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The synthesis of tryptophan derivatives, 2- and/or 3-substituted indoles, progress toward dilemmaones A-C, and synthetic studies towards fistulosin via palladium-catalyzed reductive N-heteroannulation

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**The Synthesis of Tryptophan Derivatives, 2- and/or 3-
Substituted Indoles, Progress Toward Dilemmaones A-C, and
Synthetic Studies Towards Fistulosin via Palladium-Catalyzed
Reductive *N*-Heteroannulation**

Christopher Andrew Dacko

Dissertation submitted to the Eberly College of Arts and Sciences at West Virginia

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in

Chemistry

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heteroannulation

Abstract

The Synthesis of Tryptophan Derivatives, 2- and/or 3-Substituted Indoles, Progress Toward Dilemmaones A-C, and Synthetic Studies Towards Fistulosin via Palladium-Catalyzed Reductive *N*-Heteroannulation

Christopher Andrew Dacko

Palladium-catalyzed carbon monoxide-mediated reductive *N*-heteroannulation of *o*-nitrostyrenes has emerged as a very powerful method for constructing the corresponding indole core. The Söderberg variety of this methodology has been utilized to synthesize several asymmetric tryptophan derivatives along with a collection of 2- and/or 3-substituted indoles. The same protocol has also been employed to make synthetic progress toward the construction of the marine indole alkaloids Dilemmaones A-C. Finally, this versatile cyclization was implemented in studies designed to determine the true structure of the compound isolated by Tomita *et. al.* and given the name “fistulosin”.

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Table of Contents

Title Page	i
Abstract	ii
Acknowledgment	iii
Table of Contents	iv
List of Figures	ix
List of Schemes	xx
List of Tables	xxvi

Chapter 1

Introduction to Indole, Indole History and Classic Routes to the Indole Core

1.1 Indole Background and Notable Indoles	2
1.2 Classic Routes to the Indole Core	7
1.2.1 Fischer Indole Synthesis	7
1.2.2 Madelung Indole Synthesis	10
1.2.3 Bartoli Indole Synthesis	11
1.2.4 Gassman Indole Synthesis	12
1.2.5 Leimgruber-Batcho Indole Synthesis	13
1.2.6 Nenitzescu Indole Synthesis	15

Chapter 2

Indole Formation via Palladium-Catalyzed *N*-Heteroannulation

2.1 Introduction	18
2.2 Indole Formation via <i>o</i> -Alkynylanilides and <i>o</i> -Alkynylanilines	18
2.3 Indole Formation via Intermolecular Cycloaddition with Alkynes	20
2.4 Indole Formation via <i>o</i> -Allylanilines	21
2.5 Indole Formation via <i>o</i> -Vinylanilines	22
2.6 Indole Formation via Buchwald/Hartwig <i>N</i> -Arylation Processes	22
2.7 Indole Formation via Nitrenes	24

Chapter 3

Synthesis of Tryptophan Derivatives via Palladium-Catalyzed *N*-Heteroannulation

3.1 Introduction to Tryptophan/Tryptophan Skeleton in Natural Products	42
3.2 Previous Enantioselective Syntheses of α -Amino Acid Derivatives	44
3.3 Tryptophan Derivatives via Palladium-Catalyzed <i>N</i> -Heteroannulation	54
3.3.1 Retrosynthetic Analysis	54
3.3.2 Results and Discussion	55
3.3.3 Conclusions	79

Chapter 4

Synthesis of 2- and/or 3-Substituted Indoles Utilizing Palladium-Catalyzed Reductive *N*-Heteroannulation

4.1 Attempted Synthesis of 3-Silylindoles	81
4.2 Synthesis of 2-Substituted Indoles via Hydrosilylation	82
4.3 Synthesis of 2,3- and 3-Substituted Indoles via Hydrostannylation	85
4.4 Conclusions	92

Chapter 5

Synthetic Progress Toward the Construction of Dilemmaones A-C

5.1 Introduction & Background	94
5.2 Retrosynthetic Analysis	96
5.3 Attempted Synthesis of Dilemmaone B	97
5.4 Conclusions	104

Chapter 6

Synthetic Studies Towards Fistulosin Utilizing Palladium- Catalyzed Reductive *N*-Heteroannulation

6.1 Fistulosin Background	106
6.2 Synthetic Studies Towards Fistulosin by Clawson <i>et. al.</i>	107

6.3 Synthetic Studies Towards Fistulosin by Nishida <i>et. al.</i>	115
6.4 Dimer Synthesis and Analysis via Palladium-Catalyzed <i>N</i> -Heteroannulation	123
6.5 Conclusions	129

Chapter 7

Miscellaneous Reactions Forming Novel Heterocycles

7.1 Synthesis of 3-(Halomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxides	131
7.2 Incorporation of Additives into <i>N</i> -Heteroannulations	134
7.3 Conclusions	136

Chapter 8

Supporting Information: Experimental Procedures

8.1 Supporting Information Chapter 3: Tryptophan Derivatives	139
8.2 Supporting Information Chapter 4: 2- and/or 3-Substituted Indoles	165
8.3 Supporting Information Chapter 5: Dilemmaones A-C	175
8.4 Supporting Information Chapter 6: Fistulosin	179
8.5 Supporting Information Chapter 7: Miscellaneous Reactions	184

Appendix

^1H and ^{13}C NMR Spectra

● ^1H and ^{13}C NMR for Chapter 3: Tryptophan Derivatives	200
● ^1H and ^{13}C NMR for Chapter 4: 2- and/or 3-Substituted Indoles	256
● ^1H and ^{13}C NMR for Chapter 5: Dilemmaones A-C	279
● ^1H and ^{13}C NMR for Chapter 6: Fistulosin	291
● ^1H and ^{13}C NMR for Chapter 7: Miscellaneous Reactions	317

List of Figures

Figure 1: Structure and Numbering of Indole	2
Figure 2: Structures of L-Tryptophan, Serotonin, Melatonin, and Sumatriptan	4
Figure 3: Structures of Ergoline, LSD, and Lisuride	5
Figure 4: Structures of Yohimbine, Ellipticine, and Strychnine	5
Figure 5: Structures of Eudistomin L, Dragmacidin, and Dihydroflustramine C	6
Figure 6: Typical Singlet and Triplet Nitrenes	24
Figure 7: Structures of L-Tryptophan and D-Tryptophan	42
Figure 8: Structures of Brevicompanine C and Fiscalin B	43
Figure 9: Structures of Echinulan, Fuchsiaefoline, and Alstophylline	43
Figure 10: General Structure of Tryptophan Target Molecule	54
Figure 11: Structures of Dilemmaones A-C	94
Figure 12: Structures of the Trikentrins	95
Figure 13: Structures of the Herbindoles	95
Figure 14: Tomita's Proposed Structure of Fistulosin	106
Figure 15: Naturally-Occurring Dimeric Indolinone Alkaloids	107
Figure 16: Antifungal Natural Products Containing Long Aliphatic Chains	109
Figure 17: Comparison of ^{13}C NMR Shifts of Heterocycles at C-3	122
Figure 18: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)- 2-(2-trimethylstannyl-2-propen-1-yl)pyrazine (238)	200
Figure 19: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)- 2-(2-trimethylstannyl-2-propen-1-yl)pyrazine (238)	201

Figure 20: ¹ H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)- 2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (239)	202
Figure 21: ¹³ C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)- 2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (239)	203
Figure 22: ¹ H NMR of (2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)- 2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine (241)	204
Figure 23: ¹³ C NMR of (2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)- 2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine (241)	205
Figure 24: ¹ H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2- (2-(5-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (243)	206
Figure 25: ¹³ C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2- (2-(5-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (243)	207
Figure 26: ¹ H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2- nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (245)	208
Figure 27: ¹³ C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2- nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (245)	209
Figure 28: ¹ H NMR of Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)- 3,6-dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate (247)	210
Figure 29: ¹³ C NMR of Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)- 3,6-dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate (247)	211
Figure 30: ¹ H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2- (2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (249)	212

Figure 31: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (249)	213
Figure 32: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (251)	214
Figure 33: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (251)	215
Figure 34: ^1H NMR of Bis-2,3-((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene (254)	216
Figure 35: ^{13}C NMR of Bis-2,3-((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene (254)	217
Figure 36: ^1H NMR of (3-Methoxy-2-nitrophenyl)trimethylstannane (261)	218
Figure 37: ^{13}C NMR of (3-Methoxy-2-nitrophenyl)trimethylstannane (261)	219
Figure 38: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (256)	220
Figure 39: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (256)	221
Figure 40: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (262)	222
Figure 41: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (262)	223
Figure 42: ^1H NMR of (2R,5S)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (275)	224

Figure 43: ^{13}C NMR of (2R,5S)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (275)	225
Figure 44: ^1H NMR of (2R,5S)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (279)	226
Figure 45: ^{13}C NMR of (2R,5S)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (279)	227
Figure 46: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine (276)	228
Figure 47: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine (276)	229
Figure 48: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (<i>E/Z</i>) (280)	230
Figure 49: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (<i>E/Z</i>) (280)	231
Figure 50: ^1H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1 <i>H</i> -indole (263)	232
Figure 51: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1 <i>H</i> -indole (263)	233
Figure 52: ^1H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1 <i>H</i> -indole (264)	234
Figure 53: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1 <i>H</i> -indole (264)	235

Figure 54: ¹ H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1 <i>H</i> -indole (265)	236
Figure 55: ¹³ C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1 <i>H</i> -indole (265)	237
Figure 56: ¹ H NMR of 6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole (266)	238
Figure 57: ¹³ C NMR of 6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole (266)	239
Figure 58: ¹ H NMR of Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole-6-carboxylate (267)	240
Figure 59: ¹³ C NMR of Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole-6-carboxylate (267)	241
Figure 60: ¹ H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-nitro-1 <i>H</i> -indole (268)	242
Figure 61: ¹³ C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-nitro-1 <i>H</i> -indole (268)	243
Figure 62: ¹ H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine (269)	244
Figure 63: ¹³ C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine (269)	245
Figure 64: ¹ H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-4-methoxy-1 <i>H</i> -indole (270)	246

Figure 65: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-4-methoxy-1 <i>H</i> -indole (270)	247
Figure 66: ^1H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1 <i>H</i> -indole (271)	248
Figure 67: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1 <i>H</i> -indole (271)	249
Figure 68: ^1H NMR of 3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)ethyl)-1 <i>H</i> -indole (277)	250
Figure 69: ^{13}C NMR of 3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)ethyl)-1 <i>H</i> -indole (277)	251
Figure 70: ^1H NMR of 2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole (281)	252
Figure 71: ^{13}C NMR of 2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1 <i>H</i> -indole (281)	253
Figure 72: ^1H NMR of 2-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1-hydroxyindole (282)	254
Figure 73: ^{13}C NMR of 2-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1-hydroxyindole (282)	255
Figure 74: ^1H NMR of Triethyl((E)-1-(2-nitrophenyl)hex-1-enyl)silane (290)	256
Figure 75: ^{13}C NMR of Triethyl((E)-1-(2-nitrophenyl)hex-1-enyl)silane (290)	257
Figure 76: ^1H NMR of 1,2-Bis(2-nitrophenyl)ethyne (298)	258
Figure 77: ^{13}C NMR of 1,2-Bis(2-nitrophenyl)ethyne (298)	259

Figure 78: ^1H NMR of Tributyl((E)-1-(2-nitrophenyl)-2-phenylvinyl)stannane (303)	260
Figure 79: ^{13}C NMR of Tributyl((E)-1-(2-nitrophenyl)-2-phenylvinyl)stannane (303)	261
Figure 80: ^1H NMR of 1-Methoxy-4-((Z)-1-(2-nitrophenyl)-2-phenylvinyl)benzene (306)	262
Figure 81: ^{13}C NMR of 1-Methoxy-4-((Z)-1-(2-nitrophenyl)-2-phenylvinyl)benzene (306)	263
Figure 82: ^1H NMR of Tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (308)	264
Figure 83: ^{13}C NMR of Tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (308)	265
Figure 84: ^1H NMR of Tributyl(1-(2-nitrophenyl)vinyl)stannane (311)	266
Figure 85: ^{13}C NMR of Tributyl(1-(2-nitrophenyl)vinyl)stannane (311)	267
Figure 86: ^1H NMR of 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312)	268
Figure 87: ^{13}C NMR of 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312)	269
Figure 88: ^1H NMR of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene (314) and 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312).	270
Figure 89: ^{13}C NMR of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene (314) and 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312).	271
Figure 90: ^1H NMR of 1,1-Bis(2-nitrophenyl)ethene (316)	272
Figure 91: ^{13}C NMR of 1,1-Bis(2-nitrophenyl)ethene (316)	273
Figure 92: ^1H NMR of Indolo[2,3- <i>b</i>]indole (317)	274
Figure 93: ^{13}C NMR of Indolo[2,3- <i>b</i>]indole (317)	275
Figure 94: ^1H NMR of 5H-Indolo[2,3- <i>c</i>]quinolin-6(7H)-one (318)	276

Figure 95: ^{13}C NMR of 5H-Indolo[2,3- <i>c</i>]quinolin-6(7H)-one (318)	277
Figure 96: ^{13}C NMR APT and DEPT-90 of 5H-Indolo[2,3- <i>c</i>]quinolin-6(7H)-one (318)	278
Figure 97: ^1H NMR of 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (347)	279
Figure 98: ^{13}C NMR of 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (347)	280
Figure 99: ^1H NMR of <i>N</i> -(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (348)	281
Figure 100: ^{13}C NMR of <i>N</i> -(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (348)	282
Figure 101: ^1H NMR of <i>N</i> -(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (349)	283
Figure 102: ^{13}C NMR of <i>N</i> -(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (349)	284
Figure 103: ^1H NMR of 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (346)	285
Figure 104: ^{13}C NMR of 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (346)	286
Figure 105: ^1H NMR of 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (329)	287
Figure 106: ^{13}C NMR of 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (329)	288

Figure 107: ^1H NMR of 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (350)	289
Figure 108: ^{13}C NMR of 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (350)	290
Figure 109: ^1H NMR of 2-(Icos-1-ynyl)benzenamine (396)	291
Figure 110: ^{13}C NMR of 2-(Icos-1-ynyl)benzenamine (396)	292
Figure 111: ^1H NMR of 1-(Icos-1-ynyl)-2-nitrobenzene (398)	293
Figure 112: ^{13}C NMR of 1-(Icos-1-ynyl)-2-nitrobenzene (398)	294
Figure 113: ^1H NMR of Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (399)	295
Figure 114: ^{13}C NMR of Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (399)	296
Figure 115: ^1H NMR of 2-Octadecyl-1H-indole (397)	297
Figure 116: ^{13}C NMR of 2-Octadecyl-1H-indole (397)	298
Figure 117: ^1H NMR of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	299
Figure 118: ^{13}C NMR of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	300
Figure 119: ^1H NMR Expansion of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	301
Figure 120: ^{13}C NMR Expansion of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	302
Figure 121: gHMBC of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	303
Figure 122: gHMBC Expansion (aliphatic region) of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	304

Figure 123: gHMBC Expansion (aromatic region) of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1 <i>H</i> -indol-2-yl)-1,2-dihydro-3 <i>H</i> -indol-3-one (392)	305
Figure 124: ¹ H NMR of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	306
Figure 125: ¹³ C NMR of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	307
Figure 126: ¹ H NMR Expansion of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	308
Figure 127: ¹³ C NMR Expansion (aliphatic region) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	309
Figure 128: ¹³ C NMR Expansion (aromatic region) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	310
Figure 129: gHMBC Expansion (ring linkage) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	311
Figure 130: gHMBC Expansion (diastereotopic protons) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	312
Figure 131: gHMBC Expansion (aromatics) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	313
Figure 132: gHMBC Expansion (carbonyl) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	314
Figure 133: 2D NOESY (full) of 2-Octadecyl-2-(2-octadecyl-1 <i>H</i> -indol-3-yl)indolin-3-one (404)	315

Figure 134: 2D NOESY Expansion (aromatic region) of 2-Octadecyl- 2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (404)	316
Figure 135: ¹ H NMR of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	317
Figure 136: ¹³ C NMR of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	318
Figure 137: gHMBC of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	319
Figure 138: 1D NOE of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	320
Figure 139: HETCOR of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	321
Figure 140: COSY of 3-(Bromomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (412)	322
Figure 141: ¹ H NMR of 3-(Chloromethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide (415)	323
Figure 142: ¹ H NMR of Methyl 1,2-dihydroquinoline-5-carboxylate (418)	324

List of Schemes

Scheme 1: Indigo Oxidation to Isatin	3
Scheme 2: Conversion of Isatin to Oxindole	3
Scheme 3: Synthesis of Indole from Oxindole	3
Scheme 4: Synthesis of MDL 103371 Utilizing Fischer Indole Synthesis	8
Scheme 5: Mechanism of the Fischer Indole Synthesis	9
Scheme 6: Buchwald Modification of the Fischer Indole Synthesis	10
Scheme 7: Madelung Indole Synthesis of 2-Methylindole	10
Scheme 8: Madelung-Houlihan Indole Synthesis of 5-Chloro-2-phenylindole	11
Scheme 9: Bartoli Indole Synthesis of 7-Bromo-4-ethylindole	11
Scheme 10: Mechanism of the Bartoli Indole Synthesis	12
Scheme 11: Gassman Indole Synthesis	13
Scheme 12: Leimgruber-Batcho Indole Synthesis of 5-Formylindole	15
Scheme 13: Nenitzescu Indole Synthesis	15
Scheme 14: Mechanism of the Nenitzescu Indole Synthesis	16
Scheme 15: Palladium-Catalyzed Synthesis of Indoles from <i>o</i> -Alkynylanilides	19
Scheme 16: Palladium-Catalyzed Synthesis of Indoles from <i>o</i> -Alkynylanilines	20
Scheme 17: Synthesis of Psilocin via the Larock Heteroannulation	21
Scheme 18: Palladium-Catalyzed Heteroannulation of <i>o</i> -Allylanilines	22
Scheme 19: Palladium-Catalyzed Heteroannulation of <i>o</i> -Vinylanilines	22
Scheme 20: The Buchwald/Hartwig <i>N</i> -Arylation Route to Indoles	23
Scheme 21: Willis Route to <i>N</i> -Substituted Indoles	24
Scheme 22: First Nitrene in the Synthesis of Nitrogen Containing Heterocycles	25

Scheme 23: Mechanism of Carbazole Formation via Azide Decomposition	25
Scheme 24: Singlet Nitrene vs. Triplet Nitrene in the Formation of Carbazole	26
Scheme 25: Sundberg Indole Synthesis	27
Scheme 26: Cadogan-Sundberg Indole Synthesis	27
Scheme 27: Mechanism of Cadogan-Sundberg Indole Synthesis	28
Scheme 28: Alternate Cadogan-Sundberg Reaction Pathway	29
Scheme 29: First Transition Metal Promoted Deoxygenation of Nitroaromatics	29
Scheme 30: Kasahara Heck Reaction/Indole Synthesis	30
Scheme 31: Watanabe Pd-Catalyzed Reductive <i>N</i> -Heteroannulation	31
Scheme 32: Cenini Pd-Catalyzed Reductive <i>N</i> -Heteroannulation	32
Scheme 33: Kuethe and Davies Pd-Catalyzed Reductive <i>N</i> -Heteroannulation	33
Scheme 34: Dong Transformation of Conjugated Nitroalkenes into Indoles	33
Scheme 35: Söderberg Attempted Methoxycarbonylation/Indole Synthesis	34
Scheme 36: Optimized Söderberg <i>N</i> -Heteroannulation Conditions	35
Scheme 37: Synthesis of Koniamborine Using Alternate Söderberg Conditions	35
Scheme 38: Effect of Söderberg <i>N</i> -Heteroannulation on Isomeric Mixtures	36
Scheme 39: Possible Palladium-Olefin Coordination in <i>N</i> -Heteroannulation	37
Scheme 40: Proposed Mechanistic Pathway(s) of Reductive <i>N</i> -Heteroannulation	38
Scheme 41: Watanabe <i>N</i> -Heteroannulation of Deuterated Nitro-olefin	39
Scheme 42: Mechanistic [1,5]-Alkyl Shift in Reductive <i>N</i> -Heteroannulation	39
Scheme 43: Dellaria Alkylation of Homochiral Glycine Enolate Synthon	44
Scheme 44: Leanna Biocatalytic Kinetic Resolution of a Racemic Amino Ester	45
Scheme 45: Myers Direct Alkylation of Pseudoephedrine Glycinamide Hydrate	46

Scheme 46: Hruby Asymmetric Hydrogenation of α -Enamides	47
Scheme 47: Gellerman Tryptophan Synthesis via Fischer-Indole Reaction	48
Scheme 48: Chen Synthesis of the Schöllkopf Chiral Auxiliary	49
Scheme 49: Lithiation/Alkylation of Schöllkopf's Chiral Auxiliary	50
Scheme 50: Hydrolysis/Saponification of Alkylated Pyrazine	50
Scheme 51: Sakagami Tryptophan Synthesis	51
Scheme 52: Cook Tryptophan Synthesis	52
Scheme 53: Castle Tryptophan Synthesis	53
Scheme 54: Proposed Retrosynthetic Outline to Tryptophan Derivatives	55
Scheme 55: Alkylation of Schöllkopf Auxiliary	55
Scheme 56: Alternate route to the Vinyl Stannane	57
Scheme 57: Attempted Synthesis of the Vinyl Boronate Ester	57
Scheme 58: Isomerization in Kosugi-Migita-Stille Cross-Coupling	58
Scheme 59: Söderberg <i>N</i> -Heteroannulation on the Isomeric Mixture	59
Scheme 60: Thermally Induced Isomerizations	61
Scheme 61: Cook's Isotryptophan Isomerization	62
Scheme 62: Hydrolysis/Boc-Protection of Alkylated Schöllkopf Auxiliary	63
Scheme 63: Suzuki-Type Coupling of Aryl Boronate Ester	64
Scheme 64: Synthetic Routes to Methyl 2-(2-nitrophenyl)acrylate	65
Scheme 65: Attempted Alkylation Route to Cyclization Precursor	65
Scheme 66: Utilization of Levin's Cross-Coupling Conditions	66
Scheme 67: Successful Cyclization of Amino Ester Nitrostyrene	66
Scheme 68: Successful Coupling/Cyclization with Pyrazine Moiety	67

Scheme 69: De Kimpe Palladium-Catalyzed Trimethylstannylation	68
Scheme 70: Conversion to Amino Acid-Containing Tin Derivative	68
Scheme 71: Homocoupling in the Reaction of 6-Methoxy-2-nitro-1-iodobenzene	71
Scheme 72: Successful Coupling Using Corresponding 6-Methoxy-1-stannane	71
Scheme 73: Homocoupling in the Reaction of 3-Methoxy-2-nitro-1-iodobenzene	72
Scheme 74: Successful Coupling Using Corresponding 3-Methoxy-1-stannane	73
Scheme 75: Synthesis of D-Homotryptophan	77
Scheme 76: Attempted Synthesis of D-Isotryptophan	78
Scheme 77: Alami Regioselective Hydrosilylation	81
Scheme 78: Exposure of Vinylsilane to Söderberg <i>N</i> -Heteroannulation	82
Scheme 79: Katritsky Synthesis of 2-Alkylindoles	83
Scheme 80: Synthesis of 2-Butylindole	84
Scheme 81: Synthesis of 2-Phenylindole	84
Scheme 82: Attempted Synthesis of Indolo[3,2- <i>b</i>]indole via Hydrosilylation	85
Scheme 83: Alami Regioselective Hydrostannylation	86
Scheme 84: Attempted Synthesis of 2-Phenyl-3-stannylindole	86
Scheme 85: Successful Synthesis of 2-Phenyl-3-arylindole	87
Scheme 86: Formation of Alkylstannane Using Tributyltinhydride	87
Scheme 87: Synthesis of Tributyl(1-(2-nitrophenyl)vinyl)stannane	89
Scheme 88: Synthesis of 3-(1H-Indol-3-yl)-1H-indole	89
Scheme 89: Synthesis of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene	90

Scheme 90: Cyclization of the Inseparable 3:1 Mixture of o-Nitrostyrenes	90
Scheme 91: Synthesis of Fused Heterocycles	91
Scheme 92: Retrosynthetic Route to Dilemmaone B	96
Scheme 93: Synthesis of 5-Methylindanone	97
Scheme 94: Synthesis of 6-Amino-5-methylindanone	97
Scheme 95: Nitration of 2,4-Dibromoaniline	98
Scheme 96: Mechanism of Free-Aniline Nitration	99
Scheme 97: Synthesis of Cyclohexadienone Nitrating Agent	99
Scheme 98: Unexpected Bromination of Aniline Intermediate	100
Scheme 99: Similar Indanone Bromination using $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3$	100
Scheme 100: Formation of Acetanilide using Acetyl Chloride	101
Scheme 101: Formation of 6-Halo-5-methyl-7-nitroindanones	102
Scheme 102: Construction of (E)-3-(Tributylstannyl)prop-2-en-1-ol	103
Scheme 103: Attempted Formation of Dilemmaone B Precursor	103
Scheme 104: Unattempted Hydrosilylation Pathway to Dilemmaone B	104
Scheme 105: Clawson Attempted Route to Proposed Fistulosin	108
Scheme 106: Ring-Opening Oxidative Cleavage of Methoxy-Indole	109
Scheme 107: Biodegradation of Indole with White Rot Fungus	110
Scheme 108: Synthesis of 2-(Nonadecanamido)benzoic acid	110
Scheme 109: Synthesis of 2-(Octadecanamido)benzoic acid	113
Scheme 110: Nishida Synthesis of 2-Octadecyl-3-indolinone	116
Scheme 111: Tautomerization of 3-Indolinone 354 in Acidic Medium	117
Scheme 112: Nishida Synthesis of 3-Octadecyl-2-oxindole	117

Scheme 113: Formation of Indigo via Oxidative Dimerization	119
Scheme 114: Formation of Tyriverdin via Dimerization	119
Scheme 115: Van Vranken Synthesis of Peronatin B	120
Scheme 116: Possible Dimerization of 2-Octadecyl-3-indolinone	121
Scheme 117: Failed Route to 2-Octadecylindole	123
Scheme 118: Söderberg <i>N</i> -Heteroannulation Route to 2-Octadecylindole	124
Scheme 119: Attempted Dimerization Using Van Vranken Conditions	125
Scheme 120: Preparation of Dimers via Oxidation of 2-Methylindole	126
Scheme 121: Intermediates in Dimer Formations	126
Scheme 122: Successful Synthesis of 2,2'-Biindoliny Dimer	127
Scheme 123: Attempted Synthesis of 3-Bromo-2-phenylindole	131
Scheme 124: Hydrobromination of 1,2-Bis(ethynyl)benzene	132
Scheme 125: Synthesis of 1-Ethynyl-2-nitrobenzene	132
Scheme 126: Exposure of 1-Ethynyl-2-nitrobenzene to HBr in 3-Pentanone	133
Scheme 127: Mechanism of Benzisoxazole- <i>N</i> -oxide Formation	133
Scheme 128: Synthesis of 3-(Chloromethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxide	134
Scheme 129: Reaction of HBr with 1-Nitro-2-vinylbenzene	134
Scheme 130: Attempted Incorporation of Dihydropyran into <i>N</i> -heteroannulation	135
Scheme 131: Synthesis of Dihydroquinoline 418	135
Scheme 132: Attempted Incorporation of Hexanal into <i>N</i> -heteroannulation	136

List of Tables

Table 1: Attempts to Convert to the Vinyl Stannane	56
Table 2: Attempted Couplings with Pyrazine Moiety	60
Table 3: Attempted Couplings with Amino Ester Moiety	63
Table 4: Results of Kosugi-Migita-Stille Cross-Couplings	69
Table 5: Results of Palladium-Catalyzed <i>N</i> -Heteroannulations	74
Table 6: Cross-Coupling Attempts with Alkylstannane	88
Table 7: Attempts to Nitrate Acetanilide Intermediate	101
Table 8: Comparison of Tomita's Fistulosin and Carboxylic Acid 370	112
Table 9: Comparison of Tomita's Fistulosin and Carboxylic Acid 373	114
Table 10: Comparison of Nishida's Fistulosin Candidates	118
Table 11: Comparison of Nishida's 3-Hydroxyindole and Peronatin B	121
Table 12: Comparison of Dimer 392 with Nishida's 3-Hydroxyindole	128

Chapter 1

Introduction to Indole, Indole History and Classic Routes to the Indole Core

1.1 Indole Background and Notable Indoles	2
1.2 Classic Routes to the Indole Core	7
1.2.1 Fischer Indole Synthesis	7
1.2.2 Madelung Indole Synthesis	10
1.2.3 Bartoli Indole Synthesis	11
1.2.4 Gassman Indole Synthesis	12
1.2.5 Leimgruber-Batcho Indole Synthesis	13
1.2.6 Nenitzescu Indole Synthesis	15

1.1 Indole Background and Notable Indoles

Indole (**1**) is the commonly used name for the benzopyrrole in which the benzene ring is fused to the 2- and 3-positions of the pyrrole ring.¹ Its name is an acronym from *indigo*, the natural dye it originated from, and *oleum*, which is used for the isolation.² Numbering of the atoms in indole begins with the nitrogen atom and proceeds counterclockwise around the nucleus (Figure 1).

Figure 1: Structure and Numbering of Indole

1

Indole is a planar heteroaromatic molecule. The ten-electron π -system is formed by a pair of electrons from the nitrogen atom and eight electrons from the eight carbon atoms.² Indoles are highly reactive toward electrophilic reagents, including acids and certain oxidants, with the 3-position being the most reactive site for substitution. The high reactivity of the 3-position can be predicted on the basis of π -electron density, localization energy, or frontier electron density information obtained from molecular orbital calculations.² The N-H group of indoles is relatively acidic ($pK_a = 17$) and forms the anion in the presence of strong bases.¹ Although the electron pair of this anion is orthogonal to the π -system, it nevertheless increases reactivity at C-3 toward electrophiles.¹ As a consequence, the indolyl anion has ambident properties in alkylation and acylation reactions.¹

The synthesis and reactivity of indole derivatives has been a topic of research interest for well over a century.³ As previously mentioned, the development of indole

chemistry began with extensive research on the dye indigo (**2**).¹ In 1841, indigo was oxidized to isatin (**3**) using nitric acid (Scheme 1).⁴

Scheme 1: Indigo Oxidation to Isatin

In 1866, Baeyer and Knop successfully converted isatin (**3**) to oxindole (**5**). This transformation was achieved by the reduction of isatin (**3**) with sodium amalgam in water to dioxindole (**4**), which, without isolation, could be further reduced to oxindole (**5**) with the same reagent in aqueous acidic medium (Scheme 2).⁵

Scheme 2: Conversion of Isatin to Oxindole

Later in 1866 Baeyer prepared indole (**1**) by zinc dust pyrolysis of oxindole (**5**) (Scheme 3).⁶ In 1869, he proposed the formula of indole that is accepted today.⁷

Scheme 3: Synthesis of Indole from Oxindole

Indole chemistry continued to be important in the dyestuff industry until the beginning of the twentieth century when newer dyes overtook the indoles.¹ This caused a

brief decline in indole research, but interest was quickly renewed in the 1930's when it was discovered that many useful alkaloids contained the indole nucleus.¹ This interest is even greater in modern times, considering that reports of several thousand individual indole derivatives appear annually in the chemical literature.³ In fact, the indole ring system is probably the most frequently found heterocycle in nature.⁸ The main reason for this sustained attraction is the wide range of biological activity found among indoles.³ There are several indoles involved in processes in the human body. L-Tryptophan (**6**),⁹ is one of the 20 standard amino acids, as well as an essential amino acid in the human diet. In addition, tryptophan functions as a biochemical precursor for serotonin (**7**),¹⁰ a neurotransmitter synthesized via tryptophan hydroxylase.¹¹ Serotonin can be further converted to melatonin (**8**), a neurohormone, via N-acetyltransferase and 5-hydroxyindole-O-methyltransferase activities.¹² A pharmaceutically relevant indole containing the same basic structural skeleton is sumatriptan (**9**), which is used in the treatment of migraine headaches (Figure 2).¹³

Figure 2: Structures of L-Tryptophan, Serotonin, Melatonin, and Sumatriptan

Ergoline (**10**) is an indole derivative whose structural skeleton is contained in a diverse range of alkaloids used for vasoconstriction and treatment of Parkinson's disease.¹⁴ The ergoline core is also seen in a few psychedelic drugs. For example, lysergic acid diethylamide (**11**), commonly called LSD, is a famous hallucinogen.

Lisuride (**12**) is an anti-Parkinson's drug also used to lower prolactin, a peptide hormone associated with lactation (Figure 3).¹⁵

Figure 3: Structures of Ergoline, LSD, and Lisuride

In addition, yohimbine (**13**),¹⁶ has been shown in human studies to be effective in the treatment of male impotence. Ellipticine (**14**) has received a tremendous amount of attention from the synthetic community due to its potent antitumor activity.¹⁷ Strychnine (**15**) is a very toxic indole alkaloid used as a pesticide to kill small birds and rodents (Figure 4).¹⁸

Figure 4: Structures of Yohimbine, Ellipticine, and Strychnine

Marine organisms produce an unprecedented molecular diversity by the incorporation of elements like bromine that are not readily available to terrestrial species.¹⁹ Marine indole alkaloids are often produced and are of great importance due to the significant activity that they have elicited in cancer and cytotoxicity assays.¹⁹ Eudistomin L (**16**) contains a novel oxathiazepine ring and shows antiviral activity by

inhibiting HSV-1 growth.²⁰ Dragmacidin (**17**), a bisindole alkaloid isolated from a deep water marine sponge, has shown cytotoxicity against P-388 cell lines and activity against human lung and colon cancer cell lines.²¹ Dihydroflustramine C (**18**), isolated from the marine bryozoan *F. foliacea*, exhibits a wide antibacterial spectrum including activity against *E. coli* (Figure 5).²²

Figure 5: Structures of Eudistomin L, Dragmacidin, and Dihydroflustramine C

This wealth of biologically active indole derivatives found in nature has sparked organic researchers past and present to develop numerous synthetic strategies to produce the indole core. Some of these methods, involving extremely diverse starting materials and reaction conditions, are discussed in the next section.

1.2 Classic Routes to the Indole Core

For well over 100 years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists.⁸ This interest is mostly due to the remarkable range of biological and medicinal properties displayed by indole-containing molecules.²³ Substituted indoles have been referred to as “privileged structures” since they are capable of binding to many receptors with high affinity.²⁴ The principal commercial source of indole (**1**) is extraction from coal tar, although the feasibility of industrial synthesis from starting materials such as aniline and ethylene glycol, *N*-ethylaniline, or 2-ethylaniline has been demonstrated.³ Highly substituted indoles, such as the many that appear in biologically active natural and unnatural compounds, are not as easily harvested from natural sources. These indoles, most often, must be produced synthetically using one of the numerous methods that have been developed for the preparation of the indole core. Key factors, including starting material availability and functional group tolerance, often dictate which particular indole synthesis will be suitable.⁸

1.2.1 Fischer Indole Synthesis

The Fischer indole synthesis^{25, 26} has remained an extremely useful method for the synthesis of a variety of indole intermediates and biologically active compounds.²⁷ Even though it was developed in 1883, it is still probably the most widely used of all the indole syntheses. The Fischer reaction provides a simple method for the transformation of enolizable *N*-arylhydrazones into indoles. The cyclization is usually carried out with a protic acid or Lewis acid (mainly ZnCl₂) which functions both to facilitate the formation of the enehydrazine by tautomerization and also to assist the N-N bond cleavage.^{3, 27}

Watson *et. al.*²⁸ recently developed a large-scale preparation of MDL 103371 (**23**), an *N*-methyl-D-aspartate (NMDA)-type glycine receptor antagonist for the potential treatment of stroke, based on Fischer indolization chemistry. Starting from commercially available 3,5-dichlorophenylhydrazine (**19**), treatment with ethyl pyruvate in ethanol gave the hydrazone **20** as an *E/Z* mixture. Fischer cyclization using polyphosphoric acid (PPA) provided the indole **21** in excellent yield. Next, a Vilsmeier-Haack formylation gave aldehyde **22**, which was then converted to MDL 103371 (**23**) in six steps and 49% overall yield (Scheme 4).²⁸

Scheme 4: Synthesis of MDL 103371 Utilizing Fischer Indole Synthesis

The mechanism of the reaction (Scheme 5), which is supported by spectroscopic observation of intermediates²⁹ and by isolation of examples of intermediates in specialized structures³⁰, is thought to begin with the tautomerization of hydrazone **20** to the ene-hydrazine **24**. Tautomer **24** then undergoes a [3,3]-sigmatropic rearrangement to

form bis iminobenzylketone **25**. Heteroannulation and aromatization gives indoline **26** which then loses ammonia to provide the indole product **21**.

Scheme 5: Mechanism of the Fischer Indole Synthesis

Advantages of the Fischer reaction include the acceptance of a wide range of compatible functional groups around the aromatic ring and lack of a requirement for a functional group to form the new C-C and C-N bonds⁸, while one major limitation is the availability of certain substituted aryl hydrazine or hydrazone intermediates. Buchwald and co-workers have narrowed this limitation³¹ by implementing a palladium-catalyzed coupling of hydrazones with aryl bromides as an entry to N-arylhydrazones for use in the Fischer indolization.^{8,32} For example, commercially available and inexpensive benzophenone hydrazone **27** was coupled to 1-bromo-4-chlorobenzene using palladium diacetate to give hydrazone **28**, which then gave indole **29** upon treatment with acid in the presence of cyclohexanone (Scheme 6).

Scheme 6: Buchwald Modification of the Fischer Indole Synthesis

1.2.2 Madelung Indole Synthesis

The Madelung synthesis produces the indole core by the intramolecular cyclization of *N*-phenylamides using a strong base at high temperatures.³³ Specifically, the original conditions for preparing 2-methylindole (**31**) involve heating *o*-methylacetanilide (**30**) with sodium amide at 250°C (Scheme 7).³⁴

Scheme 7: Madelung Indole Synthesis of 2-Methylindole

These conditions are so harsh that they are applicable only to indoles with the most inert substituents.³ The Houlihan modification³⁵ of the Madelung synthesis, however, utilizes *n*-butyllithium (*n*-BuLi) or lithium diisopropylamide (LDA) as bases under much milder conditions. Employing these improved conditions, the formation of 5-chloro-2-phenylindole (**34**) could be effected in excellent yield by treating *N*-(4-chloro-2-methylphenyl)benzamide (**32**) with two equivalents of *n*-BuLi in tetrahydrofuran (THF) at -20°C, producing dilithiated intermediate **33**³⁶, and then allowing the reaction mixture to gradually warm to room temperature (Scheme 8).³⁵

Scheme 8: Madelung-Houlihan Indole Synthesis of 5-Chloro-2-phenylindole

1.2.3 Bartoli Indole Synthesis

The Bartoli indole synthesis^{37,38} involves the reaction of *ortho*-substituted nitroarenes with three equivalents of a vinyl Grignard reagent to form highly-substituted indoles. It is particularly suitable for producing indoles that are substituted on both the 6- and 5-membered rings. The reaction is also a good method for synthesizing 7-substituted indoles. The presence of a group *ortho* to the nitro group is critical for the success of the reaction, but Dobbs has shown³⁹ that bromine can be used in that position and then removed under radical conditions using azobisisobutyronitrile (AIBN) and tributyltin hydride after formation of the indole. Blechert *et. al.* performed the Bartoli reaction with 1-bromo-4-ethyl-2-nitrobenzene (35) and vinylmagnesium bromide in THF to yield 7-bromo-4-ethylindole (36), which was subsequently converted to the marine natural product ($\pm$)-*cis*-trikentrin A (37) in seven steps (Scheme 9).⁴⁰

Scheme 9: Bartoli Indole Synthesis of 7-Bromo-4-ethylindole

The mechanism of the Bartoli indole synthesis⁴¹ begins with the addition of vinylmagnesium bromide to the nitroarene 35 to form intermediate 38. Intermediate 38

then decomposes to form nitrosoarene **39**. The second equivalent of Grignard reagent then reacts with nitrosoarene **39** to give intermediate **40**. Next, a [3,3]-sigmatropic rearrangement occurs to give aldehyde **41**. Cyclization and tautomerization of **41** gives indoline **43**, which reacts with a third equivalent of vinylmagnesium bromide to give dimagnesium salt **44**. Finally, reaction work-up eliminates water and gives the desired indole **36** (Scheme 10).

Scheme 10: Mechanism of the Bartoli Indole Synthesis

1.2.4 Gassman Indole Synthesis

The Gassman indole synthesis⁴² is a one-pot procedure used to synthesize substituted indoles from anilines. Under typical reaction conditions, 4-chloroaniline (**45**)

is first exposed to *tert*-butyl hypochlorite, giving *N*-chloroaniline **46**. Addition of the sulfide provided sulfonium ion **47**, which was deprotonated using triethylamine to give ylide **48**. Ylide **48** then undergoes a [2,3]-sigmatropic rearrangement to give ketone **49**. Cyclization, followed by loss of water, produces 5-chloro-2-methyl-3-(methylthio)-1H-indole (**50**) in 72% yield. If desired, the thiomethyl group can be removed using Raney-nickel to give 5-chloro-2-methyl-1H-indole (**51**) (Scheme 11).³

Scheme 11: Gassman Indole Synthesis

1.2.5 Leimgruber-Batcho Indole Synthesis

The Leimgruber-Batcho indole synthesis⁴³ is one of the most important and commonly used methods for preparing 2,3-unsubstituted indoles. This two-step method first involves the condensation of an appropriately substituted *o*-nitrotoluene with *N,N*-

dimethylformamide dimethylacetal (DMFDMA) to give an intermediate β -(dimethylamino)-2-nitrostyrene.⁸ The reaction depends on the nitro group both to acidify the toluene methyl group and to stabilize the enamine product. In the original version, the reaction was driven to completion by distillation of methanol.³ However, an improvement that has been widely adopted is the inclusion of pyrrolidine in the reaction mixture.⁴⁴ Under these conditions, the reaction is accelerated and the pyrrolidine is exchanged into the enamine product.³ The second step of the reaction involves reductive cyclization, which leads to substituted indoles. A number of reducing agents have been used, with the choice being dictated by the nature of the carbocyclic substituents.³ The two most common choices, however, are palladium on carbon/H₂ and Raney nickel/hydrazine. The reaction has been used extensively for the construction of key intermediates in pharmaceutically important compounds. Simig and co-workers⁴⁵ have demonstrated a new and practical synthesis of 5-formylindole (**56**), an intermediate in the synthesis of the antimigraine drug naratriptan (**57**). According to the authors, the 49% overall yield represents the most efficient synthetic route currently available for the preparation of 5-formylindole. The synthesis began with the conversion of 3-methyl-4-nitrobenzaldehyde (**52**) to acetal **53** using ethylene glycol and catalytic TsOH. Leimgruber-Batcho reaction of **53** using DMFDMA in DMF and subsequent hydrogenation of the nitro group with Pd/C gave indole **55** in good yield. Hydrolysis of acetal **55** with aqueous HCl provided 5-formylindole (**56**) in 91% yield (Scheme 12).

Scheme 12: Leimgruber-Batcho Indole Synthesis of 5-Formylindole

1.2.6 Nenitzescu Indole Synthesis

The Nenitzescu indole synthesis⁴⁶ involves the condensation of *p*-benzoquinones with β -aminocrotonic esters and is a highly regioselective method for the formation of 1,2,3-trisubstituted-5-hydroxyindoles.⁸ Kasai and co-workers⁴⁷ have recently reported the large-scale preparation of methyl 5-hydroxy-2-(methoxymethyl)-1H-indole-3-carboxylate (**59**), a key indole intermediate in the synthesis of the antitumor agent EO9 (**60**). Reaction of ester **58** with 3 equivalents of *p*-benzoquinone and 3.5 equivalents of AcOH, followed by the addition of Na₂S₂O₄ and adjustment of the pH using aqueous NaOH, gave indole **59** in 49% yield after recrystallization. Indole **59** was then converted to EO9 (**60**) in 10 additional steps (Scheme 13).

Scheme 13: Nenitzescu Indole Synthesis

Low yields in the Nenitzescu reaction are often attributed to its mechanism, which provides several possibilities for side reactions.⁸ The most accepted mechanism⁴⁸ (Scheme 14) begins with a Michael addition of enamine **58** to the protonated benzoquinone **61**, which, after proton transfer, provides imine **63**. Imine **63** undergoes the loss of a proton to induce heteroannulation and give indole precursor **64**. Finally, loss of water provides rearomatization, producing indole **59**.

Scheme 14: Mechanism of the Nenitzescu Indole Synthesis

The classical syntheses discussed in this chapter have been around for many years, but are still commonly used in the construction of indoles today. In addition to these syntheses, however, new methods have emerged including the fairly recent use of palladium to compose the indole core. These important indole-forming reactions are discussed in Chapter 2.

Chapter 2

Indole Formation via Palladium-Catalyzed *N*- Heteroannulation

2.1 Introduction	18
2.2 Indole Formation via <i>o</i> -Alkynylnilides and <i>o</i> -Alkynylnilines	18
2.3 Indole Formation via Intermolecular Cycloaddition with Alkynes	20
2.4 Indole Formation via <i>o</i> -Allylnilines	21
2.5 Indole Formation via <i>o</i> -Vinylilines	22
2.6 Indole Formation via Buchwald/Hartwig <i>N</i> -Arylation Processes	22
2.7 Indole Formation via Nitrenes	24

2.1 Introduction

In addition to the well-established classical methods of indole synthesis, palladium-catalyzed *N*-heteroannulation reactions have emerged as very powerful methods for producing the indole core. Since the discovery of the Wacker process⁴⁹ in the late 1950's, an ever-increasing number of organic transformations have been based on palladium catalysis. Transformations involving palladium are generally tolerant of a wide range of functionalities. In addition, they are dependent on a number of factors (ligands, bases, additives, solvents, temperature), making these types of reactions very flexible.⁵⁰ Also, since palladium processes are almost always catalytic, target molecules can be reached in fewer steps and with less waste than classical methods.⁵⁰

Heterocyclic chemistry has been greatly influenced by the discovery of palladium catalysis.⁵¹ Indole synthesis has been no exception to this trend. Numerous palladium-catalyzed approaches to substituted indoles have been developed, employing a wide variety of starting materials. *N*-heteroannulation routes to indoles utilizing palladium usually involve the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold. This is most commonly done by using nitrogen atoms (anilides, anilines, nitrenes, etc.) as nucleophiles to attack alkene and alkyne moieties. In addition, other less frequently applied strategies for the construction of the functionalized pyrrole nucleus have been described that are based on the Buchwald/Hartwig *N*-arylation process.⁵²

2.2 Indole Formation via *o*-Alkynylanilides and *o*-Alkynylanilines

A large part of the studies dedicated to the development of new sequences in the bond-making process leading to the construction of the indole pyrrole ring is based on the utilization, as precursors, of compounds containing nitrogen nucleophiles and carbon-

carbon triple bonds.⁵⁰ These alkyne based procedures provide a wide range of possibilities for indole formation. The first example of palladium-catalyzed cyclization of *o*-alkynylanilides to indoles was by Taylor and McKillop⁵³ around 1985. Their procedure, however, is rarely used today due to the toxicity of the *o*-thallated anilides used as starting materials. More modern protocols, such as that reported by Kundu *et al.*⁵⁴, are much more feasible routes to indoles (Scheme 15). In Kundu's example, the cyclization of *o*-[(3-hydroxy-3,3-dimethylprop-1-yl)trifluoroacetanilide (**65**) was effected using palladium(II) acetate to give 2-(prop-1-en-2-yl)-1*H*-indole (**66**) in excellent yield after hydrolysis of the amide bond and dehydration of the tertiary alcohol.

Scheme 15: Palladium-Catalyzed Synthesis of Indoles from *o*-Alkynylanilides

The nitrogen atom of free anilines can also be used as a nucleophile to attack alkynes in palladium-catalyzed processes. Cacchi and co-workers⁵⁵ developed an approach to 2-substituted indoles using a common acetylenic building block: *o*-ethynylaniline (**67**). The synthesis of *o*-ethynylaniline is easily accomplished by performing a Sonogashira coupling⁵⁶ of *o*-iodoaniline with ethynyltrimethylsilane followed by desilylation. Once this *o*-alkynylaniline is in hand, palladium-catalyzed couplings with vinyl and aryl triflates or halides can be carried out followed by subsequent palladium-catalyzed *N*-heteroannulations to give 2-substituted indoles. This coupling/cyclization approach can also be conducted as a one-pot process omitting the

isolation of the coupling intermediate. In a typical procedure, *o*-ethynylaniline (**67**) was coupled to 4-phenylcyclohex-1-enyl trifluoromethanesulfonate (**68**) in the presence of tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), giving the intermediate *o*-alkynylaniline **69**, which was then cyclized without isolation to give indole **70** in 98% yield (Scheme 16).^{32, 57}

Scheme 16: Palladium-Catalyzed Synthesis of Indoles from *o*-Alkynylanilines

2.3 Indole Formation via Intermolecular Cycloaddition with Alkynes

The palladium-catalyzed reaction between *o*-iodoaniline derivatives and internal alkynes for the preparation of 2,3-disubstituted indoles is referred to as the Larock heteroannulation.⁵⁸ The reaction is an extremely attractive synthesis since both starting materials (i.e. *o*-iodoaniline and internal alkyne) can possess considerable functionality, giving highly substituted indoles as products.⁸ The heteroannulation is regioselective and almost always gives 2,3-disubstituted indoles, where the more sterically hindered group of the alkyne occupies the 2-position of the indole ring. In most of the reactions studied, the more hindered acetylenic termini were silyl groups, which can either serve as

versatile intermediates for the synthesis of other indole derivatives or can be desilylated to the corresponding 3-substituted indoles.⁵⁸ In addition, substituents on the aniline nitrogen are also tolerated, leading to *N*-substituted indoles. Gathergood and Scammells⁵⁹ utilized the Larock heteroannulation in the preparation of *N,N*-dimethyl tryptamine **73** via the intermolecular cycloaddition of iodoaniline **71** and TMS-alkyne **72** in the presence of palladium(II) acetate. Indole **73** was used as an intermediate in a practical and versatile synthesis of the natural product psilocin (**74**) (Scheme 17).

Scheme 17: Synthesis of Psilocin via the Larock Heteroannulation

2.4 Indole Formation via *o*-Allylanilines

Hegedus *et. al.*^{60,61} first reported the synthesis of 2-alkylindoles via the palladium-assisted cyclization of *o*-allylanilines, although Mori⁶² and Heck⁶³ each discovered this transformation independently around the same time. The reaction proceeds by a nucleophilic attack of the aromatic amine across the palladium-coordinated olefin, resulting in a σ -alkylpalladium complex, which after β -hydride elimination and spontaneous isomerization, gives the indole moiety.⁶¹ Originally, the reaction involved using stoichiometric amounts of palladium; however, improvements were made by adding benzoquinone in order to reoxidize $\text{Pd}(0)$ to $\text{Pd}(\text{II})$, thereby allowing the reaction to be catalytic in palladium. One of the original examples is shown in Scheme 18.

Allylic aniline **75** was converted to 2-ethylindole (**76**) using $\text{PdCl}_2(\text{MeCN})_2$ in good yield.

Scheme 18: Palladium-Catalyzed Heteroannulation of *o*-Allylanilines

2.5 Indole Formation via *o*-Vinylanilines

In the same paper describing the cyclization of *o*-allylanilines to give indoles⁶¹, Hegedus and co-workers reported the successful palladium-catalyzed preparation of indole (**1**) from *o*-vinylaniline (**77**), again using $\text{PdCl}_2(\text{MeCN})_2$ (Scheme 19). To their surprise, no cyclization occurred under stoichiometric palladium conditions. This methodology was also applied to several *N*-substituted substrates (*o*-vinylacetanilides⁶⁴, *o*-vinyl-*N*-alkylanilines⁶⁵, etc.), giving *N*-substituted indoles in good yield. Despite the potential of this chemistry, it has remained essentially unexplored due to difficulty in synthesizing the starting materials (*o*-vinylanilines).

Scheme 19: Palladium-Catalyzed Heteroannulation of *o*-Vinylanilines

2.6 Indole Formation via Buchwald/Hartwig *N*-Arylation Processes

Buchwald's aryl amination technique⁶⁶, which involves a palladium-catalyzed C-N bond forming reaction between aryl halides or triflates and amines, amides, and

carbamates, has been parlayed into a simple and versatile indoline synthesis.⁶⁷ In the recent total syntheses of the marine alkaloids makaluvamine C and damirones A and B, key indole intermediate **80** was assembled using the Buchwald strategy.⁶⁸ Aryl iodide **78** underwent an palladium-catalyzed intramolecular amination to give indoline **79**, which was subsequently oxidized using Pd/C to give indole **80** (Scheme 20).

Scheme 20: The Buchwald/Hartwig *N*-Arylation Route to Indoles

Willis and co-workers have very recently implemented a Buchwald-type amination to produce *N*-substituted indoles.²³ They describe a sequential inter- and intramolecular palladium-catalyzed amination reaction used to prepare indoles bearing sterically demanding *N*-substituents. This strategy avoids having to functionalize the indole N-H, which can sometimes be problematic due to the low nucleophilicity of the indole nitrogen atom. In a typical procedure, a mixture of *cis*- and *trans*-1-bromo-2-(2-chlorovinyl)benzene (**81**) was reacted with 2-methylbut-3-en-2-amine (**82**) in the presence of Pd(OAc)₂, giving *N*-prenylated indole **83** in good yield. Indole **83** was subsequently transformed into Demethylasterriquinone A1 (**84**) in 5 steps (Scheme 21).

Scheme 21: Willis Route to *N*-Substituted Indoles

2.7 Indole Formation via Nitrenes

Nitrenes are neutral, reactive intermediates containing six electrons in their outer shell, two bonded and four nonbonded.⁶⁹ Nitrenes are believed to exist in two different forms, singlet nitrenes and triplet nitrenes. A typical singlet nitrene **85** has its nonbonded electrons arranged as two lone electron pairs, and is considered to be the lower energy state. A typical triplet nitrene **86** has its nonbonded electrons arranged as a lone pair and an unpaired biradical, and is considered to be the higher energy state (Figure 6).

Figure 6: Typical Singlet and Triplet Nitrenes

Probably the first reported generation of a nitrene intermediate in a heterocyclic synthesis was by Smith and Brown⁷⁰ in 1951. They reported the synthesis of carbazole (**88**) from the thermal decomposition of 2-azidobiphenyl (**87**) in kerosene at 180°C (Scheme 22).

Scheme 22: First Nitrene in the Synthesis of Nitrogen Containing Heterocycles

Mechanistically, the reaction is believed to proceed *via* the thermally induced loss of nitrogen from azide **87** to produce nitrene **89**. Nitrene **89** then rapidly undergoes cyclization to give tricycle **90**, which, after a [1,5]-sigmatropic rearrangement, restores aromaticity and affords carbazole (**88**) (Scheme 23).

Scheme 23: Mechanism of Carbazole Formation via Azide Decomposition

Nitrogen loss from azide **87** can also be initiated photochemically, which has led to studies of the reactive intermediates involved in the formation of carbazole (**88**) by chemical trapping⁷¹, matrix spectroscopy⁷², and flash photolysis⁷³. Swenton, Ikeler, and Williams⁷⁴ demonstrated that carbazole (**88**) is derived from the reaction of a singlet state

species, presumably singlet nitrene **89**, whereas triplet nitrene **91** dimerizes to form azo compound **92** (Scheme 24).

Scheme 24: Singlet Nitrene vs. Triplet Nitrene in the Formation of Carbazole

The Sundberg indole synthesis⁷⁵ involves the thermolysis of *o*-azidostyrenes and cyclization of the resulting nitrene to form indoles. Mechanistically, it is almost identical to the protocol used by Smith and Brown in their formation of functionalized carbazoles. Molina and co-workers employed this reaction to prepare 2-(2-azidoethyl)indole (**94**) *via* the thermolysis of arylazide **93**. The less reactive aliphatic azido group remained intact (Scheme 25).

Scheme 25: Sundberg Indole Synthesis

The Cadogan-Sundberg indole synthesis,^{76, 77} an extension of the Sundberg indole synthesis, yields indoles by the deoxygenation of *o*-nitrostyrenes with trivalent phosphorus compounds (typically triethyl phosphite) and subsequent cyclization of the resulting nitrene. Although other reactive intermediates have been suggested to result from this nitro group deoxygenation, the products derived from the Cadogan-Sundberg reaction are overwhelmingly similar to the products obtained from thermal and photochemical reactions of azides.⁶⁹ This observation suggests that a reactive, electron deficient nitrogen atom, most likely a nitrene, develops during the deoxygenation of nitroaromatics. While this reaction is very broad in scope, the extreme reaction conditions (>150°C), formation of both *N*-hydroxy- and *N*-ethoxyindole byproducts, and generation of large amounts of phosphorus waste all contribute to detract from this approach.⁸ Palmisano *et. al.*⁷⁸ utilized the Cadogan-Sundberg reaction to synthesize 2-(pyridin-2-yl)indole (**96**) by exposing 2-(2-nitrostyryl)pyridine (**95**) to boiling triethyl phosphite (Scheme 26).

Scheme 26: Cadogan-Sundberg Indole Synthesis

Mechanistically, the formation of nitrene intermediate **104** most likely occurs through a process involving the sequential removal of the nitro group oxygen atoms. Addition of triethyl phosphite to nitroarene **95**, followed by the loss of triethyl phosphate provides nitroso compound **100**. A similar addition-elimination process could occur a second time to give the nitrene **104** (Scheme 27).

Scheme 27: Mechanism of Cadogan-Sundberg Indole Synthesis

Another pathway to the indole core can also be envisioned. Although the first deoxygenation step is generally accepted, a second immediate deoxygenation to arrive at the nitrene is questionable. It has been shown that direct cyclization of *o*-nitrostyrene **100** can occur to form *N*-hydroxyindole **105** after isomerization and protonation. Hydroxyindole **105** can then be readily deoxygenated using an equivalent of triethyl phosphite to give indole **96**. Evidence for this mechanistic route is provided by the frequent isolation of *N*-hydroxy- and *N*-ethoxyindoles from the reaction mixture (Scheme 28).⁶⁹

Scheme 28: Alternate Cadogan-Sundberg Reaction Pathway

Transition metal promoted deoxygenation of nitroaromatics to give heterocycles was first realized by Waterman and Vivian⁷⁹ in the 1940's using stoichiometric iron oxalate at 215°C. Nitroarene **106** was converted to carbazole (**88**) in 63% yield (Scheme 29).

Scheme 29: First Transition Metal Promoted Deoxygenation of Nitroaromatics

The direct involvement of *o*-nitrostyrenes as substrates in the palladium-catalyzed synthesis of indoles was first observed by Kasahara *et. al.*⁸⁰ in 1989. In an attempt to

prepare *o*-nitrostyrene (**108**) *via* a Heck reaction of *o*-bromonitrobenzene (**107**) and ethylene in the presence of palladium acetate, Kasahara isolated 43% of the desired alkene along with an unexpected 22% of indole (**1**) (Scheme 30). The authors suggested a mechanism consisting of the reduction of *o*-nitrostyrene (**108**) (formed *via* Heck reaction) to *o*-vinylaniline (**77**) by a palladium hydride species (generated in the Heck reaction as well), followed by a more conventional Pd(II)-catalyzed cyclization to produce indole (**1**).

Scheme 30: Kasahara Heck Reaction/Indole Synthesis

The transition metal catalyzed reductive cyclization of *o*-nitrostyrenes employing carbon monoxide (CO) as the stoichiometric reductant has emerged in recent years as a highly versatile method for the construction of indoles.⁸ Several different metals, including ruthenium⁸¹, for example, have been examined as catalysts in this transformation and have been deemed synthetically impractical due to numerous factors including moderate yields, high carbon monoxide pressures, high reaction temperatures, and high catalyst loadings. Palladium-based systems have subsequently been identified as very efficient catalysts for this transformation. These palladium-catalyzed reductive *N*-heteroannulations are thought to resemble reactions such as the Sundberg and Cadogan-Sundberg indole syntheses in that they too involve a reactive intermediate that is nitreneoid in character. Evidence of this type of intermediate arises from similarities between products obtained using palladium/CO protocols and products obtained starting

from more conventional sources of nitrenes. Mechanistically, the palladium-catalyzed carbon monoxide-mediated reductive *N*-heteroannulation does not proceed by an initial reduction of the nitro group to an amine followed by an amino-palladation/ β -hydride elimination sequence. This Hegedus-type mechanism would require a palladium(II) species, which has to be regenerated by an added oxidant.⁶⁹ The previously mentioned palladium-catalyzed *N*-heteroannulation conditions not only lack an oxidant, but are highly reductive in nature. The proposed reaction mechanism involves (a) the deoxygenation of the nitro group of the nitroarene by carbon monoxide, (b) the attack of the resultant active transition metal nitrene intermediate to the olefinic carbon, and (c) the hydrogen transfer via [1,5]-sigmatropic rearrangement to yield the indole core.⁵⁰ This rationalization is primarily supported, again, by the product distribution from reactions of aromatic nitro compounds and their analogous azides.

Watanabe⁸² and co-workers were some of the first researchers to describe the preparation of indoles from 2-ethenyl-1-nitrobenzenes via reductive *N*-heteroannulation in the presence of carbon monoxide, catalytic amounts of $\text{PdCl}_2(\text{PPh}_3)_2$, and an excess of SnCl_2 ($\text{Sn/Pd} = 10:1$). In the simplest example, *o*-nitrostyrene (**108**) was converted to indole (**1**) in good yield, albeit under a high carbon monoxide pressure (Scheme 31).

Scheme 31: Watanabe Pd-Catalyzed Reductive *N*-Heteroannulation

Cenini⁸³ *et. al.* also used high carbon monoxide pressures to help pioneer indole formation utilizing palladium-catalyzed reductive *N*-heteroannulation. For example,

indole **96** was synthesized in good yield from 2-(2-nitrostyryl)pyridine (**95**) in the presence of 5 mol % Pd(TMB)₂ (TMB=2,5-dimethyl-2,5-diisocyanohexane) and TMPhen (TMPhen=3,4,7,8-tetramethyl-1,10-phenanthroline), under 20 atm of carbon monoxide pressure (Scheme 32).

Scheme 32: Cenini Pd-Catalyzed Reductive *N*-Heteroannulation

Kueth and Davies⁸⁴ recently developed a palladium-catalyzed reduction of *o*-nitrostyrenes to afford indoles in good to excellent yield. Their cyclization occurs under much milder conditions (1 atm CO, 80°C) and at lower catalyst loadings (0.1 mol % Pd) than those previously reported by Watanabe and Cenini. The Kueth group recently described the preparation of the highly functionalized indole **110**, which was subsequently deprotected to give the potent and selective KDR kinase inhibitor **111**. Under their optimized reaction conditions which employed 0.1 mol % Pd(TFA)₂ (TFA=trifluoroacetate), 0.7 mol % TMPhen in DMF, at 80°C, and 15 psi of CO, *o*-nitrostyrene **109** produced indole **110** as the only product in 95% isolated yield (Scheme 33).⁸⁵

Scheme 33: Kuethe and Davies Pd-Catalyzed Reductive *N*-Heteroannulation

Dong and co-workers⁸⁶ have very recently reported a new synthesis of indoles via reductive cyclization of conjugated nitroalkenes in the presence of carbon monoxide. This method differs from those previously mentioned which involved indole formation by reductive cyclization of nitroarenes. Under mild conditions⁸⁷, the amination of both electron-rich and electron-deficient aromatic sp² C-H bonds was shown to occur. This methodology is limited, however, in that the starting diaryl nitroalkenes can only be derived from the corresponding ketones. In a typical procedure, 2,2-di(4-chlorophenyl)-1-nitroethylene (**112**) was converted to 6-chloro-3-(4-chlorophenyl)indole (**113**) in almost quantitative yield employing a palladium(II) acetate/1,10-phenanthroline catalyst system (Scheme 34).

Scheme 34: Dong Transformation of Conjugated Nitroalkenes into Indoles

Similar to the conditions used by Davies, Söderberg *et. al.* have developed a mild palladium-catalyzed, carbon monoxide-mediated reductive *N*-heteroannulation route to indoles starting from the corresponding *o*-nitrostyrenes.⁸⁸ The discovery of these conditions came rather unexpectedly during an attempted palladium-catalyzed methoxycarbonylation reaction. In an effort to synthesize methyl 3-nitro-2-vinylbenzoate (**115**), which was required as a precursor in another study involving Fischer chromium carbene conversions to indoles, it was observed that none of the desired product was obtained using 1-bromo-3-nitro-2-vinylbenzene (**114**) as the starting aryl bromide. Instead, 4-bromoindole (**116**) was isolated as the sole product in 63% yield (Scheme 35).⁸⁸

Scheme 35: Söderberg Attempted Methoxycarbonylation/Indole Synthesis

After substantial optimization studies, the highest yields were obtained under slightly modified reaction conditions: 6 mol % Pd(OAc)₂, 24 mol % PPh₃, CO (60 psi), MeCN, 70°C. These conditions were subsequently used to synthesize a variety of indoles^{88,89,90} possessing functional groups on both the carbocyclic and pyrrole rings. For example, 4-methoxy-2-nitro-1-(prop-1-en-2-yl)benzene (**117**) was exposed to these adjusted conditions to yield 6-methoxy-3-methylindole (**118**) in excellent yield (Scheme 36).

Scheme 36: Optimized Söderberg *N*-Heteroannulation Conditions

In addition, Söderberg and co-workers have extensively used another palladium-catalyzed reductive *N*-heteroannulation protocol to cyclize *o*-nitrostyrenes that are resistant to the previously mentioned conditions. These alternate, slightly more harsh conditions consist of 6 mol % $\text{Pd}(\text{dba})_2$ (dba =dibenzylideneacetone), 6 mol % dppp (1,3-bis(diphenylphosphino)propane), 12 mol % 1,10-phen (1,10-phenanthroline), and CO (6 atm) in DMF at 120°C . Various types of indole cores have been synthesized utilizing this procedure including 3-alkoxysubstituted indoles⁹¹ and tetrahydrocarbazoleones⁹². Natural products have been formed in this manner as well, namely the pyrano[3,2-*b*]indole koniamborine (**120**), which was constructed via cyclization from *o*-nitrostyrene **119** in good yield (Scheme 37).⁹³

Scheme 37: Synthesis of Koniamborine Using Alternate Söderberg Conditions

The Söderberg cyclization conditions are fairly mild, proceeding at a substantially lower temperature and pressure than those of Watanabe⁸² and Cenini⁸³. Also, unlike Watanabe's protocol, no Lewis acid is required. Compared to previously mentioned

palladium-catalyzed routes to indoles employing aniline derivatives, the Söderberg annulations are more attractive because (a) nitrobenzenes are usually precursors to aniline derivatives, consequentially eliminating a synthetic step, and (b) palladium re-oxidants are not required.⁸⁸ In general, the reaction appears to be independent of the substituents on the aromatic ring. *o*-Nitrostyrenes containing either electron-withdrawing or electron-donating substituents give indoles in good to excellent yields. Also, since the only stoichiometric byproduct of the reaction is CO₂, the reductive cyclization offers significant economic and environmental advantages. In addition, the stereochemistry of the alkene moiety does not effect the reaction outcome. Cyclization of pure *trans*-2-nitrostilbene (**121**) gave 2-phenylindole (**122**) in quantitative yield, while cyclization of an equal mixture of *cis*- and *trans*-2-nitrostilbene (**123**) produced the desired indole in 91% yield (Scheme 38).⁸⁸

Scheme 38: Effect of Söderberg *N*-Heteroannulation on Isomeric Mixtures

Interestingly, exposing *trans*-4-nitrostilbene (**124**) to typical Söderberg cyclization conditions left the starting material unchanged; no alteration of the nitro group was observed (Scheme 39).⁸⁸ It appears that the close proximity of the olefin moiety to the nitro group is critical for any reaction to occur. It has been hypothesized that palladium coordination to the double bond may assist in the reduction of the nitro group.⁸⁸

Scheme 39: Possible Palladium-Olefin Coordination in *N*-Heteroannulation

A definite, concrete mechanism explaining the Söderberg *N*-heteroannulation, and others like it, remains elusive. While the exact details of the reaction continue to be mysterious, these transition metal catalyzed reductive cyclizations can be considered formally nitreneoid in character, although this is most likely an oversimplification of very complex reactions. However, combined efforts in this field, along with several mechanistic investigations have led to three plausible mechanistic routes (Scheme 40).⁹¹ To initiate any of the three routes, Pd(0) must first react with nitroarene **108** to give intermediate **125**. Intermediate **125** can then undergo an insertion of carbon monoxide to give 5-membered palladacycle **126**, which loses a molecule of carbon dioxide to yield palladium-bound nitrosoarene **127**. Two mechanistic pathways are possible from intermediate **127**. Path A⁸⁴ proceeds by reductive elimination of Pd(0) to give the free *o*-nitrostyrene **128**, which can now undergo a 6 π -electron 5 atom electrocyclic reaction, giving nitronate **129**. Subsequent [1,5]-hydrogen shift and isomerization (**129**→**130**→**131**) affords *N*-hydroxyindole (**131**), which is then reduced by a second equivalent of CO to give indole (**1**). Path B begins with a second carbon monoxide insertion into the palladium-bound nitrosoarene **127**. Loss of carbon dioxide from **132** would produce palladium-bound nitrene **133** that via a 6 π -electron cyclization could give palladacycle **134**. Reductive elimination to regenerate the palladium(0) catalyst would afford intermediate **135**. Isomerization via a [1,5]-hydrogen shift would then furnish

indole (**1**). Finally, path C arises from reductive elimination of Pd(0) from **133** to give the free nitrene **136**. An electrocyclization of **136** would produce **135**, which after a [1,5]-hydrogen shift could also yield indole (**1**).

Scheme 40: Proposed Mechanistic Pathway(s) of Reductive N-Heteroannulation

Mechanistic studies involving the [1,5]-hydride shift proposed to be involved in pathways A, B, and C above have been performed by Watanabe.⁸² He and co-workers utilized deuterium labeling experiments to further investigate the details of the reductive N-heteroannulation. Reaction of 2-(2,2-dideutero-1-methylvinyl)nitrobenzene (**137**)

afforded 3-methylindole **139** with deuterium located at the 1- and 2-positions. This result indicates that the deuterium at the β -position of the starting *o*-nitrostyrene **137** may be directly abstracted by the nitrogen atom (probably of a nitrene intermediate) in the construction of the indole skeleton. This deuterium labeling experiment also suggests evidence of a hydrogen (or in this case, deuterium) transfer via a [1,5]-sigmatropic rearrangement of intermediate **138** to afford indole **139** (Scheme 41).

Scheme 41: Watanabe *N*-Heteroannulation of Deuterated Nitro-olefin

Watanabe *et. al.*⁸² also investigated the reductive *N*-heteroannulation of β,β -disubstituted 2-nitrostyrenes, concluding that these compounds conform to a similar mechanism. For example, (2-nitrobenzylidene)cyclopentane (**140**) was transformed into 1,2,3,4-tetrahydrocarbazole (**142**) via alkyl rearrangement. In this case, results suggest that spirocyclic intermediate **141** must be produced, and then undergo a [1,5]-alkyl shift, causing ring expansion and furnishing tetrahydrocarbazole **142** after the necessary hydrogen migration (Scheme 42).

Scheme 42: Mechanistic [1,5]-Alkyl Shift in Reductive *N*-Heteroannulation.

Having a solid understanding of the mechanism of palladium-catalyzed, carbon monoxide-mediated reductive *N*-heteroannulation has provided researchers with the necessary knowledge to expand and develop this methodology to its fullest potential. Several examples of advancements in this field are presented in chapters hereafter.

Chapter 3

Synthesis of Tryptophan Derivatives via Palladium-Catalyzed

N-Heteroannulation

3.1 Introduction to Tryptophan/Tryptophan Skeleton in Natural Products	42
3.2 Previous Enantioselective Syntheses of α -Amino Acid Derivatives	44
3.3 Tryptophan Derivatives via Palladium-Catalyzed <i>N</i> -Heteroannulation	54
3.3.1 Retrosynthetic Analysis	54
3.3.2 Results and Discussion	55
3.3.3 Conclusions	79

3.1 Introduction to Tryptophan/Tryptophan Skeleton in Natural Products

Tryptophan, abbreviated Trp or W, is one of the twenty standard amino acids found in proteins and coded for in the standard genetic code as the codon *UGG*.^{94,95} The standard amino acids are also referred to as proteinogenic, or protein building amino acids.⁹⁴ These amino acids are assembled into a polypeptide, a protein subunit, through a process known as translation, the second stage of protein biosynthesis.⁹⁴ For humans, tryptophan is an essential amino acid, meaning that we cannot synthesize it and therefore must make it part of our diet. Also, as mentioned in chapter 1, tryptophan functions as a biochemical precursor for important compounds in the body such as serotonin (**7**) and melatonin (**8**) (see Figure 2). Only L-tryptophan (**6**) is used in structural or enzyme proteins, but D-tryptophan (**143**)⁹⁶ is occasionally found in naturally produced peptides (Figure 7).

Figure 7: Structures of L-Tryptophan and D-Tryptophan

By virtue of its ubiquitous distribution in plant and animal proteins, tryptophan may justifiably be regarded as the most important of the naturally occurring indoles.¹ Its skeleton can be seen in a variety of natural products, including diketopiperazines like brevicompanine C (**144**) and fiscalin B (**145**) (Figure 8). Diketopiperazines are widespread microbial products commonly found in nutrient rich cultures of both

terrestrial and marine fungi.⁹⁷ These compounds are of high interest because of their activity in various pharmacological assay systems.⁹⁸

Figure 8: Structures of Brevicompanine C and Fiscalin B

In addition, a number of ring-A (the six-membered carbocyclic ring) substituted tryptophan-based alkaloids appear in nature as well. Examples include echinulan (**146**), along with methoxylated alkaloids⁹⁹ like fuchsiaefoline (**147**) and alstophylline (**148**), which both contain an enantiopure L-tryptophan moiety (Figure 9). L-Tryptophan derivatives, including *N*-methyl-L-tryptophan, have proven to be most potent competitive IDO (indoleamine 2,3-dioxygenase) inhibitors.¹⁰⁰ Indoleamine 2,3-dioxygenase is a heme-containing enzyme that causes depletion of tryptophan which can lead to halted growth of microbes as well as T cells.⁹⁹

Figure 9: Structures of Echinulan, Fuchsiaefoline, and Alstophylline

It is important to note that almost all tryptophan derivatives and natural products that are of biological use tend to possess high enantiomeric enrichment; racemates are rarely, if ever observed in this context. For this reason, several procedures have been developed to synthesize optically active substituted tryptophans, along with chiral amino acids in general.

3.2 Previous Enantioselective Syntheses of α -Amino Acid Derivatives

Numerous methods have been reported for the asymmetric synthesis of α -amino acids. Dellaria and co-workers¹⁰¹ developed a synthesis of amino acid derivatives via the stereoselective alkylation of a homochiral glycine enolate synthon. When the glycine derivative **149** was added in dry THF to sodium bis(trimethylsilyl)amide (NaHMDS) in THF at -78°C and subsequently alkylated with benzyl bromide, the corresponding alkylation adduct **150** was obtained in good yield and excellent diastereoselectivity (>200:1). Exposure of **150** to excess refluxing ethanolic HCl provided alcohol **151**, which was then converted to the chiral amino ester **152** via palladium-catalyzed hydrogenolysis (Scheme 43).

Scheme 43: Dellaria Alkylation of Homochiral Glycine Enolate Synthon

Leanna *et. al.*¹⁰² have reported the synthesis of optically active unnatural amino acids via a tandem biocatalytic kinetic resolution of a racemic amino ester. Racemic ester **153** was treated with Subtilisin Carlsberg, an enzyme, to afford a mixture of ester **154** and carboxylic acid **155**. The now enantiopure D-ester **154** was extracted with CH₂Cl₂ after the reaction had consumed 48.5% of racemic ester **153**, as judged by C-18 HPLC. The aqueous solution containing *N*-acetyl-L-acid **155** was then treated with Porcine Kidney Acylase I to remove the acetyl group and give optically pure L-amino acid **156** in 75% over the two steps (Scheme 44).

Scheme 44: Leanna Biocatalytic Kinetic Resolution of a Racemic Amino Ester

Myers and co-workers¹⁰³ developed a practical method for the synthesis of D- or L- α -amino acids by the direct alkylation of (+)- or (–)-pseudoephedrine glycineamide hydrate. In a typical procedure, the enolate dianion of (R,R)-(–)-pseudoephedrine glycineamide (**157**) was reacted with benzyl bromide to give the asymmetric alkylation product **158** in 93% diastereomeric excess. Compound **158** was then hydrolyzed to the L-amino acid (**159**) after exposure to refluxing water (Scheme 45). It should be noted that (R,R)-(–)-**157** produces L-amino acid derivatives while the pseudoephedrine glycineamide enantiomer produces D-amino acid derivatives.

Scheme 45: Myers Direct Alkylation of Pseudoephedrine Glycinamide Hydrate

Several asymmetric syntheses have been developed specifically to produce enantiopure derivatives of both D- and L-tryptophan. These methods involve a wide variety of starting materials and reaction conditions. Hruby and co-workers¹⁰⁴ have reported a protocol for the asymmetric synthesis of both D- and L-aromatic substituted tryptophan derivatives under mild reaction conditions. The general strategy involves the asymmetric hydrogenation of α -enamides to generate functional amino acids in high optical purity (>96% ee) which serve as common intermediates from which a variety of substituted amino acid derivatives may be readily obtained through Suzuki-type couplings. α -Enamide **160**, obtained from a Horner-Emmons olefination with a commercially available indole-3-carboxaldehyde, underwent asymmetric hydrogenation using 1,2-bis((2S,5S-2,5-diethylphospholano)benzene(cyclooctadiene rhodium (I) trifluoromethane sulfonate ((S,S)-[Et-DuPHOS-Rh] OTf) to give L-amino acid derivative **161** in quantitative yield (Scheme 46). Using the enantiomer of the rhodium catalyst

gave the D-amino acid derivative **163** in excellent yield. 5-Bromotryptophan derivative **161** was then subjected to Suzuki cross couplings with a variety of boronic acids to give aryl-substituted chiral tryptophans with the general structure **162**. This overall method is limited in the number of commercially available indole starting materials. Carlier *et. al.* have also reported a similar method in constructing protected tryptophan regioisomers.¹⁰⁵

Scheme 46: Hruby Asymmetric Hydrogenation of α -Enamides

Gellerman and co-workers¹⁰⁶ have developed an approach for the asymmetric synthesis of ring-A disubstituted tryptophans based on modification and extension of the simple Fischer-indole reaction between 2,4- or 2,3-disubstituted phenylhydrazine hydrochlorides and optically active *N,N*-diprotected glutamic acid γ -aldehydes. These glutamic acid derivatives needed to be diprotected to prevent undesired intramolecular

lactamization, which would result in racemization of the asymmetric carbon. In a typical reaction, 2,4-dimethylphenylhydrazine (**164**) was refluxed with *N,N*-di-Boc protected L-glutamic acid *t*-butyl ester **165** in isopropanol to give the expected tryptophan core.

However, the second unstable Boc group was partially cleaved in the presence of HCl during the Fischer indole reaction, affording a mixture of the mono-Boc tryptophan ester **166** and di-Boc tryptophan ester **167** in 27% and 50% yield, respectively (Scheme 47).

This partial deprotection proved to be non-significant as the mixture was further treated with trifluoroacetic acid (TFA), leading to a common unprotected amino acid.

Scheme 47: Gellerman Tryptophan Synthesis via Fischer-Indole Reaction

Probably the most commonly employed tool in the field of asymmetric tryptophan synthesis is the Schöllkopf bis-lactim ether chiral auxiliary.¹⁰⁷ This method is a practical and versatile technique for the preparation of both D- and L- α -amino acids in high enantiomeric excess. The synthesis of this chiral auxiliary, developed by Chen *et. al.*,¹⁰⁸ is outlined in scheme 48. The source of chirality, L-valine (**168**), was first converted to *N*-Boc-L-valine (**169**) in excellent yield. Next, carboxylic acid **169** was treated with isobutyl chloroformate and triethylamine (NEt₃) to give an intermediate mixed anhydride, which was then converted to amide **170** upon treatment with glycine methyl ester hydrochloride. Heating amide **170** in 1,2-dichlorobenzene induced removal of the Boc group and subsequent cyclization to give 3,6-piperazinedione **171** in moderate yield. Finally, cyclic diamide **171** was treated with trimethyloxonium tetrafluoroborate to

produce Schöllkopf's bis-lactim ether chiral auxiliary, (5*S*)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine (**172**) in good yield. A similar, but less attractive Schöllkopf auxiliary synthesis has been reported by Davies and co-workers.¹⁰⁹ It should be noted that (5*R*)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine, the enantiomer of **172**, can be synthesized by starting the synthesis with D-valine.

Scheme 48: Chen Synthesis of the Schöllkopf Chiral Auxiliary

Bis-lactim ether **172** can be metalated regioselectively in the glycine moiety by butyllithium. The lithium compound **173** reacts with alkyl halides with, in part, >95% diastereoselectivity to give adducts with the general structure **174** (Scheme 49). The alkyl residue enters *trans* to the isopropyl group on C-5, *i.e.* the (*R*)-configuration is induced at C-2.¹⁰⁷

Scheme 49: Lithiation/Alkylation of Schöllkopf's Chiral Auxiliary

The alkylated pyrazine **174** can then be hydrolyzed with TFA or a dilute HCl solution to liberate the (*R*)-amino acid methyl ester **175**. Saponification of ester **175** with NaOH provides the free amino acid **176** (Scheme 50).¹⁰⁷

Scheme 50: Hydrolysis/Saponification of Alkylated Pyrazine

Sakagami *et al.*¹¹⁰ utilized the Schöllkopf method in their synthetic studies on peptides containing geranyltryptophans. Metallation of Schöllkopf chiral auxiliary **178** with *n*-BuLi in THF was followed by alkylation of chloride **177** in the presence of tetramethylethylenediamine (TMEDA) to provide geranyltryptophan derivative **179** in 78% yield (Scheme 51). The addition of TMEDA improved the diastereomeric ratio up to 30:1 (*trans*:*cis*) as detected by ¹H-NMR. Cook and co-workers¹¹¹ have also reported a similar tryptophan synthesis. Potential drawbacks to these methods are the availability of substituted indole electrophiles and the need to protect the indole nitrogen.

Scheme 51: Sakagami Tryptophan Synthesis

Cook has also developed a novel and concise synthesis of optically active tryptophan derivatives^{99,112} via a Larock heteroannulation⁵⁸ (see section 2.3) of substituted *o*-iodoanilines with an internal alkyne. The required internal alkyne **182** was prepared in greater than 96% diastereomeric excess (de) via alkylation of Schöllkopf chiral auxiliary **180** with diphenyl (triethylsilyl)propargyl phosphate (**181**). Larock reaction of alkyne **182** with 2-iodo-5-methoxyaniline (**183**) in the presence of palladium(II) acetate furnished TES-tryptophan derivative **184**. Desilylation, along with hydrolysis of the chiral auxiliary, provided amino ester **185** (Scheme 52). Some biologically important tryptophan analogs⁹⁹ were also synthesized by Cook utilizing this method, including L-isotryptophan, L-homotryptophan, and L-benz[f]tryptophan. Although this protocol is very versatile, it has a few disadvantages, including the formation of regioisomers in some cases (2-alkyl-3-silyltryptophan derivatives). Another major limitation is that the reaction fails to give tryptophan products in useful yields when 2-bromo- or 2-chloroanilines are employed and requires the use of iodoanilines which are often more expensive and less commercially available.⁸ Recently, however, Lu and Senanayake¹¹³ have reported a solution to this problem.

Scheme 52: Cook Tryptophan Synthesis

Castle and co-workers¹¹⁴ have improved upon Cook's heteroannulation strategy by employing a chiral phase-transfer-catalyzed alkylation of a glycinate Schiff base in place of the diastereoselective alkylation of a stoichiometric amount of the Schöllkopf chiral auxiliary. Chiral phase transfer catalyst **188**, containing a trifluorobenzyl moiety, promoted the alkylation of glycine derivative **186** with propargyl bromide **187** in good yield and excellent enantiomeric excess (ee). The resulting propargyl glycine **189** was converted to **192**, the central tryptophan residue of Celogentin C¹¹⁵, in three steps, with the Pd-catalyzed heteroannulation as the key transformation (Scheme 53). In addition, this process is quite economical and attractive for large-scale synthesis since the phase-transfer catalyst can be recovered from the reaction mixture.

Scheme 53: Castle Tryptophan Synthesis

3.3 Tryptophan Derivatives via Palladium-Catalyzed *N*-Heteroannulation

In an effort to improve upon the current syntheses of enantiopure tryptophan derivatives, a route was envisioned that employed the Söderberg palladium-catalyzed, carbon monoxide-mediated reductive *N*-heteroannulation reaction.¹¹⁶ The 1-(2-nitrophenyl)-1-alkene cyclization precursors are derived from Schöllkopf's chiral auxiliary. These asymmetric tryptophans have the general structure of **193**, with R being various electron-withdrawing and electron-donating substituents.

Figure 10: General Structure of Tryptophan Target Molecules

193

3.3.1 Retrosynthetic Analysis

The proposed retrosynthetic route is outlined in scheme 54. Functionalized tryptophan derivative **194** can be constructed from the aforementioned palladium-catalyzed *N*-heteroannulation of *o*-nitrostyrene **195**. This cyclization precursor **195** can be formed from a Kosugi-Migita-Stille cross coupling between aryl iodide **197** and vinyl stannane **196**. Tin compound **196** can be envisioned from a palladium-catalyzed stannylation of the corresponding vinyl bromide **198**. Finally, *trans*-pyrazine **198** results from the diastereoselective alkylation of Schöllkopf's chiral auxiliary **172** with 2,3-dibromopropene (**199**).

Scheme 54: Proposed Retrosynthetic Outline to Tryptophan Derivatives

3.3.2 Results and Discussion

The synthetic endeavor began with the diastereoselective alkylation of the commercially available (R)-Schöllkopf auxiliary **200** with commercially available 2,3-dibromopropene **199** to give *trans*-pyrazine **201**¹¹⁷ in good yield and excellent de (96%) (Scheme 55).

Scheme 55: Alkylation of Schöllkopf Auxiliary

Conversion of the vinylic bromide in **201** to the corresponding vinylic tributyltin moiety **202** was examined next. By performing this transformation, a more practical coupling partner would be created for use in upcoming Kosugi-Migita-Stille reactions with commercially available aryl halides. A variety of conditions were attempted ranging

from palladium-catalyzed protocols to procedures involving sonication; however, all failed to furnish the target stannane **202** (Table 1).

Table 1: Attempts to Convert to the Vinyl Stannane

<u>Entry</u>	<u>Conditions</u>	<u>Solvent</u>	<u>Time (hrs)</u>	<u>Temp (°C)</u>
1	(SnBu ₃) ₂ , Pd(dba) ₂ , PPh ₃	Toluene	72	115
2	(SnBu ₃) ₂ , PdCl ₂ (PPh ₃) ₂	Dioxane	19	105
3	Mg, PbBr ₂ , Bu ₃ SnCl	THF	69	25
4	Mg, 1,2-dibromoethane, Bu ₃ SnCl,)))	THF	0.5	25

An alternate route to stannane **202** was envisioned utilizing a multi-step procedure (Scheme 56). A hydrostannylation was performed on methyl propiolate (**203**) via a palladium-catalyzed procedure employing tributyltin hydride to give geminal alkene **204**. Ester **204** was reduced to the corresponding primary alcohol **205**¹¹⁸ with diisobutylaluminum hydride (DIBAL-H), followed by exposure to acetic anhydride to yield allylic acetate **206**. It should be noted that acetate **206** was pursued only after failing to synthesize both the corresponding allylic chloride¹¹⁹ and bromide¹²⁰ from alcohol **205**. Allylic acetate **206** was then exposed to lithiated Schöllkopf reagent **200** in hopes of assembling allylic pyrazine **202**. Unfortunately, free alcohol **205** was recovered as the sole reaction product owing to acetate ester cleavage.

Scheme 56: Alternate route to the Vinyl Stannane

Assembly of a vinyl boronate ester as the amino acid-containing coupling partner was also examined.¹²¹ Regrettably, palladium-catalyzed reaction of vinyl bromide **201** with bis(pinacolato)diboron failed to give boronate ester **207** (Scheme 57).

Scheme 57: Attempted Synthesis of the Vinyl Boronate Ester

After examining several options for the conversion of vinyl bromide **201** to a more versatile vinylic moiety, the decision was made to utilize **201** itself to construct the crucial *o*-nitrostyrene precursors. Kosugi-Migita-Stille cross-coupling of **201** and aryl stannane **208** using bis(acetonitrile)palladium dichloride (5 mol %), triphenylarsine, (10

Scheme 59: Söderberg *N*-Heteroannulation on the Isomeric Mixture

With knowledge that the reaction sequence was viable, an effort was made to reduce, or ideally, eliminate the amount of isomerization obtained in the Kosugi-Migita-Stille coupling step. Several different variants of the reaction were attempted by altering the catalyst, ligands, solvent, etc. Unfortunately, the reaction either did not proceed or occurred in low yield with significant isomerization. The results are summarized in Table 2.

Table 2: Attempted Couplings with Pyrazine Moiety

Entry	R₁	R₂	Catalyst	Ligand	Add^a	Solv	Temp^b	Time	Yield^c
1	H	H	PdCl ₂ (PhCN) ₂	AsPh ₃	CuI	NMP	80	72 h	46%
2	H	H	Pd(dba) ₂	PPh ₃	-	PhMe	110	120 h	0%
3	OMe	H	PdCl ₂ (PhCN) ₂	AsPh ₃	CuI	NMP	80	19 h	30%
4	OMe	H	PdCl ₂ (PhCN) ₂	AsPh ₃	CuI	NMP	100	22 h	25%
5	OMe	H	PdCl ₂ (PhCN) ₂	AsPh ₃	CuI	PhMe	110	23 h	0%
6	H	OMe	Pd(dba) ₂	AsPh ₃	CuI	THF	50	27 h	0%
7	H	OMe	Pd(dba) ₂	AsPh ₃	-	PhMe	110	19 h	0%
8	H	OMe	Pd(dba) ₂	AsPh ₃	CuI	NMP	80	72 h	20%

^a Indicates CuI as an additive (8-20%)

^b Temperature in °C

^c Yields, if any, include significant amounts of isomerization

The mechanism of this isomerization is unclear. However, it was found later to be thermally induced since heating a 12:1 trans/cis mixture of *o*-nitrostyrene **215** in DMF at 120°C for 20 hours resulted in additional racemization to a 5:1 trans/cis ratio. Furthermore, exposing indole **216** to identical conditions resulted in a similar isomerization (Scheme 60).

Scheme 60: Thermally Induced Isomerizations

Cook *et. al.* encountered a similar isomerization in their attempt to synthesize enantiopure isotryptophan (Scheme 61).⁹⁹ Organocopper compounds, such as **218**, can become quite basic when the temperature is raised. Hence, indolylcopper intermediate **218** could abstract a proton from the chiral center in the pyrazine group under the high reaction temperatures (80-90°C) to provide intermediate **219**. The reprotonation of the stabilized anion that results could occur from either face to furnish epimerized pyrazine **220**. Regeneration of CuI would give isomerized isotryptophan **221**.

Scheme 61: Cook's Isotryptophan Isomerization

Utilization of a coupling partner containing a protected amino ester was also investigated. After alkylation, the Schöllkopf auxiliary can be easily hydrolyzed with 0.1 N HCl or 0.1 N TFA, then subsequently protected as the carbamate with di-*tert*-butyl dicarbonate (Boc_2O) to furnish the corresponding Boc-protected amino ester.^{117,123} This reaction sequence was performed on pyrazine **201**. Hydrolysis of **201** with aqueous TFA gave much higher yields of amino ester **222** than did a dilute HCl solution. Protection of the resulting free amine in **222** with Boc_2O furnished vinyl bromide **223** in 68% over two steps (Scheme 62).

Scheme 62: Hydrolysis/Boc-Protection of Alkylated Schöllkopf Auxiliary

With vinyl bromide **223** in hand, some Kosugi-Migita-Stille couplings were attempted with tributyl(4-methoxy-2-nitrophenyl)stannane (**224**) while varying the reaction conditions. Again, no evidence of coupling product **225** was observed (Table 3).

Table 3: Attempted Couplings with Amino Ester Moiety

<u>Entry</u>	<u>Catalyst</u>	<u>Ligand</u>	<u>Additive</u>	<u>Solvent</u>	<u>Temp (°C)</u>	<u>Time (h)</u>
1	Pd(dba) ₂	PPh ₃	-	Toluene	110	42
2	PdCl ₂ (PhCN) ₂	AsPh ₃	CuI	NMP	80	25
3	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	CH ₃ CN	50	71

An aryl boronic ester was next examined as a possible coupling piece. Boronic acid pinacol ester **228** was synthesized in moderate yield from 1-iodo-2-nitrobenzene

(**226**) in the presence of $\text{Pd}(\text{dba})_2$ and bis(pinacolato)diboron (**227**).¹²⁴ Palladium-catalyzed coupling of **228** with vinyl bromide **201** afforded only 13% of a mixture of diastereomers (3:1, *trans:cis*) of pyrazine **215** (Scheme 63).

Scheme 63: Suzuki-Type Coupling of Aryl Boronate Ester

The synthesis of *o*-nitrostyrene **209** was also attempted via a lengthier procedure involving key methyl acrylate derivative **231** (Scheme 64). Two synthetic routes were envisioned in constructing **231**. The first route starts with conversion of commercially available carboxylic acid **229** to the corresponding methyl ester **230**.¹²⁵ Ester **230** is then condensed with formaldehyde and subsequently dehydrated to produce α,β -unsaturated methyl ester **231**. Route two begins with the palladium-catalyzed conversion of alkyne **203** to stannane **204** in the presence of tributyltin hydride. Palladium cross-coupling of stannane **204** with 1-iodo-2-nitrobenzene (**226**) using 75 mol % CuI at ambient temperature in DMF gave the target *o*-nitrostyrene **231** in excellent yield.¹²⁶

Scheme 64: Synthetic Routes to Methyl 2-(2-nitrophenyl)acrylate

Reduction of methyl ester **231** to the corresponding alcohol **232**, followed by reaction with bromine and triphenylphosphine gave allylic bromide **233**.

Disappointingly, alkylation of lithiated pyrazine **200** employing allylic bromide **233** as the electrophile failed to generate the desired 2-nitrostyrene **209** (Scheme 65).

Scheme 65: Attempted Alkylation Route to Cyclization Precursor

Recognizing that Levin's room-temperature coupling protocol¹²⁶ worked so efficiently in combining **204** and **226**, it was decided to implement the same conditions in the presence of amino ester **223** and aryl stannane **208**. Surprisingly, these conditions provided cyclization precursor **234** in high yield (Scheme 66). It should be noted that coupling partner **223**, resulting from hydrolysis/protection of the pyrazine moiety, was used in this case only due to its availability at the current time.

Scheme 66: Utilization of Levin's Cross-Coupling Conditions

Exposing nitrostyrene **234** to the Söderberg annulation conditions (6 mol % Pd(dba)_2 , 6 mol % dppp, 12 mol % 1,10-phen, and CO (6 atm) in DMF at 120°C) afforded indole **235** in 70% yield (Scheme 67).

Scheme 67: Successful Cyclization of Amino Ester Nitrostyrene

With an effective coupling/cyclization strategy in hand, reaction of pyrazine moiety **201** and stannane **208** was investigated. Using the pyrazine moiety for this transformation would save synthetic steps needed to arrive at amino ester **223**. As expected, nitrostyrene **209** was obtained as a single stereoisomer in good yield.

Palladium-catalyzed *N*-heteroannulation of **209** provided tryptophan derivative **211**

(Scheme 68).

Scheme 68: Successful Coupling/Cyclization with Pyrazine Moiety

After an exhaustive literature search, a procedure reported by De Kimpe *et al.* was discovered describing the palladium-catalyzed conversion of a vinylic bromide to the corresponding vinylic trimethylstannyl derivative using hexamethylditin.¹²⁷ Specifically, *N,N*-dibenzyl-*N*-(2-bromo-2-propenyl)amine (**236**) was transformed into *N,N*-dibenzyl-*N*-(2-trimethylstannyl-2-propenyl)amine (**237**) by reaction with hexamethylditin in the presence of 20 mol % of Hünig's base and 5 mol % tetrakis(triphenylphosphine)palladium(0) in benzene at 80°C for 15 h (Scheme 69).

Scheme 69: De Kimpe Palladium-Catalyzed Trimethylstannylation

Fortunately, very similar conditions were effective in converting bromide **198** to vinyl trimethyltin derivative **238** (Scheme 70). Note that **198** is the enantiomer of **201** and that this (2*R*,5*S*)-stereochemistry will be seen in all examples hereafter. Compound **198** was furnished from (5*S*)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine using the alkylation protocol reported in scheme 55.

Scheme 70: Conversion to Amino Acid-Containing Tin Derivative

With the key stannane and an efficient coupling protocol both in hand, a number of annulation precursors were prepared via coupling of **238** with various halonitroarenes using a slightly modified version of Levin's room temperature coupling conditions. The results of these reactions are summarized in table 4. No epimerization was apparent in any of the coupling products. Thus, methoxy-, fluoro-, carbomethoxy-, and nitro-functionalized substrates, in addition to a pyridine derivative, were obtained in 58-82% yield. Yields of isolated products appear in parentheses.

Table 4: Results of Kosugi-Migita-Stille Cross-Couplings

<u>Entry</u>	<u>o-Halonitroarene</u>	<u>o-Nitrostyrene</u>
1	<p style="text-align: center;">226</p>	<p style="text-align: center;">239 (58%)</p>
2	<p style="text-align: center;">240</p>	<p style="text-align: center;">241 (68%)</p>
3	<p style="text-align: center;">242</p>	<p style="text-align: center;">243 (69%)</p>
4	<p style="text-align: center;">244</p>	<p style="text-align: center;">245 (61%)</p>

Table 4: Results of Kosugi-Migita-Stille Cross-Couplings (cont.)

<u>Entry</u>	<u>o-Halonitroarene</u>	<u>o-Nitrostyrene</u>
5	246	247 (62%)
6	248	249 (82%)
7	250	251 (60%)

The coupling of 6-methoxy-2-nitro-1-iodobenzene (**253**) with stannane **238** was also investigated. Since **253** was not commercially available, it was synthesized starting from 2-amino-3-nitrophenol (**252**) (Scheme 71). Conversion of the amino group in **252** to the corresponding iodide using Sandmeyer-type conditions, followed by methylation of the phenolic alcohol gave **253** in 51% yield over three steps. Unexpectedly, exposure of **253** to the conditions described in table 4 gave only homocoupling dimer **254**¹²³ and recovered aryl iodide.

Scheme 71: Homocoupling in the Reaction of 6-Methoxy-2-nitro-1-iodobenzene

To solve this problem, the iodide **253** was transformed into the corresponding trimethyl tin compound **255** using a related procedure as for the preparation of **238** (Scheme 72). Coupling of **255** with vinyl bromide **198** under previously used Kosugi-Migita-Stille conditions gave *o*-nitrostyrene **256** in moderate yield.

Scheme 72: Successful Coupling Using Corresponding 6-Methoxy-1-stannane

A similar dilemma was encountered after attempting to couple 3-methoxy-2-nitro-1-iodobenzene with **238**. Again, the starting material was not available for purchase and had to be synthesized (Scheme 73). Commercially available carboxylic acid **257** was transformed to the corresponding amine **259** upon treatment with diphenylphosphoryl azide (**258**) and *tert*-butanol, followed by removal of the resulting Boc group with 6N HCl.¹²⁸ A Sandmeyer-like protocol then provided iodide **260**. Almost identical to the behavior of **253**, attempted coupling of **260** with stannane **238** gave dimer **254** as the sole product in low yield.

Scheme 73: Homocoupling in the Reaction of 3-Methoxy-2-nitro-1-iodobenzene

An identical remedy to that illustrated in scheme 72 was applied to this situation. Iodide **260** was first converted to the corresponding tin derivative **261** using a palladium-catalyzed procedure employing hexamethylditin. Stannane **261** was then coupled with pyrazine **198** using the Pd(dba)₂-PPh₃-CuI conditions at ambient temperature to furnish 3-methoxy-2-nitrostyrene **262** in good yield (Scheme 74).

Scheme 74: Successful Coupling Using Corresponding 3-Methoxy-1-stannane

With a selection of substrates having both electron-withdrawing and electron donating substituents in hand, the palladium-catalyzed *N*-heteroannulation was examined next (Table 5). All cyclizations went to 100% completion and ranged in yield from 12-88%. Depending on the functional group on the aromatic ring, a varying degree of isomerization was observed for all substrates to give diastereomeric ratios ranging from 4.5:1 $\rightarrow$ 30:1. Characteristic of the minor *cis*-isomers are the significant upfield shifts of one of their isopropyl methyl group resonances (0.02-0.38 ppm) compared to the chemical shifts of their *trans*-counterparts (0.61-0.66 ppm). This upfield shift can be explained by a conformation wherein the isopropyl group is shielded by the aromatic ring of the indole nucleus.¹²⁹ It is interesting to note that the most hindered methoxy-substituted substrate **262** gave a significantly lower yield (47%) and lower diastereomeric ratio (6:1) than the other three methoxy compounds (**241**, **243**, **256**), most likely due to steric hinderence. Electron-withdrawing groups (-F, -CO₂Me, -NO₂) were also tolerated, although the fluoro-substituted compound **245** gave **266** with the highest amount of isomerization (dr=4.5:1), albeit in excellent yield (84%). Pyridine-derived

substrate **251** cleanly produced aza-tryptophan compound **269** in 79% yield. The lowest yield by far (12%) was obtained from cyclization of nitrobenzene **249**; however, the starting material was completely consumed and no additional products were isolated.

Table 5: Results of Palladium-Catalyzed *N*-Heteroannulations

$o\text{-Nitrostyrene} \xrightarrow[\text{CO, DMF, 120}^\circ\text{C}]{\text{Pd(dba)}_2, \text{dppp, 1,10 phen}} \text{Tryptophan Derivative}$		
<u>Entry</u>	<u><i>o</i>-Nitrostyrene</u>	<u>Tryptophan Derivative^a</u>
1	<p style="text-align: center;">239</p>	<p style="text-align: center;">263 (85%, dr=15:1)</p>
2	<p style="text-align: center;">241</p>	<p style="text-align: center;">264 (70%, dr=12:1)</p>
3	<p style="text-align: center;">243</p>	<p style="text-align: center;">265 (85%, dr=22:1)</p>

Table 5: Results of Palladium-Catalyzed *N*-Heteroannulations (cont.)

Entry

***o*-Nitrostyrene**

Tryptophan Derivative^a

4

245

266 (84%, dr=4.5:1)

5

247

267 (73%, dr=10:1)

6

249

268 (12%, dr>30:1)

7

251

269 (79%, dr=11:1)

Table 5: Results of Palladium-Catalyzed *N*-Heteroannulations (cont.)

<u>Entry</u>	<u><i>o</i>-Nitrostyrene</u>	<u>Tryptophan Derivative^a</u>
8	<p>256</p>	<p>270 (88%, dr>30:1)</p>
9	<p>262</p>	<p>271 (47%, dr=6:1)</p>

^a Yield of isolated product and diastereomeric ratio (dr) in parentheses

In addition to the tryptophan derivatives assembled in table 5, two other important tryptophan analogues were pursued via a similar cross-coupling/*N*-heteroannulation strategy: D-homotryptophan and D-isotryptophan. Multistep syntheses of the racemic form of these two tryptophan analogues have been reported previously;¹³⁰ however, Cook *et. al.*⁹⁹ have reported the only enantioselective preparation of these compounds. The synthesis of D-homotryptophan, the one carbon homolog of **263**, began with exposure of commercially available 3-bromobut-3-en-1-ol (**272**) to methanesulfonyl chloride (MsCl) to provide mesylate **273** in excellent yield (Scheme 75). Finkelstein-like reaction of **273** with sodium iodide in acetone gave homoallylic iodide **274**. Successful alkylation of the lithio derivative of Schöllkopf reagent **172** with iodide **274** required the presence of two equivalents of N,N-dimethylethyleneurea (DMEU) to furnish *trans*-pyrazine **275** in low

yield.¹³¹ It should be noted that alkylation did not proceed at all employing the corresponding homoallylic mesylate **273** or bromide. Room temperature palladium-catalyzed coupling of vinyl bromide **275** with aryl stannane **208** gave cyclization precursor **276** as a single stereoisomer in good yield. Finally, *N*-heteroannulation of *o*-nitrostyrene **276** afforded D-homotryptophan derivative **277** in 72% isolated yield and 16:1 diastereomeric ratio.

Scheme 75: Synthesis of D-Homotryptophan

Preparation of D-isotryptophan via the Söderberg *N*-heteroannulation methodology began with the alkylation of lithiated Schöllkopf reagent **172** with a commercially available *cis/trans* mixture of 1,3-dibromopropene (**278**), yielding an equal *cis/trans* mixture of **279** (Scheme 76). Bromide **279** was then coupled to tributyl(2-

nitrophenyl)stannane (**208**) using the previously mentioned $\text{Pd}(\text{dba})_2\text{-PPh}_3\text{-CuI}$ conditions to give *cis/trans* alkene **280** in good yield. Annulation of **280** gave the isotryptophan derivative **281** in low yield with almost complete isomerization ($\text{dr}=1.2:1$). Also, an incomplete reduction forming *N*-hydroxyindole **282** was observed as a minor product.¹³² Given the high degree of isomerization for the indole product **281**, the diastereoselectivity for hydroxyindole **282** was surprisingly high ($>30:1$).

Scheme 76: Attempted Synthesis of D-Isotryptophan

3.3.3 Conclusions

A novel route to tryptophan derivatives using two sequential palladium-catalyzed reactions, a Kosugi–Migita–Stille cross-coupling and a carbon monoxide-mediated reductive *N*-heteroannulation, has been developed. This reaction sequence may be useful for the preparation of novel amino acids related to tryptophan having either D- or L-configuration.

Chapter 4

Synthesis of 2- and/or 3-Substituted Indoles Utilizing

Palladium-Catalyzed Reductive *N*-Heteroannulation

4.1 Attempted Synthesis of 3-Silylindoles	81
4.2 Synthesis of 2-Substituted Indoles via Hydrosilylation	82
4.3 Synthesis of 2,3- and 3-Substituted Indoles via Hydrostannylation	85
4.4 Conclusions	92

4.1 Attempted Synthesis of 3-Silylindoles

Vinylsilanes are very useful intermediates in organic synthesis, particularly for palladium-catalyzed cross-coupling reactions.¹³³ They are commonly used in the construction of natural products, especially due to their low toxicity. The most common method of preparing vinylsilanes is by hydrosilylation of the corresponding alkyne; however, stereo- and regiochemical control of the reaction is difficult, especially employing unsymmetrical internal alkynes as substrates. In response to this problem, Alami and co-workers¹³⁴ have reported a platinum-catalyzed *cis*-hydrosilylation of unsymmetrical internal alkynes which proceeds under *ortho*-substituent regiocontrol. This previously reported *ortho*-directing effect (ODE)¹³⁵ causes the silyl group to be selectively delivered to the α -carbon of the alkyne moiety, with respect to the aromatic ring containing the *ortho*-substituent. The results have been rationalized in terms of electronic polarization across the alkyne bond induced by the *ortho*-substituent, regardless of the electronic nature of this substituent. In the example which most pertains to the Söderberg cyclization chemistry, reaction of 1-(hept-1-ynyl)-2-nitrobenzene (**283**)¹³⁴ with PtO₂ and triethylsilane, in the absence of solvent, furnished only α -hydrosilylation isomer **284**¹³⁴ in excellent yield. The β -isomer was not detected (Scheme 77).

Scheme 77: Alami Regioselective Hydrosilylation

It was envisioned that exposure of *o*-nitrostyrene **284** to typical Söderberg *N*-heteroannulation conditions would produce 3-silylindole **285**. Compounds like **285** could then be transformed into more complex 3-substituted indole target molecules.¹³⁶ Upon analysis of the crude ¹H NMR, it was clear that cyclization had occurred; however, the silyl group had been unexpectedly cleaved as well to provide 2-pentylindole (**286**)¹³⁷ as the sole product in 75% yield (Scheme 78).

Scheme 78: Exposure of Vinylsilane to Söderberg *N*-Heteroannulation

This surprising discovery led to a brief investigation into the practicality of this methodology for synthesizing 2-substituted indoles.

4.2 Synthesis of 2-Substituted Indoles via Hydrosilylation

There have been very few methods reported for the synthesis of 2-alkylindoles. Probably the most commonly used protocol was reported by Katritsky and co-workers.¹³⁸ The authors showed that 2-alkyl groups of *N*-unsubstituted 2-alkylindoles could be activated toward proton loss by using carbon dioxide both to protect the N-H position and

to enable lithiation at the methyl group. Subsequent reaction with an electrophile affords the corresponding 2-(substituted alkyl)indole-1-carboxylic acid, and loss of CO₂ then occurs to reform the NH group. In this way, Katritsky prepared 2-heptylindole (**287**) from 2-methylindole (**31**) in 93% overall yield (Scheme 79). Although this method is effective, it suffers from a procedure which is quite lengthy and cumbersome.

Scheme 79: Katritsky Synthesis of 2-Alkylindoles

The much more convenient hydrosilylation/*N*-heteroannulation route to 2-alkylindoles mentioned above was also attempted on 1-(hex-1-ynyl)-2-nitrobenzene (**289**)¹³⁹, which was obtained from a routine Sonogashira coupling between 1-iodo-2-nitrobenzene (**226**) and 1-hexyne (**288**) (Scheme 80). Hydrosilylation of alkyne **289** was successful, producing vinylsilane **290** in excellent yield. Palladium-catalyzed cyclization of **290** occurred with concurrent silyl cleavage to produce 2-butyldindole (**291**)¹⁴⁰ in 54% yield over three steps.

Scheme 80: Synthesis of 2-Butylindole

This methodology also proved to be successful in the formation of 2-phenylindole (**122**)¹⁴¹, which was formed in 55% overall yield from **226** (Scheme 81).

Scheme 81: Synthesis of 2-Phenylindole

The synthesis of indolo[3,2-*b*]indole (**300**) was also attempted utilizing this newly developed protocol. In the event, 1-iodo-2-nitrobenzene (**226**) was coupled to TMS-acetylene (**295**), followed by desilylation using TBAF to give alkyne **297**¹⁴². Next, a second Sonogashira coupling was performed, in this instance between terminal alkyne

297 and **226** to furnish symmetrical internal alkyne **298** in good yield. Alami's hydrosilylation was ineffective when applied to alkyne **298**; only possible trace amounts of vinylsilane **299** were detected. It was envisioned that exposure of **299** to the Söderberg *N*-heteroannulation conditions would furnish fused indole **300** after two successive cyclizations (Scheme 82).

Scheme 82: Attempted Synthesis of Indolo[3,2-*b*]indole via Hydrosilylation

4.3 Synthesis of 2,3- and 3-Substituted Indoles via Hydrostannylation

Alami also reported a palladium-catalyzed route to stannylated stilbene derivatives by *ortho*-substituent directed regioselective addition of tributyltin hydride to unsymmetrical diaryl alkynes.¹⁴³ For example, 2-((*E*)-1-(tributylstannyl)-2-phenylvinyl)benzaldehyde (**302**) was furnished as the sole product from reaction of alkyne **301** with Bu₃SnH and 1 mol% PdCl₂(PPh₃)₂. Similar to Alami's hydrosilylation, the β-stannane was not produced (Scheme 83).

Scheme 83: Alami Regioselective Hydrostannylation

Although several functional groups were used as *ortho*-substituents in Alami's hydrostannylation study, the effectiveness of a nitro group in this position was not explored. Since *o*-nitrostyrenes of this type are typical Söderberg annulation precursors, the synthesis of compound **303** was attempted in hopes that a subsequent cyclization would occur, affording 3-(tributylstannyl)-2-phenylindole (**304**) (Scheme 84). Again, metallated indoles of this type could potentially be used as building blocks to form more structurally complicated target molecules. Regioselective hydrostannylation of alkyne **293** was successful, yielding only α -isomer **303**. The ensuing cyclization, however, was ineffective in furnishing indole **304**. Instead, the crude ^1H NMR revealed a complex mixture of unidentifiable products.

Scheme 84: Attempted Synthesis of 2-Phenyl-3-stannylindole

An alternate route to 2-phenyl-3-substituted indoles was envisioned by first performing a Kosugi-Migita-Stille coupling with stannane **303** and then cyclizing the resulting *o*-nitrostyrene to give the target indole. This approach was successful, initially affording 1,1,2-triarylethylene **306** from the Kosugi-Migita-Stille cross-coupling reaction

of stannane **303** and 1-iodo-4-methoxybenzene (**305**). Cyclization precursor **306** was then transformed into indole **307**¹⁴⁴ upon exposure to the Söderberg annulation protocol (Scheme 85).

Scheme 85: Successful Synthesis of 2-Phenyl-3-arylindole

The formation of 2-alkyl-3-substituted indoles was also explored using the same methodology. Hence, tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (**308**) was synthesized from alkyne **289** in good yield using Alami's protocol (Scheme 86).¹⁴³

Scheme 86: Formation of Alkylstannane Using Tributyltinhydride

Subsequent cross-couplings, however, proved to be problematic. Unlike the corresponding phenyl substrate **303**, alkylstannane **308** resisted all attempts to undergo

couplings with both electron-withdrawing and electron-donating aryl halides. The results are summarized in table 6. This obstacle prevented the potential formation of any 2-butyl-3-arylindoles.

Table 6: Cross-Coupling Attempts with Alkylstannane

308

309

310

<u>Entry</u>	<u>X</u>	<u>R</u>	<u>Catalyst System</u>	<u>Solvent</u>	<u>Temp (°C)</u>	<u>Time</u>
1	Br	CN	Pd(dba) ₂ , PPh ₃ , CuI	DMF	25	3 days
2	Br	CN	Pd(OAc) ₂ , XPhos ¹⁴⁵	DMF	80	42 h
3	I	OMe	PdCl ₂ (PPh ₃) ₂ , PPh ₃ , CuI	DMF	25	4 days
4	I	OMe	PdCl ₂ (PPh ₃) ₂ , PPh ₃ , CuI	DMF	80	2 days
5	I	OMe	Pd(dba) ₂ , PPh ₃	PhMe	reflux	30 h

Alami and co-workers also extended their *ortho*-directing effect to terminal arylalkynes in order to provide α -styryltributyltin derivatives.¹⁴⁶ Again, a wide variety of *ortho*-substituents were used, all giving complete α -regioselectivity in good to excellent yield. Similar to Alami's previous study¹⁴³, the effectiveness of a nitro group in this position was not explored. Thus, tributyl(1-(2-nitrophenyl)vinyl)stannane (**311**) was furnished from 1-ethynyl-2-nitrobenzene (**297**) via the previously described regioselective palladium-catalyzed hydrostannylation. The β -isomer was not detected in the crude ¹H NMR spectrum (Scheme 87).

Scheme 87: Synthesis of Tributyl(1-(2-nitrophenyl)vinyl)stannane

Stannane **311** proved to be a versatile intermediate in the synthesis of some unique 3- and 2,3-substituted indoles. For example, the palladium-catalyzed homocoupling of **311** proceeded smoothly in DMF to give dimer **312** in good yield. Exposure of dimer **312** to the Söderberg *N*-heteroannulation protocol resulted in the formation of 3,3'-bisindole **313**¹⁴⁷ (Scheme 88).

Scheme 88: Synthesis of 3-(1H-Indol-3-yl)-1H-indole

The possibility of synthesizing various 3-arylindoles was also explored by coupling stannane **311** with substituted aryl halides. Kosugi-Migita-Stille cross-coupling of stannane **311** and iodide **305** gave the desired *o*-nitrostyrene **314** as the major product;

however, the target alkene **314** was obtained in low yield (31%) as an inseparable 3:1 mixture (as determined by ^1H NMR analysis) with dimer **312** (Scheme 89).

Scheme 89: Synthesis of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene

Nevertheless, cyclization of the 3:1 mixture of **314** and **312** was successful, yielding both of the corresponding indole substrates **315**¹⁴⁸ and **313** in 61% and 75% yield, respectively (Scheme 90). It should be noted that the resulting indole products **315** and **313** were readily separable by column chromatography.

Scheme 90: Cyclization of the Inseparable 3:1 Mixture of o-Nitrostyrenes

Finally, the synthesis of indolo[2,3-*b*]indole (**317**) was envisioned via intermediate stannane **311**. Cross-coupling of 1-iodo-2-nitrobenzene (**226**) with tin derivative **311** afforded cyclization precursor **316** in good yield. As in previous palladium-catalyzed reactions involving stannane **311**, dimer **312** was also isolated as a minor product in 9% yield. Palladium-catalyzed *N*-heteroannulation of **316** gave the expected indolo[2,3-*b*]indole (**317**) in 42% yield. Surprisingly, a second product was isolated in 24% yield and determined to be quinolinone **318** (Scheme 91). It seems that

an equivalent of carbon monoxide has somehow been inserted into the substrate during the cyclization process, giving the carbonyl functionality at C-6 of **318**. Cenini *et. al.* observed a similar CO insertion in a minor product.⁸³ The mechanism of this occurrence remains unclear. The structure of **318** was determined by advanced NMR techniques along with HRMS ($m/z = 235.0867$ for $C_{15}H_{11}N_2O$ ($M+H^+$)). In addition, the experimental melting point (312-314°C) matched well with a previously reported value (314-315°C).¹⁴⁹ This marks the first example of a CO insertion into a Söderberg cyclization product.

Scheme 91: Synthesis of Fused Heterocycles

4.4 Conclusions

The hydrosilylation¹³⁴ and hydrostannylation^{143,146} procedures developed by Alami *et. al.* have proved to be useful in developing unique *o*-nitrostyrene intermediates suitable for typical Söderberg cyclizations. Utilizing this *N*-heteroannulation methodology, a variety of 2-and/or 3-substituted indoles were furnished in moderate to good yield.

Chapter 5

Synthetic Progress Toward the Construction of

Dilemmaones A-C

5.1 Introduction & Background	94
5.2 Retrosynthetic Analysis	96
5.3 Attempted Synthesis of Dilemmaone B	97
5.4 Conclusions	104

5.1 Introduction & Background

In 1997, a variety of specimens were collected off the coast of Cape Town, South Africa in order to explore the biomedical potential of South African marine invertebrates. During a preliminary cytotoxicity screening, an extract of a mixed collection of sponges was selected for investigation. A bioassay-directed fractionation of the crude extract using a brine shrimp lethality assay led to the isolation of a sphingolipid as the active metabolite. The subsequent ^1H NMR investigation of the inactive fractions led to the structural elucidation of dilemmaones A (**319**), B (**320**), and C (**321**) (Figure 11).¹⁵⁰ These unusual indole alkaloids originally got their names from the dilemma surrounding their sponge source. However, a process of elimination has since suggested that one of the sponges in the mixed collection, *Ectyonanchora flabellate*, is responsible for producing these compounds.

Figure 11: Structures of Dilemmaones A-C

The structures of dilemmaones A-C, although simple, are quite unusual, particularly with respect to the methoxymethylene and hydroxymethylene substituents at C-2. Only a few other 6,7-annulated indole natural products have been reported. The trikentrinins were isolated by Capon¹⁵¹ from the marine sponge *Trikentrion flabelliforme* and display antibacterial activity. Members of the trikentrin family include, but are not

limited to, *cis*-trikentrin A (**37**), *trans*-trikentrin A (**322**), *cis*-trikentrin B (**323**), and *trans*-trikentrin B (**324**) (Figure 12).

Figure 12: Structures of the Trikentritins

The structurally similar herbindoles were isolated by Scheuer¹⁵² from the Australian sponge *Axinella* sp. They have been shown to possess both cytotoxic and antifeedant properties. The structures of herbindole A (**325**), herbindole B (**326**), and herbindole C (**327**) are shown in figure 13.

Figure 13: Structures of the Herbindoles

The interesting biological profiles of the trikentrins and herbindoles combined with their uncommon structural motifs have made them attractive targets for total synthesis. The significant challenges associated with the construction of these complex systems are reflected in the many distinct approaches that have been reported for their racemic and enantioselective total syntheses.^{153,154,155} To date, there has been no reported

synthesis for any member of the dilemmaone family, even though their molecular skeletons resemble those of the trikentrins and herbindoies. Hence, a route to dilemmaones A-C was envisioned which involves a palladium-catalyzed reductive *N*-heteroannulation as the key step.

5.2 Retrosynthetic Analysis

Retrosynthetically, dilemmaone B (**320**) can be constructed from the palladium-catalyzed *N*-heteroannulation of *o*-nitrostyrene **328**. Compound **328** can arise from a Kosugi-Migita-Stille cross-coupling between aryl iodide **329** and vinyl stannane **330**. Alkene **330** can be formed in one step from a hydrostannylation of propargyl alcohol (**331**). Iodoindanone **329** could be fashioned through the manipulation of 2,3-dihydro-5-methylinden-1-one (**332**), which could be produced by reaction of toluene (**334**) and 3-chloropropionyl chloride (**333**) (Scheme 92).

Scheme 92: Retrosynthetic Route to Dilemmaone B

5.3 Attempted Synthesis of Dilemmaone B

The synthesis began via a Friedel-Crafts acylation of toluene (**334**) with 3-chloropropionyl chloride (**333**), resulting in β -chloropropiophenone derivative **335** in excellent yield.¹⁵⁶ The cyclization precursor **335** was dissolved in CH_2Cl_2 and refluxed in the presence of concentrated H_2SO_4 and tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4) to give 5-methylindanone (**332**) (Scheme 93).¹⁵⁷

Scheme 93: Synthesis of 5-Methylindanone

Methylindanone **332** was then subjected to typical aromatic nitration conditions to give a 2.4:1 mixture of nitration products **336** and **337**, respectively.¹⁵⁸ Pure nitroindanone **336** could be isolated via chromatography and was subsequently reduced to the corresponding aniline **338** by hydrogenation (Scheme 94).¹⁵⁸

Scheme 94: Synthesis of 6-Amino-5-methylindanone

At this stage of the synthesis, an *ortho*-nitration of aniline **338** was necessary in order to install the nitro group present in *N*-heteroannulation precursor **328**. After reviewing the literature, a study reported by Lemaire *et. al.* was discovered which described the one-step nitration of several free-aniline substrates using 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone (**340**) as the nitronium ion (NO_2^+) source.¹⁵⁹ In one example, 2,4-dibromoaniline (**339**) was nitrated using nitrocyclohexadienone **340** in acetic acid to give *o*-nitroaniline **341** in excellent yield (Scheme 95). It should be noted that the direct nitration of anilines by classical methods is frequently low yielding, due to the susceptibility of anilines to oxidation by the nitrating agent.

Scheme 95: Nitration of 2,4-Dibromoaniline

According to Lemaire and co-workers, the driving force for the reaction is the rearomatization of **340**, which results in the loss of the nitronium ion, and produces compound **342**. Cresol **342** can be easily isolated and recycled to **340** using fuming nitric acid (Scheme 96). This direct *C*-nitration of substituted anilines must be performed under acidic conditions (AcOH) for two reasons. Firstly, rearomatization of the reagent during the course of the reaction is catalyzed by Brønsted acids; secondly, the

nucleophilicity of the amine needs to be reduced in order to limit the formation of *N*-nitration by-products.¹⁵⁹

Scheme 96: Mechanism of Free-Aniline Nitration

In order to apply this methodology to aniline **338**, a synthesis of nitrating agent **340** was performed using the procedure described by Lemaire.¹⁶⁰ Hence, *p*-cresol (**345**) was tetrabrominated using iron metal as a catalyst to give compound **342**. Tetrabromocresol **342** was then exposed to fuming nitric acid to afford nitrating agent **340** in 50% yield over 2 steps (Scheme 97).

Scheme 97: Synthesis of Cyclohexadienone Nitrating Agent

Utilizing Lemaire's protocol, aniline **338** was seemingly converted to nitroaniline **346** in good yield. This transformation was originally confirmed by detecting the absence of a singlet from the aromatic region of the ¹H NMR spectrum of **346** when

compared with aniline **338**. It was assumed that this observation indicated substitution of the aromatic ring by a nitro group, most likely *ortho* to the amino group. However, upon examination of the HRMS of presumed **346**, a discrepancy was noticed. The protonated molecular ion ($M+H^+$) of **346** should have an exact mass around m/z 207 (for $C_{10}H_{11}N_2O_3$). Instead, the HRMS spectrum surprisingly displayed two high intensity peaks at m/z 240 and 242. After some calculation, it was determined that aniline **338** had extracted a bromine atom from compound **340** to give bromoindanone **347** in 59% yield (Scheme 98). The molecular formula for compound **347** ($C_{10}H_{11}BrNO$, $M+H^+$) corresponds almost exactly to the observed m/z values.

Scheme 98: Unexpected Bromination of Aniline Intermediate

Iranpoor and Firouzabadi have also reported the novel nitration of aromatic amines using a $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3$ reagent system.¹⁶¹ Interestingly, exposure of aniline **338** to these conditions also produced the undesired bromoindanone **347** as the sole reaction product in comparable yield (Scheme 99).

Scheme 99: Similar Indanone Bromination using $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3$

After the failure of these direct aniline nitration methods, a more traditional route to *o*-nitroaniline **346** was envisioned via application of a protection/nitration/deprotection protocol to aniline **338**. To commence this route, aniline **338** was converted to acetanilide **348** in good yield using acetyl chloride (AcCl) in the presence of NEt₃ (Scheme 100).

Scheme 100: Formation of Acetanilide using Acetyl Chloride

Nitration of acetanilide **348** proved to be problematic initially. However, after optimization of the reaction conditions, the most effective and concise procedure was shown to involve fuming HNO₃ and concentrated H₂SO₄ at a reaction temperature of –20°C for 90 min. In this way, the target nitroindanone **349** was furnished in 70% yield. The results of all attempts to nitrate compound **348** are displayed in table 7.

Table 7: Attempts to Nitrate Acetanilide Intermediate

<u>Entry</u>	<u>Reagents</u>	<u>Temp (°C)</u>	<u>Time (h)</u>	<u>Yield (%)</u>
1	HNO ₃ , glacial AcOH	5 → reflux	5	0
2	KNO ₃ , H ₂ SO ₄	-5 → r.t.	20	0
3	HNO ₃ , H ₂ SO ₄	0 → r.t.	4	0
4	HNO ₃	-40 → -20	1	0
5	HNO ₃ , H ₂ SO ₄	-20	0.5	45
6	HNO ₃ , H ₂ SO ₄	-20	1	50
7	HNO ₃ , H ₂ SO ₄	-20	2.5	69
8	HNO ₃ , H ₂ SO ₄	-20	1.5	70

Deprotection of acetanilide **349** proceeded smoothly using a procedure reported by Pouli and co-workers¹⁶² to give *o*-nitroaniline **346** in good yield. Subsequent diazotization/iodination of aromatic amine **346** gave a compound tentatively assigned as iodoindanone **329**. Seemingly, the corresponding bromide **350** was also synthesized from aniline **346** in low yield through a procedure described by Baik *et. al.*¹⁶³ While all ¹H and ¹³C NMR data appear to be in agreement with the proposed structures of **329** and **350**, acceptable *m/z* values were unable to be located using HRMS (Scheme 101).

Scheme 101: Formation of 6-Halo-5-methyl-7-nitroindanones

The construction of vinyl stannane **330** was addressed next. The goal was to fashion a suitable coupling partner which could undergo an ensuing Kosugi-Migita-Stille-type reaction with either aryl iodide **329** or aryl bromide **350**, forming cyclization precursor **328**. Hydrostannylation of propargyl alcohol (**331**) in the presence of AIBN at 80°C¹⁶⁴ gave three different tin isomers, as detected by analysis of the crude ¹H NMR spectrum. After chromatography using hexanes as the mobile phase, pure *trans*-stannane

330 was isolated in 23% yield, along with an inseparable 6:1 mixture of the *cis*-stannane **351** and *gem*-stannane **205**, respectively, in 7% yield (Scheme 102).

Scheme 102: Construction of (E)-3-(Tributylstannyl)prop-2-en-1-ol

With appropriate coupling pieces in hand, an effort was made to construct *o*-nitrostyrene **328** using the conditions reported by Levin¹²⁶. Unfortunately, reaction of either iodide **329** or bromide **350** with stannane **330** failed to produce the target compound **328**; only starting materials were returned in all attempts (Scheme 103). Subsequent reductive *N*-heteroannulation of **328** would produce dilemmaone B (**320**).

Scheme 103: Attempted Formation of Dilemmaone B Precursor

A possible alternative route to dilemmaone B was envisioned but not attempted to date. This pathway is based largely on Alami's hydrosilylation chemistry¹³⁴ discussed in chapter 4. As outlined in scheme 104, either iodide **329** or bromide **350** could undergo a Sonogashira coupling with propargyl alcohol (**331**) to give alkyne **352**. Hydrosilylation of alkyne **352** should produce vinylsilane **353** with the denoted stereo- and

regiochemistry. Finally, palladium-catalyzed *N*-heteroannulation of compound **353** would produce dilemmaone B (**320**).

Scheme 104: Unattempted Hydrosilylation Pathway to Dilemmaone B

5.4 Conclusions

The synthesis of the marine indole alkaloid, dilemmaone B (**320**), was envisioned utilizing the Söderberg *N*-heteroannulation as the key step. Although the target molecule was not reached, synthetic progress was achieved by furnishing key halo-intermediates **329** and **350**, along with stannane **330**. More effort involving these important intermediates is needed in the future to complete the total syntheses of these unique natural products.

Chapter 6

Synthetic Studies Towards Fistulosin Utilizing Palladium-Catalyzed Reductive N-Heteroannulation

6.1 Fistulosin Background	106
6.2 Synthetic Studies Towards Fistulosin by Clawson <i>et. al.</i>	107
6.3 Synthetic Studies Towards Fistulosin by Nishida <i>et. al.</i>	115
6.4 Dimer Synthesis and Analysis via Palladium-Catalyzed N-Heteroannulation	123
6.5 Conclusions	129

6.1 Fistulosin Background

A novel antifungal compound, fistulosin (**354**), was isolated in 1999 by Tomita *et. al.* from the roots of the Welsh onion (*Allium fistulosum* L.) (Figure 14).¹⁶⁵ The authors proposed the structure of 2-octadecyl-3-indolinone based upon their interpretation of ¹H, ¹³C, ¹H-¹H COSY, ¹H-¹³C COSY, DEPT, and selective INEPT NMR experiments. Tomita also reported an absorption at 1684 cm⁻¹ on the IR spectrum and a molecular formula of C₂₆H₄₃NO at *m/z* 385.6337 according to HRMS experiments.

Figure 14: Tomita's Proposed Structure of Fistulosin

354

Vegetables among the *Allium* species are known to be rich in flavonoids and alk(en)yl cysteine sulfoxides, which have perceived benefits for human health.¹⁶⁶ Since the late 1980's, biologically active products in the *Allium* species have been investigated and the isolation of nematicidal and antibacterial agents has been reported by Tada and co-workers.¹⁶⁷ Specifically, fistulosin exhibited antifungal activities against the wilt-producing fungi *Fusarium oxysporum*.¹⁶⁵ Antifungal agents isolated from nature, like fistulosin (**354**), are expected to be useful as a result of their safety to animals, humans, and ecosystems. The proposed fistulosin has a unique structure not found elsewhere in nature, although the indolinone core is found in some dimeric alkaloids such as indigo (**2**), peronatin A (**355**), and peronatin B (**356**) (Figure 15).

Figure 15: Naturally-Occurring Dimeric Indolinone Alkaloids

6.2 Synthetic Studies Towards Fistulosin by Clawson et. al.

In an effort to synthesize the proposed structure of fistulosin (**354**), Clawson *et. al.* envisioned a route involving the previously mentioned palladium-catalyzed *N*-heteroannulation reaction (Scheme 105). The synthesis began with the conversion of commercially available 1-nonadecanol (**357**) to 1-iodononadecane (**358**) using a known procedure.^{168,169} The reaction of 1-lithiononadecane (generated *in situ* from the reaction of 1-iodononadecane (**358**) with 2.2 equivalents of *t*-BuLi in diethyl ether at -20°C) with chromium hexacarbonyl followed by methylation using trimethyloxonium tetrafluoroborate afforded chromium carbene **359** in moderate yield.¹⁷⁰ Utilizing McDonald's procedure¹⁷¹ for the formation of α -stannyl ethers from carbenes, tributyl(1-methoxyicos-1-enyl) stannane (**360**) was obtained as a 3:1 *E/Z* mixture in good yield from the reaction of carbene **359** with triethylamine and tributyltin triflate. The palladium-catalyzed Kosugi-Migita-Stille coupling of organostannane **360** with *o*-iodonitrobenzene (**226**) afforded the anticipated 1-(1-methoxyicos-1-enyl)-2-nitrobenzene (**361**) in excellent yield as 4:1 *E/Z* mixture of isomers. Exposing *o*-nitrostyrene **361** to slightly altered Söderberg annulation conditions (6 mol% palladium acetate and 12 mol % 1,10 phenanthroline) afforded the desired 2-octadecyl-3-methoxyindole (**362**) in good yield.

Scheme 105: Clawson Attempted Route to Proposed Fistulosin

After many failed attempts to cleave the methyl ether in **362** and arrive at the proposed structure of fistulosin (**354**), an interesting transformation was observed. Adhering **362** to silica gel and allowing it to stand open to the air in an effort to cleave the methyl ether resulted instead in a ring-opening oxidative cleavage, affording methyl 2-(nonadecanamido)benzoate (**363**) in excellent yield (Scheme 106).

Scheme 106: Ring-Opening Oxidative Cleavage of Methoxy-Indole

Amide **363** was found to resemble two key natural products; both containing long aliphatic chains and both found to have remarkable antifungal properties against *Fusarium* fungi. *N*-Arachidylanthranilic acid (**364**) was isolated from aerial parts of *Ononis natrix* L., a perennial herb found in the Mediterranean region.¹⁷² Also, *N*-docosanoylanthranilic acid (**365**) was isolated from the aerial parts of *Inula oculus-christi*, the Eye of Christ flowering plant (Figure 16).¹⁷³

Figure 16: Antifungal Natural Products Containing Long Aliphatic Chains

Adding to this new discovery, Lu¹⁷⁴ reported that indole (**1**) undergoes a similar oxidative cleavage when exposed to white rot fungus (*Pleurotus ostreatus*) (Scheme 107). Isatoic acid (**366**) was evidenced as an intermediate (UV-vis, LC/MS) in ultimately forming anthranilic acid (**367**) as the major degradation product.

Scheme 107: Biodegradation of Indole with White Rot Fungus

With the hypothesis that the true structure of fistulosin (**354**) was incorrectly assigned as 2-octadecyl-3-indolinone, Clawson *et. al.* carried out a short synthesis¹⁷⁵ of 2-(nonadecanamido)benzoic acid (**370**) in order to compare its chemical properties to that of that compound isolated by Tomita (Scheme 108). The synthesis began by converting carboxylic acid **368** to the corresponding acid chloride **369** in quantitative yield. Acid chloride **369** was then condensed with anthranilic acid (**367**) in the presence of triethylamine to give 2-(nonadecanamido)benzoic acid (**370**) in good yield. The structure of **370** was confirmed by ¹H, ¹³C, and HMBC NMR experiments.

Scheme 108: Synthesis of 2-(Nonadecanamido)benzoic acid

Carboxylic acid **370** gives almost identical ^1H and ^{13}C chemical shifts when compared to Tomita's proposed fistulosin (**354**) (2-octadecyl-3-indolinone) (Table 8). The only initial difference is the lack of the amide signal in Tomita's ^{13}C NMR spectral data (observed at 172.7 ppm in **370**), although the disappearance of amide signals due to numerous factors (solution pH, temperature, proximity to a carboxylic acid moiety, etc.) has been reported.¹⁷⁶ Also, the IR signal reported by Tomita (1684 cm^{-1}) is very close to the IR signal of 2-(nonadecanamido)benzoic acid (**370**) (1673 cm^{-1}). The larger discrepancies at this point for Clawson and co-workers were the melting point difference and the HRMS dissimilarity. Clawson's proposed fistulosin **370** melted at $94\text{-}95^\circ\text{C}$ with a m/z of 417.3243 while Tomita's isolated structure **354** melted at $80\text{-}83^\circ\text{C}$ and had a m/z of 385.6337. Nevertheless, the similarities of these two compounds are remarkable.

Table 8: Comparison of Tomita's Fistulosin and Carboxylic Acid 370

354 (Tomita)^a		370 (Clawson)^b	
mp (°C)	80-83	94-95	
IR (cm⁻¹)	1684	1673	
HRMS (M⁺)	385.6337	417.3243	
¹H NMR	10.8 (br s, 1H) 8.8 (d, 1H) 8.1 (d, 1H) 7.6 (t-like, 1H) 7.1 (t-like, 1H) 2.44 (t-like, 1H) 1.74 (m, 2H) 1.63 (m, 2H) 1.4 (m, 2H) 1.25 (br s, 28H) 0.88 (t-like, 3H)	11.0 (br s, 1H) 8.77 (d, 1H) 8.13 (dd, 1H) 7.60 (dt, 1H) 7.11 (dt, 1H) 2.47 (t, 2H) 1.77 (pent, 2H) 1.40 (pent, 2H) 1.34-1.24 (m, 28H) 0.88 (t, 3H)	
¹³C NMR	171.5 142.5 135.8 131.9 122.7 120.7 113.7 38.9 32.1 29.05-29.92 25.9 23.4 14.3	172.7 172.1 142.1 135.6 131.7 122.6 120.6 113.9 38.7 31.9 29.7-29.2 25.5 22.7 14.1	

^a In CDCl₃ at 500 MHz (125 MHz for ¹³C)

^b In CDCl₃ at 600 MHz (150 MHz for ¹³C)

Clawson *et. al.* noticed a general trend that the melting point increases with increased aliphatic carbon chain length in similar compounds. This trend was observed

by comparing *N*-arachidylanthranilic acid (**364**) to *N*-docosanoylanthranilic acid (**365**) (see Figure 16). Thus, Clawson *et. al.* proposed that the length of the aliphatic chain may be shorter than Tomita's proposed octadecyl chain. This adjustment could account for a needed decrease in melting point ($94\text{-}95^{\circ}\text{C} \rightarrow 80\text{-}83^{\circ}\text{C}$).

To solve the HRMS discrepancy, the MS fragmentation patterns of the previously mentioned *N*-docosanoylanthranilic acid (**365**) were examined. Ziesche¹⁷³ and co-workers reported that the molecular ion of (**365**) ($\text{C}_{29}\text{H}_{49}\text{NO}_3$) of m/z 459.371 was only seen in 1%, where the m/z 441.359 peak seen from the loss of H_2O was seen in 12%. Additionally, Al-Khalil¹⁷² reported similar fragmentations for *N*-arachidylanthranilic acid (**364**). The molecular ion for $\text{C}_{27}\text{H}_{45}\text{NO}_3$ of m/z 431 was only seen in 2%, where the m/z 413 peak seen from the loss of H_2O was seen in 7%. Hence, Clawson *et. al.* proposed that Tomita's reported M^+ (100%) of 385 could likely be the more abundant signal resulting from the loss of water from a compound with the molecular formula $\text{C}_{25}\text{H}_{41}\text{NO}_3$ and molecular weight of 403. With this insight, Clawson and co-workers set out to synthesize 2-(octadecanamido)benzoic acid (**373**) using the same protocol as described for the preparation of 2-(nonadecanamido)benzoic acid (**370**). This compound contains one less carbon in the aliphatic chain attached to the amide and, ironically, has a molecular weight of 403.60 g/mol. Carboxylic acid **371** was transformed into 2-(octadecanamido)benzoic acid (**373**) in two steps (Scheme 109).

Scheme 109: Synthesis of 2-(Octadecanamido)benzoic acid

The data for compound **373** now matched almost exactly to Tomita's fistulosin (**354**), except again for the absence of the amide peak in the ^{13}C NMR (Table 9).

Table 9: Comparison of Tomita's Fistulosin and Carboxylic Acid 373

354 (Tomita)^a		373 (Clawson)^b	
mp (°C)	80-83 (white crystals)	81-82 (white powder)	
IR (cm⁻¹)	1684	1673	
HRMS (M⁺)	385.6337	403.3086	
¹H NMR	10.8 (br s, 1H)	10.9 (br s, 1H)	
	8.8 (d, 1H)	8.77 (d, 1H)	
	8.1 (d, 1H)	8.13 (dd, 1H)	
	7.6 (t-like, 1H)	7.60 (dt, 1H)	
	7.1 (t-like, 1H)	7.11 (dt, 1H)	
	2.44 (t-like, 1H)	2.47 (t, 2H)	
	1.74 (m, 2H)	1.77 (m, 2H)	
	1.63 (m, 2H)		
	1.4 (m, 2H)	1.40 (m, 2H)	
	1.25 (br s, 28H)	1.34-1.24 (m, 26H)	
	0.88 (t-like, 3H)	0.88 (t, 3H)	
¹³C NMR		172.7	
	171.5	172.2	
	142.5	142.2	
	135.8	135.7	
	131.9	131.8	
	122.7	122.6	
	120.7	120.6	
	113.7	113.8	
	38.9	38.7	
	32.1	31.9	
	29.05-29.92	29.7-29.2	
	25.9	25.5	
	23.4	22.7	
	14.3	14.1	

^a In CDCl₃ at 500 MHz (125 MHz for ^{13}C)

^b In CDCl₃ at 600 MHz (150 MHz for ^{13}C)

Most importantly, the melting range for compound **373** was observed at 81-82°C, matching the melting range of 80-83°C reported by Tomita. It seems that Clawson and co-workers may have elucidated the true structure of the compound isolated from the roots of the Welsh onion; however, other attempts have been made to determine its identity.

6.3 Synthetic Studies Towards Fistulosin by Nishida et. al.

Nishida *et. al.* have published a synthesis of Tomita's reported structure of fistulosin using a ruthenium-catalyzed diene cycloisomerization (Scheme 110).¹⁷⁷ The synthesis began with the Mitsunobu reaction of readily available aniline **374** with alcohol **375** to yield α,β -unsaturated ester **376**. Treatment of ester **376** with $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$ (10 mol%) provided enamide **377** in good yield. Cycloisomerization of **377** in the presence of Grubbs second generation catalyst (10 mol %) and trimethyl(vinyloxy)silane gave cyclized product **378** in 87% yield. Cyclized product **378** was reduced with DIBAL to give aldehyde **379**, which was treated with an alkyl Grignard reagent to give the corresponding secondary alcohol. Mesylation of the resulting hydroxy group followed by reduction of the mesylate with NaBH_4 gave indoline **380**, which was converted to 3-indolinone **381** by ozonolysis. Finally, treatment of **381** with concentrated H_2SO_4 at 0°C gave the deprotected product **354** quantitatively.

Scheme 110: Nishida Synthesis of 2-Octadecyl-3-indolinone

Nishida claimed that 3-indoline **354** was pure and stable enough for the structure to be characterized; however, further purifications by column chromatography or recrystallization were unsuccessful since **354** was gradually tautomerized to the more thermodynamically stable 3-hydroxyindole **382** in solution. Compound **382** provided a second candidate for the structure of the natural fistulosin. Nishida also reported that tautomerization of **354** occurred smoothly in an acidic medium, such as aqueous HCl or H₂SO₄, to give the more stable **382** (Scheme 111). According to the authors, the structure

of 3-hydroxyindole **382** was confirmed by ^1H - ^1H COSY, HMBC, and HMQC 2D-NMR experiments.

Scheme 111: Tautomerization of 3-Indolinone **354 in Acidic Medium**

Nishida also prepared 3-octadecyl-2-oxindole (**384**) as a third prospect for comparison with Tomita's isolated product from the roots of the Welsh onion. Using a short procedure developed by Overman and co-workers¹⁷⁸, oxindole (**5**) was condensed with octadecanal to give alkene **383** in good yield. Reduction with zinc afforded the desired 3-octadecyl-2-oxindole (**384**) (Scheme 112).

Scheme 112: Nishida Synthesis of 3-Octadecyl-2-oxindole

Comparing the spectral data of all three compounds synthesized by Nishida (**354**, **382**, and **384**) to the compound isolated by Tomita (**354**) clearly shows that none of the structures agree with the reported data of the compound isolated from the roots of the Welsh onion (Table 10). Nishida did not comment much further on the true structure of fistulosin, only adding that more investigation is necessary in order to determine its identity.

Table 10: Comparison of Nishida's Fistulosin Candidates (R=C₁₈H₃₇)

	354 (Tomita)^a	354 (Nishida)^b	382^b	384^b
mp (°C)	80-83	100-102	107-108	95-96
IR (cm⁻¹)	1684 (CO)	1675 (CO)	1674 (OH)	1698 (CO)
MS (M⁺)	385	385	385	385
¹H NMR	10.8 (br s, 1H) 8.8 (d, 1H) 8.1 (d, 1H) 7.6 (t-like, 1H) 7.1 (t-like, 1H) 2.44 (t-like, 1H) 1.74 (m, 2H) 1.63 (m, 2H) 1.4 (m, 2H) 1.25 (br s, 28H) 0.88 (t-like, 3H)	7.61 (d, 1H) 7.44 (dd, 1H) 6.88 (d, 1H) 6.82 (d, 1H) 4.70 (br s, 1H) 3.75 (dd, 1H) 1.8-2.0 (m, 1H) 1.5-1.6 (m, 1H) 1.3-1.4 (m, 32 H) 0.88 (t, 3H)	7.56 (d, 1H) 7.49 (ddd, 1H) 6.95 (d, 1H) 6.78 (dd, 1H) 6.08 (br s, 1H) 1.8-1.9 (m, 1H) 0.9-1.3 (m, 34H) 0.88 (t, 3H)	8.63 (br s) 7.2-7.3 (m, 2H) 7.02 (dd, 1H) 6.91 (m, 1H) 3.47 (m, 1H) 1.96 (m, 2H) 1.2-1.4 (m, 32H) 0.88 (t, 3H)
¹³C NMR	171.5 142.5 135.8 131.9 122.7 120.7 113.7 38.9 32.1 29.05-29.92 25.9 23.4 14.3	202.7 161.3 137.0 124.5 121.5 118.9 112.6 64.3 32.0 31.9 29.3-29.7 25.8 22.7 14.1	204.6 162.0 138.1 124.2 121.5 118.3 112.0 72.5 32.0 31.9 29.3-29.8 23.0 22.7 14.1	180.7 141.6 129.9 127.7 124.1 122.2 109.7 46.1 31.9 30.5 29.6-29.7 (m) 29.3 25.8 22.7 14.1

^a In CDCl₃ at 500 MHz (125 MHz for ¹³C)

^b In CDCl₃ at 400 MHz (100 MHz for ¹³C)

While Nishida's proposed structures of 3-indolinone **354** and oxindole **384** are believed to be correct, the assigned structure of 2-octadecyl-1H-indol-3-ol (**382**) raises

some doubt. Nishida claimed to be able to control the tautomerization of **354** to “the more thermodynamically stable” compound **382** via acidic media (see Scheme 111). This assertion defies literature precedence involving 3-indolinone oxidations to give the corresponding dimeric compounds. The most commonly used method to produce indigo (**2**) involves a transformation of this type. Indoxyl (**386**) is prepared from the reaction of *N*-phenylglycine (**385**) with sodium hydroxide, potassium hydroxide, and sodium amide.¹⁷⁹ Once the reaction mixture is exposed to atmospheric oxygen, indigo (**2**) is formed via a oxidative dimerization of 3-indolinone **386** (Scheme 113).

Scheme 113: Formation of Indigo via Oxidative Dimerization

2-Substituted-3-indolinones also undergo a similar dimerization. Tyrian purple (**389**) is formed from the sulfate ester **387** via tyriverdin (**388**). Compound **387** is hydrolyzed by a sulfatase to the corresponding 3-hydroxyindole (or 3-indolinone), which by oxidative coupling forms the dimeric tyriverdin (**388**) as a mixture of stereoisomers (Scheme 114).¹⁸⁰

Scheme 114: Formation of Tyriverdin via Dimerization

2-Alkyl-3-indolinones also dimerize. For example, Van Vranken¹⁸¹ reported the synthesis of natural products peronatin A (**355**) and peronatin B (**356**) using biomimetic oxidative coupling methods. The hydrogen peroxide oxidation of 2,4-dimethylindole (**390**) in the presence of acetic acid produced the intermediate 2,4-dimethylindoxyl (**391**) which immediately dimerized to produce peronatin B (**356**) (Scheme 115). Peronatin A (**355**) was formed in the same way from **390** using basic conditions (H₂O₂, NEt₃). It should be noted that Peronatin A (**355**) slowly isomerizes to the more stable *trans*-isomer Peronatin B (**356**) in anhydrous chloroform. Sterner¹⁸⁰ has shown that the *trans*-conformation is more stable due to an intramolecular H-bonding interaction between the N-1 proton and the C'-3 carbonyl oxygen of the dimer.

Scheme 115: Van Vranken Synthesis of Peronatin B

The fact that both indoxyl (**386**) and 2,4-dimethylindoxyl (**391**) undergo oxidative coupling reactions to form the corresponding dimers conflicts with Nishida's proposal that 2-octadecyl-3-indolinone (**354**), when exposed to H₂SO₄, would give 3-hydroxyindole **382**. It seems much more likely that **354** dimerizes to give compound **392**, probably with the denoted *trans*-conformation due to the size of the alkyl chain on C-2 (Scheme 116).

Scheme 116: Possible Dimerization of 2-Octadecyl-3-indolinone

Comparison of the relevant ^1H and ^{13}C NMR signals of Nishida's 3-hydroxyindole **382** (now proposed to actually be dimer **392**) with the corresponding signals belonging to dimeric peronatin B (**356**) illustrates remarkable similarities (Table 11). The only significant difference is the ^{13}C NMR signal at C-4 of Nishida's compound **382**. This difference is most likely due to the absence of a methyl group.

Table 11: Comparison of Nishida's 3-Hydroxyindole and Peronatin B

	382^a	356^b
^1H NMR	<div>H-6 7.49 (ddd, 1H)</div> <div>H-7 6.95 (d, 1H)</div> <div>H-5 6.78 (dd, 1H)</div> <div>H-1 6.08 (br s, 1H)</div>	<div>7.30 (dd, 1H)</div> <div>6.71 (dd, 1H)</div> <div>6.52 (dd, 1H)</div> <div>6.12 (bs s, 1H)</div>
^{13}C NMR	<div>C-3 204.6</div> <div>C-7a 162.0</div> <div>C-6 138.1</div> <div>C-4 124.2</div> <div>C-5 121.5</div> <div>C-3a 118.3</div> <div>C-7 112.0</div> <div>C-2 72.5</div>	<div>204.9</div> <div>161.6</div> <div>140.1</div> <div>137.5</div> <div>119.9</div> <div>118.0</div> <div>109.4</div> <div>68.4</div>

^a In CDCl_3 at 400 MHz (100 MHz for ^{13}C)

^b In CDCl_3 at 500 MHz (125 MHz for ^{13}C)

The ^{13}C shift for C-3 of Peronatin B (**356**) at 209.4 ppm matches very nicely with the corresponding signal for **382** at 204.6 ppm. This data further suggests that Nishida misassigned dimer **392** as 3-hydroxyindole **382**. ^{13}C NMR shifts for quaternary carbons of the type reported for **382** at C-3 usually appear much further upfield. For example, Clawson *et. al.* reported a ^{13}C NMR shift at C-3 of 140.8 ppm for ethoxyindole **393** (Figure 17).⁹¹ Even without the presence of an attached ethyl group, it is difficult to justify a chemical shift difference of almost 65 ppm.

Figure 17: Comparison of ^{13}C NMR Shifts of Heterocycles at C-3

Additional evidence that Nishida may have incorrectly assigned the structure of dimeric **392** as 2-octadecyl-3-hydroxyindole (**382**) can be found by examining the HRMS data and fragmentation patterns of the dimeric peronatins. Sterner has reported that peronatin A (**355**) and peronatin B (**356**) both showed a very weak molecular ion peak when analyzed by HRMS (3-4%). Both of these compounds were shown to cleave symmetrically in the ion source, where one half takes up a hydrogen and gives the base peak of $(M/2)+1$ (the monomer plus a hydrogen) with EI ionization.¹⁸⁰ The base peaks for both peronatin A and B (exact mass = 320.1525) were found to be m/z 161.0825 (or approximately $(M/2)+1$). Nishida's reported molecular ion of m/z 385 for his proposed 3-hydroxyindole **382** is most likely the $(M/2)+1$ base peak seen from the symmetrical cleavage of dimeric **392** (exact mass = 768.6533). The molecular ion peak of **392** around

m/z 768 may have been overlooked while scanning the small region where an expected base peak of m/z 385 would be found.

6.4 Dimer Synthesis and Analysis via Palladium-Catalyzed *N*-Heteroannulation

In order to confirm that Nishida's 3-hydroxyindole **382** was indeed the proposed dimer **392**, an attempt was made to synthesize **392** for further analysis. Since the peroxidation of 2-alkyl indoles is known to give dimers of this type^{182,183}, it was believed that 2-octadecylindole (**397**) would be a suitable starting material. Initially, a route was envisioned to arrive at (**397**) that involved a Sonogashira coupling/base-promoted heteroannulation strategy. Specifically, palladium-catalyzed coupling of 2-iodoaniline (**394**) with 1-eicosyne (**395**) in the presence of copper iodide gave *o*-alkynylaniline **396** in good yield. Potassium *tert*-butoxide induced cyclization of **396**, as reported by Knochel¹⁸⁴, failed to produce 2-octadecylindole (**397**) (Scheme 117).

Scheme 117: Failed Route to 2-Octadecylindole

It was then decided to attempt to synthesize 2-octadecylindole (**397**) via the Söderberg annulation route to 2-alkylindoles discussed in chapter 4. Hence, 1-iodo-2-

nitrobenzene (**226**) was coupled to 1-eicosyne (**395**) in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and CuI to give nitroalkyne **398** in near quantitative yield. Platinum-catalyzed regioselective addition of triethylsilane to the alkyne moiety in **398** afforded vinyl silane **399** as the only product in excellent yield. Finally, exposure of **399** to typical Söderberg annulation conditions caused cleavage of the silyl group and induced cyclization to produce 2-octadecylindole (**397**) (Scheme 118).

Scheme 118: Söderberg *N*-Heteroannulation Route to 2-Octadecylindole

With indole **397** in hand, dimerization was attempted using the procedures reported to synthesize Peronatin A (**355**) and B (**356**) from 2,4-dimethylindole (**390**).¹⁸¹ Thus, 2-octadecylindole (**397**) was exposed to both the acidic conditions (H_2O_2 , AcOH , r.t.) and basic conditions (H_2O_2 , NEt_3 , THF , r.t.) described by Van Vranken in an effort to arrive at dimer **392**. Unfortunately, no evidence of dimer **392** was detected; only the starting indole **397** was returned after several hours (Scheme 119).

Scheme 119: Attempted Dimerization Using Van Vranken Conditions

After searching the literature, a study was discovered which described the peroxidation of 2-alkylindoles using *meta*-chloroperoxybenzoic acid (*m*-CPBA) to give both 2,2'-biindolyl and 3-(3-oxoindolin-2-yl)indole dimers.¹⁸⁵ For example, 2-methylindole (**31**) was transformed into dimers **400** and **401** in 61% and 20% yield, respectively (Scheme 120). It should be noted that the structures of compounds **400** and **401** were confirmed by X-ray crystallographic analysis.¹⁸⁵

Scheme 120: Preparation of Dimers via Oxidation of 2-Methylindole

Since the identification of compounds like **400** and **401**, there has been much mechanistic controversy; however, agreement has been reached. Dimers **400** and **401** have been explained by the intermediate formation of 2-methylindolone (**402**). Indolone **402** could truly be the intermediate in the formation of **401**; in fact **401** could arise from the nucleophilic attack of indole **31** on indolone **402**. However, the ionic mechanism proposed is highly unlikely to explain the formation of **400**, which is more likely to arise from the dimerization of radical **403** (Scheme 121).

Scheme 121: Intermediates in Dimer Formations

Reaction of 2-octadecylindole (**397**) with *m*-CPBA proceeded in much the same manner as reported for 2-methylindole. Hence, 2-octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (**392**) and 2-octadecyl-2-(2-octadecyl-1*H*-indol-3-yl)indolin-3-one (**404**) were furnished in 33% and 36% yield, respectively (Scheme 122). These compounds were confirmed by ¹H and ¹³C NMR, along with gHMBC and NOESY 2-D NMR experiments (see Appendix). In addition, HRMS data for dimer **392** showed a peak at *m/z* 769.6606 (*M*+*H*⁺), albeit in only 3-4%. A more intense peak at 386.3422 was also detected, indicating the symmetrical cleavage of the dimer ((*M*/2)+1). These trends match well with the ones observed in the dimeric peronatins.

Scheme 122: Successful Synthesis of 2,2'-Biindolinyl Dimer

A comparison between confirmed dimer **392** and Nishida's reported 3-hydroxyindole **382** clearly indicates that they are the same compound (Table 12). All observed data, including ¹H NMR, ¹³C NMR, mp, and IR, is in almost exact accordance. This affirms that Nishida's "tautomerization" of 2-octadecyl-3-indolinone (**354**) was actually a dimerization yielding compound **392**.

Table 12: Comparison of Dimer 392 with Nishida's 3-Hydroxyindole

392^a

382^b

	392^a	382^b
mp (°C)	105-107	107-108
IR (cm⁻¹)	1674 (CO)	1674 (OH)
MS (M⁺)	768.6527	385
¹H NMR	7.56 (d, 2H) 7.48 (t, 2H) 6.95 (d, 2H) 6.78 (t, 2H) 6.02 (s, 2H) 1.85-1.90 (m, 2H) 0.94-1.30 (br m, 66H) 0.88 (t, 6H)	7.56 (d, 1H) 7.49 (ddd, 1H) 6.95 (d, 1H) 6.78 (dd, 1H) 6.08 (br s, 1H) 1.84-1.90 (m, 1H) 0.99-1.31 (m, 34H) 0.88 (t, 3H)
¹³C NMR	204.5 161.9 138.0 124.1 121.6 118.3 112.0 72.5 32.0 31.9 29.3-29.8 (m) 22.9 22.7 14.1	204.6 162.0 138.1 124.2 121.5 118.3 112.0 72.5 32.0 31.9 29.3-29.8 (m) 23.0 22.7 14.1

^a In CDCl₃ at 600 MHz (150 MHz for ¹³C)

^b In CDCl₃ at 400 MHz (100 MHz for ¹³C)

6.5 Conclusions

After much debate, it seems that the true structure of fistulosin is 2-(octadecanamido)benzoic acid (**373**) and not 2-octadecyl-3-indolinone (**354**) as originally proposed by Tomita. Nishida actually synthesized 2-octadecyl-3-indolinone (**354**) in order to verify Tomita's claim. Upon comparison, it was clear that fistulosin was not (**354**), nor was it either of Nishida's other two fistulosin candidates, 3-octadecyl-2-oxindole (**384**) or 3-hydroxy-2-octadecylindole (**382**). With the structure of Nishida's 3-hydroxy-2-octadecylindole (**382**) in question, a study was carried out to verify its identity. It was determined that the reported structure of **382** was actually dimer **392** as concluded by comparison of the obtained spectral data. Dimer **392** was obtained from the *m*-CPBA oxidation of 2-octadecylindole (**397**).

Chapter 7

Miscellaneous Reactions Forming Novel Heterocycles

7.1 Synthesis of 3-(Halomethyl)benzo[<i>c</i>]isoxazole- <i>N</i> -oxides	131
7.2 Incorporation of Additives into <i>N</i> -Heteroannulations	134
7.3 Conclusions	136

7.1 Synthesis of 3-(Halomethyl)benzo[*c*]isoxazole-*N*-oxides

Originally, a route to 3-bromoindoles was envisioned utilizing the previously mentioned Söderberg palladium-catalyzed reductive *N*-heteroannulation. These 3-bromoindoles could be used as synthetic building blocks in constructing more complex indole natural products. Thus, benzaldehyde (**405**) was converted to the corresponding 1,1-dibromo-1-alkene **406** using carbon tetrabromide (CBr₄) in the presence of PPh₃. Unfortunately, coupling of dibromide **406** with stannane **208**, using a protocol developed by Shen *et. al.* specifically for substrates of this type, was unsuccessful.¹⁸⁶ It was imagined that compound **407** would have undergone cyclization to afford 3-bromo-2-phenylindole (**408**) (Scheme 123).

Scheme 123: Attempted Synthesis of 3-Bromo-2-phenylindole

After several failed attempts to couple **406** and **208** employing variants of the above Kosugi-Migita-Stille coupling, a publication was discovered which described the regioselective hydrobromination of 1,2-bis(ethynyl)benzene (**409**) using aqueous HBr in

hot pentanone to give 1,2-bis(1'-bromoethenyl)benzene (**410**) in near quantitative yield (Scheme 124).¹⁸⁷

Scheme 124: Hydrobromination of 1,2-Bis(ethynyl)benzene

It was presumed that this protocol would be equally effective if applied to 1-ethynyl-2-nitrobenzene (**297**). Hence, the synthesis of **297** began with a Sonogashira coupling of 1-iodo-2-nitrobenzene (**226**) and trimethylsilylacetylene to give TMS-alkyne **296**. Removal of the silyl group in **296** with tetrabutylammonium fluoride (TBAF) led to the desired compound **297** in 62% yield over two steps (Scheme 125).

Scheme 125: Synthesis of 1-Ethynyl-2-nitrobenzene

Nitroalkyne **297** was then exposed to the hydrobromination conditions discussed above in hopes that bromoalkene **411** would emerge as the major product. *o*-Nitrostyrene **411** could then undergo a Söderberg cyclization to yield 3-bromoindole. Surprisingly, combining **297** with 48% aqueous HBr in 3-pentanone at 100°C did not yield any of the desired product **411**; instead, benzisoxazole-*N*-oxide **412** was produced as the major product in 37% yield (Scheme 126). The structure of **412** was confirmed by gHMBC,

Scheme 126: Exposure of 1-Ethynyl-2-nitrobenzene to HBr in 3-Pentanone

Scheme 127: Mechanism of Benzisoxazole-*N*-oxide Formation

133

Scheme 128: Synthesis of 3-(Chloromethyl)benzo[*c*]isoxazole-*N*-oxide

It is noteworthy that heteroannulation did not occur with the corresponding nitroalkene. Subjecting 1-nitro-2-vinylbenzene (**108**) to 48% aqueous HBr in hot 3-pentanone caused only starting material to be returned (Scheme 129).

Scheme 129: Reaction of HBr with 1-Nitro-2-vinylbenzene

7.2 Incorporation of Additives into *N*-Heteroannulations

In an effort to expand the scope of the Söderberg *N*-heteroannulation methodology, a series of reactions were designed to incorporate double bond moieties into the targeted indole core. Dihydropyran (**416**) was used as the solvent in a typical Söderberg annulation employing *o*-nitrostyrene **115**, in hope that **416** would be included in the structure of the final product. Unfortunately, only a standard cyclization occurred, giving indole **417** as the lone isolated species (Scheme 130).

Scheme 130: Attempted Incorporation of Dihydropyran into *N*-heteroannulation

Integrating formaldehyde into Söderberg cyclization products was examined next. Reaction of annulation precursor **115** with ten equivalents of paraformaldehyde in the presence of palladium(II) acetate and carbon monoxide gave dihydroquinoline **418** in low yield (Scheme 131). It seems that the formaldehyde carbon has been incorporated into the C-2 position of **418**.

Scheme 131: Synthesis of Dihydroquinoline **418**

The use of hexanal in this reaction was considered next. It was envisioned that **419** could be fashioned from hexanal using the conditions described to produce **418**. Disappointingly, exposure of **115** to these cyclization conditions returned only starting material. The alternate Söderberg conditions were also implemented in order to arrive at **419**; however, only indole **417** was recovered (Scheme 132).

Scheme 132: Attempted Incorporation of Hexanal into *N*-heteroannulation

7.3 Conclusions

Two novel reactions were developed forming unique nitrogen-containing compounds. A benzisoxazole-*N*-oxide synthesis was discovered by exposing an o-alkynyl nitrobenzene to aqueous HBr in 3-pentanone. Also, the Söderberg *N*-heteroannulation methodology to produce indoles was expanded by incorporating formaldehyde into the final product, giving a dihydroquinoline moiety. More effort is needed in the future to fully determine the scope and limitations of these two novel transformations.

Chapter 8

Supporting Information: Experimental Procedures

8.1 Supporting Information Chapter 3: Tryptophan Derivatives	139
8.2 Supporting Information Chapter 4: 2- and/or 3-Substituted Indoles	165
8.3 Supporting Information Chapter 5: Dilemmaones A-C	175
8.4 Supporting Information Chapter 6: Fistulosin	179
8.5 Supporting Information Chapter 7: Miscellaneous Reactions	184

General Procedures. NMR spectra were determined in CDCl_3 at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR) or at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR), respectively. The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^1H and ^{13}C) or CDCl_3 (77.0 ppm, ^{13}C) internal standards. ^1H - ^1H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexanes and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; anhydrous acetonitrile, benzene, dichloromethane, 1,4-dioxane, diethyl ether, DMF, NMP, and toluene and all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Chromatography was performed on silica gel 60 (40-63 μm , EMD). Melting points were determined on a MelTemp and are uncorrected.

8.1 Supporting Information Chapter 3: Tryptophan Derivatives

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-trimethylstannyl-2-propen-1-yl)pyrazine (238). To a solution of (2R,5S)-2-(2-bromo-2-propen-1-yl)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazine (**198**) (1.00 g, 3.30 mmol) in benzene (25 ml) at ambient temperature and under an atmosphere of nitrogen were added diisopropylethylamine (85 mg, 0.66 mmol) and hexamethylditin (2.16 g, 6.60 mmol), followed by bis(dibenzylideneacetone)palladium ($\text{Pd}(\text{dba})_2$) (95 mg, 0.16 mmol) and triphenylphosphine (PPh_3) (173 mg, 0.66 mmol). The solution was heated for 24 h at 80 °C. The reaction mixture was quenched by the addition of CuSO_4 (sat.-aqueous, 150 mL). The reaction mixture was extracted with hexane (3 x 100 mL) and the combined organic layers were washed with brine (100 mL). The combined organic phases were dried (MgSO_4), filtered through Celite, and the solvents were removed under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 99:1) to afford **238** (1.01 g, 2.61 mmol, 80%) as a colorless oil. ^1H NMR δ 0.13 (s, 9H), 0.67 (d, $J=6.6$ Hz, 3H), 1.03 (d, $J=6.6$ Hz, 3H), 2.26 (dsept, $J=7.2, 3.6$ Hz, 1H), 2.59 (dd, $J=13.2, 7.2$ Hz, 1H), 2.83 (dd, $J=13.2, 7.2$ Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.89 (t, $J=3.6$ Hz, 1H), 4.05 (pent, $J=3.6$ Hz, 1H), 5.25 (d, $J=3.0$ Hz, 1H), 5.72 (d, $J=3.0$ Hz, 1H); ^{13}C NMR δ -8.8, 16.6, 19.1, 31.7, 44.3, 52.2, 52.4, 56.4, 60.7, 128.4, 151.7, 163.5, 163.7; IR (neat) 1220, 1692 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -12.0$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{29}\text{N}_2\text{O}_2\text{Sn}$ ($\text{M}+\text{H}^+$) 389.1251, found 389.1246.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (239). To a solution of **238** (400 mg, 1.03 mmol) in DMF (10 mL) was added 2-nitro-1-iodobenzene (**236**) (214 mg, 0.861 mmol), Pd(dba)₂ (25 mg, 0.043 mmol) and PPh₃ (45 mg, 0.17 mmol). CuI (123 mg, 0.646 mmol) was added in one portion and the reaction mixture was stirred at ambient temperature for 26 h. The mixture was diluted with Et₂O (50 mL), washed with 10% aqueous NH₄OH (3 x 50 mL), H₂O (50 mL), and brine (50 mL). The organic phase was dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 97:3) to afford **239** (2R,5S/2S,5S=15:1, 173 mg, 0.500 mmol, 58%) as a yellow oil. ¹H NMR δ 0.61 (d, *J*=6.6 Hz, 3H), 0.97 (d, *J*=6.6 Hz, 3H), 2.15 (dsept, *J*=6.6, 3.6 Hz, 1H), 2.84 (dd, *J*=13.8, 6.0 Hz, 1H), 2.92 (dd, *J*=13.8, 6.0 Hz, 1H), 3.39 (s, 3H), 3.50 (s, 3H), 3.77 (t, *J*=3.6 Hz, 1H) Hz, 4.06 (q, *J*=6.0 Hz, 1H), 5.11 (s, 1H), 5.26 (s, 1H), 7.22 (d, *J*=7.2 Hz, 1H), 7.36 (t, *J*=7.8 Hz, 1H), 7.48 (t, *J*=7.2 Hz, 1H), 7.90 (d, *J*=8.4 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.4, 51.9, 52.1, 55.1, 60.9, 118.6, 124.0, 127.8, 131.9, 132.6, 138.7, 144.2, 147.9, 162.5, 163.2; IR (neat) 1233, 1242, 1350, 1515, 1693 cm⁻¹; [α]_D²⁵ = -21.8 (*c*=1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₄N₃O₄ (M+H⁺) 346.1767, found 346.1761.

Alternative method. (2S,5R)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (209). To a solution of (2S,5R)-2-(2-bromo-2-propen-1-yl)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazine **201** (310 mg, 1.02 mmol) in N-methylpyrrolidone (3 mL) was added tributyl(2-nitrophenyl)stannane **208** (506 mg, 1.23 mmol), PdCl₂(PhCN)₂ (20 mg, 0.051 mmol) and AsPh₃ (31 mg, 0.10 mmol). CuI (19 mg, 0.10 mmol) was added and the reaction mixture was stirred at 80 °C for 3 days. The mixture was diluted with EtOAc (20 mL), washed with 10% aqueous NH₄OH (3 x 20 mL), H₂O (20 mL), and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 95:5) to afford **209** (2S,5R/2R,5R=10:1, 162 mg, 0.469 mmol, 46%) as a yellow oil. ¹H NMR (partial data minor isomer) δ 0.72 (d, *J*=6.9 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 3.10 (dd, *J*=14.4, 4.9 Hz, 2H), 3.50 (s, 3H), 3.62 (s, 3H), 5.10 (s, 1H), 5.30 (s, 1H).

(2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine (241). Reaction of 1-iodo-4-methoxy-2-nitrobenzene (**240**) (240 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence

of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (51 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **241** (221 mg, 0.589 mmol, 68%) as a yellow oil. ¹H NMR δ 0.62 (d, *J*=7.2 Hz, 3H), 0.97 (d, *J*=7.2 Hz, 3H), 2.16 (dsept, *J*=7.2, 3.6 Hz, 1H), 2.80 (dd, *J*=13.8, 6.0 Hz, 1H), 2.89 (dd, *J*=13.8, 6.0 Hz, 1H), 3.45 (s, 3H), 3.52 (s, 3H), 3.78 (t, *J*=3.6 Hz, 1H), 3.85 (s, 3H), 4.04 (dt, *J*=4.2, 2.4 Hz, 1H), 5.06 (d, *J*=1.2 Hz, 1H), 5.21 (s, 1H), 7.03 (dd, *J*=8.4, 2.4 Hz, 1H), 7.13 (d, *J*=8.4 Hz, 1H), 7.42 (d, *J*=3.0 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.5, 52.0, 52.1, 55.0, 55.8, 60.8, 108.7, 118.1, 119.1, 131.0, 132.8, 143.9, 148.2, 158.9, 162.6, 163.1; IR (neat) 1220, 1528, 1692 cm⁻¹; [α]_D²⁵ = -20.2 (*c*=1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(5-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (243). Reaction of 3-iodo-4-nitro-1-methoxybenzene (**242**) (240 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (43 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **243** (224 mg, 0.597 mmol, 69%) as a yellow oil. ¹H NMR δ 0.63 (d, *J*=6.6 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H), 2.18 (dsept, *J*=6.6, 3.0 Hz, 1H), 2.86 (dd, *J*=14.4, 6.0 Hz, 1H), 2.94 (dd, *J*=14.4, 6.0 Hz, 1H), 3.45 (s, 3H), 3.52 (s, 3H), 3.79 (t,

$J=3.6$ Hz, 1H), 3.86 (s, 3H), 4.06 (dt, $J=4.2$, 1.8 Hz, 1H), 5.09 (d, $J=1.8$ Hz, 1H), 5.23 (d, $J=1.8$ Hz, 1H), 6.65 (d, $J=3.0$ Hz, 1H), 6.84 (dd, $J=9.6$, 3.0 Hz, 1H), 8.02 (d, $J=9.6$ Hz, 1H); ^{13}C NMR δ 16.5, 18.8, 31.7, 40.3, 51.9, 52.0, 55.0, 55.7, 60.8, 112.9, 116.7, 117.5, 126.8, 140.6, 141.6, 145.2, 162.5, 162.7, 163.0; IR (neat) 1230, 1336, 1513, 1693 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -17.5$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_5$ ($\text{M}+\text{H}^+$) 376.1873, found 376.1867.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2-nitrophenyl)-2-propen-1-yl)-5-

(1-methylethyl)pyrazine (245). Reaction of 4-fluoro-1-iodo-2-nitrobenzene (**244**) (230 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (30 mg, 0.043 mmol), PPh_3 (23 mg, 0.86 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (72 h), gave after extraction and chromatography (hexanes: EtOAc, 95:5) **245** (191 mg, 0.526 mmol, 61%) as a yellow oil. ^1H NMR δ 0.62 (d, $J=6.6$ Hz, 3H), 0.98 (d, $J=6.6$ Hz, 3H), 2.17 (dsept, $J=6.6$, 3.0 Hz, 1H), 2.81 (dd, $J=14.4$, 6.0 Hz, 1H), 2.91 (dd, $J=14.4$, 6.0 Hz, 1H), 3.44 (s, 3H), 3.52 (s, 3H), 3.79 (t, $J=4.2$ Hz, 1H), 4.04 (dt, $J=4.2$, 2.4 Hz, 1H), 5.09 (d, $J=1.8$ Hz, 1H), 5.27 (d, $J=1.8$ Hz, 1H), 7.21 (d, $J=2.4$ Hz, 1H), 7.23 (d, $J=1.8$ Hz, 1H), 7.64 (ddd, $J=8.4$, 1.8, 0.6 Hz, 1H); ^{13}C NMR δ 16.6, 18.9, 31.9, 40.4, 52.0, 52.1, 55.0, 60.9, 111.6 (d, $J=26.3$ Hz), 119.0, 119.8 (d, $J=20.7$ Hz), 133.5 (d, $J=7.1$ Hz), 134.8 (d, $J=3.9$ Hz), 143.3, 148.0 (d, $J=7.8$ Hz), 161.0 (d, $J=249.3$ Hz), 162.5, 163.3; IR (neat) 808, 1219, 1234, 1245, 1347, 1550, 1692 cm^{-1} ;

$[\alpha]_D^{25} = -26.5$ ($c=1.4$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_3\text{O}_4$ ($\text{M}+\text{H}^+$) 364.1673, found 364.1667.

Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate (247). Reaction of methyl 4-iodo-3-nitrobenzoate (**246**) (263 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (25 mg, 0.043 mmol), PPh_3 (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (72 h), gave after extraction and chromatography (hexanes/EtOAc, 97:3) **247** (215 mg, 0.533 mmol, 62%) as a yellow oil. ^1H NMR δ 0.62 (d, $J=6.6$ Hz, 3H), 0.97 (d, $J=6.6$ Hz, 3H), 2.16 (dsept, $J=6.6$, 3.0 Hz, 1H), 2.85 (dd, $J=13.8$, 6.0 Hz, 1H), 2.95 (dd, $J=13.8$, 6.0 Hz, 1H), 3.38 (s, 3H), 3.51 (s, 3H), 3.79 (t, $J=3.6$ Hz, 1H), 3.96 (s, 3H), 4.06 (dt, $J=4.2$, 2.4 Hz, 1H), 5.17 (s, 1H), 5.34 (s, 1H), 7.33 (d, $J=7.8$ Hz, 1H), 8.13 (d, $J=7.8$ Hz, 1H), 8.54 (s, 1H); ^{13}C NMR δ 16.6, 18.9, 31.9, 40.2, 52.0, 52.1, 52.6, 55.0, 60.9, 119.6, 125.2, 130.0, 132.2, 133.0, 142.9, 143.5, 147.9, 162.4, 163.4, 164.9; IR (neat) 1113, 1240, 1283, 1532, 1692, 1729 cm^{-1} ; $[\alpha]_D^{25} = -8.1$ ($c=1.0$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_6$ ($\text{M}+\text{H}^+$) 404.1822, found 404.1816.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (249). Reaction of 1-bromo-2,4-dinitrobenzene (**248**) (213 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (72 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **249** (276 mg, 0.707 mmol, 82%) as a yellow oil. ¹H NMR δ 0.62 (d, *J*=7.2 Hz, 3H), 0.98 (d, *J*=7.2 Hz, 3H), 2.16 (dsept, *J*=6.6, 3.0 Hz, 1H), 2.84 (dd, *J*=14.4, 6.0 Hz, 1H), 2.98 (dd, *J*=14.4, 6.0 Hz, 1H), 3.39 (s, 3H), 3.54 (s, 3H), 3.80 (t, *J*=4.2 Hz, 1H), 4.05 (dt, *J*=4.2, 2.4 Hz, 1H), 5.21 (s, 1H), 5.41 (s, 1H), 7.48 (d, *J*=8.4 Hz, 1H), 8.34 (dd, *J*=8.4 Hz, 2.4, 1H), 8.75 (d, *J*=2.4 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 32.0, 40.3, 52.1, 52.2, 55.0, 61.0, 119.6, 120.6, 126.5, 133.2, 142.7, 144.9, 146.7, 147.8, 162.3, 163.7; IR (neat) 1237, 1350, 1529, 1691 cm⁻¹; [α]_D²⁵ = −4.3 (*c*=1.1, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₃N₄O₆ (M+H⁺) 391.1618, found 391.1612.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (251). Reaction of 2-chloro-3-nitropyridine (**250**) (136 mg, 0.861 mmol) with **238** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol),

PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for **239** (24 h), gave after extraction and chromatography (EtOAc) **251** (180 mg, 0.520 mmol, 60%) as an orange oil. ¹H NMR δ 0.63(d, *J*=7.2 Hz, 3H), 0.99 (d, *J*=7.2 Hz, 3H), 2.16 (dsept, *J*=6.6, 3.0 Hz, 1H), 2.97 (dd, *J*=13.8, 6.0 Hz, 1H), 3.17 (dd, *J*=13.8, 6.0 Hz, 1H), 3.23 (s, 3H), 3.58 (s, 3H), 3.92 (t, *J*=3.6 Hz, 1H), 4.19 (dt, *J*=4.2, 2.4 Hz, 1H), 5.37 (s, 1H), 5.45 (s, 1H), 7.32 (dd, *J*=8.4, 4.8 Hz, 1H), 8.06 (d, *J*=8.4 Hz, 1H), 8.73 (dd, *J*=4.8, 1.2 Hz, 1H); ¹³C NMR δ 16.7, 18.9, 31.8, 39.3, 51.6, 52.1, 55.5, 60.9, 121.3, 121.9, 131.7, 142.7, 145.3, 151.6, 155.0, 162.2, 163.7; IR (neat) 732, 785, 1225, 1354, 1527, 1683 cm⁻¹; [α]_D²⁵ = + 4.84 (*c*=1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₇H₂₃N₄O₄ (M+H⁺) 347.1719, found 347.1714.

Bis-2,3-((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene (254). To a solution of **238** (370 mg, 0.956 mmol) in DMF (10 mL) was added 1-iodo-3-methoxy-2-nitrobenzene (**260**) (133 mg, 0.478 mmol), Pd(dba)₂ (14 mg, 0.024 mmol), PPh₃ (25 mg, 0.096 mmol) and CuI (68 mg, 0.36 mmol). The reaction was stirred at ambient temperature for 48 h. Et₂O (30 mL) was added and the organic phase was washed with NH₄OH (10%, aq., 3 x 30 mL), H₂O (30 mL), and brine (30 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 95:5) to afford **254** (47 mg, 0.10 mmol, 22%) as a yellow oil. ¹H NMR δ 0.65 (d, *J*=6.6 Hz, 6H),

1.02 (d, $J=6.6$ Hz, 6H), 2.23 (dsept, $J=7.2$, 3.6 Hz, 2H), 2.46 (dd, $J=13.8$, 7.2 Hz, 2H), 2.93 (dd, $J=13.8$, 4.2 Hz, 2H), 3.62 (s, 6H), 3.66 (s, 6H), 3.83 (t, $J=3.6$ Hz, 2H), 4.15 (pent, $J=3.6$ Hz, 2H), 4.85 (s, 2H), 5.13 (d, $J=1.8$ Hz, 2H); ^{13}C NMR δ 16.5, 19.1, 31.4, 39.0, 52.0, 52.2, 55.3, 60.6, 115.1, 145.1, 163.0, 163.2; IR (neat) 1011, 1194, 1232, 1693 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -50.8$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{39}\text{N}_4\text{O}_4$ ($\text{M}+\text{H}^+$) 447.2971, found 447.2966.

(3-Methoxy-2-nitrophenyl)trimethylstannane (261). To a solution of 1-iodo-3-methoxy-2-nitrobenzene (**260**) (1.57 g, 5.63 mmol) in toluene (25 mL) was added hexamethylditin (2.03 g, 6.19 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (39 mg, 0.056 mmol), and PPh_3 (30 mg, 0.11 mmol). The reaction mixture was heated at 80 $^\circ\text{C}$ and stirred for 4 days. It was then diluted with EtOAc (50 mL) and washed with 10% aqueous NH_4OH (3 x 50 mL), H_2O (50 mL), and brine (50 mL). The organic phase was dried (MgSO_4), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes) to afford **261** (1.02 g, 3.23 mmol, 57%) as a yellow oil. ^1H NMR δ 0.33 (s, 9H), 3.92 (s, 3H), 7.03 (dd, $J=8.4$, 1.2 Hz, 1H), 7.11 (dd, $J=7.2$, 1.2 Hz, 1H), 7.43-7.47 (m, 1H); ^{13}C NMR δ -8.3, 56.3, 113.4, 127.8, 132.4, 139.9, 146.2, 152.4; IR (neat) 775, 1269, 1519 cm^{-1} .

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (256). Reaction of (6-methoxy-2-

nitrophenyl)trimethylstannane **255** (470 mg, 1.49 mmol) with **198** (225 mg, 0.744 mmol) in the presence of Pd(dba)₂ (21 mg, 0.037 mmol), PPh₃ (39 mg, 0.15 mmol), and CuI (106 mg, 0.558 mmol) in DMF (10 mL), as described for **239** (36 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **256** (151 mg, 0.402 mmol, 54%) as a yellow oil. ¹H NMR δ 0.68 (d, *J*=6.6 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 2.17 (dsept, *J*=6.6, 3.0 Hz, 1H), 2.81 (br s, 1H), 2.97 (d, *J*=12.0 Hz, 1H), 3.38 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 3.90 (t, *J*=3.6 Hz, 1H), 4.17 (t, *J*=3.6 Hz, 1H), 5.05 (s, 1H), 5.43 (d, *J*=1.2, 1H), 7.02 (dd, *J*=7.8, 0.6 Hz, 1H), 7.28 (t, *J*=7.8 Hz, 1H), 7.33 (dd, *J*=7.8, 0.6 Hz, 1H); ¹³C NMR δ 16.9, 18.9, 32.1, 40.6, 52.1, 52.2, 55.0, 56.2, 61.0, 114.0, 115.5, 119.2, 127.2, 127.9, 138.2, 150.1, 157.4, 163.1, 163.2; IR (neat) 799, 1055, 1230, 1527, 1693 cm⁻¹; [α]_D²⁵ = -27.2 (*c*=1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (262). Reaction of **261** (142 mg, 0.449 mmol) with **198** (113 mg, 0.374 mmol) in the presence of Pd(dba)₂ (11 mg, 0.019 mmol), PPh₃ (20 mg, 0.075 mmol), and CuI (53 mg, 0.28 mmol) in DMF (10 mL), as described for **239** (72 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **262** (99 mg, 0.26 mmol, 70%) as a yellow oil. ¹H NMR δ 0.65 (d, *J*=7.2 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 2.19 (dsept, *J*=7.2, 3.6 Hz, 1H), 2.71 (dd, *J*=14.4, 7.2 Hz, 1H), 2.94 (dd, *J*=13.2, 3.6 Hz, 1H), 3.46 (s, 3H), 3.58 (s, 3H), 3.87 (s, 3H), 3.92 (t, *J*=3.6 Hz, 1H), 4.08 (dt, *J*=4.2, 3.6 Hz, 1H), 5.17 (d, *J*=1.2 Hz, 1H), 5.24 (d, *J*=0.6 Hz, 1H), 6.90 (t, *J*=7.8 Hz, 2H), 7.32 (t, *J*=7.8 Hz, 1H); ¹³C NMR δ 16.7, 18.9, 31.9, 40.7, 52.0, 52.1, 54.8, 56.4, 60.9, 110.9, 119.9, 121.5, 130.2, 136.8, 140.3, 141.0, 150.6, 162.7, 163.3; IR (neat) 1055, 1250, 1532, 1693 cm⁻¹; [α]_D²⁵ = 3.72 (*c*=1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

(2R,5S)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (275). BuLi (1.91 mL, 4.77 mmol, 2.5 M in hexane) was added to a -78 °C cold solution of (*S*)-2,5-dihydro-3,6-dimethoxy-2-methylethylpyrazine (**172**)

(800 mg, 4.34 mmol) and *N,N'*-dimethylethylene urea (0.99 g, 8.7 mmol) in dry THF (40 mL) under a nitrogen atmosphere. After 1 h, a solution of 2-bromo-4-iodo-1-butene (**274**) (1.36 g, 5.21 mmol) in dry THF (10 mL) was added over 30 min. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with a 0.1 M phosphate buffer (30 mL) and extracted with Et₂O (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexane/EtOAc 9:1) to afford **275** (419 mg, 1.32 mmol, 31%) as a pale yellow oil. ¹H NMR δ 0.70 (d, *J*=7.2 Hz, 3H), 1.04 (d, *J*=6.6 Hz, 3H), 1.86-1.92 (m, 1H), 2.19-2.17 (m, 1H), 2.25 (dsept, *J*=7.2, 3.6 Hz, 1H), 2.42-2.52 (m, 2H), 3.69 (s, 3H), 3.71 (s, 3H), 3.94 (t, *J*=3.0 Hz, 1H), 4.02 (dt, *J*=7.2, 4.2 Hz, 1H), 5.39 (d, *J*=1.8 Hz, 1H), 5.57 (d, *J*=1.8 Hz, 1H); ¹³C NMR δ 16.7, 19.0, 31.9, 32.6, 37.1, 52.4, 52.5, 54.3, 60.9, 116.5, 134.3, 163.4, 163.8; IR (neat) 1194, 1234, 1690 cm⁻¹; [α]_D²⁵ = -2.3 (*c*=1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₃H₂₂BrN₂O₂ (M+H⁺) 317.0865, found 317.0859.

(2R,5S)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-

methylethylpyrazine (279). BuLi (2.71 mL, 5.97 mmol, 2.2 M in cyclohexane) was added dropwise to a -78 °C cold solution of (*S*)-2,5-dihydro-3,6-dimethoxy-2-methylethylpyrazine (**172**) (1.00 g, 5.43 mmol) in dry THF (15 mL) under a nitrogen atmosphere. After stirring for 30 min, a solution of 1,3-dibromo-1-propene (**278**) (1.41 g,

7.06 mmol, 1:1 *E/Z*-mixture) in THF (5 mL) was slowly added. After stirring for 90 min, the reaction was quenched with water (30 mL) and the mixture was extracted with Et₂O (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexane/EtOAc 95:5) to afford **279** (1.25 g, 4.12 mmol, 76%) as a yellow oil. Spectral data from a 1:1 mixture of *Z:E*-**279**: ¹H NMR δ 0.68 (d, *J*=6.6 Hz, 3H), 0.69 (d, *J*=6.6 Hz, 3H), 1.04 (d, *J*=7.2 Hz, 6H), 2.25 (dsept, *J*=6.6, 3.0 Hz, 2H), 2.46-2.50 (m, 1H), 2.53-2.57 (m, 1H), 2.62 (dpent, *J*=6.6, 1.2 Hz, 1H), 2.75-2.79 (m, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 3.71 (s, 3H), 3.93-3.95 (m, 2H), 4.04-4.07 (m, 1H), 4.12-4.14 (m, 1H), 6.05-6.09 (m, 3H), 6.22-6.24 (m, 1H); ¹³C NMR δ 16.6, 19.0, 31.8, 34.8, 37.4, 52.4, 52.5, 54.5, 54.8, 60.9, 106.7, 109.7, 130.7, 133.4, 162.5, 163.0, 164.1, 164.3 (6 peaks overlap); IR (neat) 1010, 1235, 1691 cm⁻¹; [α]_D²⁵ = -14.4 (*c*=1.4, CH₂Cl₂); HRMS (ESI) calcd for C₁₂H₂₀BrN₂O₂ (M+H⁺) 303.0708, found 303.0703.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine (276). Reaction of tributyl(2-nitrophenyl)stannane **208** (721 mg, 1.75 mmol) with **275** (370 mg, 1.17 mmol) in the presence of Pd(dba)₂ (34 mg, 0.058 mmol), PPh₃ (61 mg, 0.23 mmol), and CuI (167 mg, 0.877 mmol) in DMF (10 mL), as described for **239** (18 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **276** (308 mg, 0.857 mmol, 73%) as a yellow oil. ¹H NMR δ 0.68 (d, *J*=6.6 Hz, 3H), 1.03 (d, *J*=7.2 Hz, 3H), 1.78-1.84 (m, 1H), 1.96-2.02 (m, 1H), 2.24 (dsept, *J*=6.6,

3.6 Hz, 1H), 2.30-2.39 (m, 2H), 3.65 (s, 3H), 3.67 (s, 3H), 3.92 (t, $J=3.6$ Hz, 1H), 4.02 (dt, $J=4.2$, 3.6 Hz, 1H), 4.99 (s, 1H), 5.19 (d, $J=1.2$ Hz, 1H), 7.30 (d, $J=7.8$ Hz, 1H), 7.40 (t, $J=8.4$ Hz, 1H), 7.53 (t, $J=7.2$ Hz, 1H), 7.85 (d, $J=7.8$ Hz, 1H); ^{13}C NMR δ 16.6, 19.0, 31.8, 31.9, 32.6, 52.3, 52.4, 54.8, 60.8, 114.4, 124.0, 127.9, 131.0, 132.4, 138.5, 146.9, 148.4, 163.5, 163.7; IR (neat) 1194, 1235, 1525, 1690 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = 4.80$ ($c=1.0$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}^+$) 360.1923, found 360.1918.

(2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl)-5-(1-

methylethyl)pyrazine (*E/Z*) (280). Reaction of **208** (1.02 g, 2.47 mmol) with **279** (500 mg, 1.65 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (47 mg, 0.083 mmol), PPh_3 (86 mg, 0.33 mmol), and CuI (236 mg, 1.24 mmol) in DMF (10 mL), as described for **239** (48 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1) **280** (444 mg, 1.29 mmol, 78%) as a yellow oil. Spectral data from the *E/Z*-mixture: ^1H NMR (*Z*-isomer) δ 0.68 (d, $J=7.2$ Hz, 3H), 1.03 (d, $J=7.2$ Hz, 3H), 2.25 (dsept, $J=7.2$, 3.6 Hz, 1H), 2.56 (dddd, $J=15.0$, 7.2, 6.0, 1.8 Hz, 1H), 2.66-2.79 (m, 1H, overlapped by 2H of *E*-isomer), 3.63 (s, 3H), 3.65 (s, 3H), 3.97 (t, $J=3.6$ Hz, 1H), 4.08 (dt, $J=4.2$, 1.8 Hz, 1H), 5.74 (dt, $J=7.8$, 4.2 Hz, 1H), 6.80 (d, $J=12.0$ Hz, 1H), 7.40 (dt, $J=8.4$, 1.8, 1H), 7.49-7.52 (m, 1H, overlapped by 2H of *E*-isomer), 7.56 (dt, $J=7.8$, 1.2 Hz, 1H), 8.01 (dd, $J=6.6$, 1.2 Hz, 1H). ^1H NMR (*E*-isomer) δ 0.69 (d, $J=7.2$ Hz, 3H), 1.03 (d, $J=6.6$ Hz, 3H), 2.25 (dsept, $J=7.2$, 3.6 Hz, 1H), 2.66-2.79 (m, 2H, overlapped by 1H of *Z*-isomer), 3.71 (s, 3H), 3.73 (s, 3H), 3.91 (t,

$J=3.6$ Hz, 1H), 4.18 (dt, $J=3.6$, 1.8 Hz, 1H), 6.08 (dt, $J=7.8$, 7.2 Hz, 1H), 6.89 (d, $J=15.6$ Hz, 1H), 7.33 (ddd, $J=8.4$, 6.0, 3.0 Hz, 1H), 7.49-7.52 (m, 2H, overlapped by 1H of 1H of Z-isomer), 7.86 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (both isomers) δ 16.5, 16.6, 19.0, 31.8, 32.8, 37.9, 52.3, 52.4, 52.4, 52.5, 55.0, 55.3, 60.8, 60.9, 124.3, 124.4, 127.6, 127.6, 127.7, 128.1, 128.6, 129.6, 131.6, 132.0, 132.6, 132.8, 132.8, 133.1, 147.7, 148.1, 162.8, 162.9, 164.0, 164.2; IR (neat) 738, 1236, 1522, 1691 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -7.68$ ($c=1.0$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}^+$) 346.1767, found 346.1761.

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1H-indole (263).

239 (140 mg, 0.405 mmol), $\text{Pd}(\text{dba})_2$ (14 mg, 0.024 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (10 mg, 0.024 mmol), and 1,10-phenanthroline (phen) (10 mg, 0.048 mmol) were dissolved in anhydrous DMF (3 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120 $^{\circ}\text{C}$ (oil bath temperature) under CO (6 atm) for 18 hours. Water (10 mL) was added and the orange solution was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried (MgSO_4), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes/EtOAc, 8:2 then 1:1) to afford **263** (2R,5S/2S,5S=15:1, 108 mg, 0.345 mmol,

85%) as a yellow solid. mp 99-102 °C; ^1H NMR δ 0.62 (d, $J=7.2$ Hz, 3H), 0.93 (d, $J=7.2$ Hz, 3H), 2.14 (dsept, $J=7.2$, 3.6 Hz, 1H), 3.29 (t, $J=3.6$ 2H), 3.37 (t, $J=3.6$ Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 4.36 (q, $J=3.6$ Hz, 1H), 6.89 (d, $J=1.8$ Hz, 1H), 7.07 (t, $J=7.2$ Hz, 1H), 7.13 (t, $J=7.2$ Hz, 1H), 7.26 (d, $J=7.2$, 1H), 7.64 (d, $J=7.2$ Hz, 1H), 8.03 (br s, 1H); ^{13}C NMR δ 16.5, 19.0, 29.5, 31.3, 52.1, 52.2, 56.7, 60.4, 110.7, 111.6, 118.9, 119.4, 121.6, 122.7, 128.4, 135.8, 163.0, 163.7; IR (neat) 725, 1010, 1222, 1236, 1660, 1697 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -54.8$ ($c=1.3$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}^+$) 314.1869, found 314.1863. Partial data for the minor isomer: ^1H NMR δ 0.12 (d, $J=6.7$ Hz, 3H), 0.84 (d, $J=6.7$ Hz, 3H), 3.71 (s, 3H).

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1H-indole (264). Reaction of **241** (112 mg, 0.298 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (10 mg, 0.018 mmol), dppp (7.0 mg, 0.018 mmol), phen (7.0 mg, 0.036 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (26 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **264** (2R,5S/2S,5S=12:1, 71 mg, 0.21 mmol, 70%) as a yellow solid. mp 111-114 °C; ^1H NMR δ 0.61 (d, $J=6.6$ Hz, 3H), 0.92 (d, $J=7.2$ Hz, 3H), 2.13 (dsept, $J=6.6$, 3.0 Hz, 1H), 3.24 (d, $J=4.8$ Hz, 2H), 3.36 (t, $J=3.0$ Hz, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 4.33 (q, $J=4.2$ Hz, 1H), 6.74 (dd, $J=8.4$, 1.8 Hz, 1H), 6.76 (d, $J=1.8$ Hz, 1H), 6.78 (d, $J=1.8$ Hz, 1H), 7.49 (d, $J=9.0$ Hz, 1H), 7.88 (br s, 1H); ^{13}C

NMR δ 16.5, 19.0, 29.6, 31.3, 52.1, 52.2, 55.6, 56.8, 60.4, 94.2, 109.0, 111.6, 120.0, 121.4, 122.9, 136.4, 156.2, 163.0, 163.7; IR (neat) 780, 1027, 1157, 1224, 1693 cm^{-1} ; $[\alpha]^{25}_{\text{D}} = -44.6$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}^+$) 344.1974, found 344.1969. Partial data of minor isomer: ^1H NMR δ 0.15 (d, $J=7.2$ Hz, 3H), 0.85 (d, $J=7.2$ Hz, 3H), 3.65 (s, 3H), 3.70 (s, 3H); ^{13}C NMR δ 30.0, 30.9, 52.0, 52.1, 57.2, 60.7, 108.9, 120.2, 121.6, 122.9.

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1H-indole (265). Reaction of **243** (145 mg, 0.386 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (13 mg, 0.023 mmol), dppp (10 mg, 0.023 mmol), phen (9.0 mg, 0.046 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (22 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **265** (2R,5S/2S,5S=22:1, 112 mg, 0.326 mmol, 85%) as a yellow oil. ^1H NMR δ 0.63 (d, $J=6.6$ Hz, 3H), 0.94 (d, $J=6.6$ Hz, 3H), 2.15 (dsept, $J=6.6$, 3.6 Hz, 1H), 3.26 (d, $J=4.8$ Hz, 2H), 3.40 (t, $J=3.6$ Hz, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 3.86 (s, 3H), 4.36 (q, $J=4.2$ Hz, 1H), 6.80 (dd, $J=8.4$, 1.8 Hz, 1H), 6.88 (d, $J=2.4$ Hz, 1H), 7.10 (d, $J=2.4$ Hz, 1H), 7.15 (d, $J=9.0$ Hz, 1H), 7.95 (br s, 1H); ^{13}C NMR δ 16.4, 19.0, 29.5, 31.2, 52.2, 52.3, 55.9, 56.7, 60.4, 101.3, 111.3, 111.4, 111.9, 123.6, 128.8, 131.0, 153.7, 163.0, 163.8; IR (neat) 794, 1012, 1232, 1435, 1692 cm^{-1} ; $[\alpha]^{25}_{\text{D}} = -49.5$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}^+$) 344.1974, found 344.1969. Partial

data for the minor isomer: ^1H NMR δ 0.15 (d, $J=6.9$ Hz, 3H), 0.85 (d, $J=6.7$ Hz, 3H), 3.72 (s, 3H).

6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-indole (266). Reaction of **245** (118 mg, 0.325 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (11 mg, 0.019 mmol), dppp (8.0 mg, 0.019 mmol), phen (8.0 mg, 0.039 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (21 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **266** (2R,5S/2S,5S=4.5:1, 90 mg, 0.27 mmol, 84%) as a yellow oil. Spectral data of 2R,5S-**266** from the mixture: ^1H NMR δ 0.62 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H), 2.13 (dsept, $J=6.6, 3.6$ Hz, 1H), 3.25 (d, $J=4.2$ Hz, 2H), 3.37 (t, $J=3.6$ Hz, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.34 (q, $J=4.2$ Hz, 1H), 6.83 (dt, $J=9.6, 1.8$ Hz, 1H), 6.86 (d, $J=1.8$ Hz, 1H), 6.93 (dd, $J=9.0, 1.8$ Hz, 1H), 7.53 (dd, $J=8.4, 5.4$ Hz, 1H), 8.03 (br s, 1H); ^{13}C NMR δ 16.5, 19.0, 29.5, 31.3, 52.1, 52.2, 56.7, 60.4, 97.0 (d, $J=25.6$ Hz), 107.7 (d, $J=24.6$ Hz), 111.8, 120.1 (d, $J=6.3$ Hz), 122.9 (d, $J=3.9$ Hz), 125.0, 135.6 (d, $J=12.0$ Hz), 159.8 (d, $J=235.6$ Hz), 162.9, 163.8; IR (neat) 799, 1012, 1140, 1194, 1220, 1692 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -41.8$ ($c=0.9$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_3\text{O}_2$ ($\text{M}+\text{H}^+$) 332.1774, found 332.1769. Partial data for the minor 2S,5S-**266** isomer: ^1H NMR δ 0.10 (d, $J=6.6$ Hz, 3H), 0.84 (d, $J=6.6$ Hz, 3H), 1.82 (dsept, $J=7.2, 3.6$ Hz, 1H), 3.64 (s, 3H), 3.70 (s, 3H); ^{13}C NMR δ 16.2, 19.4, 29.8, 31.1, 52.0, 52.2, 57.0,

60.7, 96.9 (d, $J=25.6$ Hz), 107.7 (d, $J=24.6$ Hz), 112.6, 120.3 (d, $J=6.3$ Hz), 123.1 (d, $J=4.0$ Hz), 125.1, 135.7 (d, $J=12.0$ Hz), 159.9 (d, $J=235.6$ Hz), 162.4, 163.2.

Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-indole-6-carboxylate (267**).** Reaction of **247** (87 mg, 0.22 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (7.0 mg, 0.013 mmol), dppp (5.0 mg, 0.013 mmol), phen (5.0 mg, 0.026 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (23 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **267** (2R,5S/2S/5S=10:1, 60 mg, 0.16 mmol, 73%) as a tan solid. mp 119–121 °C; ^1H NMR δ 0.61 (d, $J=6.6$ Hz, 3H), 0.91 (d, $J=7.2$ Hz, 3H), 2.12 (dsept, $J=7.2, 3.0$ Hz, 1H), 3.29 (d, $J=4.2$ Hz, 2H), 3.34 (t, $J=3.6$ Hz, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 3.92 (s, 3H), 4.35 (q, $J=4.8$ Hz, 1H), 7.08 (d, $J=2.4$ Hz, 1H), 7.66 (d, $J=8.4$ Hz, 1H), 7.76 (dd, $J=8.4, 1.2$ Hz, 1H), 8.05 (s, 1H), 8.57 (br s, 1H); ^{13}C NMR δ 16.4, 18.9, 29.4, 31.4, 51.8, 52.2, 52.3, 56.6, 60.4, 112.1, 113.3, 119.0, 120.0, 123.3, 126.3, 132.0, 135.1, 162.8, 163.8, 168.3; IR (neat) 769, 1086, 1196, 1237, 1276, 1697, 1710 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -43.1$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}^+$) 372.1923, found 372.1918.

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-nitro-1H-indole (268). Reaction of **249** (165 mg, 0.423 mmol) in the presence of Pd(dba)₂ (15 mg, 0.025 mmol), dppp (11 mg, 0.025 mmol), phen (10 mg, 0.051 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (18 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **268** (18 mg, 0.050 mmol, 12%) as a yellow oil. ¹H NMR δ 0.62 (d, *J*=7.2 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H), 2.13 (dsept, *J*=6.6, 3.6 Hz, 1H), 3.30 (d, *J*=4.8 Hz, 2H), 3.39 (t, *J*=3.6 Hz, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.35 (q, *J*=4.2 Hz, 1H), 7.23 (d, *J*=1.8 Hz, 1H), 7.70 (d, *J*=9.0 Hz, 1H), 7.98 (dd, *J*=8.4, 1.8 Hz, 1H), 8.28 (d, *J*=1.8 Hz, 1H), 8.50 (br s, 1H); ¹³C NMR δ 16.5, 18.9, 29.2, 31.5, 52.2, 52.3, 56.4, 60.6, 107.9, 113.2, 114.7, 119.5, 128.7, 133.1, 134.1, 143.2, 162.6, 164.0; IR (neat) 735, 1011, 1220, 1309, 1504, 1692 cm⁻¹; [α]_D²⁵ = -36.6 (*c*=1.3, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₃N₄O₄ (M+H⁺) 359.1719, found 359.1714. Partial data for minor isomer: ¹H NMR δ 0.02 (d, *J*=6.6 Hz, 3H), 0.81 (d, *J*=7.2 Hz, 3H), 3.66 (s, 3H), 3.70 (s, 3H), 3.93 (s, 3H), 7.14 (d, *J*=1.8 Hz, 1H), 8.03 (s, 1H), 8.50 (br s, 1H).

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine (269). Reaction of **251** (140 mg, 0.404 mmol) in the presence of Pd(dba)₂ (14 mg, 0.024 mmol), dppp (10 mg, 0.024 mmol), phen (10 mg, 0.049 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (18 h), gave after chromatography (hexanes/EtOAc, 8:2 then EtOAc) **269** (2R,5S/2S,5S=11:1, 100 mg, 0.318 mmol, 79%) as a tan solid. mp 148-151 °C; ¹H NMR δ 0.64 (d, *J*=7.2 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 2.18 (dsept, *J*=6.6, 3.0 Hz, 1H), 3.27 (dd, *J*=14.4, 6.6 Hz, 1H), 3.53 (m, 2H), 3.63 (s, 3H), 3.66 (s, 3H), 4.40 (dt, *J*=3.6, 3.0 Hz, 1H), 7.05 (dd, *J*=8.4, 4.8 Hz, 1H), 7.28 (d, *J*=1.8 Hz, 1H), 7.60 (dd, *J*=8.4, 1.2 Hz, 1H), 8.46 (dd, *J*=4.2, 1.2 Hz, 1H), 8.84 (br s, 1H); ¹³C NMR δ 16.6, 19.0, 28.4, 31.5, 52.2, 52.3, 56.4, 60.6, 112.7, 116.5, 118.0, 126.4, 128.6, 142.6, 145.9, 163.5, 163.6; IR (neat) 765, 1012, 1220, 1695 cm⁻¹; [α]_D²⁵ = -23.2 (*c*=1.1, CH₂Cl₂); HRMS (ESI) calcd for C₁₇H₂₃N₄O₂ (M+H⁺) 315.1821, found 315.1816. Partial data for the minor isomer: ¹H NMR δ 0.38 (d, *J*=7.2 Hz, 3H), 0.94 (d, *J*=7.2 Hz, 3H), 3.64 (s, 3H), 3.69 (s, 3H).

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-4-methoxy-1H-indole (270). Reaction of **256** (123 mg, 0.327 mmol) in the presence of Pd(dba)₂ (11 mg, 0.020 mmol), dppp (8 mg, 0.02 mmol), phen (8 mg, 0.04 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (23 h), gave after chromatography (hexanes/EtOAc, 8:2 then 1:1) **270** (99 mg, 0.29 mmol, 88%) as a yellow oil. ¹H NMR δ 0.66 (d, *J*=7.2 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 2.21 (dsept, *J*=7.2, 3.6 Hz, 1H), 3.18 (ddd, *J*=14.4, 7.2, 0.6 Hz, 1H), 3.59 (s, 3H), 3.61 (dd, *J*=4.2, 0.6 Hz, 1H), 3.63 (t, *J*=3.6 Hz, 1H), 3.69 (s, 3H), 3.91 (s, 3H), 4.36 (pent, *J*=3.6 Hz, 1H), 6.45 (d, *J*=7.8 Hz, 1H), 6.83 (d, *J*=1.8 Hz, 1H), 6.91 (dd, *J*=7.8, 0.6 Hz, 1H), 7.04 (t, *J*=8.4 Hz, 1H), 7.98 (br s, 1H); ¹³C NMR δ 16.5, 19.1, 31.3, 31.4, 52.2, 52.3, 55.0, 57.1, 60.4, 99.3, 104.3, 112.6, 118.0, 121.4, 122.4, 137.6, 155.0, 163.5, 164.2; IR (neat) 701, 1086, 1236, 1690 cm⁻¹; [α]_D²⁵ = -22.3 (*c*=1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₃ (M+H⁺) 344.1974, found 344.1969.

3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1H-indole (271). Reaction of **262** (107 mg, 0.285 mmol) in the presence of Pd(dba)₂ (10 mg, 0.017 mmol), dppp (7 mg, 0.02 mmol), phen (7 mg, 0.03 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (22 h), gave after chromatography (hexanes/EtOAc, 8:2) **271** (2R,5S/2S,5S=6:1, 46.0 mg, 0.134 mmol, 47%) as a yellow oil. ¹H NMR δ 0.62 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=7.2 Hz, 3H), 2.13 (dsept, *J*=6.6, 3.0 Hz, 1H), 3.26 (d, *J*=4.8 Hz, 2H), 3.37 (t, *J*=3.6 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.93 (s, 3H), 4.35 (q, *J*=4.2 Hz, 1H), 6.59 (d, *J*=7.2 Hz, 1H), 6.88 (d, *J*=2.4 Hz, 1H), 6.98 (t, *J*=7.8 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 1H), 8.18 (br s, 1H); ¹³C NMR δ 16.7, 19.2, 29.9, 31.5, 52.3, 52.5, 55.4, 55.5, 56.9, 60.6, 101.7, 112.5, 119.5, 122.5, 126.5, 130.0, 146.1, 163.2, 163.9; IR (neat) 729, 1013, 1048, 1225, 1259, 1693 cm⁻¹; [α]_D²⁵ = -25.2 (*c*=1.1, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₃ (M+H⁺) 344.1974, found 344.1969.

3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)ethyl)-1H-indole (277). Reaction of **276** (138 mg, 0.384 mmol) in the presence of Pd(dba)₂ (13 mg, 0.023 mmol), dppp (9.0 mg, 0.02 mmol), phen (9.0 mg, 0.05 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (19 h), gave after chromatography (hexanes/EtOAc, 9:1) **277** (2R,5S/2S,5S=16:1, 90.0 mg, 0.275 mmol, 72%) as a yellow oil. ¹H NMR δ 0.74 (d, *J*=6.6 Hz, 3H), 1.08 (d, *J*=7.2 Hz, 3H), 2.10-2.16 (m, 1H), 2.24-2.33 (m, 2H), 2.72-2.84 (m, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 4.01 (t, *J*=3.6 Hz, 1H), 4.14 (dt, *J*=4.8, 3.6 Hz, 1H), 6.98 (d, *J*=1.8 Hz, 1H), 7.12 (dt, *J*=7.8, 0.6 Hz, 1H), 7.19 (dt, *J*=7.2, 1.2 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 1H), 7.64 (d, *J*=7.8 Hz, 1H), 7.95 (br s, 1H); ¹³C NMR δ 16.7, 19.0, 20.2, 31.8, 34.5, 52.3, 52.4, 55.1, 60.9, 111.0, 116.3, 119.0, 119.1, 121.1, 121.8, 127.6, 136.4, 163.6, 163.9; IR (neat) 701, 1086, 1236, 1690 cm⁻¹; [α]_D²⁵ = -2.74 (*c*=0.8, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₂ (M+H⁺) 328.2025, found 328.2020. Partial data for minor isomer: ¹H NMR δ 0.79 (d, *J*=6.6 Hz, 3H), 1.10 (d, *J*=7.2 Hz, 3H), 3.71 (s, 3H), 3.76 (s, 3H), 7.02 (d, *J*=1.8 Hz, 1H).

2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1H-indole (281) and 2-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1-hydroxyindole (282).

Reaction of **280** (217 mg, 0.628 mmol) in the presence of Pd(dba)₂ (22 mg, 0.038 mmol), dppp (16 mg, 0.038 mmol), phen (15 mg, 0.075 mmol), and CO (6 atm) in DMF (3 mL), as described for **263** (22 h), gave after chromatography (hexanes/EtOAc, 95:5 then 9:1) **281** (2R,5S/2S,5S=1.2:1, 68 mg, 0.22 mmol, 35%) and **282** (22 mg, 0.067 mmol, 11%) both as a yellow oil. Spectral data for **281** from the isomer mixture: ¹H NMR (minor) δ 0.58 (d, *J*=7.2 Hz, 3H), 1.05 (d, *J*=6.6 Hz, 3H), 2.23 (dsept, *J*=6.6, 3.0 Hz, 1H), 2.91 (ddd, *J*=14.4, 9.6, 0.6 Hz, 1H), 3.49 (dd, *J*=14.4, 3.0 Hz, 1H), 3.76 (s, 3H), 3.83 (s, 3H), 4.00 (dd, *J*=4.8, 3.6, 1H), 4.30 (ddd, *J*=9.6, 4.8, 1.8 Hz, 1H), 6.28 (d, *J*=9.6 Hz, 1H), 7.06 (t, *J*=7.8 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 7.29 (d, *J*=7.8 Hz, 1H), 7.55 (s, 1H); ¹H NMR (major) δ 0.73 (d, *J*=7.2 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 2.23 (dsept, *J*=6.6, 3.0 Hz, 1H), 3.03 (ddd, *J*=14.4, 9.6, 0.6 Hz, 1H), 3.44 (dd, *J*=14.4, 3.0 Hz, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 3.91 (t, *J*=3.6 Hz, 1H), 4.24 (dt, *J*=3.0, 1.8 Hz, 1H), 6.28 (d, *J*=9.6 Hz, 1H), 7.06 (t, *J*=7.8 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 7.29 (d, *J*=7.8 Hz, 1H), 7.54 (s, 1H); ¹³C NMR δ 16.7, 16.9, 19.0, 19.4, 31.0, 32.1, 32.8, 33.6, 52.4, 52.5, 52.6, 52.7, 55.9, 56.1, 60.7, 61.1, 100.7, 100.9, 110.4, 110.5, 119.3, 119.4, 119.8, 119.9, 120.9, 121.0, 128.3, 128.4, 135.9, 137.0, 137.1, 161.9, 162.5, 164.1, 164.7; IR (neat) 732, 1229, 1243, 1688 cm⁻¹; [α]_D²⁵=0.35 (*c*=1.0, CH₂Cl₂);

HRMS (ESI) calcd for $C_{18}H_{24}N_3O_2$ ($M+H^+$) 314.1869, found 314.1863. Spectral data for **282**: 1H NMR δ 0.77 (d, $J=7.2$ Hz, 3H), 0.99 (d, $J=6.6$ Hz, 3H), 2.14 (dsept, $J=6.6$, 3.0 Hz, 1H), 3.24 (dd, $J=14.4$, 8.4 Hz, 1H), 3.65 (dd, $J=15.0$, 3.6 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.01 (t, $J=3.6$ Hz, 1H), 4.15 (dt, $J=3.0$, 1.8 Hz, 1H), 6.18 (s, 1H), 7.03 (t, $J=7.8$ Hz, 1H), 7.17 (t, $J=7.2$ Hz, 1H), 7.45 (d, $J=8.4$ Hz, 1H), 7.52 (d, $J=7.8$ Hz, 1H), 11.71 (br s, 1H); ^{13}C NMR δ 17.6, 19.0, 29.5, 32.9, 53.3, 53.6, 57.8, 62.4, 94.9, 108.1, 118.8, 120.0, 121.0, 123.1, 132.4, 133.8, 162.2, 168.5; IR (neat) 1008, 1227, 1250, 1670 cm^{-1} ; $[\alpha]_D^{25} = -8.50$ ($c=1.2$, CH_2Cl_2); HRMS (ESI) calcd for $C_{18}H_{24}N_3O_3$ ($M+H^+$) 330.1818, found 330.1812.

8.2 Supporting Information Chapter 4: 2- and/or 3-Substituted Indoles

2-Pentyl-1H-indole (286). Triethyl((E)-1-(2-nitrophenyl)hept-1-enyl)silane (**284**) (326 mg, 0.977 mmol), Pd(dba)₂ (34 mg, 0.059 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (24 mg, 0.059 mmol), and 1,10-phenanthroline (phen) (23 mg, 0.117 mmol) were dissolved in anhydrous DMF (3 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120°C (oil bath temperature) under CO (6 atm) for 20 hours. Water (20 mL) was added and the orange solution was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes: EtOAc, 95:5) to afford **286** (136 mg, 0.726 mmol, 75%) as a yellow solid. All data in accordance with previously reported literature values.¹³⁷

Triethyl((E)-1-(2-nitrophenyl)hex-1-enyl)silane (290). In a round bottom flask, PtO₂ (45 mg, 0.199 mmol) and 1-(hex-1-ynyl)-2-nitrobenzene **289** (405 mg, 1.99 mmol) were

placed under nitrogen atmosphere. Triethylsilane (462 mg, 3.98 mmol) was introduced via syringe and the mixture was stirred at 60°C in an oil bath for 3 hours in the absence of solvent. The residue was then purified directly by flash chromatography (Hexanes: EtOAc, 98:2) to give **290** (549 mg, 1.72 mmol, 87%) as a yellow oil. ^1H NMR δ 0.53-0.61 (m, 6H), 0.80 (t, $J=7.8$ Hz, 3H), 0.89 (t, $J=7.8$ Hz, 9H), 1.18-1.31 (m, 4H), 1.80-1.85 (m, 2H), 5.96 (t, $J=7.2$ Hz, 1H), 7.02 (d, $J=7.8$ Hz, 1H), 7.32 (t, $J=7.8$ Hz, 1H), 7.50 (t, $J=7.2$ Hz, 1H), 7.92 (d, $J=8.4$ Hz, 1H); ^{13}C NMR δ 3.5, 7.2, 13.9, 22.3, 30.5, 31.2, 124.2, 126.3, 130.5, 132.4, 137.4, 138.9, 143.4, 148.1; IR (neat) 704, 1039, 1523, 2878, 2954 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{29}\text{NNaO}_2\text{Si}$ ($\text{M}+\text{Na}^+$) 342.1860, found 342.1863.

2-Butyl-1H-indole (291). Reaction of **290** (299 mg, 0.936 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (32 mg, 0.056 mmol), dppp (23 mg, 0.056 mmol), phen (22 mg, 0.112 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (20 h), gave, after chromatography (hexanes:EtOAc, 95:5), **291** (115 mg, 0.664 mmol, 71%) as a yellow solid. All data in accordance with previously reported literature values.¹⁴⁰

2-Phenyl-1H-indole (122). Reaction of **294** (258 mg, 0.760 mmol) in the presence of $\text{Pd}(\text{OAc})_2$ (10 mg, 0.046 mmol), dppp (19 mg, 0.046 mmol), phen (18 mg, 0.092 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (24 h), gave, after chromatography

(hexanes:EtOAc, 95:5), **122** (106 mg, 0.549 mmol, 72%) as a white solid. All data in accordance with previously reported literature values.¹⁴¹

1,2-Bis(2-nitrophenyl)ethyne (298). In a round bottom flask, $\text{PdCl}_2(\text{PPh}_3)_2$ (26 mg, 0.037 mmol) and CuI (7 mg, 0.037 mmol) were suspended in NEt_3 (20 mL) under a nitrogen atmosphere. 1-Iodo-2-nitrobenzene **226** (184 mg, 0.741 mmol) and 1-ethynyl-2-nitrobenzene **297** (182 mg, 1.23 mmol) were added in that order and the reaction mixture was stirred at ambient temperature for 6 h. The solvent was removed in vacuo and the residue was then purified directly by flash chromatography (Hexanes: EtOAc, 8:2) to give **298** (160 mg, 0.596 mmol, 81%) as a brown solid. mp 175-177 °C; ^1H NMR δ 7.54 (dt, $J=7.5$, 1.3 Hz, 2H), 7.66 (dt, $J=7.6$, 1.3 Hz, 2H), 7.83 (dd, $J=7.8$, 1.2 Hz, 2H), 8.14 (dd, $J=8.3$, 1.0 Hz, 2H); ^{13}C NMR δ 91.9, 118.0, 124.8, 129.5, 133.1, 135.2, 149.5; IR (neat) 739, 1284, 1335, 1514 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_8\text{N}_2\text{NaO}_4$ ($\text{M}+\text{Na}^+$) 291.0376, found 291.0377.

Tributyl((E)-1-(2-nitrophenyl)-2-phenylvinyl)stannane (303). Tributyltin hydride (2.93 g, 10.08 mmol) was added dropwise at ambient temperature to a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (472 mg, 0.672 mmol) and 1-(2-(2-nitrophenyl)ethynyl)benzene **293** (1.50

g, 6.72 mmol) in THF (20 mL). The dark brown reaction mixture was stirred for an additional 3 hr and then concentrated in vacuo. Purification by flash chromatography (hexanes) gave **303** (2.93 g, 5.70 mmol, 85%) as an orange oil. ^1H NMR δ 0.86 (t, $J=7.2$ Hz, 9H), 0.90-0.97 (m, 6H), 1.27 (sext, $J=7.2$ Hz, 6H), 1.42-1.50 (m, 6H), 6.68 (s, 1H), 6.88 (d, $J=8.4$ Hz, 1H), 7.02 (d, $J=7.8$ Hz, 1H), 7.06-7.09 (m, 3H), 7.28 (t, $J=7.8$ Hz, 1H), 7.44 (t, $J=7.2$ Hz, 1H), 8.10 (d, $J=8.4$ Hz, 1H); ^{13}C NMR δ 10.9, 13.6, 27.3, 28.8, 124.8, 126.0, 126.9, 128.1, 128.6, 129.2, 133.8, 137.0, 137.2, 142.8, 146.0, 147.5; IR (neat) 1017, 1314, 1536, 2901, 2975 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{38}\text{NO}_2\text{Sn}$ ($\text{M}+\text{H}^+$) 516.1919, found 516.1919.

1-Methoxy-4-((Z)-1-(2-nitrophenyl)-2-phenylvinyl)benzene (306). To a solution of **303** (1.50 g, 2.92 mmol) in DMF (10 mL) was added 1-iodo-4-methoxybenzene (**305**) (569 mg, 2.43 mmol), $\text{PdCl}(\text{PPh}_3)_2$ (85 mg, 0.121 mmol) and PPh_3 (63 mg, 0.242 mmol). CuI (347 mg, 1.82 mmol) was added in one portion and the reaction mixture was stirred at ambient temperature for 22 h. The mixture was diluted with Et_2O (50 mL), washed with 10% aqueous NH_4OH (3 x 50 mL), H_2O (50 mL), and brine (50 mL). The organic phase was dried (MgSO_4), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/ EtOAc , 98:2) to afford **306** (503 mg, 1.52 mmol, 62%) as an orange oil. ^1H NMR δ 3.78 (s, 3H), 6.62 (s, 1H), 6.74-6.75 (m, 2H), 7.07-7.09 (m, 2H), 7.12-7.18 (m, 5H), 7.42-7.46 (m, 2H), 7.55 (dt, $J=7.8, 1.8$ Hz, 1H), 7.78 (dd, $J=8.4$ Hz, 1.2 Hz, 1H); ^{13}C NMR δ 55.1, 113.6, 124.1,

127.1, 128.0, 128.1, 129.3, 129.7, 130.5, 131.4, 132.09, 132.14, 136.8, 138.3, 139.2, 149.6, 159.1; IR (neat) 693, 1247, 1509, 1523 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{NO}_3$ ($\text{M}+\text{H}^+$) 332.1281, found 332.1282.

3-(4-Methoxyphenyl)-2-phenyl-1H-indole (307). Reaction of **306** (77 mg, 0.232 mmol) in the presence of $\text{Pd}(\text{OAc})_2$ (3 mg, 0.014 mmol), dppp (6 mg, 0.014 mmol), phen (6 mg, 0.028 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (24 h), gave, after chromatography (hexanes:EtOAc, 95:5), **307** (45 mg, 0.150 mmol, 65%) as a pale yellow solid. All data in accordance with previously reported literature values.¹⁴⁴

Tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (308). Tributyltin hydride (4.23g, 14.56 mmol) was added dropwise at ambient temperature to a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (102 mg, 0.145 mmol) and 1-(hex-1-ynyl)-2-nitrobenzene **289** (1.48g, 7.28 mmol) in THF (10 mL). The dark brown reaction mixture was stirred for an additional 1 hr and then concentrated in vacuo. Purification by flash chromatography (hexanes) gave **308** (2.44g, 4.94 mmol, 68%) as a yellow oil. ^1H NMR δ 0.79-0.91 (m, 18H), 1.19-1.46 (m,

16H), 1.82-1.84 (m, 2H), 5.73 (t, $J=6.6$ Hz, 1H), 7.02 (d, $J=7.8$ Hz, 1H), 7.26 (t, $J=7.2$ Hz, 1H), 7.48 (t, $J=7.8$ Hz, 1H), 7.94 (d, $J=8.4$ Hz, 1H); ^{13}C NMR δ 10.6, 13.6, 13.9, 22.2, 27.3, 28.8, 30.6, 31.5, 124.3, 125.6, 129.8, 132.6, 141.2, 141.6, 142.4, 146.6; IR (neat) 1340, 1520, 2923, 2955 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{42}\text{NO}_2\text{Sn}$ ($\text{M}+\text{H}^+$) 496.2232, found 496.2232.

Tributyl(1-(2-nitrophenyl)vinyl)stannane (311). Tributyltin hydride (2.74 g, 9.43 mmol) was added dropwise at ambient temperature to a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (220 mg, 0.314 mmol) and 1-ethynyl-2-nitrobenzene (**297**) (925 mg, 6.28 mmol) in THF (20 mL). The dark brown reaction mixture was stirred for an additional 24 h and then concentrated in vacuo. Purification by flash chromatography (hexanes) gave **311** (1.61 g, 3.67 mmol, 59%) as a green oil. ^1H NMR δ 0.86 (t, $J=7.2$ Hz, 9H), 0.91-0.94 (m, 6H), 1.26 (sext, $J=7.8$ Hz, 6H), 1.43-1.48 (m, 6H), 5.45 (d, $J=2.4$ Hz, 1H), 5.74 (d, $J=3.0$ Hz, 1H), 7.11 (dd, $J=7.8$, 1.2 Hz, 1H), 7.31 (dt, $J=7.2$, 1.2 Hz, 1H), 7.52 (dt, $J=7.8$, 1.2 Hz, 1H), 7.99 (dd, $J=8.4$, 1.2 Hz, 1H); ^{13}C NMR δ 10.9, 13.6, 27.3, 28.8, 124.3, 126.0, 126.3, 129.7, 133.2, 144.3, 146.0, 154.6; IR (neat) 1038, 1339, 1518, 2922 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{34}\text{NO}_2\text{Sn}$ ($\text{M}+\text{H}^+$) 440.1606, found 440.1607.

2,3-Bis(2-nitrophenyl)buta-1,3-diene (312). To a solution of **311** (348 mg, 0.794 mmol) in DMF (10 mL) was added PdCl₂(PPh₃)₂ (28 mg, 0.040 mmol), PPh₃ (21 mg, 0.080 mmol) and CuI (113 mg, 0.595 mmol). The reaction was stirred at ambient temperature for 36 h. Et₂O (30 mL) was added and the organic phase was washed with NH₄OH (10%, aq., 3 x 30 mL), H₂O (30 mL), and brine (30 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The resulting solid was purified by chromatography (hexanes/EtOAc, 95:5) to afford **312** (78 mg, 0.263 mmol, 67%) as a dark yellow solid. mp 122-124 °C; ¹H NMR δ 4.92 (s, 2H), 5.15 (s, 2H), 7.52 (dt, *J*=7.2, 1.2 Hz, 2H), 7.61 (dd, *J*=7.8, 1.2 Hz, 2H), 7.66 (dt, *J*=7.8, 1.2 Hz, 2H), 7.98 (dd, *J*=8.4, 1.2 Hz, 2H); ¹³C NMR δ 118.3, 124.0, 128.7, 132.4, 132.9, 135.3, 145.2, 149.0; IR (neat) 697, 749, 790, 911, 1332, 1514 cm⁻¹; HRMS (ESI) calcd for C₁₆H₁₂N₂NaO₄ (M+Na⁺) 319.0689, found 319.0690.

3-(1H-Indol-3-yl)-1H-indole (313). Reaction of **312** (68 mg, 0.229 mmol) in the presence of Pd(OAc)₂ (3 mg, 0.014 mmol), dppp (6 mg, 0.014 mmol), phen (6 mg, 0.028 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (39 h), gave, after

chromatography (hexanes:EtOAc, 8:2), **313** (36 mg, 0.155 mmol, 68%) as a white solid.

All data in accordance with previously reported literature values.¹⁴⁷

1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene (314). To a solution of **311** (755 mg, 1.72 mmol) in DMF (8 mL) was added 1-iodo-4-methoxybenzene (**305**) (336 mg, 1.44 mmol), PdCl(PPh₃)₂ (50 mg, 0.072 mmol) and PPh₃ (38 mg, 0.144 mmol). CuI (206 mg, 1.08 mmol) was added in one portion and the reaction mixture was stirred at ambient temperature for 30 h. The mixture was diluted with Et₂O (30 mL), washed with 10% aqueous NH₄OH (3 x 30 mL), H₂O (30 mL), and brine (30 mL). The organic phase was dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting solid was purified by chromatography (hexanes/EtOAc, 99:1) to afford an inseparable 3:1 mixture of **314** (112 mg, 0.438 mmol, 31%) and **312** (43 mg, 0.146 mmol, 17%), respectively, as a yellow solid. Data for **314**: ¹H NMR δ 3.78 (s, 3H), 5.20 (s, 1H), 5.64 (s, 1H), 6.80-6.82 (m, 2H), 7.15-7.18 (m, 2H), 7.44 (dd, *J*=7.8, 1.8 Hz, 1H), 7.48 (dt, *J*=7.8, 0.6 Hz, 1H), 7.60-7.62 (m, 1H), 7.90 (dd, *J*=7.8, 0.6 Hz, 1H); ¹³C NMR δ 113.7, 124.2, 127.7, 128.5, 131.8, 132.3, 132.7, 137.2, 145.8, 149.0, 159.6 (1 resonance not found); HRMS (ESI) calcd for C₁₅H₁₄NO₃ (M+H⁺) 256.0968, found 256.0969.

3-(4-Methoxyphenyl)-1H-indole (315). Reaction of a 3:1 mixture of **314** (50 mg, 0.198 mmol) and **312** (20 mg, 0.066 mmol), respectively, in the presence of Pd(OAc)₂ (4 mg, 0.014 mmol), dppp (6 mg, 0.014 mmol), phen (6 mg, 0.028 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (24 h), gave, after chromatography (hexanes:EtOAc, 9:1), **315** (27 mg, 0.121 mmol, 61%) as a light blue solid and **313** (12 mg, 0.052 mmol, 75%) as a white solid. All data for **315** in accordance with previously reported literature values.¹⁴⁸

1,1-Bis(2-nitrophenyl)ethene (316). To a solution of **226** (473 mg, 1.90 mmol) in DMF (10 mL) was added tributyl(1-(2-nitrophenyl)vinyl)stannane **311** (1.00 g, 2.28 mmol), PdCl₂(PPh₃)₂ (67 mg, 0.095 mmol), PPh₃ (50 mg, 0.190 mmol) and CuI (271 mg, 1.43 mmol). The reaction was stirred at ambient temperature for 24 h. Et₂O (30 mL) was added and the organic phase was washed with NH₄OH (10%, aq., 3 x 30 mL), H₂O (30 mL), and brine (30 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The resulting solid was purified by chromatography (hexanes/EtOAc, 9:1) to afford **316** (320 mg, 1.18 mmol, 62%) as a white solid. mp 132-134 °C; ¹H NMR δ 5.62 (s, 2H), 7.43-7.46 (m, 2H), 7.58-7.59 (m,

4H), 7.71 (dt, $J=7.8$, 0.6 Hz, 2H); ^{13}C NMR δ 121.3, 123.9, 129.1, 132.4, 133.1, 133.9, 142.4, 148.7; IR (neat) 716, 774, 1351, 1516 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{NaO}_4$ ($\text{M}+\text{Na}^+$) 293.0533, found 293.0534.

Indolo[2,3-*b*]indole (317) and 5H-Indolo[2,3-*c*]quinolin-6(7H)-one (318). Reaction of **316** (174 mg, 0.644 mmol) in the presence of $\text{Pd}(\text{OAc})_2$ (9 mg, 0.039 mmol), dppp (16 mg, 0.039 mmol), phen (15 mg, 0.077 mmol), and CO (6 atm) in DMF (3 mL), as described for **286** (60 h), gave, after chromatography (hexanes:EtOAc, 4:6), **317** (56 mg, 0.272 mmol, 42%) as a dark yellow solid and **318** (36 mg, 0.154 mmol, 24%) as a tan solid. Data for **317** - mp 340-343 $^{\circ}\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 7.05 (dt, $J=8.4$, 1.8 Hz, 2H), 7.10 (dt, $J=7.2$, 0.6 Hz, 2H), 7.40 (d, $J=7.8$ Hz, 2H), 7.79 (d, $J=7.2$ Hz, 2H), 11.34 (br s, 2H); ^{13}C NMR δ 99.8, 111.4, 117.4, 118.9, 119.2, 121.9, 138.6, 144.6; IR (neat) 696, 736, 1450, 3363, 3413 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2$ ($\text{M}+\text{H}^+$) 207.0917, found 207.0917. Data for **318** - mp 312-314 $^{\circ}\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 7.32 (t, $J=7.2$ Hz, 1H), 7.34 (t, $J=7.2$ Hz, 1H), 7.41 (t, $J=7.2$ Hz, 1H), 7.47 (t, $J=7.8$ Hz, 1H), 7.51 (d, $J=8.4$ Hz, 1H), 7.65 (d, $J=7.8$ Hz, 1H), 8.44 (d, $J=7.2$ Hz, 1H), 8.47 (d, $J=7.8$ Hz, 1H), 11.85 (br s, 1H), 12.34 (br s, 1H); ^{13}C NMR δ 113.0, 116.1, 118.0, 118.2, 120.7, 122.2, 122.30, 122.31, 123.0, 125.6, 125.9, 127.6, 134.9, 138.8, 155.7; IR (neat) 729, 1328, 1620, 1648, 3158, 3316 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$) 235.0866, found 235.0867.

8.3 Supporting Information Chapter 5: Dilemmaones A-C

6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (347). 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone **340** (2.13g, 4.55 mmol) was added to a stirred solution of **338** (733 mg, 4.55 mmol) in AcOH (5mL). The resulting solution was maintained for 4 hours at ambient temperature and then poured into a 10% NaHCO₃ (aq) solution (15 mL). The suspension was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organics were washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (Hexanes:EtOAc 8:2) to afford **347** (640 mg, 2.66 mmol, 59%) as a brown solid. Mp 177-179 °C; ¹H NMR δ 2.30 (s, 3H), 2.67-2.72 (m, 2H), 2.93-2.97 (m, 2H), 4.26 (br s, 2H), 7.11 (s, 1H); ¹³C NMR δ 19.2, 23.8, 37.4, 103.6, 126.7, 131.2, 132.5, 142.4, 147.4, 204.2; IR (neat) 871, 1318, 1469, 1621, 1688, 3352, 3378 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₁BrNO (M+H⁺) 240.0024, found 240.0018.

N-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (348). To a stirring solution of **338** (4.62 g, 28.66 mmol) in 100 mL of CH₂Cl₂ was added NEt₃ (3.19 g, 31.52 mmol) at ambient temperature and the solution was allowed to stir for 15 min. Acetyl chloride (2.70 g, 34.39 mmol) was then added dropwise and the reaction mixture was stirred for

22 h at ambient temperature. The crude mixture was washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc) to give **348** (4.86 g, 23.91 mmol, 84%) as a tan solid. Mp 221-223 °C; ¹H NMR δ 2.21 (s, 3H), 2.34 (s, 3H), 2.66-2.68 (m, 2H), 3.05-3.07 (m, 2H), 7.14 (br s, 1H), 7.31 (s, 1H), 7.95 (s, 1H); ¹³C NMR δ 18.9, 24.0, 25.3, 36.6, 119.2, 128.4, 135.2, 136.0, 138.8, 152.4, 168.5, 206.0; IR (neat) 864, 1527, 1656, 1691, 3310 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₄NO₂ (M+H⁺) 204.1019, found 204.1019.

***N*-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (349).** Fuming nitric acid (10 mL) was stirred at -20°C for 5 min, then 25 drops of concentrated H₂SO₄ was added and the resulting mixture was stirred at -20°C for 20 additional minutes. This mixture was added dropwise to **348** (1.0 g, 4.92 mmol), cooled to -20°C, and was stirred at the same temperature for 2 hrs before quenching with 20 mL of H₂O and then 20 mL of a sat. NH₄Cl soln (aq). The aqueous mixture was extracted with EtOAc (3 x 50 mL) and washed with H₂O (3 x 50 mL). The organic phase was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (EtOAc) to afford **349** (860 mg, 3.46 mmol, 70%) as a dark yellow solid. Mp 225-227 °C; ¹H NMR δ 2.18 (s, 3H), 2.39 (s, 3H), 2.77-2.79 (m, 2H), 3.14-3.16 (m, 2H), 7.31 (br s, 1H), 7.53 (s, 1H); ¹³C NMR δ 19.5, 23.2, 25.3, 36.8, 126.1, 126.7, 130.7, 142.4, 146.3, 154.6, 168.9, 200.4; IR (neat) 782, 1536, 1673, 1718, 3347 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₃N₂O₄ (M+H⁺) 249.0870, found 249.0871.

6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (346). A solution of **349** (140 mg, 0.564 mmol) in EtOH (15 mL) was refluxed with 5N HCl (10 mL) for 18 hours. The organic phase was removed in vacuo and the resulting aqueous solution was made alkaline (pH 8-9) with an NaOH solution (aq). It was then extracted with CH₂Cl₂ (3 x 20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (Hexanes:EtOAc 1:1) to afford **346** (98 mg, 0.475 mmol, 84%) as a bright yellow solid. Mp 229-231 °C; ¹H NMR δ 2.32 (s, 3H), 2.72-2.74 (m, 2H), 2.97-2.99 (m, 2H), 5.10 (br s, 2H), 7.31 (s, 1H); ¹³C NMR δ 18.6, 24.6, 37.1, 129.0, 131.2, 133.6, 139.7, 145.7, 200.6 (1 resonance not found); IR (neat) 887, 1313, 1518, 1634, 1689, 3362, 3460 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₁N₂O₃ (M+H⁺) 207.0764, found 207.0764.

2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (329). To a stirred solution of **346** (280 mg, 1.36 mmol) in concentrated HCl (4 mL) and ice at 0°C, a solution of sodium nitrite (103 mg, 1.49 mmol) in H₂O (3 mL) was added dropwise. The mixture was stirred at 0°C for 30 min before adding it dropwise to a stirred solution of KI (676 mg, 4.07 mmol) in H₂O (10 mL) at ambient temperature. The mixture remained stirring for 16 hours at ambient temperature and was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were washed with 10% NaOH (aq) (1 x 20 mL), 5% NaHCO₃

(aq) (1 x 20 mL), and H₂O (1 x 20 mL) before being dried over MgSO₄, filtered, and concentrated in vacuo. The resulting dark yellow residue was purified by flash chromatography (hexanes: EtOAc, 9:1 then 8:2) to afford **329** (187 mg, 0.590 mmol, 43%) as an off-white solid. Mp 173-175 °C; ¹H NMR δ 2.60 (s, 3H), 2.73-2.75 (m, 2H), 2.98-3.00 (m, 2H), 7.28 (s, 1H); ¹³C NMR δ 24.5, 31.1, 36.9, 107.4, 125.8, 131.8, 136.3, 150.5, 156.8, 201.9; IR (neat) 871, 1149, 1432, 1694, 2923 cm⁻¹; HRMS (ESI) calcd for C₁₀H₉INO₃ (M+H⁺) 317.9627 (peak not found experimentally).

6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (350). A solution of 48% aq. HBr (1.50 mL) dissolved in DMSO (10 mL) was added dropwise to a solution of **346** (453 mg, 2.20 mmol) in a mixture of 10 mL of DMSO and KNO₂ (748 mg, 8.79 mmol) at 35°C with stirring. The added mixture was stirred at 35°C for 30 min. and then transferred to a solution of K₂CO₃ (2.5 g) in 50 mL of ice water. The reaction mixture was then extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with H₂O (2 x 30 mL) before being dried over MgSO₄, filtered, and concentrated in vacuo. The resulting dark orange residue was purified by flash chromatography (hexanes: EtOAc, 9:1) to afford **350** (33 mg, 0.122 mmol, 6%) as an off-white solid. Mp 159-161 °C; ¹H NMR δ 2.57 (s, 3H), 2.74-2.76 (m, 2H), 2.98-3.00 (m, 2H), 7.32 (s, 1H); ¹³C NMR δ 24.2, 25.9, 37.2, 122.6, 127.4, 128.7, 134.3, 146.7, 156.0, 202.3; IR (neat) 862, 1147, 1309, 1440, 1587, 1702 cm⁻¹; HRMS (ESI) calcd for C₁₀H₉BrNO₃ (M+H⁺) 269.9766 (peak not found experimentally).

8.4 Supporting Information Chapter 6: Fistulosin

2-(Icos-1-ynyl)benzenamine (396). To a solution of 2-iodobenzenamine (**394**) (1.00 g, 4.57 mmol) in NEt₃ (10 mL) at ambient temperature was added PdCl₂ (41 mg, 0.228 mmol) and PPh₃ (120 mg, 0.457 mmol). The resultant suspension was stirred for 10 min followed by addition of 1-icosyne (**395**) (2.12 g, 7.62 mmol) and then CuI (44 mg, 0.228 mmol). This mixture was then stirred for 24 h under an N₂ atmosphere at ambient temperature, followed by removal of all volatiles under reduced pressure. The resulting crude product was purified by column chromatography (hexanes: EtOAc, 95:5) to afford **396** (1.21 g, 3.27 mmol, 72%) as a brown solid. Mp 39-41°C; ¹H NMR δ 0.88 (t, *J*=7.2 Hz, 3H), 1.26-1.31 (br m, 28H), 1.45 (pent, *J*=7.2 Hz, 2H), 1.62 (pent, *J*=7.2 Hz, 2H), 2.46 (t, *J*=7.2 Hz, 2H), 4.15 (br s, 2H), 6.65 (dt, *J*=7.2, 1.2 Hz, 1H), 6.67 (d, *J*=8.4 Hz, 1H), 7.06 (dt, *J*=7.8, 1.2 Hz, 1H), 7.23 (dd, *J*=7.2, 1.2 Hz, 1H); ¹³C NMR δ 14.1, 19.6, 22.7, 29.0, 29.2, 29.4, 29.5, 29.63, 29.65, 29.66, 29.69, 31.9, 95.8, 109.0, 114.1, 117.8, 128.8, 132.0, 147.6 (several resonances overlap, 1 resonance missing); IR (neat) 719, 753, 1467, 1607, 2847, 2915, 3371, 3390, 3467, 3490 cm⁻¹; HRMS (ESI) calcd for C₂₆H₄₄N (M+H⁺) 370.3474, found 370.3475.

1-(Icos-1-ynyl)-2-nitrobenzene (398). To a solution of 1-iodo-2-nitrobenzene (**226**) (2.68 g, 10.75 mmol) in NEt₃ (30 mL) at ambient temperature was added Pd(PPh₃)₂Cl₂ (377 mg, 0.537 mmol). The resultant suspension was stirred for 10 min followed by addition of 1-icosyne (**395**) (5.0 g, 17.95 mmol) and then CuI (102 mg, 0.537 mmol). This mixture was then stirred for 3 h under an N₂ atmosphere at ambient temperature, followed by removal of all volatiles under reduced pressure. The resulting crude product was purified by column chromatography (hexanes: EtOAc, 97:3) to afford **398** (4.12 g, 10.31 mmol, 96%) as a brown solid. Mp 39-42 °C; ¹H NMR δ 0.88 (t, *J*=7.2 Hz, 3H), 1.22-1.36 (br m, 28H), 1.46 (pent, *J*=7.2 Hz, 2H), 1.63 (pent, *J*=7.2 Hz, 2H), 2.47 (t, *J*=7.2 Hz, 2H), 7.38 (dt, *J*=7.2, 1.2 Hz, 1H), 7.51 (dt, *J*=7.2, 1.2 Hz, 1H), 7.57 (dd, *J*=7.8, 1.2 Hz, 1H), 7.96 (dd, *J*=8.4, 0.6 Hz, 1H); ¹³C NMR δ 14.1, 19.8, 22.7, 28.3, 28.9, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 75.9, 99.5, 119.4, 124.3, 127.7, 132.4, 134.7, 150.1 (7 peaks overlap); IR (neat) 1339, 1514, 2848, 2917 cm⁻¹; HRMS (ESI) calcd for C₂₆H₄₁NNaO₂ (*M*+Na⁺) 422.3035, found 422.3030.

Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (399). In a rb flask, PtO₂ (278 mg, 1.23 mmol) and 1-(icos-1-ynyl)-2-nitrobenzene (**398**) (4.90 g, 12.26 mmol) were placed

under a N₂ atmosphere. Triethylsilane (2.85 g, 24.52 mmol) was introduced via syringe and the mixture was stirred at 60°C in an oil bath for 3 hours in the absence of solvent. The resulting crude product was purified by chromatography (hexanes: EtOAc, 98:2) to afford **399** (5.37 g, 10.41 mmol, 85%) as a yellow oil. ¹H NMR δ 0.50-0.61 (m, 6H), 0.84-0.90 (m, 12H), 1.12-1.32 (br m, 32H), 1.74-1.85 (m, 2H), 5.95 (t, *J*=7.2 Hz, 1H), 7.01(dd, *J*=7.8, 1.2 Hz, 1H), 7.30 (dt, *J*=7.8, 1.8 Hz, 1H), 7.48 (dt, *J*=7.8, 1.2 Hz, 1H), 7.90 (dd, *J*=8.4, 1.2 Hz, 1H); ¹³C NMR δ 3.4, 7.2, 14.1, 22.7, 29.0, 29.1, 29.4, 29.5, 29.6, 29.7, 30.8, 31.9, 124.2, 126.3, 130.5, 132.3, 137.3, 138.9, 143.5, 148.1 (8 peaks overlap); IR (neat) 705, 718, 1347, 1525, 2852, 2921 cm⁻¹; HRMS (ESI) calcd for C₃₂H₅₇NNaO₂Si (M+Na⁺) 538.4056, found 538.4050.

2-Octadecyl-1H-indole (397). Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (**399**) (2.03 g, 3.93 mmol), Pd(dba)₂ (135 mg, 0.236 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (97 mg, 0.236 mmol), and 1,10-phenanthroline (phen) (94 mg, 0.472 mmol) were dissolved in anhydrous DMF (8 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120°C (oil bath temperature) under CO (6 atm) for 16 hours. Water (30 mL) was added and the orange solution was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvent was removed

under reduced pressure. The resulting crude product was purified by chromatography (hexanes: EtOAc, 98:2) to afford **397** (1.01 g, 2.73 mmol, 70%) as a tan solid. Mp 73-74°C; ^1H NMR δ 0.88 (t, $J=7.2$ Hz, 3H), 1.18-1.35 (br m, 28H), 1.36-1.42 (m, 2H), 1.71 (pent, $J=7.2$ Hz, 2H), 2.74 (t, $J=7.8$ Hz, 2H), 6.23 (d, $J=2.4$ Hz, 1H), 7.06 (dt, $J=7.2$, 1.2 Hz, 1H), 7.10 (dt, $J=7.2$, 1.2 Hz, 1H), 7.28 (d, $J=7.2$ Hz, 1H), 7.51 (d, $J=7.2$ Hz, 1H), 7.82 (br s, 1H); ^{13}C NMR δ 14.1, 22.7, 28.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 99.5, 110.2, 119.6, 119.7, 120.9, 128.9, 135.8, 140.0 (8 peaks overlap); IR (neat) 746, 1456, 1471, 2849, 2915, 3375 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{44}\text{N}$ ($\text{M}+\text{H}^+$) 370.3474, found 370.3470.

2-octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1H-indol-2-yl)-1,2-dihydro-3H-indol-3-one (392) and 2-octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (404). A solution of *m*-chloroperoxybenzoic acid (248 mg, 1.01 mmol) in dichloromethane (5 mL) was added dropwise at ambient temperature to a stirred solution of 2-octadecyl-1H-indole (**397**) (310 mg, 0.838 mmol) in the same solvent (2 mL). The mixture was stirred for 1 h, then poured into 5% NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 25mL). The combined organic phases were dried (MgSO_4), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes, then hexanes:EtOAc 98:2) to afford **392** (107 mg, 0.139 mmol, 33 %) as a bright yellow solid and **404** (113 mg, .150 mmol, 36%) as a dark yellow solid. Data for

392 - Mp 105-107 °C; ^1H NMR δ 0.88 (t, $J=6.6$ Hz, 6H), 0.94-1.30 (br m, 66H), 1.85-1.90 (m, 2H), 6.02 (s, 2H), 6.78 (t, $J=6.6$ Hz, 2H), 6.95 (d, $J=8.4$ Hz, 2H), 7.48 (t, $J=8.4$ Hz, 2H), 7.56 (d, $J=7.8$ Hz, 2H); ^{13}C NMR δ 14.1, 22.7, 22.9, 29.31, 29.35, 29.41, 29.44, 29.54, 29.62, 29.64, 29.66, 29.67, 29.68, 29.76, 72.5, 111.9, 118.3, 121.6, 124.1, 138.0, 162.0, 204.5 (4 signals overlap); IR (neat) 741, 1613, 1674, 2849, 2916, 3358 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{52}\text{H}_{85}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 769.6606, found 769.6613. Data for **404** - Mp 49-52 °C; ^1H NMR δ 0.88 (t, $J=6.6$ Hz, 6H), 1.21-1.31 (br m, 60H), 1.52-1.56 (m, 4H), 2.23 (dt, $J=12.0, 4.2$ Hz, 1H), 2.48 (dt, $J=12.6, 3.6$ Hz, 1H), 2.79-2.82 (m, 2H), 5.03 (br s, 1H), 6.82 (t, $J=7.2$, 1H), 6.87 (d, $J=8.4$ Hz, 1H), 7.03 (t, $J=7.8$ Hz, 1H), 7.09 (t, $J=7.2$ Hz, 1H), 7.24 (d, $J=8.4$ Hz, 1H), 7.46 (t, $J=8.4$ Hz, 1H), 7.63 (d, $J=7.8$ Hz, 1H), 7.77 (d, $J=8.4$ Hz, 1H), 7.81 (br s, 1H); ^{13}C NMR δ 14.1, 22.7, 23.9, 28.4, 29.36, 29.41, 29.47, 29.56, 29.61, 29.64, 29.65, 29.66, 29.68, 29.70, 29.71, 29.72, 29.9, 30.8, 31.9, 38.1, 70.9, 108.9, 110.4, 112.1, 118.8, 119.6, 120.6, 121.2, 125.0, 127.3, 128.4, 133.5, 135.2, 136.8, 137.1, 160.1, 203.3 (15 signals overlap); IR (neat) 718, 741, 1486, 1611, 2850, 2917 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{52}\text{H}_{85}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$) 753.6656, found 753.6652.

8.5 Supporting Information Chapter 7: Miscellaneous Reactions

3-(Bromomethyl)benzo[*c*]isoxazole-*N*-oxide (412). To a 3-pentanone solution (4 mL) of 1-ethynyl-2-nitrobenzene (**297**) (294 mg, 1.99 mmol) was added aqueous HBr (48 wt %, 1.0 mL), and the mixture was heated at 100°C for 3 h. The solution was concentrated, extracted with ether (3 x 20 mL), and washed with water (1 x 20 mL). The ether extract was dried over MgSO₄, and eluted through a silica column (using 95:5 hexanes: EtOAc as the mobile phase) to give **412** (167 mg, 0.732 mmol, 37%) as a brown solid. Mp 52-54°C; ¹H NMR δ 4.90 (s, 2H), 7.08 (d, *J*=8.9 Hz, 1H), 7.32 (dd, *J*=6.3, 4.8 Hz, 1H), 7.53-7.61 (m, 2H); ¹³C NMR δ 17.9, 115.8, 116.2, 118.8, 124.8, 131.0, 157.4, 162.2.

3-(Chloromethyl)benzo[*c*]isoxazole-*N*-oxide (415). To a 3-pentanone solution (2 mL) of 1-ethynyl-2-nitrobenzene (**297**) (147 mg, 1.00 mmol) was added aqueous HCl (37 wt %, 0.5 mL), and the mixture was heated at 100°C for 3 h. The solution was concentrated, extracted with ether (3 x 20 mL), and washed with water (1 x 20 mL). The ether extract was dried over MgSO₄, and eluted through a silica column (using 95:5 hexanes: EtOAc as the mobile phase) to give **415** (97 mg, 0.528 mmol, 53%) as a brown oil. ¹H NMR δ

5.03 (s, 2H), 7.06 (dd, $J=8.7$, 6.1 Hz, 1H), 7.32 (dd, $J=9.3$, 6.5 Hz, 1H), 7.56-7.61 (m, 2H).

Methyl 1,2-dihydroquinoline-5-carboxylate (418). Methyl 3-nitro-2-vinylbenzoate (**115**) (500 mg, 2.41 mmol), Pd(OAc)₂ (33 mg, 0.145 mmol), triphenylphosphine (PPh₃) (152 mg, 0.579 mmol), and paraformaldehyde (723 mg, 24.10 mmol) were dissolved in anhydrous MeCN (7 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 4 atm of CO). The reaction mixture was heated at 90°C (oil bath temperature) under CO (4 atm) for 17 hours. Water (20 mL) was added and the orange solution was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes: EtOAc, 9:1) to afford **418** (100 mg, 0.528 mmol, 22%) as a yellow solid. ¹H NMR δ 3.13 (br t, $J=5.9$ Hz, 1H), 3.95 (s, 3H), 5.61 (d, $J=6.3$ Hz, 2H), 7.11 (d, $J=3.2$ Hz, 1H), 7.22-7.28 (m, 2H), 7.66 (d, $J=8.3$ Hz, 1H), 7.90 (d, $J=7.5$ Hz, 1H).

References and Notes

- ¹ Brown, R. K. In *Indoles*; Houlihan, W. J., Ed; Wiley-Interscience: New York, **1972**, 25, 1.
- ² Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, **1970**.
- ³ *Indoles*; Sundberg, R. J., Ed.; Academic Press: London, **1996**.
- ⁴ Baeyer, A.; Knop, C. A. *Justus Liebigs Ann. Chem.* **1866**, 140, 1.
- ⁵ Muchowski, J. M. *Canadian Journal of Chemistry*. **1969**, 47, 857.
- ⁶ Baeyer, A. *Ann.* **1866**, 140, 295.
- ⁷ Baeyer, A.; Emmerling, A. *Chemische Berichte*. **1869**, 2, 679.
- ⁸ Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, 106, 2875-2911.
- ⁹ Willcock, E. G.; Hopkins, F. G. *J. Physiology*. **1907**, 35, 88-102
- ¹⁰ Rapport, M. M.; Green, A. A. *J. Biol. Chem.* **1948**, 176, 1243-1251
- ¹¹ Fernstrom, J. D. *Physiol. Rev.* **1983**, 63, 484–546.
- ¹² Wurtman, R.J.; Anton-Tay F. *Recent Prog. Horm. Res.* **1969**, 25, 493–522.
- ¹³ Feniuk, W.; Humphrey, P. P. A. *Drug Dev. Res.* **1992**, 26, 235.
- ¹⁴ Schardl, C. L.; Panaccione D. G.; Tudzynski, P. *The Alkaloids: Chemistry and Biology*. **2006**, 63, 45–86.
- ¹⁵ Mancini, T. *Endocrinology & Metabolism Clinics of North America*. **2008**, 37, 67.
- ¹⁶ Yonezawa, A.; Yoshizumii, M.; Ebiko, M.; Amano, T.; Kimura, Y.; Sakurada, S. *Biomed Res.* **2005**, 26, 201–6.
- ¹⁷ Svoboda, G. H.; Poore, G. A.; Montfront, M. L. *J. Pharm. Sci.* **1968**, 57, 1720.
- ¹⁸ Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, 76, 4749.

- ¹⁹ Gul, W.; Hamann, M. T. *Life Sciences*. **2005**, 78, 442-453.
- ²⁰ Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, 109, 3378-3387.
- ²¹ Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, 53, 3116-3118.
- ²² Laycock, M. V.; Wright, J. L. C.; Findlay, J. A.; Patil, A. D. *Canadian Journal of Chemistry*. **1986**, 64, 1312-1316.
- ²³ Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764-4766.
- ²⁴ Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem Rev.* **2003**, 103, 893.
- ²⁵ Fischer, E.; Jourdan, F. *Ber.* **1883**, 16, 2241.
- ²⁶ Fischer, E.; Hess, O. *Ber.* **1884**, 17, 559.
- ²⁷ Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, **1982**.
- ²⁸ Watson, T. J. N.; Horgan, S. W.; Shah, R. S.; Farr, R. A.; Schnettler, R. A.; Nevill, C. R.; Weiberth, F. J.; Huber, E. W.; Baron, B. M.; Webster, M. E.; Mishra, R. J.; Harrison, B. L.; Nyce, P. L.; Rand, C. L.; Gorlaski, C. T. *Org. Process Res. Dev.* **2000**, 4, 477.
- ²⁹ Douglas, A. W. *J. Am. Chem. Soc.* **1978**, 100, 6463.
- ³⁰ Mills, K.; Al Khawaja, I. K.; Al-Saleh, F. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. I.* **1981**, 636.
- ³¹ Buchwald, S. L.; Wagaw, S.; Yang, B. H. *J. Am. Chem. Soc.* **1998**, 120, 6621.
- ³² Gribble, G. W. *J. Chem. Soc., Perkin Trans. I.* **2000**, 1045-1075.
- ³³ Madelung, W. *Ber.* **1912**, 45, 1128.
- ³⁴ Allen, C. F. H.; Van Allen, J. *Org. Synth. Coll. Vol. III.* **1955**, 597.
- ³⁵ Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, 46, 4511-4515.

- ³⁶ Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.
- ³⁷ Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129–2132.
- ³⁸ Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. I.* **1991**, *1*, 2757–2761.
- ³⁹ Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638–641.
- ⁴⁰ Wiedenau, P.; Monse, B.; Blechert, S. *Tetrahedron.* **1995**, *51*, 1167.
- ⁴¹ For a review of the Bartoli synthesis, including mechanistic studies, see: Bartoli, G.; Dalpozzo, R. *Curr. Org. Chem.* **2005**, *9*, 163–178.
- ⁴² Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590–591.
- ⁴³ Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214–220.
- ⁴⁴ Maehr, H.; Smallheer, J. M. *J. Org. Chem.* **1981**, *46*, 1753.
- ⁴⁵ Fetter, J.; Bertha, F.; Poszavacz, L.; Simig, G. *J. Heterocycl. Chem.* **2005**, *42*, 137.
- ⁴⁶ Nenitzescu, C. D. *Bull. Soc. Chim. Romania.* **1929**, *11*, 37.
- ⁴⁷ Kinugawa, M.; Arai, H.; Nishikawa, H.; Sakaguchi, A.; Ogasa, T.; Tomioka, S.; Kasai, M. *J. Chem. Soc., Perkin Trans. I.* **1995**, 2677.
- ⁴⁸ Allen, Jr., G. R.; Pidacks, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 2536–2544.
- ⁴⁹ Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.
- ⁵⁰ Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920.
- ⁵¹ Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, **2000**.
- ⁵² Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287.

- ⁵³ Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, 26, 5963.
- ⁵⁴ Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997**, 53, 13397.
- ⁵⁵ Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, 30, 2581.
- ⁵⁶ Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 16, 4467–4470.
- ⁵⁷ Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, 475, 289.
- ⁵⁸ Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, 113, 6689.
- ⁵⁹ Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, 5, 921.
- ⁶⁰ Hegedus, L. S.; Allen, G. F.; Waterman, E. L.; *J. Am. Chem. Soc.* **1976**, 98, 2674.
- ⁶¹ Hegedus, L. S.; Allen, G. F.; Waterman, E. L.; Boxell, J. J. *J. Am. Chem. Soc.* **1978**, 100, 5800.
- ⁶² Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron. Lett.* **1977**, 1037.
- ⁶³ Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, 101, 5281.
- ⁶⁴ Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. *J. Heterocycl. Chem.* **1989**, 26, 1405.
- ⁶⁵ Yamaguchi, M.; Arisawa, M.; Hirama, M. *Chem. Commun.* **1998**, 1399.
- ⁶⁶ Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, 31, 805.
- ⁶⁷ Wolfe, J. P.; Rennels, R.A.; Buchwald, S. L. *Tetrahedron.* **1996**, 52, 7525.
- ⁶⁸ Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, 118, 1028.
- ⁶⁹ Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, 4, 727-64.
- ⁷⁰ Smith, P. A.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, 73, 2435.

- ⁷¹ Sundberg, R. J.; Brenner, M.; Suter, S. R.; Das, B. P. *Tetrahedron Lett.* **1970**, *31*, 2715.
- ⁷² Reiser, A.; Wanger, H.; Bowes, G. *Tetrahedron Lett.* **1966**, *23*, 629.
- ⁷³ Lehman, P. A.; Berry, R. S. *J. Am. Chem. Soc.* **1973**, *95*, 8614.
- ⁷⁴ Swenton, J.; Ikeler, T.; Williams, B. *J. Am. Chem. Soc.* **1970**, *92*, 3103.
- ⁷⁵ Sundberg, R. J.; Russell, H. F.; Ligon, W. V.; Lin, L. *J. Org. Chem.* **1972**, *37*, 719.
- ⁷⁶ Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.
- ⁷⁷ Cadogan, J. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. G. *J. Chem Soc.* **1965**, 4831.
- ⁷⁸ Daneli, B.; Palmisano, G. *J. Heterocycl. Chem.* **1977**, *14*, 839-44.
- ⁷⁹ Waterman, H. C.; Vivian, D. L. *J. Org. Chem.* **1949**, *14*, 289-297.
- ⁸⁰ Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. *J. Heterocycl. Chem.* **1989**, *26*, 1405.
- ⁸¹ Pizzotti, M.; Cenini, S.; Quici, S.; Tollari, S. *J. Chem. Soc., Perkin Trans. 2.* **1994**, 913-917.
- ⁸² Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org Chem.* **1994**, *59*, 3375.
- ⁸³ Tolari, S.; Cenini, S.; Crotti, C.; Gianelli, E. *J. Mol. Catal.* **1994**, *87*, 203.
- ⁸⁴ Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron.* **2005**, *61*, 6425-6437.
- ⁸⁵ Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555.
- ⁸⁶ Hsieh, T. H. H.; Dong, V. M. *Tetrahedron.* **2009**, *65*, 3062-3068.
- ⁸⁷ Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533.

- ⁸⁸ Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838-5845.
- ⁸⁹ Söderberg, B. C.; Chisnell, A. C.; O'Neil, S. N.; Shriver, J. A. *J. Org. Chem.* **1999**, *64*, 9731-9734.
- ⁹⁰ Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657-3660.
- ⁹¹ Clawson, R. W., Jr.; Deavers, R. E., III; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron*. **2006**, *62*, 10829.
- ⁹² Scott, T. L.; Yu, X.; Gorugantula, S. P.; Carrero-Martinez, G.; Söderberg, B. C. G. *Tetrahedron*. **2006**, *62*, 10835-10842.
- ⁹³ Clawson, R. W., Jr.; Söderberg, B. C. G. *Tetrahedron Lett.* **2007**, *48*, 6019.
- ⁹⁴ In *Tryptophan, Serotonin, and Melatonin: Basic Aspects and Applications*/ed. Huether, G.; Kochen, W.; Simat, T. J.; Steinhart, H., 1999, New York: Kluwer Academic/Plenum Publ.
- ⁹⁵ In *Recent Advances in Tryptophan Research: Tryptophan and Serotonin Pathways*/ed. Filippini, G. A.; Costa, C. V. L.; Bertazzo, A., 1996, New York: Kluwer Academic/Plenum Publ.
- ⁹⁶ Pallaghy, P. K.; Melnikova, A. P.; Jimenez, E. C.; Olivera, B. M.; Norton, R. S. *Biochemistry*. **1999**, *38*, 11553-11559.
- ⁹⁷ Sorensen, D.; Larsen, T. O.; Christophersen, C.; Nielsen, P. H.; Anthoni, U. *Phytochemistry*. **1999**, *51*, 1181-1183.
- ⁹⁸ Kozlovsky, A. G.; Marfenina, O. G.; Vinokurova, N. G.; Zhelifonova, V. P.; Adanin, V. M. *Mycotoxins*. **1998**, *48*, 37-43.
- ⁹⁹ Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525-4542.

- ¹⁰⁰ Peterson, A. C.; Migawa, M. T.; Martin, M. J.; Hamaker, L. K.; Czerwinski, K. M.; Zhang, W.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1994**, *3*, 531.
- ¹⁰¹ Dellaria, Jr., J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916-3926.
- ¹⁰² Leanna, M. R.; Morton, H. E. *Tetrahedron. Lett.* **1993**, *34*, 4485-4488.
- ¹⁰³ Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322-3327.
- ¹⁰⁴ Wang, W.; Xiong, C.; Zhang, J.; Hruby, V. J. *Tetrahedron.* **2002**, *58*, 3101-3110.
- ¹⁰⁵ Carlier, P. R.; Lam, P. C. H.; Wong, D. M. *J. Org. Chem.* **2002**, *67*, 6256-6259.
- ¹⁰⁶ Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett.* **2003**, *10*, 1411-1414.
- ¹⁰⁷ Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798-799.
- ¹⁰⁸ Chen, J.; Corbin, S. P.; Holman, N. J. *Org. Process Res. Dev.* **2005**, *9*, 185-187.
- ¹⁰⁹ Bull, S. D.; Davies, S. G.; Moss, W. O. *Tetrahedron: Asymmetry.* **1998**, *9*, 321-327.
- ¹¹⁰ Okada, M.; Sato, I.; Cho, S. J.; Suzuki, Y.; Ojika, M.; Dubnau, D.; Sakagami, Y. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 2374-2387.
- ¹¹¹ Jain, H. D.; Zhang, C.; Zhou, S.; Zhou, H.; Ma, J.; Liu, X.; Liao, X.; Deveau, A. M.; Dieckhaus, C. M.; Johnson, M. A.; Smith, K. S.; Macdonald, T. L.; Kakeya, H.; Osada, H.; Cook, J. M. *Bioorg. Med. Chem.* **2008**, *16*, 4626-4651.
- ¹¹² Ma, C.; Liu, X.; Yu, S.; Zhao, S.; Cook, J. M. *Tetrahedron Lett.* **1999**, *40*, 657-660.
- ¹¹³ Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129.
- ¹¹⁴ Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611-3614.

- ¹¹⁵ Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626-6633.
- ¹¹⁶ Dacko, C. A.; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron: Asymmetry*. **2008**, *19*, 2775-2783.
- ¹¹⁷ Papageorgiou, C.; Florineth, A.; Mikol, V. *J. Med Chem.* **1994**, *37*, 3674-3675.
- ¹¹⁸ Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857-1867.
- ¹¹⁹ Tinkova, R.; Leseticky, L. *J. Radioanal. Nucl. Chem.* **2004**, *261*, 443-449
- ¹²⁰ Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D. *J. Org. Chem.* **2002**, *67*, 1093-1101.
- ¹²¹ Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006.
- ¹²² Isopropyl methyl groups are non-equivalent in some chiral environments, see: Sorensen, T. S. *Canadian Journal of Chemistry*. **1967**, *45*, 1585-1588.
- ¹²³ Møller, B. S.; Benneche, T.; Undheim, K. *Tetrahedron*. **1996**, *52*, 8807-8812.
- ¹²⁴ Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron*. **2001**, *57*, 9813-9816
- ¹²⁵ Nadler, E. B.; Rappoport, Z. *J. Org. Chem.* **1990**, *55*, 2673-2682.
- ¹²⁶ Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211-6214.
- ¹²⁷ D'hooghe, M.; Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 2703-2710.
- ¹²⁸ Shigyo, H.; Sato, S.; Shibuya, K.; Takahashi, Y.; Yamaguchi, T.; Sonoki, H.; Ohta, T. *Chem. Pharm. Bull.* **1993**, *41*, 1573-1582.
- ¹²⁹ Caballero, E.; Avendano, C.; Menedez, J. C. *Tetrahedron: Asymmetry*. **1998**, *9*, 3025-3038.

- ¹³⁰ Yokum, T. S.; Tungaturthi, P. K.; McLaughlin, M. L. *Tetrahedron Lett.* **1997**, 38, 5111.
- ¹³¹ Adamczyk, M.; Fishpaugh, J. R.; Thiruvazhi, M. *Tetrahedron: Asymmetry.* **1999**, 10, 4151-4156.
- ¹³² Incomplete reduction has been observed in some cases, see: Tollari, S.; Penoni, A.; Cenini, S. *J. Mol. Catal. A: Chem.* **2000**, 152, 47-54.
- ¹³³ *Silicon in Organic Synthesis*: Colvin, E. W., Ed.; Butterworth: London, 1981.
- ¹³⁴ Hamze, A.; Provot, O.; Alami, M.; Brion, J. *Org. Lett.* **2005**, 7, 5625-5628.
- ¹³⁵ Liron, F.; Le Garrec, P.; Alami, M. *Synlett.* **1999**, 246-248.
- ¹³⁶ Majchrzak, M. W.; Simchen, G. *Synthesis.* **1986**, 956-958.
- ¹³⁷ Spectral data for this compound has been reported, see: Miyazaki, Y.; Kobayashi, S. *Journal of Combinatorial Chemistry.* **2008**, 10, 355-357.
- ¹³⁸ Katritzky, A. R.; Akutagawa, K. *J. Am. Chem. Soc.* **1986**, 108, 6808-6809.
- ¹³⁹ Spectral data for this compound has been reported, see: Worm-Leonhard, K.; Meldal, M. *European Journal of Organic Chemistry.* **2008**, 5244-5253.
- ¹⁴⁰ Spectral data for this compound has been reported, see: Tokuyama, H.; Makido, T.; Han-ya, Y.; Fukuyama, T. *Heterocycles.* **2007**, 72, 191-197.
- ¹⁴¹ Spectral data for this compound has been reported, see: Morales-Rios, M. S.; Espineira, J.; Joseph-Nathan, P. *Magnetic Resonance in Chemistry.* **1987**, 25, 377-95.
- ¹⁴² Spectral data for this compound has been reported, see: Mitsumori, S.; Tsuru, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *Journal of Medicinal Chemistry.* **2003**, 46, 2436-2445.

- ¹⁴³ Alami, M.; Liron, F.; Gervais, M.; Peyrat, J.; Brion, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1578-1580.
- ¹⁴⁴ Spectral data for this compound has been reported, see: Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis*. **2003**, 728-734.
- ¹⁴⁵ XPhos = 2-dicyclohexylphosphine-2',4',6'-triisopropylbiphenyl.
- ¹⁴⁶ Hamze, A.; Veau, D.; Provot, O.; Brion, J.; Alami, M. *J. Org. Chem.* **2009**, *74*, 1337-1340.
- ¹⁴⁷ Spectral data for this compound has been reported, see: Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry*. **1996**, *7*, 285-292.
- ¹⁴⁸ Spectral data for this compound has been reported, see: Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499-2502.
- ¹⁴⁹ Kanaoka, Y.; Itoh, K. *Synthesis*. **1972**, 36.
- ¹⁵⁰ Beukes, D.R.; Davies Coleman, M.T.; Kelly-Borges, M.; Harper, M.K.; Faulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 699-701.
- ¹⁵¹ Capon, R. J.; MacLeod, J. K.; Scammells, P. J.; *Tetrahedron*. **1986**, *42*, 6545-6550.
- ¹⁵² Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J.; *Tetrahedron*. **1990**, *46*, 3089.
- ¹⁵³ MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391-392.
- ¹⁵⁴ Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230-4234.
- ¹⁵⁵ Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771-5772
- ¹⁵⁶ Boberg, F.; Deters, K.; Schulz, J.; Torges, K. *Phosphorus, Sulfur, and Silicon*. **1994**, *91*, 69-80.

- ¹⁵⁷ Schaverien, C. J.; Ernst, R.; Schut, P.; Skiff, W. M.; Resconi, L.; Barbassa, E.; Balboni, D.; Dubitsky, Y. A.; Orpen, A. G.; Mercandelli, P.; Moret, M.; Sironi, A. *J. Am. Chem. Soc.* **1998**, *120*, 9945.
- ¹⁵⁸ Murineddu, G.; Lazzari, P.; Ruiu, S.; Sanna, A.; Loriga, G.; Manca, I.; Falzoi, M.; Dessi, C.; Curzu, M.; Chelucci, G.; Pani, L.; Pinna, G. *J. Med. Chem.* **2006**, *49*, 7502-7512.
- ¹⁵⁹ Lemaire, M.; Guy, A.; Boutin, P.; Guette, J. P. *Synthesis*. **1989**, *10*, 761-763.
- ¹⁶⁰ Lemaire, M.; Guy, A.; Roussel, J.; Guette, J. *Tetrahedron*. **1987**, *43*, 835-844.
- ¹⁶¹ Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N.; Firouzabadi, D. *Tetrahedron Lett.* **2006**, *47*, 6879-6881.
- ¹⁶² Panteleon, V.; Marakos, P.; Pouli, N.; Mikros, E.; Andreadou, I. *Chem. Pharm. Bull.* **2003**, *51*, 522-529.
- ¹⁶³ Baik, W.; Luan, W.; Lee, H. J.; Yoon, C. H.; Koo, S.; Kim, B. H. *Can. J. Chem.* **2005**, *83*, 213-219.
- ¹⁶⁴ Be'langer, G.; Deslongchamps, P. *J. Org. Chem.* **2000**, *65*, 7070-7074.
- ¹⁶⁵ Phay, N.; Higashiyama, T.; Masahisa, T.; Matsuura, H.; Fukushi, Y.; Yokota, A.; Tomita, F. *Phytochemistry* **1999**, *52*, 271.
- ¹⁶⁶ Griffiths, G.; Trueman, L.; Crowther, T.; Thomas, B.; Smith, B.; *Phytother. Res.* **2002**, *16*, 603-615.
- ¹⁶⁷ Tada, M.; Hiroe, Y.; Kiyohara, S.; Suzuki, S. *Agric. Biol. Chem.* **1988**, *52*, 2383-2385.
- ¹⁶⁸ Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624.

- ¹⁶⁹ Spectral data for this compound can be found in: Maukawa, K.; Takikawa, H.; Mori, K. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 305.
- ¹⁷⁰ Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.
- ¹⁷¹ McDonald, F. E.; Schultz, C. C.; Chatterjee, A. K. *Organometallics* **1995**, *14*, 3628.
- ¹⁷² Al-Khalil, S.; Maselmeh, A.; Abdalla, S.; Tosa, H.; Iinuma, M. *J. Nat. Prod.* **1995**, *58*, 760.
- ¹⁷³ Malakov, P. Y.; Papanov, G. Y.; Ziesche, J. *Phytochemistry* **1982**, *21*, 2589.
- ¹⁷⁴ Ren, D.; Zhang, X.; Yan, K.; Yuan, S.; Lu, X. *Fresenius Environmental Bulletin* **2006**, *15*, 1238.
- ¹⁷⁵ Khajavi, M. S.; Shariat, S. M. *Heterocycles* **2005**, *65*, 1159.
- ¹⁷⁶ Piccinni-Leopard, C.; Fabre, O.; Zimmerman, D.; Reisse, J.; Fulen, C. *Can. J. Chem.* **1992**, *55*, 2649.
- ¹⁷⁷ Terada, Y.; Arisawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 1269.
- ¹⁷⁸ Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.
- ¹⁷⁹ Pflieger, J. U. S. Patent. **1901**, CODEN: USXXAM US 680395 A 19010813 CAN 0:59961 AN 1906:59961
- ¹⁸⁰ Pang, Z.; Sterner, O. *J. Nat. Prod.* **1994**, *57*, 852
- ¹⁸¹ Stachel, S. J.; Nilges, M.; Van Vranken, D. L. *J. Org. Chem.* **1997**, *62*, 4756.
- ¹⁸² Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 713.
- ¹⁸³ Hassner, A.; Haddadin, M. J. *J. Org. Chem.* **1963**, *28*, 224.
- ¹⁸⁴ Rodriguez, H. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488-2490.

- ¹⁸⁵ Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *J. Chem. Soc., Perkin Trans. 2*. **2001**, 1634-1640.
- ¹⁸⁶ Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873-8879.
- ¹⁸⁷ Lo, C.; Kumar, M. P.; Chang, H.; Lush, S.; Liu, R. *J. Org. Chem.* **2005**, *70*, 10482-10487.

Appendix

^1H and ^{13}C NMR Spectra

● ^1H and ^{13}C NMR for Chapter 3: Tryptophan Derivatives	200
● ^1H and ^{13}C NMR for Chapter 4: 2- and/or 3-Substituted Indoles	256
● ^1H and ^{13}C NMR for Chapter 5: Dilemmaones A-C	279
● ^1H and ^{13}C NMR for Chapter 6: Fistulosin	291
● ^1H and ^{13}C NMR for Chapter 7: Miscellaneous Reactions	317

Figure 18: ^1H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-trimethylstannyl-2-propen-1-yl)pyrazine (**238**)

Figure 19: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-trimethylstannyl-2-propen-1-yl)pyrazine (**238**)

Figure 20: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (**239**)

Figure 21: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine (**239**)

Figure 22: ¹H NMR of (2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine (**241**)

Figure 23: ¹³C NMR of (2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine (**241**)

Figure 24: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(5-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (**243**)

Figure 25: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(5-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (**243**)

Figure 26: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (**245**)

Figure 27: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (245)

Figure 28: ¹H NMR of Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate (**247**)

Figure 29: ¹³C NMR of Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate (**247**)

Figure 30: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (**249**)

Figure 31: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (**249**)

Figure 32: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**251**)

Figure 33: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**251**)

Figure 34: ¹H NMR of Bis-2,3-((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene (**254**)

Figure 35: ¹³C NMR of Bis-2,3-((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene (**254**)

Figure 36: ^1H NMR of (3-Methoxy-2-nitrophenyl)trimethylstannane (**261**)

Figure 37: ^{13}C NMR of (3-Methoxy-2-nitrophenyl)trimethylstannane (**261**)

Figure 38: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**256**)

Figure 39: ^{13}C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**256**)

Figure 40: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**262**)

Figure 41: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine (**262**)

Figure 42: ¹H NMR of (2R,5S)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (**275**)

Figure 43: ^{13}C NMR of (2R,5S)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (**275**)

Figure 44: ^1H NMR of (2R,5S)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (**279**)

Figure 45: ^{13}C NMR of (2R,5S)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine (**279**)

Figure 46: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine (**276**)

Figure 47: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine (**276**)

Figure 48: ¹H NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (*E/Z*) (**280**)

Figure 49: ¹³C NMR of (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine (*E/Z*) (**280**)

Figure 50: ^1H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1H-indole (**263**)

Figure 51: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1H-indole (**263**)

Figure 52: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1*H*-indole (**264**)

Figure 53: ¹³C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1H-indole (**264**)

Figure 54: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1*H*-indole (**265**)

Figure 55: ¹³C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1H-indole (**265**)

Figure 56: ¹H NMR of 6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-indole (**266**)

Figure 57: ¹³C NMR of 6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-indole (**266**)

Figure 58: ¹H NMR of Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1*H*-indole-6-carboxylate (**267**)

Figure 59: ¹³C NMR of Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1*H*-indole-6-carboxylate (**267**)

Figure 60: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-6-nitro-1H-indole (**268**)

Figure 61: ¹³C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-6-nitro-1H-indole (**268**)

Figure 62: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine (**269**)

Figure 63: ^{13}C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine (**269**)

Figure 64: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-4-methoxy-1*H*-indole (**270**)

Figure 65: ¹³C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-4-methoxy-1H-indole (**270**)

Figure 66: ¹H NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1H-indole (**271**)

Figure 67: ¹³C NMR of 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1H-indole (**271**)

Figure 68: ¹H NMR of 3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)ethyl)-1H-indole (277)

Figure 69: ¹³C NMR of 3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)ethyl)-1H-indole (277)

Figure 70: ¹H NMR of 2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1H-indole (**281**)

Figure 71: ¹³C NMR of 2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1*H*-indole (**281**)

Figure 72: ¹H NMR of 2-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1-hydroxyindole (**282**)

Figure 73: ¹³C NMR of 2-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1-hydroxyindole (**282**)

Figure 74: ^1H NMR of Triethyl((E)-1-(2-nitrophenyl)hex-1-enyl)silane (**290**)

Figure 75: ^{13}C NMR of Triethyl((E)-1-(2-nitrophenyl)hex-1-enyl)silane (**290**)

Figure 76: ¹H NMR of 1,2-Bis(2-nitrophenyl)ethyne (**298**)

Figure 77: ^{13}C NMR of 1,2-Bis(2-nitrophenyl)ethyne (**298**)

Figure 78: ¹H NMR of Tributyl((E)-1-(2-nitrophenyl)-2-phenylvinyl)stannane (**303**)

Figure 79: ¹³C NMR of Tributyl((E)-1-(2-nitrophenyl)-2-phenylvinyl)stannane (**303**)

Figure 80: ¹H NMR of 1-Methoxy-4-((Z)-1-(2-nitrophenyl)-2-phenylvinyl)benzene (**306**)

Figure 81: ^{13}C NMR of 1-Methoxy-4-((Z)-1-(2-nitrophenyl)-2-phenylvinyl)benzene

(306)

Figure 82: ¹H NMR of Tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (**308**)

Figure 83: ¹³C NMR of Tributyl((E)-1-(2-nitrophenyl)hex-1-enyl)stannane (**308**)

Figure 84: ^1H NMR of Tributyl(1-(2-nitrophenyl)vinyl)stannane (**311**)

Figure 85: ¹³C NMR of Tributyl(1-(2-nitrophenyl)vinyl)stannane (**311**)

Figure 86: ^1H NMR of 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312)

Figure 87: ^{13}C NMR of 2,3-Bis(2-nitrophenyl)buta-1,3-diene (312)

Figure 88: ^1H NMR of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene (**314**) and 2,3-Bis(2-nitrophenyl)buta-1,3-diene (**312**).

Figure 89: ^{13}C NMR of 1-(1-(4-Methoxyphenyl)vinyl)-2-nitrobenzene (**314**) and 2,3-Bis(2-nitrophenyl)buta-1,3-diene (**312**).

Figure 90: ¹H NMR of 1,1-Bis(2-nitrophenyl)ethene (**316**)

Figure 91: ^{13}C NMR of 1,1-Bis(2-nitrophenyl)ethene (316)

Figure 92: ^1H NMR of Indolo[2,3-*b*]indole (317)

Figure 93: ^{13}C NMR of Indolo[2,3-*b*]indole (317)

Figure 94: ^1H NMR of 5H-Indolo[2,3-*c*]quinolin-6(7H)-one (**318**)

Figure 95: ¹³C NMR of 5H-Indolo[2,3-c]quinolin-6(7H)-one (318)

Figure 96: ^{13}C NMR APT and DEPT-90 of 5H-Indolo[2,3-*c*]quinolin-6(7H)-one (**318**)

Figure 97: ^1H NMR of 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (**347**)

Figure 98: ^{13}C NMR of 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (347)

Figure 99: ^1H NMR of *N*-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (**348**)

Figure 100: ^{13}C NMR of *N*-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (**348**)

Figure 101: ¹H NMR of *N*-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (**349**)

Figure 102: ¹³C NMR of *N*-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (**349**)

Figure 103: ¹H NMR of 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (**346**)

Figure 104: ¹³C NMR of 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (346)

Figure 105: ^1H NMR of 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (**329**)

Figure 106: ¹³C NMR of 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (**329**)

Figure 107: ¹H NMR of 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (**350**)

Figure 108: ^{13}C NMR of 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (**350**)

Figure 109: ^1H NMR of 2-(Icos-1-ynyl)benzenamine (396)

Figure 110: ¹³C NMR of 2-(Icos-1-ynyl)benzenamine (396)

Figure 111: ¹H NMR of 1-(Icos-1-ynyl)-2-nitrobenzene (398)

Figure 112: ¹³C NMR of 1-(Icos-1-ynyl)-2-nitrobenzene (398)

Figure 113: ^1H NMR of Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (**399**)

Figure 114: ^{13}C NMR of Triethyl((E)-1-(2-nitrophenyl)icos-1-enyl)silane (399)

Figure 115: ¹H NMR of 2-Octadecyl-1H-indole (**397**)

Figure 116: ¹³C NMR of 2-Octadecyl-1H-indole (397)

Figure 117: ^1H NMR of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (**392**)

Figure 118: ¹³C NMR of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1H-indol-2-yl)-1,2-dihydro-3H-indol-3-one (**392**)

Figure 119: ¹H NMR Expansion of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (392)

Figure 120: ¹³C NMR Expansion of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (392)

gHMBC spectrum

Figure 121: gHMBC of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (**392**)

gHMBC

aliphatic region

Figure 122: gHMBC Expansion (aliphatic region) of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (**392**)

gHMBC

aromatic region

Figure 123: gHMBC Expansion (aromatic region) of 2-Octadecyl-2-(2-octadecyl-3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,2-dihydro-3*H*-indol-3-one (**392**)

Figure 124: ¹H NMR of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

Figure 125: ^{13}C NMR of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (404)

Figure 126: ^1H NMR Expansion of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (404)

Figure 128: ¹³C NMR Expansion (aromatic region) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

Linkage information between
two rings

Exclusie HMBC correlations:

from 15-CH₂'s to C8 and

17-CH₂'s to C8

Figure 129: gHMBC Expansion (ring linkage) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

HMBC spectrum of
15-CH₂ and 1-NH

Figure 130: gHMBC Expansion (diastereotopic protons) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

Figure 131: gHMBC Expansion (aromatics) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

gHMBC spectrum of
15-CH₂, 1-NH and H4

Figure 132: gHMBC Expansion (carbonyl) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

NOESY spectrum
(full region)

Figure 133: 2D NOESY (full) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

NOESY spectrum
aromatic region

Figure 134: 2D NOESY Expansion (aromatic region) of 2-Octadecyl-2-(2-octadecyl-1H-indol-3-yl)indolin-3-one (**404**)

Figure 135: ^1H NMR of 3-(Bromomethyl)benzo[c]isoxazole-N-oxide (412)

Figure 136: ^{13}C NMR of 3-(Bromomethyl)benzo[*c*]isoxazole-*N*-oxide (412)

Figure 137: gHMBC of 3-(Bromomethyl)benzo[*c*]isoxazole-*N*-oxide (**412**)

Figure 138: 1D NOE of 3-(Bromomethyl)benzo[*c*]isoxazole-*N*-oxide (**412**)

Figure 139: HETCOR of 3-(Bromomethyl)benzo[*c*]isoxazole-*N*-oxide (**412**)

Figure 140: COSY of 3-(Bromomethyl)benzo[c]isoxazole-*N*-oxide (**412**)

Figure 141: ^1H NMR of 3-(Chloromethyl)benzo[*c*]isoxazole-*N*-oxide (**415**)

Figure 142: ^1H NMR of Methyl 1,2-dihydroquinoline-5-carboxylate (**418**)