

*Edited by Krishna C. Majumdar
and Shital K. Chattopadhyay*

Heterocycles in Natural Product Synthesis



WILEY-VCH Verlag GmbH & Co. KGaA

Contents

Preface XV
List of Contributors XVII

Part One Strained Heterocycles in the Synthesis of Natural Products 1

1	Aziridines in Natural Product Synthesis 3
	<i>Candice Botuha, Fabrice Chemla, Franck Ferreira and Alejandro Pérez-Luna</i>
1.1	Introduction 3
1.2	Synthesis of Natural Products Containing Aziridine Units 3
1.2.1	Synthesis of Aziridine-2,3-Dicarboxylic Acid 3
1.2.2	Synthesis of (Z)-Dysidazirine 5
1.2.3	Syntheses of Mitomycins 5
1.2.4	Syntheses of FR-900482 and FR-66979 8
1.3	Synthesis of Natural Products Involving the Transformation of an Aziridine Moiety 10
1.3.1	Nucleophilic Ring-Opening of Aziridines for Natural Product Synthesis 10
1.3.1.1	Carbon-Centered Nucleophiles 11
1.3.1.2	Nitrogen-Centered Nucleophiles 15
1.3.1.3	Oxygen-Centered Nucleophiles 18
1.3.1.4	Halogen Nucleophiles 24
1.3.1.5	Reductions 25
1.3.2	Cycloaddition Reactions and Rearrangements 25
1.3.2.1	Aziridines in [3 + 2] Cycloadditions 26
1.3.2.2	Aziridines in [2,3]-Wittig Rearrangements 27
1.3.2.3	Aziridines in Iodide-Mediated Rearrangements 27
1.3.2.4	Aziridines in Miscellaneous Rearrangements 28
1.3.3	Synthesis of Natural Products Involving the Transformation of an Aziridinium Moiety 31

1.4	Conclusion	32
	References	33
2	Azetidine and Its Derivatives	41
	<i>Hidemi Yoda, Masaki Takahashi and Tetsuya Sengoku</i>	
2.1	Introduction	41
2.2	Structural Description of Azetidines	41
2.3	Synthetic Methodologies for the Formation of Azetidine Rings	43
2.4	Synthesis of Mugineic Acids	44
2.5	Synthesis of Penaresidins	46
2.6	Structural Description of Azetidin-2-ones	50
2.7	Synthetic Methodologies for the Formation of Azetidin-2-ones	50
2.8	Synthesis of Penicillin	52
2.9	Synthesis of Cephalosporin	54
2.10	Conclusion	56
	Acknowledgment	56
	References	57
3	Epoxides and Oxetanes	63
	<i>Biswanath Das and Kongara Damodar</i>	
3.1	Introduction	63
3.2	Epoxides in Natural Product Synthesis	63
3.2.1	Synthesis of Natural Products Possessing an Epoxide Moiety	68
3.2.1.1	Synthesis of (–)-Posticlure	68
3.2.1.2	Synthesis of Natural Polyethers	68
3.2.1.3	Synthesis of (+)-11,12-Epoxyxsarcophytol A	68
3.2.1.4	Synthesis of (–)-Scyphostatine	68
3.2.1.5	Synthesis of Arenastatin A	70
3.2.1.6	Synthesis of (+)-Ambuic Acid	70
3.2.1.7	Total Synthesis of Epocarbazolin A	71
3.2.1.8	Synthesis of Multiploidine A	71
3.2.2	Synthesis of Natural Products Involving the Transformation of the Epoxide Moiety	71
3.2.2.1	Synthesis of Dodoneine	71
3.2.2.2	Synthesis of (–)-Pericosin B	73
3.2.2.3	Synthesis of (–)-Peucedanol	73
3.2.2.4	Synthesis of (+)-Bourgeanic Acid	74
3.2.2.5	Synthesis of (6S)-5,6-Dihydro-6([2R]-2-Hydroxy-6-Phenylhexyl)-2H-Pyran-2-one	74
3.2.2.6	Synthesis of Verbalactone	74
3.2.2.7	Synthesis of (2S, 3S)-(+)-Aziridine-2,3-Dicarboxylic Acid	75
3.2.2.8	Synthesis of D- <i>erythro</i> -Sphingosine	75
3.2.2.9	Synthesis of (+)-L-733,060	76
3.2.2.10	Synthesis of (+)-Chelidonine	76
3.2.2.11	Synthesis of (–)-Pironetin	76

3.2.2.12	Synthesis of (–)-Codonopsinine	77
3.2.2.13	Synthesis of Sesamin and Dihydrosesamin	77
3.2.2.14	Synthesis of (9S, 12R, 13S)-Pinellic Acid	78
3.2.2.15	Synthesis of (Z)-Nonenolide	78
3.2.2.16	Synthesis of (–)-Cubebol	79
3.2.2.17	Synthesis of (+)-Schweinfurthins B and E	79
3.2.2.18	Synthesis of (–)-Cleistenolide	80
3.2.2.19	Synthesis of Decarestricine J	80
3.2.2.20	Synthesis of (–)-Gloeosporone	82
3.2.2.21	Synthesis of (S)-Dihydrokavain	82
3.2.2.22	Synthesis of (–)-Phorocantholide-J	83
3.3	Oxetane in Natural Product Synthesis	85
3.3.1	Synthesis of Natural Products Possessing an Oxetane Moiety	85
3.3.1.1	Synthesis of Epi-oxetin	85
3.3.1.2	Synthesis of Dioxatricyclic Segment of Dictyoxetane	86
3.3.1.3	Synthesis of (–)-Merrilactone A	86
3.3.1.4	Total Synthesis of (+)-(Z)-Laureatin	87
3.3.1.5	Synthesis of Taxol	87
3.3.2	Synthesis of Natural Products Involving Transformation of the Oxetane Moiety	88
3.3.2.1	Synthesis of Erogorgiaene	88
3.3.2.2	Synthesis of <i>trans</i> -Whiskey Lactone	88
3.3.2.3	Synthesis of (\pm)-Sarracenin	89
3.4	Conclusion	89
	Acknowledgment	90
	References	90

Part Two Common Ring Heterocycles in Natural Product Synthesis 97

4	Furan and Its Derivatives	99
	<i>Alicia Boto and Laura Alvarez</i>	
4.1	Introduction	99
4.2	Natural Products Containing the Furan Ring	100
4.2.1	Occurrence of Furan Rings in Natural Products	100
4.2.2	Synthesis of Furans in Natural Products	104
4.3	Furan Derivatives as Reagents in the Synthesis of Natural Products	106
4.3.1	Metallation	107
4.3.2	Reduction and Oxidation	111
4.3.3	Furan Derivatives as Electrophiles and Nucleophiles	118
4.3.4	Furan in Cycloadditions	124
4.3.4.1	[2 + 1], [2 + 2] and [3 + 2] Cycloadditions	124
4.3.4.2	Diels–Alder ([4 + 2] Cycloadditions)	127

4.3.4.3	[4 + 3], [6 + 4], [8 + 2] and [5 + 2] Cycloadditions	133
4.3.5	Furan in Other Reactions	136
4.3.6	Other Uses of Furan in Synthesis	138
4.4	Summary	139
	References	140
5	Pyran and Its Derivatives	153
	<i>Hideto Miyabe, Okiko Miyata and Takeaki Naito</i>	
5.1	Introduction	153
5.2	Application of Pyran Moieties in the Synthesis of Natural Products	158
5.2.1	2,6-Disubstituted Pyran Natural Products	158
5.2.2	2,6-Cyclic Pyran Compounds	161
5.2.3	Complex Pyran Natural Products	165
5.2.4	Fused Pyran Compounds with Aromatic Rings	168
5.2.5	Fused Pyran Compounds with Aliphatic Rings	171
5.3	Conclusion	176
	References	176
6	Pyrrole and Its Derivatives	187
	<i>Dipakranjan Mal, Brateen Shome and Bidyut Kumar Dinda</i>	
6.1	Introduction	187
6.2	Synthesis of Pyrrole Natural Products	193
6.2.1	Monopyrrolic Natural Products	193
6.2.2	Dipyrrolic Natural Products	203
6.2.3	Tripyrrolic Natural Products: Prodigiosins	205
6.3	Synthesis of Non-pyrrole Natural Products from Pyrrole Derivatives	209
6.4	Conclusion	214
	Acknowledgments	214
	References	215
7	Indoles and Indolizidines	221
	<i>Sarah M. Bronner, G.-Yoon J. Im and Neil K. Garg</i>	
7.1	Introduction	221
7.2	Applications of Indoles and Indolizidines in the Synthesis of Natural Products	222
7.2.1	Indoles and Oxindoles	222
7.2.1.1	Total Synthesis of Actinophyllic Acid (Overman)	222
7.2.1.2	Total Synthesis of Dragmacidin F (Stoltz)	226
7.2.1.3	Total Synthesis of Penitrem D (Smith)	230
7.2.1.4	Total Synthesis of Welwitindolinone A Isonitrile (Baran, Wood)	232
7.2.2	Indolines	237
7.2.2.1	Total Synthesis of 11,11'-Dideoxyverticillin A (Movassaghi)	237

7.2.2.2	Total Synthesis of Minfiensine (Overman, Qin, MacMillan)	240
7.2.2.3	Total Synthesis of Norfluorocurarine (Vanderwal)	245
7.2.2.4	Total Synthesis of Psychotrimine (Baran)	247
7.2.3	Indolizidines	249
7.2.3.1	Total Synthesis of Myrmicarins 215A, 215B and 217 (Movassaghi)	249
7.2.3.2	Total Synthesis of Serratezomine A (Johnston)	252
7.3	Conclusion	254
	Acknowledgment	254
	References	254
8	Pyridine and Its Derivatives	267
	<i>Paula Kiuru and Jari Yli-Kauhaluoma</i>	
8.1	Introduction	267
8.2	Application of the Pyridine Moiety in the Synthesis of Natural Products	268
8.2.1	Pyridines	268
8.2.1.1	Synthesis of Noranabasamine Enantiomers	268
8.2.1.2	Synthesis of Quaterpyridine Nemertelline	268
8.2.1.3	Synthesis of Caerulomycin C	276
8.2.1.4	Synthesis of the Spongidine Isomer	277
8.2.2	2-Alkylpyridines	278
8.2.2.1	Synthesis of Montipyridine	278
8.2.2.2	Synthesis of Piericidin A1	278
8.2.3	3-Alkylpyridine, 3-Alkylpyridinium and 3-Alkyltetrahydropyridine Compounds	281
8.2.3.1	Synthesis of Xestamines	281
8.2.3.2	Synthesis of Pyrinadine A	282
8.2.3.3	Synthesis of Pyrinodemin A	282
8.2.3.4	Synthesis of Haliclamine A	284
8.2.4	Piperidines	285
8.2.4.1	Synthesis of Coniine and Pipecoline	285
8.2.4.2	Synthesis of Stenusine	286
8.2.5	Pyridones	287
8.2.5.1	Synthesis of (\pm)-Cytisine	287
8.2.5.2	Synthesis of Iromycin A	288
8.3	Conclusion	289
	Acknowledgment	289
	References	290
9	Quinolines and Isoquinolines	299
	<i>Antonio Garrido Montalban</i>	
9.1	Introduction	299
9.2	Application of Quinolines and Isoquinolines in the Synthesis of Natural Products	300

9.2.1	Quinoline-Containing Natural Products	308
9.2.1.1	Quinine	308
9.2.1.2	Sandramycin	311
9.2.1.3	Lavendamycin	313
9.2.2	Isoquinoline-Containing Natural Products	317
9.2.2.1	Morphine	317
9.2.2.2	Emetine	320
9.2.2.3	Protoberberines	326
9.2.2.4	Nitidine	331
9.3	Conclusion	332
	References	332
10	Carbazoles and Acridines	341
	<i>Konstanze K. Gruner and Hans-Joachim Knölker</i>	
10.1	Introduction to Carbazoles	341
10.2	Total Synthesis of Carbazole Alkaloids	341
10.2.1	Palladium-Catalyzed Synthesis of Carbazoles	350
10.2.1.1	Total Synthesis of Pityriazole	350
10.2.1.2	Total Synthesis of Euchrestifoline and Girinimbine	351
10.2.2	Iron-Mediated Synthesis of Carbazoles	353
10.2.2.1	Total Syntheses of the Antostatins	353
10.2.2.2	Total Synthesis of <i>R</i> -(-)-Neocarazostatin B and Carquinostatin A	355
10.2.3	Total Syntheses of Ellipticine and Staurosporinone	356
10.2.3.1	Synthesis of Ellipticine	356
10.2.3.2	Synthesis of Staurosporinone	357
10.3	Introduction to Acridines	358
10.4	Synthesis of Acridines and Acridores	361
10.4.1	Total Synthesis of Acronycine	361
10.4.2	Synthesis of Amsacrine	362
10.4.3	Total Syntheses of Amphimedine	362
	References	364
11	Thiophene and Other Sulfur Heterocycles	377
	<i>Krishna C. Majumdar and Shovan Mondal</i>	
11.1	Introduction	377
11.2	Synthesis of Natural Products Containing Thiophene	378
11.2.1	Synthesis of Natural Products from Thiophene-Based Substrates	378
11.2.2	Synthesis of Natural Products by Construction of the Thiophene Nucleus	386
11.3	Synthesis of Natural Products Containing Other Sulfur Heterocycles	393
11.4	Conclusion	395
	Acknowledgments	396
	References	397

12	Oxazole and Its Derivatives	403
	<i>David W. Knight</i>	
12.1	Introduction	403
12.2	Mono-Oxazoles	404
12.2.1	Pimprinin	404
12.2.2	Texamine and Relatives	405
12.2.3	Synthesis of Sulfomycin Fragments	406
12.2.4	Ajudazol A and B	408
12.2.5	Rhizoxin	409
12.2.6	The Calyculins	410
12.2.7	Leucascandrolide A, B and Neopeltolide	413
12.2.8	Chivosazole	416
12.2.9	Madumycin II	416
12.2.10	14,15-Anhydropristinamycin II _B	418
12.2.11	Griseoviridin	418
12.2.12	Thiangazole	419
12.3	Unconnected Bis- and Tris-Oxazoles	420
12.3.1	Disorazole C ₁	420
12.3.2	Phorboxazoles	421
12.3.3	Leucamide A	424
12.3.4	Promothiocin A	425
12.3.5	Berninamycin A	425
12.4	Cyclic Polyheterocyclic Metabolites Containing Single Oxazole Residues	426
12.4.1	Dendroamide A	426
12.4.2	Nostocyclamide	427
12.4.3	Bistratamides	428
12.4.4	Tenuecyclamides A-D	428
12.4.5	Dolastatin I	429
12.5	Conjugated Bis-Oxazoles	429
12.5.1	(-)Hennoxazole A	429
12.5.2	Muscoride A	432
12.5.3	Diazonamide A	433
12.5.4	Bengazole A	437
12.5.5	Siphonazole	439
12.6	Tris- and Poly-Oxazoles	440
12.6.1	Ulapualide A	440
12.6.2	(R)-Telomestatin	443
12.6.3	IB-01211	445
12.6.4	YM-216391	445
	References	446
13	Thiazoline and Thiazole and Their Derivatives	459
	<i>Zhengshuang Xu and Tao Ye</i>	
13.1	Introduction	459

13.2	General Methods for the Synthesis of Thiazoline and Thiazole Derivatives	460
13.2.1	Methods for the Preparation of Thiazolines	460
13.2.1.1	Using Vicinal Amino Thiols as Starting Materials	461
13.2.1.2	From Vicinal Amino Alcohol	468
13.2.1.3	Miscellaneous	473
13.2.2	Methods for Preparation of Thiazoles	474
13.2.2.1	Dehydrogenation of Thiazolines or Thiazolidines	474
13.2.2.2	The Hantzsch Method and Its Modifications	479
13.2.2.3	Alkylation of Thiazole or Thiazole Derivatives	483
13.2.2.4	Miscellaneous	483
13.3	Thiazole and Thiazoline-Containing Natural Products	485
13.3.1	Thiazoline and Thiazole Embedded in Polyketides	485
13.3.2	Thiazoline and Thiazole Embedded in Peptides	491
13.4	Conclusions	494
	References	494
14	Pyrimidine and Imidazole	507
	<i>Vipan Kumar and Mohinder P. Mahajan</i>	
14.1	General Introduction	507
14.2	Pyrimidine-Based Natural Products	507
14.2.1	Introduction	507
14.2.2	Synthesis of Pyrimidine-Based Natural Products	508
14.3	Imidazole-Based Natural Products	518
14.3.1	Introduction	518
14.3.2	Synthesis of Imidazole-Based Natural Products	520
14.4	Conclusion	527
	Acknowledgment	528
	References	529

Part Three Natural Products Containing Medium and Large Ring-Sized Heterocyclic Systems 535

15	Oxepines and Azepines	537
	<i>Darren L. Riley and Willem A.L. van Otterlo</i>	
15.1	Introduction	537
15.2	Synthesis of the Heterocyclic Core of Selected Natural Products Containing Oxepines	538
15.3	Synthesis of the Heterocyclic Core of Selected Natural Products Containing Azepines	549
15.4	Synthesis of the Heterocyclic Core of Selected Natural Products Containing Oxazapines	559
15.5	Conclusion	561

Acknowledgments	562
References	562
16 Bioactive Macroyclic Natural Products	569
<i>Siti Mariam Mohd Nor, Zhengshuang Xu and Tao Ye</i>	
16.1 General	569
16.2 Natural Products Containing Azoles	569
16.2.1 Apratoxin A	569
16.2.2 Halipeptins A and D	572
16.2.3 Largazole	573
16.2.4 Bistratamide H and Didmolamide A	575
16.2.5 IB-01211	576
16.2.6 (R)-Telomestatin	578
16.3 Pyridine- and Piperidine-Containing Natural Products	581
16.3.1 Micrococcin P1	581
16.3.2 GE2270s	584
16.4 Indole- and Imidazole-Containing Natural Products	587
16.4.1 Celogentin C	587
16.4.2 Complestatin (Chloropeptin II)	589
16.5 Pyran- and Furan-Containing Natural Products	590
16.5.1 Phorboxazole B	590
16.5.2 Sorangicin A	592
16.5.3 Kendomycin	594
16.5.4 Bryostatin 16	597
16.5.5 IKD-8344	598
16.5.6 Deoxypukalide	599
16.5.7 Norhalichondrin B	601
16.6 Piperazic Acid-Containing Natural Products	605
16.6.1 Piperazimycin A	605
16.6.2 Azinothricin and Kettapeptin	607
16.7 Mixed Heterocyclic Systems	608
16.7.1 (–)-Nakadomarin A	608
16.8 Conclusions	610
References	611