

TABLE OF CONTENTS

Dedication.....	iii
Acknowledgements	ix
Abstract.....	xi
Prologue	xii
Table of Contents.....	xv
List of Figures	xx
List of Schemes.....	xxxiii
List of Tables.....	xl
List of Abbreviations	xliii
CHAPTER 1: THE BIOLOGY AND CHEMISTRY OF THE ZOANTHAMINE ALKALOIDS.....	1
1.1.1 Introduction	1
1.2 The Zoanthamine Natural Products.....	3
1.2.1 Isolation and Structural Characterization of the Zoanthamine Natural Products.....	3
1.2.2 Biosynthesis of the Zoanthamine Natural Products.....	6
1.2.3 Reactivity Studies of Norzoanthamine.....	11
1.3 Biological Activities of Zoanthamine Alkaloids	13
1.3.1 Anti-Osteoporotic Activity	13
1.3.2 Miscellaneous Biological Activities.....	15
1.4 Synthetic Approaches Toward the Zoanthamine Natural Products.....	17
1.4.1 General Remarks	17
1.4.2 Miyashita's Synthesis of Norzoanthamine.....	18
1.4.3 Tanner's Diels-Alder Approach to the Zoanthamine ABC Ring System.....	22

1.4.4	Uemura's Approach to the Norzoanthamine ABC Ring System.....	28
1.4.5	Williams's Approach to the Norzoanthamine AB and EFG Ring Systems	28
1.4.6	Theodorakis's Annulation Approach to the Norzoanthamine ABC Ring System.....	31
1.4.7	Kobayashi's Synthesis of the Heterocyclic CDEFG Zoanthamine Ring System.....	33
1.4.8	Hirama's Strategy for the Zoanthenol ABC Ring System.....	34
1.5.1	Summary and Outlook	38
	<i>References</i>	40
CHAPTER 2: EARLY EFFORTS TOWARD THE SYNTHESIS OF ZOANTHENOL.....		43
2.1.1	Introduction and Retrosynthetic Analysis	43
2.2.1	Synthesis of the A Ring Synthon.....	45
2.2.2	Synthesis of the C Ring Synthon.....	45
2.2.3	Synthesis of the Tricyclic Core of Zoanthenol.....	47
2.3.1	Enantioselective Synthesis of the DEFG Synthon	53
2.4.1	Summary of Early Synthetic Work	55
2.5.1	Materials and Methods.....	56
2.5.2	Preparation of Compounds	58
	<i>References</i>	85
	<i>Synthetic Summary</i>	89
APPENDIX A: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: EARLY EFFORTS TOWARD THE SYNTHESIS OF ZOANTHENOL		92
CHAPTER 3: ACID-MEDIATED CYCLIZATION APPROACHES TO THE DENSELY SUBSTITUTED CARBOCYCLIC CORE OF ZOANTHENOL.....		181

3.1.1	Revised Retrosynthetic Analysis.....	182
3.2	Toward a Vicinal Quaternary Center-Containing C Ring Synthon	182
3.2.1	Synthesis and Desymmetrization of a <i>meso</i> -Anhydride	182
3.2.2	Elaboration of the Half-Ester.....	186
3.3.1	Toward a Lactone-Derived C Ring Synthon	187
3.3.2	Acid-Mediated Cyclizations of Lactone-Derived A–C Ring Systems	188
3.4.1	Functionalization of Allylic Alcohol 248	190
3.5.1	Toward a 7-Membered Acetal-Derived C Ring.....	191
3.5.2	Acid-Mediated Cyclization of the 7-Membered Acetal Substrate.....	193
3.6.1	Synthesis of a Homologated C Ring Synthon	194
3.6.2	Acid-Mediated Cyclizations of the Homologated A–C Ring System.....	195
3.7.1	Modification of the Homologated A–C Ring System	196
3.7.2	Acid-Mediated Cyclizations of Carboxylic Acid-Derived A–C Ring Systems	196
3.8.1	Mechanistic Hypotheses.....	197
3.8.2	Mechanistic Summary and Substrate Requirements.....	201
3.9.1	Summary of Brønsted Acid Cyclization Efforts	202
3.10.1	Materials and Methods.....	203
3.10.2	Preparation of Compounds	205
	References	240
	Summary Schemes	243

APPENDIX B: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: ACID-MEDIATED

CYCLIZATION APPROACHES TO THE DENSELY SUBSTITUTED CARBOCYCLIC

CORE OF ZOANTHENOL

 248

CHAPTER 4: RADICAL CYCLIZATION APPROACHES TOWARD THE TRICYCLIC CORE OF ZOANTHENOL	366
4.1.1 Introduction	366
4.2.1 Synthesis and Cyclization of a Lactone-Derived Precursor	368
4.3.1 Synthesis and Cyclization of a Homologated Nitrile-Derived Cyclization Precursor	370
4.4.1 Synthesis and Cyclization of a Homologated Ester-Derived Cyclization Precursor	371
4.5.1 Synthesis and Cyclization of a 7-Membered Acetal-Derived Cyclization Precursor	372
4.6.1 Substrate Requirements and Limits of System	373
4.7.1 Summary	376
4.8.1 Materials and Methods.....	377
4.8.2 Preparation of Compounds.....	378
References	389
Summary Schemes	390
APPENDIX C: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: RADICAL CYCLIZATION APPROACHES TOWARD THE TRICYCLIC CORE OF ZOANTHENOL	392
APPENDIX D: CURRENT AND FUTURE INVESTIGATIONS TOWARD ZOANTHENOL	417
D.1 Introduction	417
D.2 Proposed Methods for the Utilization of Tricycle 192	417
D.3.1 Development and Cyclization of a 6-Membered Acetal-Derived A–C Ring System with Inverted C(10) Stereochemistry	419
D.3.2 Advancement of Cyclopentylidene-Derived C Ring Synthons for	

Acid-Mediated Cyclization	421
D.3.3 Advancement of Cyclopentylidene-Derived C Ring for Radical Cyclization	422
D.4.1 Alternative Approaches to the Tricyclic Core of Zoanthenol.....	423
D.4.2 Allylation/Diels-Alder Approach.....	424
D.4.3 α -Arylation Approach.....	427
D.5.1 Precedence for Planned Late-Stage Side Chain Couplings.....	429
D.5.2 Alkyne Addition into Enantiopure Lactam Synthons.....	430
D.5.3 Synthesis of a Horner-Wadsworth-Emmons Reagent for Side Chain Synthesis.....	431
D.6.1 Summary	431
D.7.1 Materials and Methods.....	432
D.7.2 Preparation of Compounds	433
<i>References</i>	454

APPENDIX E: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: CURRENT AND FUTURE

INVESTIGATIONS TOWARD ZOANTHENOL	456
Comprehensive Bibliography	509
Notebook Cross-references.....	518
About the Author.....	527