

TOTAL SYNTHESIS OF CYANTHIWIGIN NATURAL PRODUCTS VIA DOUBLE
ASYMMETRIC CATALYTIC ALKYLATION

AND

INVESTIGATIONS INTO THE NATURE OF DOUBLE ASYMMETRIC PROCESSES

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To my parents

ACKNOWLEDGEMENTS

Though a single thesis is often considered a personal endeavor, it is undeniable that scientific research requires the combined contributions of many different individuals. The work detailed in this thesis is no exception; it would not have been possible without the input, guidance, and support of a great many people.

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ABSTRACT

Since the initial isolation of the cyathane molecules in 1970, considerable synthetic interest has been invested into the preparation of these diterpenoid natural products. Owing to the biological activity and intriguing molecular architecture of these compounds, the members of the cyathane family of natural products have emerged as appealing targets for total synthesis. After a brief summary of the isolation and bioactivity properties of these diterpene compounds, previous synthetic efforts toward these molecules are reviewed.

A concise and versatile approach toward the preparation of the cyanthiwigin family of cyathane natural products is described. By leveraging a unique double asymmetric catalytic alkylation procedure it is possible to quickly establish two of the most critical stereocenters of the cyanthiwigin framework with high levels of selectivity and expediency. The synthesis additionally employs a tandem ring-opening and cross-metathesis reaction, and an aldehyde-olefin radical cyclization process, to rapidly arrive at the tricyclic cyathane core of the cyanthiwigin molecules. From this unifying intermediate, the preparation of cyanthiwigins B, F, and G are attained swiftly and without the need for protecting groups.

The nature of double asymmetric transformations is investigated from a historical, mathematical, and experimental perspective. The initial findings of Langenbeck and Horeau concerning the enantioenriching effects of scalemic duplication are described, with a specific focus on the impact of this phenomenon on total synthesis. A thorough mathematical examination, based on the work of Kagan, is then presented for situations involving double asymmetric transformations of prochiral starting materials. Expressions relating the final quantities of the stereoisomeric products to the intermediary selectivity of each stereoselective process are presented based on these formulae.

Finally, experiments designed to probe the selectivity of each stage of stereoselective bond construction in a double asymmetric process are presented. The compiled results are scrutinized in keeping with the previously derived equations, and these findings are analyzed to understand the nature of the double asymmetric processes in question.

TABLE OF CONTENTS

Dedication	iii
Acknowledgements.....	iv
Abstract	xiii
Table of Contents	xiv
List of Figures	xviii
List of Schemes.....	xxii
List of Tables	xxvi
List of Abbreviations	xxvii

CHAPTER 1

1

Cyathane Diterpenoid Natural Products: Isolation, Activity, and Previous Synthetic Effort

1.1	Introduction	1
1.2	Overview of the Cyathane Diterpenoid Natural Products.....	2
1.2.1	Isolation.....	3
1.2.2	Bioactivity	5
1.2.3	Biosynthesis.....	5
1.3	Previous Synthetic Efforts	6
1.3.1	Strategy Summary.....	7
1.3.2	Cyathane Core Syntheses.....	10
1.3.2.1	Wender's Cyathane Core Synthesis	10
1.3.2.2	Desmaële's Cyathane Core Synthesis	12
1.3.2.3	Takeda's Cyathane Core Synthesis.....	15
1.3.2.4	Sarpong's Cyathane Core Synthesis	16
1.3.3	Cyathane Total Syntheses	18
1.3.3.1	Snider's (±)-Allocyathin B ₂ and (–)-Erinacine A Syntheses.....	18
1.3.3.2	Tori's (±)-Allocyathin B ₂ Synthesis	20
1.3.3.3	Piers' (±)-Sarcadonin G Synthesis	21
1.3.3.4	Ward's (±)-Allocyathin B ₃ Synthesis	23
1.3.3.5	Ward's (+)-Cyathin A ₃ Synthesis	26
1.3.3.6	Nakada's (+)-Allocyathin B ₂ Synthesis	27

1.3.3.7	Nakada's (-)-Erinacine B Synthesis	29
1.3.3.8	Nakada's (-)-Erinacine E Synthesis.....	31
1.3.3.9	Trost's (+)-Allocyathin B ₂ Synthesis	33
1.3.3.10	Danishefsky's (-)-Scabronine G Synthesis	35
1.3.3.11	Phillip's Syntheses of (+)-Cyanthiwigin U, (+)-Cyanthiwigin W, and (-)-Cyanthiwigin Z	37
1.3.3.12	Reddy's (+)-Cyanthiwigin AC Synthesis.....	40
1.3.3.13	Cha's Syntheses of (±)-Cyathin A ₃ and (±)-Cyathin B ₂	42
1.4	Conclusions	44
1.5	Notes and References	45

CHAPTER 2

52

Enantioselective Total Synthesis of Cyanthiwigin Diterpenoids

2.1	Introduction	52
2.1.1	Structure and Synthetic Challenges	52
2.1.2	Biological Activity.....	54
2.1.3	Retrosynthetic Analysis	55
2.2	Forward Synthetic Efforts	57
2.2.1	Double Asymmetric Decarboxylative Allylation	57
2.2.2	Diketone Desymmetrization and Elaboration.....	63
2.2.3	Tricycle Formation via Radical Cyclization.....	70
2.2.4	Completion of the Cyanthiwigin Natural Products.....	74
2.3	Concluding Remarks.....	78
2.4	Experimental Section	80
2.4.1	Materials and Methods.....	80
2.4.2	Preparative Procedures	82
2.5	Notes and References	116

APPENDIX 1

124

Synthetic Summary for Cyanthiwigins B, F, and G

APPENDIX 2	126
Spectra Relevant to Chapter 2	

APPENDIX 3	179
X-Ray Crystallography Reports Relevant to Chapter 2	

CHAPTER 3	188
A Mathematical Examination of Multiple Asymmetric Transformations: Statistical Amplification and the Horeau Principle	

3.1	Introduction	188
3.1.1	Preliminary Results and Initial Interest.....	189
3.2	Duplication and Multiple Asymmetric Processes	191
3.2.1	The History of Statistical Amplification	192
3.2.2	Mathematical Representation of Horeau Duplication	196
3.2.3	Synthetic Applications of the Horeau Duplication	201
3.2.4	Multiple Asymmetric Transformations	205
3.2.5	Synthetic Applications of Multiple Asymmetric Transformations	220
3.3	Experimental Investigation of Multiple Asymmetric Transformations	223
3.4	Conclusion	235
3.5	Experimental Section.....	237
3.5.1	Materials and Methods.	237
3.5.2	Preparative Procedures	239
3.6	Notes and References	253

APPENDIX 4	260
Spectra Relevant to Chapter 3	

APPENDIX 5

275

Notebook Cross-Reference

Comprehensive Bibliography.....278
Index291
About the Author296

LIST OF FIGURES

CHAPTER 1

Figure 1.1	Representative cyathane diterpenoid natural products	2
Figure 1.2	Transition metal and Lewis acid-catalyzed retrosynthetic disconnections toward the cyathane diterpenoid tricyclic core.....	8
Figure 1.3	(A) Alkylation and aldol retrosynthetic disconnections of the cyathane diterpenoid core (B) Reddy's retrosynthetic disconnection of the cyanthiwigin AC core	9

CHAPTER 2

Figure 2.1	The cyanthiwigin diterpenoid molecules	54
Figure 2.2	X-ray crystal structure of tricycle 214	74

APPENDIX 2

Figure A2.1	¹ H NMR (300 MHz, CDCl ₃) of diallyl succinate (187).....	127
Figure A2.2	Infrared spectrum (thin film/NaCl) of diallyl succinate (187)	128
Figure A2.3	¹³ C NMR (75 MHz, CDCl ₃) of diallyl succinate (187)	128
Figure A2.4	¹ H NMR (300 MHz, CDCl ₃) of diallyl succinyl succinate (189).....	129
Figure A2.5	Infrared spectrum (thin film/NaCl) of diallyl succinate (189)	130
Figure A2.6	¹³ C NMR (75 MHz, CDCl ₃) of diallyl succinate (189)	130
Figure A2.7	¹ H NMR (300 MHz, CDCl ₃) of bis(β-ketoester) 186	131
Figure A2.8	Infrared spectrum (thin film/NaCl) of bis(β-ketoester) 186	132
Figure A2.9	¹³ C NMR (75 MHz, CDCl ₃) of bis(β-ketoester) 186	132
Figure A2.10	¹ H NMR (300 MHz, CDCl ₃) of diketone 185	133
Figure A2.11	Infrared spectrum (thin film/NaCl) of diketone 185	134
Figure A2.12	¹³ C NMR (125 MHz, CDCl ₃) of diketone 185	134
Figure A2.13	¹ H NMR (300 MHz, CDCl ₃) of triflate 194	135
Figure A2.14	Infrared spectrum (thin film/NaCl) of triflate 194	136
Figure A2.15	¹³ C NMR (125 MHz, CDCl ₃) of triflate 194	136
Figure A2.16	¹ H NMR (500 MHz, CDCl ₃) of enoate 195	137

Figure A2.17	Infrared spectrum (thin film/NaCl) of enoate 195	138
Figure A2.18	¹³ C NMR (125 MHz, CDCl ₃) of enoate 195	138
Figure A2.19	¹ H NMR (500 MHz, CDCl ₃) of cyclopentadienone 196	139
Figure A2.20	Infrared spectrum (thin film/NaCl) of cyclopentadienone 196	140
Figure A2.21	¹³ C NMR (125 MHz, CDCl ₃) of cyclopentadienone 196	140
Figure A2.22	¹ H NMR (500 MHz, CDCl ₃) of spirocycle 197	141
Figure A2.23	Infrared spectrum (thin film/NaCl) of spirocycle 197	142
Figure A2.24	¹³ C NMR (125 MHz, CDCl ₃) of spirocycle 197	142
Figure A2.25	¹ H NMR (500 MHz, CDCl ₃) of alkyne 198	143
Figure A2.26	Infrared spectrum (thin film/NaCl) of alkyne 198	144
Figure A2.27	¹³ C NMR (125 MHz, CDCl ₃) of alkyne 198	144
Figure A2.28	¹ H NMR (500 MHz, CDCl ₃) of ketone 200	145
Figure A2.29	Infrared spectrum (thin film/NaCl) of ketone 200	146
Figure A2.30	¹³ C NMR (125 MHz, CDCl ₃) of ketone 200	146
Figure A2.31	¹ H NMR (500 MHz, CDCl ₃) of bicyclic enone 204(A)	147
Figure A2.32	Infrared spectrum (thin film/NaCl) of bicyclic enone 204(A)	148
Figure A2.33	¹³ C NMR (125 MHz, CDCl ₃) of bicyclic enone 204(A)	148
Figure A2.34	¹ H NMR (500 MHz, CDCl ₃) of bicyclic enone 204(B)	149
Figure A2.35	Infrared spectrum (thin film/NaCl) of bicyclic enone 204(B)	150
Figure A2.36	¹³ C NMR (125 MHz, CDCl ₃) of bicyclic enone 204(B)	150
Figure A2.37	¹ H NMR (300 MHz, CDCl ₃) of tetraolefin 183	151
Figure A2.38	Infrared spectrum (thin film/NaCl) of tetraolefin 183	152
Figure A2.39	¹³ C NMR (75 MHz, CDCl ₃) of tetraolefin 183	152
Figure A2.40	¹ H NMR (500 MHz, CDCl ₃) of bicyclic ketone 181	153
Figure A2.41	Infrared spectrum (thin film/NaCl) of bicyclic ketone 181	154
Figure A2.42	¹³ C NMR (125 MHz, CDCl ₃) of bicyclic ketone 181	154
Figure A2.43	¹ H NMR (300 MHz, CDCl ₃) of bicyclic aldehyde 208	155
Figure A2.44	Infrared spectrum (thin film/NaCl) of bicyclic aldehyde 208	156
Figure A2.45	¹³ C NMR (75 MHz, CDCl ₃) of bicyclic aldehyde 208	156
Figure A2.46	¹ H NMR (500 MHz, CDCl ₃) of bicyclic enoate 209	157
Figure A2.47	Infrared spectrum (thin film/NaCl) of bicyclic enoate 209	158
Figure A2.48	¹³ C NMR (125 MHz, CDCl ₃) of bicyclic enoate 209	158
Figure A2.49	¹ H NMR (500 MHz, CDCl ₃) of tricyclic diketone 214	159
Figure A2.50	Infrared spectrum (thin film/NaCl) of tricyclic diketone 214	160
Figure A2.51	¹³ C NMR (125 MHz, CDCl ₃) of tricyclic diketone 214	160

Figure A2.52	^1H NMR (500 MHz, C_6D_6) of tricyclic triflate 217	161
Figure A2.53	Infrared spectrum (thin film/ NaCl) of tricyclic triflate 217	162
Figure A2.54	^{13}C NMR (125 MHz, C_6D_6) of tricyclic triflate 217	162
Figure A2.55	^1H NMR (500 MHz, CDCl_3) of cyanthiwigin F (160)	163
Figure A2.56	Infrared spectrum (thin film/ NaCl) of cyanthiwigin F (160).....	164
Figure A2.57	^{13}C NMR (125 MHz, CDCl_3) of cyanthiwigin F (160)	164
Figure A2.58	^1H NMR (500 MHz, CDCl_3) of tricyclic ketone 218	165
Figure A2.59	Infrared spectrum (thin film/ NaCl) of tricyclic ketone 218	166
Figure A2.60	^{13}C NMR (125 MHz, CDCl_3) of tricyclic ketone 218	166
Figure A2.61	^1H NMR (500 MHz, CDCl_3) of tricyclic enone 220	167
Figure A2.62	Infrared spectrum (thin film/ NaCl) of tricyclic enone 220	168
Figure A2.63	^{13}C NMR (125 MHz, CDCl_3) of tricyclic enone 220	168
Figure A2.64	^1H NMR (500 MHz, CDCl_3) of allylic alcohol 221(A)	169
Figure A2.65	Infrared spectrum (thin film/ NaCl) of allylic alcohol 221(A)	170
Figure A2.66	^{13}C NMR (125 MHz, CDCl_3) of allylic alcohol 221(A)	170
Figure A2.67	^1H NMR (500 MHz, CDCl_3) of allylic alcohol 221(B)	171
Figure A2.68	Infrared spectrum (thin film/ NaCl) of allylic alcohol 221(B)	172
Figure A2.69	^{13}C NMR (125 MHz, CDCl_3) of allylic alcohol 221(B)	172
Figure A2.70	^1H NMR (500 MHz, CDCl_3) of cyanthiwigin B (156).....	173
Figure A2.71	Infrared spectrum (thin film/ NaCl) of cyanthiwigin B (156)	174
Figure A2.72	^{13}C NMR (125 MHz, CDCl_3) of cyanthiwigin B (156).....	174
Figure A2.73	^1H NMR (500 MHz, CDCl_3) of 8- <i>epi</i> -cyanthiwigin E (222).....	175
Figure A2.74	Infrared spectrum (thin film/ NaCl) of 8- <i>epi</i> -cyanthiwigin E (222)	176
Figure A2.75	^{13}C NMR (125 MHz, CDCl_3) of 8- <i>epi</i> -cyanthiwigin E (222).....	176
Figure A2.76	^1H NMR (500 MHz, CDCl_3) of cyanthiwigin G (161)	177
Figure A2.77	Infrared spectrum (thin film/ NaCl) of cyanthiwigin G (161).....	178
Figure A2.78	^{13}C NMR (125 MHz, CDCl_3) of cyanthiwigin G (161)	178

APPENDIX 3

Figure A3.1	ORTEP drawing of tricyclic diketone 214 (shown with 50% probability ellipsoids)	179
Figure A3.2	Tricyclic diketone 214 (CCDC 664430).....	182

CHAPTER 3

Figure 3.1	A graphical representation of the impact of Horeau duplication.....	200
Figure 3.2	(A) Product <i>ee</i> plotted as a function of r_1 and r_2 selectivity factors (B) Product <i>de</i> plotted as a function of r_1 and r_2 selectivity factors (C) Product <i>ee</i> and <i>de</i> plotted as a function of r_1 and r_2 selectivity factors	216

APPENDIX 4

Figure A4.1	^1H NMR (500 MHz, CDCl_3) of carbonate 281	261
Figure A4.2	Infrared spectrum (thin film/ NaCl) of carbonate 281	262
Figure A4.3	^{13}C NMR (125 MHz, CDCl_3) of carbonate 281	262
Figure A4.4	^1H NMR (500 MHz, CDCl_3) of allyl ketone 282	263
Figure A4.5	Infrared spectrum (thin film/ NaCl) of allyl ketone 282	264
Figure A4.6	^{13}C NMR (125 MHz, CDCl_3) of allyl ketone 282	264
Figure A4.7	^1H NMR (500 MHz, CDCl_3) of β -ketoester 287(A)	265
Figure A4.8	Infrared spectrum (thin film/ NaCl) of β -ketoester 287(A)	266
Figure A4.9	^{13}C NMR (125 MHz, CDCl_3) of β -ketoester 287(A)	266
Figure A4.10	^1H NMR (500 MHz, CDCl_3) of β -ketoester 287(B)	267
Figure A4.11	Infrared spectrum (thin film/ NaCl) of β -ketoester 287(B)	268
Figure A4.12	^{13}C NMR (125 MHz, CDCl_3) of β -ketoester 287(B)	268
Figure A4.13	^1H NMR (500 MHz, CDCl_3) of carbonate ester 288	269
Figure A4.14	Infrared spectrum (thin film/ NaCl) of carbonate ester 288	270
Figure A4.15	^{13}C NMR (125 MHz, CDCl_3) of carbonate ester 288	270
Figure A4.16	^1H NMR (500 MHz, CDCl_3) of carbonate ester 290	271
Figure A4.17	Infrared spectrum (thin film/ NaCl) of carbonate ester 290	272
Figure A4.18	^{13}C NMR (125 MHz, CDCl_3) of carbonate ester 290	272
Figure A4.16	^1H NMR (500 MHz, CDCl_3) of diallyl cyclohexanone 289	273
Figure A4.17	Infrared spectrum (thin film/ NaCl) of diallyl cyclohexanone 289	274
Figure A4.18	^{13}C NMR (125 MHz, CDCl_3) of diallyl cyclohexanone 289	274

LIST OF SCHEMES

CHAPTER 1

Scheme 1.1	Biosynthesis of the cyathane core tricycle from geranylgeranyl phosphate.....	6
Scheme 1.2	Preparation of the critical [5 + 2] cycloaddition precursor.....	11
Scheme 1.3	Wender's [5 + 2] cycloaddition reaction to construct the cyathane core tricycle.....	12
Scheme 1.4	Synthesis of Desmaële's alkyl iodide coupling partner.....	13
Scheme 1.5	Preparation of the crucial Heck cyclization precursor.....	13
Scheme 1.6	Heck cyclization and aluminum-promoted ring-expansion reactions to target the cyathane tricycle.....	14
Scheme 1.7	Takada's key [4 + 3] annulation to target the C-ring of the cyathane core.....	15
Scheme 1.8	Advancement of Takeda's cyathane core structure.....	16
Scheme 1.9	Sarpong's parallel kinetic resolution method for divergent cyathane tricycle construction.....	17
Scheme 1.10	Snider's carbonyl-ene strategy toward the cyathane tricycle.....	19
Scheme 1.11	Completion of (±)-allocyathin B ₂ and glycosylation to achieve (-)-erinacine A.....	20
Scheme 1.12	Tori's strategy toward allocyathin B ₂	21
Scheme 1.13	Tori's ring-closing strategy toward construction of the seven-membered C-ring and completion of the cyathane core.....	21
Scheme 1.14	Vinyl iodide construction in Pier's sarcodonin synthesis.....	22
Scheme 1.15	Still-Mitra [2,3] sigmatropic rearrangement to construct the A-ring of sarcodonin G.....	22
Scheme 1.16	Ring expansion and endgame for sarcodonin G.....	23
Scheme 1.17	Ward's cycloaddition strategy toward tricycle formation.....	24
Scheme 1.18	Ring expansion via ozonolysis and aldol reaction to target the cyathane core.....	24
Scheme 1.19	Ward's allocyathin endgame strategy.....	25
Scheme 1.20	Catalytic enantioselective Diels-Alder approach to intermediates 29 and 87	26
Scheme 1.21	Endgame synthesis for cyathin A ₃ (TTBP = 2,6-di(<i>tert</i> -butyl)-4-methylpyridine).....	27
Scheme 1.22	Fragment coupling to prepare the aldol precursor.....	28
Scheme 1.23	Intramolecular aldol reaction and ring expansion to complete the total synthesis of allocyathin B ₂	28

Scheme 1.24	Adaptation of Nakada's allocyathin B ₂ route to erinacine B	30
Scheme 1.25	Establishing the desired stereochemistry at C(14)	30
Scheme 1.26	Completion of (–)-erinacine B	31
Scheme 1.27	Synthesis of 117 from allocyathin precursor 110 via conjugate addition-elimination	32
Scheme 1.28	Intramolecular aldol reaction for Nakada's endgame of (–)-erinacine E.....	32
Scheme 1.29	Asymmetric allylic alkylation to establish stereochemistry at C(9)	33
Scheme 1.30	Ru-catalyzed cycloisomerization to establish the central B-ring of allocyathin B ₂	34
Scheme 1.31	Diastereoselectivity considerations in the Ru-catalyzed cycloisomerization.....	34
Scheme 1.32	Completion of allocyathin B ₂ via hydroxylative Knoevenagel and intramolecular aldol reactions.....	35
Scheme 1.33	Danishefsky's Nazarov strategy for cyathane A-ring construction	36
Scheme 1.34	Advancement toward Danishefsky's ring-expansion precursor	36
Scheme 1.35	Ring expansion and endgame to complete (–)-scabronine G	37
Scheme 1.36	Auxiliary-mediated Diels–Alder reaction to establish the quaternary stereocenters of the natural product.....	38
Scheme 1.37	Completion of cyanthiwigin U via ring-opening ring-closing metathesis.....	38
Scheme 1.38	Preparation of cyanthiwigin W and cyanthiwigin Z from cyanthiwigin U	39
Scheme 1.39	Spiro-annulation of Hajos–Parrish ketone derivative 30	40
Scheme 1.40	Further oxidation and transformation toward cyanthiwigin AC.....	41
Scheme 1.41	Endgame of cyanthiwigin AC	41
Scheme 1.42	Cha's spirocyclic approach to cyathin A ₃ and cyathin B ₂	43
Scheme 1.43	Cha's endgame for cyathin B ₂ and elaboration to attain cyathin A ₃	43

CHAPTER 2

Scheme 2.1	Retrosynthetic analysis of cyanthiwigin F	56
Scheme 2.2	Preparation of the bis(β-ketoester) substrate for allylation	58
Scheme 2.3	Paths of the double asymmetric decarboxylative catalytic alkylation.....	60
Scheme 2.4	Double asymmetric decarboxylative catalytic alkylation of 186	62
Scheme 2.5	Attempts toward diketone functionalization	64
Scheme 2.6	(A) Triflate formation and carboxylative attempts toward diketone elaboration (B) An unanticipated carbonylative Heck reaction, and subsequent dimerization	66

Scheme 2.7	Palladium-catalyzed cross-coupling reactions of triflate 194	66
Scheme 2.8	Ring-closing metathesis and acid hydrolysis of enol ether 202	68
Scheme 2.9	Negishi cross-coupling for the formation of an sp ² -sp ³ carbon-carbon bond	69
Scheme 2.10	Functionalization of the C(2)-C(3) olefin via olefin cross-metathesis.....	69
Scheme 2.11	Ring-closing and cross-metathesis reaction to generate bicyclic aldehyde 208	70
Scheme 2.12	Initial attempts at radical cyclization for A-ring formation.....	71
Scheme 2.13	Radical cyclization conditions developed by Tomioka and coworkers.....	72
Scheme 2.14	Application of Tomioka's methodology to A-ring formation	72
Scheme 2.15	Mechanistic hypothesis and stereochemical rationale for radical cyclization of 214	73
Scheme 2.16	Advancement of tricycle 214 toward additional cyanthiwigin natural products.....	77
Scheme 2.17	Completion of cyanthiwiggins B and G	78

APPENDIX 1

Scheme A1.1	Synthesis of tricyclic diketone 214	125
Scheme A1.2	Synthesis of cyanthiwigin F (160).....	125
Scheme A1.3	Synthesis of cyanthiwiggins B (156) and G (161).....	125

CHAPTER 3

Scheme 3.1	Double asymmetric catalytic alkylation	190
Scheme 3.2	Double asymmetric catalytic alkylation of an enol carbonate ester substrate	191
Scheme 3.3	(A) Lagenbeck's initial experiment (B) Curves depicting the optical rotation of samples of (I) L-225 and (II) 227 vs. enantioenrichment of L-menthol starting material	193
Scheme 3.4	Product pathways for Langenbeck's duplication experiment.....	194
Scheme 3.5	Duplication of <i>sec</i> -phenethyl alcohol by Horeau	196
Scheme 3.6	(A) Reaction pathways for Horeau-type dimerization (B) Mathematical representations of relevant stereoisomeric quantities	198
Scheme 3.7	Initial steps toward Mori's synthesis of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane	201

Scheme 3.8	Horeau duplication in Mori's bee hormone synthesis	202
Scheme 3.9	Corey's total synthesis of (-)-wodeshiol via Horeau-type duplication	204
Scheme 3.10	Pathways for double asymmetric transformation, route 1	207
Scheme 3.11	Pathways for double asymmetric transformation, route 2	209
Scheme 3.12	Double asymmetric transformation via two variable simplification.....	213
Scheme 3.13	Double asymmetric transformation where $r_1 = 1.0$ and $r_2 = 0$	217
Scheme 3.14	Double asymmetric transformation where $r_1 = 0$ and $r_2 = 1.0$	218
Scheme 3.15	Double asymmetric catalytic transformation toward quadrigemine C.....	221
Scheme 3.16	Total synthesis of glabrescol by Corey	222
Scheme 3.17	Total synthesis of omaezakinol by Corey	223
Scheme 3.18	Examples of double asymmetric catalytic alkylation	224
Scheme 3.19	(A) Schematic representation of intermediates in the double asymmetric alkylation of substrate 186 (B) Schematic representation of intermediates in the double asymmetric alkylation of substrate (\pm)- 223	225
Scheme 3.20	(A) Alkylation of racemic enol carbonate (\pm)- 281 (B) Mathematical treatment of alkylation of 281	226
Scheme 3.21	Asymmetric alkylation of an enantioenriched substrate.....	229
Scheme 3.22	Substrates for double asymmetric catalytic alkylation studies	231
Scheme 3.23	Stereochemical course of double alkylation for a differentially substituted carbonate.....	232
Scheme 3.24	Averaged selectivity values for double asymmetric catalytic alkylation	234
Scheme 3.25	Experiment proposed for further investigation of double asymmetric alkylation	235

LIST OF TABLES

CHAPTER 2

Table 2.1	Transition metal cross-coupling attempts toward cyanthiwigin F.....	76
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APPENDIX 3

Table A3.1	Crystal data and structure refinement for tricyclic diketone 214 (CCDC 664430).....	180
Table A3.2	Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for diketone 214 (CCDC 664430). $U(\text{eq})$ is defined as the trace of the orthogonalized U^{ij} tensor	183
Table A3.3	Bond lengths [\AA] and angles [$^\circ$] for diketone 214 (CCDC 664430).....	184
Table A3.4	Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for diketone 214 (CCDC 664430). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^* 2 U^{11} + \dots + 2 h k a^* b^* U^{12}]$	186
Table A3.5	Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for diketone 214 (CCDC 664430)	187

CHAPTER 3

Table 3.1	Stereochemical summary of Mori's synthetic efforts.....	203
Table 3.2	Selected examples of r_1 and r_2 values, and their impact on <i>ee</i> and <i>de</i>	219
Table 3.3	Study on the effect of a pre-existing stereocenter upon asymmetric alkylation.....	228

APPENDIX 5

Table A5.1	Compounds in Chapter 2 – Enantioselective Total Synthesis of Cyanthiwigin Diterpenoids.....	276
Table A5.2	Compounds in Chapter 3 – A Mathematical Examination of Multiple Asymmetric Transformations: Statistical Amplification and the Horeau Principle	277

LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
<i>aq</i>	aqueous
Ar	aryl group
atm	atmosphere(s)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl or <i>norm</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bn	benzyl
Bz	benzoyl
<i>c</i>	concentration of sample for measurement of optical rotation
¹³ C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius

calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: <i>confer</i>)
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
CSA	camphor sulfonic acid
d	doublet
D	dextrorotatory
dba	dibenzylideneacetone
pmdba	bis(4-methoxybenzylidene)acetone
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
<i>de</i>	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane

DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
<i>ee</i>	enantiomeric excess
<i>E</i>	trans (entgegen) olefin geometry
EC ₅₀	median effective concentration (50%)
e.g.	for example (Latin: <i>exempli gratia</i>)
EI	electron impact
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	and others (Latin: <i>et alii</i>)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
¹ H	proton
² H	deuterium
³ H	tritium
[H]	reduction
HMDS	hexamethyldisilamide or hexamethyldisilazide
<i>hν</i>	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	hertz
IC ₅₀	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: <i>id est</i>)
IR	infrared spectroscopy
<i>J</i>	coupling constant
<i>k</i>	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
L	levorotatory
LA	Lewis acid
LD ₅₀	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)

mL	milliliter(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/z	mass-to-charge ratio
N	normal or molar
NBS	<i>N</i> -bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
<i>o</i>	ortho
[O]	oxidation
<i>p</i>	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million

PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl
<i>n</i> -Pr	propyl or <i>norm</i> -propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
<i>R</i>	rectus
<i>r</i>	selectivity = [major stereoisomer – minor stereoisomer]/[major stereoisomer + minor stereoisomer]
ref	reference
<i>R_f</i>	retention factor
s	singlet or seconds
<i>s</i>	selectivity factor = $k_{\text{rel}(\text{fast/slow})} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where <i>C</i> = conversion
<i>S</i>	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl

temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
t_r	retention time
Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry