

Science of Synthesis Knowledge Updates 2021/3

	Preface	V
	Abstracts	VII
	Table of Contents	XV
10.24	Product Class 24: Pyrido[1,2-<i>a</i>]indoles and Azapyrido[1,2-<i>a</i>]indoles P. A. Harris	1
10.24.1	Product Subclass 1: Pyrido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	5
10.24.2	Product Subclass 2: Pyrimido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	85
10.24.3	Product Subclass 3: Pyrimido[1,6-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	109
10.24.4	Product Subclass 4: Pyrazino[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	145
10.24.5	Product Subclass 5: Pyridazino[1,6-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	181
21.11.7	Chemoselective Ligation Methods Based on the Concept of Native Chemical Ligation L. R. Malins and R. J. Payne	193
37.9	Product Class 9: 1,4-Dioxanes B. V. Vashchenko and O. O. Grygorenko	243
3.3.4	Biocatalytic Oxidation of Alcohols: An Overview F. Hollmann	429
	Author Index	457
	Abbreviations	477

Table of Contents

Volume 10: Fused Five-Membered Hetarenes with One Heteroatom

10.24	Product Class 24: Pyrido[1,2-<i>a</i>]indoles and Azapyrido[1,2-<i>a</i>]indoles P. A. Harris	
10.24	Product Class 24: Pyrido[1,2-<i>a</i>]indoles and Azapyrido[1,2-<i>a</i>]indoles	1
10.24.1	Product Subclass 1: Pyrido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	New
10.24.1	Product Subclass 1: Pyrido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems	5
10.24.1.1	Synthesis by Ring-Closure Reactions	5
10.24.1.1.1	By Annulation to an Arene	5
10.24.1.1.1.1	By Formation of Two N—C and Two C—C Bonds	5
10.24.1.1.1.1.1	With Formation of 5—6, 5—9a, 7—8, and 10—10a Bonds	5
10.24.1.1.1.1.1.1	Method 1: Synthesis from Aryltriazenes and Diarylalkynes	5
10.24.1.1.1.1.1.2	Method 2: Synthesis from Antipyrines and Alkynes	8
10.24.1.1.1.2	By Formation of Two N—C Bonds and One C—C Bond	11
10.24.1.1.1.2.1	With Formation of 5—6, 5—9a, and 9a—10 Bonds	11
10.24.1.1.1.2.1.1	Method 1: Synthesis from (2-Aminobenzyl)triphenylphosphonium Bromide and 2-Alkynylbenzaldehydes	11
10.24.1.1.1.2.2	With Formation of 5—6, 5—9a, and 7—8 Bonds	12
10.24.1.1.1.2.2.1	Method 1: Synthesis from 2-[(2-Bromophenyl)ethynyl]aniline and Boronic Acids	12
10.24.1.1.1.2.2.2	Method 2: Synthesis from 2-(Phenylethynyl)aniline and 1,2-Dihalobenzenes	14
10.24.1.1.1.2.3	With Formation of 4a—5, 5—9a, and 7—8 Bonds	16
10.24.1.1.1.2.3.1	Method 1: Synthesis from 1-Bromo-2-(phenylethynyl)benzene and 2-Bromoanilines or 1,2-Bis(2-bromophenyl)ethyne and Anilines	16
10.24.1.1.2	By Annulation to a Heterocyclic Ring	18
10.24.1.1.2.1	By Annulation to an Indole	18
10.24.1.1.2.1.1	By Formation of One N—C Bond and Two C—C Bonds	18
10.24.1.1.2.1.1.1	With Formation of 5—6, 7—8, and 9—9a Bonds	18
10.24.1.1.2.1.1.1.1	Method 1: Synthesis from Alkynes and 3-Formyl- or 3-Acetyl-1 <i>H</i> -indoles	18

10.24.1.1.2.1.1.2	With Formation of 5—6, 6—7, and 8—9 Bonds	19
10.24.1.1.2.1.1.2.1	Method 1: Synthesis from 1 <i>H</i> -Indole-2-carbaldehyde, Bromomethyl Ketones, and Alkyne Esters	19
10.24.1.1.2.1.2	By Formation of One N—C Bond and One C—C Bond	20
10.24.1.1.2.1.2.1	With Formation of 5—6 and 7—8 Bonds	20
10.24.1.1.2.1.2.1.1	Method 1: Synthesis from 2-Phenyl-1 <i>H</i> -indole and 1,2-Dihalobenzenes ·	20
10.24.1.1.2.1.2.1.2	Method 2: Synthesis from 2-(2-Bromoaryl)-1 <i>H</i> -indoles and 1,3-Diketones	21
10.24.1.1.2.1.2.1.3	Method 3: Synthesis from 2-Aryl-1 <i>H</i> -indoles and Alkynes	22
10.24.1.1.2.1.2.1.4	Method 4: Synthesis from 2-(2-Bromoaryl)-1 <i>H</i> -indoles and Malononitrile	25
10.24.1.1.2.1.2.1.5	Method 5: Synthesis from 2-Aryl-1 <i>H</i> -indoles and Allyl Methyl Carbonate ·	26
10.24.1.1.2.1.2.1.6	Method 6: Synthesis from 2-Aryl-1 <i>H</i> -indoles with Sulfoxonium Ylides ··	28
10.24.1.1.2.1.2.2	With Formation of 5—6 and 8—9 Bonds	30
10.24.1.1.2.1.2.2.1	Method 1: Synthesis from 1 <i>H</i> -Indole-2-carbaldehydes and Fumaronitrile ·	30
10.24.1.1.2.1.2.2.2	Method 2: Synthesis from 2-Methyl-1 <i>H</i> -indole-3-carbaldehydes/nitriles and 2-Fluorobenzaldehydes	31
10.24.1.1.2.1.2.2.3	Method 3: Synthesis from 1 <i>H</i> -Indole-2-carbaldehydes and (2-Halophenyl)acetonitriles	33
10.24.1.1.2.1.2.3	With Formation of 5—6 and 9—9a Bonds	35
10.24.1.1.2.1.2.3.1	Method 1: Synthesis from 1 <i>H</i> -Indoles and Diazoenals	35
10.24.1.1.2.1.2.3.2	Method 2: Synthesis from 1 <i>H</i> -Indoles and 2-Bromo-2'-iodo-1,1'-biphenyl	37
10.24.1.1.2.1.2.3.3	Method 3: Synthesis from 1 <i>H</i> -Indoles and (2-Haloaryl)alkynes	38
10.24.1.1.2.1.2.3.4	Method 4: Synthesis from 1 <i>H</i> -Indoles and 1-Bromo-2-(2-chloro-3,3,3-trifluoroprop-1-enyl)benzenes	41
10.24.1.1.2.1.3	By Formation of Two C—C Bonds	42
10.24.1.1.2.1.3.1	With Formation of 6—7 and 9—9a Bonds	42
10.24.1.1.2.1.3.1.1	Method 1: Synthesis from 2-Bromo-1 <i>H</i> -indoles and (2-Acetylphenyl)- or (2-Formylphenyl)boronic Acid	42
10.24.1.1.2.1.3.2	With Formation of 7—8 and 9—9a Bonds	44
10.24.1.1.2.1.3.2.1	Method 1: Synthesis from 1-(2-Bromophenyl)-1 <i>H</i> -indoles and Benzynes ·	44
10.24.1.1.2.1.3.2.2	Method 2: Synthesis from 1-(2-Bromophenyl)-1 <i>H</i> -indoles and Alkynes ··	46
10.24.1.1.2.1.3.2.3	Method 3: Synthesis from 1-(2-Bromophenyl)-1 <i>H</i> -indole and Norbornadiene	48
10.24.1.1.2.1.3.2.4	Method 4: Synthesis from 1-Phenyl-1 <i>H</i> -indole-3-carbaldehydes and Alkynes	49
10.24.1.1.2.1.3.2.5	Method 5: Synthesis from 2-(1 <i>H</i> -Indol-1-yl)-1-phenylethanones and 1,2-Dibromobenzenes	52

10.24.1.1.2.1.4	By Formation of One C—C Bond	54
10.24.1.1.2.1.4.1	With Formation of the 9a—9 Bond	54
10.24.1.1.2.1.4.1.1	Method 1: Synthesis from 1-[2-(2,2-Dibromovinyl)phenyl]-1 <i>H</i> -indole and Phenylboronic Acid	54
10.24.1.1.2.1.4.1.2	Method 2: Synthesis from 1-[2-(2,2-Dibromovinyl)phenyl]-1 <i>H</i> -indoles and Polyfluoroarenes	55
10.24.1.1.2.1.4.1.3	Method 3: Synthesis from 1-[2-(Arylethynyl)phenyl]-1 <i>H</i> -indoles	56
10.24.1.1.2.1.4.1.4	Method 4: Synthesis from 1-[2-(Arylethynyl)phenyl]-1 <i>H</i> -indoles and (Arylsulfonyl)hydrazines	57
10.24.1.1.2.1.4.1.5	Method 5: Synthesis from 1-[2-(Trifluoromethyl)benzyl]-1 <i>H</i> -indoles	60
10.24.1.1.2.1.4.2	With Formation of the 7—8 Bond	62
10.24.1.1.2.1.4.2.1	Method 1: Synthesis from 1,2-Diallyl-1 <i>H</i> -indoles	62
10.24.1.1.2.1.4.2.1.1	Variation 1: From 9-Allyl-1-vinyl-2,3,4,9-tetrahydrocarbazol-1-ols	63
10.24.1.1.2.1.4.2.1.2	Variation 2: From 1-(1-Allyl-1 <i>H</i> -indol-2-yl)prop-2-en-1-ols	64
10.24.1.1.2.1.4.2.2	Method 2: Synthesis from 1-(2-Bromophenyl)-2-phenyl-1 <i>H</i> -indole or 1-Aryl-2-(2-bromophenyl)-1 <i>H</i> -indoles	65
10.24.1.1.2.2	By Annulation to a Pyridine	66
10.24.1.1.2.2.1	By Formation of One N—C Bond and One C—C Bond	66
10.24.1.1.2.2.1.1	With Formation of 4a—5 and 10—10a Bonds	66
10.24.1.1.2.2.1.1.1	Method 1: Synthesis from Benzyne and 2-(Pyridin-2-ylmethylene)malonates	66
10.24.1.1.2.2.1.1.2	Method 2: Synthesis from Quinones and Ethyl 2-(2-Pyridyl)acetate	68
10.24.1.1.2.2.2	By Formation of One N—C Bond	69
10.24.1.1.2.2.2.1	With Formation of the 4a—5 Bond	69
10.24.1.1.2.2.2.1.1	Method 1: Synthesis from 2-Benzylpyridine <i>N</i> -Oxides	69
10.24.1.1.2.2.2.1.2	Method 2: Synthesis from 2-(Diphenylmethyl)pyridines	71
10.24.1.1.2.2.2.1.3	Method 3: Synthesis from Diaryl(2-pyridyl)methanols	72
10.24.1.1.2.2.2.1.4	Method 4: Synthesis from 2-(2-Bromobenzyl)pyridines	73
10.24.1.1.2.2.2.1.4.1	Variation 1: From 2-(2-Iodobenzyl)pyridines	75
10.24.1.2	Synthesis by Ring Transformation	75
10.24.1.2.1	Method 1: Synthesis from 3-(2-Pyridyl)-1,2,4-triazines and Benzyne	75
10.24.1.3	Synthesis by Substituent Modification	77
10.24.1.3.1	Substitution of Existing Substituents	77
10.24.1.3.1.1	Substitution of C-Tin	77
10.24.1.3.1.1.1	Method 1: Substitution of Trimethylstannyl via Cross-Coupling Processes	77
10.24.1.3.1.2	Substitution of C-Oxygen	79
10.24.1.3.1.2.1	Method 1: Substitution of Trifluoromethanesulfonate via Cross-Coupling Processes	79

10.24.1.3.1.3	Substitution of C-Hydrogen	81
10.24.1.3.1.3.1	Direct Substitution by Electrophiles	81
10.24.1.3.1.3.1.1	Method 1: Synthesis of C-Nitrogen Indolo[2,1- <i>a</i>]isoquinolines	81
10.24.1.3.1.3.1.2	Method 2: Synthesis of C-Carbon Indolo[2,1- <i>a</i>]isoquinolines	81
10.24.1.3.1.3.1.3	Method 3: Synthesis of C-Carbon Pyrido[1,2- <i>a</i>]indoles	82
10.24.2	Product Subclass 2: Pyrimido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	New
10.24.2	Product Subclass 2: Pyrimido[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems	85
10.24.2.1	Synthesis by Ring-Closure Reactions	86
10.24.2.1.1	By Annulation to an Arene	86
10.24.2.1.1.1	By Formation of Three N—C Bonds and One C—C Bond	86
10.24.2.1.1.1.1	With Formation of 1—2, 4—5, 5—10a, and 9a—10 Bonds	86
10.24.2.1.1.1.1.1	Method 1: Synthesis from <i>N</i> -(2-Iodophenyl)acetamides, Malononitrile, and 2-Iodobenzaldehydes	86
10.24.2.1.1.2	By Formation of Three N—C Bonds	87
10.24.2.1.1.2.1	With Formation of 5—5a, 5—10a, and 1—10a Bonds	87
10.24.2.1.1.2.1.1	Method 1: Synthesis from (2-Bromophenyl)acetonitriles and 2-Aminobenzonitriles	87
10.24.2.1.1.2.2	With Formation of 1—10a, 4—5, and 5—10a Bonds	89
10.24.2.1.1.2.2.1	Method 1: Synthesis from <i>N</i> -[2-(2,2-Dibromovinyl)phenyl]acetamide and 2-Bromo- <i>N</i> -tosylbenzylamines	89
10.24.2.1.1.3	By Formation of Two N—C Bonds	91
10.24.2.1.1.3.1	With Formation of 1—2 and 5—10a Bonds	91
10.24.2.1.1.3.1.1	Method 1: Synthesis from Diethyl 2-([2-(Cyanomethyl)-4,5-dimethoxyphenyl]amino)methylene)malonate	91
10.24.2.1.1.3.2	With Formation of 1—10a and 5—5a Bonds	92
10.24.2.1.1.3.2.1	Method 1: Synthesis from 2-Substituted 2-Aryl- <i>N</i> -[2-(azidomethyl)phenyl]ethen-1-imines	92
10.24.2.1.1.3.3	With Formation of 1—10a and 5—10a Bonds	93
10.24.2.1.1.3.3.1	Method 1: Synthesis from 2-Amino- <i>N</i> -[2-(2,2-dibromovinyl)phenyl]benzamides	93
10.24.2.1.2	By Annulation to a Heterocyclic Ring	94
10.24.2.1.2.1	By Annulation to an Indole	94
10.24.2.1.2.1.1	By Formation of Two N—C Bonds and One C—C Bond	94
10.24.2.1.2.1.1.1	With Formation of 1—10a, 2—3, and 4—5 Bonds	94
10.24.2.1.2.1.1.1.1	Method 1: Synthesis from 1-Methoxy-6-nitro-1 <i>H</i> -indole-3-carbaldehyde and (4-Chlorophenoxy)acetonitrile	94

10.24.2.1.2.1.1.2	With Formation of 1—2, 2—3, and 4—5 Bonds	96
10.24.2.1.2.1.1.2.1	Method 1: Synthesis from Ethyl 2-Amino-1 <i>H</i> -indole-3-carboxylate, Benzaldehydes, and Terminal Alkynes	96
10.24.2.1.2.1.1.2.2	Method 2: Synthesis from Ethyl 2-Amino-1 <i>H</i> -indole-3-carboxylate, Aroyl Chlorides, and Terminal Alkynes	98
10.24.2.1.2.1.2	By Formation of Two N—C Bonds	99
10.24.2.1.2.1.2.1	With Formation of 4—5 and 1—10a Bonds	99
10.24.2.1.2.1.2.1.1	Method 1: Synthesis from Methyl 1 <i>H</i> -Indole-3-carboxylates and 2-Bromobenzamides	99
10.24.2.1.2.1.2.1.2	Method 2: Synthesis from 1 <i>H</i> -Indoles and 1-(2-Iodophenyl)ethan-1-one <i>O</i> -Acetyloxime	101
10.24.2.1.2.1.2.2	With Formation of 1—2 and 4—5 Bonds	102
10.24.2.1.2.1.2.2.1	Method 1: Synthesis from Ethyl 2-Amino-1 <i>H</i> -indole-3-carboxylate and Acetylacetone	102
10.24.2.1.2.1.3	By Formation of One N—C Bond	102
10.24.2.1.2.1.3.1	With Formation of the 4—5 Bond	102
10.24.2.1.2.1.3.1.1	Method 1: Synthesis from Ethyl 2-Amino-1 <i>H</i> -indole-3-carboxylate and 3-Substituted Ethyl 4-Ethoxy-2-oxobut-3-enoates	102
10.24.2.1.2.1.3.2	With Formation of the 1—10a Bond	103
10.24.2.1.2.1.3.2.1	Method 1: Synthesis from 2-(1 <i>H</i> -Indol-1-yl)benzamides	103
10.24.2.1.2.2	By Annulation to a Pyrimidine	105
10.24.2.1.2.2.1	By Formation of One N—C Bond	105
10.24.2.1.2.2.1.1	With Formation of the 5—5a Bond	105
10.24.2.1.2.2.1.1.1	Method 1: Synthesis from 2-Benzylpyrimidine 1-Oxide	105
10.24.2.1.2.2.1.1.2	Method 2: Synthesis from Diphenyl(pyrimidin-2-yl)methanol	105
10.24.2.2	Synthesis by Ring Transformation	105
10.24.2.2.1	Method 1: Synthesis from 10-Methyl-11-oxo-10,11-dihydro-5 <i>H</i> -dibenzo[<i>b,f</i>]azepine-10-carbonitrile	105
10.24.2.2.2	Method 2: Synthesis from 3-(Pyrimidin-2-yl)-1,2,4-triazines and Benzyne	107
10.24.3	Product Subclass 3: Pyrimido[1,6-<i>a</i>]indoles and Related Benzo-Fused Ring Systems P. A. Harris	New
10.24.3	Product Subclass 3: Pyrimido[1,6-<i>a</i>]indoles and Related Benzo-Fused Ring Systems	109
10.24.3.1	Synthesis by Ring-Closure Reactions	110
10.24.3.1.1	By Annulation to an Arene	110
10.24.3.1.1.1	By Formation of Three N—C Bonds	110
10.24.3.1.1.1.1	With Formation of 1—2, 1—10, and 4a—10 Bonds	110
10.24.3.1.1.1.1.1	Method 1: Synthesis from 2,2'-(Ethyne-1,2-diyl)dianiline	110
10.24.3.1.1.1.1.2	Method 2: Synthesis from 2,2'-Dinitrostilbenes	110

10.24.3.1.1.1.2	With Formation of 1—2, 1—10, and 2—3 Bonds	112
10.24.3.1.1.1.2.1	Method 1: Synthesis from 2-(2-Bromoaryl)-1 <i>H</i> -indoles	112
10.24.3.1.1.2	By Formation of Two N—C Bonds	114
10.24.3.1.1.2.1	With Formation of 1—10 and 4a—10 Bonds	114
10.24.3.1.1.2.1.1	Method 1: Synthesis from <i>N</i> -{2-[(2-Aminoaryl)ethynyl]aryl}amides	114
10.24.3.1.1.2.1.2	Method 2: Synthesis from <i>N</i> -{2-[(2-Aminophenyl)ethynyl]phenyl}- 2,2,2-trifluoroacetamide	115
10.24.3.1.1.2.1.2.1	Variation 1: From Bis[2-(trifluoroacetamido)phenyl]acetylene	116
10.24.3.1.1.2.1.2.2	Variation 2: From Bis[2-(trifluoroacetamido)phenyl]acetylene by Cyclocarbonylation	118
10.24.3.1.1.2.2	With Formation of 2—3 and 4a—10 Bonds	119
10.24.3.1.1.2.2.1	Method 1: Synthesis from 1-[2-(Buta-1,3-diynyl)aryl]ureas	119
10.24.3.1.2	By Annulation to a Heterocyclic Ring	120
10.24.3.1.2.1	By Annulation to an Indole	120
10.24.3.1.2.1.1	By Formation of Two N—C Bonds	120
10.24.3.1.2.1.1.1	With Formation of 1—2 and 1—10 Bonds	120
10.24.3.1.2.1.1.1.1	Method 1: Synthesis from 2-(1 <i>H</i> -Indol-2-yl)aniline	120
10.24.3.1.2.1.1.2	With Formation of 1—10 and 2—3 Bonds	122
10.24.3.1.2.1.1.2.1	Method 1: Synthesis from 2-(2-Bromophenyl)-1 <i>H</i> -indoles and Cyanamide	122
10.24.3.1.2.1.1.2.1.1	Variation 1: From 2-(2-Bromophenyl)-1 <i>H</i> -indole and Amidines	124
10.24.3.1.2.1.1.2.2	Method 2: Synthesis from 2-(2-Iodophenyl)-1 <i>H</i> -indole and [(Het)arylmethyl]amines	125
10.24.3.1.2.1.1.2.3	Method 3: Synthesis from 2-(2-Bromophenyl)-1 <i>H</i> -indole and α -Amino Acids	125
10.24.3.1.2.1.1.2.4	Method 4: Synthesis from 2-Aryl-1 <i>H</i> -indoles and 1,4,2-Dioxazol-5-ones ·	127
10.24.3.1.2.1.2	By Formation of One N—C Bond and One C—C Bond	128
10.24.3.1.2.1.2.1	With Formation of 2—3 and 4—4a Bonds	128
10.24.3.1.2.1.2.1.1	Method 1: Synthesis from <i>N</i> -(Pivaloyloxy)-1 <i>H</i> -indole-1-carboxamide and Alkynes	128
10.24.3.1.2.1.2.1.2	Method 2: Synthesis from 1 <i>H</i> -Indole-1-carboxamides and α -Diazo β -Oxo Esters	130
10.24.3.1.2.1.2.1.3	Method 3: Synthesis from 1-(2-Pyridyl)-1 <i>H</i> -indoles and Alkynes	132
10.24.3.1.2.1.2.2	With Formation of 1—2 and 3—4 Bonds	134
10.24.3.1.2.1.2.2.1	Method 1: Synthesis from 3-Bromo-2-(bromomethyl)-1 <i>H</i> -indole- 1-carboxylates and Tosylmethyl Isocyanide	134
10.24.3.1.2.1.2.3	With Formation of 1—2 and 4—4a Bonds	135
10.24.3.1.2.1.2.3.1	Method 1: Synthesis from 1-Acetyldolin-3-ones and Phenylhydrazine ·	135

10.24.3.1.2.1.3	By Formation of One N—C Bond	136
10.24.3.1.2.1.3.1	With Formation of the 1—10 Bond	136
10.24.3.1.2.1.3.1.1	Method 1: Synthesis from 2-(2-Isocyanophenyl)-1 <i>H</i> -indoles and Aryl Iodides	136
10.24.3.1.2.1.3.1.2	Method 2: Synthesis from 2-(2-Amidoaryl)-1 <i>H</i> -indoles	138
10.24.3.1.2.1.4	By Formation of One C—C Bond	139
10.24.3.1.2.1.4.1	With Formation of the 4—4a Bond	139
10.24.3.1.2.1.4.1.1	Method 1: Synthesis from 2,2,2-Trifluoro-1-(1 <i>H</i> -indol-1-yl)- <i>N</i> -(2-iodoaryl)ethan-1-imines	139
10.24.3.1.2.2	By Annulation to a Pyrimidine	140
10.24.3.1.2.2.1	By Formation of One N—C Bond	140
10.24.3.1.2.2.1.1	With Formation of the 9a—10 Bond	140
10.24.3.1.2.2.1.1.1	Method 1: Synthesis from 6-Benzylpyrimidine 1-Oxide	140
10.24.3.2	Synthesis by Substituent Modification	140
10.24.3.2.1	Substitution of Existing Substituents	140
10.24.3.2.1.1	Substitution of <i>C</i> -Sulfur and <i>N</i> -Hydrogen	140
10.24.3.2.1.1.1	Method 1: Reaction of 6-(Methylsulfanyl)indolo[1,2- <i>c</i>]quinazoline with Anthranilic Acids	140
10.24.3.2.1.2	Substitution of <i>C</i> -Halogen	141
10.24.3.2.1.2.1	Method 1: Substitution of Bromide with Aryl	141
10.24.3.2.1.3	Substitution of <i>C</i> -Hydrogen	143
10.24.3.2.1.3.1	Method 1: Substitution of Hydrogen with Aryl	143
10.24.4	Product Subclass 4: Pyrazino[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems New P. A. Harris	
10.24.4	Product Subclass 4: Pyrazino[1,2-<i>a</i>]indoles and Related Benzo-Fused Ring Systems	145
10.24.4.1	Synthesis by Ring-Closure Reactions	146
10.24.4.1.1	By Annulation to an Arene	146
10.24.4.1.1.1	By Formation of Two N—C Bonds and One C—C Bond	146
10.24.4.1.1.1.1	With Formation of 1—2, 5—10a, and 9a—10 Bonds	146
10.24.4.1.1.1.1.1	Method 1: Synthesis from 2-Iodo- <i>N</i> -(2-nitrosoaryl)anilines and 1,3-Diketones	146
10.24.4.1.2	By Annulation to a Heterocyclic Ring	147
10.24.4.1.2.1	By Annulation to an Indole	147
10.24.4.1.2.1.1	By Formation of Two N—C Bonds	147
10.24.4.1.2.1.1.1	With Formation of 1—2 and 2—3 Bonds	147
10.24.4.1.2.1.1.1.1	Method 1: Synthesis from Ethyl 1-(2-Oxo-2-phenylethyl)-1 <i>H</i> -indole-2-carboxylate	147

10.24.4.1.2.1.1.1.2	Method 2: Synthesis from 2-Carbonyl-1-propargyl-1 <i>H</i> -indoles and Ammonia	148
10.24.4.1.2.1.1.1.2.1	Variation 1: From 2-Acyl-1-propargyl-1 <i>H</i> -indoles and Hydroxylamine	149
10.24.4.1.2.1.1.1.2.2	Variation 2: From 1-(Prop-2-ynyl)-1 <i>H</i> -indole-2-carbaldehyde Oxime	150
10.24.4.1.2.1.1.1.3	Method 3: Synthesis from (<i>E</i>)-3-Aryl-2-[(2-formyl-3-methyl-1 <i>H</i> -indol-1-yl)methyl]acrylic Acids	151
10.24.4.1.2.1.1.2	With Formation of 1—2 and 4—5 Bonds	153
10.24.4.1.2.1.1.2.1	Method 1: Synthesis from 1 <i>H</i> -Indole-2-carbaldehydes and 2-Iodoaniline ..	153
10.24.4.1.2.1.1.2.1.1	Variation 1: From Methyl 1 <i>H</i> -Indole-2-carboxylate and <i>N</i> -(2-Bromoaryl)-2,2,2-trifluoroacetamides	154
10.24.4.1.2.1.1.3	With Formation of 2—3 and 4—5 Bonds	154
10.24.4.1.2.1.1.3.1	Method 1: Synthesis from 2-(2-Pyridyl)-1 <i>H</i> -indole and Chloroacetaldehyde	154
10.24.4.1.2.1.2	By Formation of One N—C Bond and One C—C Bond	155
10.24.4.1.2.1.2.1	With Formation of 1—2 and 1—10a Bonds	155
10.24.4.1.2.1.2.1.1	Method 1: Synthesis from 2-(1 <i>H</i> -Indol-1-yl)anilines and Benzaldehydes ..	155
10.24.4.1.2.1.2.1.1.1	Variation 1: From 2-(1 <i>H</i> -Indol-1-yl)aniline and α -Oxo Carboxylic Acids ...	157
10.24.4.1.2.1.2.1.2	Method 2: Synthesis from 1-(2-Iodophenyl)-1 <i>H</i> -indoles and L-Alanine ...	158
10.24.4.1.2.1.2.1.2.1	Variation 1: From 2-(1 <i>H</i> -Indol-1-yl)anilines and L-Valine	159
10.24.4.1.2.1.2.1.2.2	Variation 2: From 2-(1 <i>H</i> -Indol-1-yl)anilines and Acetophenones	160
10.24.4.1.2.1.2.1.2.3	Variation 3: From 2-(1 <i>H</i> -Indol-1-yl)anilines and 2-Methylpyridine or 2-Methylquinoline	161
10.24.4.1.2.1.2.1.2.4	Variation 4: From 2-(1 <i>H</i> -Indol-1-yl)anilines and Dimethyl Sulfoxide	162
10.24.4.1.2.1.2.1.2.5	Variation 5: From 2-(1 <i>H</i> -Indol-1-yl)anilines and β -Diketones or β -Oxo Esters	163
10.24.4.1.2.1.3	By Formation of One N—C Bond	165
10.24.4.1.2.1.3.1	With Formation of the 1—2 Bond	165
10.24.4.1.2.1.3.1.1	Method 1: Synthesis from 2-(Arylethynyl)-1-(2-nitroaryl)-1 <i>H</i> -indoles	165
10.24.4.1.2.1.3.1.2	Method 2: Synthesis from Ethyl 1-(2-Nitrophenyl)-1 <i>H</i> -indole-2-carboxylates	167
10.24.4.1.2.1.3.1.3	Method 3: Synthesis from 1-(Cyanomethyl)-1 <i>H</i> -indole-2-carboxylates ..	168
10.24.4.1.2.1.3.2	With Formation of the 2—3 Bond	170
10.24.4.1.2.1.3.2.1	Method 1: Synthesis from 1-Propargyl-1 <i>H</i> -indole-2-carbonitriles and Alcohols	170
10.24.4.1.2.1.3.2.1.1	Variation 1: From 1-(Cyanomethyl)-1 <i>H</i> -indole-2-carbonitriles and Alcohols	171
10.24.4.1.2.1.3.3	With Formation of the 4—5 Bond	172
10.24.4.1.2.1.3.3.1	Method 1: Synthesis from <i>N</i> -(2-Hydroxyethyl)-1 <i>H</i> -indole-2-carboxamides	172

10.24.4.1.2.2	By Annulation to a Pyrazine	174
10.24.4.1.2.2.1	By Formation of One N—C Bond	174
10.24.4.1.2.2.1.1	With Formation of the 5—5a Bond	174
10.24.4.1.2.2.1.1.1	Method 1: Synthesis from 2-Benzylpyrazine 1-Oxide	174
10.24.4.1.2.3	By Annulation to a Quinoxaline	174
10.24.4.1.2.3.1	By Formation of One N—C Bond	174
10.24.4.1.2.3.1.1	With Formation of the 5—5a Bond	174
10.24.4.1.2.3.1.1.1	Method 1: Synthesis from 2-Benzoylquinoxalines	174
10.24.4.2	Synthesis by Substituent Modification	175
10.24.4.2.1	Substitution of Existing Substituents	175
10.24.4.2.1.1	Substitution of Chlorine with Amines or Anilines	175
10.24.4.2.1.1.1	Method 1: S _N Ar Displacement	175
10.24.4.2.1.2	Substitution of Chlorine with Carbon Nucleophiles	177
10.24.4.2.1.2.1	Method 1: Suzuki Cross Coupling	177
10.24.4.2.1.3	Substitution of N-Hydrogen	178
10.24.4.2.1.3.1	Method 1: N-Alkylation	178
10.24.4.2.1.4	Substitution of C-Hydrogen	178
10.24.4.2.1.4.1	Method 1: Vilsmeier–Haack Reaction	178

10.24.5 **Product Subclass 5: Pyridazino[1,6-*a*]indoles and Related Benzo-Fused Ring Systems**
P. A. Harris

New

10.24.5	Product Subclass 5: Pyridazino[1,6-<i>a</i>]indoles and Related Benzo-Fused Ring Systems	181
10.24.5.1	Synthesis by Ring-Closure Reactions	181
10.24.5.1.1	By Annulation to an Arene	181
10.24.5.1.1.1	By Formation of One N—C Bond and Three C—C Bonds	181
10.24.5.1.1.1.1	With Formation of 3—4, 4a—5, 5—5a, and 4a—10 Bonds	181
10.24.5.1.1.1.1.1	Method 1: Synthesis from Azobenzenes and Arylalkynes	181
10.24.5.1.1.2	By Formation of Two N—C Bonds and One C—C Bond	183
10.24.5.1.1.2.1	With Formation of 1—2, 5—5a, and 4a—10 Bonds	183
10.24.5.1.1.2.1.1	Method 1: Synthesis from 2-Alkynylbenzaldehydes and Arylhydrazines ·	183
10.24.5.1.2	By Annulation to a Heterocyclic Ring	185
10.24.5.1.2.1	By Annulation to an Indole	185
10.24.5.1.2.1.1	By Formation of One N—C Bond and Two C—C Bonds	185
10.24.5.1.2.1.1.1	With Formation of 1—2, 3—4, and 4—4a Bonds	185
10.24.5.1.2.1.1.1.1	Method 1: Synthesis from 3-Methyl-1 <i>H</i> -indol-1-amine, 1-Phenylprop-1-yne, and <i>tert</i> -Butyl Isocyanide	185

10.24.5.1.2.1.2	By Formation of One C—C Bond	187
10.24.5.1.2.1.2.1	With Formation of the 4—4a Bond	187
10.24.5.1.2.1.2.1.1	Method 1: Synthesis from 1 <i>H</i> -Indol-1-amines and Diethyl 2-(Ethoxymethylene)malonate	187
10.24.5.1.2.1.2.1.1.1	Variation 1: From 3-Methyl-1 <i>H</i> -indol-1-amine and Acetylacetone or Ethyl Acetoacetate	188
10.24.5.1.2.1.2.1.1.2	Variation 2: From <i>N</i> -Ethyl-3-methyl-1 <i>H</i> -indol-1-amine and Diketene	189
10.24.5.1.2.1.2.1.1.3	Variation 3: From 3-Methyl-1 <i>H</i> -indol-1-amine and Crotonaldehyde	190
10.24.5.1.2.2	By Annulation to a Pyrimidine	191
10.24.5.1.2.2.1	By Formation of One N—C Bond	191
10.24.5.1.2.2.1.1	With Formation of the 9a—10 Bond	191
10.24.5.1.2.2.1.1.1	Method 1: Synthesis from 6-Benzylpyridazine 1-Oxide	191

Volume 21:

Three Carbon—Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams

21.11 Product Class 11: Peptides

21.11.7	Chemoselective Ligation Methods Based on the Concept of Native Chemical Ligation	New
	L. R. Malins and R. J. Payne	
21.11.7	Chemoselective Ligation Methods Based on the Concept of Native Chemical Ligation	193
21.11.7.1	Method 1: Native Chemical Ligation (Cysteine/Thioester Ligation)	194
21.11.7.1.1	Variation 1: Use of Alternative Thiol Additives	195
21.11.7.1.2	Variation 2: Kinetically Controlled Ligation	196
21.11.7.1.3	Variation 3: Ligation–Desulfurization at Cysteine	197
21.11.7.1.4	Variation 4: Native Chemical Ligation at Cysteine Surrogates	199
21.11.7.1.5	Variation 5: Auxiliary Approaches	202
21.11.7.1.6	Variation 6: Selenocysteine/Thioester Ligation and Postligation Modification	203
21.11.7.2	Method 2: Modern Methods for the Synthesis of Peptide Thioesters	205
21.11.7.2.1	Variation 1: Synthesis of Peptide Thioesters via Fmoc-SPPS on Hyperacid- Labile Resin	205
21.11.7.2.2	Variation 2: Synthesis of Peptide Thioesters via Fmoc-SPPS Using a Side- Chain Anchoring Strategy	207
21.11.7.2.3	Variation 3: Synthesis of Peptide Thioesters via N→S Acyl Transfer	211

21.11.7.2.4	Variation 4: Synthesis of Peptide Thioesters by Activation of C-Terminal Diaminobenzoyl (Dbz or MeDbz) Linkers	219
21.11.7.2.5	Variation 5: Synthesis of Peptide Thioesters from C-Terminal Acyl Hydrazides	224
21.11.7.3	Method 3: Diselenide–Selenoester Ligation	226
21.11.7.4	Method 4: Peptide Selenoester Synthesis	229
21.11.7.5	Method 5: Serine/Threonine Ligation	235

Volume 37: Ethers

37.9	Product Class 9: 1,4-Dioxanes New	
	B. V. Vashchenko and O. O. Grygorenko	
37.9	Product Class 9: 1,4-Dioxanes	243
37.9.1	Synthesis of 1,4-Dioxanes	244
37.9.1.1	Synthesis by Formation of the C—O Bond in Intramolecular Cyclizations ..	244
37.9.1.1.1	Method 1: Intramolecular Williamson Etherification of 1,5-Halohydrins ..	244
37.9.1.1.2	Method 2: Synthesis and Reductive Ring Opening of Trioxabicyclo[3.2.1]octanes	258
37.9.1.1.3	Method 3: Intramolecular Cyclizations of 1,5-Diols	262
37.9.1.1.3.1	Variation 1: O-Sulfonylation of 1,5-Diols Followed by Intramolecular Nucleophilic Substitution	262
37.9.1.1.3.2	Variation 2: Intramolecular Mitsunobu Cyclization of 1,5-Diols	271
37.9.1.1.3.3	Variation 3: Enantioselective Iridium-Catalyzed Allylic Substitution	272
37.9.1.1.4	Method 4: Recyclization of Substituted 2-(Ethoxymethyl)oxiranes	273
37.9.1.1.4.1	Variation 1: Intramolecular Cyclization of 2-[(2-Haloethoxy)methyl]oxiranes	273
37.9.1.1.4.2	Variation 2: Recyclization of Substituted 2-(Oxiran-2-ylmethoxy)ethanols ..	276
37.9.1.1.5	Method 5: Recyclization of 2-(Oxetan-3-yloxy)alcohols	278
37.9.1.1.6	Method 6: Cyclization of δ -Hydroxy Aldehydes	281
37.9.1.1.7	Method 7: Intramolecular Cyclization of 1,5-Dicarbonyl Compounds	286
37.9.1.1.8	Method 8: Iodo- and Selenocyclization of 2-(Allyloxy)ethanols	288
37.9.1.1.8.1	Variation 1: Iodocyclization of 2-(Allyloxy)ethanols	288
37.9.1.1.8.2	Variation 2: Selenocyclization of 2-(Allyloxy)ethanols	292
37.9.1.1.9	Method 9: Palladium-Catalyzed Cyclizations	293
37.9.1.1.10	Method 10: Intramolecular Oxa-Michael Addition	297
37.9.1.1.11	Method 11: Intramolecular Cascade Cyclization of Allenyloxiranes	304
37.9.1.1.12	Method 12: Platinum-Catalyzed Propargylic Substitution	305
37.9.1.1.13	Method 13: Electrolytic Alkoxylation of Furans	306
37.9.1.1.14	Method 14: Tandem Achmatowicz Rearrangement/Acetalization of 1-(Furan-2-yl)cyclobutanols	307

37.9.1.2	Synthesis by Formation of Two C—O Bonds in Intermolecular Cyclizations	308
37.9.1.2.1	Method 1: Double Williamson Etherification of 1,2-Diols with Bisalkylating Agents	308
37.9.1.2.2	Method 2: Reaction of Two 1,2-Diol Molecules	312
37.9.1.2.2.1	Variation 1: Dimerizations of 1,2-Diols	312
37.9.1.2.2.2	Variation 2: Dimerizations of 2,2-Dimethyl-1,3-dioxolanes	314
37.9.1.2.2.3	Variation 3: Reactions of Two Different 1,2-Diol Molecules	316
37.9.1.2.3	Method 3: Reaction of 1,2-Diols with Tetrahydro-2,2'-bipyrans	319
37.9.1.2.4	Method 4: Dimerization of Oxiranes	324
37.9.1.2.5	Method 5: Reaction of 1,2-Diols with C=C Bonds	329
37.9.1.2.6	Method 6: Dimerizations of Allyl Alcohols	336
37.9.1.2.7	Method 7: Reaction of 1,2-Diols with 1,2-Dicarbonyl Compounds	338
37.9.1.2.7.1	Variation 1: Reaction of 1,2-Diols and Trimethyl Orthoformate with Butane-2,3-dione	338
37.9.1.2.7.2	Variation 2: Reaction of 1,2-Diols with 2,3-Dialkoxybuta-1,3-dienes	345
37.9.1.2.7.3	Variation 3: Reaction of 1,2-Diols with 2,2,3,3-Tetramethoxybutane	346
37.9.1.2.7.4	Variation 4: Reaction of 1,2-Diols with 1,1,2,2-Tetramethoxycyclohexane	350
37.9.1.2.7.5	Variation 5: Other Reactions	353
37.9.1.2.8	Method 8: Dimerization of α -Hydroxy Carbonyl Compounds	354
37.9.1.2.9	Method 9: Rearrangement of Oxonium Ylides	361
37.9.1.3	Synthesis by Reactions of 2,3-Dihydro-1,4-dioxin	365
37.9.1.3.1	Method 1: [2 + 2] Cycloadditions of 2,3-Dihydro-1,4-dioxin	365
37.9.1.3.2	Method 2: [3 + 2] Cycloadditions of 2,3-Dihydro-1,4-dioxin	368
37.9.1.3.3	Method 3: [4 + 2] Cycloadditions of 2,3-Dihydro-1,4-dioxin	370
37.9.1.3.4	Method 4: Other Reactions of 2,3-Dihydro-1,4-dioxin	372
37.9.1.3.4.1	Variation 1: Visible-Light-Induced Hydrobromodifluoromethylation	372
37.9.1.3.4.2	Variation 2: Catalytic Hydrogenation	373
37.9.1.3.4.3	Variation 3: Heck-Type Reactions	373
37.9.1.3.4.4	Variation 4: Cyclopropanation	374
37.9.1.4	Synthesis by Modification of the Parent 1,4-Dioxane	375
37.9.1.4.1	Method 1: C(sp ³)—C(sp ³) Coupling Reactions	375
37.9.1.4.2	Method 2: Formation of C(sp ³)—C(sp ³) Bonds by Radical Addition to Alkenes	377
37.9.1.4.3	Method 3: Formation of C(sp ³)—C(sp ³) Bonds by Radical Addition to Ketones	391
37.9.1.4.4	Method 4: Formation of C(sp ³)—C(sp ³) Bonds by Mannich-Type Reactions	391
37.9.1.4.5	Method 5: Formation of C(sp ³)—C(sp ²) Bonds via Cross-Coupling with Boronic Acids	395
37.9.1.4.6	Method 6: Formation of C(sp ³)—C(sp ²) Bonds via Substitution of Hydrogen in Alkenes	395

37.9.1.4.7	Method 7: Formation of C(sp ³)—C(sp ²) Bonds via Substitution of Other Groups in Alkenes	399
37.9.1.4.8	Method 8: Formation of C(sp ³)—C(sp ²) Bonds via Substitution at the C=O and C=N Carbon Atoms	402
37.9.1.4.9	Method 9: Formation of C(sp ³)—C(sp ²) Bonds via C(sp ³)—C(sp) Coupling Reactions	404
37.9.1.4.10	Method 10: Formation of C(sp ³)—C(sp) Bonds via C(sp ³)—C(sp) Coupling Reactions	407
37.9.1.4.11	Method 11: Formation of C—N Bonds	409
37.9.1.4.12	Method 12: Formation of C—O Bonds	410
37.9.1.4.13	Method 13: C—H Carbene Insertions	418

Special Topic

3.3.4	Biocatalytic Oxidation of Alcohols: An Overview New F. Hollmann	
3.3.4	Biocatalytic Oxidation of Alcohols: An Overview	429
3.3.4.1	The Catalysts Used	429
3.3.4.2	Regeneration Systems	432
3.3.4.2.1	NAD(P) ⁺ Regeneration Systems	432
3.3.4.2.2	Regeneration of Oxidases	433
3.3.4.3	Oxidation of Primary Alcohols	434
3.3.4.3.1	Oxidation to Aldehydes	434
3.3.4.3.2	Oxidation to Carboxylates	437
3.3.4.4	Oxidation of Secondary Alcohols	442
3.3.4.4.1	Regioselective Oxidation of Polyols	443
3.3.4.4.2	Kinetic Resolution Reactions and Deracemization Reactions	445
3.3.4.5	Conclusions and Outlook	451
	Author Index	457
	Abbreviations	477