TOWARDS THE SYNTHESIS OF A HOMOCHIRAL BIS(DIPYRROMETHENE)

by

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To Mom, Dad, Brian, and Tasha

TABLE OF CONTENTS

LIST OF TABLES ..... **ix**

LIST OF FIGURES ..... **x**

LIST OF SCHEMES ..... **xiii**

ABSTRACT ..... **xvi**

LIST OF ABBREVIATIONS AND SYMBOLS USED ..... **xvii**

Chemicals xvii
Analytical instrumentation and related xviii
Miscellaneous xviii

ACKNOWLEDGEMENTS ..... **xix**

CHAPTER 1: INTRODUCTION **1**

Natural occurrences of pyrrole 1
Named reactions involving the formation of substituted pyrrole 3
The aromatic nature of pyrrole 8
Reaction of pyrrole with electrophiles 11
Anionic chemistry of pyrrole 14
Pyrrolic functional group interconversion chemistry 15
Dipyrromethenes and their metal complexes 18
Bis(dipyrromethene)s: Architecture of the bilins 21
Helicates and their history 23

CHAPTER 2: RESULTS AND DISCUSSION **28**

Goals and general synthetic strategy 28
Stabilizing the stereocenter with a trifluoromethyl group 30
PRELIMINARY ENDEAVORS TOWARD A BIS(DIPYRROMETHENE) LIGAND *35*
An introduction to potential synthetic strategies 35
Attempted syntheses of a symmetrical 2,2′-dipyrromethane 38
An alternative homo-coupling pathway toward **20** 44
Towards 2,2′-bis(dipyrromethene)s from the synthesis of a bis-β free 2,2′-dipyrromethane precursor 48
The use of β versus α substitution to construct the required α-free pyrrole 52
A general acylation of pyrrole with mixed anhydrides 56
*DIPYRROMETHENE DERIVATIVES OF **11*** *64*
Synthesis and chiral separation of dipyrromethene complexes 64
Investigation of complex stability: HPLC 69
Investigation of complex stability: UV-VIS 73
AN ALTERNATIVE APPROACH TO BIS(DIPYRROMETHENES) *86*
Conclusions and some useful alternatives 91
A NEW ARCHITECTURE OF BIS(DIPYRROMETHENES) FROM PYRROLINONES .. *94*
α-ACYLOXYLATION OF CARBONYL COMPOUNDS *100*

CHAPTER 3: EXPERIMENTAL 106

General Experimental Procedures 106
Benzyl 1-benzyl-3,5-dimethylpyrrole-2-carboxylate (**24**) 108
Benzyl 1-benzyl -4-(2,2,2-trifluoro-1-hydroxyethyl)-3,5-dimethylpyrrole-2-carboxylate (**25**) 108
Benzyl 1-benzyl-2,5-dimethyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (**26**) 109
Benzyl 5-acetoxymethyl-4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (**28**) 110
Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-chloromethyl-3-methylpyrrole-2-carboxylate (**29**) 110

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-methoxymethyl-3-methylpyrrole-2-carboxylate (**30**) 111

Benzyl 4-(2,2,2-trifluoro-1-hydroxyethyl)-5-methoxymethyl-3-methylpyrrole-2-carboxylate (**31**) 111

4-(2,2,2-Trifluoro-1-hydroxyethyl)-3-methylpyrrole-2-benzyloxycarbonyl-5-carboxylic acid (**33**) 111

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (**37**) 112

Benzyl 4-(1-benzyloxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (**38**) 113

Diethyl 1-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-3,5-dimethylpyrrolo[3,2-*f*]indole-2,6-dicarboxylate (**41**) 113

Diethyl 3,5-dimethyl-4-trifluoromethylpyrrolo[3,2-*f*]indole-2,6-dicarboxylate (**43**) 114

Benzyl 3-methyl-1-triisopropylsilylpyrrole-2-carboxylate (**46**) 114

Benzyl 4-bromo-3-methyl-1-triisopropylsilylpyrrole-2-carboxylate (**47**) 115

General procedure for the formation of the 4-acylpyrrole-2-carboxylates 115

Ethyl 4-(3,5-dimethoxybenzoyl)-3,5-dimethylpyrrole-2-carboxylate (**51b**) 116

Ethyl 4-benzoyl-3,5-dimethylpyrrole-2-carboxylate (**51c**) 116

Ethyl 4-(4-ethoxybenzoyl)-3,5-dimethylpyrrole-2-carboxylate (**51d**) 116

Ethyl 4-hexadecanoyl-3,5-dimethylpyrrole-2-carboxylate (**51e**) 116

Ethyl 3,5-dimethyl-4-propionylpyrrole-2-carboxylate (**51f**) 117

Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (**51g**) 117

Ethyl 3,5-dimethyl-4-(2,2-dimethylpropionyl)pyrrole-2-carboxylate (**51h**) 117

Ethyl 3,5-dimethyl-4-(3-methyl-butyryl)pyrrole-2-carboxylate (**51i**) 117

Diethyl 4-(3′,5′-dimethyl-pyrrole-2′-carbonyl-4′-carboxylate)-3,5-dimethylpyrrole-2-carboxylate (**54**) 118

Ethyl 4-(4′-acetyl-3′,5′-dimethyl-pyrrole-2′-carbonyl)-3,5-dimethyl-pyrrole-2-carboxylate (**55**) 118

Diethyl 2,2′-bis(3′,5′-dimethyl-pyrrole-4′-carboxylate) carbonyl (**57**) 118

2,3-Dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrole hydrobromide (**59**) 119

Zinc bis[2,3-dimethyl-4-(1-hydroxy-2,2,2-trifluoroethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (**60**) 119

Benzyl 4-(difluoroethoxycarbonylmethyl)-3,5-dimethylpyrrole-2-carboxylate (**66**) 120

Benzyl 4-iodo-3,5-dimethylpyrrole-2-carboxylate (**67**) 121

Benzyl 3,5-dimethyl-4-oxalylpyrrole-2-carboxylate (**69**) 121

Dibenzyl 4,4′-(ethane-1,2-dione)-3,3′,5,5′-tetramethylbispyrrole-2,2′-dicarboxylate (**70**) 122

4-Ethyl-3-methyl-5-(pyrrol-2-ylmethylidene)-pyrrol-2-one (**75**) 122

4-Methoxy-5-(pyrrol-2-ylmethylidene)-pyrrol-2-one (**77**) 123

7-Methoxy-6-(2*H*-pyrrol-2-ylmethylidene)-pyrrolo[2,1-*b*][1,3]oxazine (**78**) 124

3-Ethyl-5-methoxy-4-methyl-2-(2*H*-pyrrol-2-ylmethylidene)pyrrole (**82**) 125

3-Ethyl-5-methoxy-1,4-Dimethyl-2-(2*H*-pyrrol-2-ylmethylidene)pyrrole (**83**) 125

3-Ethyl-1,4-dimethyl-5-(1-methylpyrrol-2-ylmethylidene)pyrrol-2-one (**84**) 126

References 127

LIST OF TABLES

Table 1: Acylation results using Knight's conditions. 59

Table 2: Acylation utilizing modified method. 61

Table 3: Results for some attempted acyloxylation reactions..... 104

LIST OF FIGURES

Figure 1: Pyrrole labeled according to IUPAC convention and trivial nomenclature (parentheses) 1

Figure 2: Some natural products containing pyrrolic rings..... 2

Figure 3: Resonance structures of pyrrole illustrating its electron excessive nature..... 9

Figure 4: Top – molecular model depicting the bond lengths in pyrrole. Bottom left – molecular model depicting the bond length in the cyclopentadienyl ion. Bottom right – molecular model depicting the effect nitrogen has on the orbital coefficient of the HOMO in pyrrole..... 10

Figure 5: First intermediate for the electrophilic substitution of pyrrole and benzene..... 12

Figure 6: Example of meta directing electron-withdrawing group (top) and ortho/para directing electron-donating group (bottom)..... 13

Figure 7: Pseudo-doubly-vinylogous carbamate resonance stabilization of pyrrole..... 13

Figure 8: The reactivity effect of an ionic versus a covalent N-M bond..... 14

Figure 9: The simplest dipyrromethene structure, as a hydrobromide salt 19

Figure 10: General structure of a BODIPY molecule..... 20

Figure 11: Top - examples of bilin (biliverdin) and bilidiene (bilirubin) analogues that can be compared with 2,2′-bis(dipyrromethene)s (bottom right). Bottom left - example of an unnatural 3,3′-bis(dipyrromethene)..... 22

Figure 12: Helical bilidiene isolated by Dolphin in 1966..... 23

Figure 13: The simplest bipyridine ligand..... 23

Figure 14: Two enantiomeric single-stranded helices with defining characteristics..... 25

Figure 15: General strategies toward chiral induction..... 28

Figure 16: Illustrative example of close contacts between stereocenter and coplanar ligand. 29

Figure 17: Architectures of **A** and **B** 33

Figure 18: Effects of substituents on ring substitution. Asterisk denotes preferred regiochemistry 54

Figure 19: Trifluoroacetylating reagent 57

Figure 20: Knight's general method 58

Figure 21: Isomers for the *P* series 67

Figure 22: Separation of complex **60** with a chiral HPLC column 70

Figure 23: HPLC separation of ***S*-60** with a chiral column 71

Figure 24: Compounds studied with UV-VIS 75

Figure 25: UV-VIS spectra indicating the maximum absorbance of complex 60 with varying concentration 76

Figure 26: Overlay of UV-VIS spectra of **60** at $4.5e^{-6}$ M at different time intervals 77

Figure 27: Effect of TEA addition on the UV-VIS spectrum of **60** at 4.5e-6 M 79

Figure 28: Solutions of compound **62** in non-specrophotometric grade DCM undergo a blue shift 80

Figure 29: Complex **62** at dilute concentration and the effect of added TEA. A spectrum of pure ligand is superpositioned for comparison 80

Figure 30: UV-VIS spectra of **63** at different concentrations 82

Figure 31: UV-VIS spectrum of the ligand used in the construction of **64** 82

Figure 32: First derivative spectra for complex **60** after one hour. A spectrum of complex titrated with TEA and a spectrum of the ligand are included for comparison 83

Figure 33: Retrosynthesis of **65** 87

Figure 34: Biliruben in its *M*-ridge-tile conformation 92

Figure 35: MacMillan imidazolone catalyzed enantioselective Friedel-Crafts reaction .. 94

Figure 36: Reaction sequence accomplishing α-acyloxylation 101

LIST OF SCHEMES

Scheme 1: Precursors for Pd(0) coupling towards prodigiosin synthesis 3

Scheme 2: The Knorr reaction 4

Scheme 3: The Paal-Knorr reaction 4

Scheme 4: Hantzsch synthesis of pyrrole 5

Scheme 5: The Kleihnspehn variation of the Knorr reaction 5

Scheme 6: Kenner synthesis 6

Scheme 7: Barton-Zard synthesis of pyrrole 7

Scheme 8: Arndtsen synthesis of pyrrole 7

Scheme 9: Alkylation of pyrrylthallium(I) 15

Scheme 10: SEMCl use in pyrryllithium chemistry 15

Scheme 11: The σ-complex of bromine with pyrrole 16

Scheme 12: Use of sulfuryl chloride in the oxidation of an α-methyl carbon to generate α-alkoxy (or hydroxy)methyl, aldehyde, and carboxylic acid 17

Scheme 13: A general example of Macfayden-Stevens reduction of a pyrrolyl ester 18

Scheme 14: Synthesis of a dipyrromethene via the MacDonald condensation 21

Scheme 15: Lehn's synthesis of a homochiral ligand 26

Scheme 16: Current and historic syntheses of **5** 31

Scheme 17: *O*-methylation of **5** 32

Scheme 18: Acid-catalyzed elimination of water from hematoporphyrin 34

Scheme 19: Electrophilic aromatic substitution using ethyl trifluoroacetaldehyde hemiacetal 34

Scheme 20: Retrosynthesis and early strategy to an unsymmetrical dipyrromethene 36

Scheme 21: Retrosynthetic look at the construction of a symmetrical dipyrromethane 38

Scheme 22: Attempted routes to a methyl ether derivative with a chiral center 40

Scheme 23: Attempted homocoupling of acetoxymethyl pyrrole **28** 42

Scheme 24: Mechanism for the formation of a dipyrromethane through homocoupling. 43

Scheme 25: Alternative retrosynthesis to **20** 45

Scheme 26: Attempted coupling of an extremely electron deficient series of pyrroles ... 46

Scheme 27: Attempted decarboxylation of pyrrole **33** and the inadvertent *O*-benzylation of **37** 47

Scheme 28: Methods used to produce dipyrromethane **22** 49

Scheme 29: Inadvertent synthesis of pyrrolo-indoles **41** and **43** 51

Scheme 30: Kenner synthesis used to produce desired α-free pyrrole 53

Scheme 31: Production of a dibromo-pyrrole for palladium cross coupling 55

Scheme 32: The chemistry of **46** 56

Scheme 33: Trifluoroacetylation of **7** 59

Scheme 34: The acylation process 60

Scheme 35: New synthetic method for dipyrrylketones 63

Scheme 36: Synthesis of a dipyrromethene to test both complexation and diastereoselectivity 65

Scheme 37: Synthesis of **60** 66

Scheme 38: Asymmetric synthesis of a dipyrromethene ligand and complex 69

Scheme 39: Racemization of ***S*-11** 72

Scheme 40: Differing mechanisms displayed by copper cross coupling of an α-fluorinated ester 88

Scheme 41: Synthesis of a potential precursor to **65** 90

Scheme 42: Synthesis of an unwanted 3,3′-dipyrroethandione 91

Scheme 43: Synthesis and resolution of a chiral pyrrole by Lightner and co-workers 93

Scheme 44: Melvin and coworkers synthesis of a dipyrromethene free-base 94

Scheme 45: Synthesis of a bis(dipyrromethene) using a pyrrolinone 95

Scheme 46: Attempted synthesis of a bis(dipyrromethene) free base with a pyrrolinone 96

Scheme 47: *N*-Protected pyrrolinone 97

Scheme 48: Product distribution in dipyrrinone alkylation 97

Scheme 49: Proposed mechanism of dipyrrinone alkylation under basic conditions..... 98

Scheme 50: Synthesis of a bis(dipyrromethene) from a dipyrrinone under acidic conditions 100

Scheme 51: A depiction of reactions accomplished or attempted in construction of acyloxylation reagent and oxidation of selected ketones and aldehydes... 103

ABSTRACT

With the advent of helical metal complexes involving linear tetra-pyrroles known as bis(dipyrromethene)s, the Thompson laboratory has been interested in a stereo-controlled self-assembly of diastereomerically enriched helicates. The following chapters illustrate efforts geared toward the diastereoselective formation of bis(dipyrromethene) helicates and a few projects of opportunity that arose as a result of the exploration of suitable homochiral pyrroles required to synthesize stereochemically enriched bis(dipyrromethene) metal complexes.

The synthesis of a homochiral pyrrole as a precursor in the synthesis of a homochiral bis(dipyrromethene) for the purposes of stereocontroled helicate formation was very important. In addition to the required synthesis of a homochiral pyrrole it was desired that the stereogenic center contain a useful appendage in order to provide a useful handle for derivatization. Thus, it was decided that the useful appendage suitable for the derivation of the homochiral pyrrole, and consequently the future bis(dipyrromethene) ligand, would be a hydroxyl group. The chemistry involved in the synthesis of a homochiral bis(dipyrromethene) ligand was thought to be incompatible with the hydroxyl functional group that was adjacent to the pyrrole ring due to the increased lability (under the required acidic conditions) of any "leaving group" that is influenced by the heterocyclic lone pair. Literature methods were employed in an attempt to combat the effect of the nitrogen lone pair and the results are described.

New methods involving the synthesis of bis(dipyrromethene)s from dipyrrinone architectures became of interest and this became a small project of opportunity. As well, the β-acylation of pyrrole, involving mixed phosphoryl anhydrides, was explored and a successful method was devised to construct dipyrryl ketones. To complete the list of projects, a student exchange was undertaken and a preliminary method explored towards the α-acyloxylation of carbonyl compounds.

LIST OF ABBREVIATIONS AND SYMBOLS USED

Chemicals

AC	acetyl
ATFA	acyl trifluoroacetate
bipy	bipyridine
BODIPY	boron difluoride dipyrromethene
Boc	*t*-butoxycarbonyl
DAST	(diethylamino)sulfur trifluoride
DBU	1,8-diazabicyclo[4.5.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
NaHMDS	sodium hexamethyldisilazane
NBS	*N*-bromosuccinimide
Pd/C	palladium supported on solid carbon
SEM	trimethylsilylethoxymethyl
SEMCl	trimethylsilylethoxymethyl chloride
TEA	triethylamine
THF	tetrahydrofuran
Tf	triflate
TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride

Analytical instrumentation and related

APCI	atmospheric pressure chemical ionization
CD	circular dichroism
EIMS	electron impact mass spectrometry
ESIMS	electrospray ionization mass spectrometry
HPLC	high performance liquid chromatography
ID	internal diameter
MP	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
TLC	thin layer chromatography

Miscellaneous

HOMO	highest occupied molecular orbital
ee	enantiomeric excess
E_2	elimination bimolecular
IUPAC	International Union of Pure and Applied Chemists
LUMO	lowest unoccupied molecular orbital
PCR	polymerase chain reaction
pK_a	negative log of the acid dissociation constant
S_N2	substitution nucleophilic bimolecular
MM2	molecular mechanics 2 force field
CBS	Corey-Bakshi-Shibata

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CHAPTER 1: INTRODUCTION

Pyrrole, a name taken from the Greek word meaning red, is an electron-excessive, five-membered hetero-aromatic compound that was first isolated in 1857 from the pyrrolysate of bone. Pyrrole is a colourless liquid with a boiling point of 130 °C and a melting point of 23 °C. The odour of pyrrole can be approximated to that of chloroform and pyrrole becomes coloured (brown) in air. Pyrrole has a low solubility in water but is miscible with most organic solvents. Figure 1 shows both the IUPAC numbering scheme for this molecule along with the commonly used trivial nomenclature.[1] For the remainder of this document these two nomenclature formalisms are used interchangeably so that a substituent located on the pyrrole two position can be labeled as a 2-substituent or an α-substituent, and α-and β-free pyrroles signify a hydrogen at the 2- and 3-positions, respectively.

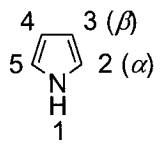
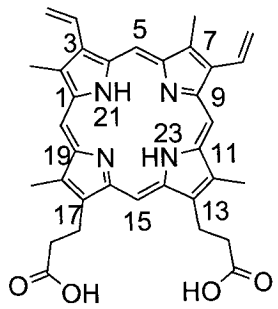


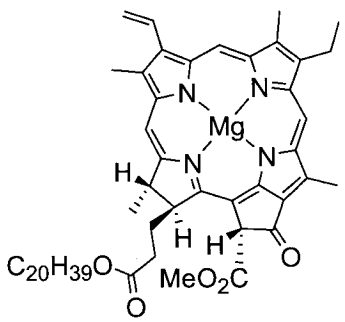
Figure 1: Pyrrole labeled according to IUPAC convention and trivial nomenclature (parentheses)

Natural occurrences of pyrrole

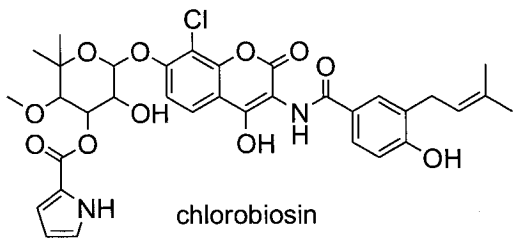
Pyrrole carboxylates are secondary metabolites for various microbial organisms and isolated molecules have displayed a wide variety of complexity. The simplest of these secondary metabolites is pyrrole-2-carboxylic acid but more complicated natural pyrroles like chlorobiocin[2] also exist. Pyrrole is found most abundantly in porphyrinogenic compounds such as protoporphyrin IX and molecules of the chlorinoid family such as chlorophyll-*a*.[3] Other examples of pyrrole monomers are porphobilinogen, the biosynthetic precursor to haemoglobin, and methyl 4-methyl-pyrrole-2-carboxylate, an ant pheromone.[4] The natural products mentioned above are illustrated in Figure 2.



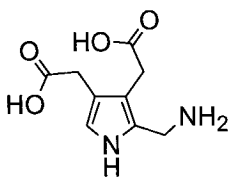
protoporphyrin IX



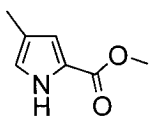
chlorophyll-*a*



chlorobiosin



porphobilinogen



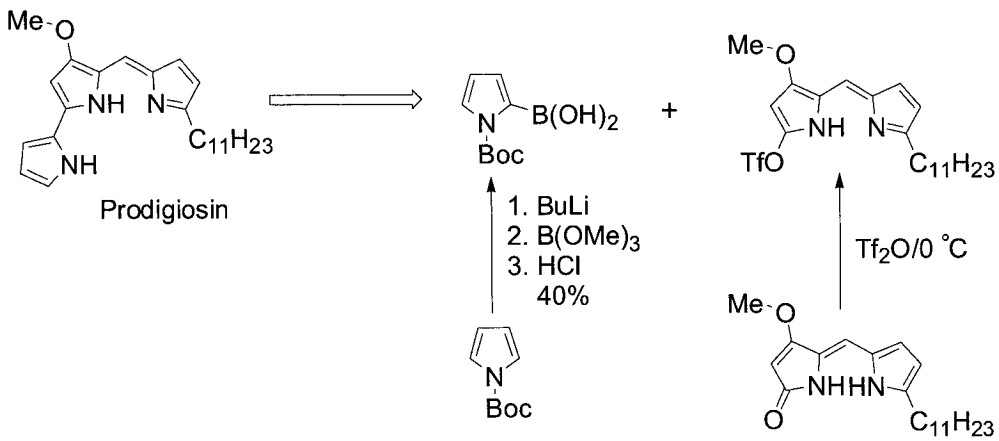
methyl 4-methyl-pyrrole-2-carboxlate

Figure 2: Some natural products containing pyrrolic rings

There are many different porphyrin molecules in nature that vary in their substitution patterns and/or their oxidation states. For example, protoporphyrin IX exists with a fully conjugated double bond network on the macrocycle and a specific substitution pattern in positions 2, 3, 7, 8, 12, 13, 17 and 18 (for numbering see Figure 2). Chlorophyll-*a*, in addition to a unique substitution pattern, is also saturated between carbons 17 and 18 and possesses an additional five-membered ring connecting positions 13 and 15. Porphyrins exist in many different protein systems in mammalian, plant and other organisms with unique biochemical characteristics (from haemoglobin to cytochrome P-450 and the chlorins) and much more can be read about these fascinating molecules in a series edited by David Dolphin called "The Porphyrins".[5]

An interesting class of pyrrole-based natural products called the prodigiosin alkaloids, generated by micro-organisms of the *Serratia* and *Streptomyces* genera, have a "prodigious" history that contributes to the name of this family of molecules.[6] The history of this family of molecules is interesting, as revealed in Furstner's review of the subject[6] and the references found therein. The synthetic construction of prodigiosin molecules provides excellent examples of classical pyrrole syntheses[7] that exploit the electron-excessive nature of the pyrrole ring. In addition to the classical routes to prodigiosin molecules and their precursors, many of these molecules have also been prepared via palladium coupling reactions involving pyrrolyltriflates and pyrrolylboronic acids (Scheme 1).[8,9] The synthesis of the prodigiosin skeleton has shown that there are many modern reactions that are compatible with even largely unsubstituted pyrroles.

Scheme 1: Precursors for Pd(0) coupling towards prodigiosin synthesis



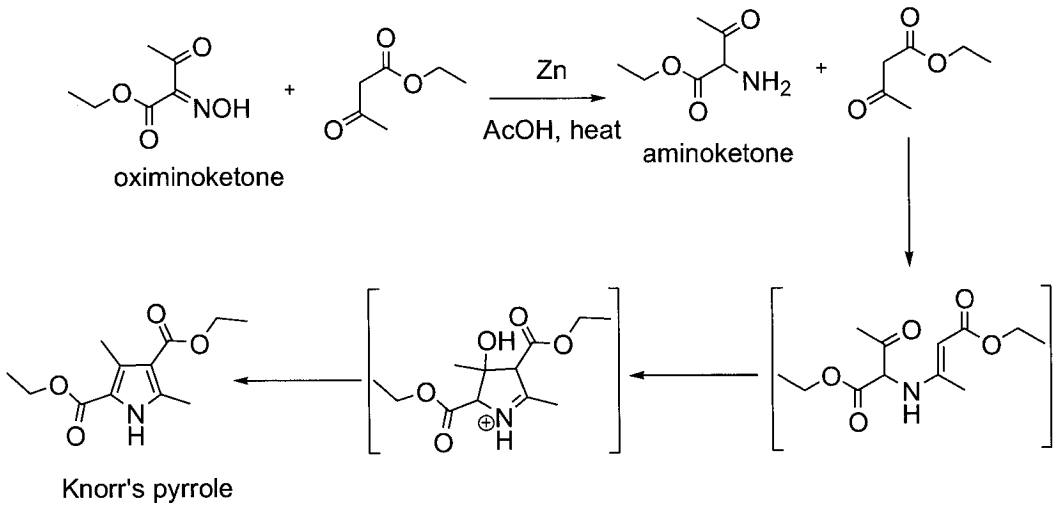
Named reactions involving the formation of substituted pyrrole

One of the most utilized syntheses of the pyrrole ring is the Knorr pyrrole synthesis,[10] which involves the condensation of a 2,4-diketone (or β-ketoester) with an α-aminoketone (or α-amino-β-ketoester) (Scheme 2). Unfortunately, self-condensation between α-aminoketones and related compounds represents a very competitive pathway to the desired pyrrole synthesis, and production of the oximino analogue of the α-aminoketone is necessary. The amine functionality is then unmasked *in situ via* a dissolving metal reduction involving powdered zinc in acetic acid. The concentration of the α-aminoketone is kept low by adding the oxime to the reaction flask in a drop-wise

fashion. The effect of the *in situ* reduction and subsequent low concentration results in the formation of the crystalline pyrrole product, albeit usually only in low to moderate yields.

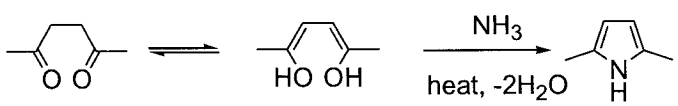
The primary advantage of this synthesis is that all starting materials and solvents are inexpensive allowing the reaction to easily be performed on multi-molar scales.[3] The reaction known as the Fischer-Fink synthesis of pyrroles can be considered a modified Knorr reaction as it proceeds *via* an alternative pathway to yield a β-unsubstituted pyrrole.[11]

Scheme 2: The Knorr reaction



The Paal-Knorr synthesis (Scheme 3) of a substituted pyrrole involves the condensation of ammonia, or a primary amine, with a 2,5-dicarbonyl compound (usually ketones or aldehydes). The mechanism of this reaction makes it very amenable to the synthesis of pyrroles that are functionalized in the 1-, 2- and 5-positions.[3]

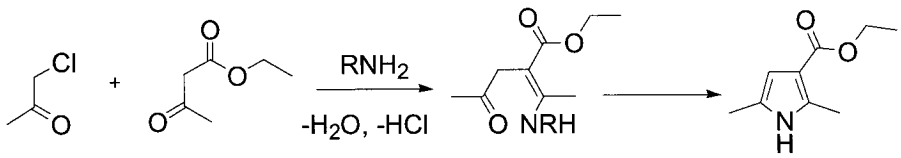
Scheme 3: The Paal-Knorr reaction



The Hantzsch synthesis of pyrroles utilizes an α-halocarbonyl compound, a β-ketoester and an amine, as seen in Scheme 4. The condensation reaction of the amine

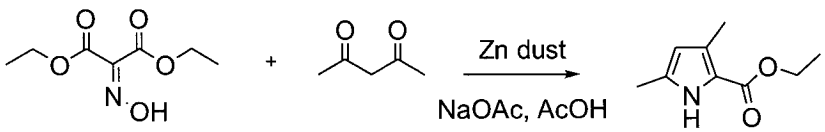
with the ketoester results in an enamine that attacks the haloketone, first displacing the halogen and then undergoing a condensation reaction to complete the cycle.[12]

Scheme 4: Hantzsch synthesis of pyrrole



The above syntheses were discovered prior to, or shortly after, the turn of the 20th century (Knorr,[13] Paal-Knorr,[14,15] Fischer-Fink,[16] Hantzsch[17]) and are thus antiquated but still very useful. A few variants of these reactions are in the literature but these reactions are largely used as they were originally published with perhaps variation in the substrates used to build a substituted pyrrole molecule. One of the more useful modifications of the Knorr reaction is the Kleinspehn[10,18] variation, which utilizes malonate esters to force the production of a β-free pyrrole (Scheme 5). The Kleinspehn variant of the Knorr reaction is far more useful than the Fischer-Fink reaction (involving the oxime of an acetoacetate and isolation of a β-free minor pyrrole) and is still in common use.

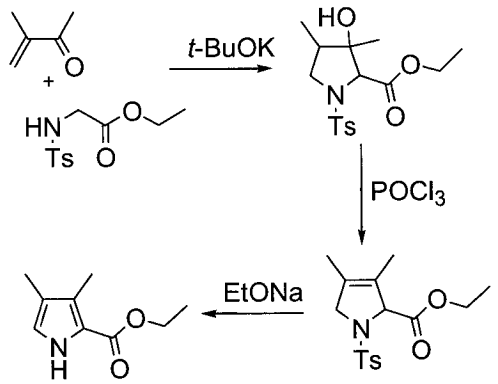
Scheme 5: The Kleihnspehn variation of the Knorr reaction



A more modern pyrrole synthesis is the Kenner[19] synthesis of pyrroles, which makes use of *N*-tosylglycine esters and α,β-unsaturated carbonyl compounds (Scheme 6). The soft nature of the stabilized anion of *N*-tosylglycinate favours 1,4-addition to the α,β-unsaturated ketone (or aldehyde) and is followed by cyclization onto the carbonyl carbon of the unsaturated ketone. Dehydration of the resulting alcohol is accomplished with phosphorous oxychloride to form the Δ^3-pyrroline. Formation of the Δ^3-pyrroline from the pyrrolidinol is favoured due to the eclipsing of the ester and tosyl groups during the formation of the Δ^2-pyrroline. The dehydration step is followed by base-promoted elimination of toluenesulfinate followed by proton transfer, resulting in aromatization to

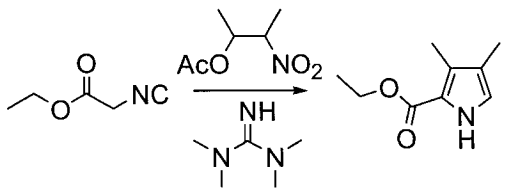
give the desired pyrrole compound. The advantage of the Kenner synthesis lies in the accessibility of a desirable substitution pattern. The Kenner procedure allows the direct synthesis of α-free pyrroles, unlike the Knorr method where one would make an α-free pyrrole from the corresponding 5-methyl substituted pyrrole through trioxidation, hydrolysis, and decarboxylation.[5]

Scheme 6: Kenner synthesis



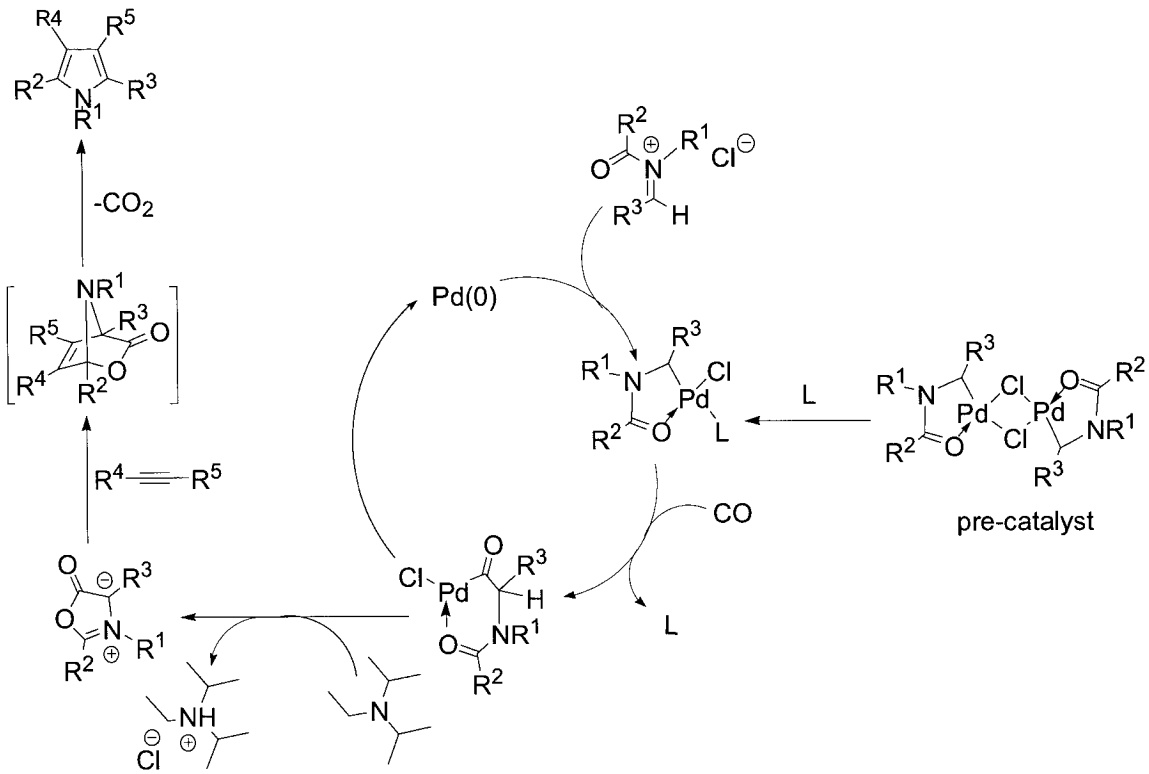
Another more recent synthesis of substituted pyrroles is known as the Barton-Zard[20] pyrrole synthesis (Scheme 7). Analogous to the Kenner synthesis, the most useful aspect of the Barton-Zard reaction, involving isocyanates, is the synthesis of α-free-2-carboxyester-pyrroles. The scale of the reaction, as published, is small but the yields are good to excellent (70-98 %). The nitro-olefins, or α-acetoxy nitroalkanes, are obtainable directly from the Henry reaction involving nitroalkane and aldehyde.[20] After the Henry reaction is performed the compound can either be dehydrated directly to the olefin or used as the acetoxy-protected species. Isocyanates can usually be obtained in reasonable quantities or at reasonable prices.

Scheme 7: Barton-Zard synthesis of pyrrole



Perhaps one of the more interesting syntheses of pyrroles, and one of the most contemporary, is a Pd-catalyzed modular construction of a substituted pyrrole (Scheme 8).[21] Arndtsen and co-workers developed this synthesis based on the propensity for 1,3-oxazolium-5-oxides to undergo 1,3-dipolar additions with alkynes, which is followed by the extrusion of carbon dioxide generating a substituted pyrrole. The yields reported are moderate to excellent (56-88 %), which is astounding considering the lack of pre-organization of the starting materials when compared to all of the previously discussed syntheses.

Scheme 8: Arndtsen synthesis of pyrrole



The aromatic nature of pyrrole

The concept of aromaticity has been very succinctly described by Katritzky:

> "Aromaticity as a qualitative concept is very well established in the teaching of organic chemistry in general. The characteristics which distinguish aromatic from non-aromatic compounds have been realized for a very long time...: cyclic with large resonance energy, substitution chemistry prevails over addition, Hückel 4n+2 π electron rule, and a diamagnetic ring current."[22]

When one compares the five-membered ring aromatic heterocycles a general observation can be made: the electronegativity of the heteroatom dictates the aromaticity of the heterocycle so that the following order of aromaticity can be established: thiophene > pyrrole > furan.[3,4,12] The diamagnetic ring currents have also been qualitatively measured on 2-methyl-heterocycles to compare downfield shifts (from calculated values) of the methyl proton resonances in the NMR spectra to establish relative aromaticity.[4] Thiophene is additionally stabilized by the larger bonding radius of sulfur, thus relieving bond angle strain, [3] and the involvement of sulfur *d*-orbitals within the bonding framework is thought to be negligible, thus allowing this molecule to be directly compared to pyrrole and furan.[4]

The same aforementioned molecules all undergo substitution chemistry but with differing rates, in the order of pyrrole > furan > thiophene,[23,24] so that the rates of reactivity and other measurements cannot be correlated directly to aromaticity. An interesting observation in terms of the comparative aromaticity of thiophene, pyrrole, and furan is the ability (or lack thereof) these molecules possess to participate in a Diels-Alder (diene) reaction; pyrrole and thiophene are generally less suitable than furan for this purpose.[12]

When one uses benzene as a benchmark for comparison of π electron distribution with five-membered aromatic heterocycles, the obvious difference is the number of atoms over which the six π electrons are distributed. Benzene has six atoms over which the six

π electrons can be distributed, as opposed to pyrrole, which has only five atoms. As in benzene, the carbon atoms within the ring of pyrrole are sp^2 hybridized with coplanar hydrogen substituents. Perpendicular to the sp^2 σ-bonded framework are *p*-orbitals, which collectively contain six delocalized electrons, resulting in a distribution of π electrons over five atomic centers. The presence of a lone pair of electrons and their delocalization can be depicted through the resonance structures shown in Figure 3. When considering the resonance structures with a formal negative charge on a carbon atom, one can appreciate why pyrroles are often described as π-electron excessive.[12] The delocalization of 4n+2 π electrons (n = 1 for pyrrole) satisfies the Hückel criteria for aromaticity.

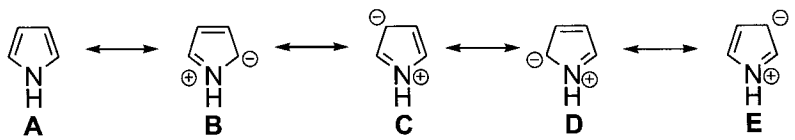


Figure 3: Resonance structures of pyrrole illustrating its electron excessive nature

One of the distinctive differences of the aromatic properties of pyrrole versus benzene is derived from the delocalization of the lone pair within the π-framework.[3] This delocalization of a lone pair has consequences to the overall shape and reactivity of the molecule. When one compares pyrrole to the iso-electronic cyclopentadienyl anion the preferential reactivity of the pyrrole α-carbon becomes more apparent. The cyclopentadienyl anion is an aromatic anion that has equal bond lengths and angles as seen in the solid state[25-27] and computationally.[28] This can be seen as a result of the symmetrical resonance distribution of charge between five carbon atoms so that each carbon bears, in effect, one fifth of a negative charge. In treating pyrrole in the same manner one notices that there are five resonance structures, four of which (**B**/**D** and **C**/**E**) exist as two equivalent pairs (due to symmetry) for a total of three different resonance forms: **A**, **B**/**D**, and **C**/**E** (Figure 3). The existence of dissimilar resonance contributors to the overall structure of pyrrole has an impact on the symmetry, and thus the structure and reactivity, of the molecule. The bonding distances of the atoms within pyrrole can be seen as alternating when compared to the structure of the cyclopentadienyl anion (as well as other aromatic hydrocarbons such as benzene) and this variation in bond length can be

seen as a measure of diene character when compared to more symmetrical (and "more" aromatic) aromatic molecules. In other words, the greater degree of alternation gives rise to a lesser degree of observed ring delocalization and thus a lesser degree of aromaticity than the cyclopentadienyl anion example (Figure 4).[4] This overall structure has an influence on the shape of the HOMO of pyrrole, which has the largest coefficient on the α-carbons, and on the reactivity of the molecule itself.

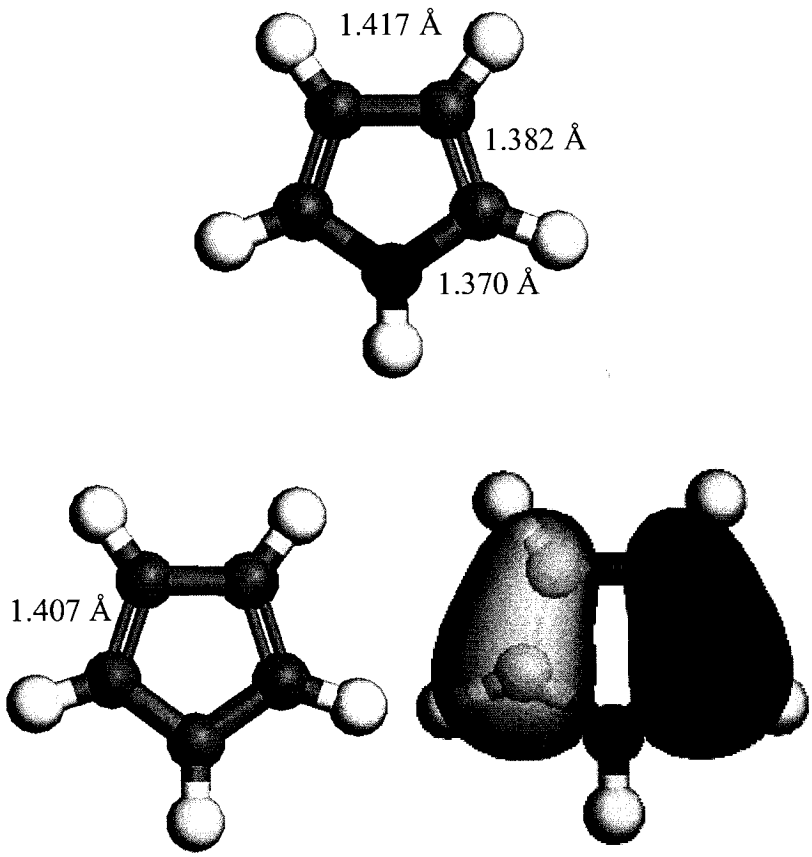


Figure 4: Top – molecular model depicting the bond lengths in pyrrole. Bottom left – molecular model depicting the bond length in the cyclopentadienyl anion. Bottom right – molecular model depicting the effect nitrogen has on the orbital coefficient of the HOMO in pyrrole

Reaction of pyrrole with electrophiles

The coefficient of the HOMO of pyrrole, as seen in Figure 4, is larger on the α-carbon due to the combination of the inductive electron-withdrawing effect and the electron-donating ability of the hetero-atom. A large coefficient at the α-carbon has the direct implication of higher electron density at that atom and therefore a greater probability of reaction at this position. Mechanistically, the interaction of pyrrole with an electrophile is a consequence of the delocalization of the lone pair of electrons (usually depicted as residing on the nitrogen atom) and resultant attack of an electrophile by either the α- or β-position. In addition to the electronic effect of the presence of nitrogen, substitution at the α-position leads to a greater delocalization of the resultant formal positive charge of the σ-complex, and the α-position is thus more reactive than the β-position. In practice, the selectivity of electrophilic attack at the α- over the β-position of pyrrole depends on the electrophile, the reaction conditions, and the substitution pattern of the pyrrolic nucleophile.[3] One of the more important reasons for the amenability of pyrrole toward substitution reactions is the full octet that all atoms possess in the addition intermediate. In comparing electrophilic attack on benzene with pyrrole one can see that a full octet will be missing for the resonance structure in the benzene σ-complex (Figure 5).

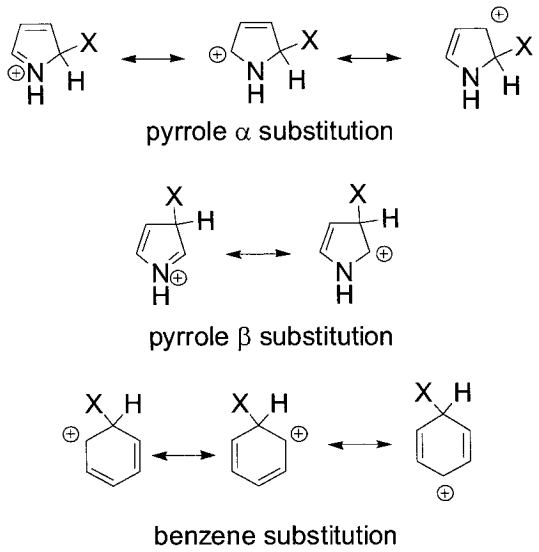
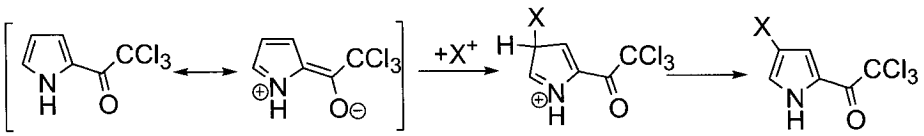
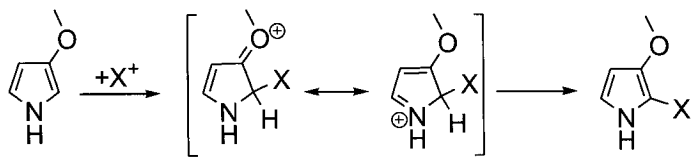


Figure 5: First intermediate for the electrophilic substitution of pyrrole and benzene

The pyrrole ring is subject to directing effects that are analogous to the benzenoid systems. Ortho-para groups have the same consequence on the pyrrole five-membered ring as they would on the benzene six-membered ring. Donation of electron density into the ring system allows for the direction of the reaction to an adjacent or ortho position. The deactivation of the ring by electron-withdrawing groups will tend to allow for more competitive meta substitution, which in the case of pyrrole is simply the nearest center that is two carbons removed from the substituted pyrrole carbon (Figure 6). The influences of activating or deactivating groups are very dependant on the ability of the functional group to either attract or donate electron density. In other words, an alkoxy carbonyl group will have little to no influence on the position of electrophilic attack while the influence of a trichloroacetyl group can be more drastic.[29] The activating or deactivating substituent must override the very strong influence of the hetero-atom lone pair of pyrrole in order for any change in regioselectivity to be observed.



meta selectivity of a strong electron-withdrawing group



ortho selectivity of an electron donating group

Figure 6: Example of meta directing electron-withdrawing group (top) and ortho/para directing electron-donating group (bottom)

Pyrrole is unstable to acidic conditions due to facile polymerization.[1,4] Friedel-Crafts acylation and alkylation reactions, which are fundamental to aromatic chemistry, are not amenable to unprotected pyrrole due to the inherent instability of pyrrole under the acidic conditions used in electrophilic aromatic substitution chemistry. Compatibility of electrophilic aromatic substitution with pyrrole in general relies on the substitution of the heterocycle with an electron-withdrawing group, the intention being to decrease the reactivity of pyrrole towards polymerization (Figure 7). This decrease in the reactivity of the protected pyrrole makes the heterocycle amenable to electrophilic reactions that produce a higher yield of the desired product due to the lack of competing polymerization. Electron-withdrawing groups, such as an ester functionality, therefore protect pyrrole through resonance stabilization. In the case of the α-ester protecting group the substituted pyrrole is stabilized through the existence of a pseudo-doubly-vinylogous carbamate resonance contributor.[30]

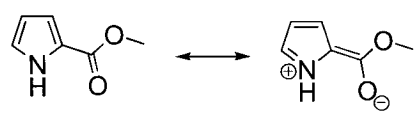


Figure 7: Pseudo-doubly-vinylogous carbamate resonance stabilization of pyrrole

Anionic chemistry of pyrrole

N-Metalated pyrroles are common precursors for *N*-substituted derivatives of pyrrole. As with any metalation reaction, both the metal used and the polarity of the solvent can have drastic effects on the position and selectivity of substitution. Generally, larger metals and more polar solvents increase the tendency for *N*-substitution due to an increased tendency for charge separation under these conditions.[11] This observed reactivity is courtesy of the ionic (or covalent) character of the pyrrole-metal bond. The more ionic the nitrogen metal bond the greater the tendency for *N*-substitution, and carbon substitution becomes more prevalent when the nitrogen-metal bond is more covalent in character; pyrrolyl Grignard reagents are usually more reactive at carbon, suggesting a more covalent metal-pyrrole nitrogen bond (Figure 8).[3] Prudence may dictate that if reaction at nitrogen is desired then all carbons should be substituted (protected) in order to minimize undesired side reactions.

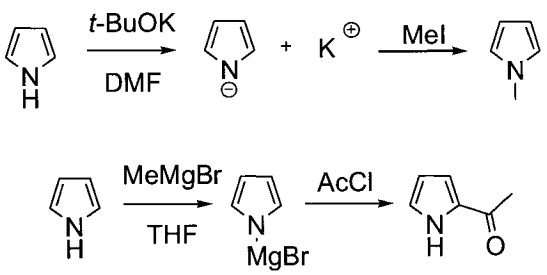
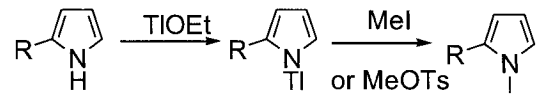


Figure 8: The reactivity effect of an ionic versus a covalent N-M bond

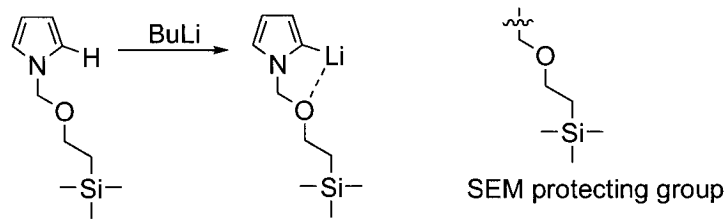
Selective *N*-alkylation has been achieved with the pyrrylthallium (I) salt in which the *N*-metalated species is stable enough to isolate in the atmosphere.[31] Alkylation of the *N*-pyrrylanion in this case usually proceeds with moderate-to-high yield, under relatively mild conditions (Scheme 9). Such alkylations were also performed in the presence of an electron-withdrawing group at the 2-position (R = CHO in Scheme 9). A useful aspect of this reaction was that methyl (and ethyl) tosylates were effectively used to produce the corresponding *N*-alkyl derivative of the pyrrylthallium (I) salt, allowing for an increased choice of reagents.[31] The major disadvantage to the practical application of this work is the extreme toxicity of thallium.

Scheme 9: Alkylation of pyrrylthallium(I)



Clever utility of the carbon-based anion of pyrrole, with the nitrogen protected, can lead to some synthetically useful manipulations. For example, the reaction of *n*-BuLi with 1-protected pyrrole (where the protecting group contains a possible chelating functionality) allows for the occurrence of regiospecific nucleophilic chemistry of the corresponding carbon-based pyrrylanion. SEM-Cl has been utilized to protect the nitrogen, and thus enables the stabilization of α-lithiated pyrrole (Scheme 10).[12,32]

Scheme 10: SEMCl use in pyrryllithium chemistry



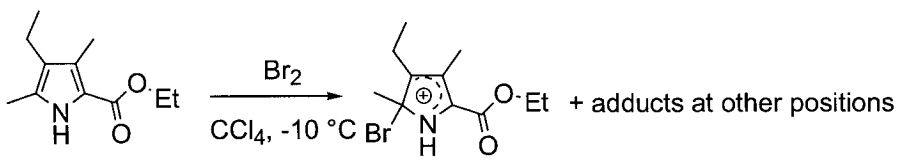
Pyrrolic functional group interconversion chemistry

The substitution chemistry of pyrrole has been briefly discussed with the description of electrophilic aromatic substitution and metalation. The following section gives a brief account of the reactivity of substituents on the pyrrole ring that are commonly exploited in the synthesis of pyrrolic derivatives.

α-Methyl substituents of pyrrole are susceptible to oxidation with a variety of oxidants. Lead tetraacetate, for example, can either oxidize the pyrrole methyl group to the acetoxy methyl or to the aldehyde in accordance with the number of equivalents used and the temperature of the reaction (higher temperatures yield higher oxidation states).[11] Lead tetraacetate will not oxidize a methyl group to the corresponding carboxylic acid and other means must be employed to reach this oxidation state. Bromination of the

methyl group can be undertaken through the addition of one equivalent of bromine, which is followed by the evolution of hydrogen bromide. The mechanism of the side-chain halogenation reaction has been studied with both bromine[33] and chlorine.[34] Nucleophilic addition of pyrrole to break the halogen-halogen bond was observed in the bromine case through the isolation of σ-complexes at -10 C[33] and an NMR spectroscopic study on the σ-adducts was performed prior to their isolation (Scheme 11). Multiple sets of signals indicated a preference for attack, probably at the one of the electron-rich α-positions, but that addition or migration to the β-carbons also probably occurred. This work helps to define the side chain halogenation mechanism as heterolytic versus the expected homolytic radical oxidation of the α-methyl group. The initial heterolytic cleavage of the bromine bond could then be followed by a series of rearrangements that end in the production of hydrogen bromide and a bromine substituted α-methyl pyrrole.

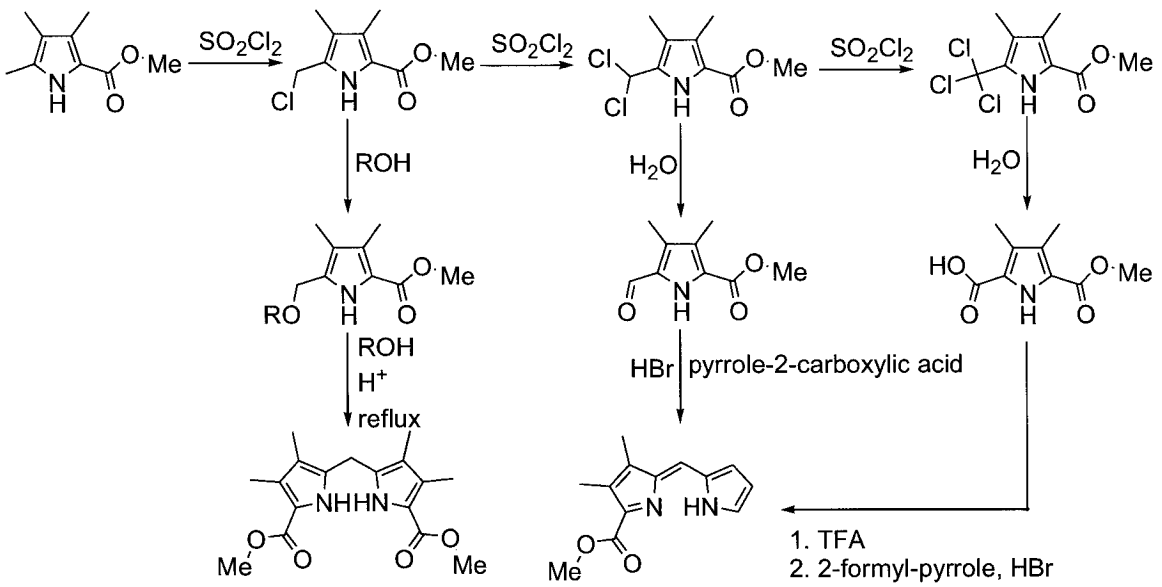
Scheme 11: The σ-complex of bromine with pyrrole



Halomethyl pyrroles are reactive precursors useful for the synthesis of various pyrrole architectures. Halomethyl pyrroles can be easily converted to α-carbinol pyrroles, formyl pyrroles and pyrrolylcarboxylic acids, depending on the number of halogen substituents on the α-methyl group.[11] Chlorination of the α-methyl group with one, two, or three equivalents of sulfuryl chloride yields the carbinol, formyl, and carboxylic acid derivatives, respectively, upon hydrolysis, from mono-, di-, and tri-chlorinated intermediates. β-Methyl groups tend to be inert under these oxidation conditions (Scheme 12). α-Carbinol or α-alkoxymethyl pyrrole, available through mono-oxidation followed by treatment with the appropriate ROH, are among the usual means of self-coupling pyrrole to form a dipyrromethane.[11] This is usually accomplished by exposing the α-halomethyl pyrrole to refluxing acidic alcoholic media. The corresponding dipyrromethene is available through the coupling of the formyl pyrrole allowing for the required oxidation state of the bridging carbon in the product. α-Free pyrroles are available through the trioxidation of the α-methyl group, hydrolysis to the

carboxylic acid and finally thermal decarboxylation. The ability to change the oxidation state of the α-methyl group is thus of tremendous importance to the pyrrole chemist interested in the synthesis of dipyrromethanes and dipyrromethenes.

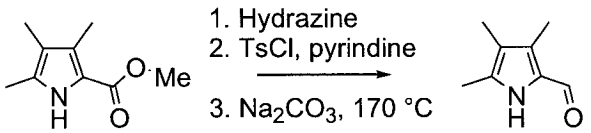
Scheme 12: Use of sulfuryl chloride in the oxidation of an α-methyl carbon to generate α-alkoxy (or hydroxy) methyl, aldehyde, and carboxylic acid



Carbonyl groups conjugated to the pyrrole ring are generally less reactive when compared to non-aromatic and benzene-appended carbonyl groups. α-Carbonyl pyrroles are in turn less reactive than analogous β-carbonyl pyrroles. The rationale for this unusual reactivity is apparent from the pseudo-doubly-vinylogous carbamate resonance structure (Figure 7), and the resonance contribution of this structure is evident in some of the physical attributes of pyrrole carbonyl compounds. Ionization constants for many pyrrol-2-carboxylates (and pyrrol-3-carboxylates) have been measured with pyrrole-2-carboxylic acid having a pK_a of 4.39[11](*c.f.* benzoic acid pK_a 4.2[35]). The addition of alkyl groups increases the ionization constant while the addition of electron-withdrawing groups decreases it. Pyrrole carboxylic acids with a greater degree of carbamate contribution can have a remarkably high pK_a, as high as 8.24 for trialkyl substituted pyrrole carboxylic acids (measurement was in methoxyethanol/water).[11]

It is possible to oxidize or reduce carbonyl substituents of pyrrole (and carbinols) without affecting the pyrrole ring. Pyrrolyl carboxylic acids and esters are, in general, stable to oxidants, and the reduction of pyrrole carbonyl groups follows the order of preference: aldehyde>ketone>acid.[1] Reduction of pyrrolyl ester groups have been achieved with the use of copper chromite as the catalyst.[11] The Macfayden-Stevens reduction has also been employed within the synthesis of prodigiosin to produce a formylpyrrole from a carboxylic acid ester precursor (Scheme 13).[6]

Scheme 13: A general example of Macfayden-Stevens reduction of a pyrrolyl ester



The reactivity of pyrrolyl carbonyl groups with nucleophiles depends upon the substitution pattern of the pyrrole ring. The ease with which the nitrogen of the pyrrole ring can donate its electrons to the carbonyl carbon is the governing force behind this type of reactivity. The presence of electron-withdrawing groups (in addition to the required reactive group) tends to increase the reactivity of an aldehyde with, for example, a carbanion. Reaction of α-formylpyrroles with malononitrile produces protected compounds from which the aldehyde can be unmasked through reaction with alkali.[36] The protection of aldehydes is important in order to avoid self-condensation under acidic conditions. Aldehydes are also important when α-free pyrroles act as the nucleophile, as seen in the MacDonald reaction in porphyrin synthesis.[37-39] This reaction consists of the acid-catalyzed condensation reaction of an α,α'-diformyl dipyrromethane with an α,α'-unsubstituted dipyrromethane and the eventual isolation of a porphyrin.[38,39]

Dipyrromethenes and their metal complexes

Porphyrin synthesis, which was pioneered by Hans Fischer in the early 1900's,[40] was one of the first processes that utilized dipyrromethene hydrobromide salts (Figure 9). In Fischer's synthesis of haemins and chlorins, dipyrromethene hydrobromide salts were often obligatory intermediates.[5,41] Among the many interesting properties of dipyrromethenes one that must be noted when working with these compounds are the

sternutatorial effects (they make you sneeze) that they possess, especially those with a β-free position.[5]

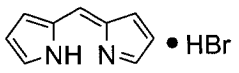


Figure 9: The simplest dipyrromethene structure, as a hydrobromide salt

Dipyrromethenes have been known to complex with metal ions since the early 1900's and these complexes have been studied in nonaqueous media since as early as 1923.[42] Structure determinations of many different dipyrromethene complexes have been performed with the intention of investigating both steric and electronic properties of the interaction between the ligands as a result of the metal within the complex.[43] These ligands are found to adopt tetrahedral or somewhat distorted tetrahedral complexes with metal(II) salts.[43] Some examples of metals that have been complexed with dipyrromethenes are Zn(II), Co(II), Ni(II), Cu(II), and Ca(II).[43] The historical conformational studies of dipyrromethene ligands are important in the broad scope of the goals of the Thompson Laboratory as they have implications to the extension of the available knowledge regarding the coordination chemistry of dipyrromethenes to the coordination chemistry of bis(dipyrromethene)s. The helical nature of the bis(dipyrromethene) metal(II) complex would benefit from an interaction at the metal that is tetrahedral and so the already identified metal(II) salts that form tetrahedral complexes with dipyrromethenes would be an appropriate start in the selection of metal ions to react with bis(dipyrromethene)s.

In recent years researchers in the Thompson Laboratory at Dalhousie University have studied the equilibria of dipyrromethene ligands with metal salts.[44] In this work it was discovered that dipyrromethenes form heteroleptic complexes with Zn(II) acetate in solution under conditions commonly used to synthesize zinc dipyrromethene homoleptic complexes. The use of NMR spectroscopy to investigate the equilibria of species within the reaction mixture was informative as the mechanism of complex formation could thus be hypothesized.

Dipyrromethenes have also come to have an important role as probes in molecular genetics (**bo**ron **di**fluoride di**py**rromethene or BODIPY dyes, Figure 10). Molecular probes used in PCR (polymerase chain reaction) can be tagged by a borondifluoride complex of any number of dipyrromethenes.[45] The dipyrromethene complex acts as a fluorescent tag, which identifies amplified genes that are the result of a PCR (polymerase chain reaction). Research into molecular optoelectronic gates has also seen the use of dipyrromethenes, and indeed porphyrins (in the same molecule), as some optoelectronic gates involve heavily conjugated polymers of porphyrins terminating in a dipyrromethene borondifluoride complex.[46]

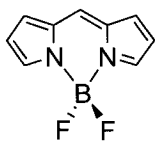
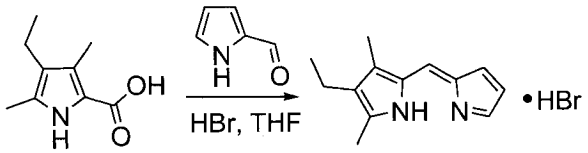


Figure 10: General structure of a BODIPY molecule

Dipyrromethenes can be synthesized via many different methods, most of which are quite antiquated. Construction of a dipyrromethane followed by oxidation of the methylene bridge to obtain the dipyrromethene compound can be achieved through the use of bromine, *t*-butyl hypochlorite, *N*-bromosuccinamide, ferric chloride, lead dioxide, and iodine monochloride.[5] It is interesting to note that iodine can sometimes be used to oxidize β-free positions of an appropriately substituted dipyrromethane without oxidizing the central methylene bridge.[5] Halogenation of 5-methyl-2-unsubstituted pyrroles in acetic acid usually affords 5-bromomethyl-5′-bromodipyrromethenes and the reaction of an α-unsubstituted pyrrole in formic acid/hydrogen bromide yields a symmetrical dipyrromethene hydrobromide salt.[5] There are many more such syntheses of dipyrromethenes that can be applied to a particular synthetic need but the method most prevalent in the literature is the condensation of an α-formyl pyrrole with an α-free pyrrole (usually formed *in situ* from its corresponding 2-carboxylate, Scheme 14).

Scheme 14: Synthesis of a dipyrromethene via the MacDonald condensation



The condensation of a bis α-free dipyrromethane and a bis-formyl dipyrromethane in order to synthesize a porphyrin is called the MacDonald reaction.[37,47] In order for the coupling reaction to be successful the "α-free" portion of the molecule must be sufficiently nucleophilic and the presence of too many electron-withdrawing groups tends to require the use of the α-free derivative itself, rather than rely on the *in situ* decarboxylation of the corresponding pyrrolyl carboxylic acid. In such instances, it is essential to find conditions for the decarboxylation of the α-alkoxycarbonyl pyrrole, and this can be a tedious process of trial and error.

Bis(dipyrromethene)s: Architecture of the bilins

Another naturally occurring class of pyrrole pigments are the linear tetra-pyrroles of the bilin and bilidiene families. These are a linear array of four pyrroles connected by one carbon atom which can be either a methylene or methyne bridge. Biliverdin and biliruben are both illustrative of bilin and bilidiene classes of molecules (Figure 11). To illustrate the frequency that these compounds can occur in mammalian biology one can isolate bile pigments from the gall bladder, blood, and, of course, bile.[5] The two most famous bile pigments are biliruben and biliverden, the latter is the consequence of the biodegredation of haeme and has a characteristic yellow colour.[48] Biliruben is an orange solid that is the result of a reduction of the central methyne carbon in biliverdin.[5] Much more can be read about this topic in David Dolphin's "The Porphyrins," volume six.[5] There are many reported examples of bis(dipyrromethene)s that were prepared synthetically. When a dipyrromethane is linked through the 3,3′-positions as opposed to the 2,2′-postions, as in naturally occurring bilins, then another series of bis(dipyrromethene)s is formed (Figure 11). 3,3′-Bis(dipyrromethene)s have been synthesized and studied by David Dolphin and his research group at the University of

British Columbia and it was found that, like the 2,2′ bis(dipyrromethenes), they form helical structures when complexed with metal ions.[49-52]

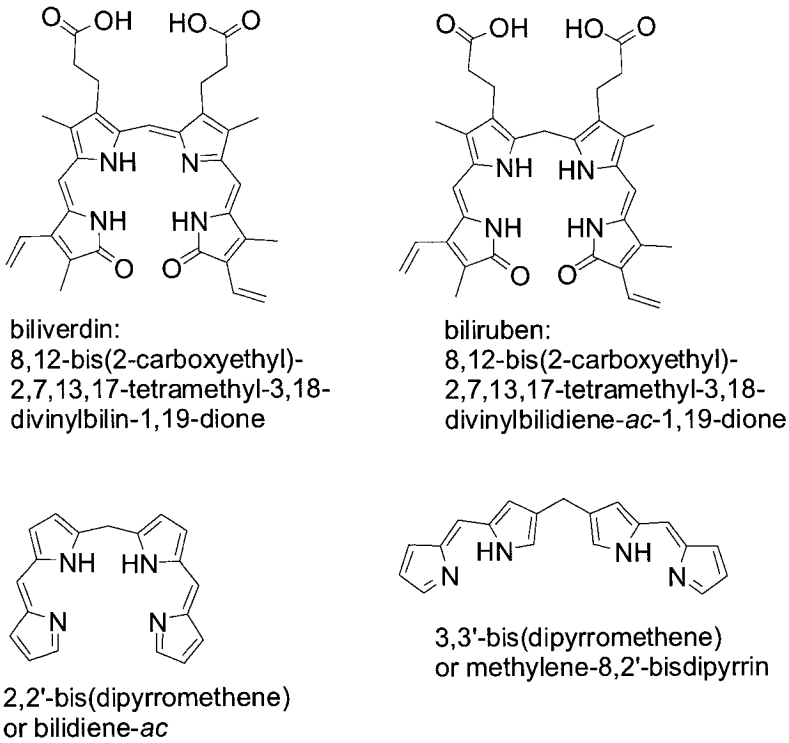


Figure 11: Top - examples of bilin (biliverdin) and bilidiene (bilirubin) analogues that can be compared with 2,2'-bis(dipyrromethene)s (bottom right). Bottom left - example of an unnatural 3,3'-bis(dipyrromethene)

Bis(dipyrromethene)s consist of two fully conjugated dipyrromethene halves separated by a methylene bridge that prevents conjugative communication between the two dipyrromethene moieties in the molecule. It must be noted that it is not a necessity to have only a methylene bridge between the two dipyrromethene subunits. By increasing the length of the spacer one introduces new coordinative properties to the ligand.[49-52]

A 2,2′ bis(dipyrromethene) helical complex was first isolated in 1966 (Figure 12)[53] in a study involving the formation of tetradehydrocorrins from 1,19-disubstituted bilidienes. One of the experiments resulted in the isolation of what was postulated to be a helical cobalt complex with two bilidiene ligands.[53] The next helical complexes reported

were those of octaethylformylbiliverdine[54] and decamethylbilidiene,[55] both as Zn(II) complexes exhibiting distorted tetrahedral geometry around the metal.

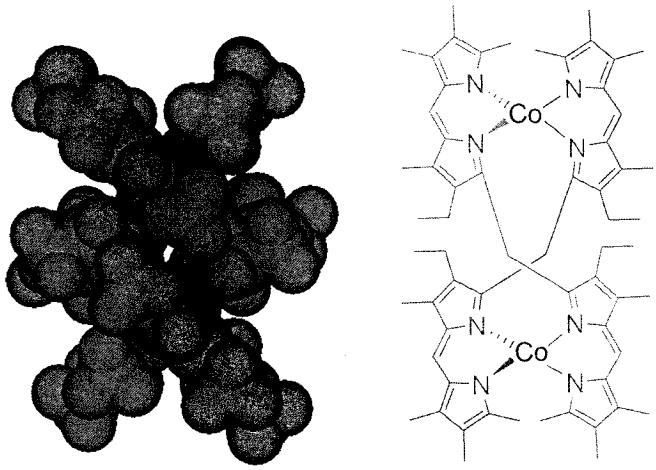


Figure 12: Helical bilidiene isolated by Dolphin in 1966

In order to appreciate the precedence of constructing helical bis(dipyrromethene) complexes and their possible uses one only has to look, in addition to the existing literature on helical bis(dipyrromethene) complexes, to Jean-Marie Lehn's reports of helical bipyridyl systems.[56-66]

Helicates and their history

Bipyridine (bipy) ligands, as shown in Figure 13, provide useful precedence for bis(dipyrromethene) ligands in that they can both form helical metal complexes. The helicates of bipy ligands have been extensively researched and the literature has been reviewed a number of times in the past decade.[67-69] The importance of the bipy system to this project lies in the accomplishments of other researchers who have done much of the ground-work regarding the analytical chemistry of this family of compounds, thus providing models for the analysis of bis(dipyrromethene) helicates.

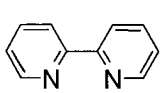


Figure 13: The simplest bipyridine ligand

Helicates are considered to be in the realm of the supramolecular. There are four points that constitute a central dogma in this realm of science: molecular recognition, self-organization, self-assembly, and molecular programming.[67,70] Molecular recognition concerns a propensity for selective interaction between two or more pieces involved in the assembly. Self-organization is a condition-specific phenomenon, which simply put means that the system will organize itself reproducibly if the conditions applied are consistent. Self-assembly refers to a discrete action within the self-organization process and constitutes the coming together of all the necessary pieces. Finally, molecular programming refers to the ability to encode information, or instruction, within the structure of one or more of the components.[70] Helicates are self-assembled entities. They are programmed by the tetrahedral (sometimes octahedral) arrangement of chosen metal ions and the preferred conformation of their bidentate organic ligands, which allows the components to come together in a helical fashion (recognition and self-organization). As an example of "programming information" into a ligand, Lehn and co-workers have designed structurally rigid ligands that form grids upon complexation.[71]

To draw a comparison between the shape of the helical structure of DNA and that of a synthetic helicate would be appropriate. Both entities have the same three-dimensional structure, in terms of helicity only, but are brought about by two different bonding motifs (hydrogen versus dative bonding, see Figure 12 for an example including a bis(dipyrromethene)). In both cases the helix can be characterized by a helical axis, a screw-sense, and a pitch.[67] The pitch of the helix is meant to illustrate the number of turns per unit length that a helix can undergo and is measured by the vertical distance between the start of the turn and the end of the turn.[67] The helix is a chiral entity of its own accord as a consequence of the chiral nature of a screw-sense. Figure 14 illustrates the helix as discussed showing that the mirror images are non-superimposable and are therefore enantiomeric, assuming there are no other sources of chirality (*i.e.* a stereocenter). Helical enantiomers are often described in terms of *M* and *P*. In analogy to the *R* and *S* priority system used in assigning the handedness of a stereocenter, the *M* and *P* system is used to describe the handedness of a helix. When one envisions the helical axis as a center of reference then observing the helix along the length of the

helical axis allows an observation of the direction of the screw sense to be made. If the screw sence is clockwise then the helix is said to be *P*, which is right handed, and conversely *M* is counterclockwise and lefthanded.

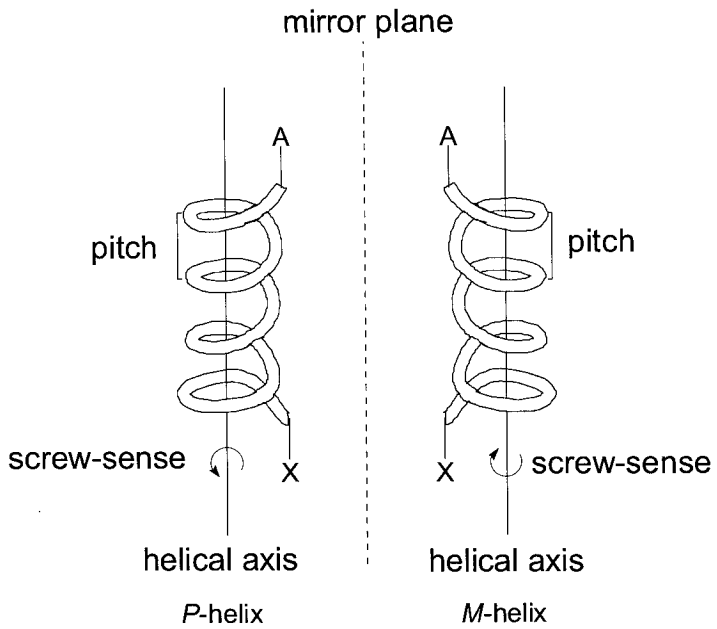
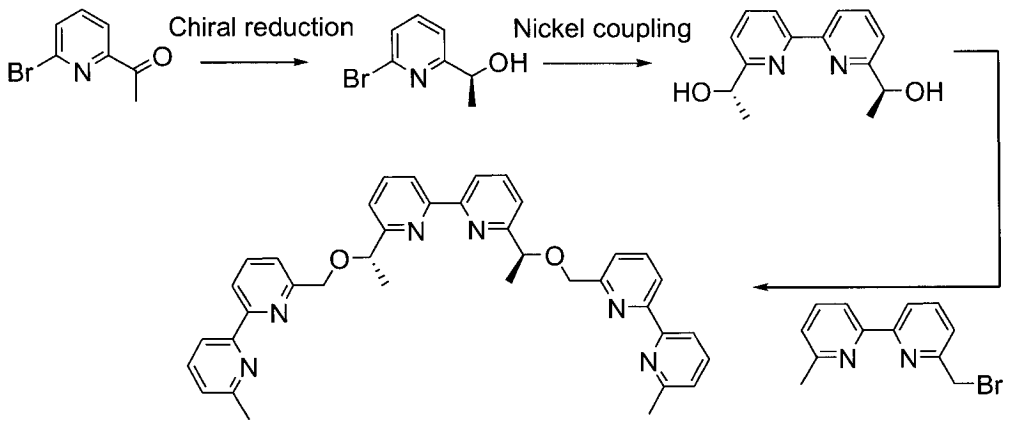


Figure 14: Two enantiomeric single-stranded helices with defining characteristics.

It has been shown with bipy ligands that the selective formation of one helix over the other is possible through stereochemical induction. Introduction of chiral centers directly to the backbone of poly-bipy ligands has been successful in the stereoselective synthesis of tri- and pentakis(bipy) ligand systems.[63] The ligands were synthesized through an asymmetric reduction of 6-bromopyridin-2-yl methyl ketone with (-)-chlorodiisopinocamphenylborane to yield the 1-pyridin-2-yl-ethanol with 90 % ee. Upon enrichment through derivatization and recrystallization, the ligand synthesis was completed through a nickel coupling and an S_N2 reaction of the sodium alkoxide (Scheme 14). These ligands were then treated with metal salts to form charged, crystalline complexes that adopted a helical structure. Lehn and co-workers postulated, with the help of space-filling models and a crystal structure of an optically active diimine ligand, that the right-handed helix formed preferentially over the left-handed helix due to energetic differences in the diastereomeric transition states.[63]

Scheme 15: Lehn's synthesis of a homochiral ligand



Bipy helicates may present some challenges in their synthesis, isolation and purification.[67] First, the propensity of the counter-ion to complex with the metal in place of the desired bipy must be investigated. Some of the highly symmetrical "noncoordinating" anions have a tendency to generate disorder in a crystal structure and in some cases the use of more than one counter-ion has been necessary.[72] Bipy helicate compounds are ionic in nature, thereby limiting purification exclusively to recrystallization as the polar nature of the complex would not be amenable to traditional column chromatography techniques. In contrast to the bipy helicates, those formed from bis(dipyrromethene)s should have an overall neutral charge. This property is advantageous for purification as chromatography becomes an option.

With a vast wealth of knowledge available in the synthesis of pyrroles, bilins, and helicates, an exploration of the construction of homochiral bis(dipyrromethene) ligands began and the strategies and outcomes are to follow. Firstly the general strategies that are being undertaken within this work and by other workers in the Thompson Laboratory will be discussed. This is followed by an exploration concerning the synthesis of a bis(dipyrromethene) ligand containing a pyrrole moiety that carries a trifluoro hydroxyethyl substituent on a β-carbon. The underlying syntheses involved in the elaboration of the groundwork, having already been undertaken by another laboratory, were seen as an advantage to the synthesis of a linear tetrapyrrolic ligand that would be amenable to desired purposes. This greatly influenced the undertaking of the chosen

chemical route.[73-75] Other, smaller projects are also described to highlight some interesting new aspects of pyrrole and dipyrrinone chemistry, followed by a very brief discussion of preliminary results obtained during a three-month student exchange at the Univeristy of Cardiff is also presented.

CHAPTER 2: RESULTS AND DISCUSSION

Goals and general synthetic strategy

The goals of the bis(dipyrromethene) ligand synthesis project in the Thompson group all converge on the diastereoselective synthesis of helical bis(dipyrromethene) complexes; specifically, the use of chiral auxiliaries for the purposes of providing a molecular impetus (through steric interactions) towards the diastereoselective formation of bis(dipyrromethene) helicate molecules. There are four strategies being investigated, as represented by the bis(dipyrromethene) hydrobromide salts in Figure 15, that may lead to the isolation of a single diastereomeric bis(dipyrromethene) helicate: (*i*) introduction of a pyrrole bearing a chiral auxiliary on the terminus of the bis(dipyrromethene),[76,77] (*ii*) introduction of an internal chiral pyrrole that is adjacent to the aliphatic linker, (*iii*) the presence of a stereocenter on the aliphatic linker between the two dipyrromethenes, and (*iv*) the utilization of a chiral template in order to induce the desired homochiral twist.[78] In the utilization of any of these methods one might envision the accomplishment of certain smaller, but essential, goals with respect to the synthesis of the chiral ligands themselves, the most important of these being the preservation of the stereocenter through variable reaction conditions.

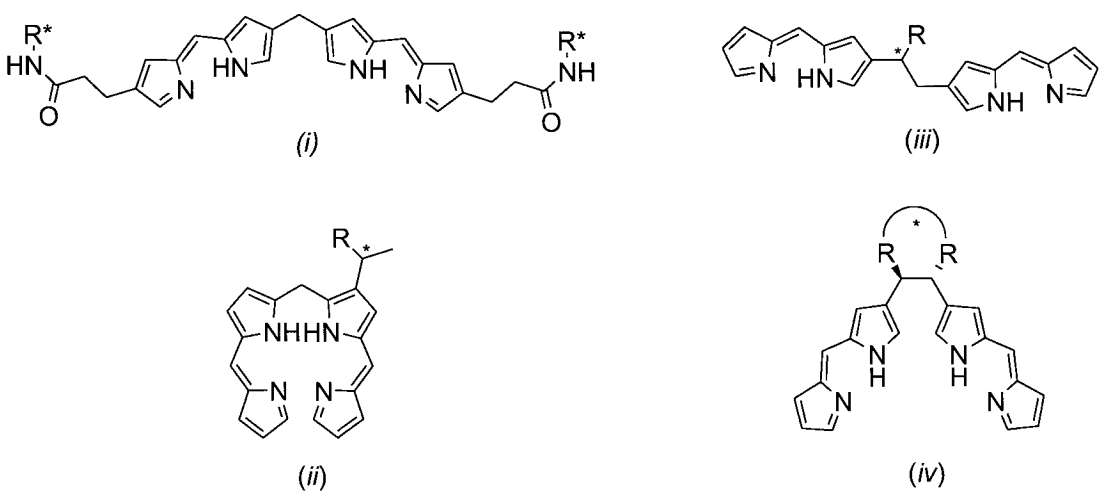


Figure 15: General strategies toward chiral induction

Any of the above four strategies can be useful in the synthesis of diastereo-pure helical complexes but each method will have advantages and disadvantages associated with its structure. In strategy (*i*) the stereocenter is too far removed from the bulk of the ligand to retard significantly the formation of one of the diastereomeric helices, thus the diastereoselectivity of complexation was poor with these ligands.[76,77] The importance of work with ligands of strategy (*i*) was a proof-of-principle study in that there could indeed be an enrichment of one helix over the other. The benefit of constructing homochiral ligands as seen in strategy (*i*) is the relative ease with which they are synthesized, and the stability of the two helices, once formed. In strategy (*ii*) (one strategy that is the aim of the research presented herein), although the stereocenter is still not a part of the ligand backbone, it may be involved in some unfavourable interactions with coplanar (Figure 16) dipyrromethene moieties within a metal complex. These interactions between dipyrromethene moieties may have sufficient influence in a helical transition state to encourage the stereoselective formation of one of the helical diastereomers since the bis(dipyrromethene) ligands present in helical systems are often necessarily coplanar, or very nearly so. In strategy (*iii*), with the stereocenter on the aliphatic linker, the energy of the transition states for the formation of the helices should be different because one helix should conform to an energy minimum with respect to the steric interactions of the atoms within the "kink" of the ligand backbone. Strategy (*iv*) has proven to be highly successful due to the conformational control a chiral template provides from a preprogrammed twist of the template molecule.[78]

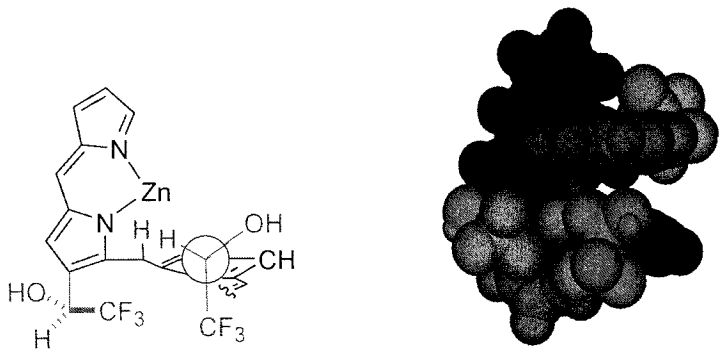


Figure 16: Illustrative example of close contacts between stereocenter and coplanar ligand. Only half of the ligand structure is shown in the stick model

A MacDonald coupling step for the synthesis of bis(dipyrromethene) hydrobromide salts, involving a condensation reaction between an α-free dipyrromethane and a 2-formylpyrrole, uses hydrogen bromide as an acid catalyst.[37,51,53] Under these conditions the use of an appropriate functional group on the stereocenter is of paramount importance to ensure the survival of the established configuration of the stereogenic center to acid-catalyzed racemization. Without intact homochirality of the stereocenter, efficient chiral induction during the formation of the helical complex cannot occur. Thus, steps toward the synthesis of a chiral bis(dipyrromethene) containing an acid stable hydroxyl-substituted stereocenter were undertaken. Herein, the sensitivity of the hydroxyl group to acid will be demonstrated, followed by a means to rectify this instability in order to utilize the hydroxyl functionality as a means to introduce structural variability through its substitution.

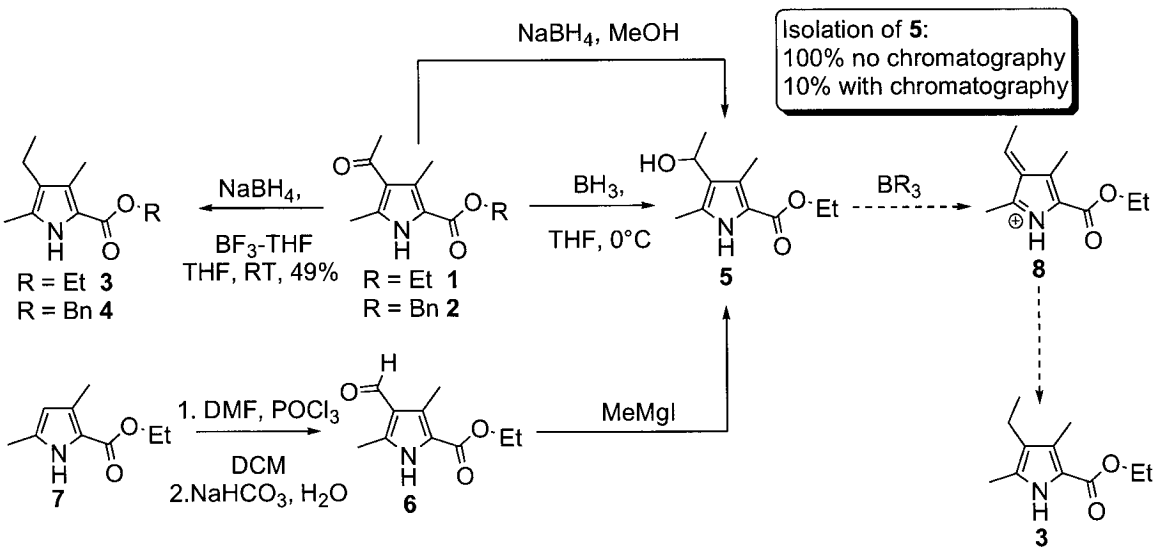
Stabilizing the stereocenter with a trifluoromethyl group

Chemistry towards the strategies (*ii*) and (*iii*) was attempted within the research described herein. The first step toward the accomplishment of either of these strategies was the establishment of the versatility and robustness of the proposed stereogenic center. The requirement of a functional group that could be easily manipulated for the purpose of changing the steric demand of the stereocenter was desired and so it was decided that the stereocenter should contain a hydroxyl functionality.

Research into the construction of a chiral bis(dipyrromethene) ligand began first with the construction of a pyrrole **1**, which is readily available from the Knorr reaction involving ethyl acetoacetate oxime with 2,4-pentandione in the presence of zinc.[10] Treatment of pyrrole **1** with borane, generated from the addition of borontrifluoride etherate to a solution containing sodium borohydride, at ambient temperatures are the usual conditions used to obtain the fully reduced pyrrole **3** (Scheme 16).[79,80] Fischer and co-workers have previously performed addition reactions on **6** with a methyl Grignard reagent[40] in order to furnish **5** but this method was less desirable due to the ready availability of pyrrole **1** compared to multi-step procedure needed for the synthesis of **6**. Sodium borohydride has also been exploited in the reduction of pyrrylketones (**1** and **3**)

to the corresponding alcohols.[81] It was thought that a reasonable intermediate in the borane reduction of **1** to **3** was through pyrrole **5**, and that the reduction to the alkane was a result of the vinylagous nitrogen atom ejecting the boron-complexed oxygen providing intermediate **8**, which was then reduced via hydride to compound **3**. Thus, the utility of lower temperatures during a borane reduction was thought to be appropriate for the isolation of **5** as this may avoid the formation and reduction of intermediate **8** to produce pyrrole **3**. The racemic compound, **5**, was thus constructed via the reduction of **1** in the presence of borane-THF at cold (0 °C) temperatures and was accomplished in quantitative yield, provided that purification via silica gel column chromatography was not undertaken.

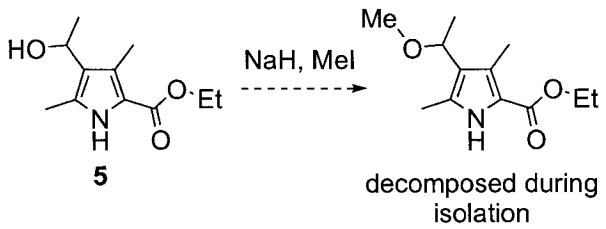
Scheme 16: Current and historic syntheses of 5



The lability of the hydroxyl goup of **5** came into question as the attempted purification of this compound by standard silica gel chromatography resulted in only a 10 % isolated yield. Conditions involving the use of neutral alumina for column chromatography and an eluent containing 0.5 % triethylamine were necessary to prevent the decomposition of pyrrole **5** (to unidentified red compound(s)) during purification. Given the ability of the pyrrolic unit to eject the hydroxyl substituent, it was desirable to protect the hydroxy pyrrole **5** through methylation of the alcohol group. Protection chemistry at this stage allowed an initial exploration of the substitution chemistry

involving a hydroxyl group substituent on a carbon adjacent to a pyrrole ring. The *O*-methylation of **5** (Scheme 17) was also problematic because TLC analysis indicated that the desired ether was most likely the major product but this compound failed to show stability during column chromatography on silica gel, which again suggested that the methoxy functionality on the carbon adjacent to the pyrrole ring was not stable. Two-dimensional TLC analysis failed to detect this instability but the extended exposure to silica during flash chromatography resulted in an outcome that was analogous to that involving the unprotected pyrrole **5**. It should be noted that the crude products were analyzed by proton NMR spectroscopy and peaks were observed that bore a similarity to more stable ethers that were prepared later.

Scheme 17: *O*-methylation of 5



Although **5** was unstable to even the mild acidic conditions of silica gel chromatography, the utilization of the hydroxyl functional group on the stereogenic carbon of a homochiral linear tetrapyrrolic ligand was still desired as a target. The presence of the hydroxyl group was attractive due to the availability of chemistry that can be exploited to derivitize this type of functional group, thus allowing for the construction of ligands with structural variability based on the hydroxyl substituent. Although it was determined that the construction of such a ligand can be accomplished through established chemistry, the stability of a hydroxyl-substituted stereogenic center adjacent to the pyrrole ring was questionable due to problems encountered with **5**. As can be seen from the structural similarities between **5** and bispyrrolyl molecules **F** and **G** (Figure 17), which have analogous stereocenters adjacent to the pyrrole ring, it was expected that the hydroxyl group in the prospective ligand would be labile. Thus, one would have to consider the repercussions of the reduction of a carbonyl species to the alcohol when future synthetic operations involve the utility of strongly acidic conditions. Acidic

conditions are necessary during the MacDonald coupling step, due to the use of HBr as a coupling reagent, to form a dipyrromethene and would prove to be more problematic than the use of silica gel due to the increased lability of the hydroxyl functional group under these conditions (Figure 17).

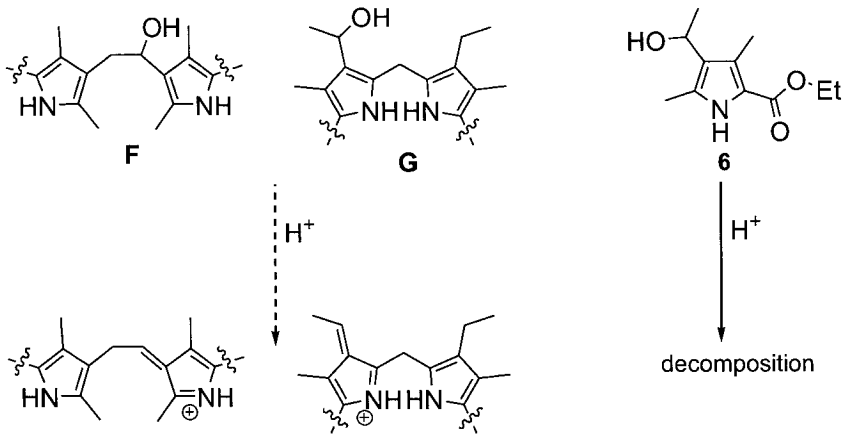
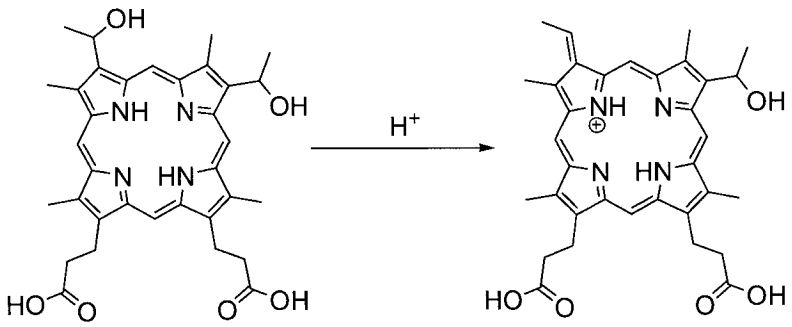


Figure 17: Architectures of F and G

Assuming a stereocenter satisfying the criterion towards strategy (*ii*) or (*iii*), which contains the desired hydroxyl substituent, can be constructed, it is expected that utilization of such homochiral ligands in diastereoselective formation of helical metal complexes will be possible. Kumadaki and co-workers suggested that due to the electron-donating ability of a porphyrin ring, the hydroxyl groups of hematoporphyrin are easily eliminated to form azafulvene intermediates (Scheme 18).[75] This is relevant to our work given the structure of pyrrole **5**. Introduction of fluoro-substituents tends to stabilize the hydroxyl group towards elimination due to the inductive electron-withdrawing effect associated with the electronegative fluorine atoms.[75,82] The chemistry involved in functionalizing a β-free pyrrole in the appropriate way has already been developed by Kumadaki and co-workers[73] and was put to use towards the development of a ligand incorporating strategy (*ii*). The use of a fluorinated linker for the 3,3′-system (strategy (*iii*)) would involve some in-house development and study, and would naturally follow from success with strategy (*ii*). Kumadaki has shown that the hydroxytrifluoroethyl-substituted pyrrole is stable to heat, acidic, and basic conditions.[75] The observed decomposition of pyrrole **5**, and the successful synthesis of stable

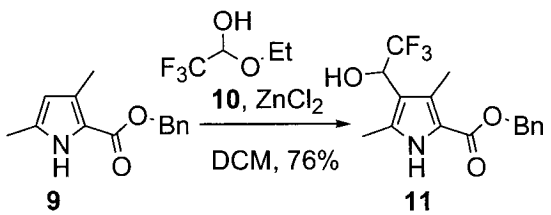
hydroxytrifluoroethyl-substituted hematoporphyrin analogues by Kumadaki, prompted us to consider the construction of bis(dipyrromethene)s bearing homochiral hydroxytrifluoroethyl substituents.

Scheme 18: Acid-catalyzed elimination of water from hematoporphyrin



A route to the introduction of a stereocenter on pyrrole **9** involves an electrophilic aromatic substitution of the β-free site with ethyl trifluoroacetaldehyde hemiacetal, **10**, in the presence of zinc(II) chloride.[73] The preparatory method utilized by Kumadaki and co-workers was found to be reproducible and allowed for the construction of **11** in 76 % yield (Scheme 19). Due to the presence of the trifluoromethyl group and Kumadaki's prior work, pyrrole **11** was expected to be stable to all conditions to which the dipyrromethene ligand would be exposed.

Scheme 19: Electrophilic aromatic substitution using ethyl trifluoroacetaldehyde hemiacetal



The envisioned bis(dipyrromethene) complex modeled in Figure 16 is illustrative of the type of ligand-metal complex that is desired in the utilization of pyrrole **11** for the construction of bis(dipyrromethene) hydrobromide salts. Geometry optimization of a [2,2′-bis(dipyrromethene)]$_2$ Si(IV)$_2$ complex that included the proposed hydroxytrifluoroethyl group (Figure 16), using molecular mechanics (MM2) was completed. Silicon was used as the "metal" due to its tetrahedral nature and available

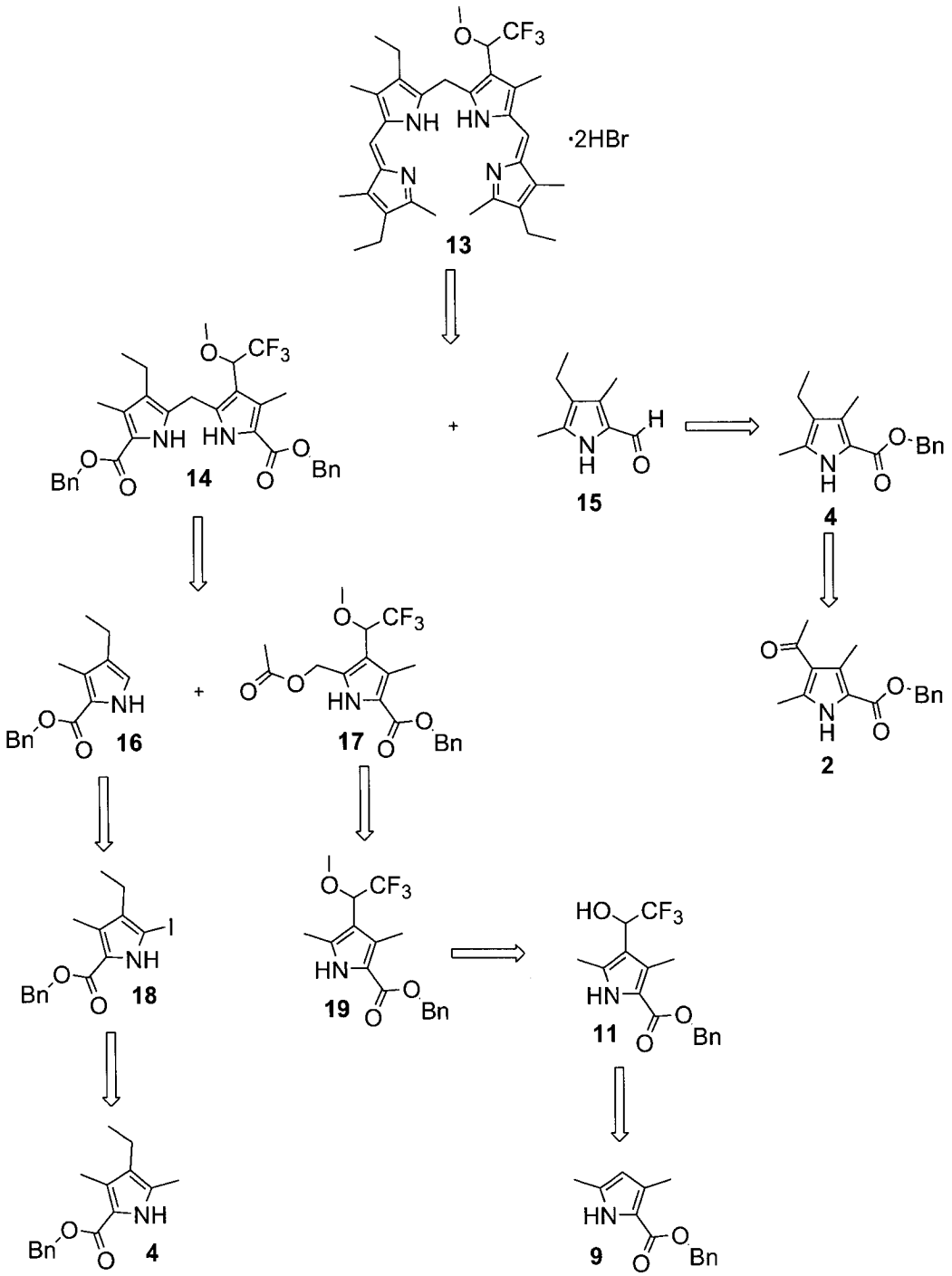
parameters within the program used for modeling.[83] The expected helical structure obtained from the MM2 force field calculation of one of the possible helicates illustrates the position of the stereocenter quite well. If the pitch of the helix can accommodate the presence of the stereogenic center, then it is anticipated that the absolute configuration of the stereocenter will be enough to encourage a helical twist in predominantly one direction. The presence of a hydrogen atom in the backbone of the 2,2'-methylene linker can be seen to be in close contact with the hydrogen atom in the stereocenter. In addition to pointing the trifluoroethyl group into space away from the complex, steric strain would be minimized through the orientation of the hydrogen on the stereogenic center to a position proximal to the hydrogen in the linker. If the trifluoromethyl group (or the oxygen atom of the hydroxyl group) were to occupy such a position, the formation of the helix should be energetically less favoured. Whether this energetic difference is enough to elicit enrichment in helical diastereomers remains to be seen upon the synthesis of a target compound. Research from this point was concerned primarily with the construction of an appropriate racemic bis(dipyrromethene) ligand to be used for complexation with a metal(II) ion.

PRELIMINARY ENDEAVORS TOWARD A BIS(DIPYRROMETHENE) LIGAND

An introduction to potential synthetic strategies

The successful synthesis of a hydroxyl trifluoroethyl-pyrrole was an important accomplishment as it is a prelude to the synthesis of a bis(dipyrromethene) ligand. With pyrrole **11** at hand as a readily available starting material, the first attempts at the synthesize a bis(dipyrromethene) containing the hydroxyl trifluoroethyl group could be undertaken. As shall be seen in the following pages there were a number of possible routes available and only the strategies that came under serious consideration are discussed.

Scheme 20: Retrosynthesis and early strategy to an unsymmetrical dipyrromethene



The optimization of the synthetic strategies to be used in the construction of homochiral bis(dipyrromethene) helicates was conducted with the racemic series of compounds to avoid any waste of homochiral material. Scheme 20 shows an early

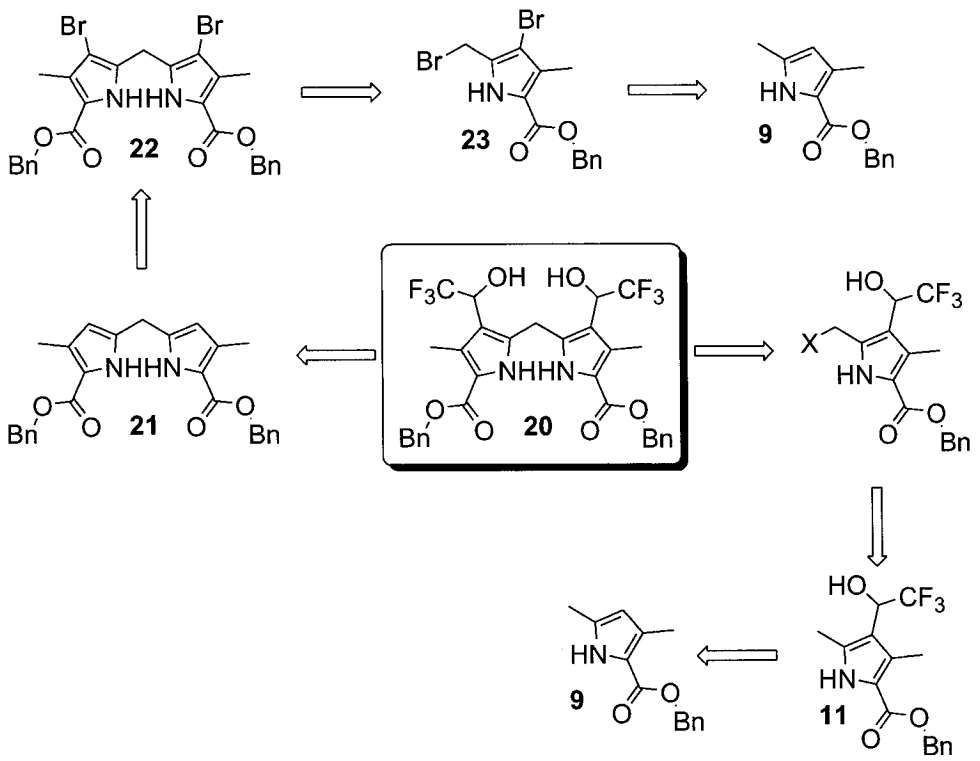
retrosynthesis of bis(dipyrromethene) **13** with strategy (*ii*) in mind: the incorporation of a chiral center onto one of the internal pyrroles of a bis(dipyrromethene). The retrosynthesis of ligand **13** indicates the MacDonald coupling of a dipyrromethane with formyl pyrrole **15**, after hydrogenolysis of the benzyl esters of **14** followed by decarboxylation. Pyrrole **15** is available ultimately from **2** through the reduction of the ketone functionality with diborane at room temperature to yield **4**. Molecule **4** could then be hydrogenolyzed (cleavage of the benzyl ester) and the resulting pyrrole-2-carboxylic acid formylated through a number of available means. Dipyrromethane **14** should result from coupling pyrrole monomers **16** and **17**, which could be synthesized from pyrroles **4** and **9**, respectively.

The architecture of the requisite ligand **13** is problematic due to the presence of a stereocenter on only one pyrrole, located on only one of the two internal rings of a linear tetrapyrrolic ligand, thus conferring the ideology of the molecule possessing a "head" and a "tail." This inherent unsymmetrical structure leads to the possibility of forming head-to-head and head-to-tail isomers of the expected dinuclear dimeric metal complex. An example of selective head-to-tail formation of a bis(dipyrromethene) complex is available in Ma's rectangular head-to-tail self-assembly of a 2,3′-bis(dipyrromethene) metal complex.[84] Ma's accomplishment of a selective synthesis of only the head-to-tail isomer may be attributed to the geometric necessity of a 2,3′-system versus a 2,2′-system desired for the current work.

In order to eliminate the possibility of head-to-head versus head-to-tail competitive complexation pathways, it would be beneficial to synthesize a ligand that possesses a C2 axis of symmetry. The axis of symmetry in the C2 symmetrical 2,2′-bis(dipyrromethene) would allow the diastereoselective complexation to be scrutinized without the added complication of head-to-tail selectivity. Introduction of symmetry to the system should also significantly shorten the synthesis required to build the ligand as only one pyrrole monomer is needed; and thus, only one synthetic pathway is required, unlike the convergent synthesis of **14**. Scheme 21 illustrates synthetic possibilities in the

realization of a symmetrical dipyrromethane, **20**, the key precursor to the desired symmetrical 2,2′-bis(dipyrromethene).

Scheme 21: Retrosynthetic look at the construction of a symmetrical dipyrromethane



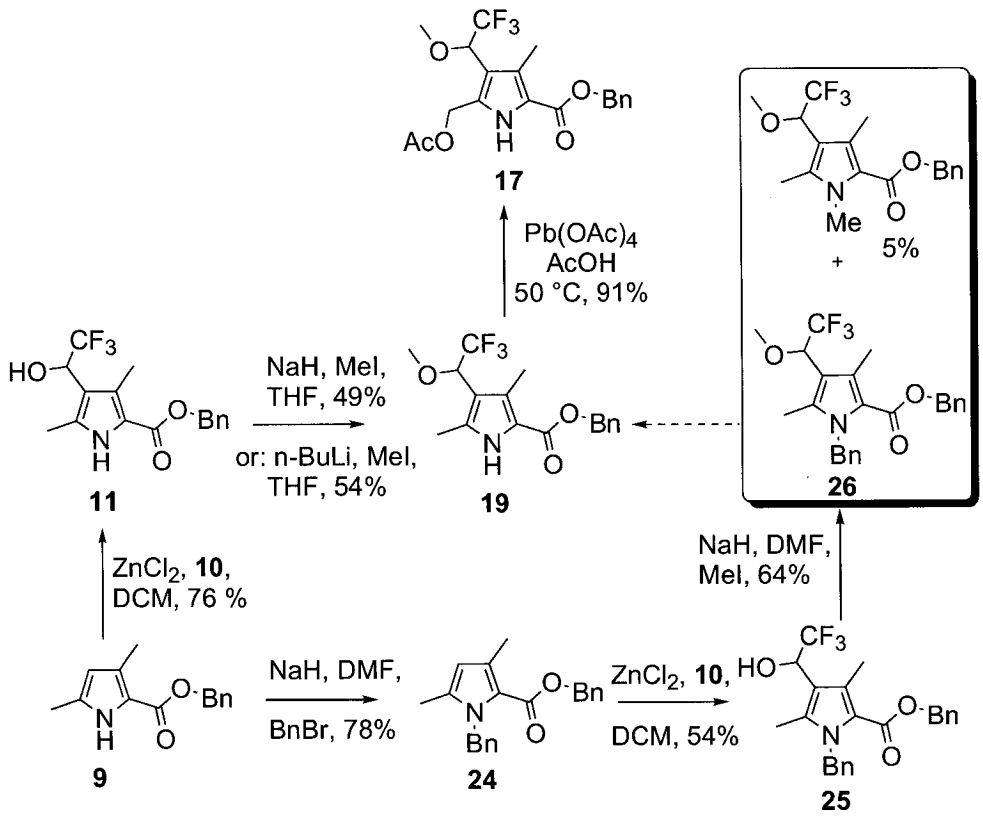
Attempted syntheses of a symmetrical 2,2′-dipyrromethane

With the retrosynthetic analysis of **20** (Scheme 21) in mind, the realization of a symmetrical dipyrromethane would allow for the construction of a homochiral 2,2′-bis(dipyrromethene) ligand. A further encouragement to the success of the eventual synthesis of **20** was the successful utility of pyrrole **11** in Kumadaki's synthesis of a homochiral variant of fluorinated hematoporphyrin.[75] It was hoped that the existing functionality of pyrrole **11** would be sufficient for the chiral induction of helix formation upon complexation of the prospective bis(dipyrromethene) ligand with a metal. Should the steric bulk of the chiral group appended to a bis(dipyrromethene) ligand synthesized from **11** be insufficient for the enriched formation of one of the possible helical

diastereomers, then the use of the oxygen atom to append larger groups should be a possible avenue for rectification. Possibilities in the synthetic elaboration of the hydroxyl group in **11** provided the impetus to the attractiveness of this molecule in the synthesis of a 2,2′-bis(dipyrromethene).

The elaboration of the hydroxyl substituent of **11** to an ether was first attempted with methyl iodide according to literature procedures.[73] The literature methylation reaction proved to be more difficult than reported as the attempted alkylation produced a mixture of *N*- and *O*-substituted products (**19** was isolated in only 49 % yield, with an equal quantity of *N*-methyl product, Scheme 22). For alkylation of the unprotected compound **11**, Kumadaki and co-workers suggested that the use of THF as a solvent is important for the selectivity of *O*-alkylation versus *N*-alkylation. The chemoselectivity observed by Kumadaki (isolated yield of 76 % of the *O*-alkylation product)[73] can be attributed to the reactivity of the nitrogenous pyrrolic anion in polar solvents as discussed in the Introduction (Figure 8); the less polar nature of THF versus DMF should ensure selective alkylation of the oxygen atom due to less efficient ion separation between the pyrrole nitrogen and the sodium counterion. Also, smaller cations tend to result in reduced alkylation at nitrogen, and thus *n*-BuLi was used as an alternative to sodium hydride in order to produce the lithium alkoxide derivative of **11** with the intention of selectively alkylating the oxygen in the absence of an *N*-protecting group. Under carefully controlled conditions, reaction of pyrrole **11** with one equivalent of *n*-BuLi and three equivalents of methyl iodide gave 54 % yield of **19**, along with the expected N-alkylated product (observed by TLC and NMR (5% by integration)), and small amounts of starting material. The reaction was repeated using a greater number of equivalents of methyl iodide, as Gartner has reported the use of up to 15 equivalents of methyl iodide to alkylate a benzyl alcohol derivative, with no change in the outcome of the reaction.[85]

Scheme 22: Attempted routes to a methyl ether derivative with a chiral center



Problems involving non-selective methylation of oxygen versus the pyrrolic nitrogen prompted the protection of the nitrogen in compound **11** with a benzyl group (**25**). In order to reduce selectivity issues the β-free pyrrole used in the construction of **11**, **9**, was benzylated to give **24** (Scheme 22). Protection of the pyrrole nitrogen prior to the aromatic substitution reaction was achieved through reaction of the pyrrolic anion of **9**, made with sodium hydride in DMF, with benzyl bromide, yielding **24** in 78 % yield. The aromatic substitution reaction of **24**, utilizing **10**, proceeded poorly (54 % yield) but the subsequent *O*-protection of the *N*-benzyl derivative, **25**, was attempted despite the poor yield of **25**. The NMR spectrum of the isolated crude material obtained from the attempted *O*-protection of **25** indicated the presence of an *N*-methyl group (peak observed at 3.74 ppm) and TLC analysis supported this. Both the chemical shift of the *N*-methyl group and the R_f as a result of a TLC analysis could be compared to an isolated sample of the desired *O*-methyl compound.

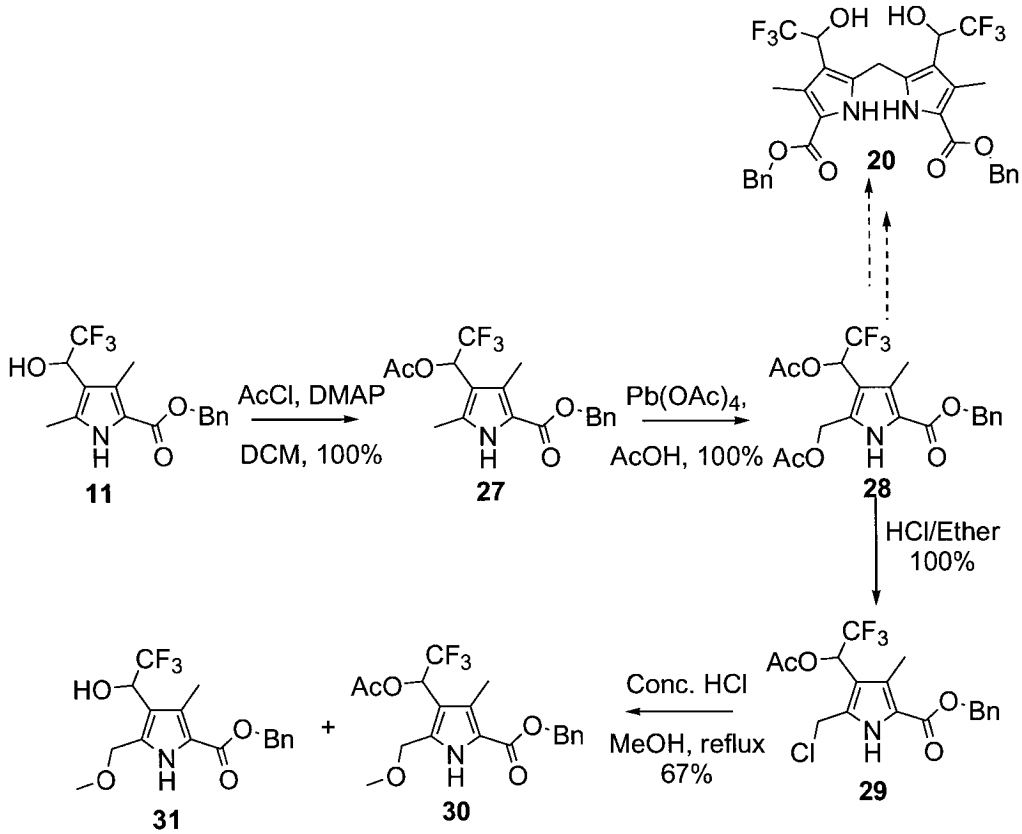
Although an intermolecular functional group exchange had occurred (*N*-*O*-dimethyl derivative of **11** was obtained as a minor product), alkylation of the oxygen at this point was successful with a moderate yield of 64 % of the product **26** (Scheme 22). The protection of the pyrrolic nitrogen rendered this synthetic pathway cumbersome and undesirable with low overall yields (27 % from **9**-**26** versus 37 % from **9**-**17** obtained without *N*-protection) and so the deprotection of **26** to form **19** was not completed. After the unsuccessful *N*-protection strategy it was decided to return synthetic efforts to the construction of pyrrole **17** from **19**. Oxidation of the α-methyl group of **19** was straightforward and synthesis of **17** was accomplished in 91 % yield.

The synthesis of a pyrrole monomer suitable for the production of dipyrromethane **20** has shown only moderate success *via* the cumbersome lengthiness (keeping in mind that this synthesis is not meant to be a total synthesis but rather the synthesis of a ligand; such syntheses are usually short and to the point as often the complex is of interest not the ligand) of the methods described above. Also, the overall yield of the acetoxymethyl pyrrole **17** was discouraging as the only high-yielding step was the oxidation of pyrrole **19**. The proposed synthesis of a symmetrical 2,2′-dipyrromethane using **17**, or another appropriately protected monomeric derivative of **11**, would utilize established oxidation chemistry of a pyrrolic α-methyl substituent. Self-coupling under acidic conditions, or the coupling an α-free pyrrole with an acetoxymethyl pyrrole, would then lead to a symmetrical dipyrromethane (**20**), and thus a symmetrical bis(dipyrromethene) upon future modification. Self-coupling strategies involving **17**, using Montmorillonite K-10 clay and tosic acid in acetic acid, failed to produce any dipyrromethane.

The elaboration of **11** to manufacture the methyl ether, **19**, was altered to instead affix an *O*-acetyl protecting group to give **27** in quantitative yield. The *O*-acylated compound **27** was easily manipulated when compared to the methyl ether compound.[75] Oxidation of **27**, using lead tetraacetate, to give **28** proceeded smoothly and occurred in quantitative yield. Attempts to self-couple pyrrole **28** using HCl/diethyl ether were met with the substitution of the α-acetoxy group with a chloro-substituent to give **29**. The isolation of **29** was disappointing but it was thought that treatment of **29** under acidic

conditions used by Clezy[86] would generate the symmetrical dipyrromethane **20**. Unfortunately, treating **29** with concentrated HCl in methanol did not effect the homo-coupling of **29** and the α-methoxymethyl compounds **30** and **31** were instead isolated, after purification by chromatography, in 67 % combined yield (as a 3:2 ratio of **31**:**30**, Scheme 23).

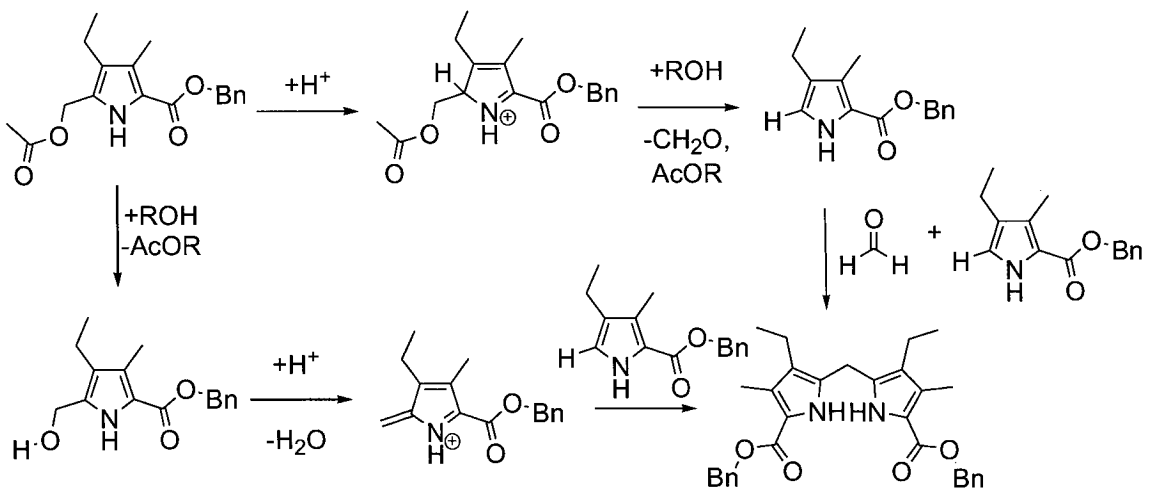
Scheme 23: Attempted homocoupling of acetoxymethyl pyrrole 28



The difference in the electron-withdrawing effect of the *O*-acyl group of **27** compared to **11** can be seen in the profound shift of the NMR signal of the lone hydrogen on the trifluoroethanol group. The NMR spectrum for pyrrole **11** shows a resonance for this proton at 5.1 ppm, while the NMR spectrum for pyrrole **27** shows a resonance of the analogous proton at 6.3 ppm. This jump in resonance frequency may be attributed, in part, to the additional electron-withdrawing effect of the *O*-acyl protecting group, which presumably deactivates the pyrrole inductively in conjunction with the trifluoromethyl group through the sigma bond network. A consequence of the *O*-acylation of pyrrole **11**,

as described, is that the extra electron-withdrawing capacity of the acyl group hampers the nucleophilicity of the pyrrole ring in compound **28**. Mechanistically, protonation of the pyrrolic ring will encourage the transesterification of the acetoxy group (to yield an ascetate ester, eg methyl acetate) followed by loss of a formaldehyde fragment (as a result of the presence of a hydroxymethyl group on the pyrrole which was formed as a result of the loss of an acetate ester) to re-aromatize the now α-free pyrrole. Thus the nucleophilicity of the pyrrole ring is of paramount importance to the self-coupling strategy (Scheme 24). Attack of the α-free pyrrole on an azafulvenium ion formed via an alternative pathway, or the combination of two α-free pyrroles with formaldehyde formed *in situ* results in a dipyrromethane. The mechanism thus highlights the necessity of a pyrrole that possesses an electron-rich nature.

Scheme 24: Mechanism for the formation of a dipyrromethane through homocoupling



The lack of success experienced in the self-coupling of pyrroles **28** and **29** is noteworthy. Pyrroles depicted in Scheme 23, and indeed the pyrroles throughout all of the attempted homo-couplings thus far, are substituted with a number of electron-withdrawing groups (only one is obvious: the ester group. The trifluoromethyl group is one carbon removed but its small affect on the electronic nature of a pyrrole is noticeable when in conjuction with a stronger withdrawing group) and are thus deactivated to the conditions usually employed to synthesize homo-coupled dipyrromethanes. During a similar synthesis of dipyrromethanes containing pyrrolic units that are substituted with deactivating groups Clezy and co-workers noted that:

> "...dipyrrylmethanes substituted with esters in the 5,5'-positions was usually achieved in reduced yield and it was anticipated that further deactivating groups in the pyrrole to be attacked by the cationic species would lower this yield to a prohibitive level."[86]

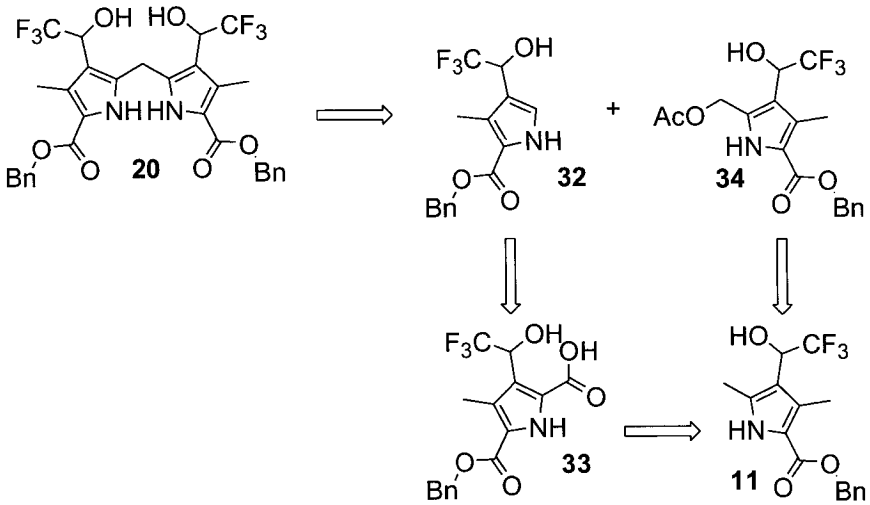
The net result of the presence of two electron-withdrawing substituents on pyrrole **27** (2-carboxylate and 4-(1-hydroxy-2,2,2- trifluoroethyl)) is that the overall deactivating effect of the substituents cannot be overcome. This deactivation effectively removes the ring electron-excessive nature of the pyrrole and thus the occurrence of established pyrrole chemistry is not observed for **28**.

The failure of the homocoupling reaction was a frustrating consequence of the over-abundance of electron-withdrawing substituents on the pyrrole monomer. As already discussed, the capacity for the trifluoromethyl substituent to behave as an inductive electron-withdrawing group was of importance to the stability of the stereogenic center on which it was appended. It was thus unfortunate that the presence of this group was hindering the self-coupling of the appended pyrroles.

An alternative homo-coupling pathway toward 20

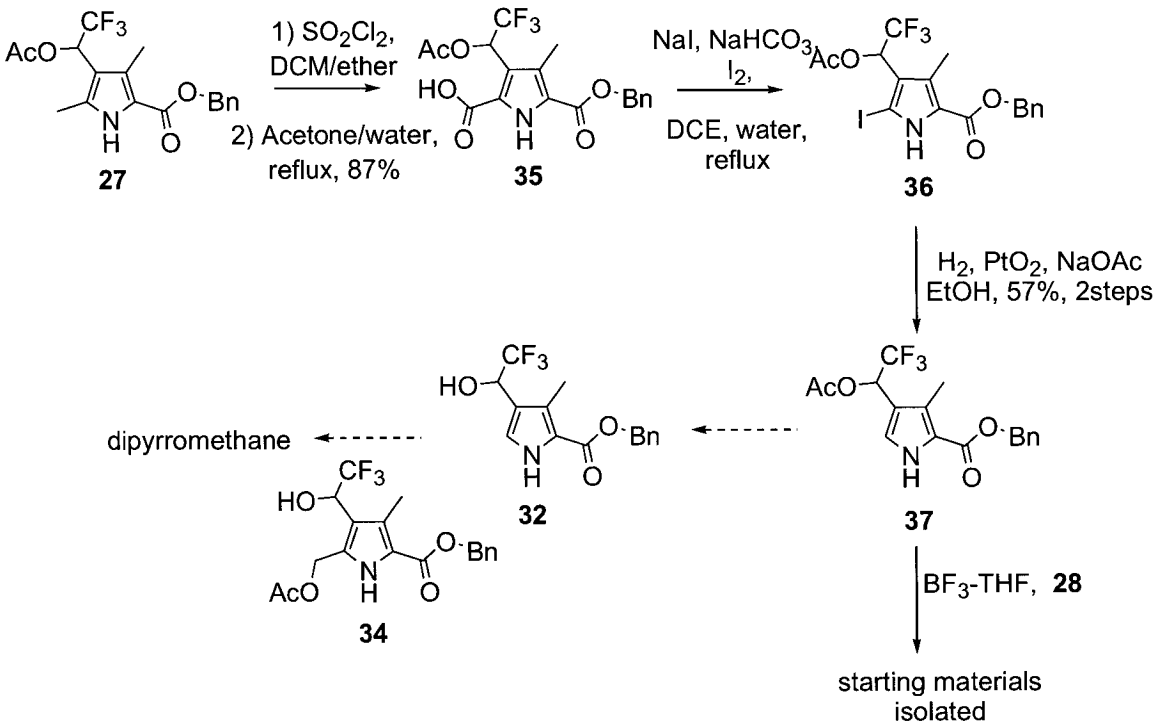
Rather than relying on self-coupling, and perhaps to expand upon the available routes within the synthesis of **20**, the strategies conceived for the construction of **13** (see Scheme 20) could also be utilized. The formation of dipyrromethane **20** is key to the production of the desired bis(dipyrromethene) ligand and could potentially be attained through the coupling of an α-free pyrrole with an α-acetoxymethyl pyrrole. Scheme 25 shows a retrosynthesis that depicts such a route.

Scheme 25: Alternative retrosynthesis to 20



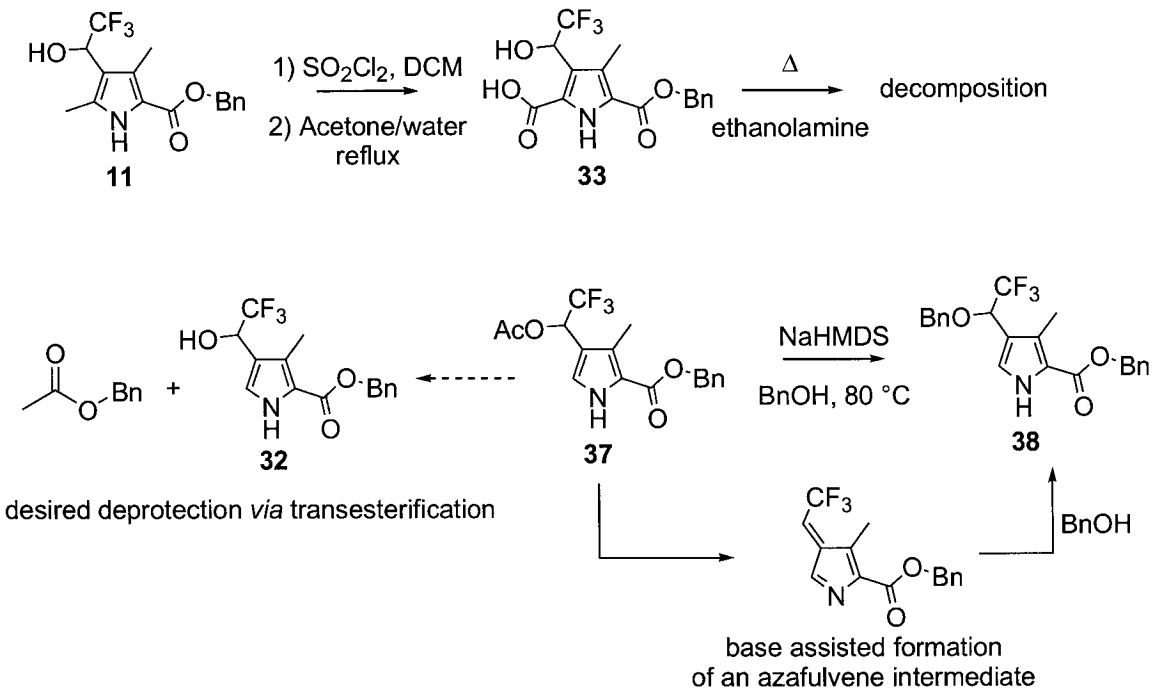
The coupling of an α-free pyrrole with an α-acetoxymethyl pyrrole is another well devised means for the preparation of a dipyrromethane, both symmetrical and unsymmetrical.[86,87] In order to produce the required α-free pyrrole the complete oxidation of the α-methyl group of **27** to the carboxylic acid (**35**) was achieved in high yield. Decarboxylation of **35** via the iodinative decarboxylation pathway yields **36** followed by hydrogenolysis of the resulting iodine-carbon bond produced α-free pyrrole **37** in 57 % yield over the two steps (Scheme 26). Pyrrole **37** was stirred, under Lewis-acidic conditions (BF_3-THF), with **28** and no discernable reaction occurred. Kumadaki and co-workers have coupled similar pyrroles via this method but their work involved the corresponding alcohols and not the *O*-acyl compounds.[75]

Scheme 26: Attempted coupling of an electron deficient series of pyrroles (*c.f.* pyrrole itself)



In an attempt to reduce the electron-withdrawing nature of the 4-substituent in pyrrole **37**, following precedent set by Kumadaki, the *O*-acyl protecting group was omitted from the synthesis (Scheme 27). *O*-Acylation proved to be prudent, however, as the attempted decarboxylation of **33** to yield **32** failed and **32** was not isolated from either iodinative decarboxylation or thermal decarboxylation in ethanolamine, which was surprising given the rapid evolution of a gas from the reaction mixture. If a route to the appropriate α-free alcohol, **32**, could be found it is suggested that this route to the dipyrromethane would be feasible due to the absence of the deactivation caused by the presence of an *O*-acyl protecting group. Kumadaki's synthesis did not require **32** but involved the synthesis of a compound in which the hydroxytrifluoroethanol substituent was in the 3-position. Locating the hydroxytrifluoroethanol substituent at the 3-position would inherently reduce the effective electron-withdrawing capacity of this functional group due to competition with the 2-benzyl ester functionality.

Scheme 27: Attempted decarboxylation of pyrrole 33 and the inadvertent *O*-benzylation of 37



The production of the deprotected pyrrole **32** from **37** would be beneficial because synthesis of a dipyrromethane could be attempted through the coupling of **32** with pyrrole **34**. During Kumadaki's chiral resolution of racemic **11** as a camphanyl ester, a basic alcoholysis was used to produce an unintended racemic mixture of ethers from the resolved camphanyl ester derivative.[74] This racemization can be explained, as seen in Scheme 27 by the formation of **38**, through an intermediate azafulvene followed by attack of a nucleophile on the terminal olefin thus producing the ether. Upon additional study alcoholysis was found to be successful, in the literature, with fast exposure times at high temperature using NaHMDS in benzyl alcohol to produce the desired homochiral alcohol.[75] A personal attempt at this reaction yielded starting material and low yields of the benzyl ether, **38** (Scheme 27). Therefore, it can be seen that the removal of the *O*-acyl protecting group is not trivial. The nitrogen lone pair is always a reactive component in pyrrole chemistry and exposure of pyrrole **37** to very basic conditions may promote the formation of an azafulvene intermediate through the deprotonation of nitrogen thus increasing the heteroatom influence on the leaving ability of the protected

alcohol in compound **37**. In this case it was hoped that the transesterification route would dominate to liberate the required pyrrole **32**.

Given the decomposition of **33** during attempts to decarboxylate, and the failed attempt to self-couple pyrroles **17** and **28**, a new method for the introduction of the 4-(hydroxytrifluoroethyl) group was desirable.

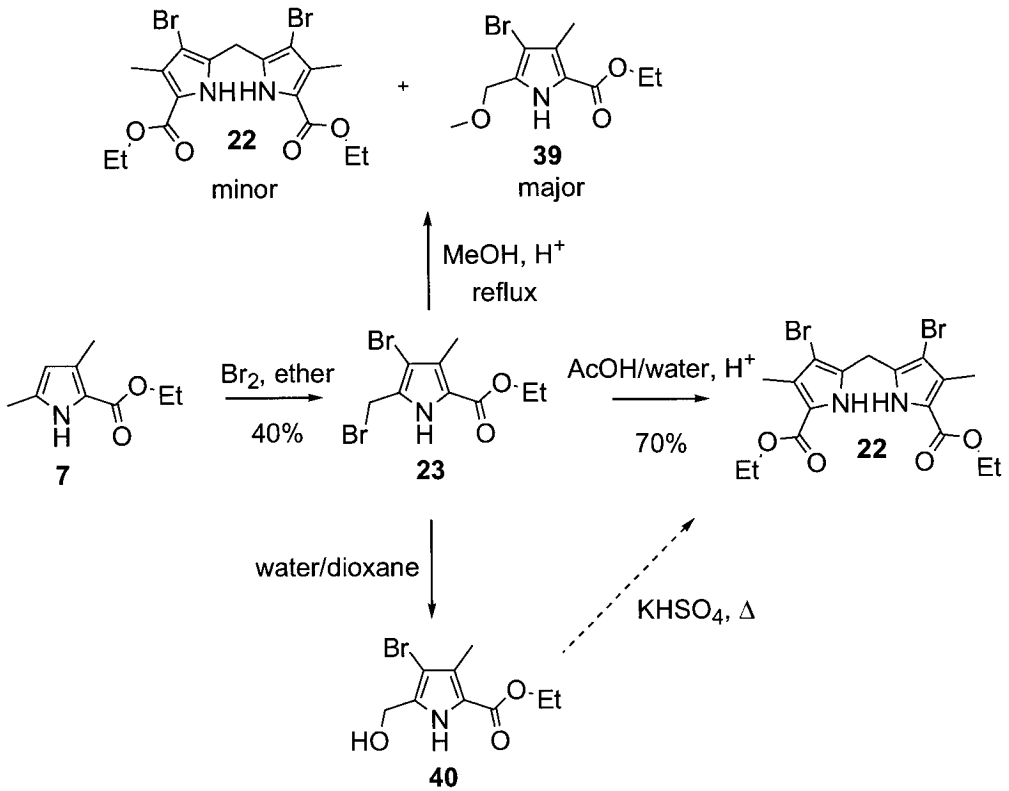
Towards 2,2′-bis(dipyrromethene)s from the synthesis of a bis-β free 2,2′-dipyrromethane precursor

Due to the difficulty experienced with the coupling of pyrroles that contain the 4-(trifluoromethyl-hydroxyethyl) substituent it became desirable to form the dipyrromethane preemptively. The formation of a di-β unsubstituted 2,2′-dipyrromethane followed by substitution of the β-free positions was seen as an alternative route to obtaining the requisite, symmetrical, bis(dipyrromethene) **20**. Construction of the dipyrromethane prior to the introduction of the trifluoroacetyl group (to be reduced to the alcohol **20**) was thus attempted (Scheme 28). This route proved to be impeded by its own challenges.

The first challenge was the construction of the dipyrromethane itself. Yields for the formation of an α-acetoxymethyl pyrrole by the oxidation of **7** with lead tetraacetate are reported to yield intractable tars so the bromination of **7** was undertaken instead.[88] Simultaneous oxidation of **7** at the β-free site and at the α-methyl group with bromine to produce **23** was very facile but the isolation of **23** was tedious due to the reactive nature of the α-bromomethyl group and only a 40 % yield was secured. After isolation, **23** was subjected to a number of conditions that typically induce self-coupling, including acidic alcohol, but only small amounts of **22** were isolated. Pyrrole **39** was the major product of the exposure of **23** to acidic conditions and similar results are reported in the literature.[86] Following a different literature procedure, the required dipyrromethane **22** was obtained in a more reasonable yield on a 1 mmol scale (37 % instead of 12 %, and less for other methods).[89] This reaction involved the suspension of **23** in acidic water at reflux followed by isolation, *via* filtration, of the suspended product after a one hour reaction

time. When the aqueous self-coupling reaction was attempted on a large scale (up to 30 mmol), clumping of the hydrophobic organic molecule precluded efficient transformation of **23** to the desired dipyrromethane and the reaction failed. Eventually, the self-coupling reaction of **23** was found to take place readily in a 1:1 ratio of acetic acid to water. The suspension was further acidified with HBr and heated to 80 °C and **22** was attained in 70% yield. Sleiter and co-workers have reported that the hydroxymethyl derivative (**40**) of **23**, can be homo-coupled by treatment with monobasic potassium sulfate (neat at the melt)[90] but due to the efficient coupling of **23** in a water/acetic acid medium this method was not attempted.

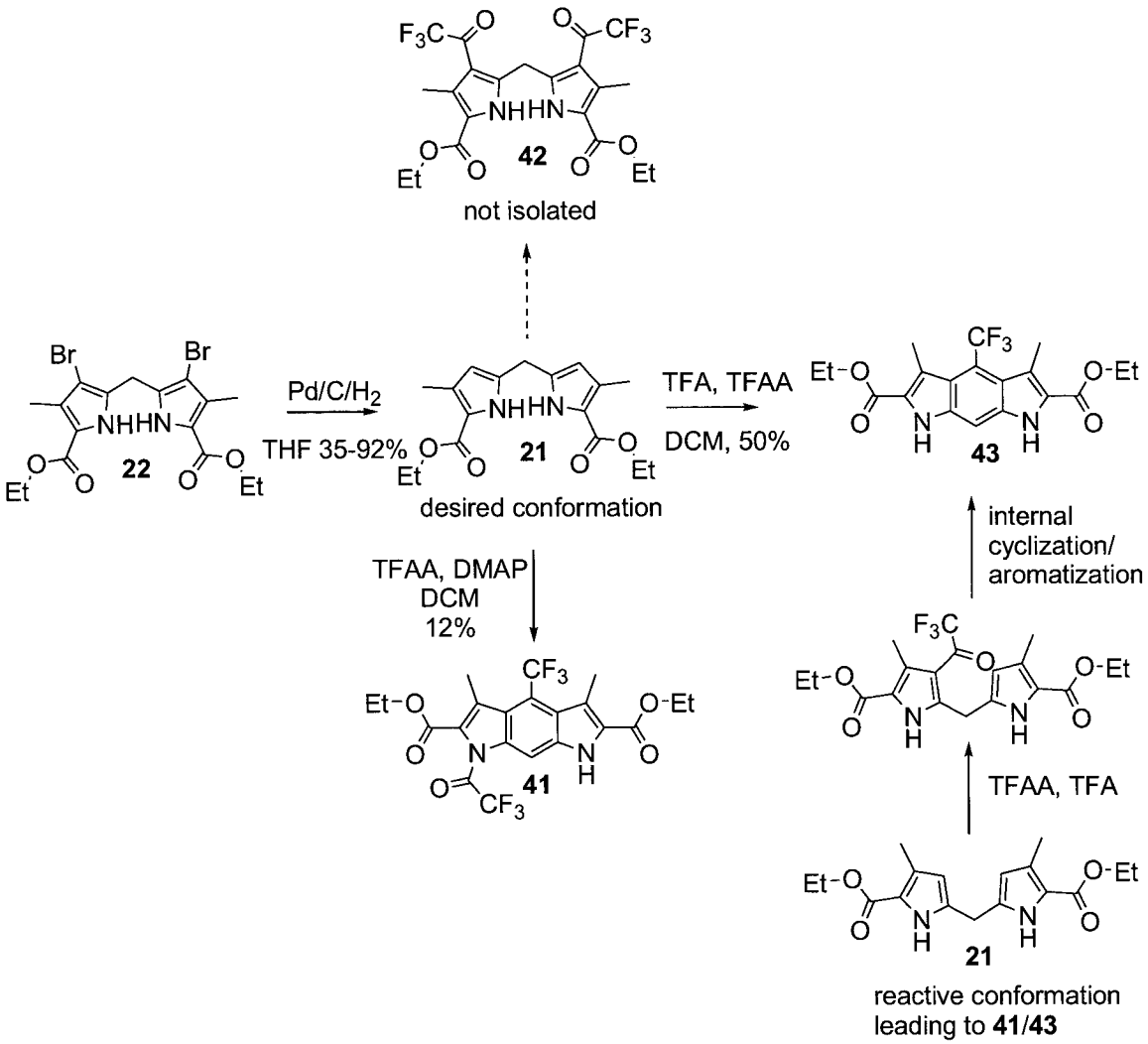
Scheme 28: Methods used to produce dipyrromethane 22



With dipyrromethane **22** in hand and the envisioned route to dipyrromethane **20** required only dehalogenation, trifluoroacylation, and reduction of the ketone functionalities to the corresponding alcohols. Work toward 2,2′-dipyrromethane **20** was slowed due to a problematic development with the precursor dipyrromethane **21** (retrosynthesis, Scheme 2). Reduction of **22** with hydrogen in the presence of palladium

on carbon was probably quantitative but yields were difficult to quantify due to the extreme insolubility of **21**, which caused difficulties with the separation of the precipitated product from the heterogeneous catalyst. As a consequence, THF is the only solvent found that is compatible (it allows partial solubility of **21** when hot) with the palladium on carbon catalyzed reduction of **22**. The trifluoroacylation of **21** utilizing TFAA and DMAP in DCM does not proceed as predicted,[91] and **41**, not the expected diketone, was isolated in 12 % yield. Elution of the compound through a flash silica column is suspected to have caused the decomposition of any other isolable product and only fluorescent by-products remained fixed to the silica and could thus not be characterized. It is hypothesized that the reaction of **21** with **19** produces the monoacyl derivative, which is then followed by internal cyclization to a pyrrolo-[3,2-*f*]-indole, **41** (Scheme 29). It is not known whether the *N*-trifluoroacyl functionality in compound **41** is appended prior to, or after, cyclization.

Scheme 29: Inadvertent synthesis of pyrrolo-indoles 41 and 43



Literature precedence for this cyclization exists in the synthesis of both pyrrolo-[3,2-*f*]-indole and pyrrolo-[2,3-*f*]-indole.[92] Chuchatprasert used Montmorillonite K-10 clay as an acidic catalyst for both the coupling and cyclization portions of his synthesis of pyrrolo-indole compounds. In contrast to acidic catalysis used by Chuchatprasert, the research presented herein utilized TFAA/DMAP to mediate the acylation of dipyrromethane **21** and then cyclization to the fluorescent yellow **41** is speculated to have occurred spontaneously (Scheme 29). The generation of a compound such as **41** is reliant on the orientation of the nitrogen atoms with respect to the methylene bridge. The conformation where the nitrogen atoms are pointing away from the methylene bridge the two β-free carbons become proximal and presumably cyclization chemistry is favoured.

It is hoped that future reactions involving the tethering of the nitrogen atoms, and thus a fixed conformation in the derivative of **21**, will inhibit the cyclization process and promote bis-acylation to give **42**. Another attempted synthesis of **42**, utilizing acidic conditions developed by Knight and co-workers,[93] only provided an efficient means of synthesizing pyrrolo-indole derivative **43**. Acidic conditions involving TFA and TFAA provided an accelerated means to produce the pyrrolo-[3,2-*f*]-indole as protonation of the ketone and subsequent alcohol facilitated both electrophilic attack and elimination. As an exemplification of the difference in mechanism achieved with the acidic method the pyrrolo-[3,2-*f*]-indole was isolated without the *N*-trifluoroacetyl group and the product (**43**) was isolated in over 50 % yield, which was a major improvement, albeit for the undesired product, over that produced with TFAA/DMAP.

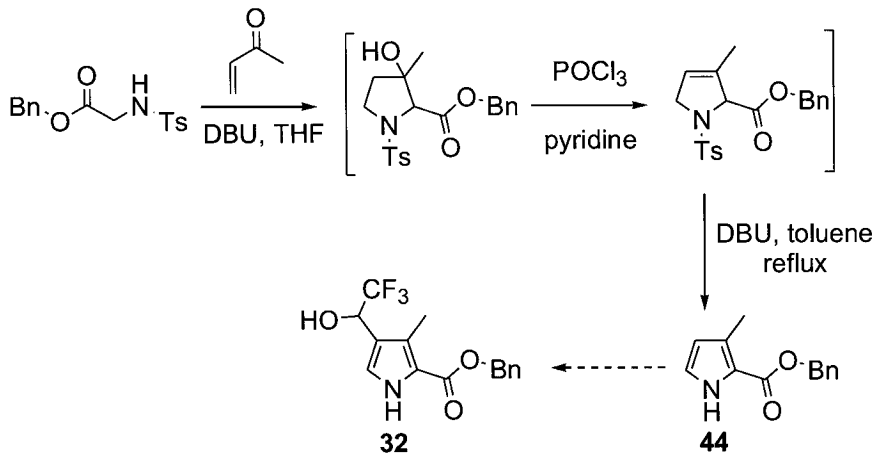
An interesting implication of the production of pyrrolo-indole **43** is the ability to produce a system from which a rigid bis(dipyrromethene) ligand might be constructed. The reactivity of a pyrrolo-indole is most likely more comparable to that of an indole than a pyrrole; indole is more reactive at the β-position than the α-position, which is opposite to pyrrole. Although further elaboration of this molecule has not been attempted it would be interesting to see if a bis(dipyrromethene) ligand based on this system would produce a rectangular molecule as a result of the complexation of four ligands to four M(II) centers.

The use of β versus α substitution to construct the required α-free pyrrole

A return to pyrrole monomers was deemed prudent as the synthesis of **32** has not yet been accomplished. If the requisite pyrrole **32** could not be synthesized from starting materials available through the Knorr synthesis (pyrrole **11** from **9** - Scheme 22 – pyrrole **9** is available through the Kleinspehn variation of the Knorr reaction[10]) then an alternative approach is required. As discussed in the Introduction, the Kenner synthesis of pyrroles is designed to produce α-free pyrroles and could theoretically be utilized to provide a pyrrolic starting material for the production of **32**. The Kenner synthesis, as

modified by Lash and co-workers,[94] was thus utilized to produce pyrrole **44** in 24 % yield from benzyl *N*-*p*-toluenesulfonylglycinate and methyl vinyl ketone (Scheme 30).

Scheme 30: Kenner synthesis used to produce desired α-free pyrrole



The use of a pyrrole such as **44** in synthesis poses some advantages and disadvantages concerning the synthesis of new molecules from this scaffold. An advantage to this system would inherently be in the existence of regioselective acylation for this family of molecules. The possible regioselective substitution of the 4-postion of **44** is thus advantageous in terms of the synthesis of **32**, especially considering the problems encountered with the decarboxylation of **33**. The second advantage that is posed by the synthesis of a molecule such as **44** lies in the lack of a need to perform any oxidation chemistry for the removal an α-methyl substituent as the α-carbon is already functionalized with the required hydrogen atom. An obvious disadvantage lies in the 2-electron-withdrawing group present within **44**. The ester functionality is known to be an inefficient directing group in pyrrole chemistry, due to the greater influence of the heterocyclic nitrogen lone pair, and this deficiency must be compensated for to ensure regioselective 4-acylation.

There are numerous routes for substituting the β-position of an α,β-unsubstituted pyrrole in preference to more usual substitution at the 5-position. For example, the use of a strong deactivating group, such as 2-trichloroacetylpyrrole, [29] or the enhancement of the electron-withdrawing ability of a weakly deactivating group[95] both result in preferential

4-substitution. When just a 2-alkoxy-carbonyl group is used to influence the regiochemistry of substitution on the pyrrole ring results are dependant on the type and the stoichiometry of Lewis acids that are often used to catalyze the substitution process.[95] The use of a strong Lewis acid to coordinate the carbonyl oxygen of the alkoxy-carbonyl group enhances the ring deactivating effect produced by the substituent.[95]

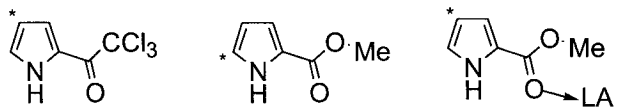
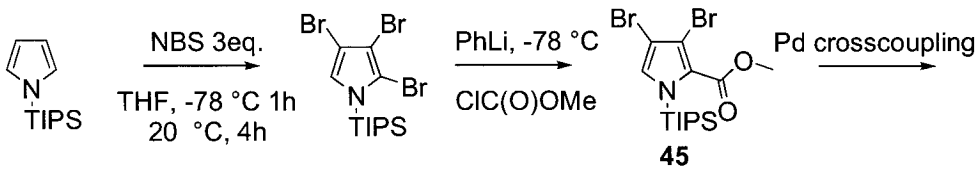


Figure 18: Effects of substituents on ring substitution. Asterisk denotes preferred regiochemistry

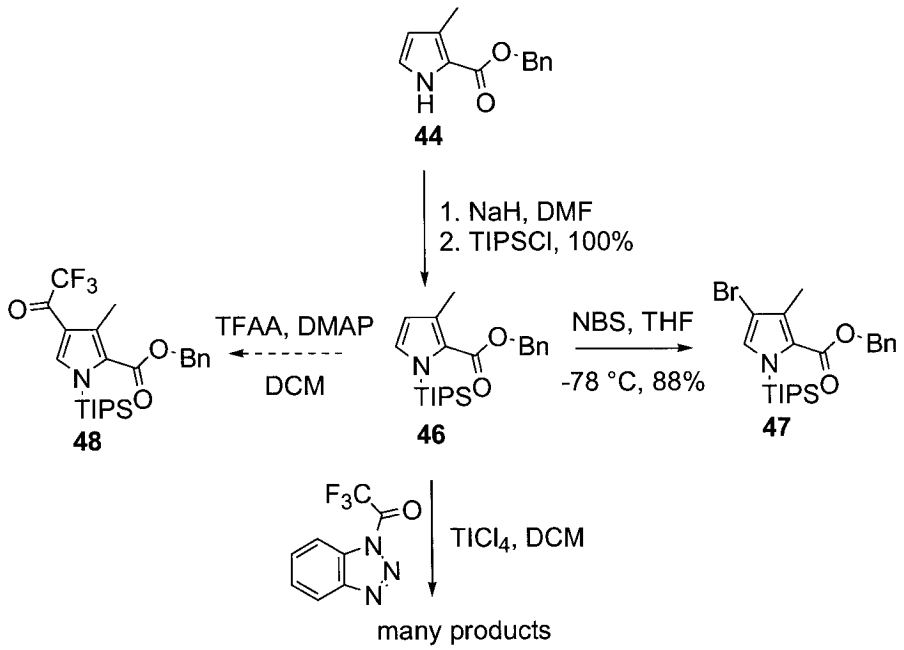
Another promising method for the β-selective substitution of pyrrole is to render the α-positions sterically inaccessible.[96] The use of the triisopropylsilyl (TIPS) group as an intentionally bulky functionality was first reported by Corey *et al.*[97] and the utility of triisopropylsilyl chloride (TIPSCl) as a nitrogen-protecting group for pyrrole was first exploited by Muchowski and co-workers.[96] Bromination of 1-TIPS-pyrrole and reaction of 1-TIPS-pyrrole with other electrophiles has been described. Particular interest lies in the reaction of 1-TIPS-pyrrole with trifluoroacetic anhydride in pyridine to produce the 3-substituted analogue.[96] It must be noted however that the use of TIPS as a protecting group in pyrrole chemistry has so far only found practical use with pyrrole itself. The utilization of *N*-TIPS protecting groups to explore the *β*-selective chemistry of 2-carboxylate-TIPS-pyrroles is rare, as few examples in the literature have been found.[98-100] Tri-bromination of *N*-TIPS-pyrrole for the express purpose of palladium cross-coupling a resultant 3,4-dibromo-2-carboxylate-pyrrole with aryl groups (Scheme 31) are among the few examples that exploit the sterically demanding attributes of the TIPS protecting group.[99,100]

Scheme 31: Production of a dibromo-pyrrole for palladium cross coupling



The protection of **44** by treatment with excess TIPSCl was straightforward and gave **46** in quantitative yield (Scheme 32). The bromination of **46** to produce **47** was facile and occurred under mild conditions as described in the literature.[96] The encouraging success of this highly regioselective reaction prompted the treatment of **46** with a mixture of TFAA and DMAP in DCM to attempt the direct synthesis of **48**. Isolation of starting material and no product from this reaction after overnight reaction in DCM was discouraging and it was decided that acidic conditions should be used. Katritzky and co-workers have developed a reagent for the trifluoroacetylation of heterocycles with titanium tetrachloride as the acid catalyst, which was also used in the presence of TIPS protection of a pyrrole nitrogen (without the 2-electron-withdrawing group).[101] Use of Katritzky's conditions on **46** resulted in a plethora of products, the isolation of which was not attempted.

Scheme 32: The chemistry of 46



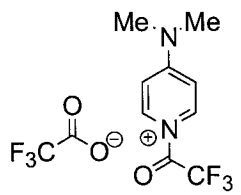
The direct trifluoroacylation of **46** was not successful in terms of the reactions attempted and the only useful reaction in this series was the β-bromination of **46** to produce **47**. With the advent of **47** the potential for the utility of the corresponding lithiated derivative to produce the desired compound was apparent. Lithium-halogen exchange reactions have provided a means to produce, regioselectively,[96,102] the lithiated pyrrole for use in the substitution of the pyrrole with electrophiles and may provide a valuable means to **32** in the future. Without an immediate means to produce the desired pyrrole **32**, the continuation of the project may be difficult from this point. The necessary alterations to the architecture of the molecule should include fewer electron-withdrawing groups in order to avoid the deactivation problems described in this chapter. Fewer electron-withdrawing groups will allow for the return to more traditional pyrrole chemistry, to achieve the target 2,2′-bis(dipyrromethene) ligands.

A general acylation of pyrrole with mixed anhydrides

During work on the self-coupling of pyrroles **28** and **17** it became necessary to produce larger quantities of **11** and the $ZnCl_2$ catalyzed electrophilic addition of **10** was

too time-consuming and cumbersome to be efficient. Direct trifluoroacetylation was therefore desired and so an optimization study was completed for the acylation of **7**.

Many different trifluoroacylating reagents are available. For example, the 1-trifluoroacylbenzotriazole developed by Katritzky and co-workers[101] may provide an alternative means to the acylation of **7**. The acylation of 2-carboxylate pyrroles is easily achieved using acid chlorides, catalyzed by Lewis acids such as $SnCl_4$.[103] Unfortunately, trifluoroacetyl chloride has a very low boiling point (-27 °C) and the corresponding acyl bromide and iodide compounds are also gases at room temperature. Due to the practical difficulties that would be encountered when utilizing a gaseous reagent, it was decided to find a higher boiling synthetic equivalent to trifluoroacetyl chloride. DMAP and TFAA were mixed in DCM and the 4-dimethylamino-1-(2,2,2-trifluoro-acetyl)-pyridinium trifluoroacetate reagent **49** was thus generated *in situ* for reaction with β-free pyrrole **7** (Figure 19, or Scheme 33). This method was utilized by Burns and co-workers to trichloroacylate a tripyrrin that proved to be extremely sensitive to acidic conditions.[91] A first attempt to synthesize **17**, through the trifluoroacetylation of **9** using **49** in DCM (analogous to the attempted derivatization of **46** with **49**, Scheme 32),[91] resulted in a disappointing yield of 51 %. A 51 % yield of an acylation product is acceptable but does little to improve the overall efficiency of Kumadaki's synthesis of **18**.



49

Figure 19: Trifluoroacylating reagent

The use of trifluoroacetic anhydride (TFAA) to produce mixed anhydrides for use in acylation chemistry is well-known[104] and the use of phosphoric acid as a catalyst in TFAA/mixed anhydride chemistry was first described by Galli.[105] The use of such reagents as an alternative to trifluoroacetyl chloride/Lewis acid catalysis is important as it greatly simplifies the acylation procedure. The phosophoric acid mixed anhydride

methodology forgoes the necessity of handling air/moisture sensitive Lewis acidic catalysts and consequently more ambient reaction conditions can be employed. Knight and co-workers have recently described a method[93] for the 2-acylation of *N*-substituted pyrroles involving carboxylic acids and TFAA (Figure 20). The reaction is thought to proceed *via* the formation of the mixed anhydride that results from the reaction of TFAA with the carboxylic acid additive. Knight's concise method is similar to those reported by Galli (thiophene)[106] and Kakushima (pyrrole),[107] and regioselectively produces good yields of 2-acyl pyrroles.

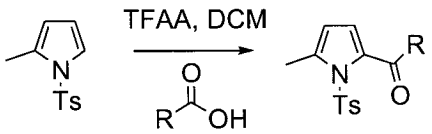
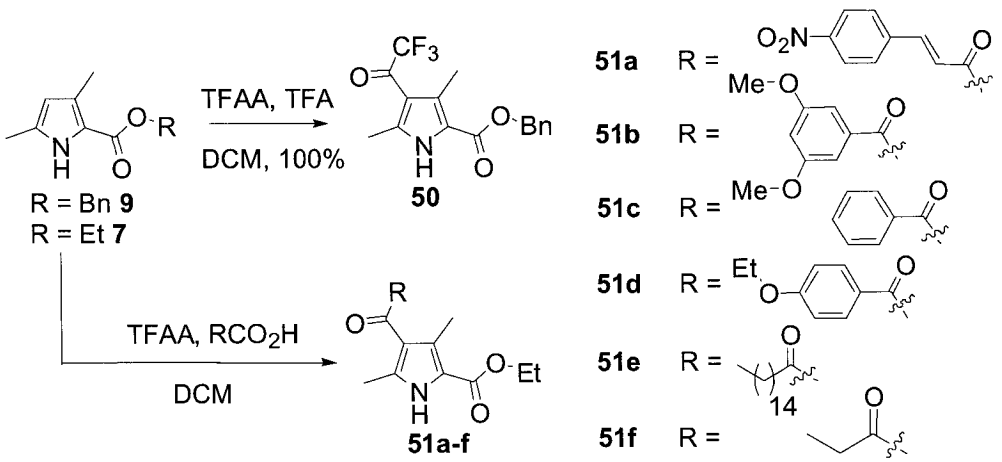


Figure 20: Knight's general method

Treating **9** with trifluoroacetic acid (TFA) in the presence of TFAA (Scheme 33), according to Knight's procedure,[93] gave the trifluoroacetyl pyrrole **50** in quantitative yield. The success of this trifluoroacetylation reaction prompted a broader exploration of Knight's methodology in the preparation of other 4-acyl pyrroles. Thus, several attempts to synthesize alternative acyl pyrroles, using different carboxylic acids in place of TFA and pyrrole **7** (this pyrrole was simply more abundant and therefore a more amenable test molecule) in place of **9**, were made and the results are presented in Table 1.

Scheme 33: Trifluoroacetylation of 7



Analysis of Table 1 reveals that electron-poor aryl acids (entries 1 and 2), and benzoic acid (entry 3) did not yield acylated pyrroles. However, electron-rich aryl acids (entry 4) and aliphatic carboxylic acids (entries 5 and 6) gave the corresponding 4-acyl pyrrole in moderate to excellent yield. Given the lack of reactivity of electron-poor carboxylic acids under these conditions, it became clear that Knight's method was not general for the 4-acylation of 2-carboxylate pyrroles. Thus, conditions were sought for an alternative strategy for the 4-acylation of 2-carboxylate pyrroles.

Table 1: Acylation results using Knight's conditions. NR – no reaction

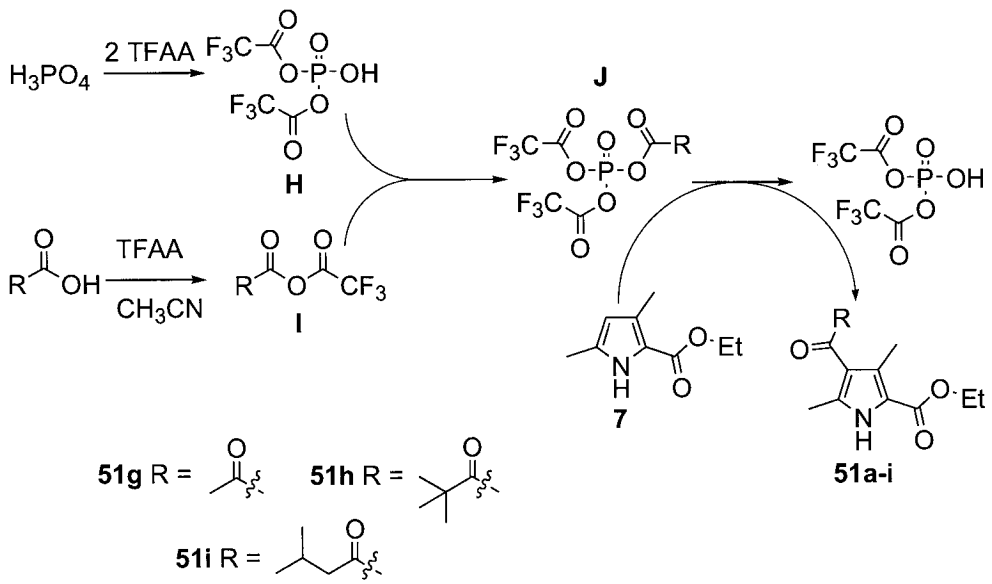
Entry	Carboxylic acid	Temp (C)	Product	Yield (%)
1	4-nitrocinnamic	20	**51a**	NR
2	3,5-dimethoxybenzoic	20	**51b**	NR
3	benzoic	20	**51c**	NR
4	4-ethoxybenzoic	20	**51d**	60
5	palmitic	20	**51e**	60
6	propanoic	20	**51f**	96

The use of acyl trifluoroacetates (ATFA) as mixed anhydrides for the acylation of aromatic heterocycles and activated benzene rings has been previously reported. Indeed, acetyltrifluoroacetate has been used as a successful acylating agent for thiophene, anisole and furan but is less successful for the acylation of pyrrole.[11,108] Clementi's work in this area indicates that the trifluoroacetylation of pyrrole becomes competitive with acylation upon a decrease in temperature, solvent polarity and reactant concentration.[109] Smyth

and co-workers have proposed that Friedel-Crafts acylations of substituted benzenes with TFAA and phosphoric acid are a clean alternative to conventional methods utilizing Lewis acid catalysts.[110-112] To increase the degree of activation phosphoric acid is used as a catalyst and the activated phosphoryl mixed anhydrides react rapidly and so Lewis acid co-catalysis is unnecessary.[112]

Considering the success of utilizing both phosphoric acid to promote acylations and the beneficial effects of polar solvents[109] to enhance the acylation of thiophene, it was decided to merge these two approaches for the 4-acylation of 2-carboxylate pyrroles (**51**). In the modified procedure, pyrrole **7** was added as a solid to a solution containing a pre-formed phosphoryl mixed anhydride **J**, synthesized step-wise in a similar manner to Smyth (Scheme 34). Smyth *et al.* mixed four equivalents of TFAA with one equivalent of the carboxylic acid, upon cooling to below 10 °C, followed by one equivalent of 85 % phosphoric acid. After complete dissolution of the phosphoric acid the substrate was added.[111] This method was modified slightly and improved yields were obtained with a variety of carboxylic acids (Scheme 34), as detailed in Table 2.

Scheme 34: The acylation process



Murakami and co-workers have reported similar phosphoric acid-promoted acylations of indole[113] and pyrroles[95] but with lower yields. The order of addition and

successful formation of the phosphoryl mixed anhydride **H** prior to the addition of the pyrrole is, presumably, the key to the higher yields obtained in this reaction. The mechanism of reaction was also studied by Smyth and co-workers utilizing anisole substrates and was followed by ^{31}P and ^{19}F NMR spectroscopy. The presumed mechanism within this work is thus unchanged from that proposed by Smyth as the nucleophilic nature of both aromatic systems (pyrrole versus anisole) is presumed to be similar. When the phosphoric acid was mixed with two equivalents of TFAA to generate **H**, **I** was generated in another flask with two equivalents of TFAA added to a solution (or suspension) of the carboxylic acid in acetonitrile. The solution of precursor **H** was then added to the solution containing **I** to generate the required phosphoryl mixed anhydride **J** and pyrrole **7** was then added as a solid. Routine work-up through quenching of the produced TFA with sodium carbonate, and purification gave the expected 4-acyl pyrroles: **51b**, **51c**, and **51e-h**. The reaction, performed under ambient atmosphere, was followed by monitoring the disappearance of **7** by TLC. Analysis of Table 2 reveals that, under these conditions, excellent yields of 4-acyl pyrroles (**51**) were obtained in cases that were previously unsuccessful or low yielding.

Table 2: Acylation utilizing modified method. NR – no reaction

Entry	Carboxylic acid	Temp (C)	Product	Yield (%)
1	palmitic	20	**51e**	77
2	propanoic	20	**51f**	90
3	acetic	20	**51g**	83
4	pivalic	20	**51h**	86
5	iso-valeric	20	**51i**	66
6	benzoic	20	**51c**	81
7	3,5-dimethoxybenzoic	20	**51b**	81[a]
8	3,5-dimethoxybenzoic	40	**51b**	62
9	4-nitrocinnamic	20	**51a**	NR

[a] – performed in the absence of solvent

The reaction was very rapid after the addition of pyrrole and usually complete (or close to completion) within five minutes. The use of aliphatic acids (Table 2, entries 1-5) gave the corresponding 4-acylpyrroles in very good yield. Benzoic acid, previously unreactive (Table 1, entry 3), gave the required acylated pyrrole in 81 % yield (Table 2, entry 6). In the case of 3,5-dimethoxybenzoic acid it was found that the yield could be significantly improved by conducting the reaction in the absence of solvent (entry 7), and

ensuring the efficient formation of **I** by heating to reflux. Unfortunately, similar attempts with *p*-nitrocinnamic acid proved fruitless (table 2, entry 9), akin to similar reports involving indoles.[113]

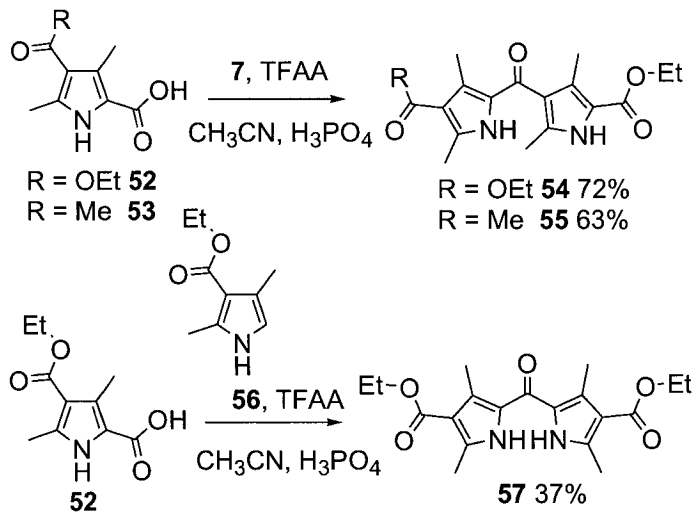
Many of the reactions could also be conducted in the absence of acetonitrile, with similar yields obtained. However, on occasion it was observed that the carboxylic acid was not miscible with TFAA and this lack of miscibility was usually indicative that the pyrrole acylation reaction would not be successful (if the reaction was carried out as usual). However, if acetonitrile was added during the formation of **I**, and the acylation carried out after the disappearance of the suspended carboxylic acid, the required 4-acyl product was isolated in good yield. It is therefore evident that the formation of the initial mixed anhydride **I** between the carboxylic acid and TFAA must occur first, before the addition of **H** and the pyrrole, if good yields are to be obtained. As such, the preferred procedure was to use, routinely, acetonitrile in the preparation of **I**.

Having established that the new procedure could be used for the efficient formation of 4-acyl pyrroles, the formation of dipyrrylketones was of interest in order to explore the usefulness of the acylation procedure. Dipyrrylketones have been used as synthetic intermediates in the synthesis of oxophlorins/oxyporphyrins, which are themselves intermediates for biologically important protoporphyrins.[86,114] Symmetric 2,2′-dipyrrylketones have previously been constructed through the use of phosgene,[115] or thiophosgene followed by reaction with basic hydrogen peroxide.[116] Other known synthetic routes to dipyrryl ketones include the oxidation of dipyrromethanes with either lead tetraacetate/lead oxide,[109] sulfuryl chloride[109] or ceric ammonium nitrate.[117]

To investigate the scope of the phosphoric acid-promoted mixed anhydride reaction for the synthesis of dipyrrylketones, pyrrolyl carboxylic acids were reacted with **7**. Thus, two pyrrolyl carboxylic acids, **52** and **53**, were used in conjunction with **7** to produce N-confused dipyrrylketones, **54** and **55**, potential precursors to N-confused and/or N-fused porphyrins. The same methodology was used for the construction of 2,2′-dipyrrylketone **57** (Scheme 35). Compounds analogous to **57** have been used to construct

oxophlorins (oxoporphyrins).[5] These results demonstrate that it is possible to prepare dipyrrylketones with a variety of architectures simply by using different pyrrolyl carboxylic acids and α/β-free pyrrole nucleophiles.

Scheme 35: New synthetic method for dipyrrylketones



A manuscript describing the accomplishment of this mixed anhydride work has recently been published.[118] The ability to produce, efficiently, 4-trifluoroacetyl pyrrole **50** and other 4-acylpyrroles is now established, allowing for a more flexible synthetic protocol in the attempted synthesis and study of a homochiral 2,2′-bis(dipyrromethene) ligand containing the trifluoro hydroxyl ethyl functional group.

DIPYRROMETHENE DERIVATIVES OF 11

Synthesis and chiral separation of dipyrromethene complexes

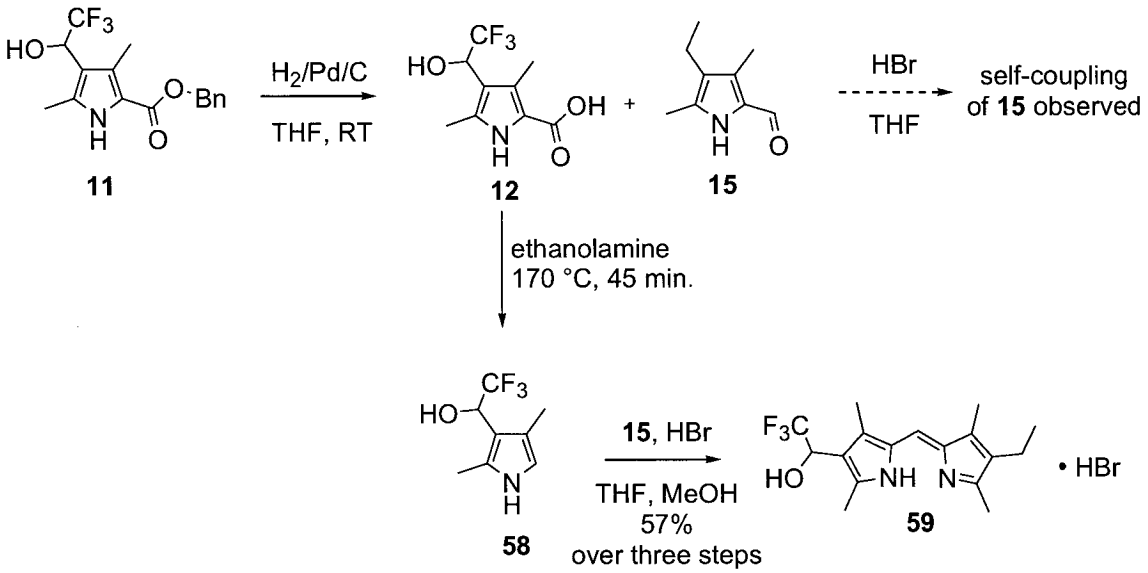
Now that the synthesis of **50** and thus **11** was two steps shorter and higher yielding, **11** could be used in the study of dipyrromethene ligands. The synthesis of dipyrromethene ligands from **11** was undertaken in part to determine the feasibility of **59** as a ligand and also if the investment of more time (and money) into the bis(dipyrromethene) project was prudent.

The synthesis and complexation of a racemic dipyrromethene containing the hydroxyl trifluoroethyl group was undertaken in an attempt to discover if the presence of the electron-withdrawing group has an influence on the complexation reaction. First and foremost in ascertaining the influence of the electron-withdrawing group is the establishment of **59** as a ligand that possesses sufficient binding strength to coordinate with the Zn(II) ion (Scheme 36). Secondly, the consequence of the presence of the stereogenic group, located on the dipyrromethene ligand **59**, is the possible existence of a simple diastereoselective complexation phenomenon when **59** is reacted with a metal salt. The separation of these diastereomers was to be accomplished with a Chiralpak®-IA chiral column. This column contains a derivatized polysaccharide that was used with other projects in the Thompson laboratory to illicit the separation of helical diastereomers of bis(dipyrromethene) complexes.[76-78]

The formation of **59** was first attempted *via* the usual method of reacting a pyrrole-2-carboxylic acid (**12**) with a 2-formyl pyrrole (**15**). This initial route was embarked upon when pyrrole **11** was first converted to the corresponding carboxylic acid by hydrogenolysis of the benzyl ester. The carboxylic acid was reacted, without purification, with **15** in the presence of hydrogen bromide. Results with this method were unsuccessful and it is suspected that **12** did not decarboxylate rapidly enough during the course of the attempted MacDonald coupling and so the competing self-coupling pathway, involving two molecules of **15**, dominated to give an unwanted dipyrromethene salt. In order to ensure the required dipyrromethene (**59**) was formed, the

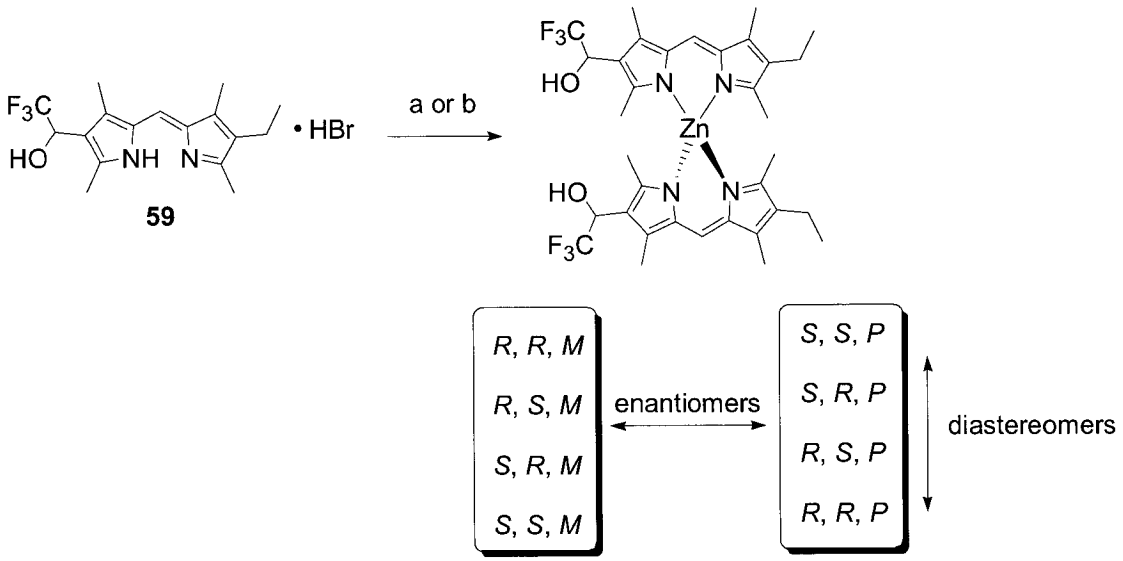
decarboxylation of **12** was undertaken *via* thermolysis in ethanolamine at 170 °C to afford the corresponding α-free pyrrole **58**. Pyrrole **58** reacted readily with **15** to complete the construction of the required dipyrromethene **59** in 57 % yield from **11**.

Scheme 36: Synthesis of a dipyrromethene to test both complexation and diastereoselectivity



Dipyrromethene **59** was then treated with a zinc acetate/sodium acetate mixture in THF/methanol solution and the dipyrromethene zinc complex **60** was isolated in 64 % yield (Scheme 37) after simple work-up. This yield was increased to 85% through the substitution of sodium acetate with lithium hydroxide as the base, and zinc perchlorate instead of zinc acetate as the source of the metal(II) ion. No separation of **60** was achieved utilizing conventional flash chromatography on silica. The analysis of the proton NMR spectrum of **60** revealed complex patterns but the larger range of chemical shifts of the ^{13}C nucleus allowed for greatly improved resolution (with respect to the separation of signals) thus making the carbon NMR spectrum more diagnostic. The stereogenic carbon (in all derivatives with the trifluoro-substituted methyl group) normally appears as a quartet in the ^{13}C NMR spectrum with $J_{CF} \approx 33$ Hz. Ligand **59** was no exception as a quartet with $J_{CF} = 32$ Hz was observed at a chemical shift of 65.8 ppm. In the case of **60** the stereogenic carbon atom gave a signal that appeared as a pair of quartets of equal intensity, presumably indicative of a mixture of isomers.

Scheme 37: Synthesis of 60



a) $Zn(OAc)_2$, MeOH/THF, NaOAc, 64% b) $Zn(ClO_4)_2$, MeOH, LiOH, 85%

The tetrahedral arrangement about the metal atom incorporates handedness (helicity) as the dipyrromethene ligand contains not only a stereocenter but is also unsymmetrical end-to-end. The use of racemic **59** in this complexation reaction allows for the possible production of eight different stereoisomers; *R* and *S* for the stereocenters on the ligands, and *M* and *P* for the metal center ($2^3 = 8$).

Two diastereomers in each of the vertical columns in Scheme 37 (*R,S,P* - *S,R,P* and *R,S,M* - *S,R,M*) are actually identical, as realized by the consideration (rotation of about an axis) of simple "stick" models (Figure 21). The identical nature of two of the complexes that could form allows for the simplification of the possible outcomes to just three stereoisomers within one enantiomeric set, which would exist in a 1:2:1 stoichiometric ratio if no stereochemical influences were in operation. As already mentioned, the ^{13}C NMR spectrum of **60** reveals only two sets of signals. The possible implications of such an observation are: 1) that there is indeed simple diasteroselectivity and one diastereomer is absent, thus giving a set of 1:1 diastereomeric complexes. Another possibility within this diastereoselectivity issue is the preferential complexation of *R* and *S* isomeric ligands on the same metal ion to form a heterleptic complex (rather than a homoleptic complexation of two *R* ligands or two *S* ligands); or 2) serendipitous

coincidence of chemical shifts for two diastereomers; and finally 3) a phenomenon known as atropisomerism may be occurring in the complex due to the proximal nature of the ligands, and thus the restricted rotation of the appended chiral functionality.[119] Atropisomerism is most commonly seen in biaryl compounds that are restricted rotationally so that they can exist as enantiomeric pairs. The restricted rotation results in chirality about an axis and is commonly exemplified by binapthalenes such as binol. This phenomenon would further complicate the isomeric constitution of the mixture **60**.

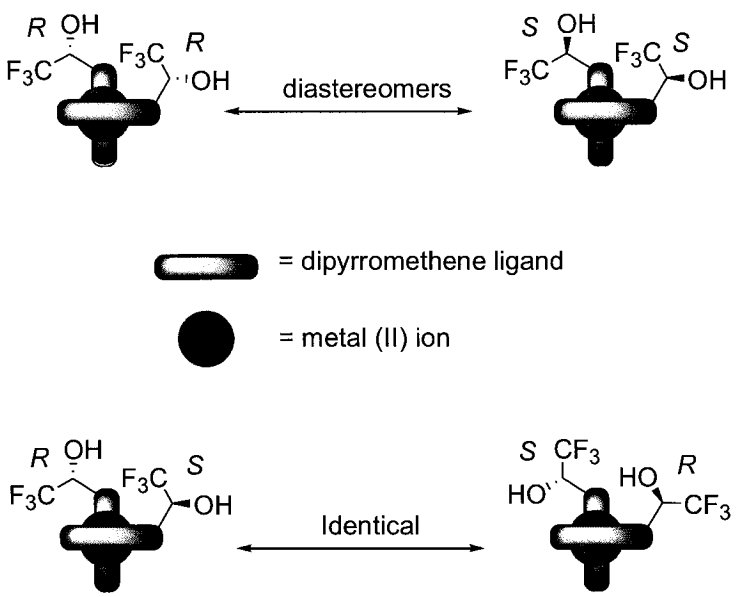
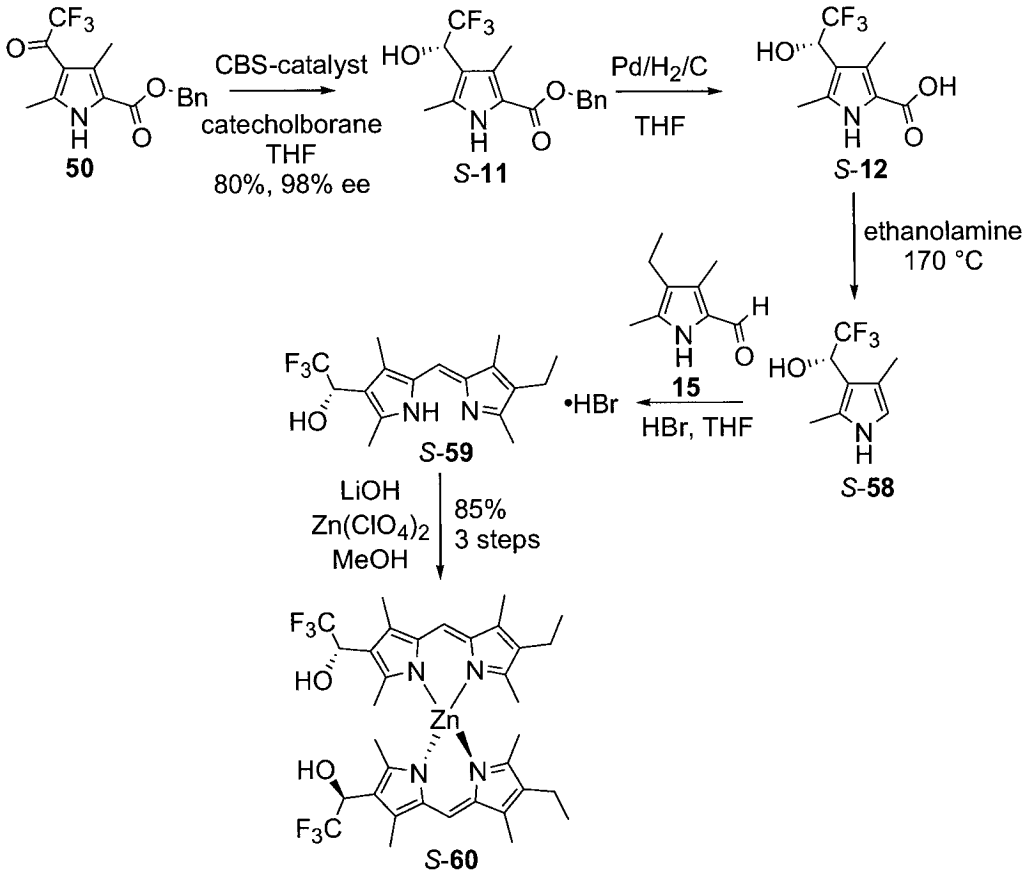


Figure 21: Isomers for the *P* series

The successful synthesis and isolation of the metal(II) complex **60** was important for the next step: a simplification of the possible stereochemical outcome of complexation by using homochiral ligands. It was expected that the use of a ligand with a defined stereocenter (*i.e.* a single enantiomer) would enable the production of complex where the metal(II) center is the only source of variation, and *M* and *P* helical diastereomers are thus expected to form. Fortunately methods have already been devised[75] to accomplish the synthesis of homochiral **11** (*S*-**11**), which was thus utilized in a synthesis of a homochiral version of **60** (*S*-**60**) (Scheme 38). Should the stereocenter have an influence (or not) on the helicity of the complex, one would expect to see a maximum of two peaks in the HPLC trace using a chiral separation, since only two

diastereomers are possible when using homochiral ligand *S*-**59** (assuming no atropisomerism).

Consequently *S*-**60** was synthesized starting from **50**, which was reduced with catechol borane in the presence of ten-mol percent CBS-catalyst to yield *S*-**11**.[75] Pyrrole *S*-**12** was decarboxylated analogously to **12** (**12**-Scheme 36 above, *S*-**12**-Scheme 38) and coupled with **15** under acidic conditions to yield chiral *S*-**59**. The ligand was then complexed to zinc (used as the perchlorate salt) in the presence of lithium hydroxide to yield the complex, *S*-**60**, in 85% yield over three steps and no separation with conventional flash chromatography was achieved. Unfortunately, the complex isolated exhibits only a small specific rotation (0.233 at a concentration of 0.016 M), due possibly to the lower than normal concentrations required with coloured compounds to acquire a reading on a polarimeter.[120] The CD-spectrum of the complex also exhibits a very small molar elipticity of 2.77×10^3 ($^\circ cm^2/dmol$), which is not encouraging (with respect to the chirality of both ligands and complex) as it makes suspect the degree of enantiopurity of *S*-**60** and thus *S*-**59**. A brief investigation of the chiroptical properties of the ligand *S*-**59** was unfruitful as neither a specific rotation (polarimetry) or a circular dichroism reading could be obtained, the former due to similar problems inherent to *S*-**60** and the difficulty of obtaining polarimetry readings with coloured compounds.[120] An explanation for the lack of *S*-**59** to yield a circular dichroism may be due to an inability of the chromophore to differentiate circularly polarized light or the lack of a homochiral influence in the molecule.



Scheme 38: Asymmetric synthesis of a dipyrromethene ligand and complex

Investigation of complex stability: HPLC

The characterization of the complex mixture obtained using racemic **60** was addressed through the attempted separation of the apparent stereoisomers through the utility of chiral HPLC. There is an abundance of chiral columns that can be utilized in the chiral separation of compounds but the columns utilized successfully in the Thompson laboratory belonged to the ChiralPak®[76-78] and ChiralCell®[77] series. Separations that were accomplished utilizing a chiral column designated as ChiralPak®-IA involving dipyrromethene ligands tethered with a binol chiral template as the substrate were considered to be similar enough to the attempted separation of **60** to warrant the use of the ChiralPak®-IA column. Results concerning the chiral separation of **60** indicated

the presence of three different compounds (whereas NMR only indicated two, presumably with corresponding enantiomers). Figure 22 illustrates the HPLC trace for mixture **60** on an analytical scale and the corresponding relative intensities from integration are: 6.83 minutes (2.6%), 7.28 minutes (86.7%), 8.20 minutes (10.7%). If, indeed, the peaks represent different isomers, as determined by the UV-VIS absorption data for each peak, it is not clear whether, from either the HPLC trace or the UV-VIS data, the peaks observed are due to enantiomers, diastereomers or both. To further investigate the compounds just isolated from the mixture containing racemic **60**, the sample was purified using preparative-scale HPLC and the complex synthesized using homochiral ligand *S*-**59** was analyzed. If simple diastereoselectivity can be attributed to the occurrence of the peaks in Figure 22, and the ratios are representative of the isomers in solution, then the expected ratio of 1:2:1 is not observed and is instead approximately 1:33:4, as calculated from the integration provided by the HPLC trace. When the second peak (the peak corresponding to the major compound) is isolated one should reasonably expect to observe one compound by NMR spectroscopy.

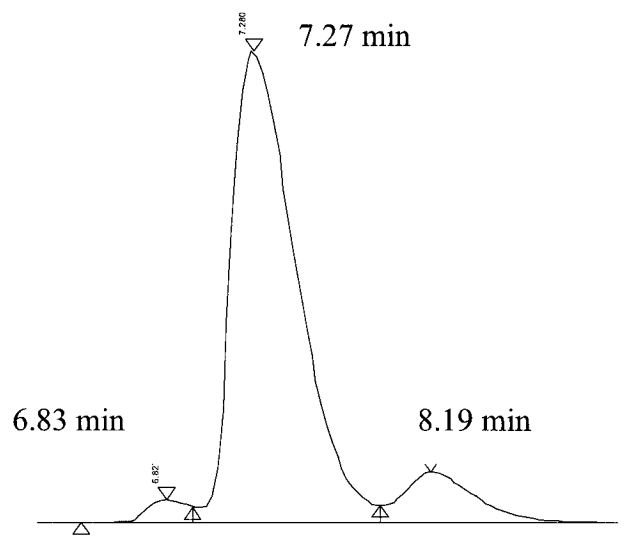


Figure 22: Separation of complex 60 with a chiral HPLC column

In order to determine the existence of chirality on the ligand/complex an HPLC trace was obtained from elution of *S*-**60** from a derivatized polysaccharide (inherently chiral) column, only to reveal that it is identical with the racemic compound **60**, with only

minor changes in retention times (Figure 23, 6.477 min (1.3 %), 6.923 min (93.6 %), 7.792 min (5.1 %): a 1:72:4 ratio). Given that use of racemic **59** could give six stereoisomers upon complexation (some of the stereochemical combinations produce identical compounds), and homochiral *S*-**59** could give only two stereoisomers (discounting atropisomerism in both cases), the two HPLC traces would be expected to be very different (assuming complete resolution). There is also the possibility that the stereocenters, homochiral or not, were unable to influence the separation of isomers on the HPLC column utilized, which, considering the goals of the complexation of analogous bis(dipyrromethene) ligands, is equally discouraging for the separation of diastereomeric complexes constructed from such homochiral ligands.

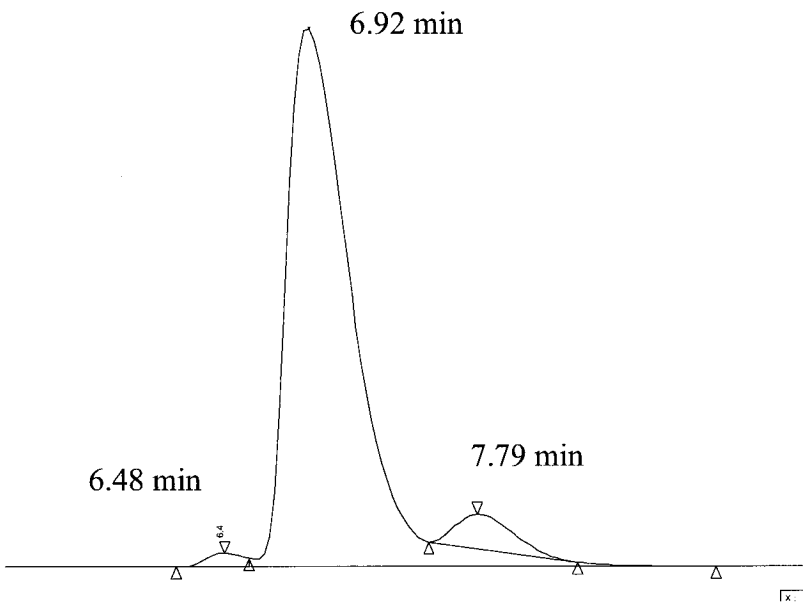
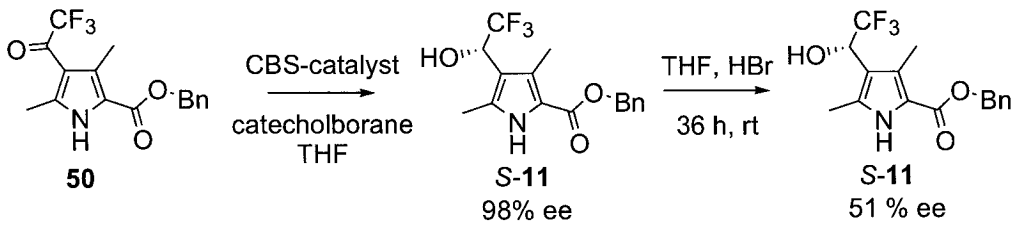


Figure 23: HPLC separation of *S*-60 with a chiral column

Literature precedence supports the stability of the trifluoro hydroxyethyl chiral center under acidic conditions,[73-75] but by reason of the HPLC results obtained with **60**, the potential racemization of the stereocenter was investigated with *S*-**11**. *S*-**11** was subjected to acidic conditions in THF over 36 hours in the presence of one equivalent of water, thus simulating the reaction conditions for the condensation of *S*-**58** with **15** (Scheme 39). Significant racemization occurred under these reaction conditions as observed by HPLC with the ee after treatment with acid being 51% versus 98% for the

starting material. This racemization must be compounded during the synthesis of *S*-**59** due to the absence of the electron-withdrawing group in pyrrole *S*-**58**, as required for the coupling of the homochiral pyrrole with **15**. The absence of the electron-withdrawing group would allow the comparatively electron-rich pyrrole *S*-**58** to more efficiently eject the leaving group to form a *β*-azafulvenium ion. The azafulvenium intermediate would then accept water as a nucleophile from either the *re* face or *si* face of the transient external olefin to form a racemate. Due to the lack of *direct* evidentiary support, however, it is inaccurate to infer that racemization did indeed occur in the synthesis of the ligand. The circumstantial evidence stated above can be used to surmise that the ligand thought to be homochiral *S*-**59** *may* have, at least partially, racemized, due to the observation of only a very small molar elipticity in compound *S*-**60**.



Scheme 39: Racemization of *S*-11

The three peaks observed by HPLC for *S*-**60** were separated. However, NMR spectra of the material eluted at 6.5 and 7.8 minutes (Figure 23) indicate that these peaks are, in all probability, not stereoismers of *S*-**60**, as they have peaks (such as β-free proton resonances) that should not occur in any isomer of *S*-**60**. If diastereomers were isolated as minor peaks from the HPLC separation performed on *S*-**60**, it would not be unexpected to see different resonances for diastereotopic groups and/or protons but the chemical shifts that are observed indicate that the compounds isolated are unrelated structurally. Also, NMR spectra obtained from a sample prior to preparative scale HPLC separation and a subsequent sample of the combined bands isolated from the eluted mixture (as seen in Figure 23) show the same pattern of proton signals. The HPLC separation is therefore that of a major compound (*S*-**60** and its corresponding stereoisomers) from associated contaminants constructed during the synthesis of a metal(II) complex. This simple comparison experiment (HPLC versus NMR spectroscopy) illustrates that the relative

ratios of major to minor products are falsely-represented on the HPLC trace and that the NMR spectrum of an apparently pure compound is deceptive at best. The ratio obtained in the HPLC traces assumes many factors are constant, one of the more important being the assumption that extinction coefficients of the three eluted compounds are the same at the wavelength in question. A difference in the magnitude of the extinction coefficients of the three compounds isolated from the chiral separations of both **60** and *S*-**60** would lead to inherently inaccurate integration of the sample and so all components of the separation would need to be corrected with respect to the extinction coefficient of the molecules under scrutiny. In other words, HPLC analysis does little to clarify what the isomeric ratio of complexation might be for complex **60** or *S*-**60** and so the three postulates (*i*)- all of the isomers elute within the major peak, (*ii*)- single compound with doubleting in the NMR spectrum, and (*iii*)- atropisomerism originating from the ^{13}C NMR spectrum of **60**, are no closer to being clarified. With chiral HPLC apparently not being able to resolve the isomers of the complex, it is extremely difficult to draw a definitive conclusion regarding the three postulates.

Investigation of complex stability: UV-VIS

The separation of *S*-**60** (major peak) from unidentified compounds (two minor peaks) using preparative-HPLC separation technology has important implications with regard to the purity of the complex. The presence of these unidentified compounds indicates either the existence of competing chemical pathways in the synthesis of *S*-**60** or a small degree of sensitivity of *S*-**60** to the environments the complex was exposed to during any chemical and/or analytical manipulation. The establishment of identical NMR spectra before and after preparative-HPLC separation rules out the possibility of decomposition on the HPLC column. Thus, concurrent with these initial HPLC separations, a UV-VIS study ensued to investigate suspected decomposition of complex **60** in chlorinated solvents.

As already mentioned **60** was synthesized in methanol and, upon completion of the reaction, the mixture could either be diluted with water and the product isolated as a precipitate, or extracted into DCM for drying and isolation. The extraction with chlorinated solvent yields an orange solution that, upon concentration, yields an orange reaction product. It is expected that **60**, or any other dipyrromethene complex, should retain this distinctive orange colour after exposure to solvents used during an extractive work-up. This has been untrue for compound **60** and a precipitative work-up (addition of water to the reaction) became the method of choice. A visual indication of decomposition was the retention of a dark residue on the surface of glassware after concentration and re-solvation of the complex in hexanes. The complex was re-synthesized, isolated and exposed to non-spectrophotometric grade DCM with the intention of performing a UV-VIS study under these conditions. Initial UV-VIS spectra conducted with non-spectrophotometric grade DCM proved to be important due to independent observations[121] involving the detrimental effects of chlorinated solvents upon some zinc(II) dipyrromethene complexes. It was noticed within this work that the λ_{max} indicative of complex was concentration-dependant in non-spectrophotometric grade DCM and it was thought that this discovery was potentially a general problem to dipyrromethene complexation during the work-up stage of the reaction.

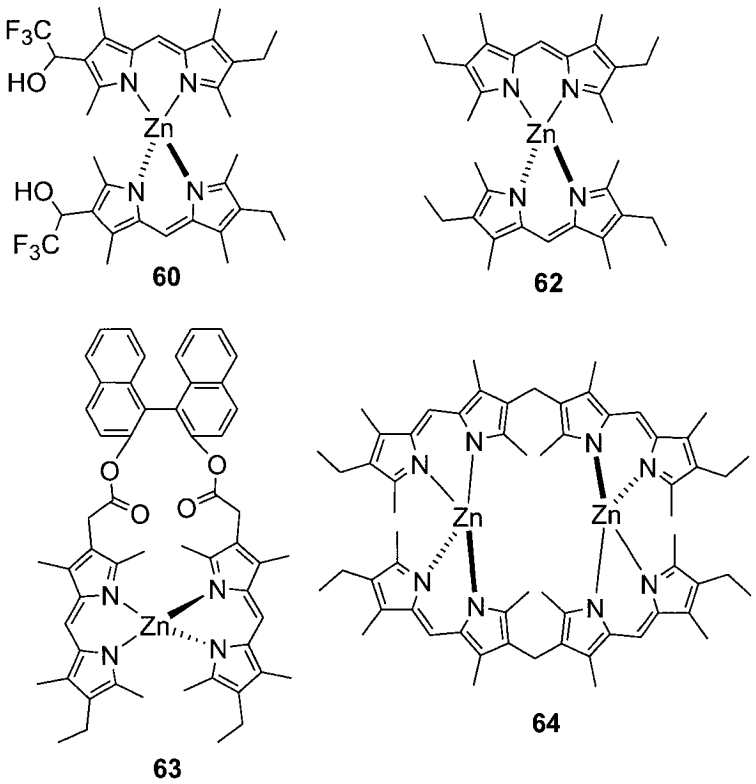


Figure 24: Compounds studied with UV-VIS

Complexes that were studied utilizing UV-VIS spectroscopy are illustrated in Figure 24. Structural variations among the dipyrromethene ligands consisted of a dipyrromethene complex with an electron-withdrawing group on the dipyrromethene ligand (**60**), a dipyrromethene complex with aliphatically substituted ligands (**62**)[122] a dipyrromethene complex with tethered ligands (**63**),[78] and a bis(dipyrromethene) complex (**64**).[122]

The non-spectrophotometric grade DCM influenced the spectra of three of the compounds studied in this brief survey. There was a concentration-dependent blue shift of the λ_{max} in each of the spectra concerned with **60**, **62**, and **63**. The blue shift of the λ_{max} was thought to coincide with the formation of ligand from complex through an unknown mechanism, seemingly because of contaminants present in the non-spectrophotometric grade DCM.

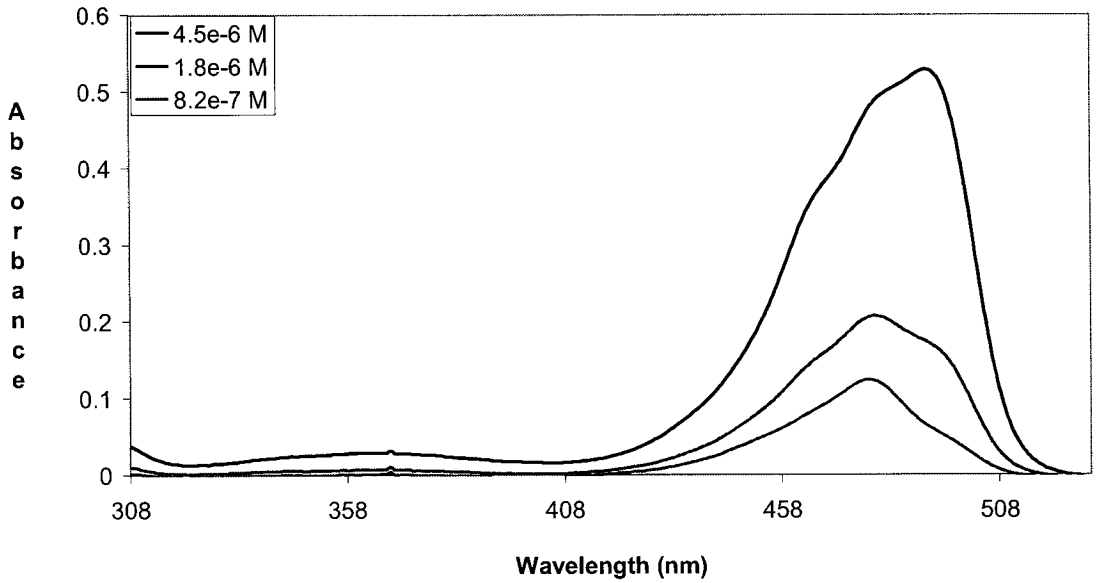


Figure 25: UV-VIS spectra indicating the maximum absorbance of complex 60 with varying concentration

Serial dilution of a stock solution (to a range of $4.5e^{-6}$ M - $8.2e^{-7}$ M) of **60** initiated a more pronounced blue shift of λ_{max} as dilution increased (Figure 25). In addition to the occurrence of a blue shift in the UV-VIS spectra of **60** at low concentrations, it was noticed that the solution of **60** at $4.5e^{-6}$ M displayed indications of blue-shifting over time (Figure 26). Thus, once a solution of complex **60** was made, and diluted to the appropriate concentration, reproducibility of the UV-VIS spectra of complex in non-spectrophotometric grade DCM was impossible and a concentration curve could not be reliably constructed.

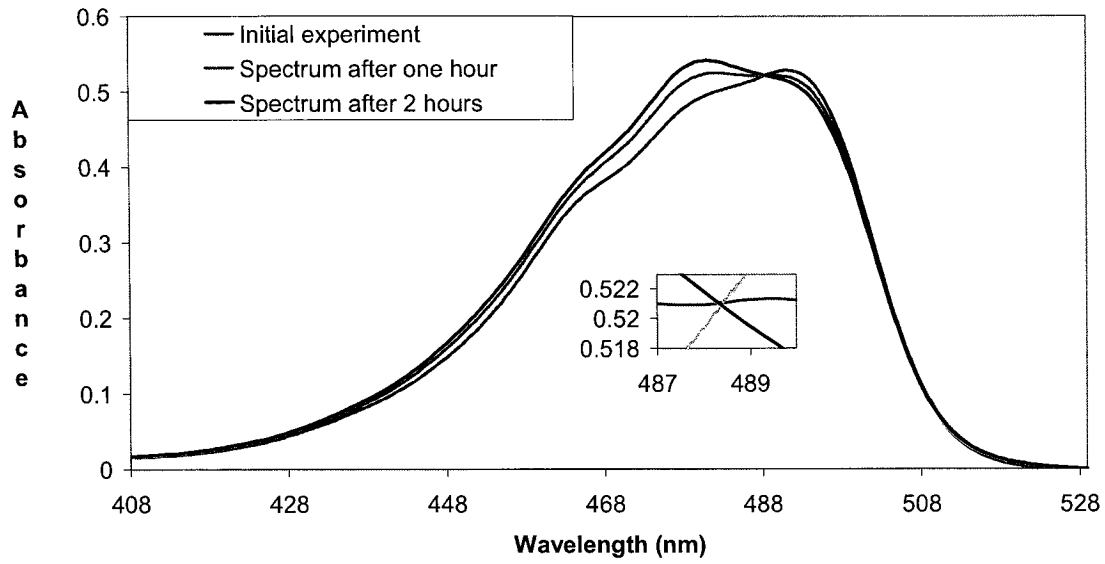


Figure 26: Overlay of UV-VIS spectra of 60 at 4.5e^{-6} M at different time intervals

One hour after the initial dilution of a solution of **60** to 4.5e^{-6} M the UV-VIS spectrum had changed significantly, and this change was even more pronounced at two hours. The overlay of the curves corresponding to the initial experiment, and the subsequent spectra after one hour and two hours were overlayed for comparison. The presence of an isosbestic point was suspected upon observing the initial overlay of the three time derived spectra of the same solution. Upon closer examination, however, there is a slight deviation of the spectrum taken after one hour from the intersection point of the other two traces. The cuvette in which the solution was maintained was not air-tight and so some of the non-spectrophotometric grade DCM may have escaped the cuvette, increasing the concentration and thus the absorbance of the sample and so the existence of an isosbestic point is still suspected. In a similar study within the Thompson laboratory the complexation of a dipyrromethene ligand through titration with small aliquots of zinc(II) acetate produced a trace overlay with similar topography to that shown in Figure 26. The lack of an isosbestic point within this study prompted an NMR study in search of a UV-VIS "unobservable" intermediate preventing the direct equilibrium between ligand and complex.[44]

An independent sample of **60** was kept in the dark for two hours in order to briefly examine the light dependence of the chromatic shifting of the UV-VIS trace upon dilution. After two hours in the dark, the shape of the resulting curve was the same as that observed with exposure to light, thus light was probably not a primary cause of the decomposition of **60** during the time-frame of the investigation. It must be noted that there is no complete spectroscopic proof in this work that can rule out the formation of heteroleptic complexes (as no UV-VIS spectrum was attained for such a species) but the existence of heteroleptic complex in solution has been demonstrated in the Thompson laboratory through NMR spectroscopic techniques.[44] Based on the UV-VIS values of the λ_{max} for both ligand and complex it is, however, it was most probable that the blue-shifted value for the diluted complex was due to ligand.

Another interesting occurrence that was observed during the course of the UV-VIS experimentation with dilute solutions of **60** in non-spectrophotometric grade DCM was the reconstitution of complex, and subsequent red shifting of the UV-VIS spectra, upon addition of TEA (Figure 27). The suspected decomposition is therefore pH dependant, and reversible upon the addition of base. The question that arose as a consequence of the basic reconstitution of **60** was: if indeed there is a conversion process in this solvent system (non-spectrophotometric grade DCM), and the reaction is acid/base dependant, then what is the source of acid?

Perhaps the acid can be traced to contaminants in the unpurified DCM solvent that are capable of oxidizing, or assisting in the oxidation of DCM to phosgene (minute amounts), which upon exposure to traces of water on the surface of glassware, or in the DCM solvent itself, can disproportionate to carbon dioxide, water and hydrochloric acid. The stability of the complex at high concentrations, or perhaps more correctly, the reduced capacity to observe decomposition readily at high concentrations is because of the high dilution of the limiting hydrochloric acid reactant. To prove that the dilution/decomplexation event was not an equilibrium under the conditions to which **60** was exposed the $8.2e^{-7}$ M solution was concentrated. Concentration of the dilute $8.2e^{-7}$ M solution of **60** did not cause a red shift in the absorbance of the dissolved compound,

which rules out an equilibrium, as there is an absence of a suitable base to reverse the process and convert the compound back to complex.

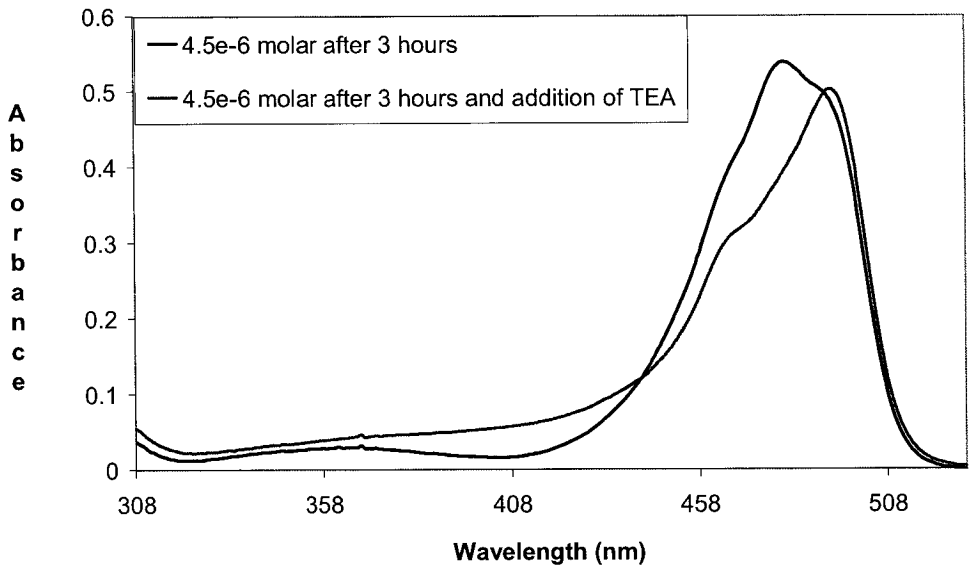


Figure 27: Effect of TEA addition on the UV-VIS spectrum of 60 at 4.5e-6 M

60 was not the only dipyrromethene complex that exemplified a concentration dependence of λ_{max} as similar results were observed for other complexes in non-spectrophotometric grade DCM. Solutions of compound **62** also underwent a blue-shift upon dilution (Figure 28). The ligand required for the synthesis of **62** has a λ_{max} of 486 nm, which can be observed as a shoulder in the UV-VIS spectrum of **62**. The addition of TEA to the solution containing the assumed mixture of compounds, presumably **62** and its parent ligand, recedes the shoulder observed at 486 nm in the original UV-VIS spectrum of the complex (Figure 29).

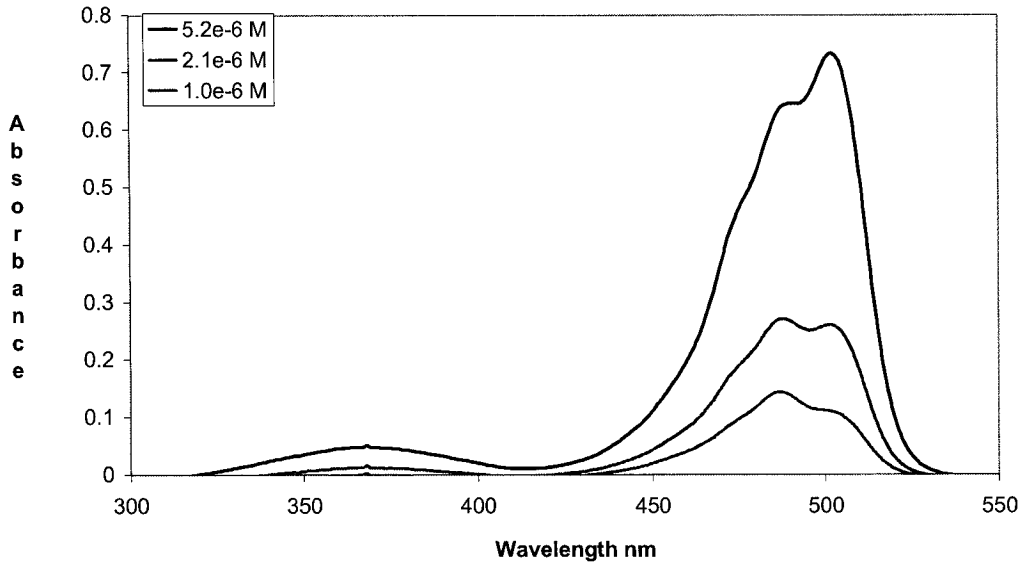


Figure 28: Solutions of compound 62 in non-spectrophotometric grade DCM undergo a blue shift

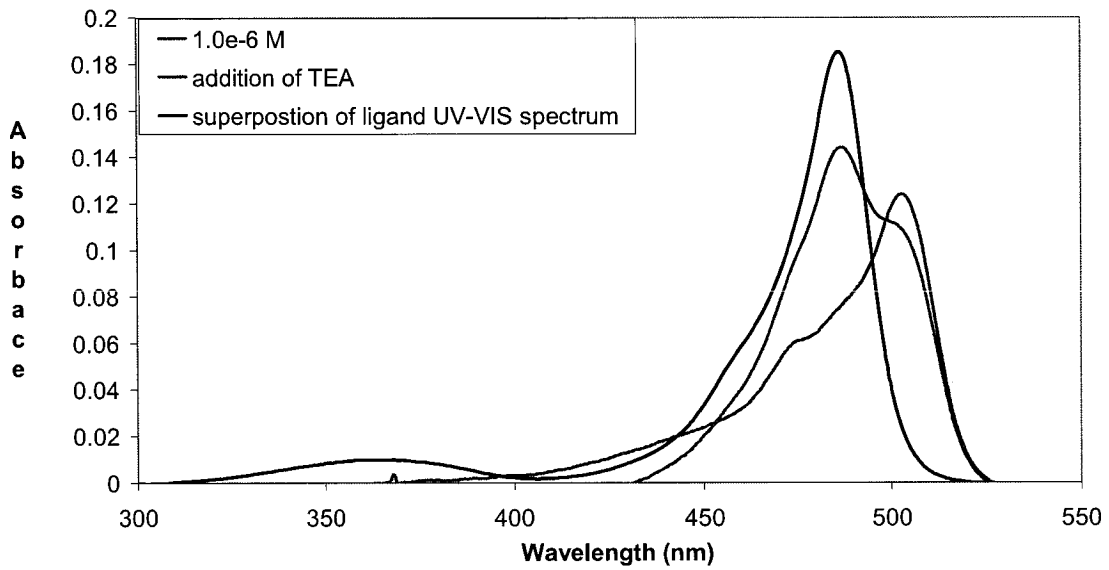


Figure 29: Complex 62 at dilute concentration and the effect of added TEA. A spectrum of pure ligand is superpositioned for comparison

Tethering of the dipyrromethenes through a linker of some description has an effect on the stability of the subsequent zinc(II) complex. The length of the spacer in the ligand used to synthesize **63** pre-determines the nature of the complex formed, which is a

monomeric/monometallic structure.[51] The shortening of such a tether, such as that seen in compound **64**, greatly enhances the stability of the dimeric/dimetalic complexes. No spectroscopic changes were observed upon dilution of **64** in non-spectrophotometric grade DCM, nor upon the addition of TEA to the dilute solution.

Complex **63**, a monomeric/monometalic complex, is also seemingly more stable than **60** or **62** in non-spectrophotometric grade DCM, and did not a display tendency for the significant loss of absorbance at a long wavelength (509 nm, not the λmax) but did show an increase at this wavelength when TEA was added (Figure 30). The confirmation of the conversion of complex to ligand, and vice-versa, is difficult in this case because the free ligand displays an absorbance that is typical of dipyrromethenes but the absorption spectrum of the complex is somewhat unique, and very different to that of **60** and **62**. Compounds **60** and **62** have a small, but characteristic, shoulder at 469 and 475 nm, respectively, but the tethered monomeric complex, **63**, displays a λ_{max} at 474 nm. The consequences of this observation are, as of yet, unknown but the variation in the spectra may be due to an intramolecular electronic transition between ligands and/or, in the case of **63**, the tethering group itself. Similarly, the bis(dipyrromethene) complex **64** shows a distinct maximum at 477 nm that may be indicative of electronic transitions that are similar to that observed in **63**, with the λmax in **64** occurring at 522 nm (Figure 31).

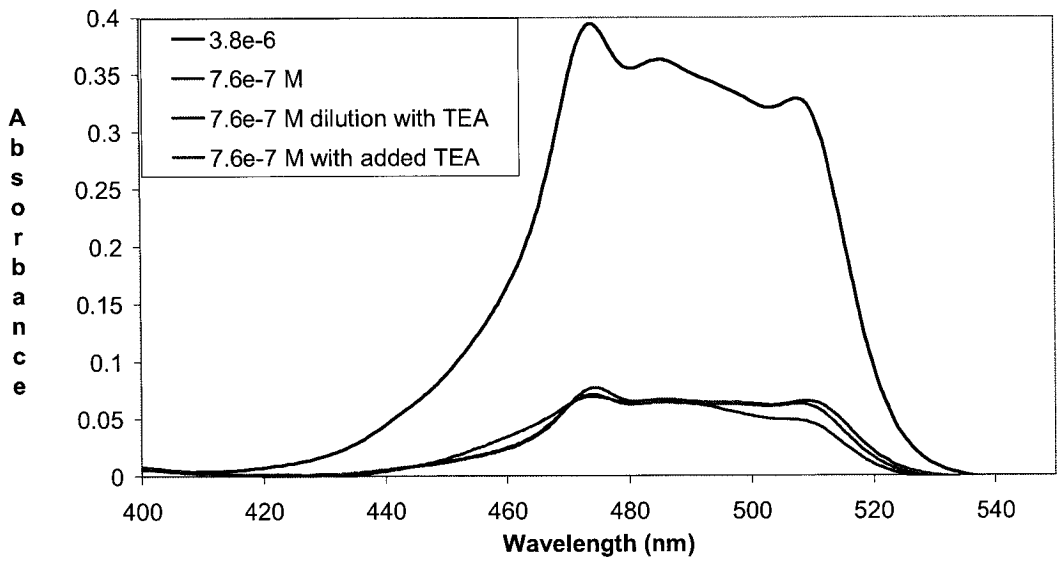


Figure 30: UV-VIS spectra of 63 at different concentrations

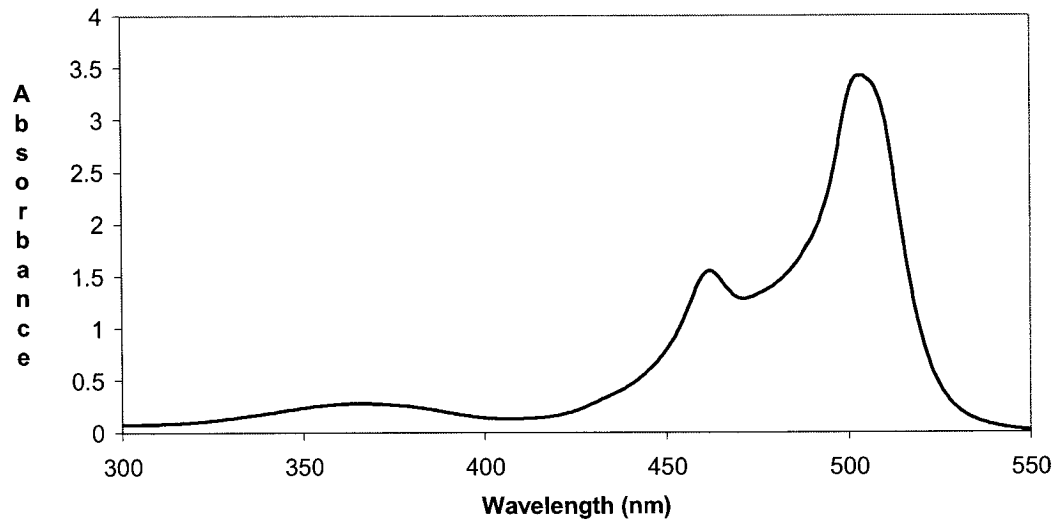


Figure 31: UV-VIS spectrum of the ligand used in the construction of 64

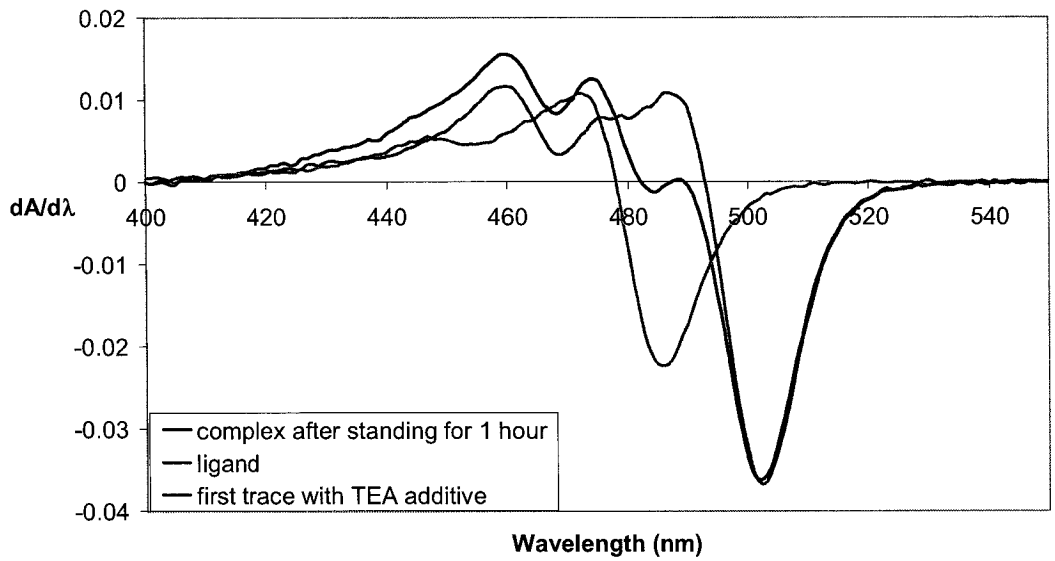


Figure 32: First derivative spectra for complex 60 after one hour. A spectrum of complex titrated with TEA and a spectrum of the ligand are included for comparison

Taking the first derivative of spectra for complexes **60**, **62-64** is a convenient method to visualize the occurrence of shoulders, maxima, and minima in a UV-VIS spectrum and is useful in the comparison of ligand, complex, and mixed UV-VIS spectra.[123] Analysis of these spectra allows one to see more accurately the differences and similarities between the discussed spectra. First derivative spectra for **60** are shown in Figure 32. The differences between first derivative traces of dilute complex and the dilute complex in the presence of TEA titrant occur in the location of the points that corresponds to the absorption maxima. In the case of the complex with added TEA, the x-intercept at 493 nm is indicative of a complex absorption maximum while the corresponding point in the complex solution with no added TEA (i.e. the original solution) is blue-shifted, due to the presence of ligand, to 490 nm. The intermediary positioning of the complex between both the ligand and the complex solution with added TEA is therefore evidence for a mixture of compounds in solution. In other words, the blue-shifting of the complex absorption maximum (and the red shifting of the ligand absorption maximum) in non-spectrophotometric grade DCM is due to a summation of two absorption spectra of two compounds present in solution.

Additionally, information involving the shoulder that is often seen in the spectra of dipyrromethene complexes can be obtained from the first derivative spectrum. The location of the minimum at around 468 nm (value obtained from the first derivative spectrum) can be attributed to the observed shoulder in the UV-VIS spectra of **60** where the slope is at its minimum grade.

Work-up of reaction mixtures containing complexes **60**, **62-64**, usually involves exposure of the reaction mixture to an aqueous wash followed by extraction with a non-spectrophotometric grade chlorinated solvent. The above UV-VIS work provides compelling evidence for the instability of some dipyrromethene complexes in low quality chlorinated solvent. In contrast to the above observations, dipyrromethenes dissolved in spectrophotometric grade DCM do not demonstrate the behavior that is observed for the low quality solvent. The importance of the lengthiness of exposure (exposures greater than two hours) of **60** in high quality chlorinated solvent was not determined in this work as prolonged exposure of these complexes to chlorinated solvent is not anticipated. Switching the solvent to a non-chlorinated system such as methanol was beneficial as the unpurified methanol (technical grade) available within the Department of Chemistry at Dalhousie University is either of sufficient quality, or methanol in general is insufficiently acidic, such that the decomposition of dipyrromethene complexes is not promoted. Switching between non-spectrophotometric grade methanol and spectrophotometric grade methanol therefore had no effect on the outcome of complexation as observed by UV-VIS spectroscopy.

Solutions of **60** were exposed to weak protic acids in both spectrophotometric grade DCM and methanol. The major observed difference in the effects of the exposure of **60** to weak protic acids in spectrophotometric grade DCM, and any grade of methanol, is the differential stability of the complex in either solvent. The addition of acetic acid to a solution of **60** in spectrophotometric grade DCM had no effect on the stability of the complex, whereas the addition of acetic acid to a solution of **60** in methanol caused the complex to revert to ligand. The decomposition reaction could subsequently be reversed, and complex reformed, through titration with TEA. Acetic acid is presumably of

insufficient strength in an aprotic medium (DCM) to elicit the decomplexation of ligand in **60**, whereas the protic solvent (methanol) allows for the existence of an efficient proton transfer mechanism that ensures the decomplexation of **60**.

Spectroscopic characterization of ligand and complex is important as the UV-VIS spectra obtained for ligand and metal complex are very different. Complexation of a dipyrromethene ligand results in a red shifting of the λ_{max} absorption signal, which is particularly useful in determining if the attempted complexation was successful. One should be wary of over-interpreting the UV-VIS spectra of dipyrromethene complexes as such spectra are by no means a measure of the completeness of the reaction and such things are best accomplished with methods such as proton-detected ^{15}N NMR spectroscopy.[124]

AN ALTERNATIVE APPROACH TO BIS(DIPYRROMETHENES)

Throughout the course of the above research interesting opportunities arose to investigate some projects in a preliminary way. Investigations into the synthesis of 3,3′-dipyrrylethane, with aspirations to strategy (*iii*) in Figure 15, bis(dipyrromethene)s utilizing pyrrolinones were undertaken, as were the α-acyloxylation of aldehydes and ketones.

Introduction of fluorine into the aliphatic chain of a 3,3′-bisdipyrromethene was desired in order to protect a stereogenic hydroxyl-functionalized carbon from the lone pair of a proximal pyrrole ring.[74,75] A convenient reagent to use in this reaction was commercially available in the form of ethyl bromodifluoroacetate. The most common use of ethyl bromodifluoroacetate is in the Reformatzky reaction for the synthesis of α-difluoroalcohols.[125] A major problem with reactions involving a difluoro-enolate compound, derived from ethyl difluoroacetate, is the tendency for the self-coupling of the reagent at the reactive carbonyl carbon.[126] However, the deoxygenation of a Reformatzky product with two α-fluoro compounds is typically difficult due to the inductive electronic effects introduced by the fluorine atoms.[125] The literature has provided some precedence for the use of ethyl bromodifluoracetate in an organometallic cross-coupling reaction.[82,125-131]

The Ullmann reaction in its original form was a coupling of aryl halides to form symmetrical bi-aryls at high temperatures.[132] Since the inception of the Ullmann reaction there have been many modifications and improvements such as the development of Cu(I) reagents that allow for the coupling to take place at much lower temperatures.[133] Reactions closely related to the Ullmann reaction involving the coupling of aryl compounds under anionic conditions usually involve transmetalation from silicon or tin to copper.[133] Copper also provides a route to the coupling of aryl halides to heteroatoms.[133] The wide range of coupling reactions that are available provided encouragement for the utility of copper in the coupling of ethyl bromodifluoroacetate with a pyrrole.

This project was envisioned to synthesize a homochiral ligand with a hydroxy substituent appended to the stereogenic center, which was to be located in the linker. As previously discussed at the beginning of the synthesis of a ligand concerning goal (*ii*), Figure 15, the desirable attribute of a hydroxyl group was its ready derivatization, which makes it possible to greatly change the steric profile of the chiral group.

A retrosynthetic analysis of the 3,3′-dipyrroethanone **65** that is needed for the synthesis of a suitable ligand suggested that Friedel-Crafts acylation of the appropriate acid chloride (derived from the carboxylic acid) with a β-free pyrrole would be the synthetic strategy of choice (Figure 33). The corresponding pyrrole carboxylic acid would be derived from the appropriate difluoroacetate ester and a β-unsubstituted pyrrole. Copper-catalyzed cross-coupling of fluorinated reagents has been developing as a method to utilize anionic fluorocarbon reagents in the chemical manipulation of halo-aryl compounds but until work by Burton the utility of reagents like trifluoromethyl copper was unreliable.[134] Fortunately, difluorinated acetates have also shown promise as methyl iododifluoroacetate was used in cross-coupling reactions of pyridine, haloolefins, and benzene derivatives were quite successful.[126-128]

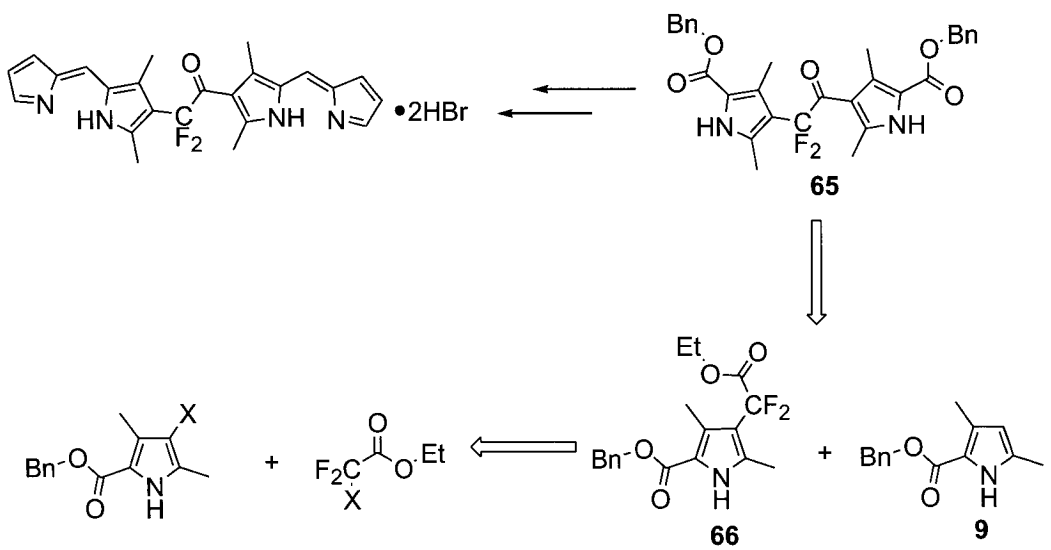
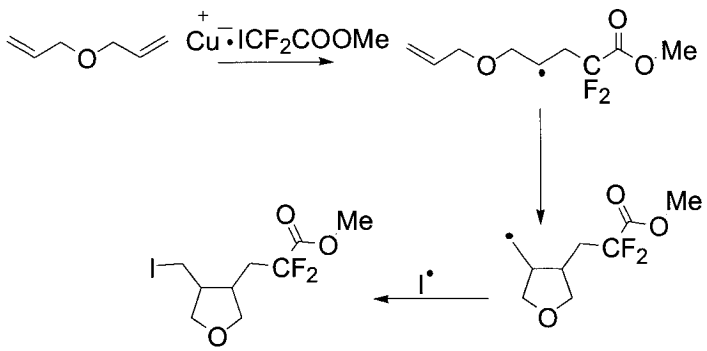


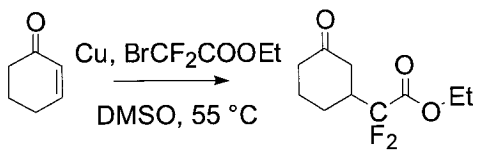
Figure 33: Retrosynthesis of 65

There are differing opinions on the mechanism of the copper coupling of aryl halides with halodifluoroacetate esters. Kobayashi noted the stability of the methyl iododifluoroacetate-copper adduct to be greatest in HMPA with a half-life of forty hours.[127] It was also noticed that the reactivity of methyl bromodifluoroacetate was markedly less than that of methyl iododifluoroacetate in DMSO under the specified conditions.[126] In addition to the stability of the reagent in polar solvents it was postulated by Kobayashi and co-workers[127] that the reaction proceeded *via* a radical pathway, supporting the work of Teguchi.[128] As an indication of the radical mechanism of the copper coupling reaction, diallyl ether was cyclized to a tetrahydrofuran derivative containing both the difluoroester moiety and a captured iodine atom (Scheme 40).[128]

Scheme 40: Differing mechanisms displayed by copper cross coupling of an α-fluorinated ester



Kobayashi's radical cyclization



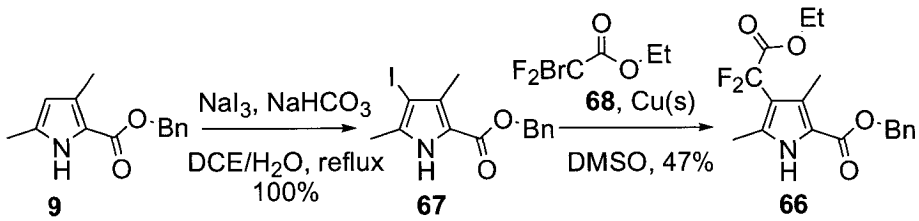
Michael addition may promote evidence for anionic mechanism

Work done by Kumadaki and co-workers with ethyl bromodifluoroacetate has contradicted the results obtained by Kobayashi. The use of ethyl bromodifluoroacetate in the elaboration of α,β-unsaturated ketones by the copper-derived reagent of the bromodifluoroacetate shows its tendency toward 1,4-addition (Scheme 40).[129] The 1,4-addition pathway was attributed to the anionic nature of the reagent and therefore an

ability to react analogously to other organocuprate reagents.[129] The isolation of an anionic copper salt derived from methyl iododifluoroacetate was accomplished as part of the work involving the radical chain mechanisms of Kobayashi. The yield was low but as a result of the isolation of the anionic copper salt, an anionic pathway for some reactions with this reagent cannot be ruled out.[128] Also, the order of addition was found to be important with ethyl bromodifluoroacetate coupling reaction. The addition of the acetate to copper prior to the haloolefin resulted in simple halogen exchange between the ethyl bromodifluoroacetate and the haloolefin.[82]

The ethyl bromodifluoroacetate reagent was utilized most effectively in DMSO with both haloolefinic and haloaryl compounds. Kumadaki's work with this reagent was a clue to the extension of the copper cross-coupling chemistry of ethyl bromodifluoroacetate to pyrroles.[82,129] In addition to the bromodifluoroacetate coupling, classical Ullmann self-coupling has been achieved with pyrrole to yield 2,2′-bispyrrole.[135] It was noticed in the self-coupling of pyrroles that the presence of electron-withdrawing groups on the starting material increased the yield of the Ullmann reaction.[135] A similar boost in yields during the coupling reaction was noticed with the reaction of *p*-nitroiodobenzene and ethyl bromodifluoracetate.[82] The copper-mediated coupling reaction of 2-halopyridines with ethyl bromodifluoroacetate was proven to be high yielding and facile due to its electron-deficient aromatic nature (*c.f.* benzene).[131] Due to the apparent success of an electron-deficient system under copper-catalyzed coupling conditions, it was decided that **67** would be suitable for the synthesis of pyrrole **66** (Scheme 41).

Scheme 41: Synthesis of a potential precursor to 65

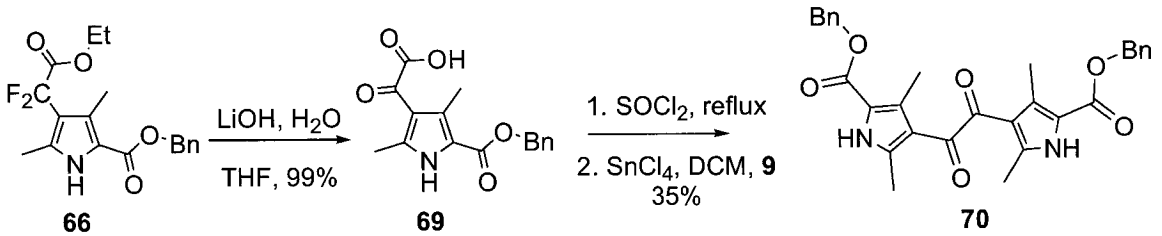


Success in the application of the copper cross-coupling reaction between **68** and **67** was achieved under anhydrous conditions and the desired product (**66**) was obtained in 47 % yield. Examination of the TLC indicated quantitative conversion but work-up with a mild phosphate buffer may have been responsible for a reduced isolated yield of 47 %. The mild aqueous acidic work-up was used to dissolve the copper halide salts but may have caused problems by way of the unwanted hydrolysis of the ester thus reducing the yield. The fluorine atoms alpha to the ethyl ester would render the carbonyl carbon more electrophilic and thus more sensitive to aqueous conditions. Utility of **66** in the construction of a bis(dipyrromethene) was to involve basic hydrolysis of the ester followed by synthesis of an acid chloride and reaction with a β-free pyrrole under Friedel-Crafts conditions.

The product of the ester hydrolysis of **66** was used as obtained without characterization, and after the completion of the Friedel-Crafts reaction, it was revealed that the NMR spectrum of the isolated product lacked the expected ^{19}F signals: no signal was observed using ^{19}F NMR spectroscopy, the ^{13}C NMR spectrum lacked coupling that is characteristic of the presence of fluorine. Furthermore, the ^{13}C NMR spectrum contained an extra carbonyl signal. These results lead to the hypothesis of hydrolysis of the fluorine-carbon bond under the basic aqueous conditions during the ester hydrolysis used to form the oxalyl pyrrole derivative **69** (Scheme 42). Literature sources revealed that the attempted synthesis of a difluoro-(indol-3-yl)-acetic acid ended in similar failure. Middleton[136] inferred that the hydrolysis of the carbon-fluorine bonds of the difluoro-(indol-3-yl)-acetic acid, producing the oxalyl derivative, was a result of the conjugated nitrogen lone pair. Similarly the lone pair in the pyrrole molecule can encourage the elimination of fluorine, a notoriously poor anionic leaving group, in exchange for a

hydroxyl group. The dihydroxy compound could then rapidly dehydrate to form the oxalyl substituted pyrrole **69**. Subsequently, compound **70** was obtained as a result of the Friedel-Crafts acylation.

Scheme 42: Synthesis of an unwanted 3,3'-dipyrroethandione



A nucleophilic fluorinating agent such as DAST could have been used to salvage the oxalyl substituted pyrrole but the re-isolation of a desired difluoro-compound may have lead to further hydrolysis further along the synthetic route. The failure to maintain fluorine substitution within the linker was disappointing. In future efforts, compound **66** must be handled under non-aqueous conditions. After the reduction of the carbonyl center, it is probable that the hydroxyl functionality will be susceptible to the same fate of the hydroxy ethyl pyrrole, **6**, due to the ready loss of the fluorine atoms. A new route to a 1,2-[3,3'-dipyrrolyl]-ethane is thus needed.

Conclusions and some useful alternatives

The introduction of many electron-withdrawing substituents severely modifies the usual nucleophilic nature of pyrrole and, akin to monosubstituted pyrroles such as 2-formyl pyrrole, substitution of pyrrole at a position adjacent to an electronic-withdrawing group is difficult. Kumadaki and co-workers have established the chemistry involved in the elaboration of hydroxyl trifluoroethyl pyrroles but have never attempted a coupling at the 5,5'-positions of two pyrroles such as **28**.[75] It is hypothesized that the 5-position of the pyrroles containing the trifluoroethanol group are electron-poor when compared to the more traditional pyrrole architecture and are therefore less susceptible to electrophilic attack. In addition to the problematic coupling chemistry with pyrroles akin to **58**, the stability of a stereocenter that is substituted with both an alcohol and a trifluoromethyl

group and attached directly to a pyrrole ring was suspect as ligand *S*-**59** and complex *S*-**60** failed to display any chiroptical tendencies that are shared with other homochiral molecules. Given the difficulty experienced with the attempted chemical synthesis of a bis(dipyrromethene) ligand it may be necessary to apply a different strategy to the same end, utilizing an alternative chiral auxiliary.

Lightner and co-workers have explored the preferred conformation of an enantiomerically pure biliruben analogue through the utility of a chiral pyrrole available through the Knorr reaction.[48,137,138] The natural biliruben XIIIα molecule is a symmetrical molecule that prefers a ridge-tile conformation due to the hydrogen bonding of a propanoic acid side-chain with the oxygen of the pyrrinone and the pyrrole/pyrrinone hydrogen atoms in bilidiene skeleton.[48] The hydrogen bonding motif of biliruben elicits a helical motif in which the molecule can exist, in equal frequency, as either a *P* or *M* helix (Figure 34).[48]

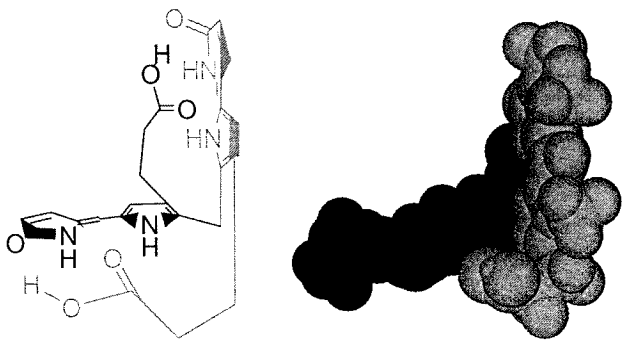
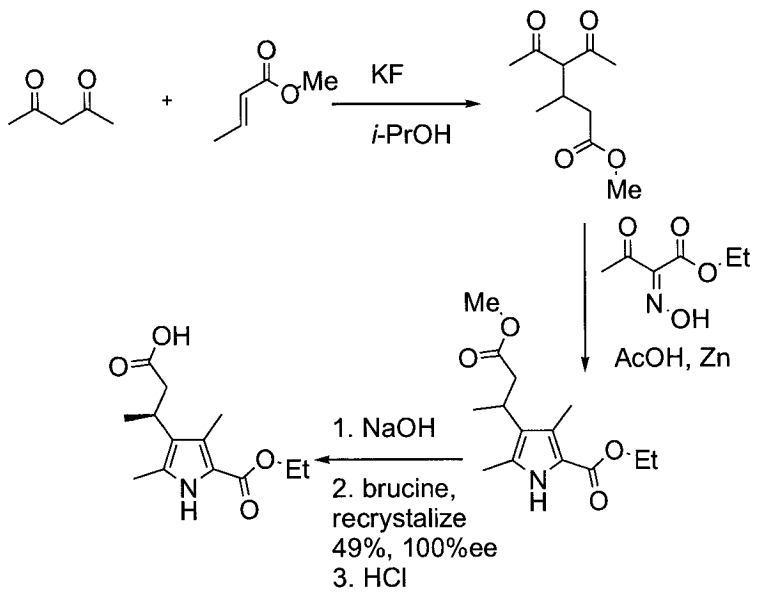


Figure 34: Biliruben in its *M*-ridge-tile conformation

The synthesis of a homochiral pyrrole, as a tool to elicit a helical preference of the resulting analogue of biliruben XIIIα, was undertaken by Lightner through the derivation of the propanoic ester side-chain of the natural tetrapyrrole. Thus, a pyrrole monomer containing a homochiral butanoic acid side-chain was fashioned. The homochiral pyrrole monomer was synthesized *via* the Knorr reaction as a racemate that was resolved, after saponification of the butanoate ester, using (-)-brucine hydrate (Scheme 43). Recrystallization of the diastereomeric salt, followed by re-acidification, resulted in the isolation of the homochiral pyrrole carboxylate in 49 % yield and 100 % ee.[48]

Elaboration of the pyrrole monomer to the chiral biliruben was followed by a study of the stereochemical properties of the isolated molecule.[48] ^{1}H NMR spectroscopy supported the presence of hydrogen bonding while CD spectra provided supporting evidence for the homochiral helical nature of the biliruben XIIIα derivative ridge-tile conformation.[48] An inherent problem with this non-convergent approach is not in its usefulness, or lack thereof, but in the necessity of a new synthesis should one wish to change the size and/or nature of substituents on the stereocenter.

Scheme 43: Synthesis and resolution of a chiral pyrrole by Lightner and co-workers



Yet another means to synthesize homochiral pyrroles is *via* the MacMillan imidazolidinone iminium catalyzed 1,4-additions to aldehydes.[139] An advantage to this phenomenal methodology is the use of pyrrole or *N*-methylpyrrole as a starting material. The implication of pyrrole as a starting material is firstly that the reaction is comparatively cheap, secondly the pyrrole used is going to be reactive and thus any chemistry to be done after the synthesis of the homochiral pyrrole should be straightforward. A disadvantage to the MacMillan chemistry is in the lack of suitable pyrrolic architecture that is viable for this reaction. Any molecule that is electron deficient relative to pyrrole is not a good substrate as the LUMO of the iminium ion is still too high in relative energy to react with the stabilized HOMO of an electron deficient pyrrole.[139]

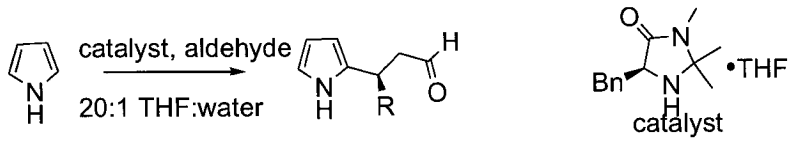
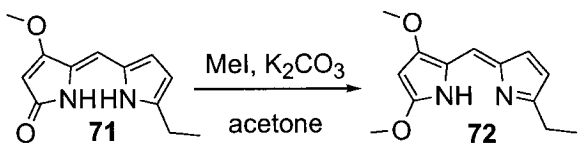


Figure 35: MacMillan imidazolone catalyzed enantioselective Friedel-Crafts reaction

A NEW ARCHITECTURE OF BIS(DIPYRROMETHENES) FROM PYRROLINONES

The synthesis of alkoxypyrroles from pyrrinones was accomplished in the 1960's via oxoniumtetrafluoroborate salts (no base necessary) or dialkyl sulfates in the presence of hydroxide.[140] The original method for the selective alkylation of the amide oxygen in a dipyrrinone involved the use of trimethyl oxoniumtetrafluoroborate.[141] Triflation chemistry has also been used to produce prodigiosin precursors for the purposes of Pd catalyzed coupling.[8,9] Thus, much of the existing work that accomplishes the derivatization of the carbamate oxygen of a dipyrrinone has usually been done under acidic conditions. The alkylation of such compounds under basic, nucleophilic conditions has also been observed.[142,143] In view of Scheme 44,[142] the alkylation of **71** to yield **72**, under basic conditions, could possibly be extended to the construction of more complicated dipyrromethene free-bases. Difunctional electrophiles such as 1,3-diiodopropane extend the possibility of constructing bis(dipyrromethene) ligands from dipyrrinones under basic conditions. Enhanced electron-donating ability of a hypothesized pyrrolyl ether family of bis(dipyrromethene) ligand should allow further means of tuning the binding capabilities of the dipyrromethene ligand and allow for a method to create new architectures with this format.

Scheme 44: Melvin and coworkers synthesis of a dipyrromethene free-base

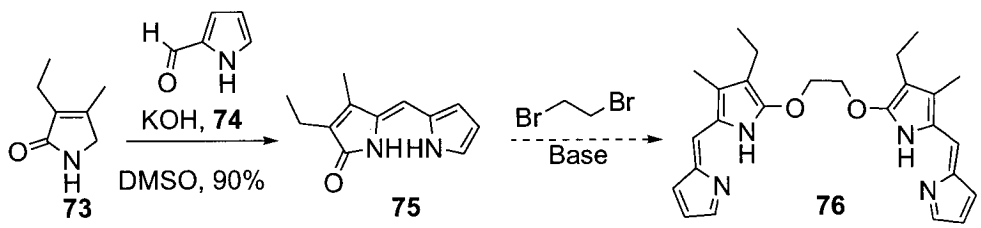


The synthesis of bis(dipyrromethene)s utilizing dipyrrinones as a starting material has not been reported. Methods that involve the condensation of formylpyrroles with α-

free pyrroles are far more common. Acid-catalyzed condensation of α-free pyrroles with formylpyrroles necessitates the isolation of product as an H-halogen salt; salts cannot be purified by chromatography but rather are precipitated from solution. Synthesis of reported dipyrrinones, from pyrrinones and formyl pyrrole precursors, have thus far been isolated as free-base compounds and purified by column chromatography or preparative TLC.[141,143] The major synthetic advantage of the isolation of the free-base is thus purification. Ease of isolation through the precipitation of a salt (by acidifying the reaction with the appropriate acid) should still be possible should this step become necessary. Preliminary results regarding the synthesis of dipyrromethenes (and bis(dipyrromethenes)) utilizing this approach has seen mixed but encouraging results. Substitution under basic conditions has indeed been successful but is subject to the isolation of multiple products (with monofunctional electrophiles) or internal cyclization products (difunctional electrophiles).

The proposed synthetic route for dipyrromethenes from dipyrrinones (**75**) starts with an aldol condensation involving **73** and **74** to produce a dipyrrinone (**75**) that bears likeness to any dipyrromethene with regards to connectivity and conjugation. Extension of the dipyrrinone system to a bis(dipyrromethene) is based on nucleophilic substitution chemistry involving the oxygen of the pyrrolinone ring as a nucleophile (Scheme 45). If the electrophile is difunctional, then one can anticipate joining two dipyrrinones through the oxygen atoms, thus producing a bis(dipyrromethene), **76**.

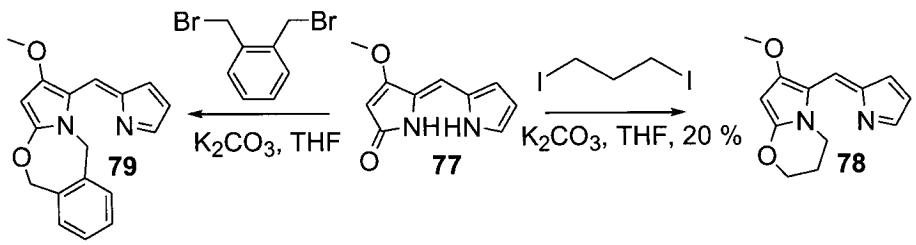
Scheme 45: Synthesis of a bis(dipyrromethene) using a pyrrolinone



It was envisioned that reaction of **77** (**77** was used initially as it is easier to synthesize than **75**) with an electrophile such as 1,3-diiodopropane would allow for the formation of the required ligand. Upon initial isolation of the product it was postulated

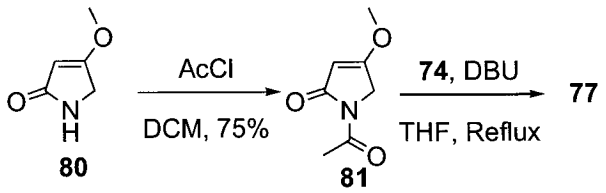
that this compound was in fact a dipyrromethene with an *O*-alkyl chain terminated with an iodo substituent. This was proven to be the incorrect structure after attempted derivatization, through endeavoring to synthesize the bis(dipyrromethene), and a subsequent closer investigation of the ^{1}H NMR spectrum indicated that the closed ring system, **78**, was obtained, in 20 % yield (Scheme 46). This architecture, although interesting, is not useful for our complexation work due to its lack of a bidenticity. Reaction of **77** with an α,α'-dibromo-orthoxylene is thought to have produced **79**, according to analysis of the NMR spectrum of the crude reaction mixture (a pure sample could not be isolated).

Scheme 46: Attempted synthesis of a bis(dipyrromethene) free base with a pyrrolinone



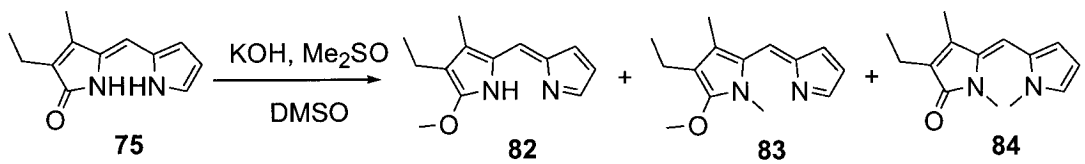
Attempts were made to *N*-protect the pyrrolinone, **80**, before reaction with 2-formylpyrrole. This was achieved with acyl chloride to give **81** in 75 % yield. Reaction of this protected amide with 2-formyl pyrrole (**74**) under basic conditions resulted in the unprotected product, **77**, as seen in Scheme 47. Reaction of the *N*-protected γ-lactam with formyl pyrrole under acidic conditions may be of use as the aldol coupling would occur through an enol equivalent and, barring the use of a nucleophilic solvent, the *N*-acyl protecting group should survive. Alternatively, the use of an α,α'-dibromo-paraxylene derivative would render internal cyclization impossible and the isolation of bis(dipyrromethene) probable, thus alleviating the need for protecting group chemistry.

Scheme 47: *N*-Protected pyrrolinone



Insight into the above results came from construction of a set of molecules needed for a collaborative study.[144,145] In synthesizing molecules needed to probe the mechanism of the anti-oxidant properties of biliruben, several *N'*, *N*, *O*, (*N'*,*N*) and (*O*, *N'*) alkylated dipyrrinones were needed (where *N'* refers to the amide nitrogen). It was decided that synthesis of the dipyrrinones under basic, nucleophilic conditions was prudent in order to facilitate the synthesis of many of these derivatives in one pot.[143] Dipyrrinone **75** was used as a substrate in the presence of potassium hydroxide, DMSO, and dimethyl sulfate. Under conditions utilizing limiting amounts of electrophile (dimethyl sulfate) the ratio of products obtained was: 3.2:3.5:1.0 for **82**, **83**, and **84**, respectively. When excess electrophile was used, only products corresponding to **83** and **84** were obtained, both in higher yield as a 1.0:1.8 ratio. The *N*-monomethyl product was prepared by the reaction of **75** with 1-methyl-pyrrole-2-carboxyaldehyde in the presence of potassium hydroxide and DMSO because the dipyrrinone product could not be isolated simply by mixing the dipyrrinone **75** with base and electrophile.[144]

Scheme 48: Product distribution in dipyrrinone alkylation

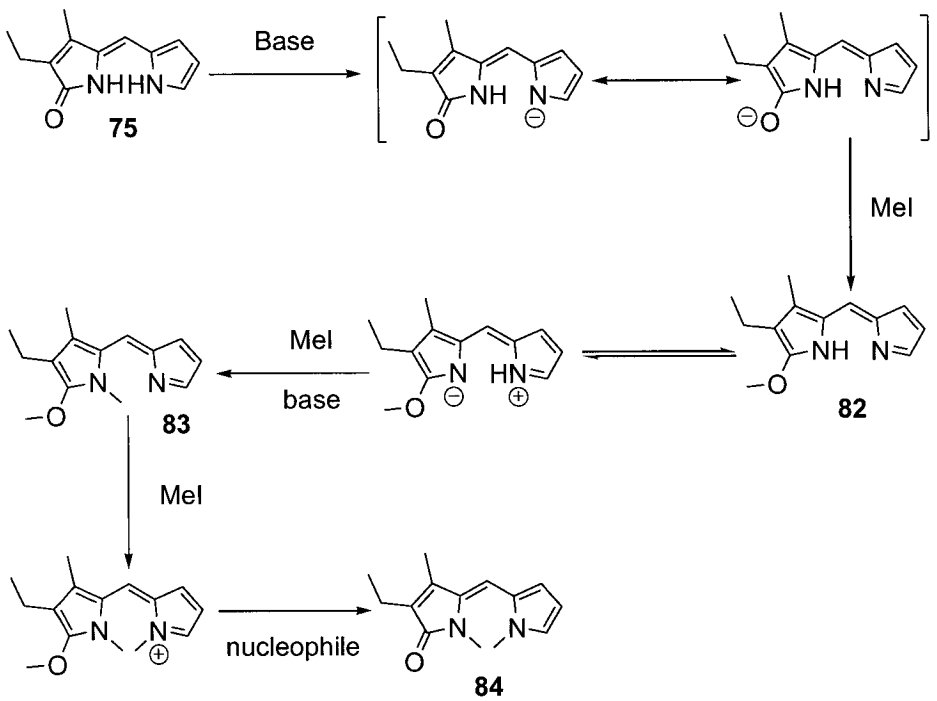


0.5 eq Me_2SO_4	19%	21%	6%
2.6 eq Me_2SO_4		24%	44%

The results of this study, in conjunction with the literature and other results obtained internally, have lead to a hypothesis towards the mechanism of addition of an

electrophile to a dipyrrinone under basic conditions, as seen in Scheme 49. Under stoichiometrically limiting conditions with respect to the alkylating agent, the dipyrrinone tends toward oxygen alkylation; the only mono-alkylated product was the *O*-methyl ether, the molecule containing the *N*-methyl group had to be prepared separately. The best route to the *N,N'*-bisalkyl product, **84**, is through the presence of an excess of electrophile. After the initial alkylation of the amide oxygen and the amide nitrogen, the addition of an electrophile to the *2H*-pyrrole nitrogen, would result in a formal positive charge, related to oxygen through resonance in this conjugated system. The presence of a nucleophile could result in the removal of the methyl group from the methyl ether, due to its oxonium character. The overall result of this is to create a molecule that is stable, non-charged, and both rings are in their more stable *1H*-pyrrole/lactam configuration. The only variable changed in these reactions was the number of equivalents of alkylating agent. Thus, with this study, oxygen alkylation should be preferred over *N*-alkylation, provided that there is no mechanism for the equilibrium of the alkylated species.

Scheme 49: Proposed mechanism of dipyrrinone alkylation under basic conditions

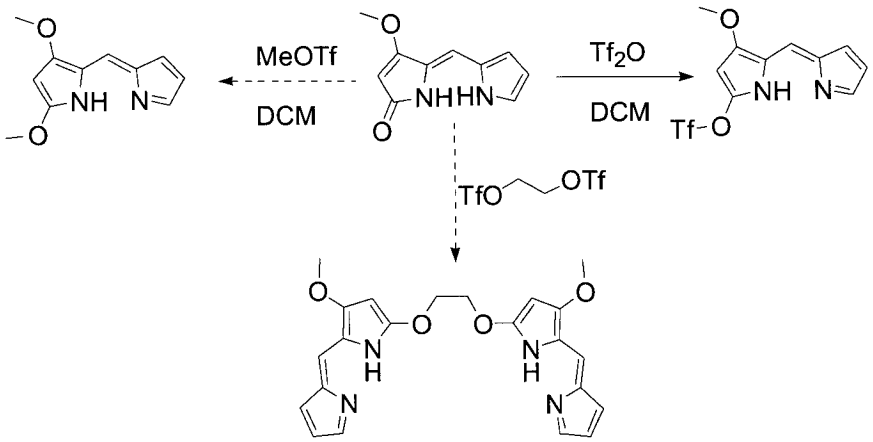


Use of a stronger base along with a more strongly binding cation and a less polar solvent, may encourage *O*-alkylation. A problem with any attempt to halt bis-alkylation

of **75** is the proximity of the *2H*-pyrrole lone pair to the new alkoxy pyrrole proton of **82**. The molecule **82** is expected to be planar and the enhancement of the pyrrole hydrogen pK_a through interaction with the *2H*-pyrrole moiety could lead to **83**. Although the outcome of this reaction was amenable to the production of many different derivatives of dipyrrinone **75** and thus its use in the synthesis of compounds for the study of biliruben structural analogues,[144] its overall usefulness in the construction of bis(dipyrromethene)s, tethered through the oxygen, is questionable. Due to the goals of this project, the synthesis of a dipyrrinone derived bis(dipyrromethene), prevention of the formation of an intramolecular bisalkylation product under basic conditions may only be achieved through initial protection of a pyrrolinone nitrogen. A more suitable protecting group than the already attempted *N*-acyl will be necessary. Alkyl protecting groups may be useful in this regard but ease of deprotection will ultimately result in the selection of a different protecting group, silyl protecting groups perhaps, as alkyl groups can be difficult to remove.

The use of a different electrophile in the dipyrrinone chemistry would be advantageous. Currently, under the basic conditions that were utilized, there are problems with the selectivity of the alkylation as well as unwanted intramolecular reactions that interfere with the desired outcome. The triflation of a dipyrrinone has already been shown to proceed to completion both in the literature [9] and in the Thompson laboratory (Scheme 50).[146] The acidic conditions involved in this triflation procedure predetermine the substitution of the electrophile at the oxygen of the dipyrrinone. It is thus hypothesized that the action of methyl triflate, analogous with trimethyloxonium tetrafluoroborate[141], on a dipyrrinone would enhance the outcome of the desired alkylation via a pathway that does not require the initial deprotonation of the dipyrrinone. Furthermore the elaboration of more exotic alkyl triflates has been reported in the literature[147] and this could allow for the synthesis of oxygen bound bis(dipyrromethene)s.

Scheme 50: Synthesis of a bis(dipyrromethene) from a dipyrrinone under acidic conditions



α-ACYLOXYLATION OF CARBONYL COMPOUNDS

During the summer of 2003 an opportunity to participate in a student exchange with the University of Cardiff (UK) presented itself. The student exchange project that was assigned by Dr. Tomkinson, the host professor at the University of Cardiff, was the synthesis of an acyloxyammonium hydrohalide salt. After a condensation reaction with an appropriate carbonyl compound, these acyloxyammonium hydrohalide salts were expected to effect the acyloxylation of the carbonyl compound *via* an aza-Claisen rearrangement. Results reported hereafter are only preliminary results obtained during the three months of the student exchange. Extension of this preliminary work by other graduate students within the Tomkinson laboratory has resulted in two publications that illustrate more efficient, optimized conditions for α-acyloxylation of carbonyl compounds.[148,149]

Recently there has been an increased interest for metal-free processes in organic chemistry.[150] Metal-free processes are expected to be both economically accessable and environmentally benign, thus benefiting both academic and industrial research programs.[150] The α-hydroxy carbonyl functional group is a prevalent architecture in many natural products (eg. fumagillol) and so there is a desire to utilize methods that can introduce this functionality chemoselectively, regioselectively, and enantioselectively.[149] The use of enolate chemistry and electrophilic oxidizing agents, for example the oxidation of enol ethers with dihydroxylating or epoxidizing reagents, are among the now

standard methods utilized to introduce the α-hydroxy carbonyl functionality.[151,152] At the forefront of the α-hydroxylation technology is the α-aminooxylation reaction,[153] which introduces a protected alcohol, enantioselectively, with proline as an organo-catalyst.

In 1969, a report was published by House that demonstrated the synthesis of α-acetoxycyclohexanone (Figure 36).[154] The synthesis of this compound was a five-step protocol which included the formation of the oxime derivative, followed by *O*-acylation and then *N*-alkylation to form the imminium ion. This iminium ion was then treated with TEA, causing the rearrangement of the iminium ion to the α-acetoxy imine, *via* an aza-Claisen rearrangement, which was hydrolyzed under mild acidic conditions to yield the α-acetoxycyclohexanone. This lengthy transformation was shortened by Coates[155] and this truncated method was utilized by Sørensen and co-workers in the synthesis of fumagillol.[156] It was thus postulated that the sigmatropic transformation could be achieved in a single step under acidic conditions (the past transformations were accomplished under basic conditions in the presence of TEA) utilizing an appropriate acoyl-amine hydrochloride reagent.

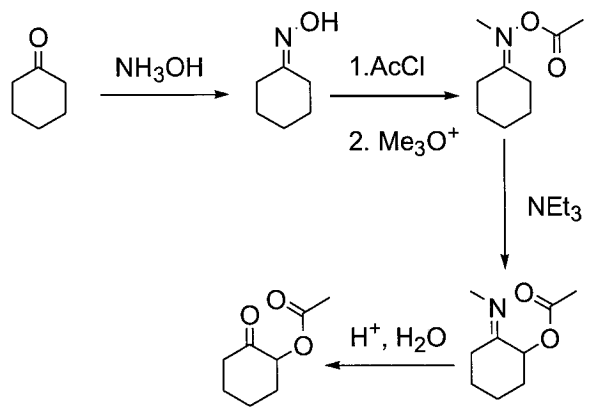
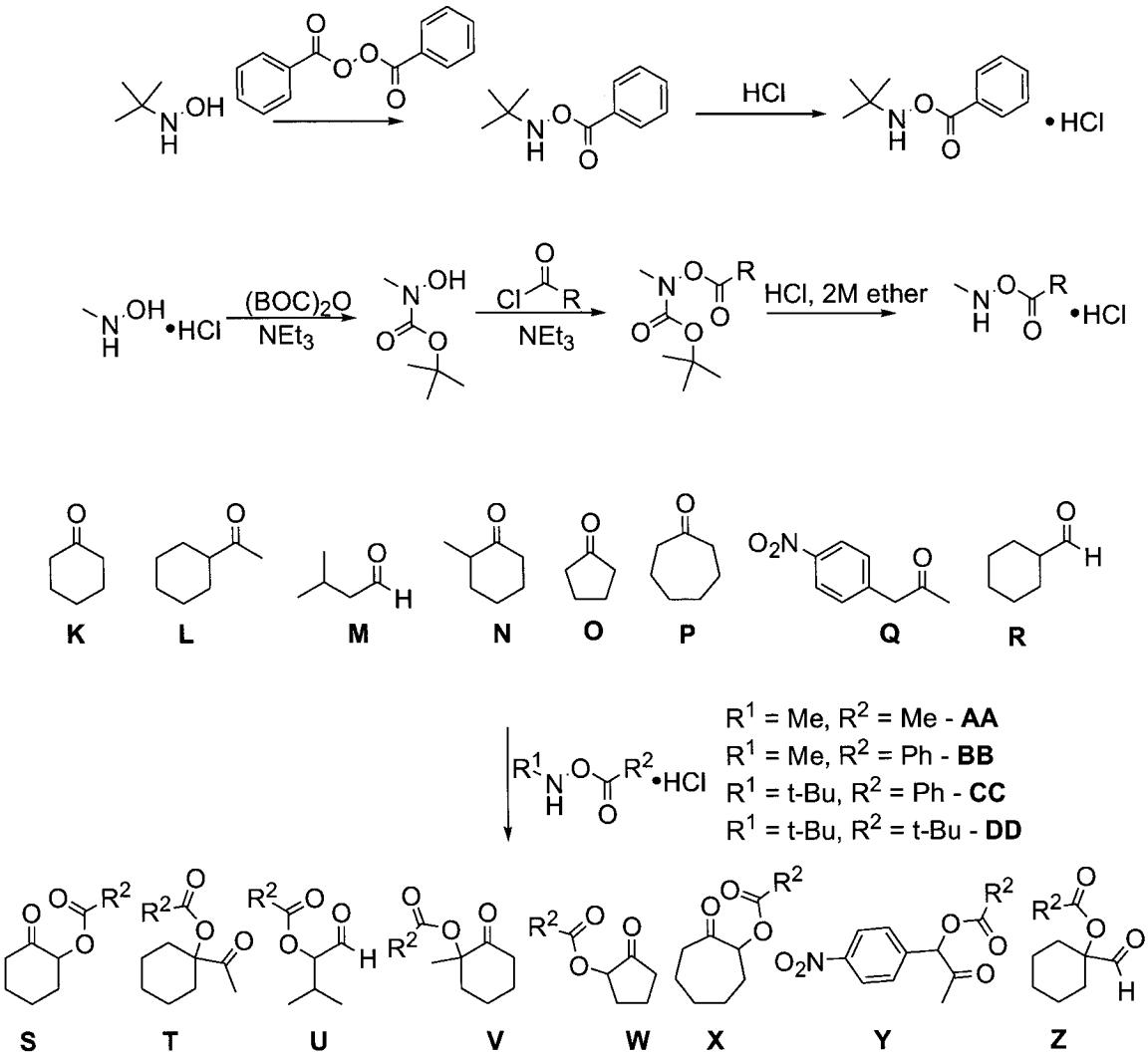


Figure 36: Reaction sequence accomplishing α-acyloxylation as described by House

With the above syntheses in mind it became the goal of this project to develop a reagent capable of performing the acyloxylation reaction in one pot and the reaction of this reagent with a variety of carbonyl compounds was also desirable. The preparation of the requisite acyloxylation reagent was accomplished in two ways. First, *N*-*t*-butyl-hydroxylamine was used in the synthesis of *N*-*t*-butyl-*O*-benzoyl hydroxylamine

hydrochloride through reaction of the amine starting material with benzoyl peroxide followed by isolation of the *O*-benzoyl hydroxylamine and acidification with HCl. Second, *N*-methyl hydroxyl amine hydrochloride was used in the synthesis of *N*-methyl-*O*-acoyl-hydroxylamine hydrochloride. The syntheses of these compounds were lengthier than that just described for the *N-t*-butyl-*O*-benzoyl hydroxylamine hydrochloride due to the necessary protection of the nitrogen with a BOC group prior acylation of the oxygen with the appropriate acid chloride. After protection and acylation, the desired *O*-acoyl-hydroxylamine hydrochloride salt was obtained by treating the *N*-methyl-*N*-BOC-*O*-acoyl hydroxylamine with ethereal hydrogen chloride. The desired hydrochloride salt precipitated from the reaction and upon isolation, *via* filtration, was ready for use in the α-acyloxylation reaction. A graphical representation of all the acyloxylation reagents and substrates follows in Scheme 51 and the results obtained during this student exchange are summarized in Table 3.

Scheme 51: A depiction of reactions accomplished or attempted in construction of acyloxylation reagent and oxidation of selected ketones and aldehydes



Although difficulties were experienced with the optimization of reaction conditions, the results obtained herein have proved to be quite promising. Cyclohexanone and cycloheptanone were adequate substrates for the transformation (Table 3 - entries 3-6 and 18). The preliminary endeavor toward the acyloxylation of 5-membered rings was not successful (Table 3 - entries 7-9). The pericyclic rearrangement was also more efficient with secondary (Table 3 - entries 1-6, 10-12, and 18) versus primary or tertiary carbons (Table 3 - entries 7-9, and 20), the exception being the isolation of a protected tertiary alcohol that was the result of the rearrangement of the acyloxy transfer reagent upon condensation with 2-methylcyclohexanone (Table 3 - entry

13). Also in the published work, a few aldehydes that only presented a tertiary option were also efficient rearrangement substrates (cylcohexane carboxyaldehyde and a Diels-Alder adduct of acrolein and cyclopentadiene).[148] Much of these data were corroborated in the published work as most rearrangements occurred on secondary centers.[149]

Table 3: Results for some attempted acyloxylation reactions

Entry	SM	solvent	Temp (°C)	Reagent	product	yield
1	**K**	DMF	RT	**AA**	**S**	72
2	**K**	DMF/H_2O	RT	**CC**	**S**	0
3	**K**	CH_3CN	60	**BB**	**S**	78
4	**K**	THF	50	**BB**	**S**	70
5	**K**	THF/H_2O (9:1)	RT	**BB**	**S**	65
6	**K**	CH_3CN/H_2O (9:1)	60	**BB**	**S**	69
7	**L**	DMF	RT	**AA**	**T**	0
8	**L**	DMF	RT-100	**CC**	**T**	0
9	**L**	DMF	100-153	**BB**	**T**	0
10	**M**	DMF	50	**DD**	**U**	68
11	**M**	DMF	60	**DD**	**U**	52
12	**M**	DMF	100	**DD**	**U**	45
13	**N**	THF	50	**BB**	**V**	64*
14	**O**	THF	50	**BB**	**W**	0
15	**O**	THF/H_2O (9:1)	RT	**BB**	**W**	0
16	**O**	CH_3CN/H_2O (9:1)	RT	**BB**	**W**	0
17	**P**	THF	50	**BB**	**X**	0
18	**P**	THF/H_2O (9:1)	RT	**BB**	**X**	68
19	**Q**	CH_3CN	60	**BB**	**Y**	N/A**
20	**R**	CH_3CN	60	**BB**	**Z**	N/A**

* product was obtained as a 6:1 mixture of regioisomers favouring **Q**. ** product was observed by NMR spectroscopy only.

The utility of different acyloxylation reagents derived from different aminoalcohols provided a route toward chemoselective α-oxidation of aldehydes versus ketones.[148,149] The bulky *t*-butyl substituent on the *N*-*t*-butyl-*O*-acoyl hydrochloride reagents (**CC** and **DD**) precluded reactivity with ketones (Table 3 - entry 2) due to the unfavourable interaction of the *t*-butyl group and any functionality α to the carbonyl (Table 3 - entry 2).[149] As a result this particular family of reagents was only useful for the functionalization of aldehyde substrates as the low steric profile of the aldehydic hydrogen was able to facilitate condensation of the *t*-butyl substituted reagent, thus

allowing for the desired pericyclic rearrangement to provide the required α-acyloxy product (Table 3 - entry 10, **M**).[148,149] In order to rectify the reactivity issues with ketones it was necessary to replace the *N*-*t*-butyl substituent with a less sterically demanding functional group.[149] For this purpose an *N*-methyl group was decided upon and the resultant acyloxylation reagent **AA** was mixed with a ketone to give the desired α-acyloxylated product (Table 3 - entry 1). It must be noted that the *N*-methyl reagents also react with aldehydes (Table 3 - entry 20).

With respect to the ketone substrates, a high degree of regioselectivity was established in almost all cases, as it was observed that the rearrangement reaction occurred at the secondary carbon, with the exception of 2-methylcyclohexanone (Table 3 - entry 18). This was confirmed by further work in the Tomkinson laboratory with the utility of ketones containing both primary and secondary carbon atoms.[149] Only products containing the α-acyloxy substituent on the secondary carbon were obtained.

During this student exchange methods were developed towards the α-acyloxylation of ketones and aldehydes including the conception of a reagent that could distinguish between these functional groups. Reaction conditions were unoptimized during this study due to time constraints but armed with the proof-of-principle methods utilized in this short student exchange project workers were able to optimize and utilize, effectively, acyloxyamines in the α-functionalization of carbonyl compounds.[148,149]

CHAPTER 3: EXPERIMENTAL

General Experimental Procedures

Reagents: All reagents were purchased from Aldrich, phosphoric acid was used as purchased from Fischer Scientific and reagent grade acetonitrile was used as purchased from Caledon. Dry THF and DCM were obtained from an Innovative Technologies solvent purification system and stored under nitrogen in a storage bomb unless otherwise indicated. Dry ether was obtained *via* distillation from benzophenone sodium ketal, dry benzyl alcohol was obtained *via* fractional distillation from magnesium sulfate under nitrogen, and dry DMSO was purchased from Aldrich.

WARNING: $Zn(ClO_4)_2$ was used as a source of M(II) cation due to the non-ligating properties of perchlorate as a ligand. Perchlorate salts can be VERY oxidizing resulting in extremely exothermic/explosive conditions. Care should therefore be taken with the use of perchlorate salts in the presence of organic material.

Experimental procedure: Unless otherwise indicated all glassware was flame-dried under vacuum prior to use followed by a nitrogen fill. All acylations for the compound **51** series were accomplished according to a general experimental except compound **51d**, which was synthesized using the method outlined by Knight and co-workers.[93]

Analysis and Purification: Silica gel used for column flash chromatography was Silicycle Ultra Pure Silica Gel 60, 230-400 mesh. TLC was performed using Silicycle Ultra Pure Silica Gel 60 aluminum-backed plates, visualized under UV light, and stained using a vanillin-in-ethanol dip. Reported R_f values for compounds **82** to **84** are from TLC plates eluted with 1:4 ethyl acetate:hexanes.

Analytical instrumentation: UV-VIS spectroscopy was performed on a Varian Cary 100Bio dual beam UV-VIS spectrometer with the sample being held in quartz cuvettes with a standard pathlength of 1 cm. HPLC separations were performed on a Varian instrument composed of two ProStar 210 solvent pumps, a ProStar 330 photodiode array detector, a ProStar 410 autosampler, and a ProStar 701 fraction collector. The HPLC

column used for attempted chiral separations of dipyrromethene metal complexes **60** and *S*-**60** was the Chiralpak®-IA column composed of amylose tris(3,5-dimethylphenylcarbamate) with particle size of 5 μm; the analytical column had an ID of 0.46 cm and the preparatory column an ID of 2 cm with both columns having a length of 25 cm. The chiral analytical column used for the determination of *ee* in compound *S*-**11** was the Chiralpak® AD-RH, also composed of amylose tris(3,5-dimethylphynylcarbamate) but with a silica support; the ID of this column was (0.46 cm) and the length was 15 cm. NMR spectroscopy utilized Bruker Avance 500 MHz, AMX 400 MHz, and AC 250 MHz spectrometers at 300 K, as indicated in parentheses (note that carbon resonates at ¼ the frequency of hydrogen and 125 MHz thus denotes the Avance 500 magnet). All ^{19}F NMR spectroscopy was performed using the AC 250. All ^{1}H and ^{13}C chemical shifts (δ) are referenced to TMS at 0 ppm and are reported on the ppm scale and all coupling constants (J) are reported in Hz. ^{19}F NMR spectra were referenced to fluorotrichloromethane as an external standard at 0 ppm. All coupling constants are reported in Hz and multiplicities are reported as: s-singlet, d-doublet, t-triplet, q-quartet, p-pentet, spt-septet, dd-doublet of doublets, qd-quartet of doublets, bs-broad singlet, m-multiplet. Mass spectra were obtained using one of the following instruments: EI, Perkin Elmer autosystem XL GC with turbomass MS; High resolution EI, CEC 21-220B double focusing magnetic sector (Dupont); ESI/APCI, Thermo Finnigan LCQ-Duo iontrap. All measurements for X-ray crystal data were obtained utilizing a Rigaku AFC5R diffractometer with graphite monochromatic Mo-Kα radiation and a rotating anode generator by Dr. T. S. Cameron, of the Dalhousie University Chem X laboratory.

The following compounds are known and were obtained following literature procedures: **1**,[10] **2**,[157] **3**,[79] **4**,[79] **5**,[81,158,159] **7**,[10] **9**,[160] **11**,[73] *S*-**11**,[75] **15**,[47] **16**,[161] **17**,[73] **18**,[161] **19**,[73] **21**,[86,89] **22**,[89,90,162] **23**,[33] **27**,[75] **34**,[75] **35**,[75] **39**,[163] **40**,[90] **44**,[94] **50**,[75] **56**,[164] **64**,[165] **80**,[166-168] **81**.[169] Compound **27** was isolated as an oil in the original reference[75] but as a solid in this work with MP of 76-77 °C. The syntheses of **52**[164] and **53**[88] were achieved by utilizing hydrogenolytic conditions[51] from the corresponding benzyl esters: 3,5-dimethyl-pyrrole-2-ethylcarboxylate-4-benzylcarboxylate[170] (yields **52**) and **4** (yields **53**). Compounds

62,[124] **63**[78] and **64**[165,171] were constructed by other researchers in the Thompson Laboratory and were originally intended for different studies. Compounds **62**, **63** and **64** were thus kindly donated in order to help facilitate the completeness of the brief UV-VIS study of the decomposition of dipyrromethene Zn(II) complexes in non-spectrophotometric grade DCM.

Benzyl 1-benzyl-3,5-dimethylpyrrole-2-carboxylate (24)

A solution of pyrrole **9** (2.099 g, 9.15 mmol) in DMF (23 mL) was added to a suspension of sodium hydride (60 % dispersion in oil, 0.460 g, 11.5 mmol), also in DMF (23 mL), at 0 °C *via* cannula. After stirring the reaction mixture at 0 °C for 0.5 hours the ice bath was removed and benzyl bromide (0.750 mL, 6.31 mmol) was added at room temperature and the resultant mixture was stirred overnight. The reaction was quenched with a saturated ammonium chloride solution (10 mL, drop-wise at first then rapidly), followed by dilution with water (50 mL) and ether (75 mL). After separation of the organic layer, the water/DMF mixture was further extracted with ether (3 x 75 mL) and the combined organic layers were washed with water (3 x 100 mL) and brine (1x 50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was recrystalized from cold pentane to give the product as light orange needles (2.159 g, 74 %). MP 46-47 °C. δ_H (*250* MHz, $CDCl_3$) 2.14 (s, 3H), 2.33 (s, 3H), 5.20 (s, 2H), 5.55 (s, 2H), 5.86 (s, 1H), 6.88 (d, $J = 5$, 2H), 7.37-7.43 (m, 8H). δ_C (*125* MHz, $CDCl_3$) 12.5, 14.8, 48.6, 65.4, 111.6, 118.7, 125.9, 126.9, 127.9, 128.1, 128.5, 128.7, 130.7, 136.3, 136.6, 138.9, 161.7. EIMS *m/z* (%): 65 (55), 91 (100), 122 (90), 168 (18), 182 (19), 184 (21), 185 (30), 228 (30), 319 (M^+, 50).

Benzyl 1-benzyl -4-(2,2,2-trifluoro-1-hydroxyethyl)-3,5-dimethylpyrrole-2-carboxylate (25)

To a solution of pyrrole **24** (0.062 g, 0.19 mmol) in DCM (1.0 mL) was added solid zinc(II) chloride (0.05 g, 0.36 mmol) followed by a jet-wise addition of hemiacetal **10** (0.09 mL, 0.77 mmol). The resultant reaction mixture was stirred at room temperature

for 11 hours after which the green reaction mixture was treated with saturated ammonium chloride (5 mL) and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organic layers were washed with water (5 mL), dried over anhydrous sodium sulfate and concentrated. The crude material was triturated with pentane (to remove grease observed by NMR spectroscopy) followed by flash column chromatography on silica using a gradient elution with 3 % hexanes in DCM to neat DCM and finally to 20 % ethyl acetate in hexanes producing compound **25** as a colourless oil (0.043 g, 54 % yield). δ_H (*250* MHz, $CDCl_3$) 2.23 (s, 3H), 2.35 (s, 3H), 2.69 (d, J_{HH} = 5, 1H), 5.12 (qd, J_{HF} = 7, J_{HH} = 5, 1H), 5.27 (s, 2H), 5.51 (d, J_{HH} = 15, 1H), 5.57 (d, J_{HH} = 15, 1H), 6.85 (dd, J_{HH} = 7.5, J_{HH} = 2.5, 2H), 7.16-7.32 (m, 8H). δ_F (*235* MHz $CDCl_3$) -79.0 (d, J_{FH} = 7).

Benzyl 1-benzyl-2,5-dimethyl-4-(2,2,2-trifluoro-1-methoxyethyl)pyrrole-2-carboxylate (26)

Pyrrole **25** (0.13 g, 0.31 mmol) in DMF (3 mL) was added *via* cannula into a suspension of sodium hydride (0.012 g, 1.2 mmol) in DMF (3 mL) and, upon the cessation of effervescence, methyl iodide (0.038 mL, 0.48 mmol) was added rapidly, drop-wise. The mixture was stirred as such for 4.5 hours followed by decanting into ice water and extraction with ether (3 x 50 mL). The combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo*. Subsequent purification with silica gel flash chromatography, using 9:1 toluene to hexanes as eluent, gave **26** as a colourless oil (0.087 g, 64 %). δ_H (*400* MHz, $CDCl_3$) 2.20 (s, 3H), 2.36 (s, 3H), 3.36 (s, 3H), 4.67 (q, J_{HF} = 7, 1H), 5.20 (s, 2H), 5.53 (d, J_{HH} = 15, 1H), 5.62 (d, J_{HH} = 15, 1H), 6.85 (d, J_{HH} = 7.5, 2H), 7.17-7.26 (m, 8H). δ_C (*100* MHz, $CDCl_3$) 10.8, 11.8, 48.6, 57.6, 65.8, 76.0 (q, J_{CF} = 32), 111.6, 118.6, 119.5, 124.9 (q, J_{CF} = 280), 125.8, 127.2, 128.2, 128.7, 128.9, 130.18, 136.5, 136.6, 138.4, 161.7. δ_F (*235* MHz, $CDCl_3$) -77.2 (d, J_{FH} = 7).

Benzyl 5-acetoxymethyl-4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (28)

To an acetic acid (1.0 mL) solution of pyrrole **27** (0.051 g, 0.14 mmol) was added Pb(IV) acetate (0.066 g, 0.15 mmol) as a solid and the resulting mixture was stirred for 3.5 hours at 50 °C. An additional aliquot of Pb(IV) acetate (0.005 g, 0.01 mmol) was added to the mixture, which was stirred at 50 °C for the reaction to be complete as indicated by TLC after an additional hour of reaction. The mixture was then cooled and diluted with ethylene glycol (0.1 mL), to quench any remaining Pb(IV) acetate. The mixture was diluted with water (2 mL) and extracted with DCM (3 x 5 mL), the combined extracts were washed with saturated sodium bicarbonate (3 x 5 mL) followed by drying over sodium sulfate and concentrated. The title compound was isolated as a clear, colourless oil (0.059 g, 99 % yield). δ_H(*500* MHz, $CDCl_3$) 2.08 (s, 3H), 2.17 (s, 3H), 2.39 (s, 3H), 5.15 (d, J_{HH} = 15, 1H), 5.17 (d, J_{HH} = 15, 1H), 5.31 (d, J_{HH} = 12.5, 1H), 5.35 (d, J_{HH} = 12.5, 1H), 6.22 (q, J_{HF} = 7.5, 1H), 7.33-7.44 (m, 5H), 9.34 (bs, 1H).

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-chloromethyl-3-methylpyrrole-2-carboxylate (29)

To a solution of pyrrole **28** (0.054 g, 0.13 mmol) in DCM (1.0 mL) was added hydrogen chloride (2 M in ether, 6.3 μL) and the reaction mixture was stirred at room temperature overnight. The mixture was washed with 5 % aqueous sodium bicarbonate (3 x 2 mL) and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification was performed using a small column (Pasteur pipette) with DCM as eluent to remove baseline polar impurities, producing the title compound as a white solid (0.047 g, 99 % yield). δ_H(*500* MHz, $CDCl_3$) 2.25 (s, 3H), 2.44 (s, 3H), 4.68 (d, J_{HH} = 12.5, 1H), 4.84 (d, J_{HH} = 12.5, 1H), 5.39 (d, J_{HH} = 12.5, 1H), 5.41 (d, J_{HH} = 12.5, 1H), 6.28 (q, J_{HF} = 7.5, 1H), 7.38-7.47 (m, 5H), 9.76 (bs, 1H). δ_C(*125* MHz, $CDCl_3$) 10.6, 20.7, 36.5, 66.1 (q, J_{CF} = 35), 66.6, 113.8, 120.1, 123.7 (q, J_{CF} = 279), 128.0, 128.4, 128.6, 128.8, 131.2, 135.9, 161.3, 168.7.

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-methoxymethyl-3-methylpyrrole-2-carboxylate (30)

Pyrrole **29** (0.330 g, 0.82 mmol) was dissolved in methanol (10 mL) to which concentrated hydrogen chloride (35 % aq, 0.45 mL) was added and the mixture was to stirred overnight under reflux. After concentration of the mixture, purification was accomplished with flash column chromatography using 20 % ethyl acetate in hexanes as an eluent to give the title compound as a white solid (0.089 g, 27 % yield). δ_H(*500* MHz, $CDCl_3$) 2.14 (s, 3H), 2.40 (s, 3H), 3.37 (s, 3H), 4.51 (d, J_{HH} = 13.5, 1H), 4.54 (d, J_{HH} = 13.5, 1H), 5.30 (s, 2H), 6.21 (q, J_{HF} = 7.5, 1H), 7.31-7.41 (m, 5H), 9.40 (bs, 1H). δ_C(*125* MHz, $CDCl_3$) 10.7, 14.2, 58.7, 66.1, 66.1, 66.3 (q, J_{CF} = 35), 111.9, 118.8, 123.9 (q, J_{CF} = 279), 128.3, 128.4, 128.8, 128.9, 133.4, 136.3, 161.1, 168.7.

Benzyl 4-(2,2,2-trifluoro-1-hydroxyethyl)-5-methoxymethyl-3-methylpyrrole-2-carboxylate (31)

Isolated in conjunction with **30** as a more polar, slowly eluting compound (0.113 g, 40 % yield). MP 91-93 °C. δ_H(*500* MHz, $CDCl_3$) 2.33 (s, 3H), 3.40 (s, 3H), 4.25 (d, J_{HH} = 7, 1H), 4.37 (d, J_{HH} = 12.5, 1H), 4.69 (d, J_{HH} = 12.5, 1H), 4.99 (p, J_{HH} = 7, J_{HF} = 7, 1H), 5.31 (s, 2H), 7.32-7.41 (m, 5H), 9.29 (bs, 1H). δ_C(*125* MHz, $CDCl_3$) 10.7, 58.7, 66.3, 66.8 (q, J_{CF} = 33), 67.2, 116.9, 118.1, 125.4 (q, J_{CF} = 281), 128.4, 128.5, 128.8, 131.7, 136.1, 161.3. δ_F(*235* MHz, $CDCl_3$) -79.4 (d, J_{FH} = 7).

4-(2,2,2-Trifluoro-1-hydroxyethyl)-3-methylpyrrole-2-benzyloxycarbonyl-5-carboxylic acid (33)

Sulfuryl chloride (1.67 mL, 20.7 mmol) was added drop-wise to pyrrole **11** (1.5 g, 4.6 mmol) in DCM (11 mL) and ether (16.5 mL) at room temperature over five minutes. After the disappearance of starting material by TLC (typically around two hours), the mixture was decanted into a one-necked round-bottomed flask and concentrated. The residue was immediately treated with water (5 mL) and acetone (25 mL), and the mixture was brought to reflux for forty minutes. After cooling the mixture to room temperature,

the mixture was concentrated, dissolved in chloroform, dried over sodium sulfate, filtered and concentrated. The concentration/dissolution process was repeated twice more, without further drying, to remove residual acetone. The product was then redissolved in a minimum amount of chloroform and stirred overnight to yield the title compound as a white solid after precipitation (0.790 g, 48%). MP 174-176 °C (dec.) δ_H (*500* MHz, acetone-d_6) 2.50 (s, 3H), 5.17 (p, J_{HF} = 7, J_{HH} = 7, 1H), 5.36 (s, 2H), 6.65, (d, J_{HH} = 7, 1H), 7.35-7.49 (m, 5H), 9.55 (bs, 1H). δ_C (*125* MHz, acetone-d_6) 15.2, 67.7, 68.0, 74.8 (q, J_{CF} = 30), 98.6, 124.8 (q, J_{CF} = 282), 126.9, 129.0, 129.2 (2 co-incident signals), 133.2, 136.2, 160.2, 170.9.

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (37)

Water (2 mL) and DCE (4 mL) were added to a flask containing pyrrole **35** (0.16 g, 0.40 mmol) and sodium bicarbonate (0.11 g, 1.3 mmol). Sodium iodide (0.16 g, 1.1 mmol) and iodine (0.48 g, 1.9 mmol) were added to the biphasic reaction mixture, which was heated at reflux for an hour. After cooling the mixture to room temperature, sodium bisulfite was added, very slowly as a solid, to quench the excess iodine (quenching was complete with loss of colour and cessation of effervescence). The mixture was then separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried with magnesium sulfate followed by concentration to give **36** as an off-white solid. The crude product was then suspended in ethanol (4 mL) followed by the addition of sodium acetate (0.045 g, 0.55 mmol) and platinum(IV) oxide (0.014 g, 0.06 mmol) through a stream of nitrogen. A hydrogen atmosphere was maintained utilizing a balloon and needle through a septum and the reaction was stirred for 0.5 hours. The product was purified by flash column chromatography on silica gel using 1:5 EtOAc in hexanes as an eluent to yield the title compound as a white solid (0.080 g, 57 % yield). δ_H (*500* MHz, acetone-d_6) 2.12 (s, 3H), 2.40 (s, 3H), 5.31 (s, 2H), 6.20 (q, J_{HF} = 7, 1H), 7.00 (d, J_{HH} = 3, 1H), 7.32-7.42 (m, 5H), 9.50 (bs, 1H).

Benzyl 4-(1-benzyloxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (38)

Pyrrole **37** (0.149 g, 0.42 mmol) was dissolved in THF (1 mL) and dry benzyl alcohol (1.0 mL, 9.7 mmol) and the solution was heated to 80 °C. Immediately after coming to temperature a NaHMDS (0.211 g, 1.15 mmol) slurry in THF (1 mL) was added *via* cannula. These conditions were maintained for five minutes after which the hot mixture was poured into ice-water and extracted with DCM (3 x 10 mL). The combined extracts were washed with water (3 x 10 mL), brine (1 x 10 mL) and dried over anhydrous sodium sulfate. Purification was achieved using a flash silica column eluted with DCM to yield the title compound as an off-white solid (0.043 g, 26 % yield). MP 76-79 °C. δ_H (*500* MHz, $CDCl_3$) 2.27 (s, 3H), 4.47 (d, J_{HH} = 12, 1H), 4.66 (d, J_{HH} = 12, 1H), 4.68 (q, J_{HF} = 5, 1H), 5.31 (s, 2H), 7.02 (d, J_{HH} = 3.5, 1H), 7.29-7.43 (m, 10H), 9.16 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 10.3, 66.1, 71.1, 71.7 (q, J_{CF} = 32), 116.9, 119.7, 122.3, 124.3 (q, J_{CF} = 279), 127.7, 127.9, 128.1, 128.3, 128.3, 128.5, 128.6, 136.1, 136.8, 161.1. δ_F (*235* MHz, $CDCl_3$) -77.5 (d, J_{FH} = 5).

Diethyl 1-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-3,5-dimethylpyrrolo[3,2-*f*]indole-2,6-dicarboxylate (41)

Dipyrromethane **21** (0.201 g, 0.63 mmol) and DMAP (0.308 g, 2.52 mmol) were suspended/dissolved in DCM (3 mL), cooled to 0 °C, and TFAA (360 μL, 4.05 mmol) was added drop-wise. The suspension promptly thickened and turned yellow and the reaction was allowed to warm to room temperature and stirred vigourously for 2 days. The reaction mixture was diluted with DCM (10 mL), washed with water (3 x 5 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel flash chromatography *via* gradient elution with 10 % - 25 % ethyl acetate in hexanes as eluent allowing for the isolation of the product as an orange solid (0.036 g, 12 %). δ_H (*250* MHz, $CDCl_3$) 1.37 (t, J_{HH} = 7, 3H), 1.47 (t, J_{HH} = 7, 3H), 2.72 (s, 3H), 2.76 (s, 3H), 4.45 (q, J_{HH} = 7, 2H), 4.52 (q, J_{HH} = 7, 2H), 8.80 (s, 1H), 9.19 (bs, 1H). δ_F (*235* MHz, $CDCl_3$) -51.7, -68.8. ESIMS (-ve) *m/z*: 491.2 (M-1)

Diethyl 3,5-dimethyl-4-trifluoromethylpyrrolo[3,2-*f*]indole-2,6-dicarboxylate (43)

TFAA (0.22 mL, 1.6 mmol) and TFA (0.040 mL, 0.52 mmol), were added sequentially, each in one portion, to a suspension of dipyrromethane **21** (0.050 g, 0.15 mmol) in DCM (0.33 mL) at room temperature. The mixture was stirred for 3 hours after which the resulting yellow precipitate was filtered and dried to produce **43** (0.030 g, 50 % yield). MP 207-209 °C dec. δ_H (*250* MHz, $CDCl_3$) 1.45 (t, J_{HH} = 7, 6H), 2.69 (q, J_{HF} = 3, 6H), 4.43 (q, J_{HH} = 7, 4H), 7.73 (s, 1H), 10.67 (bs, 2H). δ_C (*125* MHz, DMSO-d_6) 12.6 (q, J_{CF} = 7), 14.2, 60.5, 97.7, 116.5, 122.8, 125.1 (q, J_{CF} = 270), 126.8, 136.7, 158.3 (q, J_{CF} = 38), 161.4. δ_F (*235* MHz, $CDCl_3$) -47.4 (bs). ESIMS (+ve) *m/z* (%) 257.3 (25), 377.1 (63), 697.0 (17), 814.7 (2M + 23, 100), 815.8 (50), 830.6 (18).

Benzyl 3-methyl-1-triisopropylsilylpyrrole-2-carboxylate (46)

Pyrrole **44** (0.506 g, 2.35 mmol) was added to a suspension of NaH (60 % dispersion in oil, 0.23 g, 5.8 mmol) in DMF (3.4 mL) at 0 °C. The mixture was stirred at room temperature until the cessation of effervescence. TIPSCl (1.23 mL, 5.75 mmol) was then added to the reaction mixture, which was stirred until TLC indicated completion of a reaction after 14 hours. The mixture was then diluted with water (10 mL), extracted with ether (3 x 10 mL) and the combined organic fractions were washed with water (5 x 10 mL), then dried over sodium sulfate to yield a colourless oil after concentration. The product was purified by flash chromatography on silica utilizing gradient elution conditions with hexanes – 24:1 hexanes to ethyl acetate producing a colourless oil (0.863 g, 99 %). δ_H (*500* MHz, $CDCl_3$) 1.08 (d, J_{HH} = 7.5,18H), 1.70 (spt, J_{HH} = 7.5, 3H), 2.33 (s, 3H), 5.29 (s, 2H), 6.11 (d, J_{HH} = 2.5, 1H), 7.01 (d, J_{HH} = 2.5, 1H), 7.31-7.42 (m, 5H). δ_C (*125* MHz, $CDCl_3$) 13.6, 14.7, 18.5, 65.6, 113.9, 124.3, 127.9, 128.0, 128.4, 131.6, 132.6, 136.7, 162.7. ESIMS (+ve) *m/z* (%) 91.0 (100), 328.0 (M – *i*-Pr), 371.1 (0.97). HRMS *m/z* calcd for $C_{22}H_{33}NO_2Si$, 371.2280, found 371.2280 ± 0.0008.

Benzyl 4-bromo-3-methyl-1-triisopropylsilylpyrrole-2-carboxylate (47)

NBS (0.41 g, 2.3 mmol) was added to a solution of pyrrole **46** (0.86 g, 2.3 mmol) in THF (5 mL) cooled to -78 °C and the mixture was stirred for two hours. The mixture was then warmed to room temperature followed by the addition of pyridine (0.067 mL) and hexane (5 mL) and further stirring (three minutes). The mixture was immediately poured onto a plug of neutral alumina and eluted with 1:33 ethyl acetate in hexanes affording an orange oil (0.917 g, 88 %). δ_H (*250* MHz, $CDCl_3$) 1.08 (d, J_{HH} = 7, 18H), 1.67 (p, J_{HH} = 7, 3H), 2.29 (s, 3H), 5.29 (s, 2H), 7.04 (s, 1H), 7.37-7.40 (m, 5H).

General procedure for the formation of the 4-acylpyrrole-2-carboxylates

Formation of A: phosphoric acid (85 %, 0.041 mL, 0.59 mmol) was added jet-wise to TFAA (0.166 mL, 1.2 mmol) at 0 °C and the reaction mixture was stirred at this temperature until homogeneous (the reaction mixture goes through a white precipitous stage prior to the achievement of complete homogeneity). ***Formation of B***: in a separate flask, TFAA (0.166 mL, 1.2 mmol) was added to a suspension of carboxylic acid (0.59 mmol) in acetonitrile (1 mL). The reaction mixture was stirred for 10 min (or until the disappearance of the insoluble suspended carboxylic acid). ***Formation of C***: the so-formed phosphoryl mixed anhydride **A** was then added to the solution of **B** in one portion using a Pasteur pippette. ***Acylation***: mixture **C** was allowed to stir briefly (30 sec to 2 min) then pyrrole **7** (0.100 g, 0.59 mmol) was added. The mixture was stirred until the disappearance of **7** was confirmed by TLC (5 min.) and the reaction was quenched using 10 % aqueous sodium carbonate (added drop-wise slowly) until the cessation of effervescence, followed thereafter by an additional 20 mL. Extraction with DCM followed by purification using flash chromatography on silica gel and a gradient elution (19:1 hexanes: ethyl acetate – 4:1 hexanes:ethyl acetate) was then performed to give the 4-acylpyrrole.

Ethyl 4-(3,5-dimethoxybenzoyl)-3,5-dimethylpyrrole-2-carboxylate (51b)

White solid (0.121 g, 81 %). Starting material (0.025 g) was recovered under solvent-free conditions. MP 183-185 °C. δ_H (*500* MHz, $CDCl_3$) 1.38 (t, J_{HH} = 7, 3H), 2.28 (s, 6H), 3.83 (s, 6H), 4.34 (q, J_{HH} = 7, 2H), 6.64 (t, J_{HH} = 2.5, 1H), 6.90 (d, J_{HH} = 2.5, 2H), 9.05 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 12.2, 13.6, 14.5, 55.6, 60.4, 104.6, 106.5, 118.5, 123.2, 129.3, 136.6, 142.3, 160.8, 161.6, 193.4. ESIMS (*m/z*) 684.8 (2M + 23).

Ethyl 4-benzoyl-3,5-dimethylpyrrole-2-carboxylate (51c)

Light yellow solid (0.132 g, 81 %). MP 111-112 °C. δ_H (*500* MHz, $CDCl_3$) 1.37 (t, J_{HH} = 7, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 4.34 (q, J_{HH} = 7 Hz, 2H), 7.43 (t, J_{HH} = 1.5 Hz, 2H), 7.54 (t, J_{HH} = 1.5, 1H), 7.73 (d, J_{HH} = 1.5, 2H), 9.56 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 12.6, 13.9, 14.9, 60.7, 118.8, 123.5, 128.6, 129.5, 129.6, 132.5, 137.3, 140.7, 162.3, 194.3. ESIMS (*m/z*) 564.9 (2M + 23).

Ethyl 4-(4-ethoxybenzoyl)-3,5-dimethylpyrrole-2-carboxylate (51d)

Compound was synthesized utilizing the method outlined by Knight and co-workers.[93] Off-white solid (0.126 g, 67 %). MP 183-185 °C. δ_H (*500* MHz, $CDCl_3$) 1.37 (t, J_{HH} = 7, 3H), 1.44 (t, J_{HH} = 7, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 4.10 (q, J_{HH} = 7, 2H), 4.34 (q, J_{HH} = 7, 2H), 6.92 (d, J_{HH} = 5, 2H), 7.74 (d, J_{HH} = 5, 2H), 9.84 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 12.6, 13.5, 14.7, 15.0, 60.6, 64.0, 114.3, 118.6, 123.8, 129.2, 132.0, 132.9, 136.6, 162.4, 162.8, 193.4. ESIMS (*m/z*) 652.9 (2M + 23).

Ethyl 4-hexadecanoyl-3,5-dimethylpyrrole-2-carboxylate (51e)

White solid (0.185 g, 77 %). MP 93-94 °C. δ_H (*500* MHz, $CDCl_3$) 0.88 (t, J_{HH} = 7, 3H), 1.25 (m, 24H), 1.35 (t, J_{HH} = 7, 3H), 1.68 (p, J_{HH} = 7, 2H), 2.51 (s, 3H), 2.59 (s, 3H), 2.72 (t, J_{HH} = 7, 2H), 4.33 (q, J_{HH} = 7, 2H), 9.06 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 13.0, 14.6,

14.8, 15.5, 23.0, 24.6, 29.7, 29.8, 29.9, 29.9, 30.0, 32.3, 43.3, 60.7, 118.2, 124.0, 129.3, 138.0, 162.0, 198.9. ESIMS (*m/z*) 833.1 (2M + 23).

Ethyl 3,5-dimethyl-4-propionylpyrrole-2-carboxylate (51f)

White solid (0.120 g, 90 %). MP 143-144 °C. δ_H (*500* MHz, $CDCl_3$) 1.17 (t, J_{HH} = 7.5, 3H), 1.38 (t, J_{HH} = 7, 3H), 2.53 (s, 3H), 2.60 (s, 3H), 2.76 (q, J_{HH} = 7.5, 2H), 4.34 (q, J_{HH} = 7, 2H), 9.27 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 8.5, 13.1, 14.8, 15.5, 36.3, 60.7, 118.2, 123.7, 129.4, 138.2, 162.1, 199.0. ESIMS (*m/z*) 468.9 (2M + 23).

Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (51g)

White solid (0.104 g, 83 %). MP 143-145 °C. δ_H (*500* MHz, $CDCl_3$) 1.38 (t, J_{HH} = 7, 3H), 2.45 (s, 3H), 2.53 (s, 3H), 2.59 (s, 3H), 4.34 (q, J_{HH} = 7, 2H), 9.14 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 13.0, 14.8, 15.5, 31.6, 60.7, 118.3, 123.9, 129.6, 138.5, 162.0, 195.8. ESIMS (*m/z*) 440.9 (2M + 23).

Ethyl 3,5-dimethyl-4-(2,2-dimethylpropionyl)pyrrole-2-carboxylate (51h)

White solid (0.129 g, 86 %). MP 144-146 °C. δ_H (*500* MHz, $CDCl_3$) 1.24 (s, 9H), 1.39 (t, J_{HH} = 7, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 4.34 (q, J_{HH} = 7, 2H), 9.12 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 12.7, 13.4, 14.8, 27.3, 45.8, 60.4, 118.2, 125.8, 126.1, 129.5, 162.0, 213.0. ESIMS (*m/z*) 524.9 (2M + 23).

Ethyl 3,5-dimethyl-4-(3-methyl-butyryl)pyrrole-2-carboxylate (51i)

White solid (0.099 g, 66 %). MP 97-99 °C. δ_H (*500* MHz, $CDCl_3$) 0.97 (d, J_{HH} = 7, 6H), 1.37 (t, J_{HH} = 7, 3H), 2.24 (n, J_{HH} = 7, 1H), 2.51 (s, 3H), 2.57 (s, 3H), 2.61 (d, J_{HH} = 7, 2H), 4.34 (q, J_{HH} = 7 Hz, 2H), 9.27 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 12.7, 14.8, 15.0,

22.8, 25.0, 51.9, 60.4, 117.9, 124.0, 128.9, 137.6, 161.8, 198.4. ESIMS (*m/z*) 524.9 (2M + 23).

Diethyl 4-(3′,5′-dimethyl-pyrrole-2′-carbonyl-4′-carboxylate)-3,5-dimethylpyrrole-2-carboxylate (54)

Off-white solid (0.155 g, 72 %). MP 213-214 °C. δ_H (*500* MHz, $CDCl_3$) 1.35 (t, J_{HH} = 7, 3H), 1.38 (t, J_{HH} = 7, 3H), 2.22 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 2.60 (s, 3H), 4.28 (q, J_{HH} = 7 Hz, 2H), 4.35 (q, J_{HH} = 7 Hz, 2H), 9.52 (s, 1H), 10.06 (s, 1H). δ_C (*125* MHz, $CDCl_3$) 11.6, 12.3, 12.6, 14.7, 14.8, 14.8, 59.9, 60.7, 114.4, 118.8, 124.6, 128.3, 129.9, 131.7, 134.8, 141.6, 162.3, 165.8, 183.3. ESIMS (*m/z*) 742.9 (2M + 23).

Ethyl 4-(4′-acetyl-3′,5′-dimethyl-pyrrole-2′-carbonyl)-3,5-dimethyl-pyrrole-2-carboxylate (55)

Off-white solid (0.099 g, 63 %). MP 256-257 °C dec. δ_H (*500* MHz, DMSO-d_6) 1.31 (t, J_{HH} = 7, 3H), 2.10 (s, 3H), 2.16 (s, 3H), 2.24 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.24 (q, J_{HH} = 7 Hz, 2H), 11.60 (bs, 1H), 11.72 (bs, 1H). δ_C (*125* MHz, DMSO-d_6) 11.6, 12.4, 12.7, 14.8, 14.9, 31.7, 59.8, 118.0, 123.1, 124.3, 127.6, 127.8, 129.6, 135.6, 139.6, 161.2, 183.0, 195.0. ESIMS (*m/z*) 682.9 (2M + 23).

Diethyl 2,2′-bis(3′,5′-dimethyl-pyrrole-4′-carboxylate) carbonyl (57)

Orange solid (0.88 g, 37 %)(Fischer obtained colourless needles).[115] MP 226-227 °C MP lit[115] 221 °C. δ_H (*500* MHz, DMSO-d_6) 1.28 (t, J_{HH} = 7, 3H), 2.21 (s, 3H), 2.44 (s, 3H), 4.19 (q, J_{HH} = 7 Hz, 2H), 11.74 (bs, 1H). δ_C (*125* MHz, DMSO-d_6) 12.5, 14.0, 14.8, 59.3, 112.7, 128.0, 128.4, 139.9, 165.2, 179.7. ESIMS (*m/z*) 742.8 (2M + 23).

2,3-Dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrole hydrobromide (59)

Pd/C catalyst (10 % on C, 0.306 g, 10 mol %) was added to pyrrole **11** (1.00 g, 3.06 mmol) in THF (40 mL) through a stream of nitrogen and the reaction mixture was then stirred under a hydrogen (1.0 atm) atmosphere. After three days the mixture was filtered through celite and concentrated to facilitate the precipitation of the carboxylic acid (isolated in 87 % yield). The product **12** was then suspended directly in ethanolamine (25 mL) and the mixture was heated to 170 °C for 45 minutes, after which the mixture was poured into ice water and extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (50 mL) and then brine (50 mL) followed by drying over sodium sulfate and concentrated. The residue was dissolved in chloroform and re-concentrated to yield the α-free intermediate as a yellow crystalline solid **58** (72 % yield). α-Free pyrrole **58** (0.384 g, 1.99 mmol) and 2-formyl pyrrole **15** (0.190 g, 2.00 mmol) were dissolved in THF (25 mL) and concentrated (48 %) aqueous hydrogen bromide (0.300 mL) was added to the solution. After stirring overnight at room temperature, the mixture was concentrated until very little solvent remained. Ether, pre-treated with sodium borohydride, was then added until there was copious precipitate, which was then filtrated and dried to give the title compound as a red solid (0.399 g, 57 % yield). MP 190-230 °C dec. δ_H (*500* MHz, DMSO-d_6) 1.04 (t, J_{HH} = 8, 3H), 2.34 (s, 3H), 2.43 (m, 5H), 2.58 (s, 3H), 2.60 (s, 3H), 5.27 (q, J_{HF} = 8, 1H), 6.83 (bs, 1H), 7.45 (s, 1H), 12.52 (bs, 1H), 12.69 (bs, 1H). δ_C(*125* MHz, DMSO-d_6) 10.7, 11.1, 13.6, 14.2, 15.0, 17.4, 65.8 (q, J_{CF} = 32), 121.9, 122.3, 126.2, 126.4 (q, J_{CF} = 281), 128.5, 132.6, 143.9, 145.2, 151.7, 158.1 δ_F (*235* MHz, $CDCl_3$) -78.2 (d, J_{HF} = 8). ESIMS *m/z*: 327.1

Zinc bis[2,3-dimethyl-4-(1-hydroxy-2,2,2-trifluoroethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (60)

Method 1

Dipyrromethene **59** (0.050 g, 0.14 mmol), zinc(II) acetate dihydrate (0.070 g, 0.32 mmol), and sodium acetate (0.046 g, 0.34 mmol) were added to a flask and dissolved by the addition of methanol (7 mL). The mixture was stirred for 0.5 hours after which it was concentrated and redissolved in ethyl acetate. The solution was then washed with water

(3 x 5 mL), brine (5 mL) and dried over sodium sulfate. The concentrate was taken up in hot hexanes, producing an orange hexanes solution, leaving behind a dark brown residue. The solution of hexanes was concentrated to yield an iridescent orange product (0.027 g, 64 % yield).

Method 2

Dipyrromethene **59** (1.00 g, 2.5 mmol) was dissolved in methanol (80 mL) and lithium hydroxide monohydrate (0.932 g, 9 mmol) was added directly to the solution causing a dramatic shift in colour from orange/red to yellow. Zinc(II) perchlorate (**WARNING**: possible oxidizer, beware exotherm/explosion. 1.30 g, 5.0 mmol) was then added and the yellow solution turned orange immediately. The mixture was stirred for one hour followed by dilution with water to precipitate the desired product, which was isolated as a very fine orange powder after drying overnight in a vacuum oven at room temperature (0.763 g, 85%). MP 197-198 °C. δ_H (*500* MHz, $CDCl_3$) 1.01 (t, J_{HH} = 7.5, 3H), 1.02 (t, J_{HH} = 7.5, 3H), 1.89-1.94 (m, 3H), 1.95-2.20 (m, 3H), 2.20 (bs, 1H), 2.22 (d, J_{HH} = 1.5, 3H), 2.35-2.40 (m, 5H), 5.00-5.05 (m, 1H), 7.04 (s, 1H). δ_C (*125* MHz, $CDC1_3$) 10.6, 10.7, 15.1, 15.5, 15.6, 18.2, 68.4 (q, J_{CF} = 33), 68.4 (q, J_{CF} = 33), 117.9, 121.8, 125.6 (q, J = 280), 132.3, 134.8, 134.9, 137.8, 139.6, 153.3, 161.5. δ_F (*235* MHz, $CDCl_3$) -78.9 (d, J = 7.5). ESIMS (*m/z*) 327.2 (ligand), 715.1 (M + 1), 737.1 (M + 23, Na adduct).

Benzyl 4-(difluoroethoxycarbonylmethyl)-3,5-dimethylpyrrole-2-carboxylate (66)

Dry DMSO was added, *via* cannula, to a flask containing β-iodopyrrole **67** (5.00 g, 14.1 mmol) and copper metal (6.88 g, 108 mmol), after an initial room temperature induction of 20 minutes, bromodifluoroacetate **68** (5.44 mL, 42.2 mmol) was added through a septum. The reaction mixture was heated at 55 °C for four hours after which the mixture was diluted with DCM (280 mL) and the resulting precipitous solution was filtered through celite. The filtered organic solution was then washed with aqueous 1.3 M potassium phosphate monobasic buffer (2 x 500 mL), followed by water (3 x 600 mL) and brine (600 mL). The mixture was then dried over sodium sulfate, concentrated and purified by flash chromatography on silica gel using an eluent

containing a mixture of 7:2:1 hexanes:DCM:ether. The title compound isolated as an off-white solid (2.34 g, 47 %). MP 83-85 °C. δ_H (*250* MHz, $CDCl_3$) 1.33 (t, J_{HH} = 7.5, 3H), 2.37 (t, J_{HF} = 2.5, 3H), 2.42 (t, J_{HF} = 2.5, 3H), 4.31 (q, J_{HH} = 7.5, 2H), 5.32 (s, 2H), 7.37-7.45 (m, 5H), 8.94 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 11.0, 13.0, 14.1, 63.0, 66.2, 113.9 (t, J_{CF} = 248), 114.2 (t, J_{CF} = 28), 118.1, 128.0, 128.2, 128.4, 128.7, 133.5, 136.2, 161.5, 164.7 (t, J_{CF} = 37). δ_F (*235* MHz, $CDCl_3$) -102.5. ESIMS (-ve) *m/z* (%): 228.0 (17), 260.1 (26), 272.1 (27), 300.0 (93), 301.1 (20), 322.0 (29), 350.1 (M-1, 100), 366.1 (35), 443.9 (90)

Benzyl 4-iodo-3,5-dimethylpyrrole-2-carboxylate (67)

β-Free pyrrole **9** (0.053 g, 0.23 mmol) was dissolved in DCE (10 mL) and to this solution was added iodine (0.070 g, 0.26 mmol), potassium iodide (0.119 g, 0.72 mmol), and water (3 mL). The biphasic mixture was brought to reflux and sodium bicarbonate (0.200 g, 2.40 mmol) was added. The misture was heated at reflux for 3 hours and was then cooled to room temperature, followed by addition of sodium bisulfate, separation of the organic layer, drying over sodium sulfate, and concentrating to yield a crude brown product (0.068 g, 83 % yield), which was clean by NMR spectroscopy. It was found that the product could be crystallized from 49:1 hexanes to ethyl acetate but the crude product could be utilized effectively without this operation. MP 133-135 °C. δ_H (*500* MHz, $CDCl_3$) 2.27 (s, 3H), 2.30 (s, 3H), 5.30 (s, 2H), 7.32-7.41 (m, 5H), 9.01 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 14.5, 14.8, 66.1, 72.4, 118.2, 128.3, 128.4, 128.8, 131.5, 134.6, 136.4, 160.7. APCI MS *m/z* (%): 354.2 (M-1, 100).

Benzyl 3,5-dimethyl-4-oxalylpyrrole-2-carboxylate (69)

Pyrrole **66** (0.806 g, 2.29 mmol) dissolved in 1:1 THF/water and lithium hydroxide monohydrate (0.277 g, 6.60 mmol) was then added to the solution upon which the mixture turned yellow. After stirring overnight at room temperature, the mixture was concentrated and extracted with DCM (2 x 50 mL) followed by ethyl acetate (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, and concentrated yielding

a white solid (0.789 g, 99 %). A small portion was crystallized from methanol/water for identification, and the rest was used as is for the next step. MP 156 -158 °C (dec). δ_H (*250* MHz, methanol-d_4) 2.46 (s, 3H), 2.52 (s, 3H), 5.34 (s, 2H), 7.35-7.48 (m, 5H), 11.87 (bs, 1H). δ_C (*125* MHz, methanol-d_4) 10.3, 12.0, 65.7, 117.2, 118.8, 128.0, 128.0, 128.3, 131.1, 136.5, 142.1, 161.0, 168.4, 185.3. APCIMS (-ve) *m/z* (%): 228.0 (27), 299.9 (M - 1, 100).

Dibenzyl 4,4′-(ethane-1,2-dione)-3,3′,5,5′-tetramethylbispyrrole-2,2′-dicarboxylate (70)

Compound **69** (0.519 g, 1.43 mmol) was treated for 2.5 hours with neat oxalyl chloride at reflux, after which the excess was removed *in vacuo*. The residue was then chased with chloroform (2 x 5 mL) (addition of a portion of chloroform followed by immediate concentration) to yield an orange solid, which was taken up in DCM (4 mL) and injected into a flask containing pyrrole **9** (0.308 g, 1.34 mmol). The solution was stirred at room temperature and tin (IV) chloride (0.310 mL, 2.65 mmol) was added in one portion. The mixture was stirred for 0.5 hours. This was followed by quenching the reaction with HCl (20 mL of 1.6 M) for twenty minutes. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL), followed by drying of the combined organic layers over sodium sulfate, and concentration. The residue was purified using flash column chromatography on silica and a gradient elution beginning with 1:5 EtOAc in hexanes and ending with 1:2.5 EtOAc in hexanes. The title compound was obtained as an orange solid (0.238 g, 35 % yield). MP 230-233 °C. δ_H (*500* MHz, $CDCl_3$) 2.24 (s, 3H), 2.27 (s, 3H), 5.31 (s, 2H), 7.37 (m, 5H), 9.00 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 11.6, 13.0, 66.2, 118.1, 126.2, 128.2, 128.4, 128.7, 129.4, 136.2, 136.6, 161.8, 190.0.

4-Ethyl-3-methyl-5-(pyrrol-2-ylmethylidene)-pyrrol-2-one (75)

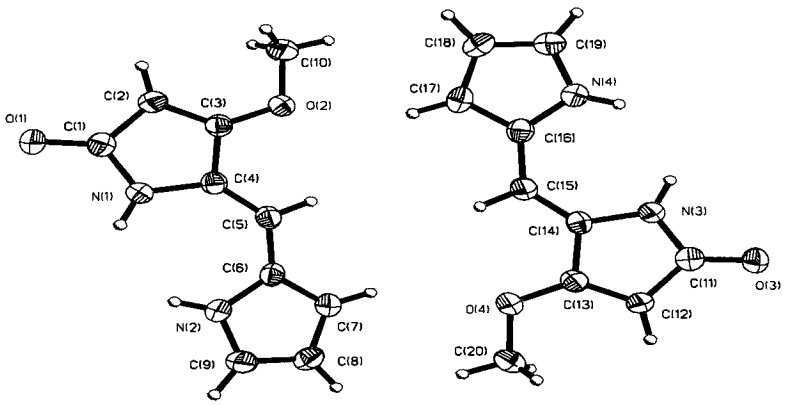
Formyl pyrrole **74** (0.96 g, 10 mmol) and pyrinone **73** (2.53 g, 20 mmol) were dissolved in dry DMSO (for purity of solvent not water content, 30 mL) and the reaction mixture was sparged with nitrogen. An aqueous solution of potassium hydroxide (10.5 mL, 4 M

solution, sparged with nitrogen) was added through a septum and the resulting orange mixture was heated to 60 °C and put under nitrogen for 12 hours with stirring. The reaction mixture was then poured into water (200 mL) and the resulting precipitate was filtered, the solid taken up in DCM, and dried over anhydrous sodium sulfate. After concentration the title compound was obtained as an orange solid (1.84 g, 90 %). MP 213-215 °C. δ_H (*500* MHz, $CDCl_3$) 1.17 (t, J_{HH} = 7, 3H,), 2.12 (s, 3H), 2.43 (q, J_{HH} = 7.5, 2H), 6.15(s, 1H), 6.26-6.29 (m, 1H), 6.42-6.45 (m, 1H), 7.02-7.05 (m, 1H), 10.7 (bs, 1H), 11.0 (bs, 1H). δ_C (*125* MHz, $CDCl_3$) 9.6, 13.4, 17.0, 103.3, 109.9, 116.0, 123.4, 127.5, 130.6, 130.7, 149.2, 174.1. EIMS *m/z* (%): 202 (100). HRMS *m/z* calcd for $C_{12}H_{14}N_2O$, 202.1106, found 202.1108 ±0.0008.

4-Methoxy-5-(pyrrol-2-ylmethylidene)-pyrrol-2-one (77)

4-Methoxy-2-pyrinone (0.42 g, 4.4 mmol) and formyl pyrrole **74** (1.0 g, 8.8 mmol) were dissolved in DMSO (14.5 mL) and the reaction mixture was sparged with nitrogen. An aqueous solution of potassium hydroxide (4.4 mL, 4M, sparged with nitrogen) was added through a septum and the resulting orange mixture was stirred at 60 °C under nitrogen for twelve hours. Water (5 mL) was added to the reaction mixture, which was then extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, followed by purification with flash chromatography on silica gel using neat EtOAc. The title compound was allowed to crystalize from the column fractions and the title compound was isolated as rectangular prismatic yellow crystals (0.837 g, 72 %). MP 210-212 °C. δ_H (*500* MHz, DMSO-d_6) 3.86 (s, 3H), 5.24 (s, 1H), 6.15-6.18 (m, 2H), 6.72 (dd, J_{HH} = 1, J_{HH} = 3, 1H), 6.93 (dd, J_{HH} = 1, J_{HH} = 3, 1H), 9.40 (bs, 1H), 11.07 (bs, 1H). δ_C (*125* MHz, DMSO-d_6) 60.0, 93.2, 99.7, 112.0, 113.4, 122.6, 127.5, 128.1, 168.6, 172.6. EIMS *m/z* (%): 190 (100), 147 (12), 133 (12), 106 (12). HRMS *m/z* calcd for $C_{10}H_{10}N_2O_2$, 190.0742, found 190.0745 ± 0.0008. Crystal data for $C_{10}H_{10}N_2O_2$, 190.2: yellow rectangular prism, monoclinic, space group $P2_1/n$ (no. 14), a = 12.955(2) Å, b = 12.152(3) Å, c = 13.228(2), α = 90 °, β = 115.905(9) °, γ = 90°, V = 1875.9(5) Å^3, Z = 8, T = 213(2) K, $2\theta_{max}$ = 60.1 °, Rigaku AFC5R diffractometer, Mo Kα (λ =0.7107 Å), reflections collected = 5973, unique reflections = 5502 (R_{int} = 0.069), final R [I>2σ(I)]

(R1 = 0.0434, wR2 = 0.0997), R indices (all data [R1 = 0.2495, wR2 = 0.1545]), gof (F^2) = 0.934



7-Methoxy-6-(2*H*-pyrrol-2-ylmethylidene)-pyrrolo[2,1-*b*][1,3]oxazine (78)

Dipyrrinone **77** (0.050 g, 0.26 mmol), potassium carbonate (0.072 g, 0.52 mmol) and 18-crown-6 (0.006 g, 0.03 mmol) were dissolved/suspended in THF (1 mL) and stirred under reflux. 1,3-Diiodopropane (0.015 mL, 0.13 mmol) was added *via* syringe and after 2 hours the reaction mixture was applied directly to a silica gel flash column, eluting with 2 % methanol in DCM. A second column was performed using 1 % methanol in ether as eluent, producing the title compound (0.087 g, 145 % yield) as a yellow film. Despite overnight exposure of the product to high vacuum not all of the solvent could be removed, hence the extraneous yield. Solvent peaks are omitted for clarity: δ_H (*500* MHz, $CDCl_3$) 1.87 (p, J_{HH} = 6, 2H), 3.54-3.52 (m, 2H), 3.89 (s, 3H), 3.97 (t, J_{HH} = 6, 2H), 5.16 (s, 1H), 6.21 (dd, J_{HH} = 5, J_{HH} = 3, 1H), 6.27 (dd, J_{HH} = 5, J_{HH} = 1, 1H), 6.31 (s, 1H), 6.69 (dd, J_{HH} = 3, J = 1, 1H). δ_C (*125* MHz, $CDCl_3$) 28.6, 30.3, 36.0, 44.5, 91.2, 109.5, 113.1, 123.8, 131.8, 166.1, 170.0. EIMS *m/z* (%) 69 (30), 106 (28), 118 (27), 145 (20), 187 (14), 199 (13), 215 (24), 230 (M^+, 100).

3-Ethyl-5-methoxy-4-methyl-2-(2*H*-pyrrol-2-ylmethylidene)pyrrole (82)

Dipyrrinone **75** (0.20 g, 1.0 mmol) and potassium hydroxide (0.27 g, 4.8 mmol, pulverized to a powder) were dissolved in anhydrous DMSO (2 mL) and the mixture was stirred for 10 minutes, under argon. Dimethyl sulfate (0.05 mL, 0.53 mmol) was added to the mixture, which was stirred for 25 minutes. The reaction mixture was diluted with water (2 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), and dried over sodium sulfate. After concentration the yellow mixture was purified by preparative TLC using 1:4 ethyl acetate in hexanes. The band with $R_f = 0.8$ was isolated using ethyl acetate and the title compound was obtained as a yellow solid after concentration (0.041 g, 19 %). MP 66-68 °C. δ_H (500 MHz, CDCl3) 1.06 (t, $J_{HH} = 7$, 3H), 2.05 (s, 3H), 2.30 (q, 2H, $J_{HH} = 7$), 4.05 (s, 3H), 6.17-6.23 (m, 1H), 6.43-6.45 (m, 1H), 6.89, (s, 1H), 11.34 (bs, 1H). δ_C (125 MHz, CDC13) 9.6, 13.8, 17.1, 55.6, 109.9, 113.1, 114.8, 122.7, 130.0, 131.0, 141.4, 145.6, 175.0. EIMS m/z (%): 216 (100), 201 (100). HRMS *m/z* calcd for $C_{14}H_{18}N_2O$, 216.1262, found 216.1262 ±0.0008.

3-Ethyl-5-methoxy-1,4-Dimethyl-2-(2*H*-pyrrol-2-ylmethylidene)pyrrole (83)

Dipyrrinone **75** (0.10 g, 0.50 mmol) and potassium hydroxide (0.13 g, 2.4 mmol, pulverized powder) were dissolved in anhydrous DMSO (1 mL) and stirred for 10 minutes under argon. Dimethyl sulfate (0.125 mL, 1.3 mmol) was added to the mixture which was left stirring for 25 minutes, after which the mixture was diluted with water (2 mL) and DCM (10 mL). After separation of the organic phase, the aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). After concentration the yellow mixture was purified by preparative TLC using 1:4 ethyl acetate in hexanes and the band with $R_f = 0.6$ was isolated using ethyl acetate and the title compound was obtained as a yellow solid after concentration (0.028 g, 24 %). MP 118-121 °C. δ_H (*500* MHz, $CDCl_3$) 1.06 (t, $J_{HH} = 7$, 3H), 2.07 (s, 3H), 2.30 (q, $J_{HH} = 7$, 2H), 3.70 (s, 3H), 4.07 (s, 3H), 6.22-6.24 (m, 1H), 6.39 (s, 1H), 6.69-6.71 (m, 1H), 7.43-7.45 (m, 1H). δ_C (*125* MHz, $CDC1_3$) 9.5, 13.7,

17.0, 34.0, 55.4, 109.7, 110.0, 116.5, 125.3, 130.0, 130.6, 141.1, 146.6, 176.0. EIMS *m/z* (%): 230 (100), 229 (18), 215 (39), 201 (12). HRMS *m/z* calcd for $C_{14}H_{18}N_2O$, 230.1419, found 230.1430 ±0.0008.

3-Ethyl-1,4-dimethyl-5-(1-methylpyrrol-2-ylmethylidene)pyrrol-2-one (84)

Dipyrrinone **75** (0.10 g, 0.50 mmol) and potassium hydroxide (0.13 g, 2.4 mmol, pulverized powder) were dissolved in anhydrous DMSO (1 mL) and stirred for 10 minutes, under argon. Dimethyl sulfate (0.125 mL, 1.3 mmol) was added to the mixture which was left stirring for 25 minutes, after which the mixture was diluted with water (2 mL) and DCM (10 mL). After separation of the organic phase, the aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). After concentration the yellow mixture was purified by preparative TLC using 1:4 ethyl acetate in hexanes after which the band with $R_f = 0.3$ was isolated using ethyl acetate and the title compound was obtained as a yellow solid after concentration (0.051 g, 44 %). MP 77-79 °C. δ_H (*500* MHz, $CDCl_3$) 1.11 (t, J_{HH} = 7, 3H), 2.09 (s, 3H), 2.37 (q, J_{HH} = 7, 2H), 3.01 (s, 1H), 3.59 (s, 3H), 5.92 (s, 1H), 6.15 (d, J_{HH} = 2, 1H), 6.69 (t, J_{HH} = 2, 1H). δ_C (*125* MHz, $CDC1_3$) 10.1, 13.7, 17.4, 28.8, 34.6, 98.8, 108.5, 112.6, 123.7, 127.1, 133.1, 140.5, 141.3, 172.9. EIMS *m/z* (%): 230 (100). HRMS *m/z* calcd for $C_{14}H_{18}N_2O$, 230.1419, found 230.1421 ±0.0008.

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