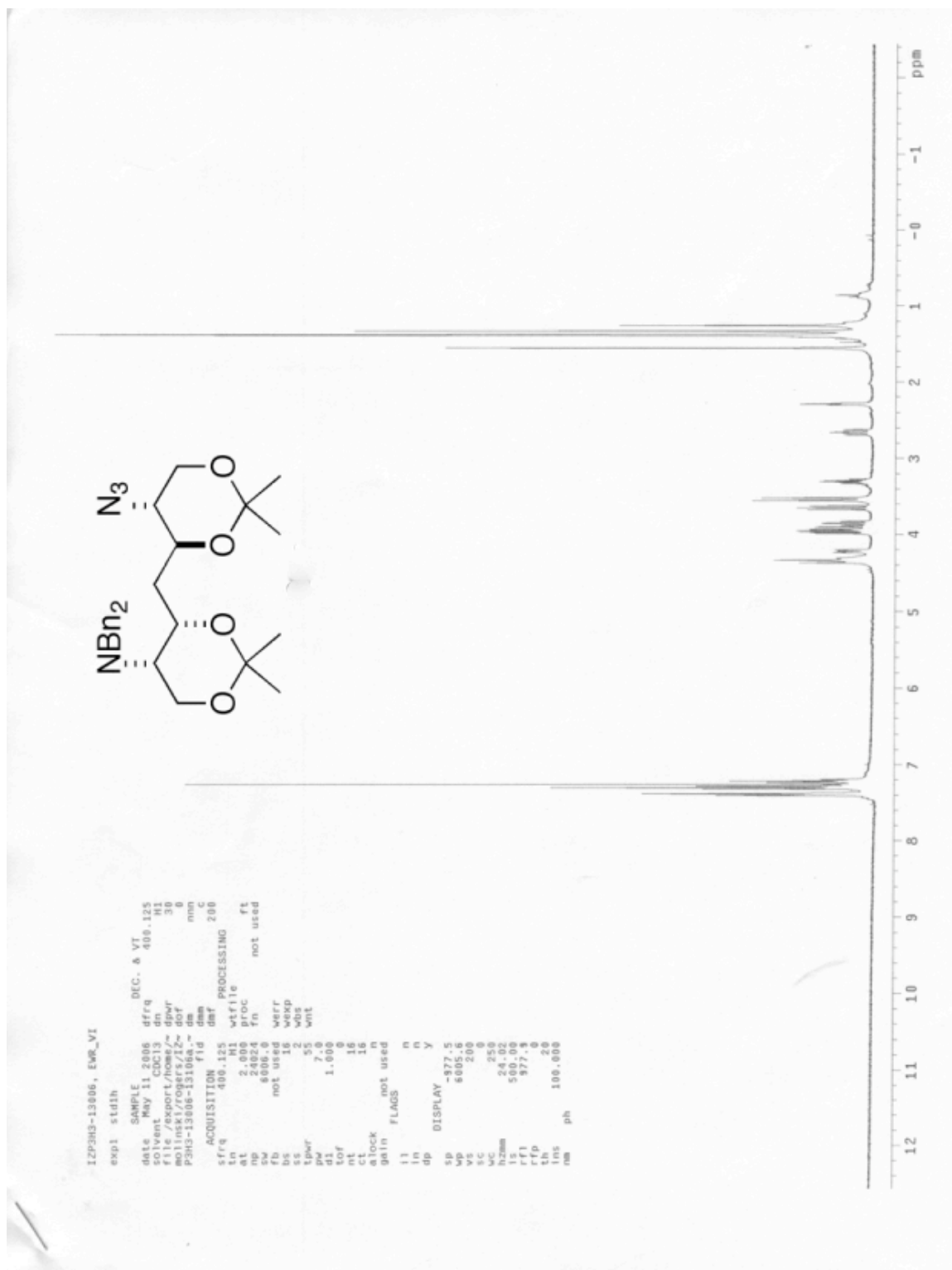
Spectrum 7.58: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 261



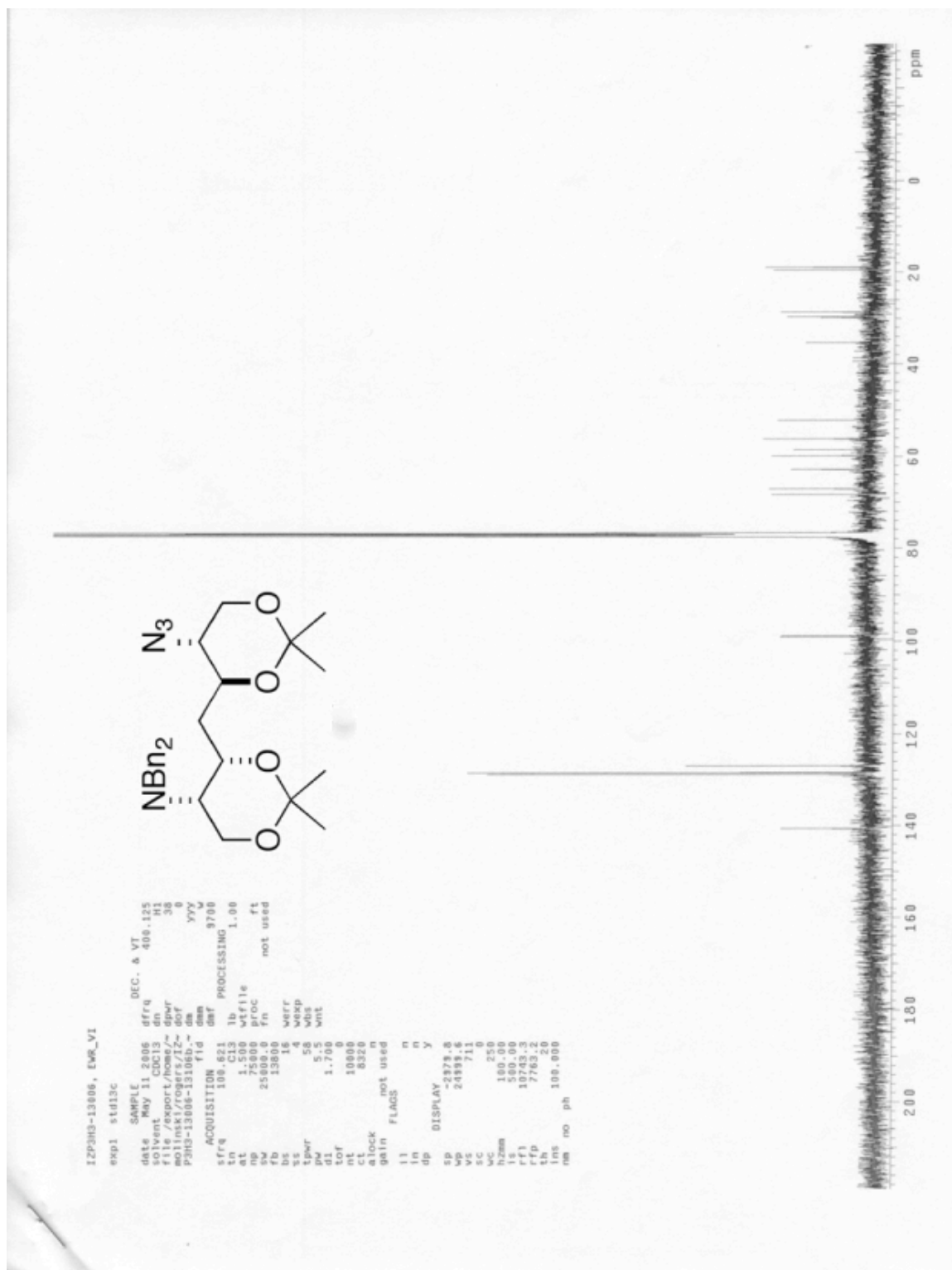
Spectrum 7.59: ^1H NMR (CDCl_3 , 400 MHz) of compound 262



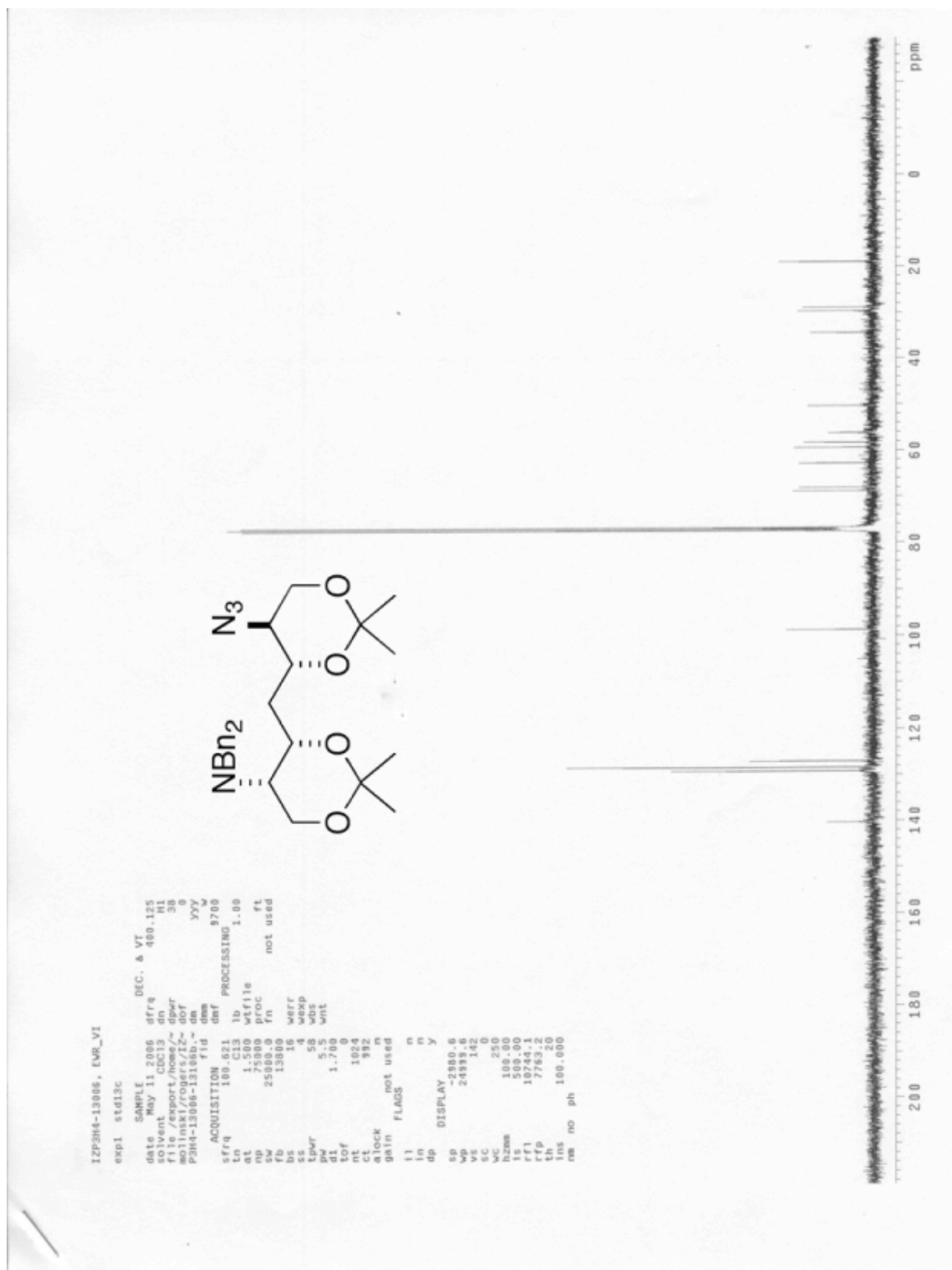
Spectrum 7.60: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 262



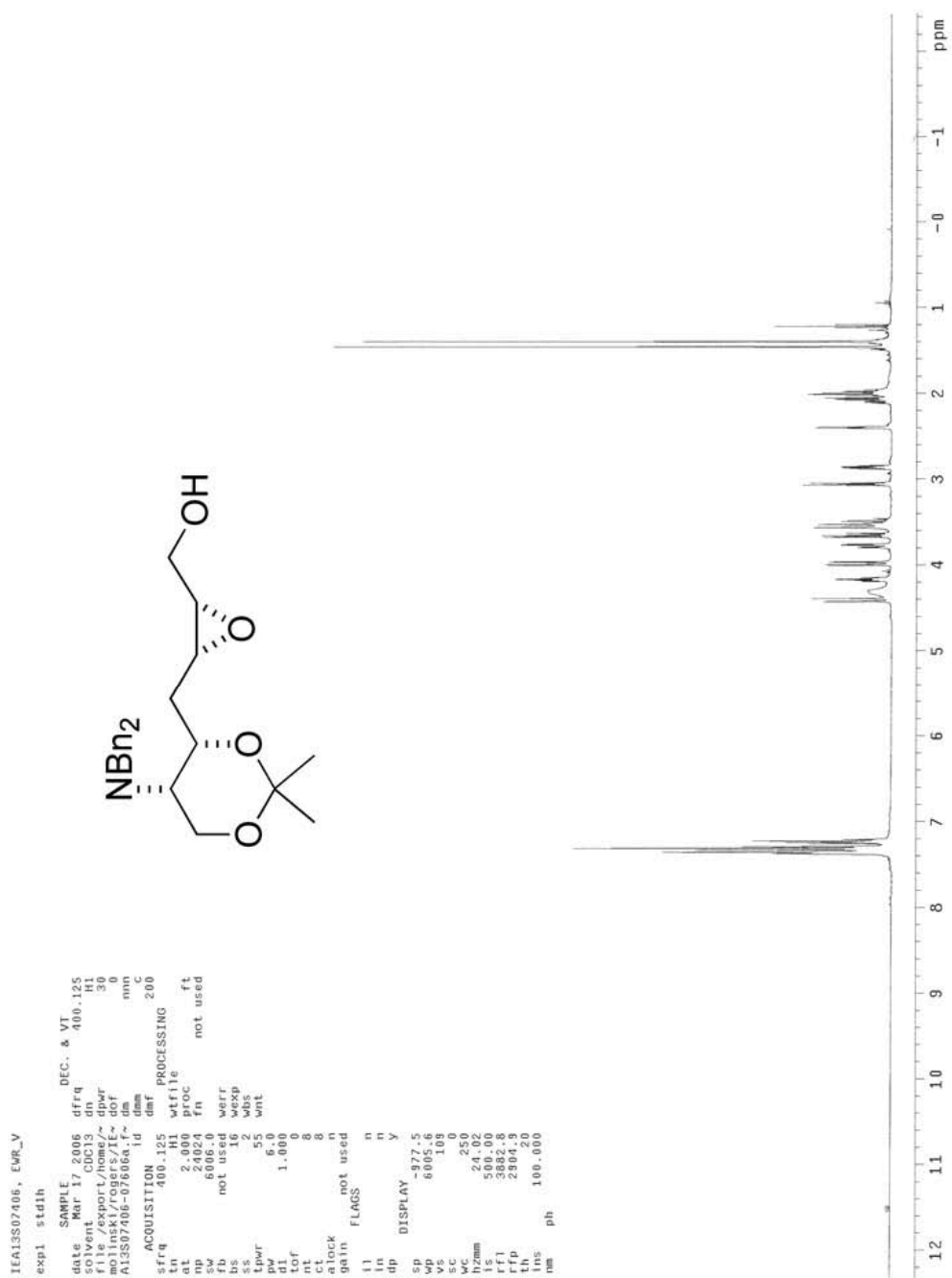
Spectrum 7.61: ^1H NMR (CDCl_3 , 400 MHz) of compound 269



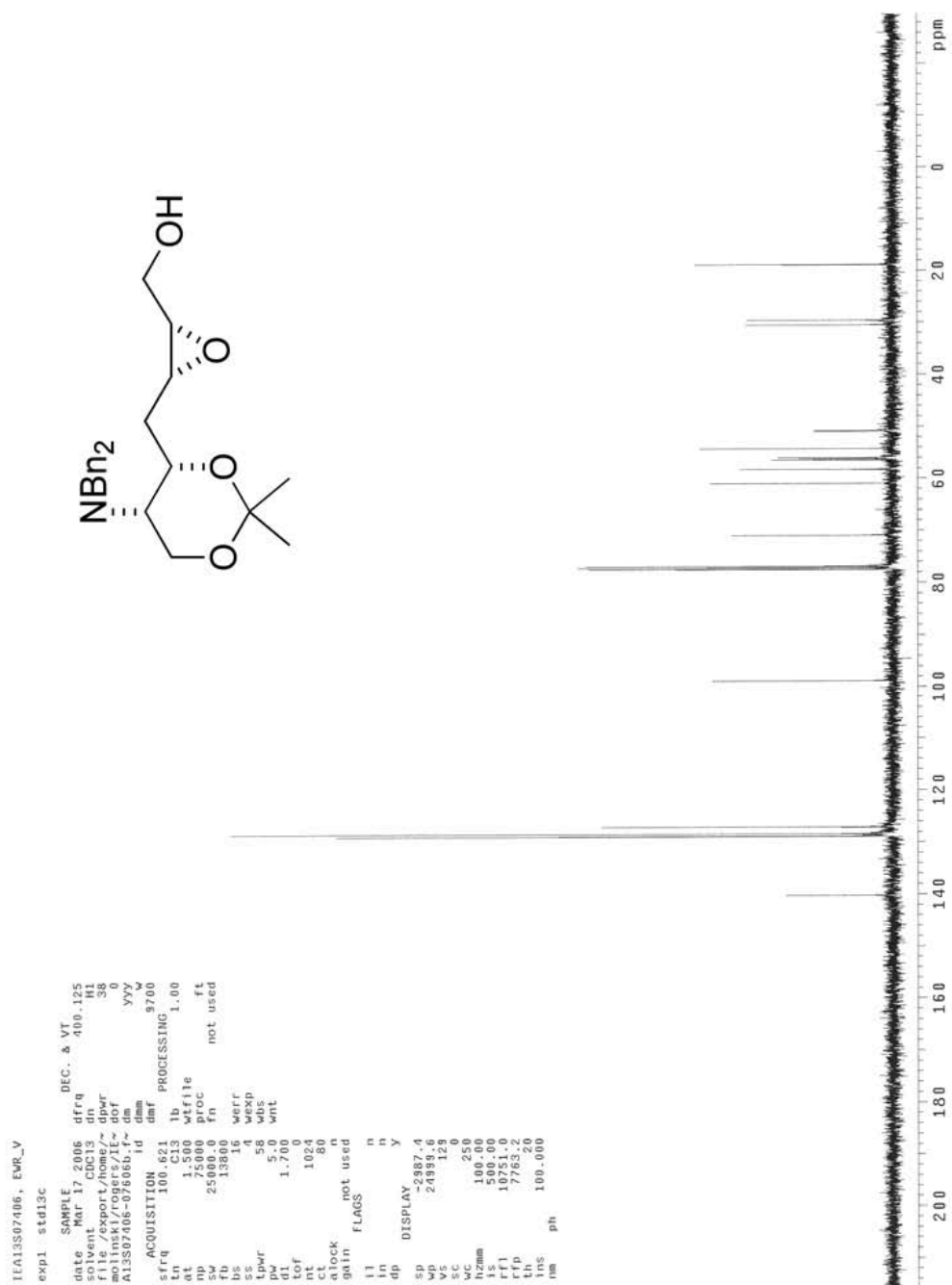
Spectrum 7.62: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 269



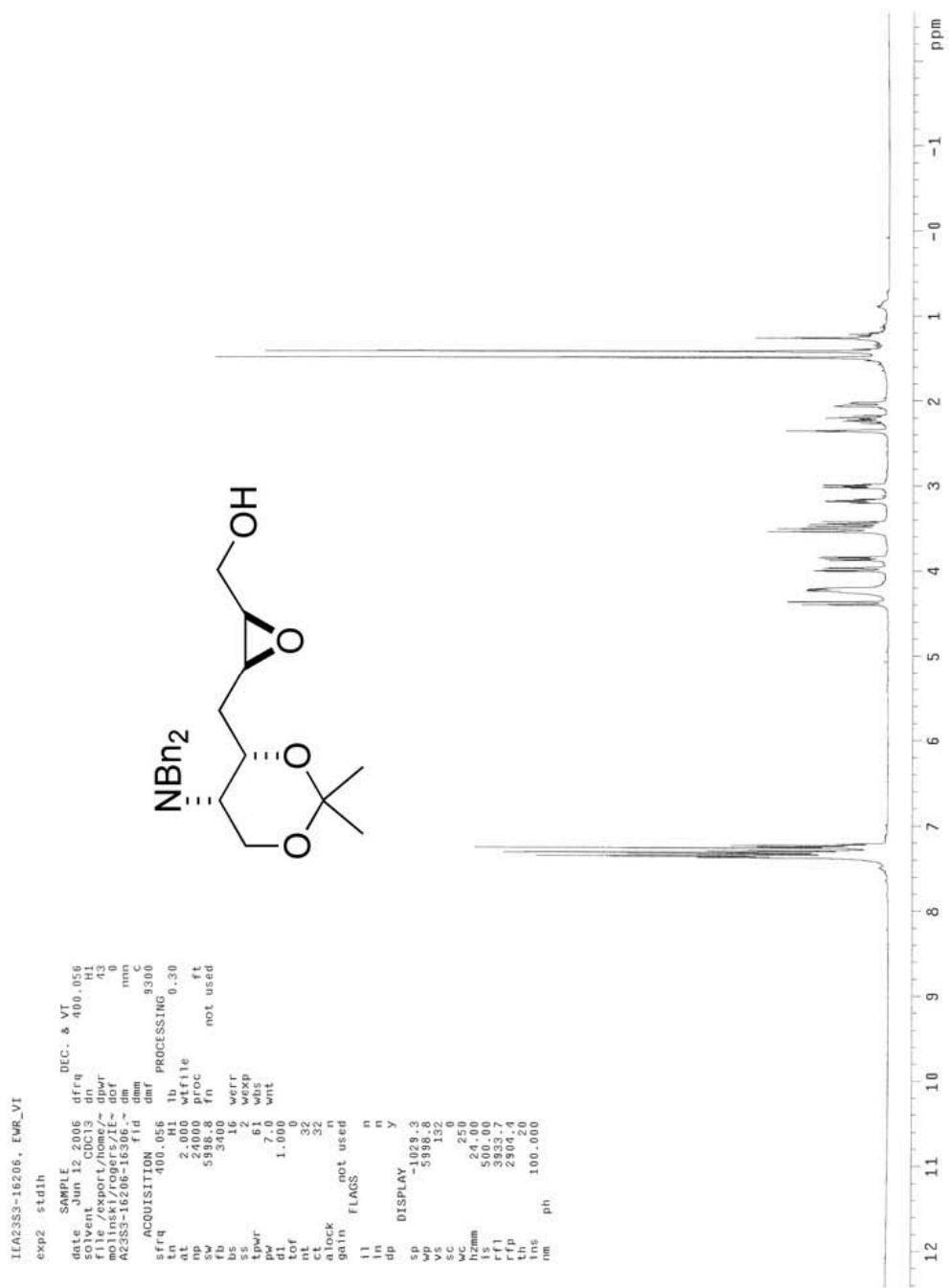
Spectrum 7.64: ^{13}C NMR (CDCl_3 , 100 MHz) of compound **271**



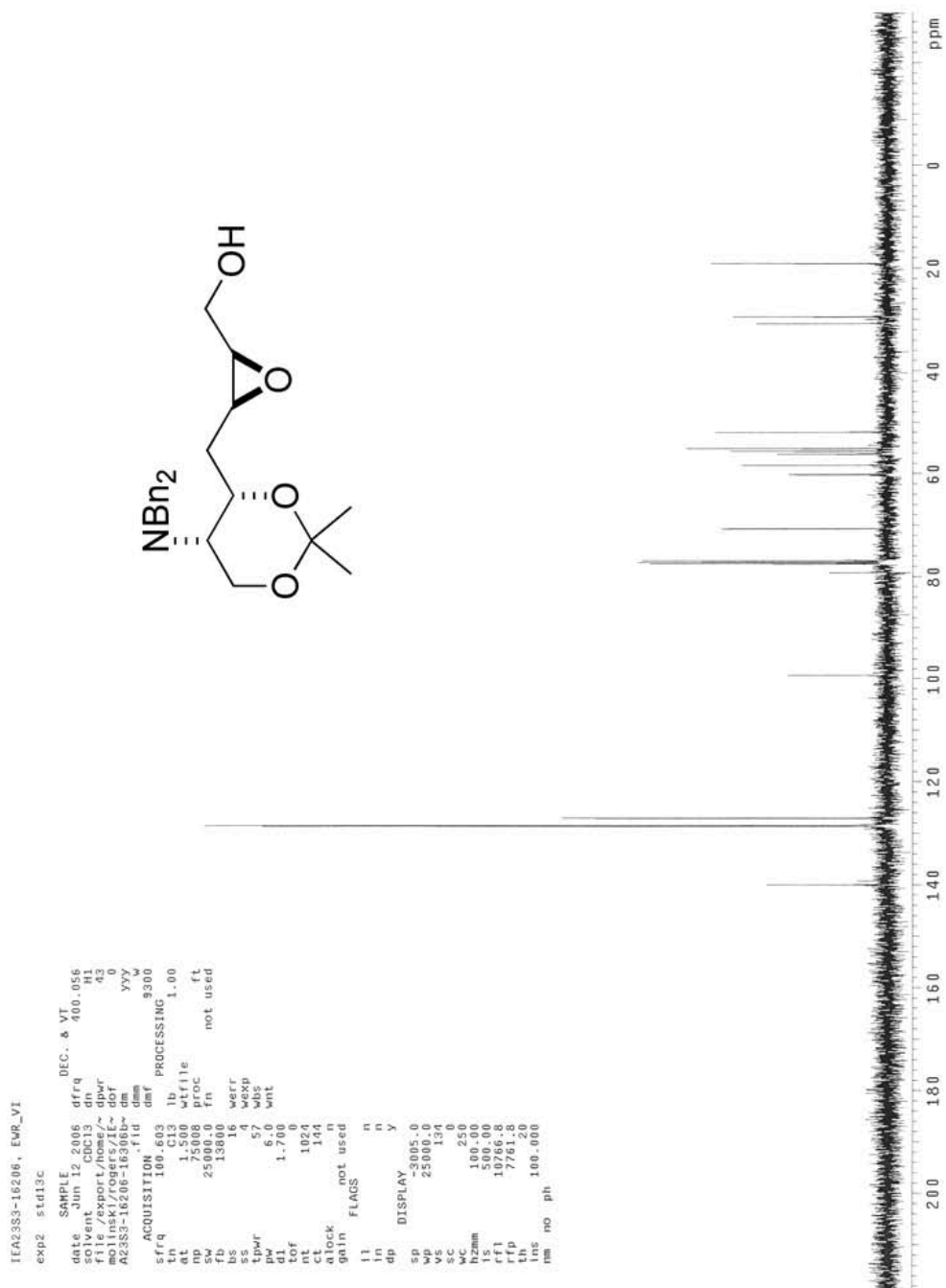
Spectrum 7.65: ^1H NMR (CDCl_3 , 400 MHz) of compound 273



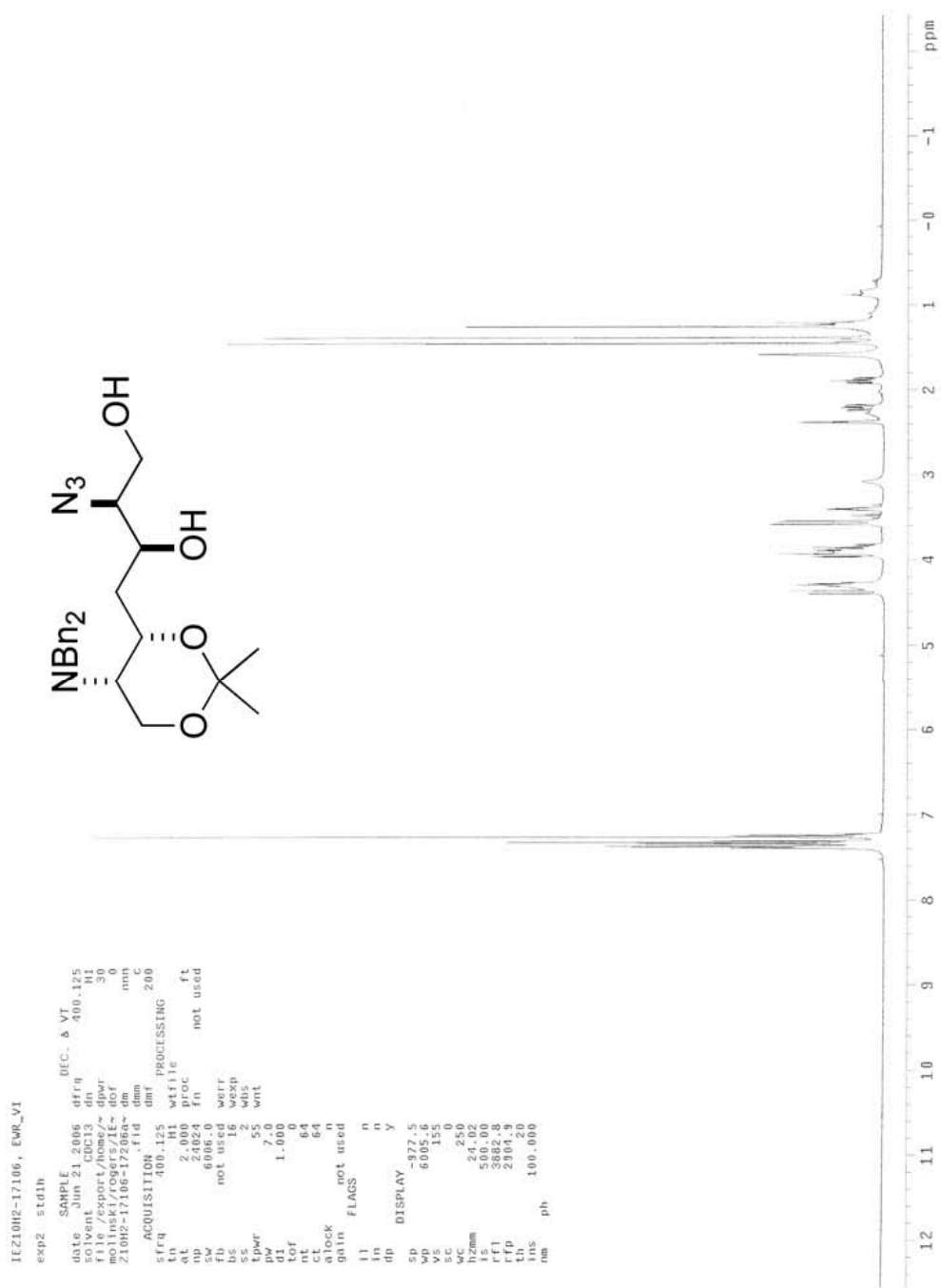
Spectrum 7.66: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 273



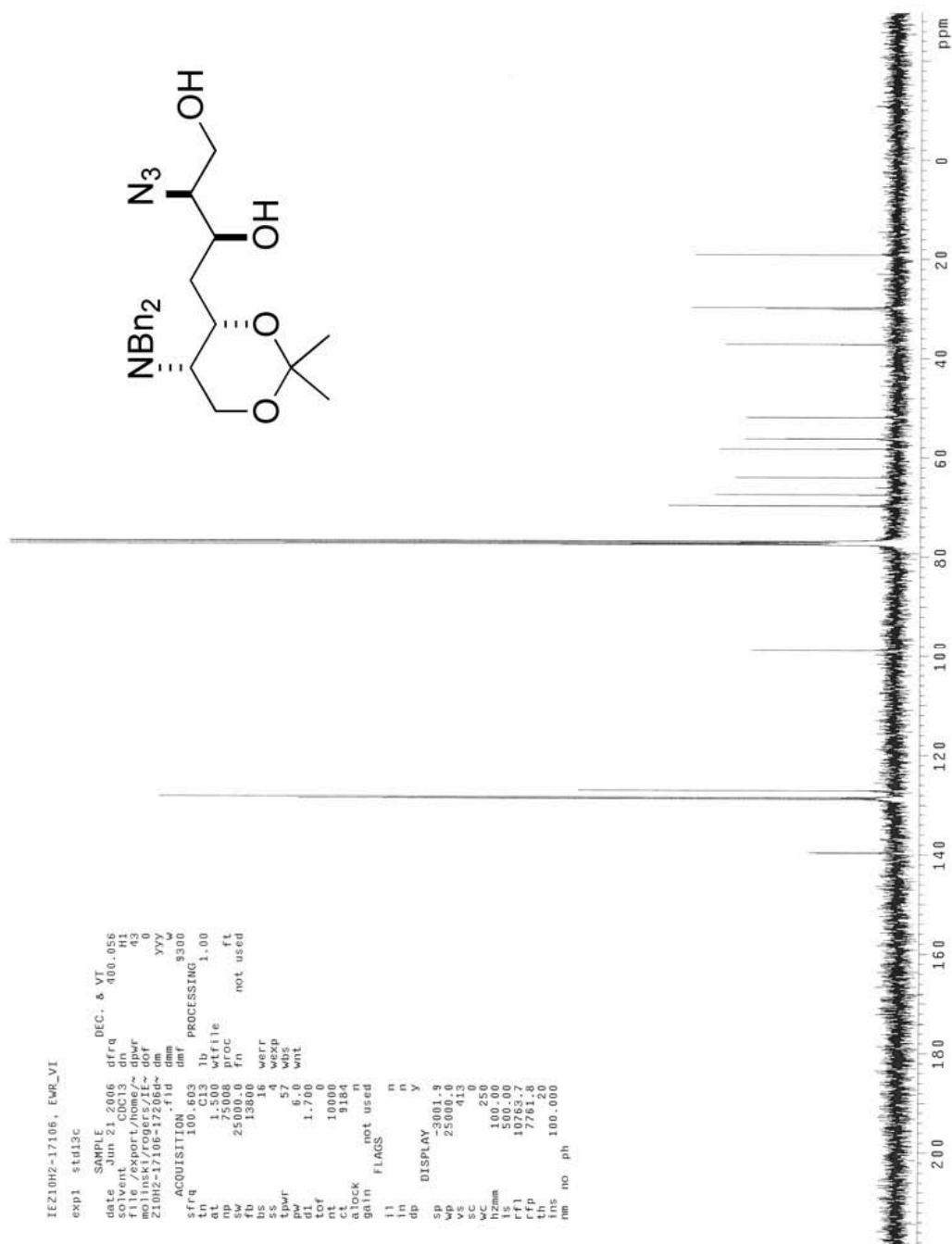
Spectrum 7.67: ^1H NMR (CDCl_3 , 400 MHz) of compound 274



Spectrum 7.68: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 274

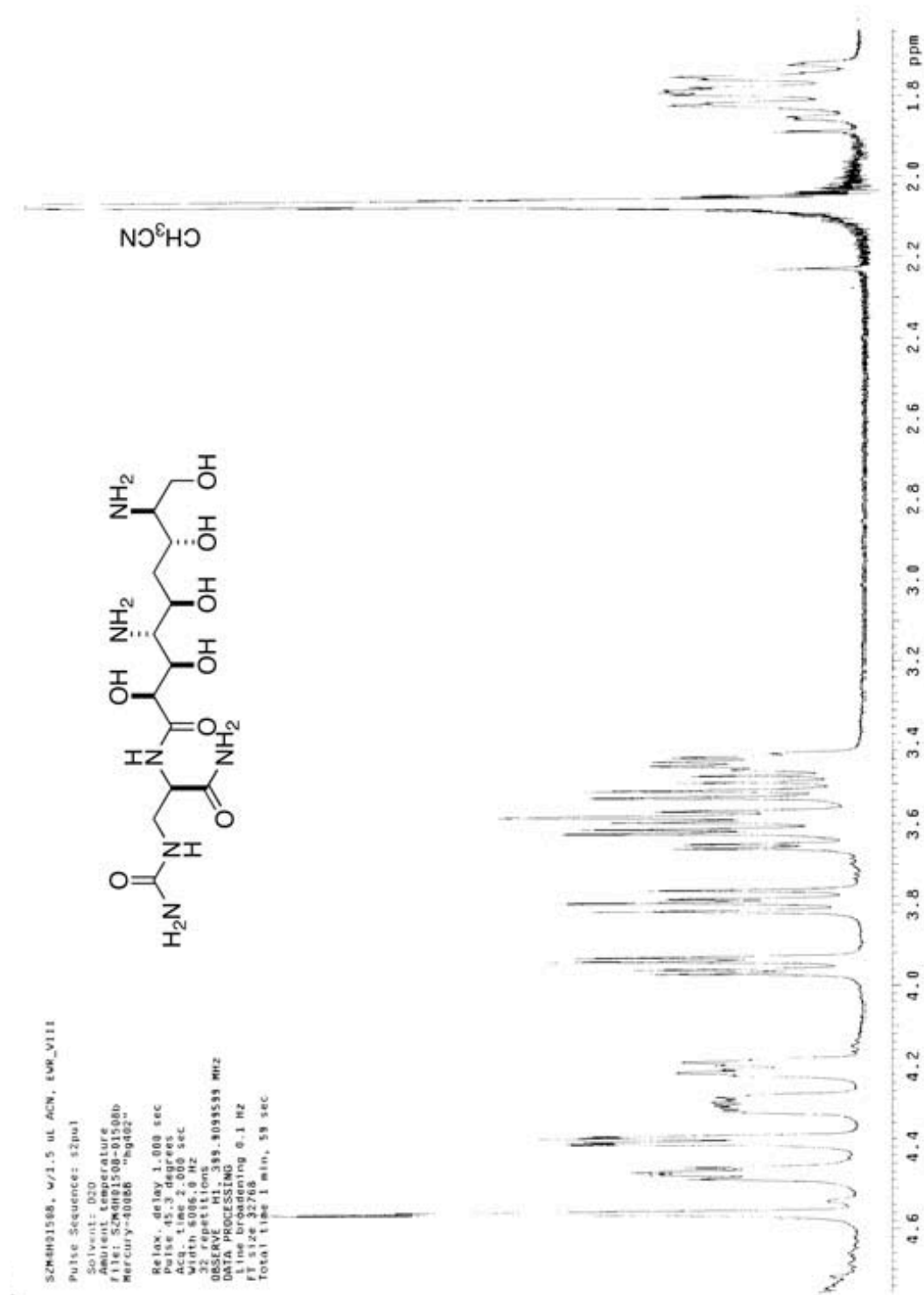


Spectrum 7.71: ^1H NMR (CDCl_3 , 400 MHz) of compound 277

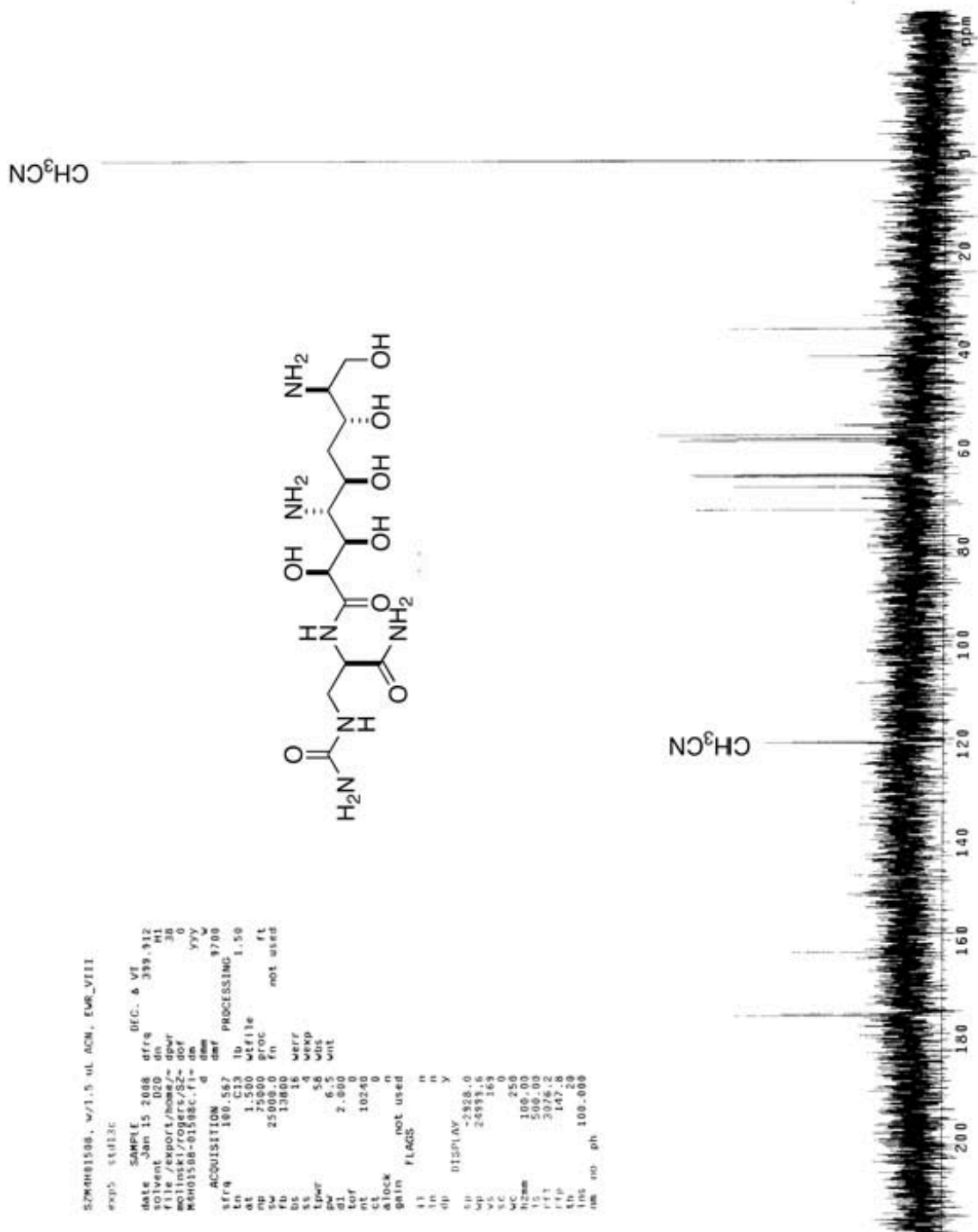


Spectrum 7.72: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 277

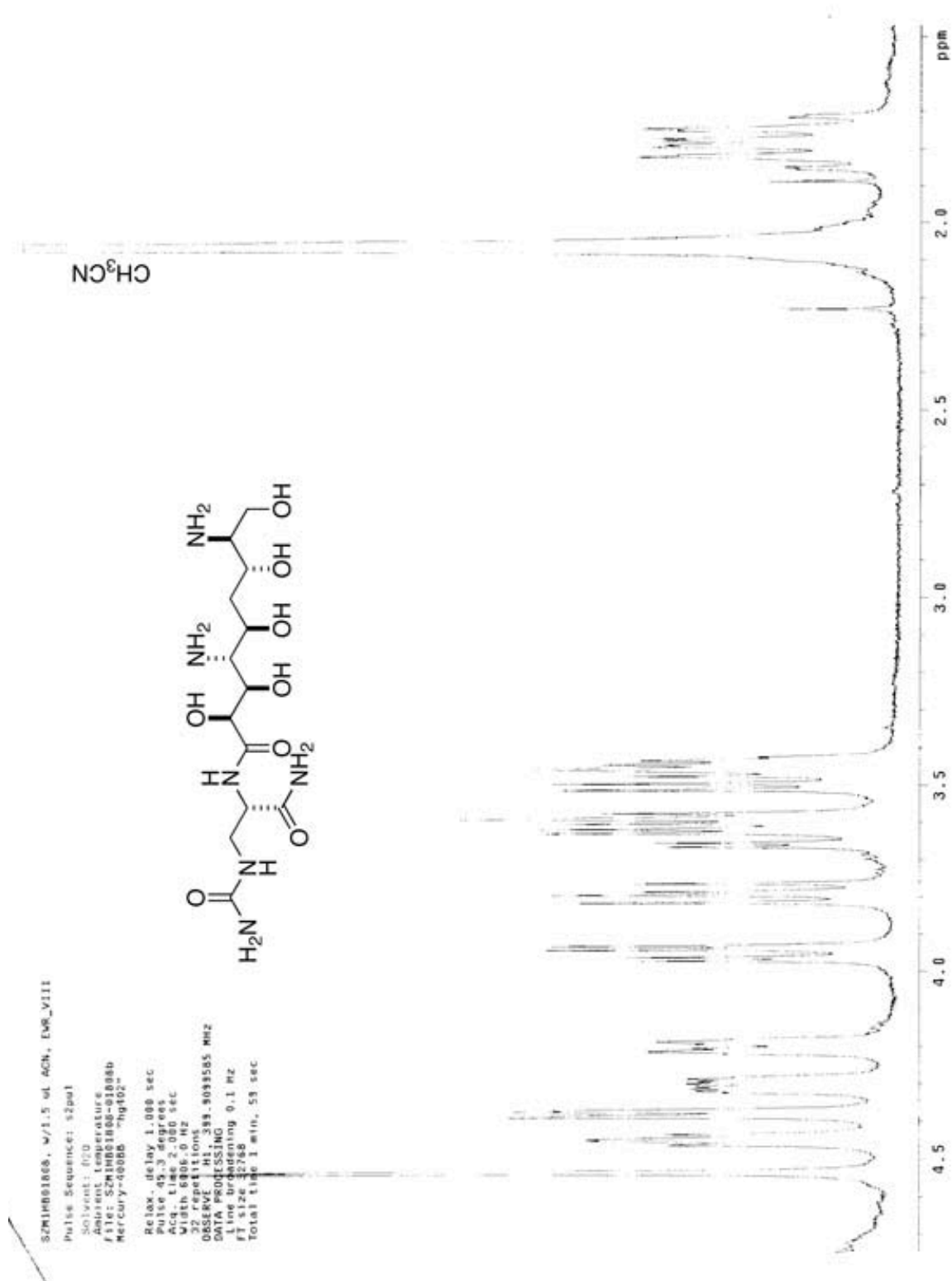
7.3.2. Chapter 3 Spectra



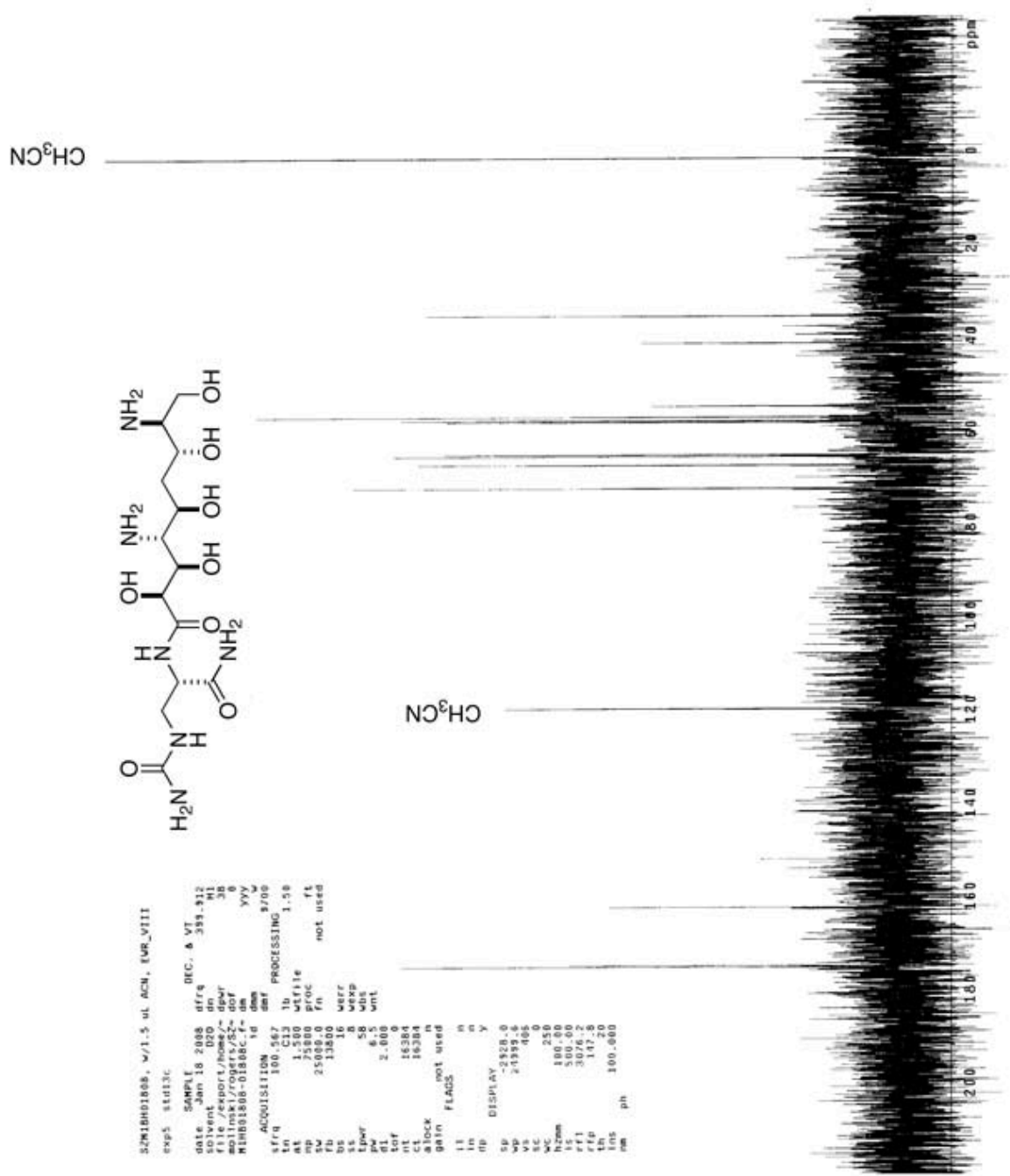
Spectrum 7.73: ^1H NMR (D_2O w/ 0.5% CH_3CN , 400 MHz) of compound (-)-1



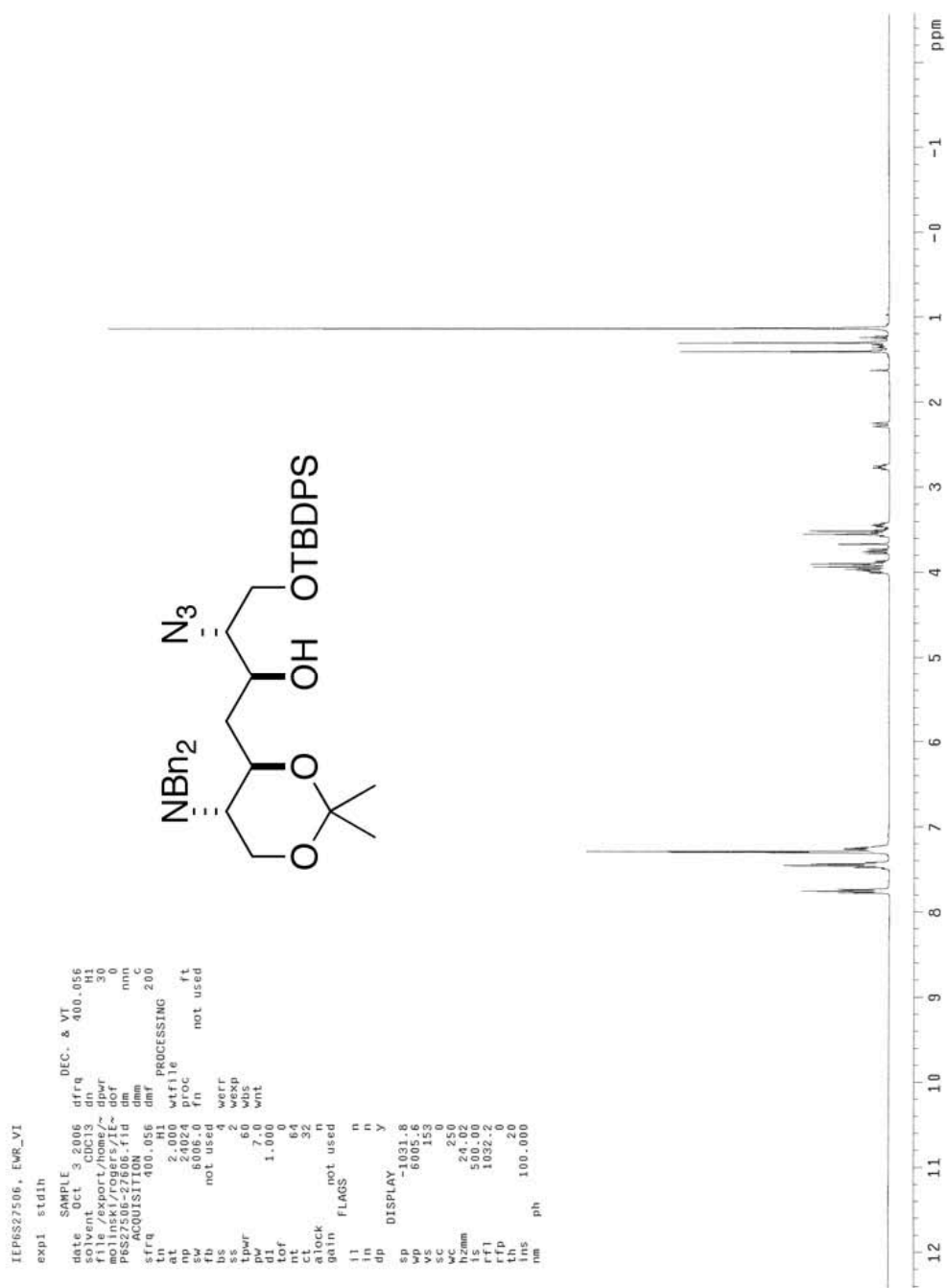
Spectrum 7.74: ¹³C NMR (D₂O w/ 0.5% CH₃CN, 100 MHz) of compound (-)-1



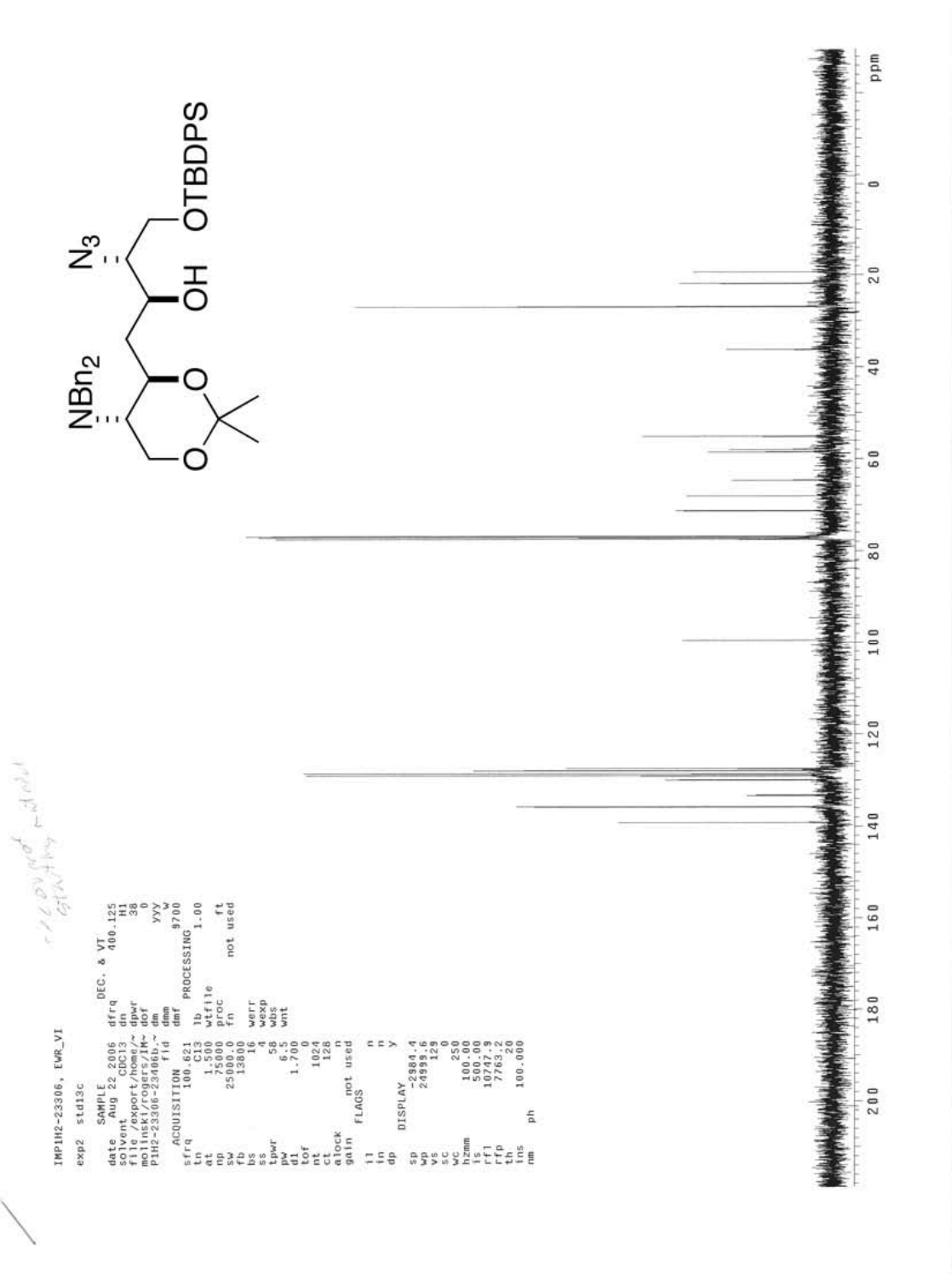
Spectrum 7.75: ¹H NMR (D₂O w/ 0.5% CH₃CN, 400 MHz) of compound (-)-279



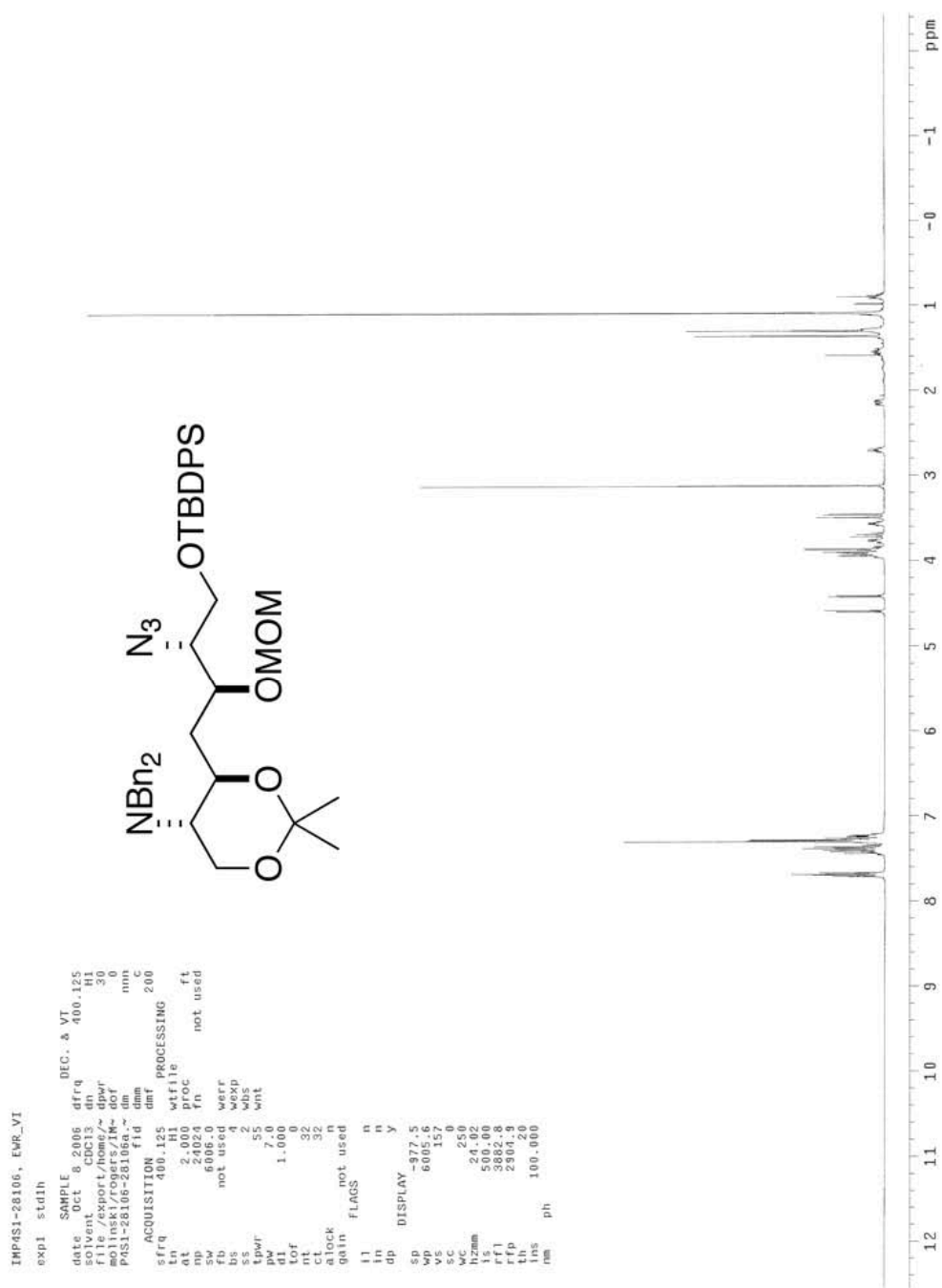
Spectrum 7.76: ¹³C NMR (D₂O w/ 0.5% CH₃CN, 100 MHz) of compound (-)-279

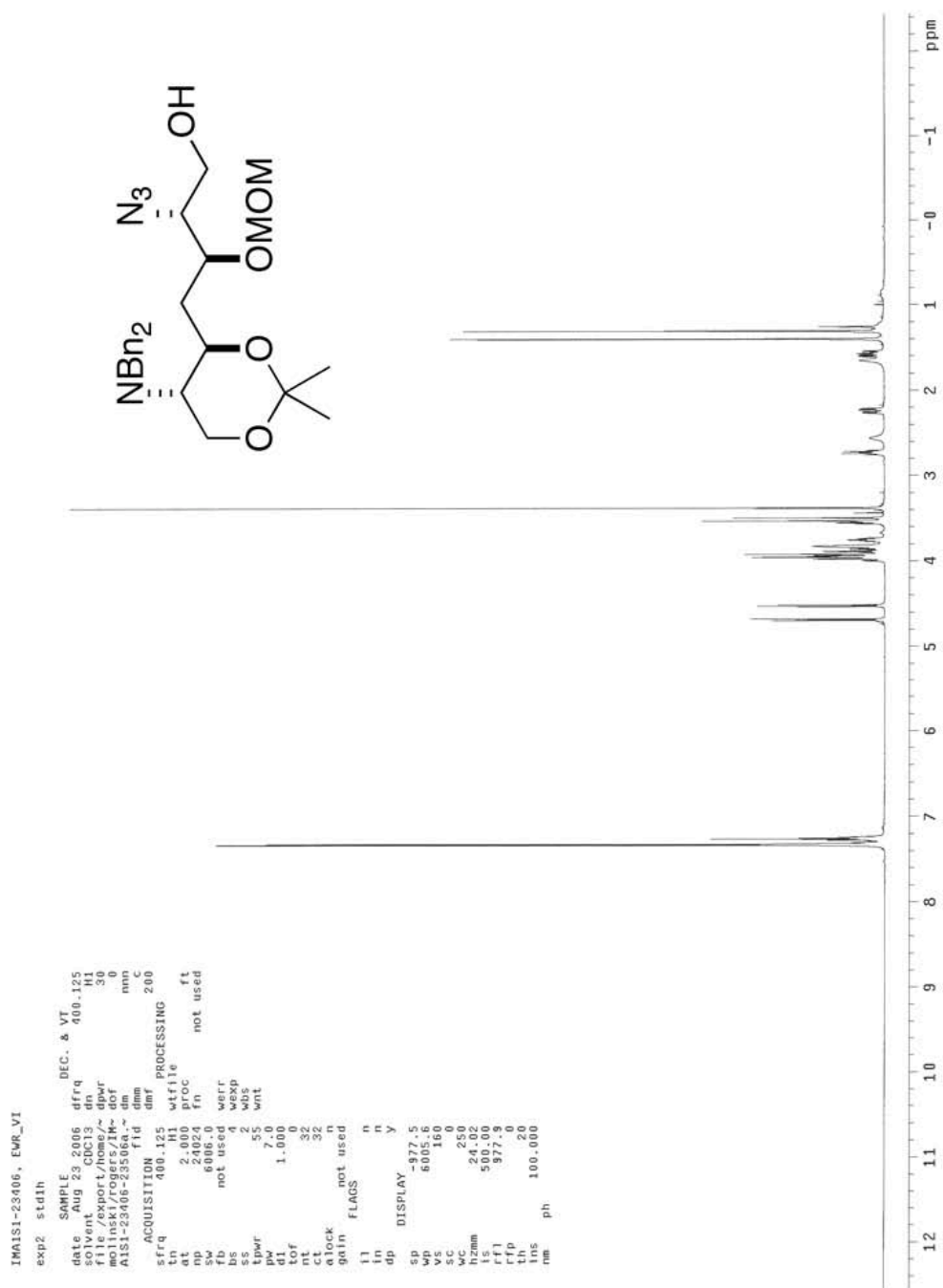


Spectrum 7.77: ^1H NMR (CDCl_3 , 400 MHz) of compound 285

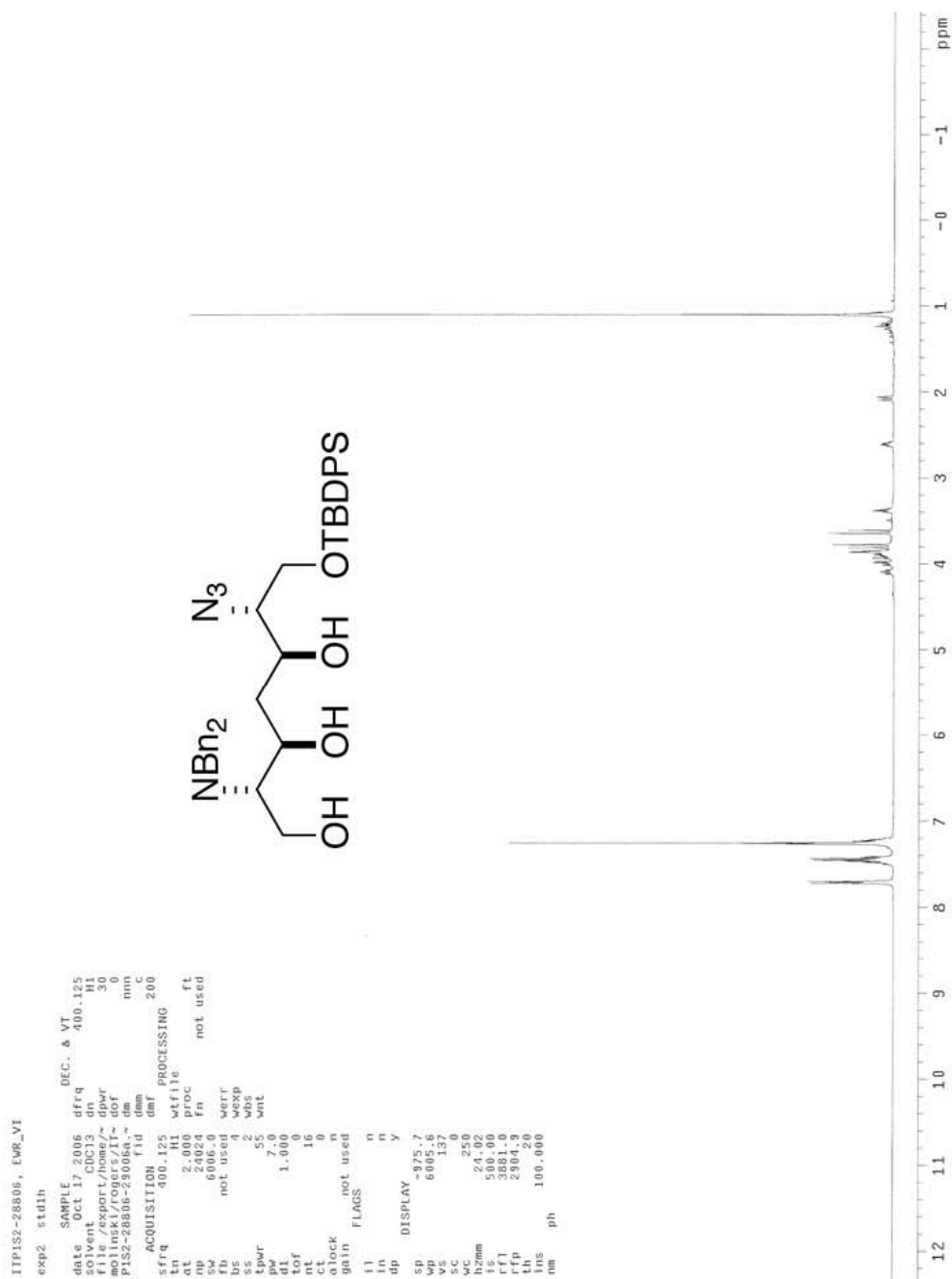


Spectrum 7.78: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 285

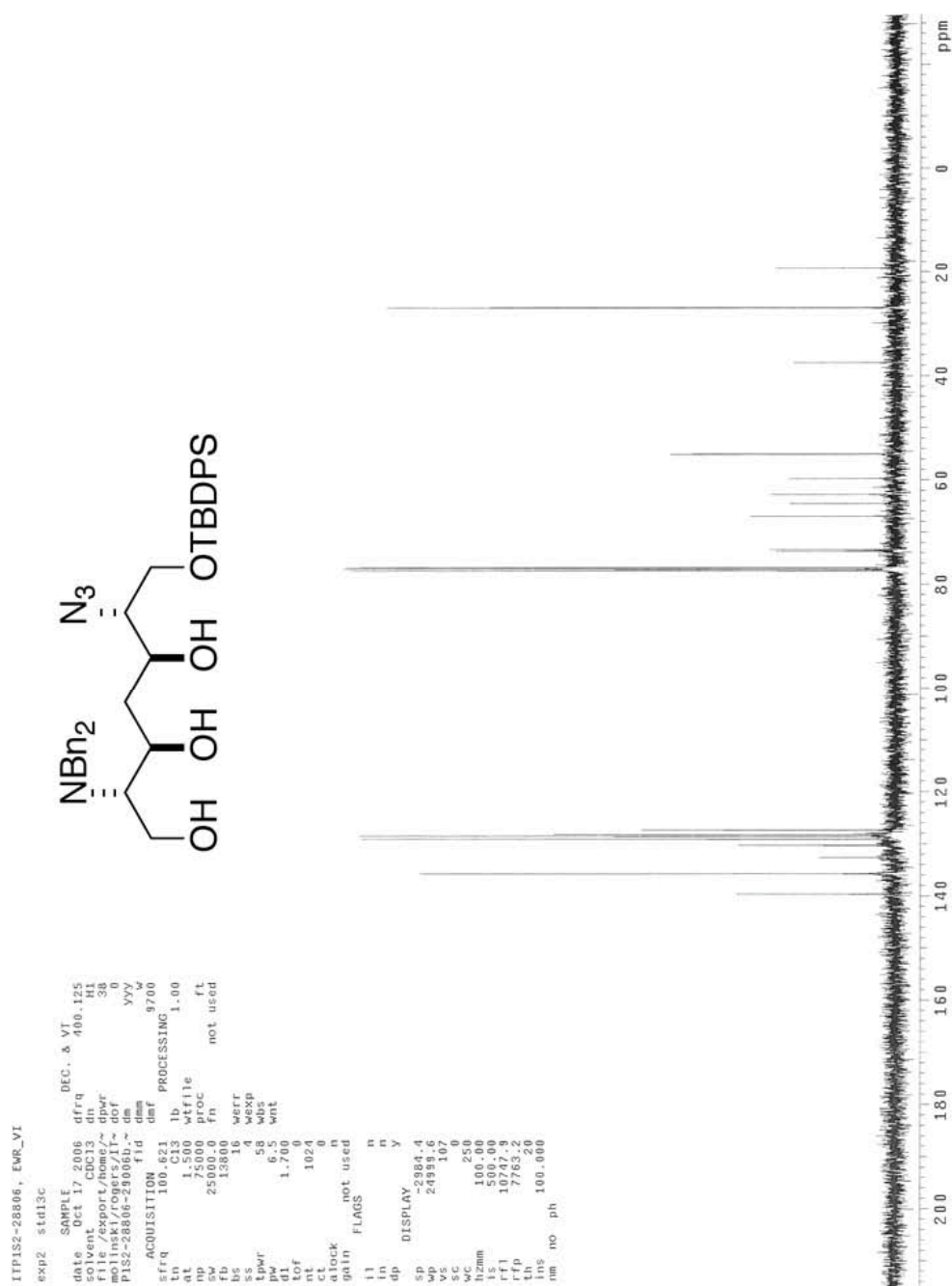




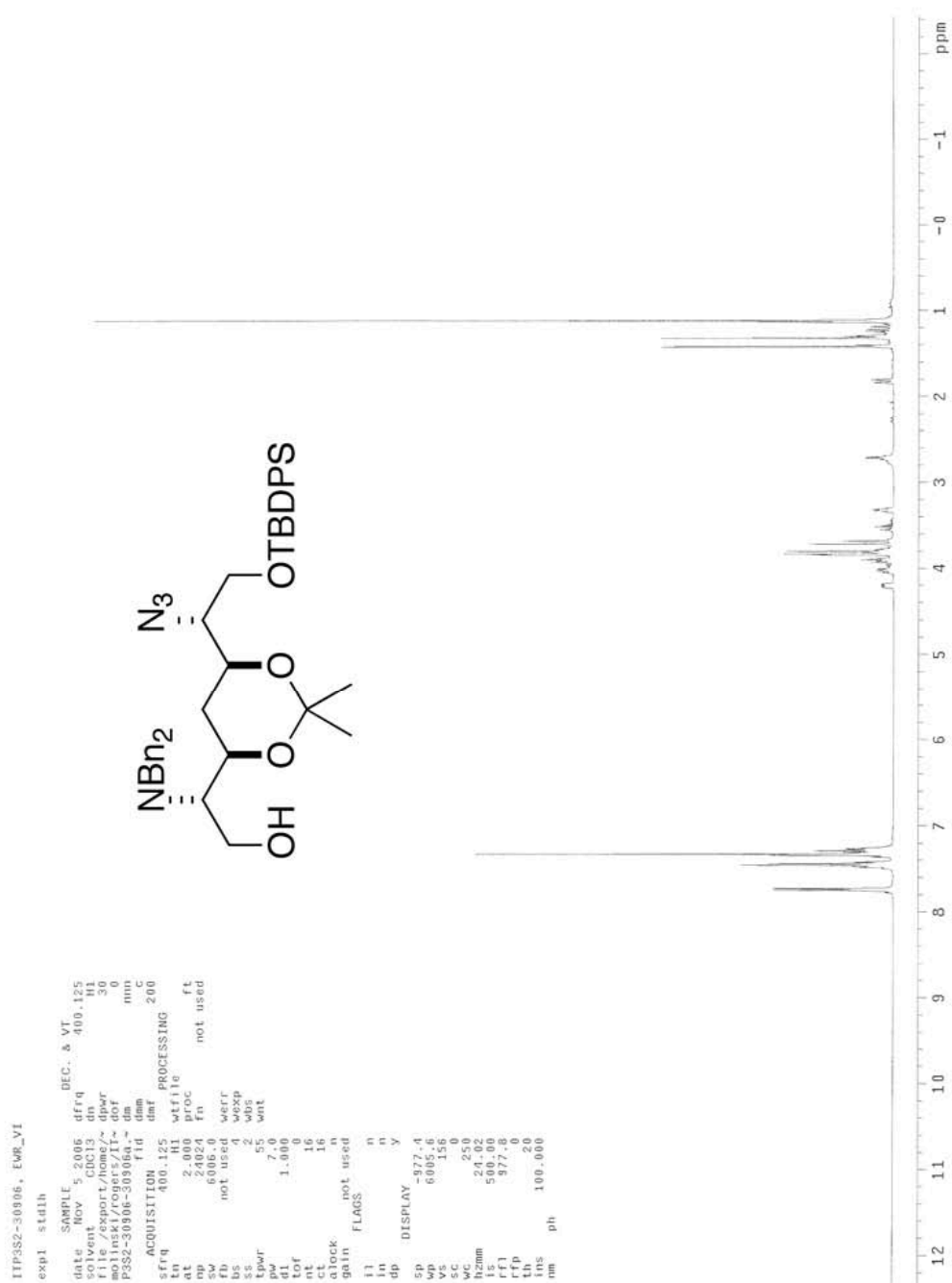
Spectrum 7.81: ^1H NMR (CDCl_3 , 400 MHz) of compound 287



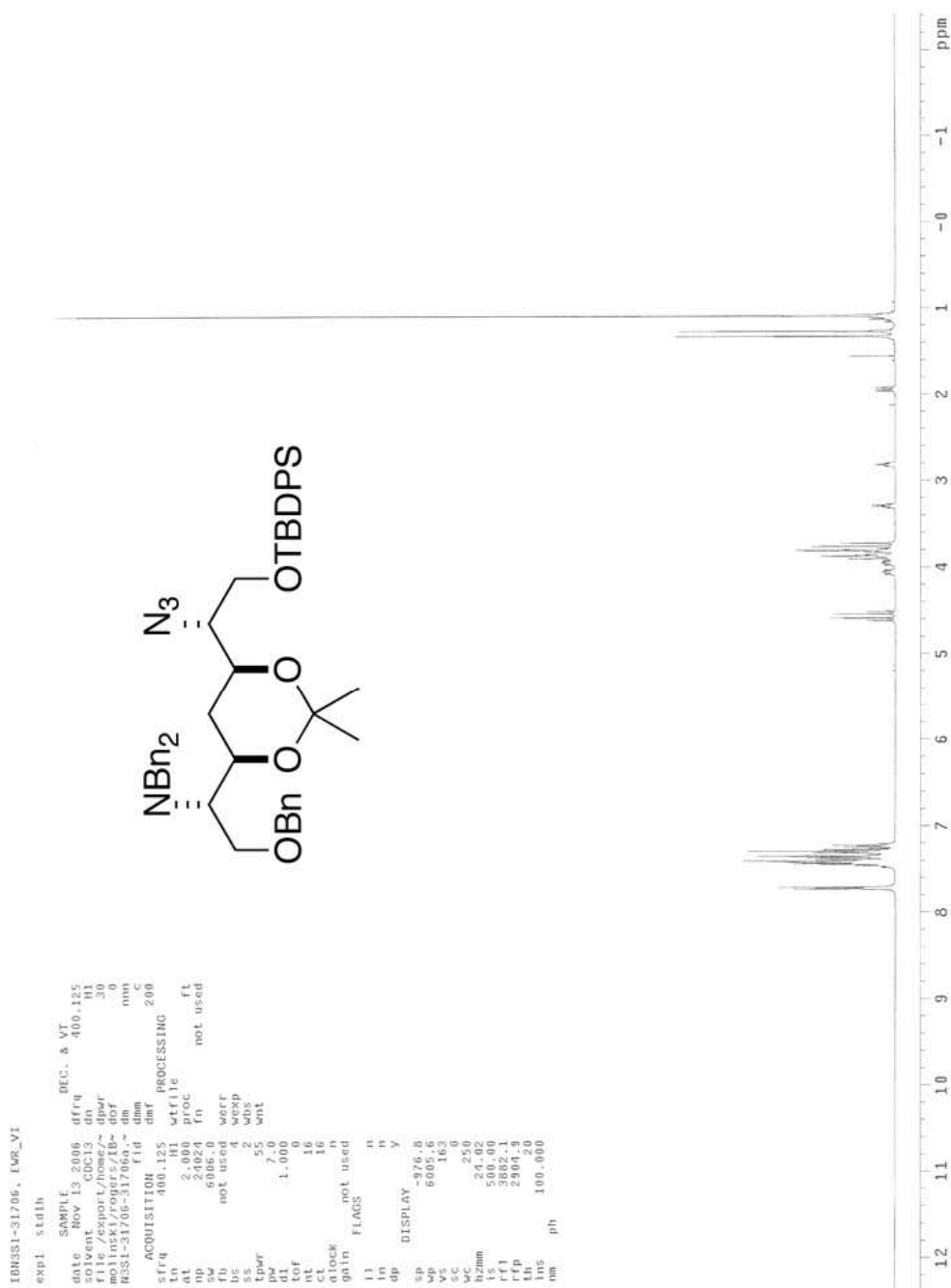
Spectrum 7.85: ^1H NMR (CDCl_3 , 400 MHz) of compound 291



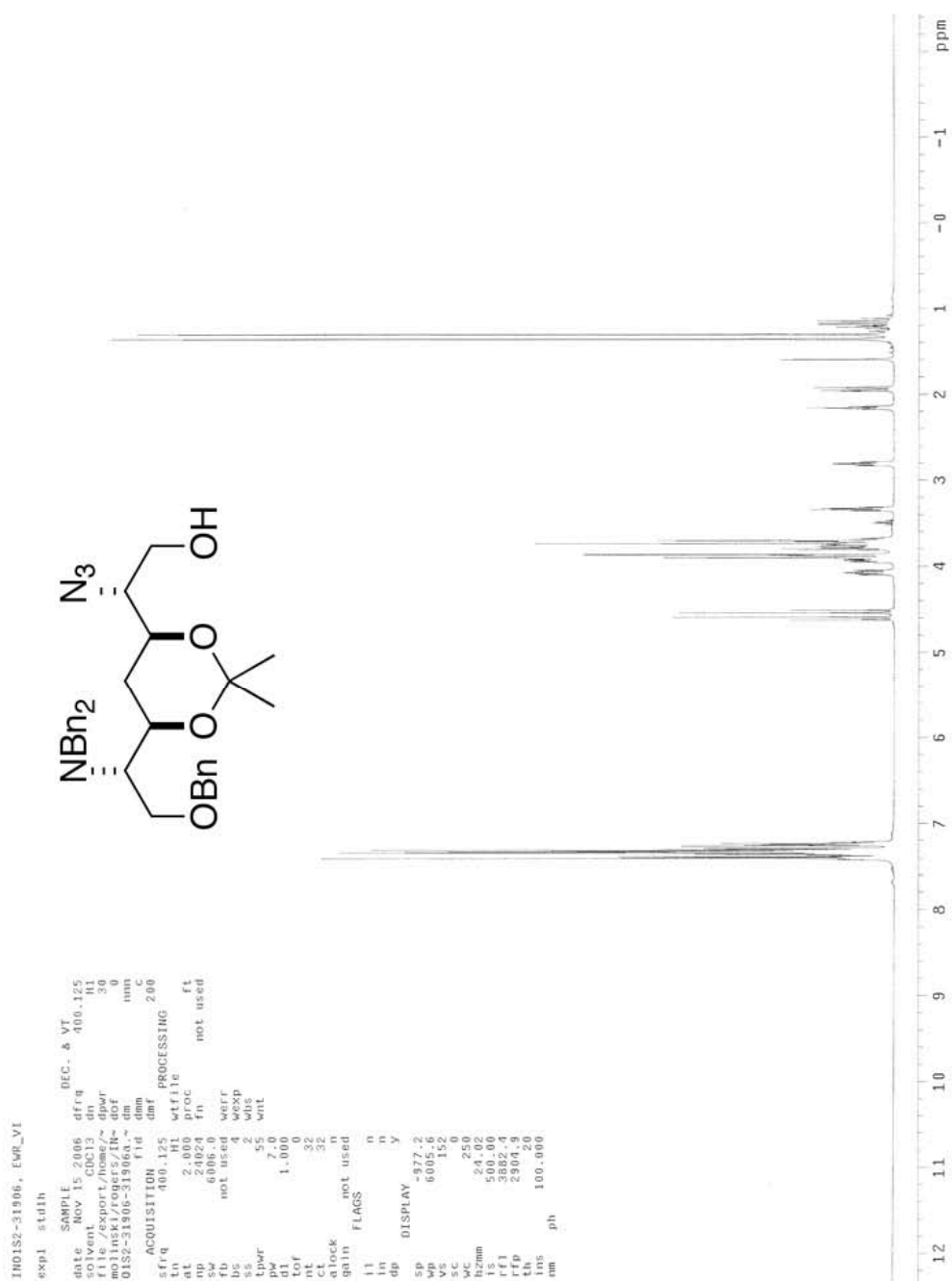
Spectrum 7.86: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 291



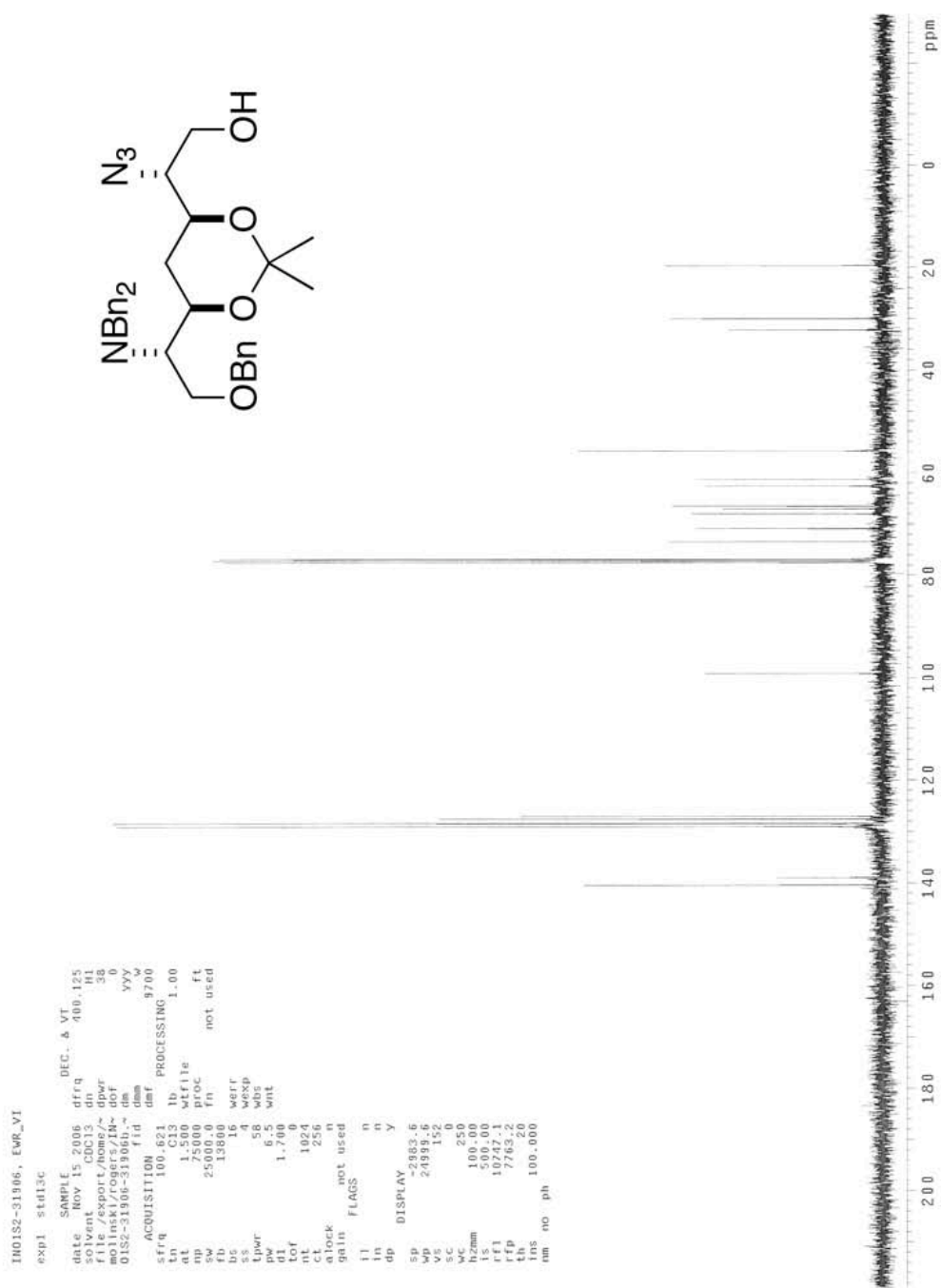
Spectrum 7.87: ^1H NMR (CDCl_3 , 400 MHz) of compound 292



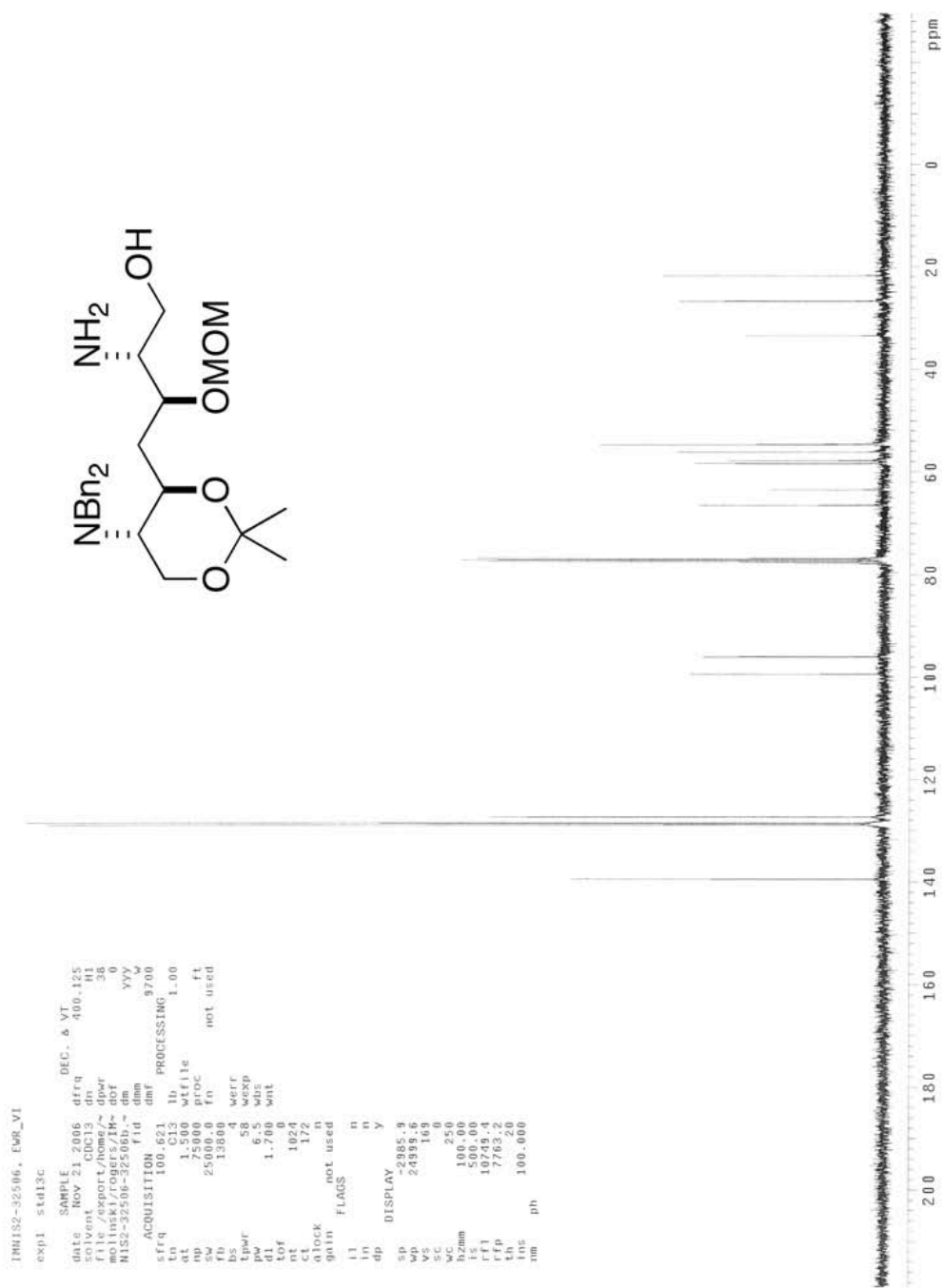
Spectrum 7.89: ¹H NMR (CDCl₃, 400 MHz) of compound 293



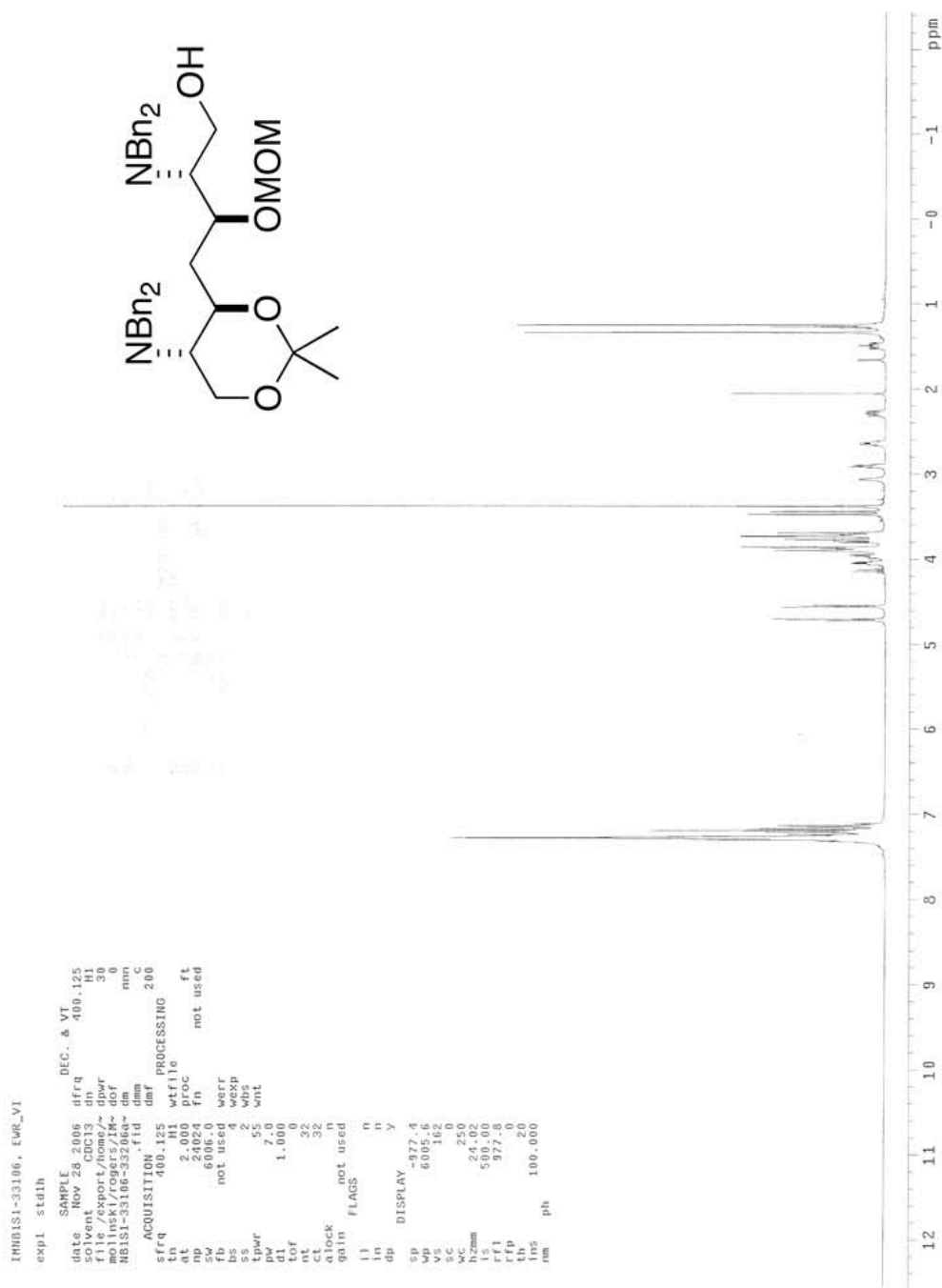
Spectrum 7.91: ^1H NMR (CDCl_3 , 400 MHz) of compound 294



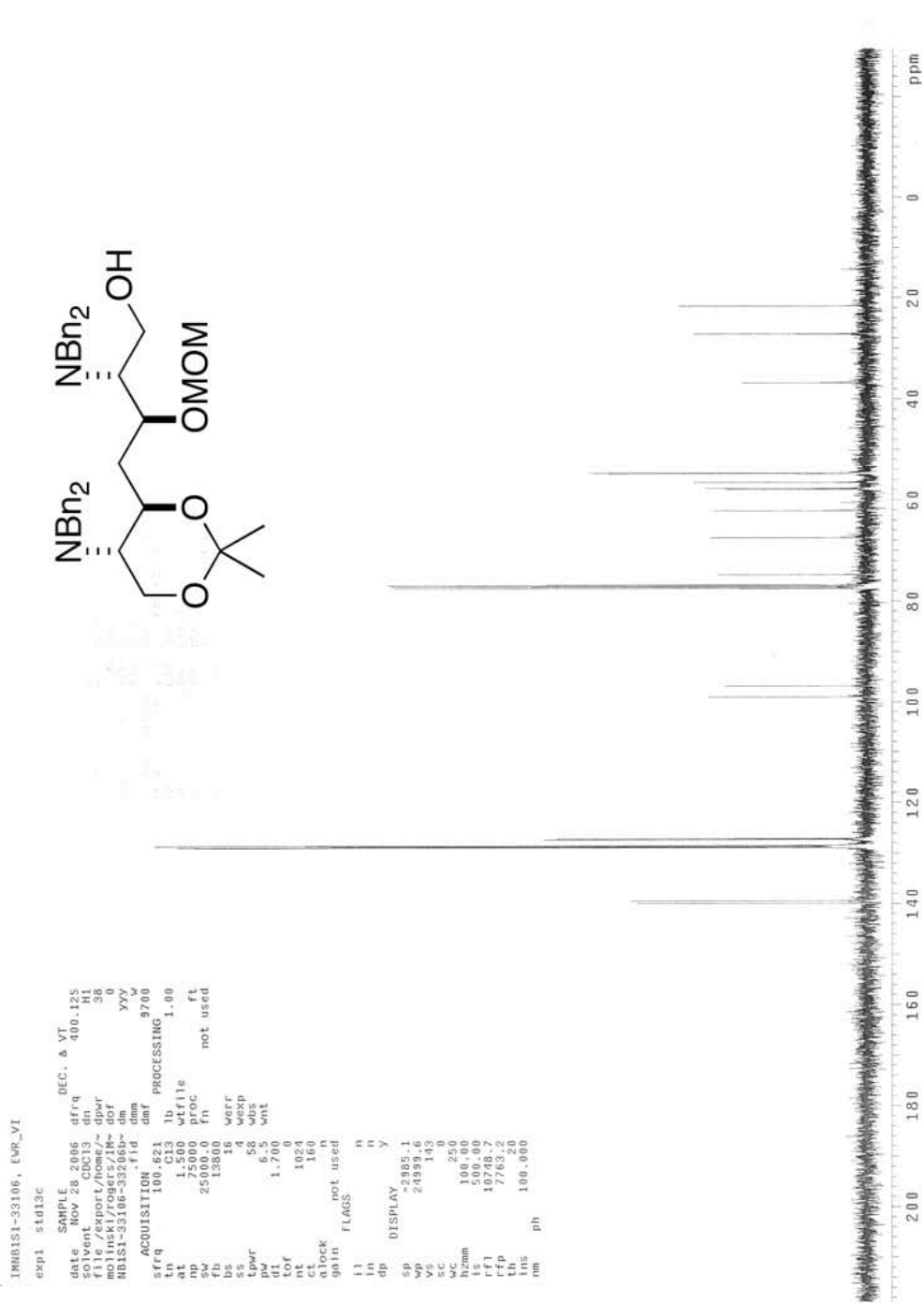
Spectrum 7.92: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 294



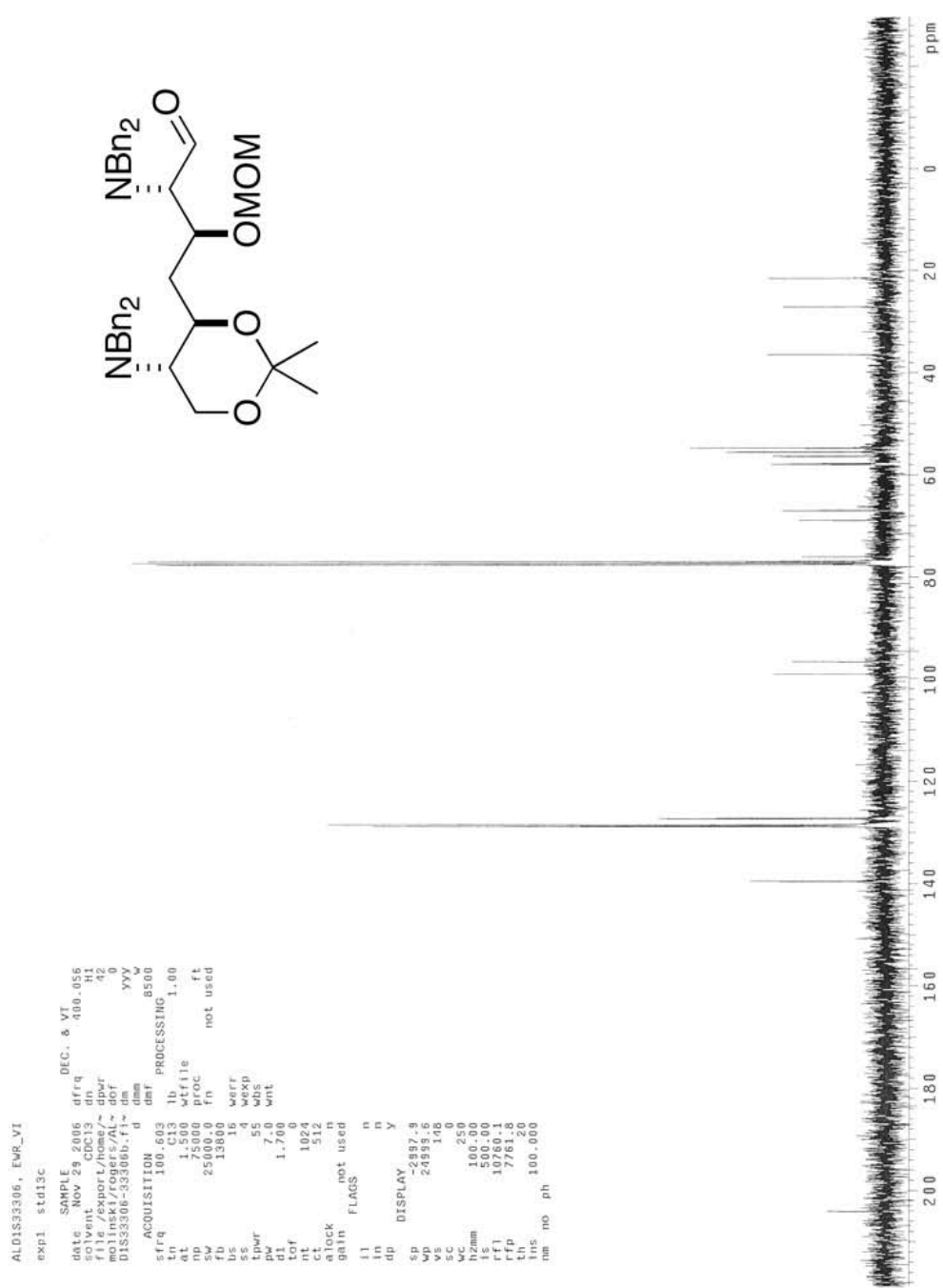
Spectrum 7.94: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 295



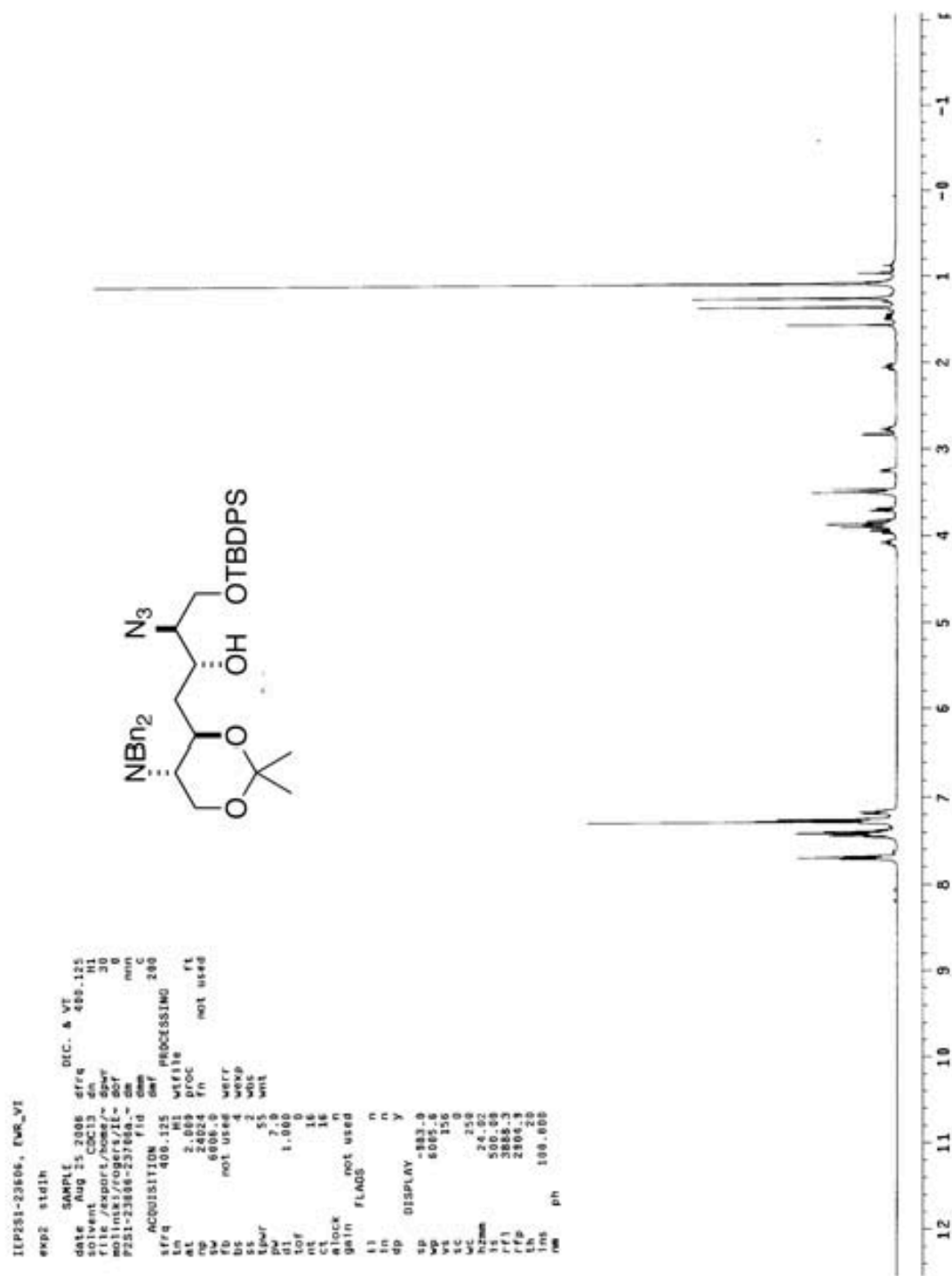
Spectrum 7.95: ^1H NMR (CDCl_3 , 400 MHz) of compound 296



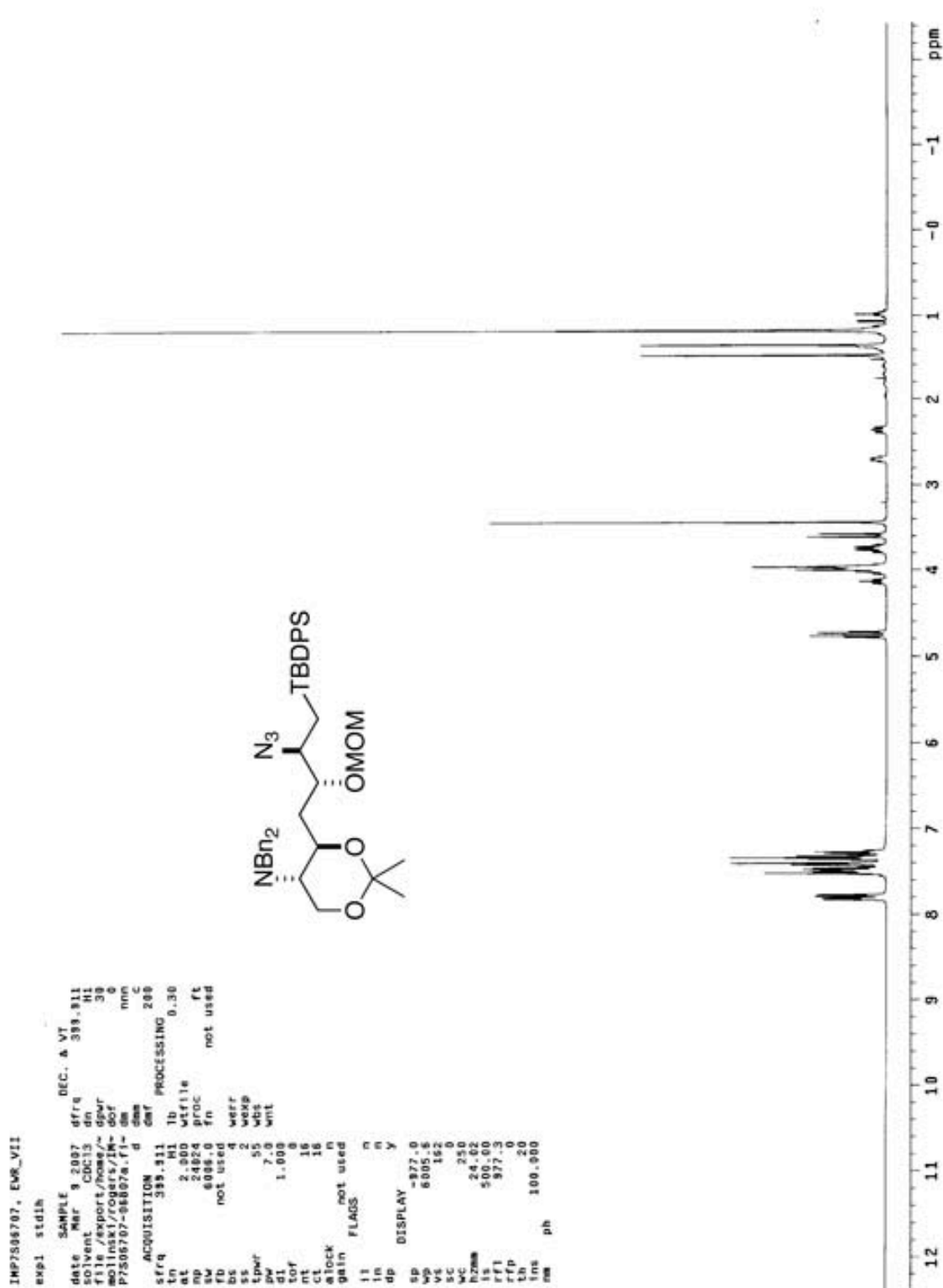
Spectrum 7.96: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 296



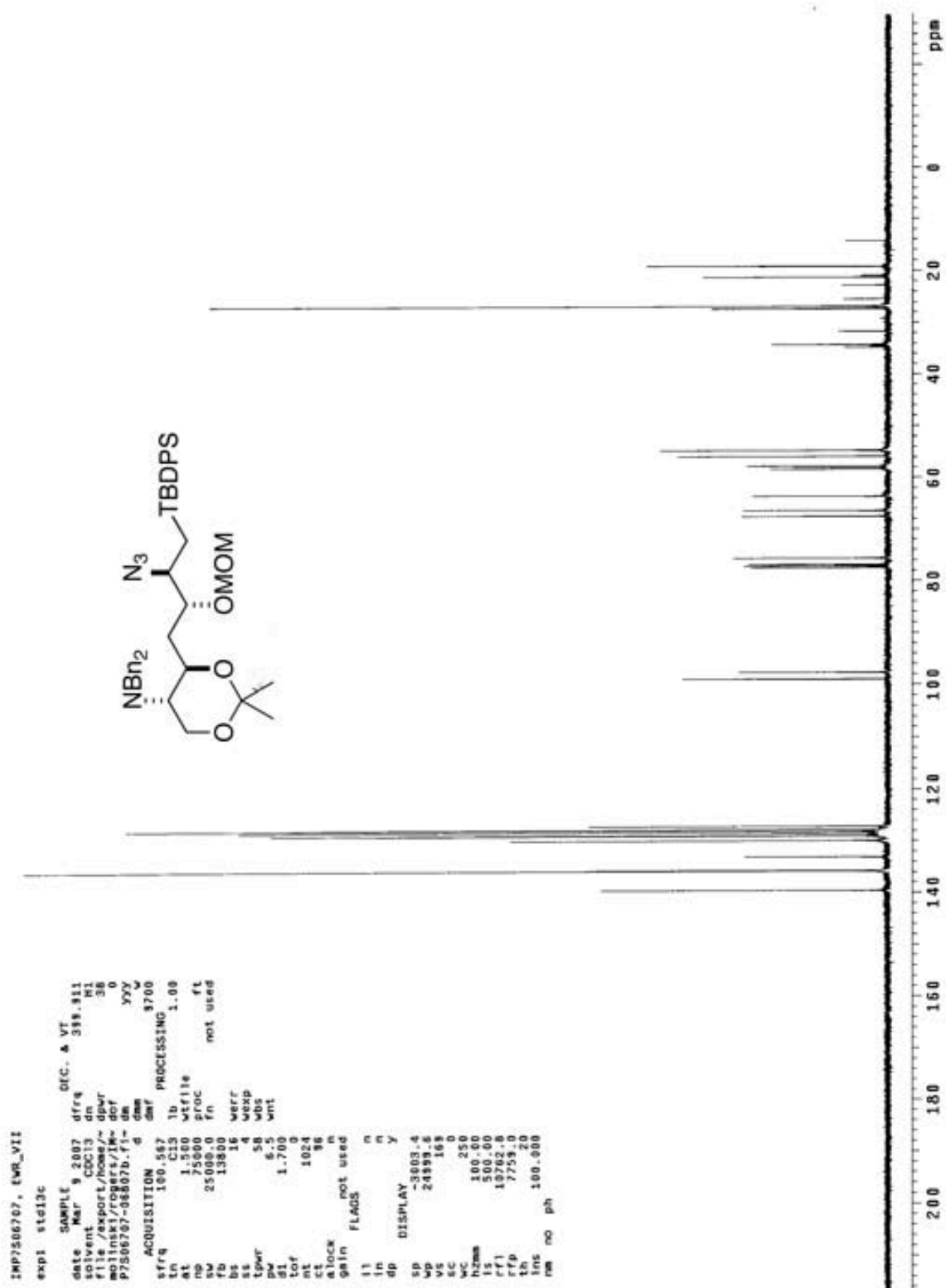
Spectrum 7.98: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 297



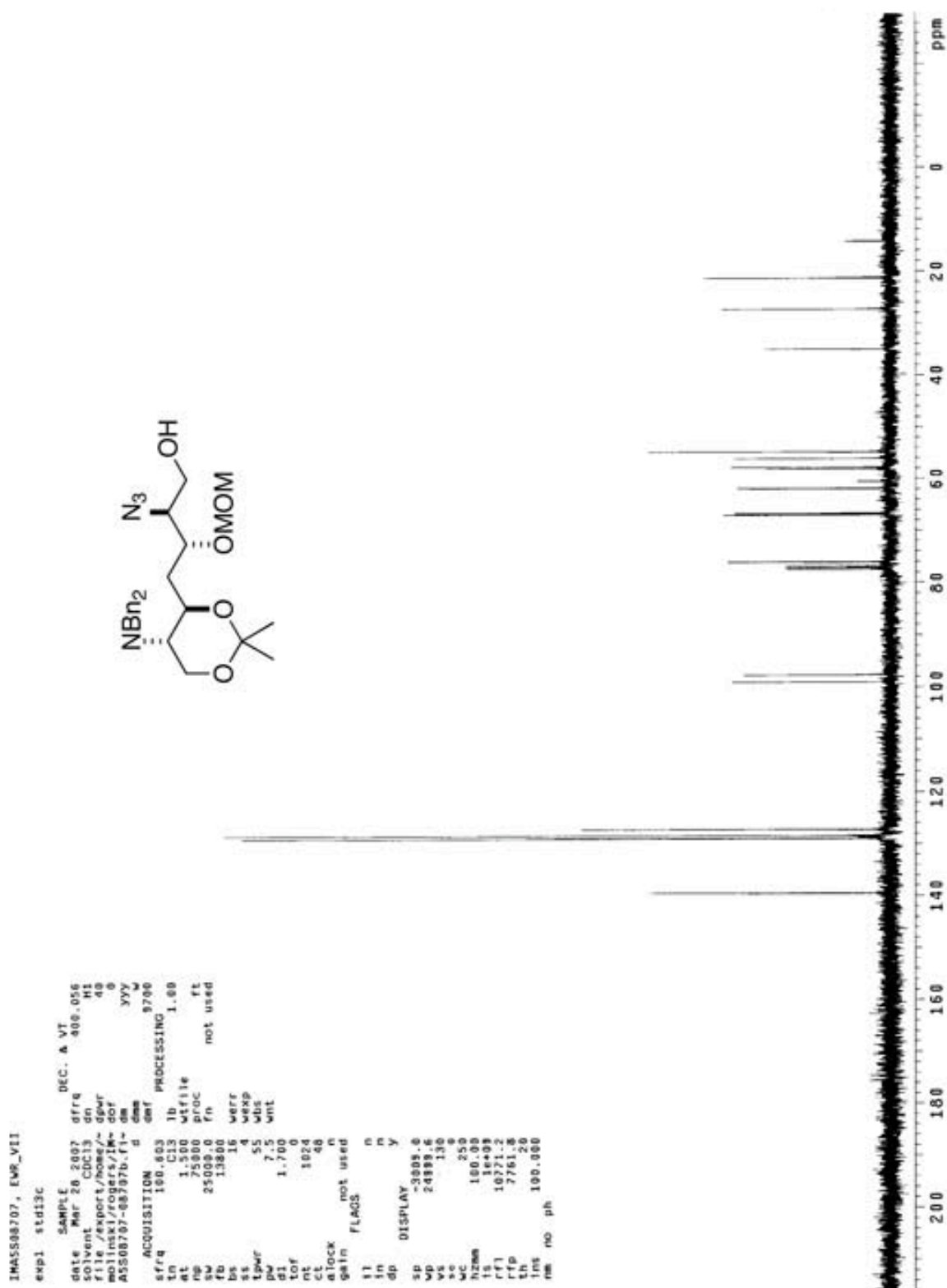
Spectrum 7.99: ^1H NMR (CDCl_3 , 400 MHz) of compound 298



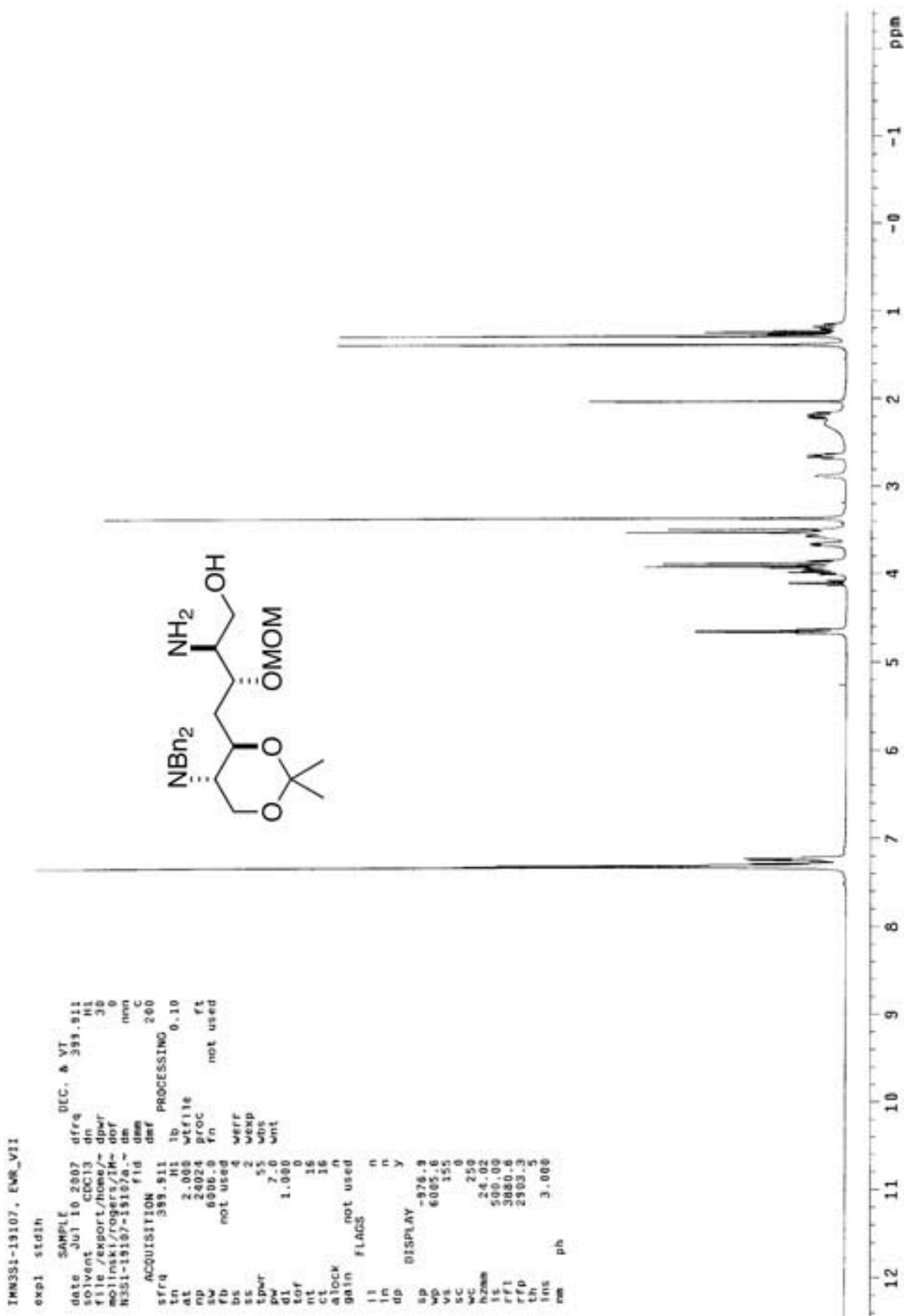
Spectrum 7.101: ^1H NMR (CDCl_3 , 400 MHz) of compound 299



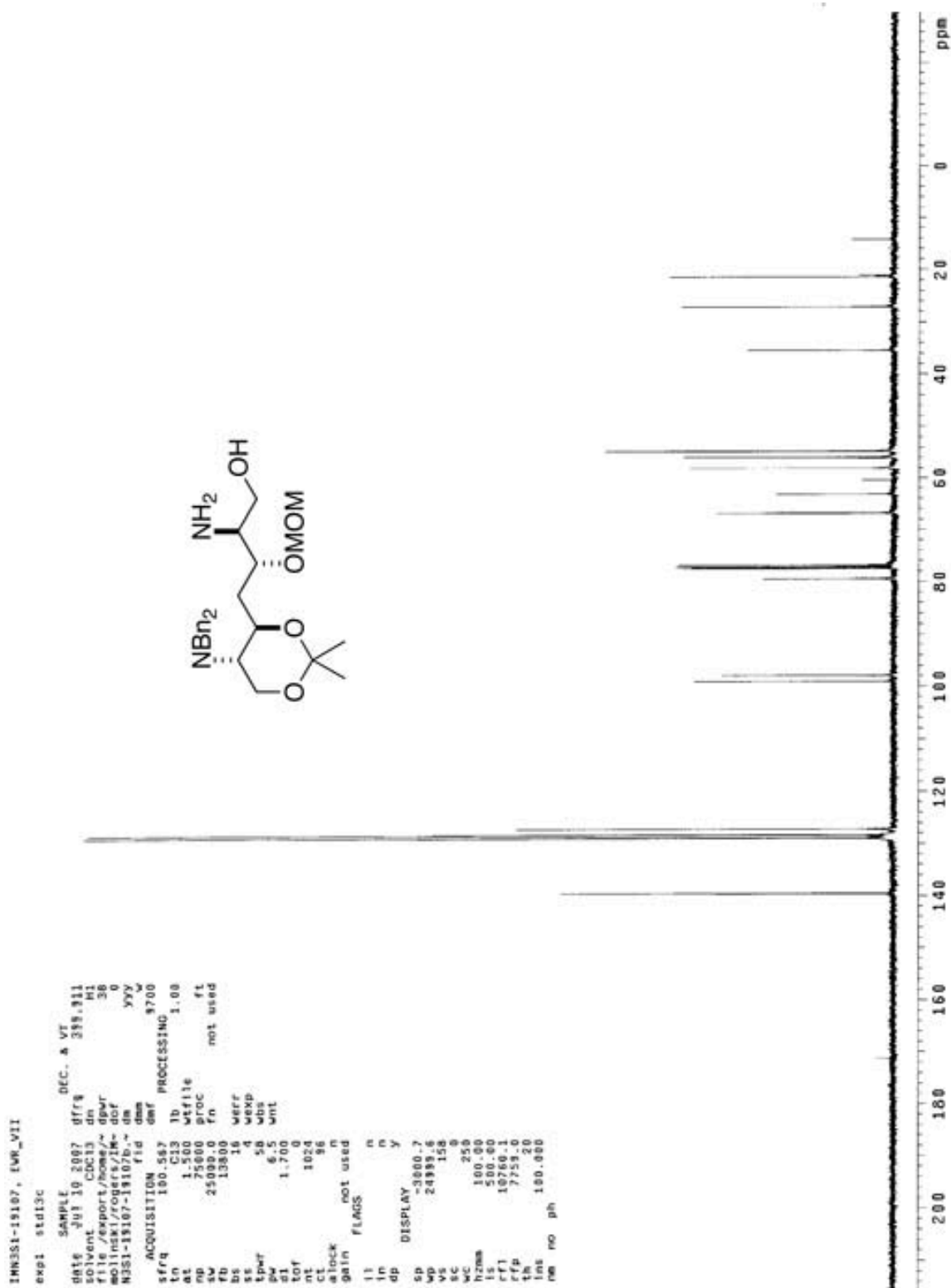
Spectrum 7.102: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 299



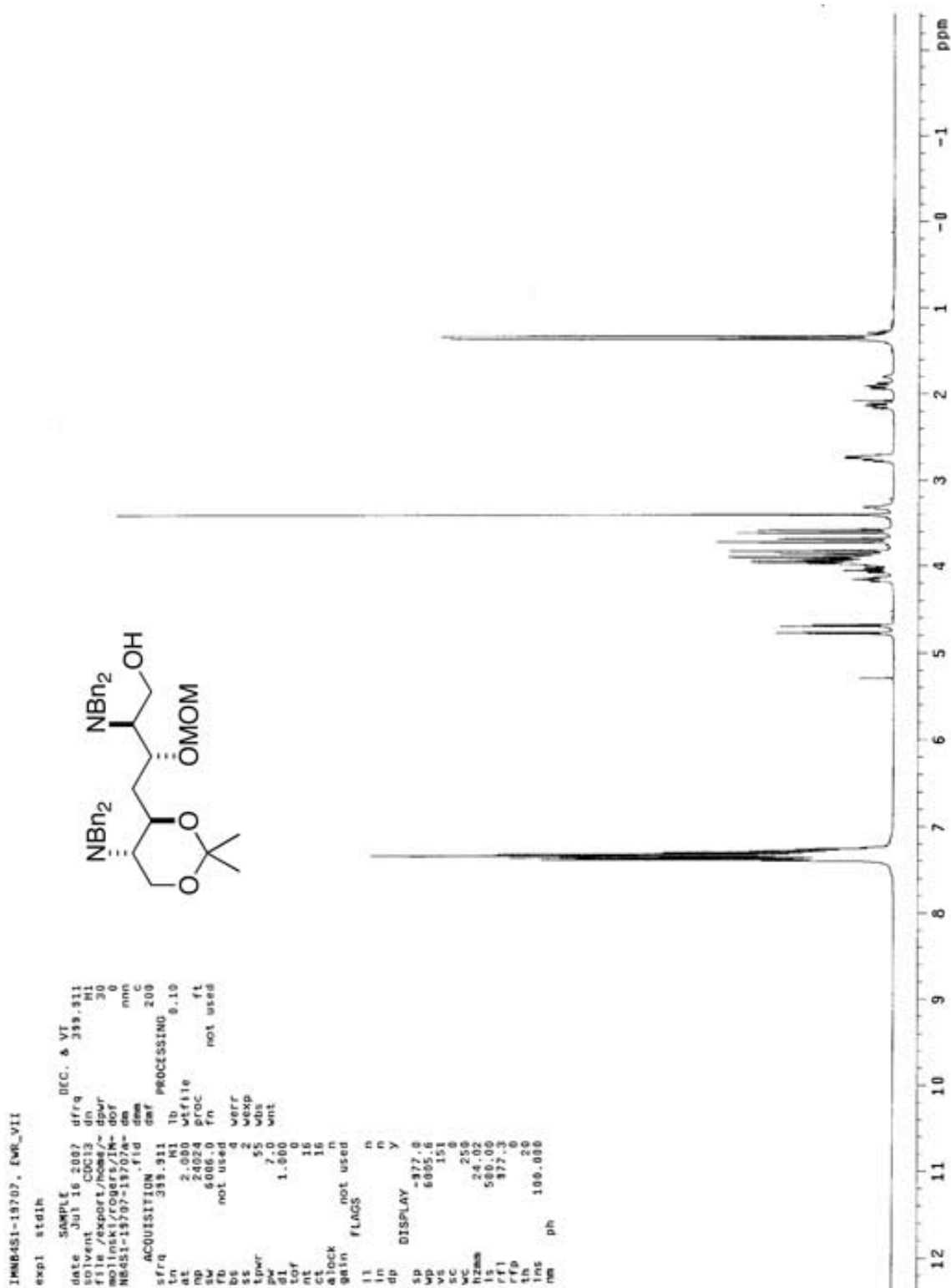
Spectrum 7.104: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 300



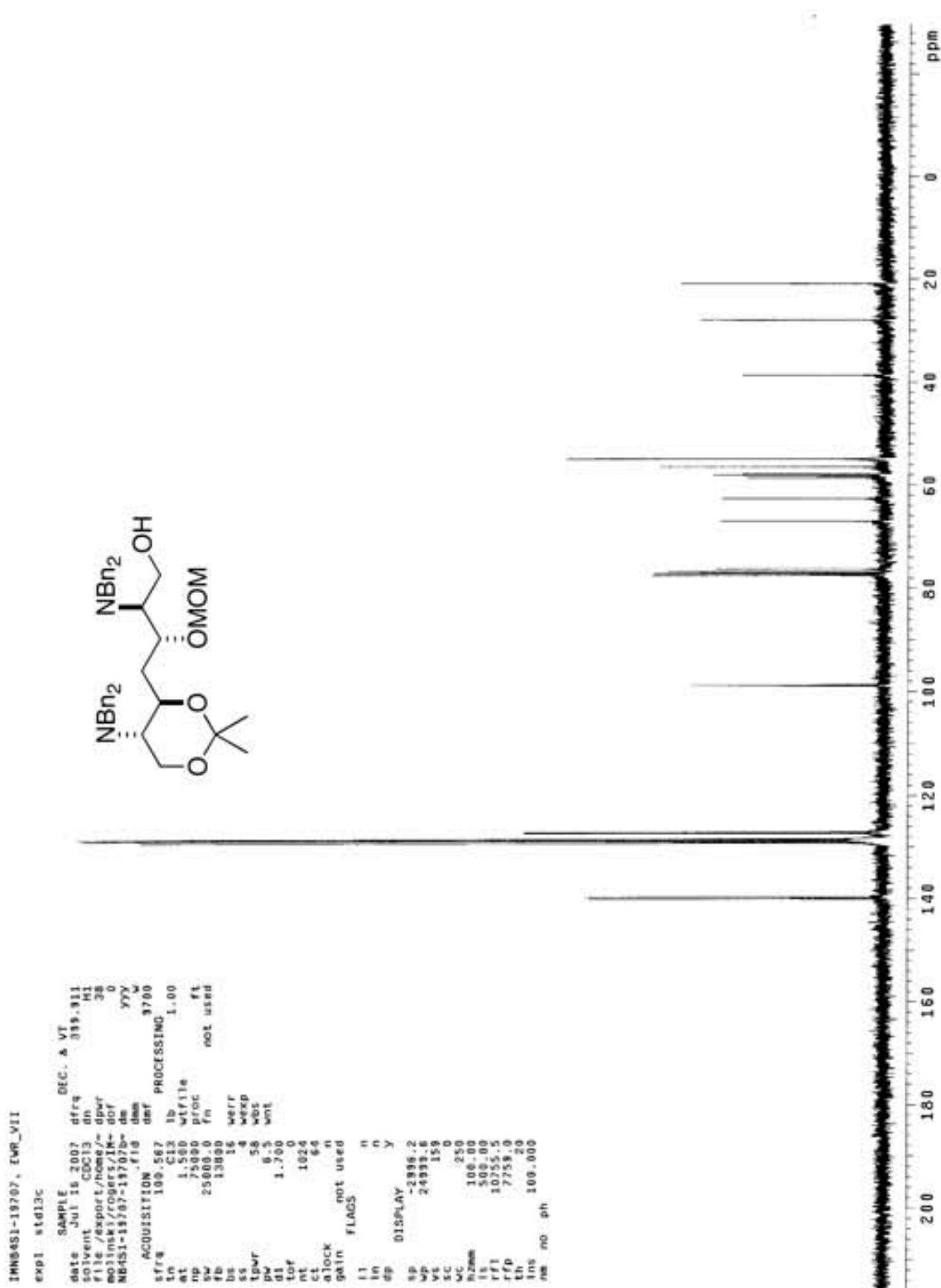
Spectrum 7.105: ^1H NMR (CDCl_3 , 400 MHz) of compound (+)-301



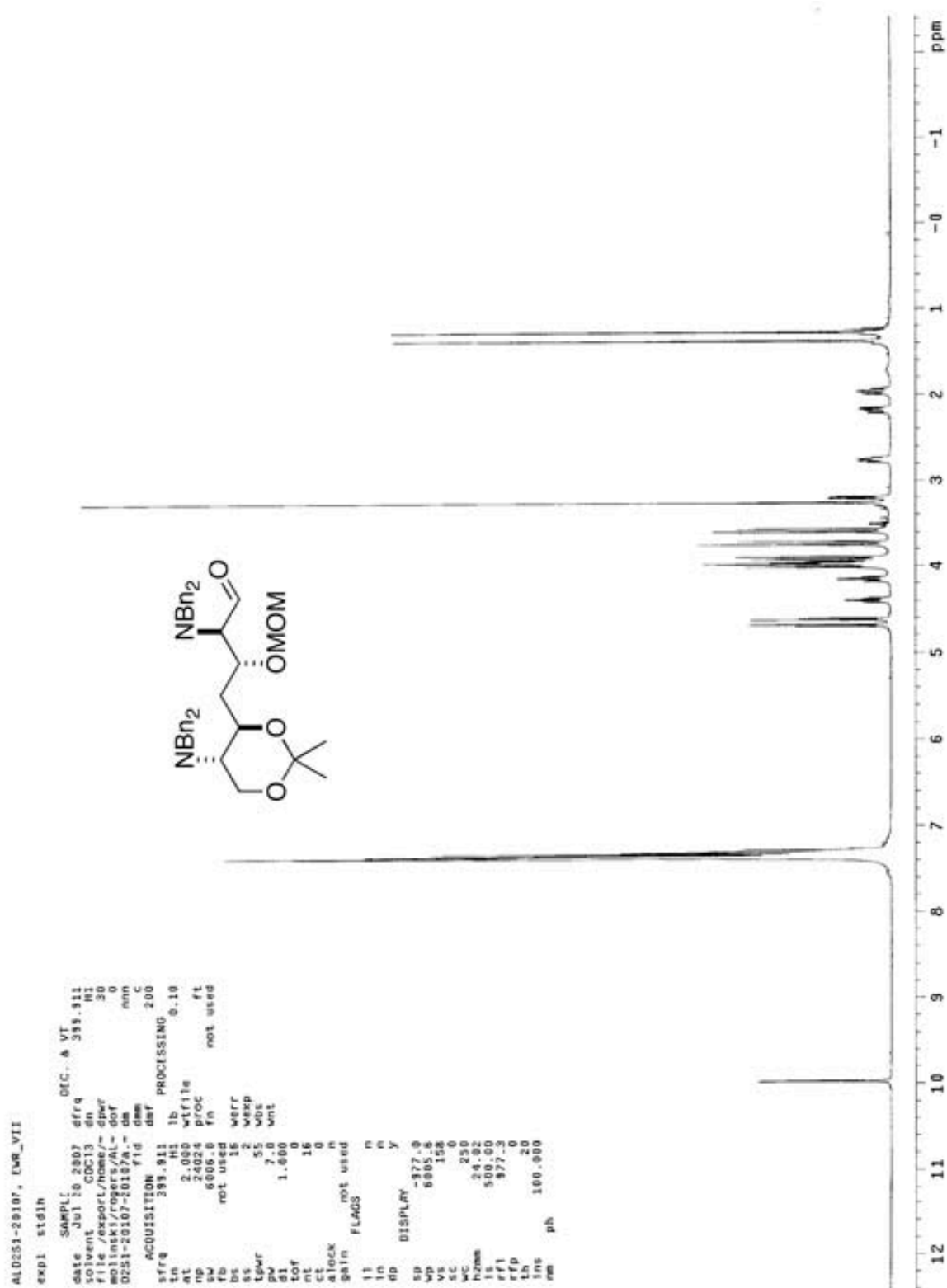
Spectrum 7.106: ^{13}C NMR (CDCl_3 , 100 MHz) of compound (+)-301



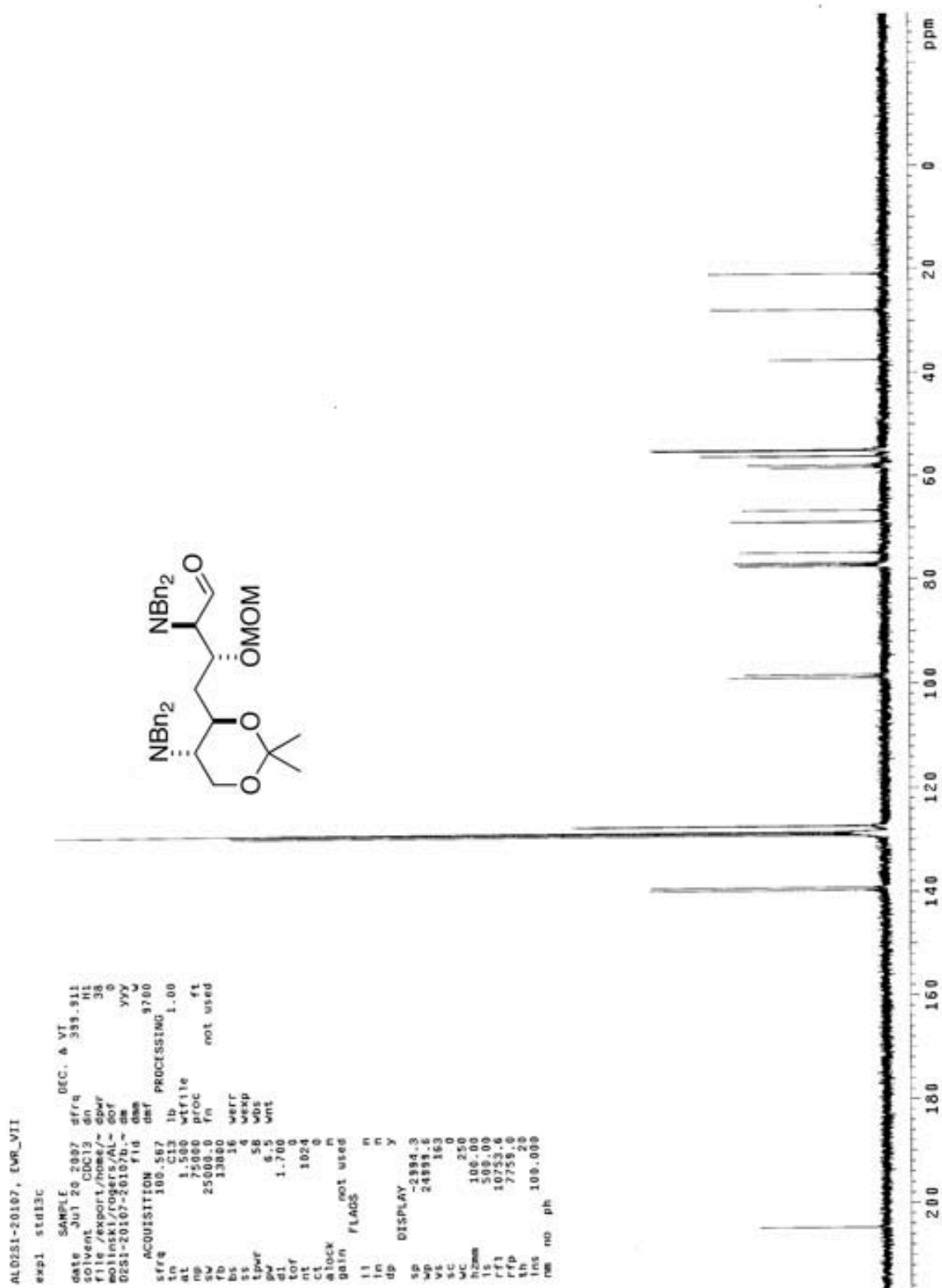
Spectrum 7.107: ^1H NMR (CDCl_3 , 400 MHz) of compound (+)-302



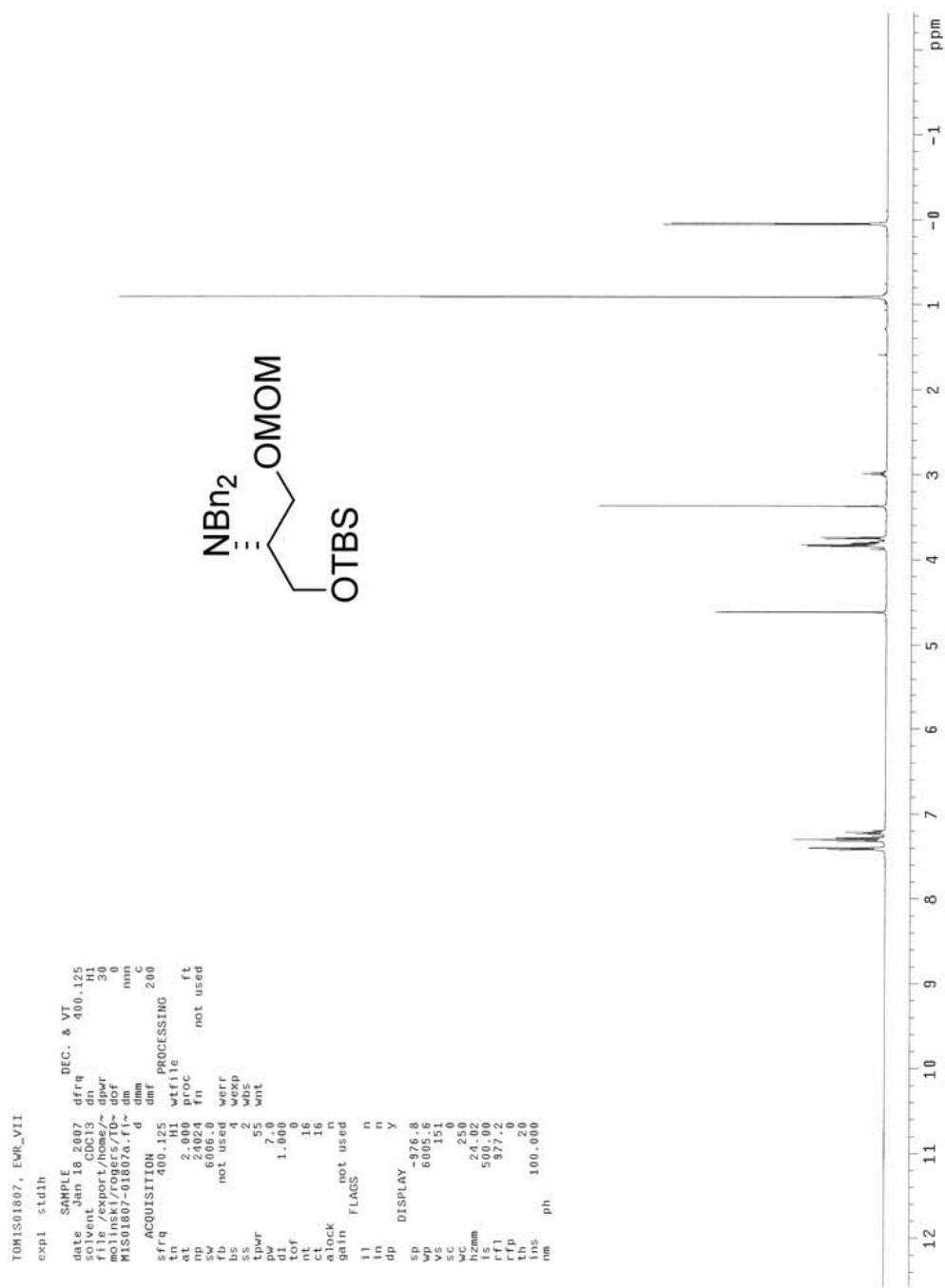
Spectrum 7.108: ^{13}C NMR (CDCl_3 , 100 MHz) of compound (+)-302



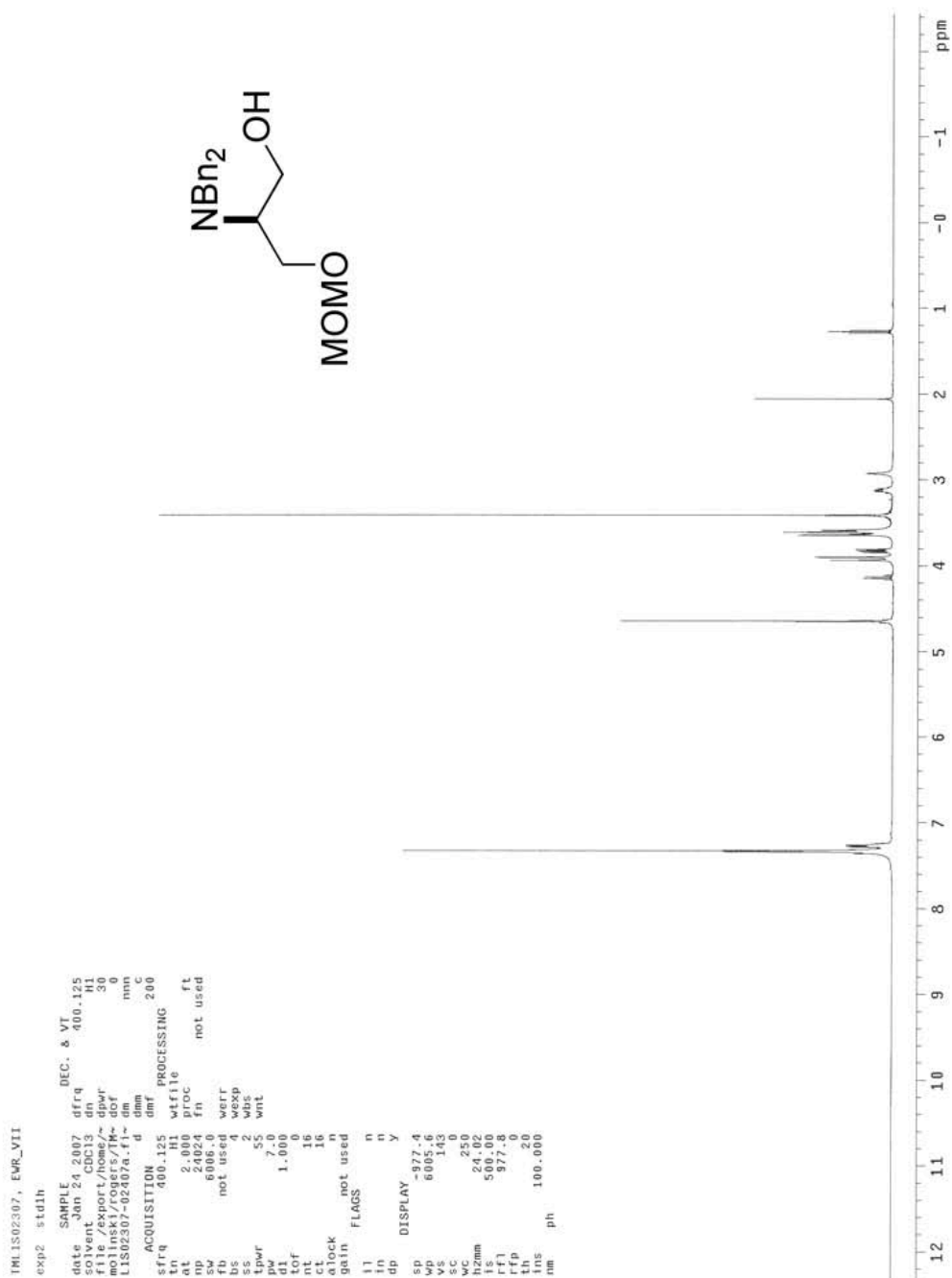
Spectrum 7.109: ¹H NMR (CDCl₃, 400 MHz) of compound 303



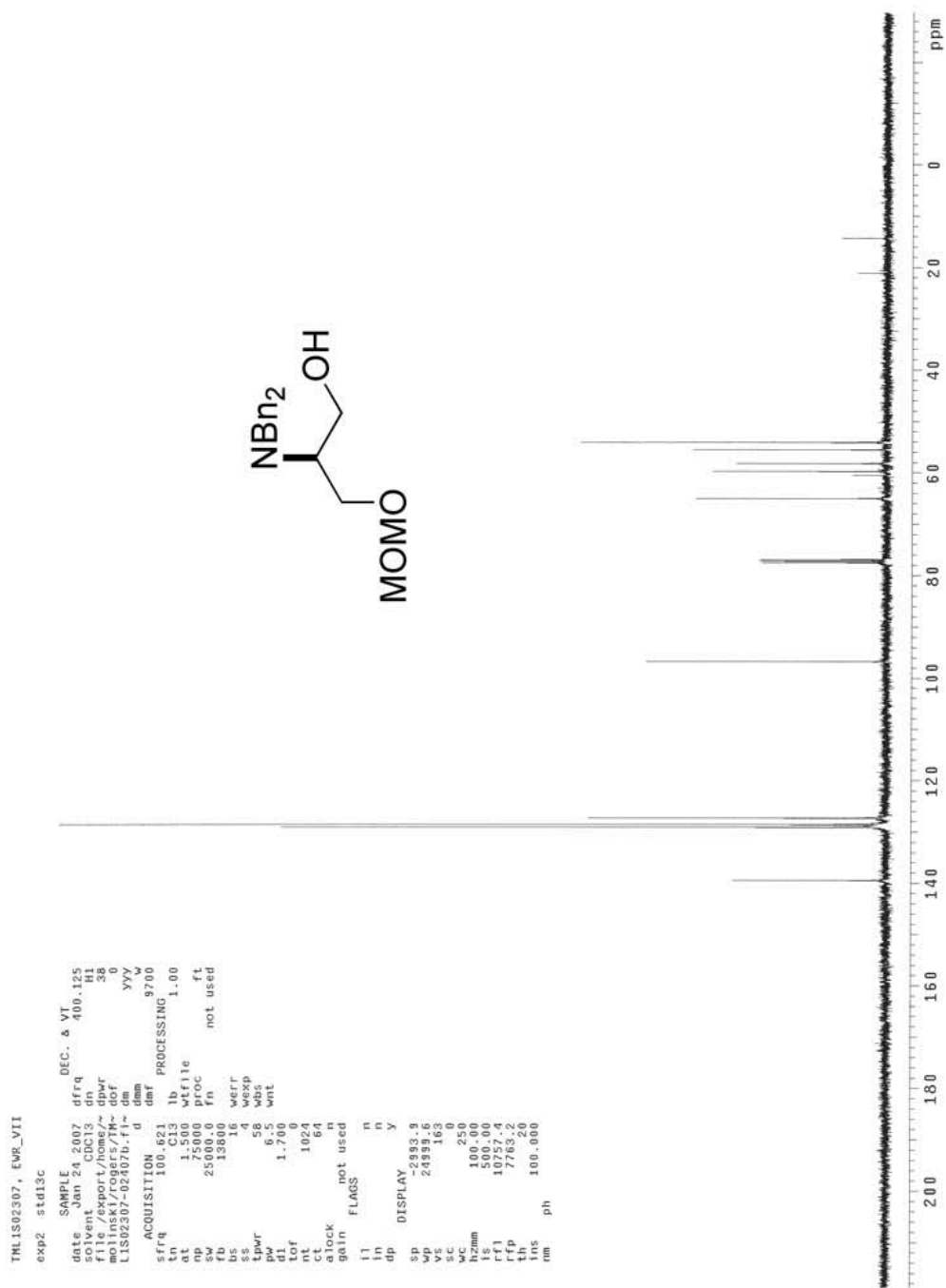
Spectrum 7.110: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 303



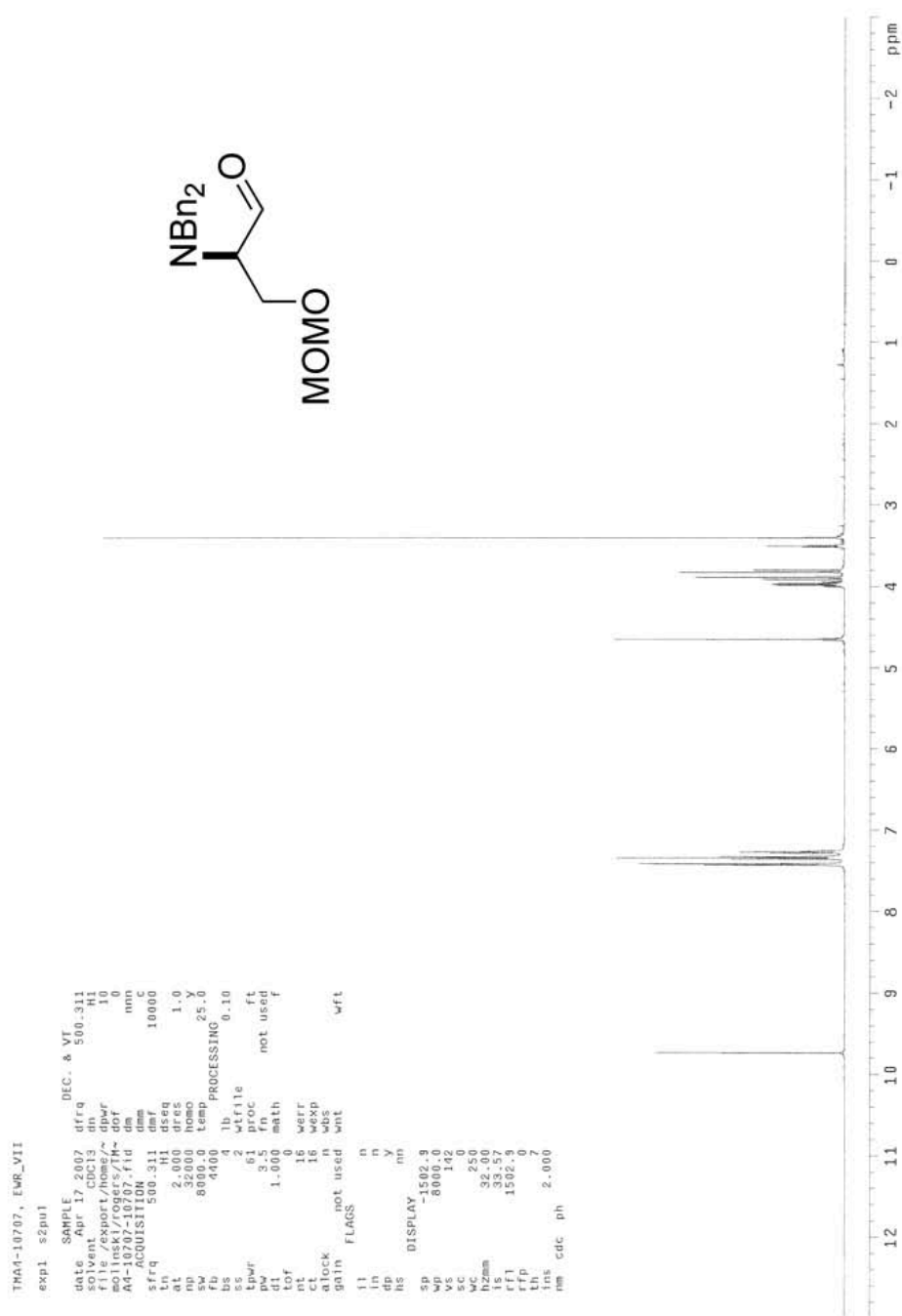
Spectrum 7.111: ^1H NMR (CDCl_3 , 400 MHz) of compound 305



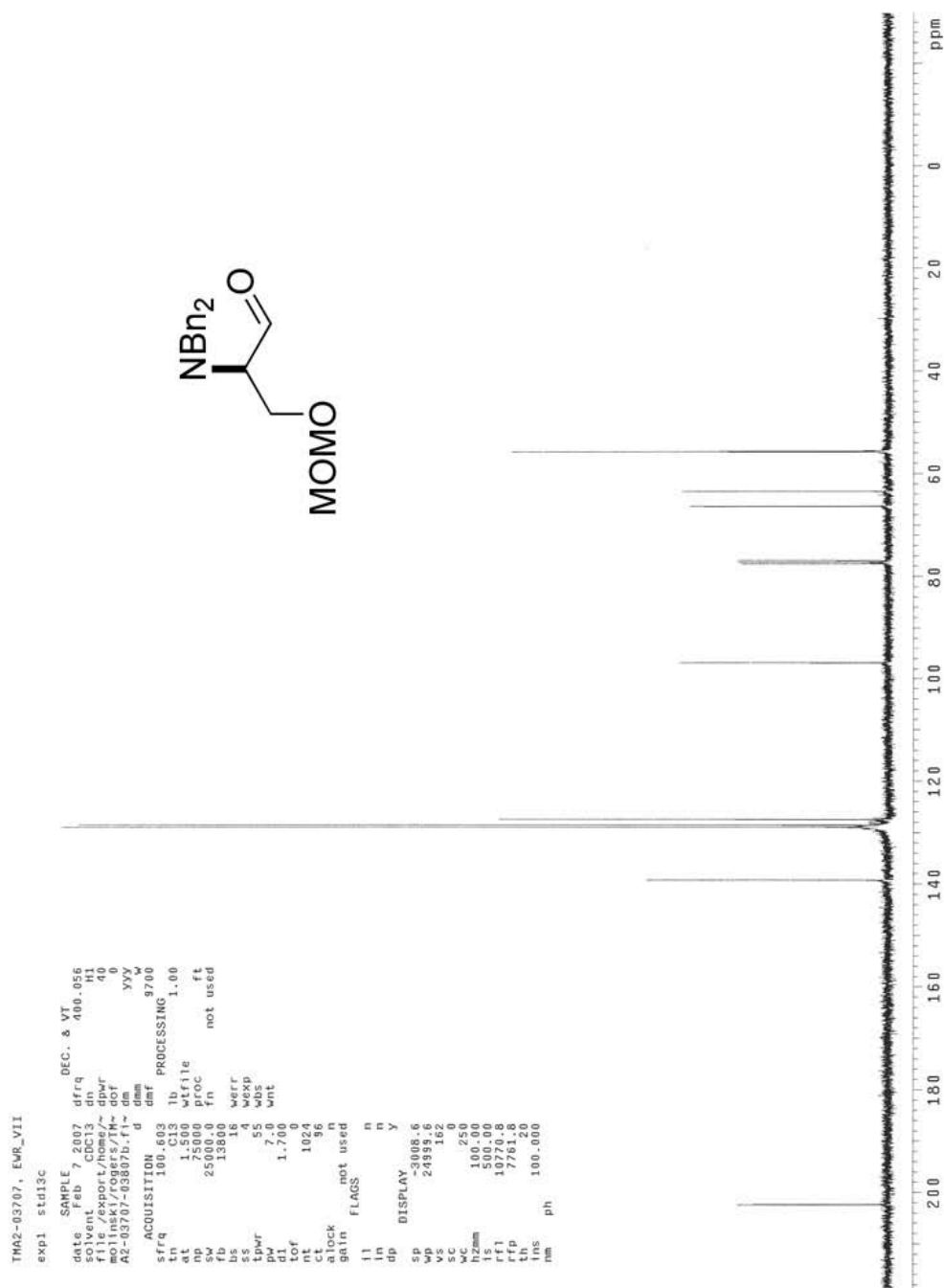
Spectrum 7.113: ^1H NMR (CDCl_3 , 400 MHz) of compound 306



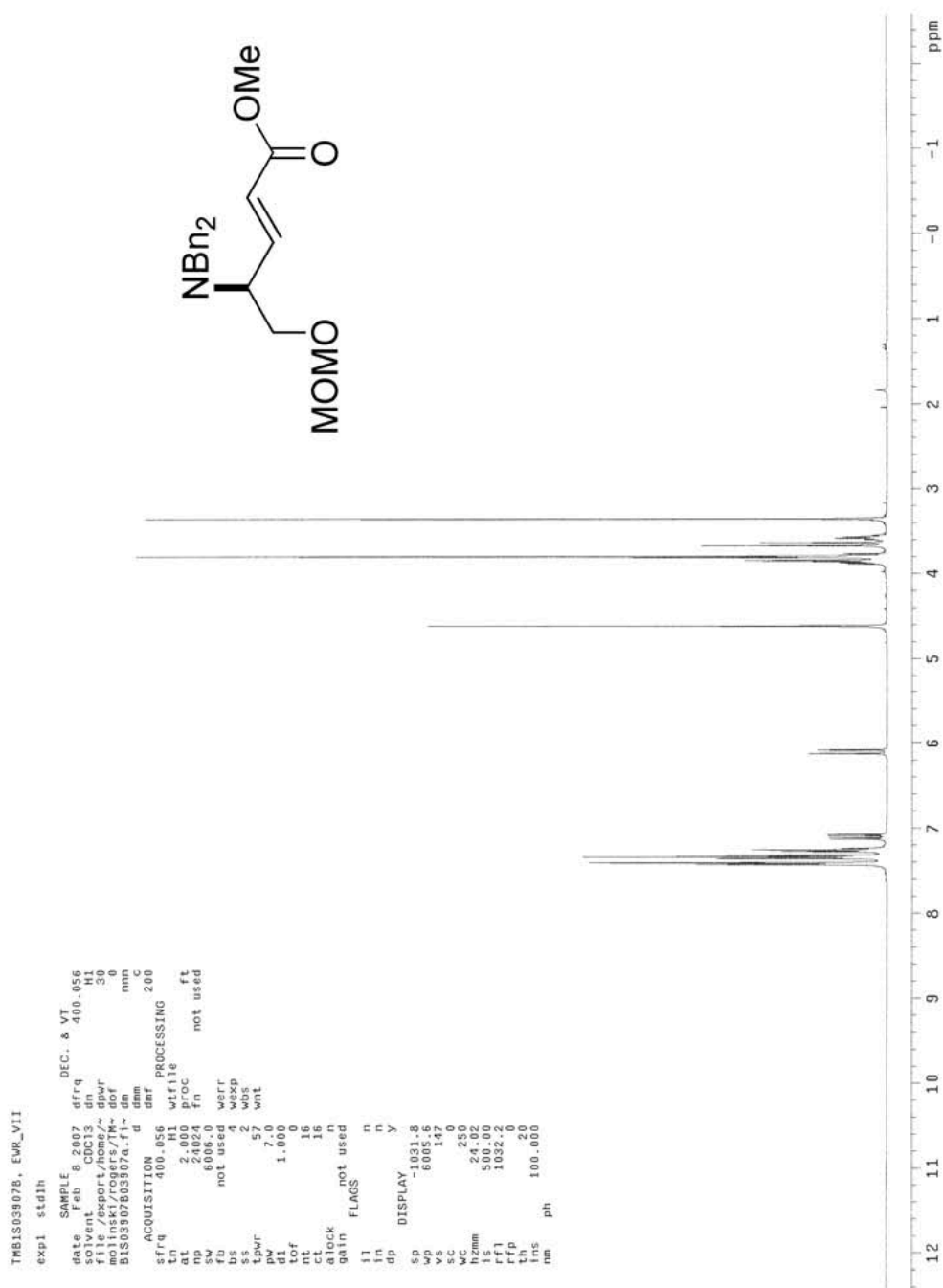
Spectrum 7.114: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 306



Spectrum 7.115: ^1H NMR (CDCl_3 , 500 MHz) of compound 307

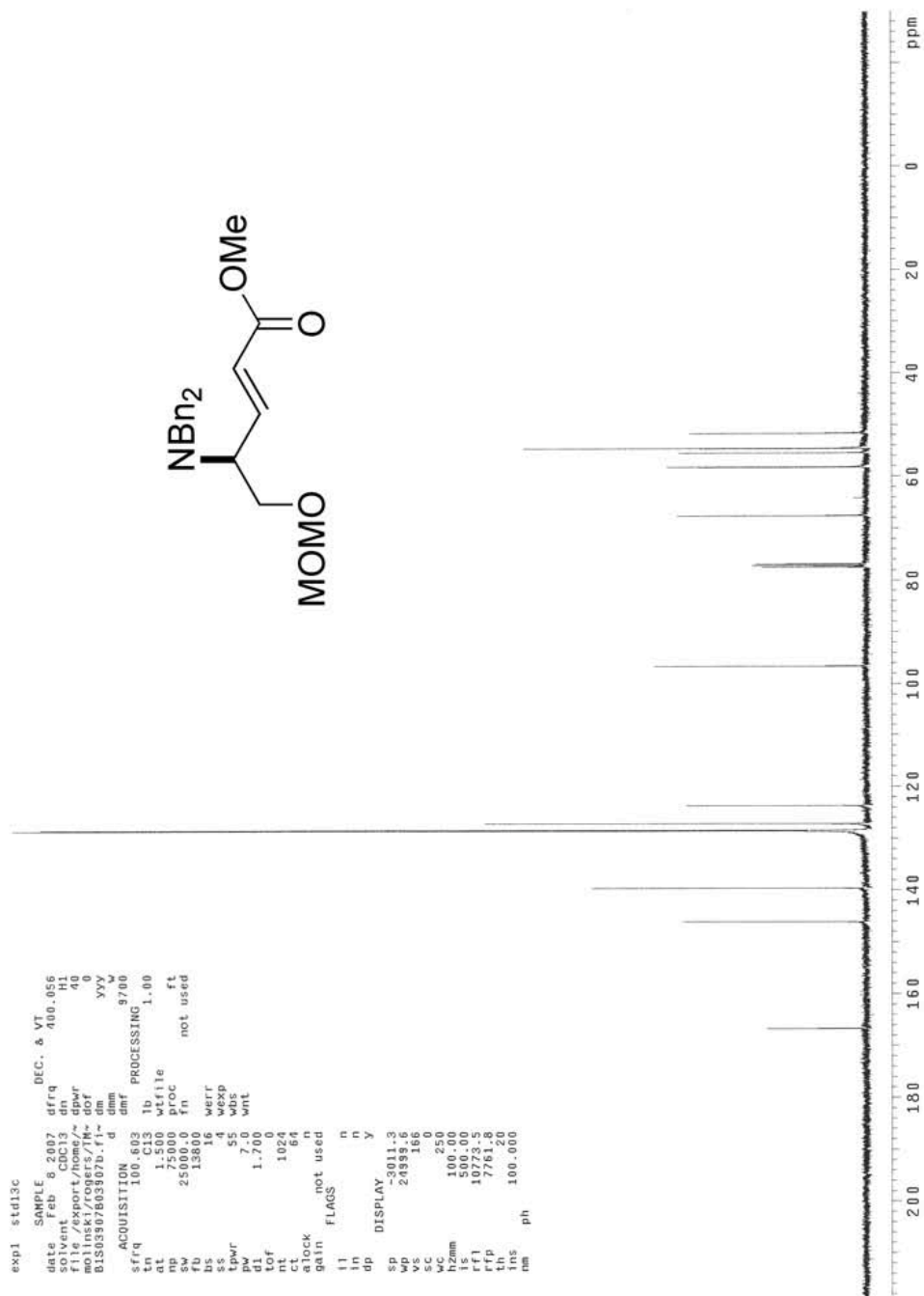
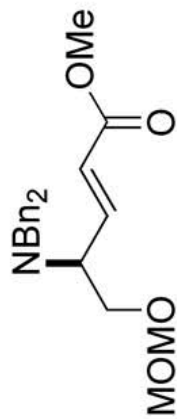


Spectrum 7.116: ^{13}C NMR (CDCl_3 , 100 MHz) of compound **307**

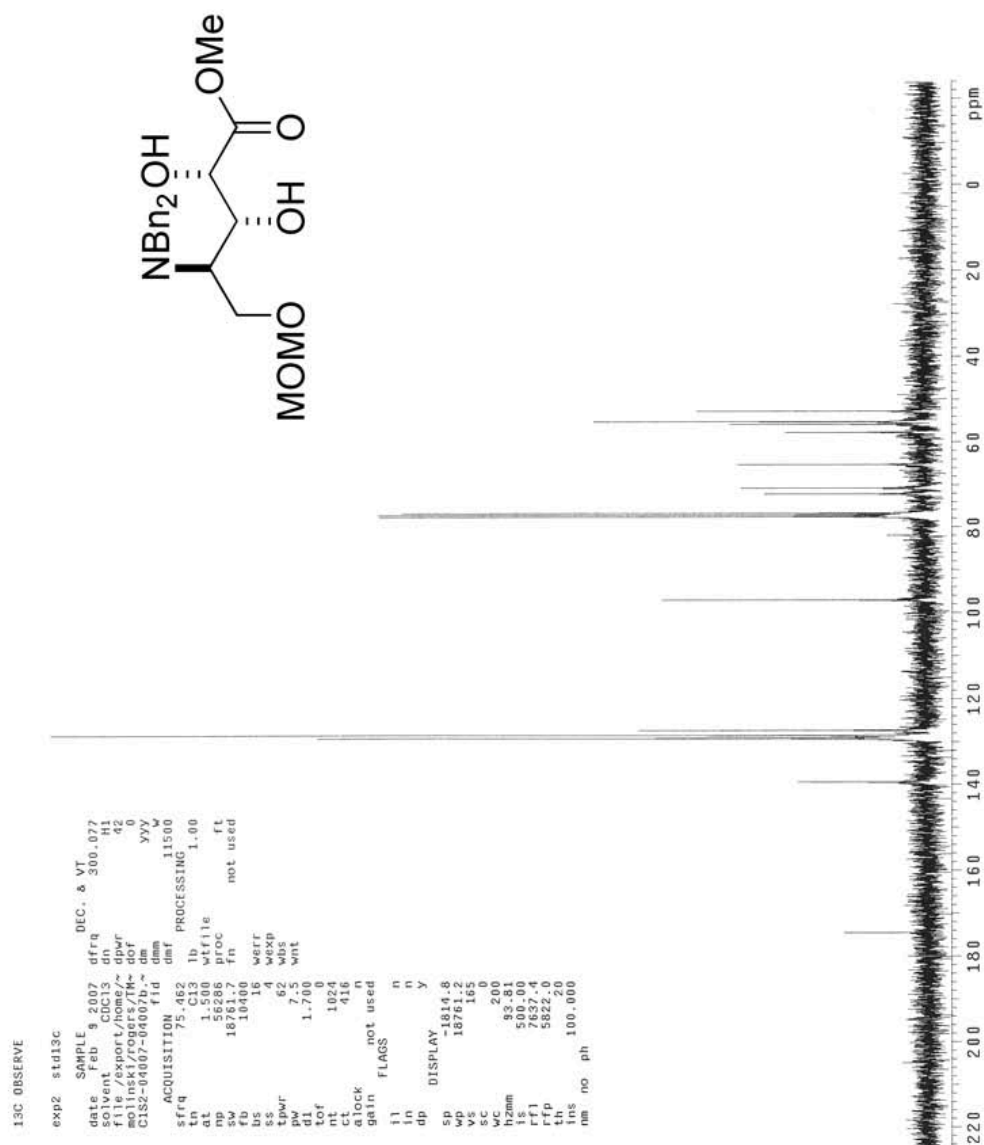


Spectrum 7.117: ¹H NMR (CDCl₃, 400 MHz) of compound 308

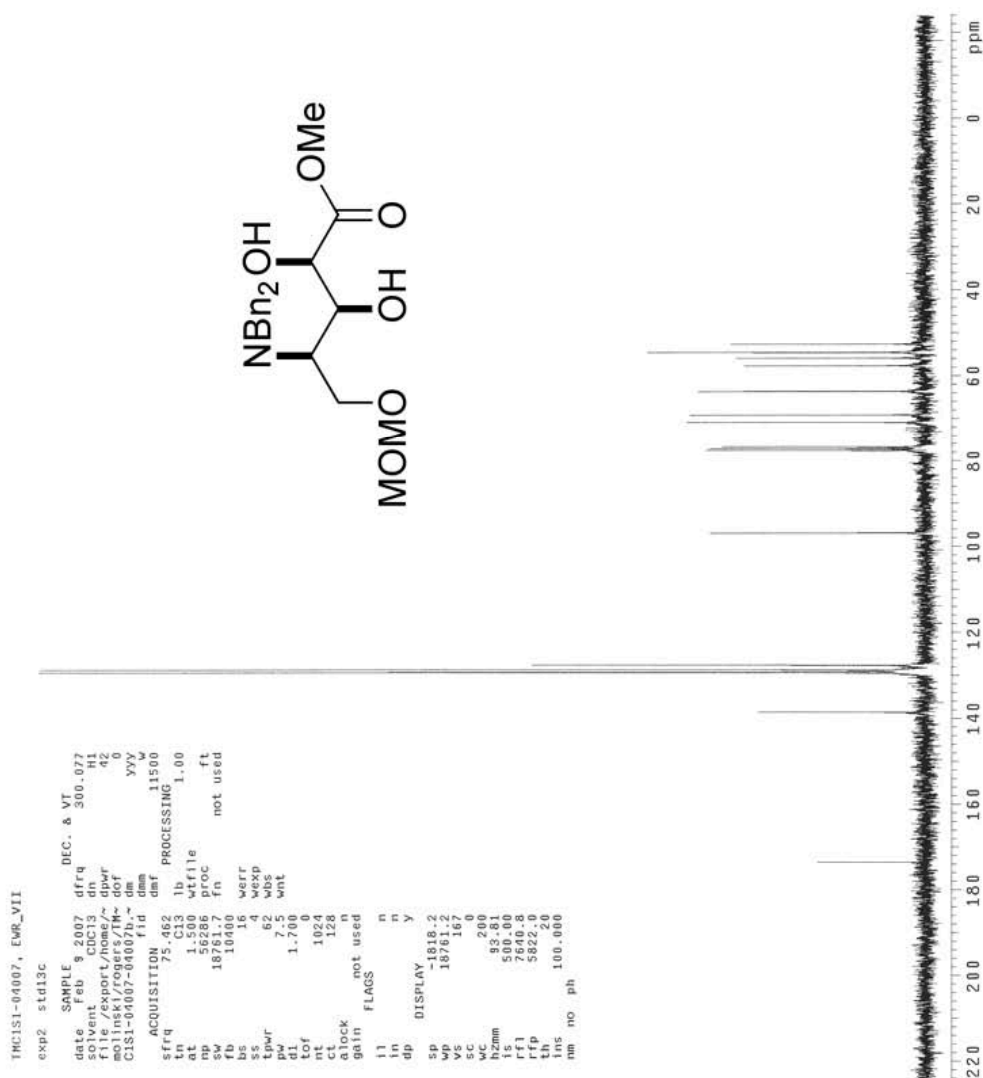
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 pulse prog zgpg30 dpr 40
 mol msk3/compes71m- dpr 40
 B1S039078039078.f1- dm yyy
 dms w
 ACQUISITION 602
 sfrq 100.613 1b PROCESSING 1.00
 tn at 1.500 wtf1le
 np 257000 proc ft
 fb 13800 fn not used
 bs 16 werr
 ss 4 wexp
 tpr 55 wbs
 dv 1.700 wnt
 lof 0
 nt 1024
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 gain not used
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 DISPLAY
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 wp 24959.6
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 rfp 7761.8
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 nm ph



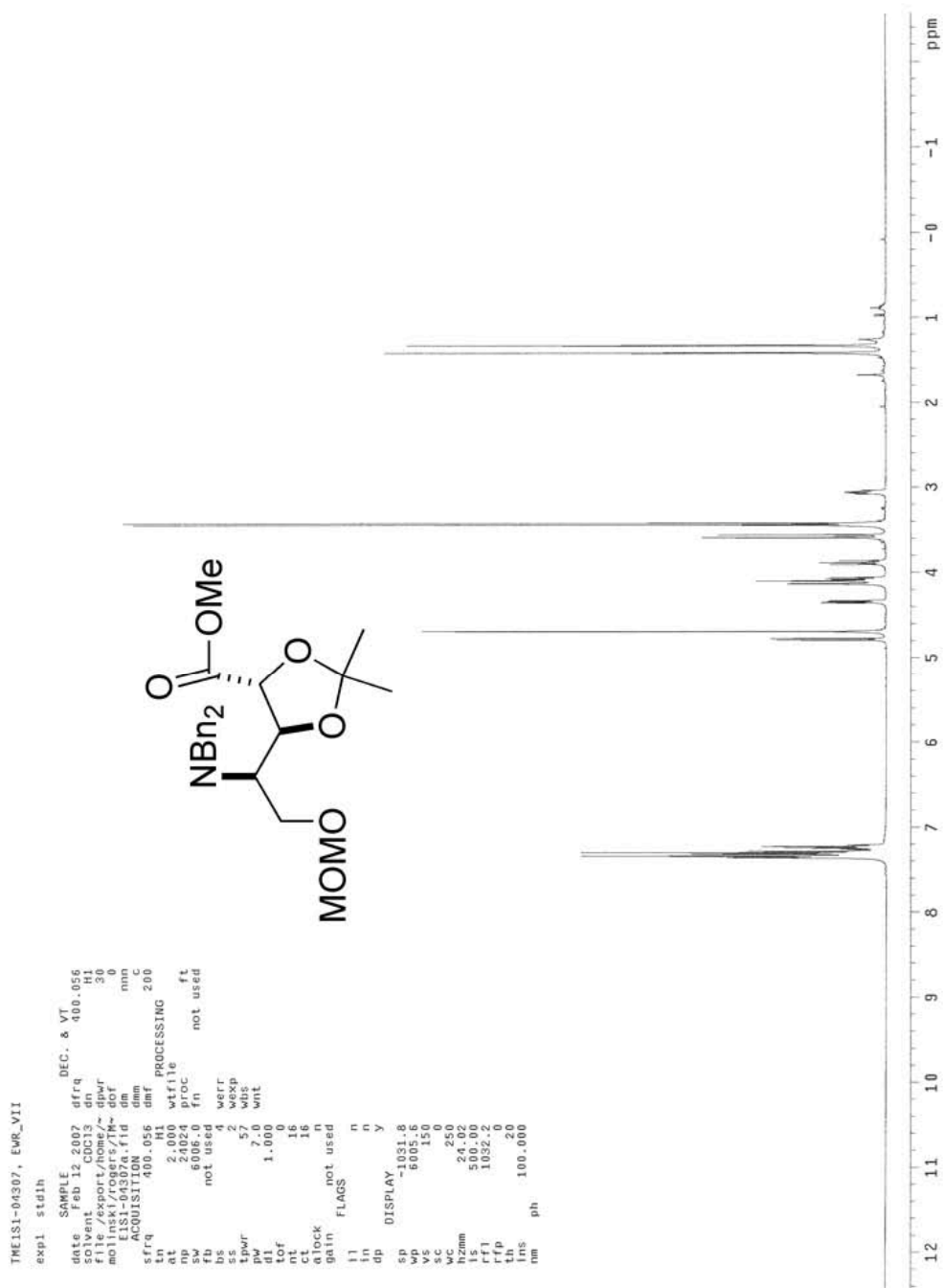
Spectrum 7.118: ¹³C NMR (CDCl₃, 100 MHz) of compound 308



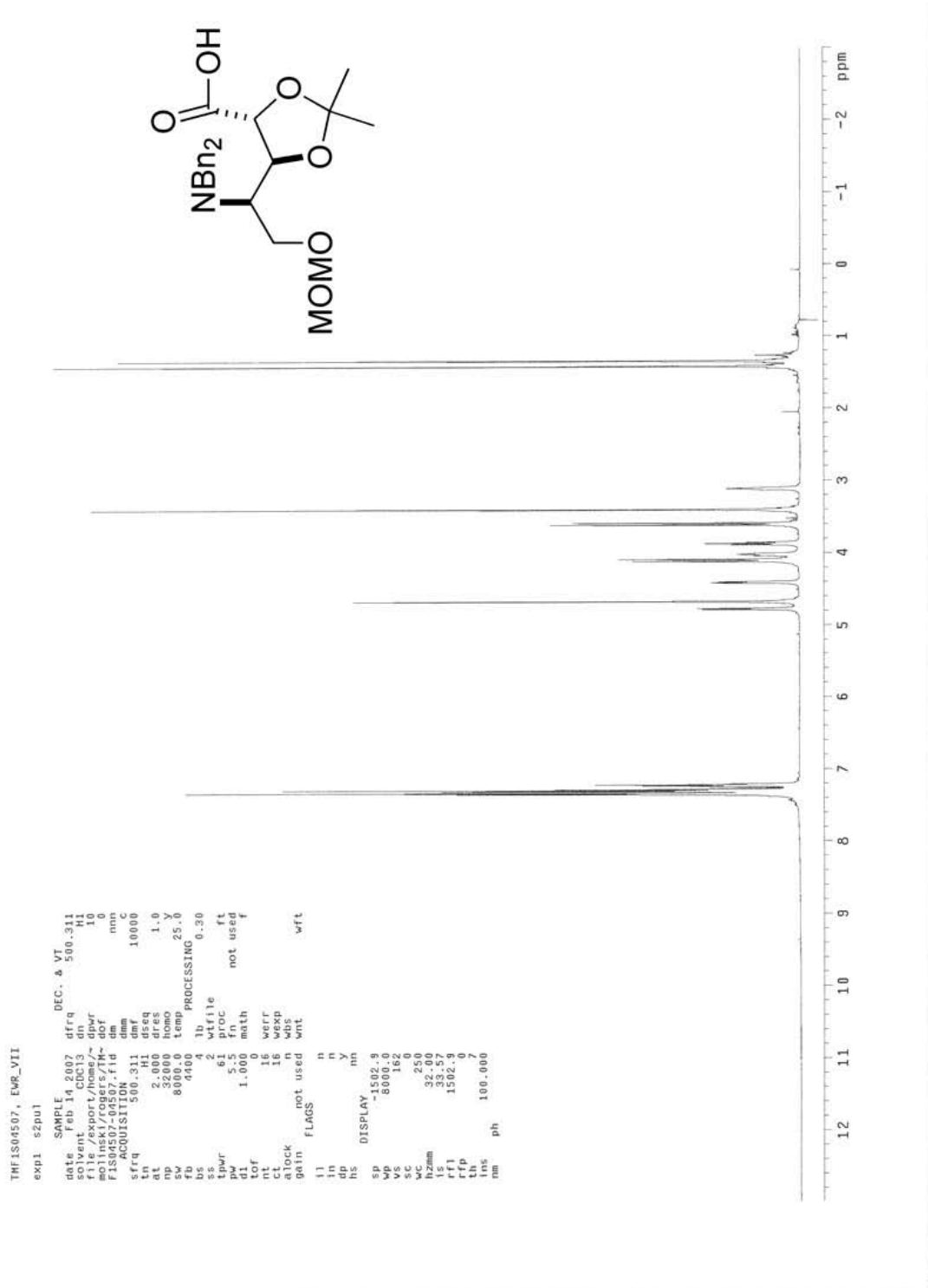
Spectrum 7.120: ¹³C NMR (CDCl₃, 75 MHz) of compound 309



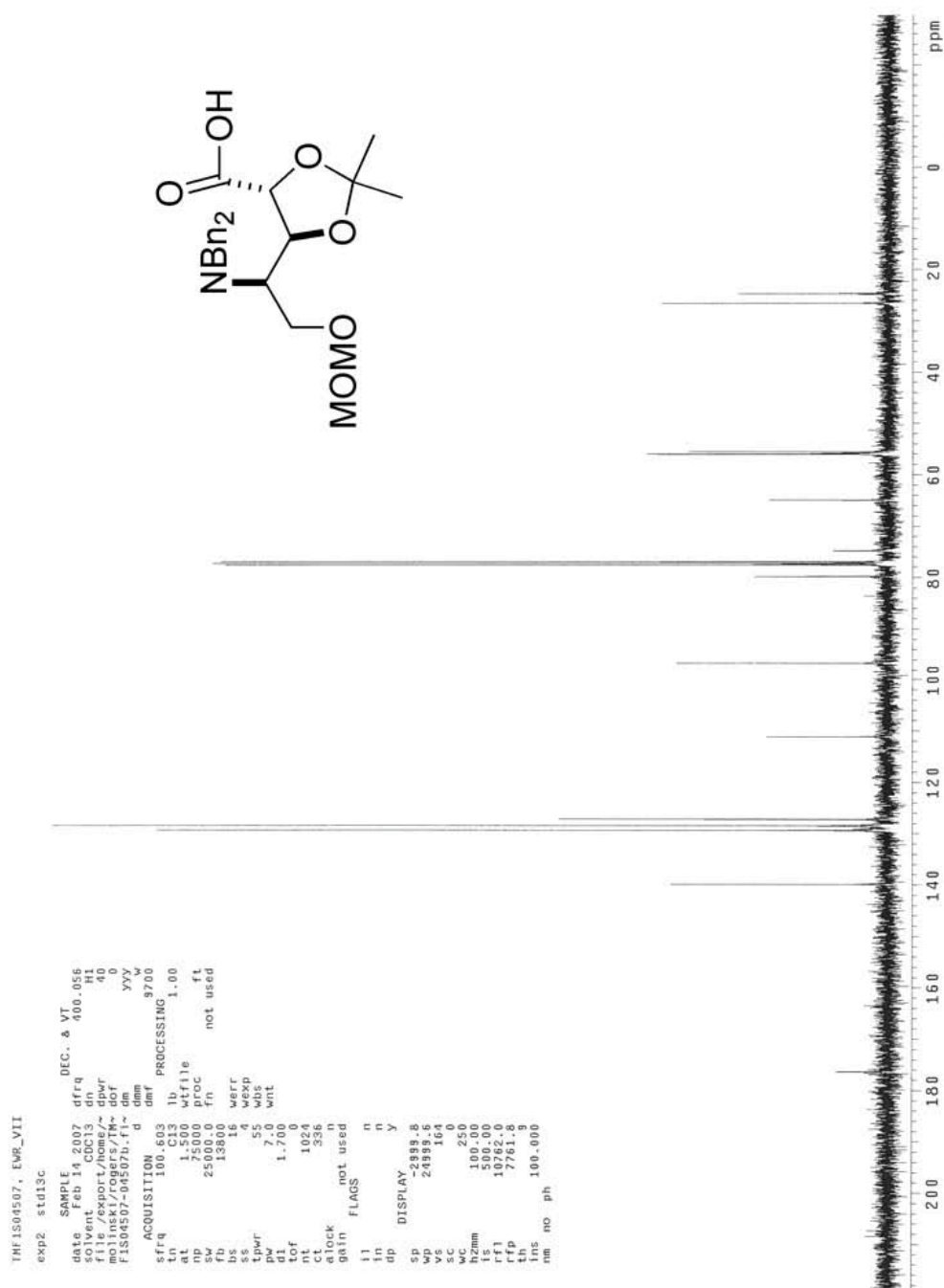
Spectrum 7.122: ¹³C NMR (CDCl₃, 75 MHz) of compound 310



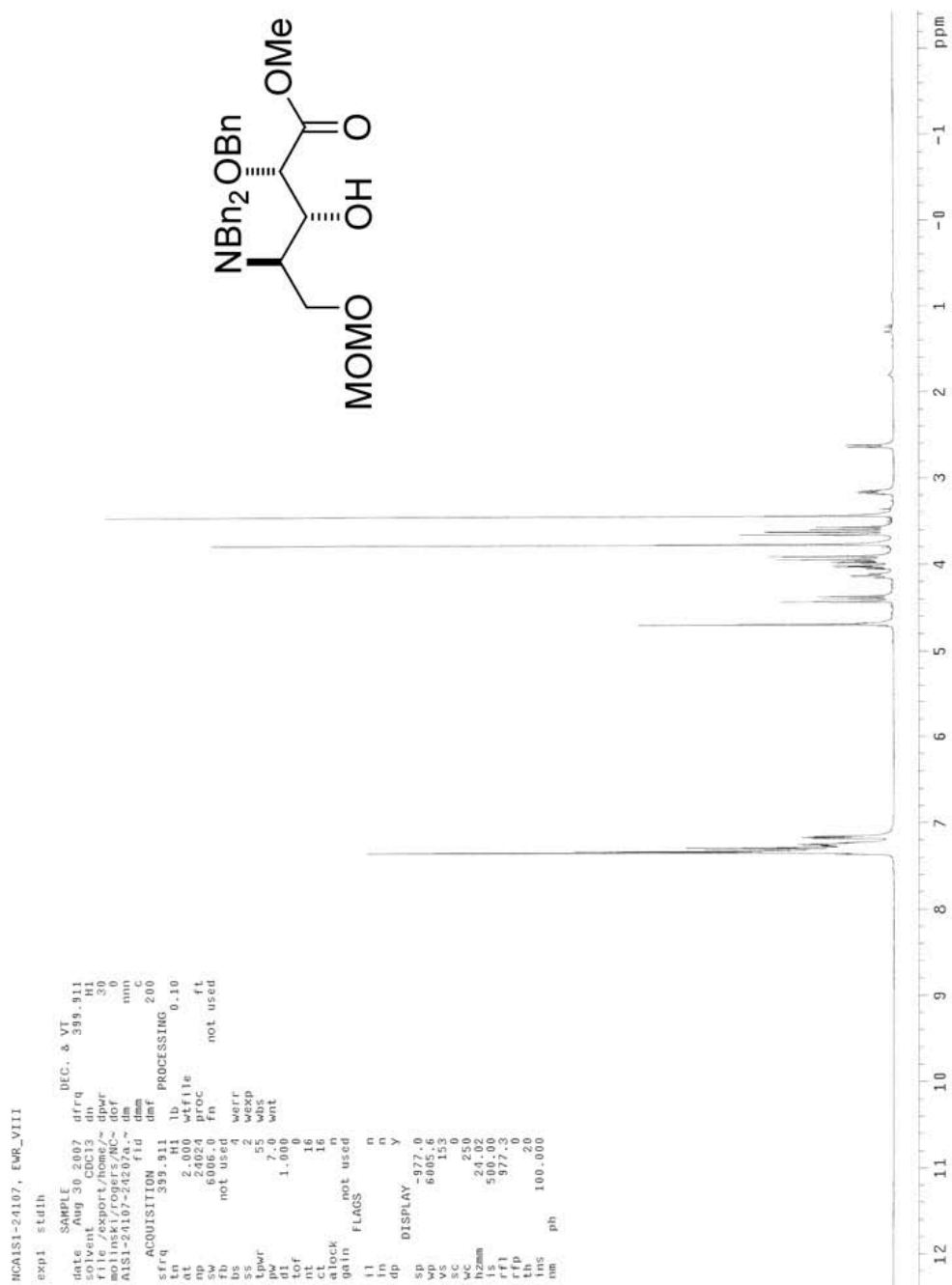
Spectrum 7.123: ^1H NMR (CDCl_3 , 400 MHz) of compound 311

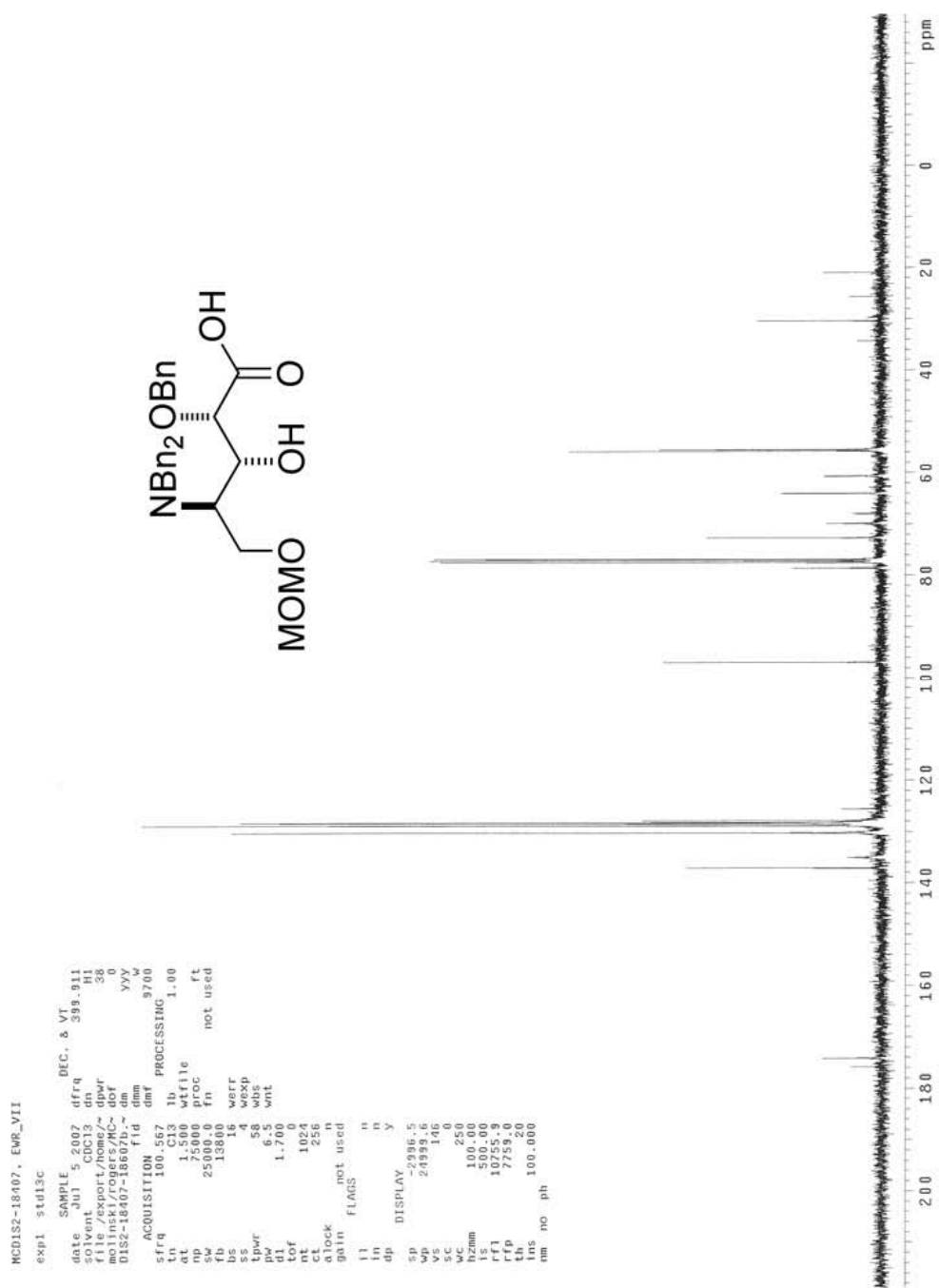


Spectrum 7.125: ¹H NMR (CDCl₃, 500 MHz) of compound 312

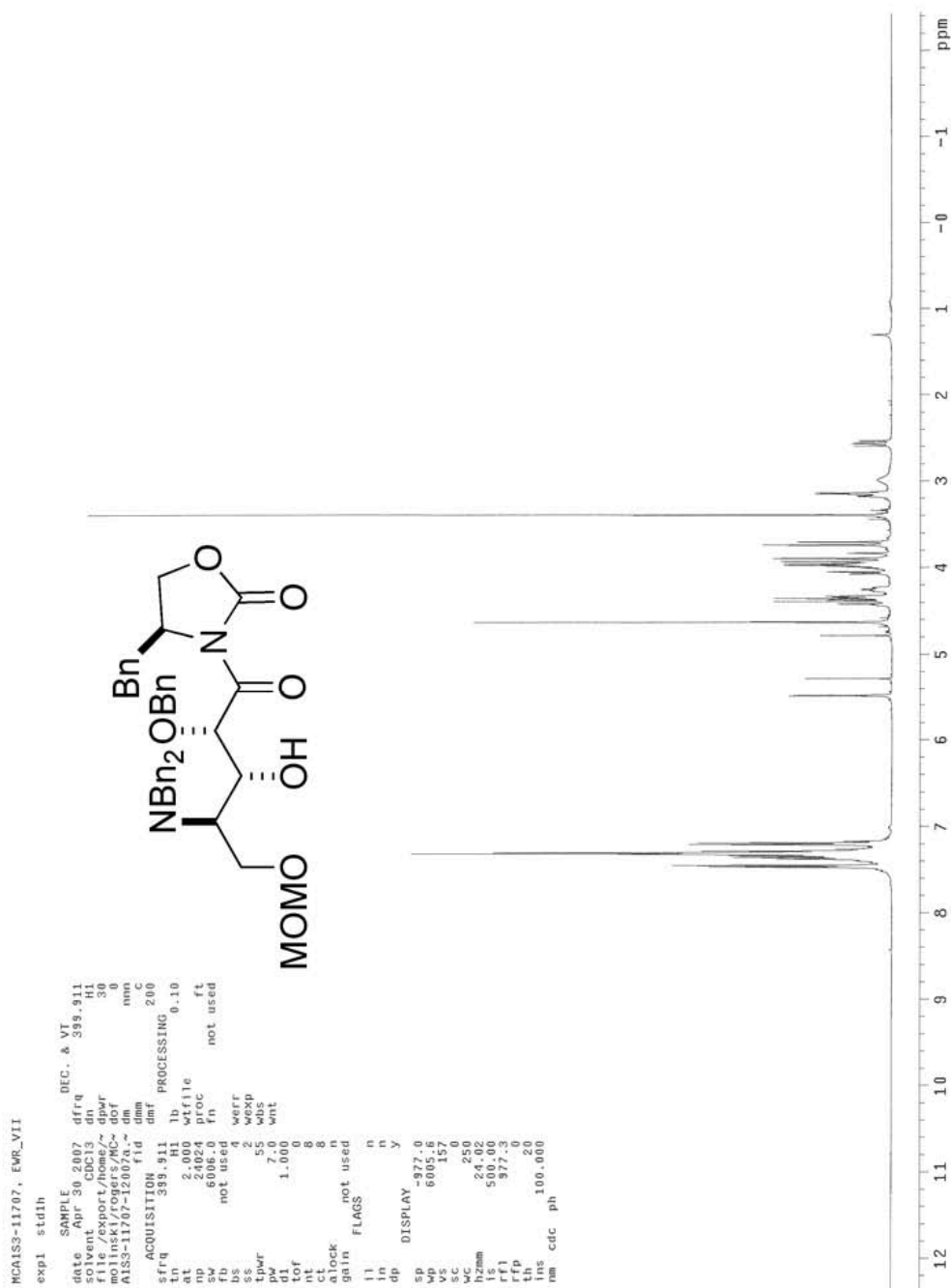


Spectrum 7.126: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 312

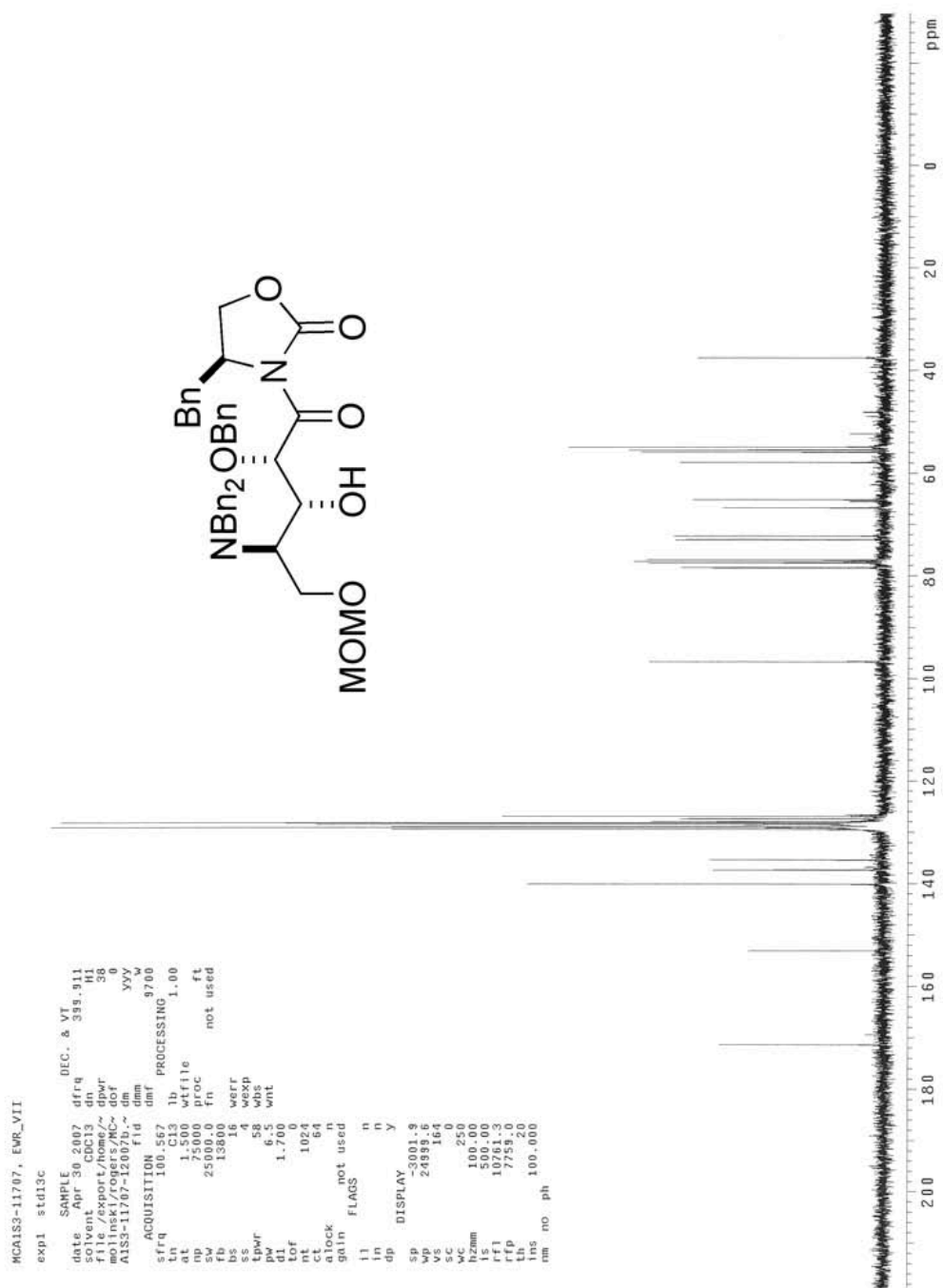




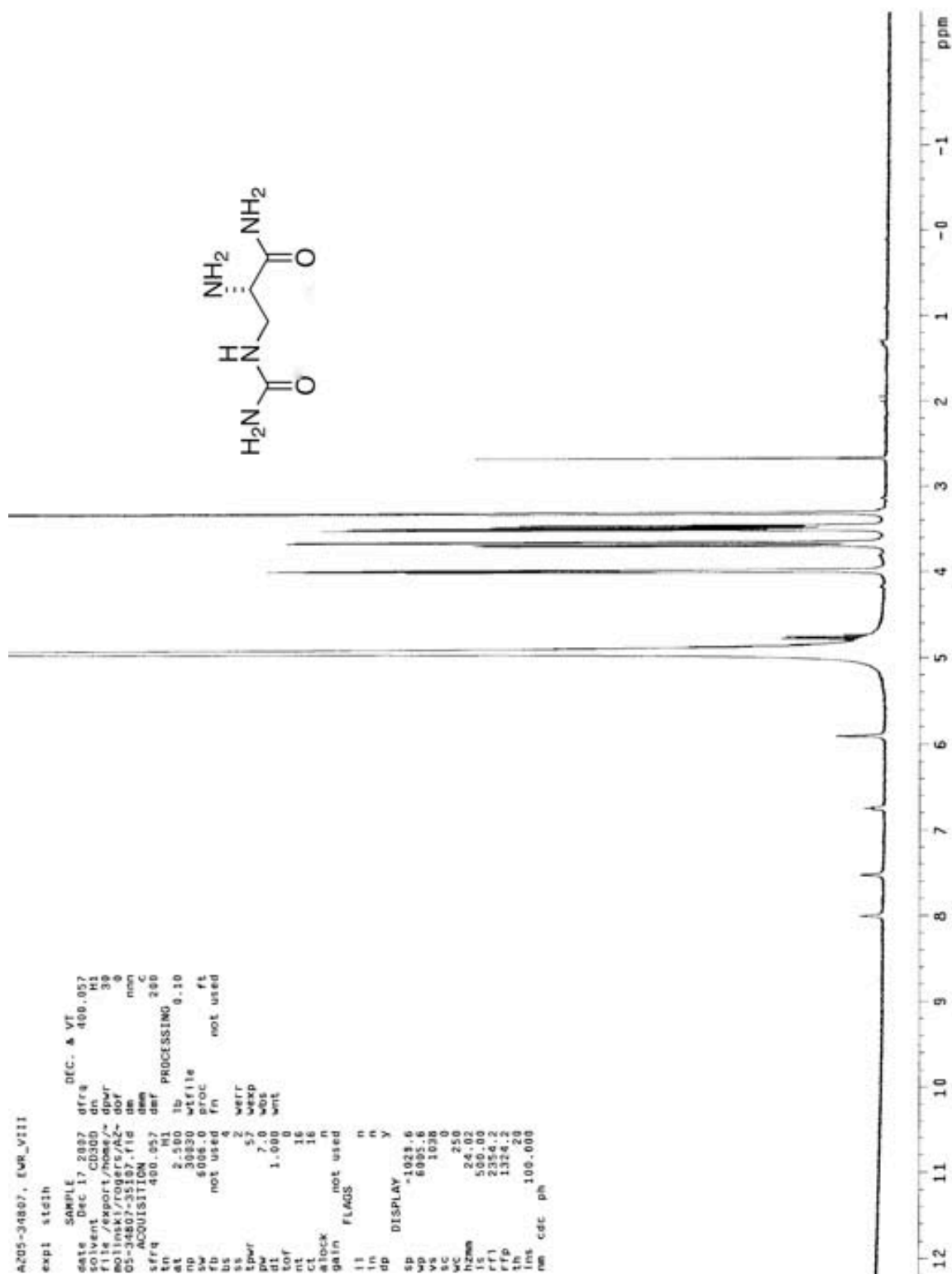
Spectrum 7.130: ¹³C NMR (CDCl₃, 100 MHz) of compound 314



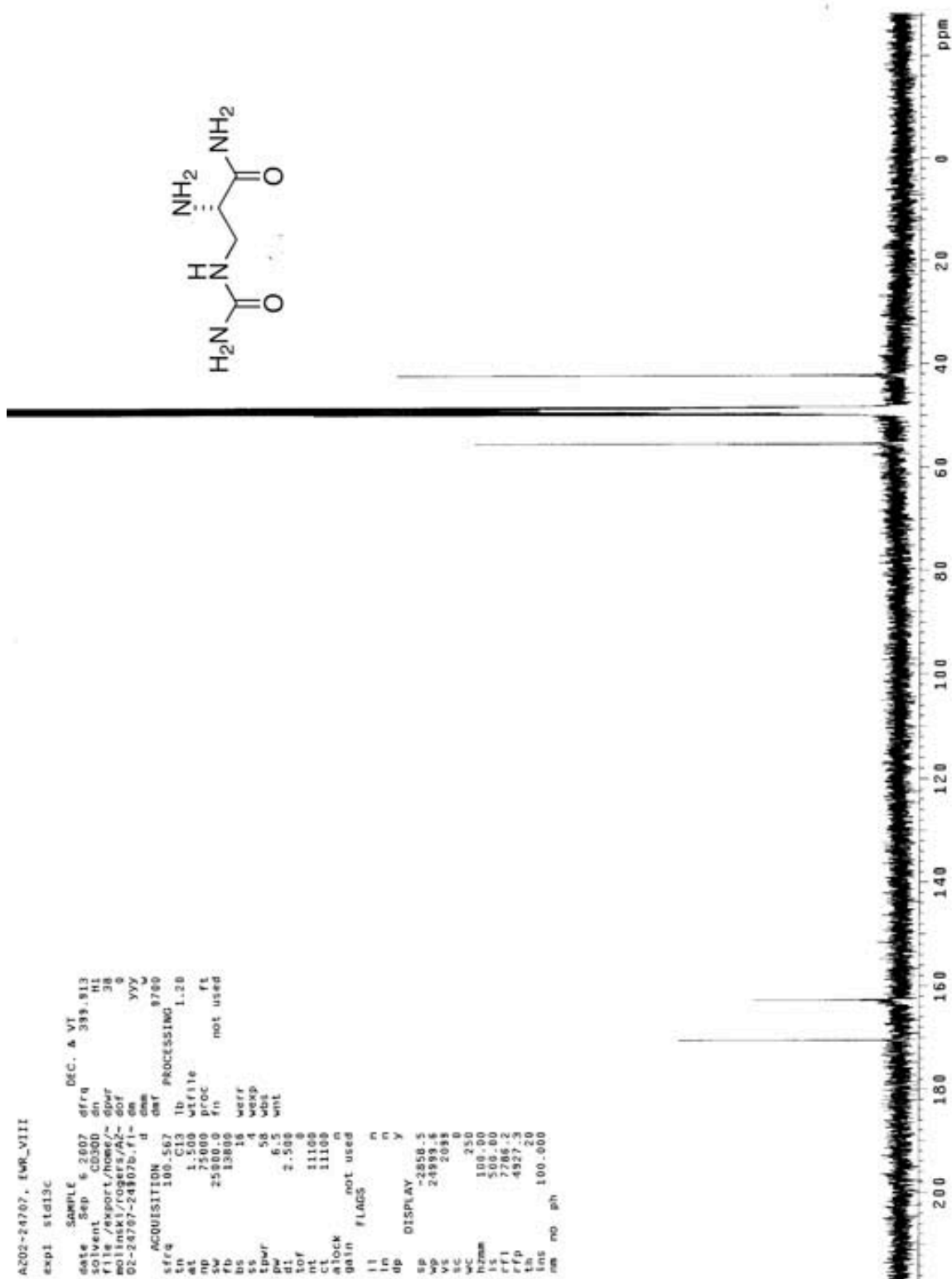
Spectrum 7.131: ¹H NMR (CDCl₃, 400 MHz) of compound **315**



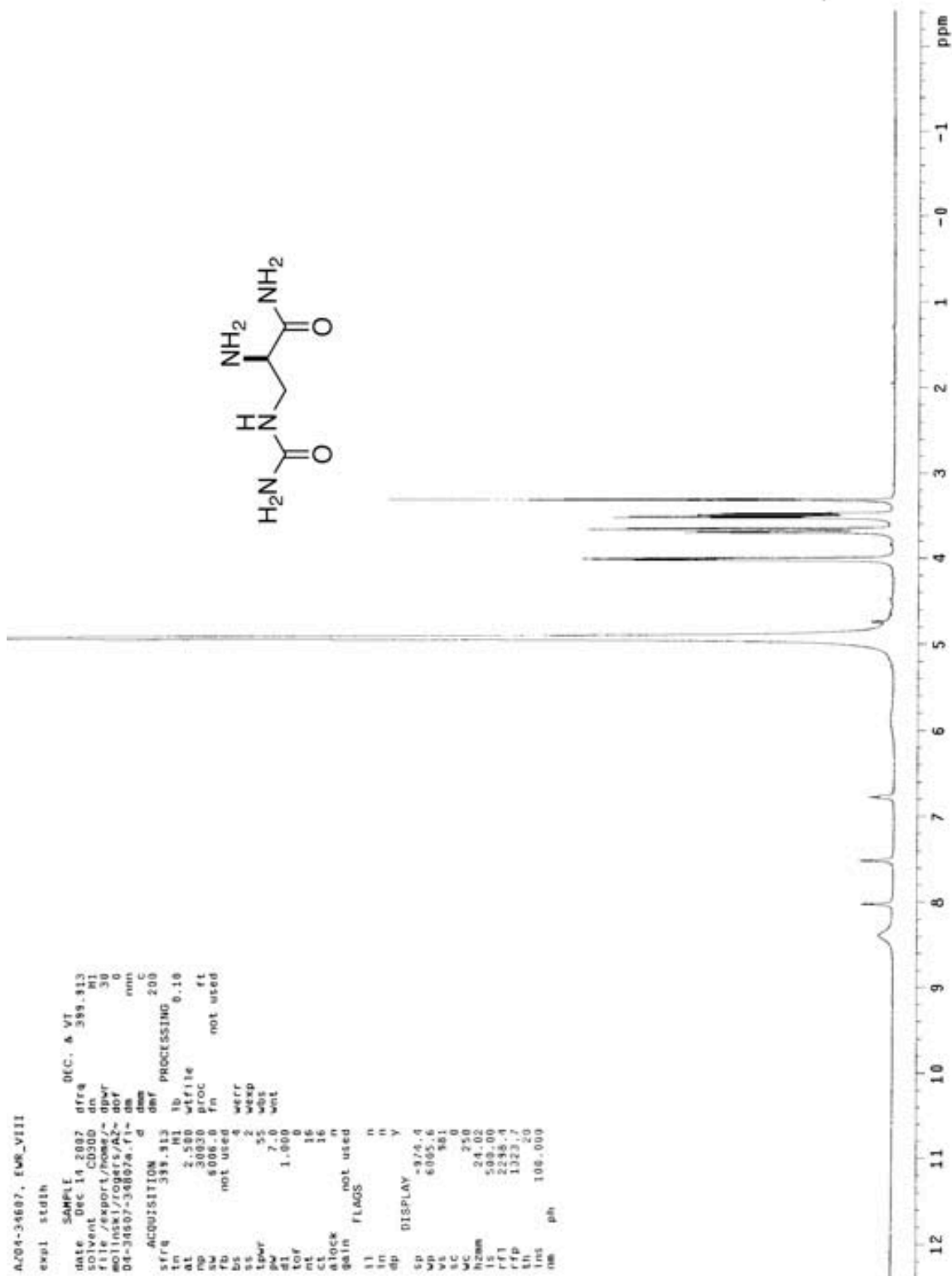
Spectrum 7.132: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 315



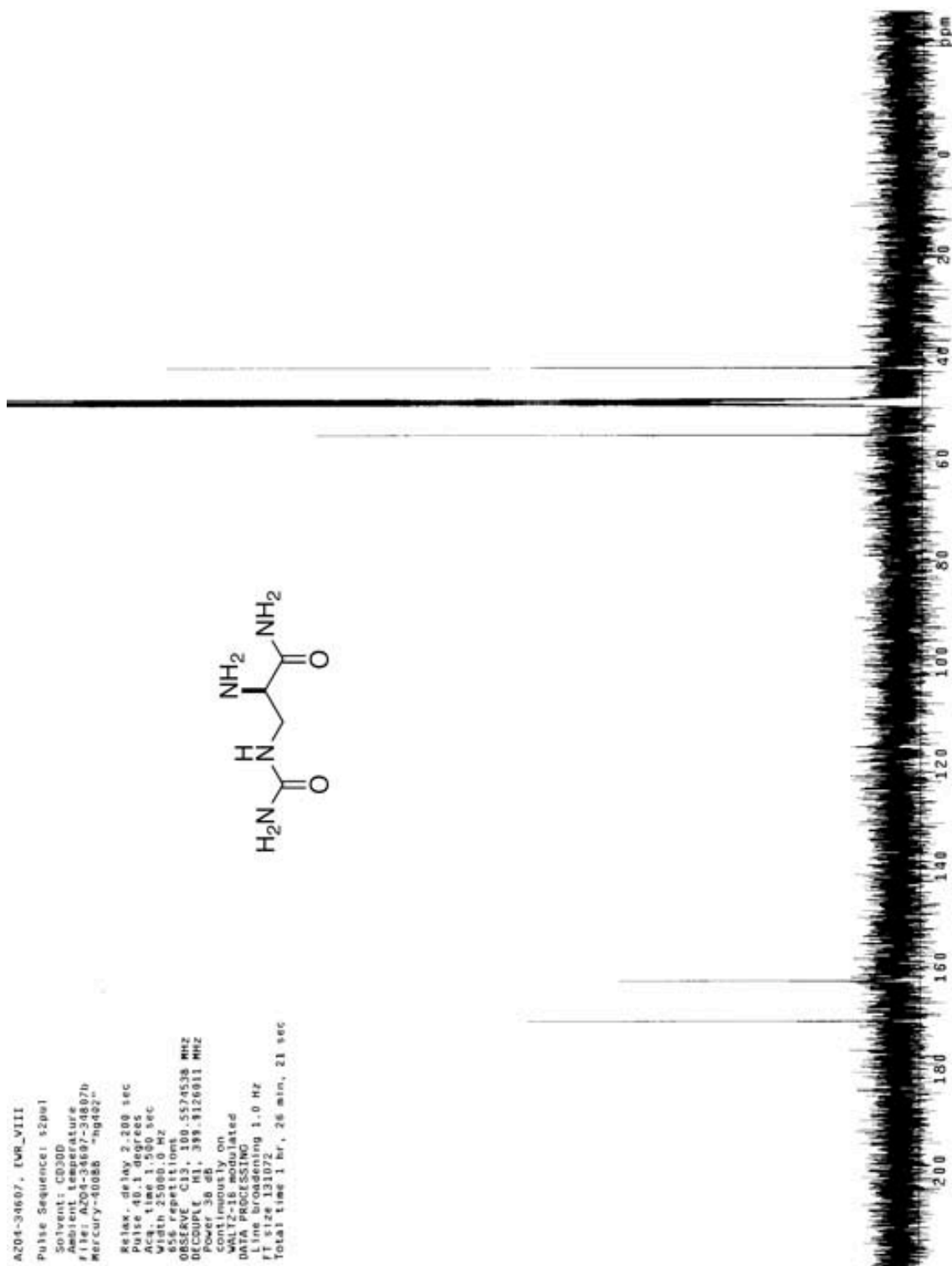
Spectrum 7.133: ^1H NMR (CD_3OD , 400 MHz) of compound (-)-319



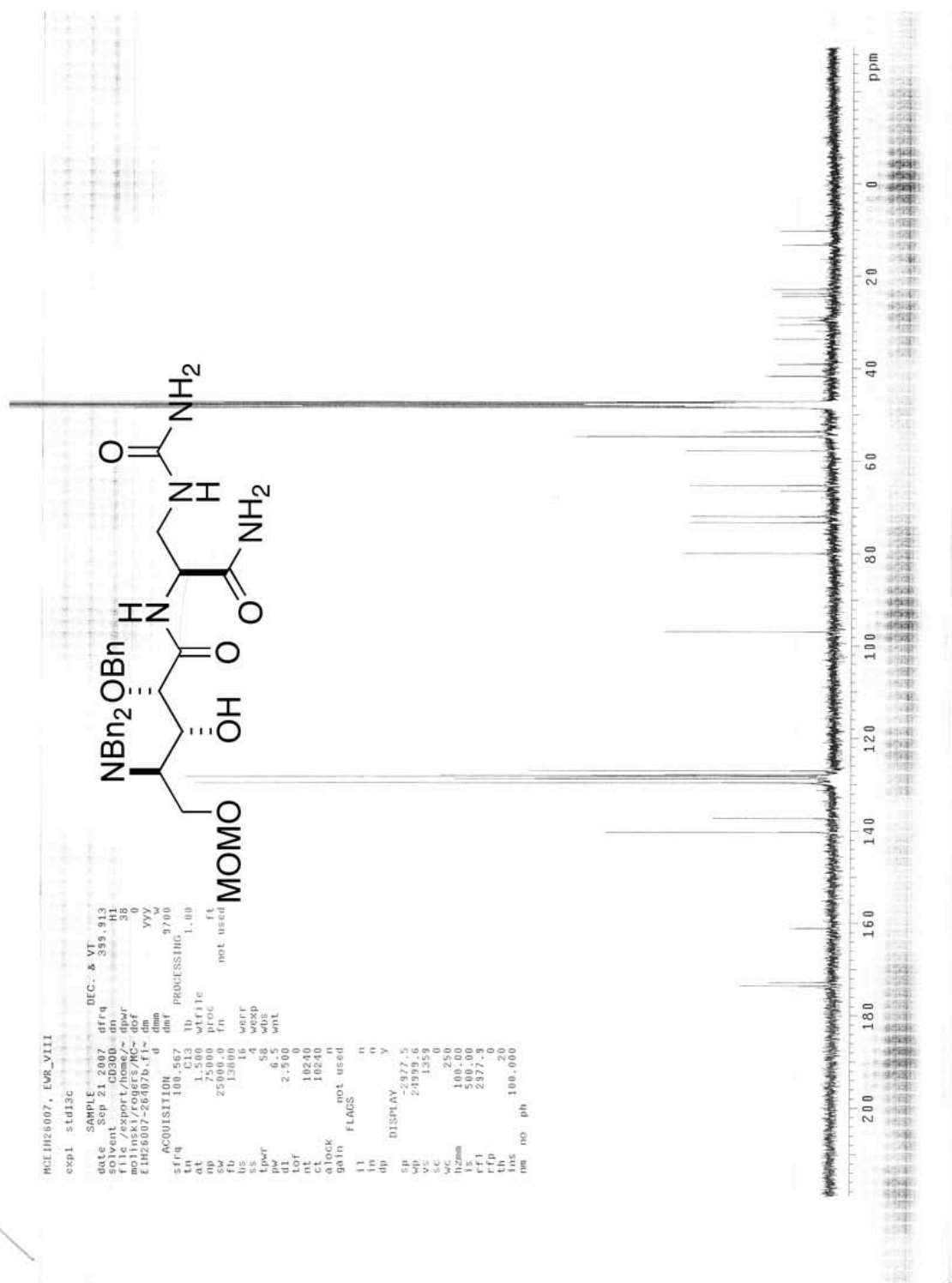
Spectrum 7.134: ^{13}C NMR (CD_3OD , 100 MHz) of compound (-)-319



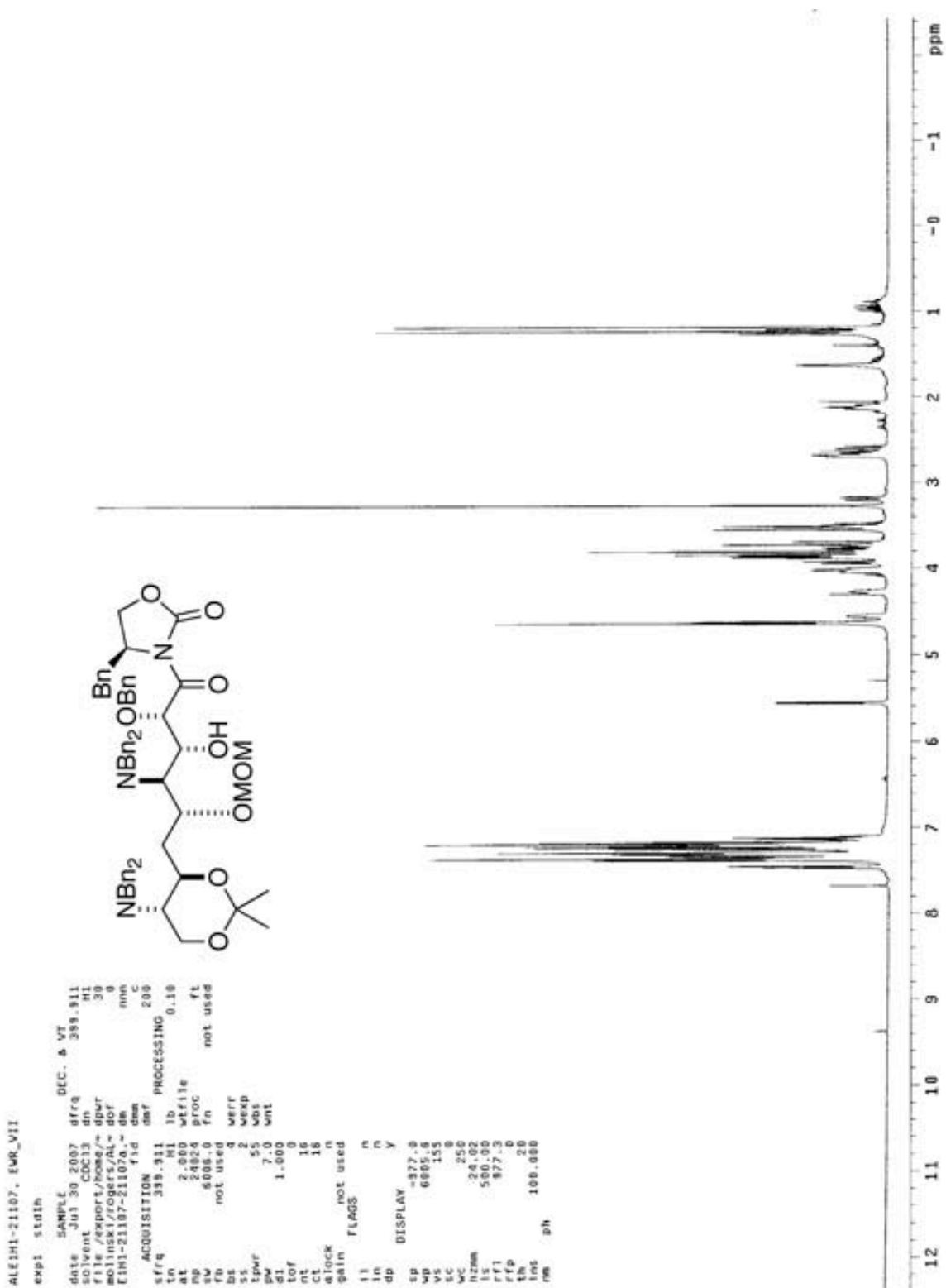
Spectrum 7.135: ^1H NMR (CD_3OD , 400 MHz) of compound (+)-319



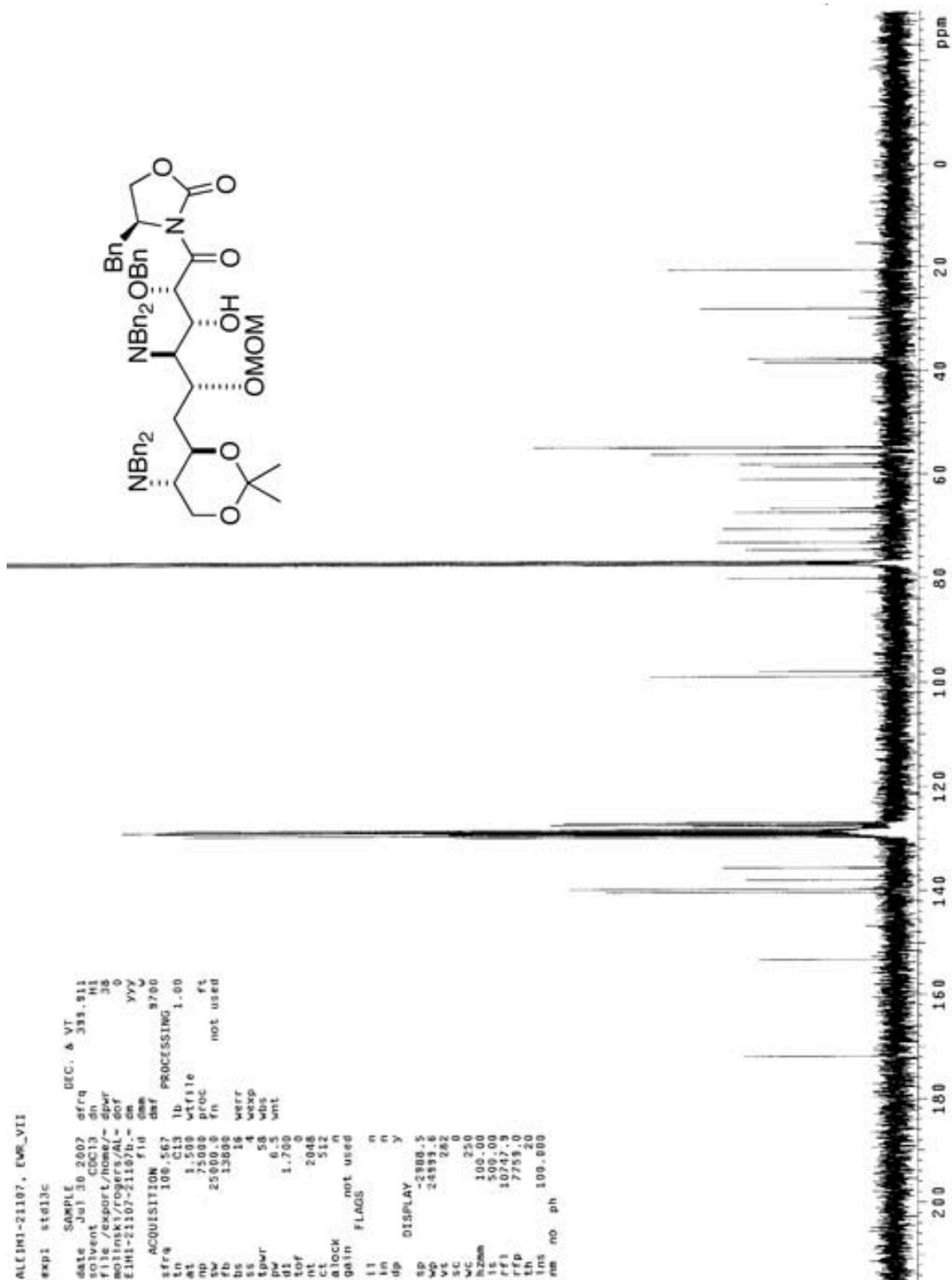
Spectrum 7.136: ^{13}C NMR (CD_3OD , 100 MHz) of compound (+)-319



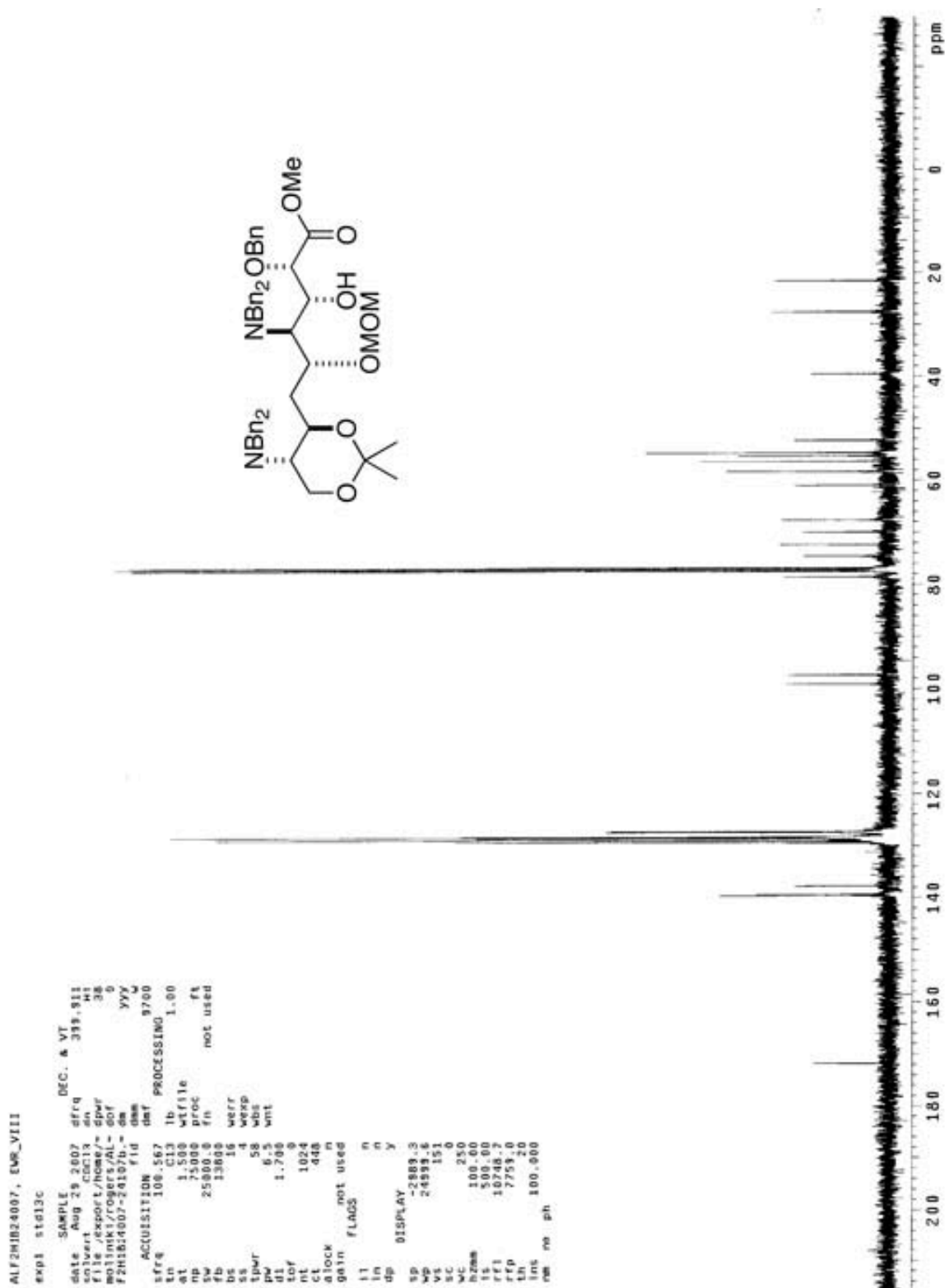
Spectrum 7.138: ¹³C NMR (CD₃OD, 100 MHz) of compound 320



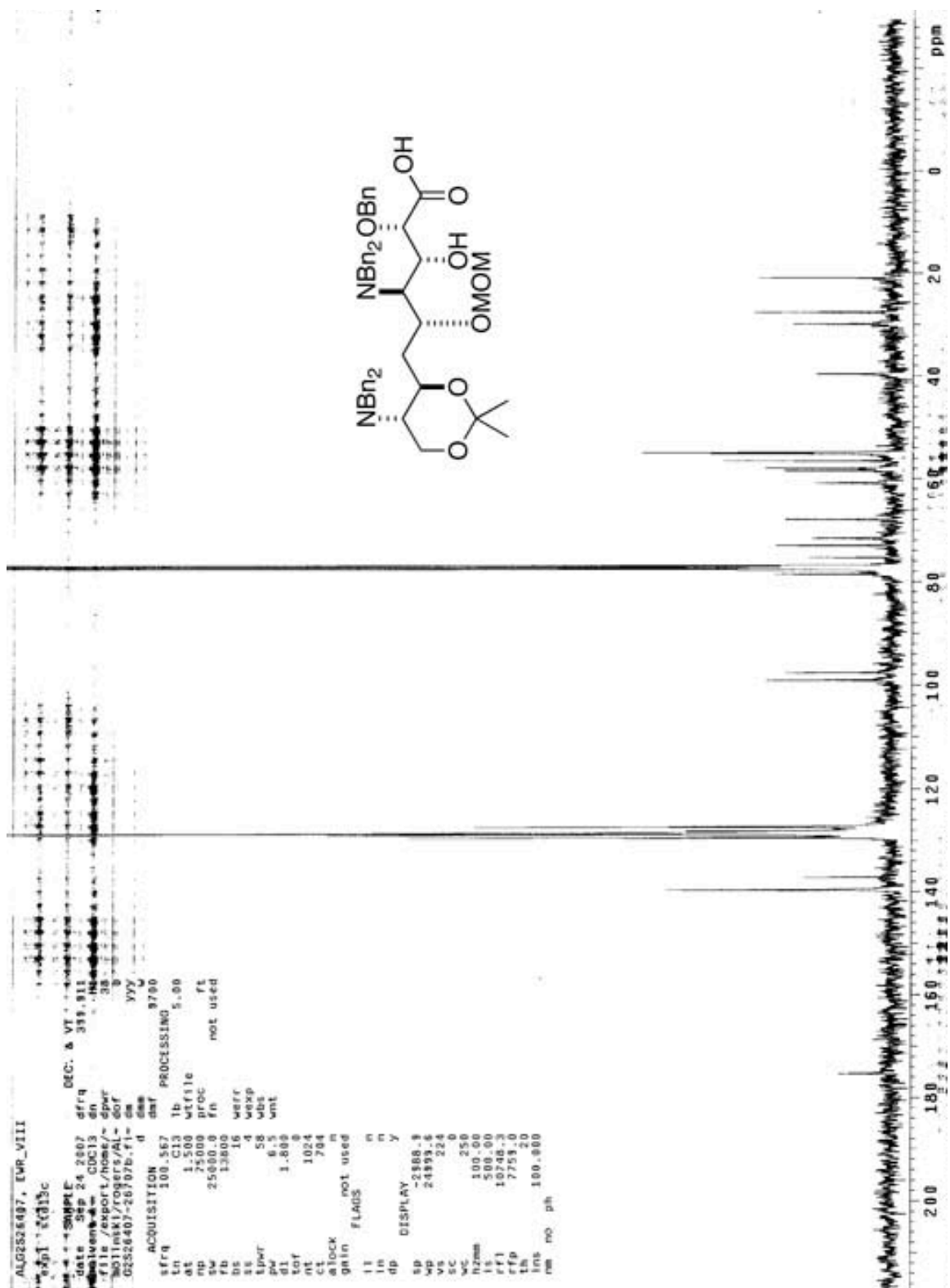
Spectrum 7.139: ^1H NMR (CDCl_3 , 400 MHz) of compound 321



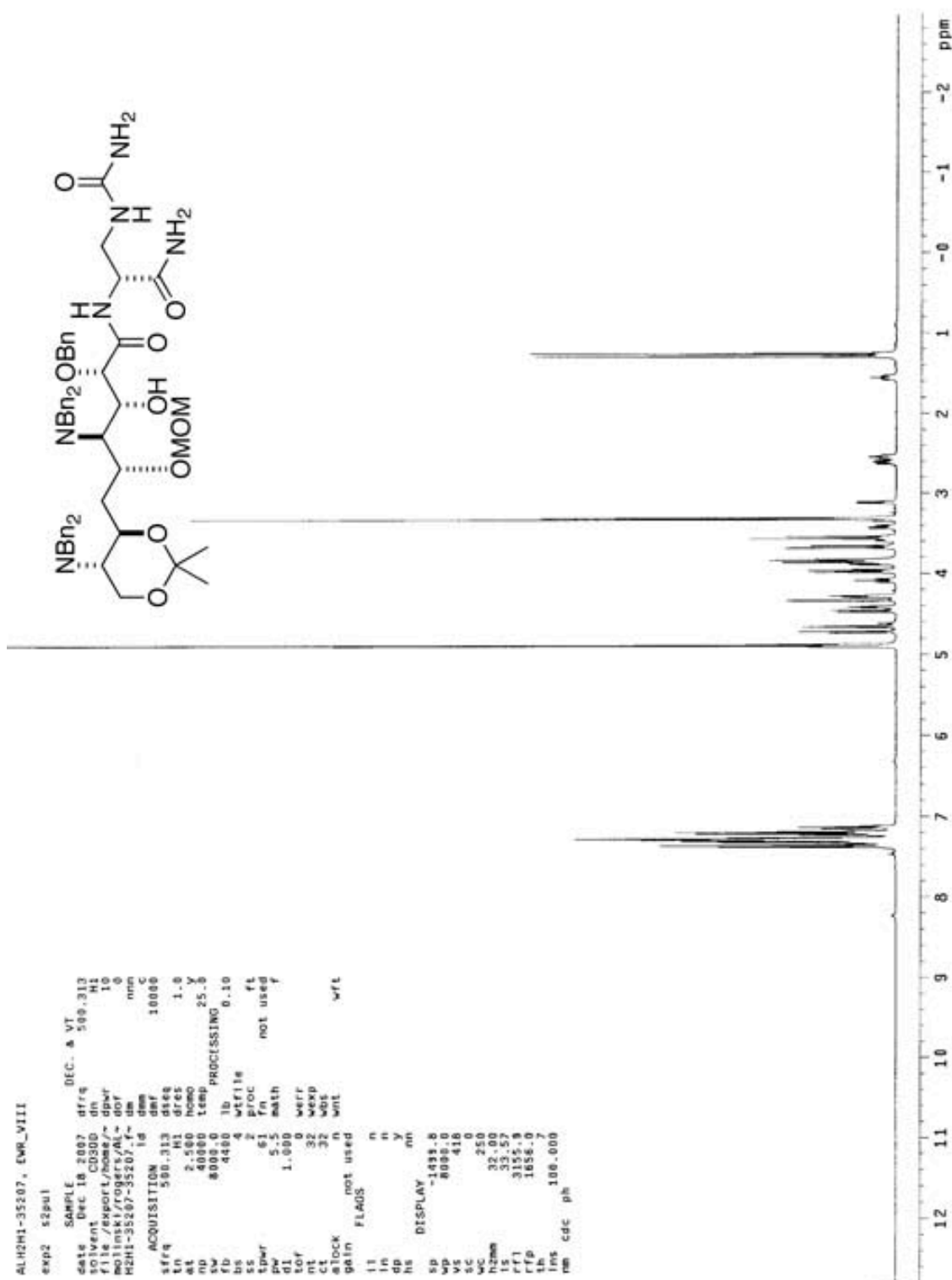
Spectrum 7.140: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 321



Spectrum 7.142: ¹³C NMR (CDCl₃, 100 MHz) of compound 322



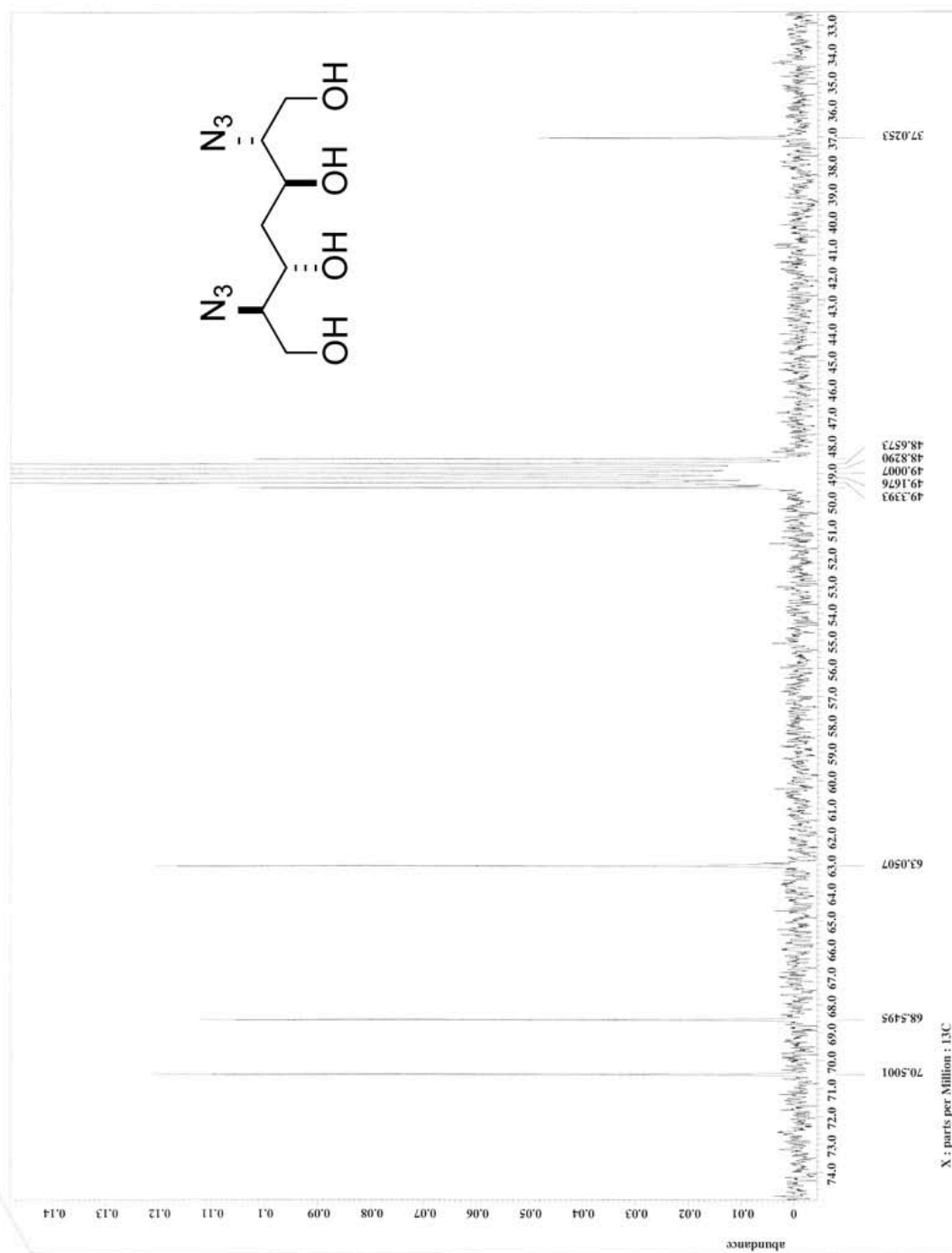
Spectrum 7.144: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 323



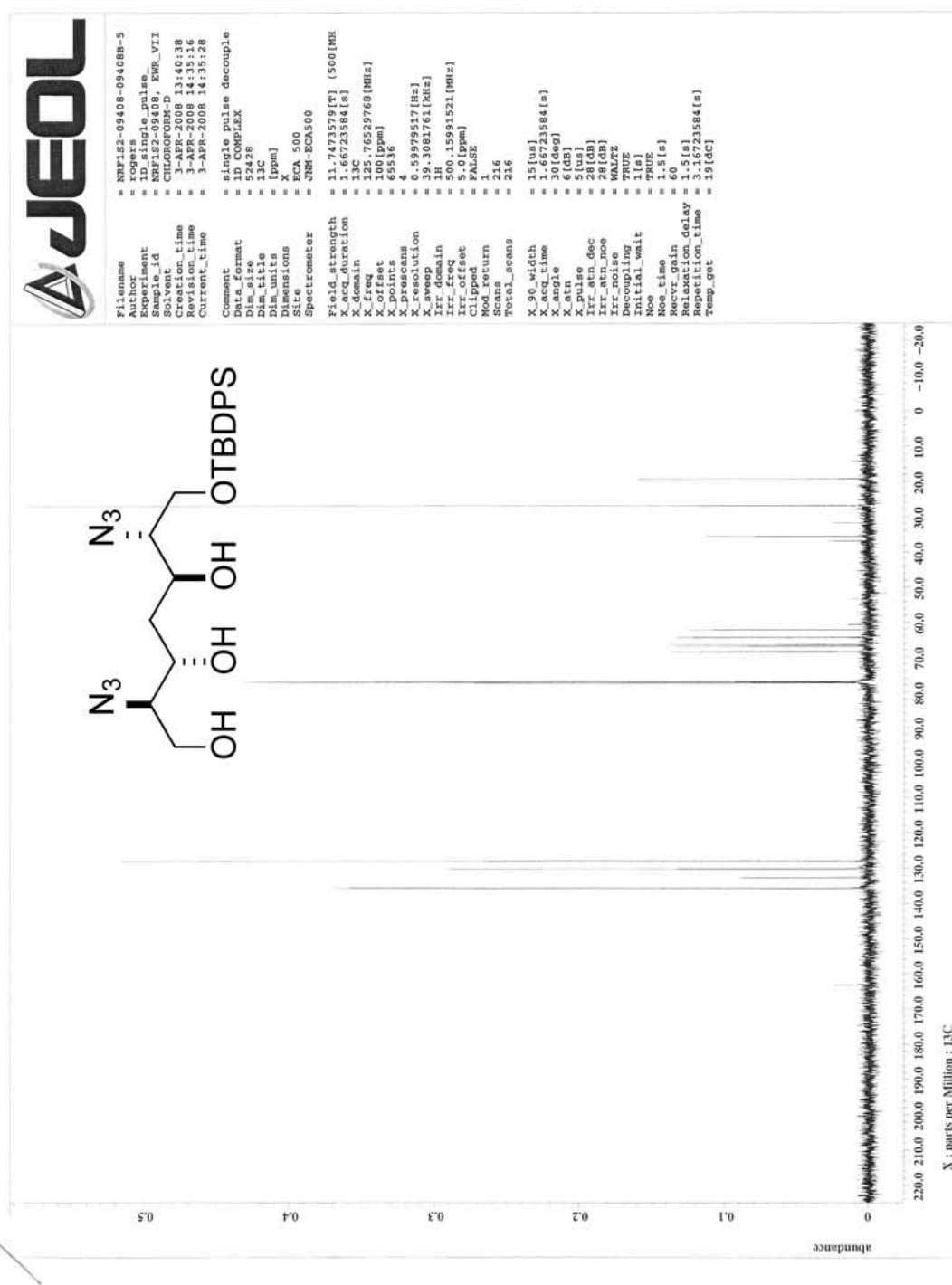
Spectrum 7.147: ^1H NMR (CD_3OD , 500 MHz) of compound 329

7.3.3. Chapter 4 Spectra

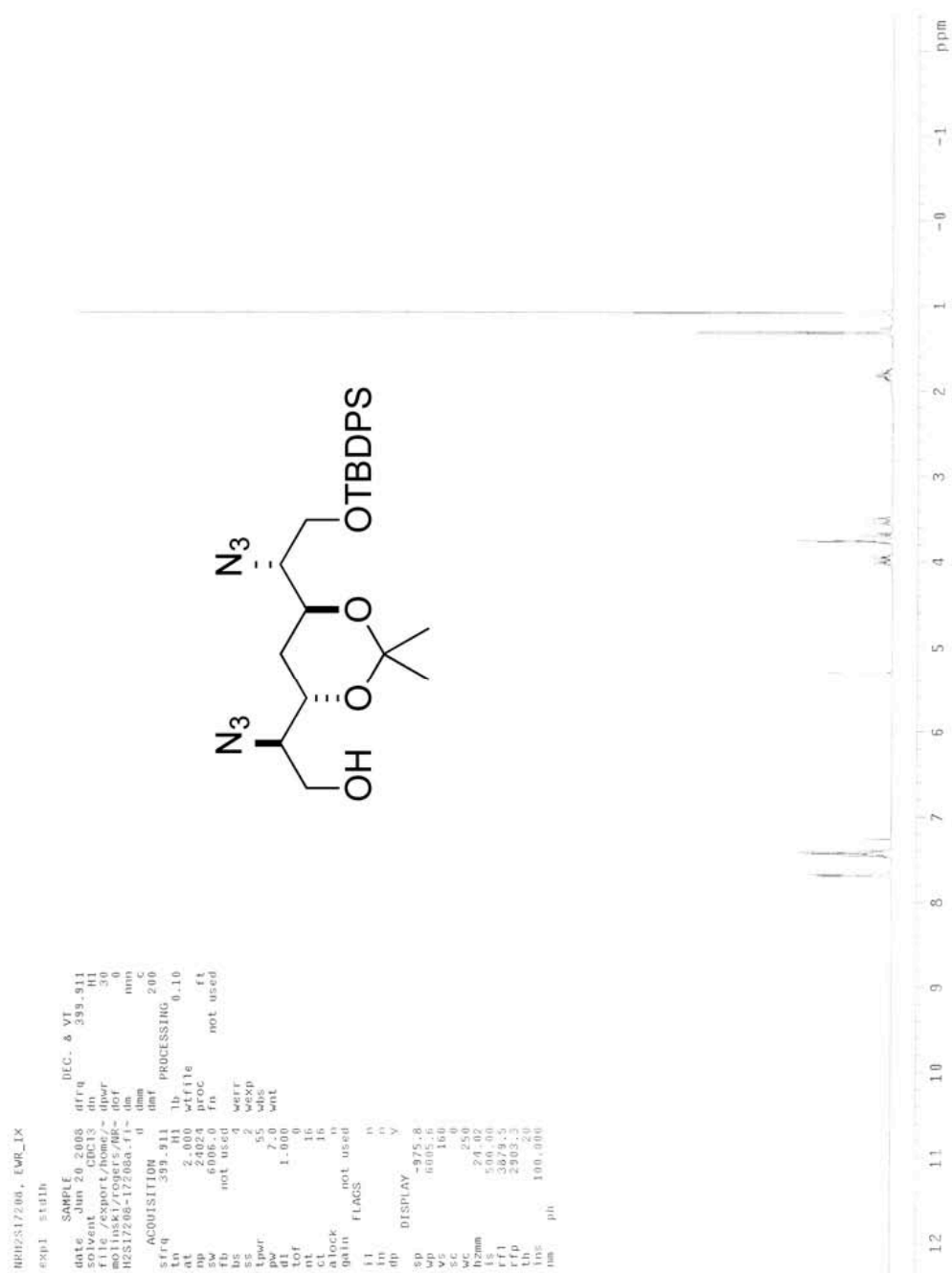
Spectrum 7.149: ¹H NMR (CD₃OD, 500 MHz) of compound 334



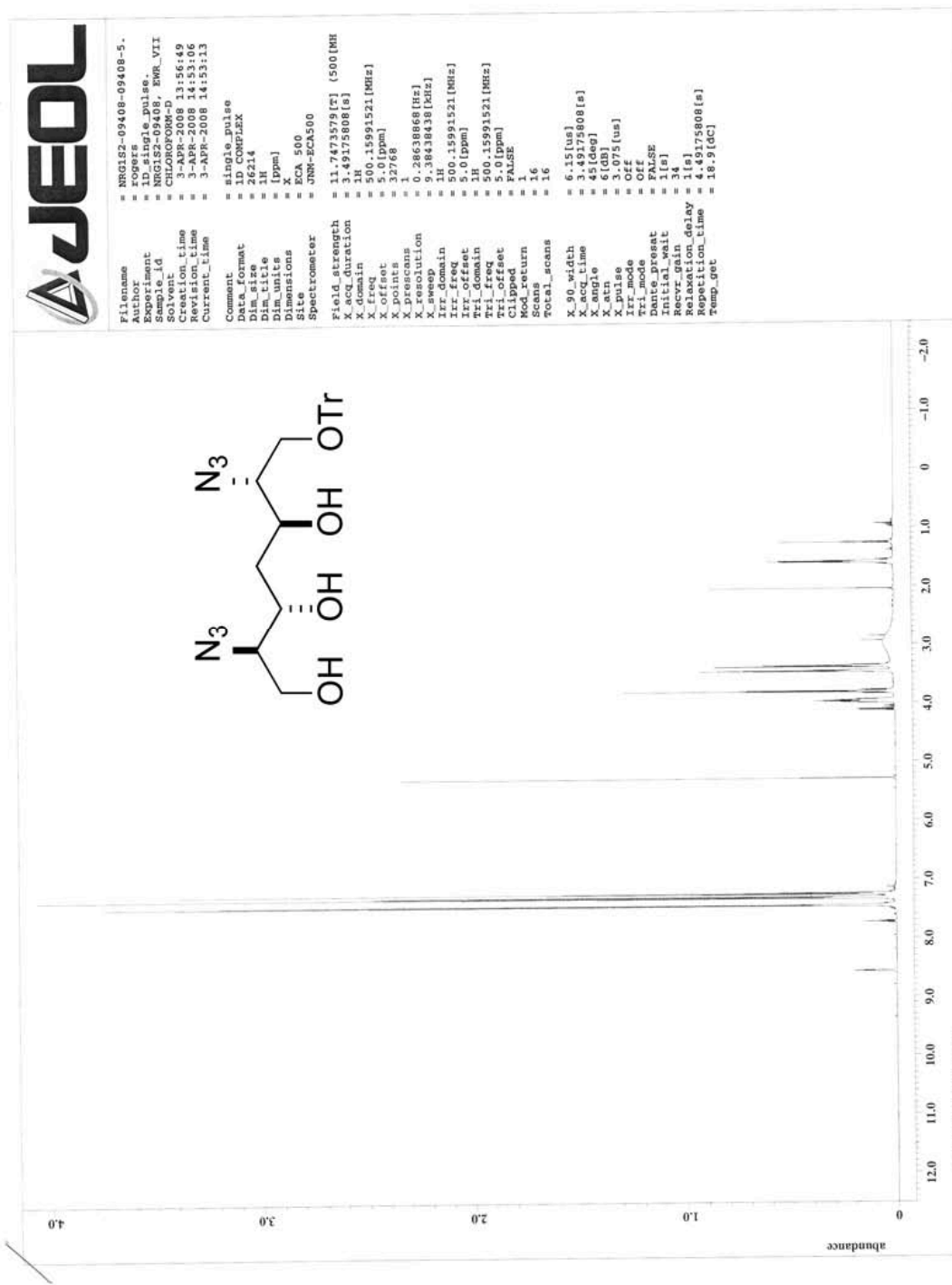
Spectrum 7.150: ^{13}C NMR (CD₃OD, 125 MHz) of compound 334



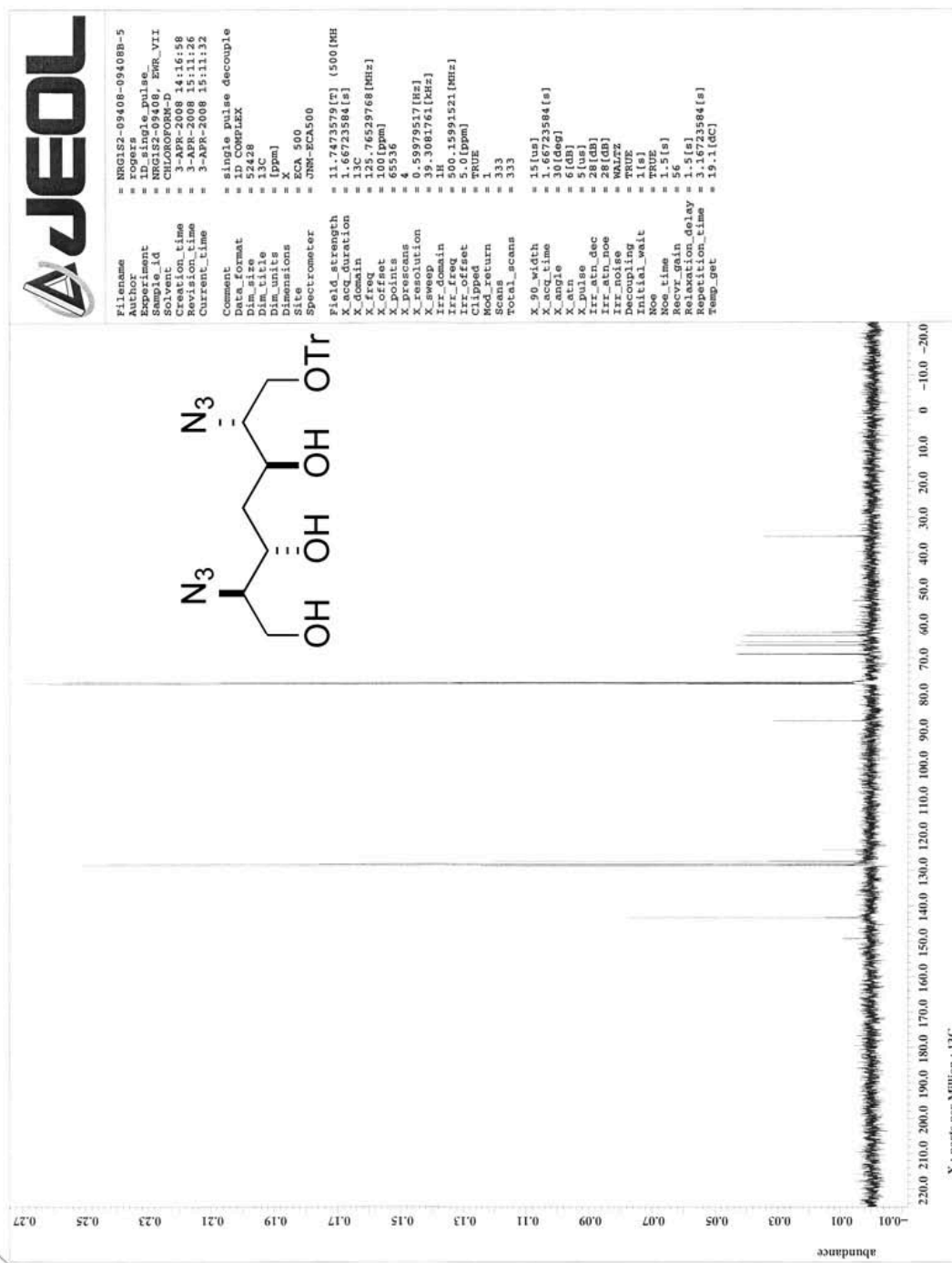
Spectrum 7.152: ^{13}C NMR (CDCl_3 , 125 MHz) of compound **339**



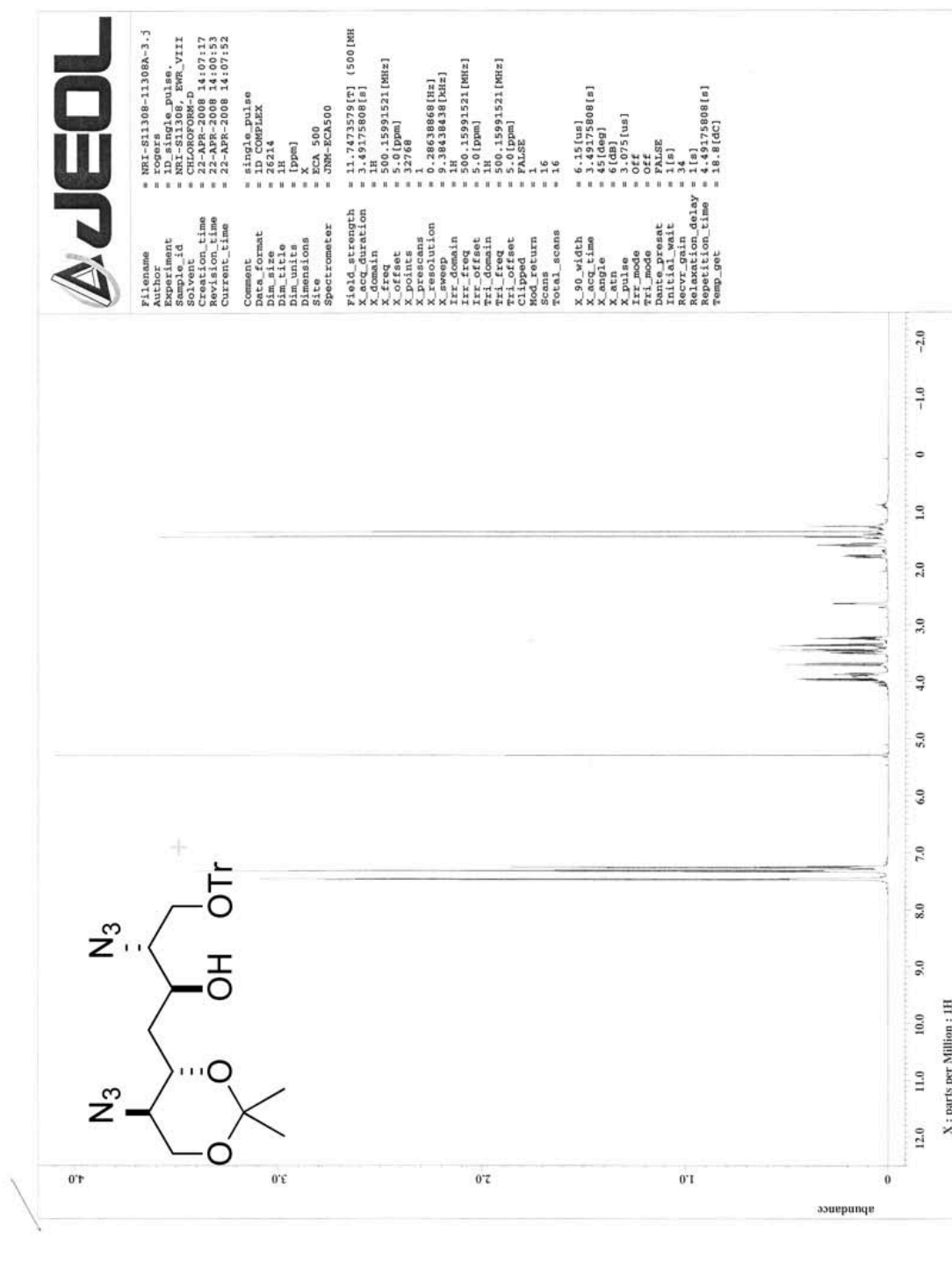
Spectrum 7.153: ^1H NMR (CDCl_3 , 400 MHz) of compound **342**



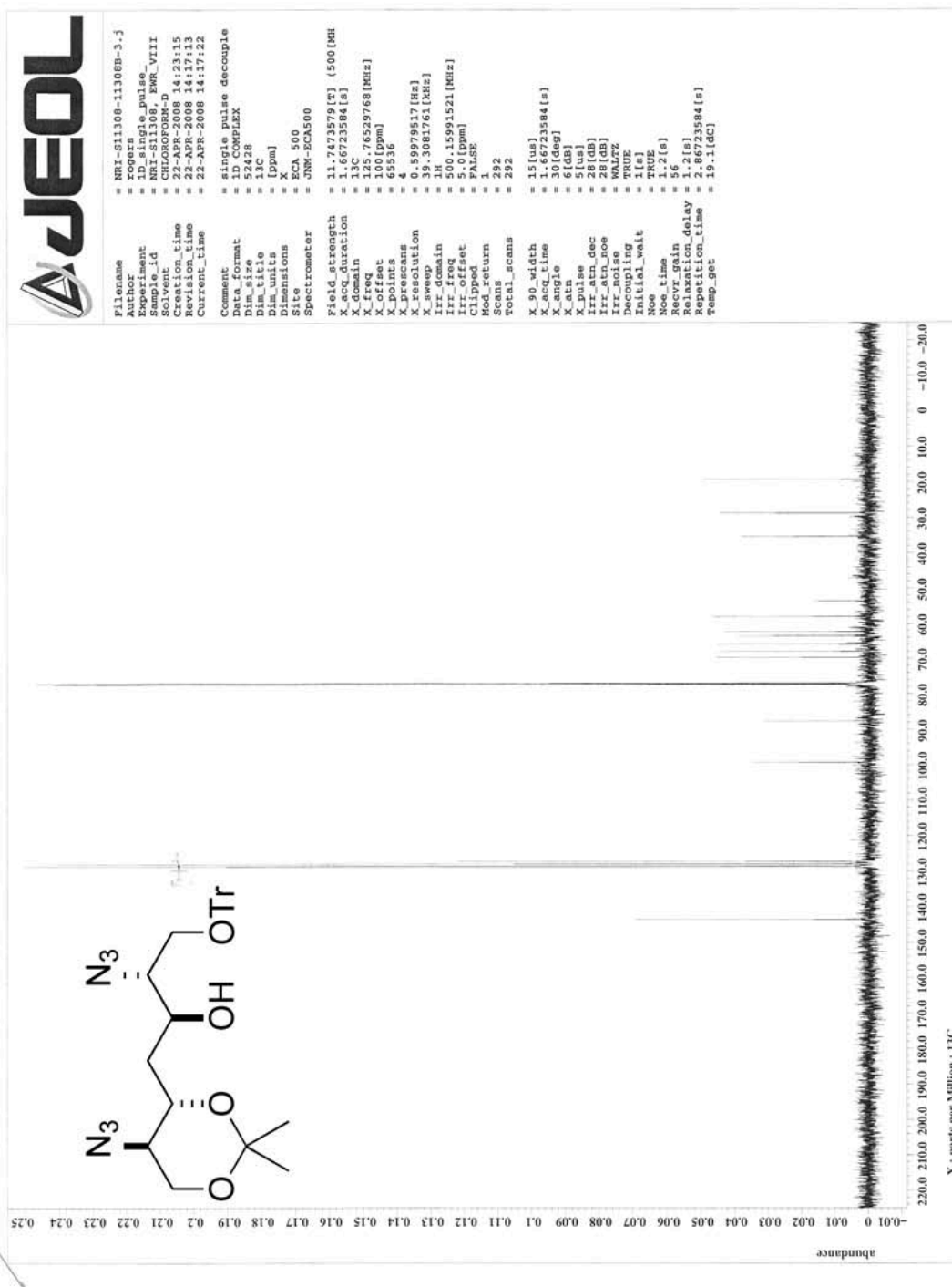
Spectrum 7.155: ^1H NMR (CDCl_3 , 500 MHz) of compound 344



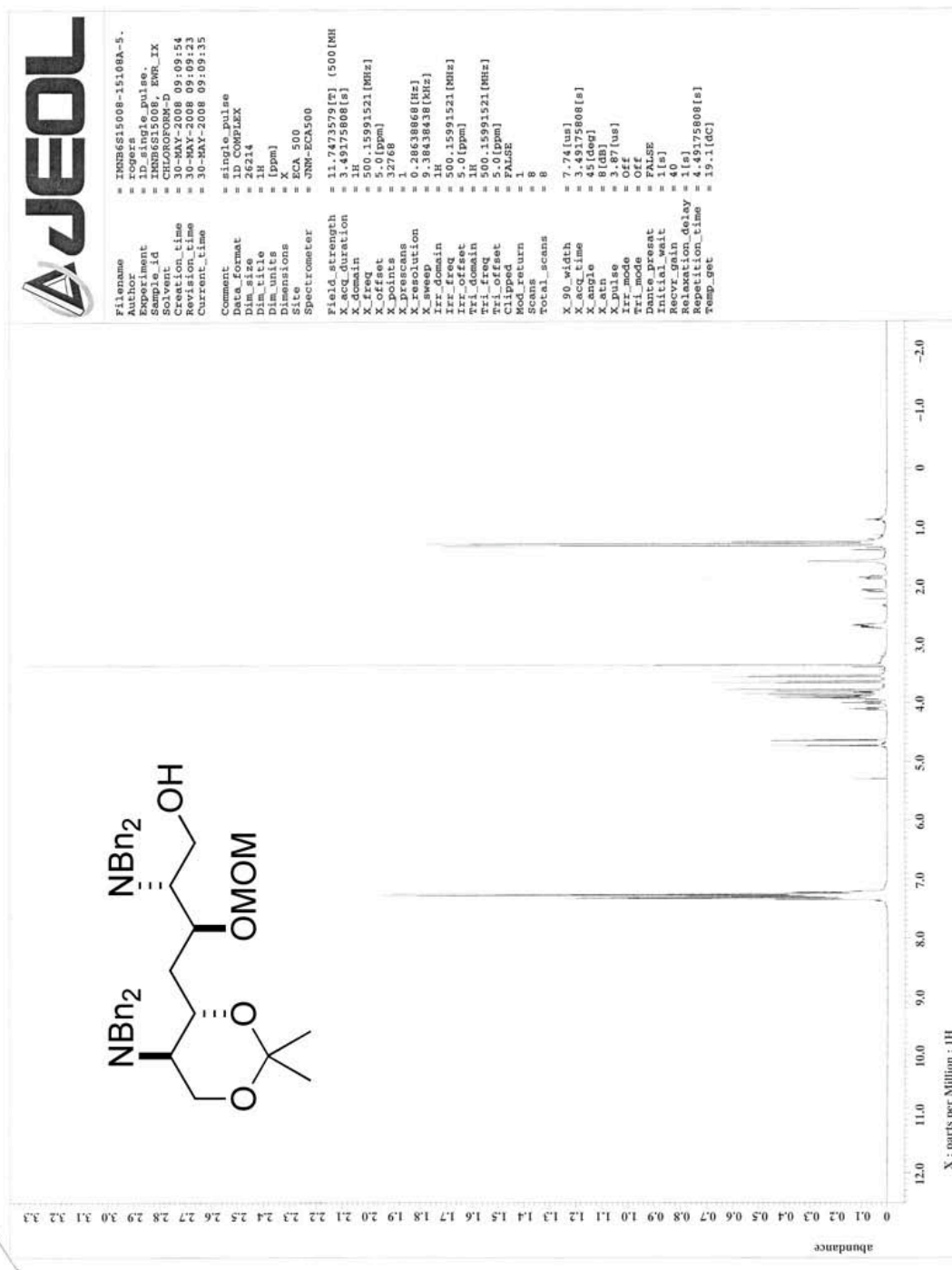
Spectrum 7.156: ^{13}C NMR (CDCl_3 , 125 MHz) of compound 344



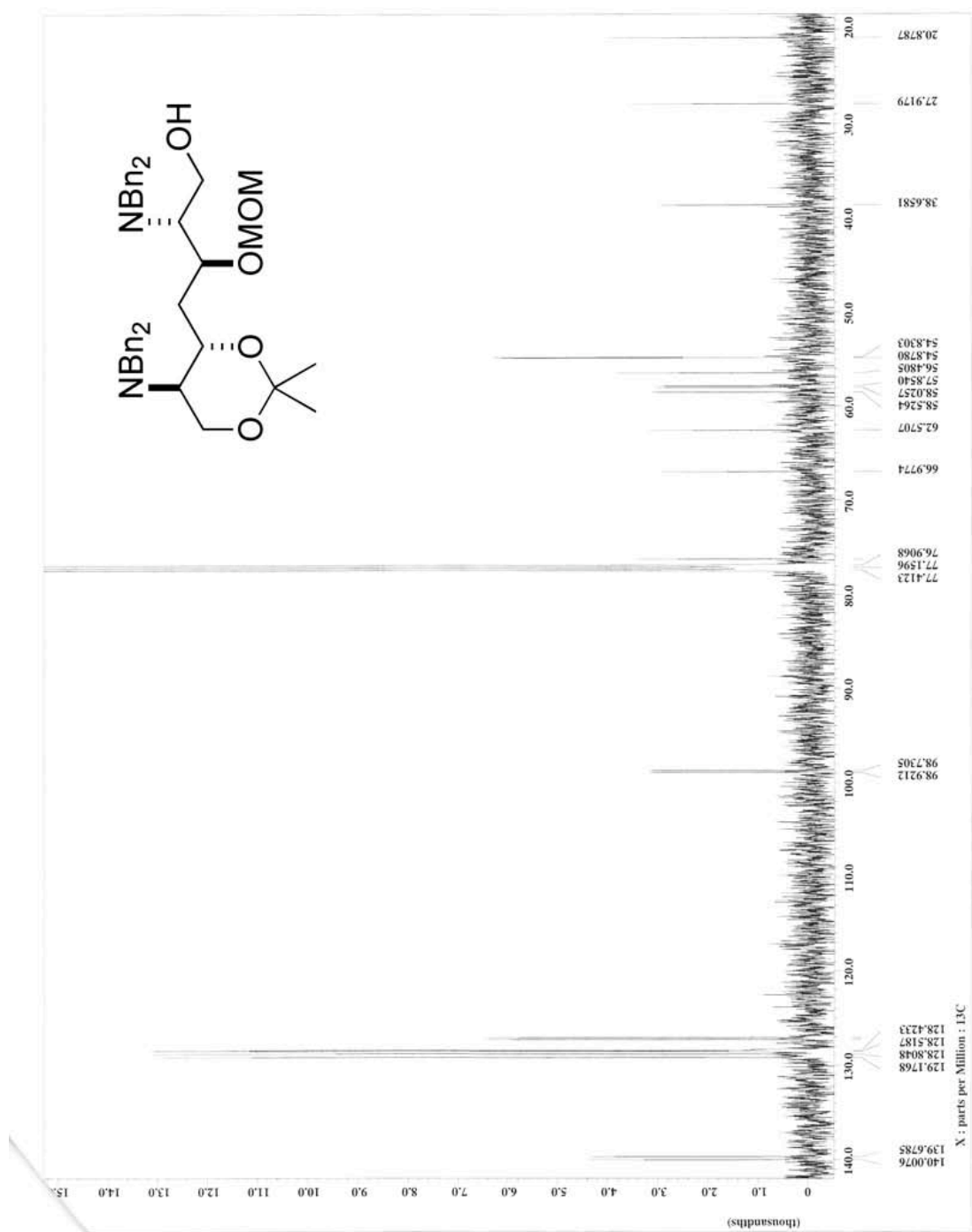
Spectrum 7.157: ¹H NMR (CDCl₃, 500 MHz) of compound 346



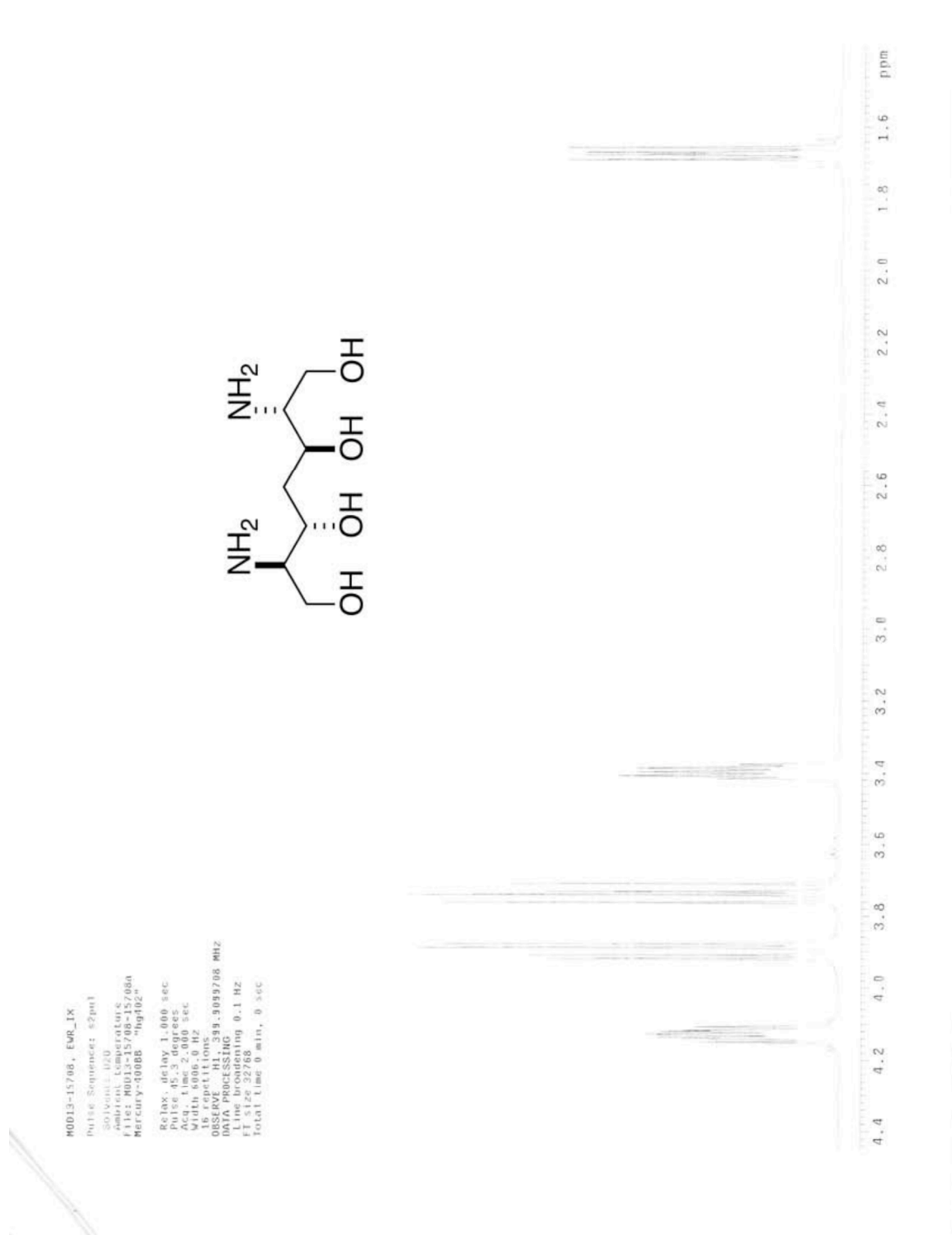
Spectrum 7.158: ^{13}C NMR (CDCl_3 , 125 MHz) of compound 346

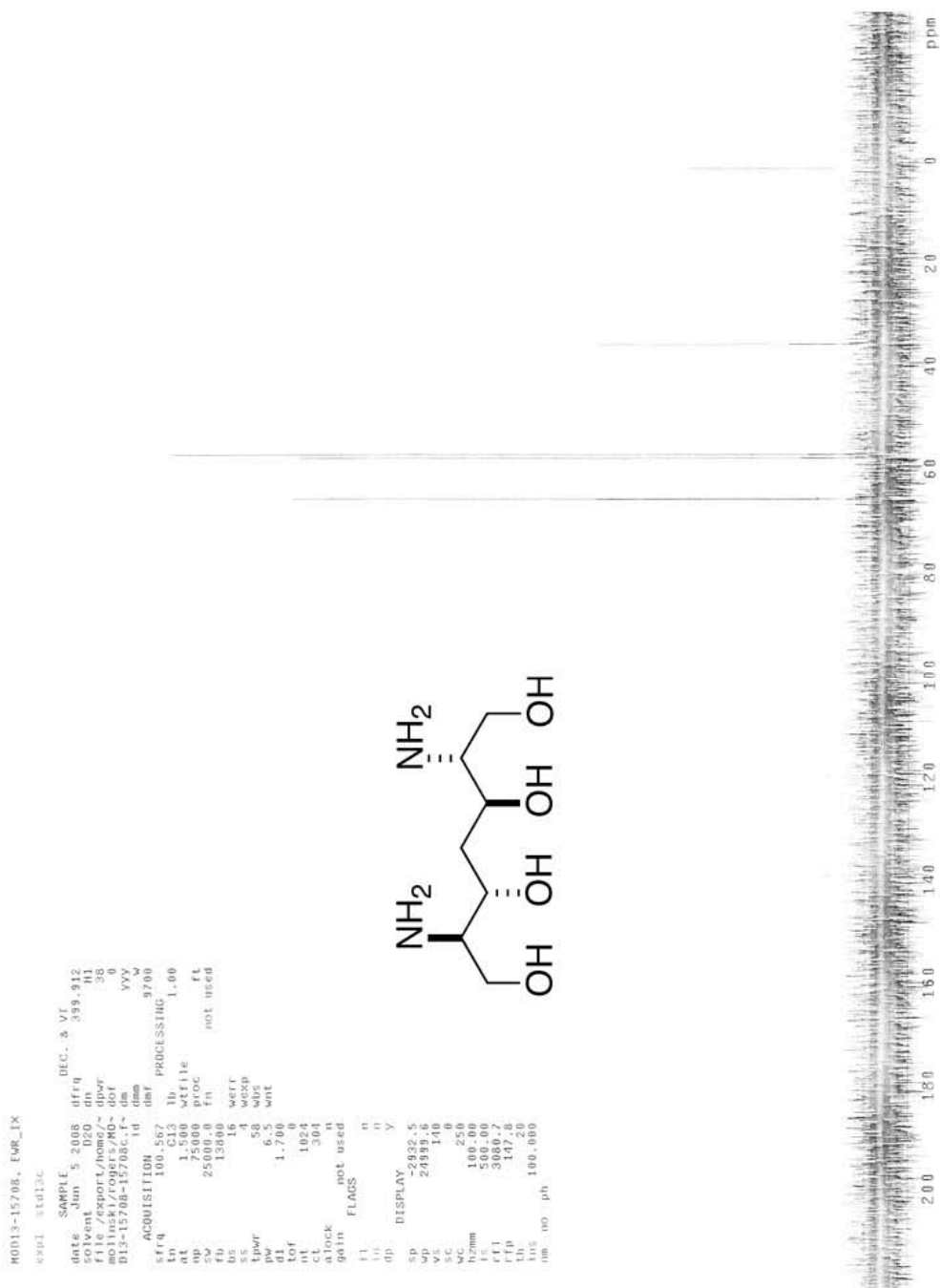


Spectrum 7.161: ¹H NMR (CDCl₃, 500 MHz) of compound (–)-302

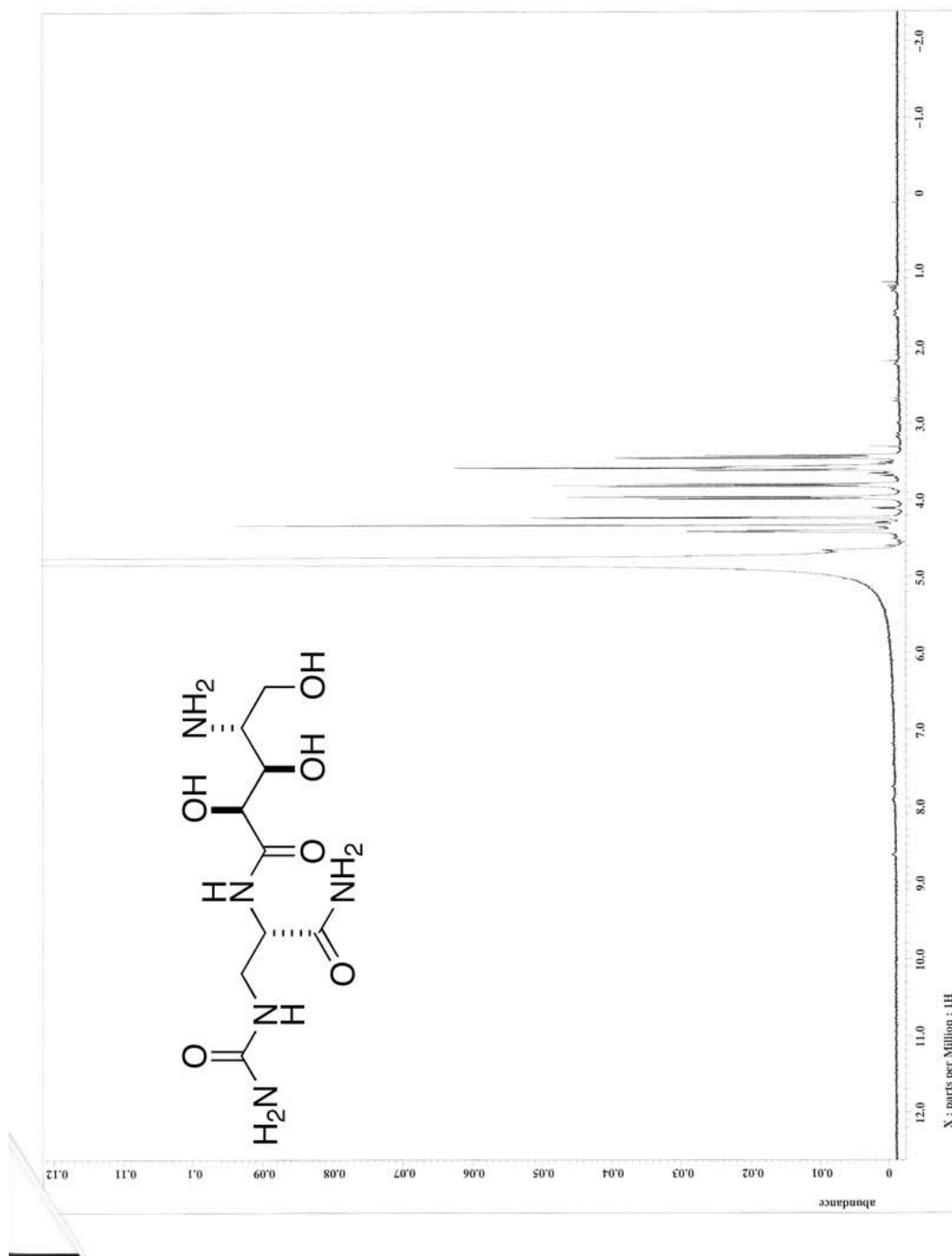


7.3.4. Chapter 5 Spectra

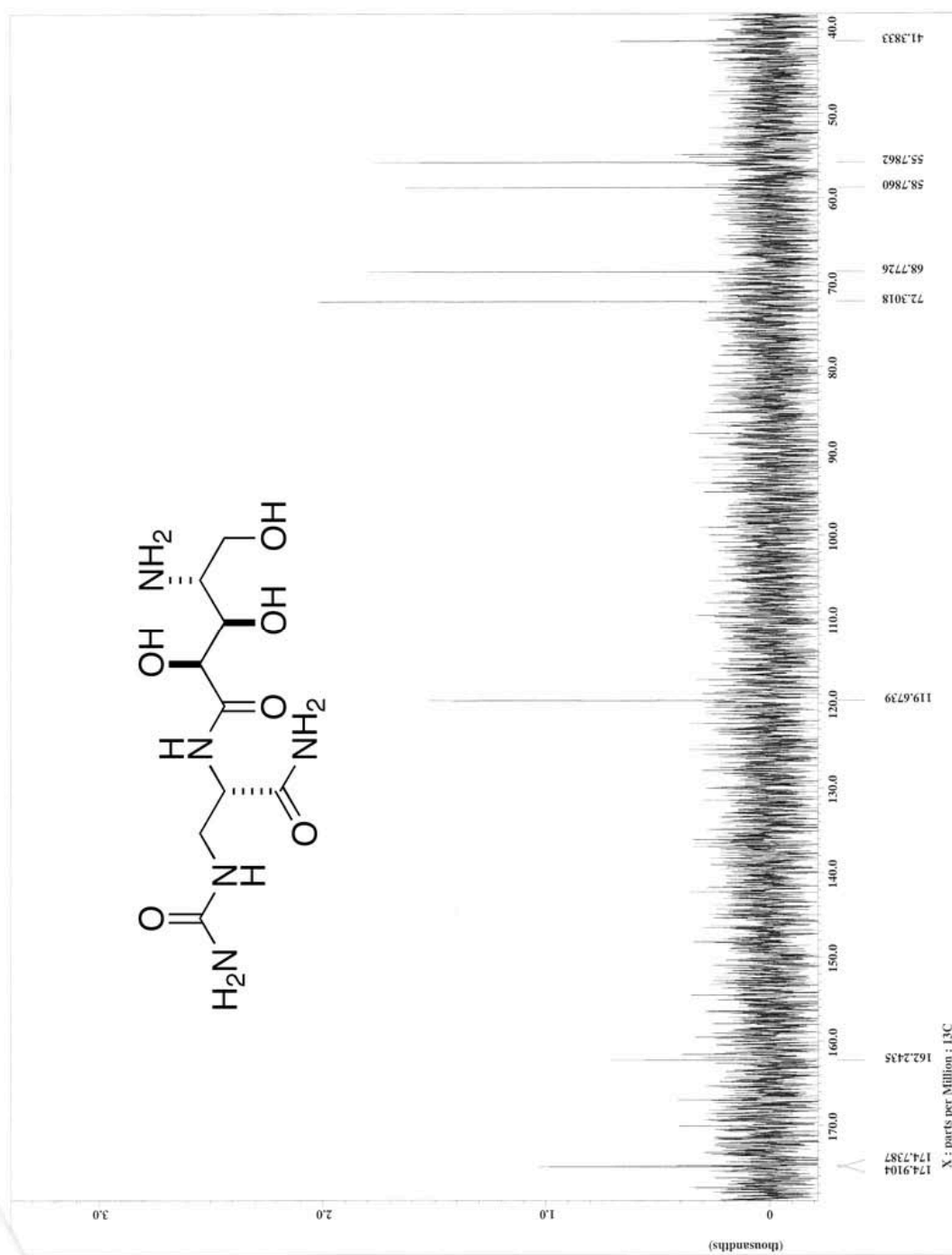
Spectrum 7.163: ^1H NMR (D_2O , 400 MHz) of compound 350



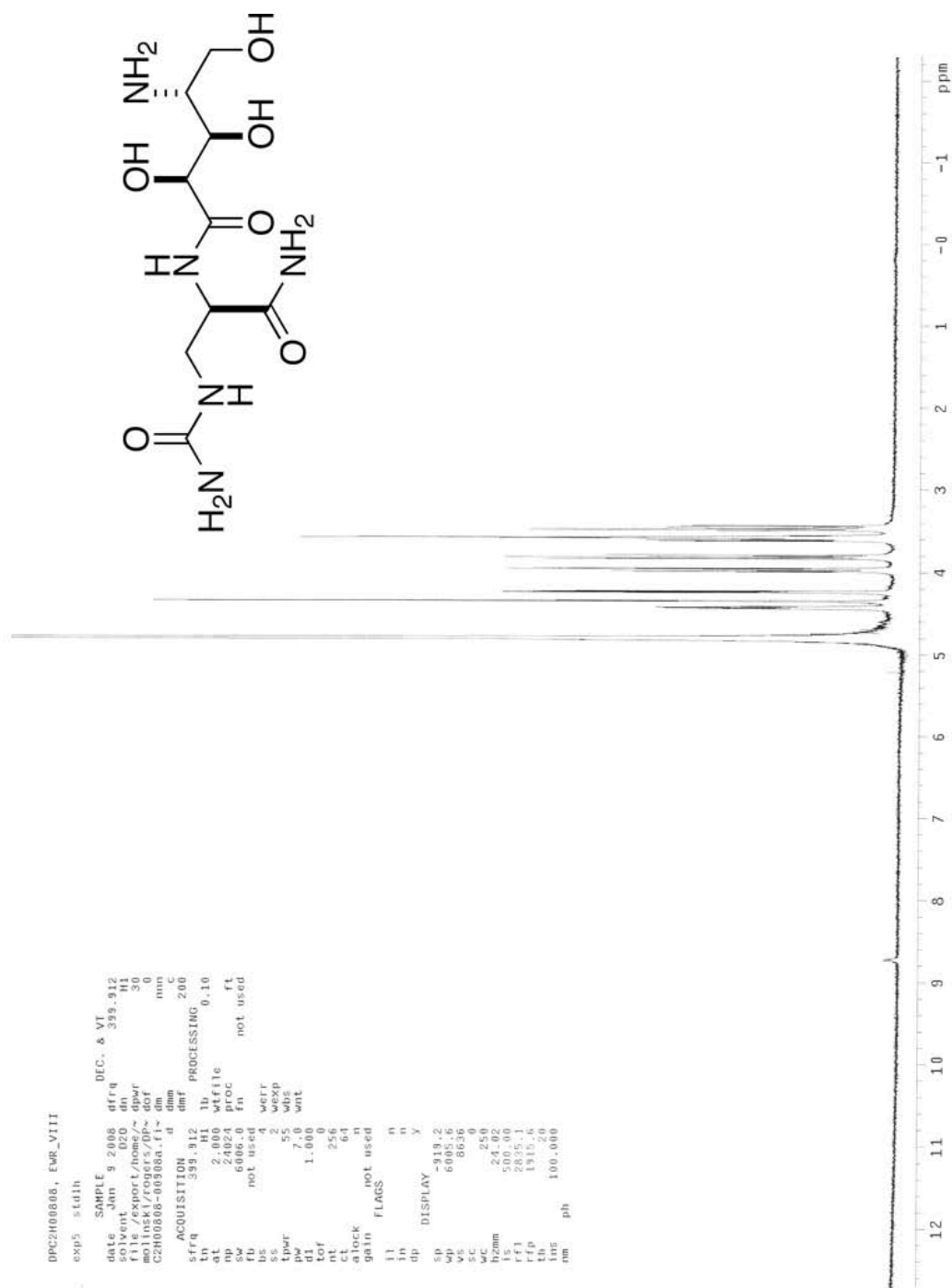
Spectrum 7.164: ^{13}C NMR (D_2O , 100 MHz) of compound 350



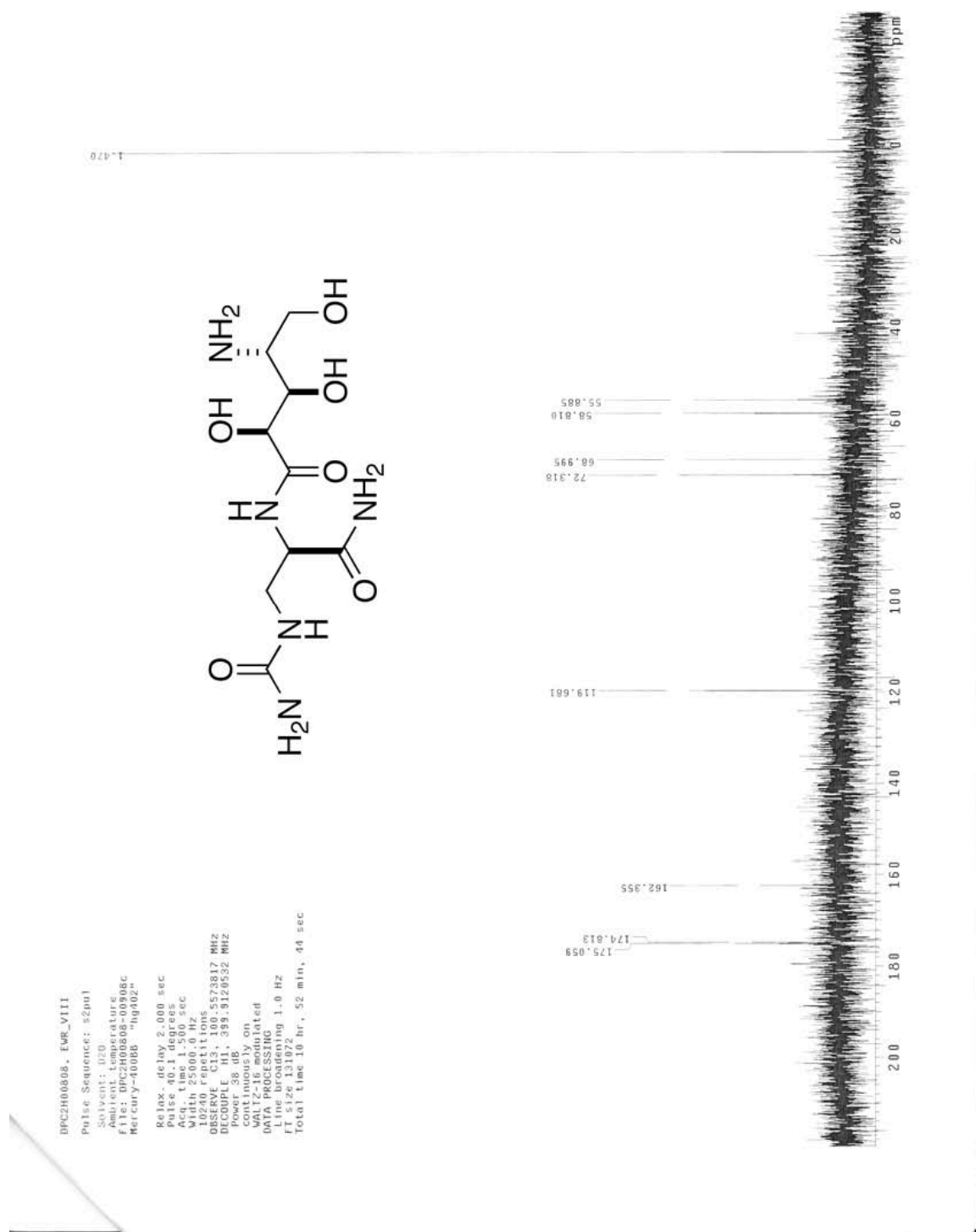
Spectrum 7.165: ^1H NMR (D_2O , 500 MHz) of compound **351**



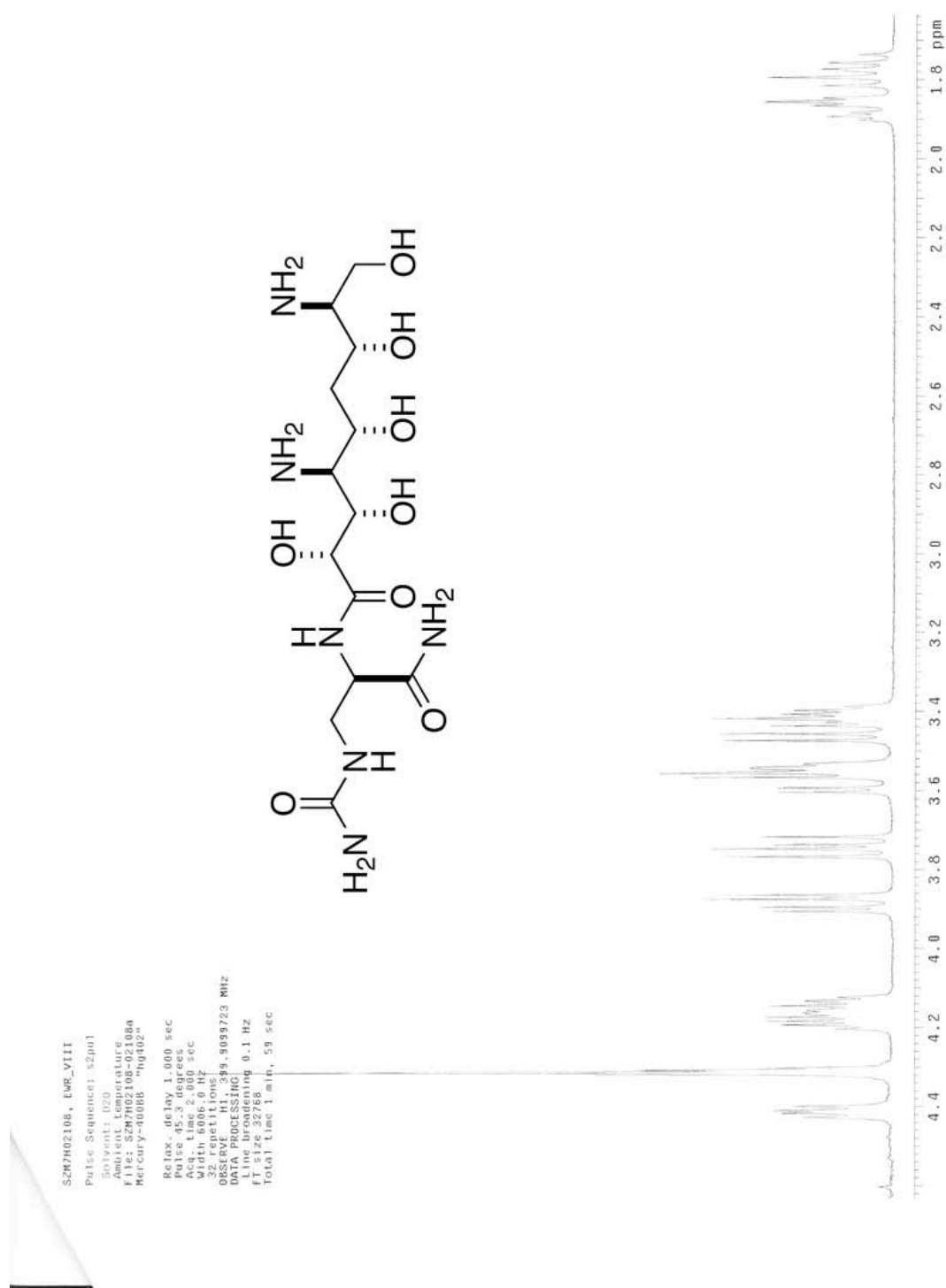
Spectrum 7.166: ^{13}C NMR (D_2O , 125 MHz) of compound 351



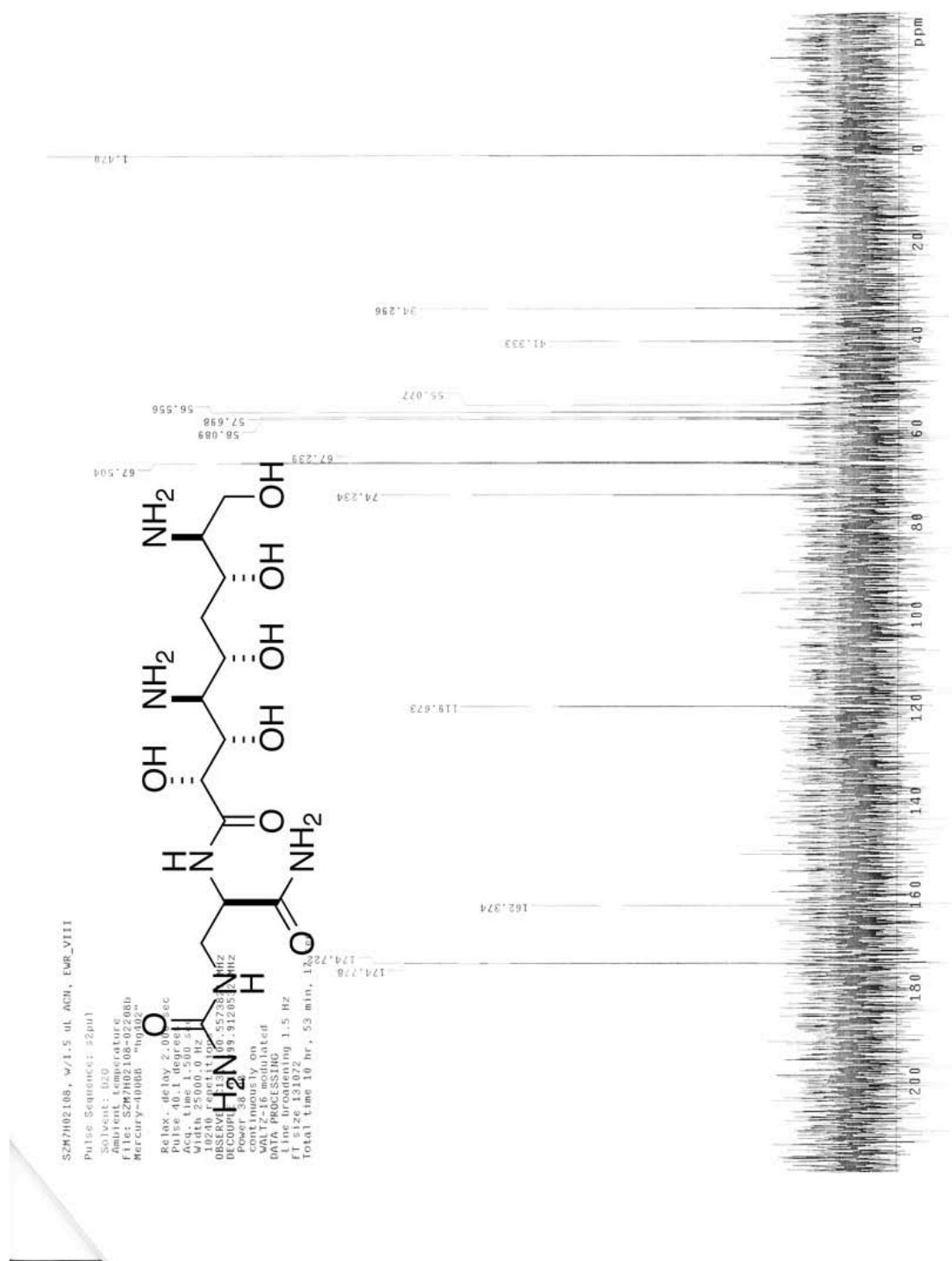
Spectrum 7.167: ^1H NMR (D_2O , 400 MHz) of compound 352



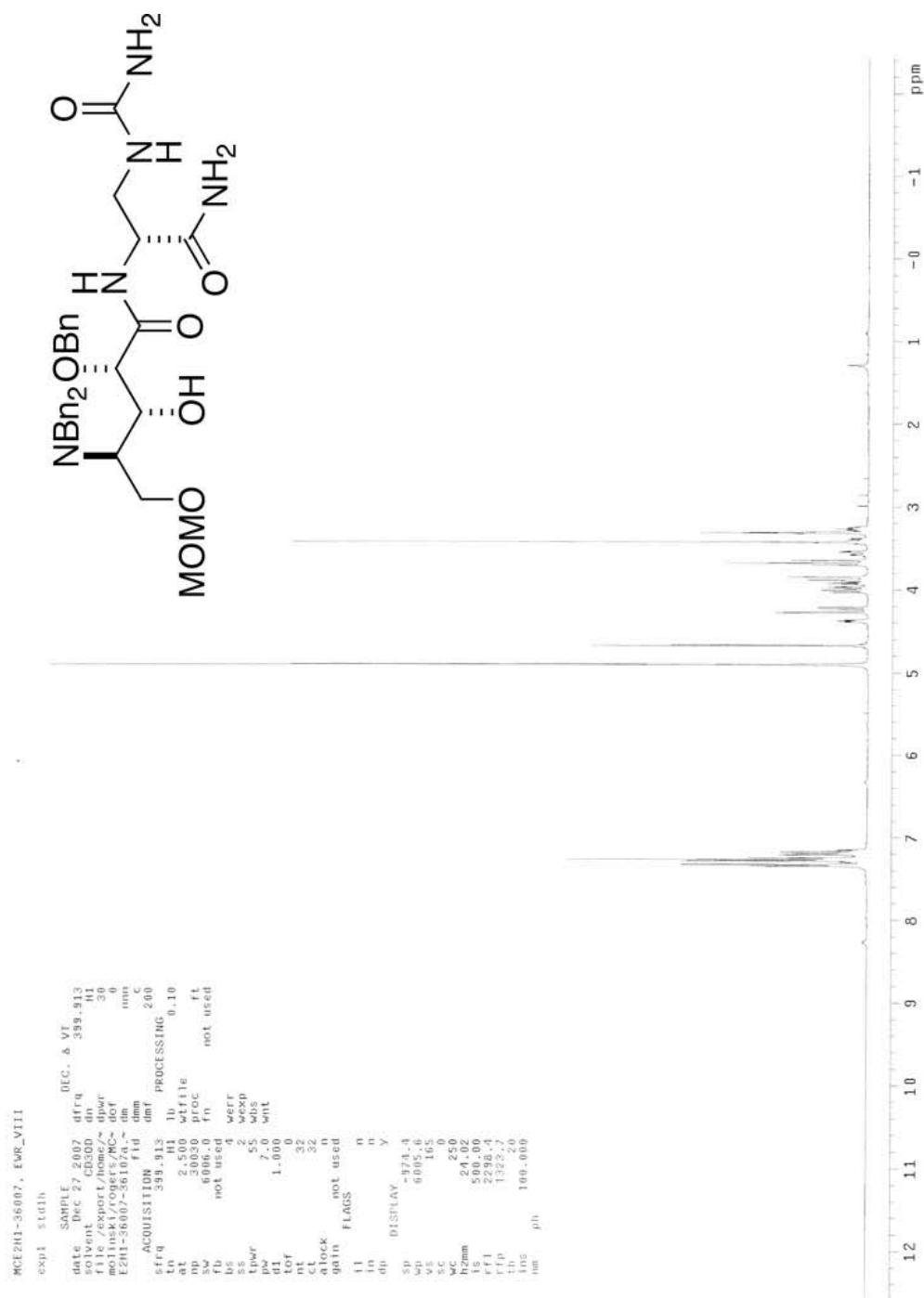
Spectrum 7.168: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 125 MHz) of compound **352**



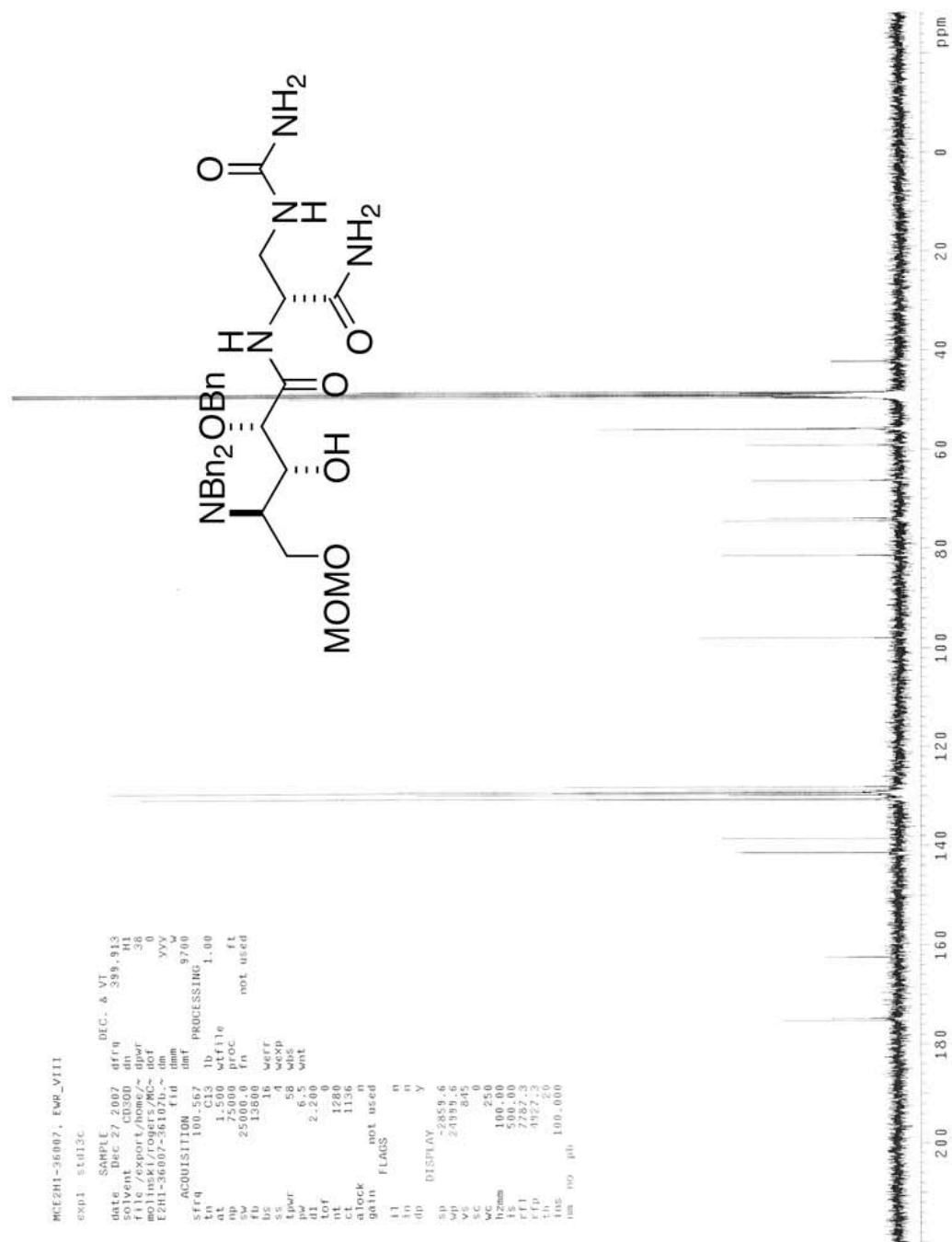
Spectrum 7.171: ^1H NMR (D_2O , 400 MHz) of compound 354

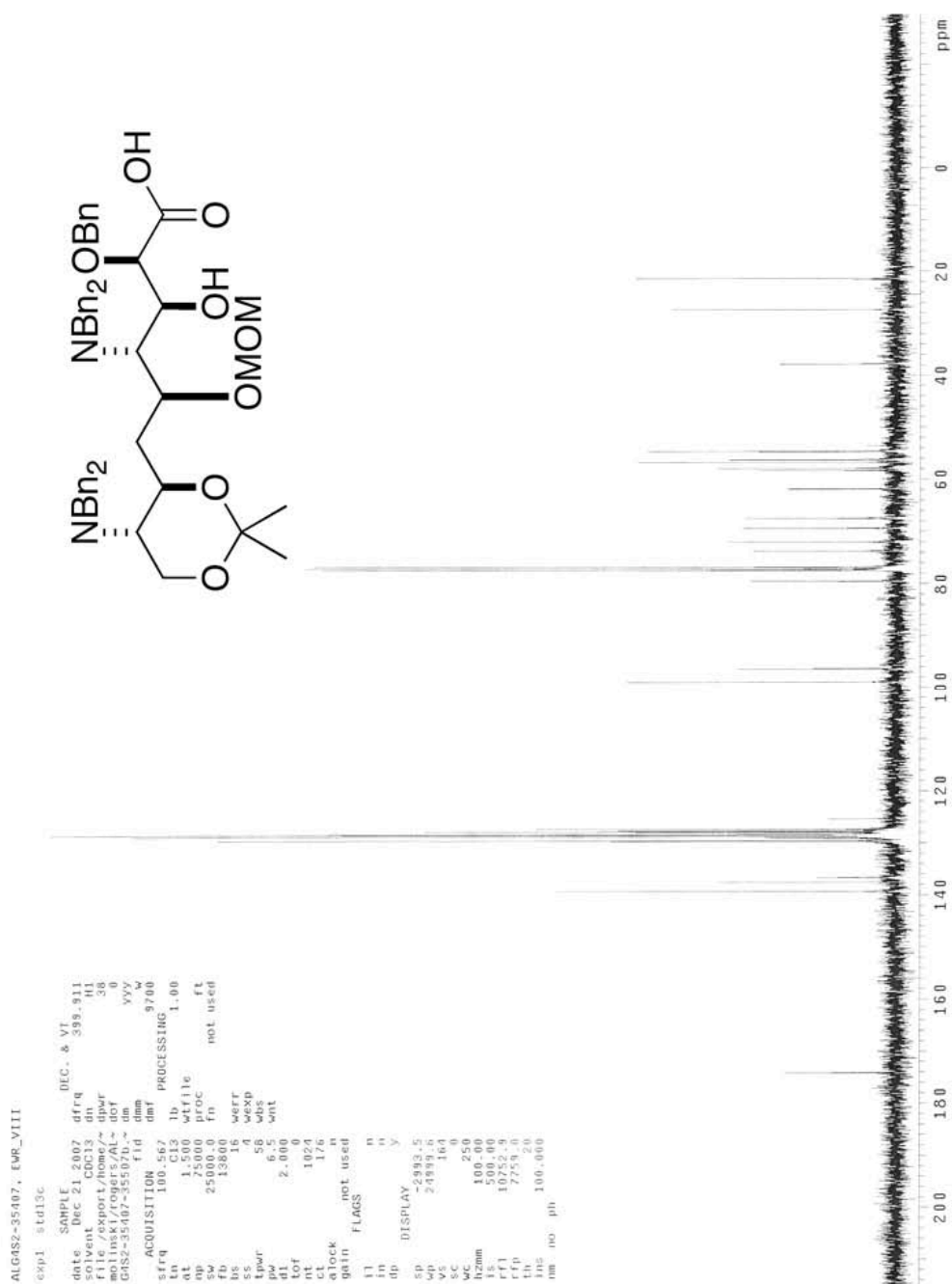


Spectrum 7.172: ^{13}C NMR (D_2O w/ 0.5% CH_3CN , 100 MHz) of compound 354

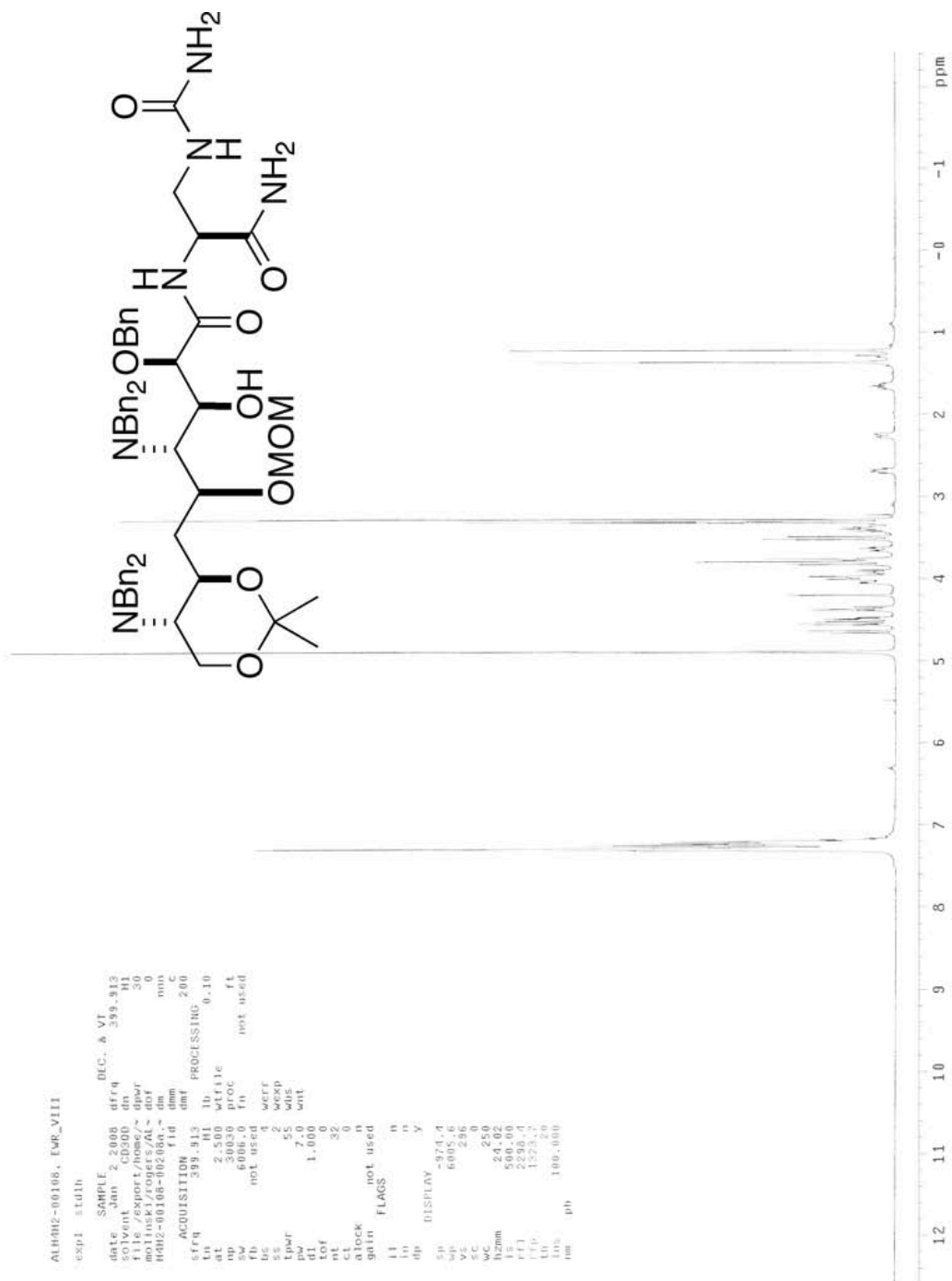


Spectrum 7.173: ¹H NMR (CD₃OD, 400 MHz) of compound 355

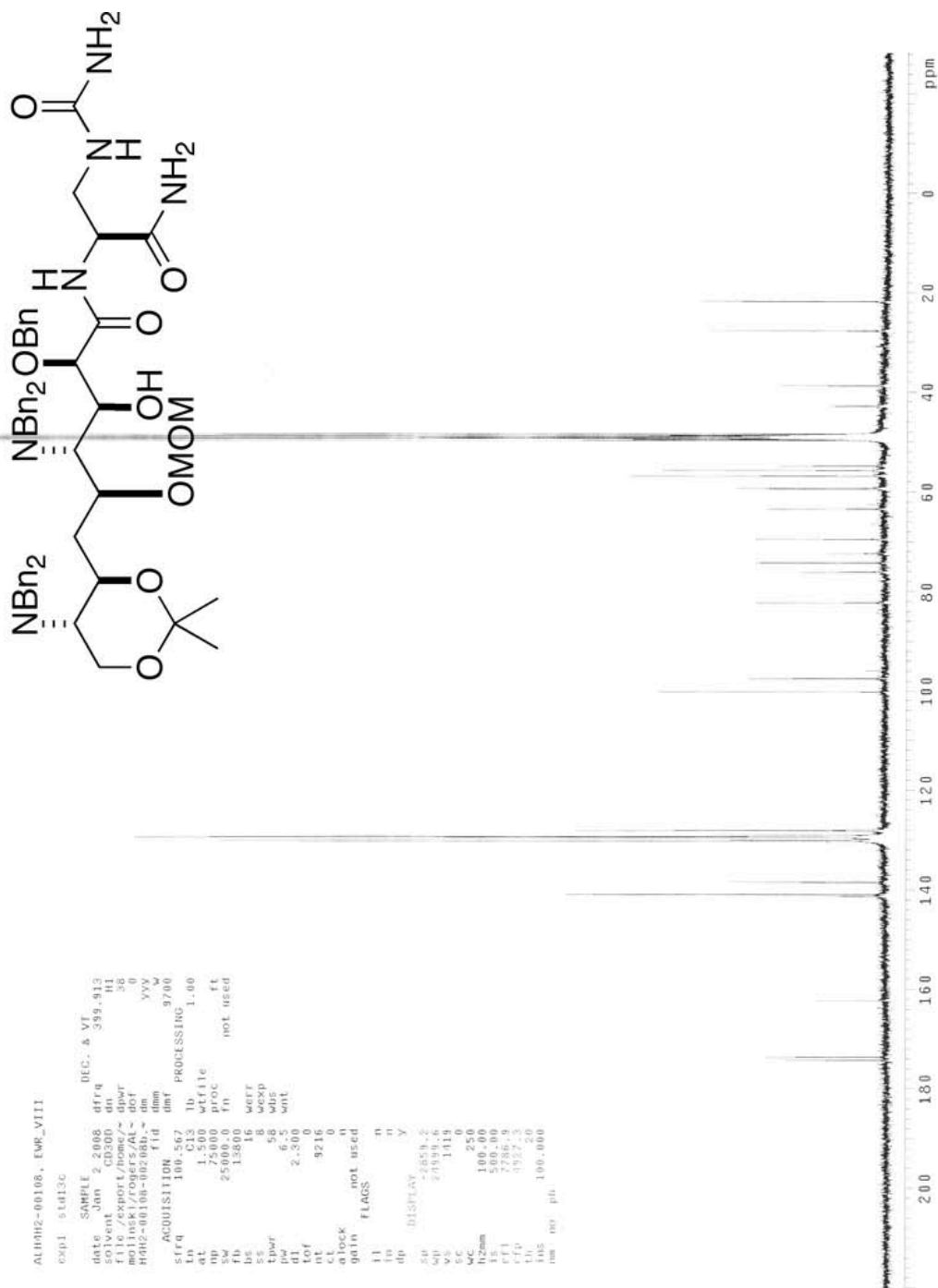




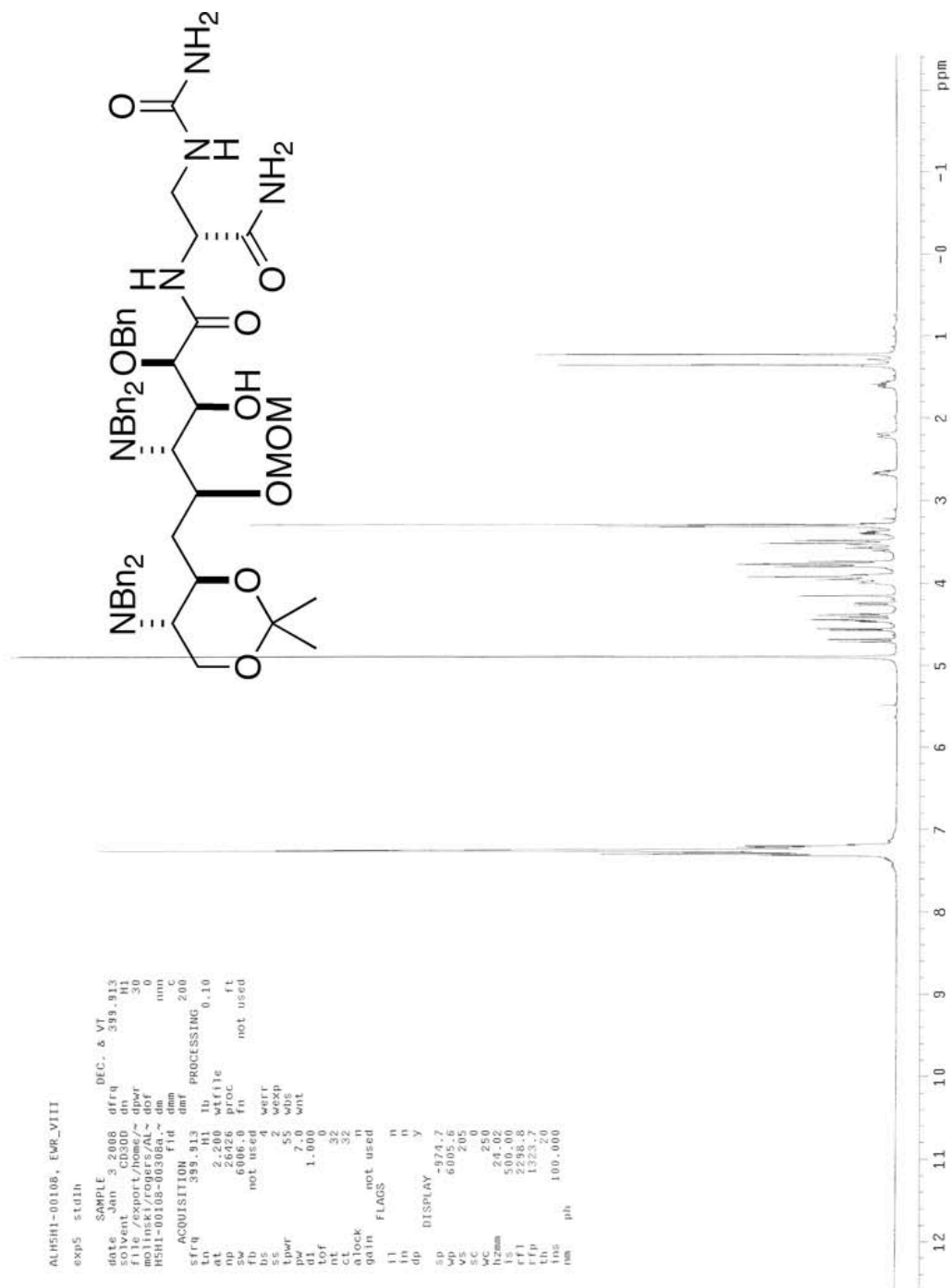
Spectrum 7.178: ¹³C NMR (CDCl₃, 100 MHz) of compound 357



Spectrum 7.179: ¹H NMR (CD₃OD, 400 MHz) of compound 358

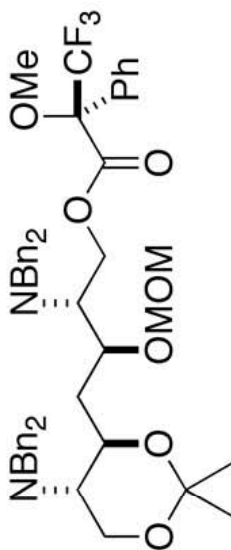


Spectrum 7.180: ¹³C NMR (CD₃OD, 100 MHz) of compound 358

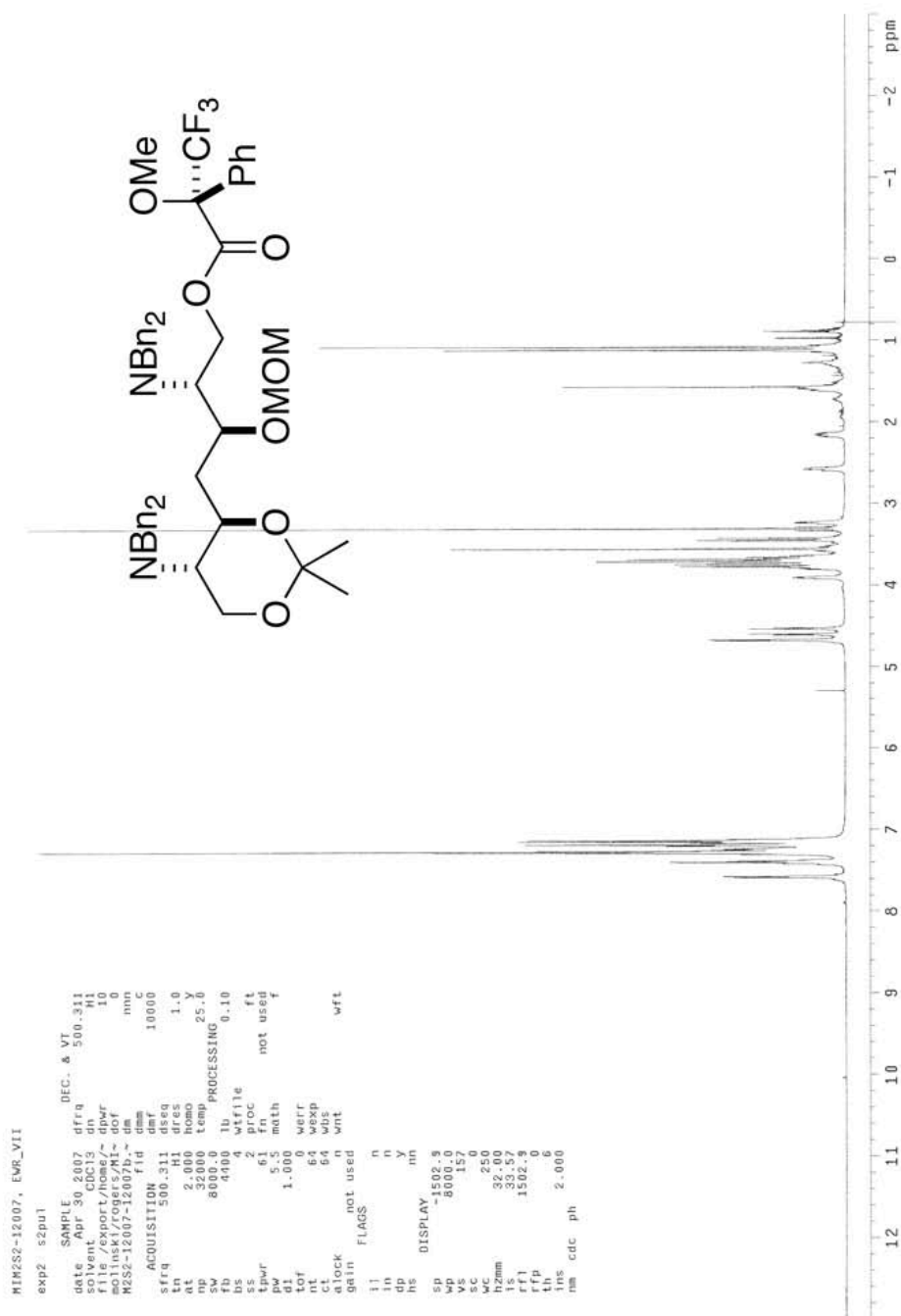


Spectrum 7.181: ¹H NMR (CD₃OD, 400 MHz) of compound **359**

MIMIS2-12007_EVR_VII
 exp1 s2pu1
 SAMPLE DEC. & VT
 date Aug 17 2007 dfrq 399.911
 solvent CDCl3 dn H1
 H1 report/cont 50
 mol Insk1/cont15/MI- novr
 MIMIS2-12007-22907-F-~ dim min
 ACQUISITION 250
 sfrq 376.250 dmf PROCESSING 200
 at 0.600 lb PROCESSING 0.10
 np 54026 wfile
 sw 45005.0 fn not used
 bs not used a werr
 ss 4 wexp
 tper 53 wbs
 dt 4.000 wnt
 nt 1024
 ct 256
 check
 gain not used
 FLAG
 ll n
 ln n
 dp n y
 DISPLAY
 sp -62636.7
 wp 45043.7
 sc 15.0
 sc 250
 hzmm 180.17
 ls 500.00
 rfn 62636.0
 rfp 0
 th 3
 ins no ph
 nm 100.000

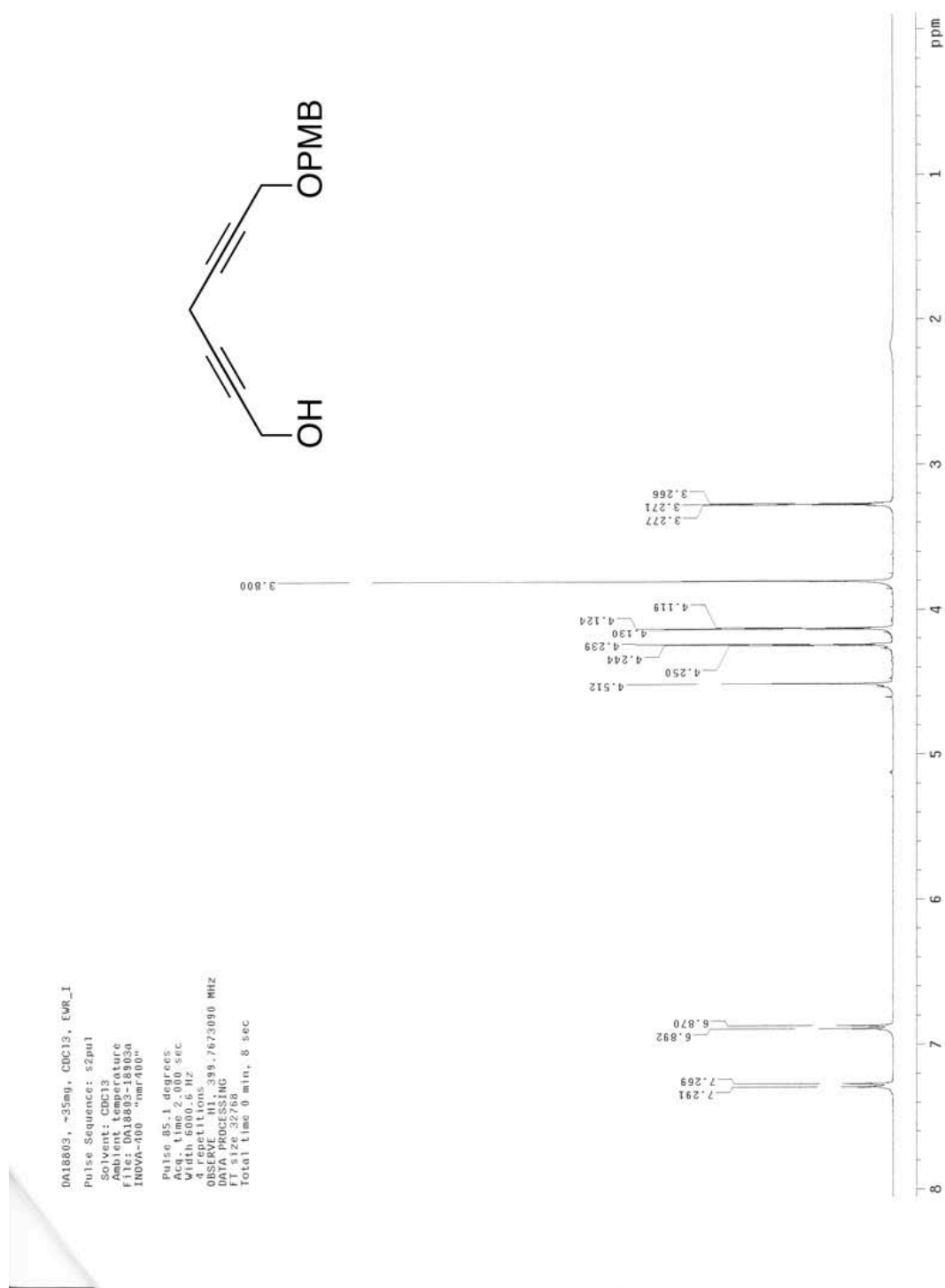


Spectrum 7.184: ^{19}F NMR (CDCl_3 , 376 MHz) of compound **361**

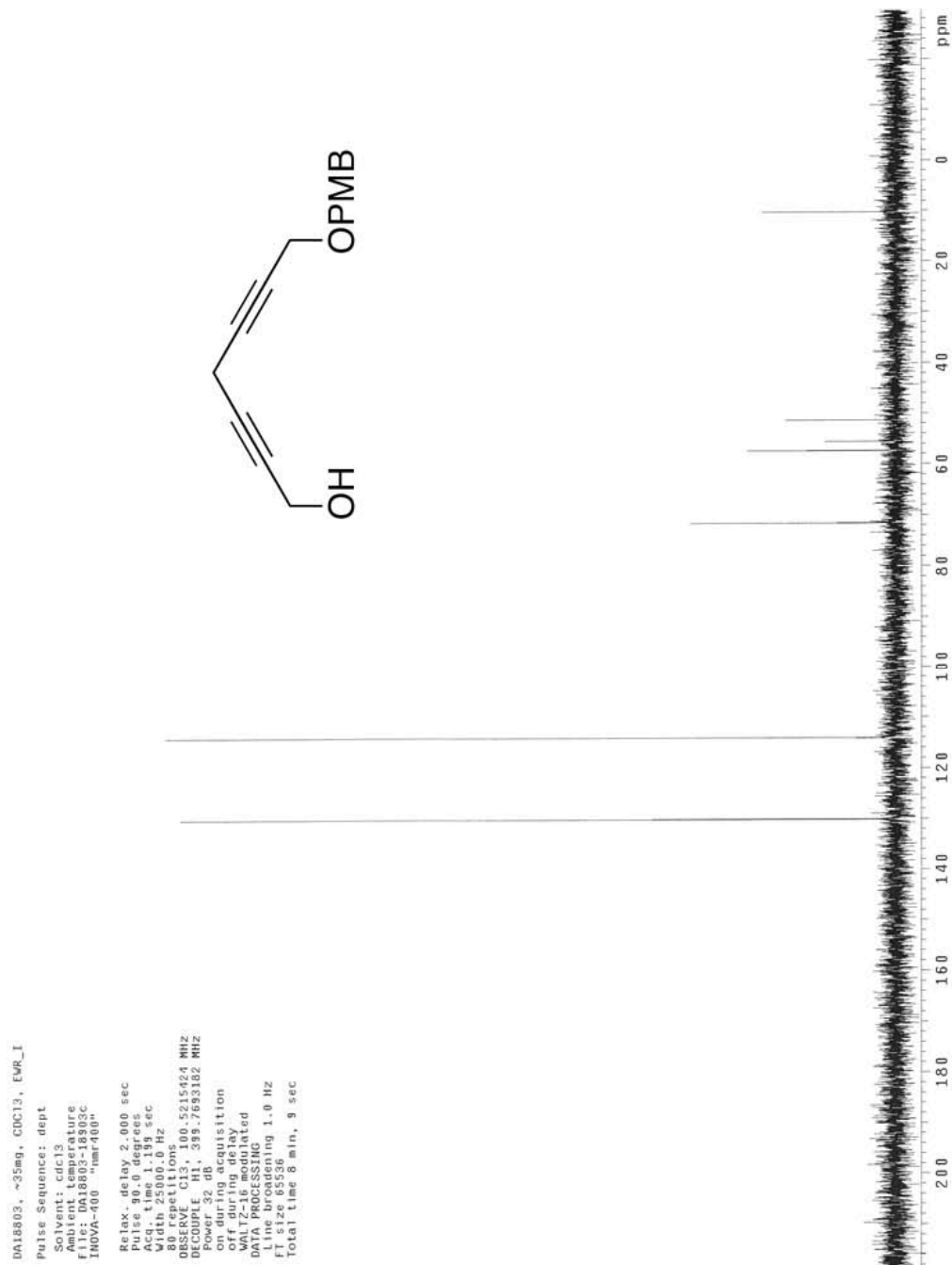


Spectrum 7.185: ^1H NMR (CDCl_3 , 500 MHz) of compound 362

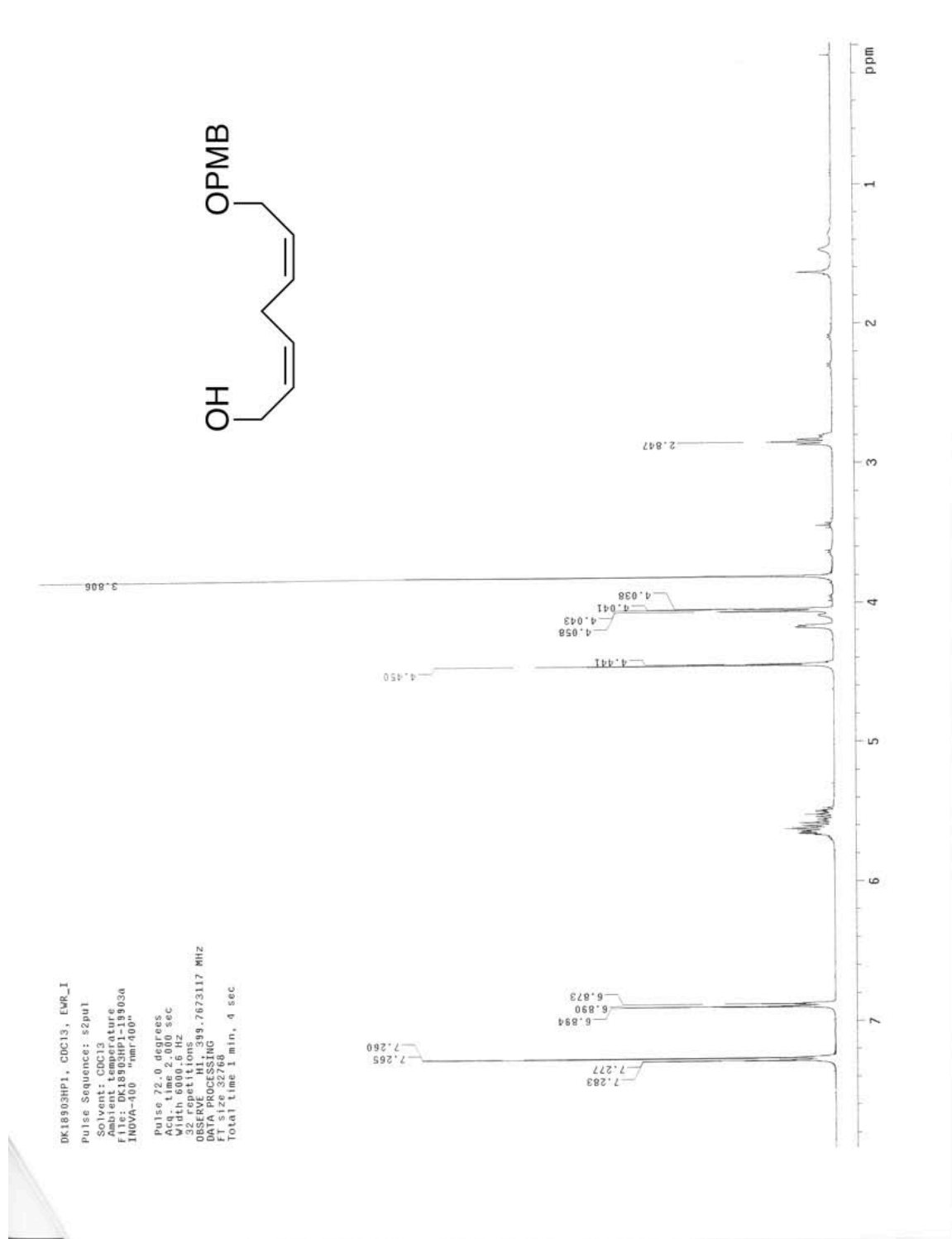
7.3.5. Chapter 6 Spectra



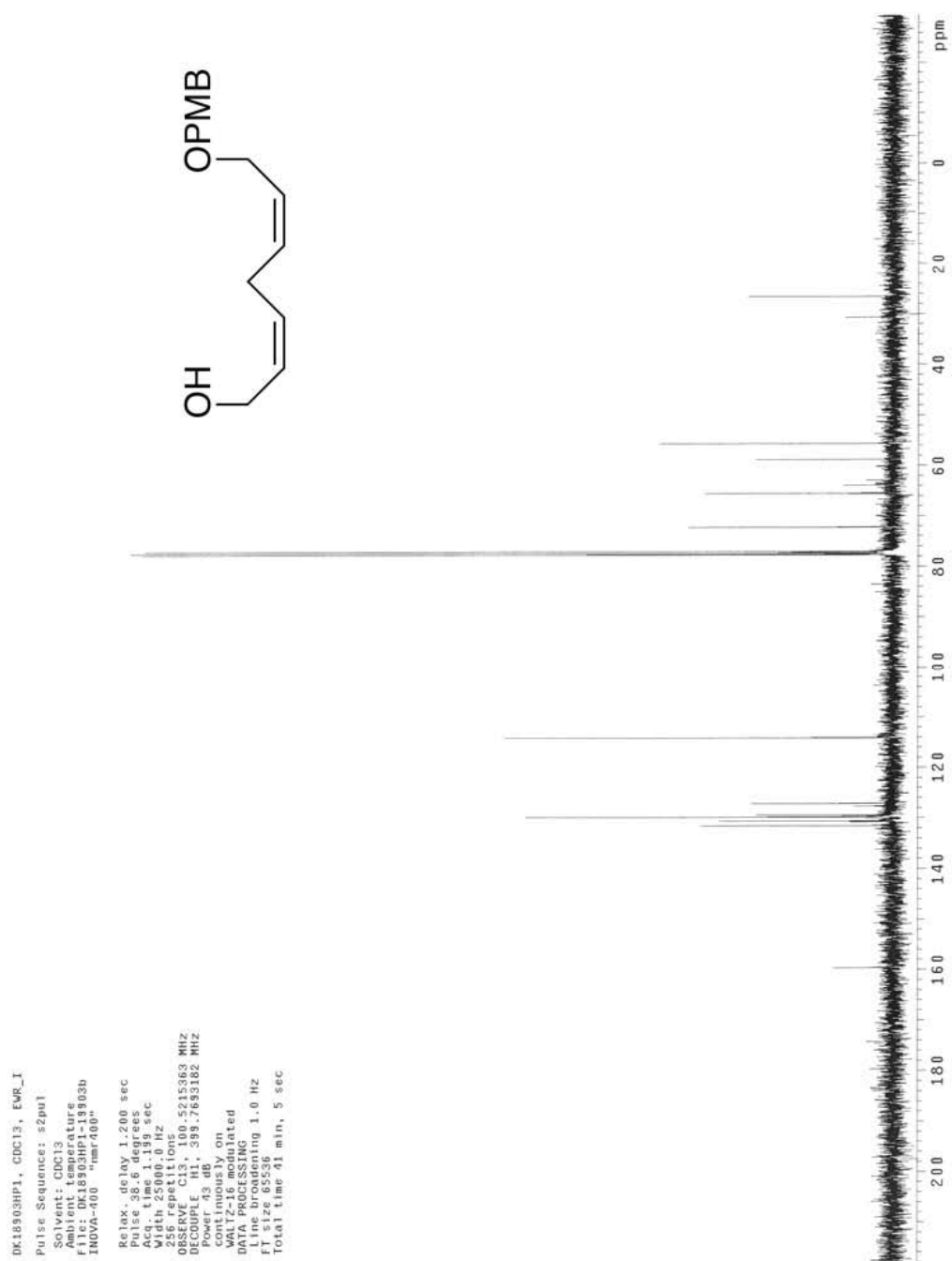
Spectrum 7.187: ¹H NMR (CDCl₃, 400 MHz) of compound 363



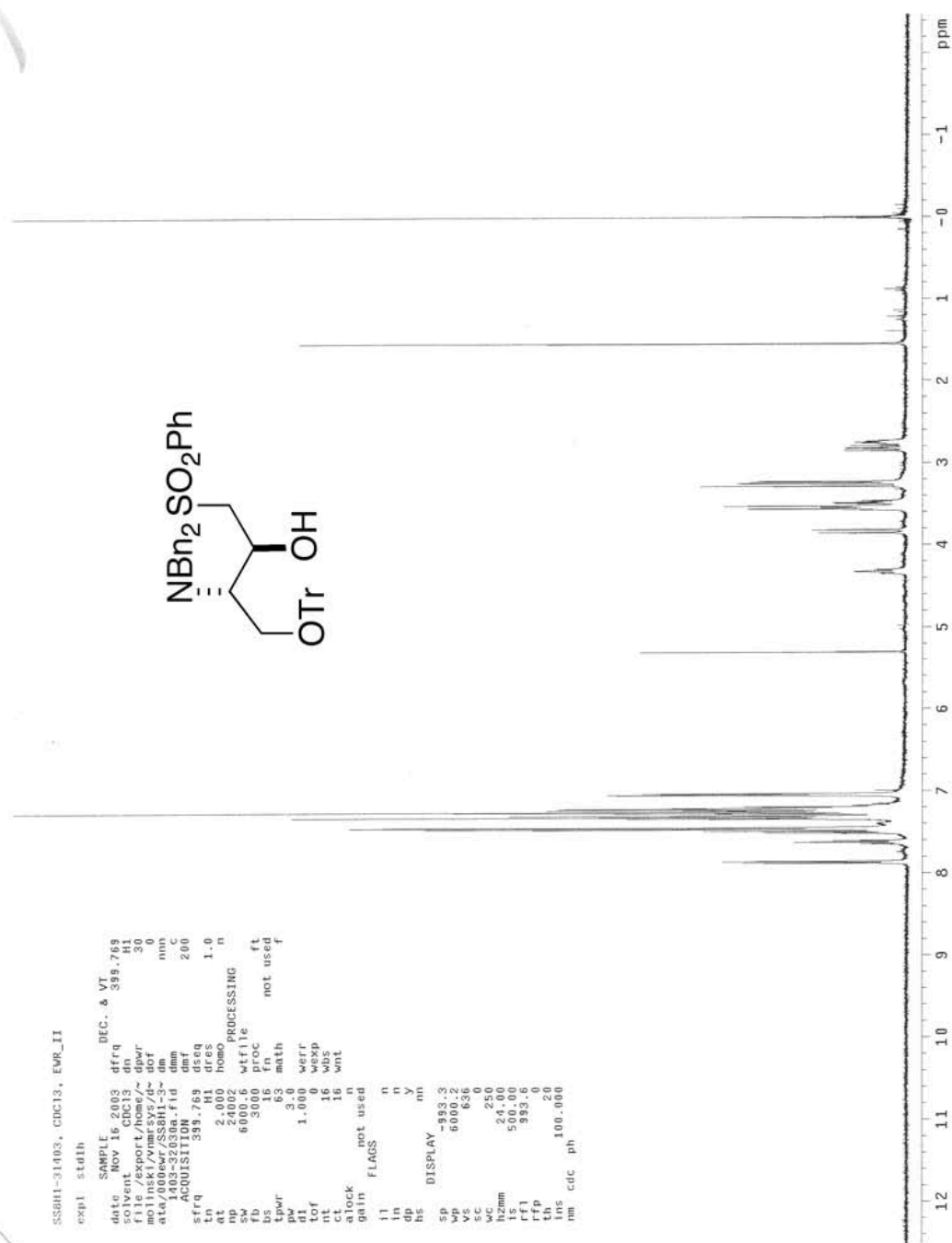
Spectrum 7.188: ¹³C NMR (CDCl₃, 100 MHz) of compound **363**



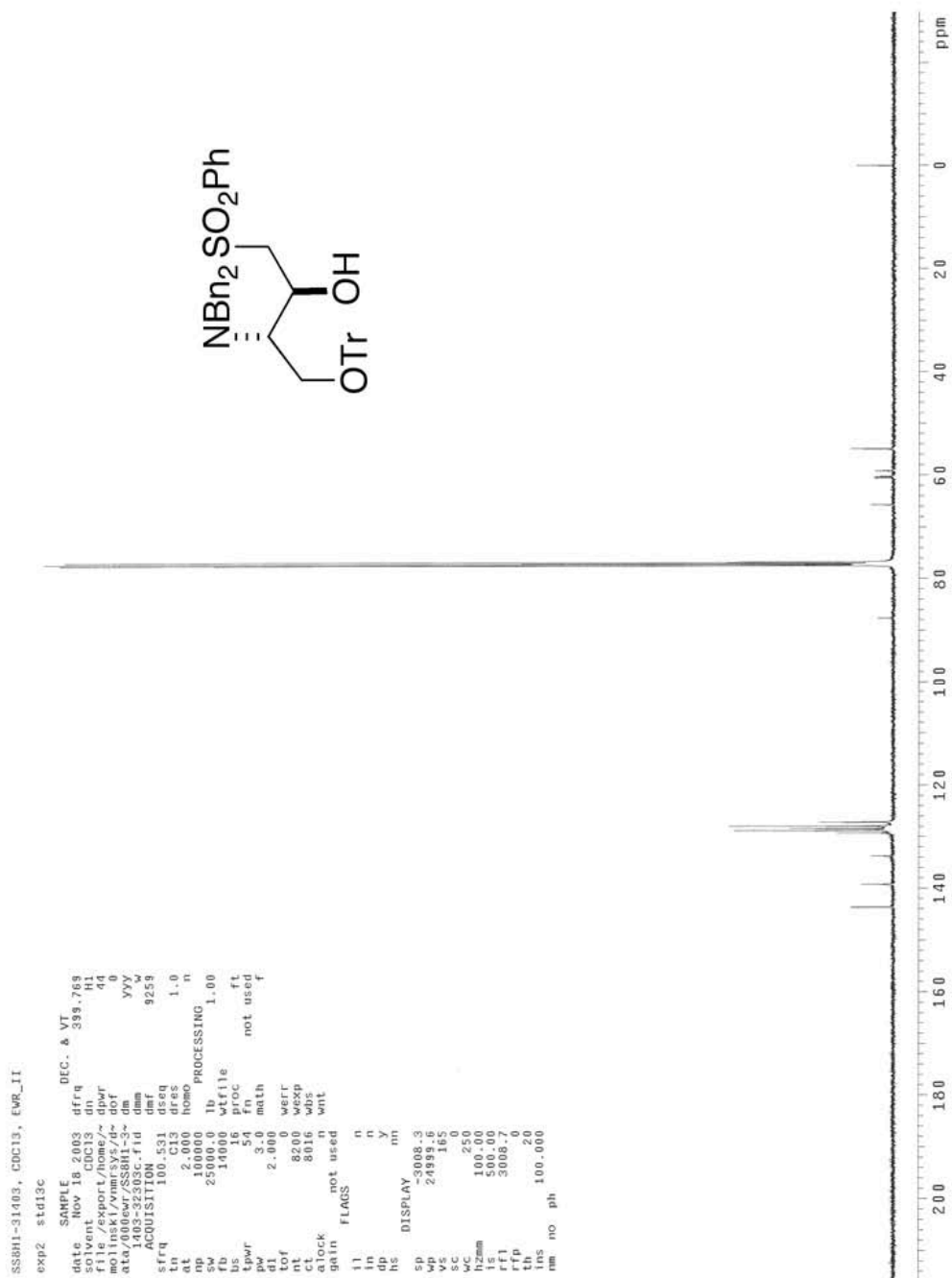
Spectrum 7.189: ^1H NMR (CDCl_3 , 400 MHz) of compound 364



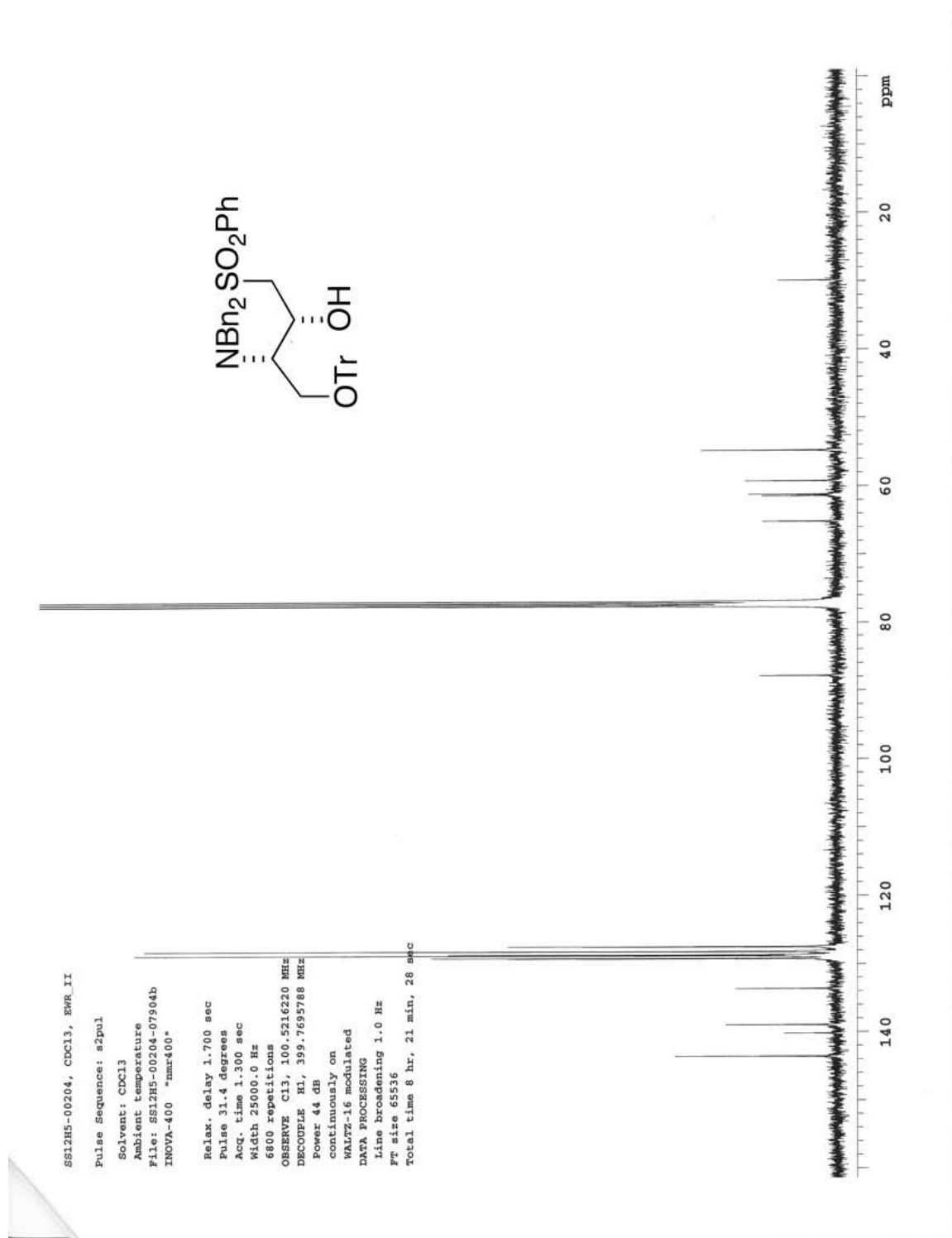
Spectrum 7.190: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 364



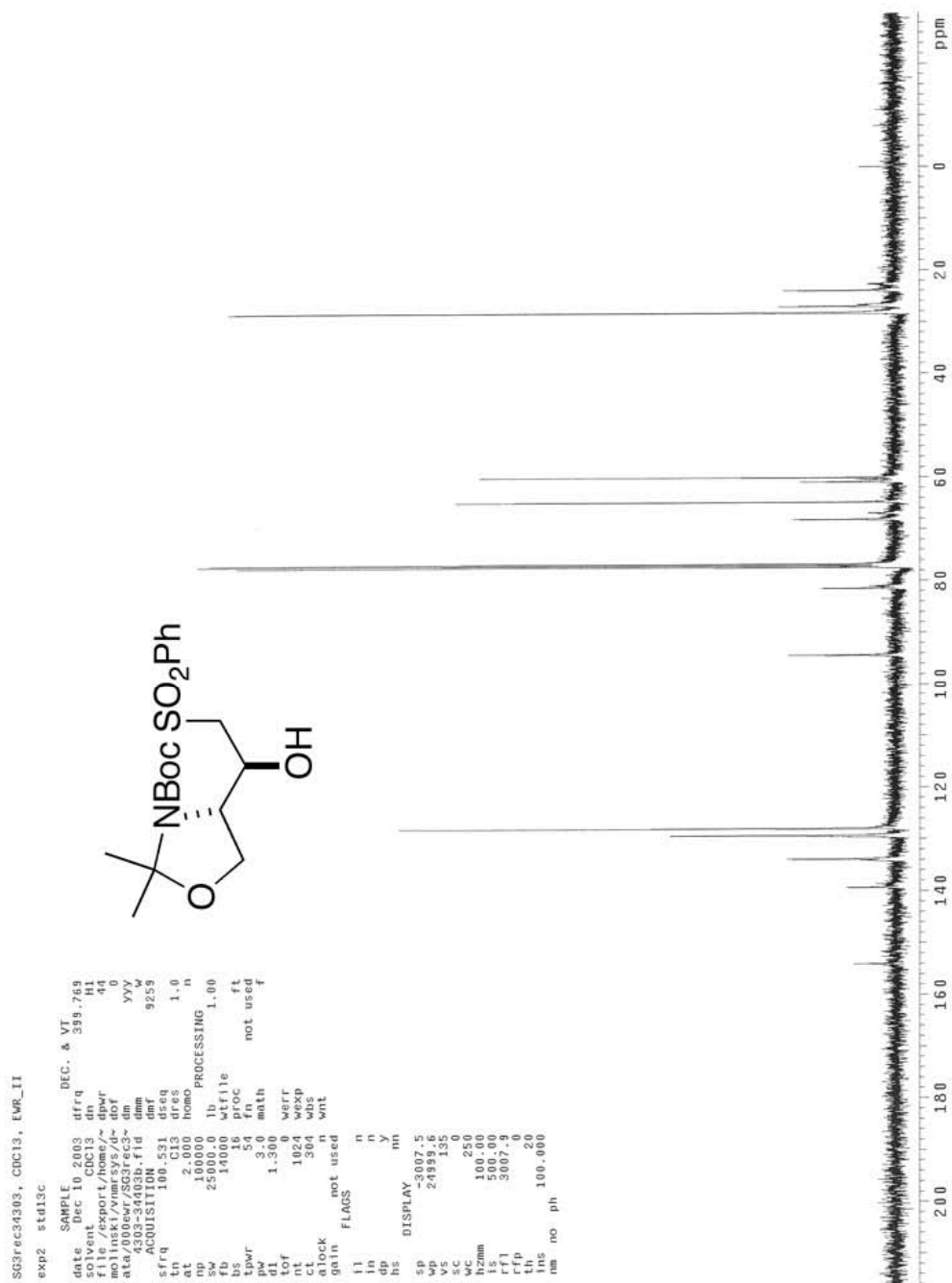
Spectrum 7.191: ^1H NMR (CDCl_3 , 400 MHz) of compound 370a



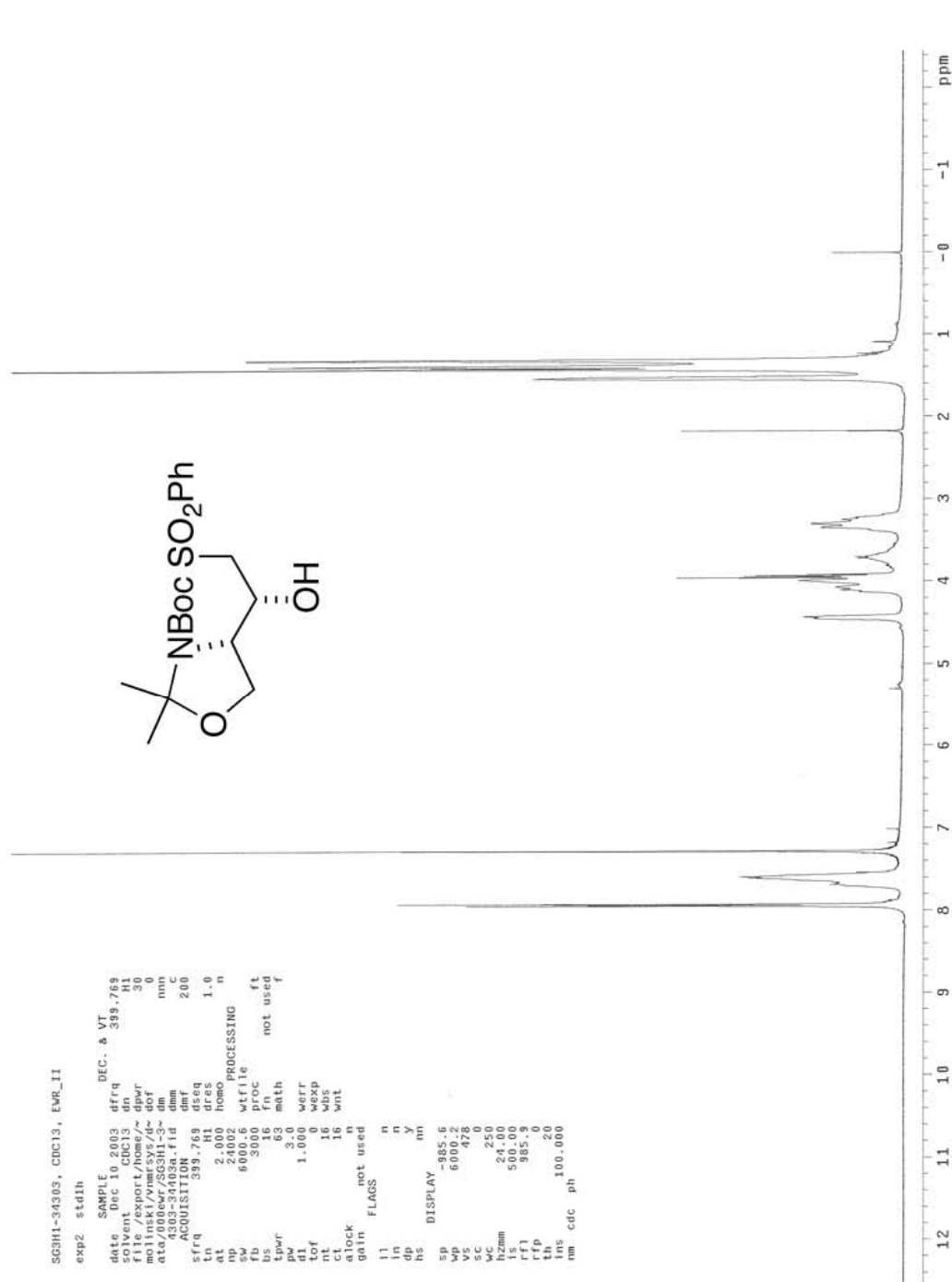
Spectrum 7.192: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 370a



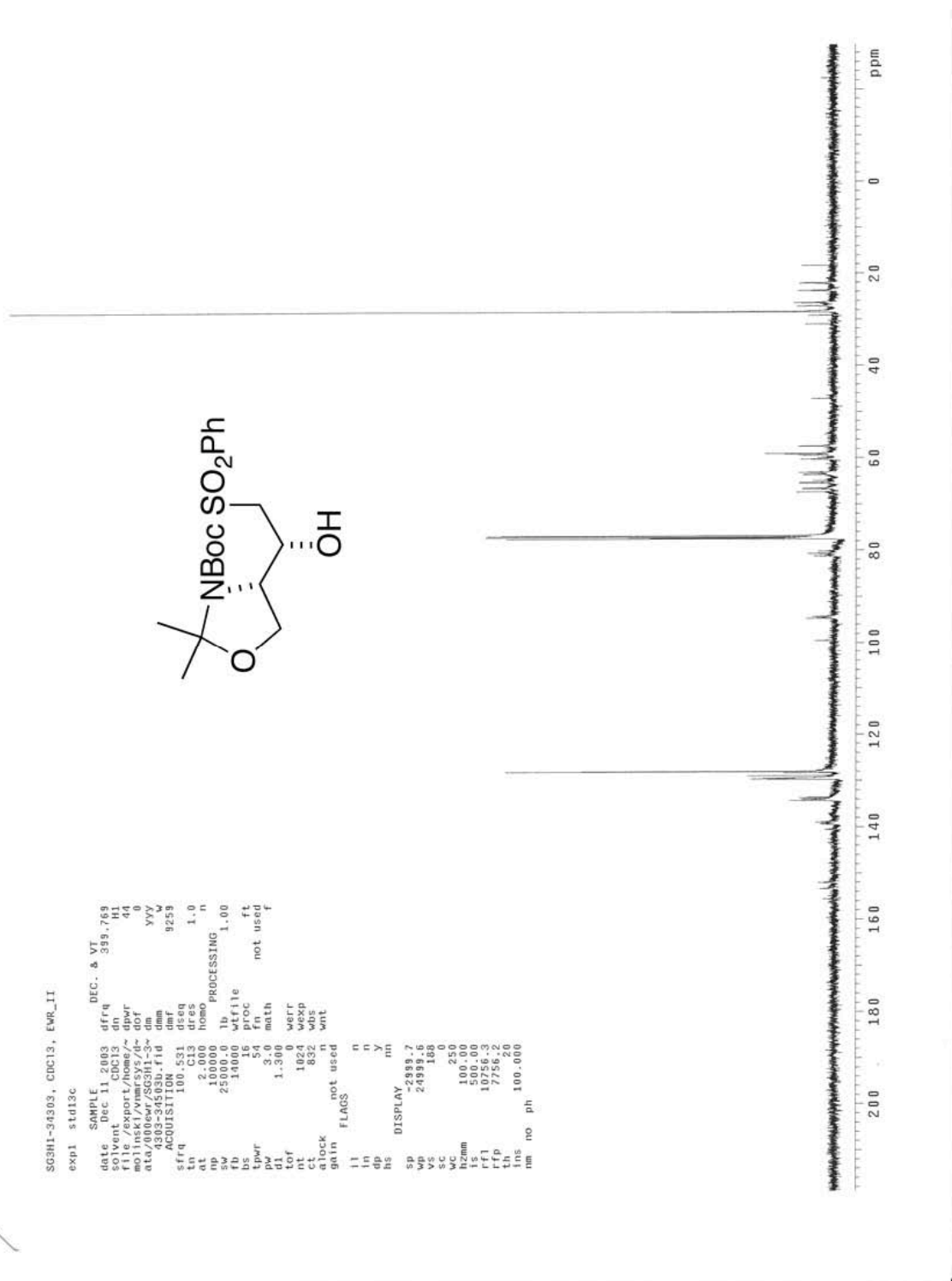
Spectrum 7.194: ¹³C NMR (CDCl₃, 100 MHz) of compound 370b



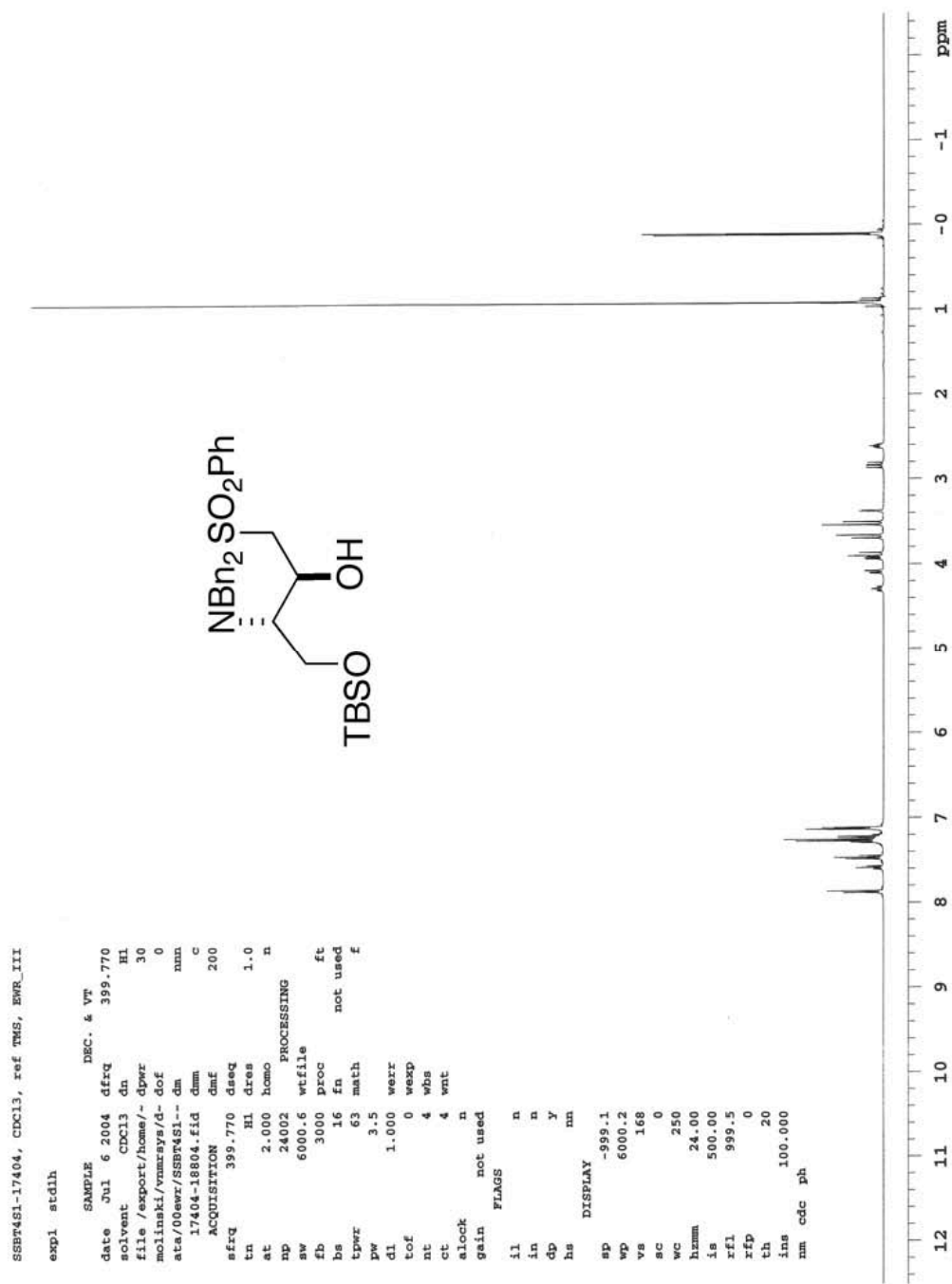
Spectrum 7.196: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 378



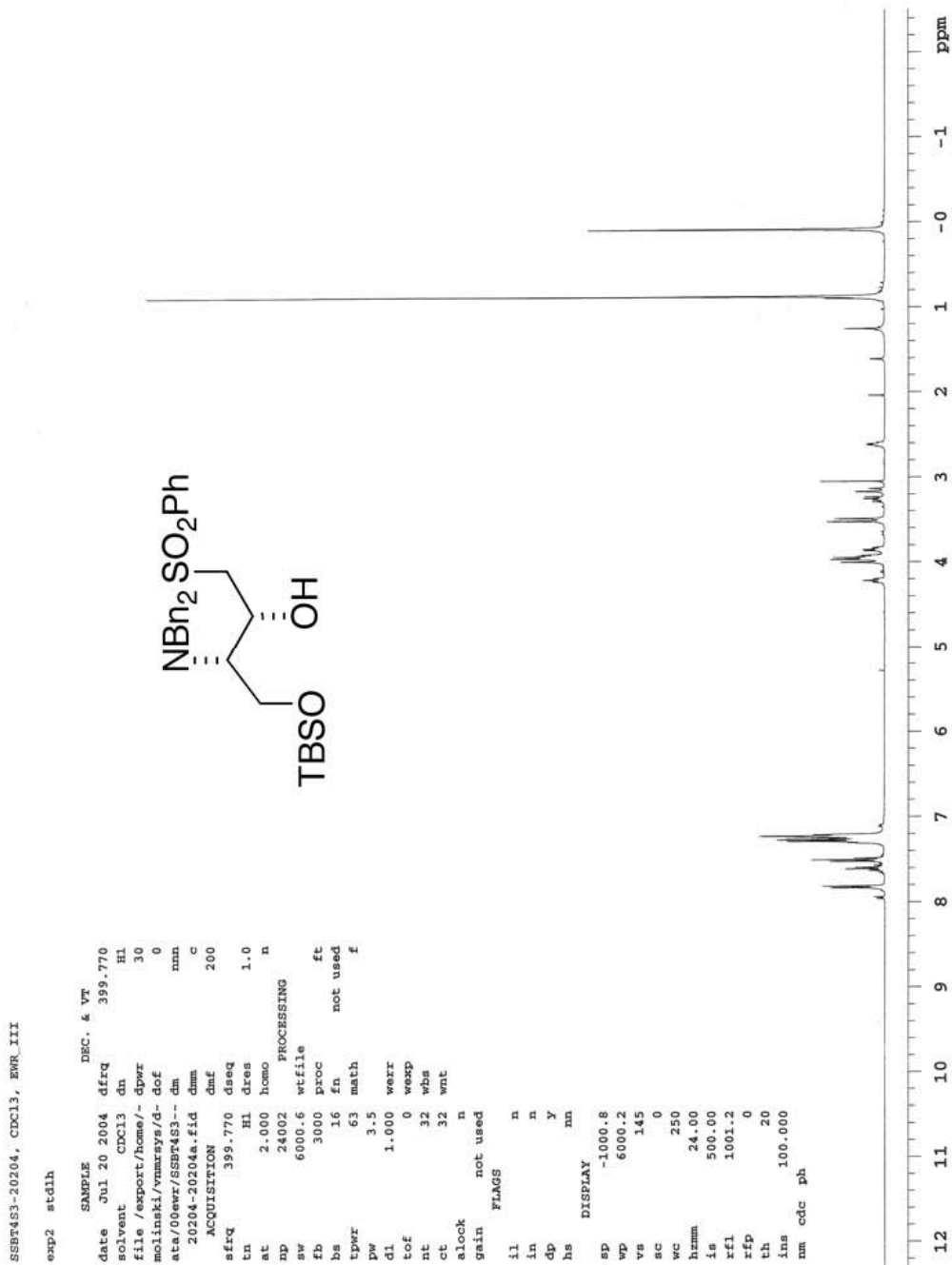
Spectrum 7.197: ^1H NMR (CDCl_3 , 400 MHz) of compound 379



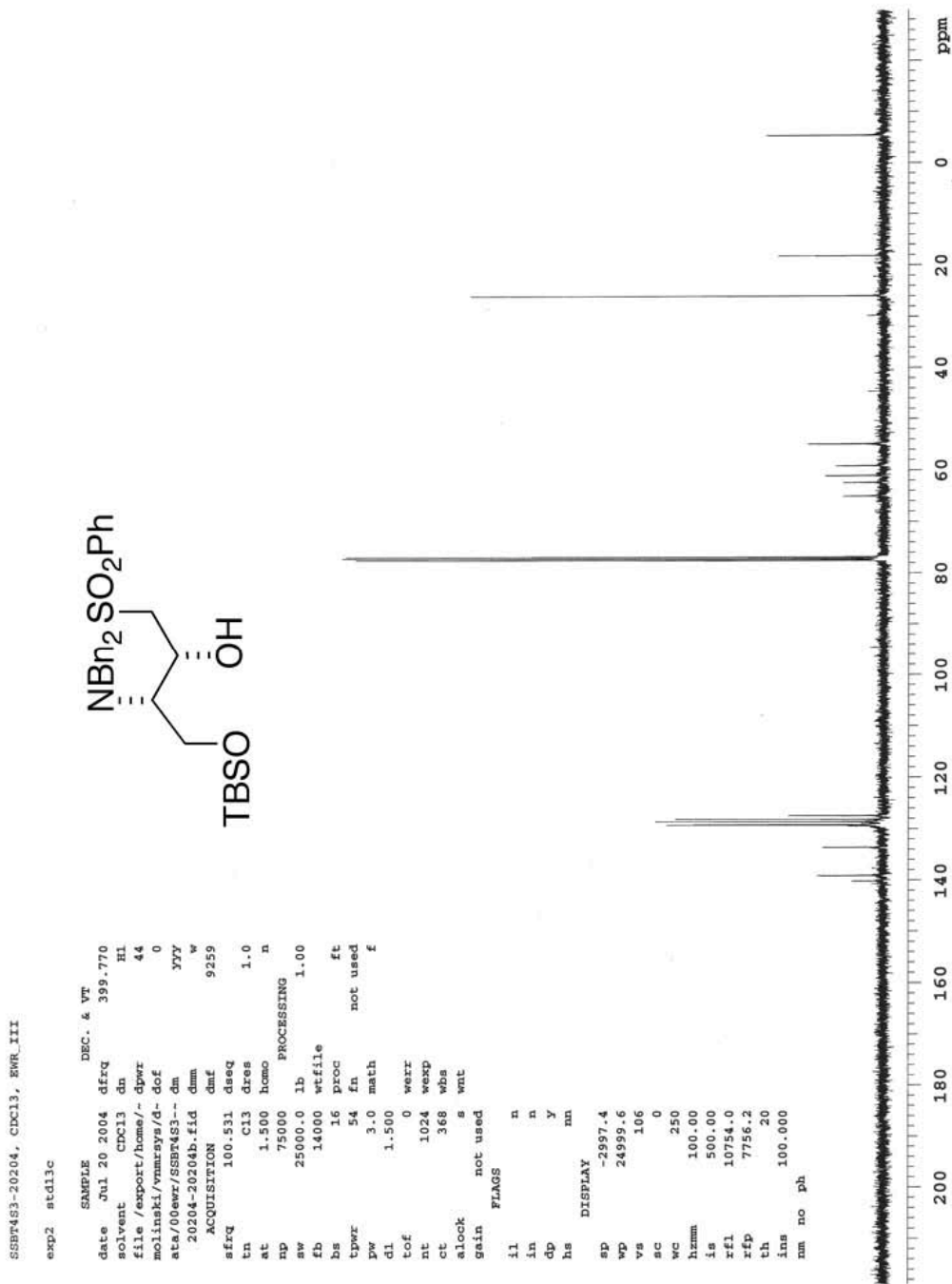
Spectrum 7.198: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 379



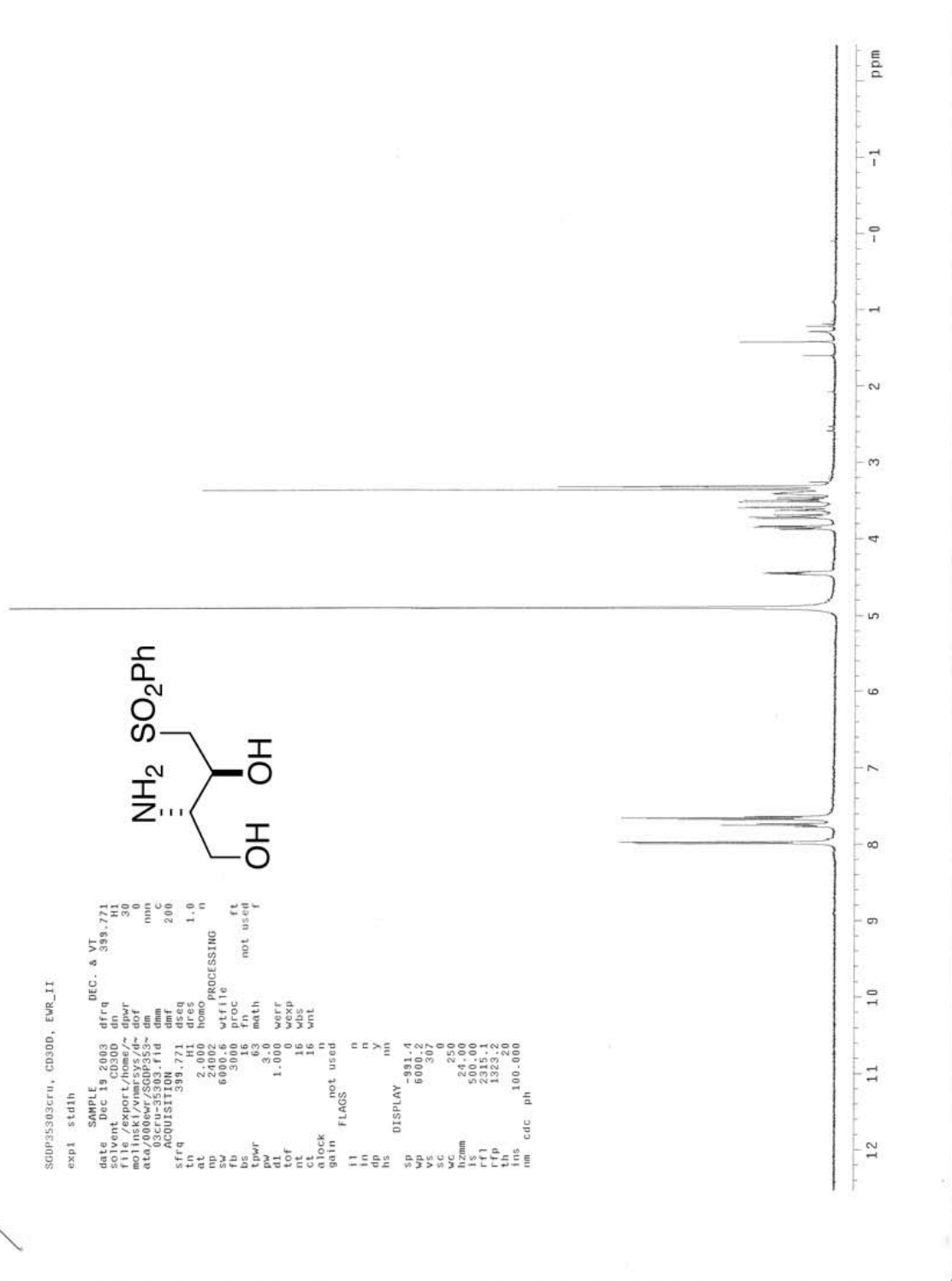
Spectrum 7.199: ¹H NMR (CDCl₃, 400 MHz) of compound 385



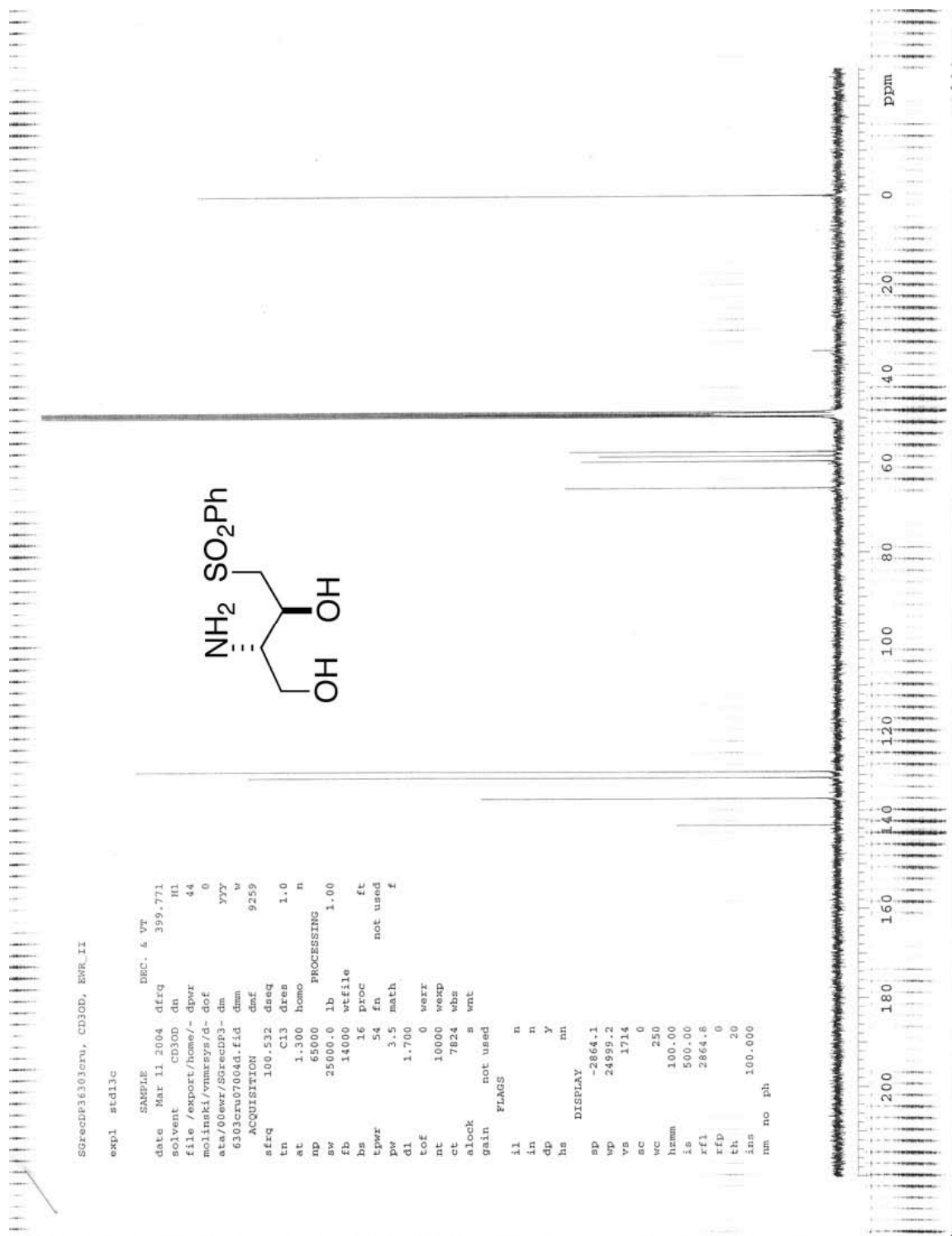
Spectrum 7.201: ^1H NMR (CDCl_3 , 400 MHz) of compound 386



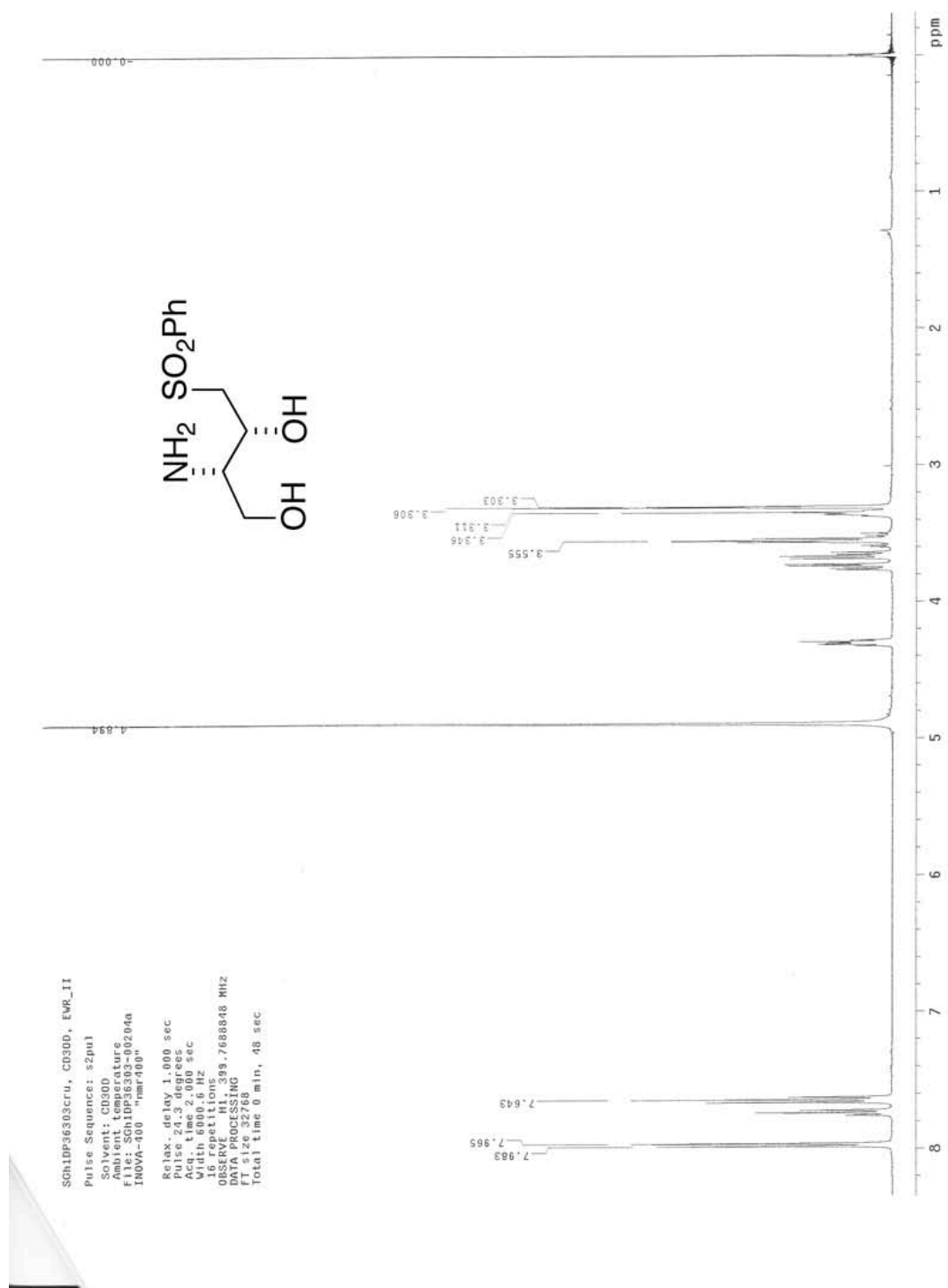
Spectrum 7.202: ¹³C NMR (CDCl₃, 100 MHz) of compound 386



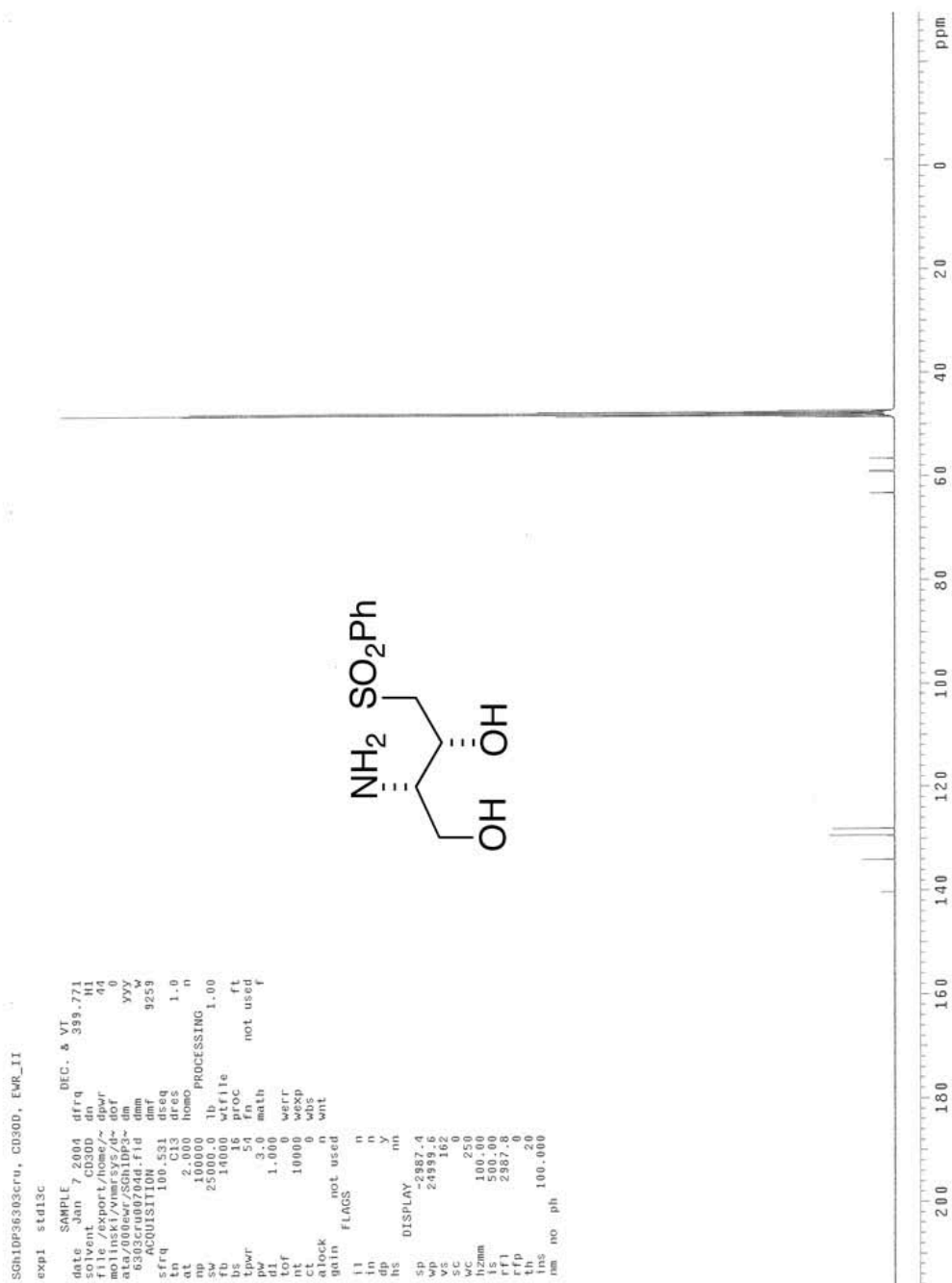
Spectrum 7.203: ^1H NMR (CD_3OD , 400 MHz) of compound 387



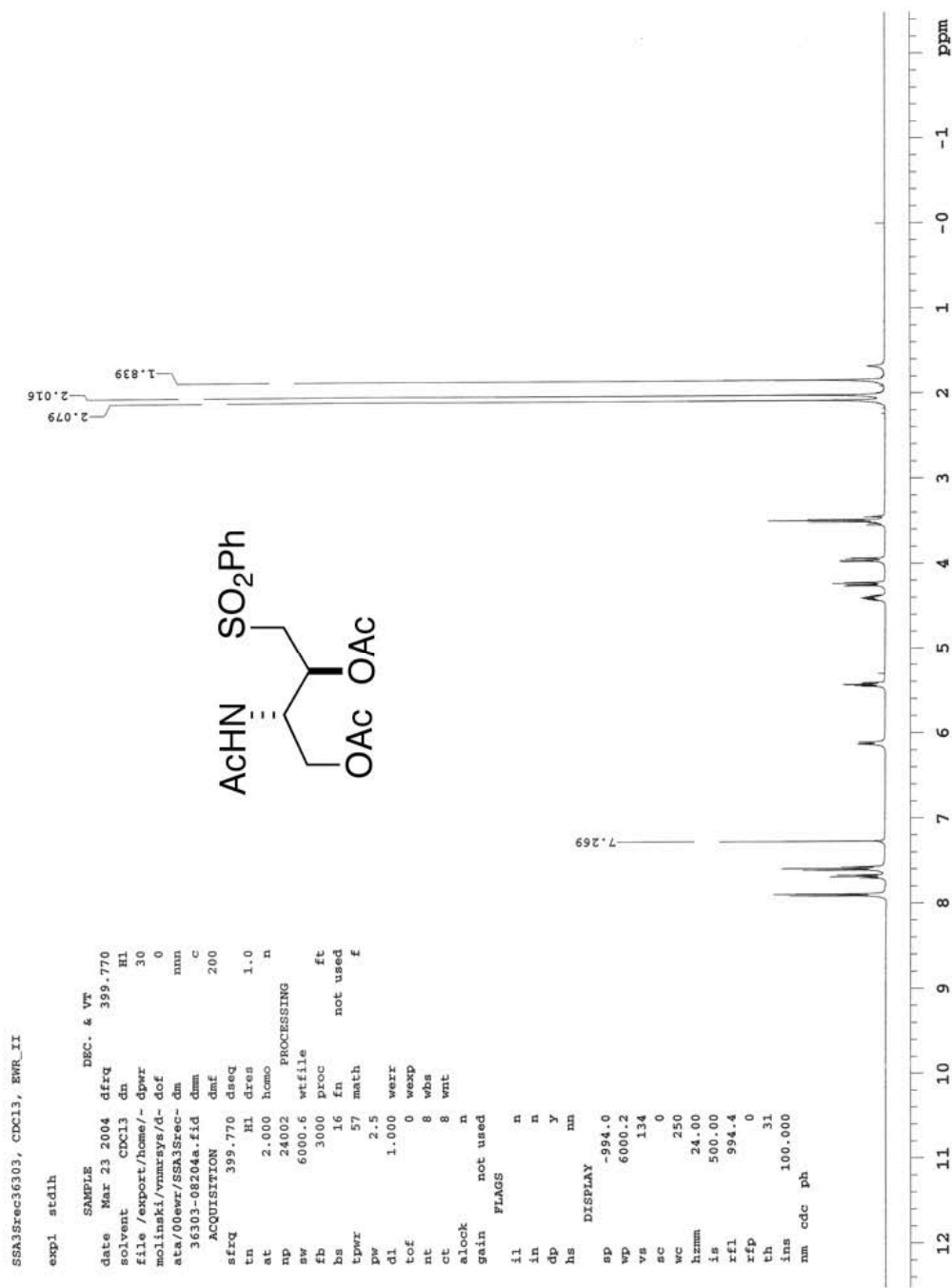
Spectrum 7.204: ^{13}C NMR (CD_3OD , 100 MHz) of compound 387



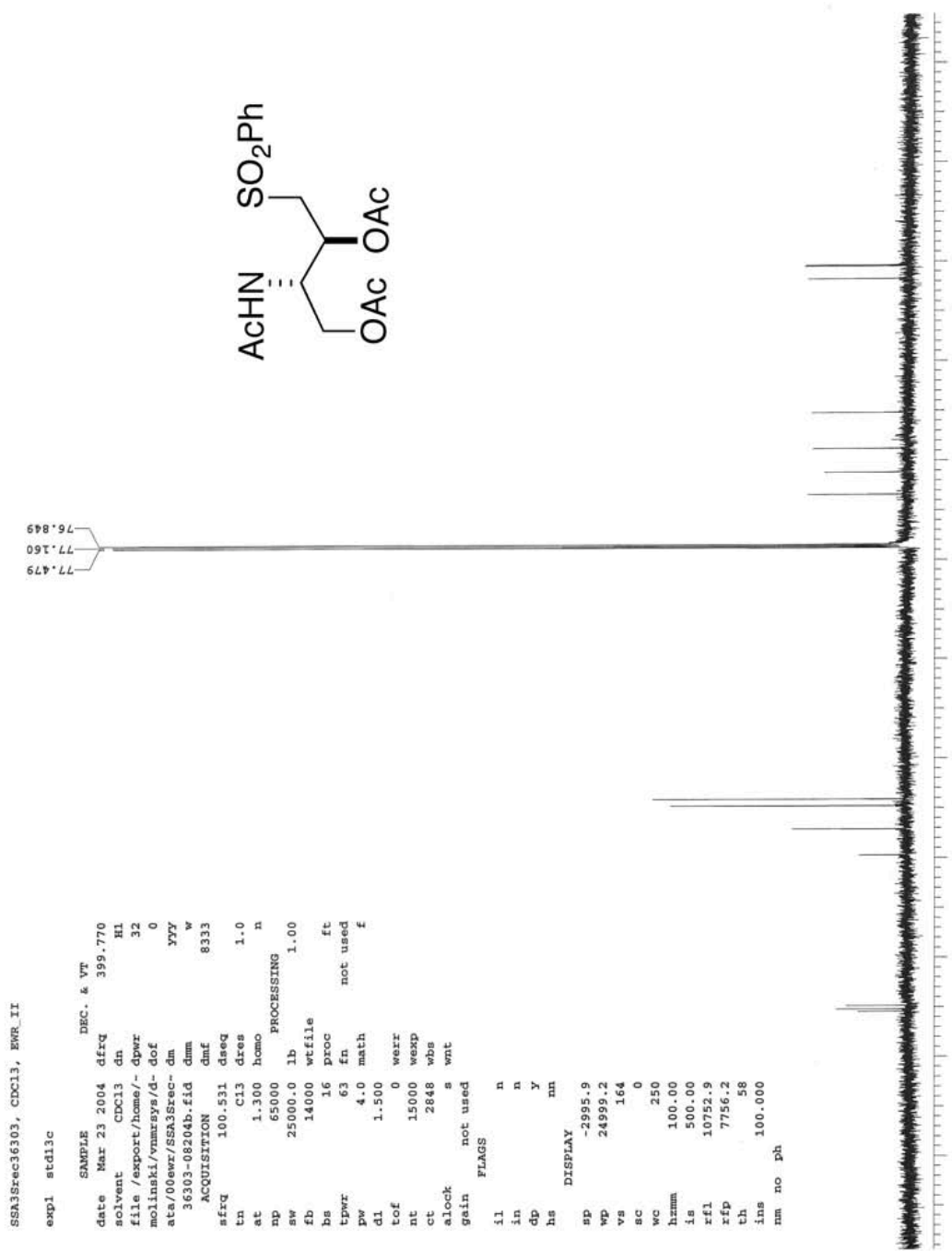
Spectrum 7.205: ^1H NMR (CD_3OD , 400 MHz) of compound **388**



Spectrum 7.206: ^{13}C NMR (CD_3OD , 100 MHz) of compound 388



Spectrum 7.207: ^1H NMR (CDCl_3 , 400 MHz) of compound 389

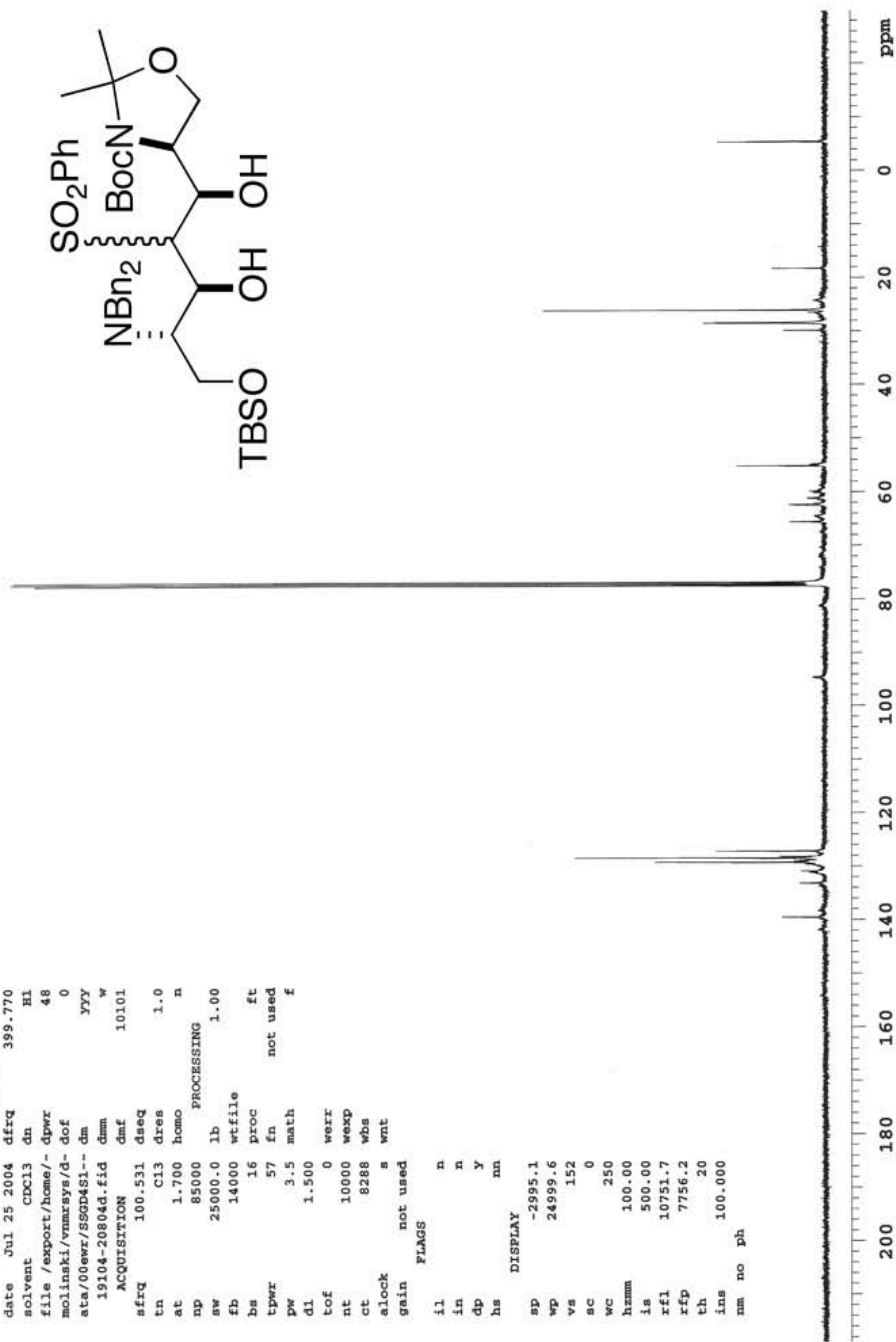


Spectrum 7.208: ¹³C NMR (CDCl₃, 100 MHz) of compound 389

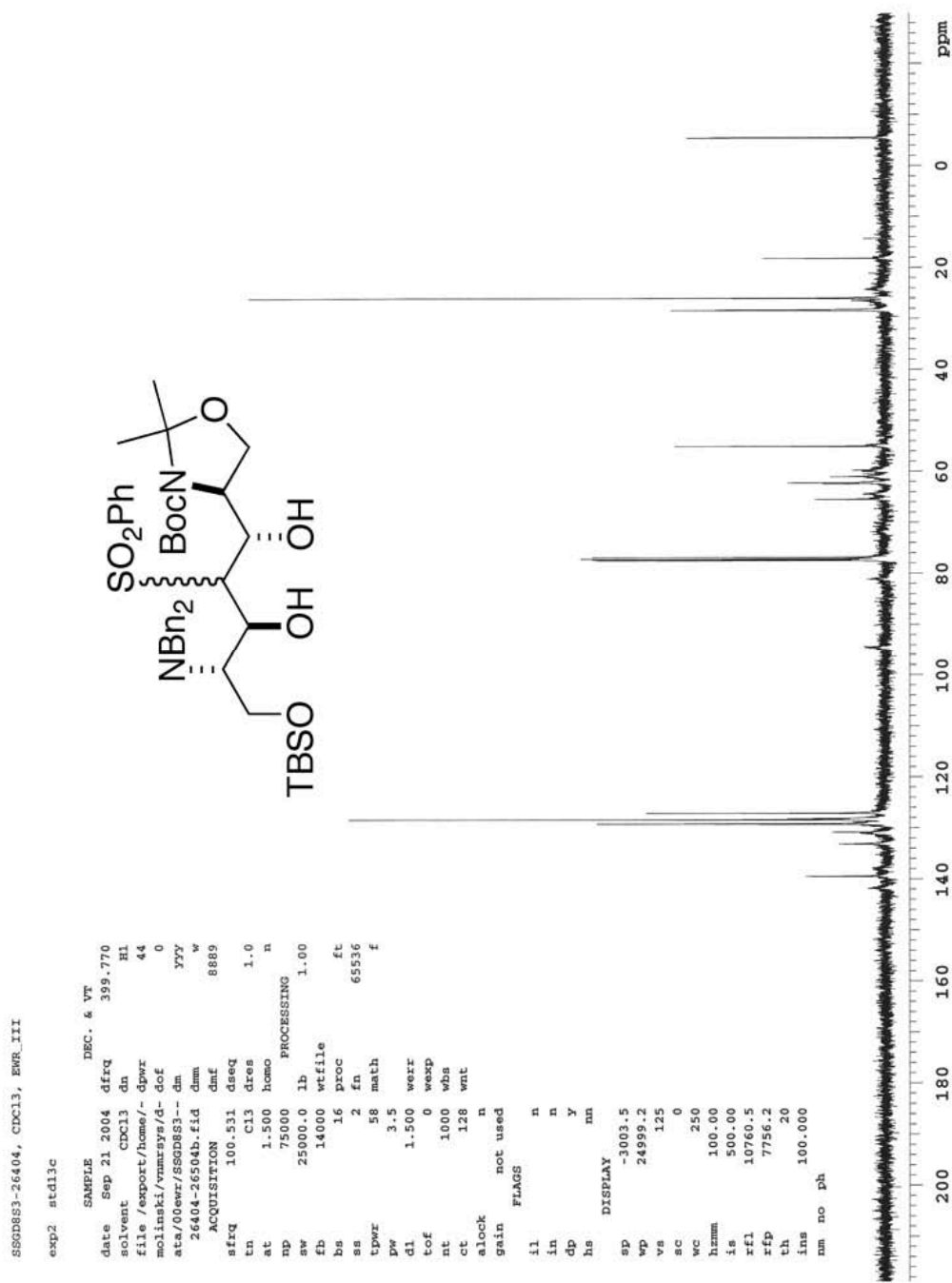
SSGD4S1-19104, CDCl3, EWR_III

exp4 std13c

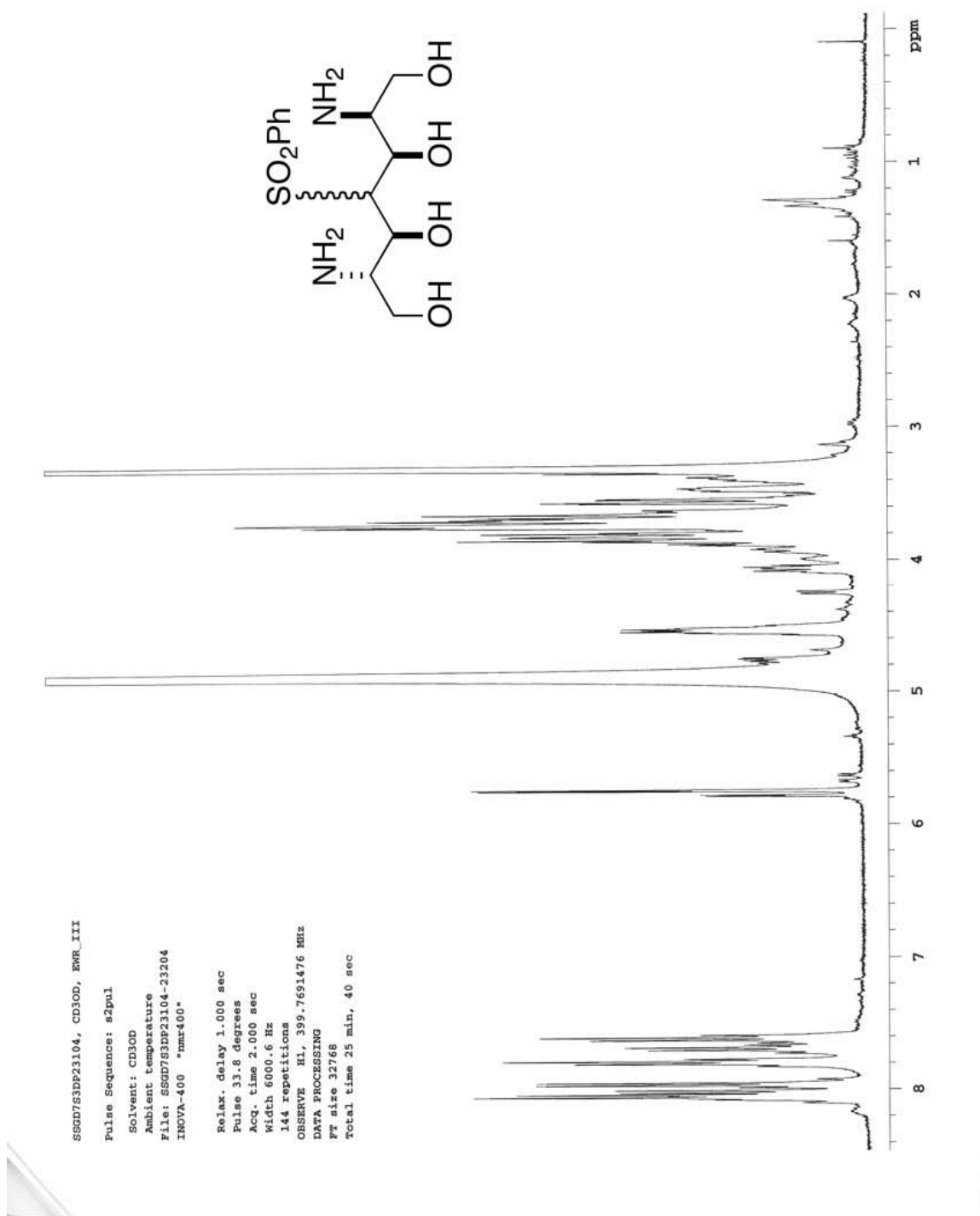
| SAMPLE | | DEC. & VT | |
|-------------------------|---------------------|------------|----------|
| date | Jul 25 2004 | dfrq | 399.770 |
| solvent | CDCl3 | dn | H1 |
| file | /export/home/- dpwr | HI | 48 |
| molinski/vmarsys/d- dof | | 0 | |
| ata/00ewr/SSGD4S1-- dm | | YYY | |
| 19104-20804d.fid | | w | |
| 19104-20804d.fid | | dm | |
| ACQUISITION | dmf | 10101 | |
| sfrq | 100.531 | dseq | |
| tn | C13 | dres | 1.0 |
| at | 1.700 | homo | n |
| np | 85000 | PROCESSING | |
| sw | 25000.0 | lb | 1.00 |
| fb | 14000 | wfile | |
| bs | 16 | proc | ft |
| tpwr | 57 | fn | not used |
| pw | 3.5 | math | f |
| d1 | 1.500 | | |
| tof | 0 | werr | |
| nt | 10000 | wexp | |
| ct | 8288 | wbs | |
| alock | s | wnt | |
| gain | not used | | |
| FLAGS | | | |
| il | n | | |
| in | n | | |
| dp | y | | |
| hs | nn | | |
| DISPLAY | | | |
| sp | -2995.1 | | |
| wp | 24999.6 | | |
| vs | 152 | | |
| sc | 0 | | |
| wc | 250 | | |
| hzmm | 100.00 | | |
| is | 500.00 | | |
| zfl | 10751.7 | | |
| rfp | 7756.2 | | |
| th | 20 | | |
| ins | 100.000 | | |
| nm | no | ph | |



Spectrum 7.210: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 390



Spectrum 7.212: ¹³C NMR (CDCl₃, 100 MHz) of compound 391



Spectrum 7.213: ^1H NMR (CD_3OD , 400 MHz) of compound 392

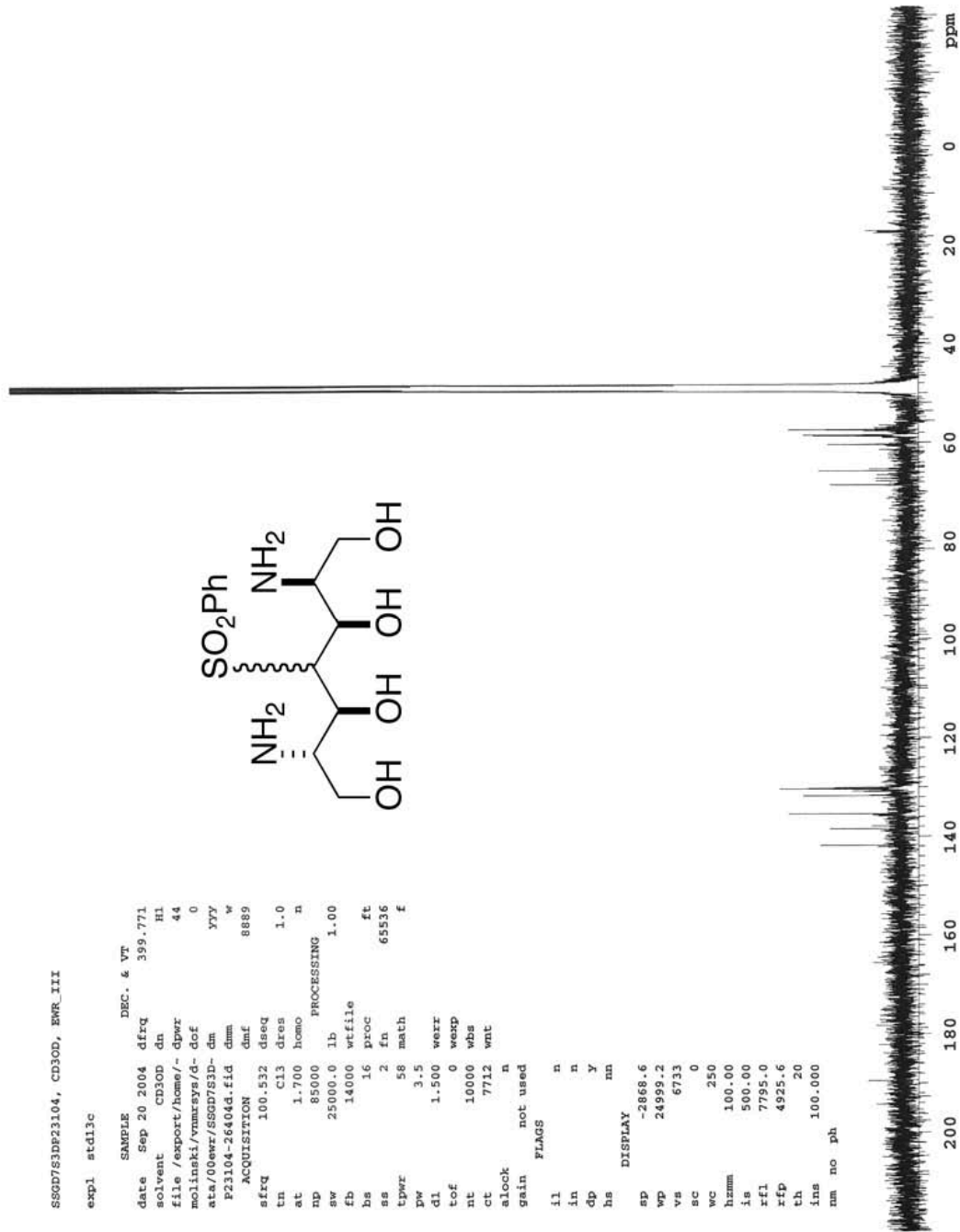
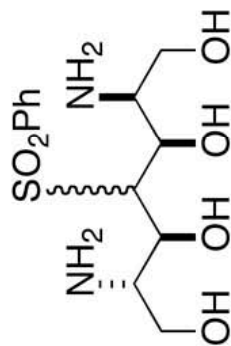
SSCD7S3DF23104, CD3OD, EWR_III

expl std13c

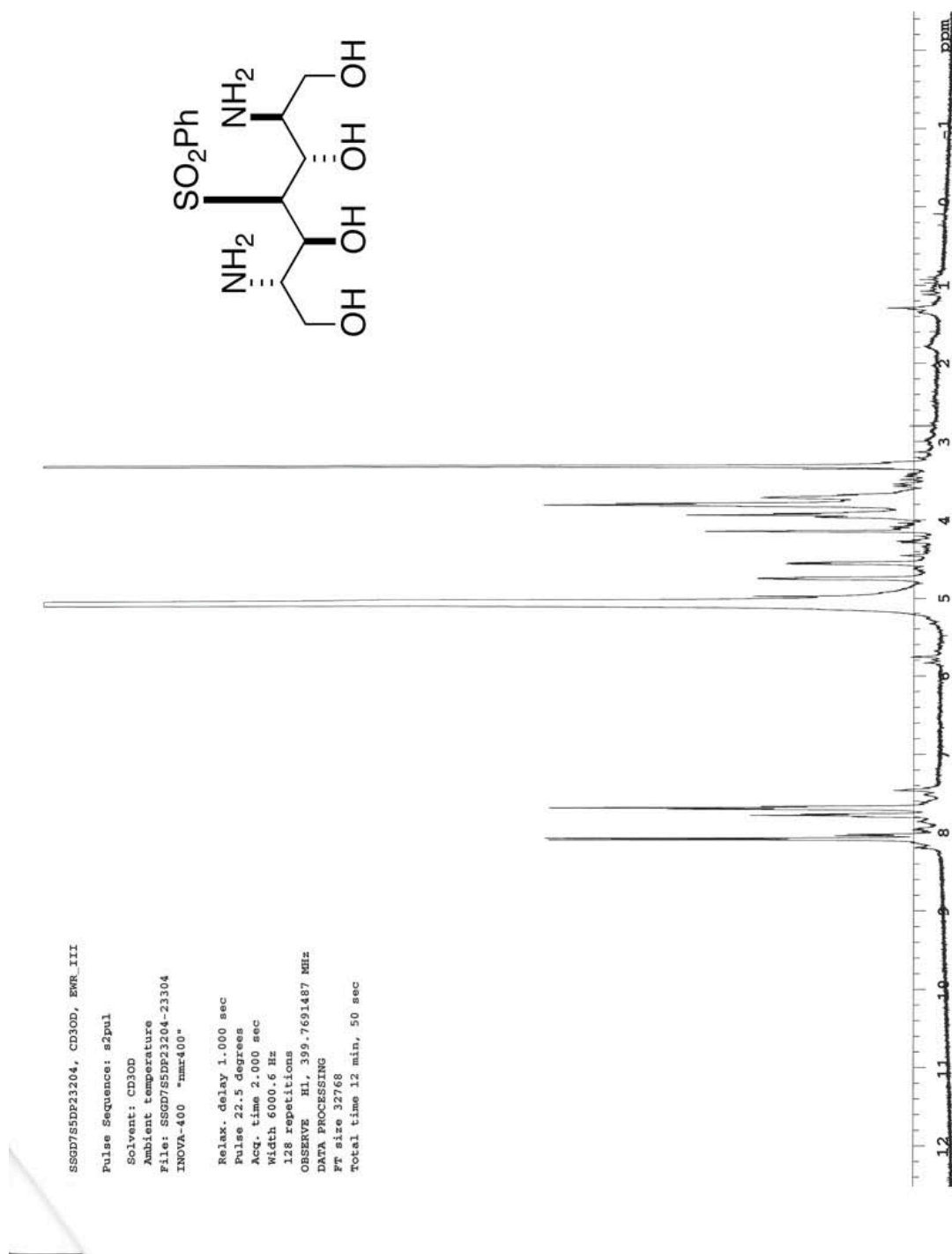
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SAMPLE          DEC. & VT
date   Sep 20 2004   dfrq   399.771
solvent CD3OD      dn      H1
file   /export/home/~ dpwr   44
molinski/vmrkys/d- dof     0
ata/00ewz/SSCD7S3D- dm    YTY
F23104-26404.fid  dnm      w
ACQUISITION      dmf      8889
sfrq   100.532   dseq
tn      C13      dres     1.0
at      1.700   homo     n
np      85000   PROCESSING
sw      25000.0 lb      1.00
fb      14000   wtfile
bs      16     proc     ft
ss      2     fn      65536
tpwr   58     math     f
pw      3.5
d1      1.500   werr
tof     0     wexp
nt      10000   wbs
ct      7712   wnt
alock   a     not used
gain
flags
il      n
in      n
dp      y
hs      nm
DISPLAY
sp      -2868.6
wp      24999.2
vs      6733
sc      0
wc      250
hzmm   100.00
is      500.00
rf1    7795.0
zfp    4925.6
th      20
ins    100.000
nm no ph

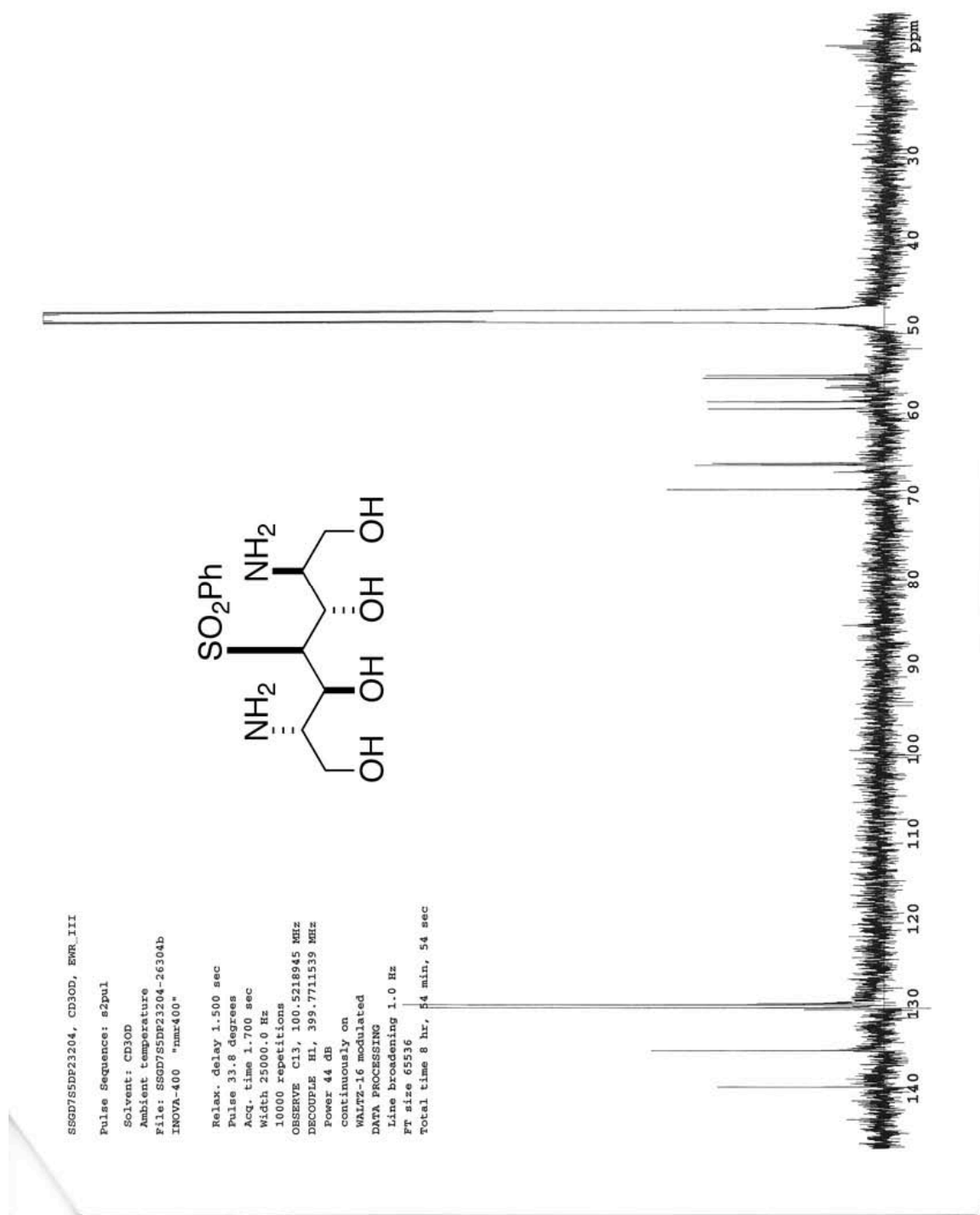
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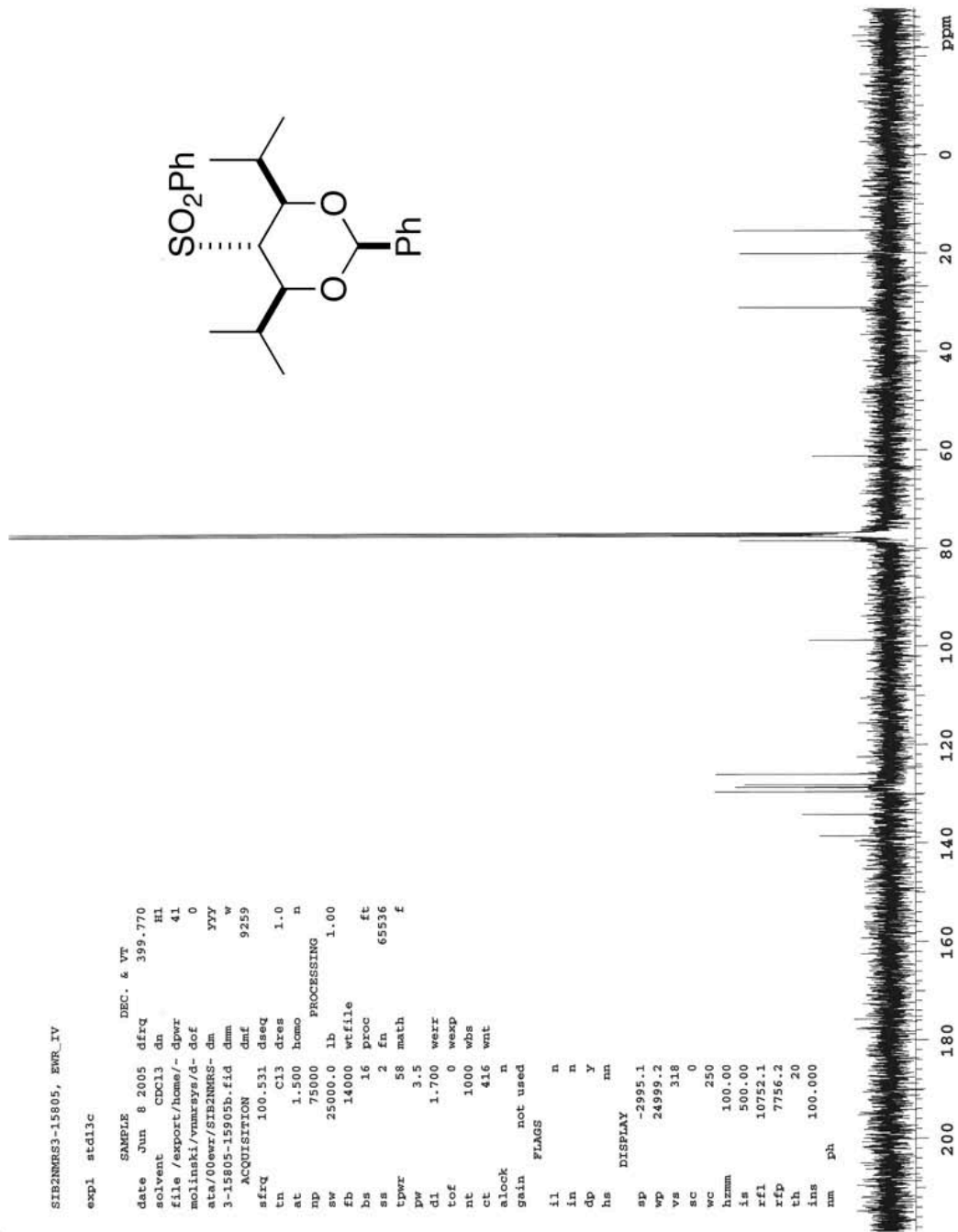
Spectrum 7.214: ¹³C NMR (CD₃OD, 100 MHz) of compound 392



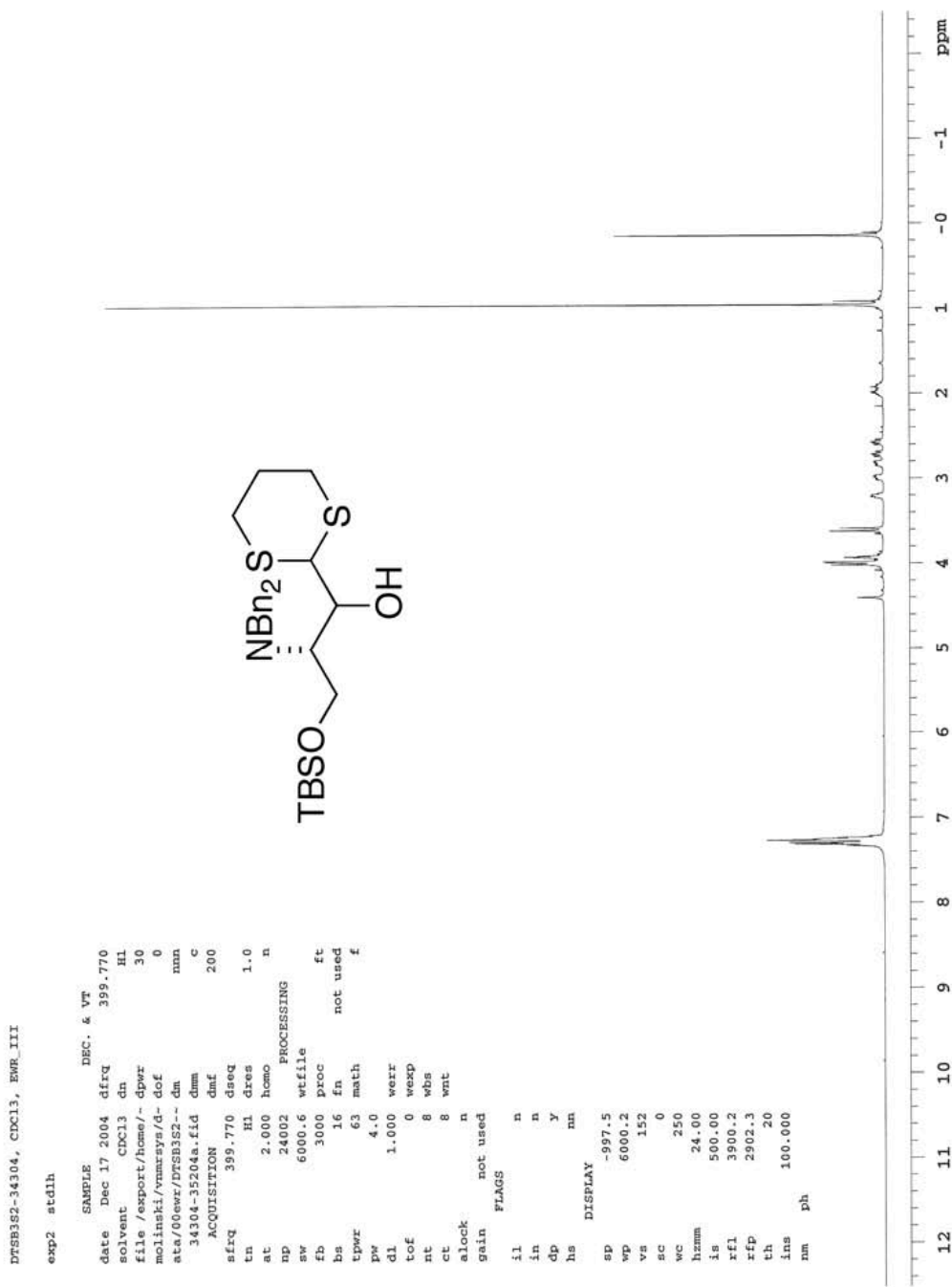
Spectrum 7.215: ^1H NMR (CD_3OD , 400 MHz) of compound 393



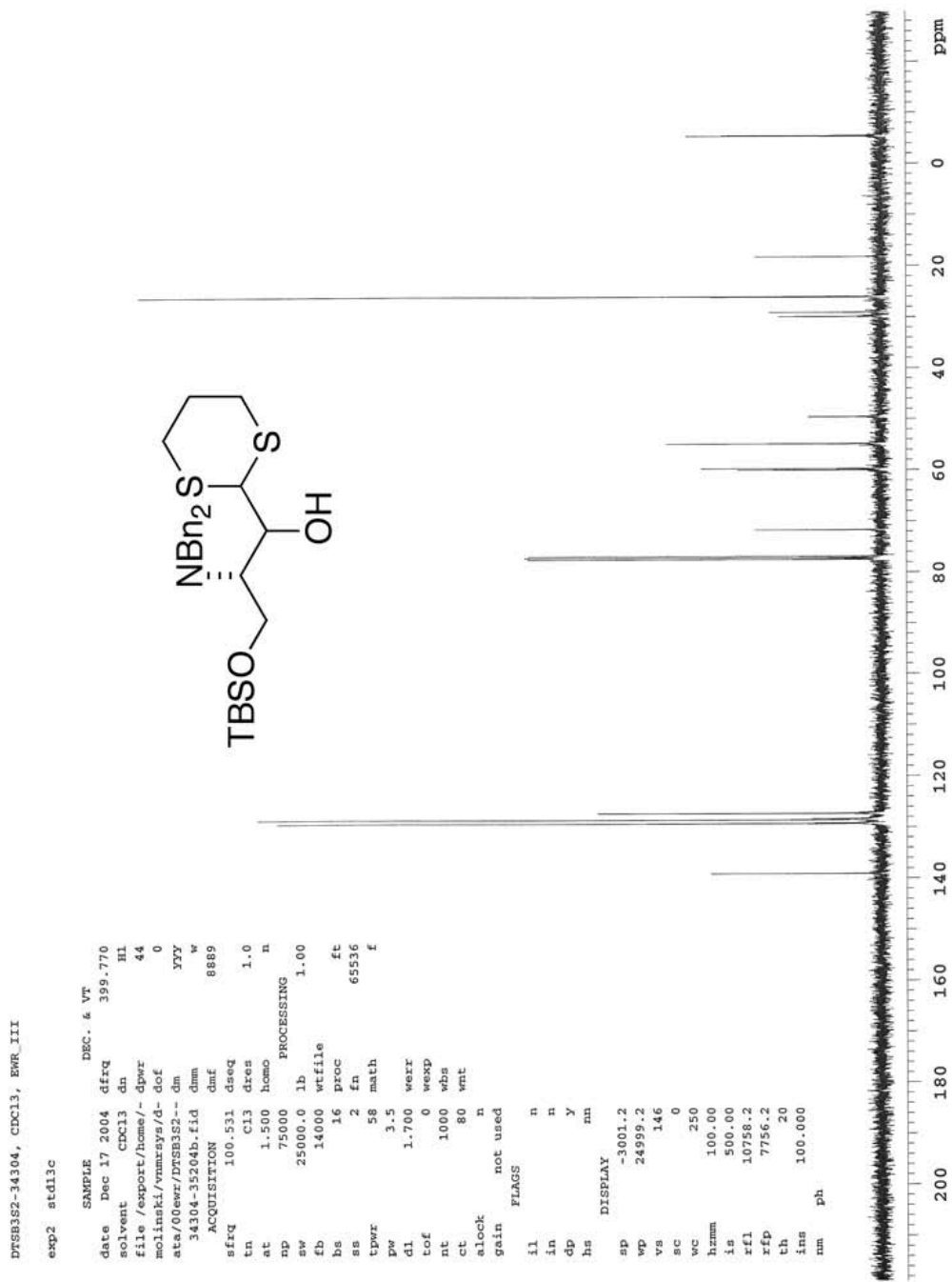
Spectrum 7.216: ¹³C NMR (CD₃OD, 100 MHz) of compound 393



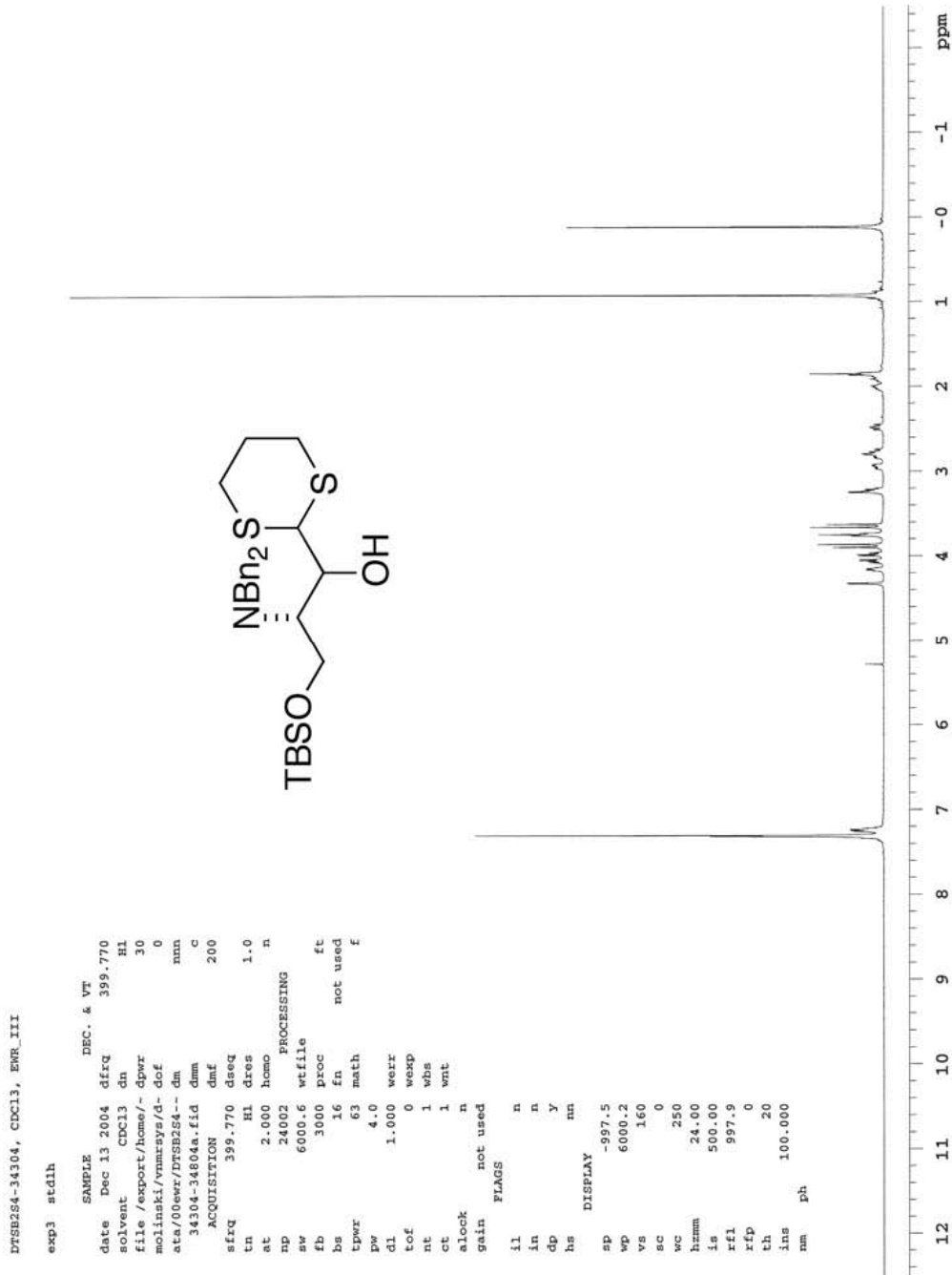
Spectrum 7.218: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 403



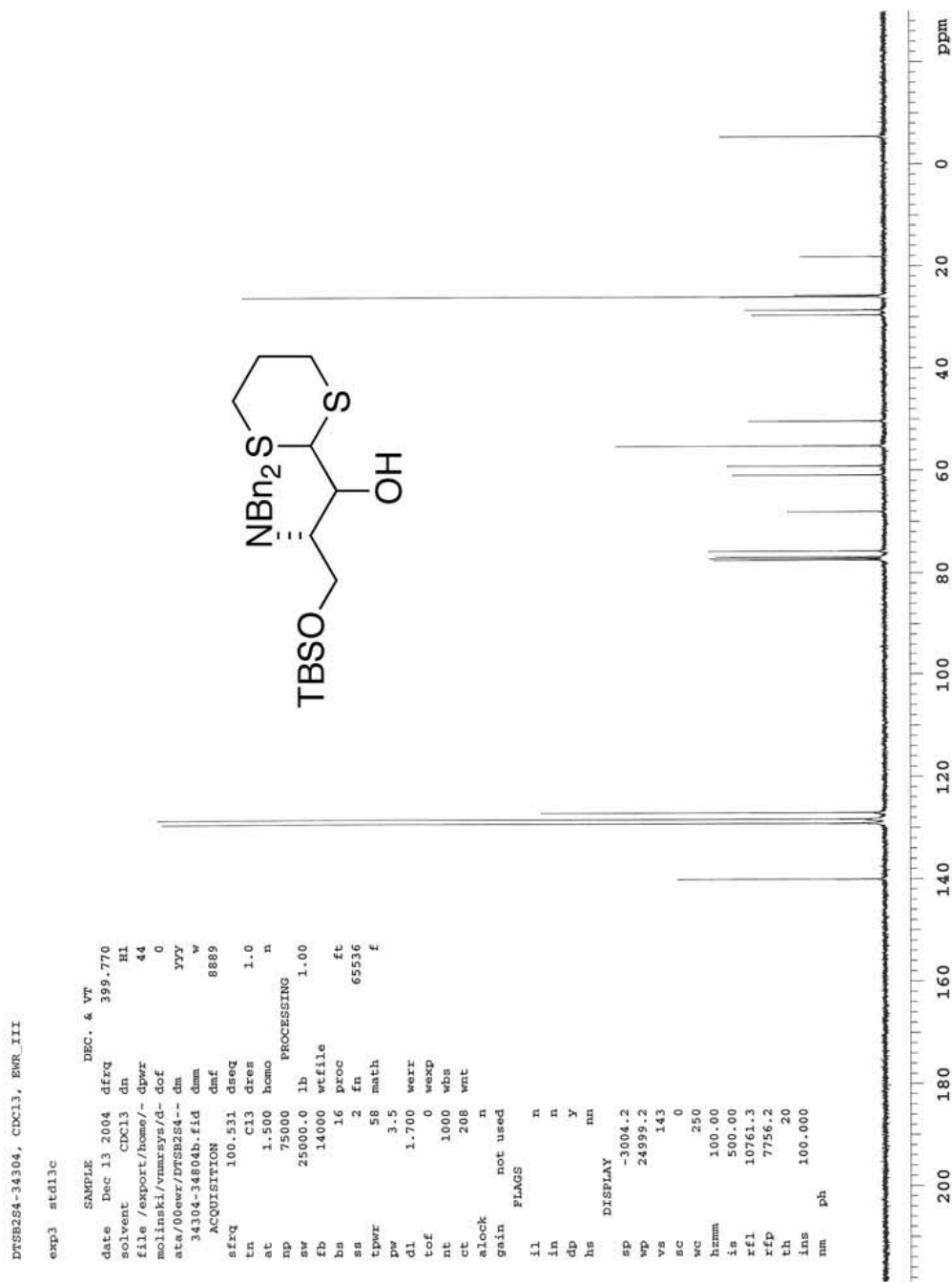
Spectrum 7.219: ¹H NMR (CDCl₃, 400 MHz) of compound 407



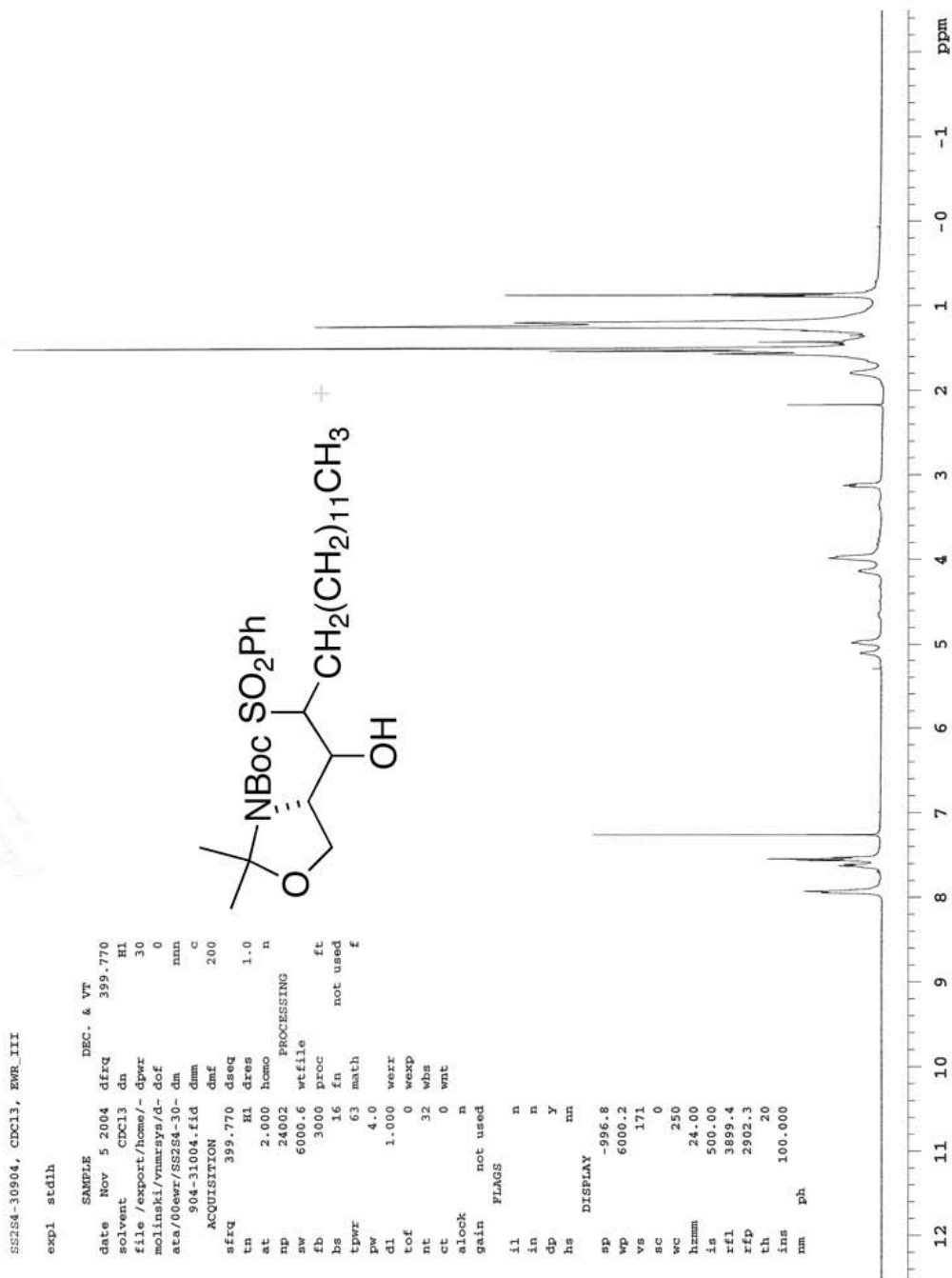
Spectrum 7.220: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 407



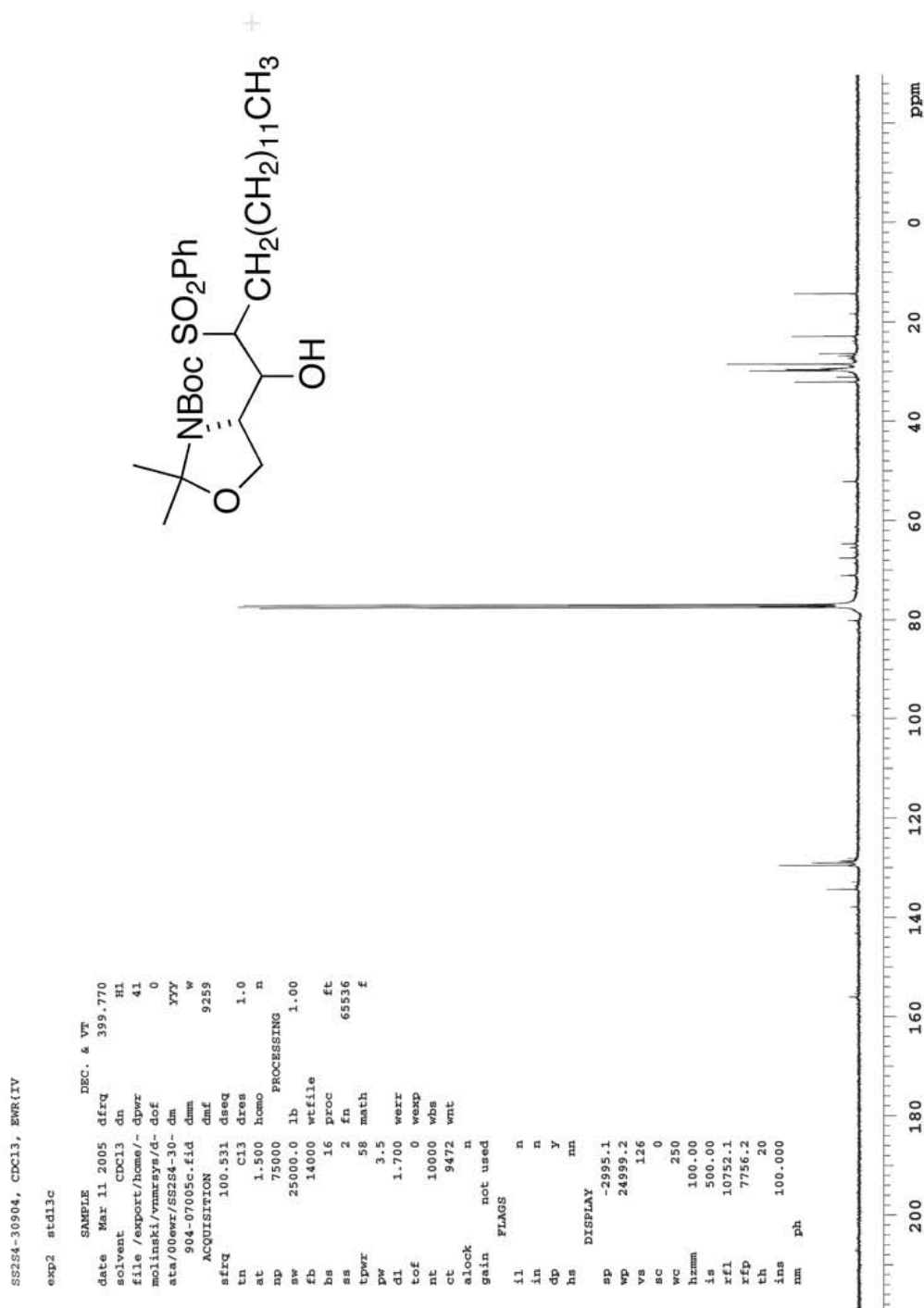
Spectrum 7.221: ^1H NMR (CDCl_3 , 400 MHz) of compound 408



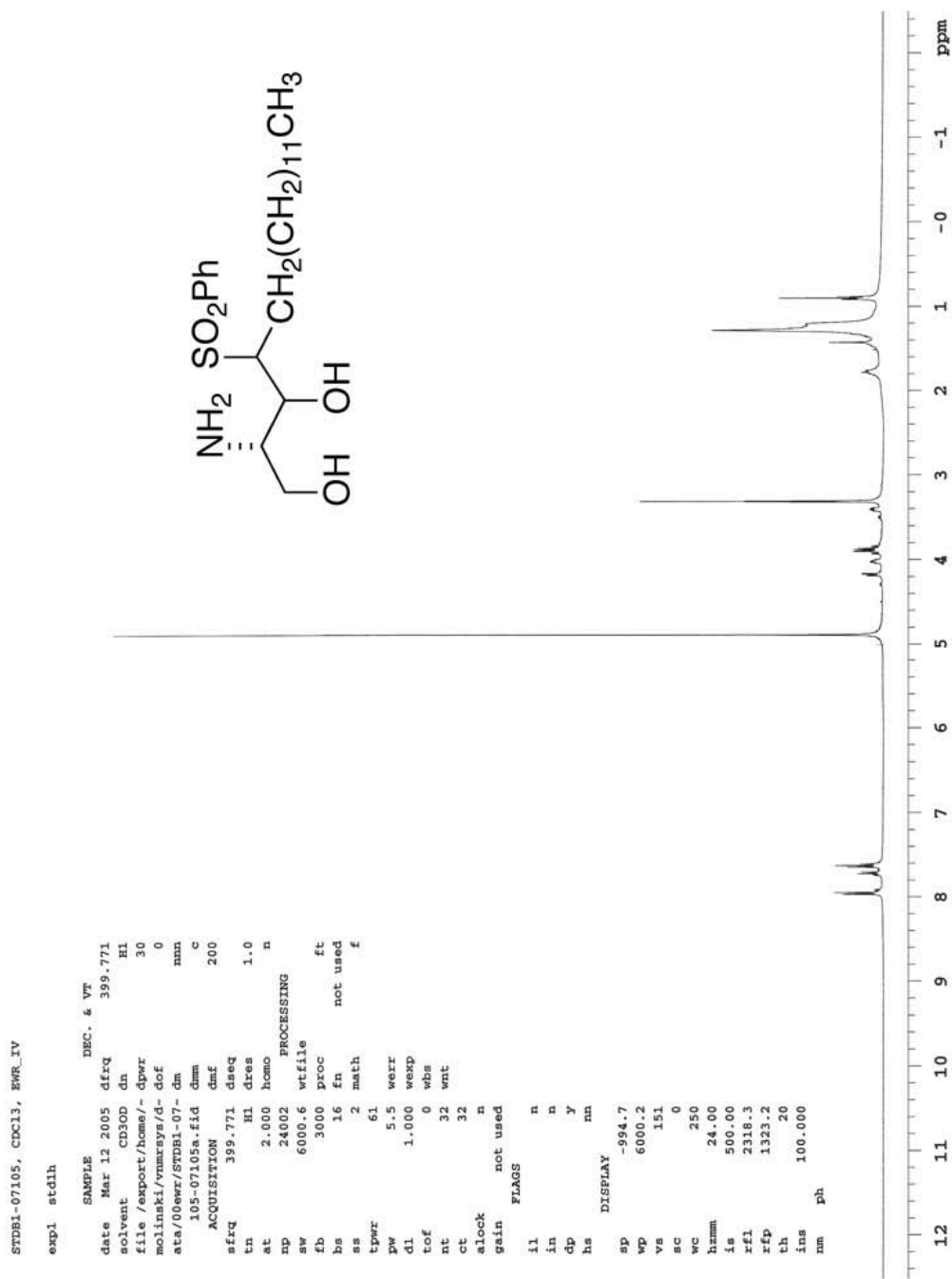
Spectrum 7.222: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 408



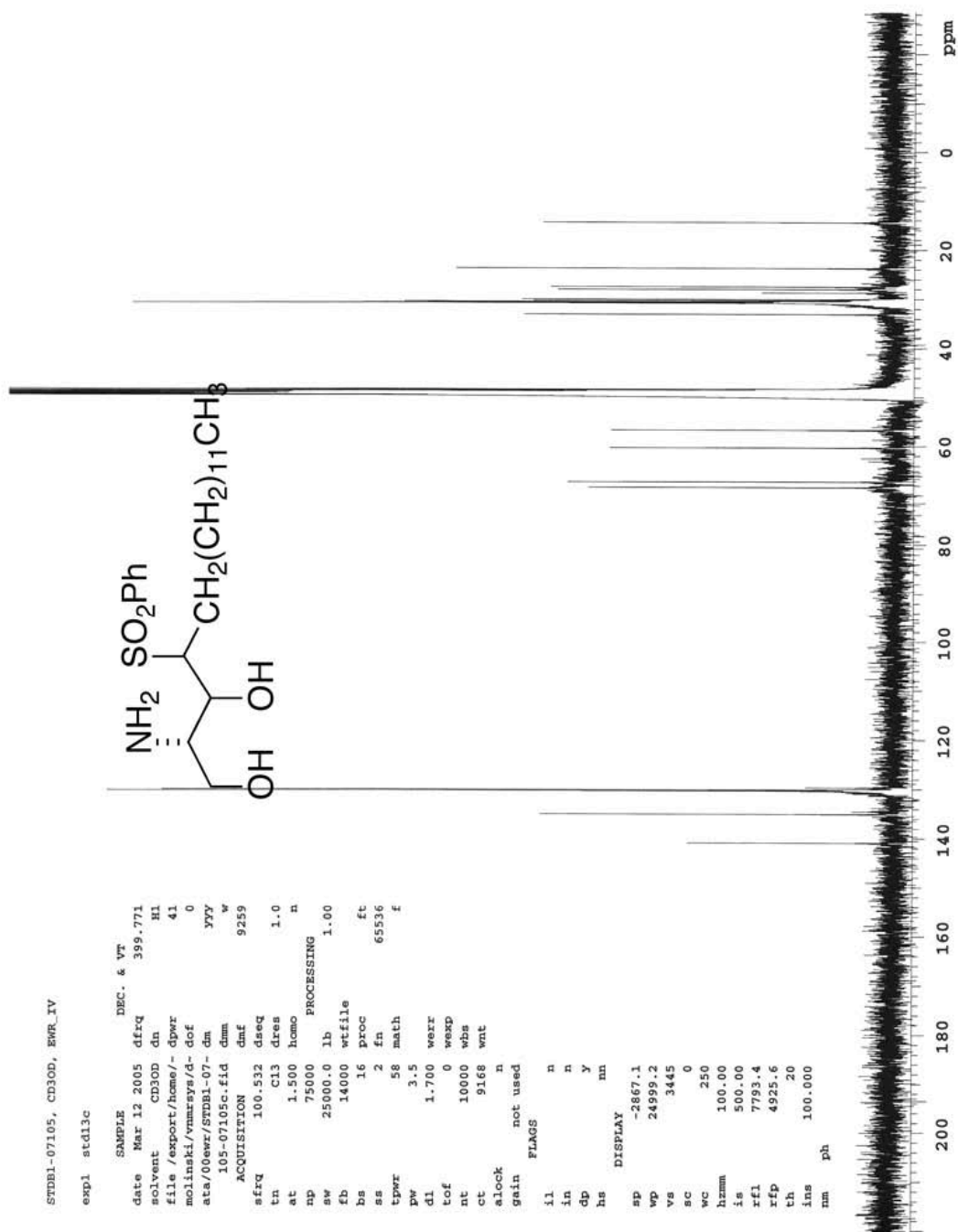
Spectrum 7.223: ^1H NMR (CDCl_3 , 400 MHz) of compound 414



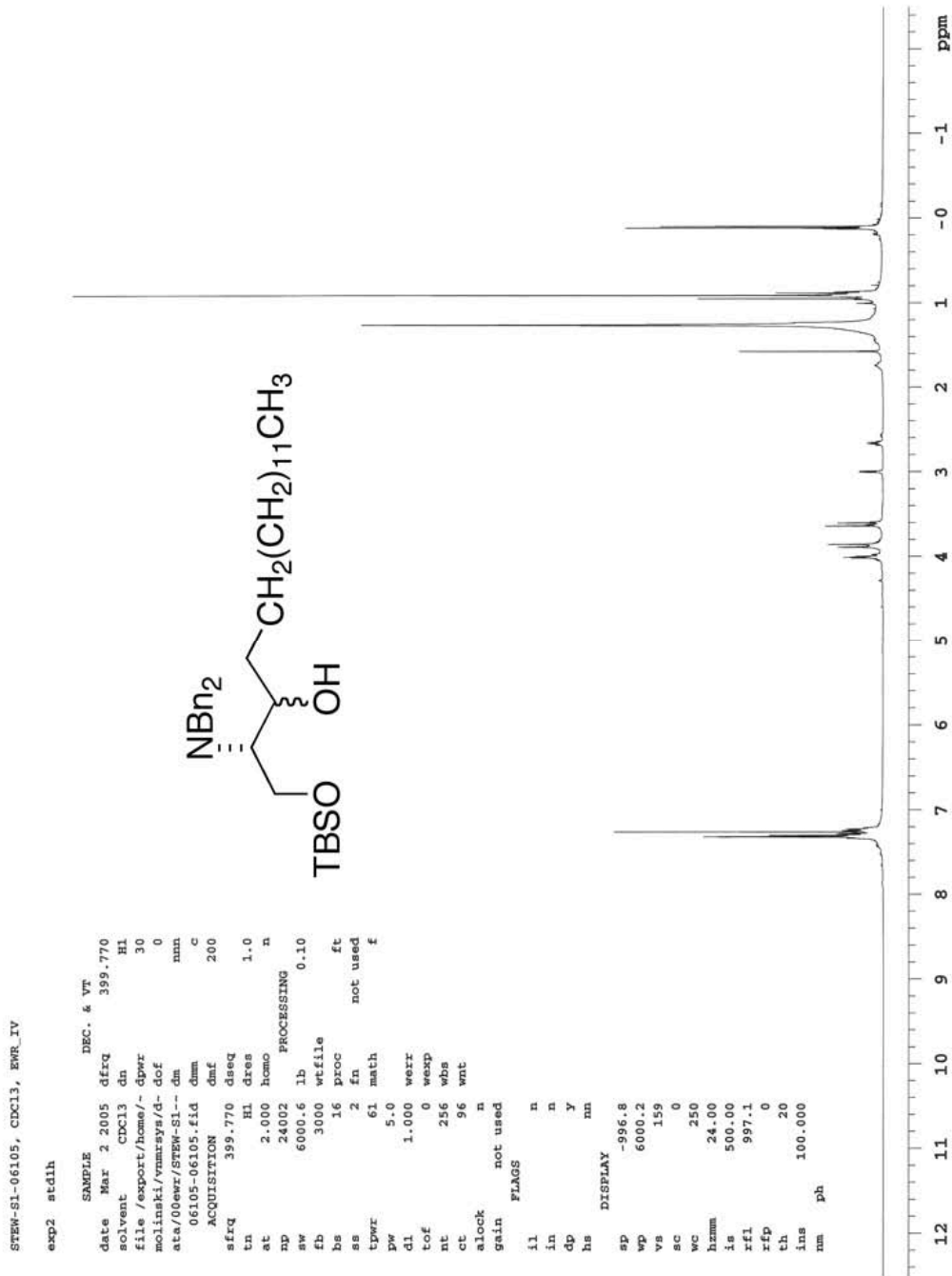
Spectrum 7.224: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 414



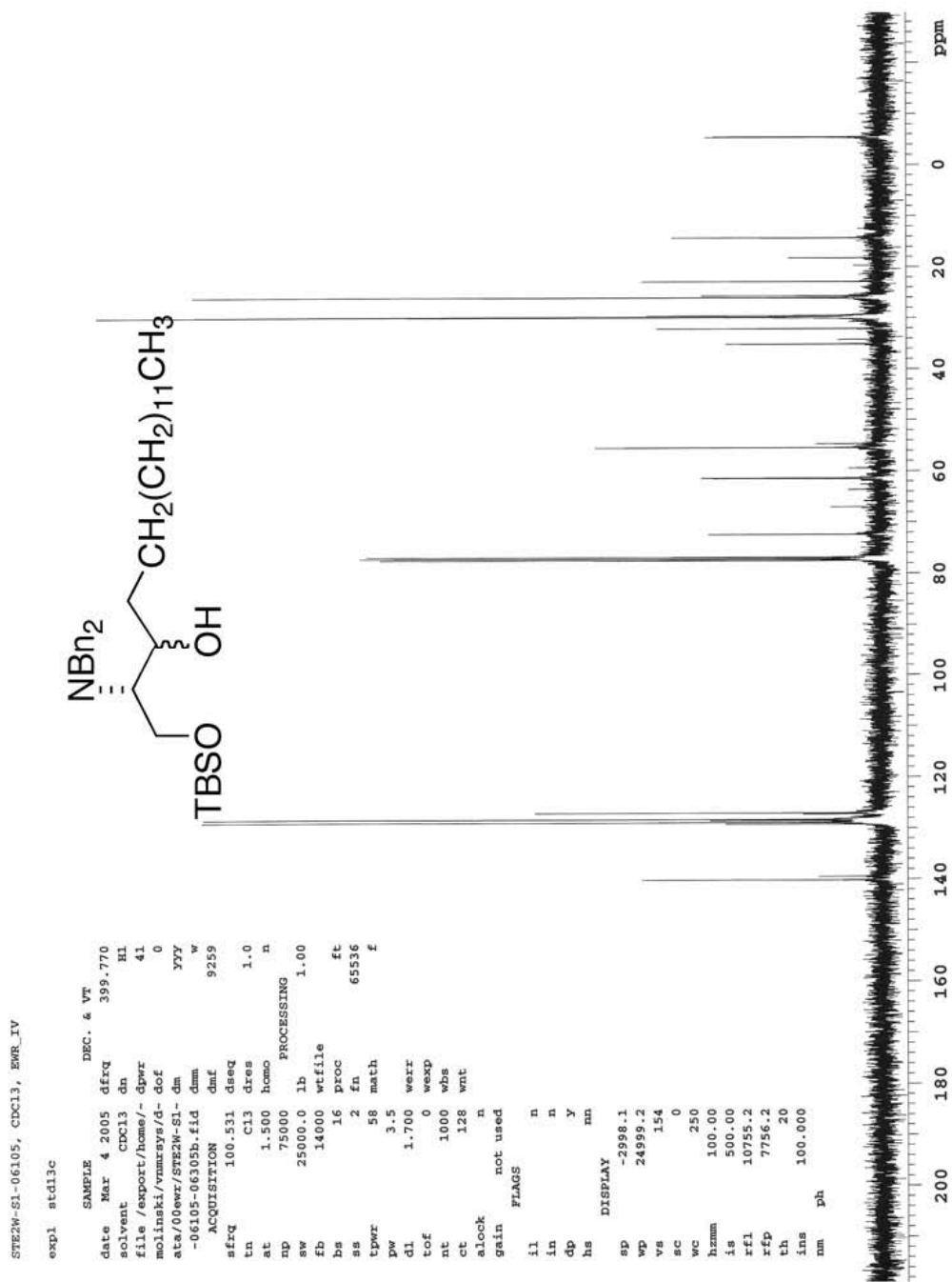
Spectrum 7.225: ^1H NMR (CD_3OD , 400 MHz) of compound 416



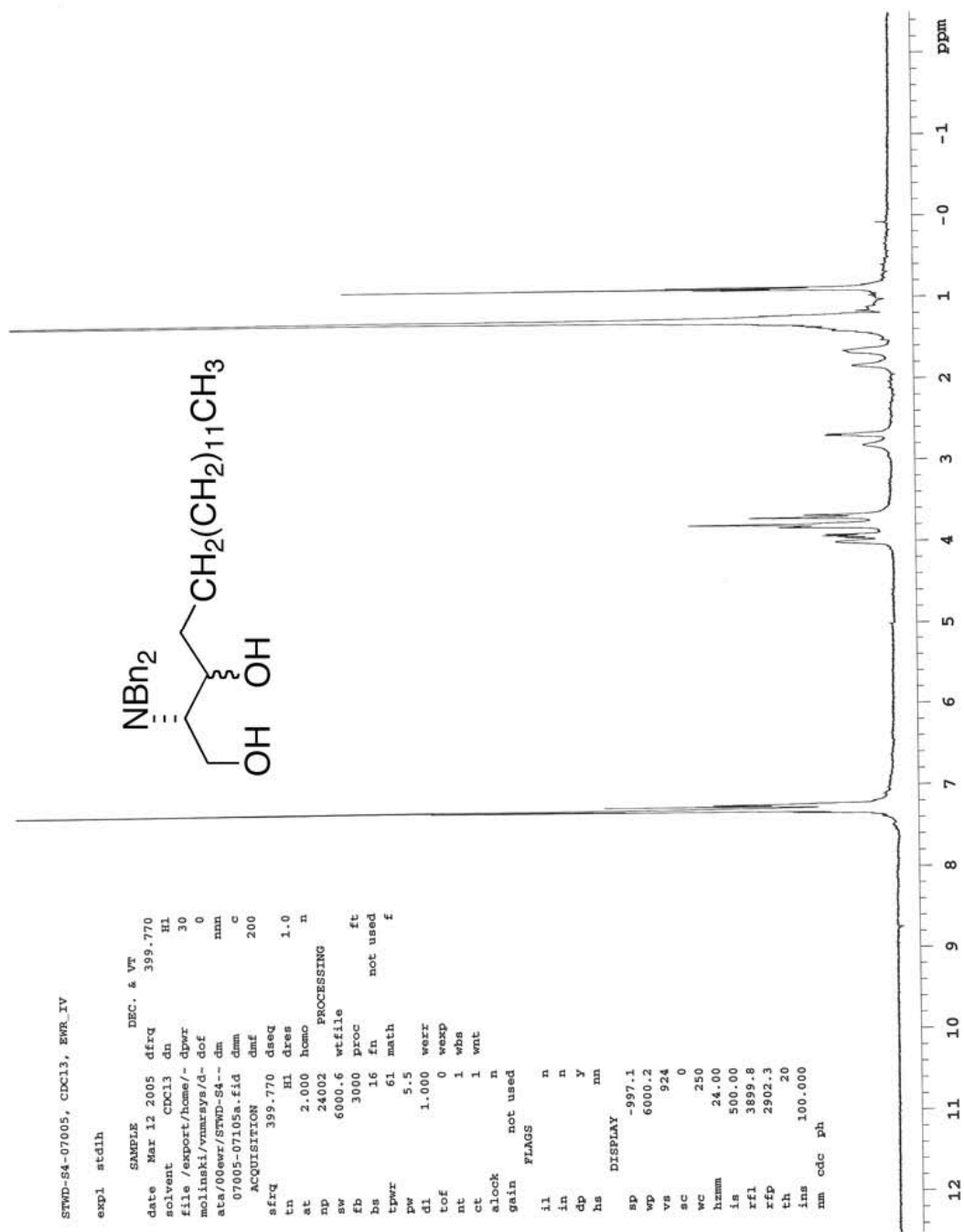
Spectrum 7.226: ^{13}C NMR (CD_3OD , 100 MHz) of compound 416



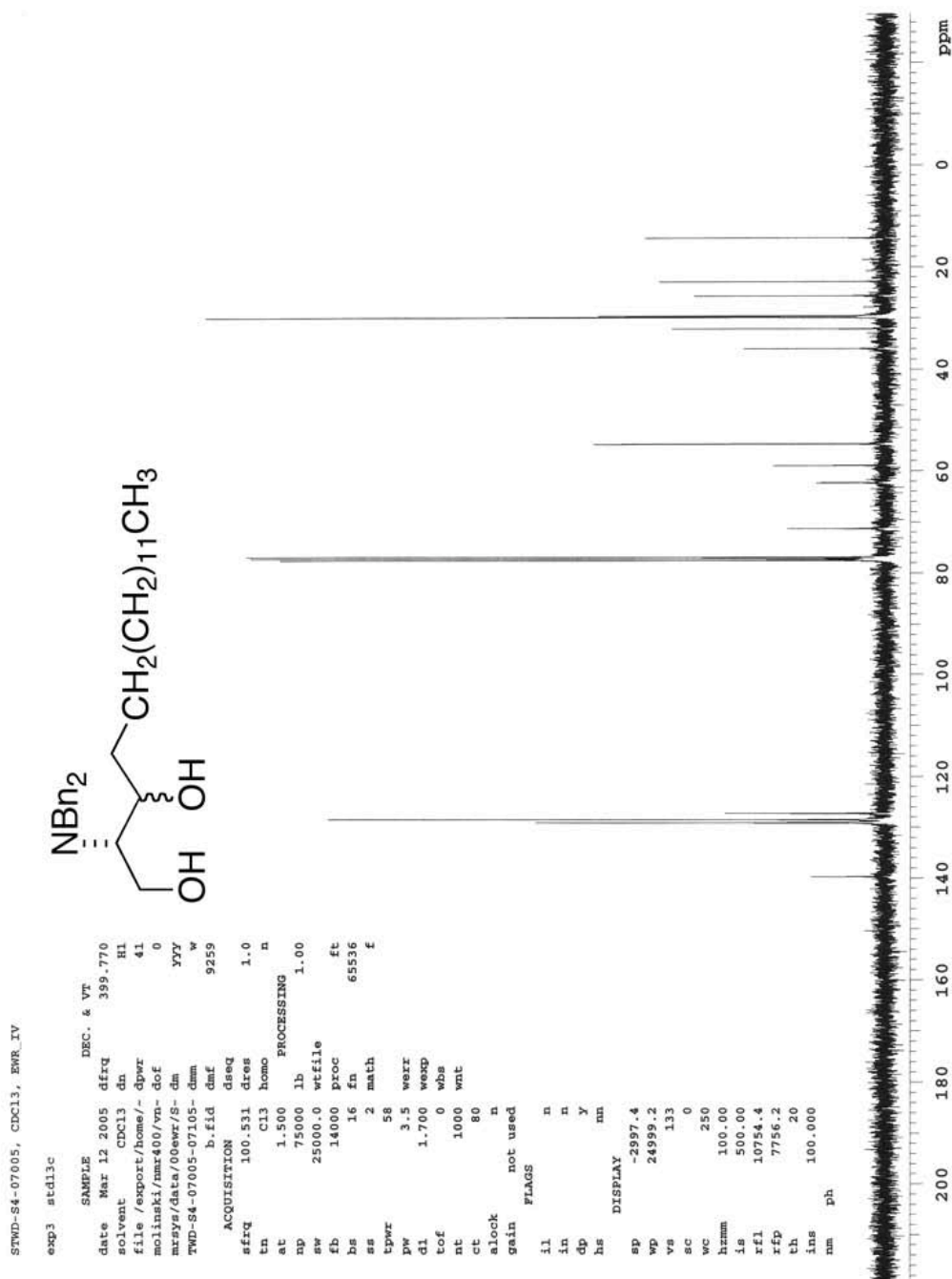
Spectrum 7.227: ^1H NMR (CDCl_3 , 400 MHz) of compound 418



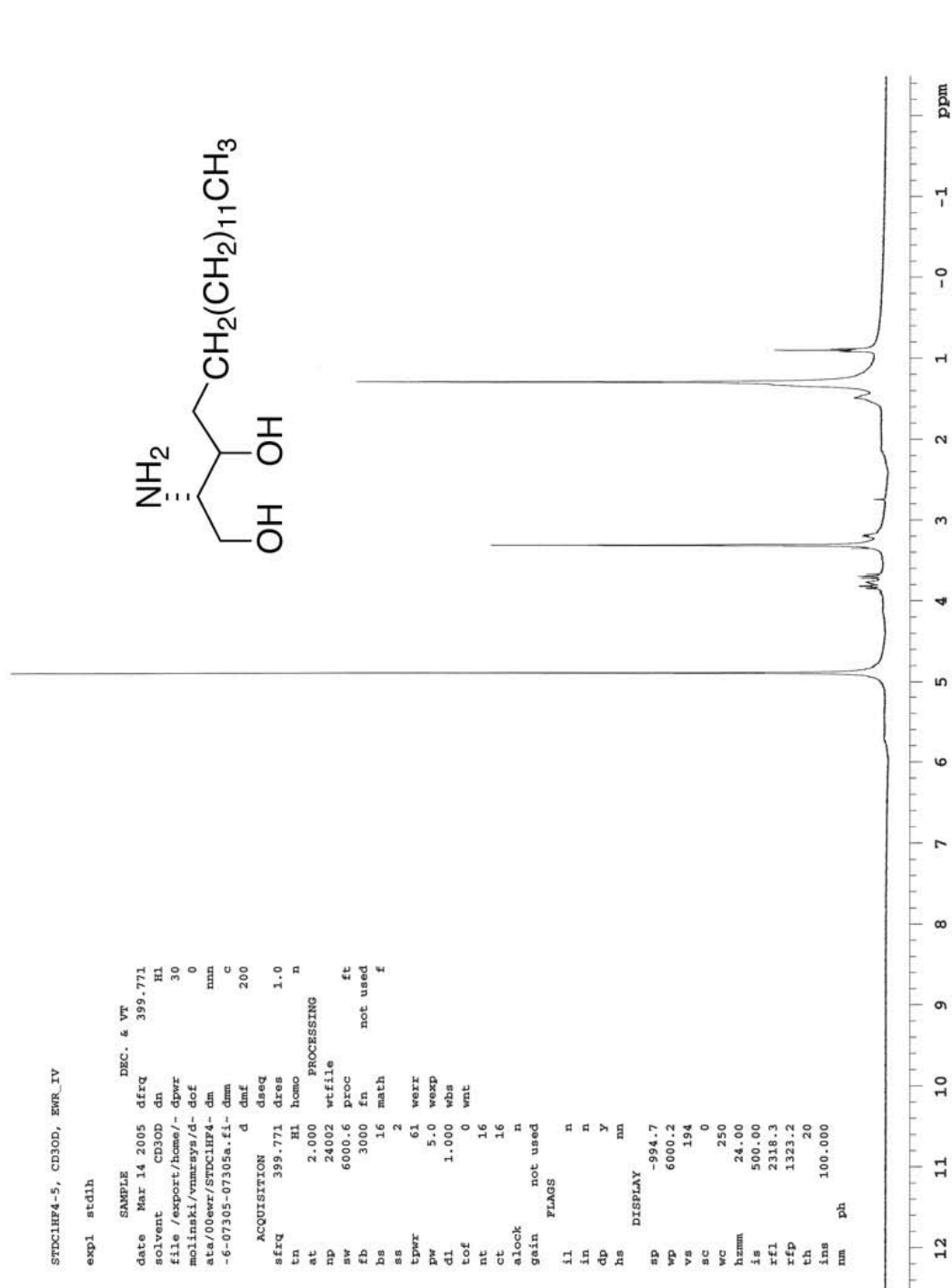
Spectrum 7.228: ¹³C NMR (CDCl₃, 100 MHz) of compound 418



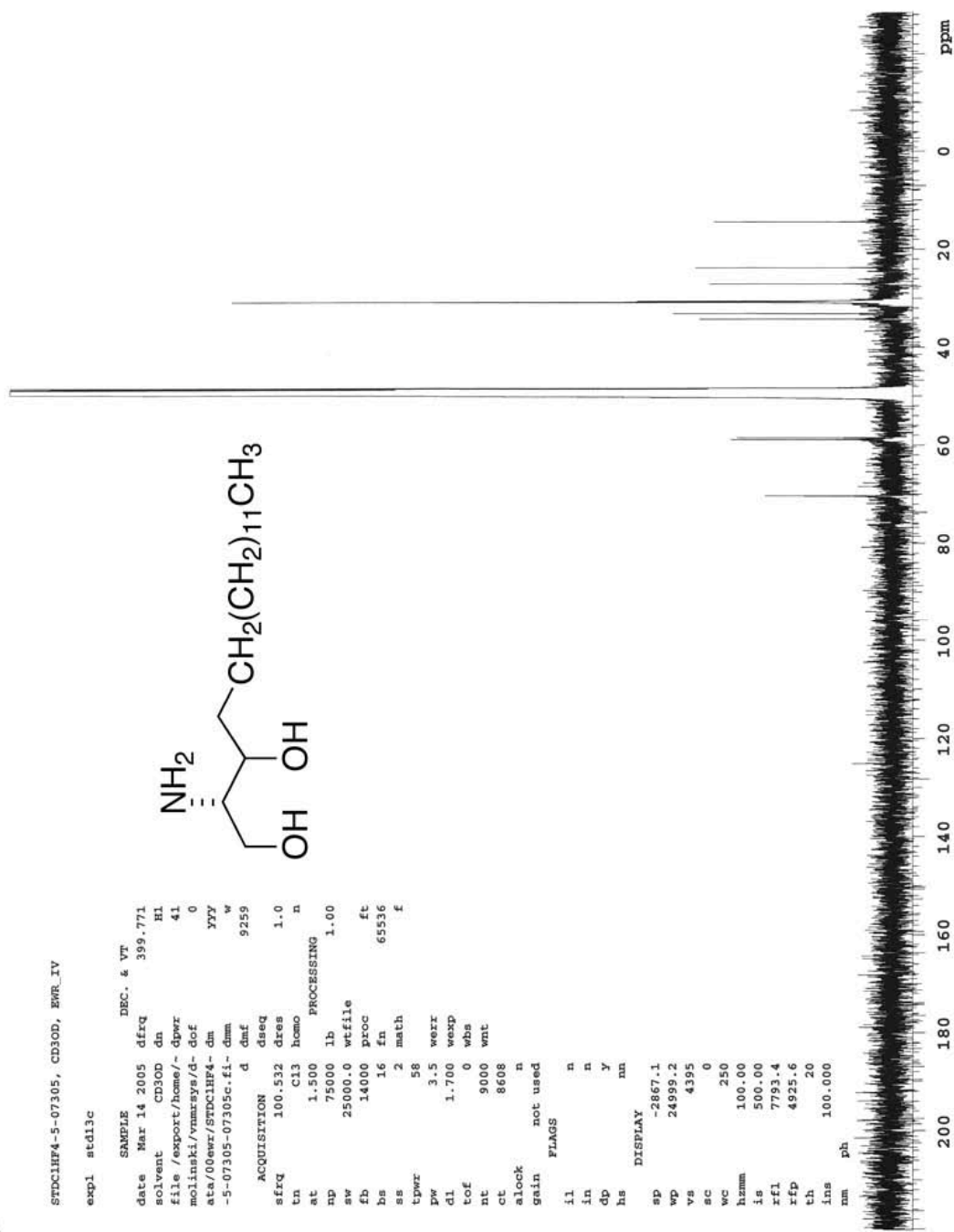
Spectrum 7.229: ^1H NMR (CDCl_3 , 400 MHz) of compound 420



Spectrum 7.230: ^{13}C NMR (CDCl_3 , 100 MHz) of compound 420



Spectrum 7.231: ^1H NMR (CD_3OD , 400 MHz) of compound 421



Spectrum 7.232: ^{13}C NMR (CD_3OD , 100 MHz) of compound 421