Oxazoloporphyrins, Oxazolochlorins, and Oxazolobacteriochlorins

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Oxazoloporphyrins, Oxazolochlorins and Oxazolobacteriochlorins

Junichi Kent Ogikubo, Ph.D.
University of Connecticut, 2012

Since the serendipitous discovery of oxazole-containing porphyrins over 30 years ago, this class of porphyrinoid macrocycles remained largely unexplored. This thesis is the first systematic study of the syntheses and optical properties of this class of macrocycles. Specifically, this thesis investigates the scope and limits of synthesizing various oxazole containing chlorin and bacteriochlorin chromophores. The multi-step syntheses described are based on the OsO₄-mediate dihydroxylation of meso-tetraphenylporphyrin (TPP) to form diolchlorin A. This diol is converted into various oxazolones and/or α-substituted oxazolines (B/C/D) via one of two principal pathways; through MnO₄⁻ mediated oxidation or NaIO₄-mediated oxidative cleavage. Similar reaction sequence also takes place on the opposing pyrrole unit for the formation of bis-oxazolochlorins and bacteriochlorins (E/F/G). These oxazole(s)-containing macrocycles are optically tunable in 20-30 nm increments in the range of 650-810 nm.
Oxazoloporphyrins, Oxazolochlorins
and Oxazolobacteriochlorins

Junichi Kent Ogikubo

B.S. Chaminade University, 2007

A Dissertation
Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy
at the
University of Connecticut
2012
APPROVAL PAGE

Doctor of Philosophy Dissertation

Presented By

Junichi Kent Ogikubo, B.S.

Major Advisor

Dr. Christian Brückner

Associate Advisor

Dr. Amy Howell

Associate Advisor

Dr. Mark W. Pecuzh

University of Connecticut

2012
# Table of Contents

List of Abbreviations ........................................................................................................... vii

List of Instruments .................................................................................................................. ix

List of Publications .................................................................................................................. x

List of Figures ......................................................................................................................... xii

List of Schemes ....................................................................................................................... xxi

List of Tables ......................................................................................................................... xxiii

1. General Introduction ........................................................................................................ 1

1.1. Porphyrins, Chlorins, and Bacteriochlorins ............................................................... 1

1.2. Optical Properties of Porphyrinic Chromophore ......................................................... 3

1.3. Porphyrin Application .................................................................................................... 6

1.3.1. Photodynamic Therapy .............................................................................................. 6

1.4. Synthesis of Porphyrins .................................................................................................. 9

1.5. Synthesis of Chlorins and Bacteriochlorins ............................................................... 11

1.5.1. Total Syntheses of Chlorins ........................................................................................ 11

1.5.2. Total Syntheses of Bacteriochlorins ......................................................................... 15

1.5.3. Syntheses of Pyrrole-Modified Chlorins and Chlorin Analogues ......................... 20

1.5.4. Syntheses of Pyrrole-Modified Bacteriochlorins and Bacteriochlorin Analogues .................. 23

1.6. References ..................................................................................................................... 27
2. **Introduction to Oxazole-Containing Porphyrinoids** ................................................................. 35
   2.1. Nomenclature Conventions ........................................................................................................ 35
   2.2. Porpholactones ........................................................................................................................ 35
   2.3. Rational Syntheses of Porpholactones .................................................................................... 37
   2.4. Reductions of Porpholactones ................................................................................................. 39
   2.5. Optical Properties of Oxazoloporphyrins and -chlorins ...................................................... 40
   2.6. Other Oxazole-Containing Porphyrinoid Macrocycles ....................................................... 42
   2.7. References .................................................................................................................................. 45

3. **Aim of this Thesis** ....................................................................................................................... 48

4. **Diphenylporpholactones** .......................................................................................................... 49
   4.1. Introduction .................................................................................................................................... 49
   4.2. Results and Discussion .............................................................................................................. 49
      4.2.1. Synthesis of 5,15-Diphenylporpholactone ............................................................................ 49
      4.2.2. Optical Properties of 5,15-Diphenylporpholactone ............................................................... 53
   4.3. Conclusion ..................................................................................................................................... 54
   4.4. Experimental Section .................................................................................................................. 54
      4.4.1. Instruments and Materials ..................................................................................................... 54
      4.4.2. Preparation and Characterization .......................................................................................... 54
      4.4.3. X-ray Crystallography Data ................................................................................................. 60
   4.5. References ..................................................................................................................................... 63
5. Oxazolochlorins ................................................................. 64

5.1. Introduction .................................................................. 64
5.2. Results and Discussion .................................................. 64
  5.2.1. –OR, –SR, and –NR Substituted Oxazolochlorins .......... 64
  5.2.2. Alternative Synthesis of –OR/NR₂ Substituted Oxazolochlorins .. 67
    5.2.2.1. Synthesis of –NR₂, and –OR substituted oxazolochlorins from diolchlorins ......................................................... 68
    5.2.2.2. Mechanistic Considerations .................................... 69
5.3. Optical Properties .......................................................... 72
5.4. Crystal structures ........................................................... 73
5.5. Conclusion .................................................................. 74
5.6. Experimental Section ...................................................... 74
  5.6.1. Instruments and Materials ......................................... 74
  5.6.2. Preparation and Characterization .................................. 74
  5.6.3. X-ray Crystallography Data ....................................... 98
5.7. References ................................................................. 101

6. Alkyl-Oxazolochlorins ...................................................... 102

6.1. Introduction ................................................................. 102
6.2. Results and Discussion .................................................. 103
  6.2.1. Synthesis of Alkylloxazolochlorins ............................. 103
  6.2.2. Optical Properties ...................................................... 107
  6.2.3. Crystal Structures of Alkylloxazolochlorins ................. 109
6.3. Conclusions.................................................................................................................. 112

6.4. Experimental Section.................................................................................................. 112
  6.4.1. Instruments and Materials...................................................................................... 112
  6.4.2. Preparation and Characterization........................................................................... 113
  6.4.3. X-ray Crystallography Data.................................................................................. 159

6.5. References.................................................................................................................... 164

7. Oxabacteriochlorins and Dioxabacteriochlorins ......................................................... 165
  7.1. Introduction................................................................................................................ 165
  7.2. Nomenclature Conventions...................................................................................... 166
  7.3. Results and Discussion ............................................................................................ 167
    7.3.1 Synthesis of Oxazolobacteriochlorins................................................................. 167
    7.3.2. Synthesis of Bisoxazolochlorins.......................................................................... 168
    7.3.3. Synthesis of Bisoxazolobacteriochlorins......................................................... 176
    7.3.4. Fluorescence Properties Oxazolochlorins and -bacteriochlorins......................... 181
  7.4. Conclusions................................................................................................................ 182
  7.5. Experimental Section ............................................................................................... 184
    7.5.1. Instruments and Materials................................................................................... 184
    7.5.2. Preparation and Characterization......................................................................... 185
    7.5.3. X-Ray Crystallography Data.............................................................................. 216
  7.6. References.................................................................................................................... 225
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>cat</td>
<td>catalytic</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>$^{13}$C nuclear magnetic resonance</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>conc</td>
<td>concentrated</td>
</tr>
<tr>
<td>CTAP</td>
<td>cetyltrimethylammonium permanganate</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DPP</td>
<td>5,15-diphenylporphyrin</td>
</tr>
<tr>
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<td>electrophilic aromatic substitution</td>
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<td>Hz</td>
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<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
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<tr>
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<td>high-resolution mass spectrometry</td>
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<tr>
<td>IR</td>
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</tr>
<tr>
<td>$\lambda$</td>
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<tr>
<td>LR-MS</td>
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<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
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<tr>
<td>NIR</td>
<td>near Infrared</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>py</td>
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<tr>
<td>TosMIC</td>
<td>toluenesulfonylmethyl isocyanide</td>
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### List of Instruments

<table>
<thead>
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<th>Instrument Type</th>
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<td>UV-visible spectroscopy</td>
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<tr>
<td>Fluorescence spectroscopy</td>
<td><strong>Varian Cary Eclipse</strong></td>
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<td>NMR spectroscopy</td>
<td><strong>Bruker Avance 300 MHz (COSY, NOESY)</strong></td>
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<td><strong>Bruker Avance III 400 MHz (^1\text{H} \text{NMR, } ^{13}\text{C NMR)</strong>}</td>
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<td><strong>Bruker Avance 500 MHz (^{13}\text{C NMR, HMBC)</strong>}</td>
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<td></td>
<td><strong>JEOL AccuTOF LC-Plus</strong></td>
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<tr>
<td>LR-MS</td>
<td><strong>Waters Quattro II</strong></td>
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<tr>
<td>IR-spectroscopy</td>
<td><strong>Thermo Nicolet Nexus 670</strong></td>
</tr>
<tr>
<td>automated chromatography</td>
<td><strong>ISCO Teledyne CombiFlash Rf</strong></td>
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List of Publications

Sections of this thesis have been published, or were submitted, as follows:


  Contributions of J.O.: Synthesis of meso-diphenylporpholactone; functionalization of meso-tetraphenyldihydroxychlorins


  Contributions: J.L.W.¹, synthesis of PEG-substituted oxazolochlorins; Y.-J. F.², mass spectrometry experiments


  Contributions: E.M.3, Synthesis of dialkyl oxazolochlorin; J.T.E.4 & C.Z.J.5, X-ray crystallography


  Contributions: E.M.3 Synthesis of dialkyl oxabacteriochlorin; J.T.E.4 & C.Z.J.5, X-ray crystallography

1: Ph.D. Candidate, Department of Chemistry, University of Connecticut
2: Mass Spectrometry Specialist, Department of Chemistry, University of Connecticut
3: Undergraduate Student (under the tutelage of JO), University of Connecticut
4: Graduate Student, Department of Chemistry, University of Akron
5: Professor, Department of Chemistry University of Akron
List of Figures

Figure 1-1. Macrocycle structure, position numbering, and naming system used in porphyrins, chlorins, bacteriochlorins, and isobacteriochlorins. ......................... 1

Figure 1-2. Examples of porphyrins, chlorins and bacteriochlorins in nature. ................. 3

Figure 1-3. Comparison of the UV-visible spectra of the four principle porphyrin and hydroporphyrin classes, in their free-base form and metalated form ......................... 4

Figure 1-4. Idealized relative position of the chromophore frontier orbitals ..................... 5

Figure 1-5. Process of photodynamic therapy ..................................................................... 7

Figure 1-6. The wavelength dependence of depth of penetration of light into a tissue ....... 7

Figure 1-7. Modified Jablonski diagram for a typical photosensitizer. ......................... 9

Figure 1-8. Examples of bacteriochlorins bearing quaternized ammonium groups ...... 19

Figure 2-1. Normalized UV-visible and fluorescence spectra of the compounds drawn (all in CH₂Cl₂ at ambient temperature) ................................................................. 41

Figure 4-1. Single crystal X-ray structures of 1-Zn and 4-II-Zn ..................................... 52

Figure 4-2. Normalized UV-vis absorption spectra comparison of 1-Zn and
4-II-Zn free-base and zinc complexes ........................................................................ 53

Figure 4-3. ¹H NMR (400 MHz, CDCl₃) of a mixture of the two regio-isomers of
5,15-diphenylporpholactones, 4-I and 4-II..................................................................... 56

Figure 4-4. ¹H NMR (300 MHz, CDCl₃) of 4-II. Assignment of proton signals as shown, and based on the 2D spectra shown below ......................................................... 56

Figure 4-5. ¹³C NMR (100 MHz, CDCl₃) of 4-II .............................................................. 57

Figure 4-6. NOESY Spectrum (300 MHz, CDCl₃) of 4-II ................................................ 57
Figure 4-7. FT-IR spectrum (neat, diffuse reflectance) of 4-II ........................................58

Figure 4-8. $^1$H NMR (300 MHz, CDCl$_3$) of 4-II-Zn. .........................................................59

Figure 4-9. FT-IR spectrum (neat, diffuse reflectance) of 4-II-Zn. ........................................59

Figure 4-10. ORTEP representation and numbering scheme used in the crystal
structure of 4-II-Zn·py. Minor disordered moieties are omitted for clarity.............61

Figure 5-1. Normalized UV-vis spectra comparison of –OR, -SR and –NR$_2$
derivatives .............................................................................................................................73

Figure 5-2. Single crystal X-ray structures of 4a-OMe .........................................................73

Figure 5-3. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-O$^1$Pr ...............................................75

Figure 5-4. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-O$^6$Hex .........................................76

Figure 5-5. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O$^6$Hex .........................................77

Figure 5-6. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-O$^1$Bu ............................................78

Figure 5-7. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O$^1$Bu ............................................78

Figure 5-8. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-O$^8$Oct ........................................79

Figure 5-9. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O$^8$Oct ........................................80

Figure 5-10. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4a-OChol ........................................81

Figure 5-11. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-OChol ........................................82

Figure 5-12. FT-IR spectrum (neat, diffuse reflectance) of 4a-OChol ........................................82

Figure 5-13. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4a-OPreg ..........................................83

Figure 5-14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-OPreg ..........................................84

Figure 5-15. FT-IR spectrum (neat, diffuse reflectance) of 4a-OPreg .......................................84

Figure 5-16. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-N$^\text{morph}$ ..................................86
Figure 5-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-N$^{\text{morph}}$ ................................................................. 86

Figure 5-18. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-N(Bn)$_2$ ................................................................. 87

Figure 5-19. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-SEt ................................................................. 89

Figure 5-20. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-SEt ................................................................. 89

Figure 5-21. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-S$^n$Hex ................................................................. 90

Figure 5-22. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4b-OEt ................................................................. 92

Figure 5-23. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4b-OEt ................................................................. 93

Figure 5-24. UV-vis spectrum (CH$_2$Cl$_2$) of 4b-OEt ................................................................. 93

Figure 5-25. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4c-OEt ................................................................. 94

Figure 5-26. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4c-OEt ................................................................. 95

Figure 5-27. UV-vis spectrum (CH$_2$Cl$_2$) of 4c-OEt ................................................................. 95

Figure 5-28. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4c-OMe ................................................................. 96

Figure 5-29. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4c-OMe ................................................................. 97

Figure 5-30. UV-vis spectrum (CH$_2$Cl$_2$) of 4c-OMe ................................................................. 97

Figure 5-31. ORTEP representation and numbering scheme of the crystal structure of 4a-OMe ................................................................. 99

Figure 6-1. UV-visible spectra of porpholactol, $\alpha$-i-propyl lactol 2c, $\alpha$-i-propyl oxazolochlorin 3c, and $\alpha,\alpha'$-bis-i-propyl oxazolochlorin 4c ................................................................. 108

Figure 6-2. Fluorescence spectra of porpholactol, $\alpha$-i-propyl lactol 2c, $\alpha$-i-propyl oxazolochlorin 3c, and $\alpha,\alpha'$-bis-i-propyl oxazolochlorin 4c ................................................................. 109

Figure 6-3. Single crystal X-ray structures of 2c, 4c, and 5cZn ................................................................. 110

Figure 6-4. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2a ................................................................. 114
Figure 6-5. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2a .................................................. 115

Figure 6-6. UV-vis and fluorescence spectra of 2a (CHCl$_3$) .................................................. 115

Figure 6-7. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2b .................................................. 117

Figure 6-8. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2b .................................................. 117

Figure 6-9. UV-vis and fluorescence spectra of 2b (CHCl$_3$) .................................................. 118

Figure 6-10. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2c .................................................. 119

Figure 6-11. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2c .................................................. 119

Figure 6-12. UV-vis and fluorescence spectra of 2c (CHCl$_3$) .................................................. 120

Figure 6-13. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2Fb .................................................. 121

Figure 6-14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2Fb .................................................. 122

Figure 6-15. UV-vis and fluorescence spectra of 2Fb (CHCl$_3$) .................................................. 122

Figure 6-16. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2Fc .................................................. 124

Figure 6-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2Fc .................................................. 124

Figure 6-18. UV-vis and fluorescence spectra of 2Fc (CHCl$_3$) .................................................. 125

Figure 6-19. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3a .................................................. 127

Figure 6-20. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3a .................................................. 127

Figure 6-21. UV-vis and fluorescence spectra of 3a (CHCl$_3$) .................................................. 128

Figure 6-22. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3b .................................................. 129

Figure 6-23. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3b .................................................. 130

Figure 6-24. UV-vis and fluorescence spectra of 3b (CHCl$_3$) .................................................. 130

Figure 6-25. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3c .................................................. 132

Figure 6-26. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3c .................................................. 132
Figure 6-27. UV-vis and fluorescence spectra of 3c (CHCl₃) ............................................. 133

Figure 6-28. ¹H NMR spectrum (400 MHz, CDCl₃) of 3⁴b .................................................. 134

Figure 6-29. ¹³C NMR spectrum (100 MHz, CDCl₃) of 3⁴b .................................................. 135

Figure 6-30. UV-vis and fluorescence spectra of 3⁴b (CHCl₃) ........................................... 135

Figure 6-31. ¹H NMR spectrum (400 MHz, CDCl₃) of 3c .................................................. 137

Figure 6-32. ¹³C NMR spectrum (100 MHz, CDCl₃) of 3c .................................................. 137

Figure 6-33. UV-vis and fluorescence spectra of 3⁴c (CHCl₃) ........................................... 138

Figure 6-34. ¹H NMR spectrum (400 MHz, CDCl₃) of 4a .................................................. 140

Figure 6-35. UV-vis and fluorescence spectra of 4a (CHCl₃) ............................................. 140

Figure 6-36. ¹H NMR spectrum (400 MHz, CDCl₃) of 4b .................................................. 142

Figure 6-37. ¹³C NMR spectrum (100 MHz, CDCl₃) of 4b .................................................. 142

Figure 6-38. UV-vis and fluorescence spectra of 4b (CHCl₃) ............................................. 143

Figure 6-39. ¹H NMR spectrum (400 MHz, CDCl₃) of 4c .................................................. 144

Figure 6-40. ¹³C NMR spectrum (100 MHz, CDCl₃) of 4c .................................................. 145

Figure 6-41. UV-vis and fluorescence spectra of 4c (CHCl₃) ............................................. 145

Figure 6-42. ¹H NMR spectrum (400 MHz, CDCl₃) of 4⁴b .................................................. 147

Figure 6-43. ¹³C NMR spectrum (100 MHz, CDCl₃) of 4⁴b .................................................. 147

Figure 6-44. UV-vis and fluorescence spectra of 4⁴b (CHCl₃) ........................................... 148

Figure 6-45. ¹H NMR spectrum (400 MHz, CDCl₃) of 4⁴c .................................................. 149

Figure 6-46. ¹³C NMR spectrum (100 MHz, CDCl₃) of 4⁴c .................................................. 150

Figure 6-47. UV-vis and fluorescence spectra of 4⁴c (CHCl₃) ........................................... 150

Figure 6-48. ¹H NMR spectrum (400 MHz, CDCl₃) of 5c .................................................. 152
Figure 6-49. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5c .............................................. 153

Figure 6-50. UV-vis and fluorescence spectra of 5c (CHCl$_3$) ............................................. 153

Figure 6-51. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5F ................................................. 155

Figure 6-52. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5F ............................................. 155

Figure 6-53. UV-vis and fluorescence spectra of 5F (CHCl$_3$) .............................................. 156

Figure 6-54. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5Zn ............................................. 157

Figure 6-55. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5Zn ............................................. 158

Figure 6-56. UV-vis and fluorescence spectra of 5Zn (CHCl$_3$) ........................................... 158

Figure 6-57. ORTEP representation of the single crystal X-ray structures of 2c .......... 160

Figure 6-58. ORTEP representation of the single crystal X-ray structures of 4c .......... 161

Figure 6-59. ORTEP representation of the single crystal X-ray structures of 5Zn .... 162

Figure 7-1. Nomenclature conventions for the regio- and stereo-isomeric
bisoxazolo- chromophores. .................................................................................................. 166

Figure 7-2. Stick representation of the molecular structures of (A) 3-cis, (B) 6-
cis, and (C) 6Zn-cis (top and side views) ................................................................. 169

Figure 7-3. (top) full and (bottom) $\lambda_{\text{max}}$ normalized UV-vis spectra of chlorins 1
(grey), 4 (purple), 3 (of -cis, blue), 6 (of -cis, lime-green), 8 (of -cis, light-
blue), 9 (of -cis, red) in CH$_2$Cl$_2$ at ambient temperature. ....................................... 174

Figure 7-4. Stick representation of the molecular structures of (A) 14-trans-E and
(B) 14-trans-Z, and (C) 13-cis (top and side views). ..................................................... 178

Figure 7-5. UV-vis spectra of 2 (red), 5 (light-blue), 14 (mixture of all isomers,
blue), 13 (cis/trans mixture, lime-green) in CH$_2$Cl$_2$ at ambient temperature. ....... 179
Figure 7-6. UV-vis spectra comparison (normalized at $\lambda_{soret}$) of the starting material 3 (red) and 15 (blue) in CH$_2$Cl$_2$ at ambient temperature.

Figure 7-7. Normalized fluorescence spectra of 2 (grey), 3 (lime-green), 5 (purple), 6 (light-blue) 8 (red) and 9 (blue) (all in CH$_2$Cl$_2$ at ambient temperature $\lambda_{excitation} = \lambda_{soret}$).

Figure 7-8. Oxazole-based chromophores sorted according to chromophore class and plot of their $\lambda_{max}$ band (spectrum of porpholactone is not shown).

Figure 7-9. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2.

Figure 7-10. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2.

Figure 7-11. UV-vis and fluorescence spectra of 2 (CH$_2$Cl$_2$).

Figure 7-12. FT-IR spectrum (neat, diffuse reflectance) of 2.

Figure 7-13. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5.

Figure 7-14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5.

Figure 7-15. UV-vis and fluorescence spectra of 5 (CH$_2$Cl$_2$).

Figure 7-16. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 7.

Figure 7-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 7.

Figure 7-18. UV-vis and fluorescence spectra of 7 (CHCl$_3$).

Figure 7-19. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3-cis.

Figure 7-20. $^{13}$H NMR spectrum (100 MHz, CDCl$_3$) of 3-cis.

Figure 7-21. UV-vis and fluorescence spectra of 3-cis (CH$_2$Cl$_2$).

Figure 7-22. FT-IR spectrum (neat, diffuse reflectance) of 3-cis.

Figure 7-23. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 6-cis.
Figure 7-24. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 6-cis. ........................................... 197

Figure 7-25. UV-vis and fluorescence spectra of 6-cis (CH$_2$Cl$_2$) ........................................ 198

Figure 7-26. FT-IR spectrum (neat, diffuse reflectance) of 6-cis. ........................................... 198

Figure 7-27. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 6Zn-cis. ........................................ 200

Figure 7-28. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 6Zn-cis. ........................................ 200

Figure 7-29. UV-vis and fluorescence spectra of 6Zn-cis (CH$_2$Cl$_2$). ................................... 201

Figure 7-30. FT-IR spectrum (neat, diffuse reflectance) of 6Zn-cis. ........................................ 201

Figure 7-31. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 8-cis. ............................................. 203

Figure 7-32. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 8-cis. ............................................. 203

Figure 7-33. UV-vis and fluorescence spectra of 8-cis (CH$_2$Cl$_2$). ....................................... 204

Figure 7-34. FT-IR spectrum (neat, diffuse reflectance) of 8-cis. ............................................. 204

Figure 7-35. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 9-cis. ............................................. 206

Figure 7-36. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 9-cis. ............................................. 206

Figure 7-37. UV-vis and fluorescence spectra of 9-cis (CH$_2$Cl$_2$). ....................................... 207

Figure 7-38. FT-IR spectrum (neat, diffuse reflectance) of 9-cis. ............................................. 207

Figure 7-39. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 14 (mixture of all isomers). .... 209

Figure 7-40. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 14 (mixture of all isomers). .... 210

Figure 7-41. UV-vis spectrum of 14 (CH$_2$Cl$_2$, mixture of all isomers). ......................... 210

Figure 7-42. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 13-cis/trans (mixture, 3:2). .... 212

Figure 7-43. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 13-cis/trans (mixture, 3:2). .... 212

Figure 7-44. UV-vis spectrum of 13-cis/trans (CH$_2$Cl$_2$, mixture, 3:2)............................. 213

Figure 7-45. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 15............................................. 215
Figure 7-46. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of $^{15}$.

Figure 7-47. UV-vis spectrum of $^{15}$ (CH$_2$Cl$_2$).

Figure 7-48. ORTEP Representation of the crystal structure of 3-cis.

Figure 7-49. ORTEP Representation of the crystal structure of 6-cis.

Figure 7-50. ORTEP Representation of the crystal structure of 6Zn-cis.

Figure 7-51. ORTEP Representation of the crystal structure of 14-trans-E.

Figure 7-52. ORTEP Representation of the crystal structure of 14-trans-Z.

Figure 7-53. ORTEP Representation of the crystal structure of 13-cis.
List of Schemes

Scheme 1-1. Adler-type synthesis of meso-tetraarylporphyrin 6. ...........................................10

Scheme 1-2. Retrosynthetic analyses for the total syntheses of chlorins and bacteriochlorins. .................................................................12

Scheme 1-3. Lindsey’s total synthesis of chlorins. ..............................................................13

Scheme 1-4. Two complementary approaches towards chlorin functionalizations. ..........14

Scheme 1-5. 5-annulated chlorin (phorbine) 22 synthesis. .................................................15

Scheme 1-6. Synthesis of bacteriochlorins and tetrahydrocorrin........................................16

Scheme 1-7. Pd-catalyzed modification of bacteriochlorins...............................................18

Scheme 1-8. Synthesis of bacteriopheophorbide.................................................................19

Scheme 1-9. Synthesis of bacteriochlorindicarboxylimides.............................................20

Scheme 1-10. Bacteriochlorins via reduction of β,β’-double bonds. ..........................21

Scheme 1-11. Chlorin-analogue synthesis via the “Breaking and Mending” approach....23

Scheme 1-12. Bacteriochlorin via OsO4⁻-mediated dihydroxylation of porphyrins. .....24

Scheme 1-13. Expanded bacteriochlorins syntheses. ....................................................25

Scheme 1-14. Bacteriochlorins via 1,3-dipolar cycloaddition and Diels-Alder reaction.26

Scheme 2-1. Literature-known syntheses of porpholactone 5...........................................36

Scheme 2-2. Synthesis of porpholactones 5 by oxidation of 2,3-dihydroxychlorins 7 ......37

Scheme 2-3. Reduction of Porpholactone 5........................................................................40

Scheme 2-4. Synthesis of 2,2-dimethyl-3-oxa-tri(1,2-benzo)tetraazachlorin (15).........43

Scheme 2-5. Synthesis of 2-oxa-21-carbaporphyrin 16, 2-oxa-3-ethoxy-21-carbachlorin 18, and 2-oxa-3-oxo-21-carbaporphyrin 19.........................................................43
Scheme 2-6. Synthesis of alkylloxazolochlorin by the group of Gurinovich via ozonolysis of octaethylporphyrin ................................................................. 44

Scheme 4-1. Synthesis of 5,15-diphenylporpholactone 4 I/II and its zinc complex

4-II-Zn .................................................................................................................. 50

Scheme 5-1. O-, N-, and S-substitution of porpholactol 4 ........................................ 65

Scheme 5-2. Step-wise synthesis of oxazolochlorins 4-OR/NR2/SR ............................. 67

Scheme 5-3. Direct synthesis of –NR2, and –OR substituted oxazolochlorins 4OR/NR2

............................................................................................................................. 69

Scheme 5-4. First example of a reaction that suggests that the oxidation of hydroxy-substituted morpholinochromeins leads to a formation of oxazolochromein. .................. 70

Scheme 5-5. Second example of a reaction that suggests that the oxidation of hydroxy-substituted morpholinochromeins leads to a formation of oxazolochromein. ............... 71

Scheme 6-1. Inadvertent oxidations at the α-carbon of oxazolochromein. .................. 102

Scheme 6-2. Synthesis of mono- and bis-alkyloxazolochromeins by alkyl-Grignard

addition to porpholactones 1 .................................................................................. 104

Scheme 6-3. Ketalization and alternative pathway towards bis-alkyloxazolochromeins ... 106

Scheme 7-1. Syntheses of oxazolobacteriochromein 2 and bisoxazolochromeins 3 ...... 168

Scheme 7-2. Syntheses of alkylbisoxazolochromeins 6, 6Zn, 7, 8 and 9 ....................... 171

Scheme 7-3. Failed routes towards dioxazolobacteriochromeins 21 ............................ 175

Scheme 7-4. Syntheses of bis-alkylbisoxazolobacteriochromeins 13 .......................... 176

Scheme 7-5. Syntheses of mono-alkylbisoxazolobacteriochromein isomers 14 ........... 177

Scheme 7-6. Synthesis of bis-alkylbisoxazolobacteriochromeins 15 ........................... 180
List of Tables

**Table 4-1.** Crystallographic and structure refinement data for 4-II-Zn·py. ................. 62

**Table 5-1.** Crystallographic and structure refinement data for 4a-OMe ......................... 100

**Table 6-1.** Crystallographic and structure refinement data for 2c, 4c and 5cZn. ............ 163

**Table 7-1.** Crystallographic and structure refinement data for 3-cis, 1-cis and 6-cis-Zn. .......................................................................................................................... 223

**Table 7-2.** Crystallographic and structure refinement data for 14-trans-E, 14-trans-Z and 13-cis. ..................................................................................................................... 224
1. General Introduction

1.1. Porphyrins, Chlorins, and Bacteriochlorins

Porphyrins are fully unsaturated macrocycles composed of four pyrrolic subunits linked by four methylene carbons. The chemical and physical properties of porphyrins are mainly determined by the presence of a closed conjugated aromatic $18\pi$ system that is cross-conjugated to two $\beta,\beta’$-double bonds. These cross-conjugated double bonds can be successively reduced—and thereby removed from macrocycle conjugation, resulting in the formation of a chlorin (one bond reduced), a bacteriochlorin (both bonds on opposite pyrroles reduced), or its isomer, an isobacteriochlorin (both bonds reduced on adjacent pyrroles) (Figure 1-1).

![Figure 1-1](image_url)  
**Figure 1-1.** Macrocycle structure, position numbering, and naming system used in porphyrins, chlorins, bacteriochlorins, and isobacteriochlorins. The macrocycle-aromatic $18\pi$ system inherent to all is shown in bold.
The ‘reduction’ of the bond can also be an oxidation or addition reaction, as long as at least one of the β-carbons is converted into an sp$^3$-carbon in the process. All reduced macrocycles still maintain a central 18 π system. The reductions result in a number of changes in their chemical and physical properties. Most profoundly, the UV-visible spectra of the chromophores change in a diagnostic fashion (for a more detailed discussion, see Section 1.2). Moreover, increasing reduction leads to increasing conformational flexibility of the macrocycle. This also affects their electronic structure as, in general, the spectra of porphyrinoids are broadened upon increase of conformational flexibility and red-shifted with increasing deviation from planarity.$^{1,2}$ Also, increasing reduction decreases significantly the basicity of the inner imine-type nitrogens. Thus, bacteriochlorins are less basic than chlorins that, in turn, are less basic than porphyrins.$^3$

In nature, porphyrins, chlorins and bacteriochlorins fulfill crucial roles in the metabolic network of all organisms. For example, heme, the iron complex of porphyrin, plays a vital role in nearly all vertebrates and some invertebrates, as it is responsible for oxygen transport through red blood cell.$^4$ Chlorophyll, a magnesium chlorin complex, is essential for photosynthesis in all plants. Similarly, bacteriochlorophyll $a$, a naturally occurring bacteriochlorin magnesium complex, is the photosynthetic pigments of photoautotrophic purple bacteria and cyanobacteria. Other examples of essential porphyrin natural products include cofactor F430, bacteriochlorophyll, and siroheme.$^4$
1.2. Optical Properties of Porphyrinic Chromophore

The optical properties of porphyrins and hydroporphyrins are illustrated in Figure 1-3. The spectra of regular porphyrins are well defined: A Soret band is followed by four Q bands in descending order of intensity. Owing to an increase of the chromophore symmetry (from two-fold symmetry to four-fold symmetry), metalation cuts the number of Q bands in half, and the longest wavelengths absorption band ($\lambda_{\text{max}}$) is now hypsochromically shifted compared to the free-base. A free-base chlorin also exhibits the Soret band and four side bands, but the $\lambda_{\text{max}}$ band is now the most intense Q-band. The bands are also broadened, reflecting the larger conformational flexibility of this chromophore. Depending on the particular chlorin, $\lambda_{\text{max}}$ may or may not be bathochromically shifted compared to the parent porphyrin. Insertion of a metal has the same principal effects on a chlorin as it has on a porphyrin (but the $\lambda_{\text{max}}$ band remains the most intense band). Metalation also rigidifies the chromophore, as seen in the sharpened optical spectrum. The Soret band of an isobacteriochlorin is hypsochromically shifted compared...
to that of a chlorin, the spectrum is chlorin-like broadened, but with a changed Q-band intensity distribution, and a hypsochromically shifted $\lambda_{\text{max}}$. The metalloisobacteriochlorin spectrum is a slightly hypsochromically shifted metallochlorin-like spectrum. The spectrum of free-base bacteriochlorin stands out for its diagnostic three-band shape, a hypsochromically shifted Soret band, and significantly bathochromically shifted $\lambda_{\text{max}}$ that possess an intensity of a similar magnitude as the Soret band (even though, in absolute terms, the extinction coefficient of the Soret band of a bacteriochlorin can be an order of magnitude lower than that of a porphyrin or chlorin).

![Figure 1-3. Comparison of the UV-visible spectra of the four principle porphyrin and hydroporphyrin classes, in their free-base form (solid trace) and metalated form (M = Zn; broken trace)](image)
The trends observed in the optical spectra of the porphyrins and their derivatives find their qualitative explanation in the relative position of the frontier orbitals of the chromophores. The longest wavelengths band ($\lambda_{\text{max}}$) in the UV-visible of a porphyrin corresponds to a HOMO$\rightarrow$LUMO transition (Figure 1-4).

Upon reduction of a porphyrin to a chlorin, the $a_{1u}$ is elevated and the relative order of the HOMO ($a_{1u}$) and the HOMO-1 ($a_{2u}$) become inverted relative to their order in porphyrins. The narrowed HOMO-LUMO gap results in a minor bathochromic shift of $\lambda_{\text{max}}$ for chlorins. The increased intensity of the chlorin $\lambda_{\text{max}}$ band is because the HOMO-LUMO transition has become more symmetry-allowed. In the isobacteriochlorin case, both the HOMO and LUMO are lifted by about the same amount, thus the $\lambda_{\text{max}}$ of

Figure 1-4. Idealized relative position of the chromophore frontier orbitals. For sake of simplification, the Zn-complexes of higher symmetry, as compared to the free-bases, are shown. Adopted from Ref. 6.
isobacteriochlorins are very similar to those of chlorins. On the other hand, the HOMO is lifted and the LUMO is slightly lowered in bacteriochlorins relative to porphyrins and chlorins. Thus, the HOMO-LUMO gap in bacteriochlorins is the smallest, translating into the longest wavelengths $\lambda_{\text{max}}$ among all four chromophores. The degeneracy of LUMO and LUMO+1 remains to be lifted, the HOMO-LUMO transition remains being symmetry-allowed and is thus correspondingly intense.

1.3. Porphyrin Application

Synthetic porphyrins and their analogues have demonstrated their value by contributing to a wide range of scientific fields such as material science (partial oxygen pressure-sensitive dyes), analytical science (high pH sensing) and environmental science (artificial light harvesting system). In biomedicine, porphyrins have shown promises as photosensitizers in photodynamic therapy (PDT) for cancer.

1.3.1. Photodynamic Therapy

Photodynamic therapy (PDT) is a non-invasive medical procedure in which a combination of light and drugs (photosensitizers) is used to remove cancerous or otherwise unwanted tissues. The process of PDT is depicted in Figure 1-5. First, a photosensitizer of negligible dark toxicity is injected systemically (A). When the preferential accumulation of the photosensitizer in tumor cells reaches the optimal level (B), the light is shone onto the target tissue for the drug activation (C). The activated
drug, through a series of photophysical processes, converts the molecular oxygen in cells to cytotoxic singlet oxygens, which eventually induces apoptosis in targeted areas (D).\textsuperscript{14}

**Figure 1-5.** Process of photodynamic therapy

The ideal PDT drug will exhibit no significant biological activity until it is activated by light. Light of longer wavelength penetrates deeper through tissues; however, at certain wavelengths, light penetration through tissues is limited due to light scattering and absorption by endogenous chromophores, mainly hemoglobin (Figure 1-6).\textsuperscript{15}

**Figure 1-6.** The wavelength dependence of depth of penetration of light into a tissue, adopted from Ref. 14
An efficient generation of singlet oxygen species is extremely crucial for the success of PDT. For this reason, ideal PDT drug is one in which can be activated at wavelength in the red or near-IR region.\textsuperscript{13}

A modified Jablonski diagram (Figure 1-7) outlines the underlying photophysical processes involved in PDT.\textsuperscript{13} Absorption of light by the photosensitizer excites the molecule to the excited states (route 1). The excited species can relax back to the ground states via fluorescence (route 2) or non-radiatively through internal conversion (route 3). Alternatively, the excited photosensitizer can partake in a non-radiative inter-system crossing (ISC, route 4) to the triplet state. Although this is a “forbidden” process and is less likely than an “allowed” process, porphyrins have a unique ability to undergo this ISC pathway with high efficiency. From the triplet state, a molecule has at least two pathways towards relaxation: radiatively via phosphorescence (route 5) and through non-radiative spin exchange with another triplet state species (i.e. molecular oxygen, route 6). This spin exchange interaction is arguably the most important step for the success of PDT. The resulting singlet oxygen is an extremely reactive species with a lifetime (in water) of \(~4\ \mu s\), it initiates a number of reactions with biological substrates. For example, oxidation of cholesterol or cycloaddition with tryptophan and guanine are all quite disruptive to the biological processes.\textsuperscript{16}
1.4. Synthesis of Porphyrins

There are a number of ways to obtain porphyrinoids (and their derivatives). Notable methods include extraction from natural sources (i.e. blood, chloroplast), semi-synthesis, and total synthesis. This thesis only focuses on the last approach, the total synthesis and manipulation of entirely synthetic porphyrin analogues. Unless mentioned otherwise, all of the syntheses described herein are based on meso-tetraphenylporphyrins (TPP).

*meso*-Tetraarylporphyrins are a synthetic class of porphyrins with no biological counterparts. The simplicity of their syntheses, however, makes them an excellent class of model compound for a wide range of porphyrin applications. The popularity of *meso*-tetraarylporphyrins also arises from their susceptibility towards a wide range of chemical modulations.

Figure 1-7. Modified Jablonski diagram for a typical photosensitizer. Adopted from Ref 13
The one-step, one-pot tetraarylporphyrin synthesis was first developed by Rothemund.\textsuperscript{17,18} In the mid-1960s, Adler and co-workers reported the acid-catalyzed modification of this reaction (Scheme 1-1).\textsuperscript{19} Several modifications of this synthesis have been reported in recent years.\textsuperscript{20} Most notably, the two-step, one-flask version, known as the Lindsey method, has been employed extensively for the syntheses of various meso-tetraarylporphyrins using a number of arylaldehydes.\textsuperscript{20,21}

\textbf{Scheme 1-1. Adler-type synthesis of meso-tetraarylporphyrin 6}

The mechanism of Adler’s tetraarylporphyrin synthesis is straightforward. An acid-catalyzed electrophilic aromatic substitution (EAS) reaction between a pyrrole and a benzaldehyde forms benzyl alcohol 1. Compound 1 is susceptible to a second EAS with another pyrrole, forming phenylidipyrromethane 2. This sequence of reactions continues on until a ring closure provides tetrpyrrolic porphyrinogen 5. Compound 5 is then rapidly oxidized \textit{in situ} until it becomes fully unsaturated, aromatic porphyrin 6, which generally crystallize out from the solution. While this reaction is low in absolute yield (~20%), it has a number of advantages: 1) simplicity and swiftness; 2) ease of
purification as it requires no chromatography; 3) its scalability for the preparation of up to ~25 grams per reaction (for TPP, it requires a 5L flask).

1.5. Synthesis of Chlorins and Bacteriochlorins

The syntheses of chlorins and bacteriochlorins are not as simple as porphyrins. There are four principal pathways to access chlorins and bacteriochlorins: firstly, they can be extracted from natural sources. Secondly, they can be made by semi-synthetic approaches. For example, the modification of chlorins and bacteriochlorins extracted from biological materials. Thirdly, a total synthesis which we consider only a synthesis that involves a porphyrinoid ring-closing step that directly results in the formation of a chlorin (Section 1.5.1) and/or bacteriochlorins (Section 1.5.2). Lastly, a synthesis in which pre-formed synthetic porphyrins are converted to chlorins (Section 1.5.3) and/or bacteriochlorins (Section 1.5.4). Hereon, we will refer to this last pathway as the pyrrole-modified approach.

1.5.1. Total Syntheses of Chlorins

The most significant progress in the total synthesis of chlorins and bacteriochlorins since the work by Woodward, Eschenmoser, or Battersby was presented in a series of publications beginning in 2000 by Lindsey and co-workers. The syntheses are based on the retrosynthetic analysis that a chlorin can be made in a [2+2] approach (Scheme 1-2) by fusion of a dipyrrromethane with a $gem$-dimethylidihydrodipyrrin. Utilizing complementary functionalities, a dipyrrromethane and a $gem$-dimethylidihydro-
dipyrrin can be ring-closed in a regioselective fashion to form, after an oxidation step, a chlorin.\textsuperscript{37-40}

Syntheses that followed this generalized scheme are characterized by several advantages: They gave access to asymmetric chlorins without any type of \(\beta,\beta'\)-double bond reduction step; they enabled the incorporation of inherent oxidation-protection by introducing the \textit{gem}-dimethyl moiety at the pyrroline \(\beta\)-position; the syntheses allowed the preparation of chlorins with unsubstituted \(\beta\)- and \textit{meso}-positions that could be modified in later steps. These advantages also translate to the related bacteriochlorin syntheses (see Section 1.5.2).

\textbf{Scheme 1-2.} Retrosynthetic analyses for the total syntheses of chlorins and bacteriochlorins

Synthesis of chlorins typically began from the functionalization of 5-aryl-dipyrrine 7.\textsuperscript{30} For instance, simple formylation (\(\text{Ar}_1 = \text{H}\)) was done under standard Vilsmeier-Haak
condition while the installment of aryl ketone (Ar₁ = p-tolyl) was done by treating 7 with 3 mol equiv. of EtMgBr followed by a reaction with pyridyl-methylbenzothioate at -78°C. The resulting carbonyl 8 (of both Ar₁ = H or p-tolyl) were subjected to further modulation, for instance regioselective NBS bromination, to complete the “eastern-half” 9 of the chlorin. A fusion of 9 with the “western half” 10 under acidic condition (TFA or TsOH·H₂O) results in, formation of free-base chlorins 11.

Scheme 1-3. Lindsey’s total synthesis of chlorins

In addition to the various functionalization of dipyrrolic fragments, Lindsey and co-workers demonstrated that the functionalization, typically transition-metal mediated coupling reactions, could also take place after the tetrapyrrolic macrocycle formation. Depicted in Scheme 1-4 are two complementary functionalization approaches. In the post-cyclization approach, regioselective NBS-bromination of 12 takes place to give 5-bromochlorin 13. A Pd-mediated coupling then introduces a new
substituent (i.e. phenyl in 14). On the other hand, a ring-fusion between two bromine-containing dipyrine halves (15 and 16) in the pre-cyclization approach directly provides dibromochlorin 17. The two bromo-groups of 17 could then undergo Pd-mediated coupling, introducing two new functional groups simultaneously (i.e. alkyne in 18).

![Scheme 1-4. Two complementary approaches towards chlorin functionalizations](image)

The two approaches mentioned above can be used sequentially for the annulation of chlorins, enabling a formation of a macrocycle known as phorbine. For example, monobromochlorin 19, made by modified pre-cyclization approach, is first acetylated via Stille coupling to provide 20. Then the selective NBS bromination, the post-cyclization modulation, takes place to provide 5-bromochlorin 21. Finally, the second palladium coupling completes the exocyclic fusion to provide phorbine 22.
1.5.2. Total Syntheses of Bacteriochlorins

Bacteriochlorins, particularly the two-fold symmetric bacteriochlorin shown (Scheme 1-2), can be made by a head-to-tail fusion of two identical *gem*-dimethyl-dihydodipyrrin building blocks. Even though this approach requires a multi-step synthesis of the dihydodipyrrin building block, it is attractive in several respects: self-condensation of a self-complementary dihydodipyrrin requires only one dipyrrolic intermediate, thus significantly reducing the number of synthetic steps; it introduces two pyrroline moieties simultaneously, furnishing a bacteriochlorin chromophore in a single step without the need for further redox steps; it enables access to bacteriochlorins carrying few β- or meso-substituents, allowing broad post-synthetic functionalization but also allowing direct access to broadly derivatized bacteriochlorins by use of appropriately substituted pyrroles (that form the dihydodipyrrin); the *gem*-dimethyl moieties provide oxidation protection in the bacteriochlorins; lastly, the synthesis of the starting materials
is scalable and the bacteriochlorin-forming reactions allow, arguably for the first time, access to significant (mmol range) quantities of synthetic regio- and stereo-chemically pure bacteriochlorins.

The bacteriochlorin macrocycle is formed by acid-catalyzed head-to-tail self-condensation of two dihydrodipyrin dimethyl acetals 23 (Scheme 1-6). In general, the reaction conditions resembled those of previous chlorin chemistry;\textsuperscript{35,36} the dihydrodipyrin-acetals were stirred in moderately polar solvents at room temperature in the presence of an acid catalyst. Since the building blocks provide all framework atoms in their proper oxidation states, no oxidation step is required.\textsuperscript{25,34}

![Scheme 1-6. Synthesis of bacteriochlorins and tetrahydrocorrin](image)

\[ \text{Scheme 1-6. Synthesis of bacteriochlorins and tetrahydrocorrin} \]
Chapter 1: General Introduction

The reaction produces three major products: The desired 5-methoxybacteriochlorin 24, bacteriochlorin 25, and tetradehydrocorrin 26. The yields and product distributions vary widely and appear to be dependent on the combination of particular β-substituents and catalyst that were used.\textsuperscript{25,34} The cyclization reaction is also subject to a considerable amount of steric effects.

Addition of functionalities onto porphyrins using transition metal-mediated coupling reactions has become standard methodology.\textsuperscript{43-47} Accordingly, meso- and β-brominated bacteriochlorins of type 27 and 29 are also susceptible to a number of reactions (Scheme 1-7). A variety of functionalities have been introduced at the 15-position of 15-bromobacteriochlorin 27 using palladium-mediated coupling reactions: Mono- and di-substituted aryl groups were added using Suzuki protocols, while Sonogashira and Buchwald-Hartwig protocols were employed for the introduction of alkyl and amide functionalities, respectively.\textsuperscript{32} Functionality such as tethers to attach bacteriochlorins to a surface (for photophysical studies) were also introduced.\textsuperscript{31}

Similarly, β-bromobacteriochlorins such as 29 can also go through a variety of standard Pd-mediated coupling reactions to provide bis-substituted bacteriochlorins 30.\textsuperscript{29} In addition, 3,13-biscyanation (concomitant with adventitious zinc insertion) was accomplished using zinc(II) cyanide,\textsuperscript{29} while a palladium-mediated carbonylation reactions in the presence of a number of nucleophiles furnished carbonyl derivatives such as acids (using sodium hydroxide as nucleophile), esters (using sodium methanolate) and aldehydes (using tri-\textit{tert}-butyl tin hydride).\textsuperscript{29} Stoichiometric amounts of palladium
reagent were required to improve the yield of these reactions. In the presence of formic acid, a palladium-mediated hydrodehalogenation took place. Subsequently, the diacids of type 30 could also be converted into the acid chlorides, and the acid chlorides reacted with amines to provide amides.

Scheme 1-7. Pd-catalyzed modification of bacteriochlorins

Bacteriochlorins 31 with two, four, or six quaternized ammonium groups (Figure 1-8) or two basic amine groups (not shown) were compared for light-mediated killing against a Gram-positive bacterium, a Gram-negative bacterium, a dimorphic fungal yeast, and human HeLa cancer cells. This report established cationic bacteriochlorins as extremely active and selective NIR-activated photoantimicrobials.
Both, the five- and six-membered annulated systems were synthesized using similar approaches mentioned above. Thus, regioselective bromination of diacetyl-bacteriochlorin 32 forms bromobacteriochlorin 33 (Scheme 1-8). The subsequent palladium-mediated α-arylation of the adjacent 13-acetyl group gives rise to the exocyclic cyclopentanone moiety, forming bacteriopheophorbide 34.

The synthesis of bacteriochlorindicarboxylimides 37 followed a similar approach (Scheme 1-9). In this case, however, the ester functionalities of 35 were introduced at the pyrrole stage of the synthesis. Selective meso-bromination gave 2,12-diethyl-3,13-diethylester-15-bromobacteriochlorins 36. Finally, palladium-mediated carbamoylation
resulted in ring-closure to provide the exocyclic dicarboxylimide moiety of bacteriochlorins 37.

**Scheme 1-9. Synthesis of bacteriochlorindicarboxylimides**

**1.5.3. Syntheses of Pyrrole-Modified Chlorins and Chlorin Analogues**

In synthetic porphyrin chemistry, many principle approaches can be taken to achieve the conversion of porphyrins to chlorins.\(^{50}\) Conceptually, the most straightforward method for converting porphyrins to chlorins, or bacteriochlorins is by reduction. However, classic reduction conditions, such as H\(_2\)/Pt or Pd-C, are unsuitable, as they tend to also reduce double bonds at the *meso*-positions.\(^{51}\)

In 1969, Whitlock and co-workers reported a hydrogenation of porphyrins 6 using diimide (HN=NH), which is generated *in situ* by heating tosyl-hydrazine in base, to produce dihydrochlorin 38 and tetrahydrobacteriochlorin 39 (Scheme 1-10).\(^3\) This reaction accomplished regioselective β,β'-double bond reduction of porphyrins but the use of it was limited, largely due to extremely difficult product isolation. Moreover, its
instability towards oxidation (facile conversion back to porphyrin 6) considerably limited the synthetic value of 38.

Scheme 1-10. Bacteriochlorins via reduction of $\beta,\beta'$-double bonds

The osmium tetroxide-mediated dihydroxylation of a $\beta,\beta'$-bond of octaalkylporphyrins was discovered by Fischer in 1940.\textsuperscript{52} This reaction highlights the pseudo-olefinic nature of the porphyrin $\beta,\beta'$-bonds and has found widespread use in the formation of chorins, bacteriochlorins, and isobacteriochlorins.\textsuperscript{53-64} However, the reaction is slow compared to the osmylation/dihydroxylation of true olefins, and no system has been reported in which the dihydroxylation of porphyrins was performed using catalytic amounts of osmium tetroxide.

Surprisingly, it took until 1995 before the application of this reaction to meso-tetraarylporphyrins was reported.\textsuperscript{65-69} meso-Tetraarylbiolchlorins 40 is obtained by the dihydroxylation of meso-tetraarylporphyrin 6 (Scheme 1-12). The reaction is performed using a stoichiometric quantity (or even a stoichiometric excess) of osmium tetroxide in the presence of pyridine (as co-solvent and accelerator of the osmylation reaction).\textsuperscript{70} The initially formed osmate ester is reduced in a separate step with H$_2$S.\textsuperscript{71} As in the diimide reduction, this oxidation is highly regioselective.\textsuperscript{65,72} The product, unlike 38, contains
functional groups that can be subjected to further synthetic modulations. Particularly, our group has utilized this functional group extensively to synthesize a number of unique chlorin-analogues. This principle approach to the synthesis of chlorin analogue will be referred hereon as the “breaking and mending approach”.

The breaking and mending approach begins by first converting simple porphyrins, typically tetraarylporphyrins 6, into diols via OsO₄-mediated dihydroxylation. The β,β’-carbon bond of diol is oxidatively cleaved using NaIO₄ or Pb(OAc)₄, initiating the “breaking” process, to form bisaldehyde secochlorins 41. This bisaldehyde sets the stage for a variety of multistep “mending” processes. For instance, a five-membered pyrrole in porphyrin can be contracted into four-membered azete in three steps (42 in Scheme 1-11). On the other hand, the bisaldehyde can be expanded into six membered rings. These examples include formation of morpholine (43) and pyrazine (44). In a more unique case, acid treatment of bisaldehyde causes the annulation to takes place with the flanking phenyl groups, giving rise to a seco-chlorin derivative known as indaphyrin (45). Alternatively, a replacement of a β-carbon atom by a heteroatom results in a formation of heterocyclic porphyrinoids. Noteworthy examples here include formation porpholactam (46), imidazoloporphyrin (47), and porpholactone (48).
All in all, this “breaking and mending” principle has proven to be a very effective way to construct a number of novel and unique synthetic porphyrinoid macrocycles. In addition, the series of synthetic methodologies developed by Brückner and co-workers also highlights the importance and the unique chemical plasticity of bisaldehyde-secochlorins.

1.5.4. Syntheses of Pyrrole-Modified Bacteriochlorins and Bacteriochlorin Analogues

The synthesis of chlorins mentioned above can also be applied to synthesize bacteriochlorins. For instance, diimide reduction of porphyrins can be pushed to form
bacteriochlorins 39 as the major product by using excess reducing agent. Likewise, meso-tetraaryl-tetraolbacteriochlorins 49 can be obtained either by the dihydroxylation of meso-tetraaryl-diolchlorin 40 or by reaction of porphyrins 6 with (at least) a two-fold molar excess of osmium tetroxide. The product is a mixture of two isomeric bacteriochlorins in a 3:1 ratio with the higher polarity trans-isomer being the major product. The two isomers vary with the relative orientation of the two vic-diol functionalities (cis/trans-isomers, shown in Scheme 1-12).

![Scheme 1-12. Bacteriochlorin via OsO₄⁻-mediated dihydroxylation of porphyrins](image)

Analogous to the pyrrole-modified chlorin syntheses, bacteriochlorins such as 49 can also be subjected to a “breaking and mending” protocol. Samankumara et al. recently reported on the expansion of one or two pyrrole(s) to form morpholine-containing bacteriochlorins 50 and 51 (Scheme 1-13). This mono- and bis-ring expansion of pyrroles can be controlled by simple methyl ether protection of the diol functional group. For instance, when one of the two diol moieties is protected (49 when R = Me), NaIO₄-
mediated cleavage results in selective formation of one morpholine ring, giving rise to
dimethoxy-morpholinobacteriochlorin 50. On the other hand, when tetraolbacteriochlorin
(49 when R = H) is treated with NaIO₄, simultaneous oxidative cleave of two diol groups
results in the formation of bismorpholinobacteriochlorin 51. Exposing the mono- and
bismorpholinobacteriochlorin to acid (i.e. TFA) causes ring fusion with the nearby
flanking phenyl group(s), forming mono- or bis-annulated morpholinobacteriochlorins,
52 and 53 respectively. 51

Scheme 1-13. Expanded bacteriochlorins syntheses

Two independent 1,3-dipolar cycloadditions to two β,β’-positions in porphyrins or
a single 1,3-dipolar cycloaddition to a β,β’-position of a chlorin are another option for the
conversion of porphyrins or chlorins into bacteriochlorins. For instance, a reaction of
porphyrin 54 with 1,3-dipoles, such as azomethine ylides, give rise to a regio-isomeric
mixtures of bacteriochlorins 55.82-85 Other examples of bacteriochlorin syntheses
involving 1,3-dipolar cycloaddition include reactions with nitrile oxides,\textsuperscript{86-89} nitrones,\textsuperscript{90} nitrile imines,\textsuperscript{91} and carbonyl ylides\textsuperscript{92}.

Similarly, bacteriochlorins can also be derived via Diels-Alder reaction. In principle, this can take place in two ways: porphyrin as dienes and as dienophiles. In either case, the porphyrin $\beta,\beta'$-double bond involved is transformed into a single bond, thus generating chlorin- and/or bacteriochlorin-type chromophores.\textsuperscript{51} One example, reported by Cavaleiro and co-workers, is the reaction of porphyrin 54 with diene-$\alpha$-benzoquinodimethane, generated \textit{in situ} by thermal extrusion of SO$_2$ from a sulfone, to form bacteriochlorin 56 (Scheme 1-14).\textsuperscript{93,94}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {Scheme 1-14. Bacteriochlorins via 1,3-dipolar cycloaddition and Diels-Alder reaction};
\end{tikzpicture}
\end{center}
1.6. References


Chapter 1: General Introduction


Chapter 1: General Introduction


2. Introduction to Oxazole-Containing Porphyrinoids

2.1. Nomenclature Conventions

There is no firmly established trivial nomenclature for most porphyrinoids. Thus, we define oxazoloporphyrins to be porphyrin-like chromophores in which a single pyrrole was replaced by an oxazole moiety (i.e. porpholactone 5) and oxazolochlorins to be chlorin-type chromophores in which a single pyrrole was replaced by an oxazoline moiety (i.e. porpholactol 11H₂).

2.2. Porpholactones

In a seminal contribution by Crossley and King more than 25 years ago,¹ it was recognized that oxidation of β-substituted porphyrins, such as dione 6 (prepared from 1 via 2, 3, or 4), can lead to the loss of one β-carbon and the formal replacement of the porphyrinic β,β’-bond by a lactone moiety, forming porpholactone 5 (Scheme 2-1). One other serendipitous finding five years later identified strongly oxidizing reaction conditions (AgNO₃ in refluxing acetic acid containing oxalate) that were suitable for converting porphyrin 1 (with Ar = C₆F₅) directly into a porpholactone.²,³ Additional specialized reaction pathways toward porpholactones have been discovered since, such as the singlet oxygen oxidation of β-aminoporphyrin 4 (Scheme 2-1).⁴ Select oxidations of dione 6 also lead to porpholactones, perhaps shedding light on a possible reaction.
Since its discovery, porpholactones have been demonstrated to be of practical value: The Fe(III) and Fe(IV)=O\(^+\) complexes of *meso*-tetakis(2,6-dichlorophenyl)-substituted porpholactone were used as model compounds for naturally occurring chlorin-type prosthetic groups.\(^4\) The catalytic activity of the Fe(III)Cl and Mn(III)Cl complexes of *meso*-tetakis(phenyl)porpholactone with respect to olefin epoxidation and sulfide oxidation reactions were tested.\(^8,9\) [*meso*-Tetakis(pentafluorophenyl)porpholactonato]Pt(II) is a promising component in pressure sensitive paints,\(^10-12\) allowing the imaging of air flow around objects.\(^13\) This complex can also be utilized as a high pH

**Scheme 2-1.** Literature-known syntheses of porpholactone 5. Only free bases are shown but some transformations may require metal complexation, or metal insertion takes place during the transformation.
sensor in the range of pH 11.5–13.\textsuperscript{14} Despite their increasing utility and the emergence of their unique reactivity, a rational, general, and high-yielding synthesis of \textit{meso}-tetraarylporpholactones was only published recently.\textsuperscript{15,16}

2.3. Rational Syntheses of Porpholactones

The process of Os\textsubscript{4}O\textsubscript{4}-mediated dihydroxylation of \textit{meso}-tetraarylporphyrin 1 to produce dihydroxychlorin 7 was first reported by Brückner and Dolphin.\textsuperscript{17} Oxidation of this diol 7 with MnO\textsubscript{4}\textsuperscript{−} produced porpholactone 5 in a single step (Scheme 2-2). The source of MnO\textsubscript{4}\textsuperscript{−} can either be an excess of powdered KMnO\textsubscript{4} suspended at ambient temperature in an organic solvent (toluene, CH\textsubscript{2}Cl\textsubscript{2}, CHCl\textsubscript{3}, THF) in the presence of the phase-transfer agent 18-crown-6, KMnO\textsubscript{4} heterogenized on silica gel or in the form of cetyltrimethylammonium permanganate (CTAP).

\[ 
\text{Scheme 2-2. Synthesis of porpholactones 5 by oxidation of 2,3-dihydroxychlorins 7} 
\]
The osmate esters were also susceptible to CTAP oxidation to the corresponding porpholactones but the reaction was slower than the reaction of the corresponding alcohols, and the fate of the osmium remained unknown. Given the high toxicity of OsO$_4$ that potentially forms as a side product,$^{18}$ the oxidation of the diol was given preference over the oxidation of the corresponding osmate ester. This methodology is considered to be fairly general as it was applicable to the oxidation of free base dihydroxychlorin 7, its Ni(II), Zn(II), Ag(II), and Pt(II) complexes, to diol chlorins carrying a variety of electron-donating and -withdrawing meso-phenyl substituents.$^{14}$

The exact mechanism of formation of the porpholactones remains unclear. Permanganate oxidation of dihydroxychlorin 7 suggests the formation of secochlorin biscarboxylate 10. In fact, Crossley already surmised that the as yet unobserved secochlorin 10 is the immediate precursor to porpholactone 5.$^1$ Other reactions that reasonably can be expected to produce the biscarboxylate species also generate porpholactones. For instance, an attempted silver ion insertion into free base bisaldehyde 9 (using excess Ag(I) in pyridine, heat) results in [porpholactonato]Ag(II) 5Ag in mediocre yield (~20%).$^6$ Independent evidence points toward 2,3-dioxochlorins of type 6 to be the key intermediates in the conversion of porpholactones.$^5,19$ Since porpholactones frequently also appear as adventitious (by)products in a number reactions that treat ($\beta$-derivatized) porphyrins under a variety of oxidizing conditions,$^{1,2,5,6}$ one may regard porpholactones as the thermodynamic sink in the $\beta,\beta'$-oxidative degradation pathway of
porphyrins. As such, it can be reasonably assumed that multiple pathways lead to this product.

2.4. Reductions of Porpholactones

The carbonyl moiety of the porpholactone is susceptible towards several types of functional group transformations.\textsuperscript{7,20-22} For instance, a DIBAl-H reduction of the porpholactone 5a\textsubscript{Zn} produces 11\textsubscript{Zn} in relatively high yield. The reduction of free base porpholactones (5H\textsubscript{2}) is complicated by the formation of aluminum containing side products, as low valent aluminum species are known to metalate free base porphyrins.\textsuperscript{23} As a result, the free base porpholactol 11H\textsubscript{2} is prepared by the reduction of the zinc complex 5a\textsubscript{Zn}, followed by an acid-mediated (HCl) demetallation. The hemiacetal moiety of porpholactol (freebase or metal-complex) can be further reduced. An acid-catalyzed (BF\textsubscript{3}⋅OEt\textsubscript{2} or Amberlyst 15, H\textsuperscript{+} form) hydro-dehydroxylation using silyl-hydride (Et\textsubscript{3}SiH) converts porpholactol 11H\textsubscript{2} to oxazolochlorin 12H\textsubscript{2} (Scheme 2-3).
Scheme 2-3. Reduction of Porpholactone 5

The methylene group of 12H₂ is located in a benzylic position with respect to the porphyrinoid aromatic system and α to an oxygen atom in the oxazole moiety. For this reason, it is highly activated and extremely sensitive toward (photo-sensitized) oxidation back to porpholactol 11H₂.

2.5. Optical Properties of Oxazoloporphyrins and -chlorins

Free base porpholactones possess UV-visible and fluorescence emission spectra that are almost indistinguishable from those of the corresponding porphyrins (Figure 2-1). The similarity of the porphyrin and porpholactone spectra, noted already upon their discovery,¹,² is surprising as the modified pyrrolic moiety has lost its cross-conjugated β,β’-double bond. Therefore, porpholactones could have been expected to possess chlorin-like spectra.²⁴ Evidently, however, the electronic effects of the carbonyl double bond mimic the presence of a β,β’-double bond. On the basis of iterative extended
Hückel calculations, Gouterman and co-workers categorized porpholactones to lie between porphyrins and chlorins.²

**Figure 2-1.** Normalized UV-visible (solid traces) and fluorescence spectra (broken traces) of the compounds drawn (all in CH₂Cl₂ at ambient temperature)
The reduced porpholactones, 3-hydroxy-2-oxachlorins $11\text{H}_2$ ($\lambda_{\text{max}} = 646$ nm) and $11\text{Zn}$, both possess chlorin-like optical spectra (cf. to the spectra for $7\text{aH}_2$, ($\lambda_{\text{max}} = 648$ nm, and $7\text{aZn}$). The influence of the 3-hydroxyl functionality on the 2-oxachlorin chromophore is profound. The removal of this group in the free base chromophore $12\text{H}_2$ results in a 22 nm red-shift ($\lambda_{\text{max}} = 668$ nm) in the UV-visible spectrum. The distinct blue-shifts caused by OH-substitution of chlorin pyrrolines has been previously reported.$^{25}$ Most surprisingly, the removal of the hydroxy group also results in a significant enhancement of the extinction coefficient of the Qx band relative to its Soret band. Thus, replacement of the CH$_2$CH$_2$ group in chlorins by a CH$_2$O group has an auxochromic effect, adding to the collection of groups that are known to substantially modify the chlorin chromophore.$^{26}$ A rationalization for this observation through computational studies has also been reported.$^{15}$

2.6. Other Oxazole-Containing Porphyrinoid Macrocycles

In 2011, an example of a 3,3-dimethyl-oxazole-containing phthalocyanine-analogue 15, made by total synthesis, was reported (Scheme 2-4).$^{27}$ Mixed condensation of either phthalonitrile (13) (or phthalimide) and 5,5-dimethyl-1,3-oxazolidine-2,4-dione (14) in the presence of nickel chloride and a ammonium molybdate catalyst (MOA) in quinoline at 250 °C led to a mixture of [phthalocyaninato]Ni(II) (PcNi) as the main product and 2,2-dimethyl-3-oxa-tri(1,2-benzo)tetraazachlorin (15) as a sparingly soluble product in 4.2% yield that required HPLC purification.
Scheme 2-4. Synthesis of 2,2-dimethyl-3-oxa-tri(1,2-benzo)tetraazachlorin (15) according to Dudkin et al.\textsuperscript{27}

Pawlicki and Latos-Grazynski reported the total synthesis of 18, the carbaporphyrin analogue to 3-methoxy-2-oxachlorin 17 (Scheme 2-5).\textsuperscript{28,29,31} Carba-porphyrins are porphyrin analogues containing a carbon atom in place of an inner nitrogen. This reaction is in contrast to our ‘breaking and mending of porphyrin’ strategy toward porpholactones 5. Multi-step oxidation of 18 led to the formation of 19, the carbaporphyrin analogue to porpholactone 5.

Scheme 2-5. Synthesis of 2-oxa-21-carbaporphyrin 16, 2-oxa-3-ethoxy-21-carbachlorin 18, and 2-oxa-3-oxo-21-carbaporphyrin 19
Crossly and King have long been regarded as the pioneers of oxazole-containing porphyrins. However, we discovered recently that Gurinovich and co-workers in fact reported the first example of oxazole-containing porphyrins in 1977. Remarkably, a standard ozonolysis at -100°C converted the starting material 20 to product 23 in one step. Presumably, the pseudo-olefinic \( \beta,\beta' \)-double bond of 20 reacts with ozone to form molozonide intermediate 21 first. Then the series of rearrangements take place to form more stable ozonide intermediate 22. The peculiar loss of one \( \beta \)-carbon (and its ethyl substituent) likely occurs at this stage to form 23 (Scheme 2-6).\textsuperscript{32}

\textbf{Scheme 2-6.} Synthesis of alkyloxazolochlorin by the group of Gurinovich via ozonolysis of octaethylporphyrin
2.7. References


Chapter 2: Introduction to Oxazole-Containing Porphyrinoids


(18) National Institute for Occupational Health and Safety Registry of Toxic Effects of Chemical Substances (RTECS): RN1140000`; TSCA 8(b) inventory


(26) See, for example, the studies relating to the optical properties of the chlorins synthesized by Lindsey and co-workers, Chapter 1, and references therein.


3. **Aim of this Thesis**

The overarching aim of this thesis is the study of the scope and limits of the syntheses of mono- and bisoxazole-containing chlorin- and bacteriochlorins-like chromophores.

Previous work has shown that a replacement of a chlorin β-carbon with an oxygen drastically intensifies and red-shifts its optical spectra but their chemical stability was low. This prompted us to develop methodologies to synthesize a class of β-alkylated oxazolochlorins that were predicted to be more stable. Furthermore, we adopted known and novel techniques to the generation of hitherto unknown oxazole(s)-containing bacteriochlorin chromophores.

![Diagram of chromophore structures]
4. Diphenylporpholactones

4.1. Introduction

During the single crystal X-ray structural evaluation of porpholactones, it was noticed that the oxazolone moiety of 1Zn, more specifically the carbonyl moiety, was not perfectly co-planar with the macrocycle.¹ We proposed that the effect may originate from a steric interaction between the carbonyl oxygen and the flanking phenyl group. To test whether other experimental evidence can be found for a significant steric interaction between the lactone carbonyl and the flanking phenyl group, we set out to prepare porpholactones from the less sterically hindered 5,15-diphenylporphyrin DPP. We hypothesized that the key MnO₄⁻-mediated oxidation step will display regioselectivity towards formation of the less sterically hindered product (4-II).

![Porphyrlactone 1 and 1Zn](image)

4.2. Results and Discussion

4.2.1. Synthesis of 5,15-Diphenylporpholactone

The 5,15-diphenylporphyrin DPP, was synthesized in a step-wise manner, following the procedure described by Boyle and co-workers.² Thus, 5-phenylidipyrro-
methanes 2 were first synthesized by reacting benzaldehyde with excess pyrrole. The phenyldipyrromethanes 2 are isolated from the side-products, namely their trimer and tetramer analogues, through sublimation at 120°C under high vacuum. These dipyrrolic fragments were then subjected to an acid-mediated condensation reaction with trimethyl-orthoformate to form the tetrapyrrolic framework of 5,15-diphenylporphyrin DPP.

OsO₄-mediated dihydroxylation, followed by H₂S-reductive cleavage transformed DPP into known 5,15-diphenyl-2,3-dihydroxychlorin 3 (Scheme 4-1).³,⁴

\[
\text{H} + \text{Ph} \xrightarrow{\text{10 mol}\% \text{TFA}} \xrightarrow{\text{N}_2} \text{Ph} \xrightarrow{\text{2. 65\%}} \text{DPP} \xrightarrow{\text{20\%}} \text{DPP}
\]

\[
\text{1. OsO}_4 \xrightarrow{2. \text{H}_2\text{S}} \xrightarrow{\text{CTAP}} 4-\text{I/II} \xrightarrow{\text{30\% \text{MeOH/CHCl}_3}} 4-\text{II-Zn}
\]

16% (combined yield) over 3 steps from 3
30% (combined yield) from DPP

**Scheme 4-1. Synthesis of 5,15-diphenylporpholactone 4 I/II and its zinc complex 4-II-Zn**

The CTAP oxidation of dihydroxychlorin 3 proceeded smoothly and rapidly,⁵ producing pink non-polar product with a porphyrin like UV-vis spectrum. Based on the previously reported syntheses of meso-tetraphenylporpholactones 1,⁵ along with the HR-MS data, the product was identified as the lactone 4. The ¹H NMR of 4 indicated the
presence of two isomers in a ~1:5 ratio. Repeated preparative plate chromatographies and recrystallizations (CHCl₃ → MeOH) allowed the isolation of a pure fraction of the majority product, but the minority product could not be isolated in pure form in high enough yields to perform a full analysis. 1D and 2D-NMR spectroscopy (see experimental section) allowed the unambiguous assignment of the majority product as the 2-oxo-3-oxa isomer 4-II, that is unaffected by any steric interaction between the lactone carbonyl and a phenyl group. This was confirmed by single X-ray crystal structure elucidation of 4-II-Zn, as its pyridine adduct, formed by zinc insertion into the free-base (Figure 4-1).

Alternatively, DPP can be directly converted into 4 at room temperature upon treatment with excess CTAP (30% combined yield). This direct-oxidation route change the regioisomeric ratio as it maintained the ~5:1 regioselectivity (favoring 4-II). This consistency of the diastereomeric ratio hints at the possibility of this reaction following a similar mechanistic path to that of the original reaction sequence (DPP → 3 → 4). To our surprise, over-oxidations to form diphenylporphodilactone were not observed even with the excessive use of oxidant and/or extended reaction time. Despite numerous attempts, direct oxidations of meso-tetraphenylporphyrins to form 1 were unsuccessful using this method. The direct oxidation to form 1, however, can be accomplished using the Ru-catalyzed system as recently reported by the group of Zhang.⁶

The fact that the seemingly less sterically inhibited isomer forms in preference over the other isomer serves as an indication for the existence of a small but noticeable steric interaction between the carbonyl and the phenyl group. Most significantly, the
Chapter 4: Diphenylporpholactone

macrocycle conformation (Figure 4-1) shows that the lactone moiety is near-perfectly co-planar with the oxazole moiety and that the macrocycle of 4-II-Zn is overall significantly more planar than that of the tetraaryl analogue 1Zn. This provides the most convincing proof for the rationalization of the non-planar arrangements of the lactone moiety with the porphyrins in 1 and 1Zn on steric grounds.

![Figure 4-1. Single crystal X-ray structures of 1-Zn (left) and 4-II-Zn (right) ](image)

We observed reduced disorder in the structure of 4-II-Zn versus that observed in porpholactone 1, and thus can more reliably determine the bond lengths in the oxazolone ring (Figure 4-1). The C=O lengths in 4-II-Zn range from 1.106(3) to 1.228(3) Å, while the C-O lengths vary between 1.357(3) to 1.486(8) Å (there are two independent molecules per unit cell). Compared to the free-base porpholactones 1, these bond length changes compared to the porpholactone free-base support a chlorin rather than a porphyrin-like electronic structure.
4.2.2. Optical Properties of 5,15-Diphenylporpholactone

Generally, the absorption spectra of 5,15-diphenylporphyrin derivatives are slightly blue-shifted compared to their tetraphenyl analogues.\textsuperscript{1,4} This also translated to the diphenyldihydroxychlorins and diphenylporpholactones (Figure 4-2).

![Normalized UV-vis absorption spectra comparison](image)

**Figure 4-2.** Normalized UV-vis absorption spectra comparison of 1-Zn and 4-II-Zn free-base (top) and zinc complexes (bottom)

The UV-visible absorption spectra of diphenylporpholactone 4-II and its zinc complex 4-II-Zn, when compared to their tetraphenyl analogues, possessed $\sim$10 nm blue-
shift at all Q-bands. Overall, the absorption spectra of 4-II and 4-II-Zn closely resembled those of their corresponding tetraphenyl analogues.

4.3. Conclusion

5,15-diphenylporpholactones were synthesized and structurally characterized, displaying their structural relationship to the corresponding porphyrins but also suggesting the presence of a steric interaction between the oxazolidone moiety with the flanking phenyl group. As hypothesized, the lactone-forming reaction displayed regioselectivity towards the formation of less-stERICally hindered isomer. The similarity of the optical properties of porphyrins and porpholactones highlight their close electronic relationship.

4.4. Experimental Section

4.4.1. Instruments and Materials

Column chromatography was performed using preparatory plate or manual glass column using normal phase silica. The fluorescence quantum yields($\phi$) were determined relative to those of meso-tetraphenylporphyrin ($\phi = 0.11$ in benzene, calculated to be 0.09 in CH$_2$Cl$_2$); $\lambda_{excitation} = \lambda_{Soret}$. For details of the instruments used, see List of Instruments.

4.4.2. Preparation and Characterization

5,15-Diphenylporpholactones 4-I and 4-II. In a 50 mL round bottom flask shielded from light with aluminum foil, diphenyldihydroxochlorin 3 (50 mg, 5.7 ×
10^{-5} \text{ mol} \) was dissolved in CHCl$_3$ (20 mL). The solution was stirred magnetically and cetytrimethylammonium permanganate (CTAP) was added (69 mg, 0.17 mmol, ~3 equiv) at ambient temperature. TLC was used to monitor the formation of a bright pink, non-polar spot. UV-visible spectroscopy was used to monitor the disappearance of the chlorin peak (at ~650 nm) and the formation of porphyrin-like peaks. The reaction was stirred until the full consumption of 3 was observed (~2 h). The products were then isolated by flash chromatography (silica, CH$_2$Cl$_2$), providing an isomeric mixture (approximate ratio 5:1 by $^1$H NMR; see ESI) of the diphenylporpholactones in high (~80%) yield. The isomers were separated by preparative TLC (silica-50% petroleum ether 30-60/CHCl$_3$) but compound 4-I could not be isolated in high purity in large enough quantity for its full characterization. 4-II. R$_f$ (silica–CH$_2$Cl$_2$) = 0.84; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 10.10 (s, 1H), 10.03 (s, 1H), 9.34 (dd, $^3J = 4.9$ Hz, $^4J = 1.8$ Hz, 1H), 9.21 (d, $J = 4.6$ Hz, 1H), 9.09 (d, $J = 4.5$ Hz, 1H), 9.03 (dd, $^3J = 4.8$ Hz, $^4J = 1.8$ Hz, 1H), 8.96 (d, $J = 8.0$, 4.7 Hz 1H), 8.85 (d, $J = 8.0$, 4.5 Hz, 1H), 8.18–8.22 (m, 4 H), 7.77–7.85 (m, 6H), −1.99 (s, 1H), −2.58 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 170.2, 155.2, 154.9, 154.7, 141.4, 140.8, 137.6, 137.4, 137.0, 136.7, 135.4, 134.7, 134.6, 132.9, 131.8, 131.1, 129.9, 129.0, 128.4, 128.3, 128.25, 127.5, 127.3, 126.3, 124.3, 107.0, 102.6, 101.1 ppm; UV-vis (CHCl$_3$) $\lambda_{\text{max}}$ (log $\varepsilon$): 409 (5.23), 511 (3.92), 549 (4.00), 581 (3.76), 633 (3.81) nm; HR-MS (ESI+, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{31}$H$_{21}$N$_4$O$_2$ (MH$^+$): 481.1665, found 481.1629.
Figure 4-3. $^1$H NMR (400 MHz, CDCl$_3$) of a mixture of the two regio-isomers of 5,15-diphenylporpholactones, 4-I and 4-II

Figure 4-4. $^1$H NMR (300 MHz, CDCl$_3$) of 4-II. Assignment of proton signals as shown, and based on the 2D spectra shown below
Figure 4-5. $^{13}$C NMR (100 MHz, CDCl$_3$) of 4-II

Figure 4-6. NOESY Spectrum (300 MHz, CDCl$_3$) of 4-II
[5,15-Diphenylporpholactonato]Zn(II) (4-II-Zn). To a stirring solution of 4-II (30 mg, 6.3 × 10^{-5} mol) in CHCl₃ (~5 mL), was added a solution of Zn(OAc)₂·4 H₂O in MeOH (27 mg, 1.3 × 10^{-4} mol, ~2 equiv). The mixture was heated to reflux for ~1 h. TLC was used to monitor the formation of a more polar green product. Upon completion, the solvents were evaporated using rotary evaporation and the product was isolated by column chromatography (silica, 1% MeOH/CH₂Cl₂) to provide 4-II-Zn in near quantitative yield (33 mg). R_f (silica, 1% MeOH/CH₂Cl₂) = 0.46; ¹H NMR (300 MHz, CDCl₃, δ): 9.84 (s, 1H), 9.69 (s, 1H), 9.16 (d, J = 4.7 Hz, 1H), 9.08 (d, J = 4.5 Hz, 1H), 8.95 (d, J = 4.3 Hz, 1H), 8.83-8.87 (m, 3H), 8.08-8.15 (m, 4 H), 7.76-7.79 (m, 6H) ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε): 416 (5.81), 514 (3.76), 553 (4.33), 597 (4.79) nm; MS (ESI+, 100% CH₃CN, 30 V cone voltage): m/z = 543.1 (MH⁺); HR-MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₃₁H₁₉N₄O₂Zn: 543.0799, found 543.0833.
Figure 4-8. $^1$H NMR (300 MHz, CDCl$_3$) of 4-II-Zn

Figure 4-9. FT-IR spectrum (neat, diffuse reflectance) of 4-II-Zn
4.4.3. X-ray Crystallography Data

X-ray crystallographic analysis (provided by Dr. Christopher Ziegler, University of Akron): X-ray intensity data were measured at 100 K (Bruker KYRO-FLEX) on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube ($\lambda = 0.71073 \, \text{Å}$) operated at 2000 W power. The crystals were mounted on a cryoloop using Paratone N-Exxon oil and placed under a stream of nitrogen at 100 K. The detector was placed at a distance of 5.009 cm from the crystals. The data were corrected for absorption with the SADABS program. The structures were refined using the Bruker SHELXTL Software Package (Version 6.1), and were solved using direct methods until the final anisotropic full-matrix, least squares refinement of $F^2$ converged.
Crystal Structure Report for 4-II-Zn-py. Purple crystals of 4-II-Zn-py were grown by diffusion of MeOH into a CH₂Cl₂ solution of the complex. A 0.10 × 0.20 × 0.20 crystal was mounted.

Figure 4-10. ORTEP representation and numbering scheme used in the crystal structure of 4-II-Zn-py. Minor disordered moieties are omitted for clarity.
Table 4-1. Crystallographic and structure refinement data for 4-II-Zn-py.

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4.5. References


5. Oxazolochlorins

5.1. Introduction

Perez and co-workers reported a high photo-toxicities of porpholactols 1 towards several cancer cell lines in 2005. This raised a question of whether modulating the hemiacetal moiety of 1 can further increase their biological activities. In this chapter, we first describe our effort to expand on the study conducted by Perez et al. thorough various functional group conversion of the hemiacetal 1. The latter part of this chapter describes the details of the improved synthesis of α-substituted oxazolochlorins.

5.2. Results and Discussion

5.2.1. –OR, -SR, and –NR Substituted Oxazolochlorins

The hydride reduction of porpholactone to form porpholactol 1 was previously described (Chapter 2). The lactol hydroxy group of 4 is susceptible to facile acid-catalyzed nucleophilic substitutions by a range of O-, N-, and S-nucleophiles, providing access to a number of stable chlorin-like derivatives of graded lipophilicity (Scheme 5-1).
Scheme 5-1. O-, N-, and S-substitution of porpholactol 4

A marked nucleophile-dependent reactivity difference is noted. Exposure of 1 to primary, secondary, and tertiary alcohols results in a rapid reaction that is essentially quantitative after 30 min to 1 h at ambient temperature. The resulting acetals 4-OR showed all the expected spectroscopic data. Diagnostic for the successful formation of acetals containing an \( \alpha \)-methylene group, this group shows a diastereotopic splitting. This can be rationalized by its relative position with respect to the macrocycle plane, exposing one of the methylene protons to a much larger degree to the diatropic ring current than
the other. Alkoxy-substituted morpholinochlorins show a very similar effect. Bulky alcohols like cholesterol or pregnenolone can also be attached to the chromophore with ease.

Secondary amines required a longer reaction time and azeotropic removal of the water formed (reflux in benzene with 3 Å mol sieves placed in a Soxhlet apparatus over several days) to push the reaction to completion. The hemiaminals 4-NR₂ showed all of the expected spectroscopic and analytical properties, including the diastereotopic split of the α-methylene protons. We did not succeed in reacting primary amines with the porpholactols under these or other conditions tested.

The reactivity of primary thiols was similar to the reactivity of the corresponding alcohols. Over time, however, the formation of side products with spectroscopic data suggestive of being the corresponding sulfoxides appeared (m/z = +16 compared to the expected compound; essentially identical ¹H and ¹³C NMR spectra).

This high reactivity of lactol 1 with respect to acetal, aminal, and thioacetal formation is of immediate interest for the potential application of the 2-oxachlorins as photochemotherapeutics. The efficacy of 1 when incorporated into a biodegradable nanoparticle for the photodynamic treatment of a tumor in a mouse model has been reported previously.¹ The facile acetalization demonstrated here suggests that the biodistribution of the hemiacetal may also be modulated by its ability to undergo derivatization with biomolecules containing alcohol and thiol groups. Such promiscuity may allow achievement of a biodistribution of the drug it would not have as a single and
stable compound. Inversely, the facile derivatization of 1 suggests the preparation of amphiphilic (pro)drugs using PEGs, carbohydrates, or similarly suitable moieties.

5.2.2. Alternative Synthesis of –OR/NR₂ Substituted Oxazolochlorins

In total, the transformation of diol 2 to oxazolochlorins 4-OR/NR₂/SR requires five discrete synthetic steps: 1. oxidation to the lactone; 2. zinc insertion; 3. hydride reduction; 4. zinc removal—the zinc is required as a protecting group for the reduction to take place; 5. acetal/aminal/thioacetal formation (Scheme 5-2). Chromatographic purification of every intermediate is necessary, with overall yields of 10-33%. Notably, the formation of aminals required forcing conditions (molecular sieve-driven water removal from the reaction taking an excess of 3 days).

Scheme 5-2. Step-wise synthesis of oxazolochlorins 4-OR/NR₂/SR

This section describes an alternative pathway that converts chlorin diol 2 in a two-step, one-pot reaction directly to a number of α-substituted oxazolochlorin derivatives of
Chapter 5: Oxazolochlorins

5.2.2.1. Synthesis of –NR₂, and –OR substituted oxazolochlorins from diolchlorins

It is known that the oxidation of diol 5 with NaIO₄ heterogenized on silica gel, in the presence of a Brønsted base (Et₃N), generates a secochlorin bisaldehyde 7.³ Further, this reaction performed in the presence of a nucleophile (alcohol, secondary amine) leads to an in situ ring-closure reaction of the bisaldehyde, forming morpholinochlorins 8 in high yields.⁴ We found that treatment of the crude mixture of 8 with MnO₄⁻, in the form of cetyltrimethylammonium permanganate (CTAP), formed, depending on the nucleophile used, oxazolochlorin acetics or aminals 4-OR/NR₂, respectively. The reaction proceeded in good to acceptable isolated yields with a range of alcohols and secondary amines (Scheme 5-3). The reaction is completed within 2 h for the meso-phenyl derivative and within 10 min for the meso-pentafluorophenyl derivative at ambient temperature using ~2 equivalents oxidant. Extended reaction time or excessive stoichiometric ratios of CTAP resulted in increased decomposition of the intermediates and reduced yields of 4-OR/NR₂.
Reactions between secondary amines and diolchlorins 2 in the absence of Et₃N led to poor conversion of the intermediate bisaldehyde 7 to morpholinochlorin 8, and the formation of substantial amounts of porpholactone 3 were noted. Aminals 4-NR₂ are susceptible to hydrolysis to the corresponding hemiacetals 1; thus slow eluting column or plate chromatography was not suited for the purification of aminal 4-NR₂. The best purification with minimal associated hydrolysis was observed on an automated flash chromatography system using a high-performance silica column (CH₂Cl₂) at rates that eluted the product within minutes.

5.2.2.2. Mechanistic Considerations

The mechanism of the single β-carbon loss from morpholinochlorin 8 remains unclear. However, it is reasonable to assume that MnO₄⁻ oxidizes 8 to form morpholinone 9. Evidently, this species extrudes a framework carbon to form oxazolochlorin 4-
OR/NR$_2$. Notably, the corresponding anhydride 10 is considerably more stable though it is also capable of fragmentation to the corresponding porpholactone 3.$^{5,6}$

There are other examples in which similar β-carbon losses take place. For instance, the CTAP oxidation of diol 2 presumably forms the corresponding secochlorin biscarboxylate that, upon decarboxylation, (oxidatively) ring-closes to form porpholactone 3 (Scheme 5-2).$^{2,7}$ Also, when the use of Ag$^{II}$ as a template was studied during the synthesis of morpholinochlorins under mildly acidic conditions (Scheme 5-4), oxazolochlorin Ag$^{II}$ complex 4Ag-OEt formed as a major product, along with diethoxymorpholinochlorin 11Ag and porpholactone 6Ag.$^8$

**Scheme 5-4.** First example of a reaction that suggests that the oxidation of hydroxy-substituted morpholinochlorins leads to a formation of oxazolochlorin

Another relevant observation was made in more recent years: Free base secochlorin bisaldehyde 7 underwent an intramolecular Cannizzaro reaction
(Scheme 5-5). This reaction mechanism was determined based on the general reactivity of aromatic aldehydes as well as an analysis of the reaction products.\(^3\)

The bisaldehyde 7, when treated with strong base, formed products 1, porpholactone 3, and dimer 1-O-1 (Scheme 5-6, Route A). Their formation was rationalized by presuming that bisaldehyde 7 underwent an intramolecular disproportionation to form acid-benzyl alcohol intermediate 12. The latter was then assumed to decarboxylate and (oxidatively) ring-close to form oxazolochlorin 13. The latter primary product 13, however, was not directly observed at any point of the reaction.\(^2\)

![Scheme 5-5](image)

**Scheme 5-5.** Second example of a reaction that suggests that the oxidation of hydroxy-substituted morpholinochlorins leads to a formation of oxazolochlorin

With the outcome of the oxidation reactions reported in Scheme 5-5 in mind, another rationalization of the reaction products offers itself (Scheme 5-5, Route B). Secochlorin bisaldehyde, when exposed to wet conditions, was noted to form a water adduct, 11-(OH)\(_2\), which was, based on its UV-vis spectrum, assigned the bis-hydroxymorpholinochlorin structure shown.\(^3\) Under the strongly basic and wet conditions of the
Cannizzaro reaction (an aqueous Et₄NOH solution was used) this compound may well have been a major intermediate before air elicited an oxidation reaction that lead to the formation of the observed product 1. In fact, similarly to bisaldehyde 7 forming acetal 4a-OEt in the presence of EtOH (Scheme 5-3), bisaldehyde 7 would directly form acetal dimer 1-O-1 in the presence of alcohol 1, indeed without evoking a Cannizzaro reaction.

5.3. Optical Properties

As expected, the –OR, -NR and -SR substitution of phorpholactol 1 did not affect the optical property in any significant manner as all derivatives maintained their characteristic chlorin-like absorption spectra. Various –OR substituted oxazolochlorins were near indistinguishable from each other as all spectra contained the \( \lambda_{\text{max}} \) of ~647 nm (4a-O\(^i\)Pr: \( \lambda_{\text{max}} = 647 \) nm, 4a-O\(^i\)Bu: \( \lambda_{\text{max}} = 647 \) nm, 4a-O\(^n\)Oct: \( \lambda_{\text{max}} = 646 \) nm, 4a-O\(^c\)Hex: \( \lambda_{\text{max}} = 647 \) nm, 4a-OChol: \( \lambda_{\text{max}} = 655 \) nm, 4a-OPreg: \( \lambda_{\text{max}} = 647 \) nm). A replacement of the hydroxy groups of porpholactol 4 with 2\(^{o}\) amines caused slight bathochromic shift of ~10 nm (4a-N\(^{\text{morph}}\): \( \lambda_{\text{max}} = 654 \) nm, 4a-N(Bn)\(_2\): \( \lambda_{\text{max}} = 655 \) nm). Likewise, a substitution of hydroxy group by thioxy group caused ~15 nm bathochromic shift (4a-S\(^n\)Hex: \( \lambda_{\text{max}} = 660 \) nm, 4a-SEt: \( \lambda_{\text{max}} = 655 \) nm). Shown in Figure 5-1 are the normalized (at \( \lambda_{\text{soret}} \)) comparisons of representative –OR, -NR and –SR substituted oxazolochlorins.
5.4. Crystal structures

The crystal structure of 4a-OMe, as its Ag(II) complex and a phorpholactol acetal dimer were previously characterized by single crystal X-ray diffraction. The crystal structure of 4a-OMe is disordered to a point that a conformational analysis is meaningless however, it is shown here as a proof of connectivity.
5.5. Conclusion

Efficient syntheses of various meso-tetraphenyloxazolochlorins from meso-tetraphenylporpholactol (1) and meso-tetraphenyldiolchlorins (2) were described. These methodologies can be regarded to be general. As a result, we have further expanded the synthetic methodologies of converting a porphyrin to pyrrole-modified porphyrins along the ‘breaking and mending of porphyrins’ strategy.

5.6. Experimental Section

5.6.1. Instruments and Materials

meso-Tetraphenyl-3-methoxy-2-oxachlorin 4a-OMe, and meso-tetraphenyl-3-ethoxy-2-oxachlorin, 4a-OEt were prepared as described previously. Flash column chromatography was performed on an automated flash chromatography system, on normal-phase silica columns (sizes of columns and solvents used are indicated; isocratic elution modes). The crude products were dry-packed onto silica gel in a pre-column. The fluorescence quantum yields(φ) were determined relative to those of meso-tetraphenylporphyrin (φ = 0.11 in benzene, calculated to be 0.09 in CH2Cl2); λ_excitation = λ_Soret. For details of the instruments used, see List of Instruments.

5.6.2. Preparation and Characterization

meso-Tetraphenyl-3-isoproxy-2-oxachlorin (4-O^iPr). General procedure for the conversion of hemiacetals to acetals. Isopropanol (1 mL) was added to a stirring solution of 1 (11.5 mg, 1.9 × 10^{-5} mol) in CHCl3 (3 mL) at room temperature. Traces of
TFA vapors (from a TFA bottle head space, delivered via pipette) were added, and the reaction was monitored by TLC. The reaction was complete within in 3 h. Upon completion, the acid was neutralized with Et₃N (1 drop), the solution washed, dried over anhydrous MgSO₄, evaporated to dryness using rotary evaporation, and purified by flash column chromatography (DCM) or preparative plate. Yield >95% (12 mg). Rf (silica–CH₂Cl₂) = 0.96; ¹H NMR (300 MHz, CDCl₃, δ): 8.60 (d, ³J = 4.2 Hz, 1H), 8.51 (d, ³J = 4.2 Hz, 1H), 8.47 (d, ³J = 4.2 Hz, 1H), 8.43 (d, ³J = 4.2 Hz, 1H), 8.35 (d, ³J = 4.2 Hz, 1H), 8.04–8.19 (m, 7H), 7.89 (br, 1H), 7.66–7.73 (m, 14H), 3.96 (m, 1 H), 1.27 (d, ³J = 6.0 Hz, 3H), 0.91 (d, ³J = 6.0 Hz, 3H), −0.73 (s, 1H), −1.09 (s, 1H) ppm; UV-vis (CH₂Cl₂) λ_max (log ε): 418 (5.38), 516 (4.21), 550 (4.26), 593 (3.97), 647 (4.63) nm; LR-MS (ESI+, 100% CH₃CN, 30 V cone voltage, TOF): m/z 677.1 (MH⁺), 634.7 (MH⁺–C₃H₇); HR-MS (ESI+ of M⁺, 100% CH₃CN): m/z calc’d for C₄₆H₃₆N₄O₂: 677.2917, found 677.3018.

Figure 5-3. ¹H NMR spectrum (300 MHz, CDCl₃) of 4a-OPr
meso-Tetraphenyl-3-cyclohexoxy-2-oxachlorin (4a-O<sup>6</sup>Hex). Prepared according to the general procedure from 1 (10 mg, 0.016 mmol) and cyclohexanol (1 mL) in >95% isolated yields 11 mg: R<sub>f</sub> (silica–CH<sub>2</sub>Cl<sub>2</sub>) = 0.98; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 8.59 (dd, <sup>3</sup>J = 4.9, <sup>4</sup>J = 1.5 Hz, 1H) 8.51 (dd, <sup>3</sup>J = 3.8, <sup>4</sup>J = 1.7 Hz, 1H), 8.46 (dd, <sup>3</sup>J = 4.9, <sup>4</sup>J = 1.7 Hz, 1H), 8.43 (d, <sup>3</sup>J = 4.5 Hz, 1H), 8.35 (d, <sup>3</sup>J = 4.5 Hz, 1H), 7.88–8.19 (m, 8H), 7.69–7.72 (m, 13H), 3.59–3.66 (m, 1H), 0.89–1.72 (m, 10H), –0.71 (s, 1H), –1.08 (s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, δ): 165.5, 154.9, 151.8, 151.4, 142.9, 142.1, 142.0, 141.1, 140.1, 139.1, 136.7, 135.3, 134.5, 134.0, 133.9, 131.7, 131.1, 129.7, 127.9, 127.85, 127.8, 127.7, 127.6, 127.5, 127.0, 126.9, 125.9, 125.0, 121.9, 121.3, 112.2, 105.1, 100.4, 79.4, 33.7, 31.9, 25.8, 24.1 ppm; UV-vis (CH<sub>2</sub>Cl<sub>2</sub>) λ<sub>max</sub> (log ε): 418 (5.31), 516 (4.14), 550 (4.19), 594 (3.88), 647 (4.55) nm; HR-MS (ESI+ of M<sup>+</sup>, 100% CH<sub>3</sub>CN, TOF): <i>m/z</i> calc’d for C<sub>49</sub>H<sub>41</sub>N<sub>4</sub>O<sub>2</sub>: 717.3230, found 717.3212.

![Figure 5-4. <sup>1</sup>H NMR spectrum (300 MHz, CDCl<sub>3</sub>) of 4a-O<sup>6</sup>Hex](image)
Figure 5-5. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O'Hex

*meso*-Tetraphenyl-3-tert-butoxy-2-oxachlorin (4a-O'Bu). Prepared according to the general procedure from 1 (12 mg, 0.019 mmol) and tert-butanol (1 mL) in 80% isolated yields (9.8 mg): R$_r$ (silica–CH$_2$Cl$_2$) = 0.92; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 8.58 (d, $^3$J = 4.7 Hz, 1H), 8.44–8.49 (m, 2H), 8.41 (d, $^3$J = 4.5 Hz, 1H), 8.34 (d, $^3$J = 4.5 Hz, 1H), 8.03–8.19 (m, 8H), 7.84–7.89 (m, 2H), 7.63–7.72 (m, 12H), 1.09 (s, 9H), –0.71 (s, 1H), –1.07 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 165.3, 154.8, 152.1, 151.7, 142.9, 142.2, 142.1, 142.0, 141.2, 140.4, 139.1, 136.7, 135.5, 134.4, 134.3, 134.1, 134.0, 133.9, 133.3, 131.6, 131.4, 129.6, 128.0, 127.96, 127.92, 127.8, 127.7, 127.6, 127.54, 127.51, 127.0, 126.9, 125.9, 125.0, 121.7, 121.2, 112.0, 105.8, 100.6, 100.4, 64.8, 28.5 ppm; UV–vis (CH$_2$Cl$_2$) $\lambda_{max}$ (log $\varepsilon$): 418 (5.20), 514 (4.05), 550 (4.08), 594 (3.79), 647 (4.46) nm; HR-MS (DART$^+$, 20 V orifice voltage, 100% CH$_3$CN, TOF): m/z calc’d for C$_{47}$H$_{39}$N$_4$O$_2$ (MH$^+$): 691.3037, found 691.3056.
Figure 5-6. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-O'Bu

Figure 5-7. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O'Bu
meso-Tetraphenyl-3-octoxy-2-oxachlorin (4a-O^8Oct). Prepared according to the general procedure from 1 (10 mg, 0.016 mmol) and n-octanol (1 mL) in 92% isolated yields (11.4 mg): R_f (silica–CH_2Cl_2) = 0.92; ^1H NMR (300 MHz, CDCl_3, δ): 8.59 (dd, 3J = 4.5, 4J = 1.5 Hz, 1H), 8.52 (dd, 3J = 4.6, 4J = 1.7 Hz, 1H), 8.45 (dd, 3J = 5.8, 4J = 1.7 Hz, 1H), 8.43 (d, 3J = 4.6 Hz, 1H), 8.35 (d, 3J = 4.5 Hz, 1H), 8.21 (dd, 3J = 5.8, 4J = 1.7 Hz, 1H), 7.85–8.18 (m, 8H), 7.64–7.77 (m, 12H), 7.59 (s, 1H), 3.64–3.67 (m, 1H), 3.42–3.45 (m, 1H), 1.24–1.28 (m, 17H), −0.73 (s, 1H), −1.09 (s, 1H) ppm; ^13C NMR (100 MHz, CDCl_3) δ 165.0, 154.9, 151.9, 151.0, 143.0, 142.1, 142.0, 140.9, 139.9, 139.0, 136.8, 135.0, 134.5, 134.2, 134.1, 134.0, 133.9, 133.5, 131.8, 131.2, 129.7, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.65, 127.0, 126.9, 125.9, 125.1, 121.9, 121.4, 112.2, 105.9, 100.3, 69.4, 32.0, 29.9, 29.5, 29.4, 26.3, 22.9, 14.3 ppm; UV-vis (CH_2Cl_2) λ_max (log ε): 417 (5.23), 515 (4.06), 550 (4.11), 593 (3.79), 646 (4.48) nm; HR-MS (ESI+ of M^+ 100% CH_3CN, TOF): m/z calc’d for C_{51}H_{47}N_4O_2: 747.3699, found 747.3705.

Figure 5-8. ^1H NMR spectrum (300 MHz, CDCl_3) of 4a-O^8Oct
**Figure 5-9.** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-O$^\text{Oct}$

*meso*-Tetraphenyl-3-(+)-cholesteroxy-2-oxachlorin (4a-OChol). Prepared according to the general procedure from 1 (33.9 mg, 0.053 mmol) and cholesterol (20.7 mg, 2 eq.) in 88% isolated yield (47 mg): $R_f$ (silica–CH$_2$Cl$_2$) = 0.96; $^1$H NMR (300 MHz, CDCl$_3$, δ): 8.63 (d, $^3J = 4.8$ Hz, 1H), 8.55 (m, 1H), 8.51 (d, $^3J = 1.5$ Hz, 1H), 8.47 (d, $^3J = 4.5$ Hz, 1H), 8.39 (d, $^3J = 4.5$ Hz, 1H), 8.10–8.25 (m, 8H), 7.9 (d, $^3J = 0.3$ Hz, 2H), 7.66–7.76 (m, 13H), 5.29–5.36 (m, 1H), 3.55–3.63 (m, 1H), 2.32–2.64 (m, 1H), 2.12–1.72 (m, 6H), 1.28–1.62 (m, 15H), 0.99–1.22 (m, 12H), 0.96 (s, 3H), 0.98 (s, 3H), 0.71 (s, 3H), -0.74 (s, 1H), -1.06 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 165.1, 165.0, 155.0, 154.9, 151.9, 151.2, 151.1, 143.0, 142.2, 142.1, 141.2, 141.1, 141.0, 140.2, 140.1, 139.1, 139.0, 136.8, 136.7, 135.4, 135.3, 134.6, 134.2, 134.1, 134.0, 133.5, 131.8, 131.1, 131.0, 129.8, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127.6, 127.1, 126.9, 126.0, 125.1, 125.1, 122.1, 122.0, 122.0, 121.9, 121.4, 121.4, 112.2, 115.3, 105.3, 105.2, 100.5, 100.4, 81.1, 81.0, 57.0, 56.4, 50.3, 42.6, 40.8, 40.0, 39.8, 38.6, 37.6, 37.4, 36.9, 36.8 36.5, 36.1,
Chapter 5: Oxazolochlorins

32.3, 32.2, 32.1, 30.1, 28.5, 28.3, 28.2, 24.6, 24.1, 23.1, 22.9, 21.4, 21.3, 19.6, 19.0, 12.1 ppm; UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ (log $\varepsilon$): 419 (5.24), 515 (4.16), 552 (4.18), 594 (3.95) 655 (3.79) nm; HR-MS (ESI+, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{70}$H$_{75}$N$_4$O$_2$ (MH$^+$):

1003.5890, found 1003.5893.

Figure 5-10. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4a-OChol
Figure 5-11. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-OChol

Figure 5-12. FT-IR spectrum (neat, diffuse reflectance) of 4a-OChol

*meso*-Tetraphenyl-3-pregnenolonoxy-2-oxachlorin (4a-OPreg). Prepared according to the general procedure from 1 (33.5 mg, 0.053 mmol) and pregnenolone (33.4 mg, 2 equiv) in 83% isolated yield (41 mg): $R_f$ (silica–CH$_2$Cl$_2$) = 0.55; $^1$H NMR
Chapter 5: Oxazolochlorins

(300 MHz, CDCl$_3$, $\delta$): 8.61 (d, $^3J = 4.5$ Hz, 1H), 8.53 (d, $^3J = 4.5$ Hz, 1H), 8.47 (t, $^3J = 4.5$ Hz, 1H), 8.44 (d, $^3J = 4.5$ Hz, 1H), 8.36 (d, $^3J = 4.5$ Hz, 1H), 7.89–8.22 (m, 9H), 7.65–7.74 (m, 13H), 5.30 (dd, $^3J = 23.3$ Hz, 4.5 Hz, 1H), 3.55–3.61 (m, 1H), 2.29–2.62 (m, 2H), 2.20 (m, 1H), 2.14 (s, 3H), 2.02–2.013 (m, 3H), 1.04–1.94 (m, 14H), 0.96 (s, 3H), 0.63 (s, 3H), −0.74 (s, 1H), −1.08 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$ $\delta$ 209.8, 151.9, 142.9, 142.1, 142.0, 141.1, 141.1, 141.0, 140.9, 136.8, 136.7, 135.4, 135.3, 134.5, 134.2, 134.1, 134.0, 133.5, 131.8, 131.1, 131.0, 129.8, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 126.9, 126.0, 125.1, 125.0, 122.0, 121.9, 121.7, 121.6, 112.2, 105.3, 105.2, 100.4, 80.9, 80.7, 63.9, 57.1, 50.1, 44.2, 40.7, 39.0, 38.5, 37.5, 37.4, 36.9, 36.8, 32.1, 31.8, 30.0, 28.1, 24.7, 23.0, 21.3, 21.2, 19.6, 19.5, 13.4 ppm; UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$ (log $\varepsilon$): 419 (5.28), 517 (4.13), 550 (4.17), 593 (3.88) 647 (4.52) nm; HR-MS (ESI+, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{64}$H$_{61}$N$_4$O$_3$ (MH$^+$): 933.4744, found 933.4733.

Figure 5-13. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4a-OPreg
Figure 5-14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-OPreg

Figure 5-15. FT-IR spectrum (neat, diffuse reflectance) of 4a-OPreg

*meso*-Tetraphenyl-3-N-morpholinyl-2-oxachlorin (4a-N$_{\text{morph}}$). General procedure for the conversion of hemiacetals to aminals. A small-scale Soxhlet containing 3 Å molecular sieves was attached to a 50 mL round bottom flask. Excess amine (5 to 10 eq) was then added to a stirring solution of 1 (30 mg, 0.043 mmol) in
benzene (10-15mL). A few drops of TFA were added and the mixture was refluxed for several days (3-5 days). The reaction progress was monitored by TLC and upon completion, the acid was neutralized with Et$_3$N (1 drop), dried over anhydrous MgSO$_4$, evaporated to dryness using rotary evaporation, and purified by flash column chromatography (CH$_2$Cl$_2$) or preparative plate to give 4a-N$^\text{morph}$ in 30% isolated yield (9 mg): $R_f$ (silica–CH$_2$Cl$_2$) = 0.60; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 8.52–8.54 (m, 1H), 8.45–8.47 (m, 1H), 8.36–8.37 (m, 2H), 8.28–8.29 (m, $^1$H), 7.84–8.15 (m, 10H), 7.64–7.70 (m, 4), 7.44 (s, 1H), 3.47–3.48 (m, 2H), 3.29–3.30 (m, 2H), 2.58–2.59 (m, 2H), 2.38–2.43 (m, 2H), –0.44 (s, 1H), –0.86 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 166.5, 154.9, 151.6, 150.6, 143.4, 142.0, 141.9, 141.2, 140.5, 139.2, 136.8, 135.2, 134.2, 134.0, 133.9, 133.8, 133.3, 131.5, 130.1, 129.7, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 126.93, 126.97, 126.1, 125.1, 121.6, 121.2, 111.6, 101.2, 99.7 ppm; UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ (log $\varepsilon$): 420 (5.08), 517 (3.91), 552 (3.91), 598 (3.16) 654 (4.34) nm; HR-MS (ESI+, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{47}$H$_{38}$N$_5$O$_2$ (MH$^+$): 704.3026, found 704.3009.
Figure 5-16. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-N$^\text{morph}$

Figure 5-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-N$^\text{morph}$
meso-Tetraphenyl-3-N-dibenzyalamine-2-oxachlorin (4a-N(Bn)₂). Prepared according to the general procedure from 1 (10.7 mg, 0.017 mmol) and dibenzyalamine (1 mL) in 70% isolated yield (9.6 mg): $R_f$ (silica–CH₂Cl₂) = 0.96; $^1$H NMR (300 MHz, CDCl₃, δ): 8.54–8.56 (m, 1H), 8.39–8.44 (m, 2H), 8.34–8.35 (m, 1H), 8.26–8.28 (m, 1H), 7.98–8.15 (m, 7H), 7.84–7.89 (m, 1H), 7.71–7.71 (m, 12H), 7.49–7.55 (m, 1H), 7.28 (s,1H), 7.11–7.12 (br, 5H), 6.84–6.86 (m, 4H), 3.47–3.61 (m, 4H), –0.33 (s, 1H), –0.70 (s, 1H) ppm; UV-vis (CH₂Cl₂) λₘₐₓ (log ε): 420 (5.16), 518 (3.97), 555 (3.97), 600 (3.69) 655 (4.39) nm; HR-MS (ESI+, 100% CH₃CN, TOF): $m/z$ calc’d for C₅₇H₄₄N₅O (MH⁺): 814.3546, found 814.3590.

Figure 5-18. $^1$H NMR spectrum (300 MHz, CDCl₃) of 4a-N(Bn)₂

meso-Tetraphenyl-3-ethoxy-2-oxachlorin (4a-SEt). General procedure for the conversion of hemiacetals to RS-based thiaacetals. Excess ethanethiol (1 to 2 mL)
was added to a stirring solution of 1 (10 mg, 0.015 mmol) in CHCl₃ (3-5 mL) at room
temperature. Traces of TFA vapors (from a TFA bottle head space, delivered via pipette)
were added, and the reaction was monitored by TLC. The reaction was complete within
in 3 to 5 h. Upon completion, the acid was neutralized with Et₃N (1 drop), the solution
washed, dried over anhydrous MgSO₄, evaporated to dryness using rotary evaporation,
and purified by silica gel flash column or preparative plate chromatography (CH₂Cl₂).
Isolated yield 90% (9.6 mg): Rₓ (silica–CH₂Cl₂) = 0.96; ¹H NMR (300 MHz, CDCl₃, δ):
8.50–8.52 (m, 1H), 8.43–8.44 (m, 1H), 8.33–8.35 (m, 2H), 8.26–8.27 (m, 1H), 7.99 (m,
8H), 7.90–7.91 (m, 1H), 7.67–7.80 (m, 12H), 2.31–2.41 (m, 1H), 2.12–2.19 (m, 1H),
0.89–0.93 (m, 3H), −0.30 (s, 1H), −0.65 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ):
165.9, 154.9, 153.1, 151.9, 143.4, 141.9, 141.8, 141.4, 139.9, 138.7, 136.8, 135.5, 134.6,
134.1, 133.9, 133.8, 133.3, 131.6, 131.1, 129.9, 128.5, 128.2, 128.0, 127.92, 127.94,
127.97, 127.8, 127.7, 127.1, 126.95, 126.9, 126.3, 124.9, 121.8, 110.6, 100.1, 90.8 ppm;
UV-vis (CH₂Cl₂) λₘₐₓ (log ε): 420 (5.31), 457 (4.43), 518 (4.13), 555 (4.07), 608 (3.88),
660 (4.51) nm; LR-MS (ESI+, 100% CH₃CN, 30 V cone voltage): m/z 679.1 (MH⁺),
upon exposure to ambient light and environment, significant peak of 695.7 (MHO⁺) is
observed; HR-MS (ESI+, 100% CH₃CN, TOF): m/z calc’d for C₄₅H₃₅N₄O₅ (MH⁺):
679.2532, found 679.2471.
Figure 5-19. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 4a-SEt

Figure 5-20. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4a-SEt
**meso-Tetraphenyl-3-hexanethioxy-2-oxachlorin (4a-SnHex).** Prepared according to the general procedure from 1 (10 mg 0.014 mmol) and hexanethiol (1 mL) in 50% isolated yields (5.8 mg): Rf (silica – CH2Cl2) = 0.92; 1H NMR (300 MHz, CDCl3, δ): 8.50–8.51 (m, 1H), 8.42–8.43 (m, 1H) 8.33–8.34 (m, 2H), 8.26–8.27 (m, 1H), 7.98–8.23 (m, 8H), 7.89–7.91 (m, 1H), 7.65–7.75 (m, 13H), 2.35–2.42 (m, 1H), 2.15–2.18 (m, 1H), 0.71–1.28 (m, 13H), −0.30 (s, 1H), −0.65 (s, 1H) ppm; UV-vis (CH2Cl2) λmax (log ε): 422 (5.17), 518 (3.99), 553 (3.93), 603 (3.65), 659 (4.35) nm; HR-MS (ESI+, 100% CH3CN, TOF): m/z calc’d for C49H43N4OS (MH+): 735.3153, found 735.3097.

![Figure 5-21. 1H NMR spectrum (300 MHz, CDCl3) of 4a-SnHex](image)

**Direct synthesis of meso-tetraphenyl-3-ethoxy-2-oxachlorins (4a-OEt) A general procedure for direct conversion of diols 5 to oxazolochlorins 4-OR/NR2.**
**Step 1:** diolchlorin (110 mg) 5a was dissolved in amylene stabilized CHCl₃ (60 mL). To the solution was added Et₃N (2 mL), ethanol (5 mL), and NaIO₄ on silica (1 g). This mixture was stirred for ~18 h or until all the starting material was consumed. The starting material consumption was monitored using TLC and UV-vis. TLC showed a polar starting material 5a which was gradually converted to 8a of intermediate polarity (Rf = 0.5 in 30% Hexane in CH₂Cl₂). UV-vis showed the appearance of a distinct morpholinochlorin spectrum, which indicated full consumption of the diolchlorin. When the reaction was completed, oxidants were filtered out and the solvent was dried using rotary evaporation. The crude product was carried to the next step without any purification. Step 2: The crude product was dissolved in CHCl₃ and to the stirring solution was added cetyltrimethylamonium permanganate (CTAP) (100 mg). This reaction typically required 1-2 h. The reaction progress was monitored by TLC as the starting material 8a of intermediate polarity is converted to a nonpolar band (indicating the formation of 4). In some instances, additional oxidants may be added to push the reaction forward. Once full consumption of starting material was observed on TLC, the oxidants were filter out using a plug of silica before the solvent was dried by rotary evaporation. The column chromatography (eluent 30% Hexane in CH₂Cl₂) of the crude mixture gave 4a-OEt in 78% yields (87 mg). The spectroscopic data (¹H NMR and ¹³C NMR) were consistent with the previously reported data. Compounds 4a-OMe (86%), 4a-N(Bn)₂ (33%), 4a-N₅morph (49%), were also synthesized following this method.

**meso-tetrakis(4-trifluoromethylphenyl)-3-ethoxy-2-oxachlorin (4b-OEt)**

4b-OEt was prepared in 73% yields (14.8 mg) from diolchlorin 4b (20 mg) as described
for the synthesis of 4a-OEt. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\): 8.58-8.56 (m, 1H), 8.49(dd, \(J = 4.8, 1.7\) Hz, 1H), 8.45 (dd, \(J = 5.1, 1.5\) Hz, 1H), 8.37 (d, \(J = 4.6\) Hz, 1H), 8.30-8.18 (m, 8H), 8.00 (t, \(J = 6.6\) Hz, 8H), 7.54 (s, 1H), 3.83-3.79 (m, 1H), 3.59-3.55 (m, 1H), 1.11 (t, \(J = 7.1\) Hz, 3H), -0.740 (s, 1H), -1.10 (s, 1H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 165.01, 154.72, 151.64, 150.96, 145.35, 143.38, 142.86, 142.39, 140.66, 136.61, 135.42, 134.23, 134.20, 134.16, 134.05, 133.95, 133.72, 132.05, 131.45, 129.96, 127.88, 125.35, 125.97, 125.03, 124.99, 124.80, 124.23, 124.20, 124.10, 124.06, 122.18, 120.31, 111.08, 105.84, 99.51, 65.59, 15.13 ppm; UV-vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (Rel. Int.): 415 (1), 513 (0.10), 547 (0.11), 594 (0.08), 648 (0.23) nm; HR-MS (ESI+) \(m/z\) calc’d for C\(_{49}\)H\(_{31}\)F\(_{12}\)N\(_4\)O\(_2\), 935.2255, obs. 935.2253.

Figure 5-22. 1H NMR spectrum (400 MHz, CDCl\(_3\)) of 4b-OEt.
Chapter 5: Oxazolochlorins

Figure 5-23. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4b-OEt.

Figure 5-24. UV-vis spectrum (CH$_2$Cl$_2$) of 4b-OEt.

**Synthesis of meso-tetrakis(pentafluorophenyl)-3-ethoxy-2-oxachlorin** (4c-OEt). Prepared from diolchlorin 5c (110 mg, 1.1 × 10^{-4} mol) according to the procedure described for the synthesis of 4a-OEt in 76% yield. Note: Step 2 for this
substrate only required 5-10 minutes for a full conversion. $^1$H NMR (400 MHz, CDCl$_3$, δ): 8.69 (d, $J = 4.6$ Hz, 1H), 8.63 (d, $J = 4.2$ Hz, 1H), 8.53 (d, $J = 4.8$ Hz, 1H), 8.47 (d, $J = 4.5$ Hz, 1H), 8.38 (d, $J = 4.5$ Hz, 1H), 8.34 (d, $J = 4.4$ Hz, 1H), 7.77 (s, 1H), 3.67-3.59 (m, 1H), 3.48 (dd, $J = 16.0$, 7.2 Hz, 1H) 1.16 (t, $J = 7.0$ Hz, 3H), -0.713 (s, 1H), -1.02 (s, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 165.74, 154.84, 153.00, 151.95, 143.03, 137.06, 134.04, 133.50, 131.83, 129.75, 127.56, 125.51, 121.79, 109.46, 106.30, 105.24, 95.97, 84.80, 63.22, 14.88 ppm; UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$ (Rel. Int.): 402 (1), 500 (0.13), 535 (0.09), 600 (0.09), 654 (0.35) nm; HR-MS (ESI+) m/z calc’d for C$_{45}$H$_{13}$F$_{20}$N$_4$O$_2$, 1023.0876, obs. 1023.0905.

Figure 5-25. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4c-OEt.
Figure 5-26. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4c-OEt.

Figure 5-27. UV-vis spectrum (CH$_2$Cl$_2$) of 4c-OEt.

meso-Tetrakis(pentafluorophenyl)-3-methoxy-2-oxachlorin (4c-OMe).

Prepared from diolchlorin 5c (100 mg, 9.91 × 10-5 mol) according to the procedure described for the synthesis of 4a-OEt in 91% yield. Note: Step 2 for this substrate only
required 5-10 minutes for a full conversion. 1H NMR (400 MHz, CDCl3, δ): 8.74 (dd, J = 4.74, 0.36 Hz, 1H), 8.68-8.67 (m, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.51 (d, J = 4.5 Hz, 1H), 8.42 (d, J = 4.5 Hz, 1H), 8.38-8.37 (m, 1H), 7.84 (s, 1H), 3.67-3.59 (m, 1H), 3.48 (dd, J = 16.0, 7.2 Hz, 1H) 1.16 (t, J = 7.0 Hz, 3H), -0.713 (s, 1H), 3.25 (s, 3H), -0.68 (s, 1H), -0.99 (s, 1H), ppm. 13C NMR (100 MHz, CDCl3, δ): 165.74, 154.84, 153.00, 151.95, 143.03, 137.06, 134.04, 133.50, 131.83, 129.75, 127.56, 125.51, 121.79, 109.46, 106.30, 105.24, 95.97, 84.80, 63.22, 29.90, 14.88 ppm; UV-vis (CH2Cl2) λ_max (Rel. Int.): 402 (1), 500 (0.13), 535 (0.09), 598 (0.09), 653 (0.33) nm; HR-MS (ESI+) m/z calc’d for C_{44}H_{13}F_{20}N_{4}O_{2}, 1009.0719, obs. 1009.0712.

Figure 5-28. 1H NMR spectrum (400 MHz, CDCl3) of 4c-OMe.
Figure 5-29. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4c-OMe.

Figure 5-30. UV-vis spectrum (CH$_2$Cl$_2$) of 4c-OMe.
5.6.3. X-ray Crystallography Data

X-ray crystallographic analysis (provided by Dr. Christopher Ziegler, University of Akron): X-ray intensity data were measured at 100 K (Bruker KYRO-FLEX) on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (\(\lambda = 0.71073 \text{ Å}\)) operated at 2000 W power. The crystals were mounted on a cryoloop using Paratone N-Exxon oil and placed under a stream of nitrogen at 100 K. The detector was placed at a distance of 5.009 cm from the crystals. The data were corrected for absorption with the SADABS program. The structures were refined using the Bruker SHELXTL Software Package (Version 6.1), and were solved using direct methods until the final anisotropic full-matrix, least squares refinement of \(F^2\) converged.
Crystal Structure Report 4a-OMe

The oxazole unit is disordered with the pyrrole units in a 3:1 ratio. In addition the methoxy group is disordered over two alternative positions above or below the plane of the macrocycle. The methoxy groups of neighboring molecules are disordered around a four-fold rotinversion axis with a combined site occupancy of 0.5. The remainder of the site is taken up by a half occupied water molecule (located directly on the four-fold rotinversion axis).

Figure 5-31. ORTEP representation and numbering scheme of the crystal structure of 4a-OMe; only one of the possible eight positions and orientations of the oxazole unit is shown for clarity.
### Table 5-1. Crystallographic and structure refinement data for 4a-OMe

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<tr>
<td>$(D/s)_{\text{max}}$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$D_{\text{r,max}}$, $D_{\text{r,min}}$ (e Å⁻³)</td>
<td>0.309, −0.182</td>
</tr>
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</table>
5.7. References


6. Alkyl-Oxazolochlorins

6.1. Introduction

One of the most challenging aspects of synthetic porphyrin chemistry is the stabilization of chlorin chromophores. Particularly, oxazolochlorin chromophores are highly unstable in oxidative conditions. For example, the α-position to the oxazoline oxygen of A (when in solution) is rapidly oxidized into B upon exposure to light. Further, OsO₄-mediated dihydroxylation of porpholactol B surprisingly results only in the oxidation of hemiacetal to lactone. This instability toward oxidation severely limited the studies and utilizations of an otherwise intriguing class of chromophores.

Scheme 6-1. Inadvertent oxidations at the α-carbon of oxazolochlorin.

In the total syntheses of chlorins and bacteriochlorins, the group of Lindsey stabilized the chlorin and bacteriochlorin chromophores by incorporating geminal-dimethyl moieties (Section 1.5). This prompted us to wonder whether the alkyl substituent can be added onto the oxazolochlorins as a stabilizer. Hence, can we reduce the carbonyl group of lactone via alkyl-Grignard addition? Further, can we gain control over mono- vs bis-alkylation? This chapter provides answers to these questions as well as the
details of their optical properties and structural conformation via single crystal X-ray
diffraction structure elucidation.

6.2. Results and Discussion

6.2.1. Synthesis of Alkyloxazolochlorins

Addition of alkyl (methyl, ethyl, i-propyl) Grignard reagents to the zinc(II) complex of porpholactone 1 under anhydrous conditions results in the formation of a more polar product. An aqueous acidic work-up using a strong enough acid to demetalate the zinc complexes provided free base porphyrinoids with a chlorin-like UV-visible spectra as the main products in good to satisfactory yields. The HR–MS (ESI+) of these compounds suggested their composition to be derived from the parent porpholactone to which a single equivalent of methane, ethane, and propane was added, respectively. Their $^1$H, $^{13}$C NMR, and IR spectra also confirmed the loss of the lactone functional group and the presence of an alkyl chain attached to the oxazole moiety. These spectroscopic data and their similarity to those of the porpholactol identified these products as the alkylated hemiketals 2. The use of 2 to 3 equivalents of Grignard reagent was found to provide the highest yields of product. The reaction is rapid (5-20 mins at ambient temperature), and can be scaled up to 1.5 g of starting porpholactone 1Zn (2.15 mmol) (or 600 mg of 1FZn, 0.62 mmol, whereby the addition of the Grignard reagent at lower temperatures, $–78^\circ$C for iPrMgBr and $–45^\circ$C for EtMgCl, was found beneficial for this
substrate). The presence of the ‘protecting group’ zinc(II) is obligatory as the alkylation
of free base porpholactones failed (Scheme 6-2).

**Scheme 6-2.** Synthesis of mono- and bis-alkyloxazolochlorins by alkyl-Grignard addition to
porpholactones 1.

Even the use of a large excess of Grignard reagent (e.g., 15-fold molar excess) did
not generate more than traces of the corresponding bis-alkylated systems. The use of the
more electron-withdrawing p-CF₃Ph-derivatives also did not improve the yield of
formation of the bisalkylated products. However, reaction of 1Zn/1FZn with an alkyl-
Grignard reagent, followed by reaction of the crude zinc complex of 2 with a Lewis acid
and further addition of alkyl-Grignard reagent furnished the dialkyl-derivatives 4 in
satisfying yields (Scheme 6-2). We screened a number of Lewis acids (BF₃·OEt₂,
TMSOTf, Sc(OTf)$_3$, InCl$_3$, Ti(O$^t$Pr)$_4$, and TiCl$_4$) for their ability to facilitate this reaction and found TMSOTf to be the best choice. The intermediacy of the TMS-ether of 2Zn was shown as it could be detected in the reaction mixture by ESI(+) LR-MS.

We have also tested methyl and $i$-propyl lithium as alkylating agents. The reactions formed the expected mono-alkylated compounds. However, the experimental conditions (reaction temperatures of $-78^\circ$C were required for both reagents) and the precautions associated with using alkyllithium reagents were not offset by higher yields, a larger fraction of bisalkylated products, or cleaner reactions when compared to the Grignard reactions. Thus, we did not develop this route toward alkyloxazolochlorins.

Analogously to porpholactol, their alkylated analogues 2/2$^F$ can be hydro-dehydroxylated using triethylsilane in the presence BF$_3$·OEt$_2$, forming mono-alkyloxazolochlorin 3/3$^F$ (For hydro-dehydroxylation of porpholactol, refer to Chapter 2). The success of this reaction is indicated by the loss of one oxygen atom in the composition of the product 3 as determined by HR–MS, the appearance of one hydrogen signal in the pyrroline region of the spectrum (6.1–7.2 ppm) that is coupled with the corresponding alkyl group (CH$_3$ of Me, CH$_2$CH$_3$ of Et, and CH(CH$_3$)$_2$ of $i$Pr), and a similar ~20 nm red-shift of the optical spectrum of alkyloxazolochlorin 3 as observed upon formation of oxazolochlorin$^1$ by dehydroxylation of hemiacetal 5. The oxazolochlorins of types 2 and 4 are distinguished by excellent solubilities but the mono-alkyloxazolochlorins of type 3 possessed markedly reduced solubilities. Also, the dimethyl-substituted oxazolochlorins possess poor solubility (good quality $^{13}$C NMR spectra, for example, could not be
recorded over 12 h acquisition times), particularly when compared to the excellent solubility of the bis-ethyl and bis-\textit{i}Pr derivatives. The generally improved solubility of the \textit{p}-CF\textsubscript{3}Ph-derivatives was not enough to overcome these solubility issues.

The hydroxy group of hemiketal 2 is susceptible to facile acid-catalyzed ketalization. This reaction is parallel to the reaction of its non-alkylated analogue. Under the right reaction conditions, this reaction is reversible, with no apparent destruction of the macrocycle, providing some evidence for the robust nature of the alkyl oxazолochlorins. Interestingly, after zinc(II) insertion into acetal 5c, a TMSOTf-mediated substitution of the methoxy group with an alkyl group gave rise to, after demetalation, an alternative synthesis of the bisalkylated product 4c (Scheme 6-3).

\textbf{Scheme 6-3.} Ketalization and alternative pathway towards bis-alkyloxazolochlorins
6.2.2. Optical Properties

Benchmark compound free base porpholactol possesses a chlorin-type UV-visible absorption spectrum ($\lambda_{\text{max}} = 646$ nm, Section 2.5.).$^1$ The spectrum of the mono-alkylated analogues ($2\text{a: } \lambda_{\text{max}} = 647$ nm, $2\text{b: } \lambda_{\text{max}} = 648$ nm, $2\text{c: } \lambda_{\text{max}} = 649$ nm, $2^F\text{b: } \lambda_{\text{max}} = 649$ nm, $2^F\text{c: } \lambda_{\text{max}} = 650$ nm) are nearly indistinguishable from that non-alkylated species (porpholactol). Likewise, the optical spectra of the methyl, ethyl, and $i$-propyl derivatives were indistinguishable from each other. The formal replacement of an alkyl group (as in $3\text{a: } \lambda_{\text{max}} = 667$ nm, $3\text{b: } \lambda_{\text{max}} = 667$ nm, $3\text{c: } \lambda_{\text{max}} = 668$ nm, $3^F\text{b: } \lambda_{\text{max}} = 669$ nm, $3^F\text{c: } \lambda_{\text{max}} = 670$ nm) significantly red-shifts the spectrum. The corresponding profound effect of the hydroxy groups located at the chlorin-specific $\beta,\beta'$-bond on the optical properties of the chromophore and a qualitatively similar auxochromic effect upon removal of the hydroxy group was observed for non-alkylated oxazolochlorins and chlorins.$^{1,2}$ The bis-alkyloxazolochlorin$^4$s possess $\lambda_{\text{max}}$ values that are similar to those of the dehydroxylated monoalkyloxazolochlorin$^3$s. However, the shapes of their Soret bands and the peak positions of the remaining Q-bands are distinctly different. Also, irrespective of whether bis-alkyloxazolochlorin$^4$s, $4\text{a}$, $4\text{b}$ or $4\text{c}$ are concerned, the UV-visible spectra of the bis-alkyloxazolochlorin$^4$s possess almost 50% lower extinction coefficients compared to the corresponding mono-alkylated species $3\text{a}$, $3\text{b}$ and $3\text{c}$ (Figure 6-1).
The fluorescence emission spectra of the alkyloxazolochlorins are all chlorin-like (Figure 6-2), with the small Stokes’ shift characteristic for porphyrins. The fluorescence yields are in the range of 0.19 to 0.30, consistent with those of regular dihydrochlorin derivatives previously reported. The presence of β-oxygen appears to have minimal effect on the florescence properties of alkyloxazolochlorins.
6.2.3. Crystal Structures of Alkyl-Oxazolochlorins

The crystal structures of mono-i-propyloxazolochlorin hemiketal 2c, its methyl ketal zinc(II) complex 5cZn, and of the bis-i-propyloxazolochlorin 4c were determined by single crystal X-ray diffraction (Figure 6-3). These structures confirm the connectivity of the oxazolochlorins but more importantly, they prove the conformation of the macrocycles (in the solid state). The conformations of all three macrocycles are essentially planar. The small deviations from planarity that can be made out vary from chromophore to chromophore but are all not large enough to affect the optical properties in any major way. Hydroporphyrins are known to be conformationally somewhat more flexible than the corresponding porphyrins. The conformational analysis of the two halves of an oxazolochlorin dimer also showed small and distinct conformation differences of the two chromophores, suggestive of a somewhat flexible macrocycle. As will be shown below,
the optical spectra of all oxazolochlorins do not show any degree of broadening, further allowing us to conclude that the conformational flexibility of oxazolochlorins is not unusually high (as, for instance, observed in the morpholinochlorin that differ from the oxazolochlorins by the presence of an additional sp$^3$-hybridized carbon atom in the non-pyrrolic moiety).\textsuperscript{5,6}

![Figure 6-3](image)

**Figure 6-3.** Single crystal X-ray structures of 2c, 4c, and 5cZn. All hydrogen atoms attached to aromatic carbons and the minor disorder contribution of 2c have been omitted for clarity.

Unlike many of the structures of the corresponding porpholactones,\textsuperscript{1} the structures of 4c and 5cZn are not disordered. The structure of 2c exhibits a small degree of disorder in the oxazole ring, which adopts two orientations with in an approximately 80/20 ratio. In all three cases, bond distances, angles and overall porphyrin planarity can be unambiguously observed. The C$_\beta$-O bond in the oxazole ring is significantly lengthened in all three compounds (1.4483(18) Å in 4c, 1.461(5) Å in 5cZn and
1.457(4) Å for the primary orientation of 2c) versus a typical Cβ-Cβ' bond length of ~1.36 Å in a normal porphyrin. The Cα-O bond distance is appreciably shorter, however, with distances of 1.3594(17) Å in 4c, 1.374(4) Å in 5cZn and 1.351(3) Å for the primary orientation in 2c, indicative of a significant degree of double bond character. The Cα-Cβ bonds in the oxazole rings are clearly single in bond character, with observed bond lengths of 1.545(2) Å in 4c, 1.518(5) Å in 5cZn and 1.578(4) Å for the primary orientation in 2c. In all three compounds, the N-C bonds in the oxazole moiety are asymmetric, with one measuring a typical distance of ~1.36-1.37 Å, and the second being shorter at 1.34 Å.

All three porphyrinoids exhibit primarily planar conformations in the solid state with some small and varying deviations. In 2c, the largest deviation from the mean 24 atom plane of the porphyrinoid is 0.27 Å, with an average deviation of 0.09 Å. In 4c, the maximum deviation is 0.23 Å with an average deviation of 0.11 Å. The zinc complex 5cZn also exhibits a predominantly planar porphyrinoid macrocycle (maximum deviation 0.27 Å, average deviation 0.10 Å); the presence of the zinc ion does not distort the conformation of the ring, although the greatest deviations from planarity are observed in the oxazole unit. The zinc ion is five coordinate with an axial pyridine, and the Zn(II) ion is pulled away from the plane of the porphyrinoid macrocycle by 0.38 Å, as is commonly observed for penta-coordinated zinc porphyrin complexes.7
6.3. Conclusions

The addition of Grignard reagents to the porphyrin-like meso-tetraarylporpho-
lactones resulted in the formation of mono- and bis-alkylated oxazolochlorins. The mono-
alkylated hemiketals can be deoxygenated or converted to ketals. As previously demons-
trated for the corresponding porpholactol (Chapter 5), this allows the facile derivati-
zation of these chromophores. The oxazolochlorins possess chlorin-like optical properties
that are slightly modulated depending on the nature of the substituents located on the sp³-
hybridized carbon α to the oxazole oxygen. Since porpholactones are readily accessible
in gram-scales and the key reactions were demonstrated at gram or half-gram scales, this
methodology offers straightforward access to significant quantities of a class of stable
chlorin-like chromophores that are endowed with somewhat tunable optical spectra.

6.4. Experimental Section

6.4.1. Instruments and Materials

[meso-Tetraphenyl-3-oxo-2-oxaporphyrinato]Zn(II) was prepared as described in
the literature. Flash column chromatography was performed on an automated flash
chromatography system, on normal-phase silica columns (sizes of columns and solvents
used are indicated; isocratic elution modes). The crude products were dry-packed onto
silica gel in a pre-column unless noted otherwise. The fluorescence quantum yields (φ)
were determined relative to those of meso-tetraphenylporphyrin (φ = 0.11 in benzene,
calculated to be 0.09 in CH$_2$Cl$_2$; $\lambda_{\text{excitation}} = \lambda_{\text{Soret}}$. For details of the instruments used, see *List of Instruments*.

### 6.4.2. Preparation and Characterization

*meso*-Tetraphenyl-3-hydroxy-3-methyl-2-oxachlorin (2a). General procedure for the conversion of lactone 1Zn to hemiketal 2. For a typical reaction, a N$_2$-flushed, oven-dried 50 mL round bottom flask was loaded with *meso*-tetraphenyl-2-oxa-3-oxoporphyrinato]Zn(II) (1Zn, 100 mg, 0.145 mmol) dissolved in dry THF (15 mL). Then, 5 equivalents of MeMgBr (3M solution in Et$_2$O, 0.24 mL) was slowly added at ambient temperature. The reaction progress was monitored using UV-vis spectroscopy (disappearance of the band at ~600 nm and development of a band at ~625 nm). The reaction was completed within 15 min. Upon completion, the reaction was quenched by addition of a saturated aq NH$_4$Cl solution (2-3 mL). The mixture was transferred into a 250 mL separatory funnel and washed with a saturated aq NH$_4$Cl, and the chlorin was extracted with CH$_2$Cl$_2$. Note: it appears critical to assure that all Grignard reagent is quenched; repeated aq NH$_4$Cl washes may be necessary. Crude 2aZn was dissolved in THF (15 mL) and stirred, and 6 M aq HCl (2-3 mL) is added. The reaction was stirred for ~2 hrs. The reaction progress was monitored by UV-vis spectroscopy. Upon disappearance of the metallochlorin spectrum of a neutralized aliquot, the green reaction mixture was transferred into a separatory funnel and a saturated aq NaHCO$_3$ solution is added (Caution, foam!). CH$_2$Cl$_2$ was added and the organic layer was extracted. The aq NaHCO$_3$ wash was repeated until the organic layer was pure purple in color. The organic
phase was isolated and dried over K$_2$CO$_3$. The product was isolated by flash chromatography (silica-CH$_2$Cl$_2$) to afford product 2a as a purple solid in good yield (76%, 72 mg). MW = 648.8 g/mol; R$_f$ = 0.55 (silica-CH$_2$Cl$_2$); UV-vis (CHCl$_3$) $\lambda_{\text{max}}$ (log $\varepsilon$): 419 (5.29), 516 (4.08), 551 (4.14), 594 (3.86), 647 (4.53) nm; Fl $\lambda_{\text{max}}$ (CHCl$_3$, $\lambda_{\text{exc}}$ = 420 nm): 652, 704 nm, $\phi$ = 0.28; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 8.57 (d, $^3J$ = 5.0 Hz, 1H), 8.46 (d, $^3J$ = 5.0 Hz, 1H), 8.41–8.39 (m, 2H), 8.33 (d, $^3J$ = 4.4 Hz, 1H), 8.15–7.60 (m, 21H), 3.72 (s, 1H), −0.67 (s, 1H), −1.1 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 162.6, 155.1, 153.5, 151.6, 143.1, 142.1, 141.9, 141.8, 139.2, 139.1, 137.1, 134.8, 134.7, 134.4, 134.1, 133.9, 133.9, 133.6, 131.6, 129.7, 128.2, 128.0, 127.9, 127.6, 127.5, 127.1, 127.0, 126.9, 126.9, 126.4, 126.3, 125.5, 122.6, 121.2, 111.5, 109.2, 100.3, 27.6 ppm; HR-MS (ESI+ of MH$^+$, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{44}$H$_{33}$N$_4$O$_2$: 649.2604, found 649.2579.

Figure 6-4. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2a
Figure 6-5. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2a

Figure 6-6. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 2a (CHCl$_3$)
meso-Tetraphenyl-3-ethyl-3-hydroxy-2-oxachlorin (2b). Prepared from [meso-tetraphenyl-2-oxa-3-oxoporphyrinato]Zn(II) (1Zn, 100 mg, 0.145 mmol) according to the reaction procedure described for the preparation of 2a, except the reaction was performed using 5 equivalents of EtMgBr (2M solution in THF, 0.145 mL). The product 2b was isolated by flash chromatography (silica-CH₂Cl₂) as a purple solid in 65% (61.5mg) yield. MW = 662.78 g/mol; R_f = 0.55 (silica-CH₂Cl₂); UV-vis (CHCl₃) λ_max (log ε): 420 (5.59), 516 (4.16), 552 (4.45), 593 (4.19), 648 (4.84) nm; Fl λ_max (CHCl₃, λ_exc = 420 nm): 652, 710 nm, φ = 0.31; ¹H NMR (300 MHz, CDCl₃, δ): 8.59 (d, 3 J = 4.4 Hz, 1H), 8.48 (d, 3 J = 3.0 Hz, 1H), 8.43–8.34 (m, 2H), 8.35 (d, 3 J = 4.0 Hz, 1H), 8.17–7.59 (m, 21H), 3.75 (s, 1H), 2.38–2.32 (m, 1H), 1.99–1.94 (m, 1H), 0.75 (t, 3 J = 7.1 Hz, 3H), −0.64 (s, 1H), −1.04 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 163.2, 155.1, 152.1, 151.6, 143.1, 142.1, 141.9, 141.8, 139.4, 138.9, 137.1, 134.9, 134.4, 134.2, 134.1, 133.9, 133.8, 133.6, 131.5, 129.7, 128.3, 128.0, 127.9, 127.9, 127.7, 127.5, 127.1, 126.9, 126.9, 126.8, 126.3, 126.2, 125.5, 122.5, 121.2, 112.2, 111.6, 100.1, 32.5, 8.67 ppm; HR-MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₄₅H₃₅N₄O₂: 663.2760, found 663.2754
Figure 6-7. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2b

Figure 6-8. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2b
Figure 6-9. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 2b (CHCl3)

*meso*-Tetraphenyl-3-hydroxy-3-isopropyl-2-oxachlorin (2c). Prepared from [meso-tetraphenyl-2-oxa-3-oxoporphyrinato]Zn(II) (1Zn, 1.5 g, 2.15 mmol) according to the reaction procedure described for the preparation of 2a, except the reaction was performed using 2 equivalents of i-PrMgBr (2M solution in THF, 2.15 mL). The product 2c was isolated by flash chromatography (silica-CH2Cl2) as a purple solid in 75% yield (1090 mg). MW = 676.80 g/mol; Rf = 0.50 (silica-CH2Cl2); UV-vis (CHCl3) λmax (log ε): 420 (5.22), 516 (4.13), 550 (4.14), 592 (3.92), 649 (4.49) nm; Fl λmax (CHCl3, λexc = 420 nm): 653, 710 nm, φ = 0.35; 1H NMR (300 MHz, CDCl3, δ) 8.59 (d, 3J = 5.0 Hz, 1H), 8.45–8.47 (m, 3H), 8.34 (d, 3J = 4.5 Hz, 1H), 7.95–8.17 (m, 7H), 7.85 (m, 1H), 7.65–7.72 (m, 11H), 7.48–7.57 (m, 3H), 2.17–2.26 (m, 1H), 1.28 (d, 3J = 6.7 Hz, 3H), 0.67 (d, 3J = 6.7 Hz, 3H), −0.60 (s, 1H), −0.99 (s, 1H) ppm; 13C NMR (100 MHz, CDCl3,
Chapter 6: Alkyl-Oxazolochlorins

\[ \delta: 163.4, 155.2, 153.6, 151.7, 143.2, 142.2, 142.0, 139.4, 139.0, 137.2, 134.9, 134.4, 
134.2, 134.1, 133.9, 133.6, 131.6, 131.0, 129.8, 128.9, 128.3, 128.0, 127.9, 127.6, 127.2, 
127.0, 126.9, 126.3, 125.6, 122.67, 121.3, 113.6, 111.4, 100.2, 36.4, 30.0, 17.8, 16.1 
ppm; LR-MS (ESI+, 30 V, CH\textsubscript{3}CN): \textit{m/z} = 677 (MH\textsuperscript{+}); HR-MS (ESI+ of MH\textsuperscript{+}, 100% CH\textsubscript{3}CN, TOF): \textit{m/z} calc’d for C\textsubscript{46}H\textsubscript{37}N\textsubscript{4}O\textsubscript{2}: 676.2917, found 677.2918.

**Figure 6-10.** \textsuperscript{1}H NMR spectrum (400 MHz, CDCl\textsubscript{3}) of 2c

**Figure 6-11.** \textsuperscript{13}C NMR spectrum (100 MHz, CDCl\textsubscript{3}) of 2c
Figure 6-12. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 2c (CHCl₃)

meso-Tetrakis(4-trifluoromethylphenyl)-3-ethyl-3-hydroxy-2-oxachlorin (2Fb). Prepared from [meso-tetrakis(trifluoromethylphenyl)-2-oxa-3-oxoporphyrinato]-Zn(II) (1FZn, 113 mg, 0.117 mmol) according to the reaction procedure described for the preparation of 2a, except the reaction was performed at −45°C using 2 equivalents of EtMgBr (2M solution in THF, 117 µL). For best yield, the reaction should be maintained at −45°C until it is quenched. The product 2Fb was isolated by column chromatography (silica-50% petroleum ether/CH₂Cl₂) as a purple solid in 78% (85 mg) yield. MW = 934.8 g/mol; Rf = 0.26 (silica-50% petroleum ether 30-60/CH₂Cl₂); UV-vis (CHCl₃) λmax (log ε): 419 (5.13), 513 (4.00), 548 (3.99), 595 (3.75), 649 (4.45) nm, Fl λmax (CHCl₃, λexc = 419 nm): 654, 702 nm, φ = 0.29; ¹H NMR (300 MHz, CDCl₃, δ): 8.59 (d, ³J = 5.1 Hz, 1H), 8.45 (d, ³J = 3.9 Hz, 1H), 8.42 (d, ³J = 5.0 Hz, 1H), 8.39 (d, ³J = 4.6 Hz, 1H),
8.32 (d, $^3 J = 4.6$ Hz, 1H), 8.18–7.99 (m, 15H), 7.87 (d, $^3 J = 8.0$ Hz, 1H), 7.77 (d, $^3 J = 8.0$ Hz, 1H), 3.84 (s, 1H), 2.38–2.29 (m, 1H), 1.92–1.86 (m, 1H), 0.74 (t, $^3 J = 7.3$ Hz, 3H) – 0.63 (s, 1H), −0.99 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 163.2, 154.9, 152.3, 151.4, 145.4, 145.2, 142.9, 142.7, 142.3, 141.6, 136.9, 135.3, 134.2, 134.0, 134.0, 133.9, 133.8, 131.8, 130.0, 129.9, 127.7, 126.0, 125.7, 125.1, 125.1, 125.0, 124.3, 124.3, 124.1, 124.1, 124.0, 123.9, 123.9, 123.3, 123.3, 123.3, 122.8, 120.1, 112.3, 110.7, 99.2, 32.7, 8.57; HR-MS (ESI+ of MH$^+$, 100% CH$_3$CN, TOF): m/z calc’d for C$_{49}$H$_{31}$F$_{12}$N$_4$O$_2$: 935.2255, found 935.2236.

Figure 6-13. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2$^F$b
Figure 6-14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2$^f$b

Figure 6-15. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 2$^f$b (CHCl$_3$)
meso-Tetrakis(4-trifluoromethylphenyl)-3-hydroxy-3-isopropyl-2-oxachlorin (2^F_c). Prepared from [meso-tetrakis(trifluoromethylphenyl)-2-oxa-3-oxoporphyrinato]-Zn(II) (1^F_Zn, up to 500 mg scale) according to the reaction procedure described for the preparation of 2a, except the reaction was performed using i-PrMgCl (2M solution in THF, 0.515 mL for 500 mg scale) maintained at –78°C. The product 2^F_c was isolated by chromatography (silica-50% petroleum ether 30-60/CH₂Cl₂) as a purple solid in 80-85% yield (up to 415 mg). MW = 948.8  g/mol; R_f = 0.32 (silica-50% petroleum ether 30-60/CH₂Cl₂); UV-vis (CHCl₃) λ_{max} (log ε): 420 (5.24), 513 (4.10), 548 (4.09), 595 (3.88), 650 (4.55) nm; Flλ_{max} (CHCl₃, λ_{exc} = 420 nm): 655, 703 nm, φ = 0.36; ¹H NMR (300 MHz, CDCl₃, δ): 8.57 (d, 3^J = 4.9 Hz, 1H), 8.42 (m, 2H), 8.36 (d, 3^J = 4.5 Hz, 1H), 8.15–7.95 (m, 19H), 3.87 (s, 1H), 2.14–2.08 (m, 1H), 1.28 (d, 3^J = 6.5 Hz, 3H), 0.65 (d, 3^J = 6.7 Hz, 3H), –0.63 (s, 1H), –0.99 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 163.2, 154.8, 153.7, 151.3, 145.4, 145.1, 142.8, 142.7, 142.4, 141.8, 141.8, 141.8, 136.9, 135.3, 134.2, 134.1, 134.0, 133.9, 133.9, 133.9, 133.7, 131.7, 129.8, 127.7, 125.7, 125.0, 124.3, 124.2, 124.2, 124.1, 124.0, 124.0, 123.9, 123.8, 123.3, 123.3, 123.3, 123.2, 122.8, 120.1, 113.6, 110.4, 99.1, 36.4, 17.5, 15.9; HR-MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₅₀H₃₃F₁₂N₄O₂: 949.2412, found 949.2431.
Figure 6-16. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of $2^F$c

Figure 6-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of $2^F$c
Figure 6-18. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of $2^f_c$ (CHCl$_3$)

*meso*-Tetraphenyl-3-methyl-2-oxachlorin (3a). General procedure for the conversion of hemiketal 9 to mono-alkyl oxazolochlorin 10. *meso*-Tetraphenyl-3-hydroxy-3-methyl-2-oxachlorin (2a, 54 mg, 0.083 mmol), was dissolved in CH$_2$Cl$_2$ and stirred at room temperature. To this solution, excess BF$_3$·OEt$_2$ (20 eq, 0.2 mL) and Et$_3$SiH (20 eq, 0.26 mL) were added slowly. The reaction was mixture was left stirring overnight. Reaction progress was monitored using UV-visible spectroscopy (formation of the diagnostic peak at ~660 nm in a neutralized aliquot). Upon completion, the reaction mixture was quenched by addition of a saturated aq NaHCO$_3$ solution. The mixture was transferred into a separatory funnel. The aq NaHCO$_3$ wash was repeated until the organic layer was purple/green in color. The organic layer was isolated, dried over Na$_2$SO$_4$, and the solvent was evaporated by rotary evaporation. The crude product was purified by
flash chromatography (silica–CH₂Cl₂) to afford the product 3a as a purple solid in 88% yield (46 mg). MW = 632.8 g/mol; Rf = 0.89 (silica–CH₂Cl₂); UV–vis (CHCl₃) λ_max (log ε): 424 (5.25), 519 (4.05), 557 (3.94), 610 (3.79), 667 (4.61) nm; Fl λ_max (CHCl₃, λ_exc = 424 nm): 672, 718 nm, φ = 0.29; ¹H NMR (300 MHz, CDCl₃, δ): 8.47 (s, 1H), 8.40 (s, 1H), 8.31–8.24 (m, 3H), 8.16–7.95 (m, 10H), 7.71 (s, 12H), 7.10 (d, ³J = 5.6 Hz, 1H), 1.60 (d, ³J = 5.4 Hz, 3H), 0.09 (s, 1H), −0.29 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 167.9, 159.7, 154.7, 151.4, 143.9, 142.1, 141.9, 141.8, 140.4, 139.2, 136.7, 134.9, 134.2, 134.0, 133.9, 133.8, 133.7, 132.9, 131.1, 129.8, 129.1, 128.2, 128.1, 128.0, 127.97, 127.91 127.8, 127.1, 126.99, 126.94, 126.4, 124.62, 121.61, 121.1, 108.7, 99.3, 83.0, 21.8 ppm; HR–MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₄₄H₃₃N₄O: 633.2654, found 633.2646.
Figure 6-19. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3a

Figure 6-20. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3a
Figure 6-21. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 3a (CHCl₃)

*meso*-Tetraphenyl-3-ethyl-2-oxachlorin (3b). Prepared from *meso*-tetraphenyl-3-ethyl-3-hydroxy-2-oxachlorin (2b, 45 mg, 0.07 mmol) according to the reaction procedure described for the preparation 3a. The product 3b was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 85% (38 mg) yield. MW = 646.8 g/mol; Rₚ = 0.92 (silica–CH₂Cl₂); UV–vis (CHCl₃) λₘₐₓ (log ε): 425 (5.36), 520 (4.18), 556 (4.06), 610 (3.92), 667 (4.70) nm; Fl λₘₐₓ (CHCl₃, λₑₓᶜₑₓ = 424 nm): 673, 718 nm, φ = 0.20; ¹H NMR (300 MHz, CDCl₃, δ): 8.45 (dd, ³J = 4.8, ⁴J = 0.8 Hz, 1H), 8.38 (dd, ³J = 4.4, ⁴J = 1.2 Hz, 1H), 8.29 (d, ³J = 4.5 Hz, 1H), 8.23 (m, 2H), 8.15–7.92 (m, 9H), 7.70–7.65 (m, 12H), 7.08 (dd, ³J = 7.9, ⁴J = 3.5 Hz, 1H), 2.06–1.99 (m, 1H), 1.75–1.69 (m, 1H), 0.69 (t, ³J = 7.4 Hz, 3H), 0.08 (s, 1H), −0.31 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 168.7, 157.9, 154.7, 151.4, 143.9, 142.1, 141.9, 141.8, 140.5, 139.3,
136.7, 134.5, 134.2, 133.99, 133.92, 133.8, 133.75, 133.70, 133.6, 132.9, 131.1, 130.8, 129.8, 129.1, 128.22, 128.18, 128.0, 127.99, 127.96, 127.92, 127.8, 127.7, 127.1, 127.0, 126.9, 126.4, 124.6, 121.6 121.1, 108.9, 99.1, 87.5, 27.7, 8.1 ppm; HR–MS (ESI+ of MH\(^+\), 100% CH\(_3\)CN, TOF): \(m/z\) calc’d for C\(_{45}\)H\(_{35}\)N\(_4\)O: 647.2811, found 647.2814.

Figure 6-22.\(^{1}\)H NMR spectrum (400 MHz, CDCl\(_3\)) of 3b
Figure 6-23. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3b

Figure 6-24. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 3b (CHCl$_3$)
meso-Tetraphenyl-3-isopropyl-2-oxachlorin (3c). Prepared from meso-tetraphenyl-3-hydroxy-3-isopropyl-2-oxachlorin (2c, 100 mg, 0.14 mmol) according to the reaction procedure described for the preparation of 3a. The product 3c was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 76% (75 mg) yield. MW = 660.8 g/mol; R₇ = 0.90 (silica–CH₂Cl₂); UV-vis (CHCl₃) λ_max (log ε): 423 (5.27), 519 (4.14), 556 (4.03), 611 (3.93), 668 (4.63) nm; Fl λ_max (CHCl₃, λ_exc = 423 nm): 674, 728 nm, φ = 0.26; ¹H NMR (300 MHz, CDCl₃, δ): 8.45 (dd, ³J = 4.7, ⁴J = 1.5 Hz, 1H), 8.38 (dd, ³J = 4.7, ⁴J = 1.8 Hz, 1H), 8.29 (d, ³J = 4.5 Hz, 1H), 8.27 (dd, ³J = 5.0, ⁴J = 1.7 Hz, 1H), 8.21 (d, ³J = 4.5 Hz, 1H), 8.13–8.17 (m, 2H), 7.92–8.02 (m, 6H), 7.64–7.72 (m, 13H), 6.90 (d, ³J = 2.3 Hz, 1H), 1.95–2.25 (m, 1H), 1.10 (d, ³J = 6.8 Hz, 3H), 0.50 (d, ³J = 6.8 Hz, 3H), 0.11 (s, 1H), −0.28 (s, 1H ) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 168.9, 158.0, 154.6, 151.3, 143.8, 142.0, 141.9, 141.8, 140.5, 139.2, 136.6, 134.5, 134.1, 133.9, 133.8, 133.7, 133.6, 133.3, 132.8, 130.9, 130.6, 129.8, 129.0, 128.1, 127.9, 127.8, 127.7, 127.5, 127.1, 126.9, 126.8, 126.3, 124.6, 121.5, 121.0, 108.9, 98.8, 91.1, 32.9, 31.8, 20.4, 14.4 ppm; HR–MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₄₆H₃₇N₄O: 661.2967, found 661.2932.
Figure 6-25. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3c

Figure 6-26. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3c
Figure 6-27. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 3c (CHCl₃)

**meso-Tetrakis(4-trifluoromethylphenyl)-3-ethyl-2-oxachlorin (3Fb).** Prepared from *meso*-tetrakis(trifluoromethylphenyl)-3-ethyl-3-hydroxy-2-oxachlorin (2Fb, 80 mg, 8.5 × 10⁻⁵ mol) according to the reaction procedure described for the preparation of 3a.

The product 3Fb was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 71% (56 mg) yield. MW = 918.7 g/mol; Rᵣ = 0.93 (silica–50% petroleum ether 30-60/CH₂Cl₂); UV-vis (CHCl₃) λ_max (log ε): 424 (5.12), 518 (3.96), 553 (3.78), 613 (3.71), 669 (4.53) nm; Fl λ_max (CHCl₃, λ_exc = 424 nm): 675, 720 nm, φ = 0.27; ¹H NMR (300 MHz, CDCl₃, δ): 8.41 (dd, ²J = 5.0, ⁴J = 1.5 Hz, 1H), 8.33 (dd, ²J = 4.7, ⁴J = 1.7 Hz, 1H), 7.95–8.25 (m, 20H), 7.05–7.07 (m, 1H), 1.99–2.06 (m, 1H), 1.66–1.73 (m, 1H), 0.70 (t, ²J = 7.4 Hz, 3H), 0.09 (s, 1H), –0.29 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ):

168.6, 158.1, 154.4, 151.1, 145.4, 145.2, 143.9, 143.7, 142.7, 141.5, 136.5, 134.7, 134.0,
Chapter 6: Alkyl-Oxazolochlorins

133.9, 133.8, 133.7, 133.1, 131.3, 131.2, 130.9, 130.7, 130.4, 130.28, 130.17, 129.9, 129.8, 128.1, 126.3, 126.2, 126.1, 126.0, 125.8, 125.3, 125.28, 125.22, 125.17, 125.14, 125.10, 125.06, 125.0, 124.9, 124.3, 124.27, 124.24, 124.20, 124.1, 124.09, 124.0, 123.4, 123.3, 123.1, 121.2, 120.5, 107.9, 98.2, 87.5, 27.9, 8.1 ppm; HR-MS (DART⁺, 100% CH₃CN, orifice voltage 20 V, TOF, of MH⁺): m/z calc’d for C₄₉H₃₁F₁₂N₄O: 919.2306, found 919.2331.

Figure 6-28. ¹H NMR spectrum (400 MHz, CDCl₃) of 3°b
Figure 6-29. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of $3^5$b

Figure 6-30. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of $3^5$b (CHCl$_3$)
meso-Tetrakis(4-trifluoromethylphenyl)-3-isopropyl-2-oxachlorin (3Fc).

Prepared from meso-tetrakis(4-trifluoromethylphenyl)-3-hydroxy-3-isopropyl-2-oxachlorin (2Fc, 52 mg, 6.0 × 10⁻⁵ mol) according to the reaction procedure described for the preparation of 3a. The product 3Fc was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 84% (43 mg) yield. MW = 932.8 g/mol; Rᵣ = 0.93 (silica–50% petroleum ether 30-60/CH₂Cl₂); UV–vis (CHCl₃) λₑₓₑₘₐₓ (log ε): 425 (5.14), 519 (3.98), 555 (3.81), 615 (3.74), 670 (4.54) nm; Fl λₑₓₑₘₐₓ (CHCl₃, λₑₓₑₜᵣₑₜ = 424 nm): 676, 722 nm, ϕ = 0.24; ¹H NMR (300 MHz, CDCl₃, δ): 8.41 (d, J = 4.7 Hz, 1H), 8.32 (d, J = 4.8 Hz, 1H), 8.07 (m, 20H), 6.95 (s, 1H), 1.90–1.95 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H), 0.48 (d, J = 6.0 Hz, 3H), 0.10 (s, 1H), −0.27 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 168.9, 158.2, 154.4, 151.1, 145.4, 145.2, 144.1, 143.7, 142.7, 141.6, 135.6, 134.7, 133.9, 133.8, 133.7, 133.1, 131.2, 130.9, 130.6, 130.4, 130.3, 130.1, 139.9, 128.1, 126.2, 126.1, 126.0, 125.3, 125.2, 125.1, 124.9, 124.3, 124.2, 124.1, 123.3, 121.2, 120.4, 107.9, 98.0, 91.3, 33.3, 20.4, 14.4 ppm; HR–MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₅₀H₃₃F₁₂N₄O: 933.2463, found 933.2433.
Figure 6-31. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of $3^F$c

Figure 6-32. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of $3^F$c
meso-Tetraphenyl-3,3-dimethyl-2-oxachlorin (4a). General procedure for the conversion of porpholactone \(4Zn\) to bis-alkyloxazolochlorin 11. Step 1: Lactone zinc(II) complex 1Zn (103 mg, 0.15 mmol) was dissolved in dry THF and stirred under \(N_2\) at room temperature and 3 equivalents of MeMgBr (3 M solution in THF, 0.15 mL) were added. The reaction progress was monitored using UV-visible spectroscopy (development of an intense peak at \(~625\) nm indicates the formation of the acetal moiety). Upon completion (~30 min), the reaction was quenched and washed with distilled \(H_2O\) in a separatory funnel. The organic phase was extracted with \(CH_2Cl_2\), the organic phase isolated, and reduced to dryness using a rotary evaporator. The residue was then dissolved in dry THF (10 mL), and passed through a plug of \(Na_2SO_4\) and dried using rotary evaporation. Step 2: The round bottom flask containing the dried residue from part
1 was purged with \( \text{N}_2 \) prior to adding dry THF (10 mL). Under \( \text{N}_2 \), 2.5 equivalents of TMSOTf (0.067 mL) was added and stirred for 5-10 min, followed by 5 equivalents of MeMgBr (0.25 mL of a 3 M solution in THF). In order to avoid incomplete reaction, the molar equivalents of alkyl-Grignard should double that of TMSOTf in this step. The reaction progress was monitored by UV-visible spectroscopy (a small aliquot is being treated with drops of 6 M HCl and neutralizing with aq NaHCO₃, the formation of a peak at ~665 nm indicates the formation of the product). Step 3: Upon completion, the reaction was quenched with water (1-2 mL), then 6M HCl (10 mL) was added to the reaction mixture to affect demetalation. The reaction mixture was stirred until the demetalation was complete (as monitored by UV-visible spectroscopy; formation of a free-base chlorin spectrum upon neutralization indicates the formation of the product). Once demetalation was achieved, the mixture was neutralized with a saturated aq NaHCO₃ solution in a separatory funnel. CH₂Cl₂ (10 mL) were added and the organic phase was isolated and dried using rotary evaporator. Product 4a was isolated and purified by column chromatography (silica–CH₂Cl₂) as a purple solid in 74% yield (71 mg). MW = 646.8 g/mol; \( R_f = 0.96 \text{ (silica–CH₂Cl₂)} \); UV–vis (CHCl₃) \( \lambda_{\text{max}} \) (log \( \varepsilon \)): 424 (5.10), 519 (3.93), 556 (3.87), 607 (3.75), 666 (4.42) nm; Fl \( \lambda_{\text{max}} \) (CHCl₃, \( \lambda_{\text{exc}} = 425 \) nm): 668, 715 nm, \( \phi = 0.19 \); 

\(^1\text{H NMR (300 MHz, CDCl₃, } \delta)\): 8.42 (dd, \( ^3J = 5.2, ^4J = 1.4 \) Hz, 1H), 8.28 (dd, \( ^3J = 4.5, ^4J = 1.9 \) Hz, 1H), 8.25 (d, \( ^3J = 4.5, 1\)H), 8.22–8.20 (m, 1H), 8.18 (d, \( ^3J = 4.5, 1\)H), 8.06–7.58 (m, 21H), 1.85 (s, 6H), 0.06 (s, 1H), –0.33 (s, 1H) ppm; due to its poor solubility, high-
quality $^{13}$C NMR spectra could not be obtained; HR–MS (ESI+ of $M^+$, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{45}$H$_{34}$N$_4$O: 646.2733, found 646.2729.

**Figure 6-34.** $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4a

**Figure 6-35.** UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 4a (CHCl$_3$)
meso-Tetraphenyl-3,3-diethyl-2-oxachlorin (4b). Prepared from [meso-tetraphenyl-2-oxa-3-oxoporphyrinato]Zn(II) (1Zn, 103 mg, 0.15 mmol) and EtMgCl according to the reaction procedure described for the preparation of 4a except for the following: In Step 1, 1.5 equivalents of EtMgCl (3 M solution in THF, 0.075 mL) was used with the reaction time of ~5 min at room temperature. In Step 2, 2 equivalents of TMSOTf (0.054 mL) were added at room temperature and stirred for ~5 min, then 4 equivalents of EtMgCl (3M solution in THF, 0.198 mL) were added and the solution stirred for additional ~5 min at room temperature. (Note: increased reaction time does not result in better yield, in fact, the opposite effect was noticed.) The product 4b was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 45% (45 mg) yield. MW = 674.8 g/mol; Rᵥ = 0.9 (silica-CH₂Cl₂); UV-vis (CHCl₃) λᵥₑₘₐₓ (log ε): 425 (5.10), 517 (3.87), 556 (3.76), 608 (3.66), 664 (4.45) nm; Fl λᵥₑₘₐₓ (CHCl₃, λₑₓᶜₑᵣ = 425 nm): 669, 719 nm, φ = 0.30;¹H NMR (300 MHz, CDCl₃, δ): 8.43 (d, ³J = 4.9 Hz, 1H), 8.30 (d, ³J = 4.2 Hz, 1H), 8.27 (d, ³J = 4.4 Hz, 1H), 8.20 (d, ³J = 4.4 Hz, 2H), 8.06 (d, ³J = 6.1 Hz, 4H) 7.96–7.91 (m, 4H), 7.69–7.56 (m, 14H), 2.15–2.04 (m, 4H), 0.78 (t, ³J = 7.2 Hz, 6H), 0.11 (s, 1H), –0.32 (s, 1H) ppm;¹³C NMR (100 MHz, CDCl₃, δ): 167.6, 157.9, 154.8, 150.9, 143.8, 142.8, 142.2, 141.8, 139.9, 139.4, 137.0, 133.9, 133.8, 133.7, 133.6, 133.5, 132.9, 130.6, 129.6, 128.4, 127.9, 127.8, 127.5, 127.4, 127.1, 126.8, 126.6, 126.5, 125.0, 121.5, 120.9, 109.0, 99.1, 97.4, 34.0, 8.3; HR–MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₄₇H₃₈N₄O: 674.3046, found 674.3031.
Figure 6-36. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4b

Figure 6-37. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4b
Chapter 6: Alkyl-Oxazolochlors

Figure 6-38. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 4b (CHCl₃)

*meso*-Tetraphenyl-3,3-diisopropyl-2-oxachlorin (4c). Prepared from [*meso*-tetraphenyl-2-oxa-3-oxophyrinato]Zn(II) (1Zn, 250 mg, 0.36 mmol) and i-PrMgCl according to the reaction procedure described for the preparation of 4a except for the following: In Step 1, 2 equivalents i-PrMgCl (2M solution in THF, 0.36 mL) were added slowly and stirred for 5 min at r.t. In Step 2, 2 equivalents of TMSOTf (0.13 mL) were added at r.t. and stirred for 5 min, then 4 equivalents of i-PrMgCl (2 M solution in THF, 0.72 mL) were added and stirred for ~5 min. Product 4c was isolated by flash chromatography (silica–CH₂Cl₂) as a purple solid in 61% (152 mg) yield. MW = 702.3 g/mol; Rᵣ = 0.9 (silica–CH₂Cl₂); UV–vis (CHCl₃) λₘₐₓ (log ε): 424 (5.06), 516 (3.88), 554 (3.75), 609 (3.66), 667 (4.38) nm; Fl λₘₐₓ (CHCl₃, λₑₓc 425 nm): 670, 726 nm, φ = 0.31;

¹H NMR (300 MHz, CDCl₃, δ): 8.43 (d, 3J = 4.8 Hz, 1H), 8.24–8.27 (m, 3H), 8.17 (m,
1H), 8.03–8.06 (m, 4H), 7.91–7.96 (m, 4H), 7.57–7.69 (m, 13H), 2.55–2.59 (m, 2H), 1.07 (d, $^3J = 6.6$ Hz, 6H), 0.66 (d, $^3J = 6.8$ Hz, 6H), 0.08 (s, 1H), –0.30 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 167.6, 161.1, 154.8, 150.8, 143.5, 142.4, 141.8, 140.3, 140.1, 137.1, 134.8, 134.1, 133.9, 133.7, 133.6, 133.4, 132.9, 130.5, 129.5, 128.4, 127.9, 127.8, 127.7, 127.5, 127.4, 127.2, 126.9, 126.8, 126.7, 126.4, 125.1, 122.1, 120.7, 108.9, 100.9, 99.2, 36.9, 19.3, 18.9; HR–MS (ESI+ of MH$^+$, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{49}$H$_{43}$N$_4$O: 703.3437, found 703.3459.

**Figure 6-39.** $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4c
Figure 6-40. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4c

Figure 6-41. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 4c (CHCl$_3$)
meso-Tetrakis(4-trifluoromethylphenyl)-3,3-diethyl-2-oxachlorin (4Fb).

Prepared from [meso-tetrakis(4-trifluoromethylphenyl)-2-oxa-3-oxoporphyrinato]Zn(II) (1FZn, 40 mg, 4.1 \times 10^{-5} \text{ mol}) and EtMgCl according to the reaction procedure described for the preparation of 4a, except for the following: In Step 1, 2 equivalents of EtMgCl (2M solution in THF, 0.041 mL) were added at –45 °C. In Step 2, 3 equivalents of TMSOTf (0.022mL) were added and the solution was stirred for ~90 min at –45 °C. Into the reaction mixture, 10 equivalents of EtMgCl (2M solution in THF, 0.205 mL) were added at -45 °C. The reaction was then stirred for ~4 h at –45°C while the progress was closely monitored as described in the preparation of 4a. The product 4Fb was isolated by chromatography (silica–60% petroleum ether 30-60/CH₂Cl₂) as a purple solid in 51% (20 mg) yield. MW = 946.8 g/mol; Rf = 0.97 (silica–50% petroleum ether 30-60/CH₂Cl₂); UV-vis (CHCl₃) \( \lambda_{\text{max}} \) (log \( \varepsilon \)): 423 (5.15), 516 (3.99), 553 (3.86), 609 (3.82), 666 (4.56) nm; Fl \( \lambda_{\text{max}} \) (CHCl₃, \( \lambda_{\text{exc}} = 424 \text{ nm})$: 671, 721 nm, \( \phi = 0.29 \); \textsuperscript{1}H NMR (300 MHz, CDCl₃, \( \delta \)): 8.41 (d, \( \textbf{J} = 4.29 \text{ Hz, 1H} \)), 8.26 (d, \( \textbf{J} = 3.40 \text{ Hz, 1H} \)), 8.2–7.08 (m, 19H), 7.61 (d, \( \textbf{J} = 3.60 \text{ Hz, 1H} \)), 2.20–2.17(m, 2H), 2.01–1.97 (m, 2H), 0.79 (t, \( \textbf{J} = 7.18 \text{ Hz, 6H} \)), 0.10 (s, 1H), –0.31 (s, 1H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl₃, \( \delta \)): 167.4, 158.2, 154.6, 150.7, 145.5, 145.5, 143.6, 143.26, 143.25, 142.98, 142.97, 142.5, 136.9, 134.0, 133.9, 133.71, 133.66, 133.5, 133.2, 130.9, 129.8, 127.7, 125.33, 125.29, 124.34, 124.31, 124.27, 124.1, 124.04, 124.01, 123.8, 123.7, 121.8, 119.8, 108.0, 98.2, 97.7, 34.1, 8.2 ppm; HR–MS (ESI+ of MH\(^+\), 100% CH\(_3\)CN, TOF): \textit{m/z} calc’d for C\(_{51}\)H\(_{35}\)F\(_{12}\)N\(_4\)O: 947.2619, found 947.2603.
Chapter 6: Alkyl-Oxazolochlorins

Figure 6-42. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4$^f$b

Figure 6-43. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4$^f$b
Figure 6-44. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of $4^F_b$ (CHCl$_3$)

*meso*-Tetrakis(4-trifluoromethylphenyl)-3,3-diisopropyl-2-oxachlorin ($4^F_c$).

Prepared from [*meso*-tetrakis(4-trifluoromethylphenyl)-2-oxa-3-oxo-porphyrinato]Zn(II) ($4^F_Zn$, 53 mg, $5.5 \times 10^{-5}$ mol) and $i$-PrMgCl according to the reaction procedure described for the preparation of $4a$ except for the following: In Part 1, 3 equivalents of $i$-PrMgCl (2M solution in THF, 0.083 mL) were added and the solution stirred for ~1 h at $-78^\circ C$. In Step 2, 3 equivalents of TMSOTf (0.03 mL) were added and the reaction was stirred for ~1 h at $-78^\circ C$. Next, 6 equivalents of $i$-PrMgCl (2M solution in THF, 0.164 mL) was added at $-78^\circ C$, then the reaction was stirred for about ~1 h at this temperature. The product $4^F_c$ was isolated by column chromatography (silica–60% petroleum ether 30–60/CH$_2$Cl$_2$) as a purple solid in 56% (30 mg) yield. MW = 974.3 g/mol; $R_f = 0.97$ (silica-50% petroleum ether 30-60/CH$_2$Cl$_2$); UV-vis $\lambda_{max}$ (log $\varepsilon$): 425 (5.29), 517 (4.11),
554 (3.95), 610 (3.92), 668 (4.67) nm; Fl $\lambda_{\text{max}}$ (CHCl$_3$, $\lambda_{\text{exc}}$ = 425 nm): 673, 718 nm, $\phi$ = 0.27; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 8.41 (d, $^3J$ = 4.4 Hz, 1H), 8.22–7.88 (m, 20H), 7.53 (d, $^3J$ = 2.5 Hz, 1H), 2.55–2.48 (m, 2H), 1.09 (d, $^3J$ = 6.2 Hz, 6H), 0.67 (d, $^3J$ = 6.6 Hz, 6H), 0.08 (s, 1H), −0.03 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 167.5, 161.4, 154.6, 150.5, 145.6, 145.0, 143.9, 143.5, 143.3, 143.0, 136.9, 134.2, 134.0, 133.7, 133.6, 133.4, 133.2, 130.9, 130.7, 129.7, 127.7, 125.3, 125.2, 124.98, 124.95, 124.33, 124.30, 124.0, 123.9, 123.8, 123.7, 122.3, 119.7, 107.9, 101.4, 98.2, 37.0, 19.3, 19.0; HR–MS (ESI+ of MH$^+$, 100% CH$_3$CN, TOF): $m/z$ calc’d for C$_{53}$H$_{39}$F$_{12}$N$_4$O: 975.2932, found 975.2901.

Figure 6-45. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4$_F$c
Figure 6-46. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of $4^F$c

Figure 6-47. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of $4^F$c (CHCl$_3$)
meso-Tetraphenyl-3-isopropyl-3-methoxy-2-oxachlorin (5c). General procedure for the conversion of hemiketals 2 to ketals 5. Hemiacetal meso-tetraphenyl-3-hydroxy-3-isopropyl-2-oxachlorin (2c, 190 mg, 0.28 mmol) was dissolved with 30% MeOH in THF (v/v), and stirred at r.t. A catalytic amount (few small drops) of TFA was added. Reaction progress was monitored using TLC and complete conversion typically required overnight stirring (15–18 h). Upon completion, the reaction was quenched by addition of Et₃N (~2-3 mL, added drop-wise until solution turns to pink/red). The neutralized solution was evaporated by rotary evaporation. The bright pink, non-polar product 5c was isolated by column chromatography (silica–CH₂Cl₂) as a purple solid in excellent yield (181 mg, 93%). MW = 690.83 g/mol; Rf = 0.88 (silica-CH₂Cl₂); UV-vis (CHCl₃) λ_{max} (log ε): 421 (4.94), 516 (3.76), 551 (3.77), 595 (3.52), 650 (4.19) nm; Fl λ_{max} (CHCl₃, λ_exc = 420 nm): 653, 702 nm, φ = 0.36; ¹H NMR (300 MHz, CDCl₃, δ): 8.61 (d, ³J = 4.9 Hz, 1H), 8.49 (d, ³J = 4.9 Hz, 1H), 8.45 (d, ³J = 5.0 Hz, 1H), 8.43 (d, ³J = 4.5 Hz, 1H), 8.36 (d, ³J = 4.5 Hz, 1H), 8.18–7.99 (m, 8H), 7.86–7.55 (m, 13H), 3.04 (s, 3H), 2.19 (m, 1H), 1.22 (d, ³J = 6.5 Hz, 3H), 0.67 (d, ³J = 6.5 Hz, 3H), −0.56 (s, 1H), −0.99 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 164.1, 155.1, 151.6, 150.9, 143.0, 142.2, 142.0, 141.8, 139.4, 138.8, 137.0, 134.2, 134.1, 133.9, 133.8, 133.5, 133.4, 131.5, 129.7, 128.2, 128.0, 127.9, 127.6, 127.5, 127.1, 126.9, 126.2, 126.1, 125.5, 122.6, 121.2, 117.5, 111.4, 99.8, 50.9, 35.8, 17.4, 16.5, ppm; HR–MS (ESI+ of MH⁺, 100% CH₃CN, TOF): m/z calc’d for C₄₇H₃₉N₄O₂: 691.3073, found 691.3062.
General procedure for the reversion of ketals 5 to hemiketals 2. Ketal 5c (100 mg, 0.145 mmol) was dissolved in 10% 3 M HCl in THF (v/v) and stirred overnight at 45 °C. The reaction was washed with aq. NaHCO₃ solution and the organic layer was extracted using CH₂Cl₂. The organic layer was evaporated by rotary evaporation and the product was isolated by flash chromatography (CH₂Cl₂) as a purple solid in 90-95% yield (88-93 mg).

Figure 6-48. ¹H NMR spectrum (400 MHz, CDCl₃) of 5c
Figure 6-49. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5c

Figure 6-50. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 5c (CHCl$_3$)
meso-Tetrakis(4-trifluoromethylphenyl)-3-isopropyl-3-methoxy-2-oxachlorin (5\textsuperscript{F}c). Prepared from meso-tetrakis(4-trifluoromethylphenyl)-3-hydroxy-3-isopropyl-2-oxachlorin (2\textsuperscript{F}c, 51 mg, 5.4 × 10\textsuperscript{-5} mol) according to the procedure described for the preparation 5c. The product 5\textsuperscript{F}c was isolated by flash chromatography (silica-CH\textsubscript{2}Cl\textsubscript{2}) as a purple solid in 70% (36 mg) yield. MW = 962.8 g/mol; R\textsubscript{f} = 0.88 (silica–30% petroleum ether 30-60/CH\textsubscript{2}Cl\textsubscript{2}); UV–vis (CHCl\textsubscript{3}) \( \lambda_{\text{max}} \) (log \( \varepsilon \)): 420 (5.22), 514 (4.11), 548 (4.11), 595 (3.60), 652 (4.54) nm; Fl \( \lambda_{\text{max}} \) (CHCl\textsubscript{3}, \( \lambda_{\text{exc}} \) 420 nm): 655, 703 nm, \( \phi = 0.35 \); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, \( \delta \)): 8.56 (d, \( ^3J = 3.8 \) Hz, 1H), 8.42 (t, \( ^3J = 3.9 \) Hz, 2H), 8.34 (d, \( ^3J = 4.5 \) Hz, 1H), 7.85–8.28 (m, 18H), 3.04 (s, 3H), 2.04–2.09 (m, 1H), 1.19 (d, \( ^3J = 6.4 \) Hz, 3H), 0.63 (d, \( ^3J = 6.8 \) Hz, 3H), –0.62 (s, 1H), –1.02 (s, 1H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, \( \delta \)): 164.0, 154.8, 151.4, 151.3, 145.4, 145.1, 142.9, 142.8, 142.3, 141.7, 136.9, 134.2, 133.95, 133.92, 133.88, 133.81, 133.7, 133.6, 131.7, 130.6, 130.4, 130.3, 129.9, 127.8, 126.1, 125.7, 125.2, 125.1, 125.05, 125.00, 124.98, 124.96, 124.4, 124.3, 124.2, 124.1, 123.4, 123.3, 123.2, 122.8, 120.1, 117.7, 110.4, 98.8, 51.0, 36.0, 17.3, 16.5 ppm; HR–MS (ESI\textsuperscript{+} of MH\textsuperscript{+}, 100% CH\textsubscript{3}CN, TOF): \( m/\zeta \) calc’d for C\textsubscript{51}H\textsubscript{35}F\textsubscript{12}N\textsubscript{4}O\textsubscript{2}: 963.2568, found 963.2539.
Figure 6-51. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5$^c$F

Figure 6-52. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5$^c$F
Figure 6-53. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of $5^6\text{c}$ (CHCl$_3$)

$[\text{meso-Tetraphenyl-3-isopropyl-3-methoxy-2-oxachlorinate}]\text{Zn(II)}$ ($5\text{cZn}$).

$\text{meso-Tetraphenyl-3-isopropyl-3-methoxy-2-oxachlorin}$ ($5\text{c}$, 67 mg, $9.7 \times 10^{-5}$ mol), was dissolved in 30% MeOH/CHCl$_3$ (v/v) and heated to reflux. A solution of Zn(OAc)$_2$$\cdot$$\text{H}_2\text{O}$ (~5-7 eq, 100-150 mg) in MeOH (5–10 mL) was added and the mixture was stirred and heated overnight. The reaction progress was monitored by TLC (silica–CH$_2$Cl$_2$; the bright pink non-polar starting material is converted to a more polar green spot). Upon completion, the product was isolated by rotary evaporation, followed by flash chromatography (silica–CH$_2$Cl$_2$). The material was obtained as crystalline material by crystallization using a slow solvent exchange from CH$_2$Cl$_2$ to MeOH or pentane as a green crystalline solid (65%, 47 mg). MW = 754.2 g/mol; $R_f = 0.50$ (silica–CH$_2$Cl$_2$); UV-vis (CHCl$_3$) $\lambda_{\text{max}}$ (log $\varepsilon$): 417 (5.36), 455 (4.07), 516 (3.76), 581 (3.88), 622 (4.58) nm; Fl $\lambda_{\text{max}}$ (CHCl$_3$, $\lambda_{\text{exc}}$ =
420 nm): 626, 679 nm, \( \phi = 0.19 \); \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \)): 8.58 (d, \(^3\)J = 4.7 Hz, 1H), 8.49 (d, \(^3\)J = 3.3 Hz, 1H), 8.41–8.33 (m, 3H), 8.13–7.88 (m, 9H), 7.78–7.58 (m, 12H), 3.1 (s, 3H), 2.26–2.17 (m, 1H), 1.25 (d, \(^3\)J = 6.4 Hz, 3H), 0.75 (d, \(^3\)J = 6.6 Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 162.2, 156.0, 155.1, 149.9, 147.9, 146.6, 145.3, 145.2, 142.4, 139.6, 139.3, 134.2, 133.9, 133.8, 133.7, 133.65, 133.60, 133.5, 133.1, 132.0, 130.3, 128.5, 128.4, 128.1, 128.0, 127.98, 127.87, 127.82, 127.7, 127.3, 127.0, 126.9, 126.8, 126.3, 126.2, 122.9, 117.6, 112.5, 98.5, 50.9, 36.1, 17.5, 16.2 ppm; HR–MS (ESI+ of MH\(^+\), 100% CH\(_3\)CN, TOF): \( m/z \) calc’d for C\(_{47}\)H\(_{36}\)N\(_4\)O\(_2\)Zn: 752.2130, found 752.2120.

Figure 6-54. \(^1\)H NMR spectrum (400 MHz, CDCl\(_3\)) of 5cZn
Figure 6-55. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5cZn

Figure 6-56. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 5cZn (CHCl$_3$)
6.4.3. X-ray Crystallography Data

X-ray crystallographic analysis (provided by Dr. Christopher Ziegler and James T. Engle, University of Akron): Single crystals of 2c, 4c, and 5cZn were coated in Fomblin® oil, mounted on a CryoLoop™ and placed on the goniometer head under a stream of nitrogen cooled to 100 K. The data were collected on a Bruker APEX2 CCD diffractometer with either IµS microfocus Cu source Kα radiation (λ = 1.54178 Å, 4c) or IµS microfocus Mo source Kα radiation (λ = 0.71073, 2c and 5cZn). The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan method (SADABS) and the structure was solved and refined using the Bruker SHELXTL Software Package until the final anisotropic full-matrix, least squares refinement of F² converged.
Crystal Structure Report for 2c

A purple plate-like specimen of 2c, approximate dimensions 0.09 mm × 0.19 mm × 0.25 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 15.15 hours.

Figure 6-57. ORTEP representation of the single crystal X-ray structures of 2c including the numbering system used. Thermal ellipsoids have been rendered at the 35% level.
Crystal Structure Report for 4c

A purple plate-like specimen of 4c, approximate dimensions 0.21 mm × 0.29 mm × 0.56 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 16.87 hours.

Figure 6-58. ORTEP representation of the single crystal X-ray structures of 4c including the numbering system used. Thermal ellipsoids have been rendered at the 35% level.
Chapter 6: Alkyl-Oxazolochlorins

Crystal Structure Report for 5cZn

A red rod-like specimen of 5cZn, approximate dimensions 0.07 mm × 0.16 mm × 0.27 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 15.15 hours.

Figure 6-59. ORTEP representation of the single crystal X-ray structures of 5cZn including the numbering system used. Thermal ellipsoids have been rendered at the 35% level.
### Table 6-1. Crystallographic and structure refinement data for 2c, 4c and 5cZn.

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<th>5cZn</th>
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<td>C₅₂H₄₄N₄O₂Zn</td>
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<td>702.87</td>
<td>833.27</td>
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<td>100(2)</td>
<td>100(2)</td>
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<td>Wavelength (Å)</td>
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<td>Crystal system</td>
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<td>Monoclinic</td>
<td>Monoclinic</td>
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<td>P2(1)/n</td>
<td>P2(1)/n</td>
</tr>
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<td>20.850(4)</td>
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<td>α, β, γ (°)</td>
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<td>90</td>
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<td>4</td>
<td>4</td>
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<tr>
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<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
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<td>6067 / 0 / 491</td>
<td>9224 / 0 / 544</td>
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<td>0.823</td>
<td>0.912</td>
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<td>R1 = 0.0408</td>
<td>R1 = 0.0609</td>
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<td>0.438 &amp; -0.270</td>
<td>0.915 and -0.315</td>
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</tbody>
</table>
6.5. References

(1) Brückner, C.; Ogikubo, J.; McCarthy, J. R.; Akhigbe, J.; Hyland, M. A.;
Daddario, P.; Worlinsky, J. L.; Zeller, M.; Engle, J. T.; Ziegler, C. J.; Ranaghan,


(3) Kratky, C.; Waditschatka, R.; Angst, C.; Johansen, J. E.; Plaquevent, J. C.;

4933.


(7) Senge, M. O. In *Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R.,
7. Oxabacteriochlorins and Dioxabacteriochlorins

7.1. Introduction

The syntheses of alkyloxazolochlorins described in the preceding chapter allowed us access to a number of oxidatively stable oxazolochlorin chromophores. In principle, this meant that we could now shift our focus onto modulating the pyrrole unit on the opposite side, without altering the pre-existing oxazole moiety, to create various bis-pyrrole modified macrocycles. Although there are few exceptions, bis-pyrrole modified porphyrinoids generally possess bacteriochlorin-like chromophores with high extinction coefficients and significant bathochromic shifts compared to their parent porphyrins.\textsuperscript{1,2} In fact, these two properties are often the essential key elements to the development of successful porphyrinoid photo-medicinal agents. For this reason, we became particularly interested in knowing whether bisoxazolobacteriochlorins can be generated. Further, can the option to modulate the tunable optical properties of the oxazolochlorins by variation of the $\alpha$-substituent be extended to the bisoxazole-systems? Presented herein are the answers to these questions. This chapter describes the systematic evaluation of the scope and limits of the synthesis of bacteriochlorin-type chromophores possessing a single or double carbon-to-oxygen replacements at opposite ring positions, their optical properties, and the crystal structures of select members.
7.2. Nomenclature Conventions

Herein we define oxazolochlorins (2-oxachlorins) to be chlorin-type porphyrinoids in which a single pyrrole was replaced by an oxazoline moiety and oxazolobacteriochlorins (2-oxabacteriochlorins) to be bacteriochlorin-type porphyrinoids in which a single pyrrole was replaced by an oxazoline moiety. Correspondingly, bisoxazolochlorins (2,12- or 2,13-dioxachlorins) are chlorin-type porphyrinoids in which two pyrroles were replaced by oxazoline and oxazole moieties. This double replacement can also result in the formation of bacteriochlorin-like chromophores; consequently, they are named bisoxazolobacteriochlorins (2,12/13-dioxabacteriochlorins).

In cases in which two oxygens are present in the chromophore of bisoxazolochlorins and -bacteriochlorins, two regioisomers are possible, designated cis (2,13-isomer) and trans (2,12-isomer) (Figure 7-1). If a mixture of isomers is present, the compound is designated as a 3,12/13 isomer mixture.

![Figure 7-1. Nomenclature conventions for the regio- and stereo-isomeric bisoxazolochromophores.](image)

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166
The sp\(^3\)-hybridized carbons of the pyrroline or oxazoline moieties are chiral centers. Moreover, the substituents on these centers can be positioned relative to each other on opposite sides defined by the macrocycle mean plane, or on the same side (Figure 7-1). Following the nomenclature chosen for these type of stereoisomers that are also observed in the tetrahydroxybacteriochlorins, we name them \(E\) and \(Z\) isomers, respectively.\(^3\)

### 7.3. Results and Discussion

#### 7.3.1 Synthesis of Oxazolobacteriochlorins

The highly regioselective OsO\(_4\)-mediated conversion of free base chlorins to form \(\beta,\beta^\prime\)-dihydroxylated bacteriochlorin is well established for \(\beta\)-octaalkyl- as well as \(meso\)-di- and tetraarylchlorins.\(^3\)-13 This reaction can also be applied to the green, non-polar alkylxazolochlorin 1 (Scheme 7-1). Thus, dihydroxylation followed by \(H_2S\)-reductive cleavage of the intermediate osmate ester produced a single major pink product in overall 34% isolated yield (with ~50% recovered starting material; the reaction was much slower than observed for the oxidation of diolchlorins but neither extended reaction times nor an excess of oxidant improved the yield significantly). Based on its composition (C\(_{49}\)H\(_{45}\)N\(_4\)O\(_3\) for MH\(^+\) as per ESI\(^+\) HR-MS) and diagnostic bacteriochlorin spectrum (with a \(\lambda_{\text{max}}\) of 750 nm; see Figure 7-5 and below for a more detailed description of the UV-visible spectra of all chromophores prepared) it was identified as 12,13-dihydroxy-2-oxabacteriochlorin 2. The \(^1\)H NMR spectrum of 2 showed \textit{inter alia} the presence of two
non-equivalent pyrroline hydrogens. The compound is chiral and presumably is found as a racemate.

![Scheme 7-1. Syntheses of oxazolobacteriochlorin 2 and bisoxazolochlorins 3.](image)

**7.3.2. Synthesis of Bisoxazolochlorins**

The oxidative conversion of a dihydroxychlorin to a porpholactone was described in Chapter 2.\textsuperscript{14-17} This reaction could also be applied to dihydroxyoxazolobacteriochlorin 2. Thus, oxidation of 2 using MnO$_4^-$ (in the form of CTAP) converted the diol functionality into a lactone moiety, as indicated by the appearance of a carbonyl stretch at 1724 cm$^{-1}$ in the IR of the product 3. In comparison, the stretching frequency is 1742 cm$^{-1}$ for the parent porpholactone. The observed shift to lower wavenumbers for 3 likely reflects the higher HOMO level for hydroporphyrins compared to porphyrins.\textsuperscript{18-20}
bacteriochlorin-type spectrum of the pink, polar starting material was replaced by a (red-shifted) chlorin-like spectrum of the much less-polar grey-colored product 3 (Figure 7-3).

Figure 7-2. Stick representation of the molecular structures of (A) 3-cis, (B) 6-cis, and (C) 6Zn-cis (top and side views). All hydrogens, disorder and solvents, when present, omitted for clarity.

The $^1$H NMR spectrum of the product indicated the presence of two diastereomers in a 7:1 ratio (see ESI), assigned to the two isomers 3-cis and 3-trans that differ in their relative orientation of the lactone moiety. The absorption spectrum of this mixture possessed equally intense $\lambda_{\text{max}}$ peaks at 695 and 705 nm. No flash column or preparative plate chromatographic separation methods were found to completely separate the two isomers but repeated column chromatography (50% hexane/CH$_2$Cl$_2$ on silica gel) enriched the mixture to a ~10:1 isomer ratio. Crystallization of this mixture resulted in the formation of a crystal of the slightly less polar majority product that was suitable for investigation by single crystal X-ray diffractometry. The structure of the compounds were determined to be of type 3, though due to disorder in the crystal, the cis-regiochemistry
could not be assigned with absolute certainty (Figure 7-2). However, the UV-visible spectra of 3 and 9-cis (derived from 6-cis) are very similar, much like the way 8 and 6 posses near-identical spectra. This information lead us to believe that the major component of the 10:1 mixture of 3 is the cis-regioisomer.

With small amounts of the separated isomers in hand, it allowed us to identify their surprisingly different UV-visible spectra. Isomer 3-cis possesses a $\lambda_{\text{max}}$ peak at 695 nm, while 3-trans possessed a much more intense $\lambda_{\text{max}}$ peak at 705 nm. Thus, the non-axial symmetric electron distribution within the oxazole moiety also affects the MOs of the oxazolone moiety across the macrocycle.

The dihydroxylation/oxidative diol cleavage reaction sequence applied to alkylloxazolochlorin 1 to generate biosoaxazolochlorin 3 can also be applied to both the hydroxy-substituted alkylloxazolochlorin 10 and its alkoxy derivative 4, to generate, via the intermediates 7 and 5, respectively, the biosoaxazolochlorins 8 and 6, respectively. However, the presence of a chiral center in these starting materials increased the complexity of the product isomer mixtures: each cis/trans isomer is formed as a racemic mixture (Scheme 7-2).
Scheme 7-2. Syntheses of alkylbisoazolochlorins 6, 6Zn, 7, 8 and 9.

All products possessed the expected spectroscopic and analytical properties with some notable features. Intermediate bacteriochlorin diol 5 formed as a separable mixture of E/Z isomers. However, since NMR spectroscopy does not allow an assignment of the isomers, their assignment remained, citing the relative polarity of related bacteriochlorin E/Z isomers for which crystal structure analyses confirmed their relative stereochemistry,
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

speculative. The UV-visible spectra of the intermediate diols 5 and 7 possess identical UV-visible spectra that are ~30 nm blue-shifted ($\lambda_{\text{max}} = 720$ nm) as compared to the spectrum of the corresponding dihydroxydialkyloxazolobacteriochlorin 2. Thus, the $\alpha$-hydroxy/methoxy-induced blue-shifts that were observed in the monooxazolochlorins (shifts of ~20 nm) are also present in the oxazolobacteriochlorin series but the shifts are somewhat more pronounced.

The MnO$_4^-$-mediated oxidation of either isomer of 5 converts the bacteriochlorin-like chromophore into a diastereomeric mixture of chlorin-type chromophores, 6. While, as expected, the sp$^2$-hybridized lactone carbon mimics the effect of a $\beta,\beta'$-double bond, the chlorin-type UV-visible spectrum of bisoxazole 6 is significantly red-shifted compared to that of the corresponding mono-oxazolochlorin 4 (Figure 7-3). As per $^1$H NMR spectrum of the regioisomeric mixture of 6-cis/trans, the formation of the 2,13-dioxachlorin 6-cis isomer was slightly favored (cis/trans diastereomeric ratio is 5:2). Again, the majority diastereomer could be enriched to ~10:1 by column chromatography and purified by fractional crystallization. The UV-visible spectrum of 6-cis (10:1 mixture) exhibited a $\lambda_{\text{max}}$ peak at 675 nm while the 5:2 cis/trans diastereomeric mixture possessed equally intense $\lambda_{\text{max}}$ peaks at 675 nm and 695 nm. Thus, the latter band was assigned to the 2,12-dioxa-substituted trans-isomer 6-trans. The structure and regio-chemistry of 6-cis was confirmed using single crystal X-ray diffractometry (Figure 7-2).
Zinc insertion into the regioisomeric mixture of grey non-polar 6 proceeded smoothly to form the more polar green product $6\text{Zn}$ of identical diastereomeric ratio. The product showed, as expected, a metallochlorin-type spectrum (see ESI).

Treatment of 6 with 2 M aq HCl in THF hydrolyzed its ketal moiety to form hemiketal 8 in near-quantitative yield. The replacement of the methoxy proton peak (at 3.1 ppm) in the $^1\text{H}$ NMR spectrum of the reactant with a hydroxy peak at 3.9 ppm (exchangeable with D$_2$O) in the $^1\text{H}$ NMR spectrum of the product, with no further significant differences in their spectra, confirmed the transformation. This reaction is reversible. Thus, hemiacetal 8 is swiftly converted back into 6 in the presence of methanol with catalytic amount of TFA at ambient temperature (Scheme 7-2). The UV-visible spectra of 6 and 8 are near-identical (see ESI). The pathway towards 8 ($4 \rightarrow 5 \rightarrow 6 \rightarrow 8$) proved to be overall higher yielding compared to the shorter alternative sequence ($10 \rightarrow 7 \rightarrow 8$) previously communicated. This is because the presence of the acetal moiety in 4 significantly improved the yield of the dihydroxylation reaction as well as the MnO$_4^-$-mediated oxidation step.

Hemiketalchlorins of type 10 could be hydro-dehydroxylated to the corresponding oxazolochlorin (Chapter 6). Likewise, treatment of 8 with Et$_3$SiH/BF$_3$·OEt$_2$ produce the less polar bisoxazolochlorin 9 in acceptable yield (Scheme 7-2). This transformation was expressed in the $^1\text{H}$ NMR spectrum of the product by the replacement of the hydroxy peak in spectrum of 8 by a diagnostic singlet for the oxazoline hydrogen (at 6.7 ppm). Once again, the removal of the $\alpha$-hydroxy group caused a bathochromic shift in the UV-
visible spectrum of 9 when compared to the spectrum of 8 and, not surprisingly, its spectrum is very similar to that of 3 (Figure 7-3).

![Figure 7-3](image)

**Figure 7-3.** (top) full and (bottom) $\lambda_{\text{max}}$ normalized UV-visi spectra of chlorins 1 (grey), 4 (purple), 3 (of -cis, blue), 6 (of -cis, lime-green), 8 (of -cis, light-blue), 9 (of -cis, red) in CH$_2$Cl$_2$ at ambient temperature.

Much to our disappointment, none of the bisoxazolochlorins 6 (as its free base or zinc complex 6Zn), 8, or 9 were susceptible to an alkylation of the lactone moiety using Grignard reagents under a variety of reaction conditions without extensive decomposition. Likewise, the double-alkylation of bisporpholactone 11$^{21,24,25}$ failed to provide...
any isolatable product (Scheme 7-3). Thus, alkylation pathways did not allow the generation of bisoxazolobacteriochlorins.

Scheme 7-3. Failed routes towards dioxazolobacteriochlorins 21.

On the contrary, an exhaustive hydride-reduction (using DIBAl-H or Et$_3$SiH) of 11 appeared to be reducing both lactones of 11 to methylene groups as the crude mixture showed a strongly red-shifted bacteriochlorin-type spectrum ($\lambda_{\text{max}} = 815$ nm) and the HR-MS indicated the presence of a product of the desired composition (signal indicative of a MH$^+$ of the composition C$_{42}$H$_{31}$N$_4$O$_2$). However, the product appeared to be extremely light- and acid sensitive and could not be isolated in a quantity allowing an unambiguous characterization. We observed the sensitivity of unsubstituted oxazolochlorins before.$^{17}$ Moreover, bis-pyrrole modified bacteriochlorin proved also to be significantly more fragile than the corresponding mono-pyrrole modified morpholinochlorins (Section 1.5.).$^1$ Nonetheless, the discovery of a fortuitous transformation eventually led to the isolation of bisoxazolobacteriochlorins.
7.3.3. Synthesis of Bisoxazolobacteriochlorins

The oxidative cleavage of a dihydroxychlorin with NaIO₄/silica gel generates the corresponding secochlorin bisaldehyde (Chapter 1).²⁶ Performed in ROH/CHCl₃, this bisaldehyde is converted in situ to a dialkoxyphospholinochlorin.¹⁴,²⁷ When we submitted polar dihydroxyoxazolobacteriochlorin 2 to these reaction conditions, the resulting non-polar product 13 showed the expected red-shifted UV-visible spectrum (λ_max = 770 nm) but it possessed a composition (as per ESI⁺-HR-MS) of C₄₉H₄₃N₄O₃ (for MH⁺), i.e., short of a C₂H₄O fragment to the composition of the expected morpholinooxazolobacteriochlorin. Further, the ¹H NMR spectrum of the product confirmed the loss of the diagnostic pyrroline hydrogen peaks of the β,β’-dihydroxy moiety but revealed the appearance of a new signal for only a single methoxy group (3.1 ppm, s, 3H) in a compound that appeared as a 3:2 mixture of two diastereomers that could not be separated by chromatography. These findings are consistent with the formation of bisoxazolobacteriochlorin 13 (Scheme 7-4).

Scheme 7-4. Syntheses of bis-alkylbisoxazolobacteriochlorins 13.
The one-step conversion of $\beta,\beta'$-dihydroxypyrrole to $\alpha$-methoxy-oxazoline conversion can also be applied to bacteriochlorin diol 5 (Scheme 7-5). However, the spectroscopic analysis of the resulting bisoxazolobacteriochlorin 14 is complicated by the presence of several regio- and stereoisomers. The molecule contains two chiral $\alpha$-oxazoline carbons. Their relative orientation to each other give rise to $E/Z$ diastereomers. In addition, the second oxazole can be arranged such that the ring oxygens are on the same side ($cis$) or on opposite sides ($trans$).

Scheme 7-5. Syntheses of mono-alkylbisoxazolobacteriochlorin isomers 14.

All diastereomers are formed with little to no regioselectivity (as per $^1$H NMR spectrum of the crude mixture). The diastereomer mixture of 14 can be further purified into the $E$- and $Z$- isomers using an automated flash chromatography system (on silica gel, 50% hexane/CH$_2$Cl$_2$) though this process also causes some decomposition of products on the stationary phase (alumina did not allow any separation). Both fractions
possess identical UV-visible absorption spectra and compositions (C_{47}H_{41}N_{4}O_{4} as per ESI\(^{+}\)-HR-MS).

Based on the relative polarity of the E/Z isomers of the tetrahydroxy-bacteriochlorins,\(^ {3}\) we presume that the less polar fraction contains the E-isomers while the more polar fraction contains the Z-isomers. This was confirmed by the single crystal X-ray structure elucidation of the two fractions; the non-polar fraction contained 14-cis/trans-E isomers while the more polar fraction contained 14-cis/trans-Z isomers. Due to disorder problems in the asymmetric unit however, we could not unequivocally determine the regiochemistry (cis vs. trans) of the major product (Figure 7-4).

![Figure 7-4](image)

**Figure 7-4.** Stick representation of the molecular structures of (A) 14-trans-E and (B) 14-trans-Z, and (C) 13-cis (top and side views). All hydrogens, disorder and solvents, when present, omitted for clarity.

The UV-visible spectra of the starting oxazolobacteriochlorin diols (2 and 5) and the bisozazolobacteriochlorins are typical bacteriochlorin-type spectra (Figure 7-5).
again, the trend that the $\lambda_{\text{max}}$ of a given chlorin or bacteriochlorin red-shifts upon replacement of a pyrroline by an oxazoline is maintained.

![UV-vis spectra of 2 (red), 5 (light-blue), 14 (mixture of all isomers, blue), 13 (cis/trans mixture, lime-green) in CH$_2$Cl$_2$ at ambient temperature.](image)

**Figure 7-5.** UV-vis spectra of 2 (red), 5 (light-blue), 14 (mixture of all isomers, blue), 13 (cis/trans mixture, lime-green) in CH$_2$Cl$_2$ at ambient temperature.

The above findings demonstrate that the $\alpha,\alpha$-dialkyl-bis-oxazolobacteriochlorins, such as 13, are chemically more robust than their mono-alkyl- or alkoxy-analogues. This further suggested to us a renewed take at the initially fruitless attempts to reduce bisoxazolochlorin (such as 6/8/9/11) to the corresponding bisoxazolobacteriochlorin. Indeed, reduction of $\alpha,\alpha$-dialkylloxazole-substituted lactone 3 could be achieved using an approx. 30-fold large excess of Et$_3$SiH/BF$_3$·OEt$_2$. The reaction was slow and full conversion (determined by the development of the diagnostic product $\lambda_{\text{max}}$ peak at 815 nm) to form bisoxazolobacteriochlorin 15 took nearly 48 h at room temp and its isolated yield were relatively low (Scheme 7-6).
Scheme 7-6. Synthesis of bis-alkylbisoaxolobacteriochlorins 15.

The disappearance of the carbonyl νC=O in the IR of the product, its composition of C_{48}H_{43}N_{4}O_{2} (as per ESI<sup>+</sup> HR-MS), and the presence of the diagnostic oxazoline peak (6.4 ppm, s, 2H) confirmed the structure of 15. Product 15 was diastereomerically pure when a 3-cis isomer-enriched (~10:1 mixture) was used as the starting material. In addition, the lack of chiral centers in 15 also greatly simplified its <sup>1</sup>H NMR spectrum. As expected, the UV-visible spectrum for 15 is a red-shifted bacteriochlorin-type spectrum (Figure 7-6).

Figure 7-6. UV-vis spectra comparison (normalized at λ<sub>soret</sub>) of the starting material 3 (red) and 15 (blue) in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature.
In part, the low yield of product is because of a pronounced (light-induced) oxidation sensitivity of the non-alkylated oxazole moiety, forming the lactol derivative (indicated by the presence of the parent mass of the MH$^+$ ion at $m/z$ 737 and possessing an UV-visible spectrum that is blue-shifted to 770 nm), or even regenerating the starting material.$^{17}$ Its stability on silica gel was also limited (and alumina proved unsuitable to separate the product from the reactant). Thus, we resorted to a fractional crystallization method (in the cold and dark) to purify product 15.

### 7.3.4. Fluorescence Properties of Oxazolochlorins and -bacteriochlorins

The fluorescence emission spectra of the dioxazolochlorins 3, 6, 8 are all chlorin-type (Figure 7-7) with the small Stoke’s shift typical for porphyrinoids, and with fluorescence quantum yields ranging between 0.11 to 0.19. The dihydroxyoxazolobacteriochlorins 2 and 5 showed also similar fluorescence emission spectra, with yields in the range of 0.07 to 0.14, but the dioxazolobacteriochlorins show a much lower fluorescence yield (0.07, 0.03, to under 0.01 respectively), as is also typical for regular bacteriochlorins.$^1$ Thus, as far as the fluorescence properties of the oxazole-derived chromophores is concerned, the replacement of one and two carbons in the chromophore framework by oxygen(s) is comparable to the effects a reduction of one or two $\beta,\beta'$-bond have.
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

Figure 7-7. Normalized fluorescence spectra of 2 (grey), 3 (lime-green), 5 (purple), 6 (light-blue) 8 (red) and 9 (blue) (all in CH$_2$Cl$_2$ at ambient temperature $\lambda_{\text{excitation}} = \lambda_{\text{soret}}$).

7.4. Conclusions

The step-wise replacement of a pyrroline moiety in a bacteriochlorin chromophore by one or two oxazolone or oxazoline moieties was described. Depending on the presence of an oxazolone or oxazoline moiety, the resulting chromophores possess chlorin (when one oxazolone moiety is present) or bacteriochlorin characteristics (when either one pyrroline and oxazoline or two oxazoline moieties are present) (Figure 7-8).

The chromophores possess UV-visible spectra that are predictably tuned based on the regioisomer and the number and position of the substituents. Thus, a stepwise modification of the porphyrin chromophore with oxazolines (variously substituted) in combination with oxazolines, oxazolones and (dihydroxy-substituted) pyrrolines allows a fine-tuning of their $\lambda_{\text{max}}$ from 650 nm to 810 nm in small increments. Thus this study defines
the structure-optical properties relationships in oxazole-derived chlorins and bacteriochlorins.

Figure 7-8. Oxazole-based chromophores sorted according to chromophore class and plot of their $\lambda_{\text{max}}$ band (spectrum of porpholactone is not shown).

As a number of crystal structures of the bisoxazole-based chromophores demonstrate that the replacement of one or two $\beta$-carbons by oxygen does not change the
overall planarity of the macrocycle. In fact, most chromophores are more planar than, for instance, the chromophore of the parent tetrahydroxybacteriochlorin (Section 1.5), implying that the tuning of the UV-visible spectra observed is an electronic substituent effect that is to no or minimal degree affected by conformational effects. Thus, the results we derived earlier for mono-oxazolochlorins can be transferred to mono- and bis-oxazolobacteriochorin series except that the bathochromic shifts that are observed in the UV-visible spectra upon replacement of a pyrrole with oxazoline are significantly more pronounced than in the chlorin series.

The relatively facile preparation of the novel bacteriochlorin analogues alkyl-oxazolobacteriochlorins, the oxidative stability of select members of this compound class, and the ability to tune their optical spectra suggests their further study with respect to their applicability as PDT agent, fluorescence tags, or in light-harvesting systems.

7.5. Experimental Section

7.5.1. Instruments and Materials

meso-Tetraphenyl-2-oxachlorins 1, 4, and 10 were synthesized as reported in the literature. Flash column chromatography was performed manually in glass columns or on an automated flash chromatography system, via dry-packing or liquid injection, on normal-phase silica (solvents used are indicated; isocratic elution modes). The fluorescence quantum yields (φ) were determined relative to those of meso-tetraphenylporphyrin
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

(\(\phi = 0.11\) in benzene, calculated to be 0.09 in CH\(_2\)Cl\(_2\)); \(\lambda_{\text{excitation}} = \lambda_{\text{soret}}\). For details of the instruments used, see List of Instruments.

7.5.2. Preparation and Characterization

**meso-Tetraphenyl-12,13-cis-dihydroxy-3,3-diisopropyl-2-oxabacteriochlorin**

(2). General procedure for the conversion of 2-oxachlorins to 2-oxabacteriochlorins.

To a solution of 1 (1.1 g, 1.57 mmol) dissolved in CHCl\(_3\) was added a solution of OsO\(_4\) in pyridine (2 eq., 796 mg). (CAUTION: OsO\(_4\) is volatile and extremely toxic, use with care; perform in fume hood and wear protective gear at all times!) Reaction progress was monitored by TLC and UV-visible spectroscopy. The conversion of starting material to product can be identified by the formation of a sharp peak at \(\sim 750\) nm in the UV-visible spectrum of an aliquot of the reaction mixture. The reaction was left stirring until no further reaction was detectable (2 to 3 days). The reaction vessel was then purged with gaseous H\(_2\)S for 5 min. (CAUTION: fume hood; use of a bleach filled H\(_2\)S scrubber is recommended.) The reaction was stirred for approximately 15-30 min under an H\(_2\)S atmosphere. The excess H\(_2\)S was purged out using N\(_2\) overnight and the remaining solvent (if any) was evaporated by rotary evaporation. Product 2 was isolated by column chromatography (silica-1% MeOH/CH\(_2\)Cl\(_2\)) in 34% yield (550 mg of the starting material 1 was also recovered). MW = 736.3 g/mol; \(R_f = 0.10\) (silica-CH\(_2\)Cl\(_2\)); UV-vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (log \(\varepsilon\)) 360 (4.65), 386 (4.74), 462 (3.49), 492 (3.66), 526 (4.28), 619 (3.31), 680 (3.69), 750 (4.39) nm; Fl \(\lambda_{\text{max}}\) (CH\(_2\)Cl\(_2\), \(\lambda_{\text{exc}} = 385\) nm): 687, 760 nm, \(\phi = 0.07\); \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\)) 8.07 (m, 2H), 7.95-8.00 (m, 2H), 7.86-7.87 (m, 5H), 7.51-7.64 (m,
15H), 6.03 (d, $^3J = 7.1$ Hz, 1H), 5.91 (d, $^3J = 7.1$ Hz, 1H), 2.46-2.49 (m, 2H), 1.06 (d, $^3J = 6.6$ Hz, 3H), 0.96 (d, $^3J = 6.6$ Hz, 3H), 0.74 (d, $^3J = 6.8$ Hz, 3H), 0.60 (d, $^3J = 6.8$ Hz, 3H), 0.36 (s, 1H), -0.21 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, δ) 165.3, 161.9, 154.2, 152.9, 149.8, 141.6, 141.1, 140.5, 140.4, 140.1, 139.6, 138.2, 133.9, 133.6, 133.3, 133.1, 131.9, 131.6, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 127.5, 127.4, 126.5, 126.5, 126.4, 125.6, 123.9, 120.3, 119.0, 118.6, 113.9, 112.1, 102.6, 100.1, 74.5, 72.8, 70.7, 36.7, 36.6, 32.1, 29.8, 29.5, 29.4, 24.9, 22.8, 19.0, 18.9, 18.5, 14.3 ppm; HR-MS (ESI$^+$ of MH$^+$, 100% CH$_3$CN): m/z calc’d for C$_{49}$H$_{45}$N$_4$O$_3$: 737.3492, found 736.3490.

Figure 7-9. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 2.
Figure 7-10. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 2.

Figure 7-11. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 2 (CH$_2$Cl$_2$).
Figure 7-12. FT-IR spectrum (neat, diffuse reflectance) of 2.

*meso*-Tetraphenyl-12,13-cis-dihydroxy-3-isopropyl-3-methoxy-2-oxabacteriochlorin (5). A diastereomeric mixture of 5 (178 mg) was prepared in 56% yield from *meso*-tetraphenyl-3-isopropyl-3-methoxy-2-oxachlorin (4) (300 mg, 0.44 mmol) according to the general procedure described for the formation of 2. The two diastereomers were separated using automated chromatography (silica, CH$_2$Cl$_2$). MW = 724.84 g/mol; $R_f$ = 0.30 (silica-CH$_2$Cl$_2$); UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ (log $\varepsilon$) 374 (4.94), 383 (5.00), 494 (3.74), 525 (4.48), 657 (3.77), 722 (4.63) nm; Fl $\lambda_{\text{max}}$ (CHCl$_3$, $\lambda_{\text{exc}}$ = 385 nm): 729 nm, $\phi$ = 0.12; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$) 8.26 (dd, $^3J$ = 4.9, $^4J$ = 1.4 Hz, 1H), 8.12 (dd, $^3J$ = 4.7, $^4J$ = 1.4 Hz, 1H), 8.12-7.69 (m, 8H), 7.66-7.51 (m, 14H), 6.08 (m, 2H), 3.05 (s, 3H), 2.07 (m, 1H), 1.11 (d, $^3J$ = 6.5 Hz, 3H), 0.58 (d, $^3J$ = 6.8 Hz, 3H), -0.38 (s, 1H), -0.88 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 162.1, 161.9, 154.5, 145.1, 141.4, 140.8, 140.7, 139.9, 138.9, 138.8, 137.1, 134.7, 133.7, 133.5, 133.4, 133.2, 132.7,
132.1, 131.7, 128.2, 128.1, 127.8, 126.7, 126.1, 125.8, 120.9, 120.4, 118.2, 116.9, 114.8, 114.5, 102.9, 74.6, 73.2, 70.8, 50.7, 35.6, 31.8, 22.9, 17.4, 16.3, 14.3 ppm; HR-MS (ESI+ of MH⁺, 100% CH₃CN): m/z calc’d for C₄₇H₄₁N₄O₄: 725.3123, found 725.3126.

**Figure 7-13.** ¹H NMR spectrum (400 MHz, CDCl₃) of 5.

**Figure 7-14.** ¹³C NMR spectrum (100 MHz, CDCl₃) of 5.
Figure 7-15. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 5 (CH₂Cl₂).

meso-Tetraphenyl-12,13-cis-dihydroxy-3-hydroxy-3-isopropyl-2-oxabacteriochlorin (7). A diastereomeric mixture (1:3) of 7 was prepared in 32% yield from meso-tetraphenyl-3-hydroxy-3-isopropyl-2-oxchlorin (10) (300 mg, 0.44 mmol) according to the general procedure described for the synthesis of 2. The diagnostic peak of product 7 was observed at ~720 nm. MW = 710.80 g/mol; Rₐ = 0.10 (silica-CH₂Cl₂); UV-vis (CH₂Cl₂) λₘₐₓ (log e) 371 (4.94), 383 (5.01), 460 (3.66), 491 (3.84), 524 (4.50), 597 (3.46), 654 (3.85), 719 (4.60) nm, Fl λₘₐₓ (CH₂Cl₂, λₜₐₜ = 383 nm): 663, 731 nm, φ = 0.14; ¹H NMR (300 MHz, CDCl₃, δ) 8.26 (d, ³J = 4.0 Hz, 0.33H), 8.23 (d, ³J = 4.2 Hz, 1H), 8.16 (d, ³J = 7.5 Hz, 1H), 8.11 (m, 1.33H), 8.01-8.06 (m, 2.3H), 7.94 (m, 4H), 7.76-7.78 (m, 3.33H), 7.50-7.78 (m, 16H), 6.14 (d, ³J = 6.9 Hz, 1H), 5.99 (d, ³J = 6.9 Hz, 1H), 2.31 (m, 0.33H), 2.07 (m, 1H), 1.22 (d, ³J = 6.5 Hz, 3H), 0.74 (d, ³J = 6.7 Hz, 3H), -0.31
(s, 1H), -0.38 (s, 0.33H), -0.79 (s, 1H), -0.85 (s, 0.33H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 162.3, 161.9, 161.3, 154.6, 154.0, 148.0, 141.5, 141.4, 140.8, 140.8, 140.7, 140.1, 139.9, 138.9, 138.9, 137.1, 137.0, 134.7, 134.7, 134.3, 134.3, 133.8, 133.6, 133.5, 133.4, 133.2, 132.1, 132.0, 131.8, 131.7, 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 126.8, 126.8, 126.7, 126.7, 126.2, 126.1, 125.8, 121.0, 120.9, 120.3, 120.2, 118.5, 114.7, 114.7, 114.5, 114.3, 113.1, 113.0, 103.2, 103.2, 102.9, 75.1, 75.1, 74.6, 73.2, 72.8, 70.8, 51.1, 36.2, 36.1, 32.2, 29.9, 29.9, 22.9, 17.9, 17.7, 15.9, 14.3 ppm; HR-MS (ESI$^+$ of MH$^+$, 100% CH$_3$CN): $m/z$ calc’d for C$_{46}$H$_{39}$N$_4$O$_4$: 711.2966, found 711.2958.

Figure 7-16. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 7.
Figure 7-17. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 7.

Figure 7-18. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 7 (CHCl$_3$).
**meso-Tetraphenyl-3,3-diisopropyl-2,12-dioxa-13-oxochlorin (3-trans) and meso-tetraphenyl-3,3-diisopropyl-2,13-dioxa-12-oxochlorin (3-cis).** General procedure for the conversion of diolbacteriochlorin to bisoxazolochlorin. Into a stirring solution of meso-tetraphenyl-12,13-cis-dihydroxy-3,3-diisopropyl-2-oxabacteriochlorin (2, 350 mg) in CHCl₃ (20 ml) were added 3 equiv of cetyltrimethylammonium permanganate (CTAP). The reaction was left stirring for ~4 h. Reaction progress was monitored using UV-visible spectroscopy and TLC. The bacteriochlorin spectrum of 2 disappeared as the formation of a chlorin spectrum (λₘₐₓ ~695 nm) was observed. Product 3 was isolated as diasteromeric mixture in 67% yield (231 mg) using column chromatography (silica-CH₂Cl₂). ¹H NMR indicated a diastereomeric ratio of 7:1 favoring the formation of meso-tetraphenyl-3,3-diisopropyl-2,13-dioxa-12-oxochlorin.

Repeated chromatography (silica-50% hexane/CH₂Cl₂) enriched the diastereomeric mixture to about ~10:1. MW = 720.86 g/mol; Rₜ = 0.95 (silica-CH₂Cl₂); UV-vis (CH₂Cl₂) λₘₐₓ (log ε): 419 (5.15), 510 (4.02), 632 (3.87), 693 (4.35) nm; Fl λₘₐₓ (CH₂Cl₂, λₑₓc = 409 nm): 703 nm, φ = 0.11; ¹H NMR (300 MHz, CDCl₃, δ, minority product peaks not listed) 8.23 (dd, ³J = 5.2, ⁴J = 1.7 Hz, 1H), 8.09 (dd, ³J = 5.2, ⁴J = 1.8 Hz, 1H), 7.90 -7.92 (m, 2H), 7.78-7.87 (m, 7H), 7.55-7.71 (m, 10H), 7.53-7.57 (m, 2H), 7.19 (dd, ³J = 4.6, ⁴J = 2.1 Hz, 1H), 2.486 (m, 2H), 1.57 (s, 1H), 1.03 (d, ³J = 6.6 Hz, 6H), 0.71 (d, ³J = 6.9 Hz, 6H), 0.69 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ) 167.9, 167.3, 157.6, 154.2, 143.9, 141.6, 141.5, 139.7, 138.4, 136.7, 133.6, 133.6, 133.2, 132.9, 131.7, 129.4, 128.6, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 126.9, 126.5, 125.0, 123.5, 120.1, 112.1, 104.4,
103.3, 100.8, 36.7, 19.1, 18.7 ppm; HR-MS (ESI+ of MH$^+$, 100% CH$_3$CN): $m/z$ calc’d for C$_{48}$H$_{41}$N$_4$O$_3$: 721.3179, found 721.3161.

Figure 7-19. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3-cis.

Figure 7-20. $^{13}$H NMR spectrum (100 MHz, CDCl$_3$) of 3-cis.
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

Figure 7-21. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 3-cis (CH$_2$Cl$_2$).

Figure 7-22. FT-IR spectrum (neat, diffuse reflectance) of 3-cis.
meso-Tetraphenyl-3-isopropyl-3-methoxy-2,13-dioxa-12-oxochlorin (6-cis)

and meso-tetraphenyl-3-isopropyl-3-methoxy-2,12-dioxa-13-oxochlorin (6-trans). A diastereomeric mixture of 6 (237 mg) was prepared in 81% yield from 5 (300 mg, 0.41 mmol) according to the general procedure described for the synthesis of 3. $^1$H NMR of the crude reaction mixture indicated the product to be in 5:2 diastereomeric ratio favoring the isomer 6-cis. The major isomer 6-cis can be further purified (up to ~10:1 d.r.) by repeated column chromatography (50% hexane in CH$_2$Cl$_2$). MW = 708.8 g/mol; R$_f$ = 0.90 (silica-CH$_2$Cl$_2$); UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ (log $\varepsilon$): 414 (5.12), 505 (3.89), 538 (3.67), 614 (3.71), 672 (4.26) nm; Fl $\lambda_{\text{max}}$ (CH$_2$Cl$_2$, $\lambda_{\text{exc}}$ = 415 nm): 683 nm, $\phi$ = 0.19;

$^1$H NMR (300 MHz, CDCl$_3$, $\delta$(minority product peaks not listed)) 8.38 (dd, $^3J$ = 5.2, $^4J$ = 1.5 Hz, 1H), 8.28 (dd, $^3J$ = 5.2, $^4J$ = 1.6 Hz, 1H), 8.01-7.87 (m, 8H), 7.72-7.60 (m, 14 H), 3.08 (m, 3H), 2.05 (m, 1H), 1.13 (d, $^3J$ = 6.6 Hz, 3H), 0.89 (s, 1H), 0.69 (d, $^3J$ = 6.8 Hz, 3H), 0.05 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 167.2, 164.8, 162.6, 154.4, 152.5, 147.8, 143.7, 141.8, 141.3, 140.4, 139.9, 138.1, 138.0, 137.9, 137.5, 136.8, 136.7, 136.6, 133.9, 133.8, 133.7, 133.3, 133.1, 133.0, 132.8, 132.5, 131.8, 131.7, 131.1, 129.5, 129.0, 128.5, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.0, 126.9, 126.3, 126.0, 125.1, 124.6, 124.3, 120.8, 117.7, 117.2, 115.1, 107.3, 104.8, 103.4, 102.7, 50.8, 35.8, 35.6, 31.1. 17.4, 17.4, 16.4, 16.3 ppm; HR-MS (ESI+ of MH$^+$, 100% CH$_3$CN): $m/z$ calc’d for C$_{46}$H$_{37}$N$_4$O$_4$: 709.2815, found 709.2825.
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

Figure 7-23. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 6-$cis$.

Figure 7-24. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 6-$cis$. 
Figure 7-25. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 6-cis (CH$_2$Cl$_2$).

Figure 7-26. FT-IR spectrum (neat, diffuse reflectance) of 6-cis.
[meso-Tetraphenyl-3-isopropyl-3-methoxy-2,13-dioxa-12-oxochlorinato]Zn(II) (6Zn-cis). Freebase 6 (100 mg of 10:1 mixture, 0.14 mol) was dissolved in 30% MeOH/CHCl₃ (v/v, 30 mL) and heated to reflux. A solution of Zn(OAc)₂·H₂O (~3-5 eq, 90-150 mg) in warm MeOH (~5 mL) was added and the mixture was refluxed overnight. The reaction progress was monitored by TLC. Upon completion, the product was isolated by rotary evaporation, followed by flash chromatography (silica–CH₂Cl₂). The material was obtained as a green crystalline solid by crystallization using a slow solvent exchange from CH₂Cl₂ to MeOH or pentane (73%, 79 mg). MW = 772.17 g/mol; Rᵣ = 0.45 (silica-CH₂Cl₂); UV-vis (CH₂Cl₂) λₘₐₓ (log ε): 424 (458), 520 (3.73), 572 (3.65), 613 (3.81), 663 (4.33) nm; Fl λₘₐₓ (CHCl₃, λₑₓᶜₑ = 414 nm): 677nm, φ = 0.08;

¹H NMR (300 MHz, CDCl₃, δ) 8.38 (m, 1H), 8.27 (m, 1H), 8.04 (m, 1H), 7.82-7.98 (m, 6 H), 7.47-7.77 (m, 16H), 2.99 (s, 3H), 2.00 (m, 1H), 1.09 (m, 3H), 0.88 (m, 3H) ppm;

¹³C NMR (100 MHz, CDCl₃, δ) 166.7, 162.5, 156.5, 153.3, 151.9, 151.3, 144.7, 144.4, 140.4, 139.4, 139.3, 139.1, 137.9, 137.6, 134.1, 134.0, 133.9, 133.3, 133.2, 132.5, 132.0, 131.9, 131.5, 128.6, 127.9, 127.8, 127.7, 127.5, 127.34, 127.32, 127.30, 126.8, 126.1, 124.5, 123.7, 118.3, 117.8, 116.3, 104.7, 101.4, 50.5, 35.7, 17.1, 17.0, 16.1; HR-MS (ESI+ of MH⁺, 100% CH₃CN): m/z calc’d for C₄₆H₂₇N₄O₄Zn: 771.1950, found 771.1950.
Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins

Figure 7-27. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 6Zn-cis.

Figure 7-28. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 6Zn-cis.
Figure 7-29. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 6Zn-cis (CH$_2$Cl$_2$).

Figure 7-30. FT-IR spectrum (neat, diffuse reflectance) of 6Zn-cis.
meso-Tetraphenyl-3-hydroxy-3-isopropyl-2,13-dioxo-12-oxochlorin (8-cis)

and meso-tetraphenyl-3-hydroxy-3-isopropyl-2,12-dioxo-13-oxochlorin (8-trans). A 10:1 diastereomeric mixture of 6 (0.08 mmol, 57 mg) was dissolved in 10% 2M HCl in THF (25 ml) and stirred overnight at 45°C. The reaction progress was monitored using TLC and the product was isolated through column chromatography (silica, CH₂Cl₂) to give 7 in 96% yield (53 mg). MW = 694.78 g/mol; Rₚ = 0.60 (silica-CH₂Cl₂); UV-vis (CH₂Cl₂) λₘₐₓ (log ε): 413 (5.03), 506 (3.83), 540 (3.60), 613 (3.63), 672 (4.16) nm; Fl λₘₐₓ (CH₂Cl₂, λₑₓᶜₑ = 414 nm): 680 nm, φ = 0.19; ¹H NMR (300 MHz, CDCl₃, δ, minority product peaks not listed) 8.36-8.34 (dd, ³J = 5.2, ⁴J = 1.9 Hz, 1H), 8.25-8.26 (dd, ³J = 5.2, ⁴J = 1.9 Hz, 1H), 7.88-8.00 (m, 6H), 7.54-7.77 (m, 16H), 3.93 (s, 1H), 2.05 (m, 1H), 1.17 (d, ³J = 6.8 Hz, 3H), 0.71 (m, 4H), -0.12 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ) 167.2, 164.2, 154.2, 150.7, 143.7, 141.3, 140.1, 138.1, 138.0, 136.7, 134.4, 133.9, 133.9, 133.8, 133.2, 131.9, 131.7, 129.6, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.1, 126.4, 125.9, 125.0, 124.4, 120.8, 115.0, 113.1, 104.7, 103.8, 35.9, 17.8, 17.7, 15.8 ppm; HR-MS (ESI+ of MH⁺, 100% CH₃CN): m/z calc’d for C₄₅H₃₅N₄O₄: 695.2658, found 695.2645.
Figure 7-31. \(^1\)H NMR spectrum (400 MHz, CDCl\(_3\)) of 8-cis.

Figure 7-32. \(^{13}\)C NMR spectrum (100 MHz, CDCl\(_3\)) of 8-cis.
Figure 7-33. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 8-cis (CH₂Cl₂).

Figure 7-34. FT-IR spectrum (neat, diffuse reflectance) of 8-cis.
meso-Tetraphenyl-3-isopropyl-2,13-dioxa-12-oxochlorin (9-cis) and meso-tetraphenyl-3-isopropyl-2,12-dioxa-13-oxochlorin (9-trans). A 10:1 diastereomeric mixture of meso-tetraphenyl-3-hydroxy-3-isopropyl-2,13-dioxa-12-oxochlorin and meso-tetraphenyl-3-hydroxy-3-isopropyl-2,12-dioxa-13-oxochlorin (8, 100 mg,) was dissolved in CH₂Cl₂ (30 mL) and stirred at room temperature. To this solution, excess BF₃·OEt₂ (10 eq, 0.17 ml of 98%+ solution) and Et₃SiH (10 eq, 0.23 ml) were added slowly.

Reaction progress was monitored using UV-visible spectroscopy (formation of the diagnostic peak at ~695 nm in a neutralized aliquot). Upon completion (~2-3 h reaction time), the reaction mixture was quenched by addition of a sat. aq. NaHCO₃ solution. The mixture was transferred to a separatory funnel. The aqueous NaHCO₃ wash was repeated until all acids were removed. The organic layer was isolated, dried using Na₂SO₄, and the solvent was evaporated by rotary evaporation. The crude product was purified by flash chromatography (silica-CH₂Cl₂) to afford the product 9 in good yield (71%, 69 mg). The product was isolated as a diastereomeric mixture (10:1 based on ¹H NMR) reflecting the diastereomeric mixture of the starting material. For the sake of simplicity, only the spectroscopic data of 9-cis are listed here. MW = 678.78 g/mol; Rf = 0.95 (silica-CH₂Cl₂); UV-vis (CH₂Cl₂) λ_max (log ε): 418 (5.02), 483 (3.41), 510 (3.82), 544 (3.45), 633 (3.66), 695 (4.25) nm, Fl λ_max (CH₂Cl₂, λ_exc 414 nm): 709 nm, φ = 0.13; ¹H NMR (300 MHz, CDCl₃, δ) 8.27 (dd, ³J = 5.2, ⁴J = 1.9 Hz, 1H), 8.14 (dd, ³J = 5.2, ⁴J = 1.9 Hz, 1H), 8.93-7.78 (m, 8H), 7.69-7.62 (m, 14 H), 6.73 (d, ³J = 2.6 Hz, 1H), 1.92 (m, 1H), 1.44 (s, 1H), 1.05 (d, ³J = 6.8 Hz, 3H), 0.68 (s, 1H), 0.59 (d, ³J = 6.7 Hz, 3H) ppm;
$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 169.4, 169.2, 154.5, 154.1, 144.4, 144.1, 139.9, 139.8, 138.3, 138.2, 137.9, 136.8, 133.9, 133.6, 133.5, 133.3, 132.9, 132.4, 132.0, 131.8, 131.7, 130.4, 129.9, 129.6, 129.2, 128.6, 128.4, 128.3, 128.0, 127.7, 127.7, 127.5, 127.5, 126.4, 125.3, 124.1, 123.8, 123.1, 118.9, 112.1, 105.1, 102.9, 90.5, 90.5, 33.1, 32.7, 20.3, 20.1, 20.0, 14.4, 14.3 ppm; HR-MS (ESI$^+$ of MH$^+$, 100% CH$_3$CN): $m/z$ calc’d for C$_{45}$H$_{34}$N$_4$O$_3$: 679.2709, found 679.2689.

Figure 7-35. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 9-$\text{cis}$.

Figure 7-36. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 9-$\text{cis}$.
Figure 7-37. UV-vis (solid red trace) and fluorescence (broken black trace) spectra of 9-cis (CH$_2$Cl$_2$).

Figure 7-38. FT-IR spectrum (neat, diffuse reflectance) of 9-cis.
meso-Tetraphenyl-3-isopropyl-3,12/13-dimethoxy-2,12/13-dioxabacteriochlorin (14-cis/trans-E/Z). General procedure for conversion of diolbacteriochlorins to dioxazolobacteriochlorins. 5 (56 mg, 0.77 mmol) was dissolved in CHCl$_3$ (7 mL) at r.t. in a round-bottom flask equipped with a magnetic stirring bar, a N$_2$ inlet and bubbler, was shielded from ambient light with aluminum foil. Excess MeOH (3 mL) was added to the solution in which was purged with N$_2$. NaIO$_4$-silica (~0.5 g) was added to the stirring reaction mixture and allowed to react for ~16 h. The reaction progress was monitored using UV-visible spectroscopy (product peak ~740 nm). A full conversion of the starting material was never observed and ~25-30% recovery of starting material was generally observed. The mixture was then filtered (glass frit M) and the filter cake washed with CH$_2$Cl$_2$. The filtrate was evaporated to dryness by rotary evaporation. The products were isolated by automated flash chromatography (silica, CH$_2$Cl$_2$). The non-polar red-pink product was isolated in 31% yield (17.5 mg, adjusted yield = 45%) as a diastereomeric mixture. MW = 724.84 g/mol; R$_f$ = 0.85 (silica-CH$_2$Cl$_2$); UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ (log $\varepsilon$): 348 (4.86), 377 (4.96), 518 (4.34), 743 (4.37) nm; Fl $\lambda_{\text{max}}$ (CH$_2$Cl$_2$, $\lambda_{\text{exc}}$ = 377 nm): 747 nm, $\phi$ = 0.07; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$, mixture of 14-cis/trans-E/Z) 8.28 (m, 2H), 8.23 (m, 2H), 8.17 (m, 2H), 7.77-8.11 (m, 33H), 7.51-7.72 (m, 44H), 3.26 (s, 3H) 3.25 (s, 3H), 3.25 (s, 2H), 3.24 (s, 2H), 3.06 (s, 2H), 3.02 (s, 2H), 3.01 (s, 3H), 2.94 (s, 3H), 2.08 (m, 2H), 1.94 (m, 2H), 1.06 (m, 5H), 0.99 (m, 2H), 0.71 (m, 2H), 0.68 (m, 6H), 0.61 (m, 3H), -1.22 (m, 2H), -1.34 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$); 162.7, 163.0, 161.0, 160.9, 160.6, 160.5, 147.9, 147.8, 147.3, 147.1, 143.0, 142.9, 142.7, 142.3,
142.2, 139.7, 139.6, 139.5, 139.4, 139.10, 139.09, 138.8, 138.63, 138.60, 138.51, 138.4, 137.94, 137.91, 137.6, 137.46, 137.45, 137.16, 137.14, 135.7, 135.6, 134.4, 134.3, 143.1, 133.9, 133.8, 133.6, 133.54, 133.52, 133.3, 133.20, 133.19, 133.0, 132.8, 132.6, 132.5, 131.2, 131.1, 130.6, 130.4, 128.1, 128.0, 127.96, 127.90, 127.74, 127.69, 127.6, 127.51, 127.49, 127.40, 127.38, 126.9, 126.8, 126.7, 126.1, 126.0, 123.7, 123.6, 123.2, 123.1, 122.64, 122.62, 118.4, 117.9, 117.8, 117.4, 117.20, 117.19, 116.6, 116.5, 116.3, 116.2, 113.97, 113.94, 113.44, 113.38, 106.24, 106.19, 105.6, 103.7, 103.6, 103.34, 103.33, 103.30, 103.27, 103.09, 103.05, 54.66, 54.5, 54.42, 54.38, 35.75, 35.73, 35.49, 35.42, 34.88, 34.73, 32.14, 25.5, 20.9, 17.6, 17.5, 16.5, 16.4, 16.3, 16.2 ppm; HR-MS (ESI+ of MH⁺, 100% CH₃CN): m/z calc’d for C₄₇H₄₁N₄O₄: 725.3128, found 725.3145.

Figure 7-39. ¹H NMR spectrum (400 MHz, CDCl₃) of 14 (mixture of all isomers).
Figure 7-40. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 14 (mixture of all isomers).

Figure 7-41. UV-vis spectrum of 14 (CH$_2$Cl$_2$, mixture of all isomers).
meso-Tetraphenyl-3,3-diisopropyl-12-methoxy-2,13-dioxabacteriochlorin

(13-cis) and meso-tetraphenyl-3,3-diisopropyl-13-methoxy-2,12-dioxabacteriochlorin

(13-trans). Prepared from diolbacteriochlorin 2 (48 mg) in 21 % yield (10 mg, with ~25% of 2 recovered) according to the general procedure described for the synthesis of 14. The diagnostic peak of 23 in UV-visible spectroscopy was observed at ~770 nm. MW = 736.89 g/mol; Rf = 0.85 (silica-CH$_2$Cl$_2$); UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$ (log ε): 390 (5.09), 356 (5.00), 528 (4.50), 774 (4.81) nm; Fl $\lambda_{max}$ (CH$_2$Cl$_2$, $\lambda_{exc}$ = 380 nm): 776 nm, $\phi$ = 0.03;

$^1$H NMR (300 MHz, CDCl$_3$, $\delta$, contains 13-cis and 13-trans at a 3:2 ratio) 8.12 (m, 1H), 8.05 (m, 3H), 7.78-8.02 (m, 15H), 7.53-7.71 (m, 23H), 3.22 (s, 3H), 3.20 (s, 2H), 2.51 (m, 2H), 2.38 (m, 1H), 1.08 (m, 3H), 1.03 (m, 3H), 0.99 (m, 2H), 0.96 (m, 2H), 0.73 (m, 2H), 0.70 (m, 3H), 0.67 (m, 2H), 0.60 (m, 3H) -0.76 (s, 1H), -0.92 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 166.0, 164.1, 163.5, 160.2, 157.7, 152.2, 146.6, 143.1, 142.7, 140.9, 140.4, 140.3, 139.9, 139.6, 139.42, 139.36, 139.1, 137.9, 137.8, 137.4, 137.1, 136.5, 134.2, 133.9, 133.79, 133.78, 133.6, 133.4, 133.3, 133.2, 133.1, 132.8, 131.2, 130.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.79, 127.76, 127.68, 127.6, 127.5, 127.4, 127.3, 126.6, 126.5, 126.4, 122.98, 122.94, 122.4, 122.1, 117.7, 117.3, 117.1, 113.8, 113.2, 111.3, 105.9, 105.4, 103.7, 103.4, 102.9, 102.3, 100.6, 99.6, 54.25, 54.1, 37.0, 36.6, 36.5, 29.9, 19.4, 19.3, 19.1, 19.0, 18.9, 18.59, 18.57; HR-MS (ESI+ of MH$^+$, 100% CH$_3$CN): m/z calc’d for C$_{49}$H$_{45}$N$_4$O$_3$: 737.3492, found 737.3504.
Figure 7-42. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 13-cis/trans (mixture, 3:2).

Figure 7-43. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 13-cis/trans (mixture, 3:2).
Figure 7-44. UV-vis spectrum of 13-cis/trans (CH$_2$Cl$_2$, mixture, 3:2).

*meso*-Tetraphenyl-3,3-diisopropyl-12,12-dihydro-2,13-dioxabacteriochlorin (15). In the dark or low light environment (important to avoid adventitious oxidation), a 10:1 diastereomeric mixture of *meso*-tetraphenyl-3,3-diisopropyl-2,12-dioxa-13-oxochlorin and *meso*-tetraphenyl-3,3-diisopropyl-2,13-dioxa-12-oxochlorin (3-cis/trans, 80 mg, 0.11 mmol) was dissolved in CH$_2$Cl$_2$ and stirred at room temperature. To this solution, excess BF$_3$·OEt$_2$ (30 eq, 0.4 ml of 98% solution) and Et$_3$SiH (30 eq, 0.53 ml) were added slowly. Reaction progress was monitored using UV-visible spectroscopy (a band ~820 nm in a neutralized aliquot, indicated the appearance of the product). The reaction was left stirring until all starting materials were consumed and additional reductants were added as necessary until the UV-visible spectrum of the reaction mixture only displayed a the bacteriochlorin spectrum with a $\lambda_{max}$ of ~820 nm. Upon completion,
the reaction mixture was quenched by addition of a sat. aq. NaHCO₃ solution. The mixture was transferred to a separatory funnel. The aq. NaHCO₃ wash was repeated until all acids were removed. The organic layer was isolated, dried using Na₂SO₄, and the solvent was evaporated by rotary evaporation. The dark residue was re-dissolved in minimal CH₂Cl₂ and crystallized via slow solvent exchange with MeOH to give 15 in 18 % yield (14 mg). MW = 706.87 g/mol; UV-vis (CH₂Cl₂) λ_max (log ε): 353 (4.65), 389 (4.79), 529 (4.24), 815 (4.6) nm; Fl λ_max (CH₂Cl₂, λ_exc = 379 nm): 819nm, φ = < 1%;

1H NMR (500 MHz, CDCl₃, δ) 8.02 (dd, 3J = 4.7, 4J = 2.0 Hz, 1H), 7.87-7.93 (m, 6H), 7.82 (dd, 3J = 4.5, 4J = 2.0 Hz, 1H), 7.76-7.78 (m, 2H), 7.41-7.68 (m, 14H), 6.4 (s, 2H), 2.47 (m, 2H), 1.04 (d, 3J = 6.6 Hz, 6H), 0.67 (d, 3J = 6.9 Hz, 6H), -0.33 (s, 1H), -0.48 (s, 1H) ppm; 13C NMR (100 MHz, CDCl₃, δ) 164.9, 163.6, 156.0, 152.4, 140.4, 140.2, 140.1, 139.4, 138.5, 137.9, 137.7, 136.8, 133.7, 133.2, 132.9, 131.6, 128.8, 128.2, 128.1, 127.8, 127.6, 127.5, 127.2, 126.4, 122.8, 122.2, 121.8, 120.1, 111.8, 109.8, 102.8, 101.9, 100.1, 36.9, 19.3, 18.8; HR-MS (ESI+ of MH⁺, 100% CH₃CN): m/z calc’d for C₄₈H₄₃N₄O₂: 707.3386, found 707.3402.
Figure 7-45. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 15.

Figure 7-46. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 15.
Figure 7-47. UV-vis spectrum of **15** (CH$_2$Cl$_2$).

### 7.5.3. X-Ray Crystallography Data

X-ray crystallographic analyses (provided by Dr. Christopher Ziegler and James T. Engle, University of Akron): Single crystals of **3-cis, 6-cis, 6-Zn-cis, 14-trans-E, 14-trans-Z** and **13-cis** were coated in Fomblin® oil, mounted on a pin and placed a goniometer head under a stream of nitrogen cooled to 100 K. The data were collected on an APEX2 CCD diffractometer with Cu source Kα radiation ($\lambda = 1.54178$). The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan method (SADABS) and the structure was solved and refined using the Bruker SHELXTL Software Package until the final anisotropic full-matrix, least-squares refinement of F$^2$ converged.
Crystal Structure Report for 3-cis

A red block-like specimen of 3-cis, approximate dimensions 0.13 mm x 0.14 mm x 0.19 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

Figure 7-48. ORTEP Representation of the crystal structure of 3-cis, side and top views. Hydrogens and disorder removed for clarity.
Crystal Structure Report for **6-cis**

A red plate-like specimen of **6-cis**, approximate dimensions 0.08 mm × 0.22 mm × 0.28 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

**Figure 7-49.** ORTEP Representation of the crystal structure of **6-cis**, side and top views. Hydrogens and disorder removed for clarity.
Crystal Structure Report for 6Zn-cis

A green specimen of 6Zn-cis, approximate dimensions 0.27 mm × 0.47 mm × 0.55 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

Figure 7-50. ORTEP Representation of the crystal structure of 6Zn-cis, side and top views. Hydrogens and disorder removed for clarity.
Crystal Structure Report for 14-trans-E

An orange plate-like specimen of 14-trans-E, approximate dimensions 0.09 mm × 0.10 mm × 0.21 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 33.52 hours.

Figure 7-51. ORTEP Representation of the crystal structure of 14-trans-E, side and top views. Hydrogens and disorder removed for clarity.
Crystal Structure Report for 14-trans-Z

A orange specimen of 14-trans-Z, approximate dimensions 0.18 mm × 0.24 mm × 0.28 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 38.48 hours.

Figure 7-52. ORTEP Representation of the crystal structure of 14-trans-Z, side and top views. Hydrogens and disorder removed for clarity.
**Crystal Structure Report for 13-cis**

A red specimen of 13-cis, approximate dimensions $0.38 \text{ mm} \times 0.42 \text{ mm} \times 0.55 \text{ mm}$, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

**Figure 7-53.** ORTEP Representation of the crystal structure of 13-cis, side and top views. Hydrogens and disorder removed for clarity.
<table>
<thead>
<tr>
<th>Identification Code</th>
<th>3-cis</th>
<th>6-cis</th>
<th>6-Zn-cis</th>
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</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₄₈H₄₀N₄O₃</td>
<td>C₉₇H₇₇N₉O₈</td>
<td>C₇₄H₆₈N₄O₅Zn</td>
</tr>
<tr>
<td>Formula weight</td>
<td>720.84</td>
<td>1496.68</td>
<td>804.18</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
<td>1.54178</td>
<td>1.54178</td>
<td>1.54178</td>
</tr>
<tr>
<td>Crystallographic and structure refinement data for 3-cis, 1-cis and 6-cis-Zn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 7-1.</td>
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<td></td>
<td></td>
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<tr>
<td>Identification Code</td>
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<td>6-cis</td>
<td>6-Zn-cis</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C₄₈H₄₀N₄O₃</td>
<td>C₉₇H₇₇N₉O₈</td>
<td>C₇₄H₆₈N₄O₅Zn</td>
</tr>
<tr>
<td>Formula weight</td>
<td>720.84</td>
<td>1496.68</td>
<td>804.18</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
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<tr>
<td>Wavelength (Å)</td>
<td>1.54178</td>
<td>1.54178</td>
<td>1.54178</td>
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<td>Crystal system</td>
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<td>Monoclinic</td>
<td>Triclinic</td>
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<td>Space group</td>
<td>P2(1)/c</td>
<td>C2/c</td>
<td>P1</td>
</tr>
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<td>11.4410(5)</td>
<td>23.6921(5)</td>
<td>111.9920(10)</td>
</tr>
<tr>
<td>α, β, γ (°)</td>
<td>90</td>
<td>126.626(3)</td>
<td>117.2340(10)</td>
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<td>β, γ (°)</td>
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<td>90</td>
<td>90</td>
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<td>Volume [Å³]</td>
<td>3718.6(3)</td>
<td>7457.3(3)</td>
<td>2192.36(12)</td>
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<tr>
<td>Z</td>
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<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Density (calc'd) [Mg/m³]</td>
<td>1.288</td>
<td>1.333</td>
<td>1.218</td>
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<td>0.640</td>
<td>0.684</td>
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<tr>
<td>F(000)</td>
<td>1520</td>
<td>3144</td>
<td>836</td>
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<tr>
<td>Crystal size [mm³]</td>
<td>0.19 x 0.14 x 0.13</td>
<td>0.28 x 0.22 x 0.08</td>
<td>0.55 x 0.47 x 0.27</td>
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<td>Theta range for data collection</td>
<td>3.59° to 62.99°</td>
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<td>-14&lt;=h&lt;=14</td>
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<tr>
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<td>21363</td>
<td>23334</td>
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<tr>
<td>Independent reflections</td>
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<td>6046</td>
<td>6348</td>
</tr>
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<td>[R(int) = 0.0480]</td>
<td>-25&lt;=k&lt;=22</td>
<td>-16&lt;=k&lt;=16</td>
<td>-14&lt;=k&lt;=11</td>
</tr>
<tr>
<td>[R(int) = 0.0303]</td>
<td>-21&lt;=l&lt;=20</td>
<td>-30&lt;=l&lt;=29</td>
<td>-16&lt;=l&lt;=16</td>
</tr>
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<td>Completeness to theta</td>
<td>96.5%</td>
<td>96.4%</td>
<td>94.7%</td>
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<td>SADABS</td>
<td>SADABS</td>
</tr>
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<td>Max. and min. transmission</td>
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<td>0.9473 &amp; 0.8320</td>
<td>0.7434 &amp; 0.5661</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
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<td>6046 / 0 / 518</td>
<td>6348 / 0 / 522</td>
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<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices</td>
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<tr>
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<td>[R(int) = 0.0303]</td>
<td>[R(int) = 0.0272]</td>
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<td>R1 = 0.0645, wR2 = 0.1748</td>
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Table 7-2. Crystallographic and structure refinement data for 14-trans-E, 14-trans-Z and 13-cis.

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<th>Identification Code</th>
<th>14-trans-E</th>
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<th>13-cis</th>
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<td>C_{47}H_{40}N_{4}O_{4}</td>
<td>C_{47}H_{40}N_{4}O_{4}</td>
<td>C_{49}H_{44}N_{4}O_{3}</td>
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<td>724.83</td>
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<td>100(2)</td>
<td>100(2)</td>
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<tr>
<td>Wavelength (Å)</td>
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<td>1.54178</td>
<td>1.54178</td>
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<td>Crystal system</td>
<td>Orthorhombic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
</tr>
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<td>P2(1)2(1)2(1)</td>
<td>P2(1)/c</td>
<td>P2(1)/c</td>
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<tr>
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<td>b = 9.5370(2)</td>
<td>a = 20.3320(5)</td>
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<tr>
<td></td>
<td>c = 30.4999(7)</td>
<td>c = 19.1964(4)</td>
<td>b = 11.1841(3)</td>
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<td>90</td>
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<td>3942.36(18)</td>
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<td>Z</td>
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<td>1.278</td>
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</tr>
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<td>-15&lt;=k&lt;=15</td>
<td>-10&lt;=k&lt;=10</td>
<td>12&lt;=k&lt;=11</td>
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<tr>
<td></td>
<td>-35&lt;=l&lt;=35</td>
<td>-21&lt;=l&lt;=20</td>
<td>-20&lt;=l&lt;=19</td>
</tr>
<tr>
<td>Reflections collected</td>
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<td>23323</td>
</tr>
<tr>
<td>Independent reflections</td>
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<td>5901</td>
<td>6350</td>
</tr>
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<td>SADABS</td>
<td>SADABS</td>
</tr>
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<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
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<td>5901/0 / 519</td>
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</tr>
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<td>R1 = 0.0808,</td>
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<td>R1 = 0.0825,</td>
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<td>wR2 = 0.2308</td>
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<td>1.444 &amp; -0.439</td>
<td>1.341 &amp; -0.423</td>
</tr>
</tbody>
</table>

Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins
7.6. References


Chapter 7: Oxabacteriochlorins and Dioxabacteriochlorins


