CONTENTS

LIST OF CONTRIBUTORS PREFACE		
		1
1.1.1 1.1.2 1.1.3 1.1.4 1.1.5 .2 From I Product 1.2.1 1.2.2 1.2.3 1.2.4	Definitions, 1 Energy Supply and Carbon Storing at the Early Stage of Metabolisms, 1 Glucose as a Starting Material Toward Key Building Blocks of the Secondary Metabolism, 1 Reactions Involved in the Construction of Secondary Metabolites, Secondary Metabolisms, 4 Biosynthesis to Total Synthesis: Strategies Toward the Natural et Chemical Space, 10 The Chemical Space of Natural Products, 10 The Biosynthetic Pathways as an Inspiration for Synthetic Challenges, 11 The Science of Total Synthesis, 14 Conclusion: A Journey in the Future of Total Synthesis, 16	3
TION I	ACETATE BIOSYNTHETIC PATHWAY	19
Françoise Scr Erica Benede 2.1 Polyko 2.1.1 2.1.2 2.1.3 2.1.4	haefers, Tobias A. M. Gulder, Cyril Bressy, Michael Smietana, tti, Stellios Arseniyadis, Markus Kalesse, and Martin Cordes etide Biosynthesis, 21 Introduction, 21 Assembly of Acetate/Malonate-Derived Metabolites, 23 Classification of Polyketide Biosynthetic Machineries, 23 Conclusion, 39	21
	rom Biosynastien Nay a 1 From F 1.1.1 1.1.2 1.1.3 1.1.4 1.1.5 .2 From I Product 1.2.1 1.2.2 1.2.3 1.2.4 References, TION I Polyketides Erica Benede 2.1 Polyke 2.1.1 2.1.2 2.1.3 2.1.4	rom Biosyntheses to Total Syntheses: An Introduction astien Nay and Xu-Wen Li 1. From Primary to Secondary Metabolism: The Key Building Blocks, 1 1.1.1 Definitions, 1 1.1.2 Energy Supply and Carbon Storing at the Early Stage of Metabolisms, 1 1.1.3 Glucose as a Starting Material Toward Key Building Blocks of the Secondary Metabolism, 1 1.1.4 Reactions Involved in the Construction of Secondary Metabolites, 1.1.5 Secondary Metabolisms, 4 2. From Biosynthesis to Total Synthesis: Strategies Toward the Natural Product Chemical Space, 10 1.2.1 The Chemical Space of Natural Products, 10 1.2.2 The Biosynthetic Pathways as an Inspiration for Synthetic Challenges, 11 1.2.3 The Science of Total Synthesis, 14 1.2.4 Conclusion: A Journey in the Future of Total Synthesis, 16 References, 16 TION I ACETATE BIOSYNTHETIC PATHWAY Polyketides Prançoise Schaefers, Tobias A. M. Gulder, Cyril Bressy, Michael Smietana, Prica Benedetti, Stellios Arseniyadis, Markus Kalesse, and Martin Cordes 2.1 Polyketide Biosynthesis, 21 2.1.1 Introduction, 21 2.1.2 Assembly of Acetate/Malonate-Derived Metabolites, 23 2.1.3 Classification of Polyketide Biosynthetic Machineries, 23

	2.2	Synthe 2.2.1 2.2.2	esis of Polyketides, 44 Asymmetric Alkylation Reactions, 44 Applications of Asymmetric Alkylation Reactions in Total Synthesis of Polyketides and Macrolides, 60	;
	Dafa	erences.		
	2.3		esis of Polyketides-Focus on Macrolides, 87	
		2.3.1	Introduction, 87	
		2.3.2	,	
			Stereoselective Synthesis of 1.3-Diols: Asymmetric Reductions, 100	5
		2.3.4	Application of Stereoselective Synthesis of 1,3-Diols in	
		2.3.5	the Total Synthesis of Macrolides, 117	
	Dof	erences,	Conclusion, 126	
	Keit	rences,	120	
3	Fatt	v Acids	s and Their Derivatives	130
			nd Trond Vidar Hansen	150
	3.1		uction, 130	
	3.2	-	nthesis, 130	
		3.2.1	•	
			Polyunsaturated Fatty Acids, 134	
		3.2.3	→	
	2.2	C41-	Fatty Acids, 135	
	3.3		esis of ω-3 and ω-6 All-Z Polyunsaturated Fatty Acids, 140	
		3.3.1	Synthesis of Polyunsaturated Fatty Acids by the Wittig	
		3.3.2	Reaction or by the Polyyne Semihydrogenation, 140 Synthesis of Polyunsaturated Fatty Acids via	
		3.3.4	Cross Coupling Reactions, 143	
	3.4	Applia	cations in Total Synthesis of Polyunsaturated Fatty Acids, 145	
	2.7	3.4.1	· · · · · · · · · · · · · · · · · · ·	
			Biomimetic Transformations of Polyunsaturated Fatty Acids, 149	
			Landmark Total Syntheses, 153	
		3.4.4	Synthesis of Leukotriene B _s , 158	
	3.5		usion, 160	
	Acknowledgments, 160			
		rences,		
4	Poly	ethers		162
	Youw	ei Xie ai	nd Paul E. Floreancig	
	4.1	Introd	uction, 162	
	4.2		nthesis, 162	
	7.2	4.2.1	Ionophore Antibiotics, 162	
		4.2.2	Marine Ladder Toxins, 165	
		4.2.3	Annonaceous Acetogenins and Terpene Polyethers, 165	
	4.3		de Reactivity and Stereoselective Synthesis, 166	
	11.5	4.3.1	Regiocontrol in Epoxide-Opening Reactions, 166	
		4.3.2	Stereoselective Epoxide Synthesis, 172	
	4.4		cations to Total Synthesis, 176	
		4.4.1	Acid-Mediated Transformations, 176	
		4.4.2	Cascades via Epoxonium Ion Formation, 179	
		4.4.3	Cyclizations under Basic Conditions, 181	
		4.4.4	Cyclization in Water, 182	
	4.5	Concl	usions, 183	
	Refe	rences,	184	

TC	

SE	ECTIO	ON II MEVALONATE BIOSYNTHETIC PATHWAY	187
5	Bios	n Acetate to Mevalonate and Deoxyxylulose Phosphate ynthetic Pathways: An Introduction to Terpenoids andros L. Zografos and Elissavet E. Anagnostaki	189
	5.1	Introduction, 189	
	5.2	Mevalonic Acid Pathway, 191	
	5.3	Mevalonate-Independent Pathway, 192	
	5.4	Conclusion, 194	
	Refe	erences, 194	
6	Mor	noterpenes and Iridoids	196
	Mari	o Waser and Uwe Rinner	
	6.1	Introduction, 196	
	6.2	Biosynthesis, 196	
		6.2.1 Acyclic Monoterpenes, 197	
		6.2.2 Cyclic Monoterpenes, 197	
		6.2.3 Iridoids, 200	
		6.2.4 Irregular Monoterpenes, 202	
	6.3	Asymmetric Organocatalysis, 203	
		6.3.1 Introduction and Historical Background, 2046.3.2 Enamine, Iminium, and Singly Occupied Molecular	
		6.3.2 Enamine, Iminium, and Singly Occupied Molecular Orbital Activation, 207	
		6.3.3 Chiral (Brønsted) Acids and H-Bonding Donors, 213	
		6.3.4 Chiral Brønsted/Lewis Bases and Nucleophilic Catalysis, 218	
		6.3.5 Asymmetric Phase-Transfer Catalysis, 220	
	6.4	Organocatalysis in the Total Synthesis of Iridoids and	
	•••	Monoterpenoid Indole Alkaloids, 225	
		6.4.1 (+)-Geniposide and 7-Deoxyloganin, 226	
		6.4.2 (-)-Brasoside and (-)-Littoralisone, 227	
		6.4.3 (+)-Mitsugashiwalactone, 229	
		6.4.4 Alstoscholarine, 229	
		6.4.5 (+)-Aspidospermidine and (+)-Vincadifformine, 230	
		6.4.6 (+)-Yohimbine, 230	
	6.5	Conclusion, 231	
	Refe	rences, 231	
7	Seso	uiterpenes	236
	_	undros L. Zografos and Elissavet E. Anagnostaki	
	7.1	Biosynthesis, 236	
	7.2	Cycloisomerization Reactions in Organic Synthesis, 244	
		7.2.1 Enyne Cycloisomerization, 245	
		7.2.2 Diene Cycloisomerization, 257	
	7.3	Application of Cycloisomerizations in the Total Synthesis of	
		Sesquiterpenoids, 266	
		7.3.1 Picrotoxane Sesquiterpenes, 266	
		7.3.2 Aromadendrane Sesquiterpenes: Epiglobulol, 267	
		7.3.3 Cubebol–Cubebenes Sesquiterpenes, 267	
		7.3.4 Ventricos-7(13)-ene, 270	
		7.3.5 Englerins, 271 7.3.6 Echinopines, 271	
		7.3.6 Echinopines, 271 7.3.7 Cyperolone, 273	
		1.5.1 Cyperoione, 215	

	7 4 Refe	7.3.8 Diverse Sesquiterpenoids, 276 Conclusion, 276 rences, 276	
8		penes Barriault	279
	8.1 8.2 8.3	Introduction, 279 Biosynthesis of Diterpenes Based on Cationic Cyclizations, 1,2-Shifts, and Transannular Processes, 279 Pericyclic Reactions and their Application in the Synthesis of Selected Diterpenoids, 284 8.3.1 Diels—Alder Reaction and Its Application in the Total Synthesis of Diterpenes, 284 8.3.2 Cascade Pericyclic Reactions and their Application in the Total Synthesis of Diterpenes, 291 Conclusion, 293 rences, 294	
9		er Terpenes and Steroids aki Ishihara	296
	9.1 9.2 9.3 9.4 9.5 Refer	Introduction, 296 Biosynthesis, 296 Cascade Polyene Cyclizations, 303 9.3.1 Diastereoselective Polyene Cyclizations, 303 9.3.2 "Chiral proton (H+)"-Induced Polyene Cyclizations, 304 9.3.3 "Chiral Metal Ion"-Induced Polyene Cyclizations, 308 9.3.4 "Chiral Halonium Ion (X+)"-Induced Polyene Cyclizations, 313 9.3.5 "Chiral Carbocation"-Induced Polyene Cyclizations, 319 9.3.6 Stereoselective Cyclizations of Homo(polyprenyl)arene Analogs, 319 Biomimetic Total Synthesis of Terpenes and Steroids through Polyene Cyclization, 319 Conclusion, 328 rences, 328	
SEC	CTION	N III SHIKIMIC ACID BIOSYNTHETIC PATHWAY	331
10	Lign:	ans, Lignins, and Resveratrols	333
	10.1	Biosynthesis, 333 10.1.1 Primary Metabolism of Shikimic Acid and Aromatic Amino Acids, 333	
	10.2 10.3 10.4 10.5 10.6 Refer	10.1.2 Lignans and Lignin, 335 Auxiliary-Assisted C(sp³)–H Arylation Reactions in Organic Synthesis, 336 Friedel–Crafts Reactions in Organic Synthesis, 344 Total Synthesis of Lignans by C(sp³)–H Arylation Reactions, 353 Total Synthesis of Lignans and Polymeric Resveratrol by Friedel–Crafts Reactions, 357 Conclusion, 375 eences, 375	

SE	CTIO		MIXED BIOSYNTHETIC PATHWAYS— THE STORY OF ALKALOIDS	381
11	Orni	thine an	d Lysine Alkaloids	383
	Sebas	tian Brau	ch, Wouter S. Veldmate, and Floris P. J. T. Rutjes	
	11.1	11.1.1	thesis of L-Ornithine and L-Lysine Alkaloids, 383 Biosynthetic Formation of Alkaloids Derived from L-Ornithine, 383 Biosynthetic Formation of Alkaloids	
		11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 Mannic L-Lysir	Derived from L-Lysine, 388 ymmetric Mannich Reaction in Organic Synthesis, 392 Chiral Amines as Catalysts in Asymmetric Mannich Reactions, Chiral Brønsted Bases as Catalysts in Asymmetric Mannich Reactions, 398 Chiral Brønsted Acids as Catalysts in Asymmetric Mannich Reactions, 404 Organometallic Catalysts in Asymmetric Mannich Reactions, 40 Biocatalytic Asymmetric Mannich Reactions, 413 ch and Related Reactions in the Total Synthesis of the- and L-Ornithine-Derived Alkaloids, 414 sion, 426	
12	-	sine Alk	aloids d Mario Waser	431
	12.1 12.2	Introdu Biosyn 12.2.1 12.2.2 12.2.3 12.2.4 12.2.5 12.2.6	thesis of Tyrosine-Derived Alkaloids, 431 Phenylethylamines, 431 Simple Tetrahydroisoquinoline Alkaloids, 433 Modified Benzyltetrahydroisoquinoline Alkaloids, 433 Phenethylisoquinoline Alkaloids, 436 Amaryllidaceae Alkaloids, 438	
	12.4	12.3.3 12.3.4 Synthe 12.4.1 12.4.2 12.4.3	Palladium-Mediated Aryl-Aryl Bond Forming Reactions, 447 Transition Metal-Catalyzed Couplings of Nonactivated Aryl Compounds, 450 sis of Tyrosine-Derived Alkaloids, 456 Synthesis of Modified Benzyltetrahydroisoquinoline Alkaloids, Synthesis of Phenethylisoquinoline Alkaloids, 460 Synthesis of Amaryllidaceae Alkaloids, 462 sion, 468	456

13 Histidine and Histidine-Like Alkaloids

473

Ian S. Young

References, 469

- 13.1 Introduction, 473
- 13.2 Biosynthesis, 473
- 13.3 Atom Economy and Protecting-Group-Free Chemistry, 480

XII	CONTENTS

		Challenging the Boundaries of Synthesis: PIAs. 488 Conclusion. 497 rences, 499	
14	Anthranilic Acid–Tryptophan Alkaloids Zhen-Yu Tang		
	14.1 14.2 14.3	Biosynthesis, 502 Divergent Synthesis-Collective Total Synthesis, 508 Collective Total Synthesis of Tryptophan-Derived Alkaloids, 510 14.3.1 Monoterpene Indole Alkaloids, 510 14.3.2 Bisindole Alkaloids, 512	
	Refer	rences, 517	
15	Future Directions of Modern Organic Synthesis Jakob Pletz and Rolf Breinbauer		519
	15.1 15.2	Introduction, 519 Enzymes in Organic Synthesis: Merging Total Synthesis with Biosynthesis, 520	
		Engineered Biosynthesis, 526 Diversity-Oriented Synthesis, Biology-Oriented Synthesis,	
		and Diverted Total Synthesis, 533 15.4.1 Diversity-oriented Synthesis, 535 15.4.2 Biology-oriented Synthesis, 536 15.4.3 Diverted Total Synthesis, 539	
	15.5	Conclusion, 541	
	Refer	rences, 545	

INDEX 548